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

E. Van den Eynde, O. Gasch, J. C. Oliva, E. Prieto, S. Calzado, A. Gomila, M. L. Machado, L. Falgueras, S. Ortonobes, A. Morón, S. Capilla, G. Navarro, J. Oristrell, M. Cervantes, and M. Navarro

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 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.

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.
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 Taulí, 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 RealAmp 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 >2000ng/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 ≥ 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 to 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.](image-url)
Table 1. Demographic and clinical characteristics of patients with severe pneumonia caused by SARS-CoV-2.

| Characteristic                                      | All patients n = 255 |
|-----------------------------------------------------|-----------------------|
| **Age, median (IQR) (years)**                       | 73.2 (61.0–79.2)      |
| **Male gender, n (%)**                              | 172 (67.5)            |
| **Origin 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 (mg/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 (%)                                  | 18 (7.1)              |
| Multi-lobar 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)            |
| Amoxycillin/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)             |
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 2A). 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 = .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.

| Baseline characteristics                  | Non-immunomodulatory n = 118 | Immunomodulatory treatment n = 137 |
|-------------------------------------------|------------------------------|-----------------------------------|
| Age, median (IQR) (years)                 | 73.7 (60.5–82.1)            | 75.6 (67.3–83.8)                  |
| Male gender, n (%)                        | 77 (65.3)                    | 27 (71.7)                         |
| Origen of infection                       |                             |                                   |
| Community acquired infection, n (%)       | 95 (80.5)                    | 32 (84.2)                         |
| Close contact with a case of COVID-19, n (%) | 23 (19.5)                  | 9 (24.3)                          |
| Comorbidities, n (%)                      |                             |                                   |
| Hypertension                              | 81 (68.6)                    | 20 (52.6)                         |
| Dyslipidemia                              | 57 (48.3)                    | 21 (55.3)                         |
| Obesity                                   | 41 (34.7)                    | 13 (34.2)                         |
| Diabetes                                  | 44 (37.3)                    | 11 (28.9)                         |
| Pulmonary Disease                         |                             |                                   |
| Cardiovascular disease                    | 48 (40.7)                    | 15 (39.5)                         |
| Chronic renal disease                     | 26 (22.0)                    | 8 (21.1)                          |
| Cancer                                    | 14 (11.9)                    | 4 (10.5)                          |
| Immunosuppressive condition               | 6 (5.1)                      | 2 (5.3)                           |
| Brain vascular disease                    | 10 (8.5)                     | 5 (13.2)                          |
| Chronic liver disease                     | 3 (2.5)                      | 1 (2.6)                           |
| Renal replacement therapy Human           | 3 (2.5)                      | 0                                 |
| Immunodeficiency virus infection          | 3 (2–5)                      | 3 (1–4)                           |
| Number of comorbidities, median (IQR)     | 5 (2.5)                      | 2 (1.3–3)                         |
| Treatment with ACE inhibitors or ARBs, n (%) | 59 (50)                     | 15 (39.5)                         |
| At admission                              | 5.5 (3–8)                    | 6 (3–8)                           |
| Days from first symptoms to SARS-CoV-2 PCR, median (IQR) | 92 (87–96) | 91 (84.5–96)                     |
| Basal oxygen Saturation, median (IQR)     | 261 (185.5–327)             | 240.5 (155–325.5)                 |
| PaFi at admission, median (IQR)           | 402 (302–443)                | 412 (183.5–443)                   |
| SpFi at admission, median (IQR)           | 30 (25.9)                    | 10 (26.3)                         |
| CURB-65 scale-score ≤ 1, n (%)            | 219 (120–278)                | 125 (116–161)                     |
| SpFi at ITD                               | 980 (780–1760)              | 710 (560–1055)                    |
| Lymphocytes count (10⁹/L)                 | 13.24 (5.45–22.11)          | 9.35 (5.91–22.43)                 |
| C-Reactive protein (mg/dL)                | 1573 (960–4662)              | 2298 (969–6845)                   |
| D-dimer (ng/mL)                           | 1192 (665–2221)             | 1299 (687–2194)                   |
| Ferritin (ng/mL)                          | 331 (264–396)                | 340 (260–487)                     |
| LDH (U/L)                                 | 69 (58.5)                    | 17 (44.7)                         |
| LDH (U/L)                                 | 980 (780–1760)              | 710 (560–1055)                    |
| C-Reactive protein (mg/dL)                | 13.24 (5.45–22.11)          | 9.35 (5.91–22.43)                 |
| D-dimer (ng/mL)                           | 1573 (960–4662)              | 2298 (969–6845)                   |
| Ferritin (ng/mL)                          | 1192 (665–2221)             | 1299 (687–2194)                   |
| LDH (U/L)                                 | 331 (264–396)                | 340 (260–487)                     |
| Outcomes, n (%)                           | In-hospital mortality        | 69 (58.5)                         |
| Discharged or ongoing on 05/19/2020       | 49 (41.5)                    | 21 (55.3)                         |

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

| Baseline characteristics | Alive<sup>a</sup> n = 139 | In-hospital mortality n = 116 | Cox regression analysis | Univariate p-value | Multivariate HR (95%IC) |
|--------------------------|-----------------------------|-------------------------------|------------------------|-------------------|------------------------|
| 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%
- Dyslipidemia: 63 (45.3%)
- Obesity: 52 (37.4%)
- Diabetes: 33 (23.7%)
- Chronic Pulmonary Disease: 39 (28.1%)
- Brain vascular disease: 7 (5.0%)
- Cardiovascular disease: 16 (11.5%)
- Chronic renal disease: 16 (11.5%)
- Cancer: 13 (9.4%)
- Chronic liver disease: 2 (1.4%)
- Diabetic kidney disease: 2 (1.4%)
- Number of comorbidities, median (IQR): 2 (1–3)
- Treatment with ACE inhibitors or ARBs, n (%): 54 (39.1%)
- At admission
  - Days from first symptoms to SARS-CoV-2 PCR, median (IQR): 7 (4–9)
  - Basal oxygen Saturation (%), median (IQR): 93 (89–96)
  - SpFi at ITD: 213.9 (120.0–271.0)
  - Days from SARS-CoV-2 PCR to ITD: 5 (2–7)
  - Lymphocytes count (10<sup>9</sup>/L): 0.92 (0.65–1.37)
  - C-Reactive protein (mg/dL): 8.35 (4.33–14.95)
  - Ferritin (ng/mL): 1425.5 (808.5–2128.4)
  - LDH (U/L): 321 (266–379)

**Immunomodulatory therapy, n (%)**

- Corticosteroids: 21 (15.1%)
- Tocilizumab: 14 (10.1%)
- Corticosteroids + tocilizumab: 55 (39.6%)

---

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.

<sup>a</sup>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).

<sup>p</sup> values smaller than .05 are marked as bold values.

lower probability of in-hospital death (Figure 2(B), Table 4).
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 compared to those in the control group, and there was no significant difference in admission to intensive care between groups [19]. The BACC Bay Tocilizumab trial enrolled 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

---

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

| 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 (%) | 42 (35.9) | 59 (96.4) |
| Non-immunomodulatory therapy (n = 101) | 18 (14.4) | 10 (11.8) | .033 |
| Tocilizumab | 11 (9.4) | 4 (4.7) | .025 |
| Corticosteroids + tocilizumab | 46 (39.3) | 12 (14.1) | <.001 |

IQR: Interquartile range; SpFi: pulse oximetry oxygen saturation/fraction of inspired oxygen ratio; ITD: Immunomodulatory treatment decision day.

*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.
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.

Acknowledgements

The authors thank Sara del Ángel, Mónica Belenguer, Enric Prats, Ona Cano, Aina Camps, René Gómez, Carla Monnerris and Cristina Mestre for their help in collecting data and Maria Centeno for her thorough revision of the final manuscript. The authors also wish to thank all the staff who fought the epidemic of COVID-19 at Consorci Corporació Sanitària Parc Taulí.

Disclosure statement

The authors report no conflict of interest.

Funding

OG received a personal research grant from the Pla estratègic de recerca i innovació en salut (PERIS) 2019–2021 (Departament de Salut. Generalitat de Catalunya). This work was supported by the Red Española de Investigación en Patología Infecciosa (REIPI).

References

[1] Zhu N, Zhang D, Wang W. China Novel Coronavirus Investigating and Research Team, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727–733.
[2] COVID-19 Situation Reports. WHO Coronavirus Disease (COVID-19) Dashboard | WHO Coronavirus Disease (COVID-19) Dashboard [cited 2020 Nov 17].
[3] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–1062.
[4] Huang X, Wei F, Hu L, et al. Epidemiology and clinical characteristics of COVID-19. Arch Iran Med. 2020;23(4):268–271.
[5] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–513.
[6] Jin YH, Cai L, Cheng ZS, for the Zhongnan Hospital of Wuhan University Novel Coronavirus Management and Research Team, Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM), et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020;7(1):4.
[7] Rizk JG, Kalantar-Zadeh K, Mehra MR, et al. Pharmacotherapeutic Analysis of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. Am J Med. 2020;80(13):1267–1292.
[8] Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients With COVID-19. Clin Infect Dis. 2020;ciaa478.
[9] Clinical Management of Severe Acute Respiratory Infection When COVID-19 Is Suspected. [cited 2020 May 27]. Available from: https://www.who.int/publications-detail/ci...infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
[10] The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. AMeta-analysis. JAMA. 2020;324(13):1330–1341.
[11] Bruno M, Tomazini BM, Maia IS, COALITION COVID-19 Brazil III Investigators, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. 2020;324(13):1307–1316.
[12] The Writing Committee for the REMAP-CAP Investigators. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317–1329.
[13] Dequin PF, Heming N, Meziani F, CAPE COVID Trial Group and the CRICS-TrIGGERsep Network, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support

ORCID

O. Gasch http://orcid.org/0000-0001-8518-458X
Among Critically Ill Patients With COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298–1306.

[14] Horby P, Lim WS, Emberson JR, et al.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med*. 2020. DOI:10.1056/NEJMo2021436

[15] World Health Organization. Corticosteroids for COVID-19: living guidance, 2 September, 2020. World Health Organization. Available from: https://apps.who.int/iris/handle/10665/334125

[16] Zhang C, Wu Z, Li JW, et al. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents*. 2020; 55(5):105954

[17] Gupta S, Wang W, Hayek SS, STOP-COVID Investigators, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181(1):32–40.

[18] Hermine O, Mariette X, Tharaux P-L, et al. 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(1):32–40.

[19] Salvarani C, Dolci G, Massari M, RCT-TCZ-COVID-19 Study Group, 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(1):24.

[20] Stone JH, Frigault MJ, Serling-Boyd MJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med*. 2020;383(24):2333–2344.

[21] GUAIS NIH NNOV 3] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [cited 2020 Nov 22]. Available from: https://www.covid19treatmentguidelines.nih.gov/.

[22] GUAIS IDSA Nov] Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. [cited 2020 Nov 18]. Available from: www.idsociety.org/COVID19guidelines.

[23] Corman VM, Landt O, Kaiser M. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020; 25(3):pii = 2000045.

[24] Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132(2): 410–417.