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Coronavirus Pandemic

Evaluation of bacterial coinfections and susceptible antibiotic profiles in hospitalized COVID-19 patients in Koya district, Iraq

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Abstract

Introduction: Bacterial coinfection among intensive care unit (ICU) COVID-19 patients is not widely studied in Iraq. Hence, the current study was performed to determine the prevalence of secondary bacterial infection and susceptible profile in ICU patients with COVID-19 infections.
Methodology: The study was conducted from November 2021 to April 2022, in Mad Center/ Shahid Doctor Khalid Hospital/Koya district. The midstream urine (MSU), sputum, and throat swab (TS) were obtained. Age, gender, clinical characteristics, bacterial identities, and antibiotic sensitivity profiles were collected for 200 COVID-19 patients. The standard biochemical tests confirmed the bacterial isolates. Antibiotic susceptibility was implemented by using the disk diffusion method.
Results: Out of 200 ICU patients, 87 (43.5%) of them had bacterial coinfection. The most predominant bacteria were isolated *Acinetobacter baumannii* (25.3%), *Escherichia coli* (18.3%), *Pseudomonas aeruginosa* (16%), *Klebsiella pneumonia* (11.5%), followed by *Staphylococcus aureus* (4.6%), and *Enterococcus spp.* (3.5%). Gram-negative bacteria showed a high level of sensitivity to Ertapenem (90.7%) and Piperacillin/Tazobactam (84.9%). Gram-positive isolates showed high sensitivity to Teicoplanin (77.2%) and Rifampicin (71%).
Conclusions: The susceptibility rate of the isolated bacteria is moderate; this indicates that early diagnosis of coinfections and more accurate use of antibiotics are necessary to mitigate the severity of COVID-19.

Key words: COVID-19; SARS-CoV-2; bacterial co-infection; ICU.

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Introduction

The novel coronavirus, known as Coronavirus-2 (SARS-CoV-2), was first reported in Wuhan, Hubei Province, China in December 2019. Since then, the virus has spread all over the world and has claimed thousands of lives. Due to serious respiratory diseases in humans, some patients require hospitalization, and in severe cases, intensive care with the support of mechanical ventilation is required (~5–15%) [1,2]. Coronaviruses are enveloped, positive-sense, large single-stranded RNA genomes ranging from 26 to 32 kb in length, and capable of rapid transformation and recombination [3]. Coronaviruses are classified into alpha and beta coronaviruses, both of which have a genetic source from bats and are mostly found in mammals such as bats, rodents, civets, and humans; and gamma and delta, both of which have an avian genetic source and are mainly found in birds [4,5]. Whole genome sequence analysis of SARS-CoV-2 showed the typical organization of beta coronavirus: 5′ untranslated region (UTR), homologous complex (orf1ab), S gene, E gene, M gene, N gene, 3′ UTR and several non-structural open reading frames that are not specific, but distinct from SARS-CoV-1 and MERS-CoV, which have caused epidemics in the past. SARS-CoV-2 together with the Bat_SARS-like coronavirus forms a distinct strain in the sarbecovirus subtype [6]. Opportunistic pathogens can bring superinfections as Urinary tract infection (UTI) and respiratory tract infection (RTI) in hospitalized patients, particularly when they coexist with viral respiratory tract infections [7]. UTI and RTI are the most common infections in hospitals, accounting for up to 35% of nosocomial infections, and the second most prevalent source of bacteremia in hospitalized patients [8]. Co-infections are typically caused by a particular group of bacterial pathogens such as *Staphylococcus species*, *Streptococcus pyogenes*, *Haemophilus influenzae*, etc., and are associated with hospital-acquired infections [9-11]. It's obvious that bacterial species spread in hospitals are highly likely to be multi-drug resistant (MDR), and it's the main challenge in managing ICU

patients [12]. Therefore, a crucial step in treating COVID-19 patients should be the quick and accurate identification of bacteria that present as pathogenic or resident microorganisms during the illness [13]. The goal of the current study was to investigate the prevalence of bacterial coinfection and their antibiotic susceptibility profile among SARS-CoV-2 cases admitted to ICU.

Methodology

Study design and setting

The study was performed in the Mad Center/ Shahid Doctor Khalid Hospital, Koya district, Iraq, collaborating with the Department of Medical Microbiology, Faculty of Sciences and Health (FSCH), Koya University, from November 2021 to April 2022, which is a referral hospital for the admission of COVID-19 patients. 200 COVID-19 patients were proved by real-time reverse transcriptase polymerase chain reaction (RT-PCR) on throat-swab samples admitted to the ICU enrolled in this study. There were 92 (46%) females and 108 (54%) males, the median age of participants was 48.43 with an age range of 28-67 years**.**

Collection of clinical samples for bacterial identification

The sources of bacterial isolation were 90 samples from mid-stream urine (MSU), 90 sputum, and 20 throat swabs (TS). In this study, we established certain criteria for inclusion. These criteria included being diagnosed with COVID-19 infection, being admitted to the ICU, receiving intubation and mechanical ventilation for more than 48 hours, and experiencing dyspnea and respiratory distress. We defined the presence of secondary bacterial infection based on the clinical symptoms indicating respiratory and urinary tract infections exhibited by the patients. The samples were collected after 5-7 days of admission and delivered to the laboratory within 30 minutes for quantitative bacterial growth. All samples were cultured on Blood Agar, Chocolate Agar, Eosin Methylene Blue (EMB), and MacConkey Agar. They were then incubated at 37 °C for 24–72 hours (chocolate agar with 5% CO_2) under standard conditions.

The colonial growth of the bacteria was preliminarily characterized by colony morphology, Gram staining, and standard biochemical tests (e.g., Catalase, Coagulase, Oxidase, Mannitol Salt Agar, Dnase, Triple Sugar Iron Agar (TSI), Sulfide Indole Motility (SIM), Methyl Red (MR)/Voges-Proskauer (VP), (Glucose, Sucrose, Mannitol, Lactose fermentation), Nitrate, Novobiocin susceptibility, Bacitracin susceptibility, Optochin Susceptibility, Bile esculin hydrolysis, Bile solubility test, Citrate, Urease, etc.) (all media were acquired from Acumedia Neogen USA). Further identification of the gram-negative organisms was made with API 20E identification System (BioMerieux, Marcy-IEtoile, France).

Determination of antimicrobial susceptibility test

Antibacterial susceptibility was performed separately on isolated bacteria from MSU, sputum, and TS samples. The test was implemented on Mueller Hinton agar (Acumedia Neogen, USA) by Kirby-Bauer's disk diffusion method according to interpretive criteria recommended by the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Susceptibility of the isolated gram-negative bacteria was performed against a panel of antibiotics: Amoxicillin/Clavulanic acid (AMC 20 + 10 µg), Aztreonam (ATM 30 µg), Cefotaxime (CTX 30 µg), Ertapenem (ETP 10 µg), Norfloxacin (NOR 10 µg), Piperacillin/Tazobactam (TZP100 + 10 µg). Susceptibility of the isolated gram-positive bacteria was tested against the following agents: Ampicillin (AMP 10 µg), Cefoxitin (CX 5 µg), Chloramphenicol (C 30 µg), Clindamycin (CD 10 µg), Rifampicin (RD 30 µg), Teicoplanin (TEC 30 µg). All antibiotic disks were obtained from (Oxoid, UK). Interpretation of results was carried out based on the diameter of the zone. *S. aureus* ATCC 25923 and *E. coli* ATCC 25922 were used as standard strains for antimicrobial susceptibility tests.

Statistical analysis

In this study, the Chi-square test was used to determine the association between the participants' gender, age group, and underlying disease of the COVID-19 cases and for identification of bacterial co-infection. Antibacterial susceptibility data were presented as a percentage of sensitivity to the total number of isolates recovered from the specimens for individual bacterial species. Also, Minitab v17.1 Software was applied for all statistical analyses [14]. A p-value < 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics of COVID-19 Patients

The percentage of males in the study was slightly higher 54% (108) than females 46% (92). Out of a total of 200 samples, 87 (43.5%) yielded significant growth

of pathogenic organisms. The positive isolates were obtained from 47 (43.5%) males and 40 (43.4%) females, ($p > 0.05$). Our study demonstrated that the older age groups had higher co-infection in the respiratory and urinary tract 37 (62.7%) than the younger groups 11 (22.4%), respectively. Regarding comorbidities of COVID-19 patients who were admitted to ICU, 43 (21.5%) of patients had diabetes, and 157 (78.5%) were non-diabetic. In common, diabetic COVID-19 patients are more susceptible to developing secondary bacterial infection [15]. Therefore, in this research, we focused on the susceptibility of patients with diabetes in the case of SARS-CoV-2 infection. Our findings indicated that the occurrence of positive bacterial coinfection was 0.9% higher in diabetic COVID-19 patients compared with non-diabetic patients ($p > 0.05$) (Table 1).

Among COVID-19 patients, there is no significant difference in the variables, gender, age groups, and bacterial coinfection ($p > 0.05$).

Identification of isolated bacterial coinfection among COVID-19 Patients

A total of 87 bacterial strains were isolated from the cultures in 200 patients. As many as 44 (48.9%) of the samples were MSU, 39 (43.3%) were sputum, and 4 (20%) were TS. Among the 87 isolates from the secondary bacterial infections, 76 (87.4%) species were gram-negative bacteria and 11 (12.6%) were gram-positive bacteria (Table 2). Results revealed that seven pathogenic gram-negative bacterial species were isolated, *A. baumannii, E. coli, P. aeruginosa, K. pneumonia, Enterobacter spp., Haemophilus spp.,* and *Proteus spp.* at a percentage of 25.3% (22), 18.3% (16), 16% (14), 11.5% (10), 8% (7), 4.6% (4), and 3.4% (3), respectively. Additionally, five pathogenic gram-positive bacterial species were isolated, *S. aureus, Enterococcus spp., S. pyogenes, S. pneumonia,* and *S. epidermidis* at a percentage of 4.6% (4), 3.5% (3), 2.3% (2),1.1% (1), and 1.1% (1), respectively (Table 2).

Antibiotic susceptibility patterns of detected bacterial isolates from ICU COVID-19 patients

Antibiotic sensitivity patterns were performed on isolated bacteria from all samples; MSU sputum and TS of SARS-CoV-2 patients. We used 6 antibiotics to evaluate the susceptibility test for isolated gram-negative bacterial species. *A. baumanii* was the major isolated gram-negative bacteria, which was most sensitive to Ertapenem (86.4%) and Cefotaxime (54.5%) followed by Piperacillin/Tazobactam (50%) (Table 3). Likewise, *E. coli* was relatively sensitive to the above antibiotics. *P. aeruginosa* showed a low susceptibility rate to Aztreonam (35.7%), Cefotaxime, and Amoxicillin/Clavulanic acid (40.7% each). Similarly, *K. pneumoniae* displayed a low level of sensitivity to Aztreonam and Cefotaxime but showed high sensitivity to Piperacillin/Tazobactam (100%), Ertapenem (96%), and Amoxicillin/Clavulanic acid (80%). The *Enterobacter spp*. revealed low sensitivity against Norfloxacin (37.1%) and Aztreonam (42.8%). However, it revealed a high rate of sensitivity for the rest of the antibiotics. Additionally, the highest-rate

Table 2. Prevalence and occurrence of bacterial co-infections isolated from MSUs, sputum, and TS of ICU COVID-19 patients.

Isolated pathogens	Percentage % (N)
Gram-negative bacterial species 76 (87.4%)	
Acinetobacter baumannii	25.3 (22)
Escherichia coli	18.3 (16)
Pseudomonas aeruginosa	16 (14)
Klebsiella pneumoniae	11.5 (10)
Enterobacter spp.	8 (7)
Haemophilus spp.	4.6 (4)
Proteus spp.	3.4 (3)
Gram-positive bacterial species 11 (12.6%)	
Staphylococcus aureus	4.6 (4)
Enterococcus spp.	3.5 (3)
Streptococcus pyogenes	2.3 (2)
Streptococcus pneumoniae	1.1 (1)
Staphylococcus epidermidis	1.1 (1)
Total	100 (87)

Table 1. Relationship between gender, age and clinical profiles of ICU COVID-19 patients.

Variables	Samples (200)		Total	*p* value
	Positive culture (87)	Negative culture (113)	200	
Gender				
Male	47 (43.5%)	61 (56.4%)	108 (54%)	0.995
Female	40 (43.4%)	52 (56.5%)	92 (46%)	
Age group				
28-37	11 (22.4%)	38 (77.5%)	49 (24.5%)	
38-47	13 (33.3%)	26 (66.7%)	39 (19.5%)	0.001
48-57	26 (49.0%)	27 (50.9%)	53 (26.5%)	
58-67	37 (62.7%)	22 (37.3%)	59 (29.5%)	
Under line disease				
Diabetic	19 (44.2%)	24 (55.8%)	43 (21.5%)	0.918
Non-diabetic	68 (43.3%)	89 (56.7%)	157 (78.5%)	

sensitivity of isolated pathogens to most tested antibiotics was observed from *Haemophilus spp*. and *Proteus spp*., which only showed low sensitivity to Aztreonam (Table 3). Notably, the total susceptibility rate of gram-negative isolated pathogens showed sensitivity to Ertapenem (90.7%) and Piperacillin/Tazobactam (84.9%).

Additionally, in our study, 6 antibiotics were used to assess the sensitivity rate of the isolated gram-positive bacterial species. The overall antimicrobial susceptibility of gram-positive isolates was revealed to be highly susceptible to Teicoplanin (77.2%), Rifampicin (71%), and Clindamycin (62.7%). Susceptibility rates of *S. aureus* were observed (92.5%) sensitive to Teicoplanin, (85%) to Rifampicin, (75%) to Clindamycin, followed by (72.5%) to Chloramphenicol and (67.5%) to Cefoxitin (Table 4). *Enterococcus spp*. was sensitive to Teicoplanin (83.3%), Chloramphenicol, and Rifampicin (50% each). In contrast, low sensitivity was detected for other antimicrobials tested. *S. pyogenes* had the lowest sensitivity rate to all commonly used antibiotics. Generally, *S. epidermidis* and *S. pneumonia* presented a low susceptibility rate to Ampicillin (0%) and Chloramphenicol (30%) respectively (Table 4).

Discussion

In this research, we concluded that the antibiotic susceptibility tests of the isolated gram-negative bacteria were more resistant than gram-positive bacteria. This could delay not only the process of treatment and recovery of SARS-CoV-2 patients but also may increase the mortality rate [16]. Thus, the choice of antimicrobial program could be more suitable for treating the infections of multidrug-resistant gram-negative bacteria [17]. The current study reported that 47 (43.5%) of patients who had bacterial coinfection were male, the mean age was 47.5 years, and 43 (21.5%) of all patients had diabetic diseases. Similar to this data, recent studies have reported that the male gender constitutes a risk factor for disease severity. Underlying diseases and age above 65 are risk factors for death in COVID-19 patients [18]. In the present study, the sample was taken from patients admitted to ICUs for 5-7 days. Indeed, this duration was an excellent opportunity for bacteria to infect the patients [11]. This is corroborated by another study that took the sample after five days of admission, which raised the rate of co-infection (6.1%) among COVID-19 patients [19,20]. In our study, among 200 patients with SARS-CoV-2, secondary bacterial infections occurred in 87 (%43.5) patients; this is in line with another study done in Lagos, Nigeria, which had a rate of coinfection (55.3%) of the study participants [21]. In this research, gram-negative isolates (87.4%) were more prevalent than gram-positive bacteria (12.6%). Building on previous findings that reported gram-negative bacteria in the majority of COVID-19 patients [22]. Our result showed that the most common gram-negative bacterial species were *A. baumanii* (25.3%), *E. coli* (18.3%), *P. aeruginosa* (16%), and *K. pneumonia* (11.5%), and the most common gram-positive bacteria were S. aureus

Table 3. Antibiotic susceptible patterns in gram-negative bacteria isolated from critically ill COVID-19 patients.

Antibiotics	Bacterial Type														Total Susceptibility Rate (%)
	A. baumanii		*E. coli*		*P. aeruginosa*		*K. pneumoniae*		*Enterobacter spp.*		*Haemophilus spp.*		*Proteus spp.*		
	N = 22	%	N = 16	%	N = 14	%	N = 10	%	N = 7	%	N = 4	%	N = 3	%	
Amoxicillin	9	40.9	7	43.7	5.7	40.7	8	80	5.5	78.6	3	75	2.5	83.3	63.2
Aztreonam	0	0	6	37.5	5	35.7	0	0	3	42.8	1.3	32.5	0	0	21.2
Cefotaxime	12	54.5	8.3	51.8	5.7	40.7	4	40	6	85.7	3.4	85	2.6	86.7	63.5
Ertapenem	19	86.4	14.2	88.7	12.4	88.6	9.6	96	6.2	88.6	4	100	2.6	86.7	90.7
Norfloxacin	0	0	4.7	29.3	9.8	70	4	40	2.6	37.1	2.3	57.5	2	66.7	42.9
Piperacillin/Tazobactam	11	50	13.6	85	12.4	88.6	10	100	5.8	82.8	3.8	95	2.8	93.3	84.9

A. baumanii; Acinobacter baumanii: E. coli: Escherichia coli; P. aeruginosa: Pseudomonas aeruginosa: K. pneumoniae; Klebsiella pneumoniae. N: frequency of isolates.

Table 4. Antibiotic susceptible patterns in gram-positive bacteria isolated from critically ill COVID-19 patients.

Antibiotics	Bacterial Type										Total Susceptibility Rate (%)
	S. aureus		*Enterococcus spp.*		*S. pyogenes*		*S. pneumoniae*		*S. epidermidis*		
	N = 4	%	N = 3	%	N = 2	%	N = 1	%	N = 1	%	
Ampicillin	1.3	32.5	0	0	0	0	0.5	50	0	0	16.5
Cefoxitin	2.7	67.5	1.2	40	0.8	40	0.6	60	0.7	70	55.5
Chloramphenicol	2.9	72.5	1.5	50	0.7	35	0.3	30	0.9	90	55.5
Clindamycin	3	75	1	33.3	0.7	35	0.8	80	0.9	90	62.7
Rifampicin	3.4	85	1.5	50	0.8	40	0.8	80	1	100	71
Teicoplanin	3.7	92.5	2.5	83.3	0.8	40	0.9	90	0.8	80	77.2

S. aureus: Staphylococcus aureus, S. pyogenes: Streptococcus pyogenes, S. pneumoniae: Streptococcus pneumoniae, S. epidermidis: Staphylococcus epidermidis. N: frequency of isolates.

(4.6%), Enterococcus spp. (3.5%), *S. pyogenes* (2.3%) and *S. pneumoniae* (%1.1). The observed prevalence of bacterial co-infection among ICU SARS-CoV-2 patients might be attributed to several factors, including compromised immunity and low standard of infection control between wards, high workload, and staff shortage. Therefore, it is crucial to view bacterial coinfection in COVID-19 patients, particularly with multi-drug resistant bacteria, to overcome hospital infections [13]. We found that *A. baumannii* (25.3%) was the main pathogen in the respiratory tract of COVID-19 patients. Another study reported that *A. baumannii* (56%) was detected in ICU SARS-CoV-2 patients [23]. Coinfection with *A. baumannii* in COVID-19 patients is significantly linked with the development of systemic infections and increased severity risk among ICU COVID-19 patients [24]. Our findings revealed *A. baumannii* strains recovered from the sputum of ICU COVID-19 patients were sensitive to Cefotaxime, Ertapenem and Piperacillin/Tazobactam. This observation is consistent with a previous study conducted in Turkey, which reported the sensitivity of *A. baumannii* from SARS-CoV-2 patients to the same antibiotics [18]. *E. coli* was the second most commonly isolated bacterial species (18.3%) in patients, mainly isolated from urine. Similarly, *E. coli* was previously identified in (16%) of COVID-19 patients [25]. *E. coli* displayed a low susceptibility rate to Norfloxacin, Aztreonam, Amoxicillin/Clavulanic acid. This is supported by previous findings that most uropathogenic *E. coli* in Hail were resistant to most antibiotics, including Norfloxacin and Amoxicillin [26]. Coinfection with *K. pneumonia* was linked with deterioration of overall health, especially in ICU COVID-19 patients [27]. *K. pneumoniae* has been reported to be the most commonly isolated bacteria from COVID-19 patients (19.4%) [28]; this is slightly higher than our findings (11.5%). Our result revealed that *S. aureus* (4.6%) was the most frequent gram-positive bacterial isolate from TS and sputum. Furthermore, our study presented that *S. pyogenes* (2.3%) was the most resistant bacterial species isolated in TS. This bacterium has high levels of antibiotic resistance and can produce various virulence factors, leading to high mortality [29]. This is comparable with another study, which recovered *S. pyogenes* (1%) from a nasopharyngeal swab of Covid-19 patients [13]. Bacterial co-infections are common in patients with viral respiratory illnesses such as influenza and COVID-19 [30]. Our data showed that bacterial co-infection is common in hospitalized patients with SARS-CoV-2, it may be useful to perform a panel test in these patients to determine whether co-infection is present. Finally, assessment of co-infection should also be considered in the clinical management of patients with COVID-19 so that treatment can be initiated for both SARS-CoV-2 and bacterial co-infection.

Conclusions

The overall prevalence of bacterial coinfection was 43.5% among ICU COVID-19 patients. The main causative agent was isolated *Acinetobacter baumannii, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia*, followed by *Staphylococcus aureus, Enterococcus spp.*,and *Streptococcus pyogenes*. The susceptible antibiotic rates against the significant isolated bacteria are generally moderate. Additional infection of a patient admitted to an intensive care unit (ICU) is a significant problem in the context of the COVID-19 pandemic, which can lead to an increase the disease severity and death. This study indicates that early detection of bacterial coinfection, and appropriate use of antimicrobial agents is needed for the treatment of ICU COVID-19 patients.

Limitations of the Study

Our study has some limitations. First, the current study focused only on ICU COVID-19 patients, not on non-ICU COVID-19 patients. Comparing these two groups of patients would give a better idea of bacterial isolation and sensitivity to antimicrobials. Second, bacterial species identification and the presence of genetic resistance determinants were not performed. Furthermore, our patients were not screened for bacterial infection upon admission. Future investigations to overcome these restrictions require to be considered.

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Ethics Statement

The Faculty of Science and Health/Koya University's Ethics Committee approved the study (reference: 11-2021).

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