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ORIGINAL ARTICLE

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Corticosteroids and tocilizumab reduce in-hospital mortality in severe COVID-19 pneumonia: a retrospective study in a Spanish hospital

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ABSTRACT

Background: There is an urgent need to reduce mortality of COVID-19. We examined if corticosteroids and tocilizumab reduce risk for death in patients with severe pneumonia caused by SARS-CoV-2.

Methods: A retrospective cohort study was performed in a single university hospital. All adult patients admitted with confirmed severe COVID-19 pneumonia from 9 March to 9 April 2020 were included. Severe pneumonia was defined as multilobar or bilateral pneumonia and a ratio of oxygen saturation by pulse oximetry to the fraction of inspired oxygen (SpFi)$<$315. All patients received antiviral and antibiotic treatment. From March 26, patients also received immunomodulatory treatment with corticosteroids (methylprednisolone 250 mg/day for 3 days), or tocilizumab or both. In-hospital mortality in the entire cohort and in a 1:1 matched cohort sub-analysis was evaluated.

Results: 255 patients were included, 118 received only antiviral and antibiotic treatment while 137, admitted after March 26, also received immunomodulators. In-hospital mortality of patients on immunomodulatory treatment was significantly lower than in those without [47/137(34.3%) *vs.* 69/118(58.5%), ($p < .001$)]. The risk of death was 0.44 (CI, 0.26–0.76) in patients receiving corticosteroids alone and 0.292 (CI, 0.18–0.47) in those treated with corticosteroids and tocilizumab. In the sub-analysis with 202 matched patients, the risk of death was 0.356 (CI 0.179–0.707) in patients receiving corticosteroids alone and 0.233 (0.124–0.436) in those treated with the combination.

Conclusions: Combined treatment with corticosteroids and tocilizumab reduced mortality with about 25% in patients with severe COVID-19 pneumonia. Corticosteroids alone also resulted in lower in-hospital mortality rate compared to patients receiving only antiviral and antibiotic treatment. Corticosteroids alone or combined with tocilizumab may be considered in patients with severe COVID-19 pneumonia.

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Introduction

The first cases of coronavirus infectious disease 2019 (COVID-19) were reported in Wuhan, China in December 2019. A novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was isolated and identified as the causative agent [1].

As of 17 November 2020, 53,766,728 laboratory-confirmed cases have been documented globally with 1,308,975 deaths [2]. Although most patients present with mild illness, approximately 10% require hospital admission for COVID-19 pneumonia, of which 10% will require admission to an intensive care unit (ICU) due to acute respiratory distress syndrome (ARDS) [3–5].

During the first months of the pandemic, the mainstay of management of patients with severe COVID-19 pneumonia was supportive therapy, including fluid management, oxygen therapy, and mechanical ventilation [6].

Given the hyper-inflammatory state in COVID-19, immunomodulatory approaches, including steroids and other immunomodulatory agents, have been used to treat ARDS and the systemic inflammation [7].

Early in the SARS-CoV-2 pandemic, based on experience with SARS and MERS, the IDSA (Infectious Diseases Society of America) and the World Health Organization (WHO) cautioned against the use of systemic corticosteroids due to risk of worsening clinical status, delayed viral clearance, and adverse events [8,9]

More recently, a meta-analysis and several studies suggested a clinical benefit of administration of steroids to critically ill patients with COVID-19 [10–13]. While different studies were under way, results of the UK-based Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial with 6425 patients on June 16 showed a strong benefit of dexamethasone over placebo [14]. The results of the RECOVERY trial led most ongoing trials assessing the impact of corticosteroids use to suspend recruitment.

Critically ill patients who received systemic corticosteroids were 34% less likely to die compared with those who received usual care or placebo in a prospective meta-analysis of seven randomized controlled trials sponsored by the WHO [10]. Based on these findings, on 2 September 2020, the WHO recommended use of corticosteroids in patients with severe and critical COVID-19 [15].

High cytokine levels have been observed in hospitalized patients with severe COVID-19 pneumonia, and serum levels of IL-6 are correlated with disease severity. Tocilizumab, an IL-6 receptor blocker, has been proposed as an effective drug [16], but it has not show conclusive benefits until now. Three randomized controlled trials showed that tocilizumab had no or only a modest benefit, contradicting a large retrospective study that suggested a more robust effect [17–20]. Based on these results, recent guidelines concluded that results were not good enough to support routine use and recommend against tocilizumab in the treatment of COVID-19, except in a clinical trial [21,22].

By the end of March 2020, the lack of antiviral drugs with confirmed efficacy prompted us to administer corticosteroids and tocilizumab to selected patients with severe COVID-19 pneumonia. The aim of this study was to compare the outcome of patients before and after the introduction of these immunomodulatory drugs.

Materials and methods

Setting

We conducted this study at Consorci Corporació Sanitaria Parc Tauli, a University tertiary-care hospital in the area of Barcelona, Spain.

Clinical records from all consecutive adult subjects admitted with SARS-CoV-2 infection from 9 March 2020 to 9 April 2020 were retrospectively reviewed. All patients were diagnosed by positive SARS-CoV-2 RT-PCR assay (GeneFinderTM COVID-19 Plus Real*Amp* Kit, OsangHelthcare Korea) in nasopharyngeal or oropharyngeal swabs. The assay detects three different regions of the SARS-CoV-2 genome: RdRp, E and N genes [23]. Data was manually extracted from the electronic medical and hospital pharmacy records.

From 9 March 2020, all patients admitted at the hospital with severe pneumonia were treated with at least one drug with *in vitro* antiviral activity (i.e. hydroxychloroquine, lopinavir/ritonavir, beta-1B interferon or remdesivir) plus antibiotics (mostly betalactams and/or azithromycin or quinolones).

On 26 March 2020, a guidance issued by a multidisciplinary board of experts and distributed to all attending staff at our medical centre suggested corticosteroids and tocilizumab as therapeutic options for patients with severe COVID-19 pneumonia. This protocol recommended corticosteroids and tocilizumab in patients presenting with severe respiratory illness and at least one of the following criteria: serum ferritin $>$700ng/ml or D-dimer $>$2000 ng/ml and clinical progression despite previous treatment (defined as increasing oxygen requirement and worsening of chest X-ray findings). No other

interventions were introduced in the clinical management of patients during the study period.

The suggested corticosteroid dosage was 250 mg/day of methylprednisolone for 3 days (or 120 mg/day when used concomitantly with lopinavir/ritonavir). Tocilizumab was given at a dose of 400 mg (if weight $<$75 kg) or 600 mg (if weight $\geq$ 75 kg), once or twice daily.

Study design

In this single-centre retrospective study, we compared patients who did not receive immunomodulatory treatment (admitted from 9 March 26 March 2020) with patients who received immunomodulatory treatment (admitted from 26 March to 9 April 2020). All patients received antibiotic and antiviral agents as well as standard care measures (supplemental oxygen, invasive or non-invasive mechanical ventilation, vasopressor support, and renal-replacement therapy, at the discretion of the responsible clinical team).

Definitions

- *Confirmed COVID-19 pneumonia* was defined as the presence of radiographic pulmonary infiltrates and positive RT-PCR SARS-CoV-2 in nasopharyngeal or oropharyngeal swabs in patients with signs and symptoms concordant with COVID-19.
- *Severe COVID-19 pneumonia* was defined as multilobar or bilateral pneumonia in patients who presented a ratio of oxygen saturation by non-invasive pulse oximetry to the fraction of inspired oxygen (SpFi) below 315 [24].
- *Immunomodulatory treatment* was defined as one of the following regimens: corticosteroids, tocilizumab or corticosteroids plus tocilizumab. The specific immunomodulatory regimen was at the discretion of the treating physician.
- *Immunomodulatory Treatment Decision (ITD) time* was defined as the date when immunomodulatory treatment was started. For patients who did not receive immunomodulatory treatment, ITD was the first day that they fulfilled the criteria to receive such treatment.

Inclusion and exclusion criteria

All adult patients admitted to the hospital with confirmed severe COVID-19 pneumonia were considered for the study. Only patients receiving treatment with *in vitro* antiviral activity (hydroxychloroquine, lopinavir/ritonavir, beta-1B interferon or remdesivir) plus antibiotics were included in the analysis.

Patients without a positive RT-PCR SARS-CoV-2 in nasopharyngeal or oropharyngeal swabs were excluded. Patients who received methylprednisolone at lower doses than 60 mg/day or any corticosteroid at equivalent dose were excluded.

Variables

The following variables were recorded for each patient: age, gender; symptoms at presentation, vital signs at admission, laboratory and chest X-ray findings, comorbidities and current diagnoses, treatment administered, maximum oxygen-administration required, ICU admission, complications during hospital stay and outcomes.

Treatment groups

Two treatment groups were defined depending on whether immunomodulatory treatment was administered. We defined three categories in the immunomodulatory treatment group: corticosteroids alone, tocilizumab alone and corticosteroids plus tocilizumab.

Outcome

The primary outcome was in-hospital mortality rate in the groups with and without immunomodulatory treatment. The secondary outcome was in-hospital mortality rate in the three immunomodulatory treatment groups (corticosteroids, tocilizumab, corticosteroids plus tocilizumab).

Statistical analysis

Continuous variables are reported as median and interquartile range (IQR) and compared using the Kruskall–Wallis or Mann–Whitney test, as appropriate. Categorical variables are reported as number and percentage and compared using the Chi-squared test. The sample size was derived from all eligible consecutive hospitalized patients during the study period. Follow-up ended at discharge or death. Patients who were still admitted to the hospital on May 19 were censored. We used bivariate and multivariable Cox-proportional hazards model analyses to test the association between in-hospital mortality and receipt of each immunomodulatory treatment. In order to control for confounding factors, covariates in the bivariate analysis with a p-value $<$.2 as

well as those with clinical rationale were included in the multivariate analysis. The final model was derived following a backward stepwise procedure. Cohorts were matched 1:1 for age, gender, number of comorbidities and SpFi at ITD, using MatchIT Package 2018 of R software (R Core Team), with the *nearest neighbour matching* method (caliper = 0.25).

A two-sided *p*-value <.05 was considered statistically significant. We used the software package IBM SPSS Statistics for Windows, Version 25.0. IBM Corp. Released 2017, Armonk, NY: IBM Corp. for statistical analysis.

Ethical considerations

The study was approved by the Institutional Review Board of Corporació Sanitària Parc Taulí. Because no direct patient contact was planned, the requirement for informed consent was waived. The data was de-identified and only then transferred for analysis.

Results

Clinical records of 486 patients admitted to our hospital with confirmed SARS-CoV-2 infection were reviewed. 255 fulfilled all the inclusion and none of the exclusion criteria and were included in the analysis (Figure 1).

Overall, 172 (67.5%) patients were male. The median age was 73,2 (IQR 61.0–79.2) years. The median number of chronic comorbidities was 3 (IQR 2–4) (Table 1). Diagnosis of SARS-CoV-2 infection was confirmed a median of 6 (IQR 3.5–8) days after onset of symptoms. The most frequent first symptoms were fever, cough and dyspnoea. Almost all patients had bilateral pneumonia (237, 92.9%), and 190 (74.9%) had a CURB-65 score above 1 at admission. At ITD, the median SpFi ratio was 178 (IQR 116–266). In-hospital death occurred in 116 (45.5%) patients.

Of all 255 patients, 118 did not receive any immunomodulatory treatment, while 137 patients did (Table 2). Seventy-eight patients received corticosteroids plus tocilizumab, 38 corticosteroids alone and 21 tocilizumab alone.

There were no significant differences in age [median 73.7 years (IQR 60.5–82.1) vs. 73.1 years (IQR 71.5–77.6), $p = .154$] or number of baseline comorbidities [median 3 (IQR 2–5) vs. 3 (IQR 1–4), $p = .356$] between patients not receiving and receiving immunomodulators, respectively. Median SpFi ratio at ITD was lower in patients on

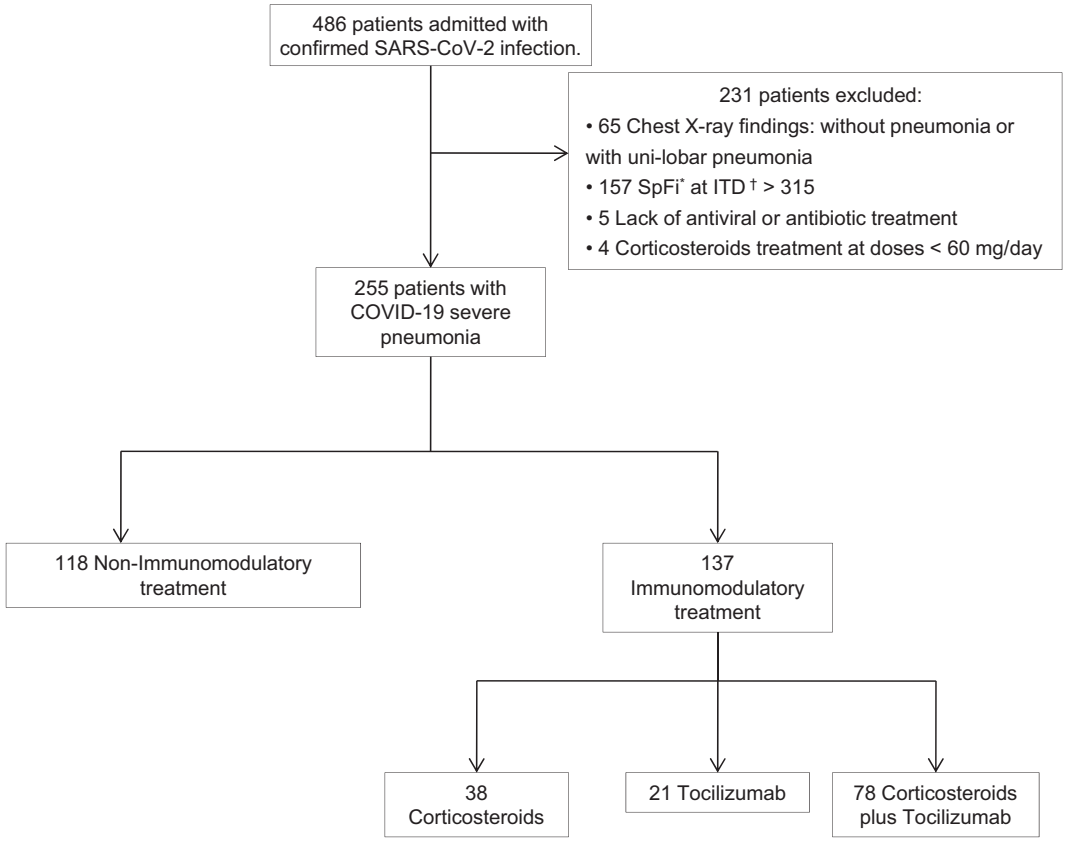

Figure 1. Study flowchart. SpFi: pulse oximetry oxygen saturation/fraction of inspired oxygen ratio; ITD: Immunomodulatory treatment decision day.

Table 1. Demographic and clinical characteristics of patients with severe pneumonia caused by SARS-CoV-2.

	All patients $n = 255$
Age, median (IQR) (years)	73.2 (61.0–79.2)
Male gender, *n* (%)	172 (67.5)
Origen of infection	
Community acquired infection, *n* (%)	215 (84.3)
Close contact with a case of COVID-19, *n* (%)	64 (25.2)
Comorbidities, *n* (%)	
Hypertension	159 (62.4)
Dyslipidemia	126 (49.4)
Obesity	94 (36.9)
Diabetes	81 (31.8)
Chronic Pulmonary Disease	80 (31.4)
Cardiovascular disease	91 (35.7)
Chronic renal disease	45 (17.6)
Cancer	30 (11.8)
Immunosuppressive condition	22 (8.6)
Brain vascular disease	19 (7.5)
Chronic liver disease	7 (2.7)
Renal replacement therapy	3 (1.2)
Human immunodeficiency virus infection	0 (0)
Number of comorbidities, median (IQR)	3 (2–4)
Treatment with ACE inhibitors or ARBs, *n* (%)	113 (44.3)
Symptoms, *n* (%)	
Fever	227 (89.0)
Cough	190 (74.5)
Dyspnoea	179 (70.2)
Asthenia	91 (35.7)
Arthromyalgia	73 (28.6)
Diarrhea	59 (23.1)
Sputum production	54 (21.2)
Nausea	43 (16.9)
Anorexia	39 (15.3)
Flu-like syndrome	34 (13.3)
Headache	19 (7.5)
Days from first symptoms to SARS-CoV-2 PCR, median (IQR)	6 (3.5–8)
Physical examination at admission, median (IQR)	
Heart rate (bpm)	86 (76–98)
Systolic blood pressure (mmHg)	127 (115–140)
Diastolic blood pressure (mmHg)	70 (60–79)
Basal oxygen Saturation (%)	91.9 (88–95.5)
PaFi	259.5 (176.6–317.4)
SpFi	407.2 (279.4–443)
Blood analysis at admission, median (IQR)	
Leucocytes count(10^9/L)	6.58 (5.14–8.93)
Lymphocytes count (10^9/L)	0.87 (0.65–1.17)
Platelets count (10^9/L)	180 (123–235)
Hemoglobin (g/L)	13.5 (12.3–14.6)
C-Reactive protein (mg/dL)	13.2 (9.2–19.1)
Prothrombin time ratio	1.18 (1.11–1.29)
D-dimer (ng/mL)	986 (540–1.599)
Creatinine (mg/dL)	1.07 (0.85– 1.35)
ALT (U/L)	28 (16–39)
AST(U/L)	34 (21.8–49.8)
Lactic acid (mg/dL)	14.5 (11.4–19.9)
CURB-65 scale-score$<=$1, *n* (%)	64 (25.1)
Chest X-ray, *n* (%)	
Multi-lobar pneumonia	18 (7.1)
Bilateral pneumonia	237 (92.9)
Diagnostic of co-infections, *n* (%)	
Influenza	1 (0.7)
Streptococcus pneumoniae	6 (2.4)
Any antibiotic treatment, *n* (%)	255 (100)
Azithromycin	224 (87.8)
Ceftriaxone	206 (80.8)
Amoxycilin/clavulanic acid	29 (11.4)
Quinolones	71 (27.8)
Piperacillin/tazobactam	38 (14.9)
Carbapenems	25 (9.8)
Any antiviral treatment	255 (100)
Lopinavir/ritonavir, *n* (%)	179 (70.2)
Lopinavir/ritonavir days, median (IQR)	3 (1.5–6)
Hydroxychloroquine, *n* (%)	245 (96.1)
Hydroxychloroquine days, median (IQR)	7 (4–9)
Beta-1B interferon, *n* (%)	85 (33.3)

(*continued*)

Table 1. Continued.

	All patients $n = 255$
Beta-1B interferon days, median (IQR)	4 (2–6)
Remdesivir, *n* (%)	6 (2.4)
Remdesivir days, median (IQR)	8 (4–10)
Need for oxygen therapy, *n* (%)	
Air-entrainment mask	55 (21.6)
Reservoir mask	47 (18.4)
High flow oxygen	4 (1.6)
CPAP	80 (31.4)
BiPAP	31 (12.2)
Tracheal intubation	38 (14.9)
SpFI at ITD, median (IQR)	178 (116–266)
PaFI at ITD, median (IQR)	124 (91–159)
Days from SARS-CoV-2 PCR to ITD, median (IQR)	4 (2–7)
Blood test at ITD, median (IQR)	
Leucocytes count(10^9/L)	8.02 (5.84–11.46)
Lymphocytes count (10^9/L)	8.10 (5.7–1.14)
Platelets count (10^9/L)	234 (177–316)
Hemoglobin (g/L)	12.2 (11.1–13.4)
C-Reactive protein (mg/dL)	9.9 (5.2–20.3)
Prothrombin time ratio (mg/dL)	1.23 (1.14–1.37)
D-dimer (ng/mL)	2.055 (1.012–7.661)
Ferritin (ng/mL)	1.383 (714–2.170)
Creatinine (mg/dL)	0.88 (0.7–1.19)
ALT(U/L)	33 (19–55.8)
AST(U/L)	36 (27–58)
LDH (U/L)	344 (272–467)
Non- Immunomodulatory treatment, *n* (%)	118 (46.3)
Immunomodulatory treatment, *n* (%)	137 (53.7)
Corticosteroids	38 (14.9)
Tocilizumab	21 (8.2)
Corticosteroids plus tocilizumab[a]	78 (30.6)
Corticosteroids dose, median (IQR)	750 (750–750)
Tocilizumab dose, median (IQR)	600 (400–600)
400 mg	26 (10.2)
600 mg	50 (19.6)
> =800 mg	23 (70.2)
Complications, *n* (%)	
Cardiac event	28 (11)
Bacteremia/fungemia	17 (6.7)
Pulmonary Thromboembolism or deep vein thrombosis	15 (5.9)
Hemodynamic shock	10 (3.9)
Need for dialysis	4 (1.6)
Admission to intensive-care unit, *n* (%)	48 (18.8)
In-hospital mortality, *n* (%)	116 (45.5)
Days from ITD to death, median (IQR)	4 (3–7)
Discharged, *n* (%)	126 (49.4)
Length of hospital stay, median (IQR)	14 (8–22)
Ongoing patients, censored on 05/19/2020, *n* (%)	13 (5)
Length of hospital stay, median (IQR)	61 (58–63)

IQR: Interquartile range; ACE inhibitors: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; PCR: polymerase chain reaction test; PaFi: partial pressure of arterial blood oxygen/fraction of inspired oxygen ratio; SpFi: pulse oximetry oxygen saturation/fraction of inspired oxygen ratio; ALT: Alanine transaminase; AST: Aspartate transaminase; CPAP: Continuous positive airway pressure; BiPAP: bilevel positive airway pressure; ITD: Immunomodulatory treatment decision day; LDH: lactate dehydrogenase.
[a]Anakinra was administered as rescue therapy to 6 (7.7%) patients.

immunomodulatory treatment [219 (IQR 120–278) vs. 123 (IQR 116–237), $p = .001$]. In-hospital mortality was significantly lower in patients receiving immunomodulatory treatment (47/137, 34.3%) than in patients who did not (69/118, 58.5%), ($p < .001$).

In-hospital mortality rate was 44.7% ($n = 17$) in the corticosteroids group, 33.3% ($n = 7$) in the tocilizumab group and 29.5% ($n = 23$) in the group that received corticosteroids plus tocilizumab (Figure 2(A)). When comparing baseline and clinical characteristics of each of the three immunomodulatory treatment groups with the group not given such treatment, some differences were observed: patients treated with tocilizumab were younger ($p < .001$), had lower SpFi ratios at ITD ($p = .029$) and higher lactate dehydrogenase (LDH) values at ITD ($p = .001$). Patients treated with corticosteroids plus tocilizuman had lower SpFi ratio ($p = .003$) and C-reactive protein (PCR) at ITD ($p = .005$), but higher LDH ($p = .025$) and D-dimer at ITD ($p = .046$). Patients treated with corticosteroids alone did not differ significantly from those not receiving immunomodulatory treatment.

Cox-regression model analysis of independent factors associated with in-hospital mortality was adjusted by the

Table 2. Comparison of patients with severe pneumonia caused by SARS-CoV-2 according to the immunomodulatory treatment administered.

	Non-immunomodulatory $n = 118$	Immunomodulatory treatment $n = 137$			*p*-Value
		Corticosteroids $n = 38$	Tocilizumab $n = 21$	Corticosteroids plus Tocilizumab $n = 78$	
Baseline characteristics					
Age. median (IQR) (years)	73.7 (60.5–82.1)	75. 6 (67.3–83.8)	61.5 (51.2–71.4)	73.3 (63.3–76.8)	**<.001**
Male gender, *n* (%)	77 (65.3)	27 (71.7)	16 (76.2)	52 (66.7)	.744
Origen of infection					
Community acquired infection, *n* (%)	95 (80.5)	32 (84.2)	20 (95.2)	68 (87.2)	.299
Close contact with a case of COVID-19, *n* (%)	23 (19.5)	9 (24.3)	4 (19.0)	28 (35.9)	.065
Comorbidities, *n* (%)					
Hypertension	81 (68.6)	20 (52.6)	11 (52.4)	47 (60.3)	.207
Dyslipidemia	57 (48.3)	21 (55.3)	7 (33.3)	41 (52.6)	.382
Obesity	41 (34.7)	13 (34.2)	5 (23.8)	35 (44.9)	.258
Diabetes	44 (37.3)	11 (28.9)	3 (14.3)	23 (29.5)	.176
Chronic Pulmonary Disease	34 (28.8)	12 (31.6)	6 (28.6)	28 (35.9)	.758
Cardiovascular disease	48 (40.7)	15 (39.5)	5 (23.8)	23 (29.5)	.249
Chronic renal disease	26 (22.0)	8 (21.1)	2 (9.5)	9 (11.5)	.185
Cancer	14 (11.9)	4 (10.5)	1 (4.8)	11 (14.1)	.692
Immunosuppressive condition	6 (5.1)	2 (5.3)	3 (14.3)	11 (14.1)	.100
Brain vascular disease	10 (8.5)	5 (13.2)	0	4 (5.1)	.233
Chronic liver disease	3 (2.5)	1 (2.6)	1 (4.8)	2 (2.6)	.950
Renal replacement therapy	3 (2.5)	0	0	0	.318
Human immunodeficiency virus infection	0	0	0	0	.150
Number of comorbidities, median (IQR)	3 (2–5)	3 (1–4)	2 (1–3)	3 (2–4)	
Treatment with ACE inhibitors or ARBs, *n* (%)	59 (50)	15 (39.5)	6 (31.6)	33 (42.3)	.353
At admission					
Days from first symptoms to SARS-CoV-2 PCR, median (IQR)	5.5 (3–8)	6 (3–8)	6 (4–8)	7 (4–10)	.242
Basal oxygen Saturation (%), median (IQR)	92 (87–96)	91 (84.5–96)	91 (86.5–95)	92 (89–95)	.937
PaFi at admission, median (IQR)	261 (185.5–327)	240.5 (155–325.5)	290 (193–323)	256 (165–304)	.336
SpFi at admission, median (IQR)	402 (302–443)	412 (183.5–443)	400.5 (251–443)	417 (294–444)	.914
CURB-65 scale-score ≤ 1, *n* (%)	30 (25.9)	10 (26.3)	7 (33.3)	17 (22.4)	.779
Immunomodulatory treatment decision day (ITD), median (IQR)					
SpFi at ITD	219 (120–278)	125 (116–161)	123 (118–227)	121 (116–235)	**.013**
Lymphocytes count (10^9/L)	980 (780–1760)	710 (560–1055)	1140 (950–1280)	570 (460–850)	.570
C-Reactive protein (mg/dL)	13.24 (5.45–22.11)	9.35 (5.91–22.43)	9.07 (4.9–22.46)	7.15 (2.31–14.42)	**.045**
D-dimer (ng/mL)	1573 (960–4662)	2298 (969–6845)	5681 (1072–23267)	2166 (1112–17516)	.125
Ferritin (ng/mL)	1192 (665–2221)	1299 (687–2194)	1326 (808–2310)	1577 (859–2128)	.892
LDH (U/L)	331 (264–396)	340 (260–487)	468 (346–607)	380 (271–516)	**.004**
Outcomes, *n* (%)					
In-hospital mortality	69 (58.5)	17 (44.7)	7 (33.3)	23 (29.5)	**.001**
Discharged or ongoing on 05/19/2020	49 (41.5)	21 (55.3)	14 (66.7)	55 (70.5)	**<.001**

IQR: Interquartile range; ACE inhibitors: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; PCR: polymerase chain reaction test; PaFi: Partial pressure of arterial blood oxygen/Fraction of inspired oxygen ratio; SpFI: pulse oximetry oxygen saturation/fraction of inspired oxygen ratio; LDH: lactate dehydrogenase.

p values smaller than .05 are marked as bold values.

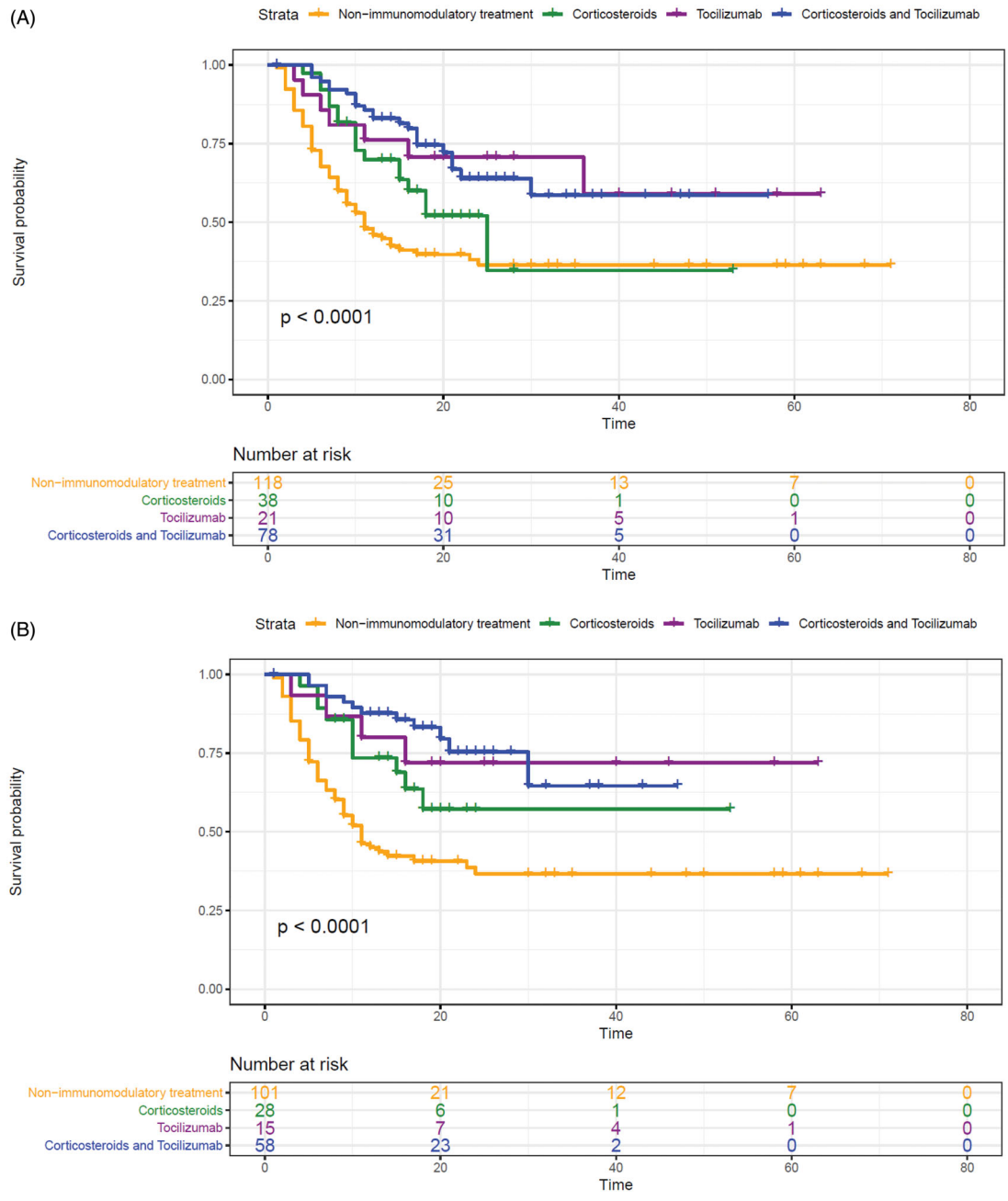

Figure 2. Kaplan–Meier survival analysis of in hospital mortality of patients with severe pneumonia caused by SARS-Cov-2, according to the immunomodulatory treatment administered. (A) Survival analysis in the whole cohort ($n = 255$). (B) Survival analysis in the paired 1:1 cohort ($n = 202$).

following variables: age, gender number of comorbidities, CURB-65 score at admission, treatment with angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers, SpFi ratio at admission and at ITD, D-dimer, ferritin, lymphocytes count and LDH at ITD and specific immunomodulatory regimen -considering the group with no immunomodulatory treatment as reference (Table 3).

Treatment with corticosteroids alone or combined with tocilizumab was associated with lower probability of death compared to not receiving immunomodulatory treatment, with a hazard ratio of 0.443 (CI, 0.257–0.761) and 0.292 (CI, 0.180–0.474), respectively (Table 3). Tocilizumab alone was not significantly associated with probability of death. The same associations were found when all patients who died during the first 24 h after ITD were excluded from analysis (data not shown). After matching patients 1:1 for age, gender, number of comorbidities and SpFi at ITD, a sample of 202 patients was obtained. When the same analysis was repeated in the matched subgroup, corticosteroids alone or in combination with tocilizumab remained associated with

Table 3. Cox-regression analysis to assess risk factors for in-hospital mortality among patients admitted with SARS-CoV-2 severe pneumonia.

	Alive[a] $n = 139$	In-hospital mortality $n = 116$	Cox regression analysis	
			Univariate *p*-value	Multivariate HR (95%IC)
Baseline characteristics				
Age, median (IQR) years	68.3 (57.3–75.3)	75.7 (69.2–83.4)	**<.001**	**1.040 (1.023–1.057)**
Male gender, *n* (%)	93 (66.9)	79 (68.1)	.950	
Non-community acquired infection, *n* (%)	12 (8.6)	28 (24.1)	**.010**	
Comorbidities, *n* (%)				
Hypertension	78 (56.1)	81 (69.8)	**.047**	
Dyslipidemia	63 (45.3)	63 (54.3)	.318	
Obesity	52 (37.4)	42 (36.2)	.642	
Diabetes	33 (23.7)	48 (41.4)	**.001**	
Chronic Pulmonary Disease	39 (28.1)	41 (35.3)	.196	
Brain vascular disease	7 (5.0)	12 (10.3)	.105	
Cardiovascular disease	31 (22.3)	60 (51.7)	**<.001**	
Chronic renal disease	16 (11.5)	29 (25.0)	**.002**	
Cancer	13 (9.4)	17 (14.7)	.252	
Immunosuppressive condition	11 (7.9)	11 (9.5)	.993	
Chronic liver disease	2 (1.4)	5 (4.3)	.215	
Number of comorbidities, median (IQR)	2 (1–3)	3 (2–5)	**<.001**	
Treatment with ACE inhibitors or ARBs, *n* (%)	54 (39.1)	59 (51.3)	.050	
At admission				
Days from first symptoms to SARS-CoV-2 PCR, median (IQR)	7 (4–9)	5 (3–8)	.462	
Basal oxygen Saturation (%), median (IQR)	93 (89–96)	91 (85–95)	**.028**	
PaFi, median (IQR)	267.9 (182.0–326.0)	252.5 (162.5–299.4)	.181	
SpFi, median (IQR)	420.7 (310–447.7)	365 (243.1–436.9)	**.013**	**0.998 (0.997–1.000)**
CURB-65 scale-score ≤ 1, *n* (%)	49 (35.8)	15 (14.0)	**.001**	
Immunomodulation therapy decision day (ITD), median (IQR)				
SpFi at ITD	213.0 (120.0–271.0)	122.0 (113.2–232.0)	**.019**	**0.996 (0.993–0.999)**
Days from SARS-CoV-2 PCR to ITD	5 (2–7)	2 (1–5)	**<.001**	
Lymphocytes count (10^9/L)	0.92 (0.65–1.37)	0.71 (0.44–0.94)	.253	
C-Reactive protein (mg/dL)	8.35 (4.33–14.95)	15.70 (6.60–21.33)	**.023**	
D-dimer (ng/mL)	1594 (857.3–6173)	4116 (1127–15,220)	**.055**	
Ferritin (ng/mL)	1425.5 (808.5–2128.4)	1346.8 (632.7–2348.2)	.124	
LDH (U/L)	321 (266–379)	443 (334–636)	**<.001**	
Immunomodulatory therapy, *n* (%)				
Non- immunomodulatory therapy	49 (35.2)	69 (59.5)		
Corticosteroids	21 (15.1)	17 (14.7)	.055	**0.443 (0.257–0.761)**
Tocilizumab	14 (10.1)	7 (6.0)	**.017**	0.479 (0.215–1.067)
Corticosteroids + tocilizumab	55 (39.6)	23 (19.8)	**<.001**	**0.292 (0.180–0.474)**

IQR: Interquartile range; ACE inhibitors: angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; PCR: polymerase chain reaction test; PaFI: partial pressure of arterial blood oxygen/fraction of inspired oxygen ratio; SpFi: pulse oximetry oxygen saturation/fraction of inspired oxygen ratio; ITD: Immunomodulatory treatment decision day; LDH: dehydrogenase lactate.

[a]16 patients still admitted on 19 May 2020 were included in this group, as they needed functional rehabilitation. All had clinical stability. Their median length of hospital stay (IQR) on 19 May 2020 was 61 days (58–63).

p values smaller than .05 are marked as bold values.

lower probability of in-hospital death (Figure 2(B), Table 4).

Discussion

This study showed that use of immunomodulatory treatment was associated with reduced in-hospital mortality in patients with severe COVID-19. The combination of corticosteroids and tocilizumab gave the greatest reduction of in-hospital mortality. Notably, patients receiving immunomodultators survived longer despite more severe respiratory parameters.

Despite the scarce evidence supporting corticosteroids or tocilizumab treatment in severe COVID-19 pneumonia by the first wave of the pandemic, both drugs were widely used.

Several studies have later found that corticosteroids are beneficial in treatment of patients with severe COVID-19 pneumonia [10–14].

In a meta-analysis assessing corticosteroid efficacy among 1703 critically ill patients with confirmed or suspected COVID-19, there were 222 deaths in 678 patients randomly assigned to corticosteroids and 425 deaths in 1025 patients randomly assigned to usual care or

Table 4. Cox-regression analysis to assess risk factors for in-hospital mortality among matched cohorts (1:1)[a].

			Cox regression analysis	
	Alive $n = 117$	In-hospital mortality $n = 85$	Univariate p-value	Multivariate HR (95%IC)
Age, median (IQR) years	68.2 (57.2–75.7)	76.0 (68.9–83.6)	**<.001**	**1.039 (1.021–1.058)**
Male gender, n (%)	79 (67.5)	56 (65.9)	.487	
Number of comorbidities, median (IQR)	2 (1–3)	3 (2–5)	**.001**	
SpFi at admission, median (IQR)	424.0 (303–447.6)	373.0 (260.8–437.8)	.135	
SpFi at ITD, median (IQR)	235.0 (120.0–271.0)	125 (113.9–236.3)	**.012**	**0.996 (0.993–0.999)**
Immunomodulatory treatment, n (%)				
Non- immunomodulatory therapy ($n = 101$)	42 (35.9)	59 (96.4)		
Immunomodulatory therapy ($n = 101$)				
Corticosteroids	18 (14.4)	10 (11.8)	**.033**	**0.356 (0.179–0.707)**
Tocilizumab	11 (9.4)	4 (4.7)	**.025**	0.397 (0.141–1.114)
Corticosteroids + tocilizumab	46 (39.3)	12 (14.1)	**<.001**	**0.233 (0.124–0.436)**

IQR: Interquartile range; SpFi: pulse oximetry oxygen saturation/fraction of inspired oxygen ratio; ITD: Immunomodulatory treatment decision day.
[a]Patients were paired 1:1 by age, gender, number of comorbidities and SpFi at ITD.
p values smaller than .05 are marked as bold values.

placebo [odds ratio of 0.66 (95% confidence interval, $0.53 - 0.82$; $p < .001$), favouring steroid treatment] [10].

In the COVID-19 dexamethasone randomized clinical trial, with 299 patients with COVID-19 and moderate-to-severe ARDS from 41 intensive care units, the addition of dexamethasone (20 mg of dexamethasone intravenously daily for 5 days), significantly improved survival and increased the number of days free of mechanical ventilation [11].

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial evaluated a fixed 7-day course of intravenous hydrocortisone (50 mg or 100 mg every 6 h) to improve organ support and mortality in 403 patients with severe COVID-19 [12]. The fixed-dose strategy was superior to no hydrocortisone therapy with regard to organ support–free days within the following 21 days. Despite these findings, REMAP-CAP investigators cautioned about drawing definitive conclusions as the trial was stopped early and significance of prespecified endpoints was not achieved.

The most relevant results in the impact of corticosteroid use came from the RECOVERY study, a randomized clinical trial in patients with severe COVID-19 that showed a significantly lower risk of death (25.7% in the usual care group vs. 22.9% in the dexamethasone group; $p < .001$). The largest benefit was observed in patients receiving invasive mechanical ventilation [14].

Contrary to the previous studies, in another randomized clinical trial on patients with acute respiratory failure, hydrocortisone therapy (at an initial dose of 200 mg/d for 7 or 4 days and then tapering until 14 or 8 days according to improvement), was not associated with a significant reduction in treatment failure rates [13].

Our results support the idea that other immunomodulatory therapies targeting cytokines involved in the excessive inflammatory response could be beneficial in SARS-CoV-2 pneumonia.

Tocilizumab is widely used to treat rheumatoid arthritis, but has been proposed to play a role in COVID-19 due to its effect in the cytokine release syndrome [16]. However, in three recent randomized clinical trials tocilizumab did not show a clear benefit in treatment of COVID-19 [17–20]. In the CORIMUNO-19 trial, patients who required at least 3 L/min of oxygen without ventilation or admission to the intensive care unit were randomly assigned to receive tocilizumab or to usual care alone. No difference was found in 28-day mortality between groups. However, at day 14, 24% of patients receiving tocilizumab (vs 36% in the usual care group) had died or required either non-invasive or mechanical ventilation [18]. The RCT-TCZ-COVID-19 Study Group trial, included patients with pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratios between 200 to 300 mmHg, fever and elevated C reactive protein levels. Of patients receiving tocilizumab, 28.3% progressed clinically within 14 days, compared to 27.0% in the control group, and there was no significant difference in admission to intensive care between groups [19]. The BACC Bay Tocilizumab trial enroled patients with severe pneumonia with analytic parameters consistent with cytokine release syndrome. Compared with placebo, patients receiving tocilizumab had similar risk for intubation, death or disease progression [20].

In contrast, in a retrospective analysis of 3924 patients, the authors found a lower risk of death in patients treated with tocilizumab compared to those who did not receive this drug (hazard ratio [HR], 0.71;95% CI, 0.56–0.92) over a median follow up period of 27 days [17].

To summarize, contrary to corticosteroids, until now tocilizumab has not shown a clear benefit to support its

use in clinical practice. Therefore, current guidelines from both the National Institutes of Health (NIH) and the IDSA recommend the use of low doses of corticosteroids but recommend against tocilizumab in treatment of COVID-19 [21,22].

According to our results, immunomodulatory therapy with corticosteroids alone or combined with tocilizumab in patients with severe respiratory illness secondary to COVID-19 improved survival. Since there is no effective antiviral that stops progression in early stages of disease, in severe COVID-19 pneumonia, the use of corticosteroids and tocilizumab to modulate the inflammatory response associated with the lung damage is, in our opinion, beneficial.

The main limitation of our study is the retrospective design. Nevertheless, the decision taken by the hospital's internal committee on March 26 to administer immunomodulatory treatment allowed us to compare patients receiving to those not receiving immunomodulators. Another limitation is that the specific immunomodulatory regimen administered to each patient was at the discretion of the treating physician.

Important questions remain to be addressed such as identification of patients likely to benefit from corticosteroids and tocilizumab, optimal dosing, and optimal timing of such therapies to maximize therapeutic outcomes. Well-designed randomized controlled trials are needed to provide evidence for treatment recommendations.

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