Association between prehospital medication and fatal outcomes in a cohort of hospitalized patients due to coronavirus disease-2019 in a referral hospital in Peru

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ABSTRACT

Background: To explore the association between the use of prehospital medications and the development of fatal outcomes in patients who required hospitalization due to coronavirus disease-2019 (COVID-19).
Methods: This retrospective cohort study included adult patients who were hospitalized due to COVID-19. Demographic, clinical, and laboratory data, prehospital medication history, and fatal outcome development (use of high-flow oxygen therapy, intensive care unit [ICU] admission, or mortality) were extracted from the medical records of patients who were admitted due to COVID-19 to the Carlos Seguín Escobedo National Hospital of Arequipa, Peru during July to September 2021, the period after the second wave of COVID-19 cases in Peru. Survival was analyzed using the Cox proportional hazards model, and crude hazard ratios and adjusted hazard ratios (aHR) with their respective 95% confidence intervals (95% CI) were calculated.
Results: A total of 192 patients were evaluated, of whom 62% were males and 46.9% did not require oxygen support at admission. Additionally, 64.6% used nonsteroidal anti-inflammatory drugs, 35.4% used corticosteroids, 28.1% used macrolides or ceftriaxone, 24.5% used ivermectin, and 21.9% used warfarin before hospitalization. Of the patients, 30.2% developed a fatal outcome during follow-up. The multivariate analysis revealed that prehospital corticosteroid use was independently associated with the fatal outcome due to COVID-19 with an aHR = 5.29 (95%CI: 1.63–17.2).
Conclusion: Prehospital corticosteroid use was associated with a 5-fold increased risk of fatal outcome development.

1. Introduction

With >260 million cases and 5 million reported deaths worldwide until December 2021 [1], the coronavirus disease-2019 (COVID-19) pandemic is still responsible for high morbidity and mortality in some regions worldwide [2]. Therefore, the scientific community developed vaccines and continued to investigate the efficacy of different drugs against the disease [3]. The COVID-19 vaccination was shown effective [4]; however, global vaccine procurement and distribution inequity [5, 6], as well as the emergence of new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7,8], mean that the pandemic persists as a public health crisis.

Until December 2021, multiple drugs have been proposed for COVID-19 management [9]; however, very few have the quality for clinical practice recommendation. The path to building this evidence was marked by recommendations, sometimes contradictory from

regulatory institutions worldwide, as well as by the withdrawal of initially recommended drugs that were not only ineffective but also potentially harmful [10,11]. These official recommendations faced barriers to their implementation, as described in different clinical practice guidelines [12,13], which resulted in different outpatient and inpatient medication schemes as the pandemic progressed. Additionally, the saturation of health systems led to self-medication in infected patients, sometimes with drugs without proven evidence and with potential adverse effects, which increased hospitalizations in health systems that are already overwhelmed in their capacity for care [14,15].

Peru is a middle-income country that, until January 2022, reported >1.5 million confirmed cases and >200,000 deaths from COVID-19, making it one of the countries with the highest mortality from this disease worldwide [16,17]. Peru has a fragmented health system, with a poor linkage between health authorities and integration of information between the sectors in charge of managing the problems during the COVID-19 crisis [16]. At the beginning of the pandemic, the lack of transparency in the preparation of therapeutic recommendations for COVID-19 management by the Ministry of Health (MINSA, by its Spanish acronym). This led to the use of Hydroxychloroquine, Ivermectin and Azithromycin as the standard regimen for the management of COVID-19, even in Peruvian Social Security institutions, which improved with the subsequent incorporation of evidence-based national recommendations during May 2021 [18,19]. This meant a variation in the use of prescribed medication by physicians in outpatients and hospitalized patients [20]; however, the use of drugs without evidence and with potential harm, both by prescription and self-medication, persists [20,21].

Studies have been published on the associated factors with mortality in hospitalized patients due to COVID-19 in Peru [22–25]; however, studies that evaluate the effects of prehospital drugs on infected patients have not been published. Therefore, this study aimed to explore the association between the use of prehospital drugs and fatal outcome development in patients who required hospitalization due to COVID-19 in a national referral hospital in Peru, during July to September 2021, the period after the second wave of COVID-19 cases in Peru [17], and when there was already not evidence of benefit from the use of drugs such as corticosteroids in mild cases [19,26].

2. Materials and methods

2.1. Study design and population

A retrospective cohort study was conducted after the second wave of the COVID-19 pandemic at the Carlos Alberto Seguín Escobedo National Hospital (HNCASE, by its Spanish acronym) of the social security (EsSalud, by its Spanish acronym) between July 23 and September 30, 2021.

The HNCASE is a regional referral hospital that is located in the province of Arequipa, Peru. The hospital had 356 beds, with 25 beds in the intensive care unit and 168 beds in the emergency department. Also, during the COVID-19 pandemic, 150 additional beds were made available [27].

The sampling was a non-probabilistic consecutive type (inclusion of all patients who met the selection criteria at the defined time). All patients who presented with emergency respiratory symptoms and were hospitalized for COVID-19 (confirmed by molecular or antigenic test) were included. Patients under 18 years of age, pregnant, reported prehospital medication use for reasons other than COVID-19, referred from another hospital center, and with incomplete data on the variables of interest (prehospital medication and fatal outcome) were excluded from the study.

2.2. Data collection

In our hospital, during the study period, a data collection form was

implemented to record prehospital medication-related data (Annex 1). This form was distributed among the physicians of the "COVID Emergency" department during the research period. At the end of each day, the forms were collected by the head of the emergency department.

Clinical and laboratory data were extracted from the electronic medical records 4 weeks after they had a record of their admission and had their prehospital medication withdrawal form. Electronic medical records were available on the governmental social security virtual platform implemented in 2019 (Servicio de Salud Inteligente del Seguro Social in Spanish, https://essi.pe/).

Variables of interest were recorded in a Microsoft Excel database for subsequent data curation.

2.3. Variables and definition

The primary outcome includes hospital discharge or fatal outcomes. Fatal outcome was constructed from the clinical development of any of the following: 1) need for high-flow oxygen; 2) intensive care unit (ICU) admission; or 3) and death of the patient. This definition was used in previous studies [28–30].

The exposure includes prehospital use of anti-COVID-19 drugs that were stratified by drug groups as follows: 1) antimicrobials (antibiotics, ivermectin, and hydroxychloroquine); 2) corticosteroids; 3) colchicine; 4) oral anticoagulants (warfarin); 5) nonsteroidal anti-inflammatory drugs (NSAIDs); and 6) other drugs or substances (inhalers, antihistamines, acetylcysteine, vitamin C, vitamin D, zinc, and chlorine dioxide). We included information from patients who reported the use of medications at any time interval prior to arrival at the hospital and that were used only for the purpose of managing respiratory symptomatology.

Other recorded variables in the data extraction form, in addition to the used prehospital medications, include the duration of using different medications, in days, before going to the hospital and the source of medications (prescribed by physicians or self-medication).

Moreover, sociodemographic data (age and sex), self-reported obesity and arterial hypertension and diabetes mellitus as comorbidities, history of receiving two doses of COVID-19 vaccine (if available in the clinical history), and oxygen support upon admission were collected from the medical records, as well as vital signs upon admission (heart rate, respiratory rate, and oxygen saturation), laboratory data within 48 h of emergency admission (blood count, creatinine, liver enzymes, *C*-reactive protein, lactate dehydrogenase, and D-dimer), and presence of pulmonary involvement on computed tomography (CT) scan upon admission.

2.4. Statistical analysis

STATA software version 16 (StataCorp, College Station, TX, USA) was used for data processing.

Descriptive analysis was used as absolute and relative frequencies for categorical variables, as well as the measures of central tendency and dispersion according to their numerical variable distribution. Bivariate analysis was performed using the chi-square test for categorical variables, and the independent *t*-test compared the means of numerical variables to find the association and the Mann–Whitney *U* test in case of non-normality of variables.

The survival function for independent variables was done using the Kaplan–Meier method and the differences between the survival functions were evaluated using the log-rank test. The crude and adjusted regression analysis used the Cox proportional hazards model to find the hazard ratios (HR) and their respective 95% confidence intervals (95% CI) to evaluate the association between the different prehospital medication groups and fatal outcomes.

A statistical approach was followed, adjusting for confounding variables, which in the bivariate regression analysis had a significant association (*p-value* <0.20), prioritizing the numerical variables over their categorized counterpart to enter the variables into the multivariate Cox

regression model. In addition, the variables oxygen support at admission, respiratory rate, Leukocytes, CRP were not considered in the final model due to theoretical collinearity. Finally, the multicollinearity between the different variables and between drug groups was evaluated to enter a single multivariate Cox regression model to evaluate the association between the corticosteroid usage and fatal outcome. Proportionality assumptions were evaluated using the Schoenfeld residuals, the assumption is considered met with the *p*-value of >0.05.

In addition, we conducted a sensitivity analysis incorporating the consumption of other drugs into the final adjusted model. Finally, we performed a sensitivity analysis considering as corticosteroid consumption only those patients who reported having consumed more than 72 h of corticosteroids. As well as, categorizing the variable in short intervals of corticosteroid use.

2.5. Ethical aspects

The study protocol was evaluated and approved by the Office of Training, Research, and Teaching of the Social Security of Peru, Red Asistencial Arequipa-EsSalud (NIT: 1161-2021-141). For greater transparency, the protocol was entered with code EI00000002461 in the national registry of Health Research Projects developed by the Peruvian National Health Institute. Informed consent was not requested due to the retrospective observational nature of the study.

3. Results

Of a total of 587 patients who presented with emergency respiratory symptoms and were hospitalized for COVID-19 from July 23 to September 30, 349 were excluded due to lack of data on the variable of interest (prehospital medication), 5 due to voluntary withdrawal, 41 due to incomplete data, thereby obtaining a final sample of 192 (32.7%) (Fig. 1).

Among the 192 participants, the median age was 47 years (RIC: 39.5–66), 62.0% were males, 14.1% were obese, 18.8% had a history of arterial hypertension, and 9.9% had a history of diabetes mellitus. Additionally, 46.9% did not require oxygen support and 75% had pulmonary involvement on chest CT upon admission. The prescription of

three prehospital medications was reported by 20.3%, whereas more than five in 20.8% (Table 1).

The median hospitalization duration was 10 days (IQR: 1–59) and the median survival time was 25 days (IQR: 14–38). A fatal outcome due to COVID-19 was found in 58 patients (30.2%). This represents a fatal outcome rate of 3.0 per 100 person-days and an incidence rate of 2.37 events per 100 person-days-risks. Fatal outcome was significantly more frequent in patients older than 65 years (45.1%; *p* = 0.003), with a history of hypertension (44.4%; *p* = 0.039), required reservoir mask on admission (60.5%; *p* < 0.001), with a high respiratory rate on admission (45.6%; *p* < 0.001), with a lactate level of >720 u/l (80.0%; *p* = 0.028), and with a D-dimer value of >500 (34.5%; *p* = 0.008). Additionally, leukocytes, neutrophil-to-lymphocyte ratio, neutrophils, lymphocytes, *C*-reactive protein, lactate dehydrogenase, and D-dimer were significantly more frequently increased in patients who presented a fatal outcome (Table 1).

Regarding the used prehospital medication, 64.6% used NSAIDs with a median duration of 5 days (range: 1–12), 35.4% used corticosteroids with a median duration of 3 days (range: 1–30), and 28.1% reported using macrolides or ceftriaxone with a median duration of 3 days (range: 0–8 for macrolides and 1–8 for ceftriaxone). Likewise, 24.5% used ivermectin with a median duration of 2 days (range: 1–5) and 21.9% used warfarin with a median duration of 3 days (range: 1–8). Corticosteroid (39.7%; *p* = 0.034) and warfarin (47.6%; *p* = 0.005) were used more frequently and were associated among patients with fatal outcomes (Table 2).

Regarding the source of prehospital medication prescription, self-medication was reported in 100%, 34.9%, 32.8%, and 14.0% of those who used chlorine dioxide, ivermectin, antibiotics, and NSAIDs, respectively. Likewise, a medical prescription was reported in 100% of those who used warfarin, colchicine, and hydroxychloroquine (Fig. 2).

The multivariate analysis revealed that the prehospital use of corticosteroids was independently associated with the fatal outcome due to COVID-19 with an HRa of 5.29 (95%CI: 1.63–17.2), adjusted for age, neutrophil level, a lymphocyte level, oxygen saturation on admission, creatinine, lactate dehydrogenase, and D-dimer levels (Table 3).

In the sensitivity analysis, we found that the use of corticosteroids continued to be associated with an increased risk of developing a fatal
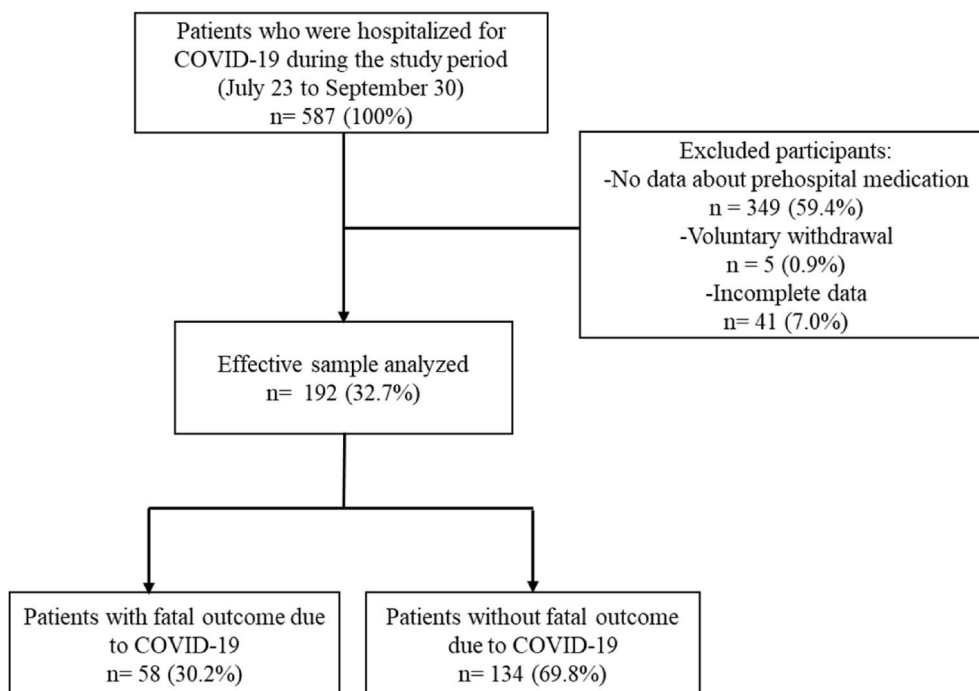

Fig. 1. Flowchart for sample selection.

Table 1
Characteristics of the population studied according to fatal outcomes.

Variables	n (%)[a] 192 (100%)	Fatal result from COVID-19		
		No[a] 134 (69.8%)	Yes[a] 58 (30.2%)	p-value[b]
Age (years)	47 (39.5–66)	45.5 (39–62)	59.5 (40–71)	**0.005**
18–49 years	111 (57.8)	88 (79.3)	23 (20.7)	**0.003**
50–64 years	30 (15.6)	18 (60.0)	12 (40.0)	
≥65 years	51 (26.6)	28 (54.9)	23 (45.1)	
Sex				
Female	73 (38.0)	51 (69.9)	22 (30.1)	0.987
Male	119 (62.0)	83 (69.8)	36 (30.3)	
Comorbidities				
None	90 (46.9)	68 (75.6)	22 (24.4)	0.102
At least one	102 (53.1)	66 (64.7)	36 (35.3)	
Type of omorbidities				
Obesity	27 (14.1)	15 (55.6)	12 (44.4)	0.082
Hypertension	36 (18.8)	20 (55.6)	16 (44.4)	**0.039**
Cardiopathy	8 (4.2)	4 (50.0)	4 (50.0)	0.213
Diabetes mellitus	19 (9.9)	11 (57.9)	8 (42.1)	0.234
Another comorbidity	61 (31.8)	45 (73.8)	16 (26.2)	0.413
Follow-up time (days)	10 (6–18)	8.5 (6–16)	12.5 (6–21)	0.082
Oxygen support at admission				
No	90 (46.9)	66 (73.3)	24 (26.7)	**<0.001**
By Binasal Cannula	64 (33.3)	53 (82.8)	11 (17.2)	
By Mask with reservoir	38 (19.8)	15 (39.5)	23 (60.5)	
Vital signs on admission				
Heart rate (lpm)[c]	88 (76–97)	86 (75.5–96)	89 (79–100)	0.849
Normal	144 (76.2)	103 (71.5)	41 (28.5)	0.366
High	45 (23.8)	29 (64.4)	16 (35.6)	
Respiratory rate (rpm)[c]	21 (20–24)	20 (20–22)	23.5 (22–26)	**<0.001**
Normal	78 (46.4)	69 (88.5)	9 (11.5)	**<0.001**
High	90 (53.6)	49 (54.4)	41 (45.6)	
Oxygen saturation (%)[c]	87 (82–90)	88 (83.5–91)	85 (80–89)	**0.007**
≥90	53 (32.1)	43 (81.1)	10 (18.9)	0.065
85–89	56 (33.9)	42 (75.0)	14 (25.0)	
81–84	28 (17.0)	20 (71.4)	8 (28.6)	
≤80	28 (17.0)	15 (53.6)	13 (46.4)	
Laboratory values at admission				
Leukocytes (cel/mm3)	7.0 (5.0–10.6)	6.8 (4.8–10.1)	8.3 (5.8–13.2)	**0.009**
<4000	24 (12.5)	17 (70.8)	7 (29.2)	0.203
4000–10000	112 (58.3)	83 (74.1)	29 (25.9)	
>10,000	56 (29.2)	34 (60.7)	22 (39.3)	
neutrophil-to-lymphocyte ratio	5.4 (3.2–12.5)	4.8 (3.0–9.5)	9.4 (4.4–20.8)	**<0.001**
Neutrophils (%)	77 (67–84)	75 (66–81)	82.7 (74–87)	**<0.001**
Lymphocytes (%)	14 (6.3–21)	15 (9–22)	9 (4–17)	**<0.001**
Creatinine (mg/dl)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.7 (0.6–1.9)	0.107
≤1	139 (72.4)	95 (68.4)	44 (31.7)	0.480
>1	53 (27.6)	39 (73.6)	14 (26.4)	
TGO (U/L)[c]	52.7 (27–81.4)	51.3 (25–79.9)	59.3 (32–92.5)	0.218
≤40	71 (40.3)	54 (76.1)	17 (23.9)	0.111
>40	105 (49.7)	68 (64.8)	37 (35.2)	
TGP (U/L)[c]	48.5 (25.7–92.2)	47.7 (24–91)	49.6 (27.8–111)	0.268
≤40	78 (41.5)	58 (74.4)	20 (25.6)	0.359
>40	110 (58.5)	75 (68.2)	35 (31.8)	
PCR (U/L)[c]	7.6 (3.5–16.4)	7.0 (2.7–15.1)	11.3 (5.0–23.0)	**0.005**
≤10	108 (57.1)	82 (75.9)	26 (24.1)	0.053
>10	81 (42.9)	51 (63.0)	30 (37.0)	
Lactic dehydrogenase (U/L)[c]	324 (252–490)	308 (250–401)	451 (294–561)	**0.003**
≤720	105 (95.5)	76 (72.4)	29 (27.6)	**0.028**
>720	5 (4.6)	1 (20.0)	4 (80.0)	
D-dimer (ug/ml)[c]	714 (465–1214)	630 (420–1033)	961 (649–2324)	**0.001**
≤500	45 (28.0)	39 (86.7)	6 (13.3)	**0.008**

Table 1 (*continued*)

Variables	n (%)[a] 192 (100%)	Fatal result from COVID-19		
		No[a] 134 (69.8%)	Yes[a] 58 (30.2%)	p-value[b]
>500	116 (72.1)	76 (65.5)	40 (34.5)	
Pulmonary Involvement in Pulmonary Tomography on admission				
No	48 (25)	35 (72.9)	13 (27.1)	0.586
Yes	144 (75)	99 (68.8)	45 (31.3)	
Prehospital drug use				
None	37 (19.2)	27 (73.0)	10 (27.0)	0.767
One	12 (19.3)	9 (75.0)	3 (25.0)	
Two	34 (17.7)	25 (73.5)	9 (26.5)	
Three	39 (20.3)	27 (69.2)	12 (30.8)	
Four	30 (15.6)	22 (73.3)	8 (26.7)	
More than five	40 (20.8)	24 (60.0)	16 (40.0)	

[a] Mean ± standard deviation, median (Interquartile range).
[b] Significant p-value of <0.05, found by chi-square test, Fisher test, T student test, or Mann–Whitney *U* test.
[c] Incomplete data.

outcome independently of other medications (Table S1). In addition, we found that a greater use of corticosteroids for 72 h increased the hazard of developing a fatal outcome (HR: 5.43; 95% IC: 1.44–20.56), adjusted for age, comorbidities, number of neutrophils, number of lymphocytes, oxygen saturation on admission, creatinine, lactate dehydrogenase and D-dimer level (Table S2). We also observed that the direction of effect was maintained in patients who reported using corticosteroids on the first two days, on days three to four and in those who used it for more than five days (Table S3).

Fig. 3 represents the survival function using the Kaplan–Meier curve for the variables of prehospital usage of macrolides, ceftriaxone, ivermectin, corticosteroids, warfarin, and NSAIDs.

4. Discussion

4.1. Main findings

Our main results show that approximately three out of four patients used some type of medication before hospital admission, including NSAIDs, corticosteroids, and antibiotics. A high rate of self-medication was observed in medications such as chlorine dioxide, ivermectin, and antibiotics. One in three patients had a fatal outcome due to COVID-19, being five times higher among those who used corticosteroids before hospital admission.

4.2. The comparison of our results with previous studies

Several studies in Peru identified the used medication before hospitalization due to COVID-19. A study in Lima revealed that 80.0% of hospitalized patients received some type of treatment before hospitalization, with antibiotics (85.8%), specifically azithromycin, and ivermectin (66.9%), as the most commonly used [31]. Corticosteroids and NSAIDs were used in 54.7% and 16% of patients, respectively [31]. Another study in Lima revealed that 33.3% of patients used azithromycin, ivermectin, or corticosteroids [32]. These studies, similar to ours, were conducted in national referral hospitals; however, they were conducted during the first wave of the pandemic, which could explain the variation in some used drugs. At that time, the recommendations issued by MINSA still suggested the use of azithromycin and did not expressly prohibit or exclude the use of ivermectin [33], as recommended by the Instituto de Evaluación de Tecnologías en Salud e Investigación of Seguridad Social de Salud (ÍETSI, EsSalud, by its Spanish acronym) [19] and by the Ministry of Health (MINSA) in May 2021 [34]. A study done in Lima between April and September 2020 revealed that before hospital admission, 44% of patients used some drug, 32% azithromycin, 28.9% ivermectin, and 20.7% corticosteroids.

Table 2
The prevalence of prehospital medication according to fatal outcomes.

Variables	n (%) 192 (100)	Consumption time (days)		Fatal result from COVID-19		
		media ±SD	median (range)	No 134 (69.8)	Yes 58 (30.2)	*p-value**
ANTIMICROBIALS						
Ivermectin						
No	145 (75.5)	2.1 ± 0.9	2 (1–5)	98 (67.6)	47 (32.4)	0.242
Si	47 (24.5)			36 (76.6)	11 (23.4)	
Macrolides						
No	138 (71.9)	3.6 ± 1.6	3 (0–8)	91 (65.9)	47 (34.1)	0.063
Si	54 (28.1)			43 (79.6)	11 (20.4)	
Ceftriaxone						
No	138 (71.9)	3.7 ± 1.7	3 (1–8)	101 (73.2)	37 (26.8)	0.101
Si	54 (28.1)			33 (61.1)	21 (38.9)	
Other antibiotics						
No	147 (76.6)	3.6 ± 1.7	3 (1–10)	107 (72.8)	40 (27.2)	0.102
Si	45 (23.4)			27 (60.0)	18 (40.0)	
Hydroxychloroquine						
No	190 (99.0)	4 ± 1.4	4 (3–5)	134 (70.5)	56 (29.5)	0.090
Si	2 (1.0)			0 (0.0)	2 (100.0)	
CORTICOSTEROIDS						
No	124 (64.6)	4.6 ± 5.0	3 (1–30)	93 (75.0)	31 (25.0)	**0.034**
Si	68 (35.4)			41 (60.3)	27 (39.7)	
COLCHICINE						
No	190 (99.0)	4 ± 1.4	4 (3–5)	134 (70.5)	56 (29.5)	0.090
Si	2 (1.0)			0 (0.0)	2 (100.0)	
WARFARIN						
No	150 (78.1)	3.4 ± 2.0	3 (1–8)	112 (74.7)	38 (25.3)	**0.005**
Si	42 (21.9)			22 (52.4)	20 (47.6)	
NSAIDS						
Aspirin						
No	181 (94.3)	5.2 ± 5.4	3 (1–20)	126 (69.6)	55 (30.4)	0.827
Si	11 (5.7)			8 (72.7)	3 (27.3)	
Other NSAIDs						
No	68 (35.4)	4.6 ± 2.4	5 (1–12)	47 (69.1)	21 (30.9)	0.880
Si	124 (64.6)			87 (70.2)	37 (29.8)	
OTHER MEDICINES						
Inhalers						
No	183 (95.3)	5.1 ± 3.5	4 (3–14)	130 (71.0)	53 (29.0)	0.090
Si	9 (4.7)			4 (44.4)	5 (55.6)	
Antihistamines						
No	160 (83.3)	3.6 ± 1.9	3 (1–8)	111 (69.4)	49 (30.6)	0.779
Si	32 (16.7)			23 (71.9)	9 (28.1)	
Acetylcysteine						
No	160 (83.3)	4.2 ± 2.3	4 (1–12)	115 (71.9)	45 (28.1)	0.160
Si	32 (16.7)			19 (59.4)	13 (40.6)	
Vitamin C						
No	182 (94.8)	6.1 ± 8.7	4 (1–30)	126 (69.2)	56 (30.8)	0.470
Si	10 (5.2)			8 (80.0)	2 (20.0)	

Table 2 (*continued*)

Variables	n (%) 192 (100)	Consumption time (days)		Fatal result from COVID-19		
		media ±SD	median (range)	No 134 (69.8)	Yes 58 (30.2)	*p-value**
Vitamin D						
No	188 (97.9)	4.8 ± 2.1	5 (2–7)	131 (69.7)	57 (30.3)	1.000
Si	4 (2.1)			3 (75.0)	1 (25.0)	
Zinc						
No	189 (98.4)	11.3 ± 16.2	3 (1–30)	131 (69.3)	58 (30.7)	0.555
Si	3 (1.6)			3 (100.0)	0 (0.0)	
Chlorine Dioxide						
No	191 (99.5)	2.0 ± 0.0	.	133 (69.6)	58 (30.4)	1.000
Si	1 (0.5)			1 (100.0)	0 (0.0)	

SD: standard deviation; NSAIDs: Nonsteroidal anti-inflammatory drugs.
Significant *p*-value of <0.05, found by chi-square test or Fisher test.

However, the frequency of some used drugs increased over the months [20]. In addition to the variation in official recommendations, the authors also suggested that drug infodemia could explain this increase [20].

Our study revealed that NSAIDs were the most commonly used drugs, contrary to previous studies, although these studies are not comparable because they were conducted in different cities and at a different stage of the pandemic. NSAIDs are widely used drugs in the country for different circumstances such as musculoskeletal pain [35], as may be found in patients with COVID-19. Some studies revealed that they were the most commonly self-medicated drugs before the pandemic, together with analgesics [21]. Although initially suspected, later reports ruled out the possibility that their use might increase the disease susceptibility [36]. Like NSAIDs, other self-medicated drugs were antibiotics; however, unlike studies during the first wave [31,32] where azithromycin was the most commonly used antibiotic, our study revealed macrolides and ceftriaxone in addition to ivermectin. A study at the Hospital Nacional 2 de Mayo in Lima also revealed an increased frequency of ceftriaxone before hospital admission during the first wave of the pandemic [20]. As noted by the authors, infodemia through social networks, conferences, chats, or daily conversations, sharing supposedly successful experiences of COVID-19 treatment, could explain the increased antibiotic usage before hospitalization, despite the known infrequent bacterial coinfections [20]. This is congruent with the persistence, almost 2 years after the beginning of the pandemic, in the discarded use of drugs by regulatory institutions, such as ivermectin or chlorine dioxide [37–39]. This means cultural and information dissemination aspects must be addressed as public health policies.

Our study revealed a significant frequency of self-medication of some medications as revealed in other investigations. A study in districts of Lima revealed that during the pandemic, self-medication included antibiotics together with anti-inflammatory drugs (39.2%), anti-inflammatory drugs alone (30.9%), antibiotics (21.6%), ivermectin (5.7%), and ivermectin in combination with other drugs (2.6%) [21]. A national referral hospital in Lima revealed that >3 out of 10 hospitalized patients self-medicated before admission [31]. In Cajamarca, a region in the northern highlands of the country, 60.3% of patients survived and 39.7% of those who died during hospitalization due to COVID-19 were self-medicated, most commonly with antibiotics, followed by corticosteroids and anticoagulants [40]. Self-medication against COVID-19 is not a problem only in Peru; a systematic review revealed that self-medication ranged from <4% to >88% in the general population, with antibiotics, chloroquine or hydroxychloroquine, paracetamol, vitamins or supplements, ivermectin, and ibuprofen as the most
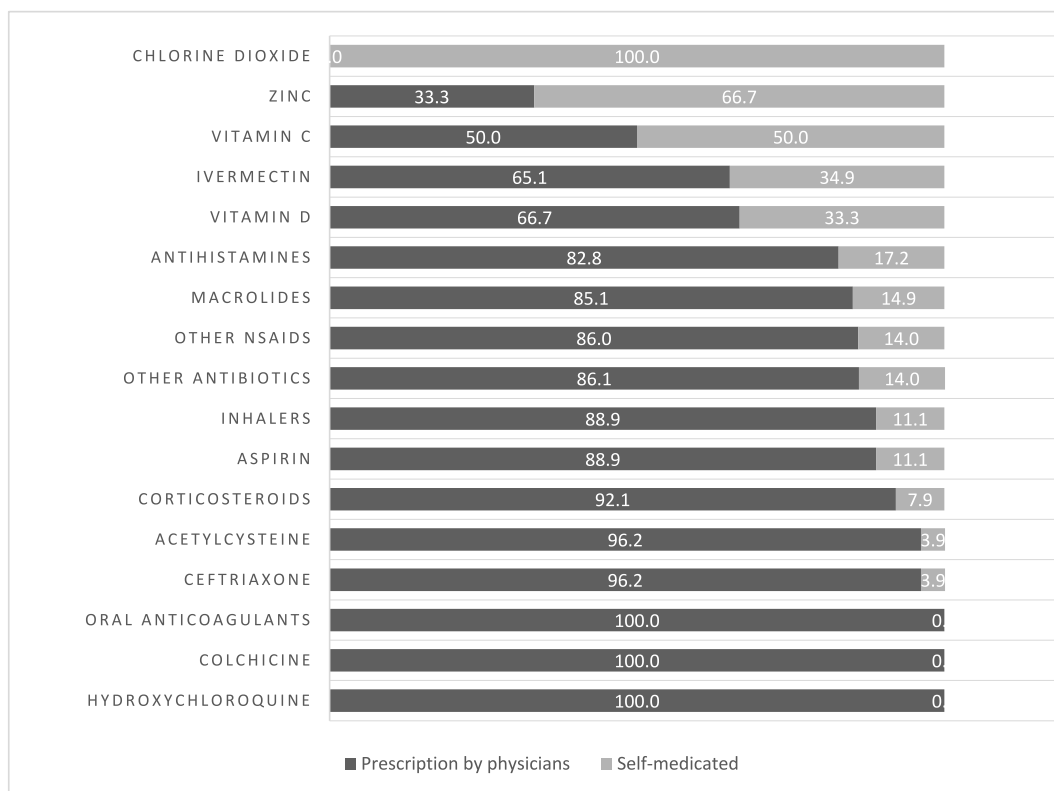
Fig. 2. Sources of procurement of prehospital medication.

Table 3
Cox regression models to assess the association between different drugs and the fatal outcome of COVID-19.

Drugs	Fatal result from COVID-19			
	Bivariate analysis cHR (95% CI)	p	Multivariate analysis aHR (95% CI)	p
Macrolides				
No	Ref.		Ref.	
Yes	0.70 (0.36–1.35)	0.283	0.47 (0.12–1.81)	0.272
Ceftriaxone				
No	Ref.		Ref.	
Yes	1.24 (0.72–2.12)	0.440	0.67 (0.22–2.02)	0.472
Ivermectin				
No	Ref.		Ref.	
Yes	0.85 (0.44–1.65)	0.628	1.75 (0.60–5.14)	0.307
Corticosteroid				
No	Ref.		Ref.	
Yes	1.57 (0.93–2.63)	0.090	4.99 (1.46–17.06)	**0.010**
Warfarin				
No	Ref.		Ref.	
Yes	1.68 (0.97–2.90)	0.062	2.44 (0.75–7.92)	0.139
Nonsteroidal anti-inflammatory				
No	Ref.		Ref.	
Yes	0.99 (0.58–1.71)	0.977	1.72 (0.60–4.95)	0.312

cHR: Crude Hazard Ratio; aHR: Adjusted Hazard Ratio; 95% CI: 95% confidence interval.
Hazard ratios and confidence intervals were calculated considering the epidemiological model. *P*-values of <0.05 are in bold.
The proportional hazards assumptions of the Cox models using Schoenfeld residuals were greater than 0.05.
*Each drug was adjusted for age, comorbidities, number of neutrophils, number of lymphocytes, oxygen saturation on admission, creatinine, lactate dehydrogenase, and D-dimer level.

commonly used medications [14]. Self-medication in patients with known chronic pathologies may be an advantage [41]; however, in anti-COVID-19 drugs, several reports warned about adverse effects without clear clinical utility [14,15]. This was aggravated by inappropriate drug prescription by physicians and self-medication in the population for the fear of contracting the disease or developing a serious condition. A nationwide study revealed that 22.1% and 83.7%, 59.7% and 80.2%, and 8.0% and 16.8% used some type of medication, medicinal plant, or chlorine dioxide for the prevention and control of COVID-19, respectively [23]. This practice was favored by the medication perception as potential "miracle cures," as well as, by the individual, social, cultural, and organizational characteristics that influence this behavior [42].

We revealed that one in three hospitalized patients due to COVID-19 developed a fatal outcome, where age, personal history of diabetes, oxygen saturation at admission, and elevated laboratory indicators of systemic inflammation were identified as significant risk factors. Therefore, these factors have been associated with mortality or severe disease due to COVID-19 in previous international [26,27,43] and national studies [31,44,45]. However, to our knowledge, none of these studies considered prehospital medication as a risk factor for fatal outcomes. This background is an important point to consider since the prehospital medication could generate the appearance of adverse reactions, drug-drug interactions, and the feeling of protection or improvement in patients with COVID-19, leading to a delay in seeking medical help in hospitals.

Fatal outcomes were five times higher among those who use corticosteroids, the second most commonly used drug before hospitalization. Previous meta-analyses showed that corticosteroid use in non-severe cases delays clearance of SARS-CoV-2 does not reduce the rate of ICU admission, and does not improve the survival rate [46,47]. Corticosteroid therapy is beneficial in patients who develop severe disease and require respiratory support [47]. This was supported by the results of the RECOVERY trial, which revealed that the use of dexamethasone improved survival in patients with severe COVID-19 [48]. Thus, the appropriate timing of corticosteroid administration is one of the main determinants for the beneficial effect of COVID-19 treatment. Thus,
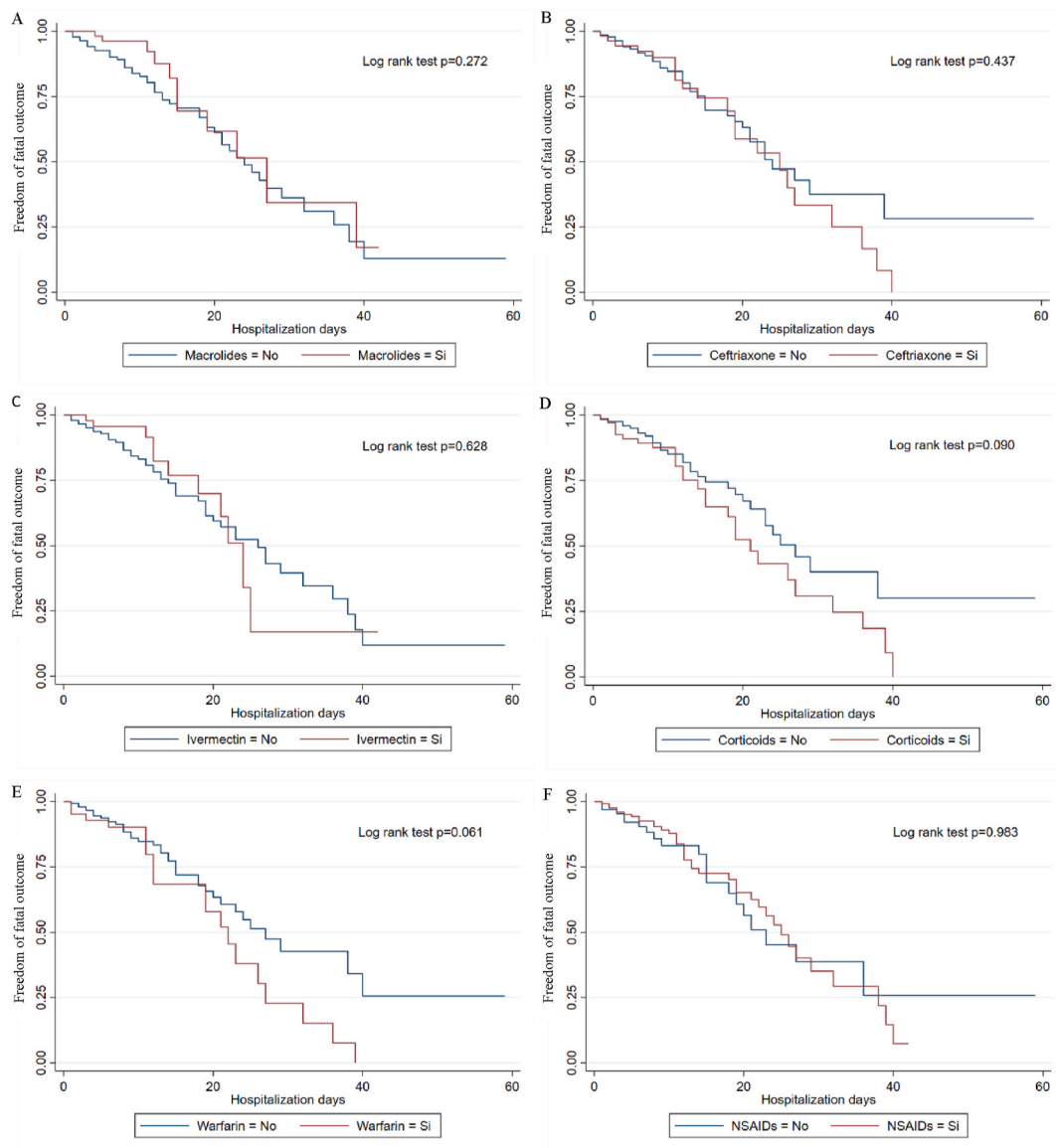
Fig. 3. Kaplan–Meier survival curve according to treatment with (A) macrolides, (B) ceftriaxone, (C) ivermectin, (D) corticosteroids, (E) warfarin, and (F) nonsteroidal anti-inflammatory drugs (NSAIDs).

outpatient use of corticosteroids without any strict control of the dose or therapeutic regimen could lead to worse outcomes, as shown in our sensitivity analyses where we considered the role of corticosteroids at different time intervals. Throughout the pandemic, corticosteroids were used for mild case management and even in asymptomatic patients, to avoid the need for high-flow oxygen, ICU admission, or mortality [49, 50], although this practice is not supported by quality evidence [9,51]. However, the indiscriminate use of corticosteroids in patients with non-severe COVID-19 disease may cause adverse effects or a negative clinical course [51–53].

4.3. Implications and recommendations for public health

At the beginning of the pandemic, the official recommendations of the Peruvian state showed little transparency in their elaboration [18]; however, with the inclusion of drugs without proven usefulness [33], there are currently evidence-based recommendations for outpatients in the country [19]. This contrasts with the used drugs in our study, which could mean a problem in socializing these documents among health professionals. This is particularly important in the case of the

recommendations regarding the type of patient with COVID-19 in whom corticoids should be used [19]. Likewise, unifying the message regarding the use of recommended medications among our health authorities is necessary, since otherwise, it may give rise to contradictory messages and encourage the use of medications without evidence or self-medication [21,54]. Many outpatients likely resort to self-medication due to our health system oversaturation, thus reinforcing strategies such as telemedicine or primary care may reduce it [55, 56]. Finally, boosting the media and governmental public messages regarding the care to prevent the disease spread and the rational use of drugs among the general population with simple and clear messages to avoid health risks.

4.4. Limitations and strengths

The main limitation of the study was its retrospective nature, thus examining some confounding variables of interest, such as clinical characteristics (weight, body mass index, nutritional status before hospitalization, time of symptoms, etc.) or personal history (harmful habits, physical activity, etc.), was impossible to record because these data were

not recorded upon hospital admission in most patients. Additionally, there were clinical (heart rate, respiratory rate, and oxygen saturation) and laboratory factors (TGO, TGP, CRP, lactate dehydrogenase, and D-money) that were not measured in all patients. However, the lack of information on the variables was not considerable. Another limitation that we found during data collection was that the information on patients with severe or critical condition was reported by family members, who may not be fully aware of the medications used by the patients. Another limitation to consider was that the study was performed in a single social security health center with non-probabilistic sampling, thus a specific part of the population with different characteristics from the general population possibly affected by COVID-19 was captured. Therefore, our results are not necessarily extrapolable to other health systems, but they are considered in other realities due to the strength of found association in the present study. Therefore, prospective studies with the inclusion of a larger number of patients, which are multicenter and have more detailed information, are needed. Finally, many of the recorded data in the clinical history were possibly not adequately measured (vital signs). However, only variables with complete data that were measured through reliable instruments were entered for the multivariate analysis.

5. Conclusion

In conclusion, three out of four patients used some type of medication before hospital admission. The fatal outcome in hospitalized patients due to COVID-19 was five times higher among those who used corticosteroids before hospital admission.

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CRediT authorship contribution statement

Brenda Caira-Chuquineyra: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Daniel Fernandez-Guzman:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Priscilla MA. Alvarez-Arias:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Ángel A. Zarate-Curi:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Percy Herrera-Añazco:** Formal analysis, Writing – original draft, Writing – review & editing. **Vicente A. Benites-Zapata:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2022.102472.

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