Discover Public Health

Research

COVID-19 vaccination and lethality reduction: a prospective observational study in Venezuela during the last two waves

David A. Forero-Peña[1,2,3] · Jéssica L. Leyva[1,2] · María V. Valenzuela[1,2] · Óscar D. Omaña-Ávila[1,2] · Oriana A. Regalado-Gutiérrez[1,2] · Daniela L. Mendoza-Millán[1,2] · Elisanny A. Sánchez-Ytriago[4] · Andrea C. Lahoud-El Hachem[1,2] · Katherine R. Farro[4] · Ana K. Maita[4] · Romina del C. González[4] · Carlis M. Rodriguez-Saavedra[1] · Fernando Hernández-Medina[5] · Natasha A. Camejo-Ávila[1,5] · Diana C. Freitas-de Nobrega[1] · Rodrigo T. Celis[2] · José L. Forero-Peña[1] · Alfonso Martínez[2] · María E. Grillet[6] · María E. Landaeta[3] · Fhabián S. Carrión-Nessi[1,2,5]

Received: 31 July 2024 / Accepted: 7 October 2024
Published online: 14 October 2024

Abstract

Background In Venezuela, the predominant vaccines administered are BBIBP-CorV and Gam-COVID-Vac. Despite robust evidence from randomized clinical trials validating the effectiveness of COVID-19 vaccines in mitigating hospitalization and mortality, there is still a lack of post-authorization safety studies conducted within this demographic population.

Methods A prospective observational study from October 5, 2021 to March 31, 2022 encompassed COVID-19 vaccinated and unvaccinated patients from four sentinel hospitals in Venezuela. Patient lethality was predicted using Charlson Comorbidity index. Clinical outcomes were assessed through WHO's COVID-19 Clinical Progression Scale.

Results Out of the 175 patients assessed, 85 (48.6%) were vaccinated. The median Charlson Comorbidity index was 3 points, with no statistically significant differences observed between the groups ($p = 0.2$). A total of 50 (28.6%) patients died during the study period, with higher proportion of deaths in unvaccinated patients (35.6% vs. 21.2%, $p = 0.035$). Advanced age (OR = 1.043, 95% CI = 1.015–1.071, $p = 0.002$) was associated with increased death risk, whereas vaccination against COVID-19 (OR = 0.428, 95% CI = 0.185–0.99, $p = 0.047$), high oxygen saturation (OR = 0.964, 95% CI = 0.934–0.995, $p = 0.024$), and enoxaparin administration (OR = 0.292, 95% CI = 0.093–0.917, $p = 0.035$) were associated with decreased death risk.

Conclusion During the third and fourth waves of the pandemic, COVID-19 vaccination was associated with a 57% reduction in lethality among patients in four public hospitals in Venezuela.

Key summary points

- Less than half (48.6%) of the patients were vaccinated against SARS-CoV-2.
- At least one out of four patients died during the study period, mainly in the unvaccinated group.

David A. Forero-Peña and Jéssica L. Leyva have contributed equally to this work and shared first authorship.

✉ David A. Forero-Peña, vacter.cv@gmail.com; ✉ Fhabián S. Carrión-Nessi, fhabiancarrion@gmail.com | [1]Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela. [2]"Luis Razetti" School of Medicine, Universidad Central de Venezuela, Caracas, Venezuela. [3]Department of Infectious Diseases, University Hospital of Caracas, Caracas, Venezuela. [4]Department of Internal Medicine, "Dr. Luis Razetti" University Hospital, Barcelona, Venezuela. [5]Instituto Venezolano de Investigaciones Científicas, Altos de Pipe, Venezuela. [6]Vector and Parasite Biology Laboratory, Tropical Ecology and Zoology Institute, Faculty of Sciences, Universidad Central de Venezuela, Caracas, Venezuela.

- Advanced age was associated with a higher risk of death.
- Vaccination against COVID-19, high oxygen, and enoxaparin administration were factors associated with a lower risk of death.

Keywords COVID-19 · Vaccines · Patients · Lethality · Waves · Venezuela

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization
COVAX	COVID-19 Vaccines Global Access
PAHO	Pan American Health Organization
RT-PCR	Reverse transcription polymerase chain reaction
SD	Standard deviation
IQR	Interquartile range
SPSS	Statistical Package for the Social Sciences

1 Background

As of September 22, 2024, the global burden of the coronavirus disease 2019 (COVID-19) has resulted in over 776 million cases and more than 7 million deaths [1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome sequencing was first published in January 2020 [2], but the limited understanding of its transmission dynamics, preventive measures, and therapeutic approaches determined a significant impact since the global emergency aroused [3]. In an endeavor to counteract the pandemic, a multitude of pharmaceutical entities embarked on the development of vaccines targeting SARS-CoV-2, culminating in a minimum of 78 confirmed active vaccine candidates by April 2020 [4]. In late 2020, phase III outcomes were disclosed for several vaccines, including Gam-COVID-Vac (Sputnik-V) with an efficacy of 94–100% [5], CoronaVac (Sinovac) with an efficacy of 50–62%, and BBIBP-CorV (Sinopharm) with an efficacy of 64–86% [6], along with Pfizer-BioNTech [7], Moderna [8], and AstraZeneca [9]. Sinopharm and Sinovac vaccines procured approval from the US Food and Drug Administration and the World Health Organization (WHO) in May 2021 [11, 12]. However, other candidates such as Sputnik-V are still awaiting WHO endorsement [13].

Vaccination efforts gradually began after the initial vaccine approvals in December 2020, with the United Kingdom, Canada, the United States, Russia, and China being among the earliest countries to initiate population vaccination [10, 14]. As of August 2023, 13.5 billion vaccine doses had been administered [15]. In Latin America, several nations undertook initiatives to expedite the process. Mexico was the first country to respond to the United Nations appeal in April 2021 to provide access to therapeutics and vaccines to combat COVID-19 [16]. Colombia emerged as the first Latin American country to receive BNT162b2 vaccines under the COVID-19 Vaccines Global Access (COVAX) initiative in March 2021 [17]. Chile donated 20,000 doses of the Chinese vaccine CoronaVac to Ecuador and Paraguay [18]. In Venezuela, the vaccination campaign against COVID-19 utilized BBIBP-CorV, CoronaVac, and Gam-COVID-Vac vaccines due to agreements with the Russian Federation [19] and global collaboration mechanisms such as COVAX [20].

The Venezuelan government initially strategized to launch the "Mass Vaccination Plan" in January 2021, but the first batch of the BBIBP-CorV and Gam-COVID-Vac vaccines arrived in February. The process was segmented into five stages, with healthcare workers prioritized in the initial stage [20]. Subsequently, the supply of vaccines to Venezuela continued sporadically and without prior planning, including the arrival of vaccine candidates such as Abdala, Soberana-2, and EpiVacCorona [20]. By September 2021, the Pan American Health Organization (PAHO) reported a vaccination coverage of 14.9% in Venezuela. As of August 2023, Venezuela had administered an aggregate of 37.9 million doses, vaccinating 66.9% of its population [15]. Although some studies have demonstrated that Gam-COVID-Vac vaccines effectively elicit a neutralizing antibody response in Venezuelan patients [21], the clinical efficacy of the available vaccines in this demographic remains to be elucidated.

While randomized clinical trials are considered the "gold standard" for evaluating the effects of a medical intervention, they have several limitations, including sample size, subgroup analysis, restrictive inclusion criteria, and a highly

controlled environment that may not be replicated during a mass launch. Suboptimal adherence to schedules and logistics also influences its effectiveness. Therefore, post-authorization safety studies are crucial for evaluating the actual efficacy and behavior in real populations [22]. This study aims to describe the clinical behavior and outcomes of vaccinated and unvaccinated patients during the third and fourth pandemic waves in four hospitals in Venezuela.

2 Methods

2.1 Study design and population

We conducted a prospective observational study involving patients aged 18 years and older who were confirmed to be infected with SARS-CoV-2 and subsequently hospitalized between October 5, 2021 and March 31, 2022. The study was conducted across multiple sentinel hospitals in Venezuela, including the University Hospital of Caracas (Capital District) (thirteen COVID-19 beds available), "Dr. Luis Razetti" University Hospital (Anzoategui state) (forty COVID-19 beds available), "Ruiz y Páez" University Hospital Complex (Bolivar state) (thirty COVID-19 beds available), and "Uyapar" Hospital (Bolivar state) (ten COVID-19 beds available). A total of 540 patients were hospitalized at the four sentinel centers during the study period (82 patients at the University Hospital of Caracas, 214 at the "Dr. Luis Razetti" University Hospital, 182 at the "Ruiz y Páez" University Hospital Complex, and 62 at the "Uyapar" Hospital). The diagnosis of SARS-CoV-2 infection was confirmed through antigen testing in 24% ($n = 42$) of patients and the rest by reverse transcription polymerase chain reaction (RT-PCR) according to resources availability [23] at the "Rafael Rangel" National Institute of Hygiene (Venezuela). A national genomic surveillance study analyzed samples from nasopharyngeal or nasal swabs confirmed positive by RT-PCR during routine COVID-19 diagnosis in Venezuela.

There were four waves of the COVID-19 pandemic in Venezuela, with the first (March to November 2020) and the second (December 2020 to May 2021) one with a hospitalization of 14.6% and 40.5% of the cases, respectively [24]. This study encompassed cases from the third (June to December 2021) and fourth (January to February 2022) waves of the pandemic in Venezuela [24], which had a hospitalization of 33.6% and 11.3% of the cases, respectively, each characterized by different SARS-CoV-2 variants. The third wave was marked by variants of both interest and concern, commencing with Gamma (B.1.1.248) and concluding with Delta (B.1.617). The fourth wave was characterized by the circulation of the Omicron variant (B.1.1.529) [25].

The severity of COVID-19 was categorized as mild (presence of various signs and symptoms of COVID-19, excluding shortness of breath, dyspnea, or abnormal chest imaging), moderate (evidence of lower respiratory disease during clinical assessment or imaging and an oxygen saturation ≥ 94% on room air at sea level), severe (oxygen saturation < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%), or critical (respiratory failure, septic shock, and/or multiple organ dysfunction). These categories were defined according to the guidelines provided by the National Institutes of Health (United States of America) [26].

2.2 Sample size

Out of the 540 patients hospitalized at the four sentinel centers during the study period, those without confirmed diagnosis of SARS-CoV-2 infection were excluded, as well as those that did not provide consent to participate. Moreover, patients with incomplete or illegible data on variables of interest in interviews and medical records were excluded. Figure. 1 shows a flow chart of patient's selection.

2.3 Epidemiological and clinical assessment

Patient data was gathered by trained staff at sentinel centers through interviews and review of medical records. This data encompassed epidemiological characteristics (such as age, sex, educational level, marital status, race, occupation, domicile), clinical characteristics (including symptoms on admission, pathological history, psychobiological habits, physical examination), paraclinical characteristics (such as hematology, blood chemistry, coagulation tests), vaccination status against COVID-19 (verified by vaccination certificate issued by the Venezuelan Ministry of Health), and treatment received for COVID-19 (including antivirals, antibiotics, antiparasitics, corticosteroids, thromboprophylaxis, immunomodulators, ventilatory support). The timely use of Remdesivir was defined as its administration within 7 days following symptom onset, while the timely use

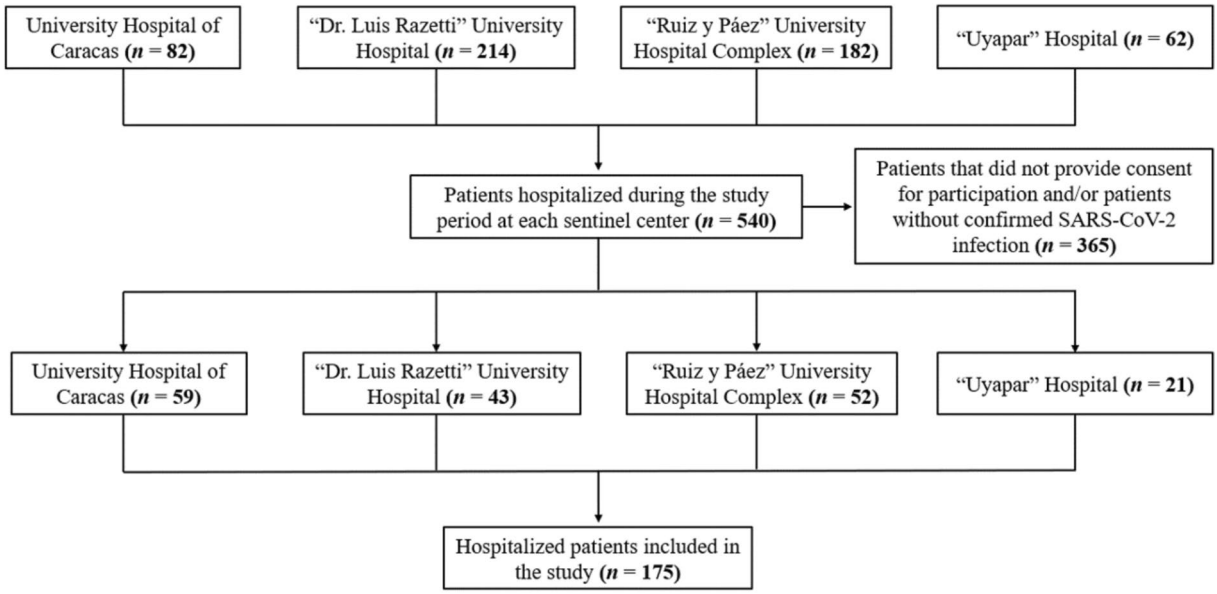

Fig. 1 Flow chart of patient's selection

of Favipiravir and Molnupiravir was defined as their administration within 5 days following symptom onset. The appropriate use of Dexamethasone and Methylprednisolone was defined as their administration for up to 10 days.

The Charlson Comorbidity index was calculated to predict patient lethality [27]. Patient outcomes were assessed at day 28 and 48 post-admission using the WHO's COVID-19 Clinical Progression Scale [28]. The date of death for those patients who died prior to evaluation were recorded. For patients discharged alive prior to day 28 or 48, assessments were performed either face-to-face or via telephone to determine their outcomes. For the purpose of analysis, patients were classified into two groups based on their vaccination status: vaccinated and unvaccinated. Individuals were defined as "vaccinated" if they had received at least one dose of a COVID-19 vaccine, at least 14 days prior.

2.4 Statistical analysis

Patients' data was summarized using descriptive statistics, including mean, standard deviation (SD), median, interquartile range (IQR), frequency, and percentage (%). The distribution of numerical variables was evaluated using the Kolmogorov–Smirnov test. For variables with a non-normal distribution, the Mann–Whitney U test was employed, whereas Student's *t*-test was used for variables with a normal distribution. Categorical variables were analyzed using Pearson's chi-squared and Fisher's exact tests. In instances where *post-hoc* analysis was required, the Bonferroni correction was applied to adjust the *p* value. A *p* value of less than 0.05 was considered statistically significant. Survival analysis was conducted using the Mantel–Cox test and visualized using Kaplan–Meier curves. Binomial logistic regression with backward stepwise selection was utilized to identify factors associated with lethality. The most valid model, which classified the highest percentage of patients and demonstrated a good fit based on R^2 Nagelkerke and the Hosmer–Lemeshow test, was selected. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26 (International Business Machines Corporation, Armonk, NY, United States of America). Figures were generated using SPSS version 26 and Microsoft® Excel® version 2019 (Microsoft, Redmond, WA, United States of America).

3 Results

3.1 Patients' sociodemographic characteristics

During the study period, a total of 175 patients were included: 59 (33.7%) captured at the University Hospital of Caracas, 43 (24.6%) at the "Dr. Luis Razetti" University Hospital, 52 (29.7%) at the "Ruiz y Páez" University Hospital Complex, and 21 (12%) at the "Uyapar" Hospital. Among these, 85 (48.6%) were categorized as vaccinated. Within the vaccinated group, 15/85 (17.6%) received one dose (86.7% received BBIBP-CorV, and 13.3% received Gam-COVID-Vac), 65/85 (76.5%) received two doses (64.6% BBIBP-CorV, and 35.4% Gam-COVID-Vac), and 5/85 (5.9%) received three doses (20% BBIBP-CorV, and 80% Gam-COVID-Vac) of the COVID-19 vaccine. All patients reported receiving homologous vaccines. The mean duration between the onset of COVID-19 symptoms and the administration of the last dose of the COVID-19 vaccine was 123.6 (SD ± 88.9) days.

The patients had a median age of 68 (IQR 28) years, with a majority being female (53.1%), of mestizo race (85.1%), and unemployed/retired (60.6%) (Table 1). Geographically, 67 (38.3%) patients resided in Bolivar state, 48 (27.4%) in Anzoategui state, 52 (29.8%) in the Metropolitan Area of Caracas, and the remaining 8 (4.5%) in other states. A significant association was observed between the categories "healthcare worker" and "vaccinated" ($p = 0.0037$).

3.2 Medical history

Less than 10% of all patients reported having at least one previous SARS-CoV-2 infection, which was less frequent among the unvaccinated compared to the vaccinated (4.4% vs. 14.1%, $p = 0.026$). Hypertension was the most common

Table 1 Sociodemographic characteristics of patients with COVID-19 according to their vaccination status

Characteristics	Total ($n = 175$, 100%)	Vaccinated ($n = 85$, 48.6%)	Unvaccinated ($n = 90$, 51.4%)	p value
Age, median (IQR), years	68 (28)	67 (27)	69 (24)	0.304*
Sex, female/male (%)	93/82 (53.1/46.9)	43/42 (50.6/49.4)	50/40 (55.6/44.4)	0.51†
Level of education, *n* (%)				0.002†
None	21 (12)	5 (5.9)	16 (17.8)	
Primary school	65 (37.1)	36 (42.4)	29 (32.2)	
High school	46 (26.3)	16 (18.8)	30 (33.3)	
Associate degree/University	43 (24.6)	28 (32.9)	15 (16.7)	
Marital status, *n* (%)				0.152‡
Married	68 (38.9)	39 (45.9)	29 (32.2)	
Single	64 (36.6)	32 (37.6)	32 (35.6)	
Widowed	29 (16.6)	10 (11.8)	19 (21.1)	
Divorced	8 (4.6)	2 (2.4)	6 (6.7)	
Cohabiting (common-law)	6 (3.4)	2 (2.4)	4 (4.4)	
Race, *n* (%)				0.045‡
Mestizo	149 (85.1)	74 (87.1)	75 (83.3)	
White	19 (10.9)	11 (12.9)	8 (8.9)	
Black	6 (3.4)	0 (0)	6 (6.7)	
Indigenous	1 (0.6)	0 (0)	1 (1.1)	
Occupation, *n* (%)				0.02†§
Unemployed/Retired	106 (60.6)	51 (60)	55 (61.1)	
Employed	29 (16.6)	15 (17.6)	14 (15.6)	
Self-employed	25 (14.3)	8 (9.4)	17 (18.9)	
Healthcare worker	11 (6.3)	10 (11.8)	1 (1.1)	
Student	4 (2.3)	1 (1.2)	3 (3.3)	

*Mann–Whitney U test; †Pearson's chi-square; ‡Fisher's exact test; §Significant association only between "healthcare worker" and "vaccinated" ($p = 0.0037$) for a value $\alpha = 0.005$ by Bonferroni correction. IQR: interquartile range

comorbidity, affecting 53.1% ($n = 93$) of patients. This was followed by diabetes (18.3%, $n = 32$), and asthma (9.1%, $n = 16$). A total of 10 patients (5.7%) had a history of oncologic conditions, including breast cancer (four patients), acute lymphoblastic leukemia (three patients), cervical cancer (one patient), lung cancer (one patient), and thyroid cancer (one patient). Additionally, three patients (1.7%) were diagnosed with the human immunodeficiency virus. One of them, which was vaccinated with BBIBP-CorV, was the only one to survive. However, no statistical differences were found. Interestingly, a higher proportion of vaccinated patients had asthma compared to unvaccinated patients (14.1% vs. 4.4%, $p = 0.026$). The median Charlson index of patients was 3 (IQR 3) points, with no significant differences observed between groups ($p = 0.2$). Furthermore, no significant differences were found between the vaccinated and unvaccinated patients in terms of smoking habits, alcohol consumption, and illicit drug use (Table 2).

3.3 Clinical characteristics upon admission

The median duration between the onset of COVID-19 symptoms and hospitalization was 6 (IQR 8) days, with no significant differences observed between the vaccinated and unvaccinated groups (7 vs. 5 days, respectively, $p = 0.343$ by Mann–Whitney U test). The most common symptoms upon admission were fever (71.4%, $n = 125$), dyspnea (69.7%, $n = 122$), and dry cough (56.6%, $n = 99$). Less common symptoms included lumbar pain (2.9%, $n = 5$), dysphonia (3.4%, $n = 6$), and dysphagia (4%, $n = 7$). A higher proportion of vaccinated patients reported myalgias compared to unvaccinated patients (29.4% vs. 14.4%, $p = 0.016$), while dyspnea was more prevalent in unvaccinated patients (76.7% vs. 62.4%, $p = 0.039$) (Fig. 2).

Upon physical examination, the median heart rate, respiratory rate, and oxygen saturation at admission were 90 (IQR 24) bpm, 22 (IQR 6) rpm, and 89 (IQR 14) %, respectively. Notably, the median respiratory rate was significantly higher in unvaccinated patients compared to vaccinated patients (24 vs. 22 rpm, $p = 0.005$). Crackles (73.1%, $n = 128$) and decreased breath sounds (50.3%, $n = 88$) were the most common pathological findings on chest auscultation, and altered consciousness was observed in 14.3% ($n = 25$) of all patients upon admission. Furthermore, the most frequently documented thoracic X-ray findings were an interstitial pattern (51.7%, $n = 62$) and lung fields with a reinforced bronchovascular tract (20%, $n = 24$) (Table 3).

Table 2 Medical history of patients with COVID-19 according to their vaccination status

Characteristics	Total ($n = 175$, 100%)	Vaccinated ($n = 85$, 48.6%)	Unvaccinated ($n = 90$, 51.4%)	p value
Previous SARS-CoV-2 infection, yes (%)	16 (9.1)	12 (14.1)	4 (4.4)	0.026*
Comorbidities, yes (%)				
Hypertension	93 (53.1)	40 (47.1)	53 (58.9)	0.117*
Diabetes	32 (18.3)	16 (18.8)	16 (17.8)	0.858*
Asthma	16 (9.1)	12 (14.1)	4 (4.4)	0.026*
COPD	10 (5.7)	4 (4.7)	6 (6.7)	0.576*
Cancer	10 (5.7)	3 (3.5)	7 (7.8)	0.226*
CKD	5 (2.9)	1 (1.2)	4 (4.4)	0.369†
Obesity	5 (2.9)	2 (2.4)	3 (3.3)	1†
CVD	4 (2.3)	2 (2.4)	2 (2.2)	1†
HIV	3 (1.7)	1 (1.2)	2 (2.2)	1†
Other	9 (5.1)	4 (4.7)	5 (5.6)	1†
Charlson Index, median (RIQ), points	3 (3)	2 (3)	3 (3)	0.2‡
Smoking, yes (%)	33 (18.9)	16 (18.8)	17 (18.9)	0.991*
Pack-year index, mean (SD)	17.7 (18.3)	21.8 (23.4)	13.8 (11.2)	0.215§
Alcoholics, yes (%)	23 (13.1)	13 (15.3)	10 (11.1)	0.413*
Illicit drug use, yes (%)	2 (1.1)	1 (1.2)	1 (1.1)	1†

*Pearson's chi-square; †Fisher's exact test; ‡Mann–Whitney U test; §Student's *t*-test for independent samples. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. COPD: chronic obstructive pulmonary disease. CKD: chronic kidney disease. CVD: cerebrovascular disease. HIV: human immunodeficiency virus. IQR: interquartile range. SD: standard deviation

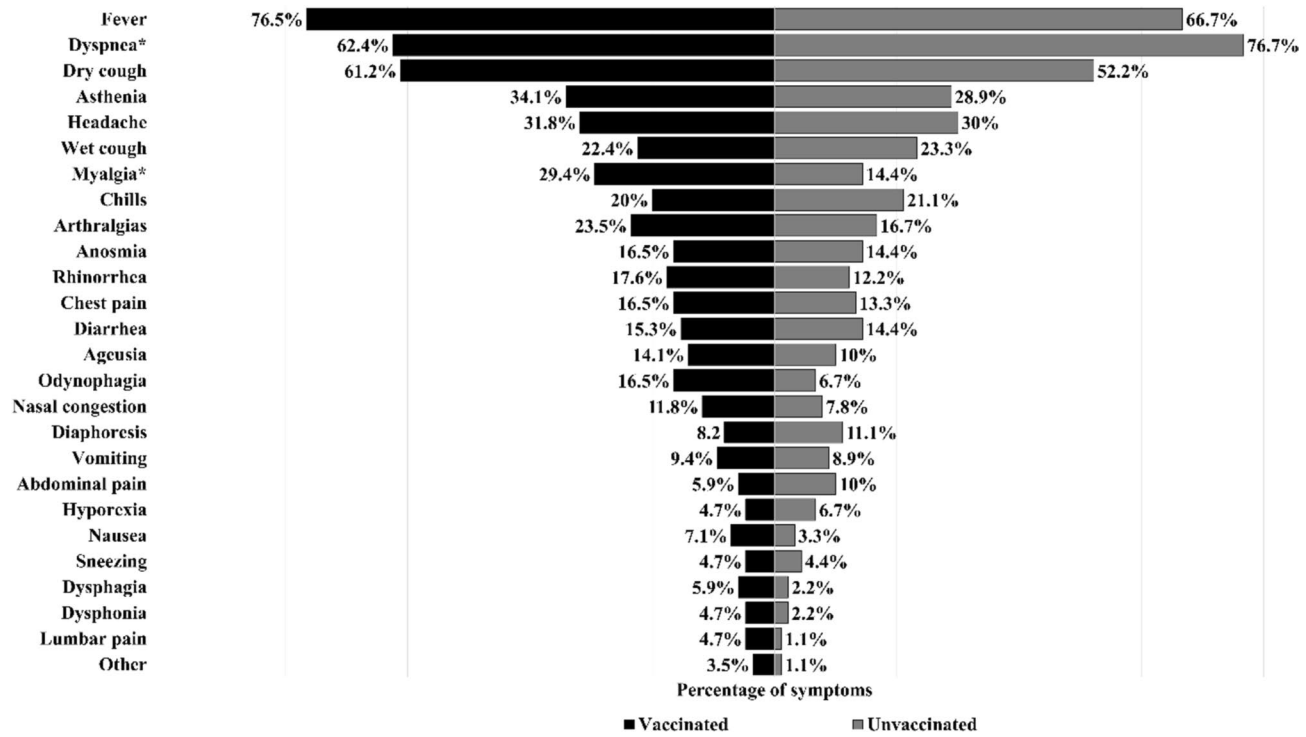

Fig. 2 Symptoms on admission of patients with COVID-19 according to their vaccination status. Data is graphed as percentage. $^{*}p < 0.05$ (*p* values by Pearson's chi-square)

Table 3 Physical exam findings on admission of patients with COVID-19 according to their vaccination status

Characteristics	Total (*n* = 175, 100%)	Vaccinated (*n* = 85, 48.6%)	Unvaccinated (*n* = 90, 51.4%)	*p* value
Hemodynamic parameters				
Heart rate, median (IQR), bpm	90 (24)	88 (23)	90 (23)	0.916[*‡]
Breathing rate, median (IQR), rpm	22 (6)	22 (6)	24 (7)	0.004[*‡]
SBP, median (IQR), mm Hg	122 (30)	124 (30)	122 (29)	0.646[*‡]
DBP, median (IQR), mm Hg	75 (18)	75 (16)	76 (20)	0.821[*‡]
Oxygen saturation, median (IQR), %	89 (14)	90 (10)	87 (14)	0.02[*‡]
Chest pathologic findings on auscultation, yes (%)				
Crackles	128 (73.1)	63 (74.1)	65 (72.2)	0.777[†*]
Decreased breath sounds	88 (50.3)	44 (51.8)	44 (48.9)	0.704[†*]
Intercostal pull	23 (13.1)	13 (15.3)	10 (11.1)	0.413[†*]
Hypoexpansible chest	20 (11.4)	8 (9.4)	12 (13.3)	0.415[†*]
Roncus	18 (10.3)	11 (12.9)	7 (7.8)	0.261[†*]
Wheezing	16 (9.1)	10 (11.8)	6 (6.7)	0.242[†*]
Other	2 (1.1)	0 (0)	2 (2.2)	0.498[‡†]
Thoracic X-ray findings, *n* (%)				0.301[‡†]
Interstitial pattern	62 (51.7)	26 (44.8)	36 (58.1)	
Lung fields with reinforced bronchovascular tract	24 (20)	16 (27.6)	8 (12.9)	
Infiltrates	19 (15.8)	8 (13.8)	11 (17.7)	
Consolidation	10 (8.3)	5 (8.6)	5 (8.1)	
Pleural effusion	5 (4.2)	3 (5.2)	2 (3.2)	
Altered neurological status, yes (%)	25 (14.3)	14 (16.5)	11 (12.2)	0.422[†*]

[*]Mann–Whitney U test; [†]Pearson's chi-square; [‡]Fisher's exact test. IQR: interquartile range. SBP: systolic blood pressure. DBP: diastolic blood pressure

3.4 Paraclinical findings upon admission

Table 4 presents the paraclinical findings of the patients upon admission. The majority of the laboratory parameters were comparable between both groups. However, an exception was the median D-dimer level, which was significantly higher in unvaccinated patients compared to vaccinated patients (7.6 vs. 1.4 µg/mL, $p = 0.015$).

3.5 Medications administered

In this cohort, the antivirals administered were Remdesivir (14.9%, $n = 26$), Favipiravir (4.7%, $n = 13$), and Molnupiravir (1.7%, $n = 3$). These were administered in a timely manner in 50% ($n = 13/26$), 84.6% ($n = 11/13$), and 66.7% ($n = 2/3$) of cases, respectively. Furthermore, 45.7% ($n = 80$) of patients received antibiotic treatment, predominantly Levofloxacin (23%), followed by Ceftriaxone and Meropenem. Meropenem was administered in a higher proportion of vaccinated patients compared to unvaccinated patients (9.4% vs. 2.2%, $p = 0.041$). Regarding corticosteroids, Dexamethasone was administered to 59.4% ($n = 104$) of patients and was used appropriately in 88.2% ($n = 60/104$) of these cases. Tocilizumab was only used in two patients (1.1%) (Supplementary Data 1).

3.6 Clinical outcome

The median duration between hospitalization and discharge was 10 (IQR 12) days, with no significant differences observed between the vaccinated and unvaccinated groups (11 vs. 10 days, respectively, $p = 0.526$ by Mann–Whitney U test). In the vaccinated group, two patients required admission to the intensive care unit, compared to four

Table 4 Paraclinical findings on admission of patients with COVID-19 according to their vaccination status

Characteristics	Total ($n = 175$, 100%)	Vaccinated ($n = 85$, 48.6%)	Unvaccinated ($n = 90$, 51.4%)	p value
Hemoglobin, mean (SD), g/dL	12.2 (2.2)	12.5 (2.4)	12 (2)	0.212*
Hematocrit, mean (SD), %	39.9 (6.7)	38 (6.8)	37.8 (6.6)	0.85*
White blood cells, median (IQR), $\times 10^3$/mL	9.4 (6.1)	10.2 (7.5)	8.9 (5.6)	0.097†
Neutrophils, median (IQR), $\times 10^3$/mL	81 (18)	81 (15)	80.9 (18.5)	0.997†
Lymphocytes, median (IQR), $\times 10^3$/mL	15 (14.8)	13.4 (12)	16.8 (17.3)	0.7†
Platelets, mean (SD), $\times 10^3$/mL	245.5 (114.2)	254.6 (118.8)	236.1 (109.5)	0.39*
Glycemia, median (IQR), mg/dL	117 (69)	117 (70)	116.9 (70)	0.856†
Urea, median (IQR), mg/dL	36.5 (25.7)	38.5 (22)	36 (24.7)	0.729†
Creatinine, median (IQR), mg/dL	1 (0.4)	1 (0.4)	0.9 (0.5)	0.695†
PT, mean (SD), sec	12.4 (3.2)	12.3 (3.4)	12.4 (3.1)	0.905*
PTT, mean (SD), sec	30.5 (12.3)	32.4 (14.7)	28.1 (8.5)	0.312*
Fibrinogen, mean (SD), mg/dL	535.5 (454.6)	469.3 (232.9)	668.1 (742.7)	0.398*
AST, mean (SD), U/L	37.5 (17.6)	39 (19.4)	35.4 (15)	0.513*
ALT, mean (SD), U/L	40 (18.5)	40.6 (20.5)	39.1 (15.8)	0.808*
Total bilirubin, mean (SD), mg/dL	1 (1.1)	0.8 (0.6)	1 (1.4)	0.702*
LDH, mean (SD), U/L	430.8 (238.6)	438.5 (271)	423.1 (204.6)	0.783*
ESR, mean (SD), mm/h	41.5 (28.8)	31.4 (22.1)	51.5 (32.8)	0.204*
CRP, median (IQR), mg/L	12 (42.4)	14.7 (54.8)	11 (26.9)	0.134†
D-dimer, median (IQR), µg/mL	2.2 (14.3)	1.4 (3.9)	7.6 (118)	0.015†
Ferritin, median (IQR), ng/mL	336.1 (406.4)	405 (243.9)	314 (287.5)	0.222†
Procalcitonin, median (IQR), ng/mL	0.4 (0.6)	0.4 (1.6)	0.4 (0.2)	1†
Albumins, mean (SD), g/L	3.3 (0.5)	3.3 (0.5)	3.3 (0.6)	0.999*

*Student's *t*-test for independent samples; †Mann–Whitney U test. SD: standard deviation. IQR: interquartile range. PT: prothrombin time. PTT: partial thromboplastin time. AST: aspartate aminotransferase. ALT: alanine aminotransferase. LDH: lactate dehydrogenase. ERS: erythrocyte sedimentation rate. CRP: C-reactive protein

patients in the unvaccinated group ($p = 0.683$ by Pearson's chi-square test). During the study period, there were 50 deaths (28.6% of patients), with a higher proportion observed among unvaccinated patients compared to vaccinated patients (35.6% vs. 21.2%, $p = 0.035$ by Pearson's chi-squared test). Furthermore, it was determined that vaccination against COVID-19 reduced the probability of death ($p = 0.028$) (Fig. 3).

3.7 Factors associated with lethality

The most valid model ($p < 0.001$, R^2 Nagelkerke = 0.341, Hosmer–Lemeshow test = 0.238) accurately classified 78.9% ($n = 138$) of patients. Factors associated with increased odds of death included advanced age (OR = 1.043, 95% CI = 1.015–1.071, $p = 0.002$), and receiving treatment at the "Dr. Luis Razetti" University Hospital (OR = 3.897, 95% CI = 1.053–14.418, $p = 0.042$) or "Uyapar" Hospital (OR = 7.317, 95% CI = 1.798–29.776, $p = 0.005$) compared to the University Hospital of Caracas. On the other hand, factors associated with decreased odds of death included vaccination against COVID-19 (OR = 0.428, 95% CI = 0.185–0.99, $p = 0.047$), high oxygen saturation (OR = 0.964, 95% CI = 0.934–0.995, $p = 0.024$), and administration of enoxaparin (OR = 0.292, 95% CI = 0.093–0.917, $p = 0.035$) (Table 5).

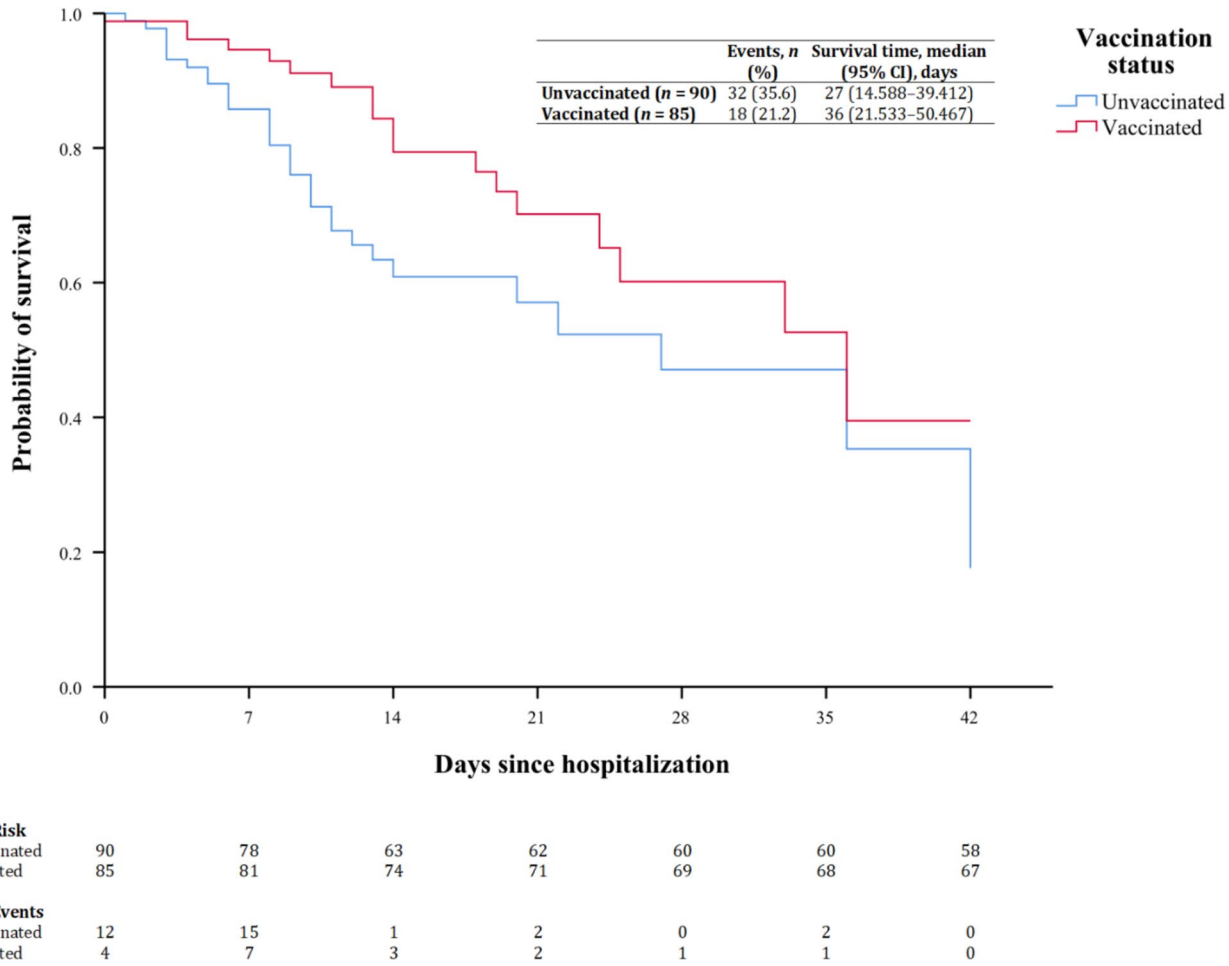

Fig. 3 Kaplan–Meier curves showing the probability of survival patients with COVID-19 according to their vaccination status. Log Rank (Mantel–Cox test) = 4.811, $p = 0.028$

Table 5 Factors associated with lethality patients with COVID-19

	β	*p* value	OR adjusted (95% confidence interval)
Vaccinated against COVID-19, yes	− 0.848	0.047	0.428 (0.185–0.99)
Age	0.042	0.002	1.043 (1.015–1.071)
Sex, male	0.412	0.307	1.51 (0.687–3.326)
Care center (reference: University Hospital of Caracas)			
"Dr. Luis Razetti" University Hospital	1.36	0.042	3.897 (1.053–14.418)
"Ruiz y Páez" University Hospital Complex	0.874	0.103	2.397 (0.839–6.846)
"Uyapar" Hospital	1.99	0.005	7.317 (1.798–29.776)
Hypertension, yes	− 0.109	0.8	0.897 (0.386–2.083)
Dyspnea, yes	− 0.234	0.614	0.791 (0.318–1.967)
Oxygen saturation	− 0.037	0.024	0.964 (0.934–0.995)
Crackles, yes	0.447	0.375	1.563 (0.583–4.191)
Dexamethasone, yes	− 0.467	0.386	0.627 (0.218–1.803)
Enoxaparin, yes	− 1.231	0.035	0.292 (0.093–0.917)

4 Discussion

This study represents the first multicenter research examining the clinical and epidemiological characteristics, including lethality rates, among vaccinated and unvaccinated COVID-19 patients in Venezuela. In Venezuela, the logistical challenges associated with vaccine distribution and storage were mitigated through the assistance of international organizations such as the United Nations Children's Fund, PAHO, and COVAX [20], culminating in the vaccination of 66% of the population by May 2023 [15]. Vaccination was correlated with a 57% decrease in lethality relative to the unvaccinated cohort.

A higher representation of healthcare workers was noted in the vaccinated group, likely attributable to this demographic being prioritized for vaccination in accordance with WHO and PAHO guidelines for risk groups [23]. Both cohorts had comparable characteristics in terms of sex, age, and comorbidities, except for bronchial asthma. However, no significant differences were observed upon calculation of the Charlson Comorbidity Index for each group. Interestingly, despite a higher incidence of asthma in the vaccinated group, this comorbidity has been linked to reduced lethality in hospitalized patients due to its association with T_H2 lymphocyte inflammation, which acts as a protective factor against COVID-19 [29].

Our study revealed a higher prevalence of previous COVID-19 infections among vaccinated individuals when compared to the unvaccinated ones. One potential hypothesis for this observation could be the risk of breakthrough infections following vaccination, particularly noted with inactivated whole virus vaccines such as BBIBP-CorV and Gam-COVID-Vac [30]. Additionally, vaccine hesitancy, often accompanied by a denial of the virus's existence or the severity of the disease, may contribute to underreporting of infection rates within the unvaccinated population [31]. The most prevalent symptoms and signs, including dyspnea, fever, dry cough, tachypnea, and decreased oxygen saturation, were consistent with previous studies [32, 33]. Unvaccinated patients had a higher prevalence of dyspnea, increased respiratory rate, and lower oxygen saturation values, corroborating findings from similar studies [34]. Consistent with prior documentation [35], D-dimer values at admission showed statistically significant differences between both groups, with higher levels observed in the unvaccinated group, indicative of a hypercoagulable state and increased risk of adverse events and death.

This study demonstrated a reduction in COVID-19 lethality among patients vaccinated with BBIBP-CorV and Gam-COVID-Vac, consistent with similar studies conducted in Qatar [36] and India [37] that reported a more than threefold increase in lethality among unvaccinated patients. However, the quality of evidence varied across vaccines [38]. A study conducted in China involving the Delta variant demonstrated effective protection following two doses of inactivated virus vaccines such as BBIBP-CorV and CoronaVac, while partial vaccination offered no significant protection [39]. Another multicenter case–control study carried out in South American countries such as Argentina, Colombia, Chile, and Brazil, evaluated the efficacy of the CoronaVac, BBIBP-CorV, and Gam-COVID-Vac vaccines (among others) by age and by the predominant circulating variant of SARS-CoV-2, demonstrating that vaccines prevented

hospitalizations and deaths even among the oldest population [40]. In a multicenter United States study, progression to death after COVID-19 hospitalization was associated with a lower likelihood of vaccination (OR = 0.41; 95% CI = 0.19–0.88) [41]. Finally, a study in Pakistan found significantly higher percent deaths in the unvaccinated group compared to the vaccinated group. However, they also documented variations according to patient age and type of vaccine. For example, the percent of COVID-19 cases who died among unvaccinated individuals > 50 years of age was 3.83- and 7.49-fold higher compared to recipients of BBIBP-CorV and Gam-COVID-Vac, respectively [42]. This is similar to our results.

High oxygen saturation, a valuable metric for classifying disease severity, was associated with lower lethality rates in both groups under study. Conversely, low oxygen saturation has been identified as a significant indicator of death risk [43]. Additionally, the administration of enoxaparin, a low molecular weight heparin, was found to decrease lethality risk within our cohort, consistent with previous research [44]. The impact of low molecular weight heparins in COVID-19 varies significantly depending on whether thromboprophylaxis or therapeutic doses are used. However, in accordance with the guidelines of the Venezuelan Ministry of Health during the time of our study [45], thromboprophylaxis dosage was employed in this population, still yielding a significant difference.

In our model, no significant association was observed between comorbidities and COVID-19 outcomes, contradicting previous findings [46]. The Charlson Comorbidity Index enabled us to evaluate patients in both groups based on their number of comorbidities and risk. However, well-managed long-term pathologies could potentially influence the accuracy of this measure and the outcomes. Increased age was associated with a higher risk of death, potentially due to older patients' susceptibility to COVID-19 as hypothesized by Ayón-Aguilar et al. [47], which could be attributed to immunosenescence and their dysregulated inflammatory response. Institutions should consider assessing COVID-19 older patient's weakness to provide appropriate care for this risk group.

Significant variations in death risk were observed across different care centers. Coupled with the disparities described in healthcare centers in Venezuela, including challenges such as access to basic needs like water supply, continuous electricity, personnel shortage, and medication availability [48], these factors do not remain constant between centers and departments within the same institution. The University Hospital of Caracas, located in the country's capital, may have had an advantage in terms of resource accessibility and allocation, resulting in better outcomes and highlighting the ethical dilemma in attention care in Venezuela. Moreover, the "Uyapar" Hospital, which had a considerably limited COVID-19 bed availability during the study period, possibly reserved those for severely ill patients, which may have also conditioned a worse outcome in these patients.

This study represents the first nationwide analysis of the impact of vaccination on lethality rates among patients with COVID-19 in Venezuela. It encompasses a comparative assessment of hospitalized individuals who have received the vaccine and those who have not from four different hospitals during two separate waves of the pandemic within the country. Institutional variables, such as availability of beds and medical supplies, accessibility to diagnostic procedures, and level of patient care, elucidate the Venezuelan healthcare landscape. These elements contribute to a more accurate description of vaccine efficacy under real-world conditions. However, this study has several limitations. Despite its multicenter nature, it only included four hospitals in major cities of the country, so the results should be extrapolated with caution, especially in sociodemographic contexts of peri-urban and rural regions. The limited sample size in this study can be attributed to several factors. Firstly, the availability of beds within the COVID-19 designated areas of the participating hospitals, specifically at the "Dr. Luis Razetti" University Hospital and "Uyapar" Hospital, was restricted. Secondly, although the third and fourth wave of the pandemic had more cases, hospitalization rates decreased in comparison to the first two, from 40.5% of cases during the second wave to 11.3% during the fourth one [24]. Lastly, prolonged hospital stays for severe cases naturally reduced the turnover of patient admissions. Moreover, there was limited access to antigen and RT-PCR testing for SARS-CoV-2 detection, particularly at the "Ruiz y Páez" University Hospital Complex and "Uyapar" Hospital. Consequently, patients without confirmed infection due to these testing limitations were excluded from the study. Furthermore, the non-randomized methodology limits our ability to estimate vaccine efficacy, and the small sample size does not allow for secondary analysis in the population that received a partial vaccination schedule or a booster dose. Additionally, we lack insights into the individual efficacy of each vaccine type.

In some cases, follow-up was conducted via telephone, but it was not possible for three patients, which could have underestimated the lethality. Finally, the lack of molecular diagnostic tools prevented the identification of specific variants associated with each case, which represents a significant limitation since we know that they may modify patient outcomes [49]. This study suggests that despite suboptimal adherence to vaccination schedules and logistical challenges in Venezuela, the deployment of COVID-19 vaccines contributed to a decrease in lethality rates among infected individuals. Using a prospective, multicenter methodology allowed the assesment of the clinical outcomes of hospitalized

COVID-19 patients. The findings revealed that, regardless of the administered vaccine, there was a significant reduction in the lethality rate, greater than 50%, among the cohort of vaccinated individuals. This discovery represents a substantial advancement in understanding the impact of immunization in practical environments and could offer critical insights for formulating public health policies. Nonetheless, further research involving a larger and randomly sampled populace is imperative to facilitate nuanced analyses based on vaccine type and dosage received. Moreover, including patients from hospitals across diverse demographic and healthcare landscapes is recommended to allow for the analysis of additional variables unique to each medical facility.

5 Conclusions

This study found an association between COVID-19 vaccination and reduced lethality among COVID-19 patients treated in four public hospitals in Venezuela during the third and fourth pandemic waves in 2021 and 2022, respectively. However, to determine the individual efficacy of each vaccine and its correlation with the number of doses administered, further multicenter studies involving larger populations are encouraged.

Acknowledgements Not applicable.

Author contributions DAFP, JLL, MVV, and FSCN conceived and designed the study. DAFP, JLL, MVV, DLMM, EASY, KRF, AKM, RdCG, DCFdN, and FSCN collected clinical data. ÓDOÁ, DLMM, ACLEH, CMRS, FHM, NACÁ, and FSCN analyzed and interpreted the data. JLL, MVV, ÓDOÁ, OARG, DLMM, ACLEH, CMRS, RTC, JLFP, AM, and FSCN wrote the manuscript. DAFP, OARG, FHM, MEG, MEL, and FSCN critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability All data generated or analyzed during this study are included in the article.

Declarations

Ethics approval and consent to participate The study protocol was reviewed and approved by the Independent Bioethics Committee for Research of the National Center for Bioethics (CIBI-CENABI, in Spanish) of Venezuela (CIBI-CENABI-14/2021). The study was conducted in accordance with the ethical principles for medical research in humans of the Declaration of Helsinki and the Venezuelan regulations for this type of research. Signed informed consent was requested from all patients at the beginning of hospitalization in the COVID-19 ward.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. WHO Coronavirus (COVID-19) Dashboard [https://covid19.who.int/]
2. Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, Hu Y, Tao Z-W, Tian J-H, Pei Y-Y, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–9.
3. Novelli G, Biancolella M, Mehrian-Shai R, Erickson C, Godri Pollitt KJ, Vasiliou V, Watt J, Reichardt JKV. COVID-19 update: the first 6 months of the pandemic. Hum Genom. 2020;14(1):48.
4. Le Thanh T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, Mayhew S. The COVID-19 vaccine development landscape. Nat Rev Drug Discovery. 2020;19(5):305–6.
5. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, Kovyrshina AV, Lubenets NL, Grousova DM, Erokhova AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021;397(10275):671–81.

6. Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. Nat Med. 2021;27(2):205–11.
7. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15.
8. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–16.
9. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881–91.
10. Basheeruddin Asdaq SM, Jomah S, Rabbani SI, Alamri AM, Salem Alshammari SK, Duwaidi BS, Alshammari MS, Alamri AS, Alsanie WF, Alhomrani M, et al. Insight into the advances in clinical trials of SARS-CoV-2 vaccines. Can J Infect Dis Med Microbiol. 2022;2022:6913772.
11. World Health O. Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing: interim guidance, first issued 8 January 2021, updated 15 June 2021, updated 19 November 2021, updated 21 January 2022. In. Geneva: World Health Organization; 2022.
12. World Health O: Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm: interim guidance, first issued 7 May 2021, updated 28 October 2021, updated 15 March 2022. In. Geneva: World Health Organization; 2022.
13. Sputnik Vaccine Efficacy Data Published in Lancet Are 'Statistically Impossible' [https://healthpolicy-watch.news/sputnik-vaccine-efficacy-data/#:~:text=To%20date%2C%20the%20World%20Health,necessary%20data%20has%20been%20submitted]
14. Bok K, Sitar S, Graham BS, Mascola JR. Accelerated COVID-19 vaccine development: milestones, lessons, and prospects. Immunity. 2021;54(8):1636–51.
15. COVID-19 Data Explorer: Global Humanitarian Operations [https://data.humdata.org/visualization/covid19-humanitarian-operations/]
16. Arrocha Olabuenaga P. Un faro en la oscuridad: México y la resolución 74/274 de la Asamblea General de las Naciones Unidas. Revista Mexicana de Política Exterior. 2021;119:239–58.
17. Colombia recibe las primeras vacunas que llegan a las Américas a través del Mecanismo COVAX [https://www.paho.org/es/noticias/1-3-2021-colombia-recibe-primeras-vacunas-que-llegan-americas-traves-mecanismo-covax#:~:text=Washington%2C%20DC%2C%201%20de%20marzo,regi%C3%B3n%20y%20en%20el%20mundo.]
18. Timeline: tracking Latin America's road to vaccination [https://www.as-coa.org/articles/timeline-tracking-latin-americas-road-vaccination]
19. Otras 500 mil dosis de Sputnik V arribaron al país para fortalecer vacunación masiva [https://www.mincyt.gob.ve/otras-500-mil-dosis-de-sputnik-v-arribaron-al-pais-para-fortalecer-vacunacion-masiva/]
20. López-Loyo ES, Urbina-Medina H, Esparza J. Aporte institucional de la Academia Nacional de Medicina de Venezuela en tiempos de pandemia: vacunación contra la COVID-19. Gac Méd Caracas. 2021;129(4):801–13.
21. Claro F, Silva D, Pérez Bogado JA, Rangel HR, de Waard JH. Lasting SARS-CoV-2 specific IgG Antibody response in health care workers from Venezuela, 6 months after vaccination with Sputnik V. Int J Infect Dis. 2022;122:850–4.
22. Dean NE, Hogan JW, Schnitzer ME. Covid-19 vaccine effectiveness and the test-negative design. N Engl J Med. 2021;385(15):1431–3.
23. WHO. Protocol: real-time RT-PCR assays for the detection of SARS-CoV-2, Institut Pasteur, Paris. Geneva: World Health Organization; 2020.
24. Arvelo MC, Montes de Oca M, Sánchez-Traslaviña L, Pujol FH, Jaspe RC, Silva IC, Stulin I, Blanco G, Quevedo J, Valera N, et al. Cambios en las características clínicas y desenlaces de pacientes hospitalizados por COVID-19 durante dos años de pandemia: experiencia en un hospital venezolano. Rev Peru Med Exp Salud Pública. 2022;39(3):292–301.
25. Jaspe RC, Loureiro CL, Sulbaran Y, Moros ZC, D'Angelo P, Hidalgo M, Rodríguez L, Alarcón V, Aguilar M, Sánchez D, et al. Description of a one-year succession of variants of interest and concern of SARS-CoV-2 in Venezuela. Viruses. 2022;14(7):1378.
26. . In: Coronavirus Disease 2019 (COVID-19) Treatment guidelines. edn. Bethesda (MD): National Institutes of Health (US); 2021.
27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
28. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020, **20**(8):e192-e197.
29. Zhang JJ, Dong X, Liu GH, Gao YD. Risk and protective factors for COVID-19 morbidity, severity, and mortality. Clin Rev Allergy Immunol. 2023;64(1):90–107.
30. Yegorov S, Kadyrova I, Negmetzhanov B, Kolesnikova Y, Kolesnichenko S, Korshukov I, Baiken Y, Matkarimov B, Miller MS, Hortelano GH, et al. Sputnik-V reactogenicity and immunogenicity in the blood and mucosa: a prospective cohort study. Sci Rep. 2022;12(1):13207.
31. Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K, Kimball S, El-Mohandes A. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med. 2021;27(2):225–8.
32. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR Jr, Nahid M, Ringel JB, et al. Clinical characteristics of Covid-19 in New York city. N Engl J Med. 2020;382(24):2372–4.
33. Forero-Peña DA, Carrión-Nessi FS, Mendoza-Millán DL, Omaña-Ávila ÓD, Mejía-Bernard MD, Camejo-Ávila NA, Flora-Noda DM, Velásquez VL, Chacón-Labrador FR, Doval-Fernández JM, et al. First wave of COVID-19 in Venezuela: epidemiological, clinical, and paraclinical characteristics of first cases. J Med Virol. 2022;94(3):1175–85.
34. Sayeed MA, Shalim E, Farooqui F, Farman S, Khan M, Iqbal A, Ahmed I, Rajput AW, Razzaque A, Quraishy S. Comparison of the disease severity and outcome of vaccinated COVID-19 patients with unvaccinated patients in a specialized COVID-19 facility: a retrospective cohort study from Karachi, Pakistan. Vaccines. 2023;11(7):1178.
35. Eljilany I, Elzouki A-N. D-Dimer, fibrinogen, and IL-6 in COVID-19 patients with suspected venous thromboembolism: a narrative review. Vasc Health Risk Manage. 2020;16:455–62.
36. Butt AA, Nafady-Hego H, Chemaitelly H, Abou-Samra AB, Khal AA, Coyle PV, Kanaani ZA, Kaleeckal AH, Latif AN, Masalmani YA, et al. Outcomes among patients with breakthrough SARS-CoV-2 infection after vaccination. Int J Infect Dis. 2021;110:353–8.
37. Balachandran S, Moni M, Sathyapalan DT, Varghese P, Jose MP, Murugan MR, Rajan C, Saboo D, Nair SS, Varkey RA, et al. A comparison of clinical outcomes between vaccinated and vaccine-naive patients of COVID-19, in four tertiary care hospitals of Kerala, South India. Clinical Epidemiol Global Health. 2022;13: 100971.

38. Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect. 2022;28(2):202–21.
39. Hu Z, Tao B, Li Z, Song Y, Yi C, Li J, Zhu M, Yi Y, Huang P, Wang J. Effectiveness of inactivated COVID-19 vaccines against severe illness in B16172 (Delta) variant–infected patients in Jiangsu, China. Int J Infect Dis. 2022;116:204–9.
40. Kahn R, Janusz CB, Castro MC, da Rocha MA, Domingues C, Ponmattam J, Rey-Benito G, Toscano CM, Helena de Oliveira L. The effectiveness of COVID-19 vaccines in Latin America, 2021: a multicenter regional case-control study. Lancet Reg Health Am. 2023;20:100474.
41. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, Ghamande S, Douin DJ, Talbot HK, Casey JD, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA. 2021;326(20):2043–54.
42. AlQahtani M, Du X, Bhattacharyya S, Alawadi A, Al Mahmeed H, Al Sayed J, Justman J, El-Sadr WM, Hidary J, Mukherjee S. Post-vaccination outcomes in association with four COVID-19 vaccines in the Kingdom of Bahrain. Sci Rep. 2022;12(1):9236.
43. Liu W, Yang C, Liao YG, Wan F, Lin L, Huang X, Zhang BH, Yuan Y, Zhang P, Zhang XJ, et al. Risk factors for COVID-19 progression and mortality in hospitalized patients without pre-existing comorbidities. J Infect Public Health. 2022;15(1):13–20.
44. Joanico-Morales B, Gaspar-Chamu AD, Salgado-Jiménez M, Rodríguez-Echeverría G. Enoxaparin dose associated with decreased risk of death in COVID-19. Revista medica del Instituto Mexicano del Seguro Social. 2022;60(1):33–9.
45. MPPS: Guía para el manejo y tratamiento de contactos y pacientes con COVID-19 - Comité Terapéutico COVID-19. In. Caracas, D.F.: Ministerio del Poder Popular para la Salud de Venezuela; 2020: 21.
46. Sezen YI, Senoglu S, Karabela SN, Yesilbag Z, Borcak D, Canbolat Unlu E, Korkusuz R, Ozdemir Y, Kart Yasar K. Risk factors and the impact of vaccination on mortality in COVID-19 patients. Bratisl Lek Listy. 2022;123(6):440–3.
47. Ayón-Aguilar J, Méndez-Martínez S, Toledo-Tapia R, García-Flores MA, Mayoral-Ortiz A, TIecuitl-Mendoza N, Toledo-Tapia M, Ortega-Aguirre M, Amaro-Balderas E. Influence of risk factors on mortality from COVID-19. Revista medica del Instituto Mexicano del Seguro Social. 2022;60(4):433–9.
48. Paniz-Mondolfi AE, Sordillo EM, Márquez-Colmenarez MC, Delgado-Noguera LA, Rodriguez-Morales AJ. The arrival of SARS-CoV-2 in Venezuela. Lancet. 2020;395(10236):e85–6.
49. Stepanova M, Lam B, Younossi E, Felix S, Ziayee M, Price J, Pham H, de Avila L, Terra K, Austin P, et al. The impact of variants and vaccination on the mortality and resource utilization of hospitalized patients with COVID-19. BMC Infect Dis. 2022;22(1):702.

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).
Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.
These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.
We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.
While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.
These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.
To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.
Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.
If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com