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Scientific update on COVID-19

Updated on December 21th 2020

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Questions:

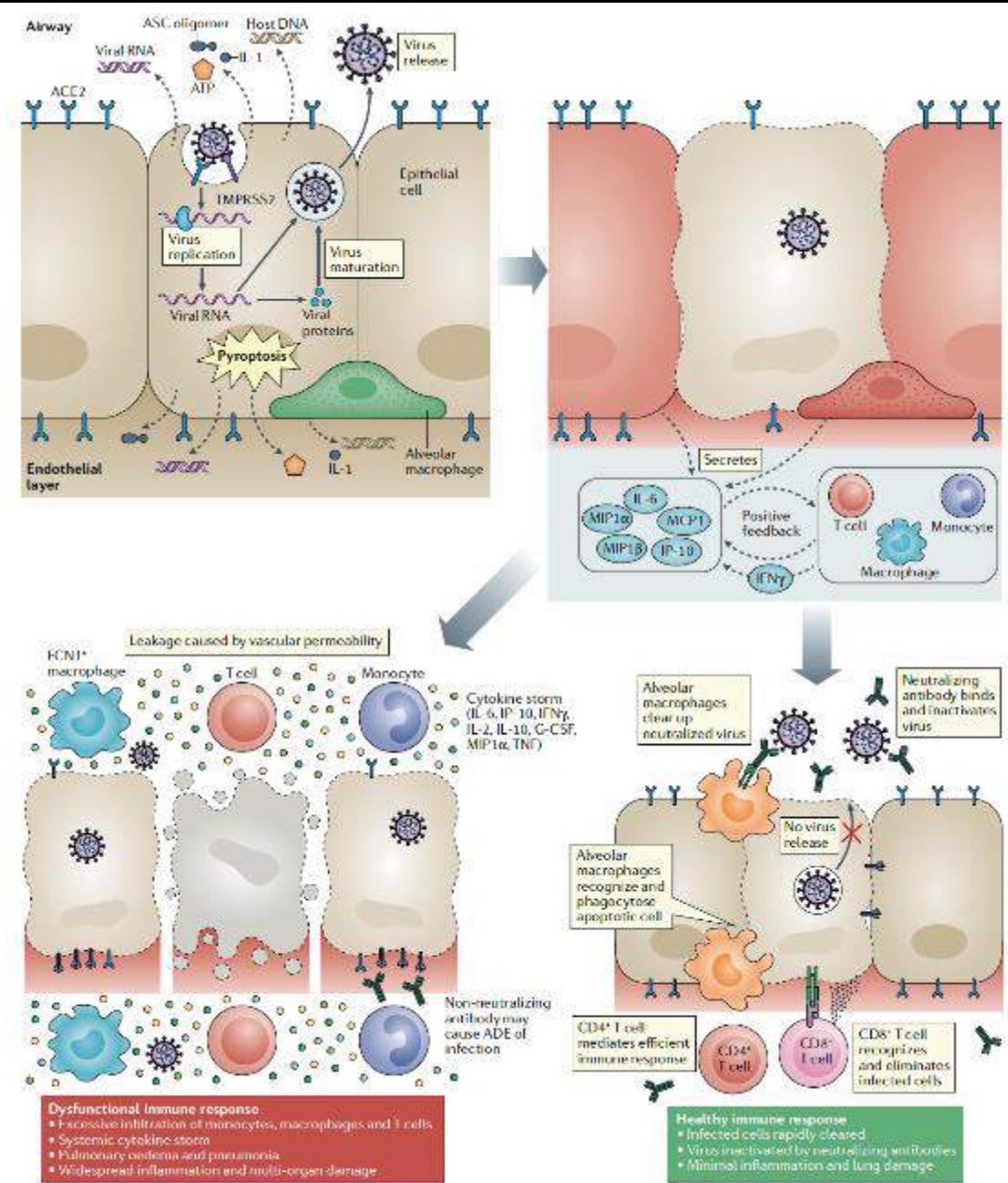
- What is the mechanism of action of SARS-CoV-2? Cell immunity?
- What is the clinical presentation of COVID-19 in adults and children?
- Is there multiple-organ damage?

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

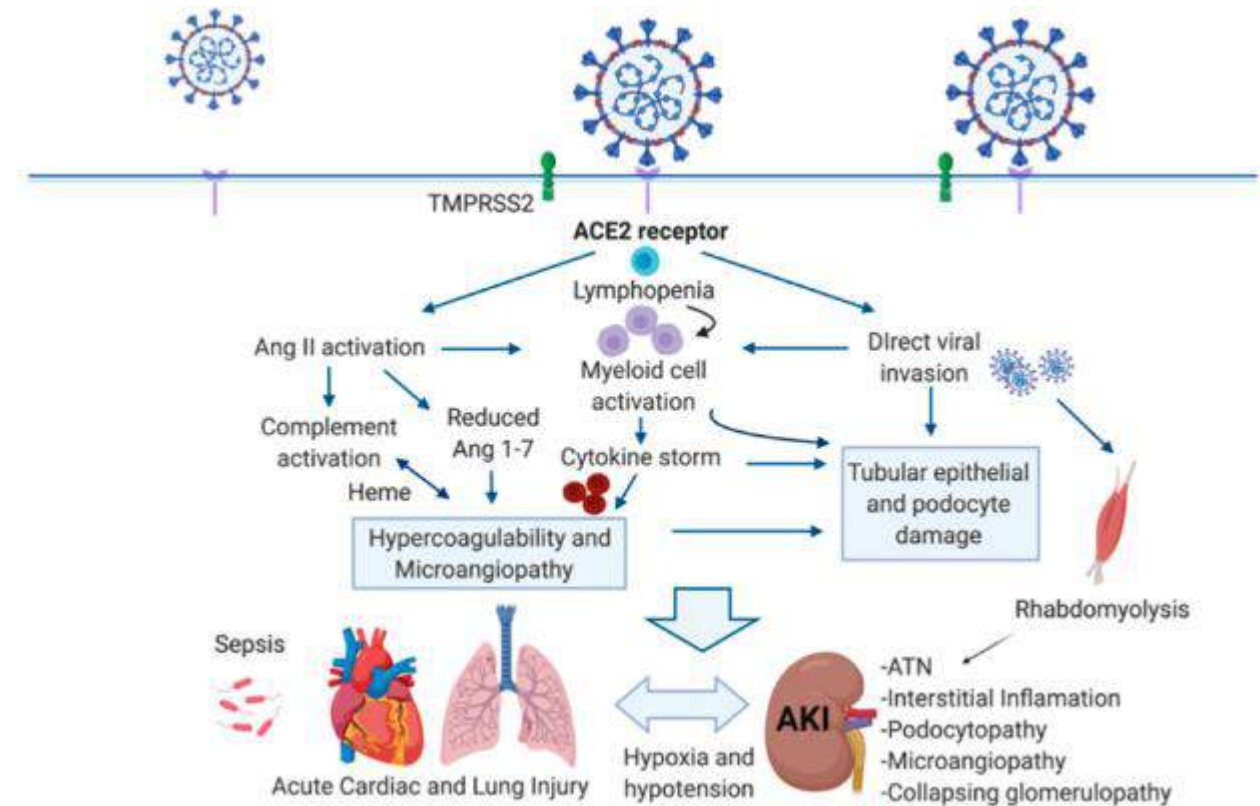
BUT sometimes (10 to 15 days after symptom onset)

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



Physiopathology

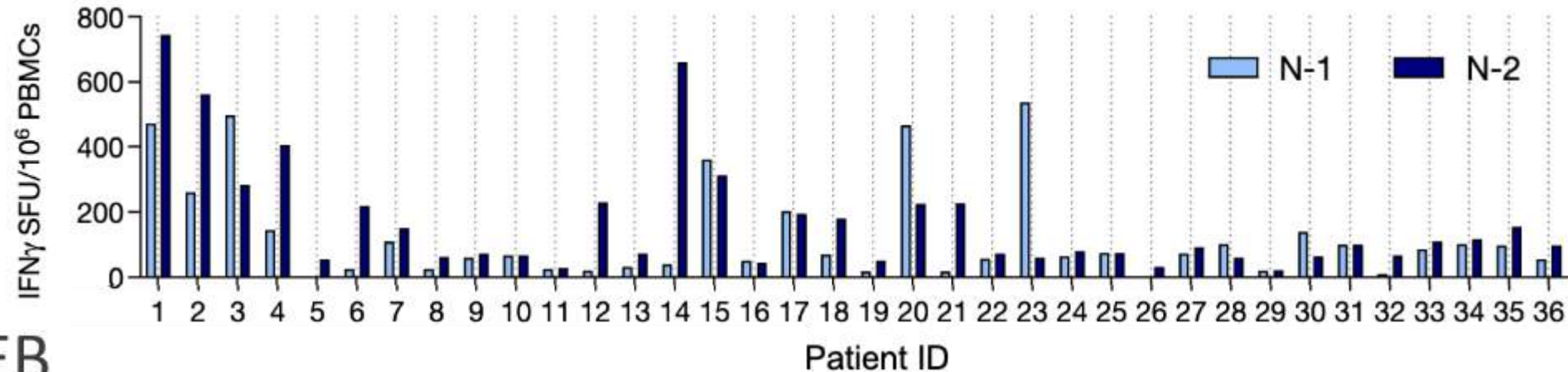
- SARS-CoV-2 targets ACE2 receptor and infected cells via « priming »
 - Renin- Angiotensin system dysregulation
 - Activation of innate and adaptative immune pathways
 - Cytokine storm
 - coagulation pathway → hypercoagulation
- Multi-organ damage
 - Kidney, heart, lungs, vessel, immune system



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.
- Peripheral 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 (IFN γ spot)**



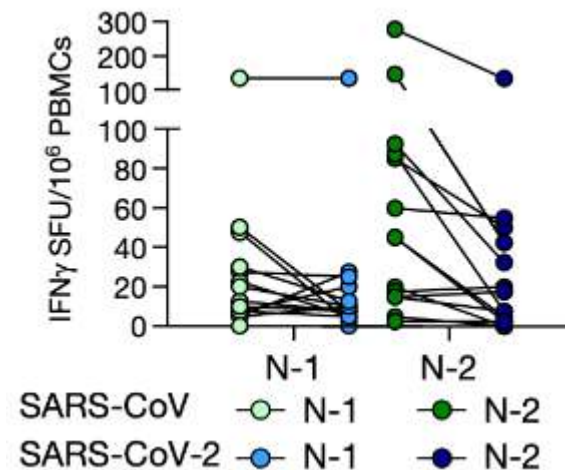
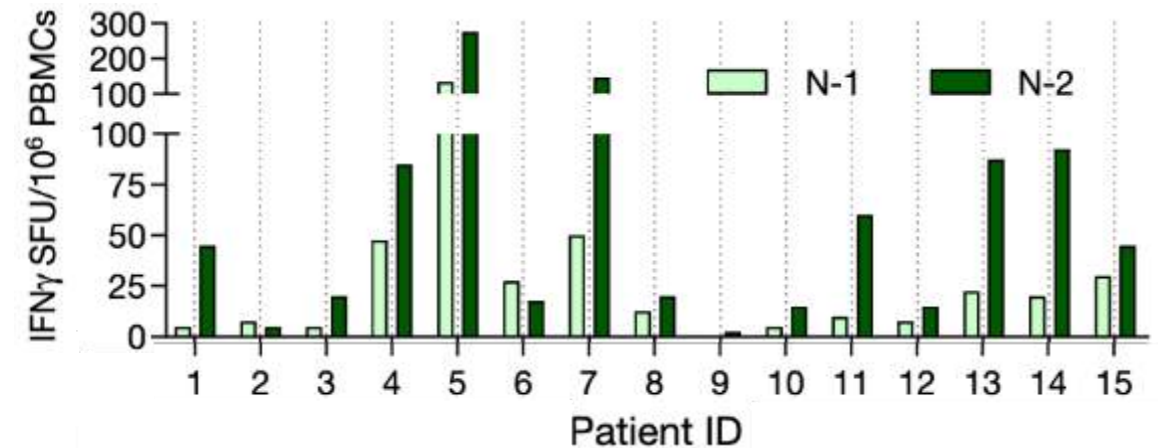
SARS-CoV-2 specific T cell immunity

SARS-CoV2 specific T cells in patients with SARS

- Patients who recovered from SARS have T cells that are specific to epitopes within different SARS-CoV proteins.
- Collected PBMCs 17 years after SARS-CoV infection from 15 individuals.
- **17 years after infection, IFN γ responses to SARS-CoV peptides were still present.**
- These T cells displayed robust cross-reactivity to the N protein of SARS-CoV-2.
- SARS-CoV-2 N-specific T cells are part of the T cell repertoire of individuals with a history of SARS-CoV infection and these T cells are able to robustly expand after encountering N peptides of SARS-CoV-2.

→ **Supporting the notion that patients with COVID-19 will develop long-term T cell immunity.**

PBMCs isolated from 15 individuals who recovered from SARS 17 years ago were stimulated with SARS-CoV



PBMCs of 15 individuals who recovered from SARS were stimulated in parallel with peptide pools covering the N proteins of SARS-CoV and SARS-CoV-2, and the frequency of IFN γ -producing cells is shown.

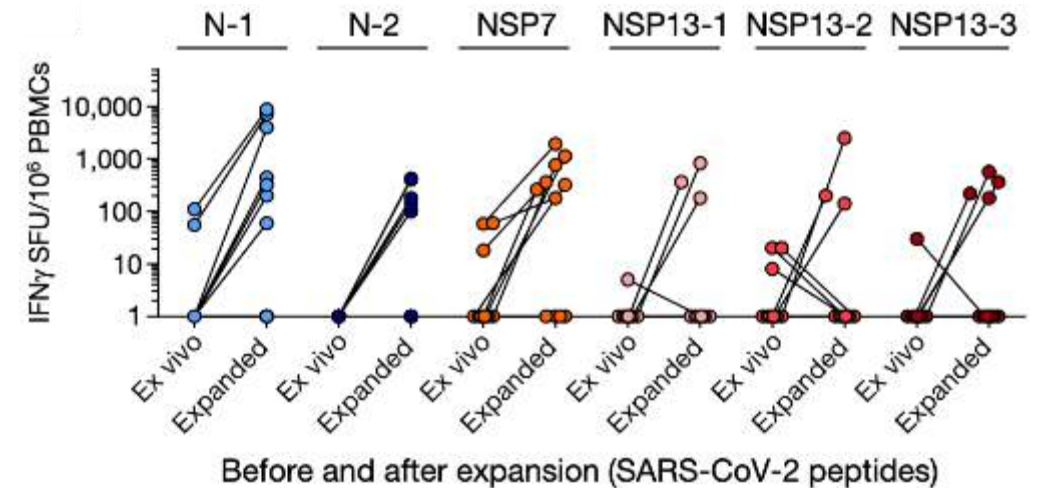
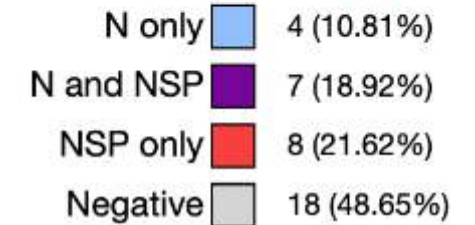
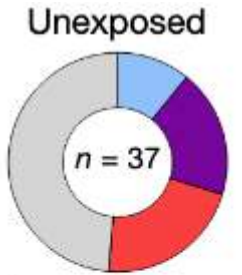
SARS-CoV-2 specific T cell immunity

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 IFN γ 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.

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

The percentage of individuals with N-specific responses



Immunological assessment

Cohort study of 178 confirmed SARS-CoV-2 infection

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

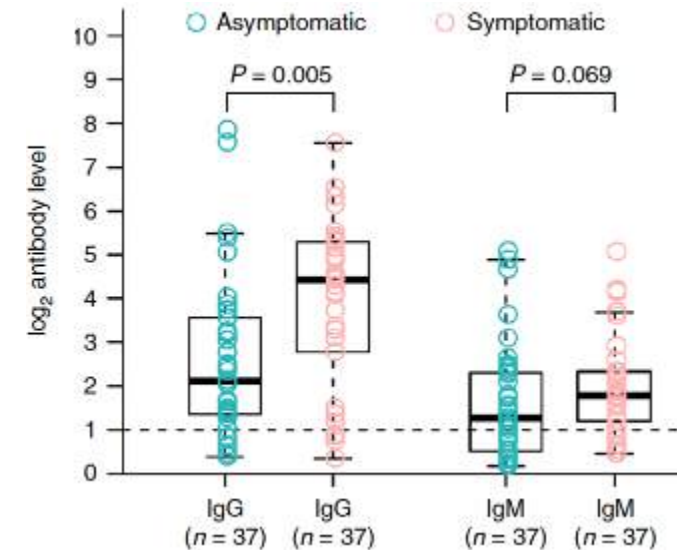
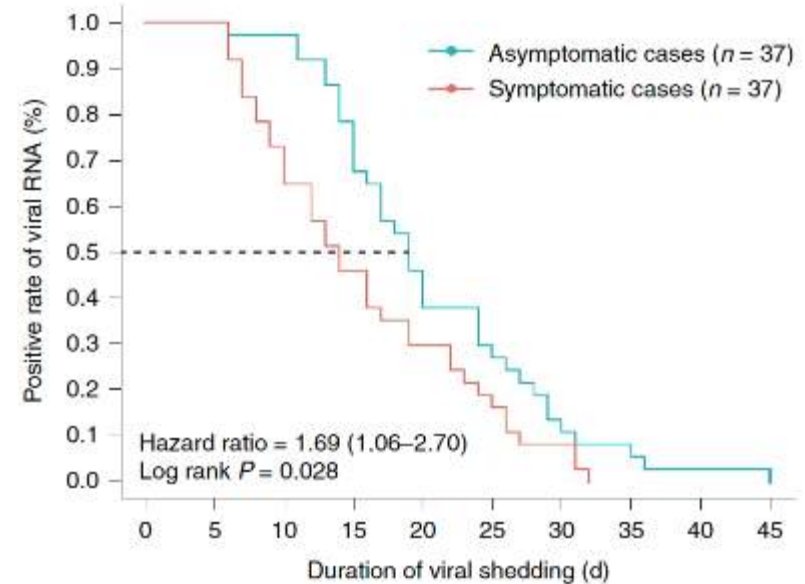
37 asymptomatic matched with 37 mild symptomatic patients

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)



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

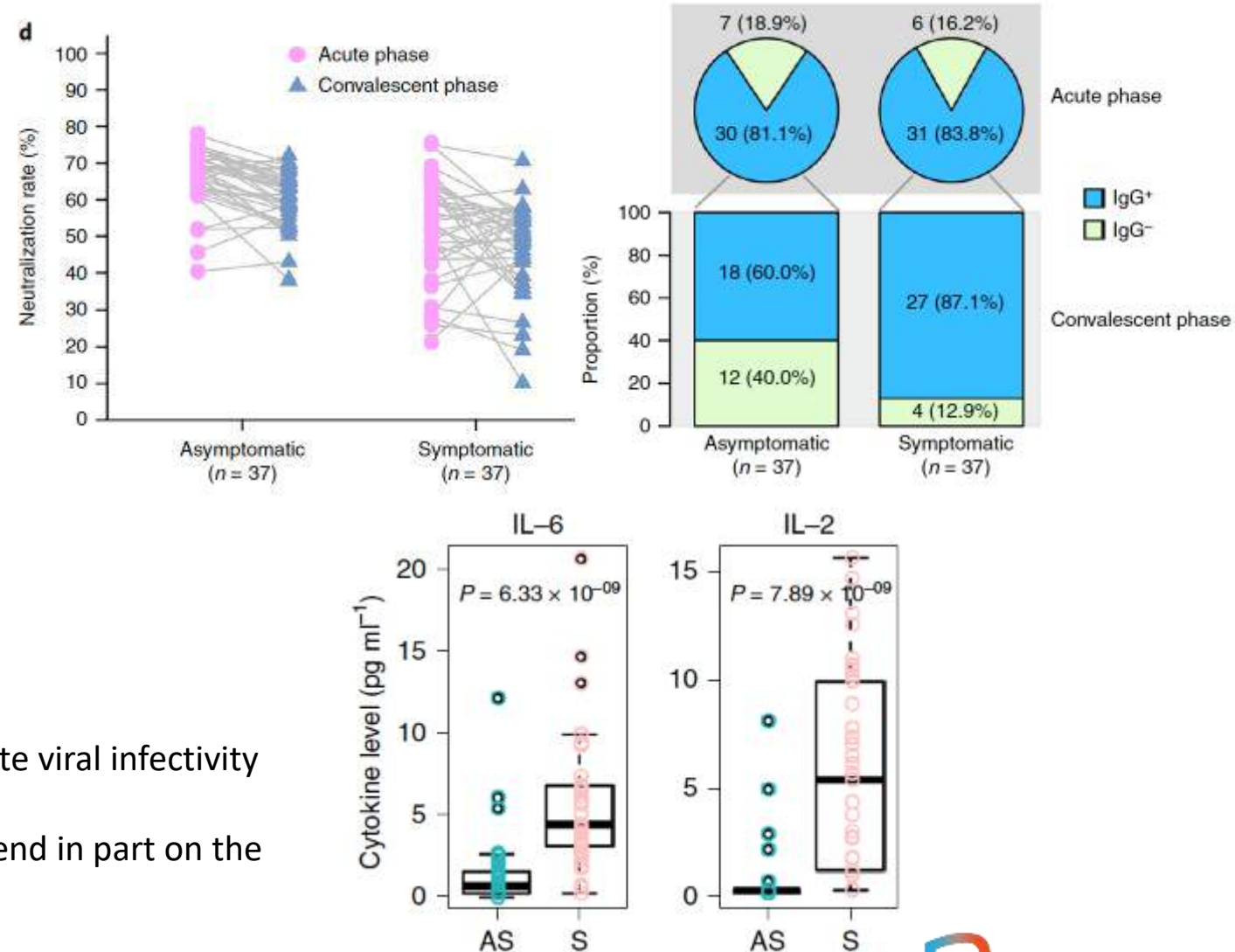
Similar observations were made for neutralizing antibodies

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



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})

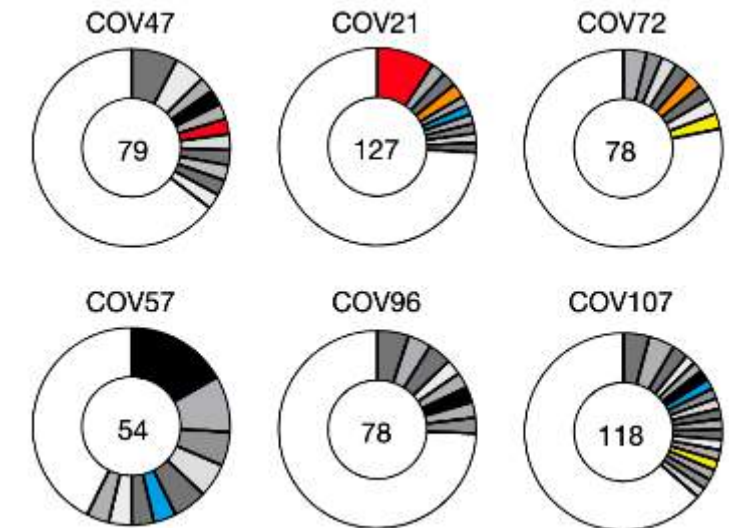
Generally low: $NT_{50} < 50$ in 33% of samples and < 1000 in 79%

- 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.*



Antibody response to SARS-CoV-2

- Do monoclonal antibodies have neutralizing activity?

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 NT₅₀ values.

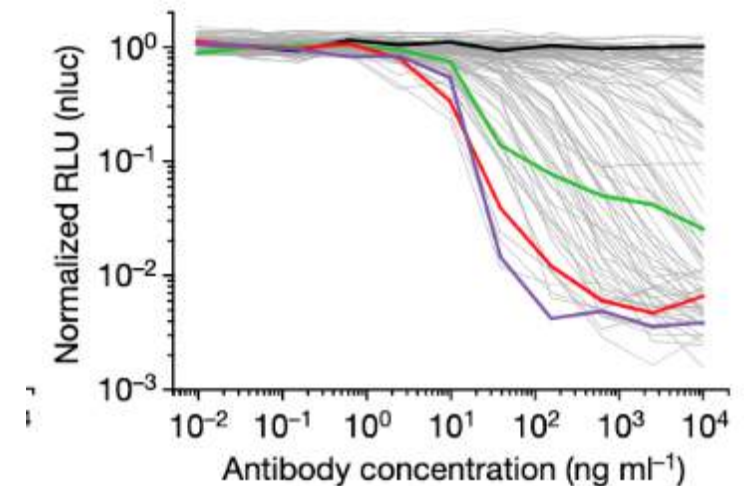
→ Even individuals with modest plasma neutralizing activity have rare IgG memory B cells that produce potent SARS-CoV-2-neutralizing antibodies.

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.

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.



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)

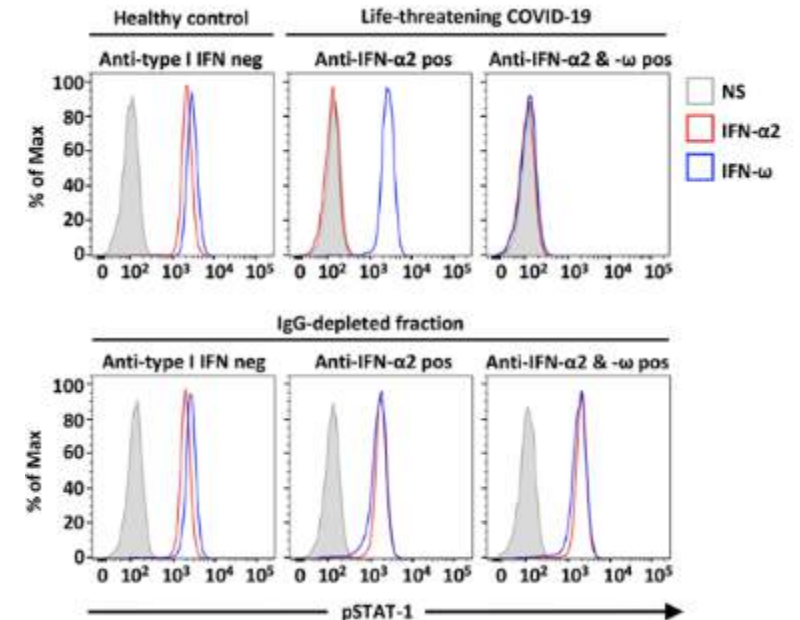
1227 healthy controls

Auto-antibodies against IFN- α 2 and/or IFN- ω ?

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

Auto-Abs neutralize IFN- α 2 and/or IFN- ω in vitro?

- 101 of 987 life-threatening COVID-19 had neutralizing IgG auto-Abs against at least one type I IFN:
 - 51% against IFN- α 2 and IFN- ω ,
 - 36% against IFN- α 2 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- α 2- or IFN- ω -induced pSTAT1 in the presence of 10% healthy control or anti-IFN- α 2/ ω - auto-Ab-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- α 2 and IFN- ω stimulation.

Auto-antibodies & type I IFN & COVID-19

Auto-Abs against all IFN- α subtypes?

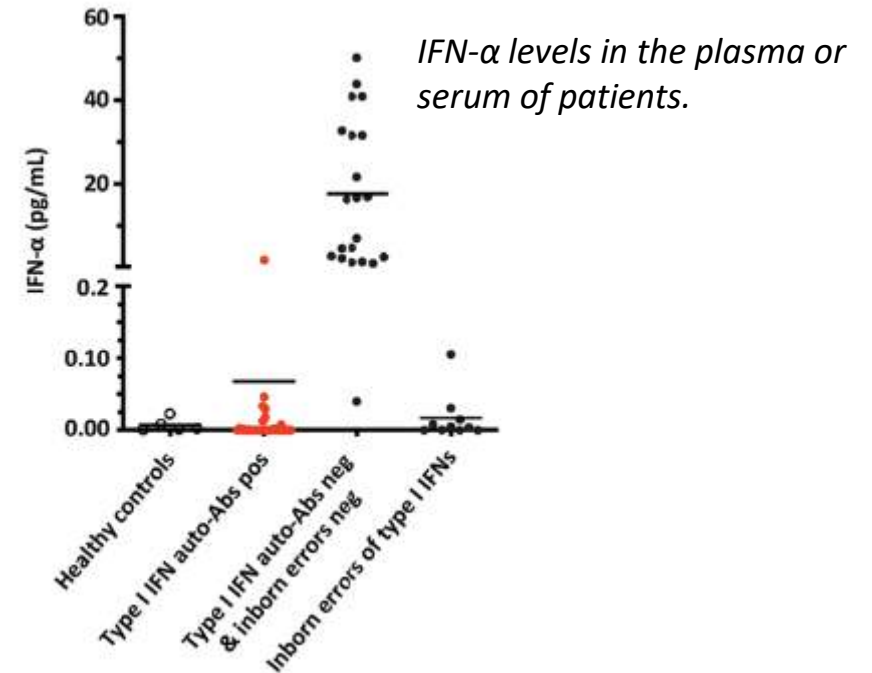
- All patients (22) with neutralizing auto-Abs against IFN- α 2 had auto-Abs against all 13 IFN- α subtypes
- **Early treatment with IFN- α is unlikely to be beneficial**

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- α 2, 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



→ 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

Neutralizing antibodies to SARS-CoV-2 infection

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

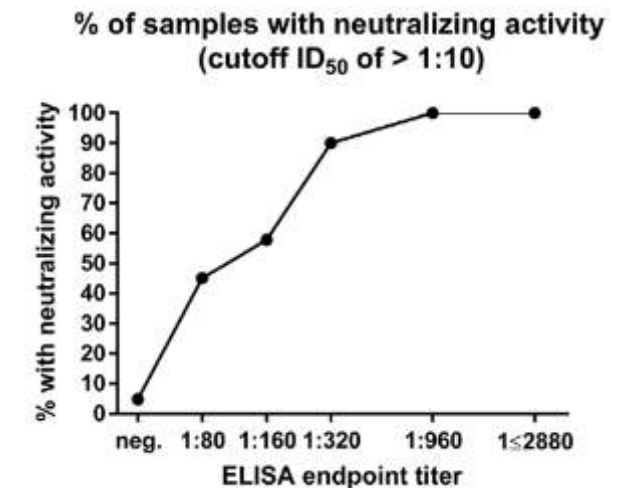
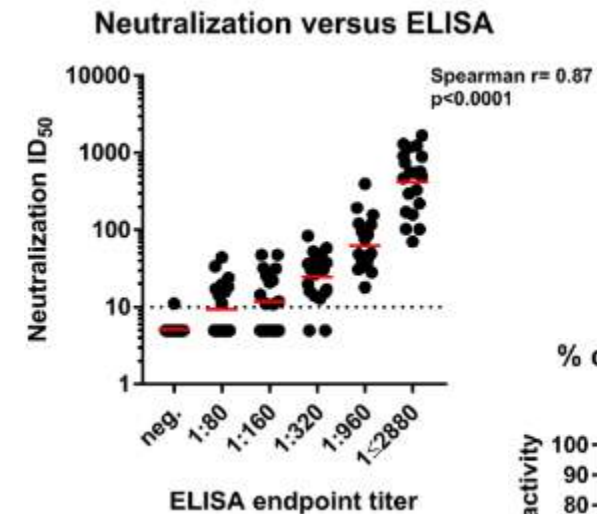
Mont Sinai Health System screen individuals for antibodies to SARS-CoV-2

- 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

Neutralizing effects \rightarrow quantitative microneutralization assay

- 120 samples of known ELISA titers ranging from negative to $\geq 1:2880$
- **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.



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?

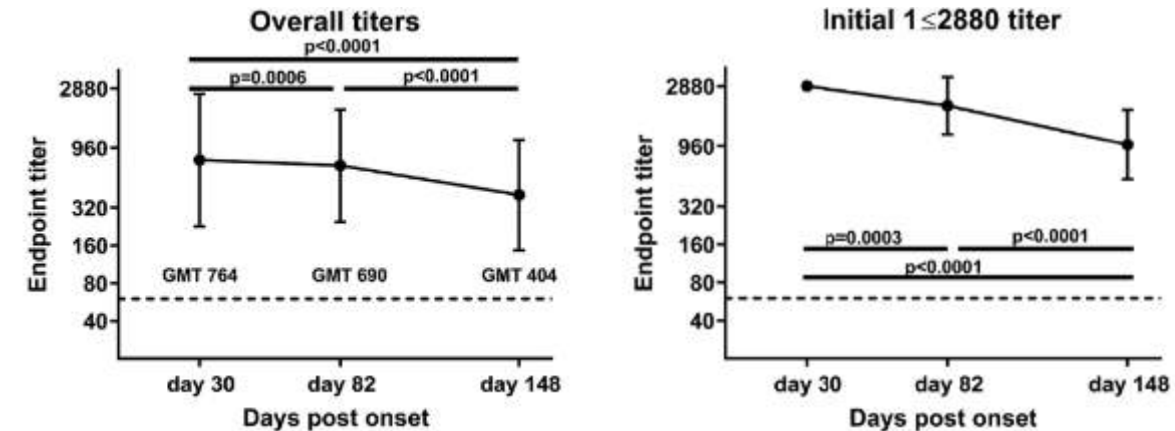
- Still unclear for infection with SARS-CoV-2 **in humans**

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

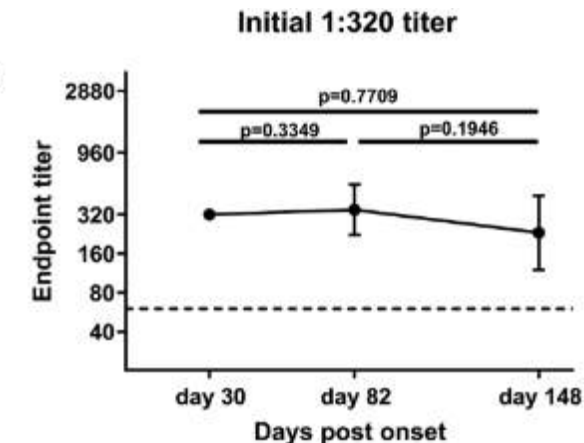
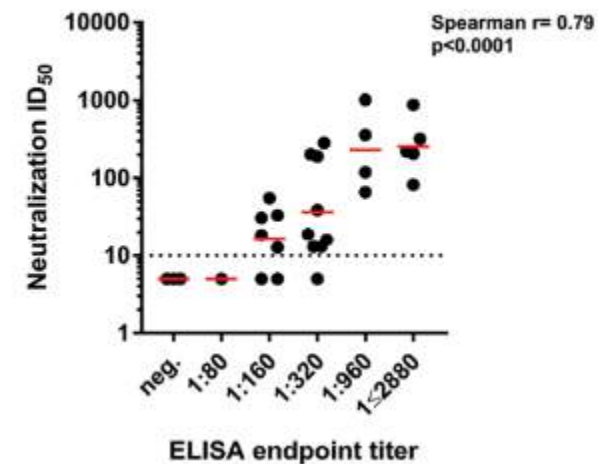
→ Correlation between spike-binding titers and neutralization titers

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

Antibody titer stability over time



Correlation of neutralization versus ELISA at day 148 time point



Cannot provide conclusive evidence : these antibody response protect from reinfection?

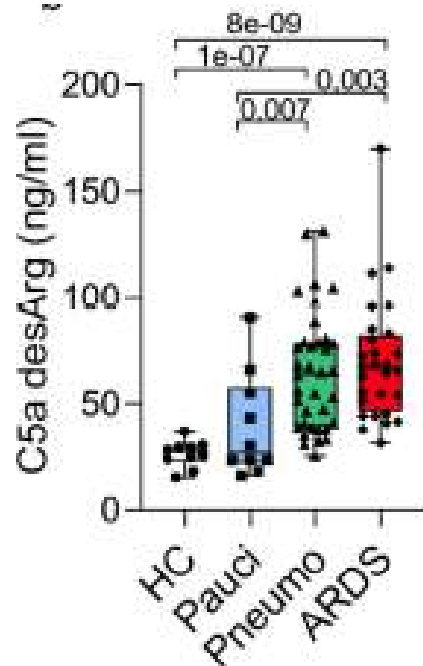
C5a-C5aR1 axis & COVID-19

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.

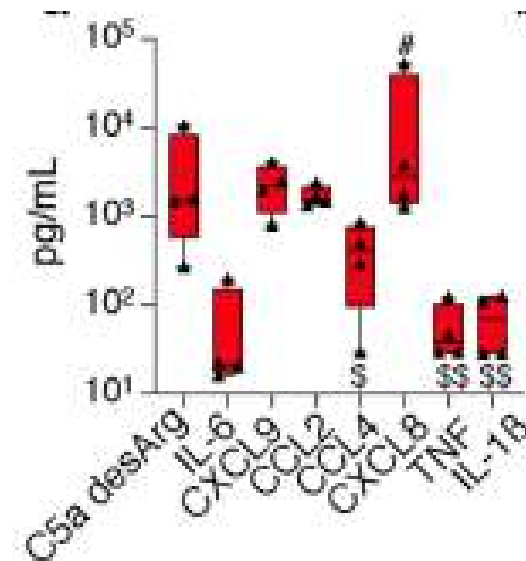
Concentration of C5a desArg in plasma



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



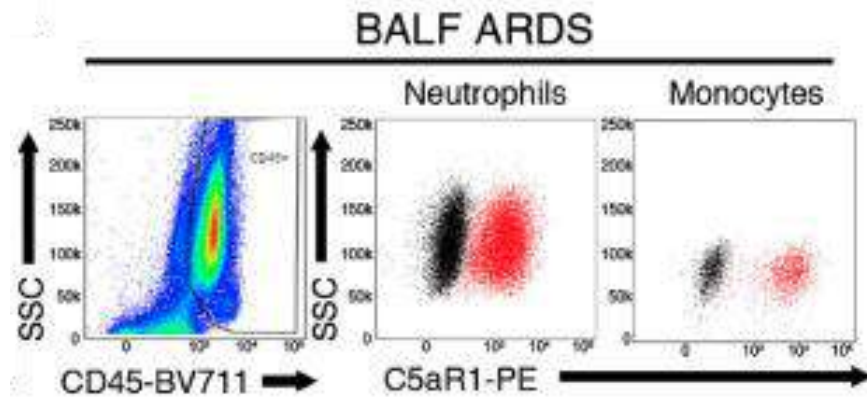
Saliva specimens could be effective in the diagnosis of COVID-19

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

Risk factors of mortality

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

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

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

30 days all cause of mortality = 5,2%

Risk factors of death:

Sex:

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

Age:

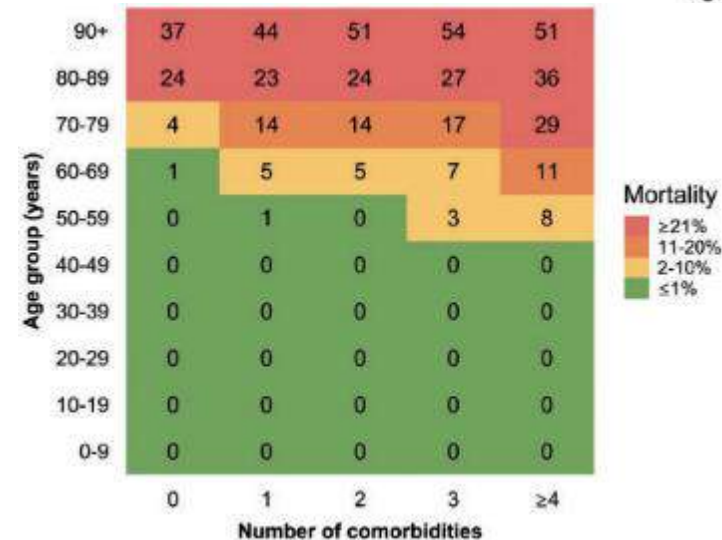
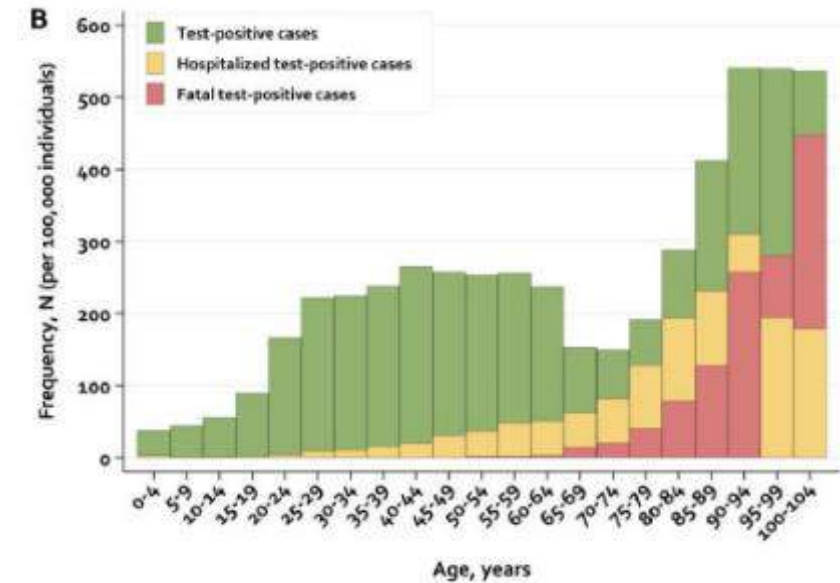
- 70 – 79 years: OR= 15; CI_{95%} [9– 26]
- 80-89 years: OR= 30; CI_{95%} [17–52]
- >90 years: OR= 90; CI_{95%} [50–162]

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



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

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

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**

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

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.^a

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. (%)	no./total no. (%)	percentage points	no./total no. (%)	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)

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

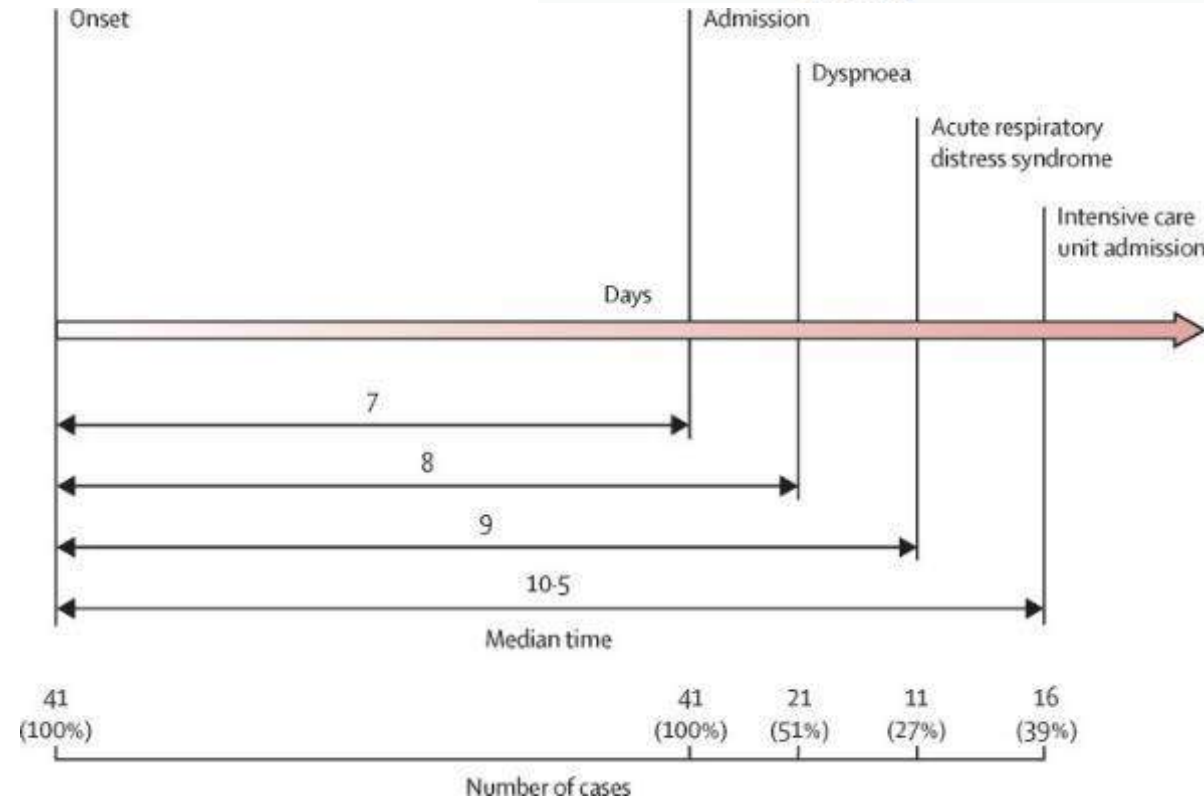
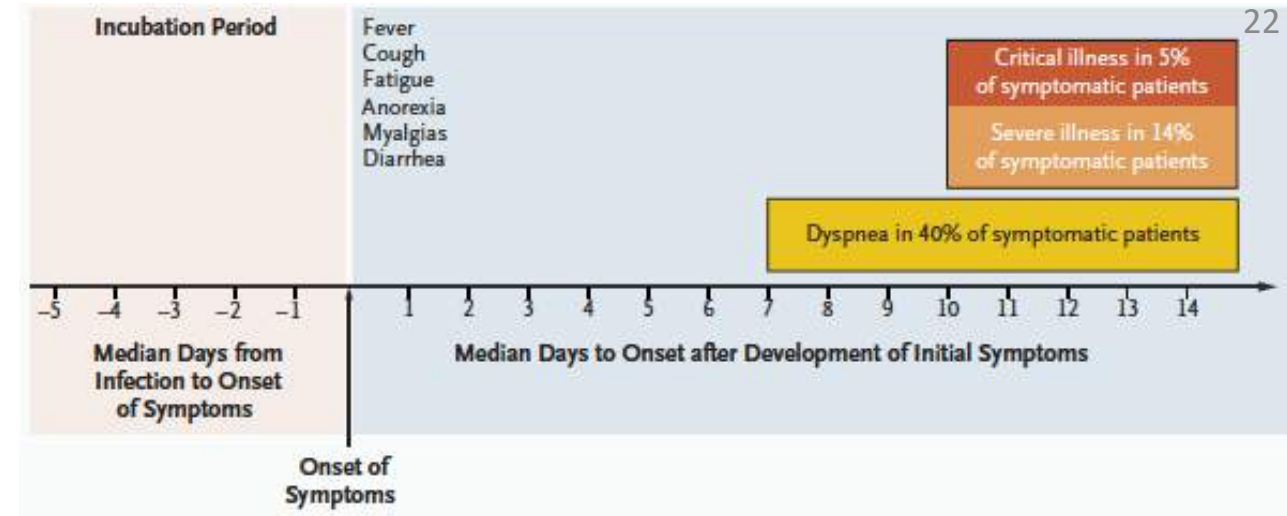
Limits

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

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]



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 %

Abnormal chest CT: 1130 (71,1 %)

Outcomes

- Pharyngalgia: 14,7 %
- Headache: 15,4 %
- Chill: 12,2 %
- Nausea/vomiting: 5,8 %
- Diarrhea: 4,2 %
- Critical illness: 131 (8,24 %)
- ICU admission: 99 (6,23 %)
- Mechanical ventilation: 50 (3,1 %)

Case fatality rate: 50 (3,1 %)

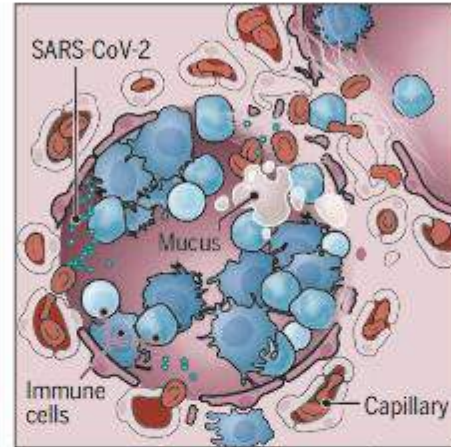
Organ damage

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.

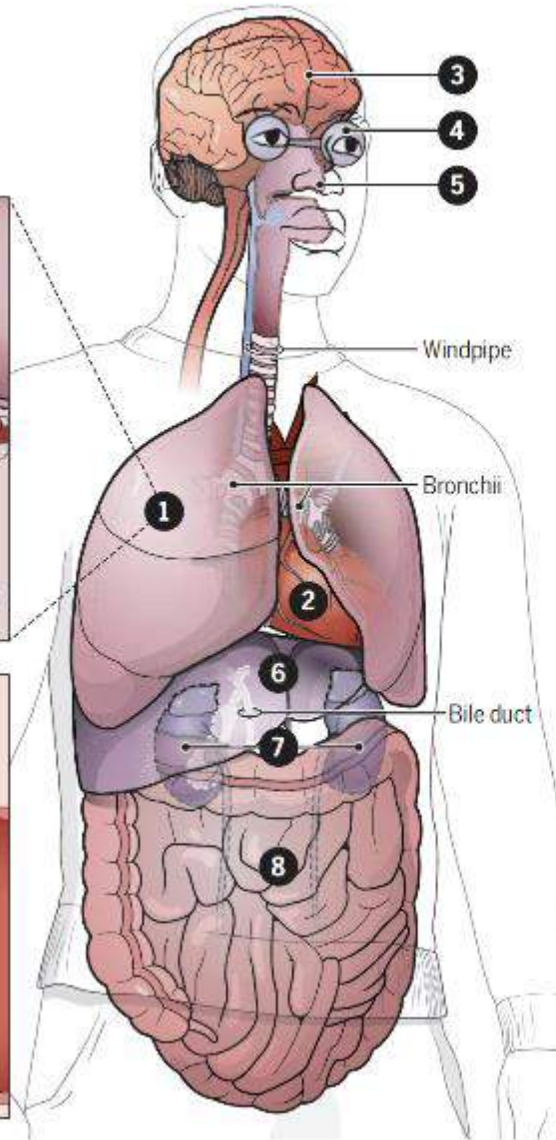
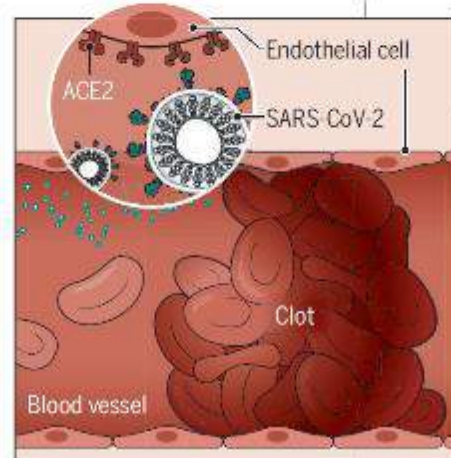
1 Lungs

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.

Radiology

Monocentric – from 16 January to 17 February

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

CT interpretation (366 CT scan)

→ Each lung divided into 3 zones

→ Overall CT score (max = 24)

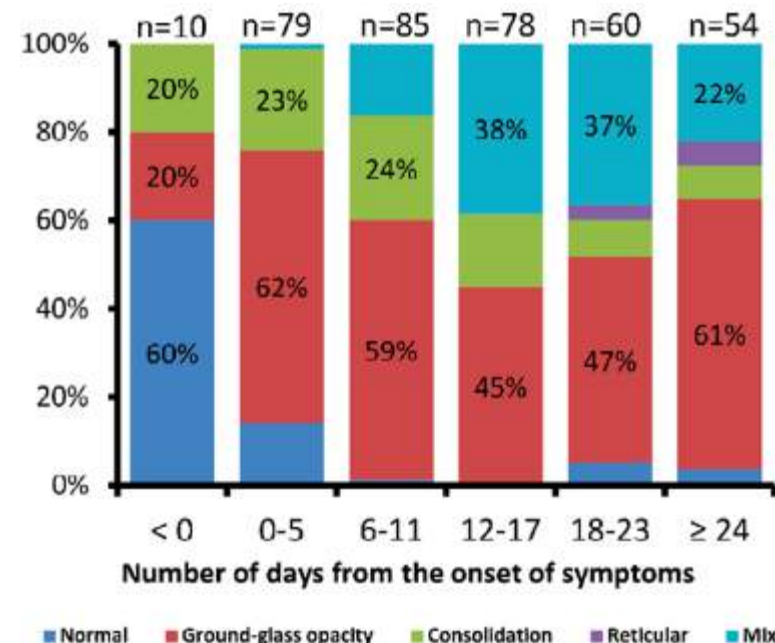
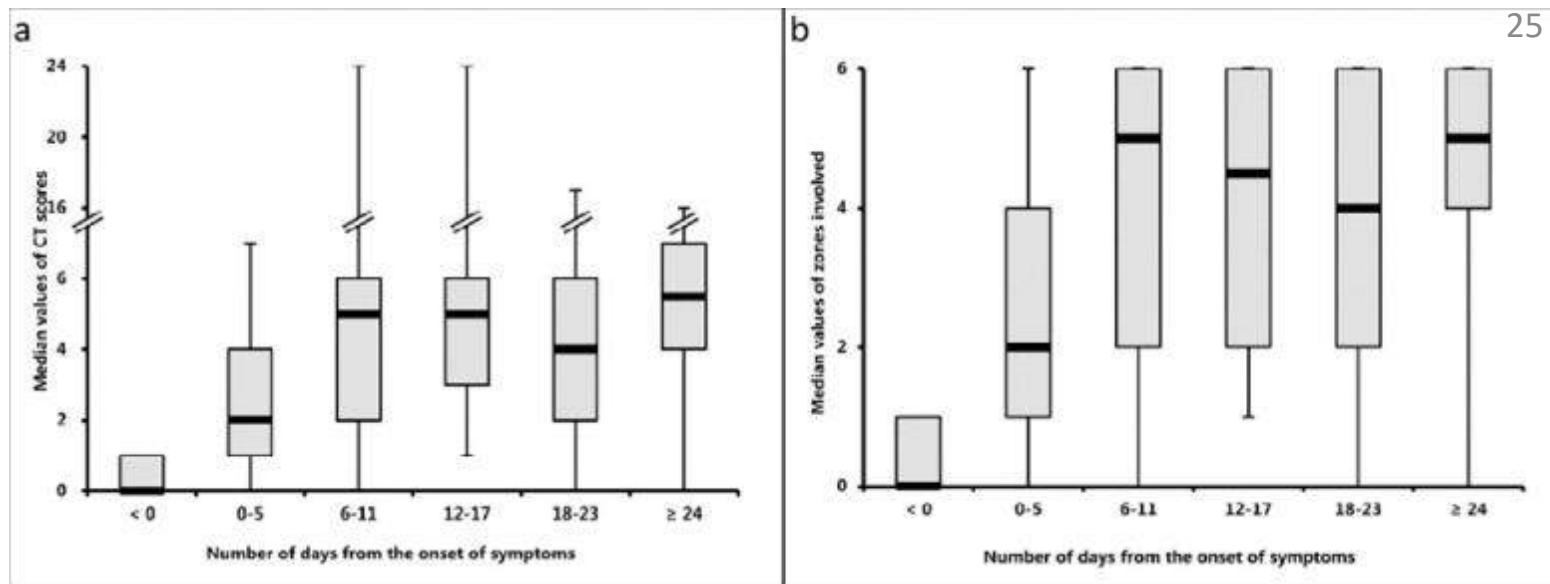
Results

- 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

Limitations : No subgroup analysis (mild and severe)

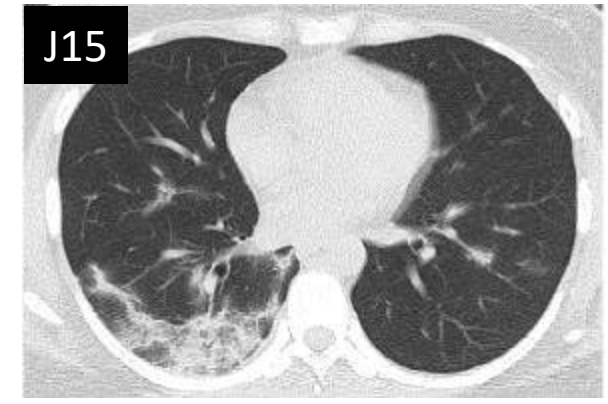
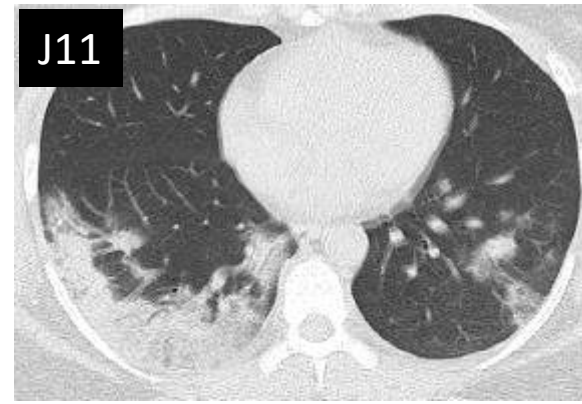
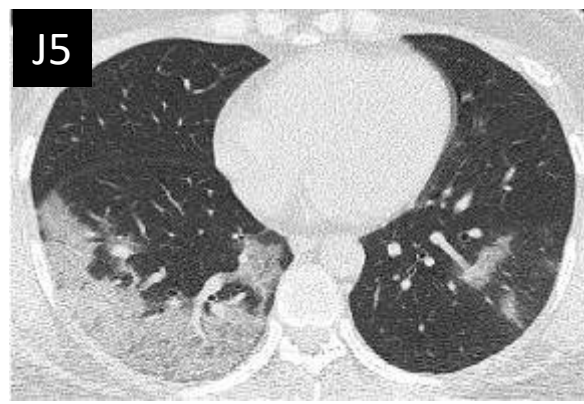
→ **Bilateral GGO is the most common manifestation**

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



Radiology

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



TIME



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

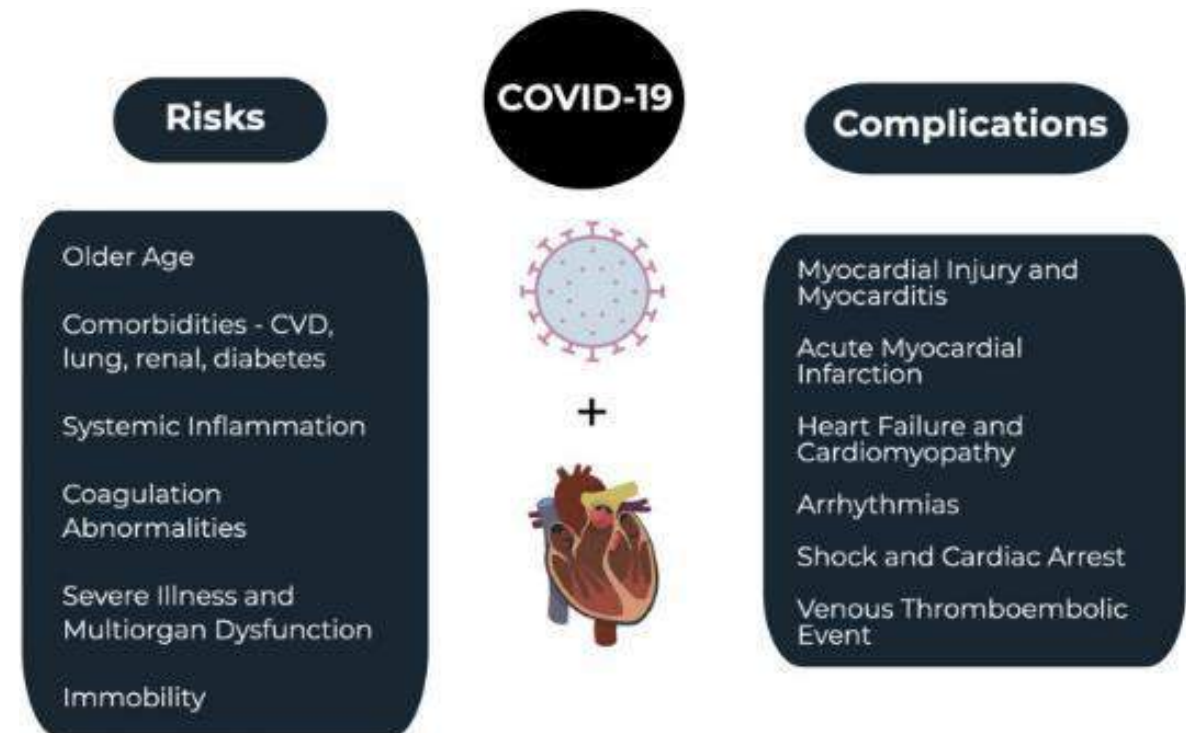
- 17% of hospitalized and 44% of ICU patients
- Hypoxia, inflammatory, abnormal metabolism

Venous thromboembolic event

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

ECG and echocardiographic abnormalities

- Correlated with worse outcomes



Kidney & COVID-19

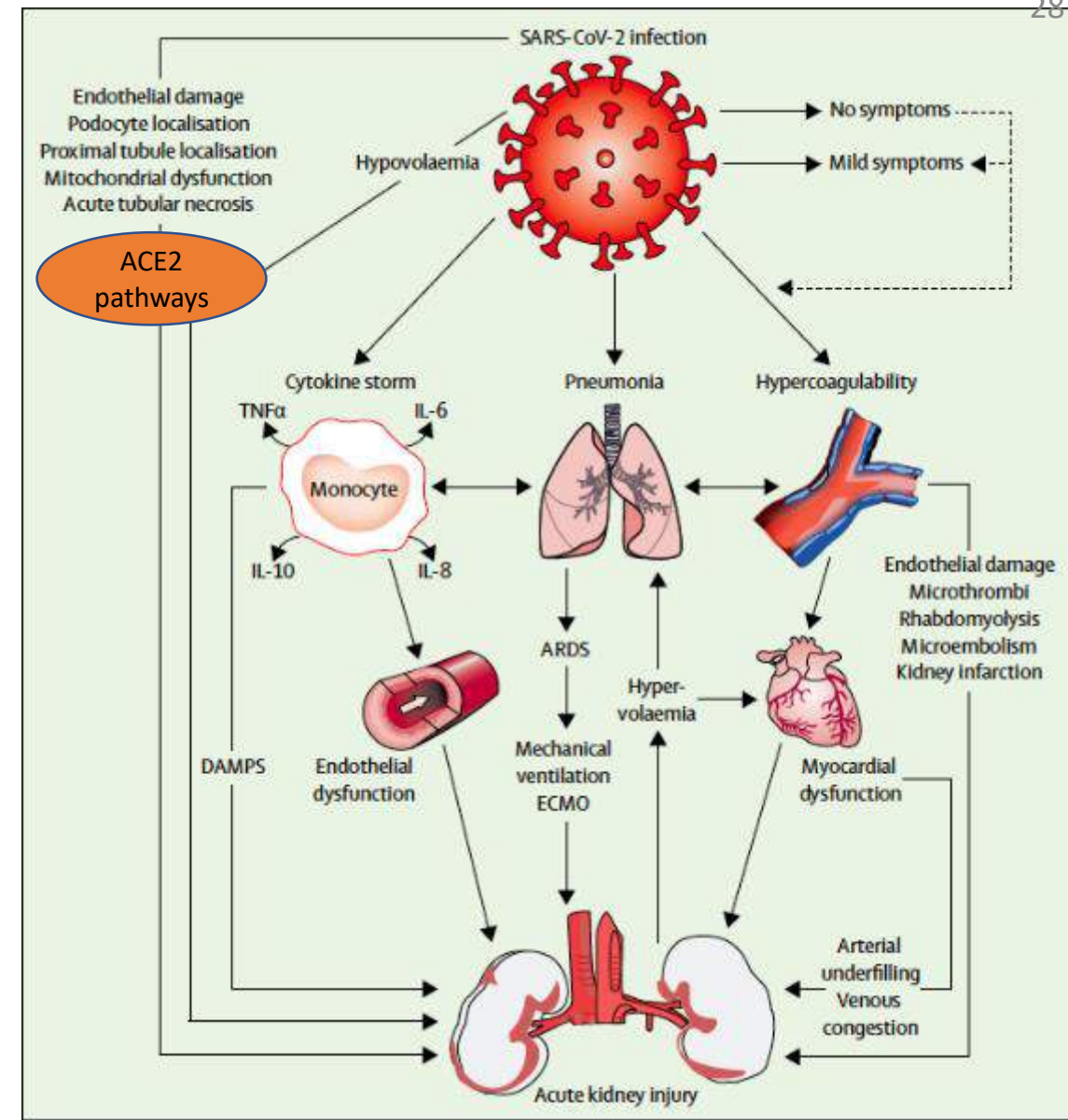
Introduction

- > 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



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

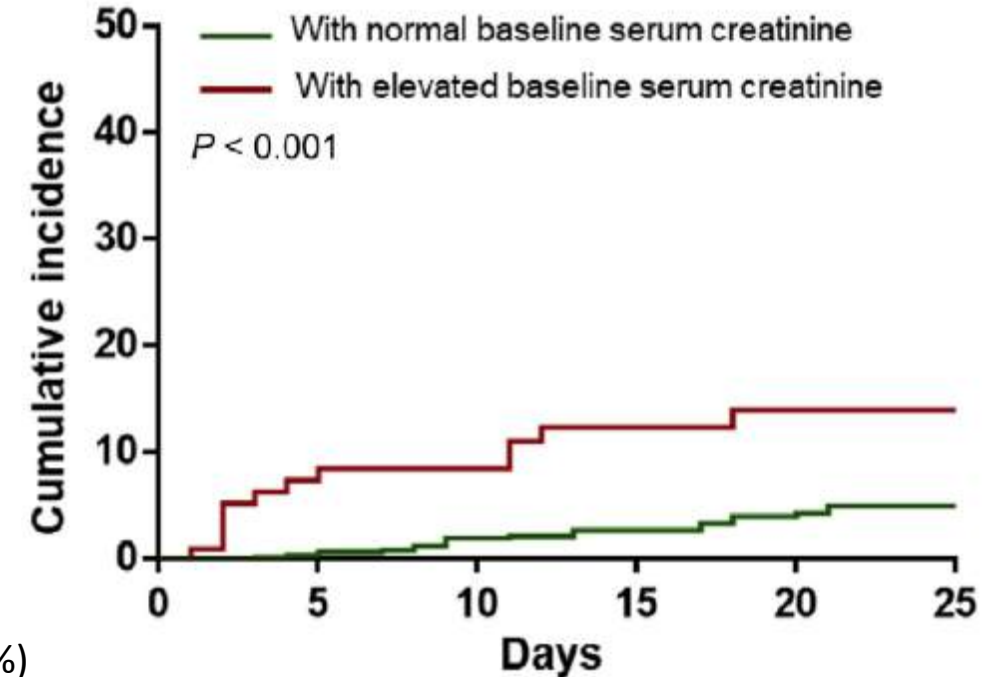
Kidney injury (at admission)

- Elevated serum creatinine (SC) at admission 14,4%
- Elevated BUN at admission 13,1%
- GFR<60 ml/min/1,73m² for 13,1%
- Proteinuria (43,9%) & hematuria (26,7%)

AKI and hospital death

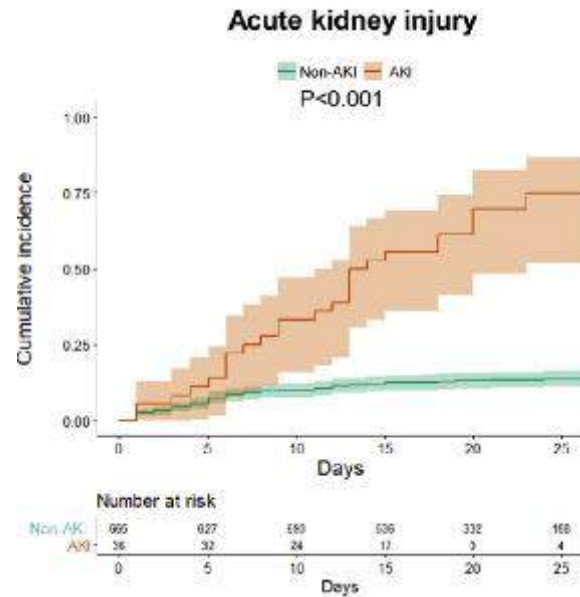
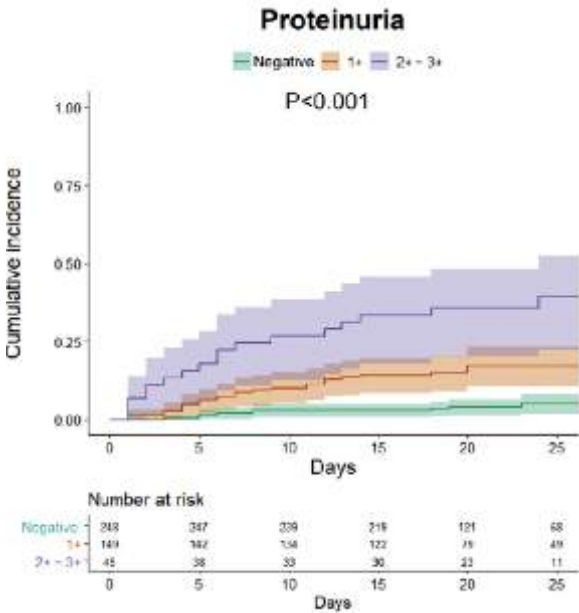
- Prevalence of AKI: 5,1% - higher in patients with elevated SC at admission(11,9%)
- In hospital death: 16,1%
 - 33,7% in patient with elevated SC at admission vs 13,2% others (p<0,05)

Cumulative incidence of AKI subgrouped by baseline serum creatinine



Kidney & COVID-19

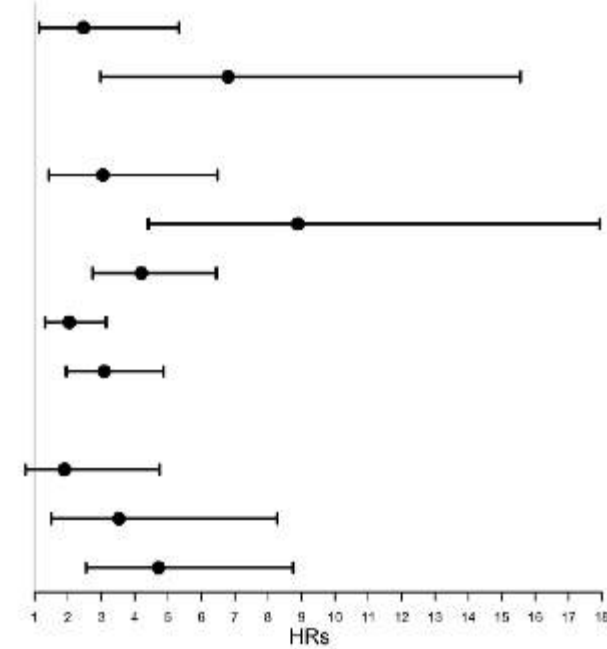
Kidney abnormalities → ↑ in hospital death



Cumulative incidence for in-hospital death

After adjusting

Variables	HRs	95% CI
Proteinuria		
1+	2.47	1.15-5.33
2+ ~ 3+	6.80	2.97-15.58
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

4 clinical syndromes associated with COVID-19

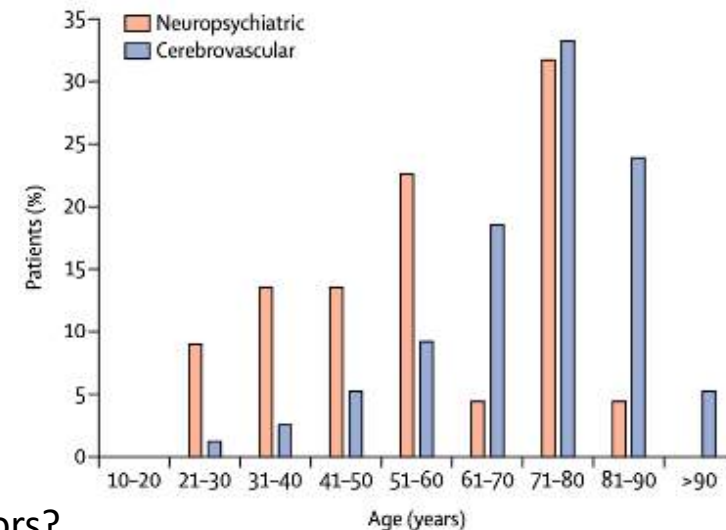
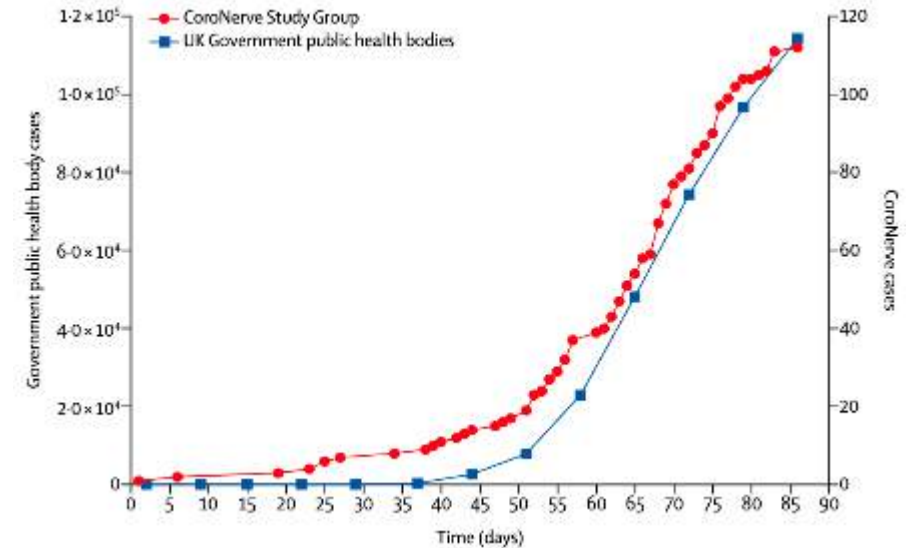
- **Cerebrovascular event** = 77 cases
 - Ischemic stroke / intracerebral hemorrhage
- **Altered mental status** = 39 cases
 - Encephalopathy /encephalitis / primary psychiatric diagnoses / ...
- **Peripheral neurology** = 6 cases
- **Other neurological disorders** = 3 cases

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

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.

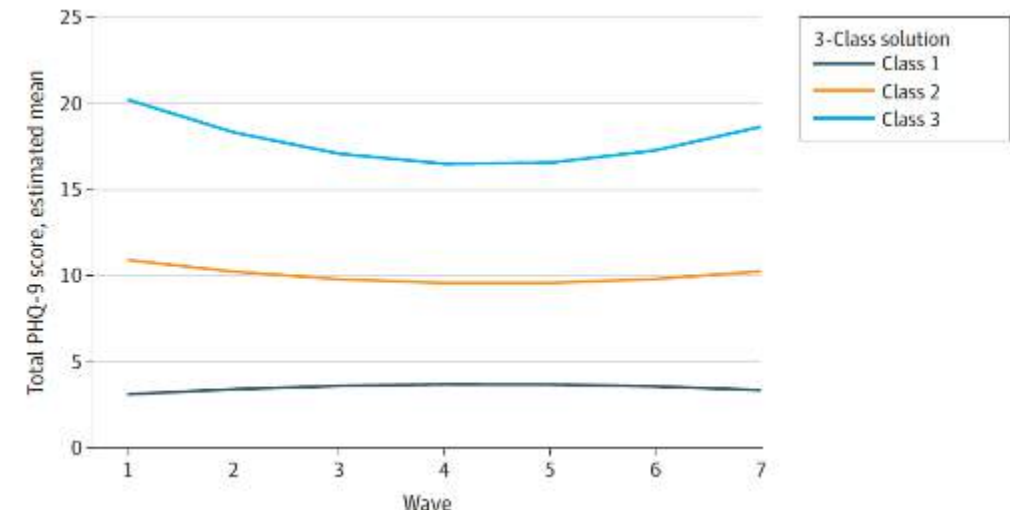
51 417 participants:

- 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 health 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

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:

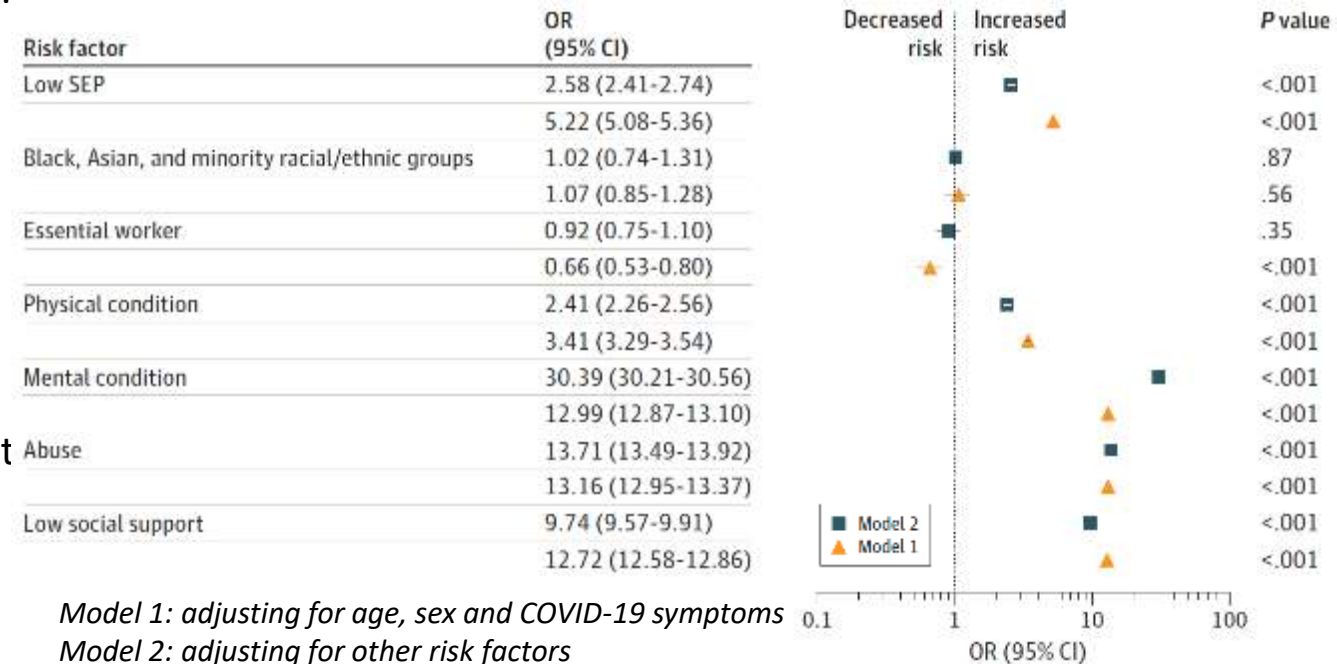
- Mean PHQ-9 score more than 2-fold higher

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

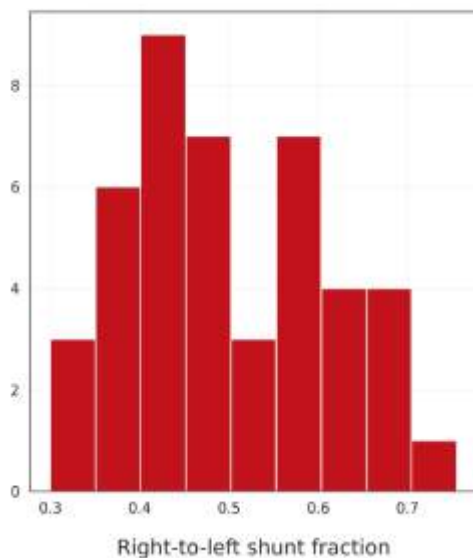
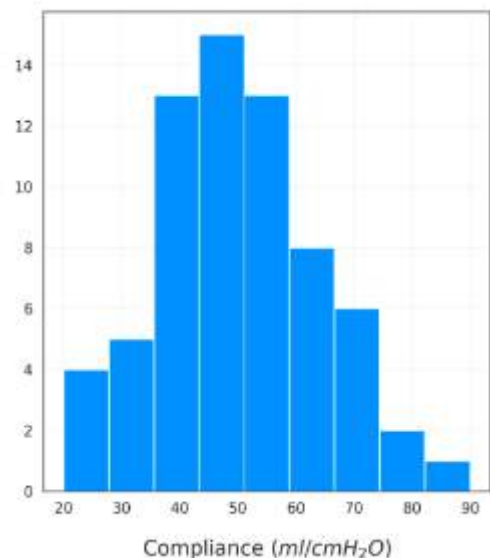


→ The odds of severe depressive symptoms were more than 5-fold higher in those facing socioeconomic disadvantage

→ Importance of developing 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



Type «L»: Low elastance

- Gas volume nearly normal
 - **Vt 7-8 ml/kg** → **DV<14cmH₂O**
- Recruitability is low
 - **PEP<12cmH₂O**
- 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<14cmH₂O**
- Recruitability is high
 - **PEP>12cmH₂O** (carefully)
- High lung weight → bilateral condensations
 - **Prone position**

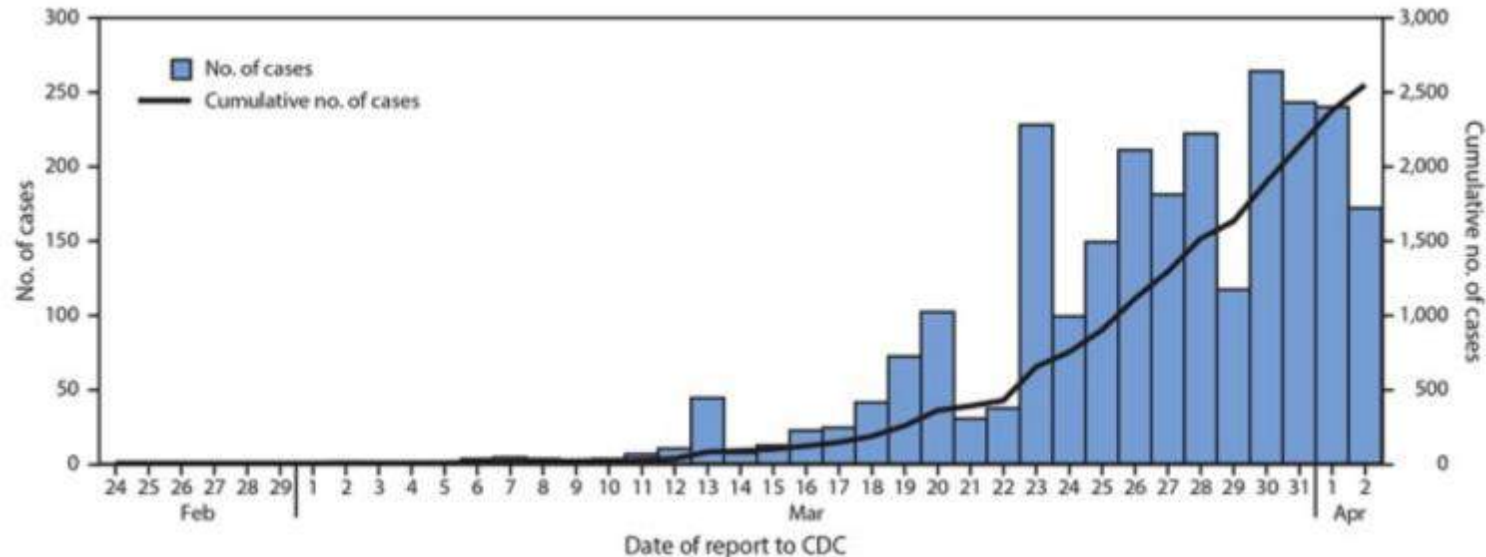
CT scan

A: spontaneous breathing

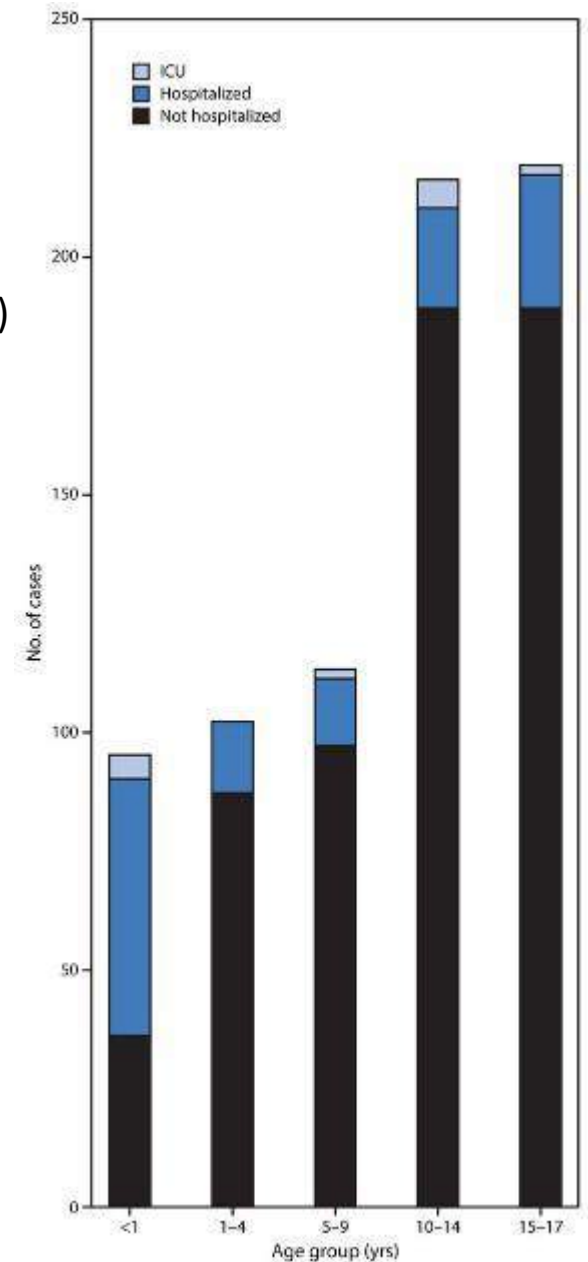
B: mechanical ventilation

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



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)

Evolution

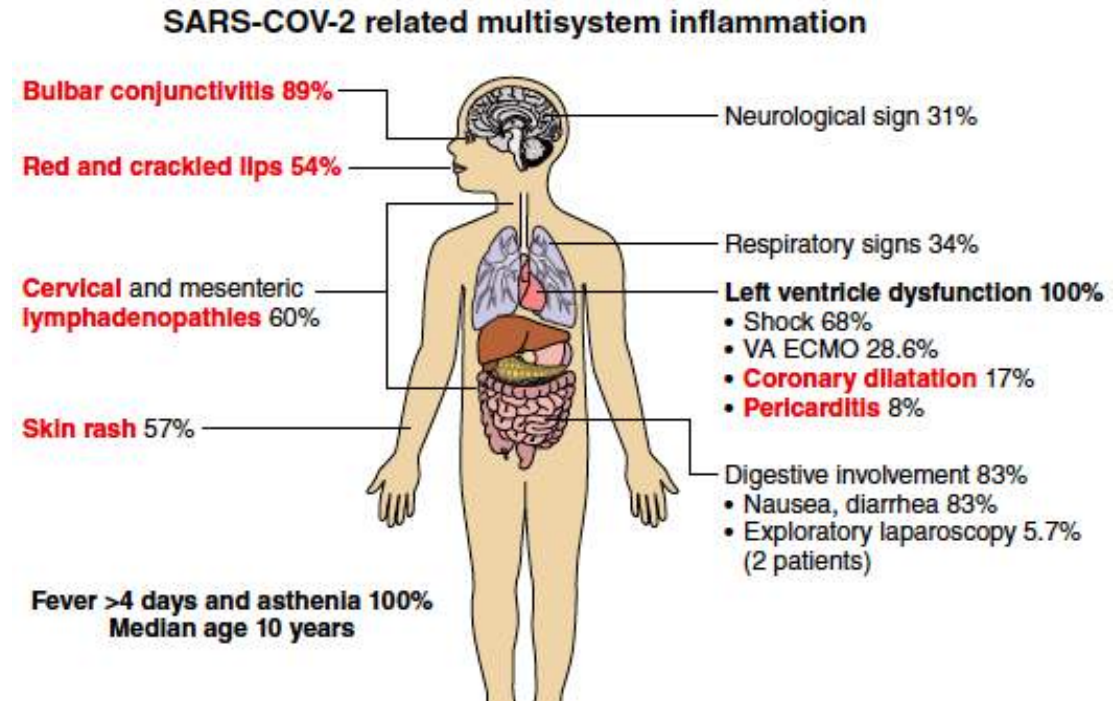
- 71% had total recovery left ventricular ejection fraction at day 7
- Time to full recovery = 2 days [2 – 5]

Treatment (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



Differences with Kawasaki disease

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

Pediatric inflammatory multisystem syndrome

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

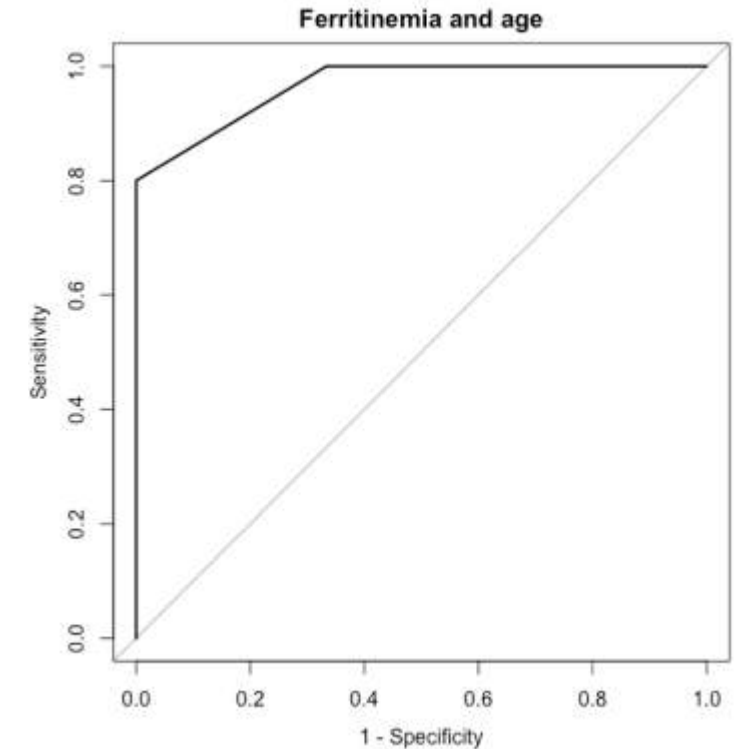
Compared with a historical cohort of «classical KD» (→ 220 patients)

Cohort of Kawa-COVID-19

- 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

Kawa-COVID-19 versus historical cohort

- 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



Factor prognostic for the development of severe disease

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

CLINICAL (December 21th 2020)

1. What is the mechanism of action of SARS-CoV-2? Cell immunity?

- Uses ACE2 receptor to enter the cell and can produce a hyper-inflammatory response
- Activation of innate and adaptive immune pathways
- Induces long lasting T cell immunity against the structural N protein
- Recurrent anti-SARS-CoV-2 RBD antibodies with potent neutralizing activity can be found in all individuals
- Auto-Abs against type I IFNs are a cause of severe SARS-CoV-2 infection
- Recovered from mild COVID-19 → robust antibody response to spike protein
- Good correlation between neutralization and ELISA titers & Stable antibody titers 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



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