Peer-reviewed version available at *Archives of Iranian Medicine* **2020**, *23*, 239-243; doi:10.34172/aim.2020.04

Co-infection of coronavirus disease 2019 and influenza: A report from Iran

Zohre Khodamoradi[1, 2], Mohsen Moghadami[3], Mehrzad Lotfi[4]

Abstract

Background: On late December 2019, a viral pneumonia known as coronavirus disease 2019 (COVID-19), was originated from China and spread very rapidly in the world. Therefore, COVID-19 became a global concern and health problem.

Methods: We presented four patients in this study. They were selected from patients who presented with pneumonia symptoms and were suspicious for COVID-19 and referred to the intended centers for COVID-19 diagnosis and management of Shiraz University of Medical Sciences in the south of Iran. Two nasopharyngeal and oropharyngeal throat swab samples were collected from each patient and tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) detection by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR), and also samples were sent for influenza viruses and all the respiratory panel.

Results: In the present report, four patients were diagnosed in the starting days of COVID-19 disease in our center in south of Iran with co-infection of SARS-CoV-2 and influenza virus.

Conclusions: This co-infection of COVID-19 and influenza highlights the importance of considering SARS-CoV-2 PCR assay regardless of other positive findings for other pathogens in the primary test during the epidemic.

Keywords: Co-infection, coronavirus disease 2019, COVID-19, Influenza

Corresponding author: Mohsen Moghadami, MD

Department of internal medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Email: moghadami@icloud.com

[1]Department of internal medicine, Namazee hospital, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Shiraz Geriatric Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[3]Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran

[4]Department of Radiology, Namazee hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Introduction

Coronaviruses are enveloped RNA viruses from *Coronaviridae* family, which can spread in humans and other mammals (*1, 2*). Two epidemics of betacoronaviruses have happened in the world with typical characteristics of a respiratory syndrome, which were named as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in the 21st century. The overall mortality rate of these two epidemics of SARS-CoV and MERS-CoV was 10% and 37%, respectively (*3-6*).

A new betacoronaviruses from *Coronaviridae* family, which was first originated and detected in Wuhan, Hubei, China, in December 2019, caused a cluster of viral pneumonia cases (*2*). The first confirmed case was recognized in the samples of the bronchoalveolar lavage fluid of a patient in Wuhan on January 3, 2020. This viral pneumonia was known as coronavirus disease 2019 (COVID-19) and has spread very rapidly in the world with cases detected in multiple countries (*1, 3, 5, 7*). About 145311 confirmed infected cases are detected, and 5416 death cases are reported till March 14, 2020, in the world, mostly detected in China. The number of infected cases and involved countries increases daily; thus, COVID-19 has become a global public health emergency. One hundred thirty seven countries have experienced COVID-19 up to now (*8*). Moreover, COVID-19 can kill healthy adults.

Peer-reviewed version available at *Archives of Iranian Medicine* **2020**, *23*, 239-243; doi:10.34172/aim.2020.04

Most of the patients infected with COVID-19 in the world presented with fever, fatigue, dry cough, and dyspnea. In addition to these symptoms, some cases were reported with gastrointestinal manifestation such as diarrhea and nausea as the initial presentation of COVID-19 (*1, 6, 9, 10*). As reported in previous studies, the most common finding in lung computed tomography (CT) scan is bilateral multifocal ground-glass opacities, a crazy-paving pattern, and consolidation, which is a typical finding in viral pneumonia. These clinical manifestations are similar to what was found in SARS-CoV and MERS-CoV patients (*6, 9, 11, 12*).

The most common laboratory findings on admission are lymphopenia, thrombocytopenia, leukopenia, and elevated C-reactive protein. Moreover, high levels of alanine aminotransferase, and aspartate aminotransferase are reported (*6*).

This report aims to describe four Iranian cases infected with COVID-19 and influenza simultaneously at the time of referral to the emergency room. We report our diagnostic protocol, clinical manifestation, laboratory data, and radiological findings of these patients with a confirmed COVID-19 infection.

Methods

Diagnostic and confirmatory test

The genetic sequence of 2019-nCoV was shared by Chinese researchers on January 7, 2020 (*13*). Patients who are suspected cases of COVID-19 should undergo testing for COVID-19 by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. Two nasopharyngeal and oropharyngeal throat swab samples were collected and tested for SARS-CoV-2 for each patient using the Chinese Center for Disease Control and Prevention (CDC) recommended Kit (BioGerm, Shanghai, China), following WHO guidelines for RT-PCR (*14, 15*).

Peer-reviewed version available at *Archives of Iranian Medicine* **2020**, *23*, 239-243; doi:10.34172/aim.2020.04

According to the protocol of COVID-19 detection in suspicious patients, samples also should be sent for influenza viruses and all respiratory panels for detection of parainfluenza virus, adenovirus, human rhinovirus, respiratory syncytial virus, *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumonia.*

Patients

The cases presented in this study were patients with confirmed samples of COVID-19 and influenza. The samples were collected from patients who presented with pneumonia symptoms and were suspicious for COVID-19; they referred to the intended centers for COVID-19 diagnosis and management of Shiraz University of Medical Sciences in the south of Iran.

Ethical Statement

The ethics committee of Shiraz University of Medical Sciences approved the study with the ethical protocol code: IR.SUMS.REC.1398.1377.

Data Gathering

The data were gathered by reviewing the patients' medical records, and the documented laboratory data were then submitted in prepared datasheets. The patients' demographic information, including age and gender, were recorded. Moreover, the patients' clinical presentations on admission were also recorded.

Case presentation

Four patients presented with pneumonia and were admitted to a hospital that is the center of COVID-19 diagnosis and management of Shiraz University of Medical Sciences.

On February 24, 2020, a 74-year-old woman (patient 1), who was a case of previous ischemic cerebrovascular accident and hypertension referred to the emergency department of our local center of COVID-19 diagnosis and management of Shiraz University of Medical Sciences. She

Peer-reviewed version available at *Archives of Iranian Medicine* **2020**, *23*, 239-243; doi:10.34172/aim.2020.04

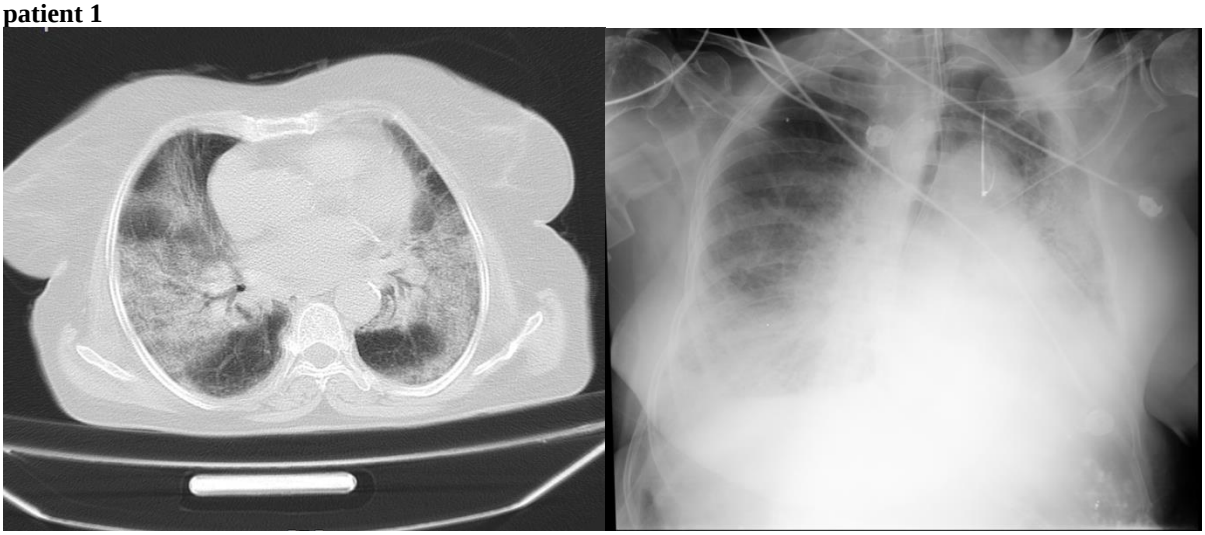
had a history of five days of dry cough, malaise, body pain, subjective fever, headache, and anorexia. She had developed dyspnea and orthopnea one day before admission. She did not report any history of gastrointestinal symptoms. She had no contact with confirmed COVID-19 patients but had contact with patients with cough in a clinic when she had referred to the physician for her routine checkup.

On admission, the physical examination revealed a blood pressure of 70/50 mm Hg, t body temperature of 38.7°C, pulse of 89 beats per minute, respiratory rate of twenty-six breaths per minute, and oxygen saturation of 90%, while the patient was breathing ambient air.

Her chest radiography on the first day of admission showed diffuse infiltrates in both lungs (Fig. 1).

Her swab sample for the detection of influenza viruses was positive. We sent another nasopharyngeal and oropharyngeal samples that were positive for SARS-CoV-2 on RT-PCR assays. This positive test for SARS-CoV-2 confirmed the diagnosis of COVID-19 in this patient, but the respiratory panel was negative.

Figure 1: Sample images of the thoracic CT scans of the lungs and posteroanteriorc chest radiography of patient 1



Peer-reviewed version available at *Archives of Iranian Medicine* **2020**, *23*, 239-243; doi:10.34172/aim.2020.04

The second patient was a 40-year-old healthy man who had travelled to the involved city with COVID-19 with higher number of confirmed cases (Qom) before the onset of his symptoms. Moreover, he stated that he had close contact with his friends who lived in that city. His symptoms started during his stay. Four days after his travel to that city, his symptoms initiated with headache and fever. This implies that the incubation period for COVID-19 may have been three days in this case. About eight hours later, his initial symptoms progressed, and he developed sweating, chills, cough, and severe compressive chest pain. On the second day of illness, he presented with dyspnea, orthopnea, and body pain. In addition to his symptoms, he reported diarrhea on the second day of the disease that lasted for three days. His chest pain worsened, so he returned to Shiraz and was admitted to our local center of COVID-19 diagnosis and management of Shiraz University of Medical Sciences in the fourth day, on February 24, 2020. On admission, he was ill with respiratory distress, sweating, and had a low-grade fever. He complained of very severe compressive chest pain, orthopnea, and body pain.

In the first visit by the physician in the emergency room, the physical examination revealed a blood pressure of 110/70 mm Hg, the body temperature of 35.4°C, pulse of 77 beats per minute, respiratory rate of 20 breaths per minute, and oxygen saturation of 97%, while the patient was breathing ambient air.

His chest radiography showed diffuse and bilateral infiltration in the lungs (Fig. 2). As was detected in patient No. 1, his swab sample for the detection of influenza viruses was positive, and samples for SARS-CoV-2 on RT-PCR assays were positive as well. Thus the second case of co-infection of influenza with COVID-19 was found.

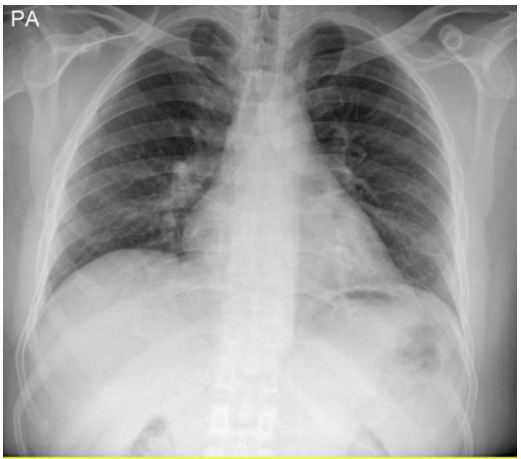
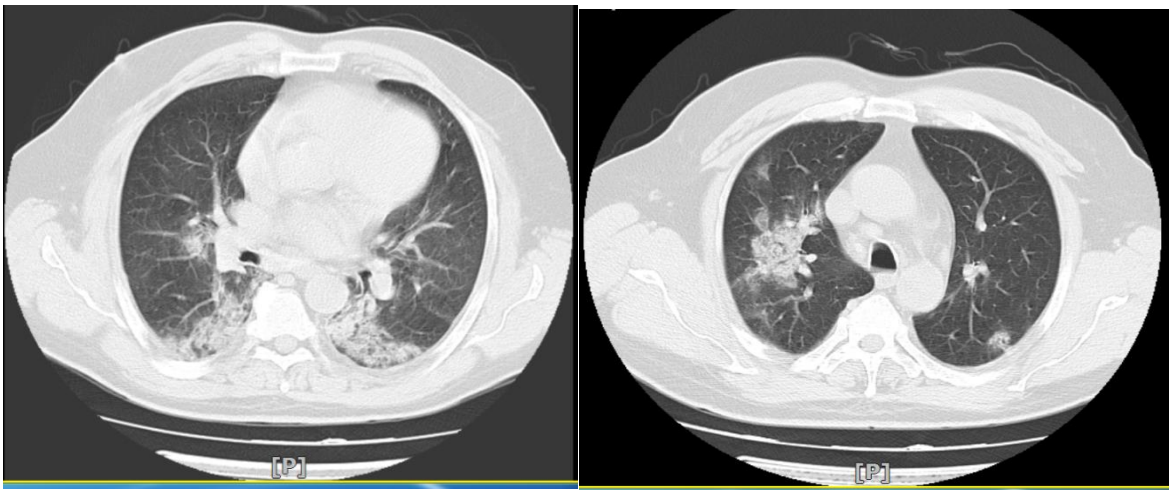


Figure 2: Posteroanterior chest radiography of patient 2

On February 25, 2020, a 64-year-old man presented to our local center of COVID-19 diagnosis and management with a complaint of dry cough, malaise, headache, and subjective fever for about five days. Additionally, he reported that he had dyspnea for a few hours. He did not report any gastrointestinal symptoms or chest pain. On admission, the physical examination revealed a blood pressure of 130/80 mm Hg, body temperature of 37.7°C, pulse of 110 beats per minute, respiratory rate of 99 breaths per minute, and oxygen saturation of 87%, while he was breathing ambient air. Chest radiography taken on the first day of admission was the same as what was found in previous patients; diffuse and bilateral infiltration was detected in the lungs (Fig. 3). As our protocol for all suspicious patients for COVID-19, rapid nucleic acid amplification test for influenza A and B and respiratory panel were sent and his influenza report was positive. Nasopharyngeal and oropharyngeal swab specimens were positive for SARS-CoV-2 on RT-PCR assays. He was the third patient with positive influenza and COVID-19 on admission in our center of COVID-19 diagnosis and management affiliated to Shiraz University of Medical Sciences.

Figure 3: Sample images of the thoracic CT scans of the lungs and posteroanterior chest radiography of patients 3

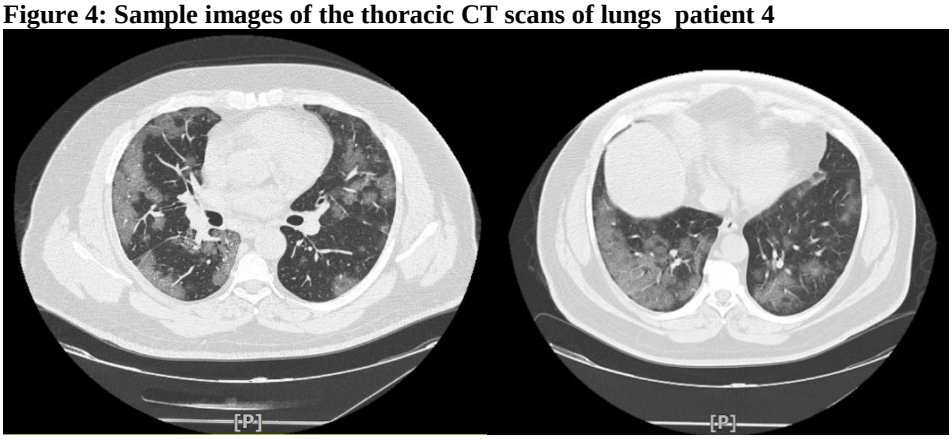


Peer-reviewed version available at *Archives of Iranian Medicine* **2020**, *23*, 239-243; doi:10.34172/aim.2020.04

The fourth patient was a 50-year-old healthy man without any underlying disease who was referred to the center of COVID-19 diagnosis and management on March 2, 2020.

He stated that he had travelled to Qom city about two weeks before the onset of his symptoms. After he returned to Shiraz, he presented with subjective fever, dry cough, and dyspnea on February 30. His dyspnea progressed, so he was admitted in our center. On admission, blood pressure of 120/65 mm Hg was found. He had body temperature of 38.0°C, pulse rate of 85 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 93%, while the patient was breathing ambient air. His chest radiography on the first day of admission showed diffuse infiltrates in both lungs (Fig. 4)

Figure 4: Sample images of the thoracic CT scans of lungs patient 4



On March 4, his positive nasopharyngeal and oropharyngeal swabs that were tested for COVID-19 and influenza confirmed that he had coinfection of COVID-19 and influenza at the same time. All demographic characteristics, clinical features, and laboratory findings of four patients are shown in Table 1.

Table 1: Summary of demographic characteristics, clinical features, and laboratory findings of the four patients presented with co-infection of coronavirus disease 2019 and influenza

Clinical characteristics	Patient 1	Patient 2	Patient 3	Patient 4

Peer-reviewed version available at *Archives of Iranian Medicine* **2020**, *23*, 239-243; doi:10.34172/aim.2020.04

Date of admission	February 24	February 24	February 25	March 2
Age	74	40	64	50
Gender	female	male	male	male
Underlying disease (risk factor)	Yes	No	No	No
Sign and symptoms (on admission)				
Cough	Yes	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes	Yes
Fever	Yes	Yes	Yes	Yes
Body pain	Yes	Yes	No	Yes
Chest pain	No	Yes	No	No
Headache	Yes	Yes	Yes	No
Sweating	No	Yes	No	No
Diarrhea	No	Yes	No	No
Nausea	No	Yes	No	No
Laboratory data				
White blood cell (× 10^9 cells per L)	4.3	4.1	6.2	4
Neutrophil count (× 10^9 cells per L)	3.8	1.6	3.9	3.1
Lymphocyte count (× 10^9 cells per L)	0.3	1.9	1.1	0.6
Platelet count (× 10^9 cells per L)	140	153	200	169
CRP (mg/L)	24	10	45	55
ESR (mm/hr)	69	7	51	44
Blood urea nitrogen (mg/dl)	67	14	16	12
Cratinin (mg/dl)	2.2	1.1	1.3	1.2
Aspartate aminotransferase (mg/dl)	2220	25	56	171
Alanine aminotransferase (mg/dl)	461	23	23	147
Radiology abnormalities	Yes	Yes	Yes	Yes

Discussion

There are several reports indicating that viral interactions have some outcomes on the course of infectious diseases (*16, 17*). However, these interactions are relatively undefined in the process and pathogenesis of most viral diseases. In this field, the majority of investigations have focused on chronic viral infections such as HIV and hepatitis B and C. (*18, 19*). Due to the comparatively short duration of viral respiratory infections, the topic of co-inefection might be less of a concern.

In the present report, in an investigation of the first twelve cases, four patients in the starting days of COVID-19 disease in our region in the south of Iran were identified with co-infection of SARS-CoV-2 and Influenza virus. We conducted this study to determine the role of various viruses in the etiology of acute viral respiratory diseases and suggest an empirical therapy for respiratory tract infectious disease in patients who referred to the primary clinics. However, the exact role of co-infection in the clinical course and whether these coinfections need improvement or change in the current treatment protocol are still unclear.

This is the first investigation that quantified the clinical severity of COVID-19 based on specific co-pathogens. Our co-infection rate of 33% is higher than what is reported in other studies (*20, 21*). It might be due to the overlap between the emergence of SARS-CoV-2 and seasonal flue in our region. This overlap emphasizes the consideration of SARS-CoV-2 PCR test regardless of other positive findings for other pathogens in primary test during the epidmic.

In our protocol, the chest CT scan is the first line of screening and diagnosing COVID-19. Fang et al. showed chest CT scan has greater sensitivity than RT-PCR for detection of COVID-19 (*22*). Ground glass opacities, multifocal patchy consolidation, especially with peripheral distribution, is the pattern of lung involvement in viral pneumonia and is non-specific for

patients infected with COVID-19. Furthermore, this pattern is similar to the abnormality of the chest CT scan that was reported in previous two coronavirus outbreaks of SARS and MERS (*12, 23-25*). Therefore, these imaging findings guided us to find suspected patients by considering clinical findings. As mentioned, the four patients presented in this study had non-specific chest CT findings for viral pneumonia, which cannot differentiate influenza from COVID-19. Therefore, in this study, chest CT scan just helped us to find the infected lungs with virus, but swab samples helped us to confirm influenza and COVID-19; then, we chose the proper management and therapeutic regimen accordingly.

Acknowledgements: The authors would like to thank Manica Negahdaripour and Shiraz University of Medical Sciences, Shiraz, Iran and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References:

1. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. New England Journal of Medicine. 2020.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine. 2020.
4. Drosten C, Meyer B, Müller MA, Corman VM, Al-Masri M, Hossain R, et al. Transmission of MERS-coronavirus in household contacts. New England Journal of Medicine. 2014;371(9):828-35.
5. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. The Lancet. 2020.
6. Chowell G, Abdirizak F, Lee S, Lee J, Jung E, Nishiura H, et al. Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study. BMC medicine. 2015;13(1):210.

7. Hoehl S, Berger A, Kortenbusch M, Cinatl J, Bojkova D, Rabenau H, et al. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. New England Journal of Medicine. 2020.
8. COVID-19 CORONAVIRUS OUTBREAK. 2020 March 14, 2020 [cited 2020 March 14, 2020]; Available from: https://www.worldometers.info/coronavirus/
9. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020;395(10223):514-23.
10. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet. 2020.
11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020.
12. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020:200370.
13. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020:1-4.
14. Organization WH. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. Interim guidance January. 2020;28.
15. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020;25(3).
16. Pou AM, Rimell FL, Jordan JA, Barua P, Shoemaker DL, Post JC, et al. Adult respiratory papillomatosis: human papillomavirus type and viral coinfections as predictors of prognosis. SAGE Publications Sage CA: Los Angeles, CA; 1995.
17. Franz A, Adams O, Willems R, Bonzel L, Neuhausen N, Schweizer-Krantz S, et al. Correlation of viral load of respiratory pathogens and co-infections with disease severity in children hospitalized for lower respiratory tract infection. Journal of clinical virology. 2010;48(4):239-45.
18. Muriuki BM, Gicheru MM, Wachira D, Nyamache AK, Khamadi SA. Prevalence of hepatitis B and C viral co-infections among HIV-1 infected individuals in Nairobi, Kenya. BMC research notes. 2013;6(1):363.
19. He N, Chen L, Lin H, Zhang M, Wei J, Yang J, et al. Multiple viral coinfections among HIV/AIDS patients in China. Bioscience trends. 2011;5(1):1-9.
20. Drews AL, Atmar RL, Glezen WP, Baxter BD, Piedra PA, Greenberg SB. Dual respiratory virus infections. Clinical infectious diseases. 1997;25(6):1421-9.
21. Nisii C, Meschi S, Selleri M, Bordi L, Castilletti C, Valli MB, et al. Frequency of detection of upper respiratory tract viruses in patients tested for pandemic H1N1/09 viral infection. Journal of clinical microbiology. 2010;48(9):3383-5.
22. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology. 2020:200432.
23. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology. 2020:200463.
24. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020:200642.
25. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for radiologists on COVID-19: an update—Radiology Scientific Expert Panel. Radiology. 2020:200527.