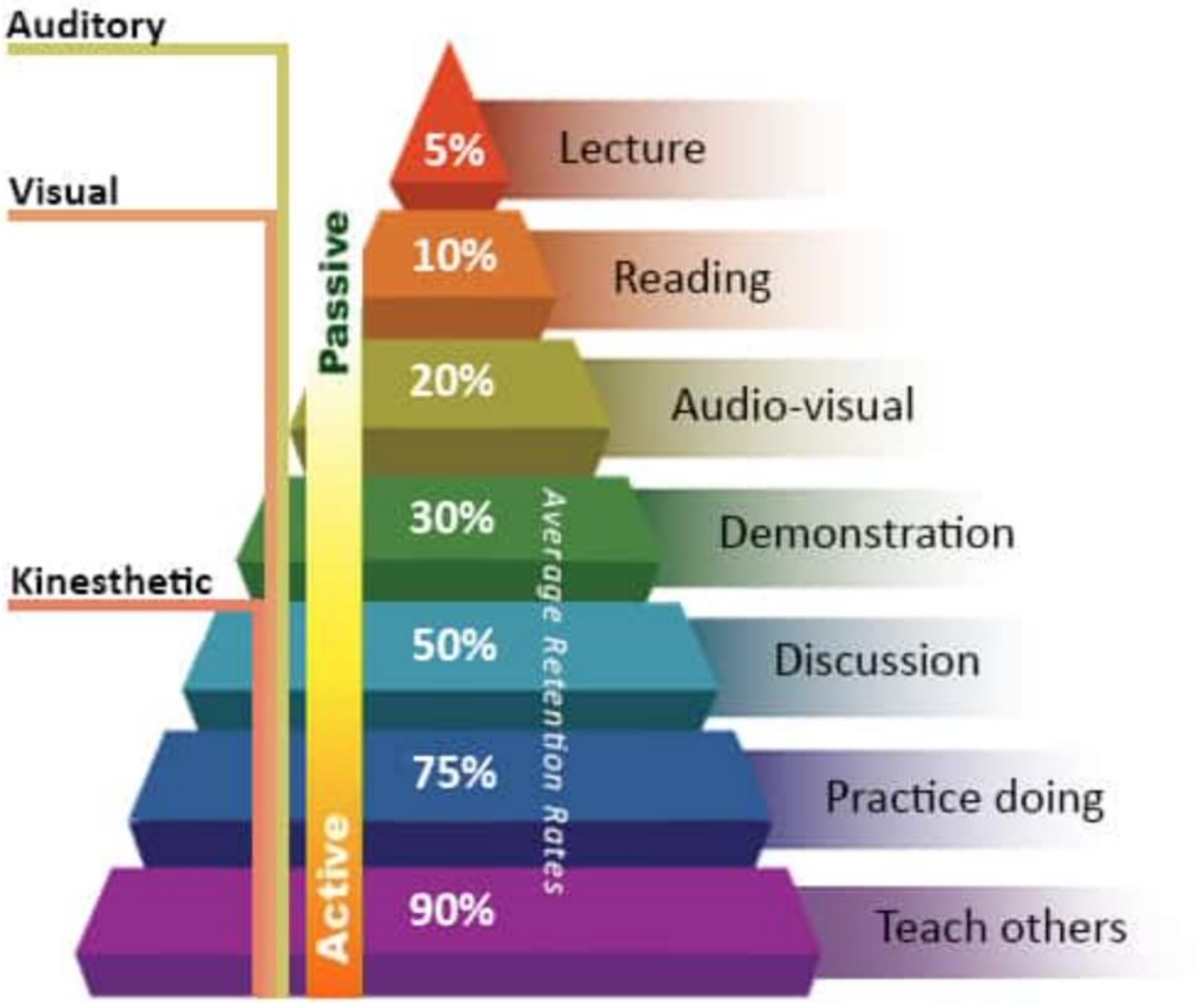
COVID-19:
aspetti clinici, terapeutici, e epidemiologici.
Long COVID

Francesco Di Gennaro

The Learning Pyramid



Adapted from the NTL Institute of Applied Behavioral Science Learning Pyramid

Cosa Sappiamo e cosa non sappiamo

Virus.a RNA,

Grande

Ubiquitario

Recettore ACE 2,

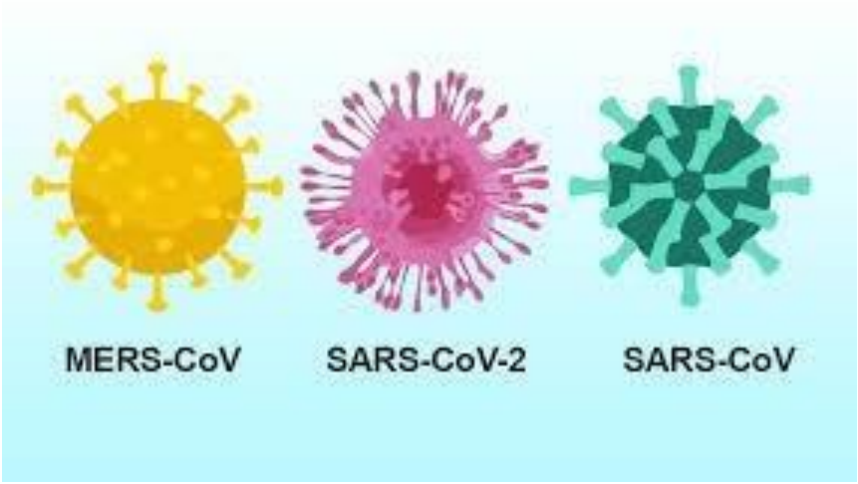
Effetto citopatico ? (NO)

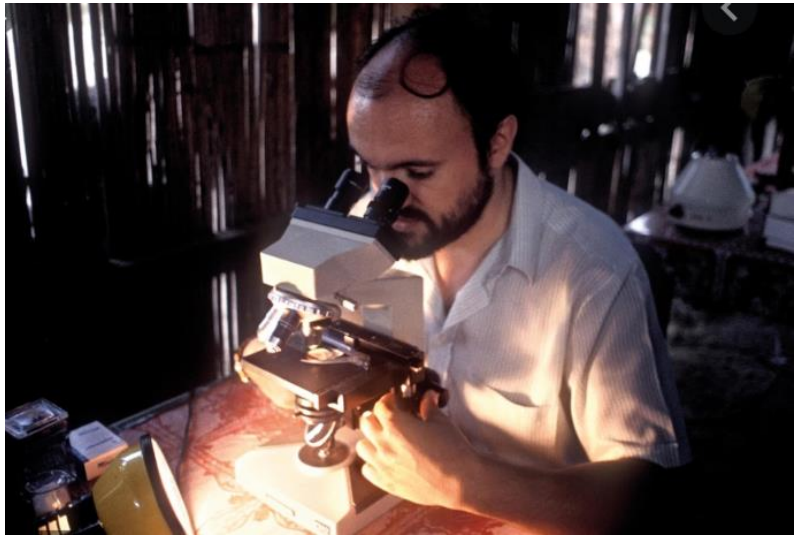
SARS CoV1 , MERS.

Long COVID (?)

La famiglia CORONAVIRUS

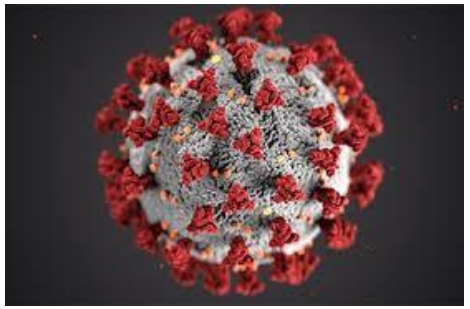
- Virus con capsula a RNA a singolo filamento
- Clinicamente
  - virus respiratori noti dai primi anni ’30
  - Spettro clinico dal raffreddore comune alle gravi infezioni delle basse vie respiratorie spec. in lattanti, anziani, immunodepressi
- Già noti in passato:
  - SARS-CoV, 2003 focolaio di sindrome respiratoria acuta grave iniziato in Cina nel 2002, letalità 10%
  - MERS-CoV, 2012 = sindrome respiratoria del Medio
    Oriente (Arabia Saudita, Quatar… letalità 34%)





SARS-CoV2 e COVID-19

- Dicembre 2019 nuovo coronavirus causa di un cluster di casi di polmonite a Wuhan, nella provincia cinese di Hubei.
- 11 Marzo 2020, WHO ha dichiarato Pandemia
- Verosimilmente di origine zoonotica. Trasmissione predominante uomo–uomo
- La *malattia* è designata come **COVID-19:** (COrona Virus Disease)-19
- Il *virus* che causa COVID-19 è designato come **sindrome respiratoria acuta grave- da CoronaVirus- 2** (SARS-CoV-2: Severe Acute Respiratory Syndrome – COronaVirus – 2)



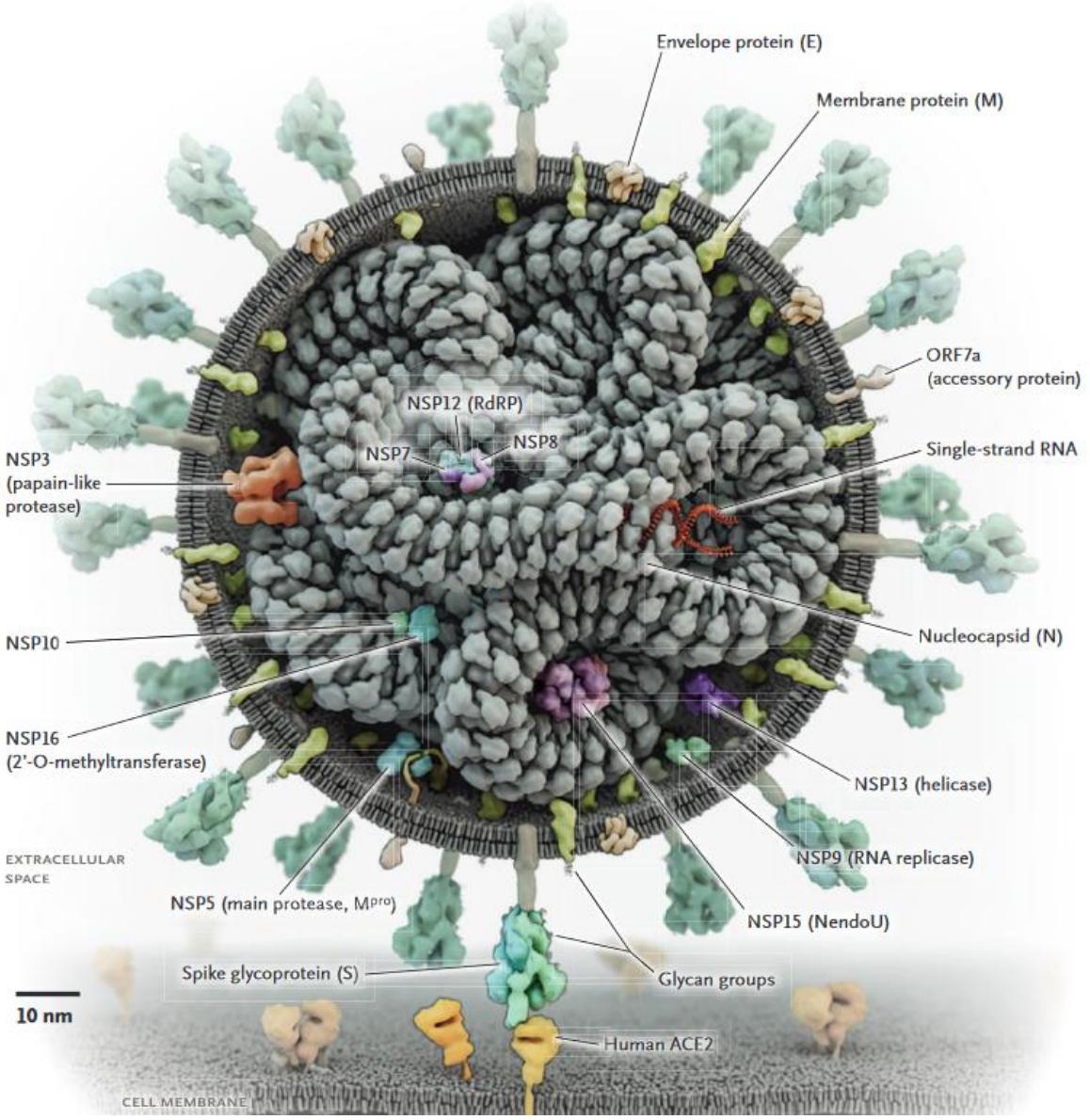
Struttura del virus SARS-CoV2

La provincia di Wuhan

Infezione da SARS-CoV2 è condizione estremamente complessa

- per i meccanismi fisiopatogenetici connessi
- per la molteplicità delle manifestazioni cliniche
- per il ruolo giocato dalla risposta immunitaria dei soggetti

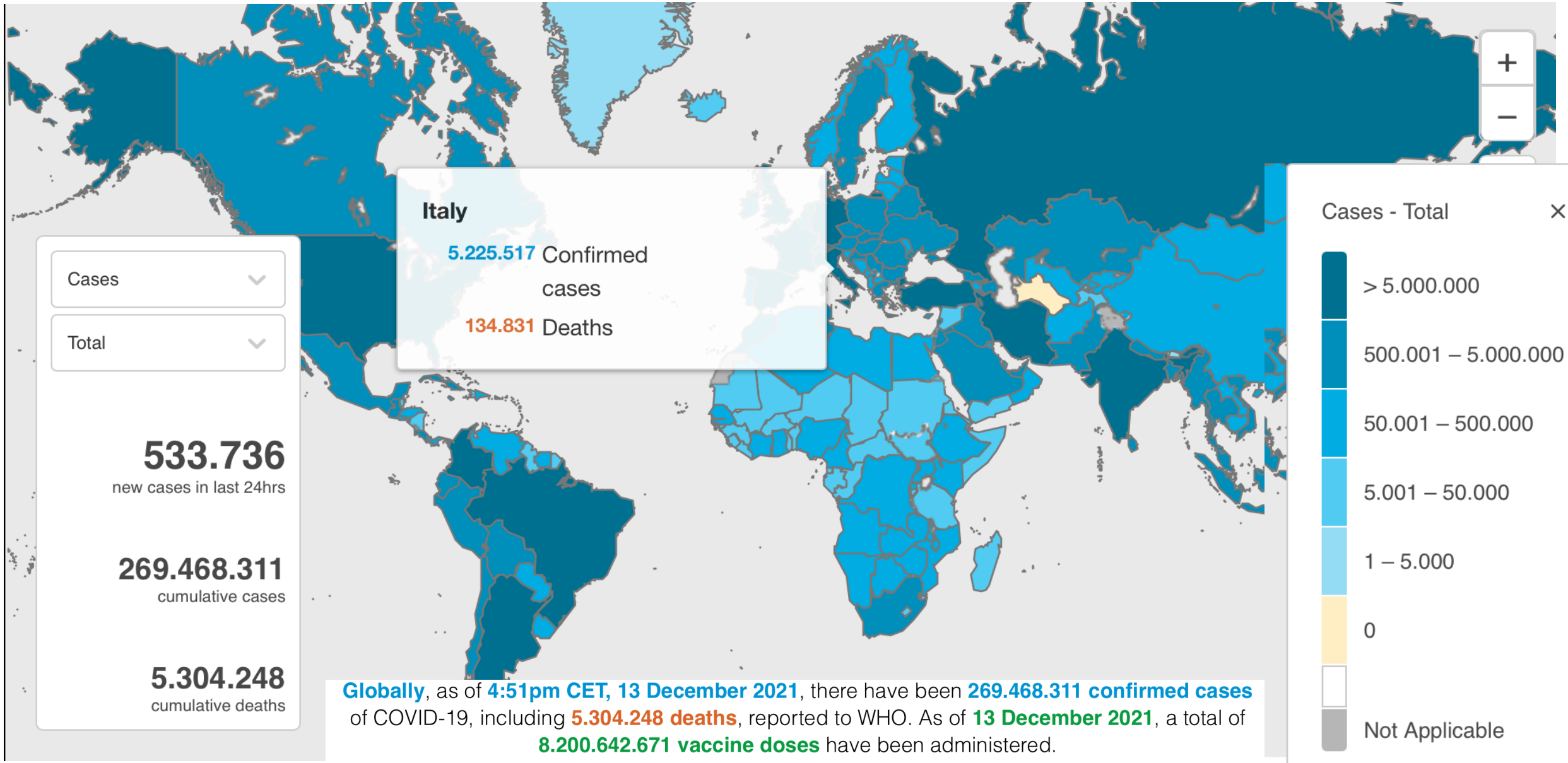
SARS-CoV-2 STRUTTURA E CICLO VITALE



- Singolo filamento di RNA a polarità positiva (28-32 Kb), RNA polimerasi RNA-dipendente
- Proteina S (*Spike*) lega il recettore sulla cellula ospite (ACE 2 identificato come recettore)
- Iniziale traduzione poliproteina non strutturale che forma il complesso di replicazione-trascrizione
- 4 proteine strutturali (*Spike,* di membrana, *envelope* e nucleocapside)
- S (Spike, permette al virus di attaccarsi alle membrane della cellula ospite), E (Involucro), M (Membrana), tutte e tre creano il CAPSIDE
- N (Nucleocapside) , contiene il genoma

World Health Organization

WHO Coronavirus (COVID-19) Dashboard



Globally, as of **4:51pm CET, 13 December 2021**, there have been **269.468.311 confirmed cases** of COVID-19, including **5.304.248 deaths**, reported to WHO. As of **13 December 2021**, a total of **8.200.642.671 vaccine doses** have been administered.

World Health Organization

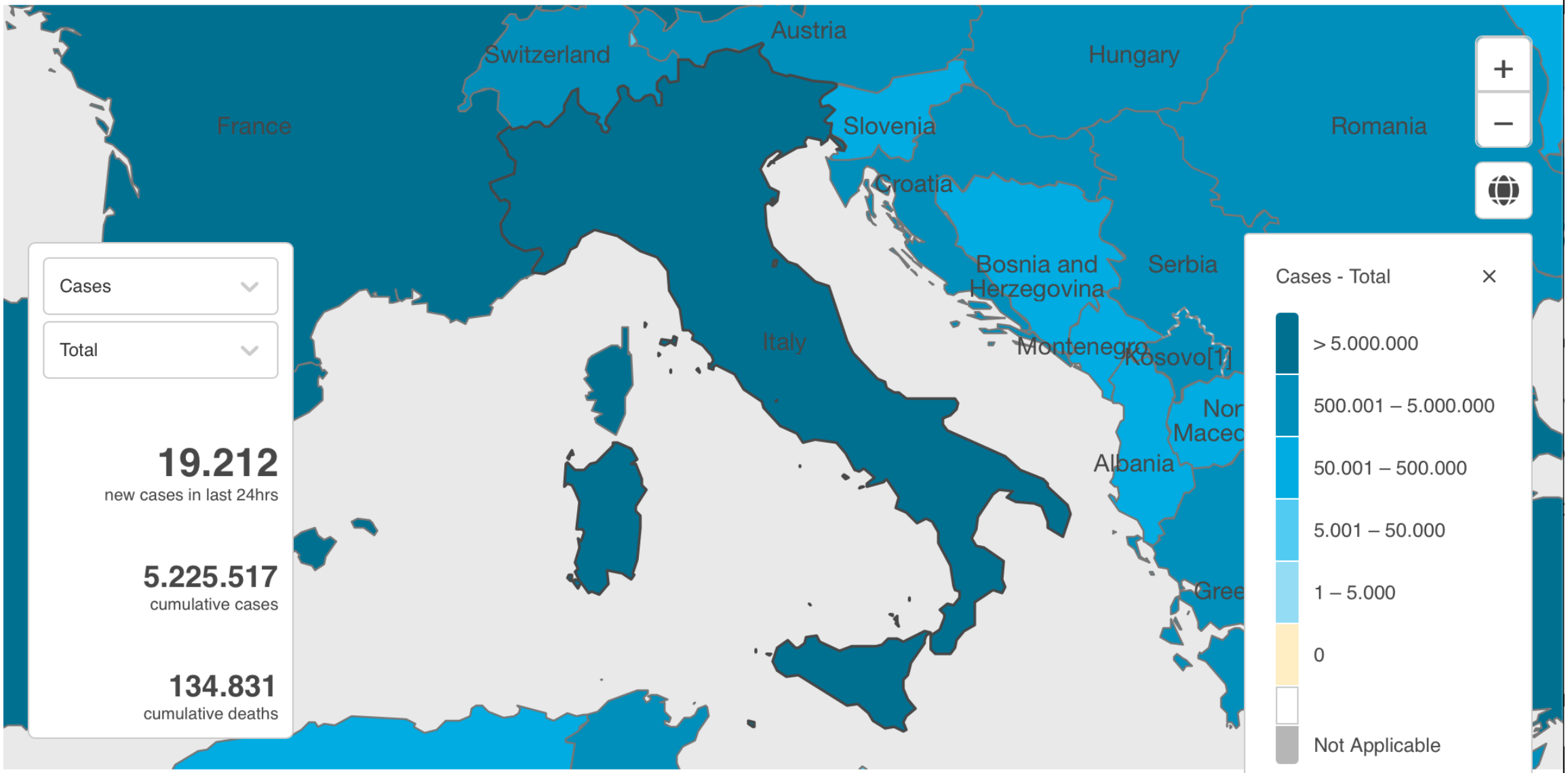
Search by Country, Territory, or Area

Covid-19 Response Fund

Donate

Global > Italy

Overview Measures Data Table Explore

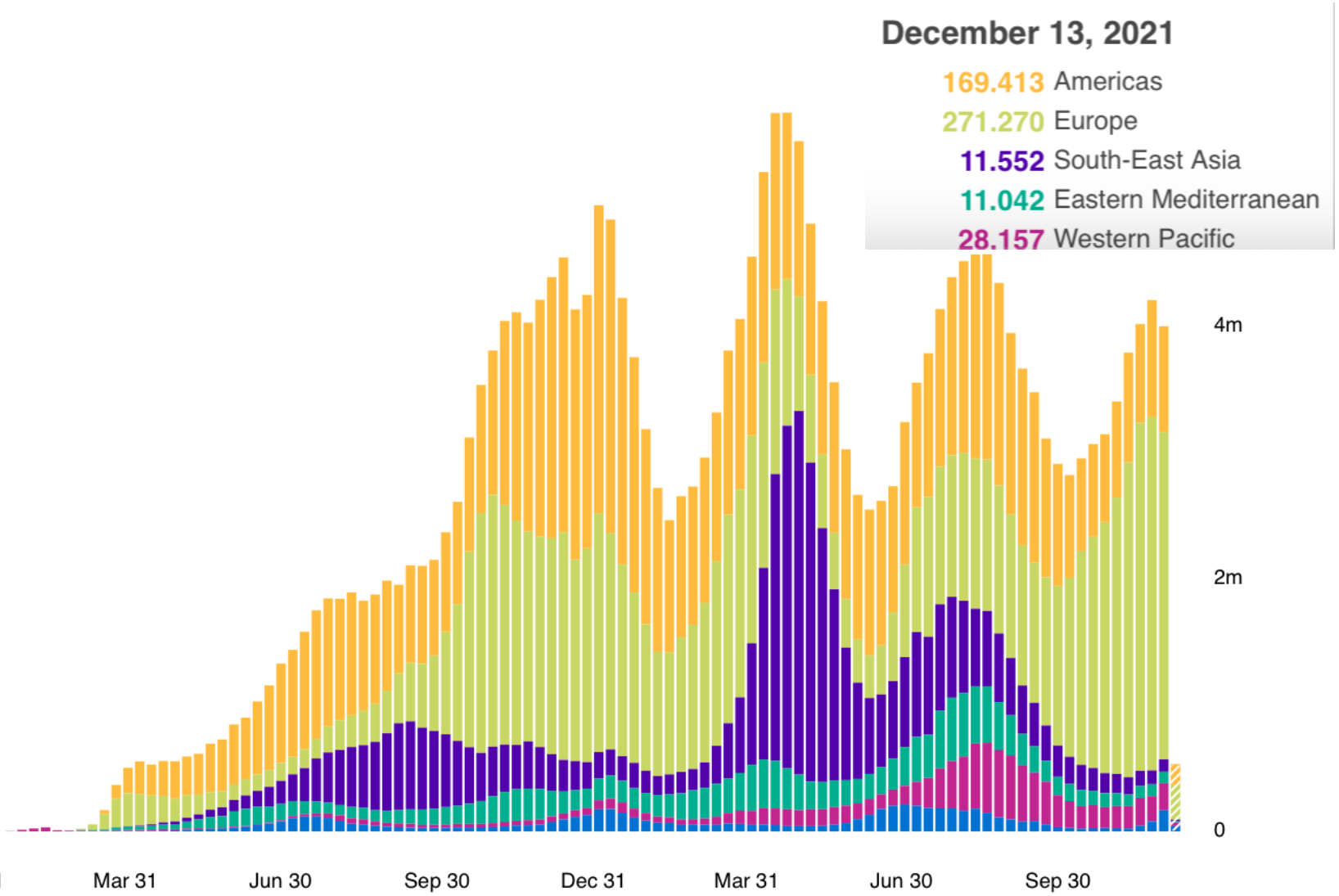


Situation by WHO Region

Situation by WHO Region

Daily | Weekly | Cases | Deaths | Count

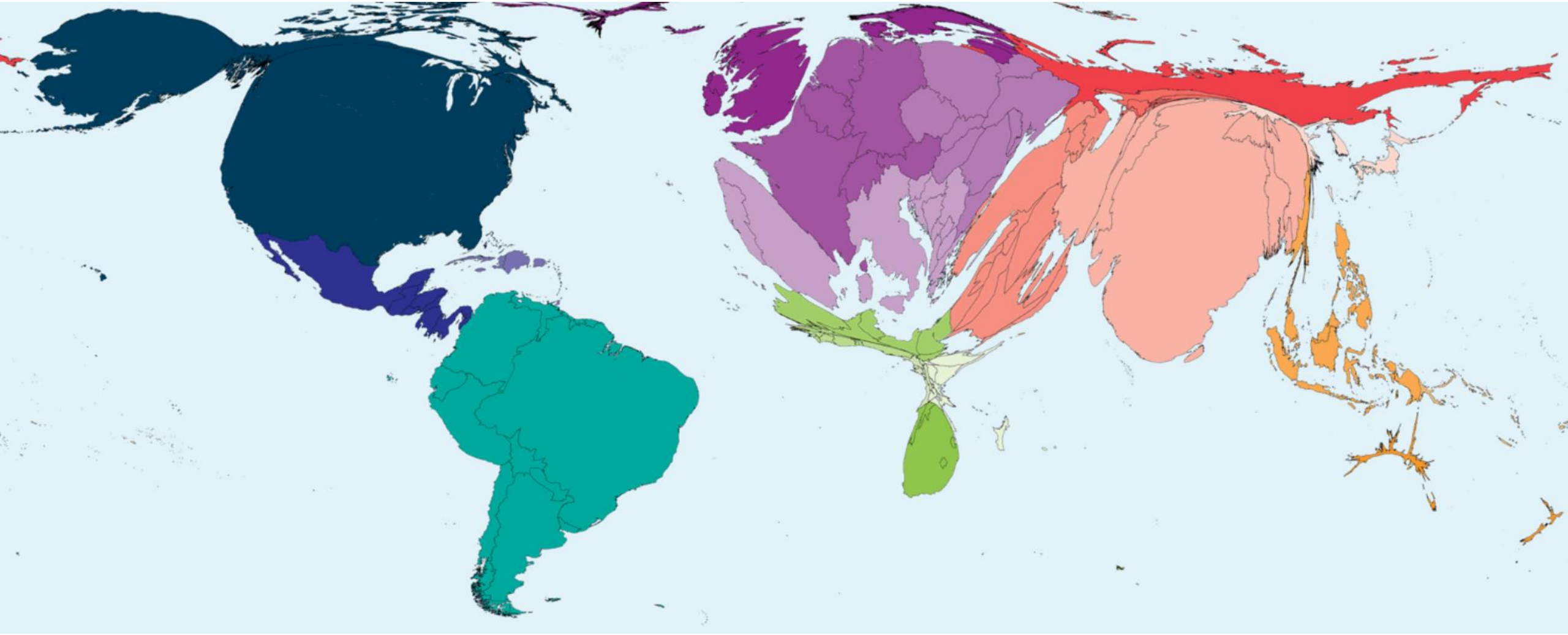
Americas	98.690.724 confirmed
Europe	91.903.122 confirmed
South-East Asia	44.748.558 confirmed
Eastern Mediterranean	16.947.823 confirmed
Western Pacific	10.612.501 confirmed
Africa	6.564.819 confirmed



Source: World Health Organization

Data may be incomplete for the current day or week.

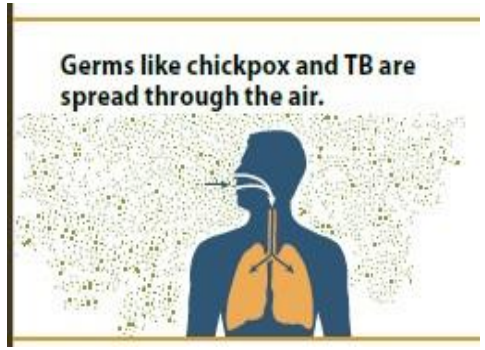
COVID 19 Global distribution



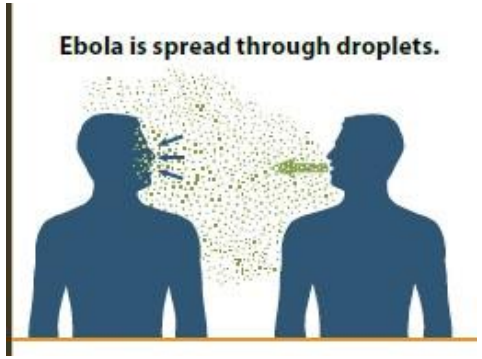
Modalità di trasmissione del virus

COVID-19 si trasmette per droplets/ per contatto con superfici contaminate

- *attraverso la saliva, tossendo e starnutendo*
- *contatti diretti personali, attraverso le mani, ad esempio toccando con le mani contaminate non ancora lavate bocca, naso o occhi*

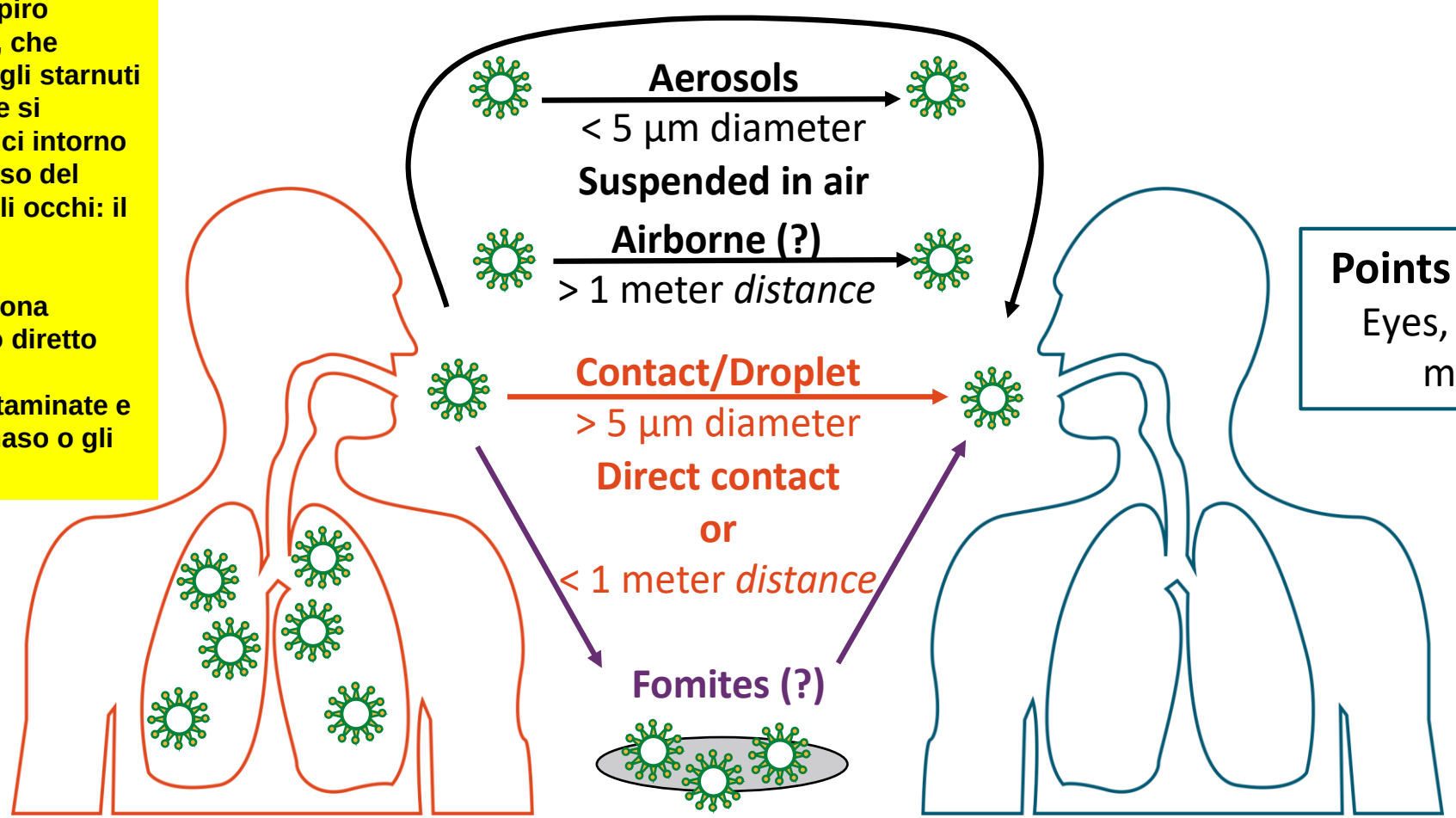


Diffusione per via aerea	Trasmissione attraverso droplets
Germe fluttua nell´aria dopo che una persona parla, tossisce, starnutisce NON è necessario il contatto diretto con la persona infetta perché qualcun altro si ammali	Goccioline respiratorie che si emettono starnutendo, tossendo o parlando, dette goccioline di Flügge
Tubercolosi, Morbillo, Varicella	Ebola

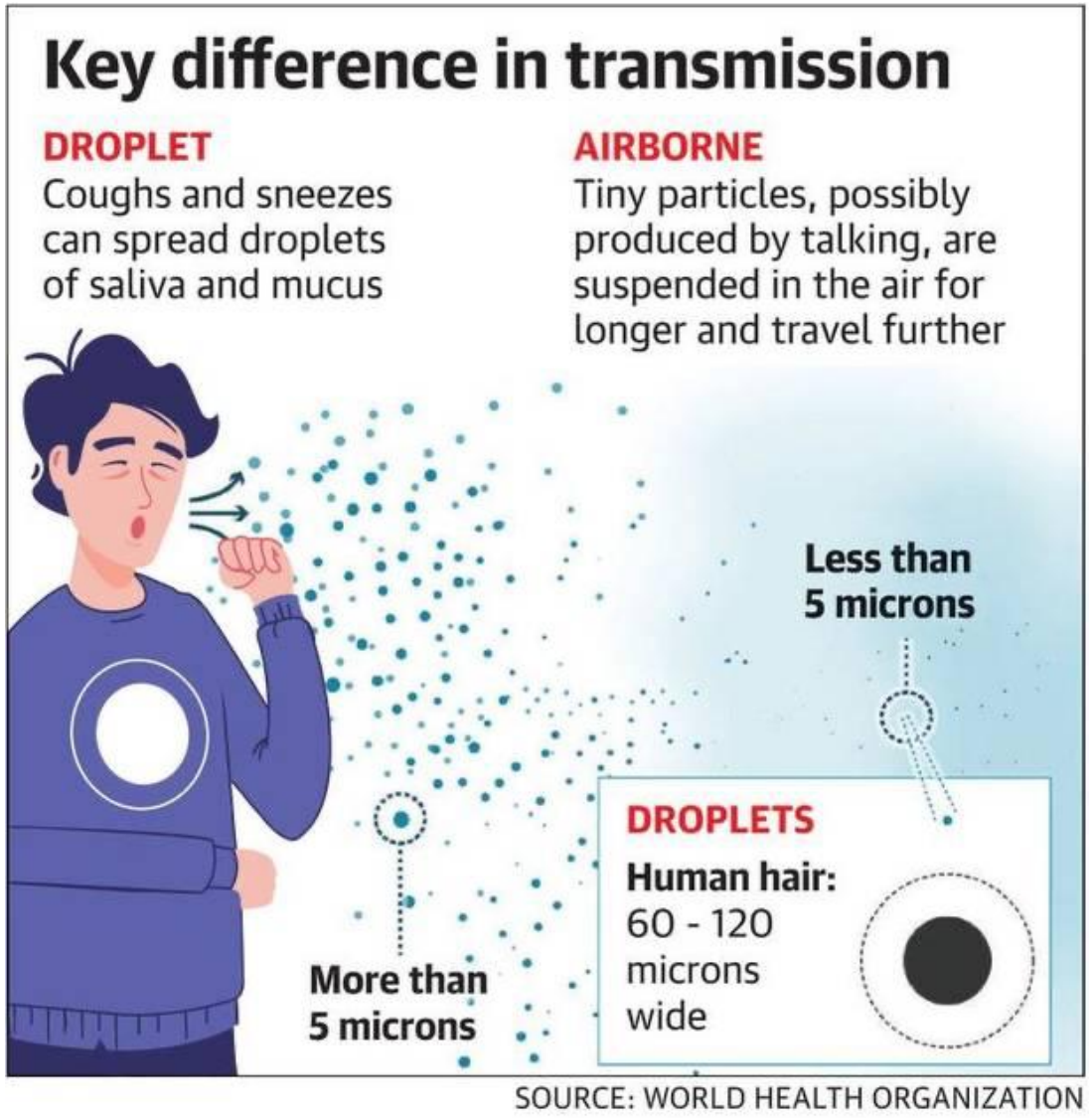


Modalità di trasmissione del virus

La trasmissione interumana avviene attraverso le goccioline del respiro (droplets) della persona infetta, che vengono espulse con la tosse, gli starnuti o la normale respirazione, e che si depositano su oggetti e superfici intorno alla persona. Le porte di ingresso del virus sono la bocca, il naso e gli occhi: il contagio avviene
inalando attraverso il respiro le goccioline emesse da una persona malata, oppure tramite contatto diretto personale,
oppure toccando superfici contaminate e quindi toccandosi la bocca, il naso o gli occhi con le mani.



Trasmission airborne



Recentemente l'OMS ha pubblicato un documento nel quale sottolinea come la **trasmissione airborne** non possa essere esclusa in ambienti affollati e inadeguatamente ventilati in cui sono presenti persone infette, come chiese, ristoranti e locali notturni in cui le persone gridano, parlano o cantano.
La possibilità di trasmissione del virus tramite aerosol è supportata da un numero sempre maggiore di evidenze scientifiche. Gli US Centers for Disease Control and Prevention (CDC), nelle loro linee guida recentemente aggiornate, riconoscono che in determinate condizioni le persone con COVID-19 possono infettare altre persone che si **trovano a più di 6 piedi (oltre 180 centimetri) di distanza**, soprattutto se ci si trova all'interno di **spazi chiusi** con ventilazione inadeguata, e la persona infetta respira pesantemente, oppure canta o svolge attività fisica

Hallmarks of COVID-19 Clinical Picture

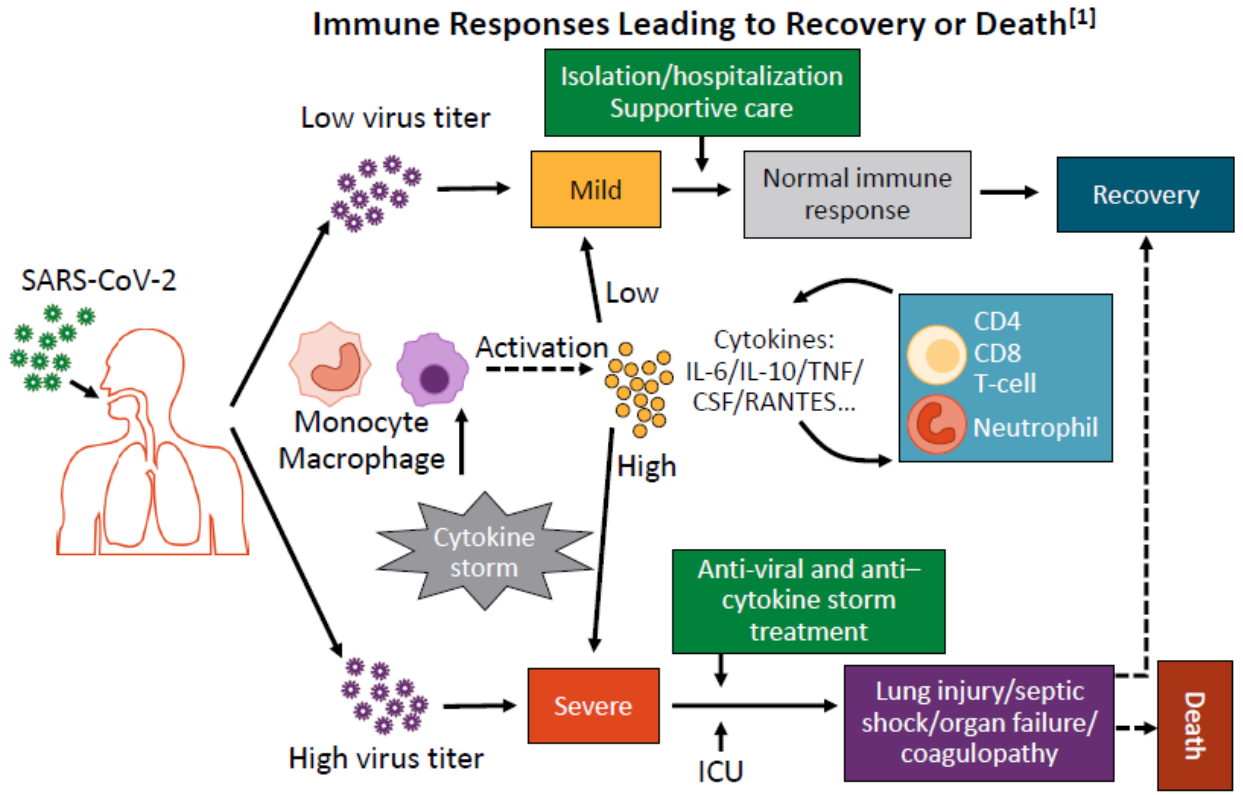
1.Cytokine Storm: **Dysregulated and excessive immune responses** may lead to significant systemic damage. Mononuclear cells such as neutrophils and monocytes in the patient's lung tissues and peripheral blood produce elevated levels of pro-inflammatory cytokines such **as interleukin-6 (IL-6), interleukin-1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

1.Cytokine Storm

Immune Response to SARS-CoV-2



Adequate immune responses[2]

- Timely innate/adaptive responses
- Quick type 1 IFN response
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

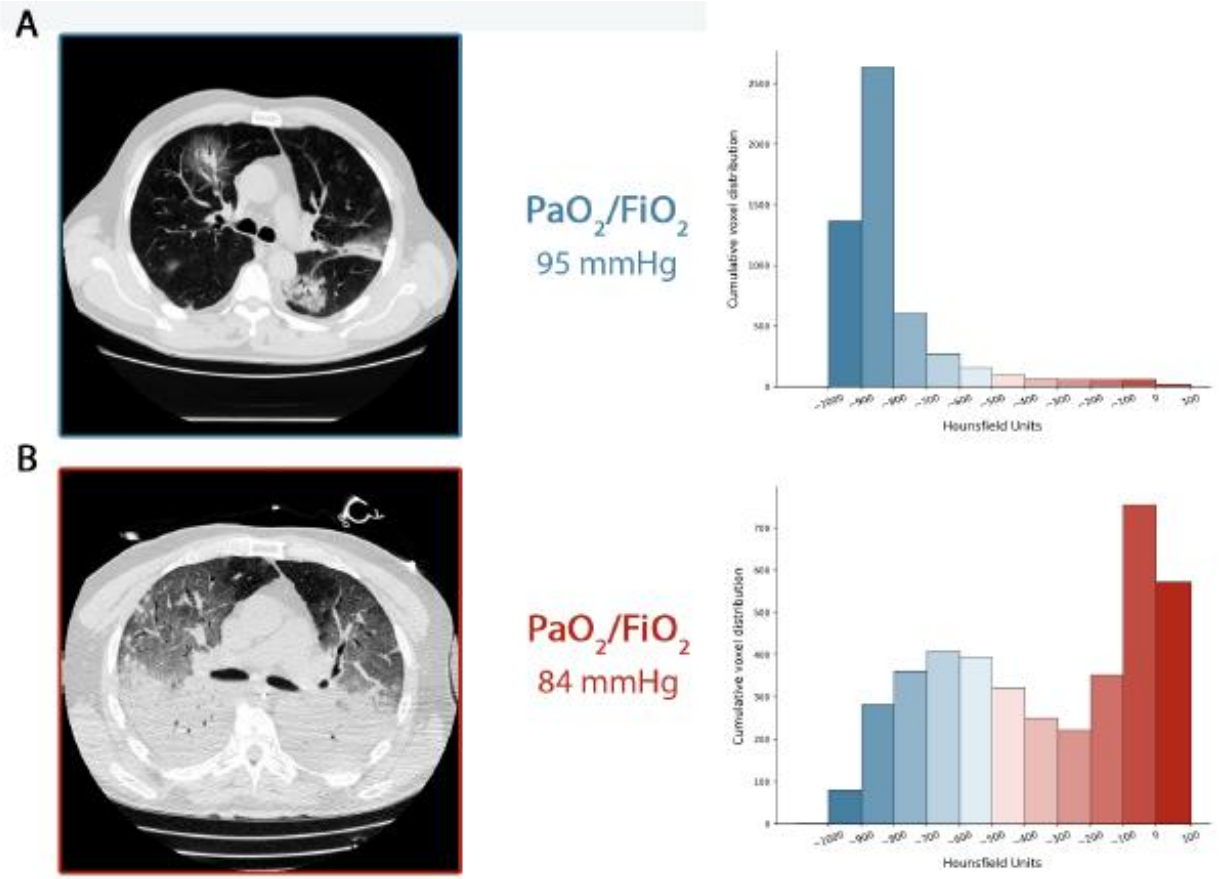
Inadequate immune responses[2]

- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

1. Wang. 2020; J Leukoc Biol. 2020;[Epub]. 2. Sokolowska. EAACI. 2020[Epub].

Slide credit: clinicaloptions.com

2.Hypoxiemic Respiratory Failure



Panel A: CT scan acquired during spontaneous breathing. The cumulative distribution of the CT number is shifted to the left (well aerated compartments), being the 0 to -100 HU compartment, the nonaerated tissue virtually 0. Indeed, the total lung tissue weight was 1108 g, **7.8% of which was not aerated** and the gas volume was 4228 ml. Patient receiving oxygen with Venturi mask, **inspired oxygen fraction of 0.8**. (**TYPE L**)

Panel B: CT acquired during mechanical ventilation at end-expiratory pressure at 5 cmH2O of PEEP. The cumulative distribution of the CT scan is shifted to the right (non-aerated compartments) while the left compartments are greatly reduced. Indeed, the total lung tissue weight was 2744 g, **54% of which was not aerated** and the gas volume was 1360 ml. The patient was ventilated in Volume Controlled mode, 7.8 ml/kg of tidal volume, respiratory rate of 20 breaths per minute, **inspired oxygen fraction of 0.7**. (**TYPE H**)

2.Hypoxiemic Respiratory Failure

EDITORIAL Open Access

COVID-19: a hypothesis regarding the ventilation-perfusion mismatch

Mario G. Santamarina[1,2], Dominique Boisier[3], Roberto Contreras[4], Martiniano Baque[5], Mariano Volpacchio[6] and Ignacio Beddings[7*]

We believe that a severe V/Q mismatch underlies the pathophysiology of moderate to severe COVID-19 cases, in which downregulation of ACE2 secondary to viral endocytosis plays a key role.

Il rapporto **ventilazione/perfusione** (V/Q) rappresenta il principale determinante della concentrazione di ossigeno nel sangue che esce dalla circolazione **polmonare** per raggiungere i tessuti attraverso il circolo sistemico.

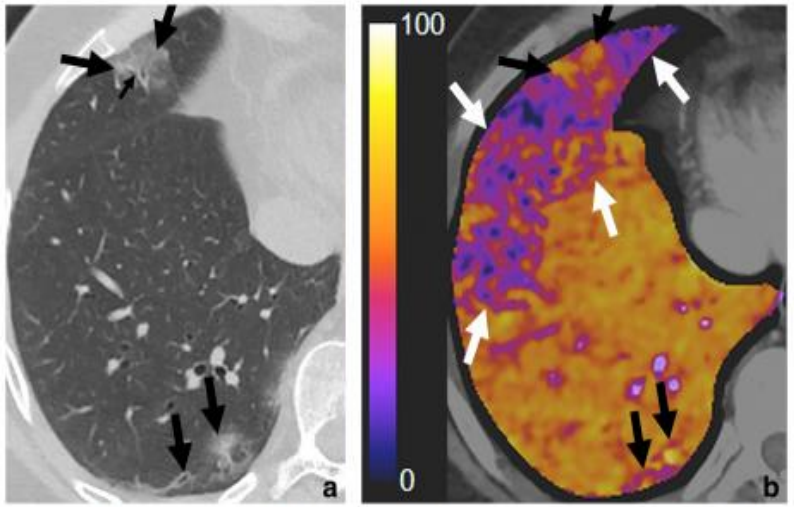


Fig. 1 a, b Slight hypoperfusion in the well-aerated lung, hyperemia, and small zones of hypoperfusion in the areas of injured lung. Fifty-nine-year-old male patient, RT-PCR-confirmed COVID-19, 11 days since symptom onset, without hypoxemia, (PaO_2/FiO_2) 538, D-dimer 340 ng/mL. There are isolated foci of ground-glass opacities associated with septal thickening, with a predominantly subpleural distribution, which correlate with areas of hyperemia (middle lobe) and small zones of hypoperfusion (lower right lobe) in subtraction CT iodine maps (large black arrows). There is an evident area of hypoperfusion in the middle lobe and lower right lobe (white arrows) that correlates with the apparently normal lung parenchyma in conventional chest CT images. The conventional CT image also shows pulmonary arterial vascular dilatation in the periphery of the ground-glass opacity in the middle lobe (small black arrow). These slight perfusion abnormalities do not impact the PaFi ratio. The ground-glass opacity in the lower right lobe shows slight peripheral hypoperfusion, probably due to compensatory vasoconstriction, an expected regulatory mechanism when vasoplegia is not fully established

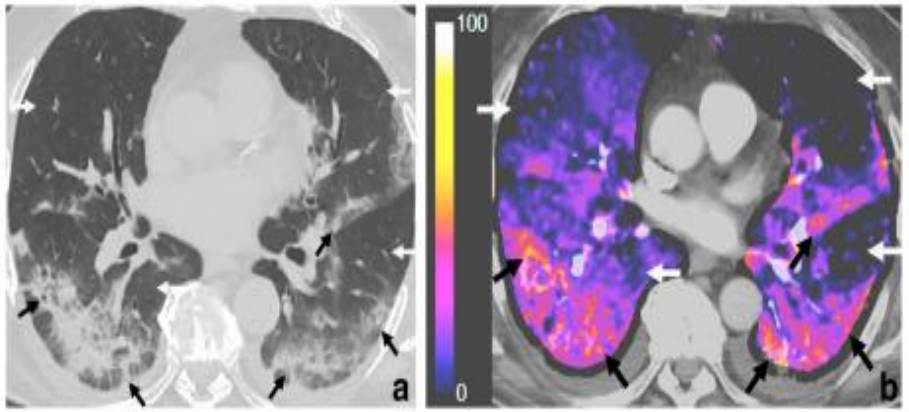
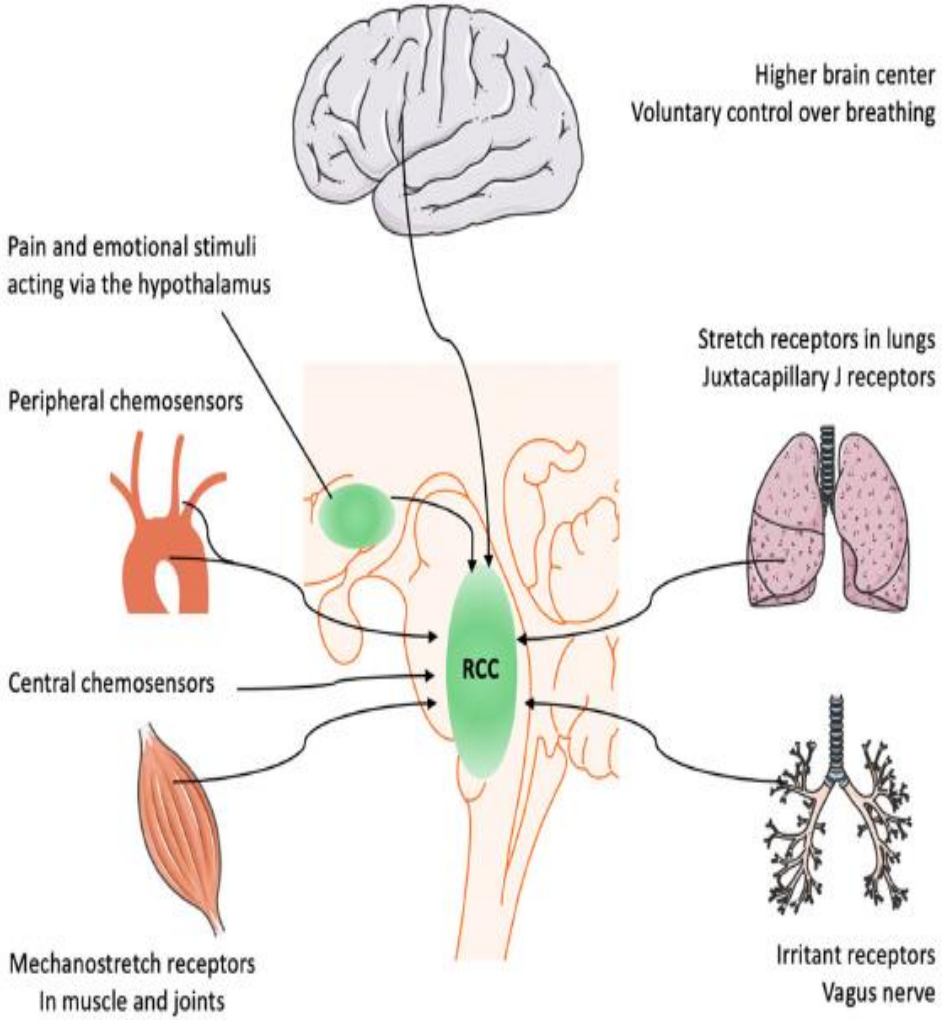


Fig. 2 a, b Prominent hypoperfusion in the well-aerated lung and hyperperfusion in areas of injured lung. Seventy-eight-year-old male patient, RT-PCR-confirmed COVID-19, 10 days since symptom onset, with hypoxemia, (PaO_2/FiO_2) 206, D-dimer 1600 ng/mL progressively increasing. There are extensive foci of consolidation and ground-glass opacities, associated with septal thickening, with a predominantly posterior and subpleural bilateral distribution, which correlate with the areas of hyperemia and iodine pooling in subtraction CT iodine maps (black arrows). There are areas of markedly decreased perfusion in both lungs, which correlate with the apparently healthy lung parenchyma in conventional chest CT images (white arrows). Bilateral pleural effusion. This could be explained by an increased blockage of ACE2 receptors in the lung endothelium, leading to increased local levels of angiotensin II, which leads to vasoconstriction and ventilation/perfusion mismatch. This patient was managed with invasive mechanical ventilation, with highly compliant lung parenchyma, in accordance with the type 1 or L phenotype described by Gattinoni et al.

2.Hypoxiemic Respiratory Failure



Dhont *et al. Respiratory Research* (2020) 21:198
https://doi.org/10.1186/s12931-020-01462-5

Respiratory Research

REVIEW Open Access

The pathophysiology of 'happy' hypoxemia in COVID-19

Sebastiaan Dhont[1*], Eric Derom[1,2], Eva Van Braeckel[1,2], Pieter Depuydt[1,3] and Bart N. Lambrecht[1,2,4]

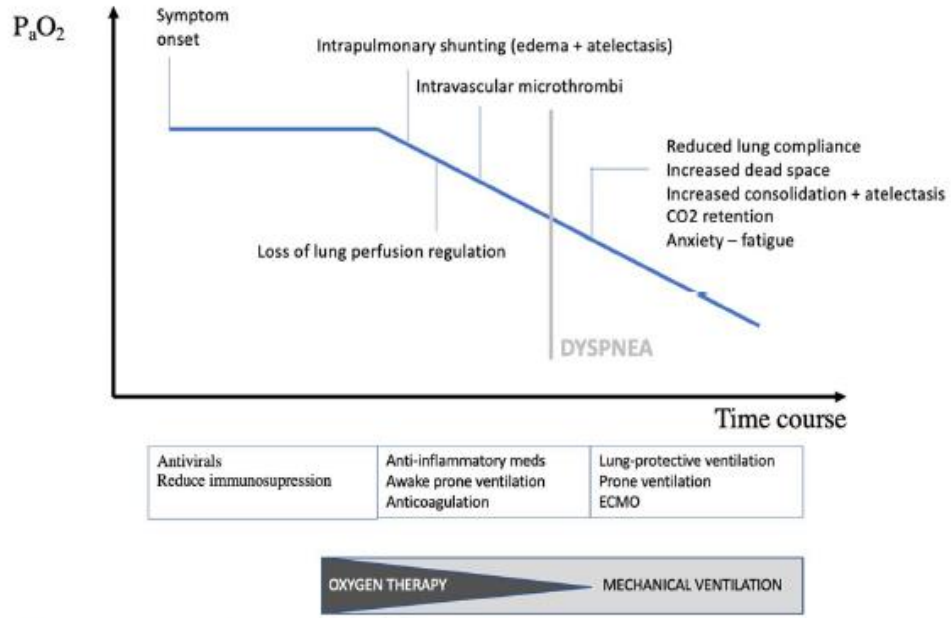
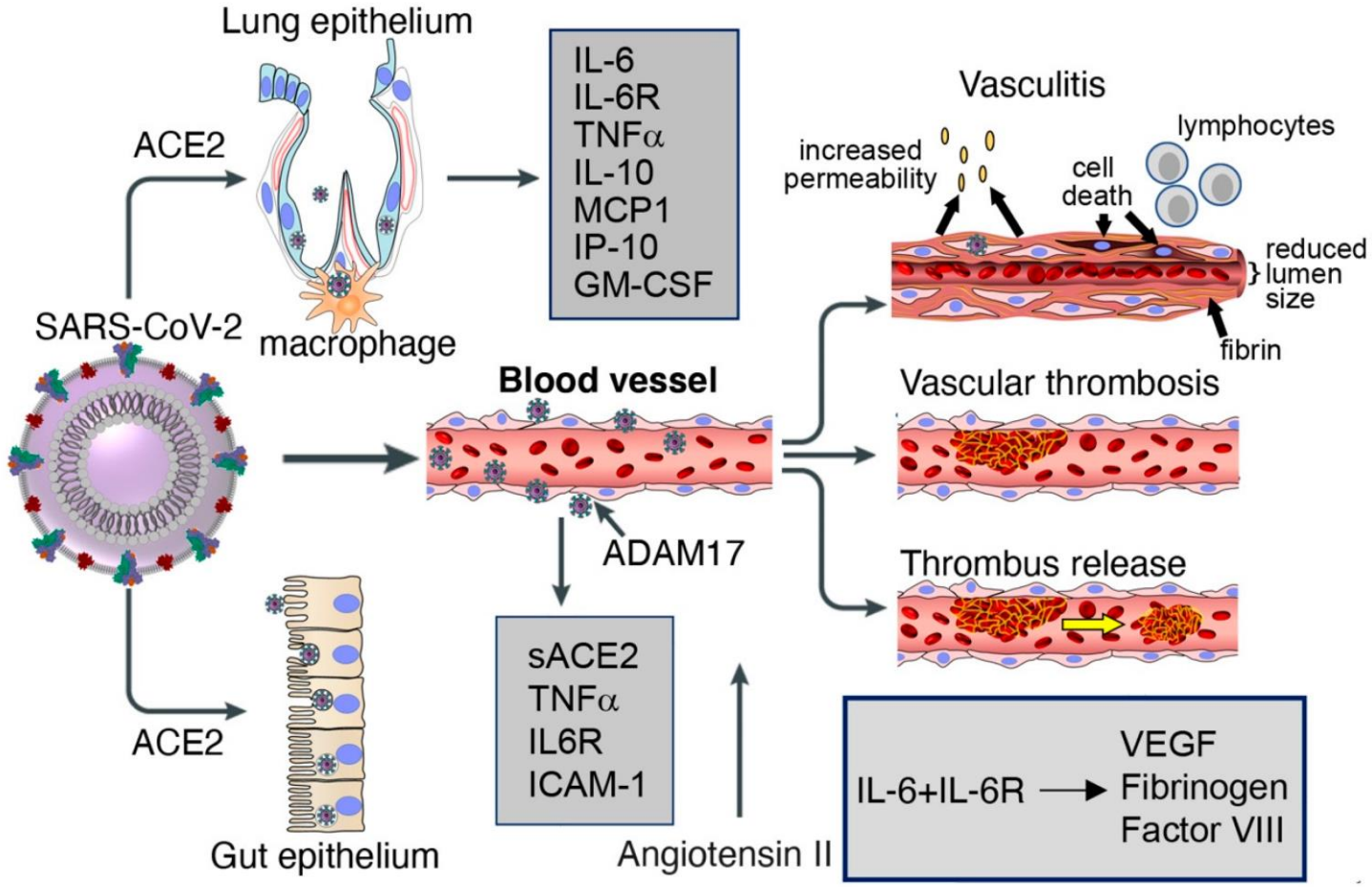


Fig. 2 Mechanisms of hypoxemia in COVID-19

3. COVID-19-related Hypercoagulability

Stato protombrotico sia dovuto al virus + tempesta citochinica



3. COVID-19-related Hypercoagulability

Angiogenesis
https://doi.org/10.1007/s10456-020-09753-7

ORIGINAL PAPER

Microvascular dysfunction in COVID-19: the MYSTIC study

Alexandros Rovas[1] · Irina Osiaevi[1] · Konrad Buscher[1] · Jan Sackarnd[2] · Phil-Robin Tepasse[3] · Manfred Fobker[4] · Joachim Kühn[5] · Stephan Braune[6] · Ulrich Göbel[7] · Gerold Thölking[1,8] · Andreas Gröschel[9] · Hermann Pavenstädt[1] · Hans Vink[10] · Philipp Kümpers[1]

Received: 16 September 2020 / Accepted: 28 September 2020

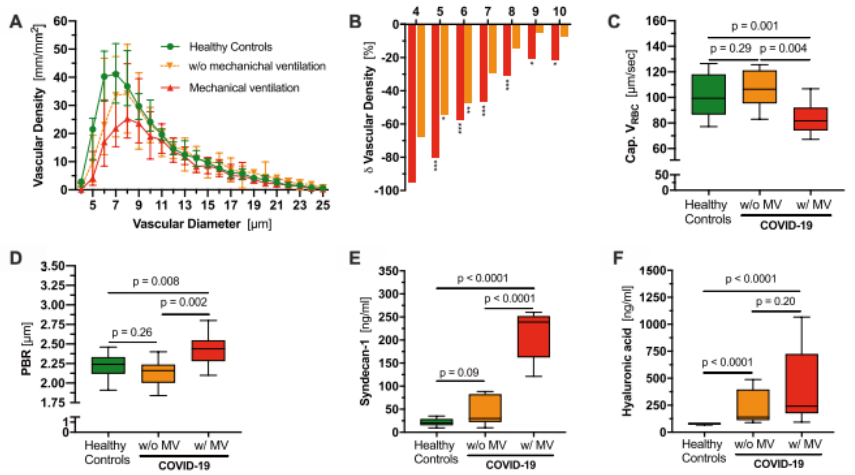


Fig. 1 Endothelial glycocalyx dimensions in vivo and in vitro and capillary density in COVID-19 patients with (w/) and without (w/o) mechanical ventilation (MV) and healthy controls.**a** Median and IQR values of vascular density of healthy controls and COVID-19 patients based on the diameter class from 4 to 25 µm. **b** Bar charts showing the percentage of loss of vascular density in COVID-19 patients with (red) and without (orange) mechanical ventilation compared to healthy controls (diameter class from 4 to 10 µm). $*q<0.05$, $**q<0.01$, $***q<0.001$ Boxplots of **c** of capillary V_{RBC}, **d** PBR values, and endothelial glycocalyx constituents **e** syndecan-1 and **f** hyaluronic acid of healthy controls (green) and COVID-19 patients with (red) or without (orange) mechanical ventilation (MV) $*p<0.05$, $**p<0.01$, $***p<0.001$

"Our data **clearly show severe alterations of the microcirculation and the endothelial glycocalyx in patients with COVID-19**. Future therapeutic approaches **should consider the importance of systemic vascular involvement in COVID-19**"

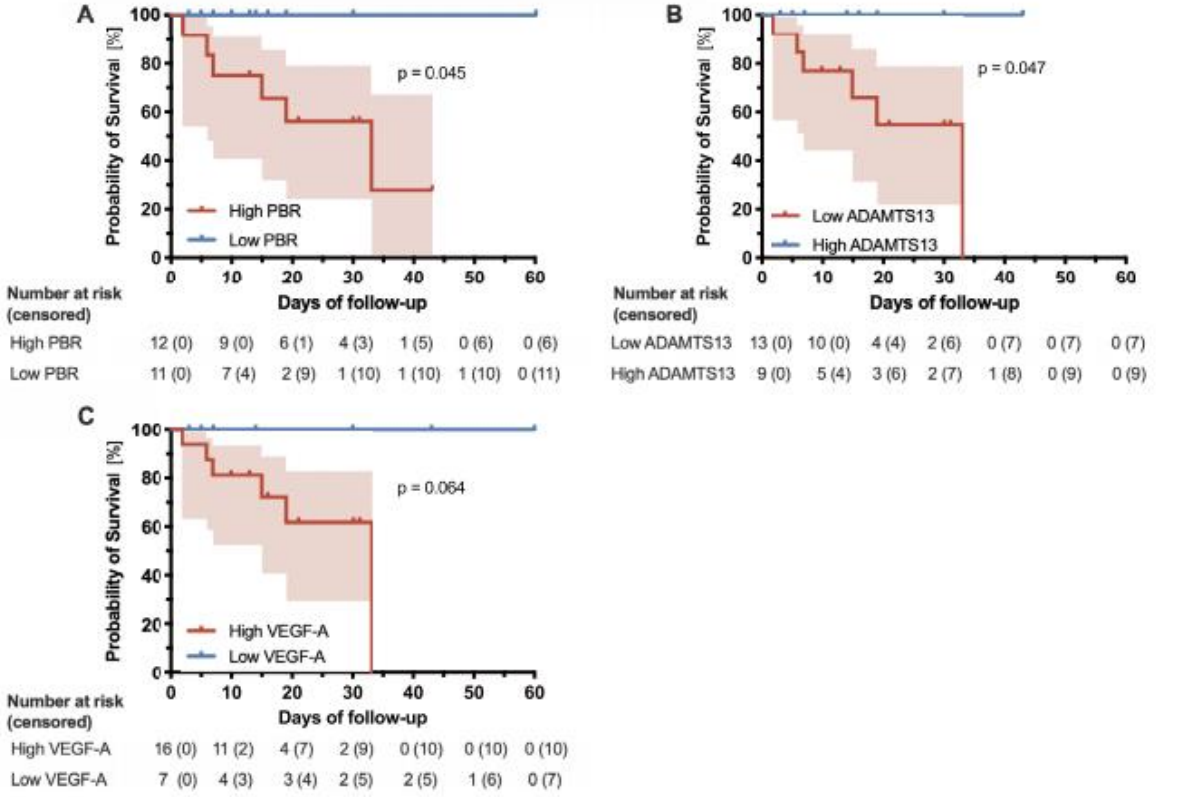


Fig. 3 Survival probability of COVID-19 patients according to different endothelial markers.Kaplan–Meier curves with 95% CIs showing survival probability of COVID-19 patients with **a** low/high PBR, **b** low/high ADAMTS13, and **c** low/high VEGF-A.#ADAMTS13 of one patient could not be measured due to technical reasons

Decorso clinico

Fase iniziale

- Legame a ACE2 → penetrazione all'interno delle cellule dell'ospite → replicazione.
- Fase dei sintomi generali, aspecifici.
- Se sistema immunitario dell'ospite riesce a bloccare l'infezione → decorso benigno

Tempesta citochinica

- Possibile evoluzione a quadro clinico ingravescente dominato da tempesta citochinica e da stato iperinfiammatorio

- A livello polmonare
  - quadri di vasculopatia arteriosa e venosa con trombizzazione dei piccoli vasi ed evoluzione verso lesioni polmonari gravi e, talvolta, permanenti (fibrosi → polmonare).

Seconda fase

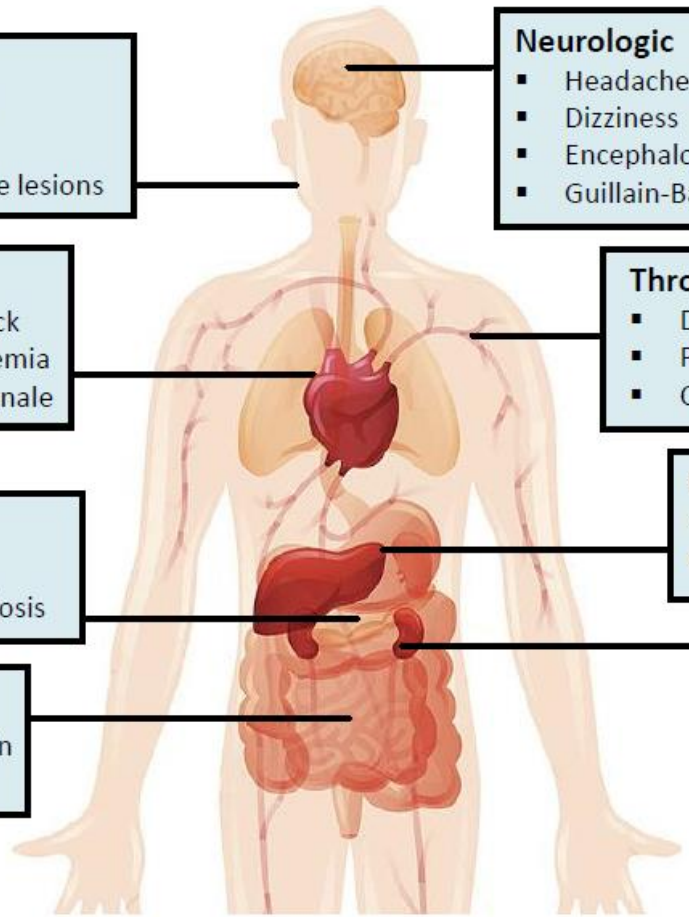
- Alterazioni morfo funzionali a livello polmonare
- Effetti diretti + risposta immunitaria dell'ospite
- Polmonite interstiziale → sintomatologia respiratoria → generalmente limitata nella fase precoce
- Possibile evoluzione a progressiva instabilità clinica con insufficienza respiratoria
- "Ipossiemia silente" → bassi valori diossigenazione → ematica in assenza di sensazione di dispnea soggettiva

ARDS

Alterazione progressiva di parametri:

- infiammatori come PCR, ferritina, citochine pro-infiammatorie (IL2, IL6, IL7, L10, GSCF, IP10, MCP1, MIP1A e TNFα)
- Parametri coagulativi come aumentati livelli dei prodotti di degradazione della fibrina, il D-dimero, consumo di fattori della coagulazione, trombocitopenia.

Extrapulmonary Manifestations



Dermatologic
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

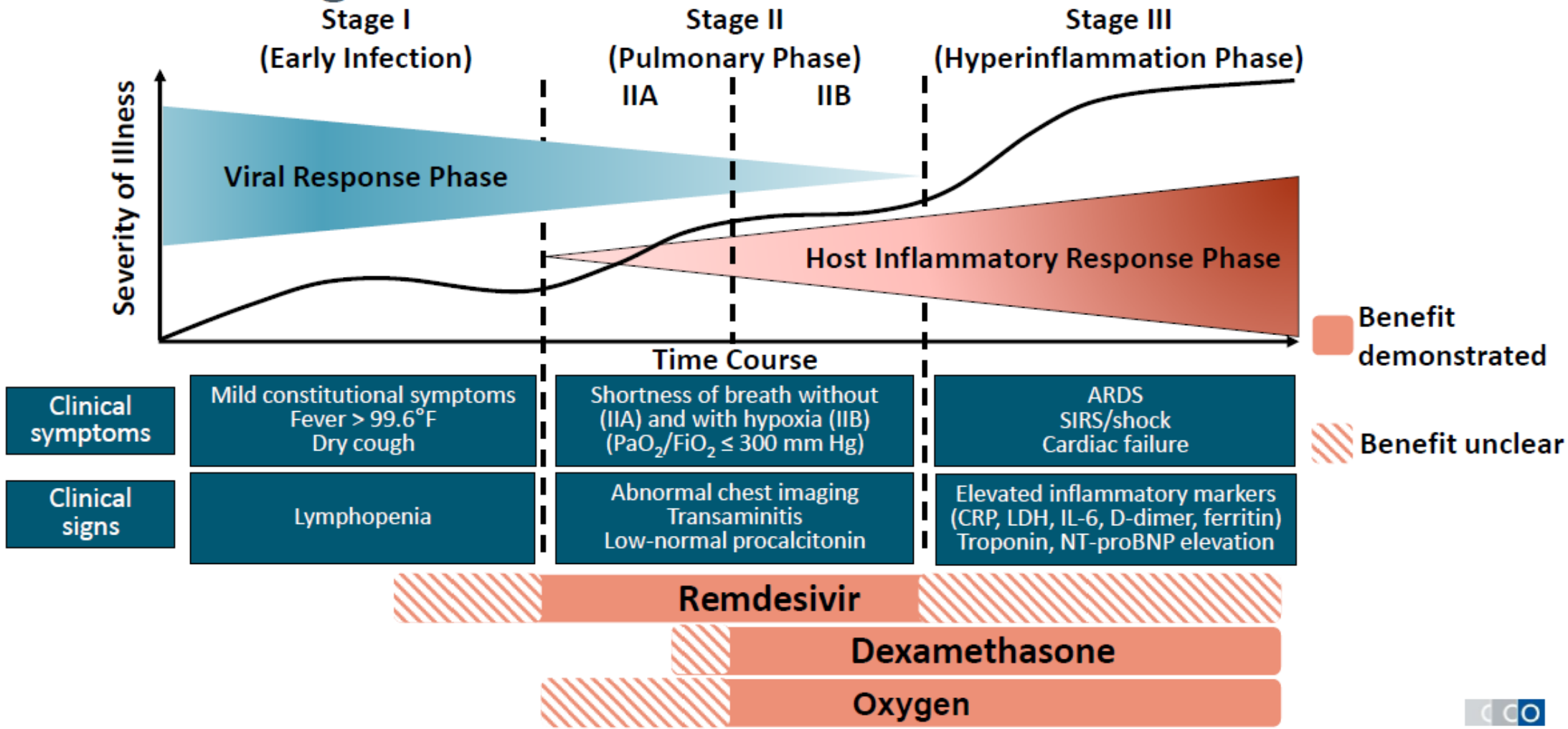
Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

Gupta. Nat Med. 2020;26:1017.

Slide credit: clinicaloptions.com

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



Siddiqi. J Heart Lung Transplant. 2020;39:405.

Slide credit: clinicaloptions.com

Decorso clinico

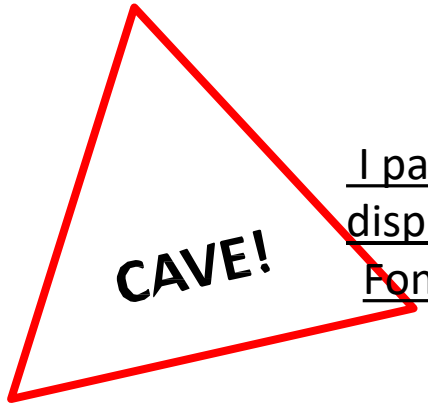
SINTOMI	%
Febbre *4-12 gg* (Tc > 38°C)	**44-94%**
Tosse *19 gg*	**68-93%**
Anosmia e/o Ageusia	79%
Sintomi delle alte vie respiratorie (mal di gola, rinorrea, congestione nasale o dei seni paranasali)	5-61%
Dispnea *13 gg*	**11-40%**
Astenia	23-38%
Mialgie	11-15%
Cefalea	8-14%
Confusione	9%
Sintomi GI (nausea, vomito, diarrea)	3-17%

Il 20% dei casi è asintomatico

L´importanza della misurazione dei parametri vitali

1. Pressione arteriosa – PA
2. Frequenza cardiaca – FC
3. Saturazione periferica - SpO2 %
4. Frequenza respiratoria – FR
5. Stato di coscienza - GCS

- Tachipnea (FR> 22 atti/min)
- Desaturazione
  - SpO2 < 94%
  - Ipossiema all'EGA
- Grave alterazione dello stato di coscienza



I pazienti COVID non "sentono" la dispnea

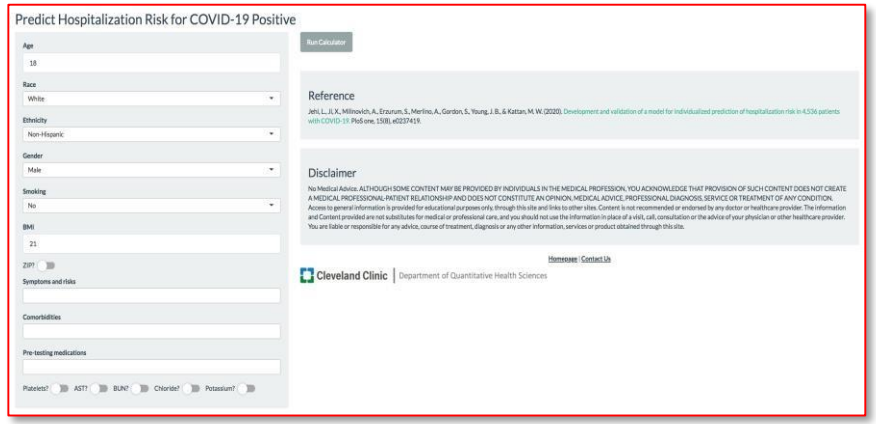
Fondamentale la frequenza respiratoria!

Fattori di rischio (per malattia severa)

- Sesso M
- Età > 60
- Ipertensione arteriosa
- Obesità BMI > 30
- Diabete
- Malattie cardiovascolari, cerebrovascolari
- Malattie degenerative neuro-muscolari
- BPCO
- Insufficienza renale
- Neoplasia maligna attiva
- Latenza tra inizio sintomi e prima valutazione medica

CRITERI DI SEVERITÁ

- Ospedalizzazione
- Trasferimento in TI
- IOT o ventilazione meccanica
- Mortalità aumentata



Cleveland Clinic: Studio su ca. 5000 Pz. per stimare il rischio di

Report sulle caratteristiche dei pazienti deceduti positivi a SARS-CoV-2 in Italia

Il presente report è basato sui dati aggiornati al 5 ottobre 2021

Figura 1. *Età mediana deceduti e diagnosticati positivi a SARS-CoV-2*

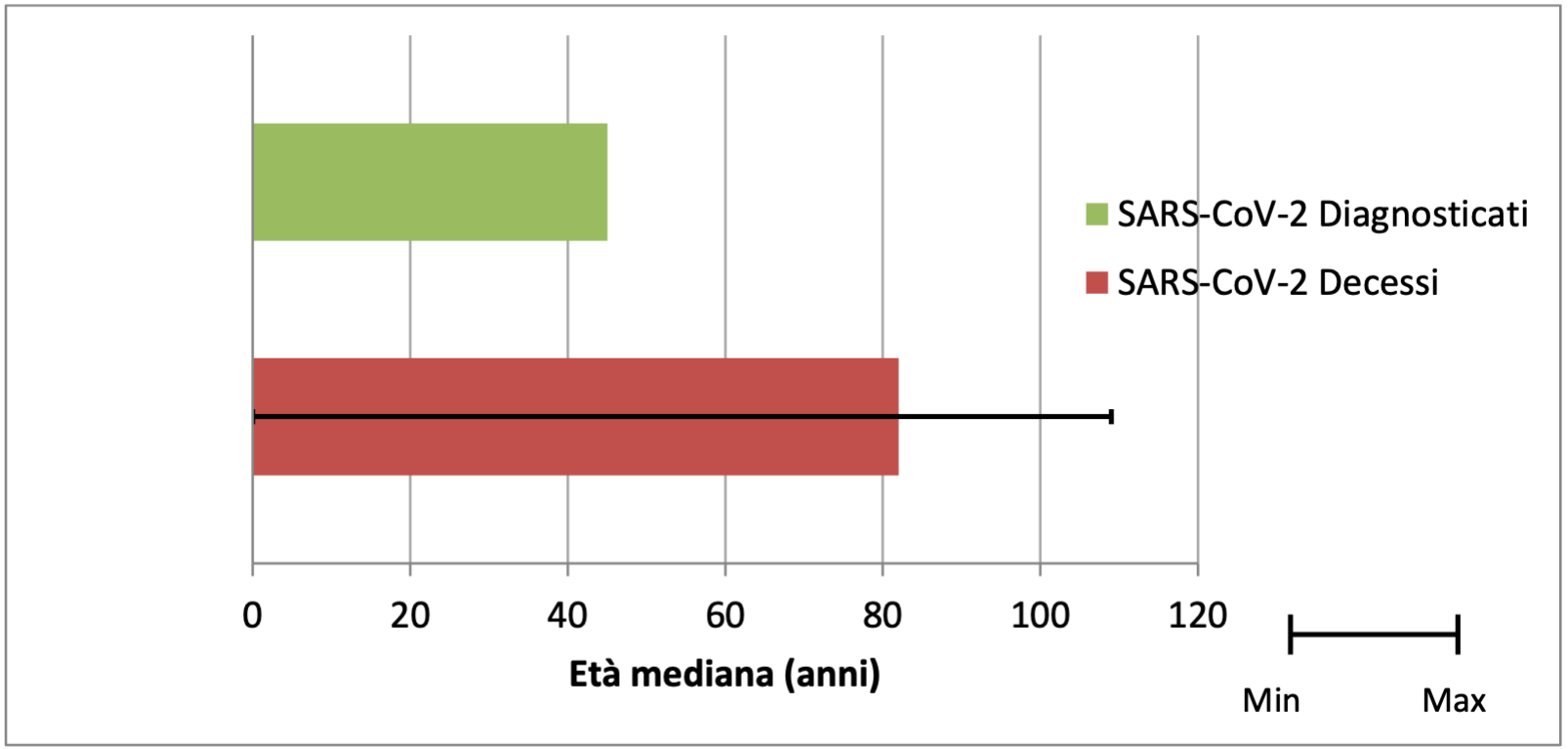


Figura 2. *Numero di decessi per fascia di età e sesso*

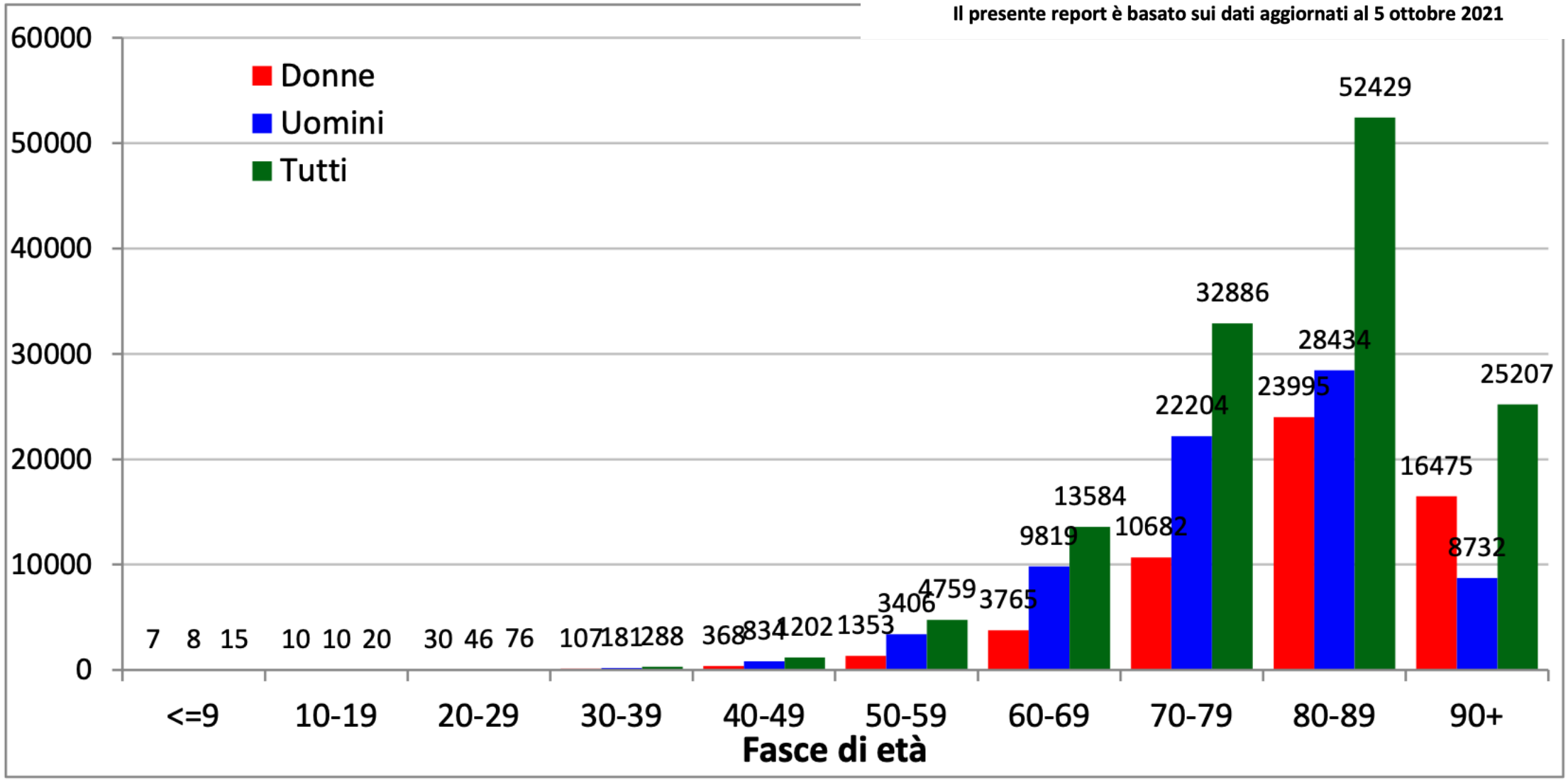
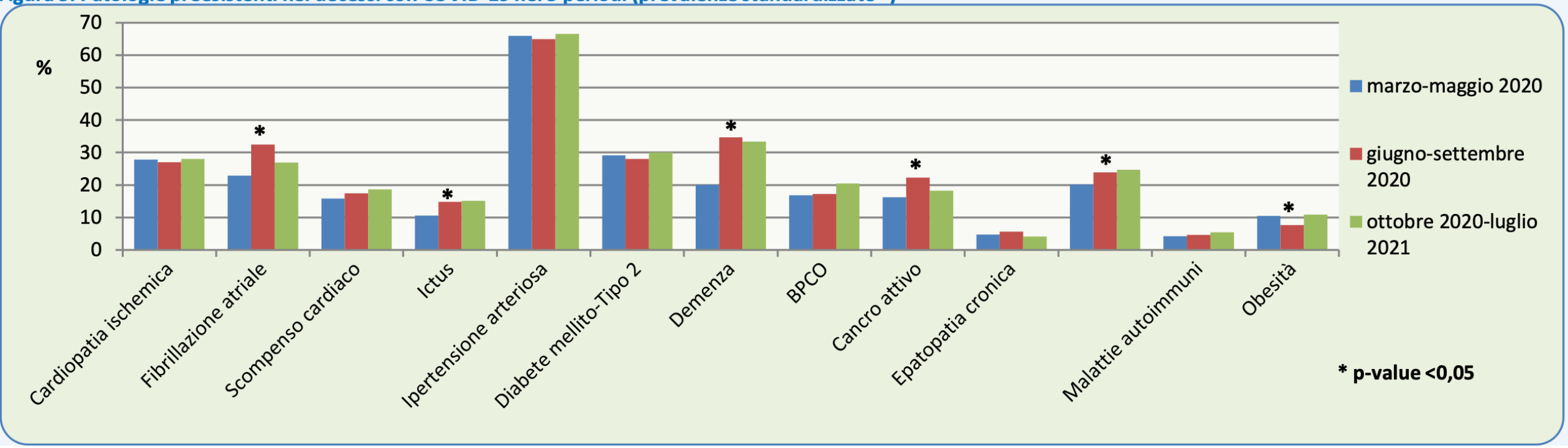


Figura 5. Patologie preesistenti nei decessi con COVID-19 nei 3 periodi (prevalenze standardizzate ^)



Diagnosi: test di laboratorio

RT-PCR

- **Tampone Nasofaringeo** (80% sensibilità 3 giorni dopo l'insorgenza dei sintomi)

- **Lavaggio broncoalveolare (BAL)**: dati ancora non conclusivi, suggeriscono un aumento del 5% nella diagnosi

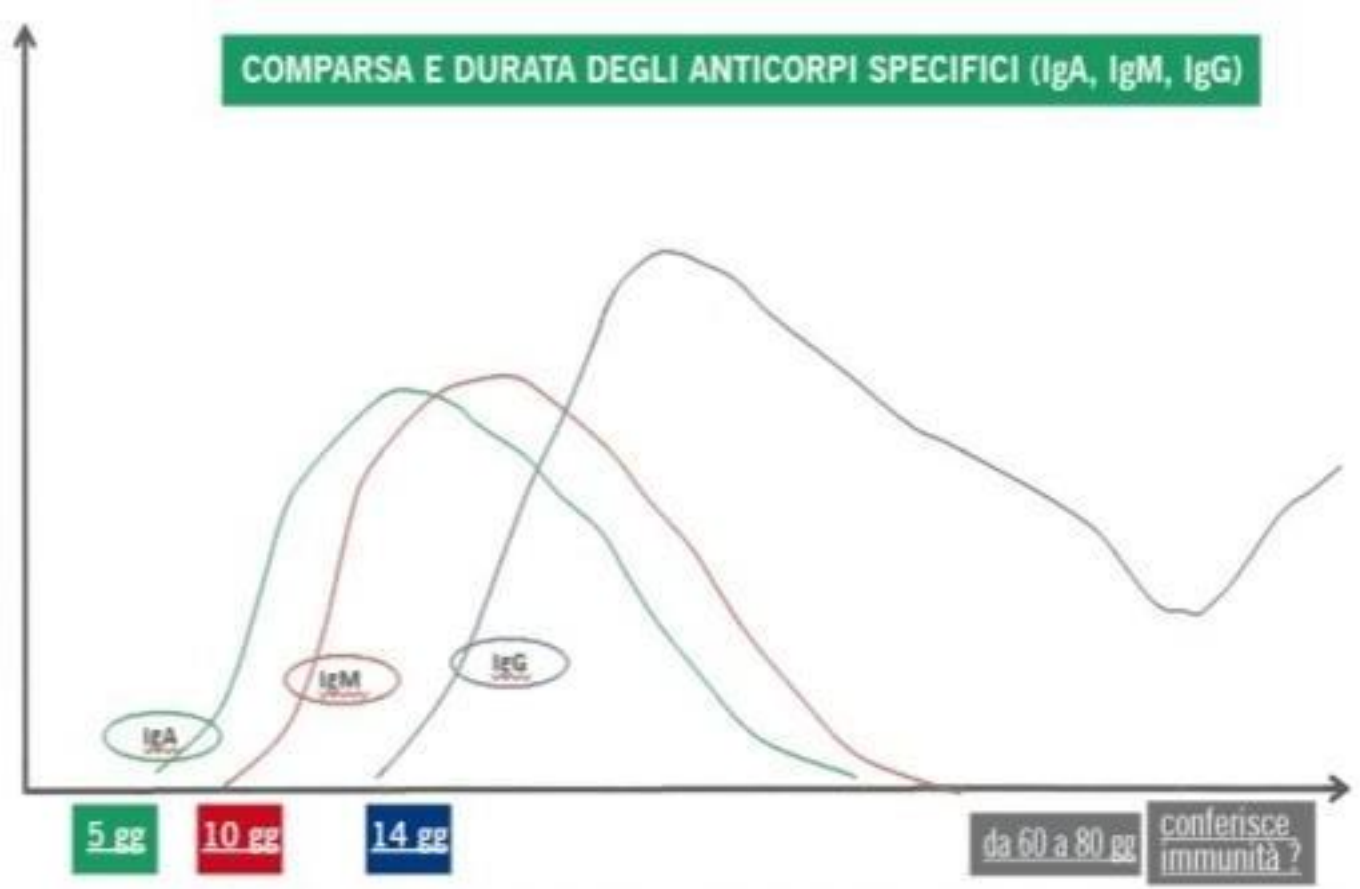
Antigen test ("rapido")

- rapido, point of care, possibili falsi negativi

TEST ANTIGENICO	PROBABILITA' PRE-TEST di infezione da SARS- CoV-2	
	BASSA *	ALTA °
NEGATIVO	INFEZIONE SARS-CoV-2 ESCLUSA / MOLTO IMPROBABILE	INFEZIONE SARS-CoV-2 INCERTA
	Non indicati test ulteriori	Ripetizione test Ag o effettuazione test RT-PCR
POSITIVO	INFEZIONE SARS-CoV-2 INCERTA	INFEZIONE SARS-CoV-2 CONFERMATA/ MOLTO PROBABILE
	Effettuazione test RT-PCR	Non indicati test ulteriori per motivi clinico-epidemiologici

Test sierologici

- Prestazioni e precisione **variabili**
  - IgA: le più precoci
  - IgM: da 5-10 giorni dall'infezione fino a 3 settimane
  - IgG: 14 giorni dopo l'insorgenza dei sintomi; alti titoli in caso di malattia severa



Esami di laboratorio di routine

Leucociti	< 4000 o > 10000/µL	**Lattati**	> 2
Linfociti	< 800/µL	**LDH**	> 250 U/L
Neutrofili	> 8000/µL	**PCR**	> 10 mg/L
PLT	< 150000/µL	**Creatinina**	> 1.5 mg/dL
Troponina	> 99° percentile	**AST/ALT**	> 40 U/L
D-dimero	> 1.5 µg/mL	**Ferritina**	> 1000 ng/mL

Fattori prognostici: Linfopenia, LDH, PCR, PCT, D-dimero, Ferritina, Troponina, IL-6

EGA: pH, P/F, PCo2, Lac

Stage	Characteristics
Asymptomatic or presymptomatic infection	▪ Positive test for SARS-CoV-2 but no symptoms
Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain) but no shortness of breath, dyspnea, abnormal imaging
Moderate illness	▪ $SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	▪ $SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	▪ Respiratory failure, septic shock, and/or multiorgan dysfunction

MEWS: Modified Early Warning Score

DATI FISIOLOGICI (indicare un solo valore per ogni fattore)							
Punteggio	3	2	1	0	1	2	3
Frequenza respiratoria (atti/minuto)		< 9		9-14	15-20	21-29	≥ 30
Frequenza cardiaca (battiti/minuto)		≤ 40	41-50	51-100	101-110	111-129	≥ 130
Pressione sistolica (mmHg)	< 70	71-80	81-100	101-199		≥200	
Temperatura corporea (°C)		≤ 35 °C		35.1-38.4		≥ 38.4°C	
Sintomi neurologici				Vigile	Risponde alla voce	Risponde al dolore	Non risponde (GCS < 9)

PUNTEGGIO TOTALE |__|__| legenda MEWS: 0-2 paziente stabile, 3-4 instabile, ≥ 5critico

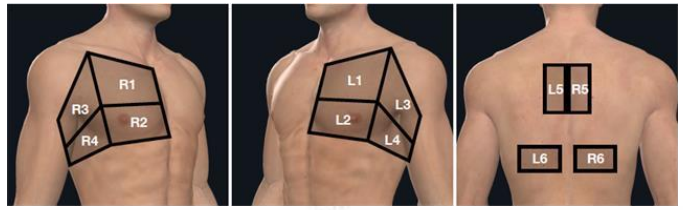
Saturazione O_2 ____ in Aria ambiente |__| in O_2 terapia |__| _____ Lt/min

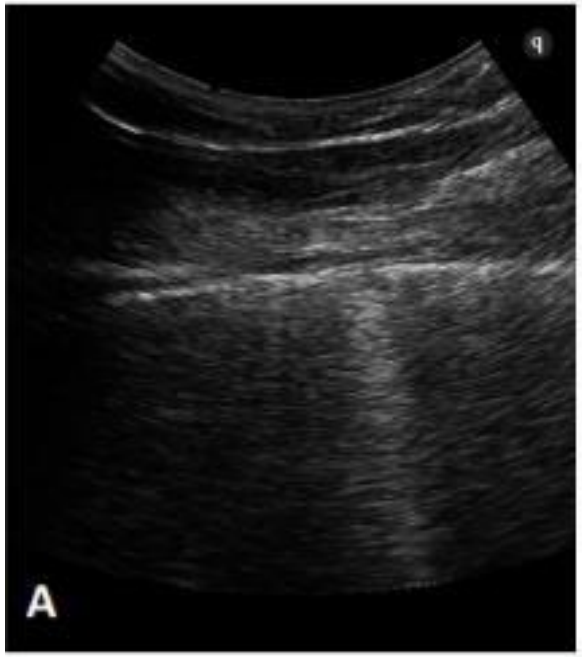
Rapporto PaO_2/FiO_2 _____

DIAGNOSTICA PER IMMAGINI

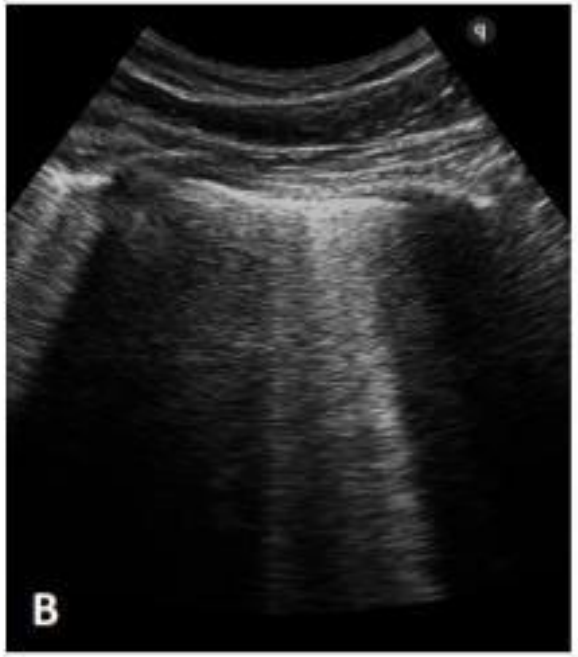
- **Ecografia polmonare**

  12 aree da esaminare

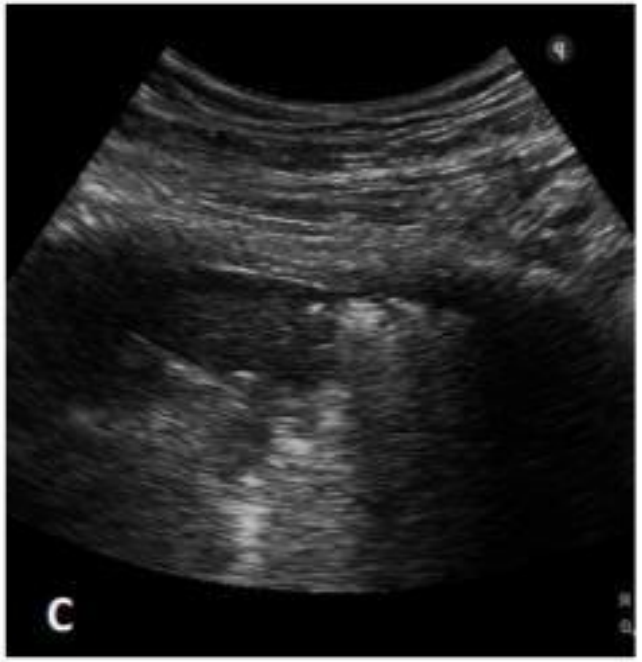




A. Rare linee B, iniziale coinvolgimento interstiziale



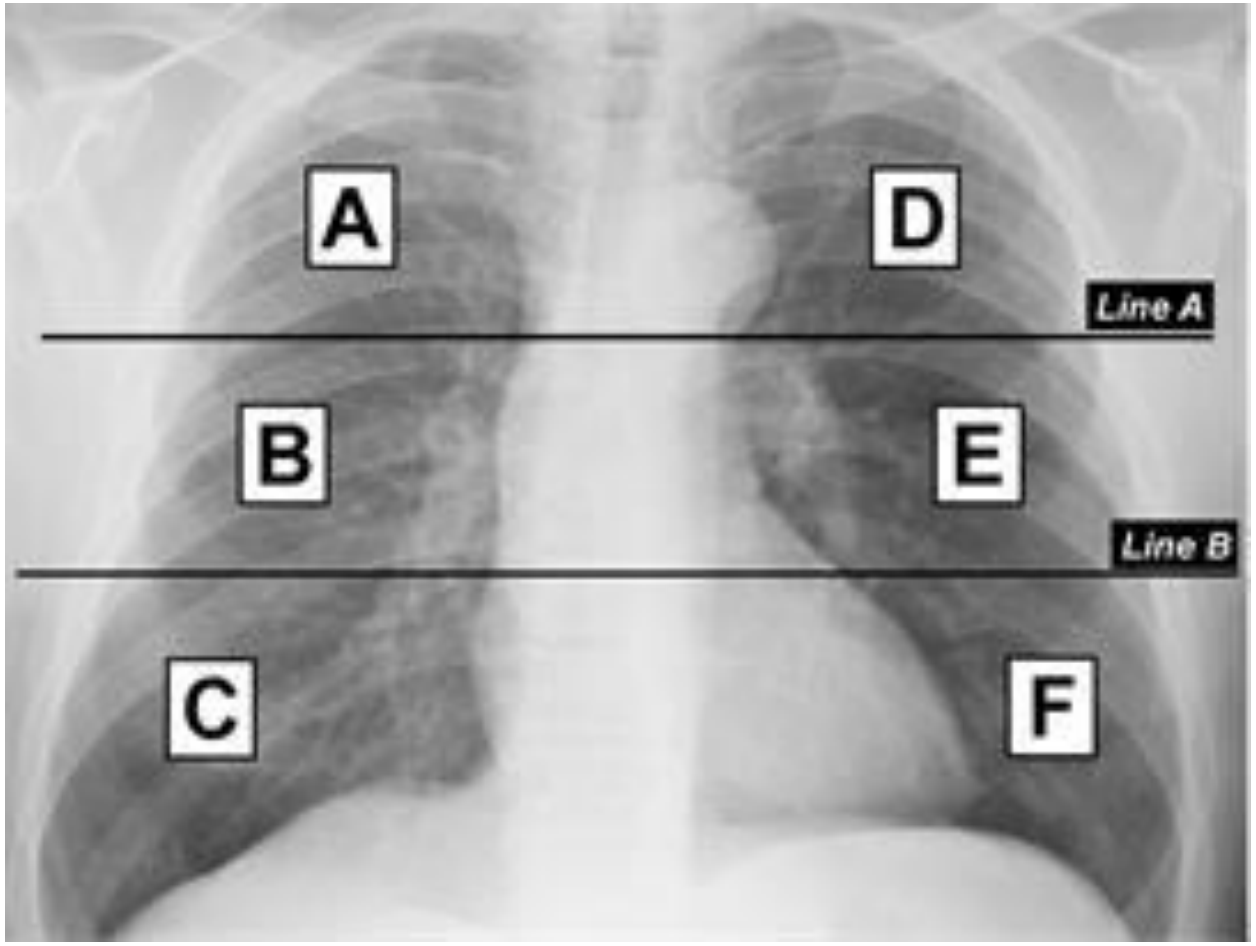
B. Coinvolgimento interstiziale con linee B confluenti e iniziali addensamenti subpleurici



C. Multipli addensamenti subpleurici

DIAGNOSTICA PER IMMAGINI

- **RX torace**
  - Valutazione del *grado di impegno parenchimale*
  - **BRIXIA score** valuta semiquantitativamente il grado di impegno parenchimale in ogni area (con punteggio totale variabile da 0 a 18):
    - 0 – nessuna alterazione
    - 1 – infiltrati interstiziali
    - 2 – infiltrati interstiziali e alveolari
    - (predominanza interstiziale)
    - 3 – infiltrati interstiziali e alveolari
    - (predominanza alveolare)



DIAGNOSTICA PER IMMAGINI

Diagnostica d' immagine: TC torace con studio ad alta risoluzione: HRTC

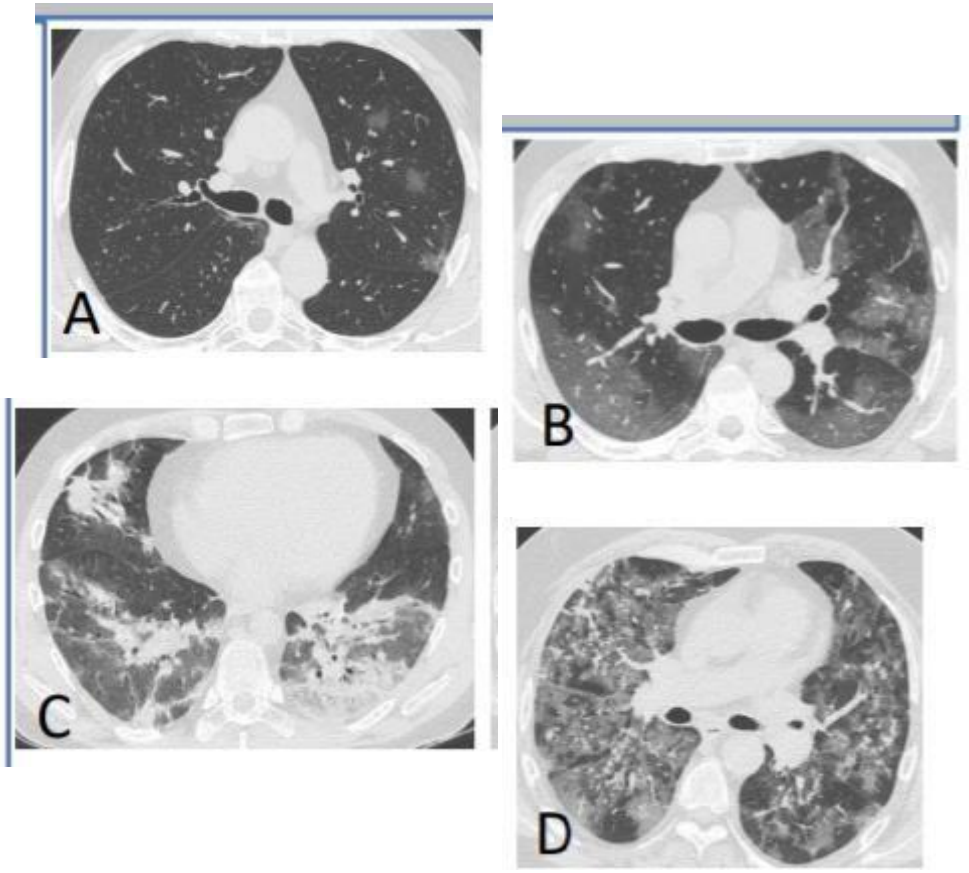
Gold standard

Fase pre-sintomatica (A): piccole aree di iperdensità con aspetto "ground glass", spesso unilaterale, pochi segmenti coinvolti

Prima settimana (B): lesioni bilaterali, più estese, più segmenti coinvolti, tipico pattern GG a distribuzione prevalentemente periferica/posteriore. Rari VPL e linfadenopatia

Peggioramento (C): aumento del pattern GG e comparsa di consolidamento parenchimale.

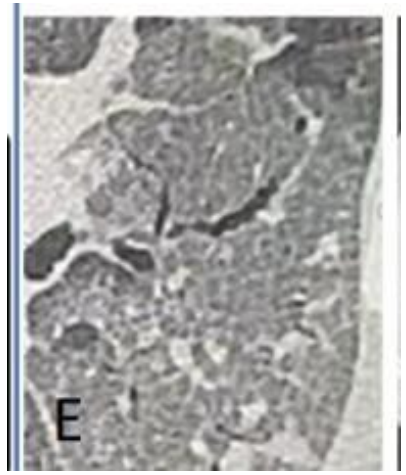
Possibile anche evoluzione a pattern ARDS **(D)**

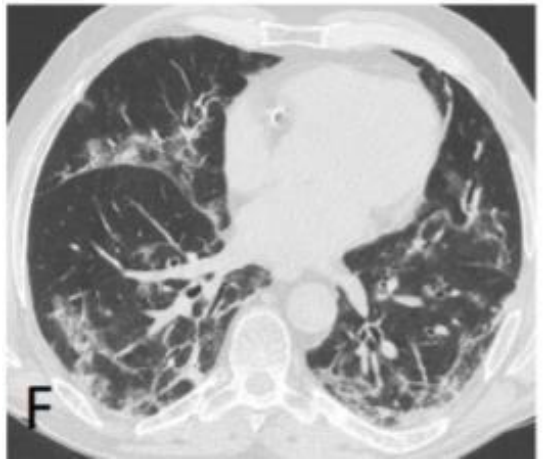


DIAGNOSTICA PER IMMAGINI

Diagnostica d' immagine: TC torace con studio ad alta risoluzione: HRTC

Evoluzione: casi non severi mostrano riduzione delle aree GG **(E)**. Ispessimento dei setti interlobulari. Nelle aree di consolidamento, sono le porzioni più periferiche che rimangono consolidate più a lungo “old spiderweb” **(F)**



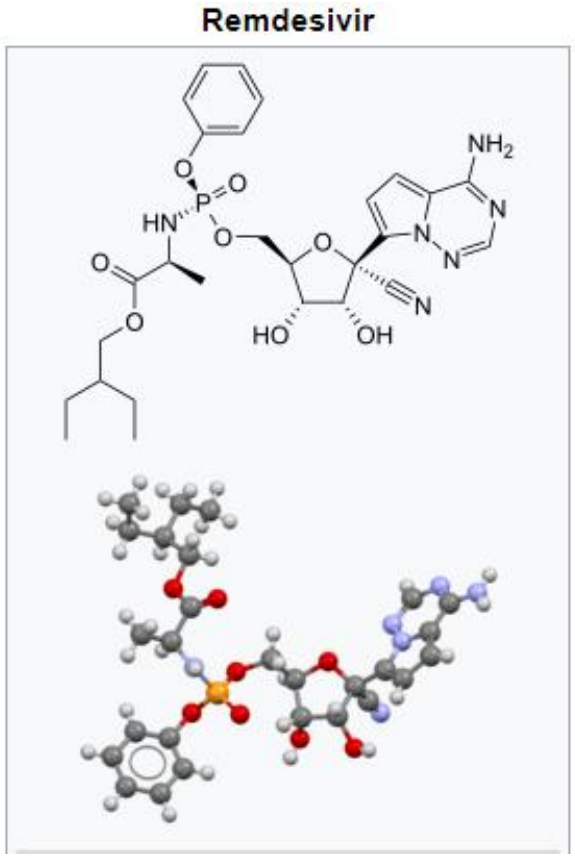


SCAN ME

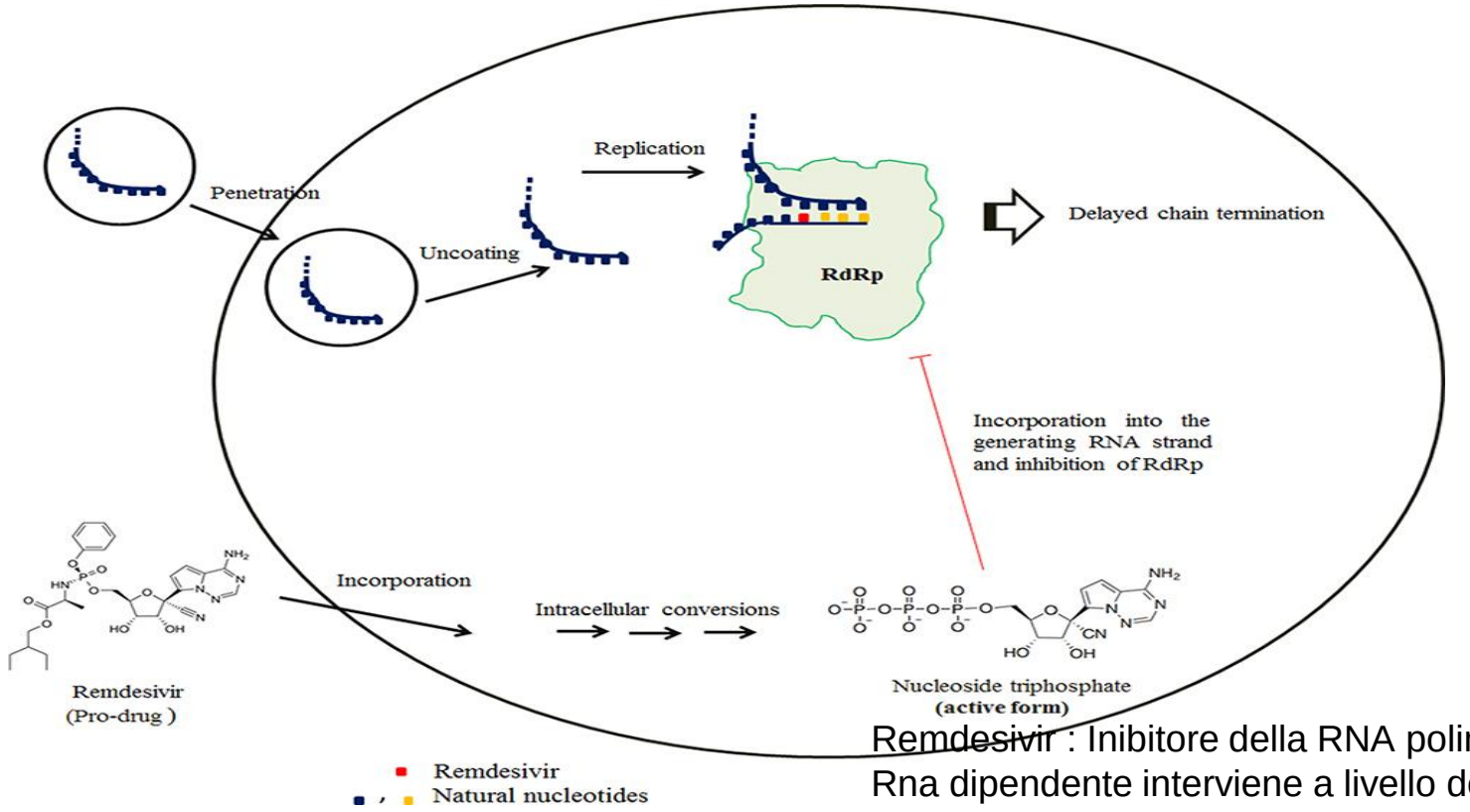
POSSIBILI APPROCCI TERAPEUTICI

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

REMDESIVIR



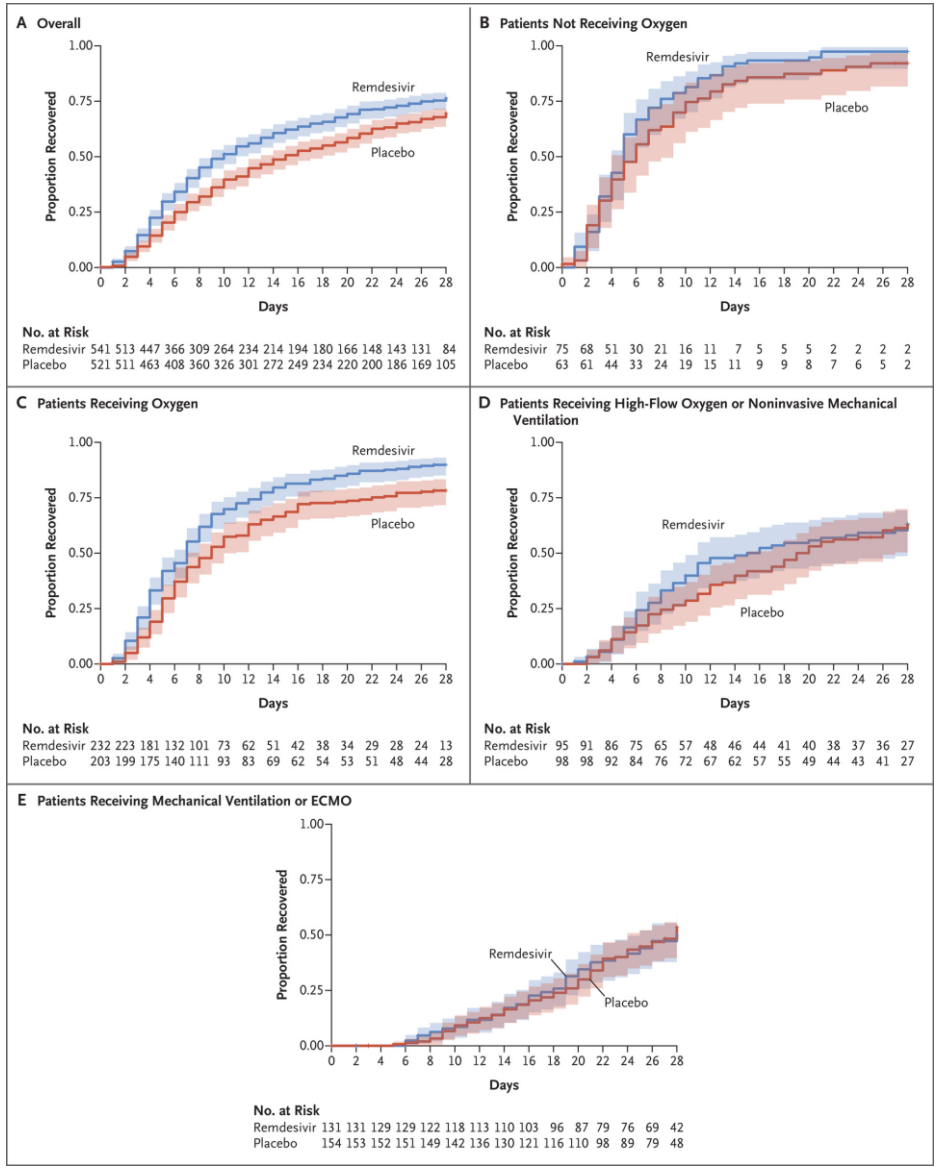
Remdesivir is a prodrug that is intended to allow intracellular delivery of GS-441524 monophosphate and subsequent biotransformation into GS-441524 triphosphate, a ribonucleotide analogue **inhibitor of viral RNA polymerase**



Remdesivir : Inibitore della RNA polimerasi Rna dipendente interviene a livello del ribosoma e blocca la replicazione del virus

chain terminator=terminatore di catena

REMDESIVIR

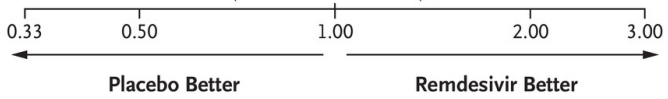


ORIGINAL ARTICLE

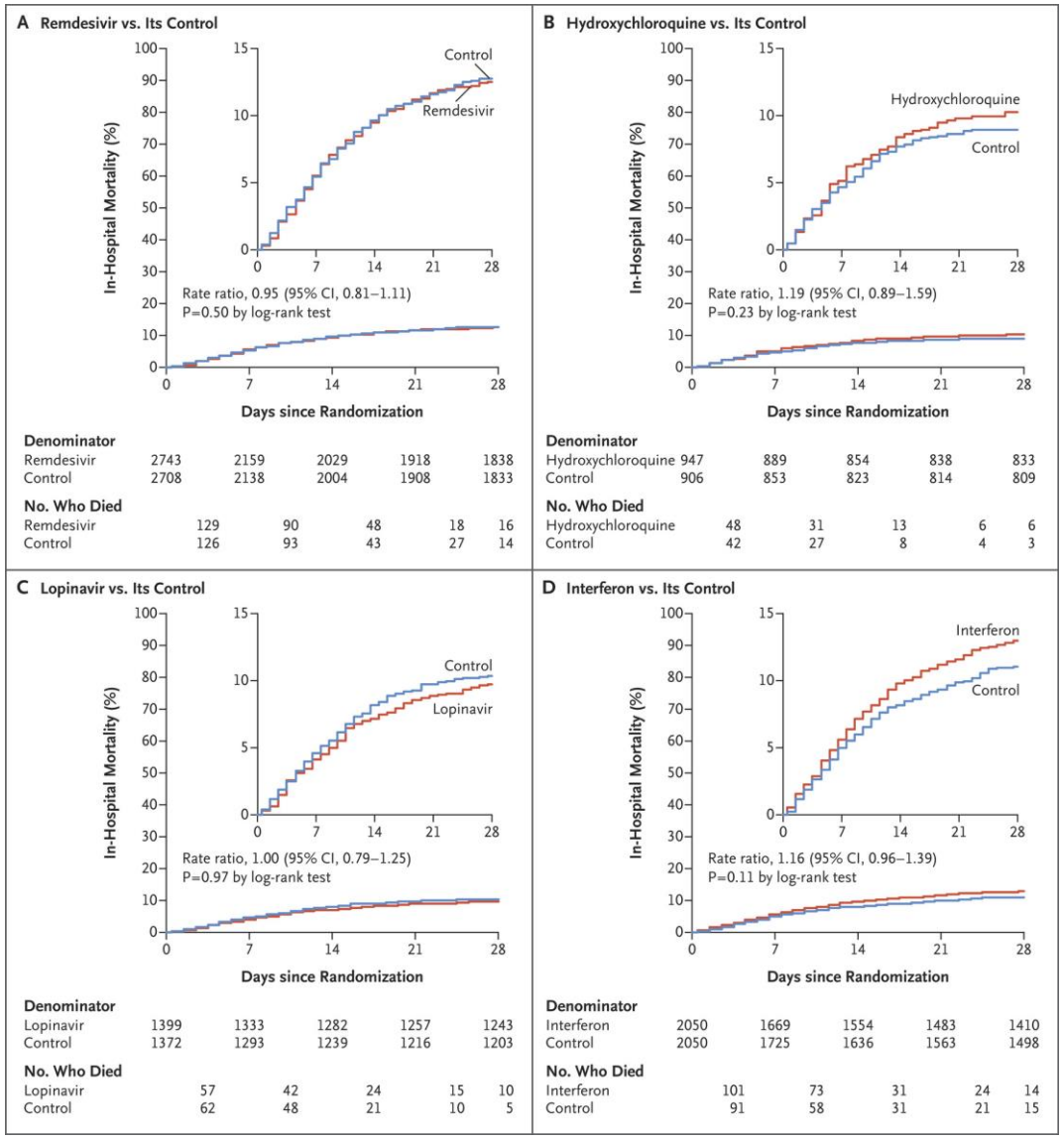
Beigel, NEJM 2020

Remdesivir for the Treatment of Covid-19 — Final Report

Subgroup	No. of Patients	Recovery Rate Ratio (95% CI)
All patients	1062	1.29 (1.12–1.49)
Geographic region		
North America	847	1.30 (1.10–1.53)
Europe	163	1.30 (0.91–1.87)
Asia	52	1.36 (0.74–2.47)
Race		
White	566	1.29 (1.06–1.57)
Black	226	1.25 (0.91–1.72)
Asian	135	1.07 (0.73–1.58)
Other	135	1.68 (1.10–2.58)
Ethnic group		
Hispanic or Latino	250	1.28 (0.94–1.73)
Not Hispanic or Latino	755	1.31 (1.10–1.55)
Age		
18 to <40 yr	119	1.95 (1.28–2.97)
40 to <65 yr	559	1.19 (0.98–1.44)
≥65 yr	384	1.29 (1.00–1.67)
Sex		
Male	684	1.30 (1.09–1.56)
Female	278	1.31 (1.03–1.66)
Symptoms duration		
≤10 days	676	1.37 (1.14–1.64)
>10 days	383	1.20 (0.94–1.52)
Baseline ordinal score		
4 (not receiving oxygen)	138	1.29 (0.91–1.83)
5 (receiving oxygen)	435	1.45 (1.18–1.79)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation)	193	1.09 (0.76–1.57)
7 (receiving mechanical ventilation or ECMO)	285	0.98 (0.70–1.36)



REMDESIVIR



Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*

*A complete list of SOLIDARITY Trial investigators is provided in the Supplementary Appendix.

CONCLUSIONS

These Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens **appeared to have little or no effect on hospitalized COVID-19**, as indicated by overall mortality, initiation of ventilation and duration of hospital stay. The mortality findings contain most of the randomized evidence on Remdesivir and Interferon, and are consistent with meta-analyses of mortality in all major trials. (Funding: WHO. Registration: ISRCTN83971151, NCT04315948)

REMDESIVIR

Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

Lancet Infect Dis 2021

Published Online
September 14, 2021
https://doi.org/10.1016/S1473-3099(21)00485-0

Florence Ader, Maude Bouscambert-Duchamp, Maya Hites, Nathan Peiffer-Smadja, Julien Poissy, Drifa Belhadi, Alpha Diallo, Minh-Patrick Lê, Gilles Peytavin, Thérèse Staub, Richard Greil, Jérémie Guedj, Jose-Artur Paiva, Dominique Costagliola, Yazdan Yazdanpanah, Charles Burdet, France Mentré*, and the DisCoVeRy Study Group*

Methods DisCoVeRy was a phase 3, open-label, adaptive, multicentre, randomised, controlled trial conducted in 48 sites in Europe (France, Belgium, Austria, Portugal, Luxembourg). Adult patients (aged ≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and illness of any duration were eligible if they had clinical evidence of hypoxaemic pneumonia, or required oxygen supplementation. Exclusion criteria included elevated liver enzymes, severe chronic kidney disease, any contraindication to one of the studied treatments or their use in the 29 days before random assignment, or use of ribavirin, as well as pregnancy or breastfeeding. Participants were

REMDESIVIR

Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

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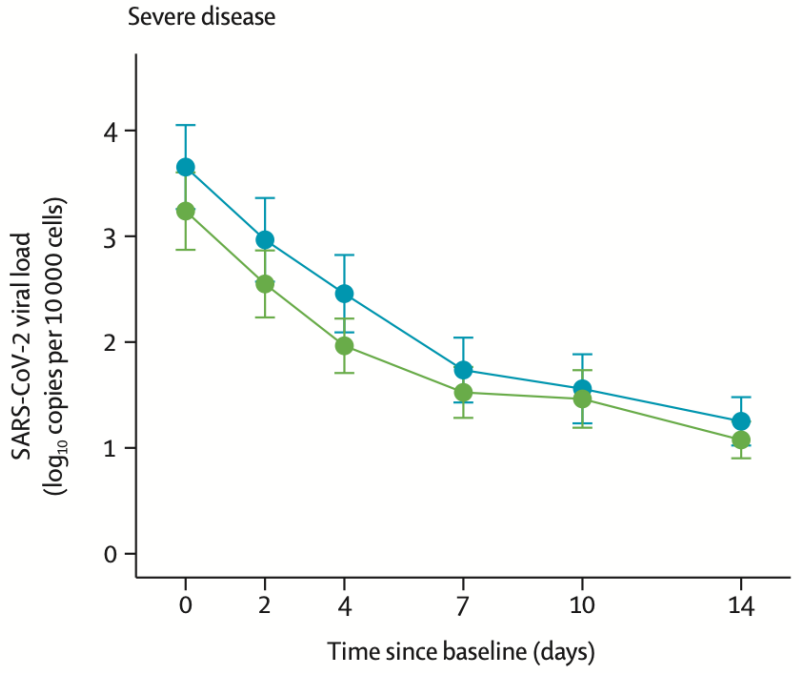
Lancet Infect Dis 2021

Published Online
September 14, 2021
https://doi.org/10.1016/
S1473-3099(21)00485-0

In this randomised controlled trial, the use of remdesivir for the treatment of hospitalised patients with COVID-19 was not associated with clinical improvement at day 15 or day 29, nor with a reduction in mortality, nor with a reduction in SARS-CoV-2 RNA.



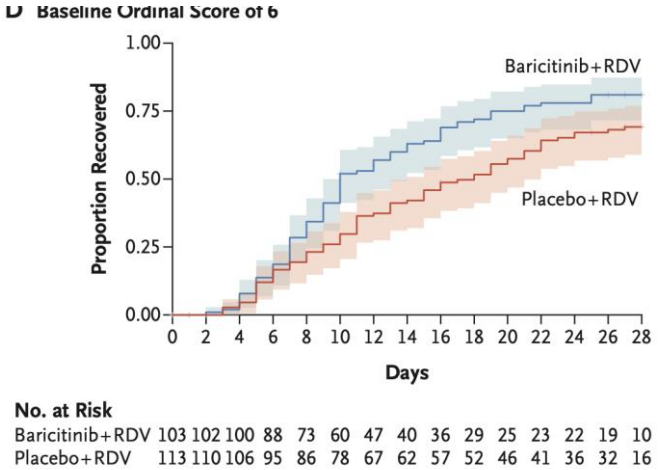
Data are mean (95% CI). Green lines show the remdesivir group. Blue lines show the control group. LSMD=least-square mean difference.

BARICITINIB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19



METHODS

We conducted a double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with Covid-19. All the patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15.

CONCLUSIONS

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT04401579.)

COVID-19 Principles of Treatment

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

OSSIGENOTERAPIA

Cenni di Terapia (1) - Ossigenoterapia

SpO2 target > 92%. Se BPCO 88-94%

- O2 terapia con cannule nasale 1-6 litri massimo
- Maschera di Venturi fino al 60%
- Maschera Reservoir 10-15 litri/min

Valvola		FiO2
Celeste	2 l/min	24%
Gialla	4 l/min	28%
Bianca	6 l/min	31%
Verde	8 l/min	35%
Blu	10 l/min	40%
Arancio	12 l/min	50%
Rosa	15 l/min	60%

Se la SpO2 non è a target o peggiora iniziare

1. **CPAP**
   - Iniziale setting a 7,5 cmH2O, incrementabile fino a massimo 10 cm H2O
   - FiO2 60-100% da titolare in base all'andamento
2. **NIV** con PEEP 5 setting iniziale come per CPAP e PSV con setting iniziale 6 cmH2O, valutando il Volume Corrente FiO2 35-80% da titolare in base alla SpO2. Questa modalità è preferibile nei BPCO o dove la CPAP non funziona o provoca ipercapnia.

- Se non controindicato e fattibile tecnicamente considerare la **pronazione a paziente sveglio per 8-12 ore al giorno**. Se difficile, modificare il decubito del paziente da un fianco all'altro ogni 2-3 ore.

CAVE!

In caso di **improvvisa desaturazione**! pensare a embolia polmonare!!

Proning in Non-Intubated (PINI) in Times of COVID-19: Case Series and a Review

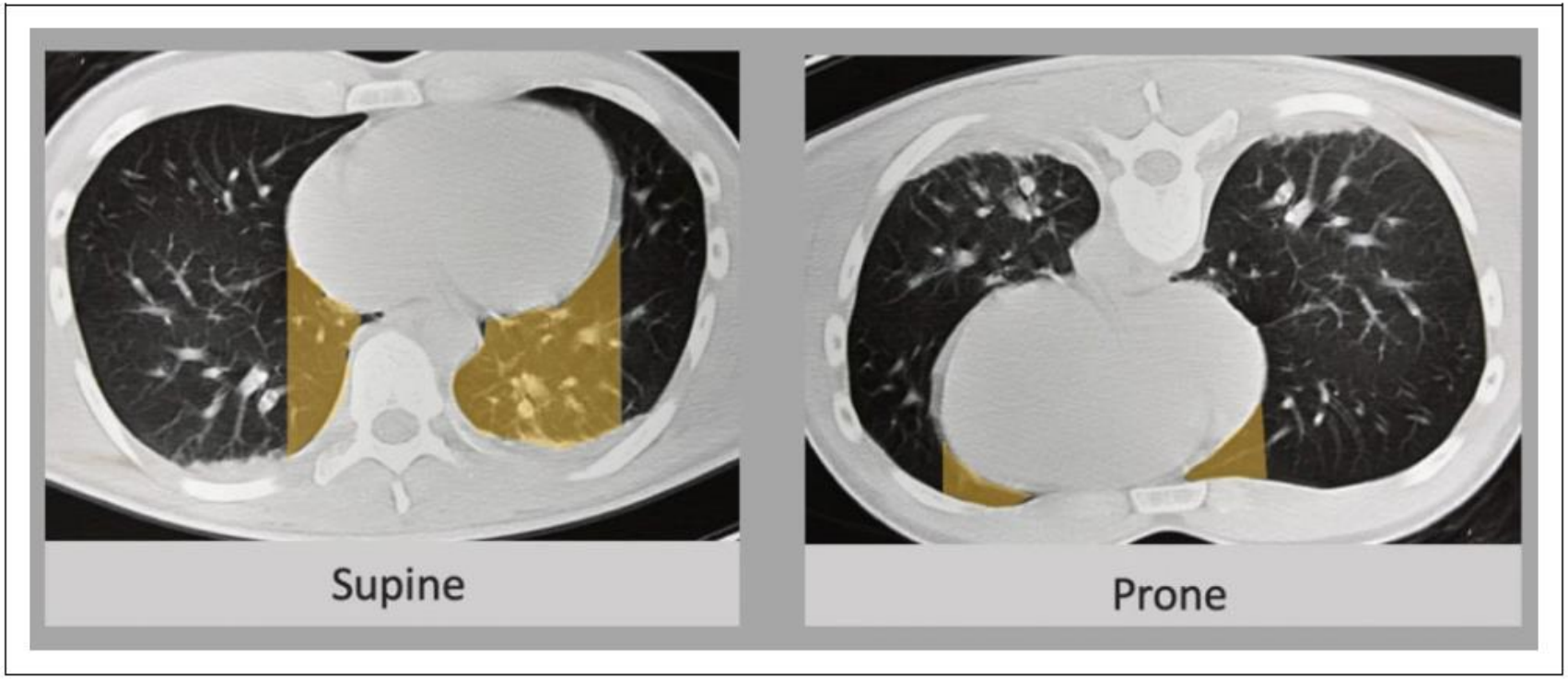


Figure 5. Comparison of lung compression by the heart in supine and prone positions (Adapted from the efficacy of prone position in acute respiratory distress syndrome patients: a pathophysiology-based review. V Koulouras, World J Crit Care Med. 2016;5(2): Page 126).

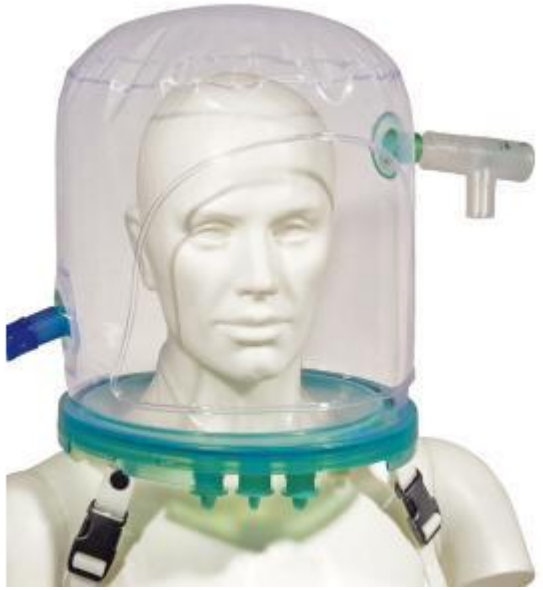
OSSIGENOTERAPIA

Ossigenoterapia

Se necessario, ventilazione non invasiva (NIV), cPAP (continuous positive airway pressure), HFNO (high-flow nasal oxygen)

Idratazione endovenosa

Terapia antibiotica empirica o mirata



COVID-19 Principles of Treatment

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

CORTICOSTEROID FOR COVID

Corticosteroids for COVID-19

LIVING GUIDANCE
2 SEPTEMBER 2020

World Health Organization

Recommendations: The panel made two recommendations: a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19, and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19.

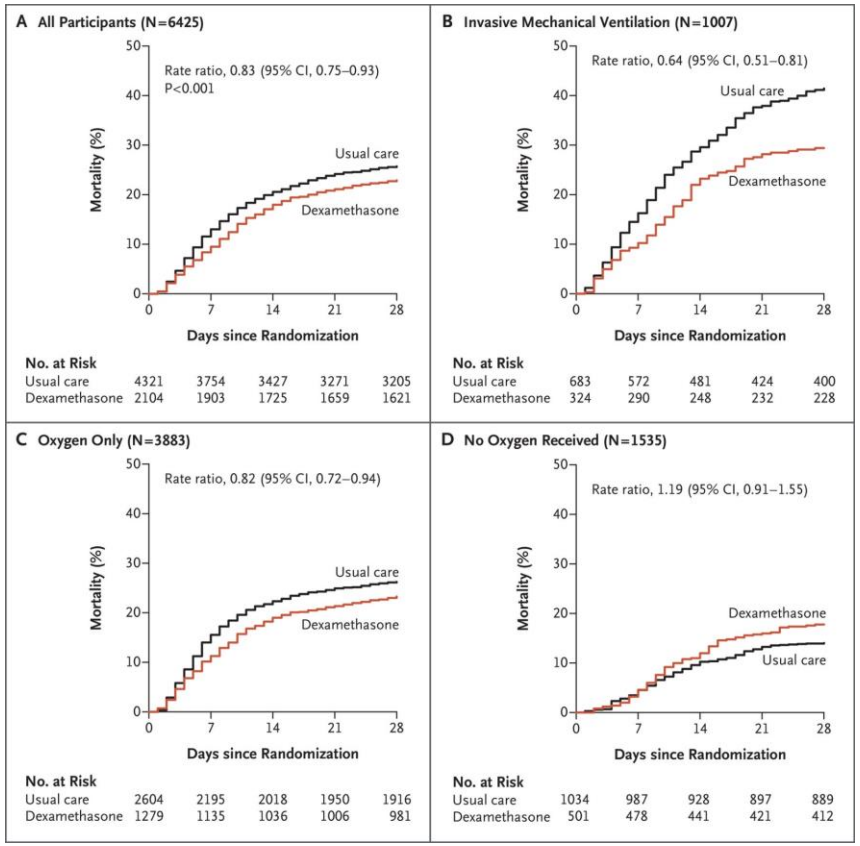
DEXAMETHASONE

ORIGINAL ARTICLE

NEJM, 2020

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*



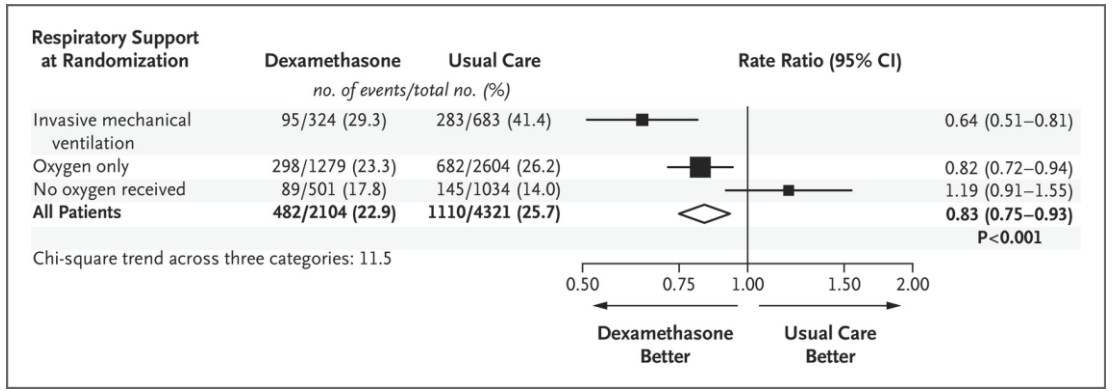


Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

COVID-19 Principles of Treatment

Internal and Emergency Medicine
https://doi.org/10.1007/s11739-021-02655-6

IM - ORIGINAL

Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients

Amit Bahl[1] · Steven Johnson[1] · Nai-Wei Chen[2]

[a]Propensity score matching analysis was Cox regression in the matched cohort

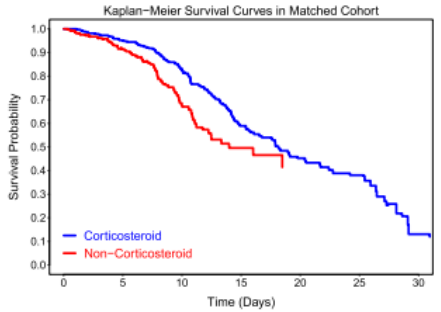


Figure 1. Kaplan-Meier survival curve for corticosteroids treatment. Figure shows overall survival for propensity score-matched patients treated with or without corticosteroids. The estimated survival curves were pooled from 20 imputed datasets

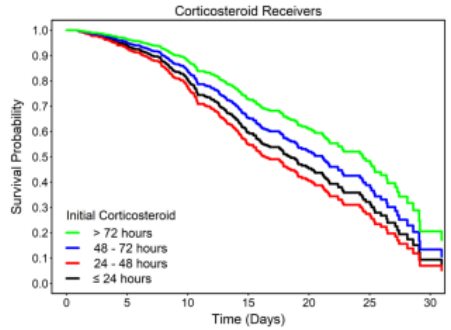


Figure 2. Survival curve for the timing of corticosteroids treatment. Figure shows overall survival of study patients associated with the initial receipt of corticosteroids treatment during the hospitalization. The direct adjusted survival curves were estimated based on a multivariable analysis and pooled from 20 imputed datasets

Patients receiving first dose of corticosteroids>72 h into hospitalization had a lower risk of death compared to patients with first dose at earlier time intervals (HR 0.56, 95% CI 0.38–0.82; p=0.003).

<u>There was a mortality beneft in patients with>7 days of symptom onset to initiation of corticosteroids</u> (HR 0.56, 95% CI 0.33–0.95; p=0.03).

In patients receiving oxygen therapy, corticosteroids reduced risk of death in mechanically ventilated patients (HR 0.38, 95% CI 0.24–0.60; p7 days should trigger initiation of corticosteroids.

In the absence of invasive mechanical ventilation, corticosteroids should be initiated if the patient remains hospitalized at 72 h

TOCILIZUMAB

SYSTEMATIC REVIEW | ARTICLES IN PRESS

Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis

Imad M. Tleyjeh • Zakariya Kashour • Moussab Damlaj • ... Rana Tleyjeh • Leslie Hassett • Tarek Kashour • Show all authors

Published: November 05, 2020 • DOI: https://doi.org/10.1016/j.cmi.2020.10.036

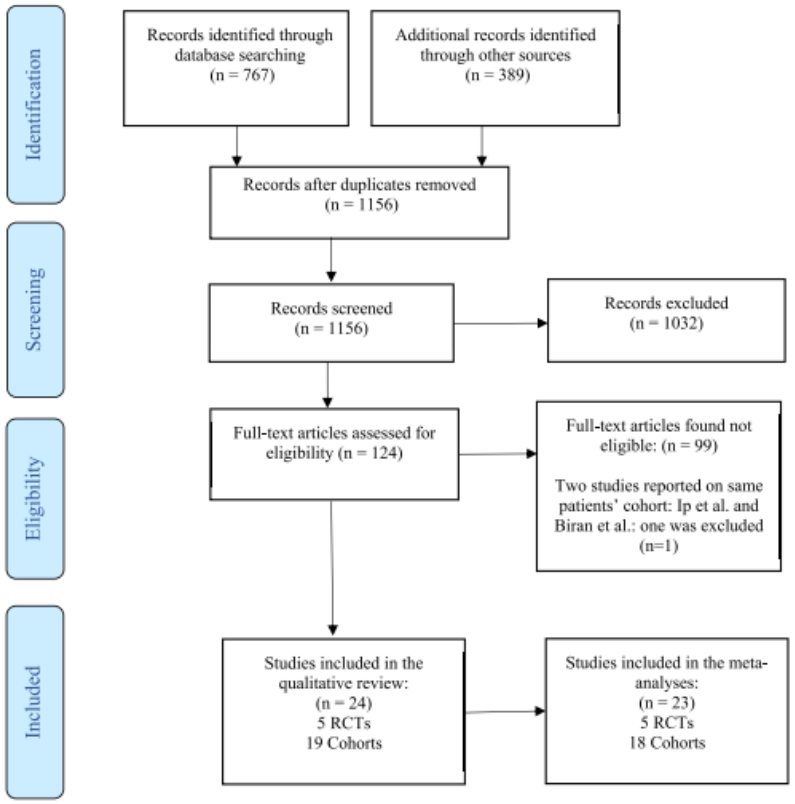
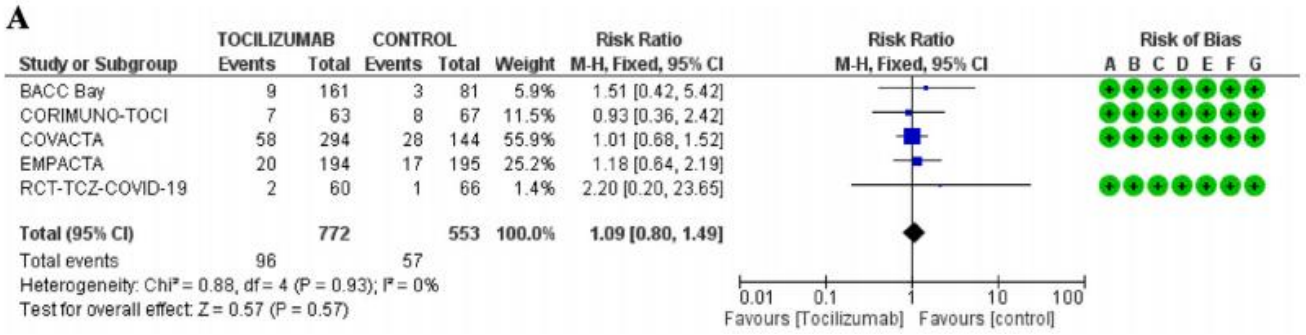
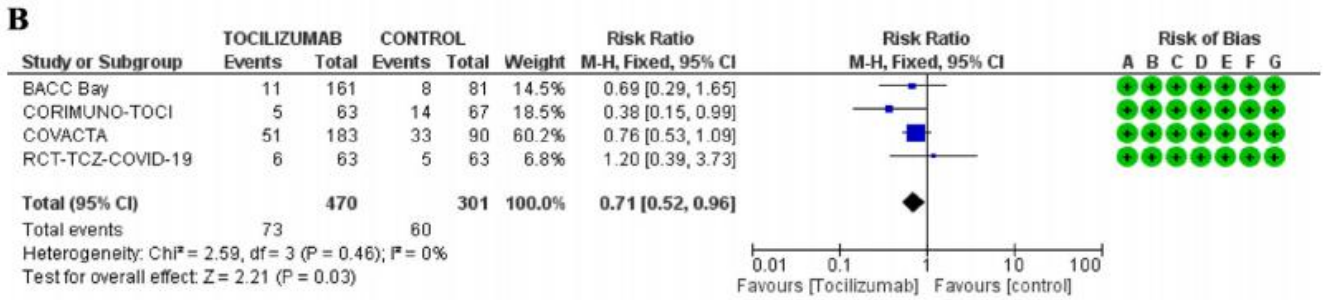
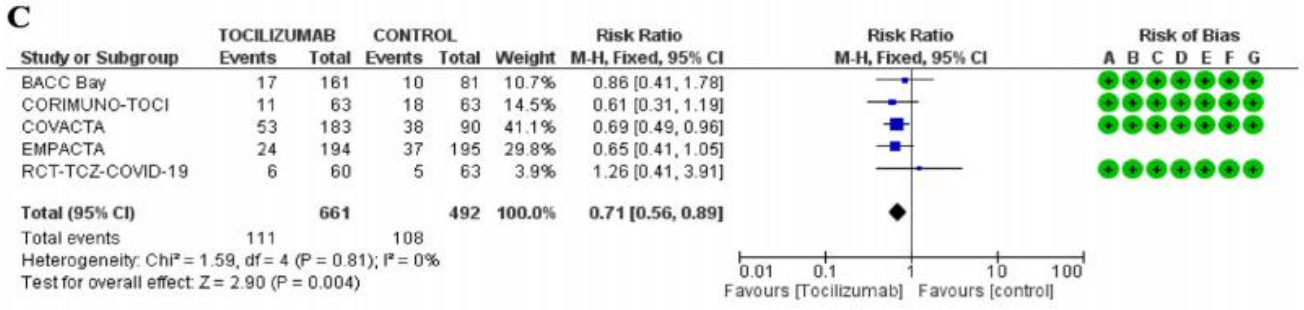


Fig. 1. Flow diagram of the assessment of studies identified in the systematic review.



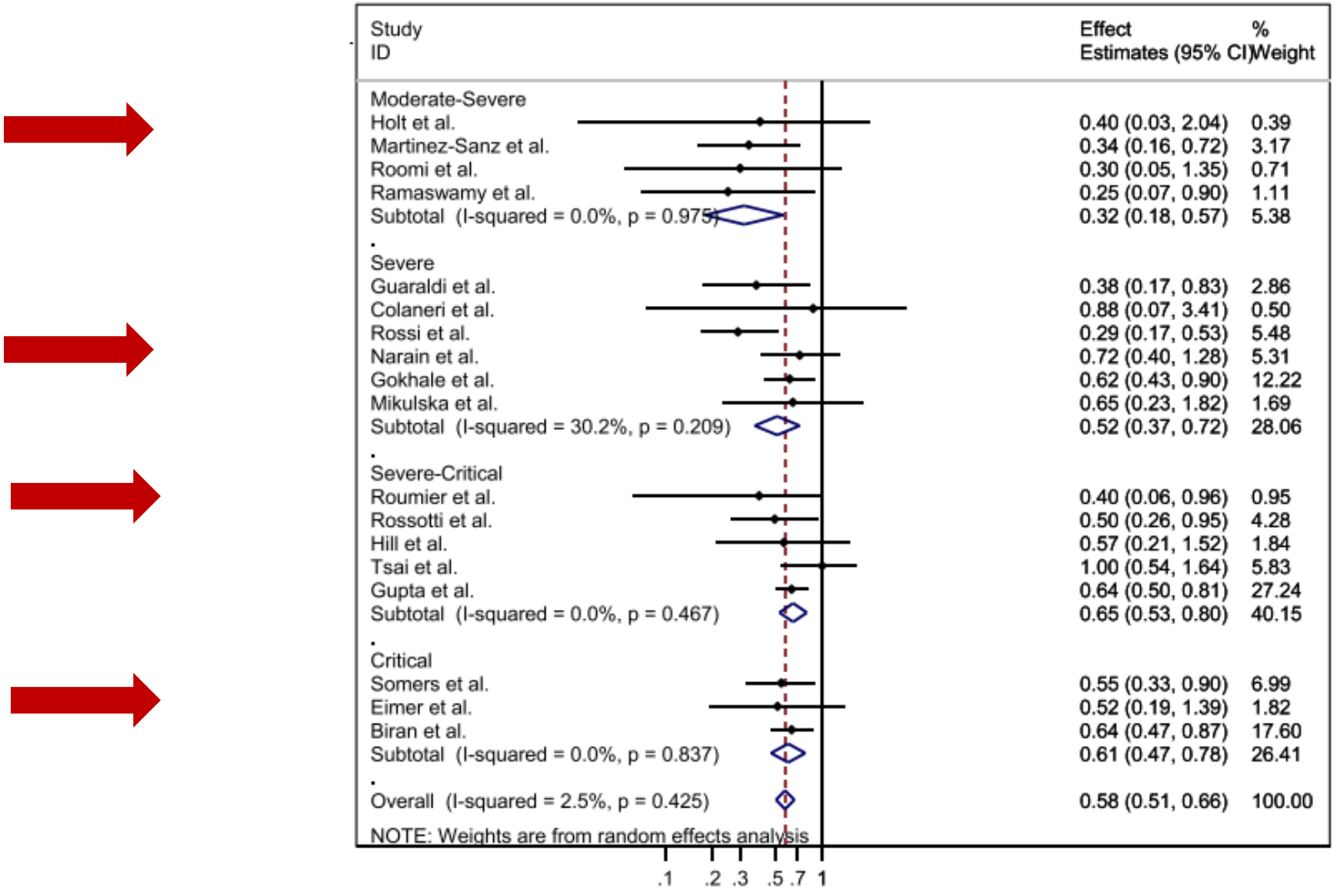




A: Forest plot for the effect of tocilizumab on 28-30 days mortality in randomized controlled trials with corresponding risk of bias. **B:** Forest plot for the effect of tocilizumab on risk for mechanical ventilation in randomized controlled trials with corresponding risk of bias. **C:** Forest plot for the effect of tocilizumab on 28-30 days composite outcome in randomized controlled trials with corresponding risk of bias

TOCILIZUMAB

Forest plot of the association between tocilizumab use and short-term mortality in COVID-19 patients from cohorts at moderate risk of bias: stratified by disease severity



TOCILIZUMAB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

METHODS

We randomly assigned (in a 2:1 ratio) patients hospitalized with Covid-19 pneumonia who were not receiving mechanical ventilation to receive standard care plus one or two doses of either tocilizumab (8 mg per kilogram of body weight intravenously) or placebo. Site selection was focused on the inclusion of sites enrolling high-risk and minority populations. The primary outcome was mechanical ventilation or death by day 28.

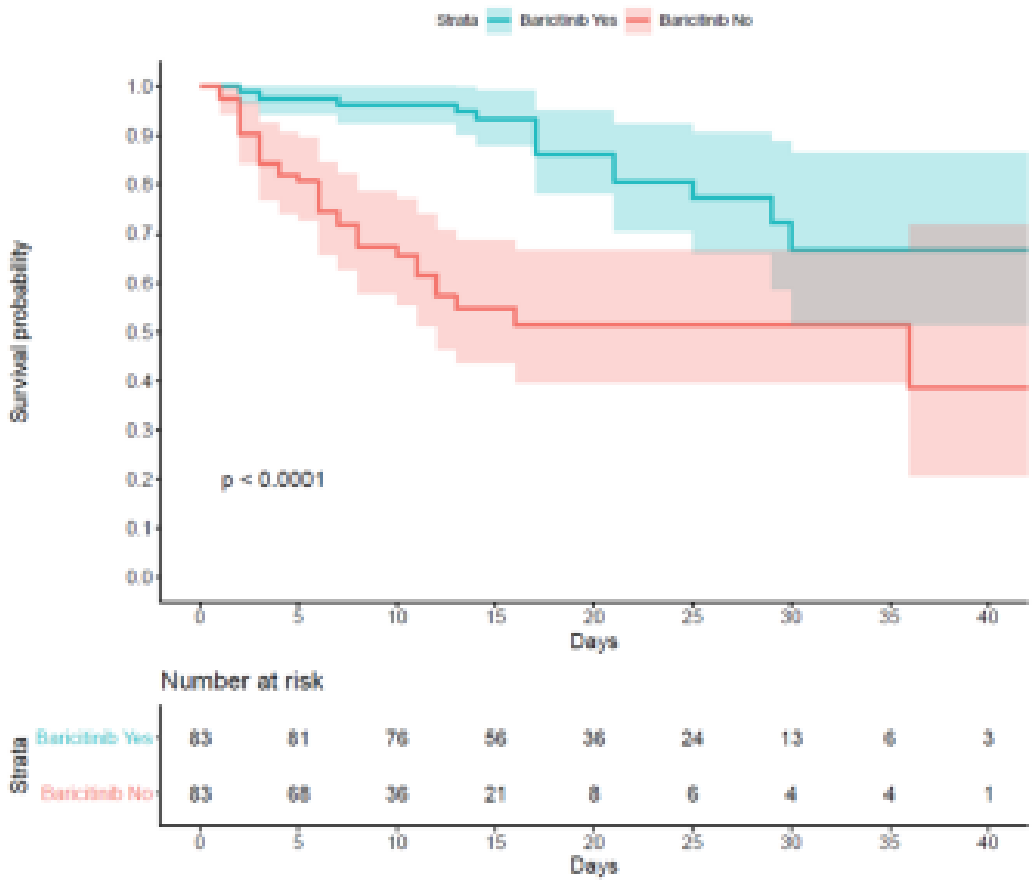
Table 2. Primary and Key Secondary Efficacy Outcomes by Day 28 in the Modified Intention-to-Treat Population.*

Outcome	Tocilizumab (N=249)	Placebo (N=128)	Hazard Ratio (95% CI)	Weighted Difference (95% CI)	P Value†
Primary outcome: mechanical ventilation or death — % (95% CI)‡	12.0 (8.5 to 16.9)	19.3 (13.3 to 27.4)	0.56 (0.33 to 0.97)	NA	0.04
Secondary outcomes					
Median time to hospital discharge or readiness for discharge (95% CI) — days§	6.0 (6.0 to 7.0)	7.5 (7.0 to 9.0)	1.16 (0.91 to 1.48)	NA	
Median time to improvement in clinical status (95% CI) — days§¶	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)	1.15 (0.90 to 1.48)	NA	
Median time to clinical failure (95% CI) — days§	NE	NE	0.55 (0.33 to 0.93)	NA	
Death — no. (% [95% CI])‖	26 (10.4 [7.2 to 14.9])	11 (8.6 [4.9 to 14.7])	NA	2.0 (–5.2 to 7.8)**	

BARICITINIB

Table 4. Multivariate Cox-regression analyses for the primary outcome in the propensity score matched populations from the University of Pisa and the Albacete Hospital. Selection bias was addressed by propensity score analysis. Briefly, this is a two-phase technique used to estimate a treatment effect in comparative groups selected by non-random means. In the first phase of a propensity score analysis, variables that influence selection to group assignment are used to model the probability of receiving treatment (or of being in the reference group, in this case, the baricitinib group). The resulting probability is the propensity score. In the second phase, the propensity score is used to adjust for pre-existing group differences in the analysis of the relevant outcomes. There are several ways to use propensity scores such as stratification variables, matching patients based on their propensity score or their use as a weighting or adjustment variable during multivariate analysis. In the current study, each baricitinib patient was matched to a control patients based on comparable propensity scores. Assuming that all relevant covariates are included in the propensity score model, the group effect observed in a propensity score analysis represents an unbiased estimate of the true treatment effect.

	HR (95% CI)	*p*
Baricitinib	0.29 (0.15-0.58)	0.0001
Age	1.01 (0.98-1.04)	0.470
Male sex	1.13 (0.54-2.34)	0.750
Hypertension	1.31 (0.52-3.32)	0.572
Diabetes	0.51 (0.23-1.17)	0.113
Chronic Obstructive Lung Disease	0.51 (0.17-1.54)	0.230
Cardiovascular disease	1.41 (0.68-2.92)	0.351
Cronic kidney disease	1.45 (0.51-4.15)	0.491
Solid cancer	1.18 (0.49-2.87)	0.709
Charlson Comorbidity Index	1.03 (0.90-1.17)	0.680
Baseline PaO_2/FiO_2	1.00 (1.00-1.00)	0.823
Lymphocyte count (/mcL)	1.00 (1.00-1.00)	0.657
Alanine aminotransferase	1.01 (1.00-1.03)	0.026
Hydroxychloroquine	2.77 (0.28-27.41)	0.384
Lopinavir/Ritonavir	1.18 (0.38-3.61)	0.776
Glucocorticoids	1.79 (0.60-5.34)	0.299
Low Molecular Weight Heparin	0.10 (0.01-1.33)	0.081
Antibiotics	2.34 (0.29-18.90)	0.427



COVID-19 Principles of Treatment

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

HEPARIN

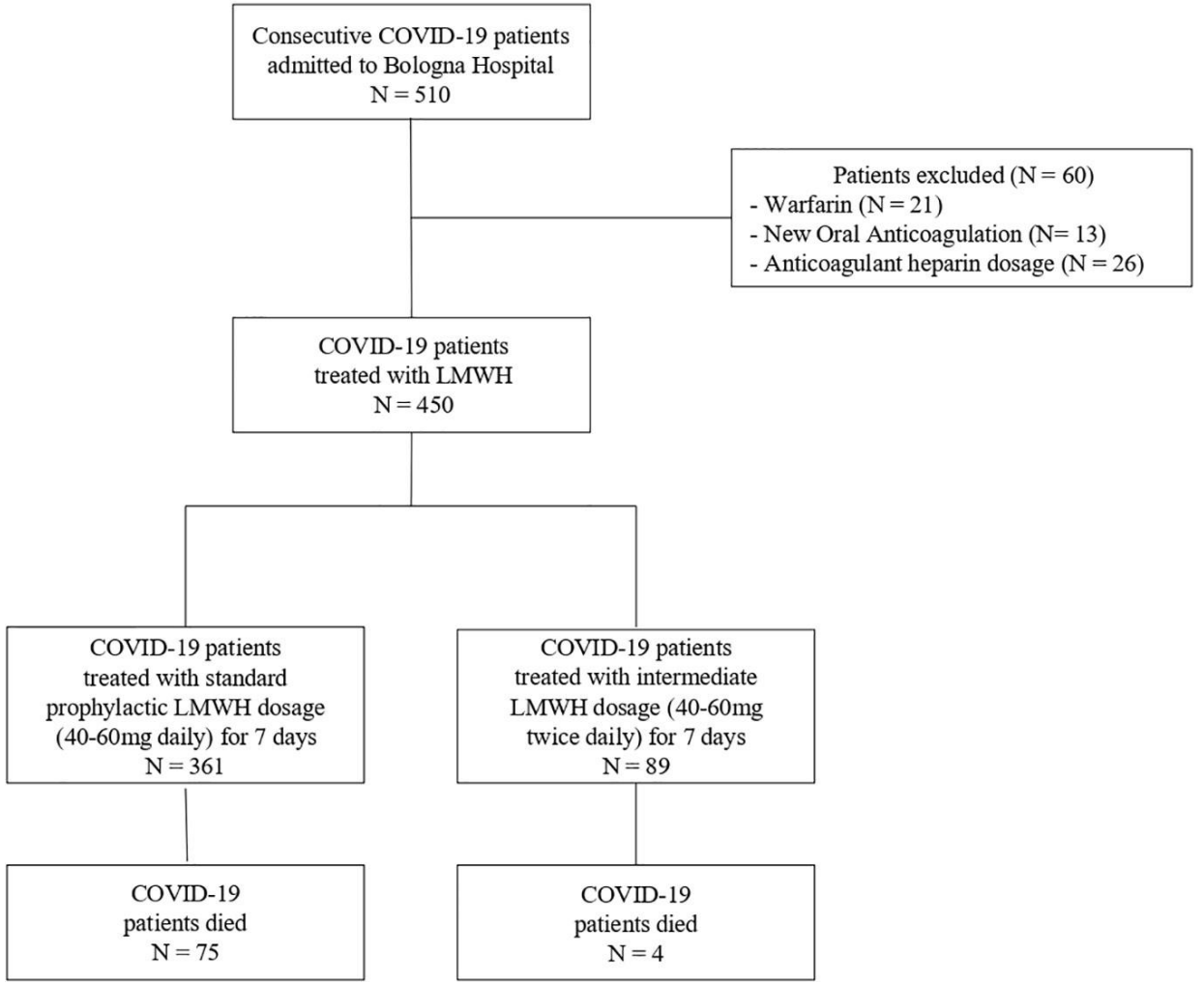
BRIEF RESEARCH REPORT ARTICLE
Front. Pharmacol., 06 August 2020 | https://doi.org/10.3389/fphar.2020.01124

Preliminary Experience With Low Molecular Weight Heparin Strategy in COVID-19 Patients

Out of 450 patients, 361 received standard deep vein thrombosis (DVT) prophylaxis enoxaparin treatment (40-60mg daily) and 89 patients received intermediate enoxaparin dosage (40–60 mg twice daily) for 7 days.

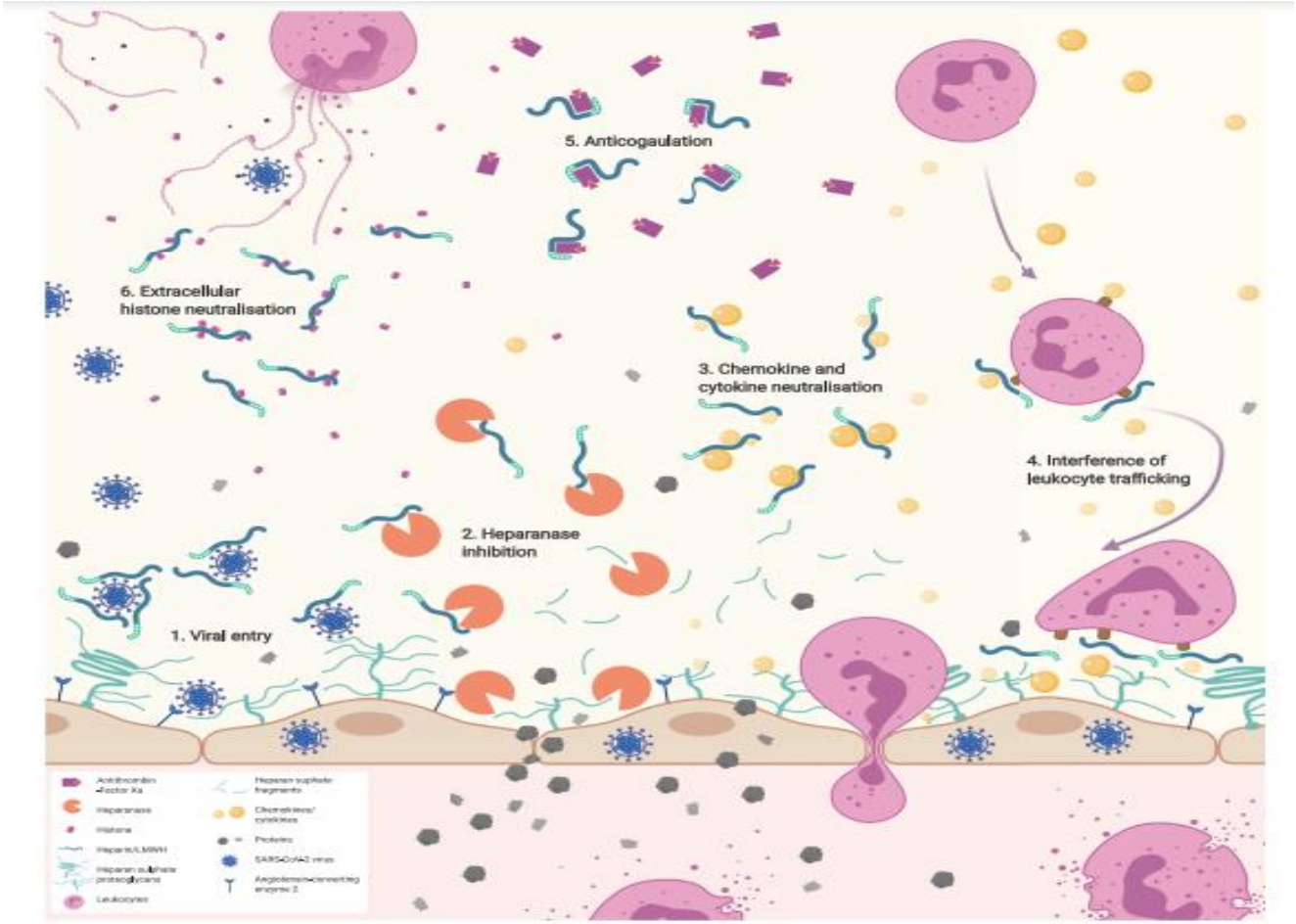
No significant differences in the main demographic characteristics and laboratory testings at admission were observed in the two heparin regimen subgroups, except for older age and prevalence of hypertension in the group treated with “standard” prophylaxis LMWH dosage.

The intermediate LMWH administration was associated with a lower in-hospital all-cause mortality compared to the “standard” prophylactic LMWH dosage (18.8% vs. 5.8%, p = 0.02). This difference remained significant after adjustment with the propensity score for variables that differed significantly between the dosage groups (OR= 0.260, 95% CI 0.089–0.758, p=0.014).



HEPARIN

Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients



Potential beneficial, non-anticoagulant mechanisms underlying treatment of COVID-19 patients with heparin/LMWH, which include:

(i) Inhibition of heparanase activity, responsible for endothelial leakage;
(ii) Neutralisation of chemokines, and cytokines;
(iii) Interference with leukocyte trafficking;
(iv) Reducing viral cellular entry, and
(v) Neutralisation of extracellular cytotoxic histones.

Baranca Buijsers et al. EBIO Medicine, SEPTEMBER 01, 2020

HEPARIN

Le proprietà dell'eparina consentirebbero in pazienti affetti da Sars-CoV-2:

– a livello polmonare, **l'inibizione dell'infiammazione**, della formazione di trombi e dello sviluppo di ARDS (in quanto l'attivazione del sistema di coagulazione risulta rilevante nella patogenesi di quest'ultima grave complicazione respiratoria)

– a livello cardiaco, una **riduzione della formazione di trombi coronarici ed intrac**ardiaci, potenziali effetti benefici inibendo lo sviluppo di miocarditi e cardiomiopatie

– a livello vascolare, una potenziale **riduzione dei processi di ischemia microvascolare** e potenziali effetti benefici sulla disfunzione multiorgano

HEPARIN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

This article was published on August 4, 2021

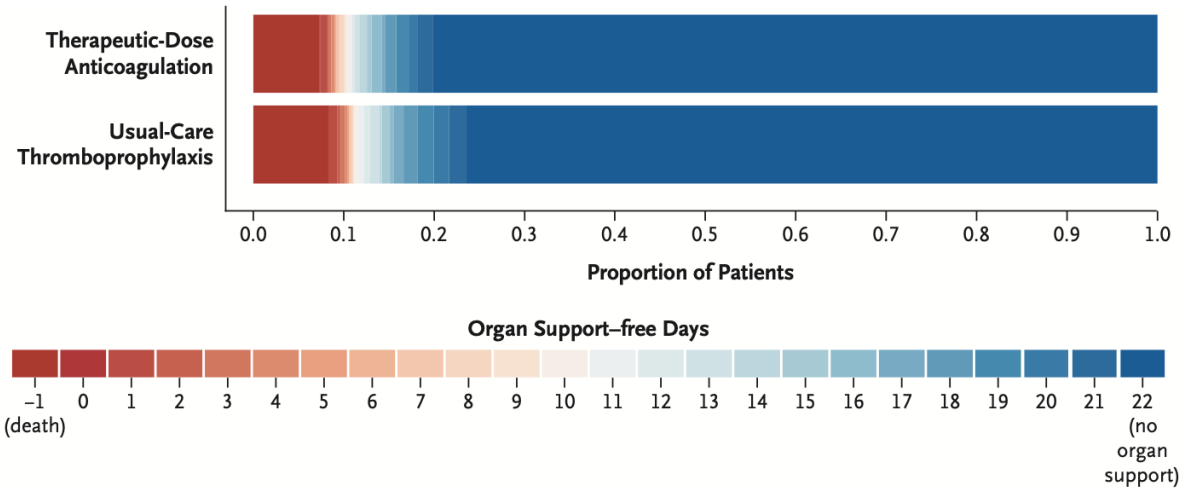


Table 3. Secondary Outcomes among All Patients with Moderate Disease.*

Outcome	Therapeutic-Dose Anticoagulation	Usual-Care Thromboprophylaxis	Adjusted Difference in Risk (95% Credible Interval)†	Adjusted Odds Ratio (95% Credible Interval)‡	Probability of Effect of Therapeutic-Dose Anticoagulation
	no. of patients/total no. (%)		*percentage points*		%
Survival until hospital discharge	1085/1171 (92.7)	962/1048 (91.8)	1.3 (–1.1 to 3.2)	1.21 (0.87 to 1.68)§	87.1¶
Survival without organ support at 28 days‖	932/1175 (79.3)	789/1046 (75.4)	4.5 (0.9 to 7.7)	1.30 (1.05 to 1.61)	99.1¶
Progression to intubation or death**	129/1181 (10.9)	127/1050 (12.1)	–1.9 (–4.1 to 0.7)	0.82 (0.63 to 1.07)	92.2¶
Major thrombotic event or death	94/1180 (8.0)	104/1046 (9.9)	–2.6 (–4.4 to –0.2)	0.72 (0.53 to 0.98)	98.0¶
Major thrombotic event	13/1180 (1.1)	22/1046 (2.1)			
Death in hospital	86/1180 (7.3)	86/1046 (8.2)			
Major bleeding	22/1180 (1.9)	9/1047 (0.9)	0.7 (–0.1 to 2.3)	1.80 (0.90 to 3.74)	95.5††

HEPARIN

JAMA Internal Medicine

October 7, 2021

Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19

The HEP-COVID Randomized Clinical Trial

Objective To evaluate the effects of therapeutic-dose low-molecular-weight heparin (LMWH) vs institutional standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19.

Main Outcomes and Measures The primary efficacy outcome was venous thromboembolism (VTE), arterial thromboembolism (ATE), or death from any cause, and the principal safety outcome was major bleeding at 30±2 days. Data were collected and adjudicated locally by blinded investigators via imaging, laboratory, and health record data.

Conclusions and Relevance In this randomized clinical trial, therapeutic-dose LMWH reduced major thromboembolism and death compared with institutional standard heparin thromboprophylaxis among inpatients with COVID-19 with very elevated D-dimer levels. The treatment effect was not seen in ICU patients.

COVID-19 Principles of Treatment

- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

ANTIMICROBIAL THERAPY

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

Recommendations for antibacterial therapy in adults with COVID-19 — an evidence based guideline

Table 2
Summary of recommendations

Recommendation	Strength	Quality of evidence
1. We generally suggest restrictive use of antibacterial drugs in patients with proven or a high likelihood of COVID-19. This especially applies for patients upon admission who are mild to moderately ill	Weak	Very low
2. We suggest that exceptions for the restrictive use of antibacterial drugs can be made for patients with proven or a high likelihood of COVID-19 who present with radiological findings and/or inflammatory markers compatible with bacterial co-infection. Other exceptions are patients who are severely ill or immunocompromised*	Weak	GPS
3. We recommend maximum efforts to obtain sputum and blood for culture as well as pneumococcal urinary antigen testing before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 upon admission	Strong	GPS
4. In case of suspected bacterial co-infection, we suggest against empirical antibiotic treatment covering atypical pathogens in patients with proven or high likelihood of COVID-19 hospitalized at the general ward. *Legionella* urinary antigen testing should be performed according to local and/or national guidelines for CAP	Weak	Very low
5. We recommend that the empirical antibiotic regimens in case of suspected bacterial co-infection depends on the severity of disease and according to local and/or national guidelines. For those fulfilling criteria of mild and moderate-severe CAP, we recommend to follow local and/or national guideline recommendations on antibacterial treatment in CAP	Weak	Very low
6. We recommend to follow local and/or national guideline recommendations on antibacterial treatment for patients with COVID-19 and suspected bacterial secondary infection	Strong	GPS
7. We suggest to stop antibiotics when representative sputum and blood culture as well as urinary antigen tests taken before start of empirical antibiotic therapy in patients with proven or high likelihood of COVID-19 show no bacterial pathogens after 48 hours of incubation	Weak	GPS
8. We suggest an antibiotic treatment duration of five days in patients with COVID-19 and suspected bacterial infection upon improvement of signs, symptoms and inflammatory markers	Weak	GPS

* immunocompromised is defined as the use of chemotherapy for cancer, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, or prolonged use of corticosteroids or other immunosuppressive medications; GPS: good practice statement.

COVID-19 Principles of Treatment

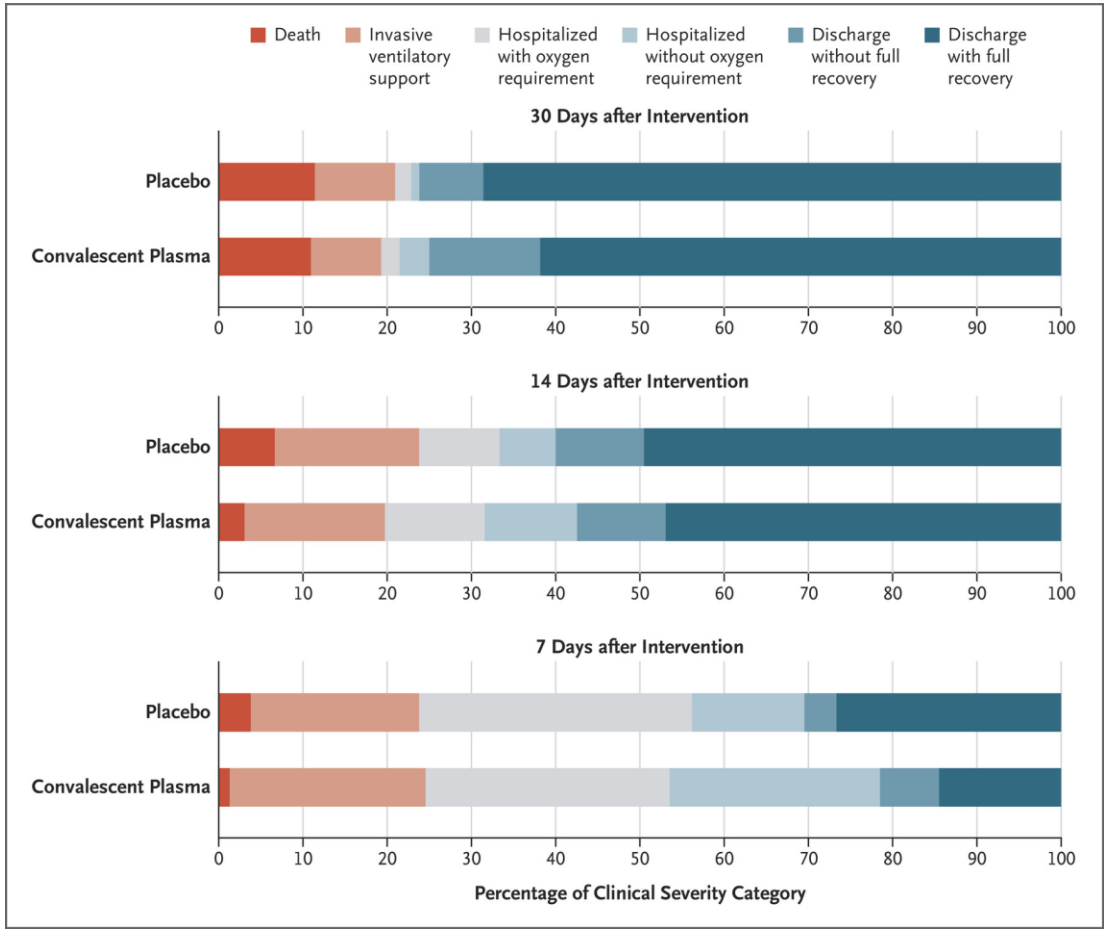
- Antiviral therapy
- Oxygen therapy
- Anti-inflammatory therapy
- Anti-thrombotic therapy
- Antimicrobial therapy
- Plasma/monoclonal antibodies therapy

PLASMA

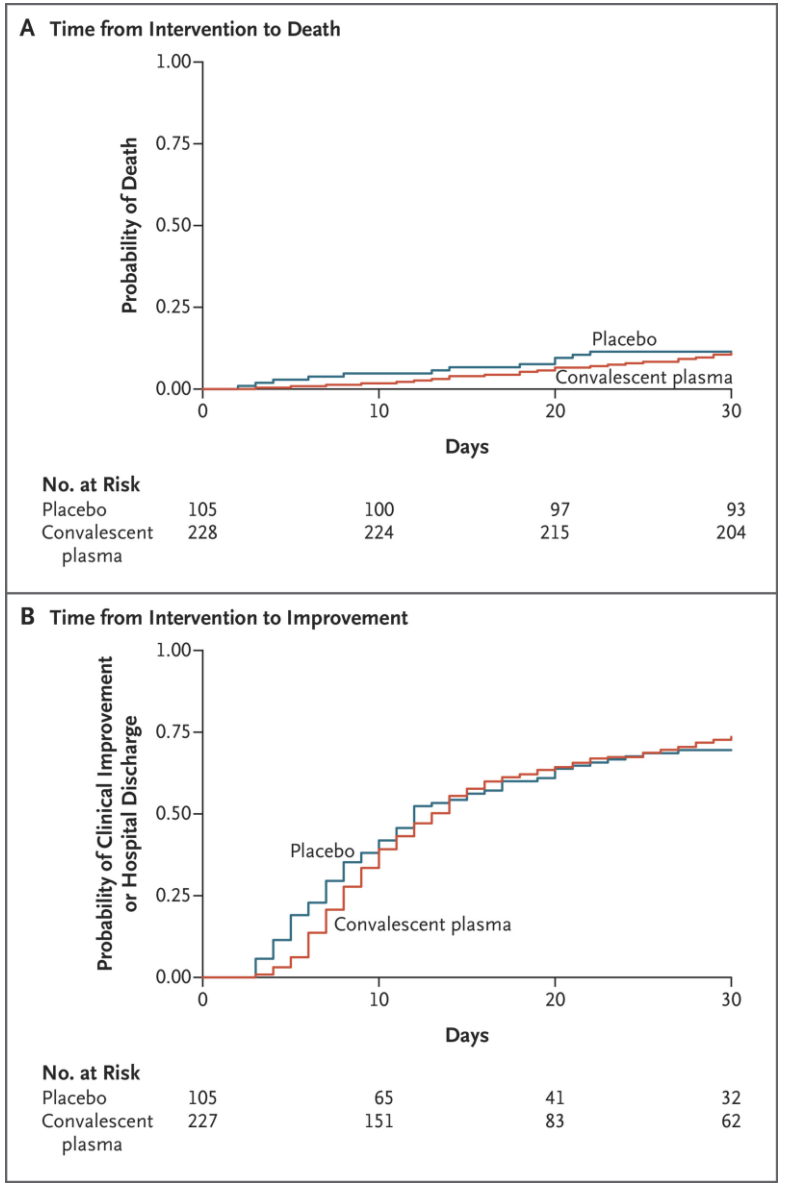
ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

Ventura A. Simonovich, M.D., Leandro D. Burgos Pratx, M.D., Paula Scibona, M.D., María V. Beruto, M.D., Marcelo G. Vallone, M.D., Carolina Vázquez, M.D., Nadia Savoy, M.D., Diego H. Giunta, M.D., M.P.H., Ph.D., Lucía G. Pérez, M.D., Marisa del L. Sánchez, M.D., Andrea Vanesa Gamarnik, Ph.D., Diego S. Ojeda, Ph.D., et al., for the PlasmAr Study Group*



Plasma delude non beneficio ma importante bias almeno il 50% non si sapeva titolo anticorpale del plasma!!!



PLASMA

ARTICLES | VOLUME 397, ISSUE 10289, P2049-2059, MAY 29, 2021

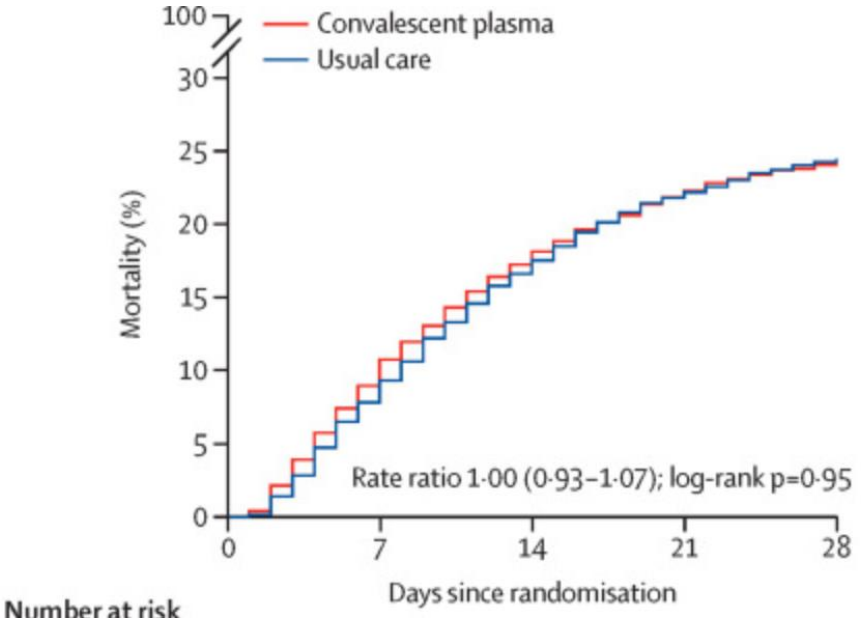
PDF [957 KB]

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial

RECOVERY Collaborative Group † • Show footnotes

Open Access • Published: May 14, 2021 • DOI: https://doi.org/10.1016/S0140-6736(21)00897-7 •

Check for updates



Interpretation

In patients hospitalised with COVID-19, high-titre convalescent plasma did not improve survival or other prespecified clinical outcomes.

TSUNAMI

Press release no. 641

8 April 2021

COVID-19: TSUNAMI STUDY, PLASMA DOES NOT REDUCE THE RISK OF RESPIRATORY DAMAGE OR DEATH

The data analysis was competed of the randomised and controlled clinical trial called TSUNAMI, promoted by the ISS and AIFA and coordinated by the ISS, on the therapeutic role of convalescent plasma in patients who have developed the COVID-19 disease. 27 clinical centres distributed throughout Italy participated in the study. 487 patients were enrolled (of which 324 in Tuscany, 77 in Umbria, 66 in Lombardy and 20 from other regions).

Overall, TSUNAMI did not show a plasma benefit in terms of reducing the risk of respiratory worsening or death in the first thirty days.

Teatment was generally well tolerated, although adverse events were more frequent in the plasma group. The results of the TSUNAMI study are in line with those (mainly negative) of the international literature, except for patients treated very early with high titre plasma.

PLASMA

PLOS MEDICINE

RESEARCH ARTICLE

Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial

Methods and findings

The study was an open-label, single-center randomized clinical trial performed in an academic medical center in Santiago, Chile, from May 10, 2020, to July 18, 2020, with final fol- low-up until August 17, 2020. The trial included patients hospitalized within the first 7 days of COVID-19 symptom onset, presenting risk factors for illness progression and not on mechanical ventilation. The intervention consisted of immediate CP (early plasma group) versus no CP unless developing prespecified criteria of deterioration (deferred plasma group). Additional standard treatment was allowed in both arms. The primary outcome was a composite of mechanical ventilation, hospitalization for >14 days, or death.

Conclusions

In the present study, we failed to find evidence of benefit in mortality, length of hospitalization, or mechanical ventilation requirement by immediate addition of CP therapy in the early stages of COVID-19 compared to its use only in case of patient deterioration.

Balcells ME, Rojas L, Le Corre N, Martínez-Valdebenito C, Ceballos ME, Ferrés M, et al. (2021) Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. PLoS Med 18(3): e1003415. https://doi.org/10.1371/journal.pmed.1003415

ANAKINRA

Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial

The CORIMUNO-19 Collaborative group†*

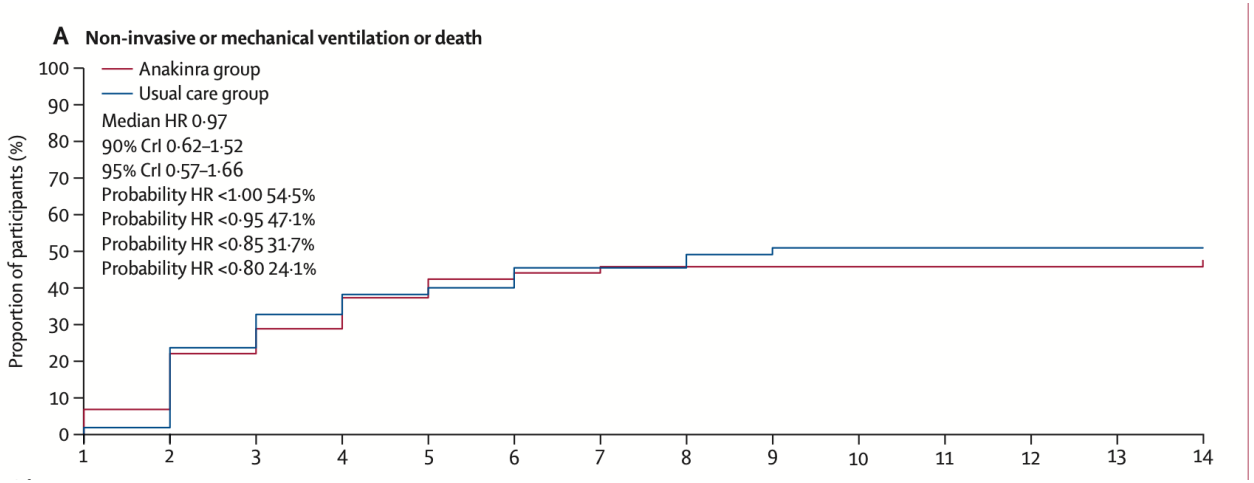
Lancet Respir Med 2021;
9: 295–304

Published Online
January 22, 2021
https://doi.org/10.1016/
S2213-2600(20)30556-7

Methods

Study design and participants

We enrolled patients with COVID-19 from University hospitals in France for a series of randomised controlled trials testing different therapeutic regimens (CORIMUNO-19 cohort). Patients with mild-to-moderate COVID-19 pneumonia and patients with severe and critical COVID-19 pneumonia were included in independent clinical trials. Here we report data from CORIMUNO-ANA-1, a CORIMUNO-19, multicentre, open-label, randomised controlled trial of patients with mild-to-moderate COVID-19 pneumonia.



In summary, this randomised clinical trial suggests that **anakinra was not effective in reducing the need for non-invasive or mechanical ventilation or death in patients with COVID-19 and mild-to-moderate pneumonia**. These results are relevant for this patient population at the dose we used and cannot be extended to other populations with other doses. Further studies are needed to assess the efficacy of anakinra in other selected groups of patients with more severe COVID-19 and at other doses.

nature medicine

ARTICLES

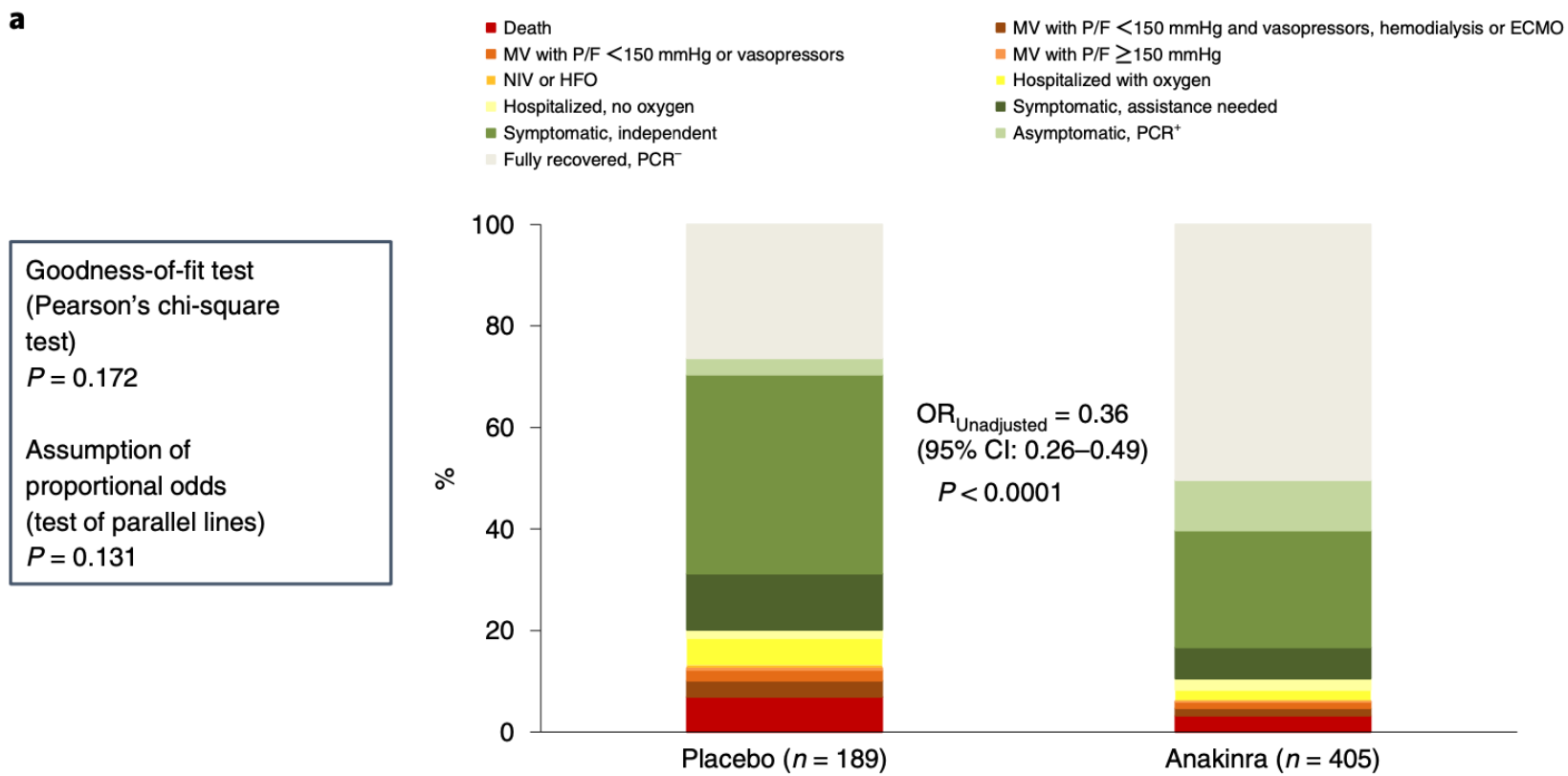
https://doi.org/10.1038/s41591-021-01499-z

Published online: 03 September 2021 Check for updates

OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

a



Clinical studies evaluating anti-SARS-CoV-2 monoclonal antibodies

Sponsors	Drug code	Status	Trial ID	Est. start	Est. primary completion
Junshi Biosciences / Eli Lilly and Company	JS016, LY3832479, LY-CoV016	Phase 2	NCT04441918; NCT04441931; NCT04427501	6/5/2020; 6/19/2020; 6/17/2020	Dec 2020; 10/2/2020; 3/11/2021
Brii Biosciences	BRII-196	Phase 1	NCT04479631	7/12/2020	Mar 2021
Brii Biosciences	BRII-198	Phase 1	NCT04479644	7/13/2020	Mar 2021
AbbVie	ABBV-47D11	Phase 1 pending	NCT04644120	11/27/2020	May 2021
Sorrento Therapeutics, Inc.	COVI-GUARD (STI-1499)	Phase 1	NCT04454398	9/17/2020	Feb 2021
Mabwell (Shanghai) Bioscience Co., Ltd.	MW33	Phase 1	NCT04533048	8/7/2020	Dec 2020
HiFiBiO Therapeutics	HFB30132A	Phase 1	NCT04590430	Oct 2020	July 2021
Ology Bioservices	ADM03820	Phase 1 pending	NCT04592549	11/16/2020	Aug 2021
Hengenix Biotech Inc	HLX70	Phase 1 pending	NCT04561076	12/9/2020	Sep 2021
U. Cologne / Boehringer Ingelheim	DZIF-10c	Phase 1 /2 pending	NCT04631705; NCT04631666	11/23/2020; 11/23/2020	6/30/2021; 6/30/2021
Sorrento Therapeutics, Inc.	COVI-AMG (STI-2020)	Phase 1 /2 pending	NCT04584697	Dec 2020	April 2021
Beigene	BGB DXP593	Phase 1; Phase 2 pending	NCT04532294; (NCT04551898	8/31/2020; 10/30/2020	10/15/2020; 2/28/2021
Sinocelltech Ltd.	SCTA01	Phase 1; Phase 2/3	NCT04483375; NCT04644185	7/24/2020; 2/10/2021	Nov 2020; 5/10/2021
Tychan Pte. Ltd.	TY027	Phase 3 pending	NCT04429529; NCT04649515	6/9/2020; 12/4/2020	Oct 2020; 8/31/2020
AstraZeneca	AZD7442 (AZD8895 + AZD1061)	Phase 1; Phase 3 pending	NCT04507256; NCT04625725; NCT04625972	8/17/2020; 11/17/2020; 11/16/2020	Sep 2021; 7/31/2021; 6/16/2021
Celltrion	CT-P59	Phase 1; Phase 2/3	NCT04525079; NCT04593641; NCT04602000	7/18/2020; 9/4/2020; 9/25/2020	Nov 2020; 12/23/2020; Dec 2020
Vir Biotechnol./GlaxoSmithKline	VIR-7831/ GSK4182136	Phase 2/3	NCT04545060	8/27/2020	Jan 2021
AbCellera / Eli Lilly and Company	LY-CoV555 (LY3819253); combination of LY-CoV555 with LY-CoV016 (LY3832479)	**EUA***	NCT04411628 (Phase 1); NCT04427501 (Phase 2); NCT04497987(Phase 3);NCT04501978 (Phase 3); NCT04518410 (Phase 2/3)	5/28/2020; 6/13/2020; 8/2/2020; 8/4/2020; Aug 2020	8/23/2020; 9/15/2020; 3/8/2021; July 2021; Nov 2020
Regeneron	REGN-COV2 (REGN10933 + REGN10987)	**EUA***	NCT04425629 (Phase 1/2); NCT04426695 (Phase 1/2); NCT04452318 (Phase 3)	6/16/2020; 6/10/2020; 7/13/2020	12/19/2020; 1/25/2021; 6/15/2021

CASIRIVIMAB AND IMDEVIMAB

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

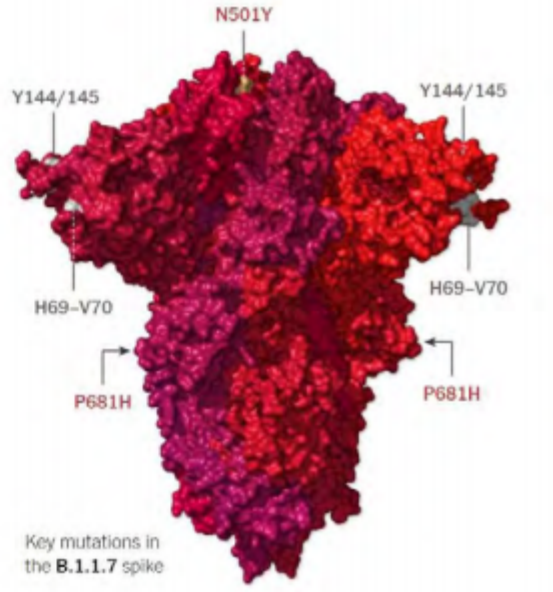
REGEN-COV is a combination of 2 monoclonal antibodies (casirivimab and imdevimab) that bind to two different sites on the receptor binding domain of the SARS-CoV-2 spike protein.
Findings: Between 18 September 2020 and 22 May 2021, 9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone,

Table 2: Effect of allocation to REGEN-COV on key study outcomes among seronegative participants

	REGEN-COV (n=1633)	Usual Care (n=1520)	RR (95% CI)
Primary outcome			
Mortality at 28 days	396 (24%)	451 (30%)	0.80 (0.70-0.91)
Secondary outcomes			
Median duration of hospitalisation, days	13 (7 to >28)	17 (7 to >28)	-
Discharged from hospital within 28 days	1046 (64%)	878 (58%)	1.19 (1.08-1.30)
Invasive mechanical ventilation or death*	487/1599 (30%)	542/1484 (37%)	0.83 (0.75-0.92)
Invasive mechanical ventilation	189/1599 (12%)	200/1484 (13%)	0.88 (0.73-1.06)
Death	383/1599 (24%)	434/1484 (29%)	0.82 (0.73-0.92)
Subsidiary outcomes			
Use of ventilation †	355/1267 (28%)	370/1143 (32%)	0.87 (0.77-0.98)
Non-invasive ventilation	341/1267 (27%)	360/1143 (31%)	0.85 (0.75-0.97)
Invasive mechanical ventilation	89/1267 (7%)	119/1143 (10%)	0.67 (0.52-0.88)
Successful cessation of invasive mechanical ventilation ‡	9/34 (26%)	12/36 (33%)	0.86 (0.36-2.03)
Renal replacement therapy §	68/1616 (4%)	64/1498 (4%)	0.98 (0.71-1.38)

B.1.1.7, 20I/501Y.V1, VOC202012/01

First detected by	United Kingdom
First appearance	20 September 2020
Key mutations	H69/V70 deletion; Y144 deletion; N501Y; A570D; D614G; P681H; S106/G107/F108 deletion in NSP6
Transmissibility*	Increased (43%-82%), increased secondary attack rate (10% to 13%)
Severity*	Likely associated with an increased risk of hospitalisation and death compared to infection with non-VOC viruses.
Neutralization capacity*	Slight reduction but overall neutralizing titers remained above the levels expected to confer protection
Potential impacts on vaccines*	No significant impact on Moderna, Pfizer-BioNTech, and Oxford-AstraZeneca
Potential impacts on diagnostics*	S gene target failure. No impact on Ag RDTs observed
Countries reporting cases (community transmission) as of 23 Feb	101 (45)



https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

nature

Article | Published: 15 March 2021

Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7

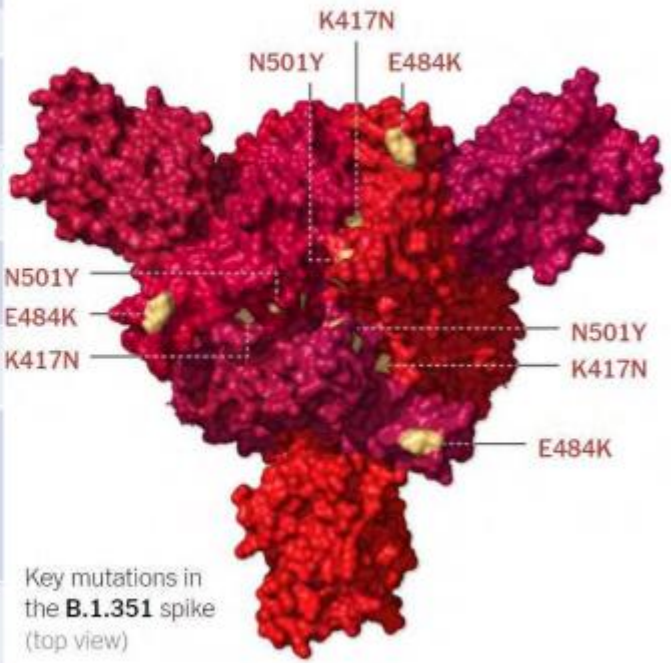
Nicholas G. Davies ✉, Christopher I. Jarvis, CMMID COVID-19 Working Group, W. John Edmunds, Nicholas P. Jewell, Karla Diaz-Ordaz & Ruth H. Keogh

B.1.1.7 infections **are associated with higher viral concentrations** on nasopharyngeal swabs, as measured by Ct values from PCR testing

Higher viral load could therefore be partly responsible for the observed increase in mortality; this could be assessed using a mediation analysis.

B.1.351, 20H/501Y.V2, VOC202012/02

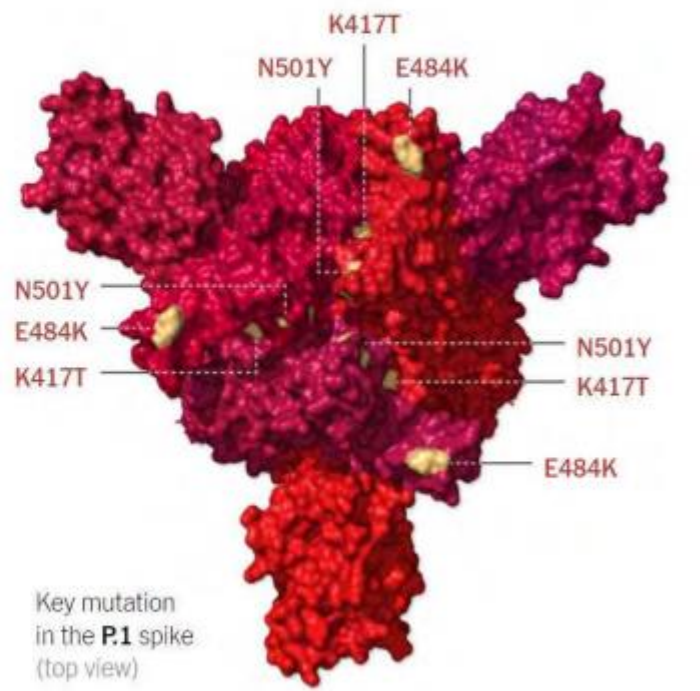
First detected by	South Africa
First appearance	Early August 2020
Key mutations	L242/A243/L244 deletion; N501Y; D614G; E484K; K417N; S106/G107/F108 deletion in NSP6
Transmissibility*	Increased [1.50 (95% CI: 1.20-2.13) times more transmissible than previously circulating variants]
Severity*	No impact reported to date, no significant change in-hospital mortality
Neutralization capacity*	Decreased, suggesting potential increased risk of reinfection
Potential impacts on vaccines*	Reduction in the neutralizing activity, but impact on protection against disease or relative importance of other immune response mechanisms (e.g., T/B-cells), not fully known. Potentially decreased based on small, prelim studies.
Potential impacts on diagnostics*	None reported to date.
Countries reporting cases (community transmissions) as of 22 Feb	51 (13)



https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

B.1.128.P.1, 20J/501Y.V3

First detected by	Brazil / Japan
First appearance	December 2020
Key mutations	N501Y; D614G; E484K; K417N; S106/G107/F108 deletion in NSP6
Transmissibility*	Suggested to be increased
Severity*	Under investigation, no impact reported to date
Neutralization capacity*	Potential decrease, small number of reinfections reported
Potential impacts on vaccines*	Under investigation
Potential impacts on diagnostics*	None reported to date
Countries reporting cases (Community transmission) as of 23 Feb	29 (3)



https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

A.23.1 2021-03-25

Description

International lineage with variants of biological significance F157L, V367F, Q613H and P681R, described fully in the preprint: Bugembe et al 2021. Q613H is predicted to be functionally equivalent to the D614G mutation that arose early in 2020.

This webpage is generated using publically available sequence data from GISAID, shared by international sequencing efforts.

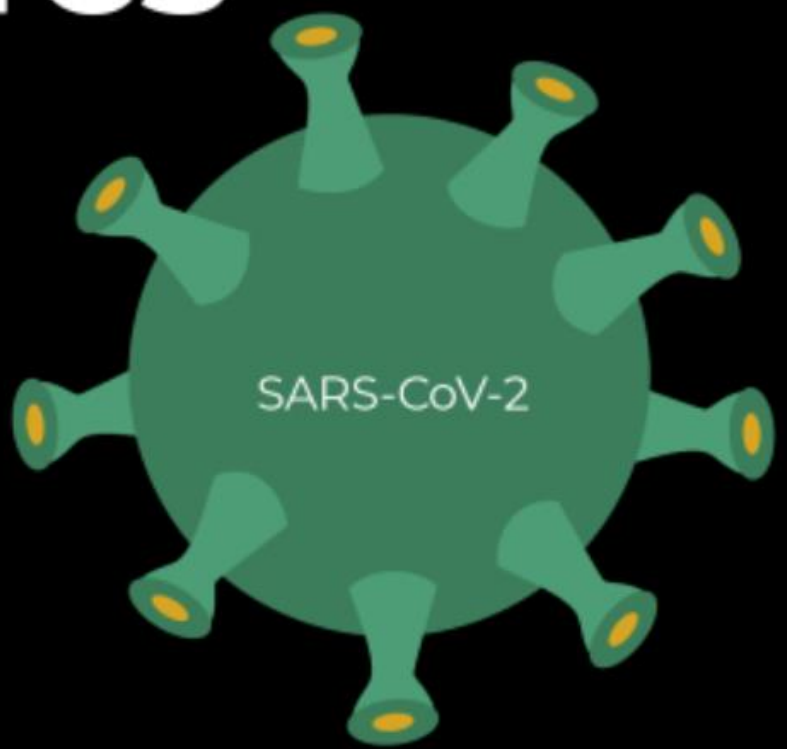
Table 1 | Summary of A.23.1 data

Statistic	Information
Countries reported	2
Countries with sequences	28
Sequence count	449
Countries	United Kingdom 163, Rwanda 88, Uganda 48, Canada 44, Belgium 21, United States of America 19, Cambodia 14, Latvia 8, Sweden 8, Denmark 6, Indonesia 5, Switzerland 3, Netherlands 3, Kenya 2, Zimbabwe 2, India 2, Germany 2, South Africa 1, United Arab Emirates 1, Italy 1, New Zealand 1, Norway 1, Australia 1, Mauritius 1, Vietnam 1, Israel 1, Ghana 1, Botswana 1
First detected	Uganda
Earliest sample date	2020-10-21
Defining SNPs	aa:S:F157L aa:S:V367F aa:S:Q613H aa:S:P681R

Infographic:

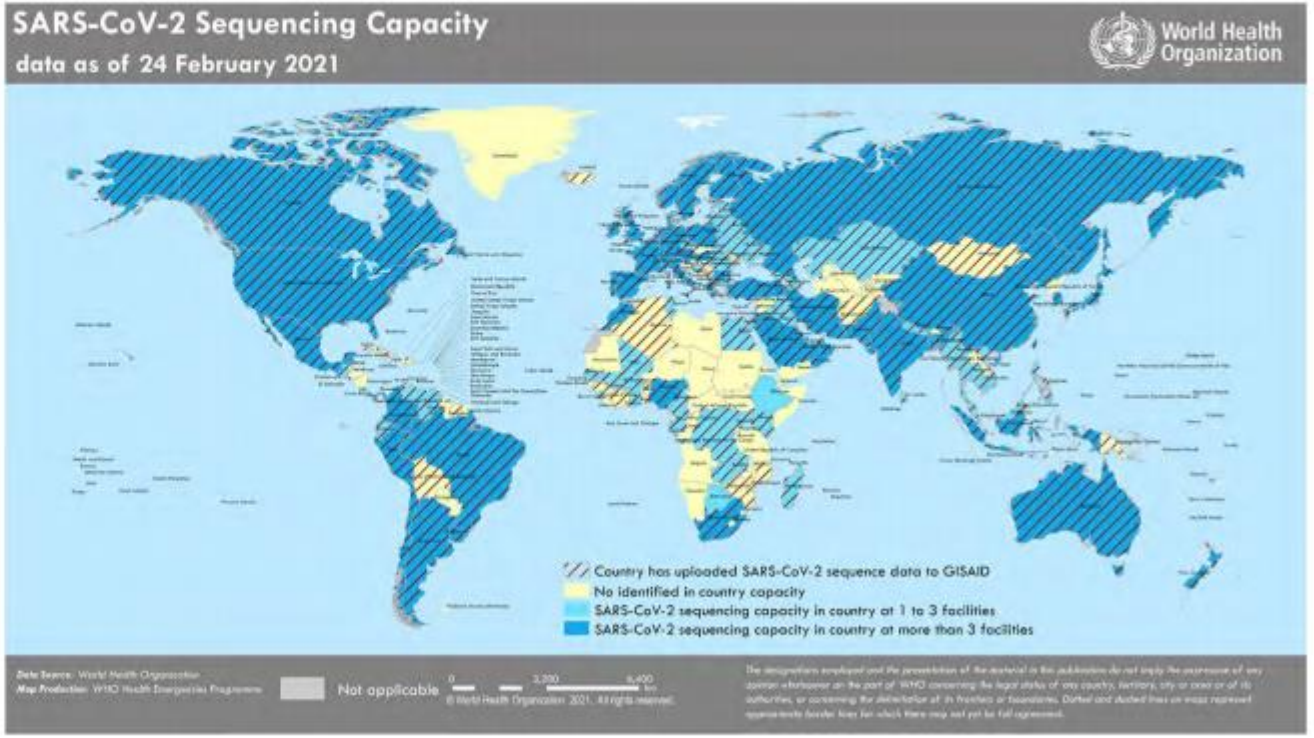
How the Omicron variant compares

Ο ο	Δ δ	Γ γ	Β β	Α α
Omicron B.1.1.529	Delta B.1.617.2	Gamma P.1	Beta B.1.351	Alpha B.1.1.7



Global SARS-CoV-2 Sequencing Capacities

- **Globally:**
  - **523,778** WGS in GISAID
  - **134/194 (69%)** countries submitted WGS
  - **5%** of sequences with metadata
- **GISRS:**
  - At least **61% GISRS labs** submitted WGS to GISAID
    - **95 labs from 78 countries**
  - **32 GISRS labs** support sequencing for other GISRS and non-GISRS labs



Emergenza Covid

Non vaccinati a quota 10 milioni: ecco chi sono

Si tratta quasi del 20% della popolazione over 12. A preoccupare di più sono i 3,3 milioni di over 50: sono infatti le persone nella fascia di età a maggiore rischio di ospedalizzazione

di Andrea Gagliardi

2 settembre 2021

Ancora 3,3 milioni gli over 50 senza dose

Dei 10,6 milioni di residenti in Italia senza nemmeno una dose di vaccino a preoccupare di più sono i 3,3 milioni di over 50. Si tratta infatti delle persone nella fascia di età a maggiore rischio di ospedalizzazione. Di questi, 1,68 milioni sono nella fascia 50-59 anni; 917mila in quella 60-69 anni; 517mila in quella 70-79 e 188mila over 80.

A livello solo numerico la fascia d'età con un maggior numero di persone senza dose è quella tra i 40-49 anni (2,1 milioni). Altri 1,9 milioni sono nella fascia 39-39; 1,4 milioni in quella 20-29 e 1,8 milioni in quella 12-19.

viruses

MDPI

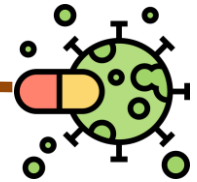
Article

Attitudes towards Anti-SARS-CoV2 Vaccination among Healthcare Workers: Results from a National Survey in Italy

Francesco Di Gennaro [1], Rita Murri [2,3], Francesco Vladimiro Segala [2,*], Lorenzo Cerruti [4], Amina Abdulle [5], Annalisa Saracino [1], Davide Fiore Bavaro [1] and Massimo Fantoni [2,3]

OUTLINE

- Lessons from SARS CoV and MERS
- A WHO consensum definition of Long COVID



- First data on Long COVID (experience from China, UK and Italy)
- Open Questions and Research Goals

Elsevier Pub

Publi

Lancet. 2020 Dec 12; 396(10266): 1861.

Published online 2020 Dec 10. doi: 10.101

Facing up to long COVID

The Lancet

Elsevier Public

nature

Explore content | About the journal | Publish with us | Subscribe

nature > correspondence > article

CORRESPONDENCE | 10 November 2020

Long COVID: don't consign ME/CFS to history

Peter White

BMJ. 2020 Sep 15;370:m3586. doi: 10.1136/bmj.m3586.

Long covid: doctors call for research and surveillance to capture disease

Jacqui Wise [1]

Affiliations – collapse

Affiliation

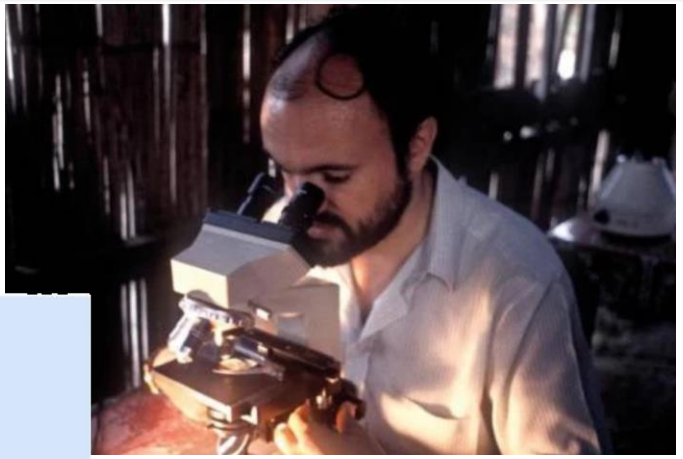
1 London.

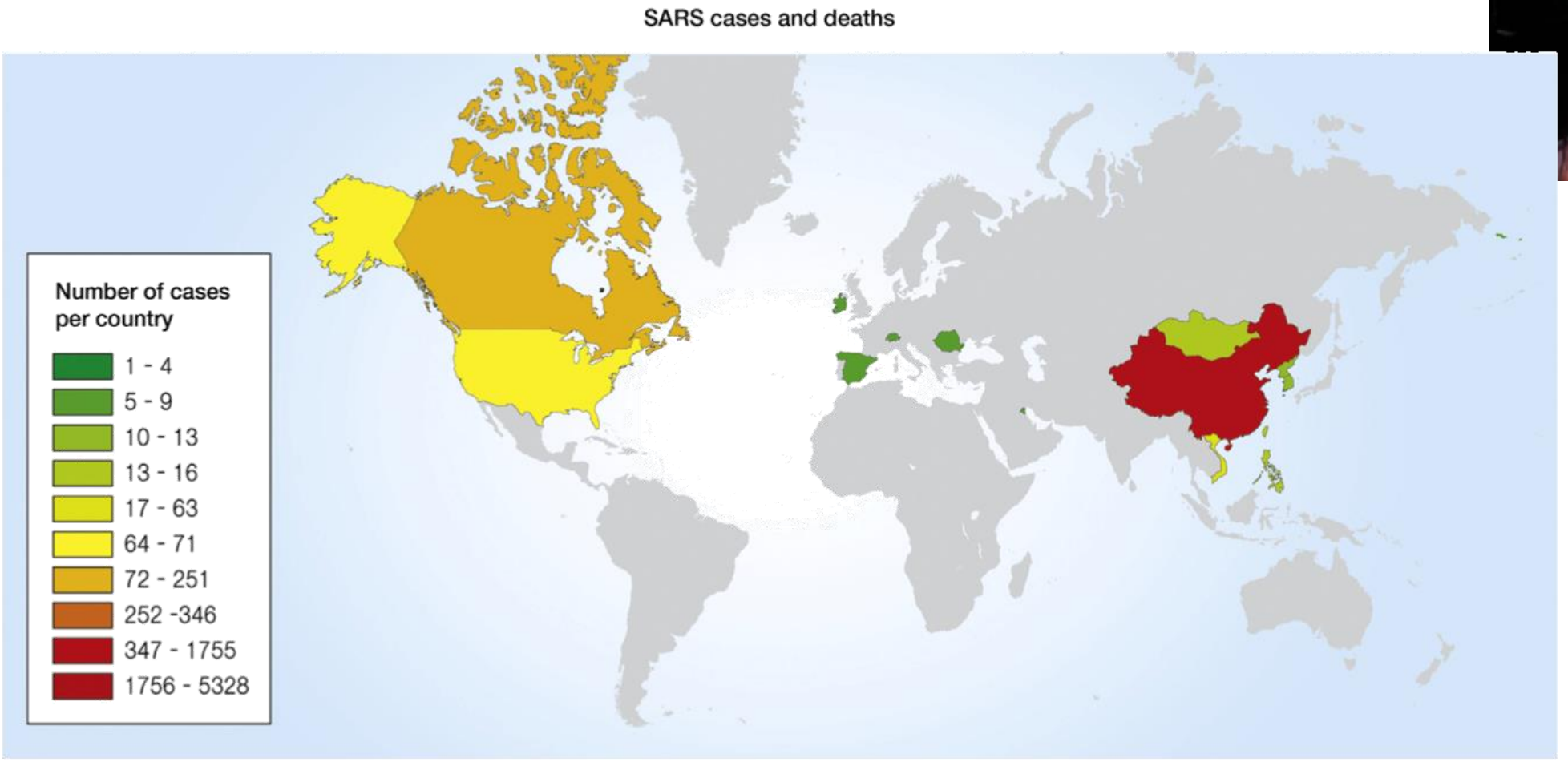
ut "long covid"?

ong lasting effects, **Elisabeth Mahase** examines the

GBD Long COVID Collaborators. Surviving COVID-19: a global systematic analysis of long COVID disability in 2020

LOOKING BACK



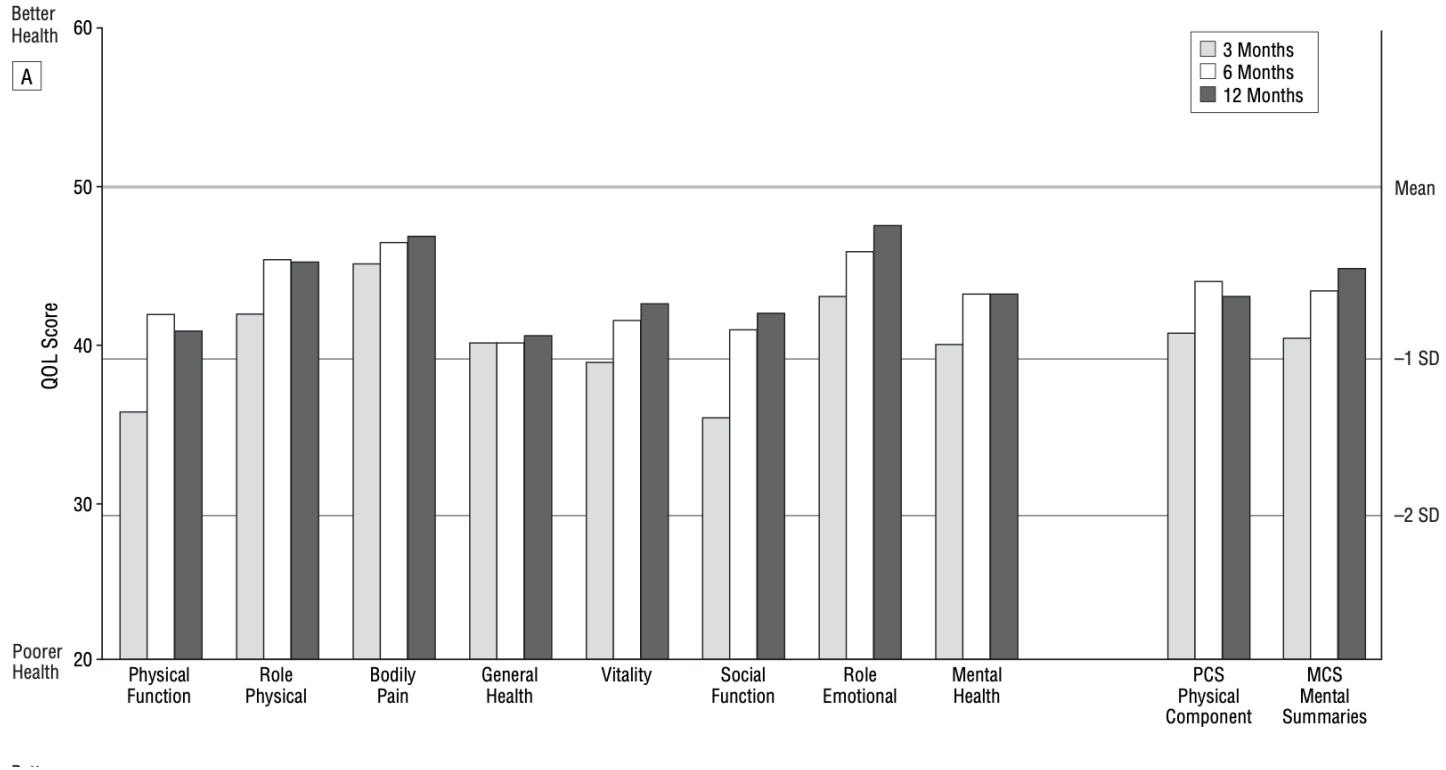


Source: Lee SH. The SARS epidemic in Hong Kong--a human calamity in the 21st century. Methods Inf Med. 2005;44(2):293-8

LOOKING BACK

One-Year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome

Catherine M. Tansey, MSc; Marie Louie, MD; Mark Loeb, MD; et al



117 patients in Toronto who had contracted SARS, with interviews, physical examnation, chest radiography, a 6-minute walk test (6MWT), QoL measures and self-reporting of healthcare utilisation at 3, 6 and 12 months . They showed that at 1 year, **18%** of individuals had a **reduced 6MWT due to shortness of breath and fatigue**.

QoL measures (SF-36) showed a **global reduction at 3 months, which had improved but not normalised at 1 year**. Most patients returned to work after a 1–2 month period of reduced hours; however, **at 1 year, 17% of patients hadn't returned and 9% had not returned to pre-SARS level of work.**

Source: Tansey CM, et al. One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. Arch Intern Med. 2007 Jun 25;167(12):1312-20.

LOOKING BACK

RESPIRATORY INFECTION

Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors

D S Hui, G M Joynt, K T Wong, C D Gomersall, T S Li, G Antonio, F W Ko, M C Chan, D P Chan, M W Tong, T H Rainer, A T Ahuja, C S Cockram, J J Y Sung

Thorax 2005;**60**:401–409. doi: 10.1136/thx.2004.030205

Table 3 Six minute walking distance (6MWD) among SARS survivors (n = 110) at 3 and 6 months after the onset of illness compared with Hong Kong normative data

Outcome		Normal	3 months	6 months	p value†
All survivors (n = 110*)	Mean (SD)		464 (83)	502 (95)	**
Age group (years)					
21–30 (n = 37)					0.01
Men	Mean (SD)	651(105), (n = 80)	487 (58), (n = 17)	549 (73), (n = 17)	
	Mean difference (95% CI)		−164 (−201 to −127)**	−102 (−155 to −49)**	
Women	Mean (SD)	600 (84), (n = 85)	461 (75), (n = 20)	493 (92), (n = 20)	0.13
	Mean difference (95% CI)		−139 (−180 to −98)**	−107 (−149 to −65)**	
31–40 (n = 40)					
Men	Mean (SD)	645 (93), (n = 78)	513 (80), (n = 19)	551 (98), (n = 19)	0.06
	Mean difference (95% CI)		−132 (−178 to −86)**	−94 (−141 to 46)**	
Women	Mean (SD)	606 (86), (n = 108)	476 (71), (n = 22)	502 (53), (n = 22)	0.11
	Mean difference (95% CI)		−130 (−169 to 91)**	−101 (−139 to −63)**	
41–50 (n = 21)					
Men	Mean (SD)	623 (80), (n = 38)	477 (82), (n = 7)	543 (112), (n = 7)	0.09
	Mean difference (95% CI)		−146 (−212 to −79)**	−80 (−151 to −9), p = 0.03	
Women	Mean (SD)	541 (67), (n = 79)	404 (83), (n = 14)	473 (76), (n = 14)	**
	Mean difference (95% CI)		−137 (−177 to −97)**	−68 (−107 to −29)**	
51–60 (n = 11)					
Men	Mean (SD)	588 (68), (n = 23)	331 (83), (n = 2)	405 (89), (n = 2)	0.18
	Mean difference (95% CI)		−257 (−361 to −152)**	−183 (−288 to −78)**	
Women	Mean (SD)	534 (89), (n = 33)	399 (92), (n = 9)	371 (99), (n = 9)	0.67
	Mean difference (95% CI)		−135 (−203 to −67)**	−163 (−232 to −94)**	

*Including one woman aged 61 years with 6MWD 492 m and 465 m at 3 and 6 months, respectively.
**p<0.01.
†6 months *v* 3 months.

110 survivors with confirmed SARS were evaluated at the Prince of Wales Hospital, HK at the end of 3 and 6 months after symptom onset.
The assessment included lung volumes (TLC, VC, RV, FRC), spirometry (FVC, FEV1), carbon monoxide transfer factor (TLCO adjusted for haemoglobin), inspiratory and expiratory respiratory muscle strength (Pimax and Pemax), 6 minute walk distance (6MWD), chest radiographs, and HRQoL by SF-36 questionnaire.

Source: Hui DS, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax. 2005 May;60(5):401-9.

LOOKING BACK

RESEARCH ARTICLE Open Access

BMC Neurology

Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study

Table 2 Sleep, Pain and Fatigue in SARS vs. FMS Subjects

Sleep Parameter	SARS (n = 22)	Fibromyalgia (n = 21)	Significance
	Mean (SD)	Mean (SD)	
Sleep onset latency (min.)	24.13 (21.63)	18.37 (35.39)	n.s.
Total sleep time (min)	370.83 (83.84)	338.54 (76.26)	n.s.
Sleep Efficiency %	77.44 (13.56)	79.34 (15.63)	n.s.
Stage 1%	9.11 (4.13)	9.76 (3.66)	n.s.
Stage 2%	60.22 (9.95)	54.61(5.41)	0.031
Stage 3%	7.83 (6.36)	7.35 (3.08)	n.s.
Stage 4%	6.27 (5.80)	9.53 (6.18)	n.s.
REM onset Latency (min.)	136.79 (63.72)	87.26 (35.78)	0.004
REM %	16.57 (5.94)	18.77 (4.81)	n.s.
Apnea/Hypopneas Index (no. per hr.of sleep)	4.70 (5.53)	3.29 (2.37)	n.s.
Periodic leg movements (no.per hr of sleep)	2.03 (5.64)	2.38 (3.81)	n.s.
Arousals per hr of sleep	14.01 (7.59)	11.31 (5.31)	n.s.
CAP rate per hr of sleep	71.64 ()(14.25)	70.39 (15.64)	n.s.
Alpha EEG sleep (1-5)	3.00 (0.63)	3.50(0.61)	0.014
Presleep Pain Presleep Fatigue (1-7)	6.24 (4.01) 4.57 (1.57)	10.95 (5.74) 4.30 (1.08)	0.005 n.s.
Presleep Sleepiness (1-7)	2.76 (1.14)	4.30 (1.08)	0.0001
Post Sleep Pain (0-24)	7.10 (3.81)	11.75 (6.45)	0.009
Post Sleep Fatigue (1-7)	4.30 (1.87)	4.60 (1.23)	n.s.
Post Sleep Sleepiness (1-7)	3.45 (1.57)	3.90 (1.12)	n.s.

Fatigue, myalgia, depression and poor sleep were seen in a cohort of 22 patients and a post-SARS syndrome, similar to **fibromyalgia** or **post viral chronic fatigue syndrome**, was suggested, possibly as a result of the **psychological trauma or neurological involvement of SARS**.

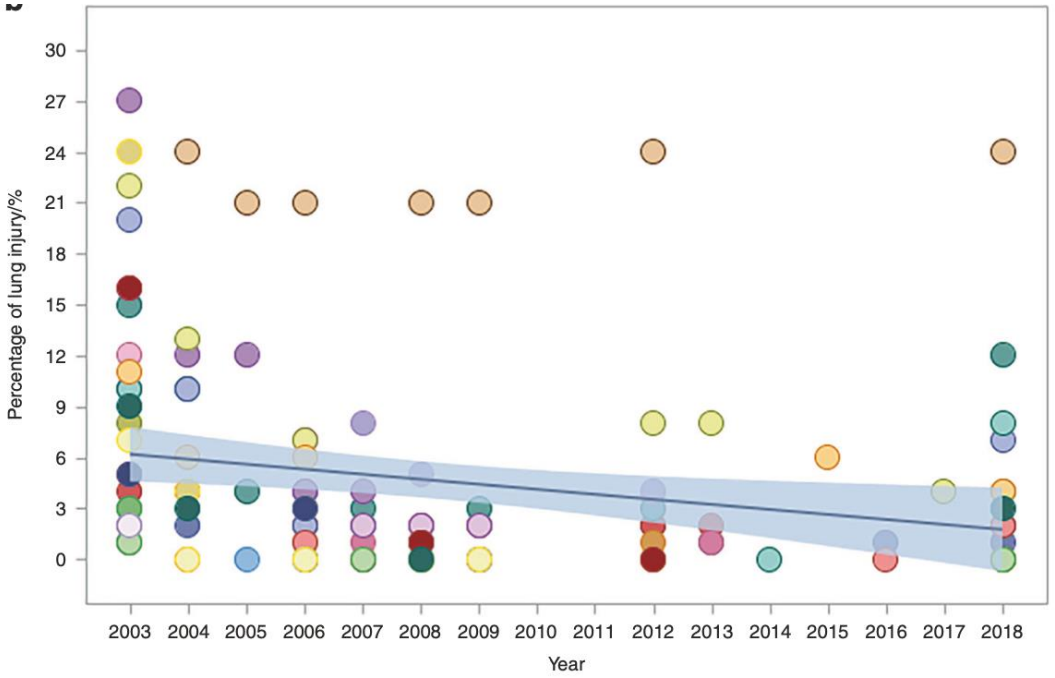
Source: Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. BMC Neurol. 2011 Mar 24;11:37.

LOOKING BACK

ARTICLE OPEN

Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study

Peixun Zhang[1], Jia Li[2], Huixin Liu[3], Na Han[4], Jiabao Ju[5], Yuhui Kou[1], Lei Chen[6], Mengxi Jiang[6], Feng Pan[6], Yali Zheng[2], Zhancheng Gao[2] and Baoguo Jiang[1]



The volume of femoral head necrosis decreased significantly from 2003 (38.83 ± 21.01)% to 2005 (30.38 ± 20.23)% (P = 0.000 2), then declined slowly from 2005 to 2013 (28.99 ± 20.59)% and plateaued until 2018 (25.52 ± 15.51)%. Pulmonary interstitial damage and functional decline caused by SARS mostly recovered, with a greater extent of recovery within **2 years after rehabilitation**. Femoral head necrosis induced by large
doses of steroid pulse therapy in SARS patients was not progressive and was partially reversible.

LOOKING BACK

Batawi *et al. Health and Quality of Life Outcomes* (2019) 17:101
https://doi.org/10.1186/s12955-019-1165-2

Health and Quality of Life Outcomes

RESEARCH Open Access

Quality of life reported by survivors after hospitalization for Middle East respiratory syndrome (MERS)

Batawi et al followed up 78 MERS survivors with questionnaires at 14 months post-hospitalisation in **Saudi Arabia.** Using the SF-36, QoL scores were reduced, with significantly lower scores in those who had had critical care admissions. Similar to SARS, **chronic fatigue** symptoms were described in **48%** of survivors at 1 year, reducing to 33% at 18 months. **88%** of MERS survivors were back at work, but the study didn't differentiate on how many were in part- or full-time work

SAGE Public Health Emergency Collection
Public Health Emergency COVID-19 Initiative

Workplace Health Saf. 2020 Mar 9 : 2165079919897693. PMCID: PMC7201205
Published online 2020 Mar 9. doi: 10.1177/2165079919897693 PMID: 32146875

Assessing the Presence of Post-Traumatic Stress and Turnover Intention Among Nurses Post–Middle East Respiratory Syndrome Outbreak: The Importance of Supervisor Support

Heeja Jung,[1] Sun Young Jung,[1] Mi Hyang Lee,[1] and Mi Sun Kim[2]

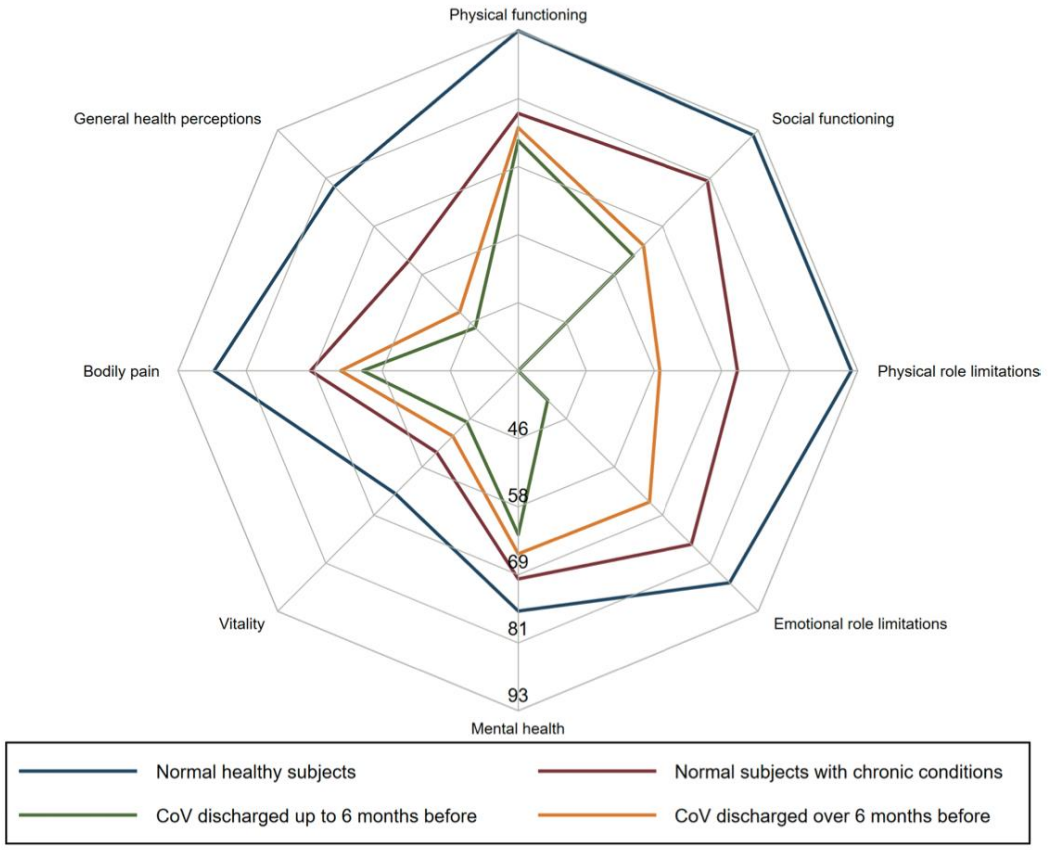
As seen with SARS survivors, there are high levels of psychiatric disorders, including anxiety, depression and PTSD, notably worse in HCWs. The study showed that at 12 months **post-MERS 27% of survivors had depression and 42% had PTSD**, which improved at 18 months but was still a problem in 17% and 27% of survivors respectively. These effects were increased in **HCWs**, where around **57% of nurses** who treated patients with MERS suffered PTSD

LOOKING BACK

Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS) outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis

Journal of REHABILITATION MEDICINE
OWNED BY THE NON-PROFIT ORGANIZATION FOUNDATION FOR REHABILITATION INFORMATION

Hassaan Ahmed, Kajal Patel, Darren C. Greenwood, Stephen Halpin, Penny Lewthwaite, Abayomi Salawu, Lorna Eyre, Andrew Breen, Rory O'Connor, Anthony Jones, Manoj Sivan
School of Medical Sciences, University of Manchester, UK
DOI: 10.2340/16501977-2694



Outcome	Number of studies	Number of participants	% Impaired function (95% CI)	Range of observed results	I^2
Up to 6 months' follow-up					
% Impaired diffusing capacity for carbon monoxide (DLCO)	8	831	27% (15 to 45)	(0% to 65%)	76%
% Impaired forced dxpiratory volume (FEV1)	5	617	6% (2 to 18)	(1% to 30%)	62%
% Impaired forced vital capacity (FVC)	3	191	12% (4 to 28)	(6% to 32%)	82%
% Impaired total lung capacity (TLC)	2	154	15% (5 to 38)	(7% to 30%)	84%
Over 6 months' follow-up					
% Impaired diffusing capacity for carbon monoxide (DLCO)	7	378	24% (11 to 45)	(0% to 82%)	70%
% Impaired forced dxpiratory volume (FEV1)	5	321	11% (4 to 24)	(0% to 32%)	79%
% Impaired forced vital capacity (FVC)	4	301	11% (5 to 22)	(4% to 30%)	86%
% Impaired total lung capacity (TLC)	3	237	10% (5 to 19)	(5% to 22%)	91%

Fig. 2. Summary Forest plot showing pooled estimate of prevalence of different lung function abnormalities in CoV survivors up to 6 months (top) and over 6 months (bottom).

Source: Ahmed H, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. J Rehabil Med. 2020 May 31;52(5):jrm00063.

LOOKING BACK

Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS) outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis

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DOI: 10.2340/16501977-2694

Outcome	Number of studies	Number of participants	%Prevalence of condition (95% CI)	Range of observed results	I^2
Over 6 months' follow-up					
% Prevalence of post-traumatic stress disorder (PTSD)	6	589	39% (31 to 47)	(26% to 55%)	96%
% Prevalence of depression	4	465	33% (20 to 50)	(9% to 48%)	88%
% Prevalence of anxiety	2	169	30% (10 to 61)	(14% to 52%)	80%

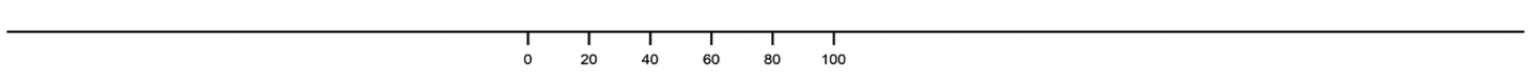


Fig. 3. Summary Forest plot showing pooled estimate of prevalence of different psychological conditions in CoV survivors over 6 months

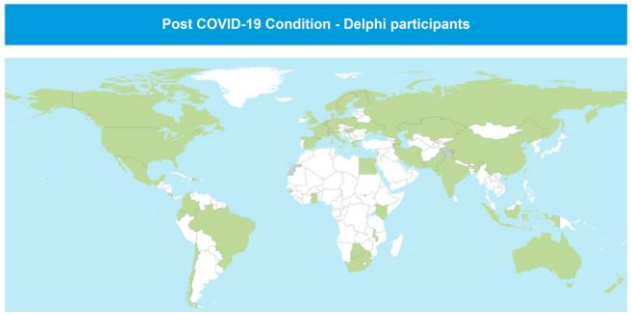
Source: Ahmed H, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. J Rehabil Med. 2020 May 31;52(5):jrm00063.

WHAT IS LONG COVID? DEFINITION MATTER

A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021

World Health Organization



WHO has developed a clinical case definition of post COVID-19 condition by Delphi methodology that includes 12 domains, available for use in all settings. This first version was developed by **patients, researchers** and others, representing all WHO regions, with the understanding that the definition may change as new evidence emerges and our understanding of the consequences of COVID-19 continues to evolve.

Post COVID-19 condition occurs in individuals:

- *with a history of probable or confirmed SARS CoV-2 infection,*
- *usually 3 months from the onset of COVID-19 with symptoms and*
- *that last for at least 2 months*
- *cannot be explained by an alternative diagnosis.*

Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness.

Symptoms may also fluctuate or relapse over time.

WHAT IS LONG COVID? DEFINITION MATTER

NICE National Institute for Health and Care Excellence

COVID-19 rapid guideline: managing the long-term effects of COV

v1.7 published on 11/23/21

- How to use this guideline
- **Identification**
- Assessment
- Investigations and referral
- Planning care
- Management
- Follow up, monitoring and discharge
- Sharing information and continuity of care
- Service organisation
- Common symptoms
- Recommendations for research
- Equality considerations
- Methods and evidence reviews

Consensus recommendation

Use the following clinical case definitions to

Acute COVID-19

Signs and symptoms of COVID-19 for up to

Ongoing symptomatic COVID-19

Signs and symptoms of COVID-19 from 4 w

Post-COVID-19 syndrome

Signs and symptoms that develop during o
12 weeks and are not explained by an alter
overlapping, which can fluctuate and chang
may be considered before 12 weeks while

In addition to the clinical case definitions, th
continue or develop after acute COVID-19.
post-COVID-19 syndrome (12 weeks or more).

Codes have been developed that align with this case definition. See the practical info section for further details.

EDITORIALS

Check for updates

1 Academic Department of Rehabilitation Medicine, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

NICE guideline on long covid

Research must be done urgently to fill the many gaps in this new "living guideline"

Manoj Sivan, [1,2] Sharon Taylor[3,4]

Standardised terms

The guideline defines long covid as "signs and symptoms that develop during or following an infection consistent with covid-19 and which continue for more than four weeks and are not explained by an alternative diagnosis."[4] Given that we are beginning to understand the underlying immunological and organ specific effects of SARS-CoV-2,[6,7] it might have been better to define it as "signs and symptoms that continue for more than four weeks and can be attributed to covid-19 infection." This definition would include all the post-acute medical complications of covid-19 under one unified definition rather than making long covid a vague diagnosis of exclusion.

NICE recommends using the term "post-covid syndrome" from 12 weeks after infection. But no evidence exists of any particular physiological changes (that predict chronicity) at 12 weeks, so it would be preferable to use the term long covid for symptoms of any duration beyond four weeks, as is strongly advocated by people with lived experience of this condition.[8] Using the prefix "post" implies that acute infection and any active disease process ave resolved, which is currently unknown.

One stop multidisciplinary clinics are recommended, led by a doctor with relevant specialist skills and experience. NHS England has also emphasised the importance of multidisciplinary assessment and diagnostics being available in long covid clinics to avoid multiple referrals to different specialists.[5] Clearer guidance on the optimal composition of multidisciplinary teams would have been helpful. Respiratory physicians, cardiologists, neurologists, general physicians (from primary care or rehabilitation medicine), neuropsychologists or neuropsychiatrists, physiotherapists, occupational therapists, speech and language therapists, and dieticians may all be required.

Interventions

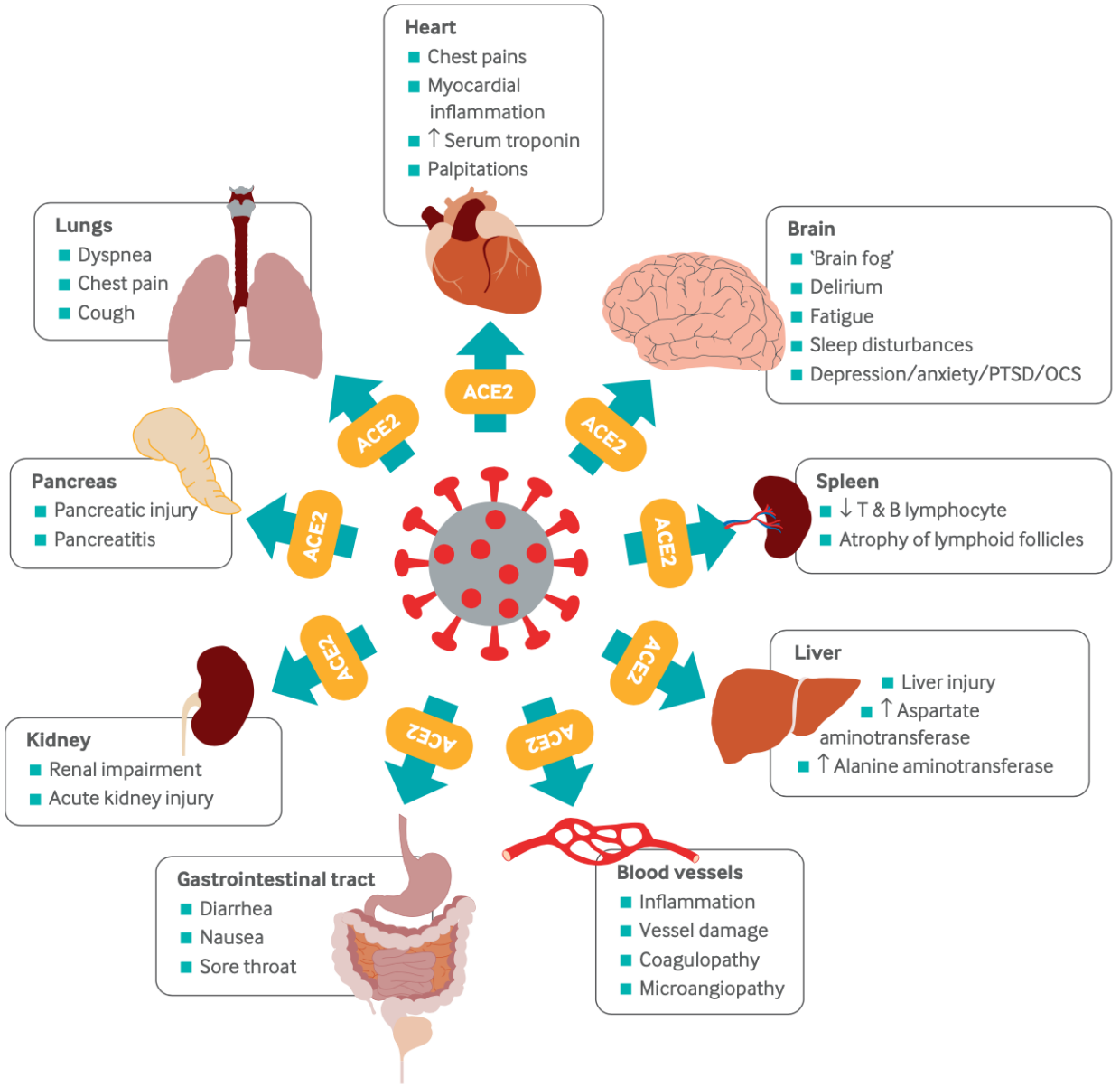
Shared decision making is appropriately emphasised in the setting of goals and the formulation of personalised management plans and care plans. The guidance lacks detail on potentially helpful rehabilitation interventions such as breathing techniques, psychological interventions (such as cognitive behaviour therapy), cognitive training (such as memory training), and occupational rehabilitation, perhaps understandably given the current paucity of supporting evidence. The dangers of exercise in some patients, such as those with undiagnosed acute

BMJ: first publis

PATHOPHYSIOLOGY

The predominant pathophysiologic mechanisms of acute COVID- 19 include the following: direct/umdirect viral toxicity; endothelial damage and microvascular injury; immune system dysregulation and stimulation of a hyperinflammatory state; hypercoagulability with resultant in situ thrombosis and macrothrombosis; and maladaptation of the angiotensin-converting enzyme 2 (ACE2) pathway

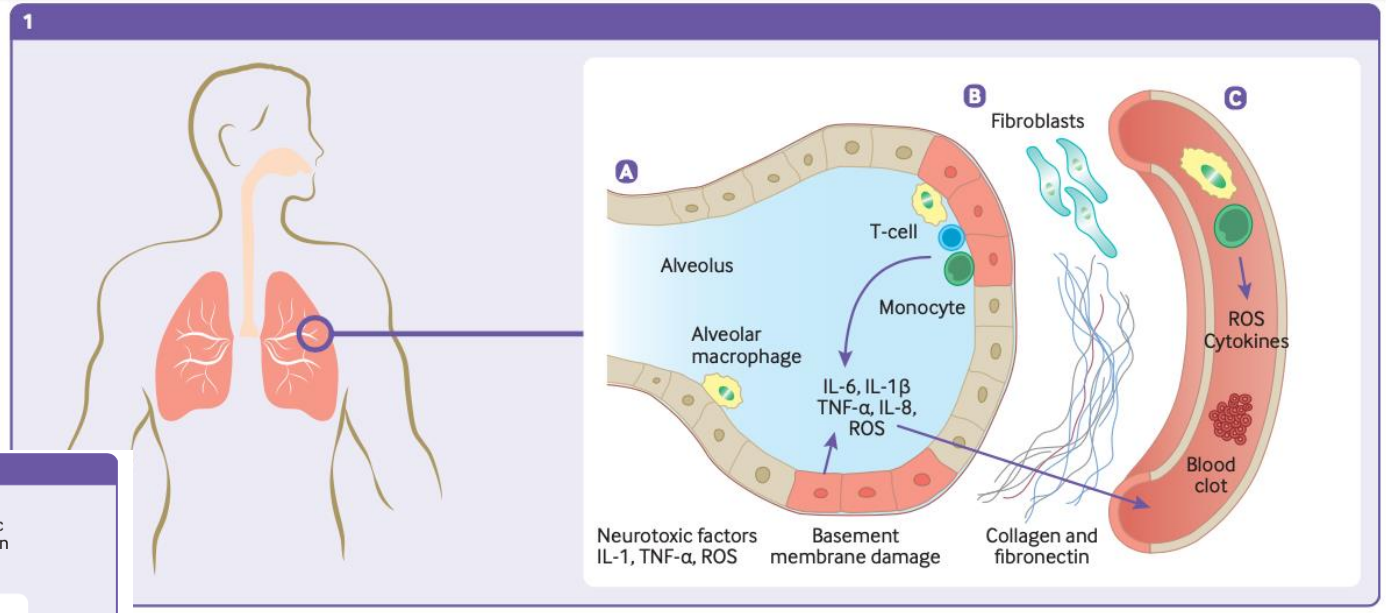
Multi-organ complications of covid-19 and long covid.
The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor. Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms, some of which are outlined here

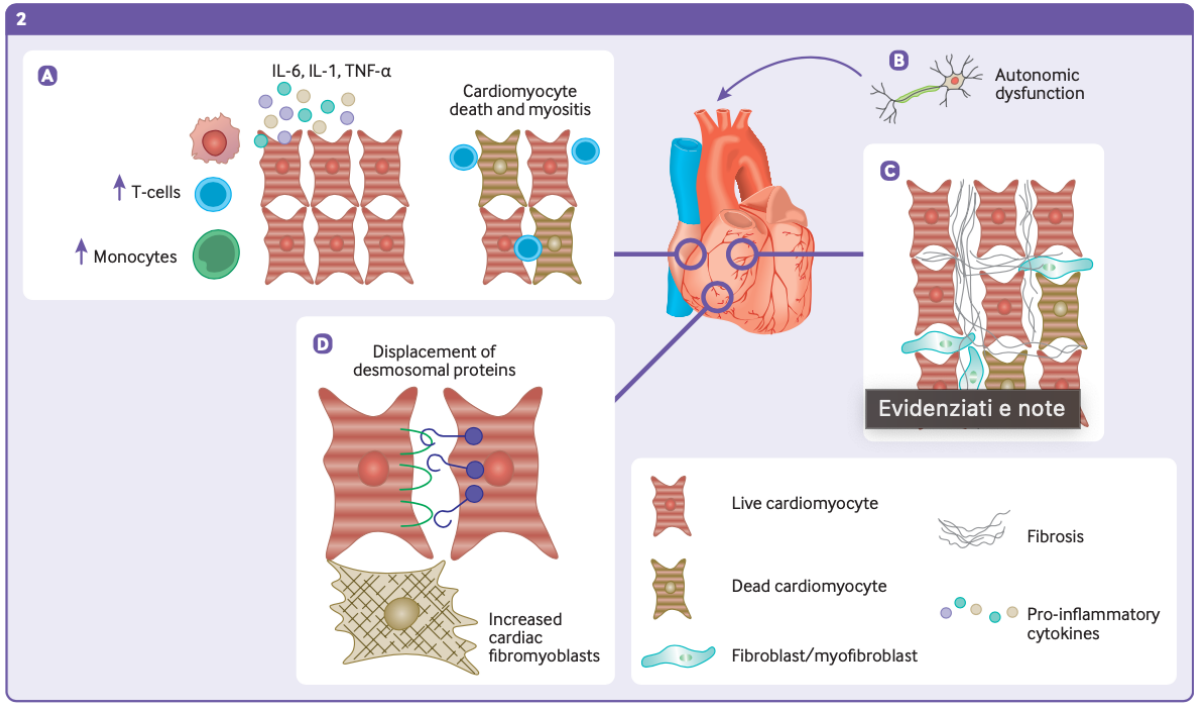


Crook H et al. Long covid—mechanisms, risk factors, and management BMJ 2021; 374 :n1648

LONG TERM SEQUALAE

In the alveoli of the lungs, chronic inflammation results in the sustained production of pro-inflammatory cytokines and reactive oxygen species (ROS) which are released into the surrounding tissue and bloodstream

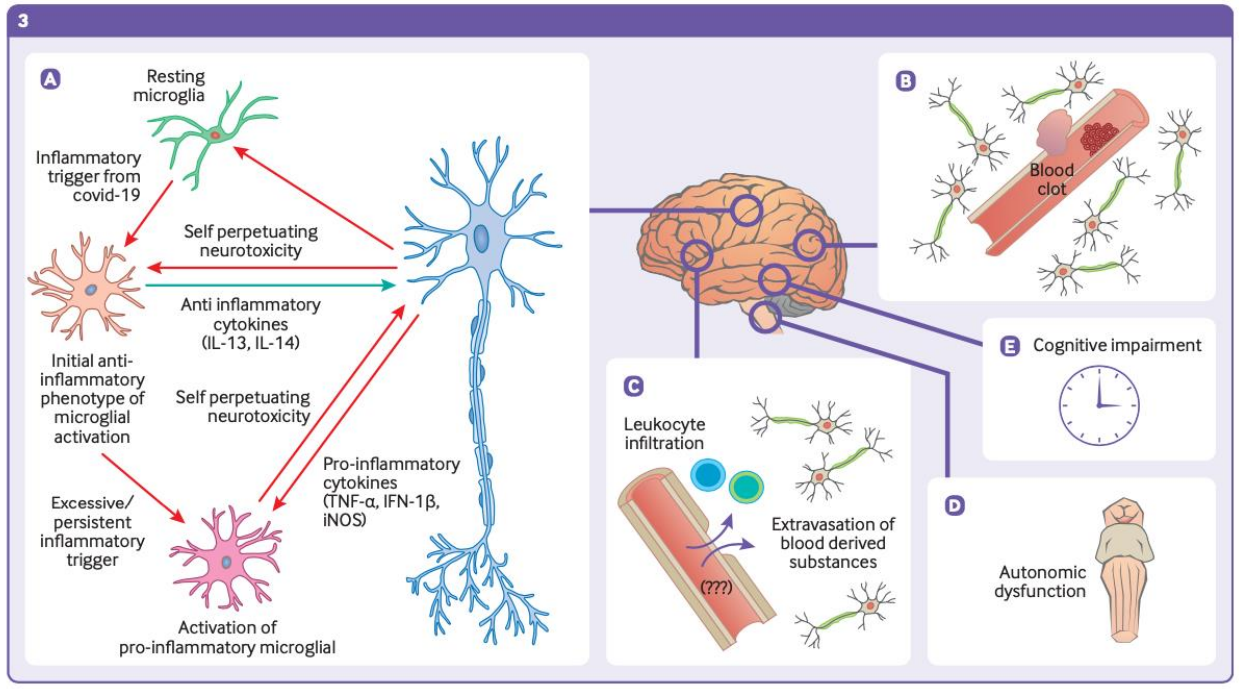




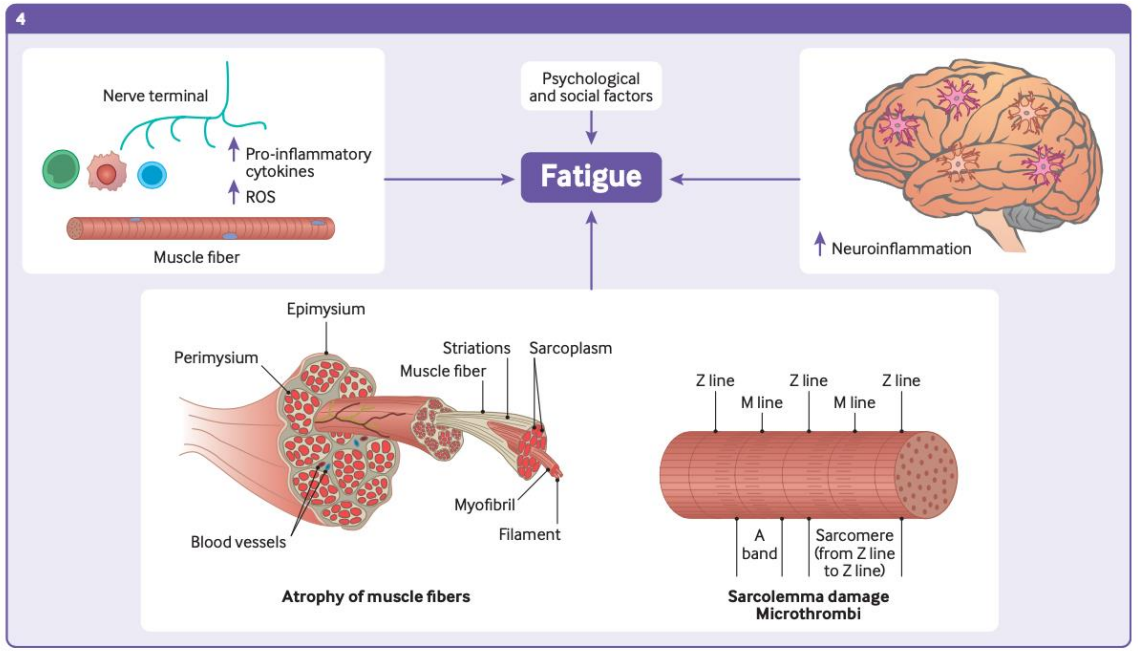
In the heart, chronic inflammation of cardiomyocytes can result in myositis and cause cardiomyocytes death. Furthermore, dysfunction of the afferent autonomic nervous system can cause complications such as postural orthostatic tachycardia syndrome

Crook H et al. Long covid—mechanisms, risk factors, and management BMJ 2021; 374 :n1648

LONG TERM SEQUALAE



In the CNS the long term immune response activates glial. Hyperinflammatory and hypercoagulable pathological permeability, cognitive impairment. Blood-brain barrier damage and dysregulation results in pathological permeability. The effects of long covid in the brain can lead to cognitive impairment

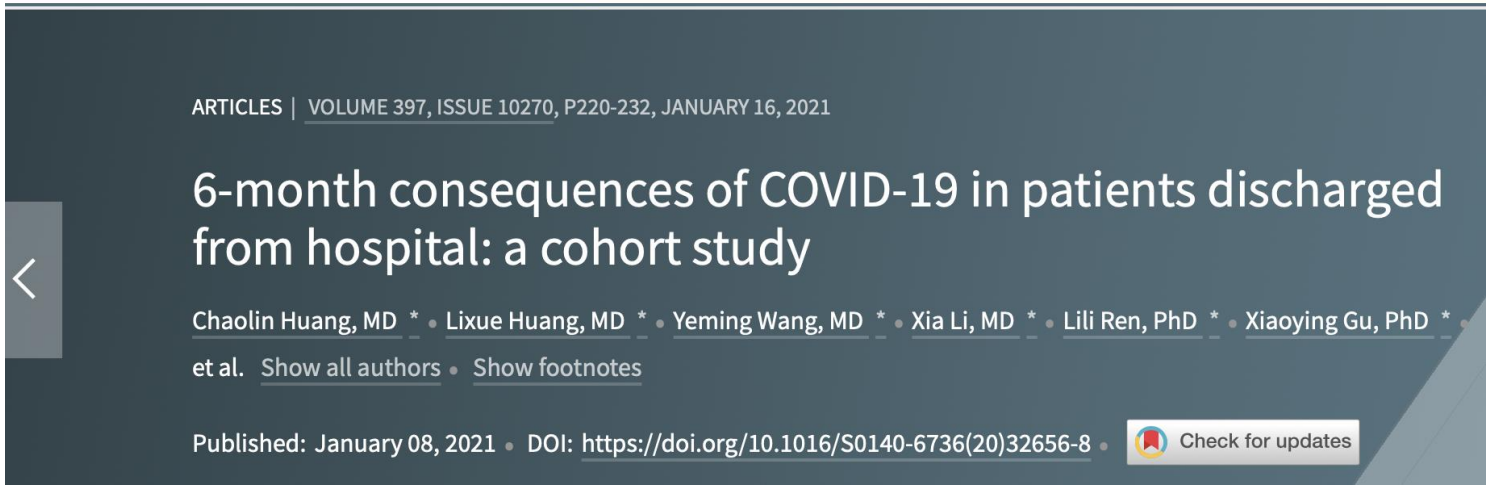


Chronic inflammation in the brain, as well as at the neuromuscular junctions, may result
in long term fatigue. In skeletal muscle, sarcolemma damage and fiber atrophy and damage may play a role in fatigue, as might a number of psychological and social factors

Crook H et al. Long covid—mechanisms, risk factors, and management *BMJ* 2021; 374 :n1648

EVIDENCES SO FAR

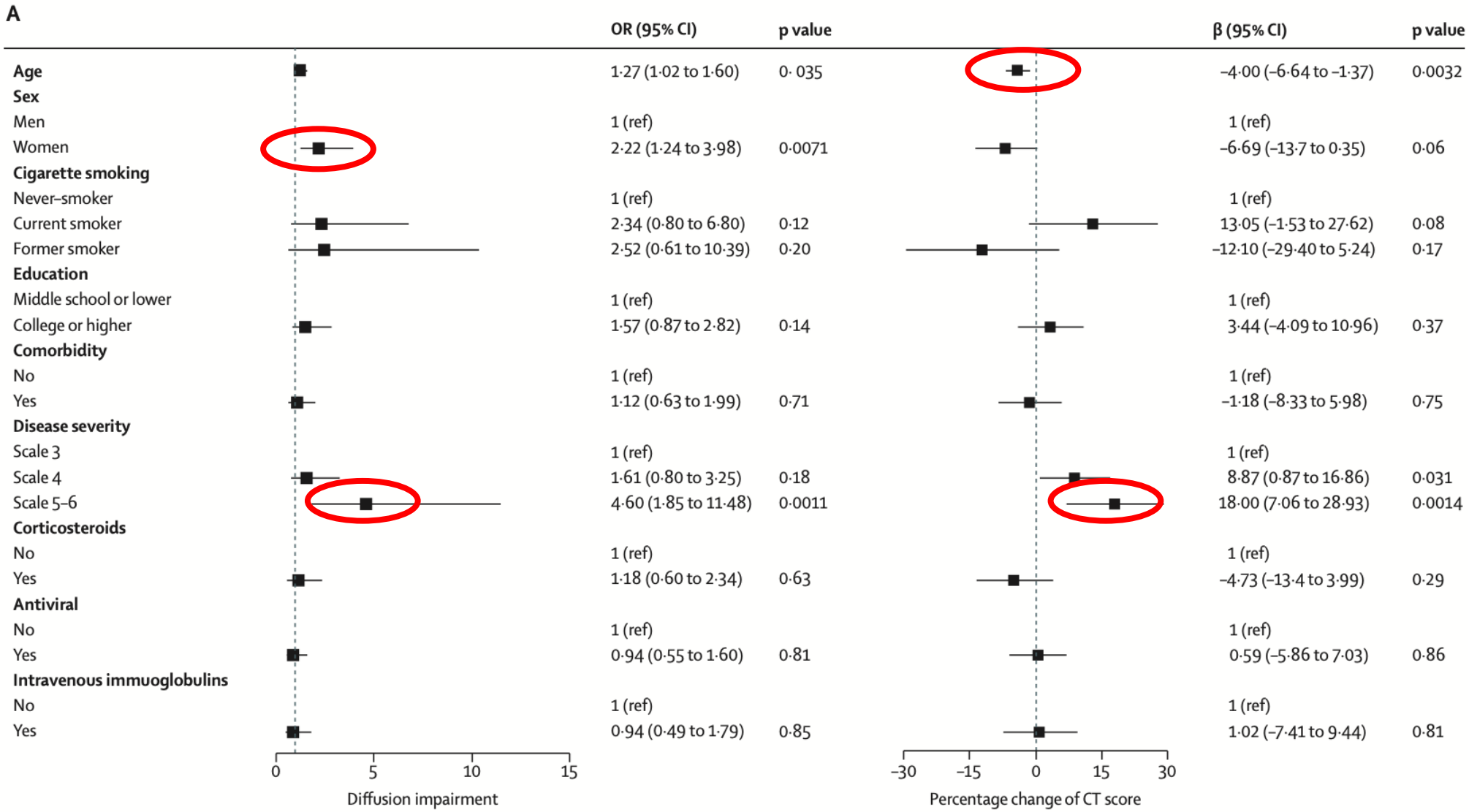
THE LANCET



→ ambidirectional cohort study of patients with confirmed COVID-19 discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, 2020, and May 29, 2020 -- follow-up from June 16, to Sept 3, 2020
→ 1733 of 2469 discharged patients with COVID-19 were enrolled after 736 were excluded
→ median age of 57·(IQR 47–65) years and 897 (52%) were men.
→ median follow-up time after symptom onset was 186 (175–199) days.
→ Fatigue or muscle weakness (**63%,** 1038 of 1655) and sleep difficulties (**26%,** 437 of 1655) were the most common symptoms.
→ Anxiety or depression was reported among **23%** (367 of 1617) of patients.
→ The proportions of median 6-min walking distance less than the lower limit of the normal range were 24% for those at severity scale 3, 22% for severity scale 4, and 29% for severity scale 5–6

Source: Huang C, et al 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220-232.

EVIDENCES SO FAR



Source: Huang C, et al 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220-232.

EVIDENCES SO FAR

Contents lists available at ScienceDirect

The Lancet Regional Health - Europe

journal homepage: www.elsevier.com/lanepe

Research paper

Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol

- → The ISARIC WHO Clinical Characterisation Protocol (CCP) first developed by international consensus in 2012 to respond to any emerging or re-emerging pathogen of public health interest
- → Patients >18 years, admitted to hospital between 17th January to 5th October 2020 with confirmed or highly suspected SARS-CoV-2 infection at **31 centres**
- → The primary outcome was **self-reported recovery at 3 to 12 months** following initial Covid-19 symptoms.
- → Secondary outcomes included persistent or new symptoms, new or worsened disability assessed using the Washington Disability Group (WG) Short Form, breathlessness measured using the Medical Research Council (MRC) dyspnoea scale, fatigue measured on a 1 to 10 visual analogue scale (VAS) where zero is no fatigue and ten is worst possible fatigue, and quality of life using the EuroQol! EQ5D-5L instrument .
- → **327 participants**

Sigfrid L, et al ISARIC4C investigators. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. Lancet Reg Health Eur. 2021 Sep;8:100186.

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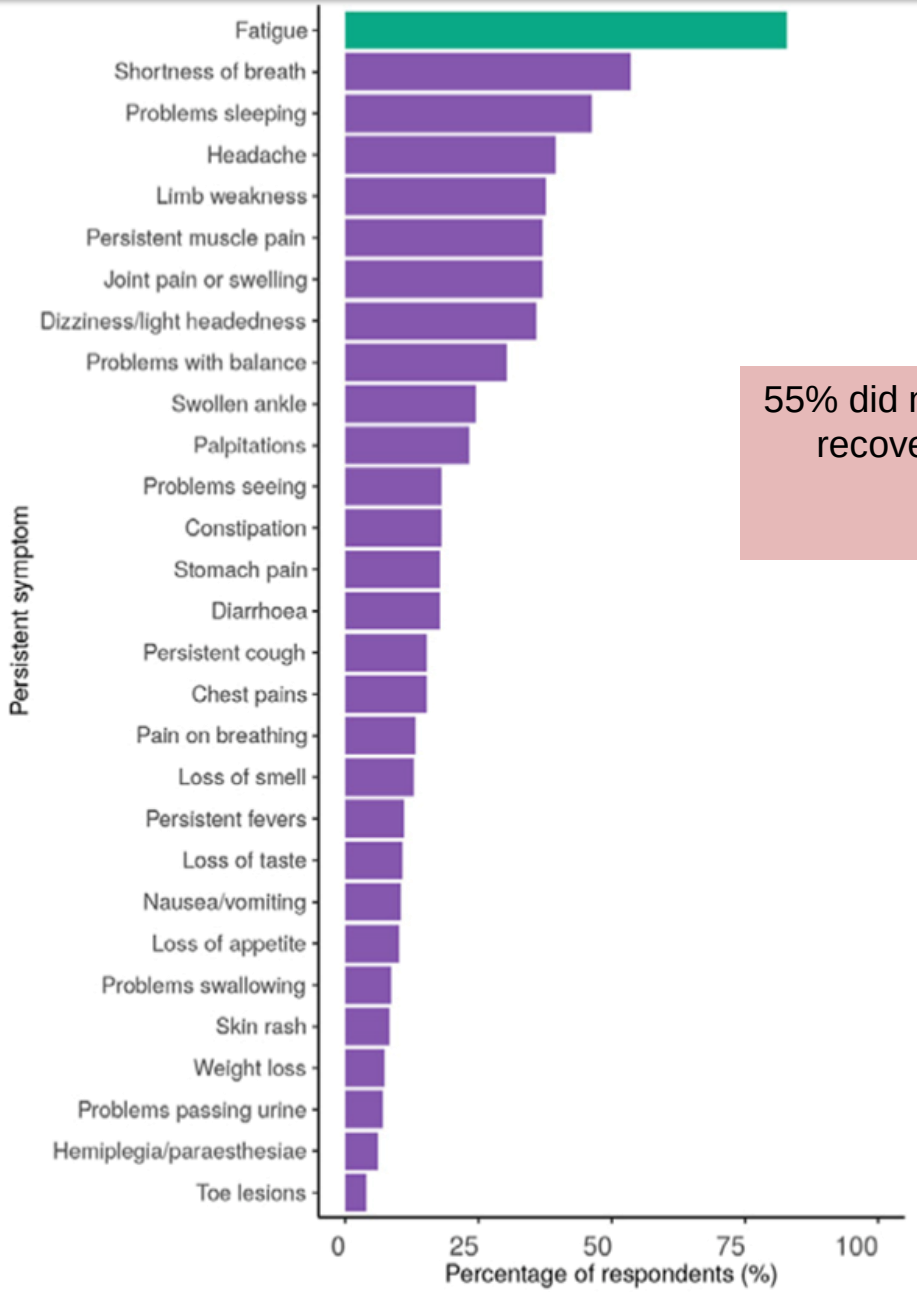
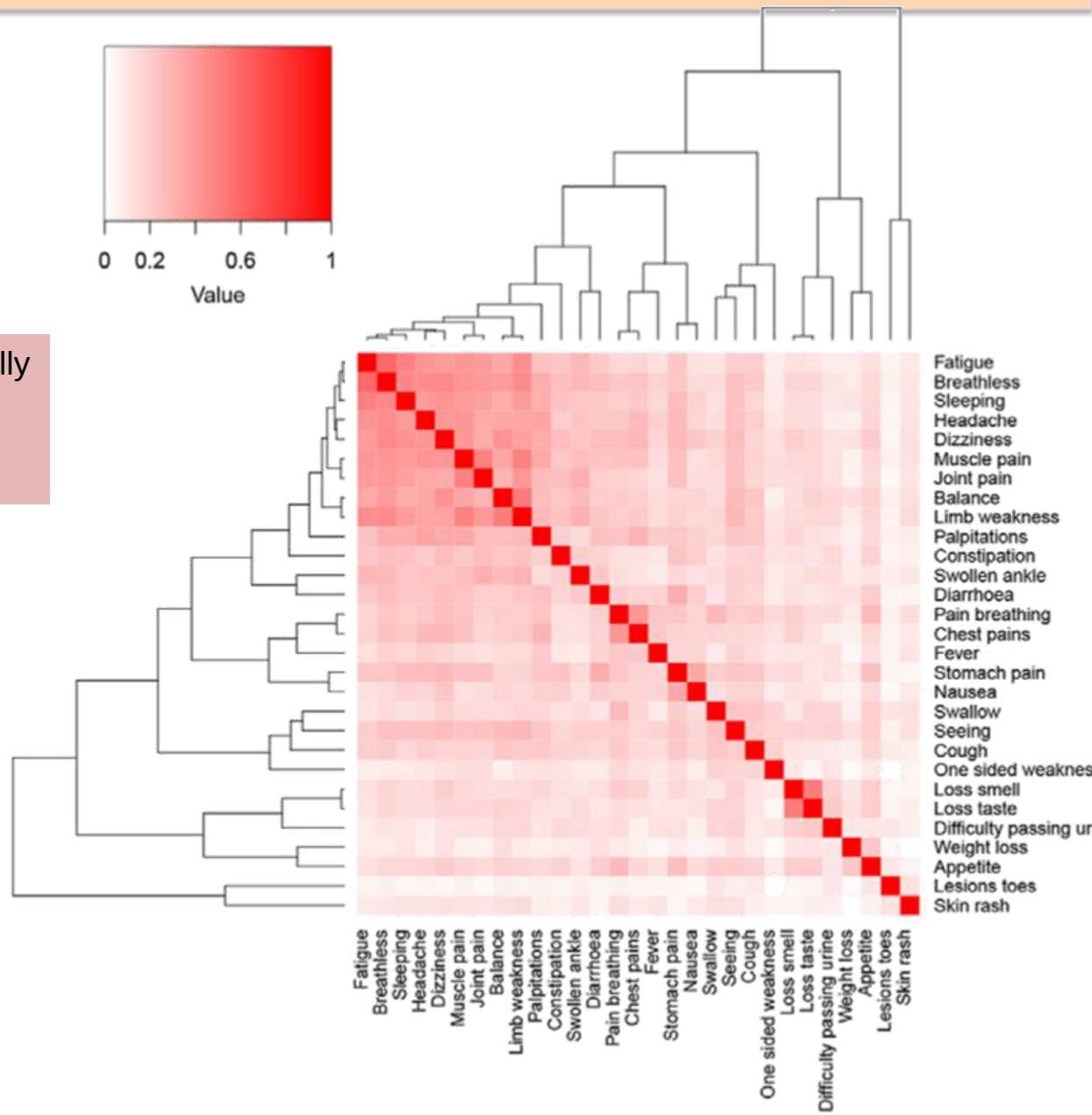


55% did not feel they had fully recovered at the time of follow-up.



L. Sigfrid et al. / The Lancet Regional Health - Europe 8 (2021) 10018

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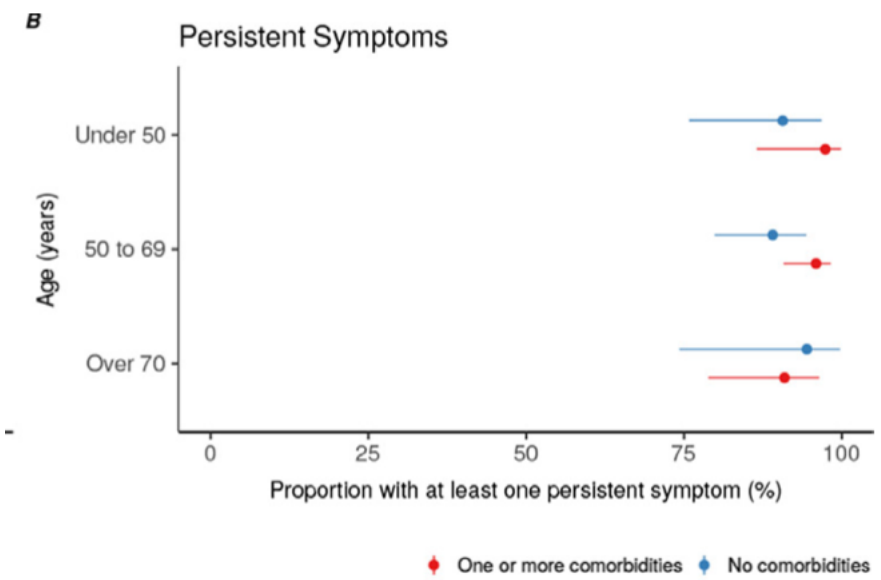

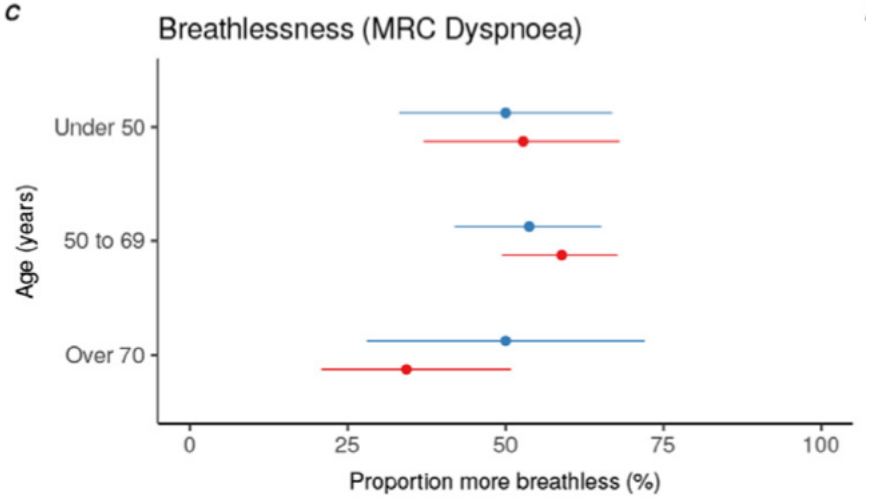

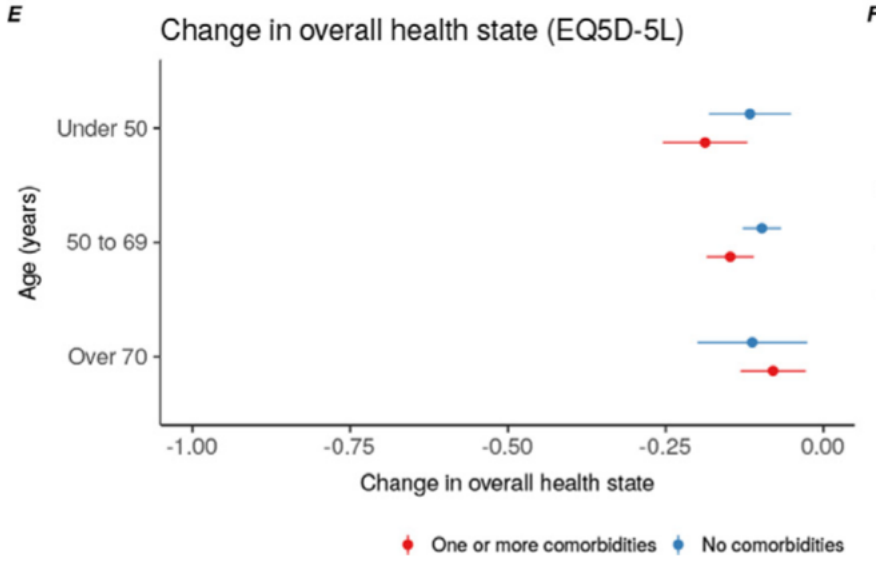

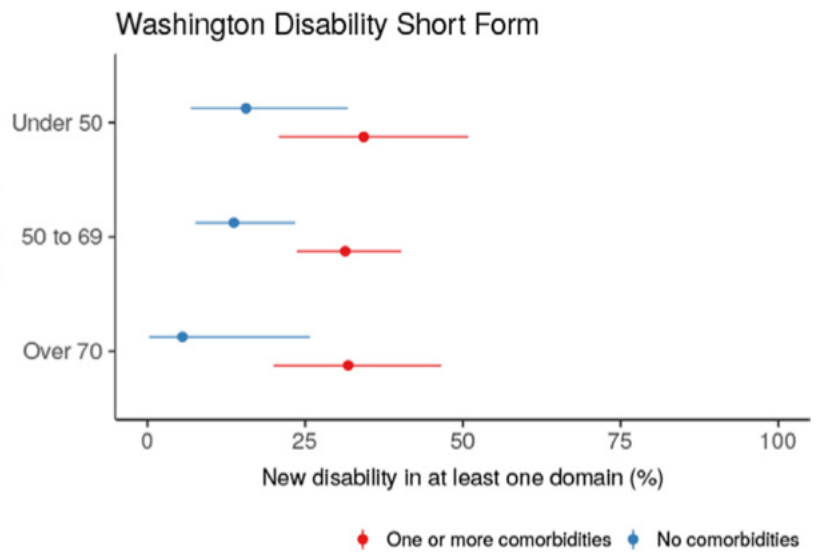

L. Sigfrid et al. / The Lancet Regional Health - Europe 8 (2021) 100186

EVIDENCES SO FAR

Table 3
Multilevel regression models for secondary outcomes of new or persistent symptoms, change in MRC dyspnoea scale, fatigue, EQ5D-5L summary index change and Washington Short Set new or worse disability.

Explanatory variable		New or persistent symptoms: OR (95% Confidence Interval)	Change in MRC Dyspnoea: OR (95% Confidence Interval)	Fatigue level: Coefficient (95% Confidence Interval)	EQ5D-5L summary index change: Coefficient (95% Confidence Interval)	Washington Short Set new or worse disability: OR (95% Confidence Interval)
Sex at Birth by Age	Male | Under 50	-	-	-	-	-
	Male | 50 to 69	0·82 (0·21-3·30, p=0·783)	2·20 (0·89-5·45, p=0·088)	0·44 (-0·56 to 1·44, p=0·194)	-0·05 (-0·11 to 0·02, p=0·093)	1·66 (0·51-5·42, p=0·401)
	Male | Over 70	0·74 (0·14-3·83, p=0·720)	2·59 (0·84-7·95, p=0·096)	0·38 (-0·84 to 1·60, p=0·272)	-0·04 (-0·12 to 0·04, p=0·184)	2·08 (0·55-7·96, p=0·283)
	Female | Under 50	2·75 (0·26-28·92, p=0·400)	7·15 (2·24-22·83, p=0·001)	2·06 (0·81 to 3·31, p=0·001)	-0·19 (-0·27 to -0·11, p<0·001)	4·22 (1·12-15·94, p=0·034)
	Female | 50 to 69	2·10 (0·39-11·37, p=0·389)	6·18 (2·28-16·78, p<0·001)	1·20 (0·15 to 2·24, p=0·012)	-0·10 (-0·17 to -0·03, p=0·003)	2·70 (0·81-9·03, p=0·107)
	Female | Over 70	1·21 (0·11-13·89, p=0·876)	0·62 (0·12-3·11, p=0·562)	0·29 (-1·33 to 1·92, p=0·362)	-0·06 (-0·17 to 0·04, p=0·109)	1·88 (0·36-9·82, p=0·452)
Any comorbidity	No comorbidities	-	-	-	-	-
	One or more comorbidities	2·28 (0·92-5·65, p=0·076)	0.74 (0·42-1·31, p=0·304)	0·95 (0·35 to 1·55, p=0·001)	-0·02 (-0·06 to 0·02, p=0·139)	2·96 (1·57-5·57, p=0·001)
Severity	Scale 3 (did not receive supplemental oxygen)	-	-	-	-	-
	Scale 4 (received supplemental oxygen)	0·61 (0·15-2·43, p=0·483)	0·51 (0·24-1·07, p=0·076)	-0·26 (-1·06 to 0·55, p=0·266)	0·04 (-0·01 to 0·09, p=0·077)	1·11 (0·51-2·40, p=0·798)
	Scale 5 (received HFNC or NIV)	0·32 (0·07-1·46, p=0·142)	0·89 (0·36-2·21, p=0·794)	-0·20 (-1·22 to 0·83, p=0·354)	0·01 (-0·06 to 0·08, p=0·371)	1·32 (0·49-3·51, p=0·583)
	Scale 6 or 7 (received invasive mechanical ventilation or critical care)	1·18 (0·24-5·95, p=0·838)	1·82 (0·79-4·22, p=0·162)	-0·18 (-1·09 to 0·74, p=0·354)	-0·05 (-0·11 to 0·02, p=0·073)	1·48 (0·63-3·52, p=0·370)

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Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

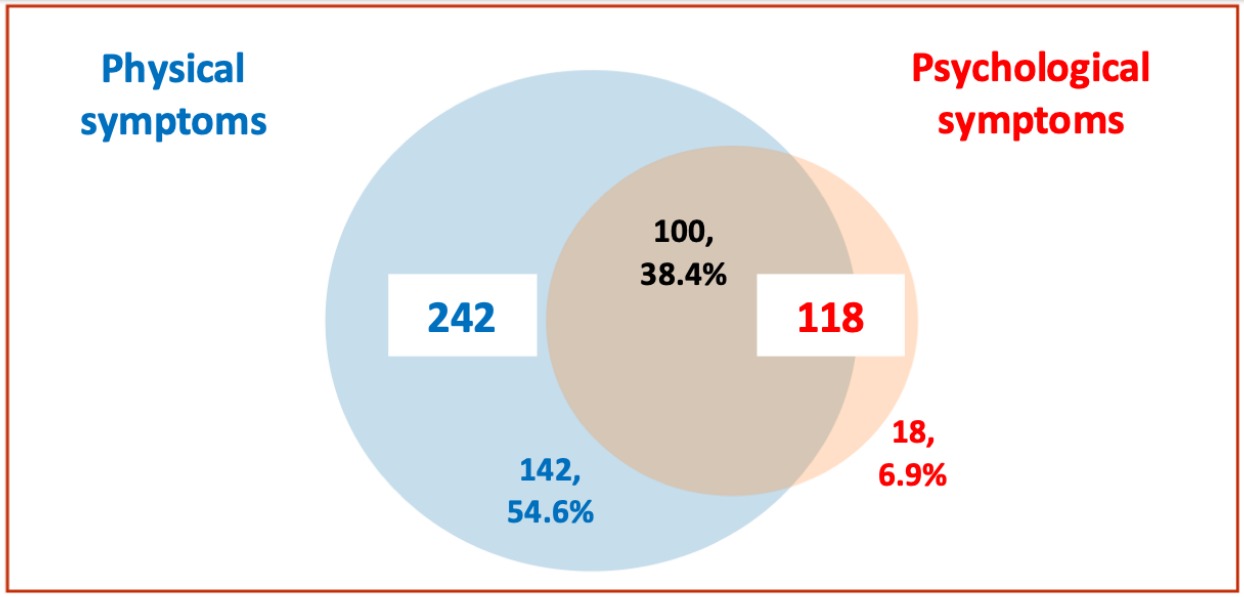
Original article

Female gender is associated with long COVID syndrome: a prospective cohort study

- → single-centre prospective cohort study conducted at San Paolo Hospital in Milan, Italy.
- → HADS was intended to measure anxiety and depression symptoms, whereas IES-R was used as a screening tool of PTSD. A total HADS score higher than 8 denoted considerable symptoms of anxiety and depression, while a IES-R score above 33 was interpreted as highly suggestive for PTSD.
- → Long COVID was defined as the persistence of physical and/or psychological symptoms at follow-up
- → Adult patients who were evaluated at the post- COVID outpatient clinic, which had been set up in April 2020, between 15 April 2020 and 15 December 2020.
- → The study includes a total of **377** patients
- → The follow-up examination was done at a median of **102** (IQR 86e126) days from acute symptom onset, a median of 79 (IQR 69e102) days from clinical recovery and a median of 56 (IQR 47e74) days from virological clearance.

Source: Bai F, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect. 2021 Nov 9:S1198-

EVIDENCES SO FAR



→ Long COVID was observed in **69%** patients; 81.7% females presented long COVID syndrome.

Within long COVID patients:

→ **37.3%** participants had only one persisting symptom, **32.3% had two** persisting symptoms and **30.4%** had three or more persisting symptoms.

→ 55% reported ongoing physical symptoms only, 38% both physical and psychological symptoms, 7% presented psychological distress solely at follow-up. Physical and psychological manifestations were similarly represented in both genders

→ Most common **physical symptoms**: fatigue 39.5%, exertional dyspnoea 28.9%, musculoskeletal pain 21.2%, “brain fog” 20.2%

→ As far as psychological sequelae: manifestations of **anxiety 18.8%,** depression symptoms **10.6%**

→ 31% of cases the IES-R score resulted pathological, possibly suggesting the presence of PTSD

→ **Women** were characterized by **a higher** proportion of most physical symptoms and all psychological symptoms than men

Source: Bai F, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect. 2021 Nov 9:S1198-

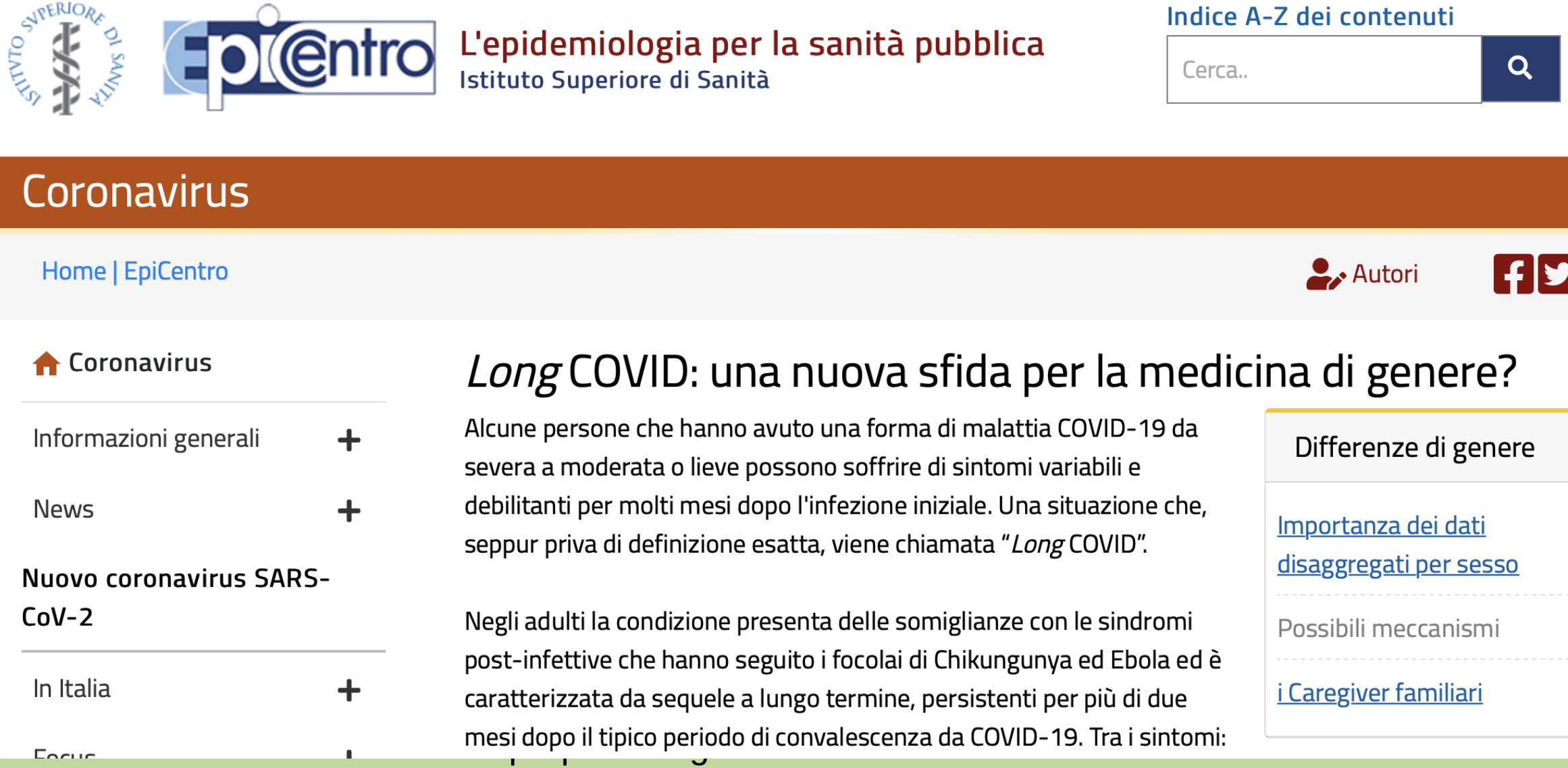
EVIDENCES SO FAR

Table 4
Factors associated with long COVID syndrome by fitting univariable and multivariable logistic regression analyses

Parameters	OR (95%CI)	p	AOR (95%CI)	p
Gender:				
Male	1		1	
Female	2.78 (1.68–4.62)	<0.0001	3.32 (1.78–6.17)	<0.0001
Age, 10 years older	1.03 (1.01–1.04)	0.001	1.03 (1.01–1.05)	0.01
O_2 therapy:				
No O_2	1		1	
O_2 therapy low–high flows	0.67 (0.38–1.19)	0.17	0.39 (0.19–0.82)	0.44
CPAP/NIV/IOT	0.97 (0.55–1.71)	0.91	0.67 (0.29–1.55)	0.85
LOS, each day more	1.01 (0.99–1.03)	0.28	0.998 (0.97–1.03)	0.92
Comorbidities:				
No	1		1	
Yes	1.35 (0.86–2.11)	0.19	1.05 (0.597–1.84)	0.87
Smoking:				
Active	1		1	
Unknown	0.13 (0.03–0.52)	0.004	0.16 (0.04–0.75)	0.31
Never	0.61 (0.37–0.997)	0.05	0.56 (0.31–1.01)	0.41
Former	0.36 (0.14–0.96)	0.04	0.19 (0.06–0.62)	0.002
BMI:				
≥30	1		1	
Unknown	0.29 (0.096–0.91)	0.03	0.13 (0.30–0.53)	0.03
<30	0.55 (2.27–5.06)	0.02	0.55 (0.31–0.98)	0.28
Time from symptoms onset to virological clearance, each day more	1.01 (0.99–1.02)	0.64	0.99 (0.98–1.01)	0.47

Source: Bai F, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect. 2021 Nov 9:S1198-

EVIDENCES SO FAR



Source: Bai F, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clin Microbiol Infect. 2021 Nov 9:S1198-

EVIDENCES SO FAR

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Research paper

Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

Hannah E. Davis[a,1], Gina S. Assaf[a,1], Lisa McCorkell[a,1], Hannah Wei[a,1], Ryan J. Low[a,b,1], Yochai Re'em[a,c,1], Signe Redfield[a], Jared P. Austin[a,d], Athena Akrami[a,b,1,*]

→ **online survey** of people with suspected and confirmed COVID-19, distributed via COVID-19 support groups (e.g. Body Politic, Long COVID Support Group, Long Haul COVID Fighters) and social media (e.g. Twitter, Facebook).

→ Data collected from September 6, 2020 to November 25, 2020.

→ **3762** participants with confirmed or suspected COVID-19, from 56 countries, with illness lasting over 28 days and onset prior to June 2020.

→ the prevalence of 203 symptoms in 10 organ systems and traced 66 symptoms over seven months was estimated. The impact on life, work, and return to baseline health was measured.

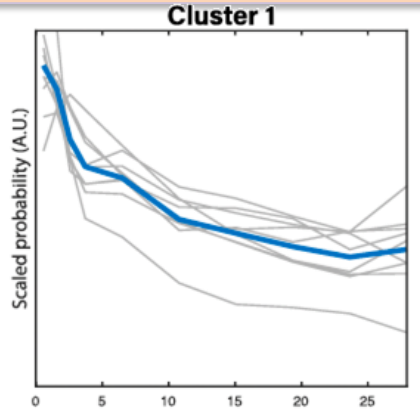
EVIDENCES SO FAR

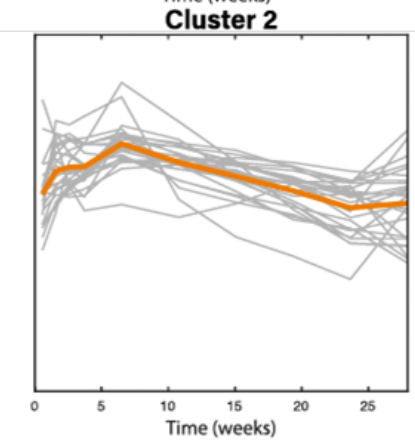
Main findings

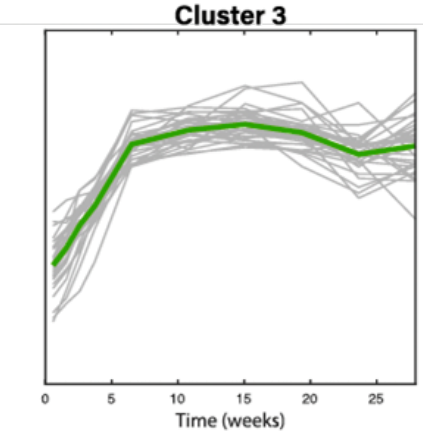
- → For >91% of respondents the time to recovery exceeded 35 weeks.
- → During their illness, participants experienced an average of 56 symptoms, across an average of 9.1 organ systems.
- → Symptoms varied in their prevalence over time, **three symptom clusters were identified each with a characteristic temporal profile.**
- → 85.9% of participants **experienced relapses**, primarily triggered by exercise, physical or mental activity, and stress.
- → 1700 respondents (45.2%) required a reduced work schedule compared to pre-illness, and an additional 839 (22.3%) were not working at the time of survey due to illness.
- → Cognitive dysfunction or memory issues were common across all age groups (~88%).
- → Except for loss of smell and taste, the prevalence and trajectory of all symptoms were similar between groups with confirmed and suspected COVID-19

Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019.

EVIDENCES SO FAR







	CLUSTER 1	CLUSTER 2	CLUSTER 3
Cardiovascular		25. Fainting 19. Pain/burning in chest 33. Tachycardia	49. Bradycardia 38. Palpitations 64. Visibly inflamed/bulging veins
Dermatologic		30. COVID toe	53. Dermatographia 55. Other Skin and Allergy 42. Peeling skin 54. Petechiae 44. Skin rashes
Gastrointestinal	9. Diarrhea 2. Loss of Appetite 4. Vomiting	26. Abdominal pain 18. Nausea	45. Constipation 43. Gastroesophageal reflux
HEENT (Head, ears, eyes, nose, throat)	7. Runny nose 6. Sore Throat		48. Hearing loss 51. Other ear/hearing issues 39. Other eye symptoms 58. Tinnitus 59. Vision symptoms
Immunologic/ Autoimmune			65. New allergies 63. New anaphylaxis reaction
Musculoskeletal		32. Bone ache or burning 21. Muscle aches 15. Tightness of Chest	37. Joint pain 40. Muscle spasms
Neuropsychiatric		20. Acute (sudden) confusion/disorientation 12. Changes to sense of smell and taste 22. Dizzines, unsteadiness or balance issues 31. Hallucinations 29. Headaches and related symptoms 35. Insomnia 27. Other sleeping symptoms 34. Sleep apnea 36. Slurring words/speech	41. All sensorimotor symptoms 47. Brain fog 61. Memory issues 50. Neuralgia (nerve pain) 62. Speech/language issues 52. Tremors 56. Vibrating Sensations
Pulmonary/ Respiratory	3. Dry cough 5. Rattling of breath	14. Breathing difficulty (normal O2 saturation level) 17. Cough with mucus production 10. Coughing up Blood 24. Other Respiratory and Sinus 16. Shortness of Breath 13. Sneezing	
Reproductive/ Genitourinary/ Endocrine			60. All menstrual/period issues 46. Bladder control issues
Systemic	8. Elevated temperature (98.8-100.4F) 1. Fever (>= 100.4F)	11. Chills/flushing/sweats 28. Fatigue 23. Low temperature	39. Other temperature issues 57. Post Exertional Malaise

Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019.

EVIDENCES SO FAR

Since being infected with SARS-CoV-2
- 2.8% (95% confidence interval 2.3% to 3.3%) of respondents reported experiencing varicella zoster reactivation,
- 6.9% reported current/recent Epstein Barr virus (EBV) infection,
- 1.7% reported current/recent Lyme infection,
-1.4% reported current/recent Cytomegalovirus (CMV) infection.

Table 6
Test results for latent disease.

Virus	Positive*	Positive (past)	Negative	Total Tested
Epstein-Barr (EBV)	40	309	231	580
Lyme Disease	7	34	366	407
Cytomegalovirus (CMV)	4	85	204	293

* Includes both current and recent cases.

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TRIALS ONGOING

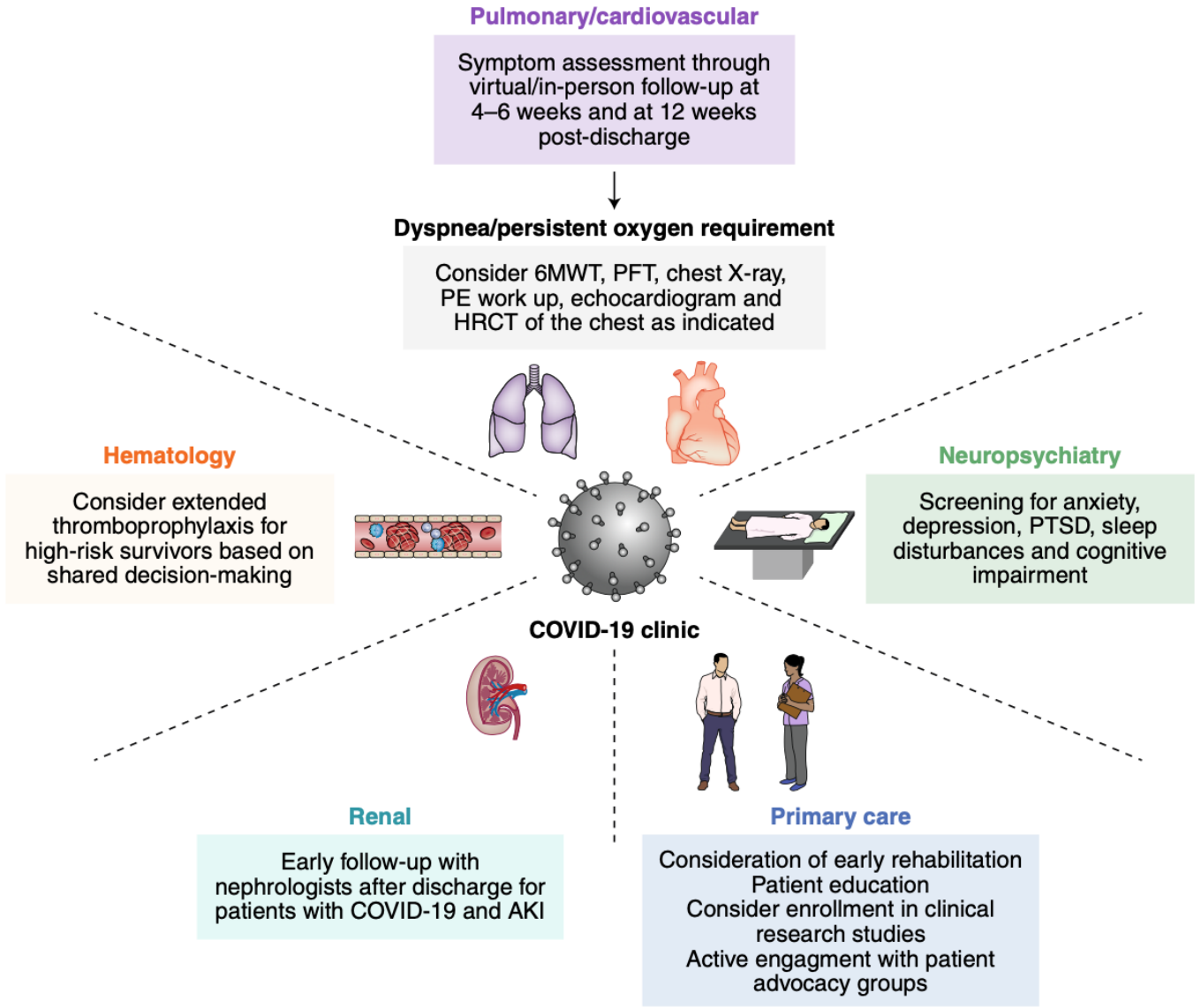
NIH U.S. National Library of Medicine
ClinicalTrials.gov

Lessening Organ Dysfunction With VITamin C - COVID-19 (LOVIT-COVID); ClinicalTrials.gov Identifier: NCT04401150, Université de Sherbrooke (Toronto). Intravenous vitamin C administered in bolus doses of 50 mg/kg mixed in a 50-ml solution of either normal saline (0.9% NaCl) or dextrose 5% in water (D5W) during 30 to 60 minutes, every 6 hours for 96 hours (i.e. 200 mg/kg/day and 16 doses in total).

The Effects of a Multi-factorial Rehabilitation Program for Healthcare Workers Suffering From Post-COVID-19 Fatigue Syndrome; ClinicalTrials.gov Identifier: NCT04841759, Medical University of Vienna. SARS-CoV2 survivor who attends the exercise program and suffers from post-COVID-19 fatigue Syndrome according to the Post-Covid-19-Functional Scale (PCFS). 8 week exercise program, nutritional & psychological consultation

Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate COVID-19; ClinicalTrials.gov Identifier: NCT04343651, University of California, Los Angeles. two-arm, randomized, double blind, placebo controlled multicenter study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with mild-to-moderate symptoms of respiratory illness caused by coronavirus 2019 infection. Patients will be randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo. Leronlimab (PRO 140) and placebo will be administered via subcutaneous injection.

Interdisciplinary management in post COVID-19 clinics



Nalbandian, A., *et al.* Post-acute COVID-19 syndrome. *Nat Med* **27,** 601–615 (2021)

RESEARCH QUESTIONS

- What is the precise epidemiology of long covid and how will novel variants of Covid-19 affect the epidemiology and severity of long Covid?
- What are the major risk factors for long Covid and how do we best reduce an individual's risk of developing long term post-Covid-19 symptoms?
- Which symptoms, or set of symptoms, can we use to classify long Covid, clinically and phenotypically, with the aim of improving diagnosis and management?
- What is the optimal treatment and management strategy for long covid and is this strategy non- specific or will it require targeting and tailoring to specific patients?
- Which presentation of long Covid in children, pregnant woman and older people?
- Which therapies possible for long Covid?
- Different virus variants differents long Covid ?
- Role of Vaccines in long covid ?
- Which models of care for taking in charge these patients?

What is going on in Italy

Il **decreto-legge Sostegni bis** approvato dal Consiglio dei Ministri in data 21 maggio 2021 istituisce un **protocollo nazionale di monitoraggio** che prevede, senza oneri a carico dell'assistito, l'esecuzione di prestazioni di **specialistica ambulatoriale**, contenute nei Livelli Essenziali di Assistenza, ritenute per il monitoraggio, la prevenzione e la diagnosi precoce di eventuali esiti o complicanze legati alla pregressa malattia da COVID-19.

Le prestazioni previste nel decreto comprendono:

- una valutazione di parametri ematochimici,
- l'emogasanalisi,
- esami che valutano la funzione cardiologica (ECG Holter, Ecocardiogramma)
- esami che valutano la funzione pneumologica (Spirometria, diffusione alveolo capillare del CO, TC del torace)
- valutazioni specialistiche.

Per pazienti più anziani, in considerazione delle condizioni di fragilità, è stata prevista **la valutazione multidisciplinare.**

Per i pazienti sottoposti a terapia intensiva/subintensiva è stato previsto il **colloquio psicologico**

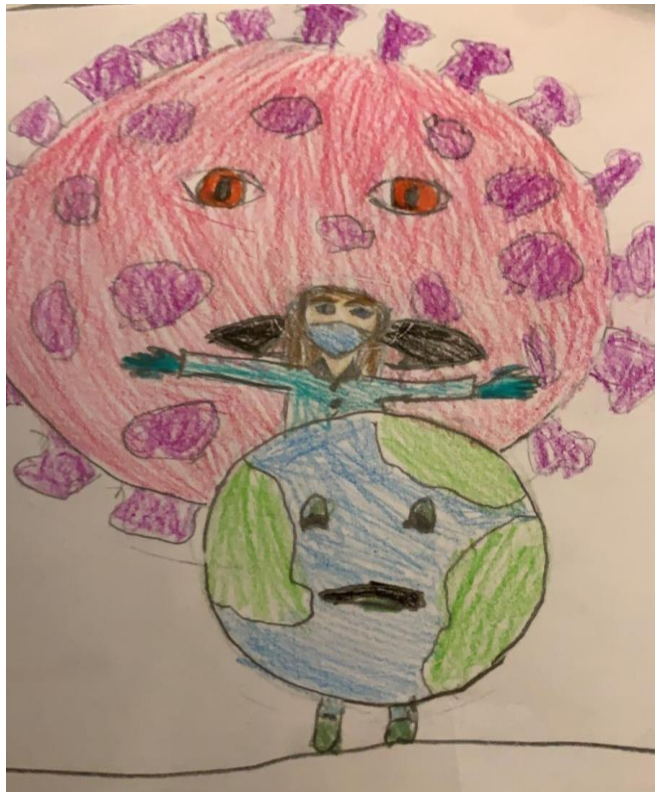
DECRETO SOSTEGNI BIS

Il protocollo si riferisce specificamente ai pazienti che hanno avuto la **necessità di un ricovero ospedaliero per un quadro severo di COVID-19** (polmonite interstiziale da SARS-CoV-2, con relativa insufficienza respiratoria con o senza necessità di terapia intensiva/subintensiva), *in quanto questi soggetti, spesso anziani e polipatologici, presentano un maggior rischio di eventuali sequele e complicanze legate alla pregressa malattia da COVID-19.*

What is going on in Italy

Il **decreto-legge Sostegni bis** indica anche l'importanza di definire studi mirati di raccolta dati per il Long COVID-19, in considerazione del fatto che l'esigenza di comprensione, analisi e studio degli esiti della malattia COVID-19 sono particolarmente rilevanti per gli effetti in termini di coordinamento risposte del Servizio Sanitario Nazionale.

Tali studi devono prevedere una raccolta dati basata su parametri clinici, laboratoristici e strumentali uniformi e omogenei sul territorio nazionale.



Grazie per l’attenzione!

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