COVID-19 Vaccination and Lethality Reduction: A Prospective Cohort Study in Venezuela

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Abstract

Background

While rigorous randomized clinical trials have substantiated the efficacy of COVID-19 vaccines in reducing hospitalization and mortality rates, there is a paucity of post-authorization analyses conducted in real-world settings. In Venezuela, the primary vaccines administered are BBIBP-CorV (Sinopharm) and Gam-COVID-Vac (Sputnik-V). However, the performance and effectiveness of these vaccines within this specific population remain to be thoroughly investigated.

Methods

A prospective cohort study was undertaken from October 5, 2021, to March 31, 2022, across four sentinel hospitals in Venezuela. The outcomes were evaluated at two time points: day 28 and day 48, utilizing the WHO's COVID-19 Clinical Progression Scale. For the purpose of analysis, patients were classified into two groups: vaccinated and unvaccinated.

Results

The study included a total of 175 patients, of which 85 (48.6%) were categorized as vaccinated, with the majority (76.5%) having received two doses. The median age of the patients was 68 years, with a slight predominance of females (53.1%), and the majority being unemployed/retired (60.6%). Hypertension (53.1%) and diabetes (18.3%) were the most prevalent comorbidities. The median Charlson index of the patients was 3 points, with no statistically significant differences observed between the groups ($p = 0.2$). Upon admission, dyspnea was more commonly observed in unvaccinated patients compared to vaccinated patients (76.7% vs. 62.4%, $p = 0.039$). Almost all laboratory parameters were comparable in both groups, with the exception of the median D-dimer level, which was significantly higher in unvaccinated patients (7.6 vs. 1.4 µg/mL, $p = 0.015$). A total of 50 patients (28.6%) died of the disease, with a higher proportion of deaths observed in unvaccinated patients compared to vaccinated patients (35.6% vs. 21.2%, $p = 0.035$). Factors such as advanced age (OR = 1.043, 95%CI = 1.015–1.071, $p = 0.002$) were associated with increased odds of death, while factors such as 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 odds of death.

Conclusion

In the course of the third and fourth waves of the pandemic, vaccination against COVID-19 was found to be associated with a 57% reduction in lethality among patients treated in four public hospitals in Venezuela.

Background

As of December 27, 2023, the global impact of the coronavirus disease 2019 (COVID-19) has resulted in over 773 million confirmed cases and more than 6.9 million deaths [1]. The initial impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was significant due to the limited understanding of its transmission, treatment, and prevention strategies [2]. In response to the pandemic, numerous pharmaceutical companies initiated the development of vaccines against SARS-CoV-2, resulting in at least 78 confirmed active vaccine candidates by April 2020 [3]. In late 2020, phase III results were reported for several vaccines, including BNT162b2 (Pfizer-BioNTech) with an efficacy of 90–97% [4, 5], mRNA-1273 (Moderna) with an efficacy of 87–97% [6], ChAdOx1-S/nCoV-19 (AstraZeneca) with an efficacy of 65–88% [7], Gam-COVID-Vac (Sputnik-V) with an efficacy of 94–100% [8], CoronaVac (Sinovac) with an efficacy of 50–62%, and BBIBP-CorV (Sinopharm) with an efficacy of 64–86% [9]. The BNT162b2 and mRNA-1273 vaccines were the first to receive emergency use authorization from the US Food and Drug Administration (FDA) in December 2020 [10–12], followed by approval from the World Health Organization (WHO) in January 2021 [13, 14]. The BBIBP-CorV and CoronaVac vaccines received approval in May 2021 [13, 15, 16]. However, other candidates such as Gam-COVID-Vac have yet to receive WHO approval [17–19].

Despite the slow progress of the vaccination process in Latin America, several countries have undertaken initiatives to expedite the process. Mexico was the first country to respond to the United Nations call in April 2021 to provide access to drugs and vaccines to combat COVID-19 [20]. Colombia became the first Latin American country to receive BNT162b2 vaccines under the COVID-19 Vaccines Global Access (COVAX) program in March 2021 [21]. Chile donated 20,000 doses of the Chinese vaccine CoronaVac to Ecuador and

Paraguay [22]. In Venezuela, the vaccination campaign against COVID-19 utilized BBIBP-CorV, CoronaVac, and Gam-COVID-Vac vaccines due to agreements with the Russian Federation [23] and global collaboration mechanisms such as COVAX [24].

The Venezuelan government initially planned to launch the “Mass Vaccination Plan” in January 2021, but the first batch of vaccines arrived in February [25]. The process was divided into five stages, with healthcare workers prioritized in the first stage [24]. Subsequently, the supply of vaccines to Venezuela continued sporadically and without prior planning, including the arrival of other vaccines such as BBIBP-CorV, Gam-COVID-Vac, and vaccine candidates such as Abdala, Soberana-2, and EpiVacCorona [24, 26]. By September 2021, the Pan American Health Organization (PAHO) reported a vaccination coverage of 14.9% in Venezuela. By May 2022, Venezuela had administered a total of 38 million doses, vaccinating 66% of its population [27]. Although some studies have demonstrated that Gam-COVID-Vac vaccines are effective in eliciting a neutralizing antibody response in Venezuelan patients [28, 29], the clinical efficacy in this population remains unknown.

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. In addition, patient inclusion is often based on their clinical stability [30]. Suboptimal adherence to schedules and logistics also influences its effectiveness. Therefore, post-authorization analyses are crucial for evaluating the actual efficacy and behavior in real populations [31]. This study aims to describe the clinical behavior and outcome of vaccinated and unvaccinated patients during the third and fourth pandemic waves in four hospitals in Venezuela.

Methods

Study design and population

A prospective cohort study was conducted including patients aged 18 and over who tested positive for SARS-CoV-2 infection and were hospitalized between October 5, 2021, and March 31, 2022, at various sentinel hospitals in Venezuela. These included the University Hospital of Caracas (Capital District), “Dr. Luis Razetti” University Hospital (Anzoategui state), “Ruiz y Páez” University Hospital Complex (Bolivar state), and “Uyapar” Hospital (Bolivar state). The diagnosis of SARS-CoV-2 infection was confirmed via antigen testing and reverse transcription polymerase chain reaction (RT-PCR) [32] at the “Rafael Rangel” National Institute of Hygiene (Venezuela). The study period included cases from the third (June to December 2021) and fourth (January to February 2022) waves of the pandemic in Venezuela [33], each characterized by different variants of SARS-CoV-2. A national genomic surveillance study analyzed samples from nasopharyngeal or nasal swabs confirmed positive by RT-PCR during routine COVID-19 diagnosis in Venezuela. The third wave presented variants of both interest and concern, starting with Gamma (B.1.1.248) and ending with Delta (B.1.617). The fourth wave was predominantly characterized by the circulation of the Omicron variant (B.1.1.529) [34]. Patients with incomplete or illegible data on variables of interest in interviews and medical records were excluded.

The severity of COVID-19 was categorized as mild (defined as the presence of various signs and symptoms of COVID-19, excluding shortness of breath, dyspnea, or abnormal chest imaging), moderate (defined as evidence of lower respiratory disease during clinical assessment or imaging and an oxygen saturation $\geq$ 94% on room air at sea level), severe (defined as 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 (defined as 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) [35].

Sample size

According to the Pan American Health Organization [36], as of October 4, 2021, there were 373,332 confirmed SARS-CoV-2 cases in Venezuela. Hence, the sample size, with a 95% confidence interval and a 5% margin of error, was at least 384 patients. The sampling method was non-probabilistic.

Epidemiological and clinical assessment

Patient data were collected by trained staff at sentinel centers through interviews and review of medical records. This data included epidemiological characteristics (such as age, sex, education 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 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 [37]. Patient outcomes was assessed at day 28 and 48 post-admission using the WHO's COVID-19 Clinical Progression Scale [38]. The dates of 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 outcome. 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 14 days prior.

Statistical analysis

Patients' data were 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, while 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).

Results

Patients' sociodemographics

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" ($p = 0.0037$).

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 α = 0.005 by Bonferroni correction. IQR: interquartile range

Medical history

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

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

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 low back 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. 1).

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 radiographic thoracic pathological findings were an interstitial pattern (51.7%, n = 62) and lung fields with a reinforced bronchovascular tract (20%, n = 24) (Table 3).

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 radiographic pathological 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

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).

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

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).

Clinical outcome

The median time between hospitalization and discharge was 10 (IQR 12) days, with no statistically significant differences between the vaccinated and non-vaccinated 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, whereas, in the unvaccinated group, four did ($p = 0.683$ by Pearson's chi-square test). During the study period, 50 (28.6%) patients died, and a higher proportion of deaths was found in unvaccinated patients compared to vaccinated patients (35.6% vs. 21.2%, $p = 0.035$ by Pearson's chi-squared test). Moreover, it was found that being vaccinated against COVID-19 decreased the probability of death ($p = 0.028$) (Fig. 2).

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 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. 2).

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).

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)

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. Vaccination was correlated with a 57% decrease in lethality relative to the unvaccinated cohort. The logistical challenges associated with vaccine distribution and storage in Venezuela were mitigated through the assistance of international organizations such as the United Nations Children's Fund, PAHO, and COVAX [24], culminating in the vaccination of 66% of the population by May 2023 [27].

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 [32, 39]. Both the vaccinated and unvaccinated cohorts had comparable characteristics in terms of sex, age, and comorbidities, with the exception of bronchial asthma. However, no significant differences were observed upon calculation of the Charlson Comorbidity Index for each group. 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 [40, 41] and Gam-COVID-Vac [42]. 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 [43]. The most prevalent symptoms and signs, including dyspnea, fever, dry cough, tachypnea, and decreased oxygen saturation, were consistent with previous studies [44–55]. Unvaccinated patients had a higher prevalence of dyspnea, increased respiratory rate, and lower oxygen saturation values, corroborating findings from similar studies [56–60]. 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 [61–65]. Consistent with prior documentation [66, 67], D-dimer values at admission showed statistically significant differences between the 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 [68] and India [69] that reported a more than threefold increase in lethality among unvaccinated patients. Prior researches have evaluated the efficacy of the BNT162b2, mRNA-1273, CoronaVac, and Gam-COVID-Vac vaccines, concluding that they are all safe and effective against all variants of interest included in their work in several countries around the world, including Chile, Brazil, Colombia, and Ecuador [70–73]. However, the quality of evidence varied across vaccines [74]. 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 [75]. 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 [76, 77]. 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) [72]. 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 [78]. 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 [51, 79]. Additionally, the administration of enoxaparin, a low molecular weight heparin, was found to decrease lethality risk within our cohort, consistent with previous research [80, 81]. The impact of low molecular weight heparins in COVID-19 varies significantly depending on whether thromboprophylaxis or therapeutic doses are used, with the latter demonstrating greater benefit [82]. However, in accordance with the guidelines of the "Ministerio del Poder Popular para la Salud" (the primary national health institute) in Venezuela during the time of our study [83], 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 [84, 85]. 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.* [86], which could be attributed to immunosenescence and their dysregulated inflammatory response. Institutions should consider assessing frailty at admission for all older patients admitted with COVID-19 to provide appropriate care for this risk group.

Significant variations in death risk were observed across different care centers. The therapeutic management of COVID-19 initially presented an uncertain pathway for providers, and guidelines remained quite open for personal suggestions and individualized treatment adapted on a case-by-case basis [83]. 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 [87, 88], 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.

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 sample size was limited. This limitation is attributable to several factors: primarily, the restricted availability of beds within the COVID-19 designated areas of the participating hospitals, notably at the "Dr. Luis Razetti" University Hospital and "Uyapar" Hospital; secondarily, the protracted hospital stays required for severe cases, which inherently reduced the turnover of patient admissions; and lastly, the limited access to antigen and RT-PCR testing for SARS-CoV-2 detection, with pronounced scarcity at the "Ruiz y Páez" University Hospital Complex and "Uyapar" Hospital. As a result, patients who could not have their infection conclusively verified due to these testing limitations were excluded from the study. Furthermore, its non-random methodology limits the estimation of 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, nor does it allow for understanding the individual efficacy of each type of vaccine. In some cases, follow-up was conducted via telephone, but it was not possible in three patients, so the lethality found in this work could be higher. Finally, the absence of molecular tools did not allow for determining the variants involved in each case, which constitutes a significant limitation since we know that they may modify patient outcomes [89, 90]. This study posited that notwithstanding 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. Employing a prospective, multicenter methodology, the study assessed the clinical outcomes of patients hospitalized for COVID-19. The findings revealed that, regardless of the vaccine variant administered, there was a notable reduction in the lethality rate, greater than 50%, among the cohort of vaccinated individuals. This finding marks a significant advancement in comprehending the ramifications of immunization within practical environments and could provide critical insights for public health policy formulation. Nonetheless, further research involving a more extensive and randomly sampled populace is imperative to facilitate nuanced analyses contingent upon the vaccine type and dosage received. Moreover, the inclusion of patients from hospitals across diverse demographic and healthcare landscapes is recommended to permit the analysis of additional variables unique to each medical facility.

Conclusions

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

Abbreviations

COVID-19 coronavirus disease 2019, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *FDA* US Food and Drug Administration, *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

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.

Availability of data and materials

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

Competing interests

The authors declare no competing interests.

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Authors' contributions

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

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Figures

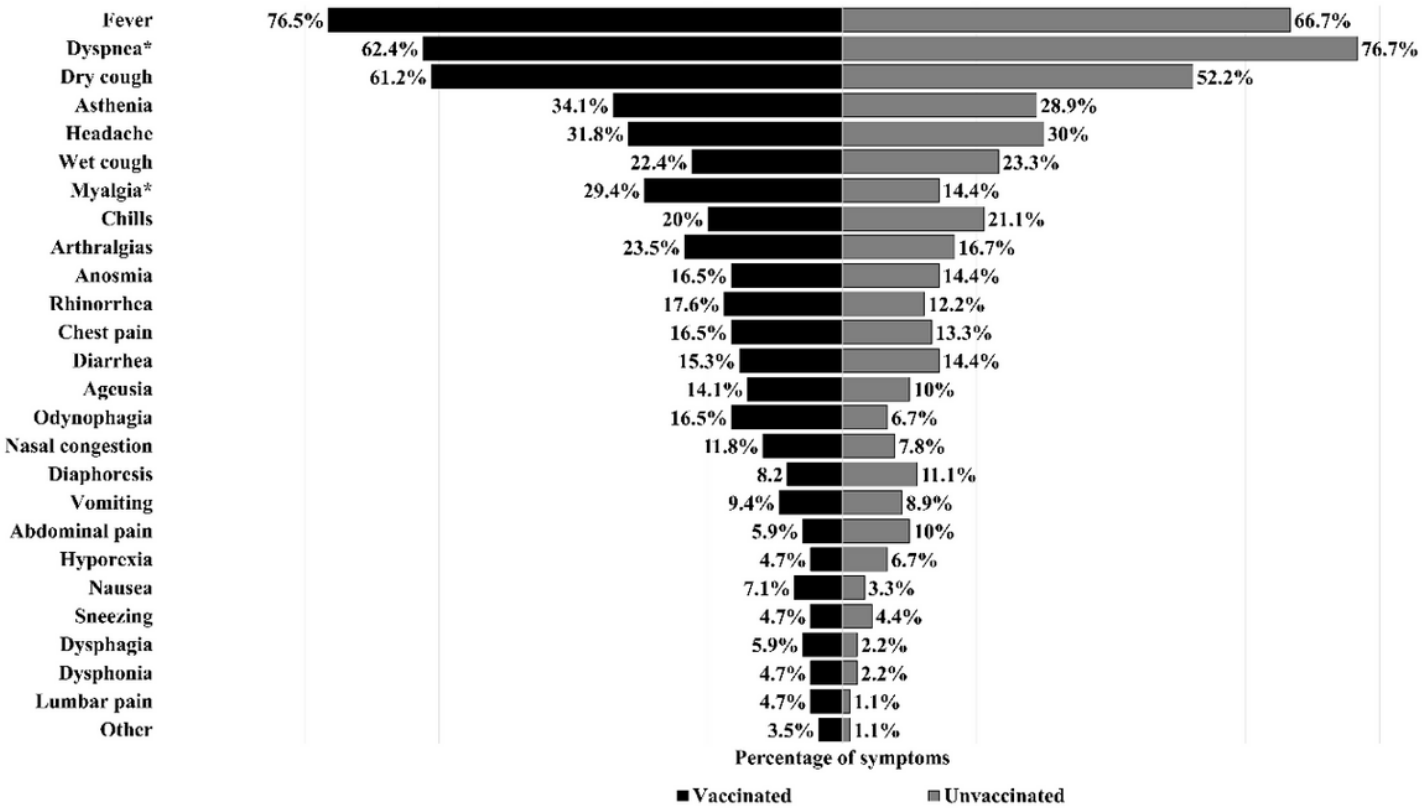

Figure 1

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

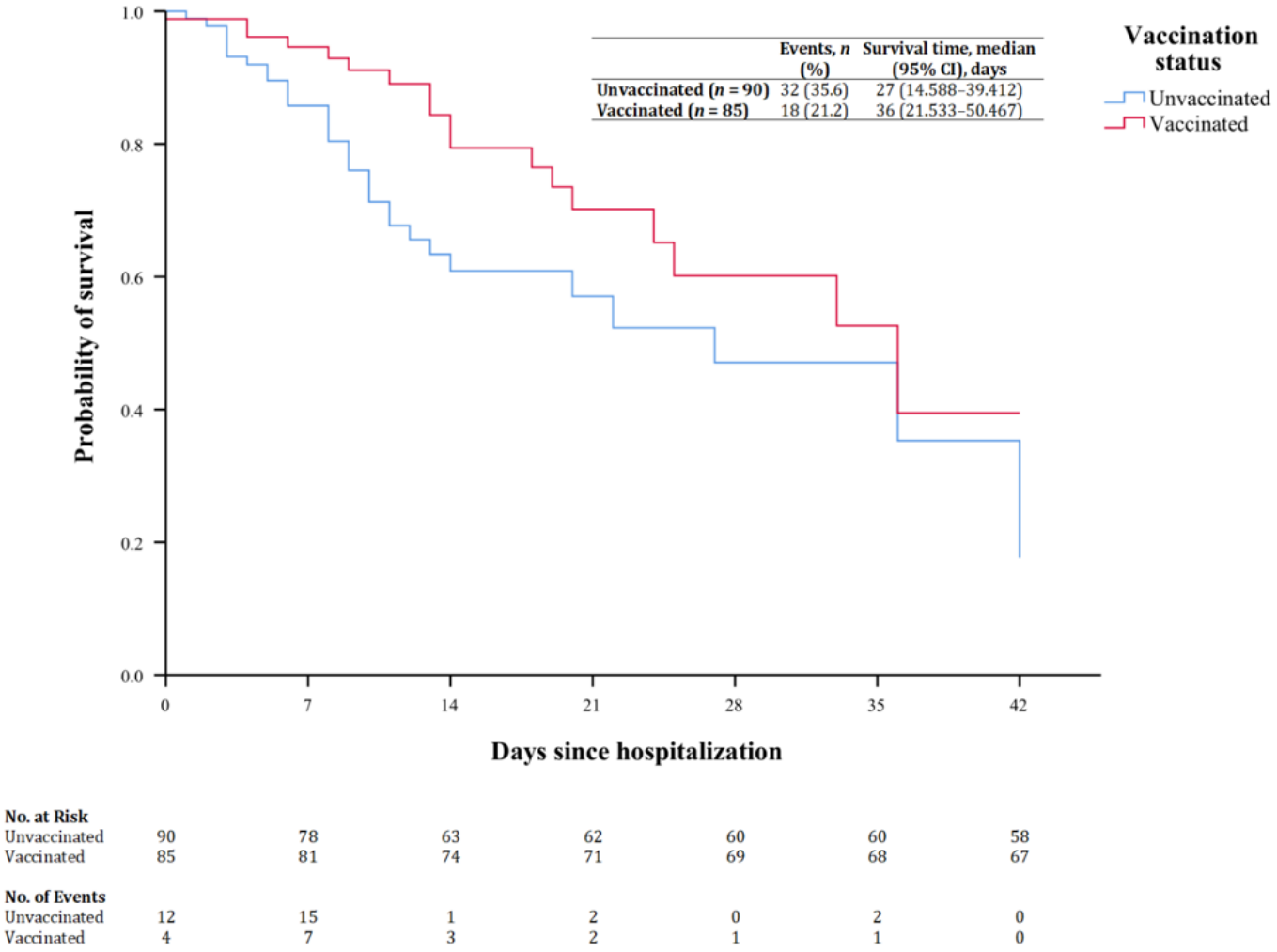

Figure 2

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

Supplementary Files

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- SupplementaryData1.docx