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Short Communication

Effectiveness of influenza vaccination against coronavirus disease (COVID)-19 outcomes in hospitalized individuals in Brazil: an epidemiological study

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ABSTRACT

Objectives: This study aimed to evaluate the impact of the flu vaccination on the mortality of hospitalized individuals with coronavirus disease (COVID)-19 in Brazil.
Study design: A retrospective cohort study was conducted based on epidemiological data released by the Brazilian Ministry of Health.
Methods: An observational study was performed using epidemiological data available at OpenDataSUS. The primary outcome was death—the study period comprised December 29, 2019, to April 6, 2023. The odds ratio with a 95% confidence interval (OR; 95% CI) was calculated to evaluate the association between the epidemiological markers, including the vaccination status against influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the outcome using a multivariable analysis.
Results: The study comprised 791,891 hospitalized individuals with COVID-19. In the study, male sex, older age, living in rural areas, and race (Black and Indigenous peoples), as well as the presence of clinical signs, comorbidities (except the presence of asthma, which was protective), need for intensive care unit, and invasive mechanical ventilation, were associated with a higher chance of death; the vaccination was protective. Among patients with COVID-19, the individuals who received vaccination against influenza [N = 138,564; OR = 0.754 (95% CI = 0.742–0.766)], SARS-CoV-2 [N = 114,628; OR = 0.630 (95% CI = 0.620–0.641)], or both vaccines [N = 55,616; OR = 0.544 (95% CI = 0.531–0.556)], when compared to the individuals who received no vaccination (N = 483,083), had a lower chance of death.
Conclusions: The flu vaccination might be responsible for decreased mortality in hospitalized patients with COVID-19 in Brazil.

Introduction

The coronavirus disease (COVID)-19 crisis ceased to be considered a global health emergency by the World Health Organization in May 2023[1]; however, it was responsible for nearly seven million deaths worldwide until September 2023,[2] and until today, new variants are arising, such as Omicron (B.1.1.529) and Gamma (P.1), thus reinforcing the need for preventive measures.[3] As the COVID-19 was a new type of viral infection, vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) took a considerable time to be developed, being the first one delivered outside a clinical trial in December 2020.[4] Concomitantly, recent data suggest that the influenza virus and SARS-CoV-2 have some grades of similar epitopes, which might lead to potential, although limited, cross-reactivity in the activation of CD8+ T cells in a process called trained immunity.[5,6] The trained immunity can be observed in a real-life scenario because some studies reported that the influenza vaccination affects COVID-19 individuals by decreasing mortality, the need for ventilatory mechanical support, and intensive care unit treatment.[6–8] However, only one study reported the effect of the flu vaccination on Brazilian individuals.[7] Thus, the study evaluated the impact of the influenza vaccination

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on the mortality of hospitalized individuals with COVID-19 in Brazil.

Methods

An observational study was performed using epidemiological data available at OpenDataSUS (https://opendatasus.saude.gov.br/). The Brazilian Ministry of Health computed the data according to the surveillance data of the SARS-CoV-2 infection in Brazil. The primary outcome was death—the study period comprised December 29, 2019, to April 6, 2023. The following information was obtained: gender (male/female), age periods [infancy (<1-year-old, yo), childhood (1–12 yo), youth (13–24 yo), maturity (25–60 yo), presenile (61–72 yo), senile (73–84 yo), and elderly (+85 yo)], race [White, Back, Asian, *Pardos* (multiracial background), and Indigenous peoples], local of residence (urban, peri-urban, and rural), presence of fever, presence of respiratory signs during admission [dyspnea, respiratory discomfort, and oxygen saturation of arterial blood (<95% or ≥95%)], presence of comorbidities [cardiopathy, hematologic disease, Down syndrome, liver disease, asthma, diabetes mellitus, neurologic disease, immunosuppression, obesity, kidney disease, and other comorbidities (any)], need for intensive care unit, need for mechanical ventilatory support (invasive, non-invasive, and none), vaccination status (none, vaccination against influenza only, vaccination against SARS-CoV-2 only, and vaccination against influenza and SARS-CoV-2) and outcome (death and clinical recovery). The Brazilian Ministry of Health included the vaccination status against influenza as positive for individuals who received the vaccine in the last flu annual vaccination campaign within a maximum period of one year before the date of admission. For better accuracy, three authors revised all epidemiological data obtained in the data set.

Before proceeding with the inferential statistical analysis, the multiple imputation for missing data was performed using the NIPALS (Nonlinear Iterative Partial Least Squares) algorithm in the XLSTAT software [Addinsoft (2020) XLSTAT Statistical and Data Analysis Solution. New York. https://www.xlstat.com]. It was performed with the inclusion of missing data for some features because there was more than 5% missingness, the missing data did not occur for the dependent variable, and it was assumed that the variables were missing completely at random. Three characteristics were excluded because they had more than 40% missingness, including the image examinations (X-ray and high solution computed tomography of the chest results) and educational level. After the multiple imputations, the multivariable analysis was performed using the Binary Logistic Regression in the Statistical Package for the Social Sciences (IBM SPSS Statistics for Macintosh, Version 27.0). Finally, the figures were drawn in GraphPad Prism Version 8.0.0 for Mac (GraphPad Software, San Diego, California, USA; www.graphpad.com). The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee (no. 67241323.0.0000.5514).

Results

The study comprised 791,891 hospitalized individuals with COVID-19 (Supplementary Figure 1, SF1). Supplementary Table 1 (ST1) presents the distributions of gender, age groups, place of residence, clinical signs, comorbidities, disease severity (need for intensive care treatment and need for mechanical ventilation support), vaccination status, and outcomes. The distribution of the hospitalized patients by notification weeks is demonstrated in Supplementary Figure 2 (SF2). The bivariate analysis is presented in Supplementary Table 2 (ST2), and the multivariable analysis result is presented in Supplementary Table 3 (ST3) and Fig. 1. In the study, male sex, older age, living in rural areas, and race (Black and Indigenous peoples), as well as the presence of clinical signs, comorbidities (except the presence of asthma, which was protective), need for intensive care unit, and invasive mechanical ventilation, were associated with a higher chance of death; the vaccination was protective. Among patients with COVID-19, the individuals who received vaccination against influenza [N = 138,564; OR = 0.754 (95% CI = 0.742–0.766)], SARS-CoV-2 [N = 114,628; OR = 0.630 (95% CI = 0.620–0.641)], or both vaccines [N = 55,616; OR = 0.544 (95% CI = 0.531–0.556)], when compared to the individuals who received no vaccination (N = 483,083), had a lower chance of death.

Discussion

The results are in accordance with previous papers that observed decreased mortality in those patients who received the influenza vaccination.[7,9,10] A retrospective study performed by Candelli et al. (2021) enrolled 602 participants diagnosed with COVID-19. The authors observed that those who received the flu vaccination were less likely to die within 60 days of follow-up.[9] In the same way, Fink et al. (2020) enrolled 53,752 hospitalized patients with COVID-19, and 31% of them received the flu vaccination. The authors observed decreased mortality, need for intensive care, and need for respiratory support after controlling for several variables (e.g., age, gender, healthcare facility, socio-economic status, and comorbidities).[7] Finally, a recent meta-analysis included data from 23 studies comprising more than 1,000,000 individuals. Su and collaborators (2022) observed that those who received the flu vaccination not only had lower rates of SARS-CoV-2 infection, but those with COVID-19 who received the flu vaccination also presented lower rates of hospitalization and mortality from COVID-19.[10] In all the studies, including the meta-analysis, decreased mortality from COVID-19 was observed in those who received the flu vaccination, which is in accordance with our results; however, none of these studies evaluated when the patient received both vaccines (COVID-19 and influenza), which in our study resulted in a better protection even when compared to one vaccine alone.

The mechanisms behind this cross-protection against COVID-19 by flu vaccines might be due to several biological factors, such as antigenic similarities between the two viruses, boosted innate antiviral response, reduced inflammation, and changes in the transcriptional profile of monocytes in response to infection.[5,11] However, one might not exclude the possibility that the flu vaccine has no biological effect on COVID-19; rather, the results may be due to the healthy user effect, in which individuals who frequently receive preventive therapies are healthier.[6]

In our results, it was also observed that those who received both vaccines, against influenza and COVID-19, might have decreased mortality when compared to those who received only one of the vaccines. Currently, there is no contraindication to give both shots simultaneously;[12] in fact, some countries, such as Brazil, even encourage both shots to be taken on the same day.[13] Even though some studies suggest a higher incidence of self-reported adverse effects when both vaccines were given, when compared to only COVID-19 or influenza alone, one may speculate individuals are more willing to receive the vaccines when they are administered together.[14,15] Furthermore, giving both vaccines at the same time might also improve logistics and decrease the financial burden on healthcare centers, ultimately impacting the well-being of the patients. Finally, asthma was also protective, maybe due to the increase in Th2 response and lower expression of the angiotensin-converting enzyme receptors,[16] and the other epidemiological markers were risk factors as previously reported in the literature.[16–19]

As a limitation, there might be underreporting of COVID-19, as demonstrated by the higher number of individuals classified as

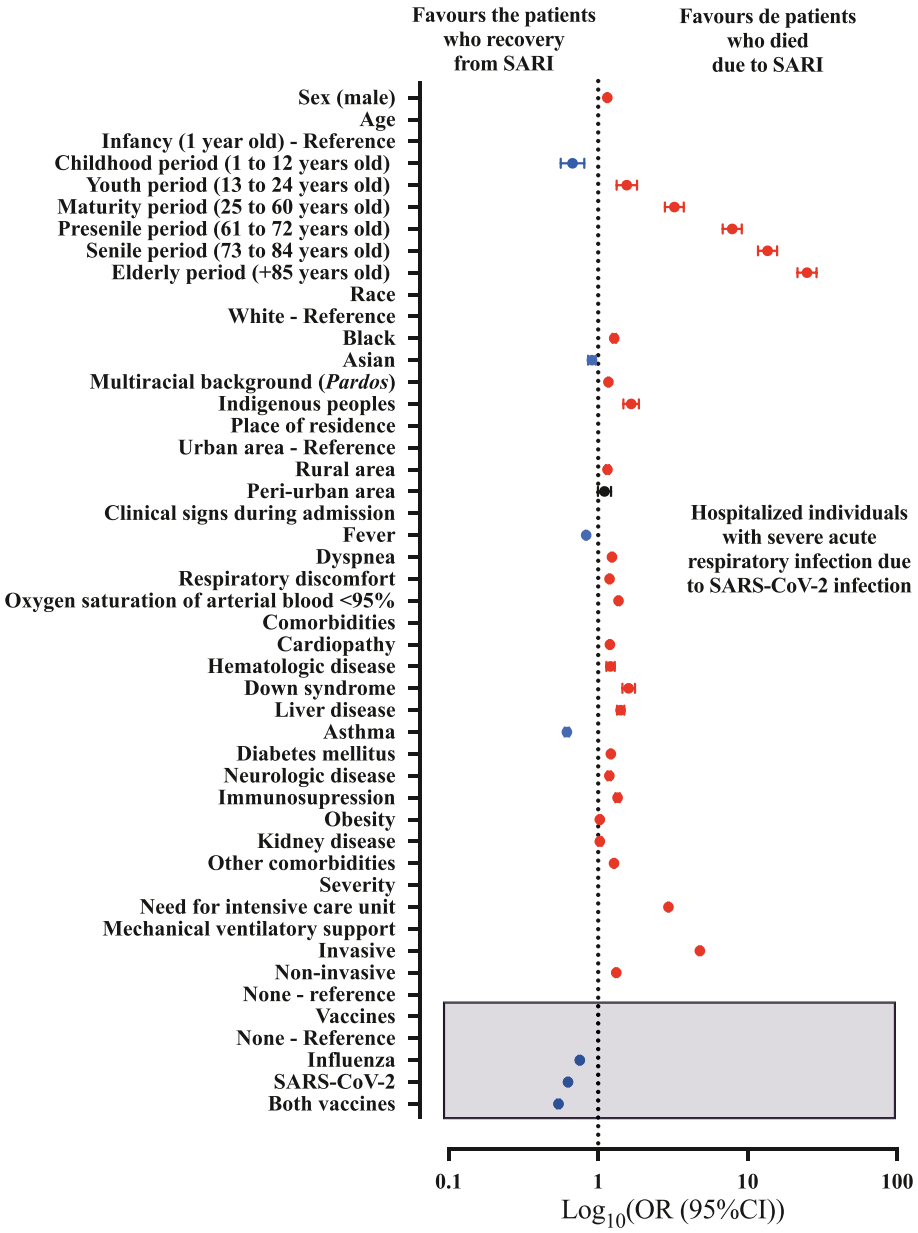

Fig. 1. Multivariable analysis using Binary Logistic Regression to identify the predictors of death among hospitalized individuals with coronavirus disease (COVID)-19 in Brazil. The data are presented using Log_{10}(OR, 95% CI) scale. OR, odds ratio; 95% CI, 95% confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARI, severe acute respiratory infection. The study period comprised December 29, 2019, to April 6, 2023. The data were obtained from OpenDataSUS (https://opendatasus.saude.gov.br/). The study included only the hospitalized individuals with complete information in the data set for vaccinations against influenza and COVID-19, outcome, and infected with SARS-CoV-2.

having a severe acute respiratory infection due to an unknown etiological agent in Brazil (**SF1**). As this is an observational study, it was impossible to infer causality between the flu vaccination and COVID-19 mortality. The authors did not have access to some epidemiological features that could strengthen the work, such as antibodies against SARS-CoV-2.

In conclusion, the flu vaccination might be responsible for decreased mortality in hospitalized patients with COVID-19 in Brazil.

Author statements

Ethical approval

The data used in our study were made publicly available, not containing consent-free personal data because they do not present risks to the research participants. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee (no. 67241323.0.0000.5514).

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Competing interests

None.

Consent to participate

Not required.

Consent for publication

The authors have approved the manuscript and agreed with the submission.

Data and material availability

The complete data can be accessed in Open DataSUS (https://opendatasus.saude.gov.br/).

Code availability

Not required.

Authors' contributions

FALM made substantial contributions to the study conception and design; and performed the acquisition, analysis, and interpretation of data for the work. NMSS, MNB, MD, and FALM drafted the work and revised it critically for important intellectual content. NMSS, MNB, MD, and FALM gave the final approval for the version to be published.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.09.015.

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