COREB mission nationale
Coordination Opérationnelle Risque Epidémique et Biologique

https://www.coreb.infectiologie.com/

CLINIC & PHYSIOPATHOLOGY

ANRS MALADIES INFECTIEUSES ÉMERGENTES

https://reacting.inserm.fr/

Scientific update on COVID-19

Updated on 22nd July 2021

Redaction committee

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CLINICAL

Questions:

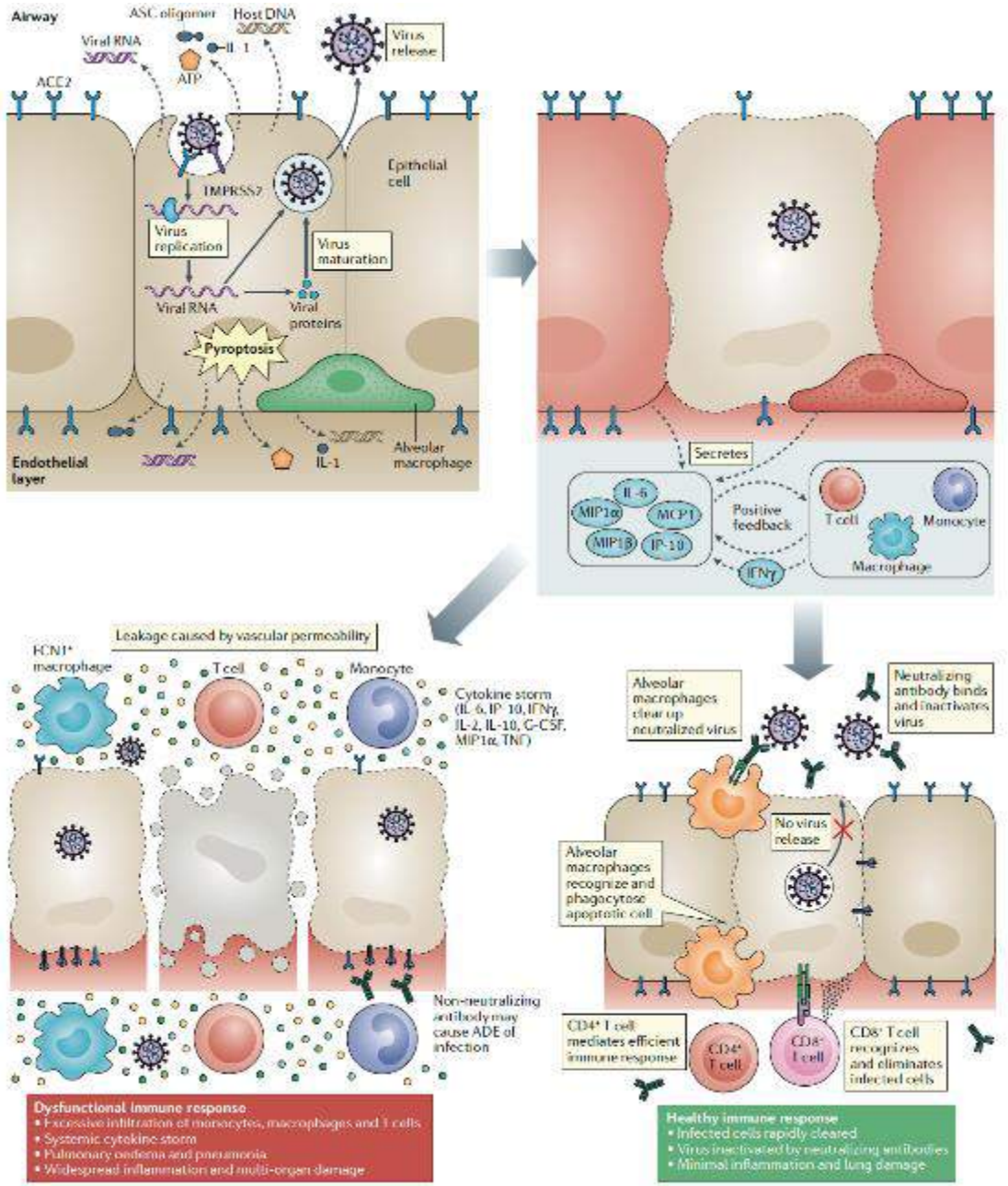
- What are the mechanisms of action of SARS-CoV-2?
- What are the cellular and humoral host responses against SARS-CoV-2 infection?
- What are the clinical features of COVID-19 in adults and children?
- Is there multiple-organ damages associated to COVID-19?
- What are the long term effects of Covid-19?

Physiopathology

- **Binding** to host cell through ACE2 receptor by spike (S) protein
  - Lung, Kidney, Heart, Brain …
- **Fusion** of the viral envelope with cellular membrane (TMPRSS2)
- Virus **hijacks** the cell machinery
- Host cell → **pyroptosis** and release damage-associated molecular
  - ATP, nucleic acid, ASC oligomer …
- **Inflammatory response**
  - Pro-inflammatory cytokines & chemokines: IL-6, IP-10, MCP1 …
- Attract other cells (monocytes, macrophage, T cells …)
  - Pro-inflammatory feedback loop
  - Eliminates the infected cells before the virus spreads

BUT sometimes (10 to 15 days after symptom onset)

- Accumulation of immune cells
  - **Hyper-inflammatory response**
  - Lung damage and multi-organ damage

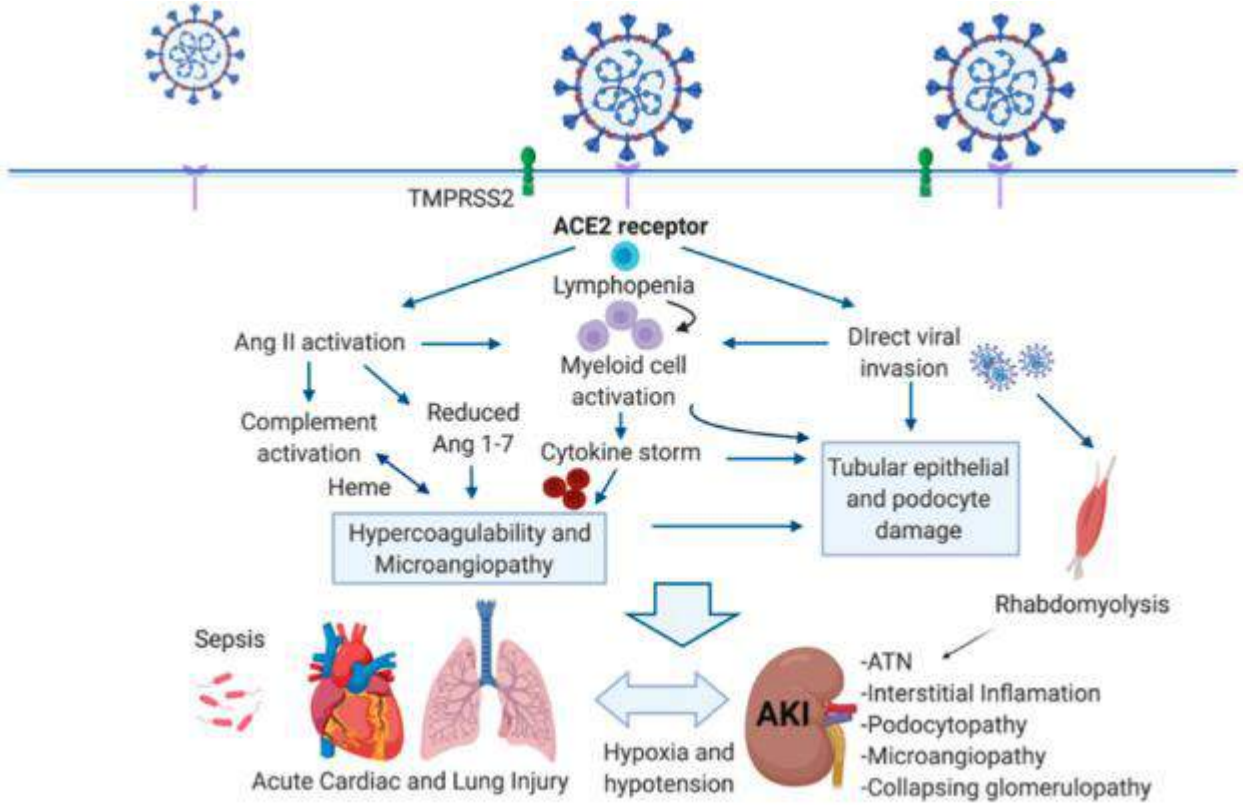


Tay MZ, *et al. Nat Rev Immunol*. Apr 2020

Physiopathology

- SARS-CoV-2 targets ACE2 receptor and infected cells via « priming »
  - Renin- Angiotensin system dysregulation
  - Activation of innate and adaptative immune pathways
  - Cytokine storm
  - coagulation pathway → hypercoagulation

- Multi-organ damage
  - Kidney, heart, lungs, vessel, immune system ….



Battle D, *et al. JASN*. May 2020

Auto-antibodies & type I IFN & COVID-19

Neutralizing auto-Abs against type I IFN could lead to life-threatening COVID-19 pneumoniae?

987 patients hospitalized for life-threatening COVID-19

663 patients asymptomatic or mildly symptomatic (COVID-19)

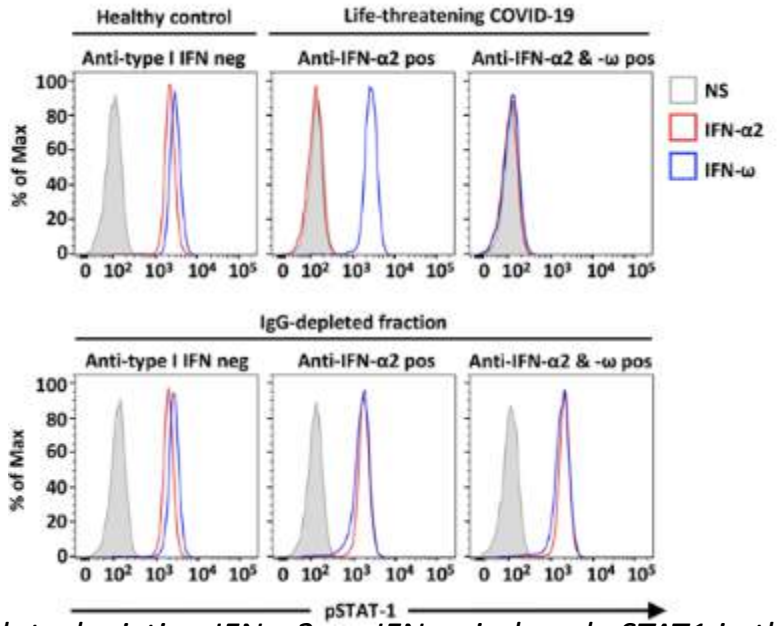
1227 healthy controls

<u>Auto-antibodies against IFN-α2 and/or IFN-ω</u>?

- 135 of 987 critically ill patients had IgG auto-Abs against at least one type I IFN.

<u>Auto-Abs neutralize IFN-α2 and/or IFN-ω in vitro</u>?

- 101 of 987 life-threatening COVID-19 had neutralizing IgG auto-Abs against at least one type I IFN:
  - 51% against IFN-α2 and IFN-ω,
  - 36% against IFN-α2 only,
  - 13% against IFN-ω only.
- Auto-Abs detected in only 4 of 1227 controls and none of 663 asymptomatic or mild-symptomatic patients.



FACS plots depicting IFN-α2- or IFN-ω-induced pSTAT1 in the presence of 10% healthy control or anti-IFN-α2/ω- auto-Abs-containing patient plasma (top panel) or an IgG-depleted plasma fraction (bottom panel).

IgG depletion from patients with auto-Abs restored normal pSTAT1 induction after IFN-α2 and IFN-ω stimulation.

Auto-antibodies & type I IFN & COVID-19

Auto-Abs against all IFN-α subtypes?

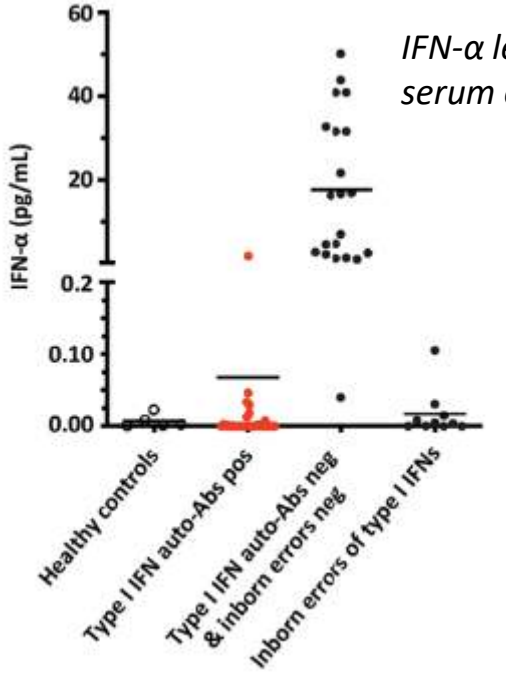
- All patients (22) with neutralizing auto-Abs against IFN-α2 had auto-Abs against all 13 IFN-α subtypes
- **Early treatment with IFN-α is unlikely to be beneficial**

Auto-Abs against IFN-β?

- 1,9% of the patients had auto-Abs against IFN-β
- All were severe COVID-19
- **Treatment with injected or nebulized IFN-β may have beneficial effects**

In vitro and in vivo?

- In patients with neutralizing auto-Abs against IFN-α2, the baseline levels of type I IFN-dependent transcripts were low,
- Neutralizing in vitro & in vivo
- Suggesting a pre-existing or concomitant biological impact in vivo



IFN-α levels in the plasma or serum of patients.

→ **Auto-Abs against type I IFNs are a cause of severe SARS-CoV-2 infection.**

→ Provides an explanation for the major sex bias in severe COVID-19 and the increase in risk with age

→ Clinical and therapeutic implications

Bastard P, et *al. Science*. Sep 2020

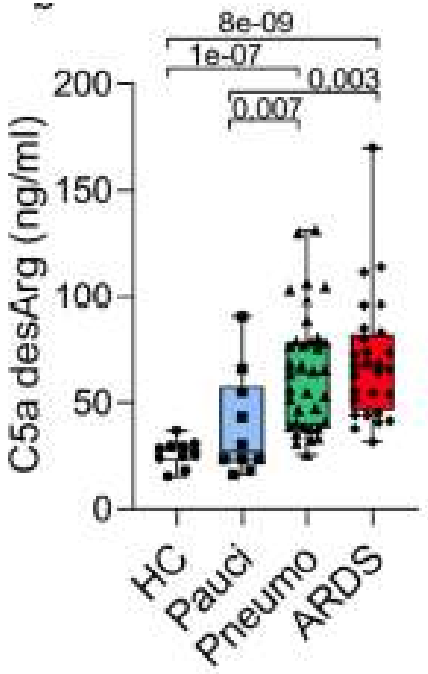
C5a-C5aR1 axis & COVID-19

C5a anaphylatoxin and its receptor C5aR1 play a key role in the initiation and maintenance of inflammatory response

- Recruiting and activating neutrophils and monocytes

82 individuals: 10 healthy control, 10 paucisymptomatic COVID-19, 34 with pneumonia & 28 with ARDS due to SARS-CoV-2.

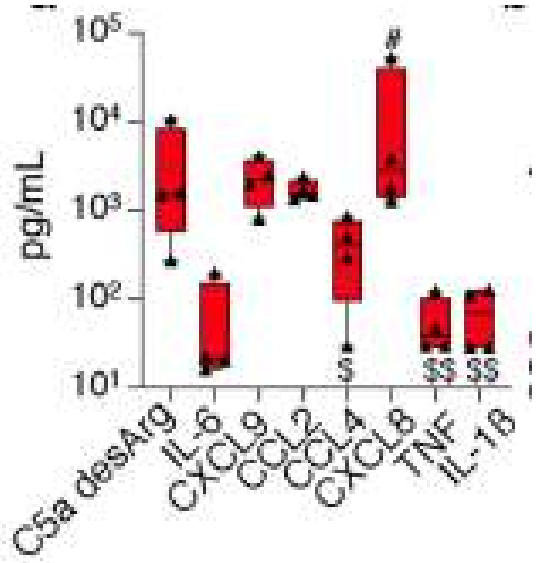
Concentration of C5a desArg in plasma



An increase in plasma C5a levels proportional to COVID-19 severity.

Increased systemic and local complement pathway activities on the peripheral blood.

C5a is detected in lung sample from COVID-19 patients



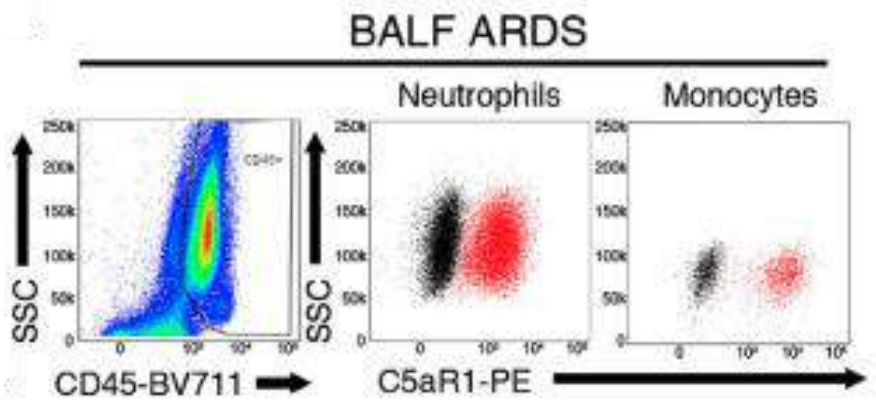
Saliva specimens could be effective in the diagnosis of COVID-19

C5a-C5aR1 axis & COVID-19

C5a production leads to the chemo-attraction and activation of myeloid cells in the lung → release of inflammatory cytokines.

Possible that the vasculitis associated with severe COVID-19 is linked to the production of C5a.

$CD45^+$ immune cell infiltration in BALF
C5a-R1 expression (red)



Neutrophils and monocytes in BALF expressed C5aR1.

Potential therapeutic strategy → C5a-C5aR1 axis blockade.

Avdoralimab = mAb against C5aR1.

In vitro:

- inhibited C5a-induced neutrophil activation,
- Inhibited the C5a-induced migration of neutrophils.

In mice:

- Mice received an intranasal instillation of recombinant human C5a → developed ALI.
- Avdoralimab prevented albumin release in BALF
- Avdoralimab inhibited the increase in IL-6, TNF and CCL2.
- Avdoralimab inhibited ALI in mice

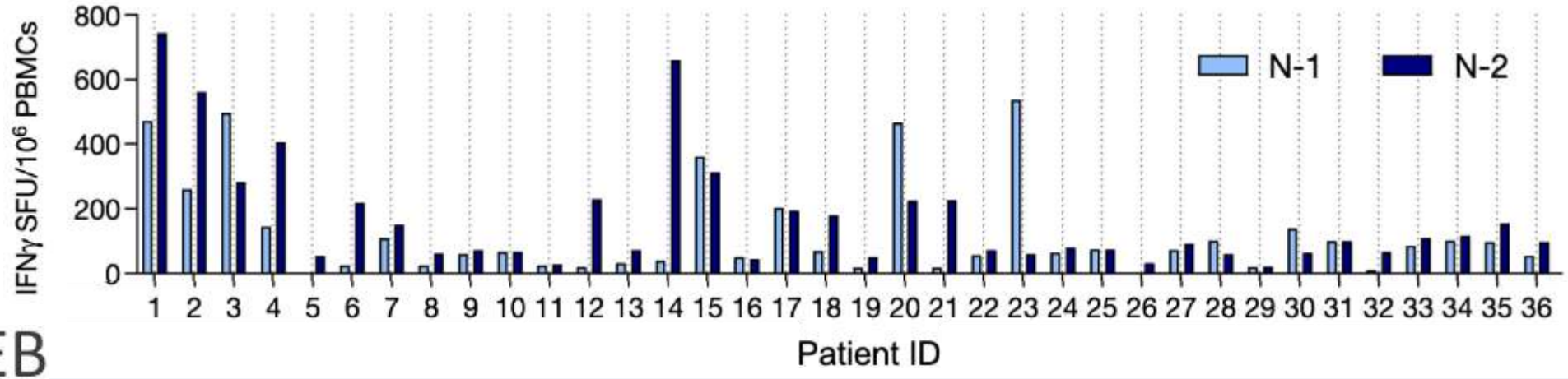
CR5a-C5aR1 axis blockade might be used to prevent the excessive lung inflammation and endothelialitis associated with ARDS in COVID-19 patients

SARS-CoV-2 specific T cell immunity

SARS-CoV2 specific T cells in patients with COVID-19

- 36 individuals after recovery from mild to severe COVID-19.
- T cell response against selected structural (N) and non-structural proteins (NSP7, NSP13 & ORF1).
- Use of an unbiased method with overlapping peptides.
- Peripherical blood mononuclear cell (PBMC) of the 36 patients were stimulated for 18h with the different peptides pools.

- **In 36 out of 36 individuals, found specific T cell that recognized multiple regions of the N-protein (IFNγ spot)**



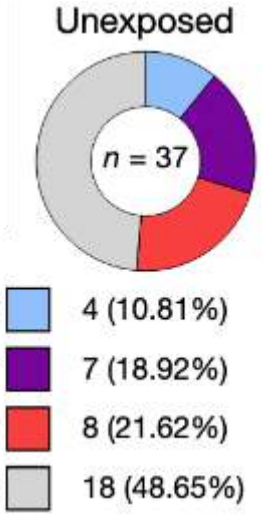
Le Bert N, *et al. Nature*. Jul 2020

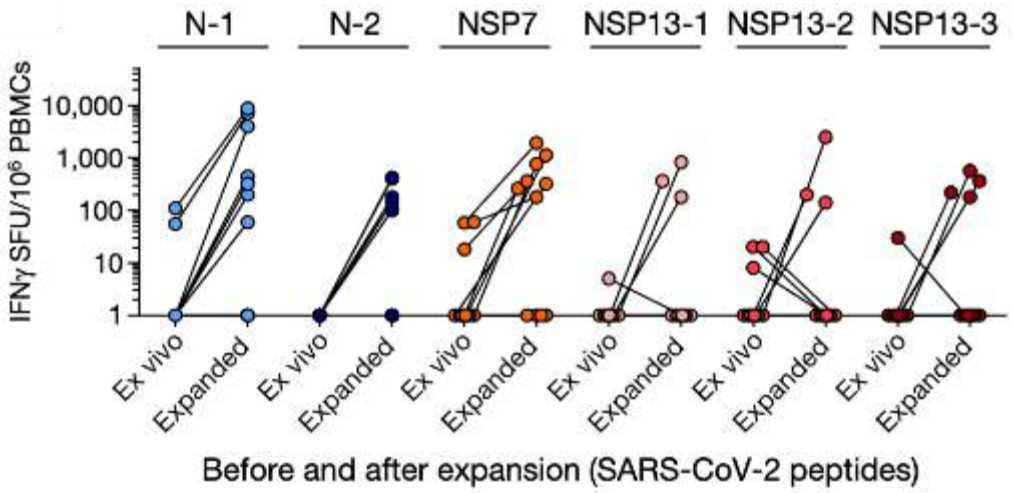
SARS-CoV-2 specific T cell immunity

SARS-CoV2 specific T cells in unexposed donors

- 37 donors: not exposed to SARS-CoV and SARS-CoV-2
- **Detection of SARS-CoV-2-specific IFNγ responses in 19 out of 37 unexposed donor.**
- The unexposed group showed a mixed response to the N protein or to NSP7 and NSP13.
- These SARS-CoV-2-reactive cells from unexposed donors had the capacity to expand after stimulation with SARS-CoV-2-specific peptides.

The percentage of individuals with N-specific responses





→ Infection with betacoronaviruses induces multi-specific and long lasting T cell immunity against the structural N protein.

Le Bert N, *et al. Nature*. Jul 2020

SARS-CoV-2 specific T cell immunity

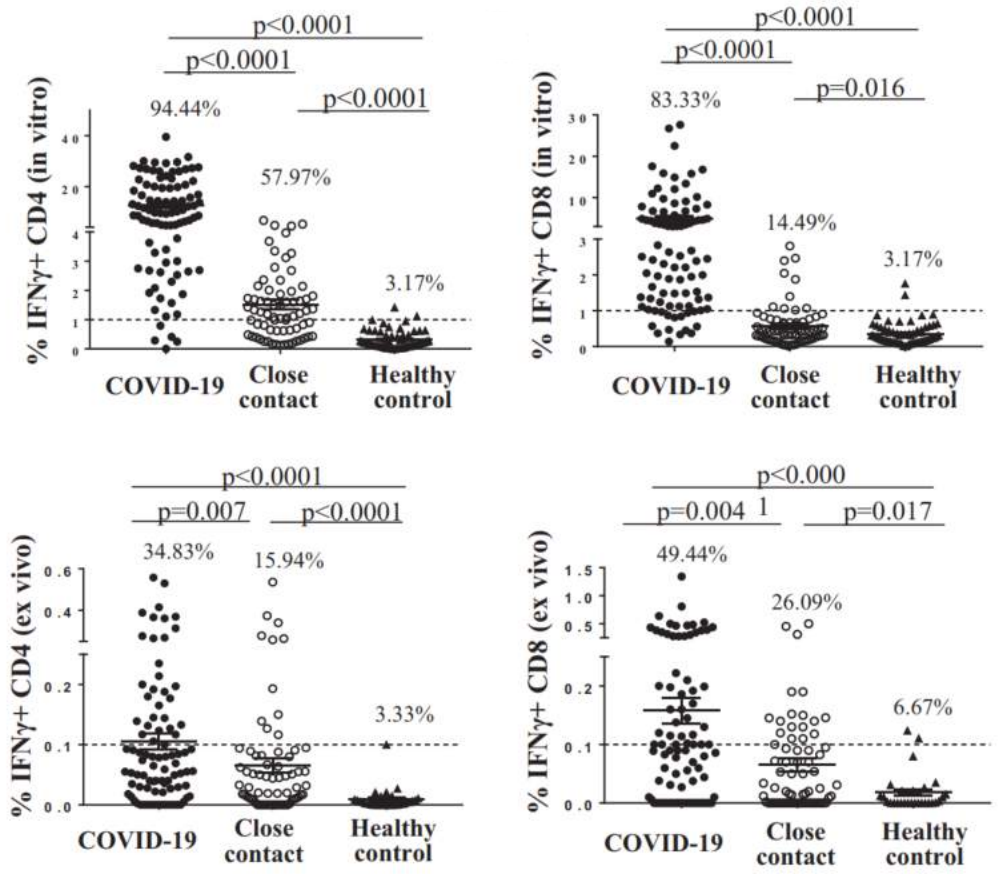
Samples: peripheral blood mononuclear cells (PBMCs) from:

- 90 COVID-19 patients, collected 48-86 days after disease onset
- 69 close contacts (NAT-neg, SARS-CoV-2 IgG/IgM-neg), collected 48-86 days after contact with COVID-19 patient
- 63 healthy donors, collected in September 2019

in vitro: PBMC expansion and 10 day-stimulation with peptide pool targeting spike, membrane and envelope glycoproteins, nucleocapsid, RNA polymerase ORF1ab

ex vivo: PBMCs stimulated overnight with peptide pool

- 94.44% CD4+ and 83.33% CD8+ SARS-CoV-2 specific T cells of COVID-19 patients, and 57.97% CD4+ and 14.49 CD8+ of close contacts underwent in vitro expansion.
- Healthy donors showed minimal cross-reactive T cells from other coronaviruses, but at a significantly lower frequency than T cell immunity of close contacts.
- *ex vivo* data corroborated these results and showed significant differences between T cell memory pools and INFγ production of patients and close contacts.
- Memory T cell immunity is detectable in both symptomatic and asymptomatic COVID-19 patients, with no significant difference in T cell pool size and qualities.
- Following *in vitro* expansion, virus-specific memory CD4+ T cell pool correlated with titers of IgG against S RBD and N protein.



INFγ expressing T cell exantion upon in vitro and ex vivo PBMC stimulation with peptide pools encompassing viral epitopes

SARS-CoV-2-specific memory T-cell immunity was observed in COVID-19 patients and close contacts at D48-86

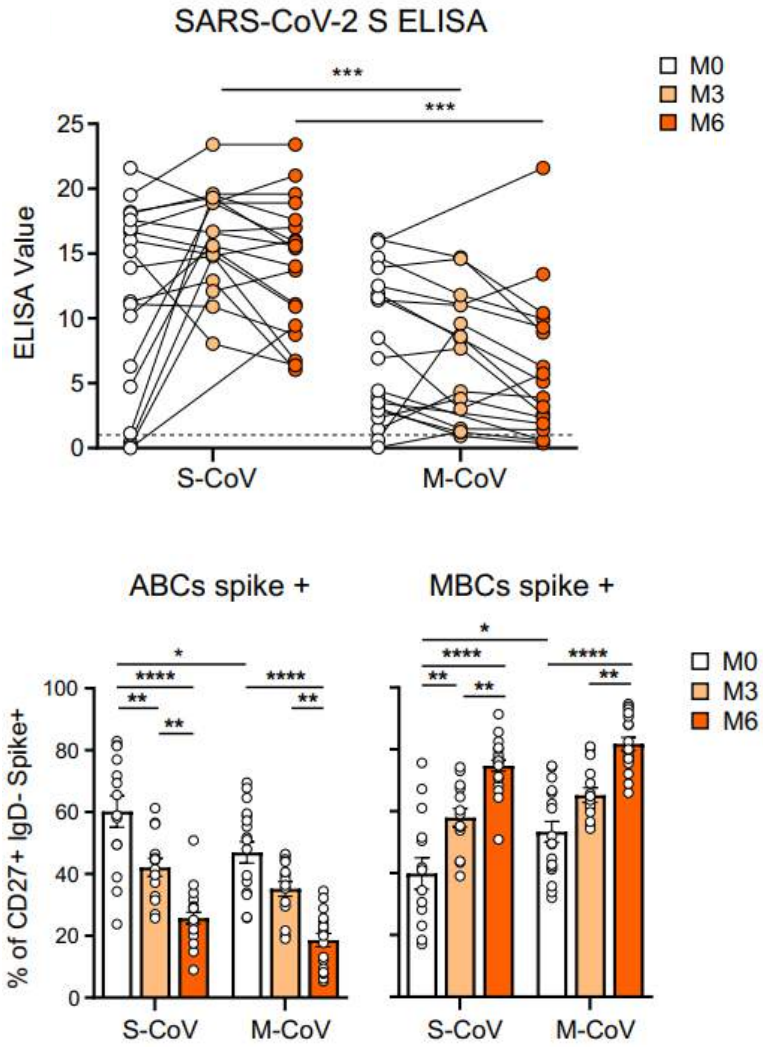
Wang Z, *et al. Nature Commun*. Mar 2021

SARS-CoV-2 specific B cell immunity

21 Severe (S)-Cov vs 18 Mild (M)-Cov patients assessed at 3 and 6 months

- S-specific IgG are stable with time in both cohorts, but appear significantly higher in S-CoV patients
- At 6 months, B cells **mostly resided in the memory B cell (MBC) compartment** in both cohorts, while S-specific antigen secreting cells were marginally detectable. S-specific MBCs were at higher frequencies S-CoV patients, but present also in M-CoVs.
- In both S-CoVs and M-CoVs, the proportion of S-specific activated B cells **(ABCs) steadily decreased over time, along with an increase of S-specific classical, resting MBCs**.

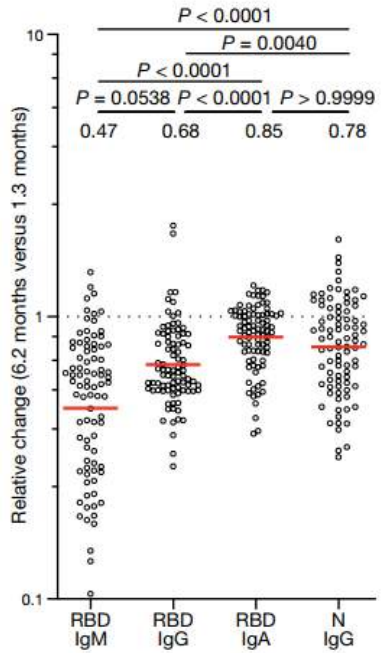
A robust and stable S-specific MBC population is induced in both M- and S-CoV patients



SARS-CoV-2 specific B cell immunity

87 participants assessed at 1.3 and 6.2 months after infection

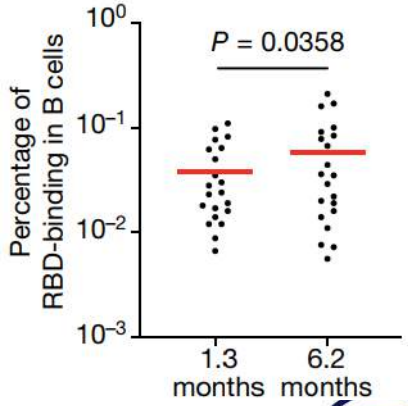
- Antibody response:
  - Anti-RBD and ELISA anti-N antibodies in plasma decreased significantly between 1.3 and 6.2 months.
  - IgM showed the greatest decrease in anti-RBD reactivity (53%), followed by IgG (32%); anti-RBD IgA decreased by only 15% and anti-N IgG levels by 22%.
  - Individuals with persistent post-acute symptoms had significantly higher levels of anti-RBD IgG and anti-N total antibody.
  - Neutralising activity: NT50 was 401 and 78 at 1.3 and 6.2 months, respectively → 5-fold decrease. Neutralizing activity was directly correlated with IgG anti-RBD.



Relative change in plasma antibody levels

- B cell response:
  - The % of RBD-binding memory B cells increased marginally between 1.3 and 6.2 months (n=21).
  - although the magnitude of the RBD-specific memory B cell compartment is conserved between 1.3 and 6.2 months after infection, there is extensive clonal turnover and antibody sequence evolution, consistent with prolonged germinal centre reactions.

Percentage of antigen-specific B cells



Gaebler C. *et al.* Nature. Jan 2021

SARS-CoV-2 specific B cell immunity

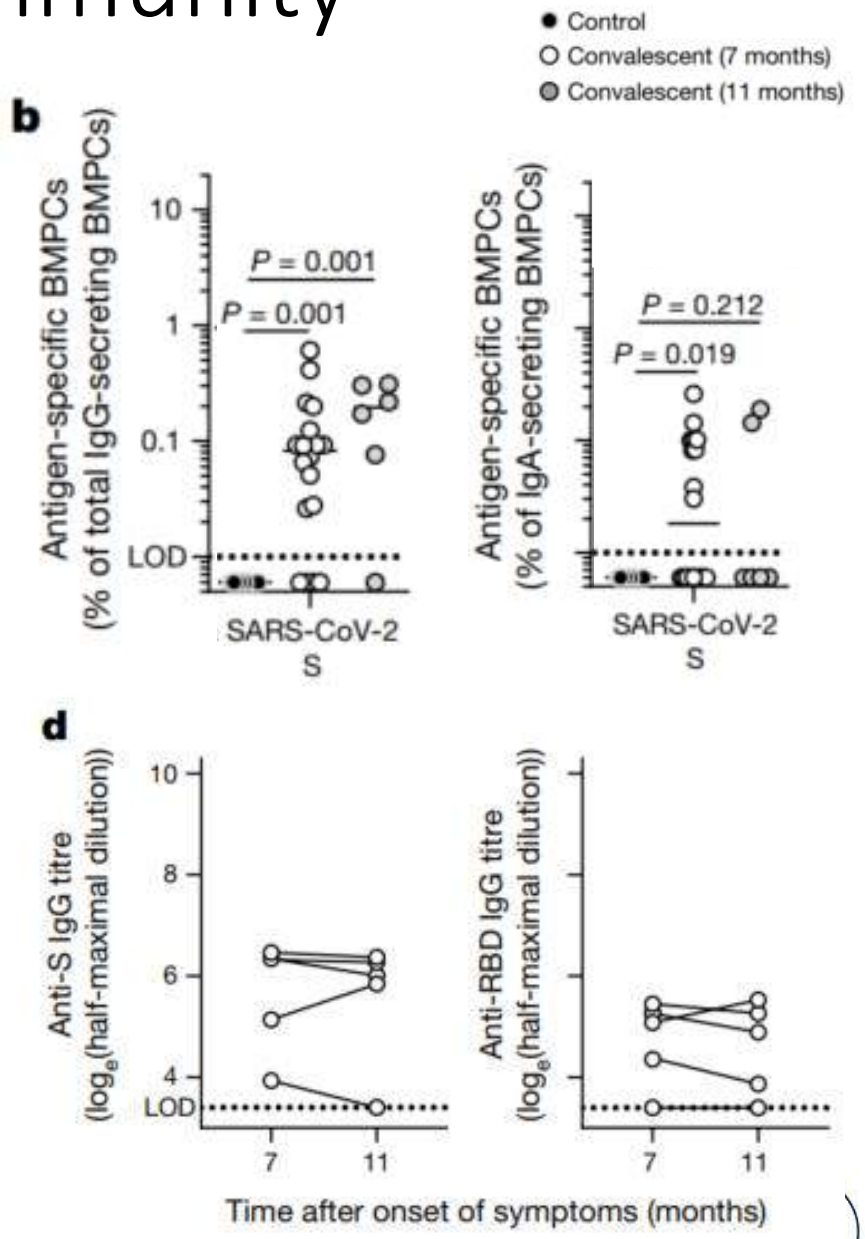
Durable serum antibody titres are maintained by long-lived plasma cells: non-replicating, antigen-specific, detected in the bone marrow long after antigen clearance

Longitudinal analysis of circulating anti-SARS-CoV-2 serum antibodies in 77 covalescent individuals:

- 74/77 has detectable serum titres 1 month after symptom onset
- Ab titres decayed rapidly between 1-4 months, then decline slowed at 4-11 months

Induction of S-binding long-lived BMPCs (analysis of bone marrow aspirates obtained 7 and 11 months after infection)

- At 7 months, IgG- and IgA-secreting S-specific BMPCs were detected in 15 and 9 of the 19 convalescent individuals, respectively, but not in any of the 11 control individuals
- At 11 months, frequencies of anti-S IgG BMPCs were stable (n=5), and frequencies of anti-S IgA BMPCs were stable in 4/5 individuals
- Frequencies of anti-S IgG BMPCs showed a modest but significant correlation with circulating anti-S IgG titres at 7-8 months after symptoms onset, consistent with the long-term maintenance of antibody levels by these cells
- BMPCs detected in convalescent individuals were in a quiescent state

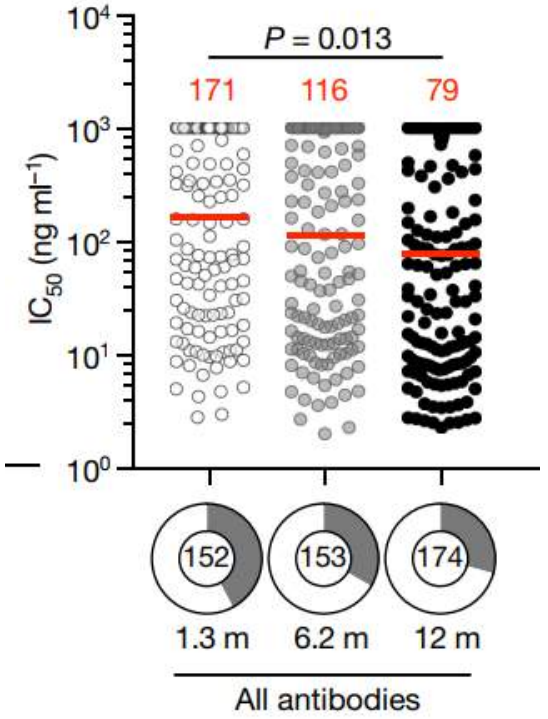


Turner JS. *et al.* Nature. May 2021

SARS-CoV-2 specific B cell immunity

- Analysis of anti-SARS-CoV-2 immune response of 63 convalescent individuals 12 months after infection (mainly mild)
- 26 of them received at least one dose of a mRNA vaccine

- **Plasma SARS-CoV-2 antibody reactivity**
  - Neutralising titres remains relatively unchanged 6-12 months after infection. Vaccination boosts this activity by nearly 50-fold
  - Neutralising activity against variants Alpha, Iota, Gamma, and especially Beta, was generally lower than against WT. Vaccination still boosted neutralising titers above those reported in infected individuals or in vaccinated naïve individuals.
- **Memory B cells**
  - RBD-specific B cells are present 12 months after infection. Vaccination boosted circulating B cells (8.6-fold average increase).
  - Clonal evolution continues 6-12 months after infection, regardless of vaccination state. Vaccination induced re-expansion of RBD-specific memory B cell clones, but not to additional accumulation of somatic mutations
- Monoclonal antibodies at 12 months after infections showed **increased affinity, avidity, and potency**, regardless of vaccination status.
- Over time, non-neutralising antibodies are removed from the repertoire, while clonal evolution allows acquisition of neutralisation breadth (increasing activity against variants).



SARS-CoV-2-neutralising activity of neutralising antibodies (pseudovirus neutralisation assay). Pie charts illustrate fractions of neutralising antibodies. Red line and numbers indicate geometrical mean values.

Immunological assessment

Cohort study of 178 confirmed SARS-CoV-2 infection

Asymptomatic infection = 20,8% (37/178 patients)

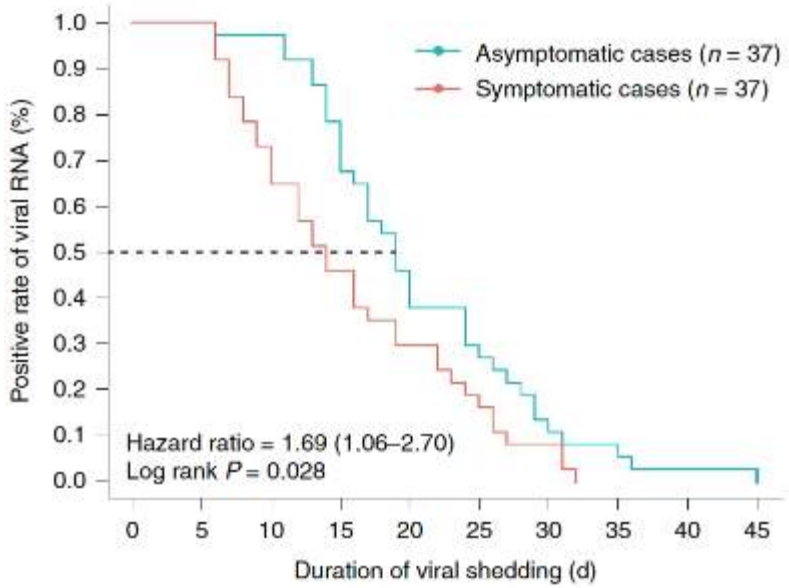
37 asymptomatic matched with 37 mild symptomatic patients

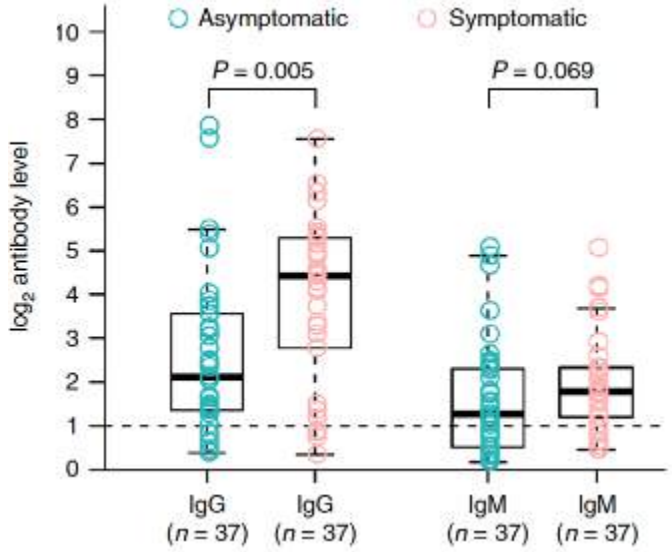
Viral shedding:

- Initial Ct value were similar in the two groups
- Asymptomatic group had a significantly longer duration of viral shedding (19 days versus 14 days; *p*=0.028)

IgG and IgM, 3 to 4 weeks after exposure (acute phase):

- IgG positivity rates similar between the two groups (81 and 84% of asymptomatic and symptomatic, respectively)
- IgG levels in the asymptomatic group (median S/CO, 3.4; IQR, 1.6–10.7) were lower than the symptomatic group (median S/CO, 20.5; IQR, 5.8–38.2; *p* = 0.005)
- IgM levels were similar in the two groups (62 and 78% of positivity of asymptomatic and symptomatic, respectively)





Long QX, *et al. Nat Med.* Jun 2020

Immunological assessment

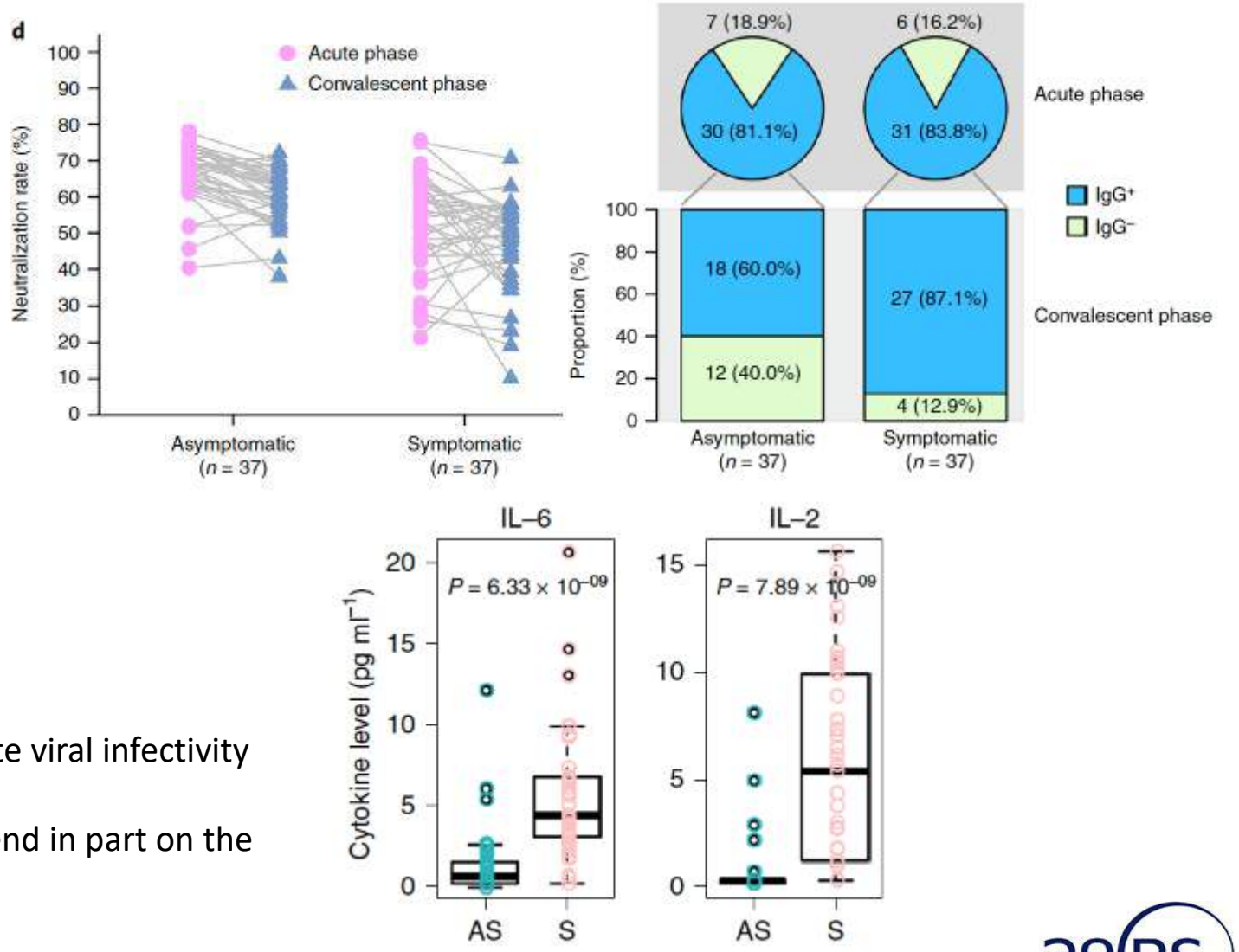
IgG and IgM, 8 weeks after exposure (convalescent phase)

- A decline of IgG is observed among >90% of patients
- 40% and 13% of asymptomatic individuals IgG+ at the acute phase became seronegative

Similar observations were made for neutralizing antibodies

Asymptomatic patients had a reduced inflammatory response with lower concentration of circulating cytokines and chemokines

The relatively low seroprevalence and its decrease within 2-3 months after infection highlights the potential limits of serology for diagnostic and the need of timely serosurvey



Limits

→Viral RNA shedding does not equate viral infectivity (not assessed in this study)

→Serological observations may depend in part on the commercial assay used

Long QX, *et al. Nat Med.* Jun 2020

Antibody response to SARS-CoV-2

Cohort of 149 cases and contacts: 111 with SAR-CoV-2 PCR positive + 46 close contacts.

Free of symptoms at least 14 days at the time of sample collection.

→ Convalescent plasma samples

- Binding to SARS-CoV-2 RBD and trimetric S protein?

IgG response: 78% showed anti-RBD and 70% anti-S

IgM response: 15% showed anti-RBD and 34% anti-S

Anti-RBD IgG levels → moderately correlated with age and severity

- Neutralizing activities? → the half-maximal neutralizing titer (NT_{50})

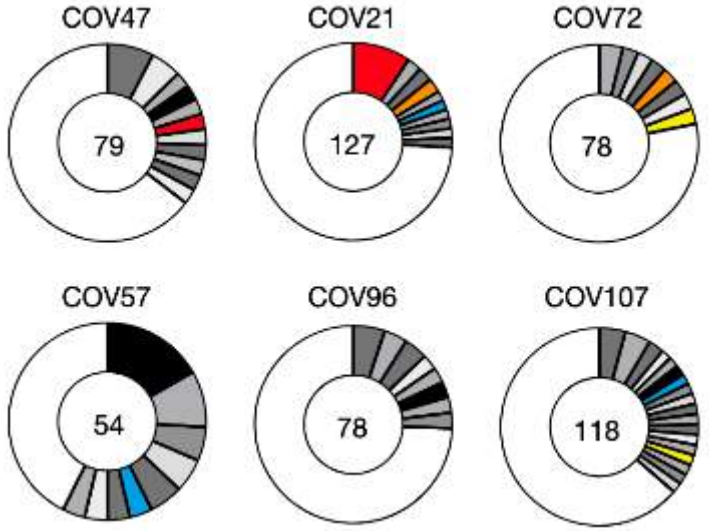
Generally low: NT_{50}<50 in 33% of samples and < 1000 in 79%

- Nature of the antibodies elicited by SARS-CoV-2 infection?

Expanded clones of viral antigen-binding B cells in all tested individuals convalescent after COVID-19.

95% of the antibodies tested bound to SARS-CoV-2 RBD with an average EC_{50} of 6,9 ng/ml

The distribution of antibody sequences from six individuals The number in the inner circle indicates the number of sequences analyzed for the individual denoted above the circle. White indicates sequences isolated only once, and grey or colored pie slices are proportional to the number of clonally related sequences.



Robbiani DF, et *al. Nature*. Aug 2020

Antibody response to SARS-CoV-2

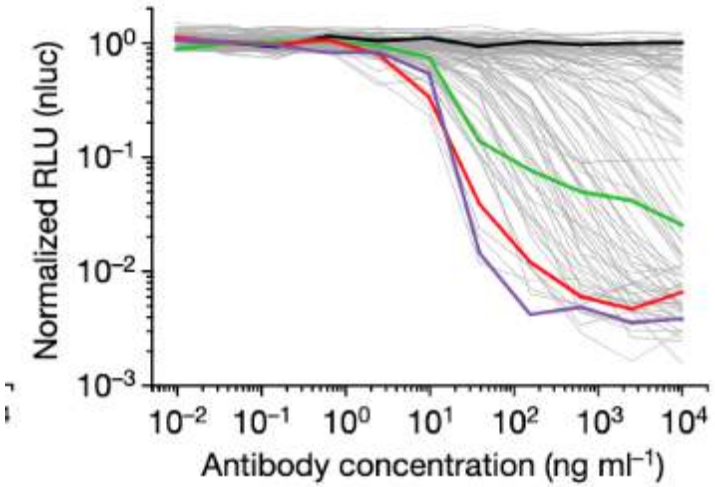
- <u>Do monoclonal antibodies have neutralizing activity?</u>

Among 89 RBD-binding antibodies tested, we found 52 that neutralized SARS-CoV-2 pseudovirus with IC50 values ranging from 3 to 709 ng/ml.

Potent neutralizing antibodies found irrespective of the NT_{50} values.

→ Even individuals with modest plasma neutralizing activity have rare IgG memory B cells that produce potent SARS-CoV-2-neutralizing antibodies.

The normalized relative luminescence values for cell lysates of 293TACE2 cells 48 h after infection with SARS-CoV-2 pseudovirus in the presence of increasing concentrations of monoclonal antibodies.



Plasma neutralizing activity is low in most convalescent individuals

Recurrent anti-SARS-CoV-2 RBD antibodies with potent neutralizing activity can be found in all individuals.

A vaccine designed to elicit such antibodies could be broadly effective.

Neutralizing antibodies to SARS-CoV-2 infection

Understanding the protective effects of the immune response ⇔ neutralizing effects of SARS-CoV-2 antibodies

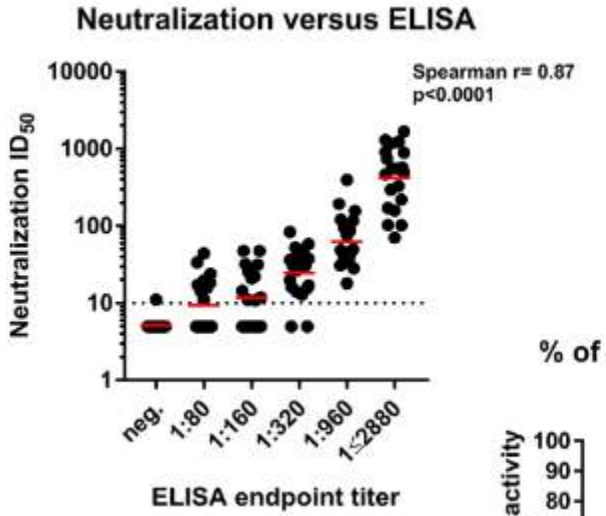
Mont Sinai Health System screen individuals for antibodies to SARS-CoV-2

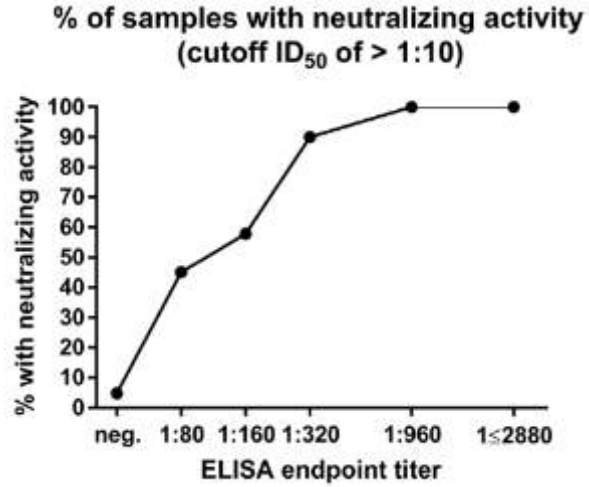
- 72,401 individuals screening : 30,082 positive & 42,319 negative
- Vast majority of positive individuals have moderate-to-high titer of anti-spike antibodies.
- Seroconverters = titer of 1:320 or higher

<u>Neutralizing effects</u> → quantitative microneutralization assay

- 120 samples of known ELISA titers ranging from negative to ≥1:2880
- **Neutralization titers significantly correlated with spike-binding titers**
- 90% of seroconverters make detectible neutralizing antibody responses

Neutralizing activity of serum samples in relation to ELISA titers.





Wajnberg A, et *al. Science*. Oct 2020

Neutralizing antibodies to SARS-CoV-2 infection

Longevity of the antibody response:

- Slow decline in titer over time
- Initial increase in individuals with a initial titer of 1:320 or lower
- Titer remains relatively stable for several months after infection (~ 5)
- Good correlation between neutralization and ELISA titers on day 148

Correlation between specific level of antibody and risk of (re)infection?

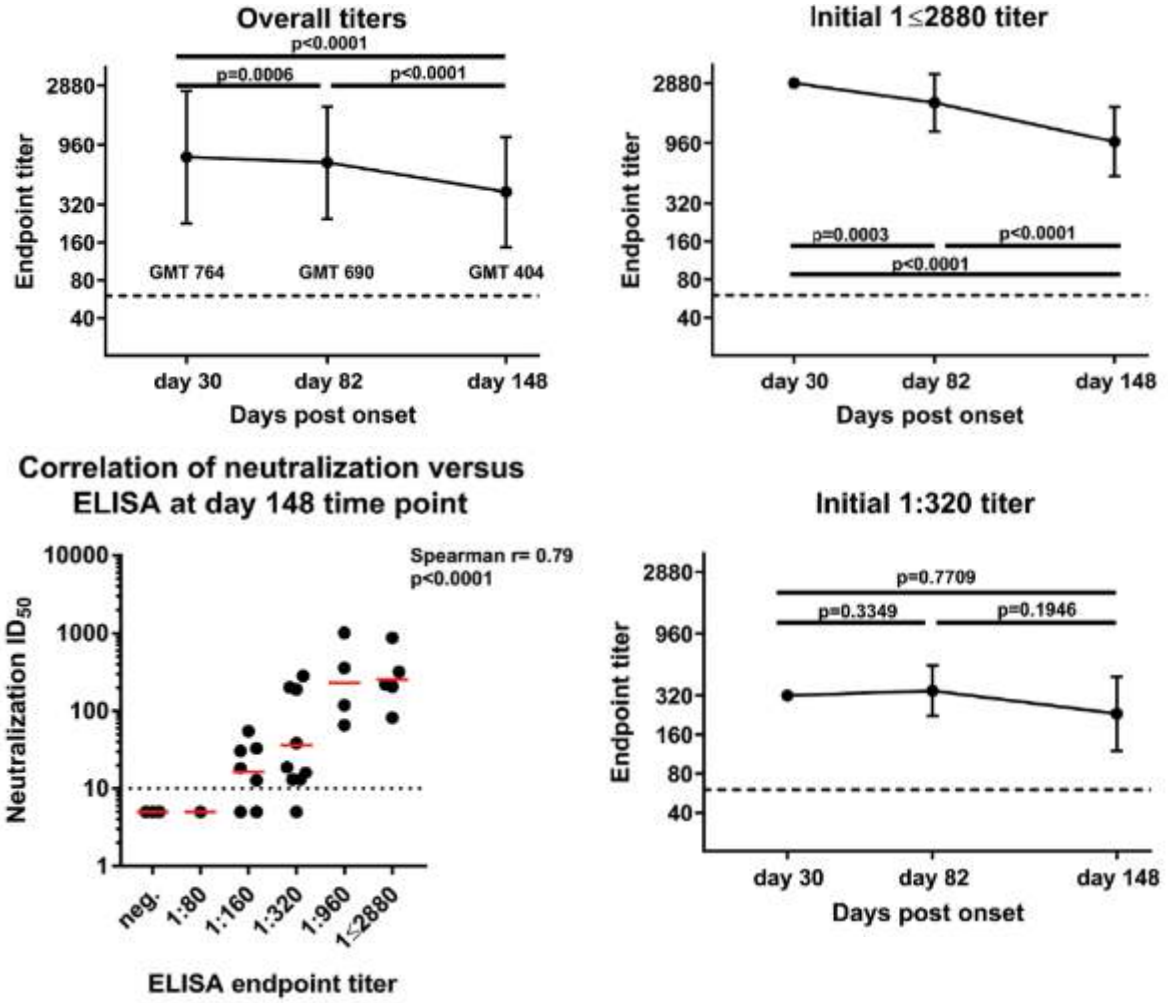
- Still unclear for infection with SARS-CoV-2 **in humans**

→ Individuals who have recovered from mild COVID-19 experience relatively robust antibody response to the spike

→ Correlation between spike-binding titers and neutralization titers

→ Stable antibody titers over 3 months and modest declines at the 5-month time point

Antibody titer stability over time



Cannot provide conclusive evidence : do this antibody responses protect from reinfection?

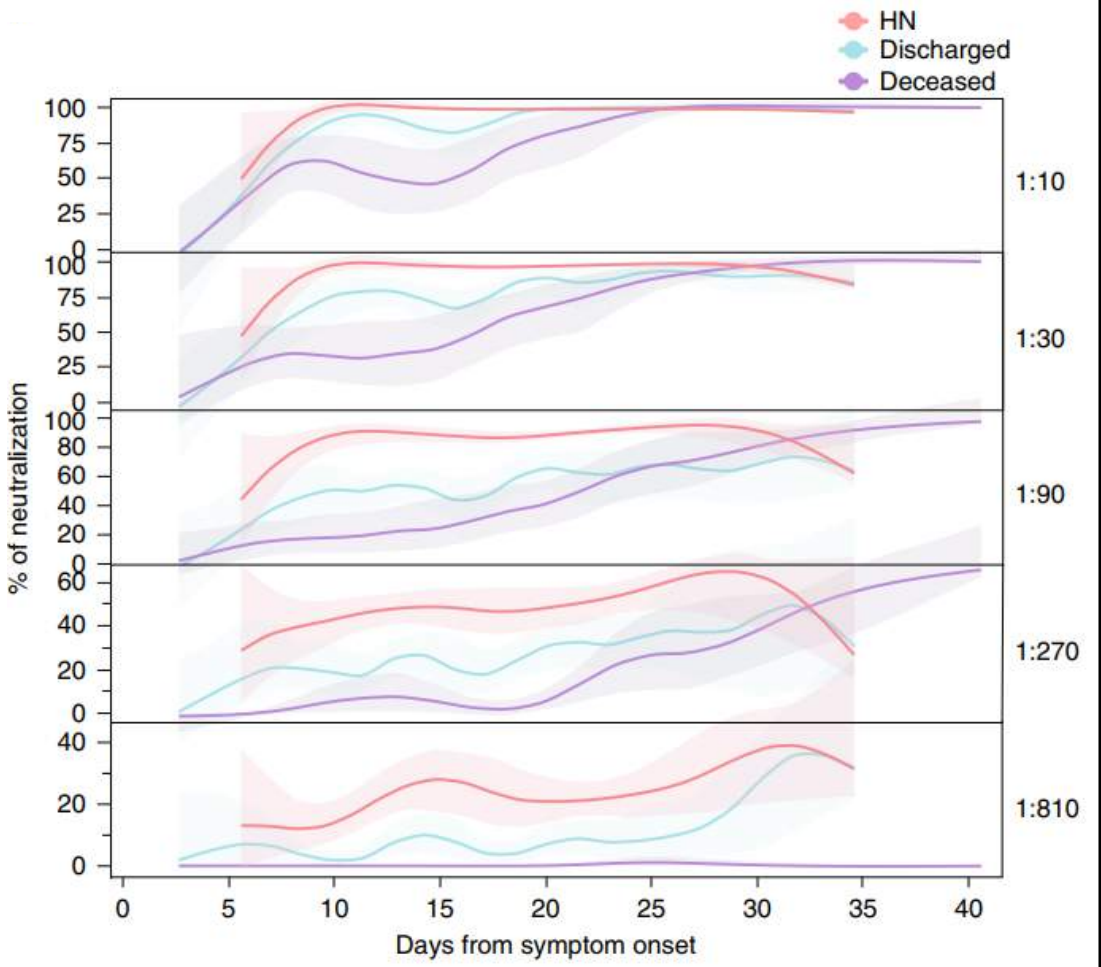
Wajnberg A, et *al. Science*. Oct 2020

Neutralising antibodies and COVID-19 outcomes

Test population: 185 hospitalised patients, 44 non-hospitalised control patients

- Anti-S IgG levels, but not anti-RDB IgGs, are positively correlated with disease severity. However, among hospitalised patients, deceased and discharged survivors did not show differences in virus-specific IgG or IgM.
- Anti-S IgG antibodies positively correlated with COVID-19 severity, along with the circulating levels of monocytes and eosinophils, but independent of circulating T cells, Tfh cells or viral load.
- Death from COVID-19 correlated with a delay in the development of virus-specific IgG and virus clearance.
- Discharged patients show faster NAb kinetics and a higher peak than deceased patients. Early NAb production correlated with improving clinical signs and lower mortality than late neutralizers.

  → Clinical trajectories and outcomes do not correlate with the levels of NAb produced over the disease course but with **the timing of NAb production**



Longitudinal data plotted over time of neutralization capacity among discharged (light blue), deceased (purple) and High Neutraliser (red) patients at the experimental six-fold serially dilutions (from 1:3 to 1:2,430)

Long term humoral response against SARS-CoV-2

Anti-SARS-CoV-2 antibody persistance in COVID-19 patients after 6 months (1/3)

- 532/9542 individuals tested positive for pan-immunoglobulins (Wuhan).
  - Seroprevalence adjusted for sex, age group and district: 6.92%
  - 1st follow-up at 2 months, 2nd at 6 months

	IgG	IgA	IgM	Neutralising Ab
Baseline (n=532)	532 (100%)	84 (15.8%)	69 (13.0%)	212 (39.8%)
1st follow-up (n=363)	354 (97.5%)	36 (9.9%)	14 (3.9%)	162 (44.6%)
2nd follow-up (n=454)	413 (91.0%)	16 (3.5%)	7 (1.5%)	187 (41.2%)

- **Titers** of pan-Ig, IgG , IgM and IgA continuosly decreased significantly accross the study period

- Seroconversion rates of neutralising Ab at baseline and second follow-up:

	Baseline	2nd follow-up	P value
Confirmed (n=27)	18 (66·7%)	16 (59·3%)	0·54
Symptomatic (n=55)	35 (63·6%)	35 (63·6%)	1·000
Asymptomatic (n=253)	88 (34·8%)	103 (40·7%)	0·38
Total (n=335)	141 (42·1%)	154 (46·0%)	0·55

- The proportion of patients positive for IgM, IgA and IgG decreased in all three subgroubs

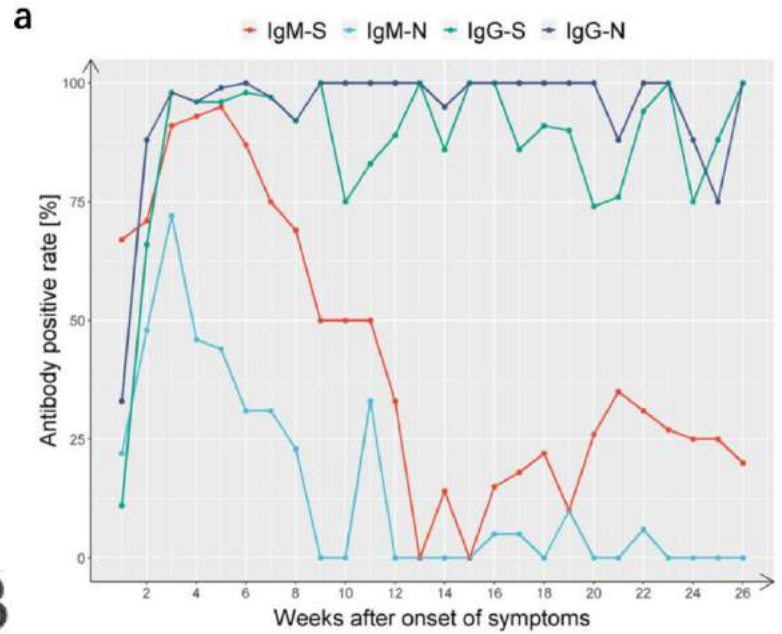
He Z. *et al. Lancet*. Mar 2021

Long term humoral response against SARS-CoV-2

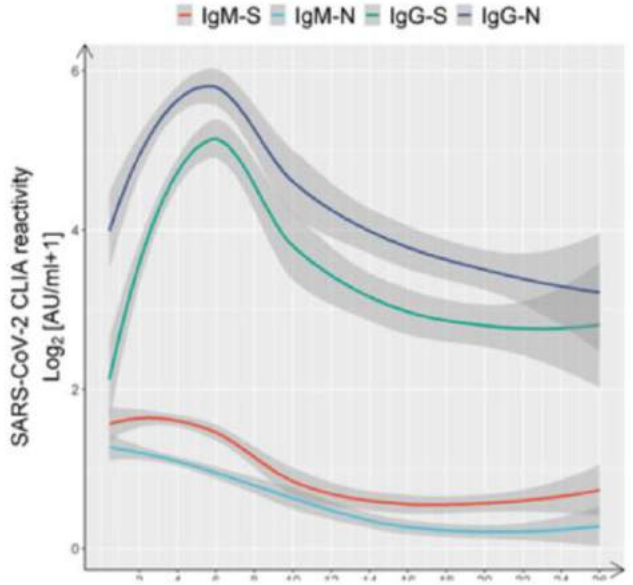
Anti-SARS-CoV-2 antibody persistance in COVID-19 patients after 6 months (2/3)

IgM and IgG responses against RBD of S and N proteins over 26 weeks (W) in 349 symptomatic COVID-19 patients, Wuhan

- Antibody positivity rate:
  - W1: IgM-S (67%) > IgG-N (33%) > IgM-N (22%) > IgG-S (11%)
  - IgM-S peaked (95%) at W5, then decreased below 35% after W13
  - IgM-N reached 72% at W3, then became undetectable at W10-12
  - IgG-N and IgG-S reached high positivity rate at W2 and 3 respectively, and remained high over the study period



- Antibody titers:
  - IgM-N and IgM-S peaked at W3 and 4, and fell below cutoff value at W9 and 12
  - IgG-N and IgG-S peaked at W4 and 5, respectively, underwent a contraction phase (W6-14) and then stabilised and high level over the study period
- IgG-RBD-S titer was highly positively correlated with neutralising activity



Wu J, *et al. Nature Commun*. Mar 2021

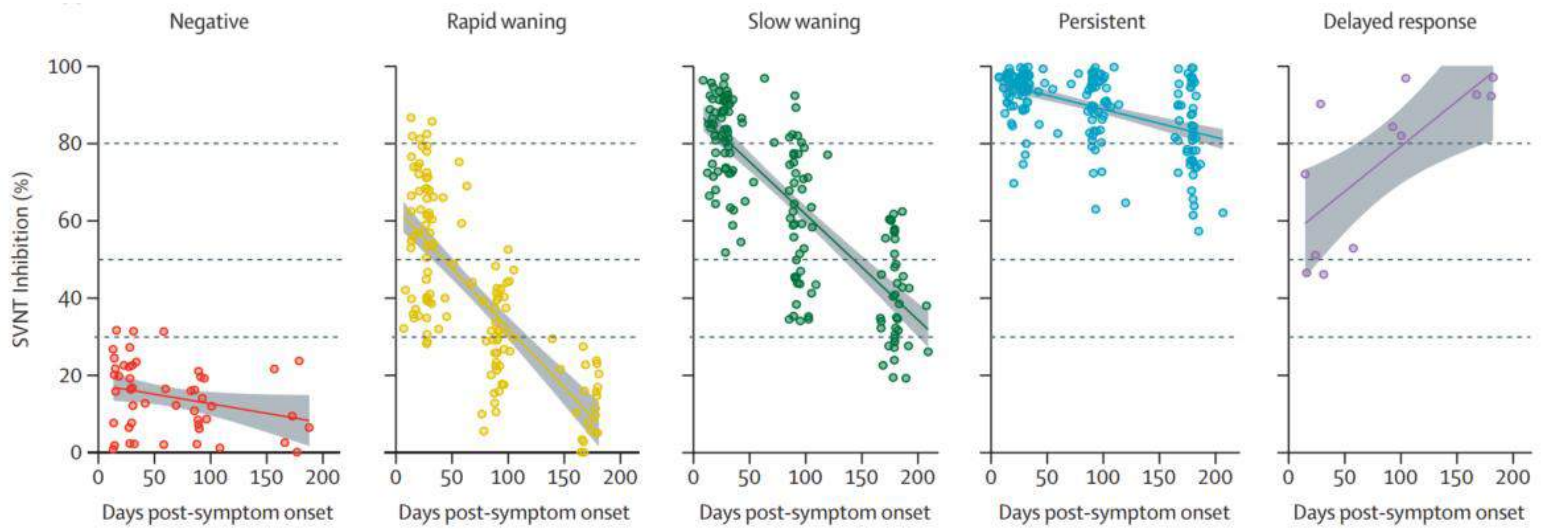
Long term humoral response against SARS-CoV-2

Anti-SARS-CoV-2 antibody persistance in COVID-19 patients after 6 months (3/3)

Neutralising antibodies (nAB) in 164 COVID-19 patients, Singapore, 180 days post symptom onset

- 5 patterns of nAb dynamics observed:
  - Negative – did not reach 30% inhibition level): 12%
  - Rapid waning – positive early on but seroverting: 27%
  - Slow waning – remain nAb-positive over study period: 29%
  - Persistent – minimal nAb decay 32%
  - Delayed response – increase of nAb ≥90 days post-symptom onset: 2%

- Persistent group showed higher levels of pro-inflammatory cytokines (IFN-γ, IL-12p70, and IL-17A) and chemokine (IP-10), and growth factors as compared with other groups at 180 days
- All patients maintained specific (NP, M, S) T-cell response at 180 days
- Disease severity independently was associated with persistent antibody levels



Linear regression model of each grouping for neutralising antibody level. Dashed lines represents 30%, 50%, and 80% of sVNT percentage inhibition.

Chia WN, *et al. Lancet Microbe*. Mar 2021

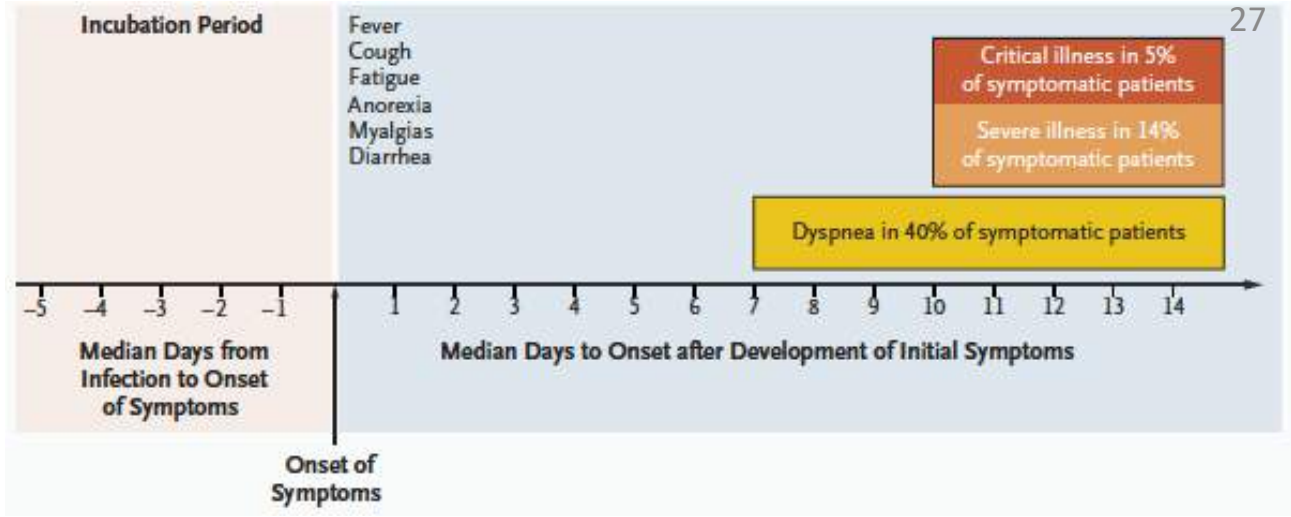
COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

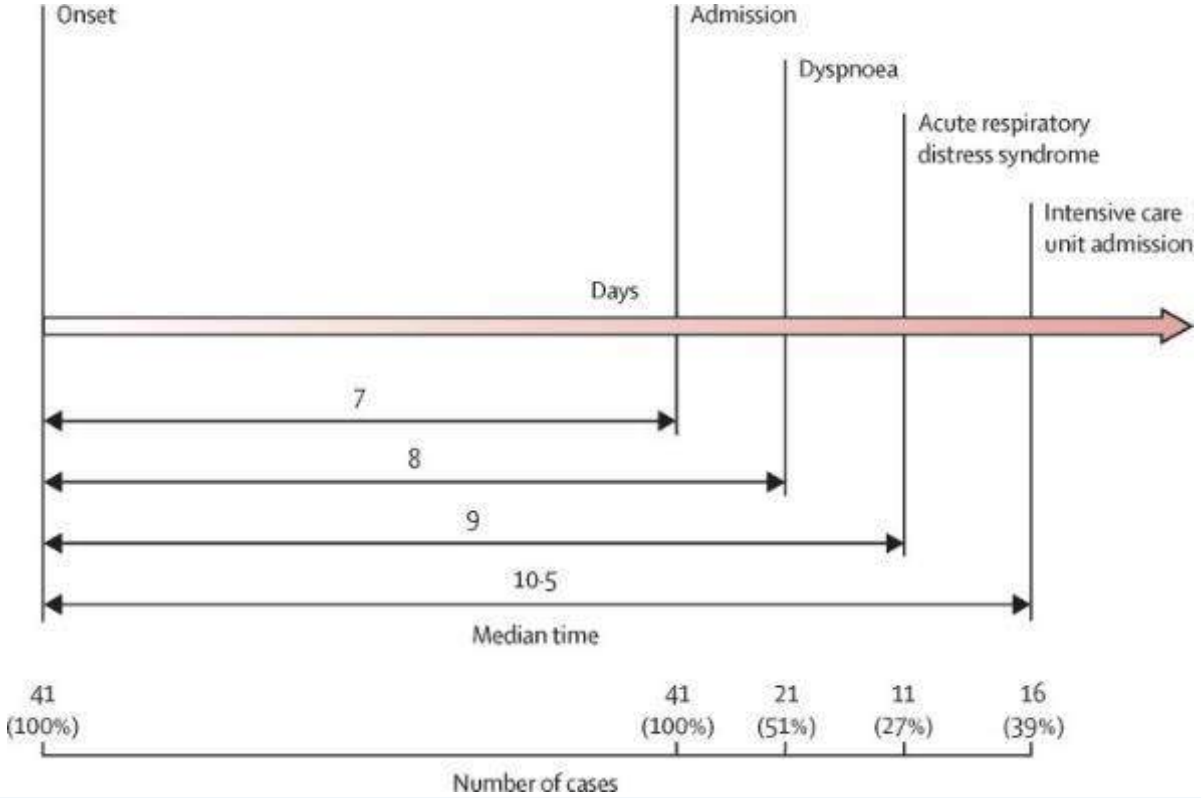
anrs MALADIES INFECTIEUSES ÉMERGENTES

Clinical features

Median time (41 patients admitted to hospital)

- From onset of symptoms to first hospital admission
  - **7 days** [4,0–8,0]
- From illness onset to dyspnea
  - **8 days** [5,0–13,0]
- To ARDS
  - **9 days** [8,0–14,0]
- To ICU admission
  - **10,5 days**
- To mechanical ventilation
  - **10,5 days** [7,0–14,0]





Huang C, *et al. Lancet*. Feb 2020

Berlin DA, *et al. NEJM*. May 2020

Clinical features

China, **1 590 hospitalized** patients (13,4% of all cases reported in China)

Age (median): 48,9 ± 16,3 years

Male: 904 (57,3 %)

Comorbidities

- Hypertension: 16,9 %
- Diabetes: 8,2 %
- CHD: 3,7 %
- Cerebrovascular disease: 1,9 %
- COPD: 1,5 %
- Chronic kidney disease: 1,3 %
- Malignancy: 1,1 %

Symptoms

- Fever: 88 %
- Cough: >70 %
- Fatigue: 42,8 %
- Shortness of breath: 20,8 %
- Myalgia/arthralgia: 17,5 %
- Pharyngalgia: 14,7 %
- Headache: 15,4 %
- Chill: 12,2 %
- Nausea/vomiting: 5,8 %
- Diarrhea: 4,2 %

Abnormal chest CT: 1130 (71,1 %)

Outcomes

- Critical illness: 131 (8,24 %)
- ICU admission: 99 (6,23 %)
- Mechanical ventilation: 50 (3,1 %)

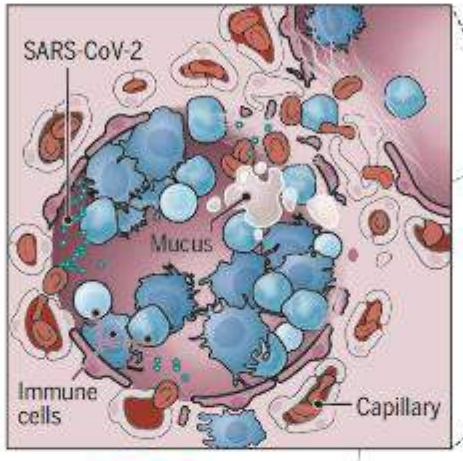
Case fatality rate: 50 (3,1 %)

Organ damage

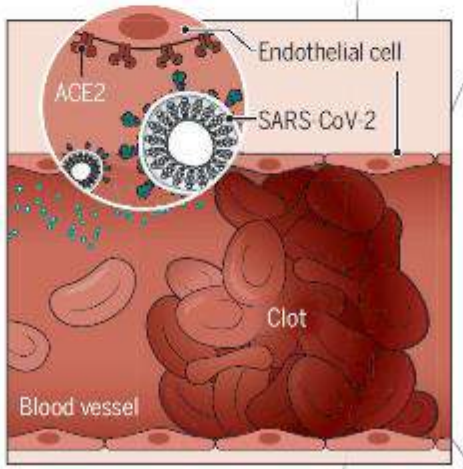
An invader's impact

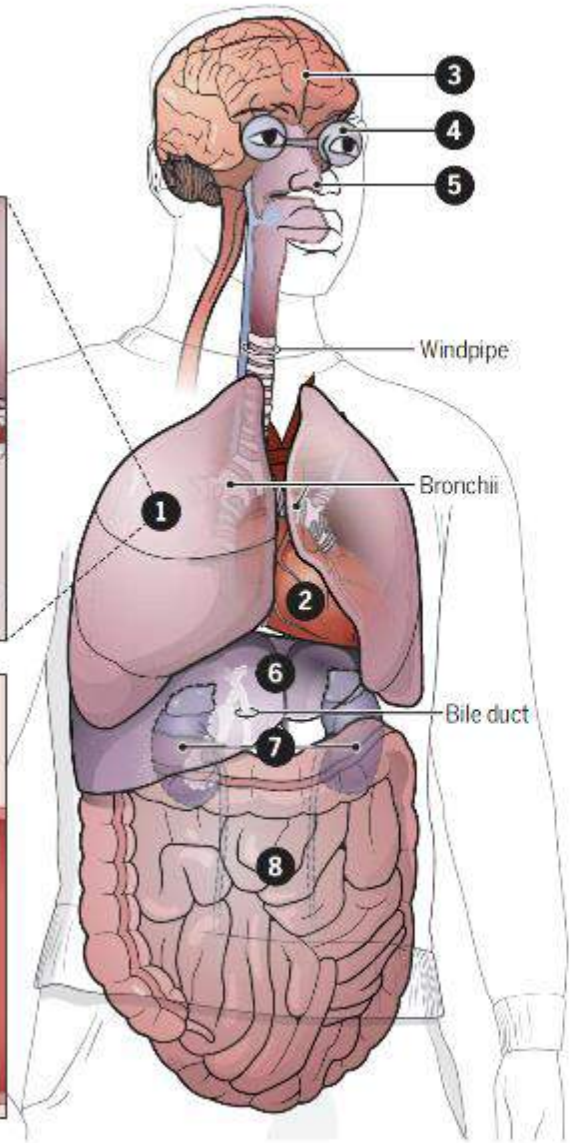
In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body's response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm.

1 Lungs
A cross section shows immune cells crowding an inflamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.



2 Heart and blood vessels
The virus (teal) enters cells, likely including those lining blood vessels, by binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.





3 Brain
Some COVID-19 patients have strokes, seizures, confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

4 Eyes
Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

5 Nose
Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose's nerve endings and damage cells.

6 Liver
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

7 Kidneys
Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

8 Intestines
Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in ACE2 receptors. Some 20% or more of patients have diarrhea.

Wadman M, *et al. Science*. Apr 2020

Radiology

Monocentric – from 16 January to 17 February

90 patients - Median follow up: 18 days [5 – 43]

<u>CT interpretation</u> (366 CT scan)

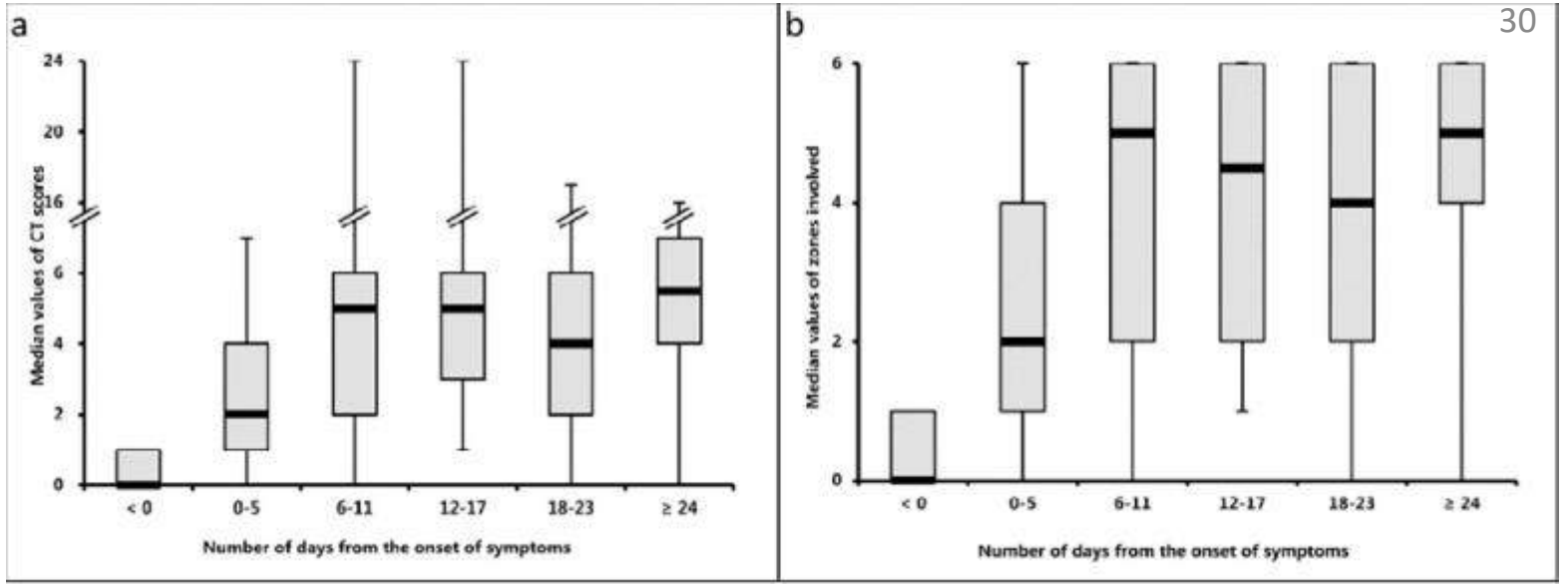
→ Each lung divided into 3 zones

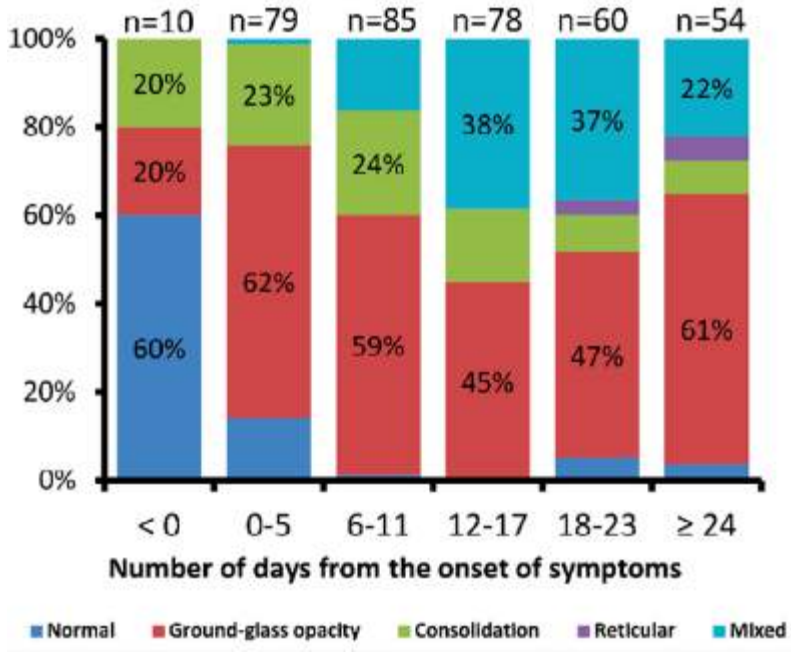
→ Overall CT score (max = 24)

<u>Results</u>

- Increase median values of CT score with time
- Peak levels of lung involvement: 6-11d from symptom onset
- Ground glass opacity (GGO) is the most common finding
- More diverse manifestations around 6-11d and after
- Sensitivity of CT for SARS-CoV-2 increase over time
- At discharge: 64% still had abnormalities

<u>Limitations :</u> No subgroup analysis (mild and severe)





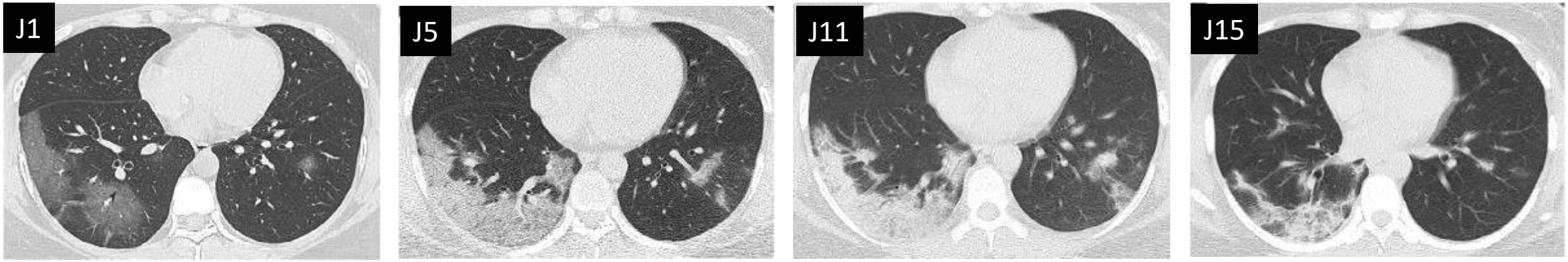
→**Bilateral GGO is the most common manifestation**

→**Rapid extension and specific pattern of evolution**

Wang Y, *et al. Radiology*. Mar 2020

Radiology

Ground glass opacity in a 35-year-old woman with COVID-19 pneumonia



Wang Y, *et al. Radiology*. Mar 2020

Heart & COVID-19

Acute myocarditis

- 7 – 17% of hospitalized patients
- 22 – 31% patients admitted in ICU
- 7% of COVID-19 related deaths

Acute myocardial infarction

- Viral illness → increase the risk
- Inflammation + hypercoagulability → increased risk

Acute heart failure

- 20-25% of patients in their initial presentation
- Increased risk of mortality
- New cardiomyopathy or exacerbation?

Dysrhythmias

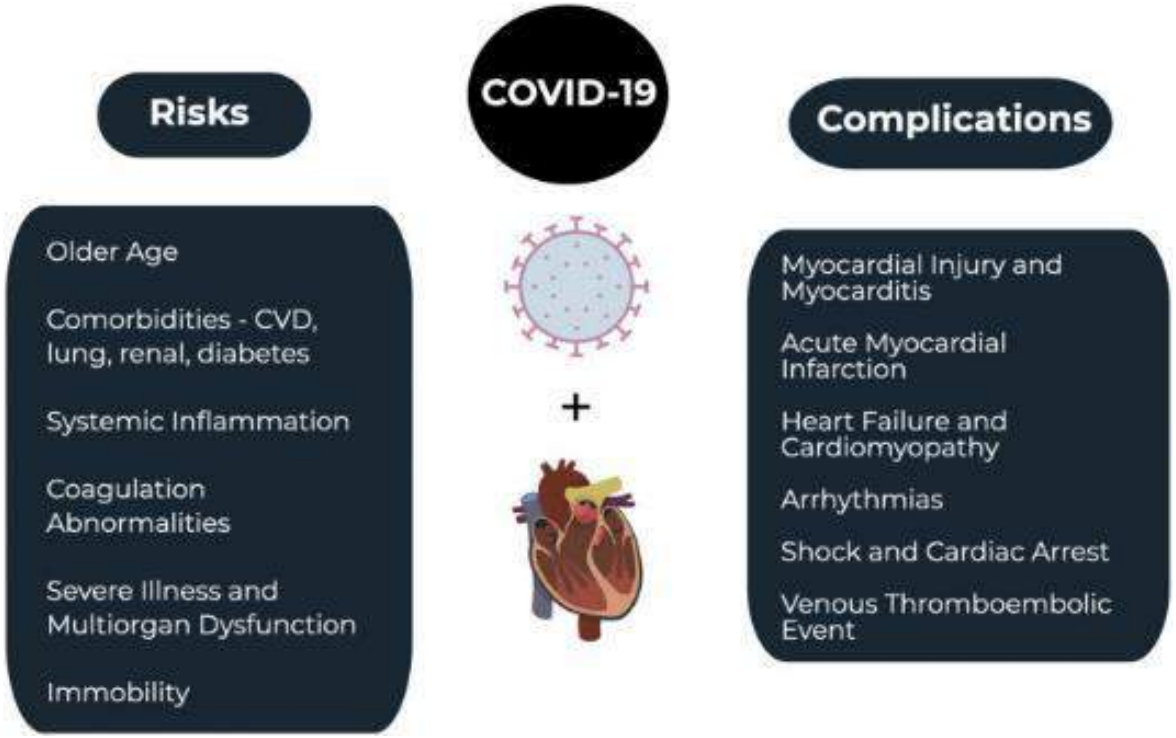
- 17% of hospitalized and 44% of ICU patients
- Hypoxia, inflammatory, abnormal metabolism

Venous thromboembolic event

- Increased risk
- Inflammation, organ dysfunction, abnormal coagulation
- 16-17% of pulmonary embolism

ECG and echocardiographic abnormalities

- Correlated with worse outcomes



Long B, *et al. Am J Emerg Med*. Apr 2020

Kidney & COVID-19

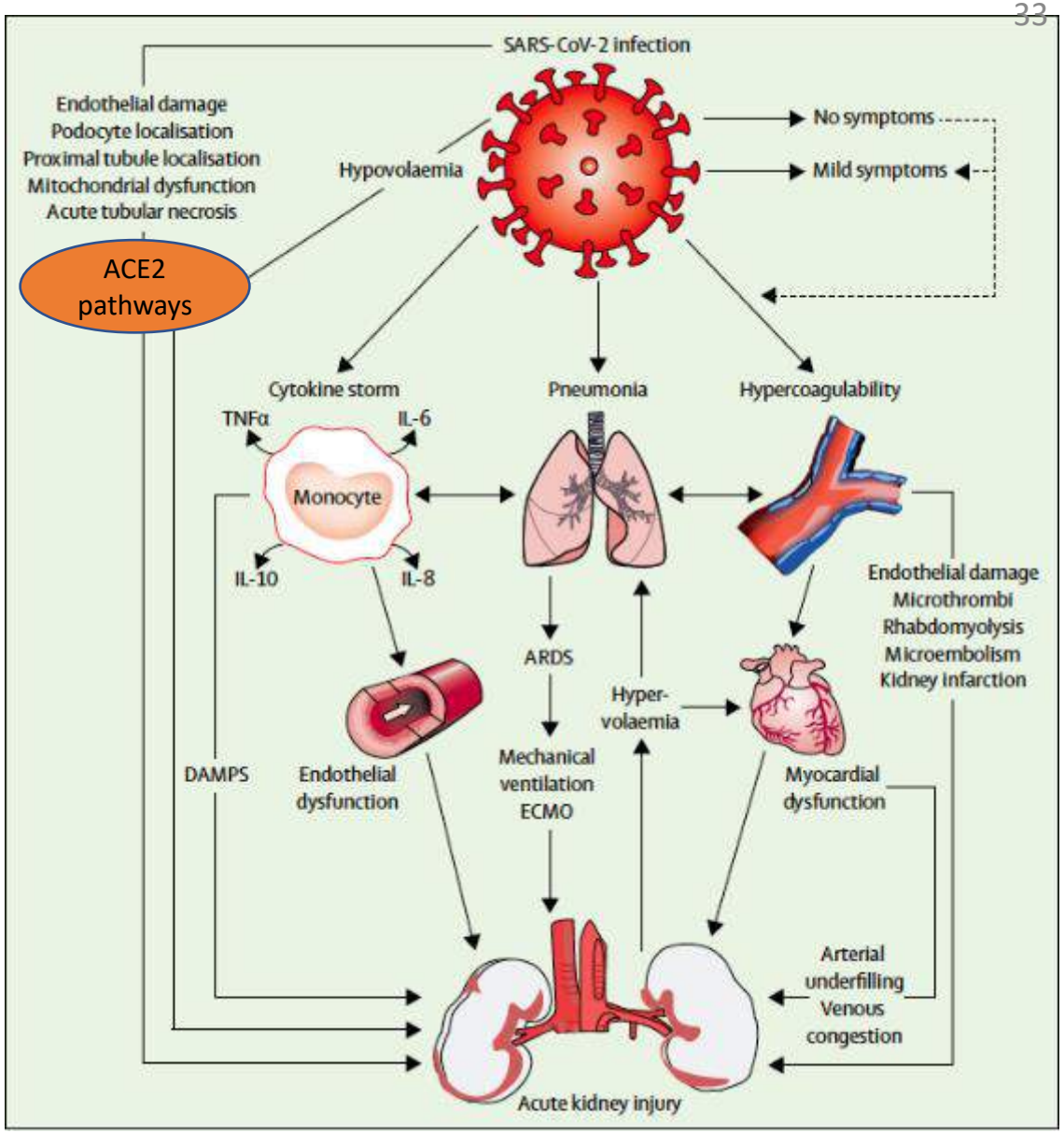
Introduction

- > 40% cases of COVID-19 have abnormal proteinuria at hospital admission
- Patients admitted to ICU with COVID-19:
  - 20 to 40% have an AKI
  - 20% require renal replacement therapy (RRT)

Pathophysiology → multifactorial with predisposing factors

Management

- Implementation of KDIGO guidelines
- Restore normal volume status
- Reduce the risk of
  - Pulmonary oedema
  - Right ventricular overload
  - Congestion
- Application of lung-protective ventilation
- RRT
  - Volume overload ± refractory hypoxemia
  - Right jugular vein
  - Anticoagulation protocols: LMWH or UFH



Ronco C, *et al. Lancet Respir Med*. May 2020

Kidney & COVID-19

Prospective cohort – 1 hospital in China – **701 patients**

- Prevalence of acute kidney injury (AKI)?
- Association between markers of kidney injury and death?

Age (median): 63 years with 52,4% male
Illness onset to admission: 10 days

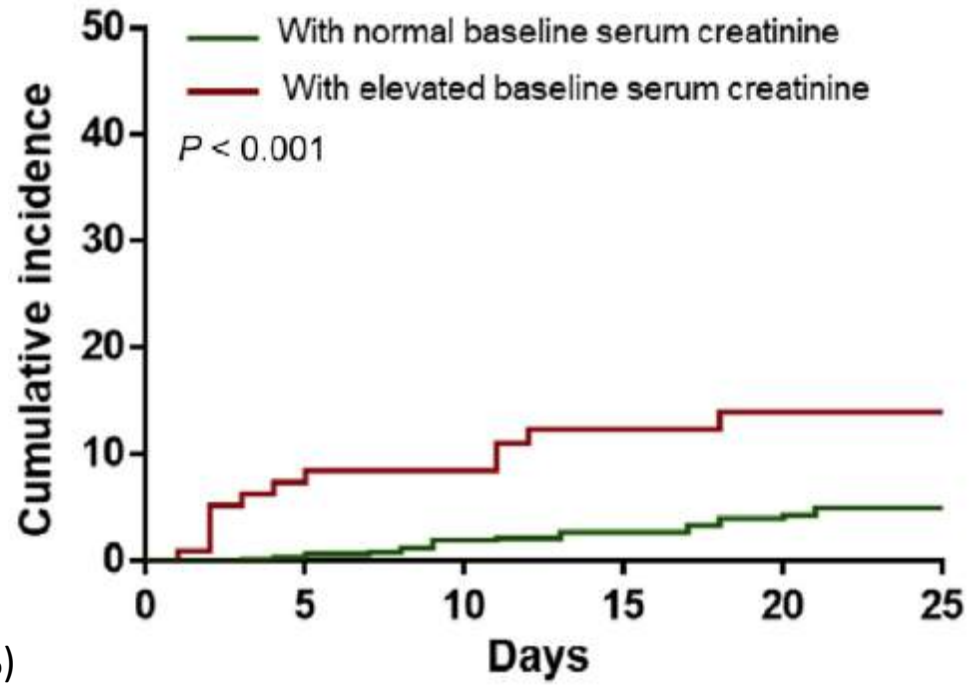
Kidney injury (**at admission**)

- Elevated serum creatinine (SC) at admission 14,4%
- Elevated BUN at admission 13,1%
- GFR<60 ml/min/1,73m^2 for 13,1%
- Proteinuria (43,9%) & hematuria (26,7%)

AKI and hospital death

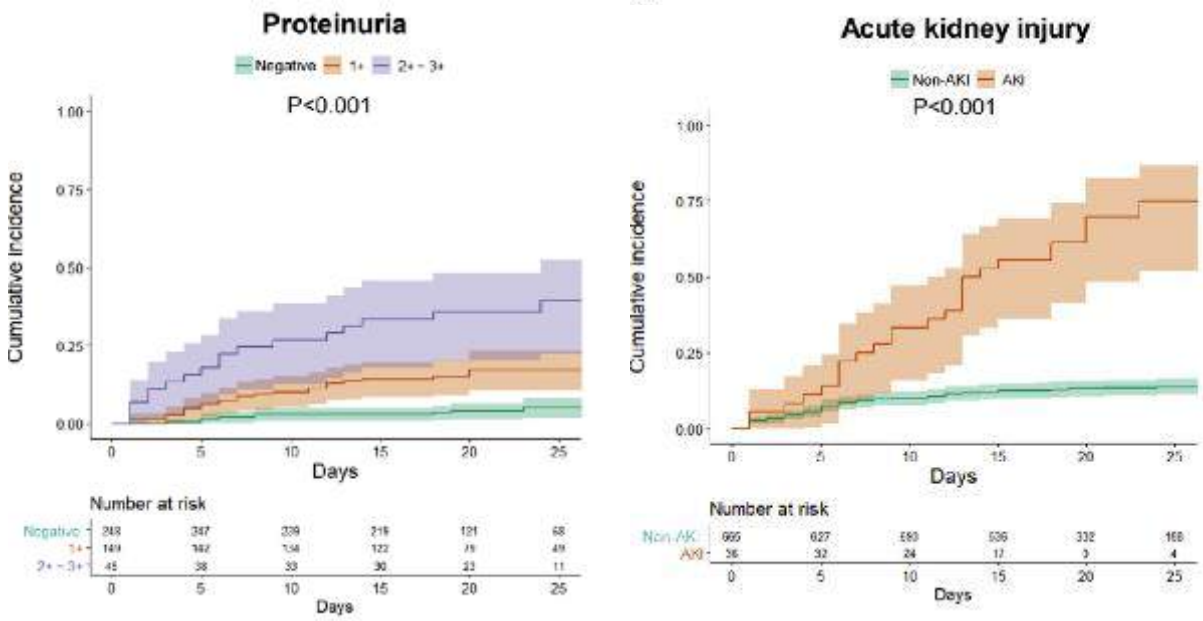
- Prevalence of AKI: 5,1% - higher in patients with elevated SC at admission(11,9%)
- In hospital death: 16,1%
  - 33,7% in patient with elevated SC at admission vs 13,2% others (p<0,05)

Cumulative incidence of AKI subgrouped by baseline serum creatine



Kidney & COVID-19

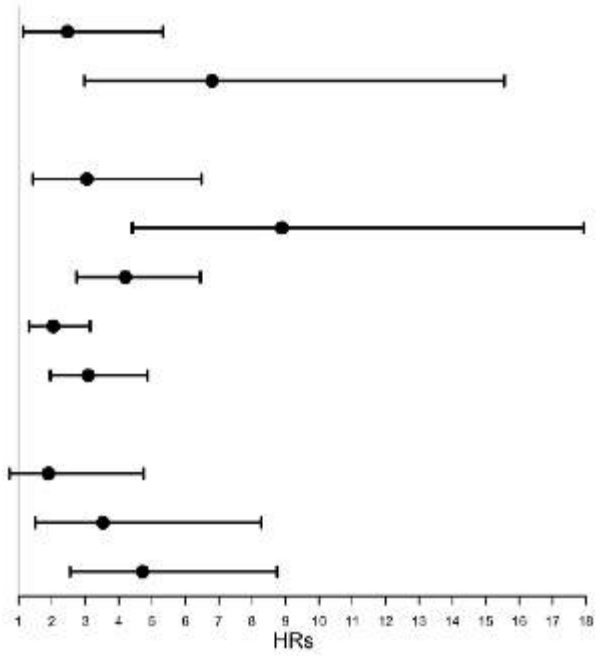
Kidney abnormalities → ↑ in hospital death



Cumulative incidence for in-hospital death

After adjusting

Variables	HRs	95% CI
Proteinuria		
1+	2.47	1.15–5.33
2+ ~ 3+	6.80	2.97–15.56
Hematuria		
1+	3.05	1.43–6.49
2+ ~ 3+	8.89	4.41–17.94
Elevated baseline blood urea nitrogen	4.20	2.74–6.45
Elevated baseline serum creatinine	2.04	1.32–3.15
Peak serum creatinine > 133 μmol/l	3.09	1.95–4.87
Acute kidney injury		
Stage 1	1.90	0.76–4.75
Stage 2	3.53	1.50–8.27
Stage 3	4.72	2.55–8.75



→ High prevalence of kidney disease among hospitalized patients with COVID-19

→ Association between kidney involvement and poor outcome
→ Early detection and effective intervention of kidney involvement

→ Impact on long-term outcomes?

Neuropsychiatric disorders & COVID-19

Online network of secure rapid-response case report notification portals (CoroNerve platforms)
From April 2 to April 26, 2020 in the UK
153 unique cases (correlated with the national case identification data)

- 114 = confirmed SARS-CoV-2 infection
- 6 = probable SARS-CoV-2 infection
- 5 = possible SARS-CoV-2 infection
- 28 excluded because missing data

<u>4 clinical syndromes associated with COVID-19</u>

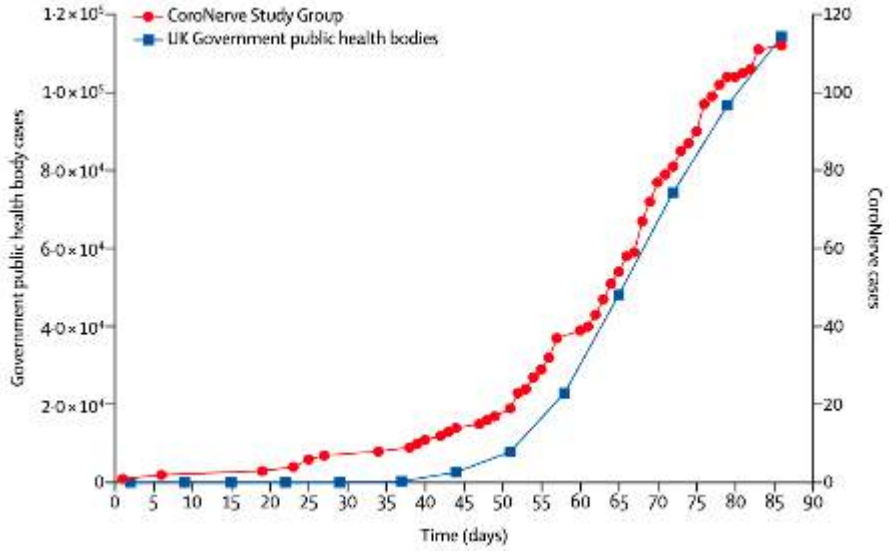
- **Cerebrovascular event** = 77 cases
  - Ischemic stroke / intracerebral hemorrhage
- **Altered mental status** = 39 cases
  - Encephalopathy /encephalitis / primary psychiatric diagnoses / …
- **Peripheral neurology** = 6 cases
- **Other neurological disorders** = 3 cases

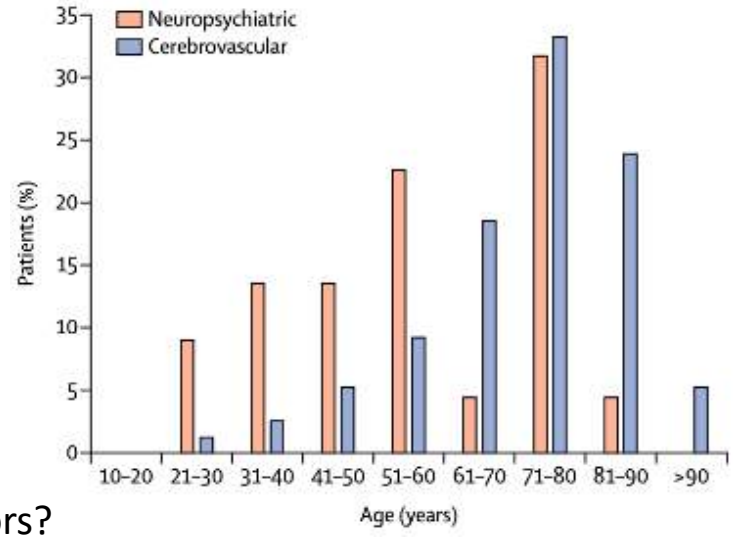
Acute alteration in mental status were overrepresented in young patients

→Cerebrovascular events in COVID-19 → vasculopathy

→Viral neurotropism? Host immune responses? Genetic factors?

Temporal distribution for cases notified to the CoroNerve Study group





Age distribution of patients – case definitions for cerebrovascular and neuropsychiatric events

Varatharaj A, *et al. Lancet Psychiatry*. June 2020

Severity of depressive symptoms & COVID-19

Who is most at risk and how their experiences are evolving as the pandemic continues?

Explore the severity levels of depressive symptoms among individuals **at high risk.**

- Cohort study (COVID-19 Social Study in the UK)
- Depressive symptoms were measured on 7 occasions: the 9-item Patient Health Questionnaire (PHQ-9)
- Exposures → self-reported during the interview

Group-based trajectories of depressive symptoms were estimated using latent growth mixture (LGM) modeling.

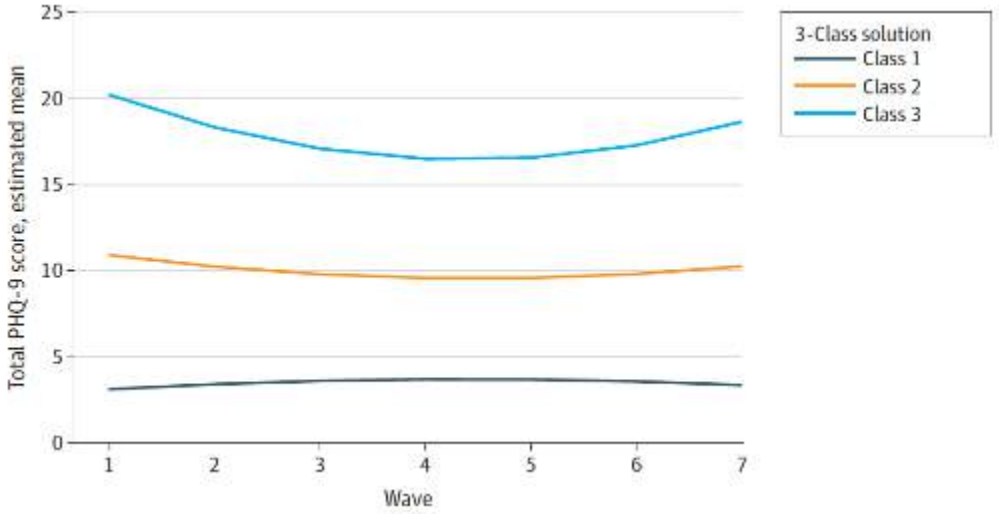
<u>51 417 participants</u>:

- Oldest age group > 60 y → 32,1% (higher proportion)
- Higher proportion of participants in the low and medium-income groups
- 22,1% were essential worker
- 19,9% had mental heakth condition
- 11,3% had psychological or physical abuse

→ Severe depressive symptoms decreased following the start of the lockdown but began to increase again

Characteristics of study participants (extract)

Depressive symptoms[c]	
Minimal or mild	35 715 (69.5)
Moderate	12 451 (24.2)
Severe	3251 (6.3)
Psychiatric medications, yes	7726 (18.0)



Group-Based Trajectories of Depressive Symptoms
Class 1: low depressive symptom trajectory
Class 2: moderate depressive symptom trajectory
Class 3: severe depressive symptom trajectory

Iob E, *et al. JAMA Netw Open*. Oct 2020

Severity of depressive symptoms & COVID-19

The risk of severe depressive symptoms was higher among people:
- Experiencing **abuse** or **low social support**
- With **low SEP**
- With **preexisting mental or physical health condition**

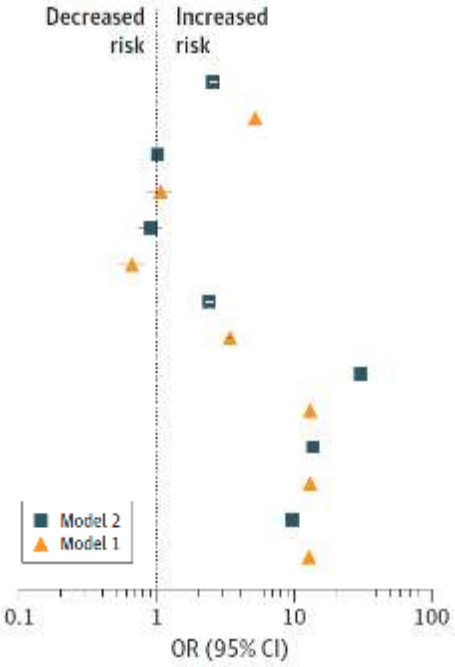
Preexisting mental health condition versus no preexisting:
- Mean PHQ-9 score more than 2-fold higher

Psychological distress experienced during this pandemic may result in an increased incidence of various adverse physical health outcomes.

Limits:
- Not random sample & not nationally representative
- Self-reported measures → bias (underreported sensitive information)
- Causality cannot be assumed
- Lack data on individuals prior to lockdown

Associations of Sociodemographic, Psychosocial, and Health-Related Risk Factors With the Severe Depressive Symptom Trajectories

Risk factor	OR (95% CI)	P value
Low SEP	2.58 (2.41-2.74)	<.001
	5.22 (5.08-5.36)	<.001
Black, Asian, and minority racial/ethnic groups	1.02 (0.74-1.31)	.87
	1.07 (0.85-1.28)	.56
Essential worker	0.92 (0.75-1.10)	.35
	0.66 (0.53-0.80)	<.001
Physical condition	2.41 (2.26-2.56)	<.001
	3.41 (3.29-3.54)	<.001
Mental condition	30.39 (30.21-30.56)	<.001
	12.99 (12.87-13.10)	<.001
Abuse	13.71 (13.49-13.92)	<.001
	13.16 (12.95-13.37)	<.001
Low social support	9.74 (9.57-9.91)	<.001
	12.72 (12.58-12.86)	<.001



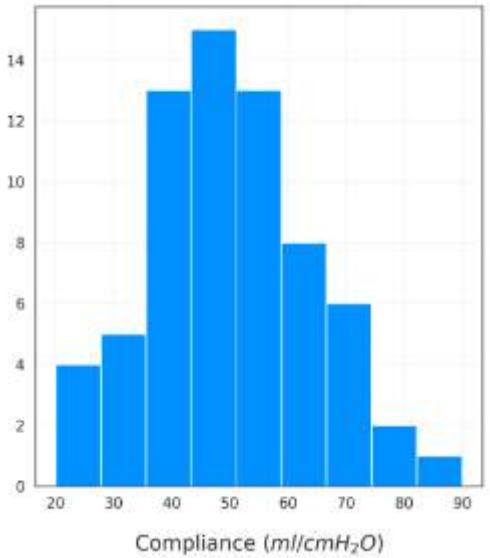
Model 1: adjusting for age, sex and COVID-19 symptoms
Model 2: adjusting for other risk factors

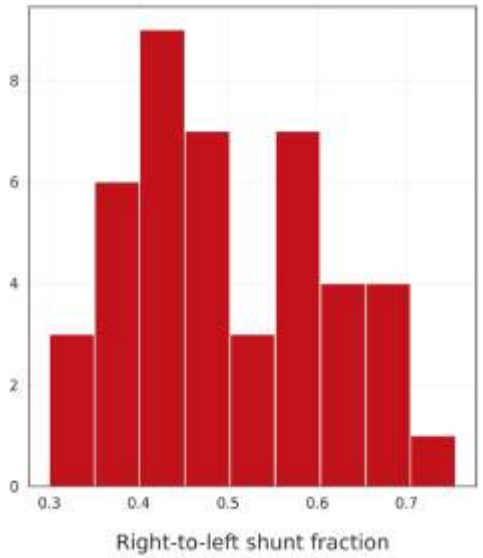
→ The odds of severe depressive symptoms were more than 5-fold higher in those facing socioeconomic disadvantage

→ Importance of developping strategies to identify at-risk person

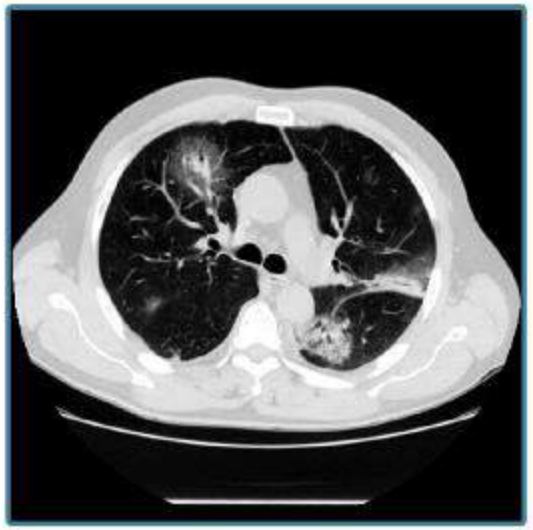
ARDS & COVID-19

- Atypical form of ARDS
- Dissociation in more than 50%:
  - Well preserved lung mechanics
  - Severity of hypoxemia



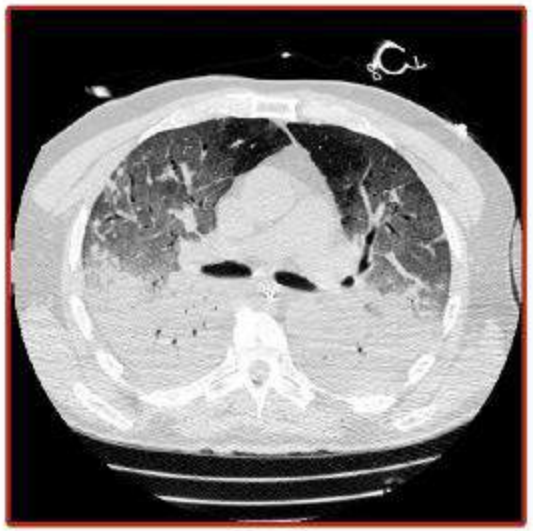


2 types of phenotypes



Type «L»: *Low elastance*

- Gas volume nearly normal
  - **Vt 7-8 ml/kg → DV<14cmH_2O**
- Recruitability is low
  - **PEP<12cmH_2O**
- Loss of hypoxic pulmonary vasoconstriction
- Ventilation/perfusion mismatch → hypoxemia
- Low lung weight → ground glass densities



Type «H»: *High elastance* *(10 – 30%)*

Evolution of the COVID-19 injury attributable to P-SILI

- Increase oedema → decrease gas volume
  - **Vt = 6ml/kg → DV<14cmH_2O**
- Recruitability is high
  - **PEP>12cmH_2O** (carefully)
- High lung weight → bilateral condensations
  - **Prone position**

CT scan
A: spontaneous breathing
B: mechanical ventilation

Antihypertensive drugs & COVID-19

- Observational study
- Lombardy Region in Italy - data extracted from the registry
- February 21 to March 11
- Patient older than 40 years
- 6272 cases matched to 30759 controls (on age, sex & municipality residence)
- Use of antihypertensive drugs
  - ARBs 22,2% among cases and 19,2% among controls
  - ACE inhibitors 23,9% among cases and 21,4% among controls

- **Neither ARBs nor ACE inhibitors had a significant association with risk of COVID-19**
  - Risk similar for women and men
  - Not modified by age – severity of clinical manifestation – course of COVID-19
  - No evidence of an independent relationship between RAAS blockers and the susceptibility to COVID-19

Table 3. Odds Ratios for Covid-19 Associated with Use of Antihypertensive Drugs Dispensed as Monotherapy or Combination Therapy.

Variable	Odds Ratio for Covid-19 (95% CI)*	
	Unadjusted	Adjusted
No use during 2019	1.00 (reference)	1.00 (reference)
Use only as monotherapy	1.39 (1.28–1.51)	1.03 (0.90–1.18)
Use as combination therapy	1.60 (1.50–1.72)	0.99 (0.90–1.09)

* Shown are odds ratios for Covid-19 associated with drug use. Nonuse was considered as the reference. Estimates were obtained by fitting conditional logistic-regression models. Both unadjusted estimates and estimates that were fully adjusted for drugs and coexisting conditions are shown.

Limits

- Change in strategy to test for coronavirus during study
- Information on drug use is limited to prescription
- Exposure to antihypertensive drug not available after December 2019
- Control group included persons with COVID-19
- Unmeasured confounders

Mancia G, *et al. NEJM.* May 2020

Antihypertensive drugs & COVID-19

- Observational study
- New-York University - Use of the NYU Langone Health
- March 1 to April 15, 2020
- All patients with Covid-19 test results recorded
- Extracted from the chart (preceding 18 months)
  - Medical history
  - Medication data
- For a given medication, used a propensity-score models that adjusted for multiple variable
- 12594 patients
  - 5894 COVID-19+
  - 4357 history of hypertension → 2573 COVID-19+
- **No association with any medication studied of**
  - **Risk of severe COVID-19**
  - **Increased likelihood of a positive test**

Table 3. Likelihood of Severe Covid-19, According to Treatment with Various Antihypertensive Agents, in Propensity-Score–Matched Patients with a Positive Test for Covid-19, with Hypertension and Overall.*

Medication	Matched Patients with Hypertension			All Matched Patients		
	Severe Covid-19 in Patients Treated with Medication	Severe Covid-19 in Patients Not Treated with Medication	Median Difference (95% CI)	Severe Covid-19 in Patients Treated with Medication	Severe Covid-19 in Patients Not Treated with Medication	Median Difference (95% CI)
	no./total no. (%)		*percentage points*	*no./total no. (%)*		*percentage points*
ACE inhibitor	139/584 (23.8)	158/583 (27.1)	−3.3 (−8.2 to 1.7)	150/627 (23.9)	169/653 (25.9)	−1.9 (−6.6 to 2.8)
ARB	161/629 (25.6)	156/612 (25.5)	0.1 (−4.8 to 4.9)	162/664 (24.4)	165/639 (25.8)	−1.4 (−6.1 to 3.3)
ACE inhibitor or ARB	252/1019 (24.7)	249/986 (25.3)	−0.5 (−4.3 to 3.2)	275/1110 (24.8)	274/1101 (24.9)	−0.1 (−3.7 to 3.5)
Beta-blocker	210/792 (26.5)	231/829 (27.9)	−1.4 (−5.7 to 3.0)	230/912 (25.2)	250/976 (25.6)	−0.4 (−4.3 to 3.6)
Calcium-channel blocker	253/950 (26.6)	207/930 (22.3)	4.4 (0.5 to 8.2)	263/992 (26.5)	235/976 (24.1)	2.4 (−1.4 to 6.2)
Thiazide diuretic	116/515 (22.5)	114/520 (21.9)	0.6 (−4.5 to 5.7)	120/549 (21.9)	149/590 (25.3)	−3.4 (−8.3 to 1.6)

* Severe Covid-19 was defined as admission to the intensive care unit, the use of noninvasive or invasive mechanical ventilation, or death.

Limits

- Variation in the diagnostic characteristic for the COVID-19 testing method
- Multiple tests for some patients
- Some patients may have been tested at other heath systems
- May not reflect actual drug exposure
- Not account for socioeconomic status, insurance, …
- Additional unmeasured confounders

→Rule out that the risk was higher among treated patients than among untreated patients

Reynolds HR, *et al. NEJM.* May 2020

Risk factors of mortality

Nationwide cohort of all Danish individuals tested for SARS-CoV-2
The study cohort was linked to the Danish administrative and health registrie

<u>11 122 cases with PCR positive:</u> 80% were community-managed & 20% were hospitalized (whereas 2,8% in an ICU)

30 days all cause of mortality = 5,2%

<u>Risk factors of death</u>:

Sex:

- adjusted for age and number of co-morbidities, ORs = 2,1;$CI_{95\%}$ [1.7–2.6] for men

Age:

- 70 – 79 years: OR= 15; $CI_{95\%}$ [9– 26]
- 80-89 years: OR= 30; $CI_{95\%}$ [17–52]
- >90 years: OR= 90; $CI_{95\%}$ [50–162]

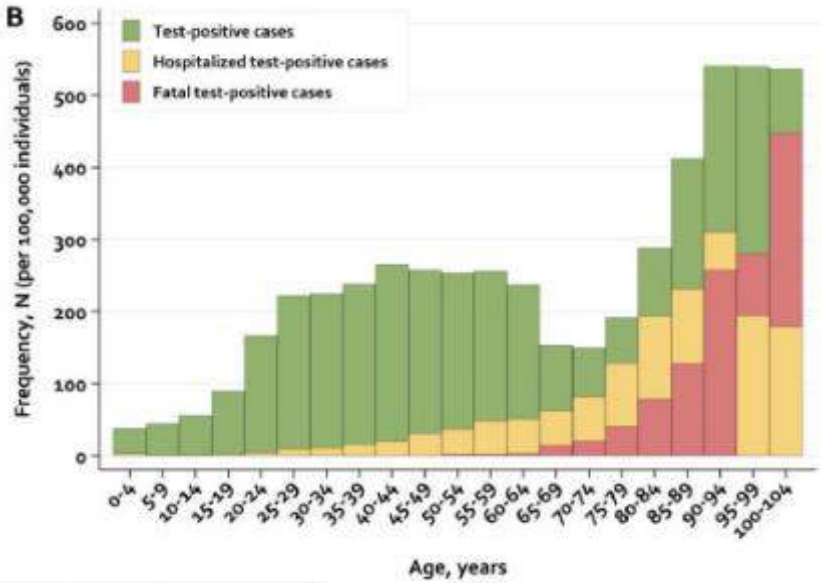
Number of co-morbidities:

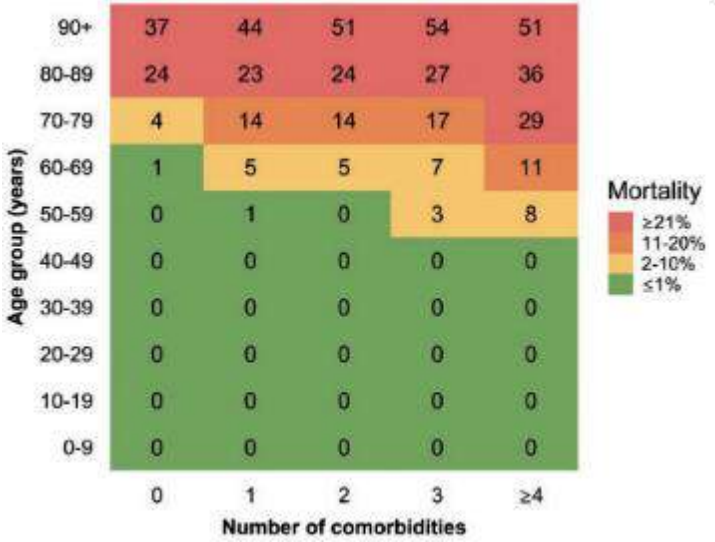
- OR=5.2; $CI_{95\%}$ [3.4–8.0], for cases with at least four co-morbidities
- 79% of deaths had at least two co-morbidities

Chronic diseases:

- Ischemic heart disease & hypertension → ORs 1,1 to 1,3
- Organ transplantation → OR 3,4

The proportion of hospitalized and fatal SARS-CoV-2 cases per 100 000 individuals relative to the total Danish population within each age group





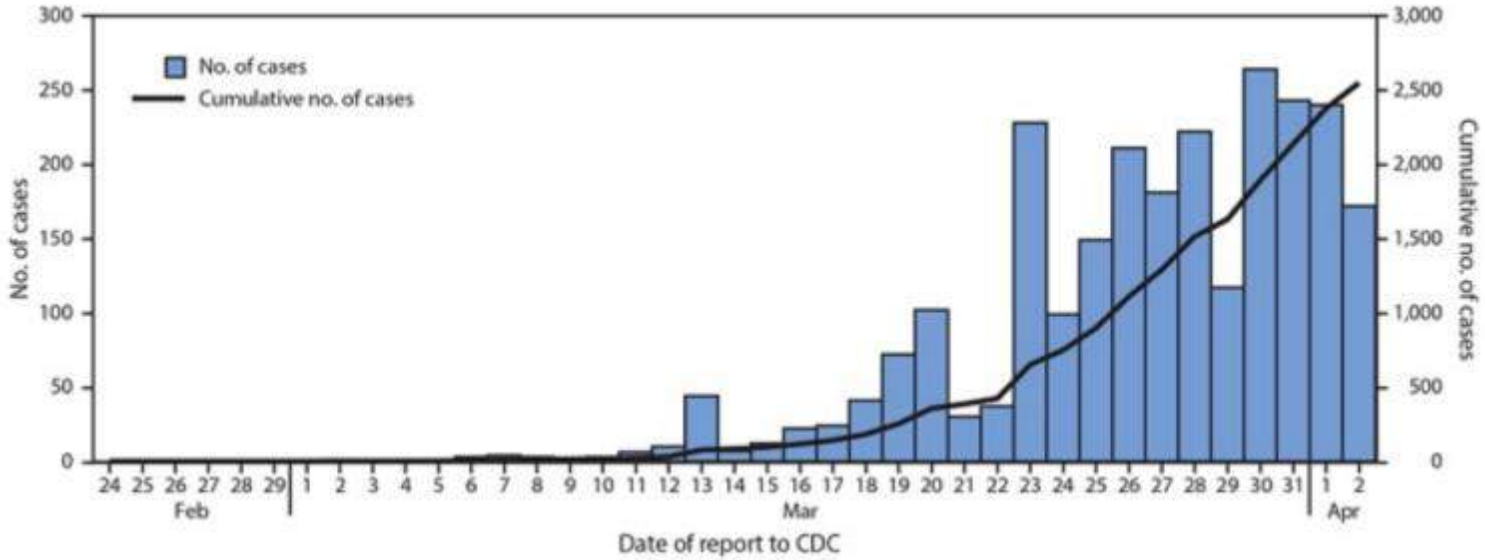
Proportion of patients dying among SARS-CoV-2 PCR-positive cases within different subgroups of age and number of comorbidities

2549 children in USA

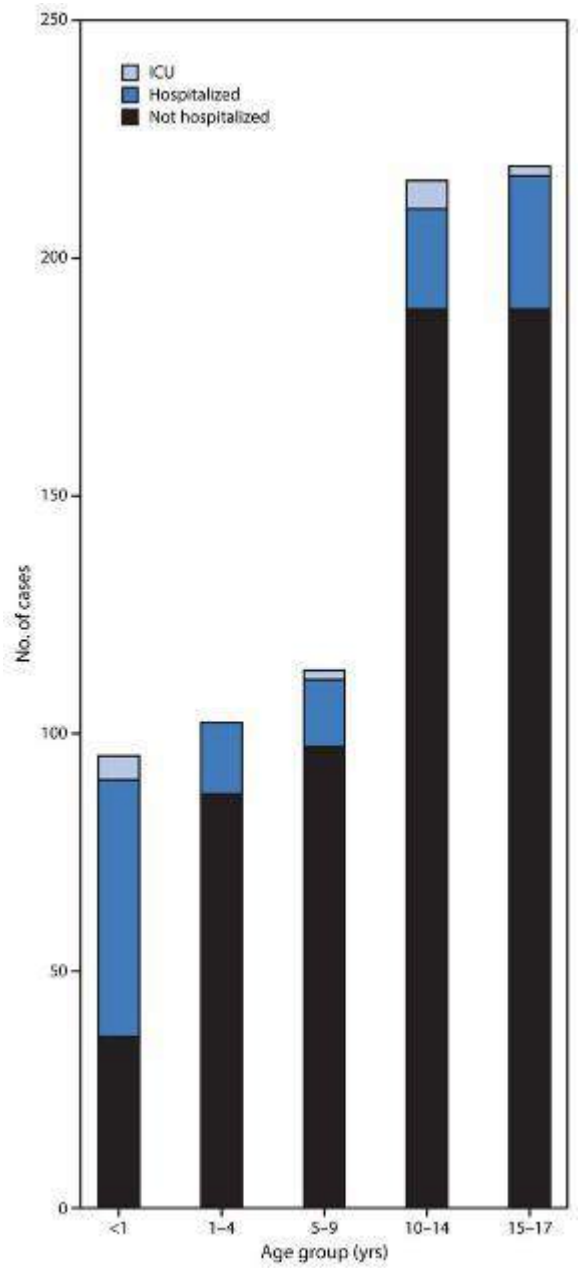
- Age (median): 11 years [0 – 17]
- Male: 57 %
- Exposure to a COVID-19 patients: 91% (household / community)

- **Symptoms** (on 291 cases)
  - Fever: 56%
  - Cough: 54%
  - Dyspnea: 13%
  - Diarrhea: 13%
  - Nausea/vomiting: 11%
  - Abdominal pain: 5,8%
  - …

- **Outcomes** (on 745 cases)
  - Hospitalized: 147
  - ICU admission: 15
- **Case fatality rate**: 0,1%



Children aged <18 years, by date reported to CDC



CDC COVID19 Response Team *MMWR*. Apr 2020

Pediatric inflammatory multisystem syndrome

Observation of a large number of children hospitalized for cardiogenic shock potentially associated with SARS-CoV-2

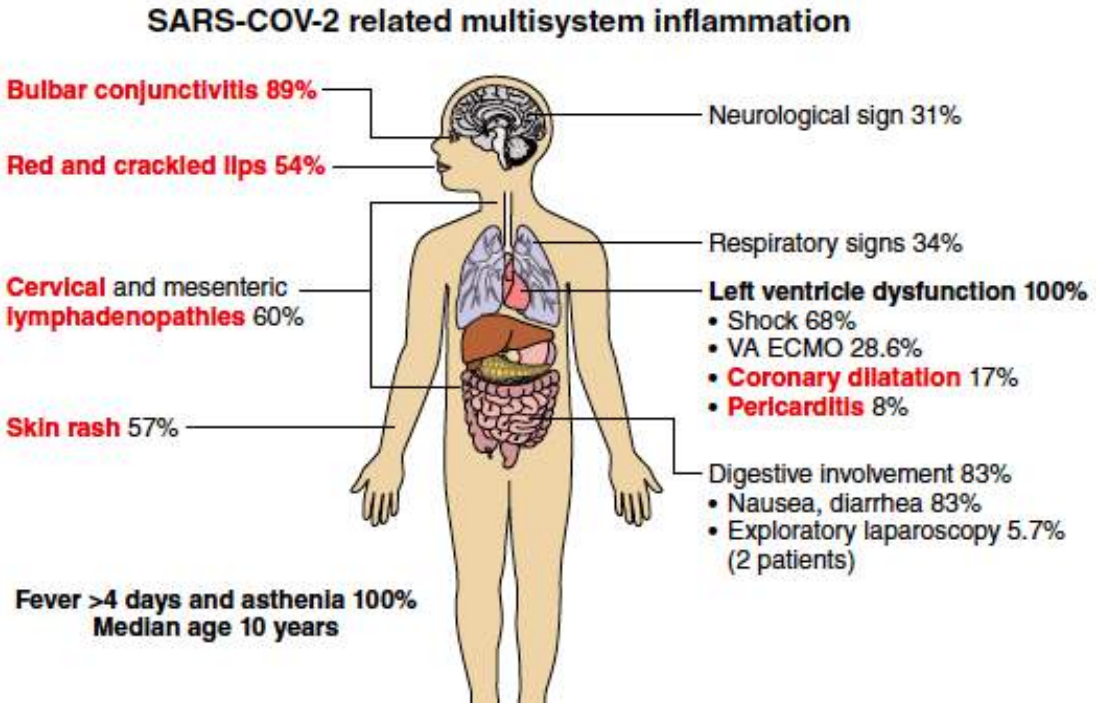
- Retrospective cohort – 2 countries (France & Switzerland) – 14 centers
- 35 children - Age (median): 10 years [2 – 16] – 51% were male
- 88% were positive for SARS-CoV-2 (nasopharyngeal swabs or serology)

<u>Evolution</u>

- 71% had total recovery left ventricular ejection fraction at day 7
- Time to full recovery = 2 days [2 – 5]

<u>Treatment</u> (no recommendation for the moment)

- 62% had invasive respiratory support
- 28% needed VA-ECMO



New disease related to SARS-CoV-2? No precise arguments
Shares some similarities with KD

→ Understanding the immune mechanisms of this disease is a priority

<u>Differences with Kawasaki disease</u>

- Older (median age: 8 to 10y)
- Incomplete forms of KD
- Limited number of coronary artery dilatation

Belhadjer Z, *et al. Circulation*. May 2020

Pediatric inflammatory multisystem syndrome

Cohort of patients with KD in Paris region associated with SARS-CoV-2 (→ 16 patients)

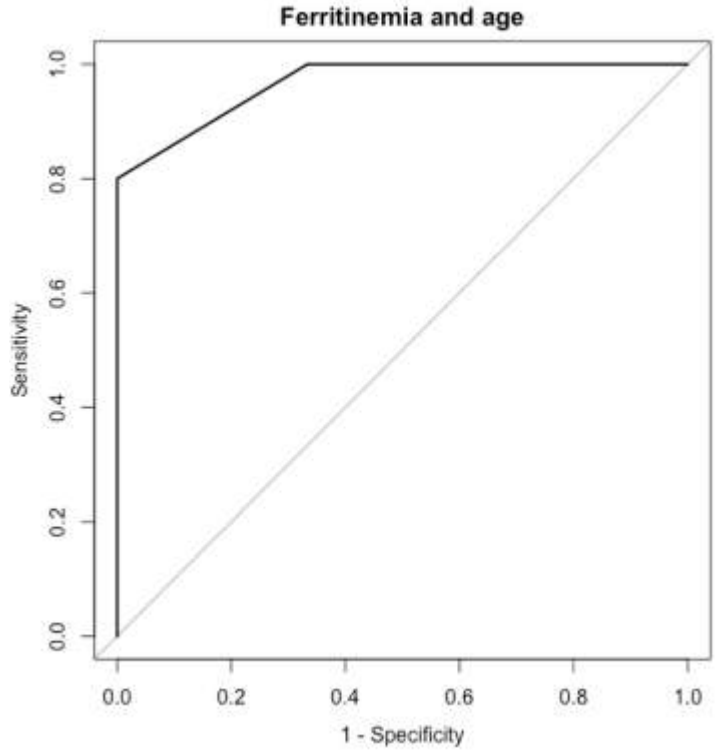
Compared with a historical cohort of «classical KD» (→ 220 patients)

<u>Cohort of Kawa-COVID-19</u>

- Median age = 10 y IQR [4,7 – 12,5]
- Median time from the onset of KD to hospitalization was 5 days
- RT PCR all site positive: 69% (11 cases)
- Cardiac ultrasound was abnormal in 11 patients
- No death – all are in remission

<u>Kawa-COVID-19 versus historical cohort</u>

- Older 10 vs 2 years (*p<0,0001*)
- Lower platelet count (*p<0,0001*)
- Lower lymphocyte counts (*p<0,0001*)
- Higher frequency of cardiac involvement: myocarditis & pericarditis

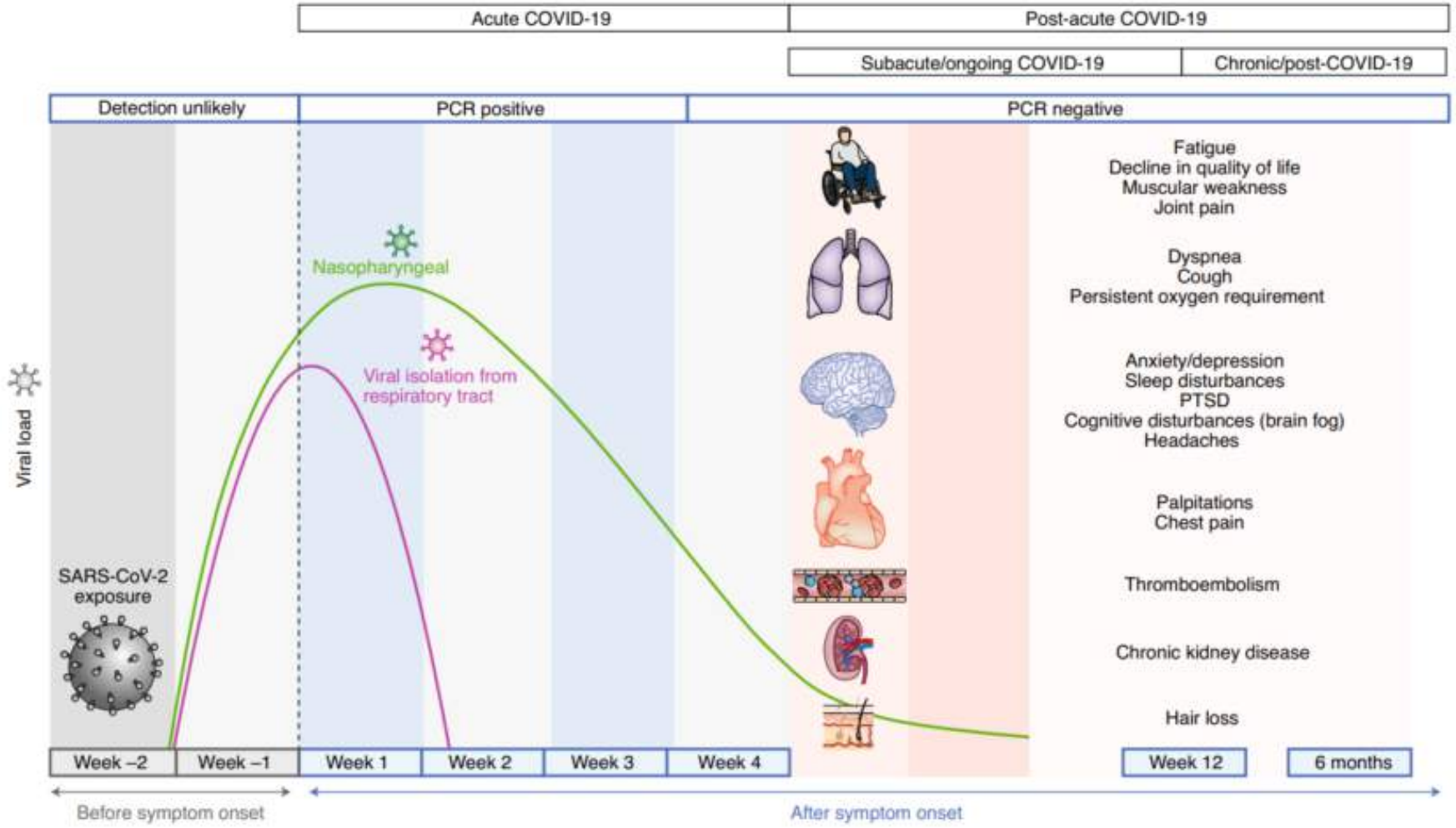


ROC curve of the severity score

<u>Factor prognostic for the development of severe disease</u>

- **Age > 5 years**
- **Ferritinaemia >1400 µg/L**

Long Covid in hospitalized patients



Timeline of post-acute COVID-19. Acute COVID-19 usually lasts until 4 weeks from symptom onset, beyond which replication-competent SARS-CoV-2 has not been isolated. Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. The common symptoms observed in post-acute COVID-19 are summarized.

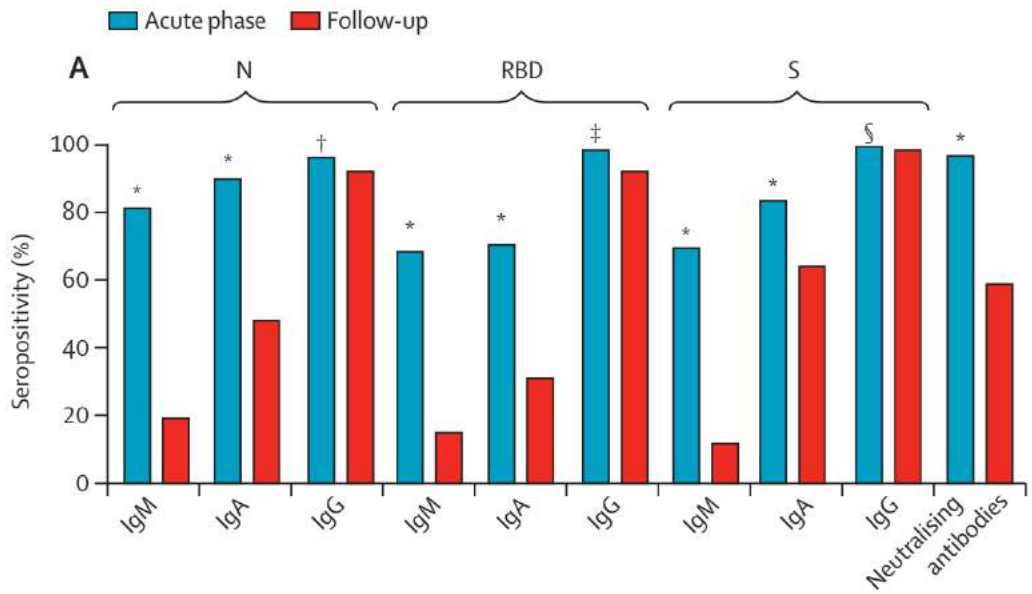
Nalbandian A, *et al. Nature Med*. Mar 2021

Long Covid in hospitalized patients

Cohort of adult Covid-19 patients hospitalized between Jan and May 2020, Wuhan (China), 1733 patients enrolled – **6-month follow-up**

	Total	Scale 3 (no supplemental oxygen)	Scale 4 (supplemental oxygen)	Scale 5-6 (HFNC, NIV or IMV)
At least one symptom	1265/1655 (76%)	344/424 (81%)	820/1114 (74%)	101/117 (86%)
mMRC score	1196/1615 (74%)	323/425 (76%)	802/1079 (74%)	71/111 (64%)
Pain or discomfort (EQ-5D-5L questionnaire)	431/1616 (27%)	111/422 (26%)	274/1082 (25%)	46/112 (41%)
Anxiety or depression (EQ-5D-5L questionnaire)	367/1617 (23%)	98/425 (23%)	233/1081 (22%)	36/111 (32%)
Quality of life (0-100)	367/1617 (23%)	98/425 (23%)	233/1081 (22%)	36/111 (32%)
Distance walked in 6 min – lower than normal range	392/1692 (23%)	103/423 (24%)	255/1153 (22%)	34/116 (29%)
eGFR <90 mL/min per 1.73m²	487/1393 (35%)	121/338 (36%)	326/967 (34%)	40/88 (45%)
Chest CT – at least one abnormal pattern	-	49 (52%)	87/161 (54%)	50/92 (54%)

Temporal changes of seropositivity of anti-SARS-CoV-2 antibodies (94 patients)



- Most common symptoms were fatigue or muscle weakness (63% of total) and sleep difficulties (26% of total)
- Pulmonary diffusion abnormality were common, risk of anxiety or depression and impaired pulmonary diffusion capacities were higher in patients with more severe illness
- The seropositivity and titres of the neutralising antibodies were significantly lower than at acute phase.

Huang C, *et al. Lancet*. Jan 2021

Long Covid in hospitalized patients

Cohort of adult Covid-19 patients hospitalized between Mar and Jun 2020, Italy, 238 patients enrolled – **4-month follow-up**

(27.7% no oxygen required; 20.6% noninvasive ventilation; 8.8% mechanical ventilation; 11.8% ICU)

Covid-19 symptoms

	Acute phase	At follow-up
Fever	215 (90.3%)	0
Cough	132 (55.5%)	6 (2.5%)
Dyspnea	129 (54.2%)	13 (5.5%)
Ageusia	70 (29.4%)	12 (5.0%)
Anosmia	63 (26.5%)	11 (4.6%)
Diarrhea	54 (22.7%)	3 (1.3%)
Arthralgia	46 (19.3%)	14 (5.9%)
Myalgia	45 (18.9%)	14 (5.9%)
Chest pain	2 (0.8%)	1 (0.4%)
Sore throat	1 (0.4%)	0
Headache	1 (0.4%)	0

Pulmonary Function Testing

- D_{LCO} <80% in 51.6% of 219 tested patients
  - Risk factors associated (OR[95% CI]) included chronic kidney disease (10.12[2.00-51.05]) and female sex (4.33[2.25-8.33]) and modality of oxygen delivery (2.20[0.57-8.48])
- D_{LCO} <60% in 15.5% of patients
  - Risk factors associated (OR[95% CI]) included ICU admission (5.76[1.37-24.25]), COPD (5.52[1.37-23.08]) and chronic kidney disease (4.75[1.19-19.00])

Physical Performance Evaluation

- A total of 52.8% patients had functional impairement
  - 22.3 patients had limited mobility based on SPPB test
  - 31.5% of all other patients had subtler impairement in 2-min walking test

Posttraumatic syndrome signs

According to IES-R questionnaire results:

- 25.6% had mild PTS symptoms
- 11.3% had moderate PTS symptoms
- 5.9% had severe PTS symptoms

Limitations:

- *Previously hospitalised patients only*
- *Potential selection bias - patients who declined study participation may have perceived full recovery*

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

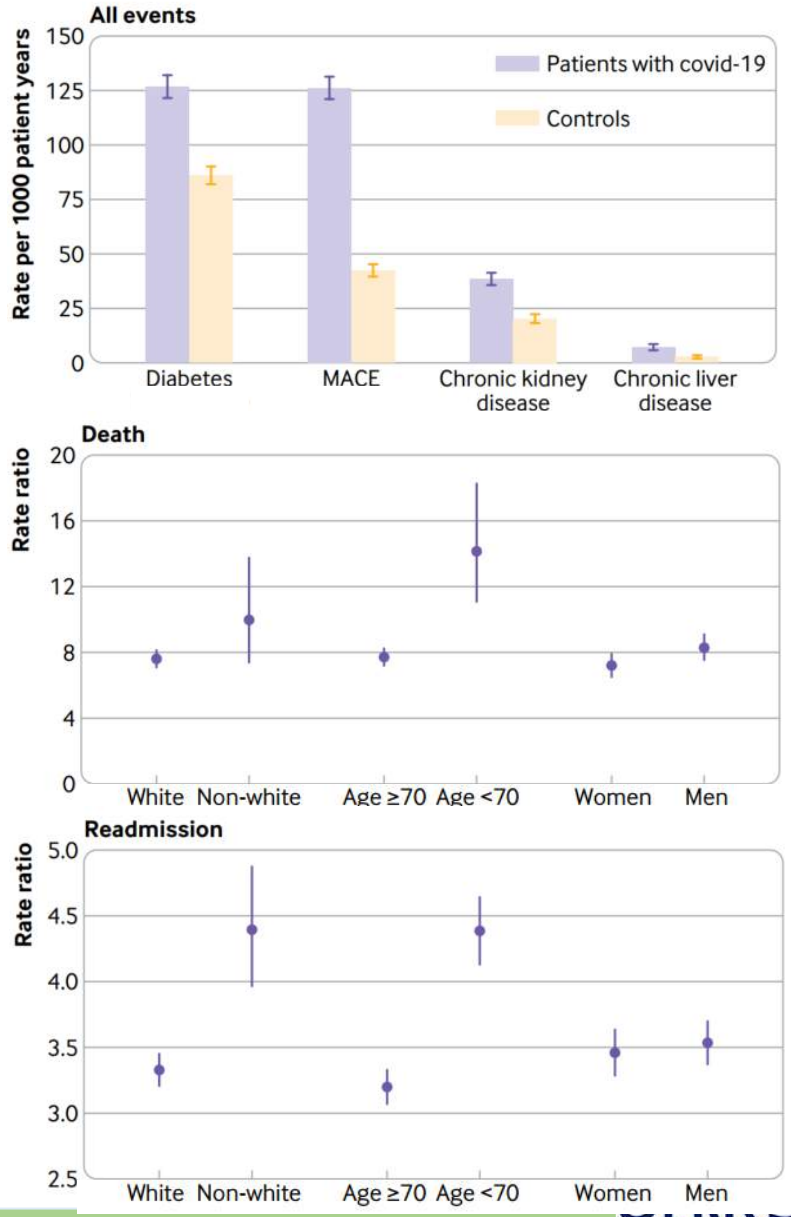
Bellan M, *et al. JAMA Netw. Open*. Jan 2021

anrs MALADIES INFECTIEUSES ÉMERGENTES

Long Covid in hospitalized patients

47 780 individuals (mean age 65, 55% men) hospitalised with covid-19 and discharged alive by 31 August 2020, exactly matched to controls from a pool of ~50 million people in England for personal and clinical characteristics.

- Admission to hospital for covid-19 was associated with an increased risk of readmission (3.5 times greater) and death (7.7 times greater) after discharge, compared to matched control.
- Rates of multiorgan dysfunction after discharge were higher in the Covid-19 cohort as compared to controls (Respiratory diseases 29% of individuals [27.3 times greater for new onset diagnoses], diabetes 4.0% [3.0], MAjor Cardiovascular Events 4.8% [2.8], chronic kidney disease 1.5% [1.9], chronic liver disease 0.3% [1.5]).
- Absolute risk of death, readmission, multiorgan dysfunction after discharge was greater in individuals ≥70 and of white ethnic background.
- Secondary analysis showed that individuals discharged from ICU after covid-19 experienced greater rates of death and readmission than those not admitted to ICUs.



Ayoubkhani D, *et al. BMJ*. Mar 2021

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MALADIES INFECTIEUSES ÉMERGENTES

Long Covid in outpatients

Analysis of occurrence of post-acute effects 2 weeks to 6 months after SARS-CoV-2 infection not requiring hospital admission in Denmark

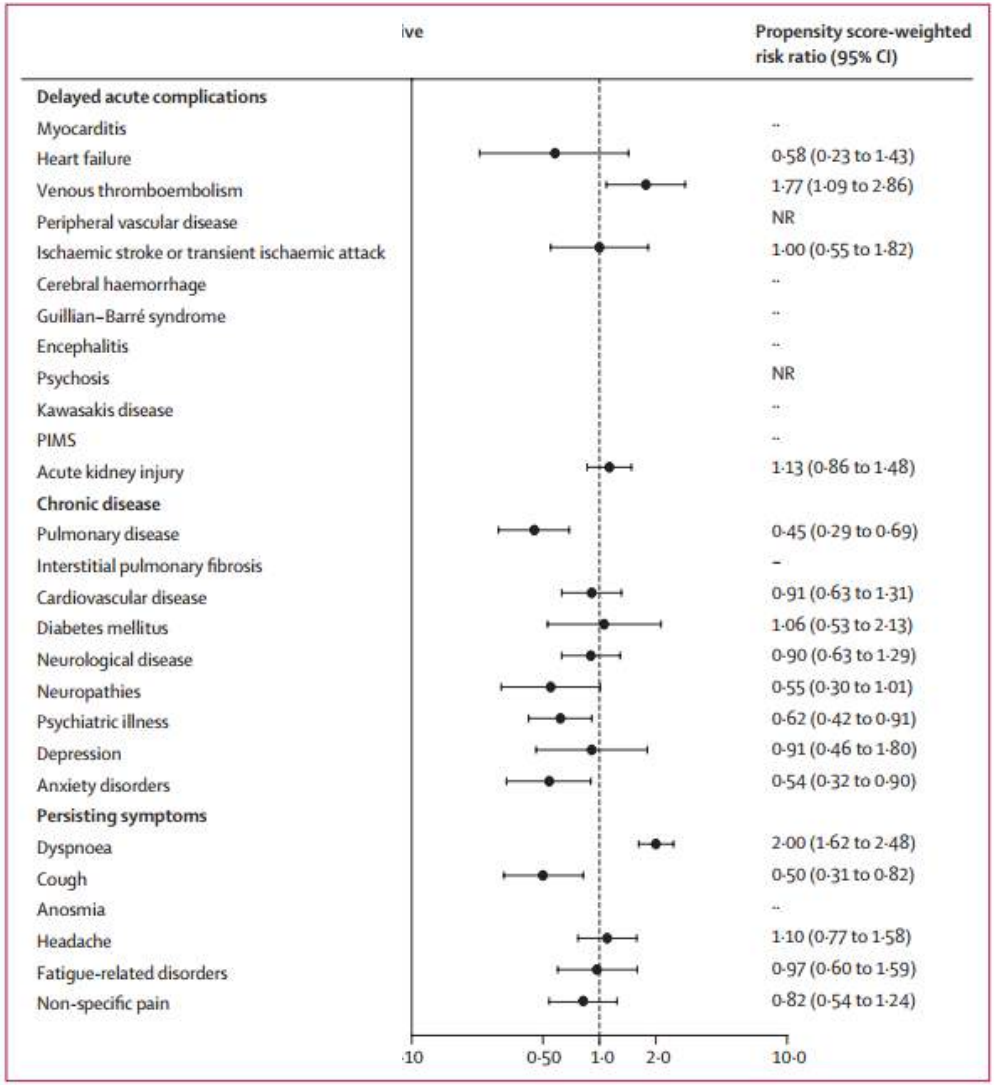
- 8983 patients alive and not admitted to hospital 2 weeks after positive SARS-CoV-2 test, atched with 80 894 SARS-CoV-2 negative individuals

➢ Crude mortality during follow-up: 0.6% for both SARS-CoV-2(+) and (-)

➢ SARS-CoV-2(+), as compared to SARS-CoV-2(-)n had increased risk of:

- Initiating brochodilating agents (1.8% vs 1.5%), specifically short-acting β2-agonists (1.7% vs 1.3%) and triptans (0.4% vs 0.3%)
- Receiving a first diagnosis of dyspnoea (1.2% vs 0.7%), venous thromboembolism (0.2% vs 0.1%)

➢ SARS-CoV-2(+) has increased PERR-adjusted rate ratios for general practitioner visits and outpatient clinic visits, but not difference for emergency department visits or hospitalisations.



Risk ratios for receiving first hospital diagnoses 2 weeks to 6 months after SARS-CoV-2(+) test in individuals not admitted to hospital

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

Lund CL. *et al.* Lancet Infect Dis. May 2021

anrs MALADIES INFECTIEUSES ÉMERGENTES

CLINIC & PHYSIOPATHOLOGY (July 2021)

1. What are the mechanisms of action of SARS-CoV-2?

- It uses ACE2 receptor to enter the cell and can produce a hyper-inflammatory response
- Activation of innate and adaptative immune pathways
- Auto-Abs against type I IFNs are a cause of severe SARS-CoV-2 infection

1. What are the cellular and humoral host responses against SARS-CoV-2 infection?

- Induces long lasting T and B cell immunity against the Spike protein and the structural N protein
- Recovered from mild COVID-19 → robust antibody response to spike protein
- Most symptomatic and asymptomatic patients present strong IgM and IgG responses, the latter lasting up to 6 months
- Anti-spike protein antibody titers appear to correlate with viral neutralization for several months

2. What is the clinical presentation of COVID-19 in adults and children?

- Most persons are asymptomatic or mildly symptomatic
- Independent risk factors of mortality: age – obesity – chronic disease
- Children are less represented than adults and have less severe or critical forms of the disease

3. Is there multiple-organ damage?

- Predominantly lung damage → prognostic of the disease
- Several cases of heart & kidney damage

4. What are the long term effects of Covid-19 (Long Covid)?

- Long term effects include fatigue, pulmonary function impairment and psychological sequelae up to 6 months after infection
- ICU admission for Covid-19 is associated to increased risks of readmission and death

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