

COVID-19 et Rein

Episode 6

Pr S. Burtey

Centre de néphrologie et transplantation rénale

AMU

AP-HM

Marseille

02/06/2020



Confluences d'intérêts

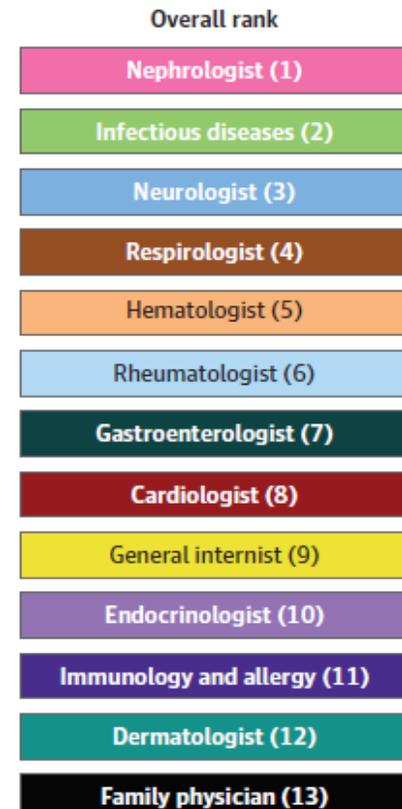


Confluence, Not Conflict of Interest

Name Change Necessary *JAMA*. 2015;314(17):1791-1792

- Otsuka
- Amgen
- Fresenius Kabi
- Baxter
- Alexion
- Bayer
- Je travaille sur les toxines urémiques
- Je suis néphrologue

Figure 2. Complexity Rankings by Physician Type

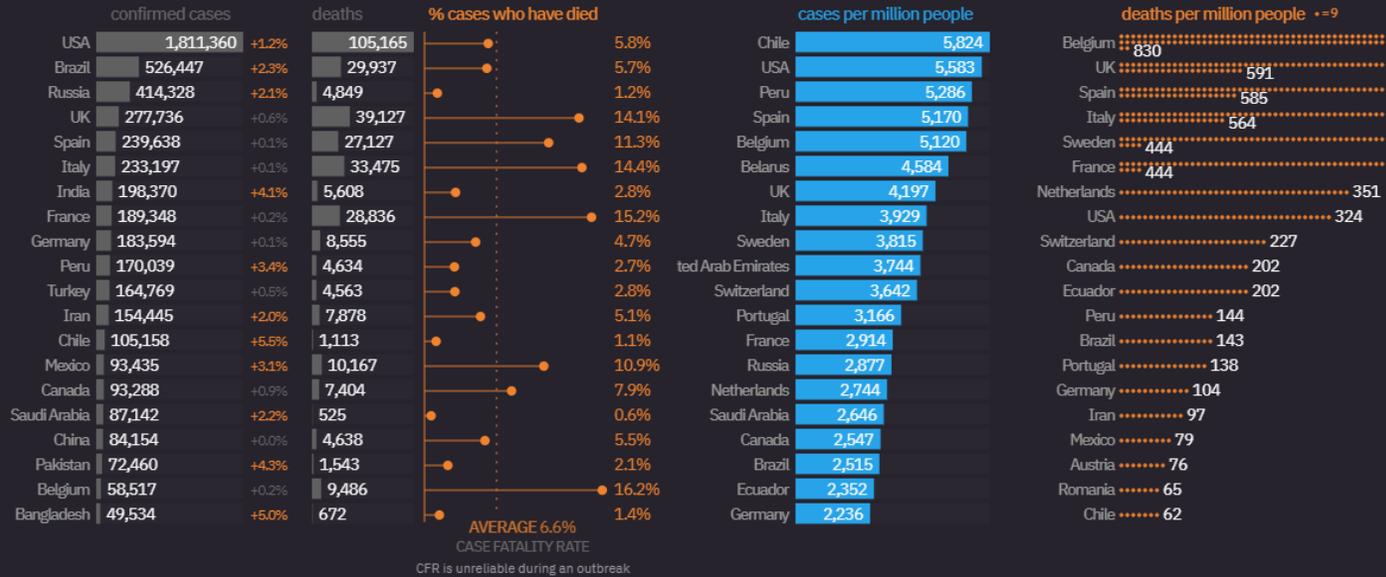


Nouvelles du front

Infection & Fatality Rates Vary by Country

Quality of healthcare, average age of population - both factors

updated 2 Jun 2020



informationisbeautiful Univrs Labs

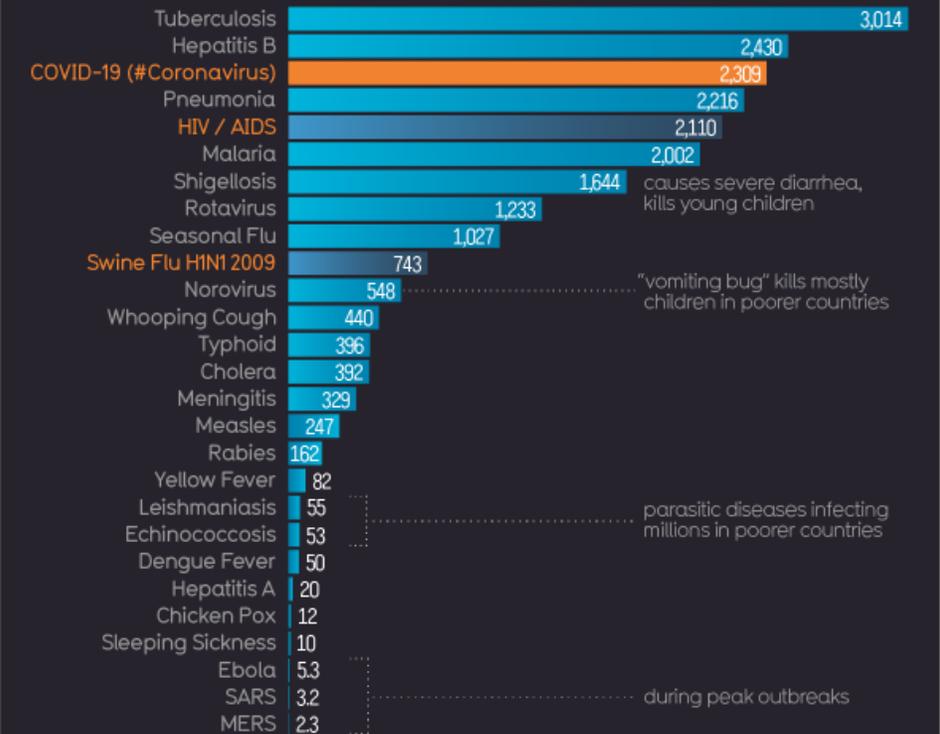
sources: Johns Hopkins University

<https://informationisbeautiful.net/visualizations/covid-19-coronavirus-infographic-datapack/>

Confirmed cases **6,121,582** Deaths **365,840**

Average Disease Deaths per Day Worldwide

updated 22nd May 2020



pandemic (global outbreak) endemic (always around)
sources: US Centres for Disease Control, WHO, The Lancet

L'infodémie, une décroissance?

- 17926 articles dans Pubmed (02/06/2020)
<https://www.ncbi.nlm.nih.gov/pubmed/?term=covid-19>
- 4501 preprints dans BioRxiv <https://connect.biorxiv.org/relate/content/181>
 - Vous êtes le reviewer... Nécessite une lecture attentive voir très attentive.
- 1077 preprints dans arXiv <https://arxiv.org/search/?query=covid-19>
- 1073 essais cliniques dans ClinicalTrials
 - 23 completed
 - Aucun avec des résultats sur le site
- Comment gérer ce flot
 - <https://www.sciencemag.org/news/2020/05/scientists-are-drowning-covid-19-papers-can-new-tools-keep-them-afloat>



SARS-COV-2 et la COVID-19 en chiffre

SARS-CoV-2 (COVID-19) by the numbers

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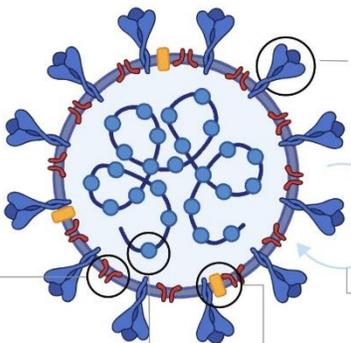
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Comments are welcome; this article is being updated on an ongoing basis at: <https://bit.ly/2W0eN64>

Size & Content

Diameter: ≈ 100 nm
Volume: $\sim 10^6 \text{ nm}^3 = 10^{-3} \text{ fL}$
Mass: $\sim 10^3 \text{ MDa} \approx 1 \text{ fg}$

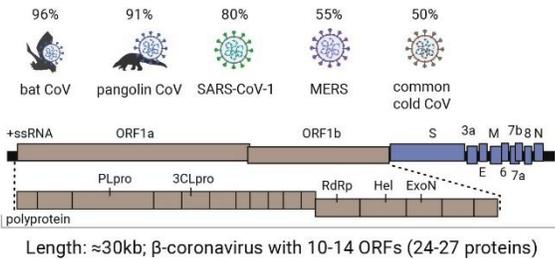


Spike trimer
Length: ≈ 10 nm
Copies per virion: ≈ 100
(300 monomers, measured for SARS-CoV-1)
Affinity to ACE2 receptor K_d : $\approx 1-40$ nM primed by TMPRSS2

Membrane protein ≈ 2000 copies (measured for SARS-CoV-1)
Nucleoprotein ≈ 1000 copies (measured for SARS-CoV-1)
Envelope protein ≈ 20 copies (100 monomers, measured for TGEV coronavirus)

Genome

Nucleotide identity to SARS-CoV-2



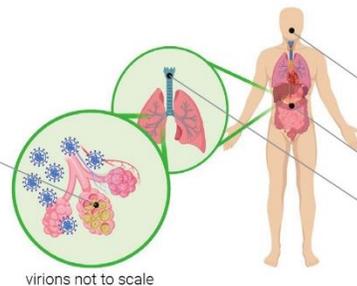
Evolution rate: $\sim 10^{-3} \text{ nt}^{-1} \text{ yr}^{-1}$ (measured for SARS-CoV-1)
Mutation rate: $\sim 10^{-6} \text{ nt}^{-1} \text{ cycle}^{-1}$ (measured for MHV coronavirus)

Replication Timescales

(in tissue-culture)
Virion entry into cell: ~ 10 min (measured for SARS-CoV-1)
Eclipse period: ~ 10 hrs (time to make intracellular virions)
Burst size: $\sim 10^3$ virions (measured for MHV coronavirus)

Host Cells

(tentative list, number of cells per person)
Type I & II pneumocytes ($\sim 10^{11}$ cells)
Alveolar macrophage ($\sim 10^{10}$ cells)
Mucous cell in nasal cavity ($\sim 10^9$ cells)
Host cell volume: $\sim 10^3 \mu\text{m}^3 = 10^3 \text{ fL}$



Concentration

(maximal observed values following diagnosis)
Nasopharynx: 10^6-10^9 RNAs/swab
Throat: 10^4-10^8 RNAs/swab
Stool: 10^4-10^8 RNAs/g
Sputum: 10^6-10^{11} RNAs/mL

RNA counts can markedly overestimate infectious virions

Antibody Response - Seroconversion

Antibodies appear in blood after: $\approx 10-20$ days
Maintenance of antibody response: $\approx 2-3$ years (measured for SARS-CoV-1)

Virus Environmental Stability

(relevance to personal safety unclear)

Half-life

(time to decrease 2-fold; not strictly constant)

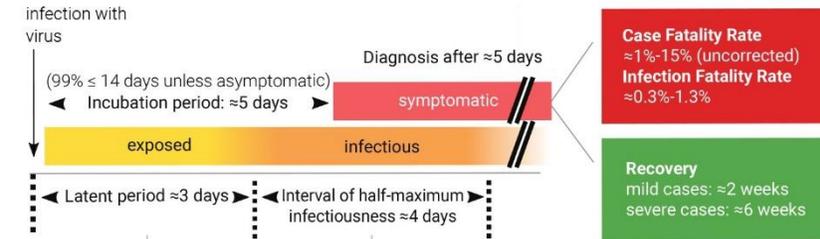
Aerosols: ≈ 1 hr
Surfaces: $\approx 1-10$ hr
e.g. plastic, glass, paper and metals

Based on quantifying infectious virions.
Numbers will vary between conditions and surface types.
Viral RNA observed on surfaces even after a few weeks.

Note the difference in notation between the symbol \approx , which indicates "approximately" and connotes accuracy to within a factor 2, and the symbol \sim , which indicates "order of magnitude" or accuracy to within a factor of 10.

"Characteristic" Infection Progression in a Single Patient

Basic reproductive number R_0 : typically 2-4
Varies further across space and time
(number of new cases directly generated from a single case)



Inter-individual variability is substantial and not well characterized. The estimates are parameter fits for population median in China and do not describe this variability.

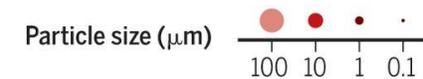
La transmission, l'émetteur

- Aérienne:
 - Gouttelette de 5 à 1000 μm
 - Aérosols $<5 \mu\text{m}$: majorité des infections transmises par les asymptomatiques (79% des infections)
 - Une minute de parole: 1000 virions
 - Gouttelette de 100 μm à 2 m en 4,6 s au sol
 - Gouttelette de 1 μm à 2 m en 12,4 h au sol
 - Le virus vit une heure dans cet aérosol
- Contact: aérien ou surface
- Selles: Possible à probable

10.1038/s41586-020-2342-5

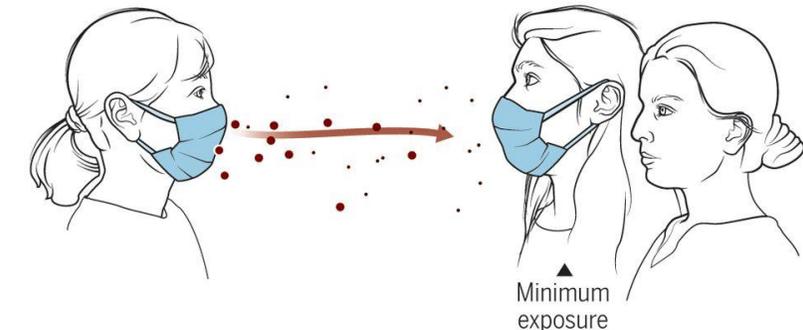
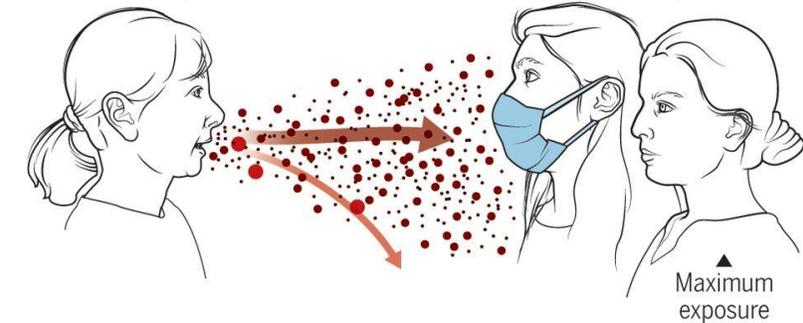
Masks reduce airborne transmission

Infectious aerosol particles can be released during breathing and speaking by asymptomatic infected individuals. No masking maximizes exposure, whereas universal masking results in the least exposure.



Infected, asymptomatic

Healthy

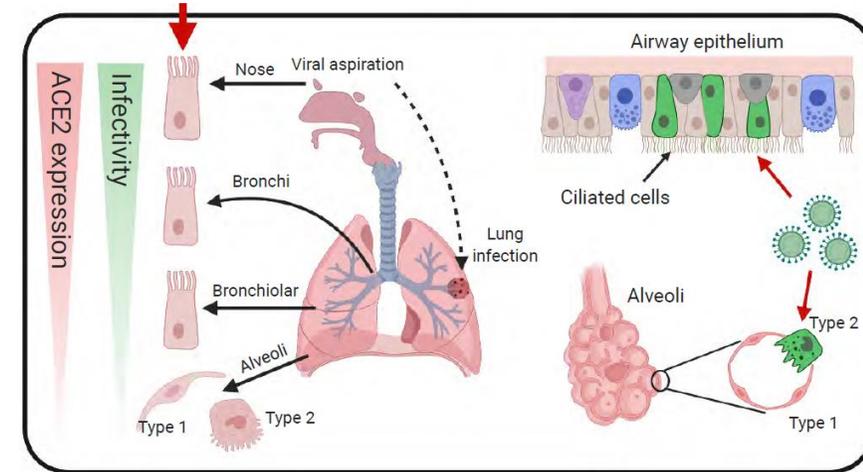


GRAPHIC: V. ALTOUNIAN/SCIENCE

<https://science.sciencemag.org/content/early/2020/05/27/science.abc6197>

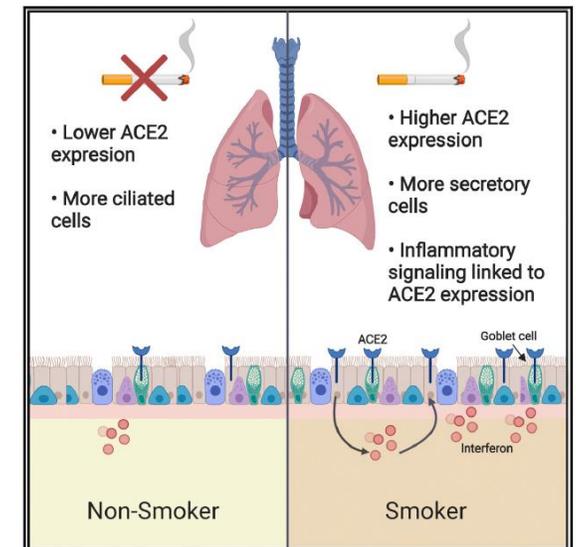
La transmission, le récepteur

- Gradient d'infectivité dans l'arbre respiratoire



<https://doi.org/10.1016/j.cell.2020.05.042>

- Dans le poumon, le tabac, comme les infections virales et l'interféron augmentent l'expression de ACE2



<https://doi.org/10.1016/j.devcel.2020.05.012>

Protection mécanique

- Distanciation sociale (masque, distance, lavage des mains)
- Malade et soignant doivent porter des masques quand ils se rencontrent
- Nettoyez les surfaces et aérer au maximum les espaces clos
- Attention au caca et aux toilettes
- Le masque

- Remarquable article historique sur l'émergence du jetable [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31207-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31207-1/fulltext)

<https://www.franceculture.fr/emissions/superfail/et-si-lerreur-cetait-de-vouloir-des-masques-jetables>

- Masque en tissus capable de bloquer les aérosols

- Importance de l'absence des espaces.
- <https://dx.doi.org/10.1021/acsnano.0c03252>

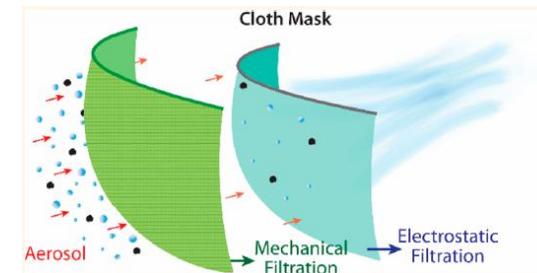


Table 1. Filtration Efficiencies of Various Test Specimens at a Flow Rate of 1.2 CFM and the Corresponding Differential Pressure (ΔP) across the Specimen^a

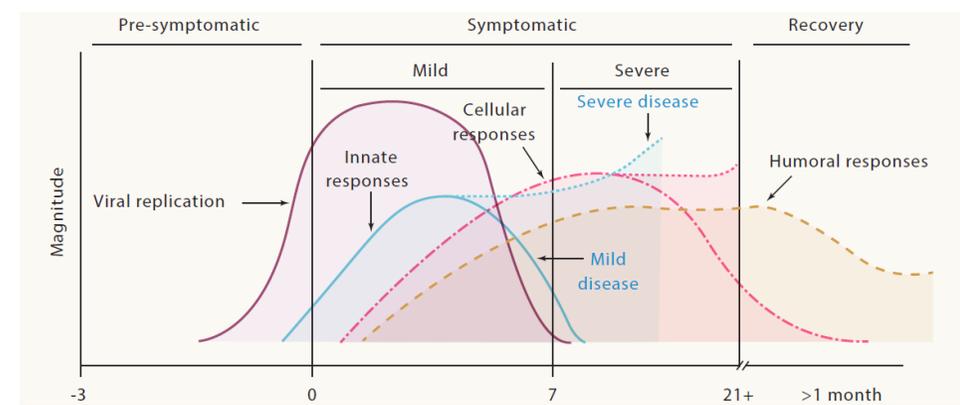
sample/fabric	flow rate: 1.2 CFM		
	filter efficiency (%)		pressure differential ΔP (Pa)
	<300 nm average \pm error	>300 nm average \pm error	
N95 (no gap)	85 \pm 15	99.9 \pm 0.1	2.2
N95 (with gap)	34 \pm 15	12 \pm 3	2.2
surgical mask (no gap)	76 \pm 22	99.6 \pm 0.1	2.5
surgical mask (with gap)	50 \pm 7	44 \pm 3	2.5
cotton quilt	96 \pm 2	96.1 \pm 0.3	2.7
quilter's cotton (80 TPI), 1 layer	9 \pm 13	14 \pm 1	2.2
quilter's cotton (80 TPI), 2 layers	38 \pm 11	49 \pm 3	2.5
flannel	57 \pm 8	44 \pm 2	2.2
cotton (600 TPI), 1 layer	79 \pm 23	98.4 \pm 0.2	2.5
cotton (600 TPI), 2 layers	82 \pm 19	99.5 \pm 0.1	2.5
chiffon, 1 layer	67 \pm 16	73 \pm 2	2.7
chiffon, 2 layers	83 \pm 9	90 \pm 1	3.0
natural silk, 1 layer	54 \pm 8	56 \pm 2	2.5
natural silk, 2 layers	65 \pm 10	65 \pm 2	2.7
natural silk, 4 layers	86 \pm 5	88 \pm 1	2.7
hybrid 1: cotton/chiffon	97 \pm 2	99.2 \pm 0.2	3.0
hybrid 2: cotton/silk (no gap)	94 \pm 2	98.5 \pm 0.2	3.0
hybrid 2: cotton/silk (gap)	37 \pm 7	32 \pm 3	3.0
hybrid 3: cotton/flannel	95 \pm 2	96 \pm 1	3.0

^aThe filtration efficiencies are the weighted averages for each size range—less than 300 nm and more than 300 nm.

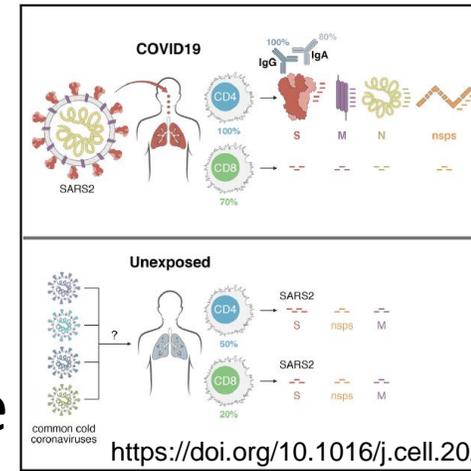
Protection biologique

- Il y a bien une réponse T avec probablement une réactivité croisée avec les autres coronavirus
- Il y a production d'anticorps neutralisants
- Une souris humanisée survivant à une première infection ne développera pas une deuxième maladie.
- Les données chez le macaque confortent la possibilité d'une immunisation efficace et d'une vaccination

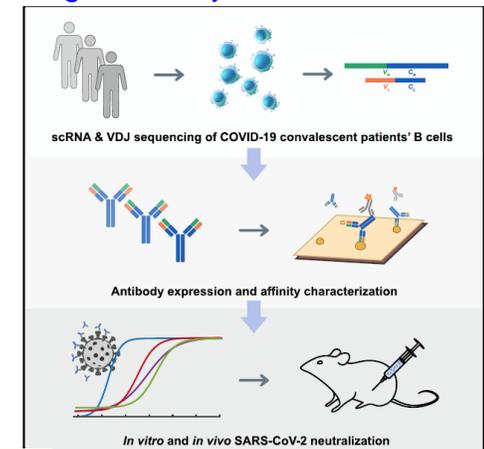
<https://science.sciencemag.org/content/early/2020/05/19/science.abc4776>
<https://science.sciencemag.org/content/early/2020/05/19/science.abc6284>



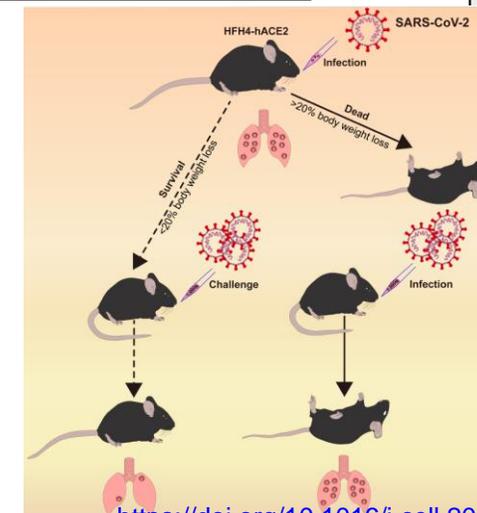
<https://doi.org/10.1016/j.immuni.2020.05.004>



<https://doi.org/10.1016/j.cell.2020.05.015>



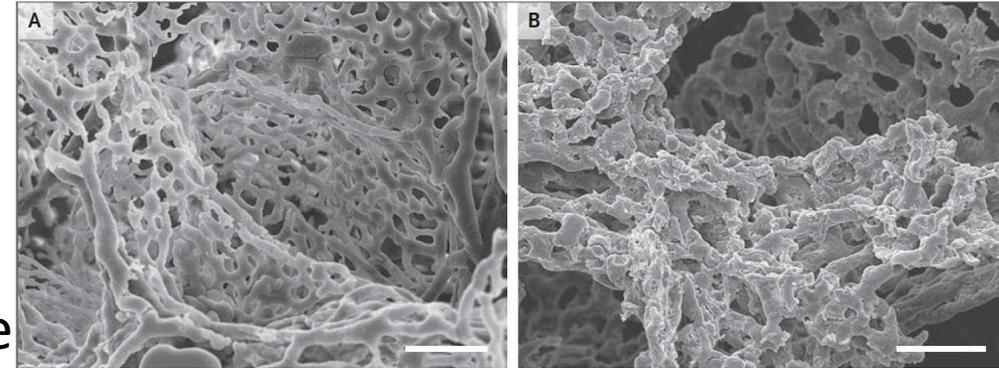
<https://doi.org/10.1016/j.cell.2020.05.025>



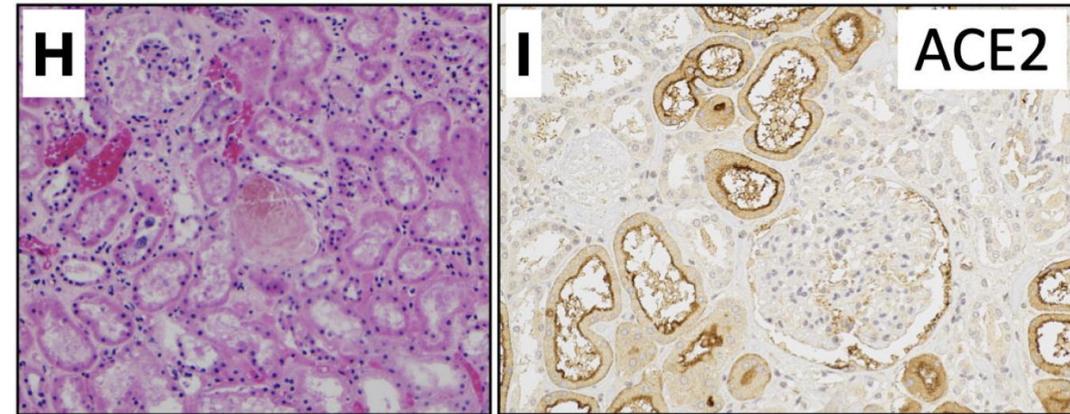
<https://doi.org/10.1016/j.cell.2020.05.027>

Un peu d'anatomopathologie

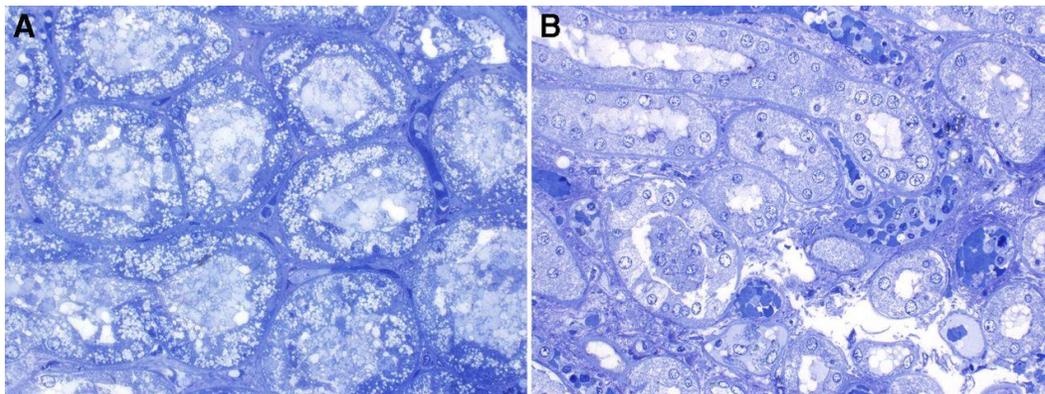
- Au niveau pulmonaire:
 - Inflammation
 - Lésion vasculaire et surtout endothéliale: thrombose
- Au niveau rénal:
 - Nécrose tubulaire aigue
 - Atteinte tubulaire proximale
 - Glomérulopathie plus anecdotique



10.1056/NEJMoa2015432



<https://www.medrxiv.org/content/10.1101/2020.05.18.20099960v1>



<https://jasn.asnjournals.org/content/early/2020/05/05/ASN.2020040432>

Une couronne n'est pas forcément un corona

- Corps microvesiculaires, vésicules à clathrine, microvésicules

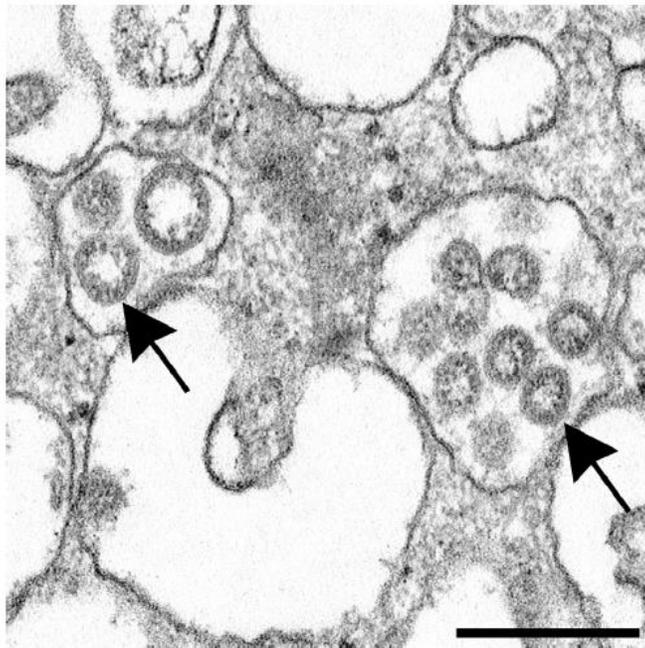


Figure 1 | Electron microscopic image of an isolate of severe acute respiratory syndrome coronavirus 2 seen here inside vacuoles (arrows). Note the dense membrane coat around the viral

<https://doi.org/10.1016/j.kint.2020.05.004>

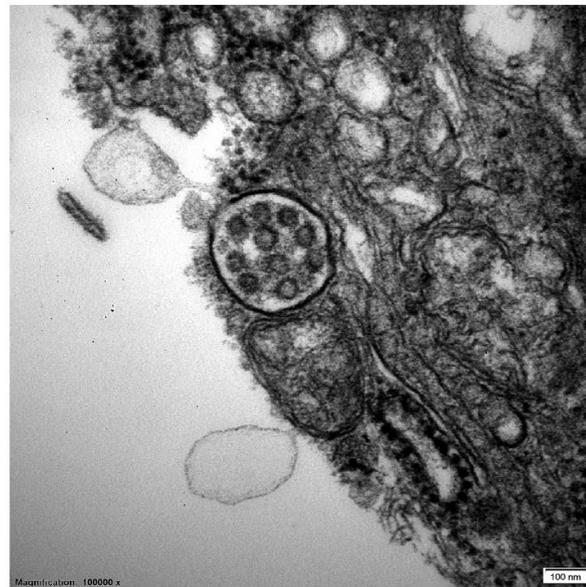
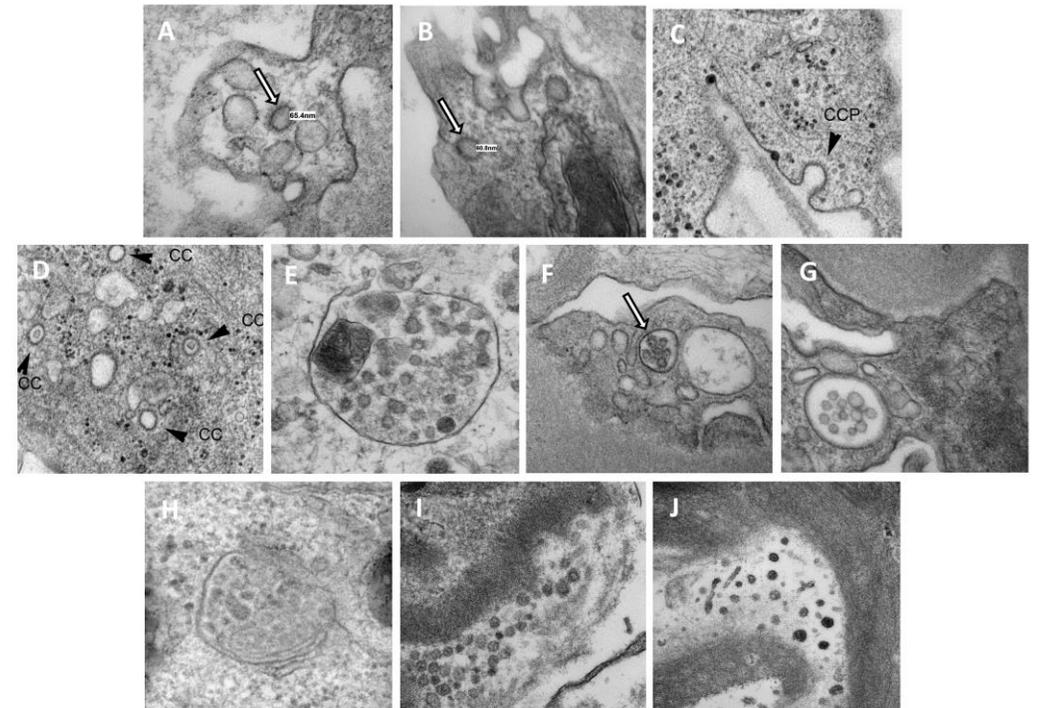


Figure 1 | Multivesicular body in a podocyte of a patient with lupus nephritis who tested negative for coronavirus disease 2019. Uranyl acetate-lead citrate, original

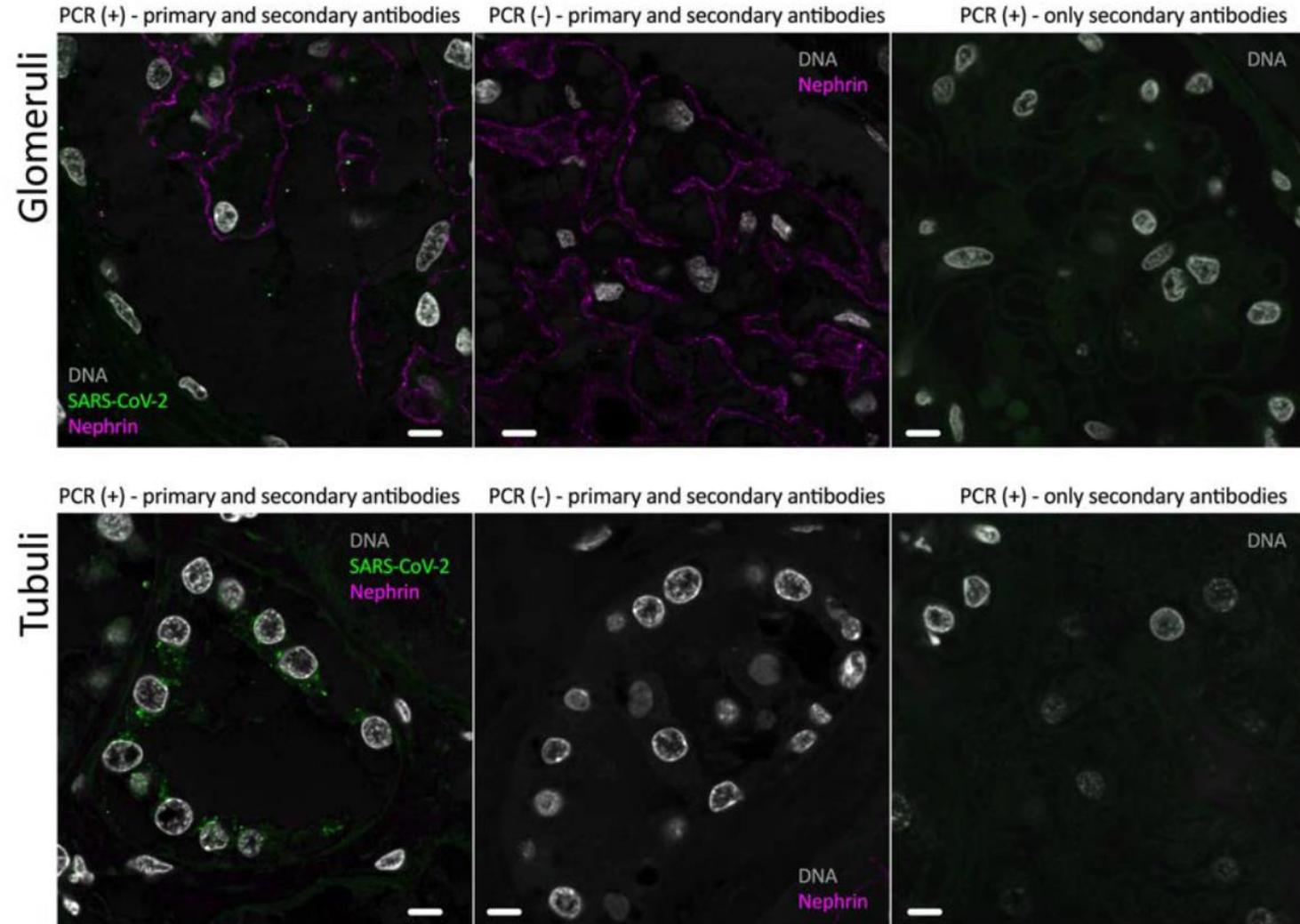
<https://doi.org/10.1016/j.kint.2020.05.003>



<https://doi.org/10.1016/j.kint.2020.05.012>

Tropisme rénal du virus

- 50% des 6 patients étudiés



Insuffisance rénale aigüe

- C'est fréquent et c'est grave...
 - Protéinurie 74% des patients
 - Leucocyturie 36%
 - Hématurie 46%
- Un guideline
 - Importance de la prise en charge de l'hypovolémie
 - *BMJ* 2020;369:m1963 doi: 10.1136/bmj.m1963

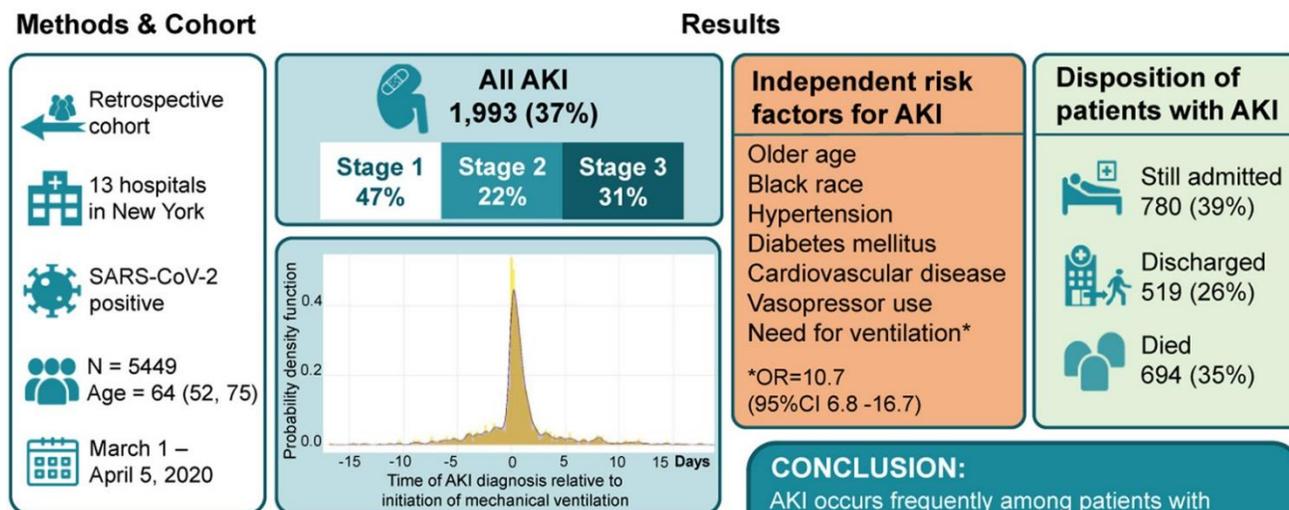
PRACTICE



GUIDELINES

Covid-19 and acute kidney injury in hospital: summary of NICE guidelines

Acute kidney injury (AKI) in patients hospitalized with COVID-19



ISN kidney INTERNATIONAL
Hirsch et al, 2020
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

10.1016/j.kint.2020.05.006

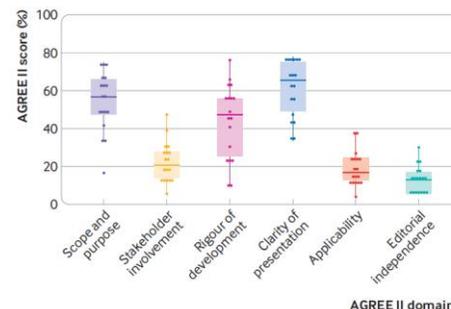


Fig 3 | Combined Appraisal of Guidelines for Research and Evaluation (AGREE) II assessment for all guidelines (n=18) as percentages of maximum possible score per domain. Vertical lines indicate range; horizontal line represents mean score for each domain

La maladie rénale chronique

- Ce n'est pas bon pour le pronostic de la COVID-19
- Le besoin en oxygène à l'entrée et la sévérité du syndrome inflammatoire ont plus d'impact que les comorbidités, hors insuffisance cardiaque et K.

BMJ 2020;369:m1966 | doi: 10.1136/bmj.m1966

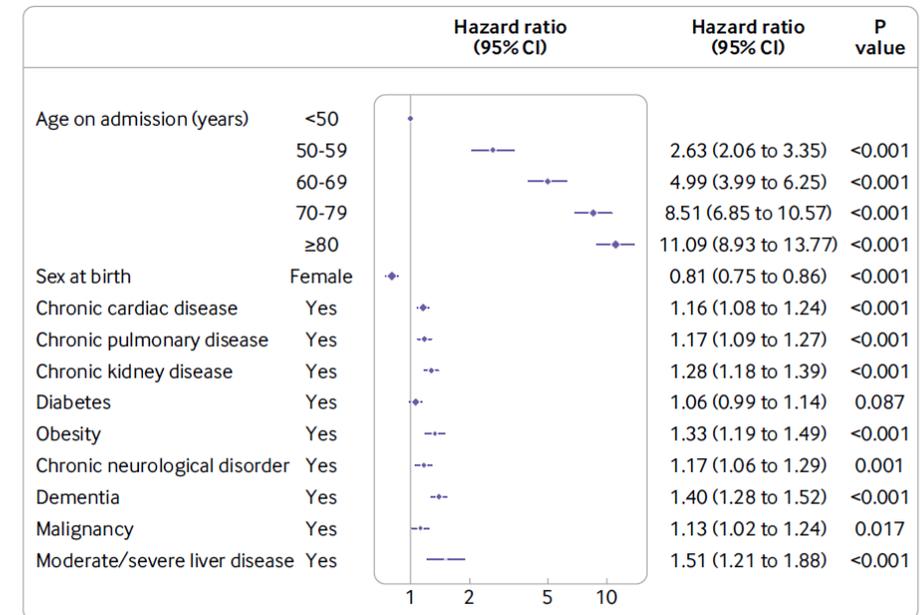


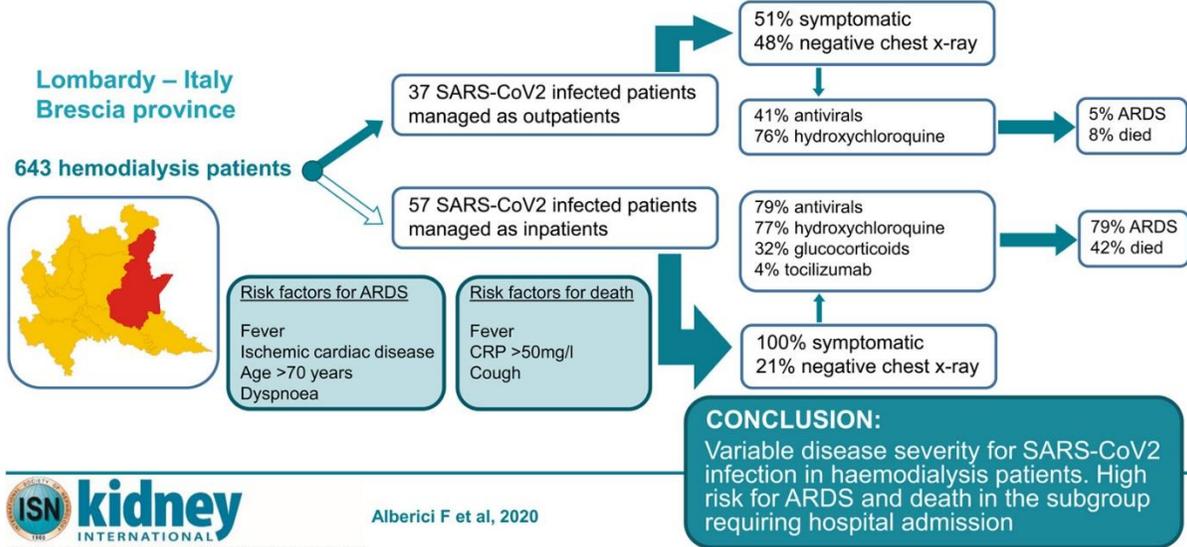
Fig 5 | Multivariable Cox proportional hazards model (age, sex, and major comorbidities), where hazard is death. Patients who were discharged were kept in the risk set (n=15 194; No of events=3911)

20000 patients au Royaume uni

BMJ 2020;369:m1985 | doi: 10.1136/bmj.m1985

En hémodialyse

A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection.

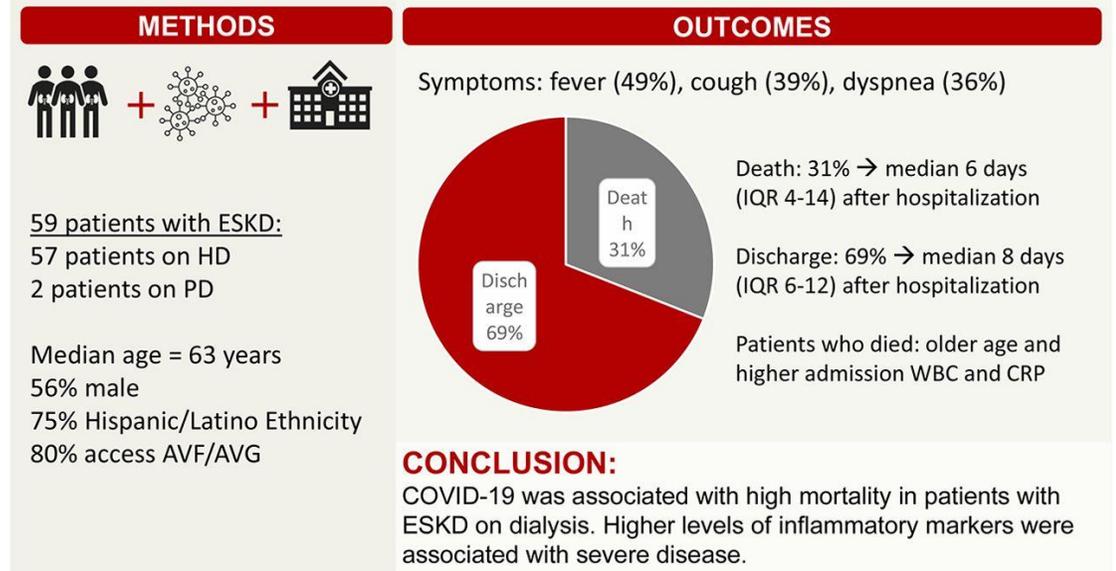


10.1016/j.kint.2020.04.030

Hemodialysis with Cohort Isolation to Prevent Secondary Transmission during a COVID-19 Outbreak in Korea

<https://jasn.asnjournals.org/content/early/2020/05/31/ASN.2020040461>

Presentation and Outcomes of Patients with End-Stage Kidney Disease and COVID-19



doi: 10.1681/ASN.2020040470

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

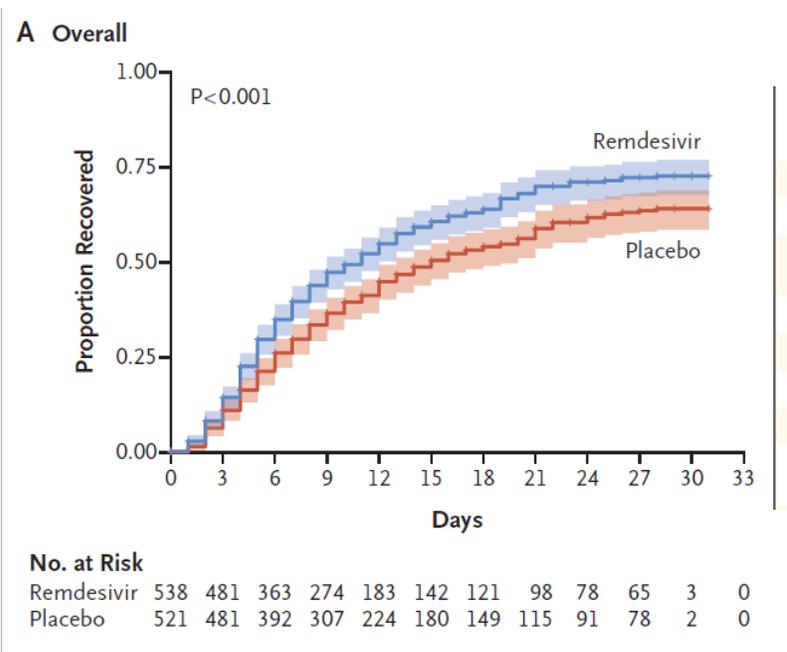
<https://jasn.asnjournals.org/content/early/2020/05/28/ASN.2020040470>



https://www.agence-biomedecine.fr/IMG/html/dashboard_covid19_n9.html

Traitement

- Pour l'instant aucune preuve publiée et reviewée d'efficacité d'une approche sur la mortalité
- Remdisivir: deux essais randomisés



	Remdesivir (N=538)	Placebo (N=521)
Recovery		
No. of recoveries	334	273
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)
Rate ratio (95% CI) †	1.32 (1.12–1.55 [P<0.001])	
Mortality		
Hazard ratio (95% CI)	0.70 (0.47–1.04)	
No. of deaths by day 14	32	54
Kaplan–Meier estimate —% (95% CI)	7.1 (5.0–9.9)	11.9 (9.2–15.4)

10.1056/NEJMoa2007764

Table 2. Clinical Outcomes According to Remdesivir Treatment Group.

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			
P=0.14 †			
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7: Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence) ‡	10	11	0.79 (0.61 to 1.01)

10.1056/NEJMoa2015301

Des résultats problématiques car préliminaires et un changement de critère principal. Un peu tôt pour conseiller cette molécule.

Gros problème pas de groupe contrôle, pas de différence entre 5 et 10 jours de traitement. Peut être mieux de prendre que 5 jours ou pas...

Traitement

- Un peu d'hydroxychloroquine

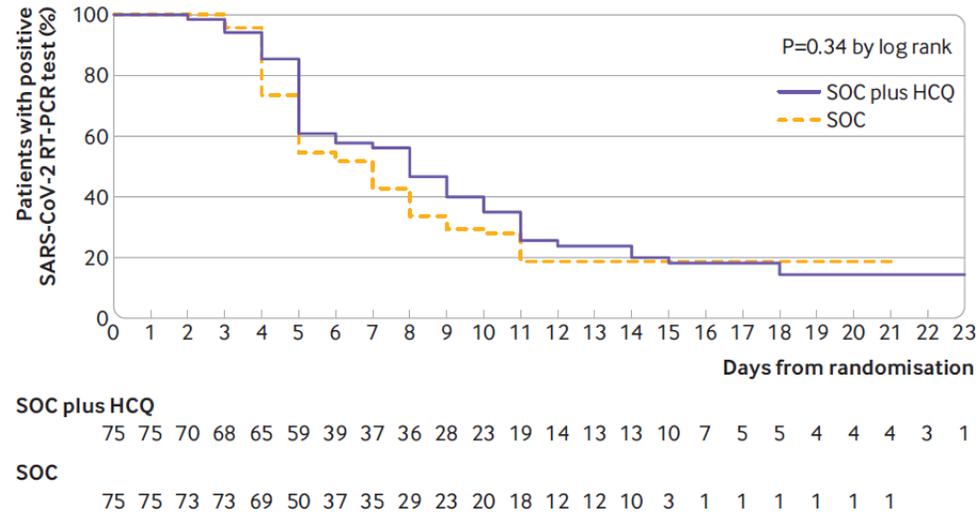


Fig 2 | Kaplan-Meier curves of time to negative conversion of SARS-CoV-2 on real time reverse transcription polymerase chain reaction (RT-PCR) test in standard of care (SOC) plus hydroxychloroquine (HCQ) versus SOC in intention to treat population. Data are shown for 75 patients assigned to SOC plus HCQ and 75 assigned to SOC. Overall probability of negative conversion by 28 days was 85.4% (95% CI 73.8% to 93.8%) in SOC plus HCQ group and 81.3% (71.2% to 89.6%) in SOC group (P=0.34). Difference between groups was 4.1% (95% CI -10.3% to 18.5%).

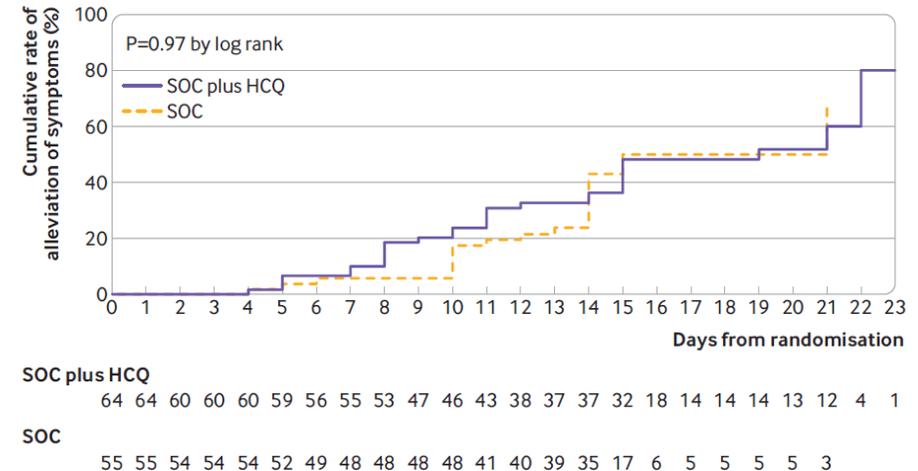
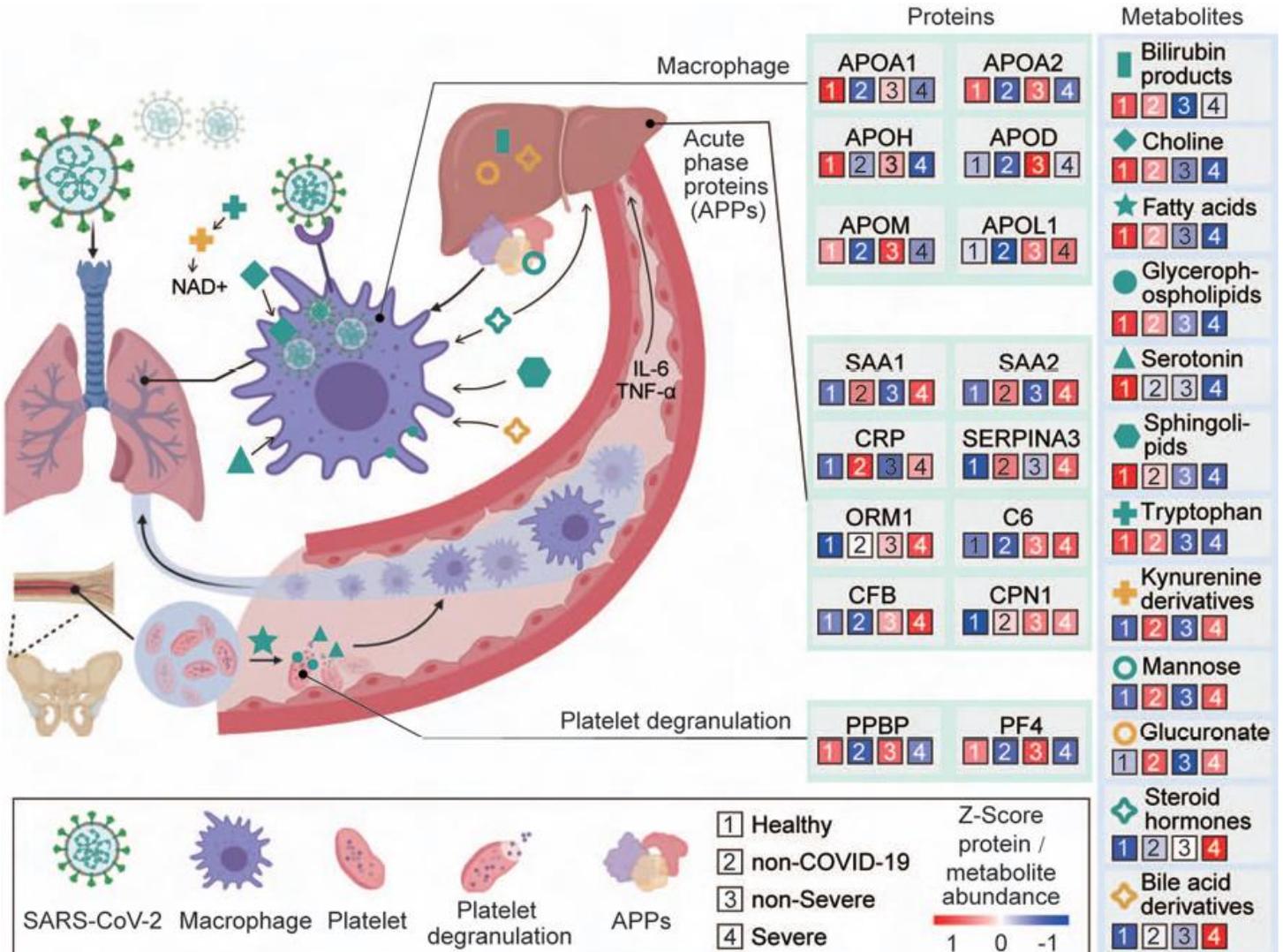


Fig 3 | Kaplan-Meier curves of time to alleviation of clinical symptoms with standard of care (SOC) plus hydroxychloroquine (HCQ) versus SOC alone in intention to treat population. Data shown are for 55 patients with symptoms assigned to SOC plus HCQ and 64 assigned to SOC. Probability of alleviation of symptoms by 28 days was similar (P=0.97) in patients with SOC with (59.9%, 95% confidence interval 45.0% to 75.3%) and without HCQ (66.6%, 39.5% to 90.9%). Difference between groups was -6.6% (95% CI -41.3% to 28.0%). Median time to alleviation of

Toute seule chez 150 patients en chine.

Ca ne marche pas dans les formes peu sévère à améliorer la symptomatologie et négativer la PCR

De nouvelles cibles



En conclusion

- Nous commençons à avoir une bonne vision de cette maladie
 - Virologique
 - Epidémique
 - Biologique
 - Clinique
- Il reste le problème de la thérapeutique
- L'immunisation est possible.
- Nous aurons appris beaucoup de choses sur l'utilisation des masques et l'importance de faire de la science de qualité.

