

Impact of systemic corticosteroids on mortality in older adults with critical COVID-19 pneumonia.

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Abstract

Background: The most susceptible population group to critical and fatal coronavirus disease 2019 (COVID-19) is older adults. In SARS-CoV-2 infection, the host immune response is thought to play a key role in the pathophysiological effects of lung damage. Therefore, corticosteroid therapy could modulate inflammation-mediated pulmonary injury and thereby reduce progression to severe respiratory failure and death. The aim of this study was to analyse the safety and clinical efficacy of corticosteroid therapy in older adults with severe COVID-19 pneumonia.

Method: We reviewed the clinical records of confirmed COVID-19 patients aged 75 years or older admitted to our hospital over a three months period (March 1, to May 31, 2020). A total of 143 patients were included in the study cohort. From 2 April, 2020, in accordance with World Health Organization (WHO) guidance on COVID-19, our hospital protocol added corticosteroid for COVID-19 treatment. We compared in-hospital mortality among patients with critical COVID-19 who received corticosteroids therapy and those who did not.

Results: 88 patients (61.5%) were treated with corticosteroids, and 55 patients (38.4%) were not. Both groups were similar in baseline characteristics. The median age was 85 years (IQR, 82–89), and 61.5% (88/143) were male. In-hospital mortality was lower in the corticosteroid group (68.2%) compared with patients in the non-corticosteroid group (81.8%). Treatment with corticosteroids was an independent survival factor (HR=0.61; 95% CI, 0.41–0.93; $P=0.006$).

Conclusions: In critically ill older adults with COVID-19 pneumonia, the use of corticosteroid treatment resulted in lower mortality without severe adverse events.

Keywords: Older adults; Critical ill patients; COVID-19 pneumonia; Corticosteroid treatment; In-hospital mortality.

Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified and linked to a cluster of patients with severe acute respiratory syndrome in Wuhan, China. On March 11, 2020, the outbreak had infected millions worldwide, and the WHO declared COVID-19 a pandemic. COVID-19 may yield severe pneumonia with acute respiratory distress syndrome (ARDS) due to a systemic inflammatory response that can lead to lung injury, multisystemic organ dysfunction and death. Older adults with multiple comorbidities have a greater risk of developing severe COVID-19. The Centers for Disease Control and Prevention (CDC) reported that patients aged 65 years or older make up 31% of COVID-19 infections, 45% of hospitalizations, 53% of intensive care unit (ICU) admissions, and 80% of deaths in the United States [1]. Previous reports show a mortality rate greater than 45% in patients older than 80 years old, admitted to hospital due to COVID-19 pneumonia [2]. Systemic corticosteroids have been suggested to benefit COVID-19 patients modulating the host inflammatory response and preventing or mitigating the inflammatory cytokine storm. The RECOVERY study, is the only prospective randomized controlled trial to analyse the effect of dexamethasone in patients hospitalized due to COVID-19. The results showed that mortality was lower among patients treated with corticosteroids who were receiving respiratory support, especially in patients with severe ARDS who were treated with invasive mechanical ventilation [3]. Recently, the WHO has recommended systemic corticosteroids for the treatment of patients with severe and critical COVID-19 [4]. This recommendation is consistent with those of other experts and governmental groups [5–9]. However, the benefits and dangers of corticosteroid treatment in older patients hospitalized due to COVID-19 pneumonia is still underexplored and evidence is scarce. Thus, the aim of this study was to evaluate the safety and clinical efficacy of corticosteroids therapy in older adults with critical COVID-19 pneumonia.

Materials and Methods

Study design, patients and data collection

This was a retrospective observational cohort study. Adults aged 75 years or older with confirmed COVID-19 pneumonia admitted to Infanta Leonor–Virgen de la Torre University Hospital complex in Madrid, Spain, from March 1, to May 31, 2020 were screened. COVID-19 diagnosis was defined by SARS-CoV-2 RNA detection in nasopharyngeal swab. The inclusion criteria were patients aged 75 years or older admitted in general wards with critical COVID-19 pneumonia. According to WHO guidance, critical disease was defined by new worsening respiratory symptoms or pneumonia, pulmonary opacities on a chest radiograph or computed tomographic scan and moderate or severe ADRS, corresponding to a PaO₂/FiO₂ (Pa/Fi) ratio lower than 200 mmHg [10]. All patients required advanced oxygen support including the need of oxygen with reservoir bag between 10 and 15 liters per minute, or noninvasive ventilation. We excluded patients who did not require supplemental oxygen or were receiving low-flow oxygen therapy during hospitalization, patients transferred to other hospital and patients who died within 24 hours after admission. Demographics, comorbidities, clinical data, oxygen saturation, complete blood count, coagulation, inflammatory and biochemical markers at admission were registered. Treatments, complications and outcomes were also collected for each patient from electronic medical records.

Local treatment protocol

During the SARS-CoV-2 pandemic, there were changes in the local treatment protocol in accordance with WHO guidance on COVID-19 and recommendations established from the Spanish Ministry of Health and the Spanish Agency of Drugs and Medical Devices (AEMPS). From 1 to 19 March, 2020, COVID-19 patients were started on lopinavir-ritonavir

(400 mg and 100 mg) twice daily for 14 days and hydroxychloroquine loading dose of 400 mg twice on the first day, followed by 200 mg twice daily for additional five days (unless contraindicated), plus ceftriaxone 2 g and azithromycin 500 mg daily for 7 days. During the second period (20 March, to 1 April, 2020), the standard of care was hydroxychloroquine plus ceftriaxone and azithromycin in mild COVID-19 patients, recommending interferon- β 1b (8 million international units every 48 hours) or tocilizumab (4 to 8 mg/kg with a maximum dose of 600 mg in a single dose) for severe or critical cases. During these periods, we did not use corticosteroid therapy for hospitalized COVID-19 patients according to our local protocol; however, they were used in patients with bronchospasm as part of routine general practice. From 2 April until the end of May, 2020, corticosteroid therapy was recommended in COVID-19-associated cytokine storm syndrome defined using the following criteria: 1) fever (temperature $>38^{\circ}\text{C}$); 2) D-dimer level $>1000\ \mu\text{g/L}$; 3) C-reactive Protein $>100\ \text{mg/dL}$ or 2-fold over basal value; 4) serum ferritin $>1000\ \text{ng/mL}$ or 5-fold over basal value; and 5) interleukin-6 $>40\ \text{pg/mL}$. Pulse therapy with intravenous methylprednisolone 125–250 mg daily for 1 to 3 days, followed by 0.5–1 mg/kg for additional five days was recommended. Tocilizumab was used at the discretion of the treating physicians, for severe and critical cases during all these periods.

Outcome

The primary outcome was in-hospital mortality. Furthermore, adverse side effects attributed to corticosteroids treatment were also analysed.

Statistical analysis

Descriptive analysis was performed to compare baseline characteristics of patients in corticosteroids and non-corticosteroids groups. Quantitative variables were expressed by mean and standard deviation when they had a normal distribution, or median and interquartile

range (IQR) when they had a non-normal distribution. Qualitative variables were defined by the frequency distribution and percentages. Quantitative variables were compared between the two periods using Student's t -test or the Mann-Whitney U, and qualitative variables were compared using Chi-squared test and Fisher's exact test depending on the normality of the variable. Kaplan-Meier analysis and log-rank tests were used to compare survival among patients in the corticosteroid and non-corticosteroid cohorts. Cox proportional hazards analysis was performed to analyse independent variables associated with mortality. A *P*-value of less than 0.05 was considered statistically significant. Results were obtained using Statistical Package for the Social Sciences software, version 26.0.

Ethical consideration

The study was conducted in accordance with the provisions of the Declaration of Helsinki and local regulations. The Institutional Investigation and Ethics Review Board of Infanta Leonor University Hospital (CEI-ILUH) approved the study (Code ILUH R 027–20). Due to its retrospective nature, the need for informed consent from patients was waived. Data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Ideas for Health Association. REDCap is a secure, web-based software platform designed to support data capture for research studies [11].

Results

Study population

From 1 March to 31 May, 2020, there were 458 patients aged 75 years or older with COVID-19 hospitalized at the Infanta Leonor–Virgen de la Torre University Hospital complex. There were 33 patients excluded because they were transferred to other hospital, 10 patients died within 24 hours after admission and 127 patients with suspected COVID-19 pneumonia had a negative SARS-CoV-2 RT-PCR at least twice. Of the remaining 288

patients, 24 did not require supplemental oxygen and 121 received low-flow oxygen therapy during hospitalization. Finally, 143 patients with critical COVID-19 were included in the study. Figure 1 shows study flow chart. 88 patients (61.5%) received corticosteroids, and 55 patients (38.4%) did not. The median age was 85 years (IQR, 82–89), and 61.5% (88/143) were male. Baseline characteristics of the patients are shown in Table 1. The median Barthel index was 90 points (IQR, 60–100); 90 patients (62.9%) had two or more comorbidities including hypertension (n = 108 [75.5%]), diabetes (n = 46 [32.2%]), coronary artery disease (n = 33 [23.1%]), chronic obstructive pulmonary disease (n = 23 [16.1%]), obesity (n = 17 [11.9%]), chronic kidney disease (n = 14 [9.8%]), dementia (n = 14 [9.8%]), and malignancy (n = 6 [4.2%]). The median number of days between symptoms onset and admission was 5 (IQR, 3–7), and the median ambient air oxygen saturation upon admission was 89% (IQR, 83–92). 21 patients (14.68%) received noninvasive ventilation; 14 patients (15.90%) in corticosteroids group, and 7 patients (12.72%) in non-corticosteroids group. 4 patients (2.79%) were admitted to ICU.

Corticosteroids treatment

Corticosteroid therapy was started at a median of 11 days (IQR, 5–15) after symptoms onset and six days (IQR, 3–8) after admission. There were 28 patients (31.8%) received intravenous methylprednisolone pulses. The median methylprednisolone daily dose was 35 mg (IQR, 25–55) and the median duration of treatment was six days (IQR, 3–9). There were no significant differences in age, gender, Barthel index, time from symptoms onset to admission, oxygen saturation at admission or comorbidities prevalence in the treated and the untreated groups. Patients who received corticosteroids showed higher levels of plasma inflammatory markers at admission versus the non-corticosteroids group (white blood cell, 8450.0 vs. 6240.0 cells/ μ L, and platelets count, 220.0 vs. 167.0 $\times 10^3/\mu$ L, respectively).

Patients receiving corticosteroids were also treated more frequently with azithromycin (87.5% versus 67.3%) and tocilizumab (15.9% versus 3.6%), and less frequently with lopinavir-ritonavir (27.3% versus 58.2%). There were 46 patients (52.2%) with any adverse event related to corticosteroid treatment. Hyperglycaemia was seen in 40 patients (45.4%), secondary infections in 6 patients (6.8%), and gastrointestinal bleeding in two patients. Among patients with corticosteroids-associated hyperglycaemia eighth patients (20%) had blood glucose level more than 250 mg/dL at least one time, and one patient developed hyperosmolar hyperglycemic state. Urinary tract infection was the most frequent secondary infections in corticosteroid group. One infection was caused by *Enterococcus faecalis*, another by *Enterobacter aerogenes*, and in two patients the microbiological etiology was not documented. There was one patient with suspicion of bacterial superinfection and *Staphylococcus hominis* bacteremia was detected in another patient. In the two patients with gastrointestinal bleeding endoscopy was not performed. Both were hemodynamically stable, but red blood cell concentrates were transfused. Physician-based criteria, only the hyperosmolar hyperglycemic state could have contributed to death.

Impact of corticosteroids on in-hospital mortality

In-hospital mortality was lower in the corticosteroid group compared with patients in the non-corticosteroid group (Figure 2). Multivariate analysis included age, gender, white blood cell, platelet count, and treatment with corticosteroids and tocilizumab. Treatment with corticosteroids (HR, 0.62; 95% CI, 0.41–0.93) and treatment with tocilizumab (HR, 0.46; 95% CI, 0.23–0.91) were independent factors associated with a lower in-hospital mortality. Table 2 compares patients treated with corticosteroids who were discharged alive and patients who died. Patients who died were older and more likely to be male sex. They also had a

lower median oxygen saturation at admission and higher median of days from symptoms onset to initialization of corticosteroid treatment.

Discussion

We analysed the impact of systemic corticosteroids on in-hospital mortality in patients aged 75 years or older with severe COVID-19 pneumonia. In this retrospective study, corticosteroid treatment was associated with a lower odds ratio of death in elderly patients.

Older adults develop more severe forms of COVID-19. The immune response decreases during aging. This phenomenon is called immunosenescence [12]. Impairment in number, function, and activation of cells involved in the immune response and aging of hematopoietic stem cells are major phenotypes of the immune system associated with immunosenescence. These changes may lead to higher SARS-CoV-2 replication [13]. SARS-CoV-2 infects bronchial epithelial through to the angiotensin-converting enzyme 2 (ACE2) receptor located on type I and II pneumocytes. Virus replication into the alveolar cells induce an inflammatory response with massive production of pro-inflammatory cytokines (such as interleukin-6, interleukin-1 and tumour necrosis factor α) producing diffuse alveolar damage [14]. Based on this, anti-inflammatory drugs could be an effective treatment for older adults with COVID-19.

Corticosteroids are well-tolerated drugs and readily available worldwide at low cost. Several studies have investigated the use of corticosteroids in COVID-19 patients with severe pneumonia and/or ARDS showing conflicting results, although the most recent reports show that they could be useful in different clinical scenarios. In a meta-analysis of seven trials including 1703 critically ill patients with COVID-19, corticosteroids reduced the 28-day mortality versus standard care or placebo (OR, 0.66; 95% CI, 0.53–0.82; $P < 0.001$) [15]. In a systematic review of 25 electronic databases and six additional Chinese databases through 20

July, 2020, for evaluating specific treatments for COVID-19, corticosteroids were associated with a reduction on mortality compared with standard care (OR, 0.87; 95% CI, 0.77–0.98) [16]. In another meta-analysis that included eight studies, corticosteroids were associated with reduced mortality exclusively in severely ill patients versus those who did not receive corticosteroids (OR, 0.65; 95% CI, 0.51–0.83; $P = 0.0006$) [17]. To date, the RECOVERY study is the largest randomized clinical trial to compare COVID-19 patients treated with and without corticosteroids [3]. The study showed that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days decreased 28-day mortality in hospitalized patients with COVID-19 compared with usual care alone, especially in patients with severe ARDS who were treated with invasive mechanical ventilation. These favourable findings are supported by two other trials of corticosteroids for COVID-19, which stopped enrolment in early June, 2020, when the RECOVERY trial results were released [18,19]. A limitation of the RECOVERY trial is that results are not detailed by age categories. Limited data are available about the usefulness of COVID-19 treatments in elderly patients. In a quasi-experimental study, hospitalized patients with moderate to severe COVID-19 that received an early short course of methylprednisolone had a reduced rate of death, ICU transfer, and mechanical ventilation [26]. In a prospective, multicenter and observational study in critically ill patients with COVID-19 admitted into ICU corticosteroids therapy showed lower mortality when compared to delayed or no use of corticosteroids [27]. In a recent systematic review and meta-analysis that included 20,197 patients, corticosteroid treatment showed a significant reduced mortality in the group (OR 0.72 (95% CI 0.57–0.87)). In our study, corticosteroid treatment reduced mortality in hospitalized patients with COVID-19 and severe respiratory failure who required high-flow oxygen therapy or noninvasive ventilation. To the best of our knowledge, this is the first study to analyse the impact of corticosteroids treatment in mortality specifically in critically ill older adults with COVID-19. In addition, in our study

the median methylprednisolone daily dose was equivalent to dexamethasone dose in the RECOVERY trial.

During hospital admission, other treatments were administered to our patients according to the current local protocol. The corticosteroid treatment group received tocilizumab more frequently compared to the non-corticosteroid treatment group. In multivariate analysis, tocilizumab was also associated with a lower mortality; however, this is non-significant difference between died and discharge alive patients in corticosteroid group.

The in-hospital mortality in our study is striking, but is similar to previous report in older adults with ADRS [20]. The reported in-hospital mortality in others studies was lower. In a Spanish study in old patients hospitalized with COVID-19 the overall case-fatality rate was 46.9% [21], and in a multicentric retrospective study in acute COVID-19 geriatric wards the in-hospital mortality was 31% [22]. In both, the probability of in-hospital mortality was increased with quick sequential organ failure assessment (qSOFA) score ≥ 2 . In contrast to these studies, in our cohort severity was defined as ADRS. The difference in mortality between our series and the previous series may reflect the critical condition of the patients. In addition, only four patients were transferred to ICU. It is remarkable that the mortality between the corticosteroid and non- corticosteroid group is similar during the first days of hospitalization, and the Kaplan-Meier curves diverges from day nine after admission. This could be related to the fact that the median time from admission to corticosteroids initial therapy was six days. The median length of hospital stay was 9 days, with lower stays observed in the corticosteroid group.

Few retrospective studies have analysed adverse events related to corticosteroids therapy in COVID-19 patients. Unfortunately, details on severity and predisposing risk factors were not available in these studies. Giacobbe et al, reported a high incidence of

bloodstream infections in patients admitted to the ICU receiving corticosteroids compared to those who did not (HR, 3.95; 95% CI, 1.20–13.03) [23]. Another observational study showed a prevalence of secondary infections in 33% (3/9) of the patients receiving corticosteroids versus 3.1% (1/32) patients who did not ($P = 0.007$) [24]. The study conducted by Zhang et al, reported hyperglycaemia in 23 of 38 patients (60.5%) with COVID-19 receiving corticosteroids versus 59 of 128 patients (46.0%) not receiving corticosteroids [25]. The RECOVERY investigators provided four serious adverse events related to dexamethasone treatment [8]. Two were hyperglycaemia, one case of steroid-induced psychosis and one participant had an upper gastrointestinal bleed. All events were solved and none of the participants died. A previous recent prospective meta-analysis reported 64 events (18.0%) among 354 patients randomized to corticosteroids, and 80 events (23.3%) among 342 patients randomized to usual care or placebo [16]. The most common adverse events were hyperglycemia and secondary infections (pneumonia, sepsis, and fungemia). Consistent with these observations, in our study hyperglycaemia and secondary infections were the most frequent side effects associated to corticosteroid treatment. Among the four serious adverse events observed in corticosteroid group (hyperosmolar hyperglycemic state, *Staphylococcus hominis* bacteremia and two cases of gastrointestinal bleeding), only hyperosmolar hyperglycemic state could have related to patient death.

Limitations

Our study has several limitations mainly due to its retrospective nature although both groups were similar in baseline characteristics, severity and respiratory support. Our results might be limited by the heterogeneity of corticosteroid dose. In addition, patients received different treatments according to the current local protocol in those moment Furthermore, this was an unicentric study and there was no long-term follow-up. Another limitation is the

generalize the results. Finally, other limitation is the lack of any data on viral clearance, but the clinical significance of this finding is unknown.

Conclusion

Our study provides evidence that elderly patients with critically COVID-19 and treated with systemic corticosteroids have a lower in-hospital mortality than patients not treated with corticosteroids. Moreover, this was a safe therapy with few severe adverse events. Until more progress in treatment is achieved or real-world data on the safety and effectiveness of vaccines against SARS-CoV-2 are available, it is recommended that elderly patients should take strong precautions during COVID-19 pandemic.

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Conflict of Interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. All other authors declare no conflicts of interest.

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Author Contributions

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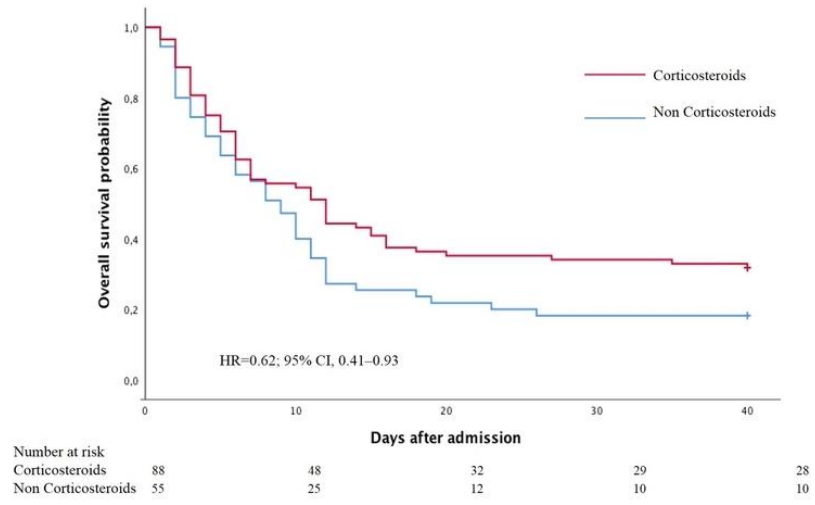
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Figure 1



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