Terapia medica nelle diverse fasi di malattia da Covid-19: dalla fisiopatologia alla clinica

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Who to treat?

When to treat?

How to treat?

Who to treat?

When to treat?

How to treat?

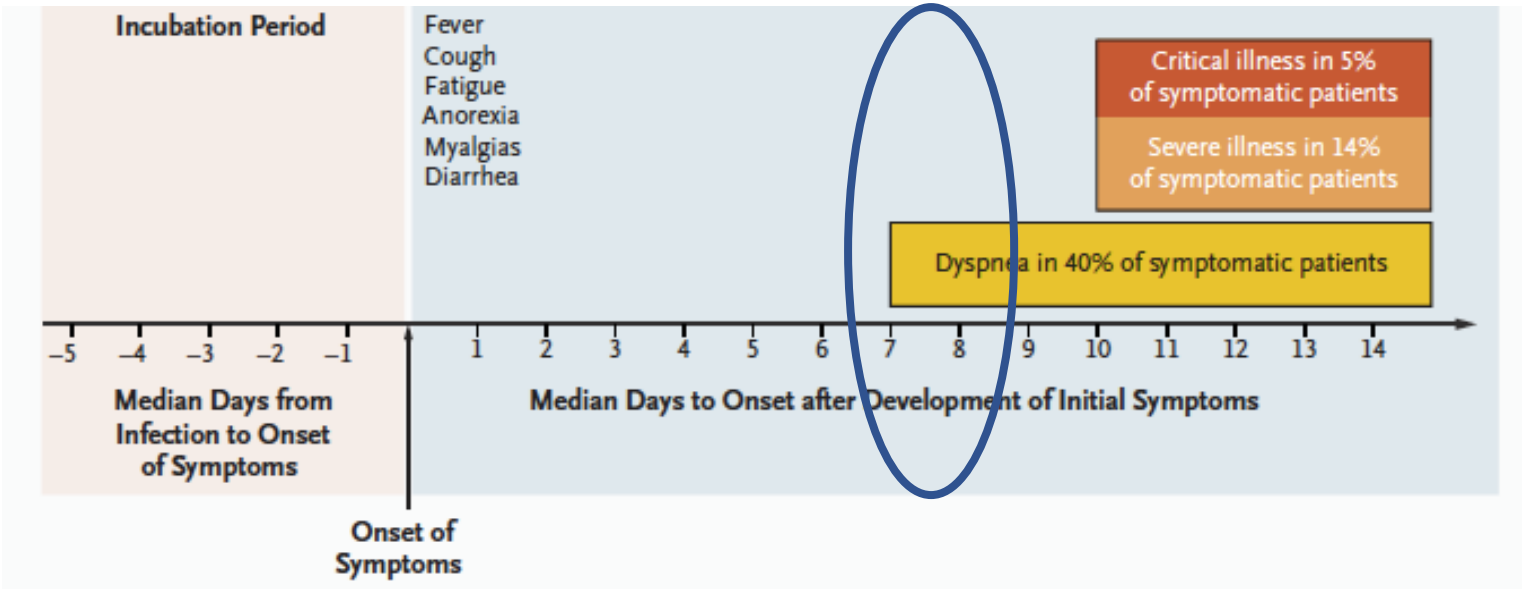
Table 1. Established and Potential Risk Factors for Severe Covid-19.*

Older age (e.g., >65 years)
Chronic lung disease
Cardiovascular disease
Diabetes mellitus
Obesity
Immunocompromise†
End-stage renal disease
Liver disease

Who to treat?

When to treat?

How to treat?



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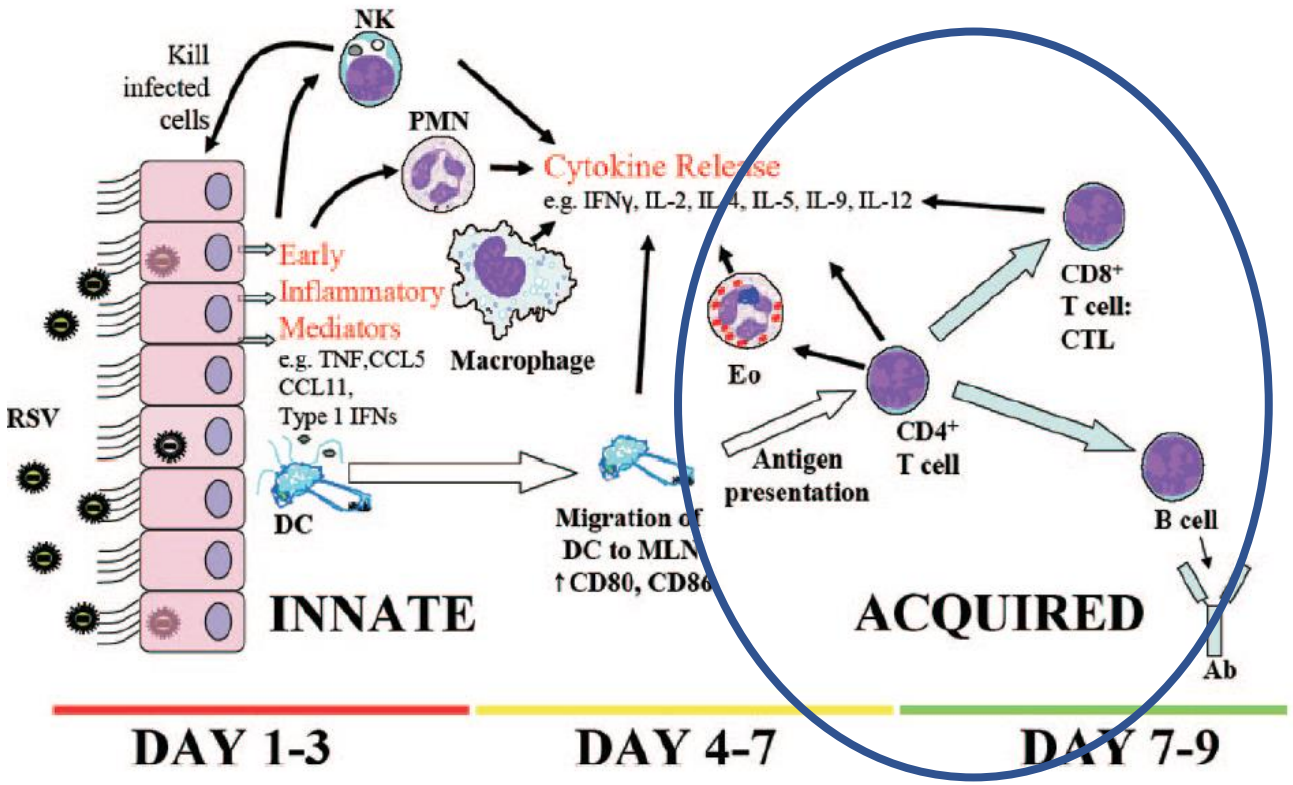
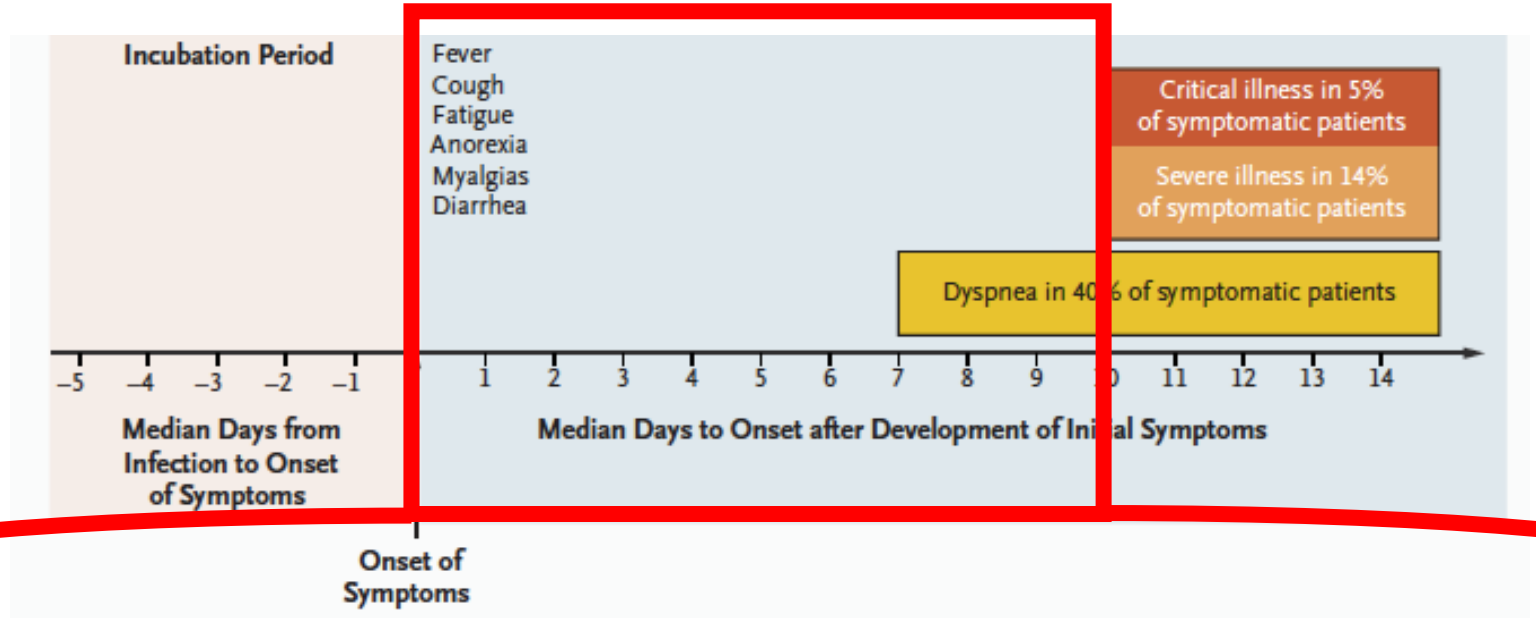


Openshaw et al. Clinical Microbiolgy Reviews 2005

Treat as early as possible

Date of onset of first symptoms drives treatment decision making (NOT the date of first positive test)



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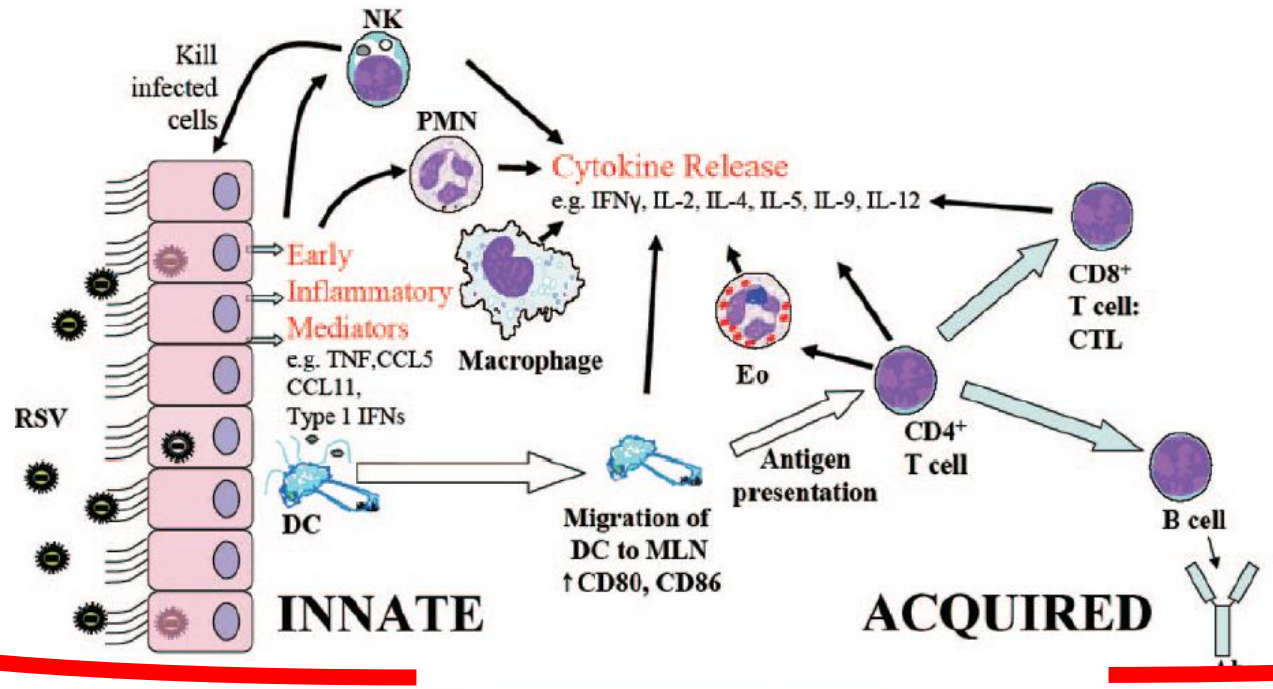


Phase 1. active viral replication

Antivirals

Openshaw et al. Clinical Microbiolgy Reviews 2005

Treatment in the outpatient setting

Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

Patient Disposition	Panel's Recommendations
All Patients	• All patients should be offered symptom management **(AIII)**. • The Panel recommends against the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] **(CIIa)**
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

Corticosteroids

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

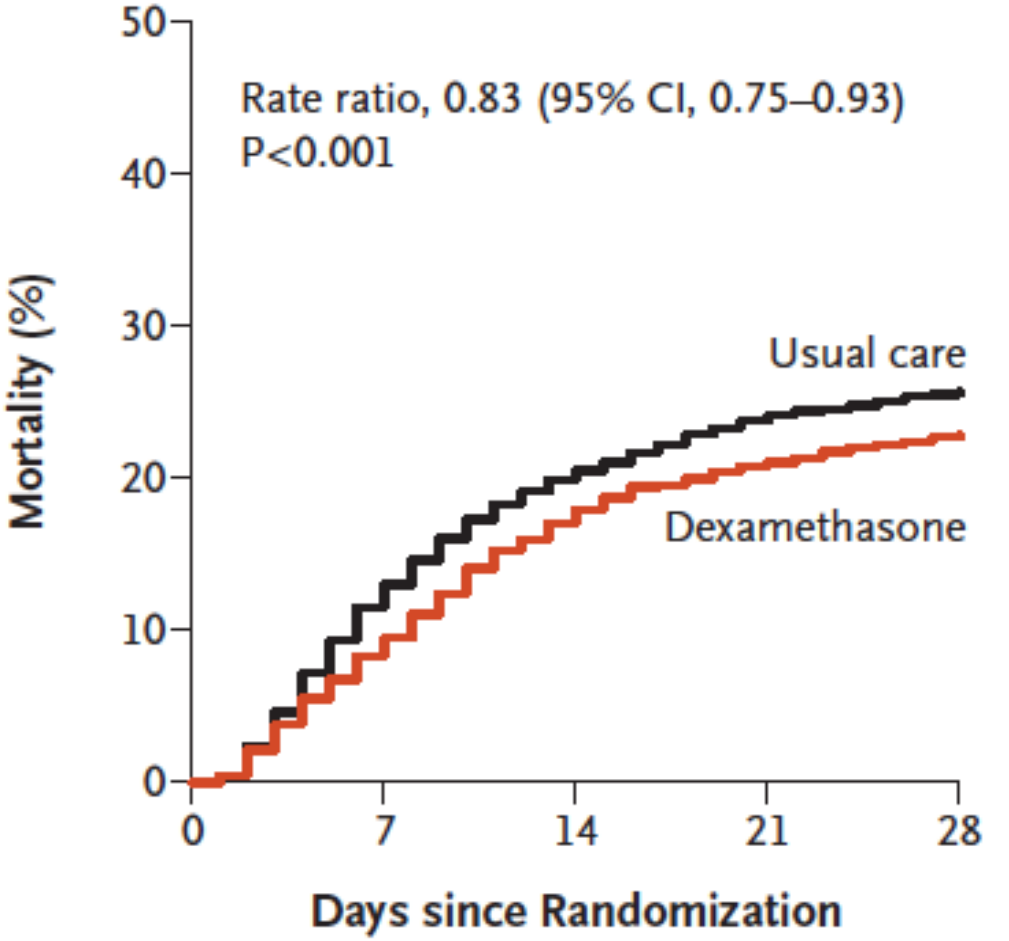
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Randomized, controlled, open label, adaptive, platform trial designed to evaluate a range of treatments for COVID-19 including dexamethasone

Dexamethasone 6 mg PO or IV once daily (n=2104) x 10 days vs usual care (n=4321)

A All Participants (N=6425)



No. at Risk					
Usual care	4321	3754	3427	3271	3205
Dexamethasone	2104	1903	1725	1659	1621

Primary outcome: mortality at day 28

Overall: 22.9% vs 25.7% (p<0.001)

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

Chi-square trend across three categories: 11.5

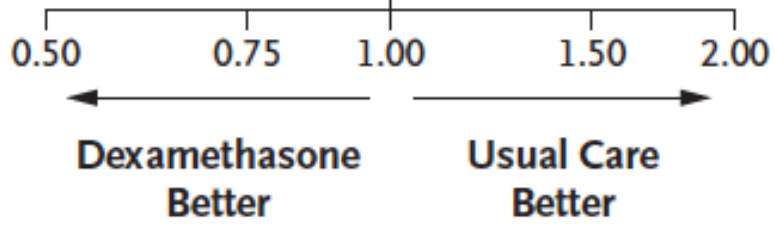


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

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

Treatment in the outpatient setting

Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

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Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

EPIC-HR Study: Evaluation of Protease Inhibition for COVID-19 in High Risk patients

Phase 2-3 randomised double-blind in unvaccinated high risk patients, under delta VOC

Symptoms 5 days before

NMV 300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 hours for 5 days

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 14, 2022 VOL. 386 NO. 15

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

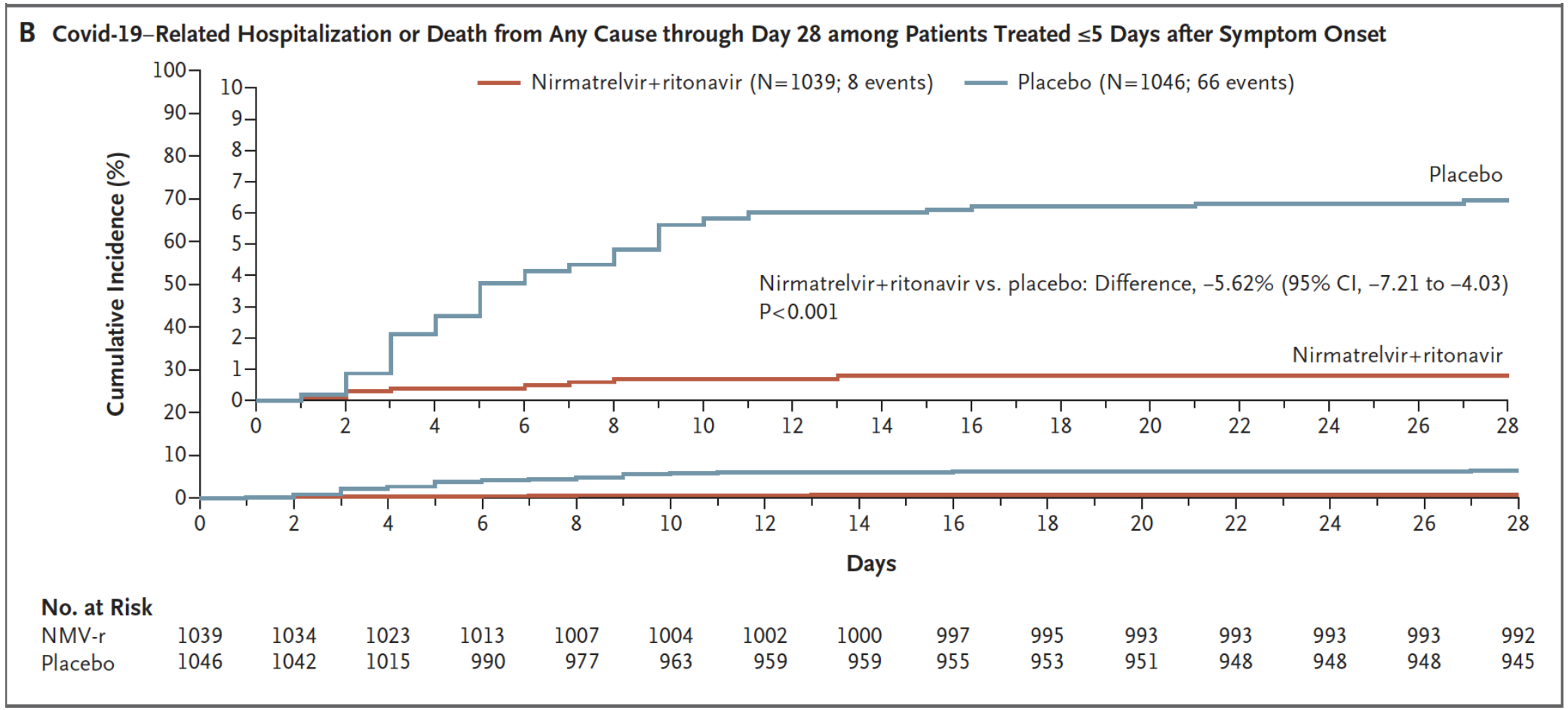
Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

Table 1. Demographic and Clinical Characteristics of the Patients (Full Analysis Population).*

Characteristic	Nirmatrelvir plus Ritonavir (N=1120)	Placebo (N=1126)	Total (N=2246)
Median age (range) at randomization — yr	45.00 (18.00–86.00)	46.50 (18.00–88.00)	46.00 (18.00–88.00)
Sex — no. of patients (%)			
Male	566 (50.5)	582 (51.7)	1148 (51.1)
Female	554 (49.5)	544 (48.3)	1098 (48.9)
Race or ethnic group — no. of patients (%)†			
White	800 (71.4)	807 (71.7)	1607 (71.5)
Black	60 (5.4)	50 (4.4)	110 (4.9)
Asian	154 (13.8)	161 (14.3)	315 (14.0)
American Indian or Alaska Native	96 (8.6)	95 (8.4)	191 (8.5)
Multiracial	1 (0.1)	2 (0.2)	3 (0.1)
Not reported	8 (0.7)	9 (0.8)	17 (0.8)
Other or unknown	1 (0.1)	2 (0.2)	3 (0.1)
Time since first symptom			
≤3 days — no. of patients (%)	754 (67.3)	735 (65.3)	1489 (66.3)
>3 days — no. of patients (%)	366 (32.7)	391 (34.7)	757 (33.7)
Mean±SD — days	2.93±1.12	2.99±1.09	2.96±1.10
Median (range) — days	3.00 (0.00–7.00)	3.00 (0.00–9.00)	3.00 (0.00–9.00)
Covid-19 monoclonal antibody treatment — no. of patients (%)			
Received or expected to receive	70 (6.2)	70 (6.2)	140 (6.2)
Not received or did not expect to receive	1050 (93.8)	1056 (93.8)	2106 (93.8)
Serology status — no. of patients (%)			
Negative	518 (46.2)	537 (47.7)	1055 (47.0)
Positive	581 (51.9)	568 (50.4)	1149 (51.2)
Median viral load (range) — $\log_{10}$ copies per milliliter	5.41 (0.00–9.16)	5.30 (0.00–9.15)	5.35 (0.00–9.16)
Viral load ≥10^4 copies per milliliter — no. of patients (%)	677 (60.4)	676 (60.0)	1353 (60.2)

* Shown are data for all patients who underwent randomization, regardless of whether the drug or placebo was administered.
† Race or ethnic group was reported by the patient.

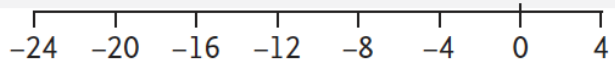
Relative risk reduction of hospitalization or death at day 28: 89.1%



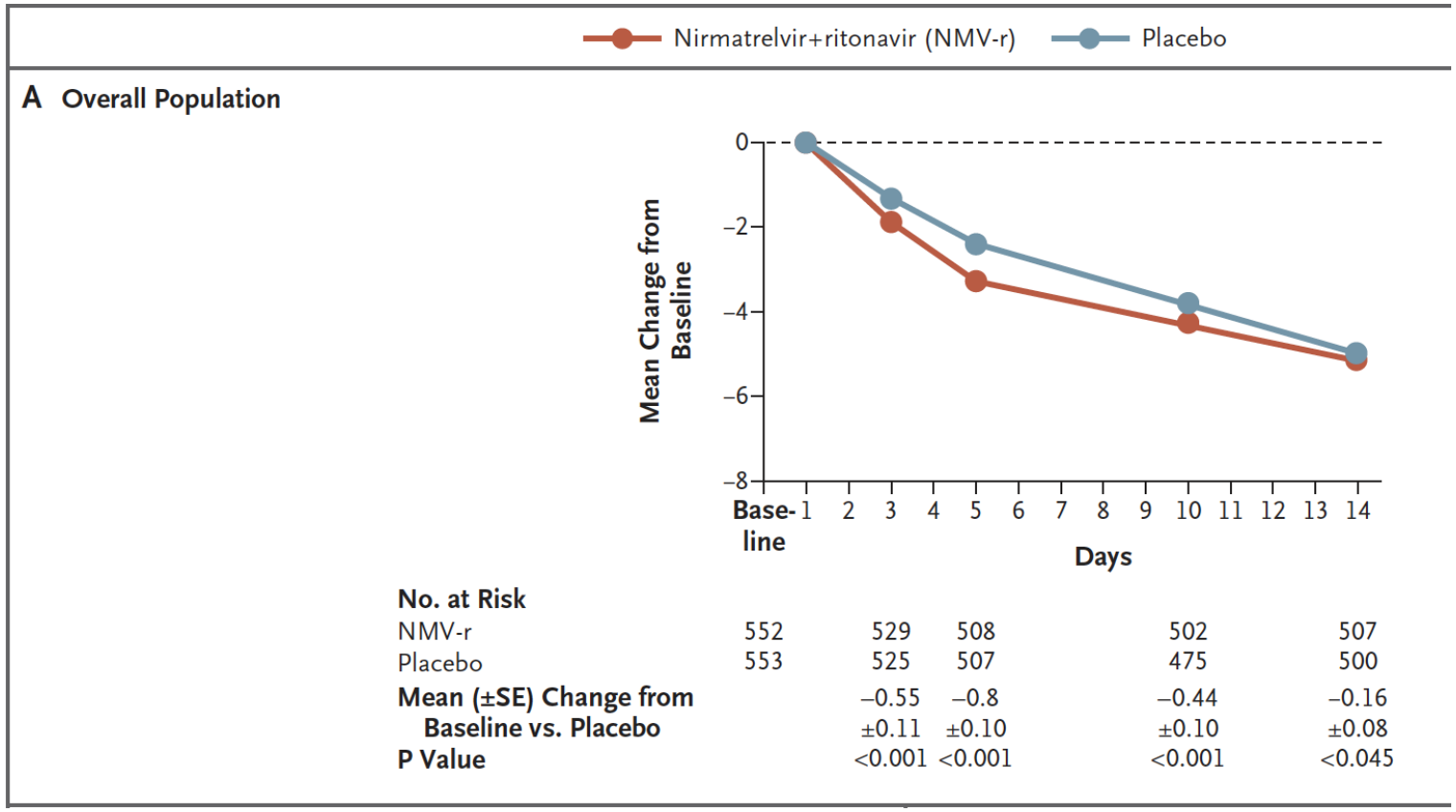
Patients treated within 5 days
from symptoms onset

C Subgroup Analysis

Subgroup	Nirmatrelvir+Ritonavir	Placebo	Difference from Placebo (95% CI)
	no. of events/total no.		*percentage points*
Overall	8/1039	66/1046	−5.62 (−7.21 to −4.03)
Time since symptom onset			
≤3 days	5/697	44/682	−5.81 (−7.78 to −3.84)
>3 days	3/342	22/364	−5.23 (−7.91 to −2.55)
Age			
<65 yr	7/908	46/909	−4.35 (−5.91 to −2.79)
≥65 yr	1/131	20/137	−13.93 (−20.07 to −7.80)
Sex			
Male	4/520	41/540	−6.93 (−9.32 to −4.53)
Female	4/519	25/506	−4.23 (−6.29 to −2.17)
Body-mass index			
<25	1/209	9/207	−3.88 (−6.83 to −0.94)
25 to <30	3/458	28/466	−5.44 (−7.75 to −3.13)
≥30	4/371	29/373	−6.85 (−9.82 to −3.87)
Diabetes mellitus			
Yes	2/125	9/127	−5.51 (−10.51 to −0.52)
No	6/913	57/919	−5.63 (−7.30 to −3.96)
Baseline SARS-CoV-2 serology status			
Negative	7/487	58/505	−10.25 (−13.28 to −7.21)
Positive	1/540	8/528	−1.34 (−2.45 to −0.23)
Received or expected to receive Covid-19 monoclonal antibody treatment			
Yes	1/70	2/69	−1.51 (−6.40 to 3.37)
No	8/1039	66/1046	−5.62 (−7.21 to −4.03)

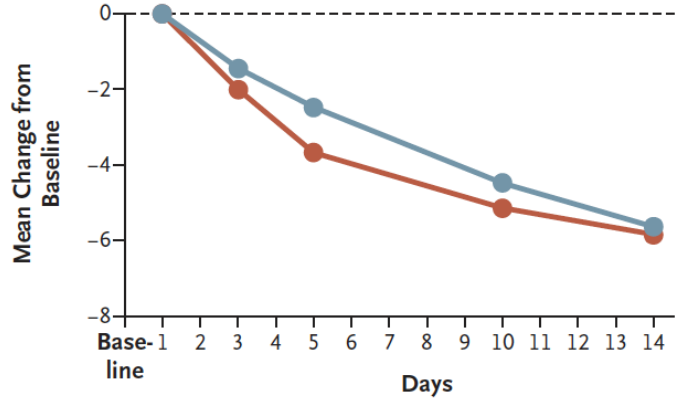


Viral load reduction



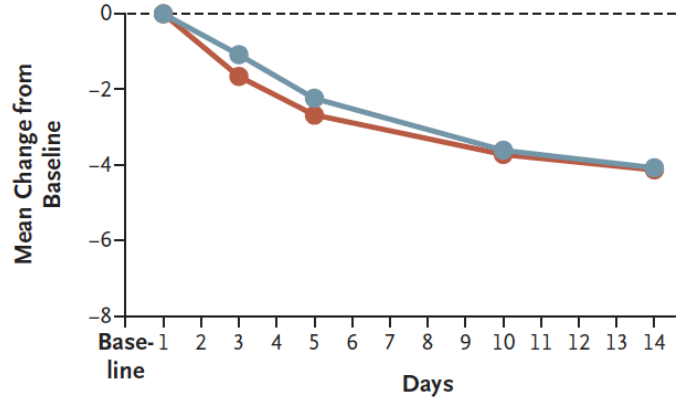
No. at Risk					
NMV-r	552	529	508	502	507
Placebo	553	525	507	475	500
Mean (±SE) Change from Baseline vs. Placebo		−0.55 ±0.11	−0.8 ±0.10	−0.44 ±0.10	−0.16 ±0.08
P Value		<0.001	<0.001	<0.001	<0.045

B Seronegative



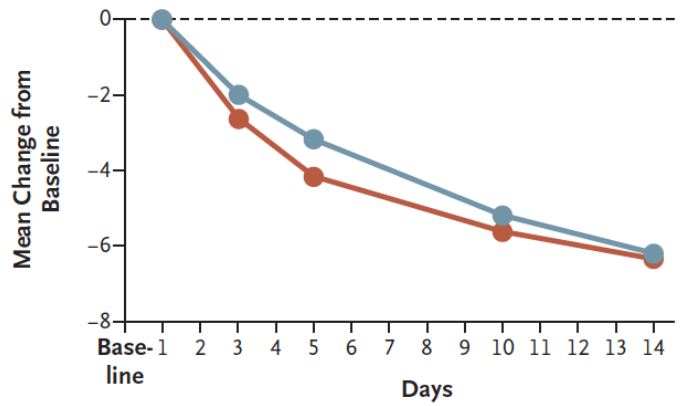
No. at Risk					
NMV-r	318	304	297	296	293
Placebo	312	294	284	267	273
Mean (±SE) Change from Baseline vs. Placebo		−0.56 ±0.14	−1.20 ±0.13	−0.67 ±0.14	−0.21 ±0.12
P Value		<0.001	<0.001	<0.001	0.07

C Seropositive



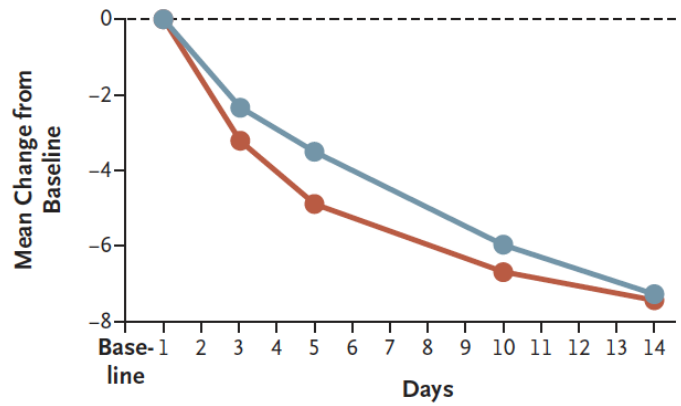
No. at Risk					
NMV-r	231	222	208	203	211
Placebo	233	223	215	200	219
Mean (±SE) Change from Baseline vs. Placebo		−0.58 ±0.18	−0.44 ±0.16	−0.11 ±0.12	−0.06 ±0.11
P Value		0.001	0.01	0.37	0.60

D Baseline Viral Load >10^4 copies/ml



No. at Risk					
NMV-r	443	424	408	408	408
Placebo	442	419	402	379	396
Mean (±SE) Change from Baseline vs. Placebo		−0.66 ±0.12	−1.00 ±0.12	−0.43 ±0.12	−0.15 ±0.10
P Value		<0.001	<0.001	<0.001	0.13

E Baseline Viral Load >10^7 copies/ml



No. at Risk					
NMV-r	224	213	209	204	208
Placebo	202	191	185	171	176
Mean (±SE) Change from Baseline vs. Placebo		−0.88 ±0.16	−1.39 ±0.15	−0.73 ±0.17	−0.16 ±0.14
P Value		<0.001	<0.001	<0.001	0.25

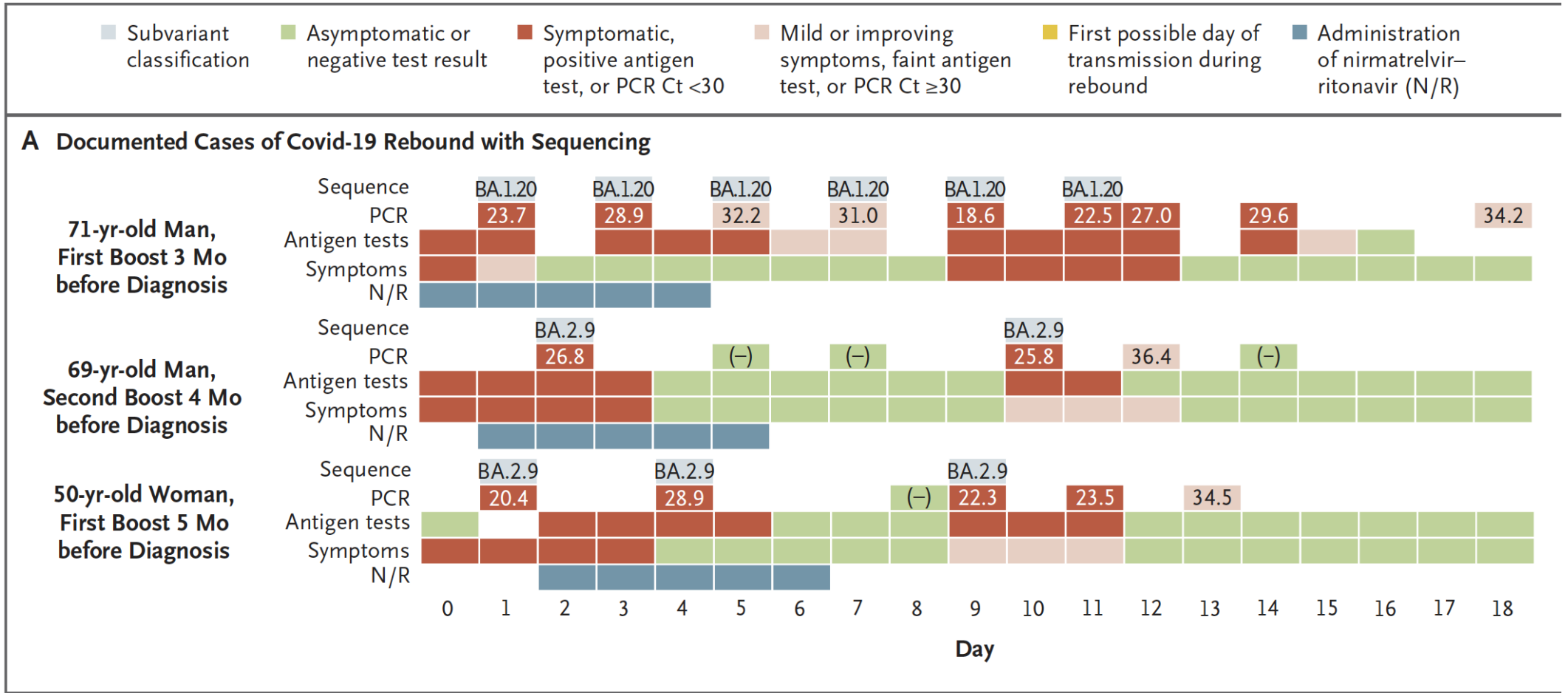
safety

Dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) more frequent with nirmatrelvir plus ritonavir vs placebo

Table 2. Summary of Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation through Day 34 (Safety Analysis Population).*

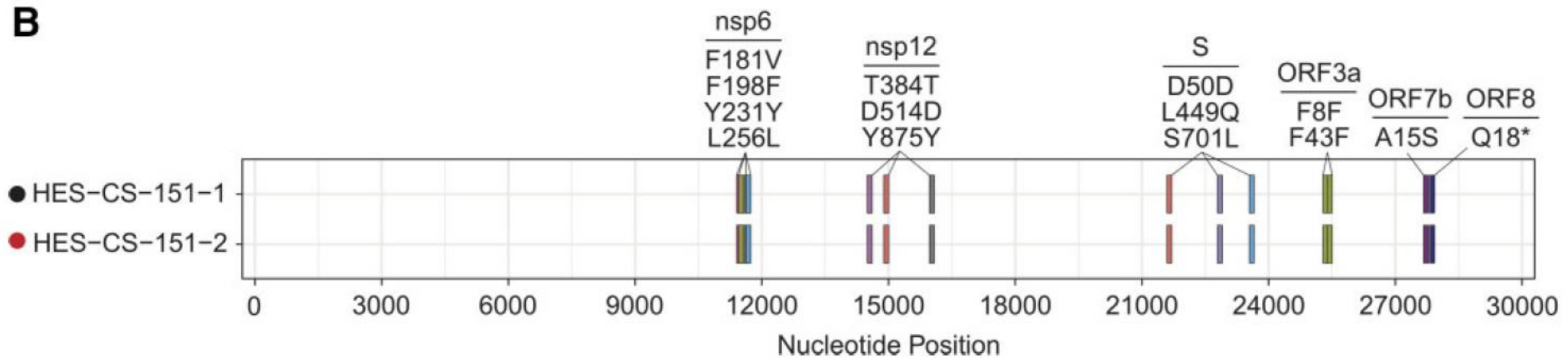
Adverse Event Category	Nirmatrelvir plus Ritonavir (N=1109)	Placebo (N=1115)
Events that emerged during treatment period		
No. of adverse events	476	525
Patients with adverse events — no. (%)		
Any adverse event	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13† (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)
Events considered to be related to drug or placebo		
No. of adverse events	123	52
Patients with adverse events — no. (%)		
Any adverse event	86 (7.8)	42 (3.8)
Serious adverse event	1 (<0.1)	0
Maximum grade 3 or 4 adverse event	5 (0.5)	5 (0.4)
Maximum grade 5 adverse event	0	0
Discontinued drug or placebo because of adverse event	9 (0.8)	7 (0.6)
Had dose reduction or temporary discontinuation owing to adverse event	2 (0.2)	3 (0.3)

Covid-19 rebound after Paxlovid – Omicrom VOC



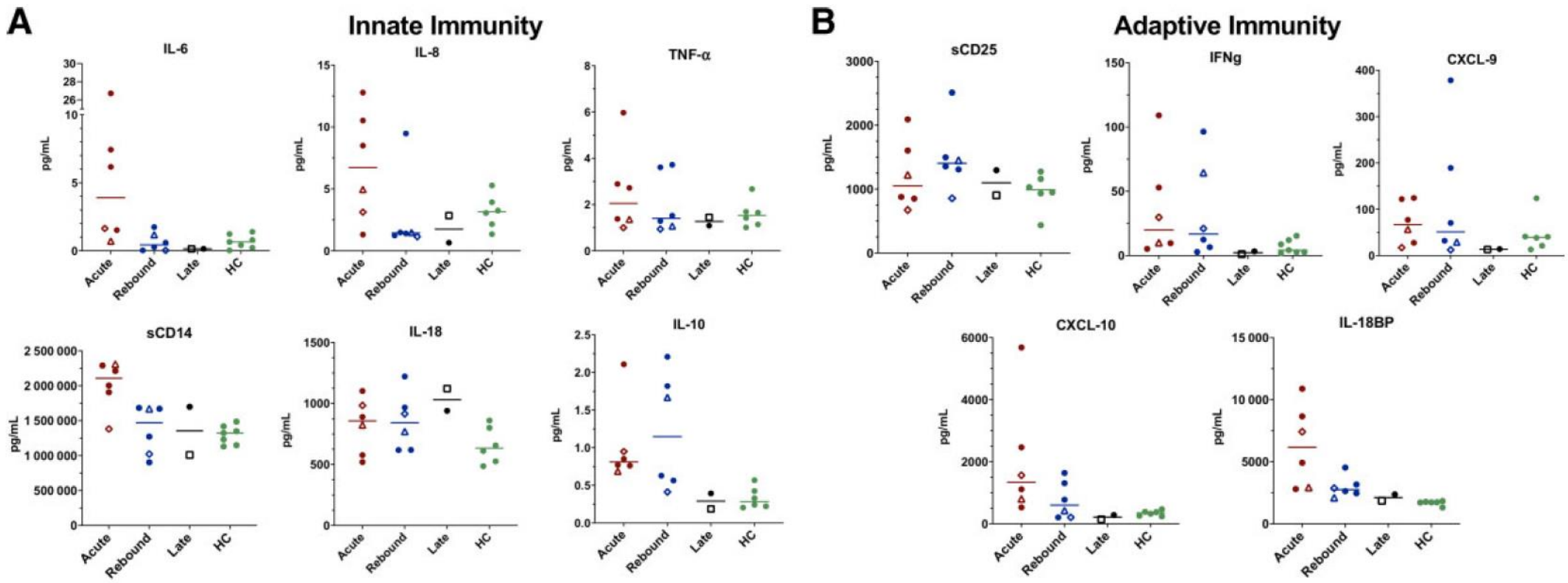
Charness et al NEJM 2022

No viral resistence at rebound



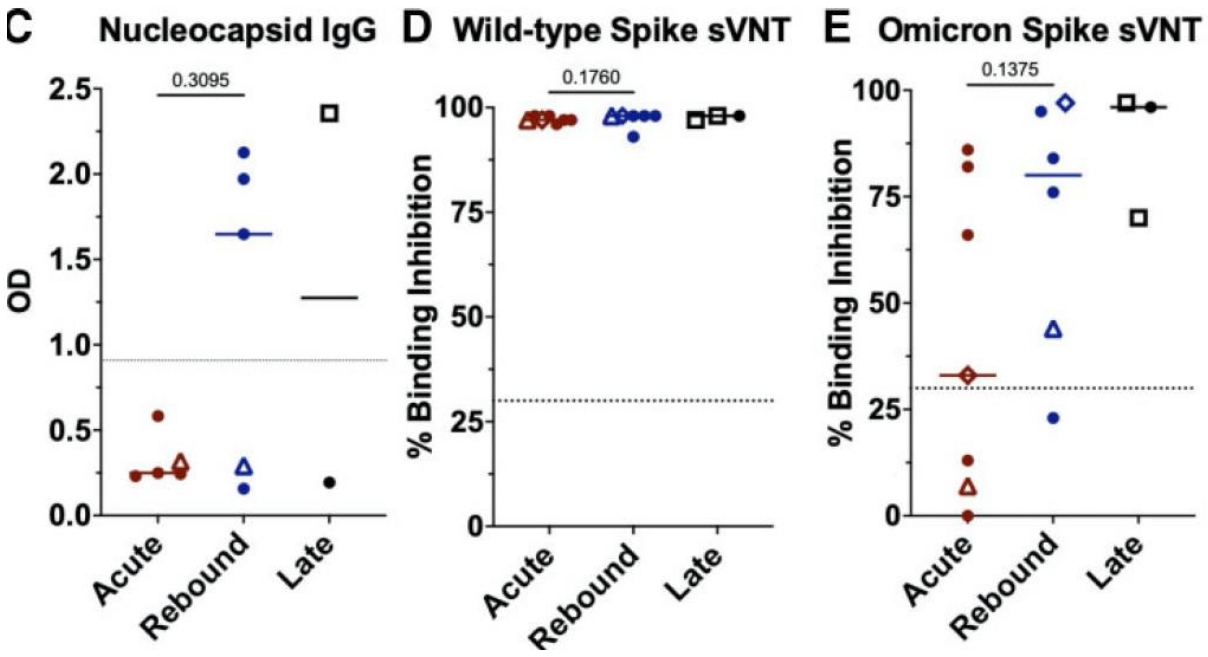
Epling et al, CID 2022

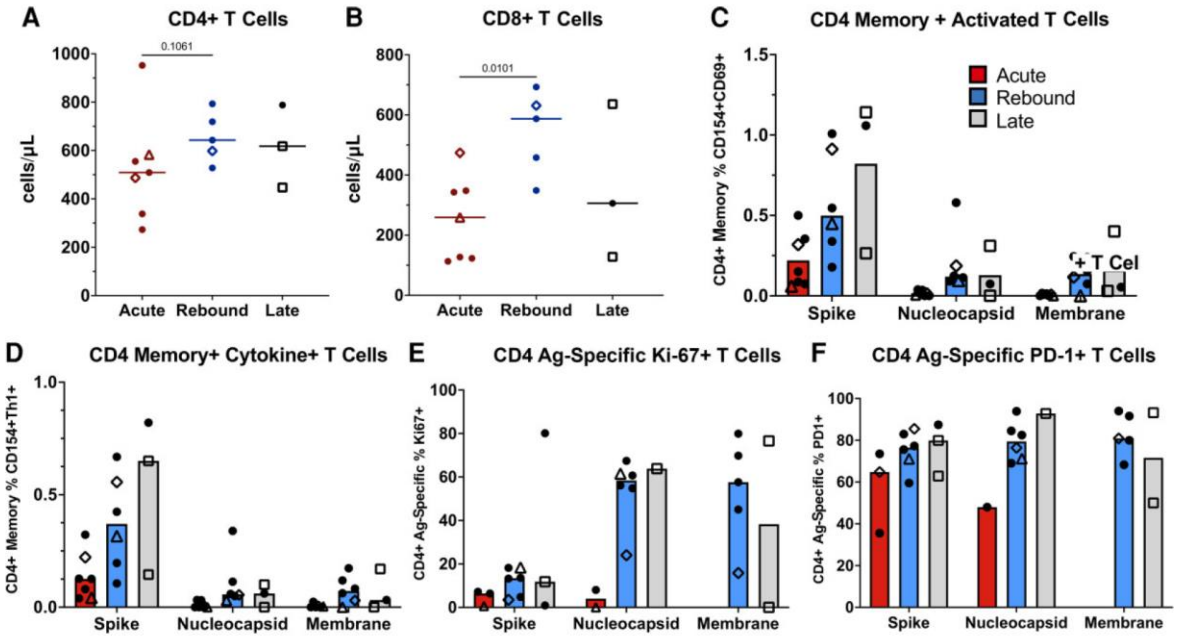
No increased inflammation in rebounding patients



Epling et al, CID 2022

Immune maturation in rebounding patients





Epling et al, CID 2022

Immune maturation at rebound

Fig 1A. Blood examination and SARS CoV-2 determination on nasopharyngeal swabs

	T1 (April, 20)	T2 (April, 27)	T3 (May, 2)	T4 (May, 16)
RBC (10^6/uL)	4.06	3.98	3.95	4.06
Hb (g/dl)	**12.3**	**11.9**	**11.8**	**12.2**
PTL (10^3/uL)	226	234	220	338
WBC (10^3/uL)	**7.55**	**4.74**	**5.75**	**6.65**
Lymphocytes (10^3/uL)	660	1170	810	1136
Monocytes (10^3/uL)	**970**	**550**	**790**	**610**
CRP (mg/L)	<5.0	5.0	<5.0	<5.0
LDH (U/L)	**250**	**200**	**205**	**180**
SARS CoV-2 (Ct)	E = 23 RdRp/S = 26 N = 20	NOT DETECTED	E = 21 RdRp/S = 25 N = 21	NOT DETECTED
SARS CoV-2 (VOC)	**B.1.1.529 BA.2 (Omicron)**	**NA**	**B.1.1.529 BA.2 (Omicron)**	**NA**

Fig 1B. Innate response

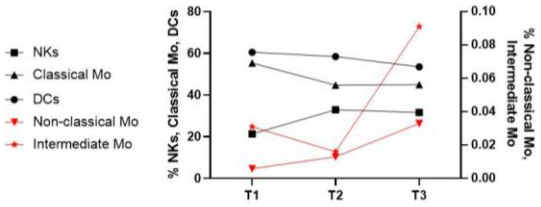


Fig 1C. SARS-CoV-2-specific CD4+ T cells

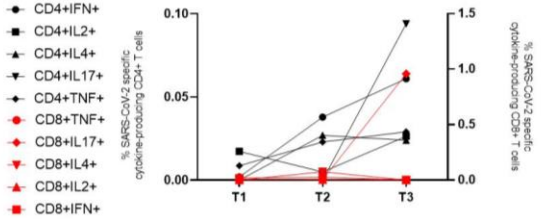


Fig 1D. Th1 - CD4+ polyfunctionality

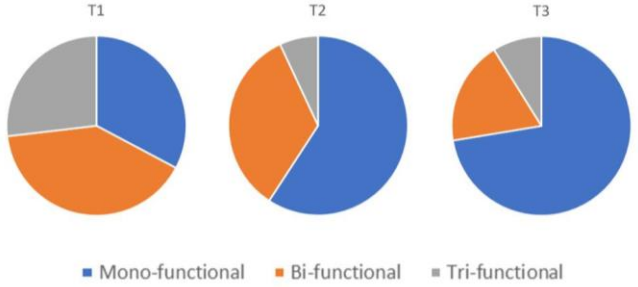
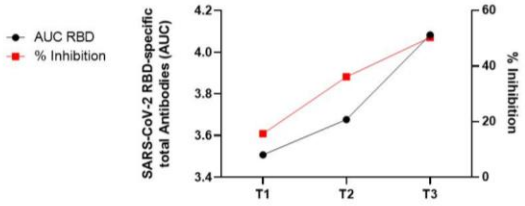


Fig 1E. SARS-CoV-2-specific Abs



Marchetti, Rovito et al, Clinical Microbiology and Infection 2023

Intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3)

Randomised double-blind in unvaccinated high risk patients.

Symptoms in the previous 7 days

The NEW ENGLAND JOURNAL of MEDICINE

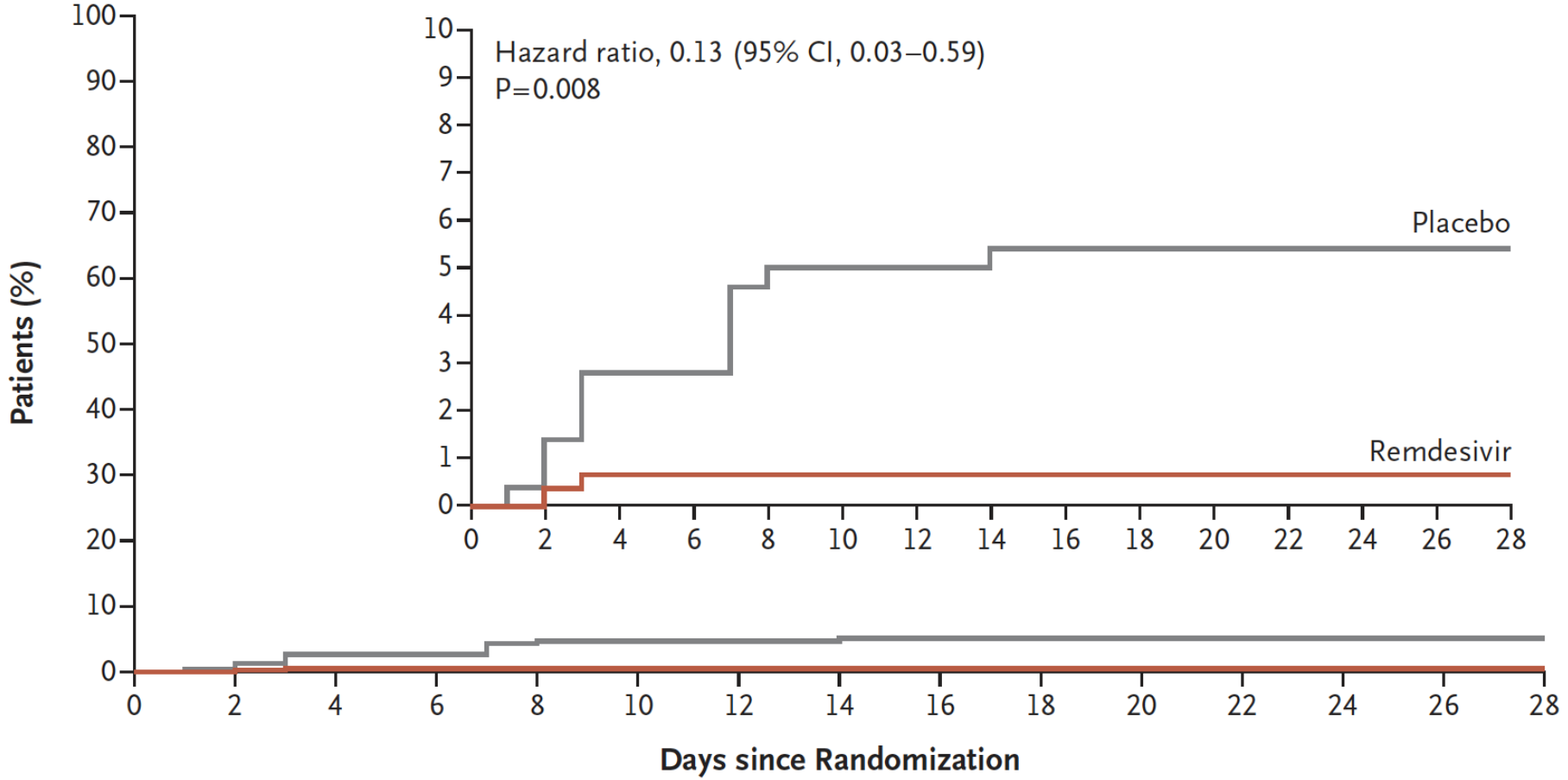
ESTABLISHED IN 1812 JANUARY 27, 2022 VOL. 386 NO. 4

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

Characteristic	Remdesivir (N=279)	Placebo (N=283)	Total (N=562)
Age — yr	50±15	51±15	50±15
Age category — no. (%)			
≥60 yr	83 (29.7)	87 (30.7)	170 (30.2)
<18 yr	3 (1.1)	5 (1.8)	8 (1.4)
Female sex — no. (%)	131 (47.0)	138 (48.8)	269 (47.9)
Residence in the United States — no. (%)	264 (94.6)	267 (94.3)	531 (94.5)
Race or ethnic group — no. (%)†			
White	228 (81.7)	224 (79.2)	452 (80.4)
Black	20 (7.2)	22 (7.8)	42 (7.5)
American Indian or Alaska Native	15 (5.4)	21 (7.4)	36 (6.4)
Asian, Native Hawaiian, or Pacific Islander	7 (2.5)	7 (2.5)	14 (2.5)
Hispanic or Latinx	123 (44.1)	112 (39.6)	235 (41.8)
Other	3 (1.1)	2 (0.7)	5 (0.9)
Body-mass index	31.2±6.7	30.8±5.8	31.0±6.2
Coexisting conditions — no. (%)			
Diabetes mellitus	173 (62.0)	173 (61.1)	346 (61.6)
Obesity	154 (55.2)	156 (55.1)	310 (55.2)
Hypertension	138 (49.5)	130 (45.9)	268 (47.7)
Chronic lung disease	67 (24.0)	68 (24.0)	135 (24.0)
Current cancer	12 (4.3)	18 (6.4)	30 (5.3)
Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)	44 (7.8)
Immune compromise	14 (5.0)	9 (3.2)	23 (4.1)
Chronic kidney disease, mild or moderate	7 (2.5)	11 (3.9)	18 (3.2)
Chronic liver disease	1 (0.4)	1 (0.4)	2 (0.4)
Residence in skilled nursing facility — no. (%)	8 (2.9)	7 (2.5)	15 (2.7)
Median duration of symptoms before first infusion (IQR) — days	5 (3–6)	5 (4–6)	5 (3–6)
Median time since RT-PCR confirmation of SARS-CoV-2 (IQR) — days	2 (1–3)	3 (1–4)	2 (1–4)
Mean SARS-CoV-2 RNA nasopharyngeal viral load — $\log_{10}$ copies/ml‡	6.31±1.75	6.28±1.79	6.29±1.77

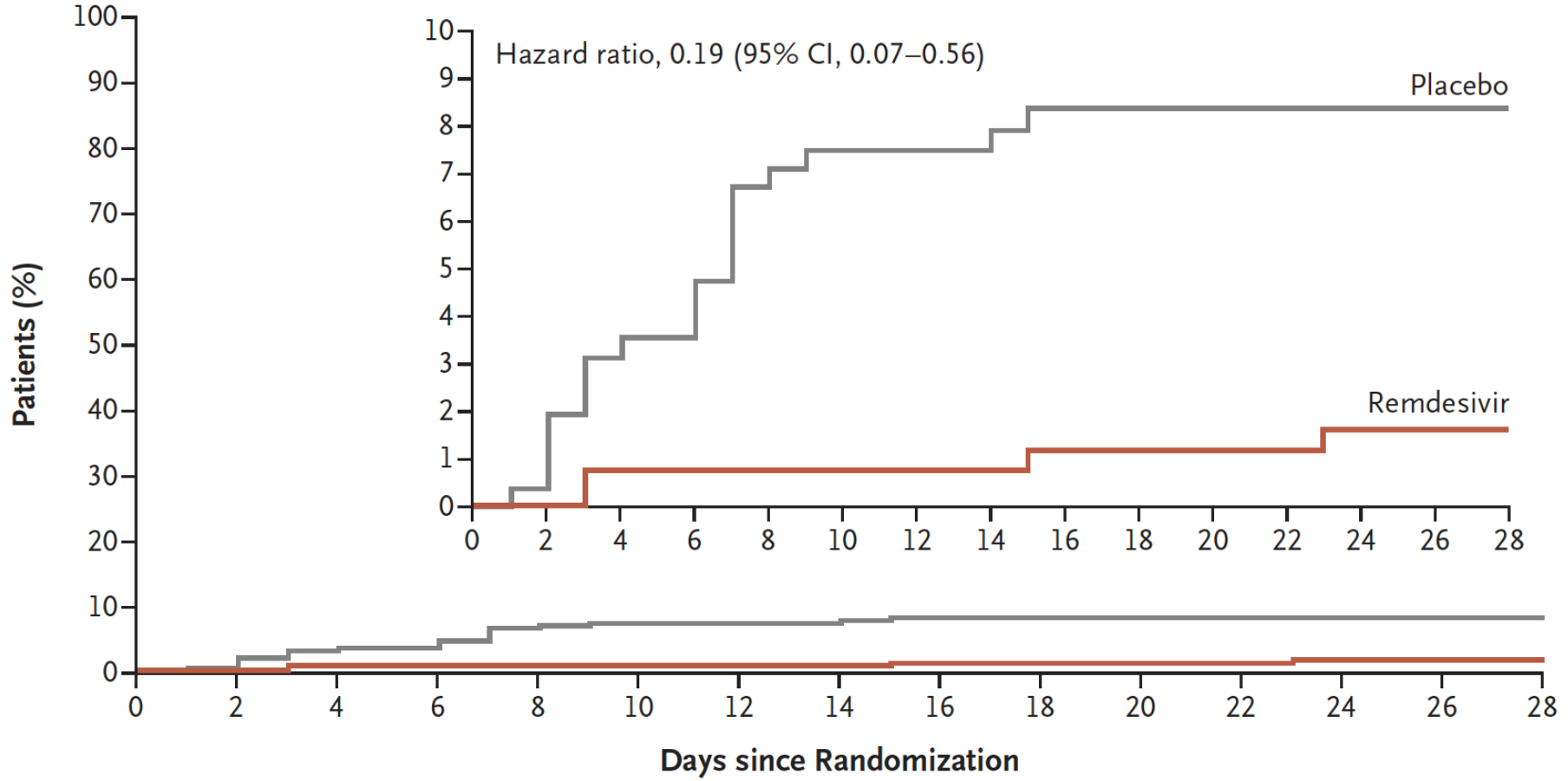
A Covid-19–Related Hospitalization or Death from Any Cause



No. at Risk

Placebo	283	280	272	271	265	264	264	263	262	261	261	260	256	250	227
Remdesivir	279	276	272	272	271	268	268	268	264	264	264	264	260	252	226

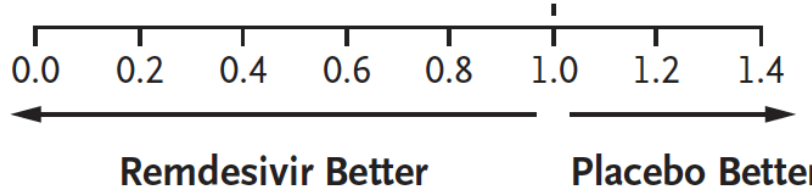
B **Covid-19–Related Medically Attended Visit or Death from Any Cause**



No. at Risk

Placebo	252	249	241	239	230	228	228	227	225	224	224	223	219	213	193
Remdesivir	246	243	239	239	239	237	237	237	232	232	232	232	227	220	197

Subgroup	Remdesivir	Placebo	Hazard Ratio (95% CI)
	no./total no. of patients (%)		
Residence in the United States	2/264 (0.8)	12/267 (4.5)	0.17 (0.04–0.76)
Age ≥60 yr	1/83 (1.2)	9/87 (10.3)	0.11 (0.01–0.86)
Male sex	1/148 (0.7)	9/145 (6.2)	0.11 (0.01–0.84)
Diabetes mellitus	2/173 (1.2)	14/173 (8.1)	0.14 (0.03–0.63)
Obesity	1/154 (0.6)	9/156 (5.8)	0.11 (0.01–0.88)
Hypertension	2/138 (1.4)	10/130 (7.7)	0.17 (0.04–0.76)
Ethnic group			
Not Hispanic or Latinx	2/146 (1.4)	8/158 (5.1)	0.26 (0.06–1.22)
Hispanic or Latinx	0/123	6/112 (5.4)	—
Chronic lung disease	0/67	4/68 (5.9)	—
Cardiovascular or cerebrovascular disease	0/20	2/24 (8.3)	—
Current cancer	0/12	2/18 (11.1)	—



800 mg of molnupiravir or placebo twice daily for 5 days.

Randomised double-blind in unvaccinated high risk patients.

Symptoms in the previous 5 days

The NEW ENGLAND JOURNAL of MEDICINE

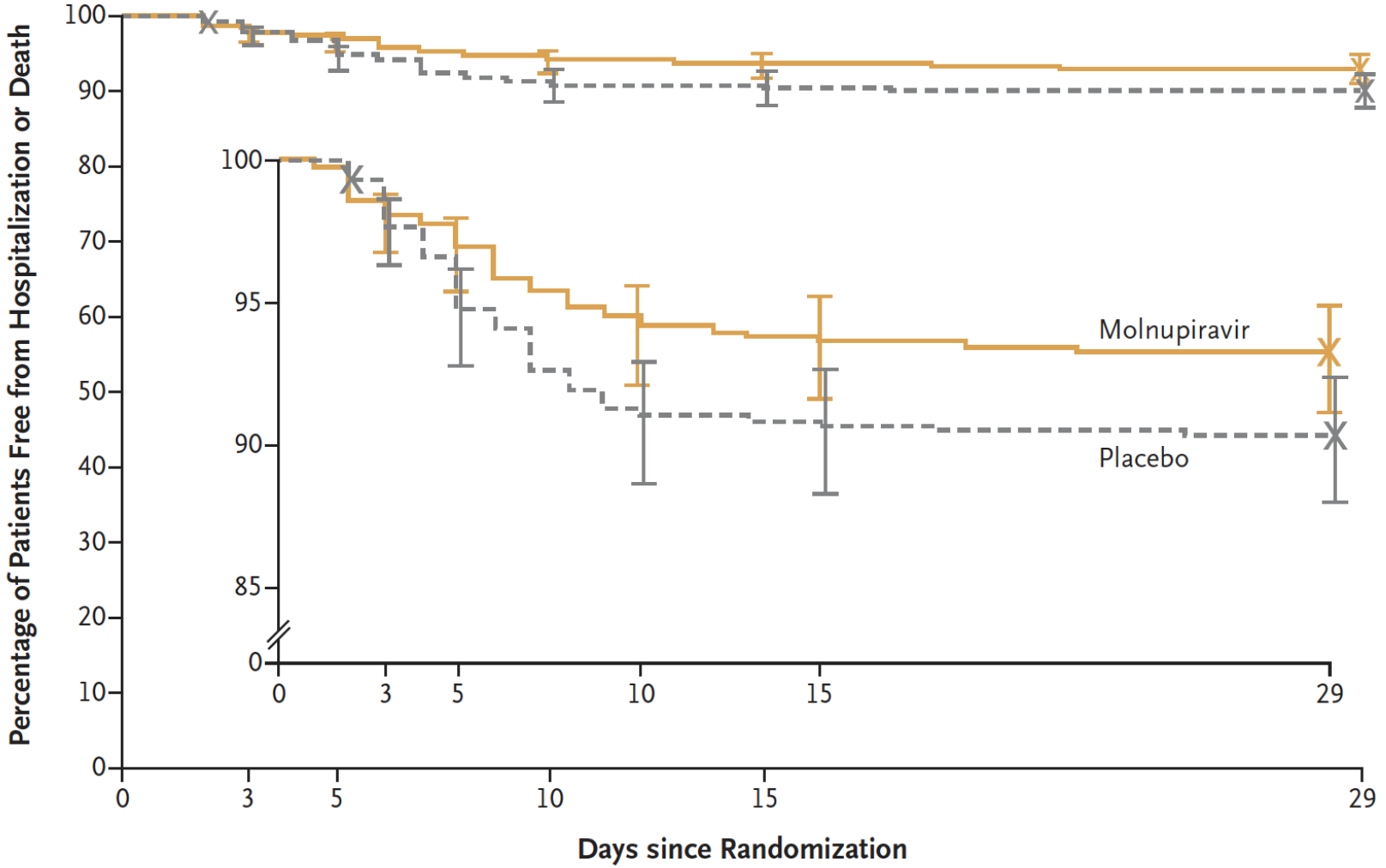
ESTABLISHED IN 1812 FEBRUARY 10, 2022 VOL. 386 NO. 6

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Molnupiravir (N=716)	Placebo (N=717)	Total (N=1433)
Female sex — no. (%)	384 (53.6)	351 (49.0)	735 (51.3)
Age group — no. (%)			
18–49 yr	484 (67.6)	465 (64.9)	949 (66.2)
≥50 yr	232 (32.4)	252 (35.1)	484 (33.8)
Median age (range) — yr	42.0 (18–90)	44.0 (18–88)	43.0 (18–90)
Risk factors for severe illness from Covid-19 — no. (%)			
At least one risk factor	712 (99.4)	712 (99.3)	1424 (99.4)
Obesity†	538 (75.1)	518 (72.2)	1056 (73.7)
Age >60 yr	119 (16.6)	127 (17.7)	246 (17.2)
Diabetes mellitus	107 (14.9)	121 (16.9)	228 (15.9)
Serious heart condition	86 (12.0)	81 (11.3)	167 (11.7)
Chronic kidney disease	38 (5.3)	46 (6.4)	84 (5.9)
Chronic obstructive pulmonary disease	22 (3.1)	35 (4.9)	57 (4.0)
Active cancer	13 (1.8)	16 (2.2)	29 (2.0)
Covid-19 severity — no. (%)			
Mild	395 (55.2)	390 (54.4)	785 (54.8)
Moderate	315 (44.0)	323 (45.0)	638 (44.5)
Severe or unknown‡	6 (0.8)	4 (0.6)	10 (0.7)
Clade designation; variant — no. (%)			
20H; beta	5 (0.7)	6 (0.8)	11 (0.8)
20I; alpha	12 (1.7)	9 (1.3)	21 (1.5)
20J; gamma	37 (5.2)	48 (6.7)	85 (5.9)
21A, 21I, 21J; delta	237 (33.1)	223 (31.1)	460 (32.1)
21G; lambda	14 (2.0)	7 (1.0)	21 (1.5)
21H; mu	76 (10.6)	86 (12.0)	162 (11.3)
Other§	16 (2.2)	16 (2.2)	32 (2.2)
Evaluable sequence data not yet available	319 (44.6)	322 (44.9)	641 (44.7)
Time from onset of Covid-19 signs or symptoms to randomization of ≤3 days — no. (%)¶	342 (47.8)	342 (47.7)	684 (47.7)
SARS-CoV-2 RNA in nasopharyngeal sample, qualitative assay — no. (%)‡			
Detectable	615 (85.9)	615 (85.8)	1230 (85.8)
Undetectable	54 (7.5)	51 (7.1)	105 (7.3)
SARS-CoV-2 nucleocapsid antibody — no. (%)‡‖			
Positive	137 (19.1)	147 (20.5)	284 (19.8)
Negative	541 (75.6)	521 (72.7)	1062 (74.1)

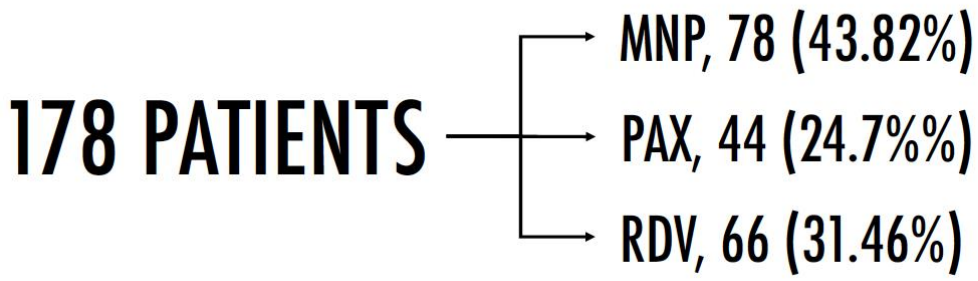


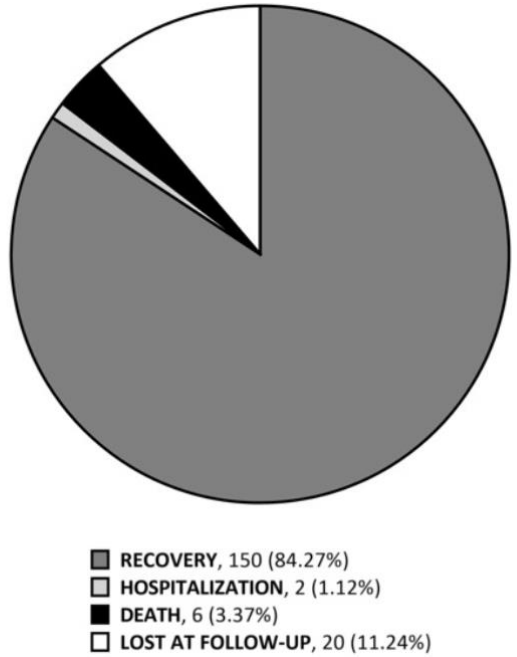
No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

Real life data

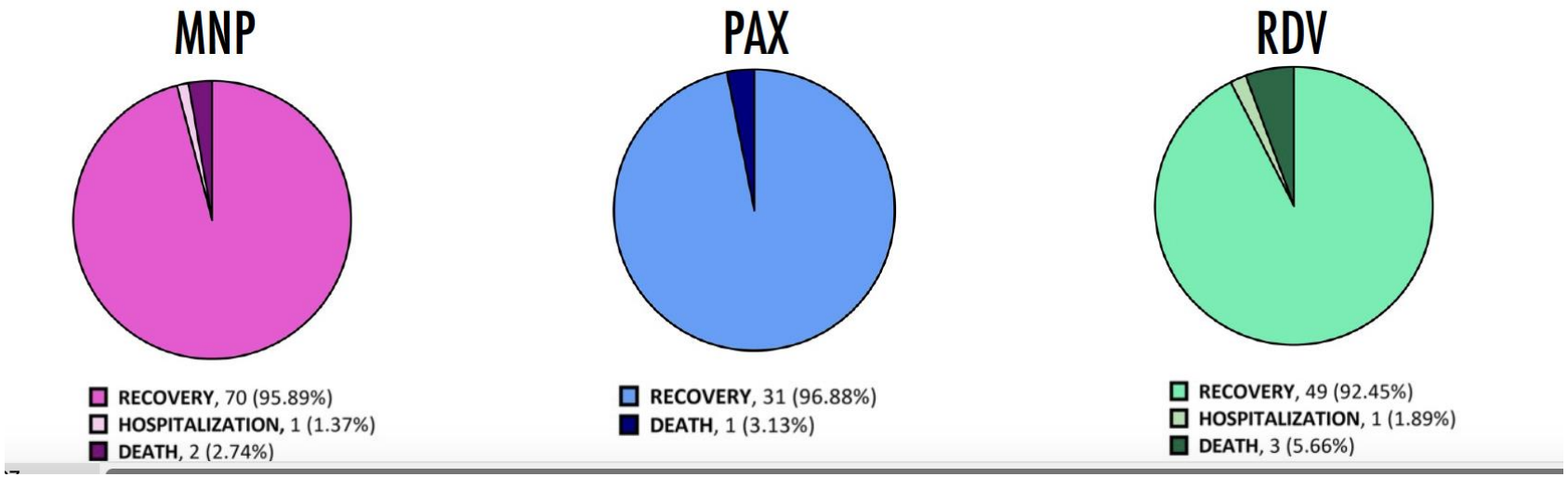
Characteristics	Study population N 178	MNP N 78 (43.8%)	PAX N 44 (24.7%)	RDV N 56 (31.5%)	p value
Age [years], median (IQR)	74 (58-82)	78 (66-84)	59 (49-78)	73 (63-83)	<0.001
Male sex, n (%)	100 (56.2%)	52 (67.5%)	20 (45.5%)	28 (50%)	0.031
COVID-19 vaccination, n (%):					
No	32 (18%)	14 (17.9%)	6 (18.8%)	12 (37.5%)	0.661
Yes (complete schedule, < 120 days)*	144 (80.9%)	64 (82.1%)	36 (25%)	44 (30.6%)	
Unknown	2 (1.1%)	0	2 (4.5%)	0	
Risk factor, n (%)					
Age > 65 years	105 (59%)	55 (70.5%)	12 (27.3%)	38 (67.9%)	<0.001
BMI >30	20 (11.2%)	7 (9%)	6 (13.6%)	7 (12.5%)	0.689
Cardio-vascular disease	75 (42.1%)	42 (53.8%)	8 (18.2%)	25 (44.6%)	<0.001
COPD or other respiratory disease	38 (21.3%)	15 (19.2%)	10 (22.7%)	13 (23.2%)	0.829
Neurological disease	11 (6.2%)	4 (5.1%)	2 (4.5%)	5 (8.9%)	0.582
Diabetes mellitus	34 (19.1%)	14 (17.9%)	5 (11.4%)	15 (26.8%)	0.141
Chronic kidney failure	10 (5.6%)	7 (9%)	0	3 (5.4%)	0.117
Cancer	12 (6.7%)	5 (6.4%)	3 (6.8%)	4 (7.1%)	0.986
Immunodeficiency	27 (15.2%)	8 (10.3%)	12 (27.3%)	7 (12.5%)	0.034
Calendar period, n (%):					
Jan-Feb 22	62 (34.8%)	35 (44.9%)	3 (4.8%)	24 (42.9%)	<0.001
Mar-Apr 22	58 (32.6%)	33 (56.9%)	17 (38.6%)	8 (14.3%)	
May-Jun 22	58 (32.6%)	10 12.8%)	24 (54.5%)	24 (42.9%)	
Treatments for COVID-19, n (%):					
Heparin	16 (9%)	3 (4%)	2 (5.6%)	11 (20.8%)	0.004
Corticosteroid therapy	4 (2.2%)	1 (1.3%)	1 (2.8%)	2 (3.8%)	0.671
Oxygen saturation, median (IQR)	97 (96-98)	97 (96-98)	97 (96-98)	96 (95-98)	0.180
Setting, n (%):					
Outpatient service	148 (83.1%)	75 (96.2%)	41 (93.2%)	32 (57.1%)	<0.001
Hospitalization for diseases other than COVID-19	30 (16.9%)	3 (3.8%)	3 (6.8%)	24 (42.9%)	
Days from symptom onset to antiviral treatment, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	2 (1-4)	0.958
Days from symptom onset to virological clearance, median (IQR)	13 (10-18)	15 (11-18)	11 (9-15)	13 (9-19)	0.015
Outcome, n (%):	N 158	N 73	N 32	N 53	
Recovery	150 (94.9%)	70 (95.9%)	31 (96.9%)	49 (92.5%)	0.850
Hospitalization	2 (1.3%)	1 (1.4%)	0	1 (1.9%)	
Death	6 (3.8%)	2 (2.7%)	1 (3.1%)	3 (5.7%)	
Adverse events, n (%):	N 148	N 67	N 30	N 51	
No	144 (97.3%)	66 (98.5%)	28 (93.3%)	50 (98%)	0.321
Yes	4 (2.7%)	1 (1.5%)	2 (6.7%)	1 (2%)	
Virological clearance at day 7 from symptoms onset, n (%):	N 133	N 60	N 26	N 47	
No	82 (61.7%)	42 (70%)	11 (42.3%)	29 (61.7%)	0.053
Yes	51 (38.3%)	18 (30%)	15 (57.7%)	18 (38.3%)	

Beringheli, Bai et al, HIV Glasgow 2022





Graphic.2 - Outcomes for each treatment, n (%)



Beringheli, Bai et al,
HIV Glasgow 2022

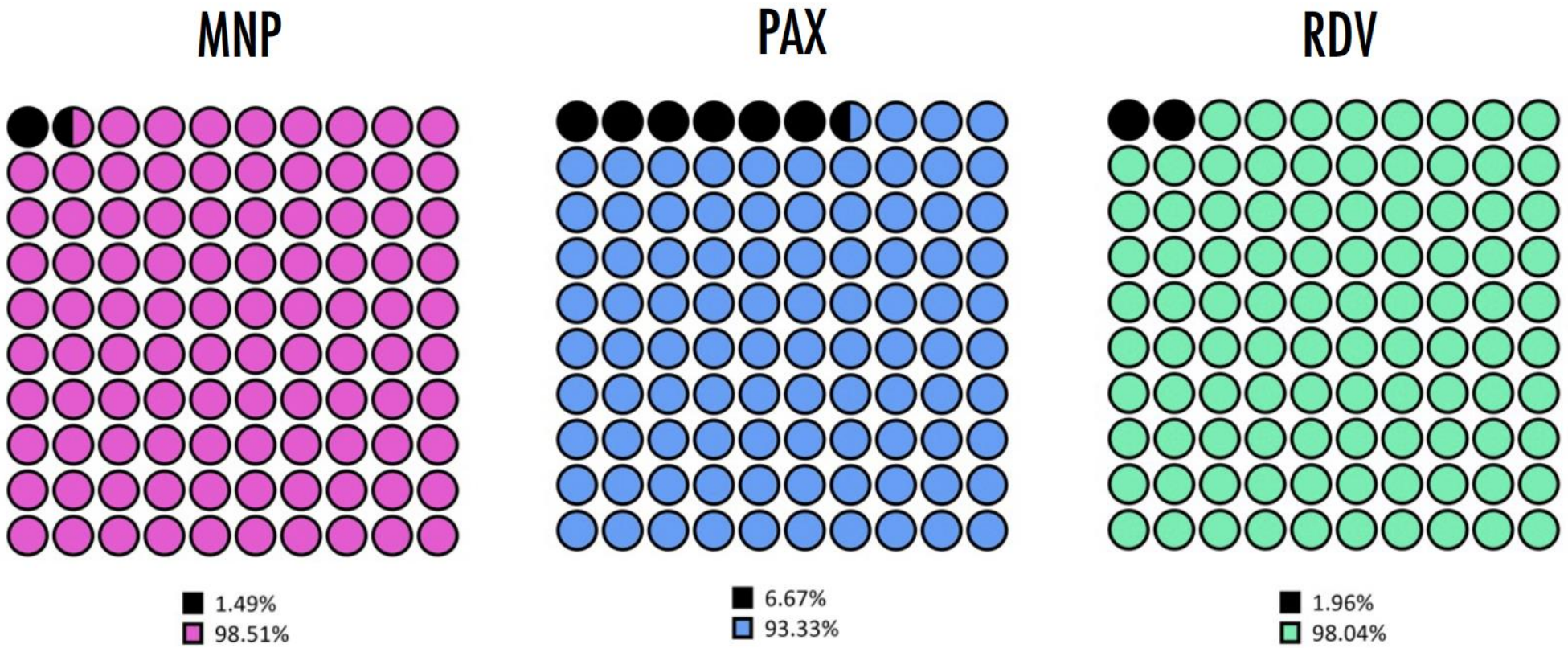
Factors associated to viral clearance at day 7

Parameters	OR	95%CI	p values	AOR	95%CI	p values
Antiviral treatment:						
Molnupiravir	1		0.059	1		0.157
Paxlovid	0.314	0.121-0.816	0.017	2.783	0.977-7.928	0.055
Remdesivir	0.690	0.308-1.547	0.368	1.425	0.633-3.206	0.392
Age, each year more	1.021	0.998-1.043	0.069	0.987	0.963-1.011	0.274
Gender,						
Female	1					
Male	1.196	0.592-2.416	0.619			
COVID-19 vaccination:						
No	1					
Yes (complete schedule, <120 days)	1.303	0.513-3.308	0.578			
Unknown						
Calendar period:						
Jan-Feb 22	1		0.032			
Mar- Apr 22	1.110	0.472-2.609	0.810			
May-Jun 22	0.364	0.150-0.883	0.025			
Risk factor for progression:						
No immunodeficiency	1	0.351-2.699	0.959	1	0.424-2.587	0.920
Immunodeficiency	0.974			1.047		
Symptoms:						
None	1					
Yes	1.730	0.437-6.846	0.435			
Setting:						
Outpatient service	1					
Hospitalization for diseases other than COVID-19	0.772	0.311-1.920	0.578			
Days from symptoms onset to antiviral treatment, each day more	0.825	0.665-1.025	0.082			

LEGEND

OR, odds ratio; AOR, adjusted odds ratio; 95%CI, 95% confidence interval. Univariable and multivariable logistic regression analysis; in the multivariable analysis the association between antiviral treatment and virological clearance at day 7th after treatment is adjusted for age and immunodeficiency.

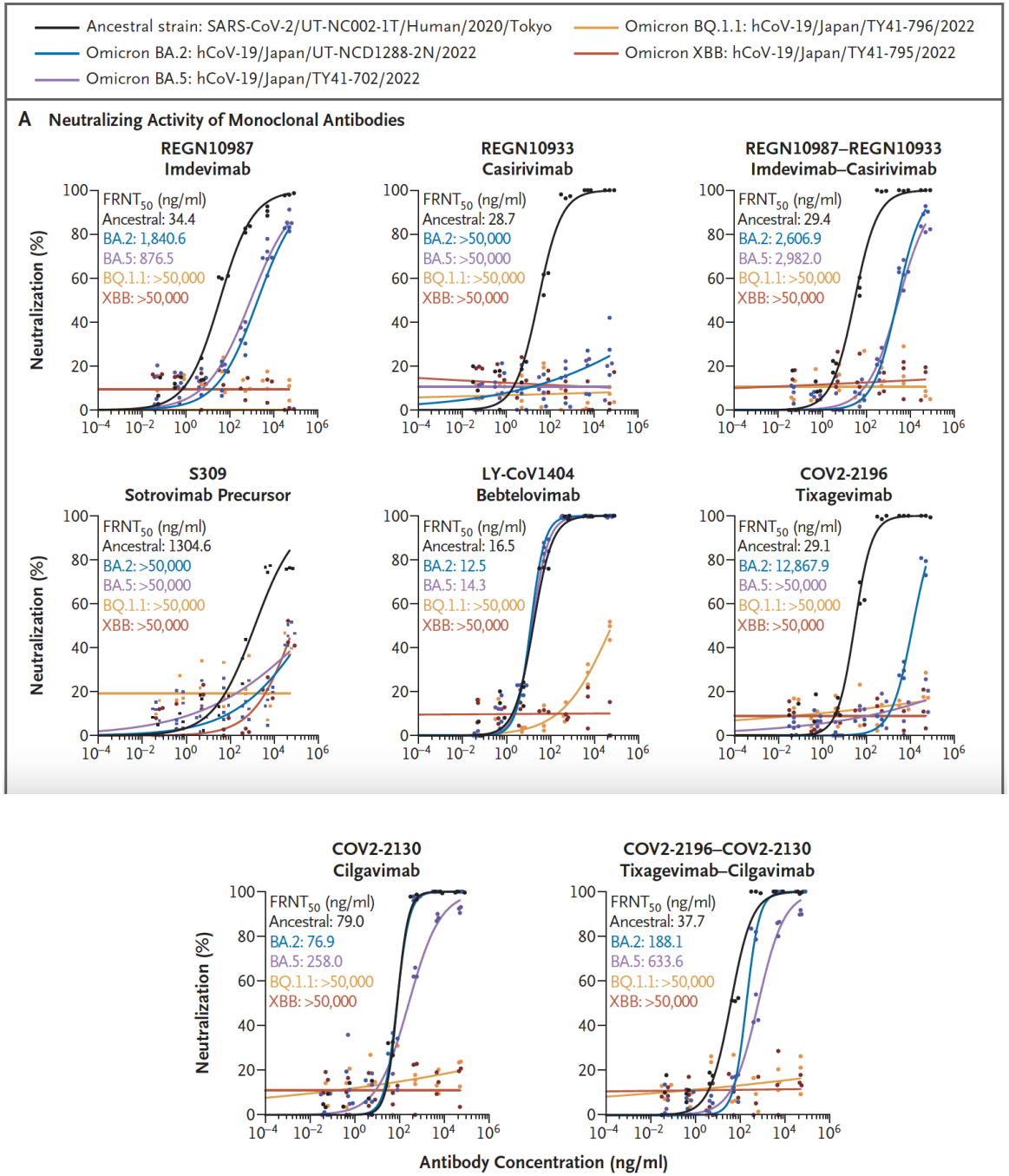
Adverse events



Beringheli, Bai et al, HIV Glasgow 2022

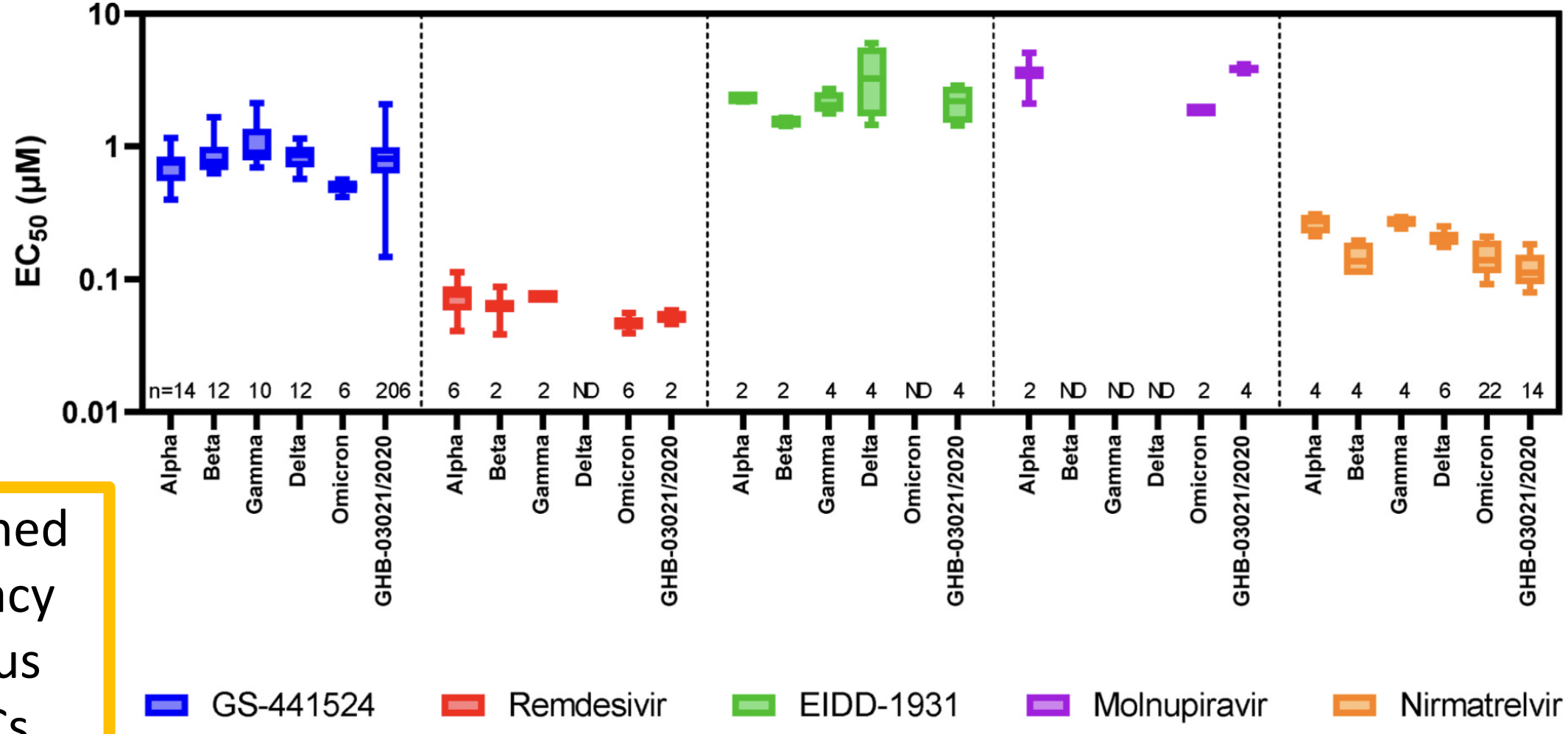
Monoclonal antibodies (?)

Years of Circulation	WHO Label and Pango Lineage	Notable Mutations	BEB		TIX Plus CIL		BAM Plus ETE		CAS Plus IMD		SOT	
			In Vitro Susceptibility[a]	Anticipated Clinical Activity	In Vitro Susceptibility[a]	Anticipated Clinical Activity	In Vitro Susceptibility[a]	Anticipated Clinical Activity	In Vitro Susceptibility[a]	Anticipated Clinical Activity	In Vitro Susceptibility[a]	Anticipated Clinical Activity
Variants Currently or Recently Circulating in the United States												
2021–present	Omicron BA.2	T376A, K417N, N440K, E484A, Q493R, N501Y	No change	Active	No change	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
2022–present	Omicron BA.4	BA.2 plus del69/70, L452R, F486V, Q493 reversion	No change	Active	Moderate reduction[b]	Active[c]	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
2022–present	Omicron BA.5	BA.2 plus del69/70, L452R, F486V, Q493 reversion	No change	Active	Moderate reduction[b]	Active[c]	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active



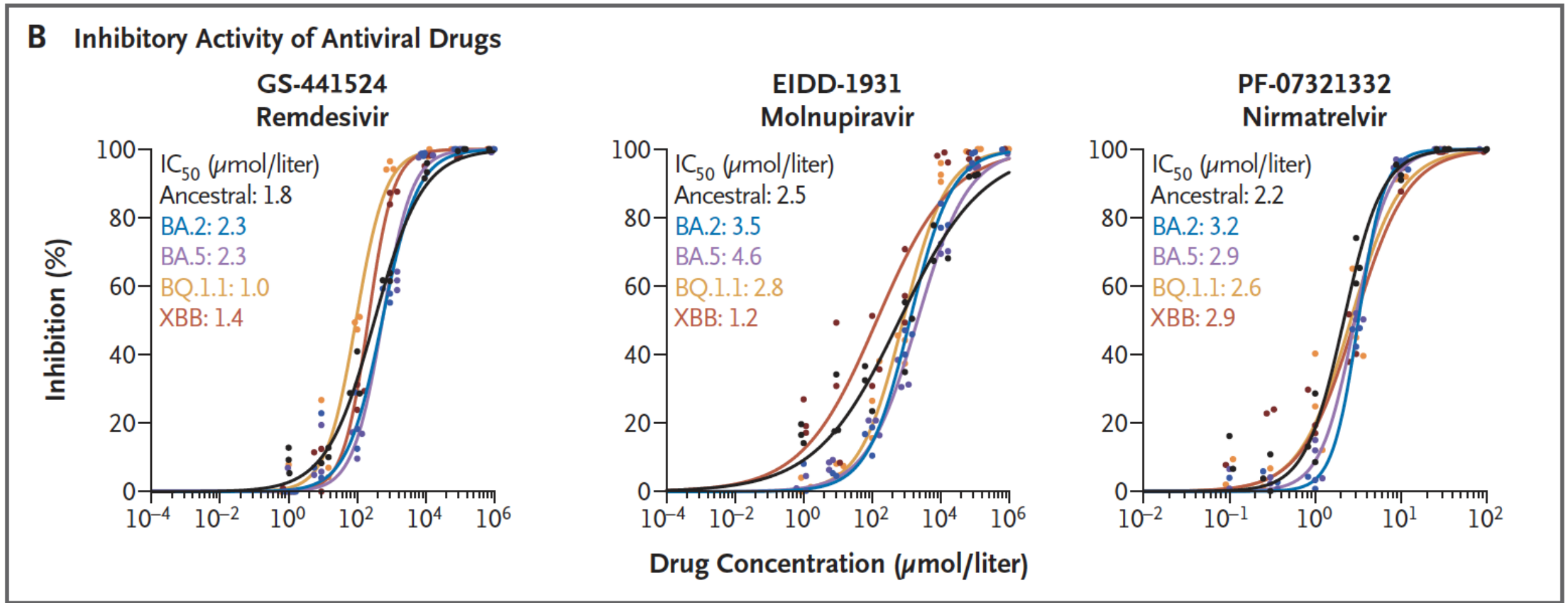
Imai et al, NEJM 2023

VeroE6-GFP cells pre-incubated O/N with compound and challenged with different SARS-CoV-2 VOC; similar EC50

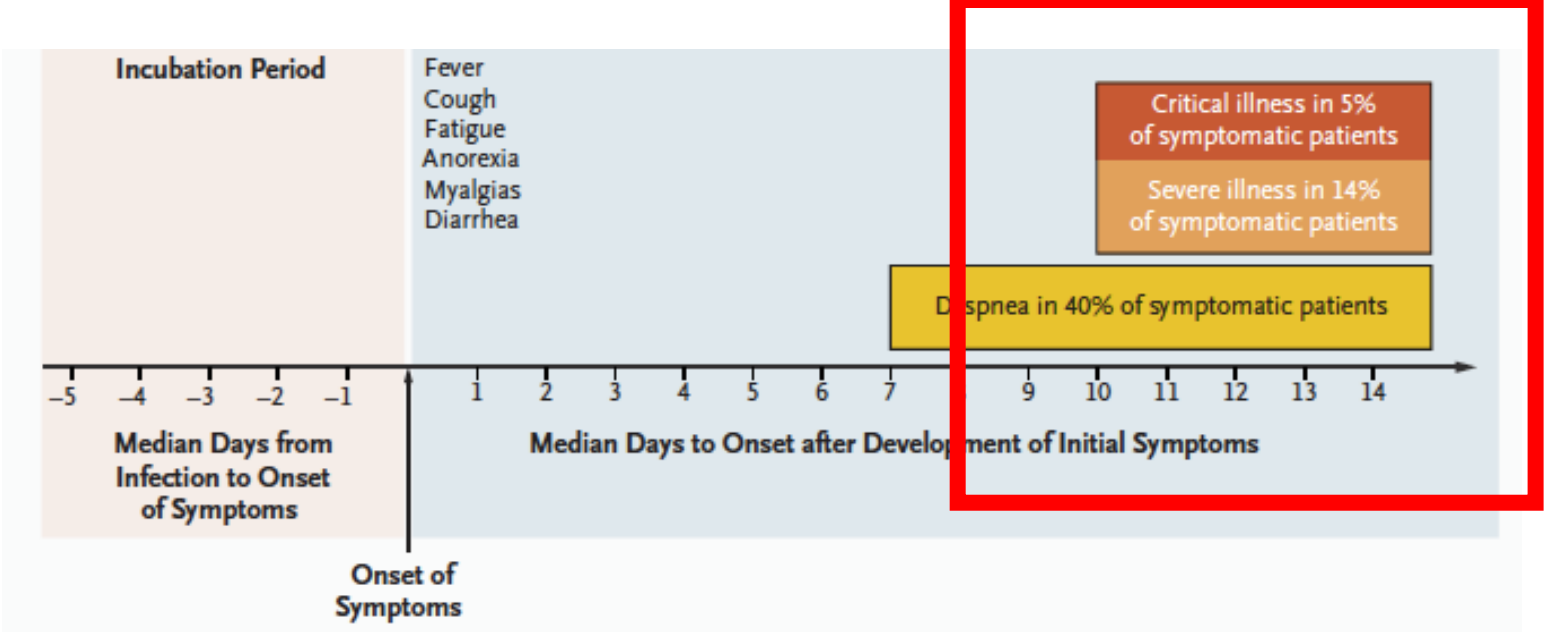


Retained efficacy versus VOCs

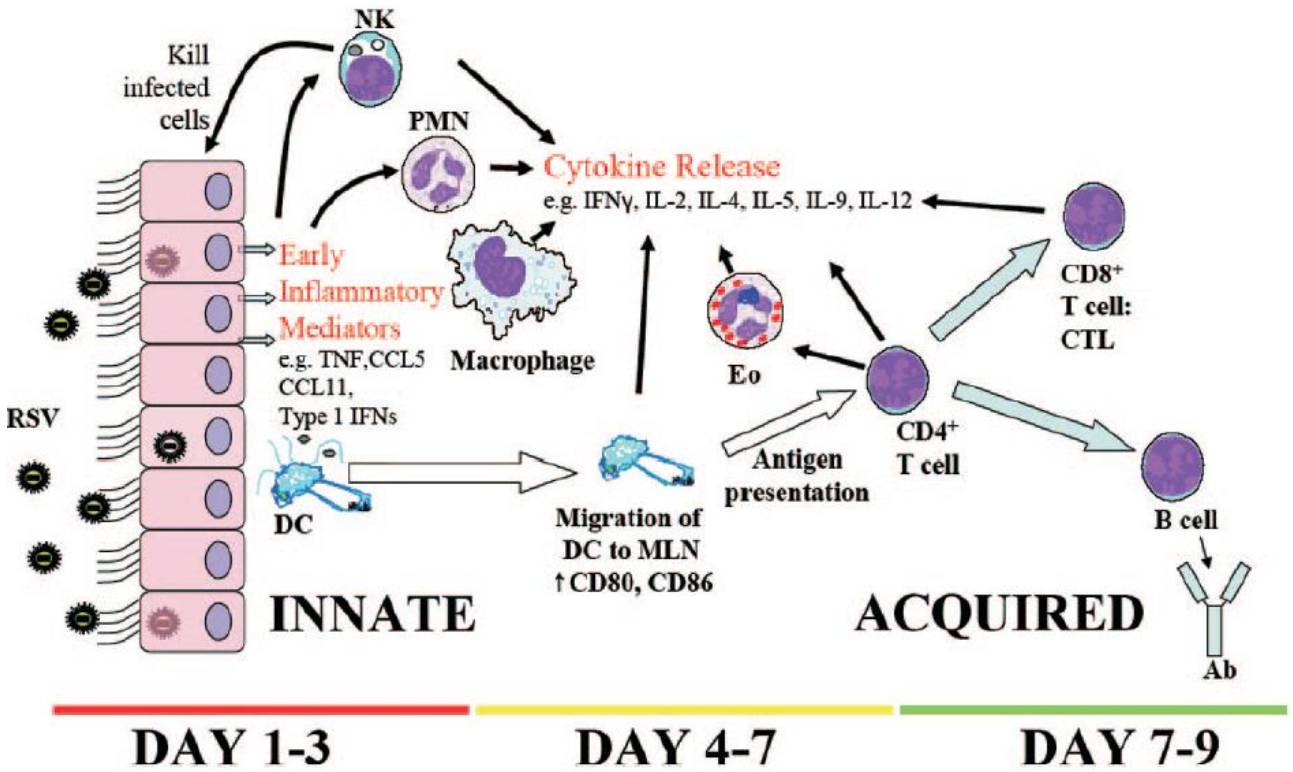
Vangeel et al, Antiviral Research 2022



Imai et al, NEJM 2023



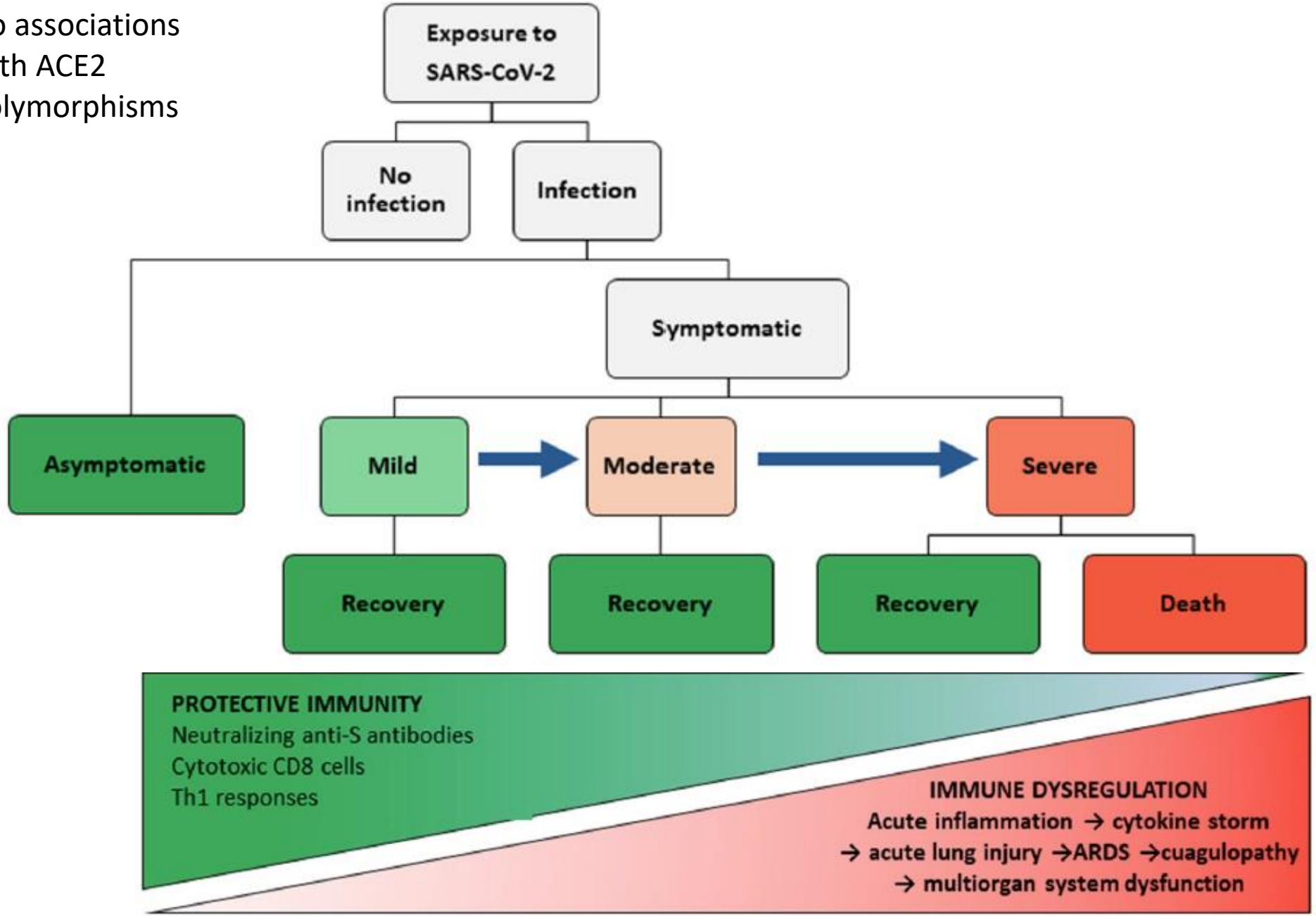
Berlin NEJM 2020



Phase 2. immune dysfunction

Openshaw et al. Clinical Microbiolgy Reviews 2005

No associations with ACE2 polymorphisms



Garcia Frontiers Immunology 2020

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REVIEW
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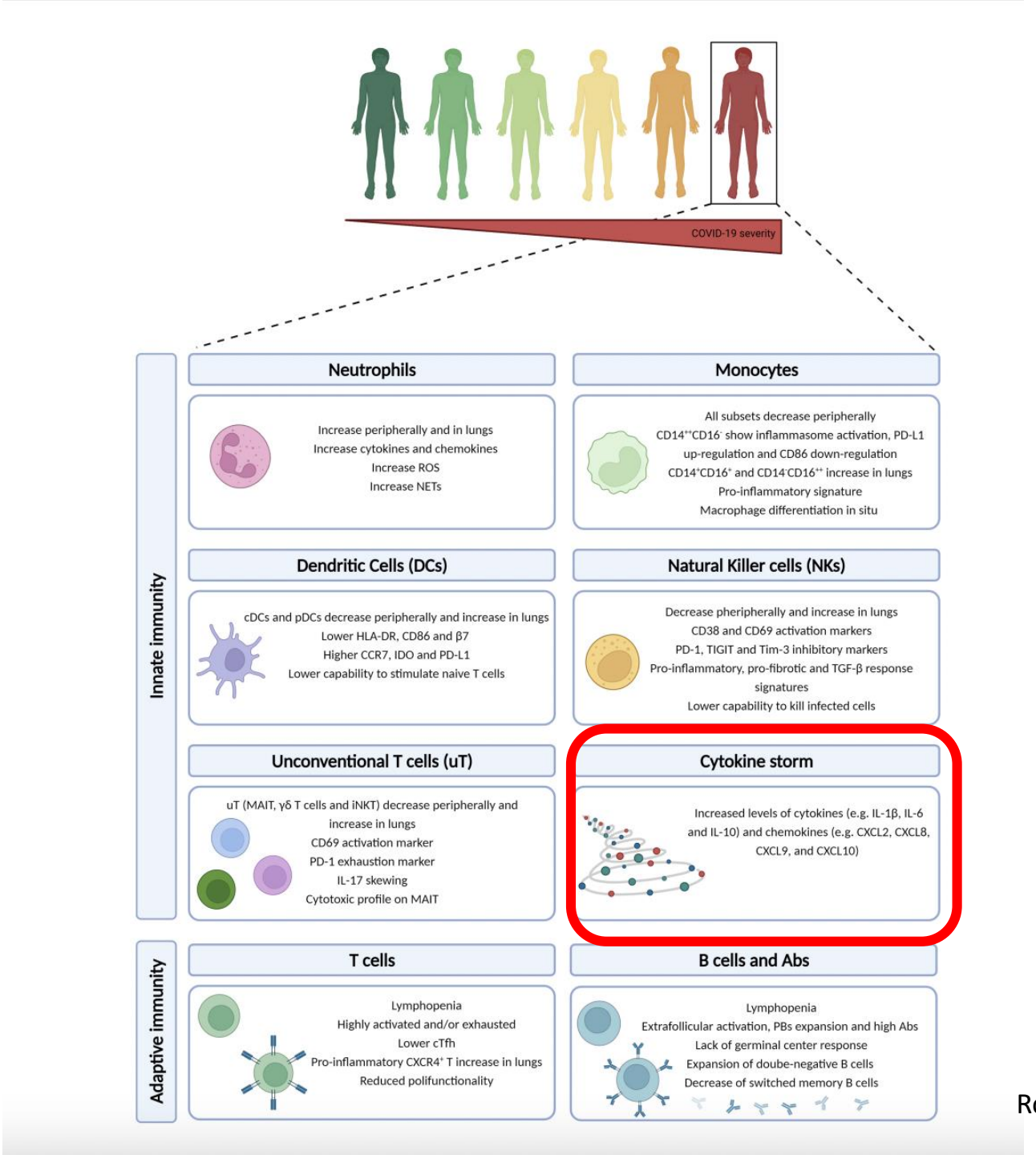
Check for updates

Hallmarks of Severe COVID-19 Pathogenesis: *A Pas de Deux* Between Viral and Host Factors

Roberta Rovito, Matteo Augello, Assaf Ben-Haim, Valeria Bono, Antonella d'Arminio Monforte and Giulia Marchetti*

Clinic of Infectious Diseases and Tropical Medicine, Azienda Socio Sanitaria Territoriale (ASST) Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milan, Italy



Rovito et al. Front Immunol 2022

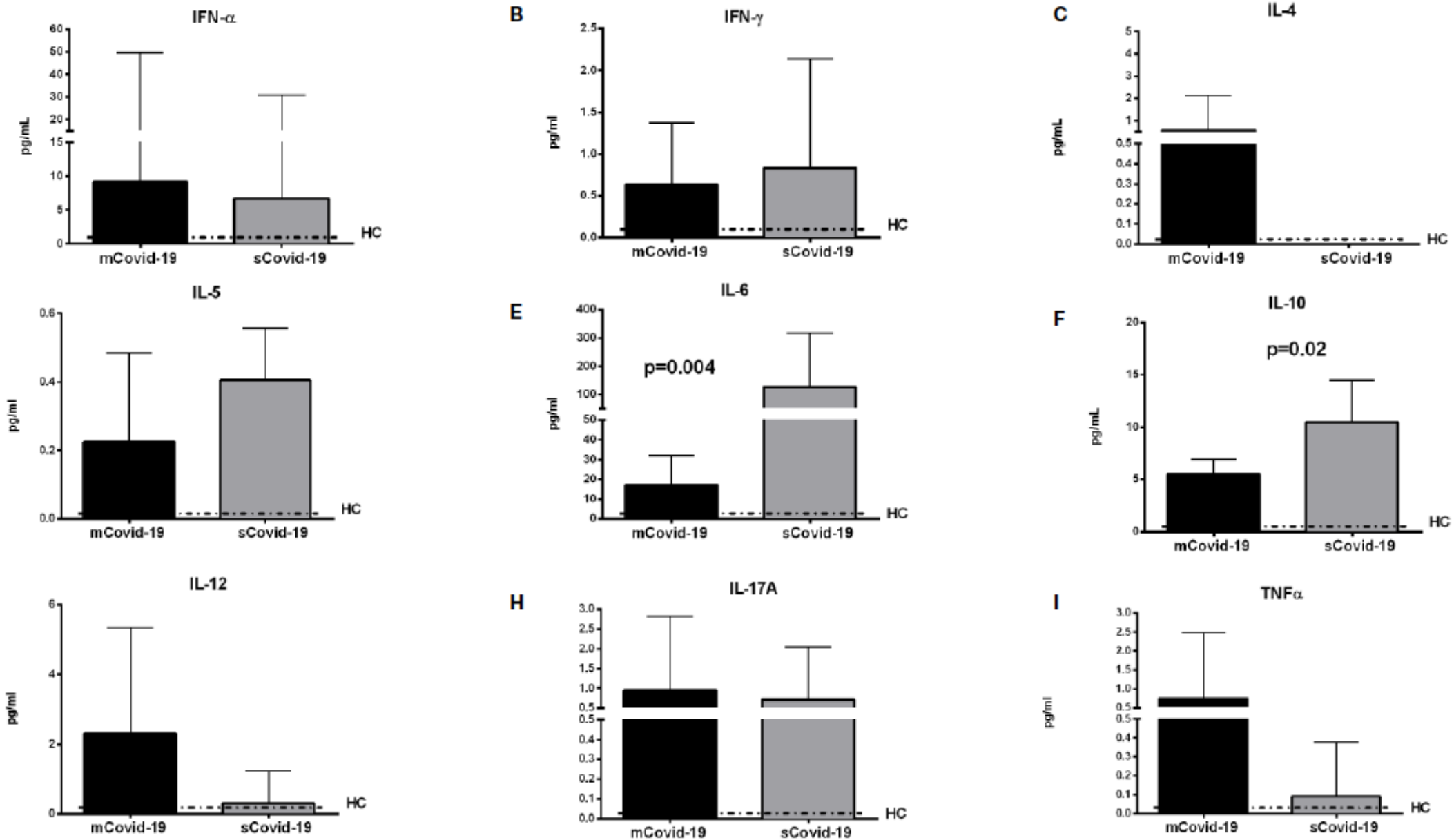
frontiers

Heightened Circulating Interferon-Inducible Chemokines, and Activated Pro- Cytolytic Th1-Cell Phenotype Features Covid-19 Aggravation in the Second Week of Illness

Camilla Tincati[1], Elvira S. Cannizzo[1], Mauro Giacomelli[2], Raffaele Badolato[2], Antonella d'Arminio Monforte[1], Giulia C. Marchetti[1*]

[1]University of Milan, Italy, [2]University of Brescia, Italy

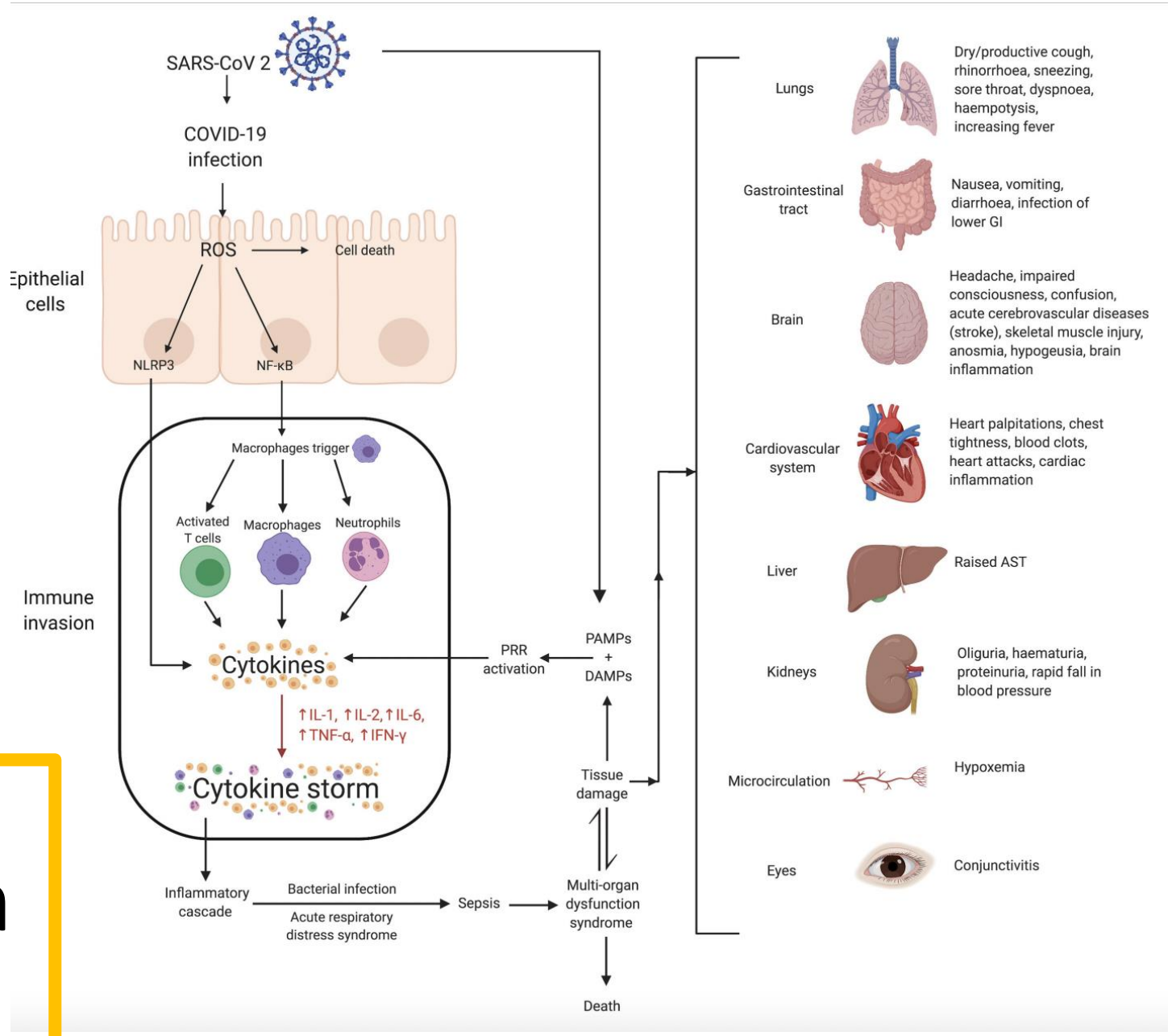
Frontiers Immunology, 2020



Tincati, Cannizzo et al. Frontiers Immunol 2020

Cytokine storm as cause of multiorgan impairment

Any role of SARS-COV2 replication in peripheral blood?



Bhaskar et al, Frontiers Immunol 2020

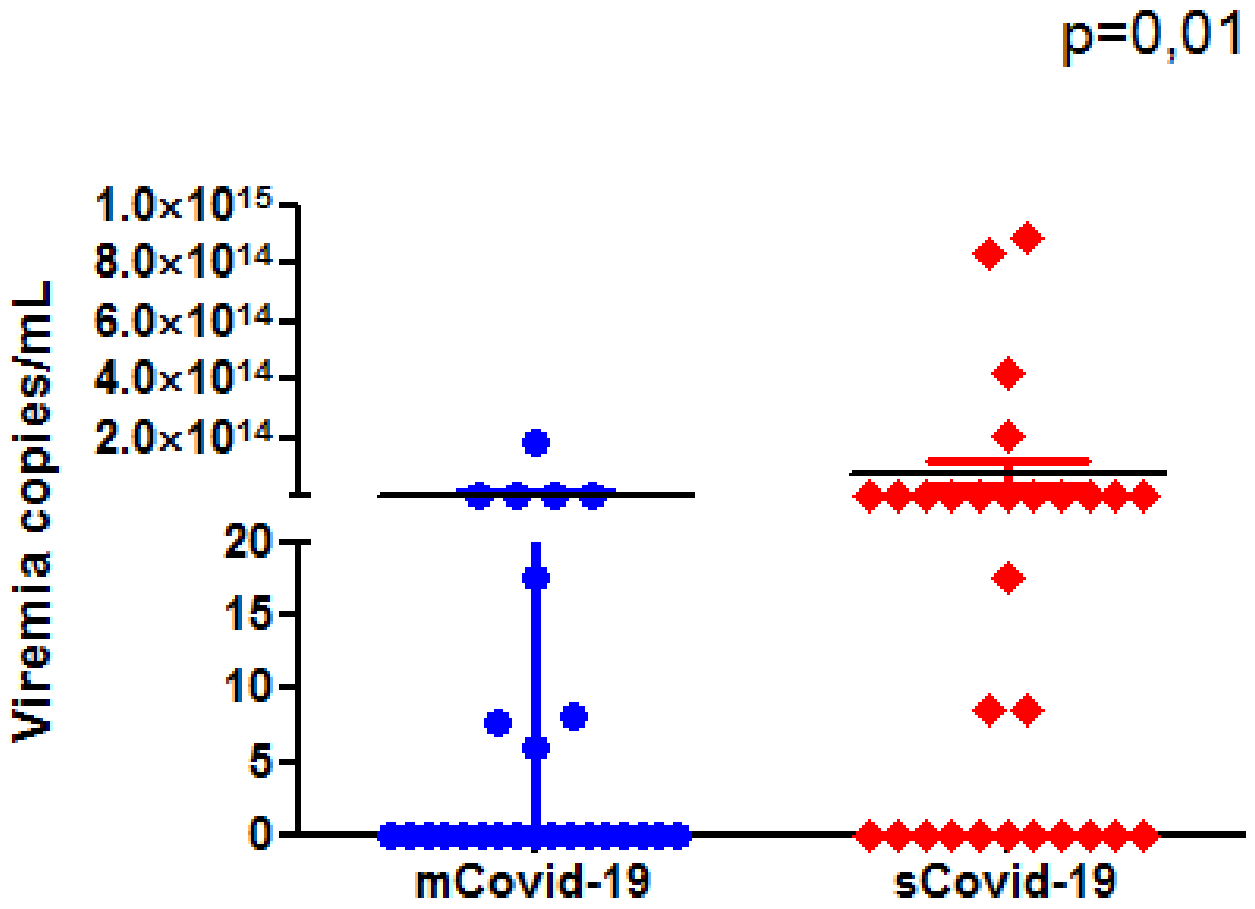
Persistent SARS-CoV-2 replication in plasma ?

	All COVID-19 patients (n=54)	Viremic COVID-19 patients (n=27)	Aviremic COVID-19 patients (n=27)	*p*-value viremic *vs* aviremic COVID-19 patients
Maximum oxygen therapy, n (%)	6 (11.1)	1 (3.7)	5 (18.5)	0.1917
None	10 (18.5)	3 (11.1)	7 (25.9)	0.2935
Low/high-flow systems	38 (70.4)	23 (85.2)	15 (55.6)	**0.0352 (*)**
CPAP/NIV/OTI				
Medical therapy, n (%)				
LPV/r or DRV/c	16 (29.6)	9 (33.3)	7 (25.9)	0.7664
Hydroxychloroquine	41 (75.9)	19 (70.4)	22 (81.5)	0.5256
Azithromycin	18 (33.3)	8 (29.6)	10 (37)	0.7734
Remdesivir	2 (3.7)	2 (7.4)	0 (0)	0.4960
Biologic drugs	12 (22.2)	7 (25.9)	5 (18.5)	0.7445
Steroids	20 (37)	12 (44.4)	8 (29.6)	0.3983
Celecoxib	7 (13)	6 (22.2)	1 (3.7)	0.1003
Interferon beta 1a	1 (1.9)	1 (3.7)	0 (0)	>0.9999
Heparin prophylaxis	41 (75.9)	21 (77.8)	20 (74.1)	>0.9999
Hyperimmune plasma	3 (5.6)	3 (11.1)	0 (0)	0.2358
Duration of hospitalization, days, median (IQR)	14.50 (6–25)	20 (8–28)	13 (6 –22)	0.4258
Outcome, n (%)				0.0994
Death	12 (22.2)	9 (33.3)	3 (11.1)	
Dismissal	42 (77.8)	18 (66.7)	24 (88.9)	

Rovito R et al. Scientific Reports 2022

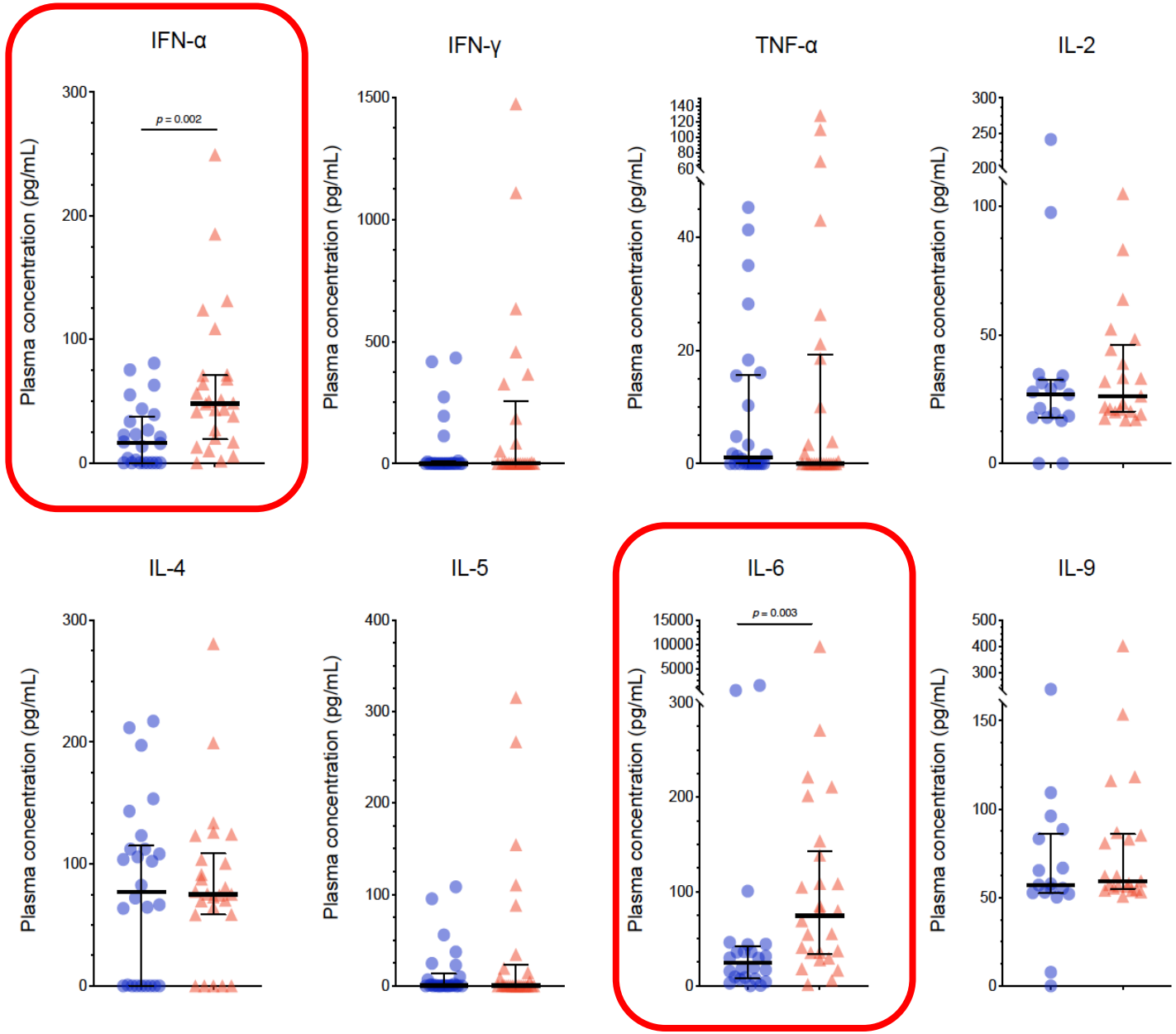
Demographic and clinical characteristics	**All COVID-19 patients (n=54)**	**Viremic COVID-19 patients (n=27)**	**Aviremic COVID-19 patients (n=27)**	***p*-value viremic *vs* aviremic COVID-19 patients**
Sex, n (%)				>0.9999
Male	39 (72.2)	20 (74.1)	19 (70.4)	
Female	15 (27.8)	7 (25.9)	8 (29.6)	
Age, years, median (IQR)	64 (52.50–75.25)	67 (55–78)	63 (45–71)	0.1659
Ethnicity, n (%)				
Caucasian	46 (82.2)	24 (88.9)	22 (81.5)	0.7040
Maghrebi/Middle Eastern	1 (1.9)	1 (3.7)	0 (0)	>0.9999
South Asian	1 (1.9)	1 (3.7)	0 (0)	>0.9999
Latin American	6 (11.1)	1 (3.7)	5 (18.5)	0.1917
Comorbidities, n (%)				
Any comorbidity	29 (53.7)	16 (59.3)	13 (48.2)	0.5857
Hypertension	20 (37)	10 (37)	10 (37)	>0.9999
Myocardial infarction	8 (14.8)	6 (22.2)	2 (7.4)	0.2501
Cardiac arrhythmia	3 (5.6)	1 (3.7)	2 (7.4)	>0.9999
COPD	1 (1.9)	1 (3.7)	0 (0)	>0.9999
Asthma	2 (3.7)	0 (0)	2 (7.4)	0.4906
Peptic ulcer	2 (3.7)	0 (0)	2 (7.4)	0.4906
Chronic kidney disease	2 (3.7)	2 (7.4)	0 (0)	0.4960
Diabetes	14 (25.9)	9 (33.3)	5 (18.5)	0.3520
Stroke	3 (5.6)	1 (3.7)	2 (7.4)	>0.9999
Dementia	1 (1.9)	0 (0)	1 (3.7)	>0.9999
Cancer	2 (3.7)	2 (7.4)	0 (0)	0.4960
Rheumatologic disease	1 (1.9)	0 (0)	1 (3.7)	>0.9999
Duration of symptoms before hospitalization, days, median (IQR)	7 (4–10)	7 (4–10)	6 (4–14)	0.4099

The detection of SARS-COV2 RNA in plasma correlates with disease severity



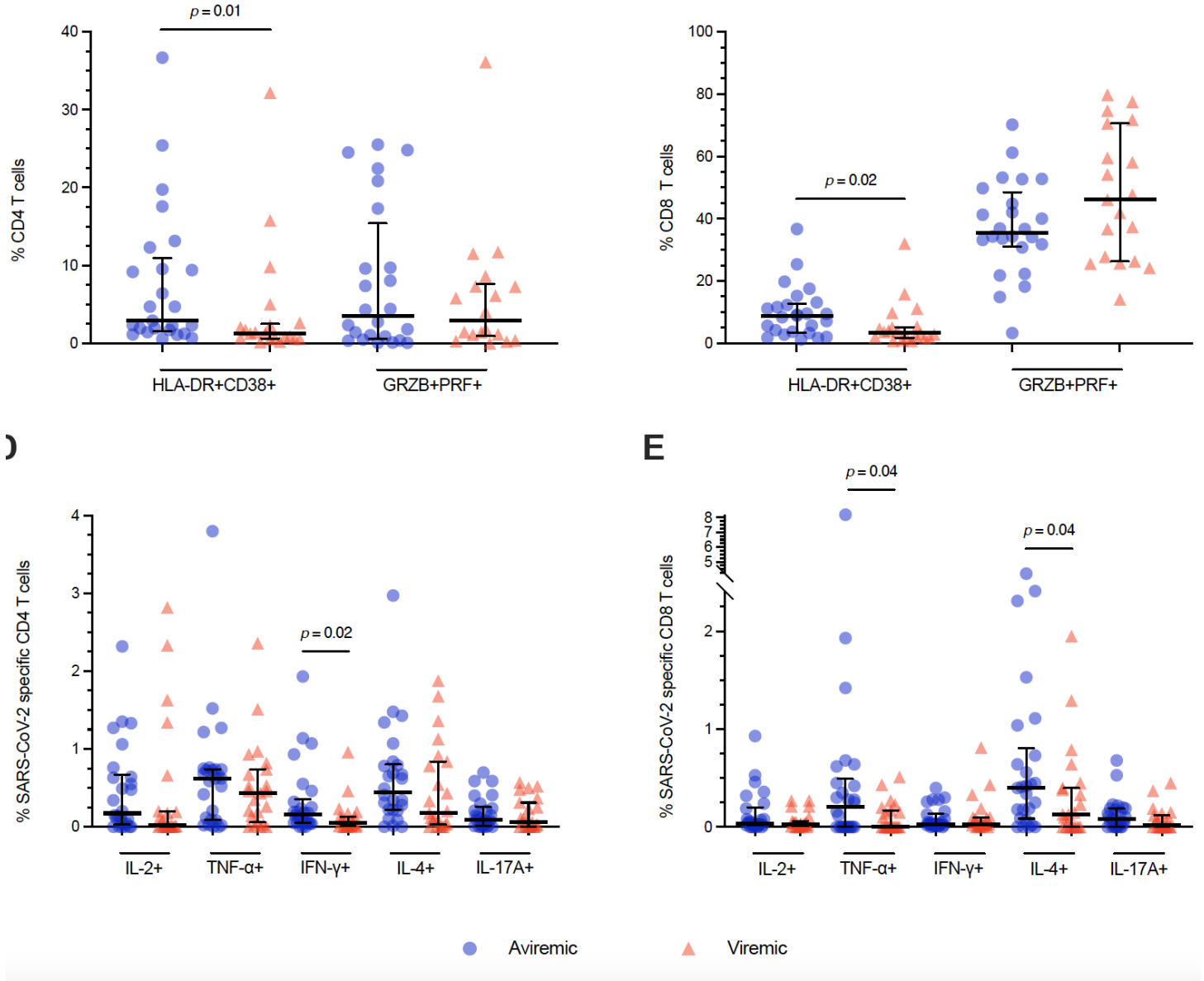
Adapted from Rovito et al, Scientific Reports 2022
Also, Chen et al. Emerg Microb and Infections 2020

Increased pro-inflammatory milieu in patients with SARS-COV2 RNA in plasma



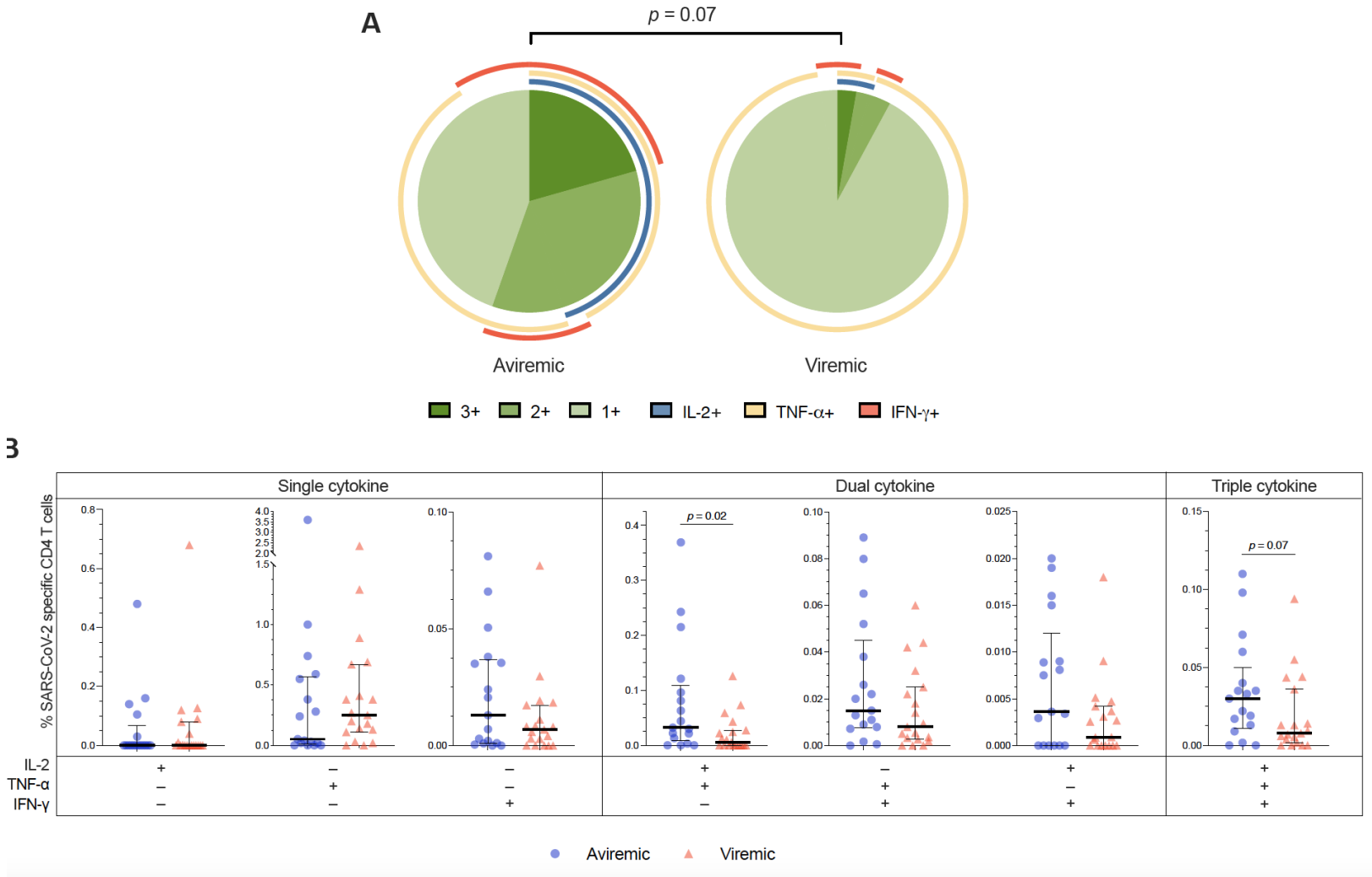
Rovito et al, Scientific Reports 2022

Lower SARS-COV2-specific T-cells in patients with SARS-COV2 RNA in plasma



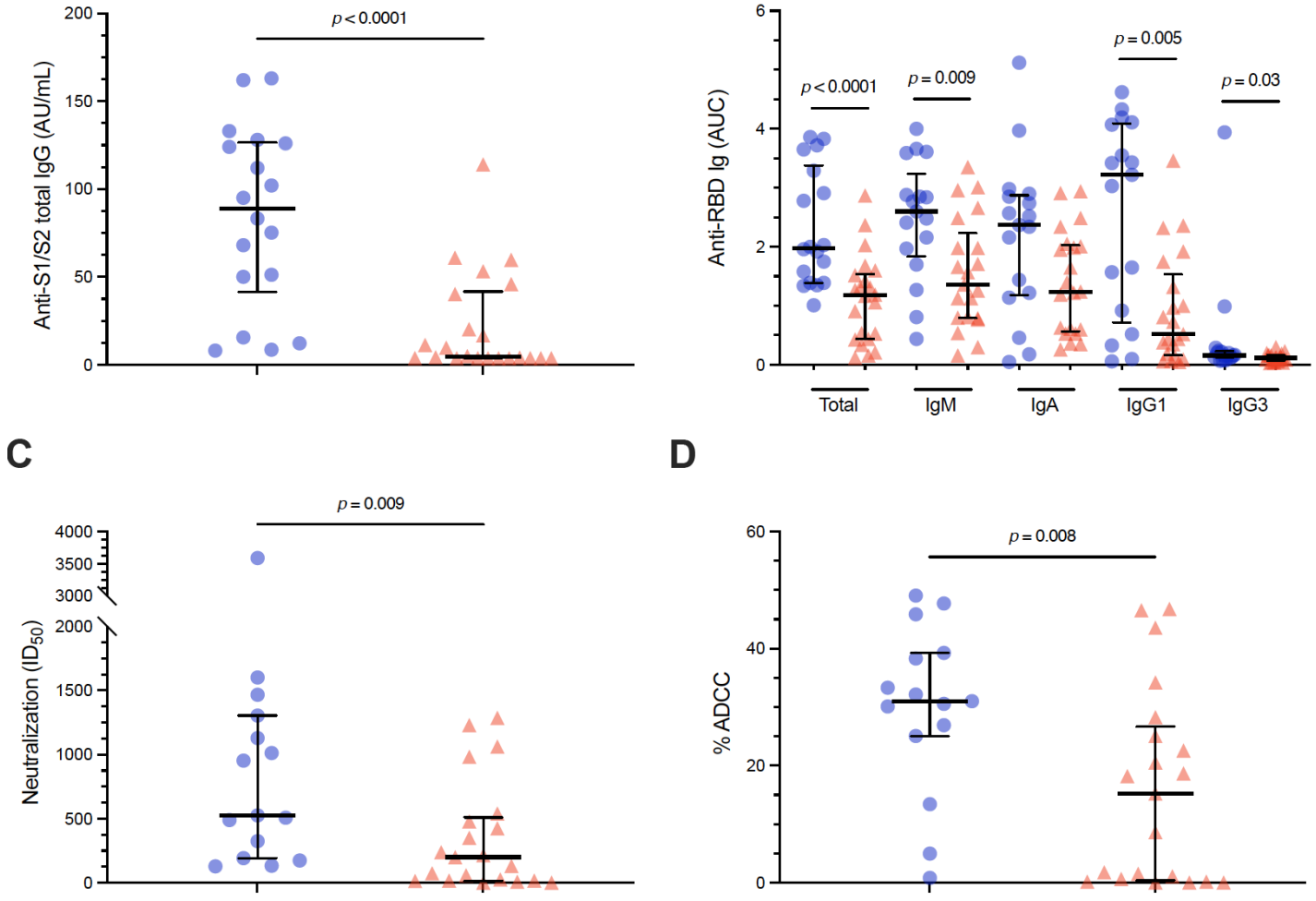
Rovito et al, Scientific Reports 2022

Lower polyfunctional SARS-COV2-specific T-cells in patients with SARS-COV2 RNA in plasma



Rovito et al, Scientific Reports 2022

Lower SARS-COV2-specific Ab response in patients with SARS-COV2 RNA in plasma



Rovito et al, Scientific Reports 2022

SARS-CoV-2 RNAemia at the end of the 1st week of disease is associated with a multi-layered dysregulated SARS-CoV-2-specific immune response

SARS-CoV-2 RNAemia: presence of viable organisms? Which effect on immune response?

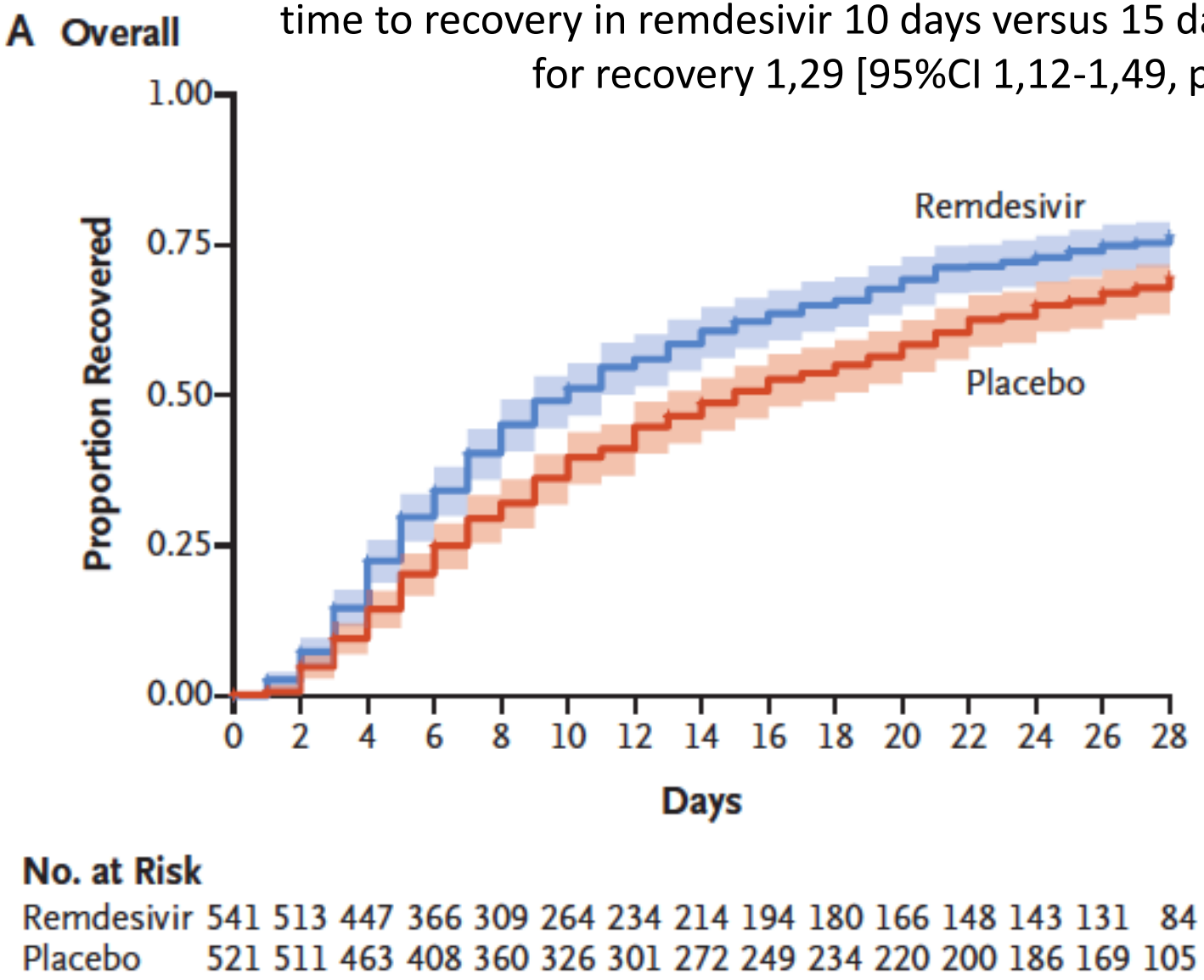
Treatment in hospitalised patients

Table 2b. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

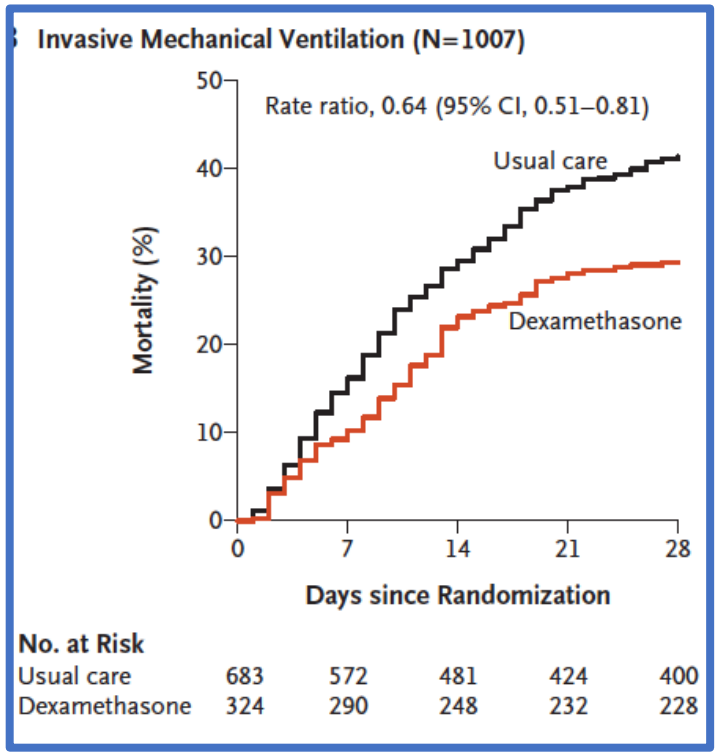
Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a]	See Therapeutic 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.[b]	
	Patients who are at high risk of progressing to severe COVID-19[a]	**Remdesivir[c] (BIII)**	
Hospitalized and Requires Conventional Oxygen[d]	Patients who require minimal conventional oxygen	**Remdesivir[e] (BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin[g] (CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir[e] (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[f]** or **IV tocilizumab[f]** to 1 of the options above **(BIIa)**.	
Hospitalized and Requires HFNC Oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib[f] (AI)** • **Dexamethasone plus IV tocilizumab[f] (BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone[h] (AI)** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**.[i]	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	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib[f] (BIIa)** • **Dexamethasone plus IV tocilizumab[f] (BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone[h] (AI)**	

Remdesivir

1062 patients,
time to recovery in remdesivir 10 days versus 15 days placebo, rate ratio for recovery 1,29 [95%CI 1,12-1,49, p<0.001)

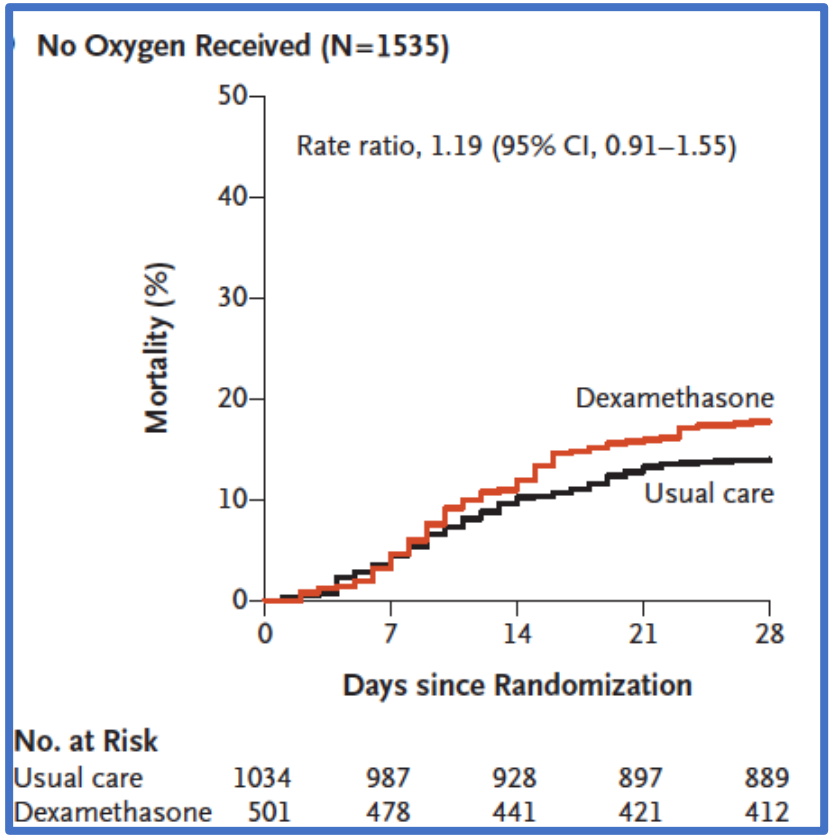


Beigel NEJM 2020

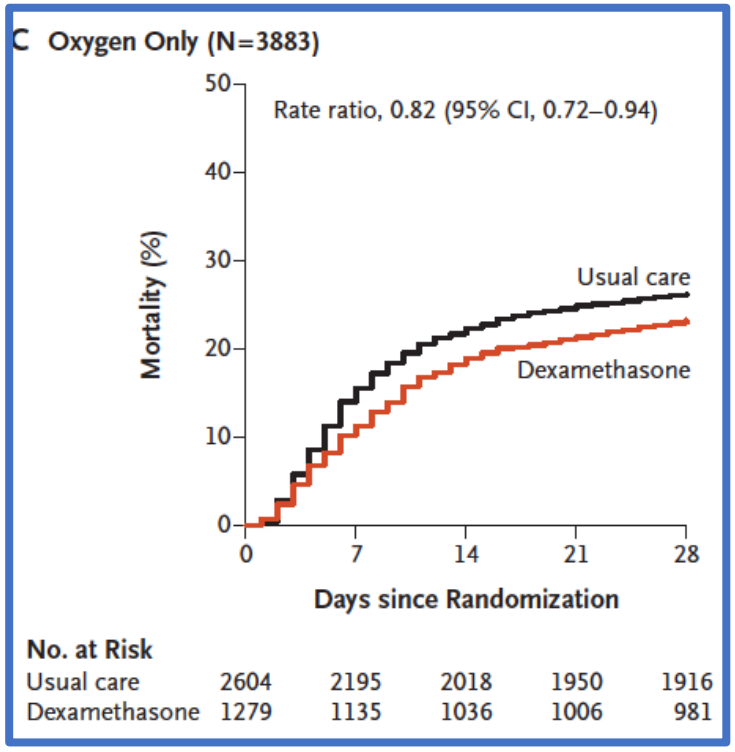


Patients **on invasive mechanical ventilation**: 29.3% vs 41.4% (rate ratio 0.64; 95% CI 0.51-0.81)

Corticosteroid



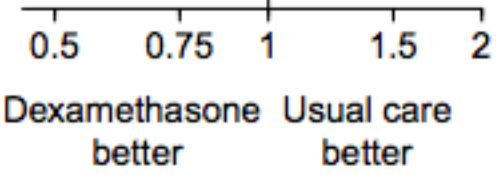
No respiratory support at randomization: 17.8% vs 14.0% (rate ratio 1.19; 95% CI 0.91-1.55)



Oxygen without invasive mechanical ventilation: 23.3% vs 26.2% (rate ratio 0.82; 95% CI 0.72-0.94)

Figure S1: Effect of allocation to dexamethasone on 28-day mortality by other pre-specified baseline characteristics

Subgroup	Dexamethasone	Usual care	RR (95% CI)	Het/trend
Age, years				
<70	129/1141 (11.3%)	428/2504 (17.1%)	0.64 (0.53–0.78)	χ^2_1=4.9
≥70 <80	155/469 (33.0%)	271/859 (31.5%)	1.03 (0.84–1.25)	
≥80	198/494 (40.1%)	411/958 (42.9%)	0.89 (0.75–1.05)	
Sex				
Men	331/1338 (24.7%)	782/2749 (28.4%)	0.80 (0.71–0.91)	χ^2_1=0.9
Women	151/766 (19.7%)	328/1572 (20.9%)	0.90 (0.74–1.09)	
Days since symptom onset				
≤7	269/916 (29.4%)	500/1801 (27.8%)	1.01 (0.87–1.17)	χ^2_1=12.3
>7	212/1184 (17.9%)	604/2507 (24.1%)	0.69 (0.59–0.80)	
Baseline risk				
<30%	150/1268 (11.8%)	377/2682 (14.1%)	0.83 (0.69–1.00)	χ^2_1=0.4
≥30% <45%	146/464 (31.5%)	334/878 (38.0%)	0.77 (0.63–0.94)	
≥45%	186/372 (50.0%)	399/761 (52.4%)	0.90 (0.76–1.07)	
All participants	**482/2104 (22.9%)**	**1110/4321 (25.7%)**	**0.83 (0.75–0.93) p<0.001**	



Treatment in hospitalised patients

Table 2b. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
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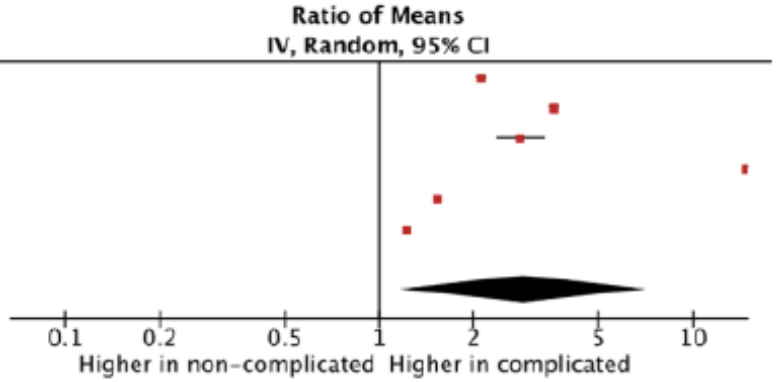
	Patients who are at high risk of progressing to severe COVID-19[a]	**Remdesivir[c] (BIII)**	
Hospitalized and Requires Conventional Oxygen[d]	Patients who require minimal conventional oxygen	**Remdesivir[e] (BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin[g] (CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir[e] (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[f]** or **IV tocilizumab[f]** to 1 of the options above **(BIIa)**.	
Hospitalized and Requires HFNC Oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib[f] (AI)** • **Dexamethasone plus IV tocilizumab[f] (BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone[h] (AI)** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**.[i]	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	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib[f] (BIIa)** • **Dexamethasone plus IV tocilizumab[f] (BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone[h] (AI)**	

Panel A. Patients with Complicated COVID-19 versus Non-Complicated

Coomes MedrXiv 2020

Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Chen et al. 2020a	0.75030559	0.01700847	14	15	16.7%	2.12 [2.05, 2.19]
Diao et al. 2020	1.2861085	0.01523892	20	479	16.7%	3.62 [3.51, 3.73]
Huang et al. 2020a	1.03489647	0.08752466	13	28	16.6%	2.81 [2.37, 3.34]
Liu 2020	2.69261639	0.00539448	69	11	16.7%	14.77 [14.61, 14.93]
Qin et al. 2020	0.42527895	0.0036103	286	166	16.7%	1.53 [1.52, 1.54]
Wu et al. 2020	0.20490848	0.00385624	84	117	16.7%	1.23 [1.22, 1.24]
Total (95% CI)			**486**	**816**	**100.0%**	**2.90 [1.17, 7.19]**

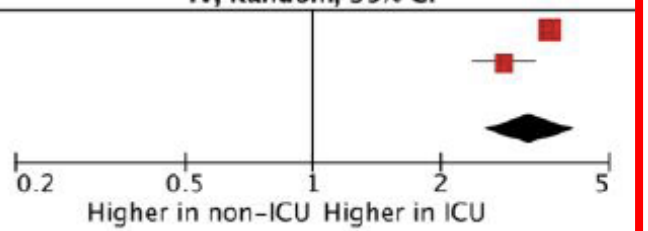
Heterogeneity: $Tau^2 = 1.28$; $Chi^2 = 158694.72$, df = 5 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 2.30 (P = 0.02)



Panel B. Patients Requiring ICU Admission versus Not Requiring ICU Admission

Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Diao et al. 2020	1.2861085	0.01523892	20	479	55.9%	3.62 [3.51, 3.73]
Huang et al. 2020a	1.03489647	0.08752466	13	28	44.1%	2.81 [2.37, 3.34]
Total (95% CI)			**33**	**507**	**100.0%**	**3.24 [2.54, 4.14]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.00$, df = 1 ($P = 0.005$); $I^2 = 87\%$
Test for overall effect: Z = 9.42 ($P < 0.00001$)



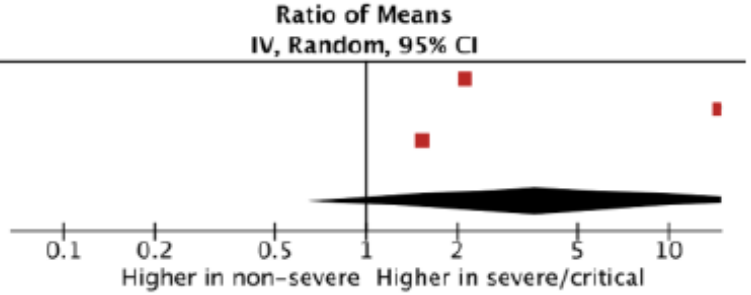
11,000 patients

Heightened IL-6 as correlate of disease severity

Panel C. Patients with Severe or Critical COVID-19 versus Mild COVID-19

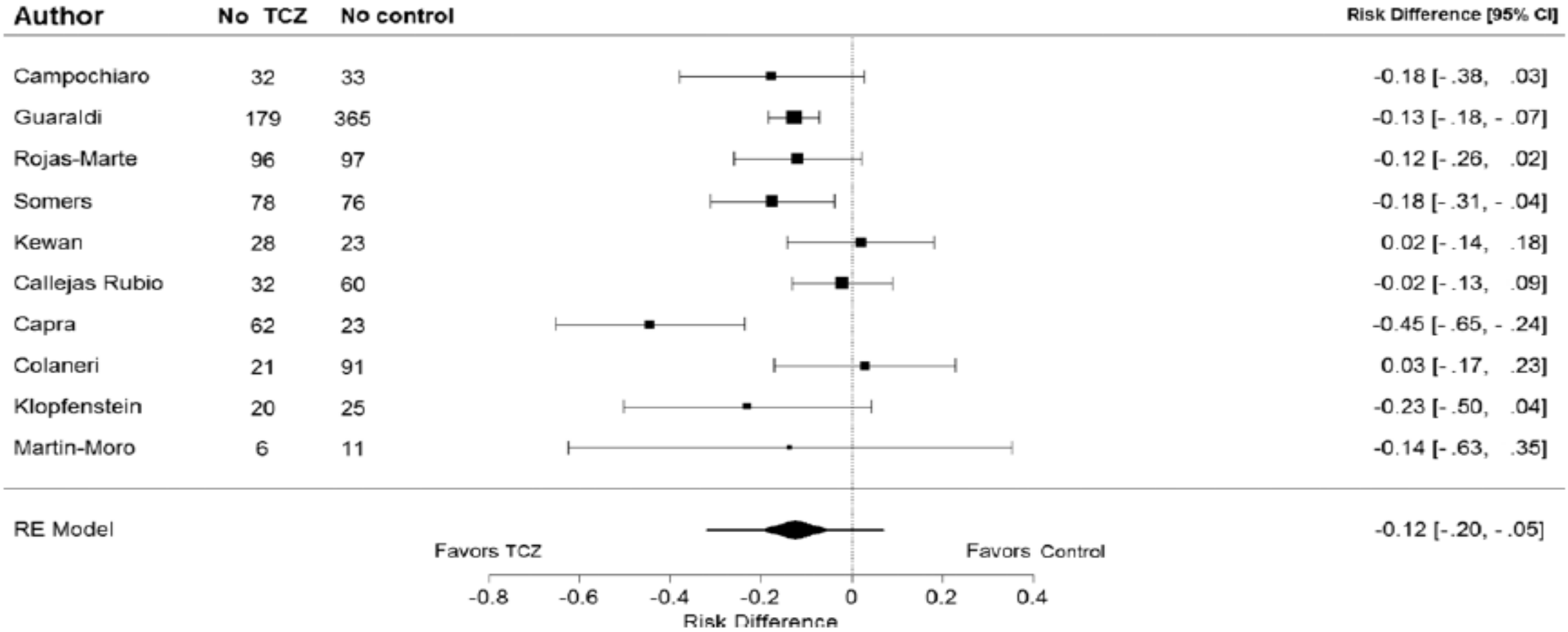
Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Chen et al. 2020a	0.75030559	0.01700847	14	15	33.3%	2.12 [2.05, 2.19]
Liu 2020	2.69261639	0.00539448	69	11	33.3%	14.77 [14.61, 14.93]
Qin et al. 2020	0.42527895	0.0036103	286	166	33.3%	1.53 [1.52, 1.54]
Total (95% CI)			**369**	**192**	**100.0%**	**3.63 [0.65, 20.37]**

Heterogeneity: $Tau^2 = 2.32$; $Chi^2 = 122484.25$, df = 2 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 1.47 (P = 0.14)



IL-6R antagonist (Tocilizumab)

Meta-analysis on 10 observational studies with 1358 patients showed 12% lower mortality in TCZ-treated patients

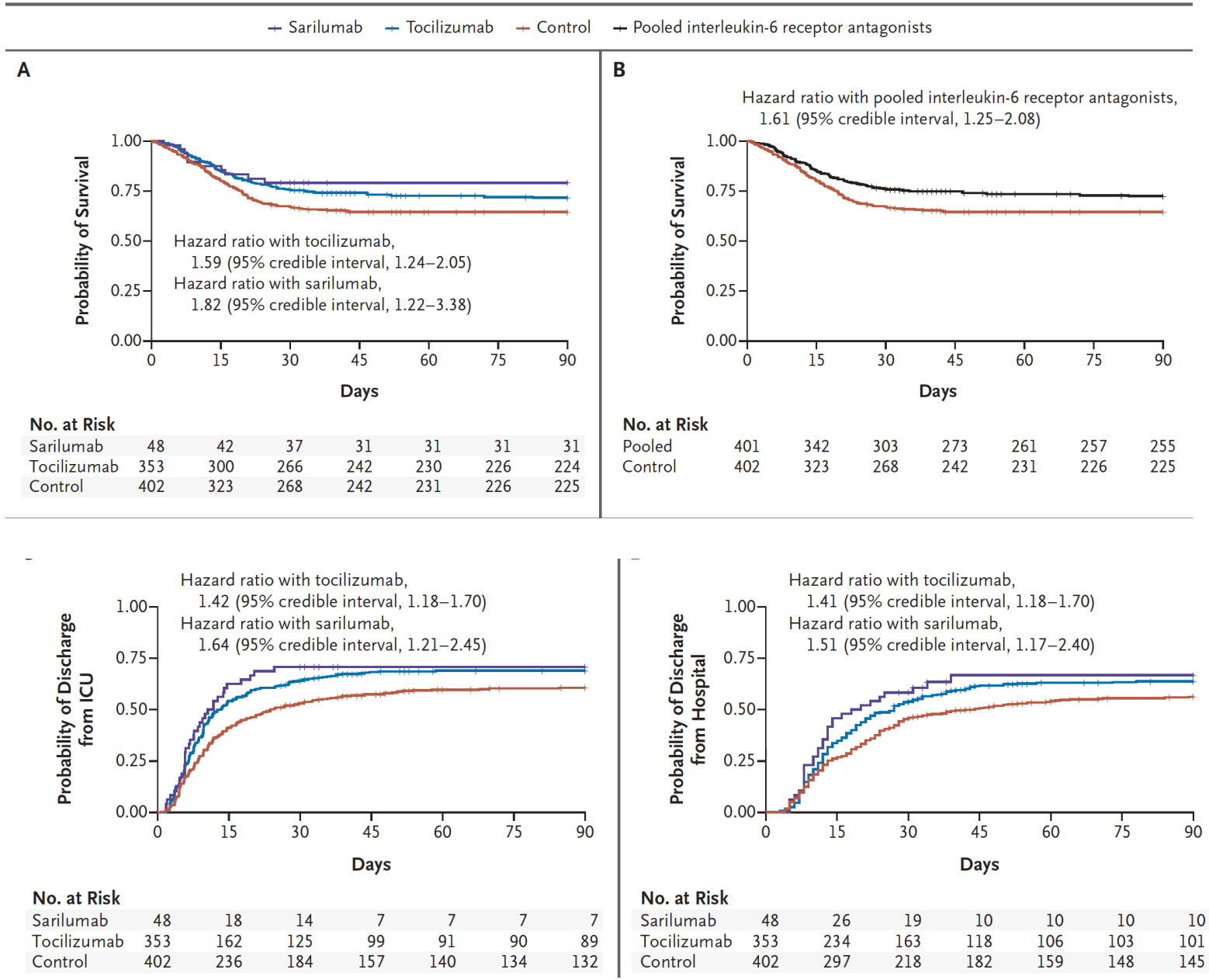


Malgie et al. CID 2020

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

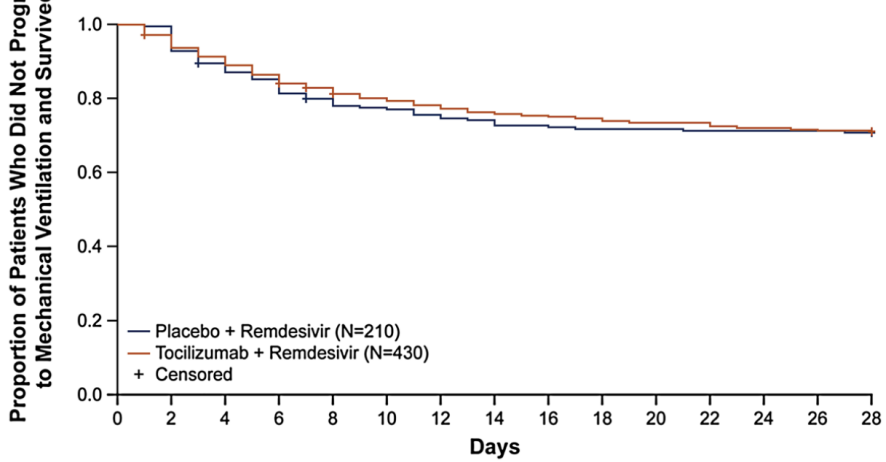
Characteristic	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)†	All Patients (N=865)‡
Age — yr	61.5±12.5	63.4±13.4	61.1±12.8	61.4±12.7
Male sex — no. (%)	261 (74)	39 (81)	283 (70)	629 (73)
Race or ethnic group — no./total no. (%)§				
White	160/228 (70)	29/39 (74)	206/279 (74)	420/580 (72)
Asian	41/228 (18)	8/39 (21)	47/279 (17)	99/580 (17)
Black	12/228 (5)	1/39 (3)	9/279 (3)	23/580 (4)
Mixed	2/228 (1)	0/39	5/279 (2)	7/580 (1)
Other	13/228 (6)	1/39 (3)	12/279 (4)	31/580 (5)
Body-mass index¶				
Patients evaluated	342	39	377	815
Median (IQR)	30.5 (26.9–34.9)	29.2 (26.0–33.8)	30.9 (27.1–34.9)	30.5 (26.8–34.9)
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)
Pao_2:FIo_2				
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)

REMAP-CAP NEJM 2021; similar data in RECOVERY trial



REMAP-CAP NEJM 2021; similar data in RECOVERY trial

b

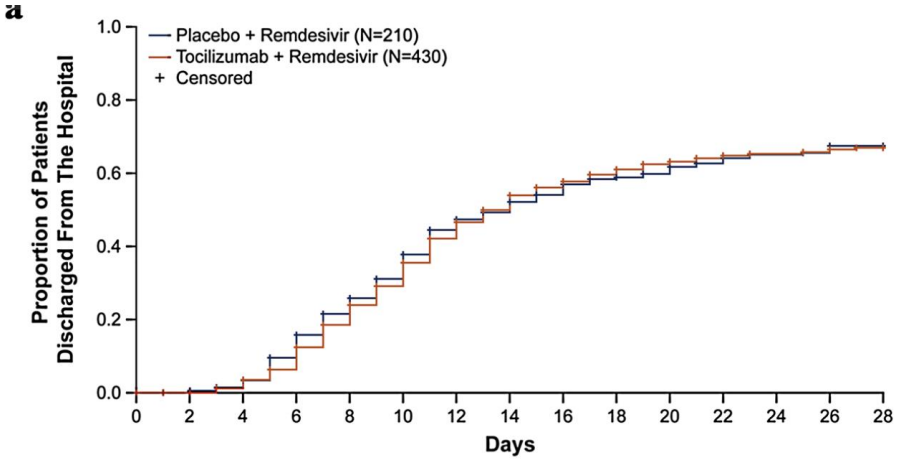


Patients remaining at risk

Placebo + Remdesivir	210	209	187	178	166	161	157	154	151	149	149	148	148	148	147
Tocilizumab + Remdesivir	430	415	390	369	352	339	331	323	319	316	311	311	305	303	302

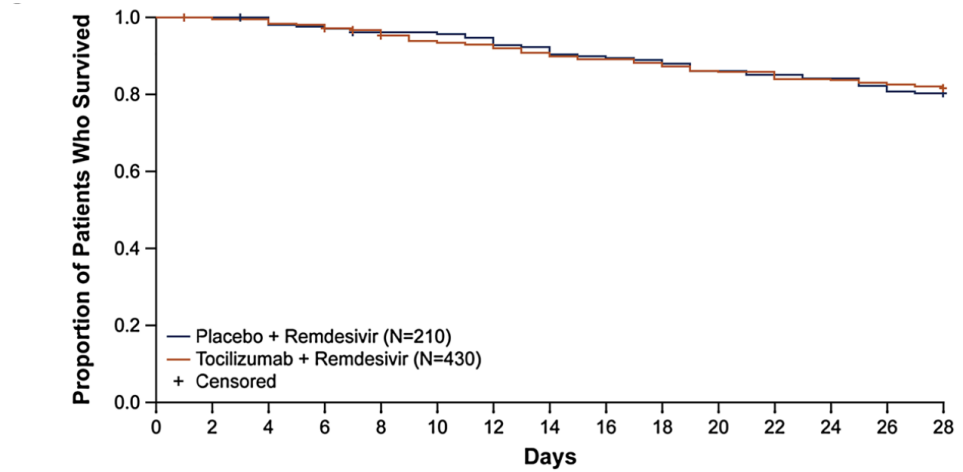
649 patient,
88% receiving
corticosteroid

a



Patients remaining at risk

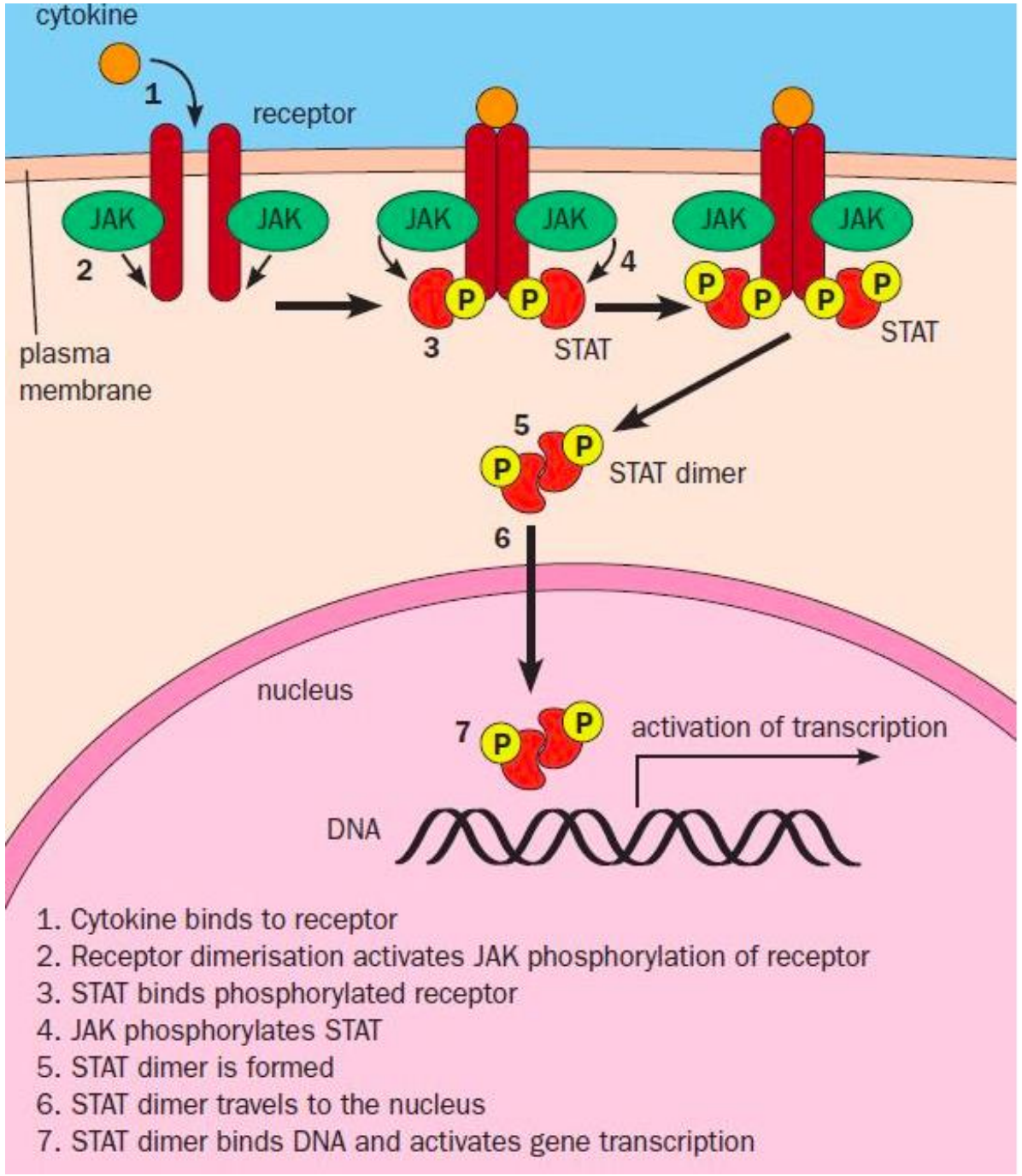
Placebo + Remdesivir	210	210	207	189	164	144	116	106	96	87	84	78	73	72	68
Tocilizumab + Remdesivir	430	428	422	400	346	300	245	212	186	171	159	152	147	145	140



Patients remaining at risk

Placebo + Remdesivir	210	210	209	204	200	200	197	192	187	185	179	177	175	171	167
Tocilizumab + Remdesivir	430	427	425	419	411	398	394	385	378	374	365	364	356	352	348

REMDACTA, Int Care Med 2021



Janus Kinase (JAK) inhibitors

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N = 1033)	Baricitinib+RDV (N = 515)	Placebo+RDV (N = 518)
Age			
Mean — yr	55.4±15.7	55.0±15.4	55.8±16.0
Distribution — no. (%)			
<40 yr	173 (16.7)	87 (16.9)	86 (16.6)
40–64 yr	555 (53.7)	281 (54.6)	274 (52.9)
≥65 yr	305 (29.5)	147 (28.5)	158 (30.5)
Sex — no. (%)			
Female	381 (36.9)	196 (38.1)	185 (35.7)
Male	652 (63.1)	319 (61.9)	333 (64.3)
Race — no. (%)†			
Asian	101 (9.8)	49 (9.5)	52 (10.0)
Black	156 (15.1)	77 (15.0)	79 (15.3)
White	496 (48.0)	251 (48.7)	245 (47.3)
Other or unknown	280 (27.1)	138 (26.8)	142 (27.4)
Ethnic group — no. (%)†			
Hispanic or Latino	531 (51.4)	263 (51.1)	268 (51.7)
Not Hispanic or Latino	486 (47.0)	246 (47.8)	240 (46.3)
Not reported or unknown	16 (1.5)	6 (1.2)	10 (1.9)
Body-mass index‡	32.2±8.3	32.2±8.2	32.3±8.4
Median time (IQR) from symptom onset to randomization — days	8 (5–10)	8 (5–10)	8 (5–11)

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Disease severity — no. (%)			
Moderate	706 (68.3)	358 (69.5)	348 (67.2)
Severe	327 (31.7)	157 (30.5)	170 (32.8)
Coexisting conditions — no./total no. (%)			
None	155/994 (15.6)	64/496 (12.9)	91/498 (18.3)
One	270/994 (27.2)	148/496 (29.8)	122/498 (24.5)
Two or more	569/994 (57.2)	284/496 (57.3)	285/498 (57.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	142 (13.7)	70 (13.6)	72 (13.9)
5. Hospitalized, requiring supplemental oxygen	564 (54.6)	288 (55.9)	276 (53.3)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	216 (20.9)	103 (20.0)	113 (21.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	111 (10.7)	54 (10.5)	57 (11.0)

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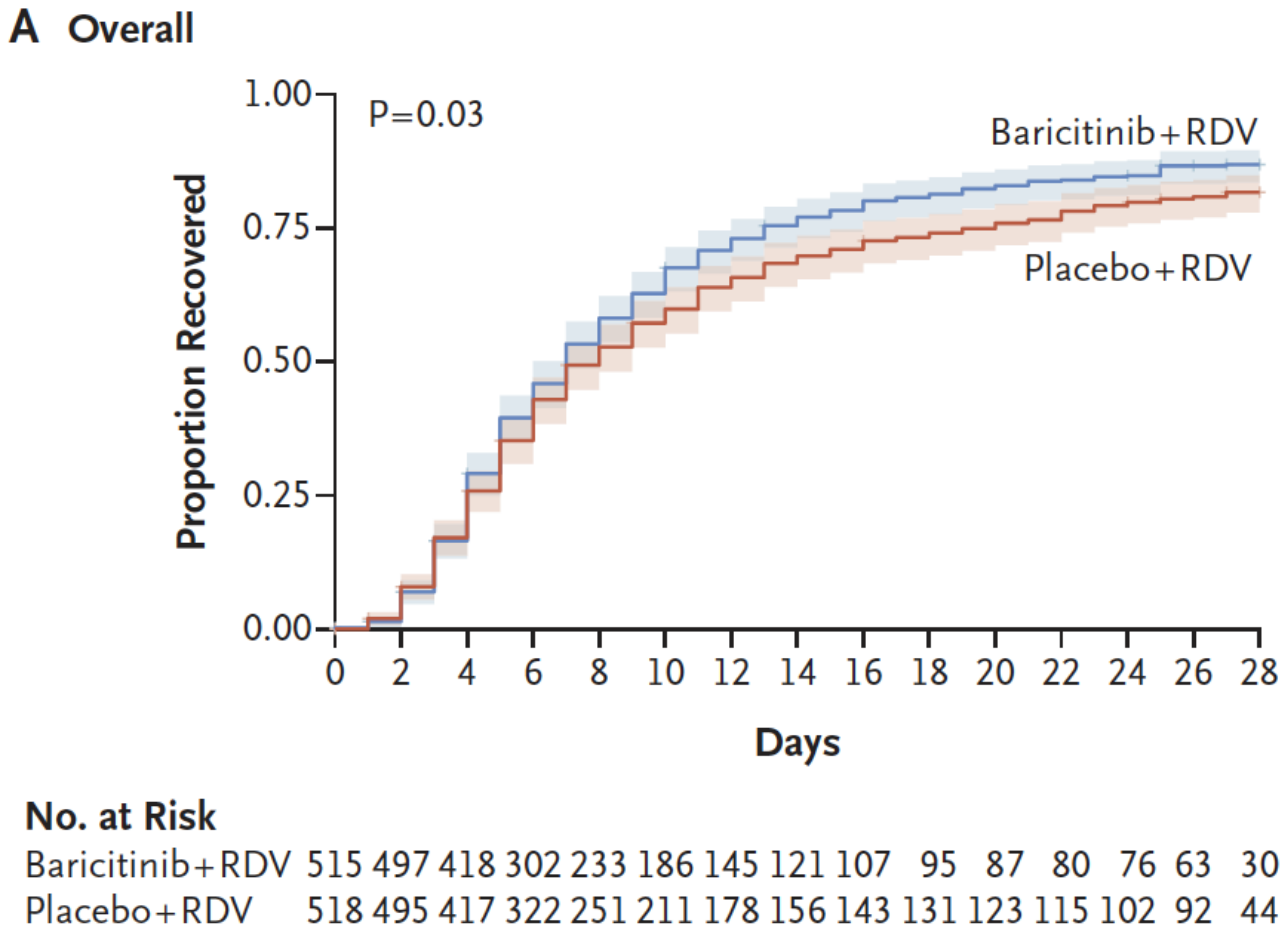
Median days to recovery: 7 in
Baricitinib+ RDV vs 8 Placebo + RDV



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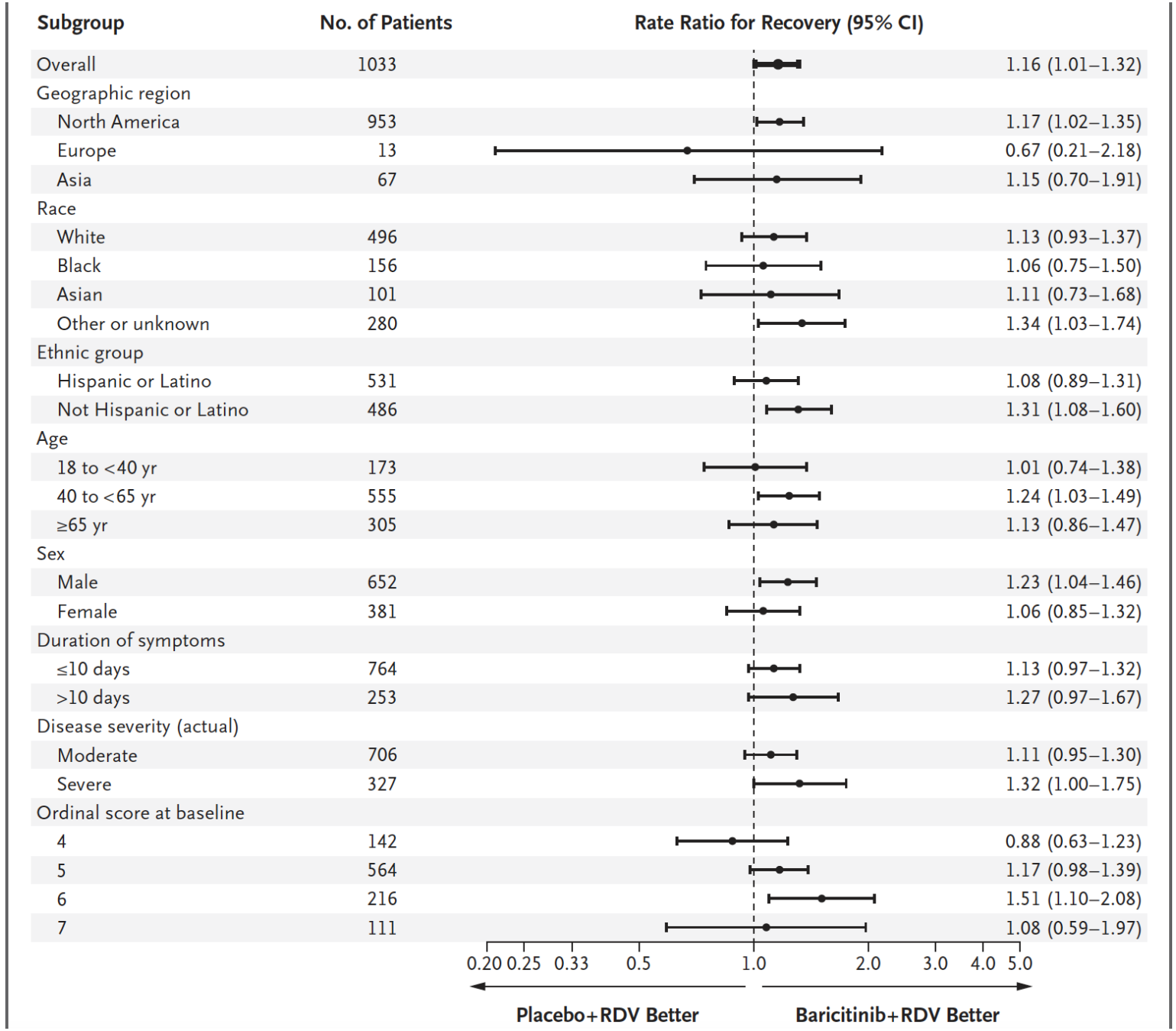

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•Patients and their families

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