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RESEARCH ARTICLE
KLİNİK ÇALIŞMA

Influenza viruses and SARS-CoV-2 in adult: 'Similarities and differences'

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ABSTRACT

Influenza viruses and SARS-CoV-2 in adult: 'Similarities and differences'

Introduction: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing a global pandemic starting from December 2019, showed a course that resulted in serious mortality in the world. In order to understand SARS-CoV-2 better, here we aimed to compare the similar and different characteristics of Influenza viruses occurring in the same season with SARS-CoV-2.

Materials and Methods: A total of 144 patients (31 patients with COVID-19, 62 patients with H1N1 influenza, and 51 patients with influenza B) were included in the study. Demographic findings, chronic diseases, laboratory values, chest x-ray, and chest CT findings of the patients were evaluated retrospectively.

Results: Median age of the COVID-19 patients and rate of male patients were higher than other patient groups (55 years; $p < 0.001$) (61% male; $p < 0.001$). The most common chronic medical conditions were hypertension and diabetes. Platelet numbers and alanine aminotransferase values were significantly higher in COVID-19 patients. Radiologically, bilateral (74.2%) and non-specific distribution (58.1%), ground-glass opacities with consolidation

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(51.6%), patchy image (25.8%), ground-glass opacities with interstitial changes (22.6%) and halo sign (22.6%) were quite evident than other groups in COVID-19 patients ($p < 0.05$).

Conclusion: We suggest that due to the higher PLT values observed in COVID-19 patients, initiation of anticoagulant therapy should be considered in the early stage and routine follow-up with d-dimer and fibrinogen should be applied for suspected patients. Moreover, attention should be paid in terms of possible liver toxicity of the drugs to be used in treatment due the higher ALT values observed in COVID-19 patients. Since we did not detect SARS-CoV-2 and influenza viruses concurrently in the same patient, it may be helpful to focus on only one virus in a patient with symptoms, and radiographic differences can be used to differentiate COVID-19 from influenza.

Key words: COVID-19; influenza A (H1N1); influenza B; diagnosis; radiology

ÖZ

Yetişkinlerde influenza virüsler ve SARS-CoV-2: 'Benzerlikler ve farklılıklar'

Giriş: Koronavirüs-2 (SARS-CoV-2) olarak bilinen virüs Aralık 2019 döneminde başlayıp tüm dünyada salgına yol açarak, ciddi mortalite oranlarına yol açmıştır. Bu çalışmada SARS-CoV-2'yi ve yol açtığı hastalığı (COVID-19) daha iyi anlamak için aynı dönemde solunum hastalığına yol açan influenza virüsler ile benzerlik ve farklılıklarını karşılaştırmayı amaçladık.

Materyal ve Metod: Bu çalışmada toplamda 144 hasta değerlendirildi (31 hasta COVID-19, 62 hasta influenza H1N1 ve 51 hasta influenza B tanılıydı). Hastaların demografik verileri, kronik hastalık hikayeleri, laboratuvar bulguları, göğüs x-ray ve toraks komputarize tomografi bulguları retrospektif olarak değerlendirildi.

Bulgular: COVID-19 hastalarının ortalama yaş düzeyleri ve erkek hasta sayıları influenza hastalarından belirgin olarak daha yüksekti (55 yaş; $p < 0,001$) (61% erkek; $p < 0,001$). Tüm gruplarda en sık rastlanan kronik hastalık hipertansiyon ve diyabetti. Kan trombosit seviyesi ve alanin amino-transferaz seviyeleri COVID-19 hastalarında influenza gruba göre daha yüksekti. Radyolojik olarak, bilateral (%74,2), non- spesifik dağılım (%58,1), buzlu cam opsitele ile konsolidasyon (%51,6), yamalı görüntü (%25,8), buzlu cam opsitele ile interstisyel değişiklikler (%22,6) ve halo işareti (%22,6) COVID-19 hastalarında diğer gruplara göre oldukça baskındı ($p < 0,05$).

Sonuç: COVID-19 hastalarında gözlenen PLT değerlerinin daha yüksek olması nedeniyle erken dönemde antikoagülan tedaviye başlanması ve şüphelenilen hastalarda d-dimer ve fibrinojen ile rutin takip yapılması gerektiğini öneriyoruz. Ayrıca COVID-19 hastalarında gözlenen ALT değerlerinin daha yüksek olması nedeniyle tedavide kullanılacak ilaçlara olası karaciğer toksisitesi açısından dikkat edilmelidir. Aynı hastada SARS-CoV-2 ve influenza virüslerini aynı anda tespit etmediğimiz için semptomları olan bir hastada sadece bir virüse odaklanmak faydalı olabilir ve COVID-19'u influenzazadan ayırt etmek için radyografik farklılıklar kullanılabilir.

Anahtar kelimeler: COVID-19; influenza A (H1N1); influenza B; tanı; radyoloji

INTRODUCTION

Many viruses that cause a pandemic in world history are known to mostly affect the respiratory system (1). H1N1 influenza virus was first reported in Mexico at the end of March 2009, spread worldwide in a short time, and still causes infections every season. Influenza B, which is a human-derived virus and also causative of seasonal flu, can also cause pandemics. Coronavirus disease 2019 (COVID-19) which appeared in Wuhan province of China in December 2019, was caused by SARS-CoV-2 and led to mortality and morbidity leading to a pandemic worldwide. While influenza is the commonly known caused a staggering pandemic in the world now (1,2).

It is believed that respiratory droplets and close contacts are the common spreading characteristics of these viruses (3). Although clinical characteristics of H1N1 influenza and influenza B are in the form of

mild disease, many studies reported that influenza viruses caused serious illnesses, even death (4). According to the World Health Organization, the disease and mortality rates of COVID-19 vary from country to country; however, they are much higher than those of Influenza viruses so far (5). Therefore, it is considered that the world may be facing a serious COVID-19 pandemic currently. Since H1N1 influenza and influenza B mostly cause mild disease and the hospitalization rate is low, imaging modalities and wide laboratory methods are not frequently used in diagnosis and follow-up. In the COVID-19 pandemic, however, chest X-ray (CXR) and computerized tomography (CT) images, as well as extensive laboratory tests, have gained vital importance in the world (6).

Recent studies have reported that COVID-19 patients have three times higher risk of in-hospital mortality, and a higher risk of secondary complications compared to seasonal influenza patients (7).

Recent studies have revealed that the presentation of patients with COVID-19 pneumonia and other causes of viral pneumonia differs considerably in terms of radiology, clinics, and mortality (8). The present study aims to compare the similar and different characteristics of influenza viruses occurring in the same season with SARS-CoV-2 by analyzing and comparing the radiological, clinical, and laboratory findings retrospectively to understand SARS-CoV-2 better and obtain a foresight for the diagnosis, follow-up, and treatment.

MATERIALS and METHODS

Patient Selection

In this retrospective study, the findings of patients, who were over the age of 18, diagnosed with H1N1 influenza, influenza B, and COVID-19, admitted to the outpatient and inpatient services of Chest Diseases, Ear, Nose and Throat (ENT), Infectious Diseases, Internal Medicine, Obstetrics, and Emergency departments of a University Hospital between October 2019 and April 2020, were evaluated retrospectively. This study was approved by the concerned tertiary University Institutional Review Board (Project no: KA20/173) and supported by University Research Fund.

H1N1 influenza and influenza B positive patients were the cases identified between October 2019 and March 2020 when COVID-19 did not appear in Turkey. After mid-March 2020, COVID-19 positive patients were evaluated. The diagnosis of H1N1 influenza and influenza B patients was made with a rapid antigen test performed by the nasopharyngeal swab specimens. Nasopharyngeal swab real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) positivity was used for the diagnosis of COVID-19 patients. Unlike H1N1 influenza and influenza B patients, CXR and chest-CT were obtained in addition to the positive PCR test for all COVID-19 patients to support the diagnosis. Influenza patients with a fever above 38°C, an underlying chronic disease, advanced age, and marked leukopenia, and all COVID-19 patients were hospitalized. Clinical and laboratory data were obtained from files and electronic medical records. Age, sex, chronic diseases, laboratory results, and findings of CXR and chest CT imaging were recorded. Laboratory results at the time of diagnosis and admission to the hospital (before beginning the treatment) are used to compare three groups.

Radiological Assessment

CXR was performed in 93 patients (33 patients with H1N1 Influenza, 29 patients with influenza B, and 31 patients with COVID-19). Admission chest radiographs in the standard posteroanterior and lateral views were obtained using Definium 6000 Dx digital x-ray system with a shooting distance of 150 cm. While obtaining roentgenogram, 251 mA, 18 mS, 80 kVp, 4.64 mAs parameters were used. Chest CT was performed in 37 patients in total. Four patients with H1N1 influenza, 2 patients with influenza B, and 31 patients with COVID-19 underwent unenhanced helical CT by a Hi-Speed scanner (Toshiba Aquilion, Computerized Tomography Medical System). After CT was performed using the CX 128 detector at 120 kV and 90 mAs with 7-mm collimation and a 7-mm reconstruction interval on the axial plane, 0.25 mm axial and coronal reconstruction images were obtained and evaluated. All radiographic data were evaluated by two radiologists, one with 3-year and the other with 8-year experience, and a consensus was reached in all cases. All radiological images were observed at the time of admission.

Radiologically, the following parameters were examined: (1) interstitial changes, (2) ground-glass opacities (GGO), (3) centrilobular nodules, (4) consolidation, (5) GGO + consolidation, (6) GGO + interstitial changes, (7) mixed pattern, (8) tree-in-bud, (9) air bronchogram, (10) interlobular septal changes, (11) crazy paving pattern, (12) halo sign, (13) pleural effusion, (14) pericardial effusion (15) lymphadenopathy. In addition, radiologists also recorded other radiological findings such as unilateral involvement, bilateral involvement, extent on initial imaging (focal, patchy, diffuse: 3 or more involved zones), predominance in upper zones, middle zones, and lower zones following the Fleischner Society Glossary terms (8,9).

Statistical Analysis

Laboratory results of H1N1 influenza, influenza B, and COVID-19 groups were compared using the one-way analysis of variance (ANOVA) or Kruskal-Wallis H test. Additional clinical and radiological characteristics of groups were compared using cross-tables with Fisher's Exact test or Chi-square test. Mean, standard deviation, minimum, median, and maximum values for continuous variables, as well as, frequency and percentage values for categorical variables were calculated. All statistical analyses and calculations were performed using the SPSS 15.0

statistical software package. Evaluations and comments were made at a significant level of p-value lower than 0.05 and indicated with bold characteristics in the tables.

RESULTS

Epidemiological Characteristics

The total number of H1N1 influenza and influenza B patients diagnosed in the 2019-2020 season was 585. All epidemiological characteristics of patients are given in Table 1. Of these, a total of 3 patients, 2 with H1N1 and 1 with influenza B, were pregnant. Also, 463 patients were under the age of 18. Six patients were both H1N1 and influenza B positive. Since those patients were excluded, 62 H1N1 influenza, 51 influenza B, and 31 COVID-19 cases were included in the study. While the number of female patients was higher in H1N1 and influenza B, the number of male patients was significantly higher in COVID-19. Mean age of the Influenza B patients (38.7) was lower than that of the H1N1 and COVID-19 patients ($p < 0.05$). COVID-19 patients were observed to have the highest mean age.

Hospital Data

Seventeen of 62 H1N1 influenza patients, 11 of 51 influenza B patients, and all 31 COVID-19 patients were hospitalized. Sixteen patients diagnosed with COVID-19 were suspected to have a concurrent influenza infection; thus, the influenza rapid antibody test Flu A&B-600409, 06/2022) was performed. However, all influenza tests were negative in patients diagnosed with COVID-19.

Chronic diseases were hypertension (HT), diabetes (DM), chronic renal disease (CRD), asthma, chronic heart disease (CHD), chronic obstructive pulmonary disease (COPD), malignancy (prostate ca), chronic

neurological disease (CND), hypothyroidism, renal transplantation, Lyme disease, and multiple sclerosis, respectively. The rate of having a chronic disease was higher in the H1N1 group (25.9%) than in the influenza B group (%18.8) ($p < 0.05$). On the other hand, COVID-19 patients were observed to have the highest rate of chronic disease (46.7%) (Table 2). While HT was the most common chronic disease in all groups, it is followed by the DM, CRD, asthma, CAD, and COPD comorbidities, respectively ($p < 0.05$) (Table 2). While the H1N1 group was observed to have the highest rate of patients with DM, this rate was observed to be the lowest in the COVID-19 group; however, this finding was not statistically significant. Although not statistically significant, no CRF comorbidity was observed in the COVID-19 group, however, it was observed in the H1N1 and influenza B groups (Table 2).

Laboratory Results

Patients' laboratory test results including leukocyte, neutrophil, lymphocyte, eosinophil, monocyte, basophil, platelet count, and hemoglobin C-reactive protein (CRP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Blood Urea Nitrogen (BUN), creatinine values were examined (Table 3).

Comparing whole blood and biochemistry values in these three patient groups, the most significant difference was observed in PLT values. PLT values were found to be significantly lower while leukocyte and neutrophil values were found to be significantly higher in H1N1 influenza, and influenza B patients compared to the COVID-19 patients ($p < 0.05$). While the mean PLT values in the H1N1 influenza group and influenza B group were very close to each other, the median values of the PLT values in the COVID-19 group were significantly higher (mean PLT count=

Table 1. Demographic characteristics of the patients included in the present study

	H1N1 influenza	Influenza B	COVID- 19
	(n)	(n)	(n)
Patient number	62	51	31
Female/male	37/ 25	36/ 15	11/ 20
Median age (year)	52	33	55
Positive test	62	51	17
Need of intensive care	3	-	-
Radiological image (+) (Chest	33	27	31

X- Ray: Computerize tomography, n: Number.

Table 2. Chronic diseases in H1N1 Influenza, Influenza B and COVID-19 patients

	H1N1 Influenza (%)	Influenza B (%)	COVID-19 (%)	Total (n)	Chi-square	p
Gender (Female/Male)	44.0/40.0	42.9/26.7	13.1/33.3	84/60	9.143	0.009
Hypertension (+/-)	45.0/41.9	20.0/38.7	35.0/19.4	20/124	3.665	0.168
Diabetes (+/-)	64.3/40.0	21.4/37.7	14.3/22.3	14/130	2.688	0.252
Chronic Renal Disease (CRD) (+/-)	77.8/40.0	22.2/37.0	0.0/23.0	9/135	4.648	0.082
Asthma (+/-)	60.0/41.7	40.0/36.0	0.0/22.3	5/139	1.210	0.723
COPD (Chronic Obstructive Pulmonary Disease) (+/-)	33.3/42.6	33.3/36.2	33.3/21.3	3/141	0.784	>0.999
Chronic Heart Disease (CHD)(+/-)	66.7/41.8	0.0/36.9	33.3/21.3	3/141	1.884	0.437
Renal Transplantation (+/-)	50.0/42.3	50.0/35.9	0.0/21.8	2/142	0.734	>0.999
Chronic Neurological Disease (CND) (+/-)	0.0/43.0	100.0/35.2	0.0/21.8	2/142	2.478	0.174
Hypothyroidi (+/-)	100.0/42.0	0.0/36.4	0.0/21.7	1/143	1.469	>0.999
Atrial Fibrillation (+/-)	100.0/42.0	0.0/36.4	0.0/21.7	1/143	1.469	>0.999
Multi Nodular Goiter (MNG) (+/-)	100.0/42.0	0.0/36.4	0.0/21.7	1/143	1.469	>0.999
Allergic Asthma (+/-)	0.0/42.7	0.0/36.4	100.0/	1/143	2.823	0.215
Malignancy (+/-)	0.0/42.7	0.0/36.4	100.0/	1/143	2.823	0.215
Lyme disease (+/-)	0.0/42.7	100.0/35.7	0.0/21.7	1/143	1.789	0.576
Multiple Sclerosis (+/-)	0.0/42.7	100.0/35.7	0.0/21.7	1/143	1.789	0.576
Chronic disease	25.9	18.8	55.3	-	11.435	0.003

n: Number. Bold values indicates a significant difference (p< 0.05).

257.516 $10^9/L$ ($p < 0.037$) (Table 3). However, mean PLT value was within the normal reference values. Thrombocytosis (PLT count $>450.0 \times 10^9/L$) was detected in only one patient with H1N1 influenza, one patient with influenza B, and one patient with COVID-19, ($495.0 \times 10^9/L$, $618.0 \times 10^9/L$, $577 \times 10^9/L$, respectively). On the other hand, the presence of leukopenia and lymphopenia events were lowest in the COVID-19 group. Leukopenia was mostly observed in the influenza B group (13.5%) ($p < 0.05$). Also, 31.9% of patients were observed to have lymphopenia. While a lower percentage (12.9%) of COVID-19 patients were observed to have lymphopenia, this figure was higher in the H1N1 influenza group (39.3%) and influenza B group (34.6%) ($p < 0.032$) (Table 4). AST values were higher ($p < 0.064$) and ALT values were significantly higher ($p < 0.037$) in the COVID-19 group. Apart from these values, there was no significant difference between the groups in terms of the eosinophil, monocyte, basophil, hemoglobin, CRP, BUN, creatinine values. Table 3 presents the results of the laboratory tests.

Radiological Imaging Findings

Radiological evaluation was performed on 33 of 62 H1N1 influenza patients, 27 of 51 influenza B patients, and 31 COVID-19 patients included in the study. Of these, 4 H1N1 influenza patients, 2 influenza B patients, and all COVID-19 patients underwent chest CT.

Three pregnant women, two with H1N1 influenza and one with influenza B, were hospitalized to follow up closely; however, radiological examination was not required, and they were discharged after recovery.

Radiologically, pneumonia findings and related radiological findings were more evident in the COVID-19 group compared to the H1N1 influenza group and influenza B group. The most common radiological findings observed in all three groups were bilateral distribution (74.2%), non-specific distribution (58.1%), GGO with consolidation (51.6%), patchy image (25.8%) GGO with interstitial changes (22.6%), and halo sign (22.6%) views, respectively

Table 3. Laboratory findings in H1N1 Influenza, Influenza B and COVID-19 patients

Parameter	Group	n	Mean	Std. Dev.	Min.	Median	Max.	Test	p
Age	H1N1 Influenza	61	48.8 (b)*	17.5	19	52	83	Chi-square= 21.005	<0.001
	Influenza B	52	38.7 (a)*	18.8	18	33	93		
	COVID-19	31	55.2 (b)	16.4	27	55	80		
Leukosyte (10 ⁹ /L)	H1N1 Influenza	61	7.996 (b)	3.331	2.09	7.44	20.40	Chi-square= 7.762	0.021
	Influenza B	52	6.520 (a)	2.545	2.72	6.71	12.90		
	COVID-19	31	6.884 (a.b)*	1.672	4.14	6.78	11.50		
Neutrophil (10 ⁹ /L)	H1N1 Influenza	61	5.478 (b)	2.900	.64	5.06	17.90	Chi-square= 9.395	0.009
	Influenza B	52	4.187 (a)	2.125	1.53	4.20	10.90		
	COVID-19	31	4.390 (a.b)	1.573	2.59	3.84	9.38		
Lymphocyte (10 ⁹ /L)	H1N1 Influenza	61	1.448	.928	.30	1.12	5.76	F= 1.826	0.165
	Influenza B	52	1.463	.784	.24	1.47	3.38		
	COVID-19	31	1.779	.728	.33	1.76	3.45		
Monocyte (10 ⁹ /L)	H1N1 Influenza	61	.630	.405	.00	0.493	2.81	Chi-square= 1.249	0.535
	Influenza B	52	.575	.314	.05	0.495	1.75		
	COVID-19	31	.652	.402	.18	0.530	1.87		
Basophil (10 ⁹ /L)	H1N1 Influenza	61	.081	.091	.01	0.060	.65	Chi-square= 3.767	0.152
	Influenza B	52	.076	.092	.01	0.051	.53		
	COVID-19	31	.080	.122	.00	0.042	.65		
Eosinophil (10 ⁹ /L)	H1N1 Influenza	61	.0787	.1165	.001	0.030	.720	Chi-square= 1.125	0.570
	Influenza B	52	.0846	.1273	.001	0.040	.635		
	COVID-19	31	.0748	.0602	.001	0.060	.220		
Hemoglobin (g/L)	H1N1 Influenza	61	14.295	1.553	9.94	14.10	17.90	F= 1.772	0.174
	Influenza B	52	13.765	1.768	9.01	13.65	16.70		
	COVID-19	31	14.300	1.517	11.50	14.30	17.10		
PLT (10 ⁹ /L)	H1N1 Influenza	59	212.469 (a)	68.715	85.50	205	495.00	Chi-square= 6.586	0.037
	Influenza B	52	215.636 (a)	94.700	27.00	209	618.00		
	COVID-19	31	257.516 (b)	96.694	128.00	247	577.00		
CRP (mg/dL)	H1N1 Influenza	58	36.085	40.799	.50	21.3	154.70	Chi-square= 3.980	0.137
	Influenza B	50	26.274	44.538	.50	14.2	218.90		
	COVID-19	31	43.283	47.397	.50	23.7	181.00		
BUN (mg/dL)	H1N1 Influenza	45	19.488	12.270	5.00	20	60.00	Chi-square= 1.368	0.505
	Influenza B	36	19.638	11.050	3.00	21	61.00		
	COVID-19	31	18.322	15.040	6.00	13	73.00		
Creatinin (mg/dL)	H1N1 Influenza	45	1.286	1.443	.50	0.86	7.00	Chi-square= 1.629	0.443
	Influenza B	36	1.019	.765	.54	0.77	4.71		
	COVID-19	31	1.247	1.508	.58	0.81	7.00		
AST (U/L)	H1N1 Influenza	45	21.111	8.183	7.00	20	45.00	F= 2.816	0.064
	Influenza B	36	24.666	10.780	9.00	24	45.00		
	COVID-19	31	26.322	10.952	8.00	25	50.00		
ALT (U/L)	H1N1 Influenza	47	22.085 (a)	9.629	6.00	19	55.00	F= 3.402	0.037
	Influenza B	36	27.250 (a.b)	13.353	8.00	25	58.00		
	COVID-19	31	29.290 (b)	15.750	8.00	28	74.00		

F: Fisher's exact test applied, *a, b, a.b: different letters show significantly different levels. n: Number. Bold values indicates a significant difference (p< 0.05).

Table 4. Leukocyte and lymphocyte rates in H1N1 Influenza, Influenza B and COVID-19 patients

		(H1N1) Influenza n (%)	Influenza B n (%)	COVID-19 n (%)	Total	Chi-square	p
Leukocyte (10 ⁹ /L)	<4	4 (36.3)	7 (63.7)	0 (0.0)	11	10.527	0.025
	4-10	45 (39.1)	40 (34.8)	30 (26.1)	115		
	>10	12 (66.7)	5 (27.8)	1 (5.5)	18		
Lymphocyte (10 ⁹ /L)	<1	24 (52.2)	18 (39.1)	4 (8.7)	46	6.877	0.032
	1>	37 (37.8)	34 (34.7)	27 (27.5)	98		

n: Number. Bold values indicates a significant difference (p< 0.05).

(p< 0.05) (Table 5). The most frequent findings in the COVID-19 group were found to be bilateral and non-specific distribution, GGO with consolidation, and patchy image, respectively. Analyzing the regions, the lower zone was found to be dominant in all three groups, and interstitial changes were observed close to it. There was no significant difference in terms of lower zone location and interstitial changes in all three groups. In the present study, GGO+interstitial changes were not observed in COVID-19 cases, while patchy appearance was not observed in influenza B cases (Figure 1). Unlike the COVID-19 group, the H1N1 influenza group and influenza B group were not observed to have a crazy-paving pattern, halo sign, pleural effusion, and LAP (Table 5).

DISCUSSION

The most prominent feature of the present study, in which the demographical, clinical, laboratory and radiological features of H1N1 influenza, influenza B, and COVID-19 patients were compared, was the higher PLT and ALT values and significant radiographic features observed in COVID-19 patients. The present study aimed to draw attention to the clinical differences between the influenza viruses that already live with people, and the deteriorating laboratory findings, and the different radiological features of the new coronavirus, which is considered to circulate among people for many years and which already lives with people.

Several studies have reported different levels of platelets in COVID-19 patients (10,11), however, PLT levels were significantly higher compared to the influenza groups. However, this increment was not at the level of thrombocytosis. The higher PLT values observed in the present study might be associated with the excess predisposition to thrombi and emboli

in different organs of these patients (12,13). Nevertheless, no COVID-19 patient in the present study was diagnosed with embolism.

ALT values were found to be the second important difference between the patients with COVID-19 and those with influenza. Drugs (such as favipiravir, hydroxychloroquine) suggested by the Ministry of Health (Turkey) for the COVID-19 patients can also cause ALT elevation, but treatment was not started for the patients when their blood samples were drawn at the time of hospitalization. Afterward, we observed a clinical improvement in our patients with a decrement in ALT value after continuing the drug treatment. Therefore, we hypothesized that ALT elevation is correlated with the disease itself rather than the effect of drugs. Previous studies have reported that the virus could damage the liver in influenza outbreaks and that a 15-20% increment in ALT and AST values was observed in patients with COVID-19 (14-17). Similarly, a significant difference in leukocyte and neutrophil levels was found also in the present study. The lowest leukocyte and neutrophil values were observed in the influenza B group, consistent with the literature (18,19). The occurrence of an event of lymphopenia was the lowest in the COVID-19 group (4 patients, 12.9%), and the highest in the H1N1 influenza group (24 patients, 39.3%). No leukopenia event was encountered in the COVID-19 group. Also, the levels of leukocytes and neutrophils were found to moderately decrease in the COVID-19 group compared to the influenza groups. These findings were also consistent with the literature (11, 20-23).

The most prominent demographic characteristic was that the average age of COVID-19 patients was significantly higher than that of the influenza groups. Despite the lower incidence of COVID-19 in older patients due to the lockdown that was applied to

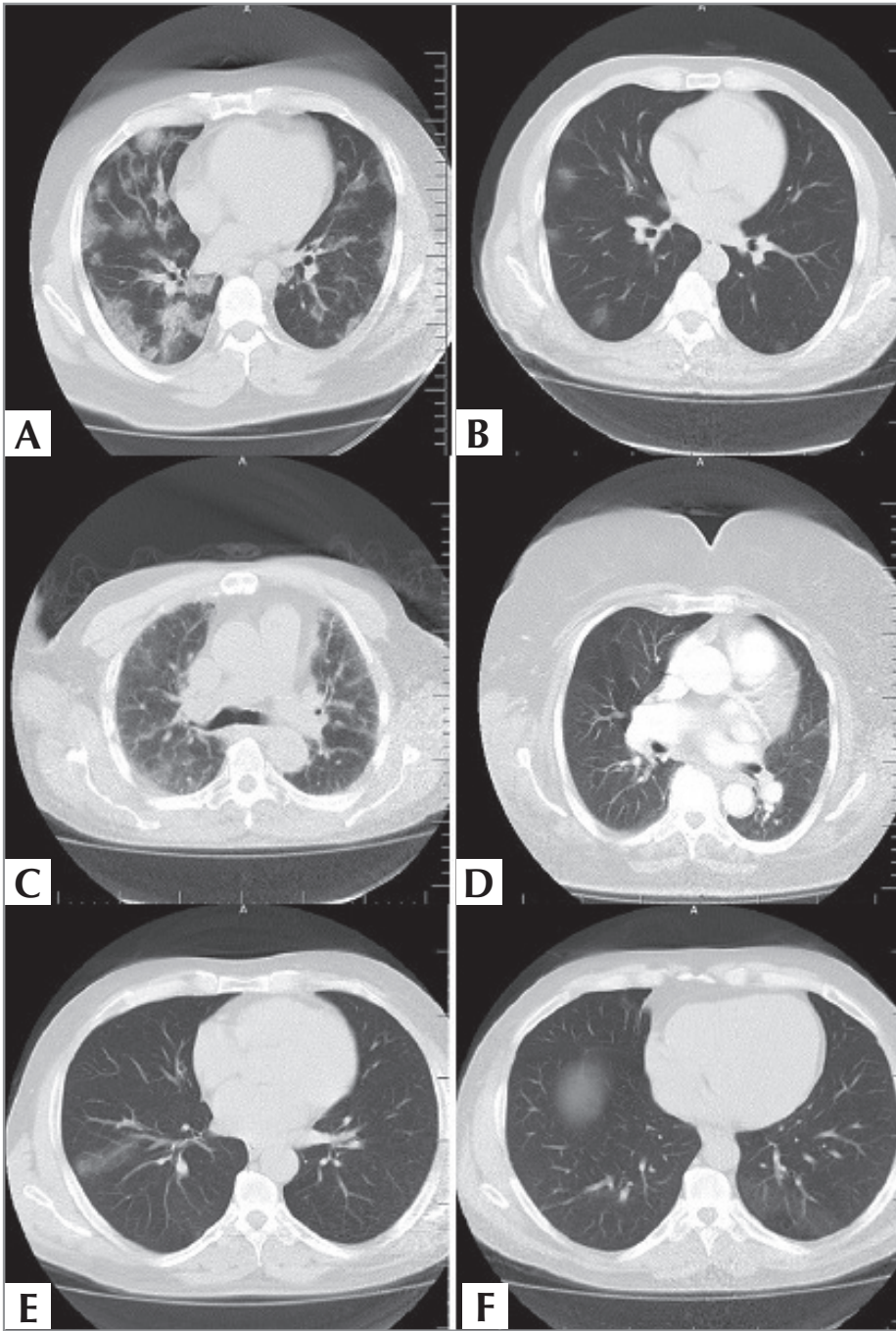


Figure 1. Computerized tomography (CT) findings of the lung of COVID-19, H1N1 influenza and B influenza. Radiological findings of COVID-19, **A.** Sharp-bound, patchy widespread ground-glass areas in both lungs, extending parallel to the pleura in the subpleural areas. **B.** Ground-glass areas that are located in the peripheral parts of the both lungs but more concentrated on the right. Radiological findings of H1N1 influenza, **C.** Subpleural ground-glass opacities accompanying peri-bronchial inflammation, interstitial pattern and minimal fibrosis, **D.** Mosaic pattern appearance in both lung parenchyma, with a pleural-based wedge-style ground glass area in the left lung and more pronounced on the right, accompanying slight prominence in the interstitial tissue. Radiological findings of influenza B, **E.** Pleural-based, ground-glass area appearance in the right lung lower lobe superior segment, **F.** Bilateral subpleural ground-glass opacities.

people above the age of 65 by the Ministry of Health (Turkey), this significantly higher average age of the COVID-19 group may imply that influenza A (H1N1) and influenza B affect significantly more children and young people compared to the COVID-19 disease. Another distinctive feature was that the rate of male patients was significantly higher in the COVID-19 group compared to the influenza groups. In the literature, the rate of male patients and average age were also found higher in COVID-19 cases (11).

Lower lobe involvement, interstitial changes, GGO and GGO, and consolidation were the most common simultaneous findings in all three groups. These findings were common in viral pneumonia and were observed in all three groups in the present study, and there was no statistically significant difference between them ($p > 0.05$) (24-26). Radiological findings in the influenza H1N1 group were observed to be more prominent compared to the influenza B group. The most common finding in patients with H1N1 influenza was bilateral involvement, which was mostly observed in the lower zones, interstitial changes, and GGO+interstitial changes. Radiological findings were more insignificant in patients with influenza B, lower zones with bilateral distribution and other symptoms were similar and less common, which was similar with other studies (20,24,25).

The duration between the onset of symptoms and the appearance of findings of radiological findings was shorter and more noticeable in the patients with COVID-19 than those in the influenza group. Radiological findings of pneumonia were also more evident in patients with COVID-19. Moreover, margin saliency of the lesions and prominent peripheral location were found to be more evident in patients with COVID-19 compared to those in the H1N1 influenza group and influenza B group. The significantly different radiological findings observed in the COVID-19 patients were bilateral (74.2%), non-specific distribution (58.1%), GGO+consolidation (51.6%), later patchy image (25.8%), halo sign (22.6%) and crazy paving patch (12.9%) ($p < 0.05$). Since no halo sign and crazy paving patch were detected in the H1N1 influenza group and influenza B group, these findings can be used to differentiate between COVID-19 pneumonia and influenza (23,24,27).

No significant difference was found between the groups in terms of the frequency of co-morbidities. HT and DM were the most common medical conditions

observed in all groups. In the present study, CRF was observed more frequently than other diseases in the influenza groups. This could be attributed to the fact that the center, where the study was conducted, was the primary center for renal transplantation in the region and the patients with chronic kidney failure received regular treatment and dialysis at this center.

In the present study conducted in this center, it was observed that patients with influenza viruses were admitted to the hospital in a higher ratio than COVID-19 patients until the end of May. It was observed that viruses appeared at different times while H1N1 influenza was observed mostly in the first months of autumn, H1N1 influenza together with the influenza B group was observed in January, and influenza B infections were mostly observed after February. As of March 2020, COVID-19 infections have been observed in our hospital. Since then, simultaneous influenza tests in COVID-19 patients were negative. We performed initial influenza tests on all COVID-19 patients included in this study at the time of hospitalization. This may also imply that while some viruses have the potential to co-infect, SARS-CoV-2's potential to infect concurrently with other viruses or infectious agents is low, which should be explored through more comprehensive studies.

This study had several limitations. First of all, we focused on the pandemic since 11 March 2020 and performed almost exclusively COVID-19 PCR test on patients. In this period, H1N1 influenza, influenza B, and other viral tests were not given much importance. Other tests except for COVID-19 were performed in small numbers during this period. However, the numbers of H1N1 influenza, influenza B, and COVID-19 cases were sufficient to make a comparison in this study, particularly under pandemic circumstances. All patients diagnosed with COVID-19 had to be hospitalized for isolation purposes for at least five days even though they did not have an additional disease and they were young patients. In addition, hospitalization criteria, duration of hospitalization, the need for intensive care and prognosis were not evaluated in this study. Although all values were evaluated retrospectively and medical records for H1N1 influenza and influenza B were limited and narrow-scaled, the differences in PLT values, leukocyte, and neutrophil values were highly significant. Thus, further biochemical tests applied in a higher

number of influenza patients will strengthen our knowledge on this subject. Moreover, two different influenza viruses have not been evaluated as subgroups in most studies in the literature, however, this distinction was made in the present study, which highlights the uniqueness of this study.

CONCLUSION

Due to higher PLT values observed in COVID-19 patients, it is suggested that initiation of anticoagulant therapy should be considered in the early stage and routine follow-up with d-dimer and fibrinogen should be applied for suspected patients. Moreover, attention should be paid in terms of possible liver toxicity of the drugs to be used in treatment due to higher ALT values observed in COVID-19 patients. While chest CT images of H1N1 influenza and influenza B were compatible with non-specific viral infection findings, radiological findings of COVID-19 were highly specific and suggestive of a differential diagnosis.

Ethical Committee Approval: This study approval was obtained from Başkent University Faculty of Medicine Clinical Researches Ethical Committee (Decision No: 94603339-604.01.02, Date: 13.05.2020).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ŞT, ŞA

Analysis/Interpretation: ŞT, ÇK, BBY, AS, ÖÖ

Data acquisition: ŞT, ÇK, BBY, ÖÖ, AS

Writing: ŞT, ÇK, ÖÖ, BBY, AS

Clinical Revision: ŞT, ŞA

Final Approval: All of authors

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