Supplementary Online Content 3

Dequin P-F, Heming N, Meziani F, et al; CAPE-COVID Trial Group and the CRICS-TriGGERSep Network. Effect of hydrocortisone on 21-day mortality or respiratory support among critically-ill patients with COVID-19: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.16761

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Detailed Inclusion and Noninclusion Criteria

Detailed Inclusion Criteria

- Age ≥ 18 year
- Patients affiliated to a social security scheme ("Sécurité sociale")
- Admission to a participating ICU or intermediate care unit
- Diagnosis of COVID19 either as certain (positive RT-PCR) or probable (evocative clinical and radiological features AND epidemic context AND absence of other microbiological documentation).
- Focal shadowing/infiltrate on chest X-ray or CT-scan
- Study drug infusion initiated no longer than 24 hours following the appearance of the first severity criterion; in case of transfer from another hospital, this period can be prolonged to 48 hours.
- Severity defined by at least one of the following:
    - Pneumonia Severity Index (PSI) > 130 (Fine class V)
    - Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more
    - Patient treated by high-flow oxygen therapy with a FiO2 of 50% or more and a PaO2/FiO2 (P/F) ratio lower than 300
    - Patient treated by oxygen therapy with a partial rebreathing-mask with a reservoir bag, provided that the PaO2 is less than (cf. table):

Oxygen flow (L/min)	6	7	8	9	10 or more
PaO2 (mmHg)	180	210	240	270	300

- Patient receiving the best available treatment as define by up-to-date scientific knowledge
- Informed consent signed by the patient, his/her legally recognized surrogate or emergency procedure

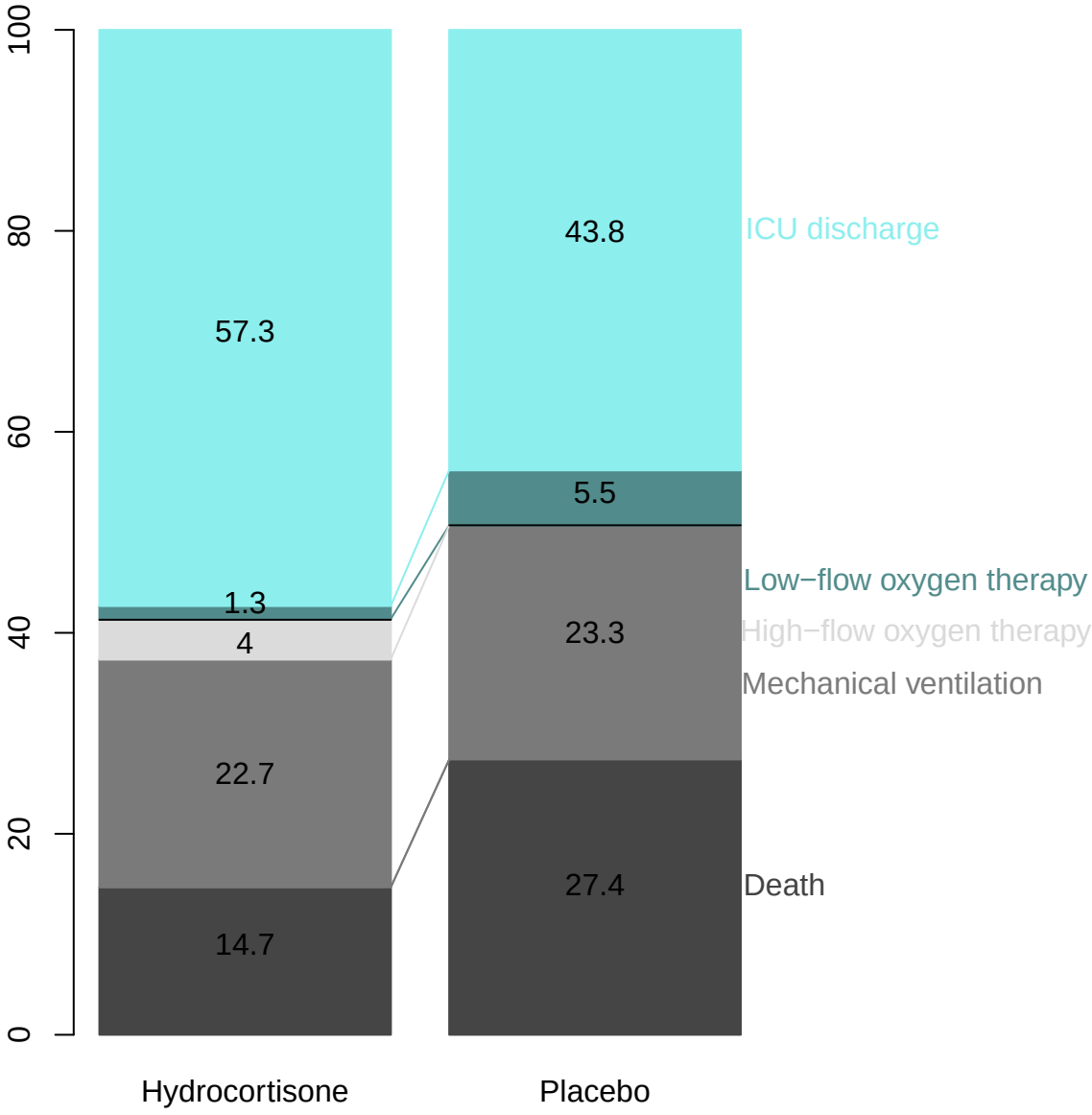
Detailed Noninclusion Criteria

- Patient treated by vasopressors for septic shock at the time of inclusion (vasopressors administered for the correction of a sedation- and high-PEEP-induced hypotension are allowed)
- Clinical history suggesting pneumonia is due to aspiration of gastric content
- History of cystic fibrosis
- Post-obstructive pneumonia
- Patients in which a rapid PCR-test is positive for influenza virus
- Active tuberculosis or fungal infection
- Active viral hepatitis or active infection with herpes viruses
- Myelosuppression
- Decision to withhold mechanical ventilation or endotracheal intubation
- Hypersensitivity to corticosteroids
- Patient needing anti-inflammatory corticosteroids or substitutive hydrocortisone for any reason
- Patients currently treatment by more than 15 mg/d of prednisone (or equivalent) for more than 30 days
- Patient already enrolled in another interventional trial with a similar end-point. If the patient is already participating in another therapeutic trial with a different endpoint, the investigator must verify that inclusion in CAPE COVID will not prejudice it.
- Pregnant or breastfeeding female
- Patient under judicial protection

eTable. Baseline Characteristics of the 149 Patients: Additional Data

	Hydrocortisone group (n_1=76)	**Placebo group** (n_2=73)
Demographics and past medical history		
Chronic Obstructive Pulmonary Disease, No. (%)	4 (5.3)	2 (2.7)
Asthma, No. (%)	3 (3.9)	2 (2.7)
Neoplastic disease, No. (%) (n_1=43, n_2=51)	2 (4.7)	3 (5.9)
Liver disease, No. (%) (n_1=43, n_2=51)	1 (2.3)	1 (2.0)
Congestive heart failure, No. (%) (n_1=43, n_2=51)	3 (7.0)	3 (5.9)
Cerebrovascular disease, No. (%) (n_1=43, n_2=51)	1 (2.3)	1 (2.0)
Renal disease (n_1=43, n_2=51)	2 (4.7)	2 (3.9)
Solid organ graft	1 (1.3)	1 (1.4)
Laboratory values at inclusion		
WBC counts, median (IQR), 10^9/L (n_1=64, n_2=63)	8.3 (6.6; 10.2)	8.2 (6.2; 10.4)
Platelet counts, median (IQR), 10^9/L (n_1=64, n_2=63)	217.0 (170.0; 279.0)	229.0 (167.0; 281.0)
Potassium, median (IQR), mmol/L (n_1=71, n_2=69)	3.9 (3.7; 4.2)	3.8 (3.5; 4.1)
Creatine Phosphokinase, UI/L, median (IQR) (n_1=45, n_2=43)	194.0 (79.0; 421.0)	157.0 (90.6; 416.0)
Cortisol, median (IQR), nmol/L (n_1=26, n_2=23)	526.0 (336.0; 613.0)	493.0 (355.0; 620.0)

WBC: white blood cells.


100
80
60
40
20
0
57.3
1.3
4
22.7
14.7
43.8
5.5
23.3
27.4
ICU discharge
Low−flow oxygen therapy
High−flow oxygen therapy
Mechanical ventilation
Death
Hydrocortisone
Placebo

eAppendix 2. Prone Position Cumulative Incidence and PaO2:FiO2 Ratios Evolution

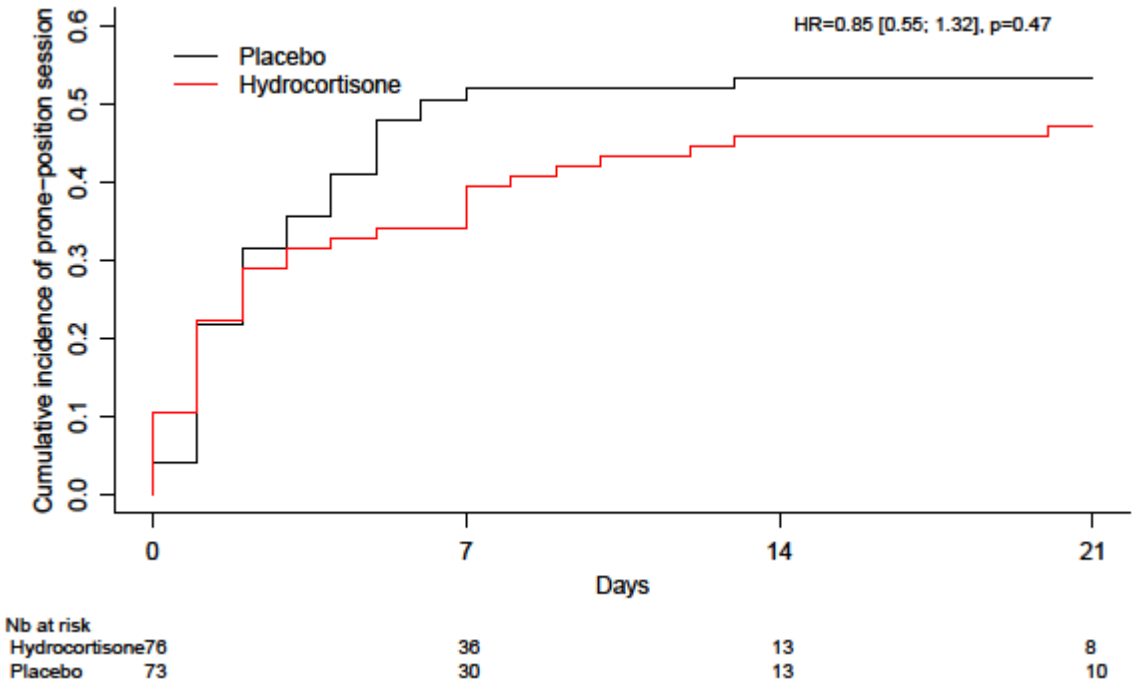
Prone Position Cumulative Incidence

The use of prone position (with the number of sessions), extracorporeal membrane oxygenation or inhaled nitric oxide (with the number of days the treatment was used) was a pre-specified secondary outcome. Cumulative incidence of patient with at least one prone-position session was estimated using a competing risk approach, with death and end of ICU stay as competing events. Given the limited number of events, analyses of extracorporeal membrane oxygenation and inhaled nitric oxide were only descriptive (Table 2 of the article). There was no significant difference in prone-positioning between both groups (p=0.47) (eFigure 2).

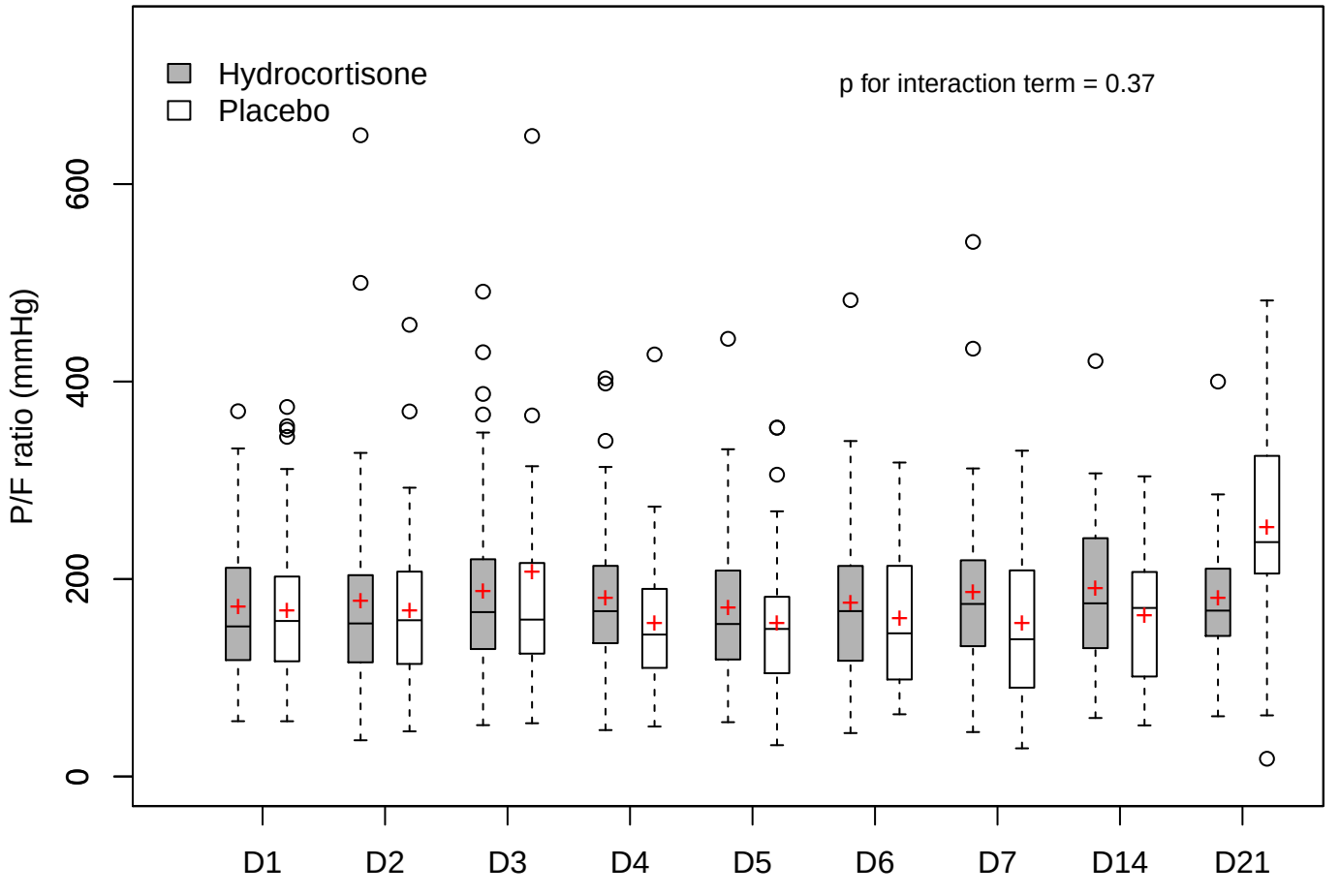
PaO2:FiO2 Ratios Evolution

The evolution of PaO2:FiO2 ratios, which were recorded daily from Day 1 to Day 7 and then on Days 14 and 21, was a pre-specified secondary outcome. PaO2:FiO2 ratios evolution was analysed using mixed linear model. It did not significantly differ between both groups (p=0.37) (eFigure 3).

eFigure 2. Prone Position Cumulative Incidence



The figure represents the cumulative proportion of patients who have had at least one session of prone-position. All patients were observed to death or 21 days (the patient who withdrew consent being censored on the last reported date).



Nb									
Hydrocortisone	71	75	73	70	66	59	62	38	23
Placebo	66	70	70	66	66	66	60	36	26

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