**ORIGINAL ARTICLE**

# Comparative Study of Clinical Symptoms, Laboratory Results and Imaging Features of Coronavirus and Influenza Virus, Including Similarities and Differences of Their Pathogenesis

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## ABSTRACT

COVID-19 has turned into one of the biggest healthcare challenges in the world. COVID-19 disease causative agent (SARS-CoV-2 virus) causes acute pneumonia and has claimed the lives of more than one million people around the world. One of the challenges the physicians face is the similarities between the symptoms of COVID-19 and influenza infection. Both viruses cause severe infection of lungs, but influenza virus has different types and some types are highly pathogenic; even more than coronavirus. Children and pregnant women are more vulnerable to influenza virus and children may experience harsher symptoms. COVID-19 symptoms on the other hand are milder in pregnant women and children. Influenza although an important pathogen of respiratory tract is mostly a seasonal virus and is in this regard dissimilar to SARS-CoV-2 virus. 1918 Influenza pandemic which claimed the lives of about 50 million people, remains the worst outbreak human beings have ever experienced. Avian flu (H5N1) has created pandemics as well. At the present study, comparative study of clinical and laboratory symptoms and imaging features of coronavirus and influenza virus and also similarities and differences in their pathogenesis is carried out.
**Keywords**: Clinical Symptoms, Laboratory, Coronavirus Imaging, Influenza

## INTRODUCTION

During the late December 2019, a new pneumonia emerged in Wuhan, china which was caused by a novel mutant coronavirus[1]. Scientific analysis indicated that this novel virus is genetically closely related to SARS coronavirus (SARS-CoV) and after creating cold-like symptoms can cause severe respiratory syndrome in infected patients. Until mid-august 2020, more than 20 million people around the world had contracted COVID-19 and about 900000 of them had lost their lives. According to statistics, mortality rate of SARS-CoV-2 infection equals 4.6% and about 5000 of infected individuals lose their lives dail[2-7].

COVID-19 symptoms highly resemble influenza symptoms and differential diagnosis of SARS-CoV-2 infection from influenza virus infection based on their clinical symptoms has become the focus of much attention. Influenza viruses are one of the most important causes of respiratory infections[8] . Since 1700, several influenza epidemics have taken place. For instance in 1889, 1918, 1957 and 1967 influenza outbreaks have occurred[9]. In 1957 this virus was responsible for the deaths of 66000 people in the United States[10]. Influenza is the worst recorded pandemic; during 1918 pandemic almost 546000 patients in the United States, and more than 50 million patients around the world succumbed to death because of this disease[10,11]. It is highly probable that a new mutant influenza virus emerges and creates yet another epidemic with high mortality rate[3,9,12,13]. In the United States, this disease resulted in hospitalization of about 959000 patients and deaths of 79000 patients during a two-year period[14]. During cold seasons, influenza mortality rate can rise dramatically[10,11]. This virus has different types with different prevalence and symptoms; type B influenza viruses can periodically cause major outbreaks. Type C influenza viruses are endemic and sporadically result in mild respiratory ailments. Type A influenza viruses result in variable death rates and generally have greater mortality risks. Pathology results indicated extensive histological modification and damages due to influenza infection and the images of pre- and post-infections differ hugely. Simultaneous or secondary bacterial pneumonia which are highly prevalent in severe influenza infections can complicate pathological analysis[9,15-19].

Considering the mentioned facts about influenza, Comparative study of influenza virus and coronavirus can contribute to better understanding of these two viruses and also improves therapeutic approaches; owing to the fact that pathological and clinical manifestations of influenza infection can also be observed in coronavirus infection. At the present study, scientific databases such as Nature, Medline, Pubmed, WHO NCBI and PsycINFO were searched thoroughly and published papers were reviewed. Searching keywords such as COVID-19 virus, influenza, viral infection, influenza types, differences between influenza and corona etc. were used and clinical records, clinical symptoms and laboratory results were analyzed.

**Comparison of COVID-19 virus and influenza virus**

**COVID-19:** Until December 2019, six pathogenic coronavirus species were identified: HCoV-229E, HCoV-NL63 of genus *Alpha*; and HCoV-OC43, HCoV-HKU1, MERS-CoV and SARS-CoV of genus *Beta.* With the addition of SARS-CoV-2 virus, currently seven types of coronavirus pathogens exist[9,20] . On December 31st 2019, World Health Organization (WHO) was informed of a pneumonia outbreak with unknown causes in Hubei province, China. Until January 3rd, 44 cases of this disease were reported to WHO by China. This outbreak initiated from seafood wholesale markets of china and on January

7th 2020, Chinese scientists identified the disease causative agent as a type of coronavirus and this disease was named 2019-nCoV or COVID-19[21,22,23]. COVID-19 virus is genetically similar to bat coronavirus (BatCoV RaTG13)[24,25]. Coronaviruses can affect a wide range of hosts, including birds, domestic animals and mammals[9,20].

**Influenza:** Influenza viruses belong to the family Orthomyxoviridae (negative strand RNA viruses) and measure 80–120 nanometers in diameter[26]. Influenza viruses are divided into three genetically close types. Among these three types, Type A influenza is the most dangerous one and is highly pathogenic[27,28]. Based on the antigenic properties of their surface glycoproteins, neuraminidase (NA) and hemagglutinin (HA) , Type A influenza viruses are further divided into subtypes. So far 16 HA and 9 NA subtypes have been identified[29]. Up to the present time, thousands of mutations have occurred in influenza viruses. WHO has issued specific guidelines for naming novel influenza viruses; according to which combinations of HN and numbers are used for naming different strains of influenza viruses (Subtypes are named by combining H and N with numbers). H1N1 influenza (type A) is more pathogenic compared to other influenza viruses. Currently, influenza viruses culpable of seasonal epidemics around the world are A/H1N1 and A/H3N2[28,29]. Types A and B influenza viruses have similar structures; however, type C influenza viruses are structurally slightly different from them. Type A and B viruses include eight gene segments; each one encodes at least one important viral protein and contributes to viral pathogenesis[26]. Influenza infects an expansive range of hosts including humans (mammals), birds and reptiles and primarily causes respiratory and alimentary ailments. Main types of influenza viruses (A, B and C) each have a specific host range and pathogenesis. Types B and C influenza viruses are isolated almost exclusively from humans (Type B influenza viruses are isolated from other vertebrates and type C influenza viruses are isolated from swine and canines)[15,30]. Type A influenza viruses infect a wide range of warm-blooded animals such as birds, swine, horses, humans and other mammals. Avian flu virus and swine flu virus are mutant forms of type A influenza viruses[29].

Table 1 comparison between common traits of SARS-CoV-2 and influenza viruses

| Parameters | COVID-19 | Influenza |
|---|---|---|
| **Structure and Family** | Coronaviruses belong to family Coronaviridae and are round, enveloped viruses and are among the biggest positive strand RNA viruses. Coronaviruses are divided into four genera *Alpha*, *Beta*, *Gamma* and *Delta*. SARS-CoV-2 measures approximately 500 nm in diameter [9, 20] | Influenza viruses belong to family Orthomyxoviridae and are negative single strand RNA viruses with segmented genomes. Influenza viruses measure 80-130 nm in diameter [26] . RNA is encapsulated in nucleoproteins and therefore forms a ribonucleotide-nucleoprotein complex. |
| **Hosts** | Coronaviruses have an expansive host range including birds, domestic animals and most mammals (humans, camels, bats etc.). They primarily cause respiratory diseases in their hosts. Some coronavirus species are limited to specific hosts, however most coronaviruses due to mutations can gain the ability to transmit to new hosts [9, 20]. | Influenza viruses infect a wide range of hosts including humans (mammals), birds and reptiles. Type B and C influenza viruses are almost exclusively isolated from humans, though type B influenza viruses were isolated from other vertebrates and type C influenza viruses were isolated from swine and canines [15, 30] . Type A influenza viruses are capable of infecting a vast range of warm-blooded animals such as birds, swine, horses, humans and other mammals [29] . |
| **Important types** | SARS and MERS are two important types of corona infections.<br>COVID-19 virus is genetically similar to bat SARS-like coronaviruses bat-SL-CoVZC45 and bat- SL-CoVZXC21(about 88% genetic similarity). Genetic similarity of COVID-19 to SARS-CoV-1viruses is 79% and to MERS-CoV is 50% [24, 25]. | Influenza viruses are divided into three types of A, B and C [15, 30]. The most dangerous type is type A which is highly pathogenic. Types A and B viruses are structurally similar, whereas type C influenza viruses have different structures. Types A and B viruses contain eight genetic segments; each one encodes at least one vital viral protein [15, 27, 30]. |
| **Outbreaks and prevalence** | Mortality is age-related. Corona infection results in more deaths in the elderly. In the United States, corona infection has a 30% mortality rate in individuals over 85 years old and the mortality rate for people between 75-84 years old equals 27%. Severe signs and symptoms are rarely recorded in the youth, infants and children [26, 27]. | Influenza has a high mortality rate among the elderly, infants and patients with chronic illnesses. Individuals over 65 and under 5 years old are at higher risk of infection and death due to influenza [10]. In addition to yearly prevalence in winters, influenza outbreaks can sometimes occur in other seasons [12, 13]. |
| **Environmental durability** | Coronavirus has more pathogenicity in low-humid, dry and cool climates. In temperatures above 30°c, its durability reduces to a few hours. Coronavirus infection has been reported from most regions of the world, but increased temperature and humidity can reduce its pathogenicity. Coronavirus infection prevalence is not latitude-related and its latency period is between 3 and 14 days [34-37] . | In low humidity and temperatures below 4°c, durability of virus increases. In temperatures above 30°c viral population decreases dramatically. Influenza pathogenicity increases at high latitudes. In the tropics influenza has low pathogenicity. Influenza prevalence is latitude- related. Influenza latency period is between 2 and 5 days [16, 31-33] . |

**Environmental durability:** Coronavirus has higher pathogenicity in low-humid, cool and dry climates. At temperatures above 30°c, its survival rate reduces to only a few hours. Coronavirus infection is not latitude- related and coronavirus infection has been reported from most regions of the world. Meanwhile, increased temperatures and

humidity can reduce infection rate. Coronavirus prevalence is not latitude-related and its latency period is between 3 and 14 days is reported to be[34-37] .

Influenza virus has higher durability in low humidity (about 20 to 40). Influenza durability increases at temperatures below 4ºc. Influenza pathogenicity is latitude-related and increases at high latitudes. In the tropics, influenza has lower pathogenicity. Membrane structure of influenza virus is sensitive to heat and in temperatures above 30ºc viral population reduces dramatically. Influenza is most prevalent in winter (dry and cold weathers), but due to their low weights viral particles remain adrift in air for several hours. Latency period of influenza is between 2 and 5 days[16,31,32,33] .

**Transmission rate and routes:** So far two main routes of coronavirus transmission have been identified; direct transmission (via cough, sneeze and breathing aerosols) and indirect [contact] transmission (via touching nose mucus, mouth and eye)[21].

Transmission via eye has not been proven yet, but analyses of infected samples have indicated that COVID-19 transmission is not limited to respiratory tract[38]. Via aerosols or saliva, coronavirus may be transmitted from human-to-human directly or indirectly[39] . Quantity of viral particles in the air is a determining factor in viral transmission; viral particles stick together in roofed populated areas and can be transmitted in large numbers[40,41]. Therefore, wearing facemasks is necessary. Unfortunately, this virus is highly pathogenic and can be transmitted from asymptomatic patients as well[42]. Airborne and fecal-oral transmissions that have caused public concerns need further investigations and proofs. Nevertheless, COVID-19 in most cases is transmitted via respiratory droplets (micro droplets)[43,44].

Influenza can also be transmitted from human-to-human directly and indirectly (via contact transmission). Direct transmission, is mostly done via micro droplets, or saliva and contact transmission occurs when healthy people come into contact with bodily secretions of infected individuals. Influenza virus can be transmitted in large numbers in roofed populated areas[45-48].

**Comparison of clinical symptoms, laboratory results and imaging features**

**Clinical symptoms and laboratory results:** Clinical signs and symptoms of coronavirus infection mainly include fever, cough, myalgia or fatigue, excess mucus production and headache. Results indicated that 32% of hospitalized patients who suffered from Acute Respiratory Distress Syndrome (ARDS), ultimately required intensive care and 15% of them lost their lives[21]. Another study indicated that almost 20% to 30% of hospitalized COVID-19 patients needed respiratory support in the intensive care unit due to pneumonia. Post-mortem biopsies have indicated severe alveolar damages[49,50]. Other clinical studies show that some patients experience mild symptoms and their radiographs look normal. At the moderate level, patients experience fever, respiratory symptoms and features of COVID-19 infection are apparent in their radiographs. At the third level, patients suffer from acute dyspnea, less than 93% oxygen saturation, respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failures[51]. In severe cases, COVID-19 can be accompanied by acute respiratory distress syndrome (ARDS), septic shock and sepsis, acute kidney injury and severe cardiac injury[52]. Laboratory results of COVID-19 include lymphopenia and increased lactate dehydrogenase, aspartate aminotransferase, alanine transaminase, blood urea and creatinine and erythrocyte sedimentation rate (ESR) levels. In more severe cases, excessive lymphopenia and increased inflammatory cytokines can also be observed[21,51].

Hospitalized influenza infected patients suffered from clinical symptoms such as sudden high fever, running nose, cough, headache, weakness, upper respiratory tract inflammation and tracheitis. In mild cases, which are usually the result of types B and C influenza infections, post-fever pneumonia is not clinically significant. Acute symptoms and fever usually last for 7 to 10 days. Weakness and fatigue on the other hand may continue for weeks. People may contract this disease at any age, but it has high prevalence among school-age children. Disease severity in infants, the elderly and patients with underlying conditions is higher[35,53,54]. Avian flu virus (H7N7) causes pulmonary inflammation which resulted in great number of deaths in 2003. It was one the deadliest viruses of that year[54,55].

Following laboratory results of influenza infections were recorded: leukopenia, thrombocytopenia, increased aspartate aminotransferase, alanine aminotransferase, creatine phosphokinase (CPK) and neutrophil. Laboratory results vary among different types of influenza. A recent clinical study about H5N1(avian flu) human infections demonstrated that compared to control group, peripheral levels of cytokines and chemokine are elevated in patients who suffered from seasonal influenza infection[33,51,53].

**Imaging features:** Patients who suffer from mild forms of coronavirus infections did not require hospitalization at the beginning and their radiographs were normal. But clinical signs and symptoms worsened as the disease progressed and the lower respiratory tract involvement occurred during the second week. Therefore, all patients should be closely examined[56,57] . CT scans indicated bilateral pneumonitis and ground-glass opacities with significant distribution of inflammation in lower lobes. Furthermore, Broncho vascular thickening and bronchoconstriction are among the side effects of this viral infection[58,59,60]. These symptoms closely resemble pneumonia symptoms. Radiographic features of influenza virus pneumonia include ground-glass opacities and Broncho vascular thickening. In some cases bronchopneumonia and local reticular shadows are also visible[61,62].

Comparison of clinical symptoms, laboratory results and imaging features

| Parameters | COVID-19 | Influenza |
|---|---|---|
| **Clinical symptoms** | On different levels of sickness, different symptoms have been observed. In mild cases patients suffer from low fever and mild weakness but pneumonia does not occur.<br>In severe cases, 40ºc fever, dyspnea or hypocalcemia, ARDS, stomachache and loss of appetite are experienced. Excessive phlegm production and pulmonary hemorrhage rarely took place [51]. | Sudden high fever, running nose, headache, weakness, upper respiratory tract inflammation and bronchitis. Depended on severity of their infections, influenza infected patients suffer from mild to severe symptoms, but in all cases sudden fever and respiratory tract inflammation are apparent. In mild cases, pneumonia and loss of appetite are not recorded.<br>Influenza pneumonia symptoms such as blood-streaked sputum have also been recorded. Excessive phlegm production and pulmonary hemorrhage were also observed [21] . |
| **Laboratory signs** | Lymphopenia, increased LDH, aspartate aminotransferase, alanine aminotransferase, blood urea and creatinine. Most patients had increased CRP and erythrocyte sedimentation rate (ESR) and normal proclcitonin.<br>In severe cases, excessive lymphopenia and increased inflammatory cytokine levels were observed.<br>The deceased: extremely high levels of neutrophils, D-dimer, blood urea and creatinine. | Leukopenia, thrombocytopenia, increased aspartate aminotransferase, alanine aminotransferase and creatine phosphokinase (CPK) and neutrophils are recorded. Laboratory results differ slightly among various types of influenza. In severe cases, inflammatory cytokine and chemokine levels are high [33, 53]. |
| **Radiological features** | Bilateral diffusion of reticular shadows and ground-glass opacities (defining attribute). radiological abnormalities can be present in a significant number of patients [58, 59]. | Pneumonia due to influenza A virus shows multiple irregular areas of consolidation (arrows) along the Broncho vascular bundles and diffuse GGO (arrowheads) with interlobular septal thickening in both lungs.<br>Radiographic findings of influenza pneumonia in adult patients included ground-glass opacities. In bronchopneumonia patchy reticulonodular opacities are visible [61, 62]. |

**Pathology:** Squamous epithelial cells of pharynx, trachea, bronchus and pulmonary alveolus are the main locations of viral reproduction. Pathological studies have indicated that coronavirus infection invariably results in inflammation and death of pulmonary cells of patients. Due to the involvement of epithelial cells of upper respiratory tract, reticular shadows and ground-glass opacities are visible in CT images of corona infected patients. Majority of COVID-19 patients only experience mild symptoms or are asymptomatic. On average 14% experience severe forms which require hospitalization and respiratory support and 5% would require intensive care. In most cases disease manifests itself with fever and does not create any respiratory complications; however pulmonary tissue damages and various levels of abnormality later occurred in all the patients and could be observed in lung scans[21,49,51].

About 20% to 30% of hospitalized COVID-19 patients had pneumonia and require intensive care and respiratory support. Post-mortem biopsies performed on a patient who succumbed to death due to ARDS, indicated severe pulmonary alveolus and squamous cells necroses[50,63].

Non-fatal influenza infections mainly infect and inflame upper respiratory tract and trachea; however in addition to these, fatal infections are also accompanied by pneumonia [64, 65]. Epithelial tissues of trachea, bronchus and pulmonary alveolus compromise the main infection sites of influenza virus. Autopsy revealed that the concurrence of secondary bacterial infection (beside fatal influenza infection) further complicated influenza patients' situation. In acute phase, multifocal destruction and epithelial cells deaths is apparent. In the majority of cases only the basal layer of epithelium remains in place. Considerable redness and swelling of pulmonary epithelium covered with mucus are found in acute phases. In 50% of severe cases, due to pulmonary cells necroses (which are probably attacked by macrophages) hemorrhage occurs also. These structural modifications of epithelium are usually unevenly distributed. During the initial phase of infection, neutrophils are absent in lymph, however as the disease progresses, neutrophils immigrate into lymph. Modifications of smaller airways are similar to those of bigger ones. In most cases neutrophils are found in bronchiole lumen and airways may be obstructed by edema, fibrin and neutrophils [25]. Congestion and sub-mucosal capillary thrombosis have been observed in severe influenza infections and bronchioles walls are sometimes completely necrotic. Focal epithelial necrosis and total necrosis of capillary wall, bronchial hemorrhage and pneumonia are reported from deceased patients [65, 66].

**Treatment:** Coronavirus infection treatment involves antiviral drugs. Currently, no specific treatment for COVID-19 is available and preventive measures such as quarantine cities and controlling infection are of up most importance. Recently FDA has recommended prescription of Ritonavir, Lopinavir and antimalarial, however the complete efficacy of these drugs for treating this disease remains unproven[62-67]. Furthermore, due to its side effects, interferon is not advised as a first-line drug. Antiviral drug of Favilavir has also been used for treating COVID-19. Recently Remdesivir and Avifavir have been use for treating COVID-19 and had yielded acceptable therapeutic results, but these drugs are merely alleviating drugs and are not considered as complete treatments. Moreover,

depended on the patient's condition, prescription of corticosteroid alongside these drugs is recommended by physicians[68-70]. Data related to production and testing of coronavirus vaccines need further analysis. Although some countries and organization have presented useful vaccines, but these vaccines have not been used routinely and for prevention and treatment of COVID-19[71,72,73].

Effective measures against influenza types A and B include infection prevention via vaccination or prescription of antiviral drugs for preventive or therapeutic purposes[37]. Studies involving healthy middle-aged people indicated that influenza vaccine is 70% to 90% effective in preventing type A influenza but its efficacy is relatively low in the elderly. Nevertheless, vaccine usually provides immunity for several months. Constant mutations of viral genomes (which gradually enable virus to escape immunity) in type A virus, is the reason that effective vaccines lose their effectiveness after several years[21]. Thus, yearly vaccination is recommended for at-risk individuals such as patients with underlying diseases and the elderly[38,74]. Fortunately, various vaccines for influenza prevention have been developed and presiding over prevention and control of influenza vaccination is an important program of WHO[39].

Antiviral drugs can have preventive and controlling effects, but in order to prevent the disease in severe cases they should be prescribed in high doses. Channel blocker medications such as Amantadine and Rimantadine are considered as highly effective drugs against influenza A; however resistant strains are found in almost one-third of the patients who receive these medications. Newly developed neuraminidase inhibitors such as Zanamivir and Oseltamivir have proven effective against both types A and B influenza viruses[21,40-44].

## CONCLUSION

Coronavirus and influenza virus signs and symptoms highly resemble each other. Both viruses infect lungs and created similar symptoms. Severity of symptoms varies in different types of influenza infections. Children and pregnant women are more vulnerable to influenza virus and influenza infection creates more severe symptoms in children. In conntrast, COVID-19 symptoms are less severe in children and pregnant women. In many cases dangerous types of influenza are more fatal than coronavirus; in the United States type A influenza has claimed more lives than coronavirus. Laboratory results and radiographic features of influenza and coronavirus are very similar. Coronavirus has higher prevalence compared to influenza virus and survives in the environment for more extended periods of time. One point with regard to initial symptoms and influenza virus pathogenesis can be mentioned. Influenza in many cases manifests itself with a sudden high fever; corona on the other hand has a longer latency period and can remain latent for up to 14 days. Tremble, running nose with dry and wet coughs are more commonplace in influenza infection. Dry coughs and dyspnea are common in coronavirus infection; pulmonary infection progress gradually and ensuing pneumonia can damage the lungs severely. Running nose is also sporadically reported in coronavirus infection.

Even with the presence of coronavirus, influenza still holds its position as a major health threat. Its constant, rapid and unpredictable mutations complicate vaccination strategies and programming. It is of vital importance that further pathological studies and autopsies of coronavirus and fatal influenza virus (as a result of endemic, seasonal or zoonotic strains such as avian flu virus) victims be performed in the future. Precise analysis of infection-resultant histological modifications in addition to molecular, genetics, viral and immunological studies can further advance our knowledge of different pathogenesis of coronavirus and influenza virus.

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