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ORIGINAL ARTICLE

# Risk factors for death and illness severity in vaccinated versus unvaccinated COVID-2019 inpatients: a retrospective cohort study

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## ABSTRACT

**Objective:** To determine the clinical profile of COVID-19 inpatients who were vaccinated prior to hospitalization and to compare the risk factors for death and the 28-day survival rate of between those inpatients vaccinated with one, two, or three doses and unvaccinated COVID-19 inpatients. **Methods:** This was a retrospective observational cohort study involving COVID-19 patients admitted to a referral hospital in the city of Recife, Brazil, between July of 2020 and June of 2022. **Results:** The sample comprised 1,921 inpatients, 996 of whom (50.8%) were vaccinated prior to hospitalization. After adjusting the mortality risk for vaccinated patients, those undergoing invasive mechanical ventilation (IMV) had the highest mortality risk (adjusted OR [aOR] = 7.4; 95% CI, 3.8-14.1; $p < 0.001$), followed by patients > 80 years of age (aOR = 7.3; 95% CI, 3.4-15.4; $p < 0.001$), and those needing vasopressors (aOR = 5.6; 95% CI, 2.9-10.9; $p < 0.001$). After adjusting the mortality risk for all patients, having received three vaccine doses (aOR = 0.06; 95% CI, 0.03-0.11; $p < 0.001$) was the most important protective factor against death. There were progressive benefits of vaccination, reducing the frequency of ICU admissions, use for IMV, and death (respectively, from 44.9%, 39.0% and 39.9% after the first dose to 16.7%, 6.2% and 4.4% after the third dose), as well as significant improvements in survival after each subsequent dose ($p < 0.001$). **Conclusions:** Vaccines were effective in reducing illness severity and death in this cohort of COVID-19 inpatients, and the administration of additional doses conferred them with accumulative vaccine protection.

**Keywords:** COVID-19; Risk factors; Hospital mortality; Vaccination.

## INTRODUCTION

Globally, until November 30, 2022, there were more than 640 million confirmed cases of COVID-19 and 6.6 million deaths; in addition, a total of 13 billion vaccine doses were administered, according to the WHO.[1] In Brazil, during the same period, there were more than 35 million cases and approximately 690,000 deaths due to COVID-19, and almost 493 million vaccine doses were administered.[1] In addition, hospitalized COVID-19 patients were the most costly for the health care system and had a high mortality rate, especially those being admitted to critical care units.[2-4]

Vaccination programs have reduced COVID-19-related hospitalizations, ICU admissions, and mortality rates.[5,6] An important observational, population-based study in Israel showed that the vaccination program against COVID-19 significantly reduced the number of asymptomatic and symptomatic cases of SARS-CoV-2 infections, hospitalizations, cases of severe disease, and deaths, even in older adults.[5] An international, randomized, double-blind, placebo-controlled phase 3 trial showed that efficacy of a single-dose vaccine for severe/critical COVID-19 cases with onset at least 14 days and at least ≥ 28 days after administration was, respectively, 76.7% and 85.4%, with decreasing numbers of hospitalizations and deaths.[7] Another study showed that fully vaccinated COVID-19 inpatients had a mortality rate of less than 50% and that the need for invasive mechanical ventilation (IMV) was less frequent in those patients than in unvaccinated patients. However, these studies did not assess the individual benefits of administering multiple doses of vaccines, even when patients were hospitalized for COVID-19.

In Brazil, the COVID-19 vaccination program started on January 17, 2021, prioritizing health professionals, the elderly population, and patients with chronic comorbidities. New outbreaks of COVID-19 may still happen in the future,[8] and it is imperative to identify the risk factors for death in vaccinated patients who are hospitalized for

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COVID-19, so that proper public health policies can be implemented. Thus, the aim of this study was to determine the clinical profile of COVID-19 inpatients who were vaccinated prior to hospitalization and to compare the risk factors for death and the 28-day survival rate between those inpatients vaccinated with one, two, or three doses and unvaccinated COVID-19 inpatients.

## METHODS

### *Study design*

In this retrospective, observational cohort study, we analyzed data from the medical records of patients admitted to at a referral hospital with 100 ICU beds and 200 ward beds for diagnosing and treating suspected or confirmed COVID-19 cases in the city of Recife, Brazil, between July 1, 2020, and June 30, 2022. Patients were enrolled in the cohort if they were 18 years of age or older, had a confirmed positive result for COVID-19 by RT-PCR SARS-CoV-2 testing, and were admitted to the hospital. Patients were grouped as vaccinated (those who were vaccinated against COVID-19 before hospitalization) or as nonvaccinated (those who did not receive any vaccine dose against COVID-19 before hospitalization).

Patients were excluded from the study if they were vaccinated after hospitalization or if vaccination data could not be identified. Patients were followed up until hospital discharge or death. The Research Ethics Committee of the *Instituto de Medicina Integral Prof. Fernando Figueira* reviewed and approved this research (CAAE no. 35243120.7.0000.5205). The Strengthening the Reporting of Observational Studies in Epidemiology guideline recommendations were used as a reference.[9]

The primary outcome was in-hospital mortality. The secondary outcomes were frequency of admission to the ICU and need for IMV. The following demographic, epidemiological, and clinical variables were evaluated: age (years), age group (< 50, 50–59, 60–69, 70–79 and > 80 years), gender (male or female), ethnicity (White or others), marital status (single [divorced, unmarried, widowed] or married [married, living with a partner]), area of residence (Recife, metropolitan area of Recife, or other), symptoms (fever, cough, dyspnea, diarrhea, and vomiting; each symptom was dichotomized as yes or no), vital signs ($Spo_2$, RR, and HR); comorbidities (systemic arterial hypertension, diabetes mellitus, obesity, chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, chronic hematologic disease, chronic neurologic disease, chronic liver disease, cancer, and immunodeficiency; each comorbidity was dichotomized as yes or no); virus variant (Gamma, Delta and Omicron; inference based on viral circulation at the period of study in Brazil), ICU admission (dichotomized as yes or no), chest CT pattern (typical or atypical for the disease), respiratory support (IMV, noninvasive mechanical ventilation, oxygen therapy, and/or none); use of vasopressors (dichotomized as yes or no), renal replacement therapy (dichotomized as yes or no); time spent on IMV (days); length of hospital stay (days); length of ICU stay (days); and in-hospital mortality rate.

### *Statistical analysis*

Data were analyzed using the IBM SPSS Statistics software package, version 28.0 (IBM Corporation, Armonk, NY, USA). Analyses were performed using only valid data. A descriptive analysis of the study population was performed using mean and standard deviation measures for continuous variables and absolute and relative frequency distributions for categorical variables. To compare continuous and categorical variables, respectively, the t-test and the chi-square test were used. We used logistic regression analyses to explore associations among the variables, with an emphasis on the vaccination status of each patient and the risk of death. Variables that showed an association with the outcomes in the univariate analyses ($p < 0.15$) were sequentially tested in a multivariate model, starting with the variable most strongly associated with the risk of death and continuing until no other variable reached significance. Variables with a p-value < 0.05 were considered statistically significant in the multivariate model.[10] We used the Kaplan-Meier method to evaluate survival within 28 days in inpatients vaccinated with one, two, or three vaccine doses versus unvaccinated inpatients, using the log-rank test to evaluate differences between the curves. Differences were considered significant at $p < 0.05$.

## RESULTS

During the period of this study, 3,930 hospitalized patients were selected from those who had confirmed COVID-19 by RT-PCR SARS-CoV-2 testing. Of these patients, 1,044 were excluded because no vaccination data could be identified, and 996 were excluded because they were vaccinated after hospitalization. Therefore, 1,921 patients were included in this study: 996 vaccinated patients (50.8%) and 925 unvaccinated patients (49.2%). Most of the patients were older (mean age = 62.2 ± 15.9 years), male (53.9%), living alone or without a partner (80.3%), non-White (71.2%), and residing in the metropolitan area of Recife (41.7%). Vaccinated patients were older than were unvaccinated patients: 66.5 ± 15.5 years vs. 57.6 ± 15.1 years ($p < 0.001$). There were no significant differences in gender, ethnicity, marital status, or area of residence between vaccinated and unvaccinated patients (Table 1).

With regard to the symptoms related to COVID-19, the most frequent ones were dyspnea (in 73.1%), cough (in 55.6%), and fever (in 42.7%). Unvaccinated COVID-19 patients showed a higher frequency of most of the symptoms ($p < 0.001$). Most of the patients had hypertension (53.5%) and diabetes (31.8%). Except for obesity and chronic pulmonary disease,

comorbidities were more often reported in vaccinated patients than in unvaccinated patients ($p < 0.001$). In our sample, of the 989 patients who underwent chest CT, 756 (76.4%) had a typical pattern for COVID-19. In addition, of the 1,921 patients, 1,022 (53.2%) were admitted to the ICU, 867 (45.1%) needed IMV, 763 (39.7%) used vasopressors, and 125 (6.5%) received hemodialysis. The overall in-hospital mortality rate was 48.7%, and this was higher among unvaccinated patients (60.8% vs. 37.4%; $p < 0.001$). Unvaccinated COVID-19 patients, in comparison with vaccinated patients, more frequently had a typical COVID-19 pattern on chest CT (84.1% vs. 70.6%; $p < 0.001$), were more frequently admitted to the ICU (60.9% vs. 46.1%; $p < 0.001$), and more frequently needed IMV (57.2% vs. 33.9%; $p < 0.001$) and vasopressors (50.1% vs. 30.1%; $p < 0.001$; Table 2).

In general, COVID-19 nonsurvivors, when compared with survivors, were older, had more comorbidities, required more ICU admissions, had more severe disease, and more often used IMV, vasopressors, and hemodialysis, in both vaccinated and unvaccinated groups (Table 3). Vaccinated COVID-19 survivors, when compared with vaccinated nonsurvivors, were younger (64.0 ± 16.3 years vs. 70.6 ± 13.2 years; $p < 0.001$), less often had dyspnea (66.3% vs. 75.3%; $p = 0.003$), had a higher mean $Spo_2$ at hospital admission (96 ± 3% vs. 94 ± 6%; $p < 0.001$), were less often admitted to the ICU (29.7% vs. 73.5%; $p < 0.001$), and less often needed IMV (8% vs. 77%; $p < 0.001$), vasopressors (5.8% vs. 70.8%; $p < 0.001$), or hemodialysis (4.2% vs. 12.1%; $p < 0.001$; Table 3).

The frequency of death, use of IMV, and ICU admission was, respectively, 60.8%, 57.2% and 60.9% for unvaccinated patients ($p < 0.001$); 39.9%, 39.0% and 44.9% for one-dose vaccinated patients ($p < 0.001$); 25.5%, 25.2% and 34.8% for two-dose vaccinated patients ($p < 0.001$); and 4.4%, 6.2%, and 16.7% for three-dose vaccinated patients (Figure 1A). As for COVID-19 variants, patients infected with the Gamma variant had a higher frequency of death, use of IMV, and ICU admission (Figure 1B).

The frequency of death, use of IMV, and ICU admission was, respectively, 38.4%, 33.0% and 46.0%, for those whose first dose was the AstraZeneca vaccine, and 37.4%, 35.1%, and 46.7% for those whose first dose was the CoronaVac vaccine ($p > 0.05$). The frequency of death, use of IMV, and ICU admission was 23.4%, 20.7%, and 38.3% ($p < 0.001$), respectively, for those whose second dose was the AstraZeneca vaccine, and 31.4%, 31.4% and 45.9% for those whose second dose was the CoronaVac vaccine ($p < 0.001$; Figure 1C). The CoronaVac, the AstraZeneca, and the Pfizer vaccines were administered as the first dose, respectively, in 45.7%, 45.0%, and 6.6% of the patients; whereas they were administered as the second dose, respectively, in 51.0%, 39.5%, and 8.8%; and, as the third dose, in 1.3%, 6.6%, and 86.1% (Figure 1D).

**Table 1.** Demographic characteristics of COVID-19 inpatients (N = 1,921) by vaccination status, 2020-2022.[a]

| Characteristic | Group | | | p* |
|---|---|---|---|---|
| | Overall sample | Vaccinated n = 996 (50.8) | Unvaccinated n = 925 (49.2) | |
| Age, years | | | | |
| Mean ± SD | 62.2 ± 15.9 | 66.5 ± 15.5 | 57.6 ± 15.1 | < 0.001 |
| Median | 63 | 68 | 57 | |
| Age group, years | | | | |
| < 50 | 446 (23.2) | 158 (15.9) | 288 (31.1) | < 0.001 |
| 50-59 | 357 (18.6) | 125 (12.6) | 232 (25.1) | |
| 60-69 | 448 (23.3) | 257 (25.8) | 191 (20.6) | |
| 70-79 | 379 (19.7) | 242 (24.3) | 137 (14.8) | |
| ≥ 80 | 291 (15.1) | 214 (21.5) | 77 (8.3) | |
| Sex | | | | |
| Male | 1,035 (53.9) | 540 (54.2) | 495 (53.5) | 0.757 |
| Female | 886 (46.1) | 456 (45.8) | 430 (46.5) | |
| Ethnicity/skin color[b] | | | | |
| White | 305 (28.8) | 143 (28.1) | 162 (29.5) | 0.625 |
| Other | 754 (71.2) | 366 (71.9) | 388 (70.5) | |
| Marital status[c] | | | | |
| Single | 1,536 (80.3) | 819 (82.4) | 717 (78.0) | 0.016 |
| Married | 377 (19.7) | 175 (17.6) | 202 (22.0) | |
| Area of residence[d] | | | | |
| Recife | 680 (35.8) | 358 (35.9) | 322 (35.6) | 0.952 |
| Metropolitan area of Recife | 793 (41.7) | 417 (41.9) | 376 (41.6) | |
| Other | 427 (22.5) | 221 (22.2) | 206 (22.8) | |

[a]Values expressed as n (%), except where otherwise indicated. [b]n = 1,059. [c]n = 1,913. [d]n = 1,900. *Chi-square test.

**Table 2.** Clinical characteristics among COVID-19 inpatients (N = 1,921) by vaccination status, 2020-2022.[a]

| Characteristic | Overall sample | Group | | p* |
|---|---|---|---|---|
| | | Vaccinated n = 996 (50.8) | Unvaccinated n = 925 (49.2) | |
| Symptoms/vital signs | | | | |
| Fever | 820 (42.7) | 393 (39.5) | 427 (46.2) | 0.003 |
| Cough | 1,068 (55.6) | 517 (51.9) | 551 (59.6) | < 0.001 |
| Dyspnea | 1,404(73.1) | 694 (69.7) | 710 (76.8) | < 0.001 |
| Diarrhea | 118 (6.1) | 61 (6.1) | 57 (6.2) | 0.973 |
| Vomit/nausea | 56 (2.9) | 32 (3.2) | 24 (2.6) | 0.421 |
| $Spo_2$ | 94.0 ± 5.7 | 95.0 ± 4.4 | 93.0 ± 6.7 | < 0.001 |
| RR, breaths/min | 22. ± 6.4 | 20.9 ± 5.4 | 23.4 ± 7.1 | < 0.001 |
| HR, bpm[b] | 88.5 ± 18.9 | 88.3 ± 18.8 | 88.7 ± 19.1 | 0.612 |
| Comorbidities | | | | |
| Hypertension | 1,028 (53.5) | 580 (58.2) | 448 (48.4) | < 0.001 |
| Diabetes | 610 (31.8) | 358 (35.9) | 252 (27.2) | < 0.001 |
| Obesity | 536 (27.9) | 252 (25.3) | 284 (30.7) | < 0.001 |
| Chronic cardiac disease | 191 (9.9) | 128 (12.9) | 63 (6.8) | < 0.001 |
| Chronic kidney disease | 176 (9.2) | 104 (10.4) | 72 (7.8) | 0.044 |
| Chronic neurologic disease | 217 (11.3) | 147 (14.8) | 70 (7.6) | < 0.001 |
| Chronic pulmonary disease | 138 (7.2) | 70 (7.0) | 68 (7.4) | 0.784 |
| Chronic hematologic disease | 24 (1.2) | 17 (1.7) | 7 (0.8) | 0.061 |
| Chronic liver disease | 29 (1.5) | 18 (1.8) | 11 (1.2) | 0.267 |
| Cancer | 62 (3.2) | 38 (3.8) | 24 (2.6) | 0.130 |
| Immunodeficiency | 63 (3.3) | 42 (4.2) | 21 (2.3) | 0.017 |
| Typical CT pattern[c] | 756 (76.4) | 397 (70.6) | 359 (84.1) | < 0.001 |
| ICU admission | 1,022 (53.2) | 459 (46.1) | 563 (60.9) | < 0.001 |
| Respiratory support | | | | |
| IMV | 867 (45.1) | 338 (33.9) | 529 (57.2) | |
| Noninvasive ventilation | 292 (15.2) | 144 (14.5) | 148 (16.0) | < 0.001 |
| Oxygen therapy | 426 (22.2) | 270 (27.1) | 156 (16.9) | |
| None | 333 (17.5) | 244 (24.5) | 92 (9.9) | |
| Vasopressor | 763 (39.7) | 300 (30.1) | 463 (50.1) | < 0.001 |
| Hemodialysis | 125 (6.5) | 71 (7.1) | 54 (5.8) | 0.252 |
| Length of hospital stay, days | 12.1 ± 11.9 | 11.8 ± 12.1 | 12.2 ± 11.8 | 0.480 |
| Duration of IMV, days | 8.5 ± 14.4 | 7.2 ± 20.3 | 9.4 ± 8.7 | 0.031 |
| In-hospital mortality rate | 935 (48.7) | 373 (37.4) | 562 (60.8) | < 0.001 |

IMV: invasive mechanical ventilation. [a]Values expressed as n (%) or mean ± SD. [b]n = 1,919. [c]n = 989. *Chi-square test.

When analyzing the adjusted risk of mortality (measured using the adjusted odds ratio [aOR]) for all patients, those undergoing IMV had the highest risk of death (aOR = 14.6; 95% CI, 8.1-26.2; p < 0.001), followed by patients > 80 years of age (aOR = 7.0; 95% CI, 3.5-13.9; p < 0.001), those admitted to the ICU (aOR = 4.6; 95% CI, 2.7-7.8; p < 0.001), those needing vasopressors (aOR = 2.8; 95% CI, 1.6-5.1; p < 0.001) and patients in the 70-79 year-old group (aOR = 4.6; 95% CI, 2.2-9.6; p < 0.001). Having received three doses of vaccine was the best protective factor against death (aOR = 0.076; 95% CI, 0.04-0.146; p < 0.001; Figure 2A).

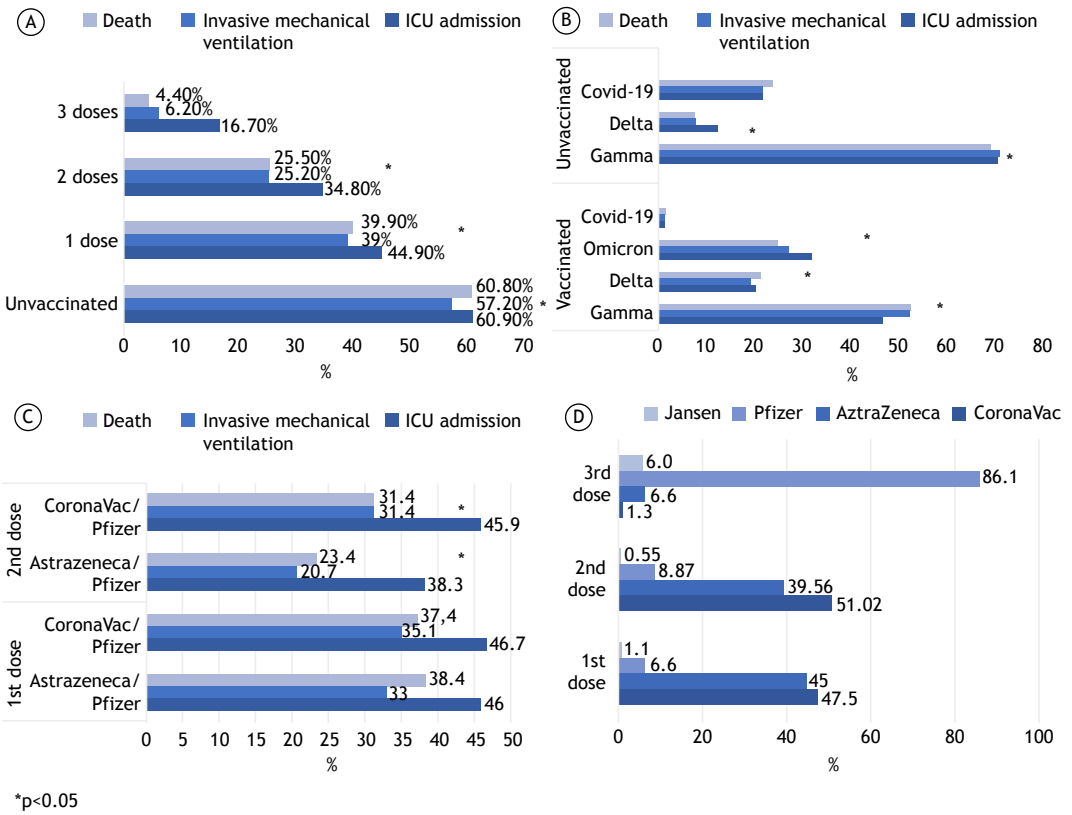
When analyzing the adjusted risk of mortality for vaccinated patients (Figure 2B), those undergoing IMV had the highest risk of death (aOR = 7.4; 95% CI, 3.8-14.1; p < 0.001), followed by patients > 80 years of age (aOR = 7.3; 95% CI, 3.4-15.4; p < 0.001), those needing vasopressors (aOR = 5.6; 95% CI, 2.9-10.9; p < 0.001), patients in the 70-79-year-old group (aOR = 4.6; 95% CI = 2.2–9.6; *p* < 0.001), those admitted to the ICU (aOR = 3.7; 95% CI, 2.2-6.1; p < 0.001), those needing hemodialysis (aOR = 3.0; 95% CI, 1.4-6.7; p < 0.001), and those in the 60-69-year-old group (aOR = 3.1; 95% CI, 1.5-6.4; p < 0.001). The presence of fever at hospital admission (aOR = 0.63; 95% CI, 0.42-0.96; p < 0.001) was a protective factor against death.

When analyzing the adjusted risk of mortality for unvaccinated patients (Figure 2C), those who underwent IMV had the highest risk (aOR = 11.2; 95% CI, 6.3-20.2; p < 0.001), followed by those needing vasopressors (aOR = 2.9; 95% CI, 1.6-5.4;

**Table 3.** Demographic and clinical characteristics among hospitalized COVID-19 survivors and nonsurvivors by vaccination status, 2020-2022.[a]

| Characteristic | Group | | | | | |
|---|---|---|---|---|---|---|
| | Vaccinated n = 996 (50.8) | | p | Unvaccinated n = 925 (49.2) | | p |
| | Survivor | Nonsurvivor | | Survivor | Nonsurvivor | |
| Age, years | 64.0 ± 16.3 | 70.6 ± 13.2 | < 0.001 | 55.3 ± 15.1 | 59.1 ± 14.9 | < 0.001 |
| Median | 66 | 72 | | 55 | 58 | |
| Age group, years | | | | | | |
| < 50 | 130 (20.9) | 28 (7.5) | | 135 (37.2) | 153 (27.2) | |
| 50-59 | 88 (14.1) | 37 (9.9) | | 92 (25.3) | 140 (24.9) | |
| 60-69 | 153 (24.6) | 104 (27.9) | < 0.001 | 72 (19.8) | 119 (21.2) | 0.004 |
| 70-79 | 136 (21.8) | 106 (28.4) | | 40 (11) | 97 (17.3) | |
| ≥ 80 | 116 (18.6) | 98 (26.3) | | 24 (6.6) | 53 (9.4) | |
| Sex | | | | | | |
| Male | 341 (54.7) | 199 (53.4) | 0.671 | 195 (53.7) | 300 (53.4) | 0.920 |
| Female | 282 (45.3) | 174 (46.6) | | 168 (46.3) | 262 (46.6) | |
| Ethnicity/skin color | | | | | | |
| White | 83 (26.1) | 60 (31.4) | 0.197 | 69 (33.3) | 93 (27.1) | 0.121 |
| Other | 234 (73.9) | 131 (68.6) | | 138 (66.7) | 250 (72.9) | |
| Marital status | | | | | | |
| Single | 509 (82) | 310 (83.1) | 0.646 | 280 (77.3) | 437 (78.5) | 0.692 |
| Married | 112 (18) | 63 (16.9) | | 82 (22.7) | 120 (21.5) | |
| Area of residence | | | | | | |
| Recife | 228 (36.6) | 130 (34.9) | 0.431 | 145 (41.3) | 177 (32) | 0.004 |
| Metropolitan area of Recife | 265 (42.5) | 152 (40.8) | | 143 (40.7) | 233 (42.1) | |
| Other | 130 (20.9) | 91 (24.4) | | 63 (17.9) | 143 (25.9) | |
| Symptoms at admission | | | | | | |
| Fever | 264 (42.4) | 129 (34.6) | 0.015 | 178 (49) | 249 (44.3) | 0.159 |
| Cough | 349 (56) | 168 (45) | < 0.001 | 222 (61.2) | 329 (58.5) | 0.429 |
| Dyspnea | 413 (66.3) | 281 (75.3) | 0.003 | 280 (77.1) | 430 (76.5) | 0.827 |
| Diarrhea | 41 (6.6) | 20 (5.4) | 0.437 | 25 (6.9) | 32 (5.7) | 0.461 |
| Vomiting | 21 (3.4) | 11 (2.9) | 0.715 | 12 (3.3) | 12 (2.1) | 0.274 |
| Vital signs at admission | | | | | | |
| $Spo_2$ | 96 + 3 | 94 + 6 | < 0.001 | 95 + 3 | 92 + 7 | < 0.001 |
| RR, breaths/min | 20 + 5 | 22 + 6 | < 0.001 | 21.6 + 6 | 24.6 + 7 | < 0.001 |
| HR, bpm | 86 + 16 | 92 + 22 | < 0.001 | 85 + 16 | 90 + 20 | < 0.001 |
| Comorbidities | | | | | | |
| Hypertension | 360 (57.8) | 220 (59) | 0.648 | 161 (44.4) | 287 (51.1) | 0.046 |
| Diabetes | 213 (34.2) | 145 (38.9) | 0.136 | 84 (23.1) | 168 (29.9) | 0.024 |
| Obesity | 162 (27.9) | 90 (27.4) | 0.737 | 113 (40.6) | 171 (41.8) | 0.472 |
| Chronic cardiac disease | 72 (11.6) | 56 (15) | 0.115 | 29 (8) | 34 (6) | 0.253 |
| Chronic kidney disease | 64 (10.3) | 40 (10.7) | 0.822 | 25 (6.9) | 47 (8.4) | 0.413 |
| Chronic neurologic disease | 79 (12.7) | 68 (18.2) | 0.017 | 27 (7.4) | 43 (7.7) | 0.905 |
| Chronic pulmonary disease | 46 (7.4) | 24 (6.4) | 0.571 | 30 (8.3) | 38 (6.8) | 0.392 |
| Chronic hematologic disease | 13 (2.1) | 4 (1.1) | 0.232 | 4 (1.1) | 3 (0.5) | 0.330 |
| Chronic liver disease | 9 (1.4) | 9 (2.4) | 0.267 | 5 (1.4) | 6 (1.1) | 0.671 |
| Cancer | 19 (3) | 19 (5.1) | 0.103 | 11 (3) | 13 (2.3) | 0.503 |
| Immunodeficiency | 26 (4.2) | 16 (4.3) | 0.930 | 11 (3.3) | 10 (1.8) | 0.212 |
| ICU admission | 185 (29.7) | 274 (73.5) | < 0.001 | 131 (36.1) | 432 (76.9) | < 0.001 |
| Invasive mechanical ventilation | 50 (8) | 288 (77) | < 0.001 | 44 (12.1) | 485 (86.3) | < 0.001 |
| Vasopressor | 36 (5.8) | 264 (70.8) | < 0.001 | 36 (9.9) | 427 (76) | < 0.001 |
| Hemodialysis | 26 (4.2) | 45 (12.1) | < 0.001 | 14 (3.9) | 40 (7.1) | 0.039 |
| CT pattern | | | | | | |
| Typical | 302 (69.9) | 95 (73.1) | 0.585 | 270 (74.4) | 195 (34.7) | < 0.001 |
| Atypical | 108 (25) | 31 (23.8) | | 93 (25.6) | 367 (65.3) | |
| Variant | | | | | | |
| Delta | 159 (25.5) | 79 (21.3) | 0.280 | 48 (13.2) | 43 (7.7) | 0.018 |
| Gamma | 303 (48.6) | 195 (52.3) | | 240 (66.1) | 386 (68.7) | |
| Omicron | 156 (25) | 93 (24.9) | | - | - | |
| Length of hospital stay, days | 11.4 ± 11.4 | 12.6 ± 13.1 | 0.134 | 12.24 ± 10.7 | 12.24 ± 13.3 | 0.998 |

[a]Values expressed as n (%) or mean ± SD.




*p<0.05

**Figure 1.** Mortality rates, use of invasive mechanical ventilation, and ICU admission by number of vaccine doses administered (in A); SARS-CoV-2 variant (in B); vaccination schedule (in C); and type of vaccine per dose (in D).

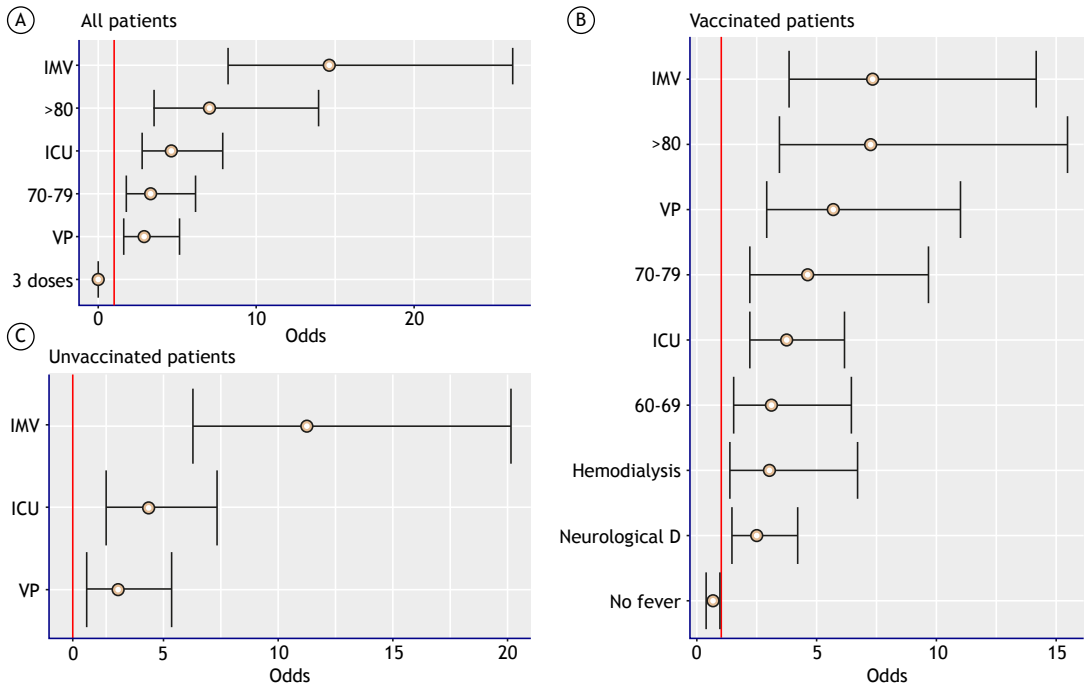



**Figure 2.** Risk factors for death among COVID-19 inpatients: all patients (in A); vaccinated patients (in B); and unvaccinated patients (in C). IMV: invasive mechanical ventilation; >80: age > 80 years; ICU: admitted to the ICU; 70-79: 70-79 age bracket; VP: vasopressor; ;60-69: 60-69 age bracket; and D: disease.

p < 0.001), and those admitted to the ICU (aOR = 4.3; 95% CI, 2.5-7.4; p < 0.001).

According to the Kaplan-Meier curves (Figure 3A), the 28-day survival rates were 38.2% and 62.9%,

respectively, in unvaccinated patients and in one-dose vaccinated patients ($p < 0.001$). The 28-day survival rates were, respectively, 74.6% and 91.8% in two-dose and three-dose vaccinated patients ($p < 0.001$ for both; Figures 3B and 3C).

## DISCUSSION

In this study, data from COVID-19 patients who were hospitalized after the initiation of the vaccination program in Brazil showed greater protection against ICU admissions, use of IMV, and death with each additional dose of vaccine, even for those who were older and had more comorbidities when compared with unvaccinated patients. Furthermore, this study also demonstrated the clinical profile of vaccinated nonsurvivors (older patients with more severe illness who were often admitted to the ICU and made greater use of IMV, vasopressors, and hemodialysis when compared with vaccinated survivors).

Older age, comorbidities, and dysfunctional organs are the most prevalent risk factors for death among hospitalized COVID-19 patients.[2-4,11,12] Vaccines against SARS-CoV-2 have been effective in reducing the number of new COVID-19 cases, hospitalizations, ICU admissions, and deaths.[5,6,13] Our study showed that, after multivariate regression analysis, the risk factors for death, even in vaccinated patients after the multivariate regression analysis, were critical illness and need for IMV, vasopressors, or hemodialysis, even though obesity and fever at admission were protective factors against death. However, the frequency of ICU admissions, the need for IMV, and the number of deaths were significantly higher in unvaccinated patients than in vaccinated patients. Thus, we can infer that the vaccination program against COVID-19 has been the most important measure for saving lives, controlling the transmission of SARS-CoV-2 and reducing health care costs, regardless of age, comorbidities, and severity of illness.

The COVID-19 vaccines have even been effective at protecting hospitalized patients.[14] Among these patients, vaccination has been effective in reducing in-hospital death,[14] risk of developing severe/critical disease,[15] emergency hospitalizations,[16] and length of hospital stay,[17] even in patients on IMV[14] and with different COVID-19 variants,[16] when compared with unvaccinated COVID-19 inpatients. Furthermore, the cumulative benefits of a higher number of vaccine doses[18] and prior infection-acquired immunity[19] have been shown to protect against severe cases,[20] the need for IMV,[21] or death,[21,22] even in older patients.[6] Our study also confirmed the progressive benefits of the vaccines because improvements were found in the overall survival rate as the number of doses administered increased, having the effect of reducing the frequency of ICU admissions, use of IMV, and death (respectively, from 44.9%, 39.0%, and 39.9% after the first dose to 16.7%, 6.2%, and 4.4% after the third dose). We would expect the vaccination program against SARS-CoV-2 to be expanded to include children and adolescents and vaccine doses to be administered twice a year in order to control possible recurrent outbreaks with new variants in the future, given that vaccine protection waned considerably after six months.[19]

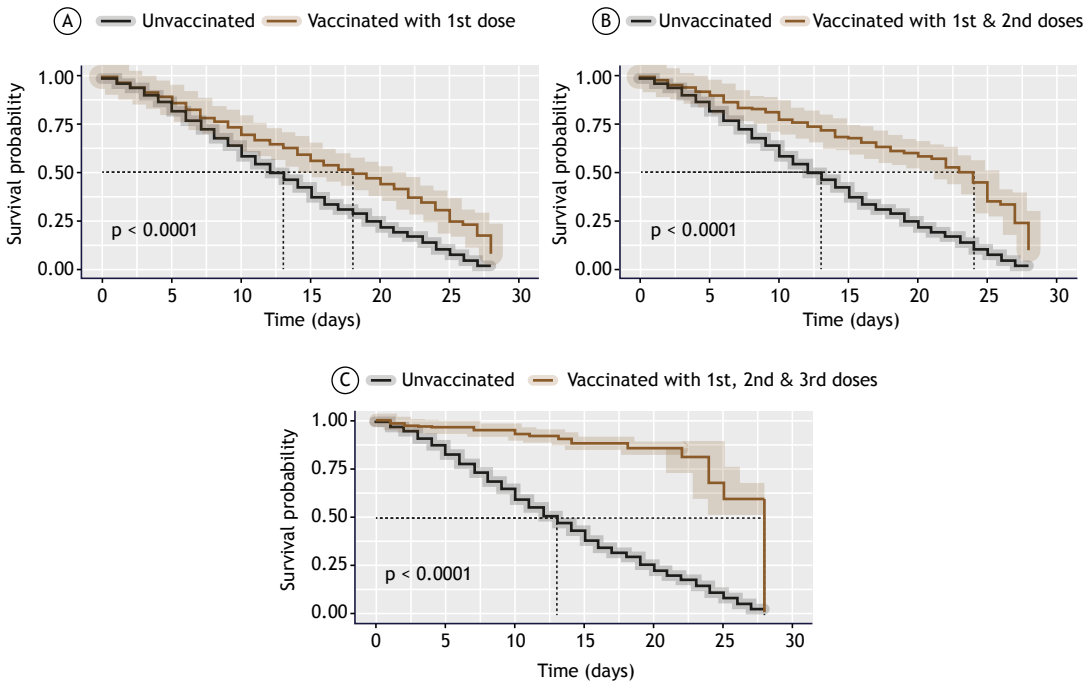



**Figure 3.** 28-day survival rates of COVID-19 inpatients by number of vaccine doses administered. In A, unvaccinated patients vs. patients vaccinated with one dose. In B, unvaccinated patients vs. patients vaccinated with two doses. In C, unvaccinated patients vs. patients vaccinated with three doses.

There are still many people either without access to vaccines[23,24] or who are avoiding taking the vaccines worldwide.[1,24] Having a large number of unvaccinated COVID-19 patients leads not only to a higher risk of death but also to a higher risk of emerging new variants of SARS-CoV-2, and, consequently, new outbreaks in the future.[8] Unfortunately, low-income countries still face challenges in vaccinating their populations completely.[25,26] Even in Brazil, by the end of November of 2022, 12-13% of the population had never received any dose of vaccine, and almost 20% had an incomplete vaccination schedule.[1] However, although systemic and local side effects from all vaccines against COVID-19 have been reported in almost one-third of vaccinated patients, the symptoms were self-limited and for a short time,[27] and therefore they do not justify avoidance or delay in taking additional vaccine doses yearly.

This study has some limitations. First, it had a retrospective observational design with data obtained from a single center, and the authors did not have full access to data regarding vaccination or history of previous COVID-19 infection for all of the COVID-19 inpatients in the study; thus, confounding factors may exist. However, the *Hospital Alfa* was created to provide specialized health assistance in COVID-19 cases and has acquired a high level of expertise by treating almost 7,000 patients with suspected or confirmed COVID-19. Second, the RT-PCR test results that confirmed the COVID-19 cases could not be reviewed, which created some bias about the patients included, albeit all patients admitted to the *Hospital Alfa* underwent the same COVID-19 diagnostic protocol. Third, the authors had no full access to information about adverse effects of the vaccines, especially after multiple doses. Finally, virus sequencing was not carried out, making it impossible to define which variant caused the hospitalization. However, our analysis might be very important for improving knowledge about the vaccines under different clinical conditions (i.e., frequency and risk of death), especially in COVID-19 inpatients because they were evaluated over a long period of time and had different levels of severity.

This important Brazilian study evaluated the clinical profile, illness severity, and risk factors for death in vaccinated versus unvaccinated COVID-19 inpatients, and it determined the overall survival rate of vaccinated patients who had received one, two, or three vaccine doses. This information might provide important support for better decision-making by governments, institutions, and/or health professionals in order to stimulate their patients to follow the vaccination program, regardless of age, gender, or clinical performance.

In conclusion, this Brazilian study showed that the vaccines against SARS-CoV-2 were effective in reducing illness severity and death even in COVID-19 inpatients, who usually have more severe disease, causing more expenses for the health care system, and have higher mortality rates. Furthermore, the use of multiple vaccine doses conferred cumulative vaccine protection to these patients.

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## AUTHOR CONTRIBUTIONS

GJC, JRSJ, CCAS, TPFL, JICJ, and MJTS: study design, conception, and planning; interpretation of evidence; and drafting and revision of the manuscript. CCAS, TPFL, MMC, MHOS, and GCSC: study conception and planning; data collection; interpretation of evidence; and data acquisition. GJC, JRSJ, CCAS, TPFL, MMC, MHOS, GCSC, JICJ, and MJTS: approval of the final version of the manuscript.

## CONFLICTS OF INTEREST

None declared.

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