

Co-infections in COVID-19 patients and correlation with mortality rate. Minireview

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ABSTRACT

Purpose: The goal of our review was to gather information on the most important community-acquired and hospital-acquired co-infections among coronavirus disease 2019 (COVID-19) patients, and to examine not only the effect of these co-infections on disease outcomes but also to identify the possible risk factors that predispose COVID-19 patients to co-infections. *Methods:* Medline (PubMed) and Google Scholar were searched for relevant articles published between January 1st, 2020, and September 31st, 2021, on the topic of co-infections among COVID-19 patients. *Results:* Among community-acquired and hospital-acquired co-infections, bacterial and fungal co-infections are equally frequent, followed by viral co-infections that affected a relatively smaller portion of patients. Overall, co-infections were more frequent in the hospital than at the community level. Risk factors for acquiring co-infections include male gender, longer length of hospital stay, presence of supportive treatment, such as ventilation, the admission to intensive care units, the administration of medications, such as steroids or antibiotics, and certain blood parameters, such as high C-reactive protein or lymphopenia. The presence of co-infections could aggravate the COVID-19 disease severity, prolong the healing time of patients, and lead to worse disease outcomes overall. *Conclusion:* Co-infections may increase the mortality of COVID-19 patients, especially in the hospital setting. Paying closer attention to hygiene, adhering to diagnostic and therapeutic protocols, implementing

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antimicrobial stewardship programs could decrease the occurrence of co-infections and lead to improved outcomes for COVID-19 patients.

KEYWORDS

COVID-19 disease, community-acquired, healthcare-associated, co-infection, death rate

INTRODUCTION

Since the beginning of the global coronavirus disease 2019 (COVID-19) pandemic, approximately 242 million confirmed cases and 4.9 million deaths were linked to the SARS-CoV-2 virus globally [1]. The COVID-19 pandemic led to a sudden overburdening of the healthcare systems due to the high number of cases worldwide [2]. The unexpected number of patients challenged the hospitals' logistical and organizational skills often resulting in difficulties in the supply of materials and the lack of adequate number of both beds and health care personnel [3].

Studies indicate that the presence of both advanced age and comorbidities greatly increase the mortality of COVID-19 patients [4–17]. Less is known about other factors, such as the prevalence and the role of co-infections in the mortality of COVID-19 patients. The proportion of COVID-19 patients affected by co-infections is not clear, as studies frequently report contradictory evidence. Moreover, the characteristics of co-infections greatly differ among community-acquired and hospital-acquired infections. Thus, the goal of our review was to gather information on the most important community-acquired and hospital-acquired co-infections among COVID-19 patients and to examine not only the effect of these co-infections, for instance on the mortality of COVID-19 patients, but also to identify the possible risk factors that predispose the individual to co-infections.

METHODS

Medline (PubMed) and Google Scholar were searched for relevant articles published on the topic of co-infections among COVID-19 patients. The following search terms were used: "COVID-19", "co-infection", "community acquired infection", "nosocomial infection", "healthcare-associated infection", "risk factor", "death rate", "mortality". We included any studies published between January 1st, 2020, and September 31st, 2021. Databases were searched by two investigators (AF, ND). Any disagreements were resolved by the inclusion of a third investigator (VFP). Articles were first selected according to their title and abstract, and this was followed by the full-text appraisal of articles. Results were summarized qualitatively.

COMMUNITY-ACQUIRED BACTERIAL CO-INFECTIONS IN PATIENTS WITH COVID-19

Approximately, 3–7% of COVID-19 patients may be affected by one or more community-acquired co-infections [18, 19]. The frequency of these co-infections, however, was overall lower compared to the community-acquired co-infection rates for influenza [20].



Among these co-infections, approximately 2.5–5% were linked to bacteria, namely *Staphylococcus epidermidis*, *methicillin-sensitive Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *methicillin-resistant S. aureus (MRSA)*, *Proteus mirabilis*, and *Klebsiella pneumoniae* [2, 18, 21–23]. These microorganisms were mostly isolated from urine, blood, respiratory tract samples, and other sources, such as from peritoneal fluid or wounds [2]. The two most common type of bacterial co-infections were urinary tract infections, which occurred among approximately 3% of cases, and pneumonia, which affected approximately 1.2–2.1% of COVID-19 cases with *Streptococcus pneumoniae* and *S. aureus* being the most common pathogens for the latter [18, 21].

Opportunistic invasive fungal infections are also considered to be frequent community-acquired co-infections in patients with COVID-19 [24, 25]. Since opportunistic invasive fungal infections are difficult to recognize because of their slower onset and atypical symptoms, these cases are often only diagnosed after death [25]. Even though the actual number of fungal co-infections among COVID-19 remains unclear, it seems that community-acquired fungal infections may affect an estimated 5.5% of COVID-19 cases [22, 24]. Aspergillosis and candidiasis (*Candida albicans*, *Candida glabrata*) were the most frequent fungal co-infections in patients with COVID-19, but mycormycosis, cryptococcosis, and other fungal pathogens have also been detected [22, 24, 25]. Cases with fungal infections have been reported to be either primary infections or secondary infections related to catheter use [24].

Community-acquired viral co-infections appear relatively rarely among COVID-19 patients. According to studies, viral co-infections were detected in only 0.2–0.6% of COVID-19 cases with *Influenza A*, *Influenza B*, *Respiratory Syncytial Virus*, and *Herpes Simplex Virus* being the most frequent viral co-infections [18, 21].

HEALTHCARE-ASSOCIATED CO-INFECTION OF COVID-19 PATIENTS

Hospital-acquired co-infections among COVID-19 patients have been reported ever since the early period of the outbreak with an evident connection to emergency procedures, such as intubation or to the placement of patients in intensive care units (ICUs) [24, 26–28]. It is not clear whether nosocomial infections appear more often among COVID-19 patients (12.5%–14.62%), as nosocomial infections usually affect 3.6–12% of patients in high income countries and 5.7–19.1% of patients in low income countries [28]. According to a study, cumulative incidence of hospital-acquired infections for COVID-19 patients was estimated to be 27% at 10 ICU-days, while incidence density of hospital-acquired infections was estimated to be 125 events per 1000 ICU-days [19]. Although COVID-19 patients have increased susceptibility to ventilation-associated lower respiratory tract infections, the incidence of reported hospital-acquired infections linked to ventilation seems to be low and mainly prevalent in critically ill patients [29, 30].

Overall, hospital-acquired bacterial infections appear less frequently among COVID-19 than in case of influenza [2, 20, 31]. According to a meta-analysis encompassing nearly 4,000 hospitalized patients with COVID-19, 7% of patients were affected by laboratory-confirmed bacterial co-infections [20]. A higher proportion (14% of COVID-19 cases) was detected among patients in ICUs [20]. In contrast to these results, another study found that bacterial co-infections may affect up to 25% of hospitalized patients [19, 32]. The most common isolated bacteria were *Mycoplasma pneumonia* (42% of bacterial co-infections), followed by



Pseudomonas aeruginosa (12%) and *Haemophilus influenza* (12%), but *K. pneumoniae*, *Acinetobacter baumannii*, *Serratia marcescens*, MRSA and *Enterococcus faecium* have been detected as well. The most frequent infections were primary infections (31%), followed by catheter-related bloodstream infections (25%), pneumonia (23%), tracheobronchitis (10%), and urinary tract infections (8%) [33]. Bacterial infections were associated with septic shock in 60% of cases, being the cause of the death in a third of these patients [33].

As for hospital acquired fungal co-infections, some studies suggest that up to 19% of COVID-19 patients may be affected by fungi in the hospital [2]. The most prevalent hospital-acquired fungal infections were caused by *Aspergillus* and *Candida* species [29]. *C. albicans* was mostly isolated from the respiratory and urinary tract of patients, while *Aspergillus flavus*, *Aspergillus fumigatus* and *C. glabrata* agents were identified primarily from respiratory samples [20]. Other fungal species (*Histoplasma* spp., *Rhizopus* spp., *Mucor* spp., *Cryptococcus* spp.) were also identified, albeit less frequently [24].

Compared to bacterial and fungal co-infections, hospital-acquired viral co-infections occurred relatively rarely, affecting approximately 3% of patients [20, 34]. Higher occurrence of viral co-infections was not identified at ICUs [20, 34]. The most frequently identified viral co-infections were caused by either *Respiratory Syncytial Virus* or the *Influenza A virus* [20, 34].

RISK FACTORS OF CO-INFECTIONS IN COVID-19 PATIENTS

Several factors may increase the risk of acquiring co-infections among COVID-19 patients. For instance, studies indicate that men are more likely to develop hospital-acquired co-infections compared to female patients [2]. Other predictors of co-infections include longer length of hospital stay, presence of supportive treatment, the administration of medication, or certain blood parameters, such as high C-reactive protein values, leukopenia, lymphopenia, and T-cell dysfunction [2, 22, 24, 26, 29, 35–38].

The longer length of hospital stay closely correlates with the appearance of co-infections. The median time from hospital admission to onset of co-infection was 16 days (IQR 9–25 days) [2]. Co-infections are also more frequent in patients treated in the ICUs and among patients receiving supportive therapy, such as intubation, ventilation, arteriovenous and urinary catheterization, continuous veno-venous hemofiltration, or hemodialysis [2, 22, 26, 35–37].

The administration of certain medications, such as steroids, immunomodulatory agents, and antibiotics, may also increase the occurrence of co-infections. Steroid therapy has been reported to increase the occurrence of hospital-acquired co-infections (OR 1.91; 95% CI, 1.42–2.57) [2]. The same has been observed for the use of immunomodulatory agents (OR 5.09, 95% CI 2.2–11.8) [37]. Previous treatment with antibiotics, such as piperacillin/tazobactam, were also linked to hospital-acquired co-infections (OR 2.85, 95% CI 1.10–7.20) [37]. According to data, the overall use of antimicrobials among COVID-19 patients can be as high as 70–87.9% [22, 38]. Most of these patients were treated with antimicrobials despite having negative blood cultures [22]. Indiscriminate antimicrobial use may enhance the spread of antimicrobial resistance [22]. The reported incidence of multi-drug resistant bacterial infections in critically ill COVID-19 patients is high, ranging between 16% and 70.4% [18, 37, 39, 40]. Apart from the fact that multi-drug resistant strains lead to higher mortality, longer hospital stay and may drive up treatment costs, previous intestinal colonization by carbapenem-resistant *Enterobacterales* (OR 16.03, 95%



CI 6.5–39.5) was also identified as a predictor for other hospital-acquired co-infections (OR 16.03, 95% CI 6.5–39.5) [37]. The use of empiric drug therapy for COVID-19 is not indicated for the prevention of bacterial co-infections, as it may lead not only to a more frequent appearance of drug resistance but also to an increased risk of adverse drug reactions, *Clostridium difficile* infections, and invasive fungal infections [2, 22].

EFFECT OF CO-INFECTIONS AMONG COVID-19 PATIENTS

Certain co-infections may greatly prolong the length of hospital stay of COVID-19 patients and increase their admission rates to ICUs [3, 20, 22, 33]. A study examining the effect of bloodstream infections among COVID-19 patients, for example, found that the median length of hospital stay was significantly longer for COVID-19 patients with a concurrent bloodstream infection than those without a bloodstream infection (18.5 vs 7 days). These patients were also more often admitted to ICUs (71.1% vs 35.6%), leading to higher mortality when compared to COVID-19 patients without bloodstream infections (53.1% vs 32.8%) [22, 35]. The latter was corroborated by other studies as well [22, 39, 41, 42]. Overall, the mortality of hospitalized COVID-19 patients may be as high as 22%, while mortality may reach 47.6% in the ICUs [38, 43]. As for the type of co-infections, fungal co-infections seem to contribute to worse outcomes in COVID-19 patients compared to viral and bacterial co-infections [22, 24, 25].

Several of these observations are in line with observations made during the influenza pandemics. During the 2009 influenza pandemic, for instance, 1 in 4 severe or fatal cases of *influenza A* (H1N1) had a bacterial co-infection, the most common being *S. pneumoniae*, *S. aureus*, and *Streptococcus pyogenes*. Bacterial co-infections have been often associated with more severe outcomes in patients affected by infectious respiratory diseases, and they are one of the main causes of mortality in influenza as well.

CONCLUSIONS

Literature suggests that co-infections aggravate COVID-19 disease severity, prolong the healing time of patients, and lead to higher mortality. Among community-acquired and hospital-acquired co-infections, bacterial and fungal co-infections are equally frequent, followed by viral co-infections that affected a relatively smaller portion of patients. Overall, a higher portion of patients were affected by coinfections in the hospital than among cases cared for in their community. Risk factors, such as gender, longer length of hospital stay, presence of supportive treatment, the administration of medications, or certain blood parameters, may be predictors of co-infections in COVID-19 patients. By paying closer attention to hygiene and adhering to diagnostic and therapeutic protocols, this could have a positive effect on the outcome of COVID-19 patients, as co-infections increase the length of hospital stay and mortality of COVID-19 patients as well. At the moment, empirical antibiotic treatment of COVID-19 patients is not indicated, as it may lead to the appearance of multidrug resistant strains and fungal co-infections. The implementation of antimicrobial stewardship programs may be an important strategy in the COVID-19 pandemic to prevent the appearance of multidrug resistant strains [23, 37, 44].



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