COVID-19 and the Liver

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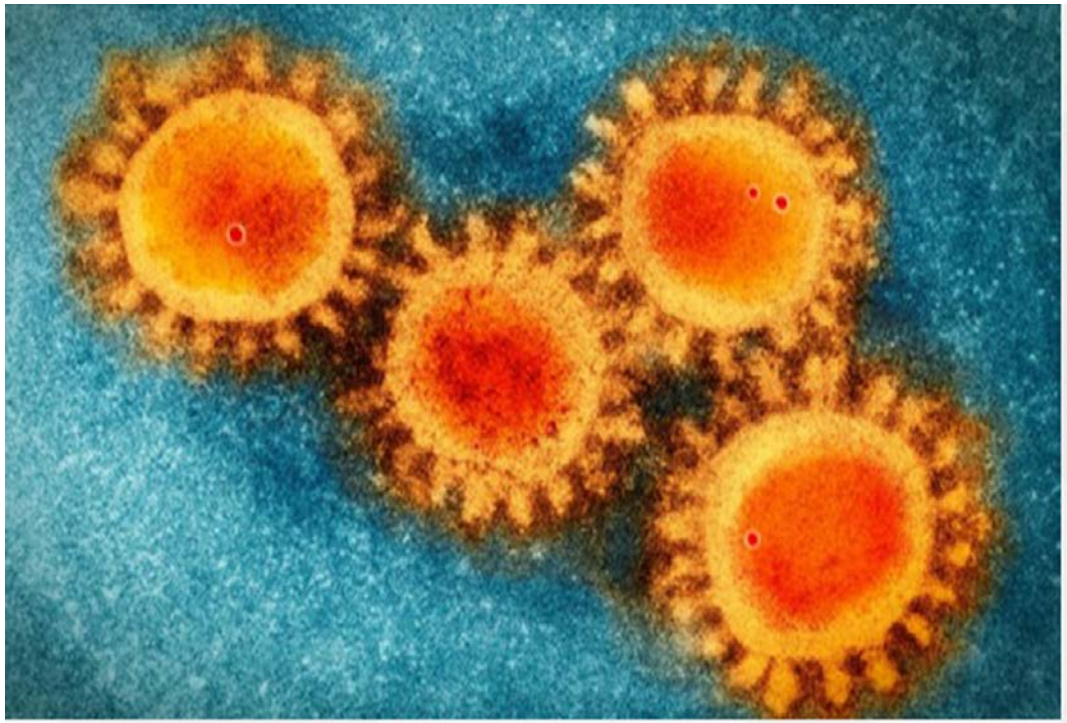
py photo of the coronavirus COVID-19 © iStockphoto

Disclosures

I have no financial disclosures

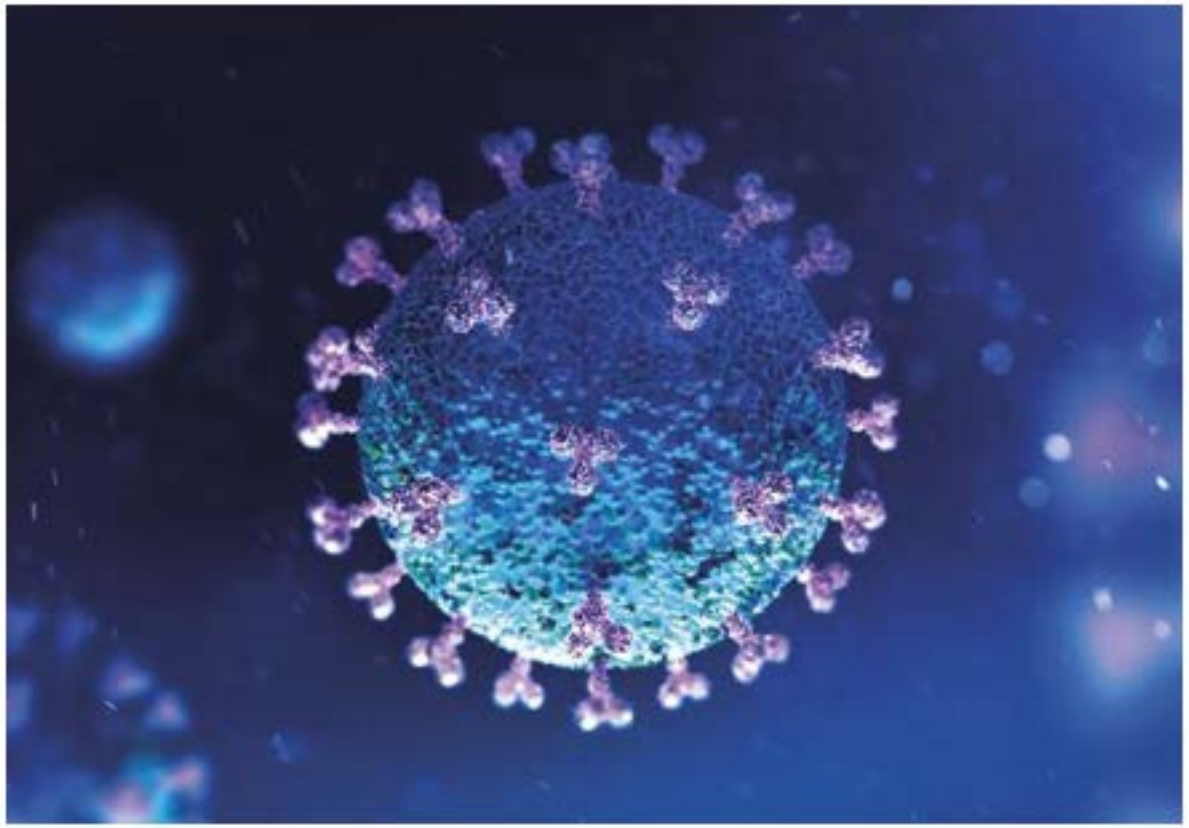
SARS-COV2 is a novel coronavirus



Colored visualisation of electron microscopy photo of the coronavirus COVID-19 © iStockphoto

- Single-stranded RNA viruses
- Common in mammals and birds
- “corona”= crown

COVID Transmission: resilient and contagious



https://www.electrooptics.com/feature/how-super-resolution-microscopy-can-reveal-coronavirus

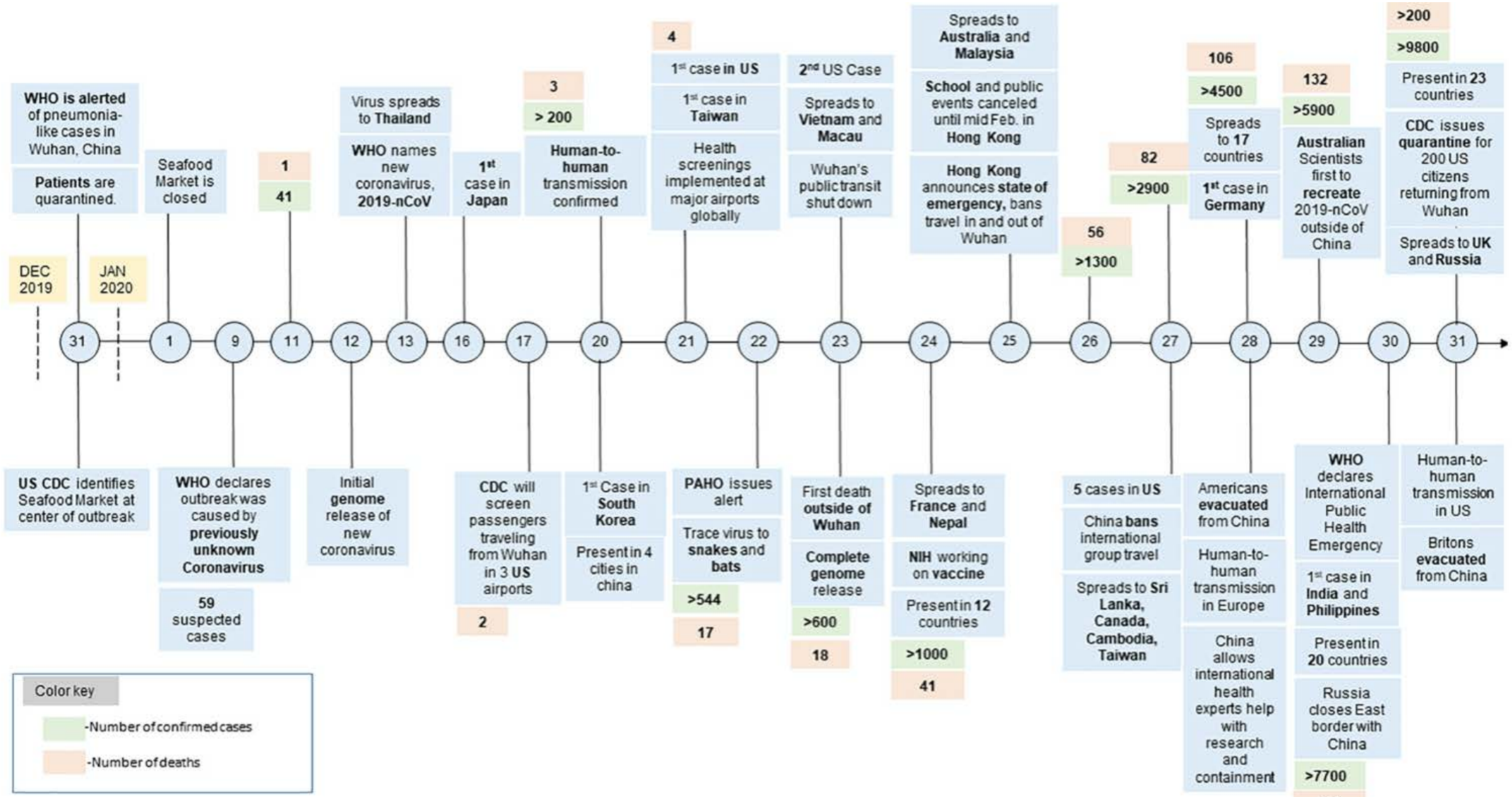
Transmission

- rapidly spreads
- spreads via sneezing, coughing and close contact
- remains viable 2 hours to 14 days
- Transmission (R0)
- R0 for COVID-19 = 2.2
- Doubling time of 7.2 days

The index COVID-19 cases identified in late December 2019

COVID-19 timeline

- Dec 2019
- Several cases of unexplained pneumonia in Wuhan, China
- Dec 31- WHO was alerted
- Jan 3-BAL from index identified presence of SARS-CoV2
- Mar 11- WHO declared a global pandemic



Zowalaty et al. Froms SARS to COVID-19: A previously unknown SARS-related coronavirus of pandemic potential infecting humans-CAll for a One Health approach: One Health, vol 9, June 2020.

SARS-CoV2 presents like a typical flu-like illness

Table 1. Spectrum of clinical manifestations and their frequency from recent studies on COVID-19 in China.

Clinical features	Wang *et al.*[22] n = 138	Zhou *et al.*[51] n = 191	Guan *et al.*[23] n = 1,099
Fever	98.6%	94%	88.7%
Cough	59.4%	79%	67.8%
Sputum	n.a.	23%	33.7%
Myalgia	n.a.	15%	14.9%
Fatigue	69.6%	23%	38.1%
Diarrhoea	n.a.	5%	3.8%
Nausea/vomiting	n.a.	4%	5.0%
Sore throat	n.a.	n.a.	13.9%
Lymphopenia ($<0.8 \times 10^9$/L)	70.3%	40%	n.a.
Prolonged PT (>13.5 seconds)	58%	n.a.	n.a.
Raised LDH (>261 U/L)	39.9%	n.a.	n.a.

COVID-19, coronavirus disease 2019; LDH, lactate dehydrogenase; PT, prothrombin time; n.a., data not available.

Journal of Hepatology **2020** vol. 73 | 1231–1240

Classification of severity may have significance when considering liver dysfunction

Table 2. Classification of COVID-19 into 3 groups based on severity of clinical manifestations by Chinese Center for Disease Control.[23]

Mild disease (reported in 81% cases)	Fever, dry cough, mild dyspnoea (respiratory rate <30/min).
Severe disease (reported in 14% cases)	Dyspnoea, respiratory rate >30 and/or lung infiltrates >50% within 24 to 48 hours.
Critical disease (reported in 5% cases)	Respiratory failure, septic shock and/or multiple organ dysfunction or failure.

COVID-19, coronavirus disease 2019.

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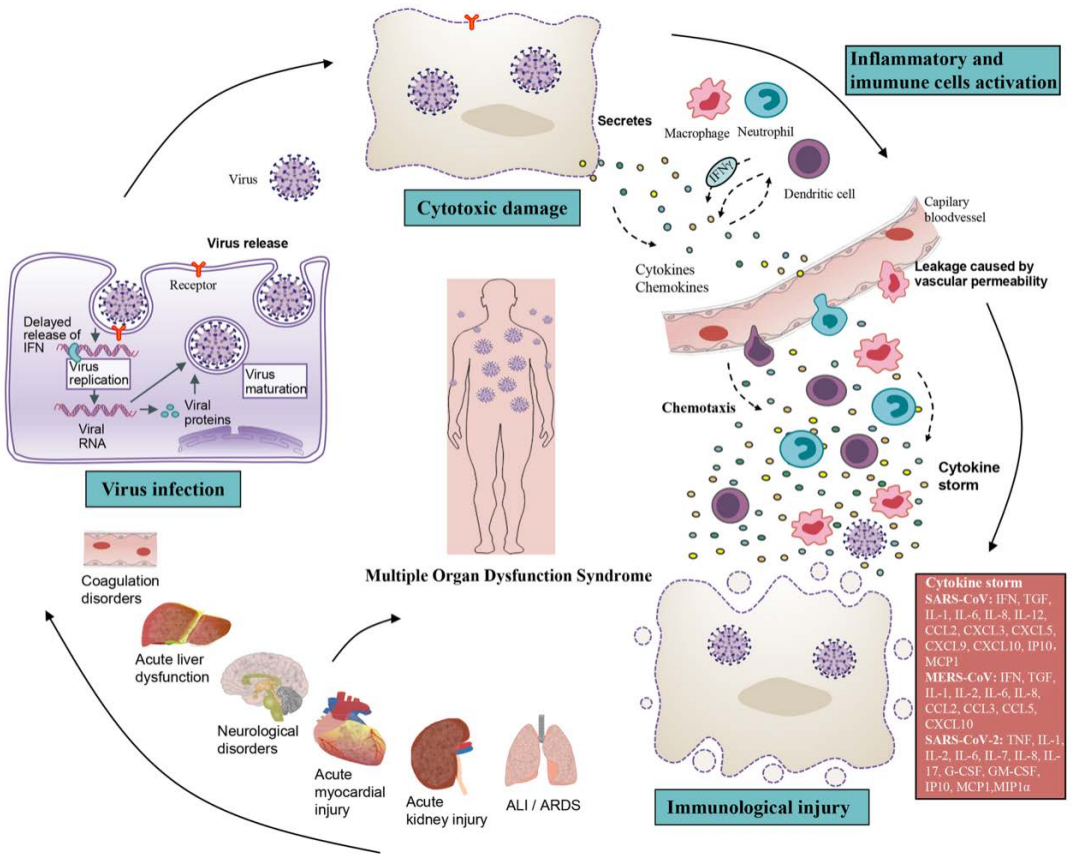
Liver function test abnormalities are one clinical feature of COVID-19 infection

	COVID-19 [94, 95, 98]	SARS [25, 97,98,99]	MERS [92, 93, 96, 98, 100]
Signs and symptoms			
Fever	56–99%	99–100%	81.7–100%
Fatigue	18–55%	31.2%	NA
Cough	39–81%	29.0–74.3%	75–85%
Sore throat	5–17%	11.0–23.2%	14
Dyspnea	12–41%	40–42%	72%
Myalgia	18–55%	49.3–60.9%	38
Diarrhea	3–17%	20–25%	26
Headache	4–23%	15.0–55.8%	NA
Complications			
ARDS	18–30%	20%	20–30%
AKI	3%	6.7%	41–50%
Laboratory findings			
Leukopenia ($< 4.0 \times 10^9$/L)	26.8%	23–35%	14%
Lymphopenia ($< 1.5 \times 10^9$/L)	55.3%	68–85%	32%
Thrombocytopenia ($< 150 \times 10^9$/L)	11.5%	40–45%	36%
Elevated LDH	55.5%	50–71%	48%
Elevated AST	17.9%	20–30%	14%
Elevated ALT	16.0%	20–30%	11%

LDH Lactate dehydrogenase, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *NA* Not available

From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses, Respiratory Research (21); article number 224. 2020

The mechanisms for liver injury is unknown

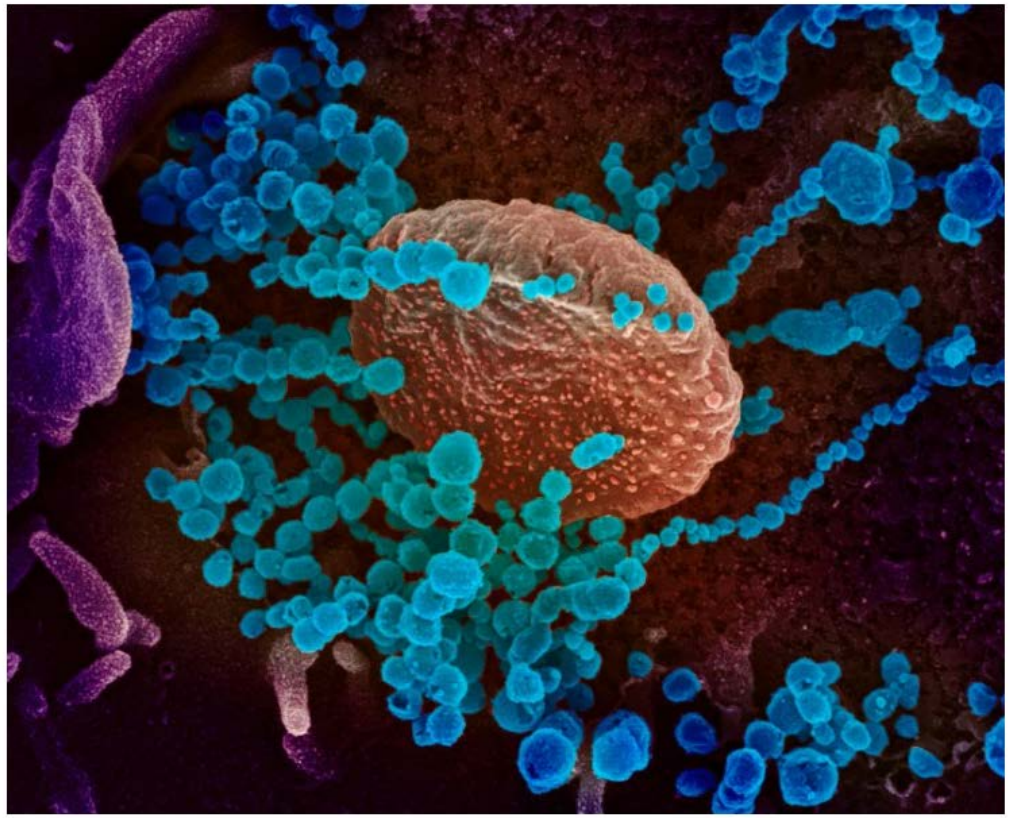


Mechanisms

- Direct cytopathic
- Uncontrolled immune reaction
- Sepsis
- Drug Induced Liver Injury

From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses, Respiratory Research (21); article number 224. 2020

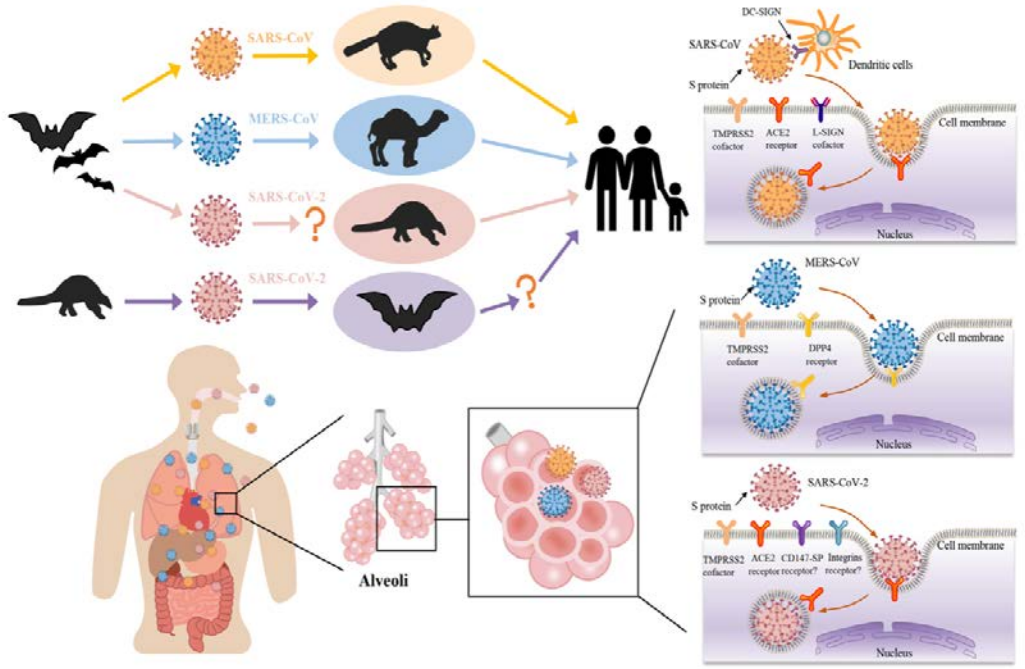
ACE-2 and TMPRSS are present in the liver



This image obtained on March 12 shows a scanning electron microscope image of SARS-CoV-2 (round blue objects) emerging from the surface of cells cultured in the lab, SARS-CoV-2, also known as 2019-nCoV, is the virus that causes COVID-19, the virus shown was isolated from a patient in the U.S. National Institutes of Health/AFP/Getty Images time. com

Fig. 1

From: From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses



The potential animal hosts, biodistribution and host cell receptors of SARS-CoV, MERS-CoV and SARS-CoV-2

From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses, Respiratory Research (21); article number 224. 2020

Liver function test may be a surrogate for severity of disease

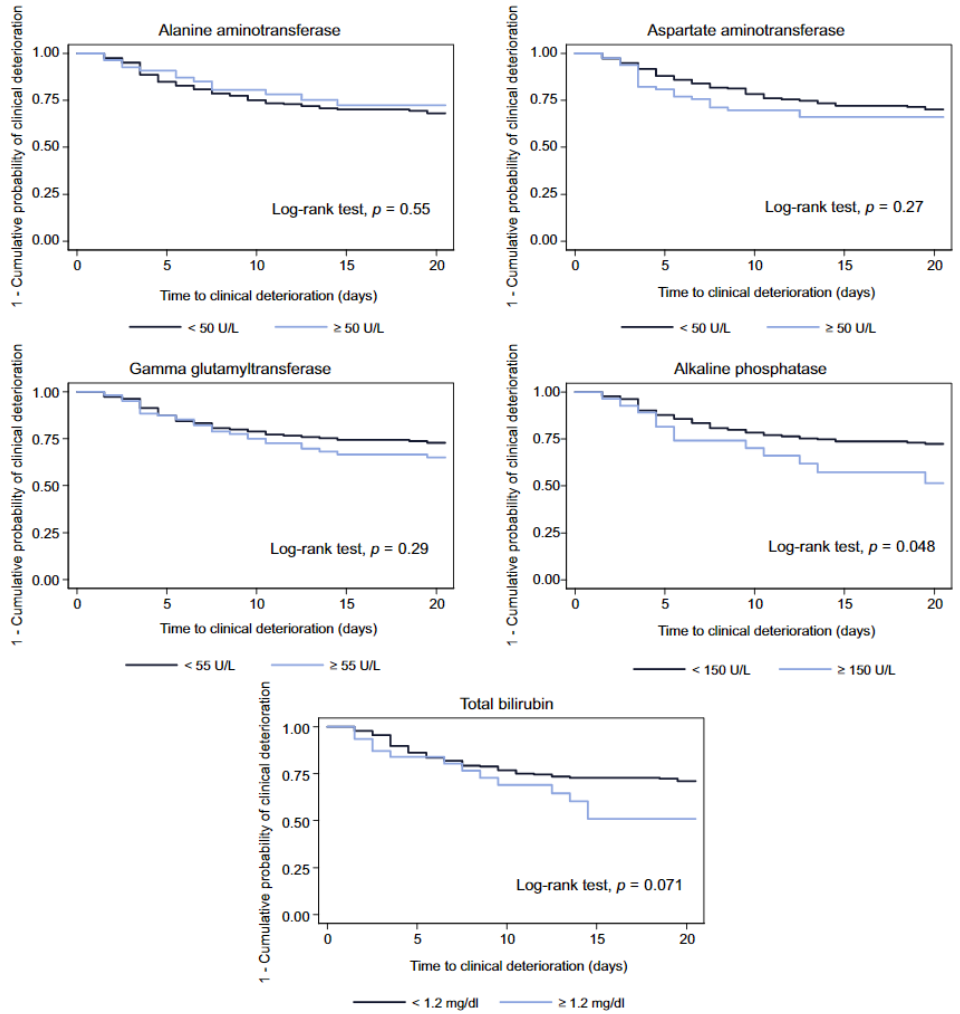


Fig. 1. Predictors of clinical deterioration leading to 'ICU transfer or death' in hospitalized patients with COVID-19: Univariable Kaplan-Meier survival curves.

Journal of Hepatology **2020** vol. 73 | 1257–1292

Remdesivir may also cause elevation in LFTs

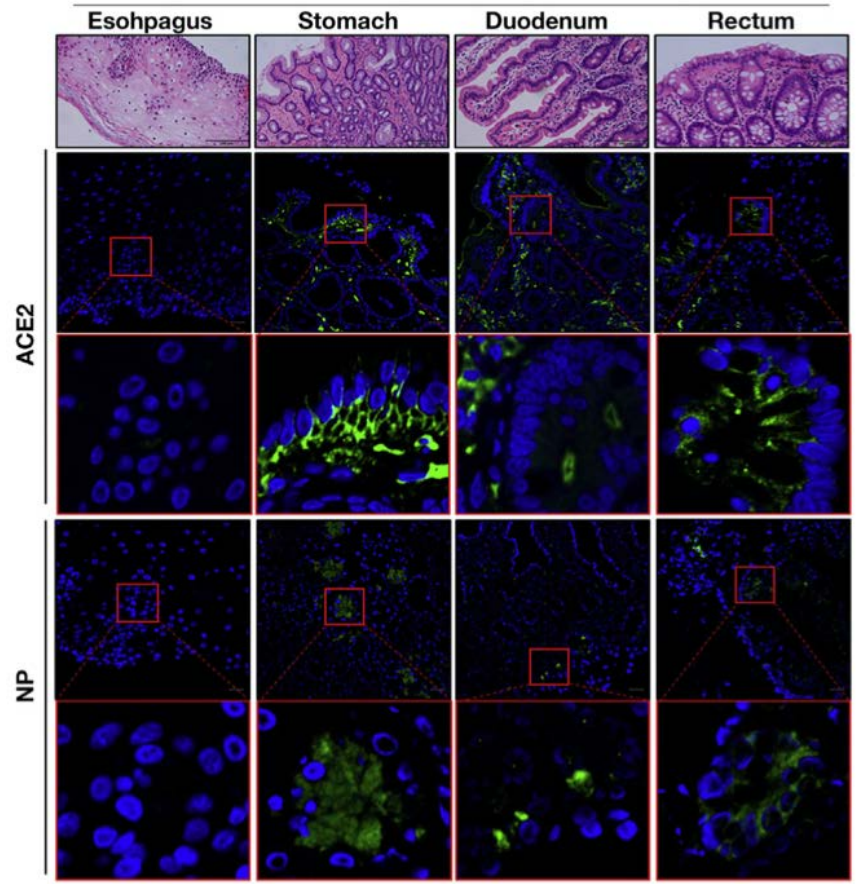
- Given intravenously
- 5 to 10 day infusion
- Converted intracellularly to an active triphosphate
- Competes with ATP for incorporation into viral RNA
- Mixed Outcomes regarding time to recovery and unclear mortality benefit
- Pattern of liver damage (predominantly hepatocellular R=12.3)
- Damage typically transient
- Some of the damage may be overshadowed and confounded by severity of COVID-19

GI tract is a possible mode of transmission

- SARS-CoV (2003) RNA was detected in stool
- Fecal-oral transmission possible
- SARS-CoV2 (3-79%) develop GI symptoms

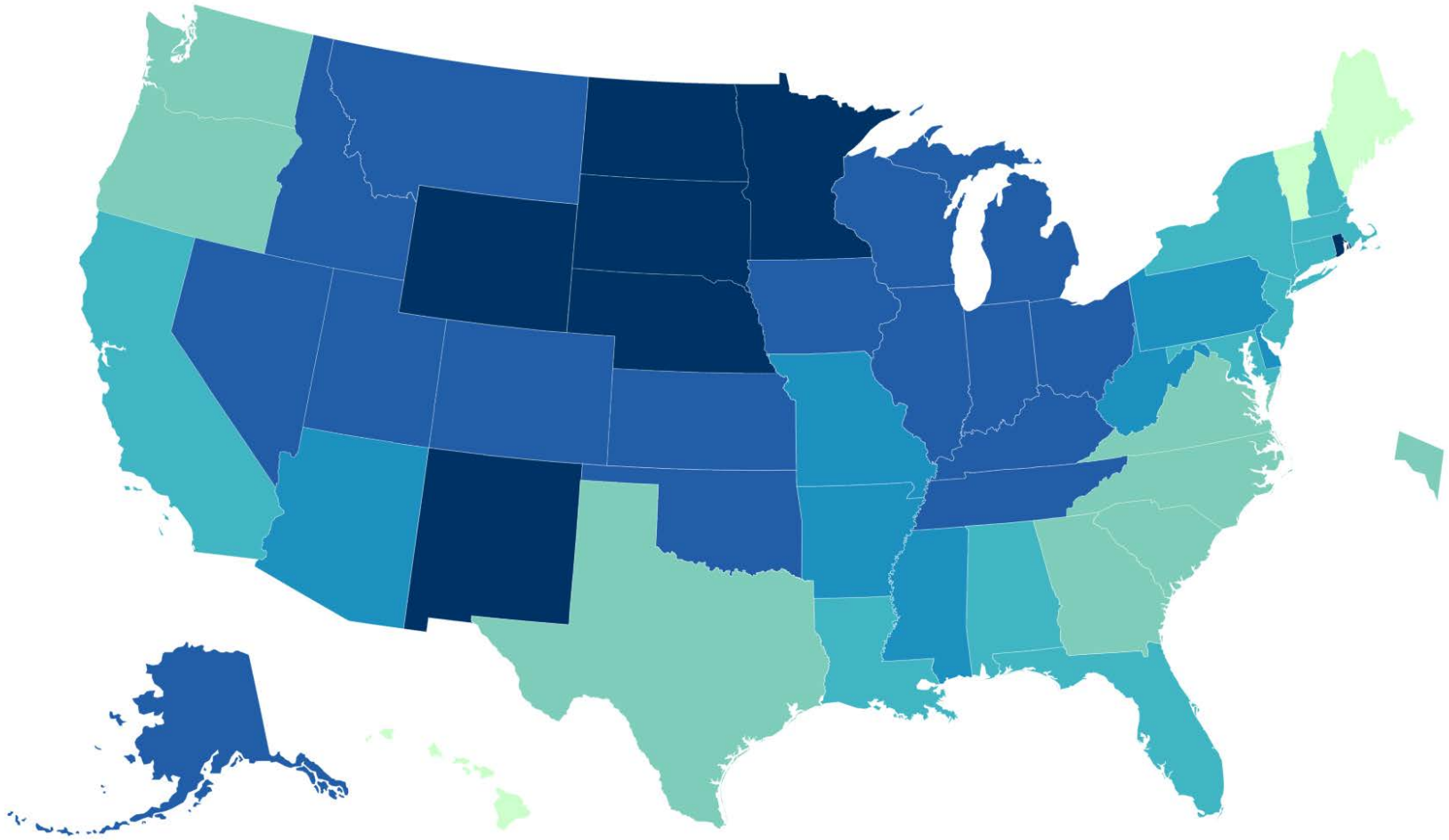
<u>73 patients (Xiao)</u>

- 53% +stool RNA
- 23% + stool RNA after negative respiratory sample



Gastroenterology 2020;158:1831–1833

US COVID-19 Average Daily Case Rate in Last 7 Days, by State/Territory (cases per 100K)



United States COVID-19 Cases and Deaths by State

Reported to the CDC since January 21, 2020

TOTAL CASES	AVERAGE DAILY CASES PER 100K IN LAST 7 DAYS	TOTAL DEATHS
13,626,022	49.2	269,763
+178,395 New Cases		+2,461 New Deaths

CDC | Updated: Dec 2 2020 12:50PM

A worldwide pandemic surging again

Worldwide

Total cases
65,686,172

New cases (14 days)

Nov 18–Dec 1: **+8,072,949**

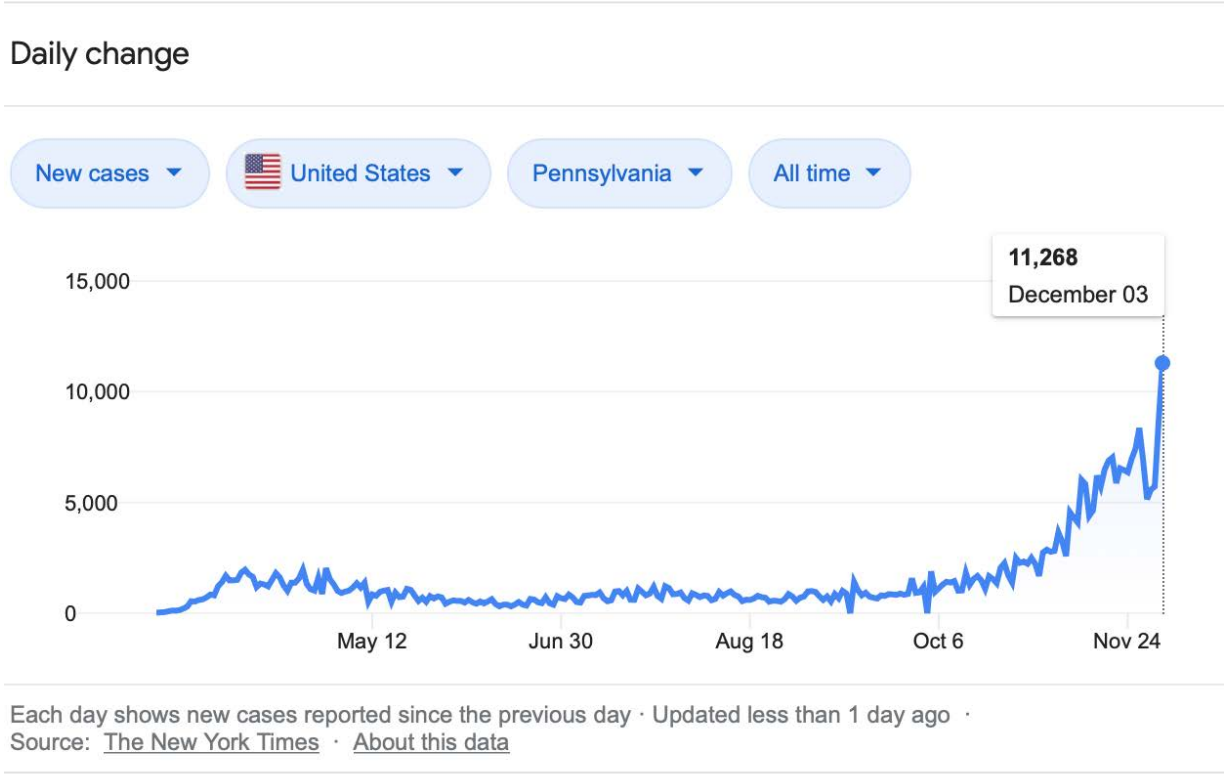
Deaths
1,514,549

Updated less than 1 hour ago • Source: Wikipedia

Cases

Location	Total cases ↓	New cases (1 day*)	New cases (last 60 days)	Cases per 1M people	Deaths
Worldwide	**65,686,172**	*No data*		**8,447**	**1,514,549**
United States	14,217,106	216,548		43,140	276,375
India	9,571,559	36,595		7,035	139,188
Brazil	6,487,084	50,434		30,695	175,270
Russia	2,354,934	27,829		16,048	41,173
France	2,255,912	12,661		33,632	53,791
Spain	1,675,902	10,127		35,581	46,038
United Kingdom	1,674,134	14,878		25,199	60,113

SARS-CoV2 has come to Pennsylvania



There are recognized disparities in liver health exacerbated by the COVID-19 pandemic

Problems

- Delay in **Diagnosis**
- Decreased **Access**
- Delay or Lack of **Treatment**
- Increased **Exposure**

Solutions

- Telemedicine
- Flexibility in resource allocation

(Human/Physical Plant/Machine/Medicine)

- Protection (PPE/Vaccinations)

COVID-19 HOSPITALIZATION AND DEATH BY AGE

FACTORS THAT INCREASE COMMUNITY SPREAD AND INDIVIDUAL RISK


CROWDED SITUATIONS


CLOSE / PHYSICAL CONTACT

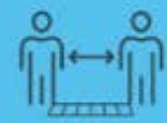

ENCLOSED SPACE


DURATION OF EXPOSURE

Rate ratios compared to 18-29 year olds	0-4 years	5-17 years	18-29 years	30-39 years	40-49 years	50-64 years	65-74 years	75-84 years	85+ years
HOSPITALIZATION[1]	4x lower	9x lower	Comparison Group	2x higher	3x higher	4x higher	5x higher	8x higher	13x higher
DEATH[2]	9x lower	16x lower	Comparison Group	4x higher	10x higher	30x higher	90x higher	220x higher	630x higher

ACTIONS TO REDUCE RISK OF COVID-19


WEARING A MASK


SOCIAL DISTANCING (6 FT GOAL)


HAND HYGIENE


CLEANING AND DISINFECTION

CDC

[1] Data source: COVID-NET (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html, accessed 08/06/20). Numbers are unadjusted rate ratios.

[2] Data source: NCHS Provisional Death Counts (https://www.cdc.gov/nchs/nvss/vsrr/COVID19/index.htm, accessed 08/06/20). Numbers are unadjusted rate ratios.

cdc.gov/coronavirus

CS319360-A 08/10/2020

COVID-19 Cases, Hospitalizations, and Deaths, by Race/Ethnicity

Rate ratios compared to White, Non-Hispanic persons	American Indian or Alaska Native, Non-Hispanic persons	Asian, Non-Hispanic persons	Black or African American, Non-Hispanic persons	Hispanic or Latino persons
Cases[1]	1.8x	0.6x	1.4x	1.7x
Hospitalization[2]	4.0x	1.2x	3.7x	4.1x
Death[3]	2.6x	1.1x	2.8x	2.8x

Race and ethnicity are risk markers for other underlying conditions that affect health, including socioeconomic status, access to health care, and exposure to the virus related to occupation, e.g., among frontline, essential, and critical infrastructure workers.

How to Slow the Spread of COVID-19

Wear a mask

Stay 6 feet apart

Wash your hands

References on back

cdc.gov/coronavirus

CS319360-A 11/30/2020

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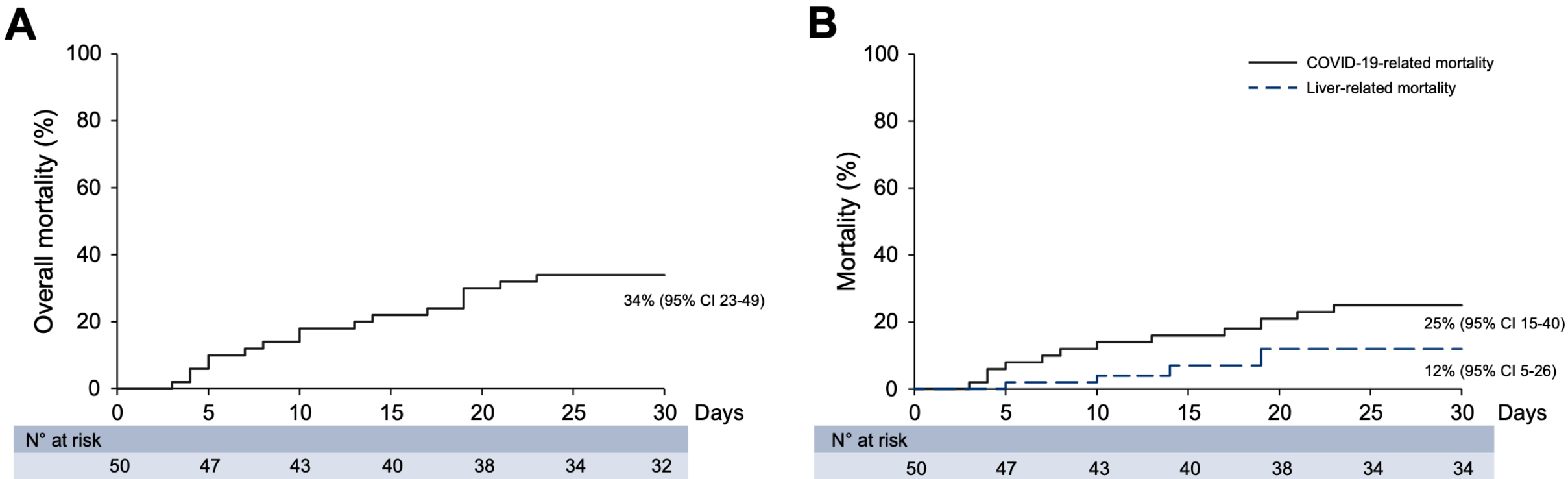

Fig. 1. 30-day cumulative probability of overall mortality and COVID-19-related or liver-related mortality. (A) 30-day cumulative probability of overall mortality and (B) 30-day cumulative probability of either COVID-19-related or liver-related mortality; survival curves were estimated by the Kaplan-Meier method.

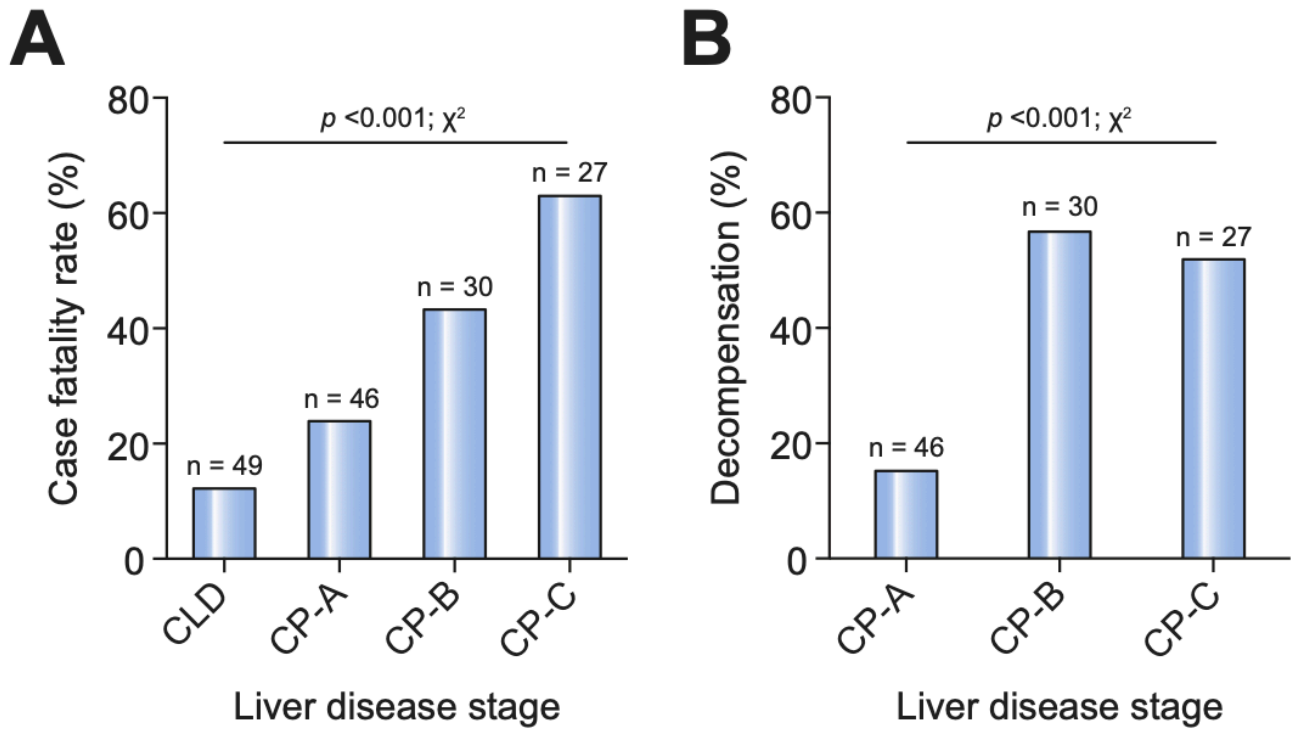

Fig. 1. Outcome in patients with non-cirrhotic chronic liver disease or cirrhosis with COVID-19. Graphs depict data from 152 submissions to COVID-Hep.net and COVIDCirrhosis.org registries between 25th March 2020 and 20th April 2020. (A) Case fatality rate by liver disease stage. (B) Rates of hepatic decompensation by stage of cirrhosis (defined as one or more of new or worsened ascites, spontaneous bacterial peritonitis, new or worsened hepatic encephalopathy, or variceal haemorrhage). *p* values derived using chi-squared test. CLD, chronic liver disease without cirrhosis; CP, Child-Pugh.

Moon et al. High mortality rates for SARS-CoV-2 infection in patients with pre-existing liver disease and cirrhosis. Journal of Hepatology, September 2020.

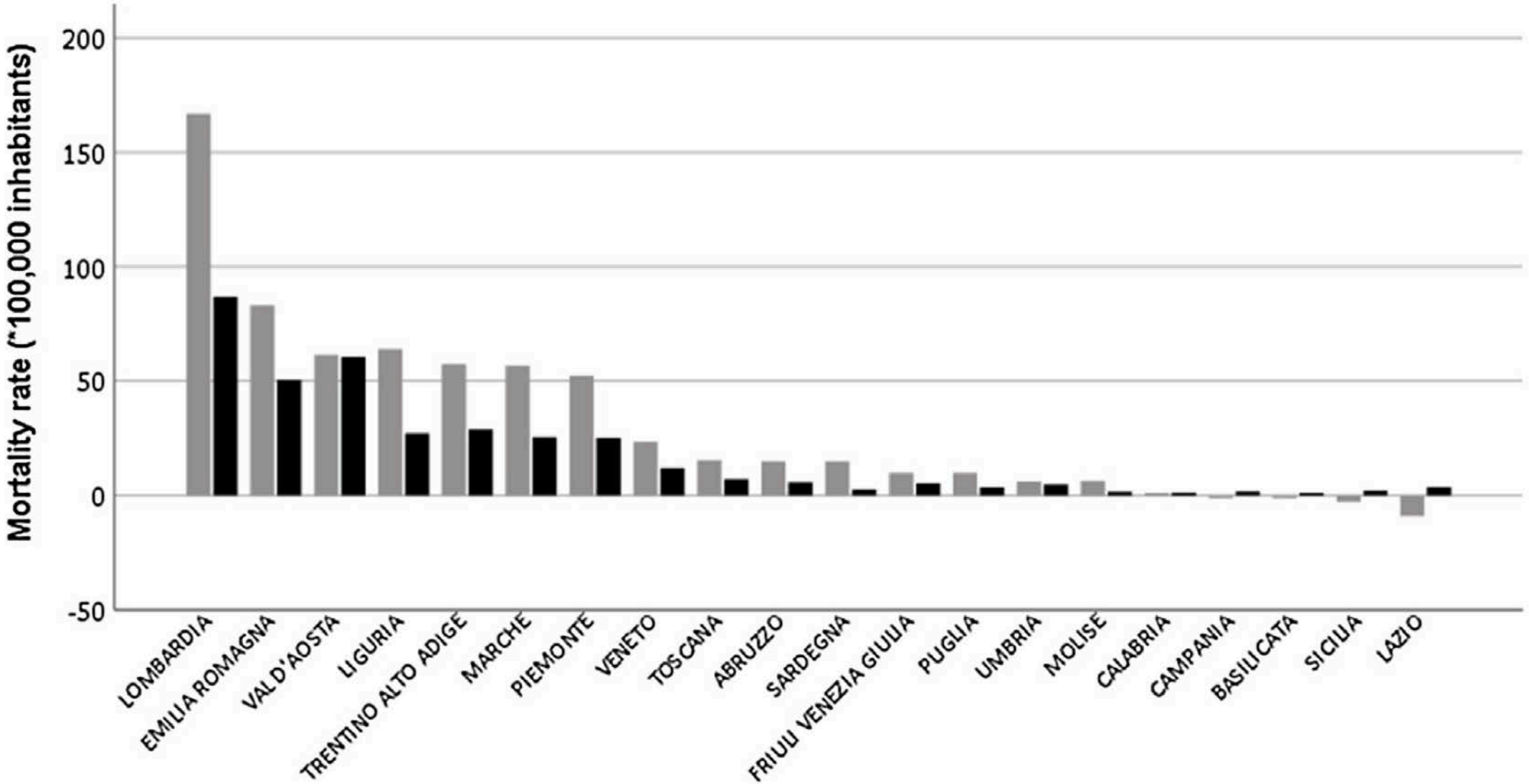

Figure 1. Excess 2020 (grey bars) and COVID-19 (black bars) mortality rates for different Italian regions.

Mannucci et al. Factors associated with increased all-cause mortality during the COVID-19 pandemic in Italy. International Journal of Infectious Diseases. September 2020.

Research Article
Viral Hepatitis

JOURNAL
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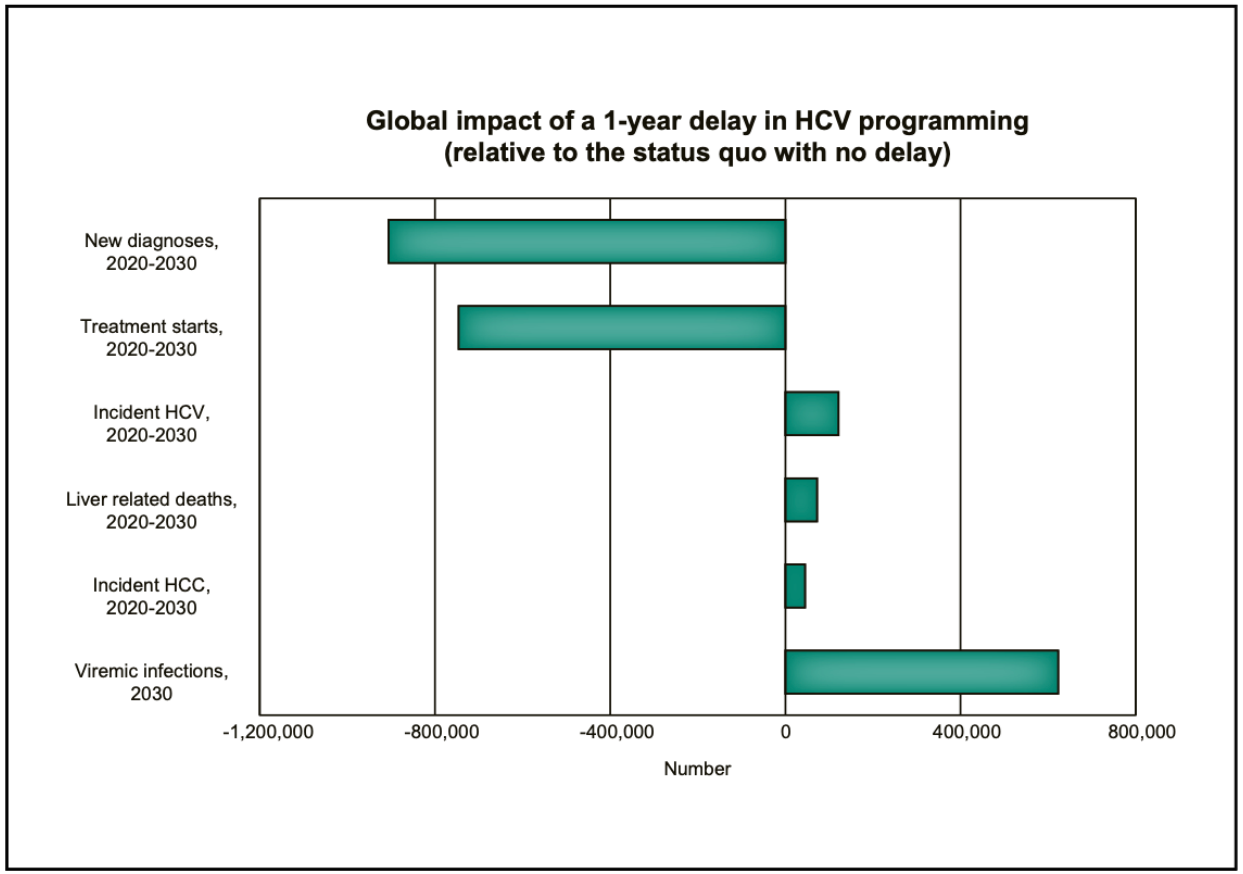
Impact of COVID-19 on global HCV elimination efforts



Organ procurement and transplantation during the COVID-19 pandemic

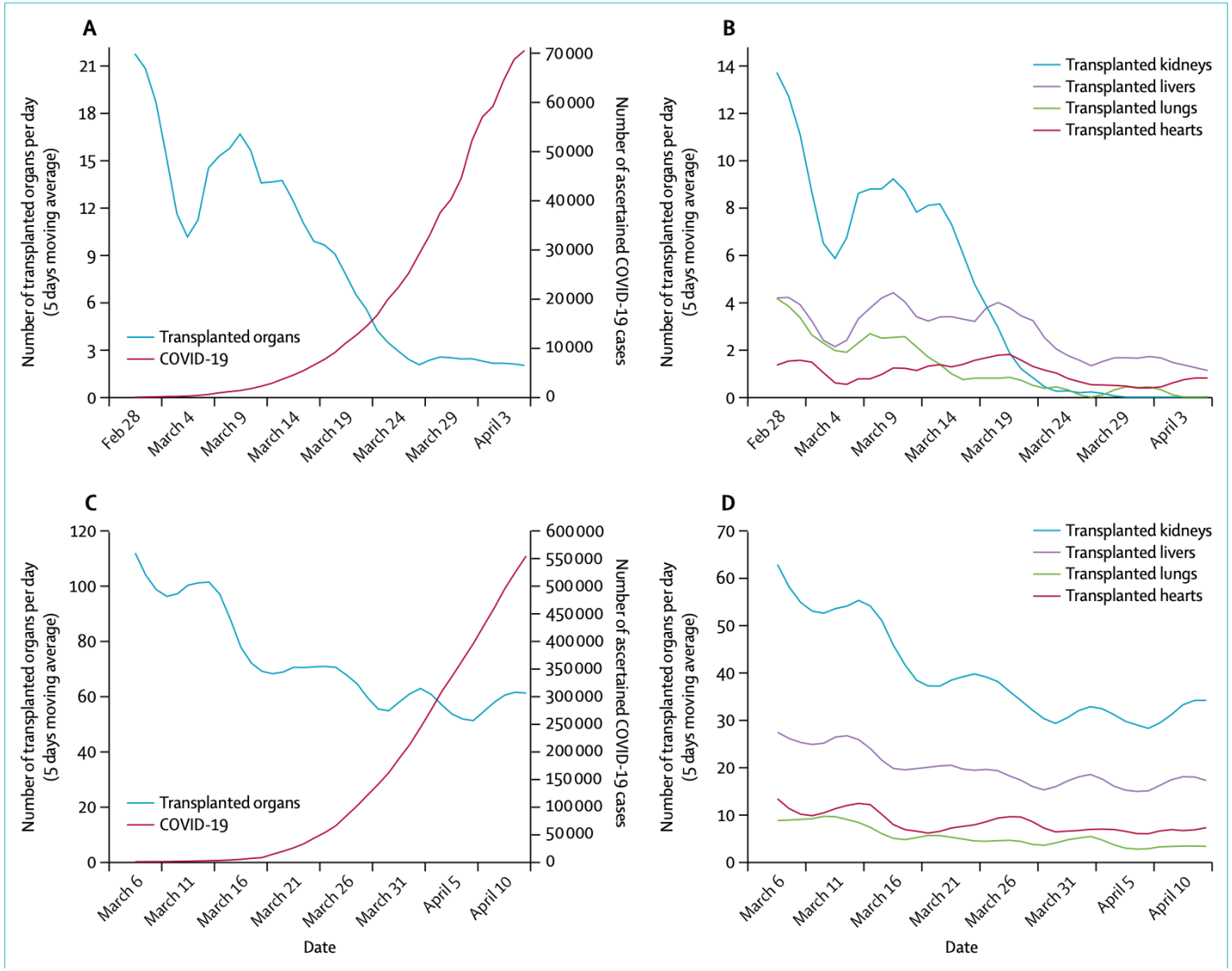


Figure: **Trends in COVID-19 spread over time in France and the USA and recovery of organs and solid-organ transplantation procedures from deceased donors**
Number of COVID-19 diagnoses and number of solid organs recovered for transplantation over time in France (A) and the USA (C). Total number of transplants from deceased donors, with separate trend lines for kidney, liver, heart, and lung, over time in France (B) and the USA (D). Data were obtained from Public Health France (A), the National Organ Procurement Agency (B), Xu et al[3] (C), and the United Network for Organ Sharing (D). Data accessed April 11, 2020. COVID-19=coronavirus disease 2019.

Loupy et al. Organ procurement and transplantation during the COVID-19 pandemic. Lancet. https://doi.org/10.1016/S0140-6736(20)31040-0

The New York Times

Covid Survivors With Long-Term Symptoms Need Urgent Attention, Experts Say

In a two-day meeting sponsored by the N.I.H., officials acknowledged an insufficient understanding of the issues and warned of a growing public health problem.

Chimére Smith, a teacher in Baltimore, has not been able to return to work since getting Covid in March. She said she has struggled for months to have her symptoms taken seriously by doctors. Schaun Champion for The New York Times

Our power to improve the health of our world lie in our equitable and sustainable solutions

- Chronic liver disease and cirrhosis have increased mortality from COVID-19
- Excess death in 2020 not fully accounted for by COVID-19
- International Hepatitis C elimination is at risk secondary to the COVID-19 pandemic
- Organ procurement and rate of transplantation decrease with the rise in COVID-19 cases
- There has been a longstanding pandemic of poverty, lack of access, treatment and diagnosis and COVID-19