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XIII congresso nazionale
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COVID 19: il percorso di cura

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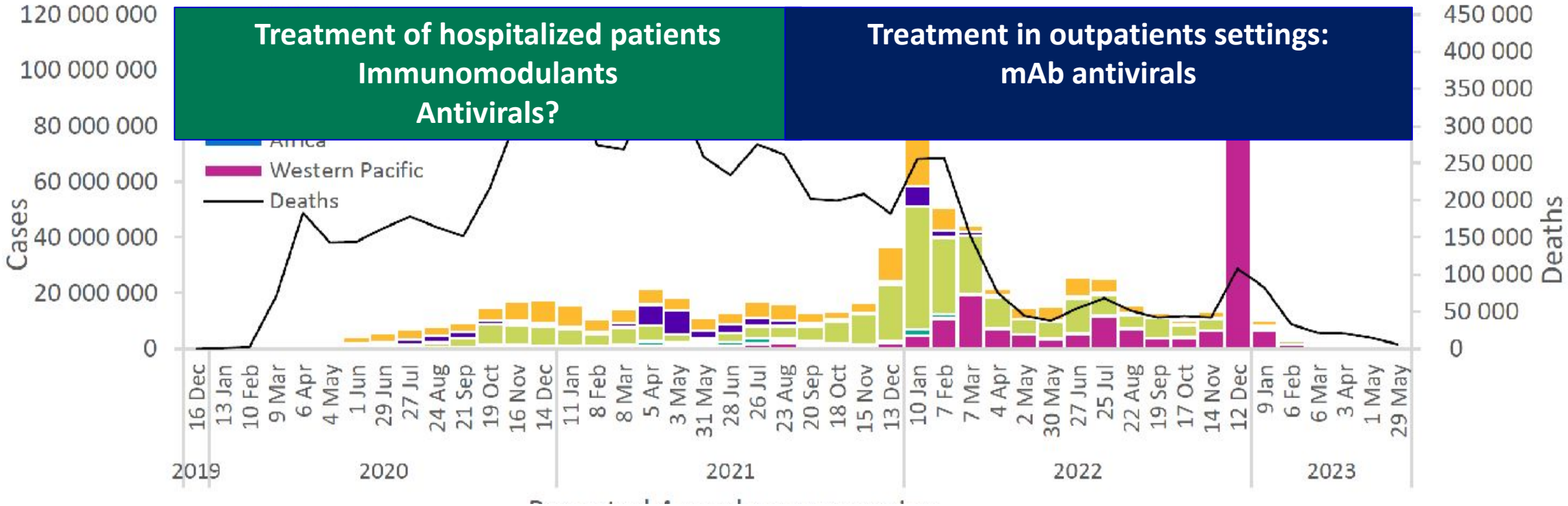
COVID-19 treatment: an evolving paradigm

Figure 1. COVID-19 cases reported by WHO Region, and global deaths by 28-day intervals, as of 25 June 2023**



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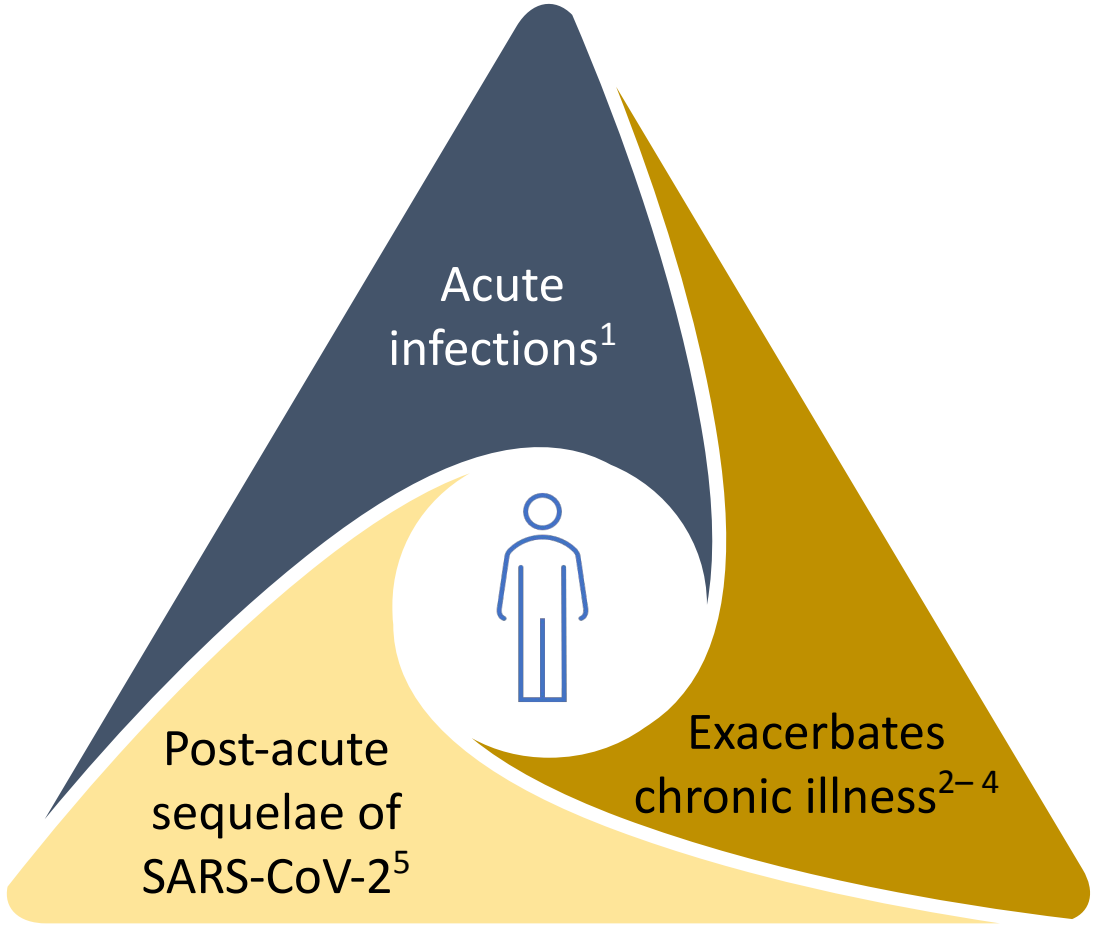
World Health Organization; July 2023

COVID-19 continues to have a significant impact on individuals, especially vulnerable patient groups



COVID-19: coronavirus disease 2019

1. https://ourworldindata.org/coronavirus (accessed Oct 2023). 2. Hyams C, *et al. J Royal Soc Med* 2023; doi: 10.1177/01410768231184162.
3. Hashem A, *et al. J Intens Care Med* 2023; doi: 10.1177/08850666231182380.
4. Lv F, *et al. EClinicalMedicine* 2022; 54:101671. 5. Tsampasian V, *et al. JAMA Intern Med* 2023; 183:566–580.

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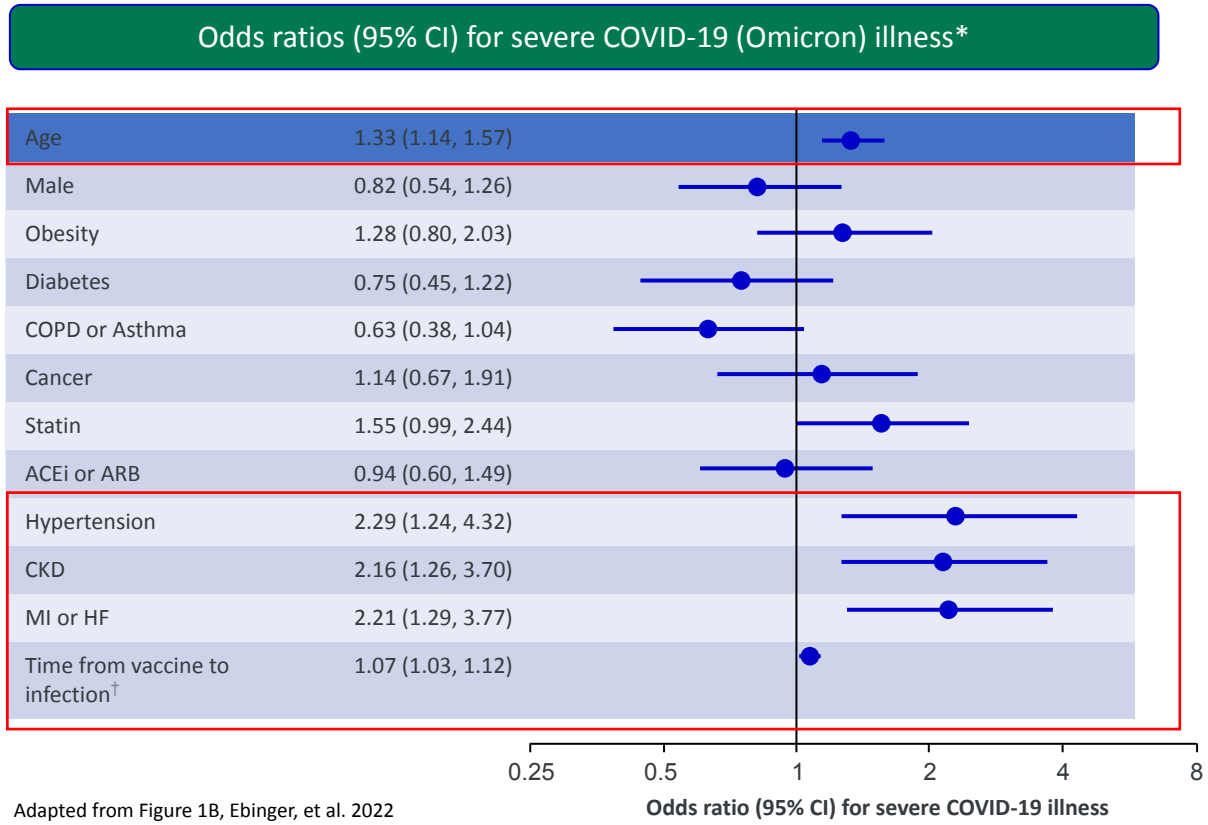
Risk factors for Omicron infection requiring hospitalisation despite receiving ≥3 vaccine doses

Characteristic	Overall (n=912)	Not hospitalised (n=767)	Hospitalised (n=145)
Age, years	56 ± 19	53 ± 18	70 ± 17
Male, n (%)	374 (41)	300 (39)	74 (51)
Race/ethnicity, n (%)			
Non-Hispanic Black	135 (15)	111 (15)	24 (17)
Non-Hispanic White	389 (43)	312 (41)	77 (53)
Hispanic/Latinx	198 (22)	170 (22)	28 (19)
Asian or Other	172 (19)	157 (21)	15 (10)
Unknown	18 (2)	17 (2)	1 (1)
Obesity, n (%)	250 (27)	208 (27)	42 (29)
Diabetes, n (%)	191 (21)	138 (18)	53 (37)
COPD or Asthma, n (%)	191 (21)	153 (20)	38 (26)
Cancer, n (%)	123 (14)	84 (11)	39 (27)
Statin, n (%)	274 (30)	192 (25)	82 (57)
ACEi or ARB, n (%)	211 (23)	156 (20)	55 (38)
Hypertension, n (%)	491 (54)	366 (48)	125 (86)
CKD, n (%)	141 (16)	82 (11)	59 (41)
MI or HF, n (%)	133 (15)	73 (10)	60 (41)
Days from vaccine to infection	72 ± 49	69 ± 47	93 ± 53

Ebinger JE, et al. *Hypertension* 2022;79(10):e132–4.



Adapted from Figure 1B, Ebinger, et al. 2022

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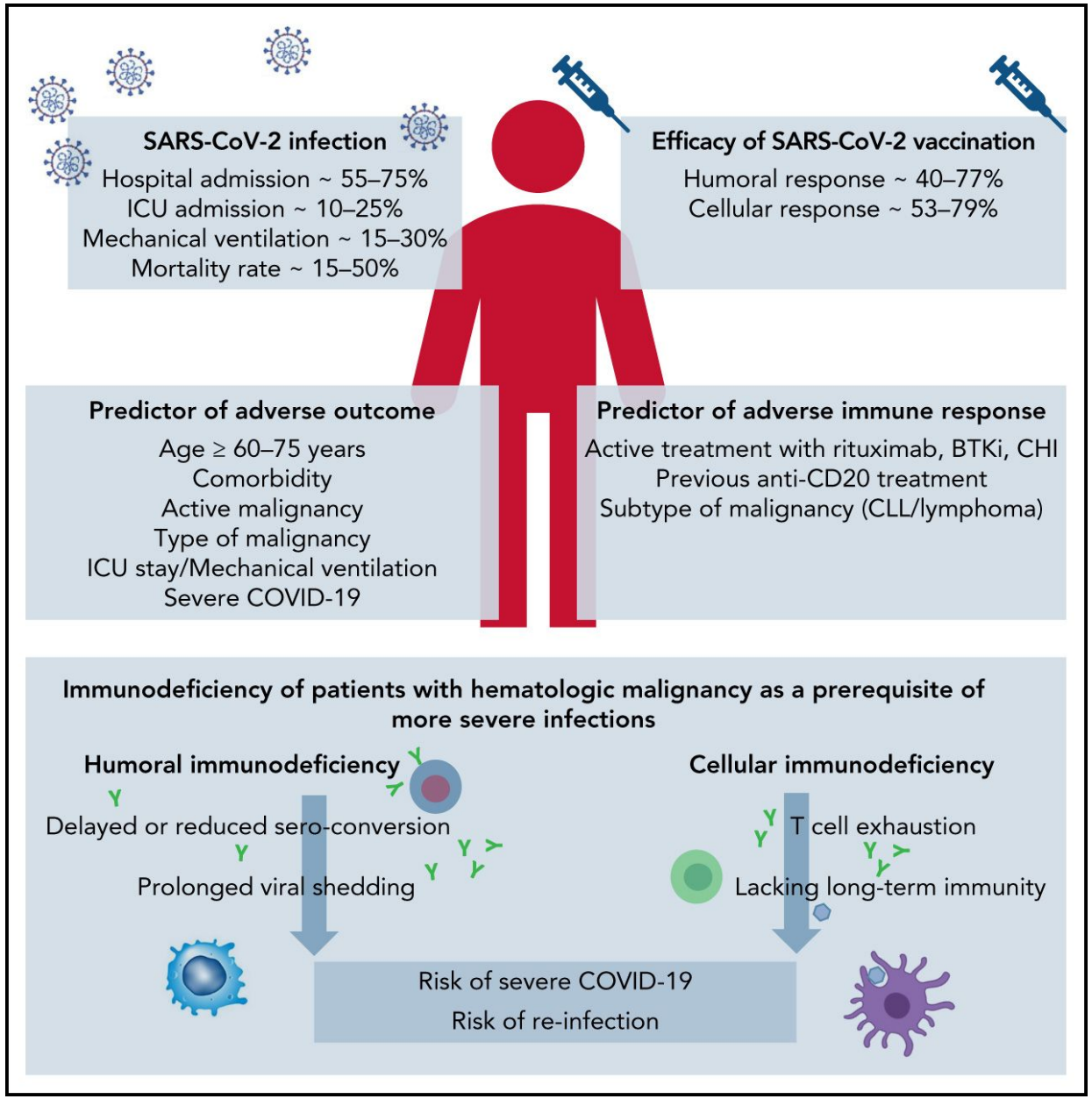
* A retrospective cohort study of adults who received at least 3 mRNA vaccine doses but were subsequently hospitalised with COVID-19 (Omicron) and had at least 2 outpatient visits within the preceding 2 years; † Time from vaccine to infection represents the interval (per 10 days) between the date of last vaccine dose received (booster) and the date of COVID-19 infection diagnosed during the Omicron surge period.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; MI, myocardial infection; mRNA, messenger ribonucleic acid.

Ebinger JE, et al. *Hypertension* 2022;79(10):e132–4.

COVID-19 in patients with hematologic malignancy



Petra Langerbeins,Michael Hallek, COVID-19 in patients with hematologic malignancy, Blood, 2022

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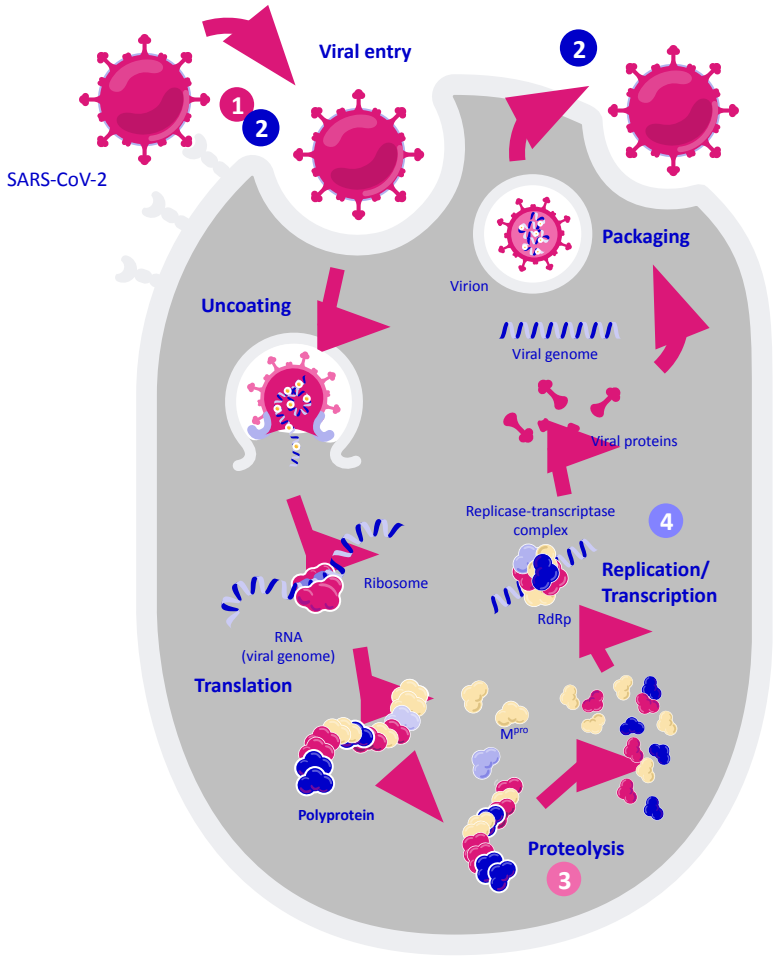
Evolution of SARS-CoV-2 treatment options



1. Binding

Prevent SARS-CoV-2 binding to ACE2 receptor:[2,3]

- Neutralising monoclonal antibodies
- Convalescent plasma or plasma-derived therapies
- Vaccines

2. Entry / exit

Inhibit viral / host interaction and endosome maturation:[2,3]

- Human protease inhibitors

3. Proteolysis

Prevent formation of proteins involved in viral replication:[3]

- Protease inhibitors (M^{pro} or PL^{pro})

4. RNA replication

Prevent replication of viral genome:[3]

- RNA polymerase inhibitors

Adapted from Figure 1, Eastman, et al. 2020[1]

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ACE2, angiotensin-converting enzyme 2; Mpro, main protease; PLpro, papain-like protease; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid.

1. Eastman RT, et al. *ACS Cent Sci* 2020;6(5):672–83; 2. Salvatori G, et al. *J Transl Med* 2020;18(1):222; 3. Tao K, et al. *Clin Microbiol Rev* 2021;34(4):e0010921.

ANTIVIRALS

Molnupiravir

RNA-polymerase inhibitor (cytidine nucleoside analogue)

Remdesivir

RNA-polymerase inhibitor (adenosine nucloside analogue)

Nirmatrelvir-Ritonavir

Nirmatrelvir is a SARS-CoV-2 main protease inhibitor (Mpro), and ritonavir is an HIV1 protease inhibitor and CYP3A inhibitor

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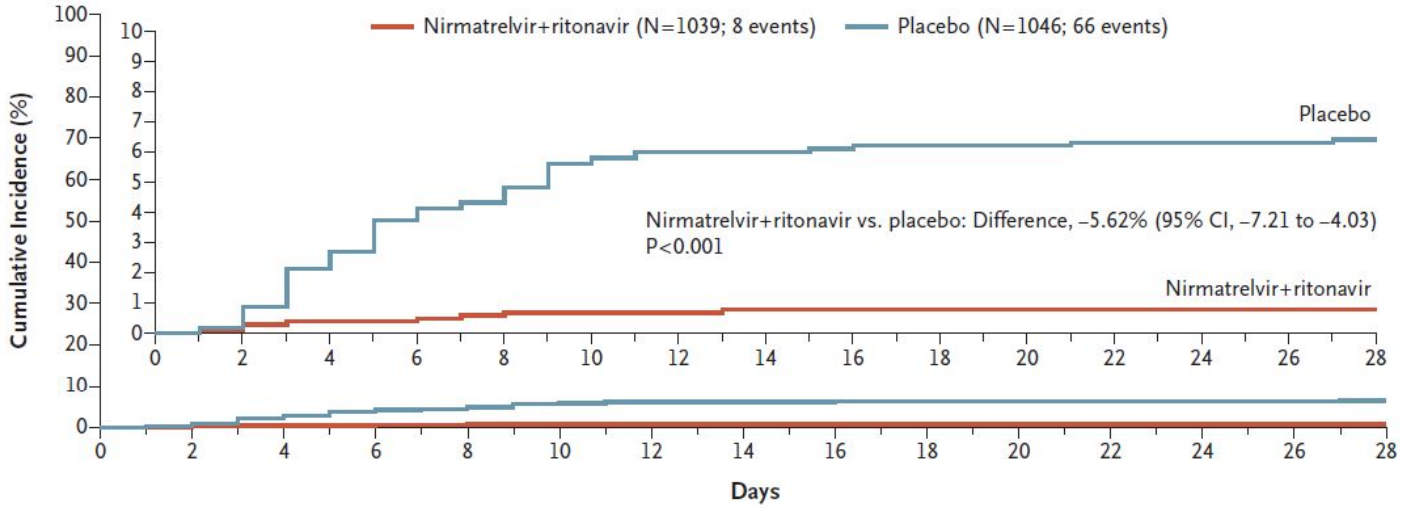
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond et al N Engl J Med 2022 Feb 16. doi: 10.1056/NEJMoa2118542.

A Outcomes According to Time Since Onset of Covid-19 Symptoms

	Treated ≤3 Days after Onset of Symptoms (modified intention-to-treat population)		Treated ≤5 Days after Onset of Symptoms	
	Nirmatrelvir+ritonavir (N=697)	Placebo (N=682)	Nirmatrelvir+ritonavir (N=1039)	Placebo (N=1046)
Patients with event — no. (%)	5 (0.72)	44 (6.45)	8 (0.77)	66 (6.31)
Hospitalization for Covid-19	5 (0.72)	44 (6.45)	8 (0.77)	65 (6.21)
Death from any cause	0	9 (1.32)	0	12 (1.15)
Average time at risk for event — days	27.29	26.19	27.05	25.97
Average follow-up — days	27.45	27.25	27.20	27.05
Estimated percentage with event (95% CI) — %	0.72 (0.30 to 1.73)	6.53 (4.90 to 8.68)	0.78 (0.39 to 1.56)	6.40 (5.06 to 8.08)
Difference (±SE) from placebo — percentage points	−5.81±1.01		−5.62±0.81	
95% CI of difference	−7.78 to −3.84		−7.21 to −4.03	
P value	<0.001		<0.001	

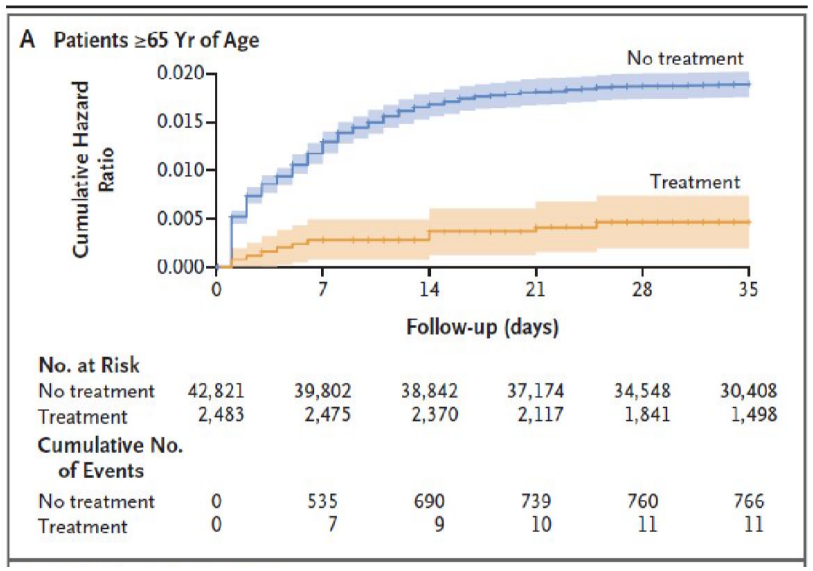
B Covid-19–Related Hospitalization or Death from Any Cause through Day 28 among Patients Treated ≤5 Days after Symptom Onset

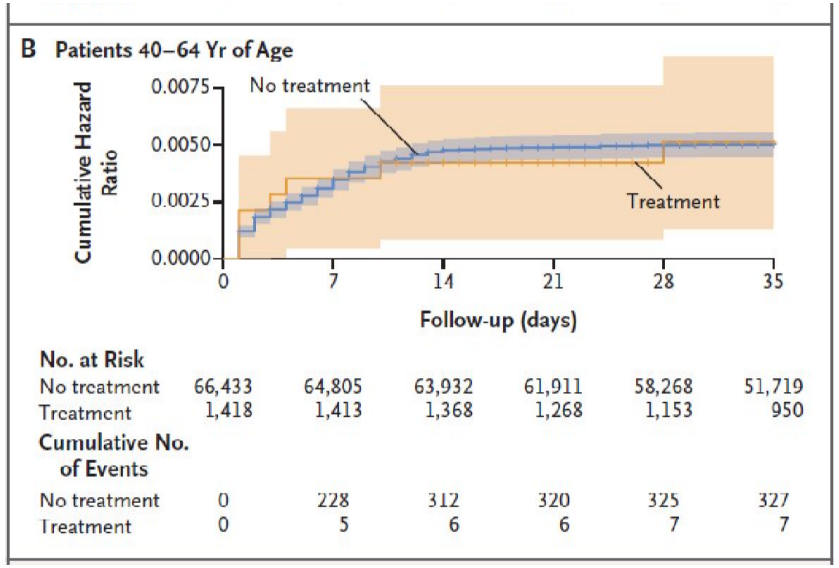


No. at Risk															
NMV-r	1039	1034	1023	1013	1007	1004	1002	1000	997	995	993	993	993	993	992
Placebo	1046	1042	1015	990	977	963	959	959	955	953	951	948	948	948	945

Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge

Arbel R N Engl J Med 2022;387:790-8. DOI: 10.1056/NEJMoa2204919





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Effectiveness of nirmatrelvir-ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system

Lewnard JA, et al. *Lancet Infect Dis* 2023; doi: 10.1016/S1473-3099(23)00118-4

Matched, observational cohort study

Location	**U.S. (Southern California)**
Follow-up	From index test to the occurrence of each study endpoint or censoring (at the scheduled end of follow-up, study end, or disenrollment)
Treatment(s)	Nirmatrelvir/ritonavir vs no nirmatrelvir/ritonavir

Outcomes assessed

Effectiveness:

- Primary: Preventing hospitalisation or death from any cause within 30 days of a positive test
- Secondary: Preventing ICU admission, mechanical ventilation or death within 60 days of a positive test*

Study cohort

Non-hospitalised COVID-19 patients who were potentially candidates for nirmatrelvir/ritonavir

Included:

- Aged ≥12 years at time of index test
- Positive SARS-CoV-2 PCR test result (defined as the index test) between 8 April and 7 October 2022†
- No prior positive test results within the preceding 90 days
- Not hospitalised at the time of index test, or within the preceding 7 days
- ≥1 year of continuous enrolment in KPSC health plans before the index test

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* Suggesting progression to severe disease; † A time when ≥5% of outpatient-diagnosed people with COVID-19 were receiving nirmatrelvir/ritonavir.
ICU, intensive care unit; KPSC, Kaiser Permanente Southern California; PCR, polymerase chain reaction; RWE, real-world evidence.
Lewnard JA, et al. *Lancet Infect Dis* 2023; doi: 10.1016/S1473-3099(23)00118-4 (Epub ahead of print).

Effectiveness of nirmatrelvir-ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system

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Effectiveness

Primary endpoint

- After adjustment* for differences in risk status among treated and untreated cases, receipt of nirmatrelvir/ritonavir 0–5 days after symptom onset was associated with an estimated effectiveness of 79.6% (95% CI 33.9% to 93.8%) against progression to the primary endpoint of hospital admission or death due to any cause within 30 days after the index test
    - Treatment courses administered at any time, regardless of the presence or timing of symptoms, were associated with an estimated effectiveness of 53.6% (95% CI 6.6% to 77.0%) against progression to the primary endpoint

Primary endpoint: All-cause hospital admission or death within 30 days from positive SARS-CoV-2 test

	Discordant sets			
Timing of dispense in relation to symptoms onset	Outcome observed for recipient, non-recipient censored (n)	Outcome observed for non-recipient, recipient censored (n)	Estimated effectiveness, % (95% CI)*	P value (two-sided)
Within 5 days of symptom onset	8	11	79.6 (33.9–93.8)	0.0080
Any time (regardless of symptoms)	26	23	53.6 (6.6–77.0)	0.031

Adapted from Table 2, Lewnard JA, et al. 2023

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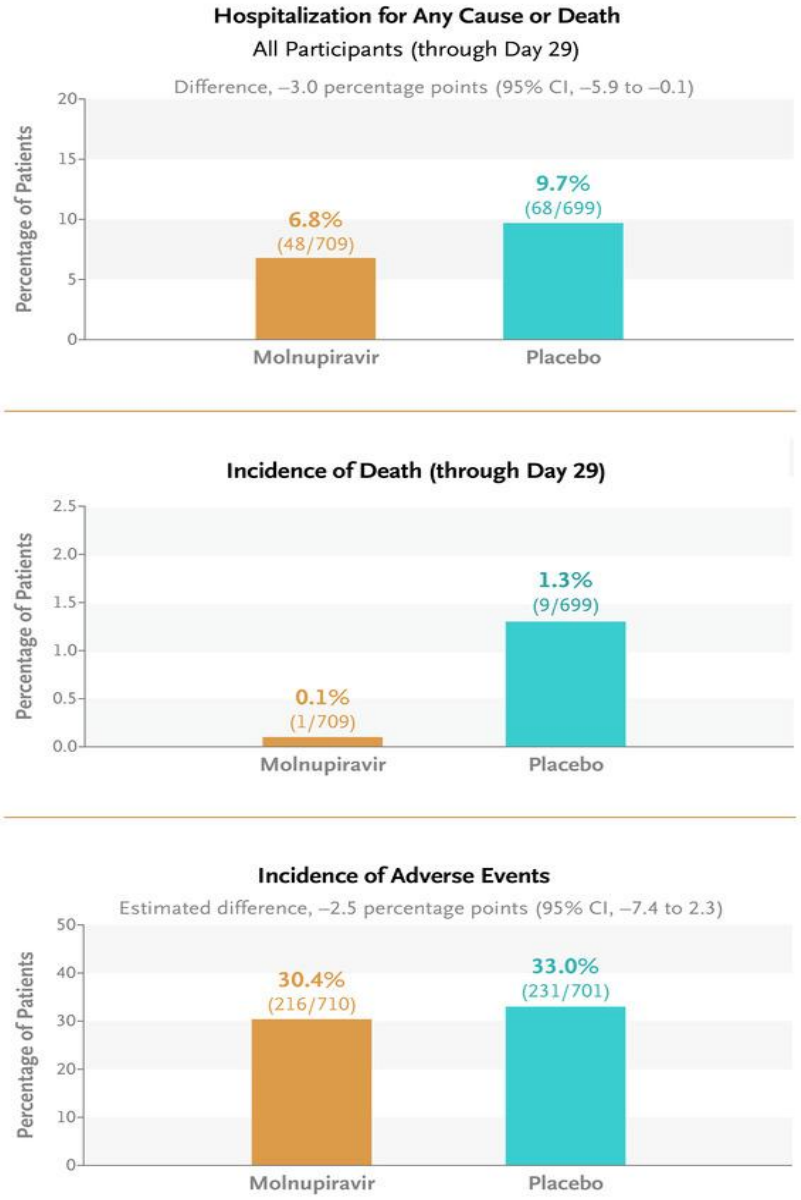
Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients



Active cancer 2%

Average efficacy 30%

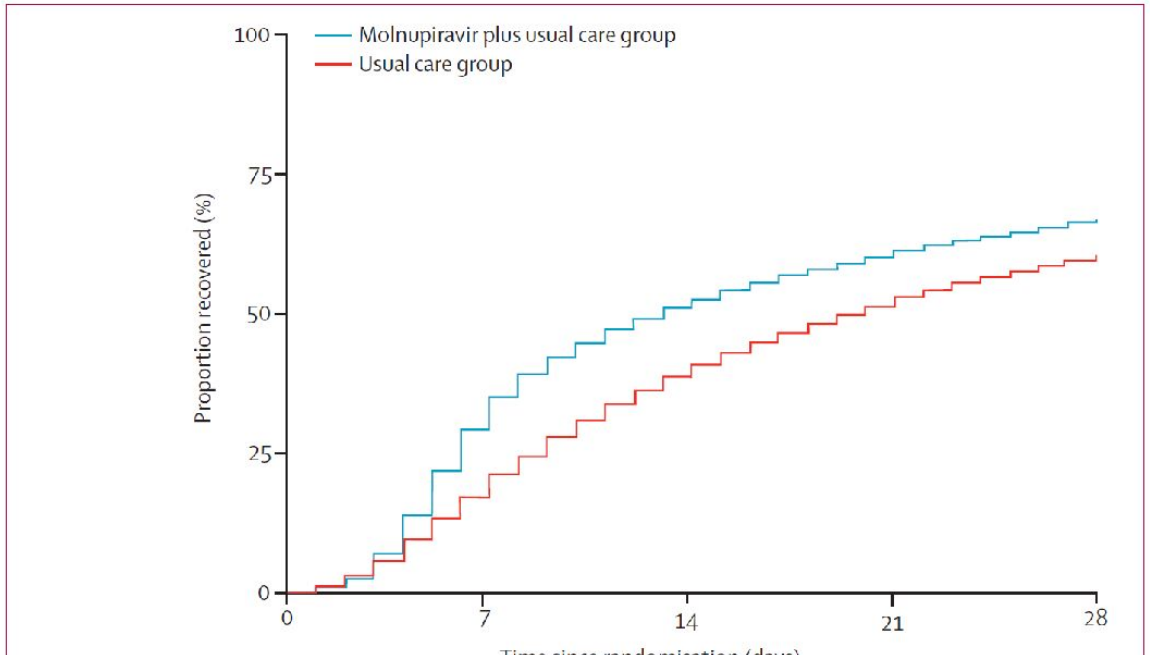
Jayk Bernal et al. N Engl J Med 2022;386:509-520

Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

Butler C et al Lancet 2023

Primary outcome:

- 103/12516 (0·8%) hospitalisations/deaths occurred in the molnupiravir group
- 96/12484 (0·8%) in usual care group



Molnupiravir plus usual care group					
Not yet recovered	12 403	7934	4661	3221	2168
Censored	0	141	260	387	594
Recovered	0	4328	7482	8795	9641
Usual care group					
Not yet recovered	12 140	9411	6121	4175	2774
Censored	0	271	542	781	1113
Recovered	0	2458	5477	7184	8253

Figure 3: Time from randomisation to first reported recovery from COVID-19

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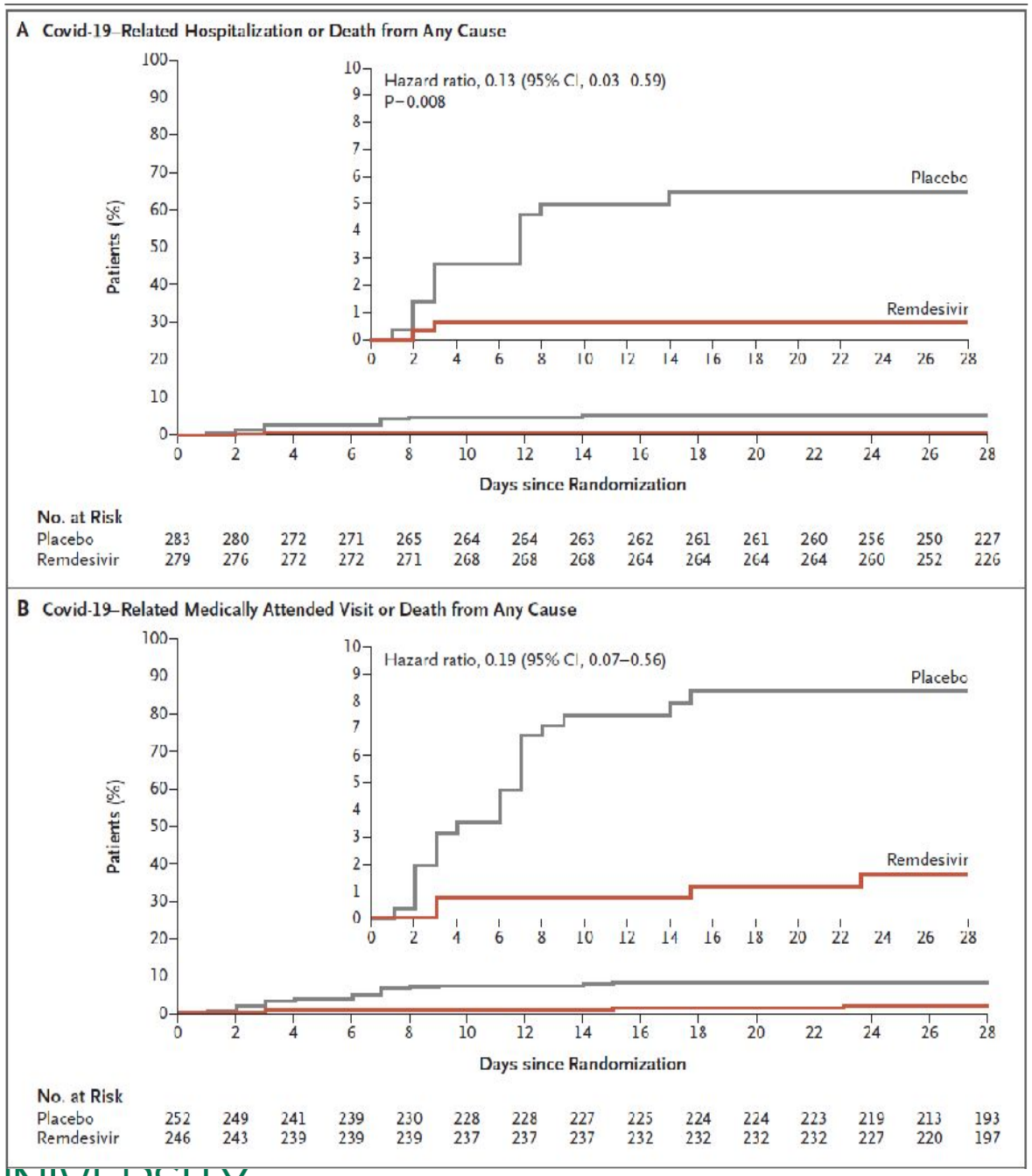

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

Gottlieb N Engl J Med 2022; 386:305-315

Immune compromise 4.1%
Cancer 5.3 %

3-day course of remdesivir had

- acceptable safety profile
- 87% lower risk of hospitalization or death than placebo.

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Remdesivir in Patients With Severe Kidney Dysfunction
A Secondary Analysis of the CATCO Randomized Trial

For patients with eGFR less than 60 mL/min/1.73m$_2$ (n = 248) at randomization, no significant difference between those receiving remdesivir or SOC in

- hospital mortality (35.2%vs 42.1%; *P* = .26),
- new mechanical ventilation (10.6%vs 15.7%; *P* = .27), or
- new dialysis (6.2%vs 5.0%; *P* = .70).

Cheng M JAMA Netw Open . 2022 Aug 1;5(8):e2229236.

Table 2. Clinical Outcomes of Patients With eGFR Less Than 30 mL/min/1.73 m^2 at Time of Randomization[a]

Variable	Remdesivir (n = 34)	Standard care (n = 25)	Difference in means (95% CI)
Hospital death, No. (%), unadjusted	13 (40.6)	13 (52.0)	RR, 0.78 (0.41 to 1.49)
New mechanical ventilation in those not ventilated at baseline, No. (%)	4 (14.8)	6 (26.1)	RR, 0.57 (0.15 to 1.80)
Total length of stay, d			
Mean (SD)	23.1 (20.5)	21.6 (28.8)	1.5 (-11.5 to 14.6)
Median (IQR)	16.5 (10-29.5)	11 (6-25)	NA
Day 5 creatinine, mg/dL[b]			
Mean (SD)	2.83 (2.15)	4.12 (2.41)	-1.29 (-2.66 to 0.09)
Median (IQR)	1.80 (1.32-3.40)	3.47 (2.02-5.99)	NA
Day 5 eGFR, mL/min/1.73 m^2[b]			
Mean (SD)	31.2 (19.2)	20.5 (13.9)	10.7 (0.20 to 21.2)
Median (IQR)	29.2 (14.2-45)	16.5 (8.5-30.9)	NA
ANCOVA for change in eGFR			-0.26 (-7.95 to 7.42)
Day 5 ALT[c]			
Mean (SD)	40.8 (36.4)	91.9 (187)	-51.1 (-177.2 to 75.0)
Median (IQR)	32.5 (15-47)	31 (22-52)	NA
New dialysis in those not receiving dialysis at baseline, No. (%)	5 (20.0)	4 (21.1)	RR, 0.95 (0.25 to 3.56)
Any adverse event, No. (%)	3 (8.8)	6 (24.0)	RR, 0.37 (0.05 to 1.33)

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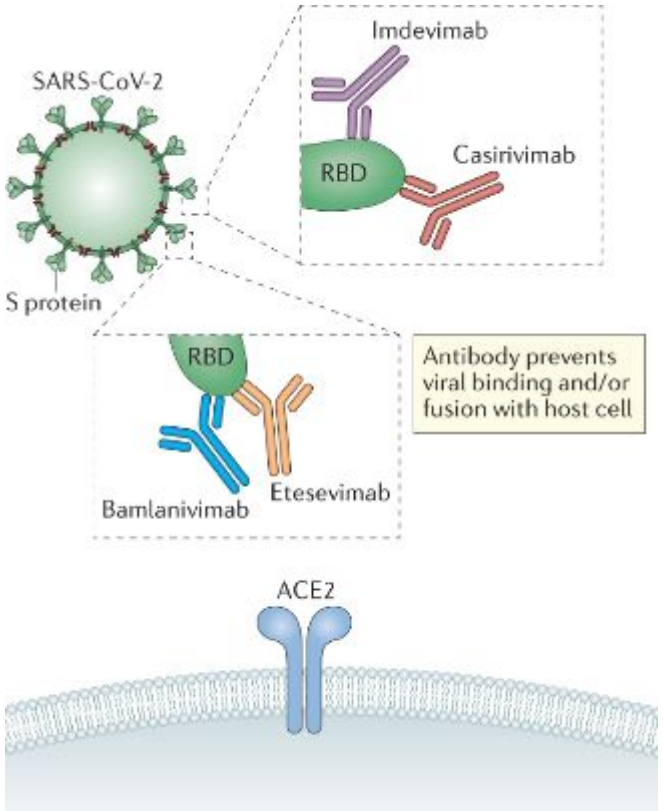
MONOCLONAL ANTIBODIES

Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein

Proposed for treatment and prophylaxis

Available in Italy
- Bamlanivimab/Etesemivab
- Casirivimab/Imdevimab
- Sotrovimab
- Cilgavimab/Tixagevimab



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Summary of COVID-19 guidelines and recommendations (hospitalized)

Drug/guideline	IDSA	WHO	AUSTRALIAN	NIH	ESCMID
Remdesivir	+ (conditional)*	+ (conditional)*	+ (conditional)*	+ (conditional)#	+ (conditional)*
Steroids (Dexa)	+ §	+ §	+ §	+ §	+ §
Tocilizumab or Sarilumab	+ (conditional)	+	+ (conditional)	+	+
Baricitinb	+ (conditional)	+	+ (conditional)	+	NA
Anakirna	-	NA	NA	-	NA
Convalenscent plasma	-	-	-	-	-
Heparin	NA	NA	Prophylactic dose	Therapeutic in criticallly ill. Prophylactic in the remainings	- Therapeutic in critically ill

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* in all patients exception for those requiring hihg-flow oxygen
#in all patients exception for those requiring hihg-flow oxygen (conditionl in immunocompromised with combination with immunomodulator
§ in patients requiring oxygen supplementation

Topics not covered by guidelines…

Higher dosage of steroids or use of steroids in immunocompromised patients?

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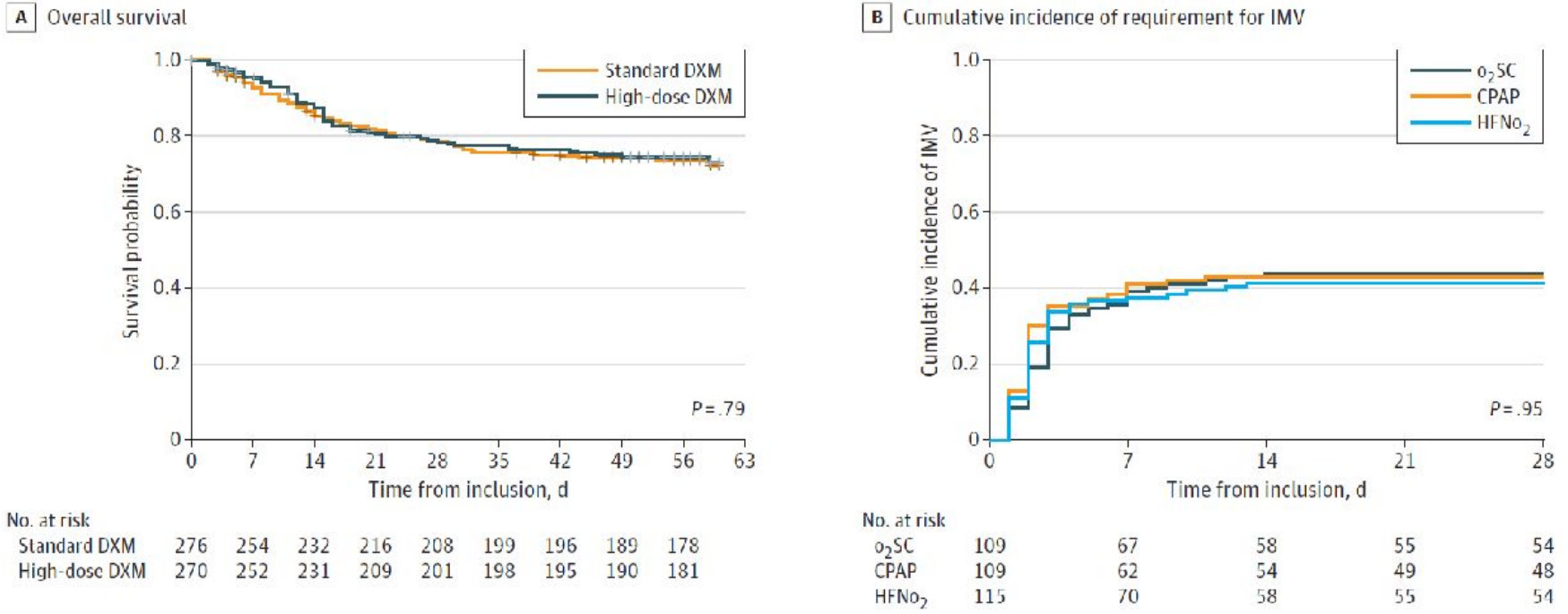
High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure The COVIDICUS Randomized Clinical Trial

Bouadma ,JAMA internal medicine 2022.

Figure 2. Primary End Points of Both Interventions



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Summary of COVID-19 guidelines and recommendations (outpatients/early treatment)

Drug/guideline	IDSA	WHO	AUSTRALIAN	NIH	ESCMID
Remdesivir	+ (conditional)	+ (conditional)	+(conditional)	+	+
Nirmatrelvir/ritonavir	+ (preferred option in most patients)	+ (preferred option in most patients)	+ (preferred option in most patients)	+ (preferred option in most patients)	+ preferred option in most patients
Molnupiravir	+ (conditional)*	+	+ (conditional)	+ (conditional)*	NA
Monoclonal antibodies	-	-	-	-	- #
Convalenscent plasma	+ (conditional)*	-	-	- (in clinical trial for immunocompromised)	-
Inhaled steroids	-	NA	+ (conditional)	Insufficient data	- Only in clinical trial

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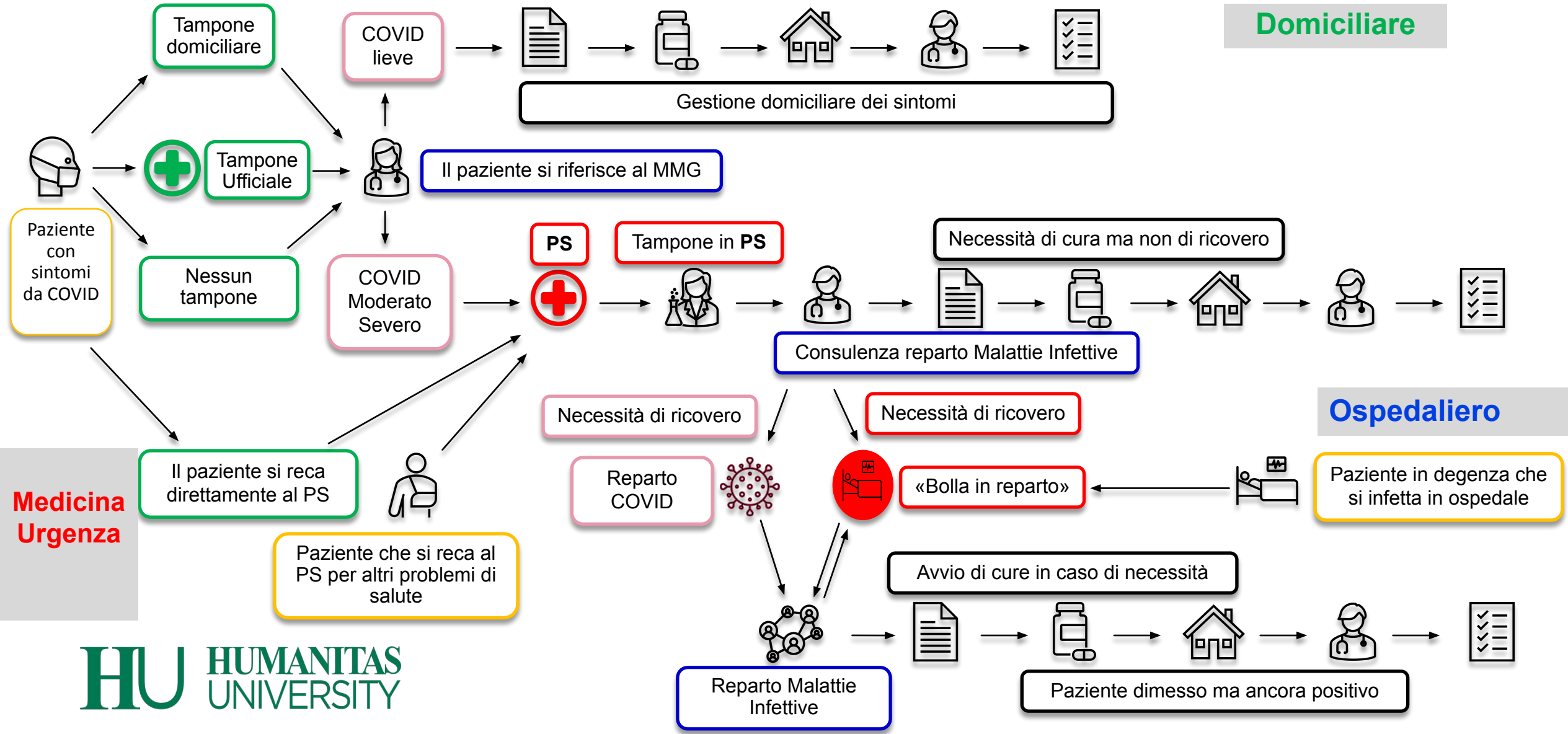
* If no other treatment options
# no reccomended in case of circulating resistant variants

Percorso Paziente positivo al Covid



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Grazie a tutti

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