ORIGINAL RESEARCH

Secondary Bacterial Infection in COVID-19 Patients and Associated Risk factors

Soumya Singh[1], Amit Kumar Singh[2], Divya Srivastava[3], Ramanath K[4*]

[1]Ph.D Scholar, Department of Microbiology, Index Medical College, Hospital & Research Centre Malwanchal University Indore, Madhya Pradesh, India.
[2]Assistant Professor, Department of Microbiology, Prasad Institute of Medical Sciences, Lucknow, Uttar Pradesh.
[3]Tutor, Department of Microbiology, Maharaja Suheldev Autonomous State Medical College, Baharich, Uttar Pradesh India.
[*4]Professor, Department of Microbiology, Index Medical College, Hospital & Research Centre Malwanchal University Indore Madhya Pradesh, India

Corresponding Author
Dr.Ramanath K
Professor, Department of Microbiology, Index Medical College, Hospital & Research Centre Malwanchal University Indore Madhya Pradesh, India.
Email: ramanath.karicheri@gmail.com

Received: 30October, 2023 Accepted: 11December, 2023

ABSTRACT

Background: Although bacterial co-infection has not been thoroughly studied in COVID-19 patients, it has been shown to exacerbate respiratory viral infections and death in influenza pandemics. Extended hospital stays, the use of mechanical ventilation, and inadequate healthcare administration can heighten the likelihood of subsequent microbial infection in cases of viral lung infections such as SARS CoV-2.**Result:**There were 114 (28.5%) females and 286 (71.5%) males among the 400 COVID-19. The majority of the male patients (n=48, 75%) belonged to the 41–45 age range. The age range of 56–60 years comprised the majority of female patients (n=24, 61.5%). A total of sixty-two patients had secondary SARS CoV-2 bacterial infections, which were more prevalent in older patients above the age of 56. Only 13 (11.4%) female COVID-19 cases had developed secondary bacterial infection, compared to 286 male cases (17.1%) with secondary bacterial infection. Gram negative bacteria was predominant bacterial isolate among gram negative bacilli , Klebsiella pneumonia (n=46; 63.1%) was predominant followed by Acinetobacter baumannii (n = 9; 12.3%), and Pseudomonas aeruginosa (n = 6; 8.2%). Among the gram positive cocci, streptococcus pneumoniae was most common(n=7; 9.6%) and followed by Staphylococcous aureus(n=5; 6.8%). Sixty-nine percent of individuals with secondary bacterial infections also had bacteremia.**Discussion and Conclusion:**Patients with diabetes and COPD had higher rates of secondary bacterial co-infection. Early identification and rapid treatment can enhance patient care and improve outcomes for COVID-19 positive individuals with secondary infections.

Key words: Secondary bacterial infection, COVID-19, Risk factors.

INTRODUCTION

The human body has a wide variety of infectious microorganisms that can cause tissue destruction through different means. These include viruses, bacteria, fungus, protozoa, and helminths. Viruses are unique among these five groups of infectious organisms because they have the ability to specifically affect the host cell's machinery and because they are always changing in order to live and proliferate in all species.[1]

The coronavirus is one of the major illnesses that mostly affects the respiratory system in humans. The coronaviruses (CoVs) that cause the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) have both been highlighted as major threats to public health in the past. In late December 2019, a number of patients received initial hospital admission diagnoses of pneumonia with unclear aetiology. These people were connected epidemiologically to a wet animal and seafood wholesale market in Wuhan, Hubei Province, China.[2, 3] Early studies predicted the start of a likely coronavirus outbreak since the anticipated reproduction number for the 2019 Novel (New) Coronavirus (COVID-19, discovered by WHO on February 11, 2020) was determined to be substantially bigger than 1 (ranges from 2.24 to 3.58).

The increase in case reports of opportunistic infections among COVID-19 patients is cause for concern, especially for individuals with underlying medical conditions and those who have taken immunosuppressive medications. Fungi are implicated in most case reports of opportunistic infections in COVID-19 patients. Virus, bacteria, protozoa, and helminth infections were the focus of other pathogen reports.[5]

Microbial coinfections are more common in SARS-CoV-2 patients due to immune system dysfunction, loss of airway epithelium, reduced mucociliary clearance, and virus-induced airway damage.[6–8] Bacterial respiratory infections are more common in COVID-19 patients.[9] After contracting COVID-19, about 14.3% of patients experience a bacterial infection.[10]

A longer stay in the intensive care unit (ICU) among severely ill COVID-19 patients may be linked to an increased risk of developing a bacterial co-infection.[11] There will probably be 700,000 deaths worldwide in 2019 as a result of the enormous challenge in managing ICU patients presented by the high probability that hospital-transmitted bacterial species will be multi-drug resistant (MDR).[12] Co-infection and super-infection are terms used to describe situations in which a second pathogen is discovered in COVID-19 patients at the time of diagnosis or hospitalization, respectively.[13] A higher percentage (41%) of super infections was observed among the ICU patients, despite the fact that the majority of SARS-CoV-2 patients were not hospitalized to the intensive care unit. One in five SARS-CoV-2 patients had co-infection at presentation.[14]

Patients with COVID-19 have been documented to develop co-infections with many microorganisms. Many bacteria, such as Streptococcus pneumoniae, Haemophilus influenzae, Serratia marscecens, Acinetobacter baumannii, Staphylococcus, Pseudomonas aeruginosa, Haemophilus influenzae, Corynebacterium spp., Bacillus spp., Micrococcus spp., Proteus spp., and Enterobacter spp. Acinetobacter baumannii, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes are among the specific class of bacterial pathogens that are commonly seen in secondary infections. Patients who get infected with SARS-CoV-2 most often are adult male patients with a median age of 34 to 59 years.[15-18] Furthermore, a person's risk of contracting SARS-CoV-2 is increased if they have long-term comorbidities including diabetes, cerebrovascular sickness, or cardiovascular disease. Severe episodes are more common in adults under 60 and in individuals with certain underlying conditions, including as diabetes, cardiovascular, and cerebrovascular diseases. Additionally, there might be a connection between bacterial and fungal coinfections and severe symptoms.[19] There have been less COVID-19 cases reported among children under the age of 15.[15-18] A study of 425 COVID-19 patients in Wuhan, published on January 29, revealed no cases of the virus in children younger than 15.[20,21] Nonetheless, 28 pediatric patients had been recorded as of January 2020.[22] While the clinical features of pediatric patients with infection can differ, most of them have mild symptoms, no fever, no pneumonia, and a good prognosis.[22] A young kid was found to have asymptomatic radiographic ground-glass lung opacities in another evaluation.[23]

In conclusion, children are either less likely than adults to get the illness or, if they do, their symptoms will probably be milder. Because of this, it's likely that their parents won't get medical help, which will cause the incidence of COVID-19 in this age group to be underestimated. Therefore, the purpose of this study is to identify co-infection in Covid-19-infected patients.

MATERIALS AND METHODS

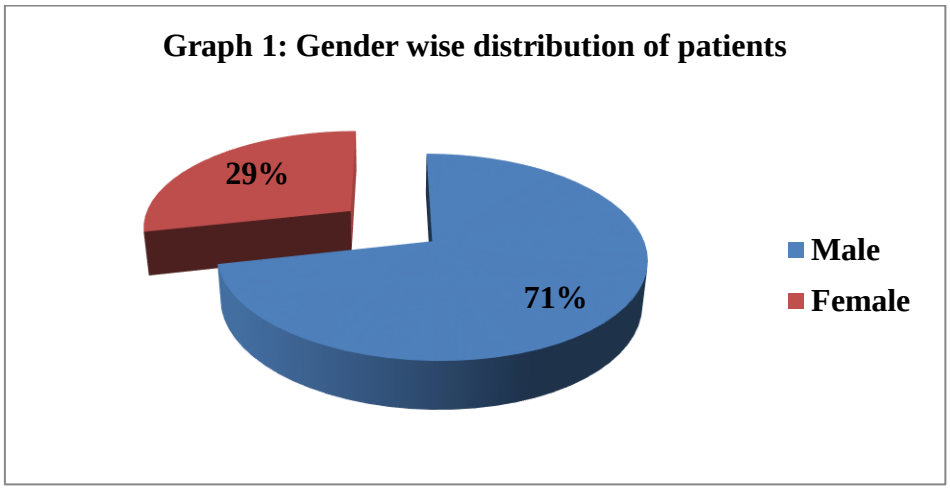
This was a three-year prospective observational study carried out in the Microbiology Department of Index Medical College and Hospital Indore, Madhya Pradesh, between January 2021 and December 2023. Clinical samples (blood, respiratory, including sputum and tracheal aspirates, and Urine) from COVID-19 patients confirmed by COVID-19 RT-PCR who were admitted to our institute's dedicated COVID hospital with a clinical suspicion of coinfections (at the time of admission) or secondary bacterial infections (after 48 hours of hospitalization) were received in the microbiology laboratory during this study period. The medical records of the patients provided the clinical and outcome data. The study included all patients with a clinical suspicion of coinfections or secondary bacterial infections (after 48 hours of hospitalization or at the time of admission) and a reverse transcriptase real-time PCR diagnosis of COVID-19. 400 clinical samples in all were obtained following the guidelines for suggested personal protective equipment. If same results were achieved, repeat samples of the same patients were not included in the study.

After being inoculated on Blood agar and MacConkey agar, respiratory samples were incubated at 37.8 ˚C for an entire night, Urine samples were cultured on CLED agar for 24 hours at 37.8 ˚C. For samples, another chocolate agar was utilised. BHI bottles were used to receive samples for blood culture.

Data collection began after January 2021 with clearance from the Ethics Committee. The patient provided written consent before any data were gathered. The patient's Performa had the pertinent information. For additional analysis, all relevant data, including oxygen saturation levels, co-morbidities that were present at the time of admission, and demographic characteristics (age, gender, etc.), were gathered and entered into a Microsoft Excel sheet for COVID-19 positive patients. Epi Info software was used to statistically analyses the data.

RESULT

In this investigation, 400 COVID-19 instances with clinical diagnoses were observed. 114 (28.5%) females and 286 (71.5%) males were present. The ratio of men to women was 2.5:1. The majority of patients were in the 56–60 age range, then 46–50 and 51–55 years.



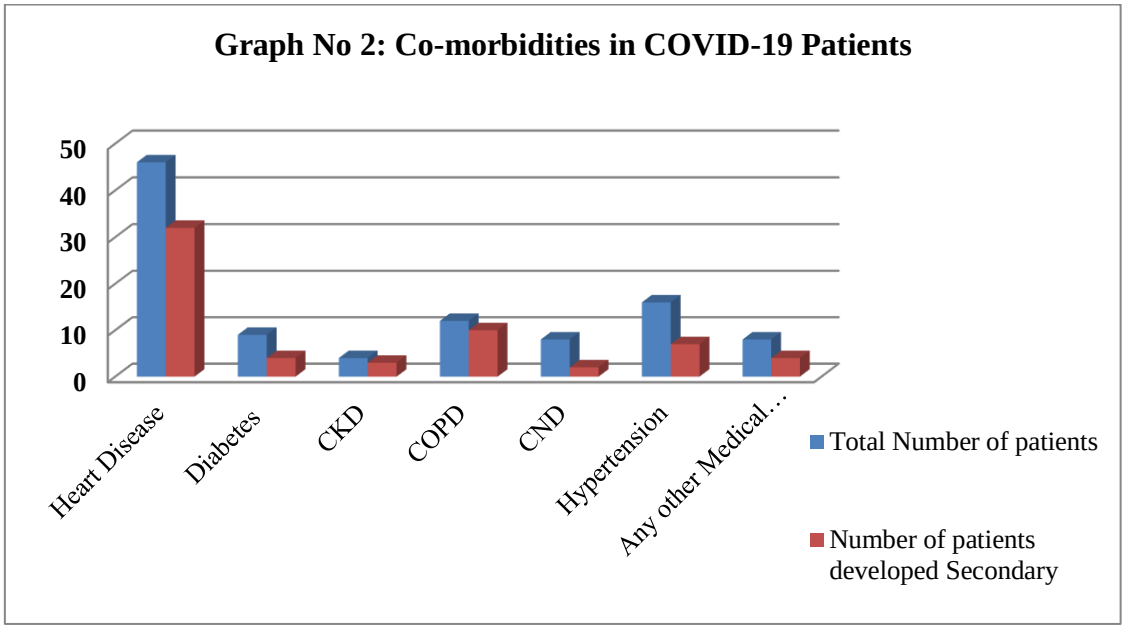
Graph 1: Gender wise distribution of patients

Of the 400 individuals that were part of the current investigation, 62 (15.5%) had various infections that were confirmed. The most common illnesses were respiratory tract infections, which were followed by urinary tract infections and blood stream infections. 43 people (69.4% of culture-positive cases) had respiratory tract infections (RTIs); 32 (74.4%) of these cases were monomicrobial RTIs, and 11 (25.6%) were polymicrobial RTIs. Nineteen patients (4.7%) had blood stream infections (BSIs), all of which were monomicrobial BSIs. Six patients (10.3% of culture-positive cases) had a urinary tract infection (UTI). Every patient with an infection of the urinary tract also had an RTI.

103 patients out of 400 had co-morbidities. 62 (60.2%; $p<0.005$) of the 103 COVID-19 patients with co-morbidities experienced secondary bacterial infection, while 41 (39.8%) of the patients with co-morbidities did not experience it. Eight patients had some form of immunosuppressive treatment, sixteen had hypertension, nine had diabetes, four had chronic kidney disease, twelve had chronic obstructive lung disease, forty-six had cardiac disease, and eight had neurological disease. A statistically significant number of 32 (69.6%) of the 46 COVID-19 patients who also had co-morbid cardiac disease had experienced secondary bacterial infections ($p<0.005$). Four (44.4%) of the nine diabetic COVID-19 patients had acquired a secondary bacterial infection. Three (75.0%; $p<0.005$) of the four individuals with chronic renal disease experienced a subsequent bacterial infection. Ten (83.3%) of the twelve patients with chronic obstructive lung disease experienced a secondary bacterial infection, a statistically significant result ($p<0.005$). Two (25.0%) of the eight individuals who had a persistent neurological illness also had a secondary bacterial infection. Seven (43.7%) of the sixteen hypertensive individuals also had a secondary bacterial illness. Four (50.0%) of the eight patients receiving a medicinal immunosuppressant went on to acquire a subsequent bacterial infection.

Table No 1: Co-morbidities in COVID-19 Patients.

Co-morbidities	Total Number of patients	Number of patients developed Secondary	*p* value
Heart Disease	46	32 (69.6%)	0.003
Diabetes	9	4 (44.4%)	0.021
Chronic Kidney Disease (CKD)	4	3 (75.0%)	0.002
Chronic Obstructive Pulmonary Disease (COPD)	12	10 (83.3%)	0.002
Chronic Neurological Disease (CND)	8	2 (25.0%)	0.003
Hypertension	16	7 (43.7%)	0.013
Any other Medical Immunosuppression	8	4 (50.0%)	0.003
Total	**103**	**62 (60.2)**	**0.004**



Graph No 2: Co-morbidities in COVID-19 Patients

62 years old was the mean age of COVID-19 patients who were at risk of developing a subsequent bacterial infection. It was determined that the odd ratio at the 95% confidence interval was 0.95 (P=0.012). Males were more likely than females to get a subsequent bacterial infection. A statistically significant 79% of male patients with secondary bacterial infections were at risk of infection (P=0.003).

Table No 2: Risk factors for the acquisition of secondary infection

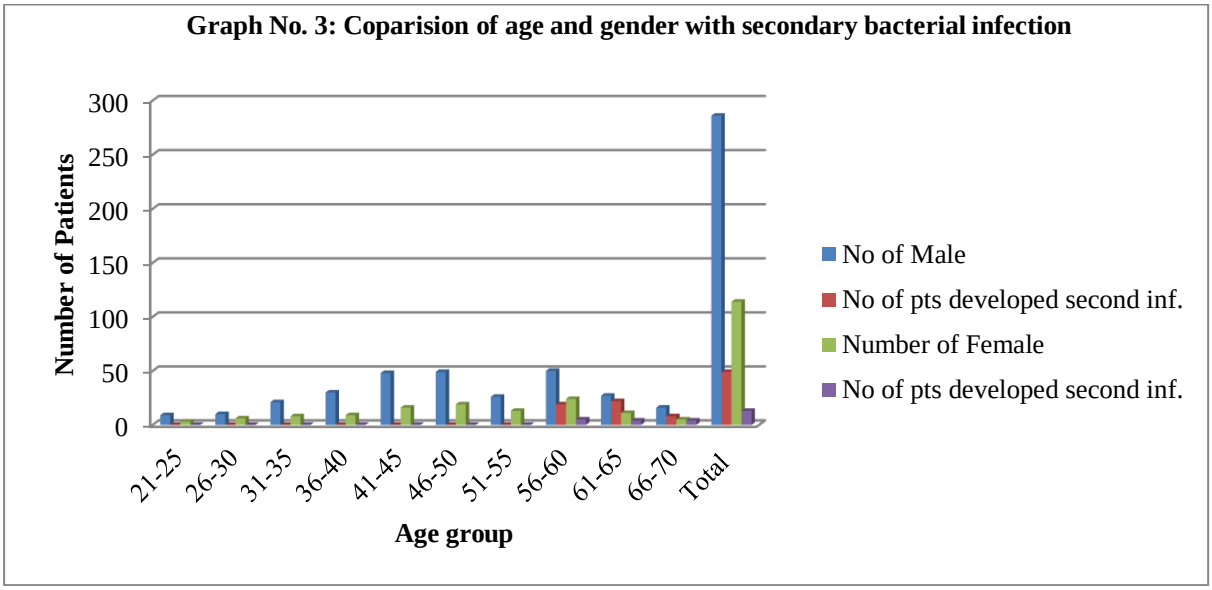
Risk Factors	Number of patients (n=62)	Odd ratio (95% CI)	*P* value
Mean Age	72 year (55-68 year)	0.95 (0.93–1.03)	0.012
Gender	49 male (79%)	0.31 (0.12–0.59)	**0.003***
Diabetes Mellitus (DM)	4 (44.4%)	0.34 (0.17–0.92)	0.043
Hypertension	7 (43.7%)	0.98 (0.91–1.34)	0.013
Cardiac disease	32 (69.6%)	0.32 (0.13–0.61)	**0.003***
Smoking	6 (75%)	0.33 (0.13–0.61)	**0.004***
APACHE score IV	42 (33–53)	0.94 (0.92–1.3)	0.032
SOFA score on admission—median	13 (9-16)	1.12 (0.94–1.26)	0.141
Immunosuppressive therapy	4 (50%)	0.84 (0.63–0.98)	0.013

Patients older than 56 years old were more likely to have secondary bacterial infections. Sixty-two (15.5%) of the 400 patients experienced a recurrent bacterial illness. Thirteen female patients and 49 male patients made up the 62 COVID-19 patients who had developed a secondary bacterial infection. Only 13 (11.4%) female COVID-19 cases had developed secondary bacterial infection, compared to 286 male cases (17.1%) with secondary bacterial infections.

Table No: 3 Comparison of age and gender with secondary bacterial infection

Age group (year)	Number of Male	Number of patients developed secondary bacterial infection	Number of Female	Number of patients developed secondary bacterial infection
21-25	9	00	3	00
26-30	10	00	6	00
31-35	21	00	8	00
36-40	30	00	9	00
41-45	48	00	16	00
46-50	49	00	19	00
51-55	26	00	13	00
56-60	50	19	24	5
61-65	27	22	11	4
66-70	16	8	5	4

Total	286	49	114	13



Graph No. 3: Comparison of age and gender with secondary bacterial infection

Gram negative bacilli (GNB) was the predominant bacterial isolate. Among gram negative bacilli, Klebsiella pneumonia (n=46; 63.1%) was predominant followed by Acinetobacter baumannii (n=9; 12.3) and Pseudomonas aeruginosa (n=6; 8.2%). Among gram positive cocci, Streptococcus pneumonia was most common (n=7; 9.6%) and followed by Staphylococcus aureus (n=5; 6.8%). Table no. 11 and graph no. 11 revealed microbial profile of secondary bacterial infection in COVID-19 Patients.

Table No: 4 Microbial profile of secondary bacterial infection in COVID-19 Patients

Name of organism	Number of isolates (n=73)	Percentage (%)
Klebsiella pneumoniae	46	63.1%
Acinetobacter baumannii	9	12.3%
Streptococcus pneumoniae	7	9.6%
Pseudomonas aeruginosa	6	8.2%
Staphylococcus aureus	5	6.8%

DISCUSSION

We are still striving to swiftly increase our knowledge of COVID-19, a recently identified potentially lethal viral disease. The ongoing COVID-19 pandemic presents a significant challenge to health systems and healthcare workers.[24, 25]

In this study, men outnumbered women, and the results corroborated those of research by Bhawna Sharma et al.[26], Sonam Vijay et al.[27], and S. Hughes et al.[28].The percentage of male participants varied between 62% and 71.5% in all the research, while the percentage of female participants varied between 24.5% and 38%.

Consistent with the present study, Sonam Vijay et al. (2021)[27] found a 53±9-year-old mean. While S. Hughes et al.[28] (2020) reported a median age of 69 (55-81), Carolina Garcia Vidal et al.[29] (2021) found a median age of 62 (48-74).

Variations in the percentages of co-morbidity were seen across study. According to the current study, in 25.75% of patients, heart illness (44.66%) and hypertension (15.53%) co-occurred. There is 53.8% co-morbidity, with diabetes (15.3%) and heart disease (21.5%) being the most common, according to Samaneh Pourajam (2022)[30]. Asthma co-morbidity, according to Prithiv J Prasad (2022)[31], is 28.51% at 13.2%. According to Sonam Vijay et al. (2021), diabetes (30%) and hypertension (25.6%) were found to co-occur in 55.7% of cases.[27]

According to the Samaneh Pourajam et al. 2022[30] study, infections of the respiratory tract were the most common, accounting for 88.6% of cases. Urine and bloodstream infections came in second, with 1.4% of cases each. A 2021 investigation by Sonam Vijay et al.[27] found that bloodstream infections were found in 44.1% of cases and respiratory tract infections in 35.1% of cases. The current study from 2023 reported respiratory tract infections at 69.4%, urinary tract infections at 10.3%, and bloodstream infections at 4.7%, which is almost exactly the same as the study by Samaneh Pourajamet al.[30]

Gram-negative bacteria were the primary cause of secondary infection in our investigation. In a similar vein, a number of investigations found that gram-negative organisms were more common than gram-positive ones.[32–36] According to Musuuza et al.[32], P.

aeruginosa and A. baumannii were the most common infections in the study. Notably, central venous catheters are present in 75.9% of COVID-19 patients with secondary fungal infection, raising the likelihood of Candida spp infection.[37]

Sonam Vijay (2021)[27], Bhawna Sharma (2021)[26], Haocheng Zhang (2020)[38], and others found 71.7%, 74%, and 57.89%, respectively. The results of the current investigation (2023), which revealed 60.19% of cases of secondary infection, were in good accord with these findings. But according to a study conducted in northern India by Khurana et al.[39], 13% of COVID-19 patients also developed secondary infections.

It is important to pay attention to secondary infection in COVID-19 patients who have severe and dangerous cases. Zhou et al.[40] reported that 50% of patients who did not survive (27/54) had secondary infections, while ventilator-associated pneumonia struck 31% (10/32) of patients requiring invasive respiratory assistance.

Pathogen-host interactions, such as pathogen virulence, immune response dysregulations, and altered microbiota, were the underlying pathogenesis of secondary infection in severe and catastrophic COVID-19 cases.[41, 42] The loss of surfactant and the sloughing of cells into the airways may promote rapid bacterial growth by providing access and an abundant supply of nutrients.[43]

CONCLUSION

In COVID-19 individuals with co-morbidities, secondary infections are more prevalent. While it could be challenging to distinguish between patients who have a coinfection or an infection acquired in the hospital and those who do not, a thorough history and physical examination should be performed to ascertain whether a bacterial co-illness is present at the time of a patient's admission with COVID-19. In all healthcare settings, strict hospital infection control protocols should be adhered to without fail.

REFERENCES

1. Almutairi MA. The coronavirus disease 2019 (COVID-19) outbreak: Challenges for pediatric dentistry. J Res Med Dent Sci 2021, 9:116-121
2. Bogoch, A. Watts, A. Thomas-Bachli, C. Huber, M.U.G. Kraemer, K. Khan, Pneumonia of unknown etiology in wuhan, China: potential for international spread via commercial air travel, J. Trav. Med. (2020).
3. H. Lu, C.W. Stratton, Y.W. Tang, Outbreak of pneumonia of unknown etiology in wuhan China: the mystery and the miracle, J. Med. Virol. 92 (4) (2020) 401–402.
4. S. Zhao, Q. Lin, J. Ran, S.S. Musa, G. Yang, W. Wang, et al., Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak, Int. J. Infect. Dis. : IJID : Off. Publ. Int. Soc. Infect. Dis. 92 (2020) 214–217.
5. Amir Abdoli, COVID-19-associated opportunistic infections: a snapshot on the current reports, Clinical and Experimental Medicine (2022) 22:327–346
6. Vareille M., Kieninger E., Edwards M., Regamey N. The airway epithelium: soldier in the fight against respiratory viruses. Clin Microbiol Rev. 2011; 24(1):210-29. doi: 10.1128/CMR.00014-10.
7. Mirzaei R. Goodarzi P., Asadi M., Soltani A., Aljanabi H., Jeda A., et al. Bacterial co-infections with SARS-CoV-2. IUBMB Life. 2020; 72(10):2097-2111. doi: 10.1002/iub.2356
8. Denney L, Ho L. The role of respiratory epithelium in host defence against influenza virus infection. Biomed J. 2018; 41(4):218-233. doi: 10.1016/j.bj.2018.08.004.
9. Calcagno A., Ghisetti V., Burdino E., Trunfio M., Allice T., Boglione L., et al. Co-infection with other respiratory pathogens in COVID-19 patients. Clin Microbiol Infect. 2021; 27(2):297-298. doi: 10.1016/j.cmi.2020.08.012.
10. Sarkar S., Khanna P., Singh A. Impact of COVID-19 in patients with concurrent co-infections: A systematic review and meta-analyses. J Med Virol. 2021a; 93(4):2385-2395.
11. Elabbadi, A.; Turpin, M.; Gerotziafas, G.T; Teulier, M.; Voiriot, G.; Fartoukh, M. Bacterial Coinfection in Critically Ill COVID-19 Patients with Severe Pneumonia. Infection 2021, 49, 559–562. [CrossRef]
12. Patel, A. Tackling Antimicrobial Resistance in the Shadow of COVID-19. Mbio 2021, 12, e0047321. [CrossRef]
13. Garcia-Vidal, C.; Sanjuan, G.; Moreno-García, E.; Puerta-Alcalde, P.; Garcia- Pouton, N.; Chumbita, M.; Fernandez-Pittol, M.; Pitart, C.; Inciarte, A.; Bodro, M.; et al. Incidence of Co-Infections and Superinfections in Hospitalized Patients with COVID-19: A Retrospective Cohort Study. Clin. Microbiol. Infect. 2020, 27, 83–88. [CrossRef] [PubMed]
14. Musuuza, J.S.;Watson, L.; Parmasad, V.; Putman-Buehler, N.; Christensen, L.; Safdar, N. Prevalence and Outcomes of Co-Infection and Superinfection with SARS-CoV-2 and Other Pathogens: A Systematic Review and Meta-Analysis. PLoS ONE 2021, 16, e0251170
15. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA 2020.
16. Wang D, Hu B, Hu C, Zhu F, LiuX, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020.
17. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020
18. Chang, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA 2020
19. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020
20. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382(13):1199–207.

21. Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of Covid19 in children in early January 2020 in Wuhan, China. N Engl J Med 2020;382(14):1370–1.
22. Shen KL, Yang YH. Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. World J Pediatr 2020.
23. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-toperson transmission: a study of a family cluster. Lancet 2020.
24. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet Lond Engl. 2020;395 (10229):1054–62.
25. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18): 1708–20.
26. Bhawna Sharma et. al.,Bacterial coinfections and secondary infections in COVID-19 patients from a tertiary care hospital of northern Indias. Qatar Medical Journal. 2021: 62; 1-10.
27. Sonam Vijay et. al., Secondary Infections in Hospitalized COVID-19 Patients: Indian Experience, Infection and Drug Resistance, 2021:14 1893–1903
28. S. Hughes et. al., Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting, Clinical Microbiology and Infection 26 (2020) 1395-1399.
29. Carolina Garcia-Vidal et. al., Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clinical Microbiology and Infection. 2021:9; 83-88.
30. Samaneh Pourajam et. al., Secondary Bacterial Infection and clinical characterstics in patients with Covid 19 admitted to two intensive care units of an Academic Hospital in Iran durin g the first wave of the pandemic,frontiers in cellular and Infection Microbiology, 2022;Volume 10:1-9.
31. Prithiv J. Prasad et. al.,Coinfections and antimicrobial use in patients hospitalized with coronavirus disease 2019 (COVID-19) across a single healthcare system in New York City: A retrospective cohort study,Antimicrobial Stewardship & Healthcare Epidemiology (2022), 2, e78, 1–8.
32. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: a systematic review and meta-analysis. *PLoS One*. 2021;16(5):e0251170. doi:10.1371/journal.pone.0251170
33. Baskaran V, Lawrence H, Lansbury LE, et al. Co-infection in critically ill patients with COVID-19: an observational cohort study from England. *J Med Microbiol*. 2021;70(4):001350.
34. Pourajam S, Kalantari E, Talebzadeh H, et al. Secondary bacterial infection and clinical characteristics in patients with COVID-19 admitted to two intensive care units of an academic hospital in Iran during the first wave of the pandemic. Front Cell Infect Microbiol. 2022;12:784130.
35. De Bruyn A, Verellen S, Bruckers L, et al. Secondary infection in COVID-19 critically ill patients: a retrospective single-center evaluation. *BMC Infect Dis*. 2022;22(1):207. doi:10.1186/s12879-022-07192-x
36. Costa RLD, Lamas CDC, Simvoulidis LFN, et al. Secondary infections in a cohort of patients with COVID-19 admitted to an intensive care unit: impact of gram-negative bacterial resistance. *Rev Inst Med Trop Sao Paulo*. 2022;64:e6. doi:10.1590/S1678-9946202264006
37. Suleyman G, Alangaden GJ. Nosocomial fungal infections: epidemiology, infection control, and prevention. *Infect Dis Clin North Am*. 2021;35(4):1027–1053. doi:10.1016/j.idc.2021.08.002
38. Haocheng Zhang et. al., Risks and features of secondary infections in severe and critical ill COVID-19 patients, Emerging Microbes & Infections 2020, VOL. 9,1958-1964.
39. Khurana S, Singh P, Sharad N, Kiro VV, Rastogi N, Lathwal A, et al. Profile of co-infections & secondary infections in COVID-19 patients at a dedicated COVID-19 facility of a tertiary care Indian hospital: Implication on antimicrobial resistance. Indian J Med Microbiol. 2020;39(2):147–53.
40. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet Lond Engl. 2020;395 (10229):1054–62.
41. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol. 2014 Apr;12(4):252–262
42. Zhang L, Forst CV, Gordon A, et al. Characterization of antibiotic resistance and host-microbiome interactions in the human upper respiratory tract during influenza infection. Microbiome. 2020 Mar 17;8(1):39.
43. Ghoneim HE, Thomas PG, McCullers JA. Depletion of alveolar macrophages during influenza infection facilitates bacterial superinfections. J Immunol. 2013 Aug 1;191(3):1250–1259