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CVV: Contributed to formulating the original idea and designed the study, analyzed the data, and wrote the original manuscript. **DFS, COA, ZDT:** Contributed to the design conception, data analysis, and manuscript writing. **GFG:** contributed to the design and development of the manuscript and supervised all research and manuscript development. All authors reviewed and approved the final version of the manuscript.

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Analysis of vaccination against SARS-CoV-2 and mortality due to COVID-19 in the Callao region, Peru during the period 2021-2022

Análisis de la vacunación contra SARS-CoV-2 y muerte por COVID-19 en la región Callao, Perú durante el periodo 2021-2022

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SUMMARY

Objective: To determine the relationship between SARS-CoV-2 vaccination dimensions and COVID-19 death rates in the Callao region. **Methods:** A cross-sectional study based on the Ministry of Health databases was carried out. A total of 44,867 records from the Callao region were analyzed for the period 2021 to 2022. To assess the association of interest, logistic regression models were constructed, reporting crude odds ratios (cOR) and adjusted odds ratios (aOR). **Results:** The logistic regression models showed that vaccination had a protective effect against death from COVID-19, with an aOR of 0.19 ($p < 0.001$) after controlling for sex, age, hospitalization, ICU admission, and pandemic wave, compared to the reference group (unvaccinated). **Conclusions:** Vaccination provides a monotonic protective effect against death from COVID-19 in the Región Callao.

KEYWORDS: COVID-19, mortality, vaccination, pandemic.

RESUMEN

Objetivo: Determinar la relación entre las dimensiones de la vacunación contra el SARS-CoV-2 y la muerte por COVID-19 en la región Callao. **Material y métodos:** Estudio transversal basado en las bases de datos del Ministerio de Salud. Se analizaron 44,867 registros referidos a la región Callao, durante el periodo 2021 al 2022. Para evaluar la asociación de interés, se construyeron modelos de regresión logística, reportando odds ratio crudas (cOR) y ajustadas (aOR). **Resultados:** Los modelos de regresión logística mostraron que la vacunación tuvo un efecto protector sobre la muerte por COVID-19 con un aOR: 0,19 ($p < 0,001$) tras controlar por sexo, edad, hospitalización, ingreso en UCI y onda pandémica, en comparación con el grupo de referencia (no vacunados). **Conclusiones:** La vacunación presenta un efecto monotónico sobre la protección frente a la muerte por COVID-19 en la región Callao.

PALABRAS CLAVE: COVID-19, mortalidad, vacunación, pandemia.

INTRODUCTION

Worldwide, the COVID-19 pandemic caused a public health crisis, considerably increasing morbidity and mortality rates. Globally, 695,781,740 cumulative cases and 6,919,573 deaths were reported ⁽¹⁾, with the USA, India, France, Germany, and Brazil being the countries with the highest numbers. This implies a wide geographical distribution of the disease. During the pandemic, there were several infection waves, in which genetic variations of the pathogen, SARS-CoV-2, have been present.

Peru was one of the most affected countries, with more than 4.5 million infected and 222,161 deaths to date ⁽¹⁾. The health system breakdown was evidenced by the lack of care and containment measures, alarming the population, which observed a discouraging panorama, due to the lack of medical oxygen, hospital beds, and the Intensive Care Unit. ⁽²⁾

The vaccine against COVID-19, as the main measure, was developed in record time, and in February 2021, an arduous nationwide vaccination campaign began. To date, a total of 89,656,595 doses have been administered, obtaining coverage of 85%. ⁽³⁾

In the Región Callao, despite being one of the most affected regions and with the highest vaccination coverage, the current adult vaccination schedule has not been extensively evaluated. This is of special interest given that Callao is the country's main gate for international trade, meaning also a potential access point for communicable diseases such as COVID-19. Similarly, there is no detailed information on the

association between vaccination variables and death from COVID-19. On the contrary, research has mainly focused on evaluating excess mortality, focusing on the calculation of the number of deaths due to COVID-19, differentiating the expected and observed numbers.

Thus, according to the Peruvian Ministerio de Salud (MoH), the Región Callao has a total of 1,711,286 cases to date, 10,983 deaths, and a case fatality rate of 6.41%, meaning that this pathology exceeded the projected epidemiological rates. The main objective was to determine the relationship between the dimensions of vaccination against SARS-CoV-2 and mortality due to COVID-19 in the Región Callao, during the period June 1, 2021, to July 31, 2022.

METHODS

Study design and population: Cross-sectional study. The population consisted of all SARS-CoV-2-infected patients from June 1, 2021, to July 31, 2022, residing in the Región Callao. The Región Callao has a total of 7 districts in an area of 148,573 km²; within its jurisdiction, there are 45 health centers, 3 hospitals of the MoH, and 8 health facilities of EsSalud ⁽⁴⁾. The inclusion criterion was records of patients belonging to the Región Callao. The exclusion criteria were records of patients under 18 years of age, registries without province of residence, records without date of infection, records with incongruent date of hospitalization, records without reported vaccination, and records of death prior to the proposed date of infection. According to the MoH database, there is a regional sample of 44,867 patients infected with SARS-CoV-2 during the period evaluated.

Data Source: The open-access databases of the Peruvian MoH were used for the analysis; the databases of infected, deceased, and vaccinated patients against COVID-19 were used. The databases were merged according to the ID information present in the databases. The ID information is unique for every patient, and it is the same for all the databases since it is generated based on the national document of identification of the person.

Data analysis: The statistical package used was STATA v. 18 (STATA Corp, Texas, USA, RRID: SCR_012763). Universidad Peruana Cayetano Heredia was the owner of the academic license, Continuous variables were expressed as average and standard deviations. Qualitative and categorical variables were expressed as absolute and relative frequencies. Likewise, the evaluation of qualitative variables was measured by the Chi-square test. Additionally, to determine the association and effect between variables, logistic regression was applied due to the behavior of the dependent variable, death by COVID-19 (dichotomous variable). The raw and adjusted coefficients were reported. In the case of the adjusted model, the co-variables of sex and age group were included. A p -value < 0.05 was considered as statistically significant.

Ethical aspects: The study was registered with SIDISI (Code: 211094), required by the Universidad Peruana Cayetano Heredia, and was reviewed and exonerated by the institutional review board (Certificate: 201-17-23).

RESULTS

In Table 1 it is shown the bivariate analysis between the variable death due to COVID-19 and the covariates. There was a significant association with vaccination, with a decrease in the relative frequency of deaths with a higher number of doses applied, from 3.34% of deaths in the unvaccinated patients compared to the 0.69% of deaths in the vaccinated group with 3 doses, or 1.56% vaccinated with 4 doses. In addition, males had a higher frequency of deaths (1.15%), while only 0.78% of infected females died. Finally, age was also statistically associated with death from COVID-19, with the deceased having an average age of 69.74 years, while the non-deceased had an average age of 40.01 years. In all statistical tests, $p < 0.001$ was obtained.

An $OR = 0.19$ (95%CI 0.15-0.26) for the effect of vaccination on COVID-19 death after adjusting for sex, age, hospitalization, ICU admission, and pandemic wave (Table 2). Of note, there was a significant reduction of COVID-19 deaths in the third ($OR = 0.48$) and fourth (0.33) pandemic waves compared to the second one.

When evaluating the association between the different number of vaccine doses with COVID-19 death (Table 3), it was found a monotonic effect starting at the second dose ($OR = 0.28$ 95%CI 0.21-0.37), being lower at the third dose ($OR = 0.08$ 95%CI 0.05- 0.10), and maintained in the fourth dose ($OR = 0.12$ 95%CI 0.02-0.66) after adjusting for covariates.

Table 1. Characteristics associated with death due to COVID-19 in bivariate analysis (n=41,641)†.

Characteristics	Total	Death by COVID-19		p
	n=41,641	No (n=41,245)	Yes (n=396)	
	n (%)	n (%)	n (%)	
Sex*				<0.001
Female	22,422 (53.8)	22,247 (53.9)	175 (44.2)	
Male	19,219 (46.2)	18,998 (46.1)	221 (55.8)	
Age (years)*, **		40.01 ± 14.97	69.74 ± 18.53	<0.001
Districts				0.202
Bellavista	8,878 (21.3)	8,796 (21.3)	82 (20.7)	
Callao	19,528 (46.9)	19,320 (46.8)	208 (52.5)	
La Perla	2,683 (6.4)	2,663 (6.5)	20 (5.1)	
La Punta	371 (0.9)	366 (0.9)	5 (1.3)	
Mi Perú	1,527 (3.7)	1,514 (3.7)	13 (3.3)	
Ventanilla	8,654 (20.8)	8,586 (20.8)	68 (17.2)	
COVID-19 vaccination dose*				<0.001
Unvaccinated	3,081 (7.4)	2,978 (7.2)	103 (26.0)	
1 dose	1,316 (3.2)	1,288 (3.1)	28 (7.1)	
2 doses	23,187 (55.7)	23,020 (55.8)	167 (42.2)	
3 doses	13,929 (33.5)	13,833 (33.5)	96 (24.2)	
4 doses	128 (0.3)	126 (0.3)	2 (0.5)	
Hospitalization				<0.001
Yes	114 (0.3)	92 (0.2)	22 (5.6)	
No	41,530 (99.7)	41,153 (99.8)	374 (94.4)	
ICU admission				<0.001
Yes	23 (0.01)	17 (0.1)	6 (1.5)	
No	41,618 (99.9)	41,228 (99.9)	390 (98.5)	
Pandemic wave				<0.001
Second	3,141 (7.5)	3,068 (7.4)	73 (18.4)	
Third	37,376 (89.8)	37,061 (89.8)	315 (79.5)	
Fourth	1,124 (2.7)	1,116 (2.7)	8 (2.0)	

* Age is presented as a continuous quantitative variable, showing the mean ± standard deviation.

† Some variables may add up to less than 41,641 due to missing data.

* Chi-square test

** Student's t-test

Table 2. Logistic regression analysis between vaccination and death from COVID-19, crude and adjusted models.

Variables	Crude model			Parsimonious Model		
	cOR	95%CI	p	aOR	95%CI	p
Vaccination						
No	Ref.			Ref.		
Yes	0.22	(0.18-0.28)	<0.001	0.19	(0.15-0.26)	<0.001
Sex						
Female	Ref.			Ref.		
Male	1.47	(1.21-1.80)	<0.001	1.54	(1.24-1.90)	<0.001
Age	1.10	(1.09-1.11)	<0.001	1.11	(1.10-1.12)	<0.001
Hospitalization						
No	Ref.			Ref.		
Yes	26.31	(16.34-42.36)	<0.001	13.63	(6.63-28.02)	<0.001
ICU admission						
No	Ref.			Ref.		
Yes	37.31	(14.63-95.13)	<0.001	1.23	(0.35-4.33)	0.738
Pandemic wave						
Second	Ref.			Ref.		
Third	0.36	(0.27-0.46)	<0.001	0.48	(0.35-0.66)	<0.001
Fourth	0.30	(0.14-0.62)	0.001	0.33	(0.15-0.73)	0.006

cOR= crude Odds Ratio

aOR= adjusted Odds Ratio.

Age as a continuous quantitative variable

DISCUSSION

This study aimed to evaluate the relationship between vaccination and death from COVID-19 in the Región Callao during the period from June 1, 2021, to July 31, 2022. For this purpose, a cross-sectional study was developed. The conclusive results showed that vaccination is a protective factor for death from COVID-19, as well as the number of doses generating an ascending protective effect.

Positive effects of vaccination have been found even with a single dose, reducing the development of COVID-19 to a critical degree or severity ⁽⁵⁾, hospitalization, and death ⁽⁶⁾. For the latter, a meta-analysis found an effectiveness of combined vaccination for COVID-19-related mortality of 68% (HR=0.32) and 92% (HR=0.08) for the first and second doses, respectively. Although a protective association was obtained with the first dose, it was considerably lower (acOR=0.74 for the first dose and acOR=0.41 for

the second dose). This difference may be due to the decrease in vaccine efficacy over days. ⁽⁷⁾

When compared with other studies conducted in Peru, a retrospective cohort study conducted with data from hospitalized patients in Lambayeque, a city in northern Peru, found that vaccination with at least one dose reduced the risk of death from COVID-19 in hospitalized patients by 42%-49% ⁽⁸⁾. This is similar to our results in which a reduction in mortality between 37%-79% was obtained with the first and second dose, however, it is important to note that the study referred to considered the first and second dose as a single group, while in the proposed study it was done as a difference, allowing the effect of the dose to be seen specifically. In another study using nationwide data, the relative vaccine efficacy of the booster dose, equivalent to the third dose, was evaluated and found to be 87.2% (84.2%-89.7%). ⁽⁹⁾

Table 3. Logistic regression analysis between the number of doses vaccinated and death due to COVID-19.

Variables	Crude Model			Parsimonious Model		
	aOR	95%CI	p	aOR	95%CI	p
Vaccination						
Unvaccinated	Ref.			Ref.		
1 dose	0.63	(0.44-0.56)	0.031	0.89	(0.55-1.44)	0.637
2 doses	0.21	(0.16-0.27)	<0.001	0.28	(0.21-0.37)	<0.001
3 doses	0.20	(0.15-0.27)	<0.001	0.08	(0.05-0.10)	<0.001
4 doses	0.46	(0.12-1.88)	0.279	0.12	(0.02-0.66)	0.014
Sex						
Female	Ref.			Ref.		
Male	1.43	(1.17-1.74)	<0.001	1.61	(1.29-2.00)	<0.001
Age	1.11	(1.10-1.12)	<0.001	1.12	(1.11-1.12)	<0.001
Hospitalization						
No	Ref.			Ref.		
Yes	17.87	(10.87-29.37)	<0.001	13.86	(6.64-28.91)	<0.001
ICU admission						
No	Ref.			Ref.		
Yes	18.65	(7.07-49.14)	<0.001	1.05	(0.29-3.76)	0.939
Pandemic wave						
Second	Ref.			Ref.		
Third	0.95	(0.69-1.33)	0.806	0.78	(0.57-1.06)	0.112
Fourth	1.28	(0.58-2.83)	0.542	0.81	(0.33-1.99)	0.654

cOR= crude Odds Ratio

aOR= adjusted Odds Ratio.

Age as a continuous quantitative variable

The COVID-19 pandemic has greatly impacted the health and economic sectors, among others. The highest mortality has occurred in the first two waves, just when most countries in the world lacked the vaccine. The third, fourth, and fifth waves have already faced a significant proportion of people with one to four doses of the vaccine. This is important to note, since Peru is within the classification of low- and middle-income countries, which generates studies such as the present one to evaluate the need to acquire vaccines and the frequency of inoculation, as can be seen in the results section, the fourth dose does not present a significant value in the crude model, this should be extrapolated to a national analysis, which supports whether the expenditure per dose is adequate, and therefore evaluate the entire vaccination scheme in general.

Booster doses have been described as effective in reducing hospitalizations and deaths from new variants. Some studies show that the immunogenicity produced by the vaccine decreases between 3 and 10 months after the third dose, suggesting that another booster dose (a fourth dose) is needed to counter SARS-CoV-2 variants ⁽¹¹⁾. However, approximately three in ten adults surveyed in Latin America and the Caribbean (LAC) reported not having received the booster vaccine ⁽¹²⁾, with a higher prevalence in Peru. ⁽¹³⁾

Our results suggest that the use of three and/or four doses of the vaccine was equally effective in reducing COVID-19 mortality. These results reveal that for our population, three doses were sufficient to reduce mortality, although it is also possible that the severity of infection resulting from the fourth and fifth waves

of infection, mainly due to the Omicron variant, was so low that mortality per se was also low ⁽¹⁰⁾. Future studies should evaluate whether more than three doses provide greater protection against death and other serious outcomes.

Vaccination is successful worldwide, however, disparities in its use have been observed, even within countries ⁽¹⁴⁾. Vaccination remains a cornerstone of the response to the COVID-19 pandemic, but broad public support remains elusive, as observed in a study in 23 countries, including Peru ⁽¹⁵⁾. Inequality in COVID-19 vaccination coverage has also been another problem observed within countries. ⁽¹⁶⁾

The main strength is the selected study area, Callao represents the point of entry and exit of Peru, therefore, it should be a region with strict Public Health surveillance. Likewise, the selected period represents a wide vaccination coverage, thus making it viable for the study of vaccination variables.

On the other hand, the weaknesses of the study are that, in the analysis of the data, no information was obtained on the history and/or comorbidities of the patients. It is also possible that some people were not identified as SARS-CoV-2 infected, especially those who were asymptomatic, reducing the population evaluated. Another limitation is that during the COVID-19 pandemic, different SARS-CoV-2 variants circulated in Peru, showing different disease severity ⁽¹⁰⁾. This limitation was partly controlled by the stratification of the study period based on the different pandemic waves. On the other hand, in the national vaccination program, different vaccine technologies were used ⁽¹⁰⁾, which could represent a differentiated effect on COVID-19 mortality. Future studies should consider these important variables.

In conclusion, the vaccination has generated a protective effect against death from COVID-19 in the Región Callao, a region with a high impact on mortality from SARS-CoV-2 infection. The analysis by number of doses shows an inverse relationship between dose and death from COVID-19, occurring up to the third dose. The fourth dose in the crude logistic regression model does not show a significant difference as a protective effect on death from COVID-19, allowing a regional evaluation of the effectiveness of the different doses applied and the scheme applied in the national territory. The study shows a significant impact on the epidemiological study of death by COVID-19 and vaccination, reinforcing the need to establish

preventive measures on conditions that affect public health in the Región Callao and the national territory. In the Región Callao, epidemiological control is imperative, accompanied by collaborative work with Public Health to ensure that pathogens do not affect the territory through the various entry and exit routes that the first port of Peru has.

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