Received: 9 March 2023 | Accepted: 1 May 2023

DOI: 10.1002/jmv.28786

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

COVID-19 vaccines reduce mortality in hospitalized patients with oxygen requirements: Differences between vaccine subtypes. A multicontinental cohort study

Ivan A. Huespe[1,2] | Augusto Ferraris[1] | Antonio Lalueza[3] | Pascual R. Valdez[4] | Maria L. Peroni[1] | Luis A. Cayetti[1] | Matias A. Mirofsky[5] | Bruno Boietti[1] | Ricardo Gómez-Huelgas[6] | José M. Casas-Rojo[7] | Juan M. Antón-Santos[7] | Jesús M. Núñez-Cortés[8] | Carlos Lumbreras[3] | Jose-Manuel Ramos-Rincón[9] | Noelia G. Barrio[3] | Miguel Pedrera-Jiménez[3] | María D. Martin-Escalante[10] | Francisco R. Ruiz[10] | María Á. Onieva-García[10] | Carlos R. Toso[2] | Marcelo R. Risk[11] | Riku Klén[12] | Javier A. Pollán[1] | David Gómez-Varela[13]

[1]Intensive Care Unit, Italian Hospital of Buenos Aires, Buenos Aires, Argentina

[2]Medicine Department, University of Buenos Aires, Buenos Aires, Argentina

[3]12 de Octubre University Hospital, Research Institute of Hospital 12 de Octubre (imas+12), Complutense University, Madrid, Spain

[4]Vélez Sarsfield Hospital, Buenos Aires, Argentina

[5]Hospital Municipal de Agudos "Dr. Leónidas Lucero", Bahía Blanca, Argentina

[6]Regional University Hospital of Málaga, Biomedical Research Institute of Málaga (IBIMA), University of Málaga (UMA), Málaga, Spain

[7]Infanta Cristina University Hospital, Madrid, Spain

[8]Gregorio Marañón University Hospital, Madrid, Spain

[9]Clinical Medicine Department, Miguel Hernadez University, Alicante, Spain

[10]Costa del Sol Hospital, Marbella, Spain

[11]Instituto de Medicina Traslacional e Ingeniería Biomédica (IMTIB), CONICET-HIBA-IUHI, Buenos Aires, Argentina

[12]Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland

[13]Department of Pharmaceutical Sciences, Division of Pharmacology and Toxicology, University of Vienna, Vienna, Austria

Correspondence

Ivan A. Huespe, Intensive Care Unit, Hospital Italiano de Buenos Aires, 4190 Tte. Gral. J. D. Perón (C1199ABB), Buenos Aires, Argentina.
Email: ivan.huespe@hospitalitaliano.org.ar

David Gómez-Varela, Department of Pharmaceutical Sciences, Division of Pharmacology and Toxicology, University of Vienna, Josef-Holaubek-Platz 2, 1090 Vienna, Austria.
Email: david.gomez.varela@univie.ac.at

Abstract

The aim of this study was to analyze whether the coronavirus disease 2019 (COVID-19) vaccine reduces mortality in patients with moderate or severe COVID-19 disease requiring oxygen therapy. A retrospective cohort study, with data from 148 hospitals in both Spain (111 hospitals) and Argentina (37 hospitals), was conducted. We evaluated hospitalized patients for COVID-19 older than 18 years with oxygen requirements. Vaccine protection against death was assessed through a multivariable logistic regression and propensity score matching. We also performed a

Funding information
Ben Barres Spotlight Award from eLife; Instituto de Salud Carlos III, Ministry of Science and Innovation, Spain; Universität Wien; Becas Salud Investiga of the Argentinian Ministery of Health

subgroup analysis according to vaccine type. The adjusted model was used to determine the population attributable risk. Between January 2020 and May 2022, we evaluated 21,479 COVID-19 hospitalized patients with oxygen requirements. Of these, 338 (1.5%) patients received a single dose of the COVID-19 vaccine and 379 (1.8%) were fully vaccinated. In vaccinated patients, mortality was 20.9% (95% confidence interval [CI]: 17.9–24), compared to 19.5% (95% CI: 19–20) in unvaccinated patients, resulting in a crude odds ratio (OR) of 1.07 (95% CI: 0.89–1.29; $p = 0.41$). However, after considering the multiple comorbidities in the vaccinated group, the adjusted OR was 0.73 (95% CI: 0.56–0.95; $p = 0.02$) with a population attributable risk reduction of 4.3% (95% CI: 1–5). The higher risk reduction for mortality was with messenger RNA (mRNA) BNT162b2 (Pfizer) (OR 0.37; 95% CI: 0.23–0.59; $p < 0.01$), ChAdOx1 nCoV-19 (AstraZeneca) (OR 0.42; 95% CI: 0.20–0.86; $p = 0.02$), and mRNA-1273 (Moderna) (OR 0.68; 95% CI: 0.41–1.12; $p = 0.13$), and lower with Gam-COVID-Vac (Sputnik) (OR 0.93; 95% CI: 0.6–1.45; $p = 0.76$). COVID-19 vaccines significantly reduce the probability of death in patients suffering from a moderate or severe disease (oxygen therapy).

KEYWORDS
COVID-19, COVID-19 vaccines, hospitalization, oxygen therapy

1 | INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) has had a calamitous impact on health systems and economies across the globe. By July 2022, 548 million COVID-19 cases were confirmed, and over 6 million people died worldwide due to this disease.[1]

Nearly 15% of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection develop severe disease with hypoxemia, and 5% developed critical disease.[2] The pathological mechanisms of severe COVID-19 disease include systemic inflammation, alveolar epithelial and alveolar cell damage, and coagulopathy.

The development of several COVID-19 vaccines proved to be effective in reducing poor clinical outcomes, including death,[3] with effectiveness above 90% for avoiding hospitalization.[4] Despite this high protection, more than 5% of vaccinated patients require hospitalization with moderate or severe illness that could progress to critical illness, reaching a mortality ratio between 14.8% and 24%, which is very similar to the one reported for unvaccinated hospitalized patients.[5–10] The majority of these vaccinated patients belong to the most sensitive groups—the elderly, people with high comorbidity burden, previous pathologies (e.g., cancer), or immunocompromised patients. These patient groups are characterized by their inability to develop a proper immune response to vaccination.[11–14] The percentage of cases that fall into this "nonresponders category" is unknown.[8]

However, the high percentage of the total population that is vaccinated (more than 80% in the most developed countries), together with the above-mentioned similarity in the mortality ratio between vaccinated and unvaccinated patients, has been used to make claims against the efficacy of the COVID-19 vaccination for saving lives. A thoughtful analysis, taking into account the unique clinical characteristics of each group of patients, on how vaccination protects patients with moderate or severe illness, is missing.

In this study, we used a multicontinental patient cohort to critically analyze the efficacy of the COVID-19 vaccines for protection against death in COVID-19 patients with oxygen requirements.

2 | METHODS

2.1 | Study design and setting

We conducted a multicontinental retrospective cohort study combining the data from 148 hospitals in both Spain (111 hospitals from the Sociedad Española de Medicina Interna COVID-19 Registry) and Argentina (37 hospitals: Argentinian COVID-19 Network, national registry). These databases included patients hospitalized between January 2020 to March 2022 with comprehensive demographic, clinical, and laboratory data. A detailed description of the databases is reported elsewhere.[15,16]

The present manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Supporting Information: Table e1).[17] Institutional Review Board approvals are provided in the Supporting Information: Material.

2.2 | Participants

Patients older than 18 years, hospitalized with a confirmed diagnosis of COVID-19, and who received oxygen therapy were included. SARS-CoV-2 infection was defined as a positive result of real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) for SARS-CoV-2 in nasopharyngeal swab specimens or sputum samples; also in the second and third waves, some patients were diagnosticated with the Panbio TM COVID-19 rapid test (Abbott) in the Spanish hospitals. We considered only the first hospitalization for COVID-19 for each patient during the study period. Patients were followed from hospital admission until death or hospital discharge.

2.3 | Variables

Data regarding demographic, clinical, vaccination status and date of vaccination, COVID therapies, and clinical outcomes during hospitalization was captured.[18–20] Clinical variables were retrieved based on International Classification of DiseasesExternal 10th Revision codes. The main exposure was vaccination status. Patients were considered vaccinated if they presented with one or more COVID-19 vaccine doses received at least 14 days before hospitalization. The main outcome was all-cause in-hospital mortality. In the Supporting Information: Material, all variables included are described.

2.4 | Statistical analyses

Data are summarized using mean and standard deviation for continuous variables and percentages for categorical variables.

2.5 | Primary outcome

To assess the relationship between COVID-19 vaccine status and death, first, we performed univariate analyses of the exposure and all the potential confounders. The potential confounders in the causal relationship between the COVID-19 vaccine and risk of death were: age, male sex, hypertension, chronic obstructive pulmonary disease (COPD), immunosuppression, cancer, diabetes, coronary heart disease (CHD) or peripheral arterial disease (PAD), asthma, heart failure, chronic kidney disease (CKD),[21] and systemic corticosteroid therapy.[22] Additionally, the belonging to a high-income country and the predominance of the Omicron variant were evaluated as potential confounders. Outcomes of patients could potentially vary in high-income when compared with middle-outcome settings due to differential resource availability.[23] Moreover, infection with the Omicron variant was of special interest for our analysis, because the Omicron variant was associated with better in-hospital outcomes, including lower mortality, when compared with other variants.[24]

Second, a multivariable logistic regression model was performed to assess the COVID-19 vaccine effects on in-hospital death while adjusting for the potential confounders. COVID-19 vaccination status was forced into the model to assess its significance in determining in-hospital death likelihood, followed by stepwise inclusion of all the potential confounders described before. Variables with $p < 0.1$ and variables with biological plausibility were maintained in the model. We tested the linear relation between continuous variables and the log odds with the Box–Tidwell test ($p = 0.23$).

Also, we know that the databases had some missing data due to the medical overload during the COVID-19 pandemic. We consider this missing data as "missing completely at random" (without systematic differences between the missing values and the observed values).[25] Hence, we performed multiple imputations by the chained equations procedure as sensitivity analysis. To reduce the sampling error due to the imputations, we set the number of 20 imputed data sets.[26]

2.6 | Propensity score matching

To assess the robustness of the vaccine's effect, we used propensity score matching. First, the individual propensities scores for COVID-19 vaccine receipt were estimated with a multivariable logistic regression model that included the same confounders used in the logistic regression model. 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 propensity score.[27] Standardized differences were estimated for all the baseline covariates before and after matching to assess prematch imbalance and postmatch balance. We consider standardized differences of less than 10.0% for a given covariate to indicate a relatively small imbalance.[28]

2.7 | Subgroup analysis

Additionally, with the propensity score matching the population, we evaluate the impact on mortality of the different vaccines such as messenger RNA (mRNA) BNT162b2 (Pfizer BioNTech), Gam-COVID-Vac (Sputnik), ChAdOx1 nCoV-19 (AstraZeneca/Oxford or Covishield), BIBP-CorV (Beijing Institute of Biological Products; Sinopharm), or mRNA-1273 SARS-CoV-2 Vaccine (Moderna). We also conducted a subgroup analysis to assess effect modifications in specific patient groups, including males, patients older than 65 years, patients with Omicron, and patients with a history of cancer.

2.8 | Population attributable risk

Additionally, we studied the attributable fraction (AF) and the population attributable risk (PAR) to quantify the contribution of the COVID-19 vaccine on death reduction after the confounder's adjustment. The AF is the proportion of the risk among exposed that is attributable to the exposure, and the PAR estimates the portion of the risk in a population that is attributable to the exposure.[29]

In the present study, AF shows the reduction in the risk of death among vaccinated that is attributable to the COVID-19 vaccine, and the PAR shows the proportion of deaths in the unvaccinated patients that would be avoided if they had been vaccinated.

The AF and PAR were estimated in the study by utilizing the "regpar" and "punaf" packages in STATA (version 16.0).[30] The package also provides standard errors, *z*-statistics, *p* values, and 95% confidence intervals (CIs) for each AF and PAR estimate. All the study data was analyzed using STATA® v16 software.

2.9 | Time-to-death comparison in vaccinated patients with and without second doses

A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association of a second COVID-19 vaccine dose with in-hospital death. The regression model was used to estimate the hazard ratio (HR) for in-hospital death due to COVID-19 in the second COVID-19 vaccine group, as compared with only one COVID-19 vaccine group. The follow-up was between the last vaccine doses and the hospitalization date. The adjusted model included sociodemographic and baseline clinical characteristics with different distributions between patients with and without a second dose (Supporting Information: Table e3).

2.10 | Sample size calculation

Assuming a mortality proportion in unvaccinated patients of 20% and 15% in vaccinated patients in the adjusted analysis, with a ratio between unvaccinated to vaccinated of 9:1,[15,16] with a power of 90%, an *α* of 0.05, and with a two-side test, we need 6767 unvaccinated patients and 677 vaccinated patients. Also, to build a logistic regression model to adjust the potential confounders with approximately 8 to 12 covariables, we would need 10 to 20 death events per variable included in the model,[31] around a total of events between 80 and 120. The observed number of vaccinated and unvaccinated patients and the number of deaths within both combined registers were far superior to this required number in all subgroups.[15,16] Sample size was calculated using STATA® v16 software.

3 | RESULTS

3.1 | Demographic characteristics

Between January 2020 and May 2022, there were 38 681 admissions of COVID-19, of whom 21 479 COVID-19 were included in the final analysis (Figure 1 shows the study flow diagram). The main reason for exclusion was the absence of oxygen supplementation. Of these, 717 (3.3%) were vaccinated with at least one COVID-19 vaccine dose, 338 (1.5%) patients received a single dose, and 379 (1.8%) were fully vaccinated.

Vaccinated patients who needed oxygen therapy during hospitalization presented a higher proportion of comorbidities such as immunosuppression, heart failure, COPD, CKD, and cancer history compared with unvaccinated patients (see Table 1). The proportion of missing data for each variable is presented in Supporting Information: Table e4.

3.2 | Primary outcome

The overall mortality in vaccinated patients was 20.9% (95% CI: 17.9–24; *n* = 150), and 19.5% (95% CI: 19–20; *n* = 4058) in

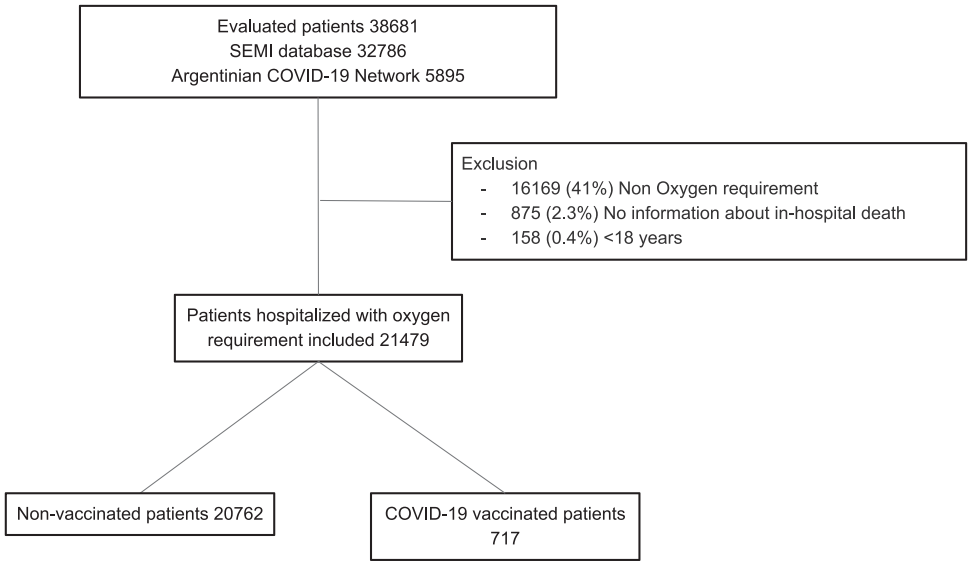

FIGURE 1 Flowchart of the analysis. COVID-19, coronavirus disease 2019.

TABLE 1 Demographic characteristics of hospitalized patients with oxygen therapy.

	All (*N* = 21 479)	Unvaccinated (*N* = 20 762)	Vaccinated (*N* = 717)	*p*, overall
Demographics				
Age, mean (SD)	66.0 (17.6)	66.2 (17.6)	60.7 (15.8)	<0.001[a]
Female sex, *n* (%)	9225 (43.8)	8914 (43.8)	311 (43.4)	0.863
Omicron variant, *n* (%)	855 (4.05)	634 (3.11)	221 (30.9)	<0.001[a]
High-income countries, *n* (%)	18920 (88.1)	18602 (89.6)	318 (44.4)	<0.001[a]
Medical history				
Hypertension, *n* (%)	9668 (45.1)	9329 (45.0)	339 (47.5)	0.208
Diabetes, *n* (%)	4494 (21.0)	4345 (21.0%)	149 (20.9)	0.977
Immunosuppression, *n* (%)	1001 (4.71)	909 (4.41)	92 (13.5)	<0.001[a]
CHD or peripheral artery disease arteriopathy, *n* (%)	1499 (6.99)	1445 (6.97)	54 (7.55)	0.597
Heart failure, *n* (%)	1358 (6.34)	1300 (6.28)	58 (8.12)	0.056
COPD, *n* (%)	1593 (7.44)	1518 (7.33)	75 (10.5)	0.002[a]
Asthma, *n* (%)	1354 (6.32)	1315 (6.35)	39 (5.45)	0.374
Stroke, *n* (%)	716 (3.38)	694 (3.39)	22 (3.14)	0.807
CKD, *n* (%)	1151 (5.38)	1096 (5.30)	55 (7.77)	0.006[a]
Cancer, *n* (%)	2320 (10.8)	2170 (10.5)	150 (21.0%)	<0.001[a]
Treatment during hospitalization				
Corticosteroids, *n* (%)[b]	5525 (68.5)[a]	5012 (67.8)[a]	513 (76.8)[a]	<0.001[a]
COVID-19 vaccine				
COVID-19 vaccine doses, *n* (%)				<0.001[a]
One COVID-19 vaccine dose	338 (1.57)		338 (47.1)	
Two COVID-19 vaccine doses	379 (1.76)		379 (52.9)	

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

[a]Statistically significant differences.

[b]The systemic corticosteroid variable has 67.4% of missing data (see Supporting Information: Table e3).

unvaccinated patients, without significant differences ($p = 0.46$). The variable distribution between survivors and in-hospital deaths is presented in Table 2.

The crude odds ratio (OR) for all-cause of in-hospital mortality of vaccination was 1.07 (95% CI: 0.89–1.29; $p = 0.41$) in the complete case analysis (data set of 6352 patients that have all analyzed covariables). However, the adjusted OR was 0.73 (95% CI: 0.56–0.95; $p = 0.02$). Variables included in the final model were age, male sex, systemic corticosteroid therapy, immunosuppression, COPD, cancer, diabetes, CHD or PAD, asthma, CKD, heart failure, country income, and omicron variant.

In the analysis of the complete data set (21 089 patients), after multiple imputations for missing data, we observed similar findings to our main analysis: we found a lower risk of in-hospital mortality for vaccinated patients when compared with unvaccinated patients (adjusted OR 0.77; 95% CI: 0.54–0.97; $p = 0.02$).

Due to the different distribution of covariables between unvaccinated and vaccinated patients in our data sets, we also perform a propensity score matching analysis. In this comparison, 601 vaccine recipients were matched with an equal number of match-weighted unvaccinated patients. Figure 2 shows the absolute standardized differences before and after propensity score matching comparing covariate values between vaccinated and unvaccinated COVID-19 patients (absolute standardized differences ranging from 0 to 0.01). This analysis shows that vaccinated patients presented a lower risk of in-hospital death compared to unvaccinated patients (OR 0.66; 95% CI: 0.5–0.87; $p < 0.01$).

The geographical breadth of our data sets enabled us to evaluate the effectiveness of different vaccine types in the matched population. As shown in Figure 3, we observed that the higher risk reduction for mortality was with the mRNA BNT162b2 (Pfizer) vaccine with an OR of 0.37 (95% CI: 0.23–0.59; $p < 0.01$),

TABLE 2 Characteristics of survivors and in-hospital death patients.

	All (*N* = 21 479)	Survivors (*N* = 17 271)	In-hospital deaths (*N* = 4208)	*p*, overall
Demographics				
Age, mean (SD)	66.0 (17.6)	63.1 (17.4)	77.8 (12.8)	<0.001[a]
Female sex, *n* (%)	9225 (43.8)	7544 (44.7)	1681 (40.0)	<0.001[a]
Omicron variant, *n* (%)	855 (4.05)	731 (4.33)	124 (2.95)	<0.001[a]
High-income countries, *n* (%)	18920 (88.1)	15386 (89.1)	3534 (84.0)	<0.001[a]
Medical history				
Hypertension, *n* (%)	9668 (45.1)	6917 (40.1)	2751 (65.7)	<0.001[a]
Diabetes, *n* (%)	4494 (21.0)	3275 (19.0)	1219 (29.1)	<0.001[a]
Immunosuppression, *n* (%)	1001 (4.71)	646 (3.77)	355 (8.55)	<0.001[a]
CHD or peripheral artery disease arteriopathy, *n* (%)	1499 (6.99)	964 (5.58)	535 (12.8)	<0.001[a]
Heart failure, *n* (%)	1358 (6.34)	762 (4.42)	596 (14.2)	<0.001[a]
COPD, *n* (%)	1593 (7.44)	1049 (6.08)	544 (13.0)	<0.001[a]
Asthma, *n* (%)	1354 (6.32)	1157 (6.71)	197 (4.71)	<0.001[a]
Stroke, *n* (%)	716 (3.38)	465 (2.73)	251 (6.02)	<0.001[a]
CKD, *n* (%)	1151 (5.38)	646 (3.76)	505 (12.1%)	<0.001[a]
Cancer, *n* (%)	2320 (10.8)	1677 (9.73)	643 (15.4)	<0.001[a]
Treatment during hospitalization				
Corticosteroids treatment, *n* (%)	5525 (68.5)	4545 (66.5)	980 (79.5)	<0.001[a]
COVID-19 vaccine				
COVID-19 vaccine, *n* (%)	717 (3.34)	567 (3.28)	150 (3.56)	0.387
COVID-19 vaccine doses, *n* (%)				0.195
One dose	338 (1.57)	259 (1.50)	79 (1.88)	
Two dosesb	379 (1.76)	308 (1.78)	71 (1.69)	
mRNA BNT162b2 (Pfizer), *n* (%)	216 (1.01)	191 (1.11)	25 (0.59)	0.004[a]
mRNA-1273 (Moderna), *n* (%)	124 (0.58)	101 (0.58)	23 (0.55)	0.857
ChAdOx1 nCoV-19 (Astrazeneca), *n* (%)	108 (0.50)	86 (0.50)	22 (0.52)	0.934
Gam-COVID-Vac (Sputnik), *n* (%)	180 (0.84)	131 (0.76)	49 (1.16)	0.013[a]
BIBP-CorV (Sinopharm), *n* (%)	76 (0.35)	55 (0.32)	21 (0.50)	0.104

Abbreviations: CHD, coronary Heart Disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; SD, standard deviation.

[a]Statistically significant differences.

[b]Some vaccinated patients had received a different vaccine type in the two doses.

second the ChAdOx1 nCoV-19 (AstraZeneca) vaccine with an OR of 0.42 (95% CI: 0.20–0.86; $p = 0.02$), mRNA-1273 (Moderna) with an OR of 0.68 (95% CI: 0.41–1.12; $p = 0.13$), Gam-COVID-Vac (Sputnik) with an OR of 0.93 (95% CI: 0.6–1.45; $p = 0.76$), and BIBP-CorV (Sinopharm) with an OR of 0.92 (95% CI: 0.5–1.69; $p = 0.79$).

Our analysis of vaccine protection against COVID-19 in different subgroups revealed that patients under 65 years old exhibited a significantly higher level of protection (OR 0.59; 95% CI: 0.39–0.89) than those over 65 years old (OR 0.84; 95% CI: 0.56–1.24). Furthermore, our data suggest that the omicron variant may elicit a higher level of protection (OR 0.55; 95% CI: 0.30–1.01) compared to other variants (OR 0.73; 95% CI: 0.53–1.00), although this finding should be interpreted with caution due to the small sample size of the subgroup analysis and the wide confidence intervals. We did not observe significant differences in vaccine protection between males (OR 0.64; 95% CI: 0.44–0.93) versus females (OR 0.74; 95% CI: 0.48–1.15), or patients without a history

of cancer (OR 0.68; 95% CI: 0.50–0.94) versus patients with cancer history (OR 0.70; 95% CI: 0.38–1.28). The subgroup forest plot is presented in Figure 4.

3.2.1 | PAR and population AF reduction of death risk in patients exposed to COVID-19 vaccine

We estimate the population AF (PAF) and the PAR assessing the contribution of the COVID-19 vaccine to the reduction of death in hospitalized patients with oxygen requirements. The adjusted PAF was 21.1% (95% CI: 7.2–32.8) and the PAR reduction was 4.3% (95% CI: 1–5). Therefore, as the death proportion in unvaccinated patients was 19.6% (95% CI: 19–20.1), if they were vaccinated the expected death proportion would have been significantly reduced to 15.3% (95% CI: 12.9–18; $p < 0.01$).

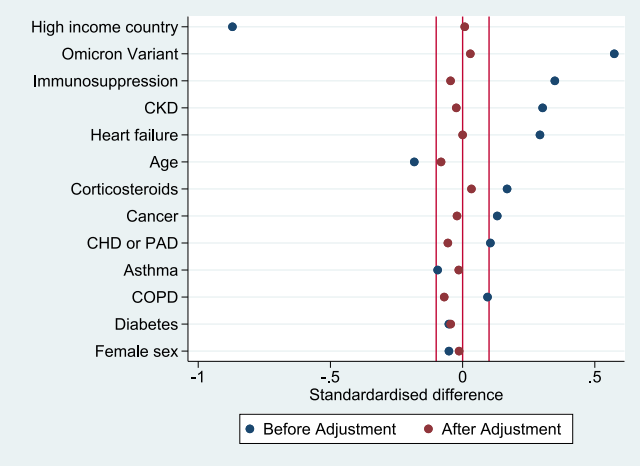

FIGURE 2 Love plot for absolute standardized differences before and after propensity score matching comparing covariate values between vaccinated and unvaccinated COVID-19, coronavirus disease 2019 (COVID-19) patients. CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease arteriopathy; SD, standard deviation.

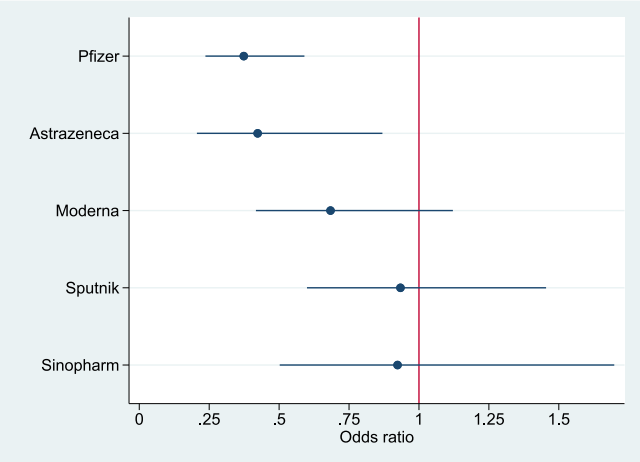

FIGURE 3 Adjusted odds ratio by propensity score matching of vaccine subtypes related to in-hospital death.

3.2.2 | Effect of vaccine doses and waning on protection against in-hospital mortality

We further evaluate clinical outcomes in the subpopulation of hospitalized vaccinated patients to compare patients with and without a second COVID-19 vaccine dose. Vaccinated patients were hospitalized 93 days mean (interquartile range [IQR]: 42–217) after the last COVID-19 vaccine doses. Patients with one dose had a mean of 54 (IQR: 25–88) days between the vaccine dose and the hospitalization, and patients with a second COVID-19 vaccine dose had 194 (IQR: 81–247) days. In Supporting Information: Table e5, we presented the time between the last vaccine doses and hospitalization depending on the vaccine subtype.

In the Cox regression analysis, the crude HR of the second COVID-19 vaccine dose was 0.26 (95% CI: 0.18–0.4), and the adjusted HR was 0.49 (95% CI: 0.28–0.88). This analysis was adjusted by the covariables with different distribution between patients with and without a second COVID-19 vaccine dose (age, omicron, high-income country, immunosuppression, CHD or peripheral artery disease arteriopathy, COPD, cancer, and corticosteroids treatment). Also, in the Kaplan–Meier graph, we observed the difference between patients with and without a second COVID-19 vaccine dose. Of note, after 200 days of the last dose, the protection seems to be reduced, and after 300 days, the proportion of in-hospital

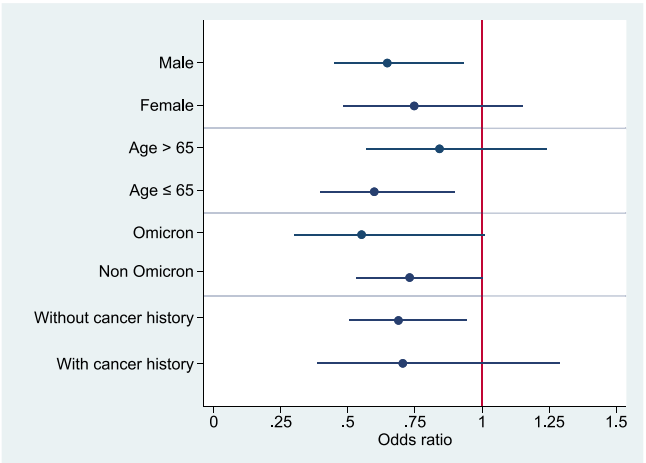

FIGURE 4 Adjusted odds ratio (OR) by propensity score matching of vaccine in-hospital mortality protection in different subgroups. OR males 0.64 (95% CI: 0.44–0.93), OR females 0.74 (95% CI: 0.48–1.15); OR patients older than 65 years old 0.84 (95% CI: 0.56–1.24), OR patients with 65 years old or younger 0.59 (95% CI: 0.39–0.89); OR patients with omicron 0.55 (95% CI: 0.30–1.01), OR patients without omicron 0.73 (95% CI: 0.53–1.00); OR patients without cancer history 0.68 (95% CI: 0.50–0.94), OR in patients with cancer history 0.70 (95% CI: 0.38–1.28).

deaths in patients with and without second COVID-19 vaccine doses was the same (Figure 5).

4 | DISCUSSION

Understanding the true mortality impact of the COVID-19 pandemic and the vaccine's protection in all groups of patients is crucial for public health decision-making. The effectiveness of the COVID-19 vaccines in the subgroup of patients that require oxygen during hospitalization (moderate illness[32]), representing the patients requiring the closest surveillance, is unknown.

Our study found that in this group of patients with an inflammatory response generated by SARS-CoV-2 with acute lung injury, the COVID-19 vaccines significantly reduced in-hospital mortality, with a PAR reduction of 4.3% from a death proportion of 19.6% in unvaccinated patients.

Various studies have reported in-hospital mortality rates ranging from 14.8% to 24% in vaccinated patients.[5–10] Tandon et al.[6] observed higher mortality in vaccinated patients than unvaccinated patients (15% vs. 9.0%; $p = 0.034$) in the United States. In Israel, Tal Brosh-Nissimov et al.[7] reported a mortality rate of 22% in hospitalized vaccinated patients without comparison to unvaccinated patients. In France, Vassallo et al.[10] reported mortality rates of 18% in patients with one vaccine dose and 15% in unvaccinated patients. Finally, Piotr Rzymski et al.[8] in Poland found a mortality rate of 6% in patients hospitalized between 0 and 14 days after vaccination, but mortality rates of 25% and 45% after 14 days of the first and second vaccine doses, respectively. These results show that the mortality rate was lower before vaccine protection antibodies started. These findings suggest that patients who require hospitalization after receiving one or two vaccine doses may have a higher mortality rate. However, it is important to note that these results may be subject to selection bias, as these studies also reported a higher burden of comorbidities in vaccinated patients who required hospitalization.[33] These comorbidities and a lower immune response to the vaccine may both contribute to the increased mortality rates observed in vaccinated patients.

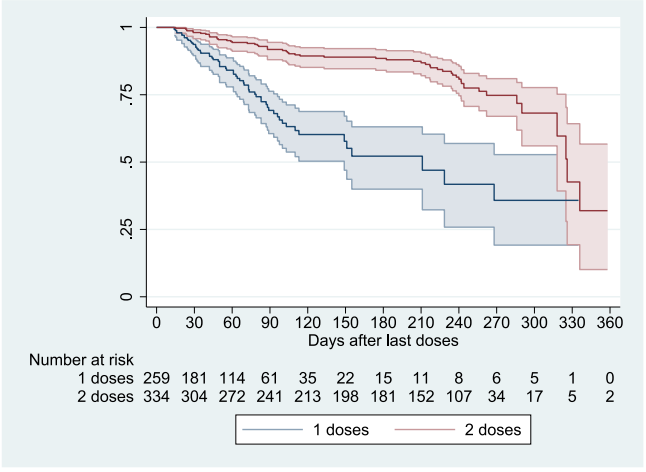

FIGURE 5 Overall survival of coronavirus disease 2019 (COVID-19) hospitalized vaccinated patients with one and two COVID-19 vaccine doses related to days after the last doses of vaccine received.

To consider these cofounders, Busic et al.[33] investigated the clinical outcomes in all types of COVID-19 patients hospitalized in one center and who received prior vaccination against a comparable matched-pair cohort of unvaccinated patients. This study reported a significantly lower 30 days mortality in vaccinated patients with an HR of 0.56 (95% CI: 0.37–0.85).

Our multicontinental study demonstrates the effectiveness of several COVID-19 vaccines in reducing the mortality of hospitalized patients that require oxygen therapy. While the crude analysis (not adjusted for the higher burden of comorbidities and risk factors in vaccinated patients) rendered similar overall mortality in the unvaccinated and the vaccinated patients (19.6% and 20.1%, respectively), the adjusted analysis clearly shows the vaccine protection against in-hospital death in COVID-19 patients with oxygen requirements.

A detailed analysis shows that the survival benefit was higher for mRNA BNT162b2 (Pfizer) in comparison with vector vaccines (ChAdOx1 nCoV-19 [AstraZeneca], Gam-COVID-Vac [Sputnik], and BIBP-CorV [Sinopharm]). This finding must be interpreted in the context of different populations vaccinated (mRNA is widely used in high-income countries) and taking into account the sample size reduction of the subgroup analysis. Our results opposed the ones reported by Busic et al., who found a lower mortality rate in hospitalized patients with vector vaccines (ChAdOx1 nCoV-19 [AstraZeneca]) in comparison to mRNA BNT162b2 (Pfizer) vaccine. However, the authors discussed that this observation could be due to the availability of exclusively mRNA vaccines by mid-February in Croatia and to the priority of vaccination among the older population and among selected patients with unfavorable prognostic characteristics.[33]

mRNA vaccines offer several advantages over DNA-based vaccines, such as faster and easier manufacturing, higher biosafety, and a safer vector as they carry a short sequence to be translated.[34] Despite their remarkable efficacy and an overall acceptable safety profile, mRNA vaccines have been associated with the development of myocarditis and pericarditis, particularly after the second dose.[35] Similarly, adenoviral vector vaccines have been linked to vaccine-induced immune thrombotic thrombocytopenia.[36] However, it is important to note that the incidence of these adverse events is relatively low, and the benefits of COVID-19 vaccination, including the prevention of severe illness and hospitalization, greatly outweigh the risks of adverse events.[37] Nevertheless, ongoing monitoring and communication of potential adverse events are crucial to ensure the safety of mRNA vaccines.[37]

Our analysis demonstrates a significant improvement in the protection with a second COVID-19 vaccine dose. However, the second COVID-19 vaccine dose protection waned after 200 days, which goes in line with similar observations reported by other authors.[4] These data strongly support the need for additional booster doses, especially among people that belong to sensitive groups (elderly, with cancer or several

comorbidities, and immunocompromised) who are 200 days or more from their initial vaccination date.

Our study has several limitations. First, the scale of missingness in some variables (i.e., corticosteroids) could affect our analysis. However, the results were robust to the imputed analysis. Second, some of the data sets used (i.e., Hospital 12 de Octubre) could carry a misclassification of some vaccinated patients as a significant number of hospitalized patients could have been previously vaccinated in other centers before their hospitalization. The lack of a centralized data service makes it impossible to track these patients. However, due to the protective effect of vaccines on the general population, the effect of this potential misclassification is to underestimate the net benefit of the vaccines in patients with the sensitive phenotype described previously. Third, we compared vaccine subtypes in the adjusted subpopulation matched by propensity score. However, the propensity score adjustment was made between vaccinated and nonvaccinated patients, rather than between vaccine subtypes. Additionally, this analysis did not adjust for the time from vaccination to hospitalization, and the availability of specific vaccines over time may have impacted the protection provided by each vaccine subtype. As a result, this analysis represents more of an exploratory overview than reliable evidence. The potential clinical differences between patients vaccinated with different subtypes were not adjusted for, and further studies will be needed to compare the effectiveness of different vaccine subtypes in this population. Finally, we consider vaccinated patients if they have at least one dose despite this being an incomplete vaccination if the vaccine scheme requires at least two doses.

Taking into account the large sample size and the geographical extension of our data set, which includes more than 140 hospitals from different continents and countries with diverse health systems, we strongly believe that our data close an important gap related to the protection benefits of COVID-19 vaccines against moderate and severe disease: a remarkable reduction of the probability of death in patients with need of oxygen therapy. Importantly, this subgroup of patients with a high burden of comorbidities represents the vast majority of hospitalized COVID-19 patients in the current pandemic waves. We expect our data to assist the public debate on the need for updated vaccination plans for the millions belonging to the most sensitive groups.

AUTHOR CONTRIBUTIONS

Ivan A. Huespe and David Gómez-Varela participated in the study design, data acquisition, data interpretation, statistical analysis, drafting of the manuscript, revising it critically for important content, and approving the final version. Augusto Ferraris participated in data interpretation, drafting of the manuscript, critically revising the manuscript for important content, and approved the final version. Luis A. Cayetti and Maria L. Peroni participated in data interpretation, drafting of the manuscript, critically revising the manuscript for important content, and approved the final version. Pascual R. Valdez, Bruno Boietti, Riku Klén, Matias A. Mirofsky, Javier A. Pollan, Ricardo Gómez-Huelgas, José M. Casas-Rojo, Juan M. Antón-Santos, Jesús M. Núñez-Cortés, Carlos Lumbreras, José-Manuel Ramos-Rincón, Noelia G. Barrio, Miguel Pedrera-Jiménez, María D. Martin-Escalante, Francisco R. Ruiz, Maria Á. Onieva-García, Carlos R. Toso, Marcelo R. Risk, and Antonio Lalueza participated in data acquisition, data interpretation, critically revising the manuscript for important content, and approved the final version. All authors fulfilled ICMJE authorship criteria and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

This work was supported by Instituto de Salud Carlos III, Ministry of Science and Innovation, Spain (COVID-19 COV20/00181)—cofinanced by the European Development Regional Fund "A way to achieve Europe" ERDF, the University of Vienna, the Becas Salud Investiga of the Argentinian Ministery of Health, and the Ben Barres Spotlight Award from eLife.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The SEMI-COVID-19 registry and the COVID registries of 12 de Octubre and the Costa del Sol hospitals have been approved by the Provincial Research Ethics Committee of Malaga (Spain; C.I.F. number: 0–9150013-B). Institutional Review Boards approved each participating site in the Argentinian COVID-19 Network study (approval numbers: 1575, 5562, and 5606).

ORCID

Ivan A. Huespe http://orcid.org/0000-0003-3445-6981
Antonio Lalueza http://orcid.org/0000-0003-2711-3817

REFERENCES

1. World Health Organization. *WHO Coronavirus (COVID-19) Dashboard*. WHO; 2022.
2. Korean Society of Infectious Diseases, Korean Society of Pediatric Infectious Diseases, Korean Society of Epidemiology, et al. Report on the epidemiological features of coronavirus disease 2019 (COVID-19) outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci*. 2020;35(10):e112. doi:10.3346/jkms.2020.35.e112
3. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111.
4. Wright BJ, Tideman S, Diaz GA, French T, Parsons GT, Robicsek A. Comparative vaccine effectiveness against severe COVID-19 over time in US hospital administrative data: a case–control study. *Lancet Respir Med*. 2022;10(6):557-565. doi:10.1016/s2213-2600(22)00042-x
5. Moffa MA, Shively NR, Walsh TL. Characteristics of postvaccination coronavirus disease 2019 hospitalizations prior to booster vaccines. *Open Forum Infect Dis*. 2022;9(4):ofac014. doi:10.1093/ofid/ofac014
6. Tandon P, Leibner ES, Hackett A, Maguire K, Mashriqi N, Kohli-Seth R. The third wave: comparing seasonal trends in COVID-19 patient

data at a large hospital system in New York City. *Crit Care Explor*. 2022;4(3):e0653. doi:10.1097/cce.0000000000000653
7. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. *Clin Microbiol Infect*. 2021;27(11):1652-1657.
8. Rzymski P, Pazgan-Simon M, Simon K, et al. Clinical characteristics of hospitalized COVID-19 patients who received at least one dose of COVID-19 vaccine. *Vaccines*. 2021;9(7):781. doi:10.3390/vaccines9070781
9. Modes ME, Directo MP, Melgar M, et al. Clinical characteristics and outcomes among adults hospitalized with laboratory-confirmed SARS-CoV-2 infection during periods of B.1.617.2 (Delta) and B.1.1.529 (Omicron) variant predominance—One Hospital, California, July 15–September 23, 2021, and December 21, 2021–January 27, 2022. *Morb Mortal Wkly Rep*. 2022;71(6):217-223. doi:10.15585/mmwr.mm7106e2
10. Vassallo M, Clement N, Lotte L, et al. Prevalence and main clinical characteristics of fully vaccinated patients admitted to hospital for Delta variant COVID-19. *Front Med*. 2022;9:809154.
11. Naleway AL, Groom HC, Crawford PM, et al. Incidence of SARS-CoV-2 infection, emergency department visits, and hospitalizations because of COVID-19 among persons aged ≥12 years, by COVID-19 vaccination status—Oregon and Washington, July 4–September 25, 2021. *Morb Mortal Wkly Rep*. 2021;70(46):1608-1612. doi:10.15585/mmwr.mm7046a4
12. Müller L, Andrée M, Moskorz W, et al. Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. *medRxiv*. Preprint posted online March 5, 2021. doi:10.1101/2021.03.03.21251066
13. Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol*. 2021;22(6):765-778.
14. Agha M, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. *medRxiv*. Preprint posted online April 7, 2021. doi:10.1101/2021.04.06.21254949
15. Boietti BR, Mirofsky M, Valentini R, et al. Descriptive analysis of 4776 patients admitted to medical clinic services for COVID-19. Results of the Argentine Multi-Center Registry—REMA-COVID-19. *Medicina*. 2021;81(5):703-714.
16. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, et al. Características clínicas de los pacientes hospitalizados con COVID-19 en España: resultados del Registro SEMI-COVID-19. *Rev Clin Esp*. 2020;220(8):480-494.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-1499. doi:10.1016/j.ijsu.2014.07.013
18. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) variants in England: a cohort study. *Lancet*. 2022;399(10332):1303-1312.
19. Ministerio de Sanidad. *Actualización de la situación epidemiológica de las variantesde SARS-CoV-2 en España*. Ministerio de Sanidad; 2022.
20. Ministerio de Salud. *COVID-19—situación de nuevas variantes SARS-CoV-2 en Argentina*. Ministerio de Salud; 2022.
21. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis*. 2021;21(1):855.
22. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/nejmoa2021436
23. Khedr A, Al Hennawi H, Rauf I, et al. Differential mortality with COVID-19 and invasive mechanical ventilation between high-income and low-and middle-income countries: a systematic review, meta-analysis, and meta-regression. *Infez Med*. 2022;30(1):51-58.
24. Bouzid D, Visseaux B, Kassasseya C, et al. Comparison of patients infected with Delta versus Omicron COVID-19 variants presenting to Paris emergency departments: a retrospective cohort study. *Ann Intern Med*. 2022;175:831-837. doi:10.7326/M22-0308
25. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
26. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377-399.
27. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med*. 2015;372(13):1213-1222. doi:10.1056/nejmoa1412168
28. Normand SLT, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly. *J Clin Epidemiol*. 2001;54(4):387-398.
29. Khan J, Shil A, Puri P. Population and sub-national (district) level diversity in missed and dropout of different doses of hepatitis-B vaccine among Indian children aged 12–59 months. *PLoS Glob Public Health*. 2022;2(5):e0000243. doi:10.1371/journal.pgph.0000243
30. Newson RB. Attributable and unattributable risks and fractions and other scenario comparisons. *Stata J*. 2013;13(4):672-698. doi:10.1177/1536867x1301300402
31. Katz MH. *Multivariable Analysis: A Practical Guide for Clinicians and Public Health Researchers*. Cambridge University Press; 2011.
32. NIH. *COVID-19 Treatment Guidelines. Clinical Spectrum of SARS-CoV-2 Infection*. NIH; 2022.
33. Busic N, Lucijanic T, Barsic B, et al. Vaccination provides protection from respiratory deterioration and death among hospitalized COVID-19 patients: differences between vector and mRNA vaccines. *J Med Virol*. 2022;94(6):2849-2854. doi:10.1002/jmv.27666
34. Jackson NAC, Kester KE, Casimiro D, Gurunathan S, DeRosa F. The promise of mRNA vaccines: a biotech and industrial perspective. *NPJ Vaccines*. 2020;5:11.
35. Kim HW, Jenista ER, Wendell DC, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. *JAMA Cardiol*. 2021;6(10):1196-1201.
36. van de Munckhof A, Krzywicka K, Aguiar de Sousa D, et al. Declining mortality of cerebral venous sinus thrombosis with thrombocytopenia after SARS-CoV-2 vaccination. *Eur J Neurol*. 2022;29(1):339-344.
37. Nashwan A, Yassin M, Soliman A, De Sanctis V, Ibrahim M. mRNA-based COVID-19 vaccines booster dose: benefits, risks and coverage. *Acta Biomed*. 2022;93(3):2022236.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Huespe IA, Ferraris A, Lalueza A, et al. COVID-19 vaccines reduce mortality in hospitalized patients with oxygen requirements: differences between vaccine subtypes. A multicontinental cohort study. *J Med Virol*. 2023;95:e28786. doi:10.1002/jmv.28786