BRIEF REPORT

Influenza Vaccination and Hospitalizations Among COVID-19 Infected Adults

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Introduction: **To date, there are no effective treatments for decreasing hospitalizations in Coronavirus disease 2019 (COVID-19) infections. It has been suggested that the influenza vaccine might attenuate the severity of COVID-19.**

Methods: **This is a retrospective single-centered cohort review of a de-identified database of 2005 patients over the age of 18 within the University of Florida health care system who tested positive for COVID-19. Comorbidities and influenza vaccination status were examined. The primary outcome was severity of disease as reflected by hospitalization and intensive care unit (ICU) admission. Logistic regression was performed to examine the relationship between influenza status and hospitalization.**

Results: **COVID-19-positive patients who had not received the influenza vaccination within the last year had a 2.44 (95% CI, 1.68, 3.61) greater odds of hospitalization and a 3.29 (95% CI, 1.18, 13.77) greater odds of ICU admission when compared with those who were vaccinated. These results were controlled to account for age, race, gender, hypertension, diabetes, chronic obstructive pulmonary disease, obesity, coronary artery disease, and congestive heart failure.**

Discussion: **Our analysis suggests that the influenza vaccination is potentially protective of moderate and severe cases of COVID-19 infection. This protective effect holds regardless of comorbidity. The literature points to a potential mechanism via natural killer cell activation. Though our data potentially is limited by its generalizability and our vaccination rate is low, it holds significant relevance given the upcoming influenza season. Not only could simply encouraging influenza vaccination decrease morbidity and mortality from the flu, but it might help flatten the curve of the COVID-19 pandemic as well. We encourage further studies into this finding. (J Am Board Fam Med 2021;34:S179–S182.)**

Keywords: **COVID-19, Hospitalization, Influenza Vaccines, Logistic Models, Morbidity, Retrospective Studies**

Introduction

By September 2020, Coronavirus disease 2019 (COVID-19) has resulted in over 200,000 deaths in the United States and 950,000 worldwide.[1] Although risk factors like older age and comorbid disease are associated with severe outcomes, no effective treatments to decrease the likelihood of hospitalizations in COVID-19 infections have been identified.[2] It has been suggested that influenza vaccination may attenuate the impact of COVID-19 potentially through a vaccine-induced change in innate immunity[3] While the influenza vaccination specifically offers protection against influenza, there is some discussion that, natural influenza infection may reduce the risk of non-influenza respiratory viruses by providing a nonspecific immunity against these viruses in a cross-reactivity strategy.[4,5] Conversely, some

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authors have suggested that influenza vaccination may create a virus interference where vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the nonspecific immunity associated with natural infection.[6–8] The data on influenza vaccination interference is mixed.[8] The objective of this project was to investigate if being up to date on influenza vaccinations is associated with a less severe response to COVID-19 infection as indicated by hospitalizations.

Methods

Data for this project was obtained from a research databank containing de-identified information from the electronic health records (EHR) of patients tested for COVID-19 in the University of Florida (UF) Health system. Usage of the databank for research is not considered human subjects research and Institutional Review Board review was not required to conduct this study. The cohort for this study consisted of all adult patients (18 years and older) with a confirmed diagnosis of COVID-19, between the dates of March and August, who established care at UF Health at least 1 year before their earliest confirmed diagnosis of COVID-19. The presence of a positive laboratory test for COVID-19 in the EHR was used to confirm COVID-19 diagnoses. Each patient's influenza vaccination status was determined using billing codes located in the EHR. Patients were considered up-to-date on their influenza vaccination if their EHR indicated administration of the vaccine within 1 year of their earliest confirmed diagnosis of COVID-19. In addition, hospital encounters and intensive care unit (ICU) stays associated with a confirmed diagnosis of COVID-19-were recorded for all patients in the cohort. Comorbidities that were found to be prevalent among hospitalized COVID-19 patients were recorded as well.[2] In total, 2005 COVID-19 patients were included in our cohort.

Unadjusted logistic regression models were used to compare the odds of COVID-19-related hospitalization or ICU admission between patients with up-to-date influenza vaccination and those without. Logistic regression analyses were subsequently adjusted for the potential confounders of gender, race/ethnicity, age, hypertension, diabetes, chronic obstructive pulmonary diseases (COPD), obesity, coronary artery disease, and heart failure in a forced inclusion model.[2] All analyses were conducted in R 3.6.3.

Results

Table 1 includes the baseline characteristics of the cohort. Of the 2005 patients included in our cohort, 214 (10.7%) patients were considered up-to-date on the influenza vaccine. This subpopulation of our cohort was found to have fewer males but had no difference in ethnic breakdown. The vaccinated group overall also had fewer comorbidities.

Hospitalization and ICU admission were used as surrogate markers for moderate and severe COVID-19 disease. Our analysis indicates that individuals, who had not received the influenza vaccination in the last year, who tested positive for COVID-19 had 2.84 (95% confidence interval [CI], 2.03-4.07) higher odds of being hospitalized when compared with patients who were vaccinated (Table 2). Similarly, the unadjusted odds of ICU admission in unvaccinated, COVID-19 positive individuals were 5.64 (95% CI, 2.11-23.01) when compared with

Table 1. Baseline Characteristics of the Cohort (n = 2005)*

	Up-to-Date Vaccination N (%)	Not Up-to-Date Vaccination N (%)
N	214 (10.7)	1791 (89.3)
Hospitalization for COVID-19	43 (20.1)	747 (41.7)
ICU Admission for COVID-19	3 (1.4)	133 (7.4)
Age (mean ±SD)	40.7±16.3	46.5±19.1
Sex		
Male	65 (30.7)	733 (40.9)
Female	149 (69.3)	1058 (59.1)
Race/Ethnicity		
Non-Hispanic White	97 (45.3)	713 (40.4)
Non-Hispanic Black	73 (34.1)	772 (43.8)
Hispanic	24 (11.3)	170 (9.6)
Other	20 (9.3)	108 (6.2)
Hypertension	22 (10.3)	385 (21.5)
Diabetes	19 (8.9)	232 (13.0)
COPD	3 (1.4)	78 (4.4)
Obesity	14 (6.5)	192 (10.7)
Coronary Artery Disease	2 (0.9)	103 (5.8)
Congestive Heart Failure	2 (0.9)	102 (5.7)

Abbreviations: COVID-19, Coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; SD, standard deviation.
*Cohort consisted of adults aged 18 years and older.

Table 2. Odds Ratios for COVID-19-related Hospitalizations between Confirmed Adult COVID-19 Patients without Up-to-Date Influenza Vaccination versus Those Who Were Up-to-Date

	Crude OR (95% CI)	Adjusted OR* (95% CI)
Hospitalization	2.84 (2.03, 4.07)	2.44 (1.68, 3.61)
ICU Admission	5.64 (2.11, 23.01)	3.29 (1.18, 13.77)

Abbreviations: CI, confidence interval; OR, odds ratio; ICU, intensive care unit.
*Model adjusted for race, age, gender, hypertension, diabetes, chronic obstructive pulmonary disease, obesity, coronary artery disease, and congestive heart failure.

vaccinated COVID-19 patients. This treatment effect was maintained for both hospital admission and ICU admission when adjusted for age, ethnicity, and medical comorbidities (Table 2).

Discussion

Our data strongly suggests that COVID-19 positive patients who are not up-to-date on the influenza vaccination have higher odds of hospitalization. A review of both peer-reviewed and non-peer-reviewed literature on the association between influenza vaccination and influenza-associated COVID-19 morbidity and mortality found no evidence that would suggest clinical manifestations in COVID-19 patients with influenza coinfection differ from those without coinfection.[9] Thus, our results, which are not focused on influenza coinfection, are the first to point to a potential protective effect of influenza vaccination for hospitalization in individuals with COVID-19.

The implications of these findings are substantial, particularly for family medicine. With limited strategies available to effectively decrease the severity of outcomes among COVID-19 patients, influenza vaccination has several attractive qualities. Influenza vaccination is inexpensive, noninvasive, and well accepted in the population. Further, the mechanisms for distribution in the population are well established. The role of the family physician in the prevention of COVID-19 outcomes with this strategy is particularly important.

It is possible to speculate that the individuals who get flu shots are healthier because of a healthier lifestyle. Everyone in the study was COVID-19 positive so a healthier lifestyle and fewer comorbidities may correlate with influenza vaccines and less severe outcomes. However, the adjusted analyses controlled for the relevant comorbidities related to COVID severity, and the effect was still quite strong. That said, we controlled only for comorbidities previously shown to be related to COVID-19 infection severity. There may be other variables that we are unaware of that may play a role in obtaining influenza vaccines and COVID-19 infection severity that could be worthy of future investigations.

There are several limitations to our study. This study is a single-centered study, which makes its generalizability to the national population unclear. In addition, though influenza vaccination status was recorded in the EHR, this is not the standard for assessing vaccination coverage.[10] There may be some misclassification of vaccinated individuals into the unvaccinated group. However, since that would likely dilute our treatment effect, the strength of the association is then particularly striking.

As stated previously, there is no clear mechanism by which the influenza vaccination might be protecting against COVID-19 infection severity. As discussed above, there is some evidence of cross-reactivity of antibodies from low-pathogenic coronavirus with COVID-19,[5] but there is no evidence of cross-reactivity of influenza induced antibodies with the SARS-CoV-2. A literature search provides 2 theories that might explain our results. The first is that an adjuvant within the flu vaccine is triggering a heightened immune response which may provide protective effects against COVID-19. We know that certain influenza vaccinations contain MF59, an oil-in-water emulsion of squalene, which has been used to potentiate the immunogenicity of the influenza vaccine. MF59 has been studied in SARS-CoV vaccines and shown to help stimulate an immune response.[11] Another intriguing theory is that the influenza vaccine could be affecting NK (natural killer cell) cytotoxicity levels. Though the exact role of NK cells in fighting a viral infection is still unclear, there have been increasing studies showing some role of NK cells in fighting virally infected cells. SARS-CoV-2 has been shown to dramatically lower NK cell activity in moderate to severe diseased patients.[12] Influenza vaccination and infection have been shown to increase NK cell activity.[13] Patients who have been vaccinated may have a more "primed" pool of NK cells and thus be able to suppress a COVID-19 infection more efficiently.

We believe that these preliminary findings are significant but require further study. When considering its widespread availability and safety profile, it

is an intriguing prospect that influenza vaccination may be effective protection against COVID-19 morbidity.

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To see this article online, please go to: http://jabfm.org/content/34/Supplement/S179.full.

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