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Procalcitonin Level and Antimicrobial Resistance among Microbial Coinfection in Hospitalized COVID-19 Patients

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Abstract

Background: Hospitalized Coronavirus Disease 2019 (COVID-19) patients are at a higher risk of bacterial and fungal infections. Procalcitonin is an inflammatory marker that has been suggested for distinguishing between bacterial and viral infections that predicting bacterial co-infection in COVID-19 and serving as a helpful indicator for determining the severity of the illness. This study aimed to evaluate procalcitonin levels and antimicrobial resistance (AMR) among microbial co-infections in hospitalized COVID-19 patients.

Methods: Clinical and microbiological data were obtained from the medical records of 100 COVID-19 patients.

Results: COVID-19 patients with bacterial infections had a 55% mortality rate. The majority of microbial cultures were detected in blood (49%), sputum (44%), and urine (7%). Among the isolates, 57.7% were Gram-negative bacteria, 31.7% were Gram-positive bacteria, 6.7% were mixed isolates, and 3.8% were fungal isolates. The predominant Gram-negative isolates were *Klebsiella pneumoniae* (37.2%), *Acinetobacter baumannii* (20.2%), and *Streptococcus pneumoniae* (14.4%). *Candida albicans* (2.9%) was the most commonly isolated fungal pathogen, followed by *Aspergillus spp.* (1%). Most of the isolates showed high resistance to broad-spectrum antibiotics. Gram-negative bacteria were detected in 29% of COVID-19 patients who died, Gram-positive bacteria in 20%, and mixed bacteria in 6%. The majority of surviving patients had procalcitonin levels below 0.25 ng/mL, whereas non- survivors had higher levels.

Conclusion: Secondary microbial infections in COVID-19 patients remain a critical concern during the pandemic. Additionally, multidrug-resistant organisms are an increasing challenge. In hospitalized COVID-19 patients, baseline procalcitonin levels were associated with patient outcomes and bacterial coinfection.

Keywords: Antibiotics resistance (AMR), COVID-19, Procalcitonin level, Secondary infection.

Introduction

SARS-CoV-2 is a novel enveloped RNA coronavirus that causes severe pneumonia, with clinical manifestations differing from those seen in other coronavirus-induced pneumonia, such as SARS-CoV (1). SARS-CoV-2 infection has spread across the world, posing a public health threat. On February 11, 2020**,** the World Health Organization (WHO) declared SARS-CoV-2-induced pneumonia as coronavirus

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disease 2019 (COVID-19) (2), and recognized it as a public health emergency of global concern**.** COVID-19 spreads rapidly, resulting in a global pandemic. Coinfection of SARS-CoV-2 with other microorganisms, such as viruses, bacteria, and fungi, plays a critical role in COVID-19. It can complicate diagnosis, treatment, and prognosis, as well as worsen symptoms and increase mortality (3). In viral pneumonia, bacterial and fungal coinfection is common, especially in critically ill individuals (4). Coinfection with bacteria and fungi significantly impacts disease progression and prognosis, particularly in severely ill patients. It can result in increased need for intensive care, antibiotic therapy, and higher mortality rates (5).

Although the transmission rate, mortality, and clinical signs of COVID-19 have been extensively established, it is necessary to clarify the immunological response to the infection (6). The Cytokine storm is one of the potential causes of the quick advancement of the disease and death of COVID-19 patients. Cytokines play important roles in controlling immunological and inflammatory responses (7). In a study conducted by Rostami-Far *et al*., (2023) it was reported that the COVID-19 patients' serum levels of IL-6 and IL-10 were elevated as expected. They added that patients hospitalized in the intensive care unit had considerably higher mean serum levels of SARS-COV-2 IgG (8). In SARS-CoV-2 infection among critically ill patients, a recent systematic review found an incidence of secondary infections ranging from 7% to 51% (9). Therefore, the goal of this study was to investigate the occurrence of secondary microbial infections and identify the most common pathogen groups along with their antimicrobial susceptibility profiles in hospitalized COVID-19 patients.

Materials and Methods

Study design and participants

Adult patients admitted to the hospital with confirmed COVID-19 infections were studied in this retrospective cohort study. All adult patients admitted to the Intensive Care Unit (ICU) with confirmed COVID-19 pneumonia experienced acute hypoxemic respiratory failure. A positive COVID-19 case was defined as a verified positive result on a nasopharyngeal swab evaluated using Real-Time Polymerase Chain Reaction (RT-PCR) (Roche, Germany) testing for SARS-CoV2. Pathogen identification and antimicrobial susceptibility testing were performed by the Vitek II Compact Automated System (bioMerieux, Lyon, France). Using the procalcitonin value, biomarker analysis (Brahms proprietary immunoassay on a Cobas e601 platform by Roche Diagnostics) was assessed for bacterial co-infection detection during hospitalization. The study was conducted in various hospitals in Erbil City from August 2021 to February 2022. Ethics approval was granted by the Erbil Polytechnic University (REF. No. 3989 in 24/5/2021). Given the urgent need to gather information during the ongoing pandemic and the retrospective nature of this study, written informed consent was waived.

Data collection

Patients were matched by gender and age, and included if they were 18 years of age or older, admitted to the hospital between August 2021 and February 2022, and had a bacterial or fungal infection confirmed in a laboratory. A substantial clinical sample with a positive culture and clinical symptoms of infection or progressive organ failure was defined as a secondary infection, limited to bacterial and fungal species.

Clinical and microbiological data were extracted from the medical records of 100 patients who showed signs and symptoms of coinfection during their COVID-19 hospitalization. Hospital laboratory software was used to collect information regarding age, gender, hospitalization outcome, bacterial culture findings, and antimicrobial susceptibility profiles at the time of enrollment. Based on the most up-to-date knowledge of COVID-19 at that time, all patients were treated according to the hospital's COVID-19 protocol.

Inclusion criteria

The inclusion criteria were: COVID-19 diagnosis, ICU hospitalization, intubation, and mechanical ventilation for more than 48 h in ICUs. Before receiving a clinical diagnosis of secondary microbial infection, none of the patients had undergone empirical antibiotic treatment.

Exclusion criteria

The study excluded neonatal and pediatric intensive care units, as well as patients who did not develop secondary infections or those for whom no microbiological specimens were collected.

Statistical analysis

For analysis, all data were compiled in Microsoft Excel. Frequencies and percentages for categorical variables were summarized. Fisher's exact and the Chi- square test were used to compare differences in the distribution of nominal variables across groups. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 20. Statistical significance was defined as a *p*-value < 0.05.

Results

During the study period (August 2021 to February 2022), 100 COVID-19 patients were admitted to hospitals and diagnosed with laboratory-confirmed coinfections. There were no significant differences in the mean of both gender (*p* value = 0.2), Males accounted for 44 (44%) of the group, while females made up 56 (56%), Mortality occurred in 55 (55 %) of COVID-19 patients with bacterial infections (p =0.47). Blood cultures (49%) was the source of the majority of microbial cultures, followed by sputum 44 (44%), and urine 7 (7%) (p=0.45). In this investigation, 60 (57.7%) gram-negative bacteria, 33 (31.7%) gram-positive bacteria, 7 (6.7%) mixed culture, and 4 (3.8%) fungal isolates were identified in hospitalized COVID-19 patients with co-infections. Although the differences were not statistically significant (p=0.29) the majority of patients were female and in the age range of 58-77 years. (Table 1).

Table 1. Demographic characteristics of hospitalized COVID-19 patients with secondary infections.

Demographic Characteristics	**(No.), %**		**P value**
Gender (Mean ± SD: 1.44 ± 0.499)			
Female	(56) 56%		0.2 (NS)
Male	(44) 44%		
Hospitalization Outcome. (Mean ± SD: 1.45 ± 0.50)			0.47 (NS)
Discharged alive	(45) 45%		
Died	(55) 55%		
Sample site (Mean ± SD: 1.58 ± 0.622)			0.45 (NS)
Blood	(49) 49%		
Sputum	(44) 44%		
Urine	(7) 7%		
Secondary Co-infection (Mean ± SD: 1.60 ± 0.854)			
Gram-negative bacteria	(60) 57.7%		
Gram-Positive bacteria	(33) 31.7%		0.05 (S)*
Mixed isolates	(7) 6.7%		
Fungus isolates	(4) 3.8%		
Age group (years)	**(Mean ± SD: 2.62±0.874)**		
	Female (Mean±SD:2.52±0.831) (No.), %	**Male (Mean ± SD: 2.75± 0.918) (No.), %**	
18-37	(7) 12.5%	(4) 9.1%	0.29 (NS)
38-57	(18) 32.1%	(13) 29.5%	
58-77	(26) 46.4%	(17) 38.6%	
78-97	(5) 8.9%	(10) 22.7%	

SD – Standard Deviation, * – Significant, NS – Not significant.

By comparing the number of bacterial species isolated from samples of hospitalized COVID-19 patients, gram-negative bacteria were found to be the most common pathogens. *Klebsiella pneumoniae* 34 (37.2%) and *Acinetobacter baumannii* 21 (20.2%) were the most frequently isolated pathogens followed by *Streptococcus pneumoniae* 15 (14.4%), *Staphylococcus aureus*10 (9.6%), *Staphylococcus haemolyticus* 5 (4.8%), *Escherichia coli* 3 (2.9%), and *Pseudomonas aeruginosa* 2 (1.9%). *Staphylococcus epidermidis*, *Stenotrophomonas maltophilia* and *Streptococcus pyogenes* were each isolated in 1(1%) case, while *Candida albicans* 3 (2.9%) and *Aspergillus spp.* 1 (1%) were the most common fungal pathogens isolated (Fig. 1).

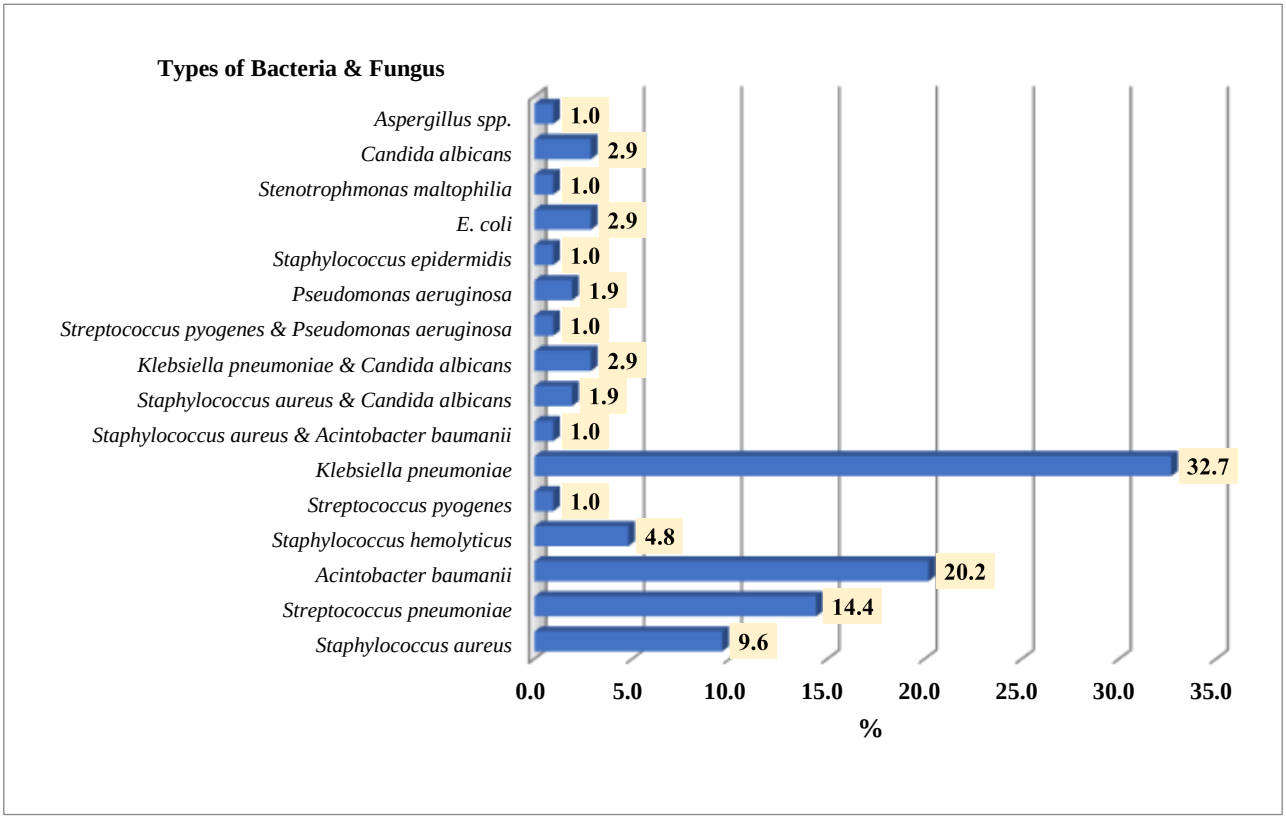


Fig. 1. Etiological distribution of secondary microbial infections caused by multiple bacteria and fungi in hospitalized COVID-19 patients.

The strongest resistance was reported among the 100 hospitalized COVID-19 patients with subsequent illnesses. Antibiotics, such as third-generation cephalosporins, beta-lactamase inhibitors like piperacillin-tazobactam, and other broad-spectrum drugs, were the most widely used in our study. We found that the isolates were resistant to each of these antibiotics. The antibiotic that showed the highest percentage of resistance was Piperacillin (51%) followed by Tri-Methoprime/Sulfamethoxazole (39%), Aztreonam (38%), Ciprofloxacin (33%), Imipenem (32%), Meropenem (32%) and Tetracycline (30%) (Figs. 2 & 3).

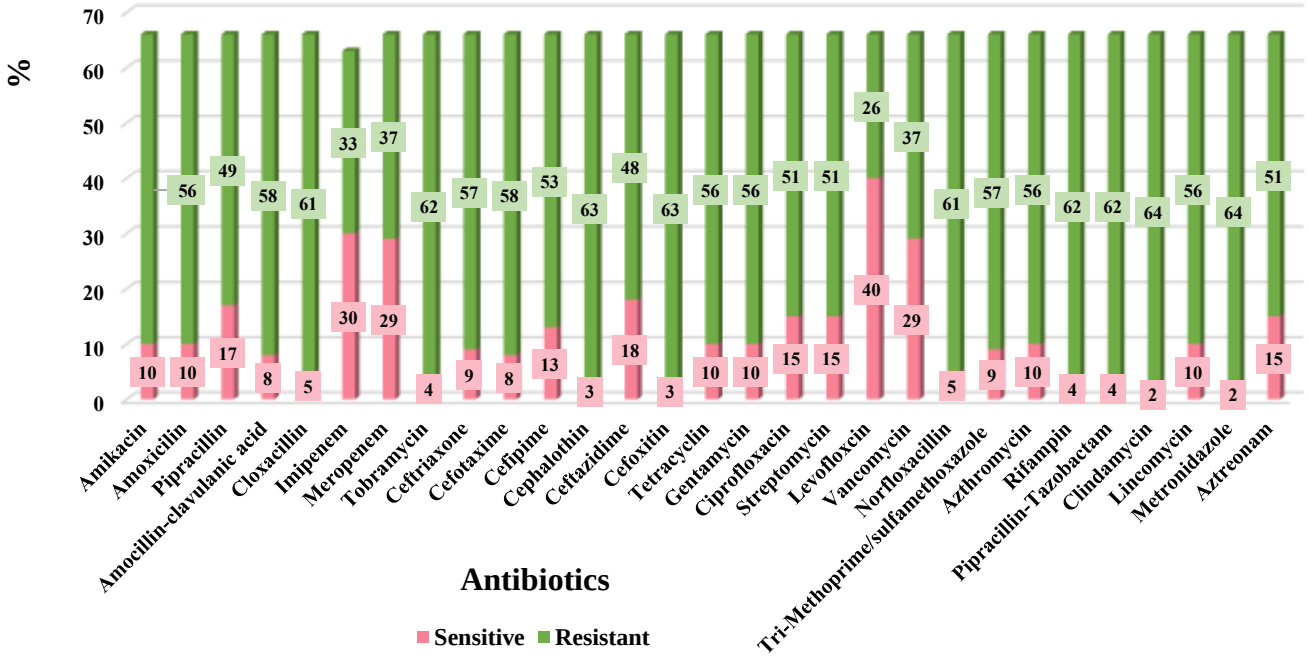


Fig. 2. Drug resistance rate of gram-negative bacteria to antibiotics causing secondary infections in hospitalized COVID-19 patients.

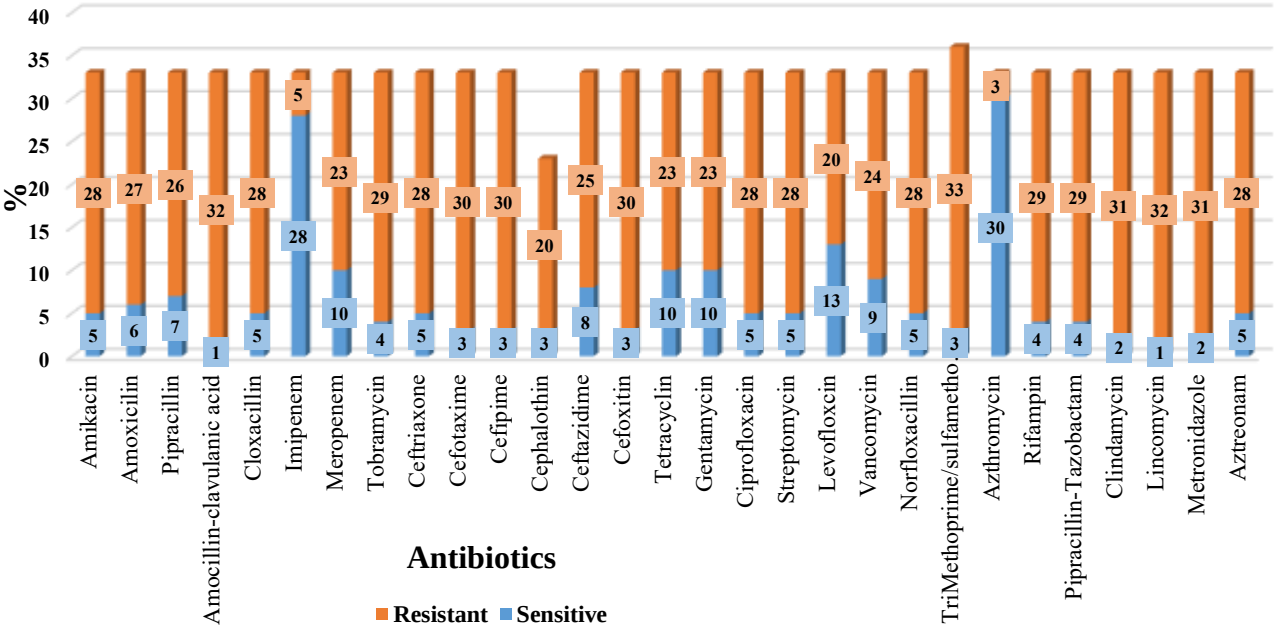


Fig. 3. Drug resistance rate of gram-positive bacteria to antibiotics causing secondary infections in hospitalized COVID-19 patients.

A total of 29 (29%) of COVID-19 patients who died had gram-negative bacterial infections, 20 (20%) had gram- positive bacterial infections, and 6 (6%) had mixed bacterial infections (p= 0.05) (Fig. 4).

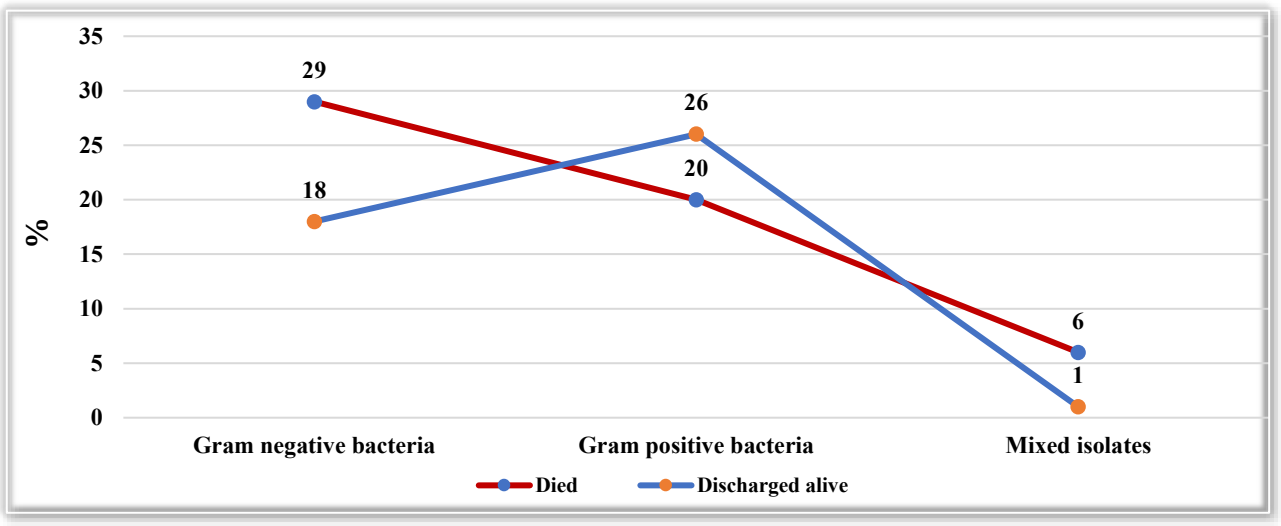
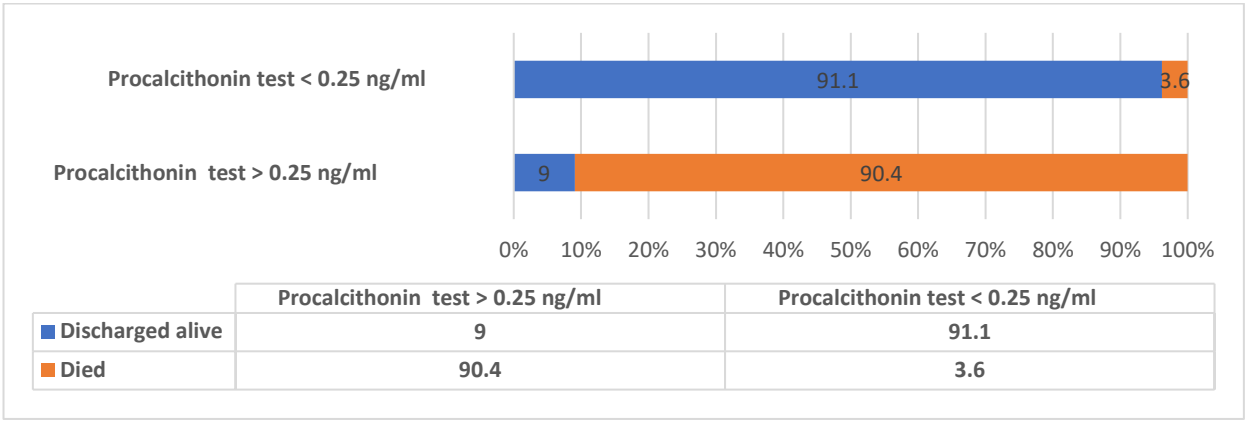


Fig. 4. The percentage of co-infections and mortality rates in COVID-19 patients admitted to the hospital**.**

The total distribution of baseline procalcitonin level was studied to better understand the role of procalcitonin in the clinical course of individuals infected with COVID- 19. The majority of patients who survived had a procalcitonin level of < 0.25 ng/mL, and as procalcitonin level increased, survival decreased (p= 0.001) (Fig. 5).



	Procalcithonin test > 0.25 ng/ml	Procalcithonin test < 0.25 ng/ml
Discharged alive	9	91.1
Died	90.4	3.6

Fig. 5. Percentage of procalcitonin concentrations and mortality rates in admitted COVID-19 patients.

Discussion

The mean age of critically ill patients and the gender ratio did not differ significantly in our study. Similar findings by other study (8). In this study, mortality rates among patients with secondary infections were significantly higher 55 (55%), which is consistent with findings from other studies (10-12). We believe that the prevalence of comorbidities may have contributed to these patients' higher fatality rates, or that patients with other infections had worse outcomes. Longer hospital stays may have predisposed patients to secondary infections, resulting in a lower discharge rate and a higher mortality rate. Additionally, patients with prolonged stays were more likely to be admitted to the Intensive Care Unit (ICU), further increasing the likelihood of mortality. These findings are in line with previous research linking co-infection with poor prognosis during respiratory virus pandemics (10-12).

Blood (49%), sputum (44%), and urine (7%) were the most common sources of

secondary infections in this study. Similar findings have been reported by other studies, which indicated that blood and lung sites were the most common sources of secondary infections in COVID-19 patients (11). One study demonstrated that positive blood cultures were identified in 46% of samples, followed by endotracheal aspirates and urine (13). Another study found 155 isolates from 82 patients with positive blood cultures (14). Additional research found that blood samples had the highest number of microbial cultures, followed by endotracheal aspirates and urine samples (15). It is known that many hospitals have experienced a 2–3-fold increase in bloodstream infections. There are several risk factors for nosocomial infections, including mechanical ventilation, central venous catheters, corticosteroid or biologic treatment, and prolonged hospitalization. During the pandemic, frequent empirical antibiotic use and the inability of some patients to produce sputum limited invasive respiratory sampling. To reduce the number of aerosol-generating procedures and protect biological sample collectors and laboratory staff, blood and sputum samples from COVID-19 patients were often avoided. COVID-19 is transmitted through virus-laden aerosols, respiratory droplets, and direct contact, further complicating infection control efforts.

Our observational study identified that the gram-negative bacteria 60 (57.7%) exhibited a significant increase in the total number of isolates, followed by gram-positive bacteria 33 (31.7%) and fungal infection 4 (3.8%), These results align with previous studies, which reported that gram-negative pathogens such as *Klebsiella pneumoniae* and *Acinetobacter baumannii* were the most common pathogens, although gram-positive and fungal cultures were also included (16). Bacterial co-infections were found in 7% of COVID-19 hospitalized patients, and gram-negative bacteria were responsible for more than 30% of healthcare-associated infections, especially in ventilator-associated pneumonia cases (47%) (17). Other studies also observed that gram-negative bacilli were the most common microorganisms responsible for secondary pneumonia, followed by gram-positive cocci (11, 12). Invasive device-associated infections caused by mechanical ventilation and central venous catheter insertion could explain the predominance of gram-negative bacteria in hospitalized patients. The fear factor of the SARS-CoV-2 virus among healthcare workers, doctors, and nurses may have contributed to practical challenges that led to increased nosocomial infection rates.

In addition to secondary bacterial infection, fungal infection was also detected in this study, with *Candida albicans* and *Aspergillus spp*. being the most common fungal isolates. Similar findings have been reported, indicating that 10-15% of COVID-19 patients develop fungal or bacterial infections in their lungs (4). Studies show that severely ill COVID-19 patients have a significantly higher incidence of bacterial (25.5%) and fungal (10.9%) co-infections, and 6% of hospitalized COVID-19 patients had *Candida spp*. (11, 18, 19). Invasive pulmonary aspergillosis, commonly detected in lower respiratory tract cultures, is more frequent in patients with viral pneumonia (12). Several studies have identified pulmonary aspergillosis as a secondary infection in critically ill patients with suspected COVID-19. Aspergillus spores, which enter the bloodstream via inhalation, are the most common source of infection. Unlike generally healthy individuals with functioning immune systems, this infection is more prevalent in immunocompromised patients (20).

Antimicrobial resistance (AMR) is a global issue, and this study found a high level of resistance to bacterial co-infections in COVID-19 patients. The most common antibiotic with the highest resistance rate was Piperacillin, followed by Tri-Methoprime/Sulfamethoxazole (39%), Aztreonam (38%), Ciprofloxacin, Imipenem, Meropenem, and Tetracycline. Other studies have reported similar findings, with a higher proportion of bacteria resistant to the tested antibiotics in COVID-19 patients. As the burden of coronavirus-induced pneumonia

exceeds ICU capacity, antibiotic resistance may become a significant source of additional illness and death globally. Consequently, prophylactic antibiotic use in COVID-19 cases may contribute to the growth of antibiotic-resistant microorganisms (20). In COVID-19 and other immunocompromised patients, the spread of resistant bacteria can have severe implications. The immune system is compromised in severe viral respiratory infections, leaving the respiratory system vulnerable to opportunistic pathogens. If a hospitalized patient becomes infected with resistant bacteria in this context, the outcomes can be fatal (20). Studies show that 30% to 40% of several common bacterial strains have already developed resistance to macrolide antibiotics, such as azithromycin (20). Furthermore, COVID-19 isolates have higher resistance to aminoglycosides like amikacin and gentamicin, monobactams like aztreonam, third-generation fluoroquinolones like levofloxacin, and beta-lactams like meropenem. These findings support the expected impact of COVID-19 on the spread of AMR infections (21). The combination of factors, including bacterial characteristics, patient health, hospital environments, and excessive antibiotic use, contributes to increased resistance. Inappropriate antibiotic prescriptions and the spread of resistant bacterial strains within hospitals via cross-colonization by healthcare professionals, and subsequent transfer between hospitals, exacerbate the issue (22). Hand hygiene practices have been notably affected during the COVID-19 pandemic, as healthcare workers often wear gloves as part of their personal protective equipment (PPE) and may feel less need to wash their hands. Additionally, there was a lack of concern about infection transmission between patients. Most secondary infections in our study were nosocomial and caused by highly drug-resistant organisms, highlighting the need for improved infection control and appropriate antibiotic therapy.

Gram-negative infections were responsible for 29% of the deaths among hospitalized COVID-19 patients, while gram-positive pathogens accounted for 20%. A recent study published in The Lancet, based on data from two hospitals in Wuhan, China, found that 50% of patients who died had secondary infections, while only 0.73% of survivors had secondary infections (23). Another study reported that 72% of COVID-19-related deaths were linked to Gram-negative infections, 10.8% to gram-positive infections, 8% to mixed infections, and 4% to fungal pathogens. Mortality rates were higher among those infected with multidrug-resistant organisms, with a mortality rate of 60.5% among these patients. The study also found that multidrug-resistant gram-negative bacteria, particularly *Klebsiella pneumoniae* and *Acinetobacter baumannii*, had high carbapenem resistance rates and were responsible for 76% and 63% of deaths, respectively (11). The high genome plasticity of *Klebsiella pneumoniae* and *Acinetobacter baumannii* has played a crucial role in their persistence, enabling the acquisition, maintenance, and spread of mobile elements encoding AMR determinants (11).

The relationship between baseline procalcitonin level and secondary bacterial superinfection was also studied. Patients who were discharged were more likely to have baseline procalcitonin level of < 0.25 ng/mL compared to those who died or remained in the hospital (23). Patients who were discharged were more likely to have baseline procalcitonin levels of < 0.25 ng/mL when compared to patients who died or were still in the hospital (24). The procalcitonin test is widely used to distinguish between bacterial and nonbacterial causes of lower respiratory tract infections and is valuable for antibiotic de-escalation in pneumonia (25). When compared to other biomarkers, procalcitonin is more effective in predicting bacterial bloodstream infections (26). The prevalence of pneumonia- like respiratory diseases, particularly in China and globally, which contributed to the public health emergency, propelled SARS-CoV-2 to the forefront (27) (28). Risk factors for bacterial infection include living in crowded conditions,

consuming contaminated food, sharing a home with sick individuals, and drinking contaminated water (29). A study by Hassan et al. reported that biofilms often exhibit enhanced antibiotic resistance or tolerance, potentially due to the environment in which microbes thrive or the exchange of genes conferring antibiotic resistance (30).

Secondary microbial infections in COVID-19 patients are a critical issue during the pandemic, posing a substantial threat to hospitalized individuals. Additionally, the rise of multi-drug-resistant organisms has become a significant concern. As a result, efforts must be made to prevent microbial co-infections in order to reduce morbidity and mortality. In hospitalized COVID-19 patients, baseline procalcitonin levels were found to be linked to patient outcomes and the risk of bacterial superinfection.

Ethics Committee Approval

The project was approved by the local ethics committee at Erbil Polytechnic University (REF. No. 3989, in 24/5/2021).

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Financial Disclosure

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Conflicts of Interest

No conflict of interest.

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