Biblio SARS-Cov2

P. Calès, 23/3/20, 2/4/20, 7/4/20, 14/4/20

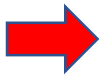
Merci de signaler les éventuelles erreurs à

paul.cales@univ-angers.fr

Introduction

- Ce diaporama est une sélection d'articles pertinents sur le COVID 19 parmi un screening exhaustif des bases Medline & MedRχiv
- Sujets abordés :
  - Biologie
  - Epidémiologie
  - Clinique
  - Hépato-gastro-entérologie
  - Recommendations
  - Traitement
- Sujets non abordés :
  - Tests diagnostiques
  - Aspects sociétaux
- Il est divisé en parties successives actualisée chacune toutes les semaines
- Il est à usage personnel

Partie I

- Biblio au 23/3/20
- Les papiers importants sont signalés par des +
- Dans les tableaux, les aspects relevant de l'HGE sont signalés par 

Plan

- Virologie
- Clinique
- Comorbidités
- Règles pratiques
- HGE

- 1342 articles le 22/3/20 à 11h25
- 1369 articles le 23/3/20 à 10h30 : > 1 article / h

Plan

- **Virologie**
- Clinique
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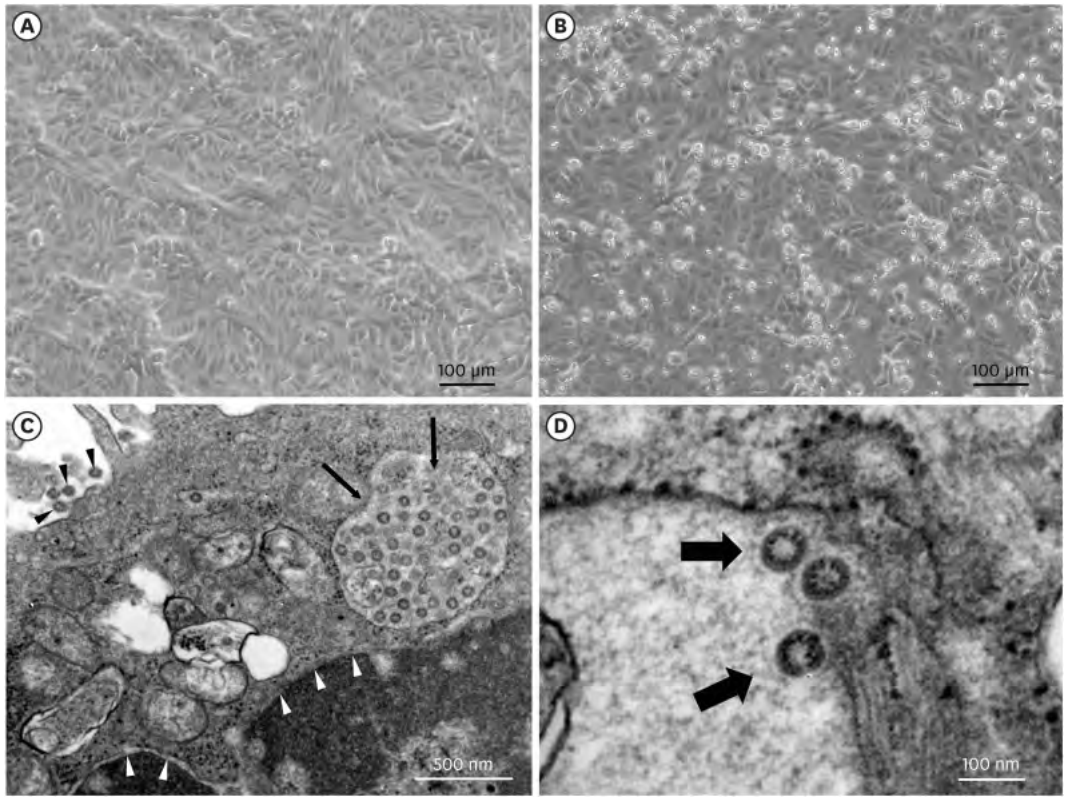
- Règles pratiques
- HGE

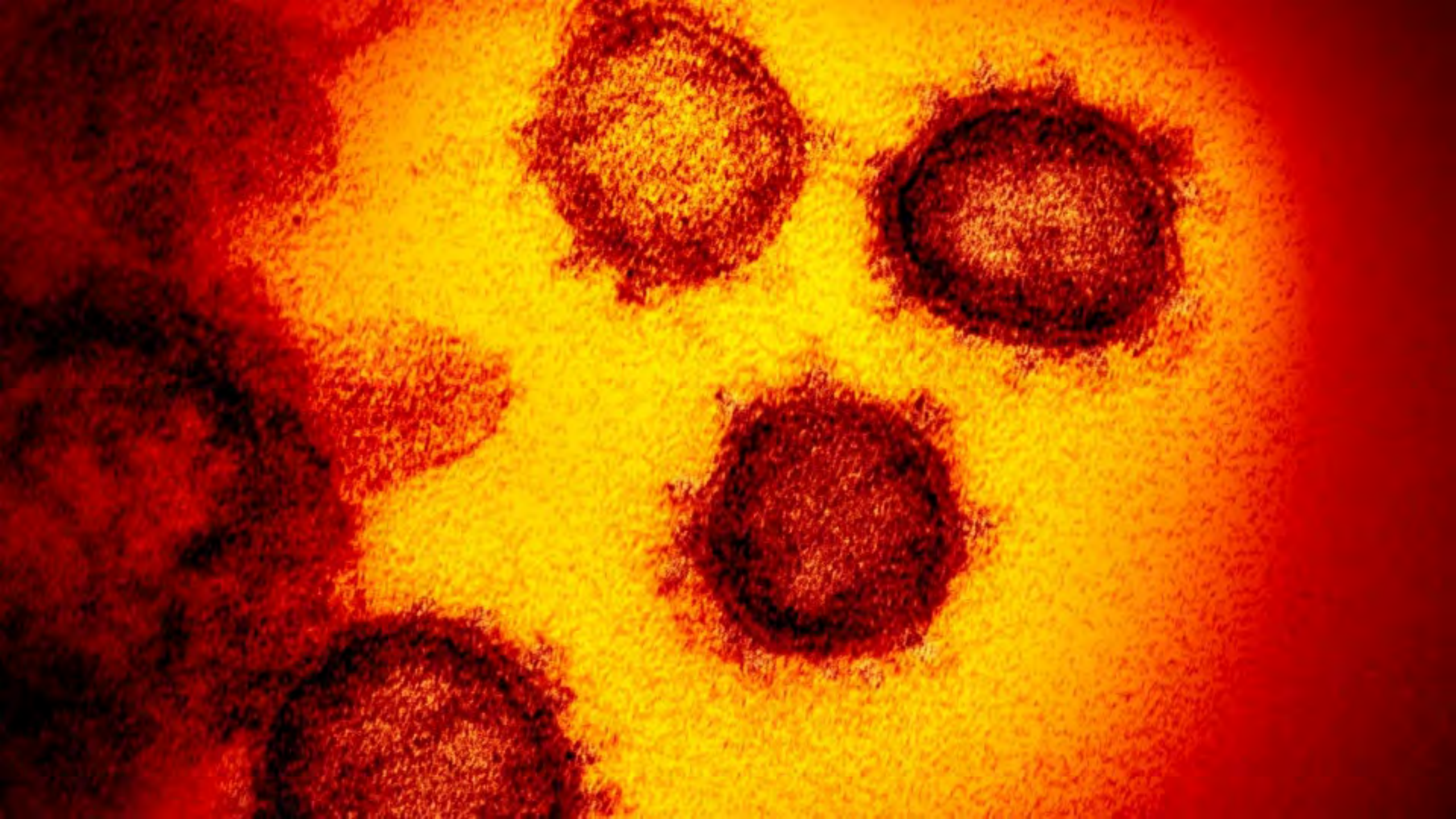
J Korean Med Sci. 2020 Feb 24;35(7):e84. doi: 10.3346/jkms.2020.35.e84.

Virus Isolation from the First Patient with SARS-CoV-2 in Korea.

Park WB[#1,2], Kwon NJ[#3], Choi SJ[2], Kang CK[1], Choe PG[1], Kim JY[4], Yun J[3], Lee GW[3], Seong MW[5], Kim NJ[1,2], Seo JS[3,6], Oh MD[1,7].



Cytopathic effects of SARS-CoV-2 in Vero cell cultures and electron microscopy image of SARS-CoV-2. Vero cells were inoculated with oropharyngeal swab sample. (A) Vero cell cultures in negative control. (B) Cytopathic effects consisting of rounding and detachment of cells in Vero cell cultures 3 days after the first blind passage. (C, D) Transmission electron microscopy image of Vero cells infected with SARS-CoV-2. White arrow head denotes nuclear membrane, black arrow head extracellular virus particles, and thin black arrow cytoplasmic vesicle including virus components (C). Thick black arrow denotes magnified virus particles with crown-like spikes (D).



Emerging Microbes & Infections

ISSN: (Print) 2222-1751 (Online) Journal homepage: https://www.tandfonline.com/loi/temi20

A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses

Sin-Yee Fung, Kit-San Yuen, Zi-Wei Ye, Chi-Ping Chan & Dong-Yan Jin

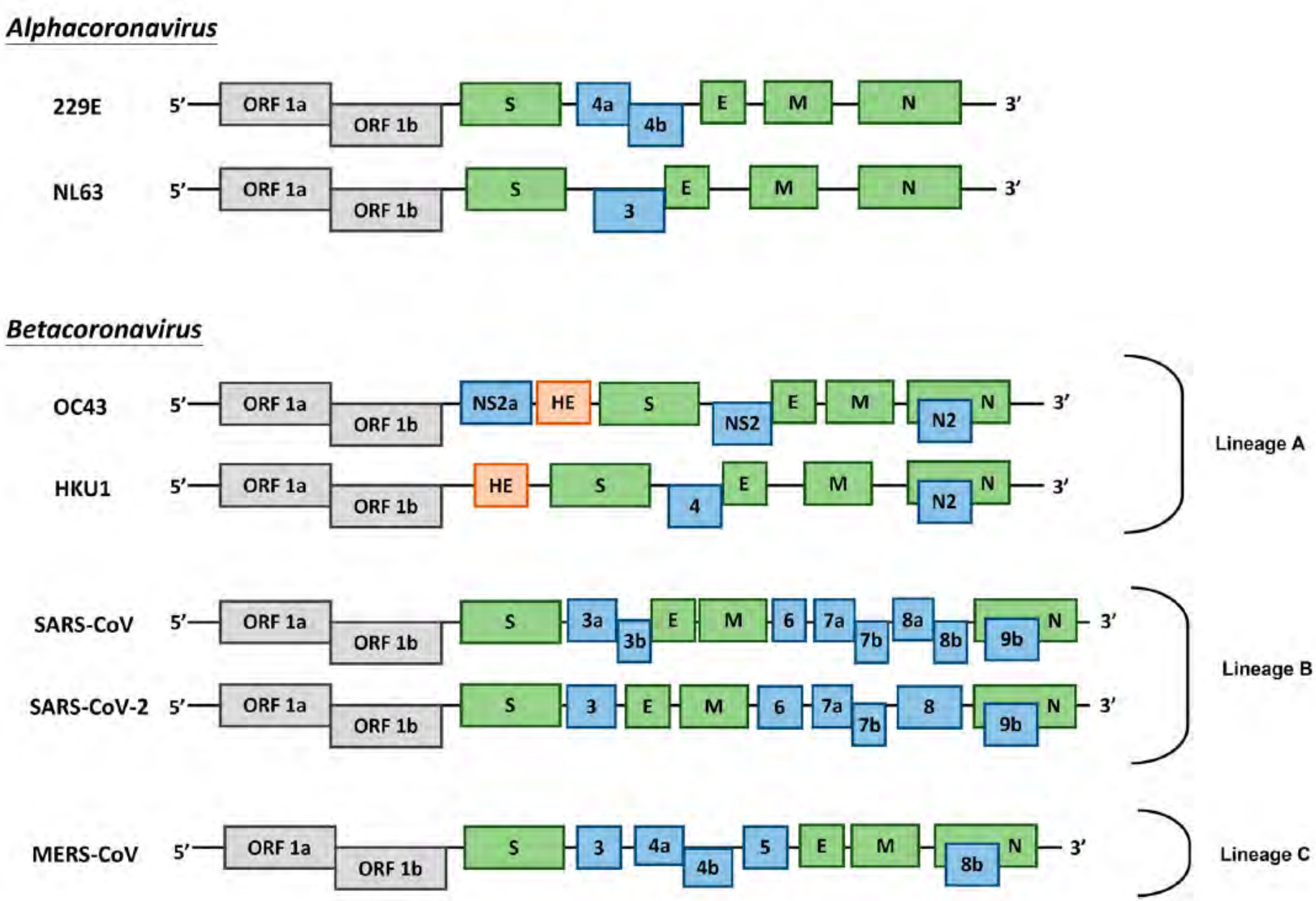


Figure 1. Genome organization of HCoVs. Schematic diagram of seven known HCoVs is shown (not in scale). The genes encoding structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N) are in green. The gene encoding haemagglutinin-esterase (HE) in lineage A of betacoronaviruses is in orange. The genes encoding accessory proteins are in blue.

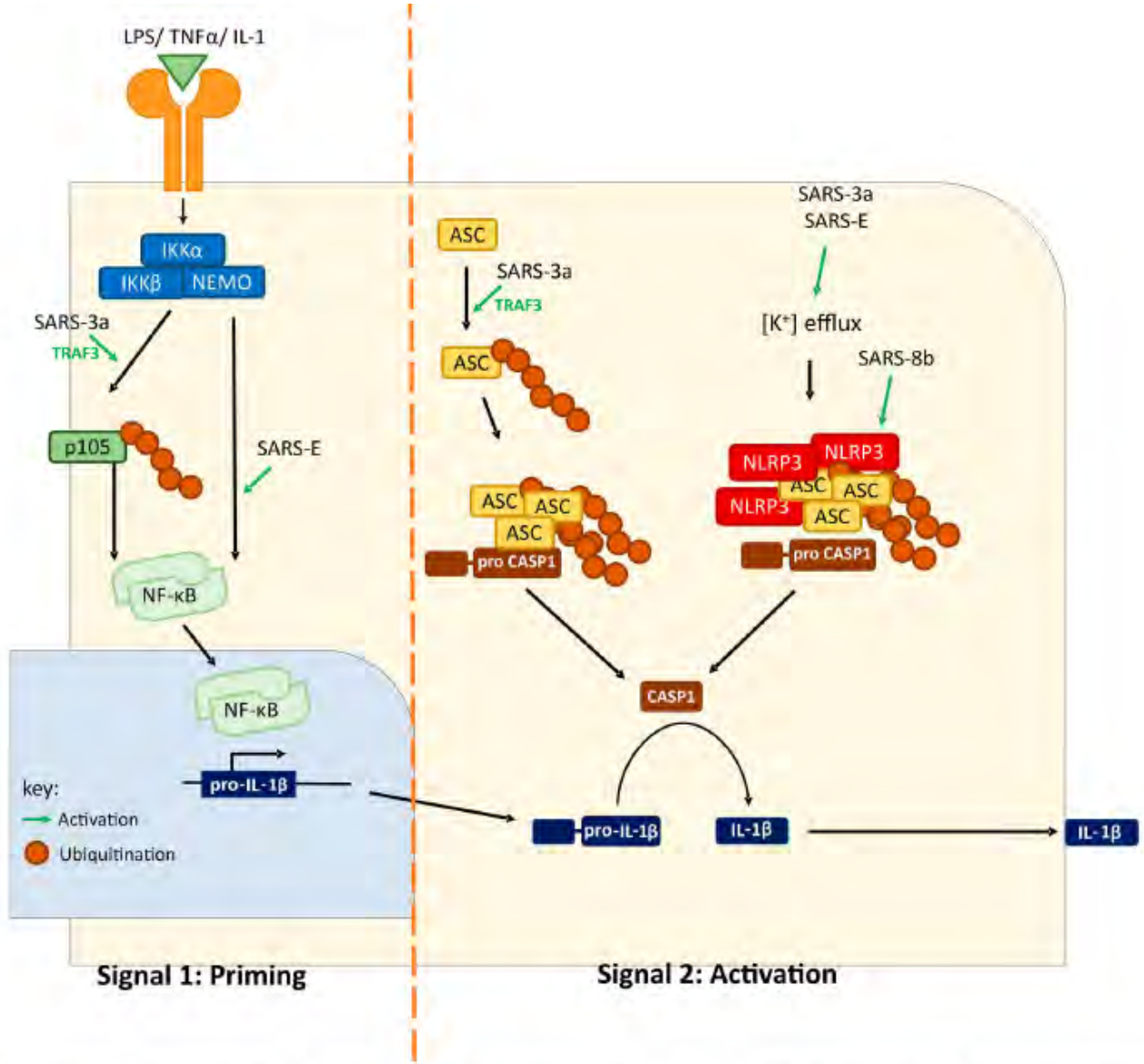
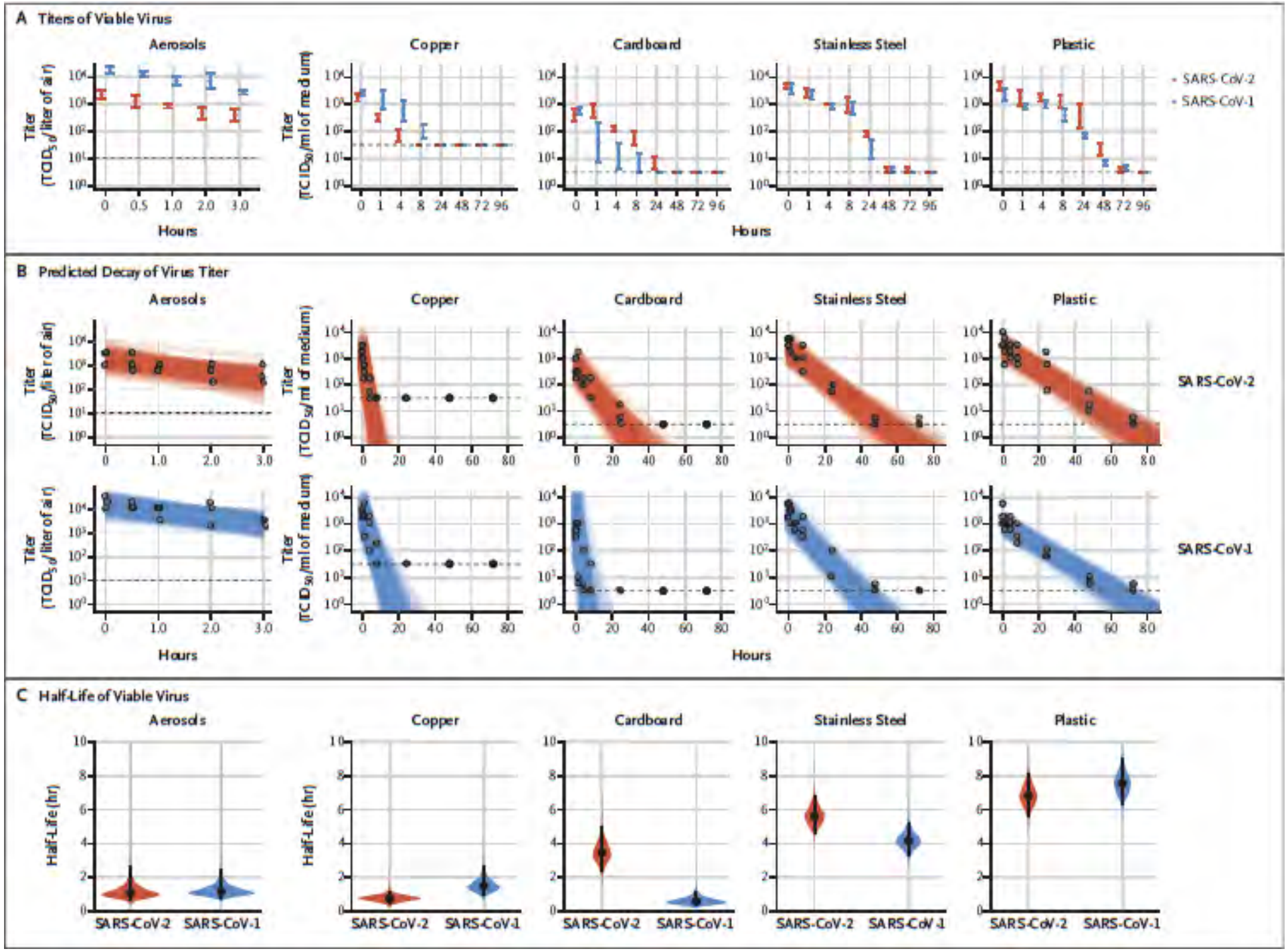


Figure 2. A working model of SARS-CoV-induced inflammasome activation. SARS-CoV can activate both signal 1 (priming) and signal 2 (activation). Upregulation of pro-IL-1β transcription is achieved by NF-κB activation. Two mechanisms of IL-1β maturation have been proposed. In the first model, potassium ion efflux is promoted by ORF3a and E proteins, leading to NLRP3 inflammasome assembly. Alternatively, ORF3a promotes ASC ubiquitination and consequent assembly of inflammasome. ORG8b interacts with and activates NLRP3. Activation of inflammasome leads to proteolytic cleavage of pro-caspase 1 and pro-IL-1β. ASC, apoptosis-associated speck-like protein containing a CARD. CASP1, caspase 1. IKK, IκB kinase. IL-1, interleukin-1. LPS, lipopolysaccharides. NLRP3, NACHT, LRR, and PYD domains-containing protein 3. NEMO, NF-κB essential modulator. TNF-α, tumour necrosis factor α.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1


A Titers of Viable Virus
Aerosols
Copper
Cardboard
Stainless Steel
Plastic
Titer (TCID50/liter of air)
Titer (TCID50/ml of medium)
Hours
SARS-CoV-2
SARS-CoV-1
B Predicted Decay of Virus Titer
C Half-Life of Viable Virus
Half-Life (hr)

Plan

- Virologie
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- Règles pratiques
- HGE

Adhikari *et al. Infectious Diseases of Poverty* (2020) 9:29
https://doi.org/10.1186/s40249-020-00646-x

Infectious Diseases of Poverty

SCOPING REVIEW Open Access

Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review

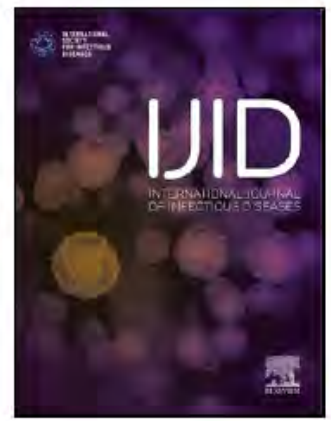
Table 4 Main epidemiological indicators of COVID-19 research articles in January 2020

Indicators	Description
Age of patients	• Cases range between 25 and 89 years, with most patients aged between 35 and 55 years and fewer cases among children and infants [14]
	• Median age of patients is 59 years, ranging from 51 to 89 [2]
	• Average age of patients was 55.5 years; age distribution: ≤ 39: 10%; 40–49: 22%, 50–59: 30%; 60–69: 22%, ≥ 70: 15% [19]
	• Cases range from 2 to 72 years [20]
Sex of patients	• More cases were males [20]
	• 59% males [2]
	• 68% males [19]
Age of the deaths	• Median age of death was 75 (with a range between 48 and 89 years) [21]
Exposure history	• Huanan Seafood Market in Wuhan [19, 22]
	• Wuhan residents or people who visited Wuhan [20]
Incubation time	• 4.8 ± 2.6 days (2–11 days) [15]
	• 5.2 days (4.1–7 days) [2]
	• Average of 7 days (2–14 days) [23]
	• Average of 10 days [22]
	• 5–6 days [24]
	• Average of 6.4 days (5.6–7.7 days) [20]
Basic Reproduction (R_0)	• 2.6 (uncertainty range: 1.5–3.5) [25]
	• 3.8 (95% *CI*: 3.6–4.0) [26]
	• 2.2 (1.4–3.8) [27]
	• 4.71 (4.50–4.92) [24]
	• 2.68 (95% *CI*: 2.47–2.86) [28]
Susceptible populations	• Elderly people [21]
	• People with poor immune function [2]
	• People with chronic co-morbidities [2, 15, 19, 21]
	• People with long-term use of immunosuppressive agents [19]
	• Surgery history before admission [21]
Mortality rate	• 3% (between 29 December 2019 to 23 January, 2020) [15]
	• 2.3% (as of 28 January 2020) [29]
	• 2.8% (as of 25 January, 2020) [21]
	• 2.9% (as of 25 January, 2020) [30]
	• 11% (as of 25 January, 2020) [19]
	• 3.1% (as of 24 January 2020) [31]

Journal Pre-proof

Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis

Jing Yang, Ya Zheng, Xi Gou, Ke Pu, Zhaofeng Chen, Qinghong Guo, Rui Ji, Haojia Wang, Yuping Wang, Yongning Zhou



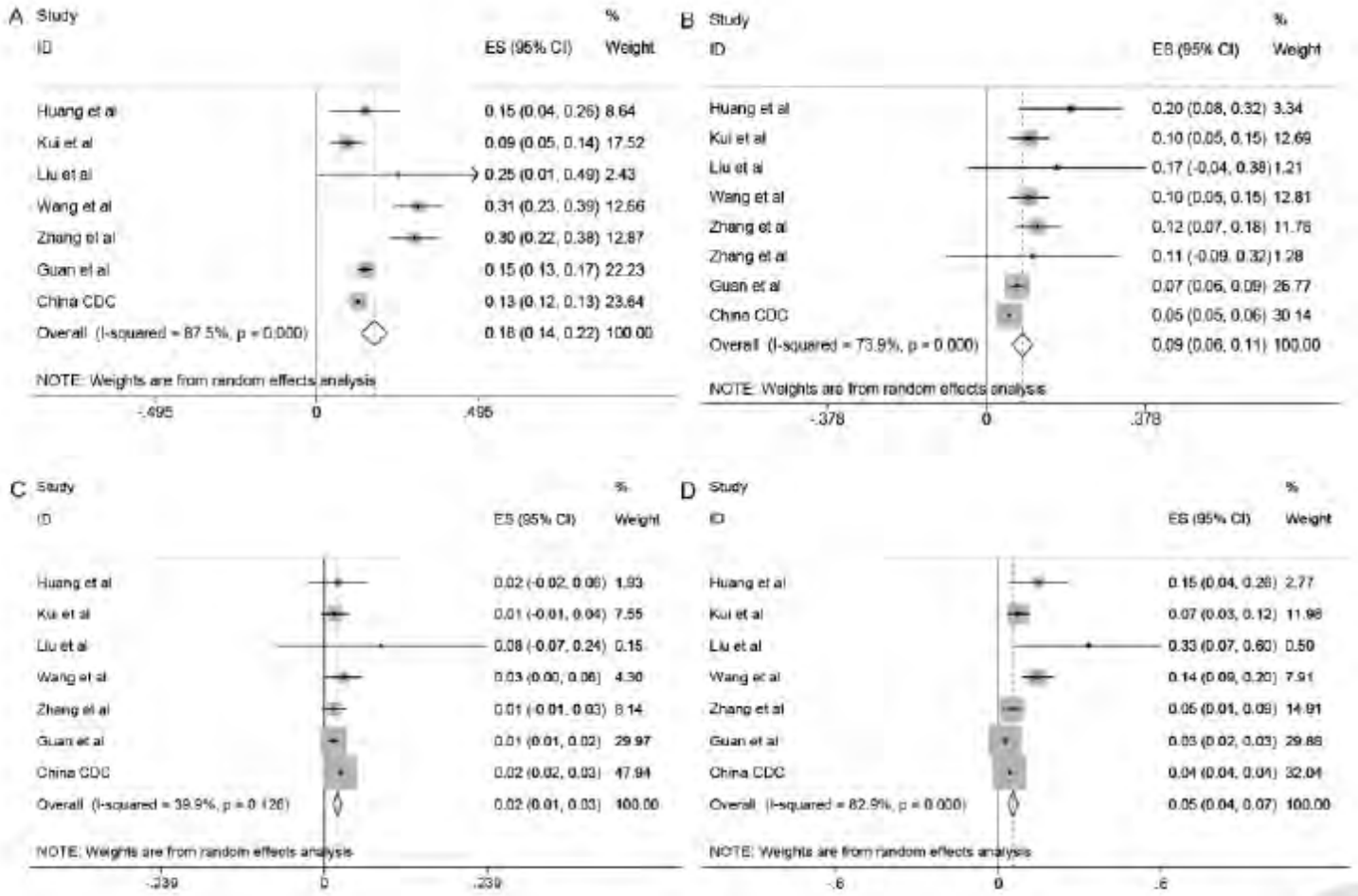


Figure 2 Meta-analysis of the proportion of comorbidities in COVID-19 cases. A, B, C, D represent proportions of hypertension, diabetes, Respiratory system disease, and Cardiovascular disease.

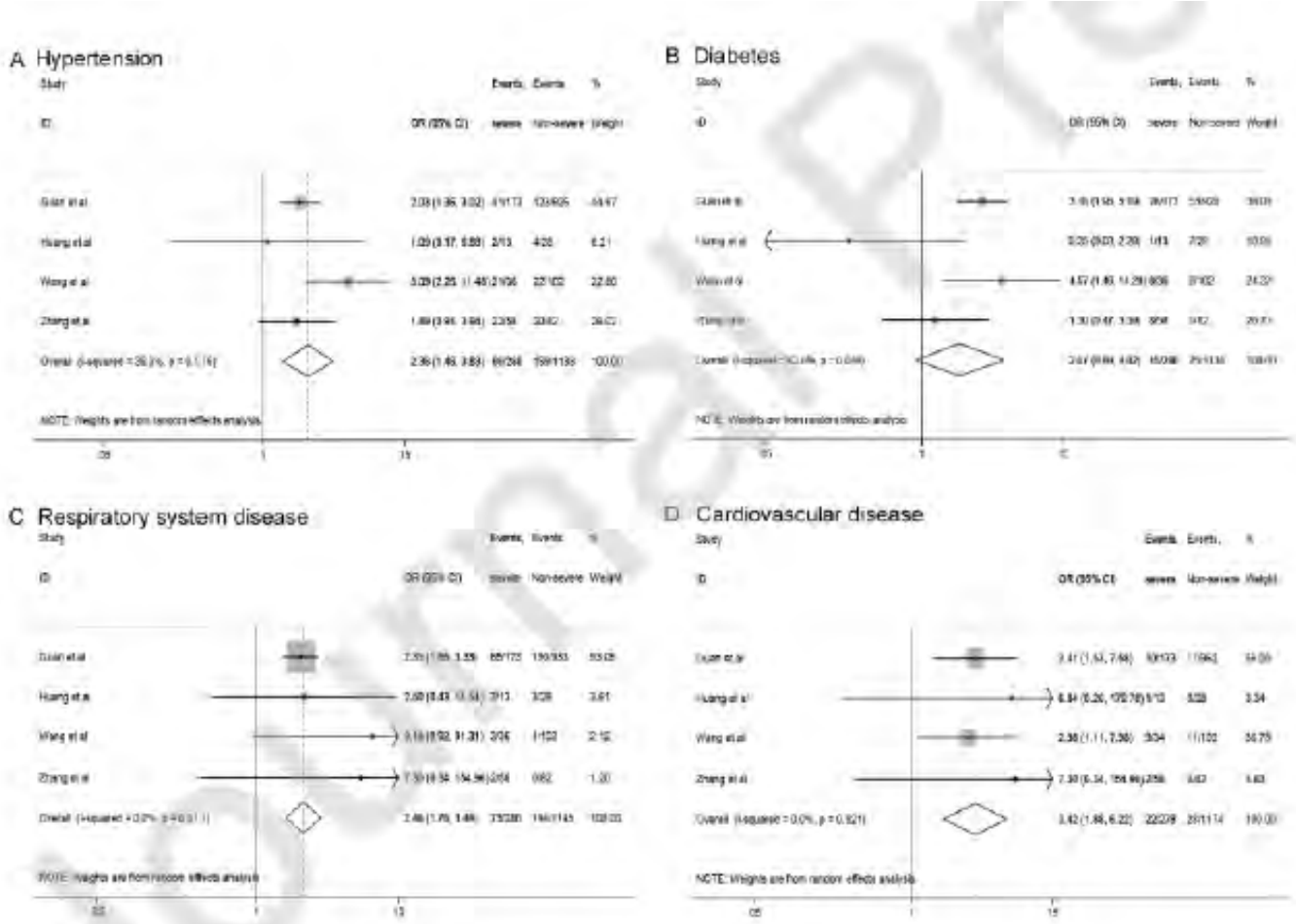


Figure 3 The risk of comorbidities in severe patients compared to Non-severe patients. (A) hypertension, (B) diabetes, (C) Respiratory system disease, (D) Cardiovascular disease.

Plan

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- Clin Infect Dis. 2020 Mar 17. pii: ciaa287. doi: 10.1093/cid/ciaa287. [Epub ahead of print]
- **Risk Factors of Healthcare Workers with Corona Virus Disease 2019: A Retrospective Cohort Study in a Designated Hospital of Wuhan in China.**
- Ran L[1], Chen X[1], Wang Y[2], Wu W[1], Zhang L[1], Tan X[1].
- Corona Virus Disease 2019 (COVID-19) originated in Wuhan, China has caused many healthcare workers (HCWs) infected. Seventy-two HCWs manifested with acute respiratory illness were retrospectively enrolled to analyze the risk factors. The high-risk department, longer duty hours, and suboptimal hand hygiene after contacting with patients were linked to COVID-19.

Emerging Microbes & Infections

ISSN: (Print) 2222-1751 (Online) Journal homepage: https://www.tandfonline.com/loi/temi20

Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0)

Working Group of 2019 Novel Coronavirus, Peking Union Medical College Hospital

+++

Protection requirements of medical personnel

Selection of front-line personnel

Front-line medical personnel are qualified only after passing the physical examinations and professional training of SARS-CoV-2. Staff with the following conditions are exempt from SARS-CoV-2 related clinical/laboratory work, including pregnancy, age over 55 years old, a past history of chronic diseases such as chronic hepatitis, renal diseases, diabetes mellitus, autoimmune diseases and tumours. Individuals affected with acute fever should also be excluded from SARS-CoV-2 related work.

Baseline tests should be arranged including the complete blood count, urine analysis, biochemical tests, creatine kinase, and chest X-ray.

Isolation and protection requirements

Isolation and observation of medical personnel after close contact with SARS-CoV-2

Effectiveness of N95 respirators versus surgical masks against influenza: A systematic review and meta-analysis.

Long Y[1], Hu T[2], Liu L[2], Chen R[3], Guo Q[1], Yang L[1], Cheng Y[1], Huang J[4], Du L[1].

J Evid Based Med. 2020 Mar 13. doi: 10.1111/jebm.12381. [Epub ahead of print]

OBJECTIVE:

Previous meta-analyses concluded that there was insufficient evidence to determine the effect of N95 respirators. We aimed to assess the effectiveness of N95 respirators versus surgical masks for prevention of influenza by collecting randomized controlled trials (RCTs).

METHODS:

We searched PubMed, EMbase and The Cochrane Library from the inception to January 27, 2020 to identify relevant systematic reviews. The RCTs included in systematic reviews were identified. Then we searched the latest published RCTs from the above three databases and searched ClinicalTrials.gov for unpublished RCTs. Two reviewers independently extracted the data and assessed risk of bias. Meta-analyses were conducted to calculate pooled estimates by using RevMan 5.3 software.

RESULTS:

A total of six RCTs involving 9 171 participants were included. There were no statistically significant differences in preventing laboratory-confirmed influenza (RR = 1.09, 95% CI 0.92-1.28, P > .05), laboratory-confirmed respiratory viral infections (RR = 0.89, 95% CI 0.70-1.11), laboratory-confirmed respiratory infection (RR = 0.74, 95% CI 0.42-1.29) and influenzalike illness (RR = 0.61, 95% CI 0.33-1.14) using N95 respirators and surgical masks. Meta-analysis indicated a protective effect of N95 respirators against laboratory-confirmed bacterial colonization (RR = 0.58, 95% CI 0.43-0.78).

CONCLUSION:

The use of N95 respirators compared with surgical masks is not associated with a lower risk of laboratory-confirmed influenza. It suggests that **N95 respirators should not be recommended for general public and nonhigh-risk medical staff those are not in close contact with influenza patients or suspected patients**.

Plan

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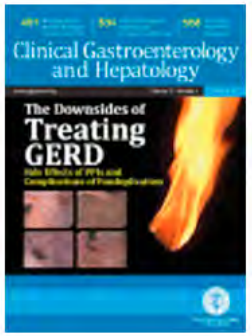
- **HGE**

- Gut. 2020 Mar 20. pii: gutjnl-2020-321051. doi: 10.1136/gutjnl-2020-321051. [Epub ahead of print] PDF
- **COVID-19 in gastroenterology: a clinical perspective.**
- Ong J[1,2], Young BE[3,4], Ong S[5,6]

- gastrointestinal symptoms appear to be infrequent in China (nausea and vomiting: 5.0% and diarrhoea: 3.7%), 17% of patients with COVID-19 in Singapore reported diarrhoea.
- RNA was detected in 50% of patients' stool samples
- In Shanghai, 50.7% (75/148) had abnormal liver function tests
- ACE2 is recognised as an important regulator of intestinal inflammation, and many hypothesise this is the mechanism by which diarrhoea in
- ACE2 receptors are also highly expressed within the biliary tree, but cholestatic liver disease is not a common feature of COVID-19.

Journal Pre-proof



What Should Gastroenterologists and Patients Know About COVID-19?

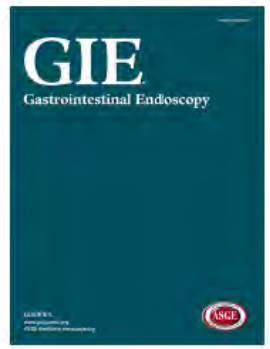
Ryan C. Ungaro, MS MS, Timothy Sullivan, MD, Jean-Frederic Colombel, MD, Gopi Patel, MD

+/-

Table: Main Points of Interest Regarding COVID-19 For Gastroenterologists

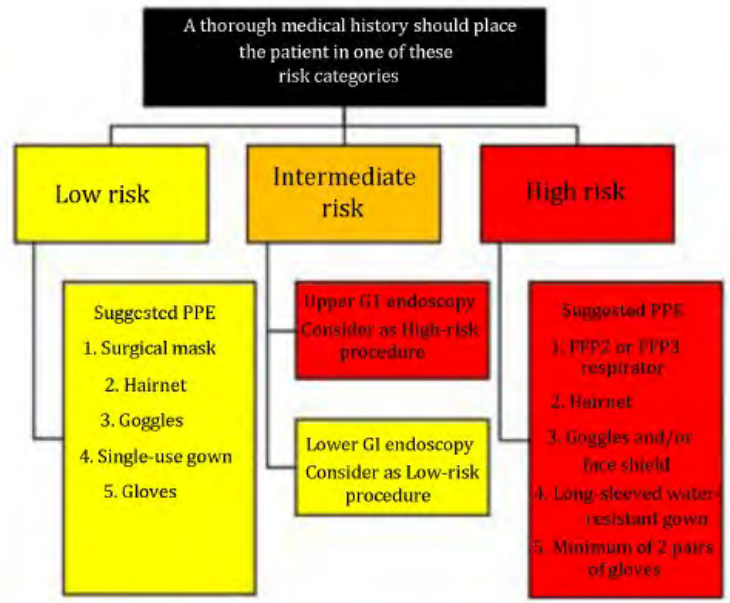
- Coronavirus Disease 2019 (COVID-19) is a respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Most cases of COVID-19 appear to be mild with the most common symptoms being fever, cough, myalgia/fatigue, and shortness of breath but can result in more severe disease
- Risk factors for more severe disease included older age and underlying chronic medical conditions such as cardiovascular or lung disease.
- Potential gastrointestinal manifestations of COVID-19 have been reported including nausea, vomiting, diarrhea, and abnormal liver function tests. SARS-CoV-2 has been detected in patient stool though unclear if there is a fecal-oral route of infection.
- There are currently no data on impact of immunosuppression on susceptibility or disease course. Patients on immunosuppression should be counseled to not stop medications for preventative reasons but should follow general precautions recommended for at risk groups by the CDC.
- Patients who potentially have COVID-19 should be isolated in a separate room and asked to wear a surgical mask. Local health authorities should be notified of possible cases.
- This is a rapidly evolving area and it is important to keep up to date with information from national and international health organizations.

Journal Pre-proof



Coronavirus (COVID-19) outbreak: what the department of endoscopy should know

Alessandro Repici, Roberta Maselli, Matteo Colombo, Roberto Gabbiadini, Marco Spadaccini, Andrea Anderloni, Silvia Carrara, Alessandro Fugazza, Milena Di Leo, Piera Alessia Galtieri, Gaia Pellegatta, Elisa Chiara Ferrara, Elena Azzolini, Michele Lagioia


A thorough medical history should place the patient in one of these risk categories
Low risk
Intermediate risk
High risk
Suggested PPE
1. Surgical mask
2. Hairnet
3. Goggles
4. Single-use gown
5. Gloves
Upper GI endoscopy
Consider as High-risk procedure
Lower GI endoscopy
Consider as Low-risk procedure
Suggested PPE
1. FFP2 or FFP3 respirator
2. Hairnet
3. Goggles and/or face shield
4. Long-sleeved water-resistant gown
5. Minimum of 2 pairs of gloves


HAIRNET
GOGGLES
SURGICAL MASK
SINGLE-USE GOWN
GLOVES OVER THE GOWN WHICH COVER THE WRIST

A


N95 or FFP2-3 RESPIRATOR
HAIRNET
GOGGLES (OR FACE-SHIELD)
LONG-SLEEVED WATER-RESISTANT GOWN
TWO PAIRS OF GLOVES, ONE OVER THE GOWN WHICH COVER THE WRIST

B

Journal Pre-proof

Effect of gastrointestinal symptoms on patients infected with COVID-19

Zili Zhou, Ning Zhao, Yan Shu, Shengbo Han, Bin Chen, Xiaogang Shu

Table1. Clinical features, treatment and prognosis of patients Infected With 2019-nCoV

		Medical staff				Non-medical staff			
	Total (254)	Total (93)	GI symptoms (23.100%)	Non- GI symptoms (70.100%)	P value	Total (161)	GI symptoms (43.100%)	Non- GI symptoms (118.100%)	P value
GI symptoms	66(26.0%)	23	23(100%)	0(0%)	-	43	43(100%)	0(0%)	-
Abdominal pain	3(1.2%)	0	0(0%)	0(0%)	-	3	3(7.0%)	0(0%)	-
Vomiting	15(5.9%)	1	1(4.3%)	0(0%)	-	14	14(32.6%)	0(0%)	-
Diarrhea	46(18.1%)	19	19(82.6%)	0(0%)	-	27	27(62.8%)	0(0%)	-
Nausea	21(8.3%)	5	5(21.7%)	0(0%)	-	16	16(37.2%)	0(0%)	-
Age	50	36	35	36	0.614	62	61	62	0.615
Median (IQR)	(36-65)	(31-41)	(30-40)	(31-42)		(49-69)	(49-67)	(49-70)	
Gender					0.45				0.033
Male	115(45.3%)	32	6(26%)	26(37%)		83	16(37%)	67(57%)	
Female	139(54.7)	61	17(74%)	44(63%)		78	27(63%)	51(43%)	

Liver injury in COVID-19: management and challenges

Lancet Gastroenterol Hepatol
2020

Published Online
March 4, 2020

	Patients with SARS-CoV-2 infection	Patients with pre-existing liver conditions	Patients with abnormal liver function	Notes
Guan et al[1]	1099	23 (2·3%)	AST abnormal (22·2%), ALT abnormal (21·3%)	Elevated levels of AST were observed in 112 (18·2%) of 615 patients with non-severe disease and 56 (39·4%) of 142 patients with severe disease. Elevated levels of ALT were observed in 120 (19·8%) of patients with non-severe disease and 38 (28·1%) of 135 patients with severe disease.
Huang et al[5]	41	1 (2·0%)	15 (31·0%)	Patients with severe disease had increased incidence of abnormal liver function. Elevation of AST level was observed in eight (62%) of 13 patients in the ICU compared with seven (25%) 25 patients who did not require care in the ICU.
Chen et al[6]	99	NA	43 (43·0%)	One patient with severe liver function damage.
Wang et al[7]	138	4 (2·9%)	NA	..
Shi et al[8]	81	7 (8·6%)	43 (53·1%)	Patients who had a diagnosis of COVID-19 confirmed by CT scan while in the subclinical phase had significantly lower incidence of AST abnormality than did patients diagnosed after the onset of symptoms.
Xu et al[9]	62	7 (11·0%)	10 (16·1%)	..
Yang et al[10]	52	NA	15 (29·0%)	No difference for the incidences of abnormal liver function between survivors (30%) and non-survivors (28%).
Our data (unpublished)	56	2 (3·6%)	16 (28·6%)	One fatal case, with evaluated liver injury.[13]

AST= aspartate aminotransferase. ALT= alanine aminotransferase. ICU=intensive care unit.

***Table*: Comorbidity with liver disease and liver dysfunction in patients with SARS-CoV-2 infection**

Prevention of SARS-CoV-2 infection in patients with decompensated cirrhosis

Lancet Gastroenterol Heptaol 2020

Published Online
March 17, 2020
https://doi.org/10.1016/S2468-1253(20)30080-7

See Online for appendix

precautions for cirrhotic complications (panel), were sent to outpatients via WeChat every 3 days for a total of 12 times. Feedback from the patient was collected every day via WeChat.

precautions for cirrhotic complications (panel), were sent to outpatients via WeChat every 3 days for a total of 12 times. Feedback from the patient was collected every day via WeChat.

As an additional comparator, we calculated the incidence of COVID-19 among 101 inpatients with decompensated cirrhosis at five other hospitals in Wuhan over the same period, where our approach had not been implemented. 17 (17%) of these 101 patients were diagnosed with COVID-19 ($p=0{\cdot}018$ *vs* our group;

Precautions sent to outpatients with decompensated cirrhosis via WeChat

- Avoid visitors and parties
- Avoid areas where severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or coronavirus disease 2019 (COVID-19) has occurred and avoid individuals with fever
- Reduce going out; wear a cap and a mask correctly if unavoidable, especially in places with a mobile population or high population density, or both
- When returning home, remove your coat and hang it on the balcony or in a special area for ventilation; thoroughly wash your hands and face (including eyes, nostrils, and ears)
- Wash your hands before and after meals for no less than 20 s
- Open windows and ventilate your room twice a day for 15–30 min
- Eat a light and balanced diet, and predominantly soft foods to reduce the risk of bleeding from oesophageal and gastric varices; eat alone
- Face the challenge with equanimity and caution, exercise properly, and avoid catching a cold after exercise
- Monitor blood pressure, heart rate, and urine volume, especially for those taking non-selective β blockers as secondary prevention
- Take medications on time, including antiviral drugs and non-selective beta β blockers
- After endoscopic treatment of gastro-oesophageal varices, continue to take oral proton pump inhibitors for 2 months
- Intervals between re-examinations can be extended if necessary
- Purchase necessary medications online or offline after contacting your doctor on WeChat
- If you have any questions, or you are not feeling well, please contact your doctor on WeChat

Measures taken for inpatients with decompensated cirrhosis

- Training about COVID-19 provided for health-care workers
- Each patient was taken care of by one attending doctor and one nurse
- Rounds changed from three times a day to once a day, except for severely ill patients
- Communication between patients and medical staff should be done online
- Hospital staff advised to carry out strict hand hygiene and disinfection
- One room for each patient, or use of isolation curtain in bigger rooms
- Air to be disinfected three times per day by medical electrostatic adsorption air steriliser
- Central air-conditioning system shut down
- Doors to be closed, except for normal medical work; windows opened regularly for ventilation
- Patients and their companions provided training on how to use surgical masks properly
- Only one companion allowed for critical patients; no companions allowed for non-critical patients
- Establish a clean area and buffer zone in the ward
- Patients and their companions not permitted to leave the ward; if unavoidable, disposable surgical caps and masks were to be worn, and hands washed on return
- Invasive examinations to be avoided; mandatory protection and disinfection according to relevant regulations if necessary
- After stabilisation, patients were encouraged to be discharged and to receive online follow-up
- Establish an emergency plan for when patients with cirrhosis are confirmed or suspected to be infected with SARS-CoV-2, including: a rapid reporting system; building multidisciplinary teams that include specialists in gastroenterology, hepatology, interventional therapy, endoscopy, infection, and intensive care; rapid transfer channel; and a quarantine observation system for close contacts

Journal Pre-proofs

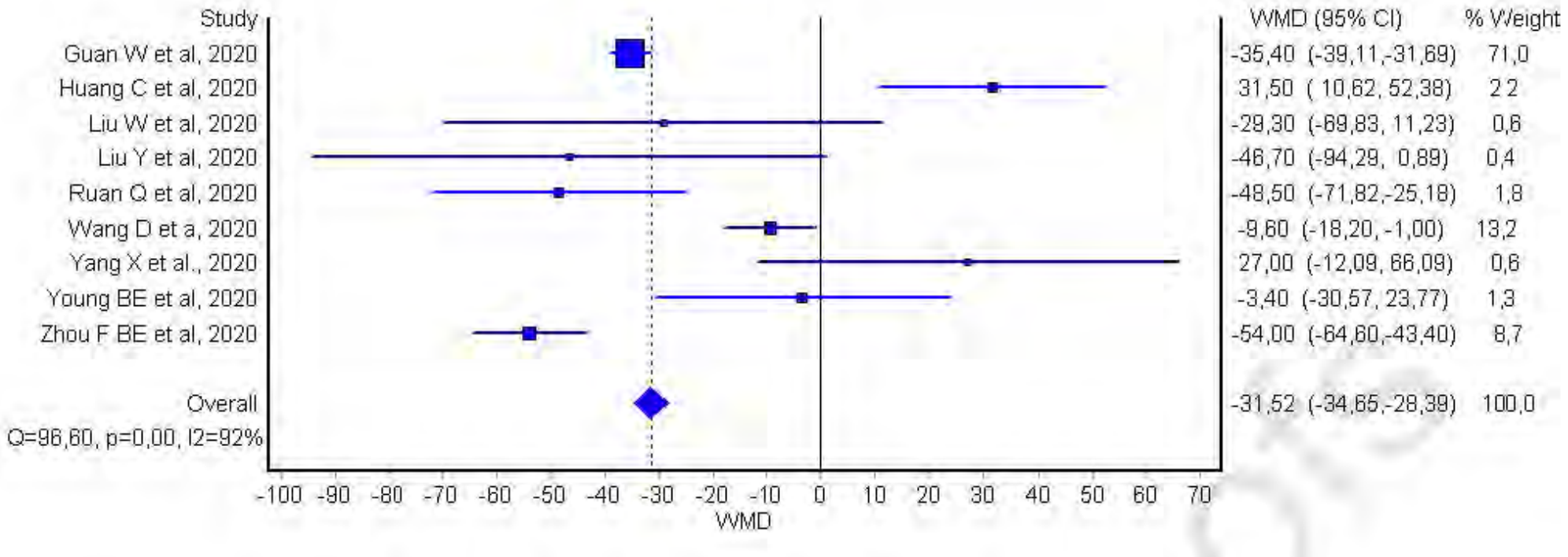
Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis

Giuseppe Lippi, Mario Plebani, Brandon Michael Henry

PII: S0009-8981(20)30124-8
DOI: https://doi.org/10.1016/j.cca.2020.03.022
Reference: CCA 16068

To appear in: *Clinica Chimica Acta*

Received Date: 8 March 2020
Revised Date: 11 March 2020
Accepted Date: 12 March 2020



a low platelet count was associated with over fivefold enhanced risk of severe COVID-19 (OR, 5.1; 95% CI, 1.8-14.6).

Implications of COVID-19 for patients with pre-existing digestive diseases

Lancet Gastroenterol Hepatol 2020

Published Online
March 11, 2020
https://doi.org/10.1016/
S2468-1253(20)30076-5

Panel: Key recommendations for managing patients with IBD during the COVID-19 epidemic

Potential risk factors for SARS-CoV-2 infection

- Patients with inflammatory bowel disease (IBD) on immunosuppressive agents
- Patients with active-stage IBD with malnutrition
- Elderly patients with IBD
- Patients with IBD frequently visiting medical clinic
- Patients with IBD with underlying health conditions, such as hypertension and diabetes
- Patients with IBD who are pregnant

Medication for patients with IBD

- Continue current treatment if disease is stable, and contact your doctor for suitable medicine if disease has flared
- Use of mesalamine should be continued and should not increase the risk of infection
- Corticosteroid use can be continued, but be cautious of possible side-effects
- A new prescription of immunosuppressant or increase in dose of an ongoing immunosuppressant is not recommended in epidemic areas.
- Use of biologics such as the anti-TNFs infliximab or adalimumab should be continued
- If infliximab infusion is not accessible, switching to adalimumab injection at home is encouraged
- Vedolizumab use can be continued due to the specificity of the drug for the intestine
- Ustekinumab use can be continued, but starting ustekinumab requires infusion centre visits and therefore is not encouraged
- Enteral nutrition might be used if biologics are not accessible
- Tofacitinib should not be newly prescribed in epidemic areas unless there are no other alternatives

Surgery and endoscopy

- Postpone elective surgery and endoscopy
- Screening for COVID-19 (complete blood count, IgM or IgG, nucleic acid detection, and chest CT) before emergency surgery

Patients with IBD and fever[*]

- Contact your IBD doctor about potential option to visit fever outpatient clinic with personal protection provisions if temperature continues over 38°C
- Suspend the use of immunosuppressant and biological agents after consultation with your IBD doctor, and follow appropriate local guidance for suspected COVID-19 if COVID-19 cannot be ruled out

- Gut. 2020 Mar 5. pii: gutjnl-2020-320891. doi: 10.1136/gutjnl-2020-320891. [Epub ahead of print]
- **SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19.**
- Song Y[#1], Liu P[#1], Shi XL[1,2], Chu YL[1], Zhang J[3], Xia J[4], Gao XZ[1], Qu T[5], Wang MY[6].

- Infect Control Hosp Epidemiol. 2020 Mar 19:1-4. doi: 10.1017/ice.2020.87. [Epub ahead of print]
- **SARS-CoV-2 enterocolitis with persisting to excrete the virus for about two weeks after recovering from diarrhea: A case report.**
- Hosoda T[1], Sakamoto M[1], Shimizu H[2], Okabe N[2].

Prolonged presence of SARS-CoV-2 viral RNA in faecal samples

Lancet Gastroenterol Hepatol 2020

Published Online
March 19, 2020
https://doi.org/10.1016/
S2468-1253(20)30083-2

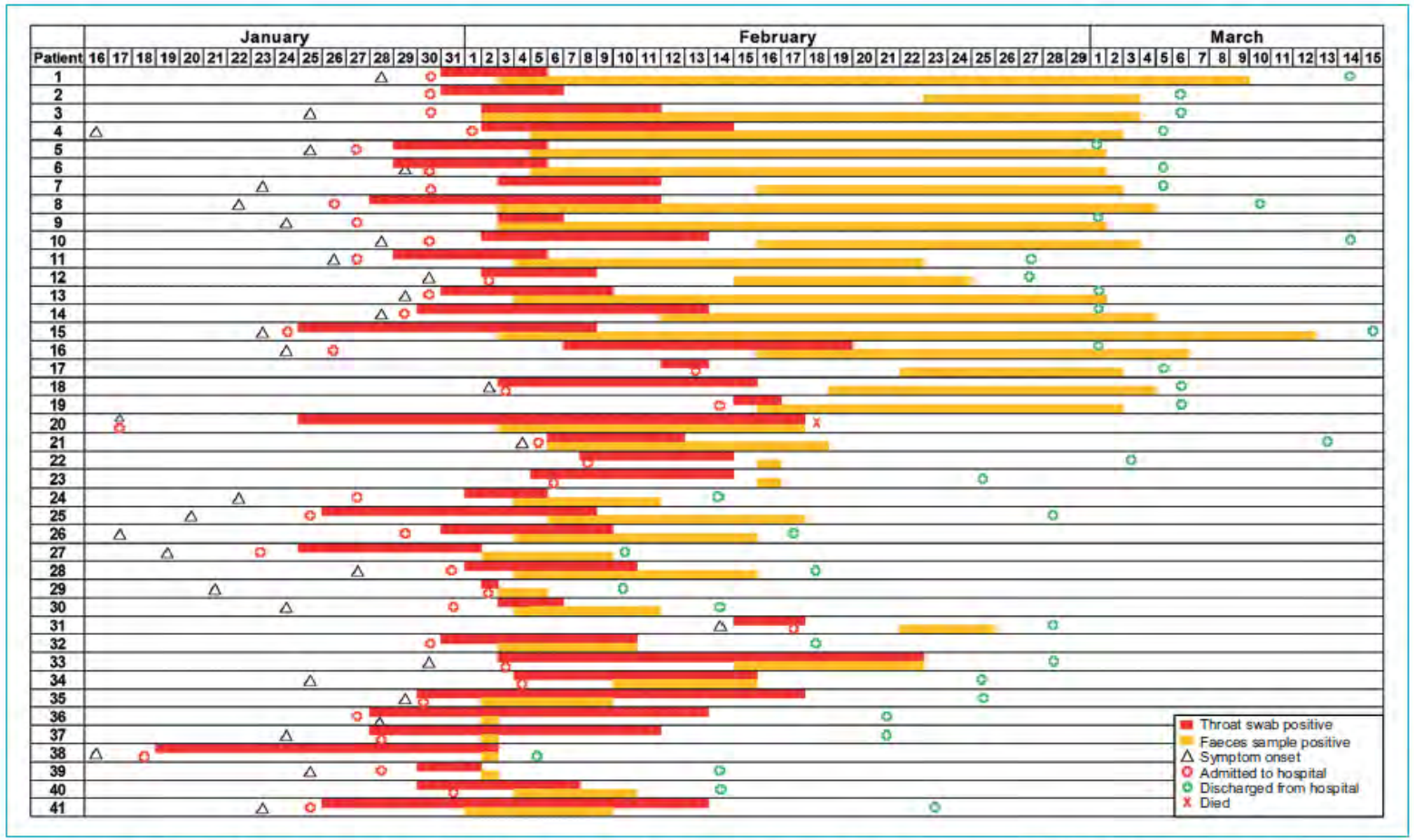


Figure: Timeline of results from throat swabs and faecal samples through the course of disease for 41 patients with SARS-CoV-2 RNA positive faecal samples, January to March, 2020

- Lancet Gastroenterol Hepatol. 2020 Mar 16. pii: S2468-1253(20)30082-0. doi: 10.1016/S2468-1253(20)30082-0. [Epub ahead of print]
- **Screening of faecal microbiota transplant donors during the COVID-19 outbreak: suggestions for urgent updates from an international expert panel.**
- Ianiro G[1], Mullish BH[2], Kelly CR[3], Sokol H[4], Kassam Z[5], Ng S[6], Fischer M[7], Allegretti JR[8], Masucci L[9], Zhang F[10], Keller J[11], Sanguinetti M[9], Costello SP[12], Tilg H[13], Gasbarrini A[14], Cammarota G[14].

- Lancet. 2020 Mar 18. pii: S0140-6736(20)30675-9. doi: 10.1016/S0140-6736(20)30675-9. [Epub ahead of print]
- **COVID-19 cacophony: is there any orchestra conductor?**
- Flahault A[1].

Partie II

- Biblio au 2/4/20

Plan

- Overview
- Epidémiologie
- Biologie
- Clinique
- HGE
- Traitements

Méthode

- 2054 articles le 1/4/20 à 15h15 dans PubMed
- Soit 3,2 articles / h sur les 9 derniers jours
- Screening de 600 articles
- Sélection des articles les + pertinents
- 197 articles in CSH Cold Spring Harbor Laboratory bioRxiv THE PREPRINT SERVER FOR BIOLOGY

News: overview

- Atteintes cardiaques
- Médicaments : IFN alpha, ribavirin, CTC…
- Récepteur virus

Epidémiologie

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 26, 2020 VOL. 382 NO. 13

Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia

Qun Li, M.Med., Xuhua Guan, Ph.D., Peng Wu, Ph.D., Xiaoye Wang, M.P.H., Lei Zhou, M.Med., Yeqing Tong, Ph.D., Ruiqi Ren, M.Med., Kathy S.M. Leung, Ph.D., Eric H.Y. Lau, Ph.D., Jessica Y. Wong, Ph.D., Xuesen Xing, Ph.D., Nijuan Xiang, M.Med., Yang Wu, M.Sc., Chao Li, M.P.H., Qi Chen, M.Sc., Dan Li, M.P.H., Tian Liu, B.Med., Jing Zhao, M.Sc., Man Liu, M.Sc., Wenxiao Tu, M.Med., Chuding Chen, M.Sc., Lianmei Jin, M.Med., Rui Yang, M.Med., Qi Wang, M.P.H., Suhua Zhou, M.Med., Rui Wang, M.D., Hui Liu, M.Med., Yinbo Luo, M.Sc., Yuan Liu, M.Med., Ge Shao, B.Med., Huan Li, M.P.H., Zhongfa Tao, M.P.H., Yang Yang, M.Med., Zhiqiang Deng, M.Med., Boxi Liu, M.P.H., Zhitao Ma, M.Med., Yanping Zhang, M.Med., Guoqing Shi, M.P.H., Tommy T.Y. Lam, Ph.D., Joseph T. Wu, Ph.D., George F. Gao, D.Phil., Benjamin J. Cowling, Ph.D., Bo Yang, M.Sc., Gabriel M. Leung, M.D., and Zijian Feng, M.Med.

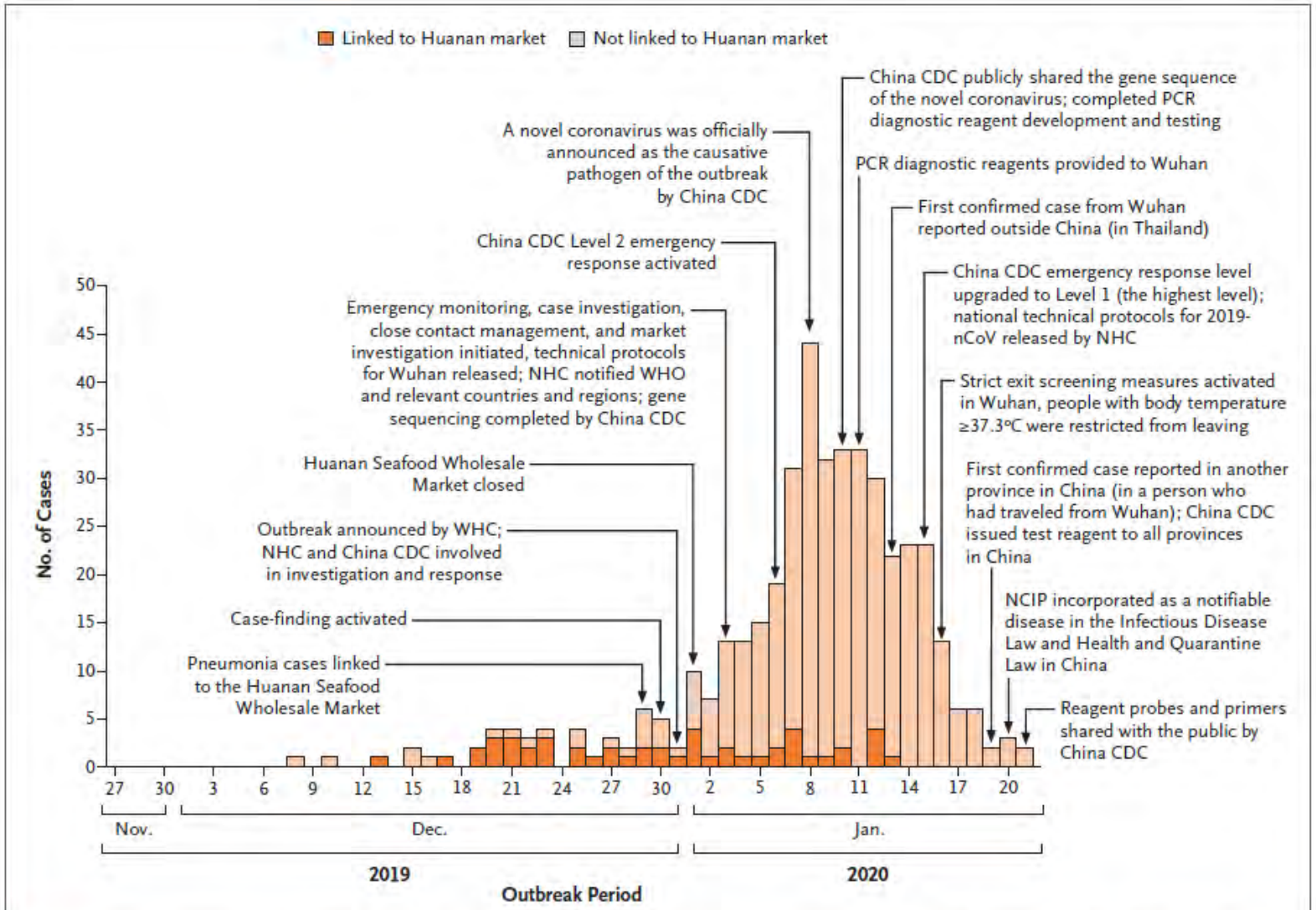


Figure 1. Onset of Illness among the First 425 Confirmed Cases of Novel Coronavirus (2019-nCoV)–Infected Pneumonia (NCIP) in Wuhan, China.

The decline in incidence after January 8 is likely to be due to delays in diagnosis and laboratory confirmation. China CDC denotes Chinese Center for Disease Control and Prevention, NHC National Health Commission of the People's Republic of China, PCR polymerase chain reaction, WHC Wuhan Health Commission, and WHO World Health Organization.

Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 27 February 2020
Cite this as: Swiss Med Wkly. 2020;150:w20212

Preliminary case report on the SARS-CoV-2 cluster in the UK, France, and Spain

Hodcroft Emma B[ab]

[a] Biozentrum, University of Basel, Basel, Switzerland
[b] Swiss Institute of Bioinformatics, Basel, Switzerland

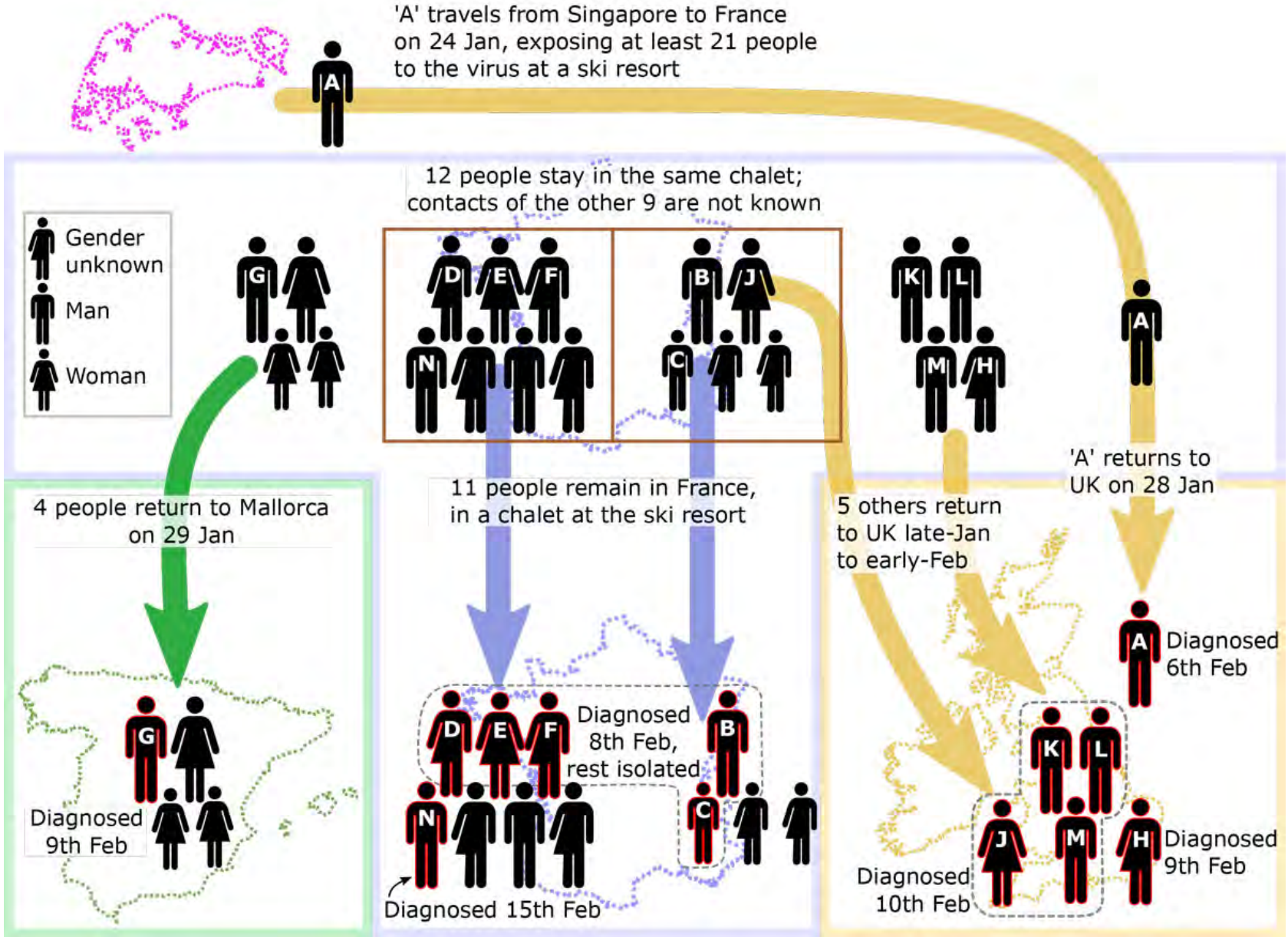


Figure 1 An overview of the "UK/France' cluster shows the travel of the twenty-one people known to be involved, and the diagnosis dates of the 13 who eventually tested positive for SARS-CoV-2. Only the dates of when focal case "A_{UK}' are in France are known definitely, and the overlap of "A_{UK}' with other cases, and the other cases with each other, is unknown.

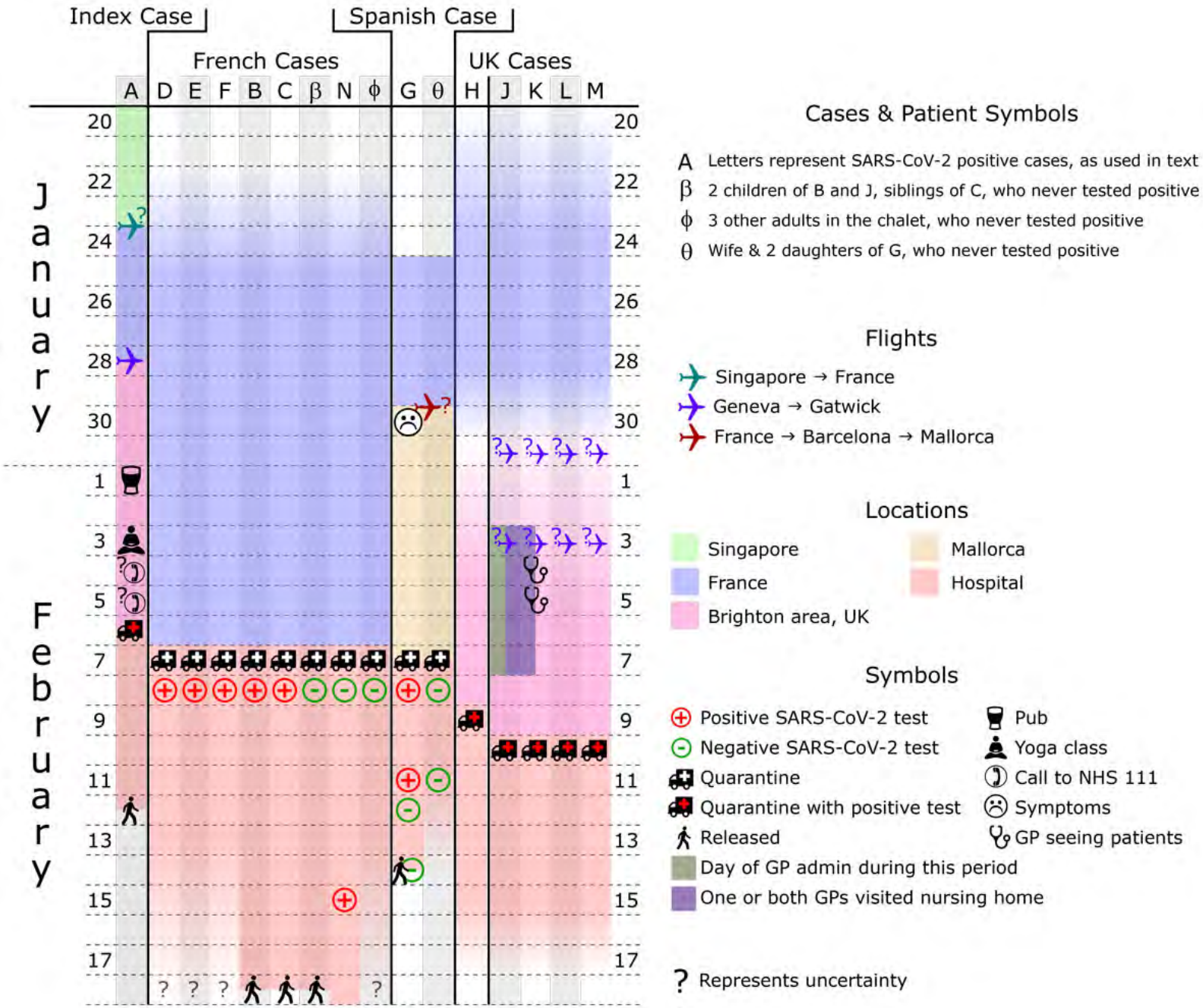


Figure 2 This detailed figure includes almost all information that is provided in the text, including travel and quarantine time, diagnoses and additional tests (if available), release date, and other important activities. Greek letters are used to represent multiple people who never tested positive for SARS-CoV-2. Questions marks show uncertainty about when or for whom an event occurred. Shading in the location colours conveys uncertainty about when individuals travelled, when they were present in a location, and by extension, when they overlapped with other individuals.

Biologie

- Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv 2020:927806.

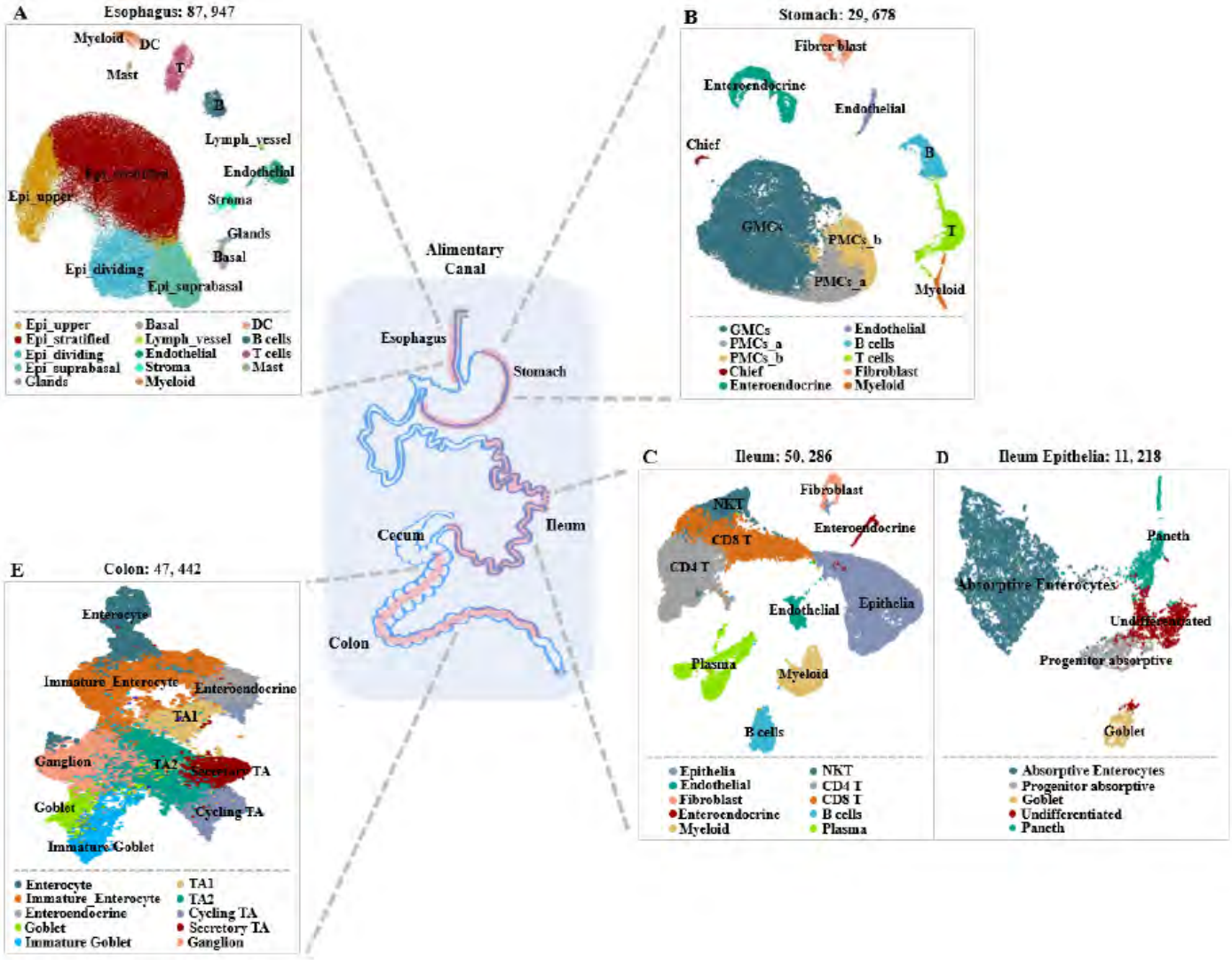


Figure 1: Single-Cell Atlas of digestive tract samples

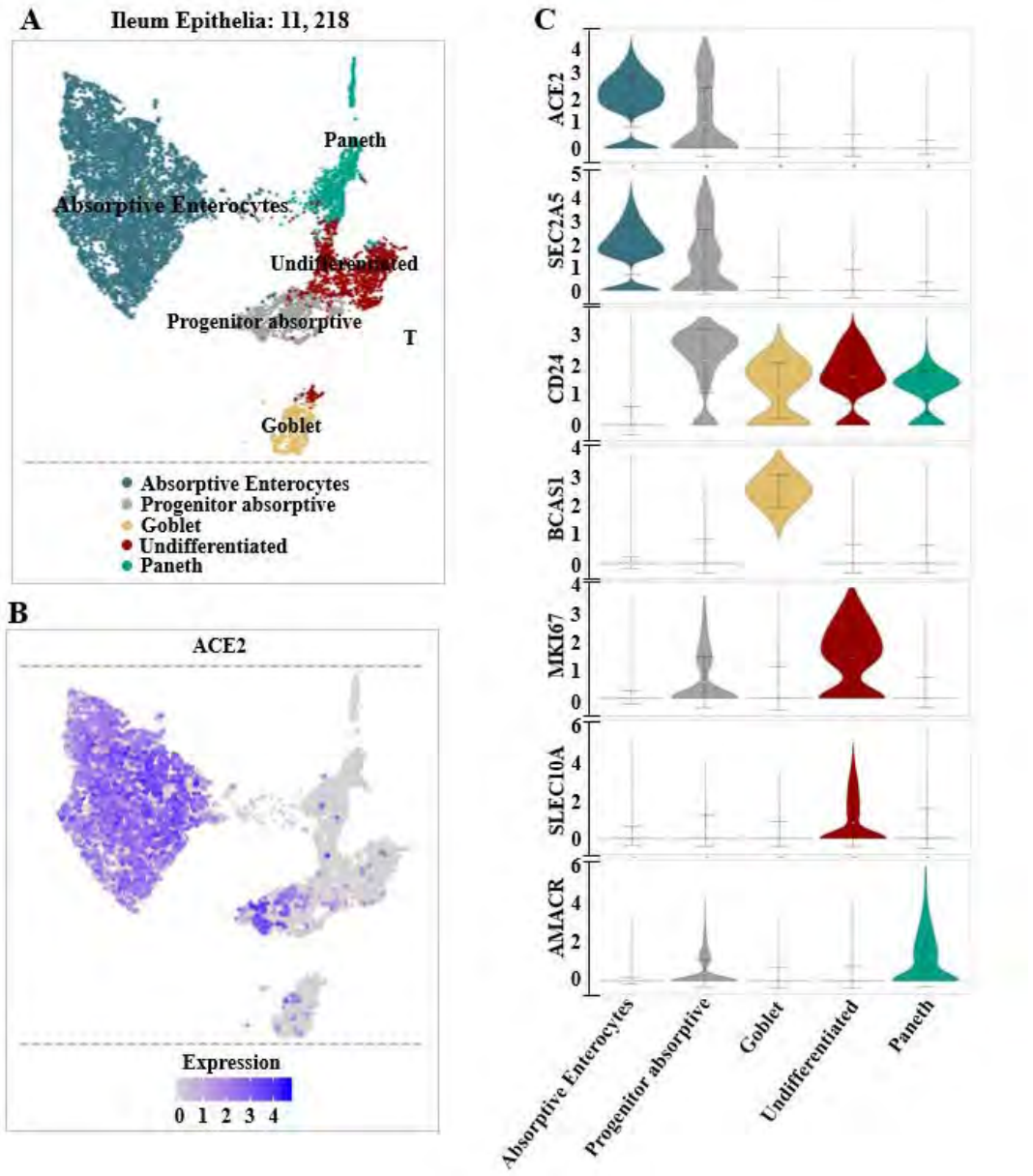


Figure 4. Single-cell analysis 2 of ileal epithelial cells
(A). UMAP plots showing the landscape of ileal epithelial cells. 10 cell clusters were identified across 11218 cells after quality control, dimensionality reduction and clustering.
(B). UMAP plots showing the expression of *ACE2* across clusters.
(C). Violin plots for ileal epithelial marker genes and *ACE2* across clusters. The expression is measured as the $\log_2$ (TP10K+1).

Journal Pre-proof

Multi-omics Evaluation of Gastrointestinal and Other Clinical Characteristics of SARS-CoV-2 and COVID-19

Mulong Du, Guoshuai Cai, Feng Chen, David C. Christiani, Zhengdong Zhang, Meilin Wang

PII: S0016-5085(20)30399-1
DOI: https://doi.org/10.1053/j.gastro.2020.03.045
Reference: YGAST 63315

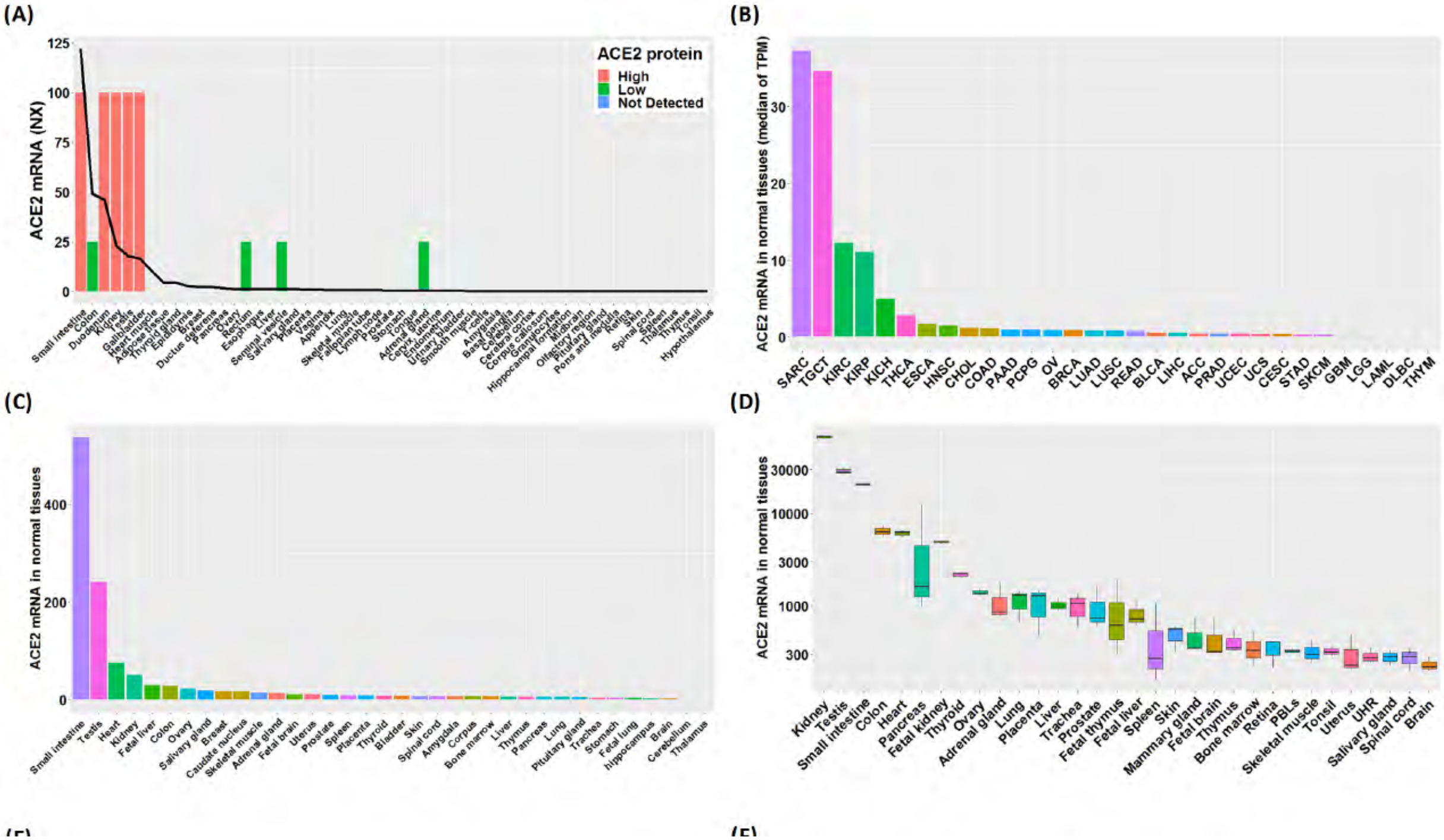
To appear in: *Gastroenterology*
Accepted Date: 17 March 2020

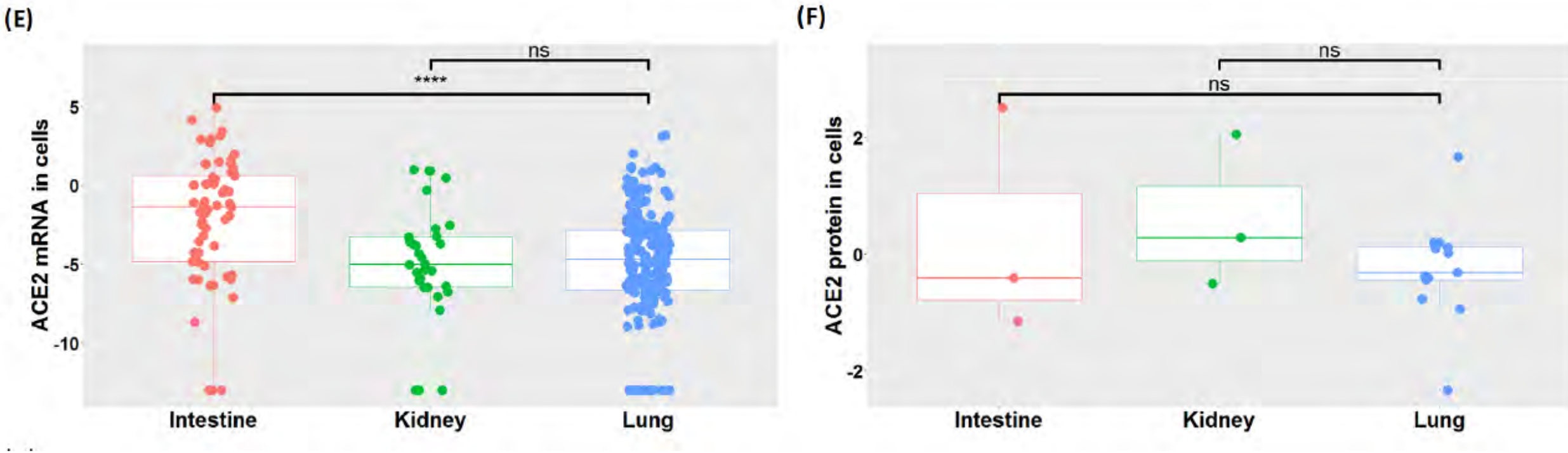
Please cite this article as: Du M, Cai G, Chen F, Christiani DC, Zhang Z, Wang M, Multi-omics Evaluation of Gastrointestinal and Other Clinical Characteristics of SARS-CoV-2 and COVID-19, *Gastroenterology* (2020), doi: https://doi.org/10.1053/j.gastro.2020.03.045.

Supplementary Figure 1. Global distribution of COVID-19 cases. Dataset was downloaded at Feb 23th, 2020 (https://tinyurl.com/s6gsq5y). (A) a total of 26,357 cases distributed around the world, among which 398 cases (39 cases derived from Hubei and 359 from the outside) recorded with complete clinical symptoms at onset of illness were marked in orange, and the non-recorded cases in blue. (B) Cases with symptoms in digestive system or asymptomatic carriers were marked in colors. A web location provided a user-friendly interface for visualization of clinical symptoms (https://mulongdu.shinyapps.io/map_covid/).

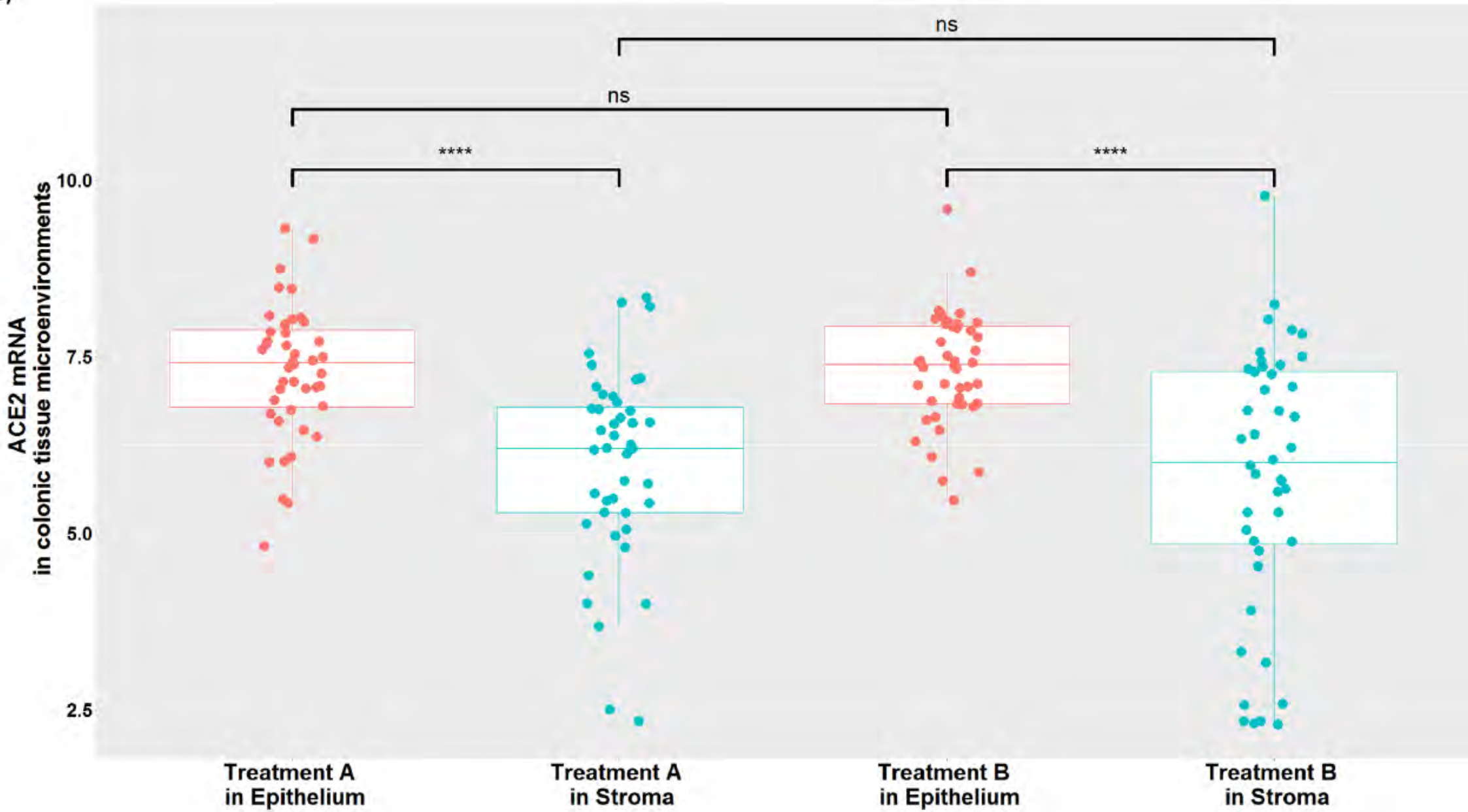
(A)

(B)

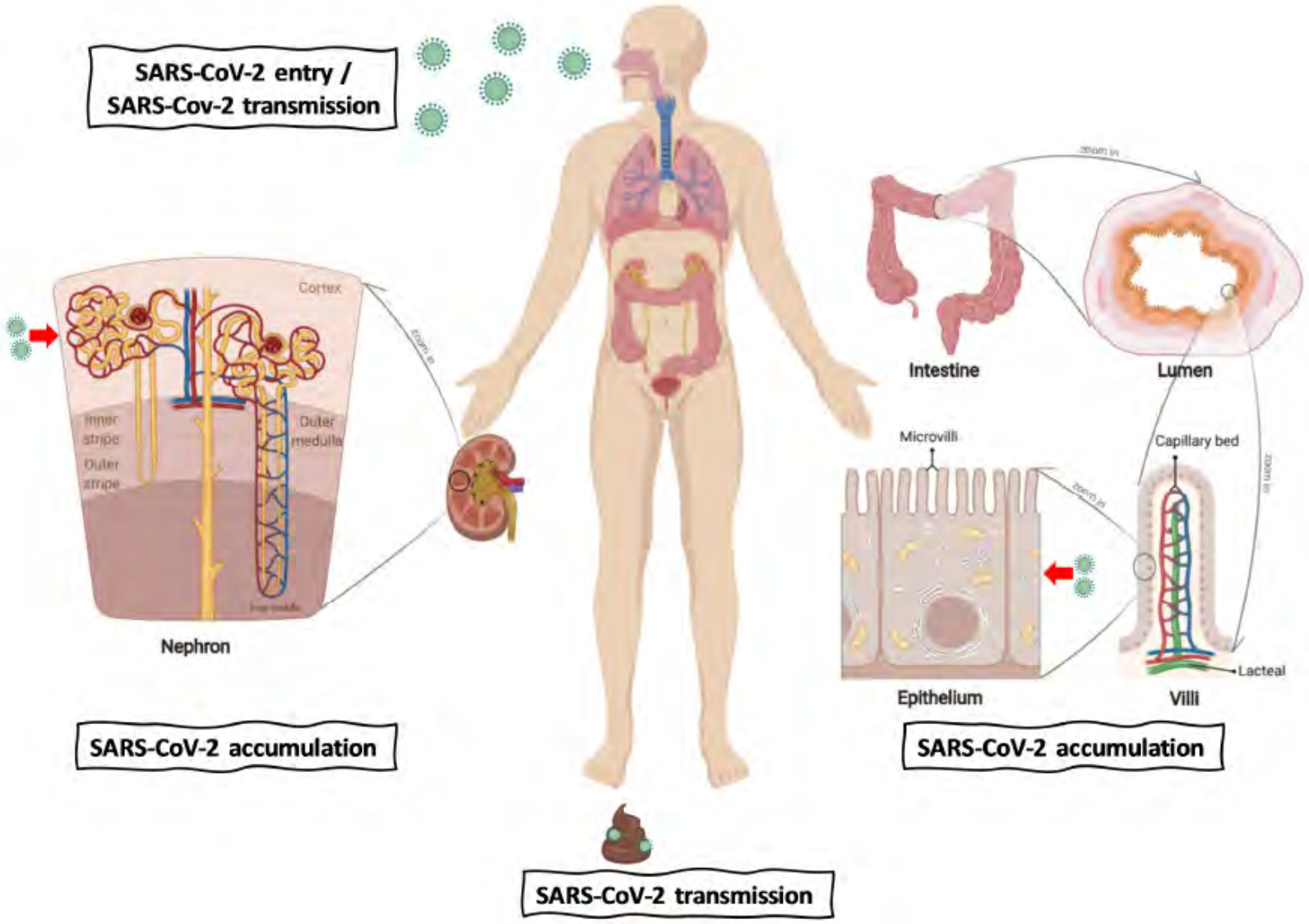

(A)
ACE2 mRNA (NX)
125
100
75
50
25
0
ACE2 protein
High
Low
Not Detected
Small intestine
Colon
Duodenum
Kidney
Testis
Gallbladder
Heart muscle
Adipose tissue
Thyroid gland
Epididymis
Breast
Ductus deferens
Pancreas
Ovary
Rectum
Esophagus
Liver
Seminal vesicle
Salivary gland
Placenta
Vagina
Appendix
Lung
Skeletal muscle
Fallopian tube
Lymph node
Prostate
Stomach
Tongue
Adrenal gland
Cervix, uterine
Endometrium
Urinary bladder
Smooth muscle
T-cells
Amygdala
Basal ganglia
Cerebellum
Cerebral cortex
Corpus callosum
Hippocampal formation
Granulocytes
Midbrain
Olfactory region
Pituitary gland
Pons and medulla
Retina
Skin
Spinal cord
Spleen
Thalamus
Thymus
Tonsil
Hypothalamus
(B)
ACE2 mRNA in normal tissues (median of TPM)
30
20
10
0
SARC
TGCT
KIRC
KIRP
KICH
THCA
ESCA
HNSC
CHOL
COAD
PAAD
PCPG
OV
BRCA
LUAD
LUSC
READ
BLCA
LIHC
ACC
PRAD
UCEC
UCS
CESC
STAD
SKCM
GBM
LGG
LAML
DLBC
THYM
(C)
ACE2 mRNA in normal tissues
400
200
0
Small intestine
Testis
Heart
Kidney
Fetal liver
Colon
Ovary
Salivary gland
Breast
Caudate nucleus
Skeletal muscle
Adrenal gland
Fetal brain
Uterus
Prostate
Spleen
Placenta
Thyroid
Bladder
Skin
Spinal cord
Amygdala
Corpus
Bone marrow
Liver
Thymus
Pancreas
Lung
Pituitary gland
Trachea
Stomach
Fetal lung
hippocampus
Brain
Cerebellum
Thalamus
(D)
ACE2 mRNA in normal tissues
30000
10000
3000
1000
300
Kidney
Testis
Small intestine
Colon
Heart
Pancreas
Fetal kidney
Thyroid
Ovary
Adrenal gland
Lung
Placenta
Liver
Trachea
Prostate
Fetal thymus
Fetal liver
Spleen
Skin
Mammary gland
Fetal brain
Thymus
Bone marrow
Retina
PBLs
Skeletal muscle
Tonsil
Uterus
UHR
Salivary gland
Spinal cord
Brain


(E)
ns
****
5
0
-5
-10
ACE2 mRNA in cells
Intestine
Kidney
Lung
(F)
ns
ns
2
0
-2
ACE2 protein in cells
Intestine
Kidney
Lung

(G)


ns
ns
****
****
ACE2 mRNA
in colonic tissue microenvironments
10.0
7.5
5.0
2.5
Treatment A
in Epithelium
Treatment A
in Stroma
Treatment B
in Epithelium
Treatment B
in Stroma

Supplementary Figure 4. Schematic of the bulk-to-cell strategy for evaluating SARS-CoV-2 infection, accumulation and transmission across hosts. The diagram was constructed with BioRender (https://biorender.com/).

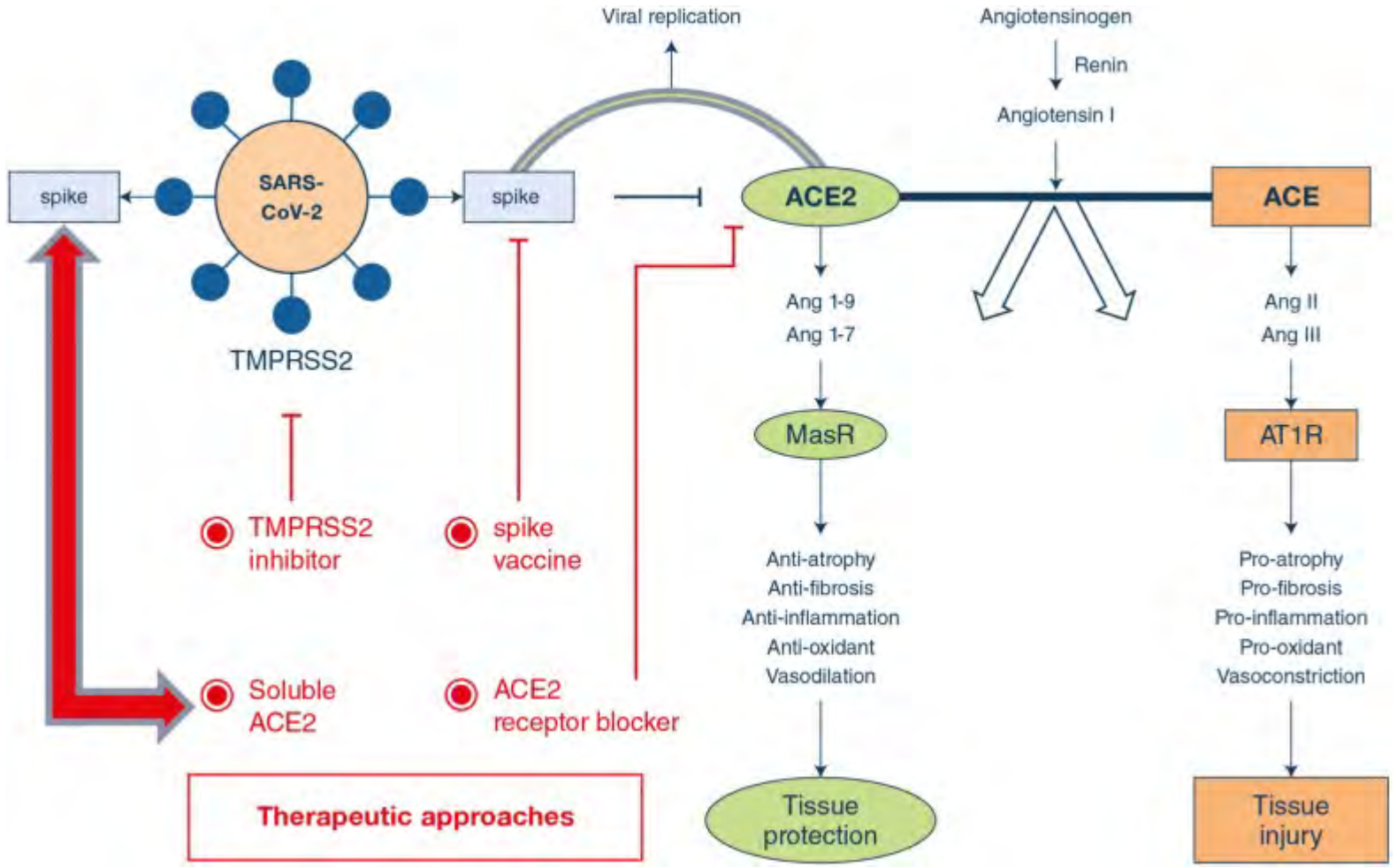


Intensive Care Med
https://doi.org/10.1007/s00134-020-05985-9

UNDERSTANDING THE DISEASE

Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target

Haibo Zhang[1,3,6], Josef M. Penninger[4,5], Yimin Li[3], Nanshan Zhong[3] and Arthur S. Slutsky[1,2,3*]



Potential approaches to address ACE2-mediated COVID-19 following SARS-CoV-2 infection. The finding that SARS-CoV-2 and SARS-CoV use the ACE2 receptor for cell entry has important implications for understanding SARS-CoV-2 transmissibility and pathogenesis. SARS-CoV and likely SARS-CoV-2 lead to downregulation of the ACE2 receptor, but not ACE, through binding of the spike protein with ACE2. This leads to viral entry and replication, as well as severe lung injury. Potential therapeutic approaches include a SARS-CoV-2 spike protein-based vaccine; a transmembrane protease serine 2 (TMPRSS2) inhibitor to block the priming of the spike protein; blocking the surface ACE2 receptor by using anti-ACE2 antibody or peptides; and a soluble form of ACE2 which should slow viral entry into cells through competitively binding with SARS-CoV-2 and hence decrease viral spread as well as protecting the lung from injury through its unique enzymatic function. MasR—mitochondrial assembly receptor, AT1R—Ang II type 1 receptor

Clinica Chimica Acta 505 (2020) 192–193

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Editorial

The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections

Clinica Chimica Acta 505 (2020) 192–193

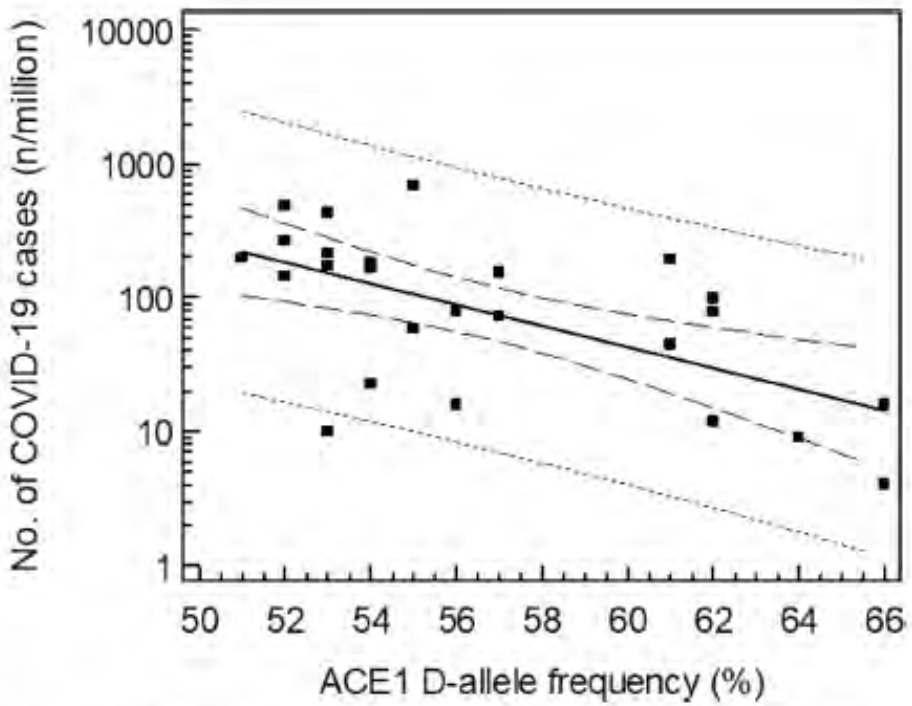


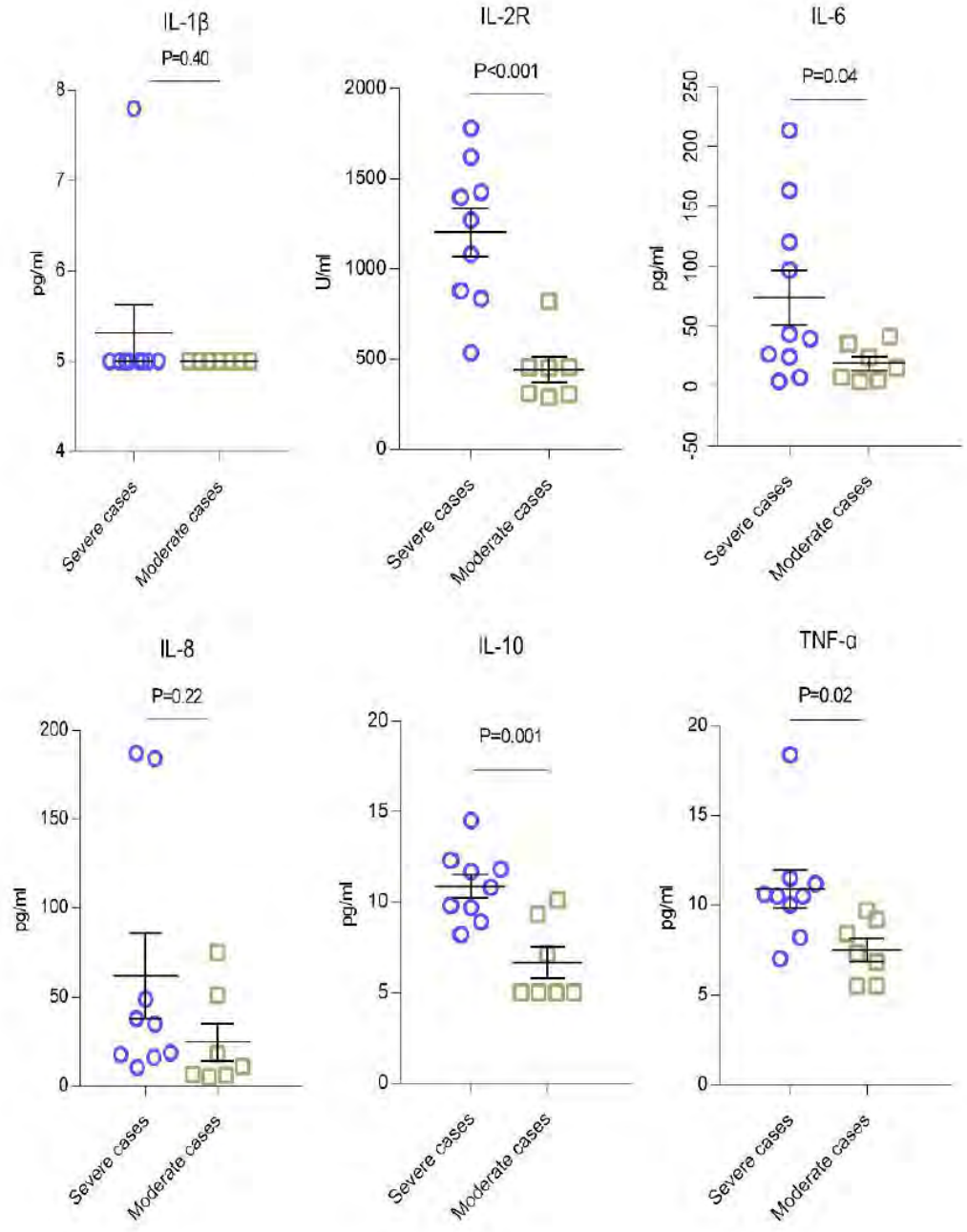
Fig. 1. Prevalence of COVID 19 in 25 European countries (on March 20, 2020 vs. ACE1 D-allele frequency (%): log (prevalence; no. of cases/10^6 inhabitants) = 6.358–0.079 (D-allele frequency, %), $r^2 = 0.378$; $p = 0.001$.

JCI The Journal of Clinical Investigation

Clinical and immunologic features in severe and moderate Coronavirus Disease 2019

Guang Chen, … , Jianping Zhao, Qin Ning

J Clin Invest. 2020. https://doi.org/10.1172/JCI137244.


IL-1β
P=0.40
pg/ml
8
7
6
5
4
Severe cases
Moderate cases
IL-2R
P<0.001
U/ml
2000
1500
1000
500
0
Severe cases
Moderate cases
IL-6
P=0.04
pg/ml
250
200
150
100
50
0
-50
Severe cases
Moderate cases
IL-8
P=0.22
pg/ml
200
150
100
50
0
Severe cases
Moderate cases
IL-10
P=0.001
pg/ml
20
15
10
5
0
Severe cases
Moderate cases
TNF-α
P=0.02
pg/ml
20
15
10
5
0
Severe cases
Moderate cases

Clinique

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, and N. Zhong, for the China Medical Treatment Expert Group for Covid-19*

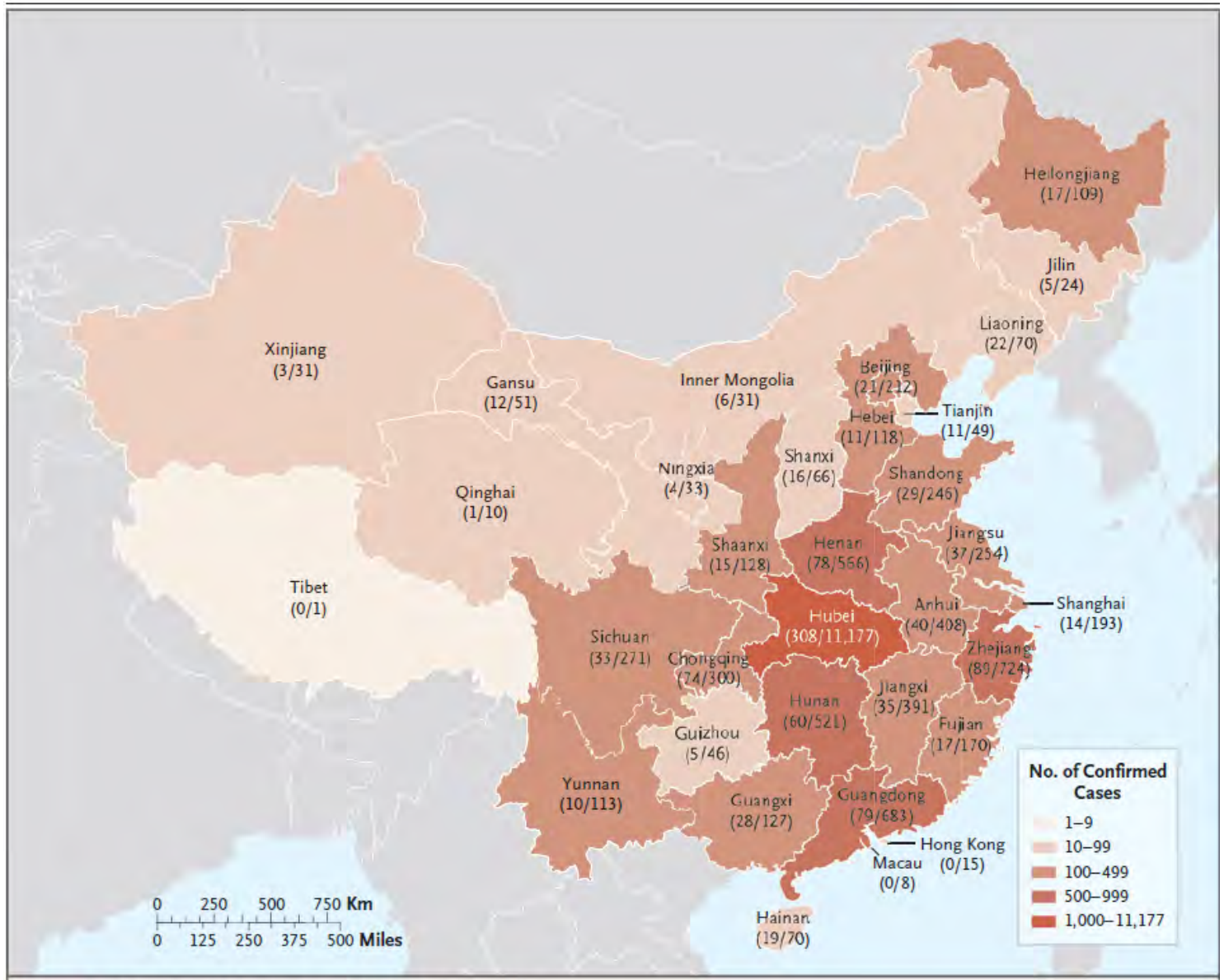


Figure 1. Distribution of Patients with Covid-19 across China.

Shown are the official statistics of all documented, laboratory-confirmed cases of coronavirus disease 2019 (Covid-19) throughout China, according to the National Health Commission as of February 4, 2020. The numerator denotes the number of patients who were included in the study cohort and the denominator denotes the number of laboratory-confirmed cases for each province, autonomous region, or provincial municipality, as reported by the National Health Commission.

Table 1. Clinical Characteristics of the Study Patients, According to Disease Severity and the Presence or Absence of the Primary Composite End Point.*

Characteristic	All Patients (N=1099)	Disease Severity		Presence of Primary Composite End Point†	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Age					
Median (IQR) — yr	47.0 (35.0–58.0)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	63.0 (53.0–71.0)	46.0 (35.0–57.0)
Distribution — no./total no. (%)					
0–14 yr	9/1011 (0.9)	8/848 (0.9)	1/163 (0.6)	0	9/946 (1.0)
15–49 yr	557/1011 (55.1)	490/848 (57.8)	67/163 (41.1)	12/65 (18.5)	545/946 (57.6)
50–64 yr	292/1011 (28.9)	241/848 (28.4)	51/163 (31.3)	21/65 (32.3)	271/946 (28.6)
≥65 yr	153/1011 (15.1)	109/848 (12.9)	44/163 (27.0)	32/65 (49.2)	121/946 (12.8)
Female sex — no./total no. (%)	459/1096 (41.9)	386/923 (41.8)	73/173 (42.2)	22/67 (32.8)	437/1029 (42.5)
Smoking history — no./total no. (%)					
Never smoked	927/1085 (85.4)	793/913 (86.9)	134/172 (77.9)	44/66 (66.7)	883/1019 (86.7)
Former smoker	21/1085 (1.9)	12/913 (1.3)	9/172 (5.2)	5/66 (7.6)	16/1019 (1.6)
Current smoker	137/1085 (12.6)	108/913 (11.8)	29/172 (16.9)	17/66 (25.8)	120/1019 (11.8)
Exposure to source of transmission within past 14 days — no./total no.					
Living in Wuhan	483/1099 (43.9)	400/926 (43.2)	83/173 (48.0)	39/67 (58.2)	444/1032 (43.0)
Contact with wildlife	13/687 (1.9)	10/559 (1.8)	3/128 (2.3)	1/41 (2.4)	12/646 (1.9)
Recently visited Wuhan‡	193/616 (31.3)	166/526 (31.6)	27/90 (30.0)	10/28 (35.7)	183/588 (31.1)
Had contact with Wuhan residents‡	442/611 (72.3)	376/522 (72.0)	66/89 (74.2)	19/28 (67.9)	423/583 (72.6)
Median incubation period (IQR) — days§	4.0 (2.0–7.0)	4.0 (2.8–7.0)	4.0 (2.0–7.0)	4.0 (1.0–7.5)	4.0 (2.0–7.0)
Fever on admission					
Patients — no./total no. (%)	473/1081 (43.8)	391/910 (43.0)	82/171 (48.0)	24/66 (36.4)	449/1015 (44.2)
Median temperature (IQR) — °C	37.3 (36.7–38.0)	37.3 (36.7–38.0)	37.4 (36.7–38.1)	36.8 (36.3–37.8)	37.3 (36.7–38.0)
Distribution of temperature — no./total no. (%)					
<37.5°C	608/1081 (56.2)	519/910 (57.0)	89/171 (52.0)	42/66 (63.6)	566/1015 (55.8)
37.5–38.0°C	238/1081 (22.0)	201/910 (22.1)	37/171 (21.6)	10/66 (15.2)	228/1015 (22.5)
38.1–39.0°C	197/1081 (18.2)	160/910 (17.6)	37/171 (21.6)	11/66 (16.7)	186/1015 (18.3)
>39.0°C	38/1081 (3.5)	30/910 (3.3)	8/171 (4.7)	3/66 (4.5)	35/1015 (3.4)
Fever during hospitalization					
Patients — no./total no. (%)	975/1099 (88.7)	816/926 (88.1)	159/173 (91.9)	59/67 (88.1)	916/1032 (88.8)
Median highest temperature (IQR) — °C	38.3 (37.8–38.9)	38.3 (37.8–38.9)	38.5 (38.0–39.0)	38.5 (38.0–39.0)	38.3 (37.8–38.9)
<37.5°C	92/926 (9.9)	79/774 (10.2)	13/152 (8.6)	3/54 (5.6)	89/872 (10.2)
37.5–38.0°C	286/926 (30.9)	251/774 (32.4)	35/152 (23.0)	20/54 (37.0)	266/872 (30.5)
38.1–39.0°C	434/926 (46.9)	356/774 (46.0)	78/152 (51.3)	21/54 (38.9)	413/872 (47.4)
>39.0°C	114/926 (12.3)	88/774 (11.4)	26/152 (17.1)	10/54 (18.5)	104/872 (11.9)

Symptoms — no. (%)					
Conjunctival congestion	9 (0.8)	5 (0.5)	4 (2.3)	0	9 (0.9)
Nasal congestion	53 (4.8)	47 (5.1)	6 (3.5)	2 (3.0)	51 (4.9)
Headache	150 (13.6)	124 (13.4)	26 (15.0)	8 (11.9)	142 (13.8)
Cough	745 (67.8)	623 (67.3)	122 (70.5)	46 (68.7)	699 (67.7)
Sore throat	153 (13.9)	130 (14.0)	23 (13.3)	6 (9.0)	147 (14.2)
Sputum production	370 (33.7)	309 (33.4)	61 (35.3)	20 (29.9)	350 (33.9)
Fatigue	419 (38.1)	350 (37.8)	69 (39.9)	22 (32.8)	397 (38.5)
Hemoptysis	10 (0.9)	6 (0.6)	4 (2.3)	2 (3.0)	8 (0.8)
Shortness of breath	205 (18.7)	140 (15.1)	65 (37.6)	36 (53.7)	169 (16.4)
Nausea or vomiting	55 (5.0)	43 (4.6)	12 (6.9)	3 (4.5)	52 (5.0)
Diarrhea	42 (3.8)	32 (3.5)	10 (5.8)	4 (6.0)	38 (3.7)
Myalgia or arthralgia	164 (14.9)	134 (14.5)	30 (17.3)	6 (9.0)	158 (15.3)
Chills	126 (11.5)	100 (10.8)	26 (15.0)	8 (11.9)	118 (11.4)
Signs of infection — no. (%)					
Throat congestion	19 (1.7)	17 (1.8)	2 (1.2)	0	19 (1.8)
Tonsil swelling	23 (2.1)	17 (1.8)	6 (3.5)	1 (1.5)	22 (2.1)
Enlargement of lymph nodes	2 (0.2)	1 (0.1)	1 (0.6)	1 (1.5)	1 (0.1)
Rash	2 (0.2)	0	2 (1.2)	0	2 (0.2)
Coexisting disorder — no. (%)					
Any	261 (23.7)	194 (21.0)	67 (38.7)	39 (58.2)	222 (21.5)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	6 (3.5)	7 (10.4)	5 (0.5)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Hypertension	165 (15.0)	124 (13.4)	41 (23.7)	24 (35.8)	141 (13.7)
Coronary heart disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (2.3)	4 (6.0)	11 (1.1)
Hepatitis B infection ¶	23 (2.1)	22 (2.4)	1 (0.6)	1 (1.5)	22 (2.1)
Cancer ‖	10 (0.9)	7 (0.8)	3 (1.7)	1 (1.5)	9 (0.9)
Chronic renal disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)
Immunodeficiency	2 (0.2)	2 (0.2)	0	0	2 (0.2)

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, and IQR interquartile range.
† The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death.
‡ These patients were not residents of Wuhan.
§ Data regarding the incubation period were missing for 808 patients (73.5%).
¶ The presence of hepatitis B infection was defined as a positive result on testing for hepatitis B surface antigen with or without elevated levels of alanine or aspartate aminotransferase.
‖ Included in this category is any type of cancer.

Table 2. Radiographic and Laboratory Findings.*

Variable	All Patients (N= 1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N =926)	Severe (N =173)	Yes (N= 67)	No (N= 1032)
Radiologic findings					
Abnormalities on chest radiograph — no./total no. (%)	162/274 (59.1)	116/214 (54.2)	46/60 (76.7)	30/39 (76.9)	132/235 (56.2)
Ground-glass opacity	55/274 (20.1)	37/214 (17.3)	18/60 (30.0)	9/39 (23.1)	46/235 (19.6)
Local patchy shadowing	77/274 (28.1)	56/214 (26.2)	21/60 (35.0)	13/39 (33.3)	64/235 (27.2)
Bilateral patchy shadowing	100/274 (36.5)	65/214 (30.4)	35/60 (58.3)	27/39 (69.2)	73/235 (31.1)
Interstitial abnormalities	12/274 (4.4)	7/214 (3.3)	5/60 (8.3)	6/39 (15.4)	6/235 (2.6)
Abnormalities on chest CT — no./total no. (%)	840/975 (86.2)	682/808 (84.4)	158/167 (94.6)	50/57 (87.7)	790/918 (86.1)
Ground-glass opacity	550/975 (56.4)	449/808 (55.6)	101/167 (60.5)	30/57 (52.6)	520/918 (56.6)
Local patchy shadowing	409/975 (41.9)	317/808 (39.2)	92/167 (55.1)	22/57 (38.6)	387/918 (42.2)
Bilateral patchy shadowing	505/975 (51.8)	368/808 (45.5)	137/167 (82.0)	40/57 (70.2)	465/918 (50.7)
Interstitial abnormalities	143/975 (14.7)	99/808 (12.3)	44/167 (26.3)	15/57 (26.3)	128/918 (13.9)
Laboratory findings					
Median Pao_2:Fio_2 ratio (IQR) †	3.9 (2.9–4.7)	3.9 (2.9–4.5)	4.0 (2.8–5.2)	2.9 (2.2–5.4)	4.0 (3.1–4.6)
White-cell count					
Median (IQR) — per mm^3	4700 (3500– 6000)	4900 (3800–6000)	3700 (3000–6200)	6100 (4900– 11,100)	4700 (3500– 5900)
Distribution — no./total no. (%)					
>10,000 per mm^3	58/978 (5.9)	39/811 (4.8)	19/167 (11.4)	15/58 (25.9)	43/920 (4.7)
<4000 per mm^3	330/978 (33.7)	228/811 (28.1)	102/167 (61.1)	8/58 (13.8)	322/920 (35.0)
Lymphocyte count					
Median (IQR) — per mm^3	1000 (700–1300)	1000 (800–1400)	800 (600–1000)	700 (600–900)	1000 (700–1300)
Distribution — no./total no. (%)					
<1500 per mm^3	731/879 (83.2)	584/726 (80.4)	147/153 (96.1)	50/54 (92.6)	681/825 (82.5)

Platelet count					
Median (IQR) — per mm^3	168,000 (132,000–207,000)	172,000 (139,000–212,000)	137,500 (99,000–179,500)	156,500 (114,200–195,000)	169,000 (133,000–207,000)
Distribution — no./total no. (%)					
<150,000 per mm^3	315/869 (36.2)	225/713 (31.6)	90/156 (57.7)	27/58 (46.6)	288/811 (35.5)
Median hemoglobin (IQR) — g/dl‡	134.0 (119.0–148.0)	135.0 (120.0–148.0)	128.0 (111.8–141.0)	125.0 (105.0–140.0)	134.0 (120.0–148.0)
Distribution of other findings — no./total no. (%)					
C-reactive protein ≥ 10 mg/liter	481/793 (60.7)	371/658 (56.4)	110/135 (81.5)	41/45 (91.1)	440/748 (58.8)
Procalcitonin ≥0.5 ng/ml	35/633 (5.5)	19/516 (3.7)	16/117 (13.7)	12/50 (24.0)	23/583 (3.9)
Lactate dehydrogenase ≥250 U/liter	277/675 (41.0)	205/551 (37.2)	72/124 (58.1)	31/44 (70.5)	246/631 (39.0)
Aspartate aminotransferase >40 U/liter	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)	26/52 (50.0)	142/705 (20.1)
Alanine aminotransferase >40 U/liter	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)	20/49 (40.8)	138/692 (19.9)
Total bilirubin >17.1 μmol/liter	76/722 (10.5)	59/594 (9.9)	17/128 (13.3)	10/48 (20.8)	66/674 (9.8)
Creatine kinase ≥200 U/liter	90/657 (13.7)	67/536 (12.5)	23/121 (19.0)	12/46 (26.1)	78/611 (12.8)
Creatinine ≥133 μmol/liter	12/752 (1.6)	6/614 (1.0)	6/138 (4.3)	5/52 (9.6)	7/700 (1.0)
D-dimer ≥0.5 mg/liter	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)	34/49 (69.4)	226/511 (44.2)
Minerals§					
Median sodium (IQR) — mmol/liter	138.2 (136.1–140.3)	138.4 (136.6–140.4)	138.0 (136.0–140.0)	138.3 (135.0–141.2)	138.2 (136.1–140.2)
Median potassium (IQR) — mmol/liter	3.8 (3.5–4.2)	3.9 (3.6–4.2)	3.8 (3.5–4.1)	3.9 (3.6–4.1)	3.8 (3.5–4.2)
Median chloride (IQR) — mmol/liter	102.9 (99.7–105.6)	102.7 (99.7–105.3)	103.1 (99.8–106.0)	103.8 (100.8–107.0)	102.8 (99.6–105.3)

* Lymphocytopenia was defined as a lymphocyte count of less than 1500 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

† Data regarding the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) were missing for 894 patients (81.3%).

‡ Data regarding hemoglobin were missing for 226 patients (20.6%).

§ Data were missing for the measurement of sodium in 363 patients (33.0%), for potassium in 349 patients (31.8%), and for chloride in 392 patients (35.7%).

Table 3. Complications, Treatments, and Clinical Outcomes.

Variable	All Patients (N= 1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Complications					
Septic shock — no. (%)	12 (1.1)	1 (0.1)	11 (6.4)	9 (13.4)	3 (0.3)
Acute respiratory distress syndrome — no. (%)	37 (3.4)	10 (1.1)	27 (15.6)	27 (40.3)	10 (1.0)
Acute kidney injury — no. (%)	6 (0.5)	1 (0.1)	5 (2.9)	4 (6.0)	2 (0.2)
Disseminated intravascular coagulation — no. (%)	1 (0.1)	0	1 (0.6)	1 (1.5)	0
Rhabdomyolysis — no. (%)	2 (0.2)	2 (0.2)	0	0	2 (0.2)
Physician-diagnosed pneumonia — no./total no. (%)	972/1067 (91.1)	800/894 (89.5)	172/173 (99.4)	63/66 (95.5)	909/1001 (90.8)
Median time until development of pneumonia (IQR) — days*					
After initial Covid-19 diagnosis	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.0 (0.0–3.5)	0.0 (0.0–1.0)
After onset of Covid-19 symptoms	3.0 (1.0–6.0)	3.0 (1.0–6.0)	5.0 (2.0–7.0)	4.0 (0.0–7.0)	3.0 (1.0–6.0)
Treatments					
Intravenous antibiotics — no. (%)	637 (58.0)	498 (53.8)	139 (80.3)	60 (89.6)	577 (55.9)
Oseltamivir — no. (%)	393 (35.8)	313 (33.8)	80 (46.2)	36 (53.7)	357 (34.6)
Antifungal medication — no. (%)	31 (2.8)	18 (1.9)	13 (7.5)	8 (11.9)	23 (2.2)
Systemic glucocorticoids — no. (%)	204 (18.6)	127 (13.7)	77 (44.5)	35 (52.2)	169 (16.4)
Oxygen therapy — no. (%)	454 (41.3)	331 (35.7)	123 (71.1)	59 (88.1)	395 (38.3)
Mechanical ventilation — no. (%)	67 (6.1)	0	67 (38.7)	40 (59.7)	27 (2.6)
Invasive	25 (2.3)	0	25 (14.5)	25 (37.3)	0
Noninvasive	56 (5.1)	0	56 (32.4)	29 (43.3)	27 (2.6)
Use of extracorporeal membrane oxygenation — no. (%)	5 (0.5)	0	5 (2.9)	5 (7.5)	0
Use of continuous renal-replacement therapy — no. (%)	9 (0.8)	0	9 (5.2)	8 (11.9)	1 (0.1)
Use of intravenous immune globulin — no. (%)	144 (13.1)	86 (9.3)	58 (33.5)	27 (40.3)	117 (11.3)
Admission to intensive care unit — no. (%)	55 (5.0)	22 (2.4)	33 (19.1)	55 (82.1)	0
Median length of hospital stay (IQR) — days†	12.0 (10.0–14.0)	11.0 10.0–13.0)	13.0 (11.5–17.0)	14.5 (11.0–19.0)	12.0 (10.0–13.0)

Clinical outcomes at data cutoff — no. (%)					
Discharge from hospital	55 (5.0)	50 (5.4)	5 (2.9)	1 (1.5)	54 (5.2)
Death	15 (1.4)	1 (0.1)	14 (8.1)	15 (22.4)	0
Recovery	9 (0.8)	7 (0.8)	2 (1.2)	0	9 (0.9)
Hospitalization	1029 (93.6)	875 (94.5)	154 (89.0)	51 (76.1)	978 (94.8)

* For the development of pneumonia, data were missing for 347 patients (31.6%) regarding the time since the initial diagnosis and for 161 patients (14.6%) regarding the time since symptom onset.
† Data regarding the median length of hospital stay were missing for 136 patients (12.4%).

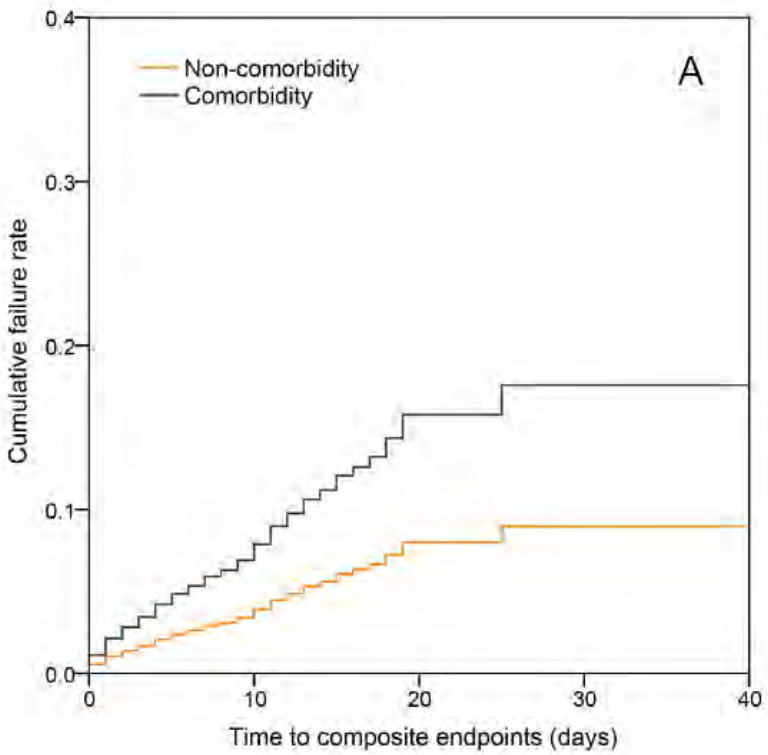
EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis



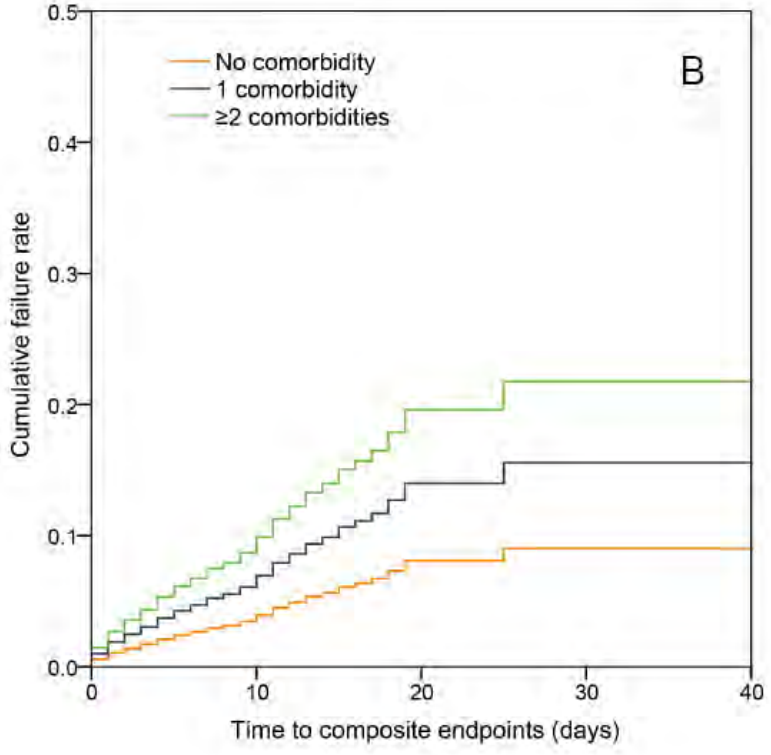


Figure 1. Comparison of the time-dependent risk of reaching to the composite endpoints

Features	Hazard Ratio (95%CI)		P Value
Type of comorbidities			
COPD	2.681	(1.424-5.048)	0.002
Diabetes	1.586	(1.028-2.449)	0.037
Hypertension	1.575	(1.069-2.322)	0.022
Malignant tumor	3.501	(1.604-7.643)	0.002
Number of comorbidities			
1	1.789	(1.155-2.772)	0.009
2 or more	2.592	(1.611-4.171)	<0.001

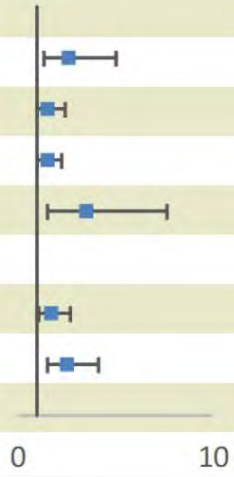


Figure 2. Predictors of the composite endpoints in the proportional hazards model
Shown in the figure are the hazards ratio (HR) and the 95% confidence interval (95%CI) for the risk factors associated with the composite endpoints (admission to intensive care unit, invasive ventilation, or death). The comorbidities were classified according to the organ systems as well as the number.

- J Crohns Colitis. 2020 Mar 26. pii: jjaa061. doi: 10.1093/ecco-jcc/jjaa061. [Epub ahead of print]
- **Are patients with inflammatory bowel disease at increased risk for Covid-19 infection?**
- Monteleone G[1], Ardizzone S[2].

- Crohn's disease (CD)] and ulcerative colitis (UC), the main inflammatory bowel diseases (IBD) in human beings, are chronic, immune-inflammatory diseases, whose pathogenesis implicates a complex interaction between environmental factors and genetic susceptibility. These disabling conditions affect millions of individuals and, together with the drugs used to treat them, can put patients at risk of developing complications and other conditions. This is particularly relevant nowadays, as coronavirus disease (Covid-19) has rapidly spread from China to countries where IBD are more prevalent and there is convincing evidence that Covid-19-mediated morbidity and mortality are higher in subjects with comorbidities. The primary objectives of this Viewpoint are to provide a focused overview of the factors and mechanisms by which the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects the cells and to illustrate the link between such determinants and the intestinal inflammation. We also provide clues about the reasons why the overall IBD population might have no increased risk to be infected with SARS-CoV-2 and highlight the potential of cytokine blockers, used to treat IBD patients, to prevent Covid-driven pneumonia.

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Special Report

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A Case of Novel Coronavirus Disease 19 in a Chronic Hemodialysis Patient Presenting with Gastroenteritis and Developing Severe Pulmonary Disease

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Table 1. Timeline of ESRD patient with COVID-19 presentation

Date	Location	Facility	Symptoms
1–13 Jan 2020	South Korea	N/A	None
24 Feb 2020	Southern California	Dialysis center	None
4 Mar 2020	Southern California	Dialysis center	None
7 Mar 2020 a.m.	Southern California	ER 1	Nausea, vomiting, subjective fever
7 Mar 2020 p.m.	Southern California	ER 2*	Nausea, vomiting, fever
9 Mar 2020 a.m.	Southern California	Dialysis center	Fever, diarrhea/loose stools
9 Mar 2020 a.m.	Southern California	Outpatient clinic	Cough, fever
10 Mar 2020 a.m.	Utah	ER 3	Cough, congestion, nausea, fever
11 Mar 2020 a.m.	Utah	Dialysis center	Cough, congestion, nausea, fever
12 Mar 2020 a.m.	Southern California	ER 2* inpatient	Cough, congestion, SOB, fever, nausea, myalgias
13 Mar 2020 p.m.	Southern California	Inpatient	Hypoxic respiratory failure Atrial fibrillation with RVR
14 Mar 2020 a.m.	Southern California	Intensive care unit	ARDS; shock

* Patients visited "ER 2" twice including upon hospital admission.
ESRD, end-stage renal disease; COVID-19, novel coronavirus disease 2019; N/A, not applicable.

OPEN ACCESS

ORIGINAL RESEARCH

Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms

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OBJECTIVE:

The SARS-CoV-2-infected disease (COVID-19) outbreak is a major threat to human beings. Previous studies mainly focused on Wuhan and typical symptoms. We analysed 74 confirmed COVID-19 cases with GI symptoms in the Zhejiang province to determine epidemiological, clinical and virological characteristics.

DESIGN:

COVID-19 hospital patients were admitted in the Zhejiang province from 17 January 2020 to 8 February 2020. Epidemiological, demographic, clinical, laboratory, management and outcome data of patients with GI symptoms were analysed using multivariate analysis for risk of severe/critical type. Bioinformatics were used to analyse features of SARS-CoV-2 from Zhejiang province.

RESULTS:

Among enrolled 651 patients, 74 (11.4%) presented with at least one GI symptom (nausea, vomiting or diarrhoea), average age of 46.14 years, 4-day incubation period and 10.8% had pre-existing liver disease. Of patients with COVID-19 with GI symptoms, 17 (22.97%) and 23 (31.08%) had severe/critical types and family clustering, respectively, significantly higher than those without GI symptoms, 47 (8.14%) and 118 (20.45%). Of patients with COVID-19 with GI symptoms, 29 (39.19%), 23 (31.08%), 8 (10.81%) and 16 (21.62%) had significantly higher rates of fever >38.5°C, fatigue, shortness of breath and headache, respectively. Low-dose glucocorticoids and antibiotics were administered to 14.86% and 41.89% of patients, respectively. Sputum production and increased lactate dehydrogenase/glucose levels were risk factors for severe/critical type. Bioinformatics showed sequence mutation of SARS-CoV-2 with m^6A methylation and changed binding capacity with ACE2.

CONCLUSION:

We report COVID-19 cases with GI symptoms with novel features outside Wuhan. Attention to patients with COVID-19 with non-classic symptoms should increase to protect health providers.

Table 1 Demographic and epidemiological characteristics of patients with COVID-19 with and without GI symptoms

Characteristic	GI symptoms (n=74)	No GI symptoms (n=577)	P value
Age	46.14±14.19	45.09±14.45	0.559
Sex (male)	37/74 (50.0%)	294/577 (50.95%)	0.902
Current smoker	3/74 (4.23%)	38/577 (6.59%)	0.610
Pre-existing conditions			
Any	25/74 (33.78%)	153/577 (26.52%)	0.212
Hypertension	12/74 (16.22%)	88/577 (15.25%)	0.864
Diabetes	7/74 (9.46%)	41/577 (7.11%)	0.477
Chronic liver disease	8/74 (10.81%)	17/577 (2.95%)	0.004
Cancer	0/74 (0%)	6/577 (1.04%)	1.00
Chronic renal disease	0/74 (0%)	6/577 (1.04%)	1.00
Heart disease	1/74 (1.35%)	4/577 (0.69%)	0.454
Pregnancy	0/74 (0%)	3/577 (0.52%)	1.00
COPD	0/74 (0%)	1/577 (0.17%)	1.00
Immunosuppression	0/74 (0%)	1/577 (0.17%)	1.00
Exposure history			
From Wuhan	38/74 (51.35%)	347/577 (60.14%)	0.167
Contact with patients	32/74 (43.24%)	230/577 (39.86%)	0.615
Family cluster	23/74 (31.08%)	118/577 (20.45%)	0.037
Clinical type on admission			
Severe/Critical type (%)	17/74 (22.97%)	47/577 (8.14%)	<0.001

Data are presented as medians (IQR), n (%) and n/N (%).
COPD, chronic obstructive pulmonary disease

Table 2 Clinical characteristics and selected laboratory abnormalities of patients with COVID-19 with and without GI symptoms

Characteristic	GI symptoms (n=74)	No GI symptoms (n=577)	P value
Fever (Y)			
Any	63/74 (85.14%)	482/577 (83.54%)	0.867
>38.5°C	29/74 (39.19%)	101/577 (17.50%)	<0.001
Cough (Y)	53/74 (71.62%)	382/577 (66.20%)	0.431
Sputum production (Y)	29/74 (39.19%)	198/577 (34.32%)	0.438
Haemoptysis (Y)	3/74 (4.05%)	8/577 (1.39%)	0.119
Sore throat (Y)	6/74 (8.11%)	93/577 (16.12%)	0.085
Nasal obstruction (Y)	2/74 (2.70%)	35/577 (6.07%)	0.419
Muscle ache (Y)	10/74 (13.51%)	61/577 (10.57%)	0.430
Fatigue (Y)	23/74 (31.08%)	96/577 (16.64%)	0.004
Shortness of breath (Y)	8/74 (10.81%)	19/577 (3.30%)	0.007
Headache (Y)	16/74 (21.62%)	51/577 (8.84%)	0.002

Table 3 Complications and treatment in patients with COVID-19 with and without GI symptoms

Variable	GI symptoms (n=74)	No GI symptoms (n=577)	P value
Complications			
Acute respiratory distress syndrome	5/74 (6.76%)	12/577 (2.08%)	0.034
Shock	1/74 (1.35%)	1/577 (0.17%)	0.215
Liver injury	13/74 (17.57%)	51/577 (8.84%)	0.035
Treatment			
Anticoronavirus treatment	66/74 (89.19%)	480/577 (83.19%)	0.239
Timing from onset of illness to antiviral therapy	5 (3–6)	4 (2–6)	0.062
Mechanical ventilation	5/74 (6.76%)	12/577 (2.08%)	0.034
CRRT	0	0	
ECMO	0	0	
Glucocorticoids	11/74 (14.86%)	63/577 (10.92%)	0.443
Antibiotic treatment	31/74 (41.89%)	246/577 (42.63%)	0.903
Admission to intensive care unit	5/74 (6.76%)	12/577 (2.08%)	0.034

Data are presented as medians (IQR), n (%) and n/N (%).
CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation .

Table 4 Multivariate analysis of risk factors for the severe/critical patients with COVID-19 with GI symptoms

Risk factor	OR (95% CI)	P value
Sputum production	11.40 (1.89 to 68.73)	0.008
From infected area	0.09 (0.02 to 0.54)	0.008
Increased LDH	24.77 (4.60 to 133.33)	0.000
Increased glucose	2.42 (1.43 to 4.10)	0.001

LDH, lactate dehydrogenase.

C

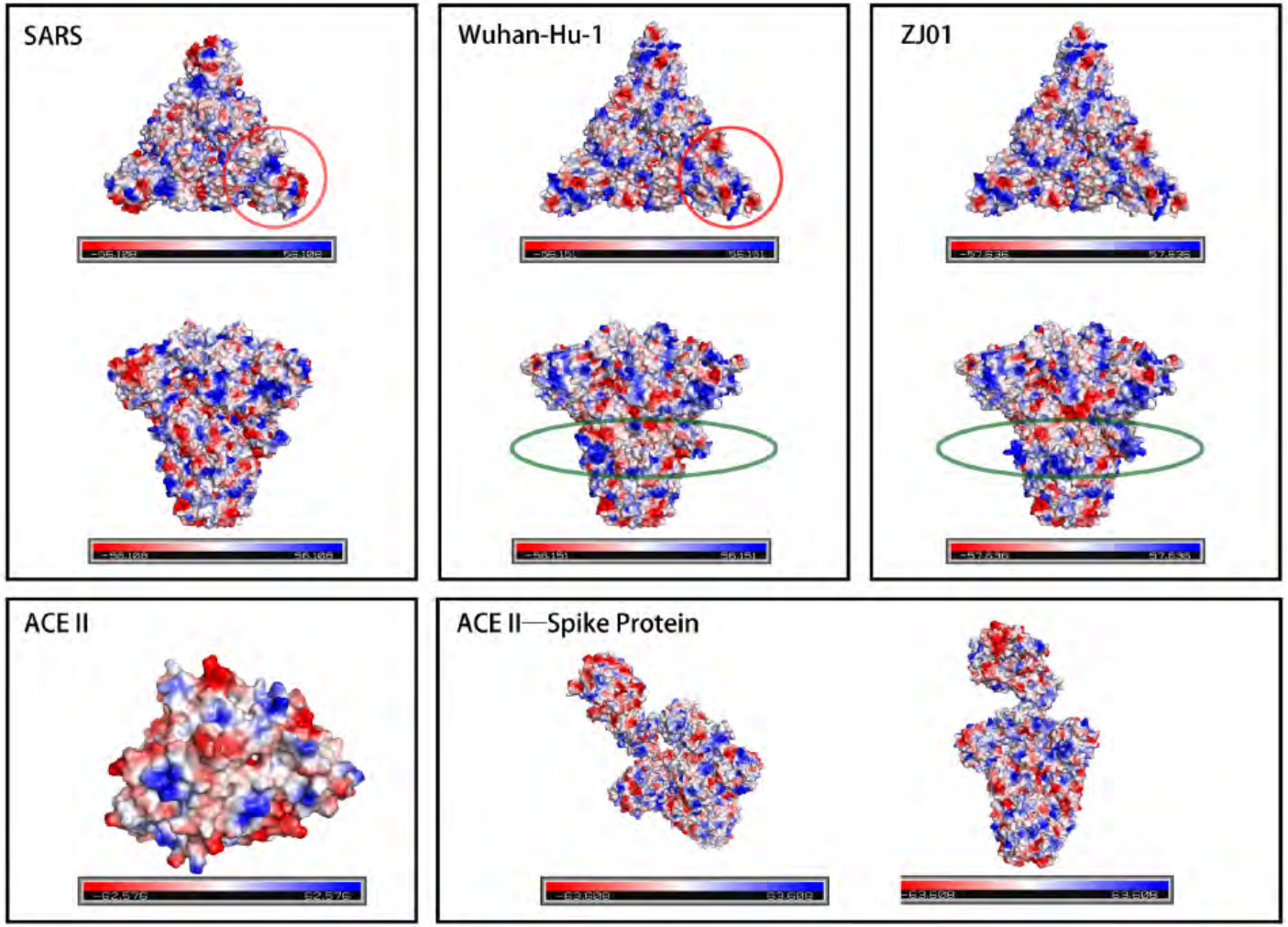


Figure 1 Sequence and protein model structure analysis of three virus strains. (A) The potential methylation sites of S protein gene sequences of SARS, Wuhan-Hu-1 and ZJ01 were analysed. The red arrows represent the positions of high-confidence methylation sites in the S protein gene sequences. Blue arrows represent conserved methylation sites in the three strains. (B) The amino acid sequences of Wuhan-Hu-1 and ZJ01 S protein are aligned. The black box marks the mutation sites. (C) The red circle marks the difference of electrostatic power distribution in receptor binding domain (RBD) region between SARS and Wuhan-Hu-1. The green ellipse indicates the change in the electrostatic distribution of the S proteins due to the mutation of the ZJ01 S protein.

Significance of this study

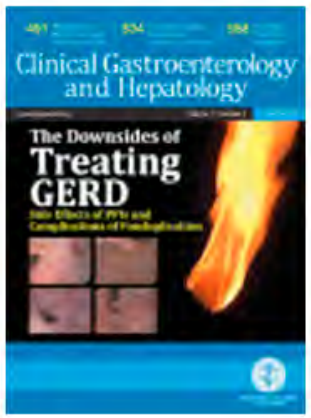
What are the new findings?

- In this study, we report for the first time on the largest cohort of patients with COVID-19 outside Wuhan with GI symptoms.
- We found that the percentage of patients with COVID-19 with GI symptoms was also higher than that in Wuhan.
- We uncovered novel characteristics of COVID-19, including increased family clustering and liver injury, severe/critical type tendency and higher rate of body temperature >38.5°C.
- The findings of novel m^6 A methylation loci in the S protein of SARS-CoV-2 may provide underlining mechanisms for its change of virulence and transmission capacity during the spread.

How might it impact on clinical practice in the foreseeable future?

- Our results indicated that global authorities should pay more attention to patients with COVID-19 with GI symptoms and its novel features, as those presentations may change the treatment strategy.
- GI doctors and other health professionals treating suspected patients with COVID-19 without respiratory symptoms and fever should take precautions.

Journal Pre-proof



Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19)

Shihua Luo, Xiaochun Zhang, Haibo Xu

PII: S1542-3565(20)30401-8
DOI: https://doi.org/10.1016/j.cgh.2020.03.043
Reference: YJCGH 57089

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 18 March 2020

- Of 1141 confirmed COVID-19 cases, 183 (16%) presented with gastrointestinal symptoms only,
- At the onset of their illness, 175 of 183 (96%) of patients had lung lesions on chest CT , which were unilateral in 61% of cases

Journal Pre-proof

Evidence for gastrointestinal infection of SARS-CoV-2

Fei Xiao, Meiwen Tang, Xiaobin Zheng, Ye Liu, Xiaofeng Li, Hong Shan

PII: S0016-5085(20)30282-1
DOI: https://doi.org/10.1053/j.gastro.2020.02.055
Reference: YGAST 63254

To appear in: *Gastroenterology*
Accepted Date: 27 February 2020

Please cite this article as: Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H, Evidence for gastrointestinal infection of SARS-CoV-2, *Gastroenterology* (2020), doi: https://doi.org/10.1053/j.gastro.2020.02.055.

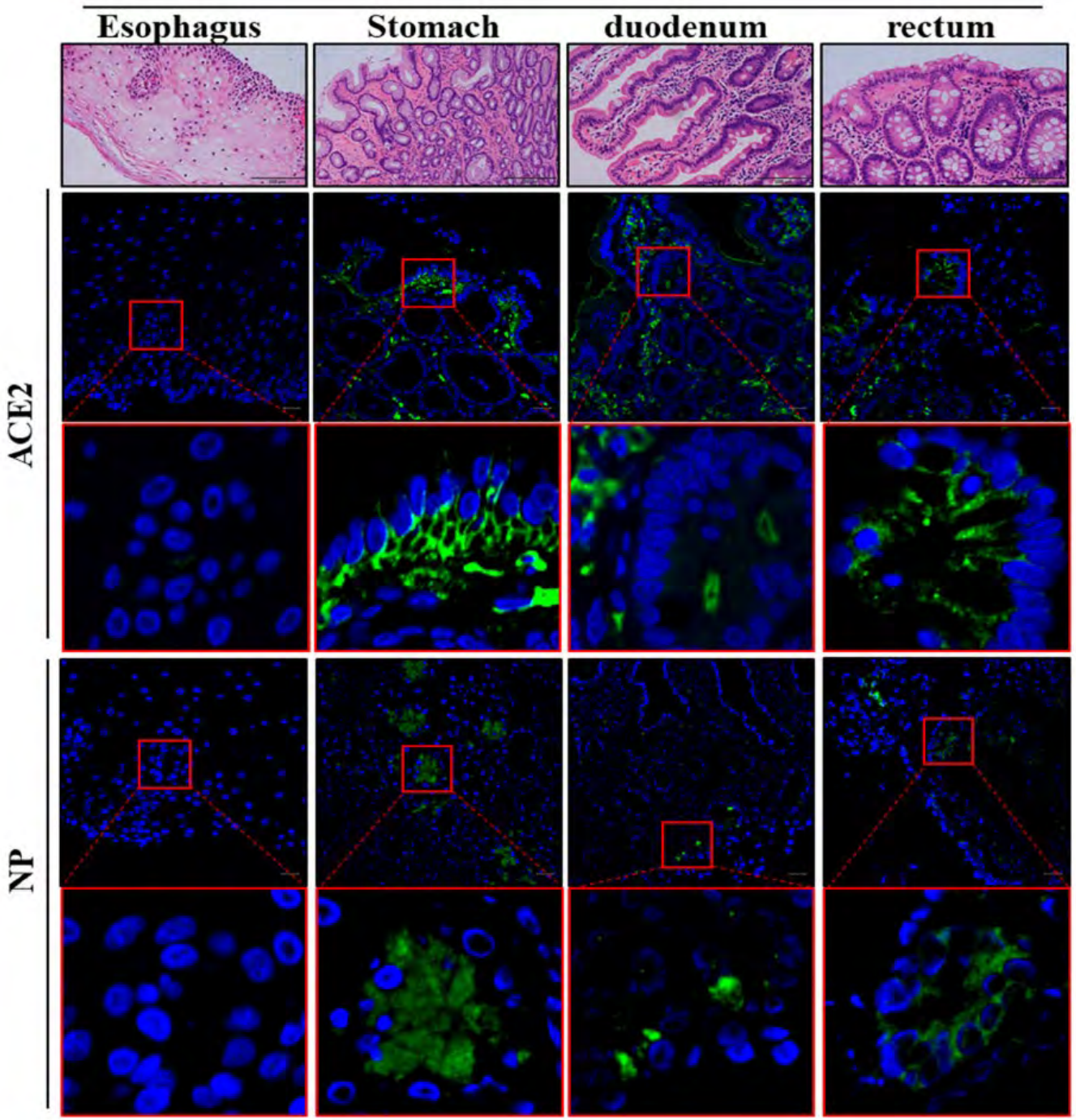


Figure 1. Images of Histological and Immunofluorescent Staining of Gastrointestinal Tissues.
Shown are images of histological and immunofluorescent staining of esophagus,
stomach, duodenum and rectum. The scale bar in the histological image represents
100 microns. The scale bar in the immunofluorescent image represents 20 microns.

intracellular staining of viral nucleocapsid protein in gastric, duodenal and rectal epithelia demonstrate that SARS-CoV-2 infects these gastrointestinal glandular epithelial cells.

- Recently, we and others have isolated infectious SARS-CoV-2 from stool (Manuscript under revision),
- We strongly recommend that rRT-PCR testing for SARS-CoV-2 from feces should be performed routinely in SARS-CoV-2 patients, and Transmission-Based Precautions for hospitalized SARS-CoV-2 patients should continue if feces tests positive by rRT-PCR testing.

Received: 19 March 2020 | First decision: 22 March 2020 | Accepted: 26 March 2020

DOI: 10.1111/apt.15731

APT Alimentary Pharmacology & Therapeutics WILEY

Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission

Yuan Tian | Long Rong | Weidong Nian | Yan He

BACKGROUND:

There is little published evidence on the gastrointestinal features of COVID-19.

AIMS:

To report on the gastrointestinal manifestations and pathological findings of patients with COVID-19 and discuss the possibility of faecal transmission METHODS: We have reviewed gastrointestinal features of, and faecal test results in, COVID-19 from case reports and retrospective clinical studies relating to the digestive system published since the outbreak.

RESULTS:

With an incidence of 3%(1/41)-79% (159/201), gastrointestinal symptoms of COVID-19 included anorexia 39.9%(55/138)-50.2%(101/201), diarrhoea 2%(2/99)-49.5%(146/295), vomiting 3.6%(5/138)-66.7%(4/6), nausea 1%(1/99)-29.4%(59/201), abdominal pain 2.2%(3/138)-6.0%(12/201), and gastrointestinal bleeding 4%(2/52)-13.7%(10/73). Diarrhoea was the most common gastrointestinal symptom in children and adults, with a mean duration of 4.1 ± 2.5 days, and was observed before and after diagnosis. Vomiting was more prominent in children. 3.6%(5/138)-15.9%(32/201) of adult patients presented vomiting and 6.5%(2/31)-66.7%(4/6) of children. Adult and children patients can present with digestive symptoms in the absence of respiratory symptoms. The incidence of digestive manifestations was higher in the later than in the early stage of the epidemic, but no differences in digestive symptoms among different regions were found. Among the group of patients with a higher proportion of severe cases, the proportion of gastrointestinal symptoms in severe patients was higher than that in non-severe patients (anorexia 66.7% vs 30.4%; abdominal pain 8.3% vs 0%); while in the group of patients with a lower severe rate, the proportion of gastrointestinal symptoms were similar in severe and non-severe cases (nausea and vomiting 6.9% vs 4.6%; diarrhoea 5.8% vs 3.5%). ACE2 receptor and virus nucleocapsid protein was detected in gastrointestinal epithelial cells, and infectious virus particles were isolated from faeces. Faecal PCR testing was as accurate as respiratory specimen PCR detection. About 36%(5/14)-53%(39/73) faecal PCR becomes positive, 2-5 days later than sputum PCR positive. Faecal excretion persisted after sputum excretion in 23%(17/73)-82%(54/66) patients for 1-11 days.

CONCLUSIONS:

Gastrointestinal symptoms are common in patients with COVID-19, and had an increased prevalence in the later stage of the recent epidemic. SARS-CoV-2 enters gastrointestinal epithelial cells, and the faeces of COVID-19 patients were infectious. PDF : + prudent

TABLE 1 Gastrointestinal manifestations in patients with SARS-CoV-2 infection

	Date	Region	Total patients	Age of affected patients average ± SD/ median (range)	Duration of diarrhoea	Disease severity of patients with GI symptoms		Gastrointestinal symptoms		Patients with GI symptoms without respiratory symptoms	Notes
Huang et al[5]	16 December-2 January	Wuhan	41	49 (IQR 41-58) y	NA	Non-ICU		Diarrhoea	1 (3%)	NA	Suggest to test faecal and urine samples to exclude a potential alternative route of transmission
Yang et al[6]	Late December-26 January	Wuhan	52	59.7 ± 13.3 y	NA	All critically ill patients		Gastrointestinal haemorrhage	2 (4%)	NA	–
								Vomiting	2 (4%)		
Liu et al[7]	1 January-15 January	Wuhan	6 children	3 (1-7) y	NA	1 critical case 5 mild-moderate cases		Vomiting	4 (66.7%)	NA	–
Chen et al[8]	1 January-20 January	Wuhan	99	55.5 ± 13.1 y (21-82)	NA	NA		Diarrhoea	2(2%)	NA	–
								Nausea and vomiting	1(1%)		
Wang et al[9]	1 January-28 January	Wuhan	138	56 (22-92) y	NA	36 ICU	102 non-ICU	Anorexia	55 (39.9%)	14 (10.1%) patients initially presented with diarrhoea and nausea before typical symptoms of fever and dyspnoea One patient presented with abdominal symptoms and was admitted to the surgical department, and infected more than 10 health care workers in this department and 4 hospitalised patients in the same ward	ICU patients were more likely to present anorexia and abdominal pain
						Anorexia 24(66.7%)	Anorexia 31(30.4%)				
						Diarrhoea 6 (16.7%)	Diarrhoea 8 (7.8%)	Diarrhoea	14 (10.1%)		
						Nausea 4 (11.1%)	Nausea 10 (9.8%)	Nausea	14 (10.1%)		
						Vomiting 3 (8.3%)	Vomiting 2 (2.0%)	Vomiting	5 (3.6%)		
						Abdominal pain 3 (8.3%)	Abdominal pain 0 (0%)	Abdominal pain	3 (2.2%)		
Ping et al[10]	17 January-24 January	Wuhan	9	35.8 (28-45) y	NA	No critical cases		Anorexia	6	All nine patients showed only digestive symptoms with no fever onset, and four patients never had respiratory symptoms or fever	The time between initial nonspecific and specific symptoms was 2-5 d Digestive symptoms occurred 1-3 days (median 2.1 d) before the patients' visit
								Nausea	1		
								Vomiting	1		
								Diarrhoea	1		
Wei et al[11]	23 January-8 February	Wuhan	20 children	2 years and 1.5 mo (1 d-14 y 7 mo)	NA	All the patients had good prognosis		Diarrhoea	3 (15%)	NA	–
								Vomiting	2 (10%)		

TABLE 1 (Continued)

	Date	Region	Total patients	Age of affected patients average ± SD/ median (range)	Duration of diarrhoea	Disease severity of patients with GI symptoms		Gastrointestinal symptoms		Patients with GI symptoms without respiratory symptoms	Notes
Fang et al[4]	27 January-14 February	Wuhan	305	57 (18-95) y	4.1 ± 2.5 d (1-14)	46 critical cases	259 noncritical cases	Diarrhoea	146/295 (49.5%)	NA	Diarrhoea appeared 1-8 d after onset, with a median time of 3.3 d The frequency of diarrhoea was up to nine times per day, median of (3.3 ± 1.6) times per day, 34.3% were watery stools 55.2% (58/105) of patients had diarrhoea after drugs estimating 22.2% of the patients had nondrug-related diarrhoea
						Digestive symptom 17/20 (85.0%)	Digestive symptom 142/181 (78.5%)	Loss of appetite	101/201 (50.2%)		
								Nausea	59/201 (29.4%)		
						Diarrhoea 17/38 (44.7%)	Diarrhoea 129/257 (50.2%)	Vomiting	32/201 (15.9%)		
								Abdominal pain	12/201 (6.0%)		
Chang et al[12]	16 January-29 January	Beijing	13	34 (IQR 34 -48) y	NA	NA		Diarrhoea	1 (7.7%)	NA	–
Guan et al[13]	11 December-29 January	30 provinces	1099	47 (IQR 35 -58) y	NA	173 Severe	926 Nonsevere	Nausea or vomiting	55 (5.0%)	NA	–
						Nausea and vomiting 12 (6.9%)	Nausea and vomiting 43 (4.6%)				
						Diarrhoea 10 (5.8%)	Diarrhoea 32 (3.5%)	Diarrhoea	42(3.8%)		
Xu et al[14]	10 January-26 January	Zhejiang province	62	41(IQR 32-52) y	>10 d	1 critical case		Diarrhoea	3 (5%)	NA	Three patients showed diarrhoea at onset
Song et al[15]	20 January-27 January	Shanghai	51	49 ± 16 y (16-76)	NA	NA		Diarrhoea	5 (10%)	NA	–
								Nausea and vomiting	3 (6%)		
Hu et al[16]	28 January-9 February	Nanjing	24 asymptomatic onset cases	32.5 (5-59) y 5 cases <15 y	NA	All cases were mild-moderate		Diarrhoea	2 (8.3%)	NA	Diarrhoea was considered as a reaction of drugs

TABLE 1 (Continued)

	Date	Region	Total patients	Age of affected patients average ± SD/ median (range)	Duration of diarrhoea	Disease severity of patients with GI symptoms	Gastrointestinal symptoms		Patients with GI symptoms without respiratory symptoms	Notes
Wang et al[17]	25 January-21 February	Six provinces in North	31 children	7 y 1 mo, (6 mo-17 y)	NA	All cases were asymptomatic or mild-moderate	Diarrhoea Vomiting	3 (9.6%) 2 (6.5%)	Three cases had diarrhoea and one case had vomiting as the first symptom without fever or cough	Three cases with diarrhoea were yellow thin faeces, two to six times per day, and no symptoms of dehydration and electrolyte disturbance
Xiao et al[18]	1 February-14 February	Guangzhou	73	10 mo-78 y	NA	NA	Diarrhoea Gastrointestinal bleeding	26 (35.6%) 10(13.7%)	NA	17/26 (65.4%) patients with diarrhoea were stool PCR positive 4/10 (40%) patients with gastrointestinal bleeding were stool PCR positive

TABLE 2 Faecal RT-PCR test in patients with SARS-CoV-2 infection

	Total patients	Patients of positive faecal PCR test	Negative in respiratory PCR test but positive in faecal test	Time Differences between negative PCR test in stool and negative PCR test in respiratory specimens (d)
Ling et al[25]	66 convalescent patients	NA	54 (81.8%)	+2(+1 to +11)*
Zhang et al[26]	14	5 (35.7%)	NA	NA
Xiao et al[9]	73	39 (53.4%)	17 (23.3%)	NA
Yang et al[24]	7	NA	3 (42.9%)	+3, +6, +7

Abbreviation: PCR, polymerase chain reaction.

*Date of negative faecal PCR test minus date of negative respiratory specimens PCR test, median (range).

Traitements

- Life Sci. 2020 Mar 25:117592. doi: 10.1016/j.lfs.2020.117592. [Epub ahead of print]
- **Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study.**
- Elfiky AA[1].

Abstract

AIMS:

A new human coronavirus (HCoV), which has been designated SARS-CoV-2, began spreading in December 2019 in Wuhan City, China causing pneumonia called COVID-19. The spread of SARS-CoV-2 has been faster than any other coronaviruses that have succeeded in crossing the animal-human barrier. There is concern that this new virus will spread around the world as did the previous two HCoVs-Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)-each of which caused approximately 800 deaths in the years 2002 and 2012, respectively. Thus far, 11,268 deaths have been reported from the 258,842 confirmed infections in 168 countries.

MAIN METHODS:

In this study, the RNA-dependent RNA polymerase (RdRp) of the newly emerged coronavirus is modeled, validated, and then targeted using different anti-polymerase drugs currently on the market that have been approved for use against various viruses.

KEY FINDINGS:

The results suggest the effectiveness of Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir as potent drugs against SARS-CoV-2 since they tightly bind to its RdRp. In addition, the results suggest guanosine derivative (IDX-184), Setrobuvir, and YAK as top seeds for antiviral treatments with high potential to fight the SARS-CoV-2 strain specifically.

SIGNIFICANCE:

The availability of FDA-approved anti-RdRp drugs can help treat patients and reduce the danger of the mysterious new viral infection COVID-19. The drugs mentioned above can tightly bind to the RdRp of the SARS-CoV-2 strain and thus may be used to treat the disease. No toxicity measurements are required for these drugs since they were previously tested prior to their approval by the FDA.

- J Med Virol. 2020 Mar 27. doi: 10.1002/jmv.25785. [Epub ahead of print]
- **Organ-protective Effect of Angiotensin-converting Enzyme 2 and its Effect on the Prognosis of COVID-19.**
- Cheng H[1], Wang Y[1], Wang GQ[1,2,3].

- This article reviews the correlation between ACE2 and severe risk factors for COVID-19 and the possible mechanisms. Angiotensin-converting enzyme 2 (ACE2) is a crucial component of the renin-angiotensin system (RAS). The classical RAS ACE-Ang II-AT1R regulatory axis and the ACE2-Ang1-7-MasR counter-regulatory axis play an essential role in maintaining homeostasis in humans. ACE2 is widely distributed in the heart, kidneys, lungs, and testes. ACE2 antagonizes the activation of the classical RAS system and protects against organ damage, protecting against hypertension, diabetes, and cardiovascular disease. Similar to SARS-CoV, SARS-CoV-2 also uses the ACE2 receptor to invade human alveolar epithelial cells. ARDS is a clinical high-mortality disease, and ACE2 has a protective effect on this type of acute lung injury. Current research shows that the poor prognosis of patients with COVID-19 is related to factors such as sex (male), age (higher than 60 years), underlying diseases (hypertension, diabetes, and cardiovascular disease), secondary ARDS, and other relevant factors. Because of these protective effects of ACE2 on chronic underlying diseases and ARDS, the development of spike protein-based vaccine and drugs enhancing ACE2 activity may become one of the most promising approaches for the treatment of COVID-19 in the future.

Partie III

- Biblio au 7/4/20
- Pubmed : n= 2780
- **COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv : n = 982**

Nouveautés

- Atteinte pancréatique
- Données sur IBD (détails non montrés)
- Meta-analyses : atteinte hépatique et digestive dont ARN génomique
- Diffusion du virus dont eaux usées
- RECOs

HGE

Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single center in Wuhan city, China

Yafei Zhang[1,2], Liang Zheng[3], Lan Liu[1,2], Mengya Zhao[4], Jun Xiao[1,2], and Qiu Zhao[1,2,*]

Liver International

Abstract

BACKGROUND:

The SARS-CoV-2 pandemic is an ongoing global health emergency. The aim of our study was to investigate the changes of liver function and its clinical significance in COVID-19 patients.

METHOD:

This retrospective, single-center study was conducted on 115 confirmed cases of COVID-19 in Zhongnan hospital of Wuhan University from Jan 18 to Feb 22, 2020. Liver function and related indexes were analyzed to evaluate its relationship with disease progression in COVID-19 patients.

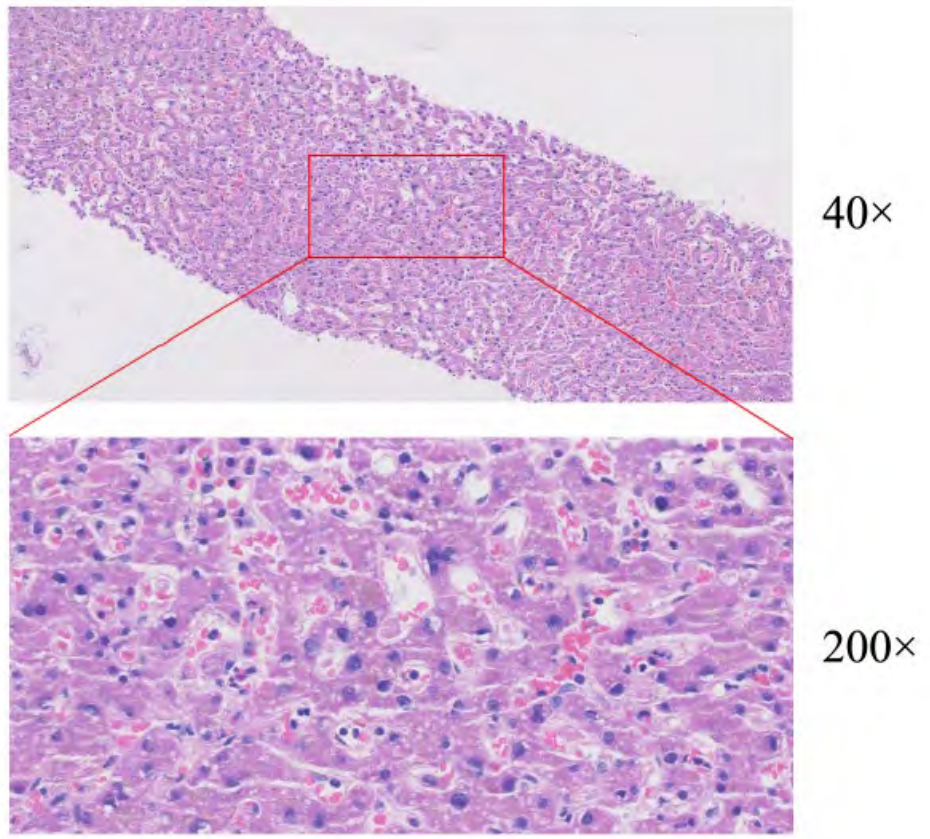
RESULTS:

Part of the COVID-19 patients presented with varying degrees of abnormality in liver function indexes. However, the levels of ALT, AST, TBIL, GGT and LDH in COVID-19 patients were not significantly different in compared with hospitalized community-acquired pneumonia patients, and the levels of albumin is even significantly higher. Levels of ALT, AST, TBIL, LDH and INR showed statistically significant elevation in severe COVID-19 cases compared with that in mild cases. However, the clinical significance of the elevation is unremarkable. Majority of severe COVID-19 patients showed significantly decreasing in albumin level and continuously decreasing in the progress of illness. Most of the liver function indexes in COVID-19 patients were correlated with CRP and NLR, the markers of inflammation. Logistic regression analysis further identified NLR as the independent risk factor for severe COVID-19, as well as age.

CONCLUSIONS:

Although abnormalities of liver function indexes are common in COVID-19 patients, the impairment of liver function is not a prominent feature of COVID-19, and also may not have serious clinical consequences.

- Histopathologic examination of the needle biopsy specimen were performed in the patient who died of COVID-19.
- The liver tissue displayed mild sinusoidal dilatation and minimal lymphocytic infiltration (Figure 1).
- No other specific damages were observed.



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Coronavirus disease 2019 (COVID-19) and prevalence of chronic liver disease: A meta-analysis

Alessandro Mantovani, MD[1], Giorgia Beatrice, MD[1], Andrea Dalbeni, MD[2]

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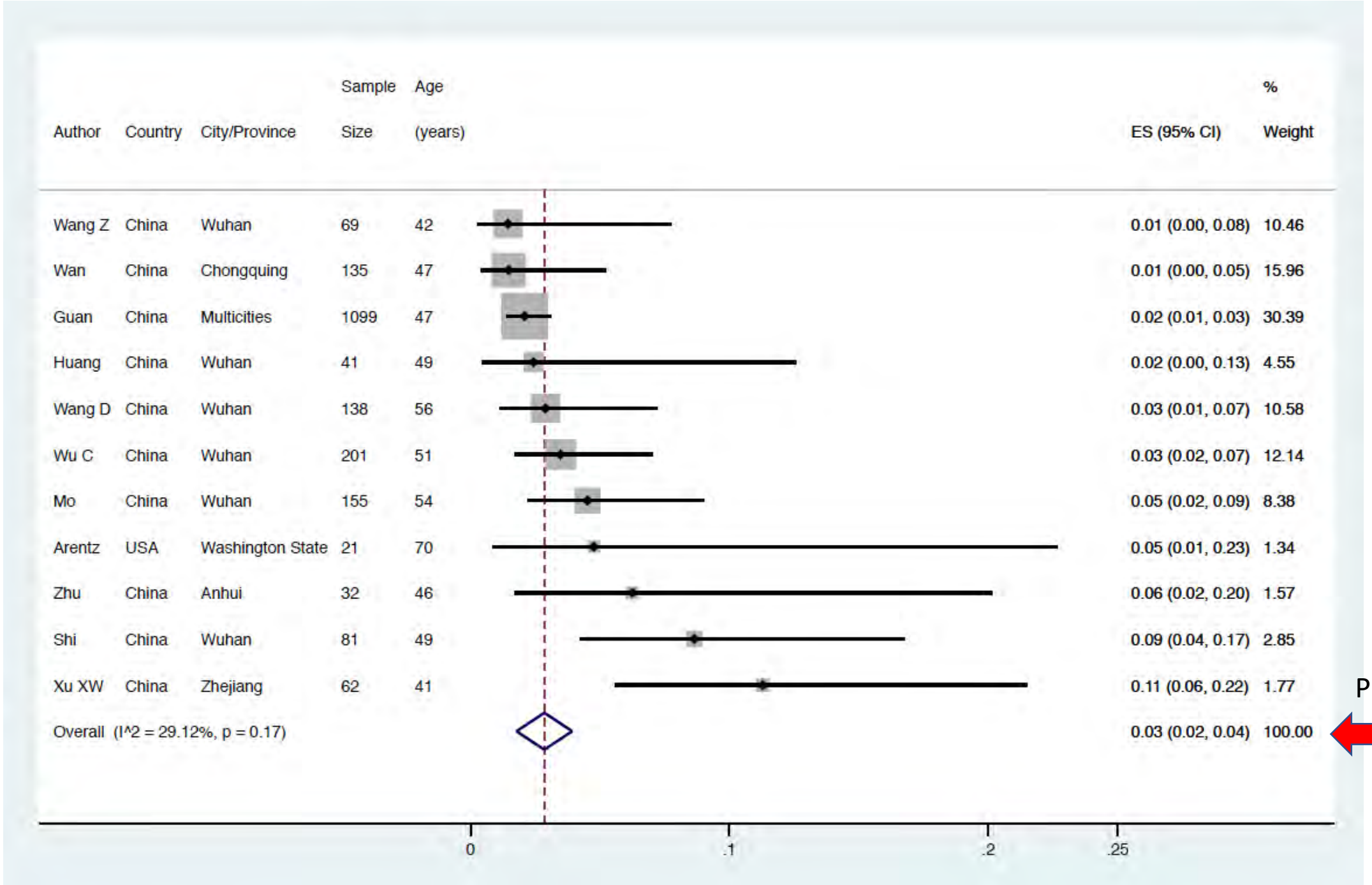
Liver International


Author
Country
City/Province
Sample Size
Age (years)
ES (95% CI)
% Weight
Wang Z China Wuhan 69 42 0.01 (0.00, 0.08) 10.46
Wan China Chongquing 135 47 0.01 (0.00, 0.05) 15.96
Guan China Multicities 1099 47 0.02 (0.01, 0.03) 30.39
Huang China Wuhan 41 49 0.02 (0.00, 0.13) 4.55
Wang D China Wuhan 138 56 0.03 (0.01, 0.07) 10.58
Wu C China Wuhan 201 51 0.03 (0.02, 0.07) 12.14
Mo China Wuhan 155 54 0.05 (0.02, 0.09) 8.38
Arentz USA Washington State 21 70 0.05 (0.01, 0.23) 1.34
Zhu China Anhui 32 46 0.06 (0.02, 0.20) 1.57
Shi China Wuhan 81 49 0.09 (0.04, 0.17) 2.85
Xu XW China Zhejiang 62 41 0.11 (0.06, 0.22) 1.77
Overall (I^2 = 29.12%, p = 0.17) 0.03 (0.02, 0.04) 100.00
0
.1
.2
.25
Prevalence

Journal Pre-proof

Pancreatic injury patterns in patients with COVID-19 pneumonia

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- Among the 52 patients with COVID-19 pneumonia, the incidence was 33% for heart injury (abnormal LDH or creatine kinase), 29% for liver injury (any abnormality in AST, ALT, GGT or ALP), 17% for pancreatic injury, 8% for renal injury (abnormal creatinine), and 2% for diarrhea.
- Cause inconnue

ORIGINAL RESEARCH

Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection

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To cite: Lin L, Jiang X, Zhang Z, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2020-321013

OBJECTIVE:

To study the GI symptoms in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients.

DESIGN:

We analysed epidemiological, demographic, clinical and laboratory data of 95 cases with SARS-CoV-2 caused coronavirus disease 2019. Real-time reverse transcriptase PCR was used to detect the presence of SARS-CoV-2 in faeces and GI tissues.

RESULTS:

Among the 95 patients, 58 cases exhibited GI symptoms of which 11 (11.6%) occurred on admission and 47 (49.5%) developed during hospitalisation. Diarrhoea (24.2%), anorexia (17.9%) and nausea (17.9%) were the main symptoms with five (5.3%), five (5.3%) and three (3.2%) cases occurred on the illness onset, respectively. A substantial proportion of patients developed diarrhoea during hospitalisation, potentially aggravated by various drugs including antibiotics. Faecal samples of 65 hospitalised patients were tested for the presence of SARS-CoV-2, including 42 with and 23 without GI symptoms, of which 22 (52.4%) and 9 (39.1%) were positive, respectively. Six patients with GI symptoms were subjected to endoscopy, revealing oesophageal bleeding with erosions and ulcers in one severe patient. SARS-CoV-2 RNA was detected in oesophagus, stomach, duodenum and rectum specimens for both two severe patients. In contrast, only duodenum was positive in one of the four non-severe patients.

CONCLUSIONS:

GI tract may be a potential transmission route and target organ of SARS-CoV-2.

What are the new findings?

- Infected patients may have no imaging features of COVID-19 pneumonia but only show GI symptoms.
- There was no significant difference in the clinical outcomes (remained in hospital, discharged or died) between patients with and without GI symptoms.
- The presence of SARS-CoV-2 RNA in faeces does not necessarily indicate more severe GI symptoms.
- SARS-CoV-2 RNA could be detected in the oesophagus, stomach, duodenum and rectum in severe patients.

Table 4 Viral RNA detection of GI system specimens in six patients underwent endoscopy examination or biopsy

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years	77	60	34	62	29	23
Sex	Male	Male	Female	Male	Male	Female
Disease severity	Severe	Severe	Non-severe	Non-severe	Non-severe	Non-severe
Viral detection						
Oesophagus	+	+	–	–	–	–
Stomach	+	+	–	–	–	–
Duodenum	+	+	+	–	–	–
Rectum	+	+	NA	NA	NA	NA
Syndromes of other organ systems	Acute respiratory distress syndrome, septic shock, multiple organ dysfunction syndrome (lung, heart and kidney).	Acute respiratory distress syndrome, respiratory failure and septic shock.	None	None	None	None
Clinical outcome	Hospitalisation	Hospitalisation	Hospitalisation	Hospitalisation	Discharged	Discharged

+, means positive; –, means negative; NA, not available.

- Chin Med J (Engl). 2020 Feb 28. doi: 10.1097/CM9.0000000000000774. [Epub ahead of print]
- **Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients.**
- Ling Y[1], Xu SB[2], Lin YX[3], Tian D[1], Zhu ZQ[1], Dai FH[1], Wu F[1], Song ZG[1], Huang W[1], Chen J[2], Hu BJ[4], Wang S[5], Mao EQ[6], Zhu L[7], Zhang WH[8], Lu HZ[1,2,8,9].
- **CONCLUSIONS:**
- In brief, as the clearance of viral RNA in patients' stools was delayed compared to that in oropharyngeal swabs, it is important to identify viral RNA in feces during convalescence. Because of the delayed clearance of viral RNA in the glucocorticoid treatment group, glucocorticoids are not recommended in the treatment of COVID-19, especially for mild disease. The duration of RNA detection may relate to host cell immunity.

Journal Pre-proof

Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis

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Abstract

BACKGROUND & AIMS:

Infection with SARS-CoV-2 causes COVID-19, which has been characterized by fever, respiratory, and gastrointestinal symptoms as well as shedding of virus RNA into feces. We performed a systematic review and meta-analysis of published gastrointestinal symptoms and detection of virus in stool, and also summarized data from a cohort of patients with COVID-19 in Hong Kong.

METHODS:

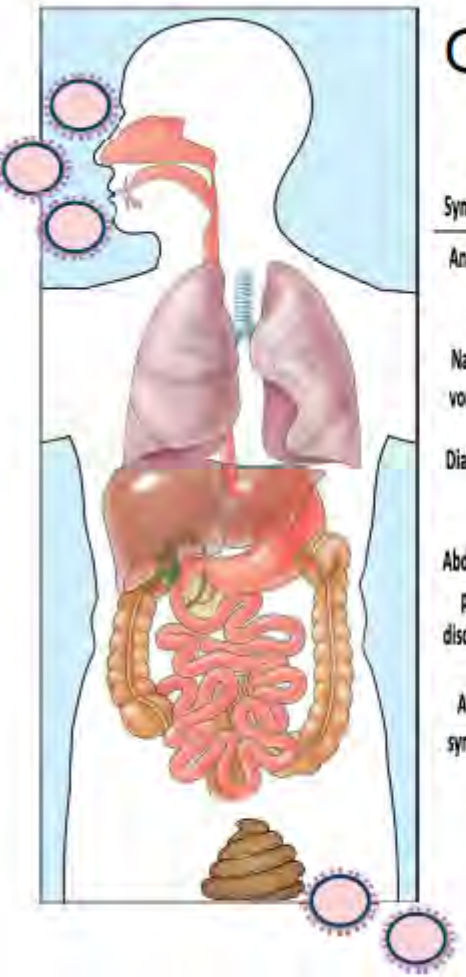
We collected data from the cohort of patients with COVID-19 in Hong Kong (n=59; diagnosis from February 2 through Feb 29, 2020), and searched PubMed, Embase, Cochrane and three Chinese databases through March 11, 2020 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We analyzed pooled data on the prevalence of overall and individual gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, and abdominal pain or discomfort) using a random effects model.

RESULTS:

Among the 59 patients with COVID-19 in Hong Kong, 15 patients (25.4%) had gastrointestinal symptoms and 9 patients (15.3%) had stool that tested positive for virus RNA. Stool viral RNA was detected in 38.5% and 8.7% among those with and without diarrhea, respectively (P=.02). The median fecal viral load was 5.1 $\log_{10}$cpm in patients with diarrhea vs 3.9 $\log_{10}$cpm in patients without diarrhea (P=.06). In a meta-analysis of 60 studies, comprising 4243 patients, the pooled prevalence of all gastrointestinal symptoms was 17.6% (95% CI, 12.3%-24.5%); 11.8% of patients with non-severe COVID-19 had gastrointestinal symptoms (95% CI, 4.1%-29.1%) and 17.1% of patients with severe COVID-19 had gastrointestinal symptoms (95% CI, 6.9%-36.7%). In the meta-analysis, the pooled prevalence of stool samples that were positive for virus RNA was 48.1% (95% CI, 38.3%-57.9%); of these samples, 70.3% of those collected after loss of virus from respiratory specimens tested positive for the virus (95% CI, 49.6%-85.1%).

CONCLUSIONS:

In an analysis of data from the Hong Kong cohort of patients with COVID-19 and a meta-analysis of findings from publications, we found that 17.6% of patients with COVID-19 had gastrointestinal symptoms. Virus RNA was detected in stool samples from 48.1% patients-even in stool collected after respiratory samples tested negative. Healthcare workers should therefore exercise caution in collecting fecal samples or performing endoscopic procedures in patients with COVID-19-even during patient recovery.



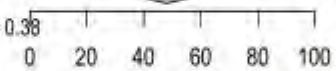
Gastrointestinal Symptoms & stool viral RNA positivity rate in COVID-19

GI Symptoms	Events	Total	Prevalence (%)	95% CI
Anorexia	216	830	26.8	16.2–40.8
Nausea/ vomiting	210	2664	10.2	6.6–15.3
Diarrhoea	326	3536	12.5	9.6–16.0
Abdominal pain/ discomfort	52	751	9.2	5.7–14.5
Any GI symptom	537	4243	17.6	12.3–24.5

Stool viral RNA positivity rate

Study	Events	Total	Prevalence (%)	95%-CI	Weight (fixed)	Weight (random)
Xiao F	39	73	53.42	[41.37; 65.20]	55.8%	45.2%
Zhang W	4	15	26.67	[7.79; 55.10]	9.0%	10.9%
Zhang J	5	14	35.71	[12.76; 64.86]	9.9%	11.9%
Wang W	5	13	38.46	[13.86; 68.42]	9.4%	11.4%
Young BE	4	8	50.00	[15.70; 84.30]	6.1%	7.7%
Kim JY	0	2	0.00	[0.00; 84.19]	1.3%	1.7%
Yang Z	3	3	100.00	[29.24; 100.00]	1.3%	1.8%
Cheng SC	0	1	0.00	[0.00; 97.50]	1.2%	1.5%
Holshue	1	1	100.00	[2.50; 100.00]	1.2%	1.5%
Cai J	5	6	83.33	[35.88; 99.58]	2.6%	3.3%
Zeng L	1	1	100.00	[2.50; 100.00]	1.2%	1.5%
Zhang Y	1	1	100.00	[2.50; 100.00]	1.2%	1.5%
Fixed effect model		**138**	**48.88**	**[40.41; 57.41]**	**100.0%**	--
Random effects model			**48.06**	**[38.33; 57.94]**	--	**100.0%**

Heterogeneity: $I^2 = 7\%$, $\tau^2 = 0.0361$, $p = 0.38$



Prevalence

Gastroenterology

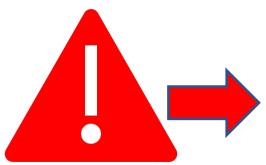
What you need to know:

BACKGROUND AND CONTEXT: Infection with SARS-Co-2 virus, which causes COVID-19, results in respiratory as well as gastrointestinal symptoms; virus RNA has been detected in fecal samples.

NEW FINDINGS: A meta-analysis of publications found that gastrointestinal symptoms have been reported in 17.6% of patients with COVID-19. Stool samples from 48.1% of patients tested positive for virus RNA; stool samples from 70.3% of these patients tested positive for virus RNA even after respiratory specimens tested negative.

LIMITATIONS: This study analyzed mostly data from reported cases from China; systematic data collection was lacking for most studies.

IMPACT: Gastrointestinal symptoms occur in almost 18% of patients with COVID-19. Virus RNA can be detected in fecal samples—even those collected after respiratory samples test negative.



Lay Summary: Many patients with COVID-19 develop gastrointestinal symptoms. The virus can be detected in stool, so patients and caregivers should take care to avoid fecal–oral transmission of the virus.

OPEN ACCESS

ORIGINAL RESEARCH

Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process

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- A rapprocher de la dia 62

Abstract

Objective Since December 2019, a newly identified coronavirus (severe acute respiratory syndrome coronavirus (SARS-C oV-2)) has caused outbreaks of pneumonia in Wuhan, China. SARS-C oV-2 enters host cells via cell receptor ACE II (ACE 2) and the transmembrane serine protease 2 (TMPRSS2). In order to identify possible prime target cells of SARS-C oV-2 by comprehensive dissection of ACE 2 and TMPRSS2 coexpression pattern in different cell types, five datasets with single-cell transcriptomes of lung, oesophagus, gastric mucosa, ileum and colon were analysed. **Design** Five datasets were searched, separately integrated and analysed. Violin plot was used to show the distribution of differentially expressed genes for different clusters. The ACE 2-expressing and TMPRRSS2-expressing cells were highlighted and dissected to characterise the composition and proportion. **Results** Cell types in each dataset were identified by known markers. ACE 2 and TMPRSS2 were not only coexpressed in lung AT2 cells and oesophageal upper epithelial and gland cells but also highly expressed in absorptive enterocytes from the ileum and colon. Additionally, among all the coexpressing cells in the normal digestive system and lung, the expression of ACE 2 was relatively highly expressed in the ileum and colon. **Conclusion** This study provides the evidence of the potential route of SARS-C oV-2 in the digestive system along with the respiratory tract based on single-cell transcriptomic analysis. This finding may have a significant impact on health policy setting regarding the prevention of SARS-C oV-2 infection. Our study also demonstrates a novel method to identify the prime cell types of a virus by the coexpression pattern analysis of single-cell sequencing data.

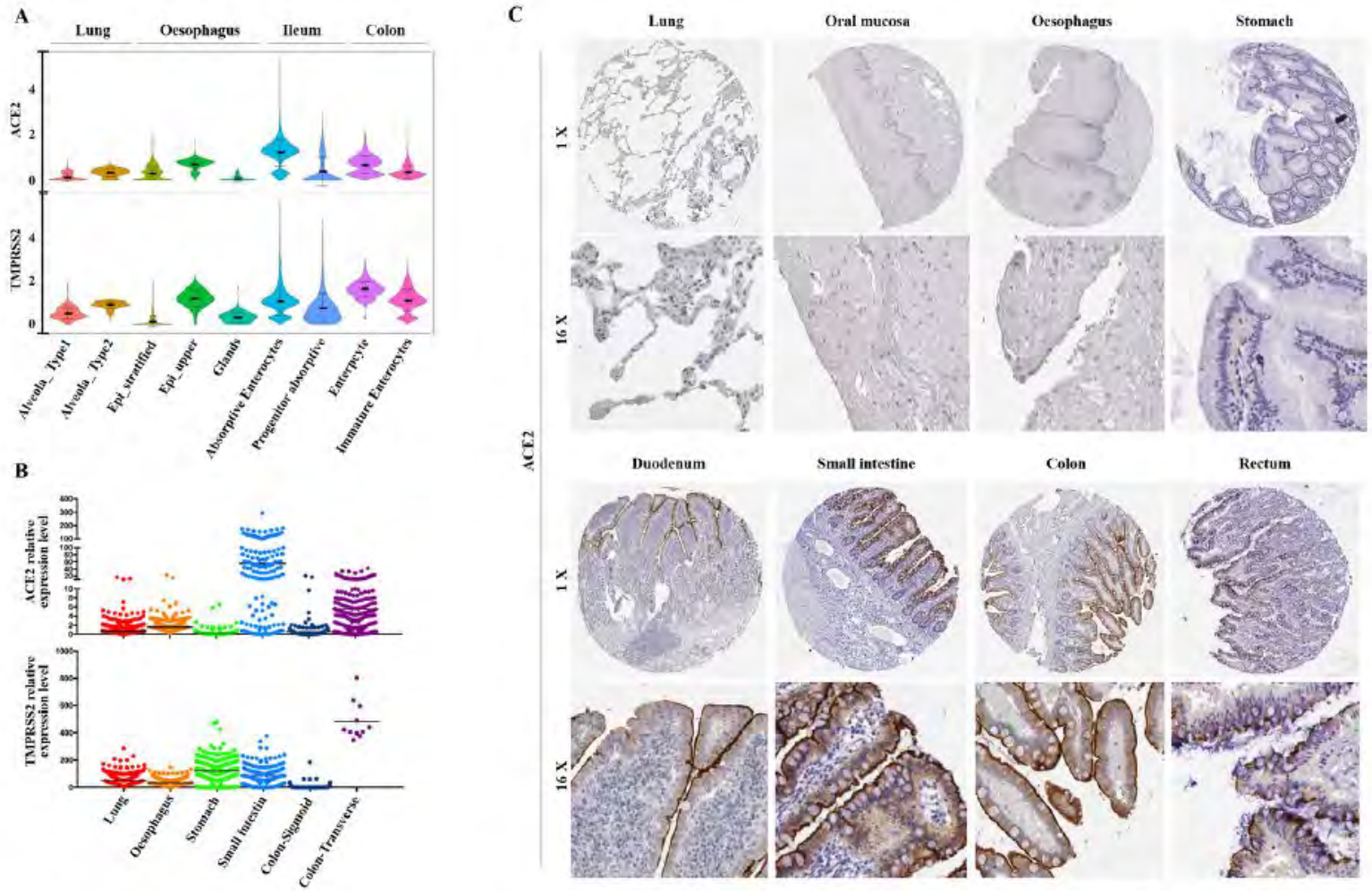

Figure 7 Expression of ACE2 and transmembrane serine protease (TMPRSS2) at RNA and protein levels in different tissues.(A) Violin plots for ACE2 and TMPRSS2 expression across two lung clusters and seven digestive tract clusters. The gene expression matrix was normalised and denoised to remove unwanted technical variability across the four datasets. (B) External validation of ACE2 and TMPRSS2 at RNA level in different tissues. The expression is measured as the pTPM value in the RNA-seq data from the Genotype-Tissue Expression database. (C) Representative immunohistochemical images of ACE2 in different tissues from the HumanProtein Atlas database.

Significance of this study

What is already known on this subject?

- Both of ACE2 and transmembrane serine protease 2 (TMPRSS2) are key proteins of severe acute respiratory syndrome coronavirus (SARS-CoV-2) cell entry process. Coexpression of these two proteins in the same cell is critical for viral entry.
- Currently, the prime target cells of SARS-CoV-2 are unclear due to incomplete knowledge of the ACE2 and TMPRSS2 coexpression pattern in the cells of respiratory tract and digestive tract.
- Though droplet transmission is considered as the main route of transmission, the other transmission routes remain unclear.

What are the new findings?

- Alveolar type 2 cells are the main cell type coexpressing ACE2 and TMPRSS2 in lung tissue.
- In addition, ACE2 and TMPRSS2 are also coexpressed in both upper epithelial and gland cells from oesophagus and absorptive enterocytes from ileum and colon.

How might it impact on clinical practice in the foreseeable future?

- This study provides the evidence of a potential route of SARS-CoV-2 in the digestive system along with the respiratory tract based on single-cell transcriptomic analysis.
- Faecal–oral transmission is a possible route of SARS-CoV-2 transmission. As such, these data may have significant impact for healthy policy setting regarding the prevention of SARS-CoV-2 infection.

What are the new findings?

- Alveolar type 2 cells are the main cell type coexpressing ACE2 and TMPRSS2 in lung tissue.
- In addition, ACE2 and TMPRSS2 are also coexpressed in both upper epithelial and gland cells from oesophagus and absorptive enterocytes from ileum and colon.

Biologie

- Encore beaucoup d’articles sur présence d’ARN dans les selles

Please cite this article in press as: Kim et al., Infection and Rapid Transmission of SARS-CoV-2 in Ferrets, Cell Host & Microbe (2020), https://doi.org/10.1016/j.chom.2020.03.023

Cell Host & Microbe

Brief Report

CellPress

Infection and Rapid Transmission of SARS-CoV-2 in Ferrets

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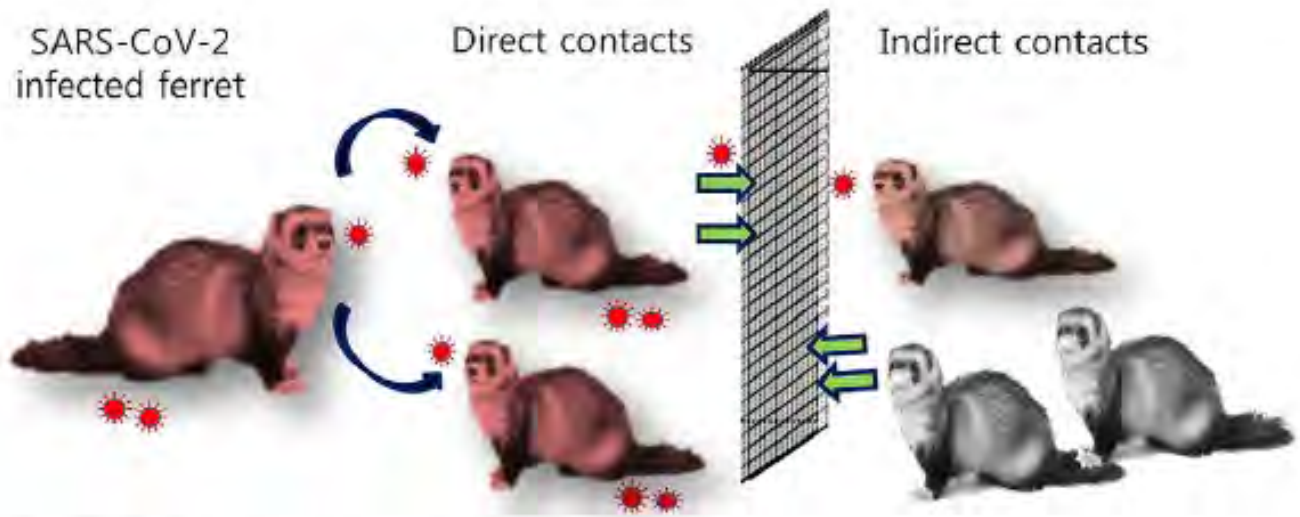
https://doi.org/10.1016/j.chom.2020.03.023

Abstract

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China and rapidly spread worldwide. To prevent SARS-CoV-2 dissemination, understanding the in vivo characteristics of SARS-CoV-2 is a high priority. We report a ferret model of SARS-CoV-2 infection and transmission that recapitulates aspects of human disease. SARS-CoV-2-infected ferrets exhibit elevated body temperatures and virus replication. Although fatalities were not observed, SARS-CoV-2-infected ferrets shed virus in nasal washes, saliva, urine, and feces up to 8 days post-infection. At 2 days post-contact, SARS-CoV-2 was detected in all naive direct contact ferrets. Furthermore, a few naive indirect contact ferrets were positive for viral RNA, suggesting airborne transmission. Viral antigens were detected in nasal turbinate, trachea, lungs, and intestine with acute bronchiolitis present in infected lungs. Thus, ferrets represent an infection and transmission animal model of COVID-19 that may facilitate development of SARS-CoV-2 therapeutics and vaccines.


SARS-CoV-2
infected ferret
Direct contacts
Indirect contacts
SARS-CoV-2 shed in nasal washes, saliva,
urine, feces

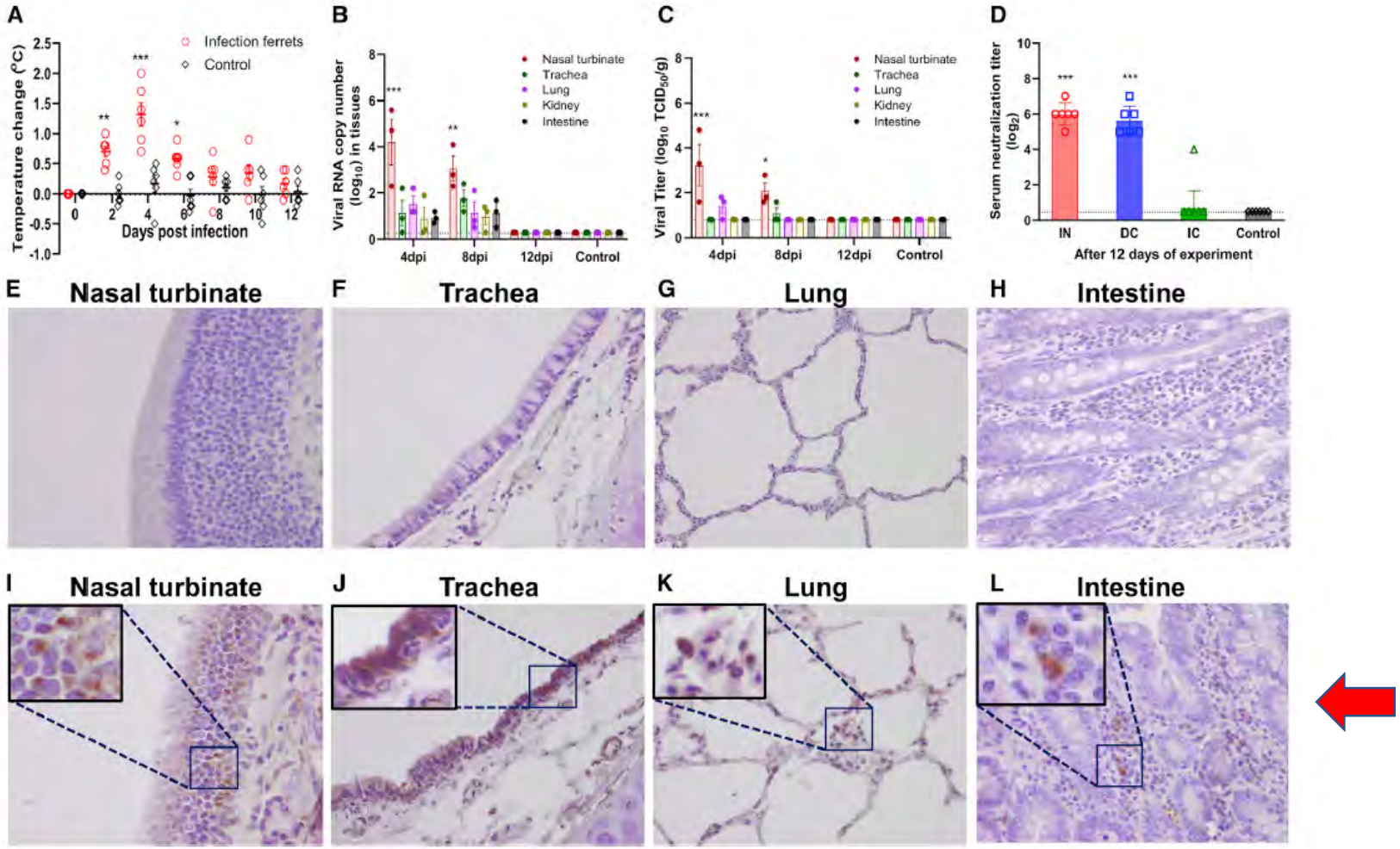


Figure 1. Temperature Changes, Weight Loss, Survival, Viral Shedding, and Immunohistochemistry of Tissues of NMC-nCoV02-Infected Ferrets

(A–C) Six ferrets were inoculated intranasally with $10^{5.5}$ $TCID_{50}$ of virus. (A) Temperature changes, (B) number of viral RNA copies, and (C) infectious virus titers were measured in tissues of NMC-nCoV02-infected ferrets (n = 6/group). Each tissue (n = 3 per group) was collected at 4, 8, and 12 dpi. Viral loads in nasal turbinate, trachea, lung, kidney, and intestine were titered using quantitative real-time PCR and $TCID_{50}$. Data are presented as mean ± SEM.

(D) Serum neutralizing (SN) antibody titers (GMT) against NMC-nCoV02 (100 $TCID_{50}$) were measured onto Vero cells after 12 days of experiment (n = 6 per group). Data are presented as geometric mean ± SD. Tissues were harvested on day 4 after inoculation and immunohistochemistry was performed with a mouse polyclonal antibody.

(E–H) Tissues of PBS control ferrets; (E) nasal turbinate, (F) trachea, (G) lung, and (H) intestine.

(I–L) Tissues of NMC-nCoV02 infected ferrets: (I) Nasal turbinate, (J) Trachea, (K) lung, and (L) Intestine.

The presence of NMC-nCoV02 antigen was determined by IHC with mouse polyclonal antibody. Magnification ×400. Asterisks indicate statistical significance compared with PBS control group by the two-way ANOVA with Sidaks multiple comparisons test (A), the two way ANOVA with Dunnett's multiple comparisons test (B and C), or one-way ANOVA Dunnett's multiple comparisons test (* indicates $p < 0.05$, ** indicates $p < 0.001$, and *** indicates $p < 0.0001$).

Presence of SARS-Coronavirus-2 in sewage.

Authors and their affiliations

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Abstract

In the current COVID-19 pandemic, a significant proportion of cases shed SARS-Coronavirus-2 (SARS-CoV-2) with their faeces.

To determine if SARS-CoV-2 is present in sewage during the emergence of COVID-19 in the Netherlands, sewage samples of 7 cities and the airport were tested using RT-PCR against three fragments of the nucleocapsid protein gene (N1-3) and one fragment of the envelope protein gene (E).

No SARS-CoV-2 was detected in samples of February 6, three weeks before the first case was reported in the Netherlands on February 27. On March 5, the N1 fragment was detected in sewage of five sites. On March 15/16, the N1 fragment was detected in sewage of six sites, and the N3 and E fragment were detected at 5 and 4 sites respectively. This is the first report of detection of SARS-CoV-2 in sewage.

The detection of the virus in sewage, even when the COVID-19 prevalence is low, indicates that sewage surveillance could be a sensitive tool to monitor the circulation of the virus in the population.

Table 1. Primer-probe sets

Assay	Target gene	Primer/Probe	Concentration	Sequence[a]	Reference
N1	Nucleocapsid (N)	2019-nCoV_N1-F	200 nM	5'-GACCCCAAAATCAGCGAAAT-3'	16
		2019-nCoV_N1-R	200 nM	5'-TCTGGTTACTGCCAGTTGAATCTG-3'	16
		2019-nCoV_N1-P	200 nM	5'-FAM-ACCCCGCATTACGTTTGGTGGACC-ZEN/Iowa Black-3'	16
N2	Nucleocapsid (N)	2019-nCoV_N2-F	200 nM	5'-TTACAAACATTGGCCGCAAA-3'	16
		2019-nCoV_N2-R	200 nM	5'-GCGCGACATTCCGAAGAA-3'	16
		2019-nCoV_N2-P	200 nM	5'-FAM-ACAATTTGCCCCCAGCGCTTCAG- ZEN/Iowa Black-3'	16
N3	Nucleocapsid (N)	2019-nCoV_N3-F	200 nM	5'-GGGAGCCTTGAATACACCAAAA-3'	16
		2019-nCoV_N3-R	200 nM	5'-TGTAGCACGATTGCAGCATTG-3'	16
		2019-nCoV_N3-P	200 nM	5'-FAM-AYCACATTGGCACCCGCAATCCTG- ZEN/Iowa Black-3'	16
E	Envelope (E)	E_Sarbeco_F	400 nM	5'-ACAGGTACGTTAATAGTTAATAGCGT-3'	17
		E_Sarbeco_R	400 nM	5'-ATATTGCAGCAGTACGCACACA-3'	17
		E_Sarbeco_P1	200 nM	5'-FAM-ACACTAGCCATCCTTACTGCGCTTCG-ZEN/Iowa Black-3'	17

[a] Y=C/T. FAM: 6-carboxyfluorescein; ZEN/Iowa Black: internal ZEN and Iowa Black double-quenched probe

Table 3. Results of screening of SARS-CoV-2 targets in 24h composite samples of incoming wastewater at different WWTP in The Netherlands 3 weeks before and approx. 1 and 2.5 weeks after the first COVID-19 case was reported in The Netherlands (February 27, 2020).

WWTP	I.E.	Date	N1	N2	N3	E	Date	N1	N2	N3	E	Date	N1	N2	N3	E
Amsterdam	1014000	7-2-2020	-	-	-	-	5-3-2020	+	-	-	-	16-3-2020	+	-	+	+
The Hague	1400000	6-2-2020	-	-	-	-	4-3-2020	-	-	-	-	15-3-2020	+	-	+	-
							5-3-2020	-	-	-	-	16-3-2020	+	-	+	-
Utrecht	530000	5-2-2020	-	-	-	-	5-3-2020	+	-	-	-	16-3-2020	+	-	+	+
							5-3-2020	+	-	-	-	16-3-2020	+	-	+	+
Apeldoorn	350000	6-2-2020	-	-	-	-	5-3-2020	-	-	-	-	16-3-2020	-	-	-	-
Amersfoort	335000	6-2-2020	-	-	-	-	5-3-2020	+	-	-	-	16-3-2020	+	-	-	-
Tilburg	375000											15-3-2020	+	-	+	+
												16-3-2020	+	-	+	-
Schiphol airport	54000	7-2-2020	-	-	-	-	5-3-2020	+	-	-	-	16-3-2020	+	-	+	+
Blanc samples		6-2-2020	-	-	-	-	6-3-2020	-	-	-	-	17-3-2020	-	-	-	-
Positive control		11-2-2020	+	+	+		10-3-2020	+	+	+		17-3-2020	+	+	+	
Negative control		11-2-2020	-	-	-	-	10-3-2020	-	-	-	-	17-3-2020	-	-	-	-

I.E.: Inhabitant Equivalents, these are design capacities of the WWTP, which is 30% higher than the number of inhabitants served by the WWTP (average of Dutch national statistics).

Table 4. Rough estimate of the observed prevalence of COVID-19 (number of infected persons per 100.000 people) in the community served by the WWTP on February 6, March 5 and 16, 2020.

WWTP	Feb 27	Mar 5	Mar 16
Amsterdam	0,0	0,3	5.5
The Hague area	0,0	0,3	3.5
Utrecht	0,0	1,6	12.9
Apeldoorn	0,0	0,0	2.9
Amersfoort	0,0	0,0	7.7
Schiphol	0,0	nd	nd
Tilburg	0,0	0.9	32.0

Transmission Potential of SARS-CoV-2 in Viral Shedding Observed at the University of Nebraska Medical Center

Authors: Joshua L. Santarpia[1,2*], Danielle N. Rivera[2], Vicki Herrera[1], M. Jane Morwitzer[1], Hannah Creager [1], George W. Santarpia[1], Kevin K. Crown[2], David M. Brett-Major[1], Elizabeth Schnaubelt[1,3], M. Jana Broadhurst[1], James V. Lawler[1], St. Patrick Reid[1], and John J. Lowe[1]

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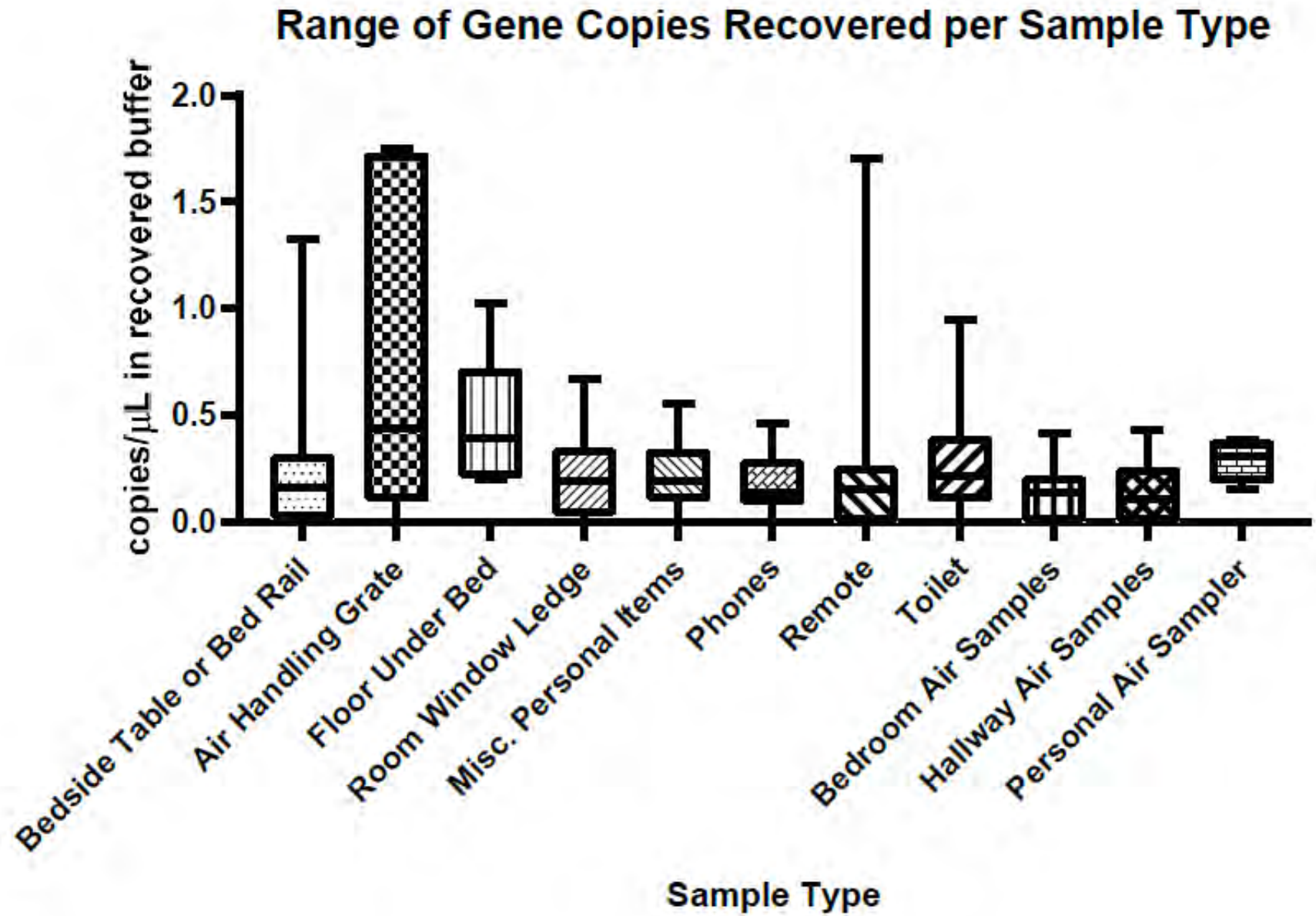
CSH Cold Spring Harbor Laboratory BMJ Yale

Lack of evidence on SARS-CoV-2 transmission dynamics has led to shifting isolation guidelines between airborne and droplet isolation precautions. During the initial isolation of 13 individuals confirmed positive with COVID-19 infection, air and surface samples were collected in eleven isolation rooms to examine viral shedding from isolated individuals. While all 15 individuals were confirmed positive for SARS-CoV-2, symptoms and viral shedding to the environment varied considerably. Many commonly used items, toilet facilities, and air samples had evidence of viral contamination, indicating that SARS-CoV-2 is shed to the environment as expired particles, during toileting, and through contact with fomites. Disease spread through both direct (droplet and person-to-person) as well as indirect contact (contaminated objects and airborne transmission) are indicated, supporting the use of airborne isolation precautions.


Range of Gene Copies Recovered per Sample Type
copies/µL in recovered buffer
2.0
1.5
1.0
0.5
0.0
Bedside Table or Bed Rail
Air Handling Grate
Floor Under Bed
Room Window Ledge
Misc. Personal Items
Phones
Remote
Toilet
Bedroom Air Samples
Hallway Air Samples
Personal Air Sampler
Sample Type

Infectiosité ?

Air samples that were positive for viral RNA by RT-PCR were examined for viral propagation inVero E6 cells. Cytopathic effect was not observed in any sample, to date, and immunofluorescence and western blot analysis have not, so far, indicated the presence of viral antigens suggesting viral replication. However, the low concentrations of virus recovered from these samples makes finding infectious virus in these samples difficult. Further experiments are ongoing to determine viral activity in these samples.

Virological assessment of hospitalized cases of coronavirus disease 2019

Roman Wölfel*, Victor M. Corman*, Wolfgang Guggemos*, Michael Seilmaier, Sabine Zange, Marcel A. Müller, Daniela Niemeyer, Terence C. Jones Kelly, Patrick Vollmar, Camilla Rothe, Michael Hoelscher, Tobias Bleicker, Sebastian Brünink, Julia Schneider, Rosina Ehmann, Katrin Zwirglmaier, Christian Drosten**, Clemens Wendtner**

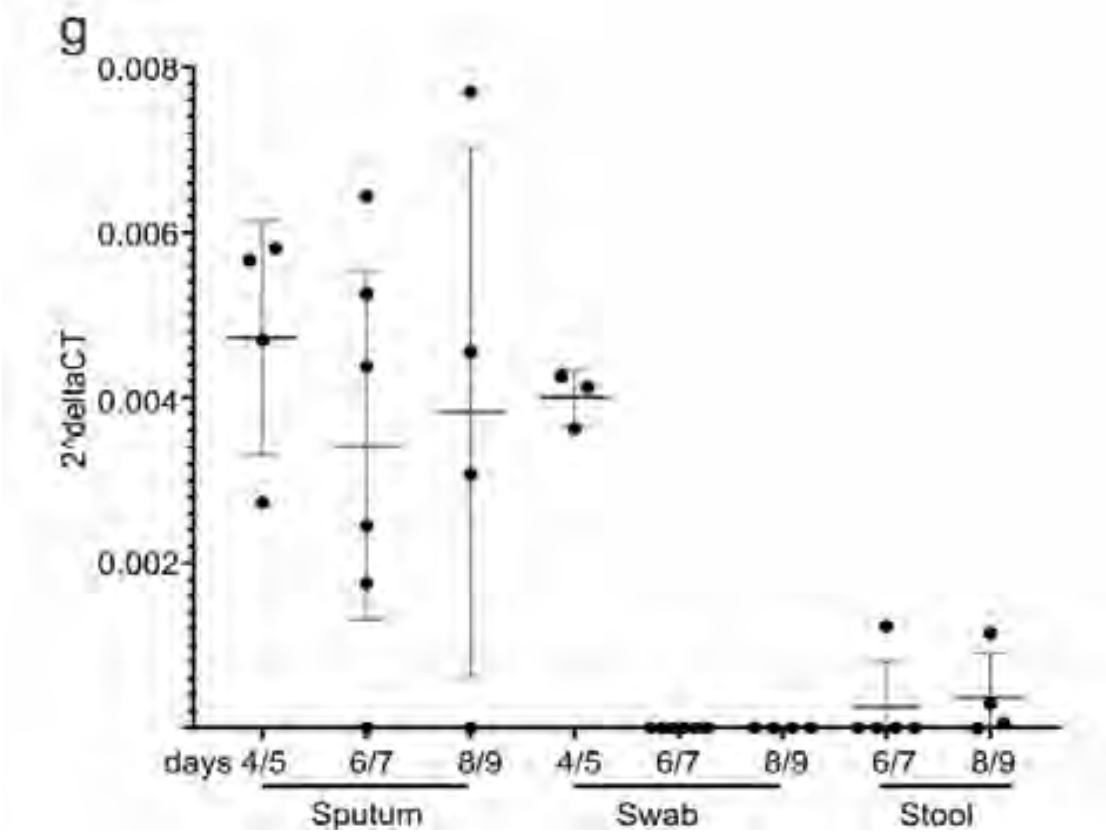
Nature. 2020 Apr 1. doi: 10.1038/s41586-020-2196-x.

+++

Abstract

Coronavirus disease 2019 (COVID-19) is an acute respiratory tract infection that emerged in late 20191,2. Initial outbreaks in China involved 13.8% cases with severe-, and 6.1% with critical courses3. This severe presentation corresponds to the usage of a virus receptor that is expressed predominantly in the lung2,4. By causing an early onset of severe symptoms, this same receptor tropism is thought to have determined pathogenicity but also aided the control of severe acute respiratory syndrome (SARS) in 20035. However, there are reports of COVID-19 cases with mild upper respiratory tract symptoms, suggesting a potential for pre- or oligosymptomatic transmission6-8. There is an urgent need for information on body site - specific virus replication, immunity, and infectivity. Here we provide a detailed virological analysis of nine cases, providing proof of active virus replication in upper respiratory tract tissues. Pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11 X 108 RNA copies per throat swab, day 4). Infectious virus was readily isolated from throat- and lung-derived samples, but not from stool samples in spite of high virus RNA concentration. Blood and urine never yielded virus. Active replication in the throat was confirmed by viral replicative RNA intermediates in throat samples. Sequence-distinct virus populations were consistently detected in throat- and lung samples of one same patient. Shedding of viral RNA from sputum outlasted the end of symptoms. Seroconversion occurred after 6-12 days, but was not followed by a rapid decline of viral loads. COVID-19 can present as a mild upper respiratory tract illness. Active virus replication in the upper respiratory tract puts prospects of COVID-19 containment in perspective.

- Virus isolation from stool samples was never successful, irrespective of viral RNA concentration, based on a total of 13 samples taken between days six to twelve from four patients. To obtain proof of active virus replication in absence of histopathology, we conducted RT-PCR tests to identify viral subgenomic messenger RNAs (sgRNA) directly in clinical samples. Viral sgRNA is only transcribed in infected cells and is not packaged into virions, therefore indicating the presence of actively infected cells in samples. No, or only minimal, indication of replication in stool was obtained by the same method (**Figure 1G**).


g
0.008
0.006
0.004
0.002
2^deltaCT
days 4/5 6/7 8/9 4/5 6/7 8/9 6/7 8/9
Sputum
Swab
Stool

- The presence of separate genotypes in throat swabs and sputum strongly supported our suspicion of independent virus replication in the throat, rather than passive shedding there from the lung.
- In only one case, independent replication in the intestinal tract seemed obvious from the course of stool RNA excretion (**Figure 2 D**).
- Stool and sputum samples remained RNA-positive over even longer periods, in spite of full resolution of symptoms.

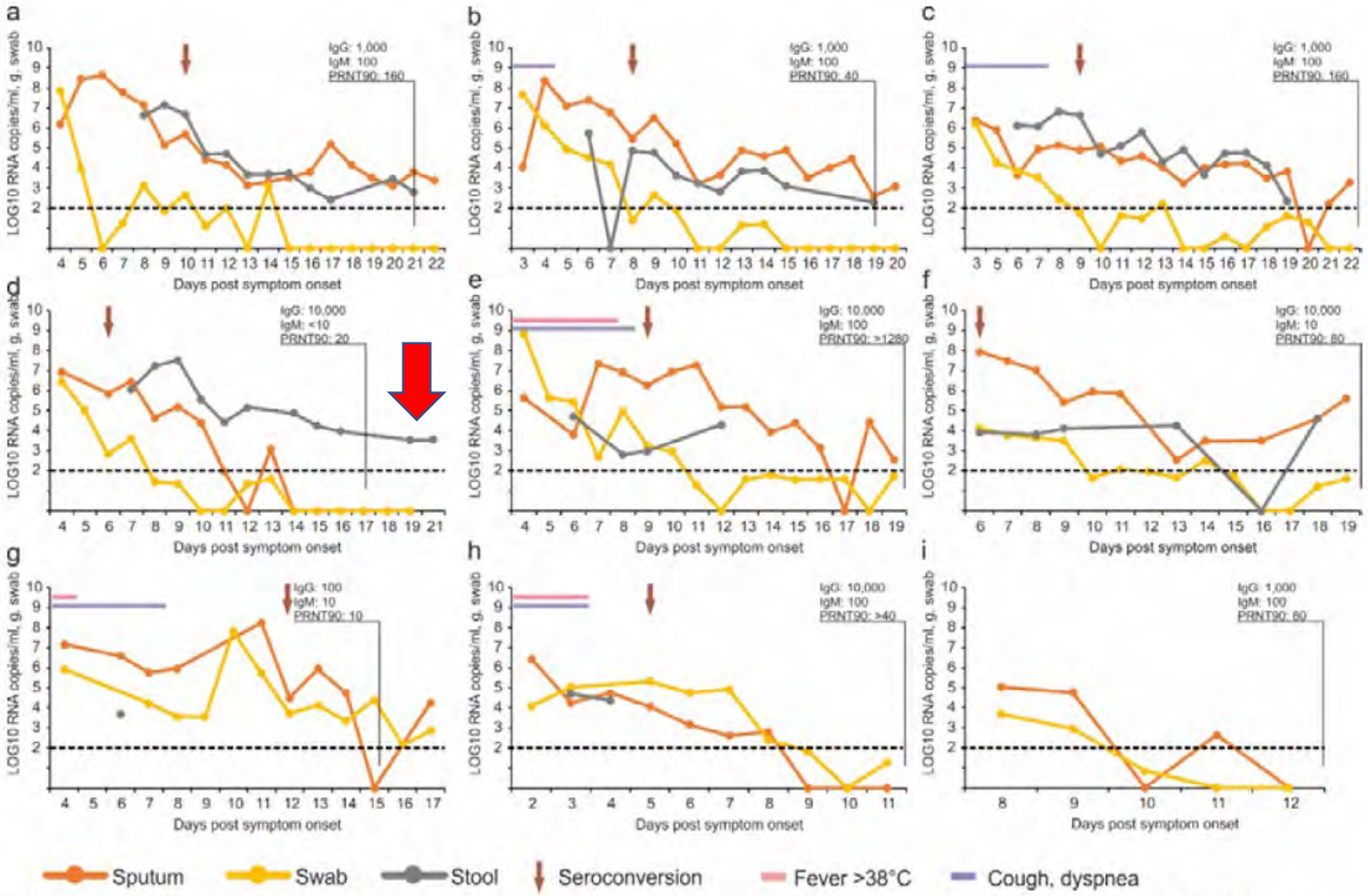


Figure 2. Viral load kinetics, seroconversion and clinical observations in individual cases. Panels A to I correspond to cases #1, #2, #3, #4, #7, #8, #10, #14, and #16 in Böhmer et al.(accompanying manuscript). Dotted lines, limit of quantification

The combination of very high virus RNA concentrations and occasional detection of sgRNA containing cells in stool indicate active replication in the gastrointestinal tract.

Active replication is also suggested by a much higher detection rate as compared to MERS coronavirus, for which we found stool-associated RNA in only 14.6% samples in 37 patients hospitalized in Riyadh, Saudi Arabia[21,22]. If virus was only passively present in stool, such as after swallowing respiratory secretions, similar detection rates as for MERS-CoV would be expected. Replication in the gastrointestinal tract is also supported by analogy with SARSCoV, which was regularly excreted in stool, from which it could be isolated in cell culture[23].

Our failure to isolate live SARS-CoV-2 from stool may be due to the mild courses of cases, with only one case showing intermittent diarrhea. In China, diarrhea has been seen in only 2 of 99 cases[24]. Further studies should therefore address whether SARS-CoV-2 shed in stool is rendered non-infectious though contact with the gut environment. Our initial results suggest that measures to contain viral spread should aim at droplet-, rather than fomite based transmission.

Synthèse : localisation digestive et biologie

- Lancet Gastroenterol Hepatol. 2020 Apr;5(4):335-337. doi: 10.1016/S2468-1253(20)30048-0. Epub 2020 Feb 20. PDF
- **Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible?**
- Yeo C[1], Kaushal S[1], Yeo D[2].

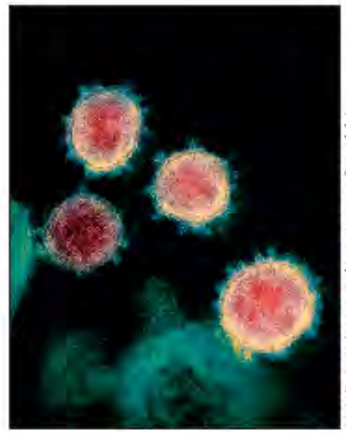
Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible?

The end of 2019 was marked by the emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused an outbreak of viral pneumonia (COVID-19) in Wuhan, China. At the time of writing, SARS-CoV-2, previously known as 2019-nCoV, has spread to more than 26 countries around the world. According to the WHO COVID-19 situation report-28 released on Feb 17, 2020, more than 71 000 cases have been confirmed and at least 1770 deaths.

Coronaviruses are a family of single-stranded enveloped RNA viruses that are divided into four major genera. The genome sequence of SARS-CoV-2 is 82% similar to severe acute respiratory syndrome coronavirus (SARS-CoV),[1] and both belong to the β-genus of the coronavirus family.[2] Human coronaviruses such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), are known to cause respiratory and enteric symptoms.

In the SARS outbreak of 2002–03, 16–73% of patients with SARS had diarrhoea during the course of the disease, usually within the first week of illness.[3] SARS-CoV RNA was only detected in stools from the fifth day of illness onwards, and the proportion of stool specimens positive for viral RNA progressively increased and peaked at day 11 of the illness, with viral RNA still present in the faeces of a small proportion of patients even after 30 days of illness.[4] The mechanism for gastrointestinal tract infection of SARS-CoV is proposed to be the angiotensin-converting enzyme 2 (ACE2) cell receptor.[2]

In the initial MERS-CoV outbreak in 2012, a quarter of patients with MERS-CoV reported gastrointestinal symptoms such as diarrhoea or abdominal pain at presentation.[5] Some patients initially presented with both



NIAID-RML/National Institutes of Health/Science Photo Library

Published Online
February 19, 2020
https://doi.org/10.1016/S2468-1253(20)30048-0

For more on the **WHO COVID-19 situation report-28** see https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200217-sitrep-28-covid-19.pdf?sfvrsn=a19cf2ad_2

*Charleen Yeo, Sanghvi Kaushal, *Danson Yeo*
danson_xw_yeo@ttsh.com.sg
Department of General Surgery, Tan Tock Seng Hospital, Singapore 308433

Extraits edito Yeo

- Data exist to support the notion that SARS-CoV and MERS-CoV are viable in environmental conditions that could facilitate faecal–oral transmission.
- SARS-CoV RNA was found in the sewage water of two hospitals in Beijing treating patients with SARS.12
- When SARSCoV was seeded into sewage water obtained from the hospitals in a separate experiment, the virus was found to remain infectious for 14 days at 4°C, but for only 2 days at 20°C.[12]

Conclusions sur réplication digestive. Parties I à III

- Possibilité d'une réplication dans le tube digestif.
- Il y a de plus en plus d'arguments très récents pour :
  - ✓ des formes digestives isolées
  - ✓ des formes digestives initialement prédominantes
  - ✓ une surexpression des récepteurs ACE2 & TMPRRSS2 dans l'intestin
  - ✓ la présence de l'ARN génomique ou de protéines virales dans les cellules intestinales
  - ✓ la présence d'ARN messagers subgénomique dans des cellules des selles
  - ✓ une présence prolongée de l'ARN du COVID 19 dans les selles après négativation dans les VADS.
  - ✓ la présence de virus infectant dans les selles est ainsi avancée
  - ✓ La présence de protéines virales du COVID 19 dans les eaux usées
  - ✓ La présence de SARS COV 1 viable dans les eaux usées à 20 °C pendant 2 j
  - ✓ Donc pour une transmission oro-fécale

Limites

- Pas de preuve directe à ce jour de la présence du virus infectant dans le tube digestif :
  - Culture cellulaire (Vero…) : doute
  - Inoculation à un modèle animal (macaque, hamster, furet)
  - Image du virus complet dans les selles ou les cellules digestives

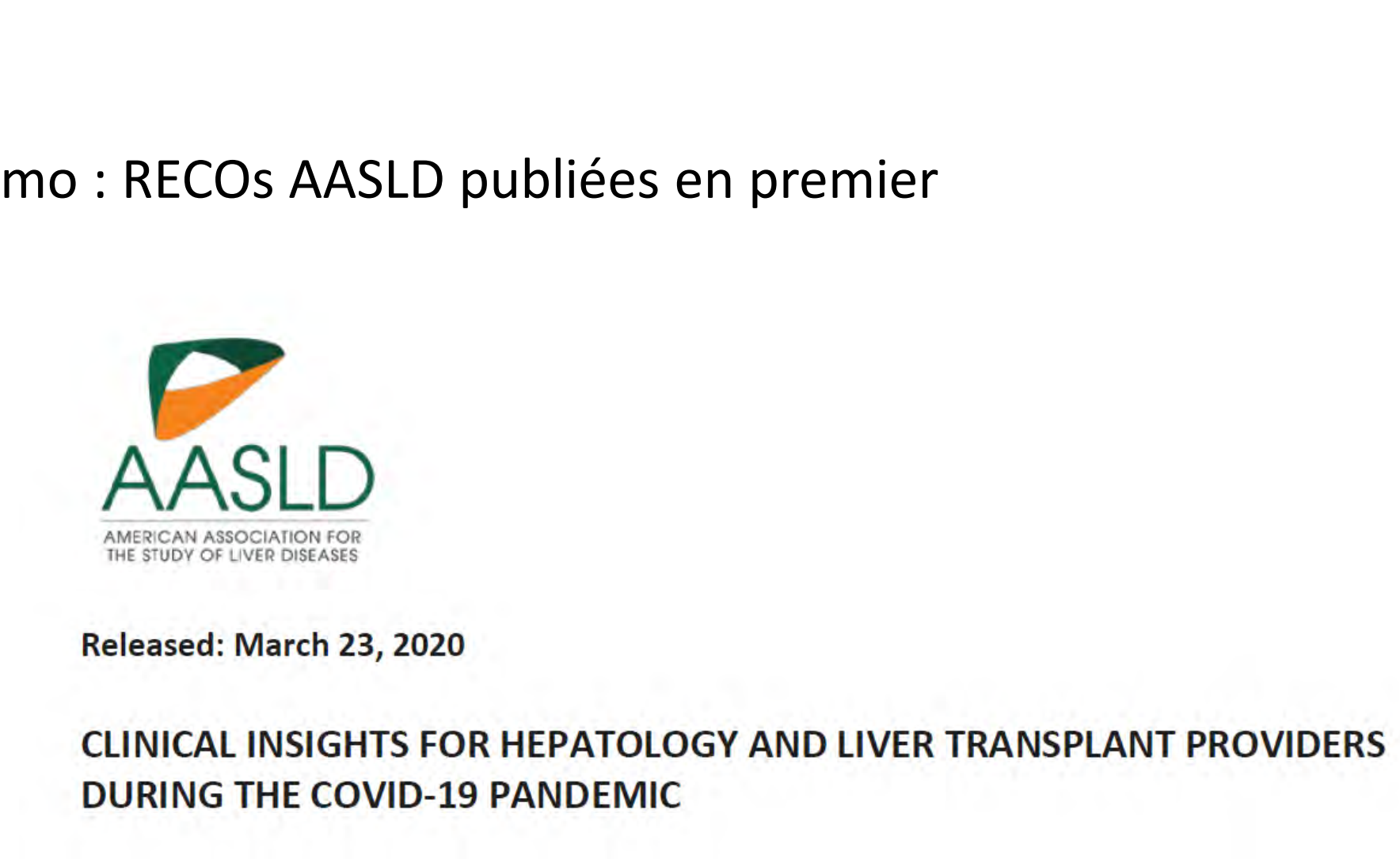
Synthèse

		Formes respiratoires (ARN VADS)	
	Covid	**Négatif**	**Positif**
Formes	**Négatif**	**?**	
digestives (ARN selles)	**Positif**		

Viabilité ?
Transmission oro-fécale ?

RECOs

- Mémo : RECOs AASLD publiées en premier



Journal Pre-proof

AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic

Shahnaz Sultan, Joseph K. Lim, Osama Altayar, Perica Davitkov, Joseph D. Feuerstein, Shazia M. Siddique, Yngve Falck-Ytter, Hashem B. El-Serag, on behalf of the AGA

PII: S0016-5085(20)30458-3
DOI: https://doi.org/10.1053/j.gastro.2020.03.072
Reference: YGAST 63343

To appear in: *Gastroenterology*

Please cite this article as: Sultan S, Lim JK, Altayar O, Davitkov P, Feuerstein JD, Siddique SM, Falck-Ytter Y, El-Serag HB, on behalf of the AGA, AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic, *Gastroenterology* (2020), doi: https://doi.org/10.1053/j.gastro.2020.03.072.

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- Très complète pour les mesures de protection et de désinfection

Journal Pre-proof

Management of Patients with Crohn's Disease and Ulcerative Colitis During the COVID-19 Pandemic: Results of an International Meeting

David T. Rubin, Maria T. Abreu, Victoria Rai, Corey A. Siegel, on behalf of the International Organization for the Study of Inflammatory Bowel Disease

PII: S0016-5085(20)30465-0
DOI: https://doi.org/10.1053/j.gastro.2020.04.002
Reference: YGAST 63348

To appear in: *Gastroenterology*

- Gastroenterology. 2020 Apr 9. pii: S0016-5085(20)30482-0. doi: 10.1053/j.gastro.2020.04.012. [Epub ahead of print]
- **AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary.**
- Rubin DT[1], Feuerstein JD[2], Wang AY[3], Cohen RD[4].

Journal Pre-proof

AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: *Expert Commentary*

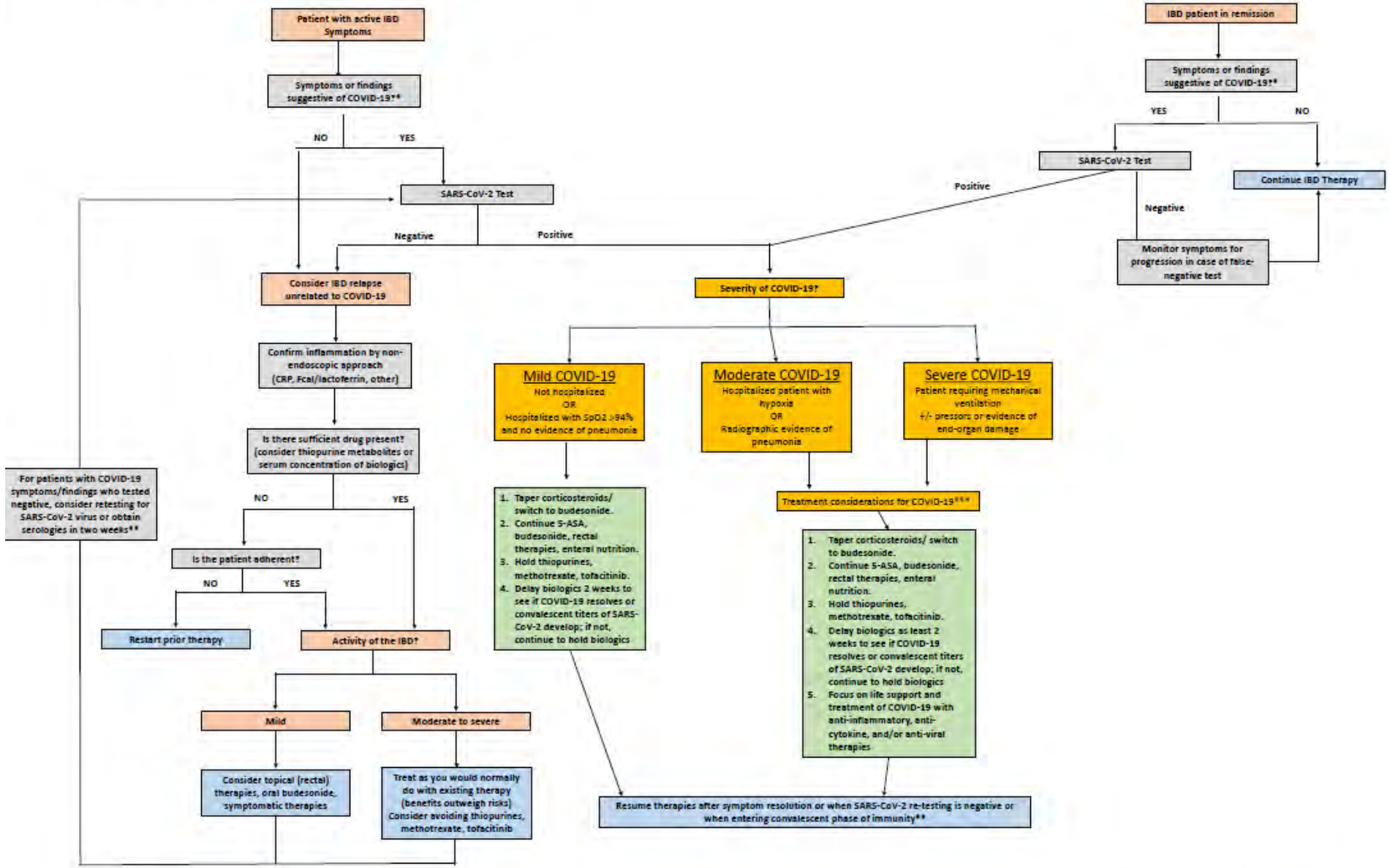
David T. Rubin, Joseph D. Feuerstein, Andrew Y. Wang, Russell D. Cohen

PII: S0016-5085(20)30482-0
DOI: https://doi.org/10.1053/j.gastro.2020.04.012
Reference: YGAST 63359

To appear in: *Gastroenterology*

Please cite this article as: Rubin DT, Feuerstein JD, Wang AY, Cohen RD, AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: *Expert Commentary*, *Gastroenterology* (2020), doi: https://doi.org/10.1053/j.gastro.2020.04.012.

Figure 1: Management of Patients with IBD during the COVID-19 Pandemic.



* Symptoms and findings of COVID-19: fever (83–99%); cough (59–82%); fatigue (44–70%); anorexia (40–84%); shortness of breath (31–40%); sputum production (28–33%); myalgias (11–35%); headache, confusion, rhinorrhea, sore throat, hemoptysis, vomiting, and diarrhea (<10%); lymphopenia (83%); CT chest: bilateral, peripheral ground glass opacities. Reference: CDC - Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed April 2, 2020.

** Clearance of SARS-Cov-2 may enable resumption of IBD therapy; role of serologic antibody testing unclear at the current time. *(Viral clearance testing may or may not be possible or appropriate, given local testing capabilities and health system-approved epidemiological testing strategies during the COIVD-19 pandemic.)*

*** Treatment of COVID-19 under investigation, consider therapies that have safety and efficacy in IBD.

Figure 1. Final results of the RAND appropriateness panel for the use of medications to treat IBD in the setting of SARS-CoV-2 or COVID-19

Statement	5-ASA	BUD	PRED (≥20mg/d)	AZA/ 6MP	MTX	Anti-TNF	VEDO	UST	TOFA
This therapy increased the risk of infection with SARS-CoV-2.									
This therapy increases the risk of COVID-19 disease.									
Patients taking this therapy should **reduce** the dose of therapy to prevent SARS-CoV-2 infection.									
Patients taking this therapy should **discontinue** therapy to prevent SARS-CoV-2 infection.									
Patients taking this therapy should **stop** therapy if they test positive for SARS-CoV-2 but don't have the COVID-19 disease.									
Patients taking this therapy should **stop** therapy if they develop COVID-19.									

Figure legend: *IBD = inflammatory bowel disease; SARS-CoV-2 = Severe Acute Respiratory Syndrome-CoronaVirus-2; COVID-19 = CoronaVirus Disease; 5-ASA = 5-aminosalicylate; Bud = budesonide; Pred = prednisone; AZA = azathioprine; 6MP = 6-mercaptopurine; MTX = methotrexate; anti-TNF = anti-tumor necrosis factor; VEDO = vedolizumab; UST = ustekinumab; TOFA = tofacitinib.*

AFEF

SOCIETÉ FRANÇAISE D'HÉPATOLOGIE

Propositions de prise en charge des patients atteints de maladies du foie à l'occasion de la pandémie de Coronavirus 2019

AFEF – Société Française d'Hépatologie

(version du 6 avril 2020)

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- Très pratique pour la PEC des différentes pathologies

Care of patients with liver disease during the COVID-19 pandemic:

EASL-ESCMID Position Paper

Tobias Boettler[1], Philip N Newsome[2,3], Mario U. Mondelli[4], Mojca Maticic[5,6], Elisa Cordero[7], Markus Cornberg[8,9], Thomas Berg[10,*]

Partie IV

- Biblio au 14/4/20
- Pubmed : n= 4077
- 1300 derniers articles screenés
- **COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv : n = 1614**

News

- Atteintes
  - Cutanés : rash
  - Cardiaques : myocardite
  - ORL
  - Neurologiques
- Traitements
  - Multiple
  - (OH) chloroquine
  - Remdesivir

Clinique

- J Pain Symptom Manage. 2020 Apr 10. pii: S0885-3924(20)30205-0. doi: 10.1016/j.jpainsymman.2020.04.008. [Epub ahead of print]
- **A comparison of burnout frequency among oncology physicians and nurses working on the front lines and usual wards during the COVID-19 epidemic in Wuhan, China.**
- Wu Y[1], Wang J[2], Luo C[3], Hu S[2], Lin X[2], Anderson AE[4], Bruera E[4], Yang X[5], Wei S[6], Qian Y[7].

Abstract

CONTEXT:

The epidemic of Coronavirus Disease 2019 (COVID-19) was first identified in Wuhan, China and has now spread worldwide. In the affected countries, physicians and nurses are under heavy workload conditions and are at high risk of infection.

OBJECTIVES:

The aim of this study was to compare the frequency of burnout between physicians and nurses on the front line and those working in usual wards.

METHODS:

A survey with 49 questions total was administered to 220 medical staff members from the COVID-19 front lines and usual wards, with a ratio of 1:1. General information such as age, gender, marriage status, and the Maslach Burnout Inventory-Medical Personnel (MBI), were gathered and compared.

RESULTS:

The group working on the front lines had a lower frequency of burnout (13% versus 39%, $P < .0001$), and were less worried about being infected compared to the usual ward group.

CONCLUSION:

Compared to medical staff working on their usual wards for uninfected patients, medical staff working on the COVID-19 front line had a lower frequency of burnout. These results suggest that in the face of the COVID-19 crisis, both front line and usual ward staff should be considered when policies and procedures to support the well-being of health care workers are devised.

- Obesity (Silver Spring). 2020 Apr 9. doi: 10.1002/oby.22831. [Epub ahead of print]
- **High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation.**
- Simonnet A[1], Chetboun M[2], Poissy J[1], Raverdy V[2], Noulette J[2], Duhamel A[3], Labreuche J[3], Mathieu D[1], Pattou F[2,4], Jourdain M[1,2]; Lille Intensive Care COVID-19 and Obesity study group.

Abstract

OBJECTIVE:

The Covid-19 pandemic is rapidly spreading worldwide, notably in Europe and North America, where obesity is highly prevalent. The relation between obesity and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has not been fully documented.

METHODS:

In this retrospective cohort study we analyzed the relationship between clinical characteristics, including body mass index (BMI), and the requirement for invasive mechanical ventilation (IMV) in 124 consecutive patients admitted in intensive care for SARS-CoV-2, in a single French center.

RESULTS:

Obesity (BMI >30 kg/m2) and severe obesity (BMI >35 kg/m2) were present in 47.6% and 28.2% of cases, respectively. Overall, 85 patients (68.6%) required IMV. The proportion of patients who required IMV increased with BMI categories ($p<0.01$, Chi square test for trend), and it was greatest in patients with BMI >35 kg/m2 (85.7%). In multivariate logistic regression, the need for IMV was significantly associated with male sex ($p<0.05$) and BMI ($p<0.05$), independent of age, diabetes, and hypertension. The odds ratio for IMV in patients with BMI >35 kg/m2 vs patients with BMI <25 kg/m2 was 7.36 (1.63-33.14; $p=0.02$) CONCLUSION: The present study showed a high frequency of obesity among patients admitted in intensive care for SARS-CoV-2. Disease severity increased with BMI. Obesity is a risk factor for SARS-CoV-2 severity requiring increased attention to preventive measures in susceptible individuals.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

COVID-19 CASES

To rapidly communicate information on the global clinical effort against Covid-19, the Journal *has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.*

Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19

Table 1. Demographic and Clinical Characteristics and Laboratory Findings.*

Characteristic	Patient 1	Patient 2	Patient 3
Demographic characteristics			
Age — yr	69	65	70
Sex	Male	Female	Male
Initial findings			
Medical history	Hypertension, diabetes, stroke	Hypertension, diabetes, coronary artery disease, no history of thrombosis	Hypertension, emphysema, nasopharyngeal carcinoma, stroke
Symptoms at disease onset	Fever, cough, dyspnea, diarrhea, headache	Fever, cough, dyspnea	Fever, fatigue, dyspnea, headache
Imaging features	Ground-glass opacity, bilateral pulmonary infiltrates	Ground-glass opacity, bilateral pulmonary infiltrates	Bilateral pulmonary infiltrates
Treatment before admission to ICU	Oseltamivir, intravenous immune globulin	Antibiotics	Antibiotics, ribavirin, rosuvastatin
Days from disease onset to thrombotic event	18	33	10
Findings on admission to ICU			
Days since disease onset	24	21	24
Disease severity	Critical	Critical	Critical

Antiphospholipid antibodies abnormally target phospholipid proteins, and the presence of these antibodies is central to the diagnosis of the antiphospholipid syndrome. However, these antibodies can also arise transiently in patients with critical illness and various infections.[1] The presence of these antibodies may rarely lead to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy.

HGE

- Eur J Gastroenterol Hepatol. 2020 Apr 10. doi: 10.1097/MEG.0000000000001742. [Epub ahead of print]
- **Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis.**
- Lippi G[1], de Oliveira MHS[2], Henry BM[3].

Journal Pre-proof

Clinical Features of COVID-19-Related Liver Damage

Zhenyu Fan, Liping Chen, Jun Li, Xin Cheng, Jingmao Yang, Cheng Tian, Yajun Zhang, Shaoping Huang, Zhanju Liu, Jilin Cheng

PII: S1542-3565(20)30482-1
DOI: https://doi.org/10.1016/j.cgh.2020.04.002
Reference: YJCGH 57116

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 3 April 2020

Please cite this article as: Fan Z, Chen L, Li J, Cheng X, Jingmao Yang Tian C, Zhang Y, Huang S, Liu Z, Cheng J, Clinical Features of COVID-19-Related Liver Damage, *Clinical Gastroenterology and Hepatology* (2020), doi: https://doi.org/10.1016/j.cgh.2020.04.002.

Abstract

BACKGROUND & AIMS:

Some patients with SARS-CoV-2 infection have abnormal liver function. We aimed to clarify the features of COVID-19-related liver damage to provide references for clinical treatment.

METHODS:

We performed a retrospective, single-center study of 148 consecutive patients with confirmed COVID-19 (73 female, 75 male; mean age, 50 years) at the Shanghai Public Health Clinical Center from January 20 through January 31, 2020. Patient outcomes were followed until February 19, 2020. Patients were analyzed for clinical features, laboratory parameters (including liver function tests), medications, and length of hospital stay. Abnormal liver function was defined as increased levels of alanine and aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, and total bilirubin.

RESULTS:

Fifty-five patients (37.2%) had abnormal liver function at hospital admission; 14.5% of these patients had high fever (14.5%), compared with 4.3% of patients with normal liver function (P=.027). Patients with abnormal liver function were more likely to be male, and had higher levels of procalcitonin and C-reactive protein. There was no statistical difference between groups in medications taken before hospitalization; a significantly higher proportion of patients with abnormal liver function (57.8%) had received lopinavir/ritonavir after admission compared to patients with normal liver function (31.3%). Patients with abnormal liver function had longer mean hospital stays (15.09±4.79 days) than patients with normal liver function (12.76±4.14 days) (P=.021).

CONCLUSIONS:

More than one third of patients admitted to the hospital with SARS-CoV-2 infection have abnormal liver function, and this is associated with longer hospital stay. A significantly higher proportion of patients with abnormal liver function had received lopinavir/ritonavir after admission; these drugs should be given with caution.

Journal Pre-proof

Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis

Dong Ji, Enqiang Qin, Jing Xu, Dawei Zhang, Gregory Cheng, Yudong Wang, George Lau

PII: S0168-8278(20)30206-3

DOI: https://doi.org/10.1016/j.jhep.2020.03.044

Reference: JHEPAT 7692

To appear in: *Journal of Hepatology*

Received Date: 27 March 2020

Accepted Date: 27 March 2020

Please cite this article as: Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G, Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis, *Journal of Hepatology* (2020), doi: https://doi.org/10.1016/j.jhep.2020.03.044.

BMI, percentage of comorbidity and NAFLD (Table). Univariate and multivariate logistic regression analysis showed that male sex (OR 3.1, 95% CI 1.1 - 9.4), age > 60 years (OR 4.8, 95% CI 1.5 - 16.2), higher BMI (OR 1.3, 95% CI 1.0 - 1.8), underlying comorbidity (OR 6.3, 95% CI 2.3 - 18.8) and NAFLD (OR 6.4, 95% CI 1.5 - 31.2), were associated with COVID-19 progression.

Patients with NAFLD had higher risk of disease progression [6.6% (5/126) vs 44.7% (34/76) $p<0.0001$], higher likelihood of abnormal liver function from admission to discharge[70% (53/76) vs 11.1% (14/126) $p<0.0001$] and longer viral shedding time(17.5±5.2 days vs 12.1±4.4 days $p<0.0001$) when compared with non-NAFLD subjects.

Journal Pre-proof

High Prevalence of Concurrent Gastrointestinal Manifestations in Patients with SARS-CoV-2: Early Experience from California

George Cholankeril, MD, Alexander Podboy, MD, Vasiliki Irene Aivaliotis, MD, Branden Tarlow, MD, PhD, Edward A. Pham, MD, PhD, Sean Spencer, MD, PhD, Donghee Kim, MD, PhD, Ann Hsing, PhD, Aijaz Ahmed, MD

PII: S0016-5085(20)30471-6
DOI: https://doi.org/10.1053/j.gastro.2020.04.008
Reference: YGAST 63354

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Accepted Date: 4 April 2020

Please cite this article as: Cholankeril G, Podboy A, Aivaliotis VI, Tarlow B, Pham EA, Spencer S, Kim D, Hsing A, Ahmed A, High Prevalence of Concurrent Gastrointestinal Manifestations in Patients with SARS-CoV-2: Early Experience from California, *Gastroenterology* (2020), doi: https://doi.org/10.1053/j.gastro.2020.04.008.

In summary, our results add to the growing body of literature that note a significant proportion of concurrent gastrointestinal manifestations related to the SARS-CoV-2.

Elevation in AST levels was the lone variable correlated to disease activity.

Journal Pre-proof

Why does SARS-CoV-2 invade the gastrointestinal epithelium?

Yoshiharu Uno, MD, PhD

PII: S0016-5085(20)30469-8
DOI: https://doi.org/10.1053/j.gastro.2020.04.006
Reference: YGAST 63352

To appear in: *Gastroenterology*
Accepted Date: 2 April 2020

These facts indicate that for individuals with blood group A, the route of viral transmission is likely to include the risk of gastrointestinal infections, in addition to those of the respiratory tract. There are also concerns that users of drugs such as proton pump inhibitors or potassium-competitive acid blockers for treating gastroesophageal reflux disease—regardless of whether they have blood type A, chronic gastritis, or HP infection—may be similarly at risk.

Biologie

- J Infect. 2020 Apr 10. pii: S0163-4453(20)30177-8. doi: 10.1016/j.jinf.2020.03.049. [Epub ahead of print]
- **Dynamics of Faecal SARS-CoV-2 in Infected Children during the Convalescent Phase.**
- Xing Y[1], Ni W[2], Wu Q[2], Li W[2], Li G[2], Wang W[2], Tong J[2], Song X[2], Wong GWK[3], Xing Q[4].

Journal Pre-proof

Dynamics of Faecal SARS-CoV-2 in Infected Children during the Convalescent Phase

Yuhan Xing , Wei Ni , Qin Wu , Wenjie Li , Guoju Li , Wendi Wang , Jianning Tong , Xiufeng Song , Gary Wing Kin Wong , Quansheng Xing

PII: S0163-4453(20)30177-8
DOI: https://doi.org/10.1016/j.jinf.2020.03.049
Reference: YJINF 4523

To appear in: *Journal of Infection*

Accepted date: 26 March 2020

Please cite this article as: Yuhan Xing , Wei Ni , Qin Wu , Wenjie Li , Guoju Li , Wendi Wang , Jianning Tong , Xiufeng Song , Gary Wing Kin Wong , Quansheng Xing , Dynamics of Faecal SARS-CoV-2 in Infected Children during the Convalescent Phase, *Journal of Infection* (2020), doi: https://doi.org/10.1016/j.jinf.2020.03.049

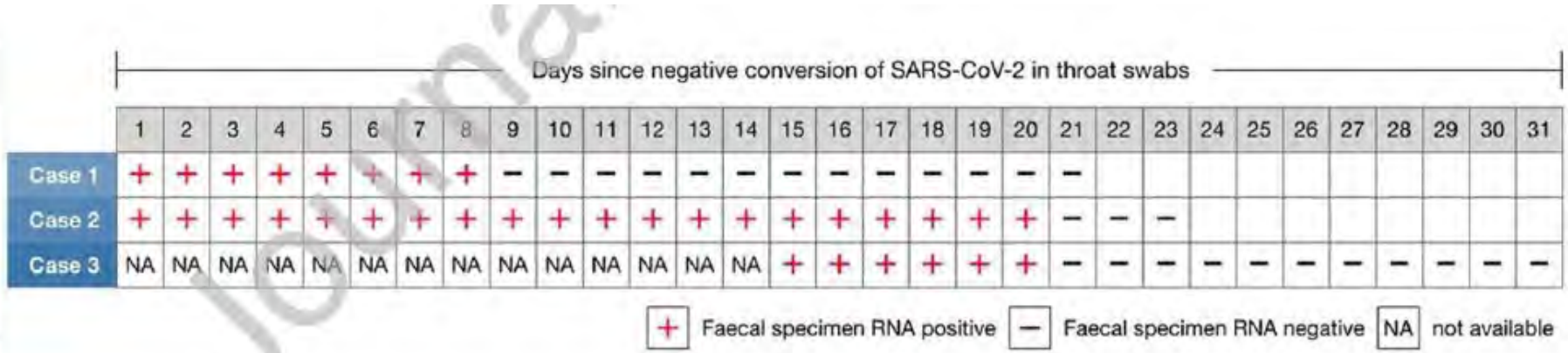

Figure 1. Timeline for Detection of SARS-CoV-2 RNA in Respiratory and Faecal Specimens

Days since negative conversion of viral RNA in throat swabs are shown in numbers with grey boxes. Boxes with red plus sign denote the days when faecal specimens were positive for reverse transcription PCR testing. Boxes with minus sign represent the days when viral RNA was not detectable in faecal samples. NA means faecal specimen was not collected from the patient on that day and laboratory result was not available.

- Infect Control Hosp Epidemiol. 2020 Apr 7:1-4. doi: 10.1017/ice.2020.114. [Epub ahead of print] **Alert for SARS-CoV-2 infection caused by fecal aerosols in rural areas in China.**
- Meng X[1], Huang X[1], Zhou P[1], Li C[1], Wu A[1].

Epidémiologie

- Cochrane Database Syst Rev. 2020 Apr 8;4:CD013574. doi: 10.1002/14651858.CD013574.
- **Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review.**
- Nussbaumer-Streit B[1], Mayr V[1], Dobrescu AI[1], Chapman A[1], Persad E[1], Klerings I[1], Wagner G[1], Siebert U[2,3,4,5], Christof C[1], Zachariah C[1], Gartlehner G[1,6].

- **AUTHORS' CONCLUSIONS:**
- Current evidence for COVID-19 is limited to modelling studies that make parameter assumptions based on the current, fragmented knowledge. Findings consistently indicate that quarantine is important in reducing incidence and mortality during the COVID-19 pandemic. Early implementation of quarantine and combining quarantine with other public health measures is important to ensure effectiveness. In order to maintain the best possible balance of measures, decision makers must constantly monitor the outbreak situation and the impact of the measures implemented. Testing in representative samples in different settings could help assess the true prevalence of infection, and would reduce uncertainty of modelling assumptions. This review was commissioned by WHO and supported by Danube-University-Krems.

- J Hosp Infect. 2020 Apr 4. pii: S0195-6701(20)30174-2. doi: 10.1016/j.jhin.2020.03.036. [Epub ahead of print]
- **Risk of nosocomial transmission of coronavirus disease 2019: an experience in a general ward setting in Hong Kong.**
- Wong SC[1], Kwong RT[2], Wu TC[2], Chan JWM[2], Chu MY[2], Lee SY[3], Wong HY[3], Lung DC[4].

Abstract

BACKGROUND:

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan in December 2019 and has rapidly spread across different cities within and outside China. Hong Kong started to prepare for COVID-19 on 31st December 2019 and infection control measures in public hospitals were tightened to limit nosocomial transmission within healthcare facilities. However, the recommendations on the transmission-based precautions required for COVID-19 in hospital settings vary from droplet and contact precautions, to contact and airborne precautions with placement of patients in airborne infection isolation rooms.

AIM:

To describe an outbreak investigation of a patient with COVID-19 who was nursed in an open cubicle of a general ward before the diagnosis was made.

METHOD:

Contacts were identified and risk categorized as 'close' or 'casual' for decisions on quarantine and/or medical surveillance. Respiratory specimens were collected from contacts who developed fever, and/or respiratory symptoms during the surveillance period and were tested for SARS-CoV-2.

FINDINGS:

A total of 71 staff and 49 patients were identified from contact tracing, seven staff and 10 patients fulfilled the criteria of 'close contact'. At the end of 28-day surveillance, 76 tests were performed on 52 contacts and all were negative, including all patient close contacts and six of the seven staff close contacts. The remaining contacts were asymptomatic throughout the surveillance period.

CONCLUSION:

Our findings suggest that SARS-CoV-2 is not spread by an airborne route, and nosocomial transmissions can be prevented through vigilant basic infection control measures, including wearing of surgical masks, hand and environmental hygiene.

Recos

Journal Pre-proof

Highlights for management of patients with Autoimmune Liver Disease during COVID-19 pandemia

Ana Lleo, Pietro Invernizzi, Ansgar W. Lohse, Alessio Aghemo, Marco Carbone

PII: S0168-8278(20)30212-9

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ACUTE AUTOIMMUNE LIVER DISEASE

CHRONIC AUTOIMMUNE LIVER DISEASE

NON-CIRRHOSIS

CURRENT KNOWLEDGE:
- AIH may present acute onset and jaundice in non cirrhotic patients
- Mild alteration of liver tests in non cirrhotic patients are not associated with a high risk of progression

LIVER CLINIC:
- Avoid invasive diagnostic procedures that require access to the hospital (i.e. liver biopsy)
- Start empiric therapy using web-based consultation
- Establish a sort term web-based follow-up to define drug efficacy

PATIENTS:
- Avoid contact with anybody who has symptoms of a respiratory infection
- Minimise the time any infected household spend in shared spaces
- Wash your hands often
- Strictly respect isolation protocols
- Contact your GP and/or hepatologist in case respiratory symptoms or fever

CURRENT KNOWLEDGE:
- Immunosuppressed patients do not seem to be at increased risk of acute respiratory distress syndrome
- a flare of autoimmune liver disease would require a high dose of steroids and potentially increased risk

LIVER CLINIC:
- Postpone medical visits until the emergency is over
- Send general information and recommendations to your patients (i.e. mailing list, medical association, ERN)
- Use web-based consultation upon request
- Organize drug dispensation with the local pharmacy

PATIENTS:
- Continue immunosuppressive drugs in unchanged doses
- Wash your hands often
- Avoid contact with anybody who has symptoms of a respiratory infection
- Strictly respect isolation protocols
- Minimise the time any infected household spend in shared spaces
- Contact your GP/hepatologist in case of respiratory symptoms or fever

CIRRHOSIS

CURRENT KNOWLEDGE:
- Acute onset AIH can rapidly progress and requires urgent care
- Acute complications in AILD, e.g. obstructive jaundice and severe cholangitis in PSC, GI bleeding, are associated with high short-term mortality.

LIVER CLINIC:
- Organize an independent flow for urgent access to the hospital; if possible, use separate ER access
- Avoid endoscopy if possible, follow local protocols if needed
- Start steroids at the usual dose for treatment and Coordinate with the Transplant Center
- in case of infection be timely in tapering steroids and immunosop.

PATIENTS:
- In case of jaundice, bleeding or ascites contact the Local Emergency Number and your hepatologist
- Strictly respect isolation protocols
- Minimise the time any infected household spend in shared spaces
- Wash your hands often
- Strictly respect isolation protocols

CURRENT KNOWLEDGE:
- Decompensated cirrhotic patients (ascites, GI bleeding, hepatic encephalopathy, and jaundice) present a poor prognosis
- Decompensated patients require strict monitoring in order to avoid further complications

LIVER CLINIC:
- Postpone non-urgent medical visits until the emergency is over
- Organize an independent flow for urgent procedures (i.e. paracentesis); if possible, use separate (COVID-free) facility or home care
- Monitor your patients using a web-based system

PATIENTS:
- Wash your hands often
- Strictly respect isolation protocols
- Minimise the time any infected household spend in shared spaces
- Continue immunosuppressive drugs in unchanged doses
- Contact your GP in case of any symptoms
- Monitor weight and urinary quantity and keep a diary

General Practitioner (GP), European Reference Network (ERN), Autoimmune Liver Diseases (AILD), Autoimmune Hepatitis (AIH), Primary Sclerosing Cholangitis (PSC), Gastrointestinal (GI), Emergency Room (ER)

Traitement

- J Infect. 2020 Apr 10. pii: S0163-4453(20)30168-7. doi: 10.1016/j.jinf.2020.03.039. [Epub ahead of print]
- **Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-1.**
- Fang X, Mei Q, Yang T, Li L, Wang Y, Tong F, Geng S, Pan A.

ARTICLE IN PRESS

JID: YJINF [m5G;April 14, 2020;12:42]

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ELSEVIER

Letter to the Editor

Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19

methylprednisolone [median hydrocortisone-equivalent dose, 250.0 mg/day (IQR, 250.0-250.0 mg/day)] was administered to 16 patients in the severe group for a median duration of 4.5 days (IQR,

In conclusion, low-dose corticosteroid therapy may not delay viral clearance in patients with COVID-19; however, this still needs to be confirmed by well-designed and large-scale RCTs with a longer follow-up duration.

The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis

Zhenwei Yang , Jialong Liu , Yunjiao Zhou , Xixian Zhao , Qiu Zhao , Jing Liu

PII: S0163-4453(20)30191-2
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Reference: YJINF 4536

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Abstract

OBJECTIVES:

An outbreak of novel coronavirus in 2019 threatens the health of people, and there is no proven pharmacological treatment. Although corticosteroids were widely used during outbreaks of severe acute respiratory syndrome and Middle East respiratory syndrome, their efficacy remains highly controversial. We aimed to further evaluate the influence of corticosteroids on patients with coronavirus infection.

METHODS:

We conducted a comprehensive literature search from January 1, 2002 to March 15, 2020 in the PubMed, Embase, Cochrane library, and China national knowledge infrastructure (CNKI). All statistical analyses in this study were performed on stata14.0.

RESULTS:

A total of 5270 patients from 15 studies were included in this meta-analysis. The result indicated that critical patients were more likely to require corticosteroids therapy (risk ratio [RR]=1.56, 95% confidence interval [CI]=1.28-1.90, P<0.001). However, corticosteroid treatment was associated with higher mortality (RR=2.11, 95%CI=1.13-3.94, P=0.019), longer length of stay (weighted mean difference [WMD]=6.31, 95%CI=5.26-7.37, P<0.001), a higher rate of bacterial infection (RR=2.08, 95%CI=1.54-2.81, P<0.001), and hypokalemia (RR=2.21, 95%CI=1.07-4.55, P=0.032) but not hyperglycemia (RR=1.37, 95%CI=0.68-2.76, P=0.376) or hypocalcemia (RR=1.35, 95%CI=0.77-2.37, P=0.302).

CONCLUSIONS:

Patients with severe conditions are more likely to require corticosteroids. Corticosteroid use is associated with increased mortality in patients with coronavirus pneumonia.

Conclusions

Patients with severe conditions were more likely to require corticosteroids.

Corticosteroids could lead to higher mortality, longer LOS, a higher rate of bacterial infection and hypokalemia.

Therefore, corticosteroid should be used with caution in the treatment of COVID-19.

Corticosteroids are not recommended for patients with mild conditions, and moderate corticosteroids can be used in patients with severe conditions to suppress the immune response and reduce symptoms.

Nevertheless, further multicenter clinical trials are needed to further verify this conclusion.

- Int J Rheum Dis. 2020 Apr 13. doi: 10.1111/1756-185X.13842. [Epub ahead of print]
- **A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in Coronavirus Disease-19 (COVID-19).**
- Shah S[1], Das S[2], Jain A[3], Misra DP[4], Negi VS[1].

Abstract

OBJECTIVE:

The pandemic Coronavirus Disease-19 (COVID-19) has pushed the global healthcare system to a crisis and amounted to a huge economic burden. Different drugs for prophylaxis against COVID-19 including chloroquine (CQ) or hydroxychloroquine (HCQ) have been tried. This study was performed to systematically review the role of CQ and HCQ in preventing the spread of COVID-19.

METHODS:

PubMed, EMBASE, ClinicalTrials.gov, ICTRP, and Cochrane Library databases were searched for studies that evaluated the prophylactic role of CQ or HCQ on SARS-CoV-2 (pre-clinical studies) or COVID-19 (clinical studies) until 30 March 2020. The available literature was critically appraised.

RESULTS:

A total of 45 articles were screened and five (three in vitro pre-clinical studies and two clinical opinions) were included. The pre-clinical studies showed the prophylactic effects of CQ and HCQ against SARS-CoV-2. On the other hand, the clinical opinions advocated the prophylactic use of CQ and HCQ against COVID-19. However, no original clinical studies on the prophylactic role of CQ or HCQ on COVID-19 were available.

CONCLUSION:

Although pre-clinical results are promising, till date, there is dearth of evidence to support the efficacy of CQ or HCQ in preventing COVID-19. Considering potential safety issues and the likelihood of imparting a false sense of security, prophylaxis with CQ or HCQ against COVID-19 needs to be thoroughly evaluated in observational studies or high quality randomized controlled studies.

- N Engl J Med. 2020 Apr 10. doi: 10.1056/NEJMoa2007016. [Epub ahead of print]
- **Compassionate Use of Remdesivir for Patients with Severe Covid-19.**
- Grein J[1], Ohmagari N[1], Shin D[1], Diaz G[1], Asperges E[1], Castagna A[1], Feldt T[1], Green G[1], Green ML[1], Lescure FX[1], Nicastri E[1], Oda R[1], Yo K[1], Quiros-Roldan E[1], Studemeister A[1], Redinski J[1], Ahmed S[1], Bernett J[1], Chelliah D[1], Chen D[1], Chihara S[1], Cohen SH[1], Cunningham J[1], D'Arminio Monforte A[1], Ismail S[1], Kato H[1], Lapadula G[1], L'Her E[1], Maeno T[1], Majumder S[1], Massari M[1], Mora-Rillo M[1], Mutoh Y[1], Nguyen D[1], Verweij E[1], Zoufaly A[1], Osinusi AO[1], DeZure A[1], Zhao Y[1], Zhong L[1], Chokkalingam A[1], Elboudwarej E[1], Telep L[1], Timbs L[1], Henne I[1], Sellers S[1], Cao H[1], Tan SK[1], Winterbourne L[1], Desai P[1], Mera R[1], Gaggar A[1], Myers RP[1], Brainard DM[1], Childs R[1], Flanigan T[1].

Abstract

BACKGROUND:

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

METHODS:

We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

RESULTS:

Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

CONCLUSIONS:

In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.).

- Ecancermedicalscience. 2020 Mar 30;14:1023. doi: 10.3332/ecancer.2020.1023. eCollection 2020.
- **COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting?**
- Russell B[1,2], Moss C[1,2], Rigg A[3], Van Hemelrijck M[1].

- **Abstract**
- Given the current SARS-CoV-2 (COVID-19) pandemic, the availability of reliable information for clinicians and patients is paramount. There have been a number of reports stating that non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may exacerbate symptoms in COVID-19 patients. Therefore, this review aimed to collate information available in published articles to identify any evidence behind these claims with the aim of advising clinicians on how best to treat patients. This review found no published evidence for or against the use of NSAIDs in COVID-19 patients. Meanwhile, there appeared to be some evidence that corticosteroids may be beneficial if utilised in the early acute phase of infection, however, conflicting evidence from the World Health Organisation surrounding corticosteroid use in certain viral infections means this evidence is not conclusive. Given the current availability of literature, caution should be exercised until further evidence emerges surrounding the use of NSAIDs and corticosteroids in COVID-19

- Nutrients. 2020 Apr 2;12(4). pii: E988. doi: 10.3390/nu12040988.
- **Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths.**
- Grant WB[1], Lahore H[2], McDonnell SL[3], Baggerly CA[3], French CB[3], Aliano JL[3], Bhattoa HP[4].

Abstract

The world is in the grip of the COVID-19 pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D_3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D_3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.

ORIGINAL ARTICLE

Early High-Dose Vitamin D_3 for Critically Ill, Vitamin D–Deficient Patients

The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network*

ABSTRACT

BACKGROUND

Vitamin D deficiency is a common, potentially reversible contributor to morbidity and mortality among critically ill patients. The potential benefits of vitamin D supplementation in acute critical illness require further study.

METHODS

We conducted a randomized, double-blind, placebo-controlled, phase 3 trial of early vitamin D_3 supplementation in critically ill, vitamin D–deficient patients who were at high risk for death. Randomization occurred within 12 hours after the decision to admit the patient to an intensive care unit. Eligible patients received a single enteral dose of 540,000 IU of vitamin D_3 or matched placebo. The primary end point was 90-day all-cause, all-location mortality.

RESULTS

A total of 1360 patients were found to be vitamin D–deficient during point-of-care screening and underwent randomization. Of these patients, 1078 had baseline vitamin D deficiency (25-hydroxyvitamin D level, <20 ng per milliliter [50 nmol per liter]) confirmed by subsequent testing and were included in the primary analysis population. The mean day 3 level of 25-hydroxyvitamin D was 46.9±23.2 ng per milliliter (117±58 nmol per liter) in the vitamin D group and 11.4±5.6 ng per milliliter (28±14 nmol per liter) in the placebo group (difference, 35.5 ng per milliliter; 95% confidence interval [CI], 31.5 to 39.6). The 90-day mortality was 23.5% in the vitamin D group (125 of 531 patients) and 20.6% in the placebo group (109 of 528 patients) (difference, 2.9 percentage points; 95% CI, −2.1 to 7.9; P=0.26). There were no clinically important differences between the groups with respect to secondary clinical, physiological, or safety end points. The severity of vitamin D deficiency at baseline did not affect the association between the treatment assignment and mortality.

CONCLUSIONS

Early administration of high-dose enteral vitamin D_3 did not provide an advantage over placebo with respect to 90-day mortality or other, nonfatal outcomes among critically ill, vitamin D–deficient patients. (Funded by the National Heart, Lung, and Blood Institute; VIOLET ClinicalTrials.gov number, NCT03096314.)

- **No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial**
- Matthieu Mahevas, Viet-Thi Tran, Mathilde Roumier, Amelie Chabrol, Romain Paule, Constance Guillaud, Sebastien Gallien, Raphael Lepeule, Tali-Anne Szwebel, Xavier Lescure, Frederic Schlemmer, Marie Matignon, Mehdi Khellaf, Etienne Crickx, Benjamin Terrier, Caroline Morbieu, Paul Legendre, Julien Dang, Yoland Schoindre, Jean-Michel Pawlotski, Marc Michel, Elodie Perrodeau, Nicolas Carlier, Nicolas Roche, Victoire De Lastours, Luc Mouthon, Etienne Audureau, Philippe Ravaud, Bertrand Godeau, Nathalie Costedoat
- **doi:** https://doi.org/10.1101/2020.04.10.20060699

Abstract

Background Treatments are urgently needed to prevent respiratory failure and deaths from coronavirus disease 2019 (COVID-19). Hydroxychloroquine (HCQ) has received worldwide attention because of positive results from small studies. Methods We used data collected from routine care of all adults in 4 French hospitals with documented SARS-CoV-2 pneumonia and requiring oxygen ≥ 2 L/min to emulate a target trial aimed at assessing the effectiveness of HCQ at 600 mg/day. The composite primary endpoint was transfer to intensive care unit (ICU) within 7 days from inclusion and/or death from any cause. Analyses were adjusted for confounding factors by inverse probability of treatment weighting. Results This study included 181 patients with SARS-CoV-2 pneumonia; 84 received HCQ within 48 hours of admission (HCQ group) and 97 did not (no-HCQ group). Initial severity was well balanced between the groups. In the weighted analysis, 20.2% patients in the HCQ group were transferred to the ICU or died within 7 days vs 22.1% in the no-HCQ group (16 vs 21 events, relative risk [RR] 0.91, 95% CI 0.47-1.80). In the HCQ group, 2.8% of the patients died within 7 days vs 4.6% in the no-HCQ group (3 vs 4 events, RR 0.61, 95% CI 0.13-2.89), and 27.4% and 24.1%, respectively, developed acute respiratory distress syndrome within 7 days (24 vs 23 events, RR 1.14, 95% CI 0.65-2.00). Eight patients receiving HCQ (9.5%) experienced electrocardiogram modifications requiring HCQ discontinuation. Interpretation These results do not support the use of HCQ in patients hospitalised for documented SARS-CoV-2-positive hypoxic pneumonia.