Beneficial effect of corticosteroids in preventing mortality in patients receiving tocilizumab to treat severe COVID-19 illness

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ABSTRACT

Objectives: To assess the characteristics and risk factors for mortality in patients with severe coronavirus disease-2019 (COVID-19) treated with tocilizumab (TCZ), alone or in combination with corticosteroids (CS).

Methods: From March 17 to April 7, 2020, a real-world observational retrospective analysis of consecutive hospitalized adult patients receiving TCZ to treat severe COVID-19 was conducted at our 750-bed university hospital. The main outcome was all-cause in-hospital mortality.

Results: A total of 1,092 patients with COVID-19 were admitted during the study period. Of them, 186 (17%) were treated with TCZ, of which 129 (87.8%) in combination with CS. Of the total 186 patients, 155 (83.3 %) patients were receiving noninvasive ventilation when TCZ was initiated. Mean time from symptoms onset and hospital admission to TCZ use was 12 (±4.3) and 4.3 days (±3.4), respectively. Overall, 147 (79%) survived and 39 (21%) died. By multivariate analysis, mortality was associated with older age (HR = 1.09, p < 0.001), chronic heart failure (HR = 4.4, p = 0.003), and chronic liver disease (HR =

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4.69, p = 0.004). The use of CS, in combination with TCZ, was identified as a protective factor against mortality (HR = 0.26, p < 0.001) in such severe COVID-19 patients receiving TCZ. No serious superinfections were observed after a 30-day follow-up.

Conclusions: In patients with severe COVID-19 receiving TCZ due to systemic host-immune inflammatory response syndrome, the use of CS in addition to TCZ therapy, showed a beneficial effect in preventing in-hospital mortality.

As of September 26, 2020, the novel coronavirus (SARS-CoV-2) has infected 32 million people worldwide, and killed more than 996,000 people (Zhou et al., 2020; http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51). The coronavirus disease-2019 (COVID-19) pandemic was confirmed to have spread to Europe on January 31, 2020 (Grasselli et al., 2020). Since then, there have been more than 700,000 confirmed cases in Spain, with more than 31,000 deaths. As a result, Spain saw one of the most draconian Covid-19 blockades in Europe, but two months after its lift, the country is on the brink of a second wave of coronavirus infections.

Although the pandemic continues to spread globally, a worrying 15% of patients will continue to transit into the third and most severe stage of disease (Siddiqi and Mehra, 2020). Unlikely to the early clinical stages in which viral replication and local respiratory involvement seem to be the norm, the advanced stage of COVID-19 appears to be triggered by the host-immune response. This third clinical stage presents as severe pulmonary injury and cytokine release syndrome with the elevation of multiorgan inflammatory markers (Siddiqi and Mehra, 2020; Aziz et al., 2020).

Accordingly, to treat this advanced stage of COVID-19 illness, the use of immunomodulatory agents such as corticosteroids (CS) or tocilizumab (TCZ), an anti-IL-6 monoclonal antibody, may be justified and has been suggested (Zhang et al., 2020; Xu et al., 2020; Di Giambenedetto et al., 2020). Currently, on the basis of the preliminary report from the RECOVERY trial, last updated (July 30, 2020) COVID-19 treatment guidelines recommend the use of dexamethasone, or alternative glucocorticoids (RECOVERY Collaborative Group et al., 2020; https://www.covid19treatmentguidelines.nih.gov/). These immunomodulatory agents are indicated in patients with severe COVID-19 who require supplemental oxygen, being or not mechanically ventilated. Conversely, as studies are still limited, current international recommendations have not taken a position either for or against the use of TCZ in such patients (Wilson et al., 2020).

In this regard, after the first short series of 21 patients reported by Xu et al., the published evidence for the use of TCZ in severe COVID-19 illness has been summarized in two existing systematic reviews and meta-analysis (SRMA). Because of the lack of randomized controlled trials (RCTs) (Mahase, 2020), both SRMA only included observational studies. The first SRMA, published by Lan SH Zhang et al., included 7 studies, with no conclusive evidence that TCZ would provide any additional benefit to patients with severe COVID-19. The second, registered in the medRxiv repository by Boregowda et al., included 16 studies, which concludes that the addition of TCZ to the SOC might reduce the mortality rate in patients with severe COVID-19.

Presently, there is an emerging number of additional observational studies of higher quality from Italy, Spain, France, and the US (Quartuccio et al., 2020; Moreno-García et al., 2020; Mikulska et al., 2020; Price et al., 2020; Maeda et al., 2020; Kewan et al., 2020; Ramaswamy et al., 2020; Rojas-Marte et al., 2020; Rossi et al., 2020; Canziani et al., 2020). These studies mostly assessed the use of TCZ in the subset of severely ill nonintubated patients with COVID-19 and were compared to a control group. Most of these recent studies concluded that TCZ may reduce intensive care unit (ICU) admissions, mechanical ventilator use, and the risk of death. Since most of the studies were performed before the RECOVERY trial, there was no standard protocol in place with regard to the use of CS in COVID-19. Thus, the use of CS only depended on the individual decision of those physicians who cared for the included patients. The potential effect of CS, in regimen combination with TCZ, was not specifically evaluated in most of such studies.

This fact prompted us to review our real-world observational data collected from routine clinical practice, during the first wave of SARS-CoV-2 infections that occurred during March-April, 2020, at our hospital setting. Our aim was to compare survivor and nonsurvivor groups from a large cohort of consecutive patients treated with TCZ, either alone or in combination with CS, to assess the characteristics and associated risk factors for in-hospital mortality in such COVID-19 patient population receiving TCZ.

Methods

The first patient with the advanced stage of COVID-19 with respiratory failure and systemic host-immune response treated with TCZ at the Bellvitge University Hospital, was on March 17, 2020. From March 17, 2020, to April 7, 2020, during the first 3 weeks of the epidemic, a retrospective cohort study was conducted at our 750-bed tertiary care public institution for adults in Barcelona, Spain. Demographic and clinical data were collected from institutional electronic medical records.

Inclusion criteria

All patients aged ≥18 years admitted at our hospital and given TCZ due to severe COVID-19 pneumonia and systemic hyperinflammation were included consecutively. All patients were diagnosed with COVID-19 by positive polymerase-chain reaction of nasal or pharyngeal swabs. All patients underwent a chest X-ray and were reported to have COVID-19 lung involvement by an expert radiologist. An electrocardiogram was also performed on all patients on admission and every 48–72 h during their stay in hospital. Patients admitted to either conventional hospital wards, semi-critical (noninvasive mechanical ventilation), or critical care units (invasive mechanical ventilation) were included.

For TCZ to be used, according to hospital guidelines, patients had to meet a PaO2 (mmHg)/FiO2 (%) $\times 100 < 300$, or its surrogate SatO2 (%)/FiO2 (%) $\times 100 < 315$ (Rice et al., 2007), and at least 2 of the following criteria: ferritin >1000 ng/ml, C-reactive protein (CRP) >100 mg/l, interleukin-6 (IL6) >70 ng/l, D-dimer >1000 mcg/l, or lactate dehydrogenase (LDH) >400 U/l. An analysis of these inflammatory parameters was performed on the day before the administration of the initial dose of TCZ (D0), and subsequently on days 1 (D1), 2 (D2), and 7 (D7) after administration. Lymphocyte count was additionally recorded.

Outcome

The primary outcome was all-cause in-hospital mortality.

Variables

As mentioned above, ancillary laboratory tests included PaO2 (mmHg), ferritin, CRP, IL-6, D-dimer, LDH, and lymphocyte count. Myocarditis was defined by clinical criteria, accompanied by sinus tachycardia, elevated troponin T (cutoff $\geq$14 ng/l), and elevated N-terminal pro-brain natriuretic peptide (NT-proBNP, cutoff $\geq$300 ng/l). Pulmonary thromboembolism (PE) was diagnosed when patients presented with disproportionate dyspnea with D-dimer elevation, and PE was confirmed by CT scan. Low-flow oxygen was defined as nasal cannula 2–3 l or oxygen mask with FiO2 < 50%. High-flow oxygen was defined as Monaghan® oxygenation with FiO2 100% and >10 l. High-flow oxygen with nasal cannula was defined as nasal cannula oxygenation with FiO2 > 50%. For noninvasive ventilation, patients were admitted in semi-critical or ICU. If invasive ventilation with endotracheal intubation was required, patients were admitted to the ICU.

Drug dosing and regimens

During the SARS-CoV-2 epidemic in Spain, the use of TCZ in patients with severe COVID-19 was regulated, authorized, and centrally supplied by the Spanish Ministry of Health, as a single iv infusion at a dose of 400 mg (weight <80 kg) or 600 mg (weight >80 kg). Exceptionally, if there was a partial or incomplete clinical response, a second infusion of TCZ at 400–600 mg at 12 h or a third at 24 h could be requested from the Spanish Central Government. Regarding the use of CS, there was no standard protocol in place for its use during the study period of the present revision. CS were indicated in combination with TCZ in the majority of cases, depending on individual physicians, using methylprednisolone at doses ranging from 0.5 mg/kg/d to 250 mg iv in 3 pulses.

The standard of care (SOC) treatments additionally administered to TCZ and CS were in accordance with available hospital guidelines at the time of the study period (March-April, 2020), and were also evaluated. SOC included hydroxychloroquine (HCQ), azithromycin, lopinavir/ritonavir (L/r), and remdesivir (R), alone or in combination regimens, given at standard recommended doses (Gautret et al., 2020; Cao et al., 2020; Grein et al., 2020; Sanders et al., 2020). Prophylactic anticoagulation therapy with low-

Table 1
Demographic, clinical, laboratory, and radiographic findings of COVID-19 patients receiving TCZ +/− CS. A comparison between survivor and nonsurvivor groups.

	All patients N = 186	Survivors N = 147	Nonsurvivors N = 39	p-Value
Age, years mean (SD)	64.3 (13)	62.1(12.7)	72.4 (10)	<0.001
Gender (males), n (%)	129 (69.4)	103 (70.1)	26 (66.7)	0.682
Body mass index, mean (SD)	29.3 (4.1)	29.6 (4.2)	28.4 (3.6)	0.105
Smoking behavior, n (%)				
Never smoker	140 (75.3)	108 (73.4)	32 (82)	0.532
Current smoker	8 (4.3)	7 (4.8)	1 (2.6)	
Former smoker	38 (20.4)	32 (21.8)	6 (15.4)	
Comorbidity n (%)				
Arterial hypertension	92 (49.5)	68 (46.3)	24 (61.5)	0.090
Diabetes mellitus	45 (24.2)	32 (21.8)	13 (33.3)	0.134
Hyperlipidemia	84 (45.2)	62 (42.2)	22 (56.4)	0.112
COPD[a]	8 (4.3)	7 (4.8)	1 (2.6)	1.000
Asthma	7 (3.8)	6 (4.1)	1 (2.6)	1.000
Chronic heart failure	7 (3.8)	2 (1.4)	5 (12.8)	**0.005**
Ischemic cardiopathy	11 (5.9)	7 (4.8)	4 (10.3)	0.246
Atrial fibrillation	6 (3.2)	3 (2)	3 (7.7)	0.108
Chronic kidney disease	16 (8.6)	10 (6.8)	6 (15.4)	0.089
Chronic liver disease	7 (3.8)	3 (2)	4 (10.3)	**0.036**
Cancer	18 (9.7)	12 (8.2)	6 (15.4)	0.175
Autoimmune disorder	14 (7.5)	10 (6.8)	4 (10.3)	0.497
Symptoms n (%)				
Fever >38 °C	174 (93.5)	140 (95.2)	34 (87.2)	0.069
Cough	144 (77.4)	110 (74.8)	34 (87.2)	0.101
Dyspnea	117 (62.9)	93 (63.3)	24 (61.5)	0.843
Anosmia	18 (9.7)	15 (10.2)	3 (7.7)	0.769
Ageusia	21 (11.3)	17 (11.6)	4 (10.3)	1.000
Sore throat	14 (7.5)	12 (8.2)	2 (5.1)	0.738
Diarrhea	63 (33.9)	53 (36.1)	10 (25.6)	0.222
Arthromyalgia	56 (30.1)	41 (27.9)	15 (38.5)	0.201
Myocarditis/MI[b], n (%)	1 (0.5)	1 (0.7)	0	1.000
Pulmonary thromboembolism, n (%)	9 (4.8)	6 (4.1)	3 (7.7)	0.399
PaO2/FiO2 D0, mean (SD)/N	188.4 (104.1)/137	194 (106)/107	169 (96)/30	0.237
SatO2/FiO2 D0, mean (SD)/N	175.7 (80.1)/129	182.6 (84.8)/101	151 (54.5)/28	**0.021**
PaO2/FiO2 <300 or SatO2 <315 D0, n (%)/N	155 (83.3)/186	119 (81)/147	36 (92.3)/39	0.144
Maximum Oxygen/ventilation required, n (%)				
Low-flow oxygen	5 (2.7)	5 (3.4)	0	0.200
High-flow oxygen (Monaghan®)	9 (4.8)	8 (5.4)	1 (2.6)	
High-flow oxygen (HFNC[c])	7 (3.8)	7 (4.8)	0	
Noninvasive ventilation	155 (83.3)	121 (82.3)	34 (87.2)	
Invasive ventilation	10 (5.4)	6 (4.1)	4 (10.3)	

[a] COPD: chronic obstructive pulmonary disease.
[b] MI: myocardial infarction.
[c] HFNC: high-flow nasal cannula.

molecular weight heparin (LMWH) was also recommended. A subset minority of patients with severe COVID-19 received sc interferon beta-1b at 0.25 mg/48 h.

Informed consent was waived because the study was performed outside the context of RCT and was retrospective in nature. Data were obtained from routine daily practice and anonymized. The confidential information of the studied patients was protected according to the European and National normative processes. The study received the ethics approval from the Research Ethics Committee of Bellvitge University Hospital (PR145/20).

Statistical analysis

Categorical variables were shown as absolute numbers and percentages. Quantitative variables were shown as mean and standard deviation. Categorical variables were compared using chi-square or Fisher's test. Quantitative variables were compared using t-test or Mann–Whitney U test, which depends on whether the variable followed a parametric distribution or not. The Cox proportional hazards model was performed with mortality as a dependent variable and which followed a backwards stepwise selection of variables. The survival time used in Cox regression is the time from hospital admission (usually coinciding with the start of the first treatment administered) to the last visit. All variables with significance <0.05 in the univariate study plus age and gender were included in the multivariate study.

Results

General data

Between March 17 and April 7, 2020, there were 1,092 patients admitted to our hospital for COVID-19 illness. Of them, 186 (17%) patients were treated with TCZ at any time of their admission and were included in the study; 129 were male (69.4%), most of them were old (64.3 yrs. ± 13). At the time of TCZ first infusion, 123 (66.1%) patients were admitted into conventional hospital wards

and 63 (33.9%) into semi-critical/critical care units. Of the total of 186 patients, 147 (79%) survived and 39 (21%) died. Both groups of patients, survivors and nonsurvivors, were comparable in the baseline. However, patients from the group of nonsurvivors were older (62.1 vs. 72.4 years and p < 0.001), more frequently had a previous diagnosis of chronic heart failure (1.4% vs. 12.8% and p = 0.005), and/or chronic liver disease (2% vs. 10.3% and p = 0.036). Significantly, survivors received CS in combination with TCZ in greater proportion than nonsurvivors (87.8% vs. 69.2% and P = 0.021) (Table 1).

Ancillary tests

Inflammatory parameters and lymphocyte count documented the day before TCZ first administration (D0), with or without CS, and its progression during the following 7 days (D1, D2, and D7) are shown in Table 2. Although the daily evolution of laboratory data was registered in a limited number of included patients, survivors showed much lower levels of abnormal inflammatory parameters and higher lymphocyte count the day before TCZ first infusion when compared with nonsurvivors. Furthermore, nonsurvivors showed a higher rapid increase of IL-6 two days after TCZ infusion (D2) as well as an evolution to worse of LDH plasmatic levels. However, none of these differences were found to be statistically significant to predict in-hospital mortality in this study.

Drug combinations and doses

All drugs in this study were given in accordance with the standard hospital protocol during the study period, based on recommended international guidelines available at that time. The number of patients receiving each of the drugs administered and the duration of such treatments are detailed in Table 3 .

The most common drugs used as SOC were HCQ (99.5%) and L/r (84.4%). The usual sequential regimen was an initial treatment with a combination of HCQ plus L/r for 5 days given on day +8.5 (±4.1) from the beginning of COVID-19 symptoms. The number of patients treated with prophylactic antibiotic (generally iv

Table 2
Laboratory tests: inflammatory parameters and lymphocyte count. Comparison between survivor and nonsurvivor groups.

	D0	D1	D2	//	D7
All patients, mean (SD)/N (N = 186)					
Ferritin ng/ml	1,927(1,245)/89	1,789(1,213)/76	1,853(1,478)/75		1,211(624)/77
CRP[a] mg/l	188(142)/148	133(106)/116	66(53)/112		21(50)/108
IL6[b] ng/l,	191(450)/32	700(1,243)/28	1,184(1,817)/19		665(711)/14
D-dimer mcg/l	2,258(6,026)/131	3,615(7,701)/108	3,717(7,391)/107	//	2,253(2,268)/106
LDH[c] U/l	459(154)/136	469(189)/109	459(184)/108		455(236)/108
Lymphocytes $\times 10^6$/l	900(1,509)/184	720(375)/113	850(873)/116		1,300(1,085)/105
Survivors, mean (SD)/N (N = 147)					
Ferritin ng/ml	1,911(1,250)/74	1,764(1,195)/65	1,854(1,485)/67		1,142(569)/70
CRP mg/l	175(110)/121	127(105)/94	62(52)/91		21(53)/98
IL6 ng/l,	188(507)/25	657(1,328)/24	688(1,112)/17	//	495(445)/12
D-dimer mcg/l	1,682(3,704)/109	2,465(5,237)/87	3,034(6,114)/87		2,042(2,017)/96
LDH U/l	442(141)/114	440(158)/88	430(167)/88		421(211)/97
Lymphocytes $\times 10^6$/l	820(396)/146	740(380)/92	910(939)/95		1,370(1,119)/94
Nonsurvivors, mean (SD)/N (N = 39)					
Ferritin ng/ml	2,006(1,258)/15	1,936(1,370)/11	1,837(1,518)/8		1,898(782)/7
CRP mg/l	246(232)/27	161(110)/22	83(55)/21		12(15)/10
IL6 ng/l,	200(132)/7	956(533)/4	5,395(24)/2	//	1,683(1,403)/2
D-dimer mcg/l	5,113(11,999)/22	8,378(13,031)/21	6,691(11,140)/20		4,280(3,475)/10
LDH U/l	551(187)/22	589(257)/21	587(203)/20		751(243)/11
Lymphocytes $\times 10^6$/l	723(431)/38	548(352)/21	548(352)/21		715(416)/11

[a] CRP: C-reactive protein.
[b] IL6: interleukin-6.
[c] LDH: lactate dehydrogenase.

Table 3
Drugs, doses, and duration. Comparison between survivor and nonsurvivor groups.

	All patients N = 186	SurvivorsN = 147	NonsurvivorsN = 39	p-Value
Hydroxychloroquine n (%)	185 (99.5)	146 (99.3)	39 (100)	1.000
Days mean (SD)	5.2 (2.9)	5.4 (1.6)	4.5 (5.5)	0.329
Lopinavir/ritonavir n (%)	157 (84.4)	127 (86.4)	30 (76.9)	0.147
Days mean (SD)	5.6 (2.5)	5.6 (2.5)	5.5 (2.9)	0.796
Azithromycin n (%)	34 (18.4)	24 (16.4)	10 (25.6)	0.893
Days mean (SD)	3.6 (1.8)	3.6 (1.6)	3.6 (2.1)	
Remdesivir n (%)	4 (2.2)	1 (0.7)	3 (7.7)	1.000
Days mean (SD)	8 (2.7)	9 (NA)	7.7 (3.2)	
Interferon-ß n (%)	22 (11.9)	13 (8.9)	9 (23.1)	0.839
Days mean (SD)	3.9 (2.6)	3.6 (2.3)	4.2 (3)	
Time from first symptom to first antiviral, days mean (SD)	8.5 (4.1)	8.5 (3.7)	8.7 (5.4)	0.727
Prophylactic antibiotic	145 (78.4)	115 (78.8)	30 (76.9)	0.804
Anticoagulation n (%)	4 (2.2)	3 (2)	1 (2.6)	0.958
None				
Prophylactic LMWH	82 (44.1)	66 (44.9)	16 (41)	
Middle doses LMWH	62 (33.3)	49 (33.3)	13 (33.3)	
High doses LMWH	38 (20.4)	29 (19.7)	9 (23.1)	
Immunomodulatory therapy				
Tocilizumab n (%)	186 (100)	147 (100)	39 (100)	1.000
Time from first COVID-19 symptom to TCZ[a], days mean (SD)	12 (4.3)	11.9 (4.2)	12.7 (4.9)	0.299
Time from COVID-19 admission to TCZ, days mean (SD)	4.3 (3.4)	4.2 (3.6)	4.6 (2.6)	0.516
Corticosteroids n (%)	156 (83.9)	129 (87.8)	27 (69.2)	**0.021**
0.5 mg/kg/d	14 (9)	14 (10.9)	0	
1 mg/kg/d	8 (5.1)	6 (4.7)	2 (7.4)	0.315
125 mg iv x3d	130 (83.3)	106 (82.2)	24 (88.9)	
250 mg iv x3d	4 (2.6)	3 (2.3)	1 (3.7)	
Time from first symptom to CS[b], days mean (SD)	11.2 (4.6)	10.9 (4.2)	12.2 (6.3)	0.192

[a] TCZ: Tocilizumab.
[b] CS: Corticosteroids.

amoxicillin-clavulanate, piperacillin-tazobactam, or ceftriaxone) and anticoagulation therapy are also indicated in Table 3 .

In those patients at risk to transit to a more severe stage, this initial regimen was subsequently followed by CS (iv pulses of 125 mg × 3 days) given on day +11.1 (±4.6) and followed by or overlapped with TCZ (single dose) given on day +12 (±4.3). In this regard, CS were also administered in combination with TCZ in 156 (83.9%) of the total 186 included patients. There were no differences between survivor and nonsurvivor groups on the doses of CS received. There was no difference in the sequential order of infusion between the TCZ and CS. With regard to TCZ administration, most patients (92.5%) received a single infusion of TCZ, 13 (7%) a second infusion 12 h after the first one, and in only 1 case (0.5%) a third infusion was administered 24 h after the second infusion. In 14 of the total 186 (7.5%) patients, despite presenting a PaO2/FiO2 greater than 300, TCZ prescription was indicated according to the serious alteration of inflammatory parameters and lymphocyte count. No noticeable adverse events related to TCZ +/– CS were shown throughout the study period and within the first 30 days of follow-up.

Finally, no differences between both survivor and nonsurvivor groups were shown according to both the indication of anti-coagulation and the different doses received, showing no higher mortality protection in the univariate study.

Risk factors of mortality

When survivors and nonsurvivors were compared in patients with COVID-19 receiving TCZ +/– CS due to severe lung injury and systemic host-immune response, the multivariate study showed statistical significance for older age (HR = 1.09, CI 95% 1.05–1.13, and p < 0.001), previous chronic heart failure (HR = 4.4, CI 95% 1,68–11.63, and p = 0.003), and previous chronic liver disease (HR =

4.69, CI 95% 1.62–13.59, and p = 0.004) as risk factors for all-cause in-hospital mortality. In contrast, the use of CS in combination with TCZ therapy showed a beneficial effect to prevent mortality in such a subset of patients with COVID-19 who receive TCZ (HR = 0.26, CI 95% 0.13–0.56, and p < 0.001) (Table 4).

Discussion

While a majority of patients with COVID-19 show a low-mild disease, a subset of 15% of patients presented with lung involvement required hospital admission. Worryingly, a 5% of the total evolve to severe respiratory failure and systemic host-immune inflammatory response, resulting in fatality in half of such cases (Zhou et al., 2020; Grasselli et al., 2020). These findings are consistent with the three stages of increasing severity proposed by Siddiqu and Mehra: stage I (incubation and early infection), stage II (pulmonary involvement), and stage III (systemic hyperinflammation and multiorgan dysfunction), which correspond with distinct clinical findings and outcomes.

In this regard, only remdesivir (Grein et al., 2020) and dexamethasone (RECOVERY Collaborative Group et al., 2020) have demonstrated evidence-based efficacy on RCTs in severe COVID-19 illness to date. These results are in accordance with the above-mentioned natural 3-stage evolution of COVID-19 disease (Siddiqi and Mehra, 2020). Therefore, it seems reasonable to propose a sequential combined therapy with effective antiviral drugs as a first step and, thereafter, immunomodulatory treatment in those patients with COVID-19 who progress into the advanced stage with severe pulmonary failure and systemic hyperinflammatory syndrome.

The knowledge about steroid use in patients with severe COVID-19 is preliminary and continues to evolve. Interestingly, a recent prospective meta-analysis of clinical trials of critically ill

Table 4
Risk factors associated with all-cause in-hospital mortality in COVID-19 patients receiving TCZ +/− CS. Cox regression analysis.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age/year	**1.07 (1.04–1.11)**	**<0.001**	**1.09 (1.05–1.13)**	**<0.001**
Gender (male)	0.77 (0.39–1.51)	0.445	–	–
BMI[a]	0.95 (0.87–1.03)	0.205		
Smoking behavior				
Never smoker (ref.)	1	–		
Current smoker	0.42 (0.06–3.09)	0.395		
Former smoker	0.48 (0.19–1.23)	0.127		
Comorbidity				
Arterial hypertension	1.59 (0.83–3.04)	0.166		
Diabetes mellitus	1.36 (0.68–2.69)	0.384		
Hyperlipidemia	1.41 (0.75–2.68)0.43 (0.06–3.13)	0.2900.404		
COPD[b]				
Asthma	0.47 (0.06–3.42)	0.454		
Chronic Heart failure	**5.86 (2.26–15.23)**	**<0.001**	**4.42 (1.68–11.63)**	**0.003**
Ischemic cardiopathy	1.81 (0.64–5.10)	0.264		
Atrial fibrillation	**4.13 (1.26–13.58)**	**0.020**	–	–
Chronic kidney disease	1.79 (0.70–4.60)	0.224		
Chronic liver disease	**3.12 (1.11–8.81)**	**0.032**	**4.69 (1.62–13.59)**	**0.004**
Cancer	**2.56 (1.06–6.17)**	**0.036**	–	–
Autoimmune disorder	1.23 (0.44–3.47)	0.696		
Lab test D0				
Ferritin >1500 ng/ml	0.88 (0.32–2.44)	0.810		
CRP[c] >150 mg/l	2.21 (0.96–5.06)	0.061		
IL6[d] >100 ng/l,	6.53 (0.78–54.31)	0.083		
D-dimer >1500 mcg/l	1.34 (0.57–3.17)	0.500		
LDH[e] >400 U/l	3.27 (0.96–11.10)	0.057		
Lymphocytes <600 × 10^6/l	1.47 (0.77–2.82)	0.242		
SatO2/FiO2	0.99 (0.99–1)	0.661		
PaO2/FiO2 < 300	1.38 (0.42–4.57)	0.597		
Pulmonary thromboembolism	1.18 (0.36–3.86)	0.788		
Anticoagulation				
None (ref.)	1	–		
Prophylactic LMWH[f]	0.93 (0.12–7.05)	0.947		
Middle doses LMWH	1.05 (0.14–8.01)	0.965		
High doses LMWH	1.11 (0.14–8.89)	0.922		
Time from first symptom to TCZ[g]	0.99 (0.95–1.03)	0.532		
Number of infusions of TCZ (1 vs. 2–3)	1.64 (0.68–3.96)	0.267		
Use of CS[h] in combination with TCZ	**0.33 (0.16–0.68)**	**0.002**	**0.26 (0.13–0.56)**	**<0.001**

[a] BMI: body mass index.
[b] COPD: chronic obstructive pulmonary disease.
[c] CRP: C-reactive protein.
[d] IL6: interleukin-6.
[e] LDH: lactate dehydrogenase.
[f] LMWH: low-molecular-weight heparin.
[g] TCZ: tocilizumab.
[h] CS: corticosteroids.

patients with COVID-19 showed that the use of steroids, when compared with SOC or placebo, was associated with lower 28-day all-cause mortality (WHO Rapid Evidence Appraisal for COVID-19 Therapies REACT Working Group et al., 2020). In this respect, the use of dexamethasone or alternative CS is currently recommended as immunomodulatory agents for the treatment of patients with severe COVID-19 requiring supplemental oxygen (https://www.covid19treatmentguidelines.nih.gov/). Conversely, updated recommendations have taken a position against the use of TCZ, alone or in combination with CS, because data from RCTs supporting the use of TCZ have not been reported yet (Lan et al., 2020; Boregowda et al., 2020).

On the other hand, recent real-world observational studies of high quality from Italy, Spain, France, and the US, indicated that TCZ might reduce ICU admissions, mechanical ventilator use, and the risk of death, when compared to the control group only treated with SOC (Quartuccio et al., 2020; Moreno-García et al., 2020; Mikulska et al., 2020; Price et al., 2020; Maeda et al., 2020; Kewan et al., 2020; Ramaswamy et al., 2020; Rojas-Marte et al., 2020; Rossi et al., 2020; Canziani et al., 2020). Moreover, Moreno-García et al. conclude that the beneficial effect of TCZ might be

particularly shown in the subset of severely-ill non-intubated patients with COVID-19 at an early stage of the systemic hyperinflammatory response. Interestingly, in a vast majority of these observational studies that assessed TCZ in COVID-19, CS were also given in addition to TCZ, ranging from 18% to 71% of included cases.

Unfortunately, the potential role of CS in combined regimen with TCZ has been less evaluated. An SRMA by Boregowda et al. found that there was no statistical difference in mortality between TCZ and SOC, when steroids are used in the treatment of severe COVID-19 illness (n = 12; pooled OR 0.76; 95% CI 0.47, 1.23; and p = 0.27). However, when steroid was not used, the TCZ group had significantly low mortality when compared with the SOC group (n = 4; pooled OR 0.24 [95% CI; 0.10–0.54] p < 0.01).

These controversial results prompted us to perform the present observational investigation, with the aim to identify those factors determining prognosis in a large real-world cohort of 186 patients receiving TCZ, with and without CS, due to severe COVID-19 illness, hospitalized during our first wave of infections. Our findings showed that, in such severe patients receiving TCZ, in-hospital mortality was associated with older age, and prior chronic heart

failure or liver disease. These mentioned factors were in accordance with those predicting a poor prognosis already found and previously reported in the general population with COVID-19 illness.

Of interest, the present study showed that in a vast majority (83.9%) of our patients with severe COVID-19 treated with TCZ, TCZ was also given in combination regimen with CS. Remarkably, the multivariate analysis identified the addition of CS to TCZ to be protective for in-hospital mortality in our series. In this respect, our results are in line with that of those reported in the SRMA by Boregowda et al., which concluded that when steroids are used in the SOC, the absence of a significant difference in mortality between those patients with COVID-19 who receive TCZ and those who do not, suggest a beneficial effect of the anti-inflammatory properties of steroids in the treatment of patients with severe COVID-19.

In the present study, TCZ and CS were both given as a second-step therapy after SOC, when the physicians who treat considered that patients were probably at a higher risk to transit into the advanced stage of COVID-19. Among the 153 included patients who receive TCZ and CS in combination, CS were most commonly given as iv pulses of methylprednisolone at 125 mg × 3 days at day +11, immediately followed by or overlapped with iv TCZ at day +12, at 8 mg/Kg (single dose). Only a minority of our patients (7.5%) received a second or third TCZ infusion, which does not appear to be related to lower mortality. Lastly, in contrast with some previous studies in which adverse events could not be evaluated due to a short follow-up, we assessed treatment safety during a 30-day follow-up after TCZ +/− CS administration, with no obvious serious adverse events or superinfections.

Finally, although survivors showed much better evolution of abnormal inflammatory parameters and lymphopenia than non-survivors, none of them were found to be statistically significant for predicting the prognosis within clinical practice. However, in the limited subset of included patients in whom laboratory data were available throughout the first days after TCZ prescription, it is noteworthy that nonsurvivors showed a worrying higher rapid increase of IL-6 two days after TCZ infusion as well as a worse evolution of LDH levels. The clinical relevance of these results might be assessed in future studies to provide better help to physicians who treat patients who are at a severe stage of COVID-19 disease.

Limitations

The results of the present study show several limitations that must be noted. First, the study is retrospective in nature using real-world observational data, outside the context of RCT. Second, we aimed to evaluate predictors of mortality in the subset of patients receiving TCZ, with or without CS, but not to assess the efficacy of TCZ in the general population with COVID-19 illness, comparing treated and untreated groups. Perhaps for this reason, the risk factors shown in our study may differ slightly from those previously recognized in other observational studies (Zhou et al., 2020; Du et al., 2020). Third, because of the emergency situation, small variations to the standard clinical management of patients with COVID-19 may not be totally ruled out as a result of hospital reorganization, which involves a wide spectrum of departments and physician specialists. Fourth, the number of patients with COVID-19 who present with PE and/or myocarditis may have been underestimated, because symptoms are difficult to ascertain in patients with severe COVID-19 and the d-dimer and troponins are almost universally elevated. Finally, the daily evolution of inflammatory parameters throughout the first days after TCZ administration was registered in a limited number of

included patients, which does not allow for firm conclusions to be drawn.

Conclusions

While waiting for RCTs, most institutions and physicians worldwide still tackle severe COVID-19 utilizing a variety of immunomodulatory drugs on the only basis of observational data. In our large series of 186 consecutive patients with COVID-19 who receive TCZ, multivariate analysis identified those patients of older age, with a previous diagnosis of chronic heart failure or liver disease to be at a higher risk for in-hospital mortality. Conversely, the addition of CS to TCZ therapy was shown to be effective in the prevention of in-hospital mortality. Unfortunately, based on the present study, it cannot be stated as to when would be the best time, not too early or too late, the best regimen, and appropriate doses, to use TCZ and CS in patients with severe COVID-19. In this respect, close monitoring of inflammatory markers, before and after treatment, may lead clinicians and researchers conducting RCTs, to select the right patients in whom immunomodulators may be beneficial.

Author contributions

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Final approval of the version to be submitted: all authors.

Conflicts of interest

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