Supplementary Online Content

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

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eMethods

Additional information on COVID-19 diagnosis

We enrolled patients with confirmed or suspected COVID-19 infection. Due to the possibility of false negative tests, especially on the first days of symptoms,[1] associated with different sensitivities depending of the site of collection (nasopharyngeal swab or tracheal aspirate), patients with negative laboratory tests included in the study were evaluated by a committee, blinded to treatment allocation, formed by three critical care physicians of the research group skilled in treating COVID-19 patients. This committee took into account the epidemiology (travel or residence in a city where community transmission is reported or contact with a confirmed case in the last 14 days prior to symptoms onset),[2] timing of testing from symptoms' onset, clinical symptoms and analysis of chest image (computed tomography scan of the lungs, or chest X-ray) to define if the patient had COVID-19 infection with negative laboratory tests (probable COVID-19 infection) or if the patient possibly had not COVID-19 infection. Patients with positive polymerase chain reaction (PCR) tests for SARS-CoV-2 or positive serology, given the clinical symptoms, were deemed to have confirmed COVID-19 infection.

Additional information on inclusion and exclusion criteria

We enrolled critically ill patients with acute respiratory distress syndrome (ARDS) due to confirmed or probable COVID-19 admitted to the ICU. After 182 patients have been enrolled, the steering committee suggested specific changes on both inclusion and exclusion criteria. The timing of ARDS diagnosis for inclusion changed from 24h to 48h. We based this decision on a pragmatic approach as ICU admission is usually delayed in Brazil as a consequence of shortage of ICU beds, thus many COVID-19 patients already have ARDS diagnosis and more than 24 hours of mechanical ventilation at ICU admission. Additionally, given the widespread use of corticosteroids in COVID-19 hospitalized patients in Brazil, we modified the previous criteria and allowed inclusion of patients who have received corticosteroids for one day during hospital stay. If the treating physician believed the patient had no indication for corticosteroids use the drug was discontinued and the patient was eligible for randomization. The exclusion criteria were refined by adding other three criteria: use of immunosuppressive drugs, cytotoxic chemotherapy in the past 21 days, and neutropenia due to hematological or solid malignancies with bone marrow invasion.

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- Each patient had to fulfill all the following inclusion criteria to be eligible for enrolment:
    - Age ≥18 years old
    - Probable or confirmed infection by SARS-CoV2
    - Intubated and mechanically ventilated
    - Moderate or severe ARDS according to Berlin criteria[3] (Partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) ratio of 200 or less, with positive end expiratory pressure (PEEP) of at least 5 cm of water, bilateral opacities and respiratory failure not fully explained by heart failure or fluid overload)
    - Within 48 hours of meeting criteria for moderate or severe ARDS

- Exclusion criteria:
    - Pregnancy or active lactation
    - Known history of dexamethasone allergy
    - Corticosteroids use in non hospitalized patients in the past 15 days
    - Indication for corticosteroids use for other clinical conditions (e.g refractory septic shock)
    - Patients who used corticosteroids during hospital stay for more than one day
    - Use of immunosuppressive drugs
    - Cytotoxic chemotherapy in the past 21 days
    - Neutropenia due to hematological or solid malignancies with bone marrow invasion
    - Patients expected to die in the next 24 hours
    - Consent refusal for participation

Additional information on randomization method and allocation concealment

The randomization list was generated by the trial statistician, not involved in patient care or enrolment, using the R software (R Core Team, Vienna, Austria, 2020).[4] The list comprised random blocks of two and four, unknown to researchers and stratified at center level and was uploaded and implemented in the on-line web-based system[5] used for randomization data collection. The group treatment was disclosed to the investigator only after all information regarding patient enrolment was

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recorded in the online system. Patients were screened for enrolment by the principal investigator and the research team at each study center.

Ventilator-free days definition

The variable ventilator-free days (VFD) until 28 days was defined as being alive and free from invasive mechanical ventilation for at least 48h (successful extubation).[6] If the patient was re-intubated within 48 hours of the extubation the variable was treated as zero VFD; if re-intubated after 48 hours, the 48 hours period was counted as VFD. Patients discharged from the hospital alive before 28 days were considered alive and free from mechanical ventilation at day 28. Non-survivors at day 28 were considered to have zero VFD. Therefore, the outcome of VFD until 28 days has the component of patients with zero VFD, either because were mechanically ventilated during the entire study period or patients who died during the study period and the component of patients who were alive at day 28 and were ventilated for less than 28 days.

Additional information on Sequential Organ Failure Assessment score calculation

The Sequential Organ Failure Assessment (SOFA) score is measured in 6 organ systems (cardiovascular, hematologic, gastrointestinal, renal, pulmonary and neurologic), with each organ scoring from 0 to 4, resulting in an aggregated score that ranges from 0 to 24. There was no mandatory measurement of the laboratorial variables used in the SOFA score (serum bilirubin, serum creatinine, platelet count and arterial blood gases). The data imputed in the electronic case report form (eCRF) was from clinical samples collected at the discretion of the treating physicians. Study centers were advised to impute the worst value of the day if more than one measurement was available.

In case of missing data on individual SOFA components, the value of 0 (normal) was imputed for that component.[7] None of the patients had missing data on all SOFA components for a specific day. However, it must be acknowledged that this approach may underestimate the final SOFA score and lead to inadequate prediction. Also, the SOFA score was calculated only for patients that were alive at the time of evaluation. Not penalizing the SOFA score for deaths might introduce survivorship bias[8] favoring the group with higher mortality (control group), which might have reduced the observed difference in the analysis.

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Therefore, although not used for predictions, the final values of each score might be underestimated and the interpretation of these data must be in the light of the limitations described.

Additional information on trial conduct

The first interim analysis with complete follow up of 96 patients was performed on June 18th. On June 16th, the Recovery trial[9] results were released as a press statement which was considered during the first interim analysis. The DSMC advised to continue enrollment until further results of Recovery were available. The steering committee inadvertently had access to unblinded raw mortality data during the first interim analysis, but with no interference with the decision of trial continuation. After the publication of the Recovery press release, the trial recruitment rate reduced substantially and, after publication of the Recovery pre-print on June 22nd, the DSMC considered that whilst the evidence presented was not a gold-standard for evidence-based research, the results were compelling and the control arm might be less safe than the treatment arm, leading to a recommendation to stop the trial. The enrollment was then suspended by the steering committee after 85% of the calculated sample size was reached.

Additional information on infections adjudication

We collected daily data on new diagnosis of infection from randomization up to 28 days for all patients. All infections reported were adjudicated by an infectious disease specialist blinded to study group. Investigators were asked to send a deidentified copy of patient's medical records (from the day the infection diagnosis was made and the day before), microbiological results of all cultured specimens between 48h before and after the diagnosis and additional radiological images (the image from the day of diagnosis and the previous available) when the diagnosis of nosocomial pneumonia or ventilator-associated pneumonia were made. After adjudication the infection status was deemed as infected, not infected or indeterminate.

Additional information on outcomes analyses

The primary model used a generalized additive model with zero-inflated beta-binomial distribution. This model is an extension of generalized linear models and assume regular residual statements of normality and homoscedasticity. The first part is a regular logistic regression model for the probability of zero value of ventilator free days (death or

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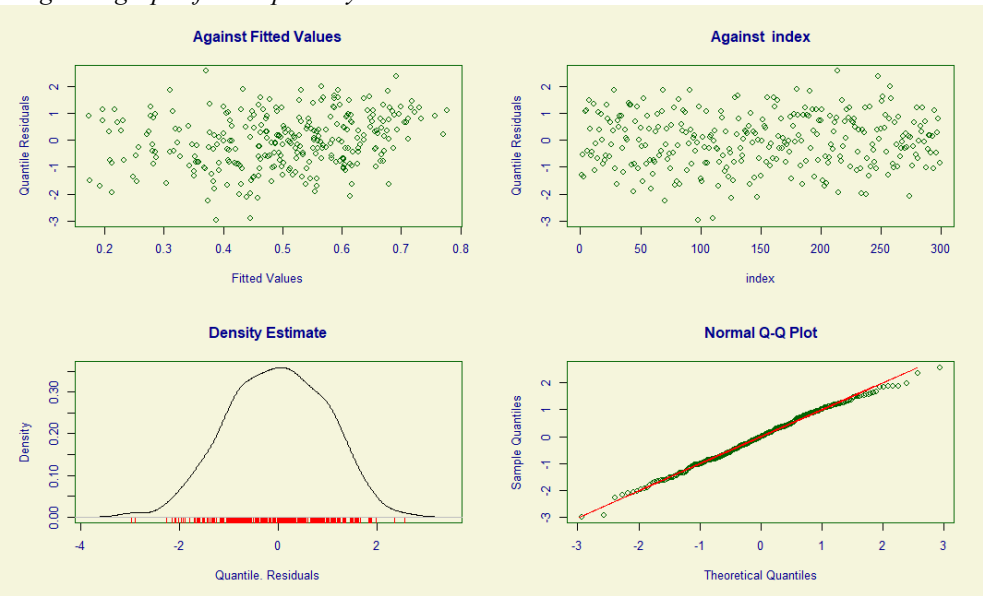
remaining 28 days in mechanical ventilation). The second part models the data distribution of the non-zero values as a beta-Binomial distribution, which is a discrete distribution in an [0, N] interval, where N = 28 (days). Both parts of the model were adjusted for age and PaO_2:FiO_2 ratio at baseline. Full model coefficients are shown in etable5. The diagnosis graphs for the primary model are shown below.

Diagnosis graphs for the primary model



For the secondary outcome of clinical status at 15 days the proportional odds ratio assumption was evaluated using the Lipsitz goodness-of-fit method, P value = 0.10, and all cumulative odds ratio were presented at eTable 6. Proportional hazard assumptions were used to evaluate mortality at 28 days and tested by Grambsch and Therneau test[10] (P value = 0.84) based on Schoenfeld's residuals and visual inspection of Kaplan-Meier curves.

We were unable to perform the pre-specified analyses of the subgroups duration of moderate to severe ARDS to randomization (≤24 hours and >24h to 48 hours) and use of corticosteroids before randomization due to the small number of patients in some groups (the >24h to 48 hours and patients without corticosteroids groups) after partitioning the sample. The subgroup analysis of HScore[11] (≥169 and <169) was not done because study centers were unable to collect data on all the HScore variables. Although all subgroup analyses were exploratory, we chose to not to analyze subgroups with small number of patients due to the risk of type I error and misinterpretation of the results.

The subgroup analysis of the Simplified Acute Physiology (SAPS) III score (<50 points and ≥50 points) was changed post-hoc to <60 and ≥60 points due to the small number of patients in the subgroup of SAPS III <50 (eFigure 1). However, we considered a subgroup analysis including the disease severity and mortality risk, although exploratory, valuable for future hypothesis generation.

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As post-hoc analyses (eTable 5) we evaluated the treatment effect on each individual component of ventilator-free days during the first 28 days and reported all two-by-two comparisons of the unfavorable vs favorable outcomes of the 6-point ordinal scale at day 15. We also analyzed the outcome of discharge from hospital alive within 28 days, which corresponds to the level 1 of the 6-point ordinal scale.

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eTable 1 – Additional data on Baseline Characteristics [a]

Characteristic	Dexamethasone (N = 151)	Control (N = 148)
Clinical Characteristics		
Temperature – ºC	36.6 (1.0)	36.6 (0.9)
Systolic blood pressure – mm Hg	119 (22)	118 (23)
Diastolic blood pressure – mm Hg	66 (12)	66 (13)
Mean arterial pressure – mm Hg	84 (13)	83 (14)
Heart rate – beats/minute	98 (19)	93 (19)
Oxygen saturation – %	94 (4)	93 (5)
Ventilation mode – no. (%)		
Pressure control ventilation	64 (42.4)	69 (46.6)
Volume control ventilation	73 (48.3)	66 (44.6)
Other	14 (9.3)	13 (8.8)
Respiratory variables at randomization		
$PaCO_2$ – mmHg	47 (14)	48 (13)
PaO_2:FiO_2 ≤100 – no. (%)	108 (71.5)	108 (73.0)
PaO_2:FiO_2 >100 and ≤200 – no. (%)	43 (28.5)	40 (27.0)
Respiratory system static compliance – mL/cm of water	32 (10)	33 (10)
Laboratory variables		
Serum pH	7.35 (0.1)	7.31 (0.1)
Serum bicarbonate – mmol/L	23.6 (5.0)	22.9 (4.6)
Bilirubin– umol/L, median (IQR)	0.44 (0.3 – 0.7)	0.49 (0.3 – 0.7)
Fibrinogen – mg/dL, median (IQR)	627 (445 – 742)	566 (467 – 711)
Triglycerides – mg/dL, median (IQR)	248 (193 – 347)	215 (146 – 343)
Ferritin – ng/mL, median (IQR)	1115 (628 – 2331)	1656 (936 – 2848)

Abbreviations: IQR interquartile range, FiO_2 fraction of inspired oxygen, PaO_2 partial pressure of arterial oxygen, $PaCO_2$ partial pressure of carbon dioxide, PaO_2:FiO_2 partial pressure of arterial oxygen to the fraction of inspired oxygen ratio. The number of patients with laboratory values available for each exam was: pH 299, bicarbonate 299, bilirubin 187, fibrinogen 155, triglycerides 101 and ferritin 104.

[a] Continuous variables are presented as mean (SD) unless otherwise indicated.

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eTable 2. Dexamethasone use in the dexamethasone plus standard of care group

Day	**Dexamethasone (N = 151)**
Daily use of dexamethasone – no. (%)	
1	146/151 (96.7)
2	148/151 (98.0)
3	143/145 (98.6)
4	134/139 (96.4)
5	128/134 (95.5)
6	123/129 (95.3)
7	111/119 (93.2)
8	103/113 (91.1)
9	93/103 (90.3)
10	83/94 (88.3)
Rate of dexamethasone use within 10 days per 100 patients-day	1212/1278 (94.8)
Use of at least one dose of dexamethasone within 10 days	150/151 (99.3)
Number of days of dexamethasone use (IQR)	10 (6 – 10)

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eTable 3. Corticosteroids use in the standard of care group

Day	**Standard of care group (N = 148)**
Daily use of corticosteroids – no. (%)	
1	3/148 (2.0)
2	11/147 (7.5)
3	15/144 (10.4)
4	21/134 (15.7)
5	23/127 (18.1)
6	20/119 (16.8)
7	25/115 (21.7)
8	29/112 (25.9)
9	31/108 (28.7)
10	30/103 (29.1)
Rate of corticosteroids use within 10 days per 100 patients-day	208/1257 (16.5)
Use of at least one dose of corticosteroids within 10 days	52/148 (35.1)
Number of days of corticosteroids use (IQR)	0 (0 – 2)
Number of protocol deviations [a]	14/148 (9.4)

[a] Two patients received corticosteroids for cryptogenic organizing pneumonia, 1 for hemophagocytic lymphohistiocytosis, 4 by the attending physicians' choice, 1 for refractory hypoxemia, 2 after the publication of the Recovery trial and in 4 the use of corticosteroids was not justified.

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eTable 4. New diagnosis of infection and adverse events at 28 days [a]

	Dexamethasone	**Control**
Infection [b] – no. (%)	33(21.8)	43(29.0)
Abdominal	0(0)	2(1.3)
Catheter-related bloodstream infection	10(6.6)	9(6.0)
Mastoiditis	1(0.6)	0(0)
Mediastinitis	0(0)	1(0.6)
Ventilator associated pneumonia	19(12.5)	31(20.9)
Sinus	1(0.6)	0(0)
Skin and soft tissue	1(0.6)	2(1.3)
Tuberculosis	1(0.6)	0(0)
Undetermined	2(1.3)	2(1.3)
Catheter-associated urinary tract infections	1(0.6)	0(0)
Bacteremia [c] – no. (%)	12(7.9)	16(10.8)
Adverse events – no. (%)	5 (3.3)	11 (7.4)
Acute myocardial infarction	1	2
Bronchospasm	0	1
Cardiogenic shock	0	1
Deep vein thrombosis	1	1
Diabetic ketoacidosis	0	1
Gastrointestinal perforation	1	0
Hyperglycemia, unspecified	1	1
Ischemic hepatitis	0	1
Nephropathy in transplanted kidney	0	1
Pneumothorax	1	1
Pulmonary embolism	0	1

[a] All investigator reported infections were adjudicated by a blinded specialist using unidentified patients records, microbiological data and radiological images.

[b] Seven patients had two infections episodes.

[c] Comprises all catheter-related bloodstream infections plus other infections with bacteremia.

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eTable 5. Primary model coefficients

Coefficients	Estimate	Standard Error	P Value
Mu link function: logit			
Mu Coefficients:			
(Intercept)	0.550	0.467	0.240
Group (Dexamethasone)	0.494	0.190	0.010
Age - yrs	-0.014	0.007	0.034
PaO_2:FiO_2	0.001	0.002	0.658
Sigma link function: logit			
Sigma Coefficients:			
(Intercept)	-0.060	0.140	0.67
Group (Dexamethasone)	-0.257	0.187	0.17
Nu link function: logit			
Nu Coefficients:			
(Intercept)	-3.664	0.754	<0.001
Group (Dexamethasone)	-0.163	0.291	0.576
Age - yrs	0.072	0.011	<0.001
PaO_2:FiO_2	0.002	0.003	0.533
Primary model was generalized using additive models for location, shape and scale, with zero-inflated beta-binomial distribution			
Mu and sigma refer respectively to the mean and standard deviation parts of the beta-binomial model			
Nu refers to the binary logistic regression for zero mechanical ventilation free days at 28 days.			

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eTable 6. Exploratory study outcomes [a]

Outcomes	Dexamethasone (N = 151)	Control (N = 148)	Effect statistic	Between Group effect		Unadjusted Group effect	
				Estimative (95% CI)	P Value	Estimative (95% CI)	P Value
Primary outcome components							
Ventilator free days for discharged alive patients or ventilator free at least one day within 28 days	19.1 (6.4) (n=54)	14.3 (8.4) (n=43)	Mean difference	3.47 (-0.15 - 6.95)	0.07	4.49 (1.43 - 7.53)	<0.01
Patients without ventilator free days within 28 days – no. (%)	97 (64.2%)	105 (70.9%)	Odds ratio	0.82 (0.46 - 1.49)	0.52	0.74(0.45 - 1.2)	0.22
Cumulative proportions of 6-point ordinal scale [b] at day 15							
Category 6	54 (35.8%)	65 (43.9%)	Odds ratio	0.74 (0.45 - 1.22)	0.23	0.71 (0.45 - 1.13)	0.15
Categories 5-6	102 (67.5%)	119 (80.4%)	Odds ratio	0.46 (0.26 - 0.81)	0.01	0.51 (0.3 - 0.860	0.01
Categories 4-6	109 (72.2%)	123 (83.1%)	Odds ratio	0.5 (0.28 - 0.89)	0.02	0.53 (0.3 - 0.92)	0.02
Categories 3-6	134 (88.7%)	140 (94.6%)	Odds ratio	0.43 (0.18 - 1.06)	0.07	0.45 (0.19 - 1.08)	0.07
Categories 2-6	134 (88.7%)	140 (94.6%)	Odds ratio	0.43 (0.18 - 1.06)	0.07	0.45 (0.19 - 1.08)	0.07
Discharged alive within 28 days – no. (%)	42 (27.8%)	25 (16.9%)	Odds ratio	1.89 (0.95 - 3.72)	0.07	1.9 (1.08 - 3.31)	0.02

Abbreviations: CI confidence interval.

[a] Values are means (95% CI) unless otherwise indicated.

[b] The 6-point ordinal scale (1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring non-invasive ventilation or nasal high-flow oxygen therapy; 5, hospitalized, requiring invasive mechanical ventilation or ECMO; and 6, dead).

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eTable 7. Sensitivity analysis for the primary outcome [a]

Primary outcome	Corticosteroids	Control	Mean difference[b]		Unadjusted mean difference	
			Estimative (95% CI)	P Value	Estimative (95% CI)	P Value
Confirmed COVID-19	6.8 (5.4 – 8.4) (n=144)	3.9 (2.7 – 5.1) (n=142)	2.7 (0.8 – 4.74)	0.01	2.94 (0.87 – 4.98)	<0.01
Confirmed or probable COVID-19	6.6 (5.3 – 8.2) (n=151)	4.1 (2.9 – 5.2) (n=147)	2.38 (0.48 – 4.33)	0.02	2.53 (0.52 – 4.47)	0.01
As treated analysis [c]	5.8 (4.6 – 7.3) (n=203)	4.1 (2.6 – 5.5) (n=96)	1.42 (-0.6 – 3.32)	0.16	1.66 (-0.48 – 3.6)	0.11
Per protocol analysis [d]	6.4 (5.1 – 8.1) (n=125)	4.1 (2.6 – 5.5) (n=96)	2.36 (-0.15 – 4.56)	0.06	2.38 (-0.04 – 4.52)	0.05

Abbreviations: IQR interquartile range, ITT intention to treat.

[a] Values are means (95% CI) unless otherwise indicated.

[b] All models are adjusted for age and baseline at PaO_2:FiO_2 ratio with random intercept by site.

[c] Patients receiving any corticosteroid versus patients not receiving corticosteroids. 203 patients in corticosteroids group and 96 in the no corticosteroids group.

[d] Patients receiving all the proposed treatment in the intervention group and patients not receiving corticosteroids in the control group. 125 patients in dexamethasone group and 96 in the control (no corticosteroids).

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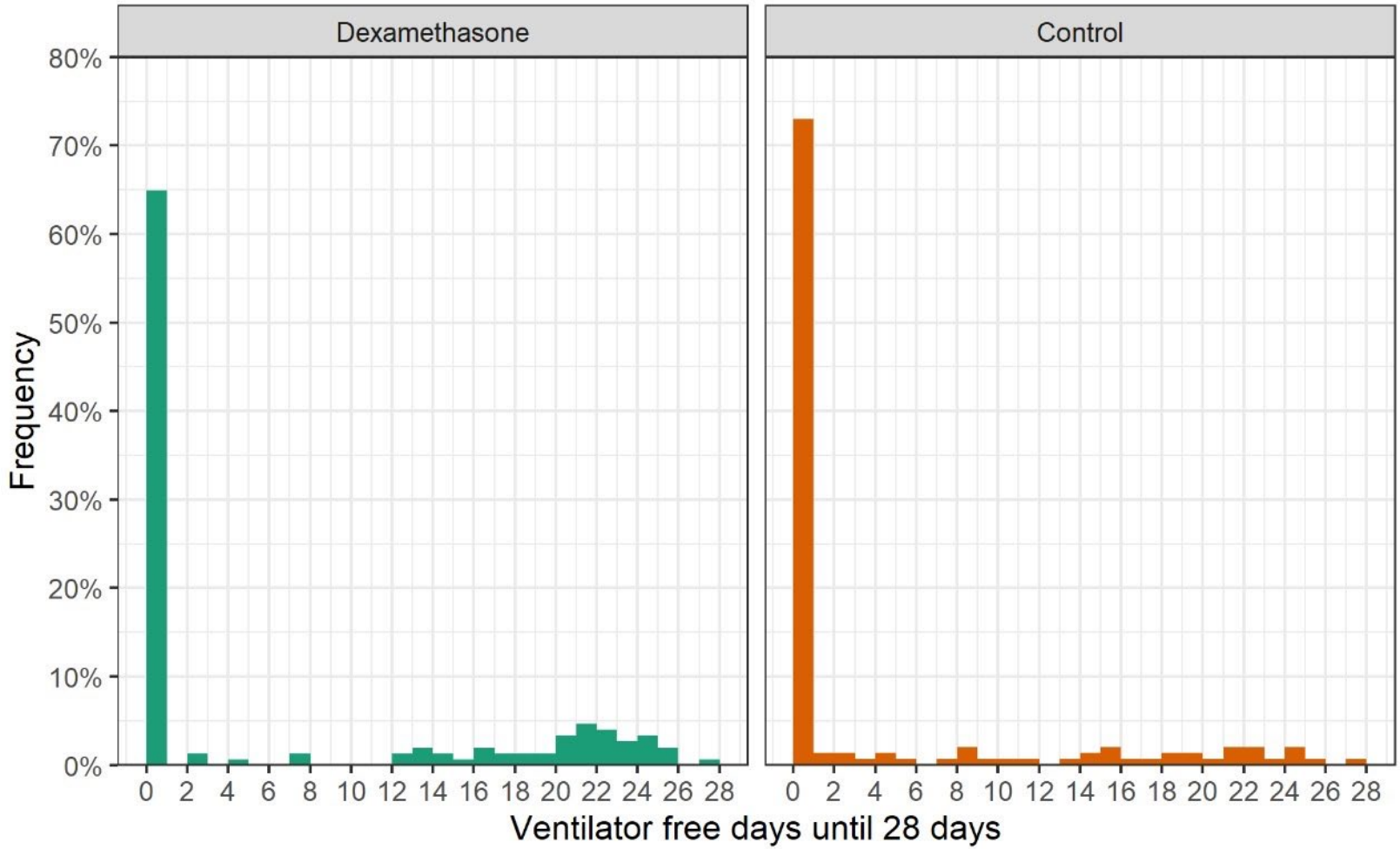
eFigure 1. Distribution of ventilator-free days according to study group



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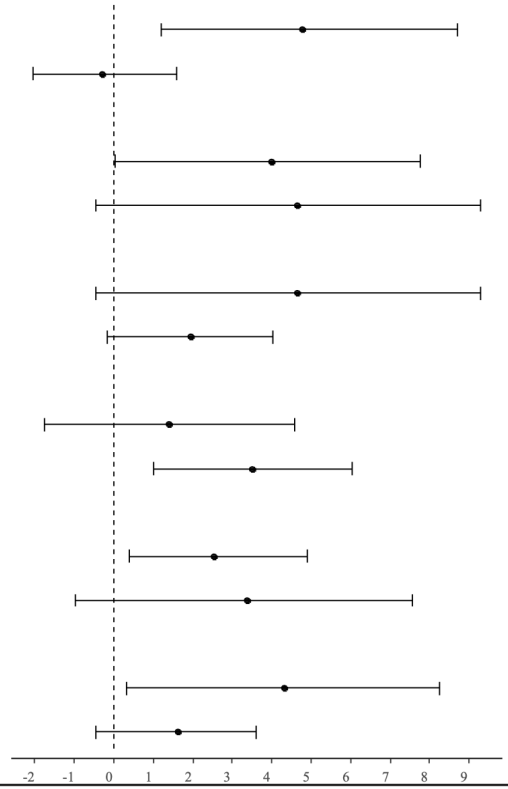
eFigure 2. Subgroup analysis

Subgroups	Dexamethasone	Control	Between group differences for ventilator free days at 28 days (95% CI)*	P-Value for interaction
	Mean (95% CI) (Number of cases)			
Age – yr				
< 60	11.7 (9.0 – 14.0) (n=68)	6.8 (4.4 – 9.7) (n=47)	4.76 (1.21 - 8.70)	0.21
≥ 60	2.5 (1.3 – 4.1) (n=83)	2.7 (1.7 – 3.8) (n=101)	-0.29 (-2.03 - 1.60)	
PaO_2:FiO_2 ratio				
≤ 100	9.0 (6.3 – 11.9) (n=43)	4.5 (2.0 – 7.7) (n=40)	4.00 (0.02 - 7.76)	0.73
> 100	5.7 (4.1 – 7.4) (n=108)	3.9 (2.6 – 5.4) (n=108)	4.63 (-0.46 - 9.28)	
SAPS III				
< 60	11.1 (6.6 – 14.2) (n=34)	6.4 (2.7 – 9.7) (n=32)	4.63 (-0.46 - 9.28)	0.75
≥ 60	5.5 (4.2 – 6.9) (n=117)	3.4 (2.1 – 5.8) (n=116)	1.94 (-0.15 - 4.03)	
Time since symptom onset – days				
≤ 7	5.4 (3.1 – 8.4) (n=54)	4.2 (2.3 – 6.6) (n=48)	1.41 (-1.75 - 4.58)	0.12
> 7	7.6 (5.7 – 9.0) (n=95)	3.9 (2.2 – 5.8) (n=99)	3.51 (1.00 - 6.03)	
Position at randomization				
Supine	6.5 (4.9 – 8.5) (n=115)	3.9 (2.7 – 5.1) (n=114)	2.52 (0.40 - 4.92)	0.89
Prone	7.3 (4.2 – 10.2) (n=33)	3.9 (1.9 – 6.8) (n=33)	3.39 (-0.98 - 7.56)	
Vasopressors at randomization				
No	10.2 (7.1 – 13.1) (n=52)	5.9 (3.2 – 7.8) (n=47)	4.32 (0.34 - 8.26)	0.81
Yes	4.8 (3.0 – 6.4) (n=99)	3.2 (2.1 – 4.5) (n=101)	1.63 (-0.44 - 3.60)	



* Generalized additive models with zero-inflated beta-binomial distribution and interaction between groups and subgroups variables.

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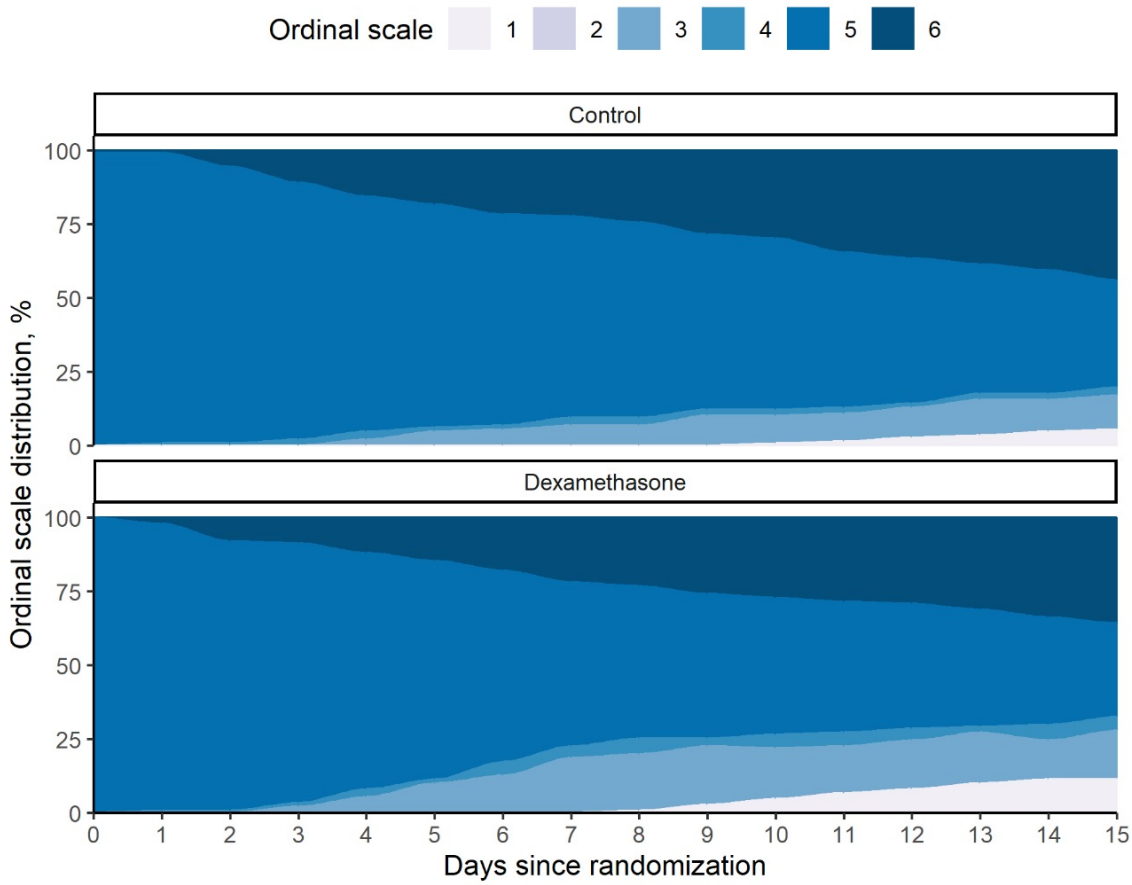
eFigure 3. Ordinal-scale results distribution over time



Shown is the course of ordinal-scale results as assessed over the time since randomization until day 15. The 6-point ordinal scale (1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring non-invasive ventilation or nasal high-flow oxygen therapy; 5, hospitalized, requiring invasive mechanical ventilation or ECMO; and 6, dead).

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