COVID-19 Pandemic: What We Know to Date

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The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D., for the China Novel Coronavirus Investigating and Research Team

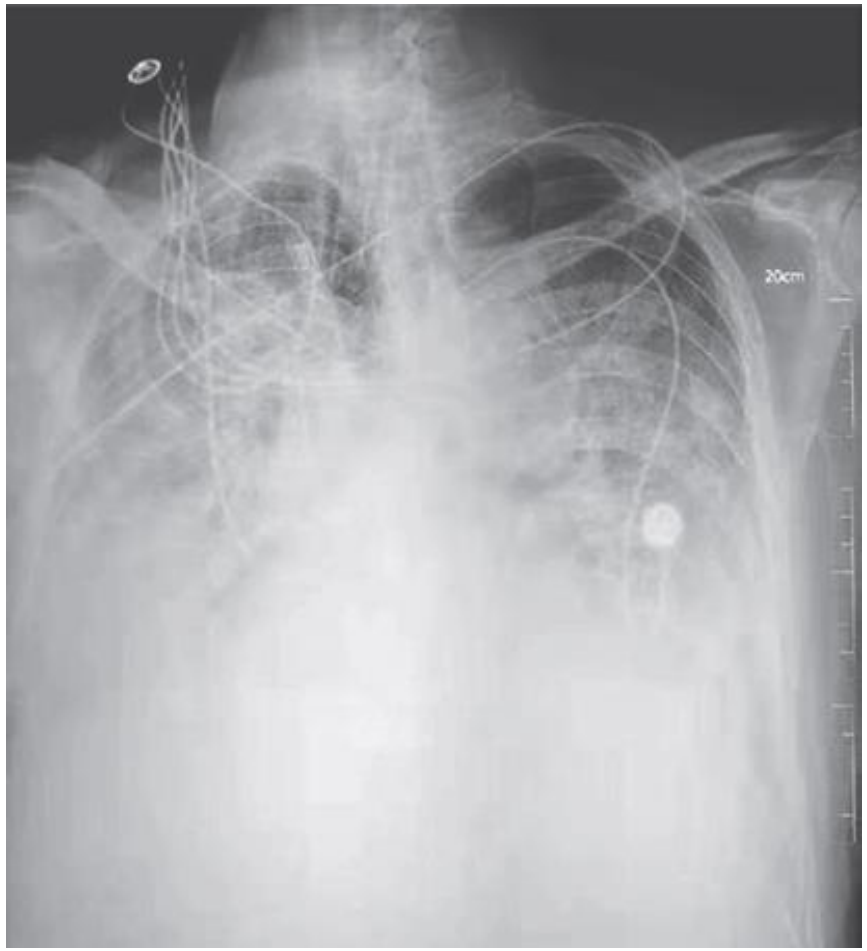
SUMMARY

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used to isolate a novel coronavirus, named 2019-nCoV, which formed a clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily. Different from both MERS-CoV and SARS-CoV, 2019-nCoV is the seventh member of the family of coronaviruses that infect humans. Enhanced surveillance and further investigation are ongoing. (Funded by the National Key Research and Development Program of China and the National Major Project for Control and Prevention of Infectious Disease in China.)

Zhu et al. NEJM 382; 8. Feb 20,2020

- 61yo M fever and cough starting 12/20/19 presented to Jinyintan Hospital (Wuhon, China) with respiratory distress 12/27/19
- Frequent visitor to the Wuhon seafood and wet animal wholesale market
- BAL 12/30/20: RPP Negative
- Died 01/20/20

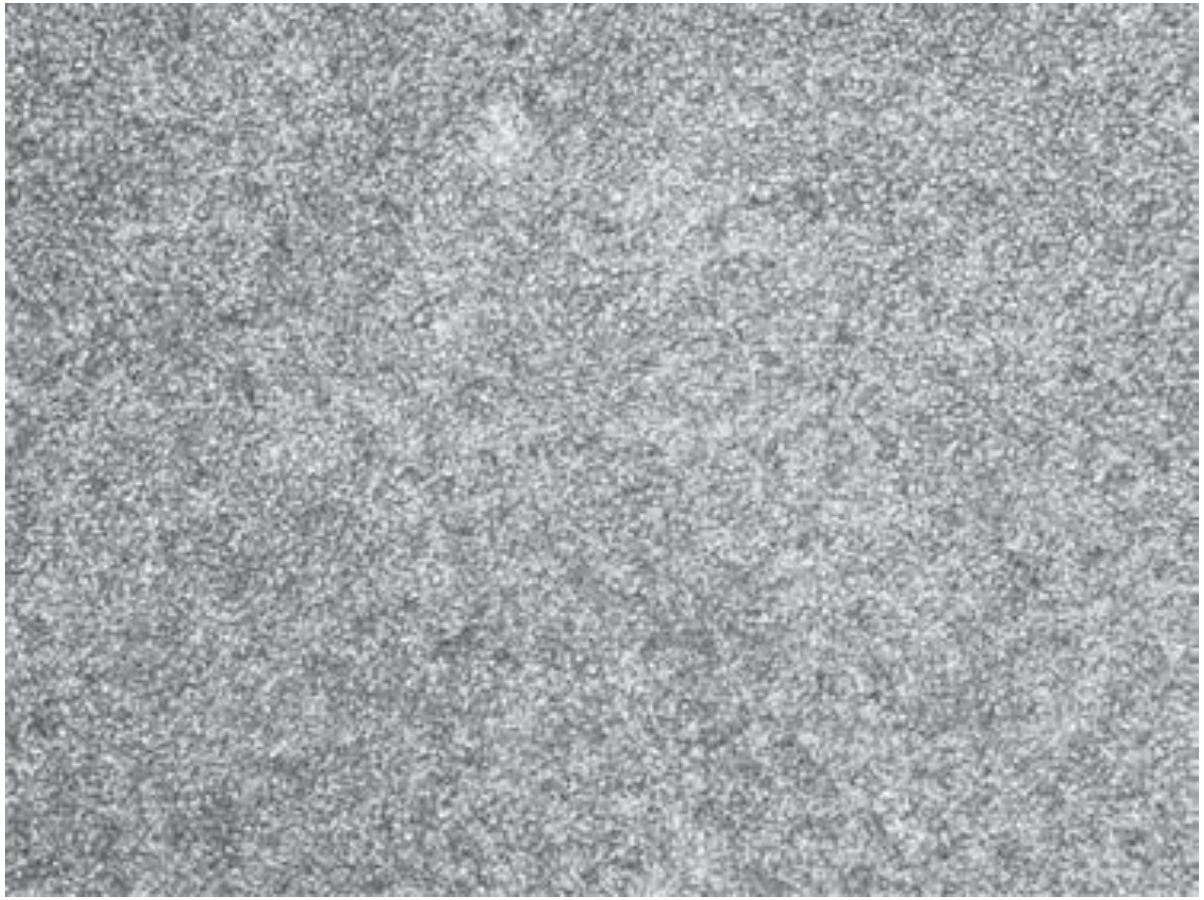
Day 8 of illness

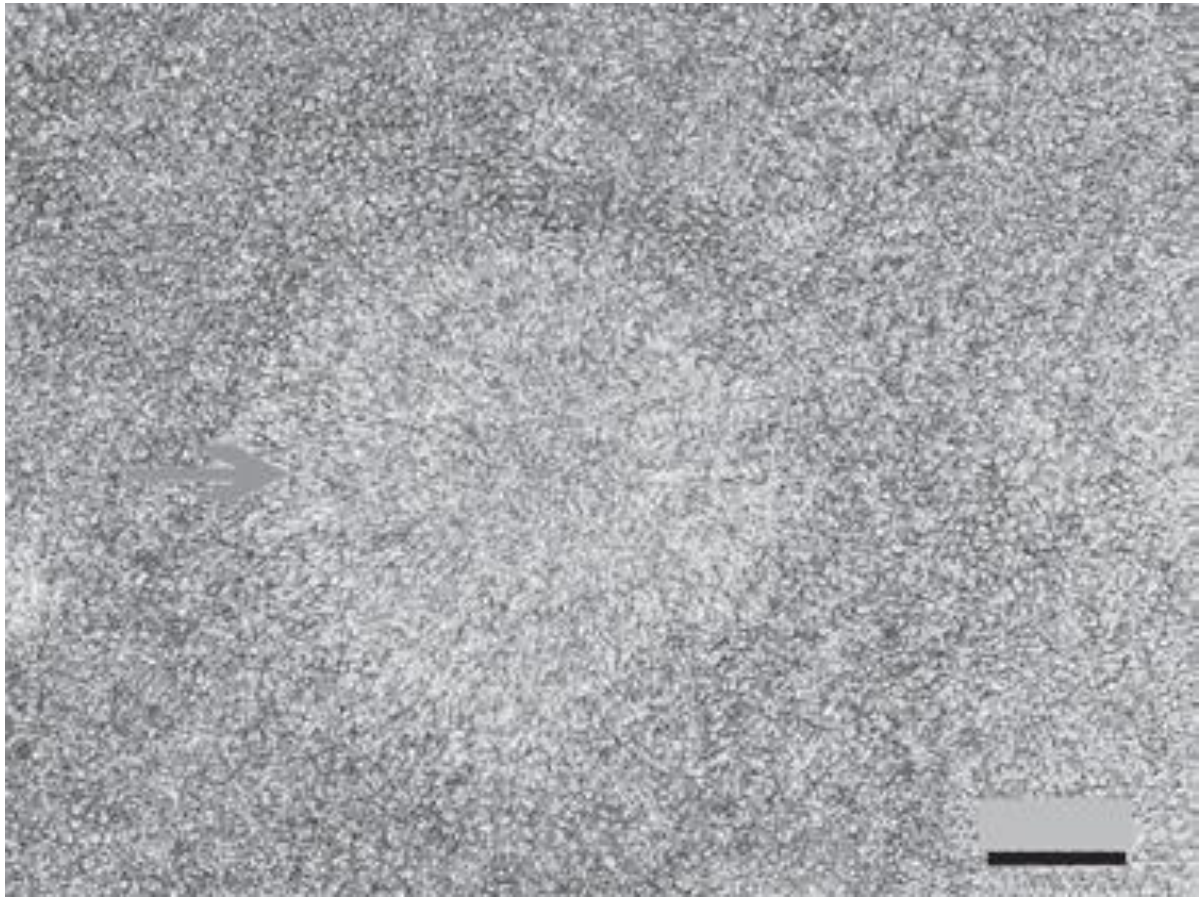


Day 11 of illness

Zhu et al. NEJM 382; 8. Feb 20,2020

Inoculation of isolated virus into human epithelial cell line

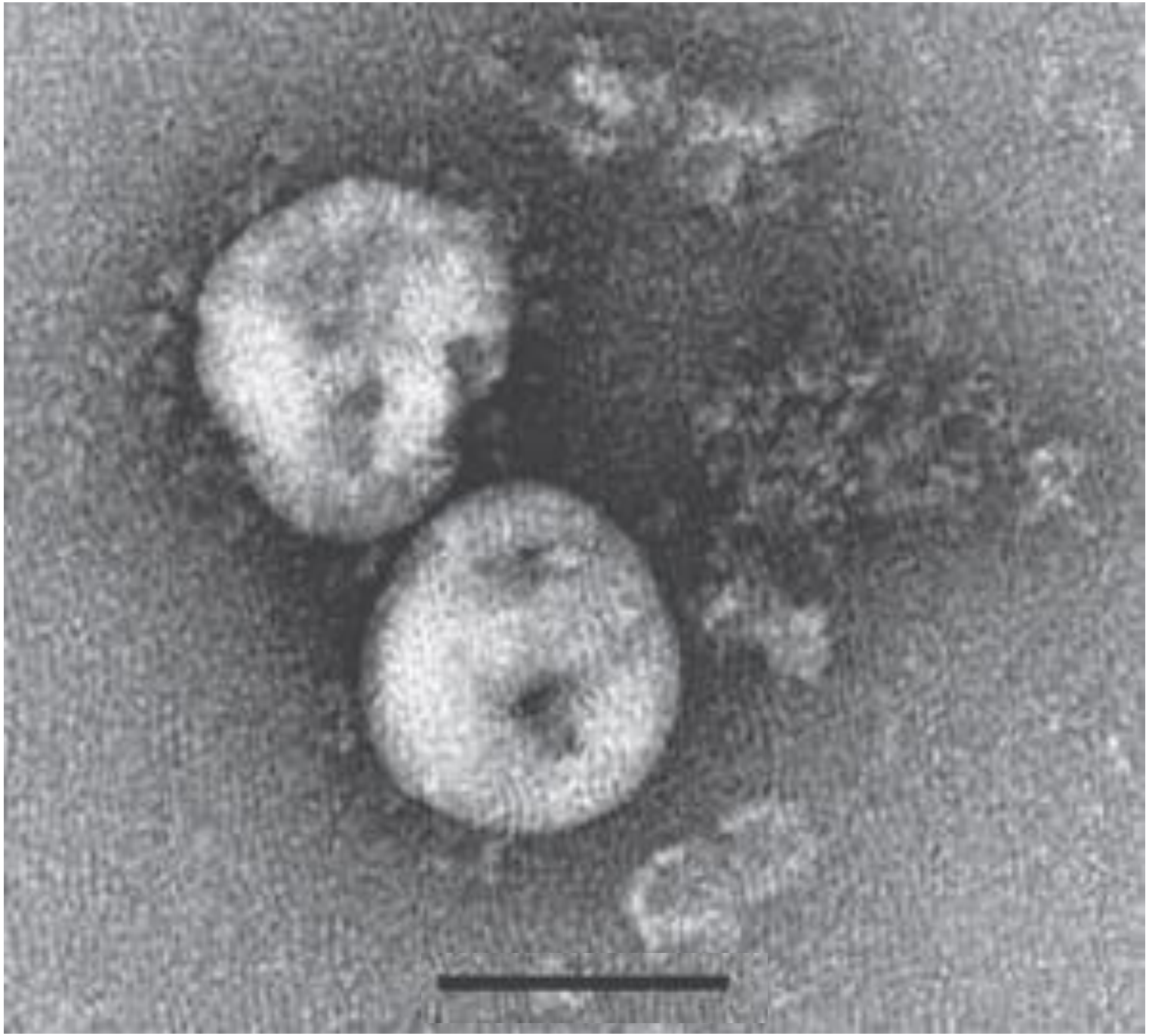




1uM

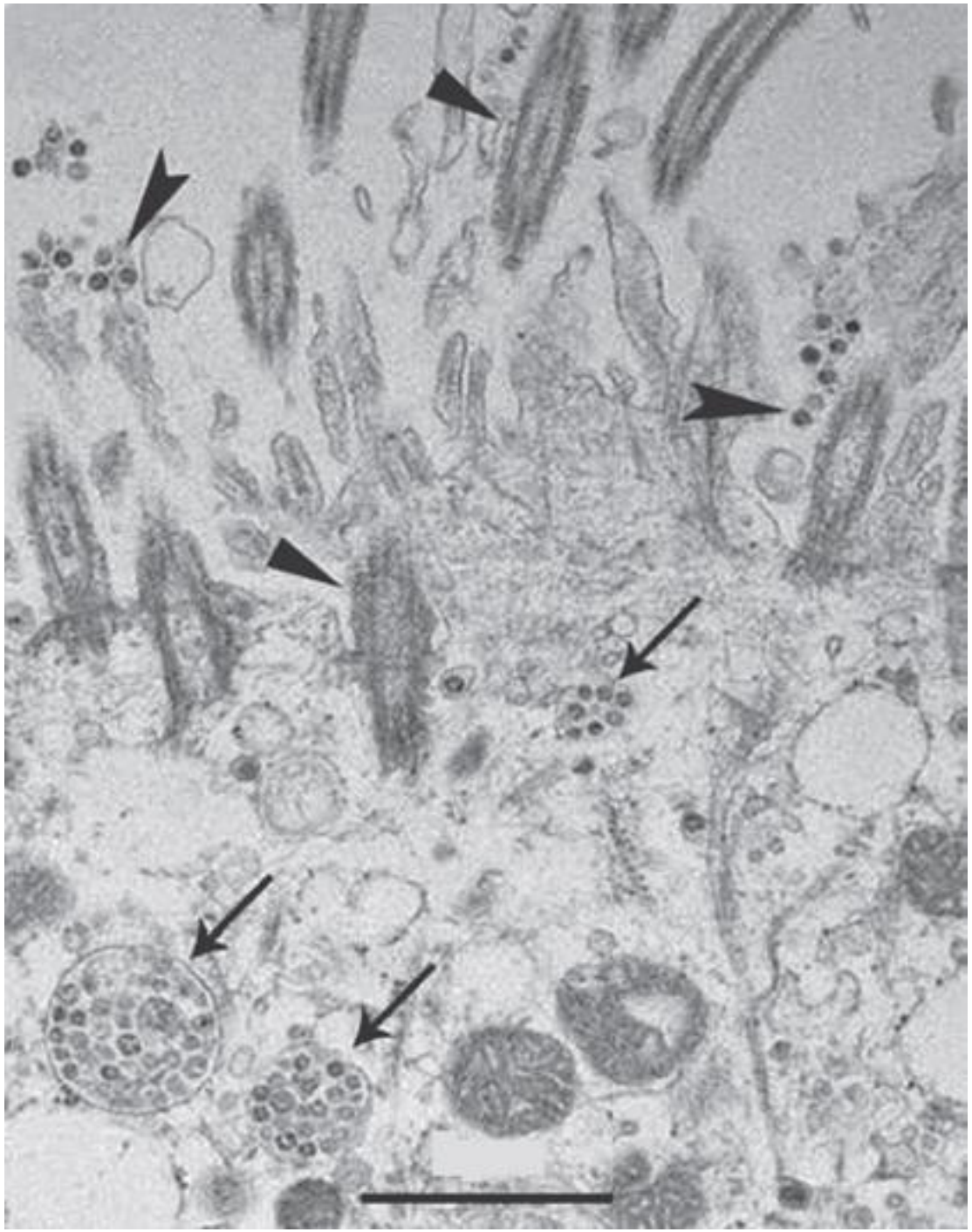
96 hours: Lack of cilium beating was seen in the center of the focus

Zhu et al. NEJM 382; 8. Feb 20,2020

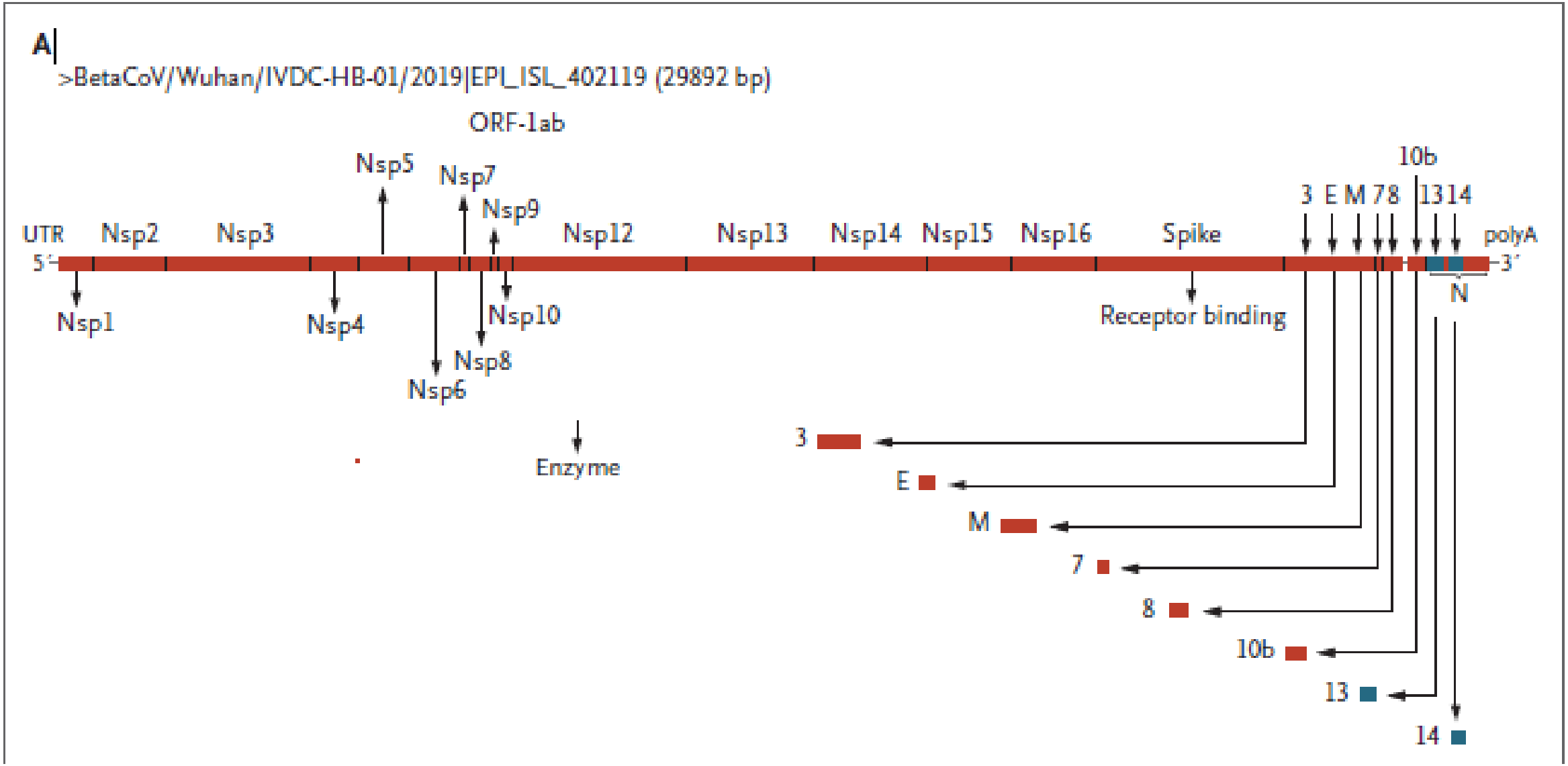


100nm

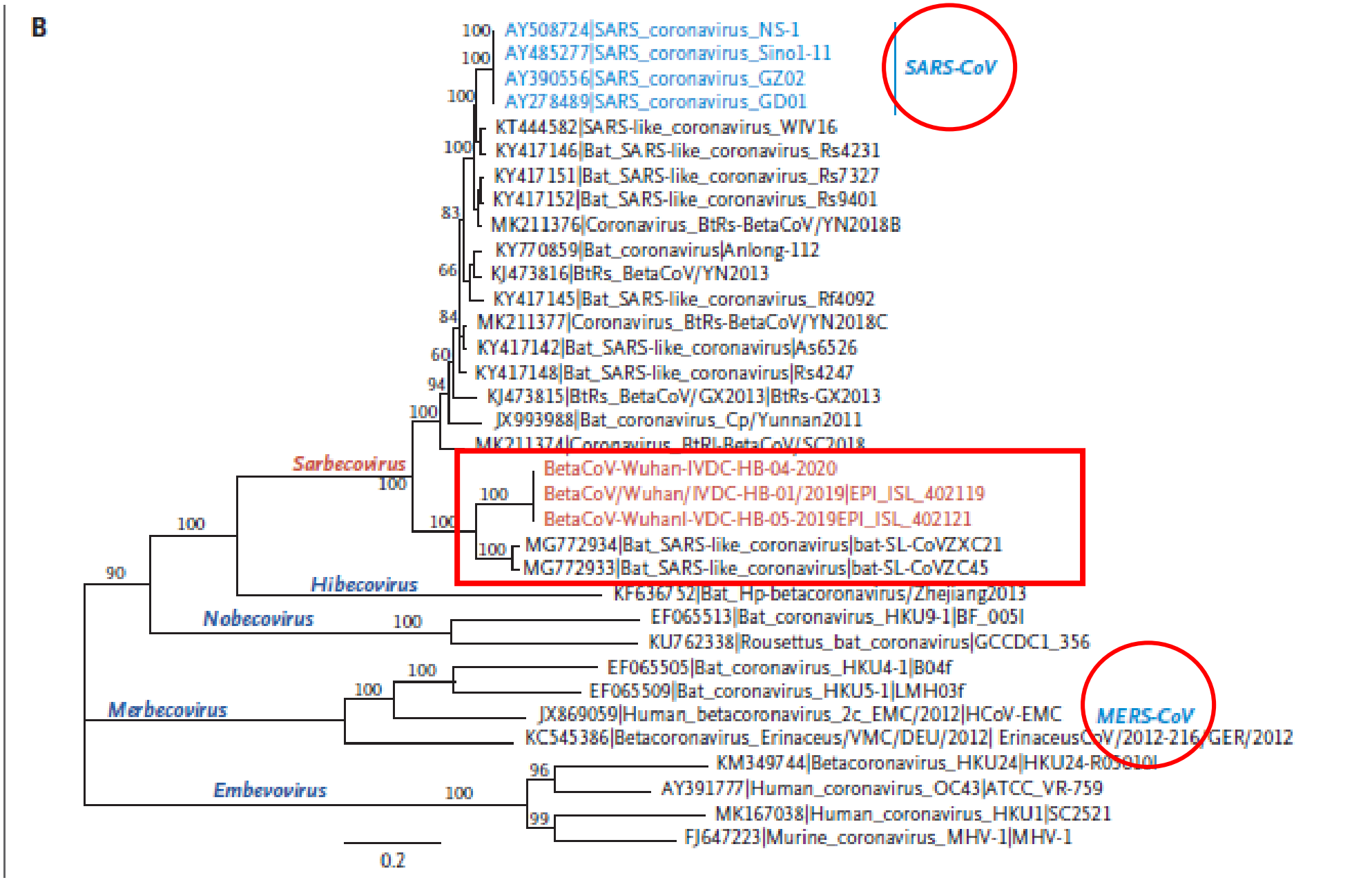
Zhu et al. NEJM 382; 8. Feb 20,2020



Zhu et al. NEJM 382; 8. Feb 20,2020



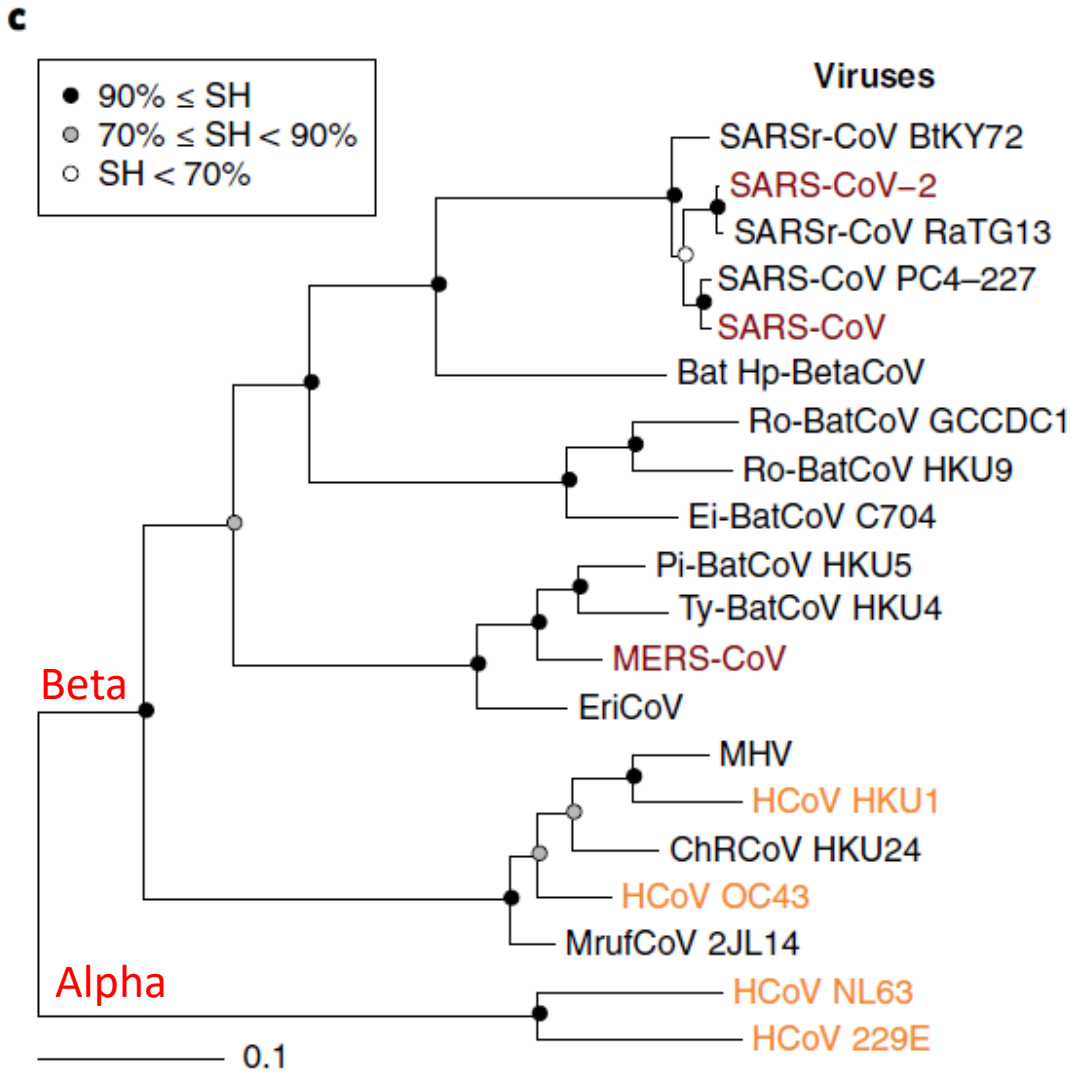
Zhu et al. NEJM 382; 8. Feb 20,2020



Zhu et al. NEJM 382; 8. Feb 20,2020

Coronaviruses

- Large +ss RNA enveloped virus in coronaviridae family
- Named for crown/halo appearance on EM
- Causes common cold (HCoVs) or deadly pneumonia after crossing species barrier (zoonotoic epidemics)
- <u>Alpha Coronaviruses:</u>
  - HCoV-229E
  - HCoV-NL63
- <u>Beta Coronaviruses:</u>
  - HCoV-OC43
  - HCoV-HKU1
  - SARS-CoV
  - MERS-CoV
  - SARS-CoV-2

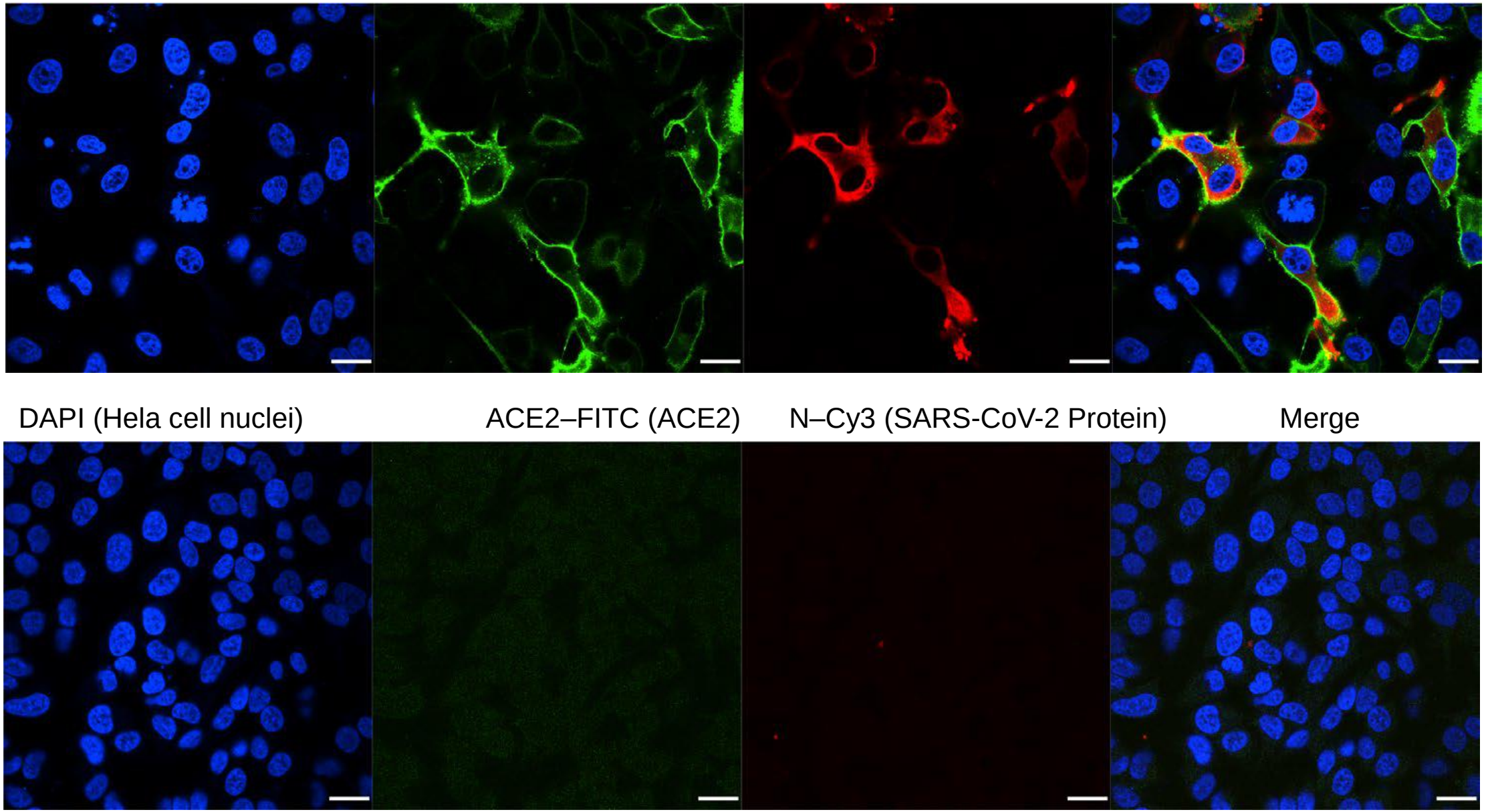


Coronavirus Study Group of the International Committee on Toxonomy of Viruses. Nature Microbiology. 2020

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)

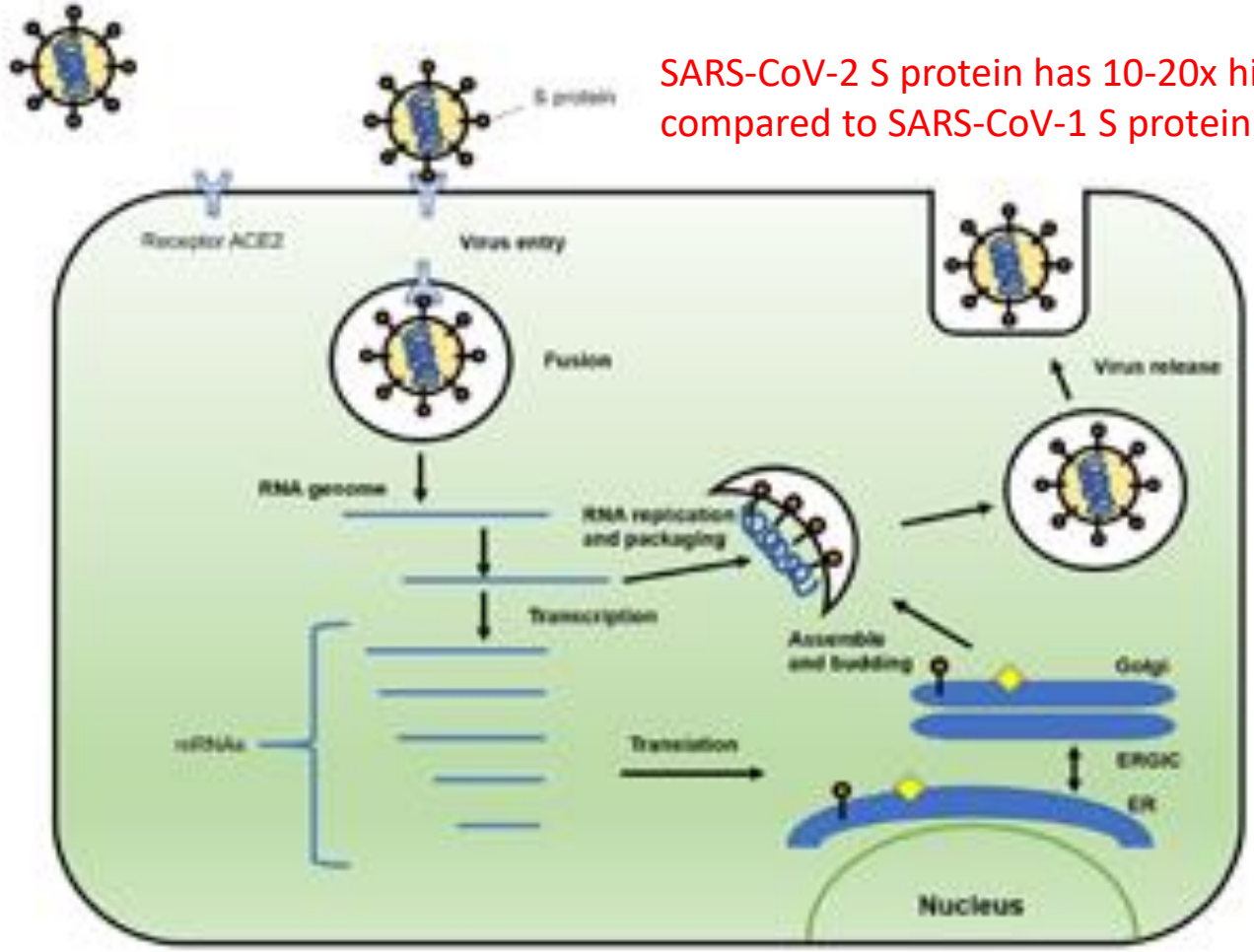
- Responsible for current COVID-19 Pandemic
- Beta Coronavirus
  - 96% genetically identical to a bat coronavirus
  - 79.6% genetically identical to SARS-CoV-1
- SARS-CoV-2 spike protein binds human ACE2 receptor for entry

SARS-CoV-2 Binds to ACE-2



Zhou et al, Nature Vol 579 March 2020

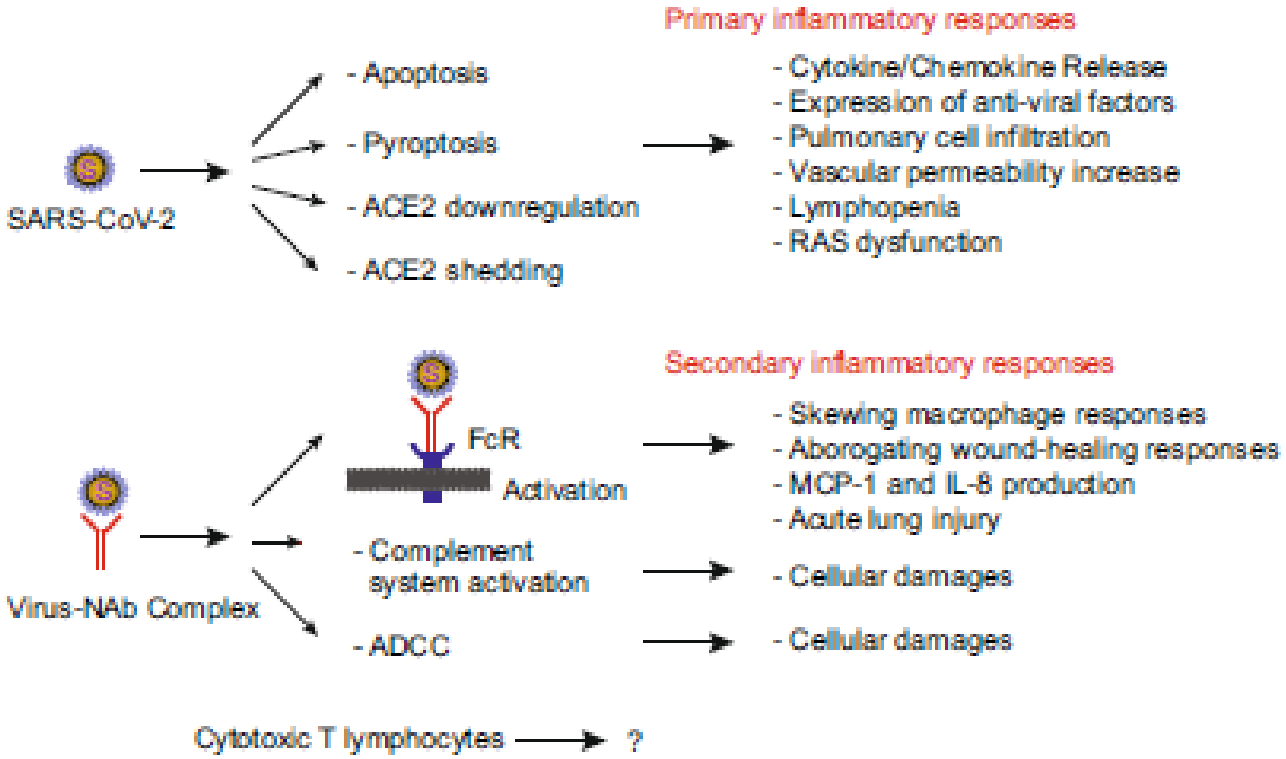
Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)

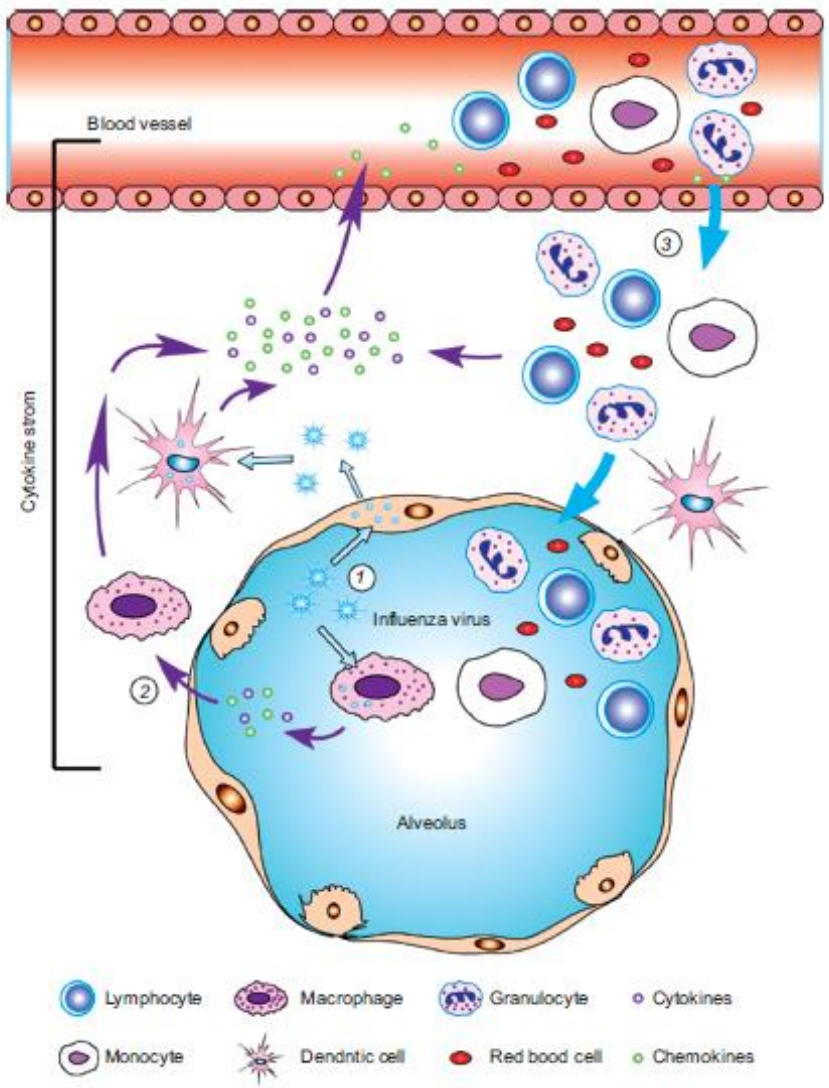


SARS-CoV-2 S protein has 10-20x higher affinity for ACE2 compared to SARS-CoV-1 S protein

He et al. JMV Epub ahead of print. 02-27-2020

Proposed SARS-CoV-2 Mediated Inflammatory Response



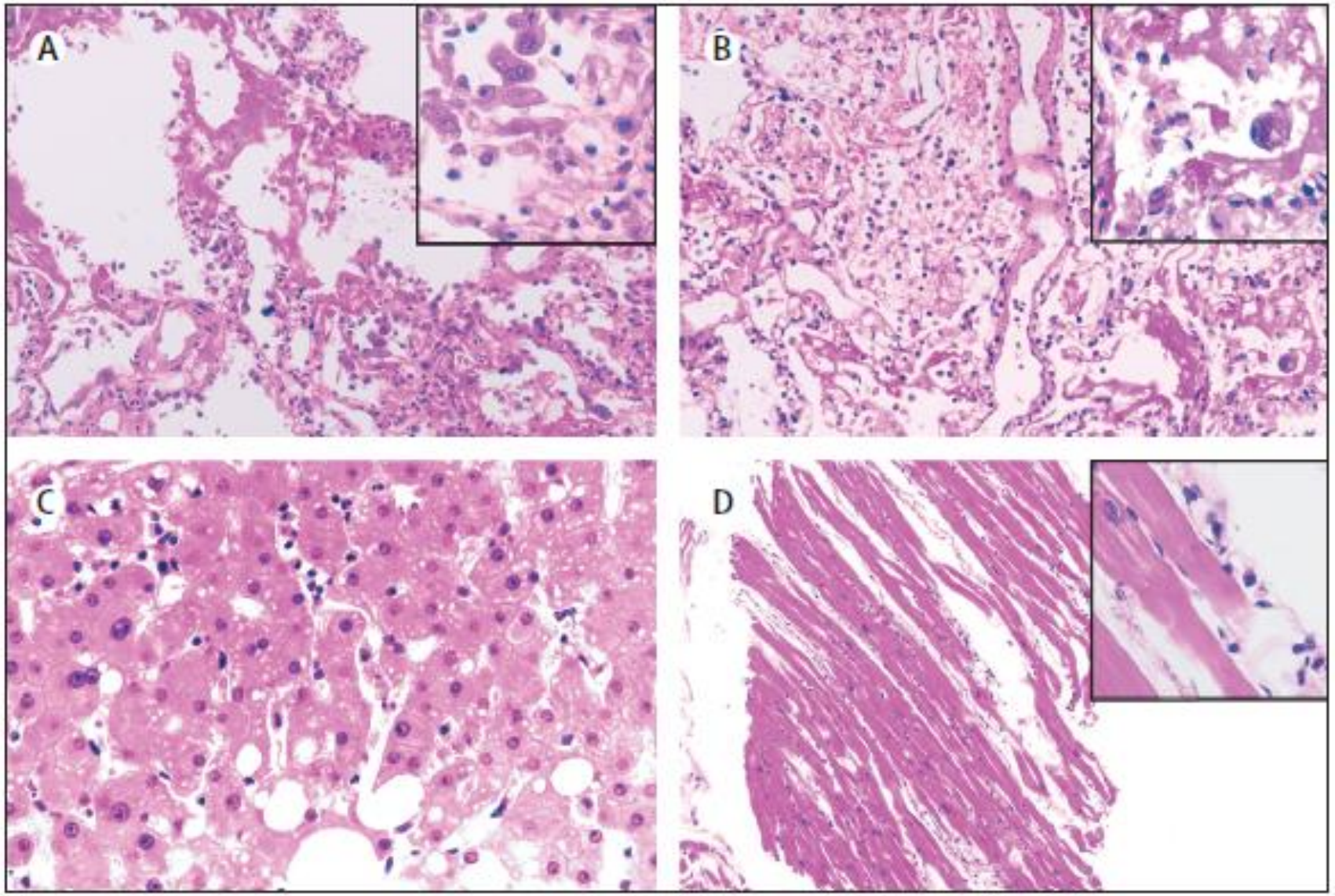


Fu et al. Virologica Sinica. Epub ahead of print. 2020

Liu et al. Cellular & Molecular Immunology (2016) 13, 3–10

SARS-CoV-2 Histological exam

Right Lung

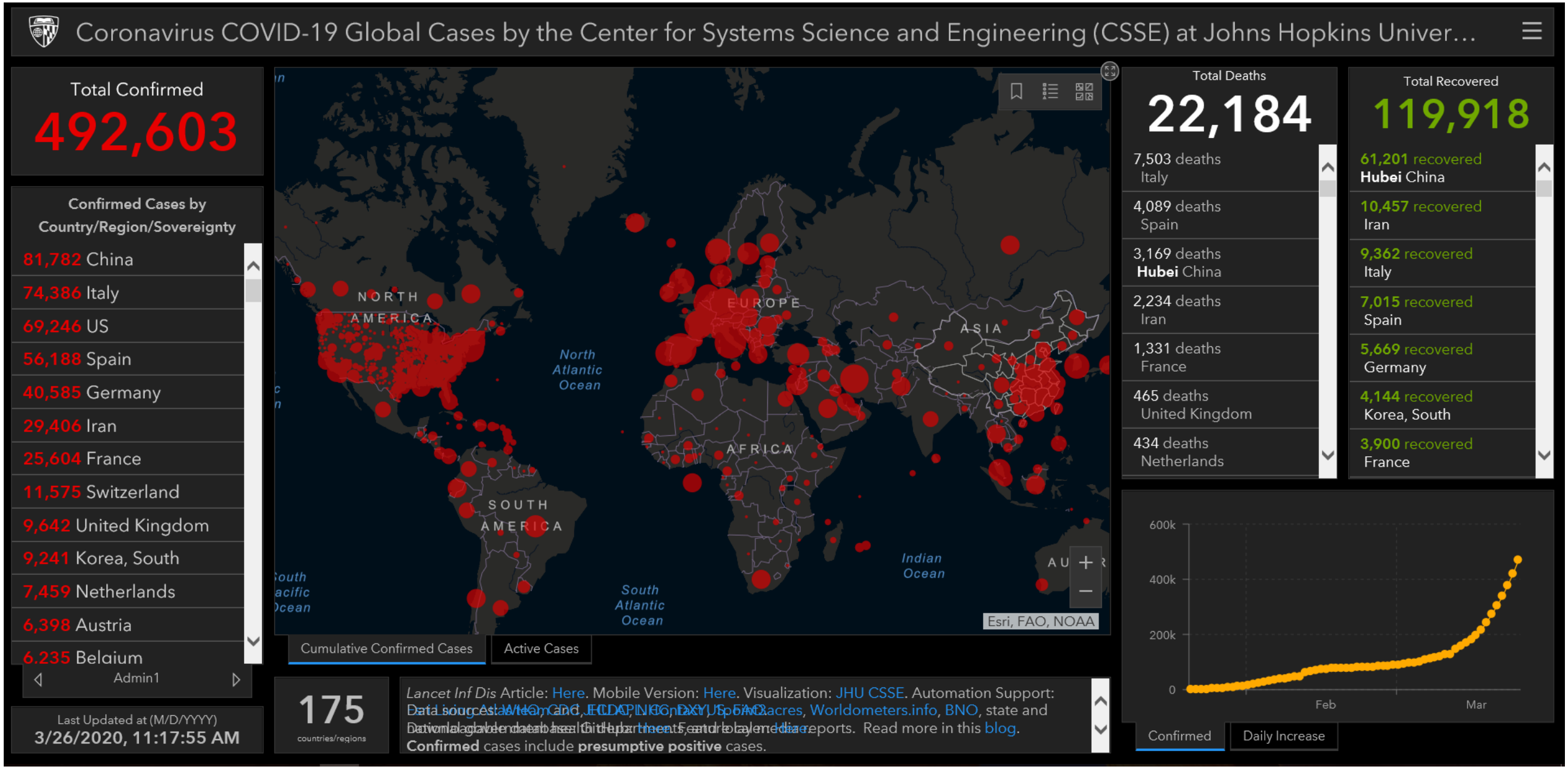


Left Lung

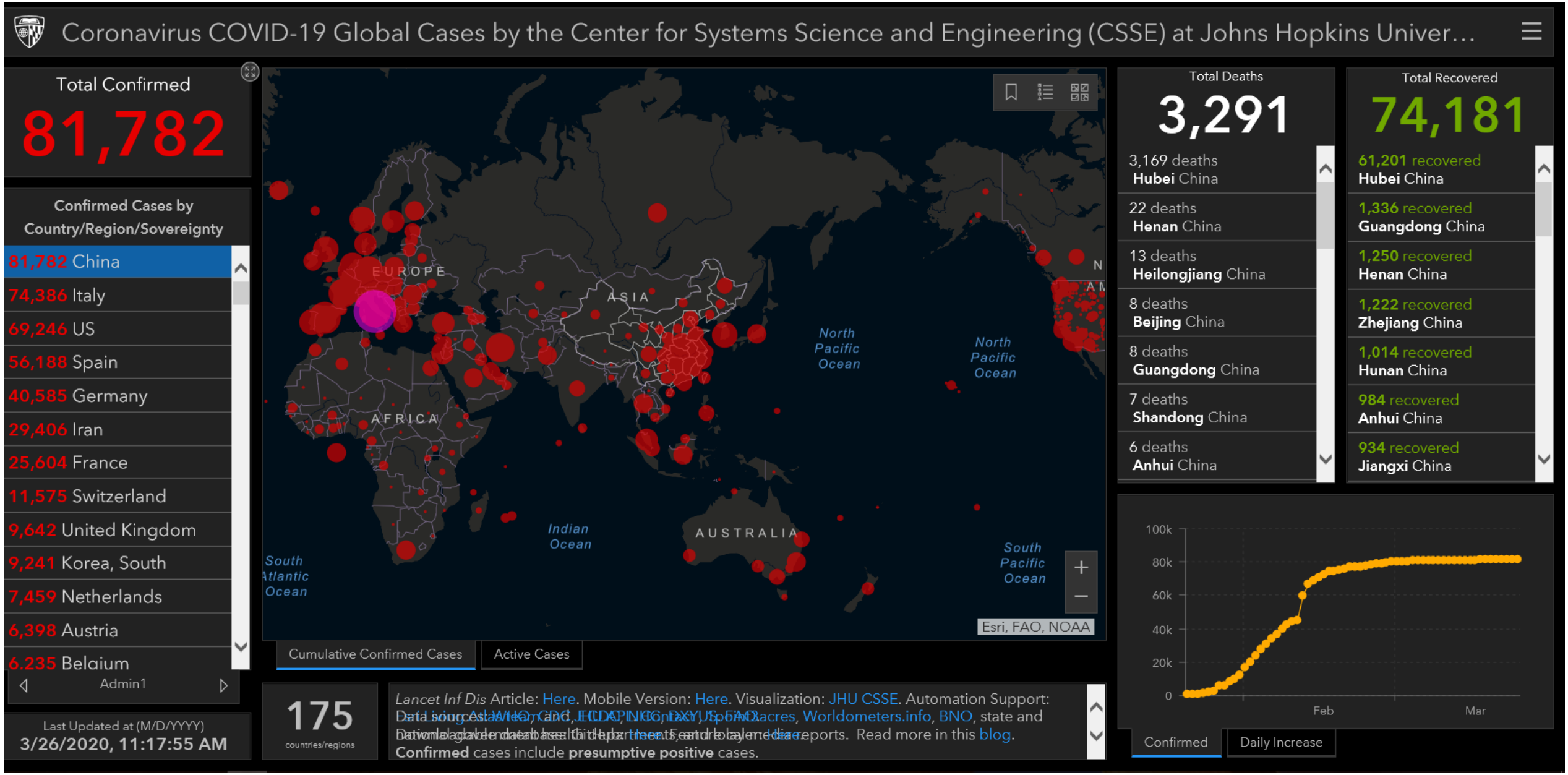
Liver

Heart

Xu et al. Lancet Epub ahead of print. 2020



Johns Hopkins COVID-19 website. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6



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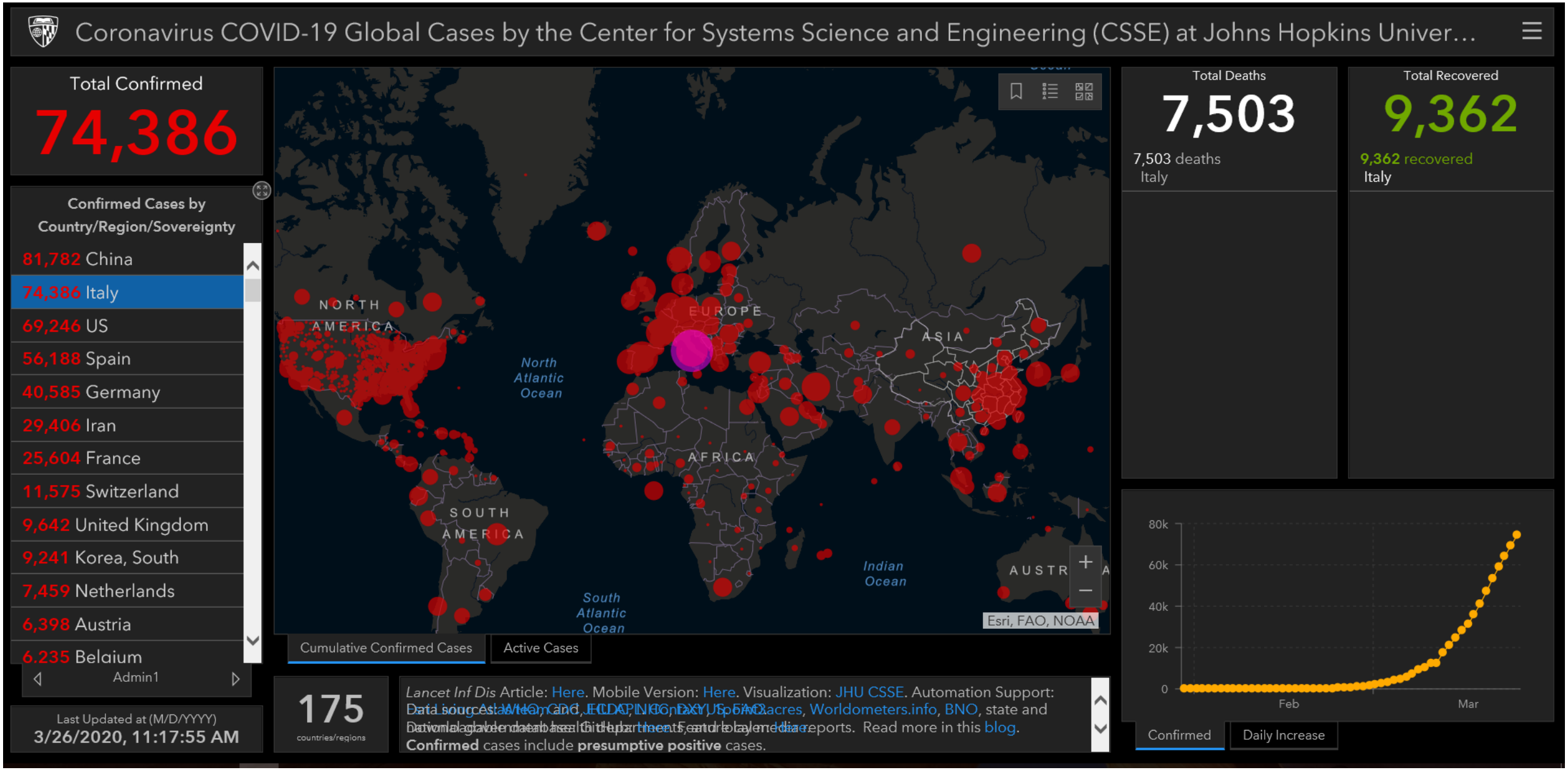
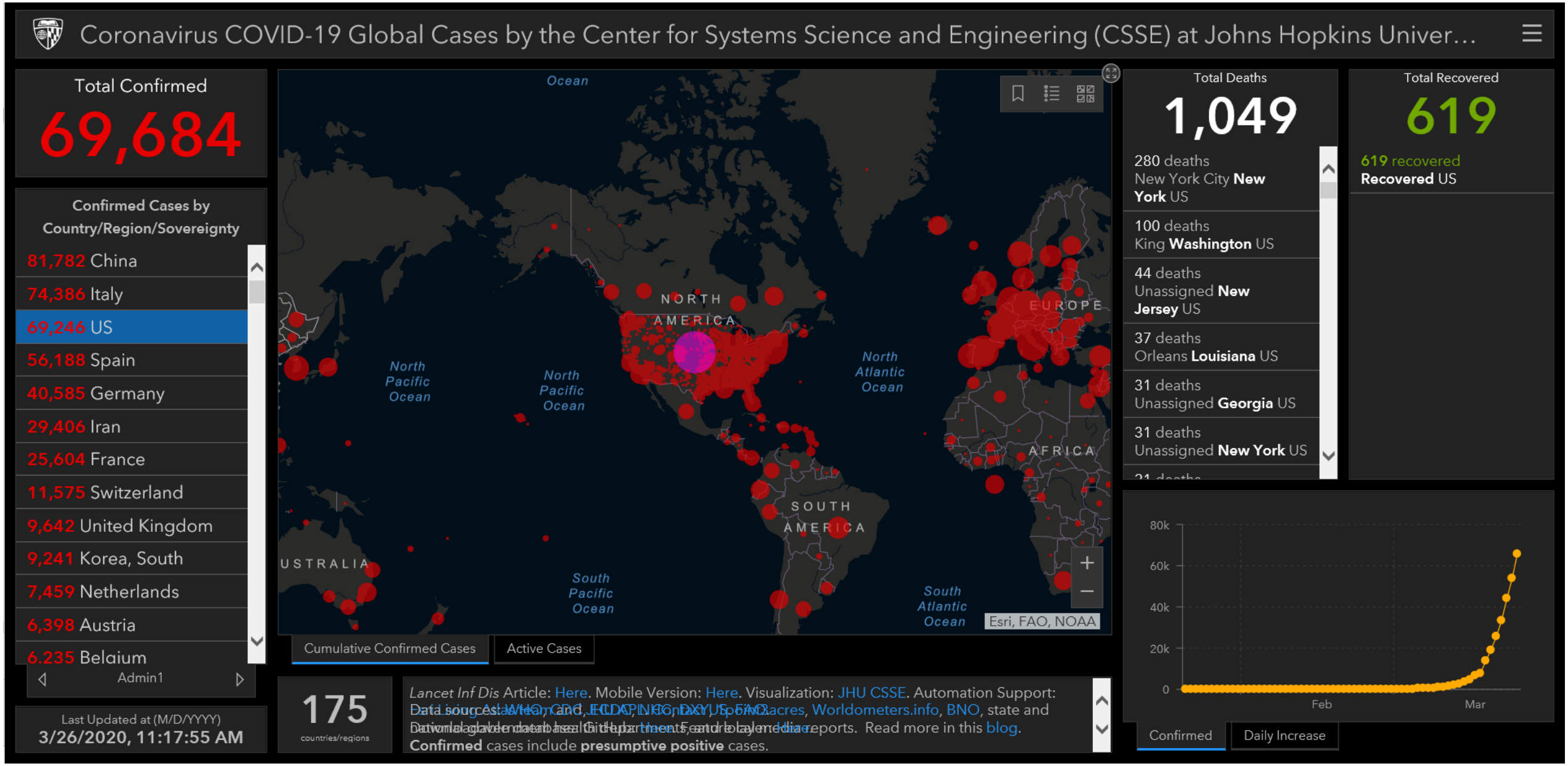


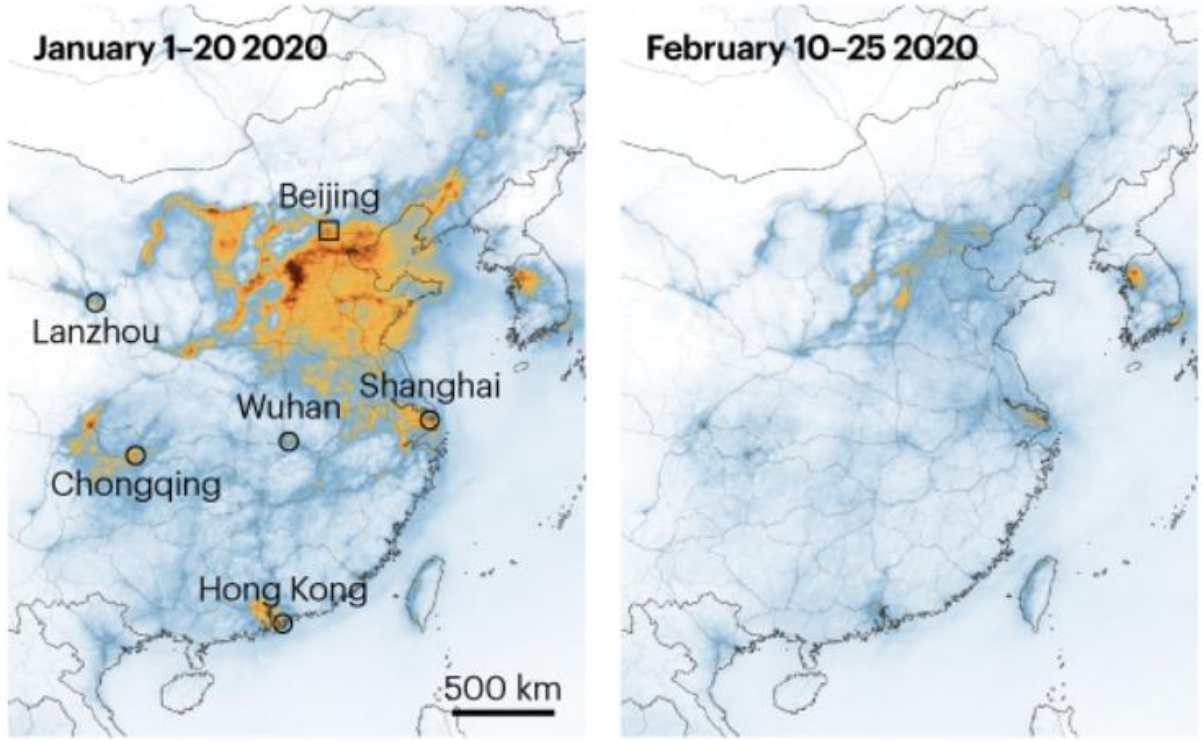
Johns Hopkins COVID-19 website. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6



Johns Hopkins COVID-19 website. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

CLEANER AIR

Measures to contain the coronavirus outbreak seem to have reduced nitrogen dioxide pollution across China.



Source: NASA Earth Observatory

Case Fatality Rate in Italy

Table. Case-Fatality Rate by Age Group in Italy and China[a]

	Italy as of March 17, 2020		China as of February 11, 2020	
	No. of deaths (% of total)	Case-fatality rate, %[b]	No. of deaths (% of total)	Case-fatality rate, %[b]
All	1625 (100)	7.2	1023 (100)	2.3
Age groups, y				
0-9	0	0	0	0
10-19	0	0	1 (0.1)	0.2
20-29	0	0	7 (0.7)	0.2
30-39	4 (0.3)	0.3	18 (1.8)	0.2
40-49	10 (0.6)	0.4	38 (3.7)	0.4
50-59	43 (2.7)	1.0	130 (12.7)	1.3
60-69	139 (8.6)	3.5	309 (30.2)	3.6
70-79	578 (35.6)	12.8	312 (30.5)	8.0
≥80	850 (52.3)	20.2	208 (20.3)	14.8

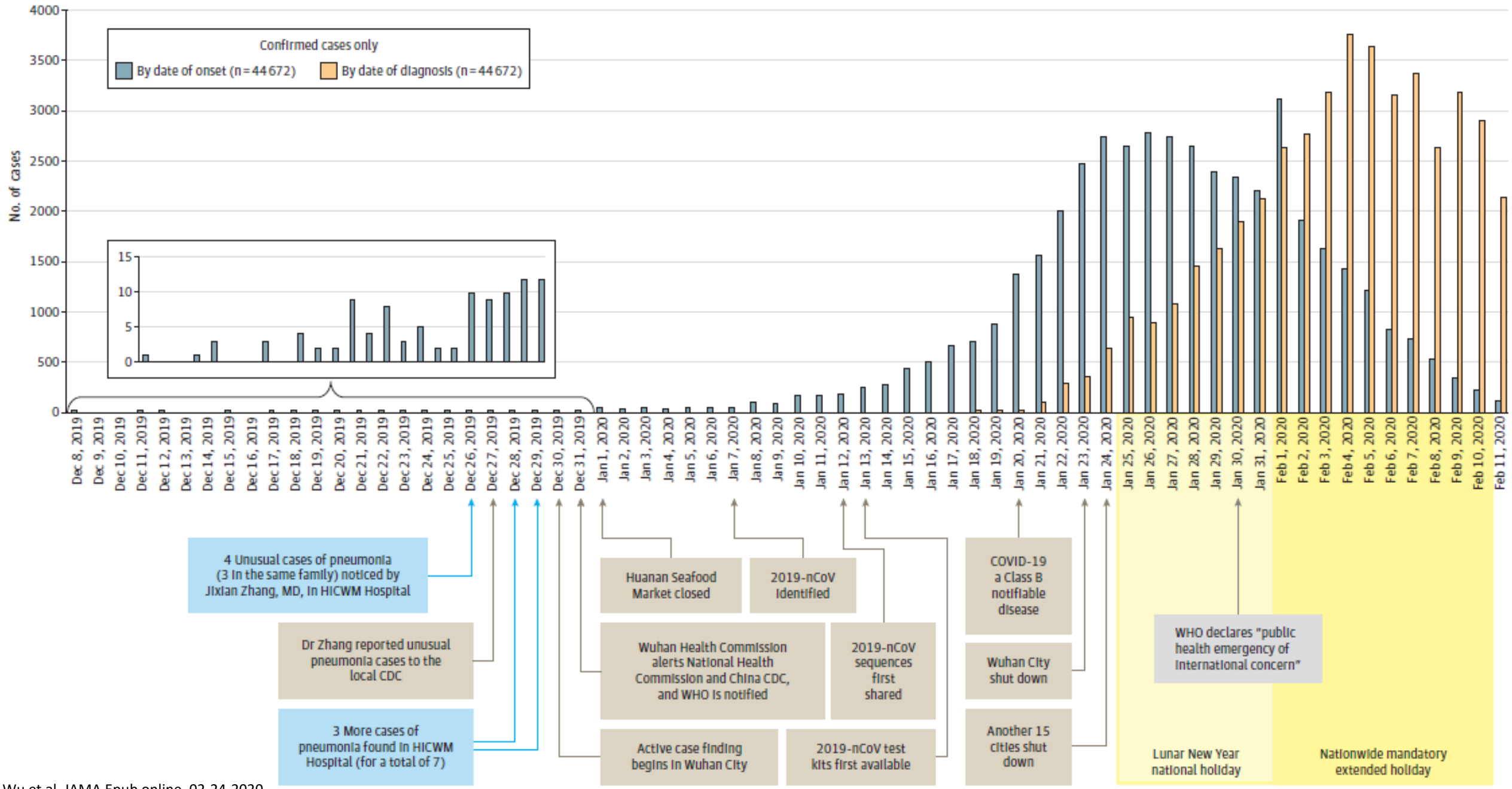
<u>% of cases >70yo:</u>
China: 11.9%
Italy: 37.6%

<u># cases >90yo:</u>
China: ?
Italy: 687 (22.7% CFR)

The overall older age distribution in Italy relative to that in China may explain, in part, the higher average case-fatality rate in Italy.

Onder et al. JAMA. Epub ahead of print. 03/2020

Figure 1. Epidemic Curve of the Confirmed Cases of Coronavirus Disease 2019 (COVID-19)



Wu et al. JAMA Epub online. 02-24-2020

Timeline for SARS vs COVID-19

Timeline	Day After First Case (SARS)	Day After First Case (COVID-19)
WHO notified	87	4
Virus Identified	151	11
Sequence shared internationally	160	16
Test available	180	**17****
WHO Global alert	116	35
WHO declares Pandemic	Never	70

Comparison to SARS and MERS CoV

[1]	SARS-CoV (SARS)	MERS-CoV (MERS)	SARS-CoV-2 (COVID-19)
Natural Virus Host	Horseshoe Bats	Bats	Bats
Intermediate Host	Masked Palm Civet	Dromedary Camels	Pangolins[3]
Median Incubation	2-10 (7d)	2-10 (5.5d)	2-14 (5.1d)
Human Cell receptor	ACE2	DPP4	ACE2
Estimated R^0	2-5	<1	2.7[2] (2.2-3.6)
Severe cases	11%	46%	18%
Countries Impacted	29	27	172
Cases world-wide	8,096	2,494	441,187
Deaths world-wide	774	858	19,784
Case Fatality Rate	9.6%	34.4%	4.5%

1. Wang et al. Qingsong Qin.
2. Wu et al. Lancet Epub ahead of print. Online 2020
3. Tsan-Yuk et al. Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China, 2020

COVID-19 Clinical Features**

- Mean incubation period: **5.1d** (1-14d; 95% by 12d) [1-2]
- Median age: 49-59yo [1,3-5]
- ~50% Male
- ~50% have comorbidities
- Symptoms[6]:
    1. Fever: 89% (65-98%)
    2. Cough:72% (45-86%)
    3. Myalgia: 43%(12-65%)
    4. Dyspnea: 35%(16-64%)
    5. Headache: 15% (9-34%)
    6. Diarrhea: 10% (2-24%)

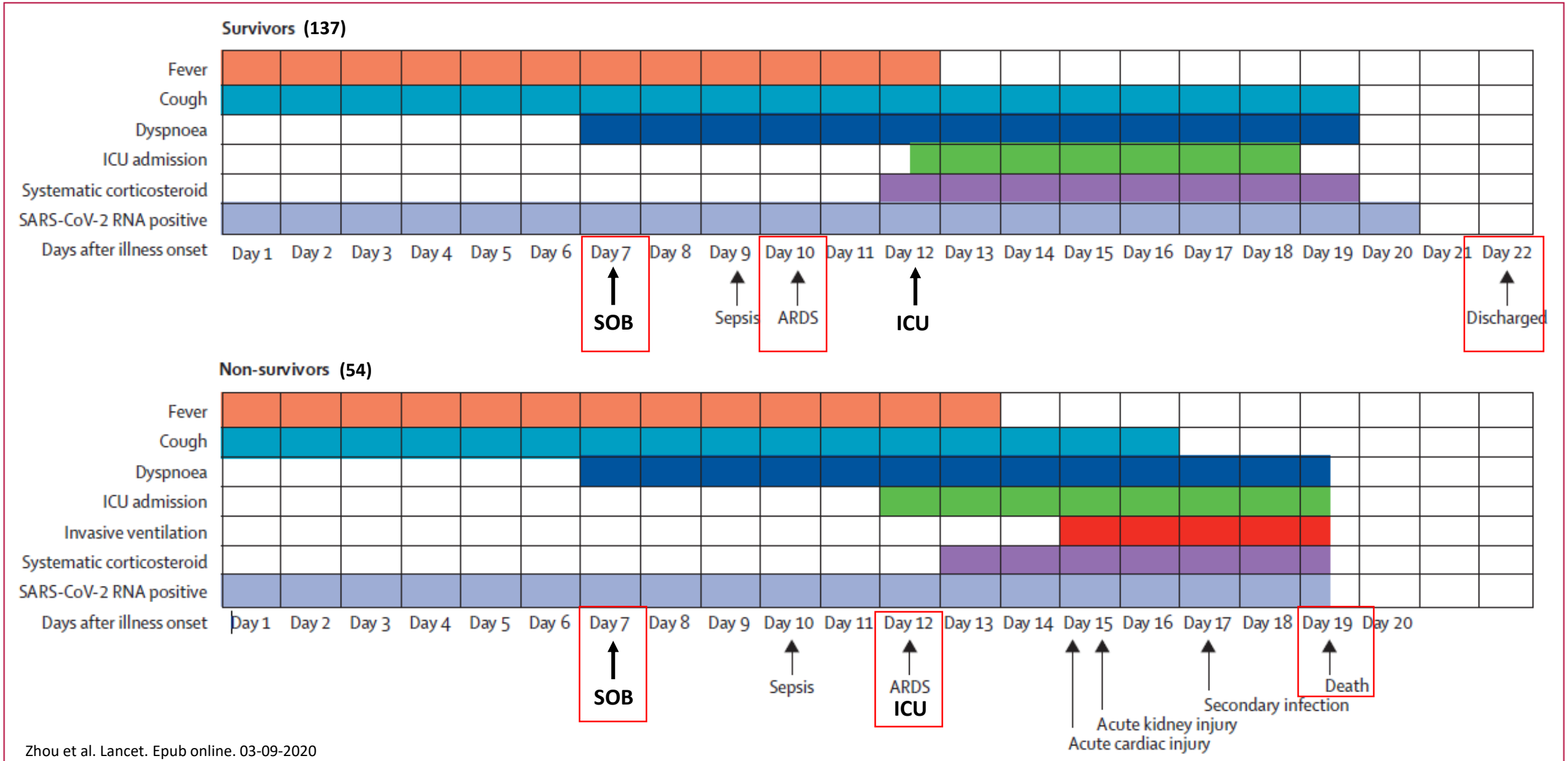
** Most published data on admitted patients. Very little outpatient data available.

1. Li et al. NEJM 2020
2. Wang et al. JAMA 2020.
3. Chan et al. Lancet 395; 10223. 2020.
4. Chen et al. Lancet 395; 10223. 2020
5. Huang et al. Lancet 395; 10223. 2020
6. Xi et al. JMV. Epub ahead of print. 2020

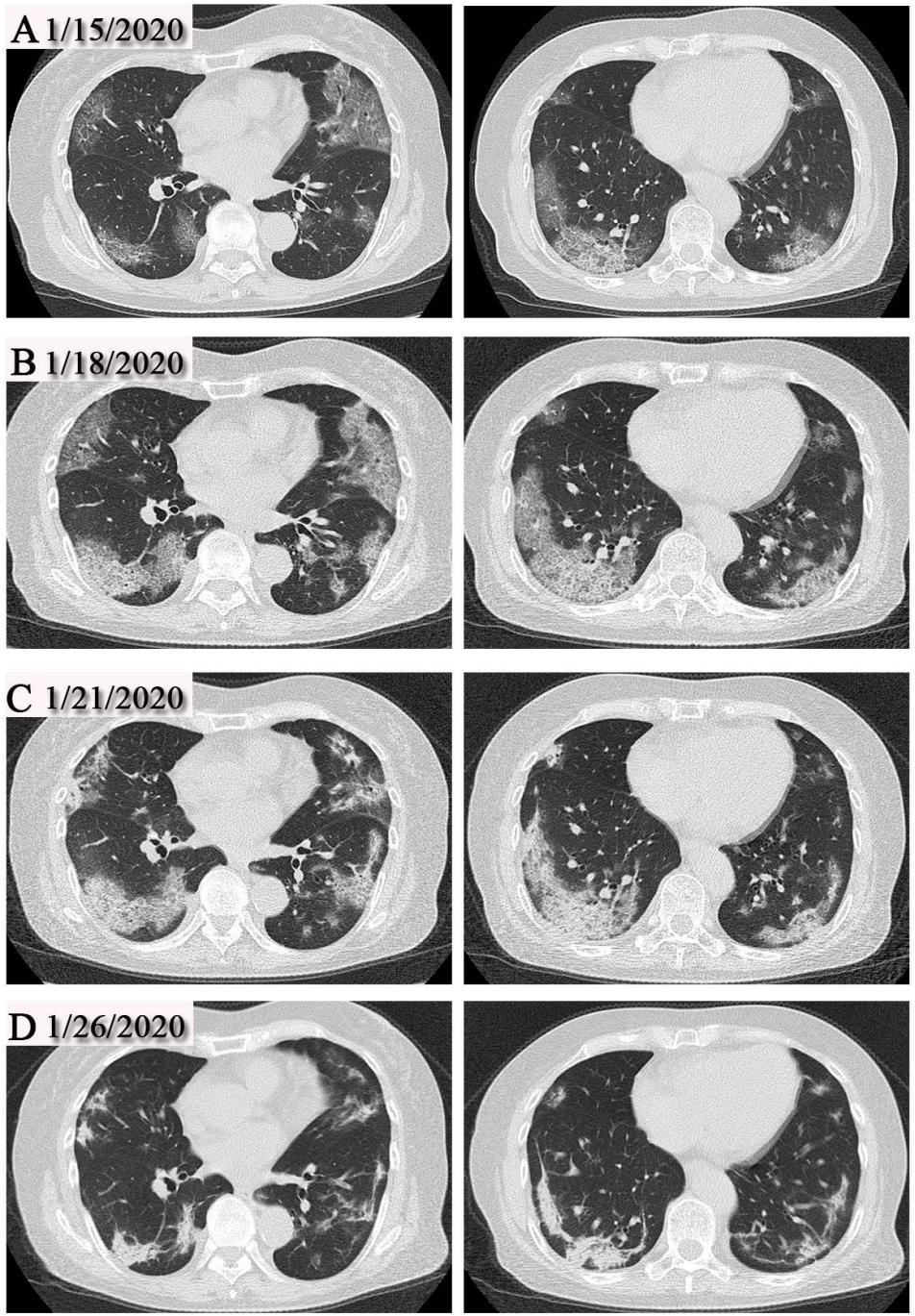
COVID-19 Case Classifications

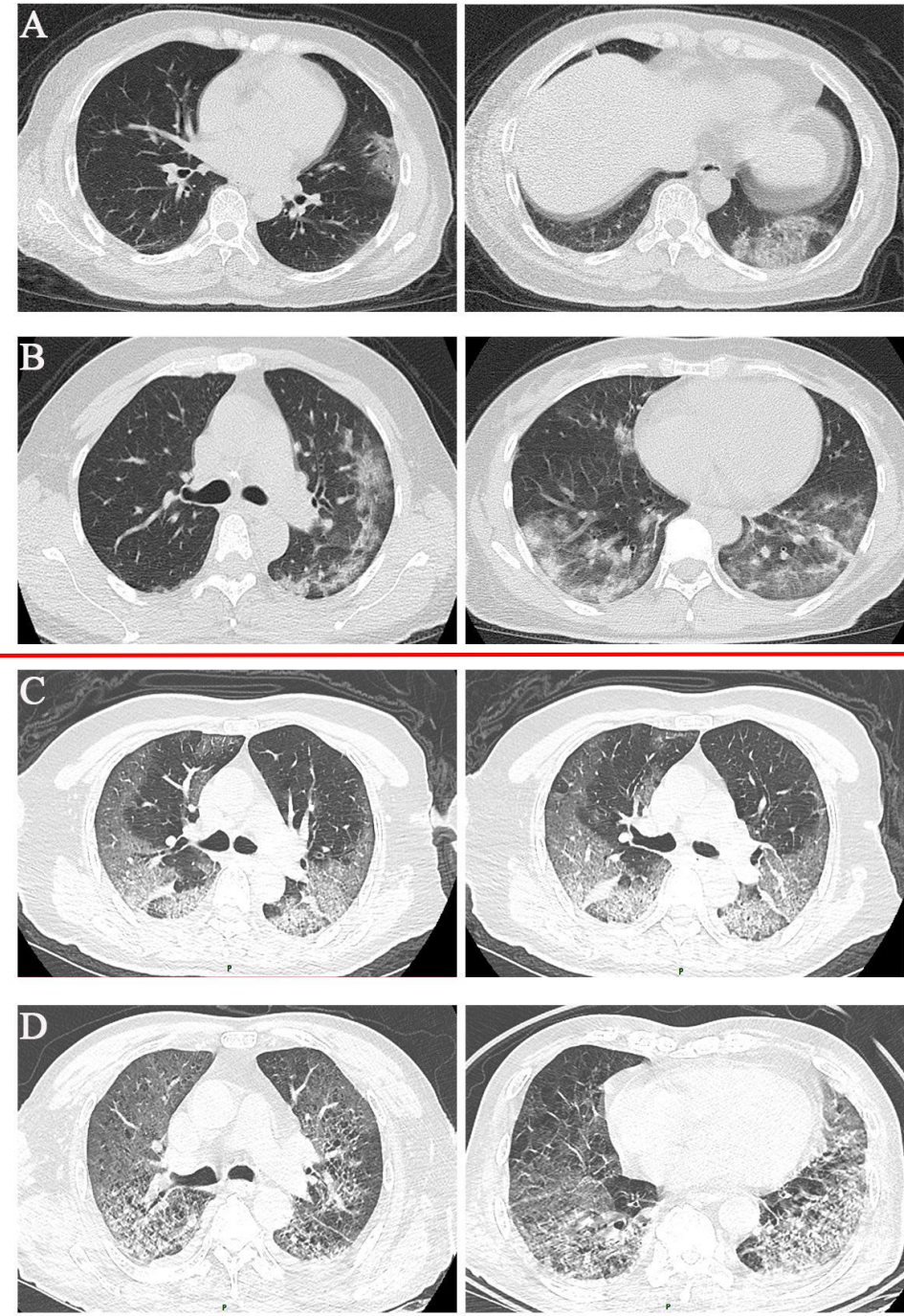
Classification	Clinical Criteria
Mild	Mild symptoms without radiographic findings
Moderate	Fever, respiratory symptoms, radiographic findings
Severe	Meet any of the following: - O2 saturation ≤93% on room air - RR>30 breaths per minute - PaO2/FiO2<300 mmHg
Critical	Meet any of the following: - Requires mechanical ventilation - Septic Shock - Multi-organ failure

COVID-19 Clinical Course: 191 admitted patients



Zhou et al. Lancet. Epub online. 03-09-2020

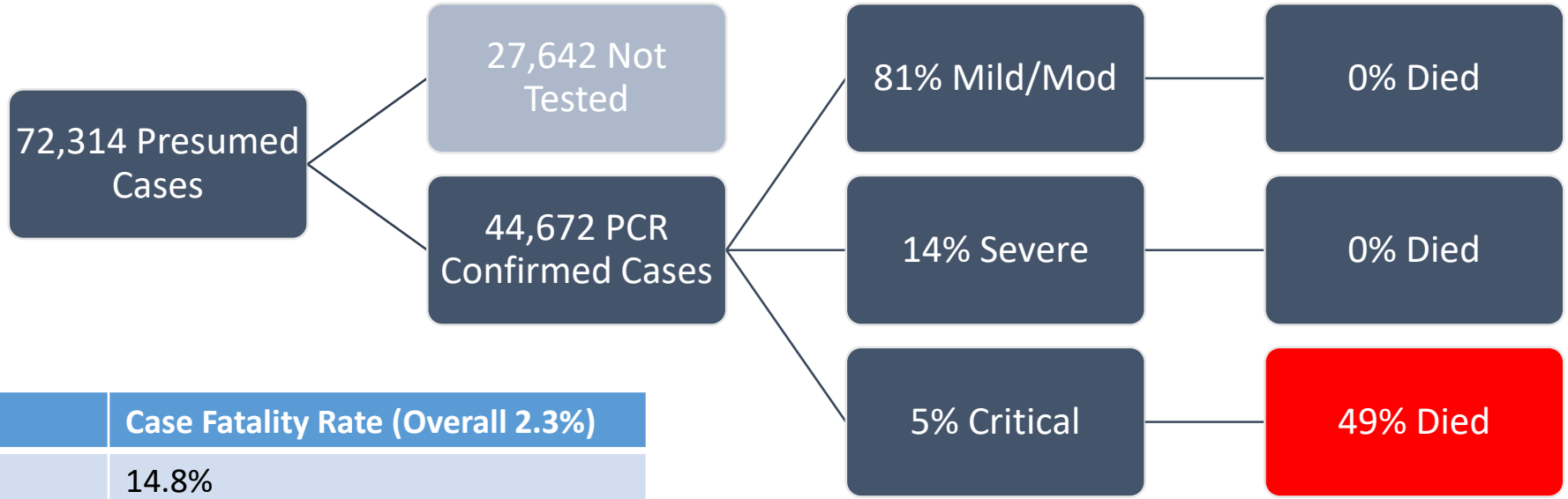




Wang et al. CID. Epub ahead of print 2020

VIEWPOINT

Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention



Risk Factor	Case Fatality Rate (Overall 2.3%)
>80yo	14.8%
CVD	10.5%
70-79yo	8.0%
Diabetes	7.3%
COPD	6.3%
Hypertension	6.0%
Cancer	5.6%
Healthcare Workers	0.3%

Wu et al. JAMA Epub online. 02-24-2020

Mortality Risk Factors

- 150 patients admitted to 2 hospitals in Wuhan China:
  - 68 Deaths
  - 82 Discharged survivors
- Older age
- Comorbidities
  - Cardiovascular Disease
  - HTN
- Complications:
  - ARDS, AKI, 2° infections
- Labs:
  - ALC, Plts, Albumin, Tbili, SCr, LDH, Trop, myoglobin, CRP, IL-6, ferritin

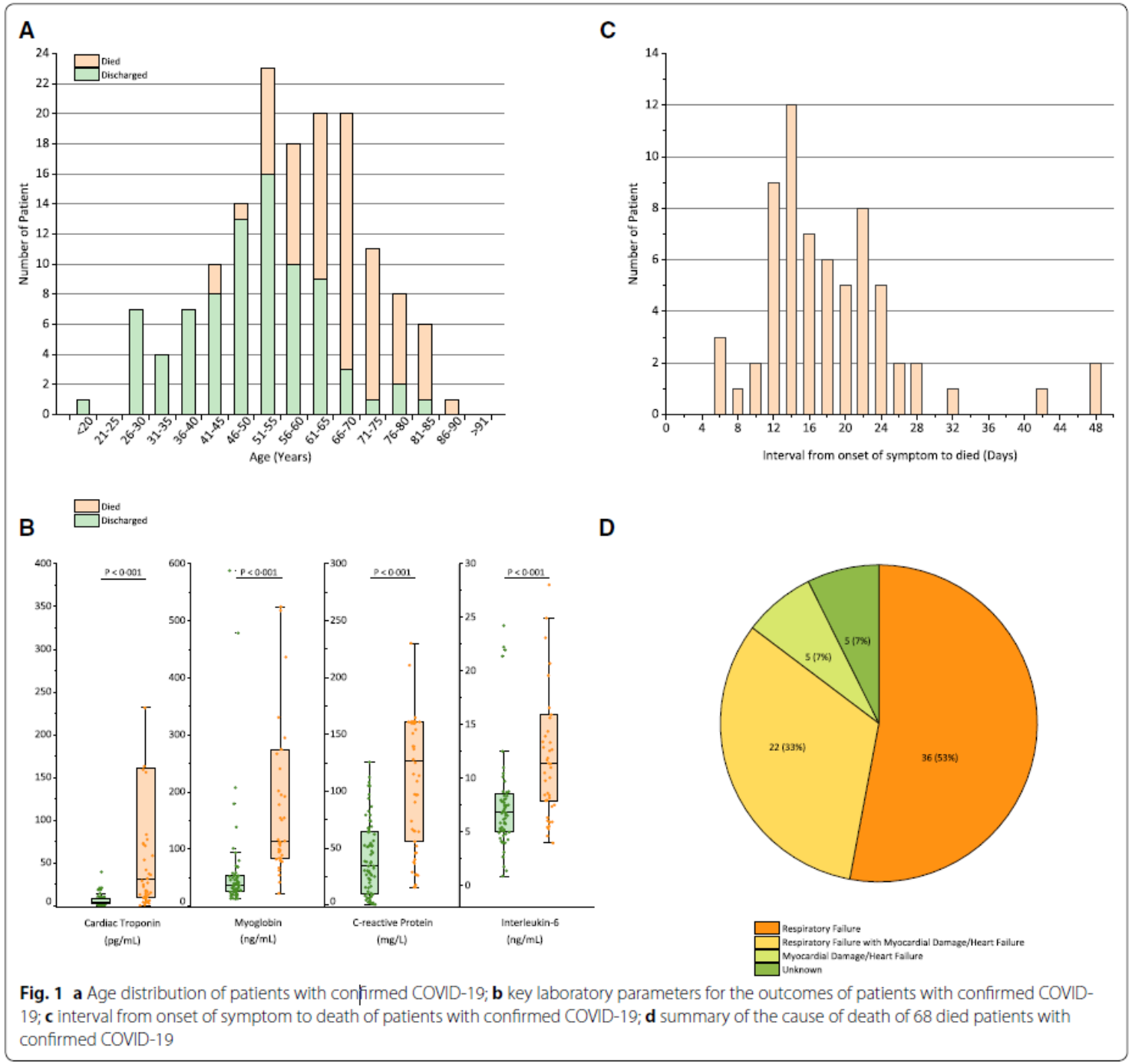


Fig. 1 **a** Age distribution of patients with confirmed COVID-19; **b** key laboratory parameters for the outcomes of patients with confirmed COVID-19; **c** interval from onset of symptom to death of patients with confirmed COVID-19; **d** summary of the cause of death of 68 died patients with confirmed COVID-19

Ruan et al. Int Care Med; Epub ahead of print. Online 03/03/2020

Risk Factor Analysis for COVID-19 Death

- 191 inpatients with moderate (38%) severe (35%) or critical (28%) disease

Univariate Comorbidities	Survived (137)	Died (54)	P value
Age	52	69	<0.01
Comorbidities	40%	67%	<0.01
Hypertension	23%	48%	<0.01
Diabetes	14%	31%	<0.01
Cor. heart disease	1%	24%	<0.01
COPD	1%	7%	0.05
CKD	0%	4%	0.02

Univariate Labs:

- ALC, HCT, Plts, Albumin, CK, LDH, SCr, Trop, PT, PTT, D-dimer, Ferritin, IL-6, PCT

Univariate Imaging:

- GGOs, consolidation

Multivariate Analysis:

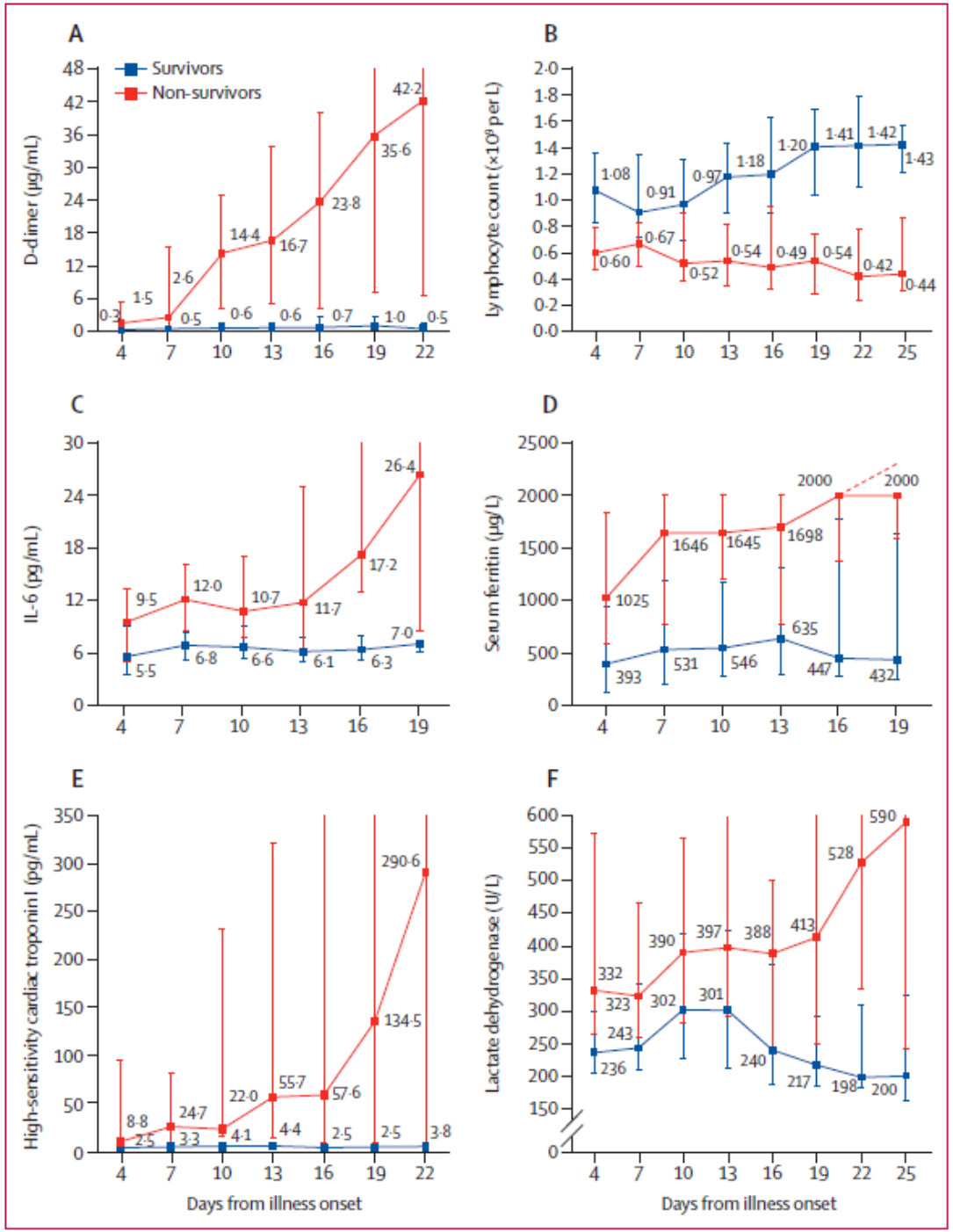
- **Older age (OR 1.1; p=0.004)***
- **SOFA score (OR 5.7; p<0.01)***
- **D-dimer >1 (OR 18.4; p=0.003)***
- Lymphocyte count (OR 0.2; p=0.13)
- Coronary Heart Disease (OR 2.1; p=0.48)

Zhou et al. Lancet. Epub online. 03-09-2020

D-Dimer

IL-6

Troponin



Absolute lymphocyte count

Ferritin

LDH

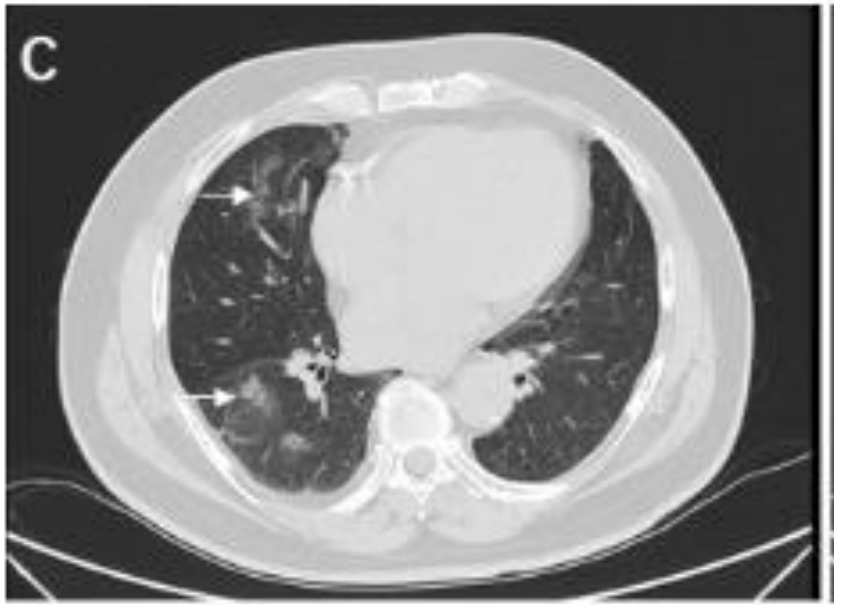
Zhou et al. Lancet. Epub online. 03-09-2020

Table 2: Main laboratory abnormalities in patients with unfavorable progression of coronavirus disease 2019 (COVID-19).

– Increased white blood cell count
– Increased neutrophil count
– Decreased lymphocyte count
– Decreased albumin
– Increased lactate dehydrogenase (LDH)
– Increased alanine aminotransferase (ALT)
– Increased aspartate aminotransferase (AST)
– Increased total bilirubin
– Increased creatinine
– Increased cardiac troponin
– Increased D-dimer
– Increased prothrombin time (PT)
– Increased procalcitonin
– Increased C-reactive protein (CRP)

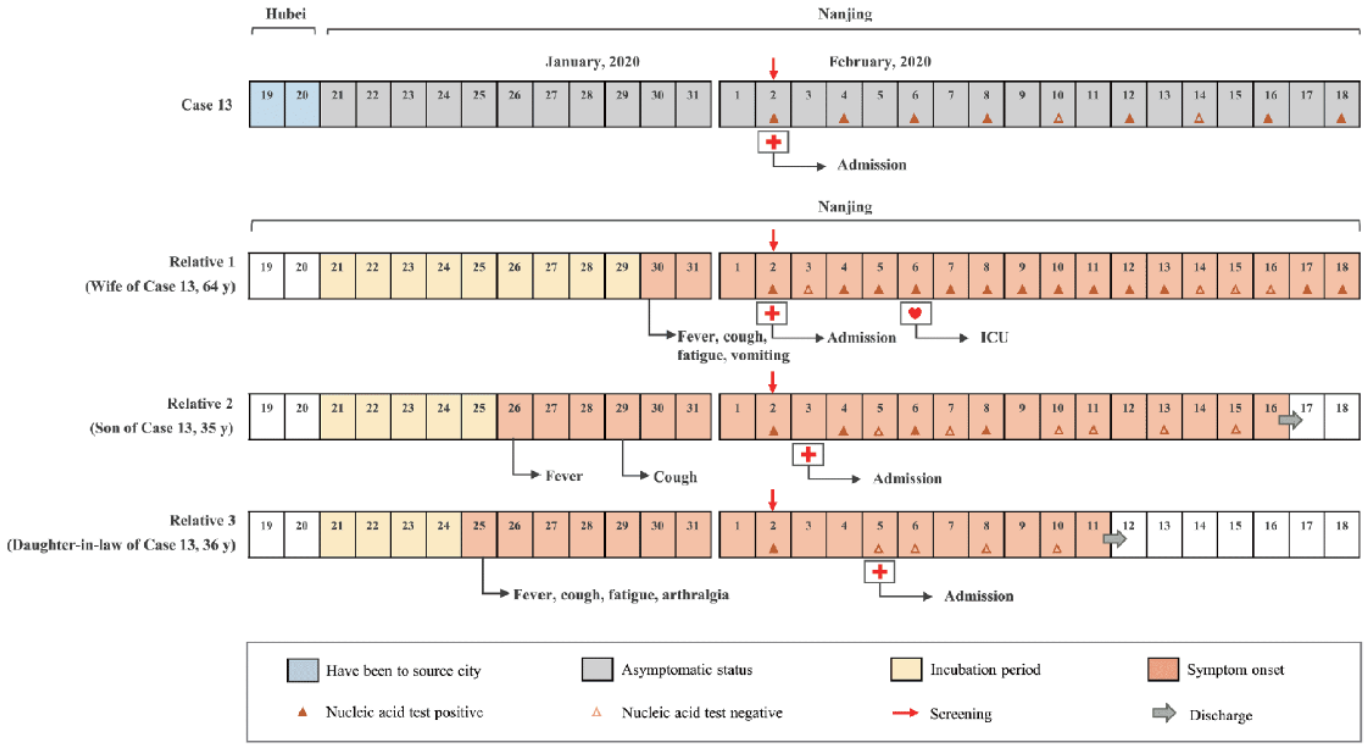
Lippi and Plebani. Clin Chem Lab Med epub ahead of print. 2020

Asymptomatic COVID-19



24 close contacts who screened COVID-19+

- Age: 32.5 (5-95yo)
- 8% had HTN and DM
- 5 (21%) developed symptoms
  - 29% abnormal LDH
  - 17% lymphopenia
  - 71% abnormal imaging
- Patients with normal CT:
  - Normal labs
  - Never symptoms
  - Young



Hu et al. Science China; Epub ahead of print. Online 03/04/2020

COVID-19 in Children

- 1% of reported cases in China were in children <10[1]

- Study of 731 children <16yo in China[2]
  - Age 10yo (evenly spread out*)
  - 97% mild/moderate; 2.5% severe; 0.4% critical, 0% deaths
    - Severe/critical disease (when occurred) more common in younger population.

- Study of 171 children <16yo in Wuhan[3]
  - Age 6yo (evenly spread out)
  - Cough 49%, Pharyngeal erythema 46%, Fever 41%, diarrhea 9%
  - Mild illness (Lymphopenia 3.5%, only 65% pneumonia, 1.8% ICU, 0% Deaths)

- Multi-site review of 31 pediatric cases[4]
  - Age 7yo
  - Fever 65%, Cough 45%, Fatigue 10%, Diarrhea 9%
  - 6% lymphopenia, 10% CRP elevation, 15% ESR elevation
  - No severe or critical illness

1. Wu et al. JAMA Epub online. 02-24-2020
2. Dong et al. Pediatrics. Epub ahead of print. 03-16-2020
3. Lu et al. NEJM. Epub ahead of print 03-18-2020
4. Zhi et al. Chinese CDC. Epub 2020.

Treatment

1. Supprortive Care
2. Chloroquine and hydroxychloroquine
3. Remdesivir
4. Lopinivir/ritonavir
5. Tocilizumab

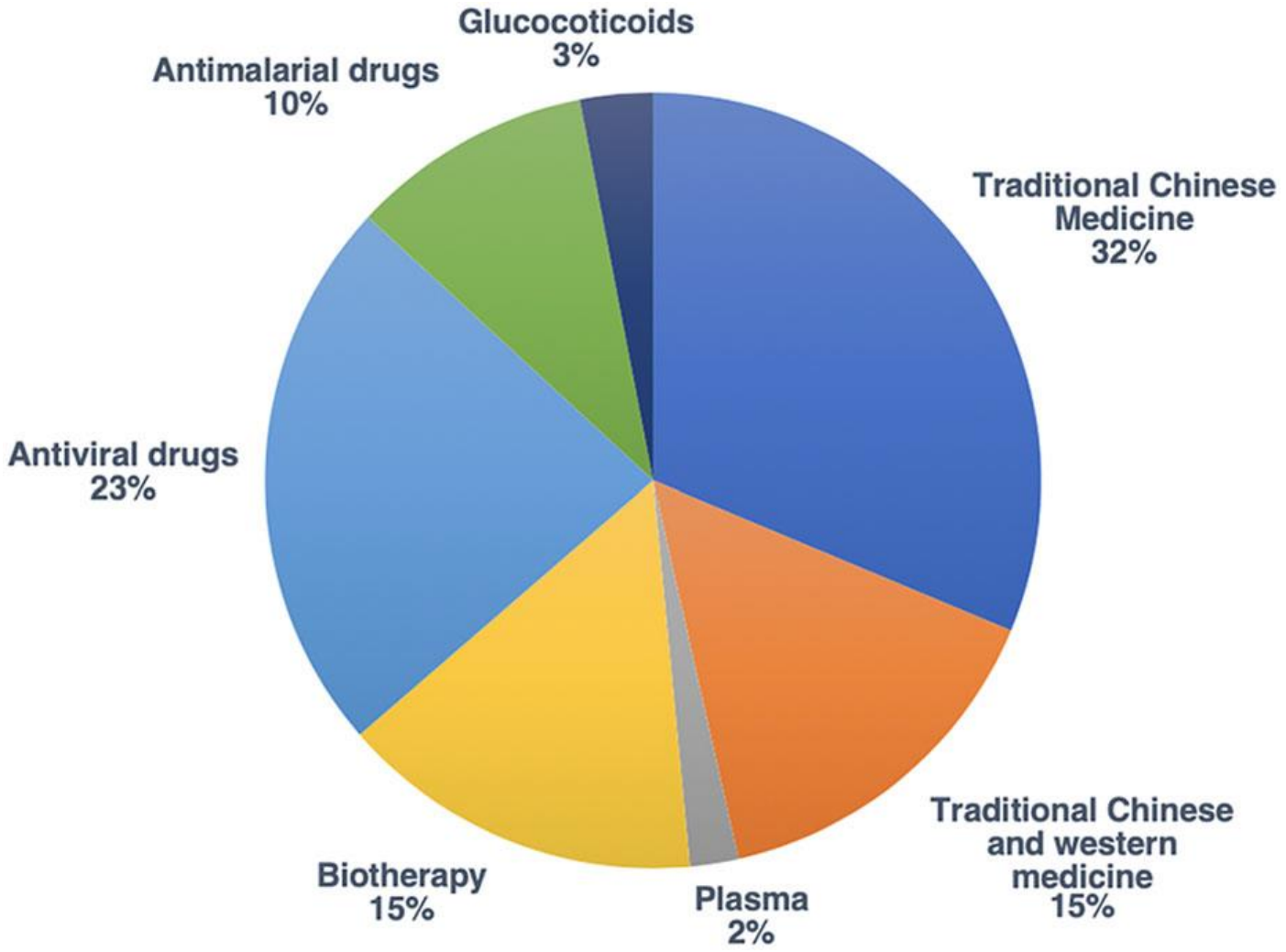
1. Therapeutic options for severe acute respiratory distress syndrome related to COVID-19

Therapy	Implementation
High-flow nasal oxygen	Might prevent or delay the need for intubation
Tidal volume	Use 6 mL/kg per predicted bodyweight (can reduce to 4 mL/kg per predicted bodyweight)
Plateau airway pressure	Maintain at <30 cm H_20 if possible
Positive end-expiratory pressure	Consider moderate to high levels if needed
Recruitment manoeuvres	Little value
Neuromuscular blockade	For ventilator dyssynchrony, increased airway pressure, hypoxaemia
Prone positioning	For worsening hypoxaemia, PaO_2:FiO_2 <100–150 mm Hg
Inhaled NO	Use 5–20 ppm
Fluid management	Aim for negative fluid balance of 0·5–1·0 L per day
Renal replacement therapy	For oliguric renal failure, acid-base management, negative fluid balance
Antibiotics	For secondary bacterial infections
Glucocorticoids	Not recommended
Extracorporeal membrane oxygenation	Use EOLIA trial criteria[3]

Matthay et al. Lancet Respiratory Medicine. Epub ahead of print. 03/2020

Targeted Therapy? Clinical Trials Underway!

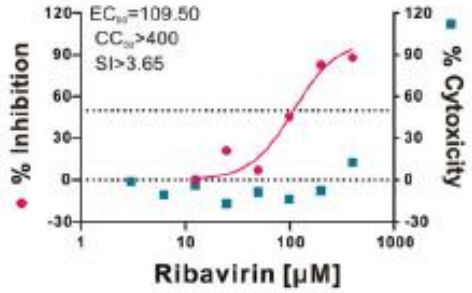
- 38 clinical trials in China
- 6 clinical in USA
- More

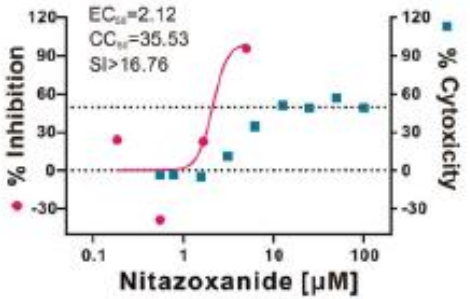


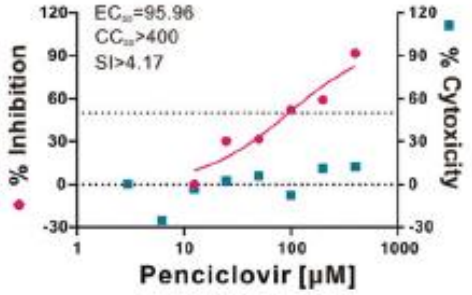
Zhang et al. JMV. 2020; Epub ahead of print. 03/2020

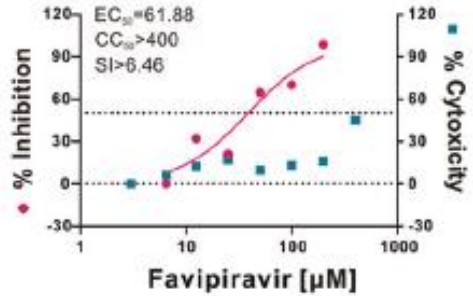
Targeted Treatment for COVID-19

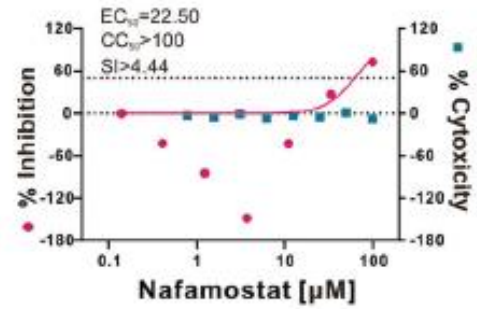
- 01-25-20 (18d*) Publication in Cell Research
- In Vitro study of 7 candidate drugs
  - Ribavirin and penciclovir required toxic doses
  - Favipiravir required high doses
  - Nafamostat and nitozoxanide inhibited virus
  - Chloroquine and Remdesivir had potent antiviral effect at low micromolar doses

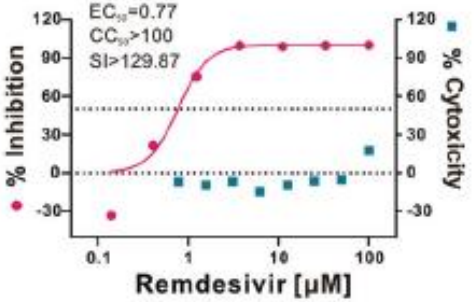


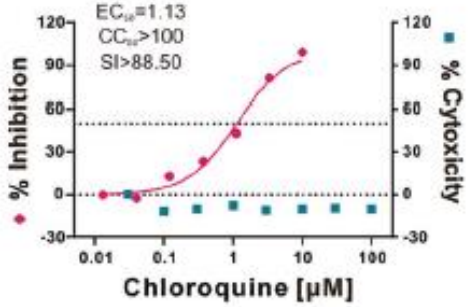




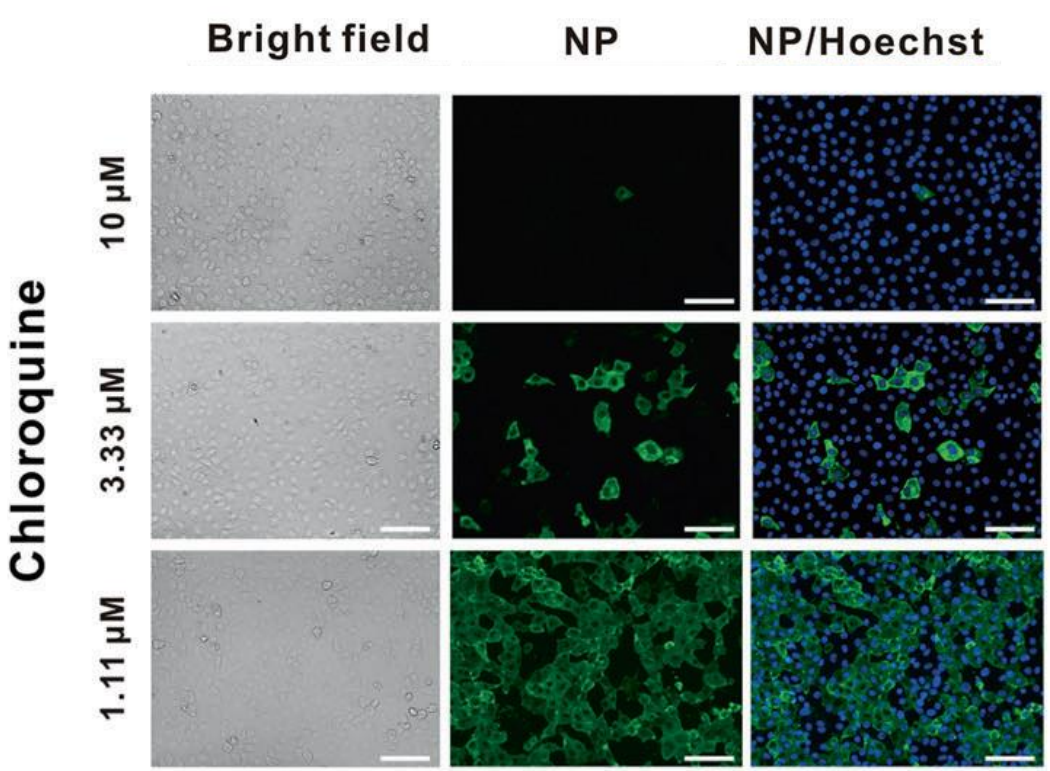


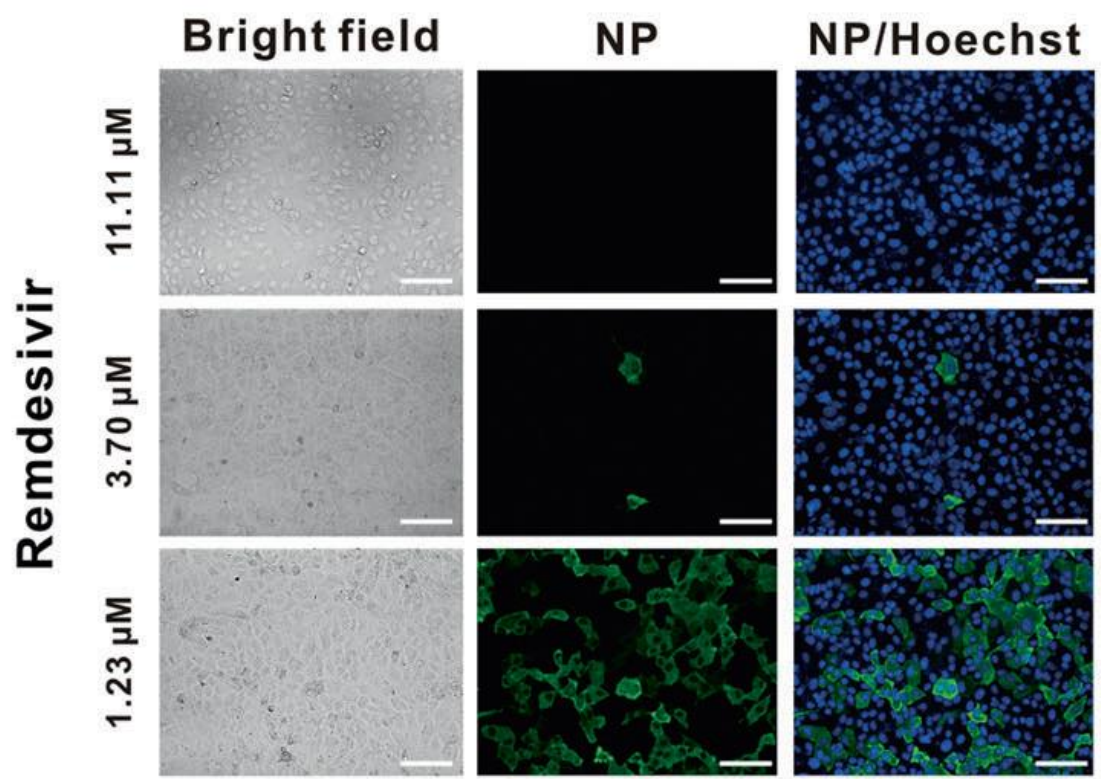


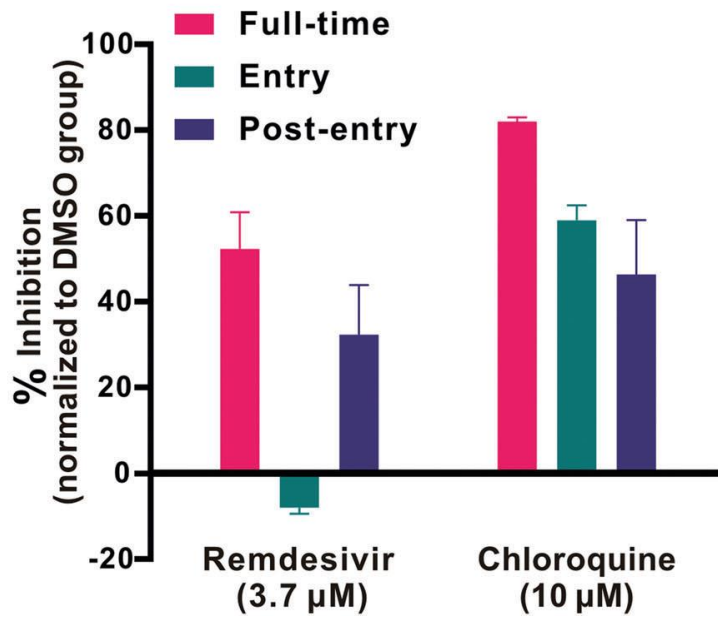




M Wang et al. Cell Research 30: 269-271. 2020







M Wang et al. Cell Research 30: 269-271. 2020

2. Chloroquine and Hydroxychloroquine for SARS-CoV-2

Rationale:

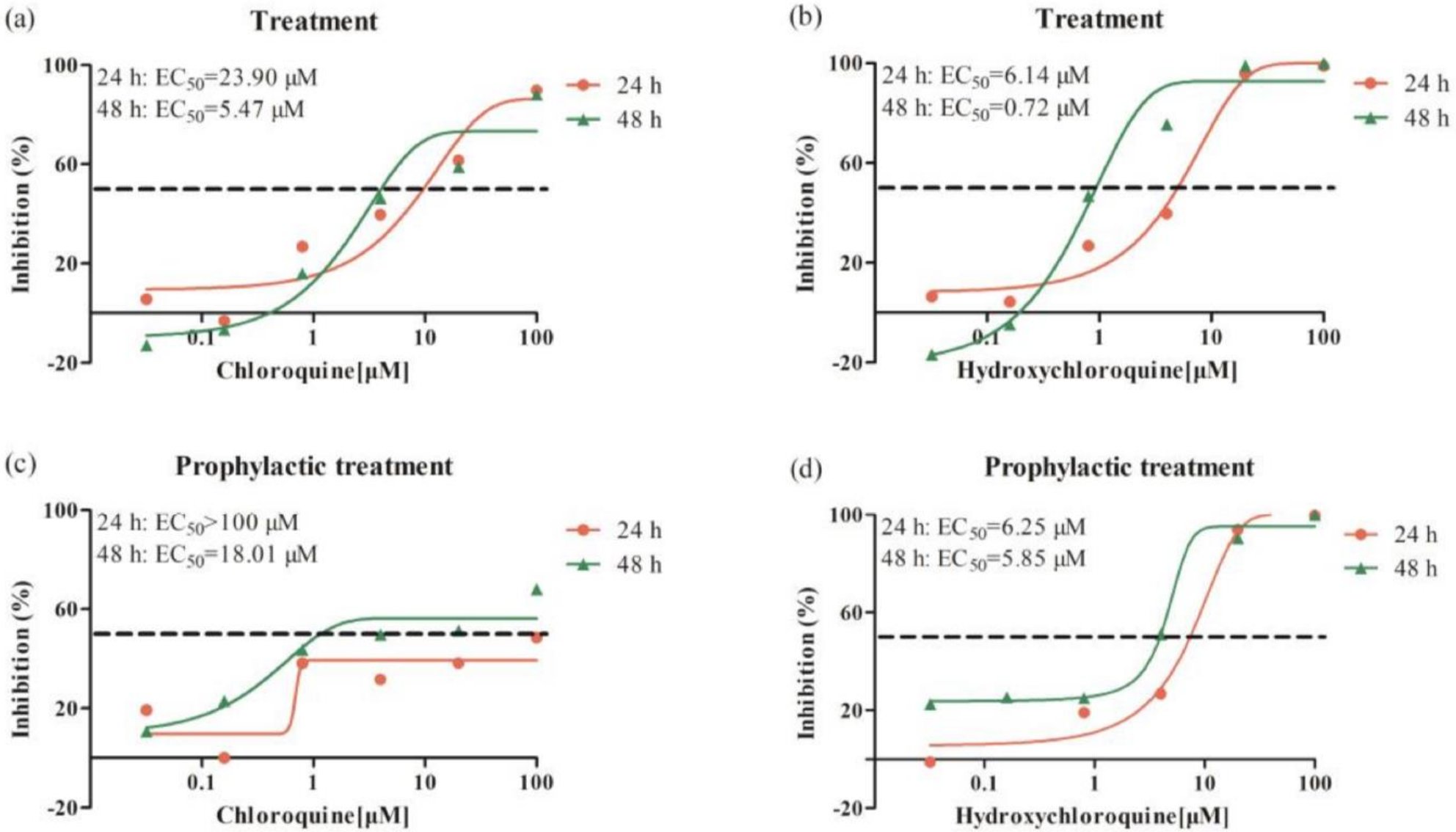
- Both are known to have immunomodulatory effects
- Hydroxychloroquine is an analog of chloroquine with fewer drug-drug interactions
- Hydroxychloroquine demonstrated activity against SARS-CoV-1 in in vitro[1]

Proposed Mechanism of Action[2]:

- Alters pH at the cell membrane surface inhibiting virus-membrane fusion
- Inhibits viral life cycle (replication, glycosylation, assembly, transport…)
- Immunomodulation

1. Biot et al. JMEdChem 2006.
2. Yao et al. CID. Epub ahead of print. 2020

Chloroquine & Hydroxychloroquine *in vitro*



Yao et al. CID. Epub ahead of print. 2020

Chloroquine & Hydroxychloroquine *in vitro*

Treatment EC50:

- Hydroxychloroquine: 0.72uM
- Chloroquine: 5.47uM

Prophylaxis EC50:

- Hydroxychloroquine: 5.85uM
- Chloroquine: 18.01uM

Hydroxychloroquine:

- Superior anti-viral and prophylactic activity

Yao et al. CID. Epub ahead of print. 2020

Chloroquine & Hydroxychloroquine Clinical Trials

- French study of 42 (non-randomized) COVID-19 patients evaluating for viral clearance for NP swabs

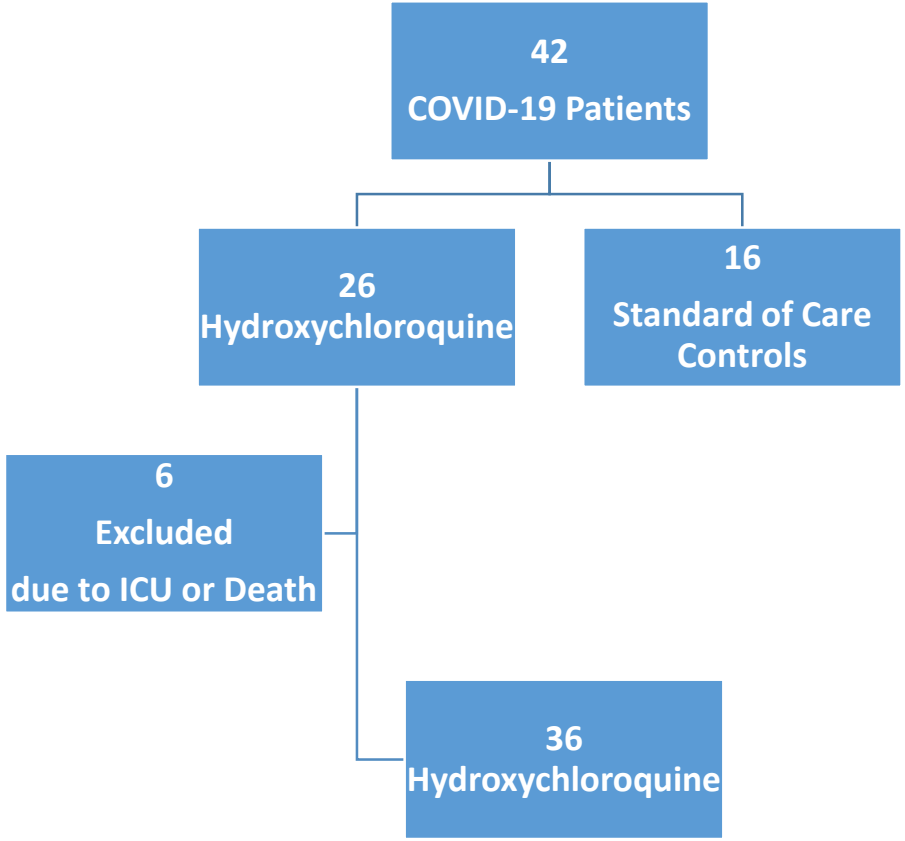
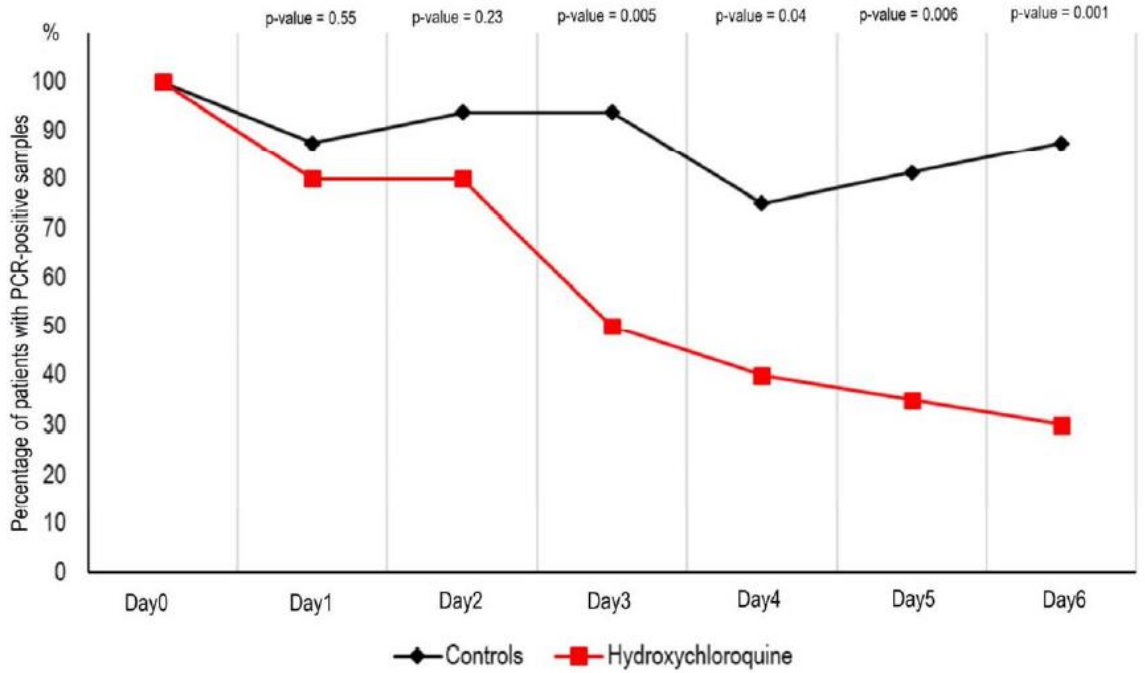


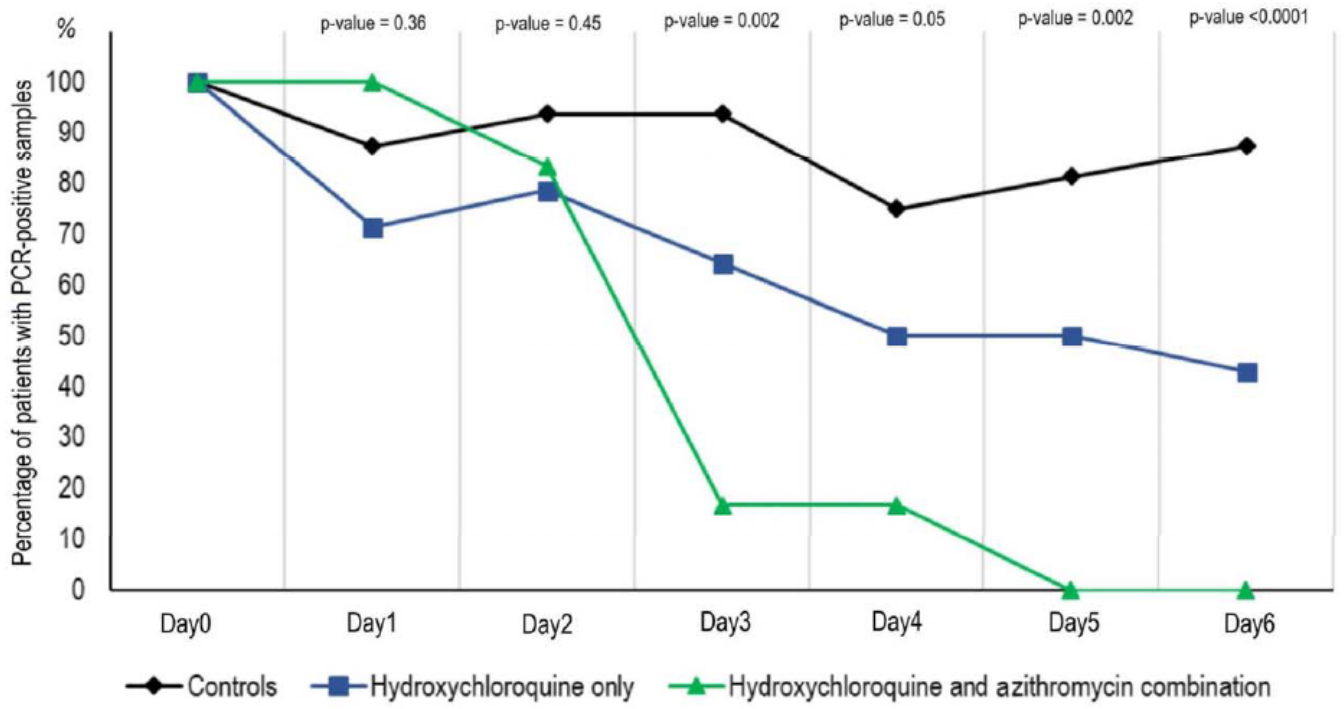
Figure 1. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.



Gautret et al. IJAA. Epub ahead of print. 3-17-2020

Chloroquine & Hydroxychloroquine Clinical Trials (French study continued)

Figure 2. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithomycin combination, and in COVID-19 control patients.



Study group	Day of illness at time of enrollment
Controls	2.8
HCQ	3.4
HCQ+Azithro	4.3

Limitations:

1. Very small sample size (6 for azithro)
2. Non-randomized
3. Location/Center Bias
4. Exclusion of ill patients
5. Outcome based on day of enrollment not day of illness

Chloroquine & Hydroxychloroquine Clinical Trials

- Multiple clinical randomized controlled trials ongoing in china and elsewhere evaluating clinical impact of chloroquine or hydroxychloroquine

- Gao et al. “Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies”
  - “Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course according”.

Gao et al. BioScience Trends. Epub ahead of print. 2020

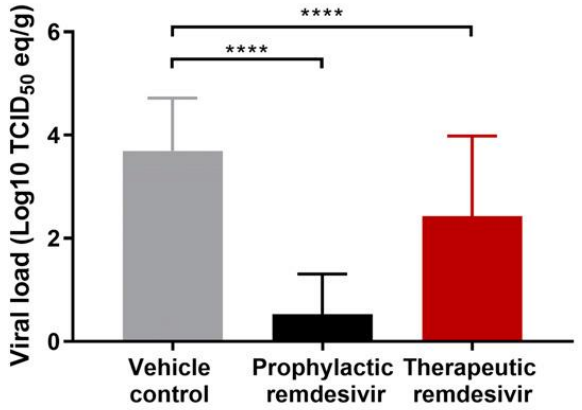
Chloroquine & Hydroxychloroquine Evidence

- Scientific rationale behind possible use with known mechanism of action and activity vs SARS in vitro
- Compelling *in vitro* evidence for hydroxychlorqouine activity against SARS-CoV-2
- Limited clinical data suggests hydroxychloroquine is better than standard of care treatment
- This is a well known drug with limited side effects, drug-drug interation, and minimal risk when prescribed in short courses

3. Remdesivir for SARS-CoV-2

Rationale:

- Experimental non-FDA approved antiviral just synthesized by Gilead in 2017
- Mechanism of action
- Demonstrated activity against Ebola in in vitro[1] and in vivo[2] (macaque)
- Demonstrated superior anti MERS-CoV activity compared to lopinavir/ritonavir[3]
- Demonstrated efficacy in vivo vs MERS-CoV in macaque model[4]



Proposed Mechanism of Action:

- Obscures viral RNA polymerase, evades viral exonucleases, decreasing viral RNA production
- Adenosine analog leading to chain termination of nascent viral RNA

1.Warren et al. Nature. 2016, 531.
2. Warren et al, OFID 2015; 2.
3. Sheahan et al. Nature communications. 2020: 11:222.
4. De Wit et al. PNAS. Epub ahead of print. Feb 2020.

Remdesivir SARS-CoV-2 *in vitro* data

- See prior slides

Remdesivir Clinical Data (One case report)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

First Case of 2019 Novel Coronavirus in the United States

Michelle L. Holshue, M.P.H., Chas DeBolt, M.P.H., Scott Lindquist, M.D., Kathy H. Lofy, M.D., John Wiesman, Dr.P.H., Hollianne Bruce, M.P.H., Christopher Spitters, M.D., Keith Ericson, P.A.-C., Sara Wilkerson, M.N., Ahmet Tural, M.D., George Diaz, M.D., Amanda Cohn, M.D., LeAnne Fox, M.D., Anita Patel, Pharm.D., Susan I. Gerber, M.D., Lindsay Kim, M.D., Suxiang Tong, Ph.D., Xiaoyan Lu, M.S., Steve Lindstrom, Ph.D., Mark A. Pallansch, Ph.D., William C. Weldon, Ph.D., Holly M. Biggs, M.D., Timothy M. Uyeki, M.D., and Satish K. Pillai, M.D., for the Washington State 2019-nCoV Case Investigation Team*

- 35yo M travelled from China to Washington.
- Presented to clinic with mild resp sx (HR 115, O2sat 96%/ra)
- COVID-19 Swab positive and admitted.
- Progressed to Pneumonia day 9
- Remdesivir compassionate use administered day 9
- Patient recovered and was discharged

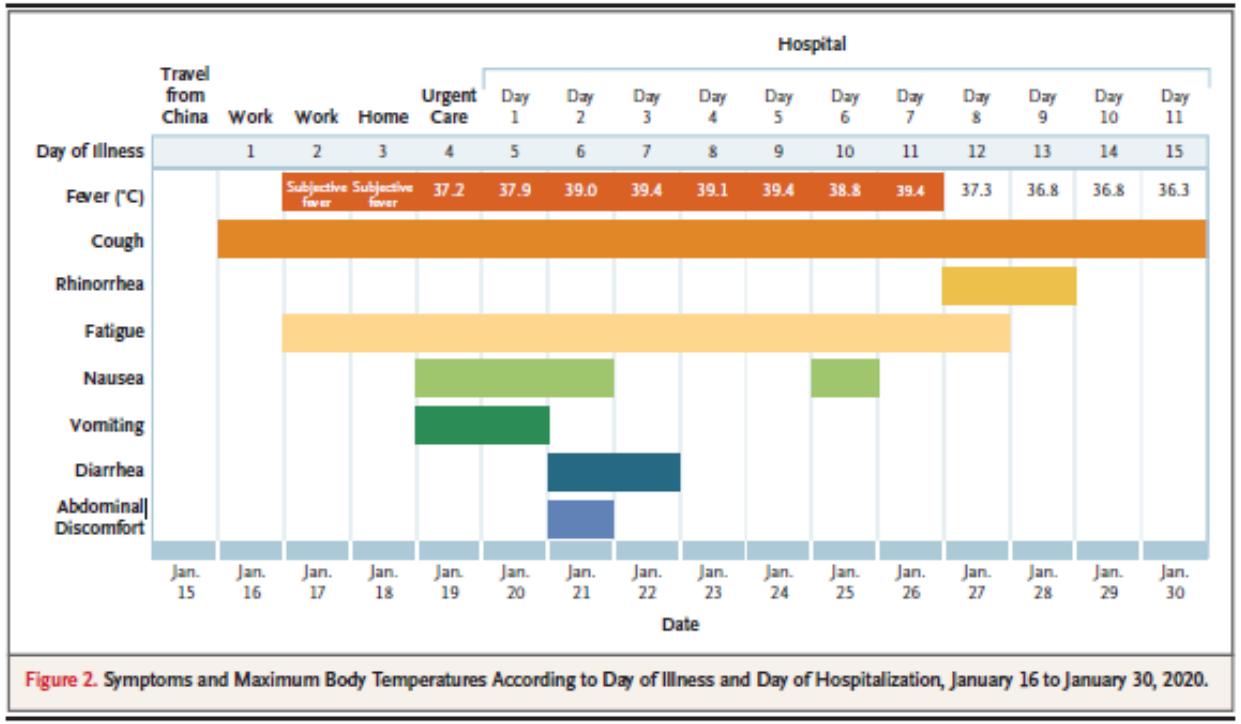


Figure 2. Symptoms and Maximum Body Temperatures According to Day of Illness and Day of Hospitalization, January 16 to January 30, 2020.

Holshue et al. NEJM. Epub Ahead of print 03-05-2020

Remdesivir Evidence

- Scientific rationale behind possible use with known mechanism of action and activity vs MERS in vitro
- Evidence of potent *in vitro* activity against SARS-CoV-2
- Limited clinical evidence though multiple RCTs ongoing
- Compassionate use is no longer available.

4. Lopinavir/ritonavir for SARS-CoV-2

Rationale:

- Experimental non-FDA approved antiviral just synthesized by Gilead in 2017
- Mechanism of action
- Demonstrated activity vs SARS *in vitro*[1]
- For SARS, Lopinavir/ritonavir + ribavirin reduced risk of adverse clinical outcomes compared to ribavirin alone[1] (non-randomized, not controlled)
- Demonstrated efficacy *in vitro* vs MERS-CoV [2]
- Case reports of MERS-CoV patients having virological clearance and survival when combined with ribavirin or interferon[3]
- Widely available and safe with extensive clinical experience in use with HIV

Proposed Mechanism of Action:

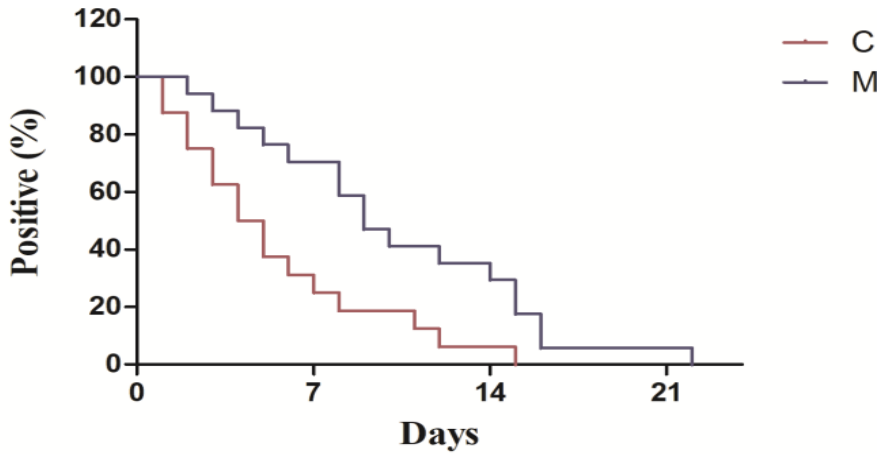
- Antiviral protease inhibitor cleaving viral 3CL protease.
- Combination with ritonavir increases drug bioavailability

1. Chu et al. Thorax 2004. 59-252-6.
2. Kim et al. Antiviral Ther 2016. 31. 455-9.
3. Min et al. Sci rep 2016; 6 25359.

Lopinavir/Ritonavir SARS-CoV-2 Clinical data

- Retrospective Case Series of 33 patients with mild/moderate infection
  - Arbidol + Lopinavir/ritonavir: 16
    - RT-PCR Negative at day 7: **75%**
    - RT-PCR Negative at day 14: **94%**
    - CT improved by day 7: **69%**
  - Lopinavir/ritonavir: 17
    - RT-PCR Negative at day 7**: 35%** P<0.05
    - RT-PCR Negative at day 14: **53%** P<0.05
    - CT improved by day 7: **29%** P<0.05

Of note:
50% pf monotherapy group on steroids** P=0.04



Limitations:

1. Very small sample size
2. We don't have arbidol in US
3. Non-randomized
4. Monotherapy group had more steroids**

Lopinavir/Ritonavir SARS-CoV-2 Clinical data

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

China RCT of 199 COVID patients

- Lopinavir/ritonavir vs standard of care
- Primary Outcome: Time to clinical improvement

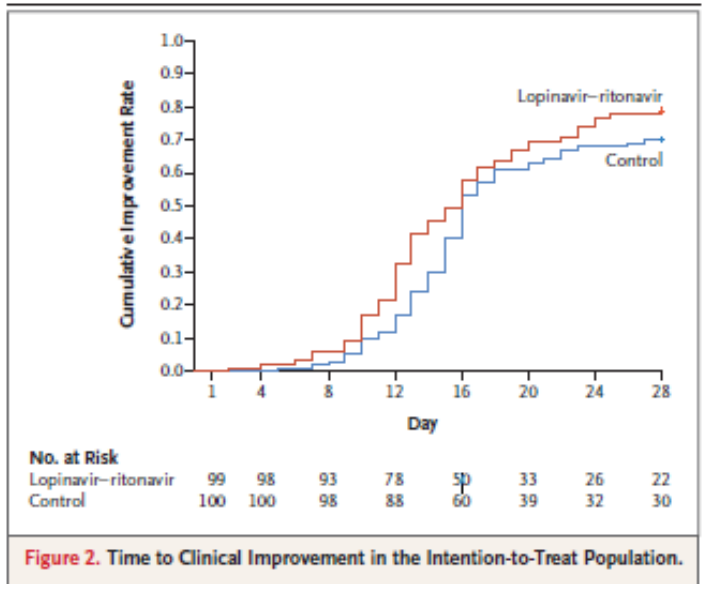


Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

Both groups:
16d (ns)

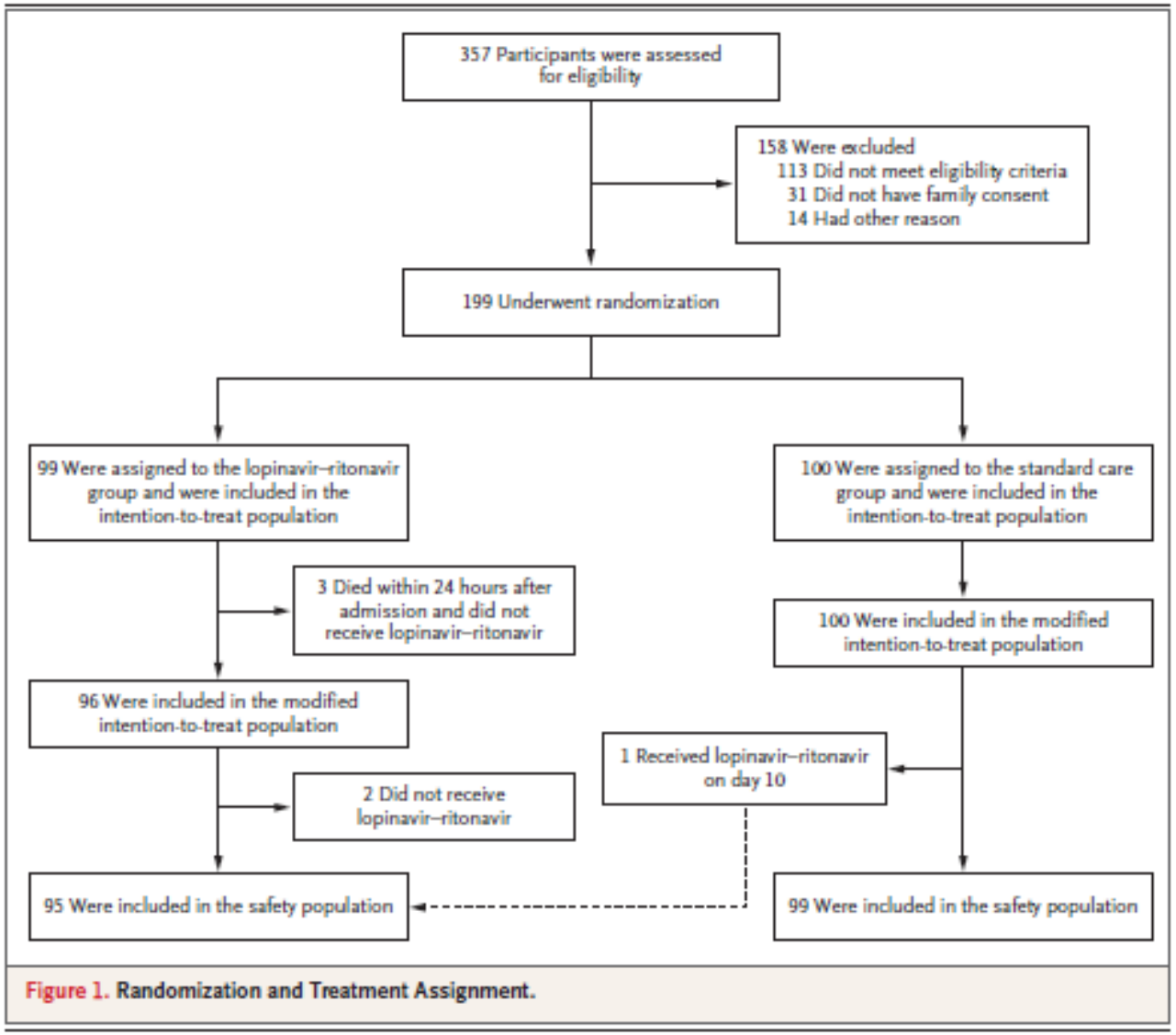


Figure 1. Randomization and Treatment Assignment.

Lopinavir/Ritonavir NEJM RCT Continued

- Mortality at 28 days:
  - Lopinavir/ritonavir: 19.2%
  - Standard of Care: 25%

Diff-5.8%; 95% CI (-17.3-5.7)

- % of Patients with detectable SARS-CoV-2 RNA at various time points were similar

Lopinavir/ritonavir Evidence

- Scientific rationale behind possible use with known anti-viral mechanism of action
- In vitro and in vivo evidence is much better when administered with other antiviral (ribavirin, interferon, arbidol…)
- Only drug with robust clinical trial data, however did not show a difference.
- Multiple RCTs ongoing with and without combination antiviral.

5. Tocilizumab for SARS-CoV-2

Rationale:

- SARS, MERS, and COVID-19 are known to cause a cytokine storm resulting in fulminant end-organ damage.
- IL-6 levels (along with other cytokine markers) are elevated in critically ill patients with COVID-19
- Patients with similar presentation following CAR T Cell therapy are routinely administered tocilizumab during cytokine storm with improved outcomes

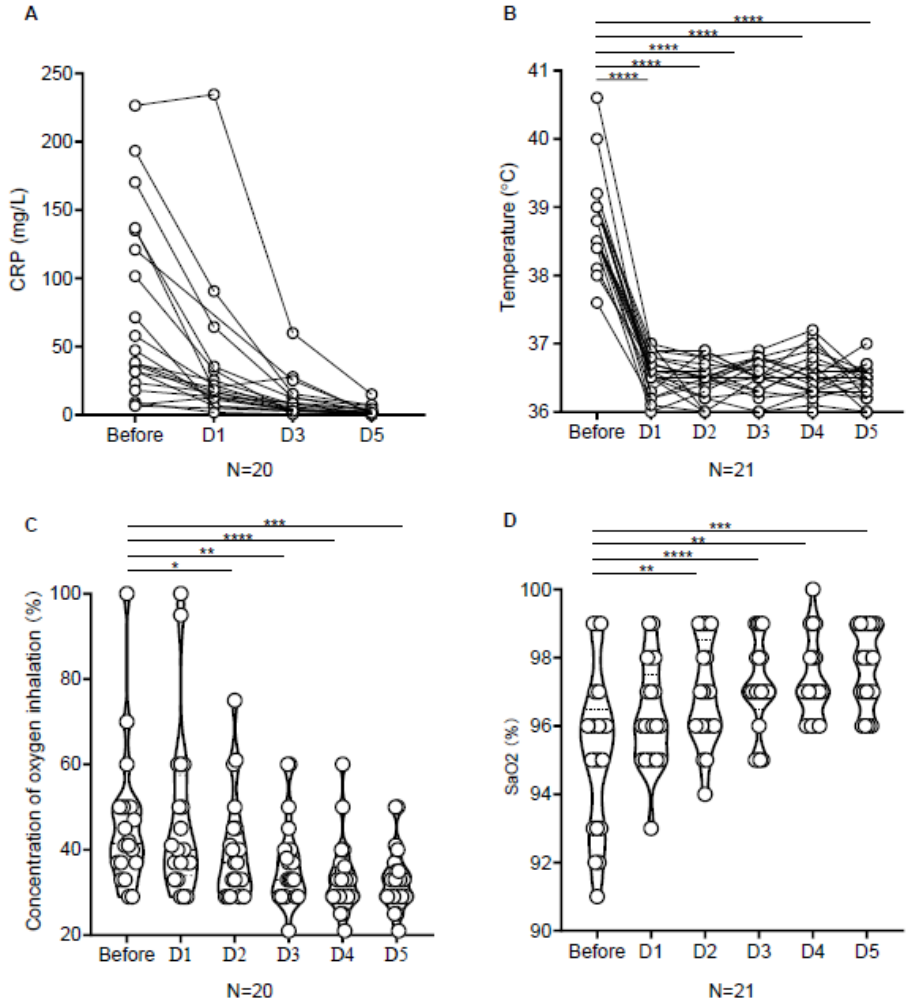
Proposed Mechanism of Action:

- Tocilizumab is recombinant humanized anti-human-IL6 receptor monoclonal antibody
- Tocilizumab binds sIL-6R inhibiting signal transduction slowing inflammatory response

1. Chu et al. Thorax 2004. 59-252-6.
2. Kim et al. Antiviral Ther 2016. 31. 455-9.
3. Min et al. Sci rep 2016; 6 25359.

Tocilizumab clinical data

- Retrospective case series of 21 severely ill COVID-19 patients in China.
- No comparator group
- Within a few days of infusion:
  - 75% had lowered O2 requirement
  - 91% had improved CT scan findings
  - 53% Lymphocyte count returned to normal
  - 84% CRP decreased significantly
- No adverse reaction observed
- 91% discharged on 13.5d following tx



Tocilizumab Evidence

- Scientific rationale behind possible use in critically ill patients with cytokine storm. No antiviral effect.
- Limited clinical evidence is promising
- Supply is limited, expensive, side effects unclear (TB, HBV)
- Needs clinical trial data

COVID-19 UAMS Targeted Treatment Considerations for Patients Admitted with COVID-19 Infections

MARCH 24, 2020

***Clinical data on potential therapies for COVID-19 infections are severely limited.

***Therapies referenced in this document should be used with caution and consideration of potential benefits and harms should be measured prior to individual use.

Potential treatment options for COVID-19 infections (see table for dosing):

1. **Mild/Moderate disease:** Admitted with minimal oxygen requirement
   a. Supportive care if does not meet high risk criteria*
   b. Consider hydroxychloroquine if meets any high risk criteria*
2. **Severe disease:** Admitted with any of the following [SpO2 <94% on room air, RR>30 bpm, PaO2/FiO2 300mmHg]
   a. Consider hydroxychloroquine
   b. Consider remdesivir. Contact Gilead (if available)
3. **Critical disease:** ICU care with mechanical ventilation, shock, or other organ failure
   a. Consider hydroxychloroquine
   b. Consider remdesivir. Contact Gilead (if available)
   c. Consider tocilizumab (contact ID)

***HIGH RISK criteria for developing severe or critical disease (any of the following apply):**

1. Age > 60yo
2. Chronic Medical Conditions such as CHF, CKD, COPD, CVD, HTN, Cirrhosis, DM, immunosuppressed
3. Any of the following lab abnormalities: ALC < 1,000, LDH >1x ULN, AST or ALT >2x ULN

Studies recommended for COVID-19 infections:

1. CBC with differential **(admission and daily)**
2. BMP **(admission and daily)**
3. Liver function tests (AST, ALT, TBili) **(admission and daily)**
4. Coags (PT, PTT, DDimer, fibrinogen) **(admission and daily if in ICU)**
5. LDH **(admission and daily)**
6. Inflammatory markers (CRP, ESR, Ferritin) **(admission and daily)**
7. Triglycerides **(admission and daily if in ICU)**
8. Troponin **(admission and prn)**
9. EKG **(admission and prn)**
10. Sputum culture **(admission and prn)**
11. MRSA nares PCR **(if starting vancomycin for VAP/HAP coverage)**
12. IL-6 level **(at ICU admission and prn if giving tocilizumab)**

Drug	Contra-Indications	Monitoring	Data
Hydroxychloroquine Dose: (tab or suspension) 400mg PO q12h x1d 200mg PO q12h x4d Adverse effects (5d-rare): - GI Disturbance - Prolonged QTc - Retinopathy	1. Prior known G6PD deficiency - consider screening for pts with Mediterranean descent Relative contra-indications: 1. Known underlying cardiomyopathy 2. Prolonged QTc	Routine: -CBC with diff - LFTs - SCr - QTc (monitor closely if >470 msec)	COVID-19 Clinical Data: - Gautret (IJAA): 20 HQ vs 16 SOC->significant viral load reduction. Excluded HQ patients who progressed COVID-19 In vitro Data: - Yao (CID): 3x more potent in vitro compared to vs chloroquine Chloroquine COVID-19 data (extrapolated for hydroxychloroquine): - Clinical Data: Gao (BioSci Trends) reports 100 pts with improved outcomes vs SOC - Chinese Treatment recs Chloroquine based on early data out of ongoing RCTs - In vitro data (Wang CellRes) shows highly effective compared to other antiviral options
Tocilizumab Dose: 400mg IV x1 If no benefit, can consider continuation up to 3 additional doses at least 8h apart. Adverse effects: - Liver failure - Cytopenias	Relative contra-indications: 1. Active hepatic disease or impairment (LFTs >3x ULN)	Screen: 1. HBV profile 2. T-Spot Routine: - LFTs (d/c if >5x ULN) - IL6 level pre and post dosing	COVID-19 Clinical Data: - Xu et al, 21 severe/critical pts (not peer reviewed; case series). All survived 91% d/c, 9% improving. By day 5, Imaging improved (91%), normalization of ALC (53%) and CRP (84%), and O2 req improved (75%). 18-1x dose; 3-2x doses.
Remdesivir Available thru Gilead: https://rdvcu.gilead.com Adverse effects: - Liver failure, AKI	Company listed Exclusion: 1. Multi-organ failure 2. Vasopressor requirement 3. ALT levels > 5 X ULN 4. CVVH CrCl<30 mL/min	Routine: - Per company	COVID-19 Clinical Data: - Holshue (NEJM case report): C1 pt clinically improved. No adverse event COVID-19 In vitro Data: - Wang: very good in vitro efficacy similar to chloroquine MERS-CoV Animal model: - De Wit, better than placebo for ppx and for treatment
Lopinavir/ritonavir Dose: 400/100mg BID x14d Adverse Events: - GI disturbance - Liver failure - Drug-drug interactions	1. Check for drug-drug interactions as ritonavir is a CYP3A inhibitor	Routine: - LFTs	COVID-19 Clinical Data: - Cao et al (NEJM) RCT vs SOC: No difference in Time to improvement (16d), mortality not statistically different SARS Clinical Data: - Chan (HongKong Med J): retrospective matched cohort with less death vs SOC

Medications without clinical data to recommend for or against use in patients with known COVID-19 infection: NSAIDS, Ace inhibitors, ARBs

Medications not recommended unless a specific indication exists other than COVID-19 infection: Corticosteroids, IVIG, Ribavirin +/-interferon-(alpha or beta)

Conclusion

- Wash your hands!

- Treatment protocol:
  - Internal: https://inside.uams.edu/coronavirus/wp-content/uploads/sites/44/2020/03/UAMS-Targeted-Treatment-Considerations-for-Patients-Admitted_032420.pdf
  - External: https://uamshealth.com/coronavirus/wp-content/uploads/sites/13/2020/03/UAMS-Targeted-Treatment-Considerations-for-Patients-Admitted_032420.pdf