Research Article

Mortality Rate and Antibiotic Resistant of the Secondary Bacterial-Infection in SARS-CoV-2 Patients

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Abstract | The main concern for SARS-CoV-2 patients is developing a bacterial secondary infection that could lead to an over whelming infections which very difficult to counteract during the course of the infection. The primary aim of the study at evaluating the most common secondary pathogens ,their antibiotic resistant profile and mortality rate of SARS-CoV-2 patients. A total of 41 patients with ventilator associated pneumonia of whom 23 were confirmed positive. for SARS-CoV-2 (infectious group) and 18 were tested negative for SARS-CoV-2 (non-infectious), were recruited in this study during the period from February to September 2022 at Al-Hussein. Teaching Hospital in Thi-Qar province, Iraq. Endotracheal aspirate samples were collected for the presence of microbes, using traditional cultivation methods along with antibiotic susceptibility testing for cultivated microbes. Using online sequential organ failure assessment score calculator to predict the outcome of the patients involved. A total of 41 patients the in I.C.U. suffers ventilator-associated pneumonia in this study, of whom 23 were infectious and 18 were non-infectious. The infectious group had higher sequential organ failure (SOFA) scores (p<0.05) and more *Acinetobacter* infections than the non-infectious group. The overuse of broad-spectrum antibiotics in treating bacterial co-infections, especially in intensive care units, is the main reasons of Multi drugs resistance (MDR) bacterial infections. These infections can worsen the clinical outcomes of SARS-CoV-2 patients, resulting in prolonged hospital stays, the need for mechanical ventilation, and higher mortality rates. Additionally, weakened immune systems due to viral infections can also make individuals more susceptible to MDR bacterial infections.

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Introduction

In the past two decades, multidrug resistance (MDR) has expanded to the point that it is now acknowledged as one of the most critical dangers to economic growth and public health. Infectious diseases by difficult to treat bacteria are progressively linked to increased mortality and high hospital expenditures in

places where antimicrobial treatment is widely used, like hospital rooms and critical care units (Ahmed *et al*., 2022). The coronavirus disease 2019 caused by the coronavirus responsible for the severe acute respiratory syndrome has posed an important threat to health throughout the globe, putting various populations at risk. With more than 650 million verified problem and a mortality toll of nearly 7 million losses worldwide.as of November 2022, the pandemic has culminated and has anxious in the healthcare system and economic system to destruction point. Severe SARS-CoV-2 has shaped the most important challenges facing medical organizations, with aging, gender identity, and complications being the most common risk factors for severe disease. Given that the airway system is the primary site of SARS-CoV-2 virus entry, the upper and lower respiration tract (Mizumoto *et al*., 2020; Baiou *et al*., 2021).

Some days after the epidemic was acknowledged, severe acute respiratory disorder coronavirus, a brand-new beta coronavirus, was found to be the cause of coronavirus disease 2019 (Bazaid *et al*., 2022). Individuals of all ages are vulnerable to SARS-CoV-2, and the majority will experience mild to moderate symptoms. The sickness is spreading quickly worldwide, and many people are dying from it. The WHO issued a Public Health Emergency of International discussion on Jan. 30, 2020. The 4 million confirmed cases and 278 892 fatalities have been reported as of May 11 throughout 213 nations, regions, or territories (Kniross *et al*., 2020; Rahmanzade *et al*., 2020).

Co-illnesses with bacteria are common in viral infections for respiratory tract like the flu and are a major source of morbidity and death. Antibacterial therapy and prompt diagnosis are therefore essential (Rehman, 2023). Uncertainty regarding bacterial co-infection prevalence, occurrence, and characteristics in SARS-CoV-2-positive patients represents a serious information gap. Antibiotics are unsuccessful in treating infection, yet for several reasons, doctors nonetheless recommended them to patients with known or suspected SARS-CoV-2 (Olsen *et al*., 2020). It is challenging to rule out the likelihood of bacterial infection throughout the disease and co-infection at the presentation time (Sharifipour *et al*., 2020). Yet, this strategy raises worries about antibiotic misuse and the negative effects of resistant pathogens. Several recommendations advocating using experimental antibiotics for patients with serious SARS-CoV-2 have been created due to increased death in patients with bacterial -infection throughout influenza pandemics (Rice *et al*., 2012). Considering the possibility of pathogenic bacteria infections in SARS-CoV-2 patients and the feature of microbes, it is crucial to responsibly treat SARS-CoV-2 patients with antibiotics to reduce the side effects of overuse (Liu *et al*., 2020).

Because SARS-CoV-2 disease is a growing issue with consequences for both the economy and world health, detecting and understanding the pattern of drug resistance in bacterial co-infections is critical to ensuring a better clinical outcome in these circumstances.

Materials and Methods

Study population and data assemblage

The study categorized the patients with ventilation associated pneumonia (VAP) into SARS-CoV-2 infected (infectious group) and non SARS-CoV-2 infected (non infectious group). The present study included patients with confirmed SARS-CoV-2 who were hospitalized at the I.C.U at Al-Hussein and other private hospitals between February and September, 2022. The patients in the I.C.U who were on mechanical ventilation and had another illness during this time were regarded as not belonging to the SARS-CoV-2 category. In these patients, V.A.P. is described as severe pneumonia occurring more than 48 hours after intensive mechanical ventilation was started.

Quantifiable culture methods for tracheal discharge aspirates are more successful when suitable parameters are used. Patients with pneumonia have at least 10^5 to 10^6 CFU/ml of pathogens in their lower respiratory system sputum. The recommended diagnosis criterion for tracheal aspirate is 106 CFU/ml.

The Kirby Bauer disk diffusion method was employed to assess the antimicrobial susceptibility of all isolates. Based on the findings, the MDR isolates, which are characterized by resistance to three or more categories of antibiotics, were chosen for additional investigations. The broth micro-dilution method utilized in this the study as delineated in the clinical and laboratory standard institute strategies, to define the MIC of antibiotics against all multi-drug resistant

(MDR) isolates. The resulting MIC values were taken by referencing standard tables modified from the CLSI informational supplement.

Endotracheal sputum samples for this study were obtained during routine clinical specimen collection and promptly inspected in the hospital's microbiological lab in accordance with the (CLSI) standards.

Statistical examination

All data were evaluated using Fisher's exact test and then expressed as numbers (%). At *P*= 0.05, differences were considered statistic significant. Online SOFA score calculator was used to predict the outcome of the patients involved using the preexisting demographic, clinical, and laboratory data from the time of admission to forecast the risk of death in I.C.U. patients.

Results and Discussion

A total of 41 patients met the principles for ventilation-Associated Pneumonia during their stay in the ICU from February 2022 to September 2022. Out of these patients, 23 tested positive for COVID-19 infection (infectious group), while the remaining 18 tested negative for COVID-19 (non-infectious group) Figure 1.

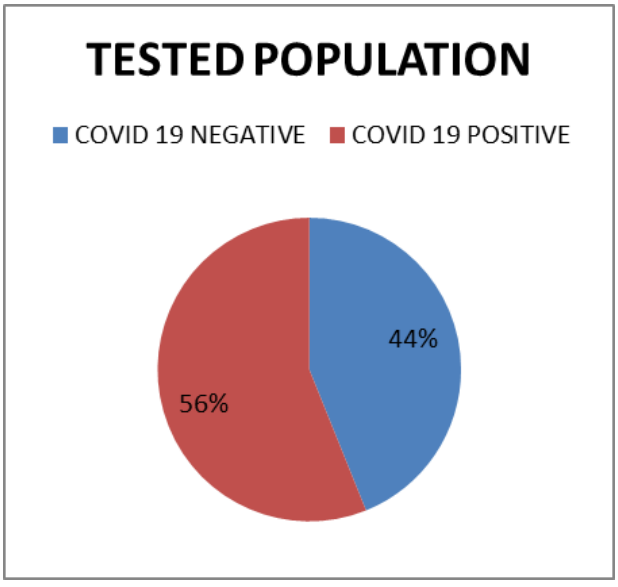

Figure 1: *Distribution of the tested population.*

The patients in the study were grouped based on their age, which fell into four categories: Forties, fifties, sixties, and seventies. Interestingly, the mainly of the patients included to the septuagenarian group Figure 2.

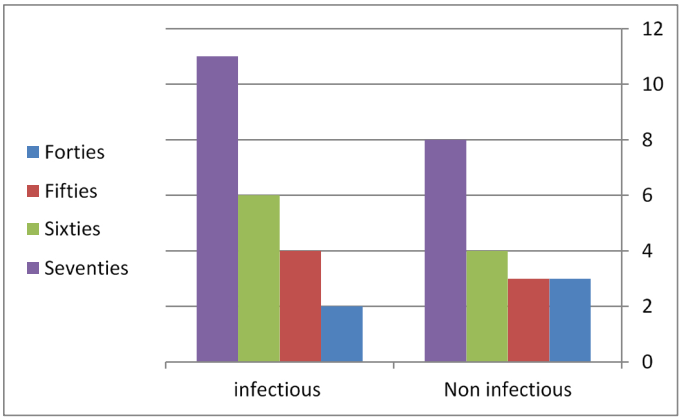

Figure 2: *Distribution of patients according to their decade of age.*

The data shows that 50% of patients in the Non-Infectious group required an extended hospital stay of over ten days. On the other hand, the infectious group had a significantly lower percentage 30.43% of patients with an extended hospital stay of over ten days Figure 3.

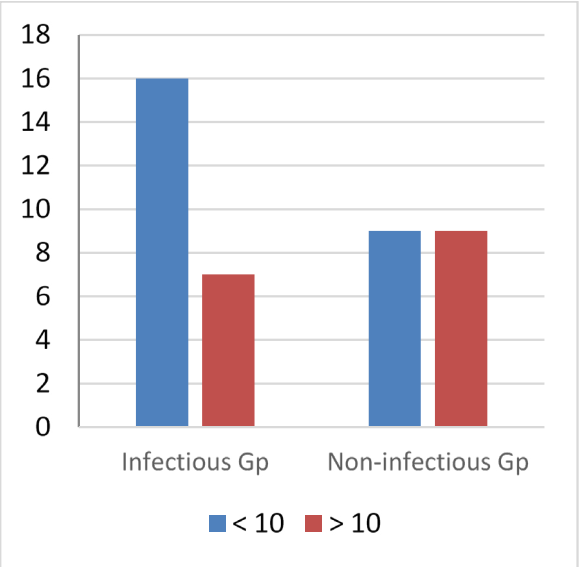

Figure 3: *The stay period (in days) for both groups in this study.*

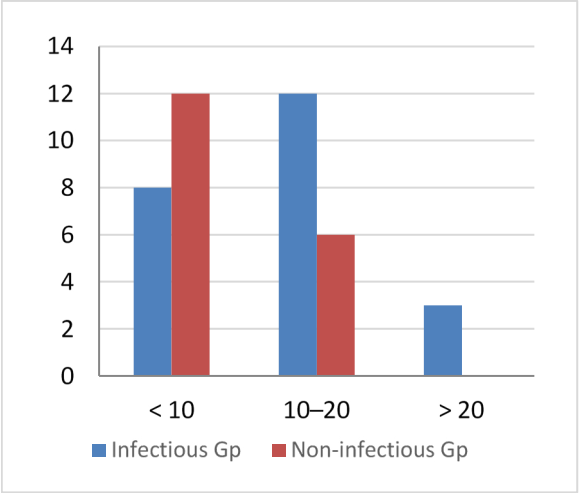

Figure 4: *The SOFA scale among both groups in this study.*

The study discovered that the SOFA score was greater than 10 in both the infectious and non-infectious categories in 65.22% and 33.33% of cases, respectively. This shows that the infectious group had a more severe sickness than the non-infectious group. With a p<0.05, the observed difference was statistically significant, indicating a high level of confidence in the findings Figure 4.

Furthermore, the study showed that infectious patients known to the ICU had a considerably higher mortality rate. The mortality rate among infectious patients was found to be 43.48%, which was much greater than the death rate among non-infectious patients, which was only 5.56% p<0.05, the alteration between the two groups was statistically significant. These findings imply that SARS-COV-2 infections play a substantial influence in the death of VAP patients Figure 5.

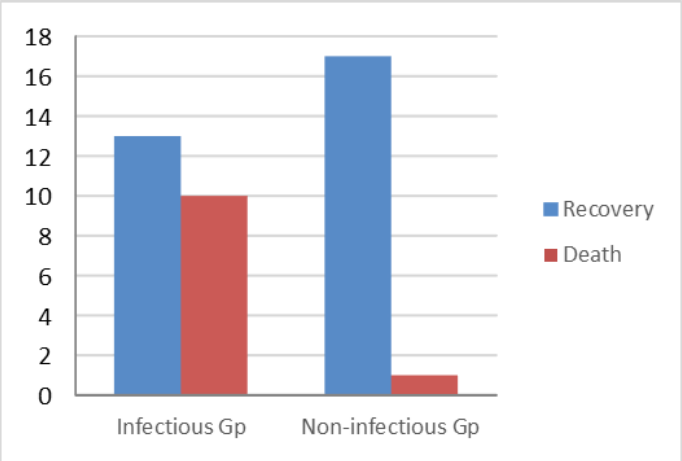

Figure 5: *The rate of recovery among both groups.*

The study found that *Acinetobacte*r spp. were the most frequently found isolates in both the infectious and non-infectious groups, accounting for 26.09% and 22.22% of cases, respectively. *Acinetobacter* spp. are gram-negative bacteria that can cause various infections, including pneumonia. *Pseudomonas aeruginosa* was the second most found isolate, accounting for 21.74% and 16.67% of cases in the infectious and non-infectious groups, respectively. *Pseudomonas aeruginosa* is also a gram-negative bacterium that can cause such infections, especially in people with weakened immune systems. *Klebsiella* spp. and *E. coli* each accounted for 13.04% of Infectious cases. *Klebsiella* spp. and *E. coli* are gram-negative bacteria. The study also isolated other microbes such as *Staphylococcus aureus*, *Staphylococcus epidermidis, Diphtheroids, Streptococcus pneumoniae, Enterococcus faecalis* which are gram-positive bacteria that are commonly found on the skin and can cause infections in skin and other infections and *Candida* spp which are fungi that can cause infections such as thrush, skin infections, and bloodstream infections. Furthermore, the statistical analysis of the study showed no significant. Differences, between the two groups regarding the type of infectious agent. The findings of the study are shortened in Table 1.

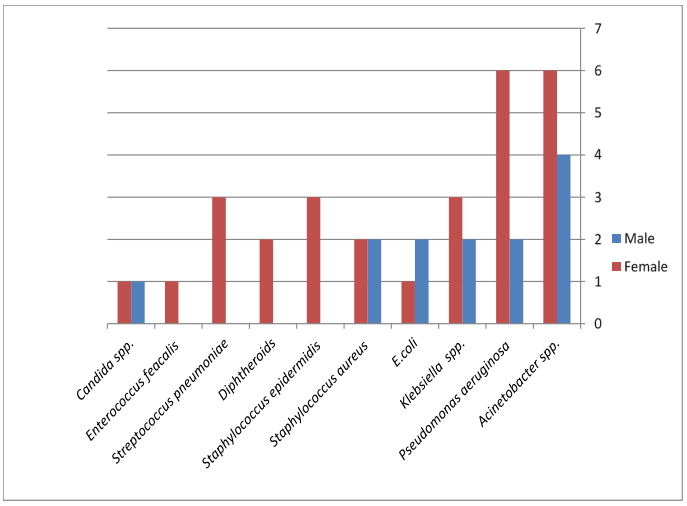

Figure 6: *Isolated pathogens according to sex.*

Table 1: *Isolated microbes from the tested groups.*

p value	%	Non-infectious group	%	Infectious group	Isolated microbe
>0.05	22.22	4	26.09	6	*Acinetobacter* spp.
	16.67	3	21.74	5	*Pseudomonas aeruginosa*
	11.11	2	13.04	3	*Klebsiella* spp.
	0.00	0	13.04	3	*E. coli*
	11.11	2	8.70	2	*Staphylococcus aureus*
	5.56	1	8.70	2	*Staphylococcus epidermidis*
	5.56	1	4.35	1	*Diphtheroids*
	11.11	2	4.35	1	*Streptococcus pneumoniae*
	5.56	1	0	0	*Enterococcus feacalis*
	11.11	2	0	0	*Candida* spp.
	100.00	18	100.00	23	Total

Table 2: *Antibiotic susceptibility testing for the isolated bacteria.*

Colistin	Ciprofolxacin	Cotrimoxazole	Amikacin	Imipenem	Gentamycin	Ceftriaxone	Cefixime	Microbes antibiotic
S	M	M	R	R	R	R	R	*Acinetobacter* spp.
S	M	M	R	M	R	R	R	*Pseudomonas aeruginosa*
S	R	M	S	S	M	M	R	*Klebsiella* spp.
R	S	R	M	S	M	S	R	*E. coli*
R	S	S	M	S	S	M	M	*Staphylococcus aureus*
S	S	S	M	S	M	S	M	*Staphylococcus epidermidis*
S	S	S	M	S	S	S	S	*Diphtheroids*
S	S	S	M	S	M	S	M	*Streptococcus pneumoniae*
M	M	M	M	M	M	S	M	*Enterococcus feacalis*

The majority of patients of both categories were females accounting for 68.29% of the entire studied population, also accounted for 72.22% and 65.22% of Noninfectious and Infectious group, respectively. Figure 6.

The study looked at eight different antibiotics, including colistin, ciprofloxacin, cotrimoxazole, amikacin, imipenem, gentamicin, ceftriaxone, and cefixime. Colistin was found to be the most efficient against multidrug-resistant gram-negative. Bacteria, such as *Acinetobacter* spp. and *Pseudomonas, aeruginosa*. Ciprofloxacin and cotrimoxazole were shown to be fairly effective against most bacteria, but not against *Acinetobacter* spp. and *Pseudomonas aeruginosa*, both of which have developed resistance to these antibiotics. Amikacin and imipenem were also discovered to be moderately to extremely effective against the majority of bacteria, with the exception of *Acinetobacter* spp., which is resistant to imipenem, and *Enterococcus faecalis*, which has moderate resistance to both antibiotics. It is not, however, effective against *Acinetobacter* spp. or *Pseudomonas aeruginosa* Table 2.

Infectious group which was co-infected with *Pseudomonas aeruginosa*, *Enterococcus faecalis*, or *Klebsiella* spp. had worse outcomes than those with co-infection with another bacteria Figure 7.

In the study of 41 patients were included in a study conducted at Al Nasiriyah Teaching Hospital between February and September, 2022. These patients had characteristics of Ventilation Associated Pneumonia (VAP). Out of all the VAP patients, 23 tested positive for COVID-19 infection and had developed secondary bacterial infections that worsened their condition. As a result, these patients had longer hospitalization periods. While this study did not bargain an important association between, the length of hospital stay and bacterial infection, This problem has been investigated in another study, Pourajam *et al.* (2022) reported a significant number of cases involving carbapenem-resistant gram-negative bacteria for COVID-19 patients who were known to the serious care, units. The majority of these cases were caused by *K. pneumoniae*, with *A. baumannii* being the second most common culprit. These cases were found to be more frequent among patients who stayed in the hospital for over 10 days. The most common age group among the patients in this study were patients in their seventies. Although there was no significant correlation found between age and secondary bacterial infection, this finding contrasts with the study by Bahceci *et al.* (2022), who concluded that elderly patients, are more vulnerable to secondary pathogenic bacteria infections after being infected with COVID-19.

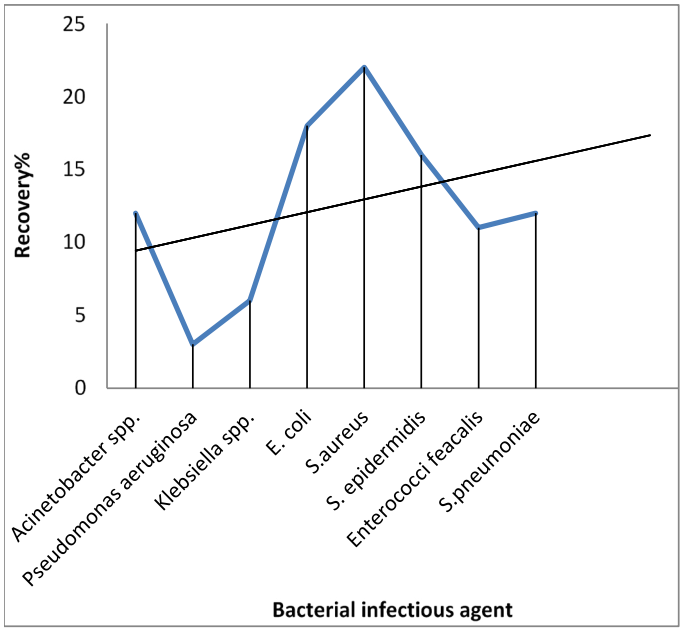

Figure 7: *The percentage of recovery among VAP infected patients.*

Acinetobacter spp. has demonstrated complete tolerance to amikacin, imipenem, gentamycin, and cefixime. Resistance to Co-trimoxazole and cefixime was discovered in *Pseudomonas aeruginosa*. Furthermore, *Klebsiella* spp. remained completely resilient to cefixime, Co-trimoxazole, gentamycin, amikacin, ciprofloxacin, and ceftazidime. Additionally, in the infectious group, *E. coli* was immune to cefixime and Co-trimoxazole (Table 2). *Klebsiella* spp. and *Acinetobacter* spp. were found to be impervious to almost all antibiotics tested, except for colistin in the non-infectious group.

Observational research indicates that COVID-19 patients experience secondary infection by pathogen bacteria, which exacerbate the condition and increase mortality, like that in those who want intrusive ventilation, the rates of pathogenic bacteria infectious diseases and subsequent infections stayed modest (5-7%), despite higher rates in severely ill ICU patients. more the readings of COVID-19, patients who were brought to the ICU indicated that the majority of patients were given antibiotics based on their symptoms, the frequency of MDR pathogens. In general, VAP rates in severely ill COVID-19 patients were found to climb above 50%. With 40% mortality rate exceeding, and an increase in the numeral of patients needing medical attention (Yadav and Ravichandran, 2023).

Several studies Chen *et al.* (2020), Mazzariol *et al.* (2021), and Zhao *et al.* (2020) have found bacterium co-infections/superinfections in 58.1% of 29.8%, and 5.1% of COVID-19 cases, respectively. Previous research from Nahav and Hospitals in Iran discovered that 12.46% of 340 COVID-19 patients acquired various bacterial illnesses. The most strains isolated bacterial species were *S. aureus, E. coli,* and *Klebsiella.* Moreover, 18 (95%) of the 19 positive COVID-19 cases were registered to I.C.U.s, according to Sharifipour *et al.* (2020). All patients had bacterial co-infections caused by *A. baumannii* (91%) and *S. aureus* (09%), which were all positively identified. In our study, 10 patients by severe COVID-19 died in the critical care unit, accounting for 43.48% of the total patients infected with COVID 19. Our findings showed that secondary bacterial infections in COVID-19 patients contributed significantly, which is agreement with previous researches (Zhao *et al.*, 2020; Mazzariol *et al.*, 2021; Yang *et al.*, 2020), discovered that thirty-two of the thirty-seven severely sick patients with mechanical ventilation who had COVID-19 perished. Four of the patients who perished had secondary diseases caused by antibiotic-resistant germs. Agreeing to Evans *et al.* (2021) 35% of COVID-19 ICU patients getting artificial breathing at a London hospital perished overall.

According to Temperoni *et al.* (2021) 64% of 48 COVID-19 patients getting artificial breathing in the Hospital's I.C.U. had multidrug-resistant microbes identified bacteria dominated gram-positive bacteria in Multidrug-resistant strains, gram-negative, which is compatible with our results. They discovered a large prevalence of *A. baumannii*, Carbapenem-resistant colonized with a 75% contagion rate. According to our outcomes, *Acinetobacter* spp. is highly resistant to antibiotics, gentamycin, amikacin, imipenem, and cefixime. The rise of resistant Gram-negative bacteria in patients is frequently linked with the extended use of outward devices such as urinary tubes, artificial ventilation, vital venous lines, and long hospital stay periods. The hazard posed by antibiotic-resistant microorganisms to human health is significant. From March 1 to May 20, 2020, Montrucchio *et al.* (2021) examined *Klebsiella pneumoniae* in COVID-19 patients admitted to the I.C.U. at the hospital, in Italy. In this investigation, three patients with V.A.P. brought on by *Klebsiella pneumonia* and *Pseudomonas aeruginosa* were shown to have bacterial co-infection. In these individuals, (CP-Kp) infected shock-related mortality was 28.7%. In a multinational investigation, V.A.P. All hospital illnesses accounted for 50% of in SARS-COV-2 patients, with Gram-negative bacteria accounting for 28 percent of V.A.P. agents. In an additional study, 2% of SARS-COV-2 patients brought to the I.C.U. had H.A.P. and thirty-three percent had V.A.P., with V.A.P. it may lead to severe respiratory distress syndrome and presence linked and more severe kidney, damage prolonged artificial breathing, and longer I.C.U. admission (Akrami *et al.*, 2023).

According to a recent investigation by Mazzariol *et al.* (2021) *Pseudomonas aeruginosa* was the most commonly detected bacteria, classes in respiratory aspirate models from automatically expressed patients with SARS-COV-2. These isolates were mostly Carbapenem-resistant. In another study, Grasselli *et al.* (2019) found that multi-drug resistance Gram-negative bacterial contamination is frequent in patients receiving extracorporeal membrane oxygenation and

is linked to more than ten-fold chances of subsequent infections linked to an elevated risk of mortality. *S. aureus* and *S. epidermidis* were the most prevalent spp. in patients across Gram-positive bacteria *Staph. Aureus, S. faecalis,* and *S. faecium* were the most dominant spp. (Salah *et al*., 2021), nonetheless, in the Temperoni *et al.* (2021) survey, additionally, 71.4% of the patients had *E. faecalis* which was M.D.R. Also, in 18.2% of cases, the development of *Candida* spp. was seen. Senok *et al*. (2021) found that the incidence of isolates carrying medication-resistance genes, the introduction of Candida species, and the treatment of patients at the General Hospital in Umm Al-Quwain are all causes for worry (Yadav and Avichandran, 2023). The high rate of occurrence of contagious and fungus infections in severe SARS-COV-2 patients is ultimately due to the widespread usage of antibiotics, immunological dysregulation, and a lack of commitment to infection management and preventive strategies.

Conclusions and Recommendations

General individuals with confirmed COVID 19 infections are developing infection outbreaks, especially by Gram-negative bacteria. Patients especially, females older than 50 years old are the most affected by COVID 19 and this due to risk factors that need to be studied, like if those exposed to occupational, environmental, and infectious factors. SOFA score needed more research as the sample size was not large for judgment since it was greater than 10 in 64.1% and 25.0% of the infectious and non-infectious groups. As demonstrated by the high frequency of antibiotic resistance among pathogens recovered from SARS-COV-2 patients getting artificial breathing in the intensive care unit, it is critical to prevent co-infections caused by this pathogen. This indicates that in SARS-COV-2 patients, a standardized strategy for antibiotic management is critical for successful therapy.

Acknowledgment

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Novelty Statement

The study outlines weakened immune systems due to viral infections can also make individuals more susceptible to MDR bacterial infections.

Author's Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ASH, MWB and AAK. The first draft of the manuscript was written by MWB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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Ethical approval
An official permission was obtained from the unit of continuous training and developments of the Thi Qar health department at Al-Nasiriyah city, Iraq.

Consent to participate
Informed consent was obtained from all individual participants to include in the study.

Consent to publish
Not applicable.

Conflict of interest
The authors have declared no conflict of interest.

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