Evidence of *Klebsiella pneumoniae* and SARS-CoV-2 Infections among patients presenting with Cough and Fever attending chest clinic, Aminu Kano Teaching Hospital, Kano

Jamilu Abubakar Bala[1,2,3*], Isah Abubakar Aliyu[1], Baba Maiyaki Musa [1], Taiwo Goluwaga Amole [1], Abdulhadi Sale Kumurya[1], Hayatu Saidu[1], Alhassan Sharif Abdullahi[4], Krishnan Nair Balakrishnan[5], Hassan Isah[1], Bilkisu Ahmed[3], Hadiza Shehu Galadanci *[3]

[1]Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Bayero University Kano, Nigeria, P.M.B. 3011, Kano, Nigeria
[2]Centre for Infectious Diseases Research, Bayero University Kano, Nigeria, P.M.B 3011, Kano, Nigeria
[3]African Centre of Excellence for Population Health and Policy, Bayero University Kano, P.M.B 3011, Kano, Nigeria
[4]Department of Medical Microbiology and Parasitology, Faculty of Clinical Sciences, Bayero University Kano, Nigeria, P.M.B. 3011, Kano, Nigeria
[5]Biotechnology Research Institute, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
*Corresponding author's email: hgaladanci@yahoo.com
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ABSTRACT

Extensive antibiotic use during early COVID-19 management may reduce bacterial co-infection but contributes to increasing antibiotic resistance, particularly in *Klebsiella pneumoniae*. Accurate detection of *K. pneumoniae* is therefore important to support diagnosis and treatment of COVID-19 patients. This study aimed to identify and detect *K. pneumoniae* and SARS-CoV-2, and to assess associated demographic characteristics and comorbidities among patients attending the chest clinic at Aminu Kano Teaching Hospital (AKTH), Kano. Demographic data and risk factors were collected using questionnaires. A total of 300 sputum samples were cultured on MacConkey agar and incubated aerobically at 37°C, followed by phenotypic identification using standard biochemical tests. SARS-CoV-2 was detected using real-time PCR. The prevalence of *K. pneumoniae* and SARS-CoV-2 infections was 17.0% and 3.3%, respectively, with a co-infection rate of 1.3%. Males showed a higher prevalence of *K. pneumoniae* infection (64.7%) than females (35.3%). Common symptoms included cough and fever. The findings highlight the association of respiratory tract infections with *K. pneumoniae* and emphasize the need for routine diagnostic testing to detect and manage co-occurring respiratory infections in COVID-19 patients.

Keywords: Bacteria; *Klebsiella pneumoniae;* antibiotics; COVID-19; RT-PCR; co-infections; SARS-CoV-2.

INTRODUCTION

Co-infection of *Klebsiella pneumoniae* and SARS-CoV-2 among patients presenting fever and cough has created major problems for social and healthcare system worldwide. The misused of antibiotic may result in increased antimicrobial resistance. This can involve bacteria becoming resistant to antibiotics (WHO 2020). The effect may be felt among the wider population and have toxic consequences, therefore, there is need to conduct research to evaluate the clinical features and characteristics of patients with SARS-CoV-2 and *Klebsiella pneumoniae* co-infections and the exact current prevalence trends of *K. pneumoniae* and SARS-CoV-2 co-infection with a view to formulating a control regimen for the environment (Guo et al., 2019).

Bacterial co-infections are commonly identified in viral respiratory tract infections. The mechanism underlying the synergy between COVID-19 and *K. pneumoniae* paves the way for the discovery of novel therapeutic agents to prevent the mortality rate in patients co-infected with COVID-19 and bacteria (CDC 2020). In the current situation, appropriate and systematic analysis of COVID-19 suspected patients diagnosed with bacterial co-infection should be implemented to choose proper antibiotics to increase the survival of patients and limit the spread of drug-resistant bacteria (Caly et al., 2020).

Despite the increase number of reports with *K. pneumoniae* infection in many regions, little is known about COVID-19 associated with *K. pneumoniae* in Nigeria especially in the North. The need for bacterial screening for *K. pneumoniae* may arise if this study reveals a significance prevalence among suspected COVID-19 patients so that transmission of this virus can be prevented (Huttner et al., 2020). Result generated from this study will not only add to the body of knowledge but will also be essential in preventing misdiagnosis and provide a helpful reference for diagnosis and clinical treatment in infected patients. Hence, there is an urgent need to carryout research to determine the occurrence of COVID-19 associated with *Klebsiella pneumoniae* infection.

MATERIALS AND METHODS

Study design and Site

This is a cross-sectional prospective study conducted at Aminu Kano Teaching Hospital, Kano, Nigeria. The hospital has a Tuberculosis-Directly Observed Therapy Unit (TB-DOTS) also known as Chest-clinic, which is situated within

Kano Metropolis. Three hundred (300) participants age between 20-79 were enrolled.

Ethical approval

Ethics approval for the study was obtained from the Research Ethics Committee of Aminu Kano Teaching Hospital, Kano Nigeria with registration number (NHREC/28/01/2020/AKTH/EC/3358). A written informed consent was obtained from the study participants after a verbal explanation was made to each participant.

Data and Sample Collection

Demographic data was collected using a design questionnaire. Detail information about the study was given to the clients and consent to participate was obtained before patient sample and data is taken. Early morning sputum was aseptically collected in a clean 20ml sterile screw-capped and wide mouthed universal container, the patient was instructed not to open the container until he/she is ready to use and prior to the sample collection, the patient was instructed to wash mouth, find an open area, the patient was instructed to inhale deeply 2 to 4 times before coughing out from the chest and to ensure it spit inside the container (Guo et al., 2019). All specimens were labeled and taken to the laboratory for culture.

Laboratory Identification of *Klebsiella pneumoniae*

The phenotypic detection of *K. pneumoniae* to the species level was performed based on standard biochemical reactions for microbial identification; these included; morphological characteristics on culture media, reaction on SH2/indole/motility (SIM) medium, triple sugar iron (TSI) agar, urease production on urea agar, growth on Simmons' citrate agar medium (Guo et al., 2019). Before analysis, all isolates were cultured on MacConkey agar medium.

Reverse transcription real-time polymerase chain reaction (RT-PCR) for the detection of COVID-19

Naso-pharyngeal samples were obtained using a specific swab and then placed in a separate collection tube containing three ml of viral transport medium and immediately sent to the coronavirus reference laboratory of the

university. First, the inactivation of the sample was achieved using lysis buffer and ethanol, extraction of the viral RNA was performed using a commercial kit according to the manufacturer's protocol (QIAGEN viral RNA mini kit). Next, RT-PCR was performed using GeneFinder™ COVID-19 Plus Real*Amp* Kit (Ochei and Kolhatkar 2008).

Inclusion and Exclusion Criteria

This study included those who do have respiratory tract infections and presented with fever and cough and excluded if they do not have respiratory tract infection and do not present with fever and cough.

Statistical Analysis

Statistical analysis was conducted with the aid of SPSS (statistical package for social sciences V22). Descriptive statistics of the categorical variables are expressed as frequency and percentage. The continuous variables were expressed interquartile ranges (IQRs). Chi-square test was used to evaluate and compare differences between patients who had other infections and those who did not. A p-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The study included 300 participants, 177 (59%) males and 123 (41%) females. The mean age average of the participants was 39.06±19 years. Eighty-nine (29.7%) and forty-two (14%) had cough and fever respectively. Among the participants, *Klebsiella pneumoniae* was found to be 51(17.0%) among the bacterial isolates, whereas other non-*K. pneumoniae* bacterial culture was 94(31.3%) and the remaining that yielded negative culture were 155(51.7%).

Male participants were found to have the higher percentage of *K. pneumoniae* infection with 33(64.7%) followed by female participants with 18(35.3%). The study shows prevalence of SARS-CoV-2 among the participants to be 10(3.3%) using real time polymerase chain reaction (RT-PCR) method. There were 4(1.3%) of *K. pneumoniae* co-infection with SARS-CoV-2 in the study. The prevalence of comorbidities was found to be for pneumonia 13.3%, Diabetes mellitus 6%, tuberculosis 5.3% and Asthma 5.0%. Clinical signs recorded among the participants with *K. pneumoniae* and SARS-CoV-2 infection reveals; 5.3% and 2.0% had cough, whereas 2.0% and 1.3% had fever respectively.

Table 1: Relationship between demography and positivity rates of SARS-CoV-2 and *K. pneumoniae* infections

Demographic characteristics	SARS-CoV-2 Positive n (%)	Negative n (%)	K. pneumoniae Positive n (%)	Negative n (%)
Gender n (%)				
Male 177 (59.0)	6 (2.0)	171 (98.0)	33 (11.0)	144 (89.0)
Female 123(41.0)	4 (1.3)	119 (98.7)	18 (6.0)	105 (94.0)
Age groups (n)				
20-30 (107)	2 (1.9%)	105 (98.1%)	21 (19.6%)	86 (80.4%)
31-40 (74)	3 (4.1%)	71 (95.9%)	11 (14.9%)	63 (85.1%)
41-50 (58)	3 (5.3%)	55 (94.7%)	9 (15.5)	49 (84.5%)
51-60 (30)	0 (0%)	30 (100%)	4 (13.3%)	26 (86.7%)
61-70 (23)	2 (8.7%)	21 (91.3%)	4 (17.4%)	19 (82.6%)
≥71 (8)	0 (0%)	8 (100%)	2 (25.0%)	6 (75.0%)
Marital status				
Single	4(1.3)	168(56.0)	19(6.3)	154(51.3)
Married	6(2.0)	122(40.7)	32(10.7)	95(31.7)
Educational status				
Primary	0(0)	12(4.0)	0(0)	122(40.7)
Secondary	4(1.3)	98(32.7)	15(5.0)	74(24.7)
Tertiary	4(1.3)	92(30.7)	29(9.7)	78(26)
Others	2(0.7)	88(29.3)	7(2.3)	85(28.3)

Table 2: *Klebsiella pneumoniae* and SARS-CoV-2 co-infection

	K. pneumoniae n (%)	SARS-CoV-2 n (%)	Co-infection n (%)	P-value
Positive	51(17)	10(3.3)	4(1.3)	0.054
Negative	249(83)	290(96.7)	296(98.7)	
Total	300	300	300	

p-value ≤0.05 was considered statistically significant.

Table 3: SARS-CoV-2 and *K. pneumoniae* infection in relation to cough and fever

Symptoms	SARS-CoV-2 n (%) Positive Negative	Total	P-value	*K. pneumoniae* Positive Negative	Total (%)	P-value
Cough Yes No	6(2.0) 83(27.7) 4(1.3) 207(84.0)	89(29.7) 211(70.3)	0.033	16(5.3) 73(24.3) 35(11.7) 176(58.6)	89(29.7) 211(70.3)	0.392
Fever Yes No	4(1.3) 38(12.7) 6(2.0) 252(84.0)	42(14.0) 258(86)	0.016	6(2.0) 36(12.0) 45(15.0) 213(71.0)	42(14.0) 258(86.0)	0.902

p-value ≤0.05 was considered statistically significant.

Table 4: Risk factors associated with SARS-CoV-2 and *K. pneumoniae* infection among the study participants

Risk factors	SARS-CoV-2 Positive Negative	P-value	*K. pneumoniae* Positive Negative	P-value
Asthma	1(0.3)	0.418	4(1.3)	0.680
Yes	14(4.7)		11(3.7)	
	9(3.0)		40(13.3)	
No	276(92.0)		245(81.7)	
Pneumonia	1(0.3)	0.733	9(3.0)	0.355
Yes	39(13.0)		31(10.3)	
	9(3.0)		20(6.7)	
No	251(83.7)		240(80.0)	
Tuberculosis	2(0.7)	0.036	4(1.3)	0.132
Yes	14(4.7)		12(4.0)	
	8(2.7)		39(13.0)	
No	276(92.0)		245(81.7)	
Diabetes	1(0.3)	0.589	2(0.7)	0.939
Yes	17(5.7)		16(5.3)	
	9(3.0)		35(11.7)	
No	273(91.0)		247(82.3)	

The overall prevalence of *Klebsiella pneumoniae* was found to be 17% which varied slightly by participant's gender, ranging from (11%) in males to (6%) in females. These agrees with studies conducted by Corman et al. 2020 in Pennsylvania with a prevalence of 16%, also in agreement with 29.2% reported by Cornelius et al. 2020 in India and in contrast with 7.8% reported by Ravichitra et al. 2014 in Lagos Nigeria, which is lower than this study. The high prevalence of *Klebsiella pneumonia* found in this study could be because the study was conducted during raining season, a period of the year where there is usually a high rate of respiratory tract infection.

The prevalence of SARS-CoV-2 among the study participants was found to be 3.3%, which is in agreement with the study conducted in the United State by Ogunsola et al. 2018, who reported the prevalence of 5.0%. However, the prevalence recorded in this study was lower compared to the prevalence recorded by Blasco et al. 2020, who reported a prevalence of 25.6% in Egypt. This could be attributed to the huge populations, low amount of screening testing, temperature and difference in the demography of the study population (Musaif et al., 2021). With regards to *Klebsiella pneumoniae*

coinfection with COVID-19 in patients presenting cough and fever, the findings in this research shows a prevalence of 1.3%. The results are in consistent with those of previously published studies in China conducted by Gomez et al. 2015 with 1% co-infection. Similar study has also been carried out in the United Kingdom, reported a prevalence of 3.2% (Liu et al., 2020). However, meta-analysis done by Hughes et al. 2020, in Washington reported a coinfection rate of 6.8% in hospitalized COVID-19 cases. This variation could be because most of the participants of this study were outpatients as such there is reduced risk of acquiring hospital-acquired infections. However, male gender demonstrated high prevalence of coinfections.

One plausible reason for the gender differences could be due to hormonal differences as estrogen may play a protective role with other susceptible factors by inhibiting the entry of SARS-CoV-2 virus into the host cells (Lansbury et al., 2020). The prevalence of comorbidities in the study participants were as follows; pneumonia (13.3%), diabetes mellitus (6%), tuberculosis (5.3%) and asthma (5.0%), which are similar to the findings reported by Ye et al. 2020 in China. The co-infected participants compared to the total COVID-19-positive population showed significantly high comorbidity rates for tuberculosis. This can be supported by the fact that tuberculosis itself downregulates the immune system by decreasing the effective T-cell and neutrophil response. It causes decreased phagocytosis, ineffective chemotaxis, and decreased killing of the invading microbes by the neutrophils and macrophages leading to increased susceptibility to secondary bacterial infection (Gomez et al., 2015).

Diabetes mellitus were observed in the co-infected participants. This might be due to the fact that diabetes mellitus is associated with elevated plasma glucose which influence SARS-CoV-2 replication through a mechanism of mitochondrial reactive oxygen species production and activation of hypoxia-inducible factor 1a (Wu et al., 2020). Therefore, the viral proliferation might also have been encouraged by hyperglycemia. On the contrary, this study shows low significant rate of 0.3% for both asthma and pneumonia, which is in line with the study conducted by Montero et al. 2020 with the prevalence of 1.5%. This might be attributed to the fact that SARS-CoV-2 enters lung cells via angiotensin-converting enzyme 2 (ACE2) receptor. Several studies suggest that interleukin-13, an important cytokine involved in T2 inflammation, reduces ACE2 expression and therefore, asthma would not be a significant risk factor for the development of COVID-19 and bacterial co-infections (Rosana et al., 2020).

The study showed that, patients on medication were (29.7%). The result is similar to reports from other countries in the African Region (47% in Kenya, 55% in South Africa and 61% in Uganda). In contrast, a study from Singapore reported a very low prevalence of 5.0% antibiotic use but higher in Spain and USA with 78% and 83% respectively (Budiarti et al., 2022).

The clinical symptoms presented by the participants were 88(29.3%) for cough and 42(14.0%) for fever and both gives a significant correlation of p-value 0.033 and 0.016 respectively. This result agrees with the report from Center for Disease Control (CDC) in the United States with 43% and 50% for fever and cough respectively (Tan et al., 2022).

CONCLUSION

The *Klebsiella pneumoniae* were isolated and identified using the standard culture and biochemical methods. The overall prevalence of the isolate among participants were 17%. Sputum sample was analyzed by real-time polymerase chain reaction (RT-PCR) kits and RNA of SARS-CoV-2 were detected among 10(3.3%) of the participants. Demographic characteristics of the participants were reported. Male gender recorded high prevalence of coinfections with 4:1 ratio. Cough (29.3) and fever (14.0%) are the most presented clinical symptoms among the participants. The possible risk factors associated with coinfection of *Klebsiella pneumoniae* and SARS-CoV-2 was identified whereby pneumonia had (13.3%), diabetes mellitus (6%), tuberculosis (5.3%) and asthma (5.0%).

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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