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Pharmacotherapy and clinical outcomes of hospitalized COVID-19 patients in Chile during the first wave of pandemic

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ABSTRACT

Background: *The largest growth in cases of COVID-19 worldwide during 2020 was in the Americas, and Chile was one of the most affected countries.* ***Aim:*** *To describe, characterize, and evaluate the use of drugs as treatment for COVID-19 in hospitalized patients in Chile during the first wave of the pandemic.* ***Methods:*** *We performed a multicenter, observational study that included 442 patients with confirmed SARS-CoV-2 infection admitted in Chilean hospitals between March 21 and September 22, 2020. The analysis included demographics, comorbidities, specific drug therapy, and outcomes over a 28-day follow-up period.* ***Results:*** *The median age of patients was 68 years (IQR 55-73), and 38.9% were women. The most common comorbidities were hypertension (57.7%) and diabetes (36.9%). Fifty-seven (12.9%) patients died. Hypertension (HR 2.99; CI 95% 1.43-6.26) and age ≥ 65 (2.14; CI 95% 1.10- 4.17) were the main predictors of mortality. Primary drugs were azithromycin (58.8%) and corticosteroids (51.1%). In this sample, azithromycin was a protective factor regarding mortality (HR 0.53; CI 95% 0.31-0.90), increasing clinical improvement and avoiding progression.* ***Conclusions:*** *The patterns of use of drugs to treat COVID-19 in Chile during the first wave of the pandemic were very dynamic and followed the international, evidence-based guidelines. The low mortality rate indicates that the clinical management of hospitalized patients was adequate.*

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Key words: *Coronavirus; Severe Acute Respiratory Syndrome; Azithromycin; Adrenal Cortex Hormone; South America.*

Farmacoterapia y desenlaces clínicos de pacientes de COVID-19 hospitalizados en Chile durante la primera ola de pandemia

Antecedentes: *Durante 2020, el mayor incremento de casos de COVID-19 se observó en el continente americano, donde Chile fue uno de los países más afectados.* ***Objetivos:*** *Describir, caracterizar y evaluar el uso de fármacos indicados para tratar el COVID-19 en pacientes hospitalizados en Chile durante la primera ola de pandemia.* ***Pacientes y Métodos:*** *Un estudio multicéntrico*

observacional incorporó a 442 pacientes con infección confirmada por SARS-CoV-2 admitidos en hospitales chilenos entre el 21 de marzo y el 22 de septiembre de 2020. Se analizaron variables demográficas, comorbilidades, terapia farmacológica específica y desenlaces clínicos para un período de seguimiento de 28 días. ***Resultados:*** *La mediana de la edad fue de 68 años (RIC 55-73), y un 38,9% fueron mujeres. Las comorbilidades más comunes fueron hipertensión (57,7%) y diabetes (36,9%). Cincuenta y siete (12,9%) de los pacientes murieron. Los principales predictores de mortalidad fueron la hipertensión (HR 2,99; IC 95% 1,43-6,26) y la edad ≥ 65 años (2,14; IC 95% 1,10- 4,17). Los fármacos más utilizados fueron azitromicina (58,8%) y corticosteroides (51,1%). En esta muestra, la azitromicina fue un factor de protección respecto a la mortalidad (HR 0,53; IC 95% 0,31-0,90), incrementando igualmente la mejoría y evitando la progresión.* ***Conclusiones:*** *Los patrones de uso de fármacos para tatar COVID-19 en Chile durante la primera ola de pandemia fueron muy dinámicos y siguieron las directrices internacionales basadas en la evidencia. La baja mortalidad sugiere que el manejo de los pacientes hospitalizados fue adecuado.*

Palabras clave: *Coronavirus; Síndrome Respiratorio Agudo Severo; Azitromicina; Corticosteroides; Sudamérica.*

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO). During 2020, the largest growth in cases of COVID-19 was in the Americas, being Brazil, Peru, and Chile, some of the countries with more cumulative cases per million inhabitants[1,2].

COVID-19 entered Chile on March 3, 2020 and a drastic increase in daily incidence rate occurred between May and July[3]. Incidence had decreased by August 2020 due to the tightening of health policy strategies such as lockdown, social distancing and facemasks. However, more than 460,000 cases of COVID-19 and 15,000 deaths was the balance for the first wave of pandemic in Chile[3,4]. A second, more severe and prolonged wave of COVID-19 was observed in Chile in 2021[5]. Fortunately, the success of the mass vaccination campaign[6] significantly reduced the number of new cases, hospitalizations and deaths[5].

Large studies on risk factors and predictors of mortality started along the first wave of pandemic, being at that time SARS-CoV-2 infection a poorly understood disease[7-10]. Given the absence of effective therapies regulatory agencies worldwide issued emergency use authorizations for new and repositioned drugs with known or putative antiviral or immunomodulating effects[11]. Consequently, disparate clinical drug regimens were used to treat COVID-19, based on early observations from China[12], France[13] and the United States of America[14]. By the end of 2020 WHO guidelines established dexamethasone as the recommended therapy to manage COVID-19 considering the results of a large clinical trial[15]. In 2021, other drugs were also recommended by WHO, such as IL-6 receptor blockers and neutralizing monoclonal antibodies[16], allowing evidence-based, more standardized treatments for COVID-19 in subsequent pandemic waves.

Since the outbreak of COVID-19 countless studies aimed to evaluate the effectiveness of specific therapies have been conducted worldwide. However, few studies have documented and characterized at a domestic level the diversity of drugs indicated as treatment for COVID-19. This information is relevant to assess the reaction of countries to sanitary crises and to improve care management facing subsequent pandemic waves. In the present study, we describe, characterize, and evaluate the use of drugs as treatment for COVID-19 in hospitalized patients in Chile during the first wave of pandemic.

Methodology

Design

A multicenter, observational study was carried out in 13 Chilean public hospitals between March and September 2020.

Ethical considerations

This study was approved by the Scientific Ethics Committee of the Valdivia Health Service (Ord. 100, April 15, 2020). Being this Committee accredited by Chilean Health Authority, their approvals have national effectiveness. Given the sanitary crisis, the approval of the study exempted researchers of obtaining informed consent from patients.

Study population

Population was comprised by confirmed of SARS-CoV-2 infected patients, with a positive result of real-time reverse transcriptase–polymerase chain reaction assay, who were admitted to high or median complexity hospitals. A non-probabilistic, convenience sampling was carried out for patients' enrollment.

Study protocol

Information was obtained from medical records and entered by the researchers into a web hosted, electronic case report form (eCRF). The eCRF was a modified version of a form developed and kindly shared by the Spanish Society of Hospital Pharmacy. The registered variables included demographic data, comorbidities, COVID-19 pharmacotherapy, signs, and symptoms at admission and during hospitalization, chest radiographic findings at admission and follow-up, development of acute respiratory distress syndrome, admission to ICU and need for mechanical ventilation. Patient clinical status was evaluated for up to 28 days of hospitalization or until discharge or death if these occurred earlier.

Outcomes

The primary outcome was mortality from all causes up to day 28. Secondary outcomes were progression of disease within the follow-up period and clinical improvement. Disease severity was categorized according to NIH COVID-19 treatment guidelines[17]. Progression was defined as transition throughout disease severity: from mild-moderate to severe or from mild-moderate/severe to critical. Clinical improvement was established as improvement of symptoms plus radiological improvement and/or PaO_2/FiO_2 <300 mm Hg and/or SpO_2 > 93% with no supplemental oxygen.

Statistical analysis

For descriptive statistics, results were expressed as frequencies and percentages. Age was expressed as median and interquartile range (IQR). For univariate analysis, comparison between categorical data was done using Chi-squared test and comparison between quantitative variables was done using Mann-Whitney U-test. For categorical variables, if the patient's eCRF did not include information on a clinical characteristic it was assumed as not present, with a limit of 20% for lost data. To study risk and protection factors, binary logistic regression and Cox proportional hazard regression analyses were performed. Odds ratio (OR) and Hazard ratio (HR) were calculated for logistic and Cox regression, respectively. All risk measures were expressed with 95% confidence interval. Statistical significance was defined as p-value < 0.05. All statistical tests were performed using IBM SPSS v.23.

Results

Demographic variables

The sample was composed of 442 patients from twelve hospitals of high-complexity and one of medium-complexity, according with Chilean classification. Patients enrolled were in seven of sixteen administrative regions of Chile and 160 (36.2%) were in the Metropolitan Region of Santiago. The median age was 68 years (IQR 55-73), with 55.9% of patients aging 65 years or older; 38.9% of patients were female. Regarding comorbidities, 29.4% of patients had none, 24.7% had one, 24.9% had two and 21% had three or more. The most common comorbidity was hypertension (57.7%), followed by diabetes (36.9%), immunodepression (9.3%), chronic obstructive pulmonary disease (COPD) (8.1%), neurological disorders (7.9%), and renal failure (6.8%) (Table 1). In this study, body mass index (BMI) was only recorded for 168 patients, accounting for 38% of the sample. Since the proportion of missing

Table 1. Demographics and comorbidities of patients

Characteristic	All patients (n = 442)	Non survivors (n = 57)
Demographic and baseline	**n (%)**	**Characteristic Y/N n (%)**
Age ≥ 65 years	247 (55.9)	45 (18.2) / 12 (6.2)
Diabetes	163 (36.9)	27 (16.6) / 30 (10.8)
Hypertension	255 (57.7)	47 (18.4) / 10 (5.3)
COPD	36 (8.1)	8 (22.2) / 49 (12.1)
Asthma	21 (4.8)	6 (28.6) / 51 (12.1)
Other respiratory disease	7 (1.6)	3 (42.9) / 54 (12.4)
Heart failure	22 (5.0)	4 (18.2) / 53 (12.6)
Ischemic cardiomyopathy	18 (4.1)	7 (38.9) / 50 (11.8)
NIC	24 (5.4)	5 (20.8) / 52 (12.4)
Renal failure	30 (6.8)	9 (30.0) / 48 (11.7)
Cirrhosis	3 (0.7)	1 (33.3) / 56 (12.8)
Neurological disorder	35 (7.9)	8 (22.9) / 49 (12.0)
Immunodepression	41 (9.3)	13 (31.7) / 44 (11.0)

COPD, chronic obstructive pulmonary disease; NIC, non-ischemic cardiomyopathy.

Table 2. Therapy against SARS-CoV-2 either monotherapy or combination

Therapy	All patients (n = 442) n (%)	ICU patients (n = 213) n (%)
No specific therapy	46 (10.4)	11 (5.2)
Lopinavir-ritonavir	32 (7.2)	31 (14.6)
Hydroxychloroquine	154 (34.8)	96 (45.1)
Azithromycin	260 (58.8)	134 (62.9)
Tocilizumab	3 (0.7)	3 (1.4)
Corticosteroids	226 (51.1)	133 (62.4)
Heparins	95 (21.5)	44 (20.7)
Convalescent plasma	8 (1.8)	6 (2.8)

data exceeded the 20%, multiple imputation was discarded, and BMI was not integrated into subsequent analyses.

Pharmacotherapeutic variables

Prior to hospitalization, 169 (38.2%) of patients were under treatment with angiotensin-converting enzyme Inhibitors or angiotensin II receptor blockers. Forty-six (10.4%) patients did not receive specific therapy for SARS-CoV-2 infection, while 119 (26.9%) were treated with a single drug, 190 (43.0%) with two drugs, and 87 (19.8%) with 3 or more drugs. The most common therapy, either as monotherapy or combination was azithromycin, followed by corticosteroids, hydroxychloroquine, and high-dose heparins (Table 2). Other therapies, such as lopinavir/ritonavir, convalescent plasma or tocilizumab, were indicated in less than 10% of patients. Monotherapy strategies were mainly based on corticosteroids (14.0%) or azithromycin (9.3%). The most common therapies for patients in intensive care units (ICU) were azithromycin (62.9%), corticosteroids (62.4%) and hydroxychloroquine (45.1%)

(Table 2). The time between onset of symptoms and the first dose was 7.0 days (IQR 5.0-11.0) for azithromycin, 7.0 days (IQR 5.0 -10.0) for hydroxychloroquine, 10.0 days (IQR 6.3-14.8) for corticosteroids and 12.0 days (IQR 8.0-16.0) for heparins. Azithromycin, corticosteroids and heparins were indicated throughout the study, while hydroxychloroquine only from March to May, disappearing by the third week of June 2020 (Figure 1).

Clinical variables

At hospital admission, 24.0% of patients were in mild to moderate condition, 69.2% in severe condition, and 6.8% in critical condition. Table 3 shows therapies against SARS-CoV-2 infection by disease severity at hospital admission. Patients admitted in mild-moderate condition were significantly more likely to be treated with hydroxychloroquine or azithromycin than with corticosteroids or heparins ($p < 0.05$).

Predictors of Mortality and Clinical Improvement

Mortality

Median age of patients was 73 (67.5-78.0) years old for those who died and 65 (53.5-73.0)

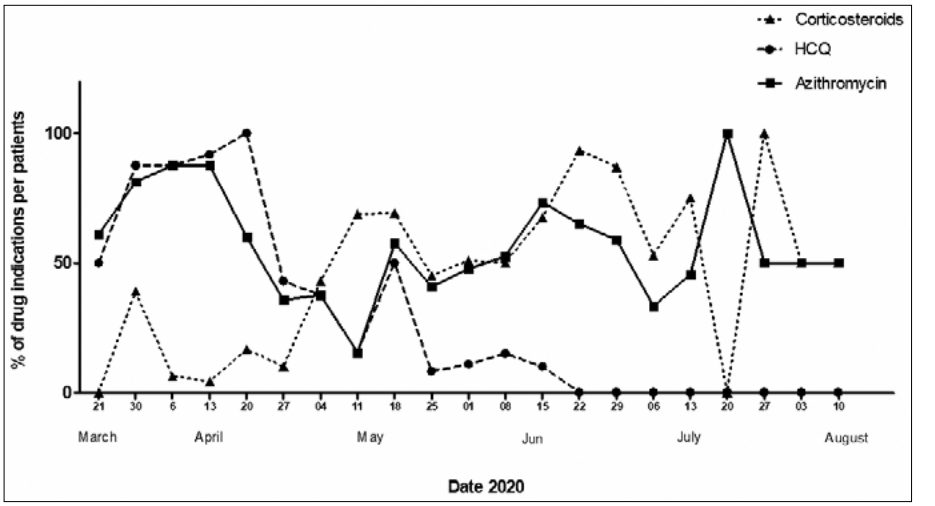

Figure. 1. Time-course of use of specific therapies in hospitalized COVID-19 patients in Chile between March and August 2020. Lines show the percentage of indications per patients enrolled that week (azithromycin and hydroxychloroquine) or the previous week (corticosteroids). HCQ: hydroxychloroquine.

Table 3. Therapies against SARS-CoV-2 infection by disease severity at hospital admission

	Disease severity No (%)		
Therapy	**Mild-moderate**	**Severe**	**Critical**
No targeted therapy	17 (37.0)	28 (60.9)	1 (2.2)
Hydroxychloroquine	47 (30.5)	102 (66.2)	5 (3.2)
Azithromycin	73 (28.2)	172 (66.4)	14 (5.4)
Corticosteroids	19 (8.4)*	181 (80.1)	26 (11.5)
Heparins	9 (9.5)*	74 (77.9)	12 (12.6)

Asterisks indicate significative differences among proportions, comparing with those of other strategies. *$p < 0.05$.

for survivors, being these medians significantly different ($p < 0.05$). Fifty-seven (12.9%) patients died over the 28-day of follow-up. In this study, 71.7% of patients achieved clinical improvement and 15.4% were still on treatment at day 28. Concerning ICU, 48.2% of the patients were admitted; among them, 15.0% died over the follow-up period and 71.4% achieved clinical improvement. There was no association between ICU admission and outcomes ($p > 0.05$).

A multivariate analysis considering main therapies and potential risk factors showed that aging, hypertension, asthma and immunodepression were independent predictors of mortality being hypertension the most relevant risk factor with an OR of 4.40 (95% CI 1.52-7.62, $p < 0.01$). Regarding therapies, azithromycin significantly reduced the risk of mortality (OR of 0.49 (95% CI 0.25-1.00, $p < 0.05$)) (Table 4). Multivariate time-to-event analyses for therapies and predictors of mortality confirmed azithromycin as a protective factor in this sample, with a HR of 0.53 (95% CI 0.30-0.91, $p<0.05$) (Figure 2). For hydroxychloroquine HR was 0.52 (95% CI 0.27-1.00), 1.02 (95% CI 0.58-1.79) for corticosteroids and 1.20 (95%CI 0.68-2.13) for heparins, all these with p values > 0.05.

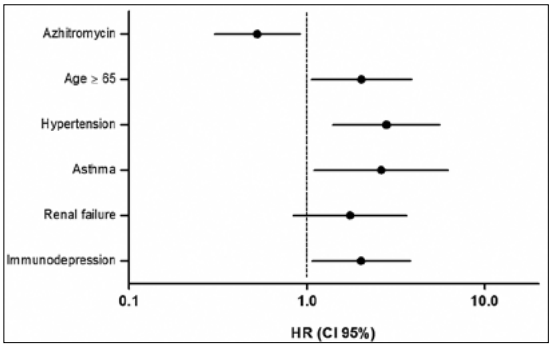

Figure 2. Azithromycin and predictors of in-hospital mortality of COVID-19 patients in Chile during the first pandemic wave. HR, hazard ratio; RD(OA), respiratory disease other than asthma (also excludes chronic pulmonary respiratory disease).

Clinical improvement and disease progression

In a multivariate analysis for the main therapies, azithromycin decreased the risk of not achieving clinical improvement, with an OR of 0.59 (95%CI 0.37-0.93 $p < 0.05$). Contrarily, heparins appeared as a risk factor, with an OR of 2.18 (95%CI 1.31-3.62 $p<0.01$) (Figure 3).

To avoid potential biases due to the uneven distribution of therapies throughout "disease

Table 4. Independent predictors of in-hospital mortality of patients receiving targeted therapy against SARS-CoV-2

	OR (95% CI)	p value
Hydroxychloroquine	0.91 (0.40-2.12)	NS
Azithromycin	0.49 (0.25-1.00)	0.046
Corticosteroids	1.48 (0.75-2.97)	NS.
Heparins	1.24 (0.60-2.54)	NS
Age ≥ 65	2.65 (0.30-5.43)	0.008
Diabetes	0.84 (0.44-1.61)	NS
Hypertension	4.40 (1.52-7.62)	0.003
COPD	0.83 (0.36-2.16)	NS
Asthma	3.21 (1.00-10.30)	0.050
Other respiratory disease	2.45 (0.48-12.55)	NS
Ischemic cardiomyopathy	1.43 (0.44-4.70)	NS
Renal failure	2.90 (1.09-7.70)	0.033
Neurologic disorder	0.76 (0.29-1.94)	NS
Immunodepression	2.59 (1.16-5.84)	0.022

COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

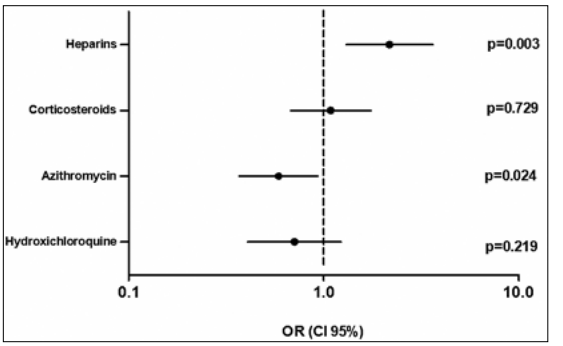

Figure 3. Specific therapies in hospitalized COVID-19 patients in Chile and the probability of not achieving clinical improvement along a 28-days follow-up. OR, odds ratio.

severity at hospital admission", the multivariate analysis was conducted according to this variable to study disease progression. For patients admitted in severe condition, a significant association between the use of azithromycin and less progression (OR 0.46, 95%CI 0.27-0.78, $p < 0.01$) was found. No associations were found for patients admitted in mild to moderate condition.

Discussion

The present study was aimed to describe, characterize, and evaluate the drugs indicated to treat COVID-19 in hospitalized patients in Chile during the first wave of pandemic. Azithromycin, corticosteroids, and hydroxychloroquine were the most widely indicated drugs, although the use of hydroxychloroquine stopped in June 2020. Azithromycin produced clinical benefits in our sample.

Clinical features of our patients tend to corroborate the representativeness of the sample. The proportion of males is concordant with a large body of literature. Whilst there is no difference in the proportion of males and females, males experience both a higher severity and fatality for COVID-19 infection[18,19]. Concerning age of patients, our observation is in agreement with international studies based on large populations[7,9,10,20] describing median ages of more than 60 years in the first pandemic wave. Preexisting hypertension and diabetes were highly prevalent in our COVID-19 patients, as it has been described in other studies[13-24]. Regarding the 12.9% mortality rate of our sample, it was very close to that previously reported in hospitalized patients in Chile[21,22]. This mortality is lower than that reported in several countries such as United Kingdom[7], Spain[9] and USA[10] for the first wave of pandemic, where mortality rates ranged from 24% to 28%. The dissimilarity was also identifiable in global data accounting cumulative confirmed COVID-19 deaths per million people[25].

Azithromycin was the most used drug for hospitalized COVID-19 patients in Chile during the first wave of pandemic, being proposed as a therapy shortly after the onset of the pandemic considering its immunomodulatory properties[26]. Early observational reports[13,27] encouraged the prescription of hydroxychloroquine plus azithromycin in Chile as in other countries, but the lack of benefit of hydroxychloroquine in subsequent clinical trials[28,29] leaved the combination unsupported in 2020. The fact that WHO warning was specific on hydroxychloroquine[30], explains that azithromycin remained as a therapeutic tool in Chile. Conversely, the time-course of corticosteroid utilization in Chile showed an increase along 2020. When SARS-CoV-2 infection arose, the precept was a lack of effectiveness and possible harm of corticosteroids in SARS[31] and its use was not recommended[32]. The clinical benefit of dexamethasone reported by RECOVERY Collaborative Group[15] promoted the gradual increase of corticosteroids utilization in Chile, which was also in agreement with WHO Guidelines. The present study shows that the pattern of use of drugs during the first wave of pandemic in Chile was dynamic and adopted evidence-based guidelines.

The diversity of drugs used during the first wave of pandemic gives a unique scenario for a discussion, considering the updated knowledge on therapies for COVID-19. Regrettably, whereas observational designs allow the study of risk factors they have inherent limitations to evaluate effectiveness of drug therapy, and results about drug protectiveness can be considered as illustrative but not predictive. In our sample hydroxychloroquine, commonly administered along azithromycin, did not produce clinical benefits. These results are in agreement with clinical trials of hydroxychloroquine in COVID-19[28,33]. Regarding corticosteroids, our results are apparently unreasonable because dexamethasone has been

an effective therapy in SARS-CoV-2 infections since 2020. Real-world analyses are different from those of clinical trials. As an example, in the RECOVERY trial for dexamethasone more than 60% of patients did not receive specific therapy against COVID-19 in the comparator arm[15], whereas in observational studies all therapies are simultaneously compared. Thus, the proper statement for our sample is that corticosteroids were less effective than azithromycin in patients with major predictors of mortality. The protectiveness of the macrolide is the true odd finding here. A number of clinical trials confirmed that azithromycin does not improve clinical outcomes in COVID-19 either in hospital[34,35] or community setting[36-38]. In RECOVERY trial for azithromycin, most of those patients received previous treatment with corticosteroids, while in Chile azithromycin started before corticosteroids when both concurred. In other clinical trial, azithromycin was evaluated as an add-on over hydroxychloroquine, which represented the standard of care in Brazil at that time[35]. Consequently, it is not responsible to discuss the present results considering those of clinical trials, not only due to the limitations of our design but because they represent disparate clinical circumstances. Otherwise, clinical trials in community settings also encompasses factors that are not part of the present study, such as unconfirmed cases and adherence issues[39,40]. Interestingly, a recent clinical trial reported therapeutic efficacy of azithromycin or clarithromycin in management of patients with mild COVID-19, not being these patients exposed to corticosteroids[41].

The present study has several limitations. As it was previously stated, observational designs cannot draw causal inferences about protectiveness. Moreover, the non-probabilistic sampling also limits the scope of conclusions.

Conclusion

The patterns of use of drugs to treat COVID-19 in Chile during the first wave of pandemic was dynamic and followed the international evidence. Consequently, hydroxychloroquine was abandoned favoring corticosteroids. Considering the low mortality rate observed in the same period, it is possible to state that the clinical management of hospitalized patients in Chile was adequate. The results on effectiveness of azithromycin in this study, although merely illustrative, are difficult to contextualize since clinical trials on this drug represent disparate clinical circumstances. The results of the present study are relevant to evaluate the domestic reaction to COVID-19 and to improve care management facing future pandemic waves which are possible despite the successful vaccination campaigns.

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