JOURNAL OF HEALTHCARE SCIENCES
Volume 2 Issue 12 2022, Article ID: JOHS2022000589
http://dx.doi.org/10.52533/JOHS.2022.21214
e-ISSN: 1658-8967

Review

Prevalence and Types of Respiratory Co-Infections found in COVID-19 Patients

Samar Alharbi [1*], Basmah Aljohani [2], Ghazi Almohmmadi [3], Abdulrahman Alsubaihi [3], Abdulaziz Alkhouzaie [4], Yasir Alrashidi[3], Shahad Alhazmi [5], Feras Beitar [6], Alanoud Althobaiti[7], Abdulaziz Alzibali [8], Fatimah Alsafwani [9]

[1] *Department of Internal Medicine, Al Thager Hospital, Jeddah, Saudi Arabia*
[2] *Department of Internal Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia*
[3] *Department of Internal Medicine, Madinah General Hospital, Medina, Saudi Arabia*
[4] *General Physician, Ministry of Health, Mecca, Saudi Arabia*
[5] *Department of Internal Medicine, Turaif General Hospital, Turaif, Saudi Arabia*
[6] *Department of Internal Medicine, Prince Mohammed bin Abdulaziz Hospital, Medina, Saudi Arabia*
[7] *College of Medicine, University of Tabuk, Tabuk, Saudi Arabia*
[8] *College of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia*
[9] *Department of Emergency Medicine, Dammam Medical Complex, Dammam, Saudi Arabia*

Correspondence should be addressed to **Samar Alharbi**, Department of Internal Medicine, Al Thager Hospital, Jeddah, Saudi Arabia. Email: dr_sam1990@hotmail.com

Received: 21 December 2022, Accepted: 25 December 2022, Published: 28 December 2022

Abstract

An unprecedented challenge to the healthcare system worldwide has resulted from the coronavirus disease 2019 (COVID-19) pandemic. As per the estimates of year 2022 over 314 million cases and over 5.5 million deaths had been reported since the pandemic began. The respiratory system is the primary system affected by COVID-19, which is a multisystem disease. It usually starts as an upper respiratory infection that spreads to the lungs and causes interstitial pneumonia, severe respiratory failure, a systemic inflammatory response, and multi-organ dysfunction in the most extreme instances. The environment that a viral infection allows concurrent or secondary bacterial co-infections has been created by the co-evolution of viral and bacterial respiratory pathogens, increasing the morbidity and mortality of respiratory viral infections and significantly increasing the burden of disease on society. Because COVID-19 mass vaccination campaigns are still in their early phases, underlying co-infections and how they are treated could have significant impact on disease morbidity and related patient care. Growing evidence of research demonstrates that microbial co-infection raises the likelihood of human illness severity. The prevalence of co-infection ranges from 0%- 20% among COVID-19 patients. *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* were the most prevalent bacterial co-infections in all COVID-19 patients along with certain other viral co-infections. Despite extensive study on viral-bacterial co-infections, there are few studies that examine how they affected the COVID-19 pandemic.

Keywords: *COVID-19, co-infection, respiratory, bacterial*

Introduction

COVID-19 is the most recent respiratory infectious illness to spread swiftly over the globe. It was originally detected in Wuhan, China, in December 2019, but rapidly spread throughout the globe, prompting the World Health Organization to proclaim it a pandemic and a public health emergency of international concern in March 2020 (1). Over 314 million diseases and over 5.5 million deaths had been reported since the epidemic began as of January 2022. In terms of cases and fatalities, the COVID-19 pandemic manifests itself differently in various parts of the world (2). COVID-19 is a multisystem illness that predominately affects the respiratory system. In the most severe cases, it begins as an upper respiratory infection that spreads to the lungs and results in interstitial pneumonia which can be identified through a computed tomography scan by the appearance of ground glass, severe respiratory failure, a systemic inflammatory response, and multi-organ dysfunction. The disease's typical signs and symptoms include fever, asthenia, a dry cough, nasal congestion, and breathing issues (3).

Multiple factors are thought to be capable of influencing the clinical course of COVID-19 infection because of the variety of clinical presentations of the disease. More complications and severity of COVID-19 has been linked to older age, male gender, the existence of concomitant conditions such as diabetes and hypertension, as well as demographic and clinical variables, according to various studies till date. In addition, certain research studies have suggested that COVID-19 infected people may also have co-infections with bacterial and viral respiratory diseases. Studies have shown that COVID-19 patients frequently have respiratory viruses such as the influenza virus, human metapneumovirus, rhinovirus, and respiratory syncytial virus. The morbidity and mortality of viral respiratory infections are also impacted by bacterial co-infections (4). Co-infection can manifest in the form of a new infection acquired secondarily as a result of a weakened immune system or as an already present pathogen that is made worse by the addition of a new pathogen (5).

Knowledge of the nature and prevalence of respiratory co-infections in COVID-19, may have consequences for diagnostic and therapeutic decisions. The presentation, clinical course, or diagnostic indicators such as laboratory investigations or computed tomography scan results used to determine prognosis in COVID-19 may be affected by co-infections, however this is uncertain. Additionally, it is feasible that treating COVID19 co-infected patients for influenza with antivirals and atypical bacteria with antibiotics can enhance their prognosis. Alternatively, some patients with co-infections cannot respond to therapy the same way as people who are not infected by COVID-19. For these reasons, understanding the prevalence and kind of respiratory co-infections has a significant impact on how COVID-19 patients are managed and how their outcomes turn out (6). *Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae* are the most prevalent pathogens determined among COVID-19 patients. Rates of co-infection with other respiratory viruses in COVID-19 individuals ranged from 0% to 20% as per various studies. Coronaviruses, rhinoviruses, enteroviruses, metapneumoviruses, parainfluenza viruses, influenza B viruses, and respiratory syncytial viruses are instances of common co-infecting viruses (7). The purpose of this research is to review the available information about prevalence and types of respiratory co-infections found in COVID-19 patients.

Methodology

This study is based on a comprehensive literature search conducted on December 12, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about prevalence and types of respiratory co-infections found in COVID-19 patients. There were no restrictions on date, language, participant age, or type of publication.

Discussion

COVID-19 pandemic is the most harmful pandemic of infectious disease since the 1918 influenza pandemic, the world experienced. The respiratory tract is the most frequent site for the occurrence of fungal or bacterial infections. The pathogenesis of lung infections caused by bacterial or fungal pathogens typically begins with colonization. Additionally, COVID-19 patients hospitalized in intensive care units are vulnerable to infections caused by bacteria and/or fungi due to a number of risk factors (8). The co-infection of COVID-19 with other respiratory pathogens, which can impede COVID-19 diagnosis, treatment, and prognosis, has

http://dx.doi.org/10.52533/JOHS.2022.21214

recently come to light as a source of worry. The disease symptoms and death rate may potentially worsen as a result of these co-infections. The beginning of the seasonal influenza season coincides with the COVID-19 and influenza epidemic overlap, which can result in two outbreaks occurring simultaneously. Similar to COVID-19, influenza virus A/B can spread by close contact, respiratory droplets, and contaminated surfaces. Both viruses can result in a variety of mild to severe illnesses, including flu-like symptoms, pneumonia, loss of taste and smell, and even death (9).

Prevalence and types of respiratory coinfections in light of literature

Earlier it was reported that co-infections with other respiratory pathogens were uncommon in COVID-19 cases. However, the co-infection incidence between COVID-19 and other respiratory viruses, according to more recent data from the United States was reported to be as high as 21%. Additionally, COVID-19 patients with more severe illness have greater rates of co-infection, indicating that co-infections can dramatically affect the clinical outcome of COVID-19. Despite this evidence pointing to the high prevalence of co-infections among COVID-19 cases and their potentially significant clinical effects on disease, the current data on co-infection remain constrained by the small number of viruses studied and the low representation of the global population (10).

Mussuza et al. revealed that co-infections affected 19% of COVID-19 patients, and superinfections affected 24% patients. Co-infection or superinfection was linked to unfavourable outcomes, including higher death rate (11). In individuals with COVID-19, co-infection with respiratory infections is a frequent and potentially significant occurrence as further demonstrated by the results which showed that pooled prevalence of 11.6% was observed while studies employing serum antibody tests indicated a pooled prevalence of 26.8%, and studies using 100% co-pathogen testing reported a pooled prevalence of 16.8% among COVID-19 patients (6). Lansbury et al. reported in their findings that a bacterial co-infection was present in 7% of COVID-19 patients who were hospitalized. Compared to patients in mixed ward/intensive care settings, a significant proportion of intensive care patients had bacterial co-infections. *Mycoplasma pneumonia, Pseudomonas aeruginosa*, and *Haemophilus influenzae* were the most prevalent microorganisms. Respiratory syncytial virus and influenza A were the most prevalent viral co-infections, accounting for 3% of the total population (12).

Results of a meta-analysis demonstrated that based on a random-effects model, the global pooled prevalence was 5.01%, with enteroviruses accounting for 1.32% cases and influenza viruses for 1.54% cases being the most common pathogens. Co-infection was substantially greater in paediatric patients (9.39%) as compared to adult patients (3.51%), as per the subgroup analysis ($p = 0.02$). Additionally, individuals with co-infections had higher odds of being dyspneic and a higher chance of dying (13).Results of an observational study showed that 12.7% patients had at least one extra pathogen, while 5.1% also had a secondary infection and 8.1% were co-infected. The majority of the cases were found in mild and moderate COVID-19 patients, including 13 *Mycoplasma pneumoniae* cases, 8 *Haemophilus influenzae* cases, 8 respiratory viruses, and 3 *Streptococcus pneumoniae* cases. Pathogens associated with hospital acquired infections were more prevalent in severely ill patients. Patients with co-infections and/or secondary infections were more likely to require antibiotics ($p <0.001$) and have raised levels of d-dimer ($p = 0.0012$), interleukin-6 ($p = 0.0027$), and procalcitonin ($p = 0.0002$) compared to those without additional pathogens. The effectiveness of traditional culture and metagenomic next-generation sequencing for the diagnosis of secondary infections was equivalent (14).

Findings of a meta-analysis showed that the overall pooled proportion was 15.9% for bacterial infections that was verified through laboratory investigations, whereas 3.7% had fungal infections and 6.6% had other respiratory viruses. COVID-19 patients in the intensive care had greater rates of co-infections nevertheless, the proportion of all COVID-19 patients with other respiratory viral co-infections was the same (6.6%) (15). Contradictory to this Karaba et al. reported the prevalence of bacterial respiratory co-infections quite low almost 1.2%; 1.1% patients had suspected bacterial community-acquired pneumonia, and 1 patient had confirmed bacterial community-acquired pneumonia. There were viral respiratory co-infections in 0.2% patients (16). Similarly results of a study by Singh et al. showed that comparing the group who tested positive for COVID-19 to the population that tested negative for the virus, a reduced overall rate of viral co-infection was observed. Co-infections with *Epstein-Barr* virus and *Staphylococcus aureus* were prevalent in the COVID-19 positive group (17).

Results of a Korean study showed that a total of 8.8% of COVID-19 patients were coinfected with respiratory

http://dx.doi.org/10.52533/JOHS.2022.21214

pathogens, including respiratory viruses in 7.9% of cases and *Mycoplasma pneumoniae* in 0.9% of cases. Out of the cases of respiratory virus coinfection, 92.6% had just one virus, and 7.4% had two metapneumovirus/adenovirus and rhinovirus/bocavirus. There were no triple COVID-19 infections with other respiratory viruses or bacteria. Viruses that co-infected COVID-19 patients include influenza A, adenovirus, bocavirus, rhinovirus, respiratory syncytial virus A and B, and metapneumovirus (18). Results of a study by Trifonova et al. demonstrated that *Human metapneumovirus* which was responsible for 25% of cases was the most common virus to cause coinfections, followed by respiratory syncytial virus (16.7%), adenovirus (16.7%), bocaviruses (16.7%), influenza A (8.3%), parainfluenza virus (8.3%), rhinovirus (4.62%), and rhinovirus + bocaviruses (4.62%). Children under the age of five were most likely to have COVID-19 coinfections followed by adults over 65 years of age. COVID-19 had a mean viral load that was higher than that of the other respiratory viruses in specimens where coinfection had been diagnosed, and influenza had a viral load that was higher than that of COVID-19 (19).

Findings of a study by Ishiguro et al. revealed that in patients with primary viral pneumonia, viral coinfection was present in 30.5% of cases, and mixed viral and bacterial pneumonia accounted for 90.3% and 9.7%, respectively, of COVID-19-associated community acquired pneumonia. The influenza virus was most prevalent accounting for 9.4% of cases. Mortality, the requirement for invasive forced breathing or high-flow nasal cannula, and severity at admission were not independently influenced by coinfection (20). Le Glass E et al. demonstrated in their findings that for at least one respiratory virus, 40% of patients who underwent testing were positive, 4.3% of the COVID-19 infected individuals also had additional respiratory viruses in their systems, with rhinoviruses being the most common responsible for 67% instances. Patients who had COVID-19 and a rhinovirus co-infection (62% versus 31%; p = 0.0008) had a considerably higher likelihood of reporting a cough than those who just had COVID-19. Additionally, they were substantially more likely to report dyspnea (45% versus 36%; p = 0.02) than patients with rhinovirus mono-infection. They also had a higher risk of dying and being admitted to an intensive care unit (16% versus 5% and 7% versus 2%, respectively) than those with rhinovirus mono-infection, but these differences were not statistically significant (21).Tang et al reported that 14.1% of COVID-19 patients were also infected with other respiratory infections, with respiratory syncytial virus in 36.4% and *Mycoplasma pneumoniae* in 45.5% of cases being the most common, 8 patients had co-infections with one other pathogen, while 3 patients had co-infections with two different pathogens. Co-infected individuals had significantly greater procalcitonin levels than mono-infected COVID-19 patients (P=0.002) (22).

Li et al reported that children with COVID-19 had a significant incidence of 33% for co-infection. *Mycoplasma pneumoniae* was responsible for 25% of co-infected pathogens, while viruses accounted for 7%, and bacteria for 5% of the cases. Only lower white blood cell, neutrophil, and lymphocyte counts were seen between patients with co-illnesses and those with monomicrobial infections; there was no discernible difference in clinical traits, laboratory tests, or length of hospital stay (23). Similarly, Wu et al. demonstrated in their findings that 45.95% of children having findings from nucleic acid testing for common respiratory infections revealed coinfection with pathogens other than COVID-19 (24). Despite extensive research on COVID-19 during pandemic era the available studies discussing incidence and types of respiratory co-infections remain quite limited and show contrasting results.

Conclusion

Patients with COVID-19 frequently develop co-infections. The co-infecting organisms can be identified at various points throughout the COVID-19 illness course and continue to be a crucial factor in patients' focused treatment plans hence critical attention shall be paid by clinicians while diagnosing and evaluating co-infections among COVID-19 patients.

Disclosure

Conflict of interest

There is no conflict of interest

Funding

No funding

Ethical consideration

Non applicable

Data availability

Data that support the findings of this study are embedded within the manuscript.

http://dx.doi.org/10.52533/JOHS.2022.21214

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

References

1. Bastani P, Mohammadpour M, Ghanbarzadegan A, Kapellas K, Do LG. Global concerns of dental and oral health workers during COVID-19 outbreak: a scope study on the concerns and the coping strategies. Systematic Reviews. 2021;10(1):45.

2. Assefa Y, Gilks CF, Reid S, van de Pas R, Gete DG, Van Damme W. Analysis of the COVID-19 pandemic: lessons towards a more effective response to public health emergencies. Globalization and health. 2022;18(1):10.

3. Biancolella M, Colona VL, Mehrian-Shai R, Watt JL, Luzzatto L, Novelli G, et al. COVID-19 2022 update: transition of the pandemic to the endemic phase. Human genomics. 2022;16(1):19.

4. Mehta P, Sahni S, Siddiqui S, Mishra N, Sharma P, Sharma S, et al. Respiratory Co-Infections: Modulators of SARS-CoV-2 Patients' Clinical Sub-Phenotype. Frontiers in Microbiology. 2021;12.

5. Devi P, Khan A, Chattopadhyay P, Mehta P, Sahni S, Sharma S, et al. Co-infections as Modulators of Disease Outcome: Minor Players or Major Players? Front Microbiol. 2021;12:664386.

6. Davis B, Rothrock AN, Swetland S, Andris H, Davis P, Rothrock SG. Viral and atypical respiratory co-infections in COVID-19: a systematic review and meta-analysis. Journal of the American College of Emergency Physicians open. 2020;1(4):533-48.

7. Sreenath K, Batra P, Vinayaraj EV, Bhatia R, SaiKiran K, Singh V, et al. Coinfections with Other Respiratory Pathogens among Patients with COVID-19. Microbiology spectrum. 2021;9(1):e0016321.

8. Rafat Z, Ramandi A, Khaki PA, Ansari S, Ghaderkhani S, Haidar H, et al. Fungal and bacterial co-infections of the respiratory tract among patients with COVID-19 hospitalized in intensive care units. Gene reports. 2022;27:101588.

9. Dadashi M, Khaleghnejad S, Abedi Elkhichi P, Goudarzi M, Goudarzi H, Taghavi A, et al. COVID-19 and Influenza Co-infection: A Systematic Review and Meta-Analysis. Frontiers in medicine. 2021;8:681469.

10. Kim KW, Deveson IW, Pang CNI, Yeang M, Naing Z, Adikari T, et al. Respiratory viral co-infections among SARS-CoV-2 cases confirmed by virome capture sequencing. Sci Rep. 2021;11(1):3934.

11. 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.

12. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. The Journal of infection. 2020;81(2):266-75.

13. Krumbein H, Kümmel LS, Fragkou PC, Thölken C, Hünerbein BL, Reiter R, et al. Respiratory viral co-infections in patients with COVID-19 and associated outcomes: A systematic review and meta-analysis. Reviews in medical virology. 2022:e2365.

14. Chen S, Zhu Q, Xiao Y, Wu C, Jiang Z, Liu L, et al. Clinical and etiological analysis of co-infections and secondary infections in COVID-19 patients: An observational study. The clinical respiratory journal. 2021;15(7):815-25.

15. Alhumaid S, Al Mutair A, Al Alawi Z, Alshawi AM, Alomran SA, Almuhanna MS, et al. Coinfections with Bacteria, Fungi, and Respiratory Viruses in Patients with SARS-CoV-2: A Systematic Review and Meta-Analysis. Pathogens (Basel, Switzerland). 2021;10(7).

16. Karaba SM, Jones G, Helsel T, Smith LL, Avery R, Dzintars K, et al. Prevalence of Co-infection at the Time of Hospital Admission in COVID-19 Patients, A Multicenter Study. Open forum infectious diseases. 2021;8(1):ofaa578.

17. Singh V, Upadhyay P, Reddy J, Granger J. SARS-CoV-2 respiratory co-infections: Incidence of viral and bacterial co-pathogens. International Journal of Infectious Diseases. 2021;105:617-20.

18. Roh KH, Kim YK, Kim SW, Kang ER, Yang YJ, Jung SK, et al. Coinfections with Respiratory Pathogens among COVID-19 Patients in Korea. The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie medicale. 2021;2021:6651045.

19. Trifonova I, Christova I, Madzharova I, Angelova S, Voleva S, Yordanova R, et al. Clinical significance and role of coinfections with respiratory pathogens among

http://dx.doi.org/10.52533/JOHS.2022.21214

individuals with confirmed severe acute respiratory syndrome coronavirus-2 infection. Frontiers in public health. 2022;10:959319.

20. Ishiguro T, Kobayashi Y, Shimizu Y, Uemura Y, Isono T, Takano K, et al. Frequency and Significance of Coinfection in Patients with COVID-19 at Hospital Admission. Internal medicine (Tokyo, Japan). 2021;60(23):3709-19.

21. Le Glass E, Hoang VT, Boschi C, Ninove L, Zandotti C, Boutin A, et al. Incidence and Outcome of Coinfections with SARS-CoV-2 and Rhinovirus. Viruses. 2021;13(12).

22. Tang ML, Li YQ, Chen X, Lin H, Jiang ZC, Gu DL, et al. Co-Infection with Common Respiratory Pathogens and SARS-CoV-2 in Patients with COVID-19 Pneumonia and Laboratory Biochemistry Findings: A Retrospective Cross-Sectional Study of 78 Patients from a Single Center in China. Medical science monitor : international medical journal of experimental and clinical research. 2021;27:e929783.

23. Li Y, Wang H, Wang F, Lu X, Du H, Xu J, et al. Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected children: A retrospective study. Medicine (Baltimore). 2021;100(11):e24315.

24. Wu Q, Xing Y, Shi L, Li W, Gao Y, Pan S, et al. Coinfection and Other Clinical Characteristics of COVID-19 in Children. Pediatrics. 2020;146(1).

http://dx.doi.org/10.52533/JOHS.2022.21214