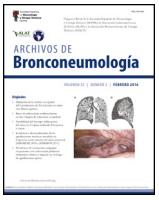
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Archivos de Bronconeumología 58 (2022) 281–283

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Scientific letter

Early Initiation of Corticosteroids Might be Harmful in Patients Hospitalized With COVID-19 Pneumonia: A Multicenter Propensity Score Analysis

El inicio temprano de corticosteroides podría ser perjudicial en pacientes hospitalizados con neumonía COVID-19: un estudio multicéntrico mediante índice de propensión

To the Director,

Although corticosteroid therapy has become a standard of care for patients with COVID-19 pneumonia, the efficacy and safety of its use remains controversial. The current widespread use of systemic corticosteroids in this clinical setting relies mostly on the results of the RECOVERY study, which showed that dexamethasone treatment reduced deaths by one-fifth in patients with COVID-19 pneumonia who needed supplemental oxygen.[1] The results of three meta-analyses supported this finding,[2–4] but it must be mentioned that the weight of the RECOVERY trial was more than 50 per cent in all of them and the magnitude of the effect was modest (OR ranging from 0.70 to 0.88). In this study, we sought to evaluate the effect of corticosteroids in preventing an unfavorable outcome in patients admitted to hospital with COVID-19 pneumonia.

Data were obtained from two different cohorts of patients admitted with COVID-19 pneumonia during the COVID-19 spring 2020 outbreak. The first cohort was composed of 1292 patients admitted to the eight Galician tertiary hospitals and the second was composed of 1548 patients admitted to four other Spanish hospitals. The study was approved by the Biomedical Research Ethics Committee of La Fe University and Polytechnic Hospital (2020-122-1) and by the Ethics Committee of Galicia (Cod. 2020/239). Data (demographic, clinical, laboratory) were collected on admission or during the first 24 h of hospitalization.

Baseline characteristics were compared between patients with and without corticosteroid treatment. Data were reported as a percentage for categorical variables and as mean ± standard deviation (SD) or median with interquartile range (IQR, 25–75%) for continuous variables. Categorical variables were compared using Fisher's exact test or Pearson's chi-square test, as appropriate, and continuous variables were compared using the Mann–Whitney *U* test or Student's t test.

To minimize the effect of a corticosteroid treatment selection bias and to control for potential confounding factors, a propensity score matching (PSM) procedure was performed. The primary outcome was a composite of in-hospital death and orotracheal intubation and the secondary outcome measure was mortality. The model included six pre-selected baseline variables that might have affected patient assignment to a corticosteroid or non-corticosteroid group, as well as clinical outcomes; specifically: room-air SpO2 for assessing the severity of respiratory failure, level of CRP for indicating systemic inflammatory response syndrome, age and sex as basic characteristics, comorbidities (using the Charlson index), and region (Galicia vs. rest of Spain). The treatment and control pairs were matched via the nearest neighbor matching approach and the caliper was set at 0.25. PSM was performed using the R package MatchIt version 3.6.2. A Cox regression model was conducted to examine the impact of corticosteroid treatment on patient outcomes. In order to examine the influence of early (<10 days from symptoms onset) versus late (≥10 days) initiation of corticosteroid therapy, a boosted multinomial logistic regression analysis was used to calculate propensity scores and to allow the comparison of three therapeutic conditions (early, late and no use of corticosteroids). Two-sided p values < 0.05 were considered statistically significant. Statistical analyses were done using the SPSS version 22.0 (IBM SPSS, Armonk, NY).

Among the 2840 screened cases, 187 were excluded for death or orotracheal intubation within 24 h after hospital admission, 301 were excluded for having received tocilizumab and 772 for absence of relevant data. Among the remaining 1580 patients, 464 were given corticosteroids. Nine hundred and twenty-eight patients were matched into 464 pairs. Clinical and laboratory characteristics in the cohort of patients exposed and not exposed to corticosteroids, before and after PSM, are shown in Table 1. Patients not receiving corticosteroids therapy were younger, less frequently male, had fewer comorbidities, better baseline SpO2 and lower CRP on admission. No significant differences were observed after matching, and characteristics for patients with or without corticosteroids were well balanced.

In the crude analysis, 122 patients (26.3%) corticosteroid-treated patients reached the composite outcome, compared to 122 patients (10.9%) who did not receive this therapy. This translated into an increased risk of death or need for mechanical ventilation (HR 1.91; 95% CI: 1.38–2.61). However, among 464 PSM pairs, there was no difference in the composite outcome (HR 1.64; 95% CI: 0.93–2.92).

With regard to the secondary outcome measure, 93 patients (20.0%) corticosteroid-treated patients died, in contrast to 98 patients (8.7%) in the non-corticosteroid group (HR 1.47; 95% CI: 1.02–2.10). Among the propensity score matched sample, mortality did not differ between corticosteroid-treated and non-corticosteroid-treated patients (HR 1.33; 95% CI: 0.94–2.28). These results are summarized in Table 2.

Due to data availability, only patients from the Galician cohort (n = 1014) were included in the boosted multinomial logistic regression analysis. Early start was associated with an increased risk of death (OR 1.52; 95% CI: 1.03–2.23) whereas this association was not found among patients with late initiation (OR 0.92; 95% CI: 0.61–1.38).

These results are in concordance with those obtained in other PSM studies that found no impact of corticosteroids on COVID-19 pneumonia outcome.[5–10] An increased mortality was observed in another report[11] and two additional PSM studies concluded that corticosteroid therapy was associated with lower mortality,[12,13] although they included critically ill patients, the specific popu-

https://doi.org/10.1016/j.arbres.2021.10.001

Table 1
Differences between subjects exposed or not to corticosteroids, before and after propensity score matching.

Variable	Unmatched			Matched		
	Not exposed to corticosteroids (n = 1116)	Exposed to corticosteroids (n = 464)	p	Not exposed to corticosteroids (n = 464)	Exposed to corticosteroids (n = 464)	p
Age, years	67 (54–76)	74 (63–83)	<0.001	74 (64–83)	74 (63–83)	0.973
Male sex	608 (54.5)	282 (60.7)	0.021	277 (59.7)	282 (60.7)	0.737
Charlson index	0 (0–2)	1 (0–2)	<0.001	1 (0–2)	1 (0–2)	0.185
SpO_2%	95 (93–97)	94 (91–96)	<0.001	94 (92–96)	94 (91–96)	0.295
*CRP**			<0.001			0.843
Below-median	633 (56.7)	215 (46.3)		212 (45.7)	215 (46.3)	
Above-median	483 (43.3)	249 (53.7)		252 (54.3)	249 (53.7)	
Region (% Galicia)	689 (61.7)	325 (70.0)	<0.001	323 (69.6)	325 (70.0)	0.886

Results are expressed as: median (interquartile range) or as number (%). SpO_2: arterial oxygen saturation. CRP: c-reactive protein.

Table 2
Estimated effect of corticosteroid treatment on the outcome measures before and after PSM.

	Unmatched	Matched
Death or orotracheal intubation	HR 1.91; 95% CI: 1.38–2.61	HR 1.64; 95% CI: 0.93–2.92
Death	HR 1.47; 95% CI: 1.02–2.10	HR 1.33; 95% CI: 0.94–2.82

lation that could benefit the most from this therapy according to the results of the RECOVERY trial.[1] Considering all the available evidence, the role of corticosteroids remains controversial in the clinical context of non-critically ill patients who need supplemental oxygen. It seems very plausible that the type, the dose, the duration and the timing of prescription (early start may increase viral replication) could influence the outcome, and the available literature has not accounted for these relevant factors. Moreover, it could be hypothesized that COVID-19 patients may suffer different histopathological patterns of lung injury, either corticosteroid-resistant (acute lung injury and diffuse alveolar damage) or steroid-responsive (i.e. organizing pneumonia), but more research is needed to investigate this possibility.

In accordance with the results of the RECOVERY trial,[1] we found a harmful effect of early (<10 days) initiation of corticosteroids, hypothetically reflecting that anti-inflammatory therapy might not be advisable during the initial, replicative, phase of the process.

The strengths of this study are the well-defined and homogenous population included, the large size, the multicenter design and the careful minimization of confounding variables related to propensity of corticosteroid treatment through a PSM analysis. The main limitations include the retrospective design, possible residual selection bias (the variables used in the PSM do not represent all of the factors that could influence an adverse prognosis, and the Charlson index is a somewhat crude measure of comorbidities) and lack of information regarding timing, type and dosages of corticosteroids.

In conclusion, we found no association between the use of corticosteroids and intubation or death in patients hospitalized with COVID-19 pneumonia. Early initiation (<10 days from symptom onset) of corticosteroids might increase the risk of mortality and this therapeutic decision must be taken with caution, weighing risks and benefits.

Author's contributions

LAPLL: Responsible for the design of the study; acquisition of data: analysis and interpretation of data; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Were principal investigators at participant sites, discussed the results and contributed to the final manuscript. RG: Responsible for the design of the study; analysis and interpretation of data; drafting the work; final approval of the version to be published. DPO: Responsible for the design of the study; drafting the work; analysis and interpretation of data; final approval of the version to be published. RM: has made substantial contributions to acquisition of data; interpretation of data; final approval of the version to be published. PPEY: has made substantial contributions to acquisition of data; interpretation of data; final approval of the version to be published; AA: has made substantial contributions to acquisition of data; interpretation of data; final approval of the version to be published. RZ: has made substantial contributions to acquisition of data; interpretation of data; final approval of the version to be published. CC: has made substantial contributions to acquisition of data; interpretation of data; final approval of the version to be published. AT: has made substantial contributions to acquisition of data; interpretation of data; drafting the work; final approval of the version to be published.

Availability of data and material (data transparency)

The database could be available upon reasonable request.

Ethics approval

The study was approved by CEIm Hospital Universitario y Politécnico La Fe (Cód. 2020-122-1) and CEIm Autonómico de Galicia (Cod. 2020/239).

Funding

This project was supported by an unconditional grant from FAES, with no role in the analysis, decision to publish or preparation of the manuscript. The design, analysis, and writing of this report are entirely the work and responsibility of the authors, and Dr. LAPLL had full access to all data and final responsibility for the decision to submit this work for publication.

Conflicts of interest

LAPLL reports grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from GSK, grants and personal fees from TEVA, personal fees and non-financial support from Novartis, personal fees and non-financial support from Chiesi, personal fees from Sanofi, personal fees from Menarini, grants and personal fees from Esteve, personal fees from ROVI, personal fees from MSD, personal fees from TECHDOW PHARMA, non-financial support from FAES, outside the submitted

work. The rest of the authors do not report conflicts of interest related to the submitted work.

Acknowledgements

The authors wish to thank SEPAR's Integrated Research Project (PII) on Respiratory Infections for its support in the preparation of this article.

References

1. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2020;383:2030–40.
2. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980, http://dx.doi.org/10.1136/bmj.m2980.
3. 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: a meta-analysis. JAMA. 2020;324:1330–41, http://dx.doi.org/10.1001/jama.2020.17023.
4. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020;24:696, http://dx.doi.org/10.1186/s13054-020-03400-9.
5. Liang MY, Chen P, He M, Tang J, Li H, He XL, et al. Corticosteroids treatment of patients with coronavirus disease 2019: a propensity score matching study. Curr Med Sci. 2021;41:24–30, http://dx.doi.org/10.1007/s11596-021-2313-6.
6. Albani F, Fusina F, Granato E, Capotosto C, Ceracchi C, Gargaruti R, et al. Corticosteroid treatment has no effect on hospital mortality in COVID-19 patients. Sci Rep. 2021;11:1015, http://dx.doi.org/10.1038/s41598-020-80654-x.
7. You X, Wu CH, Fu YN, He Z, Huang PF, Chen GP, et al. The use of methylprednisolone in COVID-19 patients: a propensity score matched retrospective cohort study. PLOS ONE. 2020;15, http://dx.doi.org/10.1371/journal.pone.0244128, e0244128. eCollection 2020.
8. Wu J, Huang J, Zhu G, Liu Y, Xiao H, Zhou Q, et al. Systemic corticosteroids and mortality in severe and critical COVID-19 patients in Wuhan, China. J Clin Endocrinol Metab. 2020;105:dgaa627, http://dx.doi.org/10.1210/clinem/dgaa627.
9. Yuan M, Xu X, Xia D, Tao Z, Yin W, Tan W, et al. Effects of corticosteroid treatment for non-severe COVID-19 pneumonia: a propensity score-based analysis. Shock. 2020;54:638–43.
10. Liu Z, Li X, Fan G, Zhou F, Wang Y, Huang L, et al. Low-to-moderate dose corticosteroids treatment in hospitalized adults with COVID-19. Clin Microbiol Infect. 2021;27:112–7.
11. Liu J, Zhang S, Dong X, Li Z, Xu Q, Feng H, et al. Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome. J Clin Invest. 2020;130:6417–28.
12. Chen Q, Song Y, Wang L, Zhang Y, Han L, Liu J, et al. Corticosteroids treatment in severe patients with COVID-19: a propensity score matching study. Expert Rev Respir Med. 2021;15:543–52.
13. Wu C, Hou D, Du C, Cai Y, Zheng J, Xu J, et al. Corticosteroid therapy for coronavirus disease 2019-related acute respiratory distress syndrome: a cohort study with propensity score analysis. Crit Care. 2020:643, http://dx.doi.org/10.1186/s13054-020-03340-4.

Luis A. Pérez de Llano [a], Rafael Golpe [a,*], Diego Pérez-Ortiz [a], Rosario Menéndez [b,c], Pedro P. España Yandiola [d], Amaia Artaraz [d], Rafael Zalacain [e], Catia Cilloniz [f,c], Antoni Torres [f,c]

[a] *Pneumology Service, Lucus Augusti University Hospital, EOXI Lugo, Monforte, Cervo. C039 Biodiscovery Research Group HULA-USC, Health Research Institute of Santiago de Compostela (IDIS), Spain*
[b] *Hospital Universitario y Politécnico la Fe, Valencia, Spain*
[c] *Biomedical Research Center Network for Respiratory Diseases (CIBERES), Madrid, Spain*
[d] *Pneumology Service, Galdakao-Usansolo University Hospital, Galdakao, Bizkaia, Spain*
[e] *Pneumology Service, Cruces University Hospital, Bizkaia, Spain*
[f] *Hospital Clinic, Barcelona, Spain*

Corresponding author.
E-mail addresses: rafagolpe@gmail.com, rafael.golpe.gomez@sergas.es (R. Golpe).