The Use of Corticosteroids or Tocilizumab in COVID-19 Based on Inflammatory Markers

Manuel Rubio-Rivas, MD PhD[1], José M. Mora-Luján, MD PhD[1], Abelardo Montero, MD PhD[1], Josefa Andrea Aguilar García, MD PhD[2], Manuel Méndez Bailón, MD[3], Ana Fernández Cruz, MD PhD[4], Isabel Oriol, MD PhD[5], Francisco-Javier Teigell-Muñoz, MD PhD[6], Beatriz Dendariena Borque, MD[7], Andrés De la Peña Fernández, MD PhD[8], Raquel Fernández González, MD[9], Ricardo Gil Sánchez, MD PhD[10], Javier Fernández Fernández, MD[11], Marta Catalán, MD[12], Begoña Cortés-Rodríguez, MD[13], Carmen Mella Pérez, MD[14], Lorena Montero Rivas, MD[15], Rebeca Suárez Fuentetaja, MD[16], Jara Eloísa Ternero Vega, MD[17], Javier Ena, MD[18], Anabel Martin-Urda Díez-Canseco, MD[19], Cristina Pérez García, MD[20], José F. Varona, MD PhD[21,22], José Manuel Casas-Rojo, MD PhD[6], and Jesús Millán Núñez-Cortés, MD PhD[23]on behalf of the SEMI-COVID-19 Network

[1]Department of Internal Medicine, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, University of Barcelona, Barcelona, Spain; [2]Department of Internal Medicine, Costa del Sol Hospital, Marbella, Málaga, Spain; [3]Department of Internal Medicine, San Carlos University Hospital, Complutense University, Madrid, Spain; [4]Department of Internal Medicine, Puerta de Hierro University Hospital, Majadahonda, Madrid, Spain; [5]Infectious Disease Unit, Department of Internal Medicine, Moisès Broggi Hospital, Sant Joan Despí, Barcelona, Spain; [6]Department of Internal Medicine, Infanta Cristina University Hospital, Parla, Madrid, Spain; [7]Department of Internal Medicine, San Pedro Hospital, Logroño, Spain; [8]Department of Internal Medicine, Son Llàtzer University Hospital, Palma de Mallorca, Spain; [9]Department of Internal Medicine, Ourense University Hospital, Ourense, Spain; [10]Department of Internal Medicine, La Fe Hospital, Valencia, Spain; [11]Department of Internal Medicine, Mataró Hospital, Mataró, Barcelona, Spain; [12]Department of Internal Medicine, Sagunto University Hospital, Sagunto, Valencia, Spain; [13]Department of Internal Medicine, Alto Guadalquivir Hospital, Andújar, Jaén, Spain; [14]Department of Internal Medicine, Ferrol Clinical University Hospital, El Ferrol, La Coruña, Spain; [15]Department of Internal Medicine, Infanta Margarita Hospital, Cabra, Córdoba, Spain; [16]Department of Internal Medicine, Monforte de Lemos Hospital, Monforte de Lemos, Lugo, Spain; [17]Department of Internal Medicine, Vírgen del Rocío University Hospital, Sevilla, Spain; [18]Department of Internal Medicine, Marina Baixa Hospital, Villajoyosa, Alicante, Spain; [19]Department of Internal Medicine, Palamós Hospital, Palamós, Girona, Spain; [20]Department of Internal Medicine, Do Salnes Hospital, Vilagarcía de Arousa, Pontevedra, Spain; [21]Department of Internal Medicine, HM Montepríncipe University Hospital, Madrid, Spain; [22]Department of Internal Medicine, Infanta Cristina University Hospital, Parla, Madrid, Spain; [23]Department of Internal Medicine, Gregorio Marañón General University Hospital, Madrid, Spain.

BACKGROUND: The inflammatory cascade is the main cause of death in COVID-19 patients. Corticosteroids (CS) and tocilizumab (TCZ) are available to treat this escalation but which patients to administer it remains undefined.

OBJECTIVE: We aimed to evaluate the efficacy of immunosuppressive/anti-inflammatory therapy in COVID-19, based on the degree of inflammation.

DESIGN: A retrospective cohort study with data on patients collected and followed up from March 1st, 2020, to May 1st, 2021, from the nationwide Spanish SEMI-COVID-19 Registry. Patients under treatment with CS vs. those under CS plus TCZ were compared. Effectiveness was explored in 3 risk categories (low, intermediate, high) based on lymphocyte count, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer values.

PATIENTS: A total of 21,962 patients were included in the Registry by May 2021. Of these, 5940 met the inclusion criteria for the present study (5332 were treated with CS and 608 with CS plus TCZ).

MAIN MEASURES: The primary outcome of the study was in-hospital mortality. Secondary outcomes were the composite variable of in-hospital mortality, requirement for high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), or intensive care unit (ICU) admission.

KEY RESULTS: A total of 5940 met the inclusion criteria for the present study (5332 were treated with CS and 608 with CS plus TCZ). No significant differences were observed in either the low/intermediate-risk category (1.5% vs. 7.4%, p=0.175) or the high-risk category (23.1% vs. 20%, p=0.223) after propensity score matching. A statistically significant lower mortality was observed in the very high–risk category (31.9% vs. 23.9%, p=0.049).

CONCLUSIONS: The prescription of CS alone or in combination with TCZ should be based on the degrees of inflammation and reserve the CS plus TCZ combination for patients at high and especially very high risk.

KEY WORDS: COVID-19; treatment; corticosteroids; tocilizumab; mortality.

Received June 22, 2021
Accepted September 8, 2021
Published online October 18, 2021

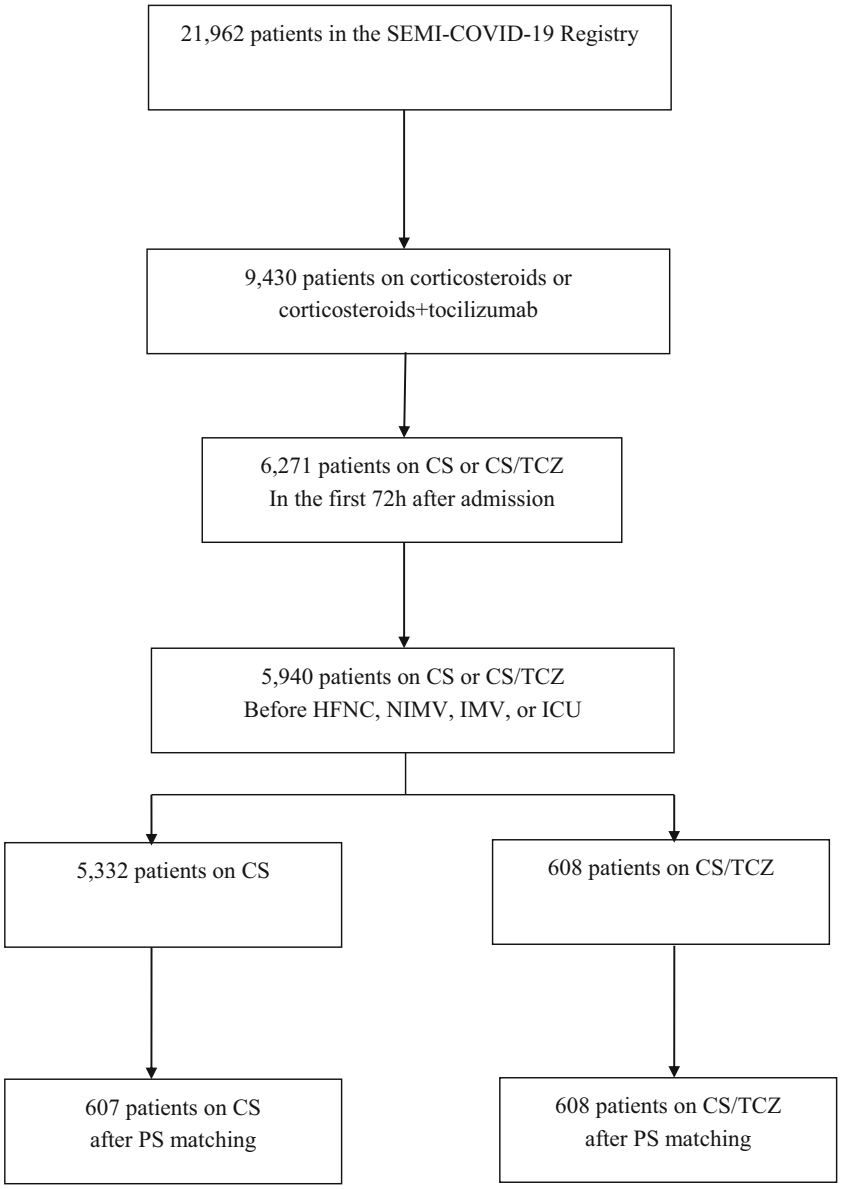

Fig. 1 Flow chart.

Abbreviations

AUC	area under the curve
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CS	corticosteroids
HFNC	high-flow nasal cannula
ICU	intensive care unit
IMV	invasive mechanical ventilation
IQR	interquartile range
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
NIMV	non-invasive mechanical ventilation
OSAS	obstructive sleep apnea syndrome
PCR	polymerase chain reaction
PSM	propensity score matching
SD	standard deviation
SEMI	Spanish Society of Internal Medicine
SOC	standard of care
TCZ	tocilizumab

J Gen Intern Med 37(1):168–75
DOI: 10.1007/s11606-021-07146-0

INTRODUCTION

It has become evident that most of the mortality due to this COVID-19 results from the so-called cytokine storm,[1] an exaggerated and uncontrolled inflammatory response that frequently leads to death if not aborted. The 2 most commonly

Table 1 General Data

	All cohort			Matched-cohort		
	CS	CS+TCZ	*p* value	CS	CS+TCZ	*p* value
n	5,332	608		607	608	
Age, median [IQR]	72.4 [59.7–82.7]	63.6 [54.8–74.2]	<0.001	63.5 [52.4–74]	63.6 [54.8–74.2]	0.542
Gender (males), *n* (%)	3,140 (58.9)	443 (72.9)	<0.001	419 (69)	443 (72.9)	0.141
Days from onset to admission, median [IQR]	7 [4–9]	7 [5–10]	<0.001	7 [4–10]	7 [5–10]	0.053
BMI, median [IQR]	28.9 [25.7–32.6]	29.1 [25.8–32.5]	0.477	29.2 [25.9–32.8]	29.1 [25.8–32.5]	0.967
Race, *n* (%)			<0.001			0.300
Caucasian	4,840 (90.8)	499 (82.1)		506 (83.4)	499 (82.1)	
Black	35 (0.7)	5 (0.8)		8 (1.3)	5 (0.8)	
Hispanic	375 (7)	83 (13.7)		70 (11.5)	83 (13.7)	
Asian	17 (0.3)	2 (0.3)		7 (1.2)	2 (0.3)	
Others	65 (1.2)	19 (3.1)		16 (2.6)	19 (3.1)	
Smoking behavior, *n* (%)			0.793			0.505
Never smoker	3,545 (66.5)	409 (67.3)		410 (67.5)	409 (67.3)	
Former smoker	1,527 (28.6)	173 (28.5)		163 (26.9)	173 (28.5)	
Current smoker	260 (4.9)	26 (4.3)		34 (5.6)	26 (4.3)	
Degree of dependency, *n* (%)			<0.001			0.072
None or mild	4,169 (78.2)	580 (95.4)		579 (95.4)	580 (95.4)	
Moderate	676 (12.7)	21 (3.5)		27 (4.4)	21 (3.5)	
Severe	487 (9.1)	7 (1.2)		1 (0.2)	7 (1.2)	
Arterial hypertension, *n* (%)	3,084 (57.8)	297 (48.8)	<0.001	304 (50.1)	297 (48.8)	0.667
Dyslipidemia, *n* (%)	2,255 (42.3)	234 (38.5)	0.072	247 (40.7)	234 (38.5)	0.432
Diabetes mellitus, *n* (%)	1,218 (22.8)	148 (24.3)	0.405	149 (24.5)	148 (24.3)	0.934
Ischaemic cardiopathy, *n* (%)	460 (8.6)	53 (8.7)	0.940	62 (10.2)	53 (8.7)	0.373
Chronic heart failure, *n* (%)	451 (8.5)	31 (5.1)	0.004	32 (5.3)	31 (5.1)	0.892
Chronic liver disease, *n* (%)	208 (3.9)	17 (2.8)	0.176	26 (4.3)	17 (2.8)	0.161
Severe chronic renal failure, *n* (%)	413 (7.7)	13 (2.1)	0.001	18 (3)	13 (2.1)	0.361
Dementia, *n* (%)	605 (11.3)	11 (1.8)	<0.001	5 (0.8)	11 (1.8)	0.132
Cancer, *n* (%)	498 (9.3)	56 (9.2)	0.917	61 (10)	56 (9.2)	0.620
COPD, *n* (%)	522 (9.8)	39 (6.4)	0.007	33 (5.4)	39 (6.4)	0.470
Asthma, *n* (%)	416 (7.8)	44 (7.2)	0.621	52 (8.6)	44 (7.2)	0.390
OSAS, *n* (%)	348 (6.5)	39 (6.4)	0.915	35 (5.8)	39 (6.4)	0.637
Charlson index, median [IQR]	1 [0–2]	0 [0–1]	<0.001	1 [0–2]	0 [0–1]	0.299

BMI body mass index, IQR interquartile range, COPD chronic obstructive pulmonary disease, OSAS obstructive sleep apnea syndrome, CS corticosteroids, CS+TCZ corticosteroids + tocilizumab. Severe chronic renal failure: creatinine >300 mg/dl or dyalisis

used drugs in the management of COVID-19 are corticosteroids (CS)[2, 3] and tocilizumab (TCZ).[3–17] While CS have been uniformly found helpful,[2, 3] TCZ efficacy has been mixed.[3–17] However, most studies have evaluated efficacy based on oxygenation/ventilation of the patients rather than inflammatory markers. Our study aims to evaluate the efficacy of these drugs based on the degree of inflammation.[18]

METHODS

Study Design, Patient Selection, and Data Collection

This is a retrospective cohort study with data on patients collected and followed up from March 1st, 2020, to May 1st, 2021, from the nationwide Spanish SEMI-

Table 2 Symptoms and Physical Examination Upon Admission

	All cohort			Matched-cohort		
	CS	CS+TCZ	*p* value	CS	CS+TCZ	*p* value
Cough, *n* (%)	3677 (69)	485 (79.8)	<0.001	434 (71.5)	485 (79.8)	0.001
Arthromyalgias, *n* (%)	1425 (26.7)	211 (34.7)	<0.001	182 (30)	211 (34.7)	0.079
Ageusia, *n* (%)	574 (10.8)	71 (11.7)	0.493	88 (14.5)	71 (11.7)	0.145
Anosmia, *n* (%)	484 (9.1)	68 (11.2)	0.090	69 (11.4)	68 (11.2)	0.920
Sore throat, *n* (%)	428 (8)	72 (11.8)	0.001	69 (11.4)	72 (11.8)	0.796
Headache, *n* (%)	608 (11.4)	96 (15.8)	0.002	74 (12.2)	96 (15.8)	0.071
Fever, *n* (%)	4118 (77.2)	523 (86)	<0.001	505 (83.2)	523 (86)	0.173
Dyspnea, *n* (%)	3625 (68)	433 (71.2)	0.105	434 (71.5)	433 (71.2)	0.913
Diarrhea, *n* (%)	1231 (23.1)	181 (29.8)	<0.001	163 (26.9)	181 (29.8)	0.259
Vomiting, *n* (%)	360 (6.8)	44 (7.2)	0.653	42 (6.9)	44 (7.2)	0.829
Abdominal pain, *n* (%)	285 (5.3)	34 (5.6)	0.798	30 (4.9)	34 (5.6)	0.612
Heart rate, bpm median [IQR]	87 [76–100]	91 [80–104]	<0.001	90 [80–101]	91 [80–104]	0.079
Respiratory rate >20 rpm, *n* (%)	2109 (39.6)	328 (53.9)	<0.001	314 (51.7)	328 (53.9)	0.439

IQR interquartile range, CS corticosteroids, CS+TCZ corticosteroids + tocilizumab

Table 3 Lab Tests Upon Admission

	All cohort			Matched-cohort		
	CS	CS+TCZ	*p* value	CS	CS+TCZ	*p* value
PaO2/FiO2, median [IQR]	285.7 [231.9–338.1]	271 [214.3–320.4]	<0.001	266.7 [209.7–319.1]	271 [214.3–320.4]	0.484
Lymphocytes $\times 10^6$/l, median [IQR]	900 [612.5–1260]	820 [600–1120]	<0.001	850 [600–1200]	820 [600–1120]	0.196
CRP mg/l, median [IQR]	84.1 [34–151.1]	131 [63.3–201]	<0.001	120 [62–192.7]	131 [63.3–201]	0.477
LDH U/l, median [IQR]	344 [262–460.4]	382.5 [306–499]	<0.001	393 [290–530]	382.5 [306–499]	0.797
Ferritin mcg/l, median [IQR]	857.4 [395.9–1596]	1120.7 [636.2–1830.9]	<0.001	1127.6 [528–1990.8]	1120.7 [636.2–1830.9]	0.855
D-Dimer ng/ml, median [IQR]	869.5 [465.3–1992.8]	717 [400–1421.3]	<0.001	842 [487–1702]	717 [400–1421.3]	0.003

CRP C-reactive protein, LDH lactate dehydrogenase, IQR interquartile range, CS corticosteroids, CS+TCZ corticosteroids + tocilizumab

COVID-19 Registry. The characteristics of the patients included in this registry have been extensively described previously.[19] This is a multicenter, nationwide registry with over 150 hospitals. All included patients were diagnosed by polymerase chain reaction (PCR) test taken from a nasopharyngeal sample, sputum, or bronchoalveolar lavage. The collection of data from each patient in terms of laboratory data, treatments, and outcomes was verified by the principal investigator of each center through the review of clinical records.

All participating centers in the register received approval from the relevant Ethics Committees, including Bellvitge University Hospital (PR 128/20).

Inclusion Criteria

The group that received only CS was considered the standard of care (SOC) for hospitalized patients. We included patients whose CS use started within the first 72 h after hospital admission and before the onset of high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV), or the requirement of intensive care unit (ICU) admission. The CS plus TCZ group included patients who received both drugs in the first 72 h after hospital admission and also before the onset of HFNC, NIMV, IMV, or ICU admission.

Exclusion Criteria

We excluded patients who did not receive CS, or received it more than 3 days after hospitalization, those with a nosocomial infection, and those who died within 24 h.

Treatments Prescribed and Definitions of Groups

We divided the cohort into 2 groups: patients who received solely CS, and patients who received both CS and TCZ. The usual dose of TCZ in our country was 4–8 mg/kg iv, generally in a single dose, although some additional doses are allowed at the discretion of the responsible physician.

Regarding antiviral treatment, the use of antivirals (lopinavir/ritonavir,[20] remdesivir[21]), hydroxychloroquine,[22] and azithromycin[22] was allowed according to the recommendations of the Spanish Ministry of Health.

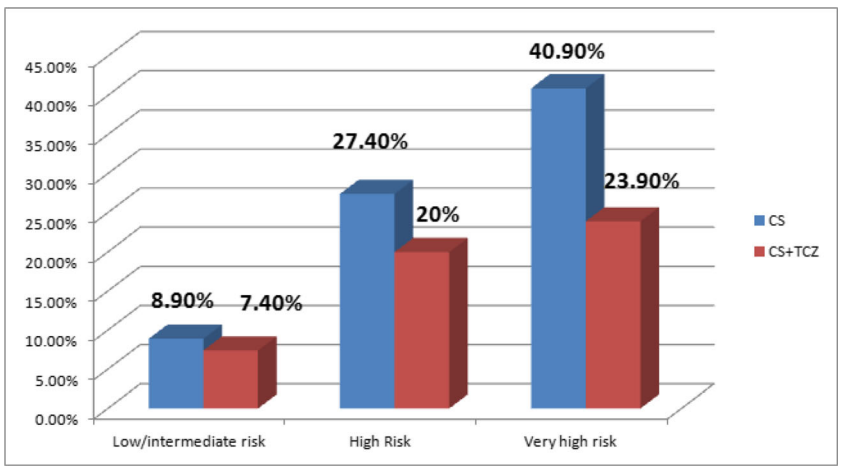

Fig. 2 In-hospital mortality (%) between groups in the general cohort.

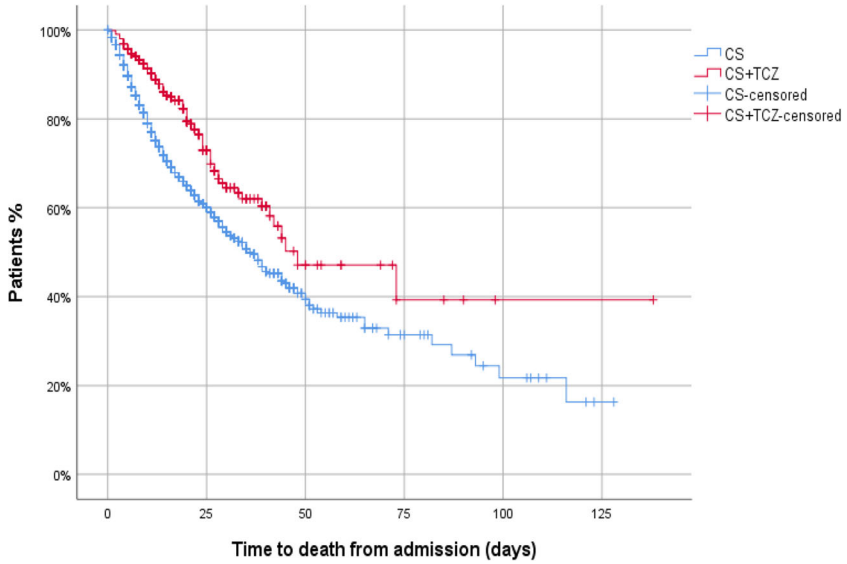

Fig. 3 In-hospital mortality (%) between groups. Kaplan-Meier. Log-rank test=44.3; $p<0.001$.

Degrees of Inflammation

We previously reported the 3 categories of risk: (low, intermediate, and high risk) based on the total lymphocyte count, and the C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer values taken at the time of admission (Table S1).[18] The high-risk category was defined based on only 1 of the 5 criteria described above the previously defined cutoff. In addition, for the present study, a very high–risk category was added, defined as the presence of 3 or more high-risk upon admission criteria (Table S1).

Outcome Definition

The primary outcome of our study was in-hospital mortality. Secondary outcomes included length of stay (LOS), and the requirement of HFNC, NIMV, IMV, and ICU admission.

Statistical Analysis

Categorical variables were expressed as absolute numbers and percentages. Continuous variables are expressed as mean plus standard deviation (SD) in the case of parametric distribution or median [IQR] in the case of non-parametric distribution. Differences among groups were assessed using the chi-square test for categorical variables and the *t*-test or Mann-Whitney test as appropriate for continuous variables. *p* values< 0.05 indicated statistical significance.

For the study of risk factors associated with in-hospital mortality, univariate and multivariate binary logistic regression was performed. For the latter, variables with $p<0.10$ in the univariate study plus age and gender were included. Differences in mortality were shown graphically using Kaplan-Meier curves with their log-rank test (event: death; censored data: hospital discharge). Missing data were treated with multiple imputations. To improve the comparability of the groups, propensity score matching (PSM) was performed. This included age, sex, body mass index (BMI), race, smoking behavior, days from onset to admission, all comorbidities, Charlson index, heart rate on admission, tachypnea on admission, PaO2/FiO2, lymphocyte count, CRP, LDH, ferritin, D-dimer, remdesivir treatment, and prescription of low-molecular-weight heparins (LMWH) during admission.

Statistical analysis was performed by IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA: IBM Corp.

Table 4 Outcomes in the General Cohort

	Low/Intermediate risk			High risk			Very high risk		
	CS, *N*=951	CS+TCZ, *N*=54	*p* value	CS, *N*=4381	CS+TCZ, *N*=554	*p* value	CS, *N*=1542	CS+TCZ, *N*=238	*p* value
In-hospital death	85 (8.9)	4 (7.4)	1.000	1201 (27.4)	13 (20)	<0.001	630 (40.9)	57 (23.9)	<0.001
HFNC	59 (6.2)	16 (29.6)	<0.001	452 (10.4)	156 (28.3)	<0.001	192 (12.5)	74 (31.2)	<0.001
NIMV	32 (3.4)	10 (18.5)	<0.001	266 (6.1)	103 (18.6)	<0.001	130 (8.4)	39 (16.4)	<0.001
IMV	30 (3.2)	9 (16.7)	<0.001	268 (6.1)	123 (22.2)	<0.001	149 (9.7)	68 (28.6)	<0.001
ICU	47 (4.9)	11 (20.4)	<0.001	375 (8.6)	168 (30.3)	<0.001	188 (12.2)	84 (35.3)	<0.001
Length of stay (days), median [IQR]	8 [5–12]	12 [8–18.5]	<0.001	9 [6–13]	14 [10–20]	<0.001	9 [5–14]	15 [10–23]	<0.001

HFNC high-flow nasal cannula, NIMV non-invasive mechanical ventilation, IMV invasive mechanical ventilation, ICU intensive care unit, IQR interquartile range, CS corticosteroids, CS+TCZ corticosteroids + tocilizumab

Table 5 Outcomes in the Matched-Cohort

	Low/Intermediate risk			High risk			Very high risk		
	CS, *N*=65	CS+TCZ, *N*=54	*p* value	CS, *N*=542	CS+TCZ, *N*=554	*p* value	CS, *N*=257	CS+TCZ, *N*=238	*p* value
In-hospital death	1 (1.5)	4 (7.4)	0.175	125 (23.1)	111 (20)	0.223	82 (31.9)	57 (23.9)	0.049
HFNC	3 (4.6)	16 (29.6)	<0.001	87 (16.1)	156 (28.2)	<0.001	50 (19.5)	74 (31.1)	0.003
NIMV	1 (1.5)	10 (18.5)	0.002	57 (10.5)	103 (18.6)	<0.001	34 (13.2)	39 (16.4)	0.322
IMV	2 (3.1)	9 (16.7)	0.022	75 (13.8)	123 (22.2)	<0.001	46 (17.9)	68 (28.6)	0.005
ICU	4 (6.2)	11 (20.4)	0.026	102 (18.8)	168 (30.3)	<0.001	59 (23)	84 (35.3)	0.002
Length of stay (days), median [IQR]	8 [4.5–12]	12 [8–18.5]	0.001	10 [6.8–16]	14 [10–20]	<0.001	11 [6–20]	15 [10–23]	<0.001

HFNC high-flow nasal cannula, NIMV non-invasive mechanical ventilation, IMV invasive mechanical ventilation, ICU intensive care unit, IQR interquartile range, CS corticosteroids, CS+TCZ corticosteroids + tocilizumab

RESULTS

General Data and Symptoms Between Groups

A total of 21,962 patients were included in the Registry by May 2021; 9430 were treated with CS or CS plus TCZ and 5940 met our inclusion criteria (5332 were treated with CS and 608 with CS plus TCZ) (Fig. 1). Table 1 shows the differences between the two groups. Those in the isolated CS group were older (72.4 vs. 63.6 years), with less male predominance (58.9% vs. 72.9%), higher prevalence of Caucasian population (90.8% vs. 82.1%), higher degree of dependency (21.8% vs. 4.7%), hypertension (57.8% vs. 48.8%), chronic heart failure (42.3% vs. 38.5%), chronic renal failure (7.7% vs. 1.1%), dementia (11.3% vs. 1.8%), chronic obstructive pulmonary disease (COPD) (9.8% vs. 6.4%), and a higher Charlson index (1 vs. 0). The groups were similar after propensity score matching (Table 1).

The CS group presented less frequently (Table 2) with cough (69% vs. 79.8%), arthromyalgia (26.7% vs. 34.7%), sore throat (8% vs. 11.8%), headache (11.4% vs. 15.8%), fever (77.2% vs. 86), and diarrhea (23.1% vs. 29.8%). There were also differences in heart rate (87 vs. 91 bpm) and tachypnea (39.6% vs. 53.9%).

Lab Tests Between Groups

The CS group had higher PaO2/FiO2 (285.7 vs. 271), lymphocytes (900×10^6 vs. 820×10^6), and D-dimer (869.5 ng/ml vs. 717 ng/ml) at admission. Alternatively, they had lower CRP (84.1 mg/l vs. 131 mg/l), LDH (344 U/l vs. 382.5 U/l), and ferritin (857.4 mcg/l vs. 1120.7 mcg/l) (Table 3). These differences disappeared after PSM except for D-dimer, which remained higher in the CS group (842 ng/ml vs. 717 ng/ml).

Treatments Between Groups

The treatments received in both groups are shown in Table S2. The CS group less frequently received remdesivir (9.8% vs. 14.3%) as well as intermediate (12.2% vs. 22.5%) or full doses of LMWH (14.3% vs. 22.2%). These differences disappeared after PSM.

The CS regimen was not standard in all patients. There were significant differences between both groups in the maximum dose of prednisone or equivalent (75 mg vs. 100 mg), days of treatment (7 days vs. 8 days), and cumulative dose (400 mg vs. 600 mg).

Outcomes Between Groups

Compared to patients receiving CS alone, in-hospital mortality was significantly lower for combination of CS + TCZ for high risk (27.4% vs. 20%, $p<0.001$) and very high–risk patients (40.9% vs. 23.9%, $p<0.001$) (Figs. 2 and 3). There was no difference for those with low/intermediate risk (8.9% vs. 7.4%, $p=1.000$) (Table 4, Figs. 2 and 3). Our PSM analysis found significantly lower mortality only in the very high–risk category (31.9%, vs. 23.9%, $p=0.049$) (Table 5; Figure S1). After PSM, we found no differences in the low/intermediate-risk (1.5% vs. 7.4%, $p=0.175$) or the high-risk category (23.1% vs. 20%, $p=0.223$).

HFNC use was lower in CS patients in all 3 risk categories: 6.2% vs. 29.6% ($p<0.001$) for the low/intermediate-risk category, 10.4% vs. 28.3% ($p<0.001$) for the high-risk category, and 12.5% vs. 31.2% ($p<0.001$) for the very high–risk category (Table 4). After PSM, we found the same differences between groups in the 3 risk categories: 4.6% vs. 29.6% ($p<0.001$), 16.1% vs. 28.2% ($p<0.001$), and 19.5% vs. 31.1% ($p=0.003$) (Table 5).

NIMV use was also lower in CS patients in all 3 risk categories: 3.4% vs. 18.5% ($p<0.001$) for the low/intermediate-risk category, 6.1% vs. 18.6% ($p<0.001$) for the high-risk category, and 8.4% vs. 16.4% ($p<0.001$) for the very high–risk category (Table 4). After PSM, we found similar differences between groups in the 3 risk categories: 1.5% vs. 18.5% ($p<0.001$), 10.5% vs. 18.6% ($p<0.001$), and 13.2% vs. 16.4% ($p=0.322$).

The use of IMV was also lower in CS patients in all 3 risk categories: 3.2% vs. 16.7% ($p<0.001$) for the low/intermediate-risk category, 6.1% vs. 22.2% ($p<0.001$) for the high-risk category, and 9.7% vs. 28.6% ($p<0.001$) for the very high–risk category (Table 4). After PSM, we found similar differences between groups in the 3 risk categories: 3.1% vs. 16.7% ($p<0.001$), 13.8% vs. 22.2% ($p<0.001$), and 17.9% vs. 28.6% ($p=0.005$) (Table 5).

Table 6 Risk Factors in the Matched-Cohort. High-Risk Category

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.07 (1.05–1.09)	<0.001	1.08 (1.06–1.09)	<0.001
Gender (female)	1.16 (0.74–1.81)	0.525	0.69 (0.47–0.99)	0.045
BMI	1.02 (0.98–1.06)	0.405		
Race			NS	
Caucasian (ref.)	1 ref.			
Black	1.10 (0.90–1.15)	0.999		
Hispanic	0.46 (0.21–1.01)	0.054		
Asian	2.37 (0.15–38.14)	0.543		
Others	0.79 (0.16–3.96)	0.774		
Moderate/severe dependency	4.90 (2.77–8.68)	<0.001	1.98 (1.01–3.90)	0.048
Arterial hypertension	2.33 (1.55–3.49)	<0.001	NS	
Dyslipidemia	1.75 (1.18–2.59)	0.006	NS	
Diabetes mellitus	1.81 (1.15–2.83)	0.010	NS	
Ischaemic cardiopathy	2.06 (1.08–3.93)	0.028	NS	
Chronic heart failure	7.59 (2.90–19.83)	<0.001	NS	
Chronic liver disease	1.10 (0.42–2.93)	0.845		
Severe chronic renal failure	4.04 (1.41–11.57)	0.009	NS	
Dementia	5.24 (0.95–28.97)	0.057	NS	
Cancer	2.54 (1.41–4.59)	0.002	NS	
COPD	2.49 (1.11–5.61)	0.027	NS	
Asthma	0.58 (0.25–1.34)	0.202		
OSAS	1.67 (0.80–3.39)	0.176		
Charlson index	1.28 (1.15–1.43)	<0.001	1.14 (1.04–1.24)	0.003
Respiratory rate >20 rpm	2.29 (1.49–3.54)	<0.001	2.01 (1.41–2.87)	<0.001
PaO2/FiO2	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
Tocilizumab	0.67 (0.45–0.99)	0.050	0.78 (0.56–1.09)	0.150

BMI body mass index, NS not significant, COPD chronic obstructive pulmonary disease, OSAS obstructive sleep apnea syndrome

The need for ICU admission was lower in patients with CS in all 3 risk categories: 4.9% vs. 20.4% ($p<0.001$) for the low/intermediate-risk category, 8.6% vs. 30.3% ($p<0.001$) for the high-risk category, and 12.2% vs. 35.3% ($p<0.001$) for the very high–risk category (Table 4). After PSM, we found similar differences between groups in the 3 risk categories: 6.2% vs. 20.4% ($p<0.001$), 18.8% vs. 30.3% ($p<0.001$), and 23% vs. 35.3% ($p=0.002$) (Table 5).

Finally, median LOS was higher in patients with CS+TCZ in all 3 risk categories: 8 days vs. 12 ($p<0.001$) for the low/intermediate-risk category, 9 days vs. 14 ($p<0.001$) for the high-risk category, and 9 days vs. 15 ($p<0.001$) for the very high–risk category (Table 4). After PSM, we found similar differences between groups in the 3 risk categories: 8 days vs. 12 ($p=0.001$), 10 days vs. 14 ($p<0.001$), and 11 days vs. 15 ($p<0.001$) (Table 5).

Risk Factors for In-Hospital Mortality

The independent risk factors for mortality in the high-risk category were age, male sex, moderate/severe dependency, higher Charlson index, tachypnea on admission, and lower PaO2/FiO2 (Table 6). The use of TCZ showed a trend of benefit that did not reach statistical significance as an independent protective factor. The very high–risk category showed similar results (data not shown). The AUC of the final model was 0.792 (Figure S2).

DISCUSSION

We found that higher degrees of inflammation responded to combination therapy, consistent with COVID-19 as an inflammatory disease. Treatment should be risk-stratified based on inflammation. At present, the approach to the disease has been heterogeneous and often based on oxygenation/ventilation status. In order to evaluate the efficacy of immunosuppressive/anti-inflammatory treatments, we have to include the degree of inflammation in patients to judge efficacy. The degree of inflammation in most studies is difficult to assess and appears to include many patients with low degrees of inflammation. It is thus difficult to know the real efficacy of these drugs and explain differences in efficacy between observational studies and clinical trials [23].

Our results suggest that the greater the inflammation, the more effective these drugs will be. Our group previously described 3 categories of inflammation based on 5 parameters at admission (lymphopenia, CRP, LDH, ferritin, and D-dimer).[18] Since the low-risk category rarely requires hospital admission, it is the least numerous in our national series.

Our study shows that the addition of TCZ does not provide benefit in the low/intermediate-risk category. While the combination reduced mortality in the high-risk group, we did not achieve statistical significance, due to inadequate power. Patients classified as very high risk (3–5 high-risk criteria) had statistically significant reduction in death.

Our secondary outcomes (use of HFNC, NIMV, and IMV, and admission to the ICU) suggest that the CS+TCZ group

had more severe disease despite PSM. The sociodemographic, clinical, and analytical data included could not fully capture patient severity. Our patients were on oxygen therapy (not high-flow) at the time of treatment initiation (CS patients or CS+TCZ patients). However, we do not know the exact FiO2 they were receiving; it is possible that the combination of CS+TCZ was used in patients requiring higher amounts of oxygen.

Our study strengths include that it is large and nationally representative. In addition, the therapeutic approach based on degree of inflammation is a good approximation to clinical practice decision-making.

Our study also has some limitations. First, it is a retrospective study. Second, it comes from a multicenter registry, with the heterogeneity that this implies, though we used standardized definitions. Another limitation to be taken into account is the heterogeneity in CS dosage and administration time as well as lack of information of important variables that might trigger addition of TCZ, such as oxygen requirement.

In conclusion, the prescription of CS alone or in combination with TCZ should be based on the degrees of inflammation and reserve the CS plus TCZ combination for patients at high and especially very high risk.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11606-021-07146-0.

Acknowledgements: *We gratefully acknowledge all the investigators who participated in the SEMI-COVID-19 Registry. We also thank the SEMI-COVID-19 Registry Coordinating Center for their quality control data, logistic, and administrative support.*

Corresponding Author: *Manuel Rubio-Rivas, MD PhD; Department of Internal Medicine, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, University of Barcelona, Barcelona, Spain (e-mail: mrubio@bellvitgehospital.cat).*

Declarations:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

REFERENCES

1. **Hu B, Huang S, Yin L**. The Cytokine Storm and COVID-19. J Med Virol. 2020. https://doi.org/10.1002/jmv.26232. Online ahead of print.
2. RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, et al.** Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021; 384: 693-704.
3. **Rubio-Rivas M, Ronda M, Padulles A, et al.** Beneficial effect of corticosteroids in preventing mortality in patients receiving tocilizumab to treat severe COVID-19 illness. Int J Infect Dis. 2020; 101: 290-7.
4. **Stone JH, Frigault MJ, Serling-Boyd NJ, et al.** Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med 2020; 383: 2333-44.
5. **Salvarani C, Dolci G, Massari M, et al.** Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia. A randomized clinical trial. JAMA Intern Med 2021; 181: 24-31.
6. **Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P**. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. A randomized clinical trial. JAMA Intern Med 2021; 181: 32-40.
7. **Malekzadeh R, Abedini A, Mohsenpour B, et al.** Subcutaneous tocilizumab in adults with severe and critical COVID-19: a prospective open-label uncontrolled multicenter trial. Int Immunopharmacol. 2020; 89: 107102.
8. **Dastan F, Saffaei A, Haseli S, et al.** Promising effects of tocilizumab in COVID-19: a non-controlled, prospective clinical trial. Int Immunopharmacol. 2020; 88: 106869.
9. **Salama C, Han J, Yau L, et al.** Tocilizumab in patients hospitalized with COVID-19 Pneumonia. N Engl J Med. 2021; 384: 20-30.
10. **Veiga VC, Prats JAGG, Farias DLC, et al.** Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021; 372: n84.
11. **Pomponio G, Ferrarini A, Bonifazi M, et al.** Tocilizumab in COVID-19 interstitial pneumonia. J Intern Med. 2021: https://doi.org/10.1111/joim.13231.
12. **Perrone F, Piccirillo MC, Ascierto PA, et al.** Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. J Transl Med. 2020; 18: 405.
13. **REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, et al.** Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med. 2021:NEJMoa2100433.
14. **Rosas IO, Bräu N, Waters M, et al.** Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med. 2021 Feb 25:NEJMoa2028700.
15. **Soin AS, Kumar K, Choudhary NS, et al.** Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021: S2213-2600(21)00081-3.
16. **Wang D, Fu B, Peng Z, et al.** Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. Front Med. 2021: 1-9.
17. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45.
18. **Rubio-Rivas M, Corbella X, Formiga F, et al.** Risk categories in COVID-19 based on degrees of inflammation. Data on more than 17,000 patients from the Spanish SEMI-COVID-19 registry. J Clin Med 2021.
19. **Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, et al.** Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry. Rev Clin Esp. 2020;220(8):480-494.
20. **Lora-Tamayo J, Maestro G, Lalueza A, et al.** Early lopinavir/ritonavir does not reduce mortality in COVID-19 patients: results of a large multicenter study. J Infect. 2021 Feb 11:S0163-4453(21)00077-3.
21. **Beigel JH, Tomashek KM, Dodd LE, et al.** Remdesivir for the treatment of COVID-19 - final report. N Engl J Med. 2020;383(19):1813-1826.
22. **Gautret P, Hoang VT, Lagier JC, Raoult D**. Effect of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, an update with an intention-to-treat analysis and clinical outcomes. Int J Antimicrob Agents. 2021;57(1):106239.
23. **Tleyjeh IM, Kashour Z, Riaz M, Hassett L, Veiga VC, Kashour T**. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis-first update. Clin Microbiol Infect. 2021 Apr 27:S1198-743X(21)00204-4.