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LETTER

Impact of late administration of corticosteroids in COVID-19 ARDS

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Dear Editor,

Acute respiratory distress syndrome (ARDS) related to coronavirus disease 2019 (COVID-19) is challenging. As pro-inflammatory patterns and cytokine storm are among the hallmarks of severe COVID-19 pneumonia, early low dose of corticosteroids (CTC) has been proved to be effective in the RECOVERY trial [1] and subsequent meta-analysis [2]. However, a large proportion of patients remained dependent of mechanical ventilation at the end of the CTC therapy, and questions about late administration and possibly high doses of CTC to prevent or treat lung fibrosis in persistent ARDS [3] are unresolved. We, therefore, aimed to evaluate the impact of late CTC for COVID-19 ARDS patients versus the absence of CTC administration.

We performed a post hoc analysis from the COVADIS project, a multicenter observational study gathering 21 French and Belgian intensive care units (ICUs) [4]. All consecutive patients (from 10/03 to 15/04/2020) with moderate to severe ARDS according to Berlin definition under invasive ventilation and positive SARS-CoV-2 RT-PCR were included. We studied patients who did not receive (no CTC group) or received CTC later than 13 days after symptoms onset (75% percentile of patients included in the RECOVERY trial [1]) (CTC group). We analyzed the effect of CTC administration on ICU 90-day survival with a Cox model by specifying the delay between intubation and administration of CTC as a time-dependent covariate. Potential confounding factors (age, gender, body mass index, hypertension, prone position, venovenous extracorporeal membrane oxygenation (VV-ECMO), comorbidities, static compliance and PaO_2/FiO_2 at intubation) were tested for inclusion in the final model. The same strategy was used to study the effect of CTC on mechanical ventilation duration, after censoring for death. The study was approved by appropriate regulatory French and Belgian committees, with the information of the patient or next of kin.

After exclusion of patients who: withdraw consent ($n=1$), were included in other studies on CTC ($n=22$), received early CTC ($n=24$), or were lost to follow-up, 348 patients were finally analyzed.

Patients received a median dose of 1 [1, 2] mg/kg of methylprednisolone equivalent, 21 [18–26] days after symptoms onset (eSupplement). Delay between intubation and late initiation of CTC was 11 [8–16] days ($n=57$ treated patients). In the final Cox model, late initiation of CTC was neither associated with lower ICU mortality (HR = 1.44; 95% CI [0.83–2.50]) nor with shorter duration of mechanical ventilation (HR = 0.89; 95% CI [0.60–1.33] (Tables 1, 2).

Early CTC treatment has demonstrated survival benefit in severe COVID-19 pneumonia, and has been endorsed by WHO [1, 2]. Conversely, no data are available on the impact of late CTC administration [5]. This post hoc analysis of a homogeneous cohort of the most severe critically ill patients found that late CTC administration did not improve the patient-centered outcomes.

To conclude, while early administration of low-dose CTC should be encouraged in severe COVID-19 pneumonia, late high-dose CTC appear to be non-beneficial in late non-resolving ARDS. Furthers trials are needed to better define the use of CTC in ARDS related to COVID-19.

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Table 1 Cox regression model for ICU 90-day mortality with late CTC administration as a time-dependent covariate

	Hazard ratio	*p* value	95% confidence interval
Late CTC administration	1.44	0.200	0.83–2.50
Age of patient	1.08	0.000	1.04–1.11
Static compliance at intubation	0.980	0.019	0.963–0.997
VV-ECMO	2.11	0.003	1.28–3.47
Charlson score	1.17	0.000	1.08–1.25
Age × time[a]	0.998	0.004	0.996–0.999

[a] Interaction term between age of patient and time (days)

Table 2 Cox regression model for MV release with late CTC administration as a time-dependent covariate

	Hazard ratio	*p* value	95% confidence interval
Late CTC administration	0.89	0.577	0.60–1.33
Age of patient	0.967	0.000	0.953–0.981
Prone position	0.51	0.000	0.36–0.71
VV-ECMO	0.30	0.000	0.19–0.49

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-020-06311-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

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