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## Original article

## Fourteen-day survival among older adults with severe infection with severe acute respiratory syndrome coronavirus 2 treated with corticosteroid: a cohort study

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## ABSTRACT

**Objective:** To assess the effectiveness of corticosteroids among older adults with coronavirus disease 2019 (COVID-19) pneumonia requiring oxygen.

**Methods:** We used routine care data from 36 hospitals in France and Luxembourg to assess the effectiveness of corticosteroids with at least 0.4 mg/kg/day equivalent prednisone (treatment group) versus standard of care (control group). Participants were adults aged 80 years or older with PCR-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or CT scan images typical of COVID-19 pneumonia, requiring oxygen  $\geq 3$  L/min, and with an inflammatory syndrome (C-reactive protein  $\geq 40$  mg/L). The primary outcome was overall survival at day 14. In our main analysis, characteristics of patients at baseline (i.e. time when patients met all inclusion criteria) were balanced by using propensity-score inverse probability of treatment weighting.

**Results:** Among the 267 patients included in the analysis, 98 were assigned to the treatment group. Their median age was 86 years (interquartile range 83–90 years) and 95% had a SARS-CoV-2 PCR-confirmed diagnosis. In total, 43/98 (43.9%) patients in the treatment group and 84/166 (50.6%) in the control group died before day 14 (weighted hazard ratio 0.67, 95% CI 0.46–0.99). The treatment and control groups did not differ significantly for the proportion of patients discharged to home/rehabilitation at day 14 (weighted relative risk 1.12, 95% CI 0.68–1.82). Twenty-two (16.7%) patients receiving corticosteroids developed adverse events, but only 11 (6.4%) from the control group.

**Conclusions:** Corticosteroids were associated with a significant increase in the overall survival at day 14 of patients aged 80 years and older hospitalized for severe COVID-19. **Laure Gallay, Clin Microbiol Infect 2021;27:1145**

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## Introduction

The RECOVERY trial showed that dexamethasone reduced mortality for patients with coronavirus disease 2019 (COVID-19) receiving oxygen with and without invasive mechanical ventilation [1]. The efficacy of corticosteroids in critically ill patients was confirmed in subsequent studies [2–4]. However, for patients with less severe disease, studies have shown variable effectiveness, associated with the severity of the disease: the more severely ill the patients, the more effective the treatment [1,5,6].

In older adults, who are at the greatest risk of severe disease and death from COVID-19, the RECOVERY trial is the only study reporting results for patients outside critical care, and it found no difference in the survival of patients according to their treatment by dexamethasone [1,7]. Nonetheless, the heterogeneity in the severity of infection within this specific subgroup does not justify strong conclusions. The unclear benefit–risk balance of corticosteroids for older patients has raised concerns (e.g. because these drugs increase the risk of confusion, hyperglycaemia, falls, drug–drug interactions), and some countries, including France, do not support the systematic use of corticosteroids for patients aged  $\geq 70$  years despite recommendations from the WHO to treat all adult patients with severe and critical COVID-19 with systemic corticosteroids [8].

In this study, we used routine care data collected during the first acute phase of the pandemic to retrospectively emulate a target trial aimed at assessing the effectiveness of corticosteroids for severe infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adults.

## Materials and methods

### Participants and settings

Physicians screened one by one all patients hospitalized between 14 March and 30 April, 2020. First, they identified all consecutive patients aged 80 years or older, with a SARS-CoV-2 infection confirmed by PCR or by typical clinical and CT scan findings. Second, they assessed whether these patients had a severe COVID-19 infection, defined by both an oxygen requirement  $\geq 3$  L/min (regardless of its duration) and C-reactive protein  $\geq 40$  mg/L [9]. Third, they excluded patients with organ failure at baseline, including those who required immediate admission to the intensive care unit (ICU) and those requiring non-invasive ventilation. Physicians and research assistants then used patients' electronic health records to abstract their data.

The Institutional Review Board of Henri-Mondor Hospital (AP-HP), France, approved this study (number: 00011,558). As it was based on data from routine care already collected at the time of the study, patients' informed consent was not required. All patients or family members were informed that their hospital data would be used for research purposes and were offered the opportunity to object to the use of their data.

### Treatment strategies

We compared two treatment strategies: receiving at least one dose of corticosteroids at  $\geq 0.4$  mg/kg/day equivalent prednisone (treatment group), or receiving the standard of care (control group). The cut-off value of 0.4 mg/kg/day was chosen to account for dose rounding by physicians. To mimic a pragmatic trial, patients in the treatment group could start corticosteroids within a 'grace period' of 72 hours from baseline.

Our causal contrast of interest was the per-protocol effect, and we compared participants who received corticosteroids in the

72 hours after baseline with those who did not receive this drug. A specific sensitivity analysis mimicking an intention-to-treat analysis was performed, analysing all patients eligible for the study; those whose data did not meet the criteria for treatment were analysed in the control group. For safety outcomes, all patients who received corticosteroids before day 14, regardless of the dose or timing, were included in the treatment group. The definition of group assignment based on patients' observational data is reported in the Supplementary material (Table S1).

### Follow up

The start of follow up (baseline or time zero) for each individual was the time when all eligibility criteria (oxygen therapy  $\geq 3$  L/min and inflammatory syndrome with a C-reactive protein level  $\geq 40$  mg/L) were met. All patients were followed up from baseline until the occurrence of one of the following events, whichever came first: (a) death, (b) loss to follow up, or (c) end of follow up, which occurred at least 14 days after baseline.

### Outcomes

The primary outcome was overall survival by day 14. The secondary outcome was the proportion of patients discharged from hospital to home/rehabilitation on day 14. The time frame of 14 days was chosen because at the time of the study and in the frail population of patients  $\geq 80$  years old, most deaths occurred before day 14 [10]. All adverse events were abstracted from electronic health records in free text and independently recoded by one physician (VT).

### Statistical analyses

Propensity-score methods were used to account for differences between the two groups at baseline. The propensity score represents the probability that patients would receive corticosteroids, given their baseline demographic and clinical covariates (see Supplementary material, Appendix S2). Estimates of the average treatment effect were calculated by inverse probability of treatment weighting (IPTW), with Cox proportional hazards models calculating hazard ratios and IPTW estimates of the relative risk for binary outcomes.

To account for immortal time bias, all patients in the control group who died during the grace period were randomly assigned to one of the two groups, given that their observational data were compatible with both groups at the time of the event (see Supplementary material, Appendix S3) [11,12].

Missing baseline variables were handled by using multiple imputation with chained equations.

## Results

### Participants

This study included 267 patients. Their median age was 86 years (interquartile range (IQR), 83–90 years), 49.8% were men, 95% had a SARS-CoV-2 PCR-confirmed diagnosis and 98 were assigned to the treatment group (see Supplementary material, Figs S1–S3 and Table S2). Co-morbidities and clinical severity at baseline were similar between the two groups. However, corticosteroids were prescribed less often to patients with low autonomy at baseline, measured with the Groupe Iso Ressource score; 14.3% of patients in the treatment group and 20.9% in the control group had a Groupe Iso Ressource score of 1 or 2, which indicates low autonomy.

The median time from symptom onset to baseline was 7 days (IQR 4–10). Among the 98 patients assigned to the treatment group, 51 (53.7%) received methylprednisolone, 22 (23.2%) prednisone, 15 (15.8%) dexamethasone, 4 (4.2%) prednisolone and 3 (3.2%) hydrocortisone. The median duration of corticosteroid treatment was 5 days (IQR 3–11) and the median dose of corticosteroids 1.1 mg/kg/day eq. prednisone (IQR 0.9–1.6), that is, 0.2 mg/kg of dexamethasone per day (Table 1).

### Follow up and outcomes

Vital status was missing at day 14 for three of the 267 patients included in the main analysis (who had, however, been discharged in

good health status before this date). During follow up, seven patients were transferred to ICU, one was intubated and 127 died before day 14.

In total, 43/98 (43.9%) patients in the treatment group and 84/166 (50.6%) in the control group died before day 14 (hazard ratio 0.81, 95% CI 0.56–1.16). After balancing the baseline covariates by IPTW, survival was significantly higher for patients from the treatment group compared with the control group (weighted hazard ratio 0.67, 95% CI 0.46–0.99) (Fig. 1). There was no significant difference between the treatment and control groups for the proportion of patients discharged to home/rehabilitation at day 14 (weighted relative risk 1.12, 95% CI 0.68–1.82) or weaned from oxygen by that date (weighted relative risk 1.00, 95% CI 0.68–1.48). Sensitivity analyses are available in the Supplementary material (Tables S3–S5, Fig. S4).

**Table 1**  
Patients' baseline characteristics (n = 267)

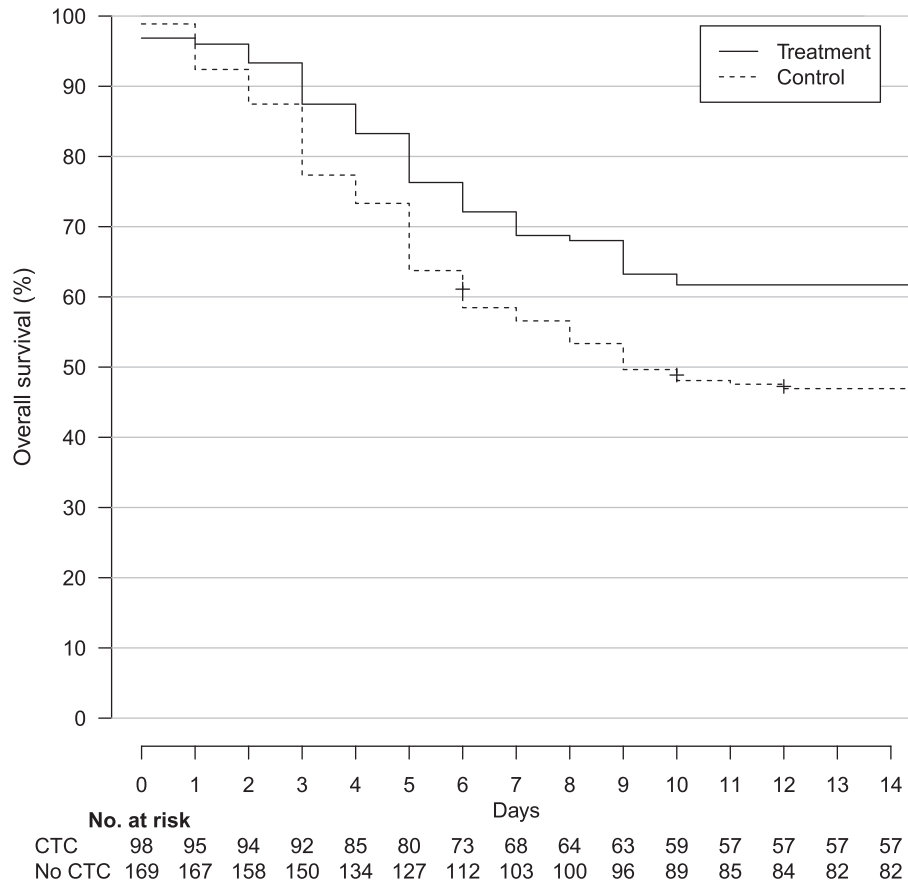
Characteristics	Total (n = 267)	Treatment group (n = 98) <sup>a</sup>	Control group (n = 169)
<b>Demographic and clinical data</b>			
Age (years), median (IQR)	86 (83–90)	86 (83–89)	87 (83–90)
Male sex, n (%)	133 (49.8)	48 (49.0)	85 (50.3)
<b>Co-morbidities, n (%)</b>			
Chronic respiratory disease (including asthma)	17 (6.4)	6 (6.1)	11 (6.5)
Chronic heart failure (n = 247)	111 (41.6)	44 (44.9)	67 (39.6)
Cardiovascular diseases (including hypertension) (n = 266)	228 (85.7)	85 (87.6)	143 (84.6)
Chronic kidney failure	48 (18.0)	21 (21.4)	27 (16.0)
Diabetes requiring insulin or complicated (n = 260)	39 (15.0)	12 (12.5)	27 (16.5)
Liver cirrhosis	2 (0.7)	1 (1.0)	1 (0.6)
Immunosuppression	10 (3.7)	4 (4.1)	6 (3.6)
Cancer	27 (10.2)	7 (7.1)	20 (11.9)
Body weight (kg), median (IQR) (n = 204)	71 (61–79)	72 (62–80)	70 (60–78)
<b>Autonomy (GIR score), n (%) (n = 261)</b>			
GIR score 1 or 2 (Low autonomy)	48 (18.4)	14 (14.3)	34 (20.9)
GIR score 3 or 4 (Moderate autonomy)	78 (29.9)	36 (36.7)	42 (25.8)
GIR score 5 or 6 (High autonomy)	135 (51.7)	48 (49.0)	87 (53.4)
<b>Usual place of residence, n (%)</b>			
Community	183 (68.5)	64 (65.3)	119 (70.4)
Retirement homes	19 (7.1)	7 (7.1)	12 (7.1)
Nursing homes/Hospital	62 (23.2)	26 (26.5)	36 (21.3)
Other	3 (1.1)	1 (1.0)	2 (1.2)
Treatment by ACEIs or ARBs, n (%) (n = 258)	119 (46.3)	39 (40.6)	80 (49.4)
<b>COVID-19 data at baseline</b>			
Time from symptom onset to baseline (days), median (IQR) (n = 262)	7 (4–10)	8 (5–11)	6 (3–10)
Confusion on eligibility date, n (%) (n = 261)	92 (35.2)	35 (35.7)	57 (35.0)
Dehydration on eligibility date, n (%) (n = 264)	84 (31.8)	27 (27.8)	57 (34.1)
Respiratory rate (breaths/min), median (IQR) (n = 211)	26 (22–31)	28 (24–32)	26 (22–30)
Oxygen flow at admission (L/min), median (IQR) (n = 261)	4 (3–7)	4 (3–6)	4 (3–7.2)
Systolic blood pressure (mmHg), median (IQR) (n = 256)	134 (119–150)	132 (120–150)	134 (116–150)
Neutrophil count (count/mm <sup>3</sup> ), median (IQR) (n = 257)	5400 (3810–8020)	5220 (3800–7600)	5575 (3832–8478)
Lymphocytes count (count/mm <sup>3</sup> ), median (IQR) (n = 258)	740 (502–1080)	680 (480–1080)	790 (520–1080)
Platelet count (count × 1000/mm <sup>3</sup> ), median (IQR) (n = 260)	204 (156–254)	211 (164–256)	199 (152–253)
C-reactive protein (CRP) > 40 mg/L, median (IQR) (n = 261)	105 (69–169)	114 (69–171)	104 (68–164)
Percentage of lung affected >50% on the CT scan (n = 168 <sup>b</sup> )	37 (13.9)	18 (18.3)	19 (11.2)
Decision to limit and stop active treatments (at baseline)	195 (73.0)	79 (80.6)	116 (68.7)
<b>Corticosteroid treatment data</b>			
<b>Corticosteroid, n (%)</b>			
Dexamethasone	15 (5.6)	15 (15.3)	—
Methylprednisolone	51 (19.1)	51 (52.0)	—
Prednisolone	4 (1.5)	4 (4.1)	—
Prednisone	22 (8.2)	22 (22.4)	—
Hydrocortisone	3 (1.1)	3 (3.1)	—
High-dose corticosteroid (≥120 mg/day) [16]	28 (10.5)	28 (28.6)	—
Corticosteroid treatment duration (days), median (IQR) (n = 94)	5 (3–11)	5 (3–11)	—
Corticosteroid dose (mg/kg/day eq. prednisone), median (IQR)	1.1 (0.9–1.6)	1.1 (0.9–1.6)	—

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; IQR, interquartile range.

The numbers in parentheses in the first column correspond to the quantity of data available before the imputation of missing baseline data by using multiple imputations with chained equations. Results are presented as % (count) unless stated otherwise.

<sup>a</sup> This corresponds to 95 patients receiving corticosteroids with at least 0.4 mg/kg in the 72 h after baseline plus one patient from the control group randomly assigned to the treatment group to account for immortal time bias (see the detailed methods in the Supplementary Appendix S3).

<sup>b</sup> Seventy-seven patients did not have a CT scan at admission.



**Fig. 1.** Kaplan–Meier curves for survival in the inverse probability of treatment sample. Abbreviation: CTC, corticosteroid treatment.

Among the 131 patients receiving corticosteroids, 22 (16.8%) developed adverse events but only 11/172 (6.4%) from the control group did. Frequent adverse events included hyperglycaemia (6.1% versus 0.6%), heart failure (2.3% versus 0.6%), confusion (3.0% versus 1.2%) and infection (1.5% versus 0%) (Table 2).

## Discussion

In this emulated trial, corticosteroids significantly improved the 14-day survival of patients aged 80 years or older and hospitalized in a non-ICU department for severe COVID-19 with reassuring data regarding harms. Indeed, despite patients treated with corticosteroids experienced more adverse events than those treated with the standard of care, those effects remained rare and we found no major cardiotoxicity or neurotoxicity. Our study did not show a reduction in hospitalization length, but the end point at day 14 might have been too early to identify this. Such an effect would be important in reducing the geriatric complications of longer hospitalizations, such as functional decline, decreased nutrition and cognitive impairment [13].

Recommendations to treat older patients with corticosteroids have been based on results from studies performed in ICU [2] and on results from the RECOVERY trial, which showed an overall effect of dexamethasone, but a non-significant difference in the population of patients aged 80 years or more. The discrepancy with our findings may be explained by the fact that our study population was more homogeneous and more severely ill than that studied in the RECOVERY trial (35% of the patients older than 80 years in the RECOVERY trial were not under oxygen at randomization). Indeed,

both the RECOVERY trial and the COCORICO study have shown that the more severely ill the patients, the more effective are the corticosteroids [1,5].

Our study has several limitations. Despite the use of robust methods to draw causal inferences, the study remains observational and potential unmeasured confounders may bias the results [14]. Second, the corticosteroid prescriptions were heterogeneous in terms of drugs, time of start, dose, and duration. Third, we could not account for the duration of corticosteroid prescriptions. For example, we may have observed only 3 days of corticosteroid

**Table 2**  
Adverse events

Adverse event	Treatment group (n = 131), n (%)	Control group (n = 172), n (%)
Any	22 (16.8)	11 (6.4)
Expected with corticosteroids		
Infection	2 (1.5)	0 (0)
Hyperglycaemia	8 (6.1)	1 (0.6)
Hypertension	1 (0.8)	0 (0)
Confusion or psychiatric manifestation	4 (3.1)	2 (1.2)
Atrial fibrillation	0 (0)	1 (0.6)
Hypokalaemia or fluid overload	1 (0.8)	0 (0)
Heart failure	3 (2.3)	1 (0.6)
Other severe adverse events		
Thromboembolic event	1 (0.8)	0 (0)
Increased serum levels of aspartate aminotransferase	1 (0.8)	2 (1.2)
Renal failure	0 (0)	1 (0.6)

Adverse events are counted in the safety population, without weighting.

treatment for a given patient because an event occurred on the fourth day. Fourth, our study population might not be representative of the population of older adults hospitalized during the first wave in France because it was recruited in centres involved in a network coordinated by REACTing (INSERM), which involved mainly non-geriatric wards. Fifth, our study was limited to the number of eligible patients available at the time of analysis. In particular, we found discrepant results between the main analysis and the sensitivity analyses. This may suggest that survivor bias is not completely accounted for in the main analysis or that our study lacked power. Finally, the follow up was limited to 14 days. Nonetheless, evidence shows that at the time of the study most deaths occurred before this cut-off point [10].

In all, our findings support the use of corticosteroids for patients aged 80 years or older with severe COVID-19. However, further research is needed to determine the right timing and dose of the treatment as well as the right indication, especially to clarify the benefit–risk balance. In particular, it would be interesting to assess whether its use in nursing homes could reduce the transfer of older adults with severe disease to the hospital. Strengthening the therapeutic arsenal for the care of older adults is critical as these patients are the most vulnerable to COVID-19 and may not fully benefit from vaccination because of the immunosenescence associated with advanced age [15].

### Transparency declaration

LG, EP, NV, FB and EF have nothing to disclose. VTT is a minority shareholder from SKEZI, this activity is outside the submitted work. MM received research funds from GSK, outside the submitted work and personal fees for lectures from LFB and Amgen, outside the submitted work. FXL received personal fees for lectures from Gilead Sciences, bioMérieux and MSD outside the submitted work.

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### Author contributions

Concept and design were by FXL, LG and VTT. Acquisition, analysis, or interpretation of data was performed by all authors from the COCO\_OLD Study Group. VTT, FXL, EF, LG, FB, NV and MM drafted the manuscript and all authors critically revised the manuscript for important intellectual content. VTT and EP performed the statistical analysis; administrative, technical and material support were by FXL, LG, VTT and EF. FXL supervised the study. VTT and EP had full access to all the data of the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

### Appendix S1. COCO-OLD (Collaborative cOhort COrticoteroids for OLD patients with COvid-19) study Group

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.03.021>.

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