



ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΠΡΟΓΡΑΜΜΑ
ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΛΟΙΜΩΞΙΟΛΟΓΙΑ» 2019-2021

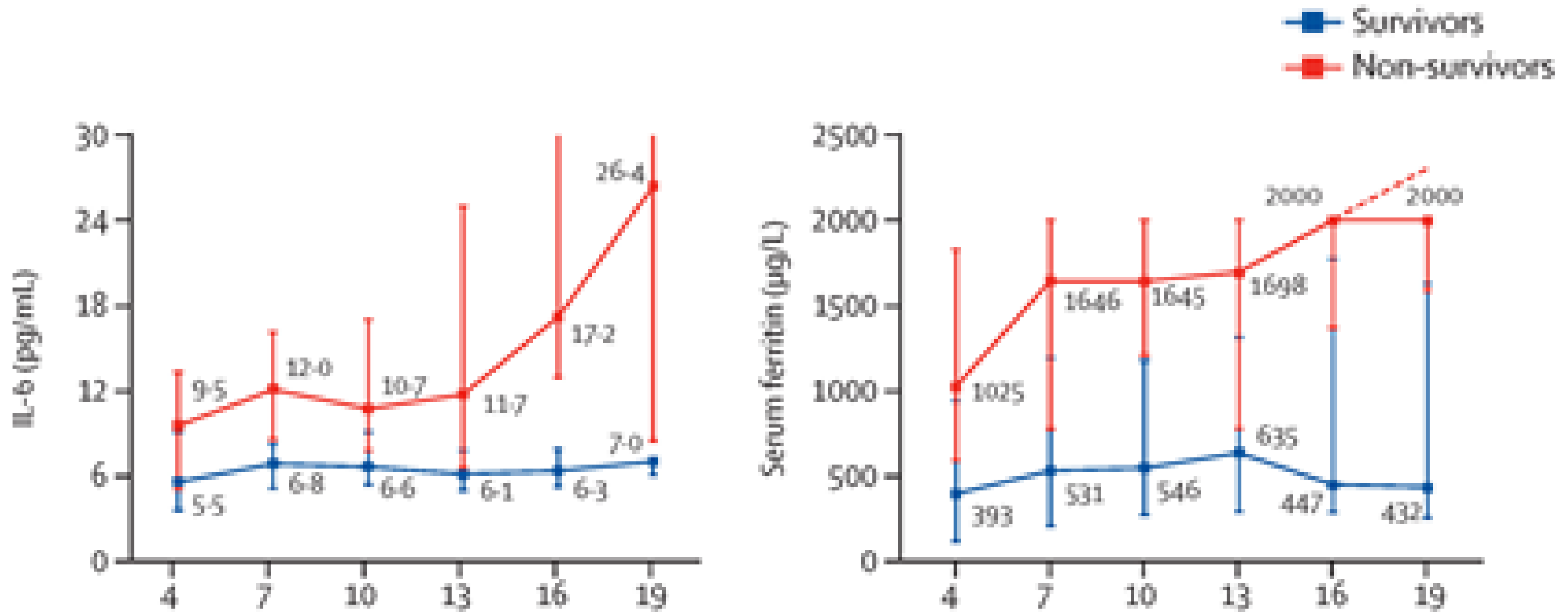
ΑΝΟΣΟΠΑΡΕΜΒΑΣΗ ΚΑΙ ΝΟΣΟΣ COVID-19

Ευδοξία Κυριαζοπούλου

*Παθολόγος-Εξειδικευόμενη Λοιμώξεων, ΜΕΛ, ΓΝΠ Τζάνειο
Επιστ. Συνεργάτης, Δ΄ Παθολογική Κλινική, ΠΓΝ ΑΤΤΙΚΟΝ*

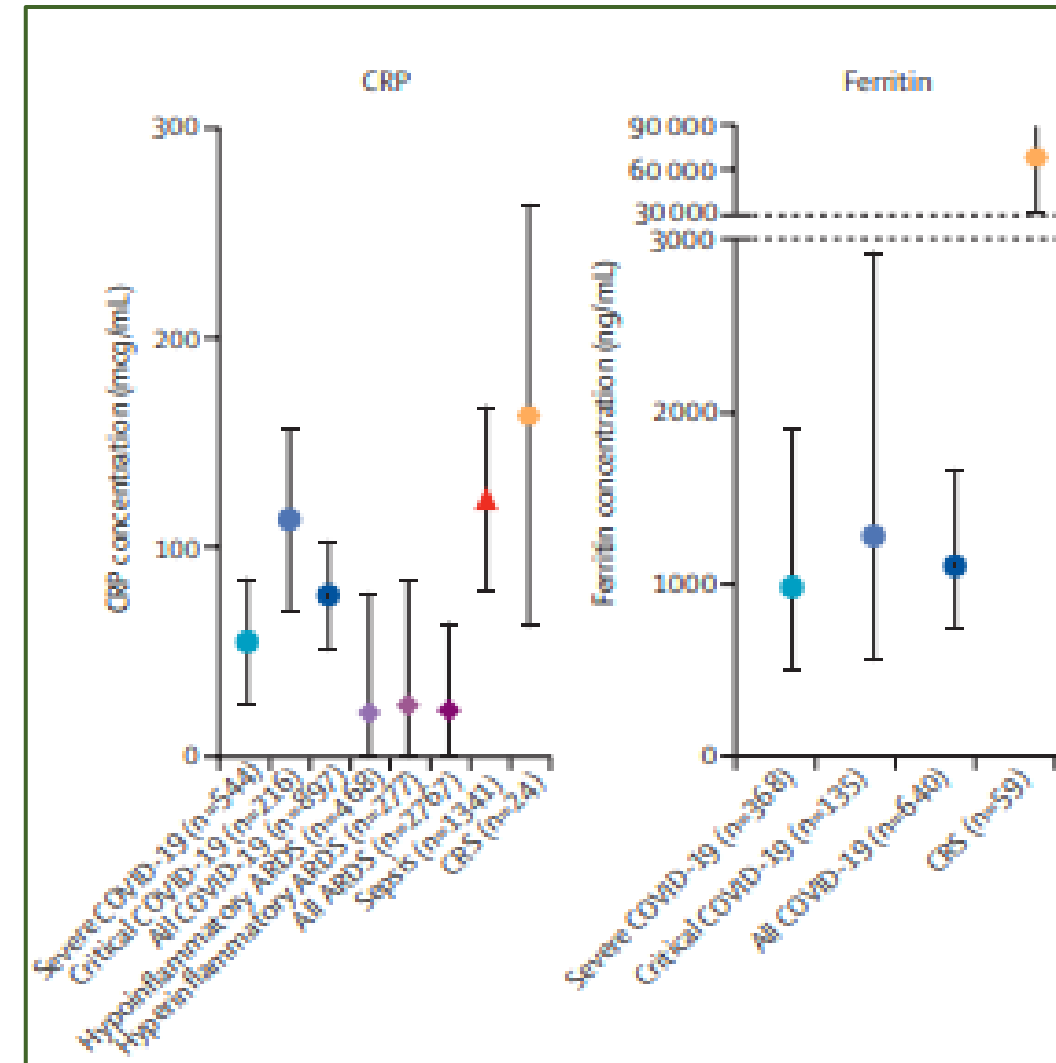
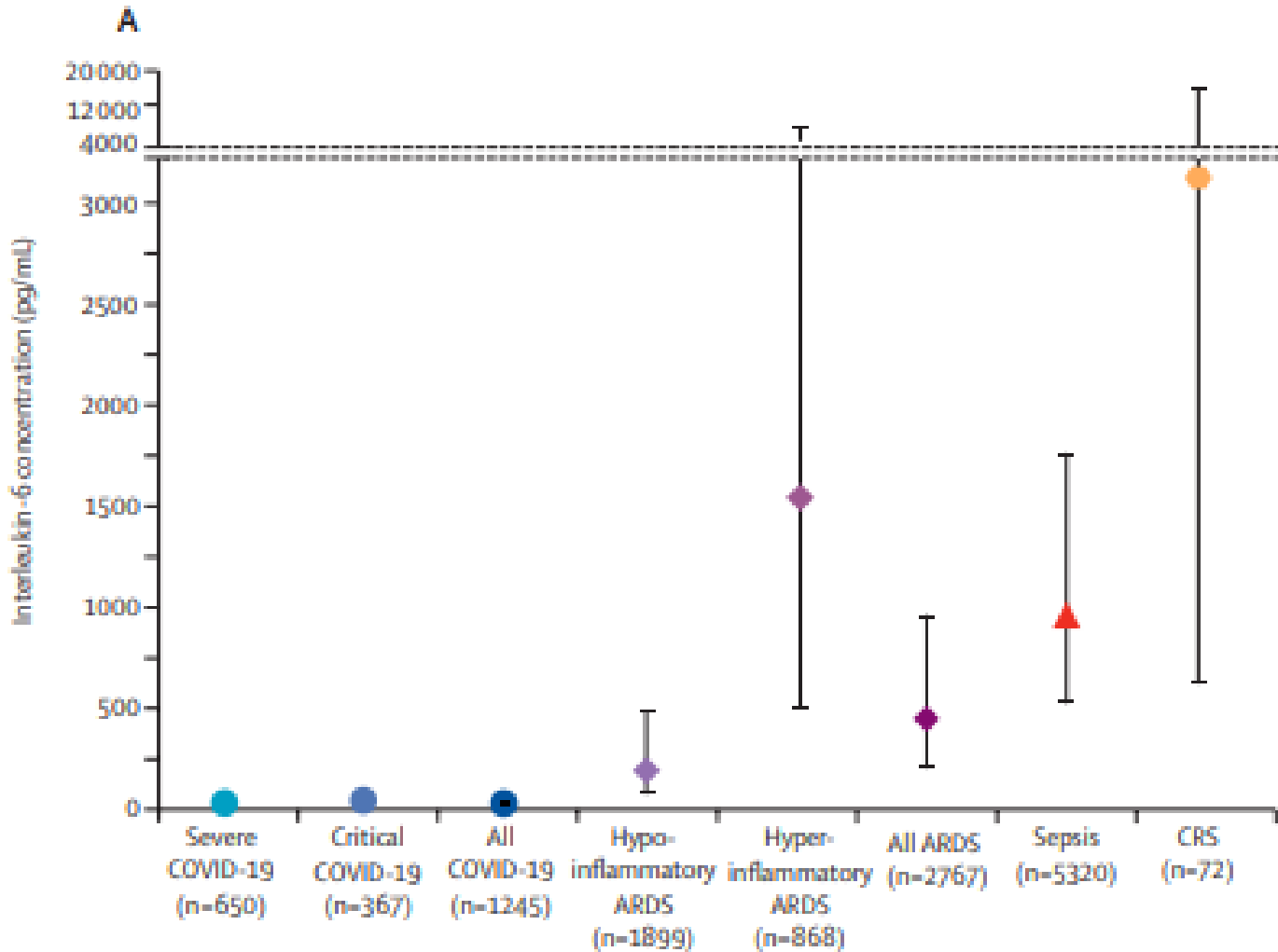
ΥΠΕΡ-ΦΛΕΓΜΟΝΗ ΣΤΗΝ COVID-19

Zhou F, et al. *Lancet* 2020; 395: 1054.



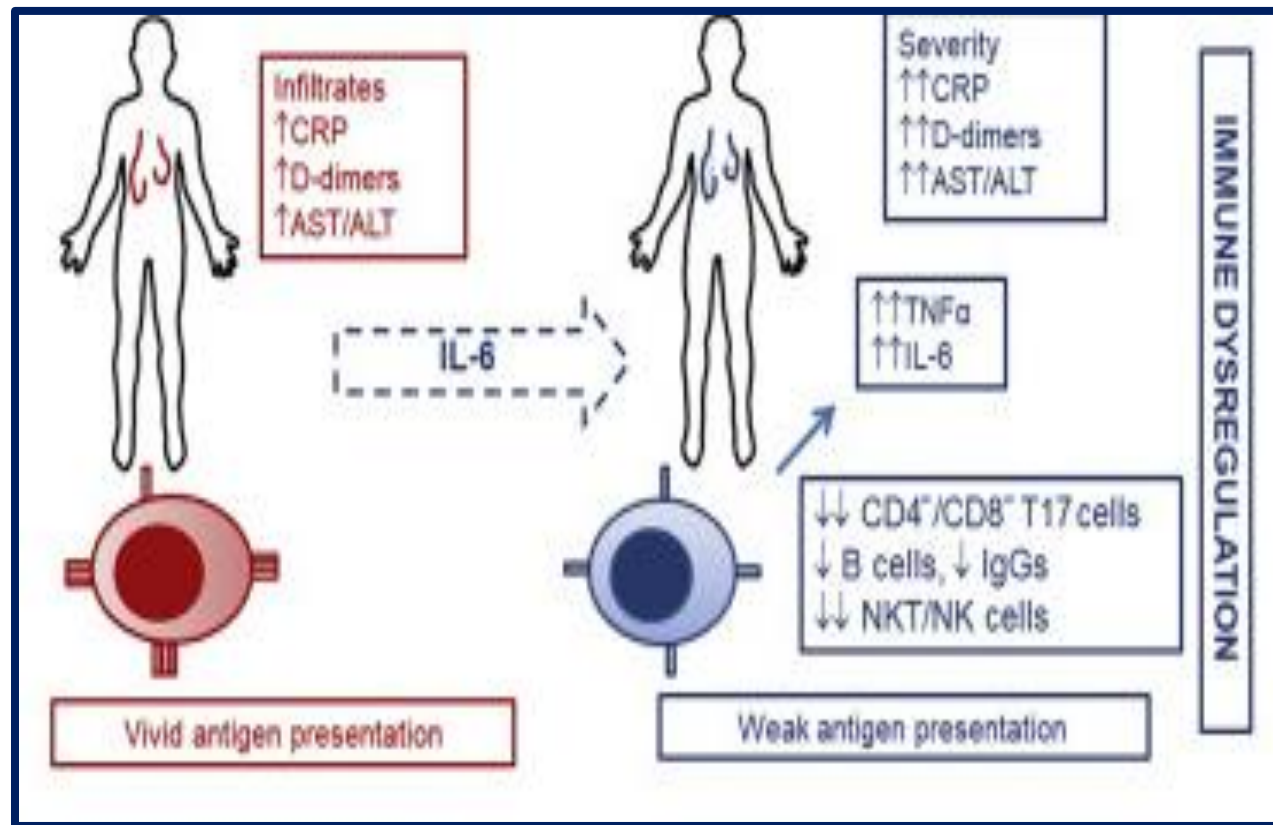
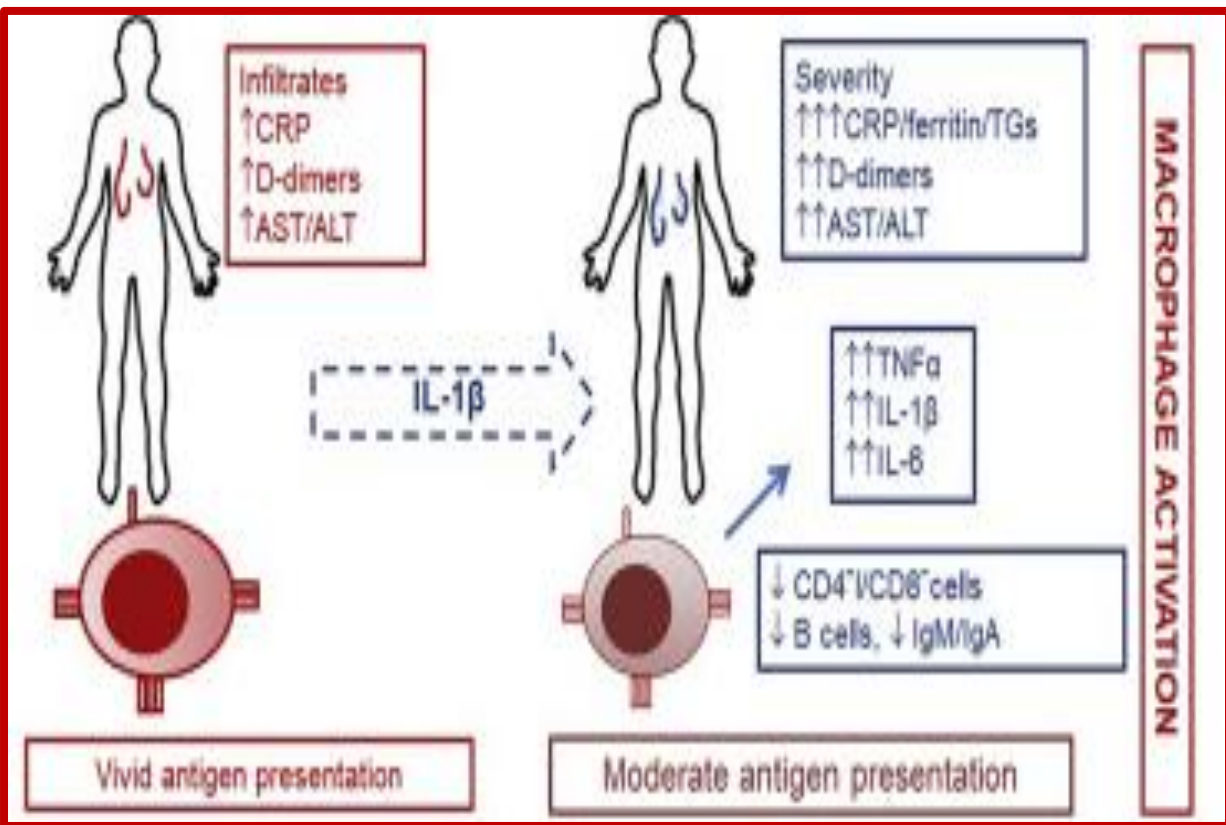
ΥΠΕΡ-ΦΛΕΓΜΟΝΗ ΣΤΗΝ COVID-19: ΝΑΙ ΜΕΝ ΑΛΛΑ...

Leisman DE, et al. *Lancet Respir Med* 2020; 8: 1233.



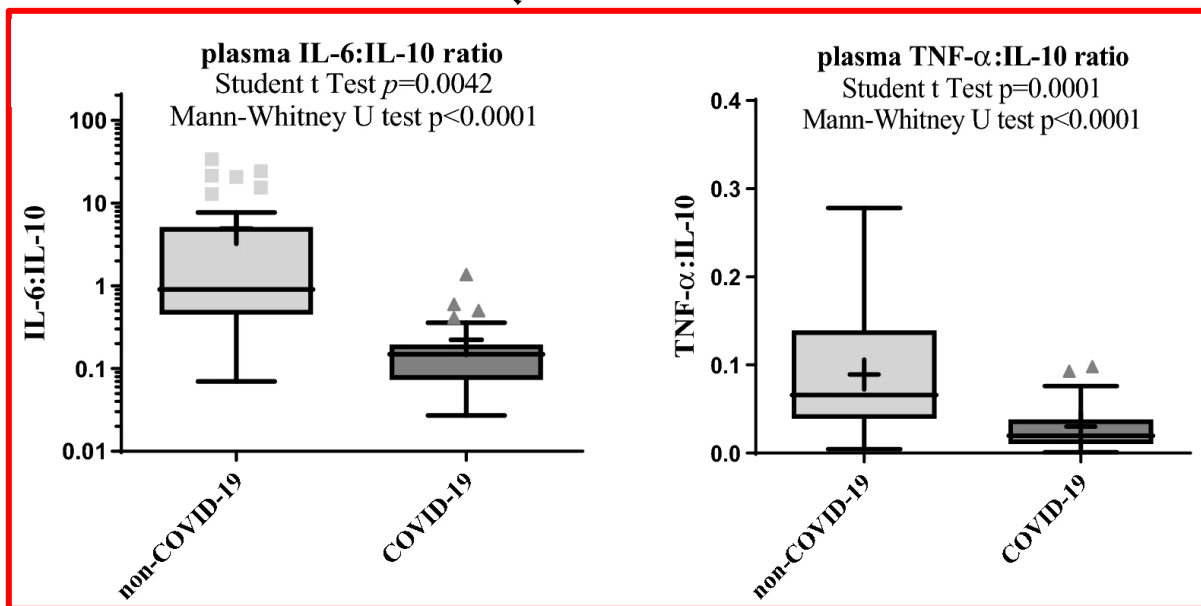
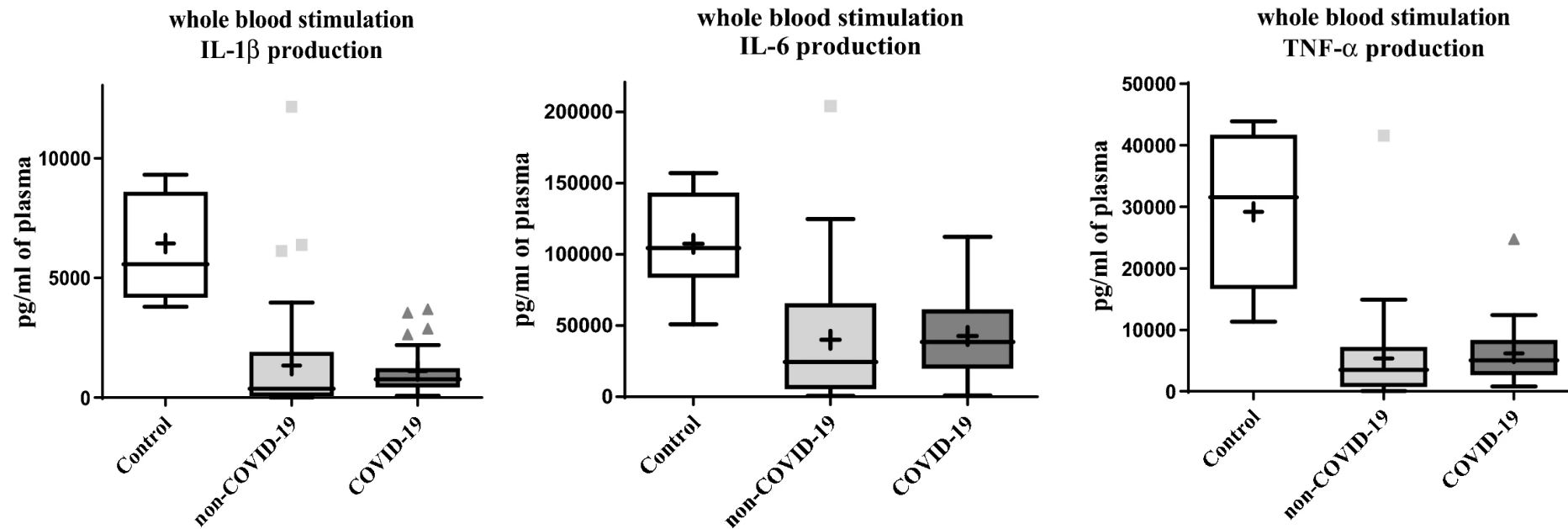
ΣΥΝΘΕΤΗ ΑΝΟΣΙΑΚΗ ΑΠΟΚΡΙΣΗ ΣΤΗΝ COVID-19

Giamarellos-Bourboulis EJ, et al. *Cell Host Microbe* 2020; 27: 992-1000.e3.

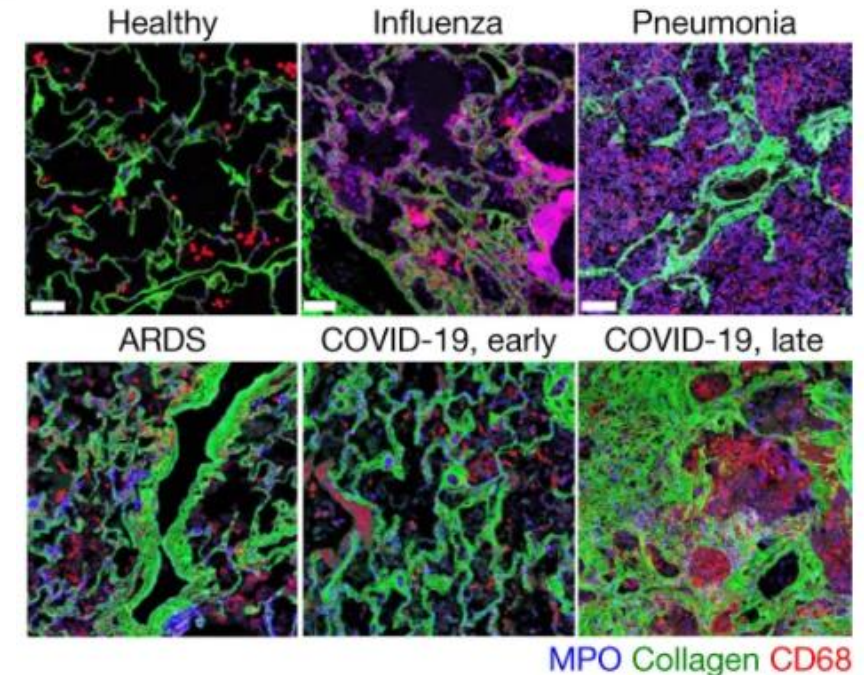
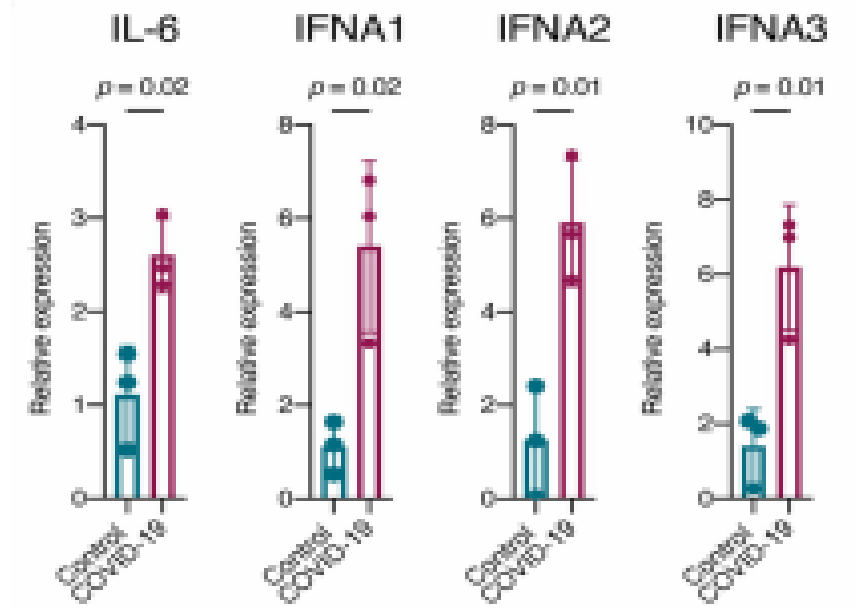
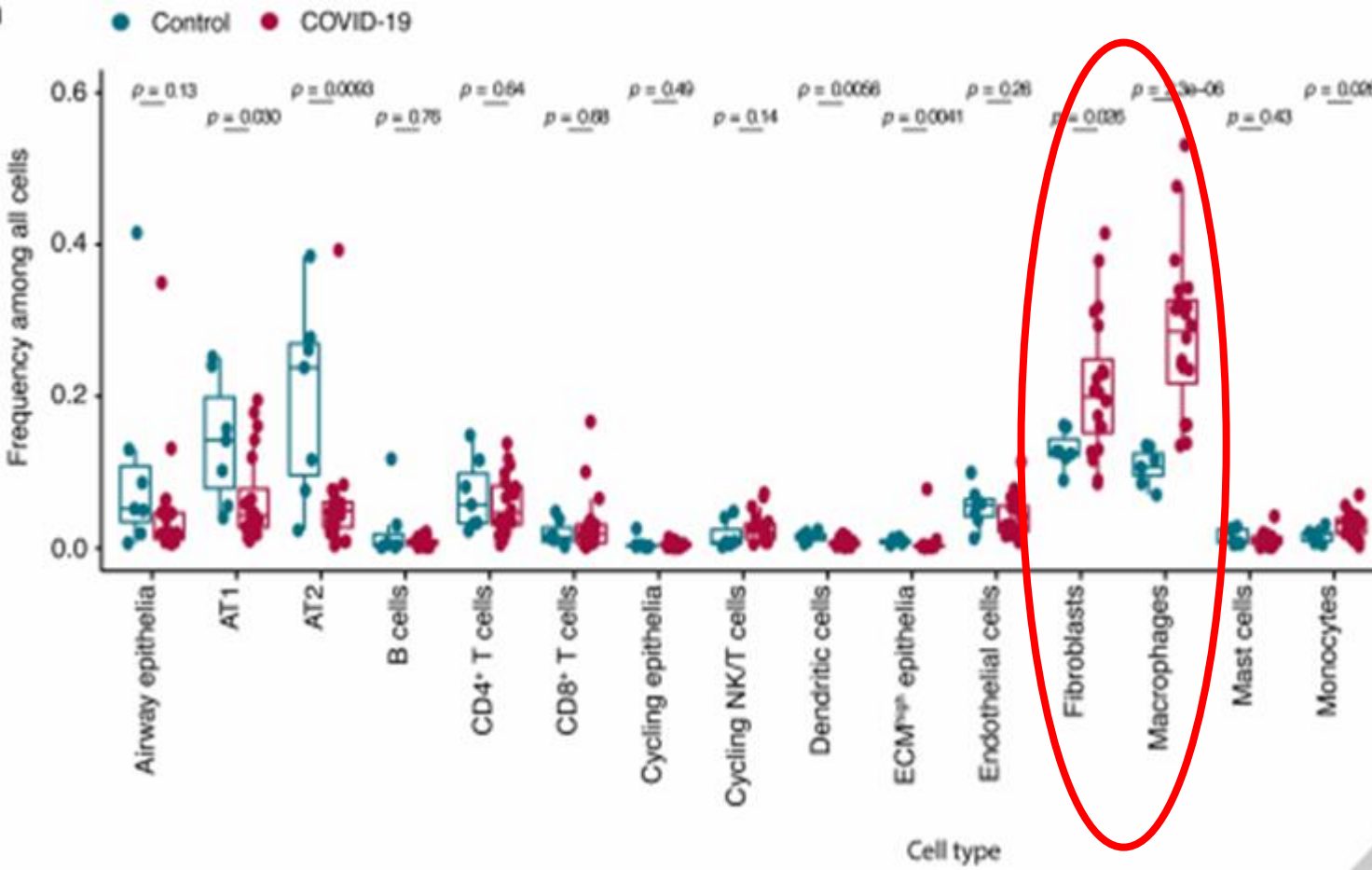


ΔΙΑΤΑΡΑΧΗ ΠΡΟ-/ΑΝΤΙ-ΦΛΕΓΜΟΝΩΔΟΥΣ ΙΣΟΡΡΟΠΙΑΣ

Blot M, et al. *J Transl Med* 2020; 18: 457.



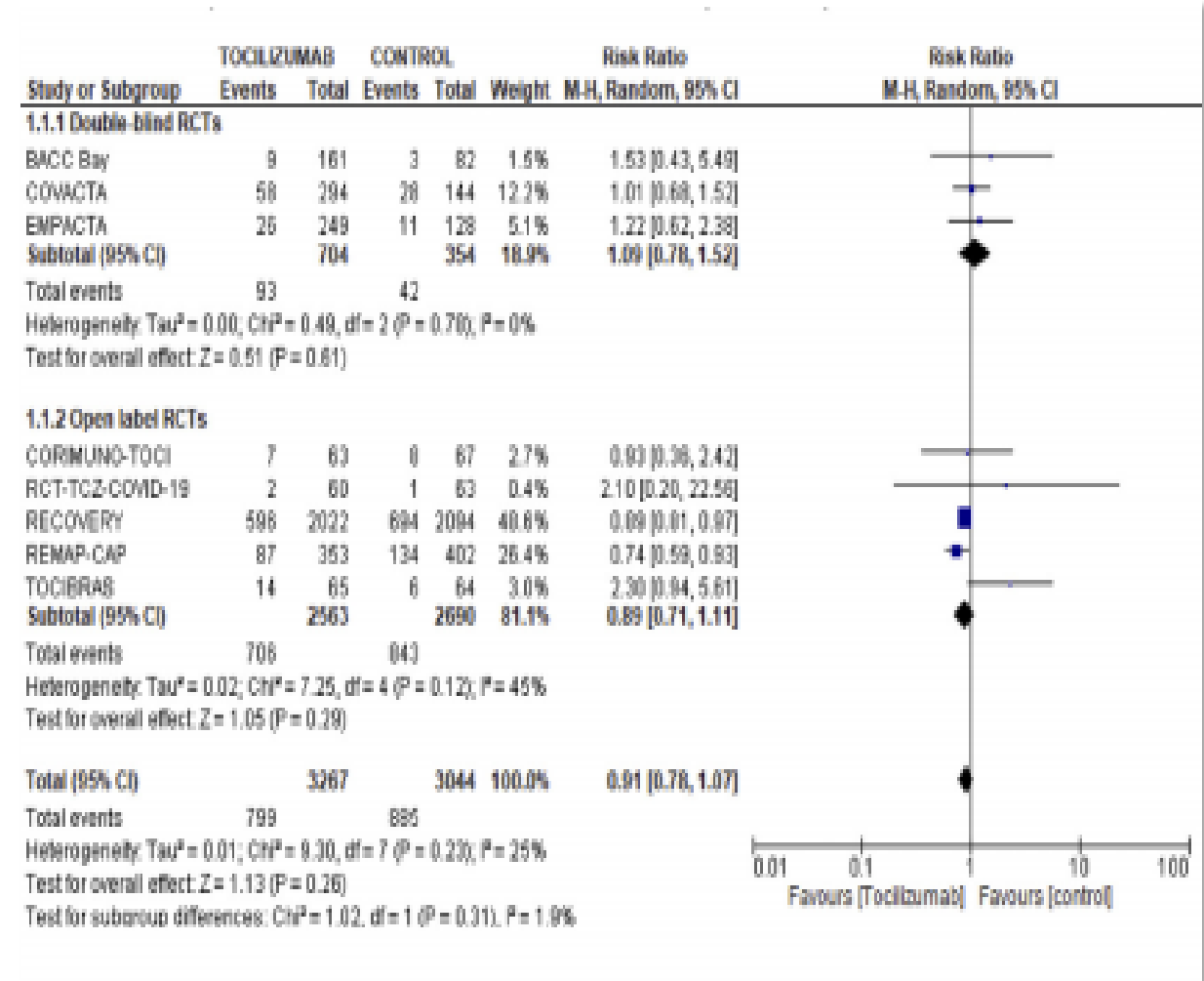
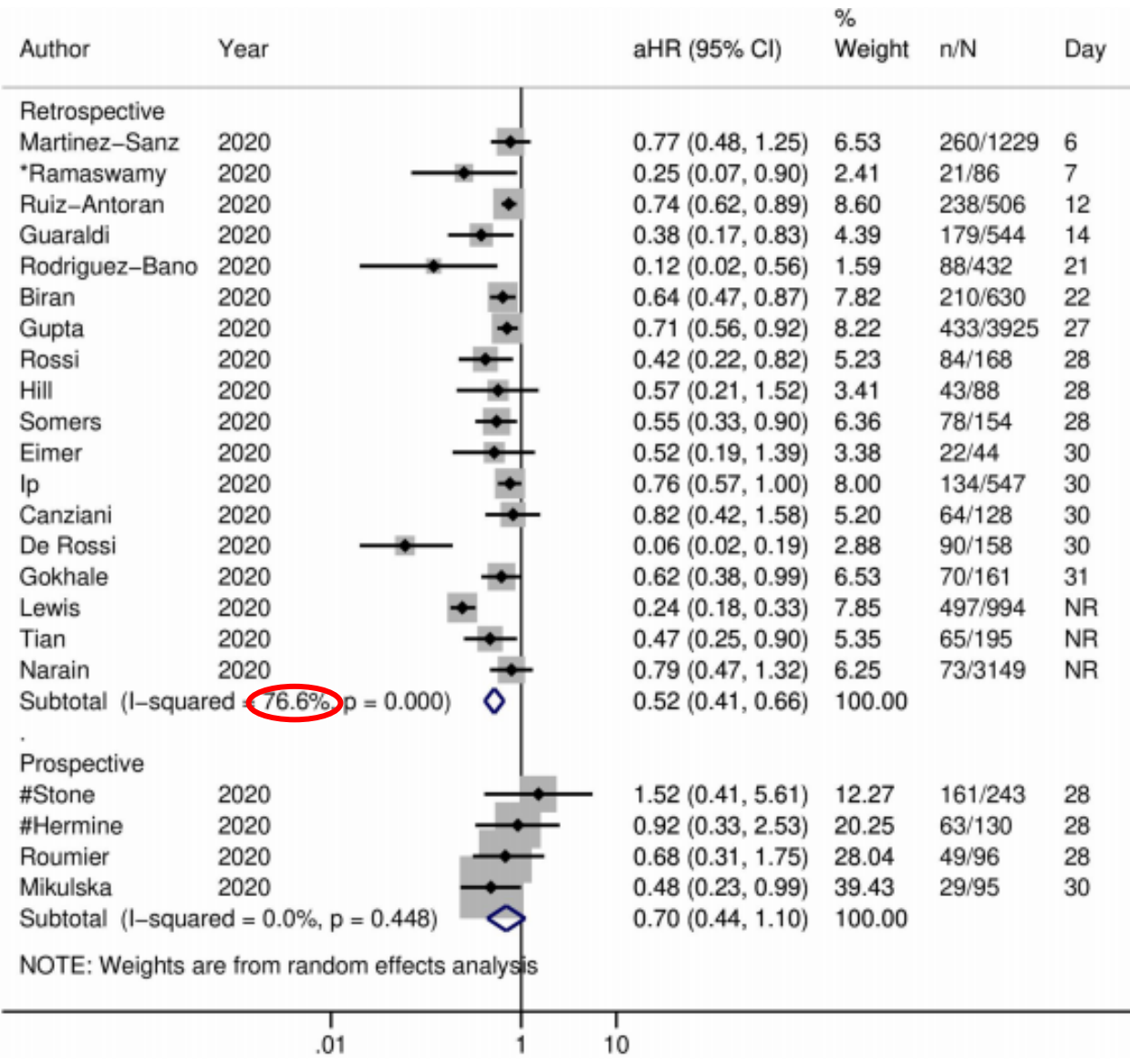
COVID-19: ΔΙΑΜΕΡΙΣΜΑΤΟΠΟΙΗΣΗ ΤΗΣ ΦΛΕΓΜΟΝΗΣ



Melms JC, et al. *Nature* 2021 doi: 10.1038/s41586-021-03569-1.

Rendeiro AF, et al. *Nature* 2021 doi: 10.1038/s41586-021-03475-6.

FOCUS ON IL-6: ANTIΦΑΤΙΚΑ ΔΕΔΟΜΕΝΑ



Khan FA, et al. *Thorax* 2021: thoraxjnl-2020-215266.

Tleyjeh IM, et al. *Clin Microbiol Infect* 2021: S1198-743X(21)00204-4.

IL-6 inhibition Tocilizumab/ Sarilumab in critical COVID-19 “REMAP CAP”

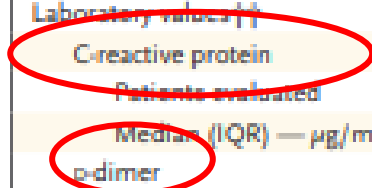
Open label RCT

- Tocilizumab 8mg/kg, n=353
- Sarilumab 400mg, n=48
- Standard-of-care, n=402

Primary Endpoint:
Organ support free days

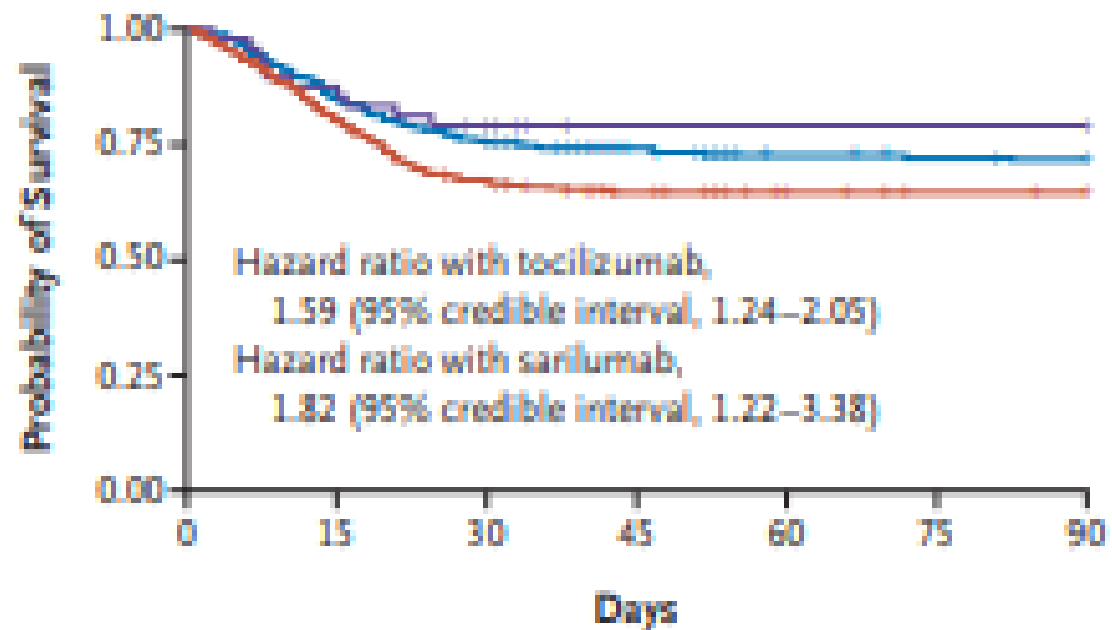
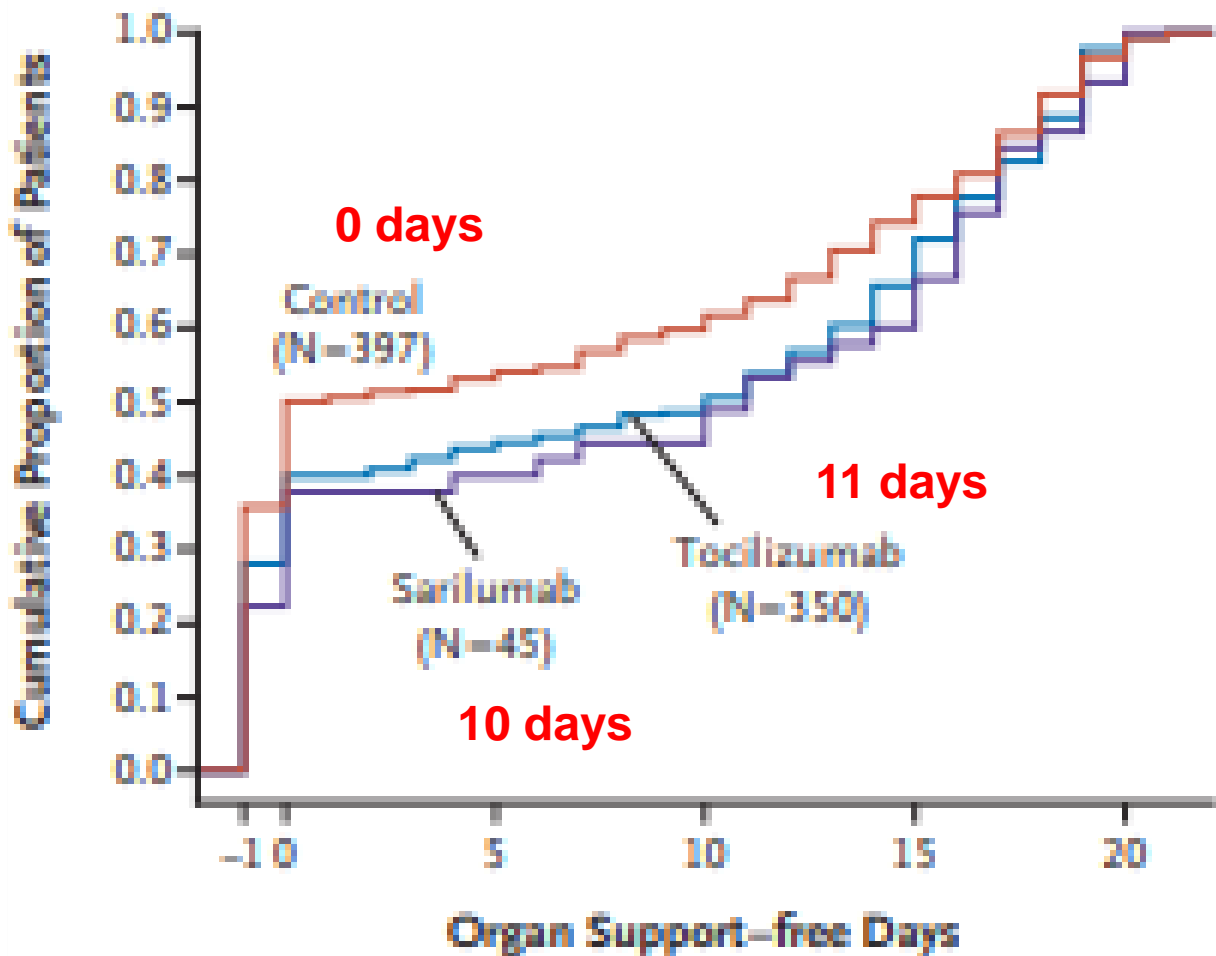
Table 1. Baseline Characteristics of the Patients in the Immune Modulation Therapy Domain.*

Characteristic	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)†	All Patients (N=865)‡
Age — yr	61.5±12.5	63.4±13.4	61.1±12.8	61.4±12.7
Male sex — no. (%)	261 (74)	39 (81)	283 (70)	629 (73)
APACHE II score 				
Patients evaluated	337	42	381	820
Median (IQR)	13 (8–19)	10 (7–16)	12 (8–18)	12 (8–19)
Confirmed SARS-CoV-2 infection — no./total no. (%)**	284/345 (82)	44/47 (94)	334/394 (85)	715/847 (84)
Median time to enrollment (IQR)				
From hospital admission — days	1.2 (0.8–2.8)	1.4 (0.9–2.8)	1.2 (0.8–2.8)	1.2 (0.8–2.8)
From ICU admission — hr	13.1 (6.6–19.0)	16.0 (11.4–20.8)	14.0 (6.8–19.5)	13.6 (6.6–19.4)
Acute respiratory support — no./total no. (%)				
None or supplemental oxygen only	1/353 (<1)	0/48	2/402 (<1)	3/865 (<1)
High-flow nasal cannulae	101/353 (29)	17/48 (35)	110/402 (27)	249/865 (29)
Noninvasive ventilation only	147/353 (42)	23/48 (48)	169/402 (42)	359/865 (42)
Invasive mechanical ventilation	104/353 (29)	8/48 (17)	121/402 (30)	254/865 (29)
Vasopressor support — no./total no. (%)	63/353 (18)	4/48 (8)	79/402 (20)	163/865 (19)
Pao₂:Fio₂				
Patients evaluated	335	35	354	780
Median (IQR)	115 (89–162)	126 (99–157)	118 (89–169)	116.5 (89–165)
Laboratory values ††				
C-reactive protein				
Patients evaluated	207	37	244	533
Median (IQR) — µg/ml	150 (85–221)	136 (105–204)	130 (71–208)	136 (79–208)
D-dimer				
Patients evaluated	159	20	172	385
Median (IQR) — ng/ml	832 (461–1763)	828 (355–1435)	1010 (500–2115)	910 (480–1916)



REMAP CAP TRIAL

REMAP-CAP Investigators. *N Engl J Med* 2021;384:1491.



No. at Risk

Sarilumab	48	42	37	31	31	31	31
Tocilizumab	353	300	266	242	230	226	224
Control	402	323	268	242	231	226	225

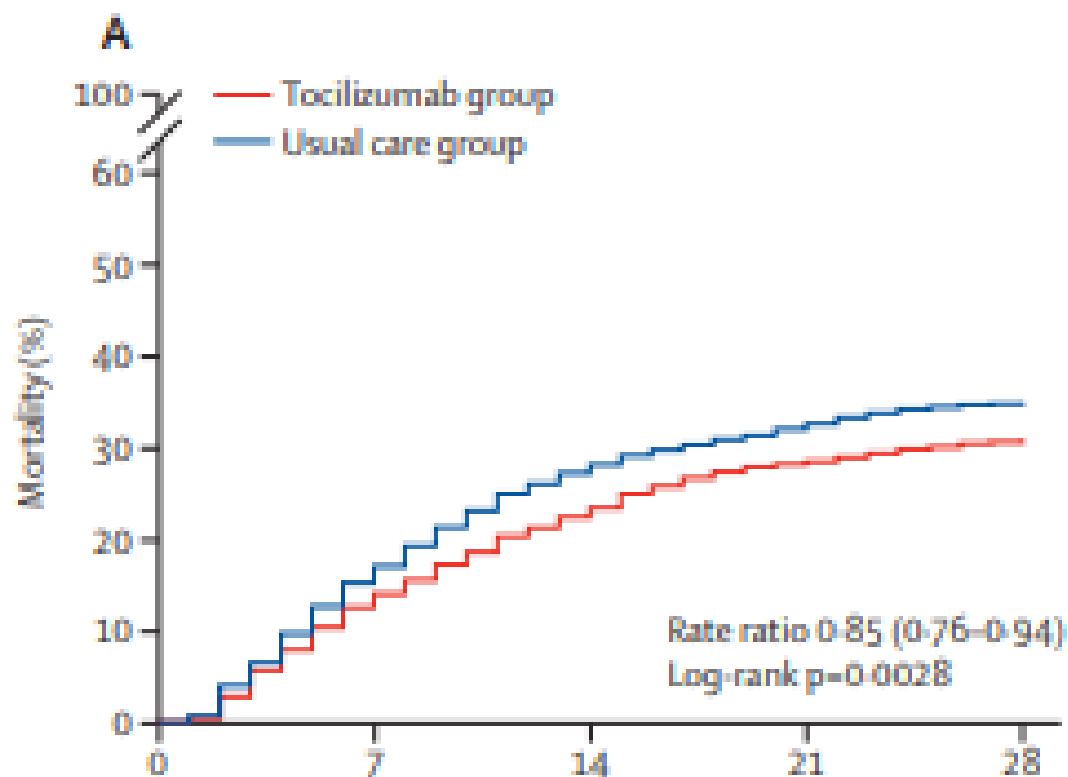
RECOVERY TRIAL

RECOVERY Collaborative Group. *Lancet* 2021; 397: 1637.

Open label RCT

Tocilizumab group: 400-800mg αναλόγως ΣΒ

SaO₂ <92% ΚΑΙ CRP ≥ 75mg/l



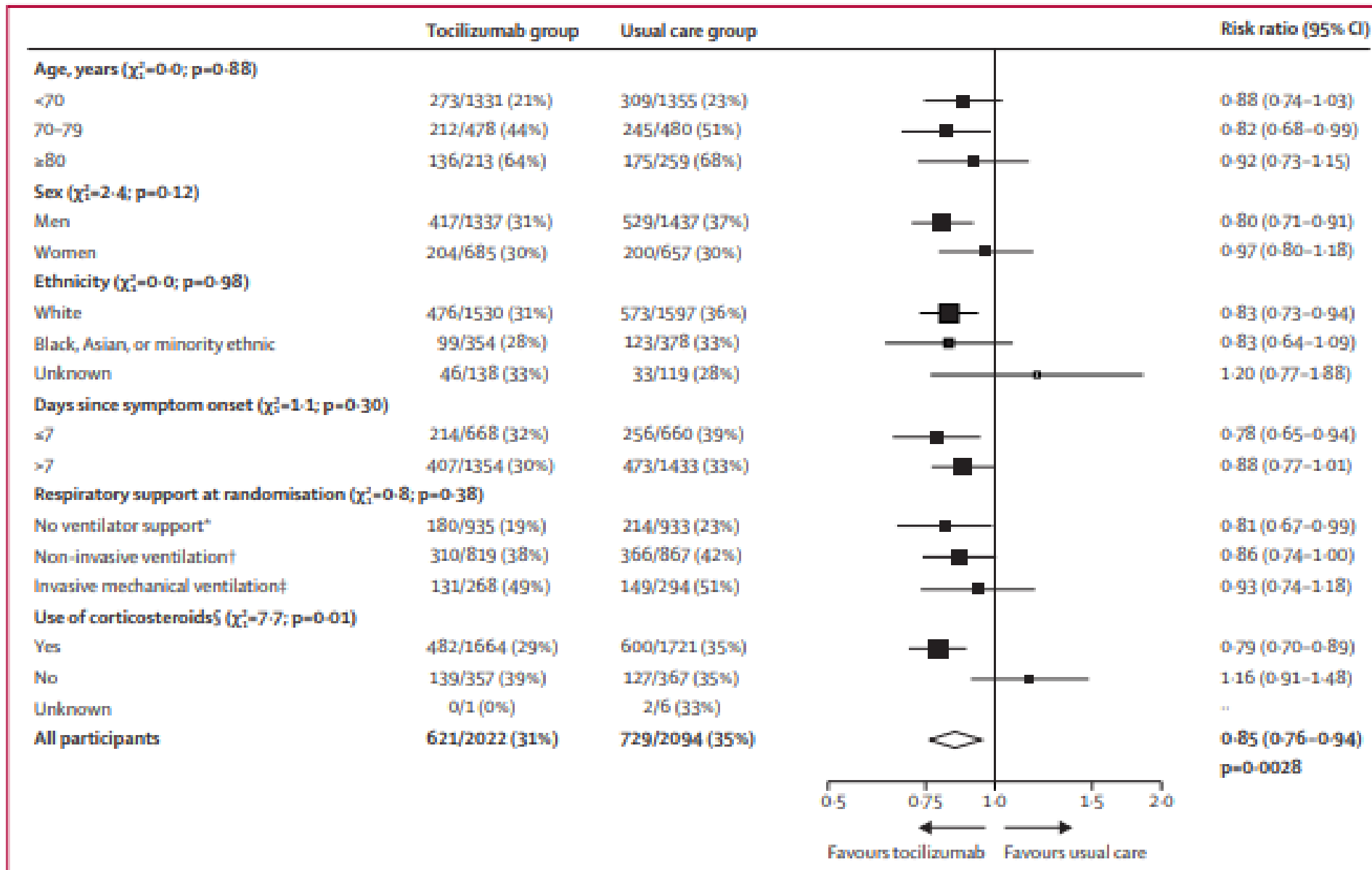
Number at risk

	0	7	14	21	28
Tocilizumab	2022	1736	1547	1445	1398
Usual care	2094	1735	1503	1410	1361

	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

anti-IL-6: ΒΕΛΤΙΣΤΗ ΧΡΗΣΗ ?

RECOVERY Collaborative Group. *Lancet* 2021; 397: 1637.

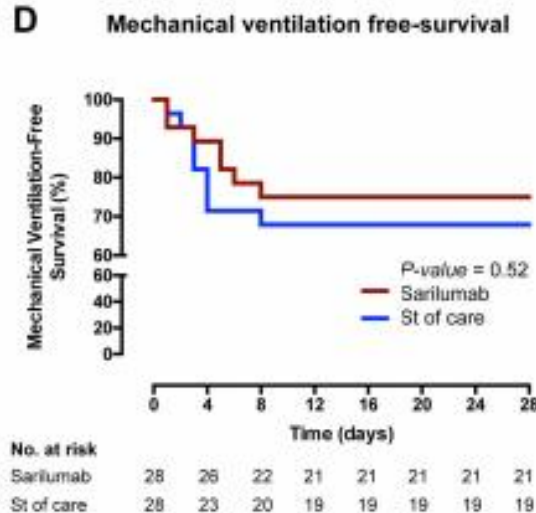
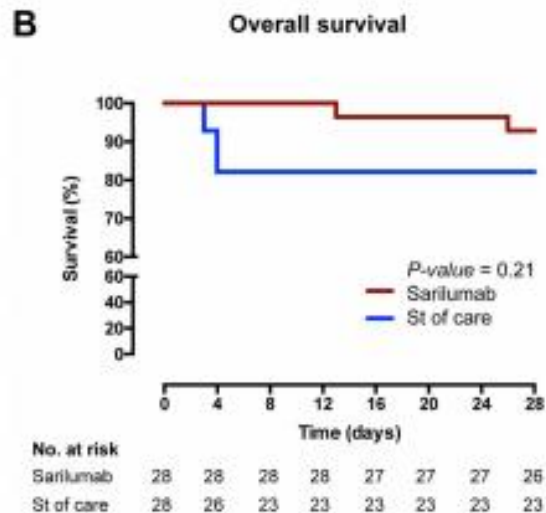
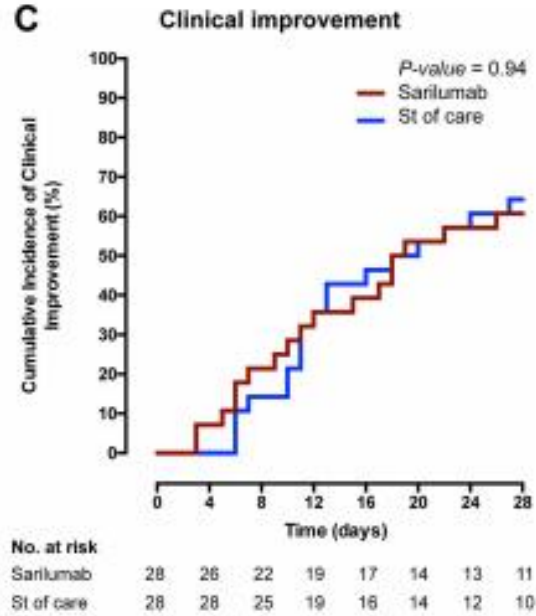


IL-6 BLOCKADE: SARILUMAB

Della-Torre E, et al. *Ann Rheum Dis.* 2020; 79: 1277.

A Patients on oxygen support, n (%)

Day 0	Sarilumab		St of care
NIV or High-flow oxygen	4	28 (100)	28 (100)
Day 28		↓	↓
Death	6	2 (7)	5 (18)
MV or ECMO	5	4 (14)	2 (7)
NIV or High-flow oxygen	4	0 (0)	0 (0)
Low-flow oxygen	3	5 (18)	3 (11)
Ambient air	2	0 (0)	1 (3)
Discharged	1	17 (61)	17 (61)



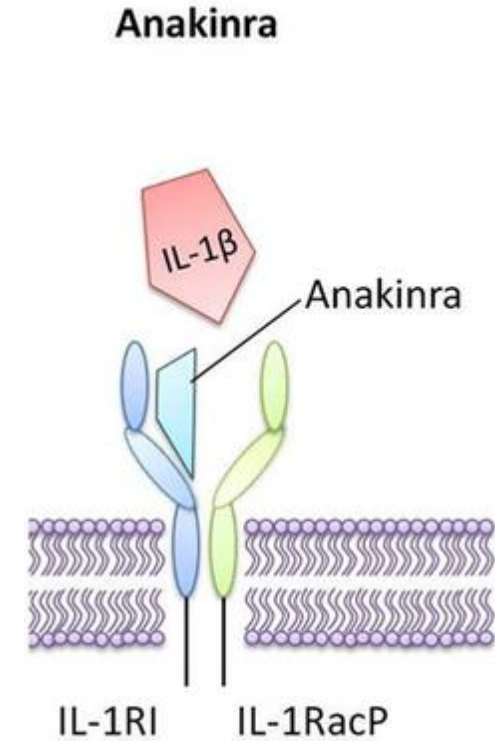
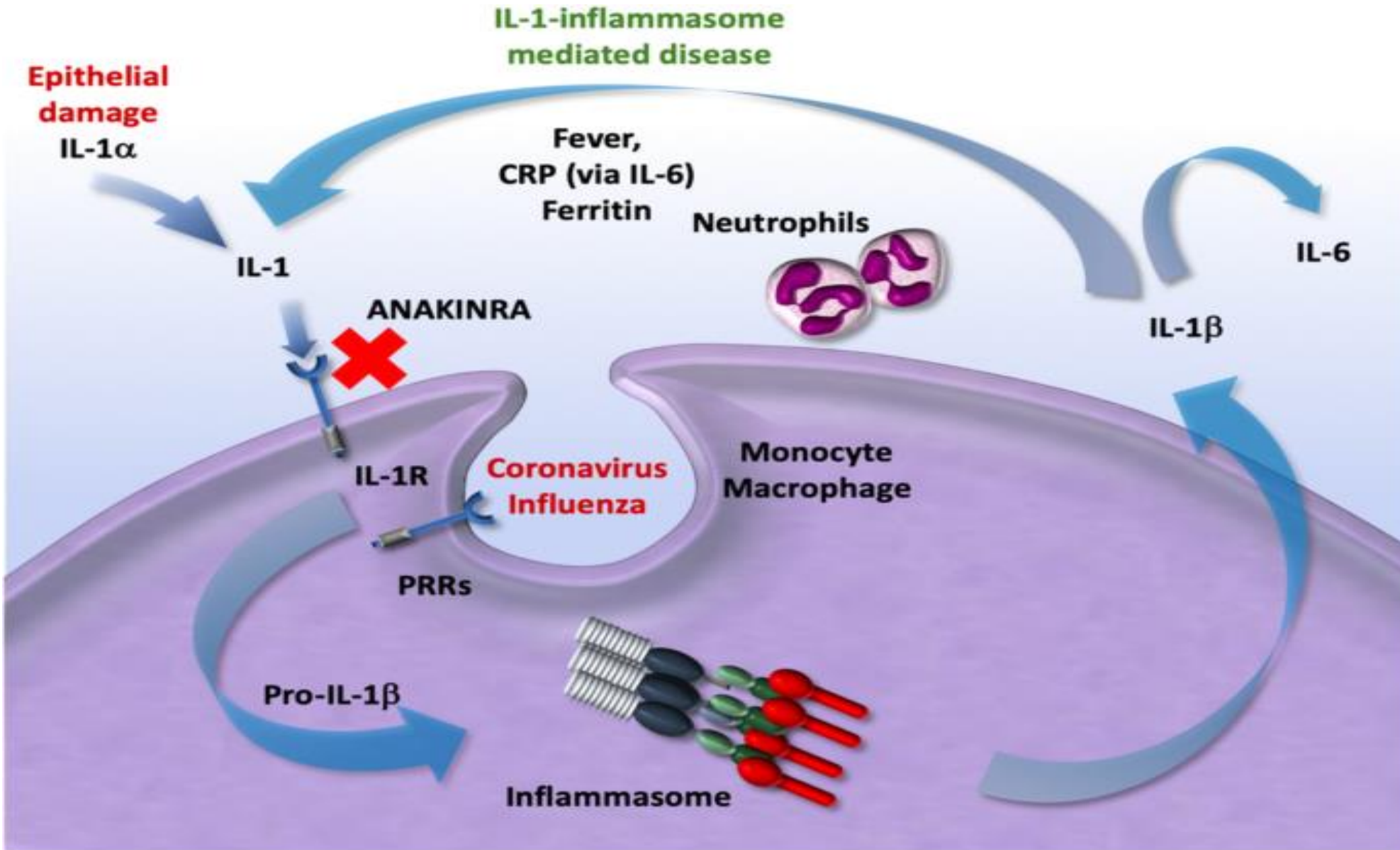
Μικρή μελέτη από το Μιλάνο

28 ασθενείς έλαβαν open-label sarilumab και 28 δε έλαβαν

Υπερφλεγμονή στα κριτήρια εισόδου:
LDH > ULN και ένα από:
CRP ≥ 100 mg/L ή
IL-6 ≥ 40 pg/ml ή
φερριτίνη ≥ 900 ng/ml

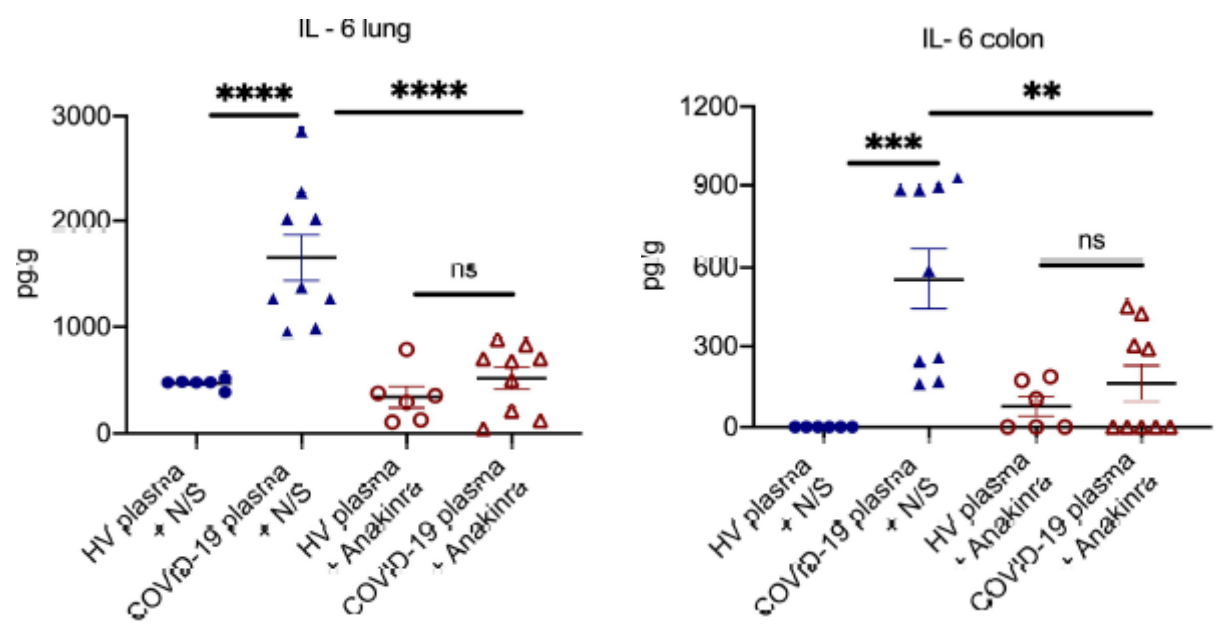
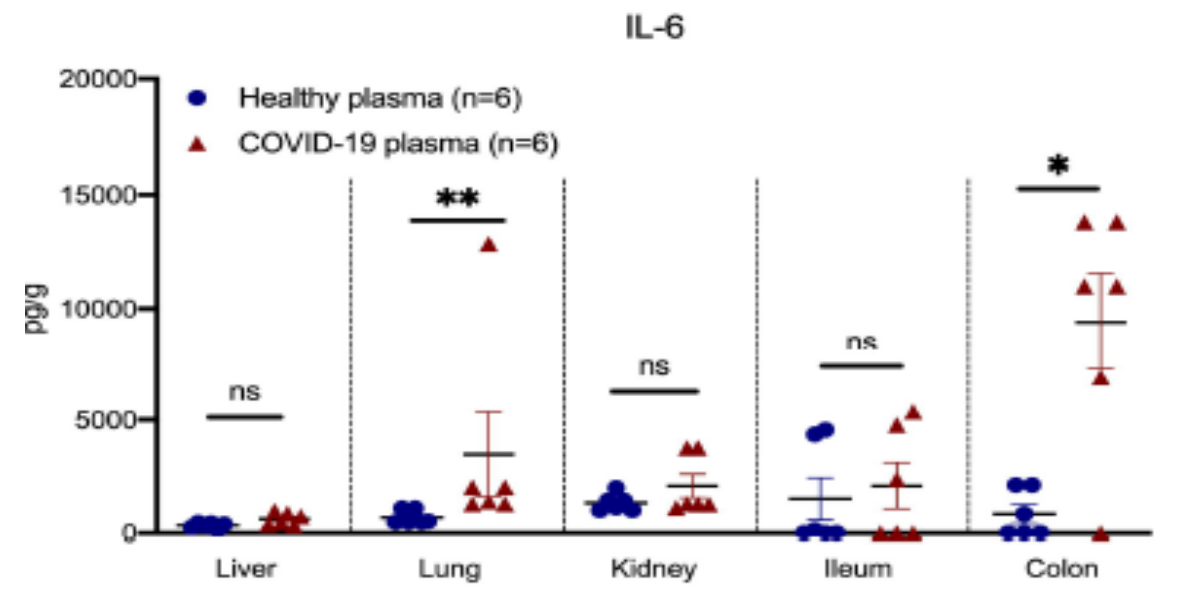
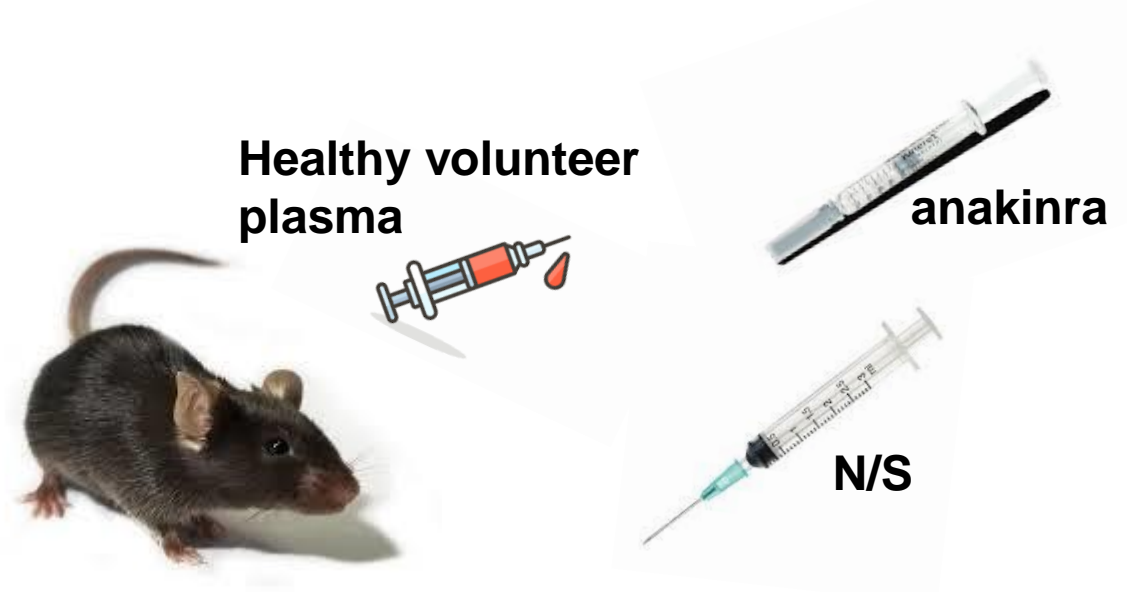
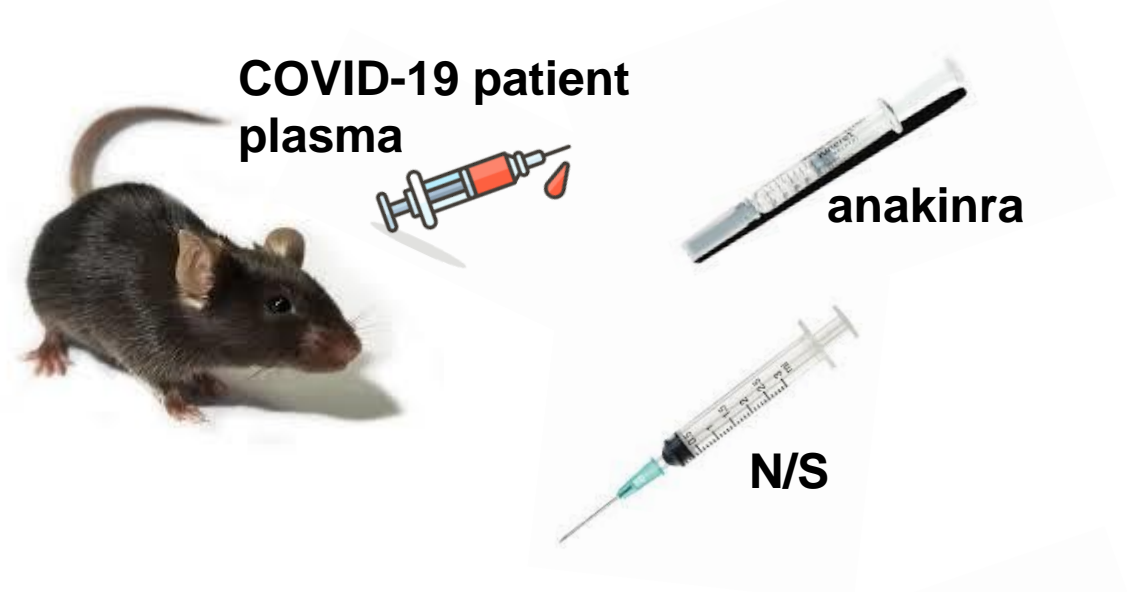
Χωρίς στατιστικά σημαντικό όφελος

ΑΝΑΣΤΟΛΗ ΤΗΣ ΙΝΤΕΡΛΕΥΚΙΝΗΣ-1: ΑΝΑΚΙΝΡΑ



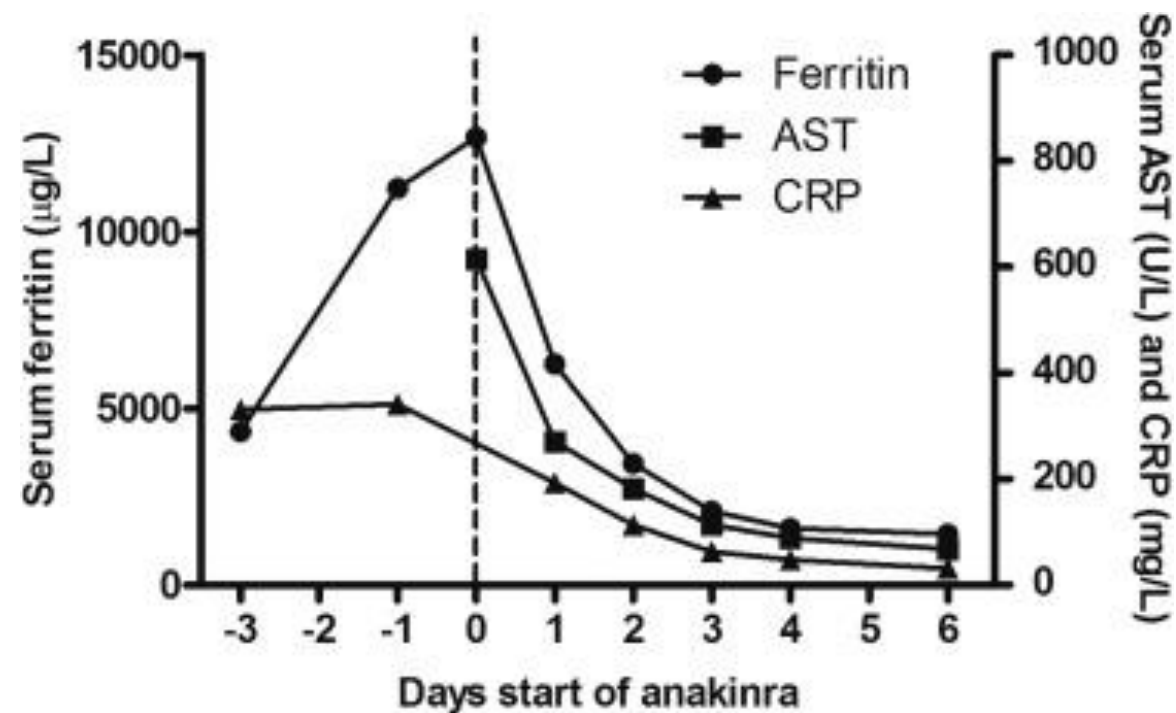
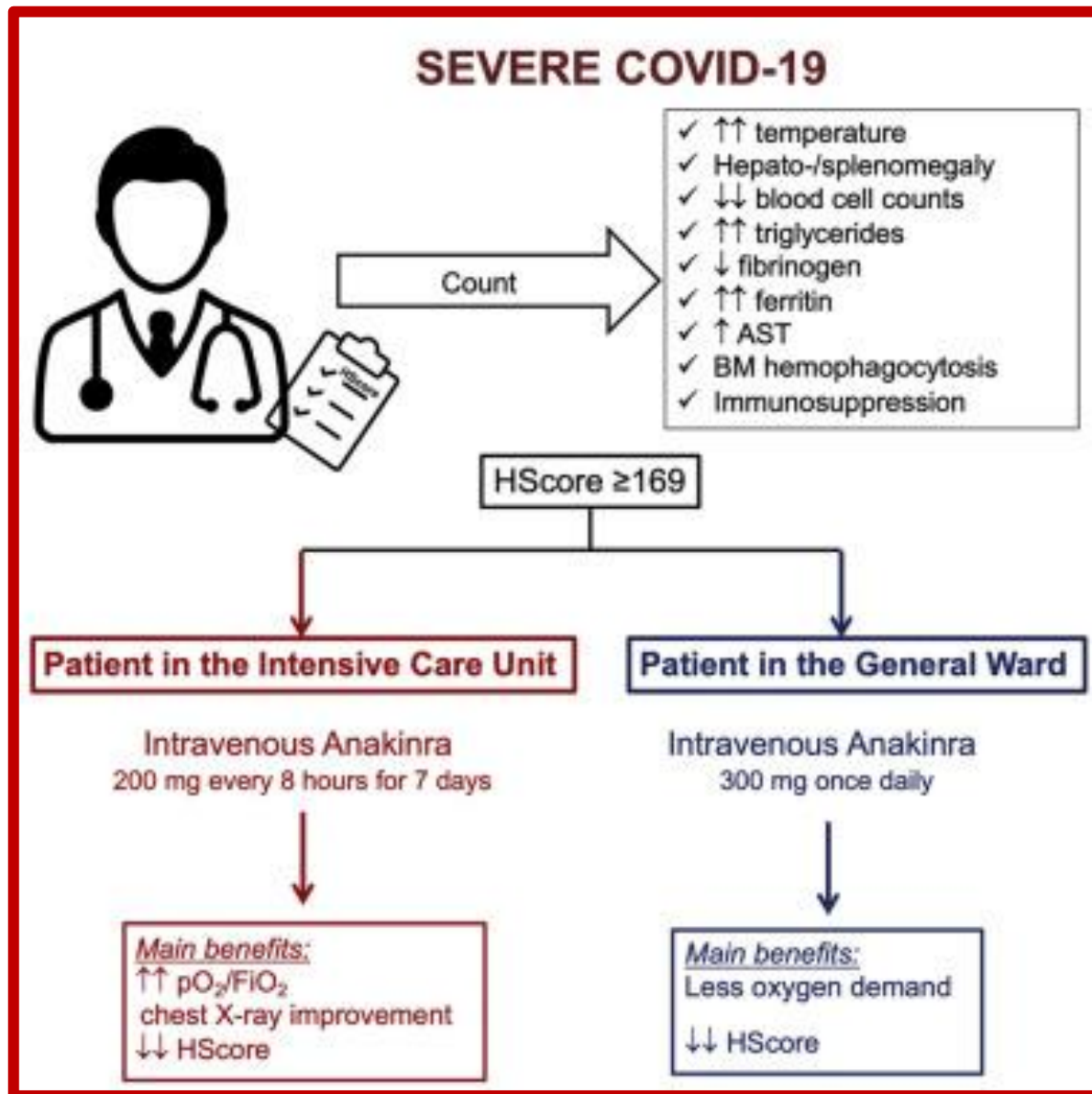
ΑΝΑΚΙΝΡΑ: ΥΠΟΘΕΣΗ ΜΗΧΑΝΙΣΜΟΥ ΔΡΑΣΗΣ

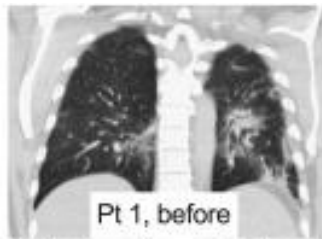
Renieris G, et al. *medRxiv* 2021.04.09.21255190.



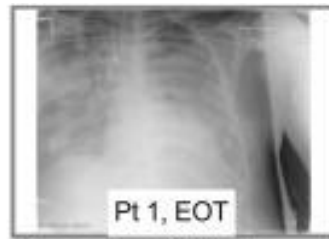
ΑΝΑΚΙΝΡΑ: ΠΡΩΙΜΗ ΘΕΤΙΚΗ ΕΜΠΕΙΡΙΑ

Dimopoulos G, et al. *Cell Host Microbe* 2020; 28: 117.





Pt 1, before
Infiltrates of lower right and left lobes
 pO_2/FiO_2 : 88mmHg, AKI(-)



Pt 1, EOT
Worsening of infiltrates
 pO_2/FiO_2 : 160mmHg, AKI(-)



Pt 2, before
Diffuse parenchymal and peribronchial infiltrates; pO_2/FiO_2 : 78mmHg, AKI(+)



Pt 2, EOT
↓ Infiltrates
 pO_2/FiO_2 : 115mmHg, AKI(+)



Pt 3, before
Diffuse infiltrates
 pO_2/FiO_2 : 68mmHg, AKI(-)



Pt 3, EOT
↓ infiltrates; ↑ aeration
 pO_2/FiO_2 : 125mmHg, AKI(-)



Pt 4, before
Diffuse infiltrates
 pO_2/FiO_2 : 89mmHg, AKI(-)



Pt 4, EOT
Unchangeable Infiltrates
 pO_2/FiO_2 : 141mmHg, AKI(+)



Pt 5, before
Diffuse infiltrates
 pO_2/FiO_2 : 88mmHg, AKI(-)



Pt 5, EOT
↓ infiltrates; ↑ aeration
 pO_2/FiO_2 : 92mmHg, AKI(-)



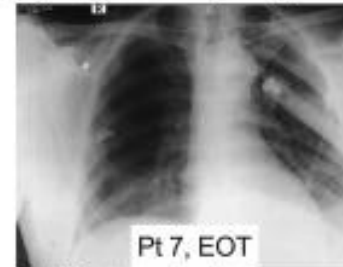
Pt 6, before
Diffuse infiltrates, predominantly right
 pO_2/FiO_2 : 92mmHg, AKI(-)



Pt 6, EOT
↓ Infiltrates
 pO_2/FiO_2 : 198mmHg, AKI(+)



Pt 7, before
Diffuse infiltrates, predominantly left
 pO_2/FiO_2 : 87mmHg, AKI(-)



Pt 7, EOT
↓ infiltrates; ↑ aeration
 pO_2/FiO_2 : 182mmHg, AKI(-)

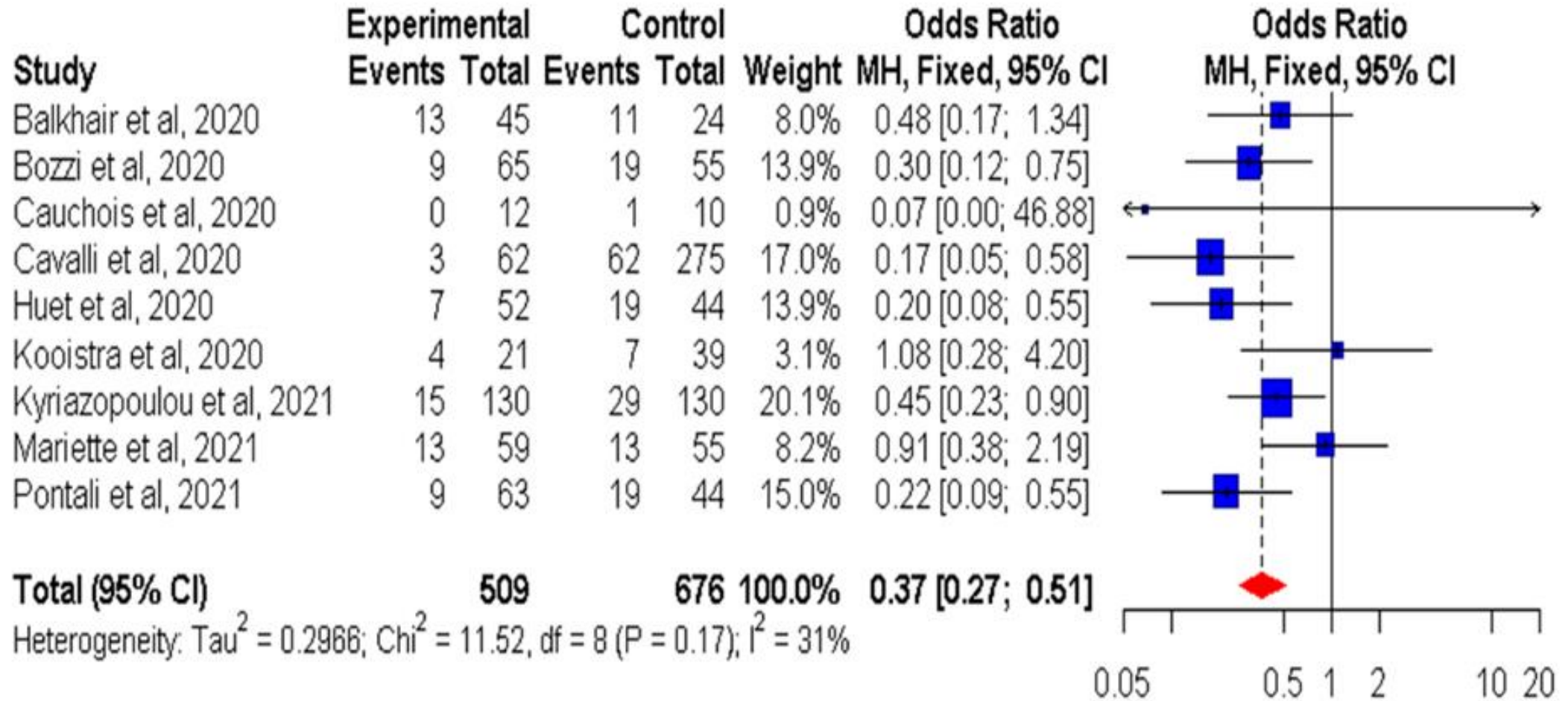
ΑΝΑΚΙΝΡΑ: ΔΙΑΘΕΣΙΜΗ ΕΜΠΕΙΡΙΑ

Kyriazopoulou E, et al. *medRxiv* 2021.04.13.21255411.

First author, year	Study type	Study country and period	Inflammation criteria for inclusion	N of patients		Admin. Route	Steroid intake
				A	C		
Balkhair, 2020	Prospective	Oman <ul style="list-style-type: none"> April 1-June 14, 2020 historical controls June 15-July 25, 2020 anakinra group 	–	45	24	SC	Some patients
Bozzi, 2020	Retrospective	Italy February 25-March 30, 2020	CRP>100mg/l Ferritin>1000μg/l	65	55	SC IV if MV	All patients
Cauchois, 2020	Retrospective	France not mentioned	CRP>110mg/l	12	10	IV	No
Cavalli, 2021	Prospective	Italy <ul style="list-style-type: none"> March 10-17, 2020 historical controls March 17-27, 2020 anakinra group 	CRP>100mg/l ferritin>900μg/l	62	275	IV	No
Huet, 2020	Retrospective	France <ul style="list-style-type: none"> March 2020 historical controls March 24-April 6, 2020 anakinra group 	–	52	44	SC	Some patients
Kooistra, 2020	Prospective	Netherlands March 11-April 27,2020	Ferritin>1800 μg/L, clinical hyperinflammation signs (fever, unexplained progression of MOF)	21	39	IV	Some patients
Kyriazopoulou, 2021	Prospective	Greece April 16-September 12, 2020	suPAR>6μg/l	130	130	SC	Some patients
Mariette, 2021	RCT	France April 8-26,2020	CRP>25 mg/l	59	55	IV	Some patients
Pontali, 2021	Retrospective	Italy February 26-April 29, 2020	CRP or ferritin > x3 normal limits	63	44	IV	Some patients

ANAKINRA KAI ΘNHTOTHTA I

Kyriazopoulou E, et al. *medRxiv* 2021.04.13.21255411.



ANAKINRA KAI ΘNHTOTHTA II

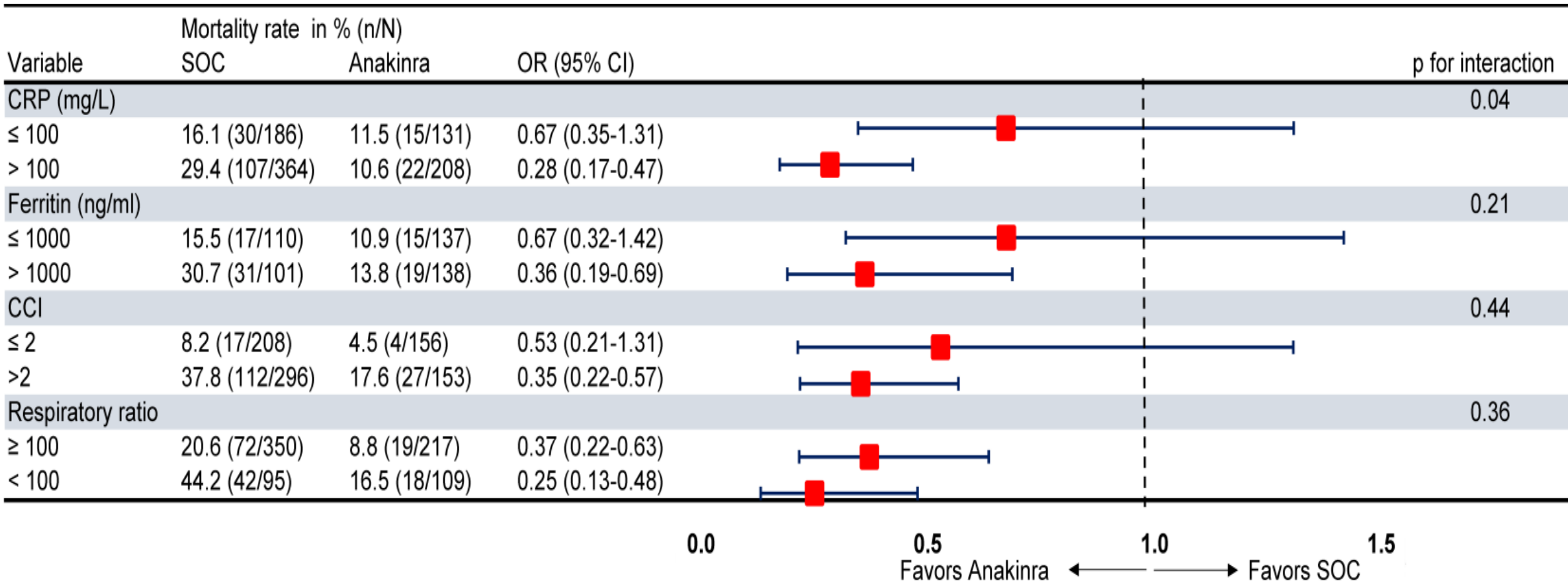
Kyriazopoulou E, et al. *medRxiv* 2021.04.13.21255411.

Individual patient data from 6 studies including 895 patients

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Anakinra treatment	0.38	(0.26-0.56)	<0.001	0.32	(0.20-0.51)	<0.001
Age >72 years*	4.97	(3.5-7.06)	<0.001	1.89	(1.12-3.20)	0.018
Charlson's comorbidity index >2*	6.35	(4.01-10.06)	<0.001	3.75	(1.99-7.07)	<0.001
Respiratory ratio <100	2.18	(1.50-3.17)	<0.001	2.89	(1.80-4.64)	<0.001
CRP>100 mg/L	1.76	(1.21-2.55)	0.003	-	-	-
Lymphocytes <580/mm ³ *	3.08	(2.12-4.49)	<0.001	3.05	(1.90-4.89)	<0.001
Study	-	-	0.147	-	-	-

ΑΝΑΚΙΝΡΑ ΒΕΛΤΙΣΤΗ ΧΡΗΣΗ

Kyriazopoulou E, et al. *medRxiv* 2021.04.13.21255411.



CCI Charlson's Comorbidity Index
 CI confidence interval
 OR odds ratio
 SOC standard of care

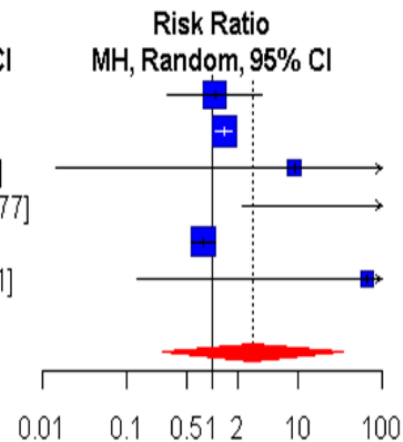
ΑΝΑΚΙΝΡΑ ΚΑΙ ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ

Kyriazopoulou E, et al. *medRxiv* 2021.04.13.21255411.

Διαταραχή ηπατικής βιοχημείας

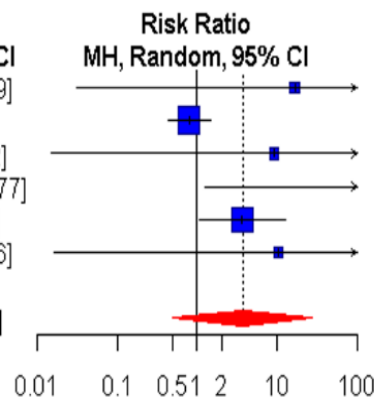
Study	Experimental		Control		Weight	Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		
Balkhair et al, 2020	6	45	3	24	24.0%	1.07 [0.29; 3.89]
Bozzi et al, 2020	57	65	35	55	26.3%	1.38 [1.11; 1.72]
Cauchois et al, 2020	1	12	0	10	7.6%	9.18 [0.01; 5634.42]
Cavalli et al, 2020	25	62	0	275	8.0%	1111.92 [2.25; 550189.77]
Kyriazopoulou et al, 2021	40	130	51	130	26.2%	0.78 [0.56; 1.10]
Mariette et al, 2021	7	59	0	55	7.9%	66.19 [0.13; 33632.31]

Total (95% CI) 373 549 100.0% 3.00 [0.26; 34.66]
 Heterogeneity: $\tau^2 = 4.3481$; $\chi^2 = 14.33$, $df = 5$ ($P = 0.01$); $I^2 = 65\%$



Study	Experimental		Control		Weight	Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		
Balkhair et al, 2020	3	45	0	24	7.0%	16.57 [0.03; 8821.89]
Bozzi et al, 2020	15	65	16	55	38.6%	0.79 [0.43; 1.45]
Cauchois et al, 2020	1	12	0	10	6.8%	9.18 [0.01; 5634.42]
Cavalli et al, 2020	14	62	0	275	7.1%	624.62 [1.25; 312056.77]
Kyriazopoulou et al, 2021	11	130	3	130	33.9%	3.67 [1.05; 12.84]
Mariette et al, 2021	1	59	0	55	6.7%	10.26 [0.02; 6574.46]

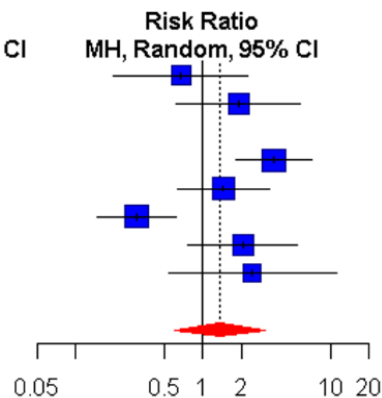
Total (95% CI) 373 549 100.0% 3.71 [0.49; 27.84]
 Heterogeneity: $\tau^2 = 2.1613$; $\chi^2 = 10.21$, $df = 5$ ($P = 0.07$); $I^2 = 51\%$



Λευκοπενία

Study	Experimental		Control		Weight	Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		
Balkhair et al, 2020	5	45	4	24	12.4%	0.67 [0.20; 2.25]
Bozzi et al, 2020	9	65	4	55	13.2%	1.90 [0.62; 5.85]
Cauchois et al, 2020	0	12	0	10	0.0%	
Cavalli et al, 2020	13	62	16	275	17.2%	3.60 [1.83; 7.10]
Kooistra et al, 2020	7	21	9	39	15.8%	1.44 [0.63; 3.32]
Kyriazopoulou et al, 2021	9	130	30	130	17.0%	0.30 [0.15; 0.61]
Mariette et al, 2021	11	59	5	55	14.4%	2.05 [0.76; 5.53]
Pontali et al, 2021	7	63	2	44	10.1%	2.44 [0.53; 11.22]

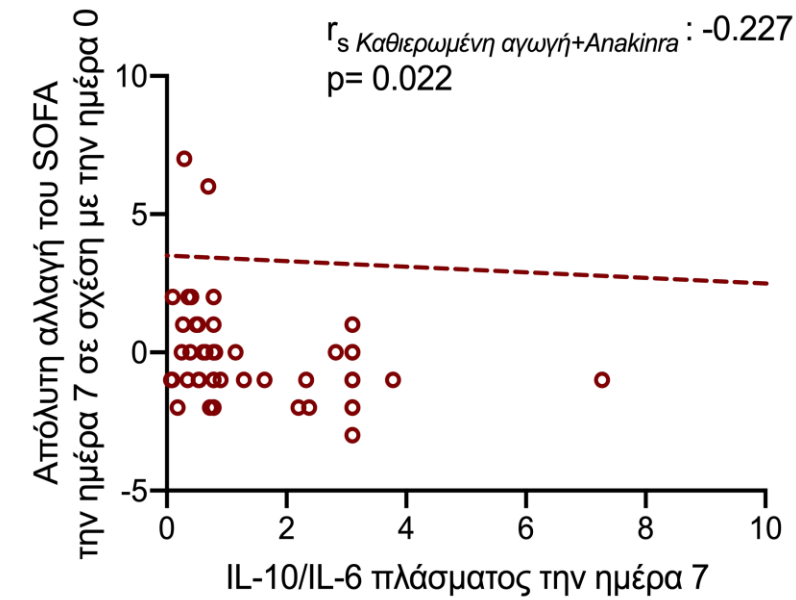
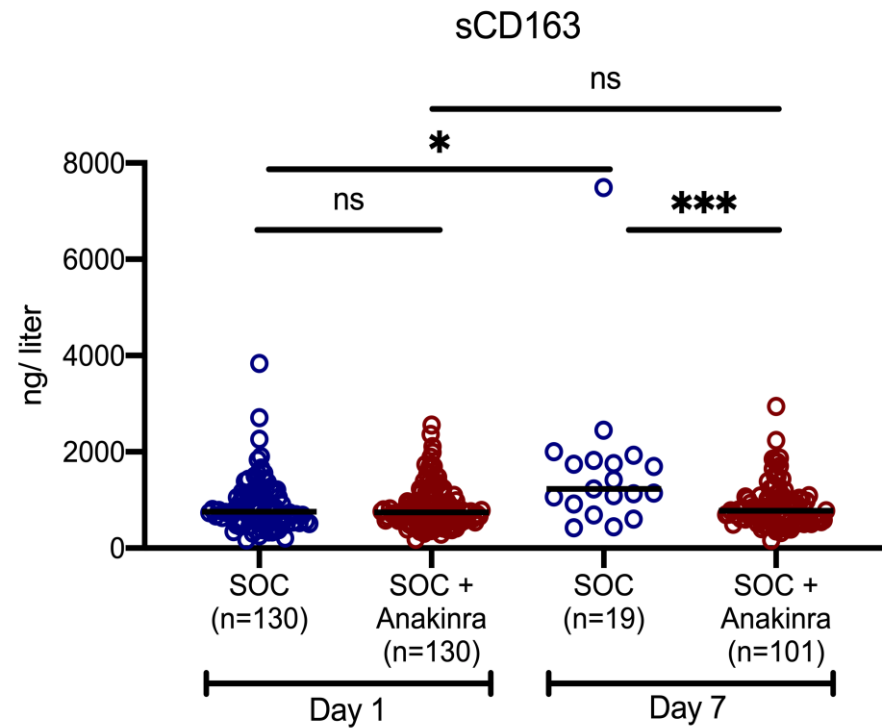
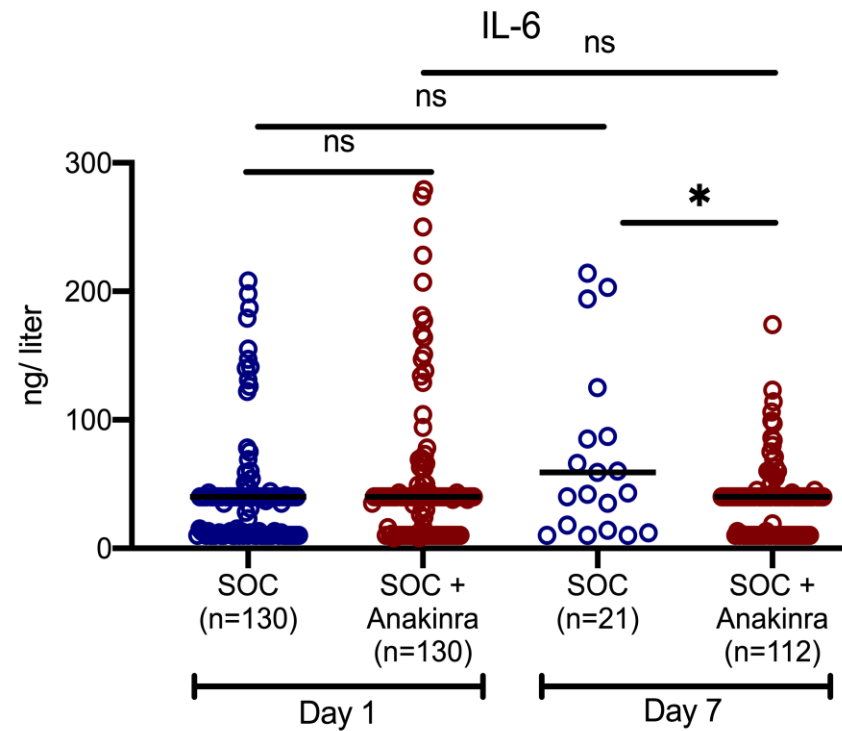
Total (95% CI) 457 632 100.0% 1.35 [0.59; 3.10]
 Heterogeneity: $\tau^2 = 0.5625$; $\chi^2 = 28.48$, $df = 6$ ($P < 0.01$); $I^2 = 79\%$



Δευτερογενής λοίμωξη

ΑΝΑΚΙΝΡΑ: ΒΕΛΤΙΩΣΗ ΑΝΤΙ-/ΠΡΟ- ΦΛΕΓΜΟΝΩΔΟΥΣ ΙΣΟΡΡΟΠΙΑΣ

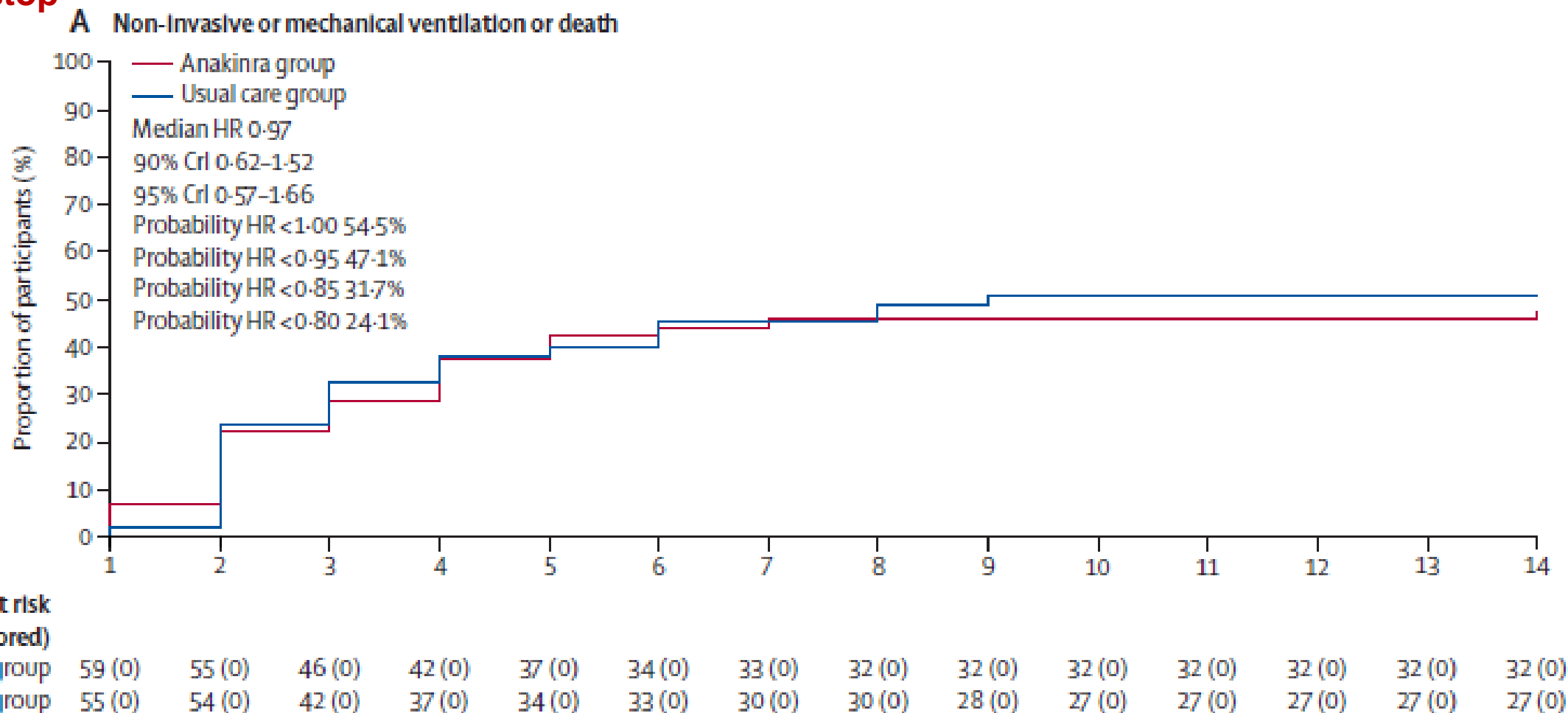
Kyriazopoulou E, et al. *Elife* 2021; 10: e66125.



CORIMUNO-ANA-1 RCT: ANAKINRA ΣΕ ΜΕΤΡΙΑ/ΣΟΒΑΡΗ COVID-19

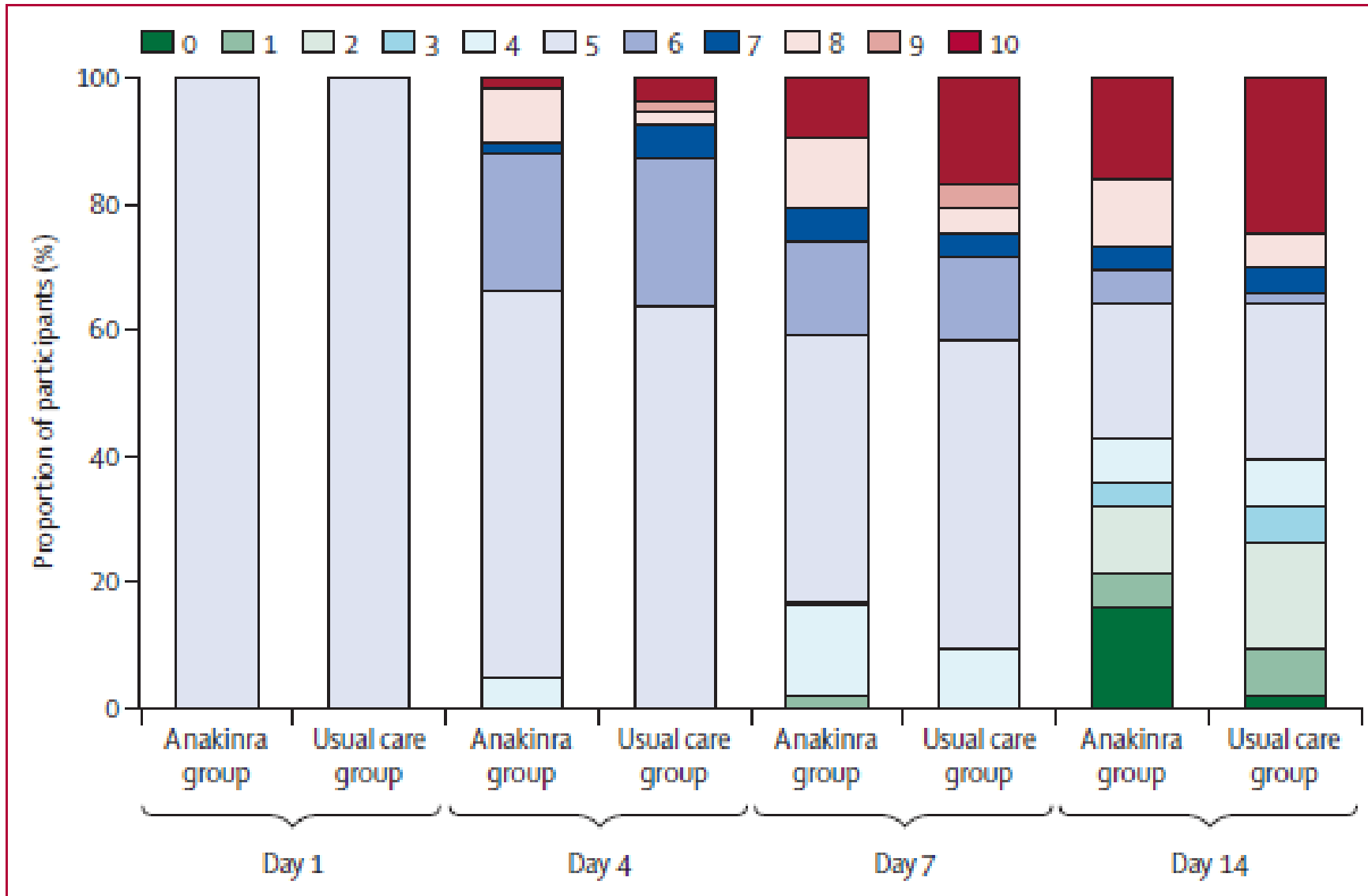
CORIMUNO-19 Collaborative group. *Lancet Respir Med* 2021; 9: 295.

- WHO CPS 5 and CRP \geq 25mg/l
- Open label RCT
- Anakinra (200 mg bid d1–3, 100 mg bid d4, 100 mg once d5) vs Standard-of-care
- Premature stop

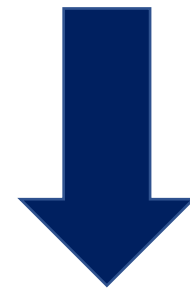


CORIMUNO-ANA-1 RCT: ANAKINRA ΣΕ ΜΕΤΡΙΑ/ΣΟΒΑΡΗ COVID-19

CORIMUNO-19 Collaborative group. *Lancet Respir Med* 2021; 9: 295.



- early stop without pre-specified stopping boundary
- CRP ≥ 25 mg/l too low?



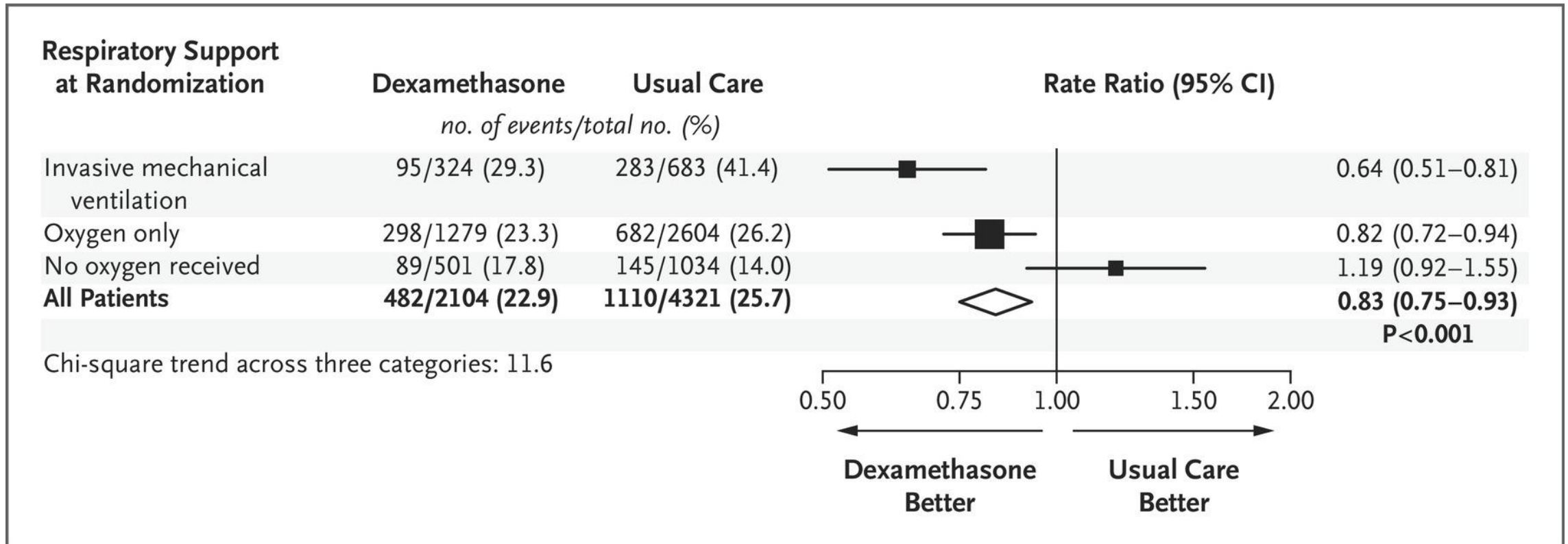
Awaited:

1. CORIMUNO-ANA-2
2. REMAP CAP
3. SAVE-MORE

ΔΕΞΑΜΕΘΑΖΟΝΗ: Η ΑΛΛΑΓΗ ΣΤΗΝ ΚΑΘΙΕΡΩΜΕΝΗ ΠΡΑΚΤΙΚΗ



RECOVERY Collaborative Group. *N Engl J Med* 2021; 384: 693.

Dexamethasone 6mg 10days (n=2104) vs SOC (n=4321)
28-d mortality 22,9% vs 25,9%




IVIg

Contents lists available at [ScienceDirect](#)

 **International Immunopharmacology** 

journal homepage: www.elsevier.com/locate/intimp



Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial

Payam Tabarsi^a, Saghar Barati^b, Hamidreza Jamaati^c, Sara Haseli^c, Majid Marjani^d, Afshin Moniri^e, Zahra Abtahian^d, Alireza Dastan^f, Sahar Yousefian^{b,c}, Raha Eskandari^c, Ali Saffaei^g, Fatemeh Monjazebi^h, Abdolbaset Vahediⁱ, Farzaneh Dastan^{b,c,*}

52 ασθενείς IVIg και 32 control
Κανένα κλινικό όφελος

Gharebaghi et al. *BMC Infectious Diseases* (2020) 20:786
<https://doi.org/10.1186/s12879-020-05507-4>

BMC Infectious Diseases

RESEARCH ARTICLE **Open Access**



The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial

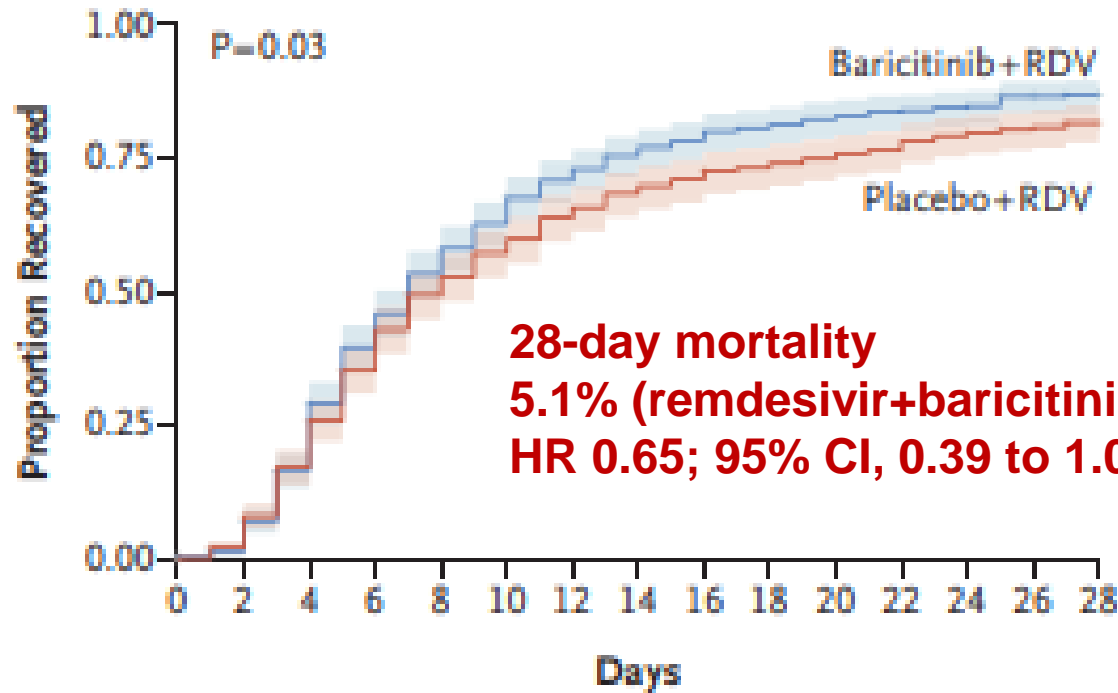
Naser Gharebaghi¹, Rahim Nejadrahim¹, Seyed Jalil Mousavi¹, Seyyed-Reza Sadat-Ebrahimi^{2*}  and Reza Hajizadeh^{3*}

30 ασθενείς IVIg και 20 placebo
Μείωση ενδονοσοκομειακής
θνητότητας

BARICITINIB

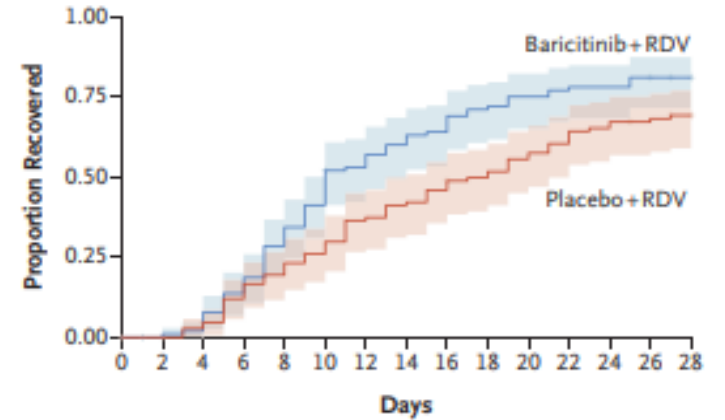
Kalil AC, et al. *N Engl J Med* 2021; 384: 795.

- RCT placebo-control
- Συγχορήγηση με ρεμντεσιβίρη
- Προ δεξαμεθαζόνης ως SOC
- Πρωτογενές καταληκτικό: Ανάρρωση (CPS 1-3)



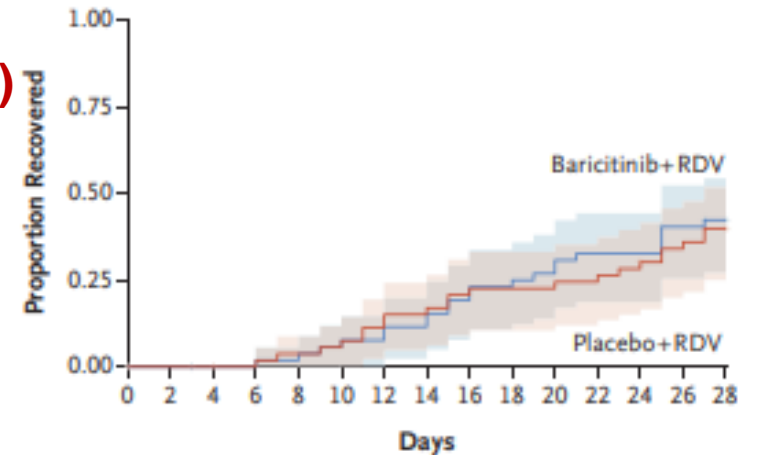
No. at Risk

Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	30
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	44



No. at Risk

Baricitinib+RDV	103	102	100	88	73	60	47	40	36	29	25	23	22	19	10
Placebo+RDV	113	110	106	95	86	78	67	62	57	52	46	41	36	32	16

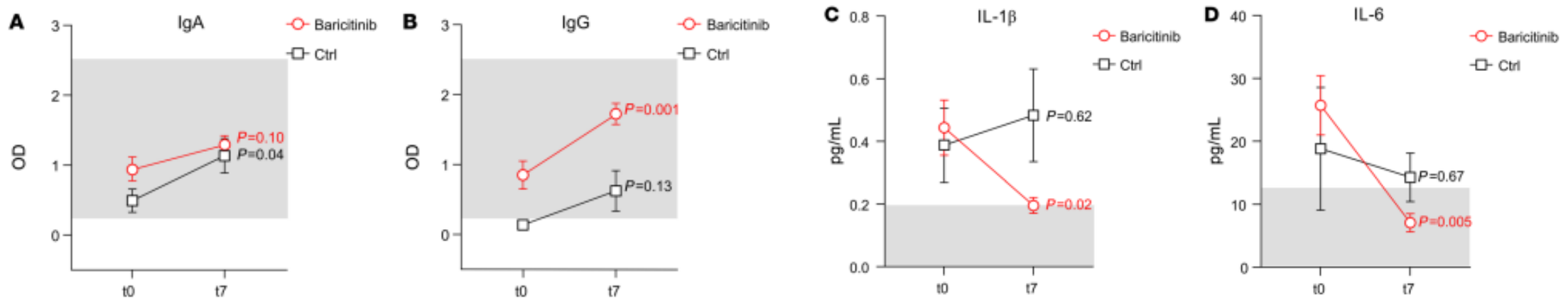
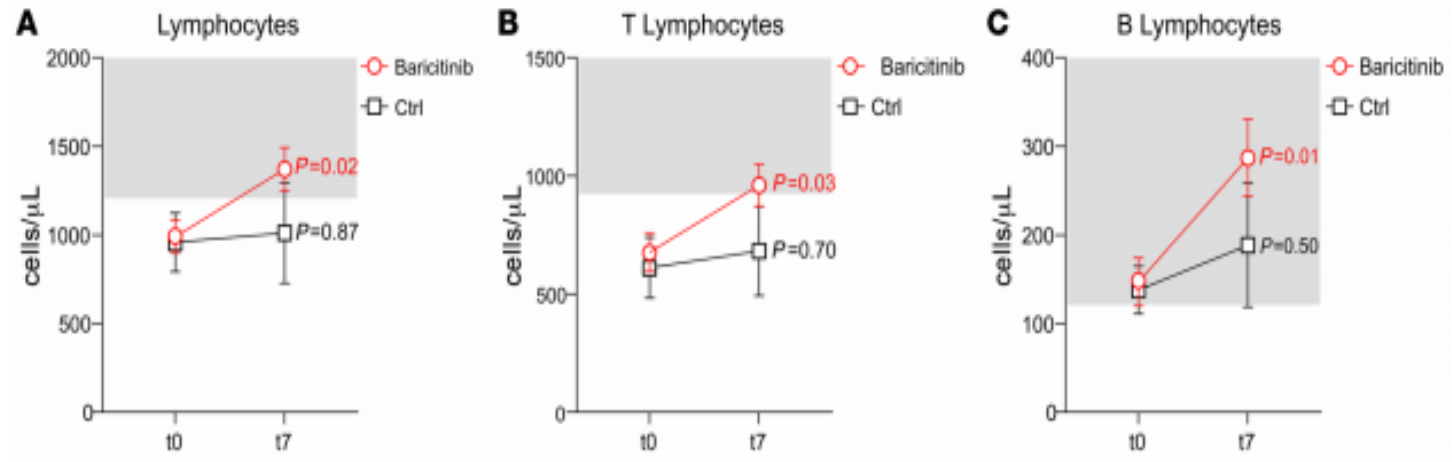
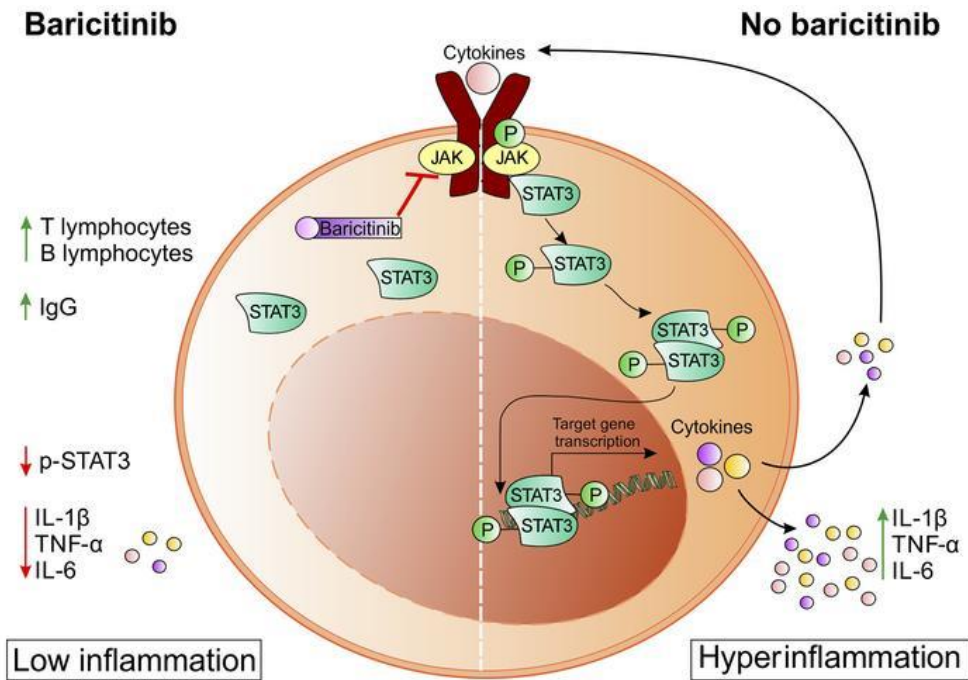


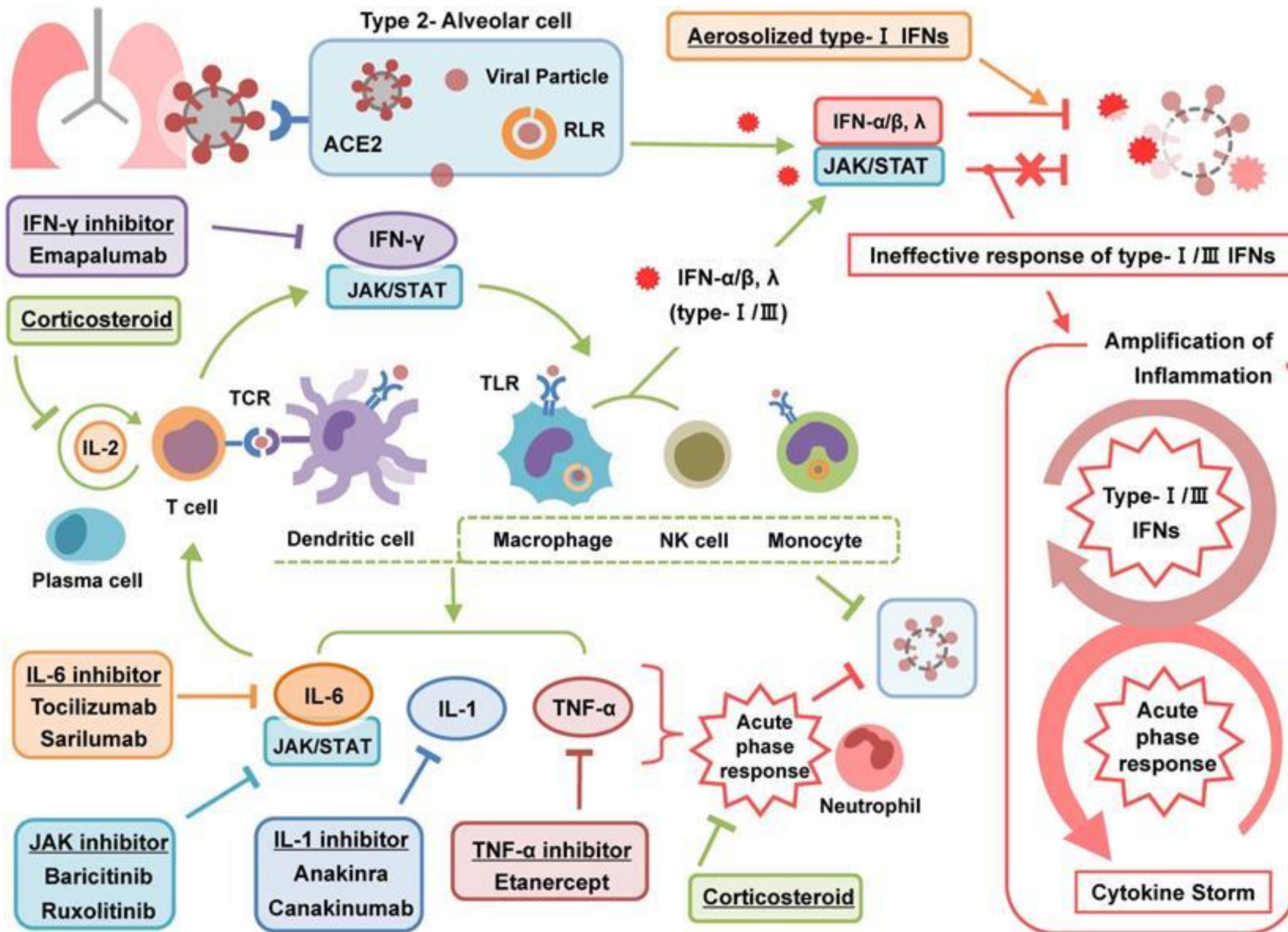
No. at Risk

Baricitinib+RDV	54	53	52	52	51	49	48	46	42	40	38	35	35	30	15
Placebo+RDV	57	54	54	53	51	50	47	45	42	41	41	40	38	34	16

BARICITINIB ΚΑΙ ΑΝΟΣΙΑΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗ

Bronte V, et al. *J Clin Invest* 2020; 130: 6409.





**ΑΝΟΣΟΠΑΡΕΜΒΑΣΗ:
Η ΘΕΣΗ ΤΗΣ ΣΤΗΝ
COVID-19**

**ΑΝΟΣΟΠΑΡΕΜΒΑΣΗ:
ΕΝΣΩΜΑΤΩΣΗ
ΠΡΟΗΓΟΥΜΕΝΗΣ
ΕΜΠΕΙΡΙΑΣ**

**ΑΝΟΣΟΠΑΡΕΜΒΑΣΗ:
ΣΕ ΠΟΙΟΝ ΑΣΘΕΝΗ**

**ΑΝΟΣΟΠΑΡΕΜΒΑΣΗ:
ΣΕ ΠΟΙΑ ΦΑΣΗ ΝΟΣΟΥ**