Clinical Outcome of Patients with COVID-19 Pneumonia Treated with Corticosteroids and Colchicine in Colombia

Miguel Alejandro Pinzón (alejandropinzon01@yahoo.es)
Clinica Medellin
Doris Cardona Arango
Universidad CES
Juan Felipe Betancur
Clínica Medellín
Héctor Holguín
Clinica Medellin
Carolina Arias Arias
Universidad CES
Bernardo Javier Muñoz
Clínica Medellín
Michael Amarillo
Clinica Medellin
Juan Felipe Llano
Clínica Medellín
Pablo Montoya
Clinica Medellin

Research

Keywords: Coronavirus, COVID-19, Colchicine, Corticosteroids, Pneumonia

Posted Date: October 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-94922/v1

Version of Record: A version of this preprint was published at Annals of Clinical Microbiology and Antimicrobials on September 14th, 2021. See the published version at https://doi.org/10.1186/s12941-021-00460-9.

Abstract

Background: To date, there is no specific antiviral therapy for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) that causes Coronavirus disease 2019 (Covid-19). Since there is no specific therapy against SARS-CoV2, current efforts aim to prevent contagion through public health measures and develop a protective vaccine. While waiting for the latter, it is necessary to evaluate the drugs that at least, in initial studies, suggested some degree of utility in the management of Covid-19 or its complications.

The Objective of the study was to describe the clinical manifestations and outcomes of patients with severe Covid-19 Pneumonia treated with corticosteroids and colchicine.

Materials and Methods: A cross sectional study of 301 adult patients with Covid-19 Pneumonia confirmed by Real-Time Polymerase Chain Reaction for SARS-CoV2 (RT-PCR SARS-CoV2), Berlin protocol, who required hospitalization in three hospitals in Antioquia, Colombia. Patients were treated according to the institutional protocol (from March 20, 2020 to June 30, 2020) with corticosteroid if the patient required supplemental oxygen. From July 1, 2020, the management protocol changed with the addition of colchicine to all patients admitted to the institutions. The treatment was supervised and monitored by the same specialist in infectology of the institutions.

We describe the clinical manifestations and outcomes of the patients who received these treatments. The patient's information was analyzed according to the outcome of interest (alive/dead) with univariate, bivariate, and multivariate measures to adjust the variables that presented statistical association.

Results: All patients had pneumonia documented by chest computed tomography with ground glass images and presented an alveolar pressure / inspired oxygen fraction (PaFi) less than 300. 240 (79.7%) of patients received corticosteroids, and 145 (48.2%) also received colchicine; of these, 14 (9.6%) died vs. 23 (14.7%) of those who did not receive it. Hospital mortality due to severe Covid-19 Pneumonia was 12.3% in three hospitals in Colombia.

Conclusions: Treatment with corticosteroids and colchicine for managing patients with severe Covid-19 pneumonia was associated with low mortality at the hospital level. Randomized, placebo-controlled studies are required to evaluate the effect of corticosteroids and colchicine on complications or death from Covid-19.

Introduction

Coronavirus disease 2019 (Covid-19) is caused by the virus classified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), an emerging pathogen initially identified in Wuhan-China, in December 2019 (1). Until August 29, 2020, 25,078,215 infected and 844,515 deaths have been identified globally. (2) with 5% lethality and greater extension than previous SARS-CoV and MERS-CoV epidemics (3).

In the Americas, as of August 29, 2020, 13,018,693 cases had been reported, 458,628 deaths with a fatality of 3.52% (4). In Colombia, the first case was reported, on March 6, 2020, in a 19-year-old patient from Milan, Italy (5). By August 29, 2020, 582,022 cases and 18,468 deaths were confirmed for a fatality of 3.1%.

The clinical manifestations are diverse; some patients present Pneumonia, with fever, cough, dyspnea, and headache as cardinal symptoms (6), but asymptomatic infections and multi-organ involvement have also been described (7).

To date, there is no antiviral drug treatment or vaccine for the prevention and treatment of Covid-19 (8). The experience obtained in the pharmacological treatment of the previous SARS-CoV and MERS-CoV epidemics has been extrapolated to the current pandemic, the results of the few studies carried out to date for COVID-19 being controversial. In vitro studies demonstrated antiviral activity against SARS-CoV-2 from Hydroxychloroquine (9) and Lopinavir/Ritonavir (10), although its clinical use did not show a decrease in mortality, as did remdesivir (11) Azithromycin was evaluated in non-randomized clinical studies for Covid-19. (12). There have also been some experimental studies with different glucocorticoids and biological drugs such as Tocilizumab. However, so far, the only therapy that has been shown to decrease mortality from Covid-19 was dexamethasone (13).

In a small randomized clinical study, Greek researchers evaluated colchicine's effect on cardiac and inflammatory markers in patients infected with Covid-19. Although they did not find differences in biomarkers concerning standard therapy, they showed less clinical deterioration determined by less mechanical ventilation and death in 55 patients who received colchicine than the conventional therapy group. (14).

Since there is no specific therapy against SARS-CoV2, current efforts aim to prevent contagion through public health measures and develop a protective vaccine. (15) While waiting for the latter, it is necessary to evaluate the drugs that at least, in initial studies, suggested some degree of utility in the management of Covid-19 or its complications, such as Acute Respiratory Distress Syndrome (ARDS) or cytokine storm. This study's objective was to describe the clinical manifestations and outcomes of patients with severe COVID-19 Pneumonia treated with corticosteroids and colchicine.

Materials And Methods

An observational study was conducted in three clinics in Antioquia (two in Medellín and one in Apartadó), a department located in the northwest of Colombia. Its capital is Medellin, the second most populated city in Colombia; aside, Apartadó is a municipality located in the Urabá subregion located 310 kilometers from Medellin, whose hospital is a second-level reference center of the region.

The included patients were older than 18 years hospitalized for Covid-19 Pneumonia, confirmed positive by Real-Time Reverse Transcription Polymerase Chain Reaction for SARS-CoV2 (RT-PCR SARS-Cov2) by Berlin protocol. The samples were taken from a nasopharyngeal swab.

The patients should also have radiological confirmation of Pneumonia, mostly chest tomography or chest X-rays, to support the diagnosis of Covid-19 Pneumonia.

In total, 301 patients met the inclusion criteria. After obtaining informed consent, patients were treated according to the institutional protocol (from March 20, 2020 to June 30, 2020) with corticosteroid if the patient required supplemental oxygen. From July 1, 2020, the management protocol changed with the addition of colchicine to all patients admitted to the institutions. The treatment was supervised and monitored by the same specialist in infectology of the institutions. Corticosteroid treatment was mostly with dexamethasone, some with prednisolone or methylprednisolone, and colchicine at a dose of 0.5 mg every 12 hours for 7 to 14 days. Upon admission, a blood count, kidney and liver function tests, arterial gases, lactate dehydrogenase, D-dimer, serum ferritin, and C-reactive protein were performed. Low molecular weight heparins were prescribed to all patients to prevent thromboembolism during their hospital stay and pronation according to tolerance if arterial oxygen pressure / expired fraction of oxygen (PaFi) less than 300.

Pneumonia was classified as mild if the patients did not have hypoxemia or need for supplemental oxygen; Severe pneumonia was defined by the presence of hypoxemia or supplemental oxygen requirement, septic shock syndrome, or multisystem compromise. The Acute Respiratory Distress Syndrome (ARDS) was defined as the presence of bilateral pulmonary infiltrates not explained by another etiology and Covid-19 and PaFi less than 300. Standardization was carried out in the researcher's observation, thus guaranteeing adequate techniques in collecting information. With these data, a database was built in Microsoft Excel, and before the analysis, it was subjected to quality control.

The variable of interest was the outcome (dead (n = 37) / alive (n = 264)) and the factors analyzed were: demographic (age and sex), comorbidities (high blood pressure, diabetes mellitus, obesity, dementia, cancer, hypothyroidism, kidney failure, coronary heart disease, chronic obstructive pulmonary disease (COPD), asthma, dyslipidemia, autoimmune disease, psychiatric disease, heart failure, smoking), clinical manifestations dyspnea, cough, fever, chest pain, asthenia, anosmia, diarrhea, headache, odynophagia; hospital care and admission to the intensive care unit, type of supplemental oxygen requirement, nasal cannula, non-invasive ventilation, high-flow cannula, ventury oxygen or non-rebreathing mask, mechanical ventilation, treatment received: corticosteroid, colchicine, findings Laboratory tests: lymphocytes, lactic dehydrogenase, serum ferritin, D-dimer, baseline and lowest PaFi during hospitalization. Once all the variables had been collected, proceed to their univariate analysis with the calculation of frequencies and statistics, bivariate analysis with the outcome variable, and the chi-square hypothesis tests were calculated, with statistical significance ($p < 0.05$).

As an epidemiological measure, the crude and adjusted OR were calculated, with their confidence intervals (95% CI); For the multivariate analysis, binary logistic regression was used, and the variables that met the Hosmer-Lemeshow criteria were entered into the final model ($p < 0.25$). All calculations were made with the SPSS version 21 package (CES University license).

Ethical considerations

The study was approved by the ethics committees of Clínica Medellín, Nueva Clínica Sagrado Corazón, and Clínica Panamericana. Informed consent was obtained from the study participants.

Results

In the period between March 20, 2020, and August 7, 2020, 1,387 patients with Covid-19 infection confirmed by RT-PCR SARS Cov2, Berlin protocol, were diagnosed from a sample taken from the nasopharyngeal swab, in 3 clinics de Antioquia, 360 at the Medellín Clinic (Medellín, Colombia), 369 at the Nueva Clinica Sagrado Corazón (Medellín, Colombia) and 658 at the Panamericana Clinic (Apartadó, Colombia). One thousand eighty-six patients were discarded because they did not have imaging findings on chest radiography or chest computed tomography compatible with Pneumonia, due to incomplete information or discharge from the emergency room for outpatient management (Fig. 1).

Of the 301 patients included for the analysis, 178 (59.1%) corresponded to male patients, and the average age was 56.8 years (SD 17.34 years). 225 (74.8%) presented some comorbidity, of which the most frequent were arterial hypertension, 137 (45.5%), and diabetes mellitus 73 (24.3%), 42 (14%) were obese. Table 1

Table 1
Frequency distribution of patients hospitalized for Covid-19 Pneumonia according to demographic characteristics and comorbidities.

Demographic characteristics and comorbilities		Absolute Frequency (n=)	Relative frequency (%)
Sex	Male	178	59,1%
	Female	123	40,9%
Age	Mean	57	
	SD	17,34	
Comorbidities	Yes	225	74,8%
	No	76	25,2%
Hypertension	Yes	137	45,5%
	No	164	54,5%
Diabetes mellitus	Yes	73	24,3%
	No	228	75,7%
Obesity	Yes	42	14,0%
	No	259	86,0%
Hypothyroidism	Yes	29	9,6%
	No	272	90,4%
Renal disease	Yes	18	6,0%
	No	283	94,0%
Coronary disease	Yes	18	6,0%
	No	283	94,0%
COPD/asthma	Yes	30	10,0%
	No	271	90,0%
Dementia	Yes	12	4,0%
	No	289	96,0%
Cancer	Yes	16	5,3%
	No	285	94,7%
Dyslipidemia	Yes	27	9,0%
	No	274	91,0%
Autoimmune disease	Yes	7	2,3%
	No	294	97,7%
Psychiatric Illness	Yes	7	2,3%
	No	294	97,7%
Neurologic disease	Yes	11	3,7%
	No	290	96,3%
Hearth Failure/Arrhythmia	Yes	7	2,3%
	No	294	97,7%
Smoking	Yes	34	11,3%
	No	266	88,7%

Most patients had symptoms such as dyspnea (74.1%), cough (66.8%), and fever (66.1%). Only 23 (7.6%) had a coinfection on admission; the most frequent were *Mycoplasma pneumoniae* infection. Table 2.

Table 2
Proportional distribution of hospitalized patients with Covid-19 Pneumonia, according to clinical manifestations and presence of coinfection

Clinical manifestation and co-infection		Absolute frequency (n=)	Relative frequency (%)
Dyspnea	Yes	223	74,1%
	No	78	25,9%
cough	Yes	201	66,8%
	No	100	33,2%
Fever	Yes	199	66,1%
	No	102	33,9%
Chest pain	Yes	33	11,0%
	No	268	89,0%
Fatigue	Yes	181	60,1%
	No	120	39,9%
Diarrhea	Yes	39	13,0%
	No	262	87,0%
Headache	Yes	40	13,3%
	No	261	86,7%
Anosmia	Yes	23	7,6%
	No	278	92,4%
Odynophagia	Yes	39	13,0%
	No	262	87,0%
Co-infection	Yes	23	7,6%
	No	278	92,4%
M. pneumoniae	Yes	16	5,3%
	No	285	94,7%
Tuberculosis	Yes	1	0,3%
	No	300	99,7%
Pneumococcus	Yes	1	0,3%
	No	300	99,7%
Salmonella	Yes	2	0,7%
	No	299	99,3%
Influenza	Yes	1	0,3%
	No	300	99,7%
Bordetella	Yes	1	0,3%
	No	300	99,7%

According to the pharmacological treatment, only 17 (5.6%) received Hydroxychloroquine and lopinavir/ritonavir. Antibiotics were prescribed to 272 (90.4%) of the patients, the most commonly used being ceftriaxone in 205 (68.1%), and azithromycin 219 (72.8%) despite the low documented coinfection rate. 240 (79.7%) of the patients received corticosteroids, mainly dexamethasone in 227 (93.4%). 105 (35.2%) of the patients were admitted to the intensive care unit, but only 57 (19.1%) need mechanical ventilation. Table 3.

Table 3
Proportional distribution of hospitalized patients with Covid-19 Pneumonia according to the treatment received.

Treatment		Absolute frequency (n=)	Relative frequency (%)
Hydroxychloroquine and lopinavir/ritonavir	Yes	17	5,6%
	no	284	94,4%
Other antibiotics	Yes	272	90,4%
	No	29	9,6%
Ceftriaxone	Yes	205	68,1%
	No	96	31,9%
Azithromycin	Yes	219	72,8%
	No	82	27,2%
Steroids	Yes	240	79,7%
	No	61	20,3%
Colchicine	Yes	145	48,2%
	No	156	51,8%
Tocilizumab	Yes	1	,3%
	No	300	99,7%
dexamethasone	Yes	227	93,4%
	No	16	6,6%
Intensive care unit management	Yes	105	35,2%
	No	193	64,8%
Conventional oxygen therapy	Yes	265	88,6%
	No	34	11,4%
High-flow nasal canula	Yes	136	45,8%
	No	161	54,2%
Mechanical ventilation	Yes	57	19,1%
	No	241	80,9%

The patients who died presented as complications ARDS (94.6%), shock (64.9%), Renal Injury (48.6%), and secondary infection (27%). Of the patients admitted to the ICU, 61.1% died. Colchicine was administered in 145 (48.2%) patients and of them 14 (9.7%) died vs 23 (14.7%) of those who did not receive it, presenting a non-significant statistical association ($p = 0.179$), but a reduction in fatal outcome was evidenced by 38.2% (OR = 0.618; 95% CI: 0.305–1.253). Table 4.

Table 4
Factors of hospital management associated with the outcome, in patients hospitalized for Covid-19 Pneumonia.

Hospital management		Outcome				Statistic test	P value	OR	CI 95%	
		Dead (n=37)		Alive (n=264)						
		n=	%	n=	%				Inf Lim	Up Lim
Steroids	Yes	32	86,5%	208	78,8%	1,190	0,275	1,723	0,642	4,626
	No	5	13,5%	56	21,2%			1,000		
Colchicine	Yes	14	37,8%	131	49,6%	1,805	0,179	0,618	0,305	1,253
	No	23	62,2%	133	50,4%			1,000		
ICU admission	Yes	22	61,1%	83	31,7%	12,014	0,001	3,389	1,651	6,954
	No	14	38,9%	179	68,3%			1,000		
Conventional oxygen therapy	Yes	34	91,9%	231	88,2%	0,446	0,504	1,521	0,441	5,248
	No	3	8,1%	31	11,8%			1,000		
High-flow nasal canula	Yes	32	88,9%	104	39,8%	30,653	0,000	12,070	4,148	35,150
	No	4	11,1%	157	60,2%			1,000		
Mechanical ventilation	Yes	20	57,1%	37	14,1%	37,050	0,000	8,141	3,830	17,315
	No	15	42,9%	226	85,9%			1,000		
ARDS	Yes	35	94,6%	180	68,2%	11,093	0,001	8,166	1,918	34,756
	No	2	5,4%	84	31,8%			1,000		
Mild ARDS	Yes	2	5,6%	70	35,0%	12,476	0,000	0,109	0,025	0,468
	No	34	94,4%	130	65,0%			1,000		
Moderate ARDS	Yes	10	27,8%	62	31,0%	0,149	0,699	0,850	0,389	1,883
	No	26	72,2%	138	69,0%			1,000		
Severe	Yes	25	69,4%	67	33,3%	16,764	0,000	4,545	2,110	9,792
ARDS	No	11	30,6%	134	66,7%			1,000		
Renal injury	Yes	18	48,6%	36	13,6%	27,022	0,000	6,000	2,879	12,503
	No	19	51,4%	228	86,4%			1,000		
Secondary infection	Yes	10	27,0%	16	6,1%	18,077	0,000	5,741	2,371	13,900
	No	27	73,0%	248	93,9%			1,000		
Shock	Yes	24	64,9%	18	6,8%	91,071	0,000	25,230	11,030	57,710
	No	13	35,1%	246	93,2%			1,000		

ARDS: Acute respiratory distress syndrome; **CI:** Confidence interval; **ICU:** Intensive care unit; **Inf Lim:** inferior limit; **N:** No; **OR:** Odds ratio. **Up Lim:** Upper limit; **Y:** Yes

The variables with a statistical association associated with death were: comorbidity, dementia, kidney injury, secondary infection, cancer, co-infection, ARDS, ICU admission, and mechanical ventilation.

After logistic regression, the variables that met the Hosmer-Lemeshow criteria and the included by medical criteria were entered—documenting an increase in the probability of dying in patients with Covid-19 Pneumonia who had some comorbidity, dementia, cancer, kidney injury, co-infection, and any degree of ARDS, which required admission to the ICU and those who had PaFi less than 200. Table 5.

Table 5
Frequency distribution of patients hospitalized for Covid-19 Pneumonia, according to the outcome (dead/alive) and its associated factors.

Variable		Outcome				Statistic test	p value	OR	IC95		Adjusted OR	CI 95%	
		dead (n=37)		Alive (n=264)									
		n=	%	n=	%				Inf Lim	Up Lim		Inf lim	Up lim
Comorbidities	Y	34	91,9	191	72,3	6,567	0,006	4,332	1,291	14,539	6,614	0,634	69,005
	N	3	8,1	73	27,7			1,000			1,000		
Hypertension	Y	20	54,1	117	44,3	1,240	0,174	1,478	0,741	2,949	0,971	0,185	5,084
	N	17	45,9	147	55,7			1,000			1,000		
Diabetes mellitus	Y	10	27,0	63	23,9	0,177	0,405	1,182	0,542	2,575	2,820	0,486	16,362
	N	27	73,0	201	76,1			1,000			1,000		
Obesity	Y	7	18,9	35	13,3	0,866	0,241	1,527	0,623	3,741	0,241	0,034	1,721
	N	30	81,1	229	86,7			1,000			1,000		
Dementia	Y	4	10,8	8	3,0	5,132	0,047	3,879	1,107	13,590	17,158	0,877	335,643
	N	33	89,2	256	97,0			1,000			1,000		
Cancer	Y	7	18,9	9	3,4	15,510	0,001	6,611	2,296	19,038	72,044	6,013	863,212
	N	30	81,1	255	96,6			1,000			1,000		
Renal Injury	Y	18	48,6	36	13,6	27,022	0,000	6,000	2,879	12,503	7,624	1,420	40,923
	N	19	51,4	228	86,4			1,000			1,000		
Secondary infection	Y	10	27,0	16	6,1	18,077	0,000	5,741	2,371	13,900	0,214	0,028	1,604
	N	27	73,0	248	93,9			1,000			1,000		
Shock	Y	24	64,9	18	6,8	91,071	0,000	25,230	11,030	57,710	189,072	11,321	3157,764
	N	13	35,1	246	93,2			1,000			1,000		
Co-infection	Y	7	18,9	16	6,1	7,603	0,006	3,617	1,377	9,499	8,627	0,987	75,373
	N	30	81,1	248	93,9			1,000			1,000		
ARDS	Y	35	94,6	180	68,2	11,093	0,010	8,167	1,919	34756,000	0,464	0,022	9,643
	N	2	5,4	84	31,8			1,000			1,000		
Mild ARDS (n=236)	Y	2	5,6	70	30,5	12,476	0,000	0,109	0,025	0,468	2,032	0,000	56122,676
	N	34	94,4	130	65,0			1,000			1,000		
Moderate ARDS (n=236)	Y	10	27,8	62	31,0	0,149	0,699	0,856	0,389	1,883	31,284	0,195	5020,334
	N	26	72,2	138	69,0			1,000			1,000		
Severe ARDS (n=237)	Y	25	69,4	67	33,3	16,764	0,000	4,545	2,110	9,792	129,456	0,707	23695,513
	N	11	30,0	134	66,7			1,000			1,000		
Mechanical ventilation	Y	20	57,1	37	14,1	37,050	0,000	8,144	3,830	17,316	0,387	0,020	7,360
	N	15	42,9	226	85,9			1,000			1,000		
ICU admission	Y	22	61,1	83	31,7	12,014	0,001	3,389	1,651	6,954	1,348	0,189	9,616
	N	14	38,9	179	68,3			1,000			1,000		
Lymphocytes	900-3300	13	35,1	138	52,3	3,812	0,051	0,495	0,241	1,013	5,030	0,963	26,279
	<900->3300	24	64,9	126	47,7			1,000			1,000		
Ferritin	< 204	2	5,4	31	11,7	1,335	0,248	0,429	0,098	1,874			

	> 204	35	94,6	233	88,3			1,000			1,000		
LDH	< 220	2	5,4	37	14	2,133	0,144	0,351	0,081	1,520			
	> 220	35	94,6	227	86			1,000			1,000		
D-Dimer	< 198	1	2,7	19	7,2	1,057	0,304	0,358	0,047	2,758	0,982	0,000	10775,748
	> 198	36	97,3	245	92,8			1,000			1,000		
Initial PaO2/FiO2	> 300	3	8,1	74	28	6,766	0,009	0,227	0,068	0,760	1,278	0,100	16,407
	< 300	34	91,9	190	72			1,000			1,000		
Lower PaO2/FiO2	> 300	0	0	43	16,3	7,031	0,008	1,167	1,111	1,227			
	< 300	37	100	221	83,7			1,000			1,000		
Initial PaO2/FiO2	> 200	9	24,3	169	64	21,156	0,000	0,181	0,082	0,399	0,836	0,148	4,735
	< 200	28	75,7	95	36			1,000			1,000		
Lower PaO2/FiO2	> 200	2	5,4	124	47	23,036	0,000	0,065	0,015	0,274	1,667	0,000	131958,323
	< 200	35	94,6	140	53			1,000			1,000		

ARDS: Acute respiratory distress syndrome; **LDH:** lactate dehydrogenase; **PaO2/FiO2:** PaO2/FiO2 ratio

Hospital mortality from severe Covid-19 Pneumonia was 12.3%. 57.1% of the patients who required mechanical ventilation died.

Discussion

To date, there is no specific treatment for COVID-19 infection, and in some countries, drugs used in previous coronavirus outbreaks (SARS-coronavirus and MERS-coronavirus) are administered despite little or no evidence of their effectiveness. For SARS-CoV2. The first experience of managing patients with drugs with antiviral activity such as Interferon α, Lopinavir/Ritonavir, Chloroquine, Ribavirin, and Umifenovir (the latter not available in Colombia) was proposed in the guide for the prevention, diagnosis, and treatment of pneumonia due to COVID- 19 from the ROC National Health Commission (6th version, released February 18, 2020) (16). Lopinavir/Ritonavir showed some activity against SARS-CoV and MERS-CoV. However, in a recent study in patients with SARS-CoV2, the use of Lopinavir/Ritonavir 400/100 mg every 12 hours for 14 days did not demonstrate statistically significant differences in mortality compared to standard treatment without drug therapy (19.2 % vs. 25.0%; 95% CI, −17.3 to 5.7). In vitro, Hydroxychloroquine was more potent antiviral than Chloroquine, making Hydroxychloroquine a possible therapeutic option (17), thanks to the inhibition of viral replication due to its immunomodulatory effects (18). However, the study by Gelesis et al. (19) in 1376 patients, of whom 811 (58.9%) received Hydroxychloroquine, there were no differences regarding intubation or death compared to the group that did not receive it (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32).

A retrospective study did not find an association between the use of macrolides and the 90-day mortality outcome or less clearance of the disease (follow-up for clinical, non-virological signs) when tested against MERS-coronavirus (20).

Although the administration of corticosteroids was controversial at the beginning of the pandemic, given the clinical studies in other viral respiratory infections (respiratory syncytial virus, influenza, SARS-coronavirus or MERS-coronavirus) that associated the use of corticosteroids with increased mortality and infections nosocomial, higher viral persistence and a higher rate of adverse reactions such as psychosis (dose-dependent), diabetes and vascular necrosis. (21), Recent evidence changed opinion about them Villar et al. (22), in a placebo-controlled, randomized, and multicenter study, found that patients with severe acute respiratory distress syndrome (ARDS) treated with dexamethasone had lower mortality (21% vs. 36%, p <0.0047) and Wu et al. (23) in patients with ARDS due to COVID-19, showed a decrease in the risk of death in patients treated with methylprednisolone (HR, 0.38; 95% CI, 0.20-0.72). More recently, the RECOVERY results (13) modified the treatment guidelines. In this study, patients who received dexamethasone had a decrease in mortality in a third of ventilated patients (frequency ratio 0.65 [95% confidence interval: 0.48 to 0.88]; p = 0.0003) and in a fifth in other patients who received oxygen only (0.80 [0.67 to 0.96]; p = 0.0021).

Different studies have documented a cytokine release syndrome in patients with severe Covid19 (24), with an increase in tumor necrosis factor-α (TNF-α), followed by an increase in Interleukin (IL) -1β, IL-2, IL-6, IL-8, IL-10, and interferon γ (IFN-γ) (25).

Colchicine, an alkaloid derivative of the Colchicum genus plants, inhibits IL-1β and IL-18 by interacting with the inflammasome Nod-like receptor protein 3 inflammasome protein complex 1 (NLRP-3), for which it is hypothesized that it could be useful in severe Covid-19 pneumonia. (26)

Mansouri et al. (27) described the improvement of a 42-year-old patient with Covid-19 pneumonia and cytokine release syndrome with early administration of colchicine, evidenced by clinical improvement and decrease in severity markers, including ferritin, D dimer, and normalization of levels of IL-6. Scarsi et al. (28) conducted a proof-of-concept study in a single hospital in Italy, where they administered colchicine to 122 hospitalized

patients with Covid-19 Pneumonia. They compared them with a standard care group without colchicine, showing a lower risk in the survival analysis of death in those patients who received colchicine (HR = 0.151 (95% CI 0.062 to 0.368).

In the GRECCO randomized clinical study (14), the use of colchicine decreased the primary endpoint of clinical deterioration in 1.8% (1 of 55 patients who received it) vs. 14.0% (7 of 50 patients who did not receive colchicine) odds ratio, 0.11; 95% CI, 0.01-0.96; P = 0.02)

According to our literature review, this is the first multicenter study reported to date, with a greater number of patients who were administered corticosteroids plus colchicine (145) for the management of Covid-19 pneumonia. 14 (9.7%) died vs 23 (14.7%) of those who did not receive it (p = 0.179), but there was a decrease in fatal outcome by 38.2% (OR = 0.618; 95% CI: 0.305-1.253). Factors that possibly affected the result can be explained by the sample's size, mainly, and to a lesser extent, the time of initiation of the drug.

Regarding mortality in our population, patients with Covid-19 Pneumonia who received management with corticosteroids and colchicine had an overall mortality of 12.3%, low compared to hospital statistics from developed countries, such as Germany, which has been recognized as one of the few countries that did not see its capacity to respond to the pandemic exceeded. In an observational study by Karagiannidis et al. ([29]) in 10,021 patients in 920 hospitals in the German country, the overall mortality was 22%, 16% for those who did not require mechanical ventilation vs. 53% for those who did.

Due to the observational nature of this study, the reported findings should be interpreted with caution. Randomized, placebo-controlled clinical studies are required to evaluate the effect of administered drug therapy.

Conclusions

Treatment with corticosteroids and colchicine for managing patients with severe Covid-19 pneumonia was associated with low mortality at the hospital level. Randomized, placebo-controlled studies are required to evaluate the effect of this therapy.

Declarations

Acknowledgements

MSc. Luz Maribel Toro. Epidemiological Surveillance Nurse. Nueva Clínica Sagrado Corazón. Medellín, Antioquia, Colombia.

MSc. Isabel Potes. Epidemiological Surveillance Nurse. Clínica Medellín, Grupo Quirón Salud, Medellín, Antioquia, Colombia.

MSc. Elizabeth Rodriguez. Health Information Technology. Clínica Medellín, Grupo Quirón Salud, Medellín, Antioquia, Colombia.

MSc. Eleannys Arroyave. Epidemiological Surveillance Nurse. Clínica Panamericana, Apartadó. Antioquia, Colombia.

They all gave permission to be mentioned in this acknowledgments section

Authors' contributions

All the authors were active participants: Conception / design of the study: MAP, DCA, HH, CAA; Data / information collection: MAP, JFB, BJM, MA, JFLL PM; Data analysis / discussion: DCA, CAA, MAP, JFB, HH; Bibliographic review: MAP, HH, DCA, CAA, JFB, BJM, MA, JFLL, PM; Manuscript preparation: MAP, DCA, HH, CAA, JFB; Final version review: MAP, DCA, HH, CAA, JFB, BJM, MA, JFLL, PM. All authors read and approved the final manuscript

Ethics approval

The study was approved by the ethics committees of Clínica Medellín (number 04-2020), Nueva Clínica Sagrado Corazón, and Clínica Panamericana. Informed consent was obtained from the study participants.

Availability of data and materials

The datasets of the current study are available from the corresponding author on reasonable request.

Consent for participate

We wish to submit the manuscript for publication in Annals of Clinical Microbiology and Antimicrobials®, and the manuscript is not currently under consideration for publication in another journal.

Competing interest

The authors declare that they have no competing interests

Funding

None declared.

References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382:727-733.
2. Coronavirus Update (Live): 30,157,437 Cases and 947,034 Deaths from COVID-19 Virus Pandemic - Worldometer [Internet]. Worldometers.info. 2020 [cited 29 August 2020]. Available from: https://www.worldometers.info/coronavirus/?zarsrc=130.
3. Mahase E. Coronavirus COVID-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. BMJ. 2020 Feb 18;368:m641. doi: 10.1136/bmj.m641.
4. Pan American Health Organization, World Health Organization. COVID -19 Information System for the Region of the Americas , as of 29 Aug 2020. Available at: https://paho-COVID19-response-who.hub.arcgis.com/ Accessed 29 Aug 2020.
5. Ministerio de Salud y Protección Social. Colombia confirma su primer caso de COVID-19. Colombia M. Colombia confirma su primer caso de COVID-19 [Internet]. Minsalud.gov.co. 2020 [cited 29 August 2020]. Available from: https://www.minsalud.gov.co/Paginas/Colombia-confirma-su-primer-caso-de-COVID-19.aspx.
6. Lupia, T.; Scabini, S.; Mornese Pinna, S.; et al. 2019 novel coronavirus (2019-nCoV) outbreak: A new challenge. J. Glob. Antimicrob. Resist. 2020, 21, 22–27
7. COVID-19 Guideline, Part 1: Treatment and Management [Internet]. Idsociety.org. 2020 [cited 29 August 2020]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
8. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Last updated April 13, 2020 at 4:39 PM EDT and posted online at www.idsociety.org/COVID19guidelines
9. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. pii: ciaa237. doi: 10.1093/cid/ciaa237.
10. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020 Feb 27. doi: 10.1002/jmv.25729. [Epub ahead of print]
11. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020 Mar 24;117(12):6771-6776. doi: 10.1073/pnas.1922083117. Epub 2020 Feb 13.
12. Philippe Gautret, Jean-Christophe Lagier, Philippe Parola et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Jul;56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.
13. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020 Jul 17:NEJMoa2021436. doi: 10.1056/NEJMoa2021436.
14. Deftereos S, Giannopoulos G, Vrachatis D, Siasos Gerasimos, Giotaki S, Gargalianos P. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA Netw Open. 2020 Jun 1;3(6):e2013136. doi: 10.1001/jamanetworkopen.2020.13136.
15. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1):58-60. doi: 10.5582/ddt.2020.01012.
16. Jin YH, Cai L, Cheng ZS et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020 Feb 6;7(1):4. doi: 10.1186/s40779-020-0233-6.
17. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. pii: ciaa237. doi: 10.1093/cid/ciaa237.
18. Colson P, Rolain J, Lagier J, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020 Mar 4:105932. doi: 10.1016/j.ijantimicag.2020.105932.
19. Joshua Geleris, Yifei Sun, Jonathan Platt, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Jun 18;382(25):2411-2418. doi: 10.1056/NEJMoa2012410. Epub 2020 May 7.

20. Arabi Y, Deeb A, Al-Hameed F et al. Macrolides in critically ill patients with Middle East Respiratory Syndrome. Int J Infect Dis. 2019 Apr; 81:184-190. doi: 10.1016/j.ijid.2019.01.041
21. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020 Feb 15;395(10223):473-475. DOI: 10.1016/S0140-6736(20)30317-2
22. Villar Jesús, Ferrando Carlos, Martínez Domingo, et al. Dexamethasone Treatment for the Acute Respiratory Distress Syndrome: A Multicentre, Randomised Controlled Trial. Lancet Respir Med. 2020 Mar;8(3):267-276. doi: 10.1016/S2213-2600(19)30417-5.
23. Wu Chaomin, Chen Xiaoyan, Cai Yanping, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Jul 1;180(7):934-943. doi: 10.1001/jamainternmed.2020.0994.
24. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034
25. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-195
26. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440(7081):237-241
27. Mansouri N, Marjani M, Tabarsi P, von Garnier C, Mansouri D. Successful Treatment of Covid-19 Associated Cytokine Release Syndrome with Colchicine. A Case Report and Review of Literature. Immunol Invest. 2020 Jul 7:1-7. doi: 10.1080/08820139.2020.1789655. Online ahead of print.
28. Scarsi M, Piantoni S, Colombo E, Airó P, Richini D, Miclini M.Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. Ann Rheum Dis. 2020 Jul 30:annrheumdis-2020-217712. doi: 10.1136/annrheumdis-2020-217712.
29. Karagiannidis C, Mostert C, Hentschker C, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med. 2020 Sep;8(9):853-862. doi: 10.1016/S2213-2600(20)30316-7. Epub 2020 Jul 28.

Figures

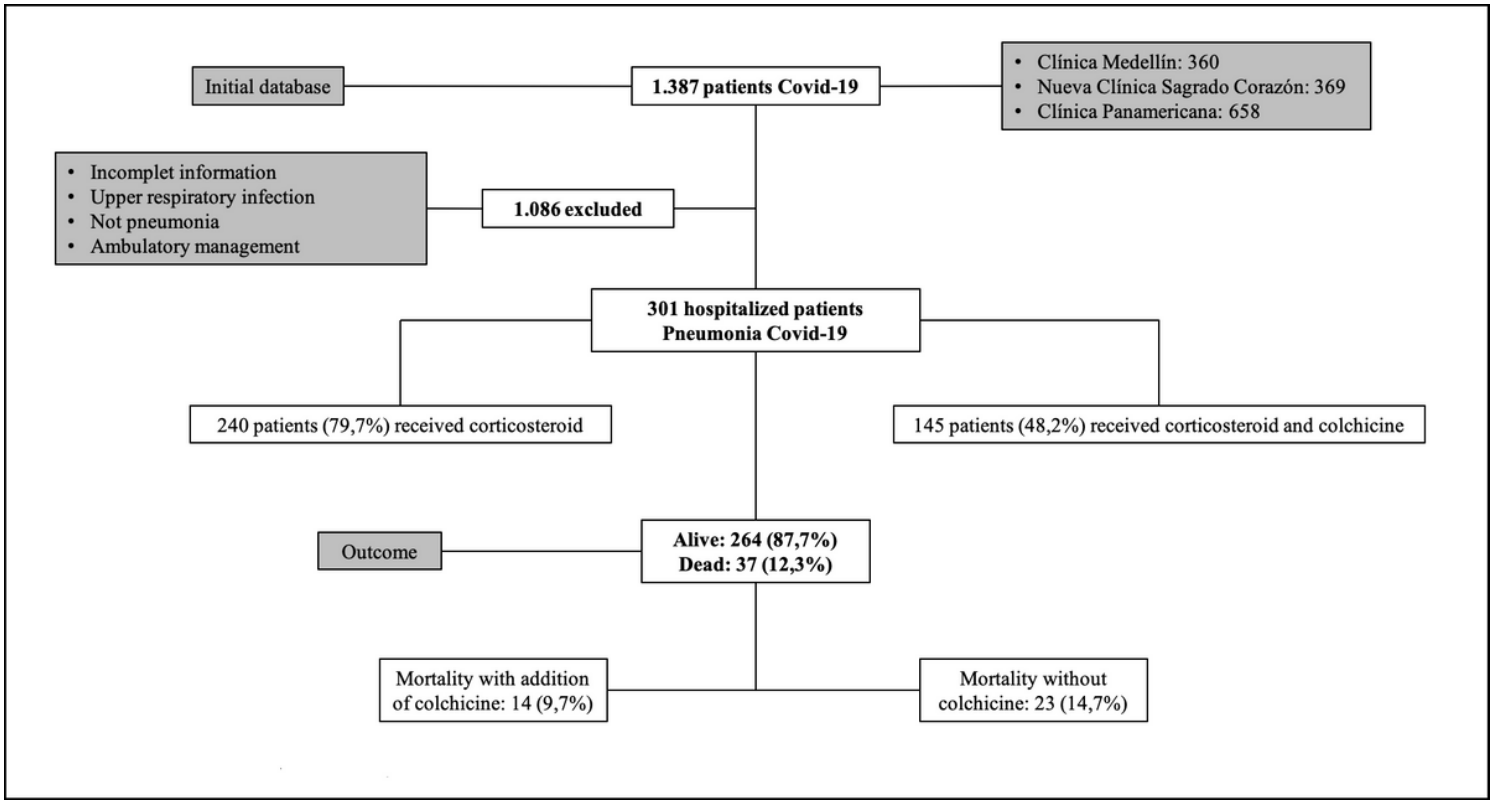

Figure 1

Patients with Covid-19 infection in three clinics in Antioquia, Colombia, between March 20 and August 7, 2020.