MINI-REVIEW

The microbial coinfection in COVID-19

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel β-coronavirus, is the main pathogenic agent of the rapidly spreading pneumonia called coronavirus disease 2019 (COVID-19). SARS-CoV-2 infects much more people, especially the elder population, around the world than other coronavirus, such as SARS-CoV and MERS-CoV, which is challenging current global public health system. Beyond the pathogenesis of SARS-CoV-2, microbial coinfection plays an important role in the occurrence and development of SARS-CoV-2 infection by raising the difficulties of diagnosis, treatment, prognosis of COVID-19, and even increasing the disease symptom and mortality. We summarize the coinfection of virus, bacteria and fungi with SARS-CoV-2, their effects on COVID-19, the reasons of coinfection, and the diagnosis to emphasize the importance of microbial coinfection in COVID-19.

Key points

• *Microbial coinfection is a nonnegligible factor in COVID-19.*
• *Microbial coinfection exacerbates the processes of the occurrence, development and prognosis of COVID-19, and the difficulties of clinical diagnosis and treatment.*
• *Different virus, bacteria, and fungi contributed to the coinfection with SARS-CoV-2.*

Keywords SARS-CoV-2 · COVID-19 · Coinfection · Microorganism

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel member of enveloped RNA β-coronavirus (Huang et al. 2020), which is the cause of a severe pneumonia with clinical symptoms different from known coronavirus caused pneumonia, such as SARS-CoV and MERS-CoV (Lu et al. 2020; Zhu et al. 2020). The SARS-CoV-2 infection has become a public health challenge for all over the world. The SARS-CoV-2 caused pneumonia was named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) on 11 February 2020 (Castagnoli et al. 2020; Ni et al. 2020). The World Health Organization has declared the novel coronavirus outbreak a public health emergency of international concern. COVID-19 spreads rapidly and becomes a global pandemic. Until 3 July 2020, 217 countries and areas have been affected, and more than 10,710,000 cases have been confirmed globally with 517,877 deaths.

Since its first detection, the infection rate and mortality rate of the SARS-CoV-2 have far exceeded that of any other common flu (Li et al. 2020a). Many drugs and vaccines specifically targeting SARS-CoV-2 infection are under different clinical phases. The coinfection of the SARS-CoV-2 with other microorganisms, such as virus, bacteria, and fungi, is a very important factor in COVID-19, and it can raise the difficulties of diagnosis, treatment, prognosis of COVID-19, and even increase the disease symptom and mortality (Ruuskanen et al. 2011) (Fig. 1). Currently, many trails and investigations

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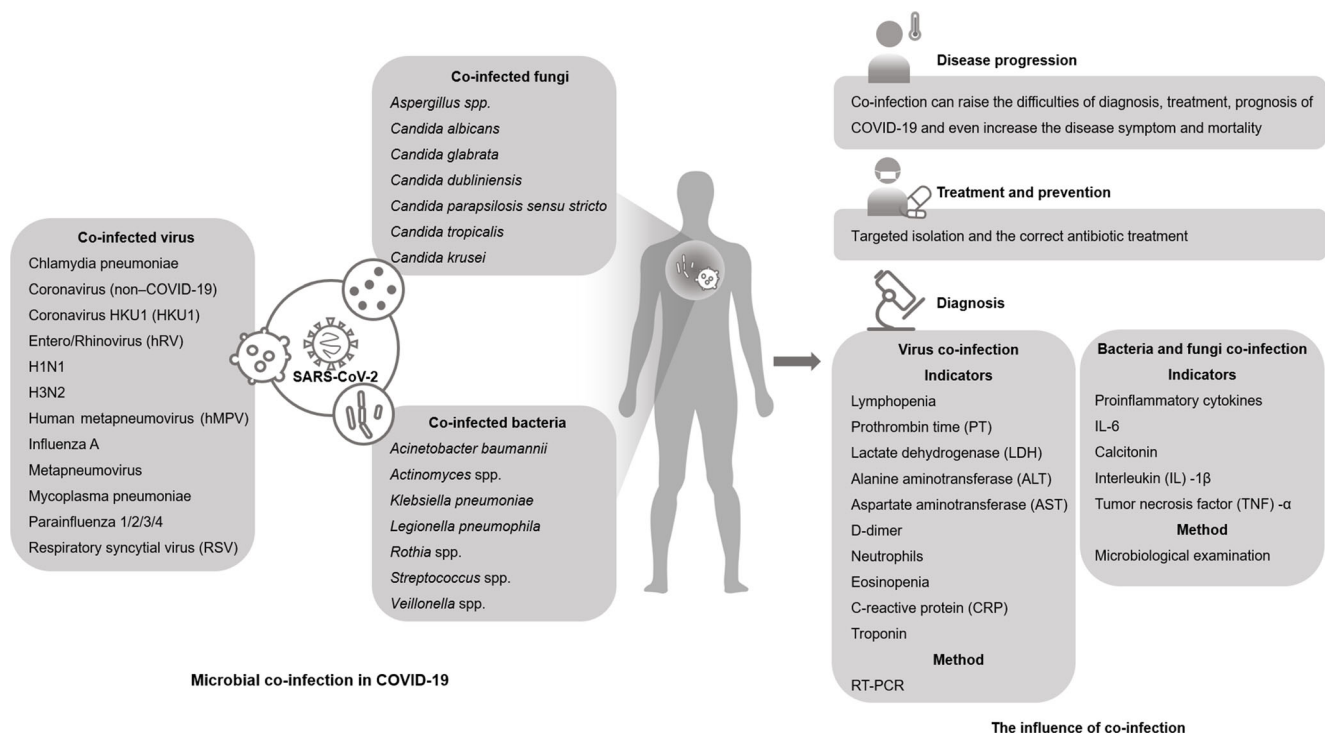
Fig. 1 In patients infected with SARS-CoV-2, coinfection of viruses, bacteria, and fungi is an important factor that cannot be ignored. Coinfection of SARS-CoV-2 with viruses, bacteria, and fungi will increase the difficulty of diagnosis, treatment, and prognosis of COVID-19, and even increase the symptoms and mortality of the disease. At the same time, coinfected microorganisms may also become a new strategy for the development of new treatments for SARS-CoV-2 infection

indicate the strong relationship between other virus, bacteria, fungi, and SARS-CoV-2 (Shen et al. 2020).

According to recent clinical studies, virus coinfection mainly includes respiratory virus such as entero/rhinovirus (hRV), human metapneumovirus (hMPV), respiratory syncytial virus (RSV), and other coronavirus (nonCOVID-19) (Lin et al. 2020). Coinfection can also change the intestinal homeostasis thus triggers the infection, and it stimulates immune cells to produce more severe inflammation. Gu et al. (2020) recently discovered that the intestinal bacterial diversity of patients with COVID-19 is significantly reduced, the relative abundance of opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* are significantly higher, while the relative of beneficial symbionts abundance, such as *Blautia*, *Romboutsia*, *Collinsella*, and *Bifidobacterium*, is lower. Meanwhile, a descriptive study held by Chen et al. (2020) showed that the coinfected fungi includes *Aspergillus* spp., *Candida albicans*, and *Candida glabrata* (Table 1). Netea et al. (2020) found that in most individuals, SARS-CoV-2 infection is mild, while coinfection can increase the susceptibility of patients to severe disease by affecting the body's immune function. Meanwhile, Kalantar-Zadeh et al. (2020) hold the view that the ecosystem of commensal microbiota can both regulate and be regulated by invading viruses, facilitating either stimulatory or suppressive effects. More importantly, the coinfected microorganisms may also be a new

strategy for the development of new treatment of SARS-CoV-2 infection. Therefore, we summarize the microbial coinfection of SARS-CoV-2, their effects on COVID-19, and the diagnosis to emphasize that the microbial co-infection is a nonnegligible factor in COVID-19, especially in the diagnosis and treatment.

Viral coinfection with SARS-CoV-2

Among viral infections of respiratory diseases, coinfection with other viruses is common. Many clinical studies have observed the viral co-infection with SARS-CoV-2 from different countries. Lin et al. (2020) conducted in vitro tests on 186 patient samples randomly selected from January 20 to February 1 in Shenzhen Third People's Hospital. Of the 92 SARS-CoV-2 positive patients, 6 patients (3.2%) respectively detected viral coinfection. Four of them (2.2%) detected at least two viruses (Lin et al. 2020). The common respiratory viruses including RSV, hRV, hMPV, parainfluenza virus type 2 (PIV2), and coronavirus HKU1 (HKU1) were also simultaneously detected. This data is consistent with a study of 5700 subjects that entero/rhinovirus and non-SARS-CoV-2 Coronavirus are the most common coinfected viruses, followed by RSV, parainfluenza 3, chlamydia pneumoniae, hMPV, influenza A, and mycoplasma pneumoniae (Richardson et al.

Table 1 The microbial coinfection in COVID-19

Microbial species	Coinfected microorganisms	References
Virus	Chlamydia pneumoniae	(Lin et al. 2020)
	Coronavirus (nonCOVID-19)	(Richardson et al. 2020)
	Coronavirus HKU1 (HKU1)	(Wang et al. 2020a, b)
	Entero/rhinovirus (hRV)	(Kim et al. 2020)
	H1N1	(Zhang et al. 2020)
	H3N2	
	Human metapneumovirus (hMPV)	
	Influenza A	
	Metapneumovirus	
	Mycoplasma pneumoniae	
	Parainfluenza 1/2/3/4	
	Respiratory syncytial virus (RSV)	
Bacteria	Acinetobacter baumannii	(Zhang et al. 2020)
	Actinomyces spp.	(Gu et al. 2020)
	Klebsiella pneumoniae	(Chen et al. 2020)
	Legionella pneumophila	
	Rothia spp.	
	Streptococcus spp.	
	Veillonella spp.	
Fungi	Aspergillus spp.	(Verweij et al. 2020)
	Candida albicans	(Chen et al. 2020)
	Candida glabrata	(Salehi et al. 2020)
	Candida dubliniensis	
	Candida parapsilosis sensu stricto	
	Candida tropicalis	
	Candida krusei	

2020). Another study in Wuhan showed that among 2745 SARS-CoV-2-positive patients, 5.8% of patients had coinfections with other coronavirus, influenza A virus, hRV, and influenza A H3N2 (Wang et al. 2020b). In Northern California, the researcher counted that in 116 specimens positive for SARS-CoV-2, 24 (20.7%) were positive for one or more additional pathogens, and entero/rhinovirus, RSV, and nonSARS-CoV-2 Coronaviridae are the most common coinfected pathogens (Kim et al. 2020). Coinfection with other respiratory viruses may be an important reason for COVID-19's early misdiagnosis as influenza for they almost have the same clinical manifestations, laboratory, and imaging findings (Lai et al. 2020b).

Due to the strong infectivity and wide spread of SARS-CoV-2, in addition to other respiratory viruses coinfect with SARS-CoV-2, many systemic infectious virus, such as HIV (Blanco et al. 2020) and hepatitis virus (Kiley et al. 2020) coinfection, are also reported and raised the serious concern, but the infection rates are still unclear.

Among the viral coinfected population, the number of middle-aged and elderly people is relatively large, which may be related to their immunity and systemic disease status (Richardson et al. 2020). Wang et al. (2020b) found that the majority of COVID-19 patients were around 30–60 years old; the overall median age was 47, while the median age of patients with coinfection was 51. However, it is worth to notice that patients with SARS-CoV-2 coinfected with other viruses are not just elders or people with systemic diseases, healthy children, youth, and middle-aged people are also at risk from the coinfection (Lim et al. 2019).

The influence of viral coinfection on disease progression and outcome

Viral coinfection may have a great influence on treatment and prognosis of the disease. Coinfection is usually connected with the need for a higher level of care, increased length of stay (LOS), and development of acute respiratory distress syndrome (Cawcutt and Kalil 2017). Due to the coinfection has caused more serious damage to the immune system (Tay et al. 2020), patients, who are positive for SARS-CoV-2 and other viruses, condition may be more serious, the treatment is more complicated, and the treatment cycle is longer in general (Yang et al. 2020). A case report about a patient coinfected by SARS-CoV-2 and HIV had a longer progression of the disease and slower generation of specific antibody because of the collapse of immune system (Wang et al. 2020a). SARS-CoV-2 infection may also cause liver damage (Li et al. 2020b). For patients who already have certain viral infections, such as hepatitis C virus and HIV, drug-induced liver injury (DILI) is more likely to occur (Boeckmans et al. 2020). The development and outcome of SARS-CoV-2 coinfected with other viruses are highly dependent on the host immune response, especially in the elderly (Nikolich-Zugich et al. 2020).

Reason of viral coinfection and prevention

The probability of respiratory virus coinfection varies from 10 to 68% (Nickbakhsh et al. 2019). Coinfection increases the levels of C-reactive protein (CRP) and procalcitonin (PCT) (Li et al. 2019). The coinfection mechanisms include virus-induced airway damage, reduced mucociliary clearance, and damage to the immune system (Vareille et al. 2011). Since many viruses can destroy the airway epithelium, this may cause an increase in viral coinfection (Denney and Ho 2018). Viruses can also cause immune system disorders to promote the possibility of infection by other viruses (Rouse and Sehrawat 2010). At present, it is difficult to determine the kinetics of viral coinfections since there is very little information about the virus kinetic parameters of SARS-CoV-2 infection. Current reports show that the coinfection rate of SARS-

CoV-2 with other viruses is not high. The reason for this may be that the competitive advantage plays an important role in the coinfection process of SARS-CoV-2 and other respiratory viruses (Nowak et al. 2020).

In order to avoid the coinfection of SARS-CoV-2 and other viruses, the most important step is the prevention and control of infection (Yuen et al. 2020). To prevent the spread of infection, social distancing should be encouraged (Li et al. 2020c; Yetmar et al. 2020). In the process of diagnosis and treatment for patients with other viral coinfections, it is best to provide a separate room for special people in the clinical setting to isolate and treat after understanding the risk of infection transmission (Alhazzani et al. 2020). Particularly, the patients, who previously infected with an HIV virus, are more likely to cause SARS-CoV-2 coinfection when the systemic immunity declines and specific antibody responses were delayed or even vanished. Therefore, for these patients, the importance of isolation should be more emphasized (Ferretti et al. 2020).

The diagnosis of viral coinfection

Among the SARS-CoV-2 patients, fever is the most common symptom, and more than 90% of patients have a fever (Singhal 2020); more than half have a cough (69.8%), followed by dyspnea (34.5%), myalgia (27.7%), pharyngalgia (17.4%), headache (7.2%), diarrhea (6.1%), sore throat (6.1%), and rhinorrhea (4.0%) (Nicola et al. 2020). The radiological imaging features of COVID-19 pneumonia include lung changes, for example, the ground-glass opacity (GGO) changes, and bronchial changes and pleural changes (Zhou et al. 2020b). These clinical symptoms and radiological imaging changes are similar to those with other respiratory viral infections. Therefore, it is difficult to determine the specific type and number of viruses the patient infected with based on imaging findings and medical history (Azekawa et al. 2020; Danis et al. 2020). These can lead to misdiagnosis of COVID-19 and other respiratory diseases. The radiographic images and clinical symptoms can only be used as an auxiliary diagnosis, and patients cannot be diagnosed based solely on these two aspects.

In addition, laboratory data indicated that SARS-CoV-2 infection included lymphopenia, prolonged prothrombin time (PT), the elevation of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer, neutrophils, eosinopenia, C-reactive protein (CRP), and troponin (Qin et al. 2020). The most common laboratory findings are a decreased lymphocyte count and an increased high-sensitivity C-reactive protein level (Li et al. 2020b). When combined with other viral infections, these results may change. The report shows that when SARS-CoV-2 and influenza A virus were coinfected, lymphocytes were increased, and C-reactive protein was often detected while the trend of lymphocytes was the opposite of SARS-CoV-2

infection alone. Of course, the results of laboratory tests are often affected by the degree of disease progression and the pathogens infected by the patient, so they can only be used as a reference for disease diagnosis.

Although there are many detection indicators, the most authoritative detection method is by using a multiplex reverse transcription-polymerase chain reaction (Mahony 2008), which can detect many respiratory tract infection viruses including the SARS-CoV-2 at the same time (D'Cruz et al. 2020). However, this method may cause some false negative results due to some factors during sample recovery, processing, or transportation. Therefore, the clinician has to repeat nasopharyngeal testing in order to confirm the diagnosis (World Health 2020). For patients with high clinical suspicion, sputum samples, or bronchoalveolar lavage should be considered in diagnosis (Rodriguez et al. 2020).

Bacterial and fungal coinfection with SARS-CoV-2

Bacterial and fungal coinfection are also common in viral pneumonia especially in critically ill patients (Zhou et al. 2020a). Among patients infected with respiratory viruses, the number of cases of primary coinfection or secondary bacterial pneumonia is between 11 and 35% (Klein et al. 2016). In 2003, according to a cohort study investigated by Prof. Zhong Nanshan research team, more than 20% of the patients who were positive for SARS-CoV have bacterial and fungal coinfection, and the coinfected patients who received invasive operation can account for 70.6% (Zheng et al. 2003). In SARS-CoV patients, there are a variety of pathogens coinfected, while the negative bacilli and *Candida* are particularly the most common types of bacteria and fungi (Gu and Korteweg 2007). For SARS-CoV-2, the phenomenon of bacterial and fungal coinfection also exists. Through a single-center, retrospective case series study including 55 severe patients and 166 nonsevere patients with laboratory-confirmed SARS-CoV-2 pneumonia, Zhang et al. (2020) found that in all 221 patients the bacterial coinfection rate is 7.7%, and the fungal coinfection rate is 3.2%. In the same situation as other viral pneumonia, the coinfection rate of severe patients is significantly higher than that of normal patients (Choi et al. 2012). In Guqin Zhang's study, the severely affected patients suffered a significantly higher rate of coinfection with bacteria (25.5%) and fungus (10.9%), while the bacterial and the fungal coinfection rates from the patients who were not severely affected are 0.8% and 0.6% respectively. Another study from Italy found that among the 16,654 patients with most severe diseases who deceased of SARS-CoV-2 infection, 11% of those cases were reported as coinfection with other bacteria and fungi (Huttner et al. 2020). In a retrospective, single-center study held by Chen et al. (2020) among the 99 cases

of 2019 novel coronavirus pneumonia in Wuhan, the coinfected bacterias include *Acinetobacter baumannii* and *Klebsiella pneumoniae* while *Aspergillus flavus*, *Candida glabrata*, and *Candida albicans* are the most common coinfect fungus. Salehi et al. (2020) investigated 53 hospitalized COVID-19 patients with oropharyngeal candidiasis (OPC) and found that *C. albicans* was the most common pathogens, which counted for 70.7%, followed by *C. glabrata* (10.7%), *C. dubliniensis* (9.2%), *C. parapsilosis sensu stricto* (4.6%), *C. tropicalis* (3%), and *C. krusei* (1.5%).

It is common to see the gastrointestinal symptoms in COVID-19 patients, and both the RNA of SARS-CoV-2 and the live virus can be detected in the fecal of the patients. The infection of SARS-CoV-2 of intestinal cells can lead to the change of intestinal microbiota. Gu et al. (2020) identified the gut microbiome by 16S ribosomal RNA (rRNA) gene V3-V4 region sequencing of 30 COVID-19 patients and found that compared with healthy people, the bacteria diversity had significantly reduced. The opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* are significantly higher, while the relative of beneficial symbionts abundance, such as *Blautia*, *Romboutsia*, *Collinsella*, and *Bifidobacterium*, is lower (Gu et al. 2020). Zuo et al. (2020) analyzed the changes of fecal fungi in 30 Hong Kong COVID-19 patients during hospitalization showed that compared with healthy controls, the pathogenic fungi such as *Candida* spp. and *Aspergillus* spp. were significantly enriched in patients, and the intestinal fungal dysregulation could be continued until 12 days after the patient's nasopharyngeal sample was cleared of SARS-CoV-2.

Currently, clinical data show that the bacterial or fungal coinfection rate of SARS-CoV-2–infected patients is lower than that of other influenza virus infections. This may be due to the relatively few relevant clinical reports and the extensive use of antibiotics in early diagnosis of SARS-CoV-2 infection. However, it is certain that the infection rate of bacterial and fungal coinfection with SARS-CoV-2 is proportional to the severity of the disease (Garazzino et al. 2020), and the coinfection can increase the mortality (Bengoechea and Bamford 2020).

Bacterial and fungal coinfection increases disease severity

Coinfection with bacteria and fungi has a great influence on the progression and prognosis of the disease, especially in severe patients, which can lead to increased needs for intensive care, antibiotic treatment, and increased deaths (Kiedrowski and Bomberger 2018; Lim et al. 2019). In 2007, in the study of *Bordetella pertussis* and SARS-CoV coinfection, the gross and histopathological lung lesions of the coinfected group were more serious, and the coinfected group significantly upregulated the expressions and periods for proinflammatory cytokines, especially IL-6 and MCP-1 (Brockmeier et al. 2008) indicating that there is a synergistic effect between *B. pertussis* and SARS-CoV, which may partially explain the increased severity of pneumonia in patients with *B. pertussis* and SARS-CoV coinfection. Coinfection can increase the degree of systemic inflammation in the patient, thereby increasing the severity of the disease and delaying the cure time. In patients with COVID-19, the number of proinflammatory cytokines associated with severe lung injury, especially IL-6, has increased significantly (Tan et al. 2020). Moreover, the bacterial and fungal coinfection was associated with a 2.5-fold increase in the risk of death in SARS-CoV-2 (Martins-Filho et al. 2020) indicating that there is a certain interaction between bacteria or fungi and SARS-CoV-2.

The reason of bacterial or fungal coinfection and the antibiotic treatment

SARS-CoV-2 infection can damage lymphocytes, especially B cells, T cells, and NK cells, which will lead to the immune system's impairment during the period of disease (Wang et al. 2020a). The decrease of lymphocytes and host immune function may be the main reason for the coinfection (Luo et al. 2019). The mortality is more significant in severe cases compared with the nonsevere group (Qin et al. 2020) due to the higher coinfection rate in severe patients. For more severely ill patients, they are more likely to receive treatment with invasive catheters, resulting in increased sensitivity to secondary infections with multidrug-resistant pathogens such as *Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterococcus* spp. (Rawson et al. 2020).

Although SARS-CoV-2 is virus-derived, based on the experience of overlapping bacterial infections in influenza, antibiotic treatment for patients with SARS-CoV-2 seemed to be the basic principle (Piva et al. 2020). According to the current data about patients with viral pneumonia, bacterial or fungal coinfection may be related to the significant risk of delaying appropriate treatment, which then lead to an increase in the mortality rate (Bengoechea and Bamford 2020). The consideration of antibiotic treatment in critically ill patients with COVID-19 is advisable as the bacterial infection cannot be excluded (Bassetti et al. 2020). A large number of studies have shown that during COVID-19 pandemic, antibiotic prescriptions were extensive and excessive during treatment, and 90% of patients prescribed empirical antibiotics (Lai et al. 2020a). However, the coinfected bacterial and fungal species in SARS-CoV-2 patients have not been fully investigated and reported so far. Of the hundreds of published articles on SARS-CoV-2 with clinical data, only a few reported the coinfections of bacteria and fungus but did not identify the detail pathogens. The widespread and inappropriate use of antibiotics is likely to lead to antibiotic resistance (AMR), which has a major impact on global health and the world

economy (Aslam et al. 2018; Prestinaci et al. 2015). Therefore, we recommend empirical treatment based on the clinical symptoms of coronavirus patients, choosing the most appropriate antibacterial agent according to local guidelines and local drug sensitivity models, and degrade as early as possible based on microbiological results or stop misapplication of antibiotics (Årdal et al. 2020).

The diagnosis of bacterial and fungal coinfection

For the diagnosis of COVID-19 patients, there are a lot of clinical guidelines. However, little attention was paid to the bacterial and fungal coinfection of this disease, and the standardized testing process of coinfection is still unavailable. It is difficult to distinguish bacterial or fungal infections from existing viral pneumonia based on clinical and radiological performance (Azoulay et al. 2020). In addition, there are articles indicating that calcitonin may also be an auxiliary means for detecting whether there is bacterial or fungal coinfection (Wiegers et al. 2019) as the concentration of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 increases, which results in the massive production and release of parathyroid-derived calcitonin during bacterial infection. However, the synthesis of parathyroid-derived calcitonin is inhibited by (TNF) -γ, which secretion is increased during viral infection (Lippi and Plebani 2020). Therefore, the large increase of calcitonin will reflect the overlapping infection of bacteria in patients who have developed serious diseases, leading to the complication of clinical conditions (Martins-Filho et al. 2020). In addition, the microbiological examination is a practical way for diagnosis, especially sputum culture (Budayanti et al. 2019). However, taking sputum or blood samples from SARS-CoV-2–infected patients may pose a significant risk to biological sample collectors and laboratory technicians as the SARS-CoV-2 does not only spread through respiratory droplets and direct contact but also through virus-laden aerosols (Peng et al. 2020; Xu et al. 2020). Therefore, it is very necessary to establish a standard detection measure for the coinfection of bacteria or fungi and to provide adequate protective measures for relevant persons.

Conclusion

The coinfection between different microorganisms and SARS-COV-2 is a serious problem in the COVID-19 pandemic. However, there are few reports about SARS-CoV-2 coinfects with bacteria, fungus, and other viruses. The clinical data of SARS-CoV-2 coinfection are of great value in guiding evidence-based treatment of COVID-19. Patients with severe SARS-CoV-2 infections, including other viruses, bacteria, and fungi, have a significantly higher rate of coinfection than those who have not been seriously affected. Therefore, under

the premise of not jeopardizing the safety of laboratory personnel, it is necessary to strengthen the investigation of the coinfection of patients with COVID-19. It provides a theoretical and factual basis for precise treatment, accurate prevention, and treatment of infectious complications and an effective reduction of the mortality rate of coronavirus-infected patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The present work did not include any animal or human samples or patient data.

Consent to participate and consent for publication All authors and institutions where the work was carried out have approved the content and authorship of the manuscript.

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