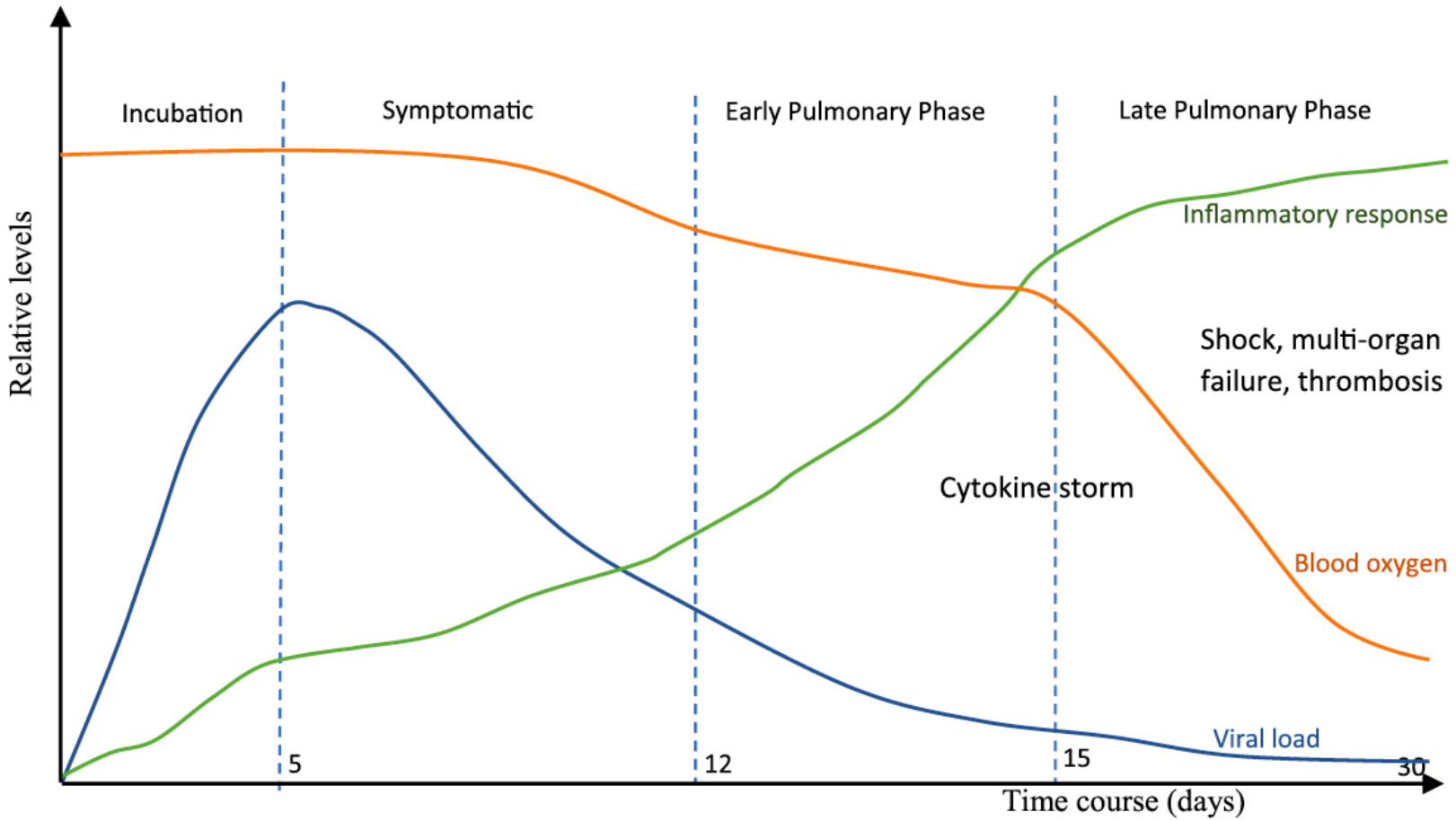
Terapie combinate nel paziente fragile con COVID-19

Carlo Torti
Istituto di Clinica delle Malattie Infettive
Dipartimento di Sicurezza e Bioetica
Università Cattolica del Sacro Cuore

SITA
Società Italiana di Terapia Antinfettiva Antibatterica Antivirale Antifungina
13° CONGRESSO NAZIONALE
PADOVA | 23-24 novembre 2023

Combination therapies for COVID-19: An overview of the clinical trials landscape

Sola Akinbolade[1] | Diarmuid Coughlan[1] | Ross Fairbairn[1] | Glenn McConkey[2] | Helen Powell[3] | Dapo Ogunbayo[1] | Dawn Craig[1]



The stages of COVID-19 showing progression of the disease.

Br J Clin Pharmacol. 2022;88:1590–1597.

Combination therapies for COVID-19: An overview of the clinical trials landscape

Sola Akinbolade[1] | Diarmuid Coughlan[1] | Ross Fairbairn[1] | Glenn McConkey[2] | Helen Powell[3] | Dapo Ogunbayo[1] | Dawn Craig[1]

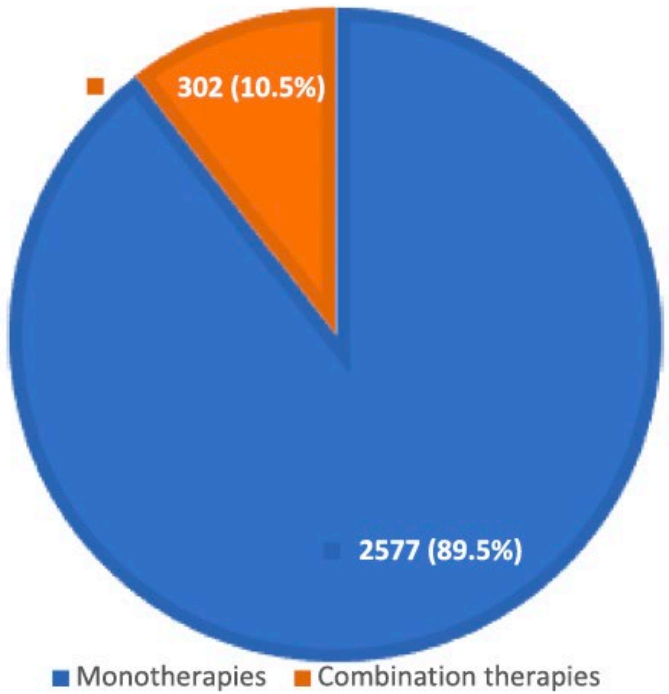


FIGURE 2 COVID-19 monotherapy and combination therapy clinical trials as of 29 March 2021

Intervention 1	Intervention 2	Trial ID	No. of subjects	Results
Bamlanivimab	Etesevimab	NCT04427501	3160	Yes
Doxycycline	Ivermectin	NCT04729140	150	No
Hydroxychloroquine	Azithromycin	NCT04336332	160	No
Hydroxychloroquine	Azithromycin	NCT04344444	600	No
Hydroxychloroquine	Baricitinib	NCT04373044	144	No
Lopinavir/ritonavir	Favipiravir	NCT04499677	240	No
Lopinavir/ritonavir	Favipiravir	2020-002106-68	240	No
Lopinavir/ritonavir	Hydroxychloroquine	NCT04386070	6400	No
Melatonin	Toremifene	NCT04531748	390	No
Methylene blue	Convalescent plasma	NCT04547127	200	No
NA-831 (Traneurocin)	Oral polio vaccine (OPV)	NCT04540185	3600	No
Naltrexone	Colchicine	NCT04756128	164	No
Oseltamivir	Vidofludimus calcium	NCT04516915	120	No
Pamapimod	Pioglitazone	2020-005849-16	144	No
Remdesivir	Bamlanivimab	NCT04501978	10000	Yes
Remdesivir	Baricitinib	NCT04401579	1034	Yes
Remdesivir	Hyperimmune immunoglobulin	NCT04546581	593	Yes
Remdesivir	Interferon beta-1a	NCT04492475	969	No
Remdesivir	Lenzilumab	NCT04583969	200	No
Remdesivir	Risankizumab	NCT04583956	200	No
Remdesivir	Tocilizumab	NCT04409262	649	Yes
Rosuvastatin	Colchicine	NCT04472611	466	No
Vitamin B- complex	Nitazoxanide	NCT04343248	800	No
Vitamin B- complex	Nitazoxanide	NCT04359680	1407	No
Vitamin B- complex	Nitazoxanide	NCT04486313	1092	No
Vitamin D	Aspirin	NCT04363840	1080	No

Br J Clin Pharmacol. 2022;88:1590–1597.

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

covid19treatmentguidelines.nih.gov

[d] Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset).

[e] Conventional oxygen refers to oxygen supplementation that is not HFNC oxygen, NIV, MV, or ECMO.

[f] If these patients progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed.

[g] If none of the preferred or alternative options are available or feasible to use, the JAK inhibitor **PO tofacitinib (CIIa)** or the IL-6 inhibitor **IV sarilumab (CIIa)** can be used in combination with dexamethasone. Sarilumab is only commercially available as a SUBQ injection; see Table 5e for information regarding the preparation of an IV infusion using the SUBQ product.

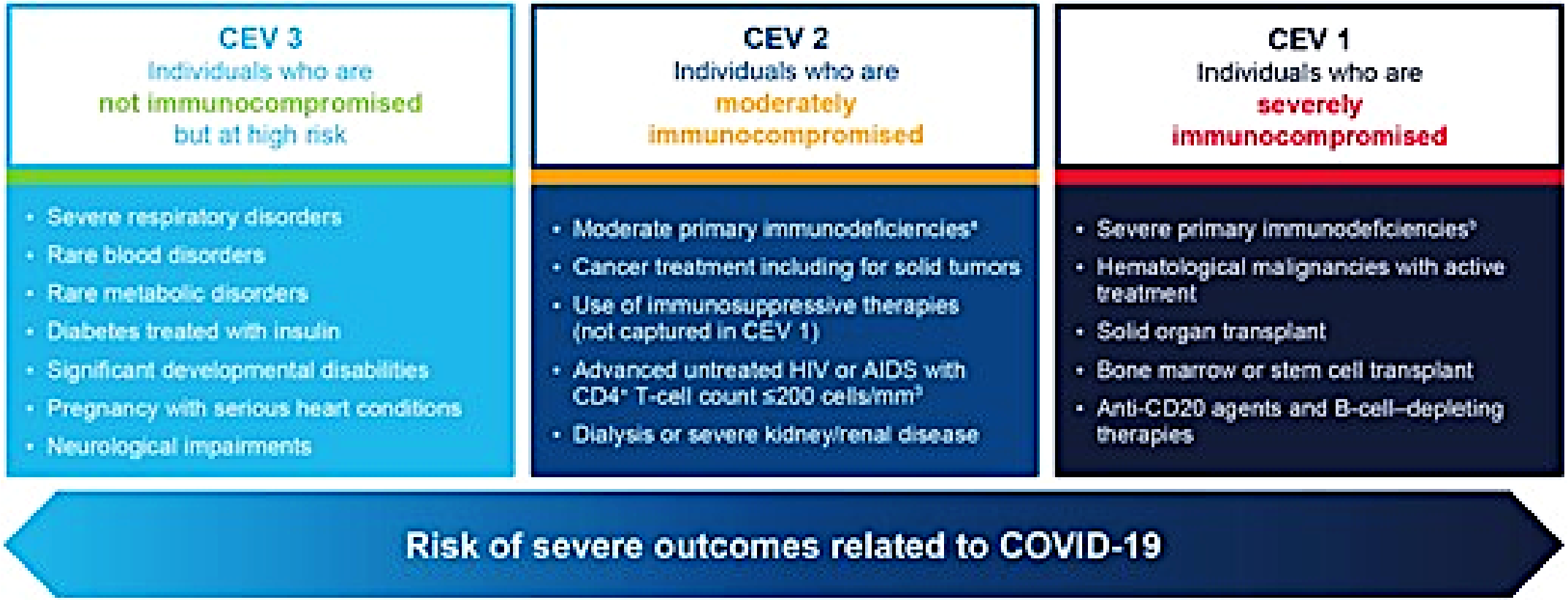
[h] Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a PLT <50 x 10^9/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder.

Hospitalized and Requires Conventional Oxygen[e]

CLOSE −

Clinical Scenario	Antiviral or Immunomodulator Therapy Recommendation	Anticoagulant Therapy Recommendation
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 1 of the following immunomodulators:[g] *Preferred* • **PO baricitinib (BIIa)** • **IV tocilizumab (BIIa)** *Alternatives* • **IV abatacept (CIIa)** • **IV infliximab (CIIa)**	

The Burden of COVID-19 in the Immunocompromised Patient: Implications for Vaccination and Needs for the Future



Antinori A, Bausch-Jurken M. The Burden of COVID-19 in the Immunocompromised Patient: Implications for Vaccination and Needs for the Future. J Infect Dis. 2023 Aug 4;228(Suppl 1):S4-S12. doi: 10.1093/infdis/jiad181. PMID: 37539764; PMCID: PMC10401620.

The unique presentation of SARS-CoV-2 Infection in patients with B-cell depletion: definition of 'persistent inflammatory sero-negative COVID'

Ana Belkin [1, 2, 3, *], Avshalom Leibowitz [1, 3], Liat Shargian [3, 4], Dafna Yahav [2, 3]

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

Diagnostic criteria of persistent inflammatory sero-negative COVID[a]

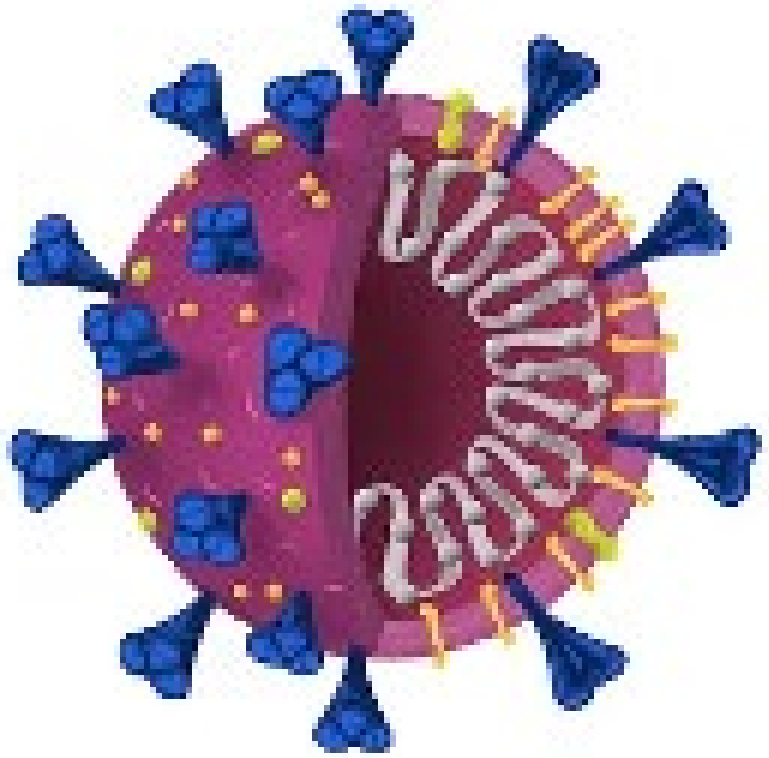
A patient is defined as having persistent inflammatory sero-negative COVID if they fulfil the following criteria and no alternative diagnosis:	
1. Host criterion	B-cell depleting disease or therapy, including the following: • Primary immunodeficiency causing hypogammaglobinaemia (X-linked agammaglobulinaemia, common variable immunodeficiency, other primary hypogammaglobinaemia). • Secondary immunodeficiency - anti-CD20 treatment in the past year; chronic lymphoblastic leukaemia, non-Hodgkin lymphoma, multiple myeloma accompanied by hypogammaglobinaemia or receiving immunotherapy directed against B cells (bi-specific antibodies or antibody-drug conjugates against CD19, CD20 or BCMA); chimeric antigen receptor T-cell therapy or allogeneic or autologous haematopoietic stem cell transplantation within 1 y.
2. Clinical criterion	Prolonged or remitting fever (total >7 d) with elevated CRP levels plus either one of the following: prostration, non-resolving cough and dyspnea (total >14 d), abnormal chest imaging showing pneumonitis (bilateral ground glass opacities).
3. Virological criterion, defined as either of the following	• Persistent or intermittent positive SARS-CoV-2 RT-PCR result over >21 d.[b] • Positive SARS-CoV-2 RT-PCR result in the last 90 d + sero-negativity for SARS-CoV-2 14 d after the initial infection in monoclonal antibody-naïve patients.[c]

B-cell maturation antigen (BCMA), CD, cluster of differentiation; COVID, coronavirus disease; CRP, C-reactive protein; Real-time PCR (RT-PCR); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Being sero-negative before and at the time of the onset of acute infection (regardless and despite vaccination) is a characteristic of this entity. It was not comprehensively included in the criteria for diagnosis because of practical reasons; the diagnosis can be made without a specialized blood test.

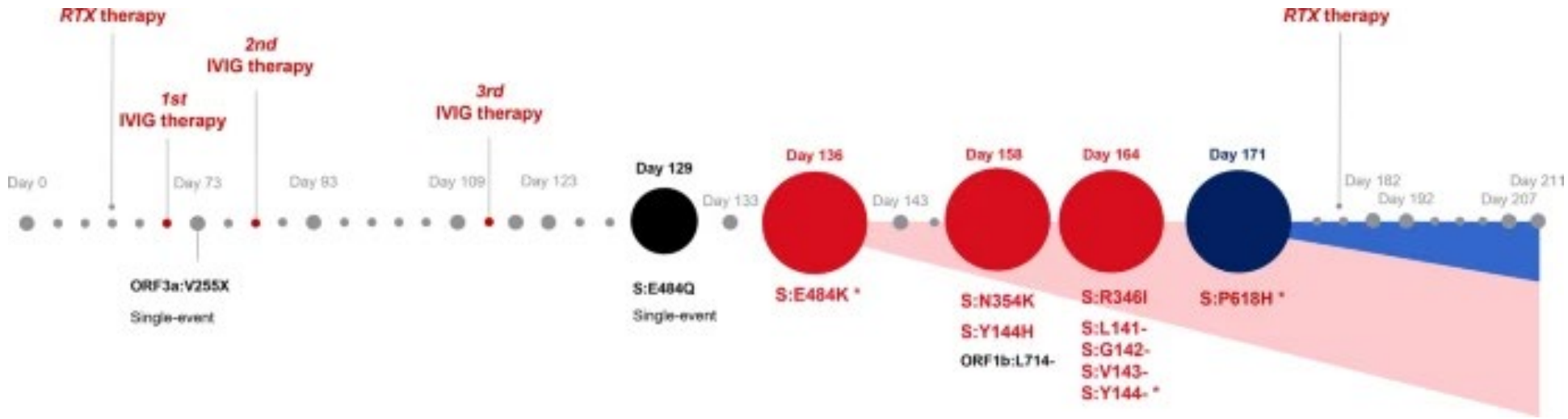
[b] A positive SARS-CoV-2 result from either a nasopharyngeal swab or lower-respiratory specimen demonstrating the same variant using sequencing supports the diagnosis but is not mandatory.

[c] Undetectable levels or low titres according to a local serology platform; patients who were treated with monoclonal antibodies for prevention may have higher titres.



It is the virus, stupid …

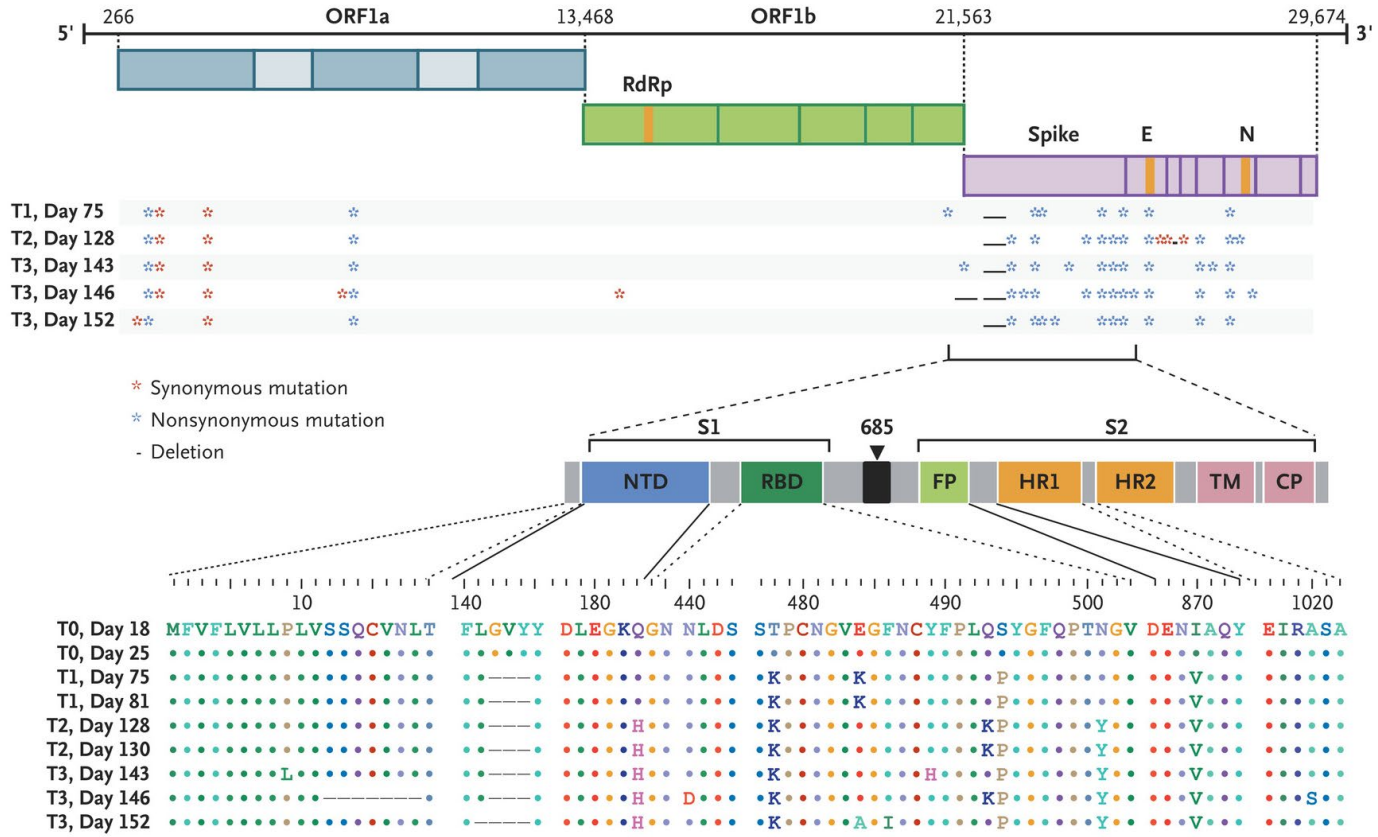
Cumulative SARS-CoV-2 mutations and corresponding changes in immunity in an immunocompromised patient indicate viral evolution within the host



Throughout the infection course, 17 non-synonymous intra-host mutations are noted, with 15 (88.2%) having been previously described as prominent immune escape mutations (S:E484K, S:D950N, S:P681H, S:N501Y, S:del(9), N:S235F and S:H655Y) in VOCs. The high frequency of these non-synonymous mutations is consistent with multiple events of convergent evolution. Thus, our results suggest that specific mutations in the SARS-CoV-2 genome may represent positions with a fitness advantage, and may serve as targets in future vaccine and therapeutics development for COVID-19.

Sonnleitner, S.T., Prelog, M., Sonnleitner, S. et al. Cumulative SARS-CoV-2 mutations and corresponding changes in immunity in an immunocompromised patient indicate viral evolution within the host. Nat Commun 13, 2560 (2022). https://doi.org/10.1038/s41467-022-30163-4

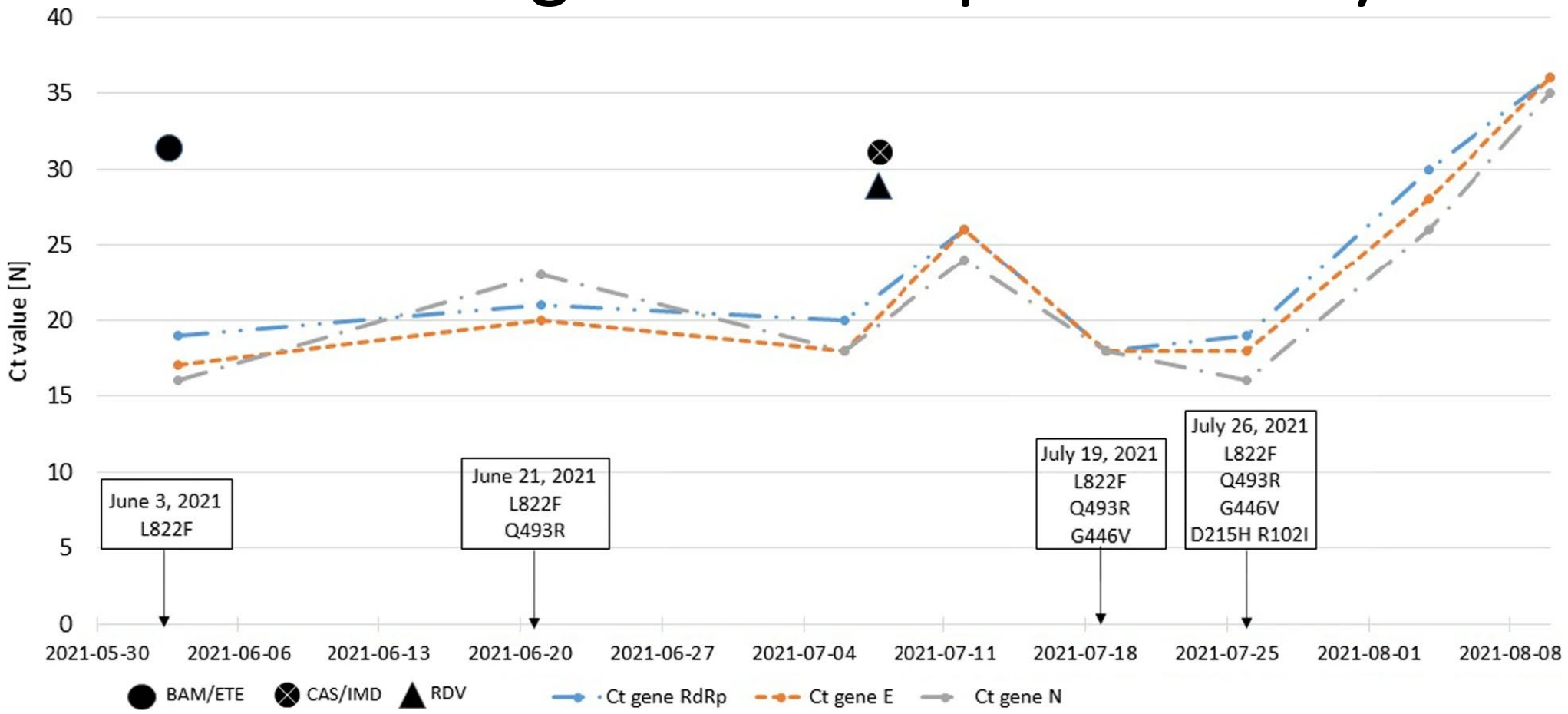
Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host



Although most immunocompromised persons effectively clear SARS-CoV-2 infection, this case highlights the potential for persistent infection and accelerated viral evolution associated with an immunocompromised state.

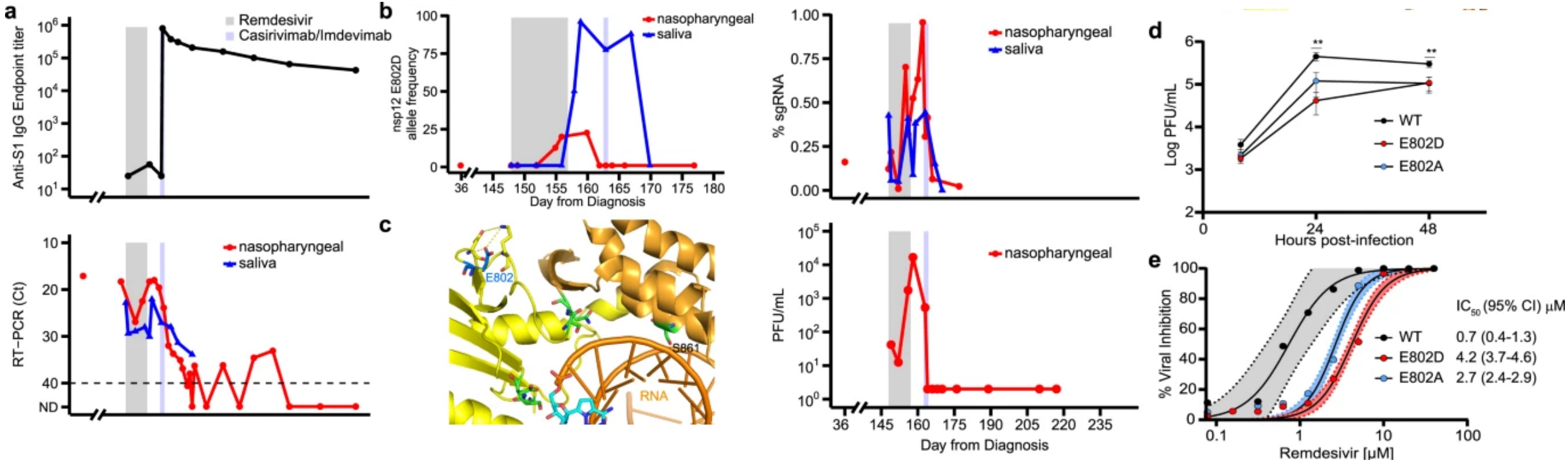
Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, Solomon IH, Kuo HH, Boucau J, Bowman K, Adhikari UD, Winkler ML, Mueller AA, Hsu TY, Desjardins M, Baden LR, Chan BT, Walker BD, Lichterfeld M, Brigl M, Kwon DS, Kanjilal S, Richardson ET, Jonsson AH, Alter G, Barczak AK, Hanage WP, Yu XG, Gaiha GD, Seaman MS, Cernadas M, Li JZ. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. N Engl J Med. 2020 Dec 3;383(23):2291-2293. doi: 10.1056/NEJMc2031364. Epub 2020 Nov 11. PMID: 33176080; PMCID: PMC7673303.

Lessons learned and implications of early therapies for coronavirus disease in a territorial service centre in the Calabria region: a retrospective study



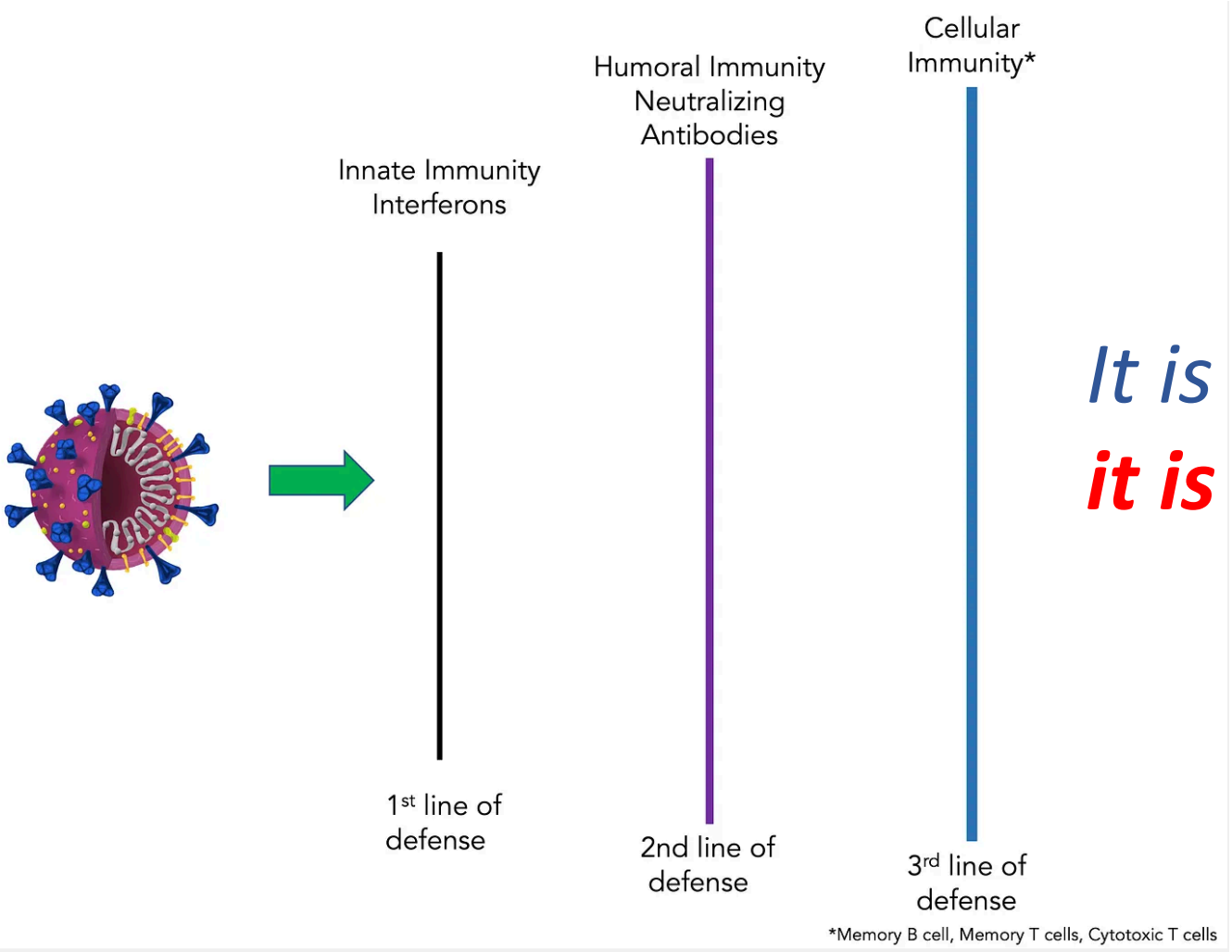
Scaglione V, Rotundo S, Marascio N, De Marco C, Lionello R, Veneziano C, Berardelli L, Quirino A, Olivadese V, Serapide F, Tassone B, Morrone HL, Davoli C, La Gamba V, Bruni A, Cesana BM, Matera G, Russo A, Costanzo FS, Viglietto G, Trecarichi EM, Torti C; IDTM U. M. G. COVID-19 Group. Lessons learned and implications of early therapies for coronavirus disease in a territorial service centre in the Calabria region: a retrospective study. BMC Infect Dis. 2022 Oct 20;22(1):793. doi: 10.1186/s12879-022-07774-9. Erratum in: BMC Infect Dis. 2022 Nov 24;22(1):883. PMID: 36266619; PMCID: PMC9583059.

De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report



Although the fitness cost observed in vitro may limit the risk posed by E802D, this case illustrates the importance of monitoring for remdesivir resistance and the potential benefit of combinatorial therapies in immunocompromised patients with SARS-CoV-2 infection.

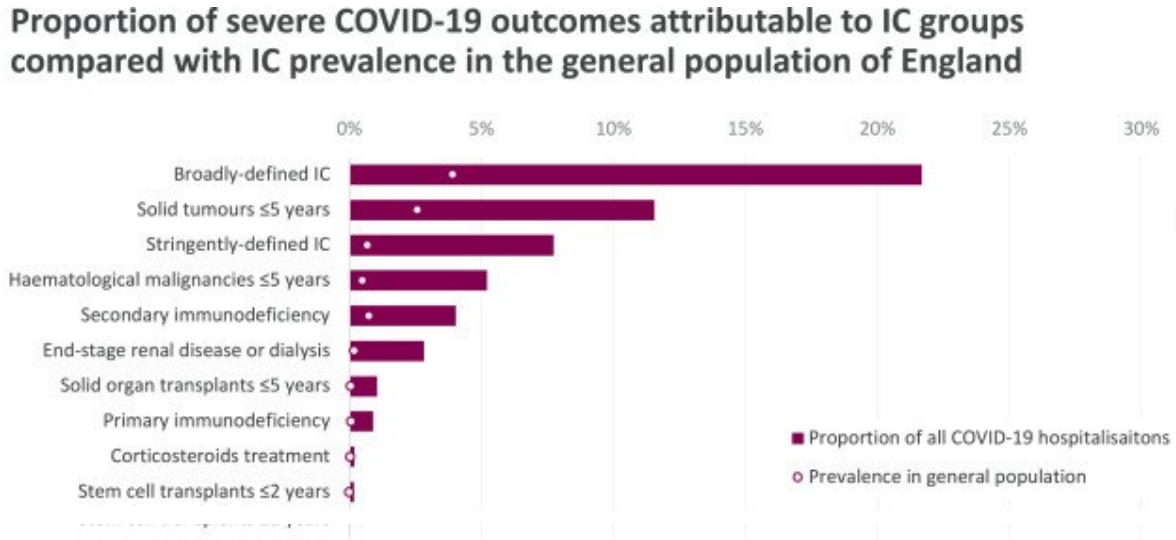
Gandhi, S., Klein, J., Robertson, A.J. et al. De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. Nat Commun 13, 1547 (2022). https://doi.org/10.1038/s41467-022-29104-y

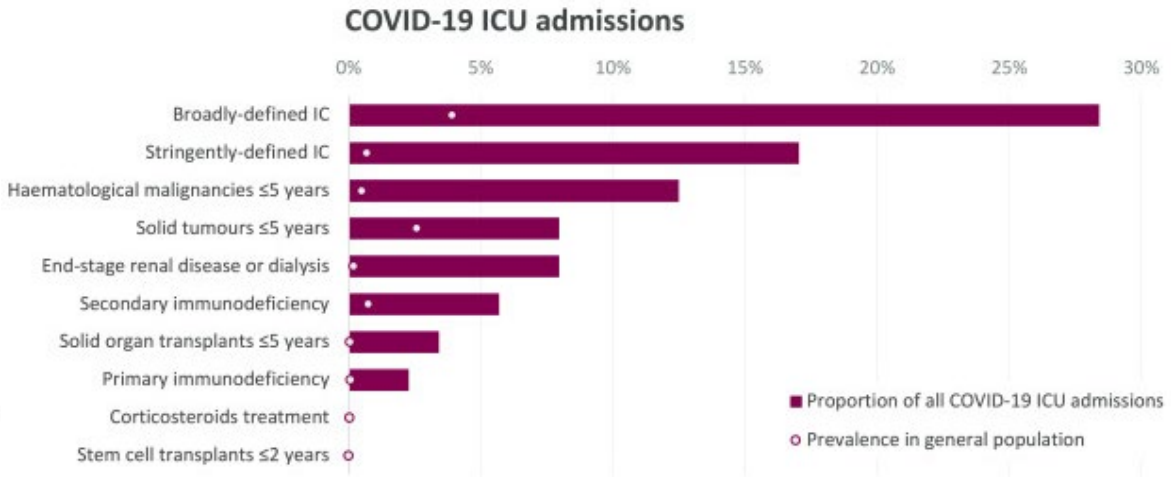


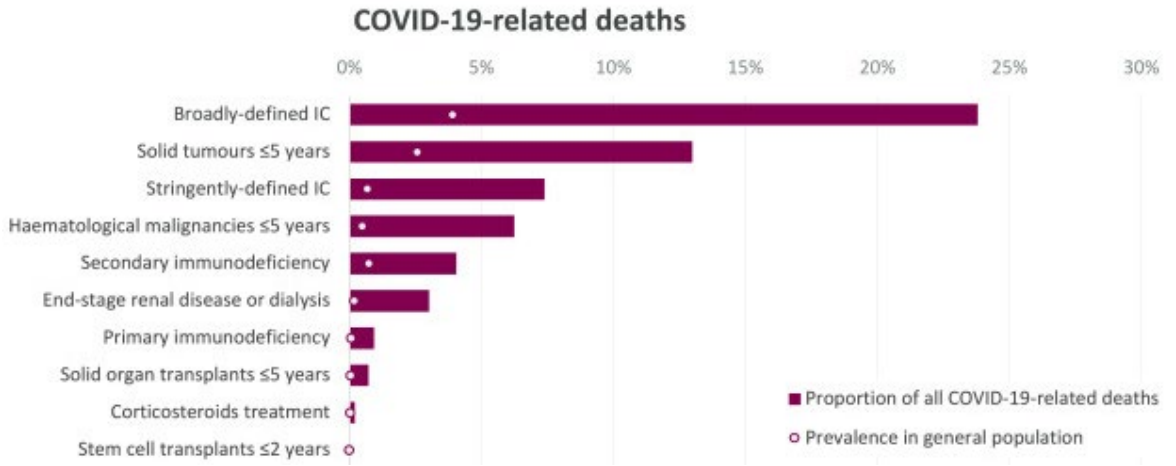
It is the virus, stupid, ***or***

it is the host?

Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study







Immunocompromised individuals continue to be impacted disproportionately by COVID-19 and have an urgent need for additional preventive measures beyond current vaccination programmes. These data can help determine the immunocompromised groups for which targeted prevention strategies may have the highest impact.

Rachael A. Evans, Sabada Dube, Yi Lu, Mark Yates, Sofie Arnetorp, Eleanor Barnes, Samira Bell, Lucy Carty, Kathryn Evans, Sophie Graham, Nahila Justo, Paul Moss, Sudhir Venkatesan, Renata Yokota, Catia Ferreira, Richard McNulty, Sylvia Taylor, Jennifer K. Quint, Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study, The Lancet Regional Health - Europe, 2023, 100747,ISSN 2666-7762, https://doi.org/10.1016/j.lanepe.2023.100747.

Incidence, Clinical Presentation, Relapses and Outcome of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Patients Treated With Anti-CD20 Monoclonal Antibodies

Patient	Recurrence Classification	Demographic	Anti-CD20	Group	No.	Time to Relapses	Status Between Episodes	Clinical Presentation	Diagnoses	Management	Outcomes
1	Relapse	35 years old, female	Multiple sclerosis	3–6 months.	2	38 days 112	Dyspnea of moderate exertion	Fever, dyspnea, cough	Nasopharyngeal RT-PCR (Ct unknown)	Corticoid	Radiological improvement. Persistent dyspnea
		No comorbidity	ocrelizumab	164 days		days		Worsening and new pulmonary infiltrates			
2	Relapse	56 years old, male	High-grade lymphoma	< 3 months	6	34 days	Asymptomatic	Fever, dyspnea, cough	Pulmonary biopsy and BAL RT-PCR (Ct 22)	Corticoid convalescent plasma remdesivir	Since plasm and remdesivir, asymptomatic and radiological resolution
		No comorbidity	rituximab	33 days		143 days		New pulmonary infiltrates			
								Superinfection			
3	Relapse	24 years old, female	Multiple sclerosis	3–6 months	5	58 days	Asymptomatic	Fever	BAL RT-PCR (Ct 23)	Corticoid	Continues with migratory infiltrates.
		DM	rituximab	135 days		287 days		Worsening and new pulmonary infiltrates			Asymptomatic
4	Possible relapse	35 years old, male	Hemolytic anemia	3–6 months	1	51 days	Asymptomatic	Fever, dyspnea, cough	No confirmation (no test done)	No specific treatment	Radiological resolution
		No comorbidity	rituximab	154 days				New pulmonary infiltrates			Asymptomatic
5	Relapse	55 years old, male	Multiple sclerosis	< 3 months	1	36 days	Dyspnea of moderate exertion	Fever, dyspnea, cough	Nasopharyngeal RT-PCR (Ct 29)	No specific treatment	Radiological improvement. Persistent dyspnea
		CF	ocrelizumab	65 days				Worsening of pulmonary infiltrates			
6	Possible relapse	53 years old, male	Multiple sclerosis	< 3 months	1	105 days	Asymptomatic	Dyspnea	Nasopharyngeal RT-PCR (Ct 21)	Corticoid	Asymptomatic
		No comorbidity	Rituximab	10 days				Worsening and new pulmonary infiltrates		Immunoglobulin	No radiological follow-up
7	Relapse	48 years old female	Rheumatoid arthritis	< 3 months	3	47 days	Asymptomatic	Fever, dyspnea, cough	BAL RT-PCR (Ct 34)	Corticoid convalescent plasma	Asymptomatic
		No comorbidity	Rituximab	7 days		83 days		New pulmonary infiltrates		Immunoglobulin	No radiological follow-up
8	Relapse	60 years old, male	Sjogren's syndrome	<3 months	1	54 days	Dyspnea of moderate exertion	Fever, dyspnea, cough,	BAL RT-PCR (Ct 23)	Corticoid	Radiological improvement. Asymptomatic
		Liver cirrhosis, CF, CRF	Rituximab	86 days				New pulmonary infiltrates		Remdesivir convalescent plasma tocilizumab	
								Acute respiratory distress			
9	Possible relapse	80 years old, female	Vasculitis	3–6 months	1	51 days	Asymptomatic	Fever, dyspnea, cough, new pulmonary infiltrates	Nasopharyngeal RT-PCR (Ct 35)	Corticoid	Asymptomatic
		HT, DM, CRF	Rituximab	95 days				Thromboembolism			No radiological follow-up

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the 6 months after anti-CD20 administration had a worse outcome and a higher mortality rate. The duration of infectivity may be longer. Relapses of COVID-19 occurred in more than 15% and were associated with viral replication. Once the infection is resolved, it is safe to restart treatment with anti-CD20.

Calderón-Parra J, Múñez-Rubio E, Fernández-Cruz A, García-Sánchez MC, Maderuelo-González E, López-Dosil M, Calvo-Salvador M, Baños-Pérez I, Valle-Falcones M, Ramos-Martínez A. Incidence, Clinical Presentation, Relapses and Outcome of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Patients Treated With Anti-CD20 Monoclonal Antibodies. Clin Infect Dis. 2022 May 30;74(10):1786-1794. doi: 10.1093/cid/ciab700.

ESCMID COVID-19 living guidelines: drug treatment and clinical management

Scope: The aim of the present guidance is to provide evidence-based recommendations for management of adults with coronavirus disease 2019 (COVID-19). More specifically, the goal is to aid clinicians managing patients with COVID-19 at various levels of severity including outpatients, hospitalized patients, and those admitted to intensive care unit. Considering the composition of the panel, mostly clinical microbiologists or infectious disease specialists with no pulmonology or intensive care background, we focus only on pharmacological treatment and do not give recommendations on oxygen supplement/support. Similarly, as no paediatricians were included in the panel; the recommendations are only for adult patients with COVID-19. Considering the current literature, no guidance was given for special populations such as the immunocompromised. **Michele Bartoletti, Clin Microbiol Infect 2022;28:222**

Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R, Paño-Pardo JR, Power NR, Sibani M, Szabo BG, Tsiodras S, Verweij PE, Zollner-Schwetz I, Rodríguez-Baño J. ESCMID COVID-19 living guidelines: drug treatment and clinical management. Clin Microbiol Infect. 2022 Feb;28(2):222-238. doi: 10.1016/j.cmi.2021.11.007. Epub 2021 Nov 22. PMID: 34823008; PMCID: PMC8606314.

Immunocompromised patients have been neglected in COVID-19 trials: a call for action

Table 1
Proportion of immunocompromised participants in registration trials of antiviral drugs

Drug	Remdesivir	Nirmatrelvir/ritonavir	Sotrovimab
Primary end point	Hospitalization or death within 28 days	Hospitalization or death within 28 days	Hospitalization or death within 29 days
Population	Symptoms ≤7 days, at least one risk factor	Symptoms <5 days, high risk patients	Symptoms <5 days, at least one risk factor
Immuno-compromized, %	5	<1	Excluded
Efficacy data, *n* (%)	2/279 (0.7) (remdesivir); 15/283 (5.3) (placebo); p = 0.008; RRR = 87%	3/389 (0.8) (nirmatrelvir); 27/385 (7.0) (placebo); p < 0.0001; RRR = 89%	3/291 (1) (sotrovimab); 21/292 (7) (placebo); p = 0.002; RRR = 85%
Publication	Gottlieb et al. [4]	Hammond et al. [5]	Gupta et al. [6]

RRR, relative risk reduction.

Trøseid M, Hentzien M, Ader F, Cardoso SW, Arribas JR, Molina JM, Mueller N, Hites M, Bonnet F, Manuel O, Costagliola D, Grinsztejn B, Olsen IC, Yazdapanah Y, Calmy A; EU RESPONSE; COMBINE. Immunocompromised patients have been neglected in COVID-19 trials: a call for action. Clin Microbiol Infect. 2022 Sep;28(9):1182-1183. doi: 10.1016/j.cmi.2022.05.005. Epub 2022 May 25. PMID: 35623577; PMCID: PMC9130310.

Special Considerations in People Who Are Immunocompromised

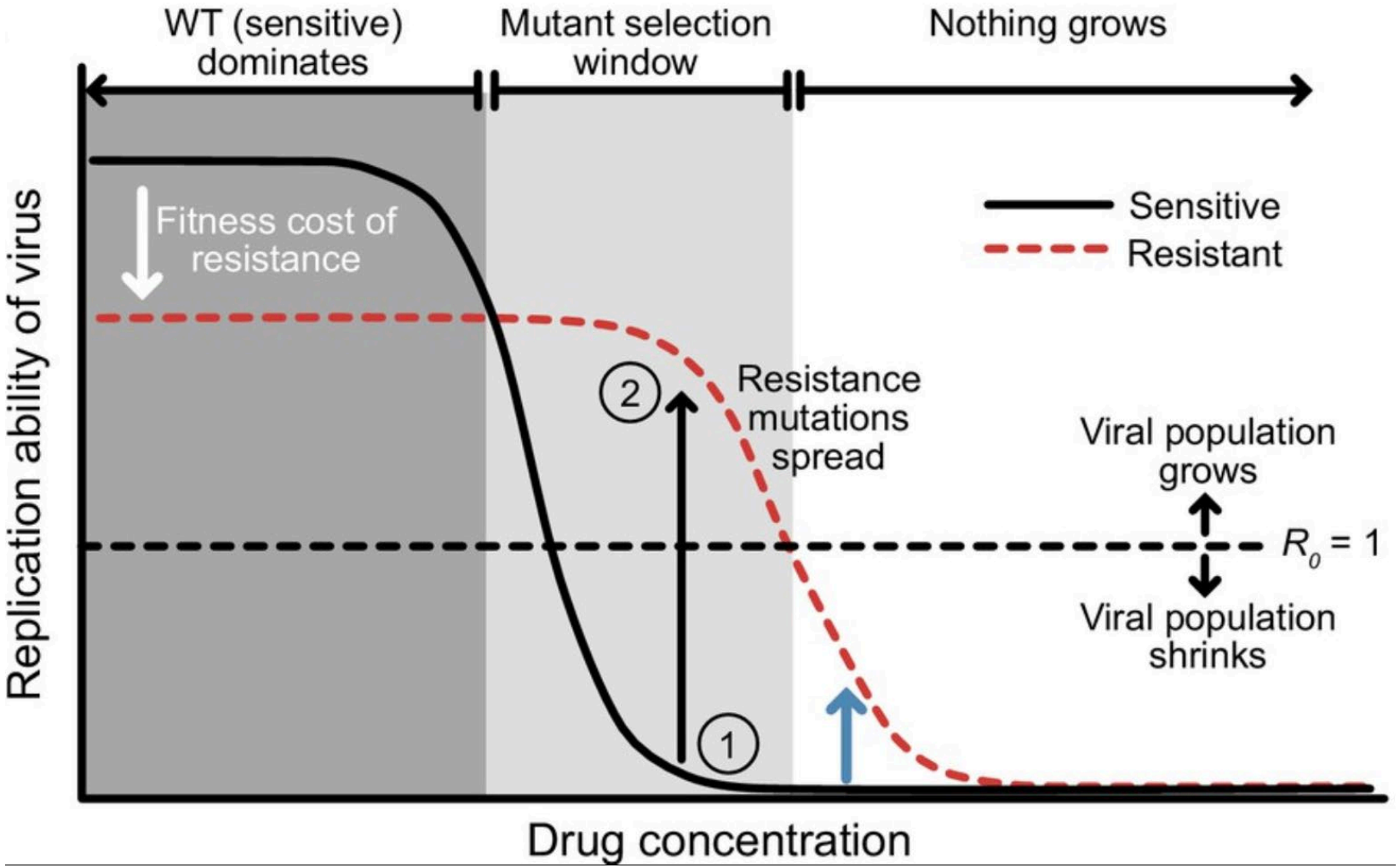
Management of Patients With COVID-19 Who Are Immunocompromised

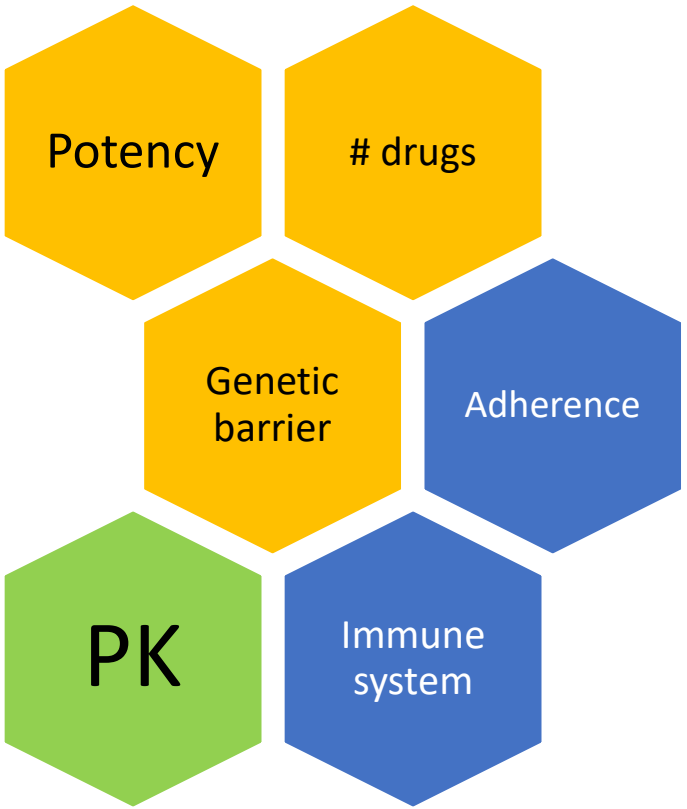
- The Panel recommends consulting with the appropriate specialists when making decisions about stopping or adjusting the doses of immunosuppressive drugs in patients with COVID-19 (**BIII**).
- When selecting treatments for COVID-19, clinicians should consider factors such as the underlying disease; the specific immunosuppressants being used; the severity of COVID-19; and the potential for drug-drug interactions, overlapping toxicities, and secondary infections.
- For nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised, the Panel recommends prompt treatment with antiviral drugs at the doses and durations recommended for the general population (**AIII**). For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19.
- For most hospitalized patients with severe or critical COVID-19 who are immunocompromised, the Panel recommends using antiviral drugs and immunomodulatory therapies at the doses and durations recommended for the general population (**AIII**). For more information, see Therapeutic Management of Hospitalized Adults With COVID-19.
- Some people who are immunocompromised have prolonged, symptomatic COVID-19 with evidence of ongoing SARS-CoV-2 replication. Without definitive data, some Panel members would use 1 or more of the following treatment options:
  - Longer and/or additional courses of ritonavir-boosted nirmatrelvir (Paxlovid)
  - Longer and/or additional courses of remdesivir
  - High-titer COVID-19 convalescent plasma from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness

eLife

Alison F Feder[1,2]*, Kristin N Harper[3], Chanson J Brumme[4,5], Pleuni S Pennings[6]

eLife 2021;10:e69032. DOI: https://doi.org/10.7554/eLife.69032





nature

Article | Published: 25 September 2023

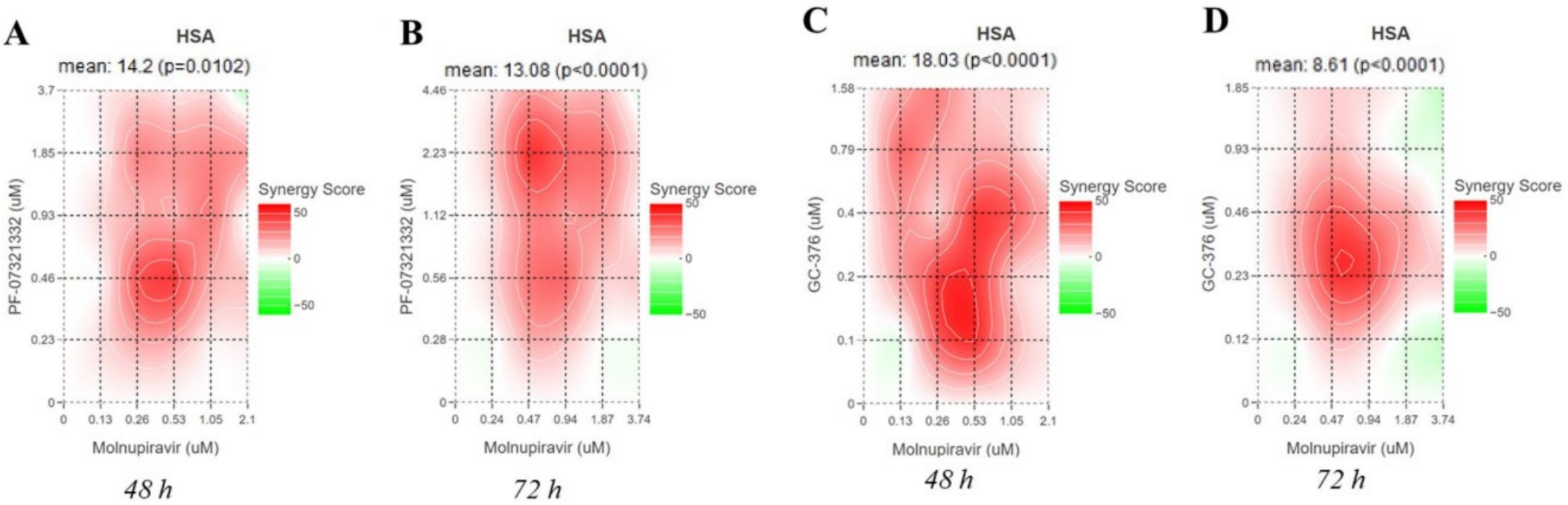
A molnupiravir-associated mutational signature in global SARS-CoV-2 genomes

Theo Sanderson, Ryan Hisner, I'ah Donovan-Banfield, Hassan Hartman, Alessandra Løchen, Thomas P. Peacock & Christopher Ruis

Abstract

Molnupiravir, an antiviral medication that has been widely used against SARS-CoV-2, acts by inducing mutations in the virus genome during replication. Most random mutations are likely to be deleterious to the virus, and many will be lethal, and so molnupiravir-induced elevated mutation rates reduce viral load[1,2]. However, if some patients treated with molnupiravir do not fully clear SARS-CoV-2 infections, there could be the potential for onward transmission of molnupiravir-mutated viruses. Here we show that SARS-CoV-2 sequencing databases contain extensive evidence of molnupiravir mutagenesis. Using a systematic approach, we find that a specific class of long phylogenetic branches, distinguished by a high proportion of G-to-A and C-to-T mutations, appear almost exclusively in sequences from 2022, after the introduction of molnupiravir treatment, and in countries and age-groups with widespread usage of the drug. We identify a mutational spectrum, with preferred nucleotide contexts, from viruses in patients known to have been treated with molnupiravir and show that its signature matches that seen in these long branches, in some cases with onwards transmission of molnupiravir-derived lineages. Finally, we analyse treatment records to confirm a direct association between these high G-to-A branches and the use of molnupiravir.

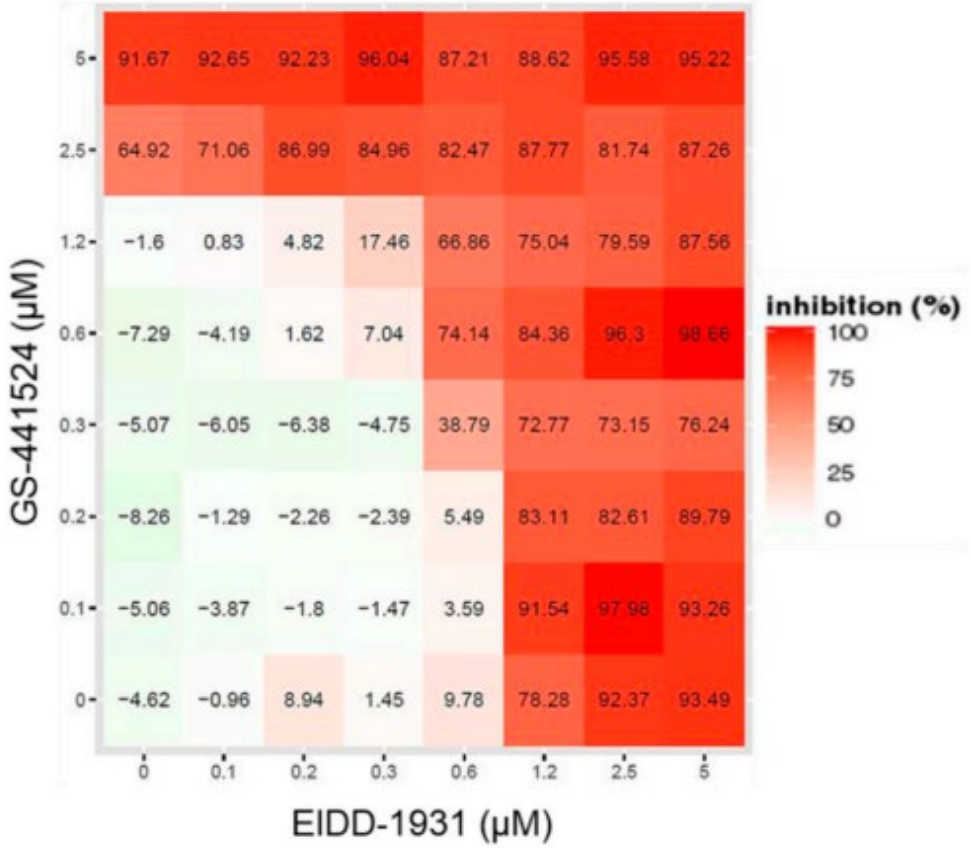
The Combination of Molnupiravir with Nirmatrelvir or GC376 Has a Synergic Role in the Inhibition of SARS-CoV-2 Replication In Vitro



Synergy distribution in pairwise combination of antivirals. Vero E6 cell viability was determined after SARS-CoV-2 20A.EU1 strain infection and treatment with molnupiravir–nirmatrelvir combinations for (A) 48 and (B) 72 h, or the combinations of molnupiravir-GC376 for (C) 48 and (D) 72 h. Rescue of virus-mediated viability reduction was used for the analysis with the SynergyFinder version 2 tool. Data are from 3 independent experiments performed in triplicate.

Gidari A, Sabbatini S, Schiaroli E, Bastianelli S, Pierucci S, Busti C, Comez L, Libera V, Macchiarulo A, Paciaroni A, Vicenti I, Zazzi M, Francisci D. The Combination of Molnupiravir with Nirmatrelvir or GC376 Has a Synergic Role in the Inhibition of SARS-CoV-2 Replication In Vitro. Microorganisms. 2022 Jul 21;10(7):1475. doi: 10.3390/microorganisms10071475. PMID: 35889194; PMCID: PMC9323947.

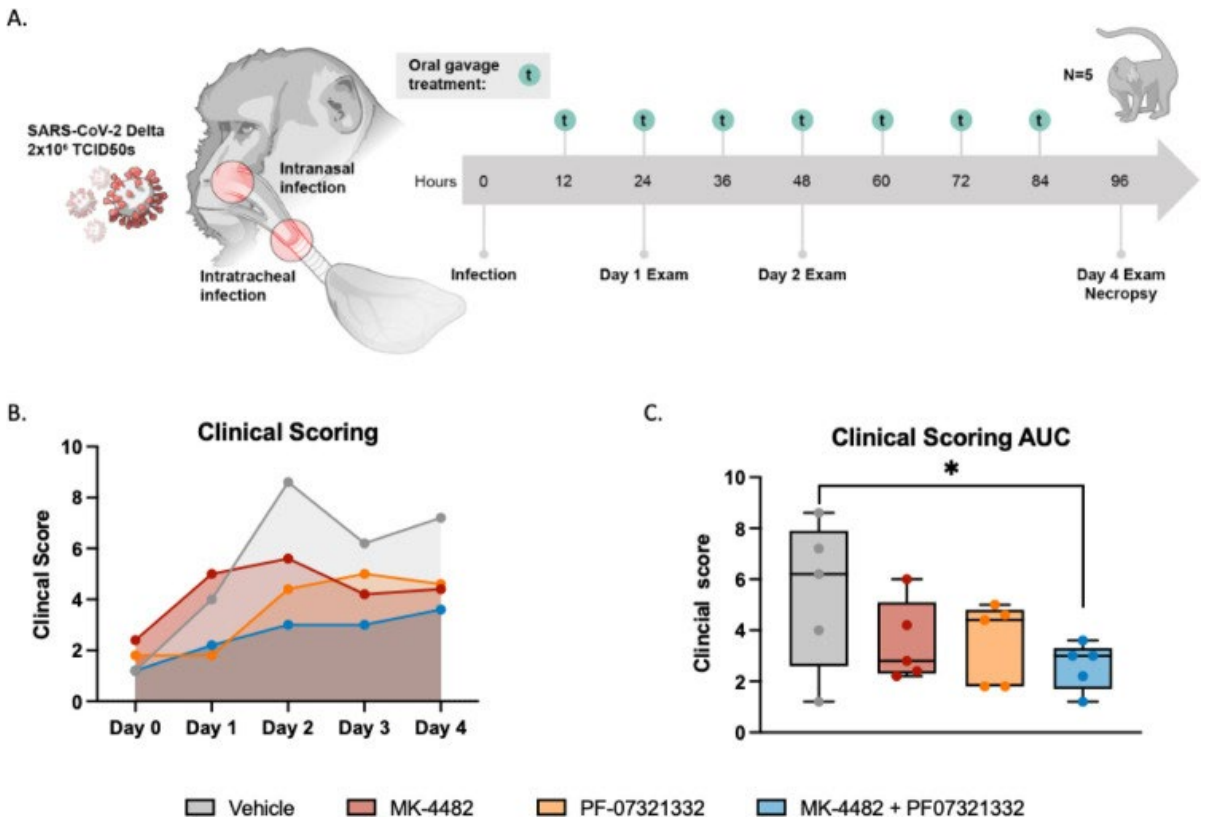
Combination of the parent analogue of remdesivir (GS-441524) and molnupiravir results in a markedly potent antiviral effect in SARS-CoV-2 infected Syrian hamsters



The combined antiviral activity of molnupiravir which acts by inducing lethal mutagenesis and GS-441524, which acts as a chain termination appears to be highly effective in reducing SARS-CoV-2 replication/infectivity. The unexpected potent antiviral effect of the combination warrants further exploration as a potential treatment for COVID-19.

Abdelnabi R, Maes P, de Jonghe S, Weynand B, Neyts J. Combination of the parent analogue of remdesivir (GS-441524) and molnupiravir results in a markedly potent antiviral effect in SARS-CoV-2 infected Syrian hamsters. Front Pharmacol. 2022 Dec 20;13:1072202. doi: 10.3389/fphar.2022.1072202. PMID: 36605401; PMCID: PMC9807602.

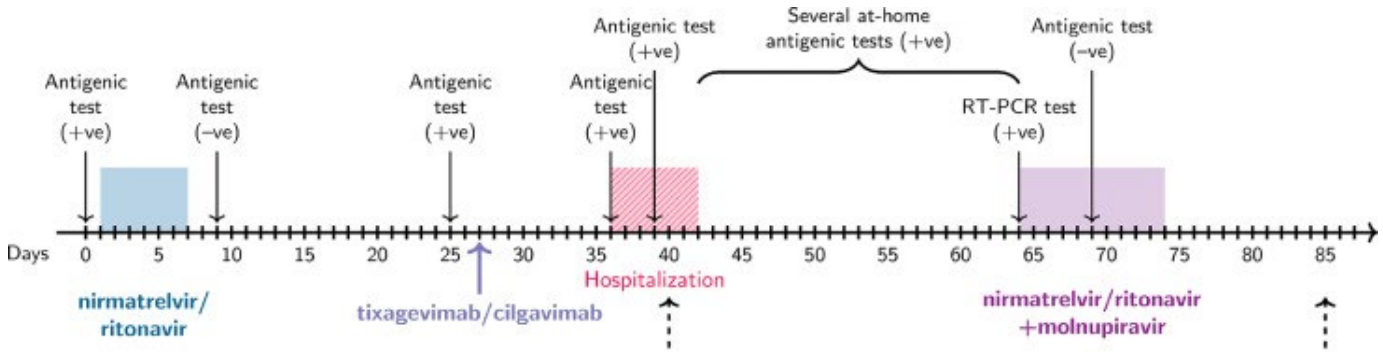
Combined Molnupiravir and Nirmatrelvir Treatment Improves the Inhibitory Effect on SARS-CoV-2 in Rhesus Macaques

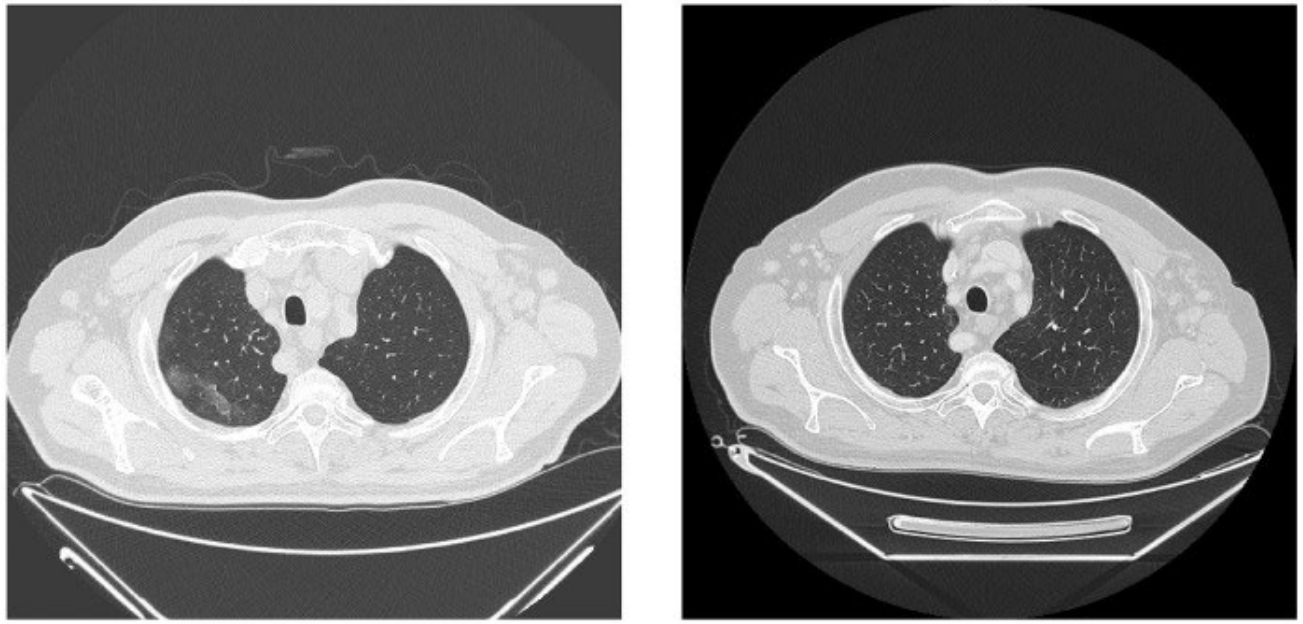


Use of MK-4482 and PF-07321332 in combination improved the individual inhibitory effect of both drugs. Combined treatment resulted in milder disease progression, stronger reduction of virus shedding from mucosal tissues of the upper respiratory tract, stronger reduction of viral replication in the lower respiratory tract, and reduced lung pathology. Our data strongly indicate superiority of combined MK-4482 and PF-07321332 treatment of SARS-CoV-2 infections as demonstrated here in the closest COVID-19 surrogate model.

Rosenke K, Lewis MC, Feldmann F, Bohrnsen E, Schwarz B, Okumura A, Bohler WF, Callison J, Shaia C, Bosio CM, Lovaglio J, Saturday G, Jarvis MA, Feldmann H. Combined Molnupiravir and Nirmatrelvir Treatment Improves the Inhibitory Effect on SARS-CoV-2 in Rhesus Macaques. bioRxiv [Preprint]. 2022 Sep 5:2022.09.03.506479. doi: 10.1101/2022.09.03.506479. Update in: JCI Insight. 2022 Dec 27;: PMID: 36263071; PMCID: PMC9580379.

Combination regimen of nirmatrelvir/ritonavir and molnupiravir for the treatment of persistent SARS-CoV-2 infection: A case report and a scoping review of the literature





Day 40 Day 85

Pending further studies on larger cohorts of patients, our report is consistent with available pre-clinical and clinical data, supporting the possible use of combination therapy in selected difficult-to-treat COVID-19 cases.

Marangoni D, Antonello RM, Coppi M, Palazzo M, Nassi L, Streva N, Povolo L, Malentacchi F, Zammarchi L, Rossolini GM, Vannucchi AM, Bartoloni A, Spinicci M. Combination regimen of nirmatrelvir/ritonavir and molnupiravir for the treatment of persistent SARS-CoV-2 infection: A case report and a scoping review of the literature. Int J Infect Dis. 2023 Aug;133:53-56. doi: 10.1016/j.ijid.2023.04.412. Epub 2023 May 5. PMID: 37150351; PMCID: PMC10198768.

Novel treatment combining antiviral and neutralizing antibody-based therapies with monitoring of spike-specific antibody and viral load for immunocompromised patients with persistent COVID-19 infection

Factors	Patient identification									
	1	2	3	4	5	6	7	8	9	10
Age (years)	51	74	49	94	51	66	72	57	51	84
Sex (male/female)	M	M	F	F	F	F	M	M	M	M
Primary disease	Follicular lymphoma	Follicular lymphoma	Myasthenia gravis	Myasthenia gravis Rheumatoid arthritis	Kidney transplant	Kidney transplant	Kidney transplant	Liver transplant	Chronic myeloid leukemia	Chronic lymphocytic leukemia
Other comorbidity	None	Hypertension	Thyrotoxicosis	Hypertension	Epilepsy	Hypertension	Hypertension Diabetes mellitus	Hypertension Diabetes mellitus Nephrotic syndrome	None	Diabetes mellitus Coronary heart disease
COVID-19 vaccination	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes
Anti-CD20 antibody	Obinutuzumab	Rituximab Obinutuzumab	None	None	None	None	None	None	None	None
Immunosuppressive agents for primary disease	Cyclophosphamide Prednisolone	Cyclophosphamide Prednisolone	Tacrolimus	Tacrolimus Prednisolone	Tacrolimus Mycophenolate mofetil Everolimus Prednisolone	Tacrolimus Mycophenolate mofetil Methylprednisolone	Tacrolimus Mycophenolate mofetil Methylprednisolone	Tacrolimus Mycophenolate mofetil Everolimus	Iguratimod Tocilizumab Prednisolone	Prednisolone
Initial antiviral therapy Switched antiviral therapy	Remdesivir	Remdesivir Nirmatrelvir/Ritonavir	Remdesivir Nirmatrelvir/Ritonavir	Remdesivir Molnupiravir	Remdesivir	Remdesivir Nirmatrelvir/Ritonavir	Remdesivir	Remdesivir Nirmatrelvir/Ritonavir	Remdesivir	Remdesivir
Neutralizing antibody-based therapy	Sotrovimab Casirivimab/Imdevimab	Sotrovimab	Casirivimab/Imdevimab	Casirivimab/Imdevimab	Sotrovimab	Sotrovimab	Sotrovimab	Sotrovimab	Casirivimab/Imdevimab	Sotrovimab
Initial Ct value	18.6	19.8	25.3	18.2	19.6	25	17.9	22.4	15	25.6
Initial spike-specific antibody	Negative	Negative	163 U/mL	Negative	Negative	Negative	Negative	Negative	Negative	1.41 U/mL
Length of antiviral and antibody-based therapy	10 days	14 days	9 days	10 days	10 days	21 days	20 days	18 days	8 days	7 days
Length of hospital stay	14 days	19 days	13 days	28 days	13 days	23 days	43 days	18 days	12 days	17 days

From February 2022, we introduced novel treatment combining antiviral therapies and neutralizing antibodies with frequent monitoring of spike-specific antibody and RT-PCR cycle threshold (Ct) values as indicators of viral load for immunocompromised patients with persistent COVID-19 infection. We applied this treatment to 10 immunosuppressed patients with COVID-19, and all completed treatment without relapse of infection. This may be a potentially successful treatment strategy that enables us to sustain viral clearance, determine optimal timing to stop treatment, and prevent virus reactivation in immunocompromised patients with persistent COVID-19.

Wada, D., Nakamori, Y., Maruyama, S. et al. Novel treatment combining antiviral and neutralizing antibody-based therapies with monitoring of spike-specific antibody and viral load for immunocompromised patients with persistent COVID-19 infection. Exp Hematol Oncol 11, 53 (2022). https://doi.org/10.1186/s40164-022-00307-9

Novel treatment combining antiviral and neutralizing antibody-based therapies with monitoring of spike-specific antibody and viral load for immunocompromised patients with persistent COVID-19 infection

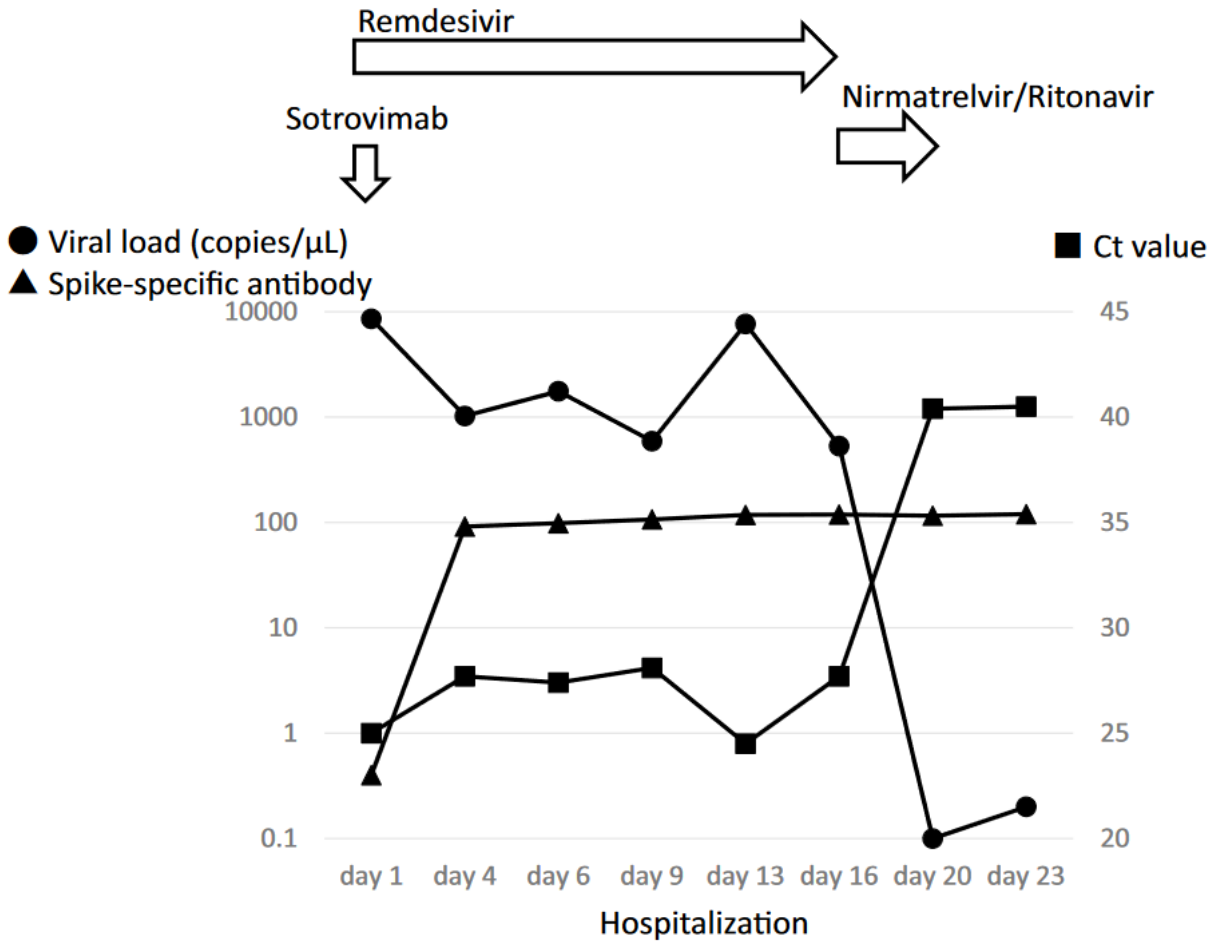


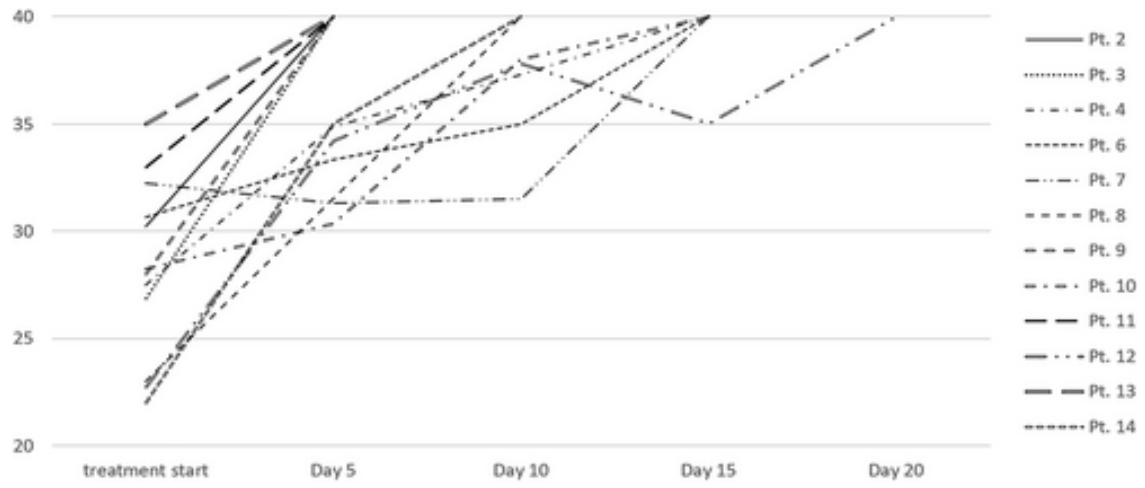
Fig. 1 The graph shows the clinical course of a COVID-19 patient taking tacrolimus hydrate and mycophenolate mofetil as immunosuppressive therapy following kidney transplantation. The round circle indicates viral load, the square indicates Ct value, and the triangle indicates the spike-specific antibody

No patients suffered relapse of the viral infection …

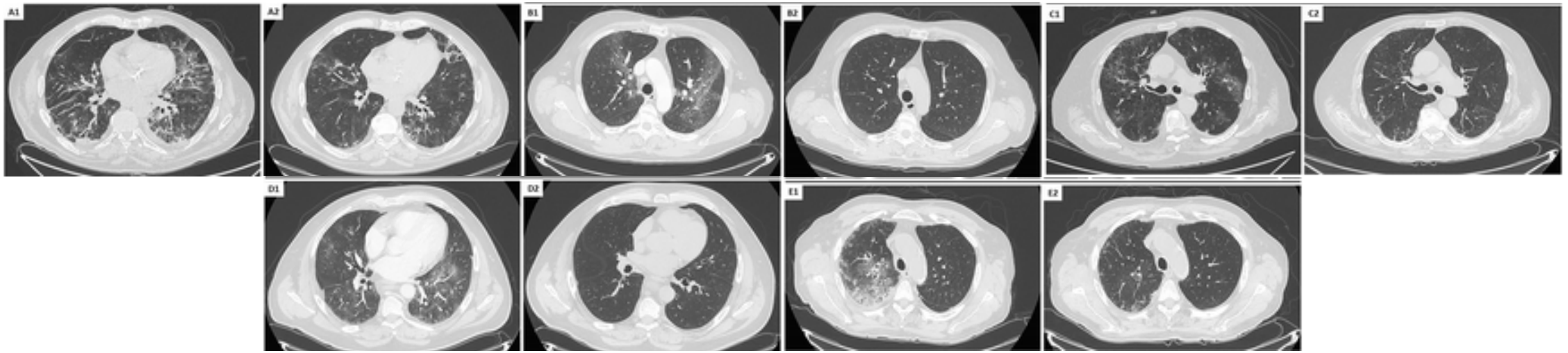
… long-term data on potential viral relapse is unknown.

Wada, D., Nakamori, Y., Maruyama, S. et al. Novel treatment combining antiviral and neutralizing antibody-based therapies with monitoring of spike-specific antibody and viral load for immunocompromised patients with persistent COVID-19 infection. Exp Hematol Oncol 11, 53 (2022). https://doi.org/10.1186/s40164-022-00307-9

Dual combined antiviral treatment with remdesivir and nirmatrelvir/ritonavir in patients with impaired humoral immunity and persistent SARS-CoV-2 infection



All patients showed resolution of COVID-19-related symptoms after a median of 6 (IQR 4–11) days and viral clearance after 9 (IQR 5–11) days. Combination therapy with remdesivir and nirmatrelvir/ritonavir is a promising treatment option for persistent COVID-19 in immunocompromized patients with humoral immunity impairment, worthy of prospective comparative trials.



Pasquini Z, Toschi A, Casadei B, Pellegrini C, D'Abramo A, Vita S, Beccacece A, Bussini L, Chionsini MC, Dentale N, Cantiani A, Lazzarotto T, Bartoletti M, Nicastri E, Zinzani P, Giannella M, Viale P. Dual combined antiviral treatment with remdesivir and nirmatrelvir/ritonavir in patients with impaired humoral immunity and persistent SARS-CoV-2 infection. Hematol Oncol. 2023 Jul 15. doi: 10.1002/hon.3206. Epub ahead of print. PMID: 37452579.

Clinical Infectious Diseases
MAJOR ARTICLE

Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients

Background. Severely immunocompromised patients are at risk for prolonged or relapsed Coronavirus Disease 2019 (COVID-19), leading to increased morbidity and mortality. We aimed to evaluate efficacy and safety of combination treatment in immunocompromised COVID-19 patients.

Methods. We included all immunocompromised patients with prolonged/relapsed COVID-19 treated with combination therapy with 2 antivirals (remdesivir plus nirmatrelvir/ritonavir, or molnupiravir in case of renal failure) plus, if available, anti-spike monoclonal antibodies (mAbs), between February and October 2022. The main outcomes were virological response at day 14 (negative Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2] swab) and virological and clinical response (alive, asymptomatic, with negative SARS-CoV-2 swab) at day 30 and the last follow-up.

Results. Overall, 22 patients (Omicron variant in 17/18) were included: 18 received full combination of 2 antivirals and mAbs and 4 received 2 antivirals only; in 20 of 22 (91%) patients, 2 antivirals were nirmatrelvir/ritonavir plus remdesivir. Nineteen (86%) patients had hematological malignancy, and 15 (68%) had received anti-CD20 therapy. All were symptomatic; 8 (36%) required oxygen. Four patients received a second course of combination treatment. The response rate at day 14, day 30, and last follow-up was 75% (15/20 evaluable), 73% (16/22), and 82% (18/22), respectively. Day 14 and 30 response rates were significantly higher when combination therapy included mAbs. Higher number of vaccine doses was associated with better final outcome. Two patients (9%) developed severe side effects (bradycardia leading to remdesivir discontinuation and myocardial infarction).

Conclusions. Combination therapy including 2 antivirals (mainly remdesivir and nirmatrelvir/ritonavir) and mAbs was associated with high rate of virological and clinical response in immunocompromised patients with prolonged/relapsed COVID-19.

Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, Labate L, Russo C, Mirabella M, Magnasco L, Di Grazia C, Ghiggi C, Raiola AM, Giacobbe DR, Vena A, Beltramini S, Bruzzone B, Lemoli RM, Angelucci E, Bassetti M. Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients. Clin Infect Dis. 2023 Jul 26;77(2):280-286. doi: 10.1093/cid/ciad181. PMID: 36976301.

Variables Associated With Response	Alive and Negative at Day +14 After Treatment (15/20[a] [75%])	Asymptomatic and Negative at Day +30 After Treatment (16/22 [73%])	Alive and Well and Negative at the Last Follow-up (18/22 [82%])
Age	ns	ns	ns
Male sex	8/11 (73)	10/13 (77)	10/13 (77)
NHL as underlying disease [vs other diseases]	10/13 (77)	12/15 (80)	14/15 (93) [vs 4/7 (57), *P* = .077]
HSCT	6/8 (75)	6/9 (67)	6/9 (67)
Active malignancy	3/6 (50)	3/6 (50)	4/6 (67)
Anti-CD20 treatment within 12 m [vs no anti-CD20]	11/13 (85)	13/15 (87) [vs 3/7 (43), *P* = .054]	14/15 (93) [vs 4/7 (57), *P* = .077]
Positive serology[b]	5/7 (71)	5/8 (62)	5/8 (62)
No. of doses of vaccine	ns	ns	***P* = .013**
Previous early therapy [vs no early therapy]	9/13 (69)	8/13 (62)	9/13 (69) [vs 9/9 (100), *P* = .115]
No response to previous treatment	6/8 (65)	5/8 (63)	5/8 (63)
COVID-19 severity WHO grade ≥4 [vs less severe]	4/7 (57)	4/8 (50) [vs 12/14 (86), *P* = .137]	5/8 (63) [vs 13/14 (93), *P* = .117]
Positive viremia	4/7 (57)	4/8 (50)	6/8 (75)
Concomitant microbiologically or clinically documented infection	4/6 (67)	4/6 (67)	4/6 (67)
Concomitant anti-inflammatory treatment [vs no anti-inflammatory treatment]	5/9 (56) [vs 10/11 (91), *P* = .12]	6/11 (55) [vs 10/11 (91), *P* = .149]	8/11 (73)
Therapy with mAbs [vs no mAbs included]	14/16 (87) [vs 1/4 (25), ***P* = .032]**	15/18 (83) [vs 1/4 (25), ***P* = .046]**	16/18 (89) [vs 2/4 (50), *P* = .135]

All data shown as No. (%). Values in bold indicate statistical significance.

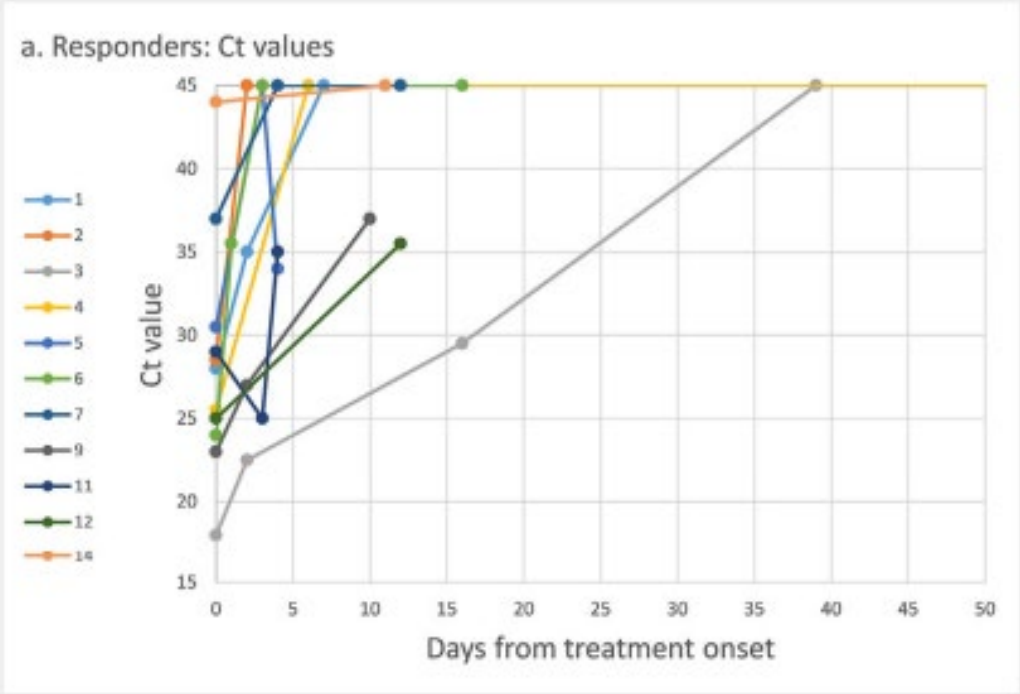
Abbreviations: COVID-19, Coronavirus Disease 2019; HSCT, hematopoietic stem cell transplant; mAbs, anti-S monoclonal antibodies; NHL, non-Hodgkin lymphoma; ns, not significant; WHO, World Health Organization.

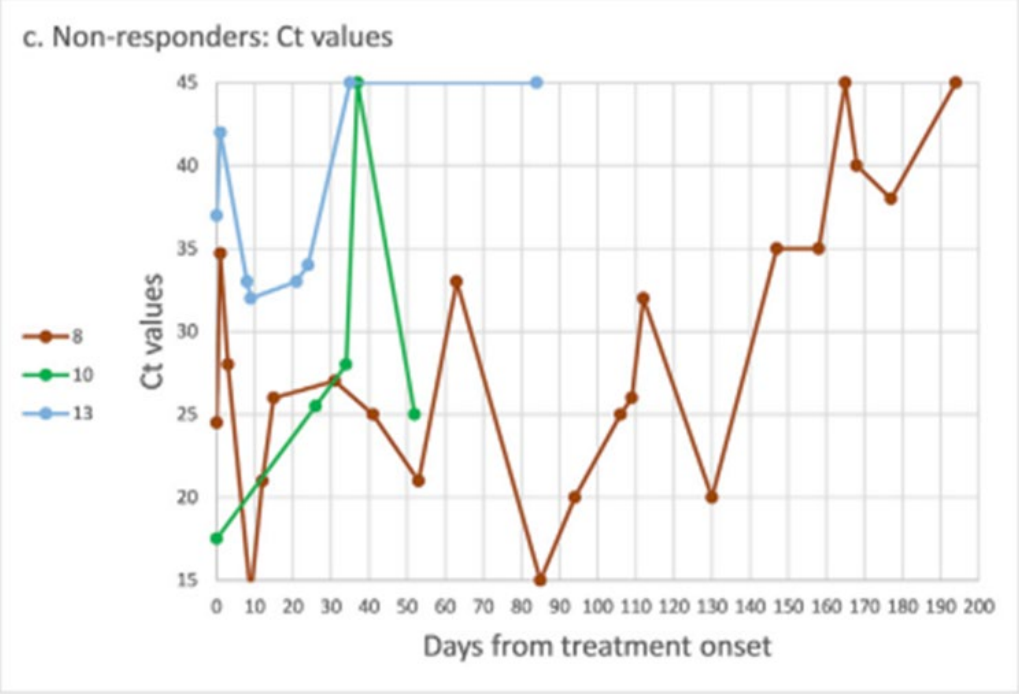
[a]Data applicable to 21 patients since 2 patients with NHL had negative swab and positive bronchoalveolar lavage fluid.

[b]Missing in 1. *P* value shown only if ≤.15.

Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, Labate L, Russo C, Mirabella M, Magnasco L, Di Grazia C, Ghiggi C, Raiola AM, Giacobbe DR, Vena A, Beltramini S, Bruzzone B, Lemoli RM, Angelucci E, Bassetti M. Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients. Clin Infect Dis. 2023 Jul 26;77(2):280-286. doi: 10.1093/cid/ciad181. PMID: 36976301.

Combination treatment of persistent COVID-19 in immunocompromised patients with remdesivir, nirmaltrevir/ritonavir and tixegavimab/cilgavimab

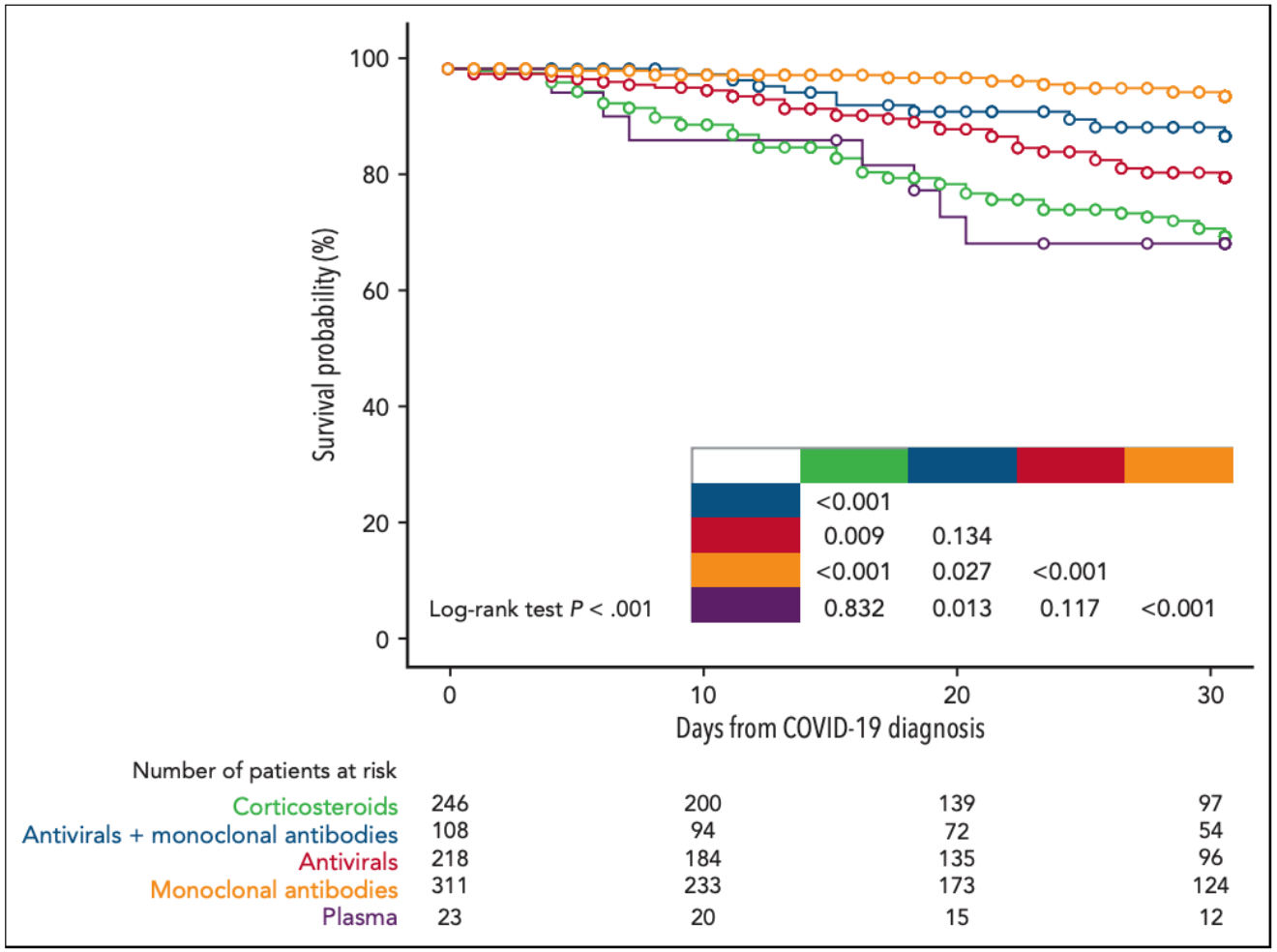




The study analyzed data from 14 patients who received a combination of tixegavimab/cilgavimab and antiviral medications after 0-77 days from symptom onset. Response was evaluated based on symptom improvement, PCR cycle-threshold values, and C-reactive protein levels. Eleven patients achieved complete clinical and virological resolution, while three showed partial responses. The study suggests a potential association between non-response and tixegavimab/cilgavimab neutralization. The findings underscore the need for tailored treatment approaches and further research on optimal strategies for managing persistent COVID-19, as well as the development of antivirals and variant-specific monoclonal antibodies.

Brosh-Nissimov T, Ma'aravi N, Leshin-Carmel D, Edel Y, Ben Barouch S, Segman Y, Cahan A, Barenboim E. Combination treatment of persistent COVID-19 in immunocompromised patients with remdesivir, nirmaltrevir/ritonavir and tixegavimab/cilgavimab. J Microbiol Immunol Infect. 2023 Sep 27:S1684-1182(23)00170-6. doi: 10.1016/j.jmii.2023.09.004. Epub ahead of print. PMID: 37805361.

Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from EPICOVIDEHA survey



Number patients at risk

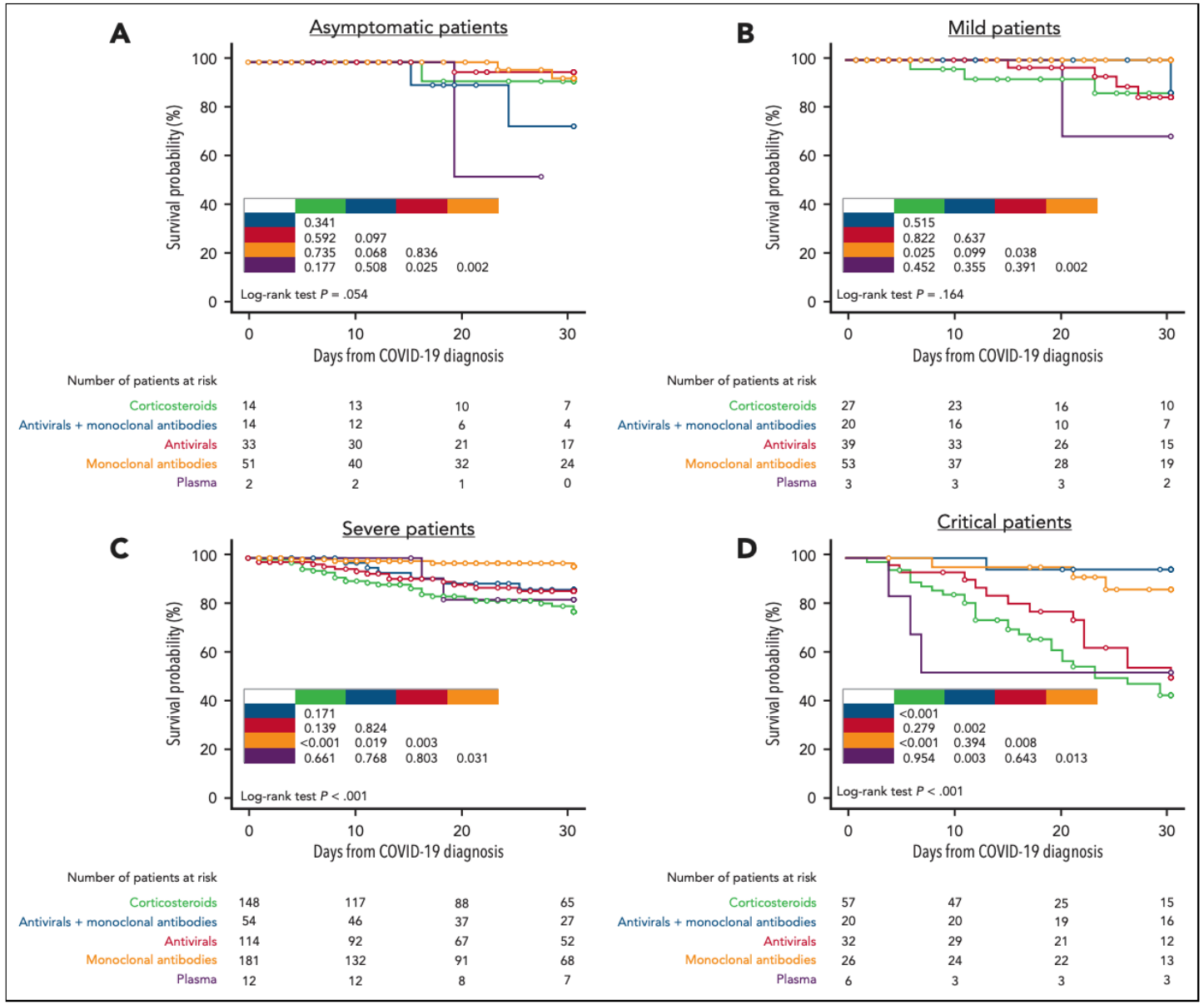
Monoclonal antibodies	311
Antivirals + MoAb	108
Antivirals	218
Corticosteroids	246
Plasma	23

blood

Pagano L, et al. Blood 2022

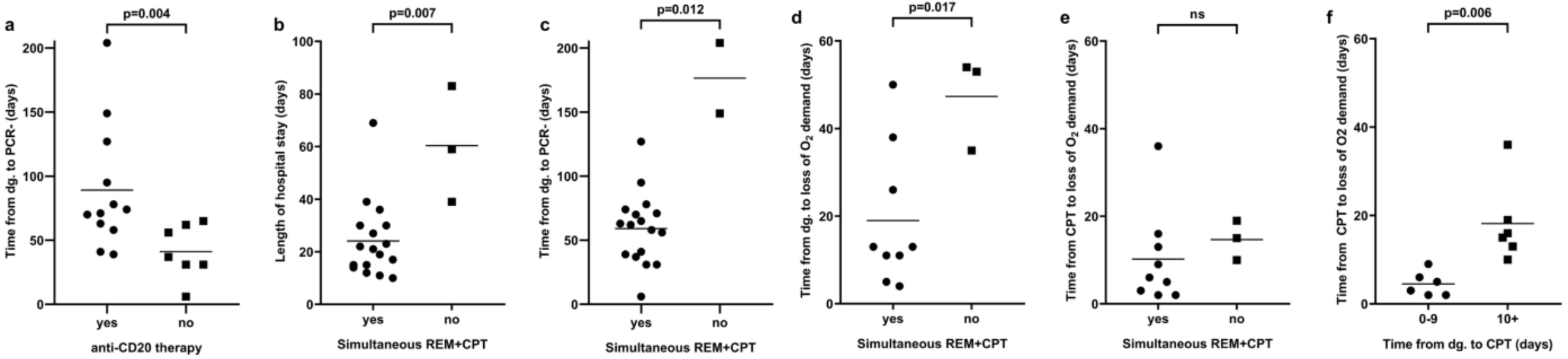
A total of 1,548 cases were included from several EU countries from 01. 2021 to 03. 2022: the mortality rate in HM patients with breakthrough COVID-19 was about 9%, lower than in the pre-vaccination era. In the multivariable model, older age, active disease, critical COVID-19, and 2-3 comorbidities were correlated with a higher mortality, whereas monoclonal antibody administration, alone ($P < .001$) or combined with antivirals ($P = .009$), was protective.

Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from EPICOVIDEHA survey



Pagano L, et al. Blood 2022

Early administration of remdesivir plus convalescent plasma therapy is effective to treat COVID-19 pneumonia in B-cell depleted patients with hematological malignancies



The combination of inhibition of viral replication with passive immunization was proved to be efficient and safe. Our results suggest the clear benefit of early, combined administration of remdesivir and convalescent plasma to avoid protracted COVID-19 disease among patients with HMs and B-cell lymphopenia.

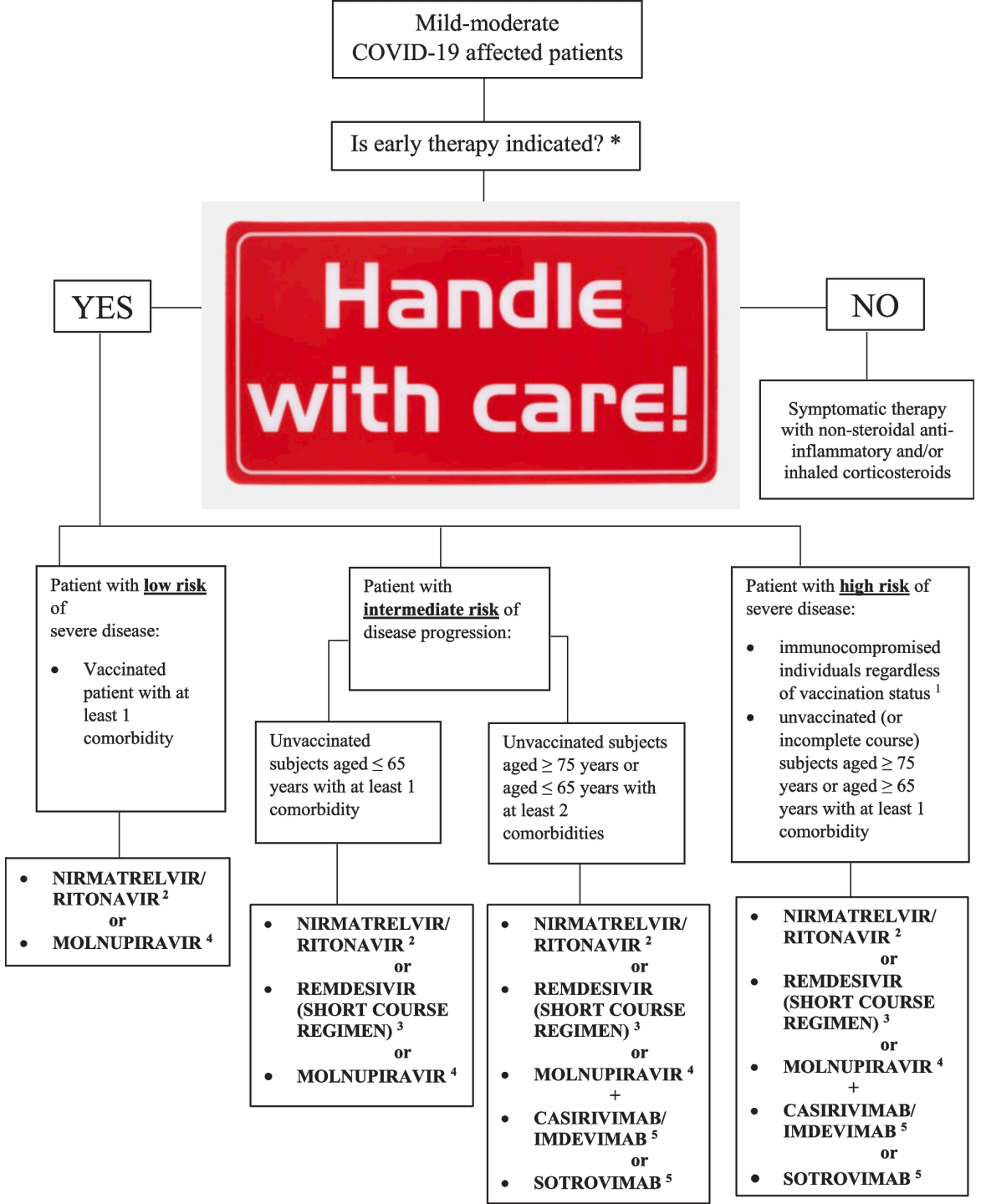
Magyari, F., Pinczés, L.I., Páyer, E. et al. Early administration of remdesivir plus convalescent plasma therapy is effective to treat COVID-19 pneumonia in B-cell depleted patients with hematological malignancies. Ann Hematol 101, 2337–2345 (2022). https://doi.org/10.1007/s00277-022-04924-6

Treat early and hard!

RESEARCH ARTICLE Open Access

Lessons learned and implications of early therapies for coronavirus disease in a territorial service centre in the Calabria region: a retrospective study

Vincenzo Scaglione[1], Salvatore Rotundo[1], Nadia Marascio[2], Carmela De Marco[3], Rosaria Lionello[1], Claudia Veneziano[3], Lavinia Berardelli[1], Angela Quirino[2], Vincenzo Olivadese[1], Francesca Serapide[1], Bruno Tassone[1], Helen Linda Morrone[1], Chiara Davoli[1], Valentina La Gamba[1], Andrea Bruni[4], Bruno Mario Cesana[5], Giovanni Matera[2], Alessandro Russo[1], Francesco Saverio Costanzo[6], Giuseppe Viglietto[3], Enrico Maria Trecarichi[1], Carlo Torti[1*] and IDTM U. M. G. COVID-19 Group



Scaglione et al. BMC Infectious Diseases 2022, 22(1):793
https://doi.org/10.1186/s12879-022-07774-9

- Median (IQR) from positive nasopharyngeal swab to treatment was 2 (1-3) days (earlier than in other studies[1-3]).
- Only 2/48 (4.2%) patients were admitted to the hospital and only 1 patient died in a short term observation up to negativisation of the NP swab.
- These outcomes were strikingly better than expected considering that our patients suffered from severe immunocompromising conditions including hematological malignancies (31/48, 64.6%), solid (8/48, 16.7%) or hematopoietic stem cell (3/48, 6.2%) transplantations, and/or were taking immunosuppressive treatments, such as anti-CD20 monoclonal antibodies (24/48, 50%).
- Patients turned negative after a median of 11 (IQR: 6–17) days from the start of combined therapy without reporting severe side effects.

1. Mikulska M, et al. Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus Infection in Immunocompromised Patients. Clin Infect Dis. 2023;77(2):280-6. 2. Tal B-N, et al. Combination treatment of persistent COVID-19 in immunocompromised patients with remdesivir, nirmaltrevir/ritonavir and tixegavimab/cilgavimab. medRxiv. 2023:2023.04.07.23288144. 3. Gentile I, et al. Early combination with remdesivir, nirmatrelvir/ritonavir and sotrovimab for the treatment of COVID-19 in immunocompromised hosts. medRxiv. 2023:2023.09.07.23295202.

Unpublished data, submitted for publication

Early combination with remdesivir, nirmatrelvir/ritonavir and sotrovimab for the treatment of COVID-19 in immunocompromised hosts

Ivan Gentile[1], Maria Foggia[1], Maria Silvitelli[1], Alessia Sardanelli[1], Letizia Cattaneo[1], Giulio Viceconte[1*], and Federico II COVID team[†]

Background: Immunocompromised patients with COVID-19 have higher morbidity and mortality than general population. Some authors have successfully used antiviral combination, but never in the early phase of the infection.

Methods: Retrospective cohort study to describe efficacy and safety of the combination of 2 antivirals, with or without a mAb, both in early (within 10 days from symptoms) and in later phase (after 10 days) of SARS-CoV-2 infection in immunocompromised patients admitted to our facility.

Results: We treated 11 patients (7 in early phase and 4 in later phase of COVID-19) with 10 days of intravenous remdesivir plus 5 days of oral nirmatelvir/ritonavir, also combined with sotrovimab in 10/11 cases.

Notably, 100% of the "early" patients reached virological clearance at day 30 from the end of the therapy and were alive and well at follow-up, whereas corresponding figures in the "late" patients were 50% and 75%. Patients in late group more frequently needed oxygen supplementation (p=0.015) and steroid therapy (p=0.045) during admission and reached higher a COVID-19 severity (p=0.017).

Discussion: The combination of antiviral and sotrovimab in early phase of COVID-19 in immunocompromised patients is well tolerated and associated with 100% of virological clearance. Patients treated later have lower response rate and higher disease severity, but a causative role of the therapy in such finding is yet to be demonstrated.

	Overall N=11	Early combination treatment N=7	Late combination treatment N=4	p-value
Age, years, median (IQR)	51 (36-57)	52 (35-56)	63 (42-77)	0.667
Females, n (%)	5 (45.5)	3 (43)	2 (50)	0.652
Charlson Comorbidity Index, median (IQR)	0.5 (0-1.25)	0 (0-1)	2 (0.25-3)	0.517
Vaccinated, n (%)	8 (72)	5 (71)	3 (75)	0.721
SARS-CoV-2 vaccine doses, median (IQR)	3 (3)	3 (3)	3 (3)	1
Hematologic malignancy				
Acute myeloid leukemia	3 (27)	3 (42)	0 (0)	0.3
Non-Hodgkin lymphoma	4 (36)	2 (28)	2 (50)	0.646
Chronic lymphatic leukemia	1 (9)	1 (14)	0 (0)	0.308
Multiple myeloma	1 (9)	0 (0)	1 (25)	0.462
Other immunodeficiencies, n (%)	2 (18)	1 (14)	1 (25)	0.538
Use of anti-CD20, n (%)	2 (18)	0 (0)	2 (50)	0.109
Deaths, n (%)	0 (0)	0 (0)	0 (0)	
Length of stay, days, median (IQR)	14 (12.5-23)	13 (11.5-16.5)	21 (12.5-38)	0.2
Early COVID-19 therapy, n (%)	1 (9)	0 (0)	1 (25)	0.364
Preventive TIX-CIL, n (%)	1 (9)	1 (14)	0 (0)	0.325
Previous therapy for COVID-19, n (%)	3 (27)	0 (0)	3 (75)	0.8
Days from COVID-19 symptoms to combination therapy, median (IQR)	9 (3.75-48)	5 (3-9)	79 (48-112)	0.017
Remdesivir 10 d + N/r, n (%)	11	7	4	
Remdesivir 10 d + N/r + Sotrovimab, n (%)	10	6	4	
SARS-CoV-2 infection duration from the end of therapy, days, median (IQR)	10 (7-22.5)	11 (8-28)	8 (3.75-16)	0.183
Negative NFS at 14d, n (%)	4 (36.4)	4 (57)	0 (0)	0.106
Negative NFS at 30d, n (%)	9 (81)	7 (100)	2 (50)	0.109
alive and well at FU, n (%)	10 (90)	7 (100)	3 (75)	0.364
Days of follow up, median (IQR)	44 (10-92)	40 (1-81)	65 (11-108)	0.183
Use of immunomodulatory drug for COVID-19, n (%)	2 (18)	0 (0)	2 (50)	0.109
COVID-19 steroid treatment, n (%)	6 (54)	2 (29)	4 (100)	0.045
Worst WHO severity grade, median (IQR)	3 (3-4.2)	3 (3)	4.5 (4-5)	0.017
Need for O2, n (%)	5 (45.5)	1 (14)	4 (100)	0.015
ADR, n (%)	1 (9)	1 (14)	0	0.636
Lowest lymphocyte value, cells/mm^3, median (IQR)	0.39 (0.15-0.9)	0.68 (0.2-1.2)	0.16 (0.07-0.32)	0.067
Highest CRP value, mg/dL, median (IQR)	3.8 (0.3-15)	2.3 (0.3-5)	17 (8-23.4)	0.117
Highest LDH value, IU/mL, median (IQR)	287 (231-446)	251 (225-436)	488 (297-708)	0.267
Highest ferritin value, median (IQR)	495 (302-1635)	424 (253-907)	2000 (542-2000)	0.286
Highest D-dimer, median (IQR)	863 (571-1580)	620 (571-1658)	1422 (1084-1931)	0.383

J Antimicrob Chemother 2023; **78**: 1454–1459
https://doi.org/10.1093/jac/dkad105 Advance Access publication 13 April 2023

Journal of Antimicrobial Chemotherapy

Current outcomes of SARS-CoV-2 Omicron variant infection in high-risk haematological patients treated early* with antivirals

*≤10 days from symptom onset

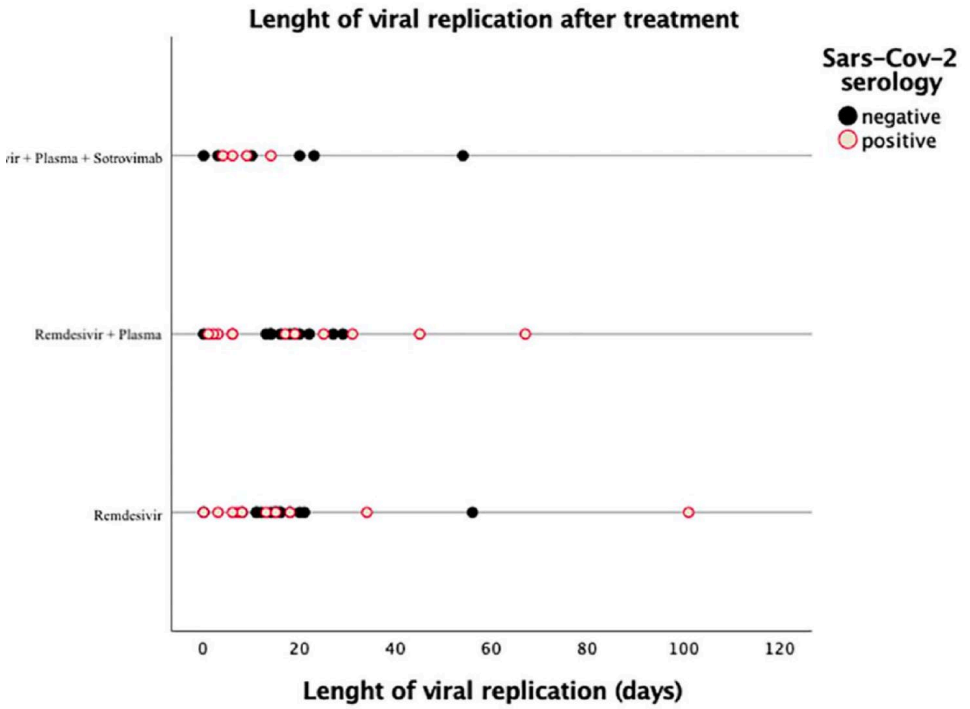
Tommaso-Francesco Aiello[1]†, Pedro Puerta-Alcalde [1], Mariana Chumbita[1], Carlos Lopera[1], Patricia Monzó[1], Albert Cortes[2], Francesc Fernández-Avilés[2], María Suárez-Lledó[2], Juan Correa[2], Valentín Ortiz-Maldonado [2], Genoveva Cuesta [3], Nuria Martinez-Cibrian[2], Jordi Esteve[2], Maria Ángeles Marcos[3], Josep Mensa[1], Alex Soriano [1,4] and Carolina Garcia-Vidal[1]*†; on behalf of 'COVID-19-researcher group'‡

Objectives: We aimed to describe the clinical outcomes and duration of viral shedding in high-risk patients with haematological malignancies hospitalized with COVID-19 during Omicron variant predominance who received early treatment with antivirals.

Methods: We conducted a prospective observational study on high-risk haematological patients admitted in our hospital between December 2021 and March 2022. We performed detection techniques on viral subgenomic mRNAs until negative results were obtained to document active, prolonged viral replication.

Results: This analysis included 60 consecutive adults with high-risk haematological malignancies and COVID-19. All of these patients underwent early treatment with remdesivir. Thirty-two (53%) patients received combined antiviral strategies, with sotrovimab or hyperimmune plasma being added to remdesivir. The median length of viral replication—as measured by real-time RT-PCR and/or subgenomic RNA detection—was 20 (IQR 14–28) days. Prolonged viral replication (6 weeks after diagnosis) was documented in six (10%) patients. Only two patients had prolonged infection for more than 2 months. Overall mortality was 5%, whereas COVID-19-related mortality was 0%.

Conclusions: Current outcomes of high-risk patients with haematological malignancies hospitalized with COVID-19 during Omicron variant predminance are good with the use of early antiviral strategies. Persistent viral shedding is uncommon.



Real-World Experience of the Comparative Effectiveness and Safety of Combination Therapy with Remdesivir and Monoclonal Antibodies versus Remdesivir Alone for Inpatients with Mild-to-Moderate COVID-19 and Immunosuppression: A Retrospective Single-Center Study in Aichi, Japan

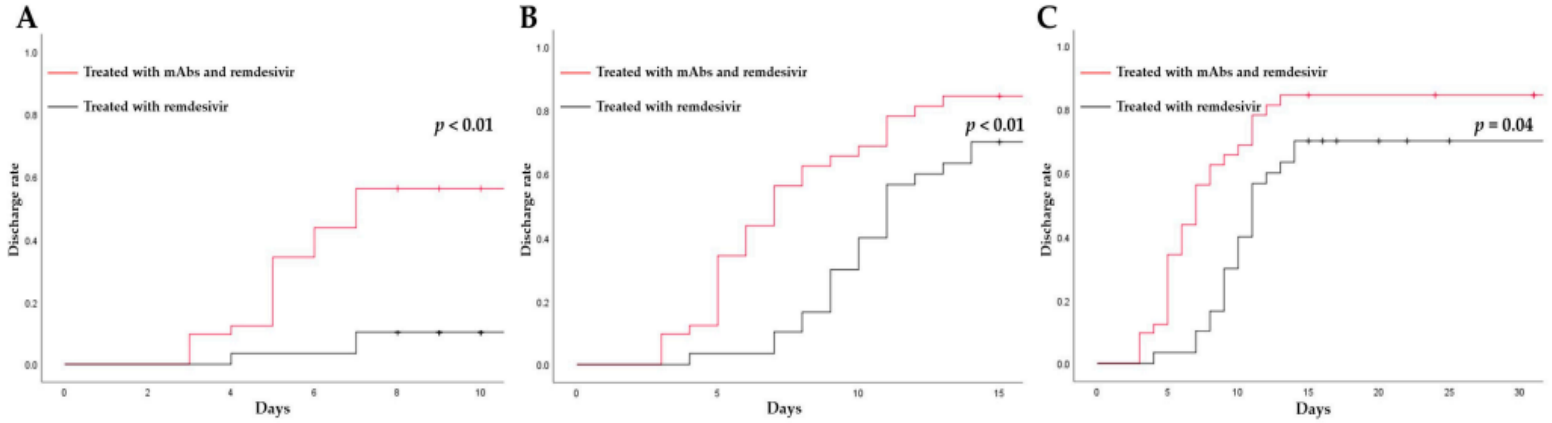


Figure 1. (**A**) The 7-day hospital discharges of CTG and MTG patients. (**B**) The 14-day hospital discharges of CTG and MTG patients. (**C**) The 28-day hospital discharges of CTG and MTG patients. CTG, combination therapy group; mAbs, monoclonal antibodies; MTG, monotherapy group.

Variables	All (n = 86)	Combination (n = 35)	Remdesivir Alone (n = 51)	p-Value
Adverse event:	4 (4.6)	2 (5.7)	2 (3.9)	0.69
-Liver dysfunction	2 (2.3)	1 (2.8)	1 (1.9)	0.78
-Kidney damage	1 (1.2)	1 (2.8)	0	0.22
-Infusion reaction	1 (1.2)	0	1 (1.9)	0.40

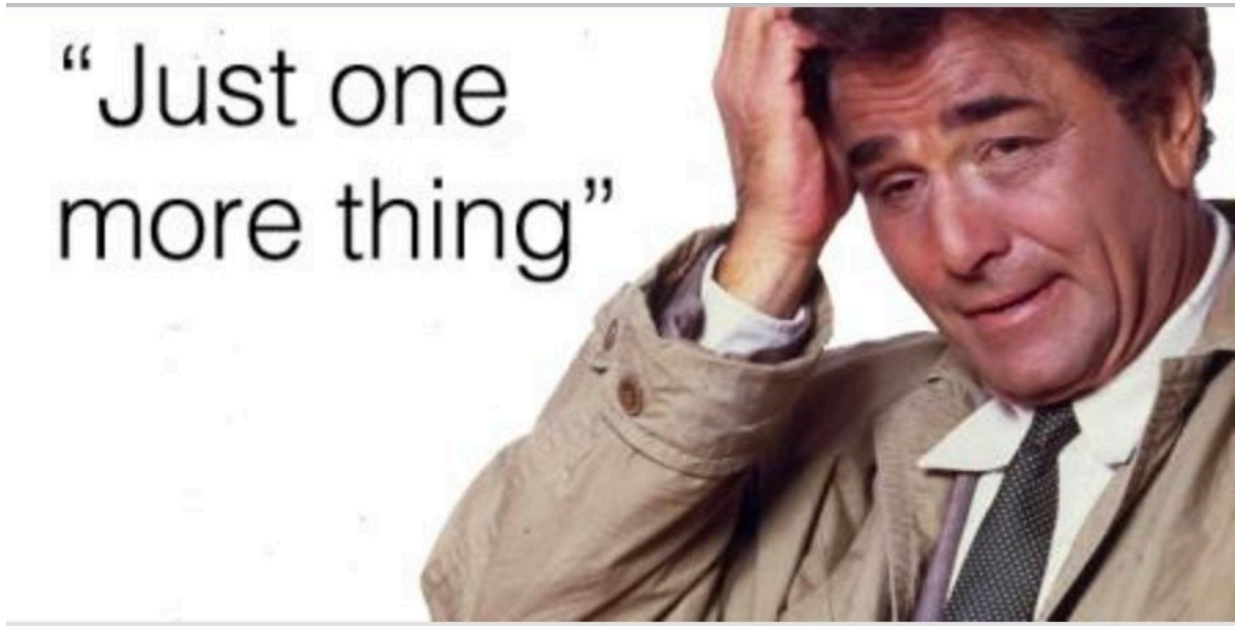
Eighty-six patients treated in July 2021–March 2023 were analyzed. The mean number of **days from COVID-19 onset to treatment was approximately 1.5 days in each group.**

The combination therapy group (CTG) showed a statistically significant reduction in viral load compared with the monotherapy group (MTG) (p < 0.01). Patients in the CTG also experienced earlier resolution of fever than those in the MTG (p = 0.02), although this difference was not significant in the multivariate analysis (p = 0.21).

Additionally, the CTG had significantly higher discharge rates on days 7, 14, and 28 than the MTG (p < 0.01, p < 0.01, and p = 0.04, respectively). No serious adverse events were observed with combination therapy.

Hirai J, Mori N, Sakanashi D, Ohashi W, Shibata Y, Asai N, Kato H, Hagihara M, Mikamo H. Real-World Experience of the Comparative Effectiveness and Safety of Combination Therapy with Remdesivir and Monoclonal Antibodies versus Remdesivir Alone for Patients with Mild-to-Moderate COVID-19 and Immunosuppression: A Retrospective Single-Center Study in Aichi, Japan. Viruses. 2023 Sep 19;15(9):1952. doi: 10.3390/v15091952. PMID: 37766358; PMCID: PMC10538070.

Whether combination therapy will prevent resistance is not yet known…



Early combination therapy: a double edge sword for emerging resistance (and dissemination)?

… toxicity/tolerability reduction or increase?

… cost reduction or cost increase?

… what is the impact on post-COVID-19 syndromes?

… can active immunization dilute its possible impact?

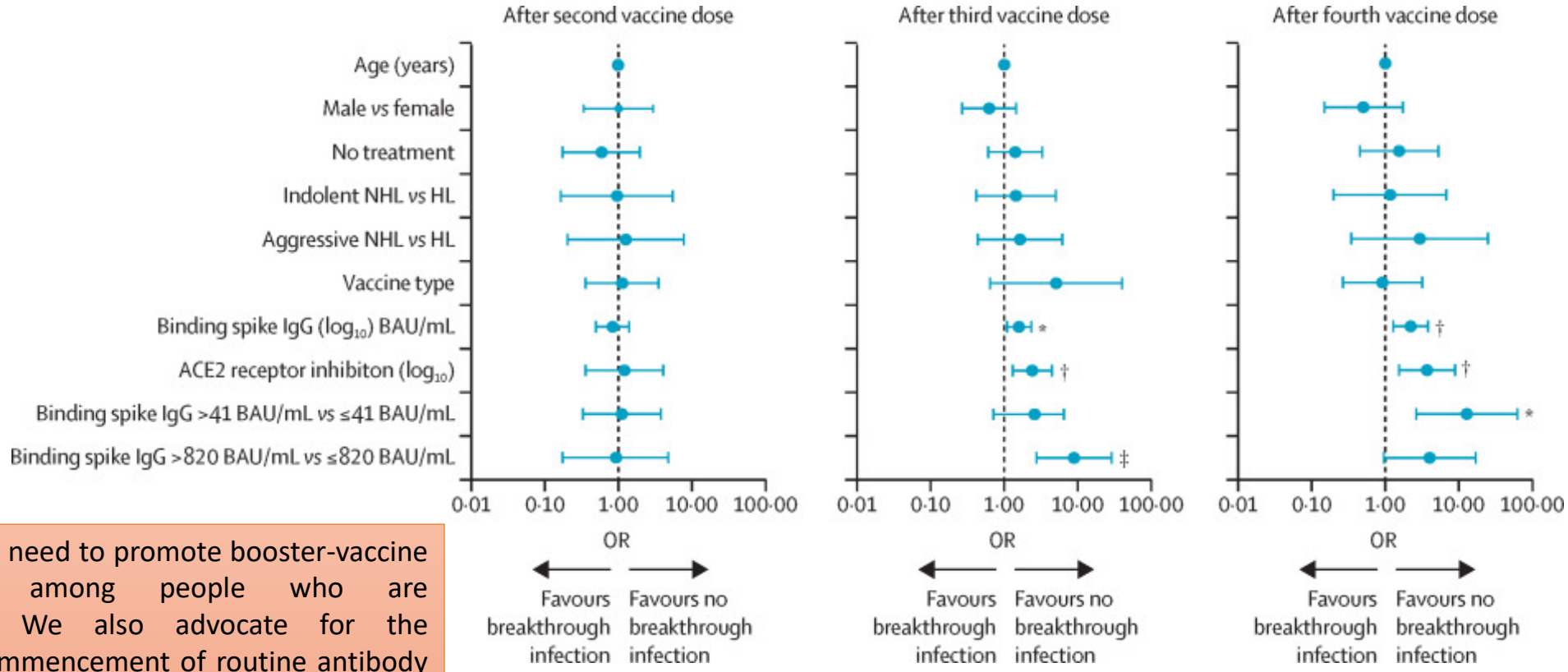
… antiviral + mAbs vs. antiviral + hyperimmune convalescent serum vs. antiviral combo? **Which combo?**

… targeted to virus and individual patient characteristics?

… who is most at risk or benefit the most?

Predicting COVID-19 infection risk in people who are immunocompromised by antibody testing

Factors associated with COVID-19 breakthrough infection after second, third, and fourth vaccine doses



These data support the need to promote booster-vaccine uptake, particularly among people who are immunocompromised. We also advocate for the standardisation and commencement of routine antibody testing in people who are immunocompromised to enable precise risk delineation for individuals and focusing of efforts to protect the most vulnerable groups.

… can active immunization dilute its possible impact?

Wijaya R, Johnson M, Campbell N, Stuart B, Kelly A, Tipler N, Menne T, Ahearne MJ, Willimott V, Al-Naeeb AB, Fox CP, Collins GP, O'Callaghan A, Davies AJ, Goldblatt D, Lim SH; PROSECO investigators. Predicting COVID-19 infection risk in people who are immunocompromised by antibody testing. Lancet. 2023 Jul 8;402(10396):99-102. doi: 10.1016/S0140-6736(23)01180-7. Epub 2023 Jun 29. PMID: 37393922.

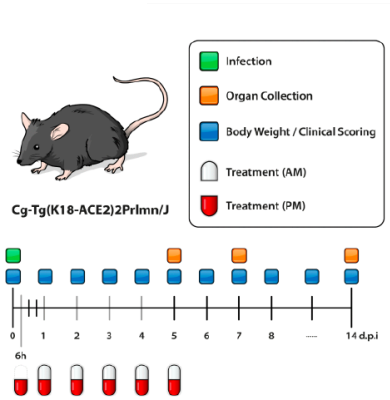
Combination therapy with nirmatrelvir and molnupiravir improves the survival of SARS-CoV-2 infected mice

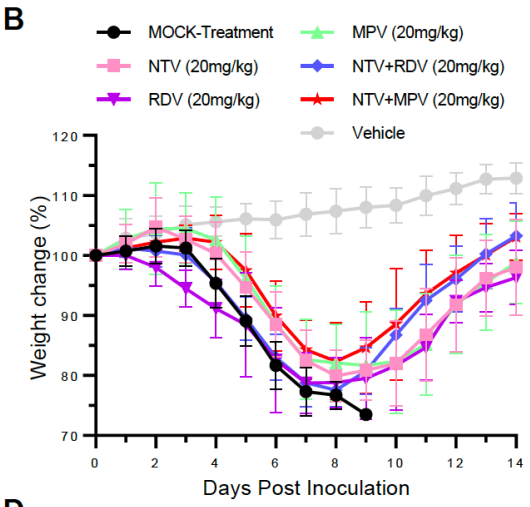
Ju Hwan Jeong [a,1], Santosh Chokkakula [a,1], Seong Cheol Min [a], Beom Kyu Kim [a], Won-Suk Choi [a], Sol Oh [a], Yu Soo Yun [a], Da Hyeon Kang [a], Ok-Jun Lee [b], Eung-Gook Kim [c], Jang-Hoon Choi [d], Joo-Yeon Lee [e], Young Ki Choi [a,f], Yun Hee Baek [a], Min-Suk Song [a,*]

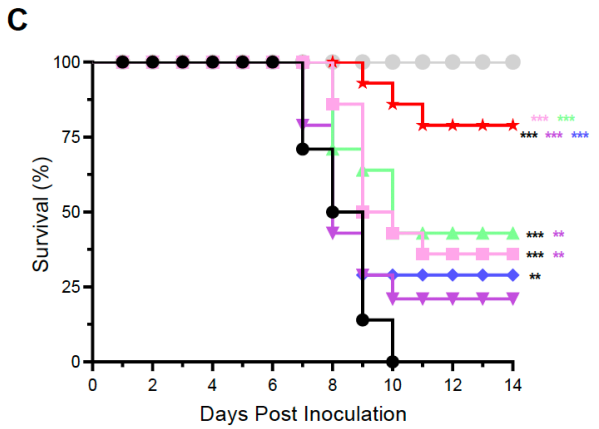
Which combo?

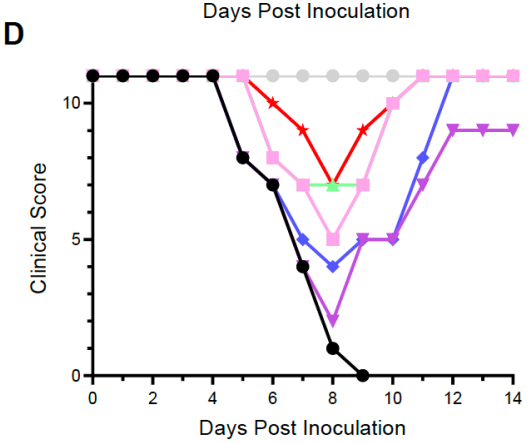
Evaluati rapeutic efficacy of nirmatrelvir, remdesivir, and molnupiravir mon tions, nirmatrelvir-remdesivir, and nirmatrelvir-molnupiravir, in SARS nsgenic mice. **(A)** Schematic illustration of the study design. Mice we RS-CoV-2 followed by administration of 20 mg/kg drugs for 5 cons and other clinical parameters were monitored until 14 DPI, and the DPI for viral titer estimation and histopathological and immunohisto eight was monitored daily for 14 days and is expressed as a percentag ht on day 0. **(C)** Kaplan–Meier plot of the survival of all the groups 0.01, ***$p < 0.001$). **(D)** The clinical score was evaluated by assessing activity, and movement from 0 DPI to 14 DPI, and the cumulative clin ce in each group is indicated.

The nirmatrelvir and remdesivir combination showed less antiviral efficacy, with lower survival compared to nirmatrelvir monotherapy, demonstrating the inefficient therapeutic effect of this combination.









Antiviral Research 208 (2022) 105430

Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2

nature

https://doi.org/10.1038/s41586-022-04482-x

Received: 22 October 2021

Accepted: 26 January 2022

Published online: 7 February 2022

David C. Schultz[1]✉, Robert M. Johnson[2,8], Kasirajan Ayyanathan[3,8], Jesse Miller[3,8], Kanupriya Whig[1], Brinda Kamalia[1], Mark Dittmar[3], Stuart Weston[2], Holly L. Hammond[2], Carly Dillen[2], Jeremy Ardanuy[2], Louis Taylor[2], Jae Seung Lee[3], Minghua Li[3], Emily Lee[4], Clarissa Shoffler[5], Christopher Petucci[5], Samuel Constant[6], Marc Ferrer[4], Christoph A. Thaiss[7], Matthew B. Frieman[2]✉ & Sara Cherry[1,3,7]✉

The SARS-CoV-2 virus has infected more than 261 million people and has led to more than 5 million deaths in the past year and a half[1] (https://www.who.org/). Individuals with SARS-CoV-2 infection typically develop mild-to-severe flu-like symptoms, whereas infection of a subset of individuals leads to severe-to-fatal clinical outcomes[2]. Although vaccines have been rapidly developed to combat SARS-CoV-2, there has been a dearth of antiviral therapeutics. There is an urgent need for therapeutics, which has been amplified by the emerging threats of variants that may evade vaccines. Large-scale efforts are underway to identify antiviral drugs. Here we screened approximately 18,000 drugs for antiviral activity using live virus infection in human respiratory cells and validated 122 drugs with antiviral activity and selectivity against SARS-CoV-2. Among these candidates are 16 nucleoside analogues, the largest category of clinically used antivirals. This included the antivirals remdesivir and molnupiravir, which have been approved for use in COVID-19. RNA viruses rely on a high supply of nucleoside triphosphates from the host to efficiently replicate, and we identified a panel of host nucleoside biosynthesis inhibitors as antiviral. Moreover, we found that combining pyrimidine biosynthesis inhibitors with antiviral nucleoside analogues synergistically inhibits SARS-CoV-2 infection in vitro and in vivo against emerging strains of SARS-CoV-2, suggesting a clinical path forward.

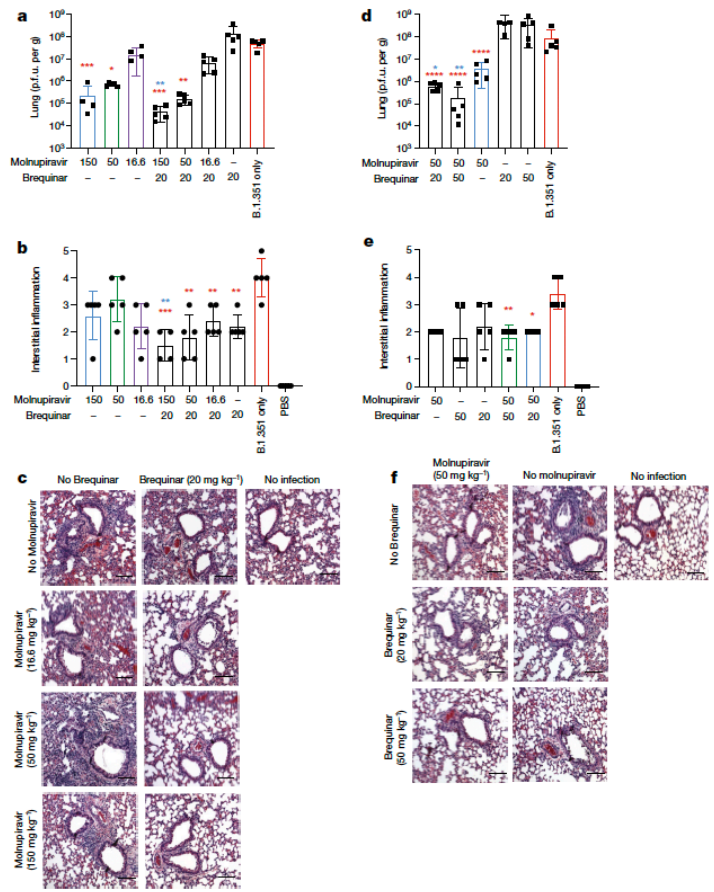
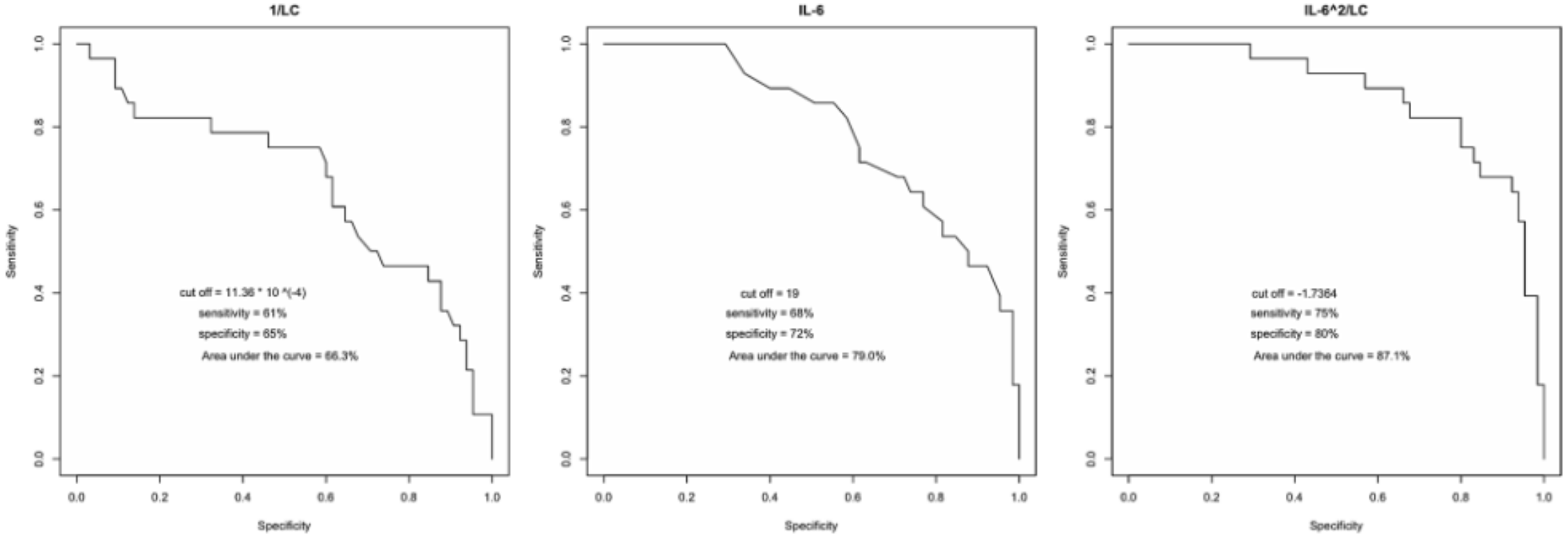


Fig. 4 | Combination of molnupiravir and Brequinar reduces SARS-CoV-2 infection and inflammation in vivo. Wild-type BALB/C mice were treated with Brequinar (intraperitoneal administration) and/or molnupiravir (oral administration) daily at the indicated concentrations starting 12 h before infection. Mice ($n = 5$ per group over 2 independent experiments) were intranasally inoculated with 1×10^5 p.f.u. per mouse of SARS-CoV-2 (B.1.351). **a**–**f**, Lungs were analysed for viral titre 2 days after infection by plaque assay (**a**, **d**) or fixed in 4% paraformaldehyde for haematoxylin and eosin staining and quantified for interstitial inflammation (**b**, **c**, **e**, **f**). $n = 5$ mice per group. Mean ± s.d. is shown. $^*P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$, using non-parametric one-way ANOVA with Dunnett's multiple comparison test. The red asterisks are compared to vehicle; the blue asterisks are compared to molnupiravir. *P* values are listed in Extended Data Fig. 8d. Scale bars, 200 µM.

Interleukin-6^2/lymphocyte as a proposed predictive index for COVID-19 patients treated with monoclonal antibodies

… targeted to virus and individual patient characteristics?



… prospective, randomized studies are needed to confirm whether interventions with new treatment strategies (for example, combining antivirals with moAbs) will further improve patient outcomes when used at earlier stages of the disease under the guide of new biomarkers.

Rotundo S, Borelli M, Scaglione V, Lionello R, Biamonte F, Olivadese V, Quirino A, Morrone HL, Matera G, Costanzo FS, Russo A, Trecarichi EM, Torti C; IDTM UMG COVID-19 Group. Interleukin-62/lymphocyte as a proposed predictive index for COVID-19 patients treated with monoclonal antibodies. Clin Exp Med. 2023 Nov;23(7):3681-3687. doi: 10.1007/s10238-023-01081-6. Epub 2023 Apr 25. PMID: 37097384; PMCID: PMC10127195.

Favipiravir, camostat, and ciclesonide combination therapy in patients with moderate COVID-19 pneumonia with/without oxygen therapy: An open-label, single-center phase 3 randomized clinical trial

… who is most at risk or benefit the most?

Jiro Terada,[a,b] Retsu Fujita,[c] Takuya Kawahara,[d] Yasutaka Hirasawa,[a] Taku Kinoshita,[a] Yuichiro Takeshita,[a] Yuri Isaka,[a,b] Toru Kinouchi,[a,b] Hiroshi Tajima,[a] Yuji Tada,[a] and Kenji Tsushima[a]*

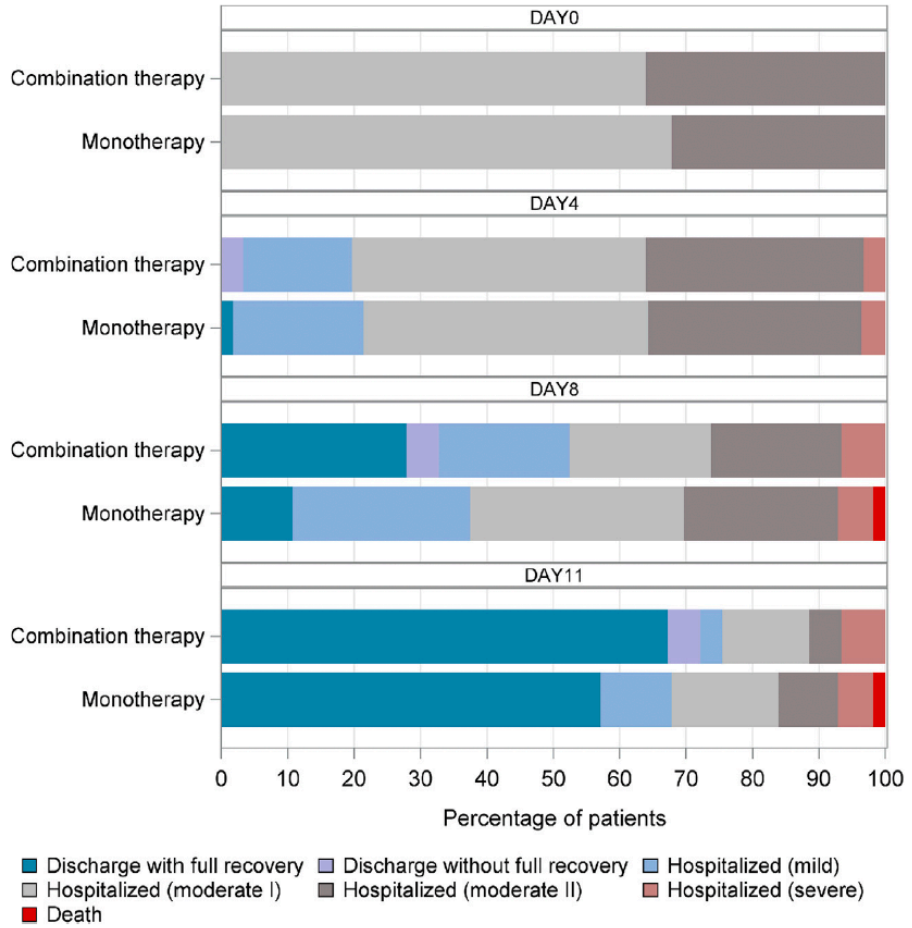


Figure 4. Proportion of Patients Discharged After Complete Recovery in Patients Receiving Monotherapy or Combination Therapy.
The higher proportion of patients discharged after complete recovery was observed in the combination therapy group compared to the monotherapy group at Day 8 and 11.

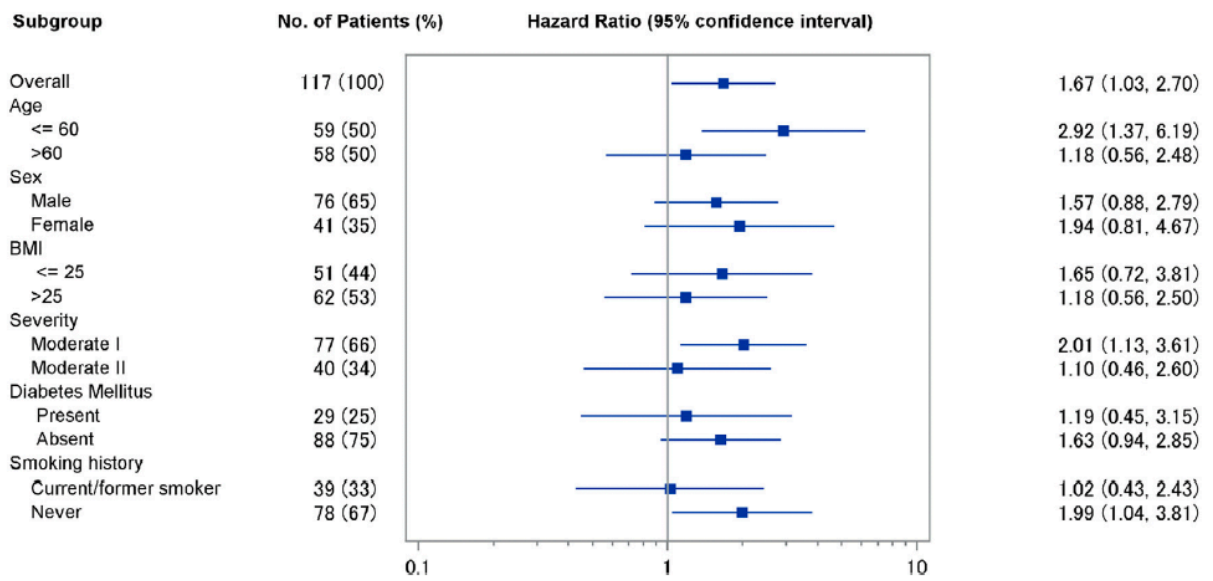


Figure 3. Hazard Ratio of Hospital Discharge Rates in the Treatment Groups Stratified by Subgroups.
The combination therapy group as compared to monotherapy group had a statistically significantly higher hospital discharge rate in patients aged ≤60 [HR, 2·92 (95% CI 1·37–6·19), with less severe disease [Moderate I, HR, 2·01 (95% CI 1·13–3·61)], and among non-smokers [HR, 1·99 (95% CI 1·04–3·81)].

eClinicalMedicine
2022;49: 101484

A tutti per l’ascolto
Al personale U.O. Malattie Infettive e Tropicali, Università «Magna Graecia» di Catanzaro per la collaborazione
Al Dr Salvatore Rotundo, Università «Magna Graecia» di Catanzaro per contributo alla preparazione delle slides