Clinical Outcomes of Hospitalized Patients with SARS-CoV-2 Omicron Variant vs. Influenza A During Influenza Season 2021 to 2022: A Retrospective Observational Study

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ABSTRACT **Background:** Influenza and coronavirus disease 2019 (COVID-19) are respiratory diseases with similar modes of transmission. In December 2021, influenza re-emerged after it had been undetected since March 2020 and the Omicron variant replaced the Delta variant. Data directly comparing the two diseases are scarce.

Objectives: To compare the outcomes of patients with both the Omicron variant and influenza during 2021–2022.

Methods: We performed a retrospective study conducted in Beilinson hospital, Israel, from December 2021 to January 2022. We included all hospitalized patients with either laboratory-confirmed COVID-19 or influenza. The primary outcome was 30-day mortality.

Results: We identified 167 patients diagnosed with Omicron and 221 diagnosed with Influenza A. The median age was 71 years for Omicron and 65 years for influenza. Patients with Omicron had a significantly higher Charlson Comorbidity Index score (4 vs. 3, $P < 0.001$). Patients with Omicron developed more respiratory failure that needed mechanical ventilation (7% vs. 2%, $P = 0.05$) and vasopressors (14% vs. 2%, $P < 0.001$) than patients with influenza. In a multivariate model, 30-day mortality was lower in patients diagnosed with influenza than in patients diagnosed with Omicron (19/221 [9%] vs. 44/167 [26%], hazard ratio 0.45, 95% confidence interval 0.25–0.81).

Conclusions: Patients diagnosed with Omicron had higher mortality than patients diagnosed with seasonal influenza. This finding could be due to differences in co-morbidities, the virus pathogenicity, and host responses to infection.

IMAJ 2023; 25: 585–589

KEY WORDS: coronavirus disease 2019 (COVID-19), influenza, mortality, Omicron vaiant, outcomes

Influenza and coronavirus disease 2019 (COVID-19) are respiratory diseases with similar modes of transmission. In December 2021, influenza activity started to increase again globally after it had barely been detected since March 2020, as reported by the World Health Organization's (WHO) Global Influenza Surveillance and Response System (GISRS). In addition, a reduction in influenza virus diversity during the COVID-19 pandemic was observed and created a genetic bottleneck with few virus clades have emerged since April 2020 and continued to diversify including two major H1N1 subclades 5a.1 (West Africa, Europe) and 5a.2 (Asia, Europe, Middle East, Australia), two major clades 2a1b.1 and 2a1b.2a, and only one B lineage, the B-Victoria lineage [1,2].

On November 2021, the WHO designated the COVID-19 strain B.1.1.529, as a variant of concern and named it *Omicron.* This variant quickly substituted the Delta variant, which was the predominant one at that time [3].

While few published studies have compared outcomes of COVID-19 with influenza from previous influenza seasons (2014–2019) [4-6], studies directly comparing Omicron and influenza at the same period (2021–2022) are lacking.

We compared the clinical outcomes, including mortality, among hospitalized patients diagnosed with the Omicron variant and hospitalized patients diagnosed with influenza during the 2021–2022 season.

PATIENTS AND METHODS

This observational retrospective study was conducted at a large academic hospital in central Israel and included all consecutive hospitalized patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or influenza virus from 1 December 2021 to 31 January 2022. Laboratory diagnosis of influenza and SARS-CoV-2 were conducted through

specific real-time reverse transcriptase polymerase chain reaction (RT-PCR) assays of nasal swab specimens. Patients with both influenza and SARS-CoV-2 positive specimens were excluded. Data regarding baseline demographics, chronic co-morbidities (including age adjusted Charlson Comorbidity Index) were retrieved. We also collected data pertaining to the index encounter (admission), such as vital signs and laboratory results at presentation. Further collected data included the necessity for invasive mechanical ventilation, vasopressors support, and intensive care unit (ICU) admission during hospitalization. The primary outcome was 30-day all-cause mortality from the diagnosis. Secondary outcomes included length of hospital stay, in-hospital mortality, and end of follow-up mortality [Figure 1]. The study was approved by the Rabin Medical Center's ethics committee.

STATISTICAL ANALYSIS

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at two-tailed comparison with a $P < 0.05$. Normality distribution was assessed through a Kolmogorov-Smirnov normality test and a Q-Q plots test. Categorical variables were tested using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were examined using Student's *t*-test if normally distributed and Mann-Whitney U test if not normally distributed. To identify individual variables associated with 30-day all-cause mortality, univariate analysis, using the Cox Proportional Hazards model was performed. Variables that were clinically significant for 30-day mortality in the univariate analysis were entered into the multivariate variate model. Hazard ratios (HRs) and 95% confidence interval (95%CI) for 30-day mortality were calculated.

RESULTS

The entire cohort included 388 hospitalized patients, 167/388 (43%) were hospitalized with Omicron and 221/388 (57%) were hospitalized with influenza. The median age of patients was 71 years for Omicron and 65 years for influenza ($P < 0.001$). Patients with Omicron were mostly male (97/167 [58%] vs. 91/221 [41%], $P = 0.001$), had higher Charlson Comorbidity Index scores (median 4 vs. 3, $P < 0.001$), needed more assistance in activity of daily living (75/167 [45%] vs. 64/221 [29%], $P = 0.008$), and more frequently presented with hypertension (55/167 [33%] vs. 51/221 [23%], $P = 0.04$), diabetes mellitus (47/167 [28%] vs. 43/221 [19%], $P = 0.05$), and solid tumors (30/167 [18%] vs. 22/221 [10%], $P = 0.02$). Those diagnosed with influenza more frequently had asthma (16/221 [7%] vs. 2/167 [1%], $P = 0.006$). All patients in the influenza group were infected with Influenza A virus [Table 1].

CLINICAL COURSE DURING HOSPITALIZATION

Half of the patients with Omicron and influenza needed oxygen supply at admission, while patients with Omicron more frequently needed oxygen supply during hospitalization (102/167 [61%] vs. 88/221 [40%], $P < 0.001$) and developed respiratory failure that needed invasive mechanical ventilation (12/167 [7%] vs. 6/221 [3%], $P = 0.05$) and vasopressors (23/167 [14%] vs. 5/221 [2%], $P < 0.001$). They were also more likely to be admitted to the ICU (23/167 [14%] vs. 4 [2%], $P < 0.001$). Patients with influenza were prescribed more antibiotics (117/221 [53%] vs. 59/167 [35%], $P < 0.001$) [Table 1].

Figure 1. Kaplan-Meier survival curve for 30-day and 10-month follow-up of hospitalized patients with COVID-19 Omicron variant vs. influenza

COVID-19 = coronavirus disease 2019

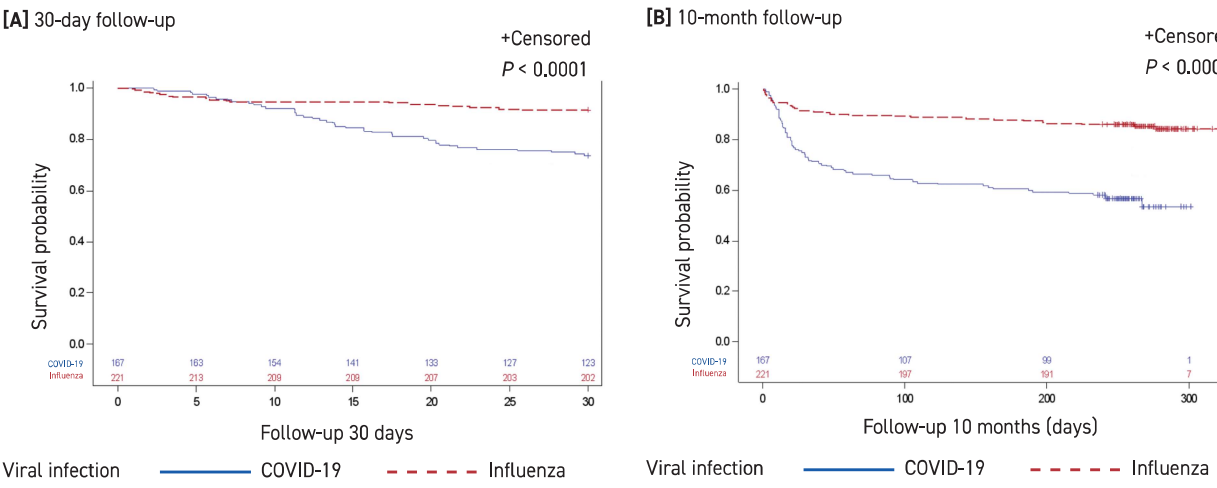

Table 1. Baseline characteristics of hospitalized patients with the COVID-19 Omicron variant versus influenza infection

	Omicron in-patients (n=167)	Influenza in-patients (n=221)	*P*-value
Age, median in years	71 (61–82)	65 (34–77)	< 0.001
Male sex, n (%)	97 (58%)	91 (41%)	0.001
Need ADL assistance, n (%)	75 (45%)	64 (29%)	0.008
Body mass index (median, kg/m^2)	25 (23–28.7)	26.7 (23.3–30)	0.2
Charlson Comorbidity Index (median)	4 (2–7)	3 (0–5)	< 0.001
Home residency, n (%)	115 (69%)	148 (67%)	0.3
Hypertension, n (%)	55 (33%)	51 (23%)	0.04
Diabetes mellitus, n (%)	47 (28%)	43 (19%)	0.05
Ischemic heart disease, n (%)	17 (10%)	17 (8%)	0.4
Chronic obstructive pulmonary disease, n (%)	13 (8%)	19 (9%)	0.8
Chronic kidney disease, n (%)	14 (8%)	12 (5%)	0.3
Active smoking, n (%)	7 (4%)	10 (5%)	1
Asthma, n (%)	2 (1%)	16 (7%)	0.006
Solid tumor, n (%)	30 (18%)	22 (10%)	0.02
Hematologic malignancy, n (%)	12 (7%)	10 (5%)	0.3
Lymphoma, n (%)	10 (6%)	6 (3%)	0.12
Acute Leukemia, n (%)	2 (1%)	4 (2%)	0.7
Solid organ transplantation, n (%)	14 (8%)	14 (6%)	0.6
Kidney transplant, n (%)	10 (6%)	10 (5%)	0.6
Heart transplant, n (%)	1 (0.6%)	1 (0.4%)	1
Lung transplant, n (%)	4 (2%)	2 (0.9%)	0.4
Liver transplant, n (%)	0 (0%)	1 (0.4%)	1
Vital signs and laboratory results at presentation			
Temperature (median)	37.2 (36.8–38)	37.8 (37.1–38.4)	< 0.0001
Oxygen saturation (%)	93 ± 6	94 ± 5	0.7
C-reactive protein (mg/dl), n (%)	7 (2.5–17)	5.5 (2–11)	0.05
Creatinine (mg/dl), n (%)	1.13 (0.86–2.02)	0.91 (0.64–1.3)	< 0.001
Platelet count (K/µcells)	203 (156–281)	202 (161–271)	0.8
White blood cells count (K/µcells)	8.5 (6–13)	8.7 (6.5–12)	0.6
Need for oxygen supply at admission, n (%)	83 (50%)	106 (48%)	0.4
Need for oxygen supply during hospital stay, n (%)	102 (61%)	88 (40%)	< 0.001
Need for mechanical ventilation during hospital stay, n (%)	12 (7%)	6 (3%)	0.05
ICU admission, n (%)	23 (14%)	4 (2%)	< 0.001
Vasopressors, n (%)	23 (14%)	5 (2%)	< 0.001
Steroid use, n (%)	106 (63%)	76 (34%)	< 0.001
Antibiotic prescription, n (%)	59 (35%)	117 (53%)	< 0.001
Remdesivir, n (%)	15 (9%)	–	–
Baricitinib, n (%)	19 (11%)	–	–
Tamiflu, n (%)	–	152 (69%)	–

ADL = activities of daily living

PRIMARY OUTCOME

The 30-day mortality was lower in the influenza group compared to the Omicron group (19/221 [9%] vs. 44/167 [26%], $P < 0.0001$) [Table 2]. On univariate and multivariate analyses of risk factors for 30-day mortality, influenza was associated with lower mortality rate (HR [hazard ratio] 0.31, [95% confidence interval [95%CI] 90.18–0.52, and HR 0.45 95%CI 0.25–0.81, respectively) [Table 3] [Figure 1A].

Risk factors for 30-day mortality were older age and higher C-reactive protein levels (HR 1.057, 95%CI 1.031–1.083, and HR 1.03, 95%CI 1.003–1.052, respectively) [Table 3].

SECONDARY OUTCOMES

Patients with Omicron had longer hospital stays than patients with influenza (median days 8 vs. 3, $P < 0.0001$). The in-hospital mortality rate was not significantly higher in the Omicron

Table 2. Clinical outcomes in hospitalized patients with the COVID-19 Omicron variant versus influenza infection

	Omicron (n=167)	Influenza (n=221)	*P*-value
Length of hospital stay in days, median (IQR)	8 (4–17)	3 (2–6)	< 0.0001
In-hospital mortality, n (%)	39 (23%)	14 (6%)	0.8
30-day mortality, n (%)	44 (26%)	19 (9%)	< 0.0001
End of follow-up mortality, n (%)	73 (44%)	33 (15%)	< 0.0001

IQR = interquartile range

Table 3. Multivariate model for risk factors of 30-day mortality

Variable	Hazard ratio	*P*-value
Age in years	1.057 (1.031–1.083)	**< 0.01**
Male sex	1.08 (0.61–1.94)	0.8
Influenza vs. Omicron	0.45 (0.25–0.81)	**0.008**
Not assisted in ADL	0.67 (0.36–1.25)	0.2
Residency in healthcare facility	1.09 (0.53–2.26)	0.8
Charlson Comorbidity Index score	0.96 (0.88–1.05)	0.4
C-reactive protein (mg/dl)	1.027 (1.003–1.052)	**0.03**
Creatinine level (mg/dl)	1.06 (0.92–1.21)	0.4

ADL = activities of daily living

Bold indicates significance

group compared with the influenza group (39/167 [23%] vs. 14/221 [6%], $P = 0.8$) [Table 2]. After 10 months of follow-up, the mortality rate continued to be higher in the Omicron group compared with the influenza group (73/167 [44%] vs. 33/221 [15%], $P < 0.0001$) [Table 2] [Figure 1B].

DISCUSSION

In the present study, we found that hospitalized patients with the Omicron variant still had a higher mortality rate than patients with seasonal influenza, even though Omicron was considered a less virulent variant with lower case fatality rates compared with the Delta and Alpha strains, as shown in several studies [7,8].

A prospective study conducted in 21 hospitals in the United States that included 5728 hospitalized COVID-19 cases found that Omicron cases were associated with less severe disease (odds ratio = 0.61, 95%CI 0.49–0.77) and lower in-hospital mortality rates than the Delta variant (7.1% vs. 12.2%) [7]. Another retrospective study from England with a large database including approximately 1 million Omicron cases and approximately 450,000 Delta cases found that the risk of severe outcomes of COVID-19 including hospital attendance, hospital admission, and death was substantially lower for Omicron than Delta with adjusted HR 0.56 (95%CI 0.54–0.58), HR 0.41 (95%CI 0.39– 0.43), and HR 0.31 (95%CI 0.26–0.37), respectively [8].

Our results show significant differences in the demographics and underlying co-morbidities in the two groups, where patients with Omicron were older and had more co-morbidities, which may have contributed to the more severe clinical course and progression to respiratory failure. Two-thirds of the Omicron patients needed oxygen support during their hospitalization and were mechanically ventilated two times more often than influenza patients. On admission, patients with Omicron were seven times more likely to be admitted to the ICU than patients with influenza. Furthermore, patients with influenza were discharged after a median of 3 days whereas, patients with Omicron remained in the hospital for a median of 8 days. Other factors that may have contributed to the differences between the outcomes in the two groups are the pathogenicity of the virus and host responses to infection.

While we are not aware of other studies that directly compared Omicron and influenza during the same period (2021–2022). We found that our results were in line with the results of several studies that compared outcomes of COVID-19 (mostly Alpha and Delta) with influenza from previous influenza seasons (2014–2019) [4-6].

A nationwide retrospective study from France comparing clinical outcomes between patients hospitalized with COVID-19 vs. influenza (influenza season 2018–2019) showed that patients hospitalized with COVID-19 had more acute respiratory failure (27.2% vs. 17.4%, $P < 0.0001$), were more often mechanically ventilated (9.7% vs. 4%, $P < 0.0001$), and had higher in-hospital mortality rate (16.9% vs. 5.8%, $P < 0.0001$) compared with influenza cases [4]. In another study from Germany, the authors compared approximately 2300 hospitalized COVID-19 cases with about 6700 influenza cases during the 2017–2019 influenza seasons. They found that COVID-19 resulted in significantly higher in-hospital mortality (14% vs. 6%) and worse clinical outcomes than influenza, including ICU admission (21 vs. 13 %), mechanical ventilation (15 vs. 9%), and severe disease (28 vs. 16%) [5]. A study from Boston, USA, included 1052 patients diagnosed with influenza from the previous five influenza seasons (2014–2019) and compared them with 582 patients diagnosed with COVID-19 during 2020. In that study, the median number of patients with COVID-19 who required mechanical ventilation per week was 17 compared to 1 patient with influenza ($P = 0.001$). Furthermore, patients with COVID-19 had significantly higher mortality (20% vs. 3%; $P < 0.001$ for all). After 10 months of follow up the mortality rate was still higher among patients with Omicron compared with influenza. This result can be explained mainly by the older age and more underlying co-morbidities in patients with Omicron compared with patients with influenza.

Our study has several limitations. First, this single center retrospective study included only hospitalized patients, raising the

possibility of selection bias, a major issue in retrospective studies. Second, data on influenza and COVID-19 vaccines were unavailable. Thus, the true effect of the vaccine on the clinical outcomes was therefore inestimable. Last, our study included only hospitalized patients, so we cannot estimate the proportion of hospitalized patients in the total number of infected patients.

CONCLUSIONS

The Omicron variant of COVID-19 was considered a less virulent variant with lower case fatality rates compared with the original strain, even though hospitalized patients with the Omicron variant still had a higher mortality rate than patients with seasonal influenza. This finding could be due to differences in underlying co-morbidities of patients, the pathogenicity of the virus, and host responses to infection.

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Capsule

A common allele of HLA is associated with asymptomatic SARS-CoV-2 infection

Studies have demonstrated that at least 20% of individuals infected with SARS-CoV-2 remain asymptomatic. Although most global efforts have focused on severe illness in COVID-19, examining asymptomatic infection provides a unique opportunity to consider early immunological features that promote rapid viral clearance. **Augusto** and colleagues postulating that variations in the human leukocyte antigen (*HLA*) loci may underly processes mediating asymptomatic infection, enrolled 29,947 individuals, for whom high-resolution *HLA* genotyping data were available, in a smartphone-based study designed to track COVID-19 symptoms and outcomes. The discovery cohort (n=1428) comprised unvaccinated individuals who reported a positive test result for SARS-CoV-2. The authors tested for association of five *HLA* loci with disease course and identified a strong association between *HLA-B*15:01* and asymptomatic infection, which were observed in two independent cohorts. Suggesting that this genetic association is due to pre-existing T cell immunity, the authors showed that T cells from pre-pandemic samples from individuals carrying *HLA-B*15:01* were reactive to the immunodominant SARS-CoV-2 S-derived peptide NQKLIANQF. The majority of the reactive T cells displayed a memory phenotype, were highly polyfunctional, and were cross-reactive to a peptide derived from seasonal coronaviruses. The crystal structure of *HLA-B*15:01*-peptide complexes demonstrates that the peptides NQKLIANQF and NQKLIANAF (from OC43-CoV and HKU1-CoV) share a similar ability to be stabilized and presented by *HLA-B*15:01*. Last, the authors showed that the structural similarity of the peptides underpins T cell cross-reactivity of high-affinity public T cell receptors, provided the molecular basis for *HLA-B*15:01*-mediated pre-existing immunity.

Nature 2023; 620: 128
Eitan Israeli