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Bacterial Coinfection in individual with COVID-19

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Abstract

The novel coronavirus infectious disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has traumatized the whole world with the ongoing devastating pandemic. A plethora of microbial domains including viruses (other than SARS-CoV-2), bacteria, archaea and fungi have evolved together, and interact in complex molecular pathogenesis along with SARS-CoV-2. However, the involvement of other microbial co-pathogens and underlying molecular mechanisms leading to extortionate ailment in critically ill COVID-19 patients has yet not been extensively reviewed. Although, the incidence of co-infections could be up to 94.2% in laboratory-confirmed COVID-19 cases, the fate of co-infections among SARS-CoV-2 infected hosts often depends on the balance between the host's protective immunity and immunopathology. Predominantly identified co-pathogens of SARS-CoV-2 are bacteria such as *Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Acinetobacter baumannii, Legionella pneumophila*. The cross-talk between co-pathogens (especially lung microbiomes), SARS-CoV-2 and host is an important factor that ultimately increases the difficulty of diagnosis, treatment, and prognosis of COVID-19.

Keywords: COVID-19, Bacterial Coinfection, Meta-analysis

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Introduction

The ongoing pandemic has clinically affected more than 113 million lives worldwide; by February 2021, India is on to the second most-affected country after the United States. Nearly 89 million of those infected have recovered, more than 2 million have died, and about 21 million are still battling the infection [1]. This pandemic is primarily caused by a coronavirus belonging to the family of *Corona viridae*. These family members are enveloped positive-sense and single-stranded RNA viruses that have caused mild respiratory diseases

in the human population. However, in some cases, they may cause severe infections, including the central nervous system, and gastrointestinal and respiratory disorders [2, 3].

There are four genera of Coronaviruses (CoVs): alpha, beta, gamma, and delta. The β-CoVs are further classified into four subgroups: A, B, C, and D. Two alpha and four β-CoVs strains are known that can infect humans.

The four major structural proteins of β-CoVs are spike (S), envelope (E), membrane (M), and nucleocapsid (N) protein, they range in size from 26 to 32 kb, the largest known viral RNA genome [4]. The latest 2019 Coronavirus Diseases (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is closely linked to SARS-CoV and is 79.5% identical to the genomic sequence [5,6]. SARS-CoV-2 is spherical and has spike-like glycoproteins (S proteins) protruding from the surface of the virion that plays a vital role in the virus binding to the host cell receptor and mediates the fusion of the host cell membrane with the virus.

The S protein subdomains S1 and S2 are responsible for initial attachment to the host cell receptor and fusion with the cell membrane. The S1 subdomain is divergent across the receptor-binding domain (RBD) coronaviruses, while S2 is more conserved and has the fusion machinery that allows the virus to reach the host cell [6]. Coronavirus infection weakens the immune system, which leads to the activation of opportunistic microbes.

Bacterial co-infections associated with COVID-19.

Bacterial co-infections develop in patients amid or after the primary infection initiated by an infectious agent. Bacterial co-infections also play a significant role during COVID-19 and are associated with an increasing rate of disease severity and case fatality [5]. Nevertheless, until now, the incidence of bacterial co-infections in patients admitted to the ICU for acute respiratory failure associated with SARS-CoV-2 pneumonia is poorly studied [6]. SARS-CoV-2 primarily enters human body through nasopharyngeal tract and then gradually move to lung to initiate infection. The pathophysiology of COVID-19 can be attributed to aberrant immune responses in clearing the virus [7].

Given the unequivocal association between viral and bacterial co-infection and respiratory disease severity, there is a pressing need to better understand how interactions of the SARS-CoV-2 with the host microbiome in the respiratory tracts correlate with viral infections that facilitate opportunistic co-infections [8]. However, little is known the outcome of the interactions of SARS-CoV-2 with nasal commensal bacteria which is thought to be critical for ultimate severity of COVID-19 disease development. The prevalence rate of bacterial co-infections in critically ill hospitalized COVID-19 patients was around 14% revealed by a meta-analysis [9].

A recent North American study reported 41% prevalence of bacterial co-infections among 17 COVID-19 patients admitted to ICU [10]. The incidence of co-infection associated with bacterial pneumonia ranged between 11% and 35% among the patients who had been infected with respiratory viruses [11].

Recently, Fu et al., (2020) reported that among ICU admitted COVID-19 patients, 13.9% were suffering from bacterial co-infections. Despite having a varying rate of bacterial co-infections among COVID-19 patients, the rate of prevalence could be as high as 50% among the non-survivors [12]. A series of retrospective case studies on SARS-COV-2 confirmed that severely and non-severely ill patients had 7.7% and 3.2%, bacterial and fungal co-infections, respectively [13]. In Italy, a study conducted among 16,654 patients with critical condition, who died of SARS-CoV-2 infection depicted that 11% of those cases were associated with bacterial and fungal co-infections [14].

Co-infections with Streptococcus pneumoniae, Staphylococcus aureus, or other colonizing bacteria during the pathophysiology of COVID-19 impairs both innate and adaptive antibacterial host defenses and temporarily compromise the physical and immunological barrier to cause secondary bacterial pneumonia, leading to severe and deadly disease in people with pre-existing comorbidities and previously healthy people [15].

Data regarding bacterial co-infections in COVID-19 pneumonia are still emerging, but an association has been made between the detection of bacterial pathogens in samples with disease severity in COVID-19 patients. The most identified coinfected bacterial pathogens include, *Acinetobacter baumannii, Klebsiella pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, and Clamydia pneumoniae* [16], [17]. In addition, bacterial pathogens such as *Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus pneumoniae, Neisseria meningitides* [16] as well as some genera of Proteus, Enterobacter, and Citrobacter species have also been reported in hospitalized COVD-19 patients.

In a recent microbiome study, Hoque et al. reported 527 and 306 bacterial genera in COVID-19 patients of Bangladesh and China, respectively [18]. Moreover, *Pseudomonas aeruginosa and E. coli* are the most frequently isolated multi-drug resistant (MDR) pathogens to be associated with hospital acquired superinfections [19]. Remarkably, SARS-CoV-2 RNA has also been detected in fecal samples of COVID-19 patients. It raises the question of gastrointestinal infection of SARS-CoV-2 and a possible fecal-oral route of disease transmission [20, 21].

Moreover, high expression levels of ACE2 mRNA in the gastrointestinal system revealed a strong interaction of SARS-CoV-2 with the gastrointestinal system that has high microbiome diversity and possible chances of immune suppression and bacterial co-infections [20, 21].

Highly qualitative and time-dependent, underlying mechanisms of these scenarios involve dynamic interactions among three (virus, host, and bacteria) different entities. However, it is evident that in a combination of viral/bacterial pneumonia, the SARS-CoV-2 immune response is probably altered. They completely postulate that any coinfection situation would eventually exacerbate the clinical outcome severity of COVID-19. SARS-CoV-2 may strengthen bacterial colonization and attachment to the host tissue, and the combined infections may lead to increased degradation and pathophysiology of the tissue. Systemic transmission of the virus/bacterial copathogens can be facilitated by airway dysfunction, cytopathology, and tissue degradation caused by SARS-CoV-2 or bacterial coinfection, significantly raising blood infection risk. Virus-mediated bacterial infection improvement is not uncommon. The airway epithelium invasion by respiratory pathogens is increased by rhinovirus and influenza virus infections [22].

The virulence factors of SARS-CoV-2 interact with the lungs and elicit an immune response. These interactions can compromise innate immunity at several levels, leading to increased bacterial attachment, growth, and dissemination. Bacterial receptors mediating bacterial attachment can be discovered by a viral infection. An exuberant inflammatory response can result from coinfection. It is also possible that the form of SARS-CoV-2-induced immune response can allow bacteria to thrive in the lungs.

On the other hand, SARS-CoV-2 infection may be predisposed to bacterial colonization because the innate immune host defenses can be down regulated, allowing survival, development, and pathology of the virus. Coinfection may aggravate tissue damage, and exuberant inflammatory response may further aggravate SARS-CoV-2-induced lung damage [23-27].

Ethical Approval

The study was approved by the Ethical Committee.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Both authors shared in conception, design of the study, acquisition of data, and manuscript writing, the critical revising and final approval of the version to be published.

References

1. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. PMCID. 2020; 16;181(2):271-280.e8.
2. Denison MR, Graham RL, Donaldson EF, Eckerle LD, Baric RS. Coronaviruses: an RNA proofreading machine regulates replication fidelity and diversity. RNA Biol. 2011; 8(2):270-279.
3. Zhou P, Yang X, Wang X Hu G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin Nature. 2020; 579 (7798):270-273.
4. Shin MD, Shukla S, Chung YH, et al. COVID-19 vaccine development and a potential nanomaterial path forward. Nat Nanotechnol. 2020; 15 (8):646-655.
5. Bengoechea JA, Bamford CG. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO Mol. Med. 2020; 12(7):e12560.
6. Huttner B, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! Clin. Microbiol. Infect. 2020; 26:808-810.
7. Yeoh YK, Zuo T, Lui GC-Y, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut, 2021; 70:698-706.
8. Hadi RN, Alfawaz MAG, Mohammed KG, et al. Hematological changes among Corona virus-19 patients: a longitudinal study. sys rev pharma. 2020; 11(5): 862-866.
9. Kaul D, Rathnasinghe R, Ferres M, et al. Microbiome disturbance and resilience dynamics of the upper respiratory tract during influenza A virus infectio Nat. Commun. 2020; 11:1-12.
10. Bassetti M, Kollef MH, Timsit J-F. Bacterial and fungal superinfections in critically ill patients with COVID-19. Intensive Care Med. 2020; 46:2071-2074.
11. Lehmann CJ, Pho MT, Pitrak D, Ridgway JP, Pettit NN. Community acquired co-infection in COVID-19: a retrospective observational experience Clin. Infect. Dis. 2020; 72 (8):1450-1452.
12. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza and other Respiratory Viruses, 2016; 10:394-403.
13. Fu Y, Yang Q, Xu M, Kong H, et al. Secondary bacterial infections in critical ill patients of COVID-19. Open Forum Infectious Diseases. 2020; 7(6):1-4.
14. Zhang G, Hu C, Luo L, et al. Clinical features, and short-term outcomes of 221 patients with COVID-19 in Wuhan, China J. Clin. Virol. 2020; 104364.

15. Lai C-C, Wang C-Y, Hsueh P-R. Co-infections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? J.Microbiol. Immunol. Infect. 2020; 53(4):505-512.
16. Yousif NG. Metastatic Cancer patients during COVID-19 pandemic: A longitudinal study of current evidence. Teikyo Medical Journal 2022; 45(04):6353-6359.
17. Ginsburg AS, Klugman KP. COVID-19 pneumonia and the appropriate use of antibiotics. The Lancet Global Health. 2020; 8:e1453-e1454.
18. Khatiwada S, Subedi A. Lung microbiome and coronavirus disease 2019 (COVID-19): possible link and implications Human Microbiome J. 2020; 17:100073.
19. Meawed TE, Ahmed SM, Mowafy SMS, Samir GM, Anis RH. Bacterial and fungal ventilator associated pneumonia in critically ill COVID-19 patients during the second wave. Journal of Infection and Public Health. 2021; 14(10):1375-1380.
20. Hoque MN, Rahman MS, Ahmed R. et al. Diversity and Genomic Determinants of the Microbiomes Associated with COVID-19 and Non-COVID Respiratory Diseases. Gene Rep. 2020; 23:101200.
21. Garcia-Vidal C, Sanjuan G, Moreno-García E. et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study Clin. Microbiol. Infect. 2020; 27(1):83-88.
22. Gao QY, Chen YX, Fang JY. Novel coronavirus infection and gastrointestinal tract J. Digestive Diseases. 2020;125-126.
23. Yousif NG. Mortality rate in cancer patients with COVID-19: meta-analysis data. American Journal of BioMedicine. 2021; 9(3):156-163.
24. Xiao F, Tang M, Zheng X, Liu X, Li H. Shan Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020; 158:1831-1833.
25. Conceição ED. Multivariate analyses of triple-negative breast cancer compare with non-triple-negative breast cancer: A multicenter retrospective study. American Journal of BioMedicine 2022;10(1):13-24.
26. Bosch TM, Biesbroek G, Trzcinski K EAM, Sanders D. Viral and bacterial interactions in the upper respiratory tract PLoS Pathog. 2013; 9(1):e1003057.
27. Bengoechea JA. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO Mol Med. 2020; 12: e12560.