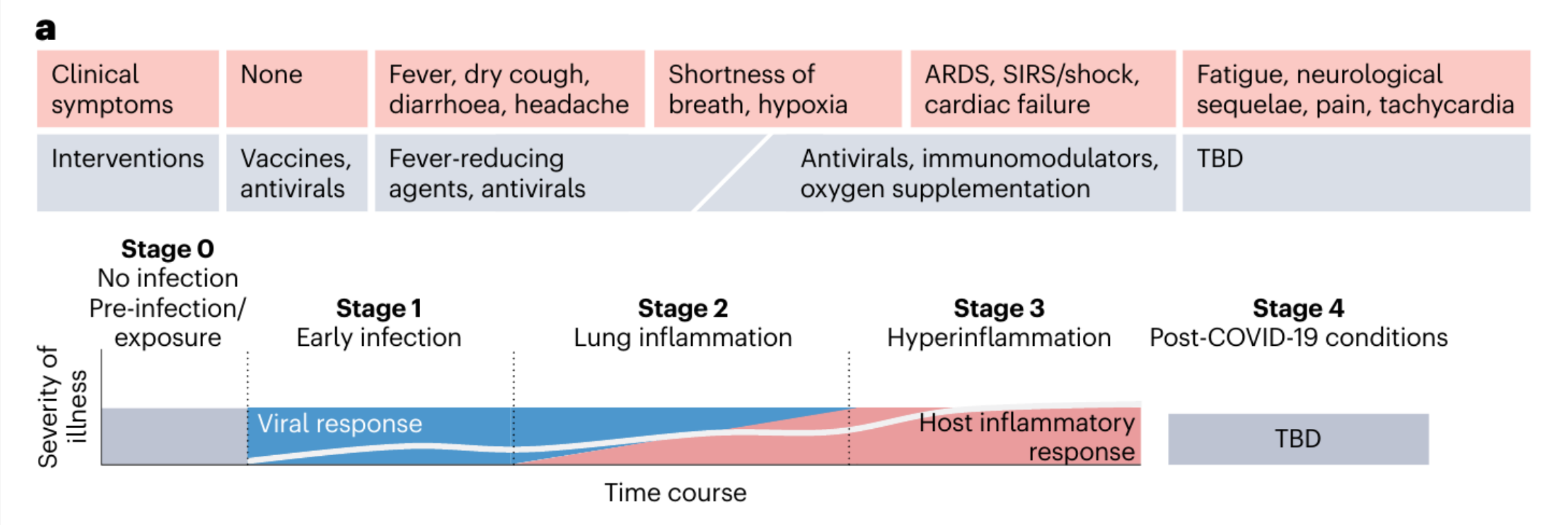
Effect and Safety of Tocilizumab in critically ill COVID-19 patients

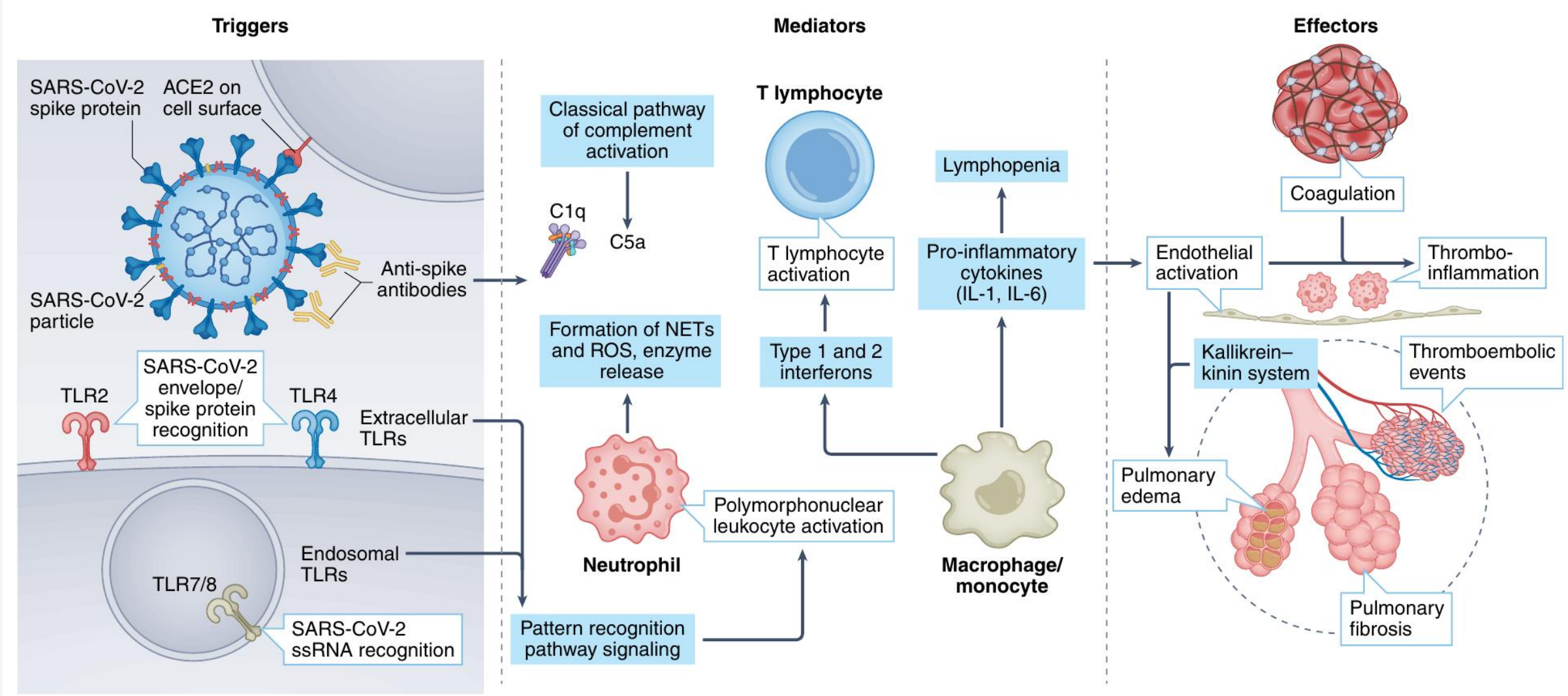
전남대학교병원 호흡기 내과
김태옥

Time course of COVID-19



Nat Microbiol **8**, 771–786 (2023)

Pathophysiological factors targeted by immune based therapies

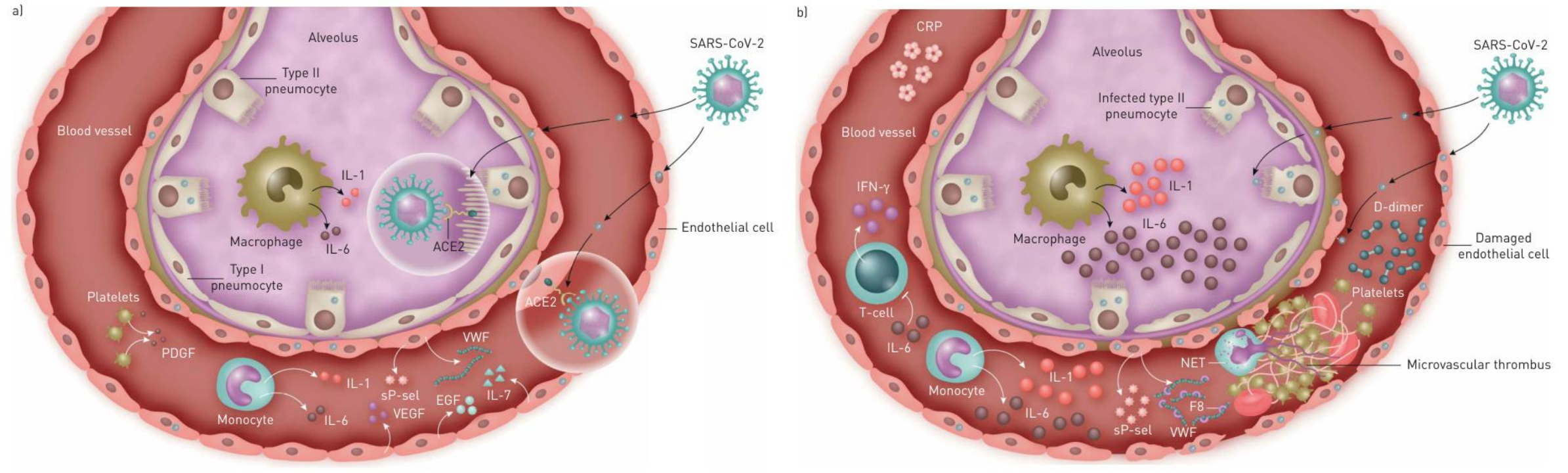


Nat Med 28, 39–50 (2022).

Cytokine Storm Syndrome

- Definition
  - ✓ immune dysregulation characterized by perpetuated activation of lymphocytes and macrophages
  - ✓ resulting in secretion of large quantities of cytokines;
  - ✓ leading to overwhelming systemic inflammation and multi-organ failure with high mortality.

Comparing mechanisms between mild and severe COVID-19

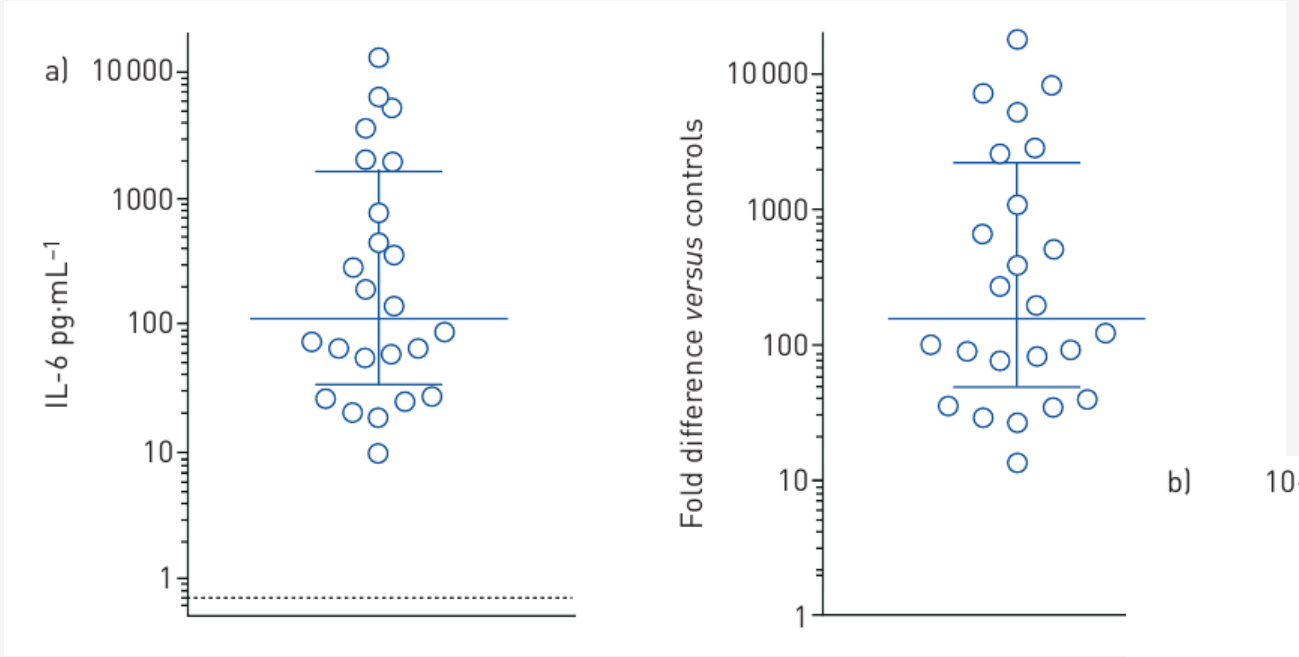


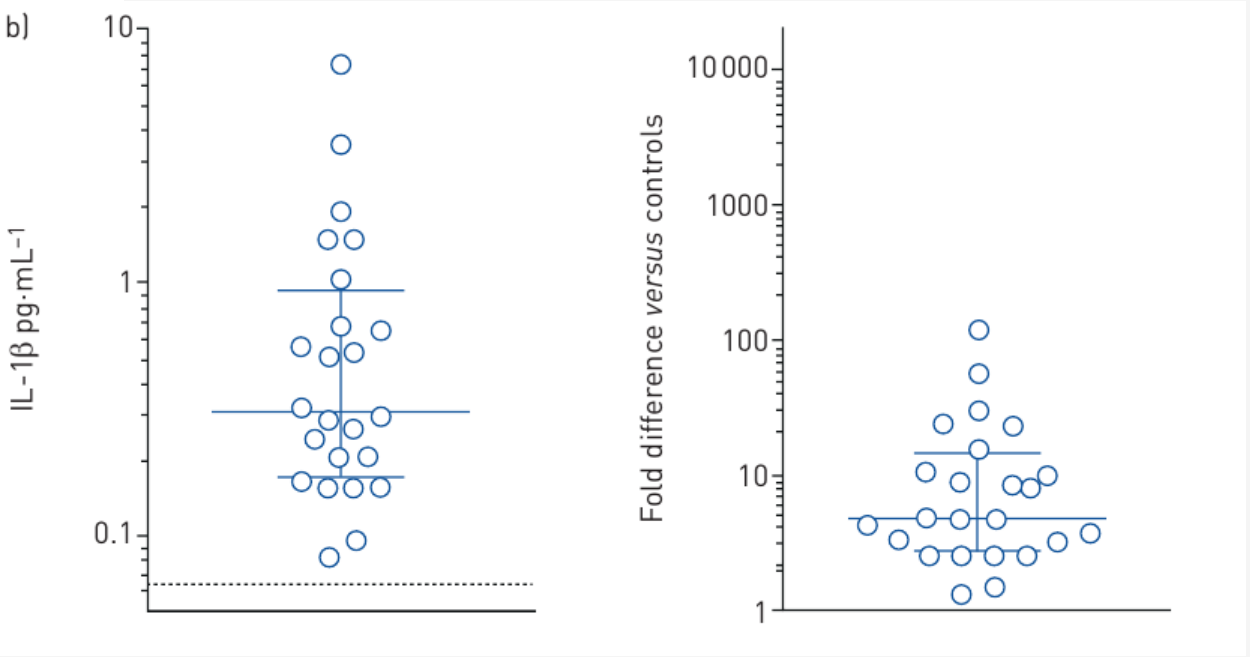
Low inflammatory cytokines and
high tissue reparative growth factors

High inflammatory cytokines and
Markers of endothelial activation

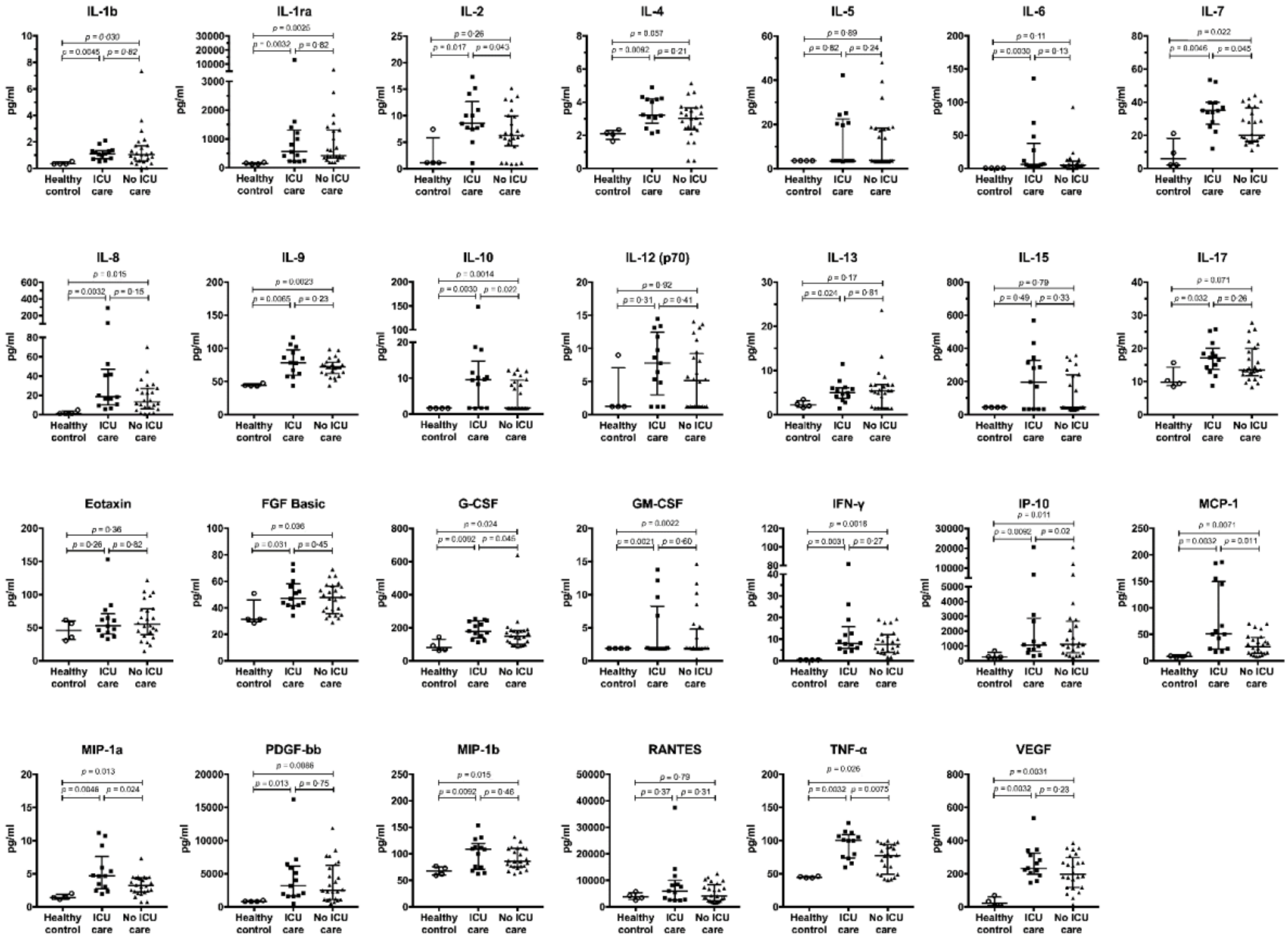
Eur Respir J 2020; 56: 2003006

Absolute cytokine levels in critically ill COVID-19 patients



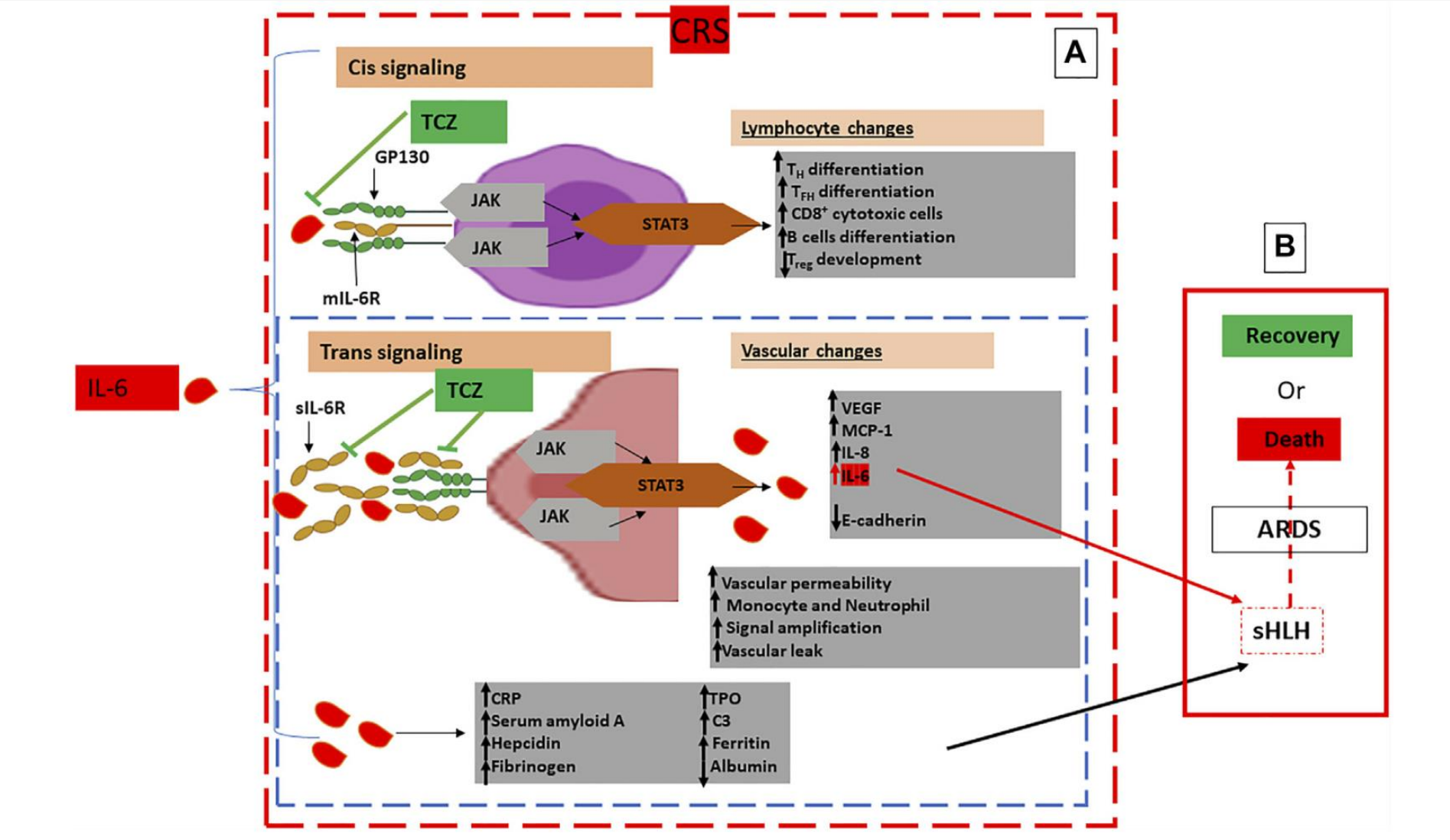


Eur Respir J 2020; 56: 2003006



10223):497-506.

Pathogenic Host Response to SARS-CoV-2 and Pathways to CRS



Front. Pharmacol. 13:825749.

Efficacy of Tocilizumab in COVID-19

Study	Key Inclusion Criteria	Primary Outcome	Characteristics of study population
COVACTA	Hypoxemia Bilateral chest infiltrates	Clinical status at Day 28, as measured by on OS	Oxygen support HFNC or NIV(30%), MV(38%) multiorgan failure(25%) Received corticosteroids at 36% in tocilizumab vs. 55% in placebo
EMPACTA	COVID-19 pneumonia	Progression to MV, ECMO, or death by Day 28	Corticosteroids: 80% in tocilizumab arm vs. 88% in placebo arm RDV: 53% in tocilizumab arm vs. 59% in placebo arm
BACC bay	1. ≥2 of the following conditions: Fever >38°C, Pulmonary infiltrates, Need for supplemental oxygen 2. ≥1 of the following laboratory criteria: CRP ≥50 mg/L, D-dimer >1,000 ng/mL, LDH ≥250 U/L, Ferritin >500 ng/mL	Progression to MV or death by Day 28	COT ≤6 L/min(80%), HFNC(4%), No oxygen(16%) Corticosteroids: 11% in tocilizumab arm vs. 6% in placebo arm RDV: 33% in tocilizumab arm vs. 29% in placebo arm
REMDACTA	COVID-19 pneumonia and requiring supplemental oxygen >6 L/min	Time to hospital discharge or readiness for discharge by Day 28	NIV or HFNC oxygen: 78% in tocilizumab vs. 83% in placebo MV or ECMO: 15% in tocilizumab vs. 11% in placebo Corticosteroid use: 83% in tocilizumab vs. 86% in placebo, during trial: 88% in both
REMAP-CAP	ICU admission Receipt of MV, NIV, or cardiovascular support	Composite of in-hospital mortality and organ support-free days to Day 21	HFNC oxygen or NIV(68%) MV(32%) Corticosteroids: 67% in SOC arm, 82% in tocilizumab arm, 89% in sarilumab arm
RECOVERY	SpO 2 <92% on room air or receipt of supplemental oxygen; CRP ≥75 mg/L	28-day all-cause mortality	COT(45%), HFNC or NIV(41%), MV(14%) Corticosteroids(82%)

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,

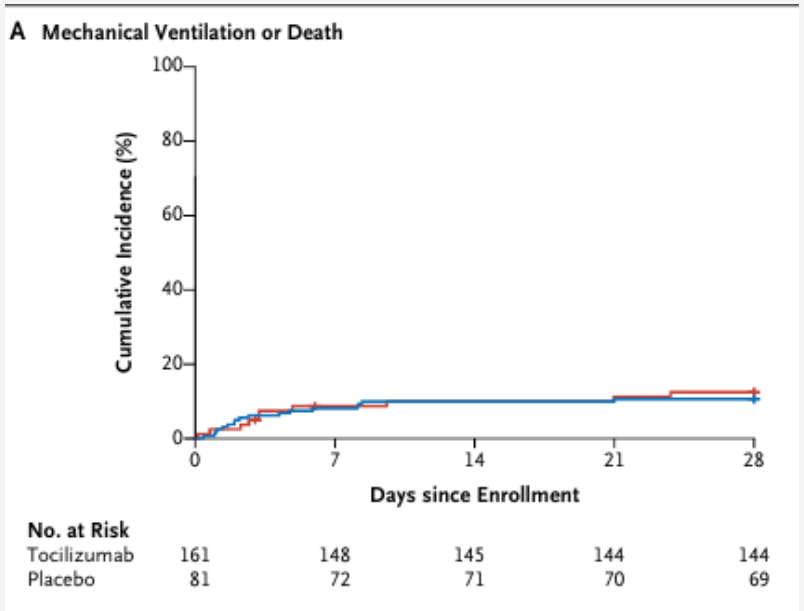
- Randomized, double-blind, placebo-controlled trial
- Hospitalized patients with fever, pulmonary infiltrates or the need for supplemental oxygen
- IV tocilizumab 8mg/kg (n=161) vs. Placebo (n=82), single dose
- Primary outcome
  - Intubation or death, assessed in a time to event analysis

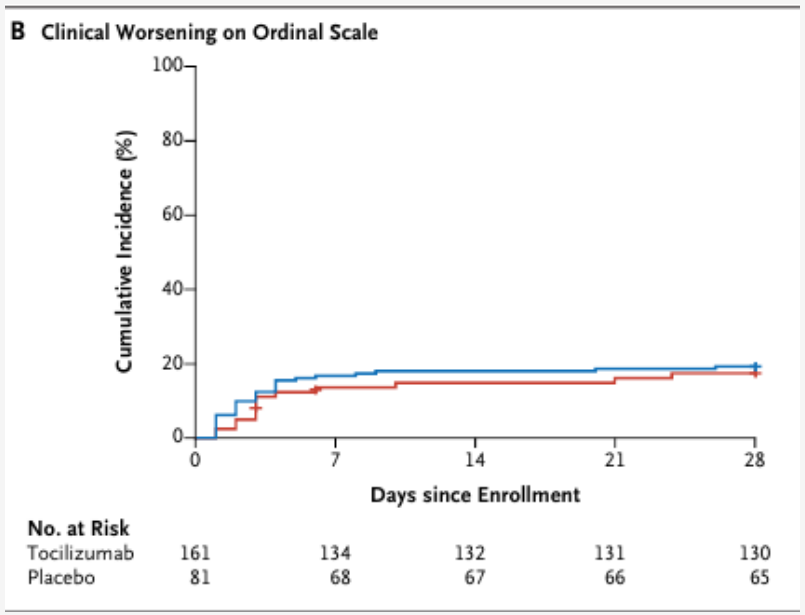
N Engl J Med 2020;383:2333-44.

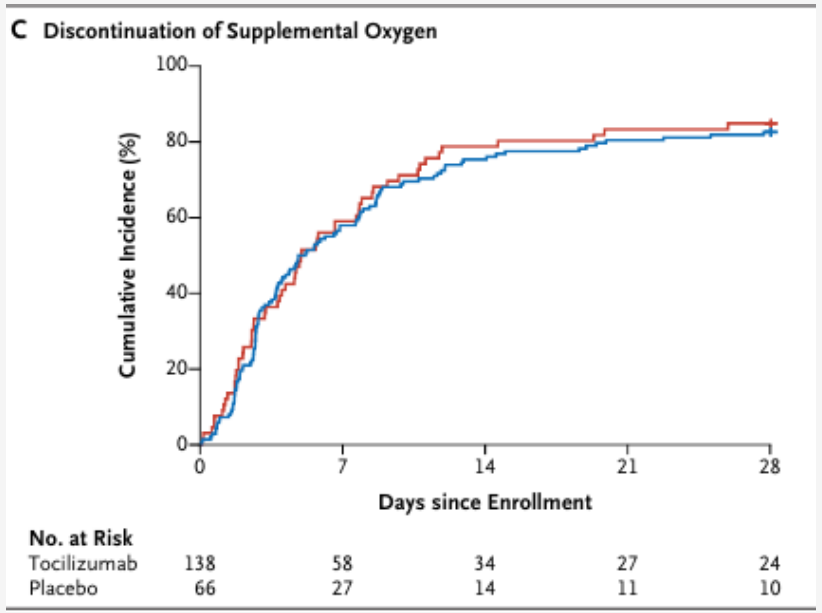
Table 2. Time-to-Event Outcomes in the Modified Intention-to-Treat Population.*

Outcome	No. of Patients with Event within 28 Days	Percentage of Patients with Event (95% CI)†		Median No. of Days to Event (95% CI)	Hazard Ratio (95% CI)	Log-Rank P Value‡
		Day 14	Day 28			
Measures of worsening						
Primary outcome: mechanical ventilation or death						
Tocilizumab	17	9.9 (6.2–15.7)	10.6 (6.7–16.6)	NR	0.83 (0.38–1.81)	0.64
Placebo	10	10.0 (5.1–18.9)	12.5 (6.9–22.0)	NR		
Secondary outcome: clinical worsening on ordinal scale§						
Tocilizumab	31	18.0 (12.9–24.9)	19.3 (14.0–26.2)	NR	1.11 (0.59–2.10)	0.73
Placebo	14	14.9 (8.7–24.7)	17.4 (10.7–27.7)	NR		
Tertiary outcome: mechanical ventilation¶						
Tocilizumab	11	6.8 (3.6–11.4)	6.8 (3.6–11.4)	NR	0.65 (0.26–1.62)	—
Placebo	8	10.0 (4.6–17.7)	10.0 (4.6–17.7)	NR		
Tertiary outcome: death						
Tocilizumab	9	4.4 (2.1–8.9)	5.6 (3.0–10.5)	NR	1.52 (0.41–5.61)	—
Placebo	3	1.3 (0.2–8.7)	3.8 (1.2–11.3)	NR		
Measures of improvement						
Secondary outcome: discontinuation of supplemental oxygen among patients receiving it at baseline						
Tocilizumab	114	75.4 (67.9–82.2)	82.6 (75.9–88.4)	5.0 (3.8–7.6)	0.94 (0.67–1.30)	0.69
Placebo	56	78.8 (68.3–87.7)	84.9 (75.2–92.2)	4.9 (3.8–7.8)		
Tertiary outcome: clinical improvement on ordinal scale§						
Tocilizumab	147	86.3 (80.6–91.1)	91.3 (86.3–95.1)	6.0 (5.0–6.0)	1.06 (0.80–1.41)	—
Placebo	72	81.5 (72.4–89.0)	88.9 (81.0–94.5)	5.0 (4.0–7.0)		
Tertiary outcome: initial discharge						
Tocilizumab	147	86.3 (80.6–91.1)	91.3 (86.3–95.0)	6.0 (4.0–7.0)	1.08 (0.81–1.43)	—
Placebo	72	81.5 (72.4–89.0)	88.9 (81.0–94.5)	6.0 (5.0–6.0)		

N Engl J Med 2020;383:2333-44.







N Engl J Med 2020;383:2333-44.

ORIGINAL ARTICLE

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

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

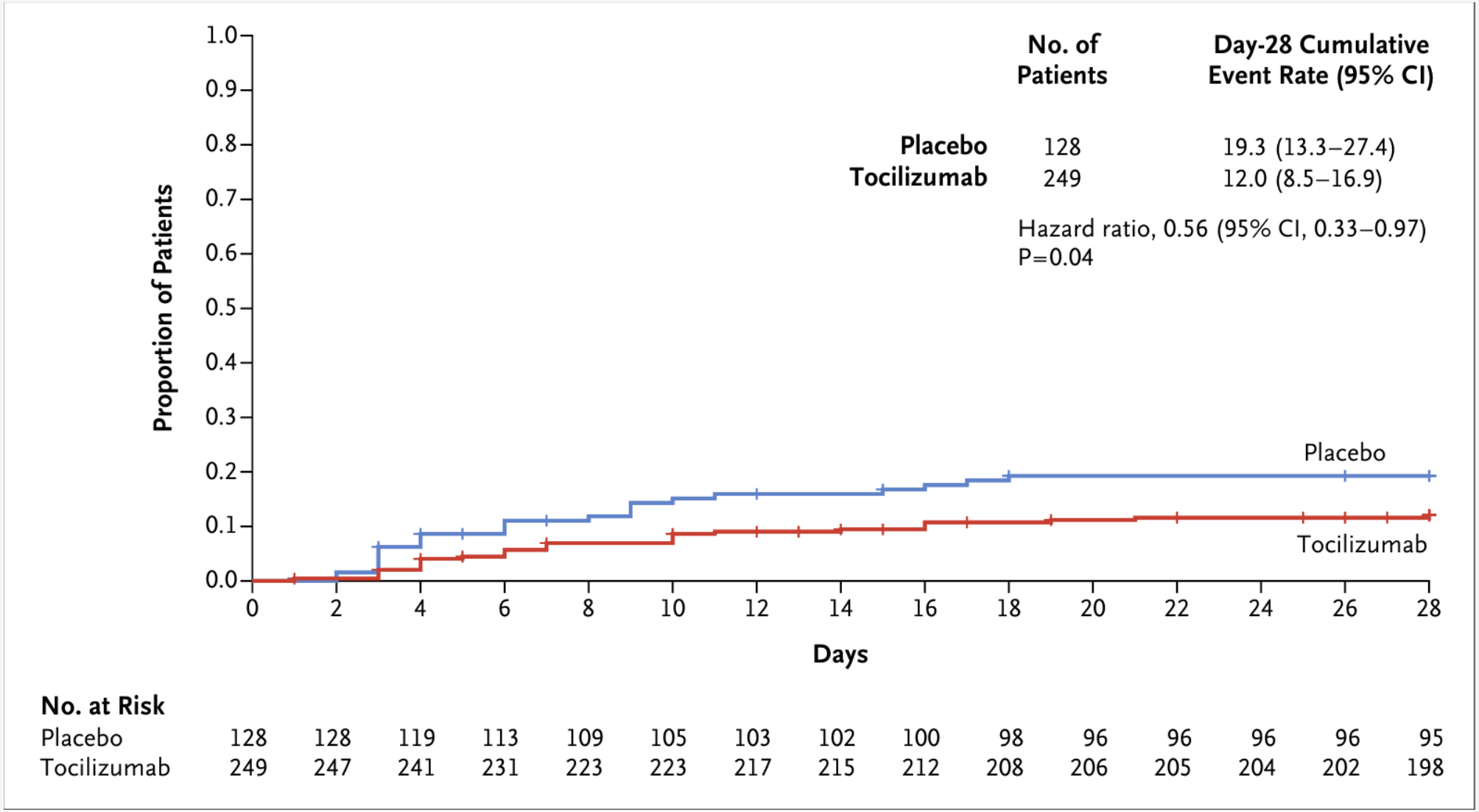
- Phase 3, Randomized, double-blind, placebo-controlled trial
- Hospitalized patients without receiving mechanical ventilation
- IV tocilizumab 8mg/kg vs. Placebo
- Primary outcome
  - Invasive mechanical ventilation or ECMO or death by day 28

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

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)**	

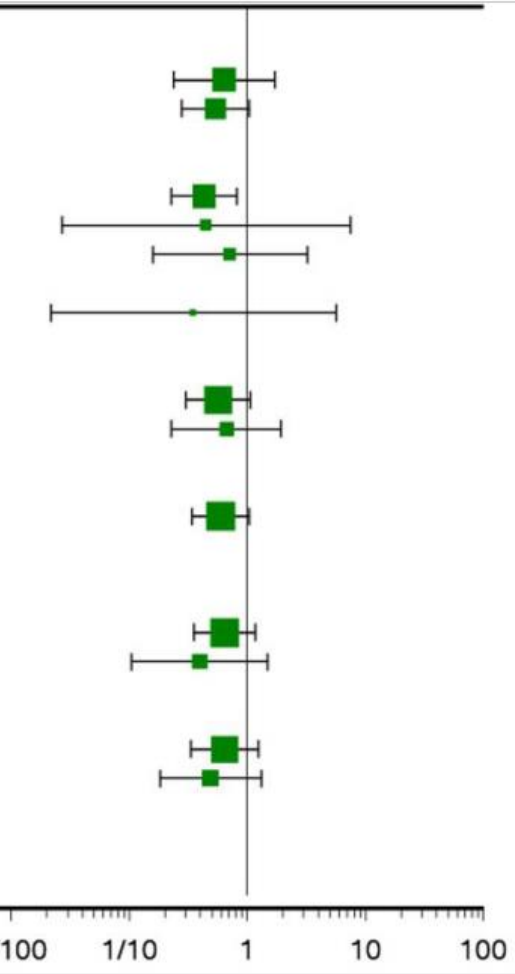
Time to mechanical ventilation or death



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

Subgroup analysis

Subgroups	Total	Tocilizumab (N=249)		Placebo (N=128)		Hazard Ratio (95% Wald CI)
	n	n	events	n	events	
Age (years)						
≤60	227	151	9	76	7	0.63 (0.23, 1.71)
>60	150	98	20	52	17	0.53 (0.28, 1.03)
Race/ethnicity combined						
Hispanic or Latino	211	143	19	68	19	0.43 (0.23, 0.82)
American Indian or Alaska Native	48	33	1	15	1	0.45 (0.03, 7.39)
Black or African American	56	35	4	21	3	0.71 (0.16, 3.21)
White	48	28	4	20	0	NE NE
Other/unknown	14	10	1	4	1	0.35 (0.02, 5.58)
Region						
USA	304	201	21	103	18	0.56 (0.30, 1.06)
Non-USA	73	48	8	25	6	0.66 (0.23, 1.93)
Systemic glucocorticoid use (within 7 days of Day 1 or concomitant)						
Yes	312	200	27	112	24	0.59 (0.34, 1.03)
No	65	49	2	16	0	NE NE
Antiviral treatment use (within 7 days of Day 1 or concomitant)						
Yes	297	196	25	101	19	0.64 (0.35, 1.16)
No	80	53	4	27	5	0.39 (0.10, 1.47)
Total number of study drug doses						
1	274	181	21	93	16	0.64 (0.33, 1.23)
2	103	68	8	35	8	0.49 (0.18, 1.30)



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

ORIGINAL ARTICLE

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

- Phase 3, Randomized, double-blind, placebo-controlled trial
- hospitalized with severe Covid-19 pneumonia
  - Bilateral pulmonary infiltrates
  - RA $SaO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg
- SoC : antiviral treatment, low-dose glucocorticoids, convalescent plasma and supportive care
- IV tocilizumab 8mg/kg (n=294) vs. Placebo (n=144)
- Primary outcome
  - Clinical status at day 28 on an 7 category ordinal scale
- 2ndary outcome
  - Mortality at day 28, time to improvement from baseline by at least 2 categories, time to hospital discharge

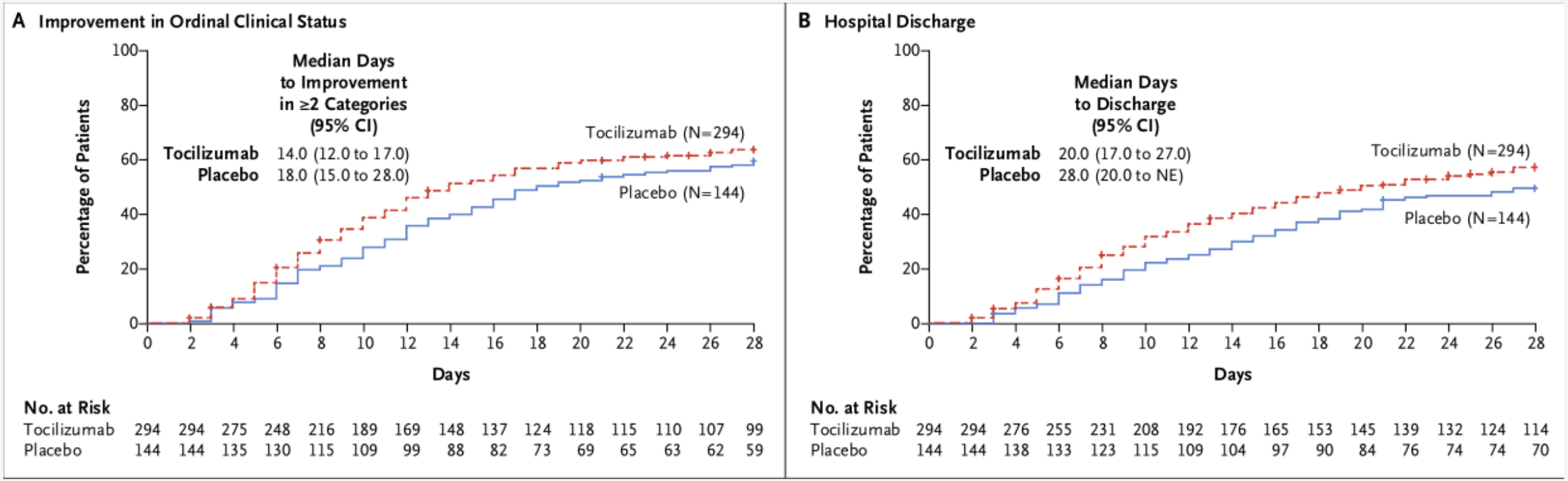
N Engl J Med 2021;384:1503-16.

Clinical status on 7-category ordinal scale at day 28

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)††	

N Engl J Med 2021;384:1503-16.



N Engl J Med 2021;384:1503-16.

The NEW ENGLAND JOURNAL of MEDICINE

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

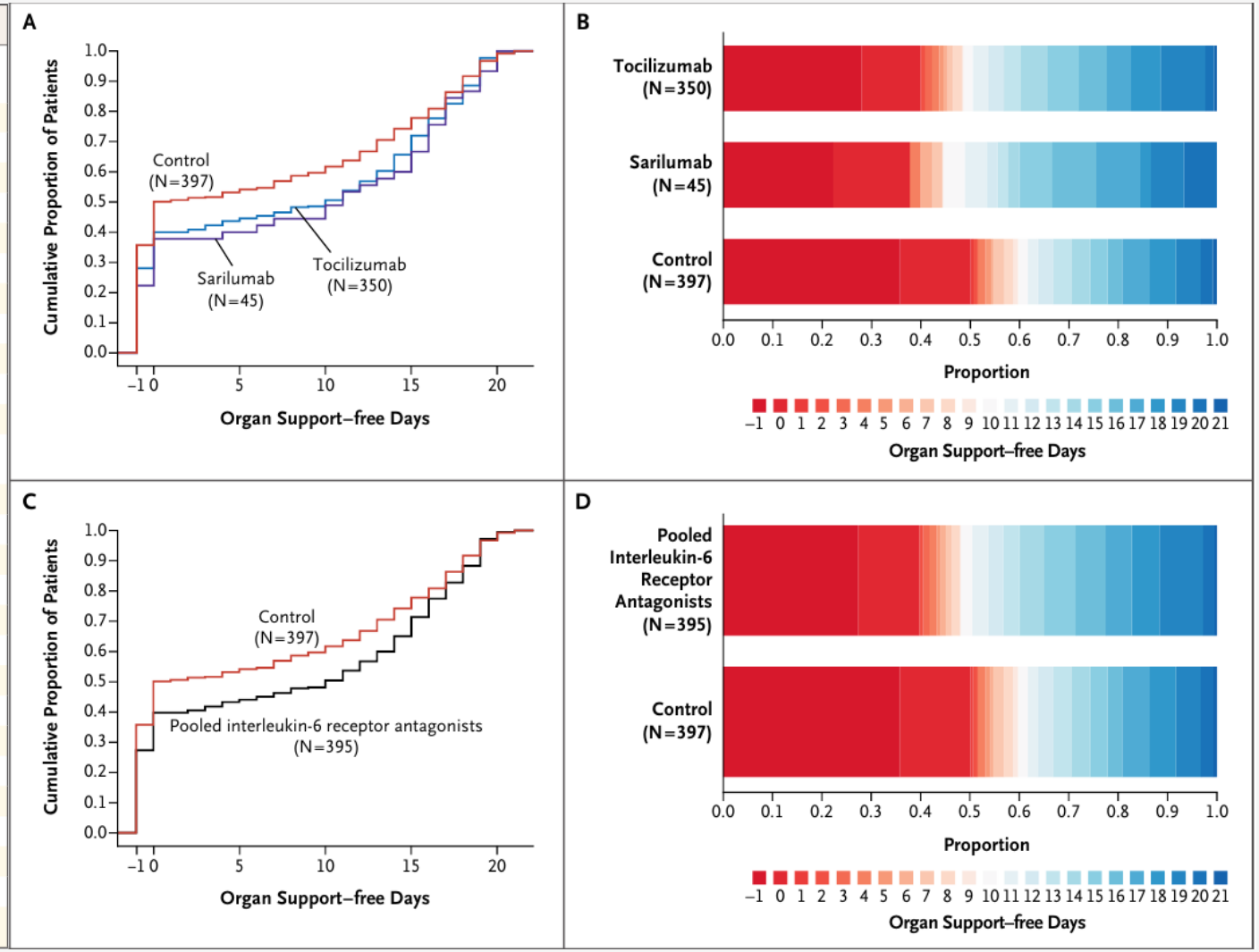
Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

- Multifactorial, adaptive platform trial
- Within 24 hours after starting organ support in ICU
  - Respiratory organ support : invasive MV or NIV or HFNC (≥ 30L/min and ≥ 0.4)
  - Cardiovascular organ support : IV infusion of any vasopressor or inotrope
- IV tocilizumab (8mg/kg) or Sarilumab (400mg) vs. Placebo
- Primary outcome
  - Respiratory and cardiovascular organ support–free days, on an ordinal scale combining in-hospital death and days free of organ support to day 21

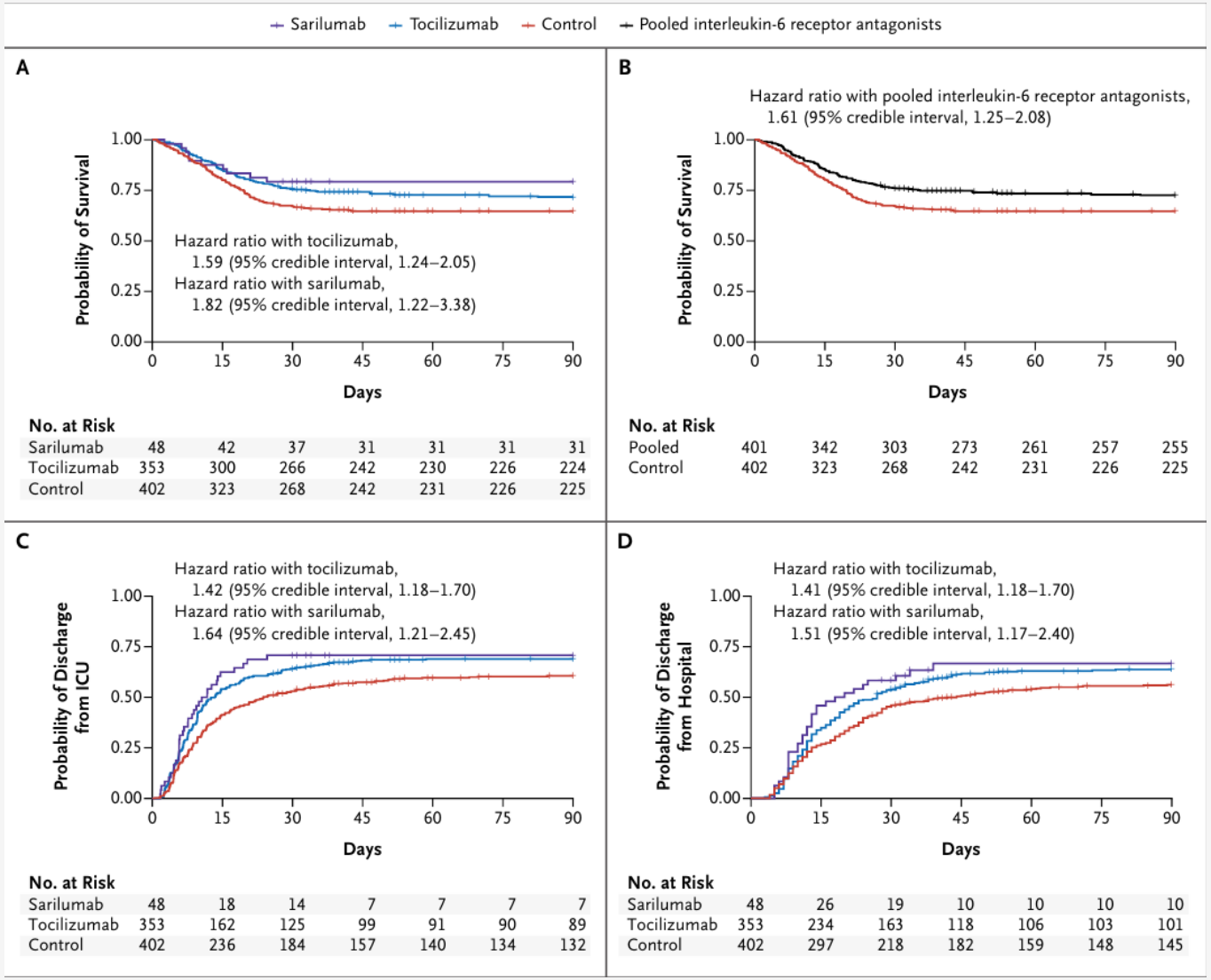
N Engl J Med 2021;384:1491-502.

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	—



Time to survival and ICU and hospital discharge



N Engl J Med 2021;384:1491-502.

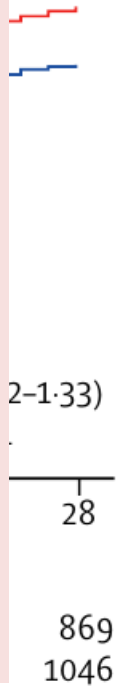
Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

- Randomized, controlled, open-label, platform trial
- Hospitalized in general ward with Covid-19
  - ✓ Hypoxia (RA SaO2 < 92%) and CRP ≥ 75 mg/L
- SoC : dexamethasone(82%)
- IV tocilizumab 400-800mg(depending on weight)
- Primary outcome
  - ✓ 28-day mortality

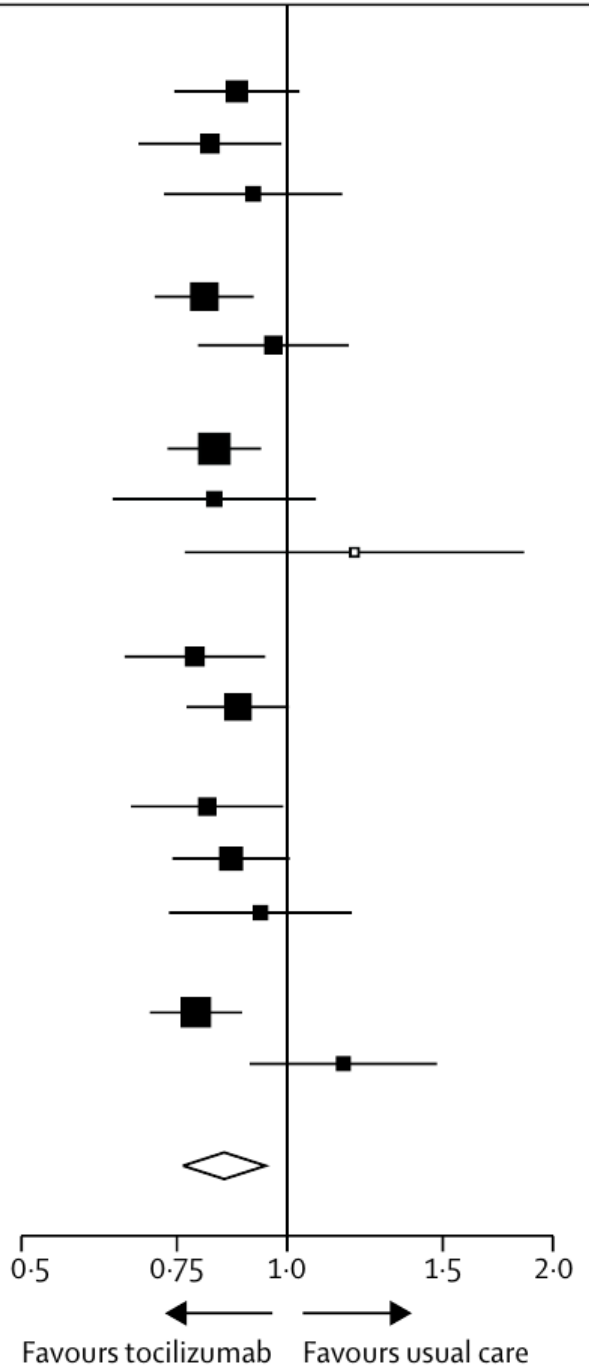
Lancet 2021; 397: 1637–45

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

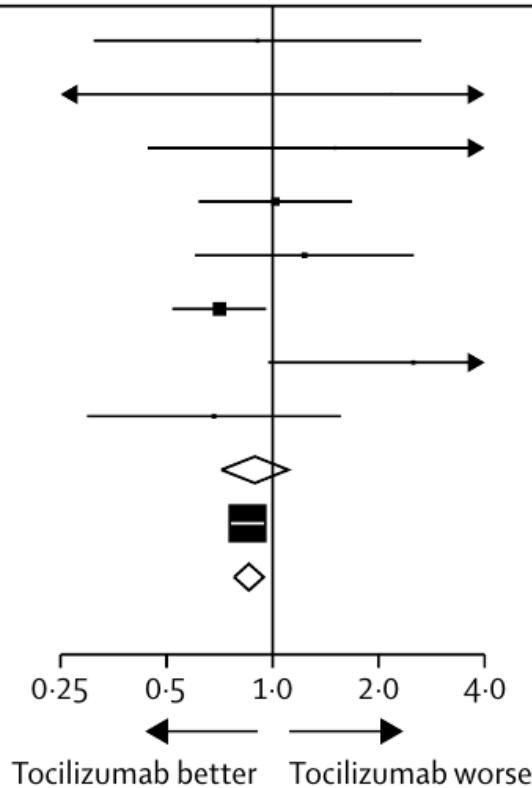


Lancet 2021; 397: 1637–45

	Tocilizumab group	Usual care group	Risk ratio (95% CI)
Age, years (χ^2_1=0·0; p=0·88)			
<70	273/1331 (21%)	309/1355 (23%)	0·88 (0·74–1·03)
70–79	212/478 (44%)	245/480 (51%)	0·82 (0·68–0·99)
≥80	136/213 (64%)	175/259 (68%)	0·92 (0·73–1·15)
Sex (χ^2_1=2·4; p=0·12)			
Men	417/1337 (31%)	529/1437 (37%)	0·80 (0·71–0·91)
Women	204/685 (30%)	200/657 (30%)	0·97 (0·80–1·18)
Ethnicity (χ^2_1=0·0; p=0·98)			
White	476/1530 (31%)	573/1597 (36%)	0·83 (0·73–0·94)
Black, Asian, or minority ethnic	99/354 (28%)	123/378 (33%)	0·83 (0·64–1·09)
Unknown	46/138 (33%)	33/119 (28%)	1·20 (0·77–1·88)
Days since symptom onset (χ^2_1=1·1; p=0·30)			
≤7	214/668 (32%)	256/660 (39%)	0·78 (0·65–0·94)
>7	407/1354 (30%)	473/1433 (33%)	0·88 (0·77–1·01)
Respiratory support at randomisation (χ^2_1=0·8; p=0·38)			
No ventilator support*	180/935 (19%)	214/933 (23%)	0·81 (0·67–0·99)
Non-invasive ventilation†	310/819 (38%)	366/867 (42%)	0·86 (0·74–1·00)
Invasive mechanical ventilation‡	131/268 (49%)	149/294 (51%)	0·93 (0·74–1·18)
Use of corticosteroids§ (χ^2_1=7·7; p=0·01)			
Yes	482/1664 (29%)	600/1721 (35%)	0·79 (0·70–0·89)
No	139/357 (39%)	127/367 (35%)	1·16 (0·91–1·48)
Unknown	0/1 (0%)	2/6 (33%)	..
All participants	**621/2022 (31%)**	**729/2094 (35%)**	**0·85 (0·76–0·94)**
			p=0·0028



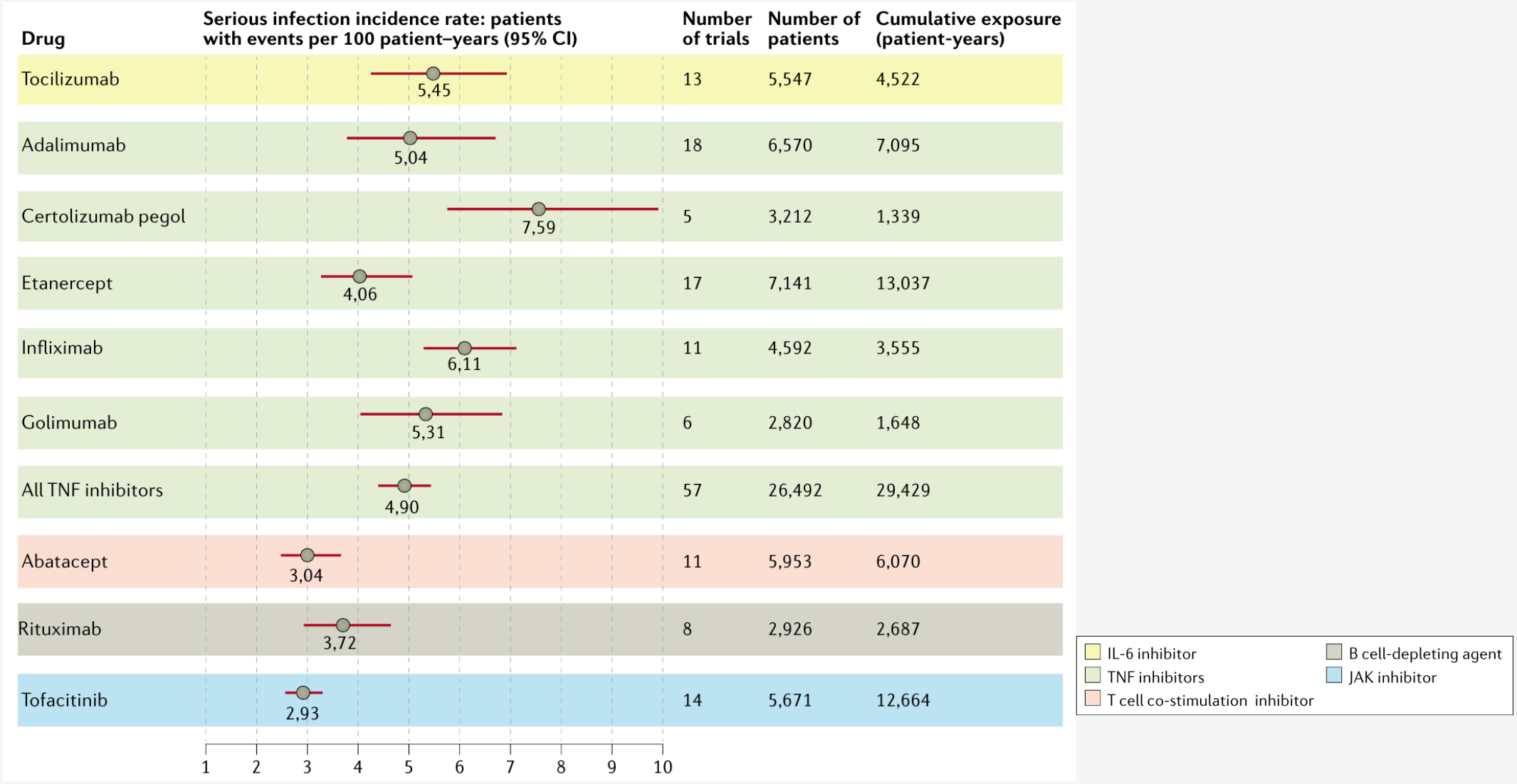
	Deaths/patients randomly assigned (%)		Observed minus expected deaths*		Ratio of death rates, rate ratio (95% CI)
	Tocilizumab group	Usual care group	(O–E)	Var (O–E)	
CORIMUNO–TOCI[10]	7/64 (11%)	8/67 (12%)	–0·3	3·3	0·91 (0·31–2·65)
RCT–TCZ–COVID-19[11]	2/60 (3%)	1/66 (2%)	0·6	0·7	2·17 (0·22–21·3)
BACC Bay[12]	9/161 (6%)	(3/82) ×2† (4%)	1·0	2·6	1·51 (0·44–5·13)
COVACTA[9]	58/294 (20%)	(28/144) ×2† (19%)	0·3	15·3	1·02 (0·62–1·68)
EMPACTA[13]	26/249 (10%)	(11/128) ×2† (9%)	1·6	7·5	1·23 (0·60–2·52)
REMAP–CAP[15]	98/353 (28%)	142/402 (35%)	–14·2	40·8	0·71 (0·52–0·96)
TOCIBRAS[8]	14/65 (22%)	6/64 (9%)	3·9	4·3	2·51 (0·97–6·50)
COVINTOC[14]	11/91 (12%)	15/89 (17%)	–2·1	5·6	0·68 (0·30–1·56)
Subtotal: eight trials	**225/1337 (17%)**	**256/1396 (18%)**	**–9·3**	**80·1**	**0·89 (0·72–1·11)**
RECOVERY	621/2022 (31%)	729/2094 (35%)	–54·4	330·6	0·85 (0·76–0·94)
All trials	**846/3359 (25%)**	**985/3490 (28%)**	**–63·7**	**410·7**	**0·86 (0·78–0·94)**
					p=0·0017



Lancet 2021; 397: 1637–45

Safety of Tocilizumab in COVID-19

Estimated serious infection rates among clinical trials of biologics in RA



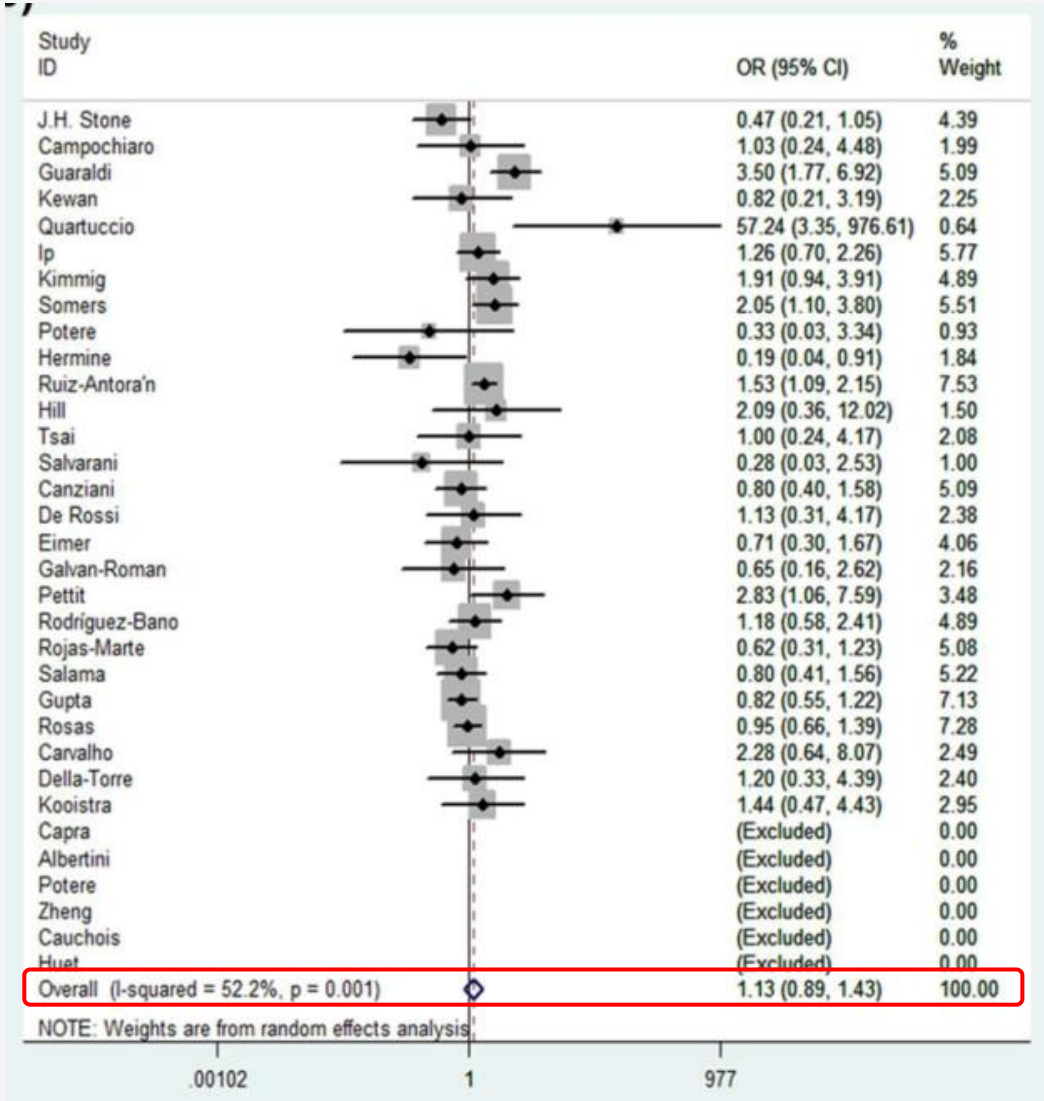
Nat Rev Rheumatol 13, 399–409 (2017)

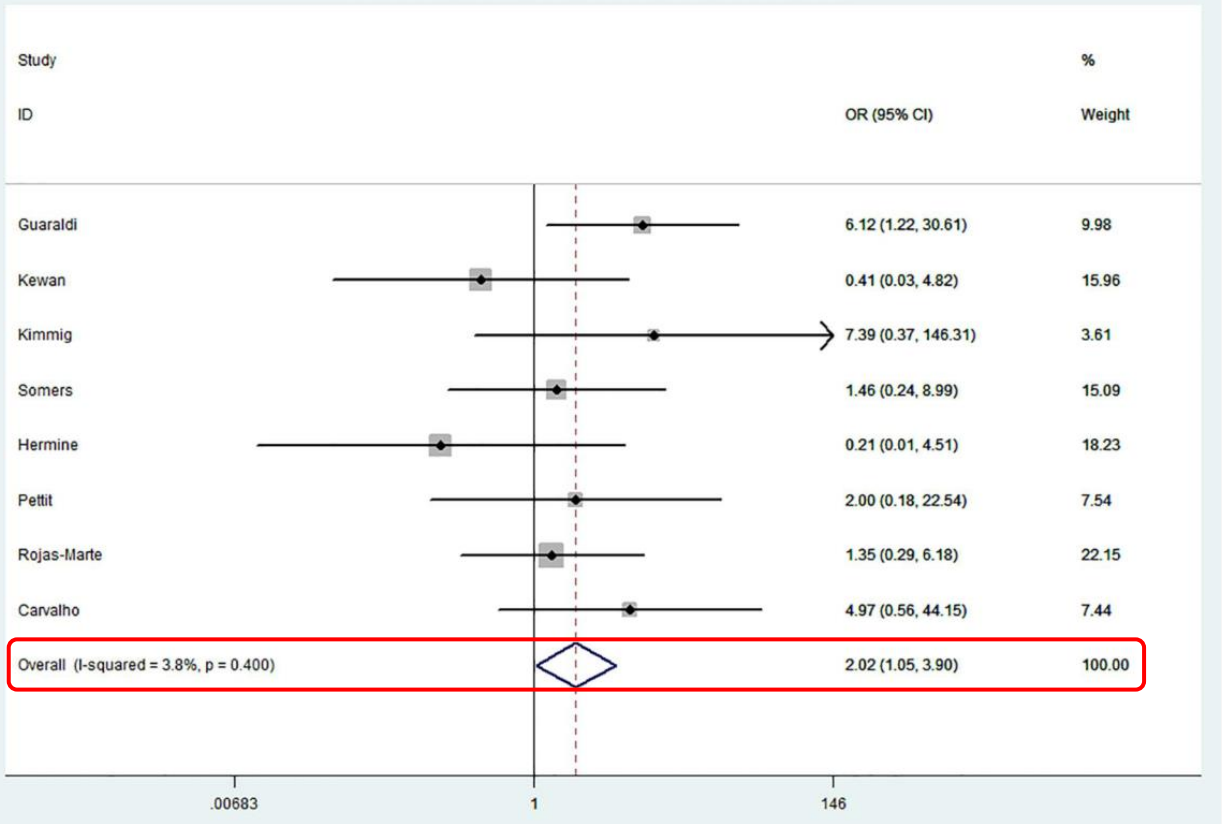
Webtable 2: Effect of allocation to tocilizumab on cause-specific 28-day mortality

	Treatment allocation		
	Tocilizumab (n=2022)	Usual care (n=2094)	Absolute percent difference (95% CI)
COVID-19	595 (29.4%)	699 (33.4%)	-3.95 (-6.79,-1.12)
Other infection	1 (0.0%)	6 (0.3%)	-0.24 (-0.49,0.01)
Cardiac	1 (0.0%)	3 (0.1%)	-0.09 (-0.28,0.09)
Stroke	2 (0.1%)	2 (0.1%)	0.00 (-0.19,0.19)
Other vascular	1 (0.0%)	2 (0.1%)	-0.05 (-0.21,0.12)
Cancer	6 (0.3%)	3 (0.1%)	0.15 (-0.13,0.44)
Other medical	14 (0.7%)	12 (0.6%)	0.12 (-0.37,0.60)
External	0 (0.0%)	0 (0.0%)	-
Unknown cause	1 (0.0%)	2 (0.1%)	-0.05 (-0.21,0.12)
All-cause	621 (30.7%)	729 (34.8%)	-4.10 (-6.97,-1.24)

Lancet 2021; 397: 1637–45

Secondary bacterial & fungal infection





Rev Med Virol. 2022;32:e2295.

Secondary infections in patients received tocilizumab

Bacterial and fungal infections amongst intensive care unit (ICU) patients at University Hospital Limerick (January—December 2021)

		COVID-19 ICU patients		General ICU patients
		Tocilizumab	No tocilizumab	
	N	41	33	332
Bacterial infection, % (*N*)	HAP	59 (24)	30 (10)	8 (27)
	BSI	46 (19)	27 (9)	5 (17)
	CAUTI	12 (5)	12 (4)	3 (9)
	Clostridioides difficile	0 (0)	3 (1)	1 (3)
	SSTI	2 (1)	0 (0)	0 (0)
Fungal infection, % (*N*)	IFD	10 (4)	3 (1)	1 (2)
	Candidemia	7 (3)	0 (0)	1 (3)
Time to detection of first bacterial infection (days)	From hospital admission			
	Median	14	22	-
	Range	3—102	3—94	-
	From tozilizumab administration			
	Median	13	-	-
	Range	1—95	-	-

Journal of Hospital Infection 126 (2022)29-36

Secondary infections in patients received tocilizumab

Table 1. Outc

	49)	*P*
Mechanical ve		0.34
Extracorporal		0.12
Secondary inf		0.02
Death (%)		0.67

Table 2. Incidence of Secondary infections in tocilizumab and control groups.

	Tocilizumab group (n = 66)	Control group (n = 49)
Gram-positive pneumonia	4 (6.1%)	4 (8.2%)
	Staphylococcus aureus (4)	*S. aureus (4)*
Gram-negative pneumonia	20 (30.3%)	7 (14.3%)
	Stenotrophomonas (4)	*Pseudomonas (4)*
	Serratia (4)	*Escherichia coli (2)*
	Pseudomonas (3)	*Acinetobacter (1)*
	Enterobacter (3)	
	Klebsiella (2)	
	Escherichia coli (2)	
	Haemophilus influenzae (2)	
Fungal pneumonia	5 (7.6%)	2 (4.1%)
	Candida (4)	*Candida (2)*
	Aspergillus (1)	
Gram-positive bacteremia	4 (6.1%)	2 (4.1%)
	S. aureus (2)	*Staphylococcus epidermidis (1)*
	Enterococcus (1)	*Micrococcus (1)*
	Streptococcus pneumoniae (1)	
Gram-negative bacteremia	5 (7.6%)	1 (2.0%)
	Enterobacter (3)	*Pseudomonas (1)*
	Pseudomonas (2)	
Fungemia	2 (3.0%)	0 (0%)
	Candida (2)	

American Journal of Therapeutics 29, e275–e278 (2022)

Secondary infections in patients received tocilizumab vs. baricitinib

Outcomes	Before Weighting		After Weighting		
	Tocilizumab	Baricitinib	Tocilizumab *vs.* baricitinib		
	% (N)	% (N)	HR[a]	95% CI	*p*-value
Clinical improvement on WHO clinical progression scale by ≥ 1 score	84.8% (165)	81.6% (76)	0.86	(0.57, 1.29)	0.459
Hospital discharge (score ≤ 3)	80.6% (165)	78.9% (76)	0.85	(0.57, 1.27)	0.418
Recovery (score ≤ 4)	75.4% (118)	68.6% (51)	1.04	(0.64, 1.67)	0.883
Viral clearance (first negative PCR result)	47.7% (155)	33.3% (72)	1.94	(1.01, 3.73)	0.048
Low viral load (Ct value ≥ 35)	46.8% (156)	35.2% (71)	1.49	(0.85, 2.60)	0.162
IgG antibody	85.5% (138)	84.9% (53)	0.97	(0.61, 1.54)	0.909
Outcomes	**% (N)**	**% (N)**	**HR[b]**	**95% CI**	***p*-value**
In-hospital death or invasive mechanical ventilation (score ≥ 7) or intensive care unit admission	33.6% (137)	27.3% (66)	0.96	(0.47, 2.00)	0.922
In-hospital death (score = 10)	17.6% (165)	19.7% (76)	0.63	(0.29, 1.35)	0.233
Severe liver injury	18.5% (162)	13.2% (76)	1.15	(0.43, 3.08)	0.778
Acute renal failure	11.6% (164)	5.3% (76)	2.33	(0.61, 8.82)	0.213
Hyperinflammatory syndrome	88.9% (18)	64.3% (14)	2.32	(0.87, 6.25)	0.091
Secondary infection	7.4% (163)	2.6% (76)	2.97	(0.62, 14.31)	0.173
Thrombotic and bleeding events	10.6% (141)	4.9% (41)	1.39	(0.32, 6.00)	0.658

Note: CI, confidence interval; Ct = cycle threshold; HR, hazard ratio; IgG = immunoglobulin G; PCR, polymerase chain reaction.

[a]HR > 1 (or <1) indicates that tocilizumab use was associated with better (worse) clinical improvement, earlier (later) hospital discharge or recovery compared to that of baricitinib.

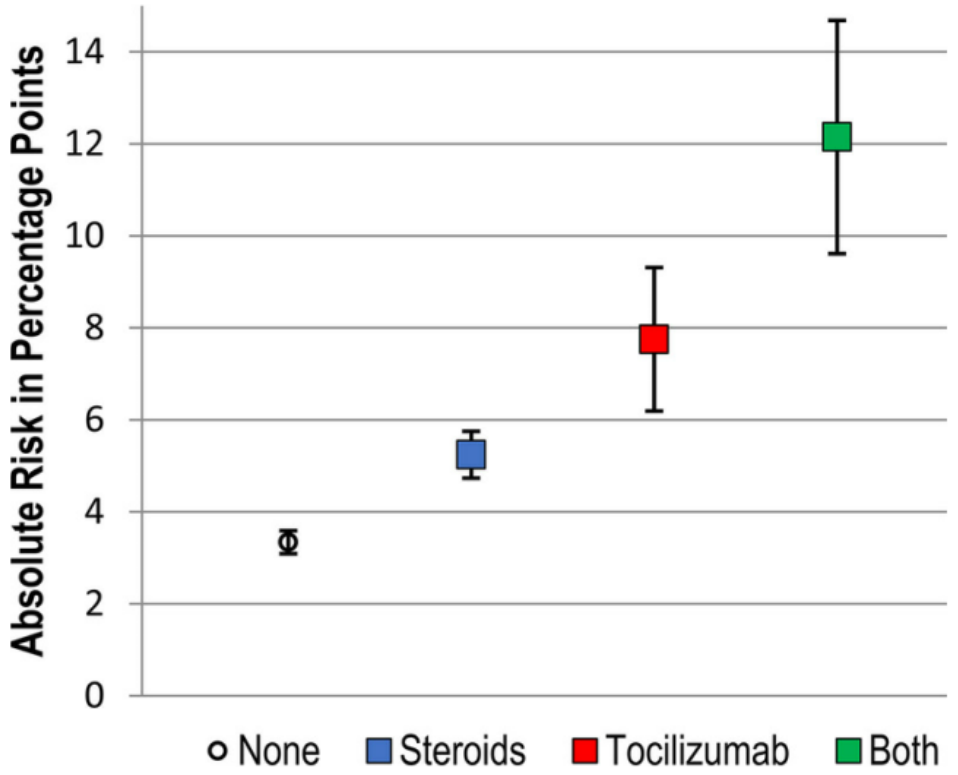
[b]HR > 1 (or <1) indicates that tocilizumab use was associated with higher (lower) risk of adverse clinical outcomes compared to that of baricitinib.

Front. Pharmacol. 13:866441.

Risk factors of bacterial infection

Immunosuppression by hospital day 2

Corticosteroids	5.2 (4.7, 5.8)
Tocilizumab	7.8 (6.2, 9.3)
Both	12.2 (9.6, 14.7)
Neither	3.3 (3.1, 3.6)



Risk and benefit of Tocilizumab in COVID-19

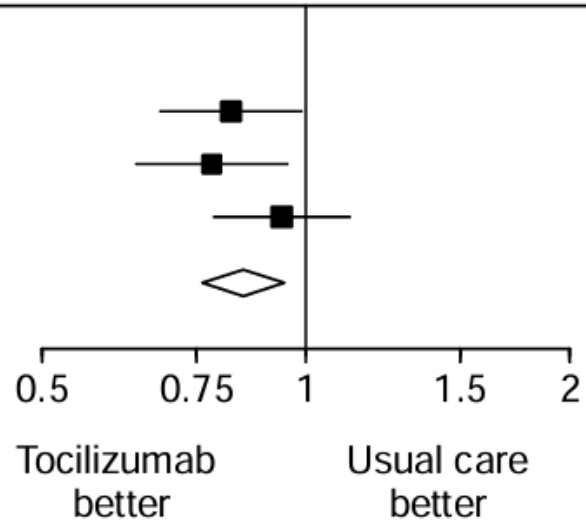
- RECOVERY
  - ✓ Hospitalized in general ward with Covid-19
    - Hypoxia (RA SaO2 < 92%) and CRP ≥ 75 mg/L

- ✓ REMAP-CAP
  - ✓ Within 24 hours after starting organ support in ICU
    - Respiratory organ support : invasive MV or NIV or HFNC (≥ 30L/min and ≥ 0.4)
    - Cardiovascular organ support : IV infusion of any vasopressor or inotrope

A high CRP is a indicator of tocilizumab's effectiveness

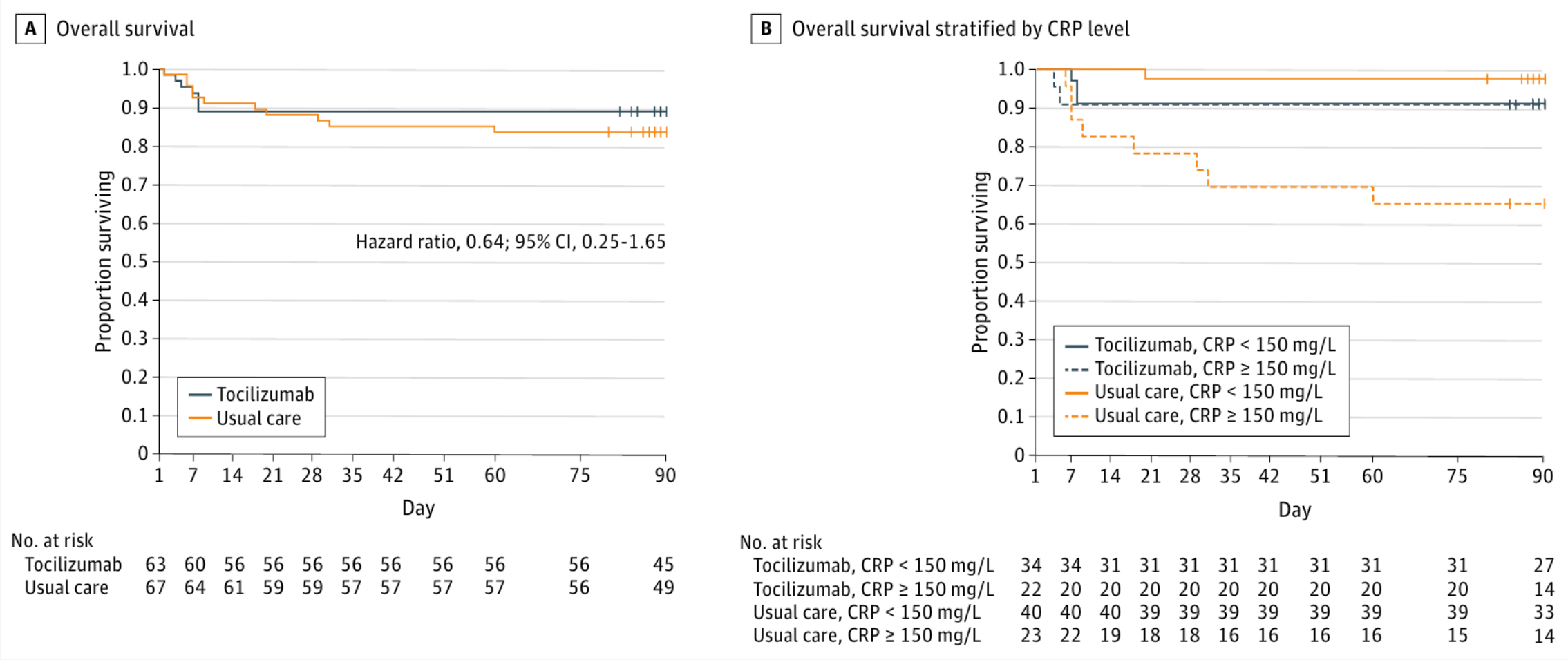
Effect of allocation to tocilizumab on 28−day mortality by baseline C−reactive protein

	Tocilizumab	Usual care	RR (95% CI)
C−reactive protein, mg/L (c_1^2=1.1; p=0.30)			
³75 <120	208/712 (29%)	248/734 (34%)	0.82 (0.68−0.99)
³120 <180	177/634 (28%)	222/645 (34%)	0.78 (0.64−0.95)
³180	236/676 (35%)	259/715 (36%)	0.94 (0.79−1.12)
All participants	**621/2022 (31%)**	**729/2094 (35%)**	**0.85 (0.76−0.94) p=0.0028**



Lancet 2021; 397: 1637–45

A high CRP is a indicator of tocilizumab's effectiveness



JAMA Intern Med. 2021;181(9):1241-1243.

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a,b]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other systemic corticosteroids **(AIII)** for the treatment of COVID-19.[c]	
	Patients who are at high risk of progressing to severe COVID-19[a,b]	**Remdesivir**[d] **(BIII)**	
Hospitalized and Requires Conventional Oxygen[e]	Patients who require minimal conventional oxygen	**Remdesivir**[d,f] **(BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] **(CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[f] **(BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[g] **(BIIa)** or **IV tocilizumab**[g] **(BIIa)** to 1 of the options above.	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	**Dexamethasone** should be administered to all patients **(AI)**. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): • **PO baricitinib**[g,i] **(AI)** • **IV tocilizumab**[g,i] **(BIIa)** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**.[j]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation **(BIII)**.
Hospitalized and Requires MV or ECMO	All patients	**Dexamethasone** should be administered to all patients **(AI)**. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • **PO baricitinib**[g,i] **(BIIa)** • **IV tocilizumab**[g,i] **(BIIa)**	

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

Windows 정품 인증

Tocilizumab in Korean critically ill COVID-19 patients

- Retrospective, multicenter study
- 1114 critically ill COVID-19 patients
- 96 patients (8.6%) received tocilizumab
- All patients received dexamethasone before tocilizumab and 89(92.7%) patients received remdesivir

	Tocilizumab(+)	Tocilizumab(-)	P-value
Sex, male	64(667%)	608(59.8%)	0.302
Age	61.2(14.3)	68.3(13.7)	<0.001
BMI	25.5(4.07)	24.8(5.15)	0.095
Underline disease			
HTN	39(40.6%)	560(55.1%)	0.014
DM	28(29.2%)	348(34.2%)	0.470
Cardiovascular disease	9(9.4%)	120(11.8%)	0.728
Chronic lung disease	6(6.3%)	84(8.3%)	0.754
Chronic kidney disease	6(6.3%)	74(7.3%)	0.898
Malignancy	5(5.2%)	75(7.4%)	0.706
LAB			
WBC	8.45(5.74)	9.02(6.71)	0.464
CRP	39.9(174.8)	22.2(46.8)	0.014
Lactate	1.64(0.76)	2.04(2.69)	0.216

	Tocilizumab(+)	Tocilizumab(-)	P-value
Treatment drug			
Remdesivir	736(72.4%)	89(92.7%)	<0.001
Dexamethasone	96(100%)	961(94.5%)	0.060
Time to tocilizumab after dexa	3.5(4.8)		
Time to tocilizumab after symptom	9.0(5.7)		
MV	57(59.4%)	581(57.1%)	0.630
CRRT	11(11.5%)	117(11.5%)	0.937
ICU LOS	19.4(23.4)	22.4(23.3)	0.242
Hospital LOS	30.6(32.5)	32.6(34.7)	0.589
ICU mortality	20(20.8%)	241(24.5%)	0.614
Hospital mortality	21(21.9%)	273(26.8%)	0.812
Blood stream infection	16(16.7%)	191(18.8%)	0.621

	Death	Survival	P-value	
HTN	175(59.5%)	423(51.6%)	0.044	<0.001
Chronic lung disease	38(12.9%)	52(6.3%)	0.002	
Cardiovascular disease	47(16.0%)	82(10.0%)	0.022	
Chronic neurologic disease	61(20.7%)	92(11.2%)	<0.001	
Chronic kidney disease	36(12.2%)	44(5.4%)	<0.001	
Malignancy	38(12.9%)	42(5.1%)	<0.001	
Remdesivir	204(69.4%)	621(75.8%)	0.023	
MV	251(85.4%)	388(47.4%)	<0.001	
ECMO	73(24.8%)	54(6.6%)	<0.001	<0.001
CRRT	99(33.7%)	29(3.5%)	<0.001	<0.001
Blood stream infection	86(29.3%)	121(14.8%)	<0.001	
Tocilizumab	21(7.1%)	75(9.2%)	0.812	
Age	74.4(12.2)	65.2(13.6)	<0.001	
WBC	10.28(9.93)	8.49(4.86)	<0.001	
CRP	27.7(104.2)	22.5(49.2)	0.258	
Lactate	2.73(4.48)	174(1.25)	<0.001	0.055
SOFA in MV	8.3(3.34)	7.2(3.1)	<0.001	

	Survival(n=75)	Death(n=21)	P-value
Sex, male	48(64.0%)	608(59.8%)	0.295
Age	57.9(13.3)	72.8(11.5)	<0.001
BMI	25.2(3.30)	25.5(4.27)	0.095
Underline disease			
HTN	28(37.3%)	11(52.4%)	0.215
DM	20(26.7%)	8(38.1%)	0.308
Cardiovascular disease	6(8.0%)	3(14.3%)	0.382
Chronic lung disease	2(2.7%)	4(19.0%)	0.020
Chronic kidney disease	4(5.3%)	2(9.5%)	0.483
Malignancy	2(2.7%)	3(14.3%)	0.068
LAB			
WBC	8.33(6.15)	8.88(4.07)	0.626
CRP	18.5(40.6)	116.9(362.2)	0.022
Lactate	1.62(0.79)	1.18(1.98)	0.666

	Survival(n=75)	Death(n=21)	P-value
Treatment drug			
Remdesivir	69(92.0%)	20(95.2%)	0.614
MV	38(50.7%)	19(90.5%)	0.001
CRRT	2(2.7%)	9(42.9%)	<0.001
Time to tocilizumab after symptom	8.6(4.2)	11.0(10.1)	0152
Time to tocilizumab after dexa	3.1(3.3)	5.2(8.3)	0.079
CRRT	11(11.5%)	117(11.5%)	0.937
ICU LOS	19.4(23.4)	22.4(23.3)	0.242
Hospital LOS	30.6(32.5)	32.6(34.7)	0.589
Blood stream infection	11(14.7%)	5(23.8%)	0.301


갸...감사합니다!
넙죽