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Severe Acute Respiratory Syndrome Coronavirus-2 and Influenza Virus Co-infection: Friend or Foe?

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ABSTRACT

Abstract: Currently, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the etiological factor of the coronavirus disease 2019 (COVID-19) pandemic condition. Based on the evidence, the number of infected patients is increasing around the world. SARS-COV2 infection could show both pulmonary and extra-pulmonary manifestations in patients. The Influenza virus is the cause of influenza disease which is a seasonal viral disease with clinical symptoms similar to COVID-19. Influenza could be a major public health problem throughout the world, as each year approximately 10%-20% of the world's population are infected and is the major cause of death, particularly among the elderly. Since influenza has an effective and preventive vaccine, maximizing influenza vaccination has been suggested. Until now (November 20, 2020) COVID-19 doesn't have any approved drug or vaccine, So the universal influenza vaccination will probably decrease the health burden of this co-infection. In this review, we will focus on the importance of COVID-19 and influenza co-infection in the COVID-19 pandemic era.

Keywords: SARS-COV-2, COVID-19, Influenza, Co-infection

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Introduction

The coronavirus disease 2019 (COVID-19) is a novel disease caused by severe acute respiratory syndrome coronavirus 2 (SARS COV 2) a member of the beta coronavirus genus (1, 2). It emerged in China and promptly widespread around the world. Soon after it was declared as a pandemic disease by the world health organization (WHO) (3, 4). The transmission occurs majorly through person to person in the course of close contact with each other (5-7). The main primary symptoms are fever, cough, and fatigue, or myalgia (8, 9). In some cases, gastrointestinal presentations were reported (10, 11). Prevention and early diagnosis are the key strategies to decrease the burden of this pandemic (12).

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Influenza is a seasonal, highly transmissible viral disease and its activity peaked in the Northern hemisphere in the autumn and winter months (13, 14). The clinical manifestations of influenza syndrome is characterized by fever, headache, cough, sore throat, myalgia, chills, nasal congestion, generalized weakness, and loss of appetite remain for 14 days(15, 16). Vaccines are the most cost-effective preventive measure, which reduces the risk of influenza infection (17-19).

At the time of the COVID-19 pandemic, the number of patients who co-infected with SARS-CoV-2 and the influenza virus in some areas may be increased as the flu season arrives, so the COVID-19-influenza co-infection serves as a major concern for public health. In this review we decided to clarify the importance of this co-infection.

SARS-CoV-2 infection

SARS-COV-2 is a new member of human coronavirus, which was initially identified in Wuhan, China in December 2019(20). World health organization declared "COVID-19" as the name of SARS-COV-2 disease on 11 February 2020(21). As COVID-19 promptly infected many people around the world, this outbreak quickly becomes a global health emergency with 50,676,072 confirmed cases and 1,261,075 deaths reported to date (22, 23).

Different members of the coronavirus family show variable clinical manifestations due to structural differences in virus proteins, affecting tropism and replication (24, 25). Coronaviruses surface spike (S) protein is responsible for virus entry to target cells by interacting with cell receptors, angiotensin-converting enzyme-2 (ACE2) (26, 27). Angiotensin-converting enzyme-2 expresses on various cells including, lung (28), liver cholangiocyte, kidney, testis, colon, esophagus keratinocytes, brain, heart, and bladder (29-31). Binding of S-protein to ACE2 contributes directly to viral pathogenesis (32). Upon viral binding to ACE2, the virus may be entering to cell and the positive-sense viral genomic RNA is then translated by the host cell, yielding the viral replication machinery and infection (33).

SARS-COV-2 infection is divided into three stages: stage I, an asymptomatic incubation period with or without detectable virus; stage II, symptomatic period but not severe and the virus is detectable; stage III, the symptomatic stage with high viral load and severe respiratory manifestations (34). After initial coronavirus infection, immune responses provoke to controlling the viral infection. Genetic differences could be accounted for various immune responses among individuals (34)

The main clinical symptoms of patients are fever, cough, and fatigue, or myalgia (9). Some patients show gastrointestinal presentations like vomiting and diarrhea (10, 35, 36). Whereas some of them have neurological symptoms like unstable walking and headache (37, 38). So, SARS-COV2 infection could show both pulmonary and extrapulmonary manifestations in patients (39, 40).

Influenza virus infection

The Influenza virus is a member of the Orthomyxoviridae family, which contains negative-sense single-stranded RNA with eight segment genome tightly enclosed by nucleoprotein (41). The haemagglutinin (HA) and the neuraminidase (NA), are the two main superficial glycoproteins that protruded above the viral envelope (42). Haemagglutinin initiates infection by attaching the virus to sialic acid (SA) or other

receptors on the surface of target cells and has a key role in endocytic membrane fusion (43, 44). While NA plays an essential role in the final stage of infection by its receptor destroying function (45, 46).

Influenza viruses enter the host bodies through the oral or nasal cavities (47). These viruses initially encounter by the mucosa that covers the respiratory tract. If the virus could be reached the mucous layer, it will then attach and invade the respiratory epithelial cells (48-50). Influenza viruses can infect diverse host species, including humans, swine, and poultry (51). Three main types of influenza viruses are (A, B, and C), that are among the most common causes of human respiratory infections(52), whereas based on the US Centers for Disease Control and Prevention (CDC) and WHO publications, mortality and morbidity caused by influenza virus have been estimated 298000 to 646000 seasonal influenza-associated deaths worldwide in 2015(44, 53). The major clinical presentations of influenza infection are, fever, cough, dyspnea in humans, like the symptoms of influenza A (H1N1) disease in the 2009 pandemic (54, 55). The activity and severity of influenza viruses are varied from different seasons and also different regions (56-58). According to the CDC announcement, each year the influenza epidemic substantially affects health care systems worldwide and has resulted in an estimated 12000 to 61000 deaths since 2010 just in the united states (59).

SARS-CoV-2 and Influenza co-infection

In the time of the COVID-19 pandemic, the number of patients who co-infected with SARS-CoV-2 and the influenza virus specifically type A, in some regions may be elevated as the flu season arrives (60). Among the various studies conducted from the onset of the SARS-COV2 pandemic era and investigated the multiple viral co-infections, influenza A virus was one of the most frequent pathogens causing co-infection among patients with COVID-19(61).

Based on a study by Iranian researchers on 105 COVID-19 positive dead patients, they found influenza co-infection 22.3% while the other viruses like Adenovirus, Respiratory syncytial virus (RSV), and parainfluenza possessed the lower percentages (62). In the study conducted by Ding et al, 3 out of 115 confirmed COVID-19 patients had influenza co-infected patients (63). In another research among 128 hospitalized patients with COVID-19 pneumonia, 64 co-infected patients were detected that 54 (84.4%) were co-infected with influenza A, and 10 (15.6%) with influenza B (64). In pediatric patients were found to have a 15% rate of SARS-COV2 co-infection with influenza A and B viruses (65).

Although SARS-COV2 and influenza virus are immensely different pathogens, they can have overlapping clinical courses. Particularly, SARS-COV2 infections may show similar symptoms as that of influenza disease, which is known as “Flu-like symptoms” (66, 67). On the other hand, as COVID-19 shows non-specific upper respiratory tract presentations, the differentiation between SARS-CoV-2 and other respiratory infections like influenza is not just a simple issue (68).

It is still not understood whether COVID-19 co-infection with other viral infections increases the severity of illness or not, but based on several investigations, since COVID-19 and influenza co-infection result in higher levels of pro-inflammatory cytokines which contributes to frequent cytokine storm may result in more severity and mortality rate in patients(60, 62, 64, 69, 70). In a study conducted by Stowe et al, a total of 43.1% of patients with coinfection lose their life compared to 26.9% of those who tested positive only for SARS-CoV-2(71). Another research by Zhang et al concluded that co-infection with other viruses can increase the rate of mortality (72).

Both viruses are primarily transmitted by respiratory droplets and close contact (73). The average duration of viral shedding was longer for patients with influenza coinfection (17 days vs 12 days) (64). While in another study the duration of viral shedding between two groups of influenza co-infected patients and patients without co-infection, were without differences (74).

One study indicated that the clinical presentations of patients with COVID-19 and influenza virus infection were similar to those who only had COVID-19 infection, but the symptoms of nasal tampon and pharyngalgia may be more prone to appear for those coinfection patients (63). Another research also found that the coinfection with influenza was not associated with an elevation in the severity of COVID-19 pneumonia (64).

Inversely, several studies showed that SARS-COV2 co-infection with other respiratory viruses may decrease the severity of the disease. It has been suggested that when SARS-COV2 infections are initiated simultaneously or after infection with another respiratory virus like influenza, it can be easily suppressed due to the activation of the host immune system. In these cases, SARS-COV2 infection is limited even if the patient is infected by a large inoculum of virus (75). Concordant with this study, another investigation found that this co-infection was associated with decreased risk of severity and death rate to 0.52 fold among COVID-19 confirmed patients (76).

Diagnosis and treatment

SARS-CoV-2 coinfection with different pathogens may prevent accurate disease diagnosis (77). It is highly suggested to adding SARS-CoV-2 to the routine diagnostic systems during the COVID-19 pandemic (78). Since both diseases have common symptoms of fever and cough, it will be difficult to distinguish COVID-19 from other respiratory viral infection only by clinical manifestations (63, 79), so they should screen for the common respiratory pathogens with proper diagnostic tests (80). To make the best decision about treatment, It's reasonable to consider testing all patients presenting with Flu-like illness for different respiratory pathogens along with SARS-CoV-2(78, 81).

As the diagnostic kits are not sufficient enough and because of the low sensitivity of tests, coinfection cases like influenza virus can be misdiagnosed, so poses several challenges to the diagnosis and treatment of COVID-19(64, 82). In the study conducted by Yu et al, among 128 hospitalized patients with COVID-19 pneumonia, 64 cases were co-infected with influenza A and B (54(84.4%) and 10(15.6%), respectively). Among influenza coinfected patients, those treated with lopinavir/ritonavir showed faster pneumonia resolution during 2 weeks after symptom initiation (64).

Prevention

In the pandemic of COVID-19 and with the onset of the influenza season, the high incidence of this co-infection is inevitable (63). As COVID-19 doesn't have any successful drug or vaccine until now (November 20, 2020), So maximizing the universal influenza vaccination will probably decrease the hospital stays due to complications especially in the at-risk groups, and therefore facilitate the hospital and health systems from the burden of dealing with both COVID-19 and influenza at the same time(71, 83, 84).

Unfortunately, according to the CDC announcement, Flu vaccination coverage among adults was 37.1%, a decrease of 6.2 percentage points from the previous flu season in the 2017-2018 season (85). People should be encouraged to take vaccines against pathogens causing respiratory infections like influenza, to reduce the risk of co-infection, diagnostic difficulties, and inappropriate managing in the context of antiviral therapy and infection control (86).

Up to now, only a few studies have investigated the relationship between influenza vaccination and COVID-19 outcomes. All of these studies declared the role of influenza vaccination in reducing the risk of COVID-19 mortality rates (87-89). Although the exact mechanism of this relationship is not clear, according to previous studies, vaccination against one microorganism may affect the host's response to other infectious agents (90-97).

Conclusion

We cannot ignore the co-infection of COVID-19 with other respiratory viruses, like the influenza virus, to make a point that we could provide the best and the most efficacious treatment to the patients. However, it is not clear COVID-19 and influenza lead to more severe disease or not, physicians and health care workers in epidemic regions, should pay more attention and consider COVID-19 as a potential diagnosis especially in combination with other viral causes, to provide the most effective treatment for patients. Actually, additional studies are needed in this area.

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