Supplemental Online Content

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

eMethods.

Study dates

Protocol - initial version:	(1) IRB approval: 8-apr-2020; (2) French Health Authority approval: 10-apr-2020
First patient in:	10-apr-2020
DXMSoC-related amendment:	(1) IRB approval: 22-jul-2020 (2) French Health Authority approval: 17-sep-2020
Last patient in:	25-jan-2021
Last Day60 follow-up:	26-mar-2021
Database lock:	26-may-2021

Blinding regarding DXM

The DXM intervention, placebo (normal saline) or dexamethasone phosphate (p-DXM), was administered intravenously. The blinding was maintained throughout the study.

All patients received the standard of care, i.e., placebo of DXM prior to the amendment implementation, then p-DXM 6 mg/d after the amendment implementation.

All patients received an additional infusion, with p-DXM if allocated to the DXM20 arm, or with placebo if allocated to the DXMSoC arm. For this additional infusion, vials of dexamethasone or placebo were prepared and masked by the central pharmacy of University Paris Hospitals (*Assistance Publique – Hôpitaux de Paris*), then the investigating sites were provided with boxes including all necessary masked vials of p-DXM or placebo, i.e., ten vials for reach day from D1 to D10. The nurses in charge squeezed the exact same amount out of the vial: 3.5 mL for the first 5 days and 1mL for the last 5 days, and signed a form for each infusion that was recorded and checked by CRO monitors.

Change in the DXM standard of care (based on the CONVERSE checklist[1])

The study protocol was finalized and approved early April 2020 (see above), i.e., at the very beginning of the COVID-19 first wave in France. At that time, the standard-of-care for ICU COVID-19 patients with severe AHRF was to not administer corticosteroids, therefore the control group received infusions of placebo of dexamethasone phosphate (p-DXM) (masked vials) from D1 to D10.

Inclusions started immediately after IRB's and French Health Authorities' approvals, on April 10, 2020.

The results of the RECOVERY trial were published on July 17, 2020 (e-publication), although they were known for a few weeks before that. On July 3, 2020, the COVIDICUS Scientific Committee prompted the study group to amend the study protocol for allowing investigators to administer p-DXM up to 6 mg/d to DXMSoC patients. In order to ensure a more robust methodology, the dose was eventually defined as a fixed dose of p-DXM 6mg/d from D1 to D10 for all DXMSoC patients. The amended study protocol was approved by the IRB on July 22, 2020, and by the French Health Authorities on Sept. 17, 2020. At that time, 73 patients were already included in the study, including 37 patients in the DXMSoC arm and 36 in the DXM20 arm. After the amendment was approved, 473 patients were included, including 239 in DXMSoC and 234 in DXM20.

Of note, no interim analysis was conducted at that time.

NIRS strategies

In all NIRS groups, oxygen support was pursued up to meeting the following predefined cessation criteria:

- SpO2 >92% and respiratory rate <25 breaths/min with minimal support, as defined by FiO2 ≤30%, for HFNO groups,
- a CPAP level ≤5 cmH2O for CPAP groups,
- no need for oxygen support for standard oxygen (02SoC) groups.

CPAP procedure

A Boussignac device (Vygon™, Ecouen, France) with a heat and moisture exchanger and connected to an oronasal mask was used. CPAP was started at 15-30 L/min oxygen (corresponding to an average pressure of 4-10 cmH_2O) [1]. CPAP was used continuously for at least the first 6 to 12 hours, then discontinuously for ≥6 hours/d, with a level modulated as needed based on clinical response and tolerance.

HFNO procedure

In the HFNO arm, oxygen was delivered through a heated humidifier (Airvo-2, Fisher and Paykel Healthcare) that was continuously applied through large-bore binasal prongs.

Prespecified criteria for intubation

Criteria for intubation might be any of the three pre-specified criteria previously described[2]:

(1) signs of persisting or worsening respiratory failure, defined by at least two of the following criteria: a respiratory rate above 35 cycles/min, lack of improvement of signs of respiratory-muscle fatigue, development of copious tracheal secretions, acidosis with a pH below 7.35, SpO_2 below 90% despite FiO_2 ≥80% for more than five min without technical dysfunction, or intolerance to NIV;

(2) hemodynamic instability defined by systolic blood pressure below 90 mmHg, mean blood pressure below 65 mmHg or vasopressor requirement;

or (3) deterioration of neurologic status with a Glasgow coma scale below 12.

Authorized and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

Open label steroids (hydrocortisone as a 50-mg intravenous bolus every 6 hours, and fludrocortisone given as a 50-µg tablet through a nasogastric tube once daily, for 7 days, without tapering) will be authorized in case of septic shock defined as follows:

- The presence of a clinically or microbiologically documented infection,

- A Sequential Organ Failure Assessment (SOFA) score of 3 or 4 for at least two organs for at least 6 hours,

- And receipt of vasopressor therapy (norepinephrine, epinephrine, or any other vasopressor at a dose of ≥0.25 µg per kilogram of body weight per minute or ≥1 mg per hour), increasing for at least 6 hours to maintain a systolic blood pressure of at least 90 mm Hg or a mean blood pressure of at least 65 mm Hg.[2]

Virological methods

All samples were collected with a virological transport media and transferred to the local laboratory.

For the measure of the viral load, the real time semi-quantitative reverse transcriptase polymerase chain reaction (RT-PCR) performed used the Charité WHO protocol (testing E gene and RdRp), or the Pasteur institute assay (testing E gene and two other RdRp targets: IP2 and IP4) or a commercial assay allowing the detection of two different SARS-CoV-2 genes, as recommended.[3] Results were provided in cycle threshold (Ct) and considered as positive if any of the tested genes was detected with a Ct value <40 or according to the manufacturer recommendations for commercial assays.

Randomization

Computer-generated randomization lists were used, with permutation blocks of varying sizes elaborated by an independent statistician. The randomization lists were implemented in the electronic case report form to ensure appropriate allocation concealment.

eAppendix. Adherence to Trial Interventions

Regarding the DXM20 intervention, 541/546 (99.1%) patients were administered at least one day of the drug or placebo, 273 (98.9%) in the DXMSoC group and 268 (99.3%) in the DXM20 group (p=1.00 by the exact Fisher test).

Regarding the oxygenation supply, there were an imbalance in adherence of the allocated group, with only 77 (70.6%) compliers in the standard oxygen group, 89 (81.7%) in the CPAP group, and 110 (95.7%) in the HFNO group (p<0.001, by the exact Fisher test). Most of these deviations concerned the administration of HFNO, either in the allocated standard oxygen group (n=29, 90.6% of the 32 non-compliers) and in the allocated CPAP group (n=12, 60% of the 20 non-compliers). Otherwise,12 patients received standard oxygen either in the CPAP group (n=7) or the HFNO group (n=5). The proportion of non-compliance in oxygenation supply ranged from 0.3% up to 27% across centers.

References

1. Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for Reporting Trial Protocols and Completed Trials Modified Due to the COVID-19 Pandemic and Other Extenuating Circumstances: The CONSERVE 2021 Statement. *JAMA.* 2021;326(3):257-265.
2. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med.* 2018;378(9):809-818.
3. Carteaux G, Pons M, Morin F, et al. Continuous positive airway pressure for respiratory support during COVID-19 pandemic: a frugal approach from bench to bedside. *Ann Intensive Care.* 2021;11(1):38.
4. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med.* 2015;372(23):2185-2196.

eTable 1. Dexamethasone Treatment and Oxygen Support Strategies in the COVIDICUS Trial

Standard of care dexamethasone	The standard of care for dexamethasone was initially placebo of dexamethasone; after 17-sep-2020, the standard of care was dexamethasone 6 mg/d from Day 1 to Day 10, administered to all included patients (DXMSoC and DXM20).
High-dose dexamethasone	An additional dose of dexamethasone 14 mg/d was administered to patients of the DXM20 arm from Day 1 to Day 5, then 4 mg/day from Day 6 to Day 10. DXMSoC patients received placebo instead.
Standard oxygen treatment	Patients assigned to the standard treatment group received oxygen delivered through a non-rebreather face mask until endotracheal intubation, death, or fulfillment of oxygen delivery cessation criteria (SpO_2 > 92% without oxygen and respiratory rate < 25 cycles/min).
CPAP treatment	Patients assigned to the CPAP plus oxygen group received periods of CPAP in addition to the standard treatment. All study centers used a Boussignac device (Vygon™) connected to an oro-nasal mask composed of a transparent mask and a soft inflatable cushion, with a heat and moisture exchanger ("Filter Boussignac CPAP"). The detailed procedure for the use of the Filter Boussignac CPAP (in French) is available at: http://www.reamondor.aphp.fr/covid19 CPAP was started at 15-30 L/min oxygen (which corresponds to an average pressure of 4-10 cm H_2O).[3] The level was decreased or increased as needed based on the clinical response and tolerance. For at least the first 6 to 12 hours, CPAP will be given continuously and then discontinuously (for at least 6 hours/day) based on patient tolerance.
HFNO treatment	In the high-flow–nasal cannula group, oxygen was delivered through a heated humidifier (Airvo-2, Fisher and Paykel Healthcare) and applied continuously through large-bore binasal prongs, starting with a gas flow rate of 30 liters per minute and adjusted based on the clinical response. FiO_2 was adjusted for the target SpO_2.
In all groups, the oxygen flow was adjusted to maintain an oxygen saturation level of 92% or more, as measured by means of pulse oximetry (SpO_2). Standard oxygen treatment, CPAP, or HFNO were continued until endotracheal intubation, death, or fulfillment of the following cessation criteria: SpO_2 above 92% and respiratory rate below 25 cycles/min with FiO_2 of 30% or less and a CPAP level ≤ 5 cmH_2O. The criteria for oxygen delivery cessation were the same as in the standard therapy group.	
Pre-specified criteria for intubation: as previously used.[4]	
Abbreviations: CPAP = Continuous Positive Airway Pressure; DXMSoC: dexamethasone standard of care; DXM20: dexamethasone at high dose; HFNO = High-Flow Nasal Oxygen	

eTable 2. Report of the Blinded Bayesian Interim Analyses

Three interim analyses (IA) were performed, on Nov. 21, 2020 (based on 384 observations), Feb. 5, 2021 (based on 436 observations enrolled before the cutoff date of Dec. 14, 2020), and Apr. 11, 2021.

NB: DSMB received information with a blinding of the randomization groups.

After blinding withdrawal, "IMV": A= DXMSoC, B= DXM20;

"Non-IMV": A=O2SoC, B= CPAP, C= HFNO

Interim Analysis (data cutoff)	Non informative prior	Skeptical prior	Enthusiastic prior
First IA (Nov., 21, 2020) (n=384)			
Analysis of DXM effect in "IMV" patients			
Pr (HR<1|data)	0.67	0.64	0.73
Pr (HR<0.75\data)	0.40	0.32	0.41
Pr (HR>1.05)	0.29	0.31	0.23
Analysis of Oxygen Supply method effect in "Non-IMV"	**B vs A**	**C vs A**	
Pr (HR<1|data)	0.62	0.92	
Pr (HR<0.75\data)	0.05	0.32	
Pr (HR>1.05)	0.30	0.06	
Second IA (Feb. 5, 2021) (n=436)			
Analysis of DXM effect in "IMV" patients			
Pr (HR<1|data)	0.52	0.52	0.60
Pr (HR<0.75\data)	0.20	0.17	0.23
Pr (HR>1.05)	0.42	0.41	0.33
Analysis of Oxygen Supply method effect in "Non-IMV" patients	**B vs A**	**C vs A**	
Pr (HR<1|data)	0.32	0.79	
Pr (HR<0.75\data)	0.005	0.12	
Pr (HR>1.05)	0.59	0.54	
Third IA (Apr., 11, 2021) (n=550)			
Analysis of DXM effect in "IMV" patients			
Pr (HR<1|data)	0.48	0.48	0.55
Pr (HR<0.75|data)	0.13	0.11	0.15
Pr (HR>1.05|data)	0.45	0.44	0.37
Analysis of Oxygen Supply method effect in "Non-IMV" patients	**B vs A**	**C vs A**	
Pr (HR<1|data)	0.28	0.51	
Pr (HR<0.75|data)	0.003	0.017	
Pr (HR>1.05|data)	0.63	0.39	

DXM: dexamethasone; HR: hazard ratio; IA: interim analysis; IMV: invasive mechanical ventilation.

eTable 3. Outcomes of Patients According to Oxygenation Strategy in the Non-IMV Group

Variable	Standard oxygen (n = 109)	CPAP (n = 109)	HFNO (n = 115)	Mean Difference (95% CI)		Hazard ratio (95% CI)[a]	
				CPAP vs o_2	HFNO vs o_2	CPAP vs o_2	HFNO vs o_2
Primary end point							
Cumulative incidence of IMV criteria at 28 d	41.4 (32.0 to 50.4)	43.0 (33.3 to 52.2)	43.8 (34.5 to 52.6)	1.6 (–11.6 to 15.0)	2.5 (1.1 to 3.7)	1.08 (0.71 to 1.63)	1.04 (0.69 to 1.55)
Secondary end points							
Cumulative incidence of actual IMV at 28 d	28.6 (20.4 to 37.3)	31.4 (22.7 to 40.4)	32.6 (24.1 to 41.3)	2.8 (1.6 to 4.0)	4.0 (3.1 to 4.9)	1.13 (0.69 to 1.85)	1.16 (0.72 to 1.87)
Overall Survival at 60 d, Kaplan-Meier estimate	71.0 (62.8 to 80.1)	71.7 (63.3 to 81.3)	73.9 (66.2 to 82.6)	0.8 (–0.0 to 1.6)	3.0 (2.2 to 3.7)	0.06 (0.58 to 1.61)	0.89 (0.54 to 1.48)
Alive free of IMV at day 28, median (IQR), d	28 (9 to 28)	28 (7 to 28)	28 (20 to 28)	–0.7 (–2.2 to 3.6)	0.0 (–2.9 to 2.9)		
Severe hypoxemia within 2 min after intubation, No. (%)	1 (0.9)	3 (2.8)	3 (2.6)	1.9 (–2.5 to 7.0)	1.7 (–2.7 to 6.6)	3.0 (0.3 to 28.4)	2.8 (0.3 to 26.9)
Cardiac arrest within 1 h after intubation, No. (%)	1 (0.9)	1 (0.9)	0	0.0 (–4.2 to 4.2)	–0.9 (–5.0 to 2.3)	1.0 (0.06 to 15.8)	0
HAI at 28 d, No. (%)	19 (17.4)	22 (20.2)	21 (18.3)	2.8 (–7.8 to 13.3)	0.9 (–9.4 to 11.0)	1.1 (0.7 to 2.0)	1.0 (0.6 to 1.8)
LOS, median (IQR), d							

ICU stay	7 (4 to 13)	8 (4 to 15)	7 (5 to 12)	2.3 (–6.1 to 1.5)	1.4 (–5.1 to 2.3)		
Hospital	15 (10 to 22)	15 (9 to 22)	14 (9 to 21)	0.4 (–4.7 to 3.8)	–0.7 (–3.4 to 4.8)		
≥1 adverse event, No. (%)	76 (69.7)	78 (71.6)	82 (71.3)	1.9 (–13.9 to 10.2)	1.6 (–12.1 to 11.6)	1.0 (0.86 to 1.22)	1.0 (0.86 to 1.21)

Abbreviations: CMV, cytomegalovirus; HAI, health care-associated infection; HSV, Herpes virus; ICU, intensive care unit; IMV, invasive mechanical ventilation; PCR, polymerase chain reaction; VAP, ventilator-associated pneumonia.

[a]Hazard ratios were stratified on the 'IMV' strata.

Standard-of-Care DXM = DXMSoC: placebo of DXM (n = 37) then dexamethasone-phosphate 6 mg/d x D1-D10. High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

eTable 4. Effects of Dexamethasone Treatment and Oxygen Support Strategies on the Main End Points Based on the As-Treated Population of the COVIDICUS Trial

Variable	Standard of care DXM (DXMSoC) N=273	High-dose DXM (DXM20) N=268		Difference (95%CI)	Hazard Ratio* (95%CI)
Whole sample					
Primary endpoint Survival at Day-60 (%)	71.8 (66.6-77.5)	72.8 (67.6-78.5)		1.0 (-2.9 to 4.9)	0.95 (0.69 to 1.32)
"Non-IMV" subset					
Variable	**Standard oxygen N=86**	**CPAP N=88**	**HFNO N=153**	**Mean Difference (95%CI)**	**Hazard Ratio* (95%CI)**
Primary endpoint Cumulative incidence of need-for-IMV criteria at D28 (%)	38.4 (28.1-48.6)	49.7 (38.7-59.8)	40.2 (32.4-48.0)	CPAP vs O2: 11.3 (-9.8 to 12.8) HFNO vs O2: 1.8 (-0.3 to 3.3)	CPAP vs O2: 1.39 (0.88-2.19) HFNO vs O2: 0.98 (0.64-1.50)

CPAP: continuous positive airway pressure; HFNO: high-flow nasal oxygen; 02: oxygen; IMV: invasive mechanical ventilation

Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

eTable 5. Effect of the Oxygen Support Strategies on the Main End Point Based on the Intent-to-Treat Population of the COVIDICUS Trial, Handling the Potential Center Effect Using a Frailty Model

	Cause-specific HR (95%CI)	
Variable	**CPAP vs O2**	**HFNO vs O2**
Primary endpoint Cumulative incidence of need-for-IMV criteria at Day28	1.04 (0.69-1.57)	1.00 (0.67-1.50)
Frailty center effect	p= 0.055	

HR: hazard ratio; CPAP: continuous positive airway pressure; HFNO: high-flow nasal oxygen; 02: oxygen; IMV: invasive mechanical ventilation
Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

eTable 6. Serious Adverse Events and Other Adverse Events at Day 28 in the Overall Study Sample, According to Dexamethasone Group

Variable	Standard of care DXM (DXMSoC) N=276	High-dose DXM (DXM20) N=270	Mean Difference (95%CI)	Risk Ratio (95%CI)
VAP	66 (23.9)	68 (24.6)	+1.6 (-5.9 to 8.5)	1.01 (0.76 to 1.35)
Bacteremia	26 (9.4)	30 (11.1)	+1.7 (-3.5 to 6.9)	1.14 (0.70 to 1.86)
Neuropathy*	8 (2.9)	10 (3.7)	+0.8 (-2.4 to 4.1)	1.28 (0.51 to 3.19)
Fungal infection	17 (6.1)	20 (7.4)	+1.3 (-3.0 to 5.5)	1.20 (0.64 to 2.24)
PCR for HSV / CMV positive	17 (6.1)	22 (8.1)	+2.0 (-2.3 to 6.3)	1.32 (0.72 to 2.43)
Digestive hemorrhage	5 (1.8)	7 (2.6)	+0.8 (-1.7 to 3.2)	1.43 (0.46 to 4.45)
Hyperglycemia (>13 mMol/mL)	66 (23.9)	69 (25.5)	+1.6 (-5.6 to 8.9)	1.07 (0.80 to 1.43)
Hyponatremia (< 130 mMol/L)	11 (4.0)	13 (4.8)	+0.8 (-2.6 to 4.3)	1.21 (0.55 to 2.65)
Hypocalcemia (< 1.5 mMol/L)	1 (0.4)	2 (0.7)	+0.4 (-0.9 to 1.6)	2.04 (0.19 to 22.4)
Septic shock**	40 (14.5)	46 (17.0)	+2.5 (-3.6 to 8.7)	1.17 (0.80 to 1.73)
Deep vein thrombosis	4 (1.4)	8 (3.0)	+1.5 (-1.0 to 4.0)	2.04 (0.62 to 6.71)
Pulmonary embolism	12 (4.3)	10 (3.7)	-0.6 (-3.9 to 2.7)	0.85 (0.37 to 1.94)
Pneumothorax, pneumomediastinum	11 (4)	16 (5.9)	+1.9 (-3.2 to 6.7)	1.49(0.70 to 3.13)
Renal failure	75 (27.2)	68 (25.2)	-2.0 (-9.4 to 5.4)	0.93 (0.70 to 1.23)
Cardiac arrest within 1 hour after intubation	3 (1.1)	2 (0.7)	-0.3 (-1.9 to 1.2)	0.68 (0.11 to 4.05)
Desaturation (SpO_2) < 80%	4 (1.4)	8 (3.0)	+1.5 (-1.0 to 4.0)	2.04 (0.62 to 6.71)

CMV: cytomegalovirus; HSV: Herpes virus; ICU: intensive care unit; PCR: polymerase chain reaction; VAP: ventilator-associated pneumonia.
* ICU-acquired neuropathy, based on investigator's reporting. **: 7 patients ((DXMSoC group, n=3; DXM20 group, n=4) received hemisuccinate of hydrocortisone within the first 10 days of the trial
Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

eTable 7. Serious Adverse Events and Other Adverse Events at Day 28 Among Non-IMV Population, According to the Oxygenation Strategy Group

Variable	Standard oxygen N=109	CPAP N=109	HFNO N=115	Mean difference, CPAP vs standard oxygen	Mean difference, HFNO vs standard oxygen
VAP	18 (16.5)	16 (14.7)	19 (16.5)	-1.8 (-11.7 to 8.0)	0.0 (-10.0 to 9.9)
Bacteremia	6 (5.5)	13 (11.9)	8 (7.0)	6.4 (-1.2 to 14.6)	1.4 (-5.4 to 8.4)
Neuropathy*	2 (1.8)	6 (5.5)	6 (5.2)	3.7 (-1.6 to 9.9)	3.4 (-1.9 to 9.3)
Fungal infection	4 (3.7)	7 (6.4)	5 (4.3)	2.7 (-3.5 to 9.5)	0.6 (-5.3 to 6.6)
PCR HSV / CMV Positive	6 (5.5)	9 (8.2)	14 (12.2)	2.7 (-4.5 to 10.2)	6.7 (-0.9 to 14.6)
Digestive hemorrhage	3 (2.8)	0	0	-2.8 (-7.8 to 0.7)	-2.8 (-7.8 to 0.5)
Hyperglycemia (>13 mMol/mL)	28 (25.7)	36 (33.0)	38 (33.0)	7.3 (-4.8 to 19.3)	7.3 (-4.6 to 19.1)
Hyponatremia (< 130 mMol/L)	2 (1.8)	8 (7.3)	4 (3.5)	5.5 (-0.7 to 12.2)	1.7 (-3.4 to 7.0)
Hypocalcemia (< 1.5 mMol/L)	0	1 (0.9)	0	0.9 (-2.5 to 5.0)	0.0 (-3.4 to 3.2)
Septic shock	12 (11.0)	17 (15.6)	15 (13.0)	4.6 (-4.6 to 13.9)	2.0 (-6.8 to 10.8)
Deep vein thrombosis	0	3 (2.8)	0	2.8 (-0.7 to 7.8)	0.0 (-3.4 to 3.2)
Pulmonary embolism	5 (4.6)	2 (1.8)	6 (5.2)	-2.8 (-8.7 to 2.4)	0.6 (-5.8 to 7.0)
Pneumothorax/pneumomediastinum	5 (4.6)	3 (2.8)	7 (6.1)	-1.8 (-6.4 to 3.2)	+1.5 (-3.1 to 7.5)
Renal failure	25 (22.9)	25 (22.9)	25 (21.7)	0.0(-11.2 to 11.2)	-1.2 (-12.2 to 9.8)

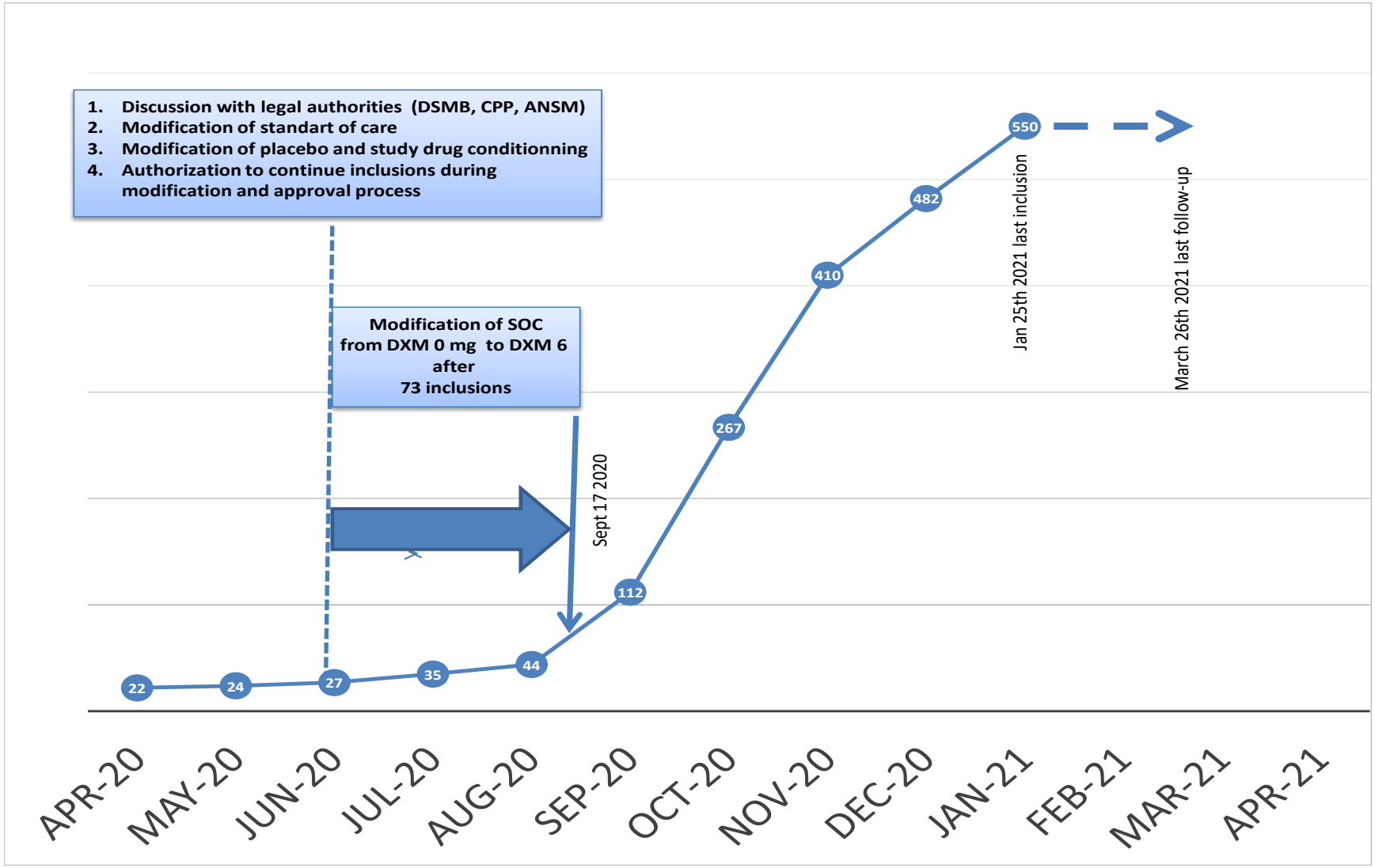
IMV: invasive mechanical ventilation; CPAP: continuous positive airway pressure; HFNO: high-flow nasal oxygen; CMV: cytomegalovirus; HAI: healthcare-associated infection; HSV: Herpes virus; PCR: polymerase chain reaction; RRT: renal replacement therapy; VAP: ventilator-associated pneumonia.

* ICU-acquired neuropathy, based on investigator's reporting.

Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.

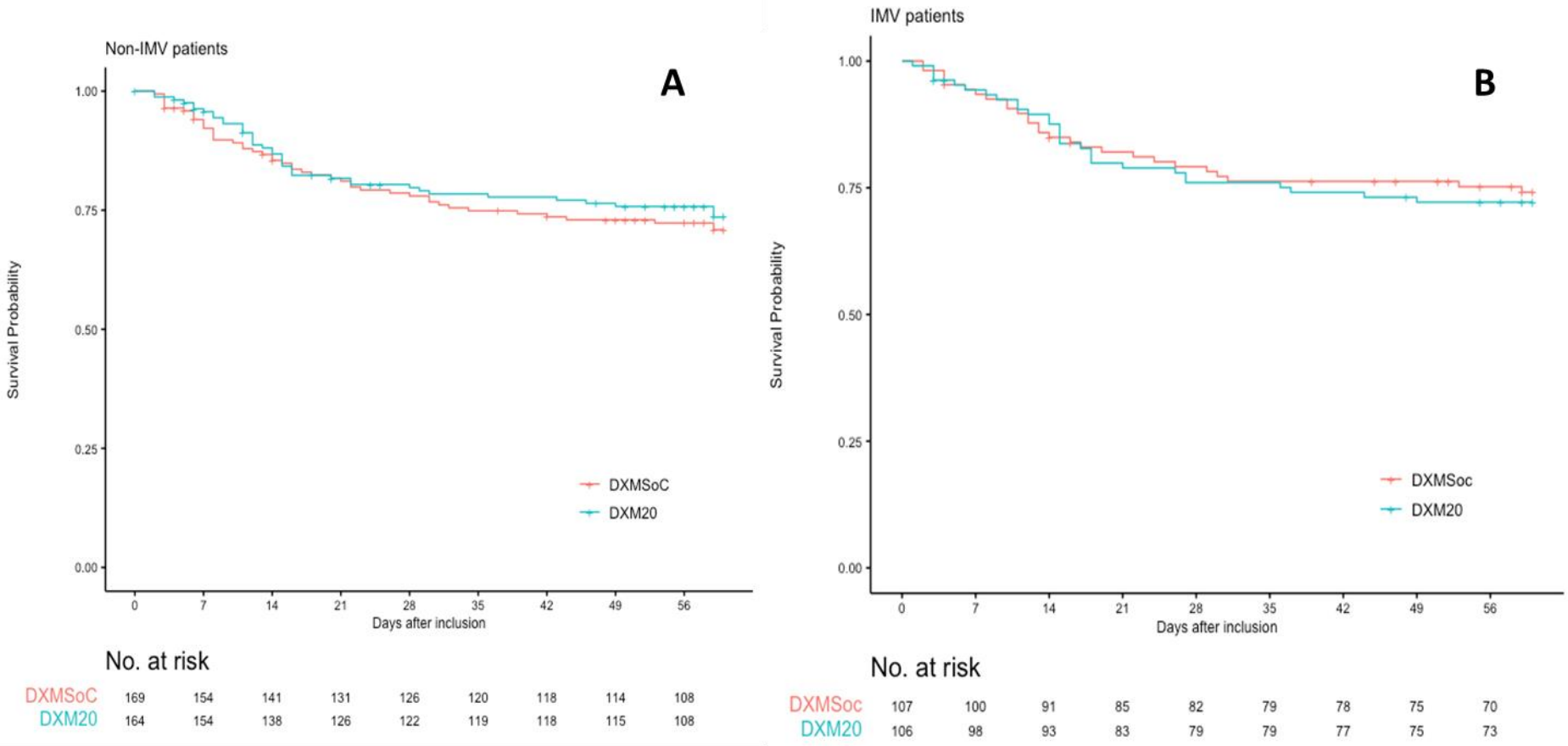
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

eFigure 1. Cumulative Inclusions in the COVIDICUS Study



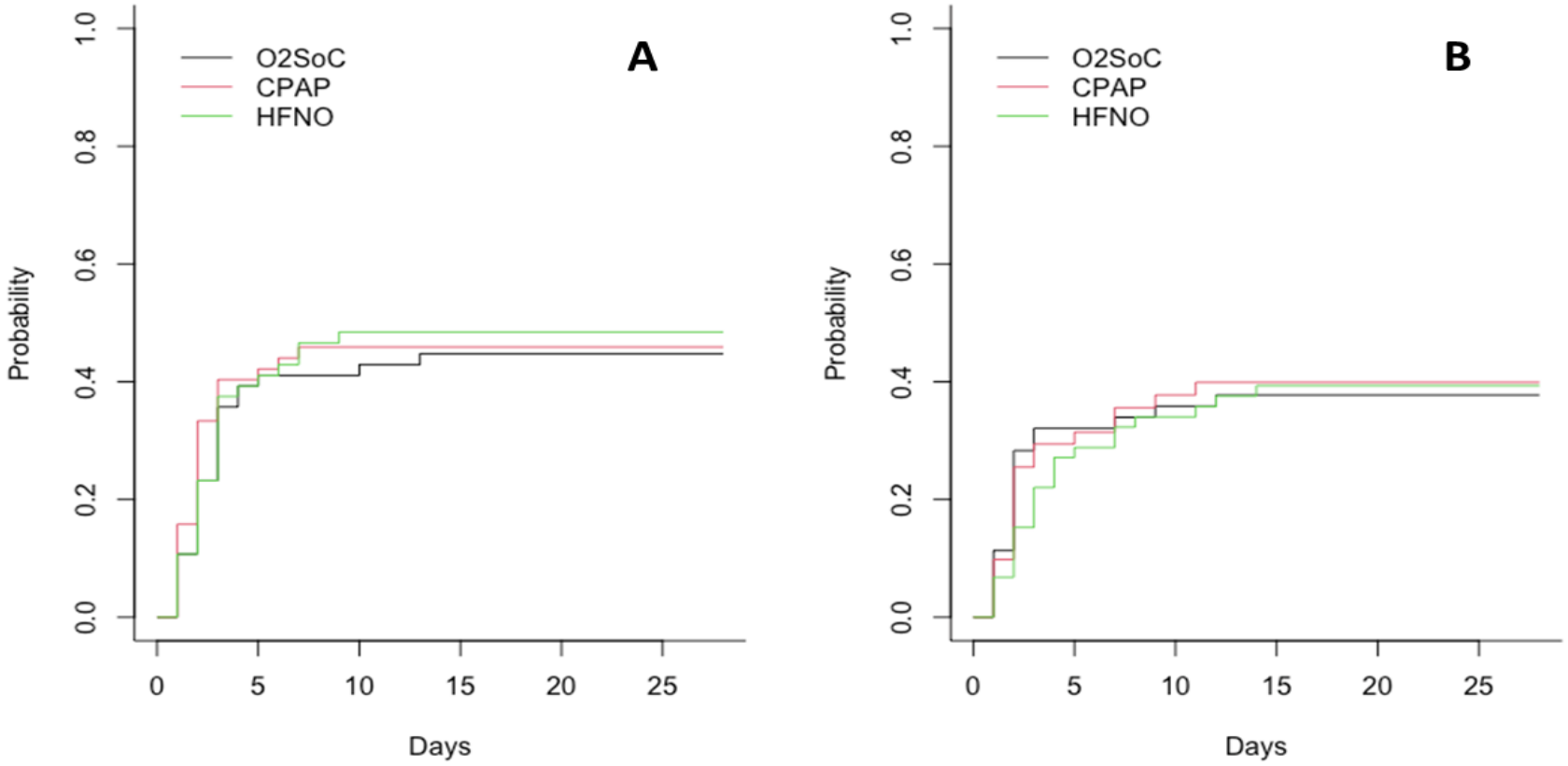
eFigure 2. Overall Survival of Patients According to Dexamethasone Group

(A) patients without IMV and eligible for oxygen support strategies at randomization (“Non-IMV” patients, DXMSoC, n= 169 vs DXM20, n=164), and (B) patients with IMV or not eligible to oxygen support strategies (“IMV” patients, DXMSoC, n=107 vs DXM20, n=106). DXMSoC: standard of care dexamethasone; DXM20: high-dose dexamethasone.
Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.



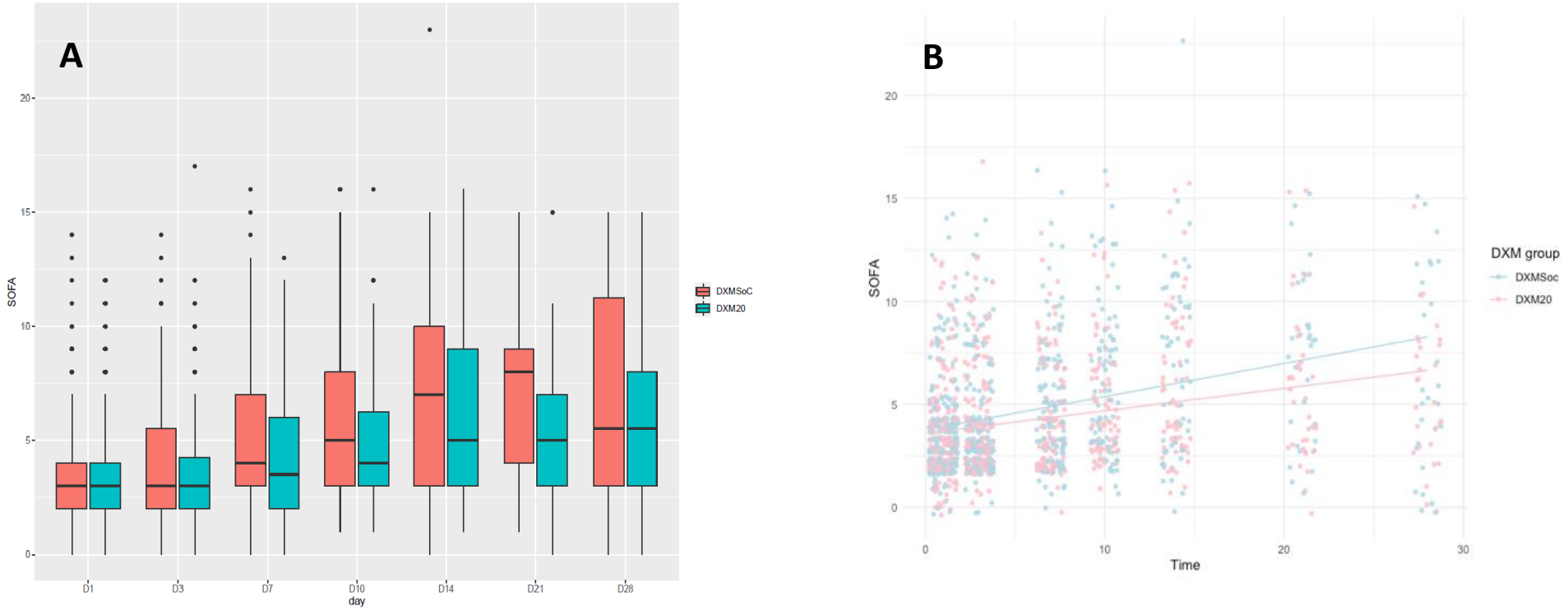
eFigure 3. Cumulative Incidence of IMV Criterion Fulfillment in Patients Without IMV and Eligible for Oxygen Support Strategies at Randomization (Non-IMV Population) According to the Oxygen Supplementation Strategy

(A) in the standard of care dexamethasone arm (DXMSoC, n=169), and (B) in the high-dose dexamethasone arm (DXM20, n=164)
Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10



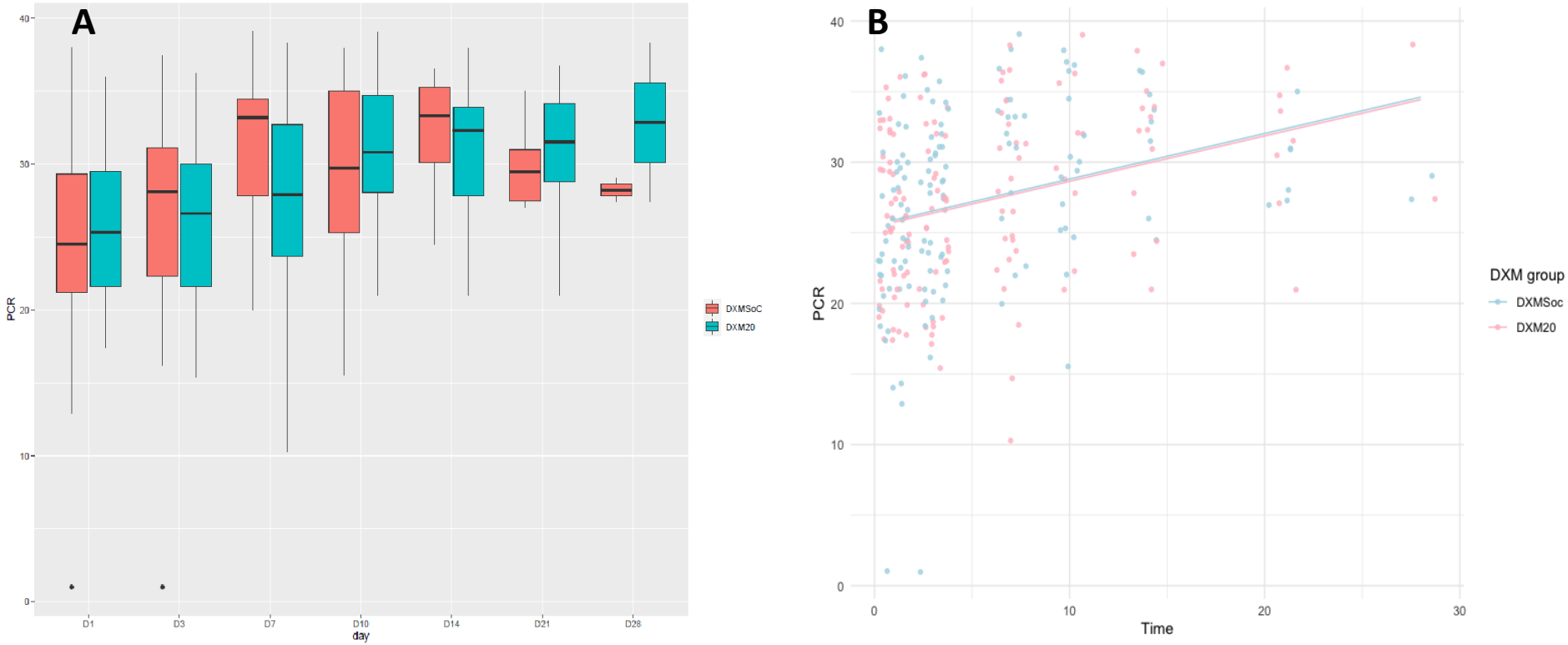
eFigure 4. Sequential Organ Failure Assessment (SOFA) Score Course Over Time According to the Dexamethasone Randomization

Standard of care dexamethasone (DXMSoC) or high-dose dexamethasone (DXM20). (A) boxplot of summary measures; (B) individual patient data with linear slopes. Difference between slopes: -0.01, 95% confidence interval (-0.05 to +0.03)
Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.



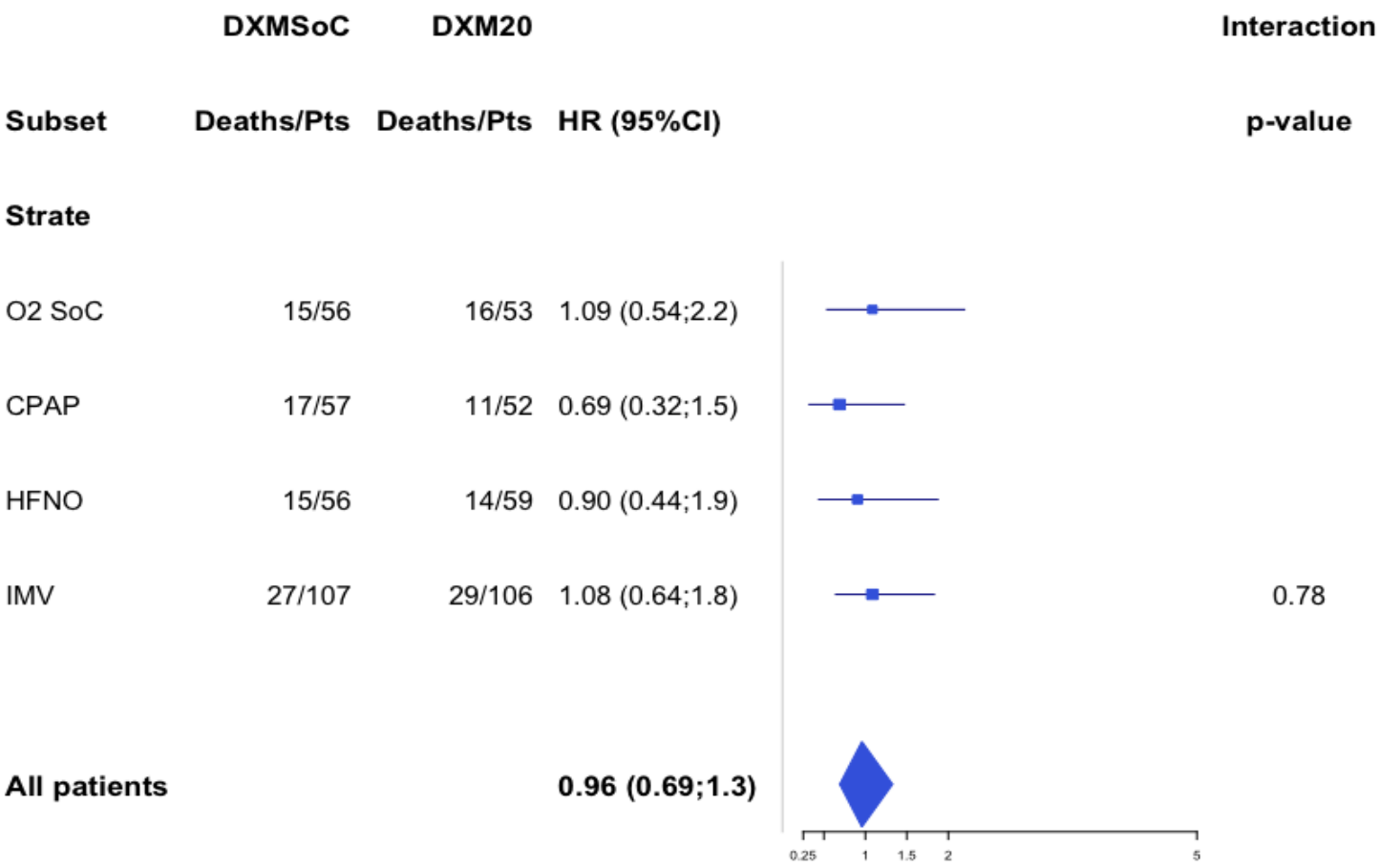
eFigure 5. Number of Cycles of the Polymerase Chain Reaction Over Time According to the Dexamethasone Group

Standard of care dexamethasone (DXMSoC) or high-dose dexamethasone (DXM20). (A) boxplot of summary measures; (B) individual patient data with linear slopes. Difference between slopes between DXM groups: 0.15, 95% confidence interval (-0.05 to + 0.35)
Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.



eFigure 6. Search for Dexamethasone Effect According to Oxygenation Group Interaction in the Effect of Dexamethasone on 60-Day Survival

Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

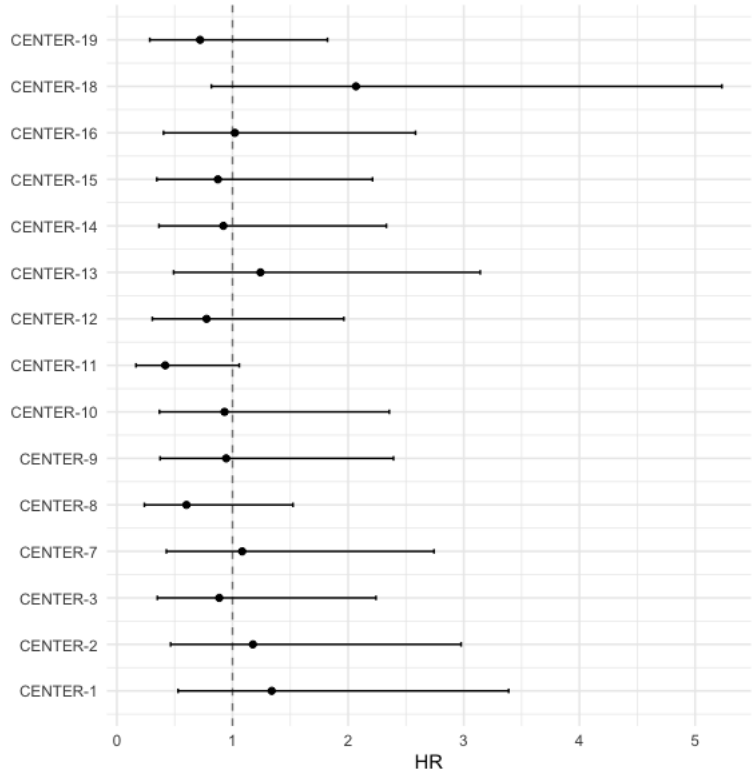


eFigure 7. Search for Center Effect on Mortality at Day 60 in the Effect of Dexamethasone on 60-Day Survival

Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

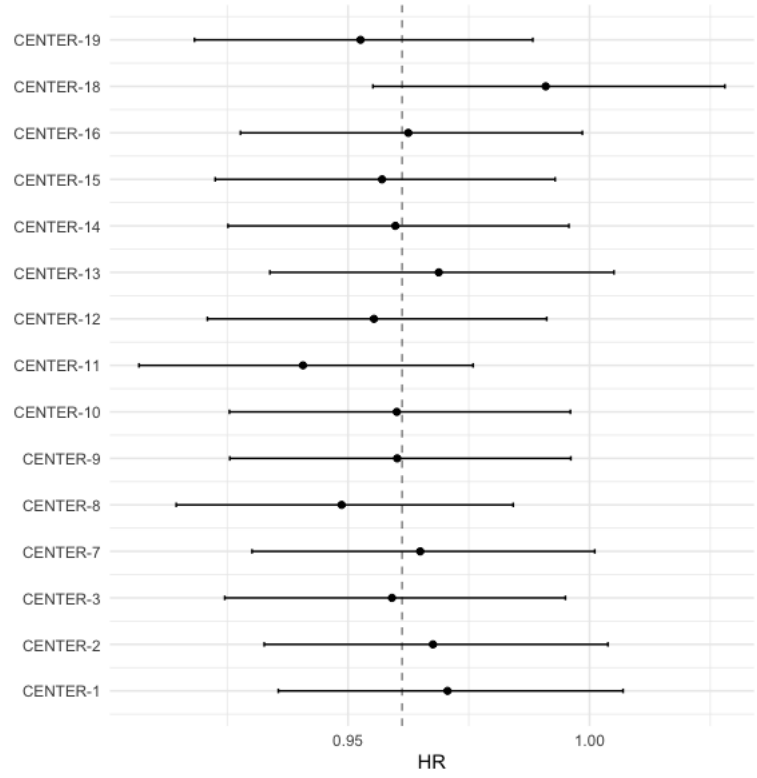
Center effect on 60-day survival

Dashed vertical line refers to the absence of effect on mortality.



DXM effect on 60-day survival according to the center

Dashed vertical line refers to the average DXM effect



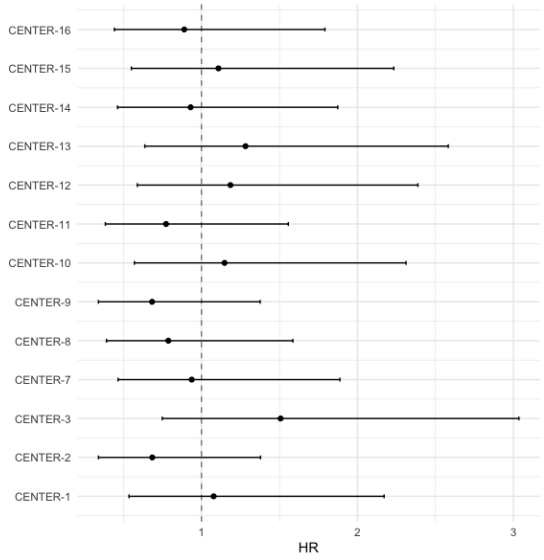
eFigure 8. Search for Center Effect on Time to Need for IMV and in the Effect of CPAP and HFNO on Time to Need for IMV

Standard-of-Care DXM=DXMSoC: placebo of DXM (n=37) then dexamethasone-phosphate 6 mg/d x D1-D10.
High-dose DXM = DXM20 dexamethasone-phosphate 20 mg/d D1-D5, 10 mg/d D6-D10.

Center effect on time-to-need for IMV

Dashed vertical line refers to the absence of

effect on need for IMV



CPAP effect on time-to-need for IMV according to the center

Dashed vertical line refers to the average CPAP or the HFNO effect

Left plot refers to the effect of CPAP, right plot to the effect of HFNO