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Original article

VACCINATION IMPACT: MORTALITY AND TIME SHIFT TO COVID-19 MAXIMUM SEVERITY IN HOSPITALIZED PATIENTS - AN ARGENTINE MULTICENTER REGISTRY

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Abstract

Introduction: The COVID-19 vaccine became an effective instrument to prevent severe SARS-CoV-2 infections. However, 5% of vaccinated patients will have moderate or severe disease. Objective: to compare mortality and days between the symptom onset to the peak disease severity, in vaccinated vs. unvaccinated COVID-19 hospitalized patients.

Methods: Retrospective observational study in 36 hospitals in Argentina. COVID-19 adults admitted to general wards between January 1, 2021, and May 31, 2022 were included. Days between symptoms onset to peak of severity were compared between vaccinated vs. unvaccinated patients with Cox regression, adjusted by Propensity Score Matching (PSM). Results in patients with one and two doses were also compared.

Results: A total of 3663 patients were included (3001 [81.9%] unvaccinated and 662 [18%] vaccinated). Time from symptom onset to peak severity was 7 days (IQR 4-12) vs. 7 days (IQR 4-11) in unvaccinated and vaccinated. In crude Cox regression analysis and matched population, no significant differences were observed. Regarding mortality, a Risk Ratio (RR) of 1.51 (IC95%

1.29-1.77) was observed in vaccinated patients, but in the PSM cohort, the RR was 0.73 (IC95% 0.60-0.88). RR in patients with one COVID-19 vaccine dose in PSM adjusted population was 0.7 (IC95% 0.45-1.03), and with two doses 0.6 (IC95% 0.46-0.79).

Discussion: The time elapsed between the onset of COVID-19 symptoms to the highest severity was similar in vaccinated and unvaccinated patients. However, hospitalized vaccinated patients had a lower risk of mortality than unvaccinated patients.

Key words: COVID-19, SARS-Cov2, comorbidities, risk factors, vaccination, mortality

Resumen

Mortalidad y tiempo entre el inicio y máxima gravedad de COVID-19, en pacientes hospitalizados vacunados y no vacunados. Registro multicéntrico argentino

Introducción: A pesar de la eficacia de la vacuna contra el COVID-19 el 5% de los pacientes vacunados presentaran una enfermedad moderada o grave. El objetivo del presente estudio fue comparar los días entre el inicio de los síntomas y la gravedad máxima de la enfermedad, en pacientes con COVID-19 vacunados vs. no vacunados.

Métodos: Estudio observacional retrospectivo en 36 hospitales de Argentina. Se incluyeron adultos con COVID-19 hospitalizados entre el 1/01/2021 y 31/5/2022. Se recolectaron datos demográficos, comorbilidades y progresión clínica de la enfermedad. Se compararon los días entre el inicio de los síntomas y el pico de gravedad entre vacunados y no vacunados mediante regresión de Cox, ajustada por emparejamiento por Propensity Score Matching (PSM). En un análisis de subgrupos, se compararon los resultados en pacientes con una y dos dosis de vacuna.

Resultados: Se incluyeron 3663 pacientes (3001 [81.9%] no vacunados y 662 [18%] vacunados). El tiempo transcurrido desde el inicio de los síntomas hasta el pico de gravedad fue de 7 días (IQR 4 - 12) en no vacunados, y de 7 días (IQR 4-11) en vacunados. Tanto en el análisis de regresión de Cox crudo como en el ajustado, no se observaron diferencias significativas entre ambos grupos (HR ajustado 1.08 [IC 95% 0.82-1.4; p = 0.56]). En cuanto a la mortalidad, el Riesgo Relativo (RR) fue 1.51 (IC95% 1.29-1.77) en los pacientes vacunados, pero en la cohorte ajustada por Propensity Score, el RR fue de 0.73 (IC95% 0.60-0.88). El RR en el grupo con una dosis de vacuna COVID-19 en el análisis PSM fue 0.7 (IC95% 0.45-1.03), y con dos dosis 0.6 (IC95% 0.46-0.79).

Discusión: El tiempo entre el inicio de los síntomas de COVID-19 y el pico de severidad fue igual en vacunados y no vacunados. Sin embargo, los pacientes vacunados hospitalizados presentaron menor mortalidad tras el ajuste por confundidores.

Palabras clave: COVID-19, SARS-CoV-2, comorbilidades, factores de riesgo, vacunación, mortalidad

KEY POINTS

Current knowledge

- The beneficial effects of SARS-CoV-2 vaccination in preventing the development of severe disease from COVID-19, reducing hospitalizations, intensive care unit admissions and mortality are known, but few data exist on the evolution in vaccinated patients who develop severe illness from COVID-19.

Contribution of the article to current knowledge

- Our results showed no benefit in time in days from symptom onset and peak disease severity in vaccinated patients who develop severe COVID-19 disease. But the mortality of vaccinated patients who develop COVID-19 disease was less than those not vaccinated.

Although social distancing and isolation were, initially, effective in limiting the spread of the virus, the absence of immunity left the people more susceptible to infection[1]. Vaccines have become an effective tool for preventing SARS-CoV-2 infections and hospitalization[2].

In Argentina, the greatest impact of the pandemic was in 2021, with overcrowding of beds in emergency services, general wards, and critical care units. At that time, the vaccination status of hospitalized patients varied from unvaccinated to incompletely or fully vaccinated. The vaccine campaign began on December 29, 2020, and, according to statis-

tics from an international database of vaccination against COVID-19 (Our World in Data, dependent on Oxford Martin School, University of Oxford and Global Change Data Lab), until October 2022, 41 322 415 people have been vaccinated in Argentina with at least one dose, and 37 808 773 people were considered as fully vaccinated[3].

So far, vaccines are known could be effective in preventing asymptomatic and symptomatic infections, as well as hospitalizations, transfer to intensive care units, severe disease, and COVID-19-related death[4-6]. Second or booster doses of vaccines are associated with increased protection against symptomatic disease[3,7,8]. Furthermore, it has been proven that, although the efficacy of COVID-19 vaccines decreased with the emergence of new variants, the prevention of hospitalization and death has remained high compared to unvaccinated patients[9,10]. These findings were also observed in studies that included healthcare workers[11].

Since the start of the pandemic, much has been studied about the impact of vaccination on the course of the COVID-19 disease. However, there remains a knowledge gap regarding the specific effect of vaccination on the time between symptom onset and peak severity. This data could be important to inform the clinical management of patients with COVID-19, particularly in terms of hospitalization and treatment decisions.

Our primary objective was to compare days from the onset of symptoms to the peak of disease severity, considering the day of Mechanical Ventilation (MV) or death (in patients who did not receive MV). Our secondary objective was to compare mortality in vaccinated and unvaccinated patients hospitalized for COVID-19 in the general ward.

Materials and methods

Study design and source of data

The Argentinian Multicenter Registry of COVID-19 (in Spanish: *Registro Multicentrico Argentino COVID-19* [REMA-COVID-19]) is a multicenter registry of COVID-19 hospitalized patients that includes 36 hospitals from 6 Argentine provinces[12]. The registry uses an ad hoc online platform that was created the 1st of March 2020 by an initiative of the Argentinean Society of Medicine to investigate the epidemiology of the SARS-CoV-2 pandemic in Argentina. The registry was created respecting the protection of the patient's identity and data, following the current legal regulations, and assigning them numerical codes. Each center could log in with its users and enter the information corresponding to each case. The data entry was carried out by physicians of each center who were in charge of the care of those patients hospitalized with COVID-19.

This registry was approved by the Institutional Review Board (Ethics Committee of the Italian Hospital of Buenos Aires #5602) and sent to all participating centers for individual approval by their respective Ethics Committees. The manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline[12,13].

Setting and participants

Patients over 18 years of age with a confirmed diagnosis of coronavirus infection admitted to different hospitals in Argentina during the period from 1st January 2021 to 31st May 2022, were included.

Inclusion criteria were: 1) patients aged 18 years or older, 2) with a diagnosis of COVID-19 confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) or other methods that detect viral RNA for SARS-CoV-2, 3) hospitalized in any general ward of a participating facility including specific respiratory care wards but not primarily involving invasive mechanical ventilator support, and 4) COVID-19 as the primary diagnosis. Patients were excluded if they were admitted directly to Intensive Care Units. Patients were followed up until in-hospital death or hospital discharge.

Variables

We divided the original variables into 9 groups: 1) demographic data, body mass index 2) comorbidities; 3) the number of doses of vaccines applied, name of the vaccine, and date of application; 4) symptoms and signs at admission and time since symptom onset at admission; 5) complementary studies; 6) specific treatment for COVID-19 infection; 7) need for admission

to Intensive Care Unit, need for MV, vasoactive support, and hemodialysis; 8) hospital discharge or death. For patients requiring admission to critical care, non-transfer was recorded due to decisions on the limitation of therapeutic effort or lack of available beds.

Statistical analysis

A descriptive analysis of all data was performed. Means with their standard deviations and medians with their interquartile intervals, according to the distribution of the variable, and confidence intervals (CI) were described.

In this study, the primary outcome examined the duration between symptom onset and the peak of disease severity (measured as mechanical ventilation (MV) utilization or death for patients who did not receive MV), using a Cox regression model. The analysis was restricted to patients who experienced the peak severity of COVID-19 disease. All patients included in this analysis had the event of interest, and no censoring or competitive risk events were accounted for. To enhance the comparability of the treatment groups, we reported both crude and adjusted coefficients using Propensity Score Matching (PSM). As a subgroup analysis we compare patients with one and two doses.

In terms of our secondary outcome, which involved evaluating mortality rates between vaccinated and unvaccinated patients, we calculated the Risk Ratio (RR). The RR was calculated first in the entire study population, and secondly in the subset of the PSM population. Each RR and the 95% confidence interval were calculated with the "cs" command in STATA v.16. For statistical significance, a p-value below 0.05 was adopted, and the estimated effects, accompanied by their corresponding 95% confidence intervals, were systematically reported.

To assess the robustness of the vaccine's effect, we used PSM to reduce the confounding effects. The potential confounders in the causal relationship between the COVID-19 vaccine and the severity of COVID-19 disease were: age, male sex, hypertension, Chronic Obstructive Pulmonary Disease (COPD), immunosuppression, cancer, diabetes, heart failure, chronic kidney disease (CKD)[14] and systemic corticosteroid therapy[15]. For the PS development, first, we estimated the individual PS for COVID-19 vaccine receipt with a multivariable logistic regression model that included all the potential confounders. Matching was performed with the use of a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width equal to 0.2 of the standard deviation of the logit of the PS[16]. Standardized differences were estimated for all the baseline covariates before and after matching to assess pre-match imbalance and post-match balance. We consider standardized differences of less than 10.0% for a given covariate to indicate a relatively small imbalance[16,17]. The data were analyzed with STATA® v16 software.

Study size

We included a consecutive sample of patients who met the inclusion criteria. Because this was a "live registry" of patients with COVID-19, we had a fixed sample size, thus we performed a power calculation for the primary and secondary outcomes.

For the primary outcome, we only evaluated patients who receive MV or died during hospitalization. In the registry, 788 patients died or received MV, of which 181 were vaccinated. With this sample size, we have a power of 99%, with an alpha of 5%, to detect a minimal significant difference (between days from the onset of symptoms to peak disease severity) of 2 days between groups (we expected 7 days in unvaccinated patients and 9 in vaccinated), with an SD of 2 in both groups.

Results

Participants

The Argentinian Multicenter Registry of COVID-19 included 5895 patients, of which 3663 were included in this study (Fig. 1). We excluded patients younger than 18 years old and hospitalized before January 1st, 2021. Of them, 3001 (81.9%) were unvaccinated patients, and 662 (18%) were vaccinated. Among the vaccinated, 421 (63.6%) received one dose and 241 (36.4%) two doses.

Descriptive data

The median age was higher in the group of vaccinated patients: 66.8 (SD 18.9) vs. 51.8 (SD

21.8); and the proportion of women was similar in both groups (45.3% in the unvaccinated and 48.3% in the vaccinated group). As for comorbidities, vaccinated patients had a higher burden of comorbidities, such as hypertension, diabetes, or cancer (Table 1).

Among vaccinated patients, Sputnik V was the most frequent (n = 304, 46%). The number of doses and type of vaccine received are shown in Table 2.

Outcome data and main results

Regarding our primary outcome, we observed that unvaccinated patients took a median of 7 days (IQR 4-11) from symptom onset to reach the peak of severity, defined as either requiring

Figure 1 | Flow chart of included patients

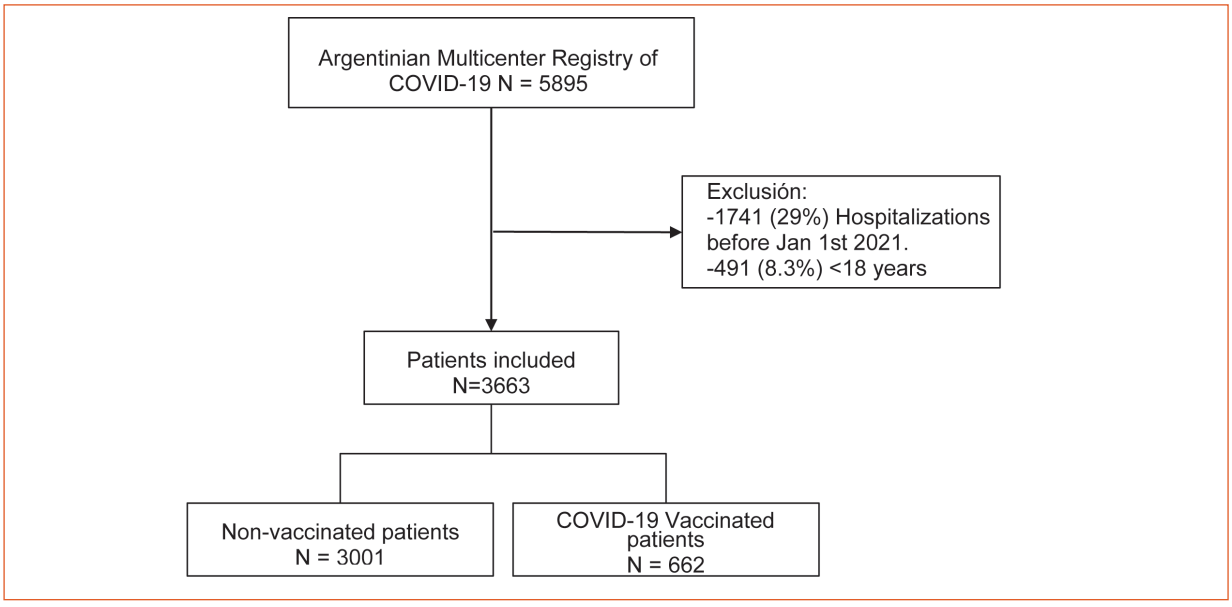

Table 1 | Baseline characteristics of patients hospitalized for COVID-19

Variables	All (n = 3663)	Unvaccinated (n = 3001) n (%)	Vaccinated (n = 662) n (%)	p-value
Age-mean (SD)	54.3 (22.1)	51.6 (22.2)	64.8 (18.3)	< 0.001
Female sex	1675 (45.7)	1361 (45.4)	314 (47.1)	0.465
Hypertension	1557 (54.3)	1123 (51.0)	434 (65.5)	< 0.001
Diabetes	615 (21.5)	454 (20.6)	161 (24.3)	0.049
Cancer	456 (15.9)	329 (14.9)	127 (19.1)	0.012
Hematologic tumors	84 (2.9)	58 (2.6)	26 (3.9)	0.113
HIV	20 (0.72)	15 (0.70)	5 (0.9)	0.792
Immunosuppression	149 (5.48)	112 (5.35)	37 (5.9)	0.652
Ischemic stroke	168 (6.28)	119 (5.84)	49 (7.66)	0.119
Hemorrhagic stroke	17 (0.64)	13 (0.64)	4 (0.62)	0.99
Smoking	112 (3.06)	89 (2.97)	23 (3.45)	< 0.001
COPD	239 (8.34)	168 (7.63)	71 (10.7)	0.015
Asthma	150 (5.23)	109 (4.94)	41 (6.17)	0.254
Cardiac failure	252 (8.78)	175 (7.94)	77 (11.6)	0.004
End-stage renal failure	13 (0.46)	10 (0.46)	3 (0.46)	0.999

mechanical ventilation or experiencing death (in patients with do-not-intubate orders). Vaccinated patients also took a median of 7 days (IQR 4-12) to reach the same peak severity. In the crude Cox regression analysis, we observed a hazard ratio (HR) of 0.93 (95% CI 0.79-1.1; p = 0.43), with no significant difference between vaccinated and unvaccinated patients. After Propensity Score Matching (PSM), the HR was 1.08 (95% CI 0.82-1.4; p = 0.56), further supporting the absence of significant differences between the two groups. These findings are presented graphically in Fig. 2, which displays the Kaplan-Meier curves, and Fig. 3, which illustrates the covariate imbalance between vaccinated and unvaccinated patients before and after matching. In tables S1 and S2 we presented the descriptive data and outcomes of the PSM population. In the subgroup analysis patients with one dose and two doses were compared against unvaccinated patients. Patients with one vaccine dose had a HR of 1.04 (95% CI 0.85-1.28; p = 0.65) and with two doses 0.84 (95% CI 0.65-1.01; p = 0.21). In the PMS population, the HR of patients with one dose was 1.19 (95% CI 0.86-1.65; p = 0.27) and with two doses 1.20 (95% CI 0.80 - 1.8; p = 0.36).

Regarding our secondary outcome, we observed that mortality was higher in vaccinated patients than unvaccinated in the univariate analysis (23.3% vs. 17.7%, p < 0.001 (Table 3). Therefore, the RR of death in vaccinated patients compared to unvaccinated patients was 1.31 (CI 95% 1.12-1.54; p < 0.001). However, in the PSM population, we observed that the relationship between vaccination and mortality was reversed, with the vaccine being protective against mortality with an RR of 0.7 (IC95% 0.56-0.84; p < 0.001). The RR in patients with one COVID-19 vaccine dose in the PSM population was 0.7 (IC95% 0.45-1.03; p = 0.063), and with two doses was 0.6 (IC95% 0.46-0.79; p < 0.001).

Table 2 | Number of doses and type of vaccines received

Variables	Vaccinated (n = 662) n (%)
Doses of vaccines received	
- 1 dose	421 (63.6)
- 2 doses	241 (36.4)
Sputnik	304 (45.6)
Oxford/AstraZeneca	194 (29.1)
Sinopharm	118 (17.7)
Moderna	24 (3.6)
No data	22 (1)

Figure 2 | Kaplan Maier time to peak of disease severity (death or MV) in ventilated patients against non-ventilated patients

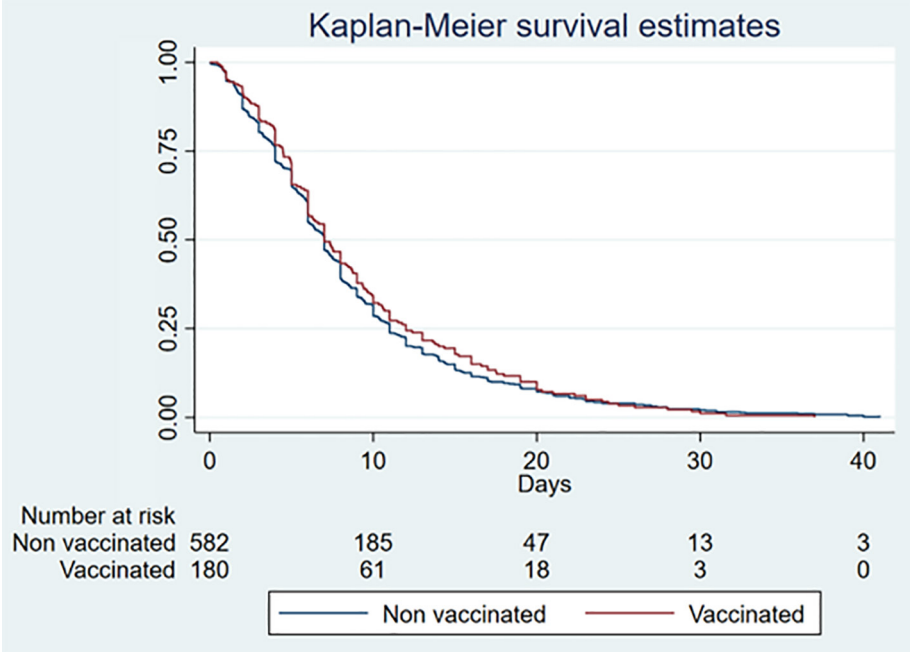

Figure 3 | Love plot for absolute standardized differences before and after propensity score matching comparing covariate values between vaccinated and unvaccinated COVID-19 patients

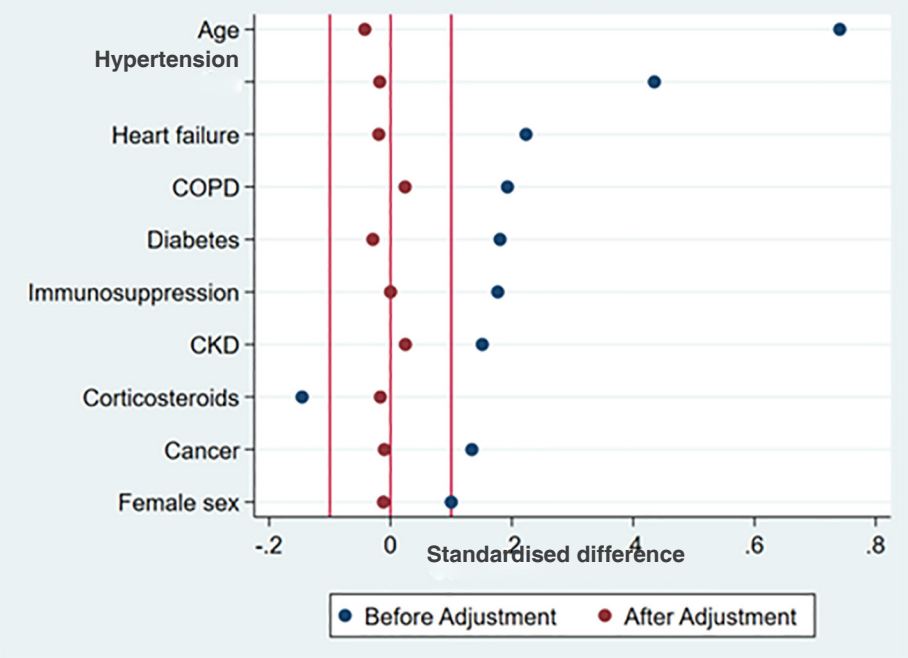

Table 3 | Clinical course of patients hospitalized for COVID-19

Variables	All (n = 3663 n (%)	Unvaccinated (n = 3001) n (%)	Vaccinated (n = 662) n (%)	p-value
Oxygen therapy	1669 (58.3)	1270 (57.6)	399 (60.5)	0.180
Corticoid treatment in hospitalization	1416 (83.2)	1066 (83)	350 (83.9)	0.616
Critical care admission	584 (15.9)	470 (15.7)	114 (17.1)	0.370
Mortality	686 (18.7)	529 (17.6)	157 (23.5)	< 0.001

Discussion

Our study has some limitations. First, we could not differentiate between SARS-CoV-2 variants. Previous studies have confirmed that the active immunity conferred by the vaccines decreased with the emergence of new variants, such as Delta, but even so, vaccinated patients had a lower risk of death compared to unvaccinated patients[18]. Secondly, we could not include booster doses of the vaccines. Current evidence has shown that patients who receive a booster dose, may have up to 90% lower risk of death compared to those who do not receive a booster dose[8, 18], even in the presence of emerging variants[9]. Third, we did not include High Flow Nasal Cannula (HFNC) therapy as a study endpoint because not all participating centers utilized this treatment strategy, and at the time of the study, there was insufficient evidence to support the benefits of using HFNC in patients with COVID.

In this study, no significant differences were observed in terms of the time elapsed between the symptom onset and peak of disease severity (MV or death) when comparing the vaccinated and unvaccinated groups. As expected, and in agreement with previous literature, we observed that the COVID-19 vaccine reduces mortality, after adjustment by confounders.

The peak of disease severity usually coincides with the cytokine storm. This is an excessive inflammatory response with the release of cytokines and pro-inflammatory chemical mediators. Clinically, it can lead to respiratory distress syndrome requiring mechanical ventilator support, multi-organ failure, or even death[17]. Previous studies reported that the time between the onset of symptoms and the cytokines storm was 7 to 10 days[19, 20]. In this sense, Khalili et al. published a meta-analysis that describes the time between the onset of symptoms to ICU admission, that was 9.8 (95% CI: 8.8, 10.9) days and 15.9 (95% CI: 13.1, 18.8) to death[20]. In our study, we observed also that the time between onset to the peak of severity was 9 days, and the difference between time to death is because the studies included in the revision of Khalili et al. evaluated time to death in ventilated patients, while we evaluate time to mechanical ventilation or death in patients with do-not-intubate orders.

Regarding our secondary objective, we observed that mortality was slightly higher in the vaccinated group, but these patients had a higher burden of comorbidities. In this sense, when a multivariate analysis was performed adjusting for age, sex, and comorbidities, we observed that vaccination is an independent protective factor against mortality (Table S2). In this way, Tenforde et al[2], reported that vaccinated COVID-19 hospitalized patients had an adjusted OR of 0.33 (CI 95% 0.19-0.5) for the outcome progression to severe disease outcomes (including respiratory failure and death). Other studies that evaluated the incidence of mortality showed a decrease in the number of cases per 100 000 persons/day in favor of patients vaccinated with mRNA vaccines[4] as well as with inactivated virus or viral vector vaccines[5]. Finally, in the study of Busic et al[21] results, the initial analysis suggests heightened mortality rates among vaccinated patients. Yet, upon meticulous confounder adjustment, COVID-19 vaccines exhibit a remarkable potential to curtail mortality in the context of hospitalized patients.

Several published articles have examined the impact of SARS-CoV-2 vaccination on mortality in Argentina. Macchia et al[5] conducted a study evaluating mortality in a group of patients over 60 years old who received either one or two doses of 4 different vaccines. The results showed favorable outcomes for vaccination. Other study (Gonzalez et al[22]) assessed the benefits of a single dose of the Sputnik V vaccine on mortality in a cohort of patients aged 60-79 from the province of Buenos Aires; and a third one (Gonzalez et al[23]) examined a cohort of children and adolescents aged 3-17 years, where vaccination demonstrated benefits in reducing mortality and hospitalization. It is important to note that all the mentioned studies were conducted on cohorts of patients without previous SARS-CoV-2 infection. In contrast, our current study focuses on a cohort of hospitalized patients with severe symptoms of COVID-19. Another local study[24] has shown an absolute risk reduction of 15.1% in mortality in hospitalized patients with a complete vaccination schedule vs. those not vaccinated or with an incomplete schedule.

In conclusion, in the present study it was observed that the COVID-19 vaccine did not change the time between symptoms onset and peak of disease severity in COVID-19 patients. It also was found that hospitalized vaccinated patients due to COVID-19 have lower mortality compared to unvaccinated patients.

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Conflict of Interest: None to declare

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SUPPLEMENTARY MATERIAL

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Table S1 | Baseline characteristics of patients hospitalized for COVID-19 in the Propensity Score Matched population

Variables	All (n = 680) n (%)	Unvaccinated (n = 340) n (%)	Vaccinated (n = 340) n (%)	p-value
Age-mean (SD)	53.9 (14.0)	54.1 (14.4)	53.7 (13.7)	0.697
Female sex	301 (44.3)	154 (45.3)	147 (43.2)	0.643
Hypertension	372 (54.7)	189 (55.6)	183 (53.8)	0.700
Diabetes	160 (23.5)	83 (24.4)	77 (22.6)	0.651
Cancer	67 (9.85)	33 (9.71)	34 (10.0)	0.999
Hematologic tumors	23 (3.38)	11 (3.24)	12 (3.53)	0.999
HIV	5 (0.74)	3 (0.88)	2 (0.59)	0.999
Immunosuppression	53 (7.79)	27 (7.94)	26 (7.65)	0.999
Ischemic Stroke	4 (0.62)	2 (0.62)	2 (0.62)	0.999
Hemorrhagic Stroke	1 (0.15)	1 (0.31)	0 (0.00)	0.499
Smoking	42 (6.18)	22 (6.47)	20 (5.88)	0.999
COPD	53 (7.79)	25 (7.35)	28 (8.24)	0.775
Asthma	25 (3.68)	16 (4.71)	9 (2.65)	0.221
Cardiac failure	85 (12.5)	43 (12.6)	42 (12.4)	0.999
End-stage renal failure	3 (0.44)	1 (0.29)	2 (0.59)	0.999

Table S2 | Clinical course of patients hospitalized for COVID-19 in the Propensity Score Matched population

Variables	All (n = 680) n (%)	Unvaccinated (n = 340) n (%)	Vaccinated (n = 340) n (%)	p-value
Oxygen therapy	589 (86.6)	296 (87.1)	293 (86.2)	0.822
Corticoid treatment in hospitalization	587 (86.3)	293 (86.2)	294 (86.5)	0.999
Critical care admission	142 (20.9)	77 (22.6)	65 (19.1)	0.299
Mortality	190 (27.9)	117 (34.4)	73 (21.5)	< 0.001