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Incidence of Co-infection and its Impact on COVID-19 Patients admitted in the Intensive Care Unit

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ABSTRACT

Background: Viral-bacterial co-infections are one of the most serious medical issues, with higher fatality rates. Few investigations have studied bacterial superinfections in individuals with coronavirus disease 2019 (COVID-19). Hence, we carried out the current research to assess the different types of secondary bacterial and fungal infections and their response to antibiotics and antifungals that affect COVID-19 patients' outcomes when admitted to the intensive care unit (ICU).

Methods: A total of 65 COVID-19 patients admitted to the ICU were studied in this cross-sectional study. Endotracheal aspirate or sputum samples and blood samples were collected using strict infection control procedures. The bacterial isolates were identified using gram staining, growth characteristics, and standard biochemical reactions with antimicrobial susceptibility testing. Fungal infections were determined by serological assays.

Results: The incidence of bacterial co-infection was 47.7%. Death was significantly higher among COVID-19 patients with secondary infection ($P < 0.001$). The clinical isolates were 34, of which 31 (91.18%) were bacteria and 3 (8.82%) were fungi. Klebsiella pneumonia and Acinetobacter baumannii were the predominant gram-negative bacteria; representing 38% and 17.65%, respectively. Staphylococcus aureus was the predominant isolated gram-positive bacteria represented 11.76%. Candida albicans were the predominantly isolated fungi. Tigecycline and amikacin were the most sensitive antibiotics for associated bacterial co-infection of COVID-19 cases (80.6% and 70.9%, respectively). Flucytosine, amphotericin B, caspofungin, and micafungin were all found to be sensitive against candida Albicans isolates.

Conclusions: Mortality was significantly higher among COVID-19 patients with secondary bacterial and fungal co-infection. Klebsiella pneumonia and Acinetobacter baumannii were the most common co-infecting agents. Tigecycline and amikacin displayed the highest sensitivity patterns.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (COVID-19) was first discovered in Wuhan, Hubei Province, China, in December 2019. The virus has spread worldwide and threatened thousands of people's lives [1]. Some patients had been hospitalized as a result of a severe respiratory illness, and intensive care with mechanical ventilation support was required in critical conditions (5–15%) [2,3].

Despite the fact that most COVID-19-related mortality has occurred in elders with serious underlying diseases [4]. In intensive care units (ICUs), nosocomial pneumonia (NP) is still a considerable risk factor for patients, especially when they are intubated. It could be accompanied by lower respiratory tract infections that worsen the patients' conditions. Nosocomial infections (NIs) are infections acquired within 48–72 hours of hospital admission. They are disseminated mostly through face-to-face interactions, medical equipment, and devices [5]. Acinetobacter baumannii spp., Escherichia coli, Klebsiella pneumonia, Enterobacter spp., Enterococcus spp., Staphylococcus spp., and Pseudomonas aeruginosa spp. are the most frequently discovered leading causes of NIs among microorganisms [6].

Co-infections can also be caused by these organisms in hospitalized patients when associated with viral respiratory tract infections. Also, patients without any chronic diseases and in any age group can be at risk of co-infections [7,8].

Viruses such as influenza viruses have been related to secondary bacterial pneumonia, which can develop during hospitalization and lead to mortality in persons

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with or without preexisting respiratory diseases, according to several studies [9]. Damage of ciliated cells has also been related to respiratory syncytial viral infection. This can result in decreased mucociliary clearance, facilitated bacterial adhesion to mucins, and increased airway bacterial colonization. Furthermore, following the loss of airway epithelial cells due to viral infection, novel receptors for bacterial adhesion may arise [10].

After an immediate inflammatory process and respiratory tissue destruction, induced by a viral infection, the lung tissue passes through a resolving/repair phase. This period may increase vulnerability to respiratory bacterial infections because of variable immunological responses in different cases. As a result, bacterial superinfection can develop following a viral infection, potentially increasing morbidity and mortality [11].

The role of bacteria in the pathogenesis of infectious disorders due to the new coronavirus is still vague. There have been a few researches about co-infections with COVID-19 patients [12,13]. So, our research aims to add knowledge regarding co-infection and its impact on determining outcomes of COVID-19 patients. As a result, our goal was to identify the types of secondary bacterial infections and their antibiotic sensitivity, as well as their impact on the outcome of COVID-19 patients in the ICU.

2. Patients and methods

This cross-sectional analytic study was carried out on 65 positive COVID-19 critically ill patients admitted to the ICU. The study was started after obtaining the Ethical Committee approval from Suez Canal University, Ismailia, Egypt. Informed consent was taken from confirmed COVID-19 participants or their first-degree relatives after an explanation of the whole procedure. Inclusion criteria included adult patients with confirmed COVID-19 by positive polymerase chain reaction (PCR) test and admitted to ICU according to WHO severity criteria [14]. Pregnant women and patients on regular steroids or immunosuppressant drugs were excluded from the study.

Patients were subjected to full history taking, general examination, hemodynamics and O_2 saturation measurement, and local chest examination. Laboratory tests and chest computed tomography (CT) scans were done and reviewed by two physicians independently. On admission, a blood sample was taken for ABG, CBC, PTT, PT, D dimer, S. ferritin, S. electrolytes, CRP, liver, and kidney functions.

2.1. Collection of the sample for the detection of secondary bacterial infection

The gathering of samples was done within 72 hours of admission and repeated when bacterial infection was suspected with at least three-day intervals between the two collected samples for each ICU patient.

Bacterial infection was suspected when fever persisted or increased leucocytic count with neutrophilia [15].

An endotracheal aspirate (ETA) specimen or sputum and a blood sample were all gathered in sterilized containers. The samples were immediately sent to a microbiological lab, where they were analyzed using conventional methods [16].

Samples were cultured on Blood agar (HiMedia, M001) containing 5% mammalian blood, Chocolate Agar (HiMedia, M001), Mannitol salt agar (HiMedia, M118) and on MacConkey agar (HiMedia, M081) and then incubated at 37°C for 24–72 hrs under standard conditions. The bacteria's colonial growth was confirmed by gram staining, other culture characteristics and biochemical reaction testing (e.g., catalase, citrate, oxidase, urease, sensitivity to some antibiotic disks, Methyl Red [MR]-Voges-Proskauer [VP], Triple Sugar Iron Agar [TSI], Sulfide Indole Motility [SIM], Dnase).

Ten mL of venous blood for blood culture was obtained after taking stringent infection control measures and then inoculated the blood into both aerobic and anaerobic bottles (Salix and Spectrum) [17].

Incubation of blood cultures occurred for up to 10 days at 37 ℃. Discard as negative when the 10-days incubation period has been completed. Subculture onto Blood agar aerobically and anaerobically, and Chocolate agar with CO2 (5–10%) and MacConkey agar aerobically have been performed. Isolated bacteria were identified by staining, culture characteristics, and biochemical reactions.

2.2. Antimicrobial susceptibility testing (AST)

At each stage of sampling, AST was conducted individually on isolated bacteria and identified by streaking out on Mueller–Hinton agar by the Kirby–Bauer disc diffusion method and evaluated in accordance with the Clinical & Laboratory Standards Institute's (CLSI) requirements [18].

The antibacterial discs utilized were cefepime (30 µg), cefoxitin (30 µg), imipenem (10 µg), ceftazidime (30 µg), amikacin (30 µg), meropenem (10 µg), gentamicin (10 µg), tetracycline (30 µg), doxycycline (30 µg), Tigecycline (15 µg), ceftriaxone (30 µg), linezolid (5 µg), ciprofloxacin (5 µg), trimethoprim/sulfamethoxazole (1.25/23.75 µg), levofloxacin (5 µg), rifampicin (10 µg), chloramphenicol (10 µg), tienam (imipenem + cilastatin) (10/10 µg), ofloxacin (5 µg) erythromycin (15 µg), ampicillin-sulbactam (10/10 µg), piperacillin-tazobactam (10/10 µg) amoxicillin (30 µg), cefoperazone (30 µg) clindamycin (30 µg), and cefotaxime (30 µg). To identify the minimum inhibitor concentration (MIC) for colistin and vancomycin, the CLSI methodology was utilized [19].

For detection of fungal infection, serological assays including a (1,3)-β-D-glucan (BDG) test and a galactomannan (GM) test were used. The tests were carried out on a Dynamiker Automatic ELISA Workstation (A200; Tianjin, China), and the results were reported as per the manufacturer's instructions.

2.3. Statistical analysis

We used SPSS v27 (IBM, Chicago, IL, USA) for statistical analysis. The normality of the data distribution was assessed using the Shapiro–Wilks test and histograms. The mean and standard deviation (SD) of quantitative parametric data were presented and evaluated using an unpaired Student's t-test. The Mann Whitney-test was utilized to assess quantitative non-parametric data reported as the median and interquartile range (IQR). The Chi-square test or Fisher's exact test was utilized to assess qualitative variables and reported as frequency and percentage. To examine the relative odds of the desired outcome occurring, an odds ratio was calculated. A two-tailed P value <0.05 was considered statistically significant.

3. Results

The incidence of bacterial co-infection among COVID-19 patients admitted to ICU was 47.7%. There was an insignificant difference in the epidemiological risk factors (age, sex, and smoking) between COVID-19 patients with co-infection and those without co-infection (controls). The mode of infection transmission was insignificantly different between both groups (P > 0.05).

Reported co-morbidities (DM, hypertension, cardiovascular diseases, respiratory diseases, renal diseases, central nervous diseases, gastrointestinal diseases, and malignancy) showed an insignificant difference between both groups (p > 0.05) (Table 1).

Symptoms observed among COVID-19 patients with secondary infection were insignificantly different compared to those without except rhinorrhea, which was higher among patients with bacterial or fungal growth (P = 0.026) (Table 2).

Laboratory findings (neutrophil, lymphocyte, Hb, PTT, PT, ALT, AST, D dimer, urea, creatinine, glucose, ferritin, and CRP) were insignificantly different between both groups (p > 0.05) (Table 3).

Death was significantly higher among COVID-19 patients with secondary infection compared to the control group (35% vs. 0%, respectively, p < 0.001 with an odd's ratio of 2.7 (95% CI: 1.9–3.8)) (Table 4).

There were 34 clinical isolates obtained, 31 of which were bacteria and 3 of which were fungi. Gram-negative isolates were found to be more prevalent 26 (76.47%) than Gram-positive bacteria 5 (14.71%). Gram-negative isolates included Klebsiella pneumoniae (38.24%), Acinetobacter baumannii (17.65%), Escherichia Coli (11.76%), Pseudomonas aeruginosa (5.88%), and Citrobacter (2.94%). Gram-positive bacteria included Staphylococcus aureus (11.76%) and Streptococcus pneumoniae (2.94%). In addition, three cases (8.82%) showed fungal infections. All isolated fungi were Candida albicans (Table 5).

Tigecycline and amikacin were the highest sensitive antibiotics for associated bacterial co-infection of COVID-19 cases (80.6%, 70.9%), respectively). Flucytosine, amphotericin B, caspofungin, and micafungin were all effective against Candida albicans isolates; however, fluconazole was resistant (Table 6).

Table 1. Epidemiological risk factors of secondary infection among ICU COVID-19 cases (n = 65).

		No bacterial co-infection (n = 34)	Bacterial co-infection (n = 31)	P value	Odd's ratio (95% CI)
Age	<60	13 (38%)	6 (19%)	0.095	2.58 (0.84–7.97)
(years)	>60	21 (62%)	25 (81%)		
Sex	Male	16 (47%)	10 (32%)	0.224	1.867 (0.68–5.13)
	Female	18 (53%)	21 (68%)		
Smoker		5 (15%)	8 (26%)	0.264	2.02 (.58–7.0)
Mode of transmission					
From Work					
Work with public		6 (18%)	5 (16%)	0.87	1.114 (0.30–4.09)
No work with public		28 (82%)	26 (84%)		
From other Sources					
Infection from Family member		5 (15%)	5 (16%)	0.87	.897 (0.23–3.45)
Visit a hospital		29 (85%)	26 (84%)		
Co-morbidities					
DM2		20 (59%)	25 (81%)	0.43	1.53
Hypertension		4 (12%)	4 (13%)	0.17	2.2
CV diseases		8 (24%)	8 (26%)	0.83	0.89
Respiratory diseases		5 (15%)	9 (29%)	0.16	0.42 (0.12–1.439)
Renal diseases		2 (6%)	2 (6%)	0.92	0.91 (0.12–6.86)
CNS diseases		3 (9%)	3 (10%)	0.91	0.90 (0.17–4.85)
GIT diseases		2 (6%)	2 (6%)	0.92	0.91 (0.12–6.86)
Malignancy		0 (0%)	3 (10%)	0.06	2.2 (1.7–2.9)

CI: confidence interval, DM2: Diabetes Mellitus Type 2, CV: Cardiovascular, CNS: Central Nervous System GIT: Gastrointestinal tract.

Table 2. Associated symptoms in COVID-19- cases with and without secondary infection.

	No bacterial co-infection (n = 34)	Bacterial co-infection (n = 31)	P value	Odd's ratio (95% CI)
Fever	31 (91%)	25 (81%)	0.22	2.48(0.56–10.92)
Cough	28 (82%)	20 (65%)	0.10	2.57 (0.81–8.09)
Dyspnea	24 (71%)	23 (74%)	0.75	0.84 (0.28–2.49)
Muscle ache	17 (50%)	11 (35%)	0.24	0.55 (0.20–1.49)
Confusion	1 (3%)	5 (16%)	0.06	0.16 (0.02–1.43)
Headache	16 (47%)	11 (35%)	0.34	0.62 (0.23–1.68)
Sore throat	21 (62%)	15 (48%)	0.28	1.72 (0.64–4.62)
Rhinorrhea	2 (6%)	8 (26%)	0.026	0.18 (0.04–0.93)
Chest pain	18 (53%)	12 (39%)	0.25	1.78 (0.66–4.78)
Diarrhea	3 (9%)	2 (6%)	0.72	1.4 (0.22–9.01)
Vomiting	4 (12%)	5 (16%)	0.61	0.69 (0.17–2.86)
Taste lost	30 (88%)	30 (97%)	0.2	4 (0.42–37.91)

CI: confidence interval

Table 3. Laboratory results of COVID – cases with and without secondary infection.

Subject	No bacterial co-infection (n = 34)	Bacterial co-infection (n = 31)	P value	Odd's ratio (95% CI)
TLC				
Decreased	15 (44%)	17 (55%)	0.033	NA
Normal	19 (56%)	10 (32%)		
Increased	0 (0%)	4 (13%)		
Neutrophil				
Normal	6 18%	10 (32%)	0.17	2.2 (0.7–7.1)
Increased	28 82%	21 (68%)		
Lymphocyte				
Decreased	24 71%	25 (81%)	0.35	0.58 (0.18–1.8)
Normal	10 29%	6 (19%)		
HB				
Decreased	13 (38%)	13 (42%)	0.53	NA
Normal	21 (62%)	17 (55%)		
Increases	0 (0%)	1 (3%)		
PTT				
High	10 (29%)	11(35%)	0.60	0.76 (0.27–2.15)
Normal	24(71%)	20 (65%)		
PT				
High	11 (32%)	12 (39%)	0.59	0.76 (0.27–2.1)
Normal	23 (68%)	19 (61%)		
ALT				
High	14 (41%)	7 (23%)	0.11	2.4 (0.81–7.1)
Normal	20 (59%)	24 (77%)		
AST				
High	15 (44%)	8 (26%)	0.12	2.3(0.79–6.5)
Normal	19 56%	23 (74%)		
D dimer				
High	32 94%	25 (81%)	0.11	3.8 (0.71–20.68)
Normal	2 6%	6 (19%)		
Urea				
High	11 32%	11 (35%)	0.79	0.87 (0.31–2.43)
Normal	23 68%	20 (65%)		
Creatinine				
High	10 29%	7 (23%)	0.53	1.43 (0.47–4.38)
Normal	24 71%	24 (77%)		
Glucose				
High	25 (74%)	23 (74%)	0.95	0.97 (0.32–2.93)
Normal	9 (26%)	8 (26%)		
Ferritin				
High	33 (97%)	28 (90%)	0.26	3.54 (0.35–35.9)
Normal	1 (3%)	3 (10%)		
CRP				
High	31 (91%)	27 (87%)	0.60	1.53 (.031–7.46)
Normal	3 (9%)	4 (13%)		

CI: confidence interval, TLC: Total Leukocyte Count, HB: Hemoglobin, PTT: Partial thromboplastin time, PT: Prothrombin Time, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein

4. Discussion

COVID-19, an uncommon pandemic of viral pneumonia, is being viewed as a breaking global public health risk. Recently, hospital-acquired infections have received less attention, possibly as a result of the COVID-19 pandemic and the resulting long-term hospitalization of patients [15].

In the present study, we found that the incidence of bacterial co-infection among COVID-19 patients admitted to ICU was 47.7%.

Table 4. Outcome of COVID-19 Cases with and without secondary infection.

	No bacterial co-infection (n = 34)	Bacterial co-infection (n = 31)	P value	Odd's ratio (95% CI)
Alive	34 (100%)	20 (65%)	<0.001	2.7 (1.9–3.8)
Dead	0 (0%)	11 (35%)		

CI: confidence interval

Table 5. Most common reported bacteria and fungi in COVID-19 cases with secondary infection.

Gram- negative bacteria	26 (76.47%)
Acinetobacter baumannii	6 (17.65%)
Citrobacter	1 (2.94%)
Escherichia coli	4 (11.76%)
Klebsiella pneumonia	13 (38.24%)
Pseudomonas aeruginosa	2 (5.88%)
Gram- positive bacteria	5 (14.71%)
Streptococcus pneumonia	1 (2.94%)
Staphylococcus aureus	4 (11.76%)
Fungi	3 (8.82%)
Candida albicans	3 (8.82%)

E. coli: Escherichia coli, K. pneumoniae: Klebsiella pneumoniae, S. pneumoniae: Streptococcus pneumoniae, Pseudomonas aeruginosa: Pseudomonas aeruginosa aeruginosa, Staph. aureus: Staphylococcus aureus.

Other investigations conducted in the US and several European and Asian countries have discovered that in COVID-19 patients; there was a wide range of bacterial superinfection prevalence, ranging from 1% to 50% [20–24].

Sharifipour et al. concluded that bacterial and fungal superinfections are more common in critically ill hospitalized cases and those admitted to ICU with underlying systemic diseases and other risk factors [15].

Also, in an American study, among a total of 375 hospitalized patients diagnosed with severe COVID-19, 128 (34.13%) had secondary bloodstream infections (sBSI); of which 117 (91.4%) were bacterial, and 7 (5.5%) were fungal during the hospitalization. They found that cases with sBSI were more likely to have been admitted to the ICU compared with controls who had not [25].

Li J. et al. [26] reported 102 (6.8%) who developed secondary bacterial infections among COVID-19 patients.

A meta-analysis included 24 studies reported that bacterial infection was 6.9% yet the percentages varied slightly depending on the patient demographic, ranging from 5.9% in hospitalized patients to 8.1% in seriously ill patients. [27]

The difference in the incidence of secondary infection could be explained by the discrepancies in the race, patients' demographics and the used diagnostic criteria tests.

Additionally, we noted, among patients admitted to ICU, that there was an insignificant difference in epidemiological risk factors and co-morbidities between patients with COVID-19 associated with secondary infection and controls. In agreement with our results, Nasir et al. [28] carried out a case–control investigation on a total of 50 subjects with bacterial infection and 50 controls to investigate risk factors for bacterial infection in COVID-19 patients with mild to severe disease. Their results demonstrated an insignificant difference between COVID-19 patients with bacterial infections in terms of age, sex, and DM2 in comparison to patients who did not have bacterial infections. Similarly, Bhatt et al. [25] noted that among those with sBSI and controls, no significant difference was reported in terms of malignancy and lung disease.

Nonetheless, Cataño-Correa et al. [29] found that, in participants above the age of 59, bacterial superinfection was 36% greater (compared to those under the age of 60), 58% higher in immunosuppressed patients and that ICU stay and the use of steroids was the clinical aspects that are most strongly linked to secondary bacterial infection.

This discrepancy can be interpreted as Cataño-Correa et al. included immunosuppressed patients and those on steroids while we excluded those patients. So Cataño-Correa et al. concluded that these patients were the most liable to secondary infection, which was expected to us so they were excluded.

Our results highlighted that death was significantly higher among COVID-19 patients with secondary infection 35% compared to controls 0%.

Similarly, Li J. et al. reported that about 49% of the patients who had secondary infections died, and critically ill patients had a higher mortality rate of 65% than less severely ill patients 15.2%. [26]

In addition, a study of 179 hospitalized patients in China, 21 (11.7%) of the patients' clinical conditions deteriorated rapidly and ended with mortality. The existence of a secondary bacterial infection was cited as the cause [30].

Further, Nasir et al. [28] documented that in comparison to controls, patients with COVID-19 who had bacterial co-infections had a higher percentage of fatalities (42% vs. 18%, p = 0.011). Hence, there is an urgent need to form effective antimicrobial stewardship protocol.

In our laboratory findings, an insignificant difference was observed between COVID-19 patients with co-infection and controls. Only total leukocytic count (TLC) showed a statistical difference between both groups.

It was documented in many studies that the C-reactive protein (CRP), procalcitonin, and neutrophil-to-lymphocyte ratio (NLR) were significantly higher in COVID-19 patients with bacterial infection [26,31,32]. This discrepancy may be attributed to the difference in the timing of blood sampling throughout the disease

Table 6. Antimicrobial sensitivity test for coinfected COVID-19 cases.

Antimicrobial agent	Sensitivity	Organism
Amoxicillin	0	
Amoxicillin/clavulanic acid	0	
Piperacillin-tazobactam	0	
Ampicillin/sulbactam	0	
Cefuroxime	0	
Cefoxitin	0	
Cefotaxime	2 (6.5%)	Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Ceftriaxone	2 (6.5%)	Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Cefoperazone	2 (6.5%)	Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Ceftazidime	3 (9.7%)	Staphylococcus aureus & Streptococcus pneumoniae (gr +ve), Acinetobacter baumannii (gr -ve)
Cefepime	8 (25.8%)	2 cases Staphylococcus aureus, 1 case S. pneumonia, 1 case Acinetobacter baumannii, 4 case Escherichia coli (gr -ve)
Meropenem	15 (48.4%)	4 cases Klebsiella pneumoniae, 3 E. coli, 6 Acinetobacter baumannii, 1 Pseudomonas aeruginosa, 1 Citrobacter (all Gr – ve)
Imipenem	7 (22.6%)	5 Cases Acinetobacter baumannii, 1 Pseudomonas aeruginosa, 1 Citrobacter (all Gr – ve)
Clindamycin	4 (12.9%)	1 case Acinetobacter baumannii (gr -ve), 3 Staphylococcus aureus (gr +ve)
Ciprofloxacin	10 (32.3%)	1 case Escherichia coli& 6 Acinetobacter baumannii (gr -ve), 2 Staphylococcus aureus & 1 Streptococcus pneumoniae (gr +ve)
Levofloxacin	11 (35.5%)	2 cases Escherichia coli & 6 Acinetobacter baumannii (gr -ve), 2 Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Ofloxacin	6 (19.4%)	2 cases Escherichia coli & 1 Pseudomonas aeruginosa (gr -ve), 2 Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Amikacin	22 (70.97%)	5 cases Klebsiella pneumoniae, 4 cases Escherichia coli& 6 Acinetobacter baumannii, 1 Pseudomonas aeruginosa, 1 Citrobacter (all Gr – ve), 4 Staphylococcus aureus, 1 Streptococcus pneumoniae (gr +ve)
Gentamicin	8 (25.8%)	3 cases Klebsiella pneumoniae, 2 case Escherichia coli& 2 Acinetobacter baumannii, 1 Pseudomonas aeruginosa (all gr – ve)
Erythromycin	0	
Vancomycin	5/31 (16.1%)	4 cases Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Linezolid	5/31 (16.1%)	4 cases Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Trimethoprim/ Sulphamethoxazole	5/31 (16.1%)	1 case Acinetobacter baumannii (Gr – ve), 4 cases Staphylococcus aureus (gr +ve)
Tetracycline	1 (3.2%)	1 case Acinetobacter baumannii (Gr – ve).
Doxycycline	9 (29%)	2 cases Klebsiella pneumoniae, 2 E. coli, 2 Acinetobacter baumannii (all gr – ve), 4 cases Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Tigecycline	25 (80.6%)	9 cases Klebsiella pneumoniae, 4 E. coli, 6 Acinetobacter baumannii, 1 Citrobacter (all gr – ve), 4 Staphylococcus aureus & Streptococcus pneumoniae (gr +ve)
Colistin	16 (51.6%)	10 cases Klebsiella pneumoniae, 4 E. coli, 1 Acinetobacter baumannii, 1 Citrobacter (all Gr – ve)
Chloramphenicol	12 (38.7%)	1 case Klebsiella pneumoniae, 3 E. coli, 4 Acinetobacter baumannii (all gr – ve), 4 cases Staphylococcus aureus (gr +ve)
Rifampicin	4 (12.9%)	4 cases Staphylococcus aureus (gr +ve)
Tienam	2 (6.5%)	2 cases Klebsiella pneumoniae (gr -ve)
Fosmycin	0	
Flucytosine, amphotericin B, caspofungin, micafungin	S (3)	Candida albicans
Fluconazole	R	

S: Sensitive, R: Resistant, gr +ve: gram-positive, gr – ve: gram-negative

course, the unavailable resources for some lab as S. procalcitonin and the difference in hospital capabilities.

According to our study, the most isolated bacteria was gram-negative bacteria represented 76.47%. Klebsiella pneumoniae and Acinetobacter baumannii were the dominant gram-negative bacteria 38.24% and 17.65%, respectively. Gram-positive bacteria represented 14.71%, of which 11.76% was Staphylococcus aureus. Candida albicans was the isolated fungi 8.82%.

Similarly, in Egypt, Ramadan et al. [33] documented that the most commonly isolated bacteria were Klebsiella pneumoniae, Acinetobacter baumannii, and Staphylococcus aureus. The most commonly isolated fungus were Candida albicans and Candida glabrata.

Further, Khurana et al. [34] noted, after studying pathogens identified from 290 clinical samples of COVID-19 patients' pathogen profiles, the dominant pathogen was K. pneumoniae (33.3%), then A. baumannii (27.1%).

Also Li J. et al. [26] agreed with us as they reported 159 strains of bacteria isolated from the SBIs, of which 85.5% were Gram-negative. The commonest bacteria were A. baumannii (35.8%), and K. pneumoniae (30.8%),

Our study found that tigecycline and amikacin were the highest sensitive antibiotics for associated bacterial co-infection of COVID-19 cases (80.6%, 70.9% respectively). This result was similar to Ramdan et al. who found that Gram-positive isolates had moderate resistance against amikacin 37.5% and highly sensitive to tigecycline.

While for gram-negative strains, they observed that tigecycline and amikacin had the highest sensitivity, 82.7%, and 79.3%, respectively, [33].

A systematic review showed that tigecycline was one of the broad-spectrum antibiotics that were routinely administered to ICU patients [35]. In Brazil, amikacin was recorded to be used among ICU patients in the

COVID-19 era due to concerns in the context of multi-drug-resistant (MDR) infections [36].

Additionally, Said et al. recorded that the bacterial isolates were intermediately resistant to tigecycline, and amikacin displayed the highest effectiveness (75.4%) [37].

On the other side, during the COVID period, some researchers found that Pseudomonas aeruginosa had strong resistance to amikacin [38–40]. Further, Saini et al. [41] noted after evaluating the paradigm shift in bacterial antimicrobial resistance patterns during COVID-19 against the pre–COVID-19 period, amikacin showed reduced effectiveness against Acinetobacter baumannii, so caution should be advocated, especially in the use of reserve drugs such as tigecycline and amikacin.

This discrepancy regarding the efficacy of antibiotic findings could be attributed to various factors. These may be the geographic location that appears to influence the prevalence of bacterial/fungal co-infection in subjects with coronavirus disease, antimicrobial guidelines, antibiotics misuse, antibiotic resistance monitoring, and surveillance for healthcare-associated diseases.

There were certain limitations to our research. First, the observational approach makes clinical judgments difficult to comprehend. Second, the virus novelty makes the pathogenesis process difficult to be understood and the factors affecting the outcome may be interfering with each other. Third, we did not use a nationally representative sample in our research.

To validate our observations and increase our understanding of the prevalence and treatment ofinfections aggravating the medical setting of COVID-19, data from large, well-designed trials are needed.

5. Conclusion

In COVID-19 patients who required intensive care admission, bacterial co-infections were common. The most prevalent co-infecting agents were Klebsiella pneumoniae and Acinetobacter baumannii. Also, our findings revealed that tigecycline and amikacin displayed the highest sensitivity patterns and emphasized the need to administer antibiotics promptly in accordance with antimicrobial sensitivity reports.

Author's contributions

Fatma Rageh, Shaymaa Abdelraheem, Mohamed A. Sakr, and Shimaa A. Al-Touny shared in Idea conceptualization and writing the protocol

Aiman Al-Touny, Eman Riad, Shimaa A. Al-Touny shared in data collection

Mohamed A. Sakr, Shaymaa Abdelraheem, and Rasha Elgamal revised lab results and supervised the cultures

Samar Ahmed performed statistical and data analysis and integrated the results into the manuscript.

All authors reviewed the literature and wrote the first drafts of respective sections of the manuscript.

Aiman Al-Touny, Fatma Rageh, Mohamed A. Sakr, and Shimaa A. Al-Touny integrated the sections and formed the final version

All authors read and approved the final manuscript.

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Disclosure statement

None

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