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Original

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COVID-19 and Acute Respiratory Distress Syndrome. Impact of corticosteroid treatment and predictors of poor outcome

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ABSTRACT

Objectives. To assess the impact of corticosteroids on inflammatory and respiratory parameters of patients with COVID-19 and acute respiratory distress syndrome (ARDS).

Methods. Longitudinal, retrospective, observational study conducted in an ICU of a second level hospital. Adult patients with COVID-19 were included. Baseline characteristics, data on SARS-CoV-2 infection, treatment received, evolution of respiratory and inflammatory parameters, and ICU and hospital stay and mortality were analyzed.

Results. A total of 27 patients were included, 63% men, median age: 68.4 (51.8, 72.2) years. All patients met ARDS criteria and received MV and corticosteroids. After corticosteroids treatment we observed a reduction in the O_2 A-a gradient [day 0: 322 (249, 425); day 3: 169 (129.5, 239.5) p<0.001; day 5: 144 (127.5, 228.0) p<0.001; day 7: 192 (120, 261) p=0.002] and an increase in the pO_2/FiO_2 ratio on days 3 and 5, but not on day 7 [day 0: 129 (100, 168); day 3: 193 (140, 236) p=0.002; day 5: 183 (141, 255) p=0.004; day 7: 170 (116, 251) p=0.057]. CRP also decreased on days 3 and 5 and increased again on day 7 [day 0: 16 (8.6, 24); day 3: 3.4 (1.7, 10.2) p<0.001; day 5: 4.1 (1.4, 10.2) p<0.001; day 7: 13.5 (6.8, 17.3) p=0.063]. Persistence of moderate ARDS on day 7 was related to a greater risk of poor outcome (OR 6.417 [1.091-37.735], p=0.040)

Conclusion. Corticosteroids appears to reduce the inflammation and temporarily improve the oxygenation in COVID-19 and ARDS patients. Persistence of ARDS after 7 days treatment is a predictor of poor outcome.

Key words: COVID-19, ARDS, mechanical ventilation, corticosteroids, ICU

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COVID-19 y Síndrome de Distress Respiratorio Agudo. Impacto del tratamiento con corticoides y predictores de mal pronóstico

RESUMEN

Objetivos. Evaluar el impacto del tratamiento con corticoides en los parámetros inflamatorios y respiratorios de los pacientes con Síndrome de Dificultad Respiratoria Aguda (SDRA) secundario a COVID-19

Métodos. Estudio longitudinal, retrospectivo, observacional en una UCI de un hospital de segundo nivel. Se incluyeron los pacientes adultos ingresados en UCI por COVID-19. Analizamos características basales, datos de la infección por SARS-CoV-2, tratamiento recibido, evolución de los parámetros respiratorios e inflamatorios y estancia y mortalidad en UCI y hospitalaria.

Resultados. 27 pacientes, 63% hombres, mediana de edad: 68.4 (51.8, 72.2) años. Todos recibieron ventilación mecánica y cumplieron criterios de SDRA. Todos recibieron corticoides. Tras la administración de corticoides observamos una reducción del gradiente A-a de O_2 [día 0: 322 (249, 425); día 3: 169 (129.5, 239.5) p<0.001; día 5: 144 (127.5, 228.0) p<0.001; día 7: 192 (120, 261) p=0.002] y un aumento en la relación pO_2/FiO_2 en los días 3 y 5, pero no al día 7 [día 0: 129 (100, 168); día 3: 193 (140, 236) p=0.002; día 5: 183 (141, 255) p=0.004; día 7: 170 (116, 251) p=0.057]. La PCR descendió a los días 3 y 5 volviendo a subir al día 7 [día 0: 16 (8.6, 24); día 3: 3.4 (1.7, 10.2) p<0.001; día 5: 4.1 (1.4, 10.2) p<0.001; día 7: 13.5 (6.8, 17.3) p=0.063]. La persistencia de SDRA moderado al día 7 se relacionó con un peor pronóstico (OR 6.417 [1.091-37.735], p=0.040)

Conclusión. Los corticosteroides parecen reducir la inflamación y mejorar temporalmente la oxigenación en pacientes con SDRA y COVID-19. La persistencia de SDRA moderado tras 7 días de tratamiento es un predictor de mal pronóstico.

Palabras clave: COVID-19, SDRA, ventilación mecánica, UCI, corticosteroides, ICU

INTRODUCTION

On 11 March 2020 the World Health Organization announced that the outbreak of the disease caused by coronavirus SARS-CoV-2 (*severe acute syndrome coronavirus 2*), known as COVID-19, can be characterized as a pandemic, after having first appeared in late 2019 in China.

COVID-19 has been a challenge for health systems all over the world; especially for ICUs that have had to expand to assume a number of patients that exceeded the number of beds available. At the same time, the lack of a known, effective treatment has led to a spate of treatment recommendations [1–4], which are not always backed by sufficient scientific evidence [5].

It has been suggested that the clinical course of COVID-19 evolves over several phases. The initial phase would be marked by a high viral load. The subsequent inflammatory response (evaluated by means of determination of interleukins but also estimated using C reactive protein [CRP], lactate dehydrogenase [LDH], D-dimer, ferritin, etc.) would be the cause of clinical worsening in some patients [6] This theory has not been confirmed and other researchers have cast doubt about the existence and importance of the "cytokine storm"[7].

According to this theory, different treatments targeted at modulating the inflammatory response, including corticosteroids, have been suggested. In a retrospective analysis of 84 patients with COVID-19 and ARDS (treated at one hospital in Wuhan) lower mortality was observed in those patients who had received methylprednisolone (HR 0.38; 95% CI 0.20-0.72) [8]. The recommendation to administer corticosteroids early during moderate-severe ARDS [9] carries more weight after publication of the results of a randomized clinical trial in which dexamethasone was shown to reduce the duration of mechanical ventilation (MV) and the mortality, compared to routine intensive care [10]. Data also exist that suggest a benefit of corticosteroid treatment in patients with community-acquired pneumonia and an intense inflammatory response [11] and, even, in patients with influenza-related pneumonia and ARDS [12]. However, unfavorable results have been notified in patients with respiratory infections of viral etiology, such as MERS (Middle East Respiratory Syndrome) [13] and also in influenza-related pneumonia [14, 15], which means we must be circumspect with its administration [16].

The Surviving Sepsis Campaign suggests using systemic corticosteroids in patients subjected to MV and ARDS following COVID-19 [2].

Recently, results of RECOVERY clinical trial have showed that use of dexamethasone resulted in lower 28-day mortality among COVID-19 patients who were receiving invasive mechanical ventilation [17].

The main objective of our study is to analyze the effects of a short course of corticosteroids on the respiratory and inflammatory parameters of patients undergoing MV because of ARDS following COVID-19. Our secondary objective is to identify predictors of poor outcome (death or prolonged MV).

MATERIAL AND METHODS

Scope of study. A second level Spanish hospital ICU with 22 beds (14 of which are suitable for patients on MV). Patients received treatment in accordance with our center's protocol, which included a recommendation for methylprednisolone (0.5 mg/kg/12 hours, 3 days) if the patient was receiving MV and complied with ARDS criteria [18]. Our protocol recommended performing a control PCR for SARS-CoV-2 10 days from admission (if the patient had no fever); in the event of a positive result a new test at 5 days was recommended.

Study period. Patients admitted during the first wave of the COVID-19 pandemic (March-June 2020).

Study design. Longitudinal, retrospective, observational study.

Inclusion criteria. Adult patients admitted to the ICU because of respiratory failure secondary to COVID-19, diagnosed by a positive PCR for SARS-CoV-2.

Exclusion criteria. Not applicable.

Ethical aspects. The study was approved by the Galicia Ethics Committee for Research into Medicines (CEIm-G) (code 2020/246).

Measures. We assessed sociodemographic data (age and sex), comorbidities, data on SARS-CoV-2 infection (duration of the disease at admission, time until a negative PCR test for SARS-CoV-2), severity scores at admission (SOFA and APACHE II), treatments received, respiratory support, evolution of respiratory and inflammatory parameters during the first week of MV and duration of the MV and ICU and hospital stay; in addition to the incidence of coinfections at admission and superinfections during stay in the ICU (defined by positive cultures and/or significant elevation in procalcitonin: ≥0.5 ng/mL).

Comorbidities were recorded according to the data obtained from the clinical history. They were grouped according to the system affected: cardiovascular (history of ischemic cardiopathy, heart failure or severe valvular disease), respiratory (diagnosis of COPD or asthma), central nervous system (history of cerebrovascular disease with or without sequelae), and liver (cirrhosis at any stage). Hematologic malignancy included those patients with a history of any kind of leukemia or lymphoma, regardless of time from diagnosis. Cancer included those patients who had received treatment for their neoplasia in the last 5 years.

Patients who needed MV for 21 days or less were classified as Group A (*good outcome*). Patients who died or needed MV for more than 21 days were classified as Grupo B (*poor outcome*).

The main objective was to analyze evolution of respiratory (pO_2/FiO_2 ratio and O_2 alveolo-arterial gradient) and inflammatory parameters (CRP, LDH, D-dimer, ferritin, lymphocyte count) after administration of corticosteroids. To homogenize our data, we used arterial blood gas results obtained daily while the patient was in supine position. We consider resolution of moderate ARDS when the pO_2/FiO_2 ratio remained above 200 for at least 48 hours.

Our secondary objective was to identify the variables present at admission or during the first week under MV that predict a poor outcome (death or need for MV for more than 21 days). We evaluated the existence of a relationship between the poor result and the main inflammatory and respiratory parameters, viral persistence and the presence of coinfection upon admission to the ICU.

Statistical analysis. Continuous variables are shown as median and p25, p75; qualitative variables are shown as number and percentage. To compare medians, we used the Mann-Whitney U test, and we compared percentages using the chi-squared test. We used logistic regression to assess the relationship between the risk of poor outcome and the variables selected. We have assumed an α error of 0.05. We used the statistical software package IBM SPSS Statistics, Version 19.0 (IBM Corp., Armonk, NY, USA) for statistical analysis and to plot graphs.

RESULTS

Up to June 16, 2020, 27 patients were admitted to our center's COVID-ICU. 63% were men and their median age was 68.4 (51.8, 72.2) years. Comorbidities and basal characteristics of patients are shown in Table 1.

Figure 1 summarizes both MV and ICU and hospital stay times for each patient.

Patients were admitted to the ICU after spending a median of 3 (1, 4) days on the hospital; 4 (2.2, 7.7) days in Group A (0, 3) and 2 (0, 3) days in Group B, (p=0.047). Both antiviral and anti-inflammatory treatment received by patients are summarized in Table 2.

All patients received MV and 15 patients (55.5%) received non-invasive ventilation (NIV) prior to onset of MV. Parameters related to respiratory support are shown in Table 3.

Ferritin levels at the time of onset of MV were 548 (280.5, 1970.5) mg/mL, 282 (220, 2281) in Group A and 1151 (496.2, 2108.2) in Group B (p=0.242).

A total of 12 (44.4%) patients presented a positive control SARS-CoV-2 PCR; 7 (58.3%) patients in Group A and 5 (33.3%) patients in Group B (p=*0.194*). 6 (22.2%) patients presented two positive control SARS-CoV-2 PCR; 4 (33.3%) patients in Group A and 2 (13.3%) patients in Group B (p=*0.214*), and four patients did not have a negative control PCR before leaving hospital (14.8%), 3 (25%) patients in Group A and 1 (6.7) patient in Group B (p=0.183).

A total of 27 patients (100%) complied with ARDS criteria at the time of starting MV and received treatment with 0.5 mg/kg/12h of methylprednisolone. Treatment lasted 3 (3, 4) days, with a median of 3 (2, 4) in Group A patients and 3 (3, 4.2) in Group B patients (p=0.294).

Corticosteroids was started at the same time as mechanical ventilation in 26 patients (96,3%). Figure 2 shows the evolution of inflammatory and respiratory parameters from starting corticosteroid treatment to day 28, and Table 4 shows the comparison of baseline values with those measured on days 3, 5 and 7 after starting corticosteroids. We have not made comparisons beyond the seventh day due to the small number of patients and high variability, which is probably related to the presence or absence of complications, especially infectious complications.

Figure 3 shows the evolution of inflammatory and respiratory parameters in group A and group B patients. In table 5 we compare those parameters in group A and group B patients on admission and on days 3, 5 and 7, in order to explore early differences between the two groups.

When we searched for factors that predict poor outcome (death or need for prolonged MV) during the first week of MV, we found that only moderate ARDS criteria persisting 7 days from MV onset predicts a poor outcome (OR: 6.417, 95% CI 1.091-37.735, p=0.040) (Table 6).

DISCUSSION

In this study we describe 27 patients admitted to our ICU because of COVID-19 from March to June 2020. A total of 1880 cases were diagnosed in our healthcare area up to June 16 (approximate incidence of 652 cases per 100,000 inhabitants); of these 132 died (7.0%). ICU admission represents 1.4% of all cases diagnosed and 5.1% of COVID-19-related hospital admissions. The percentage of patients admitted to the ICU is far from the 11.3% reported by Rodríguez et al. [19], although close to the 7% published by Yang et al [20].

The sample is a predominantly male population with few comorbidities. Our data are similar to other series published on critically ill COVID-19 patients, although the median age and percentage of patients with onco-hematologic diseases is slightly higher in our study [19–26].

The role of NIV in these patients has been a moot point during the pandemic; both because of the high rate of failure and the risk of infecting healthcare staff. In over half our patients (55.6%) NIV was tested and failed; MV was required in 100% of patients. Other authors have reported high levels of failure of NIV: 85.2% in the Tarragona study [19]. In the Lombardy and Washington series barely 11% and 19% respectively only received NIV, while the number of patients receiving MV after having received NIV is not specified [25] and Hua et al. report 32.5% of patients treated with NIV. None of the studies published to date attain 100% of patients under MV. However, the Vitoria study exceeds 90% [22] and both the Lombardy and Tarragona studies are close (88% and 86%, respectively) [19, 25]. At the other extreme, just 24% of patients from the Hua et al. series and 42% of the Yang et al. series received MV [20, 26].

The severity of respiratory failure is notable (median pO_2/FiO_2 ratio of 129, and O_2 A-a gradient of 322 mmHg O_2, at MV onset) with a high percentage of patients meeting moderate (88.9%) and severe (25.9%) ARDS criteria. Only Yang et al. have observed a lower pO_2/FiO_2 ratio, however, they report that only 67% of patients comply with ARDS criteria and just 42% of their patients

Table 1 Comorbidities, basal characteristics, evolution and results

	Overall	Group A	Group B	p
n	27	12	15	
Male sex	17 (63)	7 (58.3)	10 (66.7)	0.656
Age	68.4 (51.8, 72.2)	60.1 (45.2, 71.9)	70.8 (58.7, 72.9)	0.841
Comorbidities				
Arterial hypertension	11 (40.7)	6 (50)	5 (33.3)	0.381
Dyslipidemia	11 (40.7)	5 (41.7)	6 (40)	0.930
Diabetes mellitus	5 (18.5)	1 (8.3)	4 (26.7)	0.223
Cardiovascular	1 (3.7)	1 (8.3)	0	0.255
Respiratory	5 (18.5)	1 (8.3)	4 (26.7)	0.233
CNS	1 (3.7)	0	1 (6.7)	0.362
Liver	2 (7.4)	1 (8.3)	1 (6.7)	0.869
Hematologic malignancy	2 (7.4)	2 (16.7)	0	0,100
Cancer	3 (11.1)	2 (16.7)	1 (6.7)	0.411
BMI	28.5 (25.2, 32.6)	29.0 (25.5, 34.2)	27.4 (25.2, 31.3)	0.902
Disease course and duration				
Ss-H admission (d)	7.0 (3.5, 9.0)	5 (2, 8)	7 (4.75, 10)	0.798
Ss-ICU admission (d)	10 (7.0, 12.5)	10 (9, 12)	9.5 (7, 13.2)	0.063
Ss-MV onset (d)	12 (9, 14)	12 (10, 13)	11.5 (8.5, 14.2)	0.056
Days PCR + until PCR -	21 (16, 29)	21 (10.5, 38.5)	22.5 (18.5, 27.5)	0.419
Symptoms until PCR - (d)	33 (28, 36)	34.5 (21.7, 46.2)	31 (28, 36)	0.943
Severity scores				
APACHE II	14 (10, 17)	14 (9.2, 17.7)	14 (11, 17)	0.580
SOFA 24 h	4 (4, 7)	5.5 (4, 6.7)	4 (4, 7)	0.092
Oxygenation parameters at the onset of mechanical ventilation				
$pO_2/FiO_2 < 300$	27 (100)			
$pO_2/FiO_2 < 200$	24 (88.9)	10 (83.3)	14 (93.3)	0.411
$pO_2/FiO_2 < 100$	7 (25.9)	3 (25)	4 (26.7)	0.922
Coinfection and superinfection in the ICU				
Coinfection	13 (48.1)	5 (41.7)	8 (53.3)	0.547
Superinfection	18 (66.7)	4 (33.3)	14 (93.3)	0.001
MV onset-superinfec (d)	14 (8.7, 22.2)	10.5 (8.5, 11)	17 (8.7, 23.5)	0.151
Results				
Deceased at 28 d	2 (7.4)	0 (0)	2 (13.3)	0.189
Under MV at 28 d	10 (37)	0	10 (66.7)	<0.001
ICU at 28 d	12 (44.4)	0	12 (80)	<0.001
Hospital ward at 28 d	12 (44.4)	11 (91.7)	1 (6.7)	<0.001
Home at 28 d	1 (3.7)	1 (8.3)	0	0.255
ICU mortality	3 (11.1)	0	3 (21.4)	0.088
ICU LOS	26 (19, 39)	19 (10.2, 23.5)	35 (28, 45)	<0.001
Hospital LOS	47 (35, 54)	41 (35.7, 47.5)	53 (35, 58)	0.067

CNS: central nervous system, BMI: body mass index, Ss: symptoms, H: hospital, MV: mechanical ventilation, d: days, LOS: length of stay.

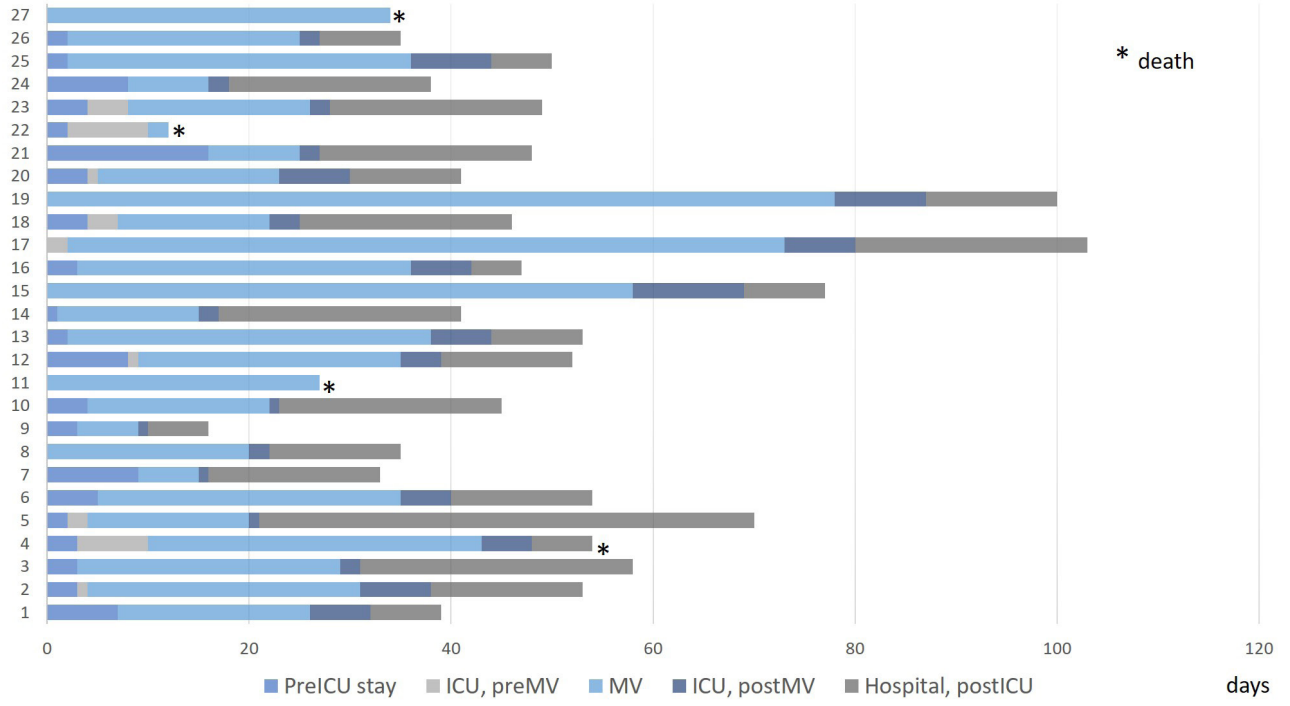

Figure 1 | **Mechanical ventilation and ICU and hospital stay times for each patient (MV: mechanical ventilation; ICU: intensive care unit)**

Table 2 | **Treatment received**

	Overall	Group A	Group B	p
Lopinavir-ritonavir	20 (74.1)	10 (83.3)	10 (66.7)	0.326
Interferon ß-1b	11 (40.7)	6 (50)	5 (33.3)	0.381
Corticosteroid bolus (preICU)	6 (22.2)	2 (16.7)	4 (26.7)	0.535
Tocilizumab (preICU)	3 (11.1)	2 (16.7)	1 (6.7)	0.411
Tocilizumab (in ICU)	8 (29.6)	0	8 (53.3%)	0.003
Hydroxychloroquine	27 (100)			
Methylprednisolone	27 (100)			
Days methylprednisolone	3 (3, 4)	3 (2, 4)	3 (3, 4.2)	0.294
Antibiotic	27 (100)			

receive MV. For the remaining series, the pO_2/FiO_2 ratio at the onset of MV varies between 130 and 169, and incidence of ARDS is around 70%. In our series, 55% of patients continue to comply with moderate ARDS criteria after 7 days under MV. Median time until a pO_2/FiO_2 ratio above of 200 is 9 days. The severity of respiratory failure of our patients is also reflected in the percentage of patients requiring ventilation in prone position (96.3%), in the high number of sessions they received, with a median of 7, and the duration of MV (median 23 days); only the Blake et al. and Rodríguez et al. series are close, with 79% and 82%, respectively, of patients that receive ventilation in prone position. The remaining series vary between 11.5% [20] and 50% [22,23].

Contrary to the severity of respiratory failure, we have barely observed other cases of organ failure, as reflected in the median SOFA score: 4 (4, 7). Both the Vitoria and Tarragona studies reported a higher score (7 and 6, respectively) [19,22] and Yang et al. published an incidence of renal failure and liver dysfunction of 29% [20].

Table 3 Respiratory therapy

	Overall	Group A	Group B	p
NIV	15 (55.6)	8 (66.7)	7 (46.7)	0.299
Days NIV	1 (0, 3)	0.5 (0, 2.7)	1 (0, 7)	0.435
MV	27 (100)			
Days MV	23 (15, 33)	15.5 (8.2, 18)	33 (26, 36)	<0.001
Prone ventilation	26 (96.3)	11 (91.7)	15 (100)	0.255
Prone vent sessions	7 (4.7, 9.2)	6 (3, 8)	7 (5, 17)	0.076
pO_2/FiO_2 < 200 at 7 d	15 (55.5)	4 (36.4)	11 (78.6)	0.032
Days moderate ARDS	9 (4, 16)	5 (2.2, 12.7)	15 (9, 21)	0.014
Tracheotomy	12 (44.4)	0	12 (80)	<0.01

NIV: non-invasive respiratory support, MV: mechanical ventilation, d: days

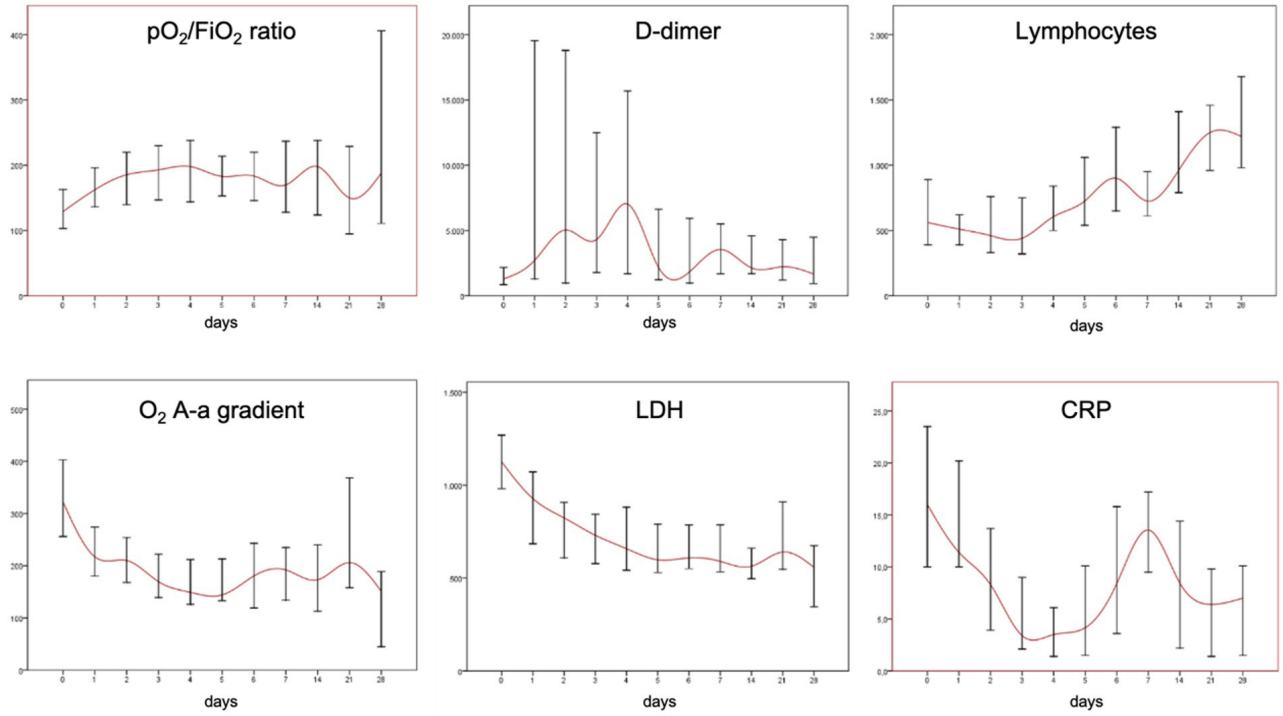

Figure 2 Evolution of inflammatory and respiratory parameters from starting corticosteroid treatment: D-dimer (ng/mL); LDH, lactate dehydrogenase, U/L); Lymphocytes count, cells/mL); CRP, C-reactive protein, mg/dL); O_2 A-a gradient, mmHg; pO_2/FiO_2 ratio

Barrasa et al. and Rodríguez et al. [19,22] reviewed treatments administered to their patients. In both studies and ours, treatment most commonly administered were hydroxychloroquine (>90%) and lopinavir-ritonavir (74.1% in our case, above the 90% in the other two series). Less homogeneous is the interferon β-1B treatment, received by less than 50% of patients from Rodríguez et al's. study and ours, and 85% of patients from the Barrasa et al. series; and tocilizumab treatment (40.7% in our study, less than 5% in the other two). All our patients received corticosteroids after onset of MV, as opposed to 35% of the Vitoria et al. study, 2.3% of the Tarragona study, and 58% of patients from the Yang et al. study [19, 20, 22].

When attempting to evaluate the impact of the treatment with corticosteroids, we observed a significant reduction in

Table 4 Evolution of respiratory and inflammatory parameters

		Day 0	Day 3	Day 5	Day 7
D-dimer (ng/mL)	Value	1290 (843, 2865.5)	4308 (1776, 12485)	2166.5 (1228.2, 8281.2)	3541 (1673, 5507)
	p (compared to day 0)		0.067	0.096	0.033
LDH (U/L)	Value	1126 (817.5, 1361)	730.5 (542, 871.7)	598.5 (528.2, 793.5)	590.0 (525.5, 800)
	p (compared to day 0)		<0.001	<0.001	<0.001
Lymphs count (cells/mL)	Value	560 (380, 900)	440 (315, 800)	725 (518.7, 1182.5)	725 (540.9, 1122.5)
	p (compared to day 0)		0.296	0.078	0.031
CRP (mg/dL)	Value	16 (8.6, 24.0)	3.4 (1.7, 10.2)	4.1 (1.4, 10.2)	13.5 (6.8, 17.3)
	p (compared to day 0)		<0.001	<0.001	0.063
O_2 A-a grad (mmHg)	Value	322 (249, 425)	169 (129.5, 239.5)	144 (127.5, 228.0)	192 (120, 261)
	p (compared to day 0)		<0.001	<0.001	0.002
pO_2/FiO_2	Value	129 (100, 168)	193 (140, 236)	183 (141, 255)	170 (116, 251)
	p (compared to day 0)		0.002	0.004	0.057

LDH: lactate dehydrogenase, lymphs: lymphocytes, CRP: C reactive protein, grad: gradient

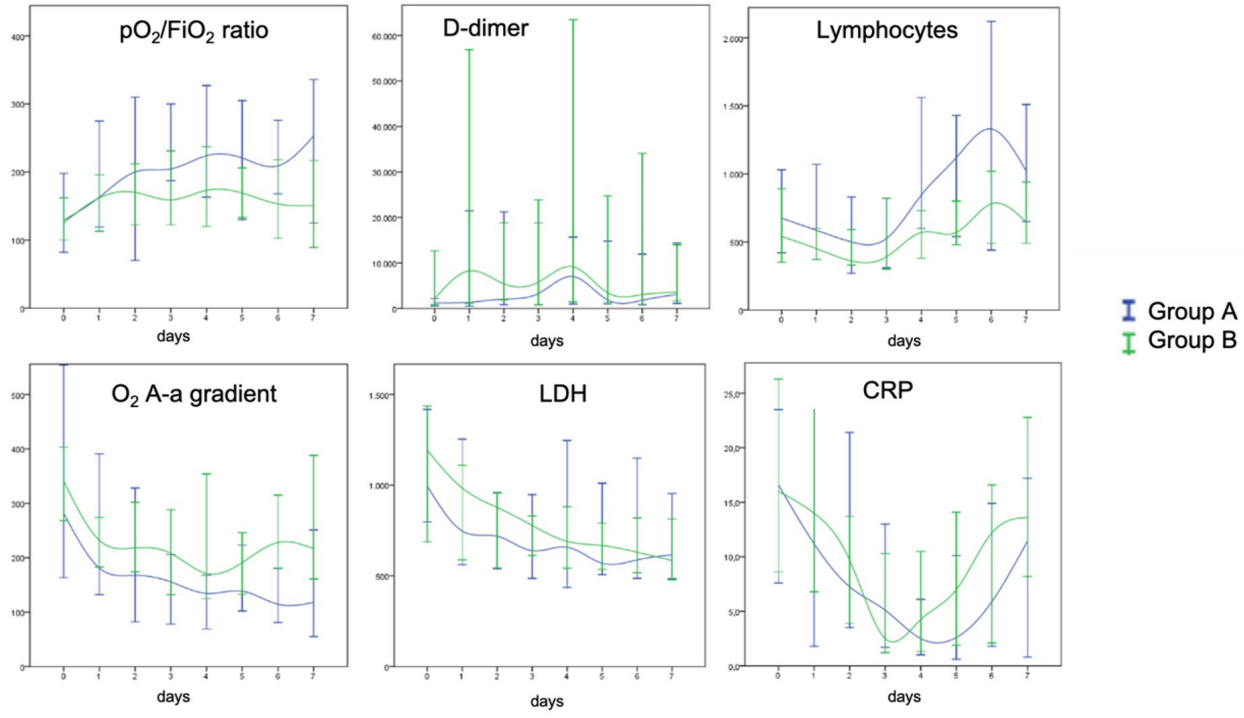

Figure 3 Evolution of inflammatory and respiratory parameters in group A and group B patients: D-dimer (ng/mL); LDH, lactate dehydrogenase, U/L); Lymphocytes count, cells/mL); CRP, C-reactive protein, mg/dL); O_2 A-a gradient, mmHg; pO_2/FiO_2 ratio

Table 5 Comparison of the evolution in respiratory and inflammatory parameters between Group A and B

		Day 0	Day 3	Day 5	Day 7
D-dimer	Group A	1290	3321	1874	3082
(ng/mL)		(663, 2028)	(1806, 9177)	(1228.2, 13631.7)	(1226.7, 5503.2)
	Group B	2797	9144	3435	3541
		(862, 10437)	(1504.5, 21219.7)	(1217.7, 4741)	(1788, 11450)
	p	0.099	0.462	1	0.563
O_2 A-a	Group A	282	155.5	138.5	118
grad		(166.7, 521.7)	(83.5, 205.5)	(103.2, 208.5)	(70, 225)
	Group B	341	191	191	216.5
		(268, 403)	(136.5, 239.5)	(136.5, 239.5)	(170, 340)
	p	0.626	0.190	0.157	0.006
LDH	Group A	995.5	638.5	569.5	616
(U/L)		(804.5, 1363.5)	(497, 941.2)	(511.7, 959.2)	(522.2, 943.5)
	Group B	1205	778	667	585
		(1019, 1345)	(618, 820.2)	(557, 785.5)	(518, 787)
	p	0.495	0.954	0.644	0.439
Lymphs count	Group A	675	525	1120	1020
(cells/mL)		(427.5, 997.5)	(312.5, 810)	(590, 1420)	(665, 1440)
	Group B	540	390	570	645
		(350, 890)	(310, 785)	(506.2, 762.5)	(497.5, 880)
	p	0.421	0.785	0.040	0.051
pO_2/FiO_2	Group A	129	204.5	220.5	253
		(87.5, 191.5)	(189.7, 290)	(135, 296.2)	(145.332)
	Group B	125	159	169	150.5
		(100, 162)	(125, 227.2)	(143, 205.5)	(97.2, 187.7)
	p	0.660	0.051	0.211	0.027
CRP	Group A	16.6	5.1	2.6	11.4
(mg/dL)		(8.2, 22.9)	(2, 12.3)	(1.2, 9)	(1.2, 16.6)
	Group B	16	2.5	7	13.6
		(8.6, 26.3)	(1.5, 9)	(2, 13.6)	(9.5, 21.1)
	p	0.626	0.498	0.224	0.190

Grad: gradient, LDH: lactate dehydrogenase, lymphs: lymphocytes, CRP: C reactive protein

LDH, CRP and O_2 A-a gradient, in addition to an increase in pO_2/FiO_2 ratio. CRP levels decreased initially and went up again once methylprednisolone treatment ended. No statistically significant differences between median CRP on day 7 and at onset of treatment were detected. The pO_2/FiO_2 ratio also increased initially and then reduced until there were no statistically significant differences between days 0 and 7 of MV. These trends appear to coincide with the time when patients received methylprednisolone; given the results of clinical trials with lopinavir-ritonavir and hydroxychloroquine [27–29], it does not appear that this effect can be attributed to the remaining treatments received by our patients. On the other hand, the initial favorable course with subsequent worsening leads us to suspect that this is not natural disease course, but rather can be impacted by the administration of methylprednisolone. Wu et al. observed that patients with COVID-19 and ARDS who had received methylprednisolone presented longer survival [8], and preliminary results of RECOVERY trial show that low doses of dexamethasone reduce the mortality of COVID-19 patients that require respiratory support, especially MV [17]

Table 6 Poor outcome predictors. Univariate analysis

	OR	CI	p
Positive control PCR	2.8	0.582-13.478	0.199
Positive control PCR x 2	3.25	0,480-21,997	0.227
Coinfection on admission	1.6	0.346-7.401	0.548
Severe ARDS day 0 MV	2.8	0.222-35.288	0.426
Moderate ARDS day 0 MV	1.091	0.192-6.196	0,922
Moderate ARDS day 7 MV	6.417	1.091-37.735	0.040
CRP > 10 mg/dL day 0 MV	1.375	0.262-7.220	0.707
CRP > 10 mg/dL day 7 MV	1.429	0.297-6.977	0.656
< 500 lymphocytes day 0 MV	1.225	0.265-5.667	0.795
< 500 lymphocytes day 7 MV	3	0.269-33.487	0.372

ARDS: acute respiratory distress syndrome, MV: mechanical ventilation, CRP: C reactive protein

One differentiating aspect of our series is the high incidence of co-infection at ICU admission (48.1%). Following our protocol, 100% of patients received empiric antibiotic treatment. Similar data were observed in the series by Yang et al. and Barrasa et al. in which 94% and 88% of patients received antibiotics [20, 22]. Conversely, in the Tarragona study no case of coinfection was identified and only 11.6% of patients received antibiotics at ICU admission. Arentz et al. report an incidence of bacterial and viral coinfection of 4.8% and 14.3%, respectively. Bhatraju et al. did not find any cases of coinfection despite an active search [24]. It is possible that the differences observed are due to the definition used, including both cultures/serology results and elevation of biomarkers.

We were unable to detect any variable at MV onset that could help us predict worse clinical course either from the point of view of age or comorbidities, or from the viewpoint of inflammatory or respiratory parameters. Hua et al. observed that patients who required MV presented a lower lymphocytes count, and CRP levels were higher [26]. Wang et al. detected that also D-dimer was higher in patients requiring MV [30]. We have observed that patients from group B presented a higher O_2 A-a gradient and a lower pO_2/FiO_2 ratio after 7 days under MV. Persistence of moderate ARDS after 7 days of MV increases the risk of poor outcome (OR 6.417, CI 95% 1.091-37.735, p=0.040). This finding coincides with that published by Rodríguez et al. who reported that among patients who died, the pO_2/FiO_2 ratio did not improve after 7 days of treatment [19]

A notable aspect of our series is the low 28 days mortality rate (7.4%). Blake et al. presented ICU mortality of 21% (with 15 of the 39 patients still in the ICU) [21]. In the Italian and the Tarragona series, they also reported ICU mortality of 26% and 23.3% (28.1% among patients who received MV), respectively [19, 25]. Mortality was significantly higher in the remaining studies: 36% at 28 days in the Barrasa et al. series [22], 50% hospital mortality in the Bhatraju et al. [24] and Wang et al. series [30], 52.4% at 5 days in the Arentz et al. study [23], 61.5% at 28 days in the Yang et al. series [20] and up to 92% in patients with MV reported by Hua et al. [26]. This lower mortality does not appear to be related to less severity in our patients. As we have discussed, it is possible that the incidence of non-respiratory organ failure is lower for our patients, however, the respiratory failure is more severe and lasts longer. It could be considered that the reduced number of patients in our series did not entail an exceptional overload for our ICU, but 22 patients requiring MV simultaneously were treated, meaning an occupation of 157% of the beds usually available for MV. Once we know the results of RECOVERY trial, the use of corticosteroids may have been a reason for this low mortality (although 28 days mortality in mechanical ventilated patients receiving dexamethasone in this trial is 29.3%). We believe that some factors such as the experience managing ARDS patients of staff treating these patients, in addition to organization of the COVID-ICU, may have played an important role. However, we would not go so far as to attribute the reduction in our mortality to a specific single aspect.

Our study presents significant limitations. First, the reduced sample size, which hinders detecting possible discrepancies between groups. Second, the high survival observed prevents comparisons of groups based on mortality and led us to use a composite outcome (mortality or prolonged MV). Third, absence of a control group makes it impossible to draw definitive conclusions about methylprednisolone effect. Fourth, this is a single hospital series with some specific characteristics and some solutions applied in our hospital context, which complicates extrapolation of our results to another type of patient or center.

To conclude, our COVID-19 patients presented severe and long lasting ARDS; a short course of low dose corticosteroids appears to reduce the inflammation and temporarily improve the oxygenation. Only persistence of ARDS after 7 days under MV was a predictor of poor outcome.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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