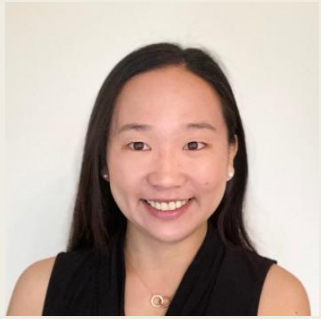


June-Wha Rhee, MD, FACC

Practicing Cardiologist with Specialty in Cardio-oncology; Instructor, Stanford Cardiovascular Institute, Stanford University School of Medicine

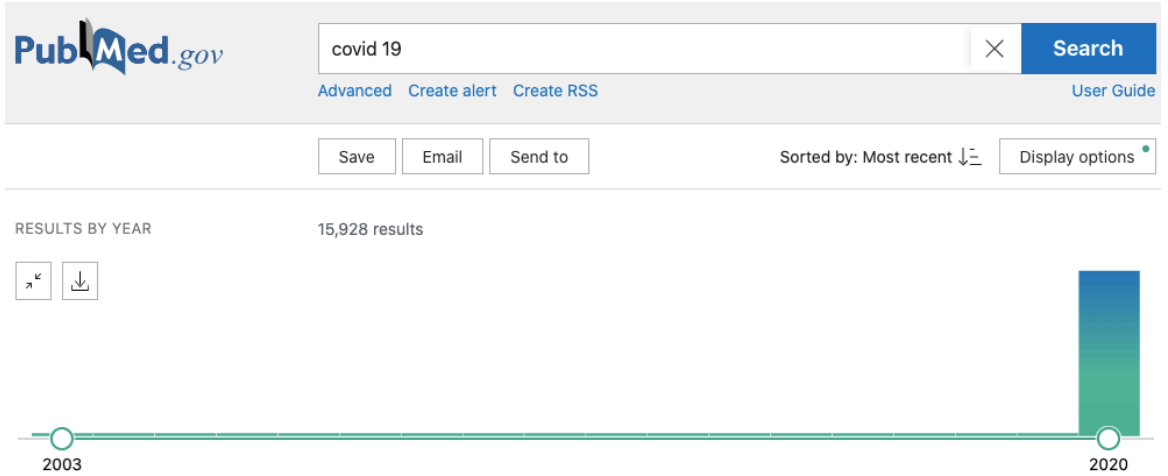
Dr. Rhee is a general cardiologist with specialized clinical and research training in cardiovascular drug toxicity and pharmacogenomics. She completed clinical cardiology fellowship and internal medicine residency training at Stanford University School of Medicine. During her post-doctoral training, Dr. Rhee's research focused on elucidating cardiotoxic effects of iron overload and of multiple chemotherapeutic agents using patient-specific induced pluripotent stem cells (iPSCs) derived models. Her current research employs clinical data, population genomics, and patient-derived iPSCs models to study genetic determinants and mechanisms of drug-induced cardiovascular toxicities. Dr. Rhee's clinic sees cardio-oncology patients and focuses on devising new methods for minimizing cardiovascular complications in that population.

Updates on Cardiovascular Complications of COVID-19

June-Wha Rhee, MD, FACC
Stanford University School of Medicine

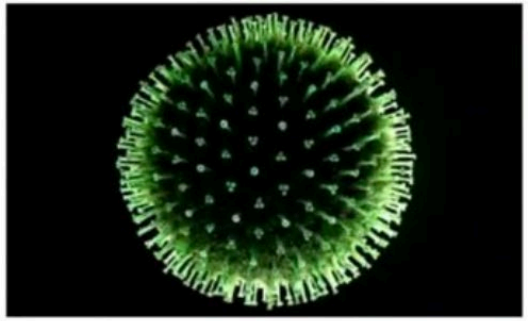
Outline

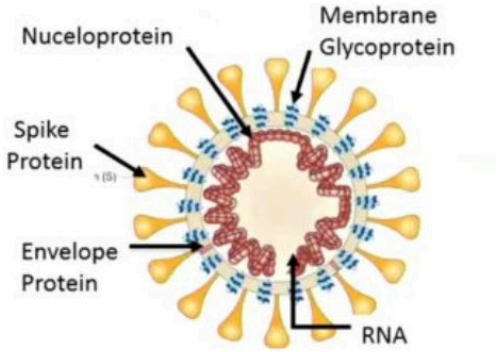
- Brief biology of COVID-19
- Overall epidemiology & spectrum of cardiac complications related to COVID-19
- Cardiac complications
  - Myocardial injury & heart failure
  - Arrythmia and cardiac arrest
- Available/experimental treatment options
- ACEI/ARB considerations



Since 2020, 15,928 articles have been published on COVID-19!

Basics of SARS-CoV-2

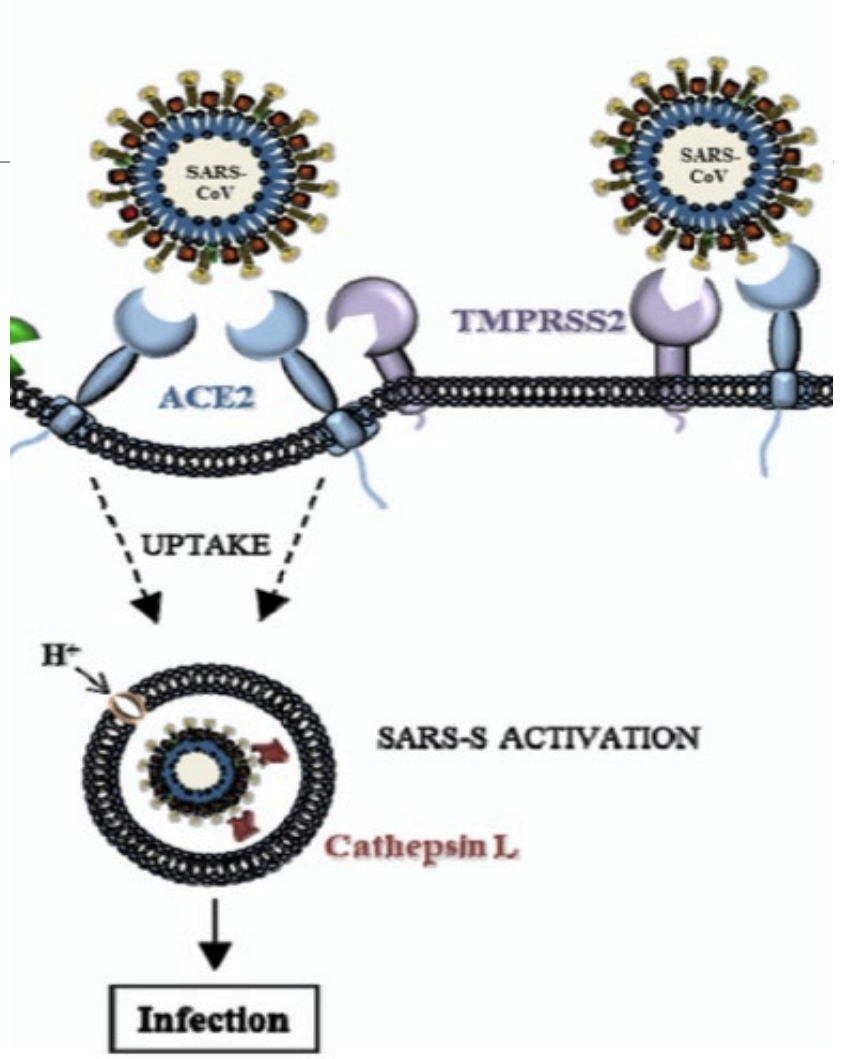




Enveloped + sense ssRNA virus

Genome sequence suggest bat-derived source

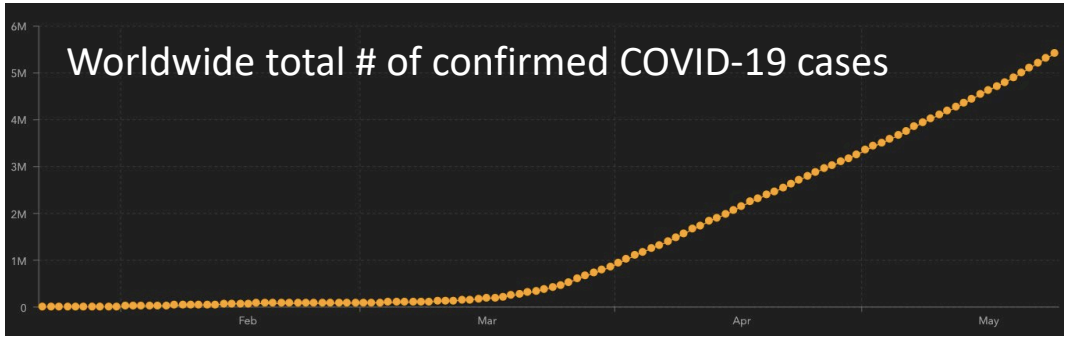
96% identical in nucleotide sequence to SARS-CoV, the cause of SARS in 2003



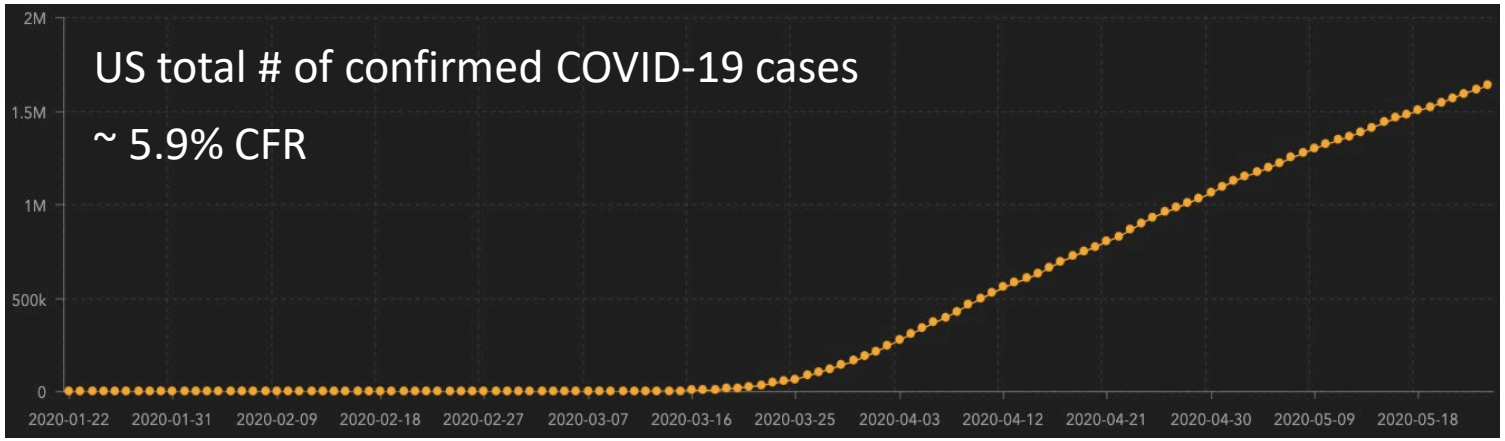
Lung Epithelial Cells
(Type II Pneumocyte)

COVID-19 is still on going

- Thus far, there have been in total of 5,460,747 confirmed cases worldwide



- COVID-19 cases have been rapidly rising in the US
  - As of May 25, 2020: there are
    - 1,622,114 total cases (>90K in California)
    - 97,049 deaths (>3700 deaths in California)



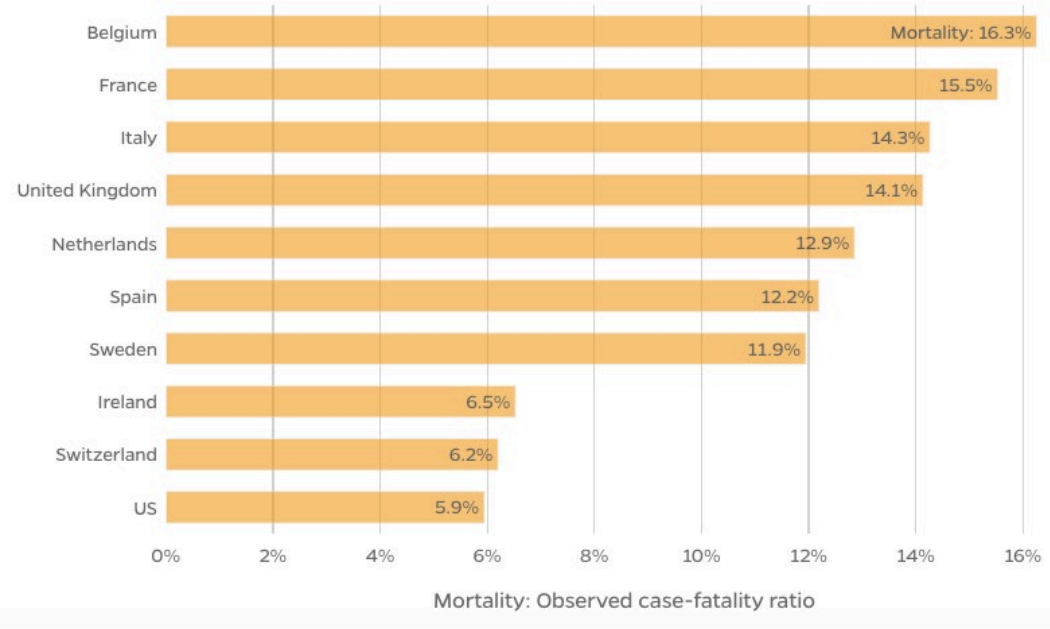
At Stanford:

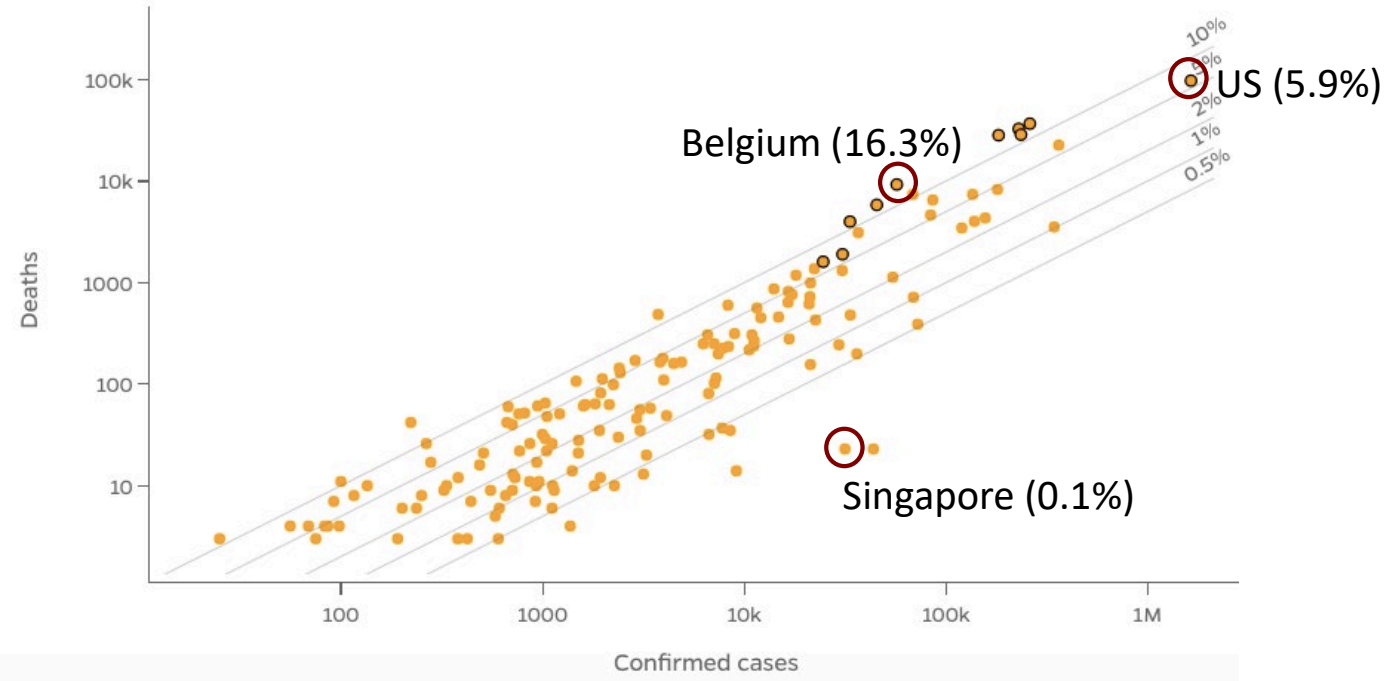
- ~ 90 in patient cases (~20 in ICU).
- 4 deaths.
- 2 cardiac complications (in patients with pre-existing CVD): 1 electrical storm + 1 RV failure
- 1 PE

https://coronavirus.jhu.edu/data & https://www.cdc.gov/coronavirus/2019-ncov/cases-updates

Case Fatality Rates of COVID-19

- The overall case fatality rate (CFR) of COVID-19 is ~6.3% but varies widely
- More than 80% of infected patients experience mild symptoms and recover without intensive medical intervention → difficult to know the overall prevalence of infection
  - In the case of Diamond Princess: 46.5% asymptomatic at the time of testing

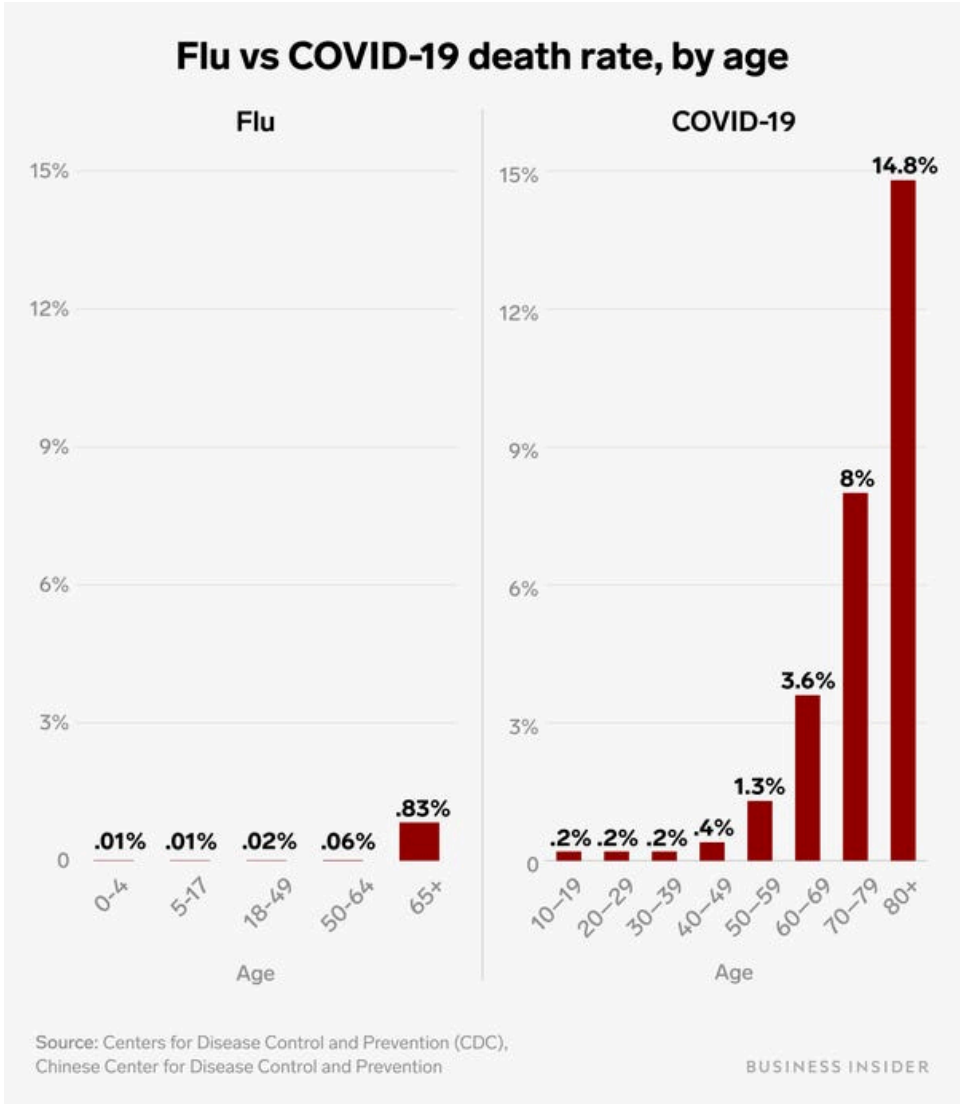


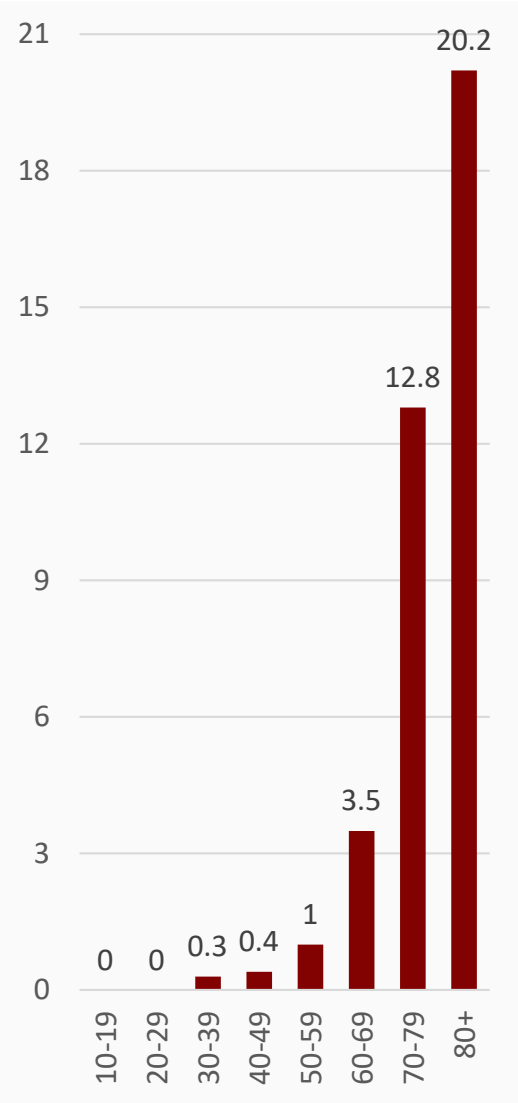


https://coronavirus.jhu.edu/data/mortality

Flu & COVID-19 death rates by age

Elderly patients are particularly vulnerable!

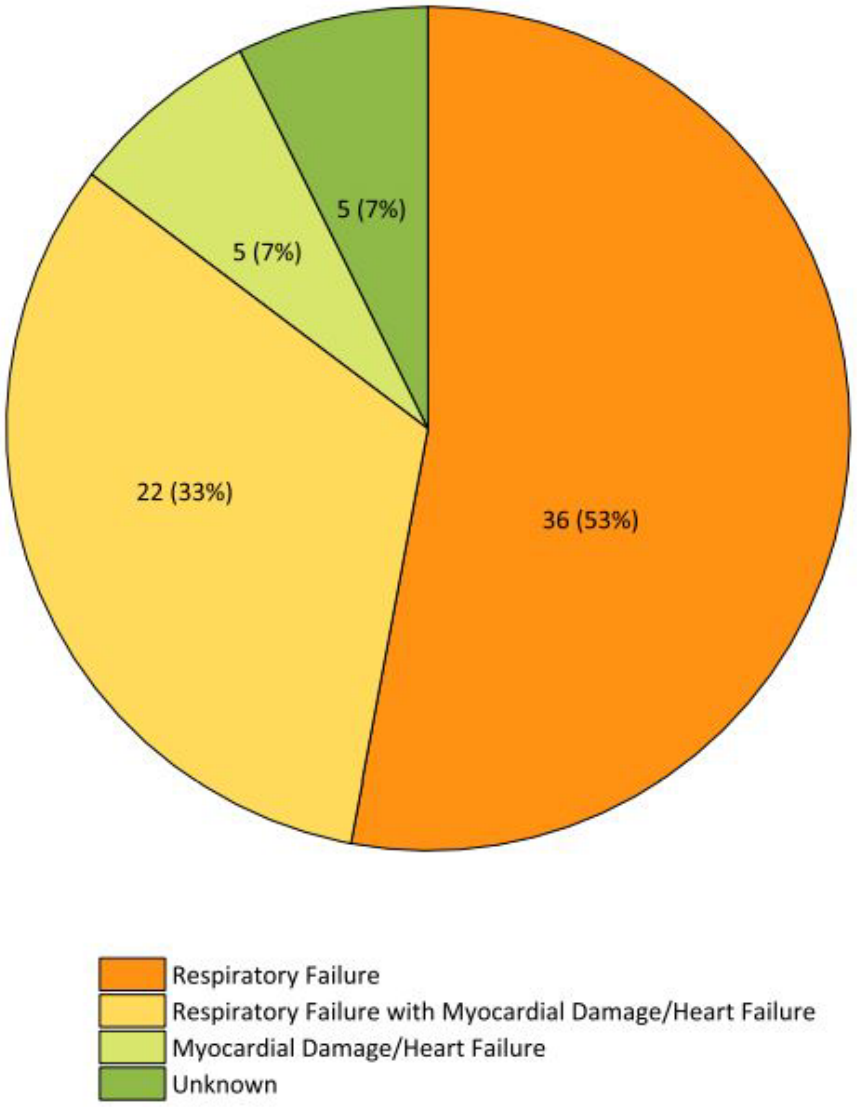




Onlder G et al. JAMA 2020

Causes of COVID-19 associated death

- Cardiac complications are the leading cause of death following respiratory failure



Ruan Q et al. Intensive Care Med 2020.

Underlying CVD comorbidities may increase risk for contracting COVID-19 and portend worse outcome

Chronic medical illness	50 (51%)
Cardiovascular and cerebrovascular diseases	40 (40%)
Digestive system disease	11 (11%)
Endocrine system disease†	13 (13%)
Malignant tumour	1 (1%)
Nervous system disease	1 (1%)
Respiratory system disease	1 (1%)

High burden of underlying CVD in patients with COVID19 (China)

Lancet. 2020;395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7.
Chen N. et al.

Case fatality rates for comorbid patients are materially higher than the average population:

- Cancer: 5.6%
- Hypertension: 6.0%
- Chronic respiratory disease: 6.3%
- Diabetes: 7.3%
- **Cardiovascular disease: 10.5%**

ACC COVID-19 Clinical Guidance
For the Cardiovascular Care Team

High burden of underlying CVD among critically ill patients and non-survivors

		ICU	No-ICU	
Comorbidities	64 (46.4)	26 (72.2)	38 (37.3)	<.001
Hypertension	43 (31.2)	21 (58.3)	22 (21.6)	<.001
Cardiovascular disease	20 (14.5)	9 (25.0)	11 (10.8)	.04
Diabetes	14 (10.1)	8 (22.2)	6 (5.9)	.009
Malignancy	10 (7.2)	4 (11.1)	6 (5.9)	.29
Cerebrovascular disease	7 (5.1)	6 (16.7)	1 (1.0)	.001
COPD	4 (2.9)	3 (8.3)	1 (1.0)	.054
Chronic kidney disease	4 (2.9)	2 (5.6)	2 (2.0)	.28
Chronic liver disease	4 (2.9)	0	4 (3.9)	.57
HIV infection	2 (1.4)	0	2 (2.0)	>.99

High burden of underlying CVD among critical ill COVID-19 patients (China)

JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1 Wang D et al.

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Age, years	56·0 (46·0–67·0)	69·0 (63·0–76·0)	52·0 (45·0–58·0)	<0·0001
Sex	..	..	..	0·15
Female	72 (38%)	16 (30%)	56 (41%)	..
Male	119 (62%)	38 (70%)	81 (59%)	..
Exposure history	73 (38%)	14 (26%)	59 (43%)	0·028
Current smoker	11 (6%)	5 (9%)	6 (4%)	0·21
Comorbidity	91 (48%)	36 (67%)	55 (40%)	0·0010
Hypertension	58 (30%)	26 (48%)	32 (23%)	0·0008
Diabetes	36 (19%)	17 (31%)	19 (14%)	0·0051
Coronary heart disease	15 (8%)	13 (24%)	2 (1%)	<0·0001
Chronic obstructive lung disease	6 (3%)	4 (7%)	2 (1%)	0·047
Carcinoma	2 (1%)	0	2 (1%)	0·37
Chronic kidney disease	2 (1%)	2 (4%)	0	0·024
Other	22 (12%)	11 (20%)	11 (8%)	0·016

High burden of underlying CVD among non-survivors (China)

Lancet 2020, Zhou et al

Table 1. Demographic Characteristics and Coexisting Conditions among Survivors and Nonsurvivors of Covid-19.*

Characteristic or Condition	Survivors (N=8395)	Nonsurvivors (N=515)	Difference (95% CI)†
Age — yr	48.7±16.6	55.8±15.1	−7.1 (−8.4 to −5.7)
Age >65 yr — no. (%)	1327 (15.8)	147 (28.5)	−12.7 (−16.0 to −9.4)
Female sex — no. (%)	3392 (40.4)	179 (34.8)	5.6 (1.3 to 10.0)
Race or ethnic group — no. (%)‡			
White	5306 (63.2)	351 (68.2)	−5.0 (−9.1 to −0.8)
Black	672 (8.0)	34 (6.6)	1.4 (−0.8 to 3.6)
Hispanic	529 (6.3)	32 (6.2)	0.1 (−2.0 to 2.3)
Asian	1637 (19.5)	84 (16.3)	3.2 (−0.2 to 6.5)
Native American	34 (0.4)	1 (0.2)	0.2 (−0.3 to 0.8)
Other	219 (2.6)	13 (2.5)	0.1 (−1.4 to 1.4)
Coexisting conditions — no. (%)			
Coronary artery disease	907 (10.8)	103 (20.0)	−9.2 (−12.8 to −5.7)
Congestive heart failure	160 (1.9)	29 (5.6)	−3.7 (−5.8 to −1.8)
Cardiac arrhythmia	269 (3.2)	35 (6.8)	−3.6 (−5.8 to −1.4)
Diabetes mellitus	1175 (14.0)	97 (18.8)	−4.8 (−8.3 to −1.3)
Hypertension	2216 (26.4)	130 (25.2)	1.2 (−2.8 to 5.1)
Hyperlipidemia	2535 (30.2)	180 (35.0)	−4.8 (−9.0 to −0.5)
COPD	193 (2.3)	32 (6.2)	−3.9 (−6.1 to −1.8)
Current smoker	445 (5.3)	46 (8.9)	−3.6 (−6.2 to −1.1)
Former smoker	1410 (16.8)	83 (16.1)	0.7 (−2.6 to 4.0)
Immunosuppressed condition	227 (2.7)	22 (4.3)	−1.6 (−3.4 to 0.2)

* Plus–minus values are means ±SD. The 95% confidence intervals (CIs) have not been adjusted for multiple testing and should not be used to infer definitive effects. COPD denotes chronic obstructive pulmonary disease, and Covid-19 coronavirus disease 2019.
† For mean age, the difference is given in years; for all other characteristics, the difference is given in percentage points.
‡ Race and ethnic group were reported by the patient.

Data from the Surgical Outcomes Collaborative (Surgisphere), an **international registry, including data from 169 hospitals located in 11 countries in Asia, Europe, and North America.**

Total **8910** patients with Covid-19

- 8395 survived to discharge
- 515 died in the hospital

Interestingly, HTN not different between survivors and non-survivors

MR Mehra et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2007621

Acute cardiac complications of COVID-19

Existing data suggest COVID-19 leads to

- **Myocardial injury +/- cardiac dysfunction**
  - Direct myocardial insult from the virus
  - Myocarditis
  - Myocardial infarction vs microvascular events
  - Stress CM, demand ischemia
  - Cytokine storm + hemodynamic consequence
  - Hypoxia-induced injury
- **Pulmonary hypertension and RV dysfunction**
- **Arrhythmia, cardiac arrest**

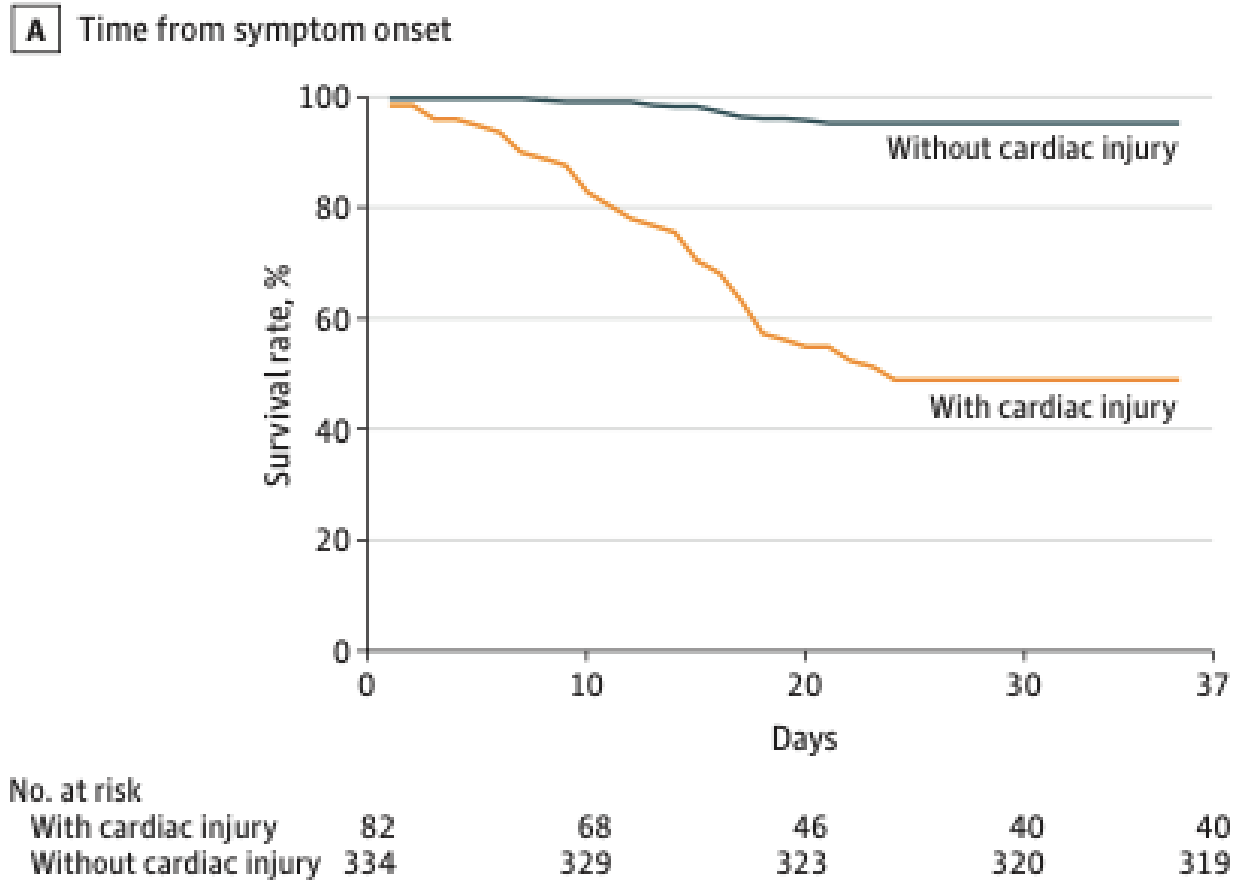
Cardiac injury portends worse outcomes

JAMA Cardiology | Original Investigation

Association of Cardiac Injury With M in Hospitalized Patients With COVI

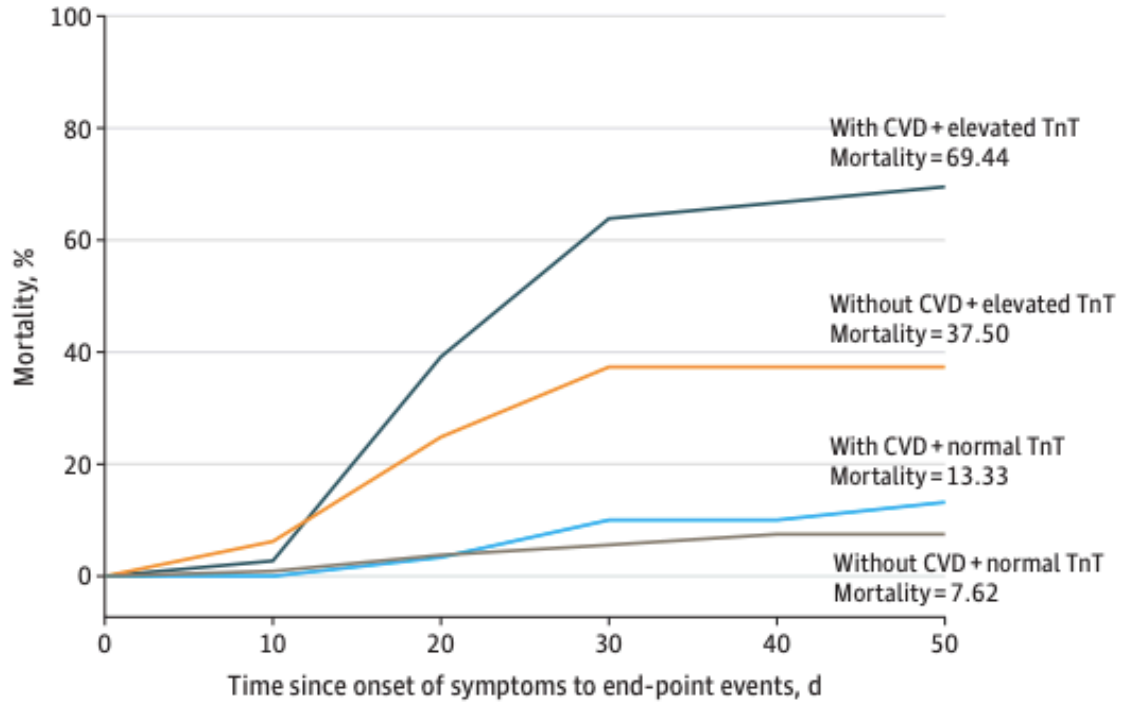
Shaobo Shi, MD; Mu Qin, MD; Bo Shen, MD; Yuli Cai, MD; Tao Liu, MD; F
Qinyan Zhao, MD, PhD; He Huang, MD, PhD; Bo Yang, MD, PhD; Congxir

- Myocardial injury, defined as cTn conc. >99th percentile upper-reference limit, is common and prognostic in COVID-19



Pre-existing CVD + cardiac injury = BAD

Figure 2. Mortality of Patients With Coronavirus Disease 2019 (COVID-19) With/Without Cardiovascular Disease (CVD) and With/Without Elevated Troponin T (TnT) Levels



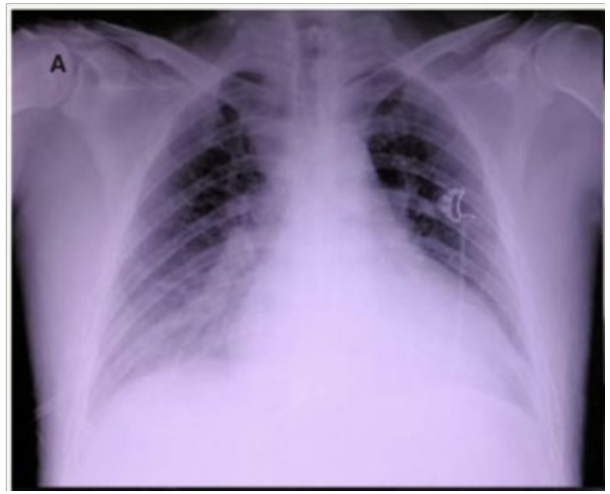
No. at risk

Without CVD + normal TnT (n = 105)	102	86	41	10	0
Without CVD + elevated TnT (n = 16)	15	12	7	1	0
With CVD + normal TnT (n = 30)	29	25	10	4	0
With CVD + elevated TnT (n = 36)	34	20	8	2	0

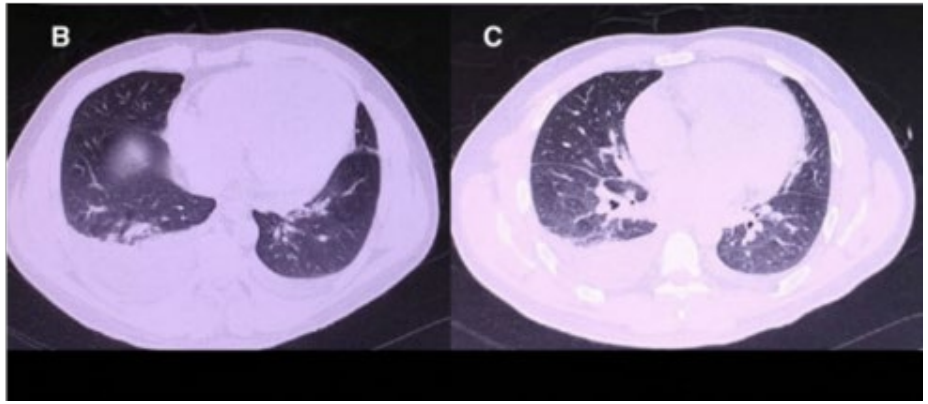
Case: 37 yo M with CP & Dyspnea x 3 days

- Admitted with 3 days chest pain, dyspnea, and diarrhea
- Hypotensive with BP 80/50 mmHg

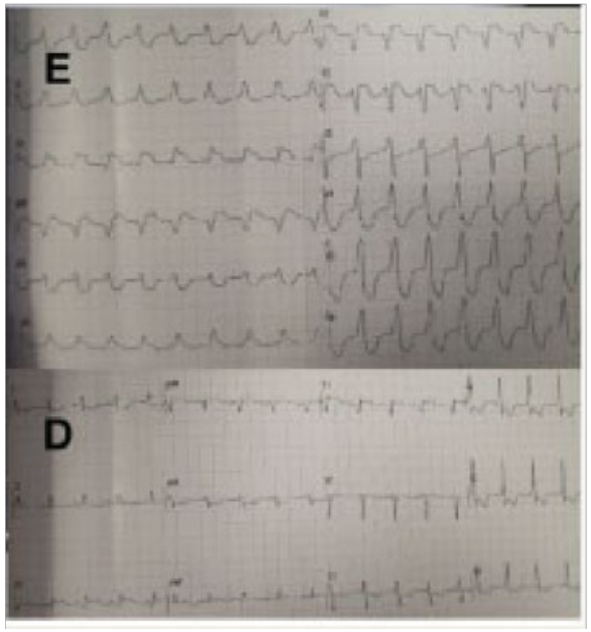
CXR



CT



EKG



Hu H et al. Eur Heart J. 2020. doi: 10.1093/eurheartj/ehaa190.

Case #1: 37 yo M with CP & Dyspnea x 3 days

- Sputum positive for SARS-CoV-2 (negative for extensive viral panel)
- Marked cardiac biomarker elevation
  - Troponin T > 10,000 ng/L
  - CKMB elevated at 112.9 ng/L
  - NT-proBNP 21,025 ng/L
- No significant coronary artery disease per CT coronary angiogram
- Echo showing markedly decreased cardiac function (LVEF 27%)

→ Diagnosed with presumed myocarditis with cardiogenic shock in the setting of COVID-19. Treated with supportive care + immune modulators with subsequent improvement

Mechanisms of Cardiac Injury

Overall, irrespective of the underlying mechanism, the presence of cardiac injury portends significantly worse outcome.

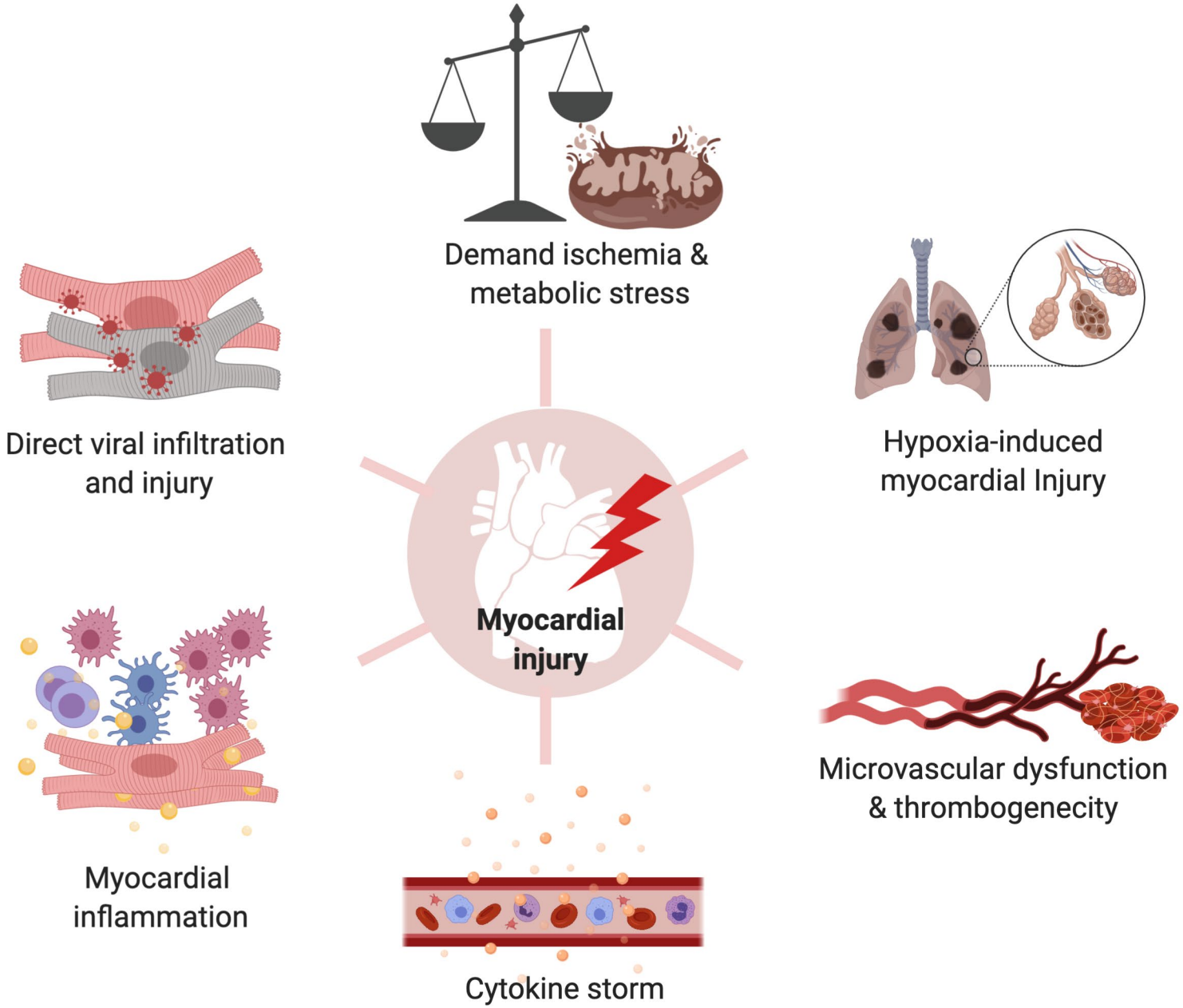


Figure modified from Cheng P et al. Curr Cardiol Rep. 2020 Apr 29;22(5):34.

Is there Increased Risk of Arrhythmia with SARS-CoV-2 Infections?

ACC Updates Suggest Possible Increased Arrhythmia in COVID-19 patients

Acute Cardiac Complications of COVID-19

- **In a recent case report on 138 hospitalized COVID-19 patients, 16.7% of patients developed arrhythmia and 7.2% experienced acute cardiac injury, in addition to other COVID-19 related complications[iv]**

Table 4. Complications and Treatments of Patients Infected With 2019-nCoV

	No. (%)			
	Total (N = 138)	ICU (n = 36)	Non-ICU (n = 102)	*P* Value[a]
Complications				
Shock	12 (8.7)	11 (30.6)	1 (1.0)	<.001
Acute cardiac injury	10 (7.2)	8 (22.2)	2 (2.0)	<.001
Arrhythmia	23 (16.7)	16 (44.4)	7 (6.9)	<.001
ARDS	27 (19.6)	22 (61.1)	5 (4.9)	<.001
AKI	5 (3.6)	3 (8.3)	2 (2.0)	.11

JAMA 2020, Wang et al

<u>Major Caveat</u>: Exact arrhythmia not defined in the JAMA study.

Lack of Reports on Arrhythmia

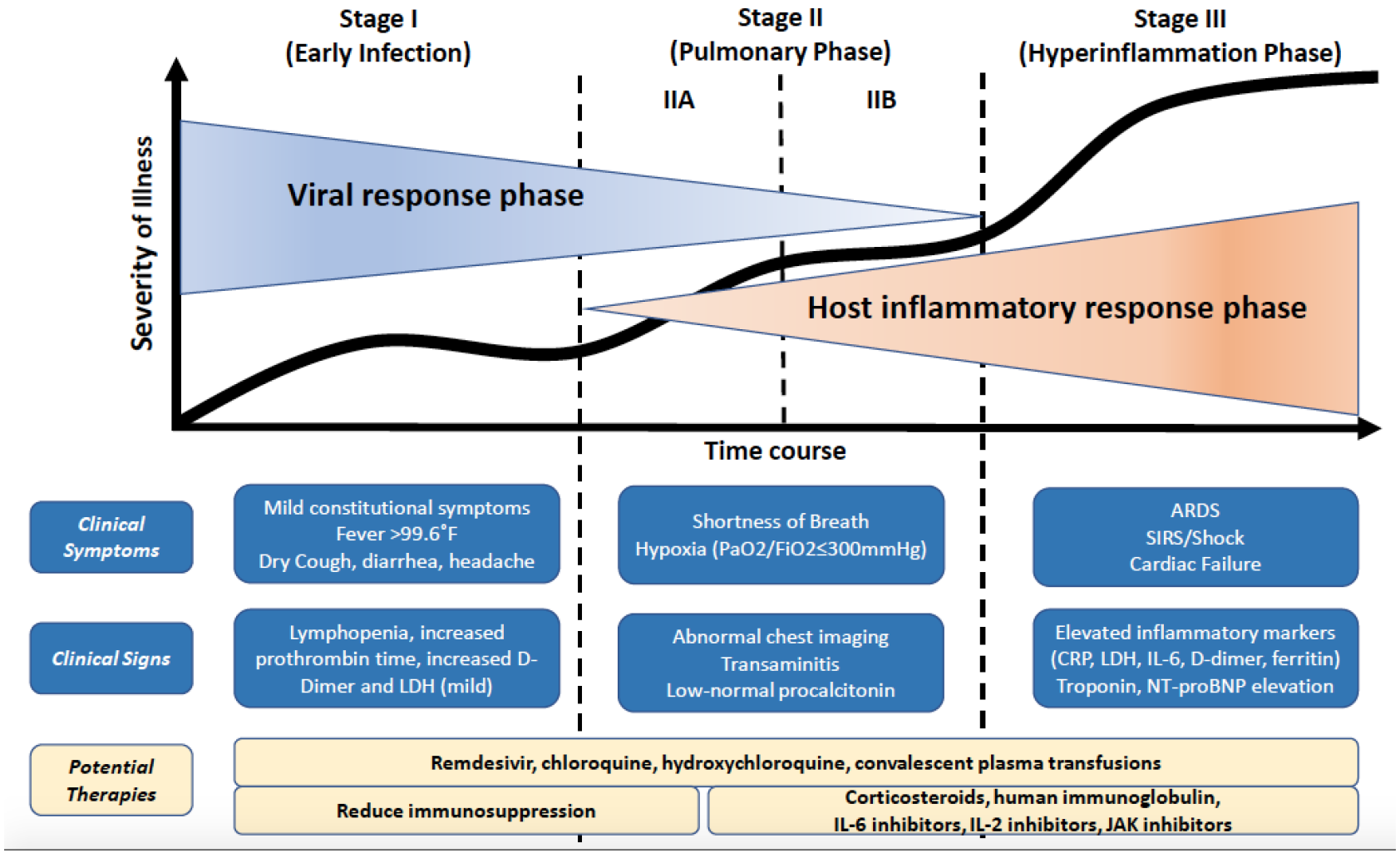
- **Clinical Characteristics of Covid-19 in New York City** (Goyal et al, NEJM 2020)
  - first 393 consecutive patients with Covid-19 in 2 hospitals in New York City: **atrial arrhythmias (17.7% vs. 1.9%, intubated vs no intubated)**
- **Clinical Characteristics of Coronavirus Disease 2019 in China** (Guen et al, NEJM 2020)
  - 51 centers, 1099 patients, no reported incidence of arrhythmia
- **Epidemiological and clinical features of 2019-nCoV acute respiratory disease cases** in Chongqing municipality, China: a retrospective, descriptive, multiple-center study. (Qi et al, Medrixv)
  - 267 pt, 3/50 severe pt had trop >0.03, no arrhythmia reported
- **Clinical features and outcomes of 2019 novel coronavirus-infected patients with cardiac injury (41 pts)** (Liu et al, medrxiv) (Guangzhou)
  - 5 % with trop > 0.03 (15/291), no arrhythmia reported

Summary of COVID-19 cardiac complications

- Patients with underlying CVD have overall poor prognosis
- Patients who suffer from myocardial injury have overall worse outcome
- Potential cardiovascular complications include:
  - myocardial injury and cardiac dysfunction
  - possible arrhythmia, cardiac arrest

Accumulating data suggest that any degree of myocardial injury marked by elevated troponin level, irrespective of the underlying mechanisms, portends significantly worse outcome

Are there any treatments?



Siddiqi, Journal of Heart & Lung Transplantation, 2020

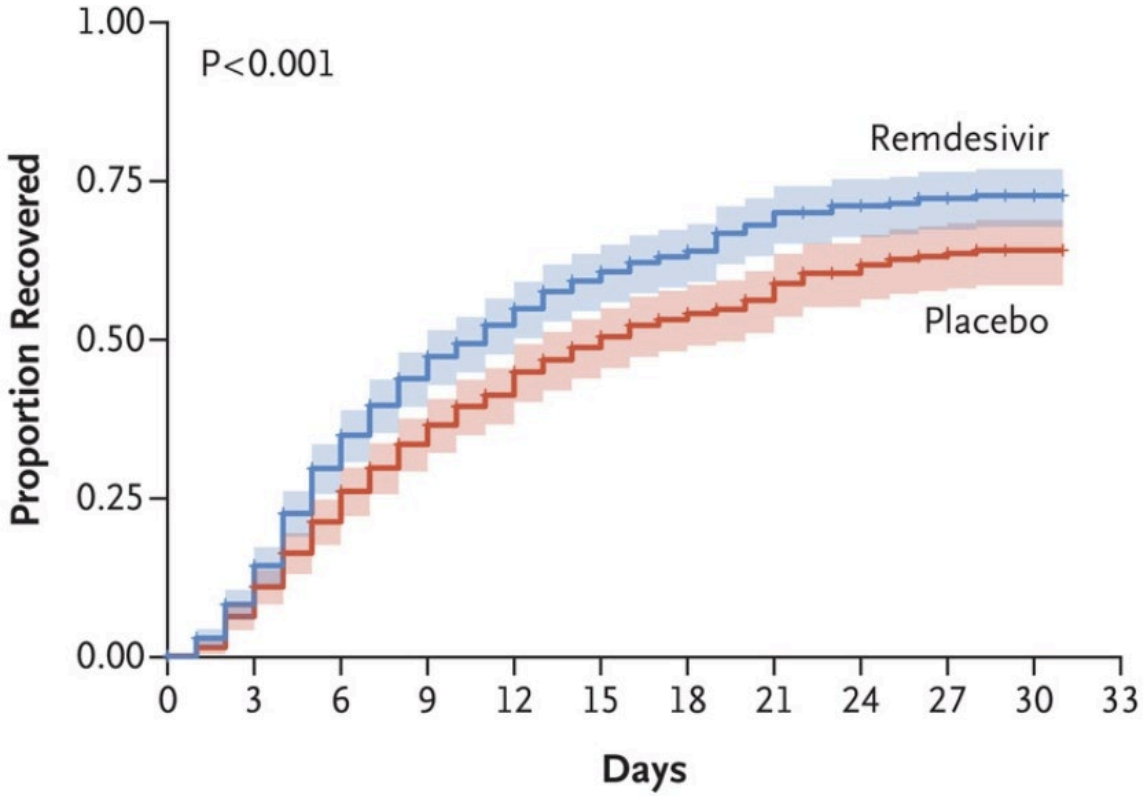
Remdesivir (Gilead)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

- Designed to inhibit Ebola RNA-dependent RNA polymerase (RdRp).
- Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo)
  - Median recovery time: 11 days vs 15 days (RR 1.32, P<0.001).
  - Mortality: 7.1% vs 11.9% (HR 0.7, CI: 0.47 to 1.04)



No. at Risk

Remdesivir	538	481	363	274	183	142	121	98	78	65	3	0
Placebo	521	481	392	307	224	180	149	115	91	78	2	0

Lopinavir-Ritonavir (anti-HIV)?

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

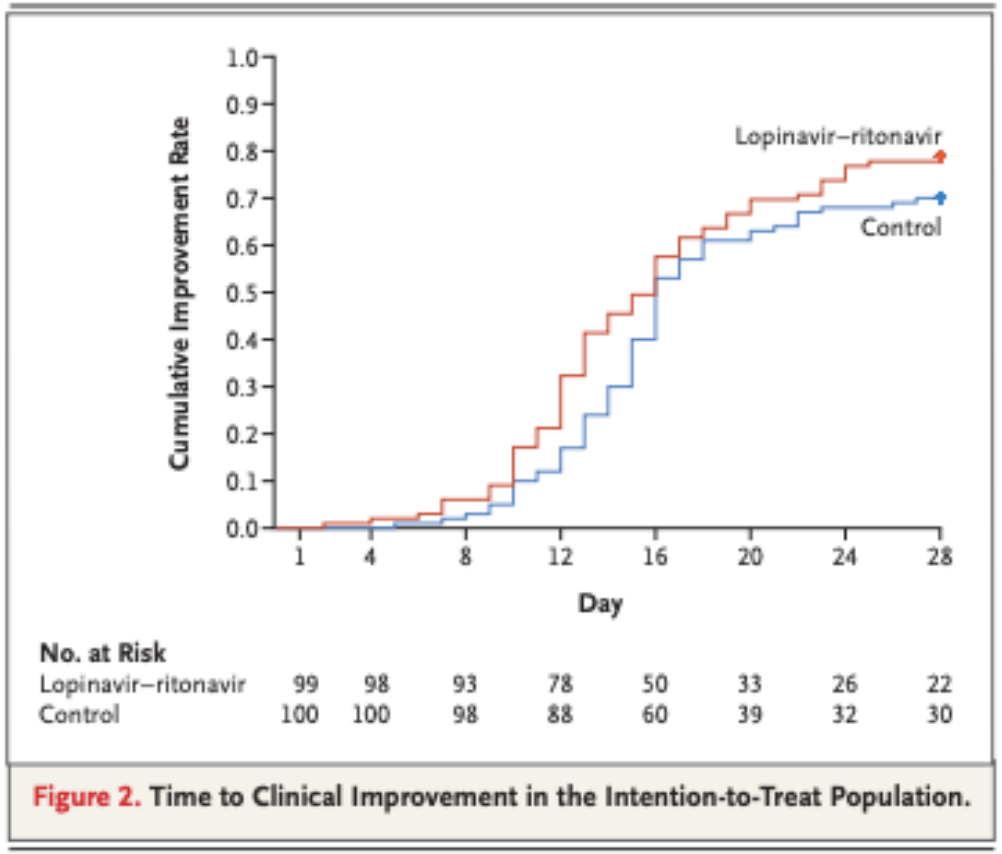


Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

Chloroquine (anti-malaria)?

- Generally used for treatment of malaria and amebiasis.
- Thought to work via multiple mechanisms but the exact mechanism remains unknown
- Potential cardiotoxicities:
  - QT prolongation ("Quinidine effects") + cardiac arrest: increasing risk of torsades de pointes
  - Cardiac dysfunction (has negative inotropic effects)
  - Possible conduction abnormalities when overdosed

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Analysis	Intubation or Death
No. of events/no. of patients at risk (%)	
Hydroxychloroquine	262/811 (32.3)
No hydroxychloroquine	84/565 (14.9)
Crude analysis — hazard ratio (95% CI)	2.37 (1.84–3.02)
Multivariable analysis — hazard ratio (95% CI)*	1.00 (0.76–1.32)
Propensity-score analyses — hazard ratio (95% CI)	
With inverse probability weighting†	1.04 (0.82–1.32)
With matching‡	0.98 (0.73–1.31)
Adjusted for propensity score§	0.97 (0.74–1.28)

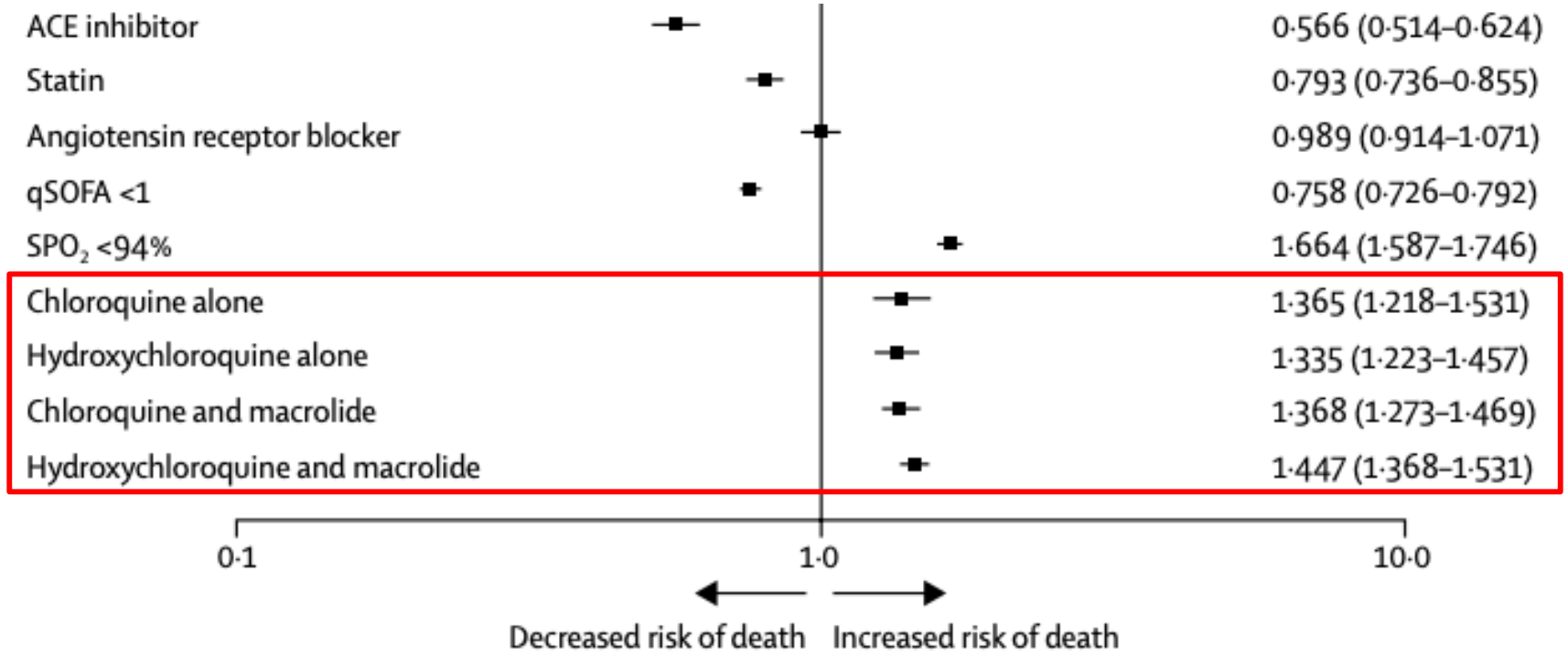
THE LANCET

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

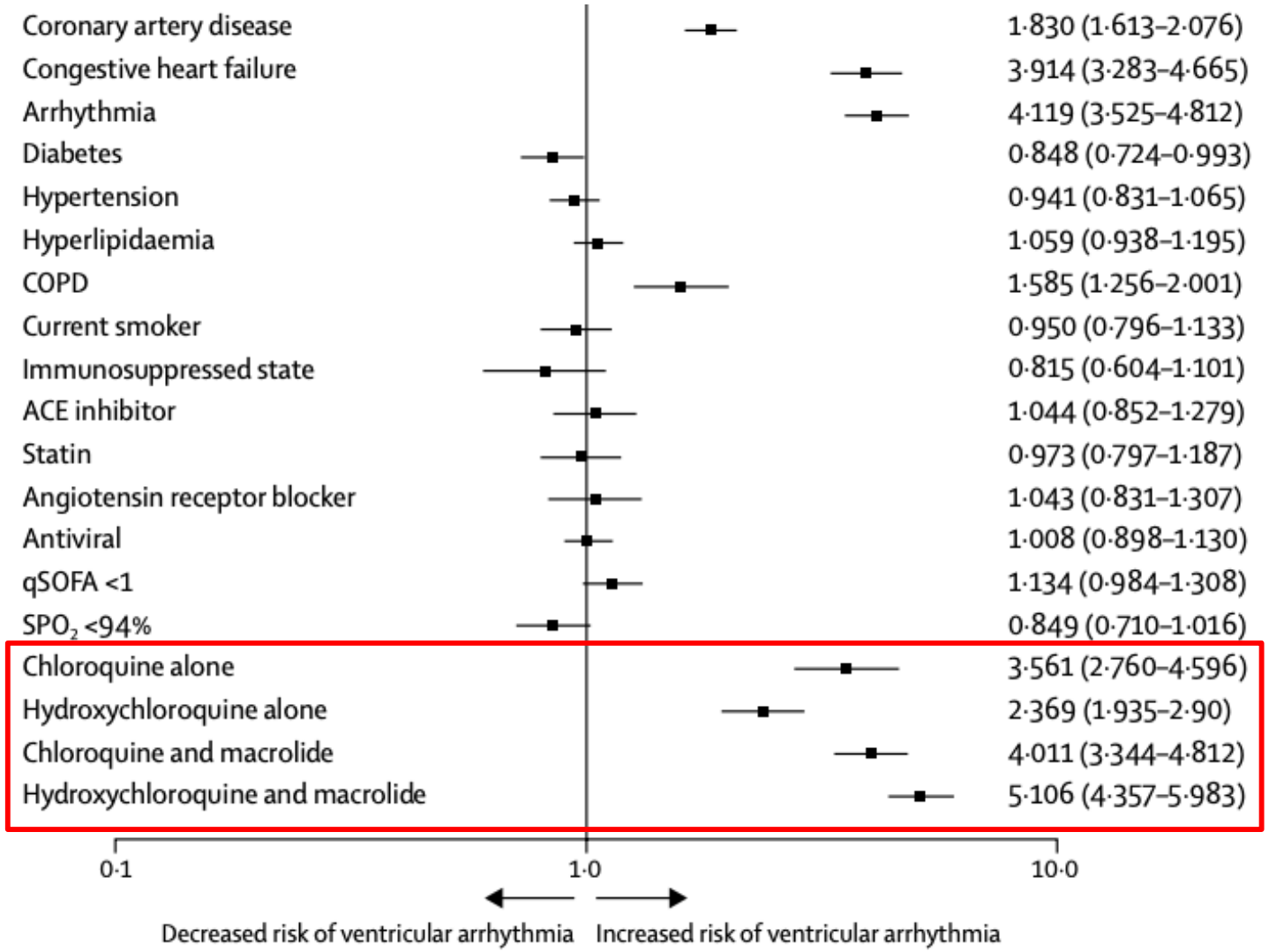
Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Multinational registry analysis of the use of hydroxychloroquine or chloroquine

- Total: 96,032 patients with COVID-19
- Hydroxychloroquine: 14,888 patients



Treatments with hydroxychloroquine led to significantly increased risk of ventricular arrhythmia!



Due to safety concern, WHO subsequently advised to temporarily pause ongoing hydroxychloroquine trial (Solidarity)

How about immunomodulators?

THE LANCET

CORRESPONDENCE | ONLINE FIRST

COVID-19: consider cytokine storm syndromes and immunosuppression

Puja Mehta • Daniel F McAuley • Michael Brown • Emilie Sanchez • Rachel S Tattersall • Jessica J Manson • et al.

Show all authors

Published: March 16, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30628-0

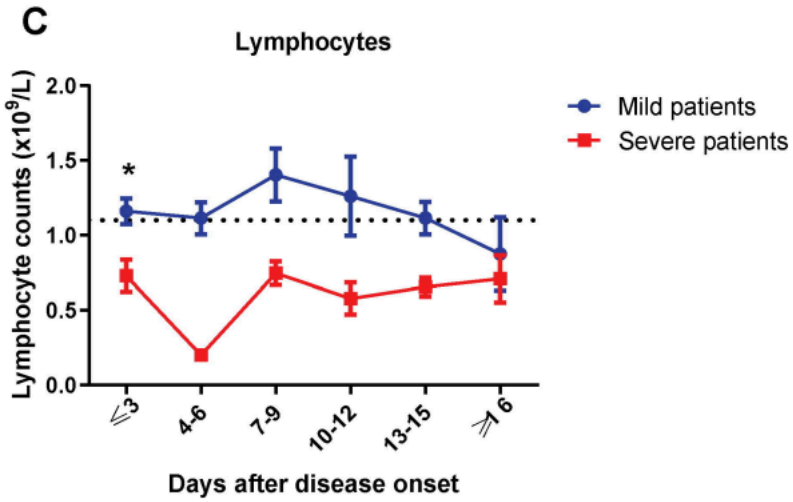
COVID-19 and cytokine storm

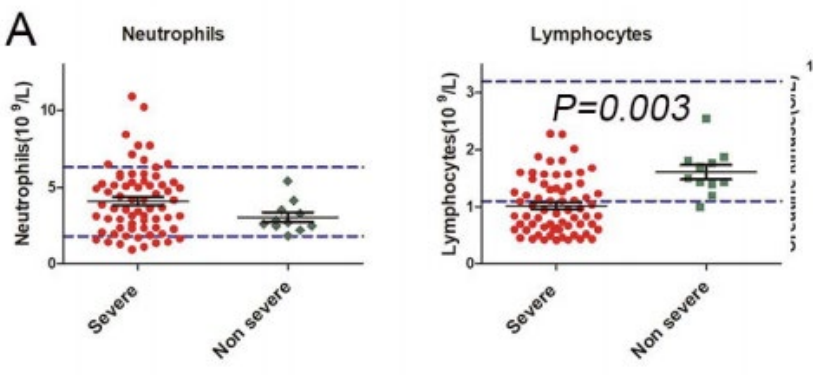
Premise:

- Prominent lymphopenia, with **normal WBC count**
- Degree of lymphopenia correlating with severity
- Acute multi-organ failure with high fevers mimic those seen in drug-induced cytokine storm

Hypothesis:

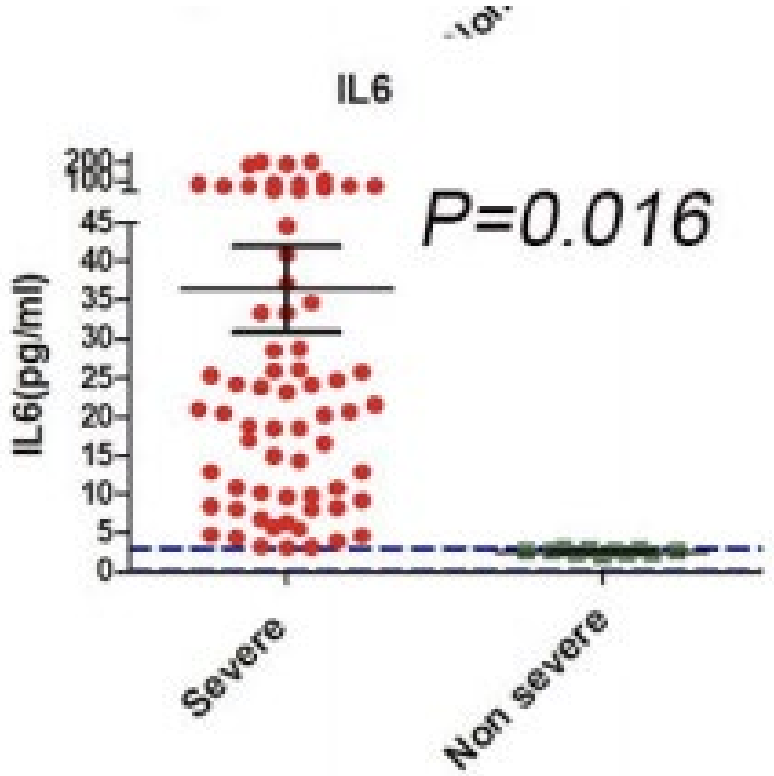
- "Cytokine storm" induced by the virus contribute to the impaired immune response, and hyper-inflammation is part of pathogenesis





IL-6 Level Correlate with Disease Severity Better than other Inflammatory Markers

- Anecdotal effective treatment with Tocilizumab from Italy and China
- Current ongoing trial for IL-6 blockade in COVID19 pts
  - NCT04315298 (New York , **Sarilumab)**
  - ChiCTR2000029765 (Hubei, China, **Tocilizumab**)



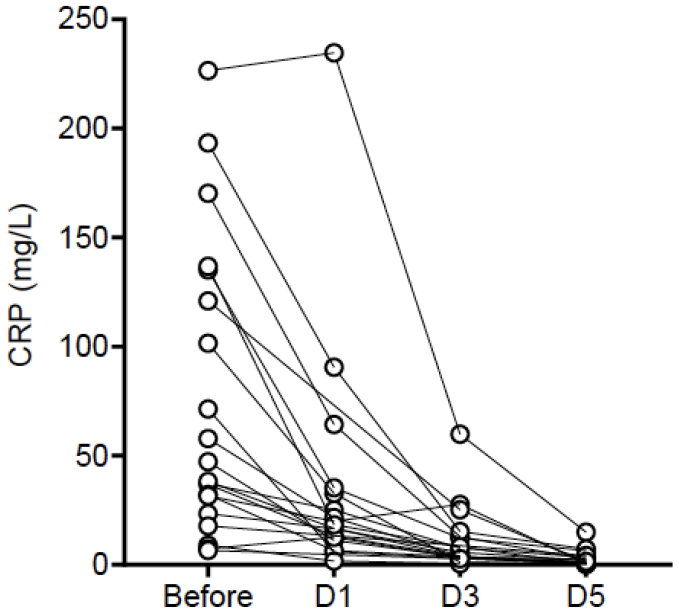
Tocilizumab Treatment With Some Promise

Effective treatment of severe COVID-19 patients with tocilizumab

Xiaoling Xu[a,1,2], Mingfeng Han[b,1], Tiantian Li[a], Wei Sun[b], Dongsheng Wang[a], Binqing Fu[c,d], Yonggang Zhou[c,d], Xiaohu Zheng[c,d], Yun Yang[e], Xiuyong Li[f], Xiaohua Zhang[b], Aijun Pan[e], and Haiming Wei[c,d,2]

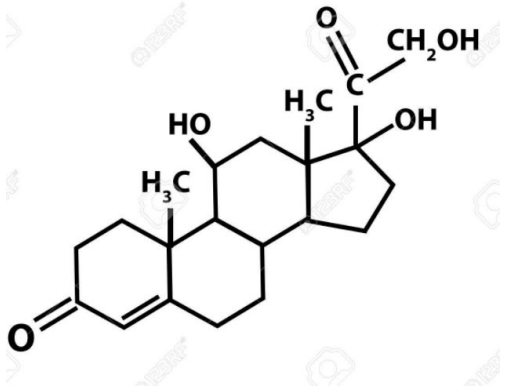
PNAS May 19, 2020 117 (20) 10970-10975;

- 21 consecutive "severe" patient
- 19 discharged from hospital with "rapid improvement."



Additional Immunomodulators

Glucocorticoids

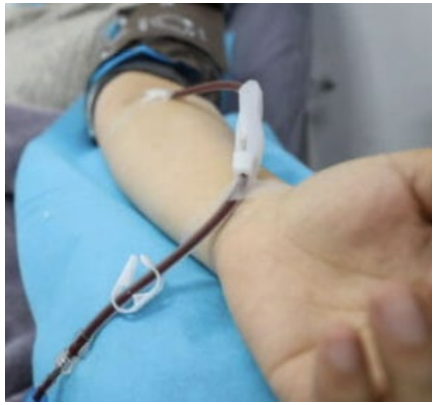


- Suppress inflammatory cytokines
- Delayed viral clearance; WHO recommends advises against for Sars-CoV-2 ARDS unless another indication
- Phase 2 RCT: Solumedrol 40 mg q12h for 5 days in ICU level pts w/ PaO2/FiO2 < 200 mmHg (NCT04244591)

IVIG

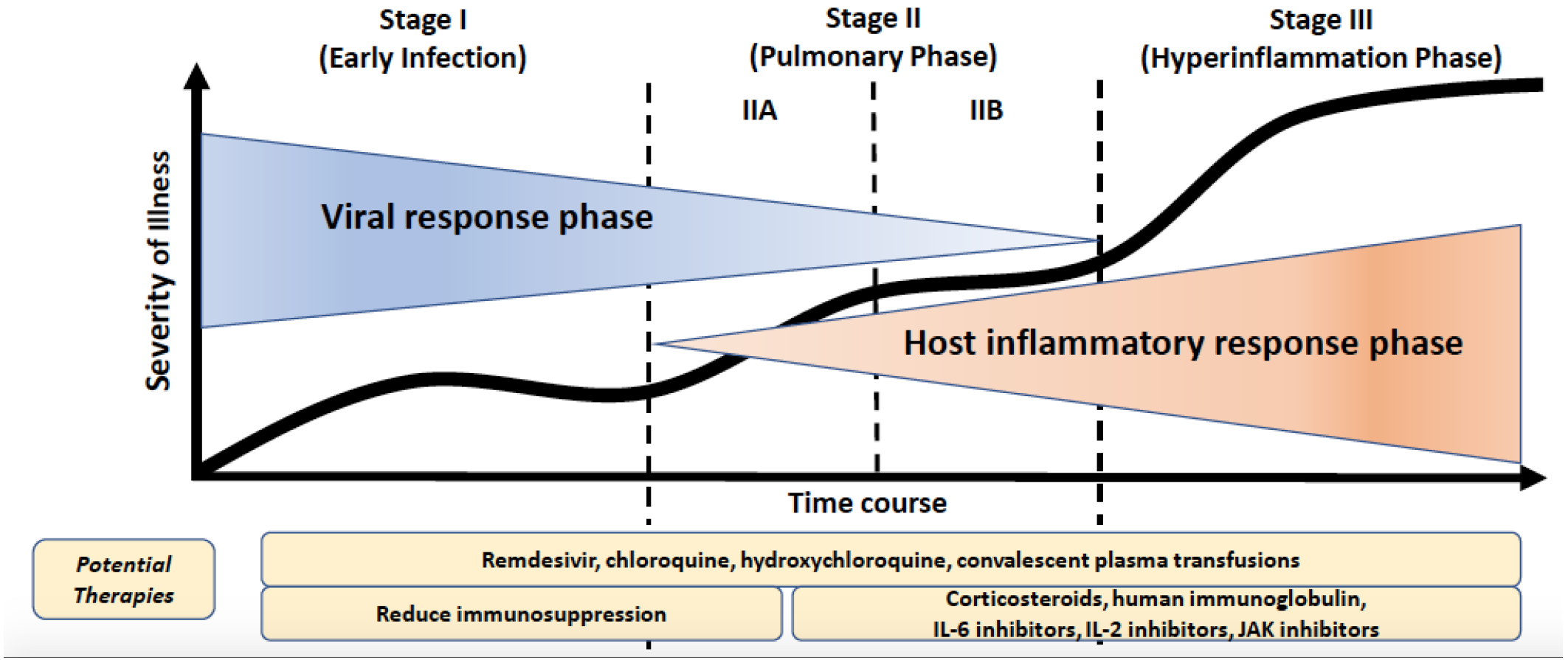
- Complement activation; saturation of Fc receptors on macrophages; and suppression of cytokines/chemokines
- Good safety profile, benefit in MERs & SARS
- Phase 2 RCT: IVIG 0.5g/kg/d for 5 days in pts w/ PaO2/FiO2 < 200 mmHg and/or multi-organ failure (NCT04261426)

Convalescent Plasma

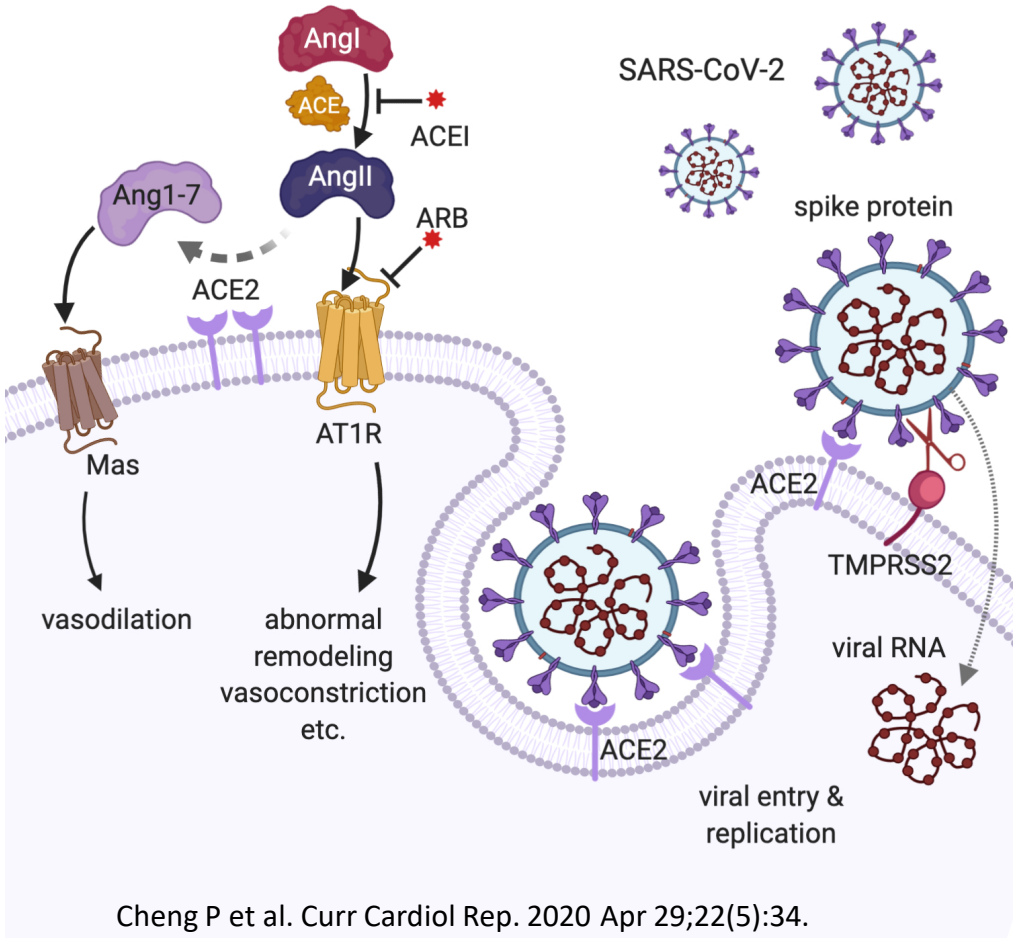


- Plasma of recovered donors (protective antibodies)
- Donors: recovered patients > 14 days; females HLA Ab neg; male donors
- FDA expanded access for respiratory failure or shock

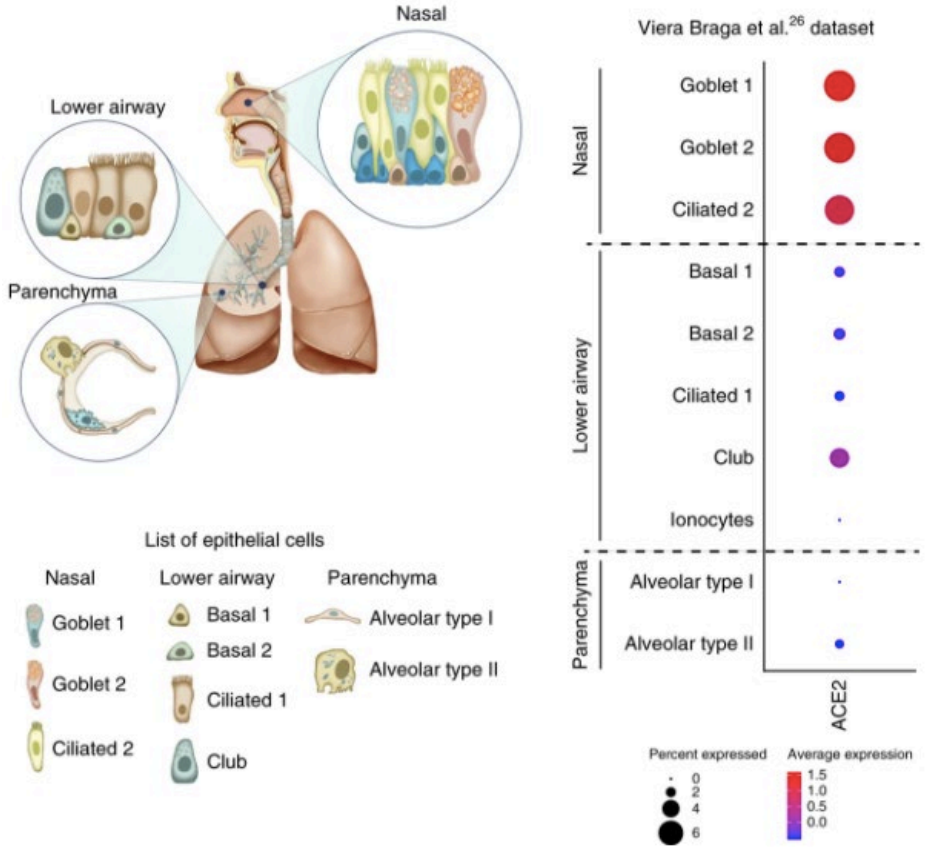
Summary of COVID-19 treatments



ACE2 and COVID-19



Cheng P et al. Curr Cardiol Rep. 2020 Apr 29;22(5):34.



SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells

Sungnak et al. Nature Medicine vol 26, p681–687(2020))

Concerns regarding ACEI/ARB

- Are patients taking ACEI/ARB more likely to get infected with SARS-CoV-2?
- Are COVID-19 patients taking ACEI/ARB worse off?

ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

- A population-based case–control study in the Lombardy region of Italy.
- A total of 6272 case patients with COVID-19 were matched to 30,759 beneficiaries.

Use of ARBs or ACEI did not show any association with Covid-19 among case patients for both ARB and ACEI.

Table 2. Odds Ratios for Covid-19 Associated with Use of RAAS Blockers, Other Blood-Pressure–Lowering Drugs, Drugs for Other Disease, and Other Features.*

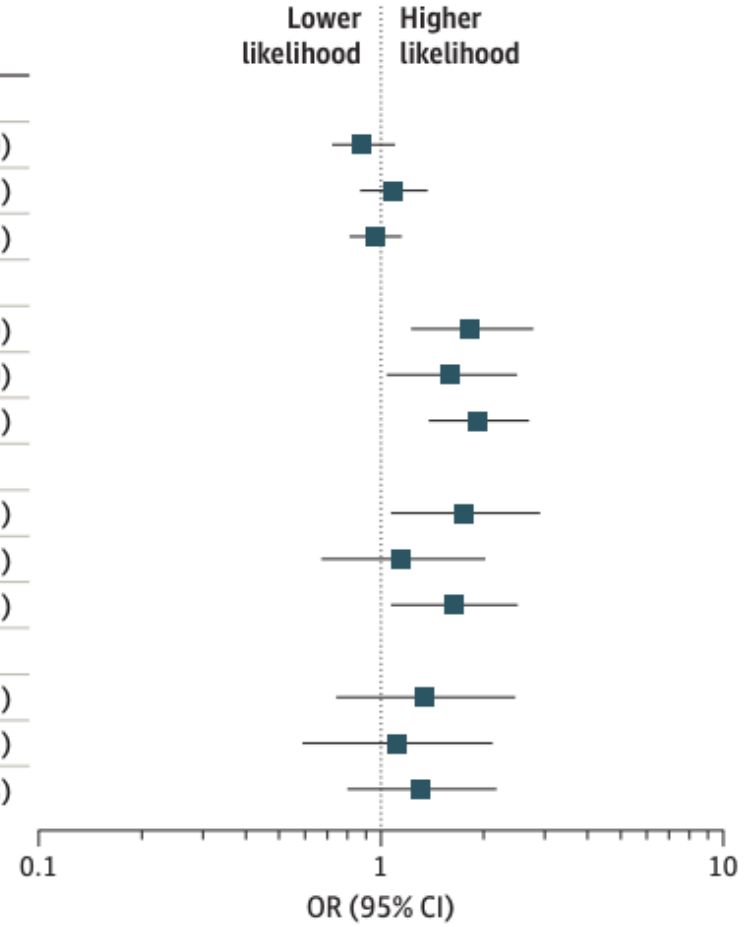
Variable	Odds Ratio for Covid-19 (95% CI)†	
	Unadjusted	Adjusted
Drugs‡		
Antihypertensive drugs overall	1.53 (1.43–1.63)	
ACE inhibitors	1.16 (1.08–1.24)	0.96 (0.87–1.07)
ARBs	1.20 (1.12–1.29)	0.95 (0.86–1.05)
Calcium-channel blockers	1.28 (1.18–1.38)	1.03 (0.95–1.12)
Beta-blockers	1.42 (1.33–1.51)	0.99 (0.91–1.08)

JAMA Cardiology | Original Investigation

Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19)

- Retrospective cohort study conducted at the Cleveland Clinic Health System in Ohio and Florida
- 18 472 patients tested for COVID-19, 1,735 patients were tested pos.
- No association between ACEI or ARB use and COVID-19 test positivity

Outcome	OR (95% CI)
Test positive	
ACEI vs no ACEI	0.89 (0.72-1.10)
ARB vs no ARB	1.09 (0.87-1.37)
ACEI/ARB vs no ACEI/ARB	0.97 (0.81-1.15)
Hospital admission	
ACEI vs no ACEI	1.84 (1.22-2.79)
ARB vs no ARB	1.61 (1.04-2.50)
ACEI/ARB vs no ACEI/ARB	1.93 (1.38-2.71)
ICU admission	
ACEI vs no ACEI	1.77 (1.07-2.92)
ARB vs no ARB	1.16 (0.67-2.02)
ACEI/ARB vs no ACEI/ARB	1.64 (1.07-2.51)
Use of ventilator	
ACEI vs no ACEI	1.35 (0.74-2.47)
ARB vs no ARB	1.12 (0.59-2.12)
ACEI/ARB vs no ACEI/ARB	1.32 (0.80-2.18)



ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

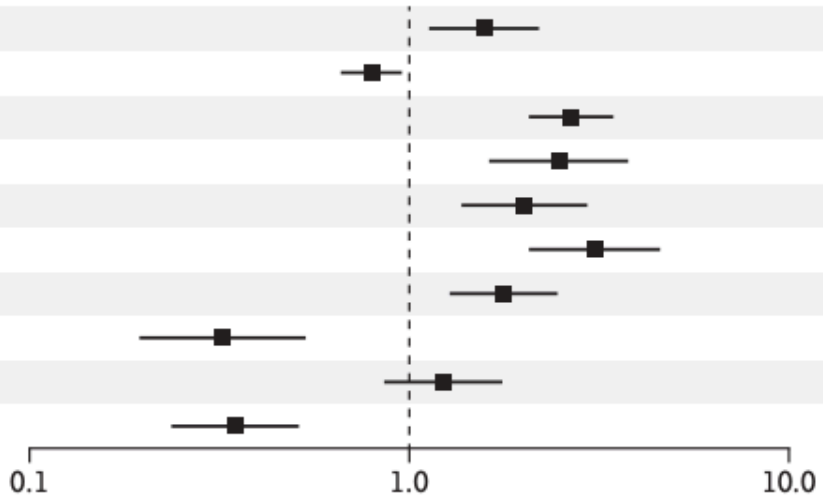
Mandeep R. Mehra, M.D., Sapan S. Desai, M.D., Ph.D.,
SreyRam Kuy, M.D., M.H.S., Timothy D. Henry, M.D., and Amit N. Patel, M.D.

Data from the Surgical Outcomes Collaborative (Surgisphere), an **international registry, including data from 169 hospitals located in 11 countries in Asia, Europe, and North America.**

Total **8910** patients with Covid-19 (515 death)

No increased risk of in-hospital death was found to be associated with the use of ACE inhibitors (2.1% vs. 6.1%; OR, 0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (6.8% vs. 5.7%; OR, 1.23; 95% CI, 0.87 to 1.74).

Risk Factor	Risk Factor Present	Risk Factor Absent	Odds Ratio (95% CI)
	no. of patients who died/total no. (%)		
>65 yr of age	147/1474 (10.0)	368/7436 (4.9)	1.93 (1.60–2.41)
Female sex	179/3571 (5.0)	336/5339 (6.3)	0.79 (0.65–0.95)
Coronary artery disease	103/1010 (10.2)	412/7900 (5.2)	2.70 (2.08–3.51)
Congestive heart failure	29/189 (15.3)	486/8721 (5.6)	2.48 (1.62–3.79)
Arrhythmia	35/304 (11.5)	480/8606 (5.6)	1.95 (1.33–2.86)
COPD	32/225 (14.2)	483/8685 (5.6)	2.96 (2.00–4.40)
Current smoker	46/491 (9.4)	469/8419 (5.6)	1.79 (1.29–2.47)
Receiving ACE inhibitor	16/770 (2.1)	499/8140 (6.1)	0.33 (0.20–0.54)
Receiving ARB	38/556 (6.8)	477/8354 (5.7)	1.23 (0.87–1.74)
Receiving statin	36/860 (4.2)	479/8050 (6.0)	0.35 (0.24–0.52)

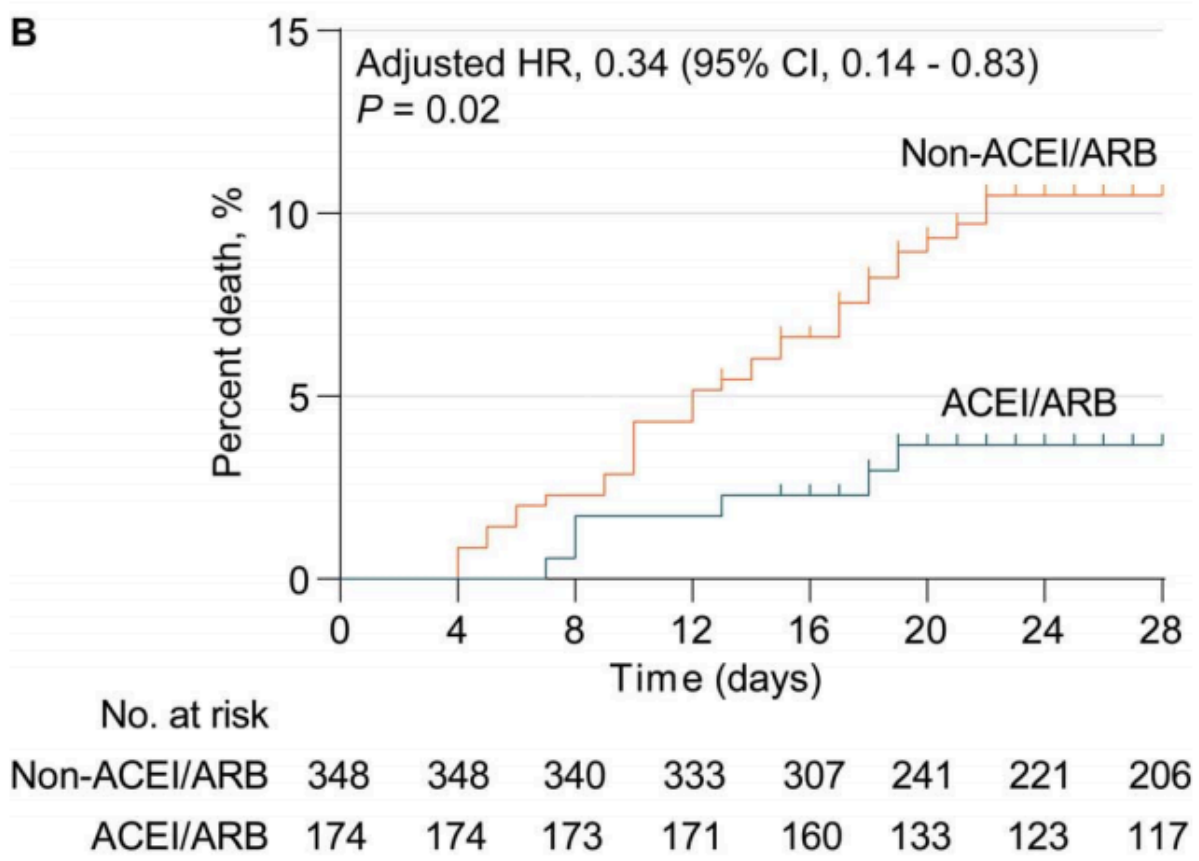


Circulation Research

Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19

- Retrospective analysis of multicenter data from China including 1128 adult patients with hypertension diagnosed with COVID-19

- The incidence of the 28-day all-cause death among patients who had inpatient treatment with ACEI/ARB is significant lower compared with ACEI/ARB non-users.



Current recommendations regarding ACE/ARB Use During COVID-19 Out Break

AHA/ACC/HFSA Joint Statement

"We understand the concern – as it has become clear that people with cardiovascular disease are at much higher risk of serious complications including death from COVID-19. However, we have reviewed the latest research – the evidence does not confirm the need to discontinue ACE-i or ARBs, and we strongly recommend all physicians to consider the individual needs of each patient before making any changes to ACE-i or ARB treatment regimens," said Robert A. Harrington, M.D., FAHA, president of the American Heart Association, Arthur L. Bloomfield Professor of Medicine and chair of the department of medicine at Stanford University.

Statement of the European Society of Hypertension (ESH) on hypertension, Renin Angiotensin System blockers and COVID-19
March 12th 2020

- Currently there is no clear evidence that hypertension *per se* is associated with an increased risk of infection by COVID-19. Therefore, patients with hypertension should apply the same precautions as subjects of the same age category and with the same profile of comorbidities (https://www.ecdc.europa.eu/en/novel-coronavirus-china).
- In stable patients with COVID-19 infections or at risk for COVID-19 infections, treatment with ACEIs and ARBs should be executed according to the recommendations in the 2018 ESC/ESH guidelines. [1]
- The currently available data on COVID-19 infections do not a support a differential use of RAS blockers (ACEI or ARBs) in COVID-19 patients.
- In COVID-19 patients with severe symptoms or sepsis, RAS blockers and other blood pressure lowering drugs should be used or discontinued on a case-by-case basis, taking into account current guidelines.

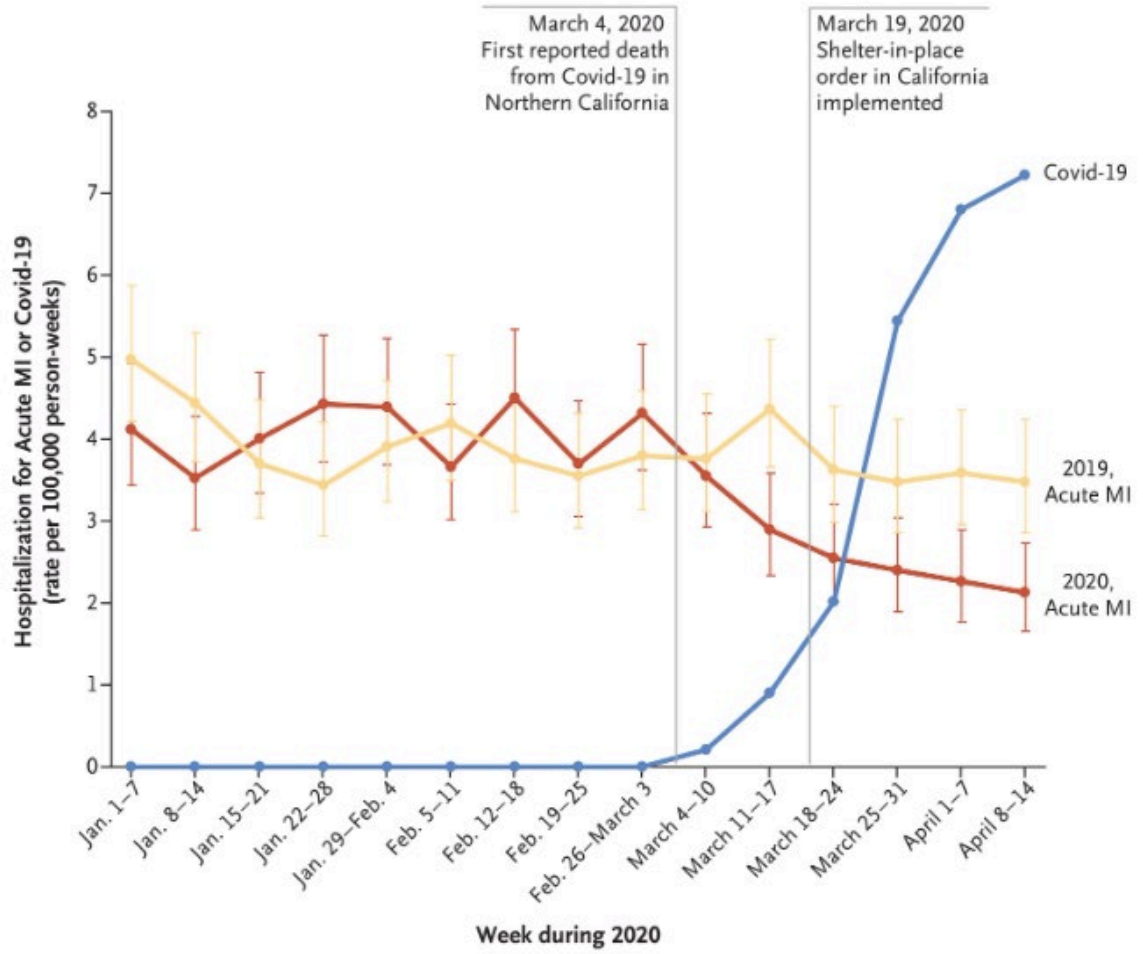
Don't change and continue taking them!!

Incidence of hospitalization for acute MI is dropping…

Data from Kaiser Northern CA (43,017,810 person-weeks from January 1 through April 14, 2020) note that significant drop in acute MI during the COVID-19 period

- The weekly rates of hospitalization for acute MI decreased by up to 48%.

Need to remind patients to seek medical attention for acute heart care!



No. of Patients															
2019, Acute MI	140	125	104	97	110	118	106	100	107	106	123	102	98	101	98
2020, Acute MI	118	101	115	127	126	105	129	106	124	102	83	73	69	65	61
2020, Covid-19	0	0	0	0	0	0	0	0	0	6	26	58	156	195	207

NEJM May 19, 2020 DOI: 10.1056/NEJMc2015630

In Summary…

1. Patients with underlying CVD have overall poor prognosis
2. Patients who suffer from myocardial injury have overall worse outcome, irrespective of the underlying mechanisms.
3. Many treatments are on the horizon, but effectiveness may depend on overall disease stage of COVID-19.
4. Currently, there is no data to support increased infectivity or worse outcome with the use of ACEI/ARB. Therefore, please continue!
5. It is important to remind patients to seek medical attentions for any symptoms or signs concerning for acute MI

Thank you for your attention!