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COVID-19 and H1N1 Influenza: Are They 2 Sides of the Same Coin?

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Abstract

Background: Swine flu (H1N1) and Coronavirus diseases (COVID-19) have been compared in the past few months. Both pandemics sparked a worldwide major panic. Although both have some common symptoms and diagnoses, they are quite different in many aspects. The current study aimed to investigate the differences in clinical and viral behaviors between H1N1 Influenza and COVID-19 pneumonia.

Methods: This was a retrospective study of adult patients hospitalized with H1N1 influenza pneumonia between January 2019 and February 2020, and patients hospitalized with COVID-19 during the outbreak. A demographic and clinical characteristic of H1N1 influenza and COVID-19 patients were recorded. Both groups were compared—using an independent samples student t test for continuous variables and a chi-square test for categorical data—to identify significantly different parameters between the 2 diseases.

Results: A total of 78 patients were included and divided into 2 groups: 33 patients (42.3%) with H1N1 and 45 patients (57.7%) with COVID-19. The mean age of the patients was 43.3 ± 10.6 years. Bronchial asthma was significantly higher among patients with H1N1, while diabetes mellitus was significantly higher among patients with COVID-19. Right lower lobe affection was significantly present among those with H1N1 than those with COVID (100% vs 0%). The monocytic count was significantly higher among those with H1N1 than COVID-19 (11.63 ± 1.50 vs 7.76 ± 1.68; $P < 0.001$). Respiratory rates of more than 22 c/min significantly increased in patients with HINI than in those with COVID-19 (18.2% vs 4.4%; $P = 0.05$). Mortality increased in patients with HINI than in those with COVID-19 (18.2% vs 6.7%). However, the difference did not reach statistical significance ($P = 0.15$).

Conclusion: Clinically, it is difficult to distinguish between H1N1 and COVID-19. Thus, a polymerase chain reaction is recommended for all patients suffering from influenza-like symptoms to rule out influenza A subtype H1N1 and/or SARS-CoV2.

Keywords: Pneumonia, Swine Flu, Acute Respiratory Distress Syndrome, Influenza, Polymerase Chain Reaction

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Introduction

Swine flu (H1N1) and coronavirus diseases (COVID-19) have been repeatedly compared in the past few months. These 2 illnesses have some signs and symptoms in common. However, they are quite different on many levels. Every year, there are 1 billion cases of influenza, with 3 to 5 million severe cases and up to 650,000 influenza-related respiratory deaths worldwide. The COVID-19 pandemic has affected more than 100 million people worldwide, with an estimated mortality of more than 2 million (1).

Immediately after the World Health Organization (WHO) announced the COVID-19 pandemic in March

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↑What is "already known" in this topic:
Swine flu and COVID-19 are 2 viral epidemics affecting the respiratory system. Both conditions may be overlapped, and they share many clinical signs and symptoms. However, their outcome is widely different. Both diseases were compared. However, no conclusive results were reached.

→What this article adds:
Clinically and even with laboratory workup, it is still difficult to differentiate the 2 diseases. Polymerase chain reaction remains the only clue to differentiate between the 2 conditions. Prevention remains a vital measure to guard against infection.

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2020, comparisons were made to the 2009 H1N1 influenza-A pandemic. The swine flu originated in the United States. The infection spread all over the country and then transmitted to other countries. It had a blend of specific flu genes that had not been previously seen in animals or humans. The Centers for Disease Control and Prevention (CDC) Organization stated, "It was a new virus that jumped from pigs to humans. Similarly, COVID-19 is also a zoonotic disease that jumped from animals to humans although there is no clear path up to this point in time." Thus, COVID-19 has been likened to the H1N1 influenza pandemic (2).

By the end of May 2009, 41 countries had reported 11,000 cases and 85 deaths due to H1H1, prompting the WHO to declare its first Public Health Emergency of International Concern (PHEIC). In 2018, global cases of influenza-associated respiratory mortality were at a higher rate than previously recorded (3-5).

However, "the COVID-19 pandemic had a more devastating impact, which could be explained by the following: (1) There was no existing treatment or prophylaxis for COVID-19; (2) People over 65 had some natural immunity to other H1N1 influenza viruses due to previous exposure; and (3) COVID-19 was more infectious with a higher case fatality rates. The CDC stated that "despite high levels of testing, flu activity was unusually low throughout the 2020-2021 flu season in both the United States and globally, with significantly fewer flu illnesses, hospitalizations, and deaths when compared with previous flu seasons. The vast majority of patients suspected of having influenza will not require hospitalization. Admissions are confined to those with clinical or radiological evidence of pneumonia, as well as those at increased risk of disease complications (eg, people >65 years, children <5 years), pregnant women, and people with certain chronic medical conditions). In the elderly, confusion, anorexia, and shortness of breath may be the only symptoms of influenza. This is in contrast to the SARS-CoV-2 mortality rates, which have remained higher than 2% in most parts of the world (1).

Furthermore, unlike the 2009 H1N1 pandemic, which killed primarily young people, the majority of COVID-19 deaths have been among the elderly (6).

The mode of transmission is similar for influenza and SARS-CoV-2 viruses (droplet and direct contact). However, the incubation period and transmissibility are quite different between the 2 viruses (eg, SARS-CoV-2 has a longer incubation period and higher transmissibility) (7).

The mechanism of viral pneumonia in COVID-19 is complex. Studies indicate that viral infection can cause an excessive immune response in the host. However, extensive tissue damage was reported in some cases due to dysfunctional coagulation, which is also known as a "cytokine storm" and can result in acute respiratory distress syndrome (ARDS) and multiorgan failure, ultimately leading to death (8).

Even though ARDS is common in influenza pneumonia (9), the case fatality rate is higher with COVID-19 (10).

Chills, cough, rhinorrhea, fever, sore throat, coryza, myalgia, shortness of breath, headache, dizziness, abdominal pain, decreased appetite, and malaise were the most commonly reported symptoms of influenza, similar to COVID-19. The H1N1 strain was also associated with an increase in the number of people reporting vomiting and diarrhea (11, 12).

Although some studies have focused on differences in symptoms of seasonal influenza viruses, few studies have compared clinical characteristics and complications of COVID-19 and influenza-A subtype H1N1, which have similar clinical presentations. Seasonal overlaps of H1N1 influenza-A pneumonia and COVID-19 pneumonia are expected. As a result, it is critical to recognize the similarities and differences between these 2 viral diseases to provide better care to patients and identify those at higher risk of complications.

We conducted this study to determine whether there were any differences in clinical manifestations and viral behaviors between patients with H1N1 influenza pneumonia and COVID-19 among those hospitalized at the new Najran general hospital in the Kingdom of Saudi Arabia (KSA).

Methods

In a 200 beds secondary care hospital in the city of Najran, KSA, we conducted a retrospective study of adult patients hospitalized with real-time reverse transcriptase polymerase chain reaction (RT-PCR) confirmed H1N1 influenza pneumonia during seasonal outbreaks between January 2019 to February 2020, and patients hospitalized with RT-PCR confirmed COVID-19 during the outbreak beginning in March 2020. Most of the patients were adults, over 20 years of age (45 with COVID-19 and 33 with influenza). A structured data sheet was used to collect demographic and clinical characteristics of patients—including underlying medical and respiratory comorbidities, laboratory and radiological investigations, treatment, and complications during hospitalization—from the information management system of the hospital. We compared these results between both groups and identified the most significant parameters between these 2 diseases.

Diagnosis of H1N1 influenza-A and SARS-CoV-2

Nasopharyngeal swabs were processed for H1N1 influenza virus detection using RT-PCR and the influenza virus PCR assay. Nasopharyngeal swabs were processed for RT-PCR detection of the SARS-CoV-2 virus in March 2020, following the WHO protocol for the 2019 nCoV RT-PCR assay. The radiological diagnosis of pneumonia was made based on the presence of infiltrates (a substance denser than air, such as pus, blood, or protein, which lingers within the parenchyma of the lungs) on X-ray imaging of the chest. A multidisciplinary team of intensivists, pulmonologists, and internal medicine consultants was included in diagnosing and managing conditions.

To determine disease severity, 2 scores were used—the Murray score and the quick Sequential Organ Failure Assessment (qSOFA) score. The qSOFA scoring system is useful in the clinical outcome prediction of critically ill patients. It includes 3 assessment parameters, instead of the 6 in the original SOFA, which include low blood pres-

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sure (SBP ≤ 100 mmHg), high respiratory rate (≥ 22 breaths/min), and altered mentation (GCS ≤ 14)). The score ranges between 0 and 3 and the presence of 2 or more qSOFA points near the onset of infection is associated with a greater risk of death or prolonged stay in the intensive care unit (13).

The Murray score is used to assess the severity of lung injury. A score of >2.5 indicates acute respiratory distress syndrome (ARDS), a score between 1 and 2.5 is a marker for mild to moderate lung injury, and a score of zero rules out lung injury. The score is based on 4 criteria: hypoxemia, respiratory compliance, chest radiographic findings, and the level of positive end-expiratory pressure. Each criterion receives a score from 0 to 4 according to condition severity and those numbers are summed to create the Murray score (14).

Statistical Analysis

We analyzed the data using SPSS Version 24. Categorical data were described by relative frequencies and percentages. Numerical data were described in terms of mean and standard deviation. The Kolmogorov-Smirnov test was used to test the normality of data. The chi-square test was used to test the association between categorical variables and the Fissure exact test was used in case of violation of the assumptions. An independent sample t test was used to test the difference between the 2 means of parametric tests and the Mann-Whitney U test was used for nonparametric data. Paired sample t test and Wilcoxon signed ranks were used to test the same variable at 2 different points in time. $P < 0.05$ was considered statistically significant.

Results

A total of 78 patients participated in the study, of whom 33 patients (42.3%) had H1N1 and 45 (57.7%) had COVID-19. The mean age of the patients was 43.3 ± 10.6 years, with men representing 67.9% of all the studied patients, and with no significant difference between the 2 groups regarding age or sex (Table 1).

In addition, both groups were comparable regarding hypertension, ischemic heart disease, cough and other clinical manifestations, blood pressure, respiratory rate, and oxygen saturation. However, there was a significant increase in bronchial asthma, heart rate, and temperature, while there was a statistically significant decrease in diabetes mellitus and diarrhea in the H1N1 group than in the COVID-19 group (Table 1).

Table 1. Comparisons between H1N1 and COVID-19 groups regarding patient demographics, associated comorbidities, clinical manifestations, vital signs, and results of imaging studies

Variable	Measures	HINI (n=33)	COVID-19 (n=45)	Total (78)	Test	*P* Value
Age (years)	Mean±SD	41.6±11.8	44.6±9.5	43.3±10.6	1.26	0.211
Gender	Male	20 (60.6%)	33 (73.3%)	53 (67.9%)	1.41	0.172
(n,%)	Female	13 (39.4%)	12 (26.7%)	25 (32.1%)		
Associated	Hypertension	8 (24.2%)	9 (20.0%)	17 (21.8%)	0.20	0.654
Comorbidity	Bronchial asthma	8 (24.2%)	2 (4.4%)	10 (12.8%)	FE	0.012*
	Diabetes mellitus	4 (12.1%)	16 (35.6%)	20 (25.6%)	FE	0.017*
	Ischemic heart disease	2 (6.1%)	4 (8.9%)	6 (7.7%)	FE	0.492
Clinical	Cough	30 (90.9%)	38 (84.4%)	68 (87.2%)	0.71	0.391
Manifestation	Fever	31 (93.9%)	32 (71.1)	63 (80.8%)	6.38	0.011*
	Vomiting	2 (6.1%)	5 (11.1%)	7 (9.0%)	FE	0.441
	Anorexia	1 (3.0%)	0 (0.0%)	1 (1.3%)	FE	0.417
	Abdominal pain	3 (9.1%)	1 (2.2%)	4 (5.1%)	FE	0.302
	Periorbital puffiness	1 (3.0%)	0 (0.0%)	1 (1.3%)	FE	0.417
	Sore throat	4 (12.1%)	7 (15.6%)	11 (14.1%)	FE	0.752
	Shortness of breath	8 (24.2%)	9 (20.0%)	17 (21.8%)	0.20	0.654
	Bone ache	1 (3.0%)	0 (0.0%)	1 (1.3%)	FE	0.417
	Dizziness	1 (3.0%)	1 (2.2%)	2 (2.6%)	FE	1.00
	Headache	0 (0.0%)	2 (4.4%)	2 (2.6%)	FE	0.501
	Diarrhea	0 (0.0%)	5 (11.1%)	5 (6.4%)	FE	0.050*
	Atypical Chest pain	0 (0.0%)	1 (2.2%)	1 (1.3%)	FE	1.00
	Fatigue	0 (0.0%)	2 (4.4%)	2 (2.6%)	FE	0.501
Vital signs	HR	103.88±8.47	95.40±8.28	98.98±9.32	4.42	<0.001*
	SBP	120.76±8.11	121.89±8.41	121.41±8.25	0.60	0.553
	DBP	75.76±7.72	76.89±6.68	76.41±7.11	0.69	0.492
	RR	20.42±1.90	19.87±1.14	20.10±1.53	1.61	0.113
	Temperature	37.72±0.38	37.46±0.37	37.57±0.40	2.93	0.004*
	O2 saturation	94.76±1.44	94.04±2.37	94.35±2.05	1.53	0.132
Imaging	N (Normal CXR)	2 (6.1%)	2 (4.4%)	4 (5.1%)	FE	<0.001*
	U (CXR not available)	7 (21.2%)	8 (17.8%)	15 (19.2%)		
	one quadrant right lower zone	8 (24.2%)	0 (0.0%)	8 (10.3%)		
	One quadrant right mid zone	0 (0.0%)	7 (15.6%)	7 (9.0%)		
	Two upper quadrants lung zones	0 (0.0%)	1 (2.2%)	1 (1.3%)		
	Bilateral lung basal quadrants zones	8 (24.2%)	0 (0.0%)	8 (10.3%)		

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Imaging Results

On analyzing chest X-ray imaging results, we found that the 2 groups were significantly different from one another ($P < 0.001$). Right lower lobe affection was significantly present among those with H1N1 when compared with those with COVID-19 (100% vs 0%), respectively (Figure 1, a, b, and c). Also, affection of lower lung bilaterally was significantly present among those with H1N1 when compared with COVID-19 patients (Figure 2, a, b, and c) and (Table 1).

Laboratory investigations showed that both groups were comparable for all results, except for a significant increase of monocytes in the H1N1 group compared with the COVID-19 group (Table 2).

Using the Murray score, both groups were comparable, while the Quick SOFA score showed that a respiratory rate of more than > 22 cycles/minute was significantly increased in the H1N1 group compared with the COVID-19 group (18.2% vs 4.4%). However, other variables showed nonsignificant differences. The duration of hospital stay was longer in COVID-19 patients than in H1N1 patients; however, the difference did not reach statistical significance. Furthermore, mortality was increased in the H1N1 group compared with the COVID-19 group (18.2% vs 6.7%), with no statistically significant differences (Table 3).

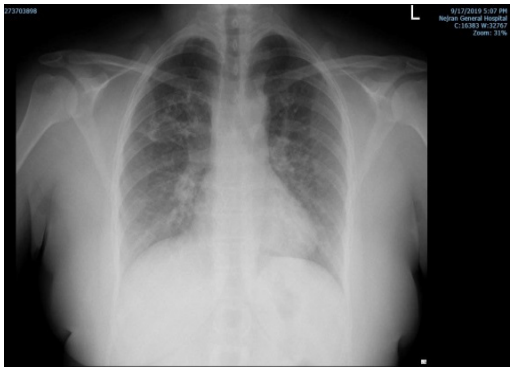

Figure 1 a. A case of positive influenza (H_1N_1) pneumonia, showing right lower zone paracardiac consolidation.

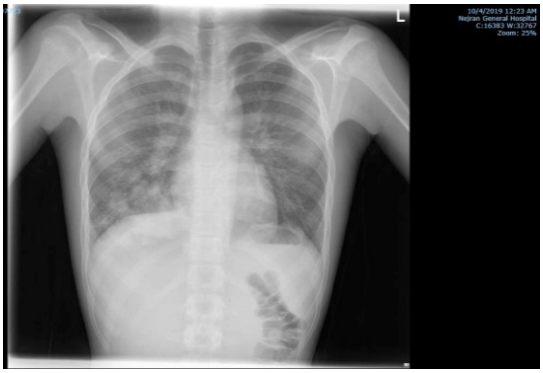

Figure 1 b. A case of positive influenza (H1N1) pneumonia, showing right lower zone consolidation.

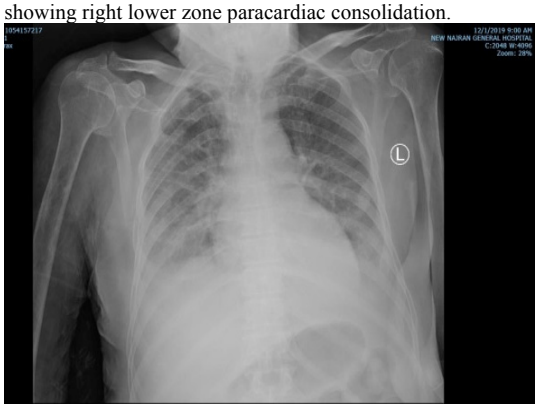

Figure 1 c. A case of positive influenza (H1N1) pneumonia, showing bilateral lower zone consolidations mainly on the right side.

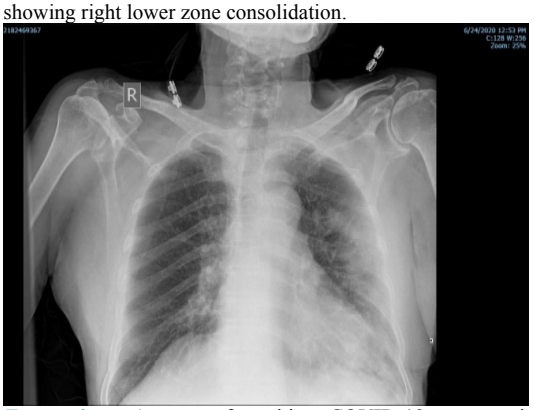

Figure 2 a. A case of positive COVID-19 pneumonia, showing left mid and lower (retrocardiac) zone consolidations.

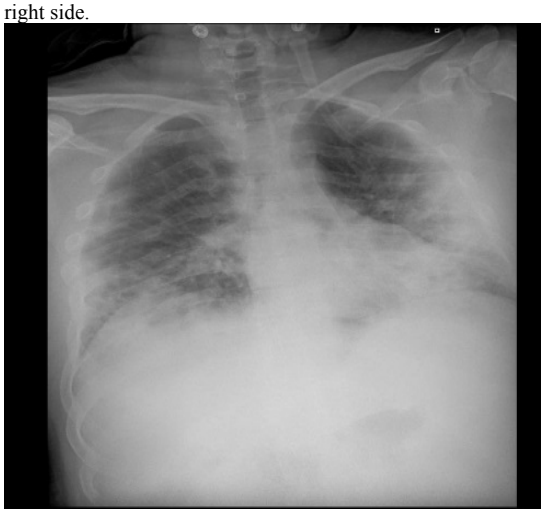

Figure 2 b. A case of +ve COVID-19 pneumonia, showing bilateral diffuse infertility (mainly lower zones).

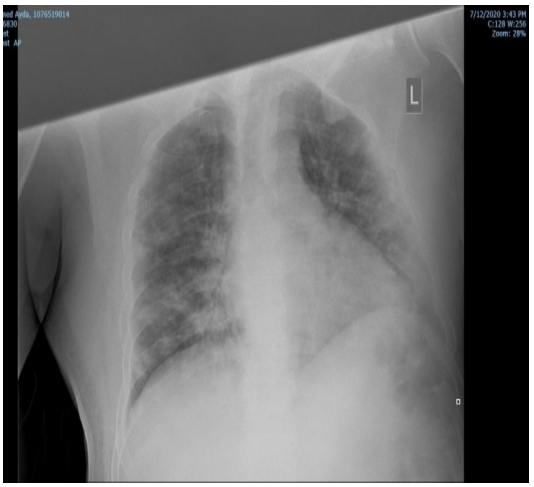

Figure 2 c. A case of positive COVID-19 pneumonia, showing bilateral diffuse infertility.

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Table 2. Comparisons between H1N1 and COVID-19 groups regarding blood cells, differential white cell count, sodium, potassium, renal, and liver function tests

Variable	HINI (n=33)	COVID-19 (n=45)	Test	*P* Value
WBCs x 10^3/CC	5.74±1.56	5.62±1.32	0.35	0.722
Neutrophils	56.03±9.35	58.64±8.11	1.32	0.191
Lymphocytes	33.39±6.20	31.89±5.68	1.11	0.271
Monocytes	11.63±1.50	7.76±1.68	10.51	<0.001*
Eosinophils	0.51±0.36	0.41±0.32	1.32	0.182
Basophils	0.27±0.09	0.26±0.08	0.19	0.844
RBCs x 10^6/ CC	4.16±0.39	4.03±0.42	1.31	0.192
Hemoglobin	12.29±0.58	12.08±0.76	1.37	0.173
Platelets x 10^3 / CC	207.67±24.84	210.38±25.41	0.47	0.640
Na	135.93±2.37	134.82±3.54	1.57	0.123
K	3.92±0.18	3.99±0.15	1.60	0.111
Creatinine	0.83±0.25	0.74±0.22	1.64	0.103
Urea	64.36±16.51	60.71±13.34	1.08	0.283
AST	37.27±10.62	33.38±8.88	1.76	0.093
ALT	35.48±6.07	35.71±8.39	0.13	0.893
Total bilirubin	1.11±0.36	1.00±0.45	1.15	0.272

Table 3. Comparisons between H1N1 and COVID-19 groups regarding murray score, quick SOFA score, hospital stay, and mortality

Variable	Measures	HINI (n=33)	COVID-19 (n=45)	Total (78)	Test	*P* Value
Murray	Cannot be assessed	7 (21.2%)	8 (18.6%)	15 (19.7%)	5.30	0.383
score	No lung injury detected	2 (6.1%)	2(4.7%)	4 (5.3%)		
	G1	8 (24.2%)	7 (16.3%)	15 (19.7%)		
	G2	10 (30.3%)	8 (18.6%)	18 (23.7%)		
	G3	4 (12.1%)	10 (23.3%)	14 (18.4%)		
	G4	2 (6.1%)	8 (18.6%)	10 (13.2%)		
Quick SOFA	RR > 22 cycles/min.	6 (18.2%)	2 (4.4%)	8 (10.3%)	FE	0.050*
score	Mental state (Awake)	33 (100.0%)	45 (100.0%)	78 (100.0%)	-	-
	SBP ≤ 100 mmHg	0 (0.0%)	1 (2.2%)	1 (1.3%)	FE	1.00
Hospital stay	Mean ± SD	4.85±0.56	5.04±1.33	4.96±1.07	0.79	0.433
	Min. – Max.	4-6	3-8	3-8		
Mortality		6 (18.2%)	3 (6.7%)	9 (11.5%)	FE	0.151

Table 4. Paired comparisons of laboratory values on admission and after 3 days (just before discharge) in the 2 groups

Group	Variable	On Admission	After 3 days	Paired (t)	*P* Value
H1N1	WBCs x 10^3/CC	5.74±1.56	4.93±1.07	6.53	<0.001*
	Neutrophils	56.03±9.35	43.57±5.06	9.72	<0.001*
	Lymphocytes	33.39±6.20	41.12±4.34	6.60	<0.001*
	Monocytes	11.63±1.50	9.41±0.79	8.20	<0.001*
	Eosinophils	0.51±0.36	1.42±0.42	10.91	<0.001*
	Basophils	0.27±0.09	0.28±0.08	4.50	<0.001*
	RBCs x 10^6/ CC	4.16±0.39	4.18±0.37	1.09	0.283
	Hemoglobin	12.29±0.58	12.32±0.59	0.62	0.538
	Platelets x 10^3 / CC	207.67±24.84	207.94±23.69	1.83	0.076
COVID-19	WBCs x 10^3/CC	5.62±1.32	5.72±1.23	1.92	0.062
	Neutrophils	58.64±8.11	59.67±7.34	4.17	<0.001*
	Lymphocytes	31.89±5.68	31.33±5.00	3.02	0.004*
	Monocytes	7.76±1.68	7.78±1.63	0.64	0.52
	Eosinophils	0.41±0.32	0.48±0.39	2.56	0.014*
	Basophils	0.26±0.08	0.31±0.11	3.37	0.002*
	RBCs x 10^6/ CC	4.03±0.42	3.97±0.42	0.74	0.46
	Hemoglobin	12.08±0.76	12.06±0.63	4.85	<0.001*
	Platelets x 10^3 / CC	210.38±25.41	215.09±23.67	0.95	0.39

In the H1N1 group, white blood cells, neutrophils, and monocytes were significantly reduced after 3 days of admission when compared with their values at admission, while lymphocytes and basophils were significantly increased. However, in the COVID-19 group, neutrophils, eosinophils, and basophils were significantly increased, while lymphocytes and hemoglobin concentrations were significantly reduced after 3 days of admission compared with values at admission (Table 4).

Discussion

The overlap of the flu season with the COVID-19 pandemic complicates the clinical management of patients with respiratory diseases. Direct clinical and laboratory comparison studies of these 2 infectious diseases are not common. Tang X et al (15) compared hospitalized patients with COVID-19 and influenza H1N1 ARDS. When adjusted for SOFA scores, the authors concluded that COVID-19-positive ARDS patients had lower severity of illness at presentation and lower mortality. The study, on the other hand, used data from 2 separate institutes, which may have resulted in some bias. It is also unclear why these patients' clinical and laboratory results differed while they were in the hospital. We discovered significant

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differences in laboratory results between hospitalized patients with COVID-19 and influenza when we tracked their temporal changes in our study. The most significant difference in COVID-19 patients over the course of hospitalization was worsening laboratory results when compared with influenza patients.

In our study, the similarities and differences between COVID-19 and H1N1 influenza pneumonia are highlighted. There was a significant male predominance among COVID-19 patients, which is consistent with databases from other parts of the world. In contrast, there was nearly equal gender distribution in H1N1 cases (12). It was also noteworthy that both infections necessitated hospitalization in nearly similar age groups. This is consistent with previous reports from the 2009 H1N1 pandemic, which indicated that younger age groups who became infected with influenza A subtype H1N1 experienced greater severity (5).

Many countries have reported a 2-wave pattern in COVID-19 cases during the 2020 pandemic, with a first wave in the spring followed by the second wave in late summer and autumn. Differences in age and disease severity have been reported, but the comparative characteristics of the 2 waves are still largely unidentified. Corresponding to a portion of the second wave, which is still active at the time of writing this article, patients in the second wave were younger, with shorter hospital stays, and a lower-case fatality rate than those in the first wave (11). In regards to H1N1 cases in our study, the peak incidence was reported during the winter, mainly between October and the beginning of January.

Also, in our study, we found that patients with COVID-19 had a longer duration of illness before presentation than H1N1 influenza patients. Tang et al (15) found a similar difference in hospital stay duration, with COVID-19 patients taking a longer course and becoming critically ill later than influenza patients. Because the influenza A virus binds to two 6-linked sialic acid receptors, which are expressed in the respiratory tract and are likely responsible for the shorter incubation period than COVID-19 infection, it has been hypothesized that this variation is due to differences in the distribution of virus entry receptors. The receptor actively involved in SARS-CoV-2 infection, on the other hand, is the ACE2 protein, which is largely found on alveolar epithelial cells and accounts for the long incubation period of COVID-19 infection (16).

In our study at the time of presentation, we found that right lower lobe affection was significantly present among those with H1N1 when compared with those with COVID-19. COVID-19, unlike H1N1, can later cause normal chest radiographs as well as strictly unilateral chest involvement (17).

Regarding disease severity according to the Murray score, in our study, we found that among patients diagnosed with H1N1, mild to moderate pulmonary symptoms (grade 2) were the most found degree among participants (30.3%). On the other hand, severe lung injury, whether a third- or fourth-degree, was the most common sign found in patients diagnosed with COVID-19 (22.2%).

In addition, in our study during analyzing associated symptoms and signs, we found that cough was more relatively present among patients with COVID-19 when compared with those with H1N1. While fever was higher in the H1N1 group than in the COVID-19 group, it was different than what was reported by the CDC, where they reported comparable distribution of fever among the 2 groups. Vomiting was more common among those with COVID-19, and this was statistically insignificant. Similarly, shortness of breath and sore throat were found more among those with COVID-19. On the other hand, we found that abdominal pain was more common among those with H1N1 when compared with those with COVID-19. We also found that anorexia, periorbital puffiness, and bone ache were exclusively present among those with H1N1 when compared with those with COVID-19. Also, headache, diarrhea, atypical chest pain, and fatigue were exclusively present among those with COVID-19 when compared with those with H1N1. However, this was also statistically insignificant. The most relevant comorbidity was type 2 diabetes mellitus for COVID-19 patients, while bronchial asthma was predominant in H1N1 cases as risk factor. Asthma and influenza are common diseases that affect millions of people worldwide. Although pathogens such as respiratory syncytial virus and rhinovirus are known to cause and exacerbate asthma, the link between asthma and influenza was unclear. Asthma was identified as a risk factor for hospitalization during the 2009 influenza pandemic, putting these 2 conditions in the focus as a duo for poor outcomes. Researchers proposed that hypersensitivity-based immune responses may protect the host during pathogen encounters, and this was confirmed during the swine flu pandemic when those with asthma were less likely to suffer from severe influenza complications (18).

Instead of comparing clinical endpoints to assess risks, as most previous studies do, we stratified both patient groups by clustering their laboratory results that were most significantly different from influenza patients (ie, complete blood count) during the first 3 days of hospitalization. The study found no specific laboratory marker that was useful in distinguishing between either infection, except monocytic count, which was significantly higher among those with H1N1 when compared with COVID-19 patients. This is consistent with previous studies that compared the 2 infections, although their number was limited (19).

According to Mei et al, serial monitoring of laboratory parameters, such as neutrophil to lymphocyte ratio, may be able to elicit the differences (20). However, in our study, for the follow-up laboratory findings for H1N1 patients, we found that there was a significant change in complete blood count (CBC) parameters over the admission period. We found that both neutrophilic count and monocytic count significantly decreased over the admission period ($P = 0.001$, $P = 0.012$). We also found that both lymphocytic count and eosinophilic count significantly increased over the admission period ($P < 0.001$, $P = 0.003$), respectively. However, we found no significant change in CBC parameters of COVID-19 patients over the admission period.

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Other clinical and laboratory data that could distinguish between mild and severe COVID-19 patients were ineffective when we assessed the risks in the current cohort. There were no differences between the 2 groups in terms of daily minimum oxygen saturation or maximum temperature. During the study, there were no statistically significant differences between the 2 groups in alanine transaminase, aspartate aminotransferase, sodium, potassium, creatinine, urea, and total bilirubin (direct & indirect). These laboratory indicators may be useful in distinguishing between hospitalized and nonhospitalized patients, which is beyond the main focus of the present study.

There was no difference between the 2 groups in the mortality rates based on SOFA scores . Previous studies have found that patients with either infection (COVID-19 or H1N1) have similar prognoses (16).

In both groups, there was a predominance of patients receiving systemic steroids. In our study, however, patients with COVID-19 were more likely to be treated with steroids than those with H1N1. This is also consistent with other studies that have reported the use of systemic steroids in the management of these infections.

According to a Cochrane review published in 2019, a greater number of COVID-19 patients were treated with steroids than influenza patients, as the risk of mortality was higher among patients with influenza who received steroids as adjunctive treatment when compared with those who did not receive steroids. This could be attributed to an increase in hospital-acquired infections (21). The RECOVERY trial for COVID, on the other hand, demonstrated a mortality benefit with the use of steroids.

The immunosuppressive effects of steroids may have an impact on the occurrence of nosocomial infections. Patients developed these infections at a higher rate in the current work (11%) than those in previous studies. The nosocomial infection rate was comparable in the 2 groups. However, patients with H1N1 were more likely than COVID-19 patients to be treated with antibiotics in addition to oseltamivir, which is consistent with other studies (22, 23).

Study Limitations

This was a one-site, retrospective study. However, the study described important and common characteristics of COVID-19 and H1N1 influenza infections. The results of this study may be useful in providing care to patients in the context of these viral outbreaks. Second, patients were restricted to a single healthcare facility (New Najran general hospital) in the Najran area, near the southern borders of KSA. Third, a sufficient number of H1N1 patients were not available. Fourth, despite appearing to be different, several laboratory parameters did not show statistical significance between COVID-19 and H1N1 patients for the same reason. Overall, our findings help predict the risk groups for further management in hospitalized COVID-19 and H1N1 patients from the Middle East Area. Further prospective studies with independent groups will be useful to confirm these findings.

Conclusion

Our findings highlight the difficulty in distinguishing these 2 infections clinically. The only difference was that COVID-19 patients had been sick for a longer period before being admitted to the hospital. As a result, patients suffering from influenza-like symptoms may require PCR testing to diagnose/rule out influenza A subtype H1N1 and/or SARS-CoV2. Furthermore, steroid treatment has the potential to increase the number of opportunistic and superimposed infections and should be used with caution in the COVID-19 subset that requires oxygen support and/or has ARDS. Despite the availability of advanced-stage H1N1 influenza treatment and the use of steroids in COVID-19, our study found no difference in mortality. As a result, we recommend implementing and employing influenza prevention strategies (ie, immunization) as well as COVID-19-specific measures such as universal masking and social distancing.

Authors' Contribution

All Authors contributed to all stages of this article, except the data collection phase (completed by authors 1 to 3).

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None.

Ethical Approval

The study protocol was reviewed and approved according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP) guidelines by the Ethical and Research Committee (IRB registration number with KACST' KSA: H-I1-N-081. IRB Log Number 2021-048).

Conflict of Interests

The authors declare that they have no competing interests.

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