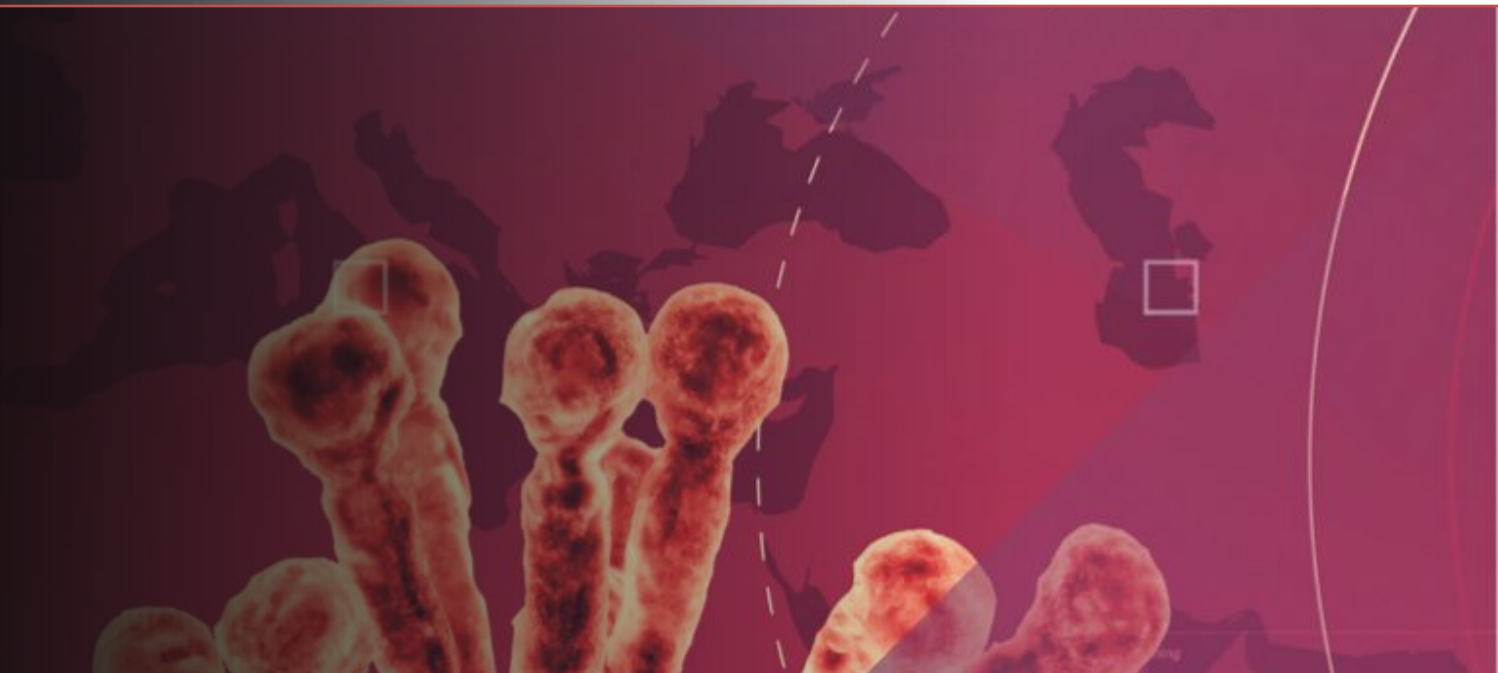
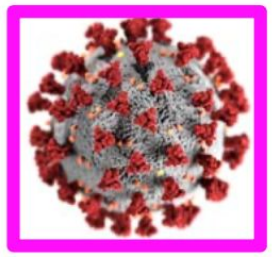
La terapia della fase infiammatoria: ruolo attuale degli steroidi e dei farmaci ad azione anticitochinica

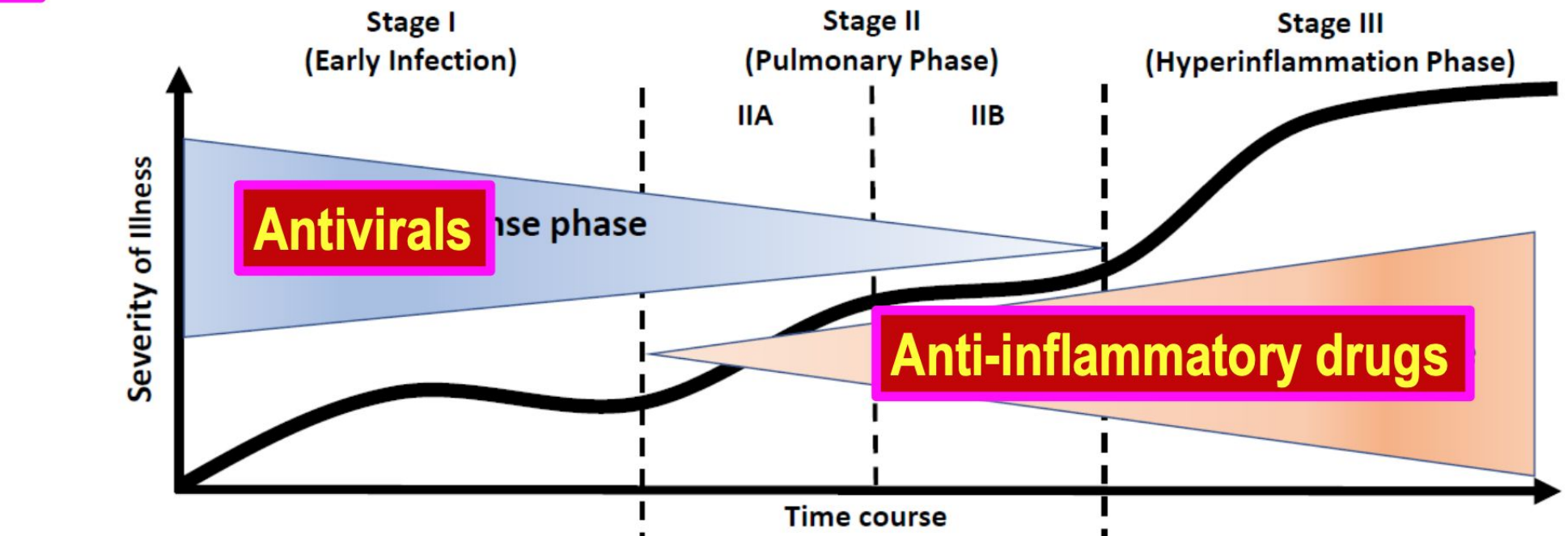
UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Cristina Mussini





Classification of COVID-19 Disease Stages



Clinical Symptoms	Mild constitutional symptoms Fever >99.6˚F Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO2/FiO2≤300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

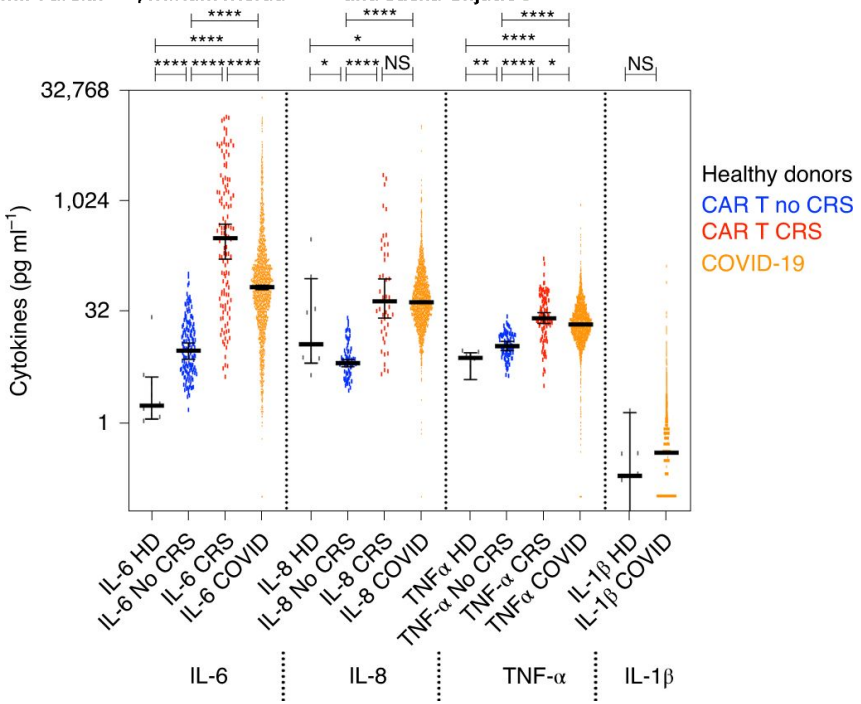
Siddiqu HK, Mehra MR. J Heart Lung Transplant. March 25th 2020 doi: 10.1016/j.healun.2020.03.012

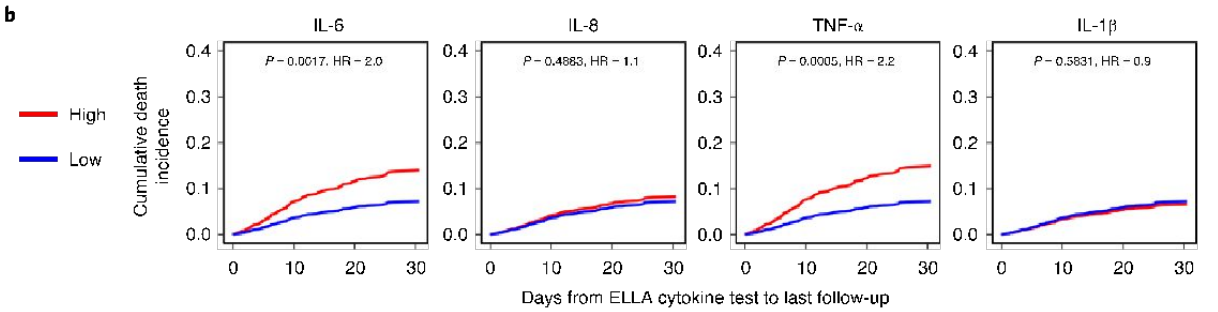
Markers of inflammation as prognostic factors for mechanical ventilation and death in COVID-19

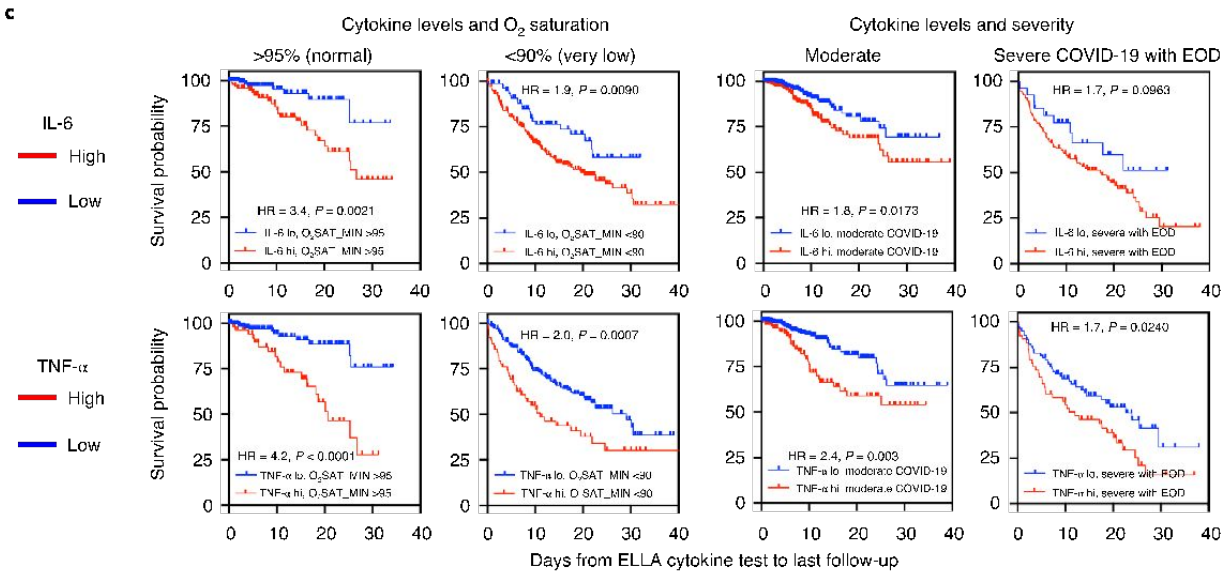
ARTICLES
https://doi.org/10.1038/s41591-020-1051-9
nature medicine
Check for updates

An inflammatory cytokine signature predicts COVID-19 severity and survival

Diane Marie Del Valle[1,2,3,14], Seunghee Kim-Schulze[1,2,3,4,14], Hsin-Hui Huang[5,6,7,14], Noam D. Beckmann[8], Sharon Nirenberg[8,9], Bo Wang[10], Yonit Lavin[10], Talia H. Swartz[10], Deepu Madduri[10], Aryeh Stock[11], Thomas U. Marron[2,3,10], Hui Xie[1], Manishkumar Patel[1], Kevin Tuballes[1], Oliver Van Oekelen[8], Adeeb Rahman[1,2,3,8], Patricia Kovatch[8,9], Judith A. Aberg[10], Eric Schadt[8], Sundar Jagannath[10], Madhu Mazumdar[5,6,7], Alexander W. Charney[8], Adolfo Firpo-Betancourt[11], Damodara Rao Mendu[11], Jeffrey Jhang[11], David Reich[12], Keith Sigel[10], Carlos Cordon-Cardo[11], Marc Feldmann[13], Samir Parekh[3,4,10], Miriam Merad[1,2,3,4,10] and Sacha Gnjatic[1,2,3,4,10,11] ✉







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

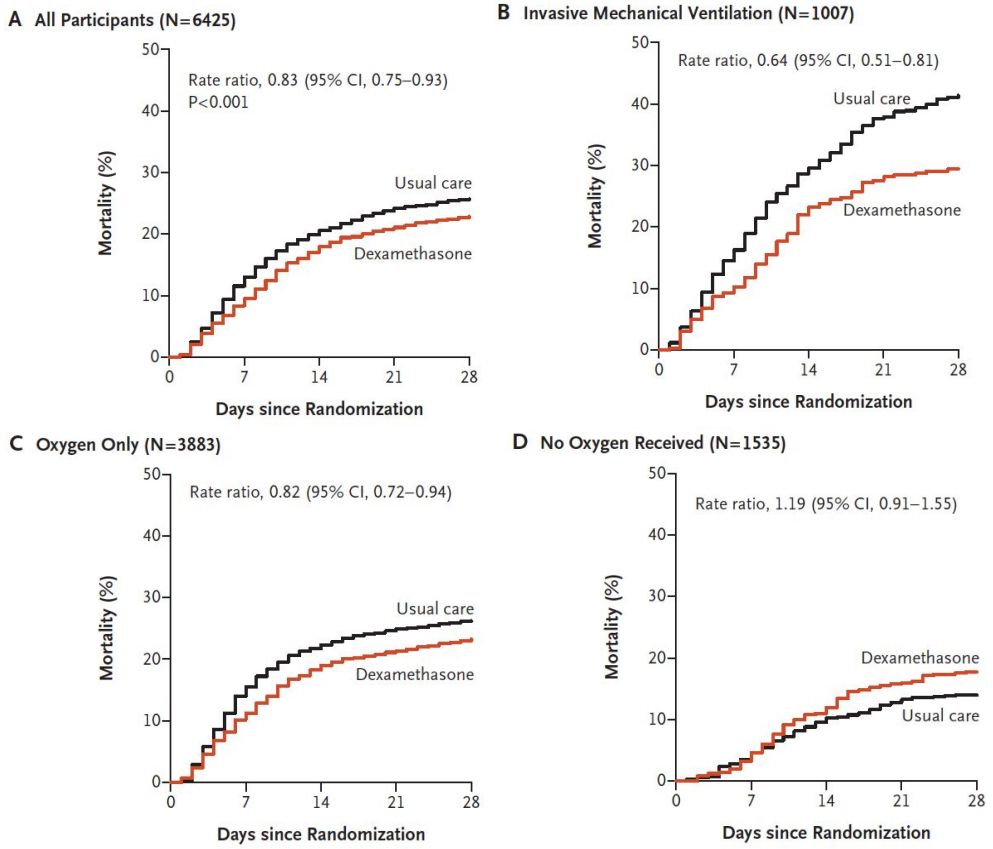
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

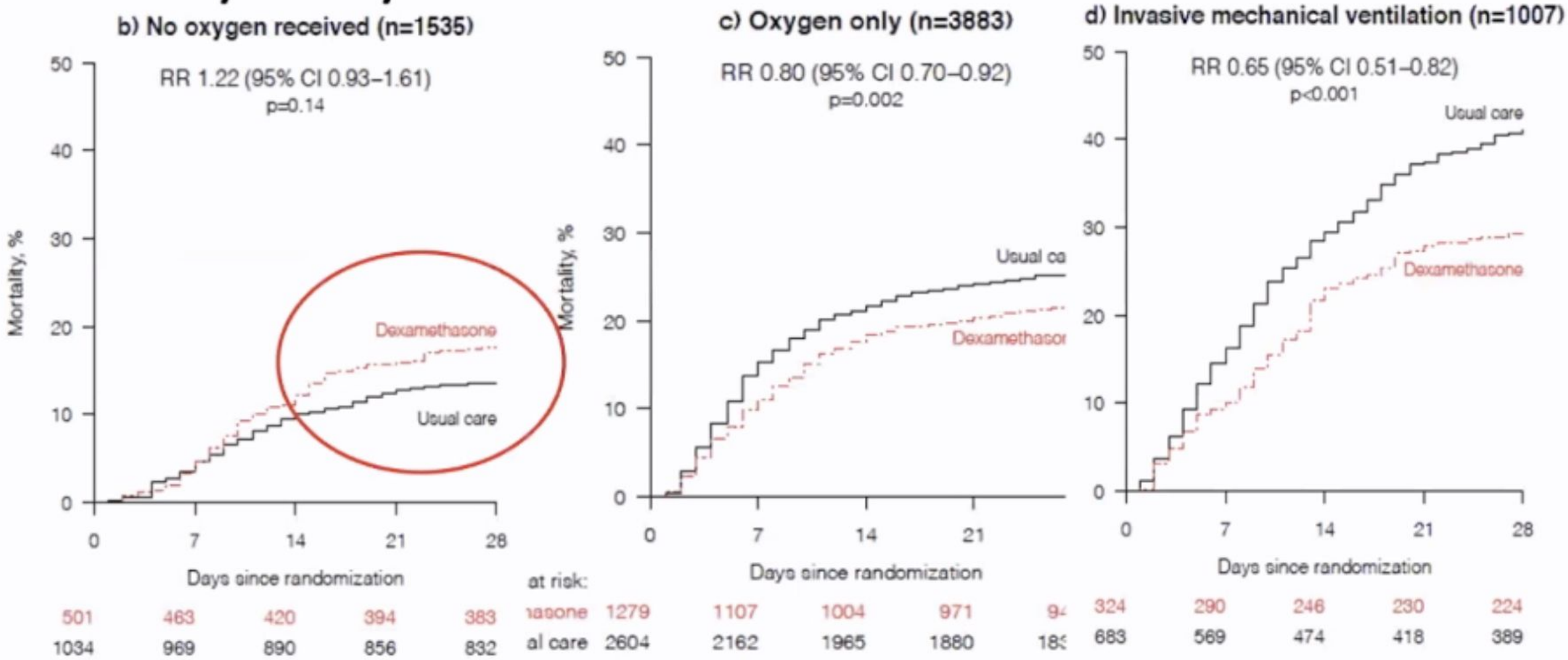
In this controlled, open-label trial were assigned to receive dexamethasone (2104) receive usual care (4321).

Oral or intravenous dexamethasone (at a dose of 6 mg once daily) was used for up to 10 days or to receive usual care alone.

The use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.



RECOVERY Dexamethasone – sub-group analysis by baseline clinical status



N Engl J Med, July 2020 DOI: 10.1056/NEJMoa2021436

Metabolic side-effects

Routine care data from 51 hospitals in France and Luxembourg to assess the effectiveness of corticosteroids at 0.8 mg/kg/day eq. prednisone (CTC group) versus standard of care (no-CTC group) among adults 18-80 years old with confirmed COVID-19 pneumonia requiring oxygen without mechanical ventilation.

Table 3
Adverse events (counted in the safety population, without weighting)

Adverse event	CTC group ($n = 283$)	No-CTC group ($n = 682$)	Difference (95%CI)
Any	53.0 (150)	46.0 (314)	7.0 (0.0–13.9)
Expected with corticosteroids:			
Infection (incl. ventilator-associated pneumonia) [a]	17.7 (50)	18.8 (128)	−1.1 (−6.4–4.2)
Bacterial	7.1 (20)	7.5 (51)	0.4 (−4.0–3.2)
Viral	0.7 (2)	0.7 (5)	0 (−1.2–1.1)
Fungal	1.1 (3)	0.7 (5)	0.3 (−1.0–1.7)
Undocumented [b]	9.5 (27)	9.5 (77)	−1.7 (−5.9–2.4)
Ventilator-associated pneumonia	6.0 (17)	8.9 (61)	−2.9 (−6.4–0.6)
Hyperglycaemia	22.6 (64)	12.6 (86)	10.0 (4.5–15.5)
Hypertension	10.6 (30)	11.1 (76)	−0.5 (−4.8–3.8)
Confusion or psychiatric manifestation	1.4 (4)	1.9 (13)	−0.5 (−2.2–1.2)
Atrial fibrillation	4.6 (13)	3.8 (26)	0.8 (−2.0–3.6)
Hypokalaemia or fluid overload	1.1 (3)	1.3 (9)	−0.3 (−1.7–1.2)
Other severe adverse events:			
Thromboembolic event (incl. pulmonary embolism)	2.8 (8)	3.5 (24)	−0.7 (−3.1–1.7)
Pulmonary embolism	2.1 (6)	2.6 (18)	−0.5 (−2.6–1.5)
Increased serum levels of aspartate aminotransferase	5.3 (15)	4.4 (30)	0.9 (−2.1–3.9)
Renal failure	2.5 (7)	2.6 (18)	−0.2 (−2.3–2.0)

Results are presented as % (absolute number).
[a] Total number of infections differs from the sum of subcategories because a patient may have had multiple infectious adverse events of different nature.
[b] Undocumented infections refer to clinical and biological presentations suggestive of an infectious episode without formal identification of a specific pathogen.

Tran V-T Clin Microbiol Infect 2021

Drug-drug interactions

Risks of potential drug–drug interactions in COVID-19 patients treated with corticosteroids: a single-center experience

D. Cattaneo[1,2] · L. Pasina[3] · F. Conti[4] · A. Giacomelli[4] · L. Oreni[4] · L. Pezzati[4] · C. Bonazzetti[4] · M. Piscaglia[4] · G. Carrozzo[4] · S. Antinori[4] · C. Gervasoni[1,4]

Seventy-five percent of the patients (*n* = 471) were treated with a corticosteroid, mainly dexamethasone (87%), prednisone (4%), beclomethasone (3%) or methylprednisolone (2%).
Potential DDIs with concomitant therapies (*n* = 781) were found in 345 out of the 471 patients (73%) on corticosteroids. No class D DDIs were recorded. Conversely, 25 and 756 class C and class B potential DDIs involving corticosteroids were, respectively, identified.

Table 1 Potential class C drug–drug interactions ($n=25$) in hospitalized COVID-19 patients treated with corticosteroids ($n=471$)

Potential adverse event	Interacting agent	*N* (%)
Reduction of the exposure and efficacy of caspofungin	Caspofungin	15 (60)
Reduction of the exposure and efficacy of voriconazole	Voriconazole	6 (24)
Increased risk of infections	Adalimumab	1 (4)
Increased risk of gastrointestinal adverse effects	Deferasirox	1 (4)
Reduction of exposure to efavirenz and/or corticosteroids	Efavirenz	1 (4)
Increased risk of gastrointestinal adverse effects	Ketorolac	1 (4)

Table 2 Potential class B drug–drug interactions ($n=756$) in hospitalized COVID-19 patients treated with corticosteroids ($n=471$)

Potential adverse event/interacting agents	*N* (%)
Antagonism of the action of antihypertensive drugs	267 (35%)
Beta-blockers	110
ACE inhibitors	82
Angiotensin II receptor antagonists	50
Alpha 1 blockers	15
Calcium channel blockers	7
Diuretics	3
Hypokalemia (lethargy, asthenia, arrhythmias)	139 (18%)
Diuretics	105
Beta agonists	34
Bleeding	130 (17%)
Acetylsalicylic acid	116
Vitamin K inhibitors	14
Reduced exposure and efficacy of remdesivir	97 (13%)
Reduced exposure and efficacy of hypoglycemic agents	81 (11%)
Metformin	65
Glinides	9
Incretin mimetics	7
Increased risk of tendon rupture	15 (2%)
Fluoroquinolones	15
Others	27 (4%)
Quetiapine	16
Antiepileptic drugs	6
Others	5

J Endocrinol Invest 2021

Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes

Judith van Paassen[1], Jeroen S. Vos[1], Eva M. Hoekstra[2], Katinka M. I. Neumann[2], Pauline C. Boot[2] and Sesmu M. Arbous[1,3*]

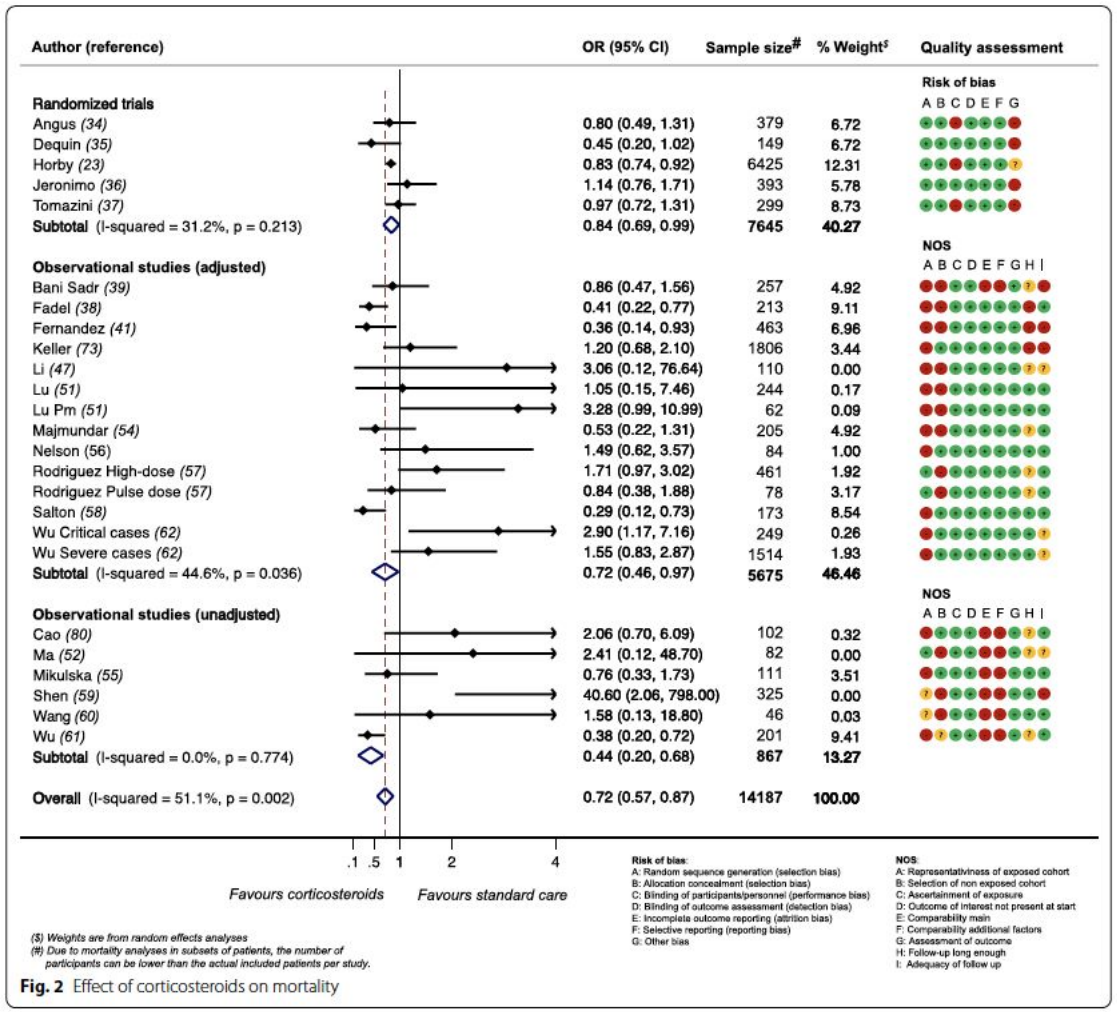


Fig. 2 Effect of corticosteroids on mortality

Abstract

Background: In the current SARS-CoV-2 pandemic, there has been worldwide debate on the use of corticosteroids in COVID-19. In the recent RECOVERY trial, evaluating the effect of dexamethasone, a reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation was shown. Their results have led to considering amendments in guidelines or actually already recommending corticosteroids in COVID-19. However, the effectiveness and safety of corticosteroids still remain uncertain, and reliable data to further shed light on the benefit and harm are needed.

Objectives: The aim of this systematic review and meta-analysis was to evaluate the effectiveness and safety of corticosteroids in COVID-19.

Methods: A systematic literature search of RCTS and observational studies on adult patients was performed across Medline/PubMed, Embase and Web of Science from December 1, 2019, until October 1, 2020, according to the PRISMA guidelines. Primary outcomes were short-term mortality and viral clearance (based on RT-PCR in respiratory specimens). Secondary outcomes were: need for mechanical ventilation, need for other oxygen therapy, length of hospital stay and secondary infections.

Results: Forty-four studies were included, covering 20.197 patients. In twenty-two studies, the effect of corticosteroid use on mortality was quantified. The overall pooled estimate (observational studies and RCTs) showed a significant reduced mortality in the corticosteroid group (OR 0.72 (95%CI 0.57–0.87). Furthermore, viral clearance time ranged from 10 to 29 days in the corticosteroid group and from 8 to 24 days in the standard of care group. Fourteen studies reported a positive effect of corticosteroids on need for and duration of mechanical ventilation. A trend toward more infections and antibiotic use was present.

Conclusions: Our findings from both observational studies and RCTs confirm a beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation. And although data in the studies were too sparse to draw any firm conclusions, there might be a signal of delayed viral clearance and an increase in secondary infections.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, Corticosteroids, Mortality, Viral clearance, Mechanical ventilation

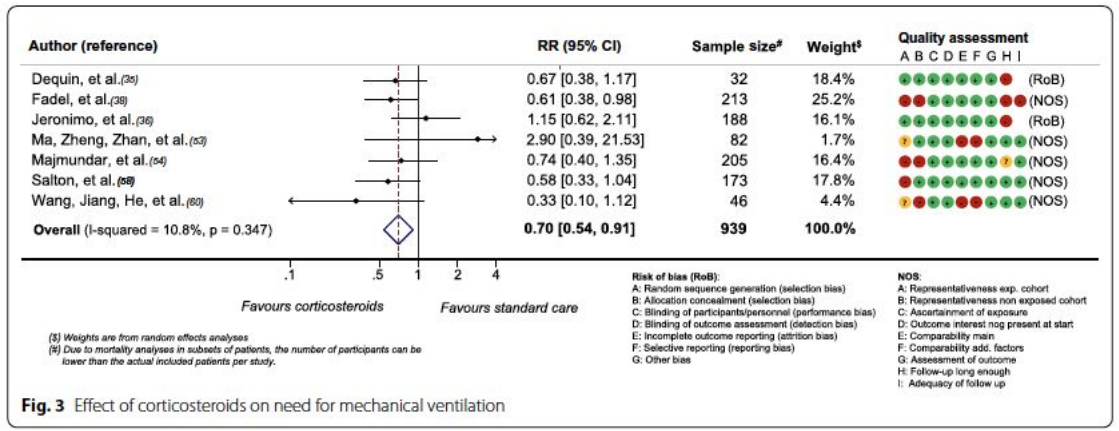


Fig. 3 Effect of corticosteroids on need for mechanical ventilation

IL-1 receptor blockade with anakinra for COVID-19 (1)

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

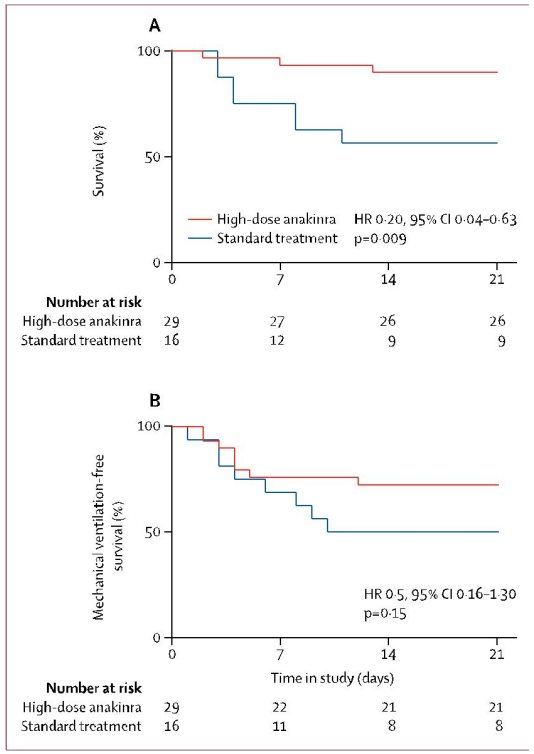
Cavalli G, De Luca G, Campochiaro C, et al.

The Lancet Rheumatology, 2020

	Day 0		Day 21	
	Standard treatment	High-dose anakinra	Standard treatment	High-dose anakinra
Discharged from hospital with resumption of normal activities (1)	0	0	7 (44%)	13 (45%)
Discharged from hospital but unable to resume normal activities (2)	0	0	0	0
Hospitalised, not requiring supplemental oxygen (3)	0	0	0	3 (10%)
Hospitalised, requiring supplemental oxygen (4)	0	0	1 (6%)	3 (10%)
Hospitalised, requiring non-invasive mechanical ventilation, high-flow supplemental oxygen, or both (5)	16 (100%)	29 (100%)	0	2 (7%)
PaO_2:FiO_2 >200 mm Hg	0	0	0	2
PaO_2:FiO_2 100–200 mm Hg (moderate ARDS)	7	4	0	0
PaO_2:FiO_2 <100 mm Hg (severe ARDS)	9	25	0	0
Hospitalised, requiring invasive mechanical ventilation (6)	0	0	1 (6%)	5 (17%)
Death (7)	0	0	7 (44%)	3 (10%)

Data are n (%). Clinical status was graded on a 7-point scale at the time of treatment initiation (day 0) and after 21 days. PaO_2=partial pressure of oxygen in arterial blood. FiO_2=fractional concentration of oxygen in inspired air. ARDS=acute respiratory distress syndrome.

Table 3: **Assessment of clinical status in patients receiving standard treatment (n=16) and high-dose anakinra (n=29)**



IL-1 receptor blockade with anakinra for COVID-19 (3)

Anakinra for severe forms of COVID-19: a cohort study

Huet T, Beaussier H, Voisin O, et al.

The Lancet Rheumatology, 2020

Anakinra combined with methylprednisolone in patients with severe COVID-19 and hyperinflammation: an observational cohort study.

Bozzi G, Mangioni D, Minoia F, et al.

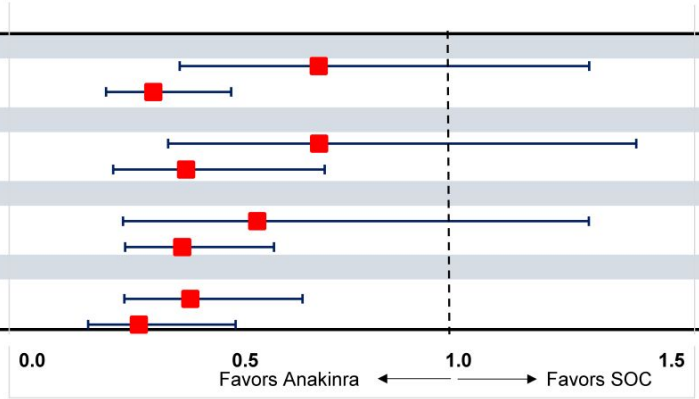
Journal of Allergy and Clinical Immunology, 2021

Effect of anakinra on mortality in COVID-19: a patient level meta-analysis

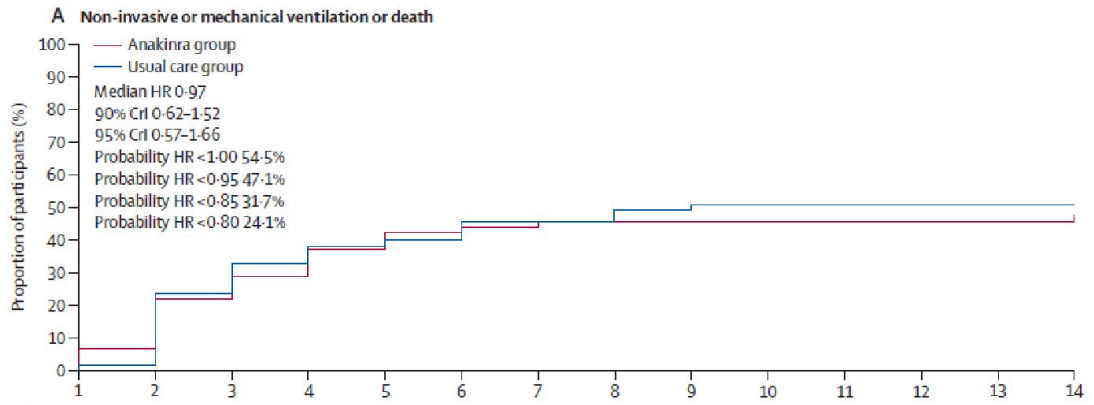
Kyriazopoulou E, Huet T, Cavalli G et al.

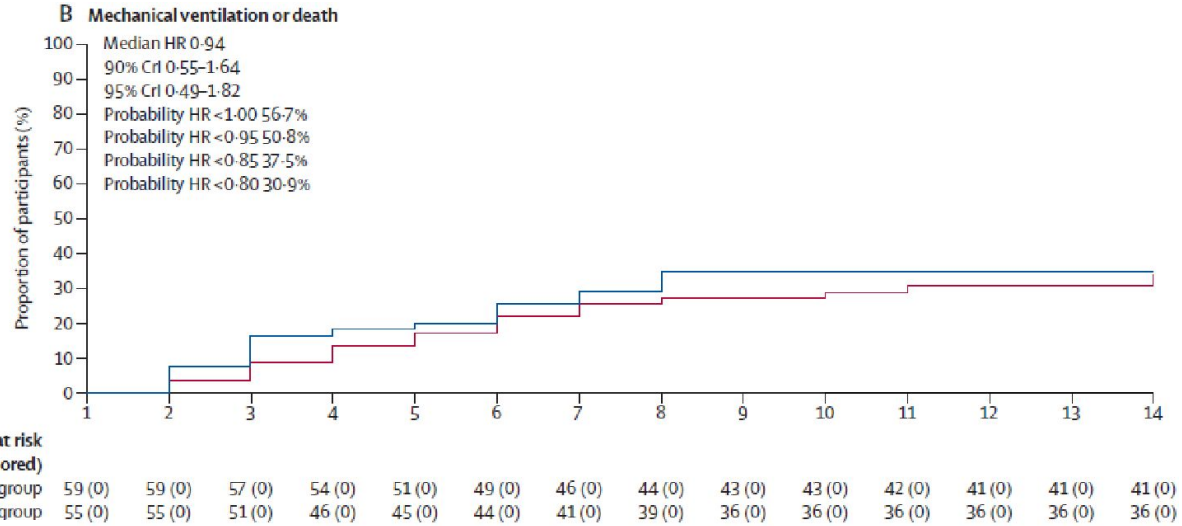
The Lancet Rheumatology, 2021 (in press)

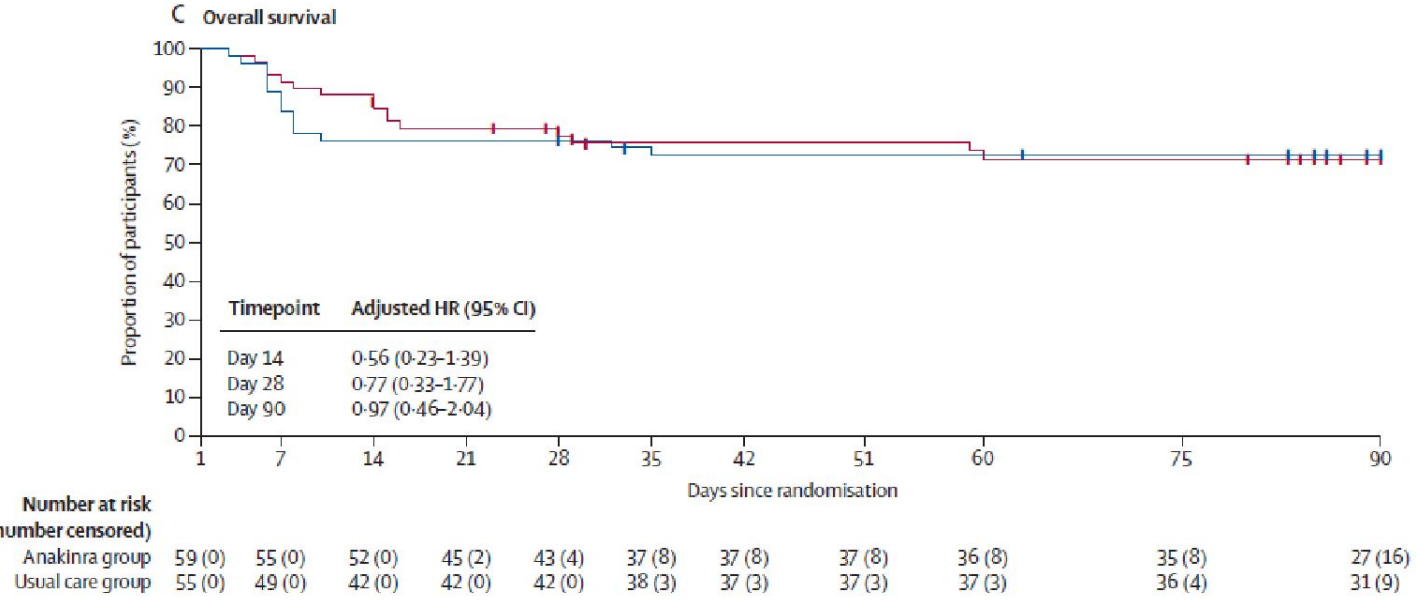
Variable	Mortality rate in % (n/N) SOC	Anakinra	OR (95% CI)	p for interaction
CRP (mg/L)				0.04
≤ 100	16.1 (30/186)	11.5 (15/131)	0.67 (0.35-1.31)	
> 100	29.4 (107/364)	10.6 (22/208)	0.28 (0.17-0.47)	
Ferritin (ng/ml)				0.21
≤ 1000	15.5 (17/110)	10.9 (15/137)	0.67 (0.32-1.42)	
> 1000	30.7 (31/101)	13.8 (19/138)	0.36 (0.19-0.69)	
CCI				0.44
≤ 2	8.2 (17/208)	4.5 (4/156)	0.53 (0.21-1.31)	
>2	37.8 (112/296)	17.6 (27/153)	0.35 (0.22-0.57)	
Respiratory ratio				0.36
≥ 100	20.6 (72/350)	8.8 (19/217)	0.37 (0.22-0.63)	
< 100	44.2 (42/95)	16.5 (18/109)	0.25 (0.13-0.48)	



Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial







Anakinra did not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia. Further studies are needed to assess the efficacy of anakinra in other selected groups of patients with more severe COVID-19.

Lancet Respir Med 2021, January 22, 2021

Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis

	Anakinra		Control		Weight	Odds ratio (95% CI)
	Events	Total	Events	Total		
Balkhair et al (2021)[30]	13	45	11	24	8·0%	0·48 (0·17–1·34)
Bozzi et al (2021)[25]	9	65	19	55	13·9%	0·30 (0·12–0·75)
Cauchois et al (2020)[22]	0	12	1	10	0·9%	0·07 (0·00–46·88)
Cavalli et al (2021)[26]	3	62	62	275	17·0%	0·17 (0·05–0·58)
Huet et al (2020)[23]	7	52	19	44	13·9%	0·20 (0·08–0·55)
Kooistra et al (2020)[28]	4	21	7	39	3·1%	1·08 (0·28–4·20)
Kyriazopoulou et al (2021)[29]	15	130	29	130	20·1%	0·45 (0·23–0·90)
The CORIMUNO-19 Collaborative group (2021)[24]	13	59	13	55	8·2%	0·91 (0·38–2·19)
Pontali et al (2021)[27]	9	63	19	44	15·0%	0·22 (0·09–0·55)
Total (95% CI)		509		676	100·0%	0·37 (0·27–0·51)

Heterogeneity: τ^2= 0·2966; χ^2=11·52, df=8 (p=0·17); I^2=31%

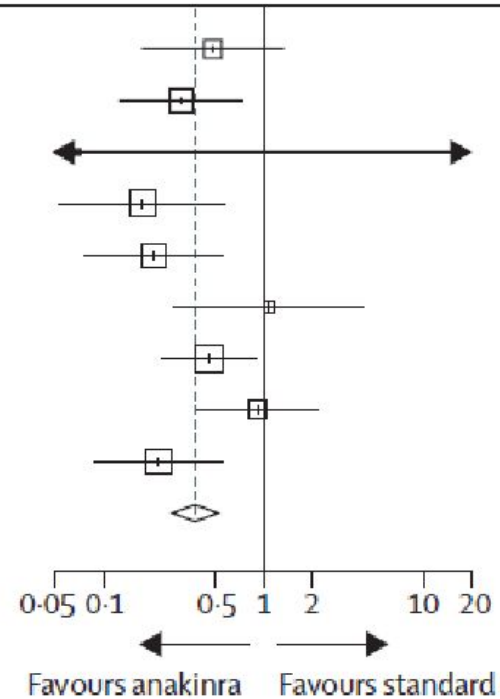
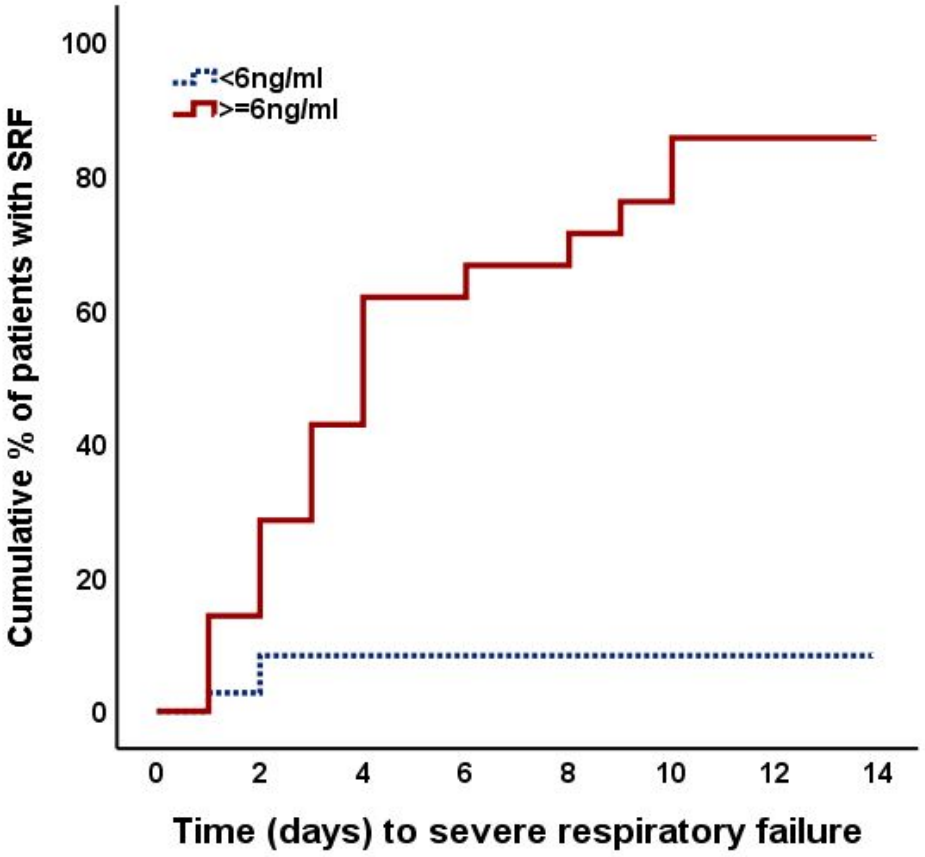


Figure 2: Forest plot showing mortality from aggregate data meta-analysis

Admission suPAR ≥6ng/mL may predict severe respiratory failure in patients with COVID-19 pneumonia



Cox regression analysis (57 patients from Greece)

(gender, co-morbidities, suPAR, neutrophils, CRP)

	HR (95%CIs)	p-value
Male gender	7.80 (1.75-34.76)	0.007
suPAR≥ 6ng/ml	16.43 (4.56-59.19)	<0.0001

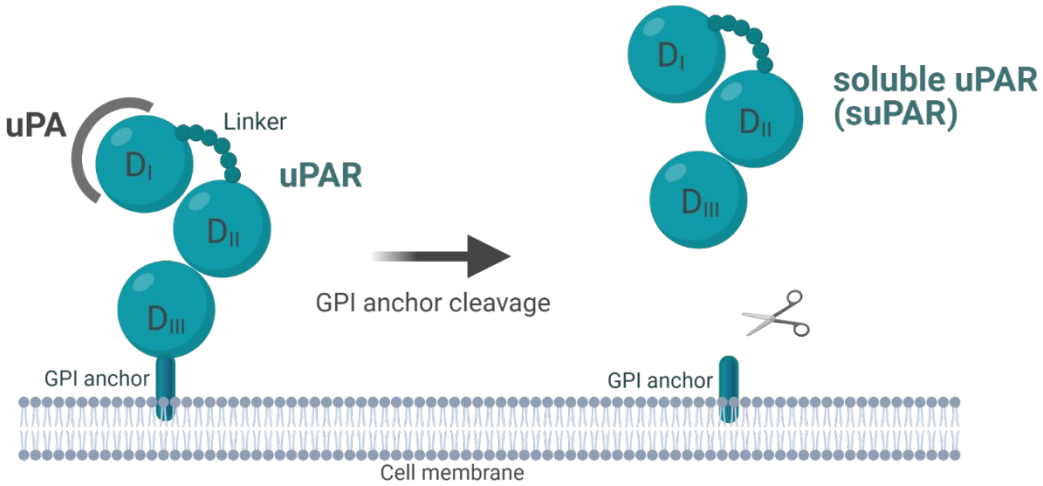
- CE-IVD approved
- Point-of-Care test for patient triaging (25 minutes)
- Roche Diagnostics Cobas c501/2 and c701/2 system; Siemens ADVIA Chemistry XPT system; & Abbott Architect c system

Rovina et al. Crit Care 2020.

What is suPAR?

suPAR - soluble **u**rokinase **p**lasminogen **a**ctivator **r**eceptor[1,2,3]

- Results from the **cleavage and release of membrane-bound uPAR** (expressed on **endothelial cells, smooth muscle cells and immune cells**) following activation of the kallikrein system
- Concentration correlates positively to the **activation level of the immune system** and **inflammation**
- Present in plasma, urine, blood, serum, and cerebrospinal fluid



Why measure suPAR?

- suPAR is elevated in numerous pathological conditions[2,3]
- suPAR is a biomarker of disease progression and may predict increased risk of mortality[4,5]
- suPAR is a potential new biomarker of COVID-19 progression[6,7]

1. Clinicaltrials.gov NCT04357366. 2. Virogates/What is suPAR. 3. Lin *et al. Exp & Mol Med* 2020 4. Velissaris D, Infect Dis Ther 2020. 5. Rasmussen et al. Emerg Med J. 2016. 6. Drug Discov Today 2020. 7. Rovina et al. Critical Care (2020)

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

nature medicine

Background In a previous open-label trial early anakinra treatment guided by elevated soluble urokinase plasminogen activator receptor (suPAR) prevented progression of COVID-19 pneumonia into respiratory failure.

Methods In the SAVE-MORE multicenter trial, hospitalized patients with moderate and severe COVID-19 pneumonia and plasma suPAR 6 ng/ml or more and receiving standard-of-care (SoC) were 1:2 randomized to subcutaneous treatment with placebo or 100mg anakinra once daily for 10 days. The primary endpoint was the 11-point World Health Organization ordinal Clinical Performance Scale (WHO-CPS) by day 28. The changes of the WHO-CPS and of the sequential organ failure assessment (SOFA) score were the main secondary endpoints. The trial was designed following advice by the COVID-ETF of the European Medicines Agency.

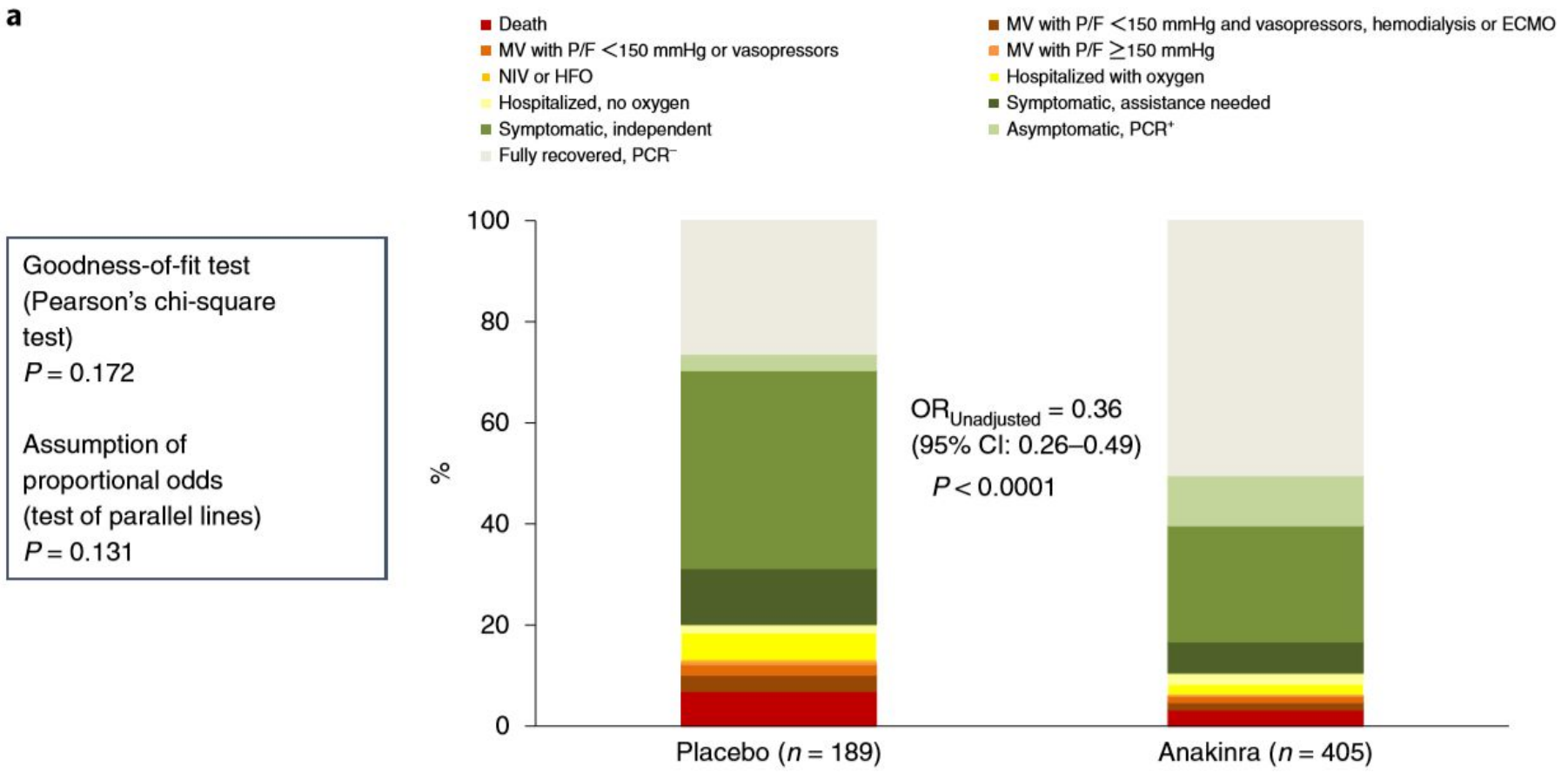
Results Anakinra-treated patients were allocated to significantly lower strata of disease severity by day 28 (adjusted odds ratio-OR 0.36; 95%CI 0.26-0.50; P<0.0001). Significantly lower disposition into severe disease or death (6 or more points of WHO-CPS) was found (OR: 0.46; P: 0.01). The median absolute changes of WHO-CPS in the placebo and anakinra groups from baseline was -3 and -4 at day 28 (OR 0.40; P<0.0001); and -2 and -3 at day 14 (OR 0.63; P: 0.003); the absolute change of SOFA score was 0 and -1 (OR 0.63; P: 0.004). Hospital stay was shorter.

Conclusions Early start of anakinra treatment guided by suPAR is leading to 64% global improvement in moderate and severe COVID-19 pneumonia .

(Sponsored by the Hellenic Institute for the Study of Sepsis ClinicalTrials.gov identifier, NCT04680949) Consider adding the mortality benefit and the shorter ICU stay.

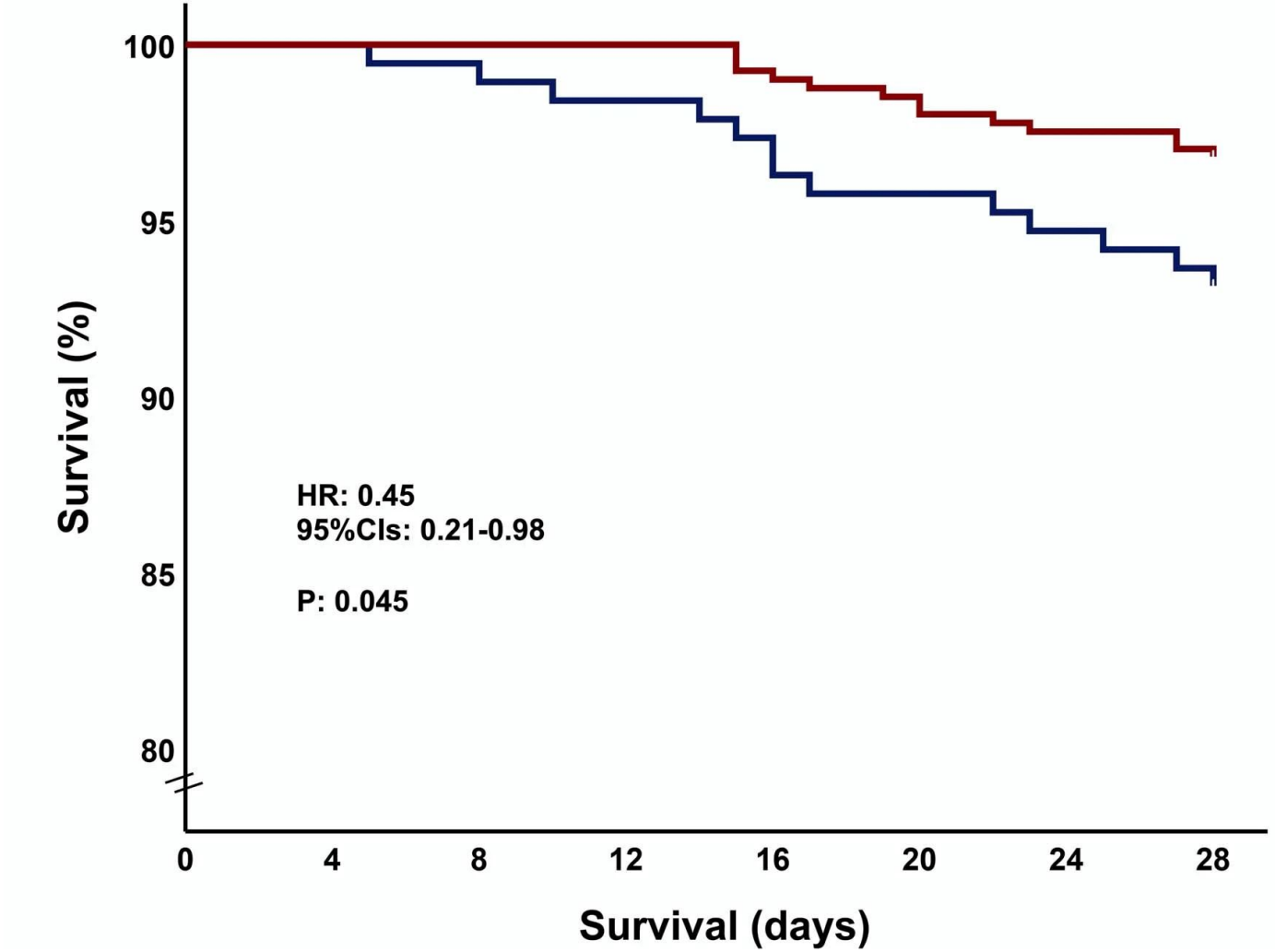
Kyriazopoulou, E., Poulakou, G., Milionis, H. et al. Nat Med (2021). https://doi.org/10.1038/s41591-021-01499-z

PRIMARY ENDPOINT: distribution of the WHO-CPS scores at day 28 (primary outcome) of patients allocated to treatment with placebo and to treatment with anakinra



50.4% (204/405) of patients receiving anakinra had fully recovered with no viral RNA detected on day 28 compared to 26.5% (50/189) of patients receiving placebo, and 3.2% (13/405) and 6.9% (13/189) of patients in the anakinra and placebo arms, respectively, died.

PRIMARY ENDPOINT: Survival analysis of enrolled patients at day 28 (univariate Cox regression analysis)



Survival analysis showed that anakinra treatment significantly reduced the risk of death by day 28 compared to placebo
(3.2% versus 6.9% in the anakinra and placebo arms, respectively; hazard ratio = 0.45, 95% CI 0.21–0.98, *P* = 0.045)

Patients at risk (n)

Placebo	189	189	187	186	182	181	179	176
Anakinra	405	405	405	405	401	397	395	392

Kyriazopoulou, E., Poulakou, G., Milionis, H. et al. Nat Med (2021). https://doi.org/10.1038/s41591-021-01499-z

Laboratory values before start of the study drug, median (Q1–Q3)			
White blood cell count, cells per mm^3	5,910 (4,280–8,300)	5,980 (4,320–8,180)	5,950 (4,310–8,200)
Lymphocyte count, cells per mm^3	730 (560–1,090)	815 (570–1,110)	800 (565–1,100)
CRP, mg L^{-1}	51.4 (25.2–98.5)	50.5 (25.2–100.2)	50.6 (25.3–99.7)
IL-6, pg ml^{-1}	20.1 (7.4–45.0)	15.5 (6.7–39.3)	16.8 (7.0–39.8)
Ferritin, ng ml^{-1}	628.6 (293.5–1,062.3)	558.9 (294.1–1,047.0)	585.2 (294.5–1,047.0)
Serum soluble uPAR, ng ml^{-1}	7.5 (6.9–9.3)	7.6 (7.0–9.1)	7.6 (6.9–9.1)
PaO_2/FiO_2	223 (168–297)	239 (186–302)	237 (181–301)

Kyriazopoulou, E., Poulakou, G., Milionis, H. et al. Nat Med (2021). https://doi.org/10.1038/s41591-021-01499-z

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G.A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, and J.H. Beigel, for the ACTT-2 Study Group Members*

ABSTRACT

BACKGROUND

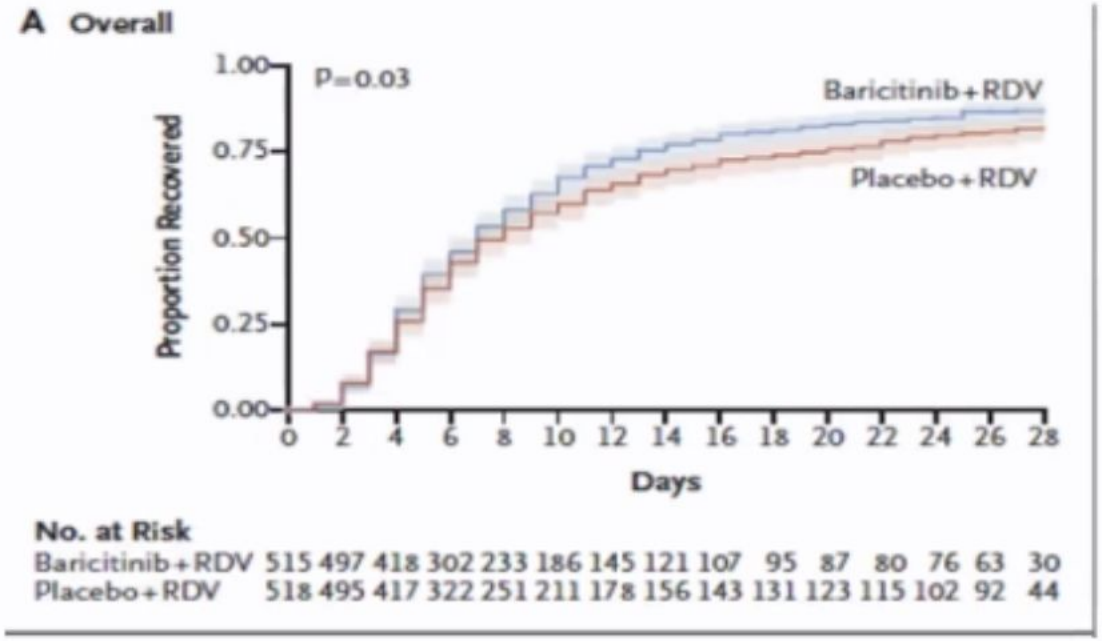
Severe coronavirus disease 2019 (Covid-19) is associated with dysregulated inflammation. The effects of combination treatment with baricitinib, a Janus kinase inhibitor, plus remdesivir are not known.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with Covid-19. All the patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15.

RESULTS

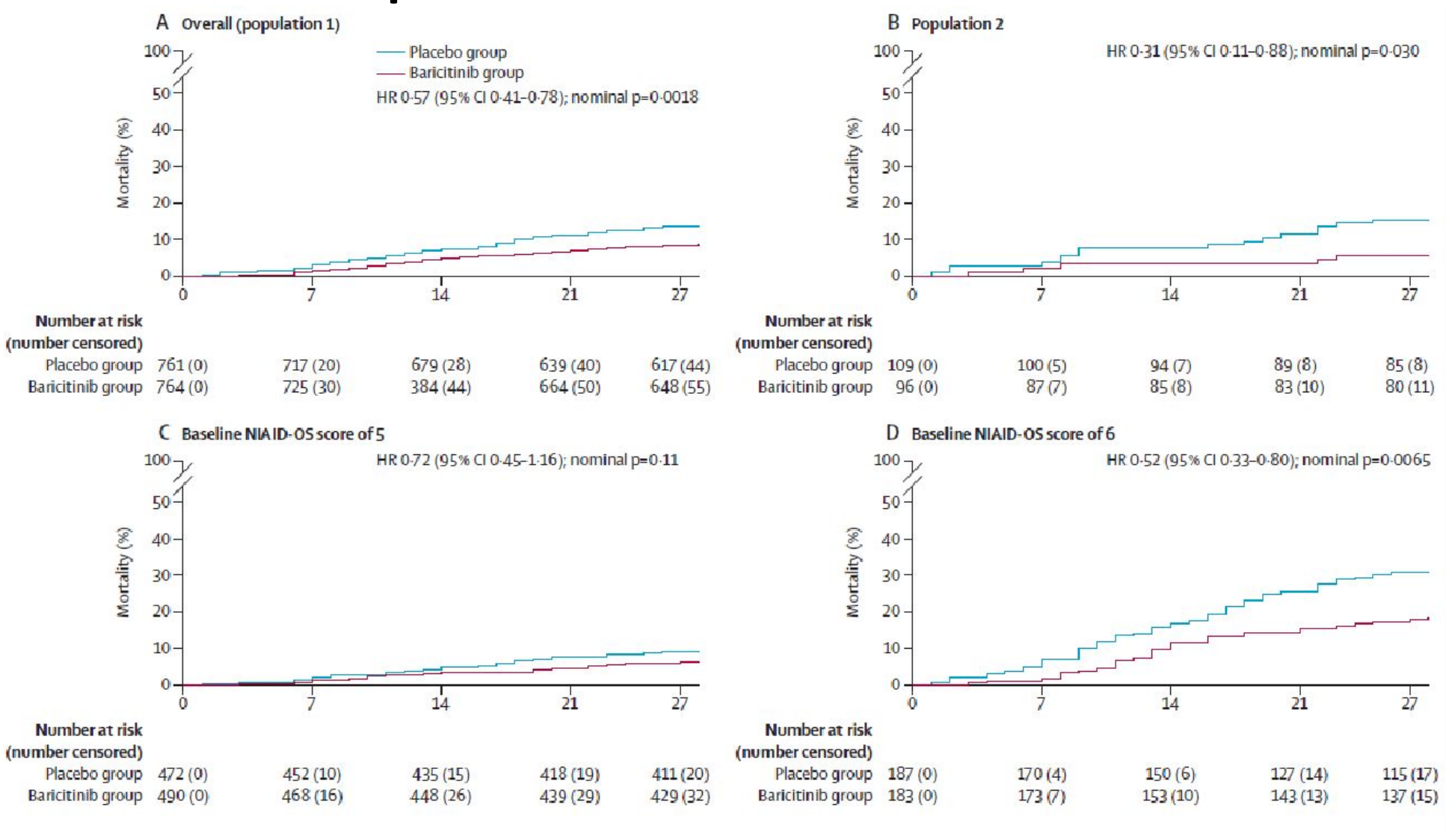
A total of 1033 patients underwent randomization (with 515 assigned to combination treatment and 518 to control). Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03), and a 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the combination group and 7.8% in the



- Overall median time to Recovery of 7 days compared to 8 days for control (RRR 1.16 95% CI 1.01-1.32)
- 30% higher odds of improvement in clinical status by day 15
- 28-day mortality 5.1% combination vs. 7.8% control (HR 0.65 95% CI 0.39 – 1.09)
- FDA grants 'Emergency Use Authorisation'

- ACTT-4: RDV+BCT vs. RDV+DEX

Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

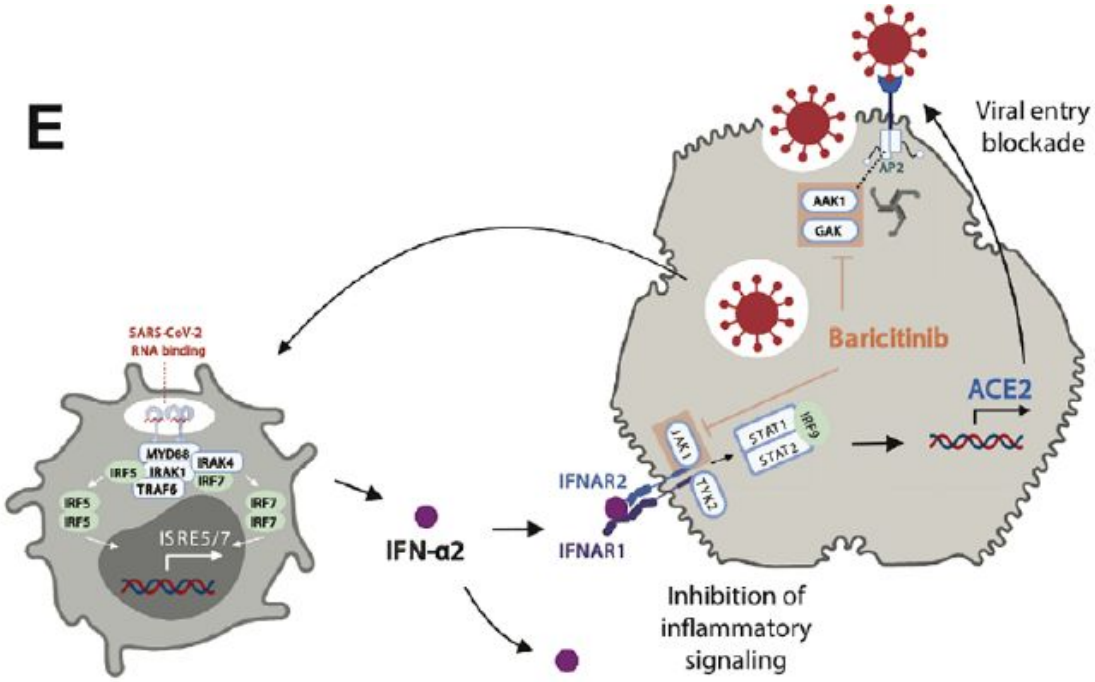


Lancet Respir Med Sept 1, 2021

JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality

Justin Stebbing[1†*], Ginés Sánchez Nievas[2†], Marco Falcone[3†], Sonia Youhanna[4†], Peter Richardson[5], Silvia Ottaviani[1], Joanne X. Shen[4], Christian Sommerauer[6], Giusy Tiseo[3], Lorenzo Ghiadoni[3], Agostino Virdis[3], Fabio Monzani[3], Luis Romero Rizos[7,8], Francesco Forfori[9], Almudena Avendaño-Céspedes[7,8], Salvatore De Marco[10], Laura Carrozzi[9], Fabio Lena[11], Pedro Manuel Sánchez-Jurado[7,8], Leonardo Gianluca Lacerenza[11], Nencioni Cesira[12], David Caldevilla-Bernardo[13], Antonio Perrella[12], Laura Niccoli[14], Lourdes Sáez Méndez[15], Daniela Matarrese[16], Delia Goletti[17], Yee-Joo Tan[18], Vanessa Monteil[19], George Dranitsaris[20], Fabrizio Cantini[14], Alessio Farcomeni[21], Shuchismita Dutta[22], Stephen K. Burley[22], Haibo Zhang[23], Mauro Pistello[24], William Li[25], Marta Mas Romero[7], Fernando Andrés Pretel[26], Rafaela Sánchez Simón-Talero[27], Rafael García-Molina[7], Claudia Kutter[6], James H. Felce[28], Zehra F. Nizami[28], Andras G. Miklosi[28], Josef M. Penninger[29,30],Francesco Menichetti[3‡], Ali Mirazimi[18‡], Pedro Abizanda[7,8‡] and Volker M. Lauschke[4‡*]

Fig. 5. Baricitinib blocks viral entry of SARS-CoV-2. Super-resolution dSTORM microscopy of short-term (4h) infected liver spheroids stained for nucleocapside treated with vehicle control (A) or baricitinib (100 nM; B). C, Relative mean fluorescence



Science Advances 2020

JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality

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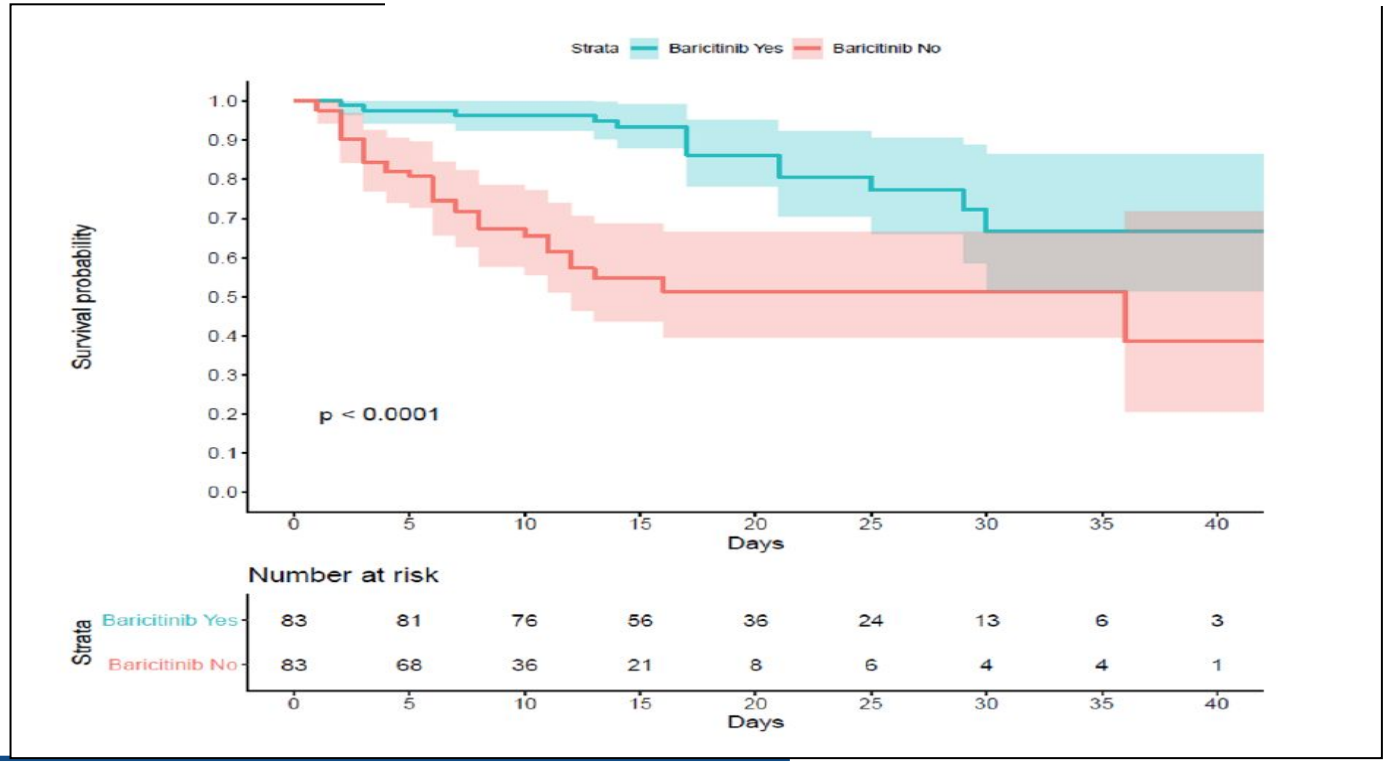
Fig. 2. Kaplan-Meier analysis of the propensity score matched cohorts from Pisa University and Albacete Hospital cohorts.



Science Advances 2020

Anakinra versus Baricitinib: Different Strategies for Patients Hospitalized with COVID-19 †

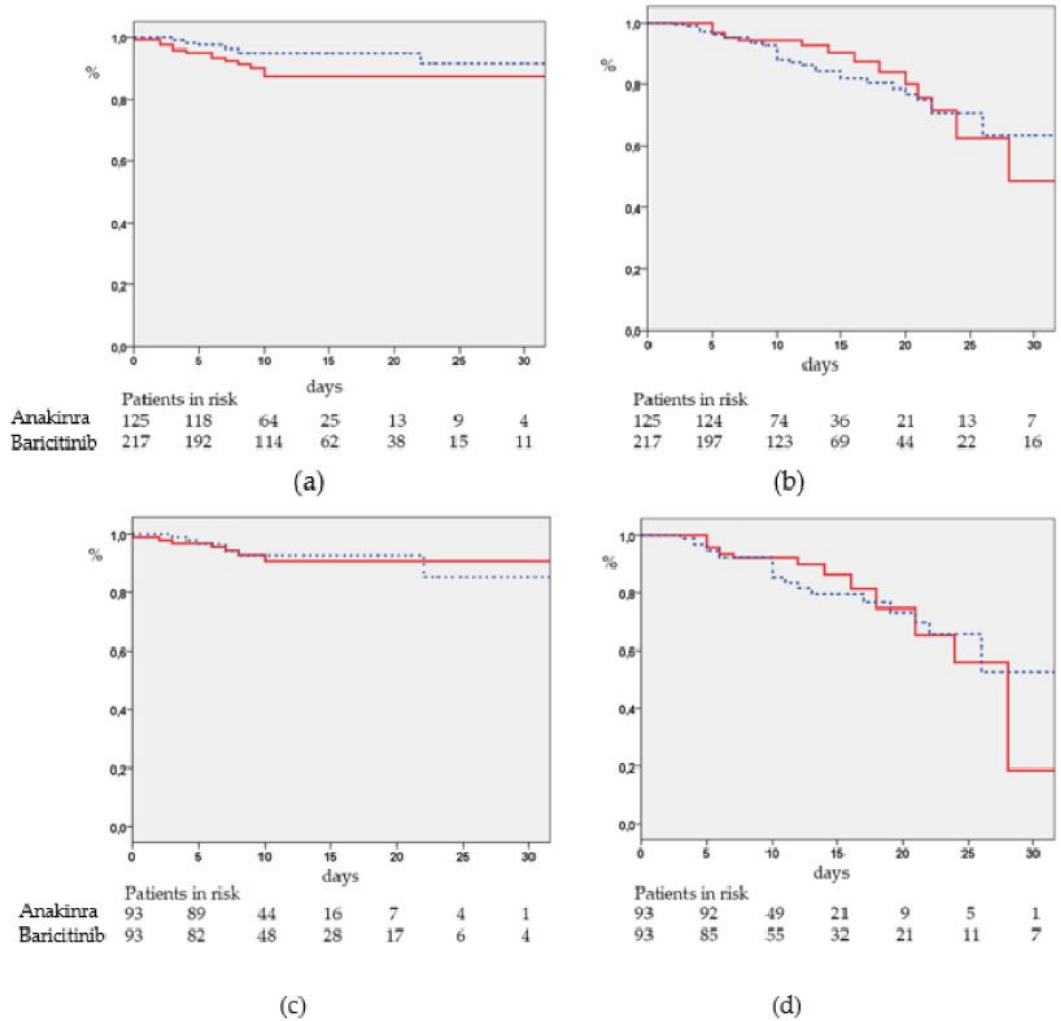
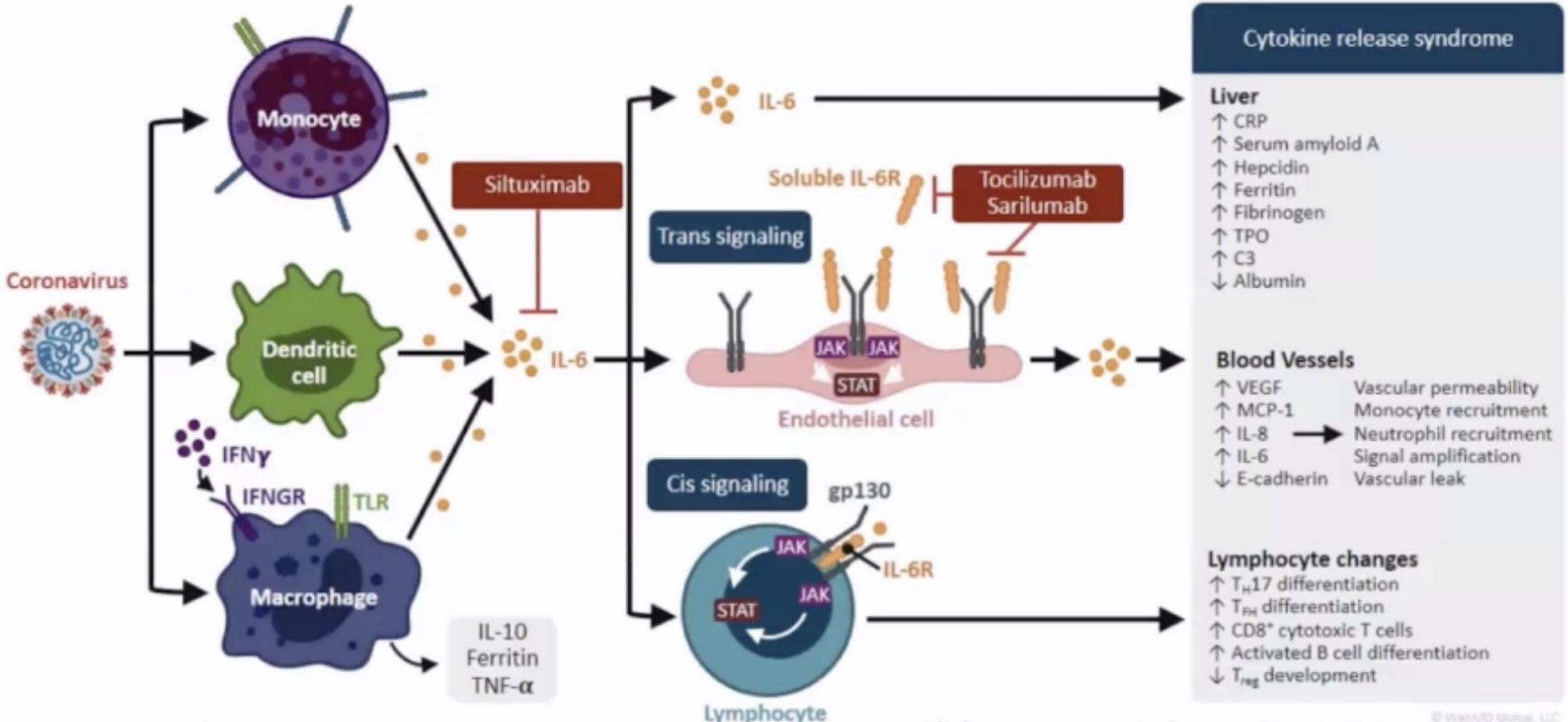


Figure 5. Probability of remaining free of invasive mechanical ventilation (**a**) and death (**b**) in the anakinra (continuous line) and baricitinib (dashed line) groups. Kaplan–Meier curves for IMV (**c**) and mortality (**d**) according to the immunomodulatory

J. Clin. Med. **2021**, *10*, 4019. https://doi.org/10.3390/jcm10174019

What about IL-6 inhibitors?



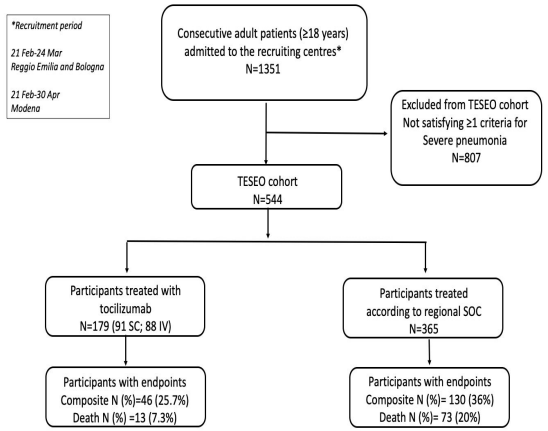
Moore JB, et al. *Science*. 2020;1;368:473-474.

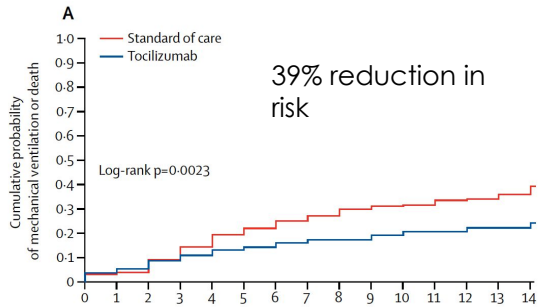
Slide courtesy: Medscape EDUCATION GLOBAL

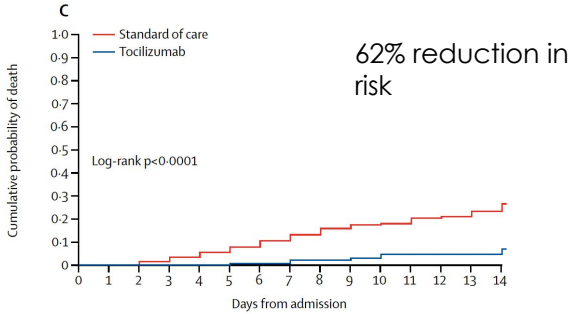
Tocilizumab in patients with severe COVID-19: a retrospective cohort study

Giovanni Guaraldi*, Marianna Meschiari*, Alessandro Cozzi-Lepri, Jovana Milic, Roberto Tonelli, Marianna Menozzi, Erica Franceschini, Gianluca Cuomo, Gabriella Orlando, Vanni Borghi, Antonella Santoro, Margherita Di Gaetano, Cinzia Puzzolante, Federica Carli, Andrea Bedini, Luca Corradi, Riccardo Fantini, Ivana Castaniere, Luca Tabbi, Massimo Girardis, Sara Tedeschi, Maddalena Giannella, Michele Bartoletti, Renato Pascale, Giovanni Dolci, Lucio Brugioni, Antonello Pietrangelo, Andrea Cossarizza, Federico Pea, Enrico Clini, Carlo Salvarani, Marco Massari, Pier Luigi Viale, Cristina Mussini

The aim of this multicentre cohort study was to assess the role of tocilizumab in reducing the risk of invasive mechanical ventilation and/or death in patients with severe COVID-19 pneumonia who received standard of care (SoC) treatment.







Implications of all the available evidence

Tocilizumab, regardless of IV or SC administration may be capable of reducing invasive mechanical ventilation or death in severe COVID-19 pneumonia.

Guaraldi G. et al. 2020. Lancet Rheumatology

Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia

ROCHE Press release 29/7/20

- **COVACTA trial did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality**
- **The study is the first global, randomised, double-blind, placebo-controlled phase III trial investigating Actemra/RoActemra in this setting**
- **Roche remains committed to continuing the Actemra/RoActemra clinical trial programme in COVID-19 to further explore Actemra/RoActemra in other treatment settings, including in combination with an antiviral**

JAMA Internal Medicine | Original Investigation

Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia

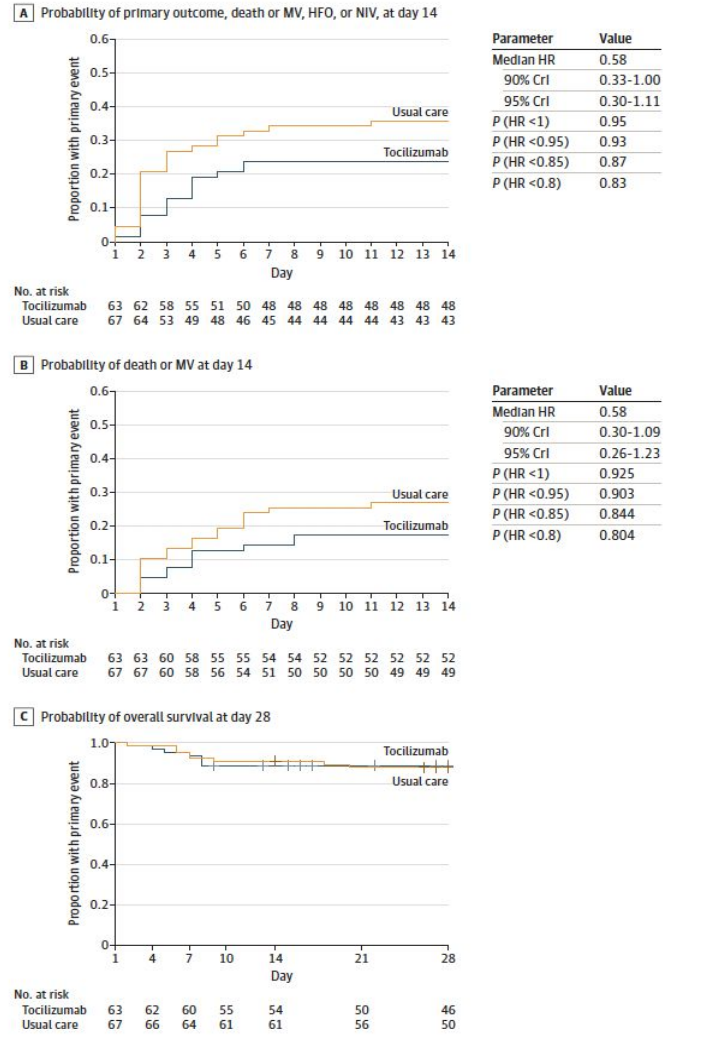
A Randomized Clinical Trial

Olivier Hermine, MD, PhD; Xavier Mariette, MD, PhD; Pierre-Louis Tharaux, MD, PhD; Matthieu Resche-Rigon, MD, PhD; Raphaël Porcher, PhD; Philippe Ravaud, MD, PhD; for the CORIMUNO-19 Collaborative Group

Table 1. Patient Characteristics at Baseline

Characteristic	No.	Tocilizumab, No./No. (%)	No.	UC, No./No. (%)
No.		63		67
Age, median (IQR), y		64.0 (57.1-74.3)		63.3 (57.1-72.3)
Male		44/63 (70)		44/67 (66)
Female		19/63 (30)		23/67 (34)
Weight, median (IQR), kg		80.0 (70.0-90.0)	55	78.0 (70.0-90.0)
BMI,[a] median (IQR)	46	27.9 (23.3-30.8)	46	27.4 (24.5-31.3)
WHO-CPS score (0-10) = 5		63/63 (100)		67/67 (100)
rRT-PCR-confirmed SARS-CoV-2 infection		56/63 (89)		61/67 (90)
Temperature, median (IQR), °C		37.3 (36.8-38.2)		37.9 (37.0-38.6)
Respiratory rate, median (IQR), bpm	56	24.0 (22.0-30.0)	57	26.0 (24.0-30.0)
Flow, median (IQR), L/min		5.0 (3.0-8.0)		5.0 (3.0-6.0)
SpO_2, median (IQR), %		95.0 (93.0-96.0)		95.0 (93.0-97.0)
Time from symptoms onset to randomization, median (IQR), d	62	10 (7-13)	66	10 (8-13)
Time from hospital admission to randomization, median (IQR), d	63	1 (1-4)	67	1 (1-2)
Coexisting conditions				
Chronic cardiac disease		20/61 (33)		20/67 (30.0)
Diabetes		20/61 (33)		23/67 (34)
Chronic kidney disease (stage 1 to 3) or dialysis		5/61 (8)		13/67 (19)
Asthma		5/61 (8)		3/67 (5)
Chronic pulmonary disease (not asthma)		3/61 (5)		3/67 (5)
Active malignant neoplasm		4/61 (7)		5/67 (8)
Smoking				
No		55/61 (90)		62/67 (93)
Current		1/61 (2)		2/67 (3)
Former		5/61 (8)		3/67 (4)
Laboratory values, median (IQR)				
CRP, mg/L	56	119.5 (74.5-219.5)	63	127.0 (84.0-171.0)
D-Dimer, µg/L	50	869 (524-1380)	50	1250 (780-1812)
Neutrophil count, G/L	60	4.9 (3.9-7.5)	63	5.1 (3.4-6.6)
Lymphocyte count, G/L	60	1.0 (0.7-1.4)	60	1.1 (0.6-1.2)
Lymphocytes to neutrophils ratio	48	0.2 (0.1-0.3)	40	0.2 (0.1-0.3)
Hemoglobin, g/dL	62	12.8 (11.9-13.8)	65	12.3 (10.9-13.4)
Platelet count, g/L	62	230 (187-324)	65	226 (163-286)
ALT/SGPT, IU/L	57	40.0 (30.0-67.0)	62	35.0 (22.0-55.0)
AST/SGOT, IU/L	58	50.0 (34.0-66.0)	62	55.0 (36.0-74.0)
Albumin, g/L	43	30.0 (27.0-36.0)	42	32.2 (28.0-36.0)
Creatinine, µmol/L	61	71.0 (56.0-87.0)	64	75.0 (59.5-119.5)
Blood urea, mmol/L	62	5.8 (4.4-7.7)	65	5.1 (4.2-8.6)
Ferritin, mg/L	43	1292 (424-2484)	46	1070 (563-1790)
LDH, IU/L	46	401 (313-582)	51	434 (351-558)
CPK, IU/L	42	136.0 (48.0-284.0)	41	105.0 (67.0-236.0)

Figure 2. Occurrence of Primary Outcome Events During Follow-up



Kaplan-Meier cumulative estimates of probability of (A) the primary outcome, death or ventilation support (mechanical ventilation, high-flow or noninvasive ventilation); B, death or mechanical ventilation; (C) overall survival in the tocilizumab arm compared with the usual care arm. In panel A, events occurring on day 1 occurred on the same day as but after randomization. For the primary event and death or mechanical ventilation, data are analyzed in a bayesian framework, and median posterior HR and 90% credible intervals (CrIs) are presented, together with posterior probabilities of achieving specified effects, in the tables on the right. Overall survival was analyzed in a frequentist framework, so these probabilities were not relevant. HFO indicates high-flow oxygen; MV, mechanical ventilation; NIV, noninvasive ventilation.

EMPACTA

ORIGINAL ARTICLE

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

Carlos Salama, M.D., Jian Han, Ph.D., Linda Yau, Ph.D.,

Table 2. Primary and Key Secondary Efficacy Outcomes by Day 28 in the Modified Intention-to-Treat Population.*

Outcome	Tocilizumab (N=249)	Placebo (N=128)	Hazard Ratio (95% CI)	Weighted Difference (95% CI)	P Value†
Primary outcome: mechanical ventilation or death — % (95% CI)‡	12.0 (8.5 to 16.9)	19.3 (13.3 to 27.4)	0.56 (0.33 to 0.97)	NA	0.04
Secondary outcomes					
Median time to hospital discharge or readiness for discharge (95% CI) — days§	6.0 (6.0 to 7.0)	7.5 (7.0 to 9.0)	1.16 (0.91 to 1.48)	NA	
Median time to improvement in clinical status (95% CI) — days§¶	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)	1.15 (0.90 to 1.48)	NA	
Median time to clinical failure (95% CI) — days§	NE	NE	0.55 (0.33 to 0.93)	NA	
Death — no. (% [95% CI])‖	26 (10.4 [7.2 to 14.9])	11 (8.6 [4.9 to 14.7])	NA	2.0 (–5.2 to 7.8)**	

N Engl J Med 2021;384:20-30.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 22, 2021 VOL. 384 NO. 16

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

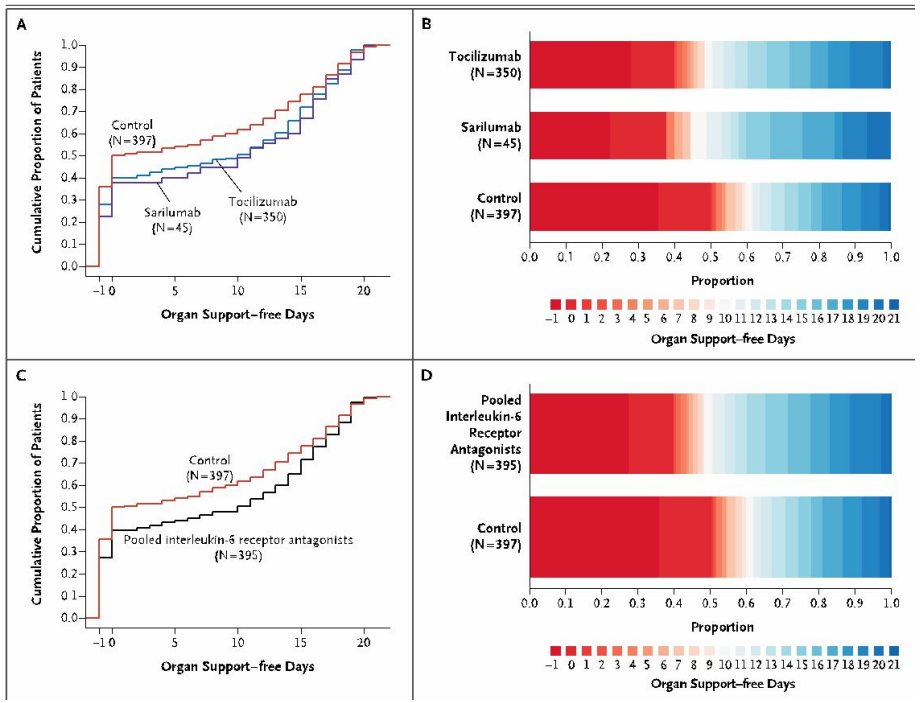


Table 2. Primary and Secondary Outcomes.*

Outcome or Analysis	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
Primary outcome			
Organ support–free days			
Median (IQR)	10 (−1 to 16)	11 (0 to 16)	0 (−1 to 15)
Adjusted odds ratio			
Mean	1.65±0.23	1.83±0.44	1
Median (95% credible interval)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control — %	>99.9	99.5	—
Subcomponents of organ support–free days			
In-hospital death — no./total no. (%)	98/350 (28)	10/45 (22)	142/397 (36)
Concurrent with tocilizumab randomization	—	—	127/355 (36)†
Concurrent with sarilumab randomization	—	—	19/63 (30)†
Median no. of days free of organ support in survivors (IQR)	14 (7 to 17)	15 (6 to 17)	13 (4 to 17)
Primary in-hospital survival			
Adjusted odds ratio			
Mean	1.66±0.31	2.25±0.96	1
Median (95% credible interval)	1.64 (1.14 to 2.35)	2.01 (1.18 to 4.71)	1
Probability of superiority to control — %	99.6	99.5	—
Secondary analysis of primary outcome			
Adjusted odds ratio			
Mean	1.68±0.24	1.84±0.44	1
Median (95% credible interval)	1.66 (1.26 to 2.18)	1.77 (1.18 to 2.90)	1
Probability of superiority to control — %	>99.9	99.6	—
Secondary analysis of primary in-hospital survival			
Adjusted odds ratio			
Mean	1.67±0.31	2.24±0.94	1
Median (95% credible interval)	1.65 (1.15 to 2.34)	2.00 (1.17 to 4.69)	1
Probability of superiority to control — %	99.6	99.4	—

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

*RECOVERY Collaborative Group**

	Treatment allocation		RR (95% CI)	p value
	Tocilizumab group (n=2022)	Usual care group (n=2094)		
Primary outcome				
28-day mortality	621 (31%)	729 (35%)	0·85 (0·76–0·94)	0·0028
Secondary outcomes				
Median time to being discharged, days	19	>28	..	..
Discharged from hospital within 28 days	1150 (57%)	1044 (50%)	1·22 (1·12–1·33)	<0·0001
Receipt of invasive mechanical ventilation or death*	619/1754 (35%)	754/1800 (42%)	0·84 (0·77–0·92)	<0·0001
Invasive mechanical ventilation	265/1754 (15%)	343/1800 (19%)	0·79 (0·69–0·92)	0·0019
Death	490/1754 (28%)	580/1800 (32%)	0·87 (0·78–0·96)	0·0055
Subsidiary clinical outcomes				
Receipt of ventilation†	290/935 (31%)	323/933 (35%)	0·90 (0·79–1·02)	0·10
Non-invasive ventilation	281/935 (30%)	309/933 (33%)	0·91 (0·79–1·04)	0·15
Invasive mechanical ventilation	67/935 (7%)	86/933 (9%)	0·78 (0·57–1·06)	0·11
Successful cessation of invasive mechanical ventilation‡	95/268 (35%)	98/294 (33%)	1·08 (0·81–1·43)	0·60
Use of haemodialysis or haemofiltration§	120/1994 (6%)	172/2065 (8%)	0·72 (0·58–0·90)	0·0046

Data are n (%), n/N (%), or median (IQR) unless stated otherwise. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. *Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. †Analyses include only those on no ventilator support at second randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at second randomisation. §Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

Table 2: **Effect of allocation to tocilizumab on main study outcomes**

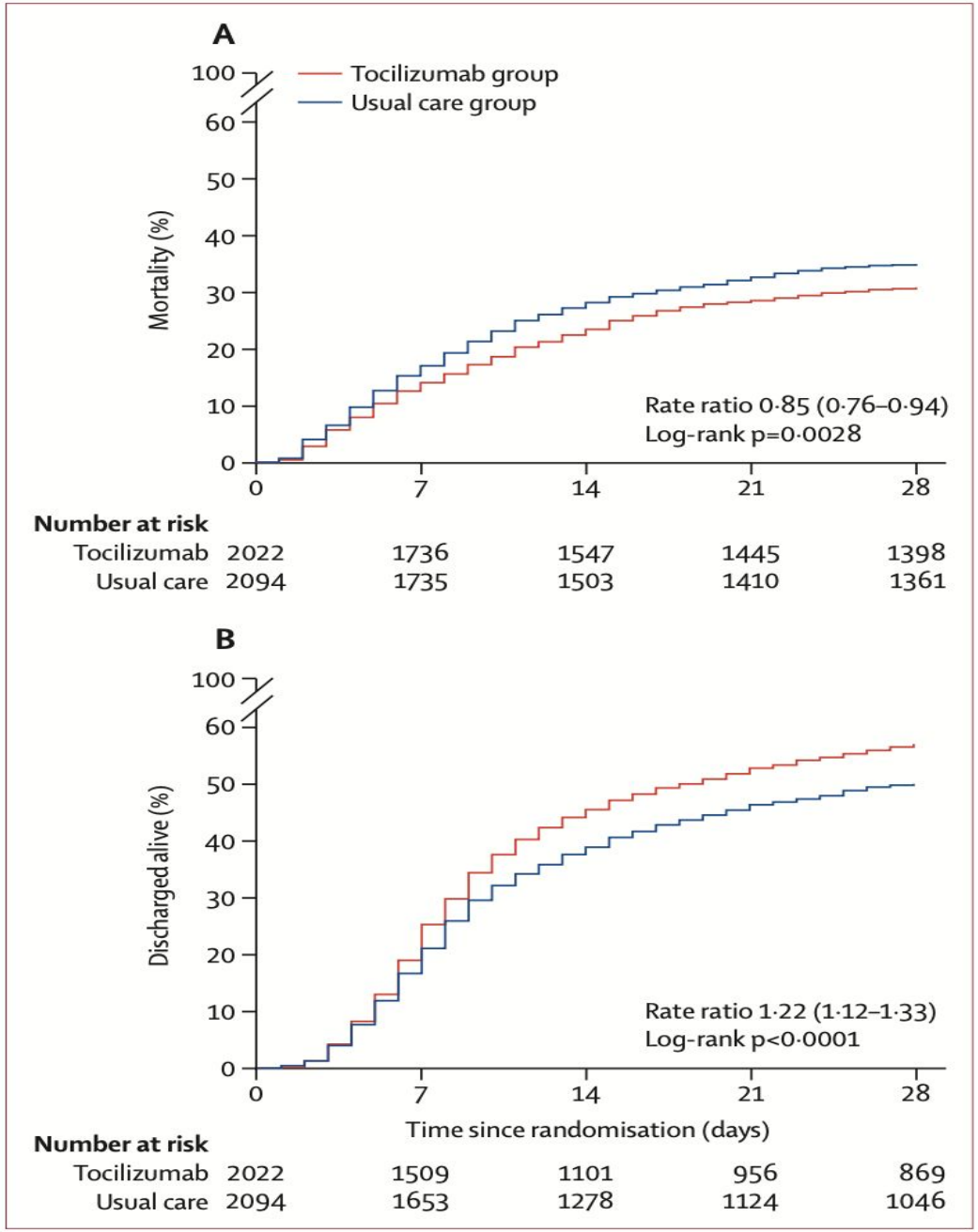


Figure 2: **Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)**

Open questions

….Too early?

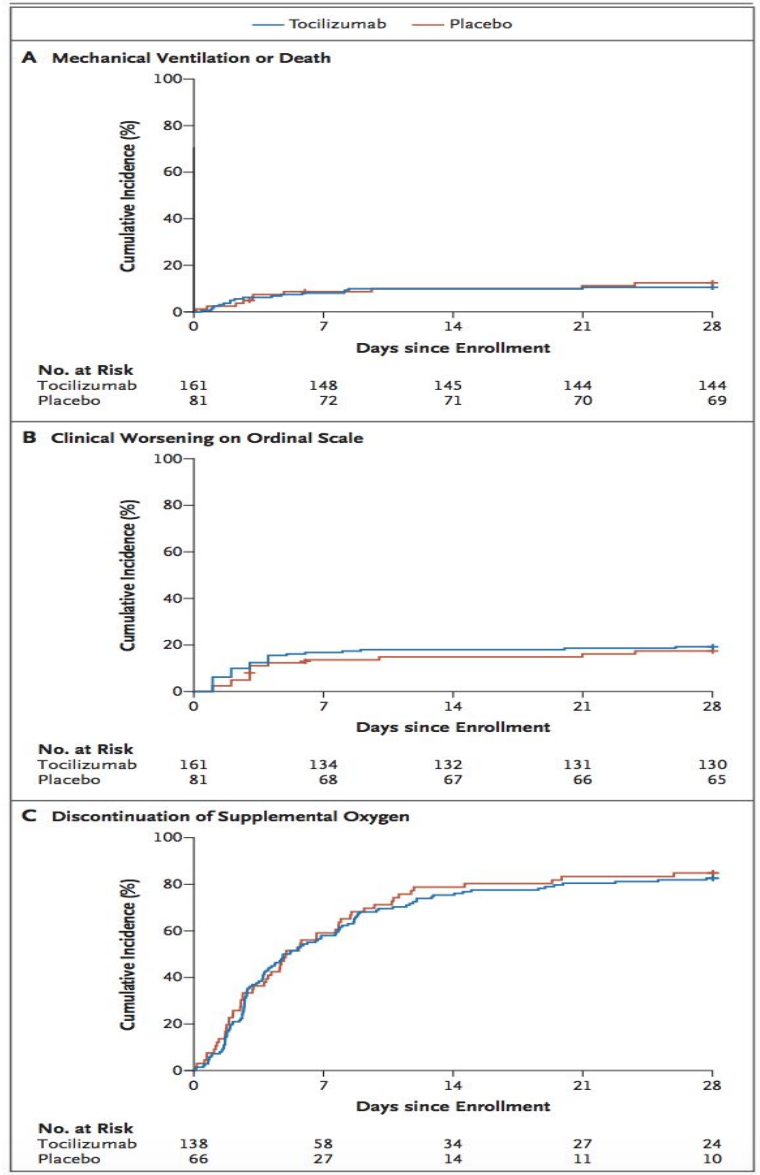
ORIGINAL ARTICLE

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.-D. Halvorsen,

Table 1. (Continued)

Characteristic	Tocilizumab (N=161)	Placebo (N=82)	All Patients (N=243)
Ordinal scale score — no. (%)§			
2	23 (14)	15 (18)	38 (16)
3	133 (83)	61 (74)	194 (80)
4	5 (3)	5 (6)	10 (4)
5	0	1 (1)	1 (<1)
Median laboratory values (IQR)¶			
Absolute lymphocyte count — cells/mm^3	1040 (700–1400)	1030 (680–1360)	1030 (700–1400)
C-reactive protein level — mg/liter	116.0 (67.1–190.6)	94.3 (58.4–142.0)	110.0 (64.9–175.3)
Ferritin level — ng/ml	723 (413–1212)	686 (382–1228)	708 (411–1225)
D-Dimer level — ng/ml	857 (536–1695)	980 (500–1739)	884 (527–1730)
Lactate dehydrogenase level — U/liter	351 (287–420)	324 (290–395)	340 (289–413)
Serum interleukin-6 level — pg/ml	23.6 (14.0–49.9)	25.4 (14.6–40.3)	24.4 (14.1–45.5)
Erythrocyte sedimentation rate — mm/hr	61 (42–90)	63 (42–87)	61 (42–88)
Troponin level — ng/liter	8 (6–22)	9 (6–24)	9 (6–22)
NT-proBNP level — pg/ml	110 (50–438)	93 (33–431)	108 (38–437)
Procalcitonin level — ng/ml	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.2 (0.1–0.4)



JAMA Internal Medicine | Original Investigation

Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia

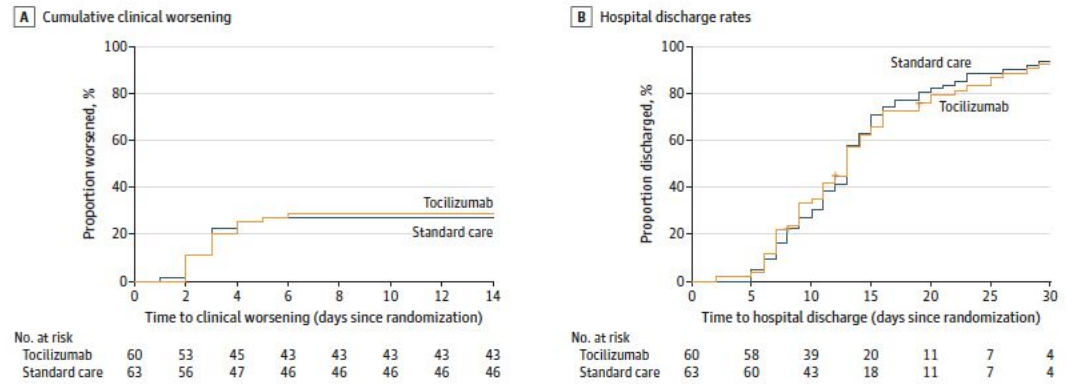
A Randomized Clinical Trial

Carlo Salvarani, MD; Giovanni Dolci, MD; Marco Massari, MD; Domenico Franco Merlo, PhD; Silvio Cavuto, BSc; Luisa Savoldi, BSc; Paolo Bruzzi, MD, PhD; Fabrizio Boni, MD; Luca Braglia, BSc; Caterina Turrà, MSc; Pier Ferruccio Ballerini, MD; Roberto Sciascia, MD; Lorenzo Zammarchi, MD; Ombretta Para, MD; Pier Giorgio Scotton, MD; Walter Omar Inojosa, MD; Viviana Ravagnani, MD; Nicola Duccio Salerno, MD; Pier Paolo Sainaghi, MD; Alessandro Brignone, MD; Mauro Codeluppi, MD; Elisabetta Teopompi, MD, PhD; Maurizio Milesi, MD; Perla Bertomoro, MD; Norbiato Claudio, MD; Mario Salio, MD; Marco Falcone, MD; Giovanni Cenderello, MD; Lorenzo Donghi, MD; Valerio Del Bono, MD; Paolo Luigi Colombelli, MD; Andrea Angheben, MD; Angelina Passaro, MD; Giovanni Secondo, MD; Renato Pascale, MD; Ilaria Piazza, MD; Nicola Facciolongo, MD; Massimo Costantini, MD, PhD; for the RCT-TCZ-COVID-19 Study Group

Table 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristic	No. (%)		
	All (n = 126)	Tocilizumab (n = 60)	Standard care (n = 66)
Age, median (IQR), y	60.0 (53.0-72.0)	61.5 (51.5-73.5)	60.0 (54.0-69.0)
Sex			
Male	77 (61.1)	40 (66.7)	37 (56.1)
Female	49 (38.9)	20 (33.3)	29 (43.9)
Days from symptom onset to randomization, median (IQR)	8.0 (6.0-11.0)	7.0 (4.0-11.0)	8.0 (6.0-11.0)
Days from hospital admission to randomization, median (IQR)	2 (1-3.2)	2 (1-3)	2 (1-4.2)
Coexisting conditions			
Diabetes mellitus	19 (15.1)	10 (16.7)	9 (13.6)
Obesity (BMI ≥ 30)[a]	38 (32.2)	16 (28.1)	22 (36.1)
Hypertension	56 (44.4)	27 (45.0)	29 (43.9)
COPD	4 (3.2)	2 (3.3)	2 (3.0)
Body temperature, median (IQR), °C	38.0 (36.9-38.5)	38.0 (37.0-38.4)	38.0 (36.8-38.5)
Respiratory rate, median (IQR), breaths/min	20.0 (18.0-24.0)	20.0 (18.0-24.0)	20.0 (18.0-24.0)
Unknown	13 (10.3)	7 (11.7)	6 (9.1)
C-Reactive protein, median (IQR), mg/dL	8.2 (3.7-13.5)	10.5 (5.0-14.6)	6.5 (3.2-11.8)
White blood cell count, median (IQR), /μL	5700 (4600-7500)	5800 (4400-7600)	5600 (4700-7200)
Unknown	2 (1.6)	1 (1.7)	1 (1.5)
Lymphocyte count, median (IQR), /μL	900 (700-1300)	1000 (800-1300)	900 (700-1200)
Unknown	13 (10.3)	8 (13.3)	5 (7.6)
Platelet count, median (IQR), $\times 10^3$/μL	200.5 (158.0-253.5)	213.0 (165.0-268.0)	188.0 (152.0-246.0)
Unknown	2 (1.6)	1 (1.7)	1 (1.5)
Pao_2/Fio_2 median (IQR), mm Hg	264.5 (243.0-290.0)	262.5 (241.0-286.5)	268.2 (244.0-290.0)
Ferritin, median (IQR), ng/mL	569.0 (317.0-1136.0)	648.0 (289.2-1107.5)	533.5 (351.0-1184.0)
Unknown	17 (13.5)	9 (15.0)	8 (12.1)
D-Dimer, median (IQR), μg/mL	0.566 (0.367-0.956)	0.756 (0.480-1.070)	0.455 (0.326-0.810)
Unknown	11 (8.7)	6 (10.0)	5 (7.6)
IL-6, median (IQR), pg/mL	42.1 (20.6-74.9)	50.4 (28.3-93.2)	34.3 (19.0-59.3)
Unknown	20 (15.9)	9 (15.0)	11 (16.7)
Hydroxychloroquine	115 (91.3)	53 (88.3)	62 (93.9)
Heparin and LMWH	81 (64.3)	41 (68.3)	40 (60.6)
Antiretrovirals[b]	52 (41.3)	21 (35.0)	31 (47.0)
Azithromycin	26 (20.6)	10 (16.7)	16 (24.2)

Figure 2. Kaplan-Meier Estimates of Cumulative Clinical Worsening and Hospital Discharge



Kaplan-Meier estimates of cumulative clinical worsening (A) and hospital discharge (B).

…..or too late?

ORIGINAL ARTICLE

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M.S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, and A. Malhotra

Ordinal scale for clinical status — no. (%)§		
2	9 (3.1)	6 (4.2)
3	78 (26.5)	44 (30.6)
4	94 (32.0)	39 (27.1)
5	45 (15.3)	15 (10.4)
6	68 (23.1)	40 (27.8)¶

This article was published on February 25, 2021, at NEJM.org.

EVALUATIONS

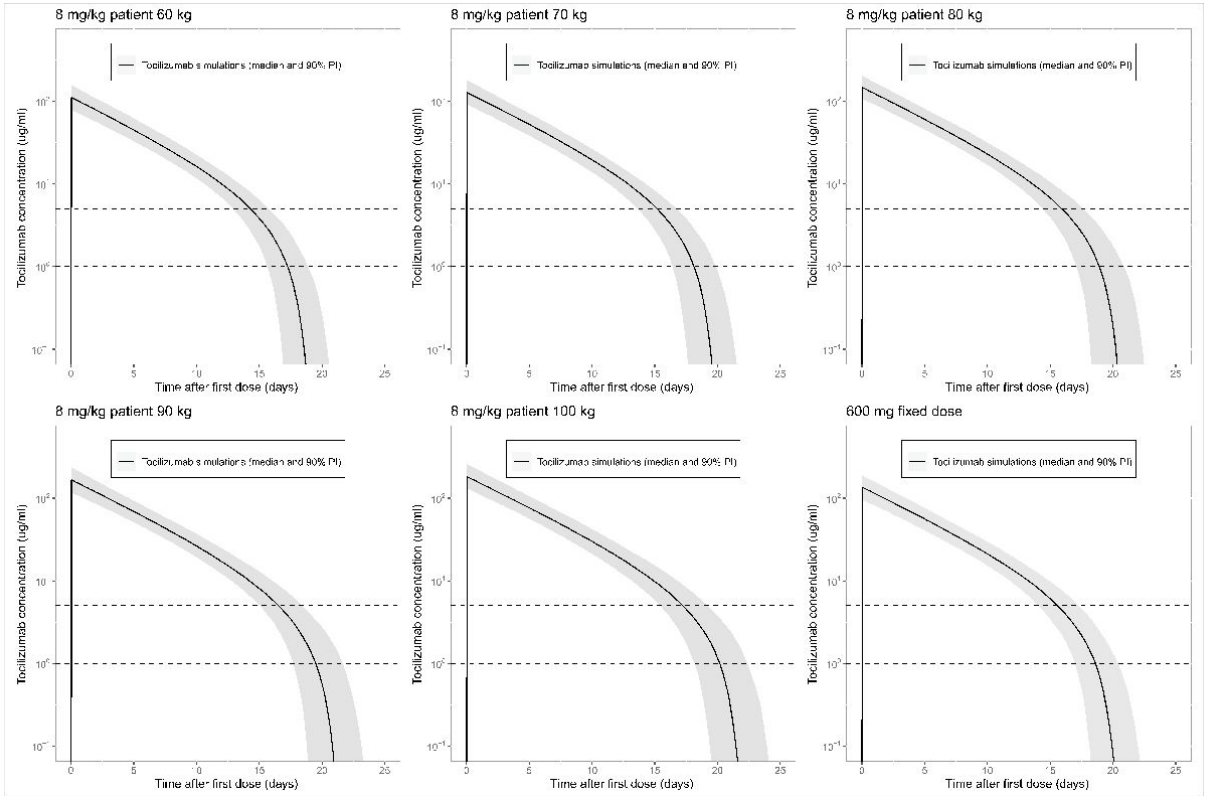
For the evaluation of patients in this trial, baseline was defined as the last observation before the administration of tocilizumab or placebo on day 1. The patients' clinical status was assessed on an ordinal scale according to the following categories: 1, discharged or ready for discharge; 2, hospitalization in a non–intensive care unit (ICU) without supplemental oxygen; 3, non–ICU hospitalization with supplemental oxygen; 4, ICU or non–ICU hospitalization with noninvasive ventilation or high-flow oxygen; 5, ICU hospitalization with intubation and mechanical ventilation; 6, ICU hospitalization with extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; and 7, death. Clinical status was recorded at baseline and every day during hospitalization.

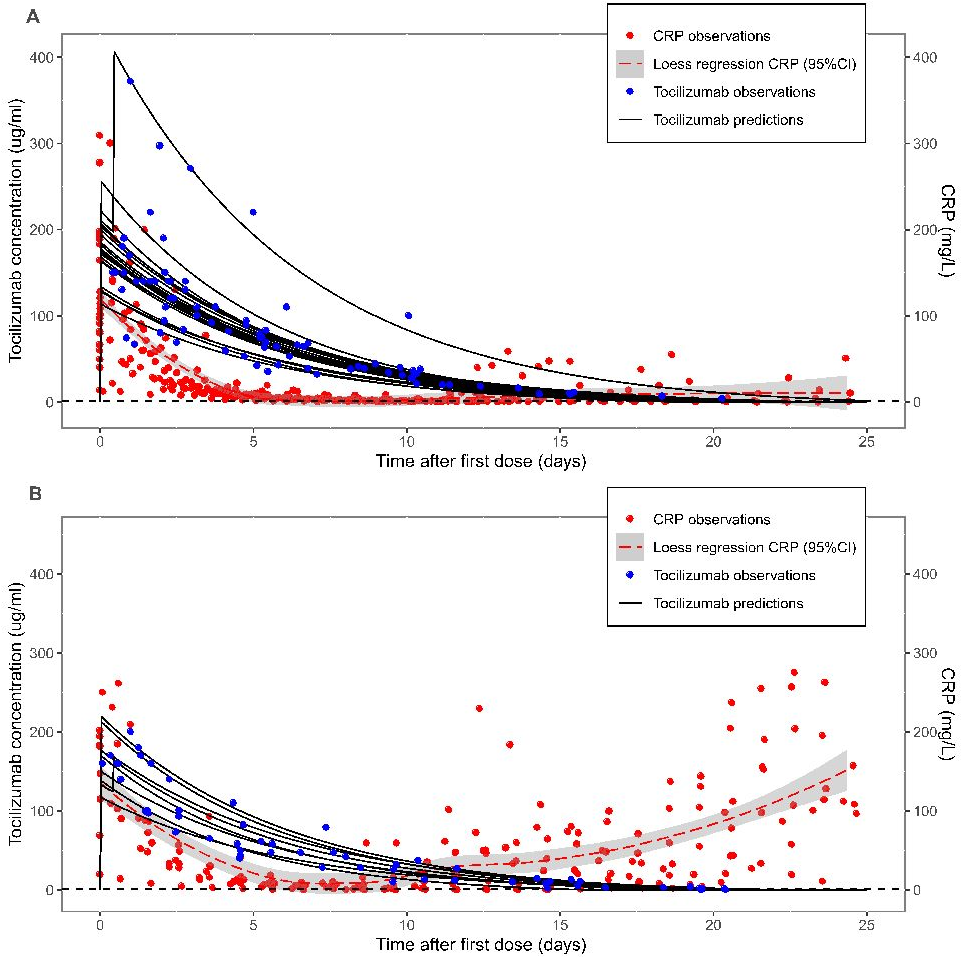
Table 2. **Primary and Secondary Efficacy Outcomes.***

Outcome	Tocilizumab (N=294)	Placebo (N=144)	Difference or Hazard Ratio (95% CI)	P Value
Primary outcome				
Median value for clinical status on 7-category ordinal scale at day 28 (95% CI)	1.0 (1.0 to 1.0)	2.0 (1.0 to 4.0)	−1.0 (−2.5 to 0.0)	0.31†
Secondary outcomes				
Median value for clinical status at day 14 on 7-category ordinal scale (95% CI)‡	3.0 (2.0 to 4.0)	4.0 (3.0 to 5.0)	−1.0 (−2.0 to 0.5)	
Death at day 28 — no. (%)	58 (19.7)	28 (19.4)	0.3 (−7.6 to 8.2)§	0.94
Median no. of days until hospital discharge or readiness for discharge (95% CI)	20.0 (17.0 to 27.0)	28.0 (20.0 to NE)	1.35 (1.02 to 1.79)¶	
Median no. of days until improvement by ≥2 categories on 7-category ordinal scale in clinical status (95% CI)	14.0 (12.0 to 17.0)	18.0 (15.0 to 28.0)	1.26 (0.97 to 1.64)¶	
Median no. of days in ICU (95% CI)	9.8 (7.0 to 15.7)	15.5 (8.7 to 25.5)	−5.8 (−15.0 to 2.9)	
Incidence of ICU stay among patients not in ICU at baseline — no./total no. (%)	27/127 (21.3)	23/64 (35.9)	−14.8 (−28.6 to −1.0)‖	
Median no. of ventilator-free days at day 28 (95% CI)	22.0 (18.0 to 28.0)	16.5 (11.0 to 26.0)	5.5 (−2.8 to 13.0)	
Incidence of mechanical ventilation among patients not receiving mechanical ventilation at randomization — no./total no. (%)	51/183 (27.9)	33/90 (36.7)	−8.9% (−20.7 to 3.0)‖	
Clinical failure among patients not receiving mechanical ventilation at randomization — no./total no. (%)**	53/183 (29.0)	38/90 (42.2)	0.61 (0.40 to 0.94)††	

Other issues?

Pharmacokinetic issues





The current proposed dose of tocilizumab 8 mg/kg (800 mg maximum) is based on the standard loading dose of rheumatoid arthritis, however evidence is lacking that this is also the optimal dose for COVID-19 ARDS.

Pharmacokinetic and pharmacodynamic parameters of medications are often found to be different in severely ill patients when compared with mild or moderately ill patients.

Moes DJ Clinical Pharmacokinetics 2021

Methods This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. Those trial participants with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein ≥75 mg/L) were eligible for random assignment in a 1:1 ratio to usual standard of care alone versus usual standard of care plus tocilizumab at a dose of 400 mg–800 mg (depending on weight) given intravenously. A second dose could be given 12–24 h later if the patient's condition had not improved. The primary outcome was 28-day mortality, assessed in the intention-to-treat population. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

CRP

Table. Outcomes According to Baseline CRP Level

Table. Outcomes According to Baseline CRP Level

Characteristic	No./total No. (%)[a]		Adjusted HR (95% CI)
	Tocilizumab (n = 63)	Usual care (n = 67)	
Received noninvasive or invasive ventilation or death until day 14			
CRP, >15.0 mg/dL	4/22 (18)	13/23 (57)	0.18 (0.06-0.59)
CRP, ≤15.0 mg/dL	8/34 (24)	9/40 (23)	0.99 (0.38-2.56)
P value for interaction	NA	NA	.045
Death until day 90			
CRP, >15.0 mg/dL	2/22 (9)	8/23 (35)	0.18 (0.04-0.89)
CRP, ≤15.0 mg/dL	3/34 (9)	1/40[2]	NA
P value for interaction	NA	NA	.02

And now what do guidelines say?

SIMIT

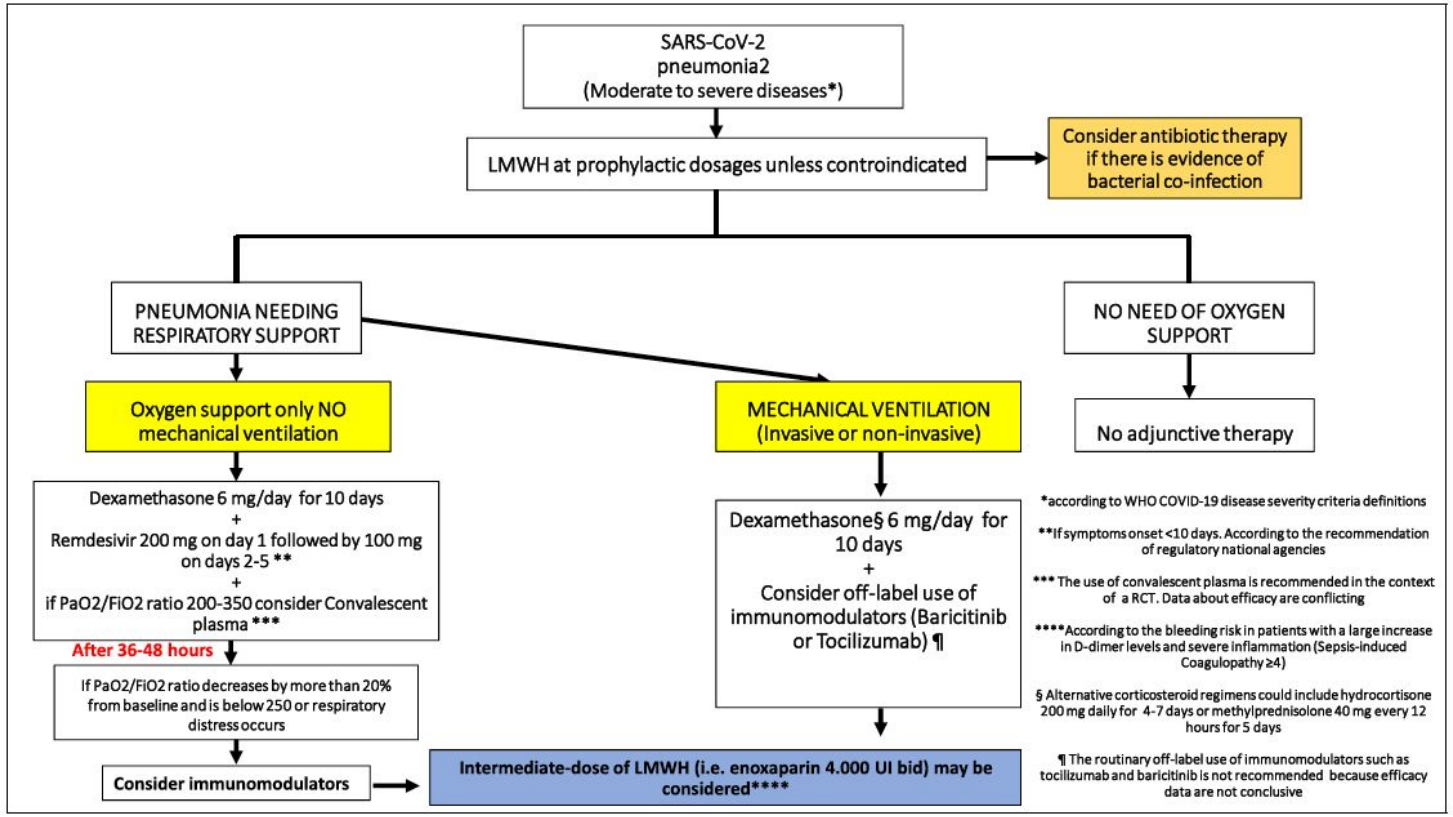


Fig. 1. Flowchart for treatment of severe cases of coronavirus disease 2019 (COVID-19).

Please cite this article as: Mussini C et al., Therapeutic strategies for severe COVID-19: a position paper from the Italian Society of Infectious and Tropical Diseases (SIMIT), Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2020.12.011

Terapia con immunomodulanti secondo indicazioni AIFA update del 28.09.21

		Indicazioni	dosaggio	Controindicazioni
Tocilizumab	anti IL-6	Soggetti adulti ospedalizzati con COVID-19 grave e/o con livelli elevati degli indici di infiammazione sistemica. • ricoverati in terapia intensiva da < di 24/48 h in ventilazione meccanica o ossigeno ad alti flussi; oppure • recentemente ospedalizzati con fabbisogno di O2 in rapido aumento in ventilazione meccanica NON invasiva o ossigeno ad alti flussi + elevati indici di flogosi (PCR ≥7.5 mg/dL). • rapida progressione clinica dopo 24/48 h di desametasone, o altri cortisonici. Fabbisogno di ossigeno in rapido aumento, pur senza necessità di ventilazione non invasiva o ossigeno ad alti flussi, e con elevati livelli di indici di flogosi (CRP≥7,5 mg/dL).	8 mg/kg ev in 60min Seconda dose dopo almeno 8 ore se non migliora (max 800 mg ad infusione)	- Infezioni attive in atto (diverse da COVID-19) che potrebbero peggiorare con l'utilizzo di tocilizumab (vedi quantiferon e PCT) - Storia di ulcerazione intestinale o diverticolite epatopatia attiva e compromissione epatica
Baricitinib	Anti JAK1/JAK2	Pazienti recentemente ospedalizzati con fabbisogno di ossigeno in rapido aumento (condizioni cliniche rapidamente ingravescenti) che richiedono ventilazione meccanica NON invasiva o ossigeno ad alti flussi in presenza di elevati livelli di indici di flogosi (PCR ≥7.5 mg/dL).	4 mg per o.s./die per 14 giorni (o fino a dimissione dall'ospedale per risoluzione clinica, se antecedente) eGFR 30-<60: 2 mg PO QD eGFR <30: non somministrare	- Neutropenia e infezioni gravi - Eventi epatici - Diverticolite e di perforazione gastrointestinale - Tromboembolismo venoso (Usato con attenzione nei pazienti con fattori di rischio per TVP/EP. Se compaiono manifestazioni cliniche di TVP/EP deve essere interrotto). - Trattamento con altri inibitori delle interleuchine o con altri JAK-inibitori
Anakinra	anti IL 1	Soggetti adulti ospedalizzati con polmonite da COVID-19 moderata/severa (con pO2/FiO2>150, e NON sottoposti a CPAP o ventilazione meccanica) e con (suPAR) ≥ 6ng/ml.	100 mg/die per 10 giorni SC	- Neutropenia e infezioni gravi - Eventi epatici - Trattamento con altri inibitori delle interleuchine o con altri JAK-inibitori
Sarilumab	Anti IL-6	si ritiene che sarilumab possa essere utilizzato in alternativa a tocilizumab quando quest'ultimo non fosse disponibile	400 mg ev in 60 min	

https://www.aifa.gov.it/-/aifa-rende-disponibili-i-medicinali-anakinra-baricitinib-e-sarilumab-per-il-trattamento-del-covid-19

Conclusions

- Despite we do not have a specific treatmet for severe COVID19 we have may information that can help clinicians. In particular, after failure of dexamethasone monoclonal antibodies active on the cytokine storm are probably the most promising drugs for severe COVID19 pneumonia. Nevertheless, for them and for glucocorticoids it is still to be determined in order to have an impact on mortality:

- The right patients
- The right dose
- The right moment in the course of the disease