Corticosteroids for COVID-19

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Digital Congress of COVID-19 Management and Treatment

جمهوری اسلامی ایران
وزارت بهداشت، درمان و آموزش پزشکی
ستاد مقابله با کرونا در کلانشهر تهران

کنگره دیجیتال مدیریت و درمان
COVID-19

دانشگاه علوم پزشکی
و خدمات بهداشتی درمانی تهران

Rationale for Use of Corticosteroids in Patients With COVID-19

- Evidence is accumulating that much of the morbidity and mortality associated with COVID-19 disease is related to a dysregulated host immune response and it has been described and clinically observed that COVID-19 often follows a biphasic pattern with an initial viral phase followed in susceptible individuals with a second “host inflammatory” phase that may be associated with respiratory failure and the development of ARDS.

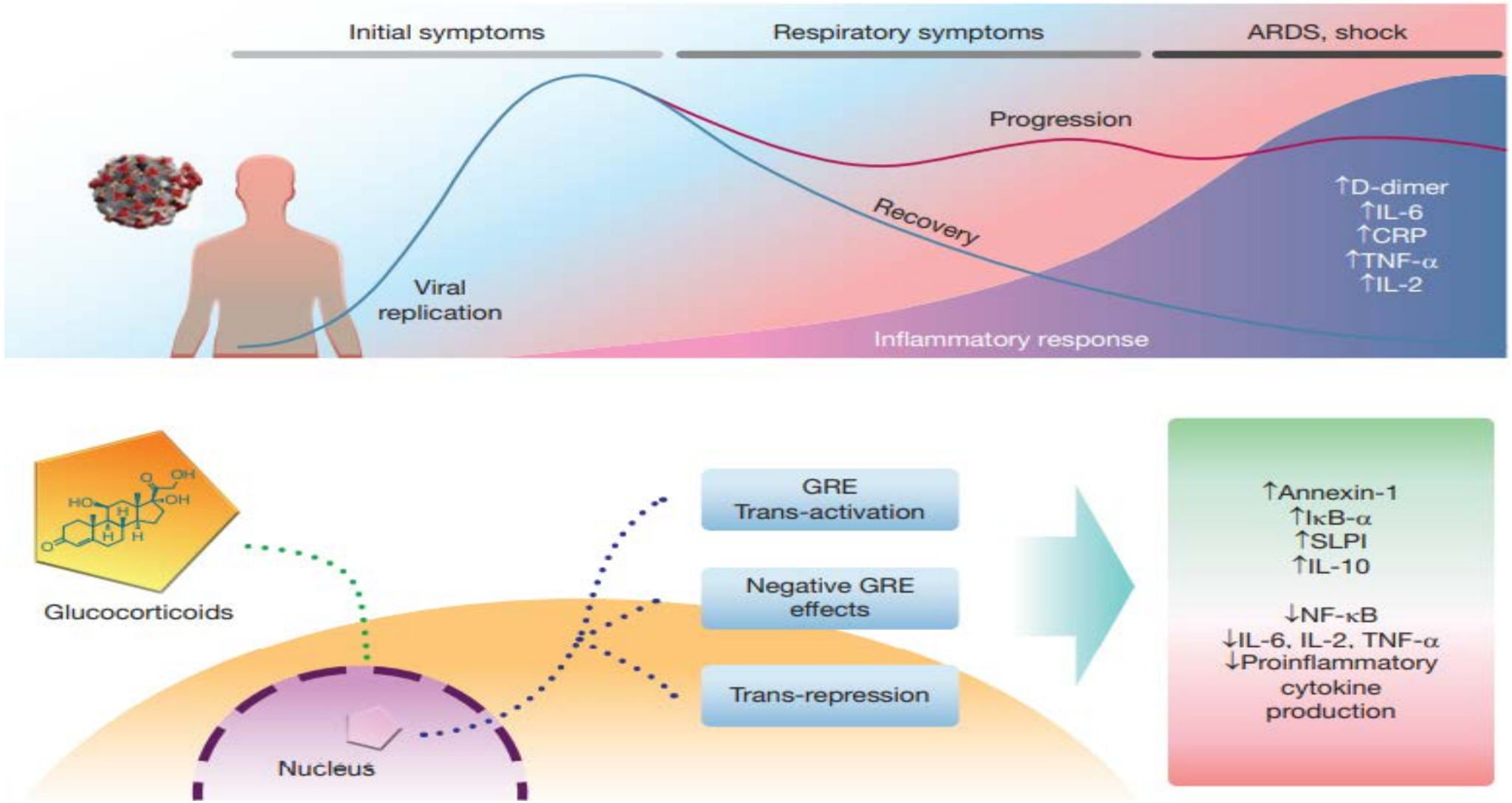
- Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects.

  Am J Respir Crit Care Med 2020; 202: 812–821

- Autopsy studies in COVID-19 patients showed lymphocyte alveolitis, acute fbrinous injury and organizing pneumonia, which are all probably steroid-sensitive.

  Crit Care. 2020;24:495

Diagram showing clinical phases of COVID 19 & immunomodulatory effects of glucocorticoid therapy



- Over the past 3 years, accruing data from larger, well conducted randomized clinical trials (RCTs) have suggested benefit of corticosteroids in ARDS and septic shock:

- APROCCHSS trial (N Engl J Med. 2018;378(9):809-818)
- ADRENAL trial (N Engl J Med. 2018;378(9):797-808)
- DEXA-ARDS trial (Lancet Respir Med. 2020;8(3):267-276)

- In meta-analyses that incorporated these recent RCTs, corticosteroid use was associated with more rapid resolution of shock and mechanical ventilation in septic shock and possible lower mortality in both septic shock and ARDS. (JAMA Intern Med. 2019;179(2):213- 223)

Multicenter Study > Am J Respir Crit Care Med. 2018 Mar 15;197(6):757-767.
doi: 10.1164/rccm.201706-1172OC.

Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome

Yaseen M Arabi [1 2], Yasser Mandourah [3], Fahad Al-Hameed [4], Anees A Sindi [5],

Conclusions: Corticosteroid therapy in patients with MERS was not associated with a difference in mortality after adjustment for time-varying confounders, but was associated with delayed MERS coronavirus RNA clearance

Am J Resp Crit Care 2018 Mar 15;197(6):757-756

OPEN ACCESS Freely available online

PLOS MEDICINE

SARS: Systematic Review of Treatment Effects

Lauren J. Stockman[1,2*], Richard Bellamy[3], Paul Garner[4]

1 Centers for Disease Control and Prevention, Respiratory and Enteric Viruses Branch, Atlanta, Georgia, United States of America, **2** Department of Veterans' Affairs, Atlanta Research and Education Foundation, Decatur, Georgia, United States of America, **3** James Cook University Hospital, Middlesbrough, United Kingdom, **4** Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Conclusions: In 29 studies of steroid use, 25 were inconclusive and four were classified as causing possible harm.

Ni *et al. Critical Care* (2019) 23:99
https://doi.org/10.1186/s13054-019-2395-8

Critical Care

RESEARCH Open Access

The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis

- Ten trials involving 6548 patients were pooled in final analysis.
- Compared with placebo, corticosteroids were associated with:

  Higher mortality (RR 1.75, 95% CI 1.30 ~ 2.36, Z = 3.71, P = 0.0002),

  Longer ICU LOS (MD 2.14, 95% CI 1.17 ~ 3.10, Z = 4.35, P < 0.0001),

  Higher rate of secondary infection (RR 1.98, 95% CI 1.04 ~ 3.78, Z = 2.08, P = 0.04),

  But not MV days (MD 0.81, 95% CI − 1.23 ~ 2.84, Z = 0.78, P = 0.44)
- Conclusions: In patients with influenza pneumonia, corticosteroid use is associated with higher mortality.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Randomized Evaluation of Covid-19 Therapy (RECOVERY)

- Multicenter, open-label, sponsored by the NHS in the UK.
- At 176 NHS organizations in the UK from March 19 to June 8, 2020.
- Clinically suspected or lab. confirmed SARS-CoV-2 infection.
- Initially, recruitment was limited to patients who were at least 18 years of age, but the age limit was removed starting on May 9, 2020. Pregnant or breastfeeding women were eligible.
- Eligible and consenting patients were assigned in a 2:1 ratio to receive either the usual SOC alone or the usual SOC plus oral or IV. dexamethasone (at a dose of 6 mg once daily) for up to 10 days (or until hospital discharge if sooner).

- primary outcome:

  All-cause mortality within 28 days after randomization

- Secondary outcomes:

  The time until discharge from the hospital

  Subsequent receipt of invasive mechanical ventilation

  Cause-specific mortality

  Receipt of renal hemodialysis or hemofiltration

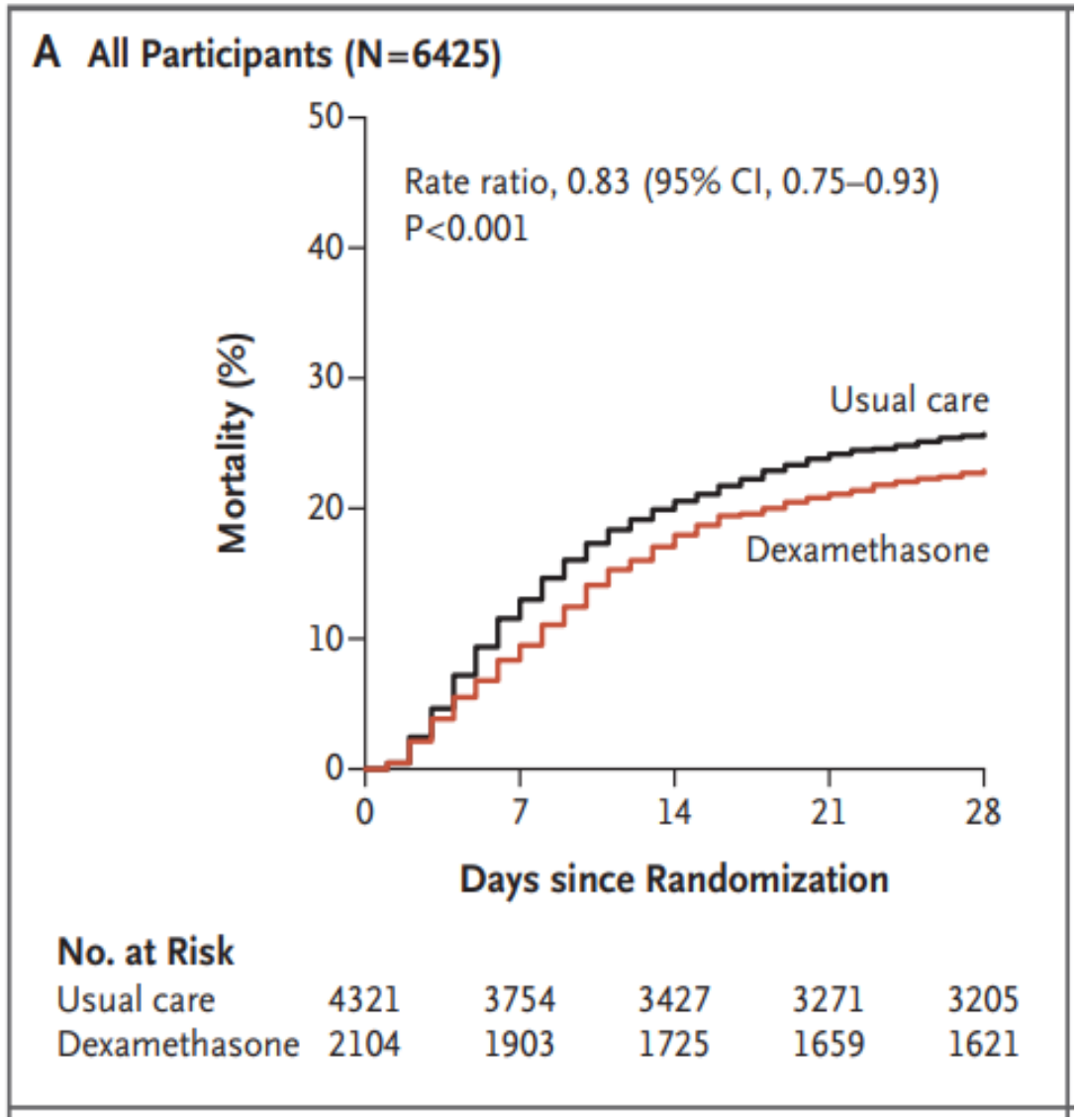
  Major cardiac arrhythmia

  Duration of ventilation

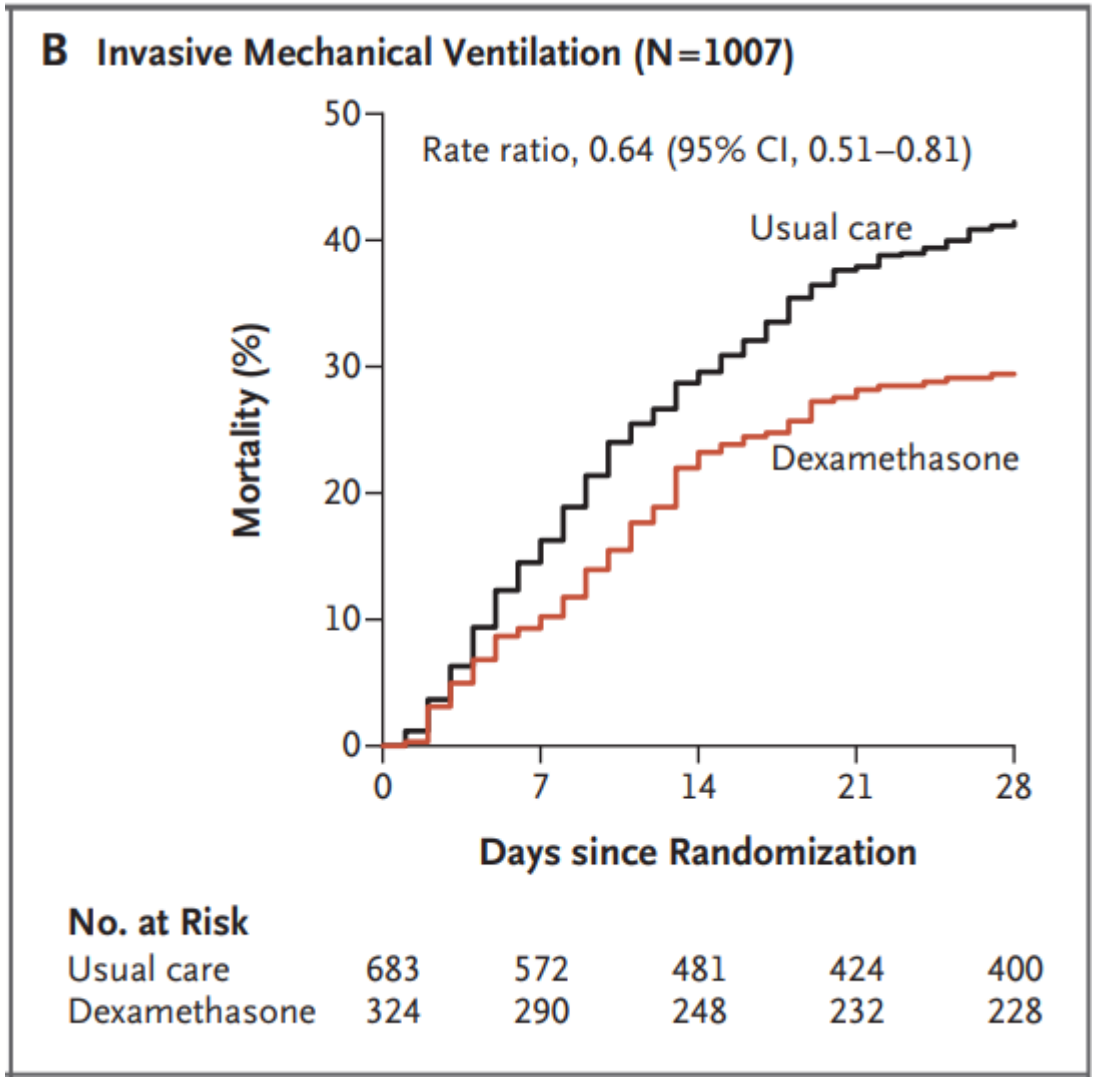
Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

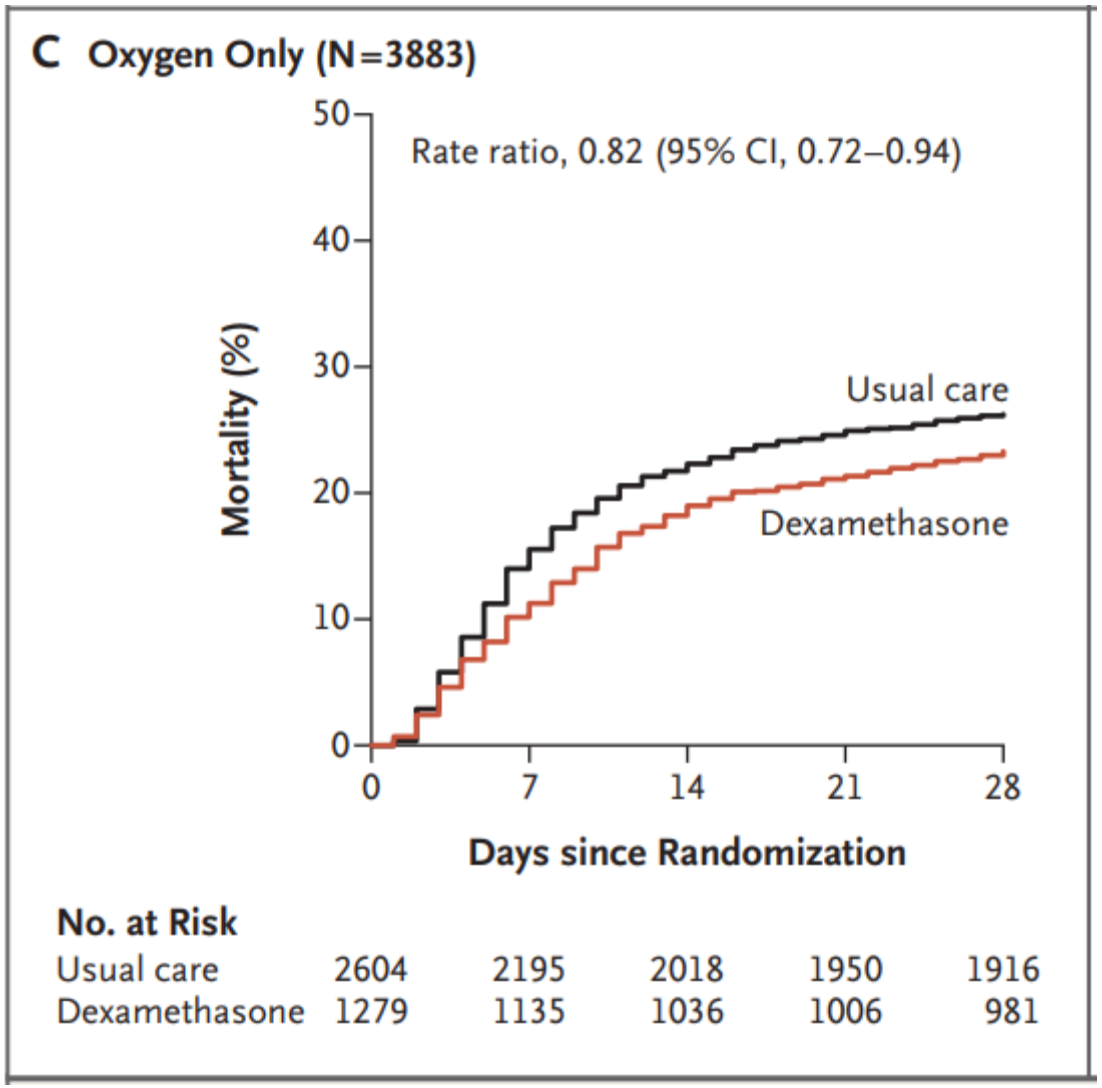
Deaths reported in 482 of 2104 patients (22.9%) in the Dexamethasone group and in 1110 of 4321 patients (25.7%) in the usual care group



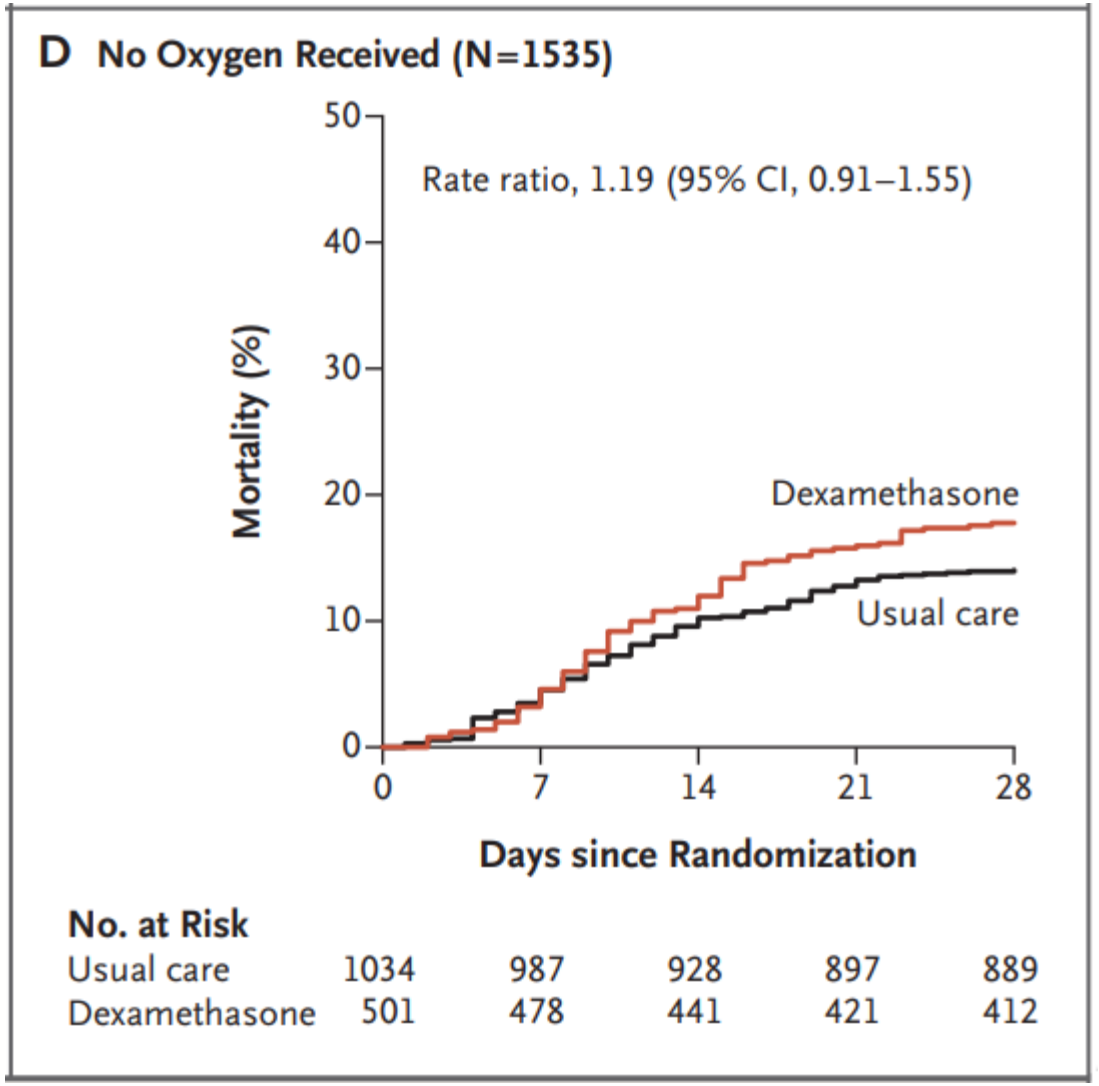
29.3% in the Dexamethasone group vs. 41.4% in the usual care group



23.3% in the Dexamethasone group vs. 26.2% in the usual care group



17.8% in the Dexamethasone group vs. 14% in the usual care group



Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

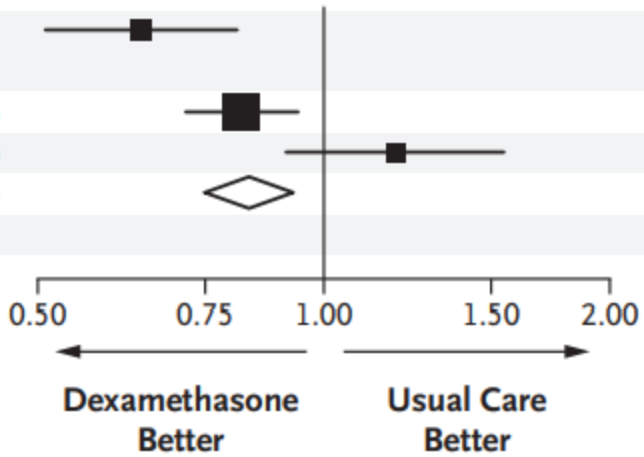


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

- Unlike with SARS, in which viral replication peaks in the second week of illness, viral shedding in SARS-CoV-2 appears to be higher early in the illness and declines thereafter. (Lancet Infect Dis 2020;20:565- 74)

- The receipt of dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with a more recent symptom onset.

- Dexamethasone is on the list of essential medicines of the World Health Organization and is readily available worldwide at low cost.

Research

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Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19

The CoDEX Randomized Clinical Trial

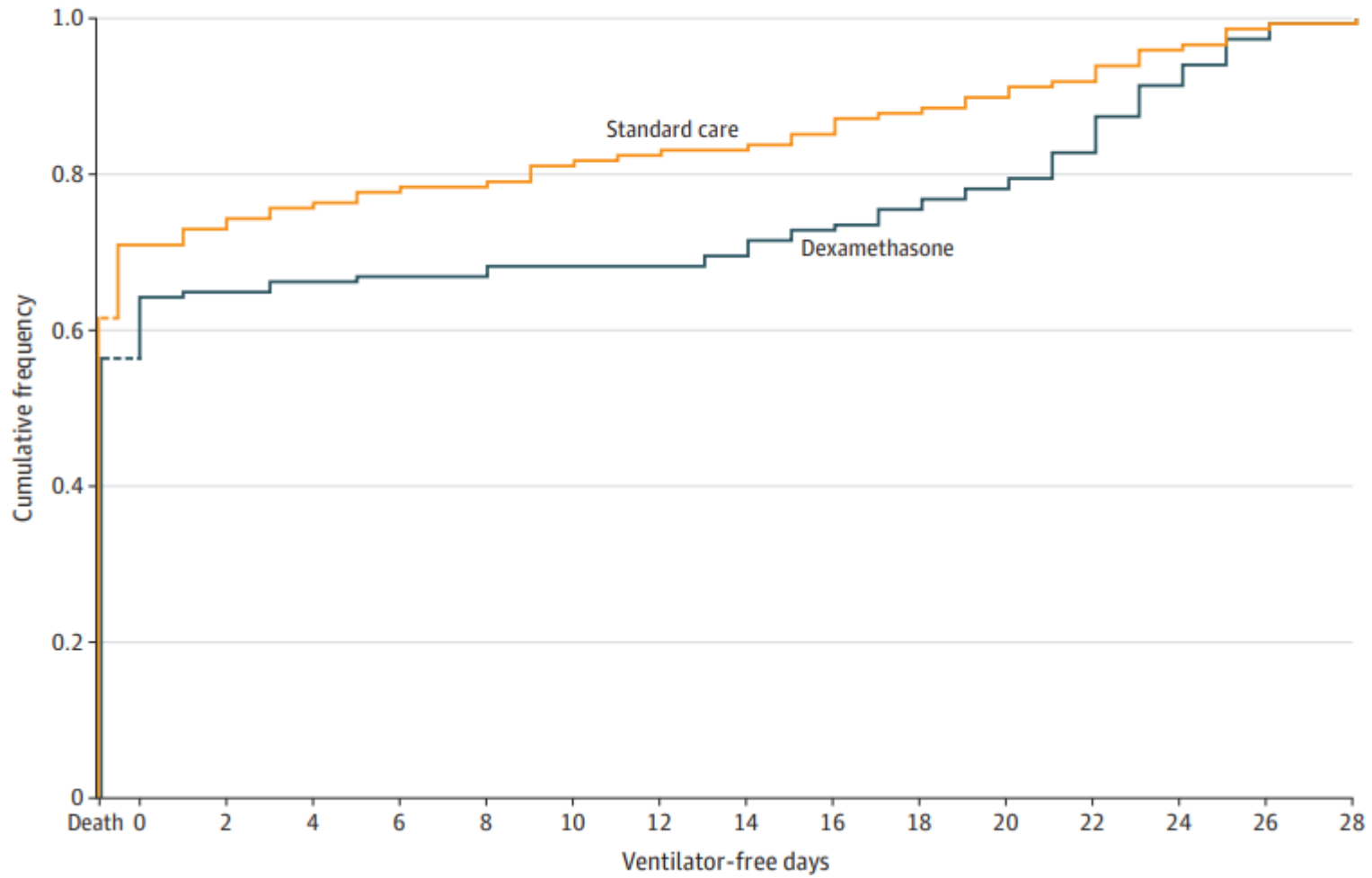
Bruno M. Tomazini, MD; Israel S. Maia, MD, MSc; Alexandre B. Cavalcanti, MD, PhD; Otavio Berwanger, MD, PhD; Regis G. Rosa, MD, PhD; Viviane C. Veiga, MD, PhD; Alvaro Avezum, MD, PhD; Renato D. Lopes, MD, PhD; Flavia R. Bueno, MSc; Maria Vitoria A. O. Silva; Franca P. Baldassare; Eduardo L. V. Costa, MD, PhD; Ricardo A. B. Moura, MD; Michele O. Honorato, MD; Andre N. Costa, MD, PhD; Lucas P. Damiani, MSc; Thiago Lisboa, MD, PhD; Letícia Kawano-Dourado, MD, PhD; Fernando G. Zampieri, MD, PhD; Guilherme B. Olivato, MD; Cassia Righy, MD, PhD; Cristina P. Amendola, MD; Roberta M. L. Roepke, MD; Daniela H. M. Freitas, MD; Daniel N. Forte, MD, PhD; Flávio G. R. Freitas, MD, PhD; Caio C. F. Fernandes, MD; Livia M. G. Melro, MD; Gedealvares F. S. Junior, MD; Douglas Costa Morais; Stevin Zung, MD, PhD; Flávia R. Machado, MD, PhD; Luciano C. P. Azevedo, MD, PhD; for the COALITION COVID-19 Brazil III Investigators

The CoDEX Randomized Clinical Trial

- DESIGN, SETTING, AND PARTICIPANTS: Multicenter, randomized, open-label, clinical trial conducted in 41 intensive care units (ICUs) in Brazil.
- Patients with COVID-19 and moderate to severe ARDS, according to the Berlin definition, were enrolled from April 17 to June 23, 2020.
- INTERVENTIONS: Twenty mg of dexamethasone intravenously daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n =151) or standard care alone (n = 148).

- **The primary outcome:**
- Ventilator-free days during the first 28 days,
- **Secondary outcomes:**
- All-cause mortality at 28 days,
- Clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death),
- ICU-free days during the first 28 days,
- SOFA scores at 48 hours, 72 hours, and 7 days

Figure 2. Ventilator-Free Days at 28 Days



Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; P = .04)

- At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, −1.16; 95% CI, −1.94 to −0.38; P = .004).
- There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, or the 6-point ordinal scale at 15 days.

Research

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Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19

A Randomized Clinical Trial

Pierre-François Dequin, MD, PhD; Nicholas Heming, MD, PhD; Ferhat Meziani, MD, PhD; Gaëtan Plantefève, MD; Guillaume Voiriot, MD, PhD; Julio Badié, MD; Bruno François, MD; Cécile Aubron, MD, PhD; Jean-Damien Ricard, MD, PhD; Stephan Ehrmann, MD, PhD; Youenn Jouan, MD, PhD; Antoine Guillon, MD, PhD; Marie Leclerc, MSc; Carine Coffre, MSc; Hélène Bourgoin, PharmD; Céline Lengellé, PharmD; Caroline Caille-Fénérol, MSc; Elsa Tavernier, PhD; Sarah Zohar, PhD; Bruno Giraudeau, PhD; Djillali Annane, MD, PhD; Amélie Le Gouge, MSc; for the CAPE COVID Trial Group and the CRICS-TriGGERSep Network

(CAPE COVID)

- Multicenter randomized double-blind sequential trial conducted in a 9 participating French ICUs,
- Patients admitted to the intensive care unit (ICU) for COVID-19–related acute respiratory failure were enrolled from March 7 to June 1, 2020, with last follow-up on June 29, 2020.
- INTERVENTIONS: Patients were randomized to receive low-dose hydrocortisone (n = 76) or placebo (n = 73).
- Treatment was continued at 200 mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days.

(CAPE COVID)

- One of 4 severity criteria had to be present:

  Need for mechanical ventilation with a PEEP of 5 cm H20 or more;

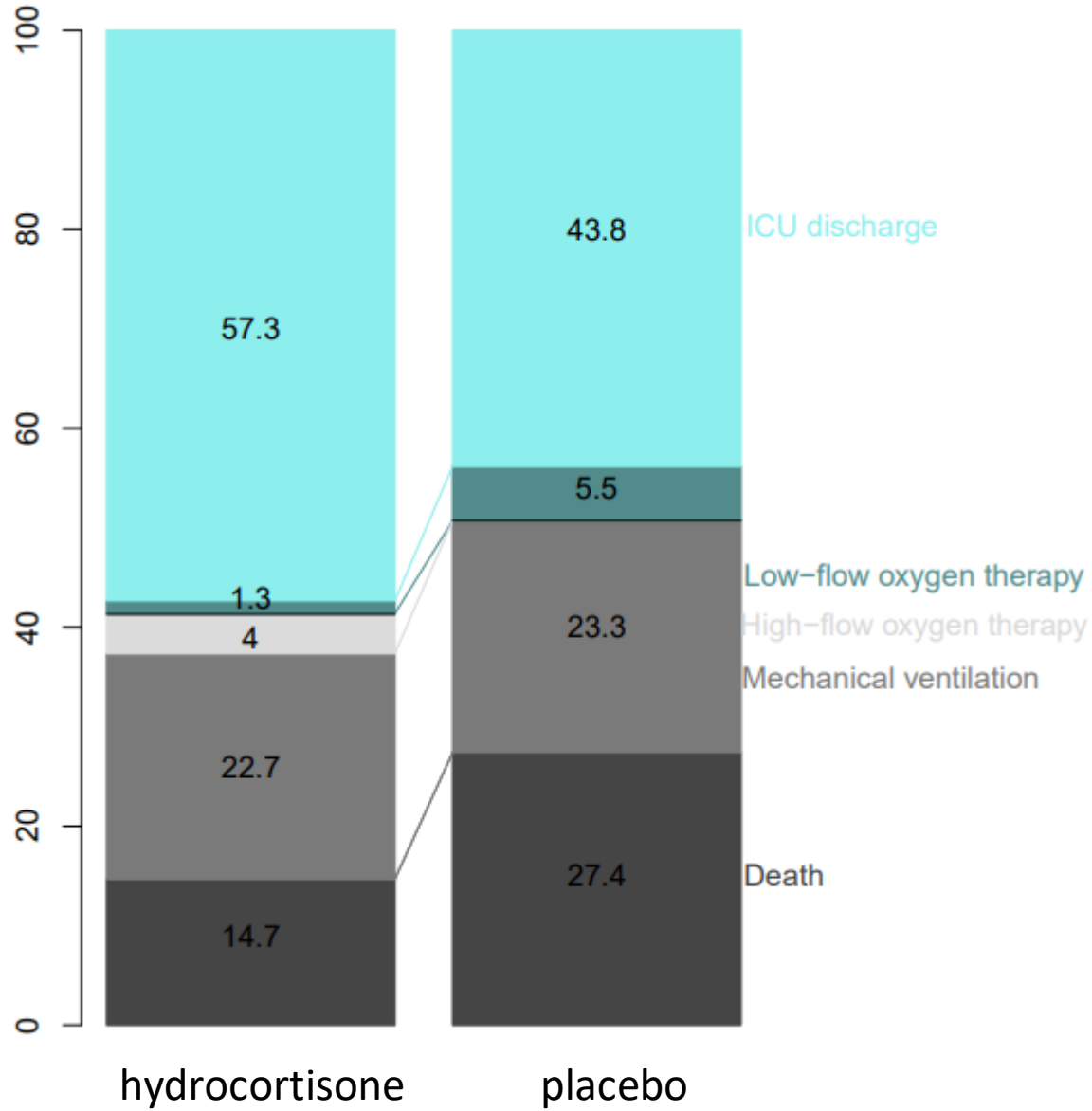
  A PaO2:FIO2 ratio less than 300 on high-flow oxygen therapy;

  A PaO2:FIO2 ratio less than 300 through a reservoir mask;

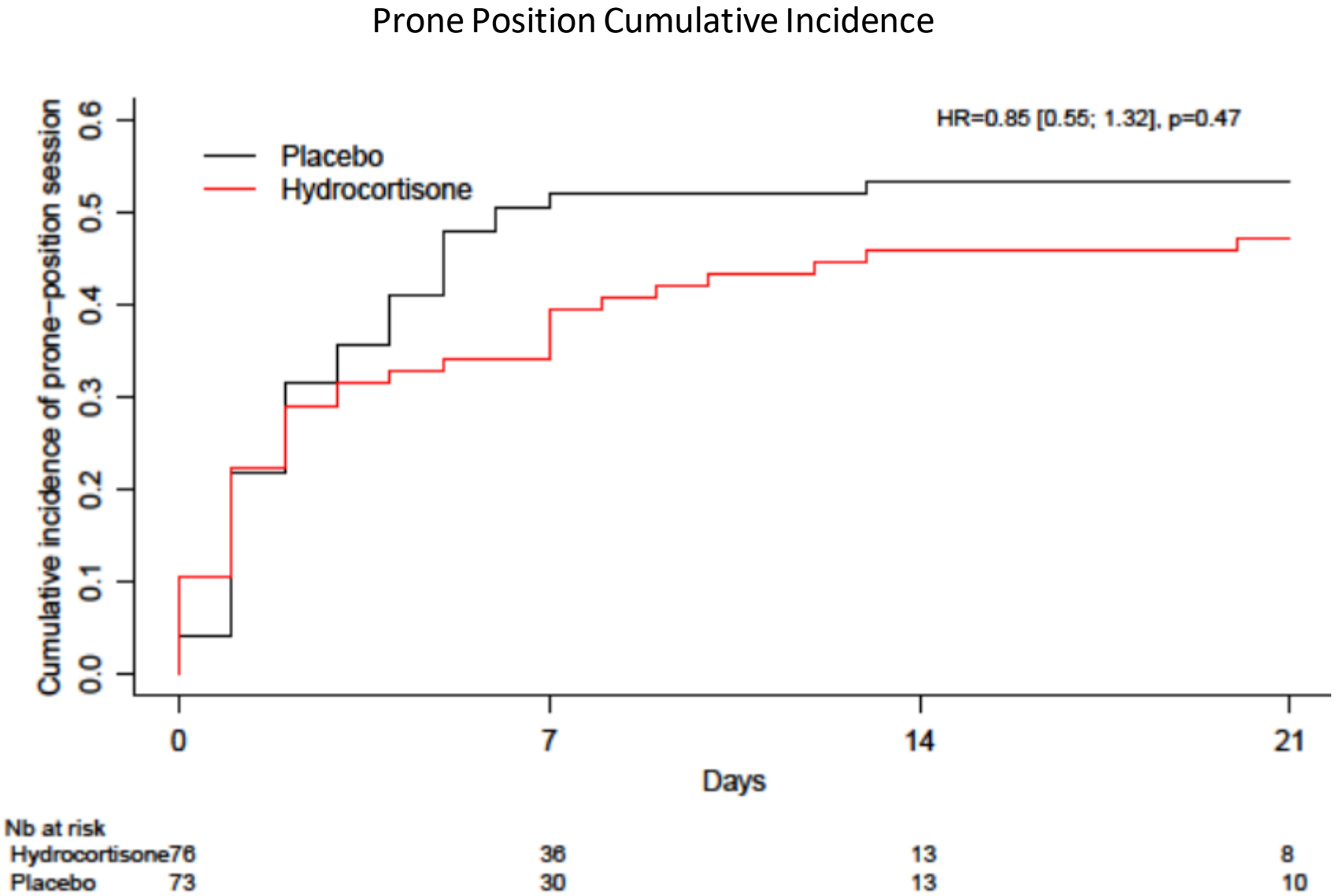
  Pulmonary Severity Index greater than 130.

- primary outcome:
- treatment failure on day 21, was defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy
- secondary outcomes:
- The need for tracheal intubation
- Cumulative incidences (until day 21) of prone position sessions,
- ECMO and inhaled nitric oxide;
- PaO2:FIO2 ratio measured daily from day 1 to day 7, then on days 14 and 21
- The proportion of patients with secondary infections during their ICU stay

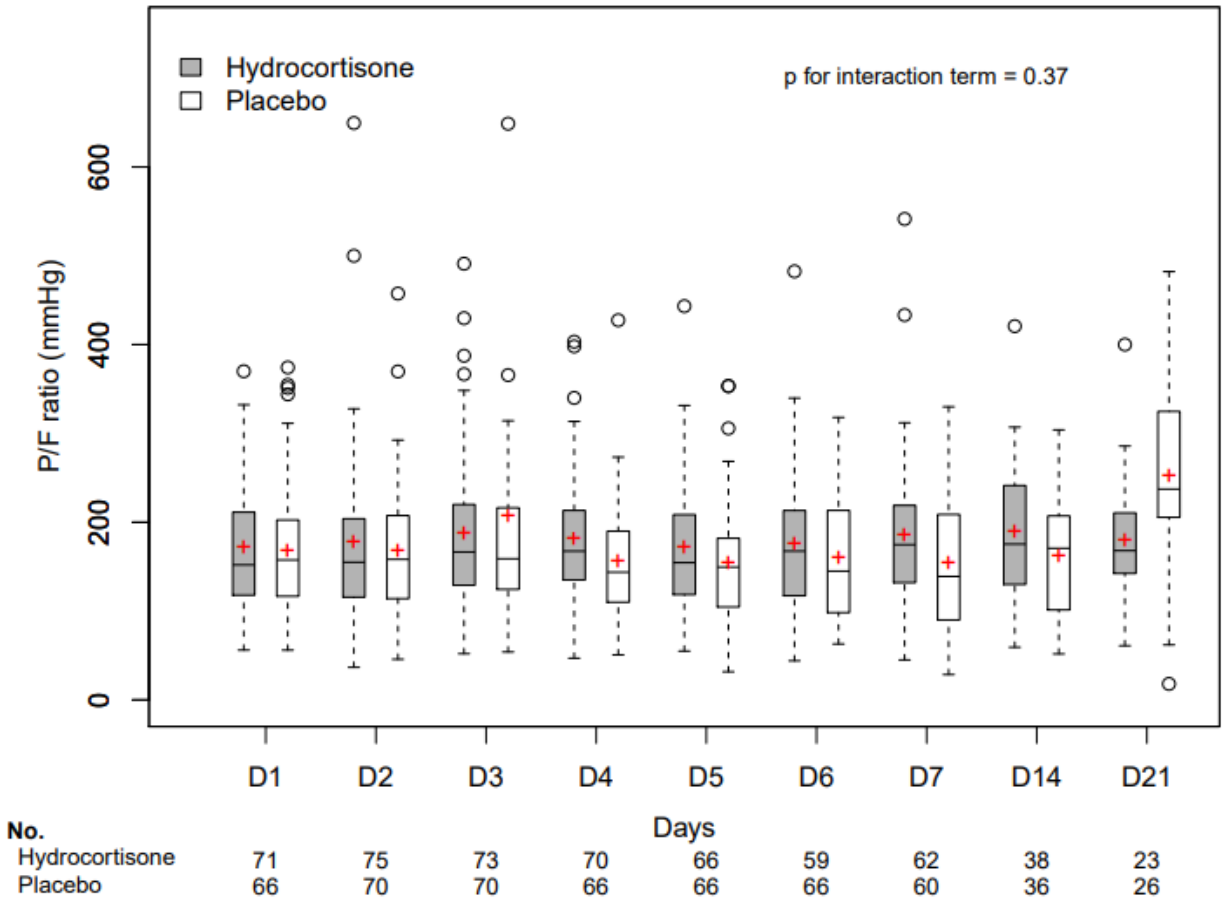
Treatment failure on day 21 occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, –8.6% [95.48% CI, –24.9% to 7.7%]; P = .29)



There was no significant between-group difference in rates of prone positioning (36/76 patients [47.4%] in the hydrocortisone group vs 39/73 [53.4%] in the placebo group; hazard ratio, 0.85 [95% CI, 0.55 to 1.32]; P = .47

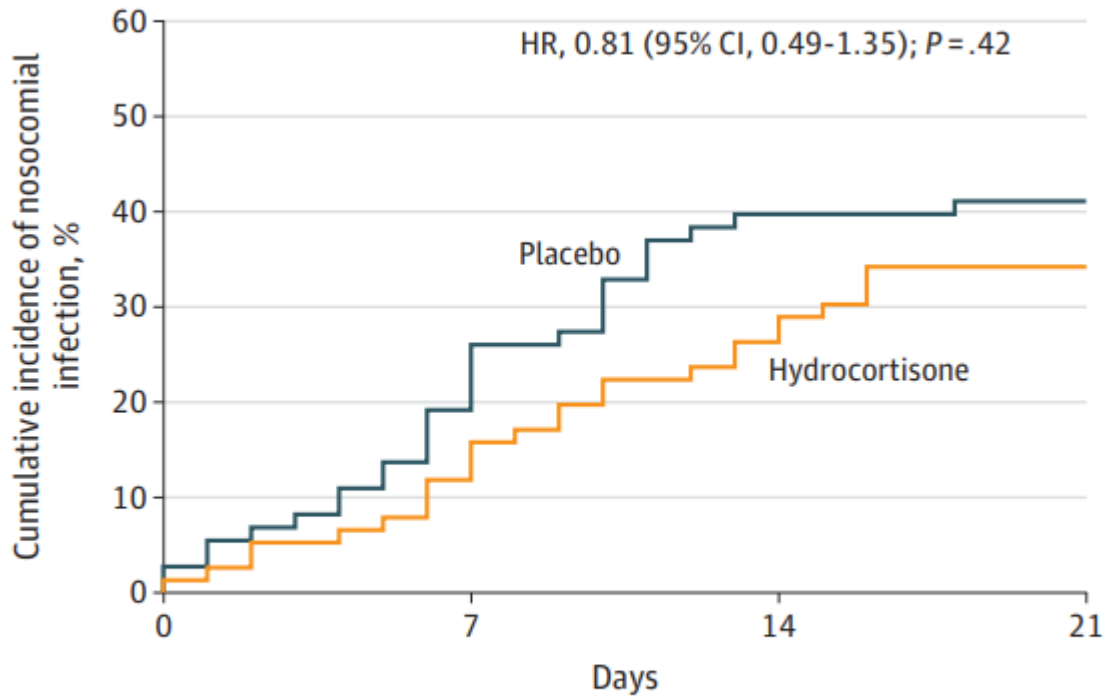


Daily evolution of Pa02:FIO2 ratio during the first week and on days 14 and 21 did not significantly differ between the groups (P = .37)



On day 28, 58 patients (38.9%) had at least 1 episode of nosocomial infection, 28 of 75 (37.3%) in the hydrocortisone group vs 30 of 73 (41.1%) in the placebo group

Figure 2. Nosocomial Infections Cumulative Incidence



No. at risk				
Hydrocortisone	76	52	23	12
Placebo	73	53	15	6

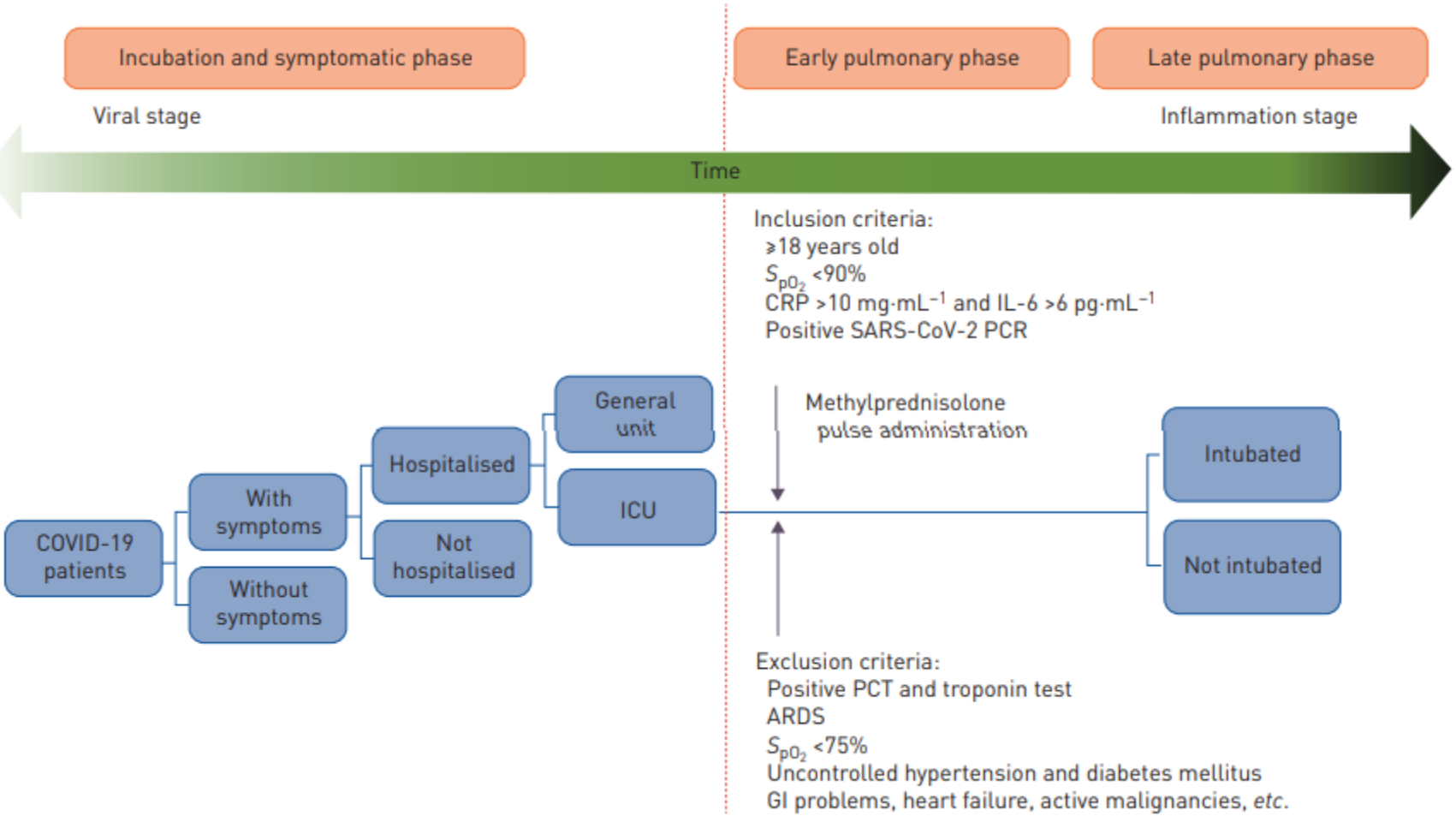
ORIGINAL ARTICLE
PULMONARY INFECTIONS

Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial

Maryam Edalatifard[1,17], Maryam Akhtari[2,3,17], Mohammadreza Salehi[4], Zohre Naderi[5], Ahmadreza Jamshidi[2,18], Shayan Mostafaei[6], Seyed Reza Najafizadeh[7], Elham Farhadi[2,3], Nooshin Jalili[8], Masoud Esfahani[9], Besharat Rahimi[1], Hossein Kazemzadeh[1], Maedeh Mahmoodi Aliabadi[10], Tooba Ghazanfari[11], Mohammadreza Sattarian[12], Hourvash Ebrahimi Louyeh[13], Seyed Reza Raeeskarami[14], Saeidreza Jamalimoghadamsiahkali[15], Nasim Khajavirad[16], Mahdi Mahmoudi[2,3,18] and Abdolrahman Rostamian[7,18]

Eur Respir J 2020; 56: 2002808

- a single-blind, randomized controlled clinical trial involving severe hospitalized patients with confirmed COVID-19 at the early pulmonary phase of the illness in Iran
- The patients were randomly allocated in a 1:1 ratio by the block randomization method to receive standard care with methylprednisolone pulse (intravenous injection, 250 mg·day−1 for 3 days) or standard care alone
- The study end-point was the time of clinical improvement or death, whichever came first. Primary and safety analysis was done in the intention-to-treat (ITT) population.



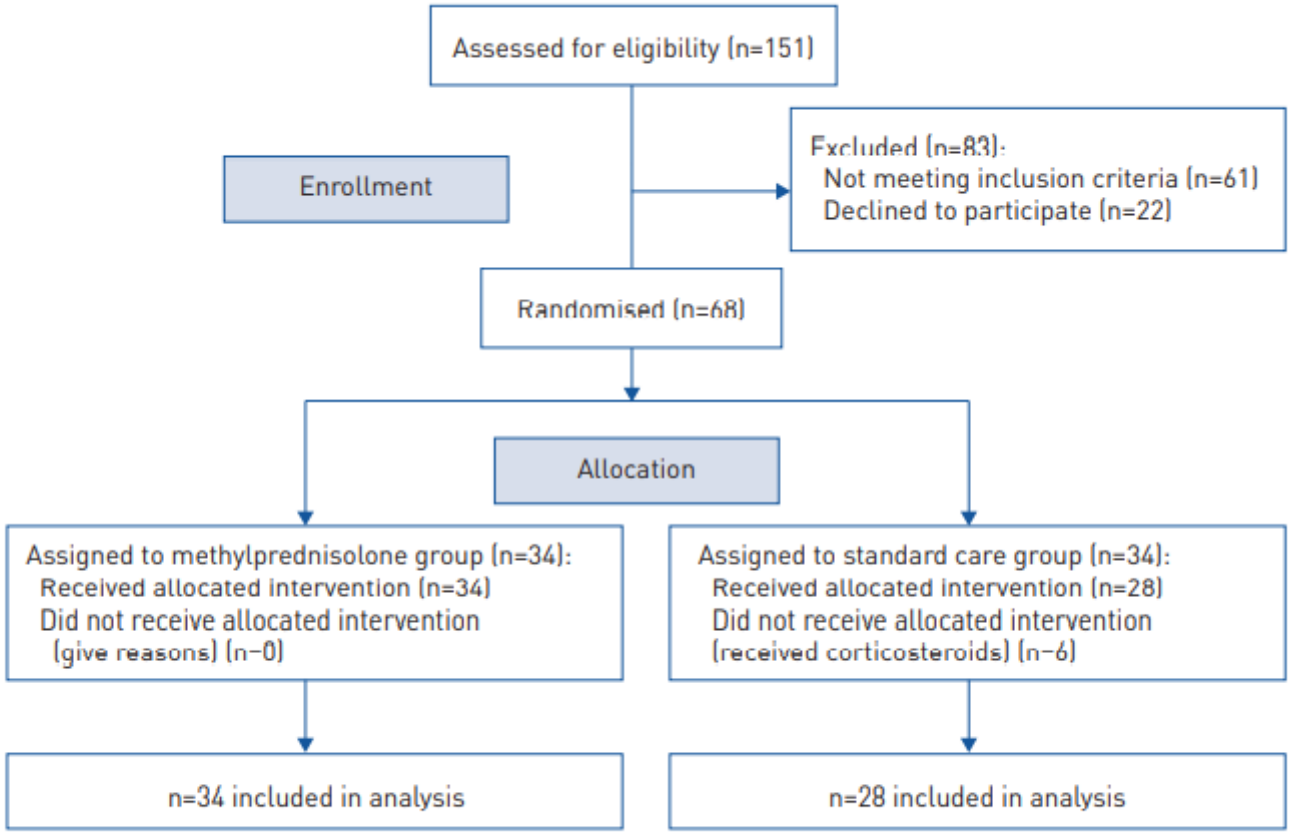


FIGURE 2 Randomisation, enrolment and treatment assignment.

TABLE 3 Primary outcomes in the methylprednisolone and standard care groups

	Methylprednisolone	Standard care	p-value
Subjects	34	28	
Time to event (discharge or death) days#	11.62±4.81	17.61±9.84	0.006*
Time to improvement days#	11.84±4.88	16.44±6.93	0.011*
Outcome			<0.001*
Recovery	32 (94.1)	16 (57.1)	
Death	2 (5.9)	12 (42.9)	

Data are presented as n or n (%), unless otherwise stated. #: median±range. *: p<0.05.

Research

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Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

	DEXA-COVID 19		CoDEX		RECOVERY		CAPE COVID		COVID STEROID		REMAP-CAP[a]		Steroids-SARI[b]	
	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid
Patients randomized by June 9, 2020	7	12	128	128	324	683	76	73	15	14	105	92	24	23
Age, median (IQR), y	62 (48-68)	60 (52-69)	62 (50-70)	64 (57-73)	59 (52-66)	60 (52-68)	63 (52-71)	66 (54-73)	57 (52-75)	62 (55-71)	59 (53-68)	62 (50-72)	67 (61-74)	62 (54-68)
Female sex, No. (%)	3 (42.9)	3 (25)	47 (36.7)	44 (34.4)	91 (28.1)	182 (26.6)	22 (28.9)	23 (31.5)	2 (13.3)	4 (28.6)	30 (28.6)	25 (27.2)	7 (29)	5 (22)
PCR-confirmed SARS-CoV-2 infection, No. (%)	7 (100)	12 (100)	120 (93.8)	122 (95.3)	301 (92.9)	647 (94.7)	72 (94.7)	72 (98.6)	15 (100)	14 (100)	80 (76.2)	75 (81.5)	24 (100)	23 (100)
Treatments at randomization, No. (%)														
Mechanical ventilation	7 (100)	12 (100)	128 (100)	128 (100)	324 (100)	683 (100)	62 (81.6)	59 (80.8)	7 (46.7)	8 (57.1)	68 (64.8)	49 (53.3)	13 (54)	14 (61)
Vasoactive	3 (42.9)	7 (58.3)	83 (65.4)	88 (68.8)	Not recorded	Not recorded	18 (23.7)	13 (17.8)	5 (33.3)	5 (35.7)	46 (43.8)	27 (29.3)	14 (58)	18 (78)
Any antiviral[c]	6 (86)	10 (83)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	24 (100)	23 (100)
Remdesivir	Not recorded	Not recorded	0	0	1 (0.3)	0	1 (1.3)	0	0	4 (28.6)	1 (1.0)	0	Not recorded	Not recorded
Lopinavir or ritonavir	Not recorded	Not recorded	0	1 (0.8)	0	0	8 (10.5)	9 (12.3)	0	0	0	2 (2.2)	Not recorded	Not recorded
Favipravir	Not recorded	Not recorded	0	0	0	0	0	0	0	0	0	0	Not recorded	Not recorded
Hydroxychloroquine	7 (100)	12 (100)	30 (23.4)	22 (17.2)	0	0	29 (38.2)	32 (43.8)	1 (6.7)	0	5 (4.8)	2 (2.2)	0	0
Azithromycin	0	0	83 (64.8)	81 (63.3)	59 (18.2)	81 (11.9)	19 (25.0)	24 (32.9)	Not recorded	Not recorded	9 (8.6)	6 (6.5)	Not recorded	Not recorded
Convalescent plasma	0	0	Not recorded	Not recorded	0	0	0	0	0	2 (14.3)	0	0	Not recorded	Not recorded

The analysis included 1,703 critically ill patients with COVID-19 who were participants in trials conducted in 12 countries from February 26 to June 9, 2020.

The median age of the patients was 60 years (IQR 52–68 years); 488 (28.7%) were women

Overall, 1,559 of the patients (91.5%) were on mechanical ventilation

Table 1. Characteristics of Included Trials

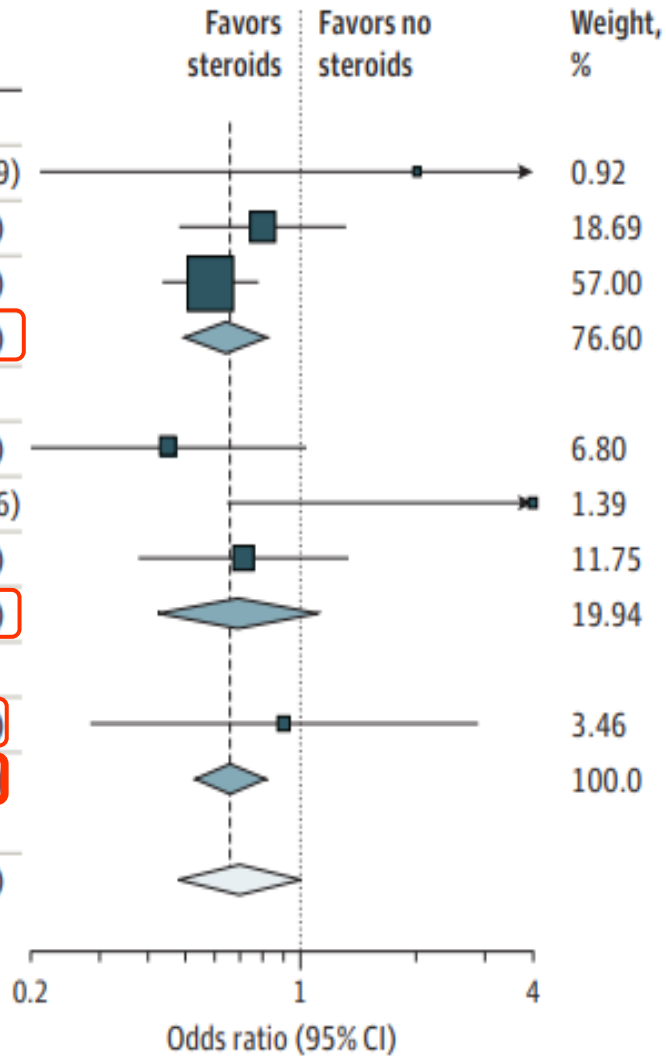
	DEXA-COVID 19	CoDEX	RECOVERY	CAPE COVID	COVID STEROID	REMAP-CAP	Steroids-SARI[a]
ClinicalTrials.gov identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned sample size	200	350	NA	290	1000	NA[b]	80
Eligibility criteria	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[a] • Confirmed COVID-19	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[a] • Onset of ARDS <48 h before randomization • Probable or confirmed COVID-19	Criteria[c] used for this meta-analysis: Intubation Suspected or confirmed COVID-19	• Minimal severity • Admitted to ICU or intermediate care unit • Oxygen (≥6 L/min) • Probable or confirmed COVID-19	• Oxygen (≥10 L/min) • Confirmed COVID-19	• Admitted to ICU receiving high-flow nasal oxygen with Fio_2 ≥0.4 at ≥30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors • Probable or confirmed COVID-19	• Admitted to ICU with Pao_2:Fio_2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min • Confirmed COVID-19
Corticosteroid							
Drug name	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone
Dosage and administration	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	6 mg/d orally or intravenously	Continuous intravenous infusion × 8 d or 14 d (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d)	200 mg/d intravenously × 7 d (continuous or bolus dosing every 6 h)	50 mg intravenously every 6 h × 7 d[d]	40 mg intravenously every 12 h × 5 d
Dose classification	High	High	Low	Low	Low	Low	High
Control intervention	Usual care	Usual care	Usual care	Placebo	Placebo	Usual care	Usual care
Primary outcome	60-d mortality	Ventilator-free days	28-d mortality	21-d treatment failure (death or persistent requirement for mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at 28 d	Composite of hospital mortality and ICU organ support-free days to 21 d	Lower lung injury score at 7 d and 14 d
Mortality outcome, d	28	28	28	21	28	28	30
Serious adverse event definitions	• Secondary infections of pneumonia, sepsis, or other similar • Pulmonary embolism	• Mortality • Infections • Insulin use	• Cause-specific mortality • Ventilation • Dialysis • Cardiac arrhythmia (in a subset) • Other that were believed to be related to study treatment	• Any • Excluded some listed in protocol • Excluded expected adverse events related to the patient's disease or comorbidity	• New episodes of septic shock (Sepsis-3 criteria) • Invasive fungal infection • Clinically important gastrointestinal bleeding • Anaphylaxis	• Per ICH good clinical practice guidelines (events not already captured as a trial end point; eg, mortality) • When the event may reasonably have occurred because of study participation	• Secondary bacterial infections • Barotrauma • Severe hyperglycemia • Gastrointestinal bleeding requiring transfusion • Acquired weakness
Location	Spain	Brazil	UK	France	Denmark	Australia, Canada, European Union, New Zealand, UK, US	China

Across the studies, 678 patients received corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone), and 1,025 received usual care or placebo.

Mortality was assessed at 28 days (five trials), 21 days (one trial), and 30 days (one trial).

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



- Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo.
- CONCLUSIONS AND RELEVANCE: In this prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

WHO Recommendation

Recommendation 1

We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation).

Recommendation 2

We suggest not to use systemic corticosteroids in the treatment of patients with non-severe COVID-19 (conditional recommendation).

- It is likely that the beneficial effect of glucocorticoids in severe viral respiratory infections is dependent on a selection of the
- Right dose
- Right time
- Right patient

High doses may be more harmful than helpful, as may such treatment given at a time when control of viral replication is paramount and inflammation is minimal.

Corticosteroid Equivalency

Compound	Equivalent Dose	Anti-inflammatory Potency	Mineralocorticoid Potency	Biological Half-life
Cortisone	250 mg	0.8	0.8	Short
Hydrocortisone	200 mg	1	1	Short
Prednisone	50 mg	4	0.6	Intermediate
Prednisolone	50 mg	4	0.6	Intermediate
Triamcinolone	40 mg	5	0	Intermediate
Methylprednisolone	40 mg	5	0.25	Intermediate
Betamethasone	8 mg	25	0	Long
Dexamethasone	8 mg	25	0	Long
Fludrocortisone	-	0	125	Intermediate

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, tuberculosis).
- The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well-defined. When initiating dexamethasone, appropriate screening and treatment to reduce the risk of Strongyloides hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities) or fulminant reactivations of HBV should be considered.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen to assess potential interactions.
- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.

Considerations in Pregnancy

- A short course of betamethasone and dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.
- Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for a short course of dexamethasone therapy, the Panel recommends using dexamethasone in hospitalized pregnant women with COVID-19 who are mechanically ventilated (AIII) or who require supplemental oxygen but who are not mechanically ventilated (BIII).

Clinically important questions

- Do the benefit and optimal dosing of corticosteroids differ between different ARDS subphenotypes?
- Should corticosteroid administration be individualized, with initiation, dosing, and duration guided by clinical response or biomarkers, such as C-reactive protein?
- Does inflammation rebound after cessation of corticosteroids in some patients and would tapering them improve outcomes?
- What are the true incidence and optimal management of adverse effects?

Clinically important questions

- Should less severely ill or nonhospitalized patients be treated with corticosteroids?
- What is the threshold of illness severity at which corticosteroids are now indicated?
- Do corticosteroids delay clearance of SARS-CoV-2, especially in less ill patients not hospitalized, and if so, does this affect clinical outcomes?
- Should remdesivir or other potentially active therapeutics be administered with corticosteroids?

Thank You for Your Attention

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COVID-19