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The Prevalence and Clinical Features of Co-Infection with SARS-CoV-2 and Influenza Virus during the COVID-19 Pandemic in Semnan, Iran

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Abstract

Background: COVID-19 and influenza are both contagious respiratory diseases. Influenza virus can increase the severity of COVID-19 infection in the cold months of the year through damage to respiratory ciliated cells, which may cause an increase in hospitalization, disease symptoms and mortality rate. Therefore, the purpose of this study was to ascertain the frequency of co-infection with the influenza virus and SARS-CoV-2, as well as the impact of co-infection on clinical outcomes in hospitalized patients suffering from respiratory problems within Semnan City, Iran.

Methods: In this cross-sectional descriptive study, we investigated 1267 hospitalized patients with respiratory problems between September 2021 and March 2022. Two nasopharyngeal and oropharyngeal throat swab samples were collected from each patient and tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A, and influenza B viruses using real-time reverse-transcriptase– polymerase-chain-reaction (RT-PCR). The collected data were analyzed with χ^2 test, ANOVA, paired Student's t-test, and Pearson's correlation coefficient test in different groups. Analyzes were done with SPSS 26.0 software.

Results: In total, 29.6% (n = 375) of patients had confirmed positive results for SARS-CoV-2, and their median age was 55.4 ± 24.63 years. It was found that 1.9% (n = 7) and 0.5% (n = 2) of COVID-19 patients had co-infections with influenza viruses A and B, respectively. In 2.4% of the cases, co-infection with COVID-19 and influenza was found. 8 out of 9 patients (88.8%) recovered, while one patient (11.1%) died. Co-infection did not significantly correlate with cancer (P = 0.588), diabetes (P = 0.202), hypertension (P = 0.530), or any other illness.

Also, Associations of death and co-infection with diabetes, cardiovascular disease, or CKD showed that a statistically significant correlation was present only between diabetes and death. Based on the ANOVA test to look at associations of death and co-infection with diabetes, cardiovascular disease, or CKD, it showed that there was no significant association of co-infection with diabetes (P = 0.202), hypertension (P = 0.530), cancer (P = 0.588), and other diseases.

Conclusion: Although a low proportion of COVID-19 patients have influenza co-infection, the importance of such co-infection, especially in high-risk individuals and the elderly, cannot be ignored. Given the prevalence of influenza co-infection, increased coverage of flu vaccination is encouraged to mitigate the transmission of the influenza virus during the ongoing COVID-19 pandemic and reduce the risk of severe outcomes and mortality.

Keywords: COVID-19, Influenza A and B, Co-infection

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↑What is "already known" in this topic:
COVID-19 co-infections with other respiratory infections, especially influenza infection may complicate the diagnosis, treatment and prognosis of COVID-19. Influenza infection can facilitate COVID-19 through damage to respiratory ciliated cells.

→What this article adds:
Our study has shown that SARS-CoV-2 and influenza co-infection was not common in Semnan city because health care during the COVID-19 pandemic may have helped to reduce the transmission of seasonal influenza virus.

Introduction

Respiratory virus infections account for significant morbidity and mortality across the globe (1, 2). Two pandemic diseases caused by respiratory viruses in the last two decades, H1N1 influenza, and SARS-CoV-2 (3, 4). Both COVID-19 and influenza diseases present with similar clinical symptoms including cough, sore throat, headache, muscle aches, breathlessness, fever, acute respiratory distress syndrome, and death (5, 6). Bao et al. showed that co-infection with these viruses increases the duration of clinical symptoms of COVID-19 and increases lung damage (7). Moreover, another study has found that the influenza virus can cause aggravate SARS-CoV-2 infection. Increased viral load of SARS-CoV-2 and aggravated lung damage occur in mice infected with influenza virus. However, increased infectivity of SARS-CoV-2 has not been observed in infections with other respiratory viruses, possibly because the influenza virus is associated with increased ACE2 expression (8). The combined effects of SARS-CoV-2 and influenza virus infection may be due to the fact that both viruses predominantly affect alveolar type II cells.Therefore, SARS-CoV-2 and influenza co-infection may aggravate respiratory epithelial damage. In addition, other studies showed that patients with Co-infection of these viruses are more likely to need mechanical ventilation (9, 10). Therefore, SARS-CoV-2 and influenza virus co-infection increases patient risk and complicates patient condition. The aim of this research is to determine the frequency of co-infection between influenza and COVID-19 viruses and assess their correlation with patient demographics and clinical data.

Methods

Study Design, Participants, and Sample Collection

This study was conducted cross-sectionally. A total of 1267 nasopharyngeal and oropharyngeal throat samples were collected between December 2021 and March 2022 in Kausar and Amir-Al-Momenin hospitals affiliated with Semnan University of Medical Sciences with approval certificate from the medical ethics committee of the university.

RNA extraction, SARS-CoV-2, influenza A and influenza B PCR detection

Using the Roje kit, viral RNA was isolated from samples. Using the Viga SARS CoV-2 and influenza A/B molecular diagnostic kit, RNA was obtained and then submitted to Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) . All molecular tests were carried out in accordance with the manufacturer's instructions (ROJE Technologies, Iran). All the RT-PCR reactions were carried out in the QIAquant 5-Plex 96 Real-Time PCR System (Qiagen, Hilden, Germany).

Data Collection and Statistical Analysis

All data and laboratory parameters were collected. Descriptive statistics were calculated for all of the variables. We calculated the prevalence of COVID-19 and influenza by the entire study group. We used the χ^2 test to compare the rates of sex, Comorbidities, Dexamethasone, and Remdesivir consumption, In-hospital deaths and use of mechanical ventilation in different age groups. The mean of age, first SpO_2 and second SpO_2 in each of the groups were analyzed by analysis of variance (ANOVA) and paired Student's t-test. Furthermore, the relationship between the use of dexamethasone and remdesivir and the survival rate of patients was investigated by Pearson's correlation coefficient test. All variables with p-values of ≤ 0.05 were considered statistically significant. The SPSS statistic software (version 26) was used to perform the analysis.

Results

Demographic and clinical characteristics

A total of 1267 individuals from Semnan, Iran who had symptoms similar to the flu were evaluated. Of them, 614 females (48.4%) and 653 males (51.5%) had mean ages of 65.38 ± 110.83 and 59.40 ± 63.41, respectively (Figure 1). A positive rate of 29.6% (n = 375) for SARS-CoV-2 was seen in 375 patients, with a median age of 55.4 ± 24.63 years. 10.2% (n = 35) of the SARS-CoV-2-positive patients were under 20, 41.5% (n = 142) were between 21 and 60 years old, and 48.2% (n = 165) were over 61. Compared to men (47.5%, n = 178), females had a greater prevalence of SARS-CoV-2 (52.5%, n = 197).

Influenza and COVID-19 co-infection were detected in 2.4% (n = 9) of the cases. According to influenza subtypes, in 375 COVID-19 RT-PCR-positive patients, the types of influenza in the form of co-infection were influenza A (1.9%, n = 7) and influenza B (0.5%, n = 2) was determined. Demographic and clinical information concerning the SARS-CoV-2 virus and co-infection with influenza virus are reported in Table 1.

Regarding comorbidities, the prevalence of diabetes was 18.9% (n = 71), hypertension 26.7% (n = 100), cancer 3.5% (n = 13), coronary artery bypass graft (CABG) 1.9% (n = 7), hyperlipidemia (HLP) 12.6% (n = 47), ischemic heart disease (IHD) 12% (n = 45), cerebrovascular accident (CVA) 5.6% (n = 21) and asthma 3.7% (n = 14) among positive COVID-19 patients. There was no significant association of co-infection with diabetes ($P = 0.202$), hypertension ($P = 0.530$), cancer ($P = 0.588$), and other diseases. In addition, the mean of the first SpO_2 level in patients with positive COVID-19 and co-infected was 91.4 ± 9.58 and

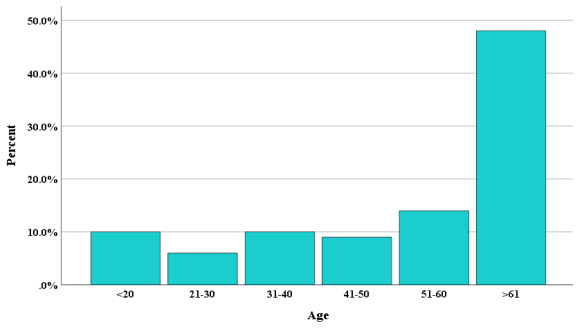

Figure 1. Age range of patients with respiratory symptoms

Table 1. Characteristics of the patients with COVID-19 and influenza co-infection

Variable	Levels of variables	No. of patients (%) with only COVID-19	No. of patients (%) with influenza and SARS-CoV-2 coinfection	*P*-value
No. of total (%)		366 (97.6%)	9 (2.4%)	
Sex				0.218
	Male	173 (47.2%)	5 (55.5%)	
	Female	193 (52.7%)	4 (44.4%)	
Age group				
	<20	35 (9.2%)	1 (11.11%)	
	21-30	23 (6.1%)	0 (0%)	
	31-40	43 (11.3%)	2 (22.22%)	
	41-50	37 (9.7%)	0 (0%)	
	51-60	39 (10.3%)	3 (33.33%)	
	>61	165 (43.4%)	3 (33.33%)	
Influenza type				
	A	-	7 (77.7%)	
	B	-	2 (22.2%)	
Comorbidities				
	Cancer	13 (3.5%)	0	0.725
	Diabetes	68 (18.5%)	3 (33.3%)	0.500
	Hypertension (HTN)	97 (26.5%)	3 (33.3%)	0.775
	Coronary artery bypass graft (CABG)	6 (1.6%)	1 (11.1%)	0.061
	Hyperkeratosis lenticularis perstans (HLP)	46 (12.5%)	1 (11.1%)	
	Ischemic heart disease (IHD)	44 (12%)	1 (11.1%)	0.762
	Cerebrovascular accident (CVA)	21 (5.6%)	0	0.590
	Asthma	14 (3.7%)	0	0.706
Blood oxygen saturation level				
	The mean of the first SpO2	91.4	83.7	0.057
	The mean of the second SpO2	95.2	94.2	0.592
Medication				
	Dexamethasone	125 (34.1%)	4 (44.4%)	0.813
	Remdesivir	109 (29.7%)	3 (33.3%)	0.378
In-hospital deaths		34 (9.2%)	1 (11.1%)	0.752

83.7 ± 7.83, respectively, and this difference was not significant.

Analysis of severity and treatment of patients with COVID-19 and coinfected with influenza

Among the positive COVID-19 patients, 35 people (9.3%) died, one of whom was coinfected with influenza and COVID-19. The mean age in dead patients was 68.46 ± 20.18 years, and in living patients was 54.09 ± 24.687 years (P = 0.001). Figure 2 shows that among the people who died due to COVID-19, most of them were 61 years old or older. In addition, among the people who died due to co-infection of COVID-19 and influenza, one person was older than 61 years.

An analysis of the relationships between death and co-infection with diabetes, cardiovascular disease, or chronic kidney disease (CKD) using the ANOVA test revealed (Table 1) that only the relationship between diabetes and death was statistically significant (P = 0.020).

Comparing the mean of first SpO_2 and second SpO_2 in people with only COVID-19 positive and people with co-infection showed that there is no significant difference in these two groups (respectively P = 0.057 and P = 0.592). However, the comparison between the COVID-19-positive patients in both survivor and deceased groups showed that there is a significant difference in the mean age, mean of first SpO_2, and second SpO_2 in these two groups (Table 2).

In addition, the relationship between first SpO_2 levels and co-infection with influenza viruses was investigated, and the findings showed that there is a negative correlation between co-infection with influenza in COVID-19-positive patients and first SpO_2 levels (Table 3).

The results of examining the relationship between the use of dexamethasone and remdesivir and the survival rate of patients (Pearson's correlation coefficient test) showed that there was no significant correlation between them. However, there was a negative correlation between remdesivir drug use and second SpO_2 levels in patients (P = 0.011, Pearson Correlation = -0.281) (Table 4).

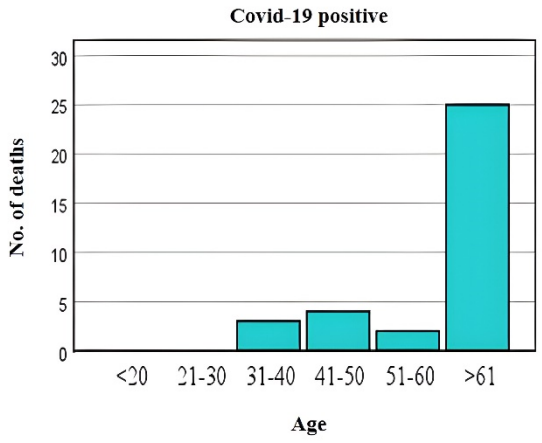

Figure 2. The mortality toll of Covid-19 positive patients by age

Table 2. Comparison of age average, first SpO_2, and second SpO_2 in dead and alive COVID-19-positive patients

	Alive patients	Dead patients	*P*-value
Age mean	54.09 (±24.686)	68.46 (±20.187)	0.001
The mean of the first SpO2*	92.15 (±8.981)	84.23 (±11.664)	<0.001
The mean of the second SpO2*	96.12 (±2.333)	86.75 (±6.670)	0.005

* First SpO_2 defines SpO_2 at the time of admission to the hospital and second SpO_2 is the patient SpO_2 at the time of discharge from the hospital.

Table 3. Mechanical ventilation used in people with positive COVID-19 and co-infection

	Not Use	O_2 therapy by mask 5_8 Lit/min	O_2 therapy by reserve bag mask	O_2 therapy by venturi mask	O_2 therapy nasal cannula
COVID-19-positive	330	16	13	5	2
Influenza co-infection	7	2	0	0	0

Table 4. Comparison of influenza and SARS-CoV-2 coinfection, Demographic data, and laboratory parameters

		Age	Sex	Cancer	Diabetes	Hypertension	First SpO_2	Second SpO_2	Survival status
Influenza coinfection	Pearson Correlation	-0.019	-0.048	0.028	0.066	-0.033	-0.120*	-0.084	-0.001
	P-value	0.720	0.354	0.588	0.202	0.530	0.038	0.453	0.981

The relationship between the use of dexamethasone and remdesivir and the survival rate of patients was investigated by Pearson's correlation coefficient test.

Discussion

COVID-19 and influenza are both contagious respiratory diseases. The influenza virus can increase the severity of COVID-19 infection in the cold months of the year through damage to respiratory ciliated cells, which may cause an increase in hospitalization, disease symptoms and mortality rate (11, 12). Co-infection with COVID-19 and influenza can therefore represent a major risk to one's health. We aimed to study the epidemiology of COVID-19 and influenza co-infection in a cross-sectional study. COVID-19 and influenza co-infection were detected in 2.4% (n = 9) of the cases. Additionally, 1.9% and 0.5% of influenza A and B patients, respectively, were infected with the virus. Moreover, the relationship between first SpO_2 levels and co-infection with influenza viruses was investigated, and the findings showed that there is a negative correlation between co-infection with influenza in COVID-19-positive patients and first SpO_2 levels. In Guan W et al. report from China, In 28 patients, 50.0% of patients were severe type and 14.3% died, which was higher than those reported in COVID-19 (13). Furthermore, a study from Northeastern Iran showed 22.3% of dead cases were co-infected with COVID-19 and influenza co-infection (14), indicating co-infection with COVID-19 and influenza co-infection may result in more severe conditions. These studies show that patients with COVID-19 and influenza co-infection developed more severe clinical conditions while having shorter hospital stays. In our opinion, the possible reason may be attributed to the timely use of effective antiviral drugs such as oseltamivir. In one study, 1.3% of COVID-19-positive patients also tested positive for influenza virus, which was lower than the results of our study (15). In the investigated studies, the rate of co-infection between COVID-19 and influenza has been observed to range from 0.24 to 44%. (6, 14, 16-20). This dispersion and difference can be due to the study population, the underlying conditions of the patients, and the method of confirming the infection as well as the time and place of the investigation in terms of the prevalence of Influenza. In this investigation, in patients with COVID-19, Hypertension (26.7%), diabetes mellitus (18.9%), cancer (3.5%), asthma (3.7%), and cardiovascular diseases were the most common underlying diseases, consistent with other recent reports (21-23). Previous studies reported 9% to 14% prevalence of diabetes in COVID-19 patients (21, 23-25). Here, we reported a higher prevalence rate of diabetes in these patients, which might be due to the larger proportion of geriatric COVID-19 patients in our study. In general, aged people are more susceptible to COVID-19 and more likely to be severe than people younger than 50 years; this may be due to more health issues and comorbidities in this population. Ding and colleagues (17) identified 5 COVID-19 and influenza co-infection patients out of 115 SARS-CoV-2 positive hospitalized patients. These 5 patients did not need ICU admission or IMV and all were discharged alive. On the other hand, Alosaimi and colleagues (26) identified 30 co-infected patients out of 48 hospitalized (14 ICU) SARS-CoV-2 positive patients and found that influenza co-infection was associated with mortality.

In this study, the death rates were 9.3% for COVID-19-positive patients and 11.1% for COVID-19 and influenza co-infection patients. These findings demonstrated that there is no discernible link between the co-infection of COVID-19 and influenza and the patient death rate. According to research, COVID-19 individuals who had previously gotten an influenza vaccination had far decreased probabilities of both critical outcomes and death (27, 28). This might imply a potential competitive mechanism between COVID-19 and influenza like competitively bound to the receptors and thereby contributing to the reduction or block of SARSCoV-2 entry into lung cells. It is also possible that influenza vaccination could stimulate a short-term non-specific immune response that provides temporary protection against SARSCoV-2. Thirdly, a considerable reduction of cytokines among co-infection patients was detected in some studies, indicating that patients with co-infection might have a lower degree of hyper-inflammation and therefore lower risk for adverse outcomes (29).

In our study, there was no significant association of co-infection with diabetes (P = 0.202), hypertension (P = 0.530), cancer (P = 0.588), and other diseases. In addition, in this study, among the dead positive COVID-19 patients, 34.2% had Hypertension (HTN), 31.4% had Ischemic heart

disease (IHD), 11.4% had diabetes, and 5.7% had cancer. Also, there was a patient with a co-infection of COVID-19 and Influenza who had IHD.

The study found that COVID-19 patients with diabetes were more likely to develop severe or critically ill subtypes, including more complications with Adult Respiratory Distress Syndrome (ARDS), and acute cardiac injury, resulting in receiving more antibiotic therapy and mechanical ventilation (30).

Furthermore, high blood pressure (hypertension) is one of the most common conditions in severe COVID-19 patients (31). In Ref. (32), systematic reviews show that hypertension is one of the major comorbidities of fatality in COVID-19 cases. Although, it should be noted that further studies of other comorbidities connected to hypertension are necessary.

Covid-19 problems are more common in cancer patients, according to published studies. It has been suggested by Liang et al. (33) that COVID-19 risk may be higher in cancer patients than in non-cancer patients. They also demonstrated worse COVID-19 outcomes for cancer patients. As a result of the COVID-19 infection, Zhang et al. (34) noted that cancer patients' circumstances are getting worse.

Also, regarding the relationship between heart diseases and death caused by COVID-19, ten observational studies have reported mortality data of acute influenza concurrent with cardiac abnormality upon presentation. Mortality in individuals hospitalized due to influenza or influenza-like illness ranged from 3.8 to 50% in these studies, except for one study by Chacko et al. (35) evaluating cardiac manifestations in patients with severe H1N1 virus during the 2009 pandemic, where a 92% overall mortality rate was observed. In contrast to acute Influenza, for the last 5 months, many (n = 16) observational studies have reported mortality data for patients with COVID-19 infection. The overall mortality in this patient cohort has ranged from 1.4 to 61.5%, which is higher than that observed in patients with acute Influenza.

The results of examining the relationship between the use of dexamethasone and remdesivir and the survival rate of patients showed that there was no significant correlation between them. However, there was a negative correlation between remdesivir drug use and second SpO_2 levels in patients. There was no significant relationship between the use of dexamethasone and the second level of SpO_2 in patients. The results of other studies have shown that among hospitalized patients with COVID-19 requiring supplemental oxygen at baseline, the use of remdesivir, compared to the best supportive care, is likely to improve the risk of mortality, recovery, and require oxygen assistance in patients receiving low-flow oxygen (LFO_2) and any additional oxygen ($AnyO_2$) (36).

Limitations

The following are some of the study's limitations: Firstly, the current study has a rather tiny sample size. Second, certain information was not recorded, which made it impossible for us to get precise and comprehensive clinical data on every patient. Furthermore, the absence of some data could have an impact on the study's findings. Third, we were unable to determine which patient had contracted which virus initially. In summary, our study's findings show that co-infection with SARS-CoV-2 and influenza was uncommon in Semnan City.

Conclusion

COVID-19 and influenza co-infection is predictable, especially during the cold season of the year. Because influenza viruses and COVID-19 share many similarities in terms of how they spread and clinical manifestations, we should investigate management strategies in the early diagnosis and treatment of these viral infections. We also encourage the rapid evaluation of patients presenting in respiratory distress to emergency departments for both SARS-CoV-2 and influenza and, if co-infected, treatment with antiviral agents both for influenza A and B and for SARS-CoV-2. Future research is desperately needed to gather data on SARS-CoV-2 subtypes, influenza subtypes, and the sequence of infection in order to undertake stratified analysis and provide more specific information, given the ongoing co-circulation of these two viruses.

Authors' Contributions

H.GH and M.E designed and administrated the project. M.T and MS.SH wrote the manuscript. P.P, M.V and F.H collected the patient's data and samples. R.N and M.Z analyzed the data. All authors read and approved the final version of the manuscript.

Ethical Considerations

All procedures performed in this work followed the ethical standard of the committee of the Semnan University of Medical Sciences (Ethical Code: IR.SEMUMS.REC. 1400.334).

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Conflict of Interests

The authors declare that they have no competing interests.

References

1. Troeger C, Blacker B, Khalil IA, Rao PC, Cao J, Zimsen SR, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18(11):1191-210.
2. Chen L, Wang Q, Gao Y, Zhang J, Cheng S, Chen H, et al. The global burden and trends of maternal sepsis and other maternal infections in 204 countries and territories from 1990 to 2019. BMC Infect Dis. 2021;21(1):1-15.
3. Atamna A, Babich T, Froimovici D, Yahav D, Sorek N, Ben-Zvi H, et al. Morbidity and mortality of respiratory syncytial virus infection in hospitalized adults: Comparison with seasonal influenza. IJID. 2021;103:489-93.
4. Hemati M, Soosanabadi M, Ghorashi T, Ghaffari H, Vahedi A, Sabbaghian E, et al. Thermal inactivation of COVID-19 specimens improves RNA quality and quantity. J Cell Physiol. 2021;236(7):4966-72.
5. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed

asymptomatic carrier transmission of COVID-19. Jama. 2020;323(14):1406-7.
6. Iqbal MM, Abid I, Hussain S, Shahzad N, Waqas MS, Iqbal MJ. The effects of regional climatic condition on the spread of COVID-19 at global scale. Sci Total Environ. 2020;739:140101.
7. Bao L, Deng W, Qi F, Lv Q, Song Z, Liu J, et al. Sequential infection with H1N1 and SARS-CoV-2 aggravated COVID-19 pathogenesis in a mammalian model, and co-vaccination as an effective method of prevention of COVID-19 and influenza. Signal Transduct Target Ther. 2021;6(1):200.
8. Bai L, Zhao Y, Dong J, Liang S, Guo M, Liu X, et al. Coinfection with influenza A virus enhances SARS-CoV-2 infectivity. Cell Res. 2021;31(4):395-403.
9. St John AL, Rathore AP. Early insights into immune responses during COVID-19. J Immunol. 2020;205(3):555-64.
10. van Riel D, Munster VJ, de Wit E, Rimmelzwaan GF, Fouchier RA, Osterhaus AD, et al. Human and avian influenza viruses target different cells in the lower respiratory tract of humans and other mammals. Am J Pathol. 2007;171(4):1215-23.
11. Konala VM, Adapa S, Gayam V, Naramala S, Daggubati SR, Kammari CB, et al. Co-infection with Influenza A and COVID-19. Eur J Case Rep Intern Med. 2020;7(5).
12. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. Lancet Microbe. 2020;1(1):e11.
13. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
14. Hashemi SA, Safamanesh S, Ghasemzadeh-moghaddam H, Ghafouri M, Azimian A. High prevalence of SARS-CoV-2 and influenza A virus (H1N1) coinfection in dead patients in Northeastern Iran. J Med Virol. 2021;93(2):1008-12.
15. Swets MC, Hardwick HE, Baillie JK. Coinfection with influenza viruses is associated with worse outcomes in severe COVID-19, an ISARIC4C/CO-CIN Report. 2022.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group* P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
17. Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol. 2020;92(9):1549-55.
18. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Euro Surveill. 2020;25(18):2000600.
19. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA. 2020;323(20):2085-6.
20. Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of coronavirus disease 2019 and influenza: a report from Iran. Arch Iran Med. 2020;23(4):239-43.
21. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
22. 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. Lancet. 2020;395(10223):497-506.
23. 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;323(11):1061-9.
24. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
25. Zhang J-j, Dong X, Cao Y-y, Yuan Y-d, Yang Y-b, Yan Y-q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-41.
26. Alosaimi B, Naeem A, Hamed ME, Alkadi HS, Alanazi T, Al Rehily SS, et al. Influenza co-infection associated with severity and mortality in COVID-19 patients. Virol J. 2021;18(1):1-9.
27. Fink G, Orlova-Fink N, Schindler T, Grisi S, Ferrer APS, Daubenberger C, et al. Inactivated trivalent influenza vaccination is associated with lower mortality among patients with COVID-19 in Brazil. BMJ Evid Based Med. 2021;26(4):192-3.
28. Draper B, Yee WL, Pedrana A, Kyi KP, Qureshi H, Htay H, et al. Reducing liver disease-related deaths in the Asia-Pacific: the important role of decentralised and non-specialist led hepatitis C treatment for cirrhotic patients. Lancet Reg Health West Pac. 2022;20.
29. Cheng Y, Ma J, Wang H, Wang X, Hu Z, Li H, et al. Co-infection of influenza A virus and SARS-CoV-2: A retrospective cohort study. J Med Virol. 2021;93(5):2947-54.
30. Zhang Y, Cui Y, Shen M, Zhang J, Liu B, Dai M, et al. Comorbid diabetes mellitus was associated with poorer prognosis in patients with COVID-19: a retrospective cohort study. MedRxiv. 2020:2020.03. 24.20042358.
31. Guan W-j, Liang W-h, Zhao Y, Liang H-r, Chen Z-s, Li Y-m, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5).
32. Chen Y, Gong X, Wang L, Guo J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. MedRxiv. 2020:2020.03. 25.20043133.
33. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
34. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020;31(7):894-901.
35. Chacko B, Peter JV, Pichamuthu K, Ramakrishna K, Moorthy M, Karthik R, et al. Cardiac manifestations in patients with pandemic (H1N1) 2009 virus infection needing intensive care. J Crit Care. 2012;27(1):106. e1-. e6.
36. Beckerman R, Gori A, Jeyakumar S, Malin JJ, Paredes R, Póvoa P, et al. Remdesivir for the treatment of patients hospitalized with COVID-19 receiving supplemental oxygen: a targeted literature review and meta-analysis. Sci Rep. 2022;12(1):9622.