



## SARS-CoV-2 and seasonal influenza: similarities and disparities

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Received: 13 April 2022 / Accepted: 18 August 2022 / Published online: 21 October 2022  
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### Abstract

This report describes the differences in disease severity and clinical presentation between hospitalized patients with coronavirus disease 2019 (COVID-19) and others with seasonal influenza. A total of 136 influenza and 152 COVID-19 patients were included. Patients with influenza more frequently had dyspnea ( $p = 0.004$ ), hypoxemia ( $p < 0.001$ ), underlying diseases ( $p = 0.046$ ), and elevated liver enzymes ( $p = 0.028$ ). In contrast, patients with COVID-19 were overweight ( $p < 0.001$ ), lymphopenic ( $p < 0.001$ ), had elevated CRP ( $p = 0.011$ ), and radiological abnormalities ( $p < 0.001$ ). Patients with influenza were more severely ill on admission (NEWS  $> 5$ ) ( $p < 0.001$ ). However, length of hospital stay, ventilatory support, and 30-day-mortality were similar. Despite differences in clinical presentation and disease severity between influenza and COVID-19 patients, both groups had similar clinical outcomes.

Respiratory illness caused by influenza viruses shares clinical and radiological findings with SARS-CoV-2 infection [1]. The distinction between the two diseases is important as health care systems struggle with the ongoing SARS-CoV-2 pandemic and seasonal influenza. Although both viruses spread primarily via droplets, some variants of SARS-CoV-2 are more infectious and spread more rapidly [2]. It has also been reported that SARS-CoV-2 is associated with worse

clinical outcomes compared with influenza [3]. However, this may change depending on the SARS-CoV-2 variant [2].

The epidemiological impact of SARS-CoV-2, the special infection prevention measures, and the fear of contracting SARS-CoV-2 among health care workers are major concerns in the current pandemic [4–6].

The primary objective of this study was to compare clinical, laboratory, and radiological features that distinguish influenza from COVID-19 on admission to allow early triage and treatment of these patients. The secondary objective was to evaluate the severity of COVID-19 compared with seasonal influenza in hospitalised patients.

This retrospective study was conducted at a tertiary hospital in northern Israel. All patients  $> 18$  years of age, admitted with confirmed SARS-CoV-2 respiratory illness during the second "wave" of COVID-19 in Israel between June 1, 2020 and August 31, 2020, were compared with patients admitted with respiratory illness caused by influenza viruses between November 1, 2019 and August 31, 2020. Different time frames for influenza and COVID-19 were used for the reason that the study was initiated in 2020, a year when seasonal influenza was absent, so the 2019 influenza season was included instead. Clinical and laboratory data were obtained from the hospital's electronic medical records. Radiological findings on chest radiographs were reviewed by a pulmonary specialist. Disease severity was graded using the National Early Warning Score 2 (NEWS2), with a score  $\geq 5$  as an indicator of severe disease [7].

Handling Editor: William G Dundon .

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Univariate analysis was performed using the  $\chi^2$ -test or Fisher's exact test for categorical variables and the independent *t*-test for continuous variables. All tests were two-tailed, and  $p < 0.05$  was considered statistically significant. The study was approved by the local ethics committee.

A total of 136 patients with influenza and 152 patients with COVID-19 were included. The mean age was similar for influenza ( $60.25 \pm 19.65$  years) and COVID-19 ( $60.32 \pm 18.24$  years),  $p = 0.266$ . The ratio of males to females was similar in the two groups. Patients with influenza had a 4-fold higher risk of hypoxemia ( $O_2$  saturation  $< 92\%$ ) on admission than patients with COVID-19 (39.5% vs. 12.9%,  $p < 0.001$ ). In addition, influenza was more frequently associated with runny nose ( $p < 0.001$ ), cough ( $p < 0.001$ ), dyspnea ( $p = 0.004$ ), and myalgia ( $p = 0.039$ ), as well as higher rates of smoking (42.6% vs. 13.8%,  $p < 0.001$ ) and underlying diseases (73.5% vs. 62.5%,  $p = 0.046$ ) compared to patients with SARS-CoV-2. Being overweight was

more frequent in patients with COVID-19 than in influenza patients (80.0% vs. 56.3%,  $p < 0.001$ ) (Table 1).

Patients with influenza had an 8-fold higher risk of elevated liver enzymes (5.7% vs. 0.7%,  $p = 0.028$ ). However, patients with SARS-CoV-2 had a 54-fold higher risk of lymphopenia  $< 1,500$  (88% vs. 11.9%,  $p < 0.001$ ). Elevated CRP  $> 5$  mg/dL ( $p = 0.011$ ) and abnormal radiological findings (77.9% vs. 56.2%,  $p < 0.001$ ) were also more common in COVID-19 patients. Of the COVID-19 patients with abnormal radiological findings, 104 (92%) had bilateral findings that were consistent with viral pneumonia, as assessed by a pulmonologist (Table 2).

Patients with SARS-CoV-2 were more likely to require intravenous fluid administration (12.5% vs. 3.7%,  $p = 0.011$ ) but less likely to require inhalation therapy (19.1% vs. 40.4%,  $p < 0.001$ ).

Although patients with influenza had a threefold higher risk of severe illness (NEWS  $\geq 5$ ) (43.4% vs. 19.1%,  $p < 0.001$ ), the length of hospital stay, need for ventilatory

**Table 1** The demographic and clinical characteristics of adult patients with influenza (between November 1, 2019 and August 31, 2020) compared to patients with COVID-19 (between June 1, 2020, and August 31, 2020) in Israel

	Influenza (n = 136)	SARS-CoV-2 (n = 152)	<i>p</i> -value	OR (95%CI)
Age, mean $\pm$ SD (median)	60.25 $\pm$ 19.65 (64.30)	60.32 $\pm$ 8.24 (60.75)	0.266	
Age $> 60$ years	81 (59.6)	80 (52.6)	0.237	
Sex (male)	63 (46.3)	80 (52.6)	0.285	
Clinical presentation (on admission)				
Fever $> 38$ °C	61 (44.9)	79 (52)	0.227	
Oxygen saturation $< 92$ %	60 (39.5)	31 (12.9)	<b><math>&lt; 0.001</math></b>	<b>4.42 (2.69-7.25)</b>
Symptom duration $> 7$ days	30 (22.1)	14 (12.7)	0.058	
Runny nose	32 (23.5)	6 (3.9)	<b><math>&lt; 0.001</math></b>	<b>7.46 (3.02-18.52)</b>
Cough	109 (80.1)	80 (52.6)	<b><math>&lt; 0.001</math></b>	<b>3.64 (2.14-6.17)</b>
Fatigue	52 (38.2)	62 (40.8)	0.658	
Headache	19 (14)	16 (10.5)	0.372	
Dyspnea	76 (55.9)	59 (38.8)	<b>0.004</b>	<b>2.00 (1.25-3.19)</b>
Sore throat	17 (12.5)	9 (5.9)	0.052	
Diarrhea	15 (11)	18 (11.8)	0.829	
Nausea/vomiting	27 (19.9)	20 (13.2)	0.125	
Myalgia	26 (19.1)	16 (10.5)	<b>0.039</b>	<b>2.01 (1.03-3.94)</b>
Comorbidities				
Any underlying condition	100 (73.5)	95 (62.5)	<b>0.046</b>	<b>1.67 (1.01-2.75)</b>
Hyperlipidemia	39 (28.7)	57 (37.5)	0.113	
Hypertension	64 (47.1)	63 (41.4)	0.338	
Diabetes mellitus	51 (37.5)	47 (30.9)	0.239	
Ischemic heart disease/ congestive heart failure	44 (32.4)	21 (13.8)	<b><math>&lt; 0.001</math></b>	<b>2.99 (1.66-5.35)</b>
Immunosuppression/malignancy	37 (24.3)	13 (5.4)	<b><math>&lt; 0.001</math></b>	<b>5.65 (2.88-10.99)</b>
COPD/asthma	42 (30.9)	12 (7.9)	<b><math>&lt; 0.001</math></b>	<b>5.21 (2.60-10.42)</b>
Chronic kidney disease	29 (21.3)	23 (15.1)	0.173	
Smoking	58 (42.6)	21 (13.8)	<b><math>&lt; 0.001</math></b>	<b>4.63 (2.62-8.20)</b>
Overweight (BMI $> 25$ )	63 (56.3)	96 (80)	<b><math>&lt; 0.001</math></b>	<b>0.32 (0.18-0.58)</b>

**Table 2** The laboratory measures and imaging of adult patients with influenza (between November 1, 2019 and August 31, 2020) compared to patients with COVID-19 (between June 1, 2020, and August 31, 2020) in Israel

	Influenza (n = 136)	SARS-CoV-2 (n = 152)	p-value	OR (95%CI) Chi <sup>2</sup> /Fisher exact test/ t-independent test
<b>Laboratory measures</b>				
WBC × 10 <sup>9</sup> /L	7.69 ± 4.40	7.42 ± 4.91	0.627	
Lymphopenia <1.5 × 10 <sup>9</sup> /L	16 (11.9)	125 (88)	<b>&lt;0.001</b>	<b>54.688 (26.424-113.183)</b>
CRP>5 (mg/dL)	50 (39.1)	77 (54.6)	<b>0.011</b>	<b>1.877 (1.155-3.051)</b>
Creatinine >2 (mg/dL)	25 (18.7)	28 (19.3)	0.889	
Albumin (g/dL)	20 (18)	8 (9.9)	0.114	
ALT or ALT >5 ULN* (unit/L)	7 (5.7)	1 (0.7)	<b>0.028</b>	<b>0.120 (0.015-0.990)</b>
Bilirubin (mg/dL)	0.56 ± 0.489	0.53 ± 0.453	0.673	
<b>Radiological findings (chest x-ray)</b>				
Normal	57 (43.8)	32 (22.1)	<b>&lt;0.001</b>	<b>2.757 (1.634-4.654)</b>
Abnormal	73 (56.2)	113 (77.9)		
Unilateral	15 (11.5)	5 (3.4)		
Bilateral	52 (40)	104 (71.7)		
Other	6 (4.6)	4 (2.8)		

\*ULN, upper limit of normal

support, in-hospital mortality, and 30-day mortality were similar in both groups ( $p = 0.26, 0.47, 0.83,$  and  $0.50,$  respectively) (Table 3).

This study showed that respiratory symptoms and hypoxemia, comorbidities, and smoking were predominant in patients with influenza compared with being overweight and laboratory and radiological abnormalities in COVID-19 patients. Although patients with influenza had more-severe disease on admission, outcomes, including length of hospital

stay, need for ventilatory support, and mortality were similar to patients with SARS-CoV-2.

Respiratory manifestations were less common in COVID-19, which may be related to the wide spectrum of extrapulmonary manifestations in patients infected with SARS-CoV-2 [8]. A previous study comparing severe acute respiratory infections (SARI) with COVID-19 contradictorily showed a similar frequency of respiratory symptoms in COVID-19 and non-COVID-19 SARI [9].

**Table 3** Management and outcome of adult patients with influenza (between November 1, 2019 and August 31, 2020) compared to patients with COVID-19 (between June 1, 2020, and August 31, 2020) in Israel

	Influenza (n = 136) (%)	SARS-CoV-2 (n = 152) (%)	p-value	OR (95% CI)
<b>Therapeutic support</b>				
Oxygen	61 (44.9)	68 (44.7)	0.984	
Inhalation	55 (40.4)	29 (19.1)	<b>&lt;0.001</b>	<b>0.347 (0.204-0.590)</b>
BiPAP/CPAP/HFNC	10 (7.4)	20 (13.2)	0.104	
Invasive ventilation	7 (5.1)	11 (7.2)	0.465	
Fluid support	5 (3.7)	12 (12.5)	<b>0.011</b>	<b>3.743 (1.273-1.007)</b>
Hemodynamic instability	7 (5.1)	17 (11.2)	0.064	
Inotropes	6 (4.4)	10 (10.4)	0.075	
<b>Outcome measures</b>				
NEWS-2 ≥ 5	59 (43.4)	29 (19.1)	<b>&lt;0.001</b>	<b>0.308 (0.181-0.522)</b>
LOS >3 days	103 (75.7)	107 (70.4)	0.309	
LOS (days) mean ± SD	9.40 ± 15.32	7.87 ± 6.988	0.266	
30-day mortality	9 (6.6)	15 (9.9)	0.500	
In-hospital mortality	10 (7.3)	14 (9.2)	0.833	

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HFNC, high-frequency nasal cannula

The lower rate of comorbidities in COVID-19 compared with patients with influenza is probably due to the permissive admission policy for patients with COVID-19 at the beginning of the pandemic in Israel, compared with the stricter admission policy for patients with influenza, in which only complicated cases were admitted. This may also be due to the fact that fear of the emerging virus led patients to seek medical attention earlier, regardless of their health status.

The higher proportion of smokers among influenza patients may indicate that smoking is associated with severe influenza infection resulting in admission to the hospital [10]. A low prevalence of smoking in hospitalized COVID-19 patients compared to the sex-adjusted population has been demonstrated previously [11]. However, smoking cannot yet be considered a protective measure for COVID-19.

The extent of lymphopenia was the most striking laboratory finding in patients with COVID-19. This may be explained by direct infection of lymphocytes by the virus due to expression of ACE2 receptors on their cell membrane or by induced lymphocyte deficiency due to proinflammatory cytokines [12, 13]. There is stronger correlation between the presence of viral RNA in plasma of hospitalized patients with COVID-19 and disease severity and lymphopenia [14] than in patients with influenza [15].

Patients with COVID-19 were more dehydrated on admission. This may be due to intravascular depletion caused by the direct action of the virus on ACE2 receptors in the kidneys [16] and difficulty in maintaining oral fluid intake, especially in elderly patients [17].

Patients with COVID-19 were more likely to have radiological findings of bilateral infiltrates. This was consistent with previously published studies [9, 18] and in contrast to another study, which showed greater consolidation and pleural effusion in chest computed tomography in patients with influenza, although this study included only a limited number of patients with COVID-19 [19].

The similar results shown in this study for COVID-19 and influenza patients contradict previous reports that hospitalized patients with COVID-19 had higher in-hospital mortality rates and worse clinical outcomes, including prolonged ventilation, longer hospital stay, acute respiratory distress syndrome, and acute kidney injury [3]. The discrepant results could be due to the fact that only insured patients were included, in contrast to the present study, which included all hospitalized patients. This could lead to selection bias, as insured patients might be at higher risk for concomitant diseases. Another study showed similar results to the current study in terms of disease severity and mortality, but with longer hospital stays for COVID-19 patients [8].

The main limitations of this study are, first, its retrospective design, which may affect the availability and quality of the data and follow-up. Second, only the second

"wave" of the COVID-19 pandemic in Israel was included, without accounting for differences in disease severity between waves caused by different variants. Future studies should include the entire cohort of COVID-19 and influenza patients throughout the pandemic. Third, there was potential selection bias from using different time frames for influenza and COVID-19. However, looking at different time frames allowed comparison of the two diseases without overlapping morbidity or coinfection.

Despite the assumption that these are two respiratory diseases with similar presentation, this study points out different characteristics of influenza and COVID-19 that allow them to be distinguished at the time of admission so that the necessary precautions and infection control measures can be taken upon arrival at the hospital. Although the severity of influenza is higher at the time of admission, in-hospital mortality and clinical outcomes of influenza patients are comparable to those of COVID-19 patients.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Drs. Halima Dabaja-Younis, Eyal Fuchs, Nadeem Shorbaji, Tal Appel, Noah Carmon, Yael Shachor-Meyouhas, Manfred Green, and Khetam Hussein. The first draft of the manuscript was written by Dr. Halima Dabaja-Younis, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding** The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

**Data availability** The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethical approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the institutional ethics committee.

**Consent to participate** Informed consent was required in this study.

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