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Coronavirus Pandemic

Clinical and epidemiological evaluation of influenza and SARS-CoV-2 coinfected cases

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Abstract

Introduction: Coinfection of COVID-19 with influenza pathogens, may complicate the diagnosis, treatment, and prognosis, which is a new concern. This study aims to evaluate COVID-19 and influenza coinfected cases during the flu season, while the SARS-CoV-2 pandemic continues.

Methodology: The study was conducted between November 2021 and January 2022. A total of 1987 (1752 outpatients, 235 inpatients) patients were included, and 44 simultaneous COVID-19 and influenza laboratory-confirmed diagnoses.

Results: During the study period, 1553 patients were diagnosed with COVID-19, 390 influenza, and 44 were diagnosed with coinfection. The incidence of coinfected cases was 2.2% (n = 44) in all patients, When coinfected cases were examined, there was a statistically significant difference between the disease duration in the inpatients (19.86 ± 10.78 days) and the disease duration in the outpatients (7.63 ± 2.25 days) ($p < 0.05$). 31.8% (n = 14) of coinfected cases were hospitalized, and the mortality rate was 50.0% (n = 7) in hospitalized patients.

Conclusions: Coinfection with SARS-CoV-2 and Influenza was not uncommon. Data on coinfected cases are limited in the literature. The coinfection with SARS-CoV-2 and influenza A should be considered in patients with complaints such as fever, myalgia, weakness, shortness of breath, and cough during the flu season. Using the diagnostic test showing two diseases in a single sample may contribute to protecting patient and community health in follow-up and treatment.

Key words: Coinfection; SARS-CoV-2; influenza; flu.

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Introduction

Infections from Influenza virus type A in the general population result in higher rates of morbidity and mortality compared to all other respiratory pathogens [1]. Coronavirus disease, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in 2019 (COVID-19) in the city of Wuhan, China. COVID-19 is a health problem of global significance because of its transmissibility and high mortality rates [2]. As of July 26, 2023, 768,560,727 confirmed cases of COVID-19 were reported to the World Health Organization of which 6,952,522 resulted in death [3].

Diagnosing SARS-CoV-2 in a patient who presents with nonspecific features of respiratory viral infection during the flu season depends on clinical and epidemiological criteria. A positive test result for one virus does not exclude infection with another respiratory virus [4]. SARS-CoV-2 and the influenza virus are droplet-mediated pathogens that mainly affect the respiratory tract. COVID-19 and influenza often present with signs and symptoms of nonspecific upper respiratory tract infections. Although both infectious agents have similar clinical features, such as fever, cough, dyspnea, myalgia, headache, sore throat, and nasal discharge, different epidemiological and clinical features can also be observed. While influenza is mostly mild or moderate, COVID-19 can cause severe infection, especially in high-risk patients [5]. Acute respiratory distress syndrome is more common in COVID-19 and mortality is from 3-4% [6].

It is thought that the use of masks in public places, the closure of schools and shopping areas, and the restrictions on movement, which have been applied almost everywhere in the world, cause a decrease in both SARS-CoV-2 and influenza cases to varying

degrees. It has been shown that there was a temporary decrease in the incidence of influenza from January–May 2020 [7]. Data regarding coinfected cases are limited in the literature. This study aims to evaluate COVID-19 and influenza coinfected cases during the flu season while the SARS-CoV-2 pandemic continues.

Methodology

Study design

The present research was a retrospective, descriptive study. It was carried out at Bingöl State Hospital, a secondary-level public hospital. The study was conducted from November 2021–January 2022. A total of 1,987 (1,752 outpatients, 235 inpatients) patients were included. 44 simultaneous COVID-19 and influenzas laboratory-confirmed diagnoses (30 outpatients and 14 inpatients) patients were part of the study.

Pregnant women, those under 18 years, and patients with dementia were excluded. Patient management was carried out according to the "COVID-19 Diagnosis and Treatment Guidelines" published by the Ministry of Health of the Republic of Turkey [8].

Age, gender, comorbidity, history of smoking, symptoms, laboratory tests and radiological images, disease duration, treatment, and clinical results of the patients were obtained from the hospital database. Influenza and SARS-CoV-2 vaccination status were recorded from the national vaccine follow-up system.

Laboratory analysis

The presence of SARS-CoV-2 was evaluated from combined throat/nasopharyngeal swab samples using real-time polymerase chain reaction (RT-PCR). The samples were transferred to the laboratory by placing them in tubes containing vNAT (viral nucleic acid buffer that enables extraction). Bio-Speedy® SARS-CoV-2 Emerging + kit (Bioeksen, Turkey) was amplified in the Bio-Rad CFX96 Real time PCR device (Bio-Rad, USA) and studied in accordance with the recommendations of the manufacturer. Results with a quantification cycle value of < 33 and forming a sigmoidal curve were reported as positive. For the laboratory diagnosis of influenza, nasopharyngeal swab samples were studied immediately, using the immunochromatographic-based Influenza Antigen Card Plus (Humasis, Korea) test following the manufacturer's recommendations.

Statistical analysis

Data from the study were analyzed using SPSS 24 software. Descriptive statistics for the variables of the study were provided. Continuous variables were expressed as mean ± standard deviation (min–max). Categorical data were presented along with the number of cases and percentages. The Mann–Whitney U-test was used to compare the means of two independent groups, as they did not comply with the parametric assumptions. The chi-square test was used in the

Table 1. Demographics and clinical characteristics of patients.

Characteristics/Infections	Coinfection	Influenza A/B	SARS-CoV-2	Total
Age (years) (mean ± SD)	48.5 ± 20.4	38.6 ± 18.0	41.3 ± 19.0	40.9 ± 18.9
Age groups (years) n (%)				
18-30	10 (22.7)	165 (42.3)	575 (37.1)	750 (37.8)
31-40	7 (15.9)	91 (23.3)	352 (22.7)	450 (22.7)
41-50	9 (20.5)	38 (9.7)	173 (11.2)	220 (11.1)
51-60	6 (13.6)	34 (8.7)	141 (9.1)	181 (9.1)
61-70	3 (6.8)	28 (7.2)	118 (7.6)	149 (7.5)
71-80	5 (11.4)	26 (6.7)	136 (8.8)	167 (8.4)
81-90	3 (6.8)	7 (1.8)	42 (2.7)	52 (2.6)
> 90	1 (2.3)	1 (0.3)	13 (0.8)	15 (0.8)
Sex n (%)				
Male	23 (52.3)	218 (55.9)	694 (44.7)	935 (47.1)
Female	21 (47.7)	172 (44.1)	859 (55.3)	1052 (52.9)
Comorbidities n (%)				
Yes	24 (54.5)	93 (23.8)	587 (37.8)	704 (35.4)
No	20 (45.5)	297 (76.2)	965 (62.2)	1282 (64.6)
Hospitalization n (%)				
Yes	14 (31.8)	95 (24.4)	126 (8.1)	235 (11.8)
No	30 (68.2)	295 (75.6)	1427 (91.9)	1752 (88.2)
Duration of illness (days) (mean ± SD, extremes)	11.5 ± 8.5	7.9 ± 2.7	8.9 ± 2.7	8.8 ± 3.0
Outcome n (%)				
Improved	37 (84.1)	389 (99.7)	1537 (99.0)	1963 (98.8)
Died	7 (15.9)	1 (0.3)	16 (1.0)	24 (1.2)
Total n (%)*	44 (2.2)	390 (19.6)	1553 (78.2)	1987 (100.0)

analysis of categorical variables, and Fisher's exact test was employed when more than 20% of the cells were expected to have frequencies lower than 5. As a result of all the analyses, a p value of < 0.05 was considered statistically significant.

Ethics committee approval

In order to conduct the study, approval was obtained from the Gazi Yaşargil training and research hospital decision number 62 dated April 7, 2022.

Results

During the study period, 1553 patients were diagnosed with COVID-19, 390 influenza, and 44 patients were diagnosed with coinfection, and the demographic and clinical characteristics of the patients are presented in Table 1.

The incidence of coinfected cases was 2.2% (n = 44) of 1987 patients, 1.7% (n = 30) of 1752 outpatients, and 6.0% (n = 14) of 235 inpatients. Although there were influenza B positive patients, all of the co-infected patients were influenza A. The mean age of the patients was 48.50 ± 20.42 (minimum 18, maximum 94); the men's mean age was 53.71 ± 20.50 (minimum 18, maximum 94), and the women's mean age was 43.74 ± 19.57 (minimum 18, maximum 83). The mean age was 56.57 ± 14.90 (min 39, max 81) in patients who recovered, and 74.57 ± 12.52 years (min 60, max 94) in cases of death.

The mean age of the inpatient group (65.57 ± 16.19 years) was higher than that of the outpatient group (40.53 ± 17.15 years) ($p < 0.05$). There was a statistically significant difference between the disease duration in the inpatients (19.86 ± 10.78 days) and the disease duration in the outpatients (7.63 ± 2.25 days) ($p < 0.05$). There was a statistically significant difference between comorbidity in the inpatients (85.7%) and comorbidity in the outpatients (40.0%) ($p < 0.05$). There was no difference between the inpatient and outpatient groups in terms of gender, history of smoking, influenza, and SARS-CoV-2 vaccination status ($p > 0.05$) (Table 2). Of the coinfection cases, 31.8% (n = 14) were hospitalized and the mortality rate in hospitalized patients was 50.0% (n = 7).

The most common comorbidities in the hospitalized patients were hypertension at 57.1% (n = 8), coronary artery disease at 35.7% (n = 5), and diabetes mellitus at 28.6% (n = 4). Outpatients had hypertension, coronary artery disease, arrhythmia, and benign prostatic hyperplasia with an equal frequency of 6.7% (n = 2).

Fever (85.7%), shortness of breath (78.6%), myalgia (64.3%), and cough (57.1%) were common in hospitalized patients; Myalgia (76.7%), fever (60.0%), cough (56.7%) and fatigue (36.7%) were common symptoms in outpatients, while anosmia (26.7%) was seen only in outpatients.

Oseltamivir treatment was given to all 20 coinfected patients who were in the risk group and admitted to the hospital within the first 48 hours of

Table 2. Characteristics of coinfected patients

	Inpatient (n = 14)	Outpatient (n = 30)	Test	*p*
Age (years) (mean ± SD)	65.57 ± 16.19 (min 39, max 94)	40.53 ± 17.15 (min 18, max 83)	Mann Whitney U = 58.000	0.000*
Sex n (%)				
Female	6 (42.9)	17 (56.7)	Chi-square = 0.281	> 0.05
Male	8 (57.1)	13 (43.3)		
Comorbidity n (%)				
Yes	12 (85.7)	12 (40.0)	Chi-square = 6.308	0.012*
No	2 (14.3)	18 (60.0)		
Use of cigarettes n (%)				
Yes	3 (21.4)	3 (10.0)	Fisher's exact	> 0.05
No	11 (78.6)	27 (90.0)		
Vaccination Influenza n (%)				
Yes	4 (28.6)	3 (10.0)	Fisher's exact	> 0.05
No	10 (71.4)	27 (90.0)		
Vaccination SARS-CoV-2 n (%)				
2 doses Sinovac	8 (57.2)	2 (6.7)		
3 doses Sinovac	1 (7.1)	-		
1 dose biontech	1 (7.1)	-	Fisher's exact	> 0.05
2 doses biontech	2 (14.3)	19 (63.3)		
2 doses sinovac 1 biontech	2 (14.3)	9 (30.0)		
Duration of illness (day) (mean ± SD)	19.86 ± 10.78 (min10, max 50)	7.63 ± 2.25 (min 5, max 14)	Mann Whitney U = 20.500	0.000*

*$p < 0.05$ was considered statistically significant.

symptom onset. Oseltamivir treatment was not given because 3 patients applied on the 5th day of symptom onset and 21 patients were not in the influenza risk group. Enoxaparin Sodium, dexamethasone, tocilizumab was given together with Methylprednisolone to 5 patients with Covid-19, 5 patients were treated with Enoxaparin Sodium 4000 antiXa IU/0.4 and dexamethasone 8 mg/2 mL, 2 patients were treated with only Enoxaparin Sodium 4000 antiXa IU/0.4 treatment, and 32 patients were followed without medical treatment.

Discussion

The basic symptoms of SARS-CoV-2 and influenza A/B viruses are similar. Without the epidemiological data on COVID-19, it seems very difficult to suspect COVID-19 during flu season. Coinfection of COVID-19 with influenza pathogens, which may complicate the diagnosis, treatment, and prognosis, is a new concern. It is predicted that these coinfections may increase the death rate together with the severity of the disease [9]. In the meta-analysis of 14 studies reporting viral coinfection with SARS-CoV-2 and other respiratory pathogens, respiratory syncytial virus (RSV) was the most common viral pathogen (16.9%), followed by influenza A (15.5%) [10]. Incidence of COVID-19 and influenza coinfected cases was between 0.54%-64% [11-19] has been reported. In the present study, the incidence of coinfected cases was 2.2%. We think that the difference in the results may be because the studies were conducted in populations with different characteristics and that the COVID-19-19 and influenza diagnostic test was not performed simultaneously in all patients.

In the study of Gold *et al*. [20] the frequency of comorbid disease was hypertension at 47%, diabetes mellitus 24%, and respiratory diseases 10%; In the meta-analysis by Dadashi *et al.* [11] hypertension 58.6%, diabetes mellitus 48.3%, and haemodialysis 17.2%; In the study by Alosaimi *et al.* [14] diabetes mellitus 54%, chronic kidney disease 10%, cardiovascular disease 4%; Antony *et al.* [21] was reported hypertension 57.4%, cardiovascular disease 28.6% hepatitis B virus 28.6%. In this study, the frequency of comorbidity in hospitalized patients (81.8%) was found to be considerably higher than in outpatients (45.8%) and the most common three comorbidities in hospitalized patients were hypertension 57.1%, coronary artery disease 35.7%, diabetes mellitus 28.6%; in outpatients, hypertension, coronary artery disease, arrhythmia, and benign prostatic hyperplasia were seen with an equal frequency of 6.7%. The findings were compatible with the previous data.

In the study conducted by Dadashi *et al.* [11], the three most common symptoms were fever, cough, and shortness of breath (89.4%, 79.3%, and 24.1%, respectively); It was found in the study of Antony *et al.* [21] (87.5%, 87.5%, 68.75%, respectively). In the present study, the three most common symptoms in hospitalized patients were fever 85.7%, dyspnea 78.6%, myalgia 64.3%; in outpatients' ratios were myalgia 76.7%, fever 60.0%, and cough 56.7%. These results were compatible with the literature.

In the literature, the mortality rate of coinfected cases has been reported as 6.9% and 19% [11-14]. In the present study, 7 (15.9%) of 44 co-infected cases died, and 14 (31.81%) patients were hospitalized. A higher mortality rate may be due to the older age of the patients and the difference in comorbidities. In addition, influenza A was reported as the only pathogen associated with mortality [15]and the other reason for the high mortality rate in our study may be that all of our co-infected cases were positive for influenza A and we did not have any cases of influenza B positive co-infection.

Oseltamivir and zanamivir are antiviral drugs that act by blocking neuramidase and are used in patients and contacts in the risk group. Influenza mortality and morbidity can be reduced with effective vaccination and early antiviral treatment [22]. In the study conducted by Antony *et al.*, (68.75%) of patients were treated with oseltamivir, and 3 with glucocorticoids [21]. Oseltamivir (41.4%), hydroxychloroquine (31%), and azithromycin (24.1%) were the three most used drugs in coinfected patients [10]. In our study, only 20 patients admitted in the first 48 hours were given oseltamivir. Oseltamivir treatment was not given to 3 patients who applied on the 5th day of symptom onset and 21 patients who were not in the risk group for influenza. In the study oksapar, dexamethasone, and/or tocilizumab were the most commonly used drugs. These results indicate that there is no consensus in the treatment approach in coinfected cases.

There are some limitations in the study. The results of the study cannot be generalized due to the lack of comparison between influenza, SARS-CoV-2, and co-infected cases, data from a single hospital, and no simultaneous diagnostic testing from all patients. All patients could not be tested for influenza due to limited testing facilities. Differential analysis designs and larger samples may be required to understand co-infection dynamics.

Conclusions

Coinfection with SARS-CoV-2 and influenza A was not uncommon. Data on coinfected cases are limited in the literature. The coinfection with SARS-CoV-2 and influenza A should be considered in patients with complaints such as fever, myalgia, weakness, shortness of breath, and cough during the flu season. Using the diagnostic test showing two diseases in a single sample may contribute to protecting patient and community health in follow-up and treatment.

In addition, the fact that the vaccination rates were determined as 15.9% for influenza and 27.2% for SARS-CoV-2 in the study reveals that social awareness for vaccination should be increased with education.

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Authors' Contributions

YÇ, HS, DİY, and MÖ: performed the experiments, YÇ: designed and performed the experiment, and wrote the manuscript, YÇ, HS, DİY, and MÖ: devised the project, scientific suggestions, and conceived this study.

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