

Appendix

Additional analyses

Considering the steroid group, we found a progression of the disease between hospital admission and steroid therapy beginning in terms of CRP and PaO₂/FiO₂. As illustrated by Appendix Figure 1, CRP was increased by 9.5 mg/L between admission and steroid therapy beginning in patients who died or underwent MV (Panel A; p=0.008), while CRP was reduced by 3.4 mg/L in patients who survived without MV (Panel B; p=0.017).

The difference of PaO₂/FiO₂ between CPAP first trial and steroid administration was not significant in patients with bad composite outcome, even if a trend in reduction from 176 to 145 mmHg is present (Panel C; N=8; p=0.162), while was 53 mmHg (from 212 to 159 mmHg; Panel D; N=44; p<0.001) in those with the good outcome.

A-posteriori excluded patients

Between the a-posteriori excluded patients for adjusting results for immortal time bias (N=191), 1 was excluded because intubated after 6 days since admission and transferred to another hospital so missing the follow-up, 96 needed mechanical ventilation and were admitted to the ICU ward after 3 days from admission (SD ±2), while 94 were treated in a medical ward; mortality was respectively 30 and 72%. In this subgroup only 9 patients (4,7%) had corticosteroids.

As summarized in Appendix Table 3 this population was particularly heterogeneous:

- Patients who died in the medical ward in less than 8 days since admission were older, had more comorbidity and had a more severe pulmonary and systemic disease. These patients were not candidates for mechanical ventilation due to the poor expected prognosis.
- Patients who de-escalated CPAP therapy before 8 days since admission and had a good outcome had better performance in terms of PaO₂/FiO₂ and milder inflammatory response (defined by CRP)
- Patients who were admitted to ICU had similar PaO₂/FiO₂ at CPAP and CRP at hospital admission compared to those treated in a medical ward (p=0.200 and p=0.212 respectively). These patients were intubated on average after 2 days. They have had a rapid clinical deterioration, as shown by the reduction of PaO₂/FiO₂ from 212 to 104 mmHg and the increase of CRP from 16.4 to 20.2 mg/L (p<0.001 for both the parameters).

Appendix Table 1. Secondary outcome and relative Odds Ratio.

Missed data for primary and secondary outcome: 171 cases of 180 (53/57 in steroid group, 118/123 in standard care alone group).

CRP: C-Reactive protein; *: $p < 0.05$; £: Value recorded at hospital admission; †: Value recorded at first CPAP trial; ¤: Value recorded at hospital admission.

Effect of steroid treatment – Main results	Adjusted Odds Ratio (95% CI)
Secondary outcome: in hospital mortality	
Steroid treatment	0.269 (0.097-0.743) *
Age - years	1.152 (1.091-1.217) *
PaO ₂ /FiO ₂ † - mmHg	0.997 (0.993-1.001)
CRP £ - mg/L	1.068 (1.006-1.133) *

Appendix Table 2. Whole population baseline characteristic comparison between usual care alone and usual care + steroid. CCI: Charlson Comorbidity Index; SOFA: Sequential Organ Failure Assessment; CRP: C-Reactive protein; *: p<0.05; £: Value recorded at hospital admission; †: Value recorded at first CPAP trial; IQR: Inter-Quartile Range.

	Treatment		P-value
	Control group (N=305)	Steroid group (N=66)	
Age - years	65±11	69±10	0.011*
Female - no. (%)	72 (24)	18 (27)	0.529
Days of symptoms before admission	7±5	7±5	0.737
Days between admission and CPAP therapy (IQR)	1 (0-2)	1 (0-4)	0.021*
CCI	3.7±2.0	3.9±1.4	0.387
SOFA score	3.9±1.6	3.4±1.2	0.013*
CRP £ – mg/L	12.4±9.1	11.9±7.9	0.673
CRP † - mg/L	14.0±8.6	13.6±7.4	0.704
PaO ₂ /FiO ₂ † - mmHg	223±113	207±111	0.298
Admission time since first patient admission - days	23±10	30 ±10	<0.001*

Appendix Table 3. Characteristics of excluded patients: 191 patients were excluded from the primary analysis because they reached the primary endpoint before 8 days of admission, the median days of steroid therapy start. The table represents the data from 190 patients because one patient was intubated after 6 days since admission and transferred to another hospital where we missed the follow-up. CCI: Charlson Comorbidity Index; SOFA: Sequential Organ Failure Assessment; CRP: C-Reactive Protein; * $p < 0.05$.

	Medical ward			ICU		
	Alive (N=26)	Dead (N=68)	P-value	Alive (N=67)	Dead (N=29)	P-value
Age - years	57±11	75±8	<0.001*	59±8	66±6	<0.001*
CCI	2.4±1.8	5.5±1.8	<0.001*	2.5±1.2	3.9±1.2	<0.001*
SOFA score	2.4±1.2	5.0±1.5	<0.001*	4.1±0.9	4.4±0.9	0.138
CRP at hospital admission – mg/L	10.2±5.5	14.1±11.1	0.112	13.9±9.6	17.2±9.4	0.125
CRP at CPAP - mg/L	11.1±5.1	15.4±8.1	0.016*	16.5±10.7	16.5±9.1	0.999
CRP at ICU admission - mg/L	-	-	-	10.4±11.0	22.9±10.3	0.164
PaO ₂ /FiO ₂ at CPAP - mmHg	265±81	167±85	<0.001*	218±123	208±114	0.718
PaO ₂ /FiO ₂ at ICU admission – mmHg	-	-	-	110±47	92±32	0.066

Appendix Figure 1. Steroid group CRP and PaO₂/FiO₂ variation between hospital admission (or CPAP positioning for PaO₂/FiO₂) and steroid therapy beginning. CRP: C-Reactive Protein; CPAP: Continuous Positive Airway Pressure.

