Il tempo conta: le terapie precoci nell'infezione da SARS-CoV-2

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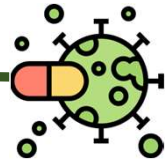
U.O.C. Malattie Infettive – Università degli Studi di Bari

OUTLINE

- **Why are specific populations at risk of developing severe COVID-19?**
- **Role of inflammatory cytokines**



- **Use of Remdesivir, Nirmatrelvir plus ritonavir, Sotrovimab,**
- **Take home message**

Hallmarks of COVID-19 Clinical Picture

1.Cytokine Storm: **Dysregulated and excessive immune responses** may lead to significant systemic damage. Mononuclear cells such as neutrophils and monocytes in the patient's lung tissues and peripheral blood produce elevated levels of pro-inflammatory cytokines such **as interleukin-6 (IL-6), interleukin-1 and tumor necrosis factors**, **directly related to the severity and mortality of the disease**

2.Hypoxemic Respiratory Failure: Direct cytopathic effects of the virus and virus-induced decrease in surfactant levels causing atelectasis are some of the unique pathologic findings seen in patients with COVID-19. **Hypoxemia is the hallmark of the pulmonary derangement of the disease**, with no signs of respiratory distress **("silent or happy hypoxemia")**

3.COVID-19-related Hypercoagulability: A distinct **prothrombotic state** as opposed to a consumptive coagulopathy has been described in COVID-19 patients, secondary to a **markedly increased levels of fibrin and fibrinogen**. **This mechanism is synergistic with the cytokine storm and the virus-induced endothelial dysfunction**. Consequently, **serum levels of D-dimer are a strong prognostic factor of poor outcomes**

Risk factors for severe disease

People with certain uncommunicable underlines conditions are at increased risk of disease progression, and should be more closely monitored for *worsening symptoms*: light headedness, difficulty breathing, chest pain, dehydration, …

- Age > 65 years

- Cardiovascular disease
- Chronic lung disease
- Sickle cell disease
- Diabetes
- Cancer
- Obesity
- Chronic kidney disease

- Pregnant women

- Smokers

NIH COVID-19 Treatment Guidelines. Last updated April 21, 2021. www.covid19treatmentguidelines.nih.gov.

Inflammatory cytokines as a risk factors for severe COVID-19

Diabetes

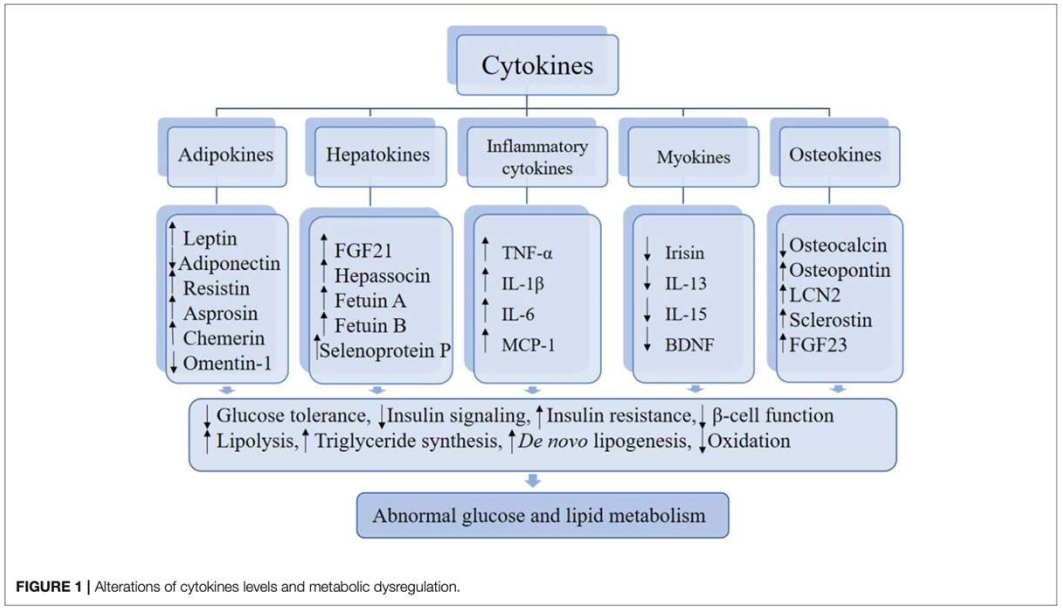
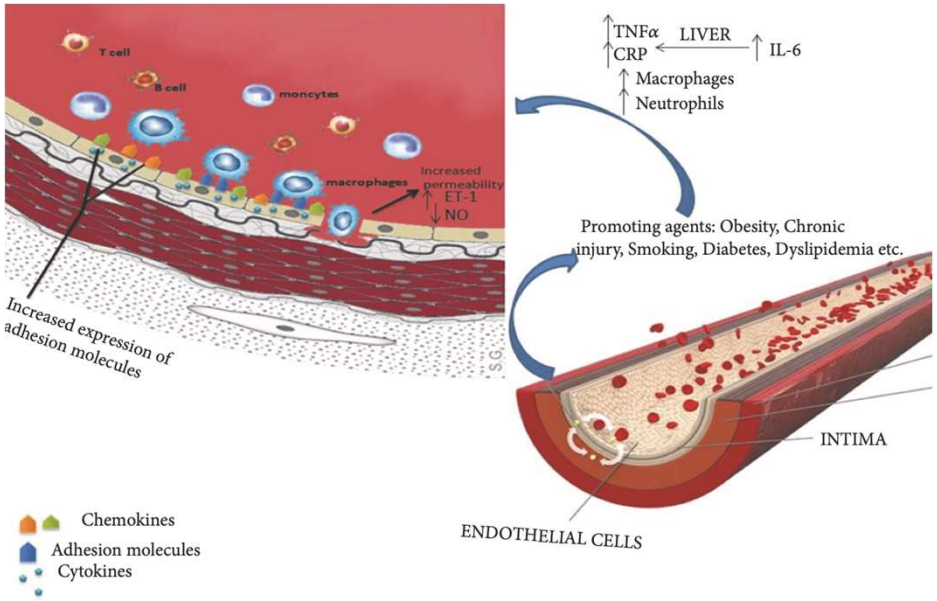


FIGURE 1 | Alterations of cytokines levels and metabolic dysregulation.

Inflammatory cytokines

[b]TNF-α	Mediates insulin resistance, stimulates of lipolysis, pro-inflammatory	↑T2D	(60–67)
[b]IL-1β	Stimulates triglycerides, cholesterol accumulation, and lipid droplet formation; reduces insulin-stimulated glucose uptake and lipogenesis	↑obesity,↑T2D, ↑NAFLD	(68–80)
IL-6	Has a dual role in modulating insulin action	↑T2D	(62, 81–89)
[b]MCP-1	Induces insulin resistance, elevates hepatic triglyceride content	↑T2D	(90–95)

Arterial Hypertension



- A key component in the pathophysiology of HTN is inflammation.
- Inflammation, in turn, promotes endothelial dysfunction and atherosclerosis through reactive oxygen species (ROS), a downstream product of cellular and soluble immune factors.
- Consequently, ROS stimulates proinflammatory cytokine secretion, increasing IL-6 expression and decreasing NO availability Studies have shown that inhibition of these ROS led to blood pressure reduction through endothelial function improvement via increased nitric oxide (NO) production

Shi J, et al. Cytokines and Abnormal Glucose and Lipid Metabolism. Front Endocrinol (Lausanne). 2019 Oct 30;10:703. doi: 10.3389/fendo.2019.00703.

Tanase DM,. Arterial Hypertension and Interleukins: Potential Therapeutic Target or Future Diagnostic Marker? Int J Hypertens. 2019 May 2;2019:3159283. doi: 10.1155/2019/3159283.

Inflammatory cytokines as a risk factors for severe COVID-19

Role of Interleukins in Inflammation and HTN Development.

Table 1: Cytokines, cytokine receptors, and their vascular impact. HTA-arterial hypertension, ATS-atherosclerosis, ST-stroke, IM-myocardium infarction, CHD-coronary heart disease, AF-atrial fibrillation, CH-cardiac hypertrophy, LVD-left ventricule dilatation, HTP-pulmonary hypertension, UA-unstable angina, CHF-chronic heart failure.

Interleukine	Receptor	Cell source	Cell Target	Cardiovascular Impact
IL-1α,β	Type I IL-1r, Type II IL-1r	Monocytes/macrophage, fibroblast, endothelial cells, B cells, epithelial cells including thymic epithelium.	All cells	HTA [52, 58], ATS [53, 54, 60], IL-1β polymorphism and HTA [61–64, 66, 67], ST [73]
IL-4	IL-4 α, common γ	Mast cells, T cells, basophils.	Endothelial cells, T cells, B cells fibroblast, NK-cells, monocytes, macrophages	Anti-inflammatory action on T cells [161]
IL-6	IL-6r, gp130	fibroblast, endothelial, Mono-cytes/macrophages, most epithelial cells including thymic epithelium.	Hepatocytes, macrophages, monocytes, T cells, B cells, epithelial cells	HTA [40, 82, 85, 88], ATS [106], IM [30], CHD [112, 113, 125], AF [126], CH [90], LVD [91], HTP [103, 105, 106], ST [119, 120]
IL-10	IL-10r	T cells, B cells, monocytes macrophages, keratinocytes, mast cells	T cells, B cells, NK cells, mast cells, monocytes macrophages	Anti-inflammatory action on T cells [120, 156, 157]
IL-17	IL-17r	CD4+ T cells	Endothelium, epithelium, fibroblast, macrophages	HTA [11], ATS [12, 131], IM and UA [135], CHF [137]
IL-23	IL-12Rb1/IL23R	Macrophages, other cell types	T cells	ATS [12, 131]

Inflammation as a Potential Therapeutic Target in Arterial Hypertension

Table 2: Anti-inflammatory effects of cardiovascular drugs.

	Effects on inflammatory cytokines	Antihypertensive mechanisms	Proposed References
Statins	↓ IL-1β ↓ IL-6 ↓ MCP-1 ↓ ICAM-1 ↓ MMP-2 ↓ MMP-9 ↓ hs-CRP ↓ PAI-1 ↑ NO	NF-κB inhibition AT1R downregulation HMC CoA inhibition (G protein coupled signalling inhibition) PPAR-γ inhibition Upregulates NO synthase	[162, 164, 166, 167, 174]
ARBs/ACEIs	↓ IL-1β ↓ IL-6 ↑ TGF-β (losartan) ↑ NO (AT2R)	NF-κB inhibition AT1R downregulation Decreased ACE synthesis	[8, 56, 164]
Calcium channel blockers	↓ MMP-2 ↓ MMP-9 ↓ IL-1β ↓ IL-18 ↓ CRP ↓ MCP-1 ↓ ICAM-1	Protein kinase pathway (MMP-2)	[174, 176]

- Increased IL-1β, IL-6, IL-8, IL-17, IL-23, TGFβ, and TNFα in hypertensive patients has been associated with either increased blood pressure values and/or end-organ damage.
- Moreover, some cytokines (i.e., IL-6) seem to determine a hypertensive response to angiotensin II, regardless of blood pressure values.
- Understanding hypertension as an inflammatory-based pathology gives way to new therapeutic targets

Tanase DM,. Arterial Hypertension and Interleukins: Potential Therapeutic Target or Future Diagnostic Marker? Int J Hypertens. 2019 May 2;2019:3159283. doi: 10.1155/2019/3159283.

Inflammatory cytokines as a risk factors for severe COVID-19

Obesity

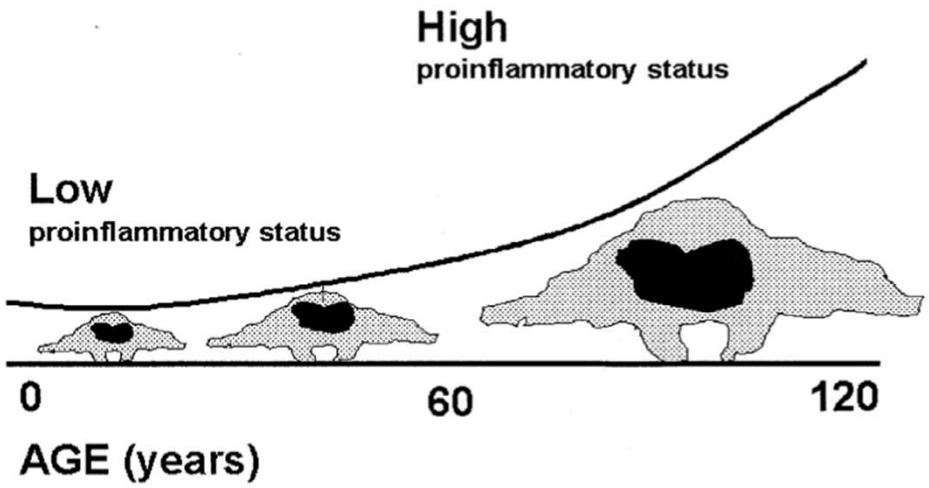
Cytokine [A]	General Obesity determined by BMI				Central Obesity determined by WHR			
	Non-Obese (Mean ± SD)	Obese (Mean ± SD)	ANOVA [B] (p-value) [D]	ANCOVA [C] (p-value) [D]	Obese (Mean ± SD)	Non-Obese (Mean ± SD)	ANOVA [B] (p-value) [D]	ANCOVA [C] (p-value) [D]
IL-2 [pg/ml]	1.45 ± 0.99	1.64 ± 1.15	0.2399	0.4388	1.50 ± 1.07	1.69 ± 1.13	0.2428	0.4917
IL-4 [pg/ml]	1.45 ± 0.45	1.51 ± 0.48	0.4289	0.7455	1.46 ± 0.46	1.53 ± 0.48	0.2742	0.5850
IL-5 [pg/ml]	1.02 ± 0.57	1.36 ± 0.54	< 0.0001	0.0001	1.13 ± 0.55	1.38 ± 0.60	0.0033	0.0100
IL-10 [pg/ml]	1.13 ± 1.03	1.43 ± 0.86	0.0267	0.0539	1.17 ± 0.83	1.57 ± 1.10	0.0041	0.0104
IL-12 [pg/ml]	1.89 ± 0.99	2.28 ± 0.89	0.0047	0.0072	1.96 ± 0.84	2.41 ± 1.08	0.0013	0.0020
IL-13 [pg/ml]	1.48 ± 0.81	1.78 ± 0.61	0.0031	0.0053	1.56 ± 0.67	1.85 ± 0.77	0.0051	0.0089
GM-CSF [pg/ml]	3.34 ± 0.55	3.45 ± 0.70	0.2258	0.4055	3.34 ± 0.60	3.51 ± 0.72	0.0820	0.1902
IFN- γ [pg/ml]	4.53 ± 0.72	4.79 ± 0.62	0.0071	0.0161	4.60 ± 0.68	4.83 ± 0.65	0.0216	0.0507
TNF-α [pg/ml]	3.17 ± 0.58	3.39 ± 0.70	0.0194	0.0590	3.24 ± 0.61	3.40 ± 0.75	0.1043	0.2897

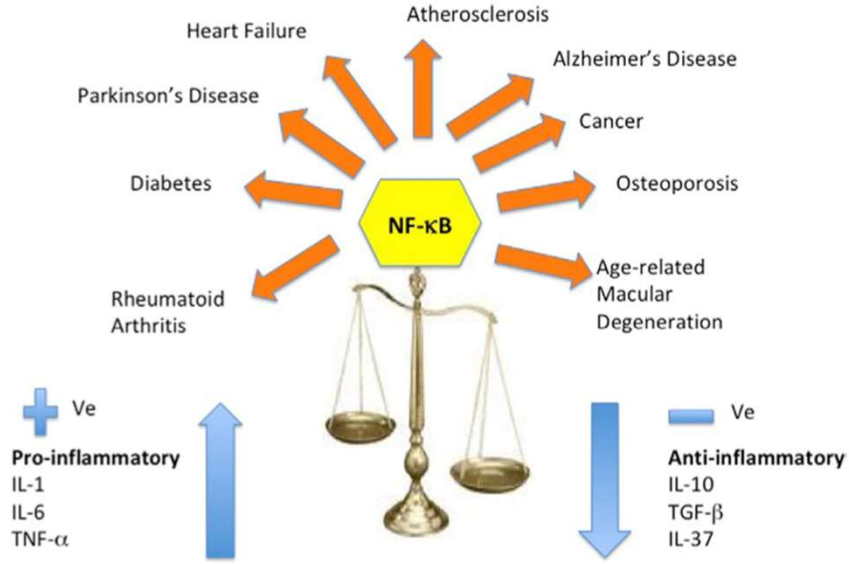
- A cross-sectional study comprising 117 obese patients (body mass index (BMI) 30) and 83 non-obese community-based volunteers;
- General obesity was associated with significantly elevated levels of IL-5, IL-10, IL-12, IL-13, IFN-γ and TNF-α, central obesity with significantly elevated IL-5, IL-10, IL-12, IL-13 and IFN-γ-levels.
- Results confirm up-regulation of certain pro- and anti-inflammatory cytokines in obesity

Schmidt FM et al Inflammatory cytokines in general and central obesity and modulating effects of physical activity. PLoS One. 2015 Mar 17;10(3):e0121971. doi: 10.1371/journal.pone.0121971.

Inflammatory cytokines as a risk factors for severe COVID-19

Inflamm-aging





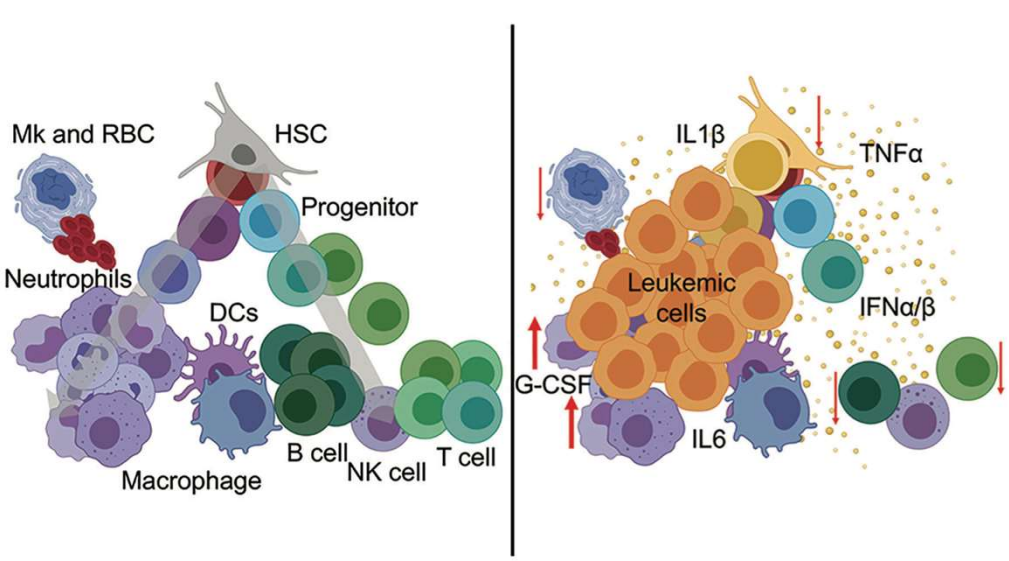
The major pro-inflammatory cytokines, such as IL-6, TNF- α, and IL-1α contribute significantly to the phenomenon of inflamm-aging in healthy elderly individuals , while also playing a major role in many age-related diseases

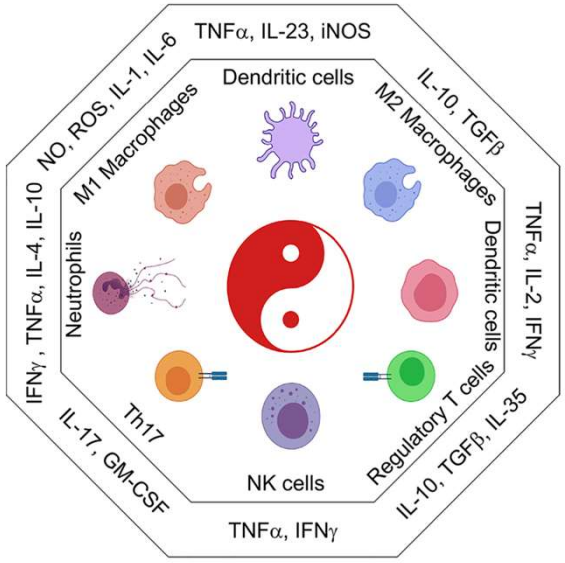
Cytokine dysregulation and NF-κB inflammation pathway

Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000 Jun;908:244-54. doi: 10.1111/j.1749-6632.2000.tb06651.x. Rea IM,. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Front Immunol. 2018 Apr 9;9:586.

Inflammatory cytokines as a risk factors for severe COVID-19

Inflammatory Cytokines Shape in Myeloid Malignancies





Increased IL-6 levels drive LSC expansion and associated pathologies and in CML, increased IL-1b predicts a poor prognosis.

it is likely that the efficacy for IL-10 might be best targeted in the early stages of diagnosis, where this cytokine could interrupt inflammatory cascades and alleviate leukemia-promoting inflammation.

Camacho V, Kuznetsova V, Welner RS. Inflammatory Cytokines Shape an Altered Immune Response During Myeloid Malignancies. Front Immunol. 2021 Nov 3;12:772408. doi: 10.3389/fimmu.2021.772408

Susceptibility, severity and clinical course

What did we learn from the previous epidemic?

Other Articles

June 3, 1961

Observations on Excess Mortality Associated with Epidemic Influenza

Theodore C. Eickhoff, M.D.; Ida L. Sherman, M.S.; Robert E. Serfling, Ph.D.

Author Affiliations

mortality pregnant women was 10%, and twice as high as that of non-pregnant women

ORIGINAL RESEARCH

Severity of 2009 Pandemic Influenza A (H1N1) Virus Infection in Pregnant Women

Creanga, Andreea A. MD, PhD; Johnson, Tamisha F. MD; Graitcer, Samuel B. MD; Hartman, Laura K. MD; Al-Samarrai, Teeb MD, MS; Schwarz, Aviva G. MPH; Chu, Susan Y. PhD, MSPH; Sackoff, Judith E. PhD; Jamieson, Denise J. MD; Fine, Anne D. MD; Shapiro-Mendoza, Carrie K. PhD, MPH; Jones, Lucretia E. MPH; Uyeki, Timothy M. MD, MPH; Balter, Sharon MD; Bish, Connie L. PhD, MPH; Finelli, Lyn DrPH; Honein, Margaret A. PhD

484 people in USA died from the 2009 H1N1 influenza, 28 (5.8%) were pregnant women, who accounted for only 1% of the US population

THE LANCET
Global Health

COMMENT | VOLUME 6, ISSUE 6, E607-E608, JUNE 01, 2018

Malaria in pregnancy: a call for a safe, efficient, and patient-centred approach to first-trimester treatment

V Bhargavi Rao • Tomas O Jensen • B Carolina Jimenez • Jo Robays • Estrella Lasry • Esther Sterk • et al.

Show all authors

Clinical Infectious Diseases

BRIEF REPORT

Middle East Respiratory Syndrome Coronavirus Infection During Pregnancy: A Report of 5 Cases From Saudi Arabia

Abdullah Assiri,[1] Glen R. Abedi,[2] Malak Al Masri,[1] Abdulaziz Bin Saeed,[1] Susan I. Gerber,[2] and John T. Watson[2]

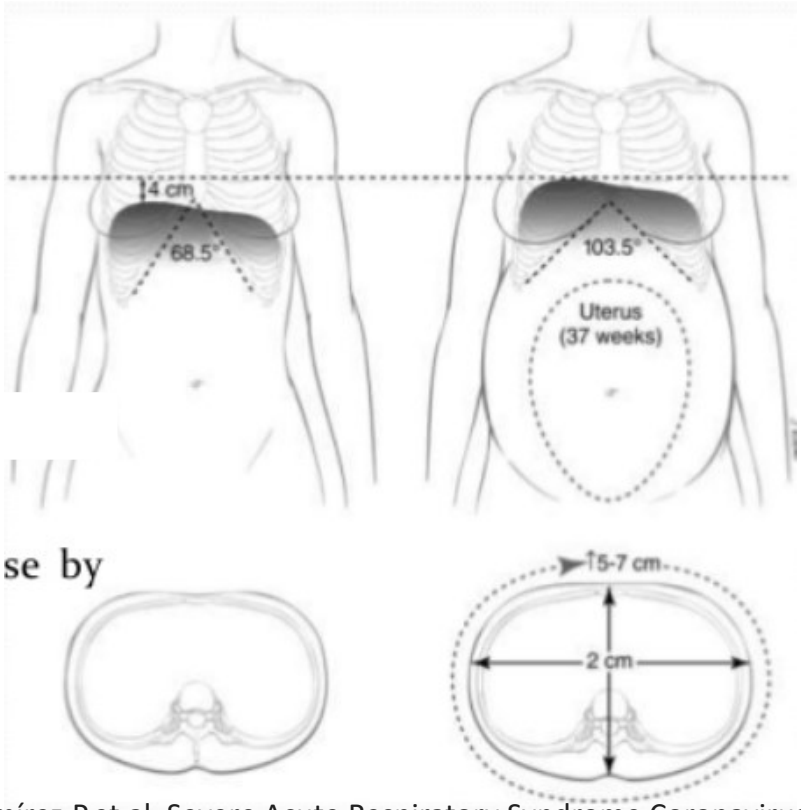
Table 1. Patient Characteristics and Pregnancy and Birth Outcomes in Confirmed Cases of Middle East Respiratory Syndrome Coronavirus in Saudi Arabia

Patient Characteristics and Outcomes	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Patient age, y	34	32	31	27	30
Gravida (G), para (P)	G7, P6	G2, P1	G1, P0	G1, P0	G1, P0
Gestational age at illness onset, wk	34	38	24	22	23
ICU admission	Yes	Yes	Yes	Yes	Yes
Maternal comorbid conditions	Preeclampsia	None	Asthma, pulmonary fibrosis, recurrent spontaneous pneumothoraces	None	None
Maternal outcome	Survived	Died	Died	Survived	Survived
Fetal outcome	Died	Survived	Died	Survived	Survived
Delivery details	Intrauterine fetal demise at 34 wk gestation	Vaginal delivery at 38 wk gestation	Surgical delivery at 24 wk gestation	Delivery at term	Delivery at term

Abbreviation: ICU, intensive care unit.

Susceptibility, severity and clinical course

Respiratory Changes in Pregnancy & Potential COVID Impact



- Less lung volume
- Increased secretions
- Increased minute ventilation
- Nasal mucosa

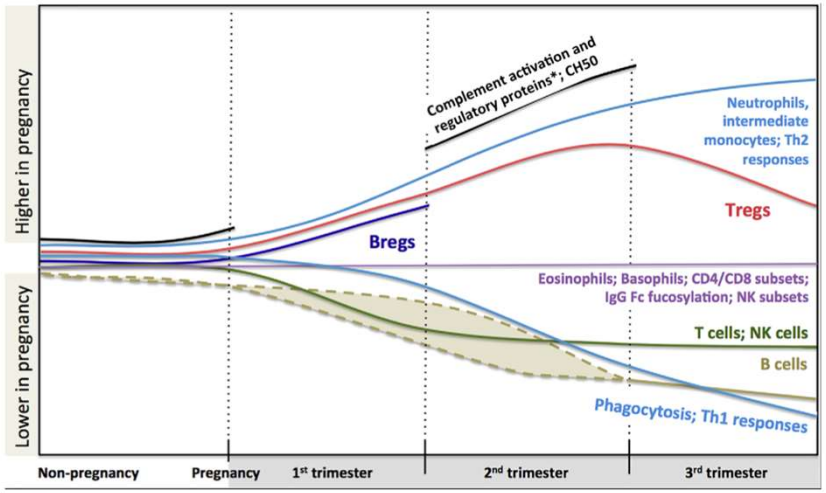
* Altered cellular immunity

Arterial blood gas measurement	1st trimester	3rd trimester	Nonpregnant
pH	7.42–7.46	7.43	7.4
↑ PaO2 (mm Hg)	105–106	101–106	93
↓ PaCO2 (mm Hg)	28–29	26–30	37
↓ Serum HCO3 (mEq/L)	18	17	23

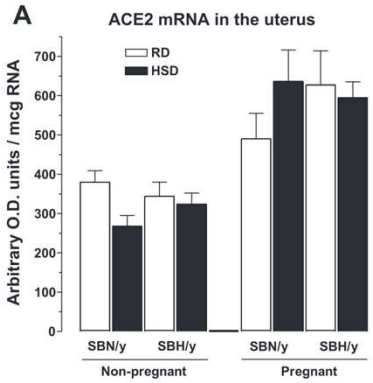
Ayala-Ramírez P,et al. Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Pregnancy. A Non-systematic Review of Clinical Presentation, Potential Effects of Physiological Adaptations in Pregnancy, and Placental Vascular Alterations. Front Physiol. 2022 Mar 30;13:785274. doi: 10.3389/fphys.2022.785274

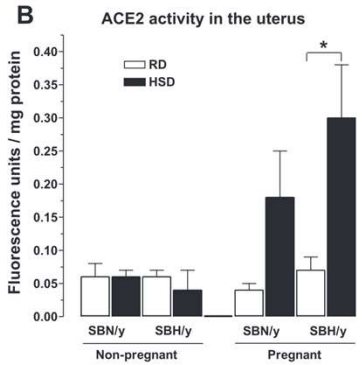
Susceptibility, severity and clinical course

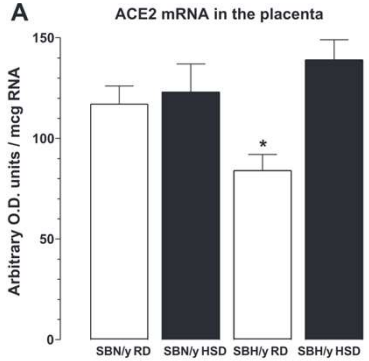
Changes in the immune system and ACE 2 receptor & Potential COVID Impact



- ↑ complement activity during pregnancy (↑ Plasma levels of C3a, C4a, C5a, C4d, C3a, C3, C9, and the Serum Complement Membrane Attack Complex SC5b9)
- hypercoagulable state, with a four-fold increased risk for deep vein thrombosis when compared to non-pregnant women
- A shift from the typically predominant T-helper 1 (Th1) system (pro- inflammatory cytokines including Interferon-g, Tumor Necrosis Factor-α, and Interleukin (IL)-2), toward Th2 system dominance (characterized by presence of anti-inflammatory cytokines includ-ing IL-4, IL-5, IL-10, and IL-13). This shift occurs in the interest of fetal protection, it does so at the expense of maternal vulnerability to viral infection, which is better contained by the Th1 system







The relative levels of ACE2 mRNA in the pregnant animal were placenta > kidneys > or = uterus and of ACE2 activity kidney > placenta > uterus

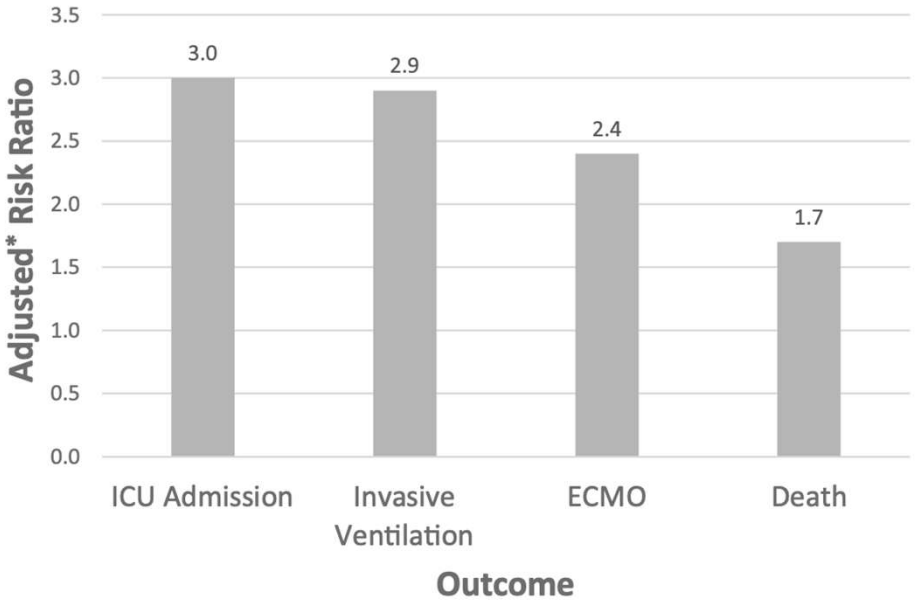
During pregnancy, the placentas, in particular, but also the uterus, constitute important sources of ACE2, in addition to its normal production in the kidney, leading to an estimated twofold increase in total ACE2 activity.

Abu-Raya B, et al. Maternal Immunological Adaptation During Normal Pregnancy. Front Immunol. 2020 Oct 7;11:575197

Levy A, et al. ACE2 expression and activity are enhanced during pregnancy. Am J Physiol Regul Integr Comp Physiol. 2008 Dec;295(6):R1953-61. doi: 10.1152/ajpregu.90592.2008

Susceptibility, severity and clinical course

FIGURE
Risk of severe COVID-19 among pregnant persons compared with non-pregnant women[9]



ECMO, extracorporeal membrane oxygenation; *ICU*, intensive care unit. *Adjusted by age, race and ethnicity, and underlying medical conditions.

Jamieson. COVID in pregnancy. Am J Obstet Gynecol 2022.

TABLE 3
Comparison of primary and secondary outcomes between the 2 groups after applying the propensity score matching

Variable	Control group 1 (n=107)	Case group 2 (n=83)	Adjusted *P* value
Primary outcome			
ICU admission	2.38	11.08	.024
Secondary outcomes			
Hospital admission for COVID-19	17.4	58.21	<.001
Need for oxygen therapy	17.24	36.04	.006
Endotracheal intubation	1.67	10.16	.022

Data are presented as percentage.

COVID-19, coronavirus disease 2019; *ICU*, intensive care unit.

Badr. Coronavirus disease 2019 in pregnancy. Am J Obstet Gynecol 2020.

- Multicentric, France and Belgium, 4 hospitals
- From January 1, 2020, and May 13, 2020
- Pregnant women were at higher risk for ICU admission than nonpregnant women (11.08% vs 2.38%; P¼.024).
- In addition, they were also at higher risk for hospital admission because of COVID-19 respiratory decompensation such as dyspnea and hypoxemia (58.21% vs 17.4%; P<.001)
- However, there were no cases of mortality in either of the 2 groups.

Jamieson DJ, Rasmussen SA. An update on COVID-19 and pregnancy. Am J Obstet Gynecol. 2022 Feb;226(2):177-186. doi: 10.1016/j.ajog.2021.08.054
Badr DA, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol. 2020 Nov;223(5):764-768. doi: 10.1016/j.ajog.2020.07.045
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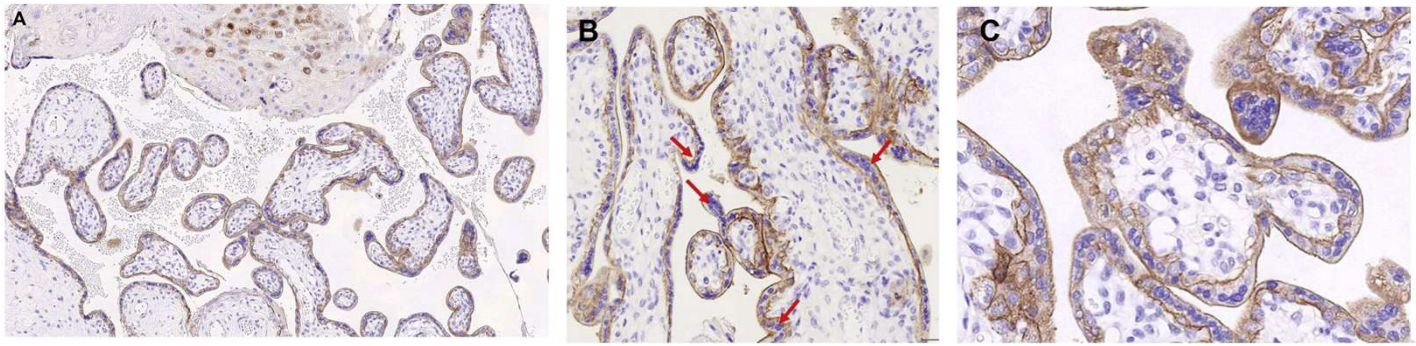
Transmission of SARS-CoV-2 to the fetus and neonate



Diffuse membranous staining of villous cytotrophoblast and syncytiotrophoblast cells (arrows) with monoclonal Anti-ACE2 antibody (clone CL4035), dilution 1/1000 in a COVID-19 positive mother, 19 weeks of amenorrhea.

Clinical Microbiology and Infection 27 (2021) 489–490

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

SARS-CoV-2 ACE-receptor detection in the placenta throughout pregnancy

Carole Gengler [1], Estelle Dubruc [1], Guillaume Favre [2], Gilbert Greub [3], Laurence de Leval [1], David Baud [2, *]

[1] Institute of Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[2] Materno-fetal and Obstetrics Research Unit, Department Woman-Mother-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[3] Center for Research on Intracellular Bacteria, Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, CH-1011, Lausanne, Switzerland

Hypothetically, two conditions are necessary for transplacental transmission to be possible:

(a) the receptor for the virus, angiotensin-converting enzyme 2 (ACE2),

(b) must be present in the placenta the virus must reach the placenta;

In situ analyses **by specific immunohistochemistry and SARS-CoV-2 detection by RT-PCR** indicate a possible placental infection by SARS-CoV2. **Trophoblastic cells**, which are in direct contact with the maternal blood in the intervillous space, show **strong expression of ACE2 throughout pregnancy**, supporting that SARS-CoV2 is able to infect the placenta via a receptor-mediated mechanism.

Gengler C, Dubruc E, Favre G, Greub G, de Leval L, Baud D. SARS-CoV-2 ACE-receptor detection in the placenta throughout pregnancy. Clin Microbiol Infect. 2021 Mar;27(3):489-490. doi: 10.1016/j.cmi.2020.09.049.

Transmission of SARS-CoV-2 to the fetus and neonate

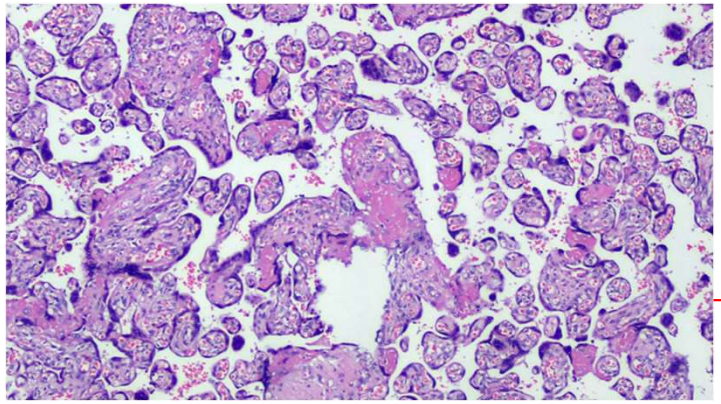
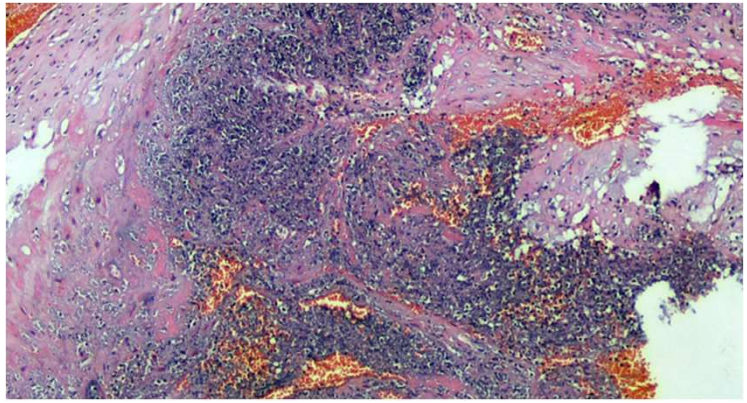


Table 2. Placental findings in SARS-COV-2 and control groups.

Placental Finding	SARS-COV-2 Group (71 Cases)	Control Group (142 Cases)	Uncorrected *p* Values	FDR-Corrected *p* Values
Weight (grams), means ± sd (range)	515 ± 84 (240–760)	499.2 ± 176.6 (130–1020)	0.48	0.48
Maternal malperfusion, n (%)	38 (54.3)	62 (43.7)	0.15	0.19
Decidual arteriopathy, n (%)	29 (40.9)	2 (1.4)	<0.0001	<0.0001
Fetal malperfusion, n (%)	15 (21.1)	6 (4.2)	<0.0001	<0.0001
Decidual inflammation, n (%)	23 (32.4)	1 (0.7)	<0.0001	<0.0001
Perivillous fibrin deposition, n (%)	26 (36.6)	5 (3.5)	<0.0001	<0.0001
Terminal villous hyperplasia n (%)	14 (19.7)	30 (21.1)	0.81	0.81
Villous hypervascularization, n (%)	9 (12.7)	49 (34.5)	0.0007	0.0011
Thrombi in fetal vessels, n (%)	16 (22.2)	1 (0.7)	<0.0001	<0.0001
Chorioamnionitis, n (%)	5 (7)	7 (4.9)	0.37	0.41

FDR correction was performed separately for means comparisons and for proportion comparisons. *n* = number of cases.

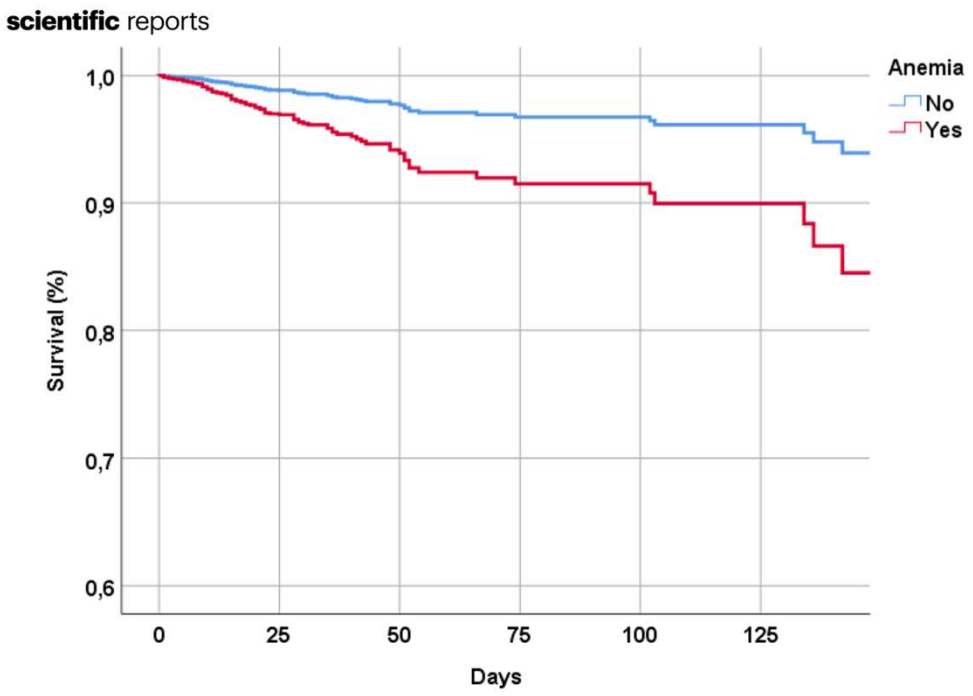


- there are some more frequent characteristics in the placentas of infected women, in particular, maternal thrombosis and deciduous, increased intervillous fibrin, and, in rare cases, fetal thrombosis.
- The immunohistochemical investigation demonstrates **positivity for the anti-SARS-CoV-2 spike glycoprotein** antibody both among maternal cells (including inflammatory intervillary cells) and in the trophoblast, and rarely in the endothelium.
- The ultrastructural investigation demonstrated both the suffering of fetal endothelia and the presence of particles attributable to SARS-CoV-2 in the trophoblast, in conjunction with its degeneration.

Resta L, et al. SARS-CoV-2 and Placenta: New Insights and Perspectives. Viruses. 2021 Apr 21;13(5):723. doi: 10.3390/v13050723.

Anemia and risk for disease progression

www.nature.com/scientificreports

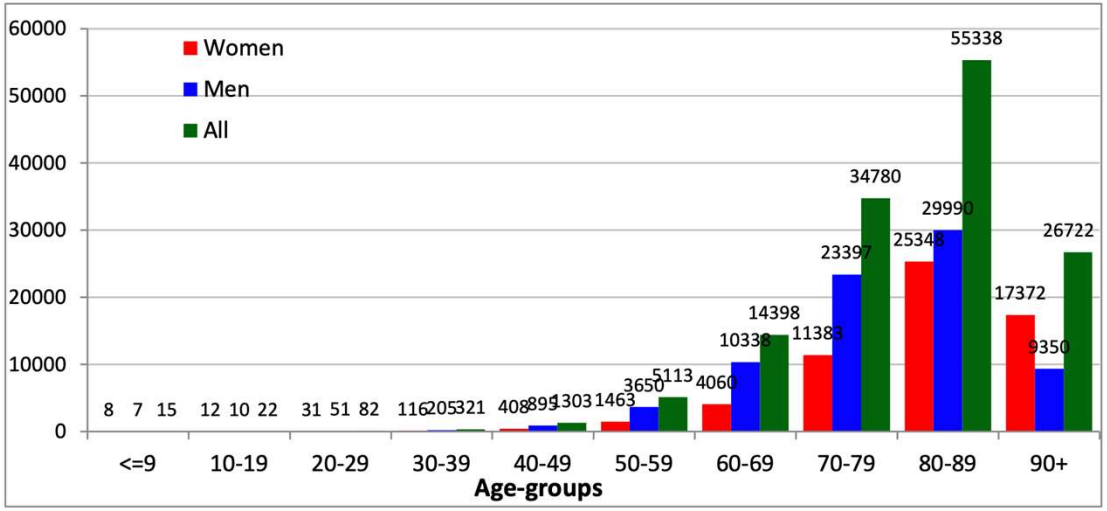


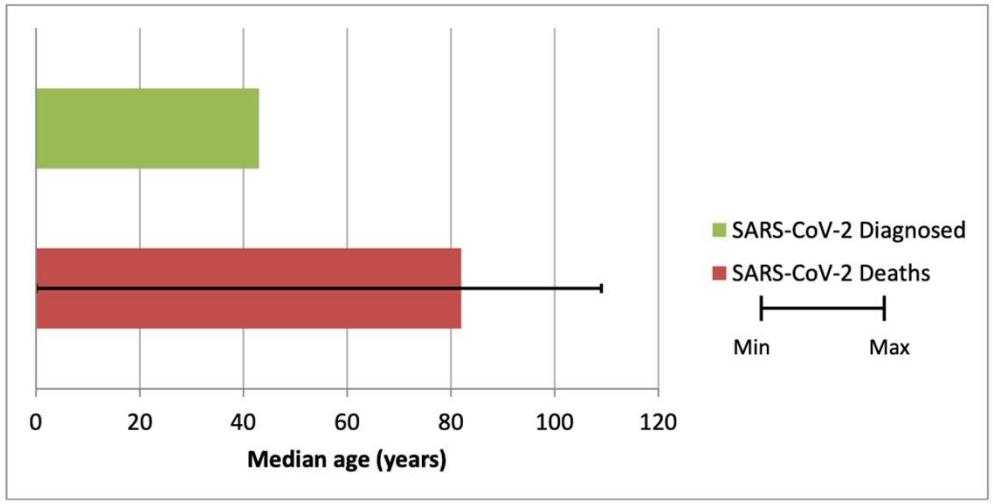
	No anemia	Anemia	
		All sample	Propensity score[4]
Mortality, incidence rate[1]	243 (135–439)	934 (610–1434)	–
Risk of mortality, model 1[2]	1, reference	3.19 (1.97–5.14)	–
Risk of mortality, model 2[3]	1, reference	2.68 (1.59–4.52)	1.91 (1.10–3.32)
Risk of severe COVID-19, model 1[2]	1, reference	6.59 (5.11–8.49)	–
Risk of severe COVID-19, model 2[3]	1, reference	2.31 (1.65–3.24)	1.77 (1.26–2.48)

Parameter (n = 1562)	No anemia (n = 857)	Anemia (n = 705)	*p*-value
Age, mean (± SD)	57.1 (16.0)	60.2 (16.4)	< 0.0001
Females, n (%)	372 (43.4)	**312** (44.3)	0.74
Comorbidities, n (%)			
At least one comorbidity	339 (39.6)	416 (59.0)	< 0.0001
Hypertension	360 (42.0)	351 (49.8)	0.002
Actual smoking	86 (10.0)	68 (9.7)	0.313
Previous smoking	32 (3.7)	17 (2.4)	
Dyslipidemia	99 (11.6)	80 (11.3)	0.9
Diabetes mellitus	161 (18.8)	176 (24.9)	< 0.0001
Renal failure	32 (3.7)	223 (10.1)	< 0.0001
Clinical presentation, n (%)			
Dyspnea	373 (43.5)	21 (31.6)	< 0.0001
Anosmia	59 (6.9)	71 (3.0)	< 0.0001
Dysgeusia	117 (13.7)	177 (25.1)	< 0.0001
Fever	609 (71.1)	379 (53.8)	< 0.0001
Cough	318 (37.1)	253 (35.9)	0.610
Gastrointestinal symptoms	179 (20.9)	238 (33.8)	< 0.0001
Oxygen saturation < 92% (%)	150 (17.5)	247 (35.0)	< 0.0001
Laboratory parameters, n (%)			
Elevated Procalcitonin	148 (17.3)	253 (35.9)	< 0.0001
Elevated D-Dimer	501 (58.5)	446 (63.3)	0.011
Elevated CRP	688 (80.3)	633 (89.8)	< 0.0001
Elevated Troponin	97 (11.3)	120 (17.0)	< 0.0001
Elevated Transaminases	132 (15.4)	107 (15.2)	0.99
Elevated IL6	372 (43.4)	293 (41.6)	< 0.0001
Elevated Ferritine	294 (34.3)	331 (47.0)	< 0.0001
Elevated LDH	252 (29.4)	252 (35.7)	< 0.0001
Low platelets levels	122 (14.2)	96 (13.6)	0.725
Presence of pneumonia at the CT scan or chest X-ray, n (%)	803 (93.7)	675 (95.7)	0.074
Use of Venturi's mask during hospitalization, n (%)	440 (51.3)	568 (80.6)	< 0.0001
Use of high flow oxygen, n (%)	156 (18.2)	456 (64.7)	< 0.0001

Saracino & team. Anemia as a risk factor for disease progression in patients admitted for COVID-19: data from a large, multicenter cohort study. Sci Rep. 2023 Jun 3;13(1):9035. doi: 10.1038/s41598-023-36208-y.

Characteristics of SARS-CoV-2 patients dying in Italy Report based on available data on January 10th, 2022



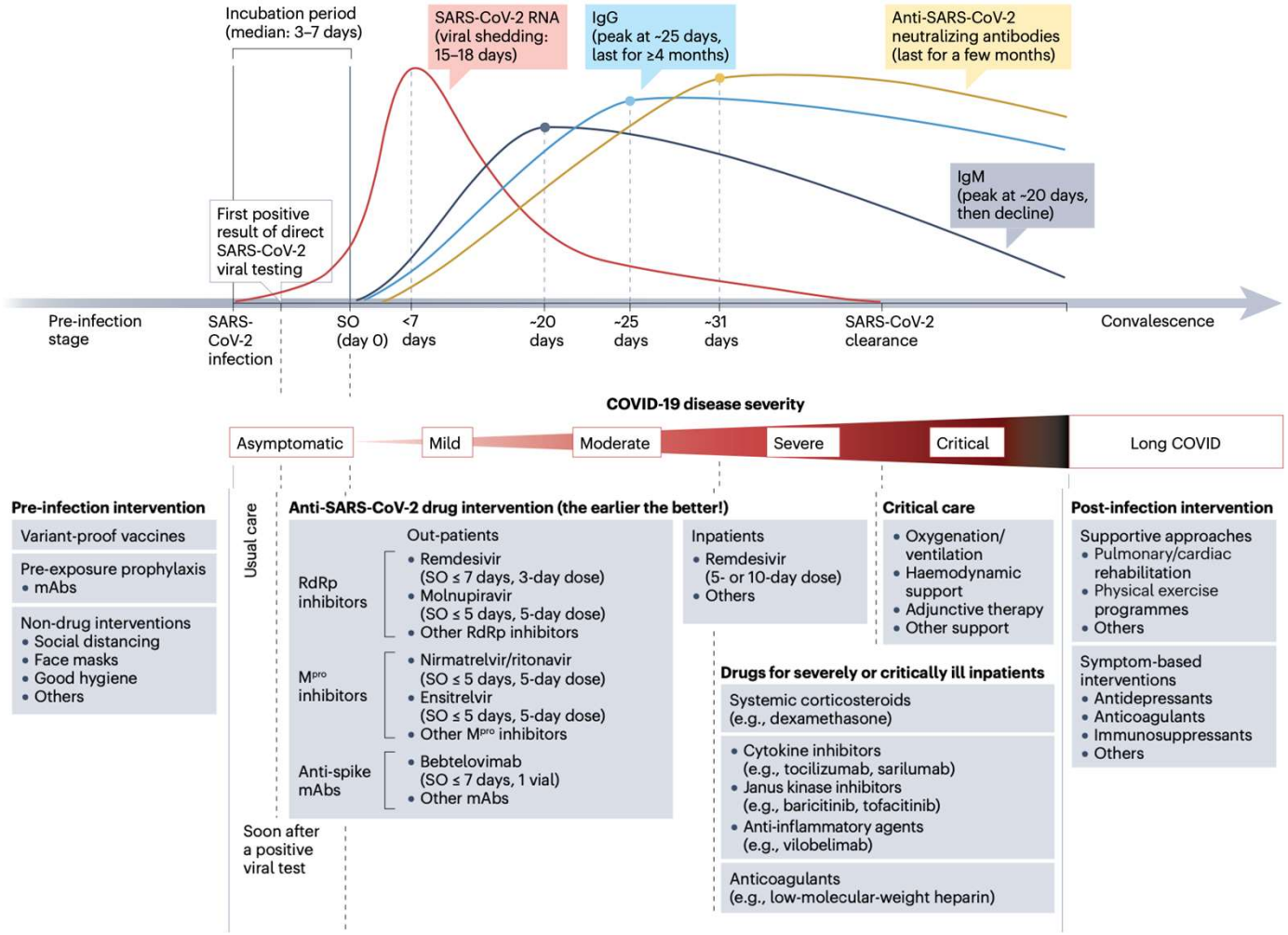


	All		Women		Men	
Diseases	***N***	***%***	***N***	***%***	***N***	***%***
Ischemic heart disease	2,379	*28.2*	810	*23.7*	1,569	*31.3*
Atrial Fibrillation	2,114	*25.1*	901	*26.3*	1,213	*24.2*
Heart failure	1,349	*16.0*	623	*17.8*	726	*14.2*
Stroke	950	*11.3*	419	*12.2*	531	*10.6*
Hypertension	5,550	*65.8*	2,327	*68.0*	3,223	*64.3*
Type 2-Diabetes	2,459	*29.1*	934	*27.3*	1,525	*30.4*
Dementia	1,987	*23.6*	1,095	*32.0*	892	*17.8*
COPD (Chronic Obstructive Pulmonary Disease)	1,476	*17.5*	487	*14.2*	989	*19.7*
Active cancer in the past 5 years	1,362	*16.1*	490	*14.3*	872	*17.4*
Chronic liver disease	427	*5.1*	145	*4.2*	282	*5.6*
Dialysis	198	*2.3*	66	*1.9*	132	*2.6*
HIV Infection	19	*0.2*	2	*0.1*	17	*0.3*
Autoimmune diseases	397	*4.7*	221	*6.5*	176	*3.5*
Obesity	981	*11.6*	391	*11.4*	590	*11.8*

Con la fine dello stato di emergenza, al 30 marzo 2022, i centri clinici non hanno più inviato le cartelle cliniche e i certificati, pertanto i report di approfondimento sulle caratteristiche dei decessi **non sono stati più elaborati**.

https://www.epicentro.iss.it/coronavirus/sars-cov-2-decessi-italia-archivio

Anti-SARS-CoV-2 drug intervention (the earlier the better!)



Li G, et al. Therapeutic strategies for COVID-19: progress and lessons learned. Nat Rev Drug Discov. 2023 Jun;22(6):449-475. doi: 10.1038/s41573-023-00672-y.

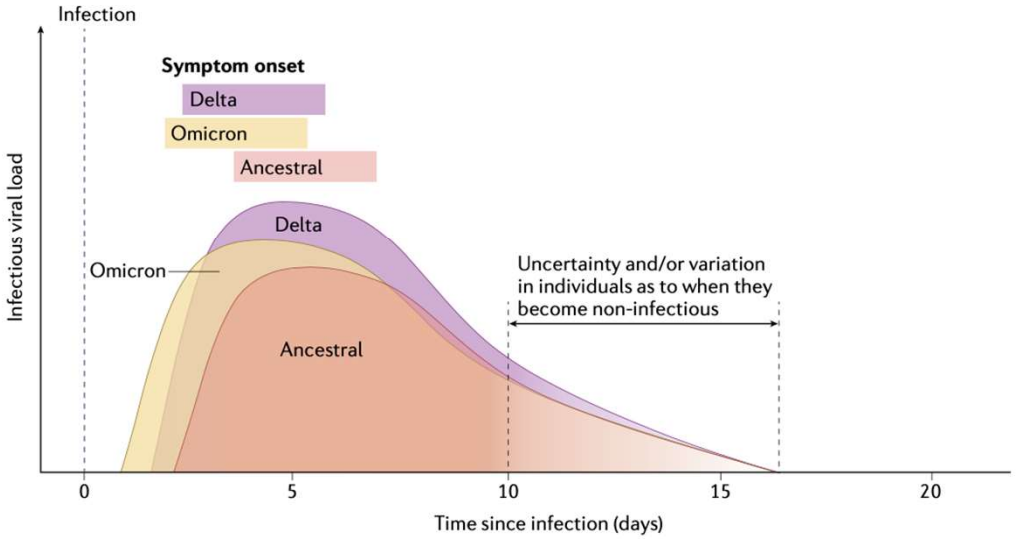
SARS-CoV-2 viral load and shedding kinetics

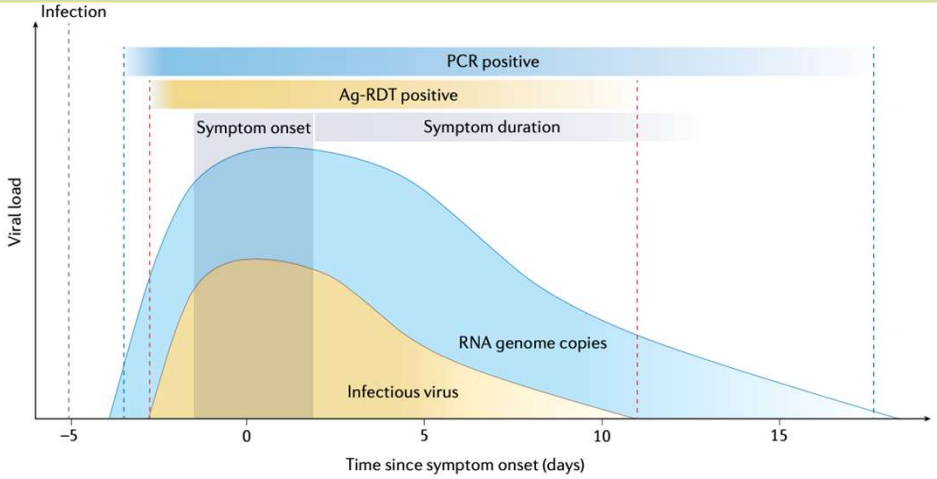
nature reviews microbiology
https://doi.org/10.1038/s41579-022-00822-w

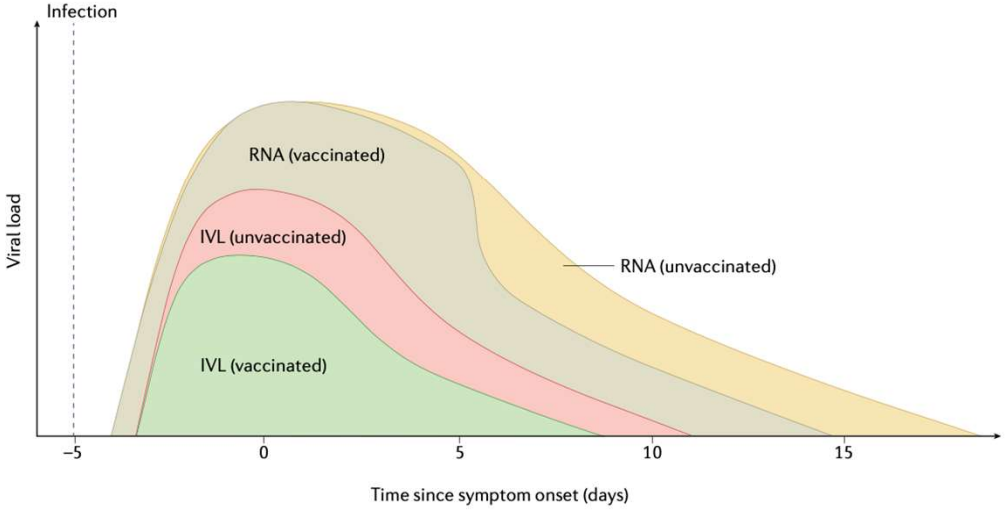
Review article
Check for updates

SARS-CoV-2 viral load and shedding kinetics

Olha Puhach[1], Benjamin Meyer[2] & Isabella Eckerle[1,3,4]

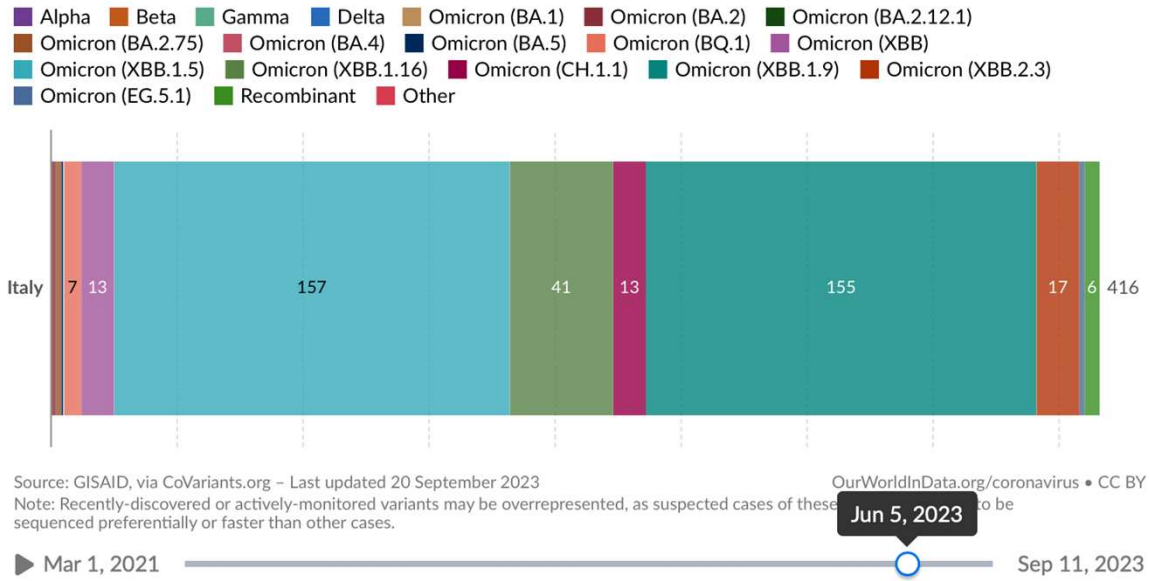






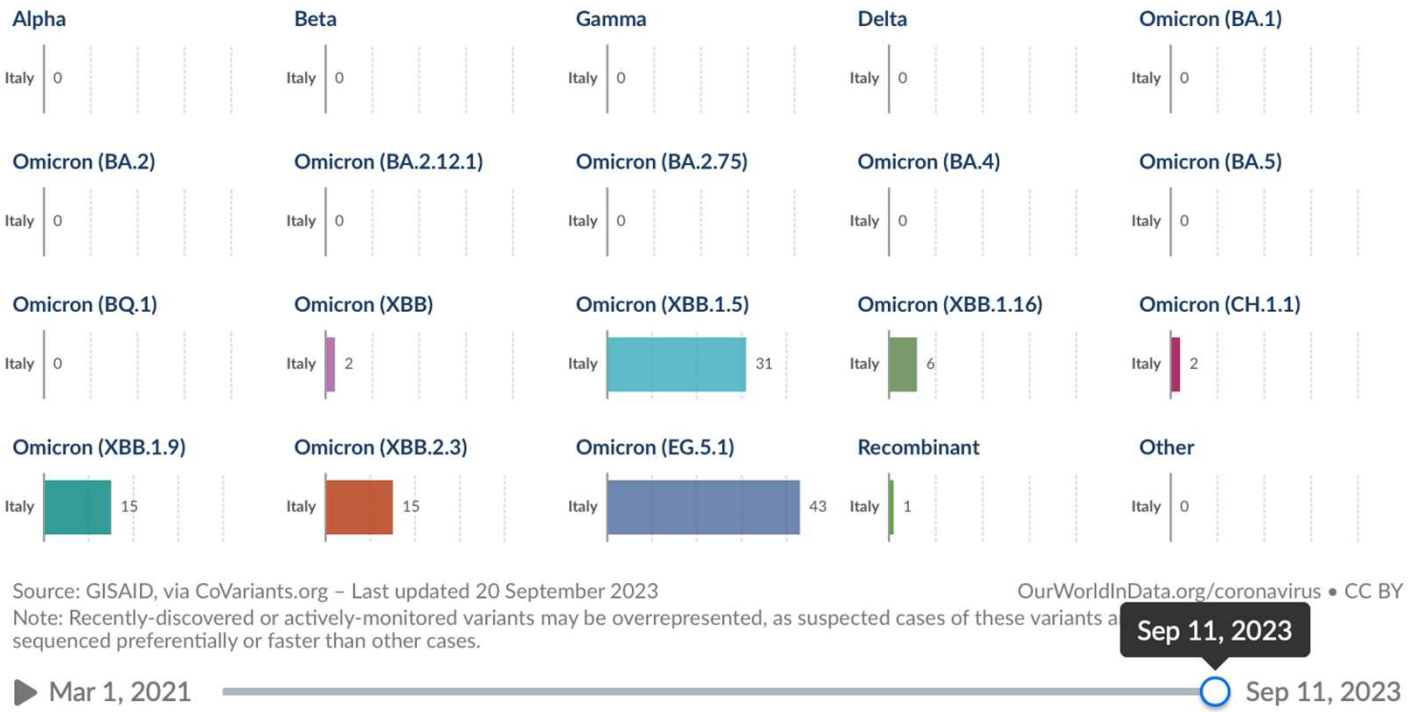
Puhach, O., Meyer, B. & Eckerle, I. SARS-CoV-2 viral load and shedding kinetics. *Nat Rev Microbiol* **21**, 147–161 (2023). https://doi.org/10.1038/s41579-022-00822-w

SARS CoV-2 sequences by variant



https://ourworldindata.org/grapher/covid-variants-bar?country=~ITA

SARS CoV-2 sequences by variant



New versions of the Moderna, Novavax, and Pfizer boosters, expected in the coming weeks, were designed to work against XBB.1.5, a close cousin of EG.5's ancestor XBB.1.9.2.

They are expected to offer better protection than existing vaccines against the EG.5 lineage.

Check for updates

Montreal

Cite this as: *BMJ* 2023;382:p1900
http://dx.doi.org/10.1136/bmj.p1900
Published: 16 August 2023

Covid-19: Infections climb globally as EG.5 variant gains ground

Owen Dyer

Neutralisation sensitivity of SARS-CoV-2 lineages

THE LANCET
Infectious Diseases

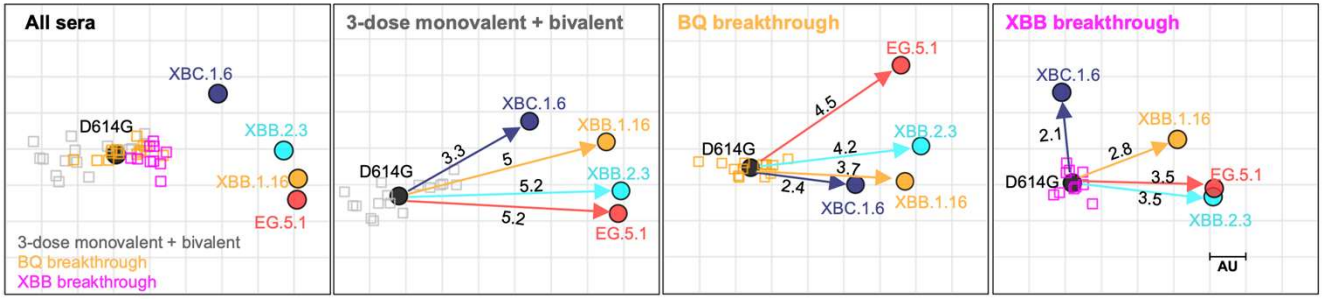
CORRESPONDENCE | ONLINE FIRST

Antibody neutralisation of emerging SARS-CoV-2 subvariants: EG.5.1 and XBC.1.6

Qian Wang • Yicheng Guo • Richard M Zhang • Jerren Ho • Hiroshi Mohri • Riccardo Valdez • David M Manthei • Aubree Gordon • Lihong Liu • David D Ho • Show less

Published: September 11, 2023 • DOI: https://doi.org/10.1016/S1473-3099(23)00555-8

VOCs	Q52	E180	G252	D253	F456	K478	S486	P521
XBB								
XBB.1.5			V				P	
XBB.1.16		V	V			R	P	
XBB.2.3				G			P	S
EG.5			V		L		P	
EG.5.1	H		V		L		P	



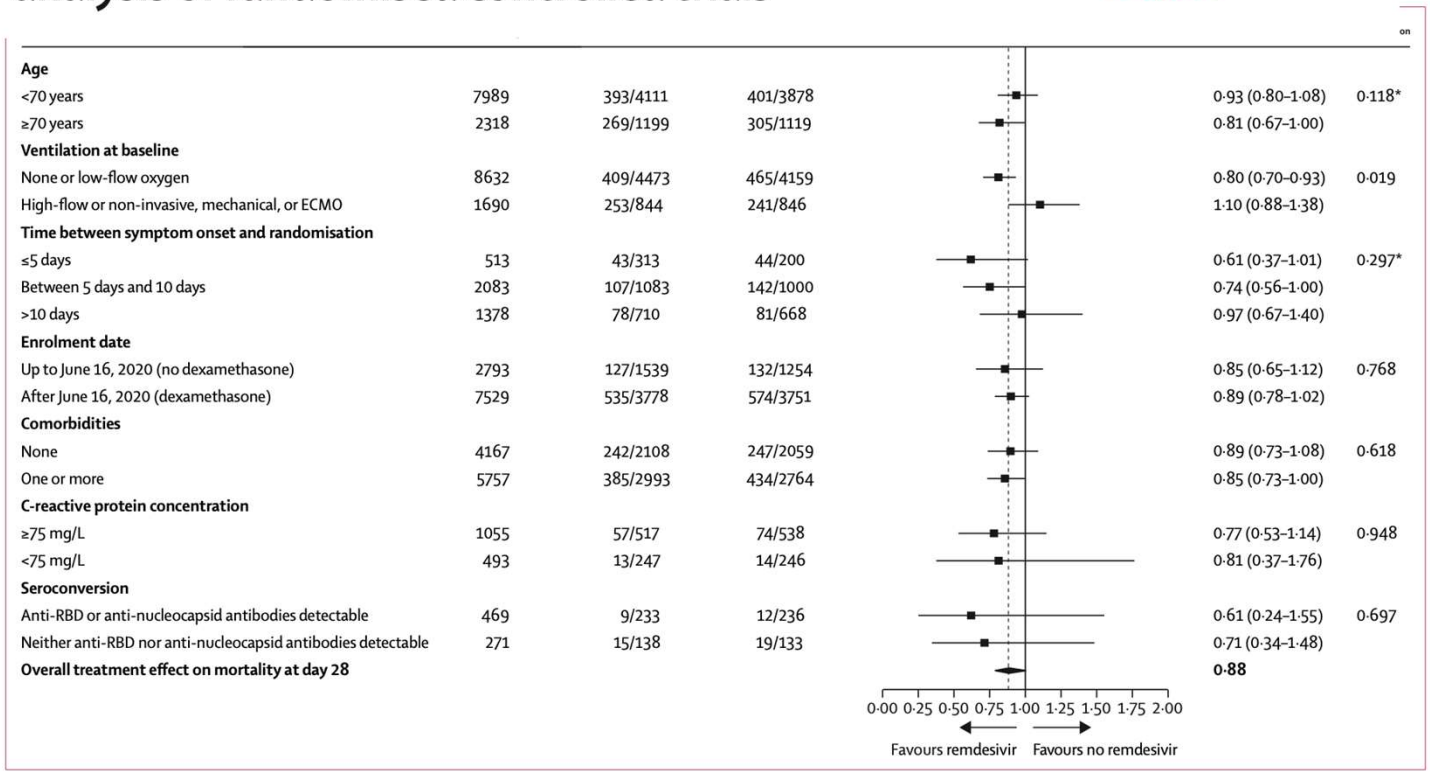
The first cohort comprised individuals who received one of the BA.5 bivalent COVID-19 mRNA vaccines after receiving three doses of one of the original COVID-19 mRNA vaccines. The other two cohorts included individuals who had a BQ or XBB subvariant breakthrough infection after multiple vaccinations.

Subvariants EG.5 and EG.5.1 are only modestly (1·7-fold) more resistant to neutralisation by serum antibodies than the previously dominant subvariant XBB.1.5

Remdesivir patients hospitalised: the role of time

Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials

Lancet Respir Med 2023; 11: 453–64



Age					
<70 years	7989	393/4111	401/3878	0·93 (0·80–1·08)	0·118*
≥70 years	2318	269/1199	305/1119	0·81 (0·67–1·00)	
Ventilation at baseline					
None or low-flow oxygen	8632	409/4473	465/4159	0·80 (0·70–0·93)	0·019
High-flow or non-invasive, mechanical, or ECMO	1690	253/844	241/846	1·10 (0·88–1·38)	
Time between symptom onset and randomisation					
≤5 days	513	43/313	44/200	0·61 (0·37–1·01)	0·297*
Between 5 days and 10 days	2083	107/1083	142/1000	0·74 (0·56–1·00)	
>10 days	1378	78/710	81/668	0·97 (0·67–1·40)	
Enrolment date					
Up to June 16, 2020 (no dexamethasone)	2793	127/1539	132/1254	0·85 (0·65–1·12)	0·768
After June 16, 2020 (dexamethasone)	7529	535/3778	574/3751	0·89 (0·78–1·02)	
Comorbidities					
None	4167	242/2108	247/2059	0·89 (0·73–1·08)	0·618
One or more	5757	385/2993	434/2764	0·85 (0·73–1·00)	
C-reactive protein concentration					
≥75 mg/L	1055	57/517	74/538	0·77 (0·53–1·14)	0·948
<75 mg/L	493	13/247	14/246	0·81 (0·37–1·76)	
Seroconversion					
Anti-RBD or anti-nucleocapsid antibodies detectable	469	9/233	12/236	0·61 (0·24–1·55)	0·697
Neither anti-RBD nor anti-nucleocapsid antibodies detectable	271	15/138	19/133	0·71 (0·34–1·48)	
Overall treatment effect on mortality at day 28				**0·88**	

Figure 2: **Forest plot presenting subgroup analyses for the primary endpoint**

RCTs of remdesivir in adult patients hospitalised with COVID-19 until April 11, 2022

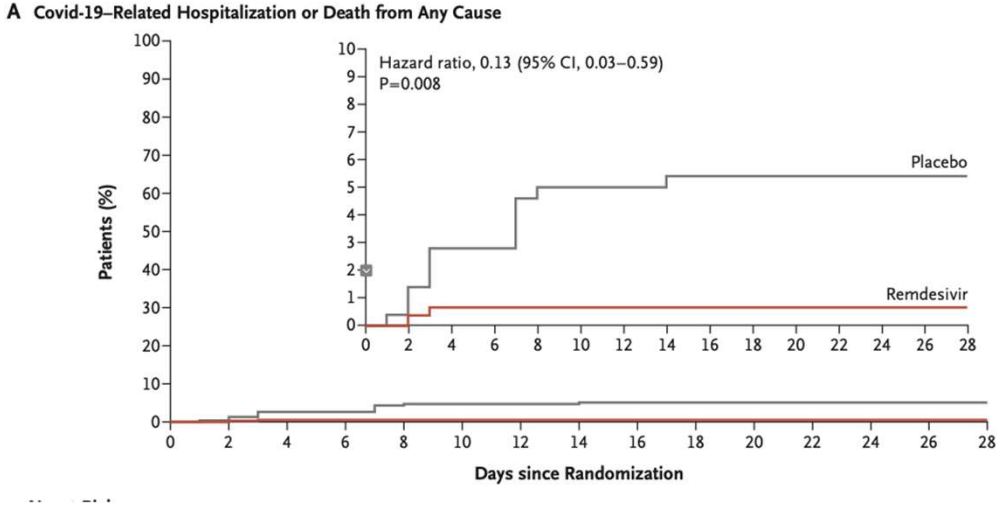
10 480 patients hospitalised with COVID-19

Remdesivir reduced mortality in patients hospitalised with COVID-19 who required no or conventional oxygen support, but was underpowered to evaluate patients who were ventilated when receiving remdesivir

Remdesivir did not increase the frequency of severe or serious adverse events

Amstutz A, Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet Respir Med. 2023 Aug;11(8):e77.

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



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)	—

Remdesivir Better — Placebo Better

Figure 2. Covid-19–Related Hospitalization or Death from Any Cause at Day 28 in More Than 5% of the Trial Population, According to Demographic and Clinical Characteristics at Baseline.

From September 18, 2020, through April 8, 2021, patients were enrolled at 64 sites in the United States, Spain, Denmark, and the United Kingdom. A total of 562 patients who underwent randomization and received at least one dose of remdesivir or placebo were included in the analyses: 279 patients in the remdesivir group and 283 in the placebo group

A randomized, double-blind, placebo-controlled trial involving non- hospitalized patients with Covid-19 who had symptom onset within the previous 7 days and who had at least one risk factor for disease progression.

Patients were randomly assigned to receive intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo.

The primary efficacy end point was a composite of Covid-19– related hospitalization or death from any cause by day 28. The primary safety end point was any adverse event. A secondary end point was a composite of a Covid-19– related medically attended visit or death from any cause by day 28.

Gottlieb RL, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2022 Jan 27;386(4):305-315. doi: 10.1056/NEJMoa2116846.

Real life experience on the use of Remdesivir Bari

Table 1. Baseline characteristics by use or not of remdesivir, after the matching using a propensity score.

Parameter	Controls (n=365)	Remdesivir (n=365)	p-value
Demographics			
Age (mean, SD)	55.4 (15.0)	56.2 (17.1)	0.52
Females (%)	59.7	52.6	0.06
Current smokers (%)	9.3	3.0	<0.0001
Comorbidities			
Any comorbidity	47.1	52.1	0.21
Hypertension	48.8	40.3	0.03
Dyslipidemia	20.5	26.6	0.07
Type 2 diabetes	20.8	14.2	0.03
Obesity	16.4	9.0	0.005
COVID-19 clinics			
Dyspnea	36.7	28.5	0.02
Anosmia	4.9	6.6	0.43
Dysgeusia	18.1	28.5	0.001
Fever	58.9	76.2	<0.0001
Cough	34.2	41.4	0.06
Gastrointestinal symptoms (%)	14.8	20.5	0.05
SpO2 <92%	71.0	71.0	1.00
Presence of pneumonia	93.2	94.0	0.76
Vaccinated against COVID-19 (%)	62.5	24.9	<0.0001
Other therapies			
Use of corticosteroids	72.6	81.6	0.05
Use of heparins	80.0	81.6	0.64
Use of monoclonal antibodies	8.9	11.8	0.25

The initial cohort included a total of 1,883 patients hospitalized for COVID-19. Of them, 1,070 used remdesivir during the hospital stay.

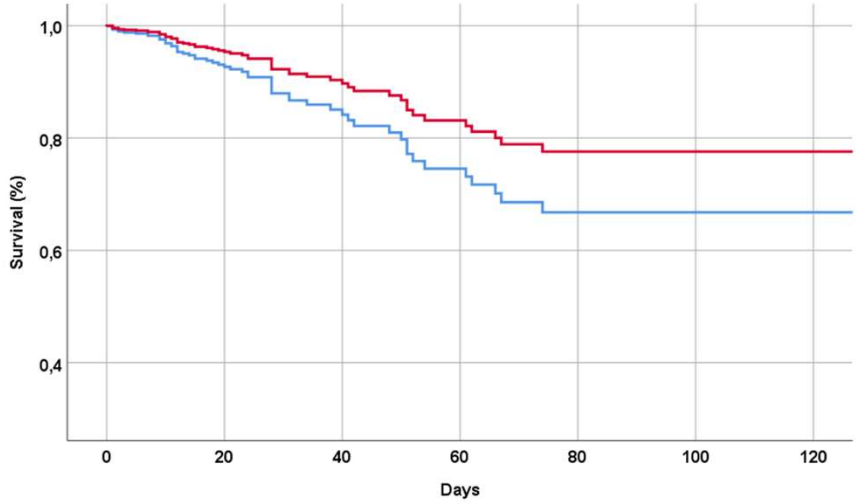
The 1,070 participants taking remdesivir differed for several clinical characteristics compared to the 813 controls, particularly regarding comorbidities and presence of pneumonia radiologically identified ($p<0.0001$ for all the comparisons).

Therefore, a propensity score matching was proposed for better accounting of these baseline differences.

Saracino group. Real life experience on the use of remdesivir in patients admitted to covid-19 in two referral italian hospital: a propensity score matched analysis. Under review on Scientific Report.

Real life experience on the use of Remdesivir Bari

Figure 1. Association between use of remdesivir and mortality during the follow-up period.



In red patients taking remdesivir, in blue controls. The analyses were made after matching using a propensity score our sample.

Table 2. Association between remdesivir and outcomes of interest, after the matching using a propensity score.

Outcome	Cumulative incidence in controls	Cumulative incidence in remdesivir	HR/OR, 95%CI	p-value
Mortality	11.2	4.7	0.63 (0.35-0.92)	0.01
Use of non-invasive ventilation during hospitalization	81.6	52.7	0.25 (0.18-0.35)	<0.0001
Severe COVID[1]	85.5	71.0	0.42 (0.29-0.60)	<0.0001

Notes: 1. Severe COVID-19 was defined as qSOFA scores ≥2 or CURB-65 scores ≥3 or admission in intensive care unit. The results are reported as hazard ratios (HRs) with their 95% confidence intervals (CIs), after a propensity-score analysis, including vaccination status at the baseline.

The use of Remdesivir was associated with a reduction in disease progression with a lower incidence of non-invasive ventilation and severe COVID-19 cases, with a reduction in these risks of almost 75%.

365 patients taking Remdesivir, we observed two cases of mild renal failure requiring a reduction in the dosage of Remdesivir and two cases in which the physicians decided to interrupt Remdesivir for bradycardia and for QT elongation.

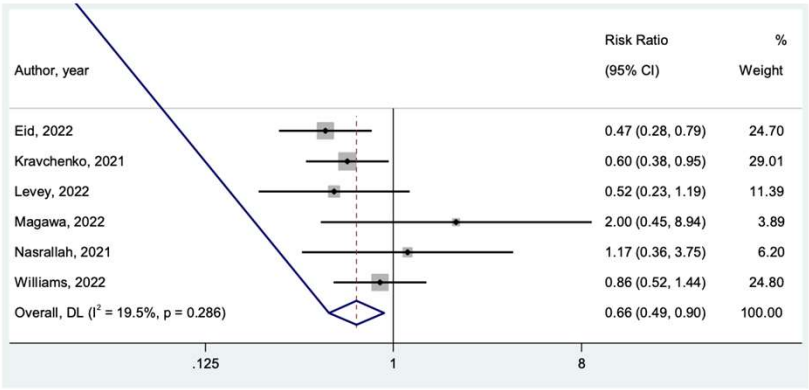
Saracino group. Real life experience on the use of remdesivir in patients admitted to covid-19 in two referral italian hospital: a propensity score matched analysis. Under reviw on Scientific Report.

Efficacy and safety of therapies for covid-19 in pregnancy

Table 2. Meta-analysis of the delivery outcomes for the studies included

Outcome	Number of studies	Sample size	Risk ratio (95% CI)	p-value	I2	Egger's test (SE), p-value
Cesarean section	6	1627	0.665 (0.491-0.899)	0.008	19.5	1.62 (1.10) P=0.22
Preterm delivery	7	2501	0.874 (0.591- 1.294)	0.50	43.5	-1.09 (1.17) P=0.40
Admission to neonatal ICU	4	2284	1.099 (0.810-1.490)	0.54	4.2	-1.47 (1.00) P=0.28
Stillbirth/ perinatal loss	4	1449	0.932 (0.200-4.347)	0.93	15.4	2.99 (5.19) P=0.62
Obstructed labor	Not reported					

Figure 2. Meta-analysis of medications versus standard care in preventing Cesarean section



After excluding 897 works from their titles and abstracts, we assessed the full-texts of 40 articles, finally including ten studies, 2,463 pregnant women

In particular, in six studies including 1627 pregnant women, the use of casirivimab/imdevimab (four studies), remdesivir (one study) and IFN alpha 2b (one study) significantly decreased the need of Cesarean section (RR=0.665; 95%CI: 0.491-0.899; p=0.008; I^2=19.5%)

Saracino group. Efficacy and safety of therapies for covid-19 in pregnancy: a systematic review and meta-analysis. BMC Infectious Diseases, accepted

Nirmatrelvir plus ritonavir during the Omicron era in Italy

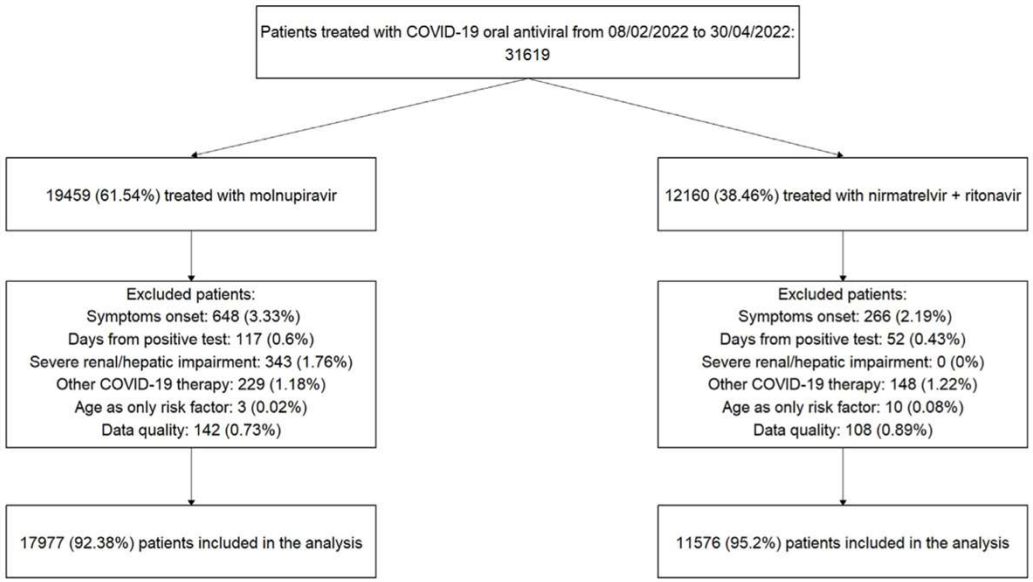
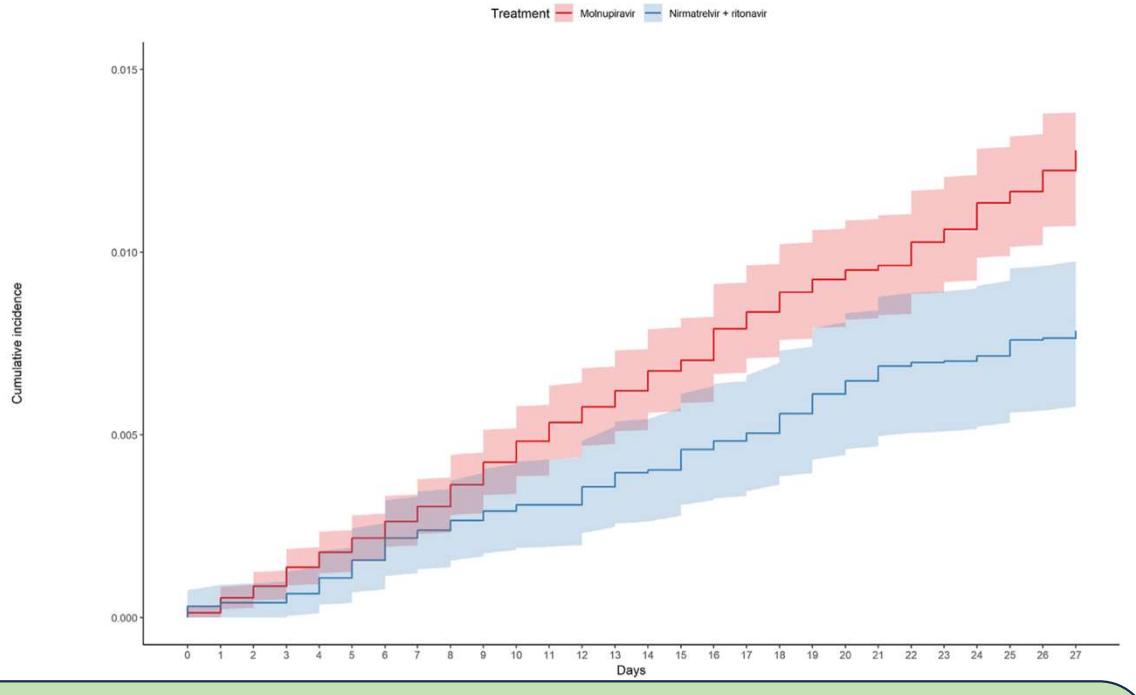


Fig. 1: Study profile.



The present study provides strong support to nirmatrelvir plus ritonavir rather than molnupiravir as a preferred option for early treatment of SARS-CoV-2 infected patients at risk of clinical progression not with standing receipt of a full vaccine course in the Omicron era.

Torti C et . Real-life comparison of mortality in patients with SARS-CoV-2 infection at risk for clinical progression treated with molnupiravir or nirmatrelvir plus ritonavir during the Omicron era in Italy: a nationwide, cohort study. Lancet Reg Health Eur. 2023 Jul 14;31:100684. doi: 10.1016/j.lanepe.2023.100684.

Nirmatrelvir plus ritonavir during the Omicron era in Italy

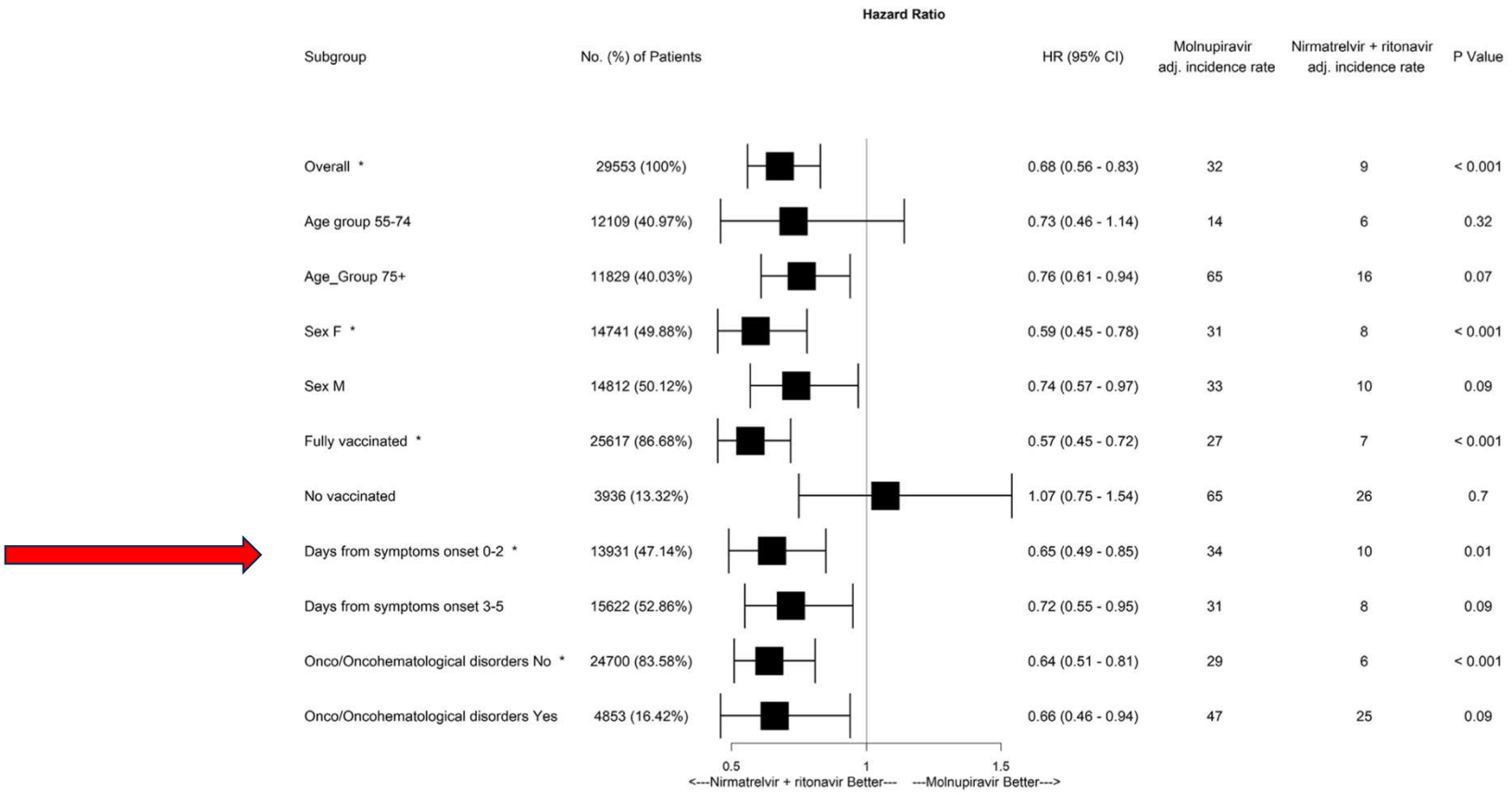


Fig. 3: Hazard ratios for death after 28 days since drug administration (nirmatrelvir plus ritonavir compared to molnupiravir) in the overall population of patients and in subgroups of selected variables.

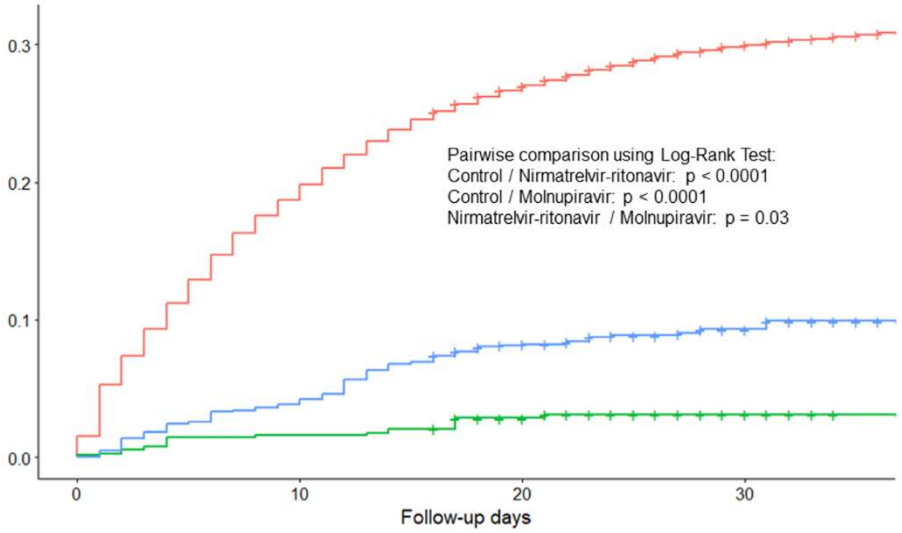
Torti C et . Real-life comparison of mortality in patients with SARS-CoV-2 infection at risk for clinical progression treated with molnupiravir or nirmatrelvir plus ritonavir during the Omicron era in Italy: a nationwide, cohort study. Lancet Reg Health Eur. 2023 Jul 14;31:100684. doi: 10.1016/j.lanepe.2023.100684.

Nirmatrelvir plus ritonavir… significant cost savings

Association of Molnupiravir and Nirmatrelvir-Ritonavir with preventable mortality, hospital admissions and related avoidable healthcare system cost among high-risk patients with mild to moderate COVID-19

Abraham Ka-Chung Wai,[a,b,c,1] Crystal Ying Chan,[d,1] Annie Wai-Ling Cheung,[d] Kailu Wang,[d] Sunny Ching-Long Chan,[a] Teddy Tai-Loy Lee,[a] Luke Yik-Fung Luk,[e] Edmond Tsz-Fung Yip,[e] Joshua Wing-Kei Ho,[e] Omar Wai-Kiu Tsui,[a] Kelly Wing-Yin Cheung,[a] Shiyeow Lee,[a] Chak-kwan Tong,[f] Tafu Yamamoto,[g] Timothy Hudson Rainer,[a] and Eliza Lai-Yi Wong [d]**

Nirmatrelvir-ritonavir reduced mortality by 23.0 percentage points, indicating the incremental cost-effectiveness ratio (ICER) of USD 5502.53



	Standard care (without any antiviral medication)	Molnupiravir	Nirmatrelvir-ritonavir
Outpatient setting			
Cost per person (USD)	367.86	1724.56	1285.02
Outpatient (designated clinic visit) [b]	168.28	178.89	175.86
Subsequent emergency room visit [b]	50.14	37.61	18.80
Antiviral medications	0.00	1391.11	1044.88
Subsequent inpatient healthcare costs [b]	149.44	116.95	45.48
Effectiveness: Probability of surviving during observation period	99.723%	99.998%	100.000%
Incremental cost (USD)	-	1356.70	917.16
Incremental effectiveness	-	0.275%	0.277%
ICER[a] (USD per death averted)	-	493,345.09	331,105.27
Inpatient setting			
Cost per person (USD)	8306.35	8755.92	7040.77
Inpatient healthcare costs [b]	8290.68	8,440.12	6,828.77
Antiviral medications	0.00	306.40	205.94
Subsequent emergency room visit [b]	15.67	9.40	6.06
Effectiveness: Probability of surviving during observation period	74.00%	91.10%	97.00%
Incremental cost (USD)	-	449.57	−1265.58
Incremental effectiveness	-	17.10%	23.00%
ICER[a] (USD per death averted)	-	2629.08	−5502.53

***Table 4*: Cost-effectiveness analysis outcomes for outpatient and inpatient settings.**

[a] ICER: Incremental Cost-Effectiveness Ratio.

[b] The cost includes costs occurred for doctor consultation, medical examinations, nursing and prescriptions.

Sotrovimab and Eris Variants

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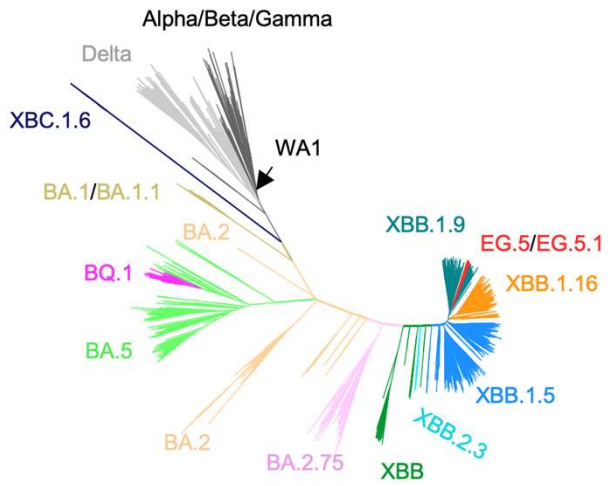
Neutralisation sensitivity of SARS-CoV-2 lineages EG.5.1 and XBB.2.3

Lu Zhang • Amy Kempf • Inga Nehlmeier • Anne Cossmann • Alexandra Dopfer-Jablonka • Metodi V Stankov • Sebastian R Schulz • Hans-Martin Jäck • Georg M N Behrens • Stefan Pöhlmann • Markus Hoffmann ✉ • Show less

Published: September 13, 2023 • DOI: https://doi.org/10.1016/S1473-3099(23)00547-9



Next, we assessed EG.5.1$_{pp}$ and XBB.2.3$_{pp}$ neutralisation by therapeutic antibodies. All S protein-bearing particles were efficiently inhibited by sotrovimab (Xevudy, GlaxoSmithKline, London, UK), with inhibition of particles bearing XBB S proteins being less efficient as compared with B.1$_{pp}$

Use of Sotrovimab in pregnant women

Use of Sotrovimab in a cohort of pregnant women with a high risk of COVID 19 progression: a single-center experience

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Table 2. Clinical and hematochemical profiles before and 72 h after the Sotrovimab administration.

	Before administration	After administration	p-value
Hemoglobin (g/dL)	12,9 (1.4)	12,5 (1.3)	0.569
PLT (Platelets) x10^3/uL	299 (78)	303 (64)	0.485
WBC (White Blood cells) (10^3µL)	12,07 (1.33)	9,98 (3.22)	0.140
Lymphocytes %	19,85 (2.89)	18,7 (3.01)	0.334
eGFR (ml/min)	121 (4.8)	123 (5.2)	0.712
AST (Aspartate Transaminase)(U/L)	25	22	0.810
ALT(Alanine Transaminase) (U/L)	23	24	0.980
Gamma GT (U/L)	18	17	0.912
D-Dimer (µg/l)	3418 (680)	1011 (780)	**0.015**
PCR (mg/L)	11,3 (5.2)	12 (7.5)	0.686
Ferritin, Mean (SD)	45 (21)	39 (29)	0.529
Blood Pressure, (mmHg), Mean (SD)	125/73	124/73	1.000
Temperature (°C), Mean (SD)	36.5 (36.0–36.9)	36.4 (36.0–36.8)	0.788
Heart rate (beats/minute), Mean (SD)	80	80	1.000
SpO2 (%), Mean (SD)	98 (97,99)	99 (98,99)	-
Ab Anti SARS-CoV-2, Mean (SD)	345	18462	**<0.001**
Adverse events	0	0	-

Table 1. The main features of 13 pregnant women treated with Sotrovimab.

	Total N (%)
Age, median [Min, Max]	32 [18.0, 41.0]
Educational level	
High level	8 (61.5)
Low-medium level	5 (39.5)
Race/Ethnicity	
Italian	11 (85.0)
East Europe	1 (7.5)
Latin America	1 (7.5)
Gestational age (weeks), median	30.5 [13.0, 40.0]
First trimester	1 (8.0)
Second trimester	5 (38.0)
Third trimester	7 (54.0)
Days from symptoms onset to mAbs administration, median	1 [0,2]
Comorbidity pre-pregnancy	
BMI (≥24.9)	8 (61.5)
Hematologic diseases	2 (15.0)
Hypertension	2 (15.0)
Immunity disorder	1 (8.0)
COPD,Asthma	0 (0.0)
Complications during pregnancy	
Gestational diabetes	2 (20.0)
Premature rupture of membranes (PROM)	1 (10.0)
Fetal anomaly	1 (10.0)
Oligohydramnios	1 (10.0)
Predominant COVID symptom	
Fever	4 (30.0)
Asthenia	7 (54)
Headache	2 (16)
Cold	3(23)
Need for ICU admission	0 (0.0)
Variant predominance period	
Delta	2(15,4)
Omicron BA.1	5(38,5)
Omicron BA.2	6(7.6)
BA 4/5	0(0.0)
Vaccination status and timing of vaccine receipt	
Not vaccinated	4(30,6)
1dose	3(23,1)
2 doses	5(38,4)
3 doses	1(7,7)
Type of Vaccine Received	
Pfizer	8(61,5)
Moderna	1(7,7)
Johnson	0 (0)
Astrazeneca	0 (0)
Vaccine administration	
Before pregnancy	9(69.0)
During pregnancy	0(0.0)
Hospital length of stay (days), median	4.1 (2.0, 21.0)

Frallonardo L, et al. Use of Sotrovimab in a cohort of pregnant women with a high risk of COVID 19 progression: a single-center experience. Pathog Glob Health. 2023 Jul;117(5):513-519. doi: 10.1080/20477724.2023.2188839.

Use of Sotrovimab in pediatric unit

Clinical and demographic features	*ALL (n = 33)*	*ON-LABEL (n = 14)*	*OFF-LABEL (n = 19)*	*p*
Sex (male), n (%)	17 (51.5%)	5 (35.7%)	12 (63.2%)	0.118
Age (years), median (IQR)	11.9 (6.67-14.9)	14.9 (13.3-16.3)	7.4 (3.8-11.1)	**<0.001**
Malignant disease	17 (51.5%)	7 (50%)	10 (52.6%)	1
Immunosuppressive conditions	23 (69.7%)	10 (71.4%)	13 (68.4%)	1
Vaccinated for SARS-CoV-2	8 (24.2%)	7 (50%)	1 (5.3%)	**0.005**
Asymptomatic prior Sotrovimab infusion	9 (27.3%)	4 (28.6%)	5 (26.3%)	1
Symptomatic 7 days after Sotrovimab	4/30 (13.3%)	3/13 (23.1%)	1/17 (5.9%)	0.29
Negativization 7 days after Sotrovimab	5/25 (20%)	3/11 (27.2%)	2/14 (14.2%)	0.59
Median time of negativization (days), median (IQR)	23 (9.5-30)[a]	17 (8-24)[b]	23.5 (13.5-33)[c]	0.31
Sotrovimab side effects	2 (6.1%)	2 (14.3%)	0 (0%)	0.17
COVID-19 complications	4 (12.1%)	2 (14.3%)	2 (10.5%)	1

Comorbidity	N
Lymphoma	4
Leukaemia	9
Systemic Lupus Erythematosus	3
Thalassemia Major	1
22q11.2 deletion syndrome	2
Ewing sarcoma	1
Soft tissue sarcoma	1
Osteosarcoma	1

Sotrovimab was prescribed in line with EMA) and AIFAindications in children over 12 years and weighing more than 40 kg. In selected cases of children under 12 years and weighing less than 40 kg Sotrovimab was prescribed off-label, subject to parental consent, according to the local hospitals' procedure.

Overall, the infusion was well tolerated with no significative differences in those receiving an off-label prescription

Venturini E, et al. Safety of Sotrovimab use in children with COVID-19: an Italian experience. J Chemother. 2023 Aug 21:1-4. doi: 10.1080/1120009X.2023.2250138. Epub ahead of print. PMID: 37605372.

Use of Sotrovimab in frail patients

Contents lists available at ScienceDirect

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Mortality and risk factors of vaccinated and unvaccinated frail patients with COVID-19 treated with anti-SARS-CoV-2 monoclonal antibodies: A real-world study

Univariate and multivariate analysis[a] of risk factors associated with mortality in patients with COVID-19 treated with anti-SARS-CoV-2 monoclonal antibodies.

	Univariable model				Multivariable model			
Parameter	OR	95% CI		*P*-value	OR	95% CI		*P*-value
Age	1.06	1.03	1.10	0.001	1.06	1.03	1.10	0.001
Sex:	1				1			
Male (reference)	0.92	0.38	2.14	0.841	1.26	0.45	3.53	0.657
Female								
Vaccination	0.95	0.37	2.92	0.927				
Monoclonal antibody:								
Sotrovimab (reference)	1	0.34	1.88	0.582				
Casirivimab-imdevimab	0.79							
≤5 days from nasopharyngeal swab positive to monoclonal administration	1.25	1.05	1.46	0.007				
Steroids	3.45	1.47	8.27	[illegible]				
Hypertension	0.96	0.36	2.54	0.935				
Heart failure	3.50	0.78	11.38	0.058				
Atrial fibrillation	1.58	0.24	5.82	0.553				
Ischemic heart disease	0.99	0.15	3.61	0.99				
Active solid neoplasia	1.74	0.27	6.43	0.473				
Active hematological neoplasia	12.67	5.02	30.77	0.001	1.14	3.67	35.37	0.001
Cardiovascular/chronic obstructive pulmonary disease diseases	2.07	0.70	5.54	0.161				
Dyslipidemia	0.76	0.12	2.74	0.713				
Chronic Renal Insufficiency	6.41	2.03	17.07	0.001	4.41	0.89	16.97	0.041
Diabetes	1.05	0.29	3.04	0.926				
Obesity	0.42	0.06	1.49	0.247				
Number comorbidity	1.38	1.07	1.72	0.007				
Need O_2 therapy	24.26	9.48	69.97	0.001	2.31	8.40	72.11	0.001

Among 1026 COVID-19 patients enrolled, 60.2% received casirivamab/imdevimab and 39.8% sotrivimab.

Median age was 63 years,

No differences in outcomes were observed between the two mAbs used.

Early administration of mAbs was associated with lower mortality (*P* <0.007)

Nevola R, et al. Mortality and risk factors of vaccinated and unvaccinated frail patients with COVID-19 treated with anti-SARS-CoV-2 monoclonal antibodies: A real-world study. Int J Infect Dis. 2023 Jun;131:155-161. doi: 10.1016/j.ijid.2023.03.030.

Take home message

- Early recognition of patient with risk factors to desease progression;
- time is an ally not an enemy;
- safe drugs ;
- monthly updates on variants and escape phenomena;
- needs quality research

To further information

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