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Prevelance of Co-infection by Multidrug-Resistant *Klebsiella pneumoniae* in COVID-19 Patients: Multi-centric Cross Sectional Study

Ahmed A Maklad*

Department of Microbiology, Alexandria University, Egypt

ABSTRACT

A relationship between COVID-19 and bacterial infection began to appear in severe cases. Numerous investigations documented the spread of Multi-Drug Resistant (MDR) *Klebsiella pneumoniae* as a coinfection among severely ill COVID-19 patients.

Subjects and methods: The study was conducted from October 2021 to October 2022 in multi-centers in Alexandria governate, Egypt. This study included 522 patients from Intensive Care Unit (ICU) and inpatient departments in 12 acute care hospitals. Data on demographics, comorbidities, microbiologic results, antimicrobial susceptibility, and outcomes were collected directly from medical health records for hospitalized COVID-19 patients.

Results: Most COVID-19 cases were in the age group over 60 years, representing 56.5% of cases. Recent exposure to antimicrobials was the most common in COVID-19 cases co-infected with *K. pneumoniae* (99%) followed by invasive devices (95.7%), and a history of previous hospitalization (80%). The most common samples isolate of *K.pneumoniae* was tracheal aspirate 60.1%. Most *K. pneumoniae* coinfections (46%) occurred in severe COVID-19 cases. There was a significant difference in mechanical ventilation requirements and recent antibiotic exposure between COVID-19 cases co-infected and non-coinfected with *K. pneumoniae* ($p<0.00001$). *K. pneumoniae* has no sensitivity to almost all antimicrobials but is sensitive to Colistin and Tigercillin.

Conclusion: The elderly and critically ill patients are at high risk for SARS-CoV-2 infection and coinfection with *K. pneumoniae*. Recent hospitalization and prior antimicrobial exposure are the risk factors for coinfection with *K. pneumoniae*. An increase in dependence on mechanical ventilation for those co-infected with *K. pneumoniae*.

Keywords: *K. pneumonia*; Co-infection; Multi-drug resistant; COVID-19; SARS CoV-2

ABBREVATIONS

Klebsiella pneumoniae (*K. pneumonia*); Intensive Care Unit (ICU); Multi-Drug Resistant (MDR); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

INTRODUCTION

On December 31, 2019, the WHO Western Pacific Regional Office received reports of 'pneumonia of unclear cause' cases in Wuhan, China. The causative agent was called Coronavirus disease 2019 because it was discovered to be caused by a novel strain of Coronavirus known as severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) (COVID-19). The disease's very quick international spread and spike in COVID-19 cases prompted WHO to declare it a pandemic on March 11, 2020. As of May 23, 2021, WHO had recorded approximately 166 million illnesses and over 3.4 million projected deaths across 186 countries linked to COVID-19. They recognized fever and cough as prevalent signs of the condition [1].

With more studies, a relationship between COVID-19 and bacterial infection began to appear in severe cases of COVID-19. In an analysis of 191 hospitalized adult COVID-19 patients in Wuhan, found that sepsis was the most frequently observed complication in both non-survivors and survivors of the disease. The stud-

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Corresponding author Ahmed A Maklad, Department of Microbiology, Alexandria University, Egypt, E-mail: Mri.Ahmed.Microbiology18@alexu.edu.eg

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ies reported that sepsis could have resulted from viral infection in these patients and hence, specific data confirming bacterial involvement in COVID-19 were still needed. In 712 hospitalized adult COVID-19 patients in Valladolid, Spain, 16% were reported as presenting with bacterial/fungal coinfections or superinfections [2,3].

Numerous microorganisms, including rhinovirus, flu infection, other CoVs, para-influenza, meta-influenza, and human orthopneumovirus, have been identified as potential co-infectious agents in COVID-19 patients. The Klebsiella species is one of the top 10 bacteria that cause nosocomial infections, and it is one of the most common infectious agents in intensive care units [4].

The increased incidence of antibiotic-resistant clinical bacterial isolates is one of the most significant strains on healthcare systems worldwide. *K. pneumoniae* is one of the top 6 pathogens contributing to healthcare-associated infections and medication resistance among these MDR bacteria. *K. pneumoniae*, an opportunistic infection composed of Gram-negative bacilli and a member of the enterobacterales family, primarily affects immunocompromised patients or those admitted to hospitals. *K. pneumoniae* has been linked to a variety of illnesses, including sepsis, bacteremia, pneumonia, and urinary tract infections [5-7].

Pneumonia is one of the most common infectious diseases, and can be the primary cause of hospitalization and mortality in older individuals. In clinical practise, MDR *K. pneumoniae* infections have been associated with high pneumonia incidence and mortality rates of 40%-50%, particularly among critically ill patients and solid organ transplant recipients, and delayed prescription of sufficient antibiotic treatment is a recognized risk factor for increased mortality [8,9].

Asymptomatic rectal carriage of MDR *K. pneumoniae* is now thought to be the principal reservoir for continuous transmission and is an important site for infection control measures to be implemented. Despite the fact that various risk factors for MDR *K. pneumoniae* colonisation have been identified, prior exposure to broad-spectrum antibiotics, notably carbapenems, seems to be the most clinically important determinant of MDR *K. pneumoniae* colonisation [10,11].

Numerous investigations documented the spread of Multi-drug resistance *K. pneumoniae* as a coinfection among severely ill COVID-19 patients, particularly during hospitalization. The identification of risk factors and the prevalence of *K. pneumoniae* is critical for *K. pneumoniae* prevention and control. The aim of this study is to investigate the prevalence of risk factors for MDR *K. pneumonia* among those who are infected with SARS CoV-2 as well as the antibiogram of *K. pneumoniae*.

PATIENTS AND METHODS

This study was conducted from October 2021 to October 2022 in multi-centers in Alexandria governate, Egypt. The institutional ethics committee of the hospitals approved the study; the committee waived the need for receipt of verbal consent from individual patients.

Study Design

Cross-sectional.

Study Subjects

This study included 522 patients from Intensive Care Units (ICU) and inpatient departments in 12 Acute care hospitals.

Data Collection

Data on demographics (age, gender), comorbidities, microbiologic results (blood and urine cultures, respiratory samples, and antimicrobial susceptibility), and outcomes Intensive Care Unit (ICU) admission, Mechanical ventilation requirement) were collected directly from medical health records for all COVID-19 patients hospitalized. To determine clinical significance, all patients with positive microbiologic results had their records reviewed.

Inclusion Criteria

All patients with SARS-CoV-2 ribonucleic acid (RNA) detection in a nasopharyngeal, respiratory swab or clinical specimen utilizing a diagnostic molecular amplification test done by a qualified provider.

Illness Severity Classifications of Covid-19 Cases

COVID-19 was divided into five various levels of illness based on the severity of the presenting illness as follows:

Individual who have positive SARS-CoV-2 ribonucleic acid (RNA) test, but:

- Asymptomatic: Wthout any clinical signs or symptoms.
- Mild illness: With clinical signs or symptoms but not shortness of breathing.
- Moderate illness: With clinical signs or symptoms but oxygen saturation $SpO_2 \geq 94\%$.
- Severe illness: $SpO_2 \leq 94\%$ associated with marked tachypnea and radiological chest infiltrate.
- Critical illness: Acute Respiratory failure, septic shock and multiple organ failure.

Bacterial Strains and Culture Conditions

Blood, tracheal aspirate, urine, and sputum samples were obtained from various infection sites and rapidly sent to the Microbiology Department laboratory for further analysis. Gram staining demonstrated that positive culture media containing Gram-negative bacteria were sub-cultured into Mac-Conkey agars. These isolates were detected using standard clinical microbiological methods, including traditional techniques and/or the API 20E system (BioMe'rieux, Marcy l'E'toile, France). The disc diffusion method was used to examine antimicrobial susceptibilities in accordance with the National Committee for Clinical Laboratory Standards' performance methods and interpretation criteria [12,13].

Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, NY, USA, 2017) was used to analyse the data. Chi-square test and Yates continuity correction to test association. To present qualitative data, numbers and percentages were used. To evaluate statistical significance, a p-value of ≤ 0.05 was utilised.

RESULTS

Majority of COVID-19 cases were in age group more than 60 years representing 56.5% of cases, of them 17% were co-infected with *K. pneumoniae* and 39.5% were not co-infected with *K. pneumoniae*, while only few cases were below 30 years (1.3%) and all of them were not co-infected with *K. pneumonia* (Figure 1). As well, the majority of COVID-19 cases were male (62.3%), of them 18.8% Co-infected with *K. pneumoniae* cases, while 37.7 were female patients (Table 1).

Table 1: Distribution of the studied cases according to the demographic data

Characteristics	COVID-19 cases Co-infected with *K. pneumoniae*	COVID-19 cases non Co-infected with *K. pneumoniae*	No.	%
		Age*		
Less than 30	0	7	7	1.3
From 30 to <40	2	13	15	2.9
From 40 to <50	17	41	58	11.1
From 50 to <60	55	92	147	28.2
≥ 60	89	206	295	56.5
		Sex		
Male	98	227	325	62.3
Female	65	132	197	37.7
Total (%)	163 (31.2)	359 (68.8)	522	100

*Age in years

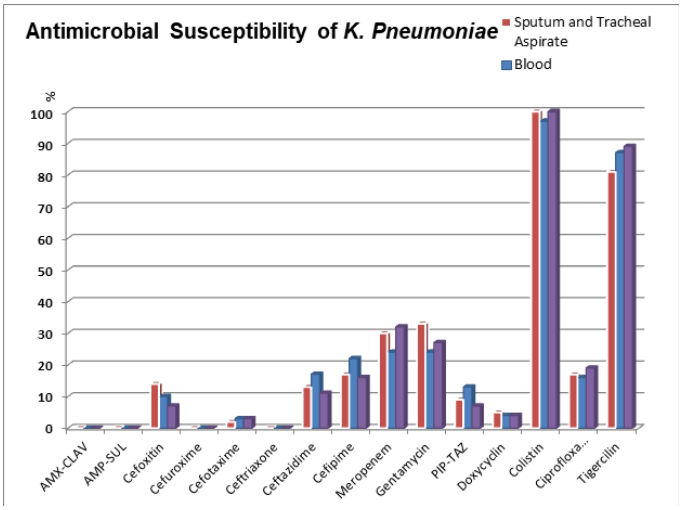

Figure 1: The clustered bar chart shows differences in the Sensitivity of *K. pneumoniae* to different antibiotics. There is no sensitivity to Amoxicillin-Clavulanic, Ampicillin-Sulbactam, Cefuroxime, and Ceftriaxone. As well, *K. pneumoniae* was sensitive only to Colistin and Tigercillin.

The current study shows that among risk factors reported, recent exposure to antimicrobial was the most common in COVID-19 cases co-infected with *Klebsiella pneumoniae* (99%) followed by invasive devices (95.7%), history of previous hospitalization (80%) and smoking (49.1%), there are no cases co-infected with *K. pneumoniae* without risk. While the most common risk factor among non-coinfected COVID-19 cases was smoking. However, in (1.9%) no risk factors could be identified (Table 2).

Table 2: Percentage of risk factors among the studied cases

Risk factors	COVID-19 cases Co-infected with *K. pneumoniae* N=163 (%)	COVID-19 cases non Co-infected with *K. pneumoniae* N=359 (%)
Diabetes Mellitus	8 (4.9)	28 (7.8)
Hypertension	7 (4.3)	19 (5.3)
Corticosteroids	13 (8)	14 (3.9)
Recent Antimicrobial exposure	161 (99)	39 (10.9)
Smoking	80 (49.1)	249 (69.4)
Previous Hospitalization	130 (80)	25 (7)
Invasive devices	156 (95.7%)	36 (10%)
No risk factors	0	7 (1.9)
Total (multiple risk factors)	555	417

The most common samples isolate *k.pneumoniae* was tracheal aspirtate 60.1% followed by sputum (22.7%), blood (19%) and urine (11%) (Table 3).

Table 3: Distribution of isolated *K. pneumoniae* in different clinical samples

Distribution of isolated *K. pneumoniae* in clinical samples	COVID-19 cases Co-infected with *K. pneumoniae N=163*	Percent %
Urine	18	11%
Sputum	37	22.70%
Tracheal aspirate	98	60.10%
Blood	31	19%

The table shows that most *K. pneumoniae* coinfections (46%) occurred in severe COVID-19 cases, while 5.8% of severe cases were not co-infected with *K. pneumoniae*. Although almost all non-coinfected with *K. pneumoniae* were asymptomatic cases (26.7%) and mild illness cases (25.6%) (Table 4).

Table 4: Percentage of COVID-19 disease severity level among *K. pneumoniae* coinfected and non coinfected

Severity levels of COVID-19 infection	Cases co-infected with K. pneumoniae N=163 (%)	Cases non Co-infected with K. pneumoniae N=359 (%)	Total
Asymptomatic	2 (1.2)	96 (26.7)	98
Mild Illness	6 (3.6)	92 (25.6)	108

Moderate illness	18 (11)	87 (24.2)	105
Severe illness	62 (38)	63 (17.5)	115
Critical illness	75 (46)	21 (5.8)	96

The current study showed that there was a significant difference in mechanical ventilation between COVID-19 cases co-infected and non-coinfected with *K. pneumoniae* (p<0.00001). Likewise, COVID-19 cases with recent antibiotic exposure had a significantly higher rate of coinfection with *K. pneumoniae* than COVID-19 cases without antibiotic exposure (p<0.00001) (**Table 5**).

Table 5: Comparison of mechanical ventilation and antimicrobial exposure among *K. pneumoniae* coinfected and non coinfected

Covid-19 infected patient	COVID-19 cases N (%)			Test of significance (Chi-square test)
	Cases co-infected with *K. pneumoniae*	Cases non co-infected with *K. pneumoniae*	Total	
On mechanical ventilation	139 (85.3)	124 (34.5)	243 (46.6)	X^2=115.43
Non-mechanical ventilation	24 (14.7)	235 (65.5)	279 (53.4)	P<0.0000**
Total	163 (31.2)	359 (68.8)	522 (100)	X^2 Yates=113.41
				P<0.0000**
Recent Antimicrobial exposure	161 (98.8)	39 (10.9)	200 (38.3)	X^2=366.5
				P<0.0000**
Non Recent Antimicrobial exposure	2 (1.2)	320 (89.1)	322 (61.7)	X^2 Yates=362.84
Total	163 (31.2)	359 (68.8)	522 (100)	P<0.0000**

DISCUSSION

Among 522 patients from ICU and inpatient departments in 12 Acute care hospitals in Alexandria Governorate who were infected with SARS Cov-2 infection, the age group of more than 60 years was at risk to infect with SARS Cov-2 and coinfection with *K. pneumonia*, and they were representing 56.5% of cases. Although only a minority of cases were under the age of 30 (1.3%) were infected with SARS Cov-2, and none of them were co-infected with *K. pneumoniae*.

In a similar Italian's study, a total of 80 COVID-19-affected patients were hospitalized in the two ICUs. Among them, 14/41 patients (34%) were 65 years patients and infected with Carbapenemase-producing *K. pneumoniae* [14].

A concordant analysis by Rawson et al. of investigations from China and the USA, reported that 8% of 806 COVID-19 patients had a bacterial or fungal co-infection. Another study reported that coinfections and secondary infections varied from as low as 0.6% to as high as 45% of COVID-19 patients [15,16].

The current study shows that among risk factors reported, recent exposure to antimicrobial was the most common in COVID-19 cases co-infected with *K. pneumoniae* (99%) followed by invasive devices (95.7%), history of previous hospitalization (80%) and smoking (49.1%), there are no cases co-infected with *K. pneumoniae* without risk. While the most common risk factor among non-coinfected COVID-19 cases was smoking. However, in (1.9%) no risk factors could be identified.

As well, there was a significant difference in mechanical ventilation dependence between COVID-19 cases co-infected with *K. pneumoniae* and those without *K. pneumoniae* co-infection (p<0.00001). Likewise, COVID-19 cases with recent antibiotic exposure had a significantly higher rate of coinfection with *K. pneumonia* than COVID-19 cases without antibiotic exposure (p<0.00001).

Similar to our findings, Zhou et al. reported in an extensive multi-center review inquiry that auxiliary bacterial coinfection occurred in 50% of the afflicted persons who died of COVID-19 due to their hospitalization for treatment [2].

Unsimilar results by Hughes et al. that observed a low frequency of bacterial coinfection during early COVID-19 hospitalization (3.2% at 0-5 days after admission) in a United Kingdom study of 836 patients with SARS-CoV-2 illness [17].

An opposite result reported by Garcia et al, Coinfection at the time of COVID-19 diagnosis is infrequent. During their stay, only a few patients got superinfections [18].

The most common samples isolate *k. pneumoniae* was tracheal aspirtate 60.1% followed by sputum (22.7%), blood (19%) and urine (11%).

Similar results was obtained by Arcari et al, 7 COVID-19 patients developed CPE co-infection (five bronchoalveolar lavages and two blood cultures tested positive for carbapenemase-producing *K. pneumoniae*) [14].

In contrast, a recent PCR-based analysis of 50,419 respiratory samples from nasopharyngeal, oro-pharyngeal and sputum swabs in the United States of America reported that *S. aureus* infected SARS-CoV-2-positive patients at a significantly higher rate than SARS-CoV-2-negative individuals (13.17% versus 11.64%, p<0.05).

The current study showed that most *K. pneumoniae* coinfections (46%) occurred in severe COVID-19 cases, while 5.8% of severe cases were not co-infected with *K. pneumoniae*. Although almost all non-coinfected with *K. pneumoniae* were asymptomatic cases (26.7%) and mild illness cases (25.6%).

Similar results were obtained by Lin et al. some COVID-19 patients especially severely ill ones, had coinfections of bacteria and fungi. Common bacterial cultures of patients with secondary infections included *A. baumannii*, *K. pneumoniae*, *A flavus*, *C. glabrata*, and *C. albicans* [19].

Similar study by Zhang et al. reported that severely affected patients, for example those who required Intensive Care Unit (ICU) admission and mechanical ventilation therapy, exhibited a significantly higher rate of bacterial co-infection compared with patients with non-severe COVID-19 disease (25.5% versus 1.8%; p<0.001) [20].

According to the study by Sakurai et al., at the time of diagnosis, 58% of the 712 individuals confirmed to have COVID-19 were asymptomatic. Ma et al. mentioned that individuals with asymptomatic infections represented in 40.50% of cases. During the outbreak of the Omicron variant in South Africa, an important investigation assessed that 31% of the confirmed cases were asymptomatic. Montrucchio et al. reported patients with COVID-19 related acute respiratory distress syndrome who developed invasive infections due to carbapenemase-producing *Klebsiella pneumoniae* [21-23].

This study reported that, there is no sensitivity to amoxicillin-Clavulanic, Ampicillin-Sulbactam, Cefuroxime, and Ceftriaxone. As well, *K. pneumoniae* was sensitive only to Colistin and Tigercillin.

Similar data were reported by Yahya, 99.4% of the *K. pneumoniae* isolates exhibited resistance to cefotaxime, while 99% showed resistance to amoxicillin-clavulanic acid and ceftazidime. Furthermore, 98.1% of the isolates exhibited resistance to each of cefuroxime and ceftriaxone, whereas 95% and 94.4% were resistant to trimethoprim-sulfamethoxazole and cefepime, respectively. It was observed resistance to piperacillin-tazobactam and ciprofloxacin as the next highest among 81.8% of the isolates, followed by cefoxitin (60%). While the lowest resistance rate corresponding to imipenem and ertapenem (31.3%), followed by meropenem (30%) [24].

In corcondant study by Oliveira et al., reported that *K. pneumoniae* increased the development of resistance against Ceftazidime, cefoperazone/sulbactam, Ceftolozane, and cefepime but the resistance trend declined in the case of Amoxicillin+clavulanic acid, Ceftriaxone, and Cefoxitin. The increased resistance against the cephalosporin group may result from the overuse of antibiotics during the pandemic [25].

In a study, high resistance rates in commonly used antibiotics like amoxicillin/clavulanic acid at 72%. Ampicillin showed a resistance rate of 99.9% while, Piperacillin showed a high resistance rate as well at 80.4%. A piperacillin/tazobactam combination, however, had lower resistance at 58.7%. Another combination (trimethoprim/sulfamethoxazole) showed high resistance at 67%. Fluoroquinolone showed lower resistance rates, with levofloxacin being the lowest of the class with 57.7% and ciprofloxacin at 61.1%. Aminoglycosides also showed lower resistance rates, especially with amikacin at 36.3% [26].

Such findings could be critical in defining the role of empiric antibiotic therapy or stewardship efforts in hospitalised COVID-19 patients.

There are several limitations in this study. First, there are many patients did not get sputum bacteriologic or fungal examination on admission because medical resources were overburdened in some hospitals. Sputum samples from COVID-19 patients may also be challenging to obtain because they are not always available from individuals who do not have a productive cough, and stimulation of cough may enhance viral transmission. As a result, the infection was not classified as either community or hospital acquired. Second, more specific patient information, particularly about clinical outcomes, was unavailable at the time of analysis; however, the data in this study allow for an early assessment of the epidemiological and clinical features of *Klebsiella pneumoniae* co-infection.

Given the wide range of positivity for coinfection or secondary infection across different studies, it is clear that larger studies are needed that are specifically designed to ascertain the levels of bacterial infection in COVID-19 patients, and that the data obtained should be stratified with respect to variables including infection site and bacterial species.

CONCLUSION

The elderly and critically ill patients are at high risk for SARS-CoV-2 infection and coinfection with *K. pneumoniae*. Recent hospitalization and prior antimicrobial exposure are the main risks for coinfection with *K. pneumoniae*. An increase in dependence on mechanical ventilation is highly significant for those who are co-infected with *K. pneumoniae*. *K. pneumoniae* was sensitive only to Colistin and Tigercillin.

RECOMMENDATIONS

Vaccination against SARS CoV-2 is highly recommended to prevent serious disease stages. The empiric antibiotic therapy or stewardship efforts in hospitalised COVID-19 patients are highly important to reduce MDR *K. pneumoniae* transmission, various infection control and antimicrobial stewardship methods are advised, including Active Surveillance Culture performance in high-risk patients. Implementation of Hand Hygiene, Contact Precautions, patient isolation and education programmes, as well as restrictions on antibiotic usage, particularly for carbapenems. A combination is supported by sufficient facts. In the treatment of these infections, therapy is used. However, the function of novel medications, such as ceftazidime-avibactam, which was recently approved for use in the MDR *Enterobacteriaceae* treatment should be evaluated.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the institutional ethics committee of the hospitals. Patients included in this study provided verbal consent to review their medical reports.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analysed during the current study are not publicly available due confidentiality reasons and institutional policies.

COMPETING INTEREST

None is declared.

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