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LETTER

Impact of influenza A co-infection with COVID-19

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Dear Editor,

The overlap between the influenza season and the ongoing COVID-19 pandemic has created a unique and difficult challenge. COVID-19 and influenza are both contagious respiratory illnesses and share many common characteristics, with similar modes of transmission and symptoms. Co-infections with respiratory pathogens in patients with COVID-19 have been observed in varying frequencies.[1,2] With the ongoing winter season in the northern hemisphere, it is expected that the seasonal influenza virus will be in circulation along with SARS-CoV-2. Due to their similar presentations, there may be delays in diagnosis and initiation of proper treatment for the two conditions. Here, we report on the rate of co-infection with influenza A in a cohort of COVID-19 patients and its impact on the clinical course and outcome. This study was approved by the Institutional Ethical Board of Fortis Escorts Hospital, Jaipur, India vide letter No. FEHJ/IEC/20/18 dated 28 December 2020.

Between 1 August 2020 and 31 December 2020, 101 patients with moderate, severe or critical COVID-19 were admitted to our unit at Fortis Escorts Hospital. All patients were tested

for influenza viruses and its strains using real-time reverse transcription polymerase chain reaction (rRT PCR) from upper respiratory tract samples. Of these, 92 (91.1%) had only COVID-19 disease and 9 (8.9%) patients had COVID-19 and influenza A co-infection. Interestingly, 8 of the 9 patients had contracted the H3N2 subtype of influenza A, while 1 had H1N1 influenza A. Previous cohorts have demonstrated influenza A co-infection with COVID-19 in varying frequencies ranging from 0.54% and 0.9% in studies from respectively northern California and Turkey,[2,3] through to 22.3% from an Iranian study among deceased patients of COVID-19,[4] and 47.3% and 49.8% in two study cohorts from Wuhan, China. Many factors may have led to this variability. Decreased influenza activity during the 2020 flu season in the southern hemisphere and the United States has been attributed to the implementation of COVID-19 preventive measures (e.g., social distancing, mask wearing, hand hygiene).[5] Currently, India is gradually relaxing COVID-19 preventive measures, and it is expected that influenza circulation will therefore increase. The circulating strain of influenza will also have an effect; in out cohort H3N2 was the dominant strain. H3N2 was also frequently observed in Wuhan during the early course of the COVID-19 pandemic,[6] whereas in Iran, the dominant strain was H1N1.[4] This is concerning because H3N2 can cause more severe disease compared to H1N1.[7]

We also compared the epidemiological and clinical parameters of co-infected patients with those with only COVID-19 (Table). The median age of our cohort was 58 years (IQR 48–65); 71.7% were males. There was no significant difference in the age and sex distribution among the two groups. Pre-existing comorbidities were present in 77 (76.2%) patients, with hypertension being the most common comorbidity, followed by type 2 diabetes. In both groups, patients presented with similar symptoms — fever, cough, malaise and dyspnoea. This reinforced the fact that co-infection with influenza can be easily masked due to similar symptoms.

We observed that co-infected patients had a significantly higher median total leukocyte count (TLC) of 13,000/mcL compared to a TLC of 9300/mcL in the COVID-19-only group (P = 0.043, Mann-Whitney U-test). Moreover, the median neutrophil-lymphocyte (NL) ratio was also significantly higher in the co-infection group (10.9 vs. 6.9 in the COVID-19-only group; P = 0.032). Similarly, a higher neutrophil count, along with an increase in pro-inflammatory markers and organ dysfunction, has been observed in non-survivors with COVID-19-influenza A co-infections.[8] A high NL ratio, often reported in case of hyperinflammation which can occur both due to severe COVID-19 as well as influenza A infection,[1,9] has consistently been associated with

adverse COVID-19 outcomes;[10] it is also seen in severe influenza and serves as a screening tool for certain high fatality influenza strains such as avian influenza H7N9.[11] Thus, these findings likely represent a synergistic effect of COVID-19 and influenza, leading to greater degree of hyperinflammation. To note, inoculation of hamsters with SARS-CoV-2 and influenza simultaneously has been found to lead to a longer clinical course, severe pulmonary damage and higher cytokine levels.[12] In our cohort, inflammatory markers such as median serum C-reactive protein levels were higher in co-infected patients than in those with only COVID-19 (89 mg/L vs. 57 mg/L); however, this difference was not statistically significant.

All patients underwent high-resolution computerized tomography (HRCT) of the chest to discern pulmonary involvement. Radiological findings, including severity, were similar in both groups. The contribution of COVID-19 and influenza A could not be differentiated, re-iterating the need for specific testing in order to detect influenza co-infection.

For treatment, respectively 94 (93.1%) and 93 (92.1%) patients received remdesivir and dexamethasone for COVID-19; 24 (23.8%) patients received COVID-convalescent plasma. In addition, oseltamivir was prescribed to all nine patients with influenza A co-infection. A total of 26 (28.3%) patients with COVID-19 and 4 (44.4%) patients with co-infections required admission to the intensive care unit (ICU). Complications during the disease course were common, the most common being acute respiratory distress syndrome (ARDS), seen in 25 (27.2%) patients with only COVID-19 and 4 (44.4%) patients with co-infections. Cytokine storm syndrome (CSS) was diagnosed based on clinical deterioration, when accompanied by supportive laboratory results suggestive of cytopenias and increase in D-dimer, lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and ferritin levels; CSS was observed in 24 (26.1%) patients with only COVID-19 and in 4 (44.4%) patients with co-infection. Interleukin (IL) 6 levels (normal <7 pg/ml) were measured in 64 patients in the cohort, and those with CSS predictably had significantly higher median IL-6 levels than those without CSS (210.2 pg/ml vs. 23.6 pg/ml; $P<0.001$). Levels in co-infected patients and those with only COVID-19 were comparable; however, because IL-6 levels were not measured for all patients, this may have confounded this observation. Patients with CSS were managed with tocilizumab or intravenous immunoglobulin decided on a case-by-case basis and drug availability. Other complications observed were acute myocardial injury, acute kidney injury, secondary bacterial infection and ventilator-associated pneumonia. Recovery was defined as discharge from the hospital based on stable vitals and ability to maintain oxygen saturation in

room air, along with radiological evidence of resolution. A total of 83 (90.2%) patients with only COVID-19 and 6 (66.7%) with co-infections recovered. Importantly, we observed that co-infected patients had a significantly longer median hospital stay than those with only COVID-19 (7 days, IQR 6–13 vs. 6 days, IQR 5–7; $P = 0.040$). This may be explained by the additional burden of influenza infection. Mortality rates in the two groups were 33.3% (3/9 patients) for co-infections and 9.8% (9/92 patients) for only COVID-19; this difference was not statistically significant ($P = 0.072$). A recent systematic review found that concurrent influenza infection in patients with COVID-19 leads to increased risk of mortality;[13] another study reported higher rates of adverse outcomes with influenza B co-infections.[14] In our study cohort, all co-infected patients were promptly treated with antiretrovirals (oseltamivir), which may explain why outcomes were better.

Our study had certain limitations due to its small sample size, the low number of patients ($n = 9$) in the co-infection group and the fact that it is a single-centre study from one geographical area. Larger studies are warranted to study the interaction between COVID-19 and influenza A, especially during the ongoing flu season.

In conclusion, we report that influenza A co-infection is not an uncommon occurrence in COVID-19 patients, and leads to significantly higher hyperinflammation and longer disease course. With the ongoing flu season and gradual relaxation of COVID-19 restrictions in many parts of the world, rates of co-infection are likely to increase despite ongoing vaccination, because inoculation of a sufficient proportion of the population takes time. Because the influenza A test is widely available and specific treatment options are available for influenza, screening of high-risk patients for seasonal flu should be considered.

Conflicts of interest: none declared.

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Table. Comparison of epidemiological, clinical and laboratory parameters of patients with COVID-19 only and those with influenza A-COVID-19 co-infections

Variable	COVID-19 only (*n* = 92) *n* (%)	Co-infection (*n* = 9) *n* (%)	Total (*n* = 101) *n* (%)	*P* value
Age, years, median [IQR]	58 [48–65]	64 [41–70.5]	58 [48–65]	0.543
Male	66 (71.7)	5 (55.6)	71 (71.3)	0.445
Comorbidities	69 (75)	8 (88.9)	77 (76.2)	0.682
• Hypertension	46 (50)	5 (55.6)	51 (50.5)	
• Diabetes mellitus	36 (39.1)	3 (33.3)	39 (38.6)	
Laboratory results, median [IQR]				
Total leukocyte count, x 10^3/μL	9.3 [6.35–13.975]	13 [10.65–18.4]	9.6 [7–14]	0.043*
Neutrophil-lymphocyte ratio	7.63 [4.77–13.55]	10.90 [7.75–18.00]	7.2 [4–12.7]	0.032*
Platelet count, x 10^3/μL*	277 [188–400]	240 [219–338]	276 [210–382]	0.739
CRP, mg/L	57.4 [22.5–116.4]	89 (46–191]	60 [23–124]	0.148
D-dimer, ng/mL	505 [277–1134]	390 [341–4100]	488 [280–1149]	0.685
IL-6 level, pg/mL	43.3 [15.1–202.2]†	39.1 [21.2–150]‡	42.7 [17.6–166.1]	0.950
CT severity score (0–25)	11 [7–15]	13 [8-18]	11 [7–15]	0.127
Cytokine storm, yes	24 (26.1)	4 (44.4)	28 (27.7)	0.258
ICU admission	26 (28.3)	4 (44.4)	30 (29.7)	0.445
Mechanical ventilation	9 (9.8)	3 (33.3)	12 (11.9)	0.072
Length of hospital stay, days, median [IQR]	6 [5–7]	7 [6–13]	6 [5–8]	0.040*
Mortality	9 (9.8)	3 (33.3)	12 (11.9)	0.072

* Statistically significant ($P<0.05$).

† Among those with only COVID-19, 57/92 patients had their IL-6 levels measured.

‡ Among those with co-infections, 7/9 had their IL-6 levels measured.

IQR = interquartile range; CRP = C-reactive protein; IL = interleukin ; CT = computed tomography; ICU = intensive care unit.