Cardiovascular Manifestations of COVID 19

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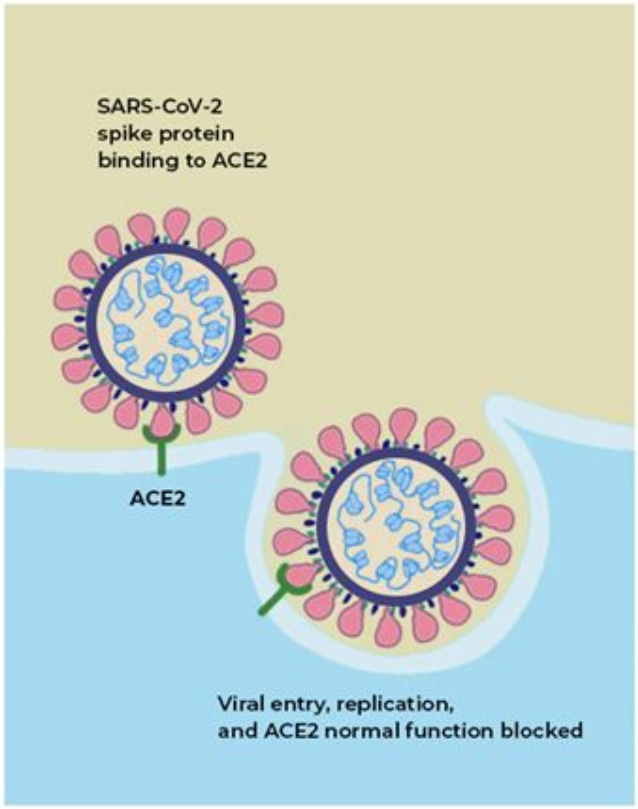
Overview

- Pathophysiology and Epidemiology
- Acute CV Complications
  - Heart failure / myocarditis
- Arrhythmia
- Thrombosis
- Cardiac Medications and COVID
  - ACEI / ARB
  - Anti-coagulants
  - Statin
  - Colchicine

Pathophysiology

- COVID-19 caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), a single strand RNA virus
- Binds to target cells via ACE2 receptor
- ACE2 expressed on surface of multiple tissues:
  - Lung, esophagus, ileum and colon, myocardial cells, kidney proximal tubules, bladder, oral cavity, testis, thyroid, adipose tissue

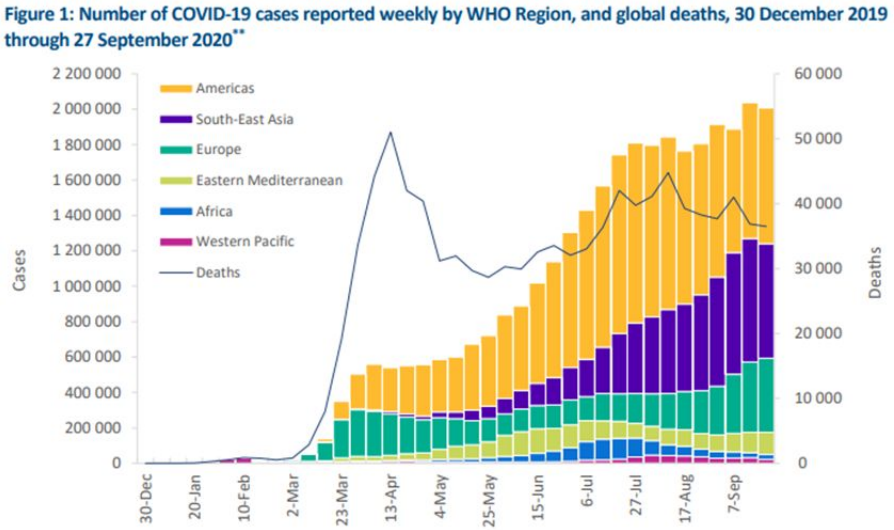


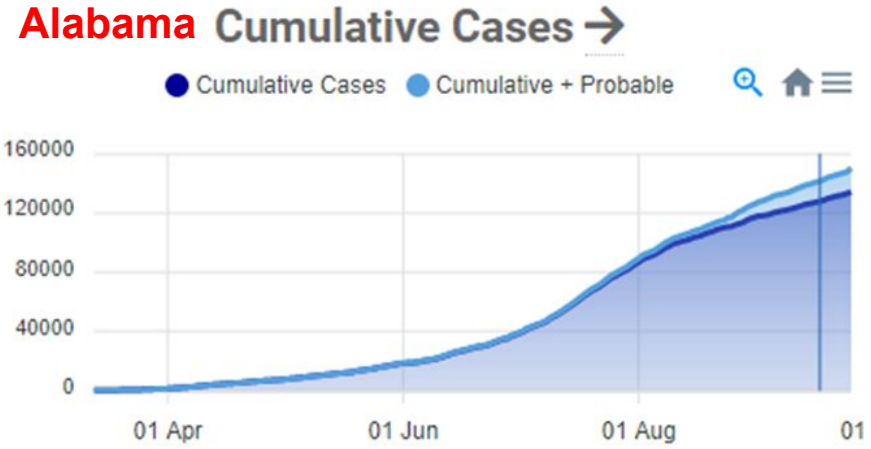
Epidemiology

- Spreads primarily thru respiratory droplets and airborne particles, hand to mouth transmission also possible
  - Documented mRNA persistence on surfaces for days after exposure, whether live virus and clinical importance uncertain
  - Live virus isolated from fecal specimens, orofecal transmission possible
- Infected individuals contagious prior to symptom onset
  - Infection risk starts 2-3 days prior to symptoms, peaks 0.7 day before symptom onset, declines within 7 days (He X et al Nat Med 2020;26(5):672)
  - Persistence of mRNA does not necessarily indicate presence of infectious virus

Epidemiology

- World-wide
  - Cumulative thru 9/29/20:
    - 32.7 million cases
    - 1 million deaths
  - Week Sep 7 -13th
    - 1.8 million cases
    - 40 K deaths
- Alabama
  - Cumulative (thru 9/24/20):
    - 150 K cases
    - 2491 deaths

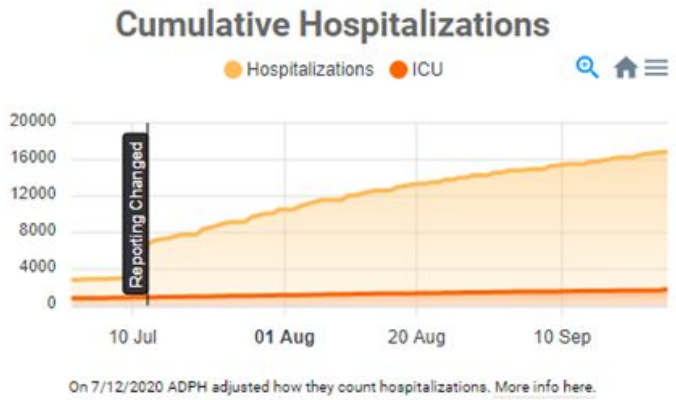


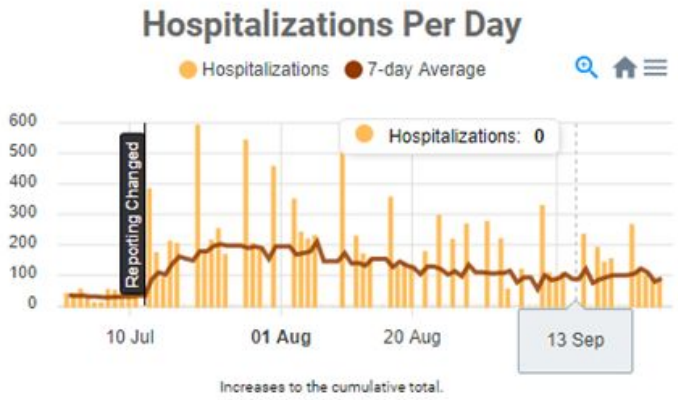


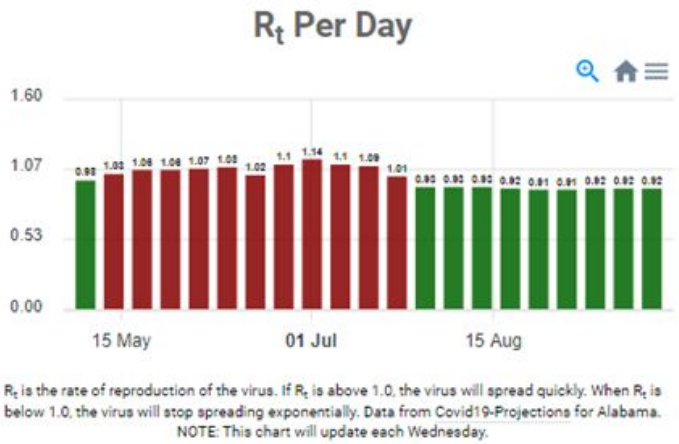
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200914-weekly-epi-update-5.pdf?sfvrsn=cf929d04_2

BamaTracker.com Accessed 9/25/20

Alabama Hospitalizations and R_t







Case Growth Per Day

Doubling Time (In Days)

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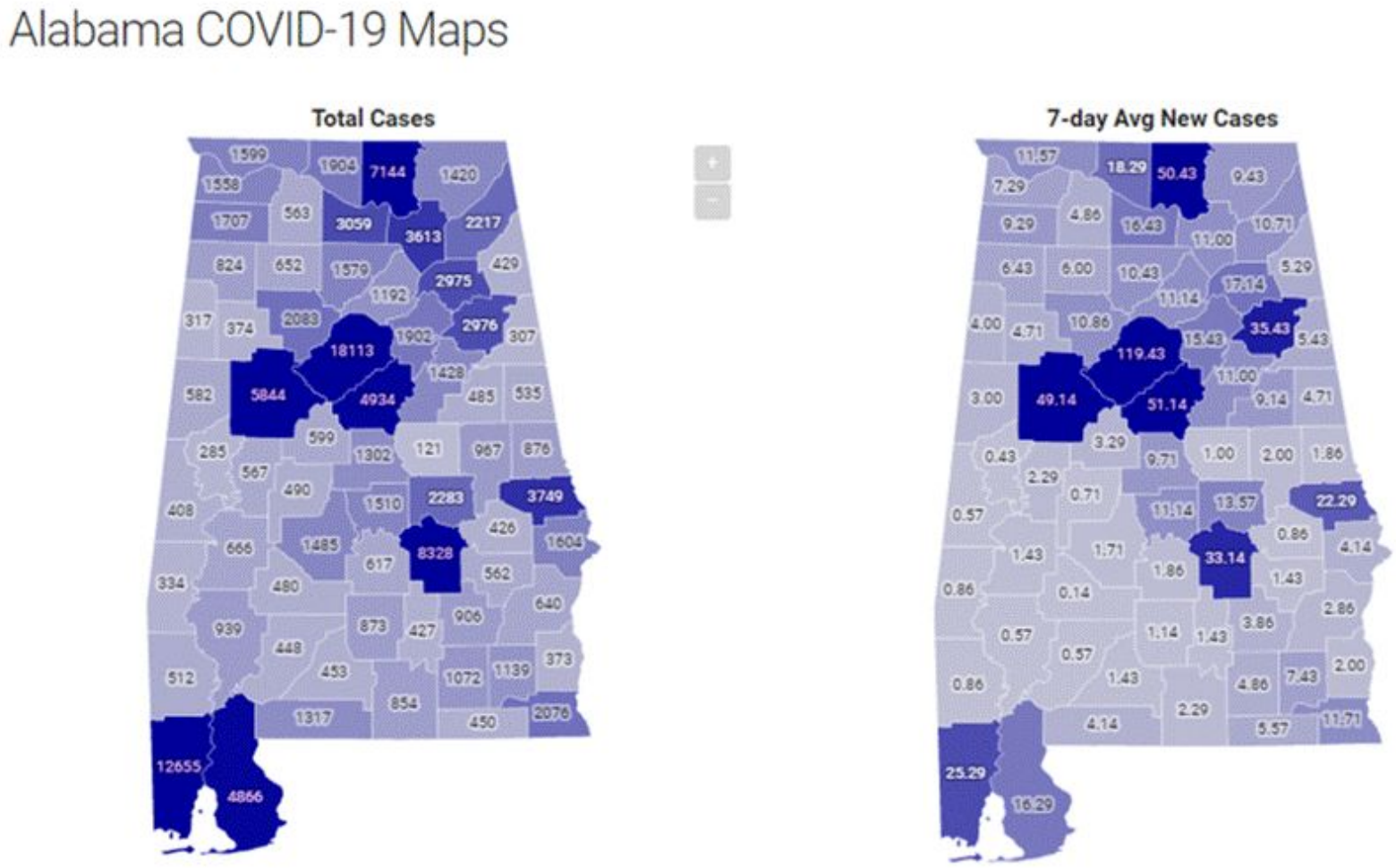
BamaTracker.com Accessed 9/25/20

Alabama COVID-19 by County



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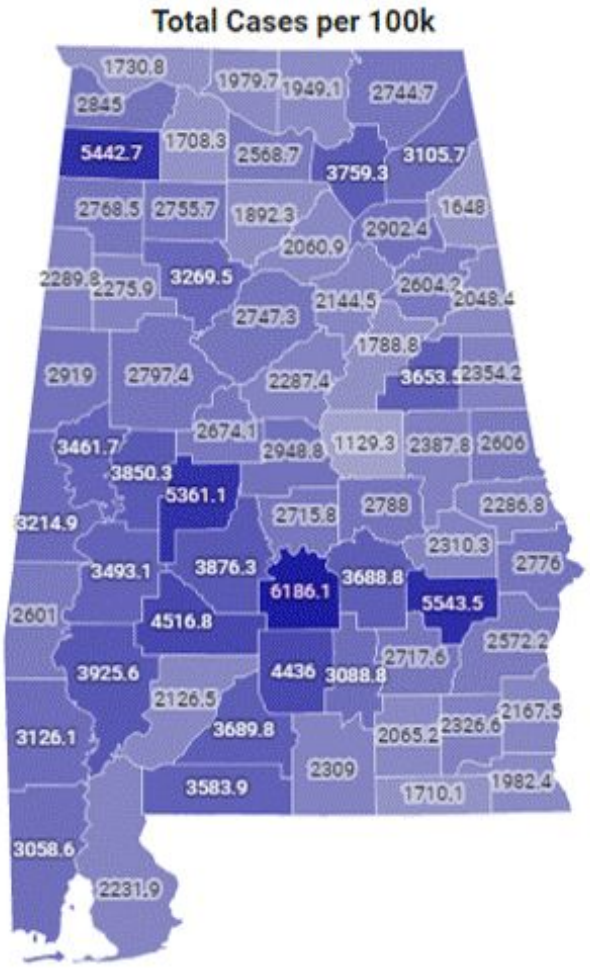
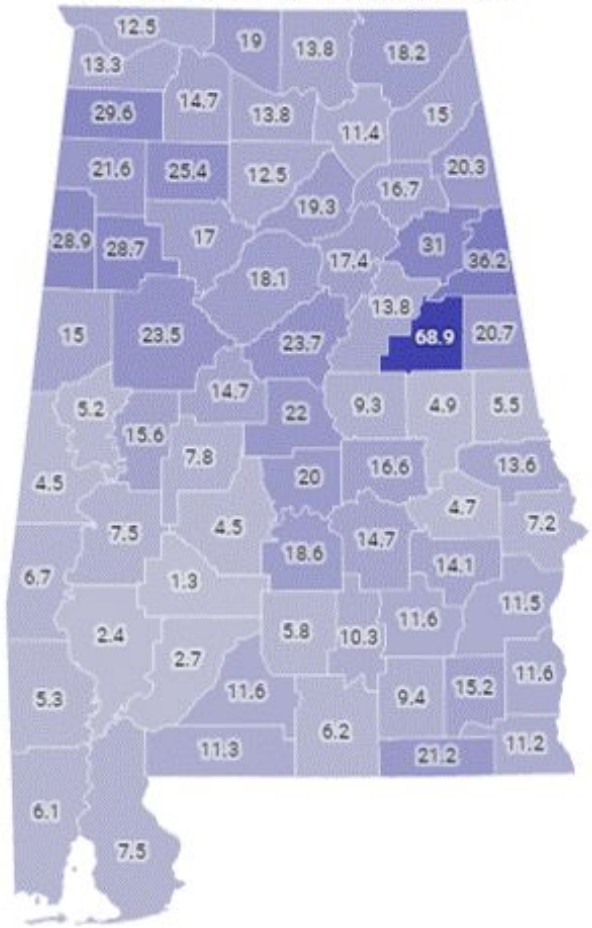
Alabama COVID-19 per 100K





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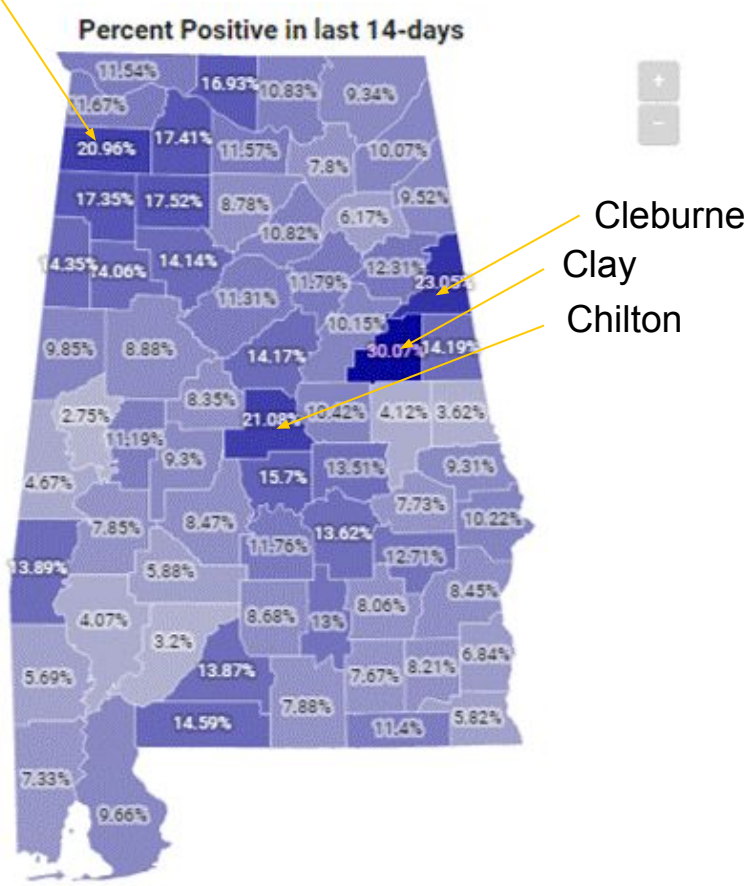
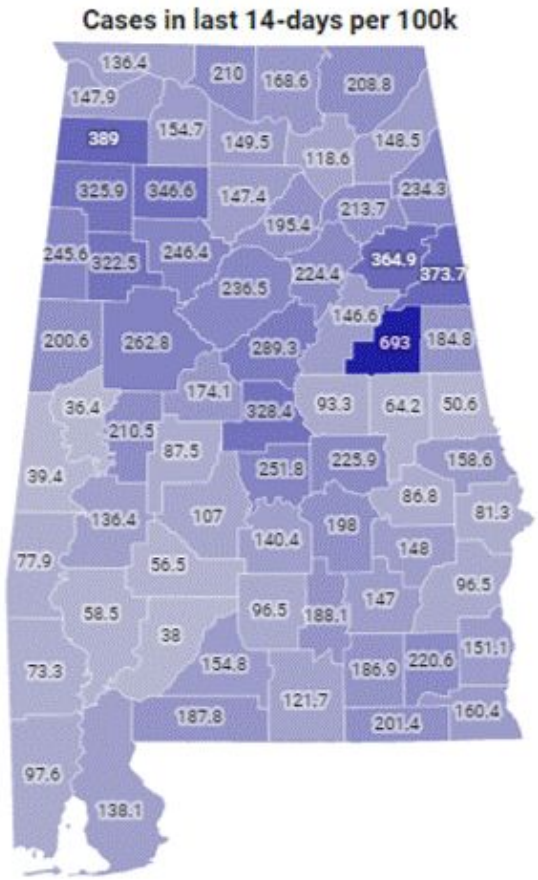
BamaTracker.com Accessed 9/19/20

Alabama "Hotspots"
High Cases + High Positive Test Rate

Franklin





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BamaTracker.com Accessed 9/19/20

COVID Deaths / 100 K by State

Gross US CFR = 2.86%
Gross AL CFR = 1.63%

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Covid.CDC.gov/covid-data-tracker/#cases_casesinlast7days
Accessed 9/29/20

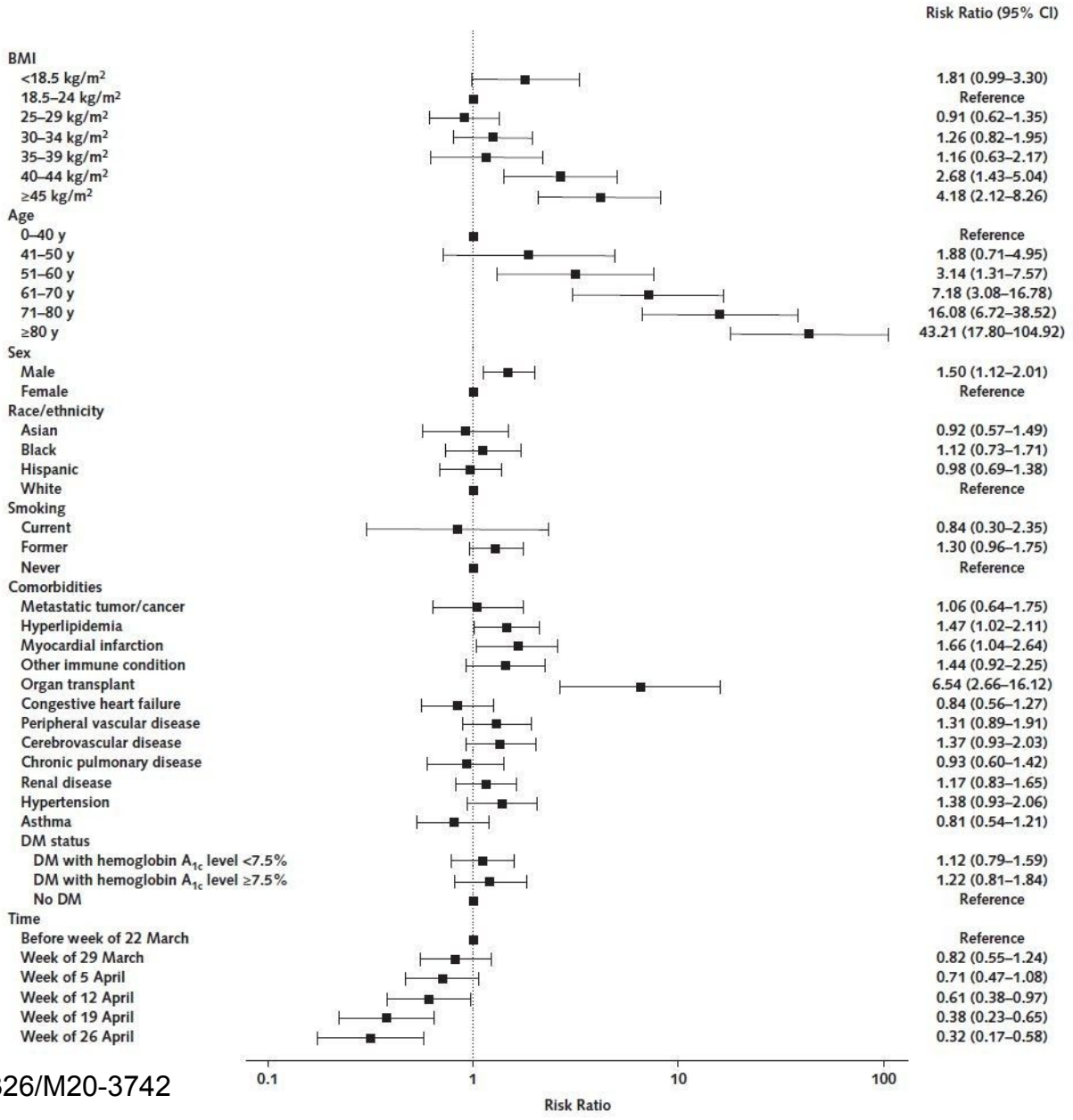
Risk Factors for COVID-19 Mortality

Kaiser Permanente
Southern California
6916 patients
Feb – May 2020

Age, BMI, sex most important risks
CV risk factors lesser effect after multivariable adjustment but highly prevalent

Race, ethnicity, socio-economics not risk in multivariable model (insured population)

Treatment got better over time



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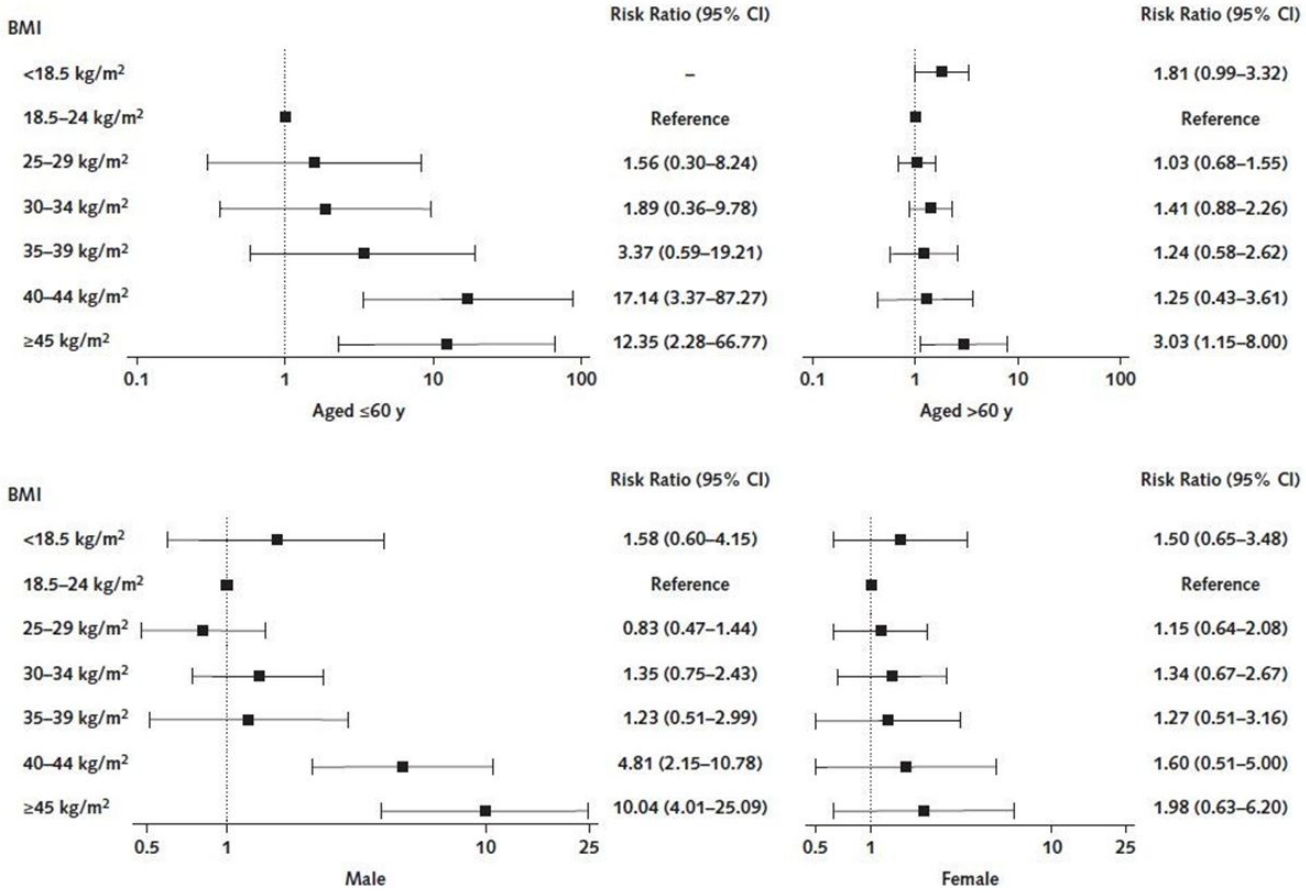
https://doi.org/10.7326/M20-3742

Risk Factors for COVID-19 Mortality

Kaiser Permanente
Southern California
6916 patients
Feb – May 2020

Obesity is an important risk factor

BMI interaction more important with younger patients and men



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https://doi.org/10.7326/M20-3742

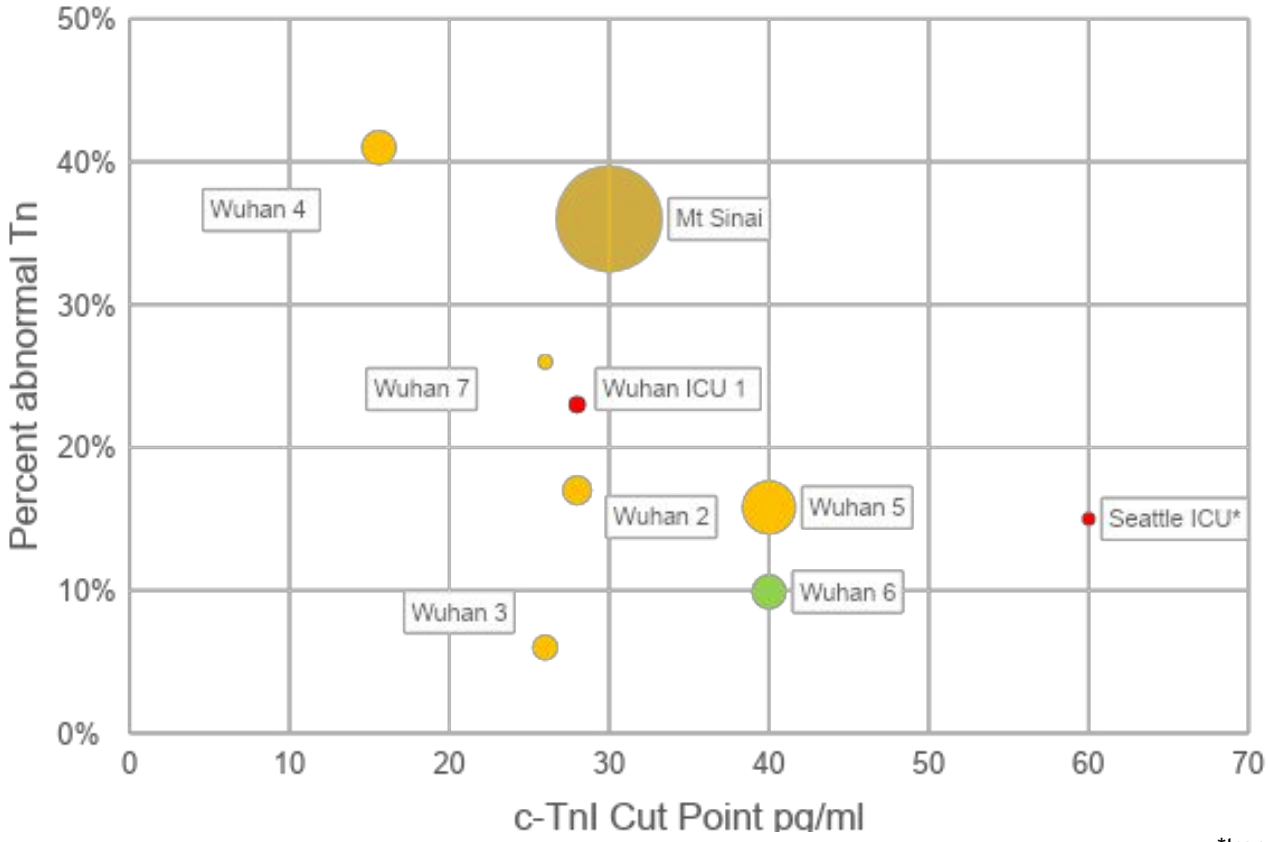
Cardiovascular Complications in COVID-19

- Primary acute cardiac involvement
  - Acute Coronary Syndromes
  - Myocarditis
  - Arrhythmia
- Secondary acute cardiac involvement
  - Acute myocardial injury
    - cytokines, microvascular dysfunction, arrhythmia
  - Heart failure
    - Pre-existing or new onset
    - LV or RV
- Hypercoagulable state
- Subacute cardiovascular risk
  - Thromboembolic risk?
  - Myocarditis / heart failure risk?

Myocardial injury and COVID 19

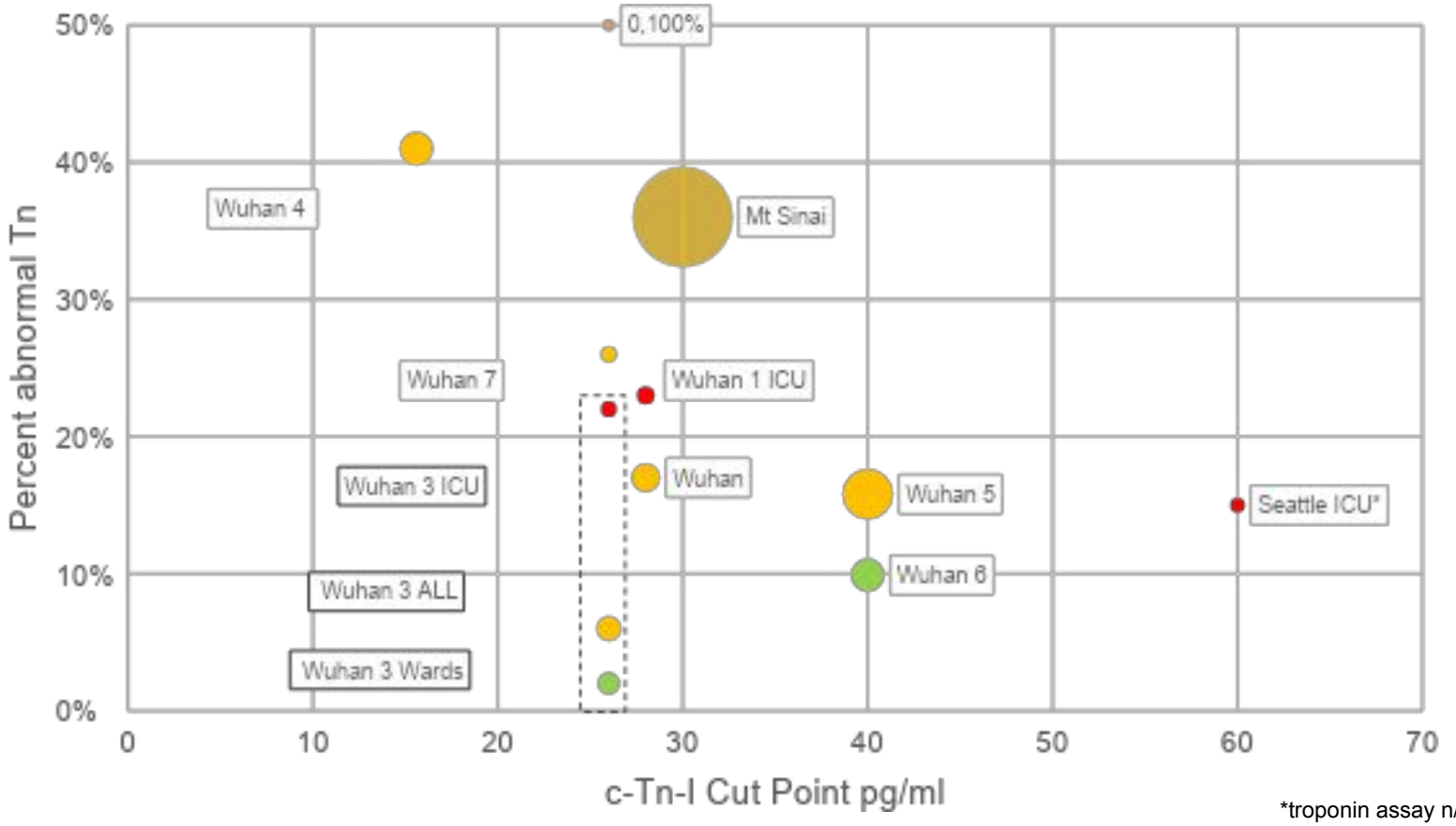
- Myocardial injury defined as c-troponin < 99th percentile ULN
- Myocardial injury is common in hospitalized patients with COVID-19
- Troponin elevation mostly mild but has prognostic implications
- Prevalence and magnitude of troponin elevation highly variable depending on assay used, prevalence of underlying cardiovascular disease, and severity of illness

Prevalence of Tn-I Elevation in Hospitalized Patients with COVID 19



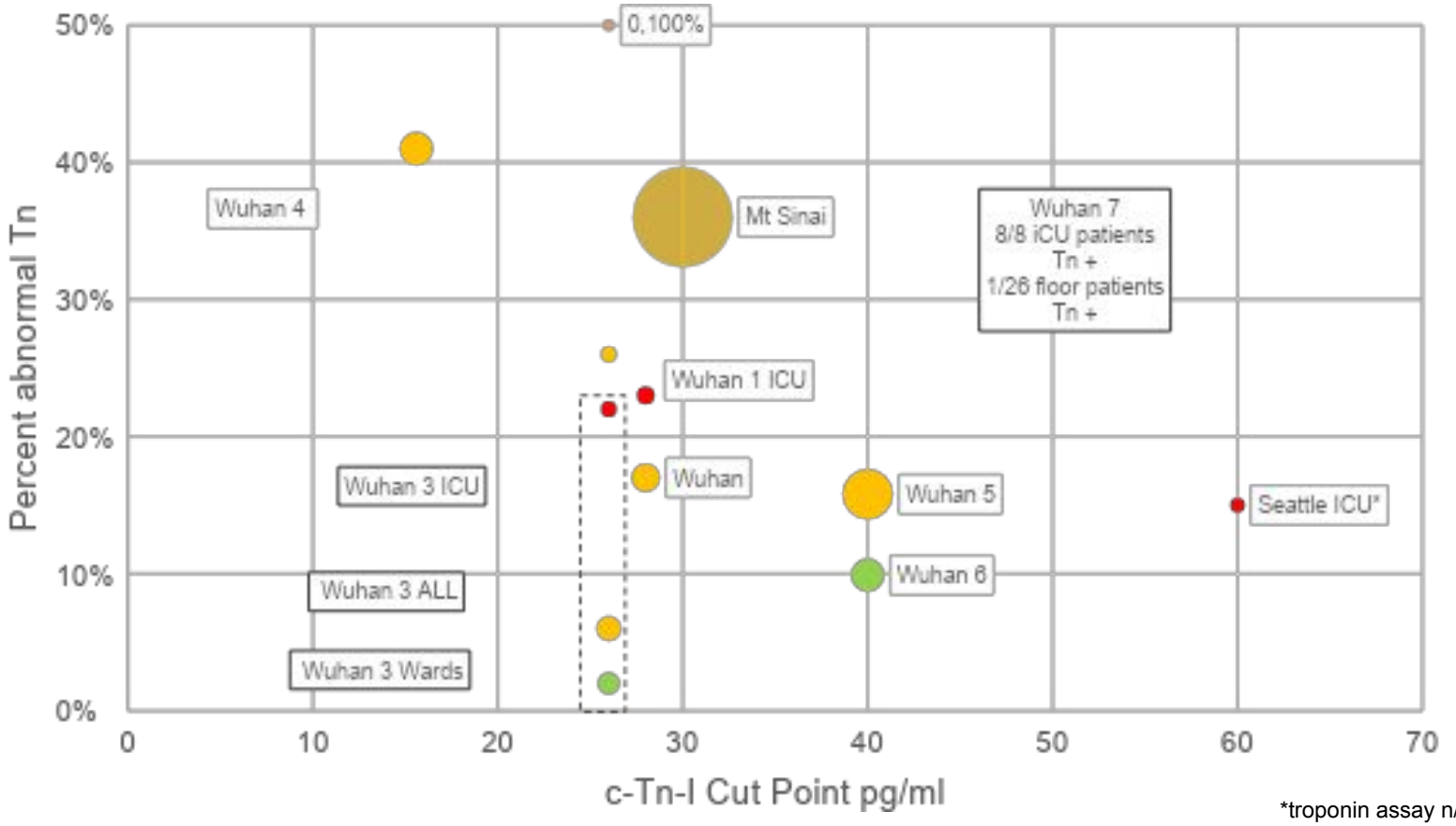
*troponin assay n/a

Prevalence of Tn-I Elevation in Hospitalized Patients with COVID 19



*troponin assay n/a

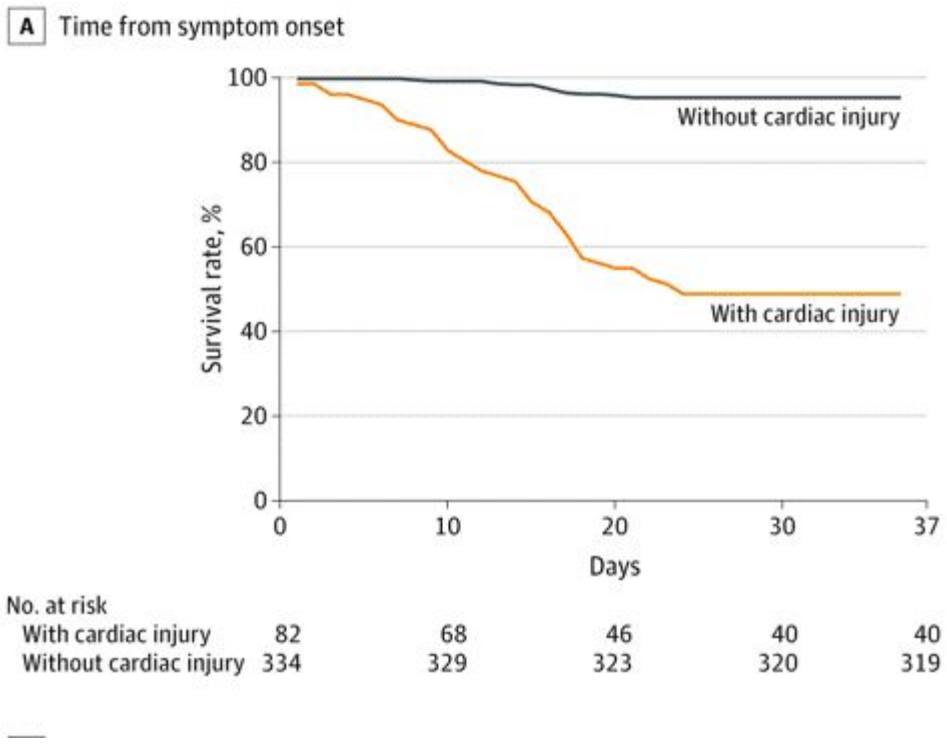
Prevalence of Tn-I Elevation in Hospitalized Patients with COVID 19



*troponin assay n/a

From: **Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China**

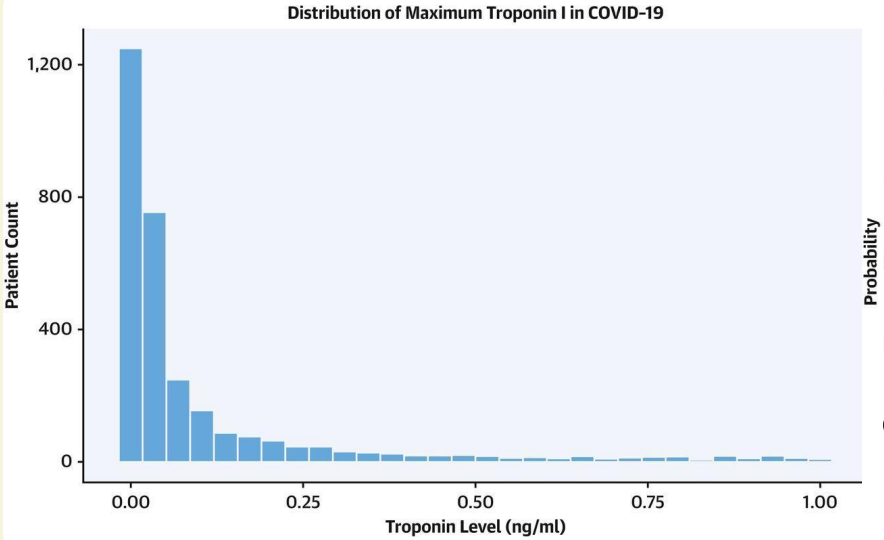
JAMA Cardiol. 2020;5(7):802-810. doi:10.1001/jamacardio.2020.0950

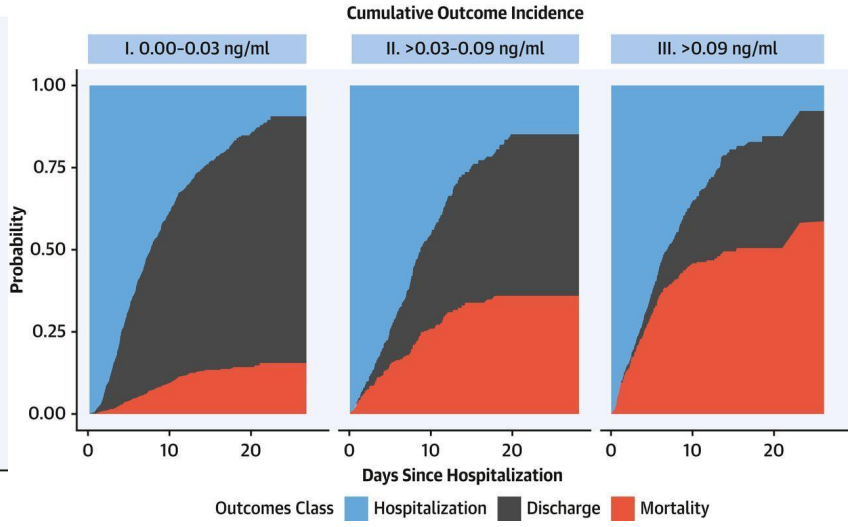


- 416 patients hospitalized in Wuhan Jan-Feb 2020, 20% had myocardial injury (hs-cTnT > 9 pg/ml)
- Patients with myocardial injury older, more CV co-morbidities
- ARDS, and requirement for invasive ventilation higher with injury
- Mortality hazard ratio of myocardial injury 3.41 after multi-variable adjustment

Myocardial Injury: Mt Sinai Cohort

- 2736 COVID-19 patients median age 63 admitted to Mt Sinai Health System Feb-April 2020 with troponin measurements within 24 hours of admission
- 36% had elevated troponin-I (>0.03 ng/ml)
  - More prevalent in patients with hypertension or diabetes
  - Increased risk of death
    - Adjusted hazard ratio 1.75 for troponin 0.03 – 0.09
    - Adjusted hazard ratio 3.03 for troponin > 0.09
    - Rising troponin over time associated with 24% mortality





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Lala A, Johnson KW, et al Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. J Am Coll Cardiol 2020;76:533-546.

Myocardial injury and COVID 19

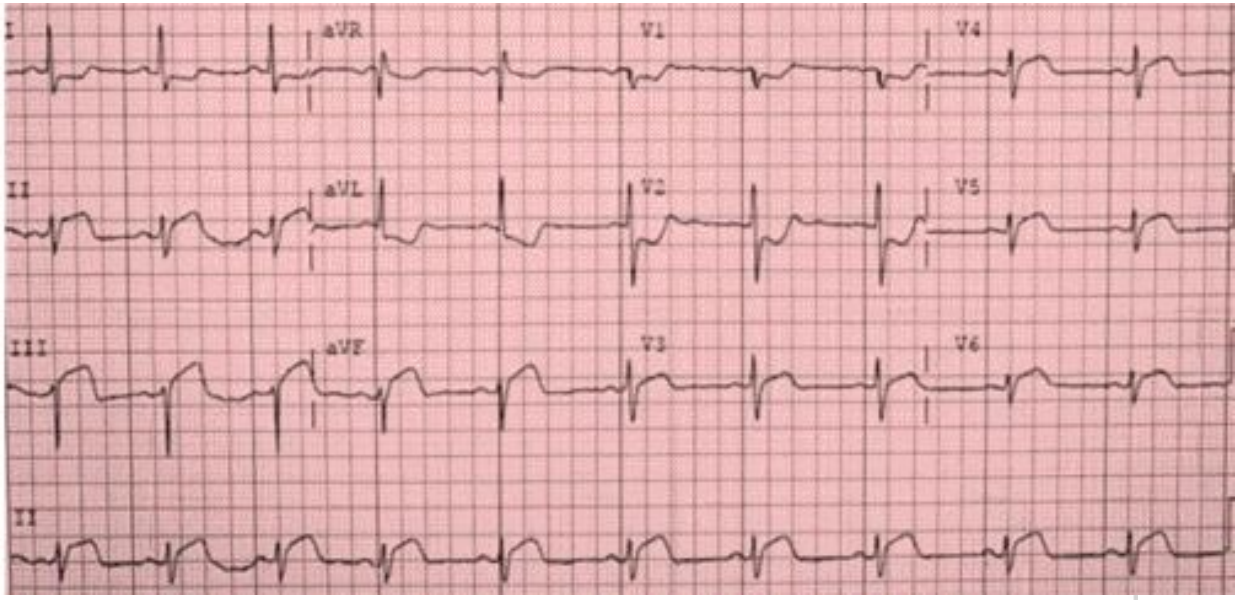
- Wide variation in detection of myocardial injury depending on assay, severity of illness, and CV co-morbidities
- Troponin elevation and rising troponin has prognostic import
- Hs-Troponin elevation common in non-COVID ICU patients
  - 42% had c-Tn > 10 pg/ml in 878 consecutive admissions to Mayo ICU
- Potential mechanisms of myocardial injury in COVID-19:
  - Ischemic
    - Type 1 MI due to plaque rupture
    - Type 2 MI due to hypoxemia and hemodynamic stress, or microvascular damage from thrombosis, DIC, inflammation
  - Non-ischemic
    - Myocarditis due to viral infection
    - Direct myocardial injury due to inflammatory cascade or cytokine release
    - Stress cardiomyopathy

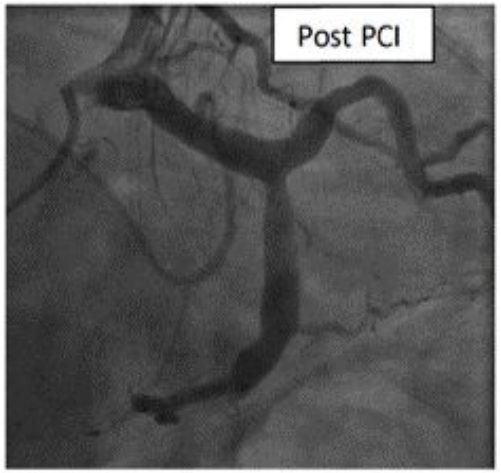
Acute Coronary Syndrome and COVID 19

- Acute coronary syndrome incidence is increased 3-10 fold in setting of viral infections generally
  - STEMI or NSTEMI
- Case series of 18 patients with ST elevation and COVID 19 in NY area hospitals
  - Mean age 63, 83% male, 50% Hispanic
  - 33% had chest pain
  - 10/18 ultimately found not to have acute coronary syndrome

N Engl J Med 2020; 382:2478-2480 DOI: 10.1056/NEJMc2009020

STEMI and COVID 19





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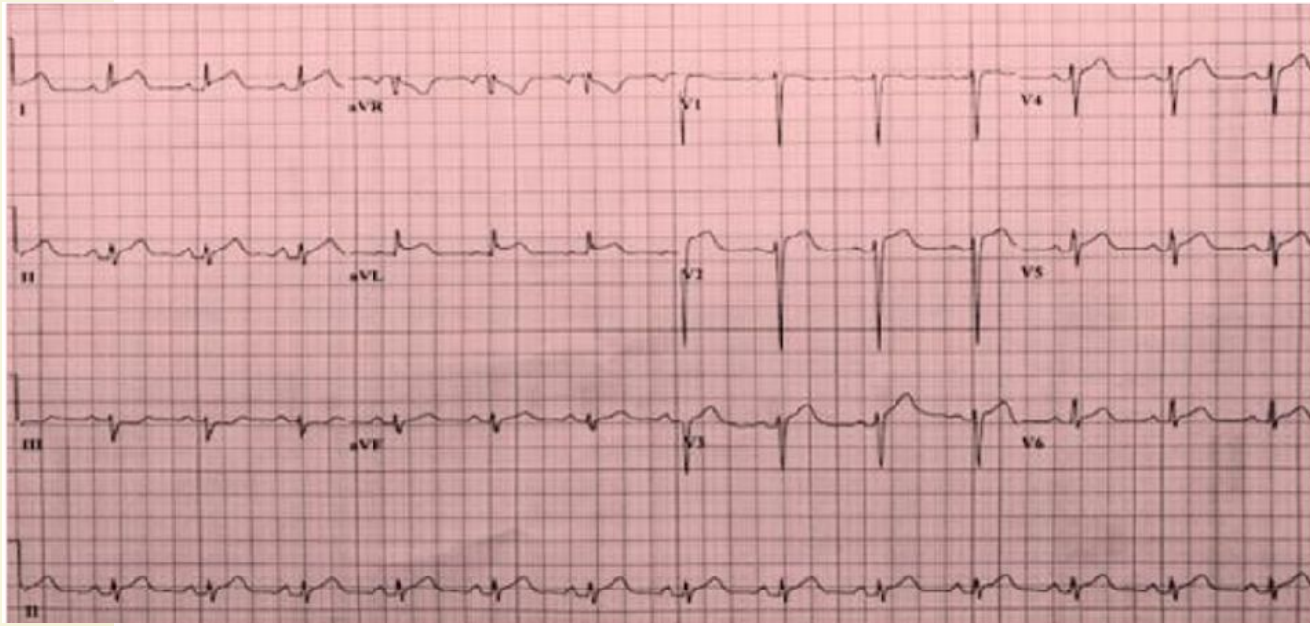
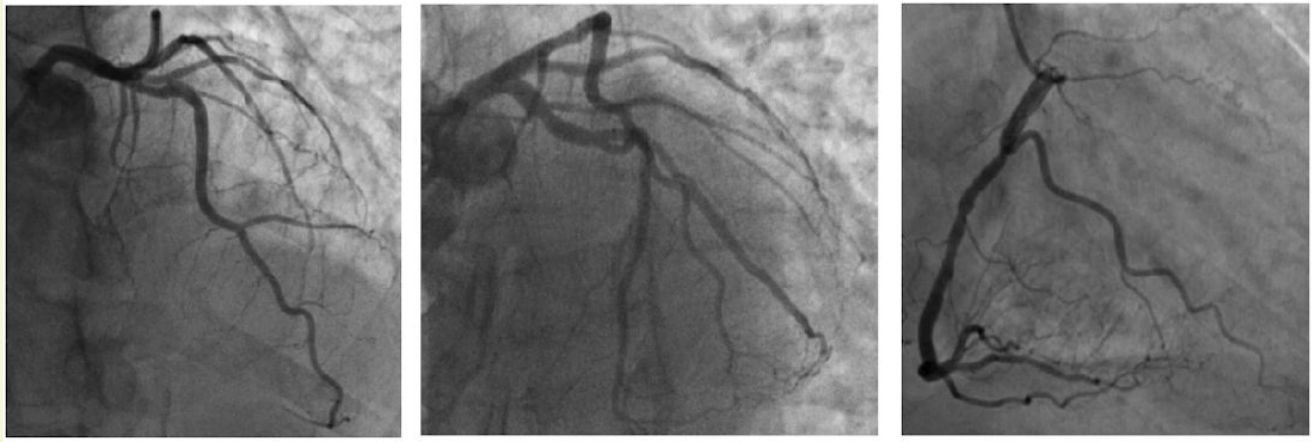
ST Elevation and COVID 19



- Patient with diffuse ST elevation on ECG



- Coronary arteriograms: no obstruction

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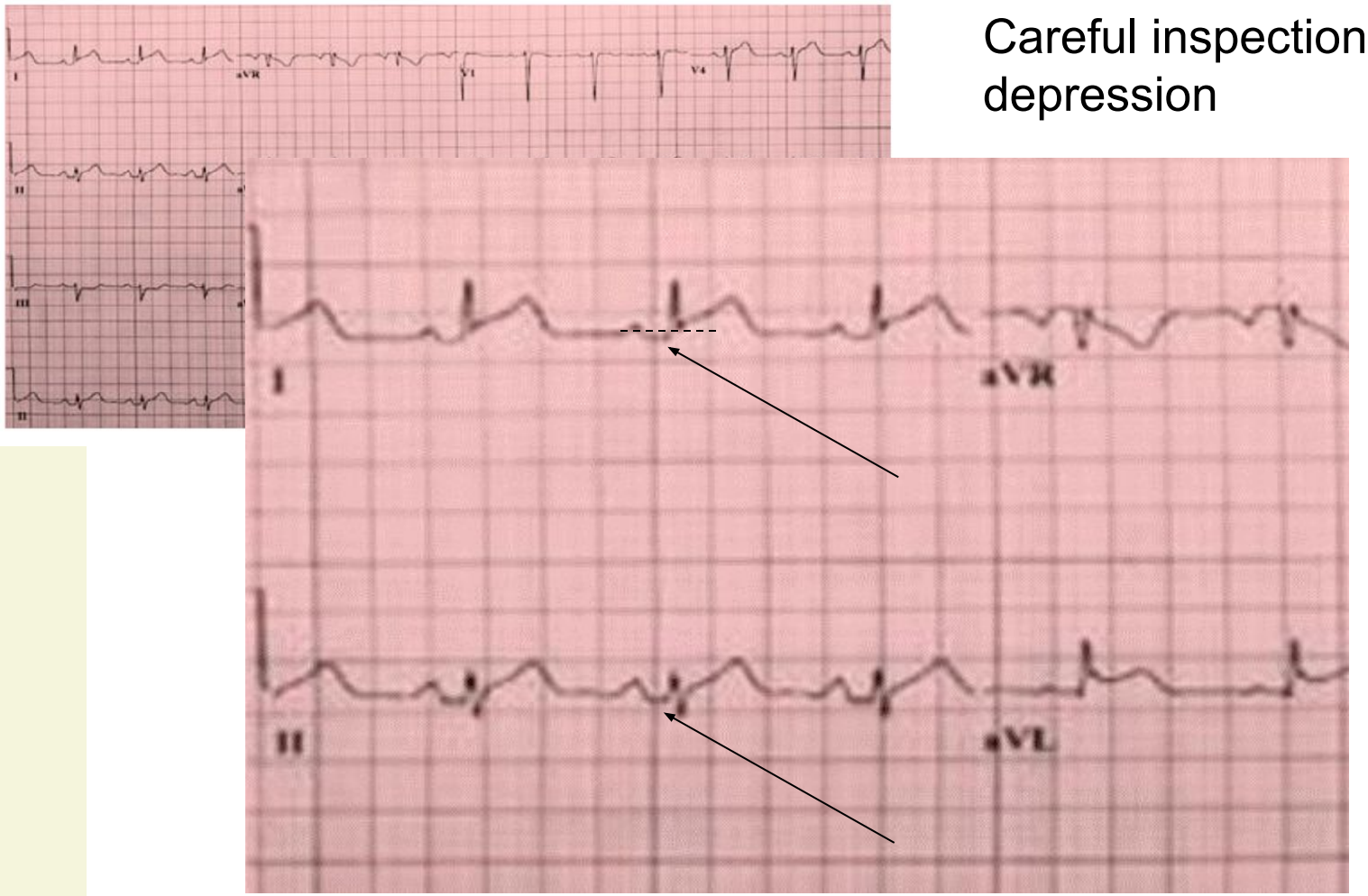
N Engl J Med 2020; 382:2478-2480 DOI: 10.1056/NEJMc2009020

ST Elevation and COVID 19

Patient #9



Careful inspection show PR depression

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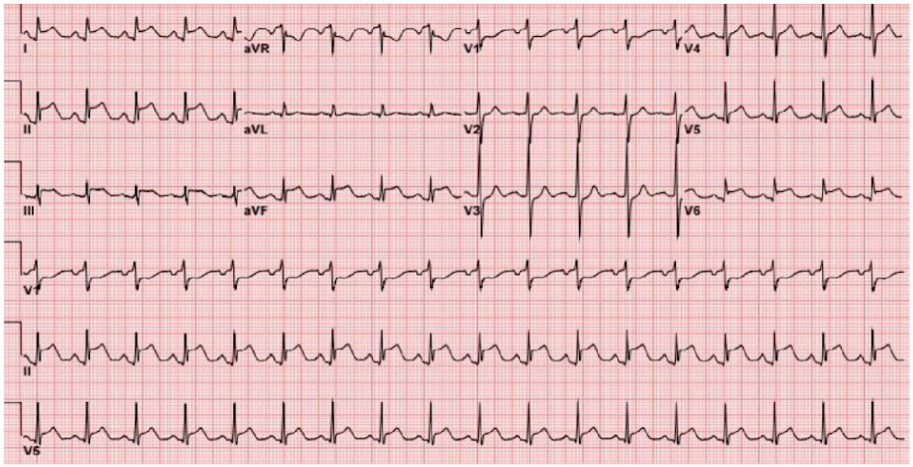
N Engl J Med 2020; 382:2478-2480
DOI: 10.1056/NEJMc2009020

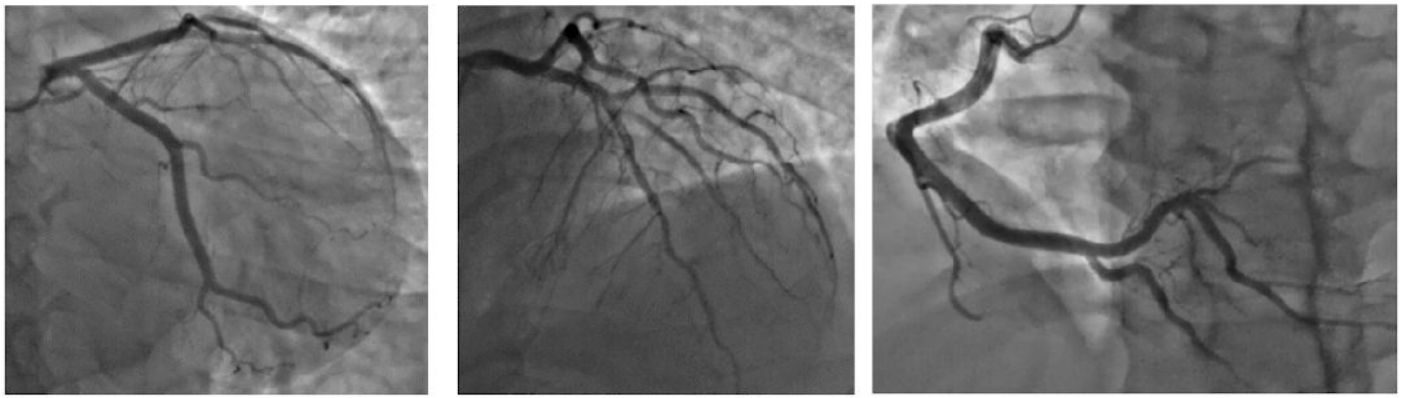
ST Elevation and COVID 19

Patient #12



Patient #14

Patient #14



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ST Elevation and COVID 19

Characteristic	Myocardial Infarction	Myocardial Injury (non-ACS)
n	8	10
Median Age (IQR)	60 (56 – 73)	66 (54-73)
Male (%)	7 (88)	8 (80)
Chest pain (%)	**5 (62)**	**1 (10)**
Shock (%)	2 (25)	5 (50)
Intubated (%)	5 (62)	7 (70)
ECG pattern (%) Diffuse ST elevation Focal elevations	 0 8 (100)	 **4 (40)** 6 (60)
Echo (%) **Normal EF** **Regional WMA**	 **1/8 (12)** **6/8 (75)**	 **7/9 (78)** **0/9**
Death in hospital (%)	4 (50)	9 (90)

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N Engl J Med 2020; 382:2478-2480 DOI: 10.1056/NEJMc2009020

ST Elevation in Lombardy Italy

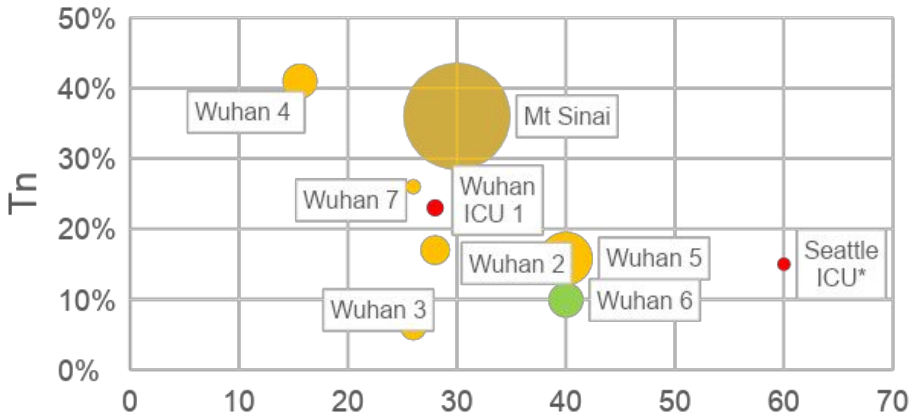
- Case series of all COVID-19 patients presenting with ST elevation and undergoing LHC in hospitals in Lombardy Italy Feb 20 – March 30 2020
- All patients met definition of STEMI with segmental ST elevation (n = 25) or new LBBB (n = 3)
- Mean age 68, 71% male, 78% chest pain, 82% with regional wall motion abnormalities by echo
- 39% did not have obstructive coronary disease at catheterization, of which:
  - 64% had regional WMA
  - 18% normal LV function
  - 18% diffuse LV dysfunction

Circulation. 2020;141:2113–2116. DOI: 10.1161/CIRCULATIONAHA.120.047525

Myocardial injury and COVID 19

- Potential mechanisms of myocardial injury in COVID-19:
  - Ischemic
    - ✔ Type 1 MI due to plaque rupture
      - ♦ Type 2 MI due to hypoxemia and hemodynamic stress, or microvascular damage from thrombosis, DIC, inflammation
  - Non-ischemic
    - ✔ Acute myocarditis
      - ♦ Myocardial injury due to inflammatory cascade or cytokine release
      - ♦ Stress cardiomyopathy

COVID-19 Myocardial Injury: Is it myocarditis?



- 20 – 40% of hospitalized patients in various series have evidence of myocardial injury
- Overwhelming majority don't have ACS clinically
- What is the mechanism of injury in these patients
  - Type 2 NSTEMI?
  - Myocarditis?
  - Takatsubo?

Myocarditis

- Definition: inflammatory disease of the heart muscle cells
- Clinical presentations
  - Acute fulminant: LV systolic dysfunction, cardiogenic shock
  - Non-fulminant: acute or chronic, may progress insidiously
- Diagnosis
  - Definitive diagnosis requires endomyocardial biopsy:
    - Lymphocytic infiltration of myocardium with cell necrosis
  - Clinical diagnosis based on presentation and MRI findings:
    - Increased T2, early gadolinium enhancement, LGE, native T1 mapping
- Can be triggered by infectious agents, especially viral, as well as toxins or hypersensitivity reactions
  - Viral genome detected in myocardium in 25-50% of suspected myocarditis in various biopsy / autopsy series

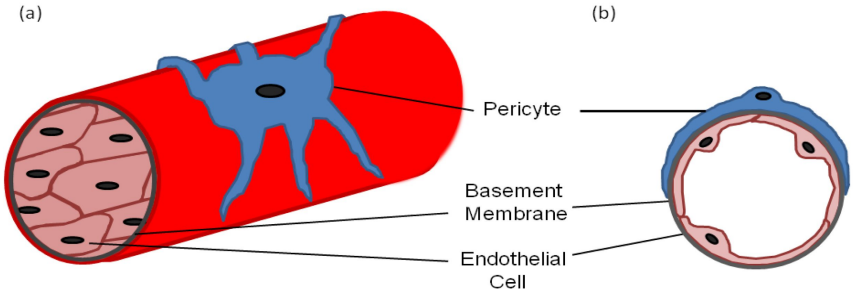
Circulation Research. 2016;118:496–514

COVID-19 Myocardial Injury: Is it myocarditis?

- Cardiomyocytes express the ACE-2 receptor, and infection of cardiomyocytes by SARS-CoV-2 had been demonstrated in-vivo
- Demonstrated in cardiomyocytes post mortem in a child[1]
- Autopsy and biopsy series have demonstrated SARS-CoV-2 in the heart, but mostly not in cardiomyocytes
  - Found in cardiac macrophages on biopsy[2]
  - Autopsy series of 22 patients did not find evidence of myocarditis[3]
    - Clinically did not have diagnosis of fulminant myocarditis
    - Most patients had mild troponin elevation, but no lymphocytic infiltrate
    - Severely dilated right ventricle
    - Viral particles observed in **myocardial endothelial compartment**, but **not in cardiomyocytes**
    - Authors hypothesized elevated troponin in COVID-19 due to stress from acute pulmonary disease rather than myocarditis

1. Lancet Child Adoles Health 2020 doi.org/10.1016/S2352-4642(2030257-1)
2. Eur J Heart Fail 2020;22:911-15
3. JAMA Cardiol doi 10.1001/jamacardio.2020.3551

COVID-19 Myocardial Injury: Is it myocarditis?



- Cardiac pericytes might be the myocardial cells most likely to be infected[1,2]
  - Localize around endothelial cells and make up 10% of total cardiac nuclei
  - ACE2 much more highly expressed in pericytes than cardiomyocytes
  - Pericytes regulate myocardial micro-circulation
  - Authors hypothesized that pericyte infection might lead to microvascular dysregulation and myocardial injury

1. JAMA Cardiol doi 10.1001/jamacardio.2020.3551
2. Cardiovasc Res 2020;116:1097-1100

Mechanisms of Myocardial Injury in COVID-19

- Potential mechanisms of myocardial injury in COVID-19:
  - Type 1 MI
  - Type 2 MI
    - hypoxemia and hemodynamic stress, especially acute RV failure
    - ? microvascular dysfunction (pericytes?, cytokines)
  - ? Myocarditis: does not appear to account for bulk of myocardial injury in COVID-19
    - clinical myocarditis occurs (ST elevation), but uncommon
    - viral genome demonstrated in heart but not in adult cardiomyocytes
    - lymphocytic infiltrates uncommon by autopsy or biopsy Direct myocardial injury due to inflammatory cascade or cytokine release
  - Stress cardiomyopathy
    - 4.2% of 118 consecutive hospitalized COVID-19 patients who underwent clinically indicated echo[1]

1. DOI: 10.1016/j.jacc.2020.05.068

Important Unanswered Questions

The elephant in the room

- IS IT SAFE TO PLAY FOOTBALL?

JAMA Cardiology | Original Investigation

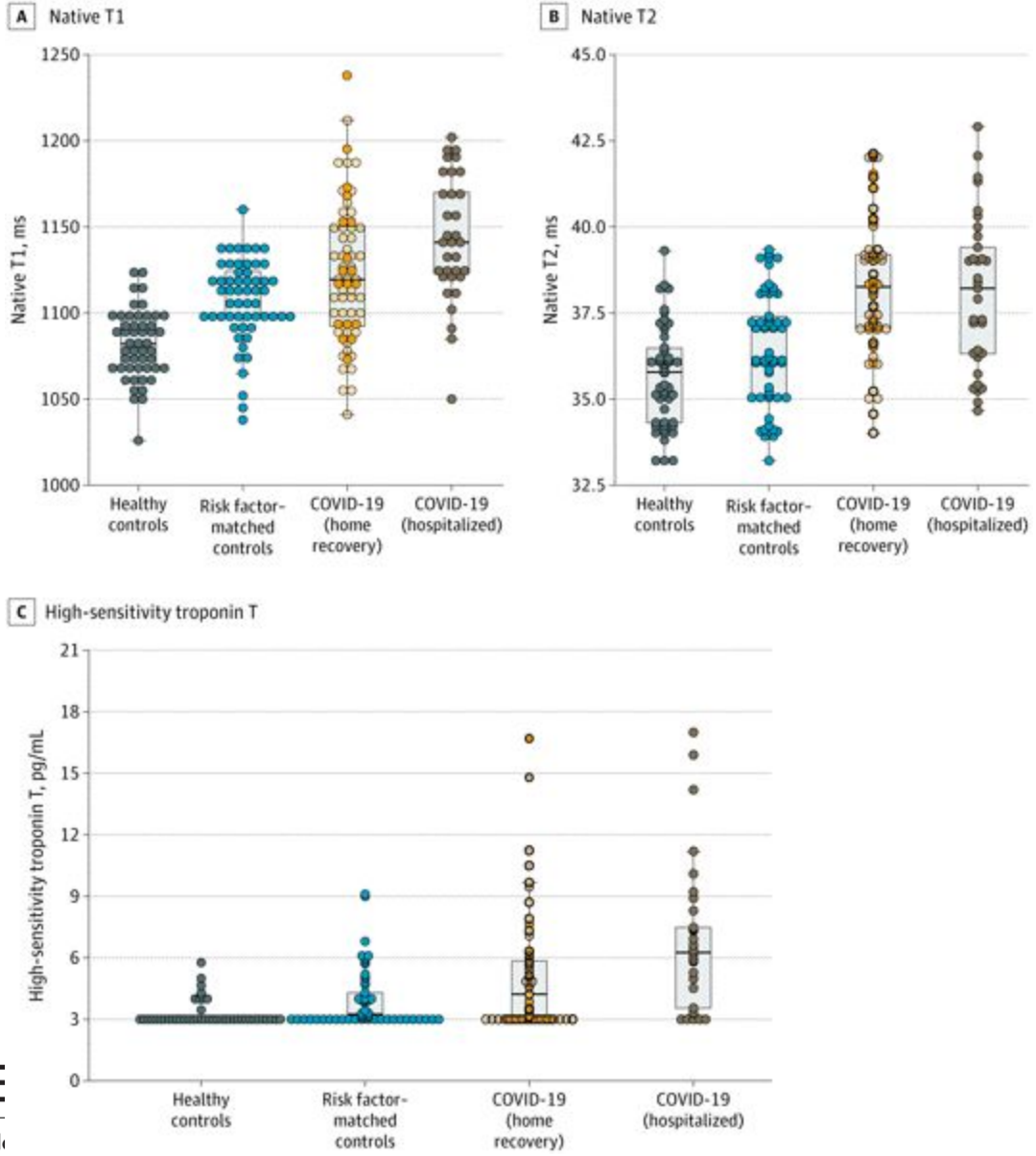
Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

Valentina O. Puntmann, MD, PhD; M. Ludovica Carerj, MD; Imke Wieters, MD; Maria Fahim; Christophe Arendt, MD; Jedrzej Hoffmann, MD; Anastasia Shchendrygina, MD, PhD; Felicitas Escher, MD; Mariaca Vasa-Nicotera, MD; Andreas M. Zeiher, MD; Maria Vehreschild, MD; Eike Nagel, MD

The study that cancelled Big 10 Football

- 100 patients mean age 49 years, 53% male
- MRI 71 days (64 – 92) post COVID-19 diagnosis
- 67% managed at home, 33% had been hospitalized
- Atypical chest pain (17%), dyspnea (36%; 25% NYHA III)
- Troponin detectable (> 3 pg/ml) 71 %, abnormal (>13.9 pg/ml) 5% at time of MRI
- “78% had evidence of cardiac involvement by MRI”
- Abnormal CMR (raised native T1 or T2, LGE, pericardial enhancement) more frequent in COVID patients than age / risk factor matched controls
- 3 patients with severe abnormalities underwent biopsy which showed lymphocytic infiltration

JAMA Cardiol doi:10.1001/jamacardio.2020.3557



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JAMA Cardiol doi:10.1001/jamacardio.2020.3557

Safety of Competitive Atheletics after COVID-19 Infection

- Significant percentage of middle age Germans have at least some abnormality on MRI 2 – 3 months after COVID infection
  - So do a lot of age / risk matched controls
- Abnormalities more prevalent in patients who were initially hospitalized, but also seen in patients who were treated at home
- Severe abnormalities were seen in a smaller percentage of patients, including at least one who had minimal symptoms with initial infection
- Relevance of study of middle age Germans to young healthy athletes?
  - Eduardo Rodgiruez: Baseball pitcher felt “like I was 100 years old”, developed myocarditis and missed 2020 season
  - Michael Ojo: International basketball player who died suddenly while training 1 month post-COVID
  - Press reports of “35% incidence of myocarditis in Big-10 athletes post-COVID”

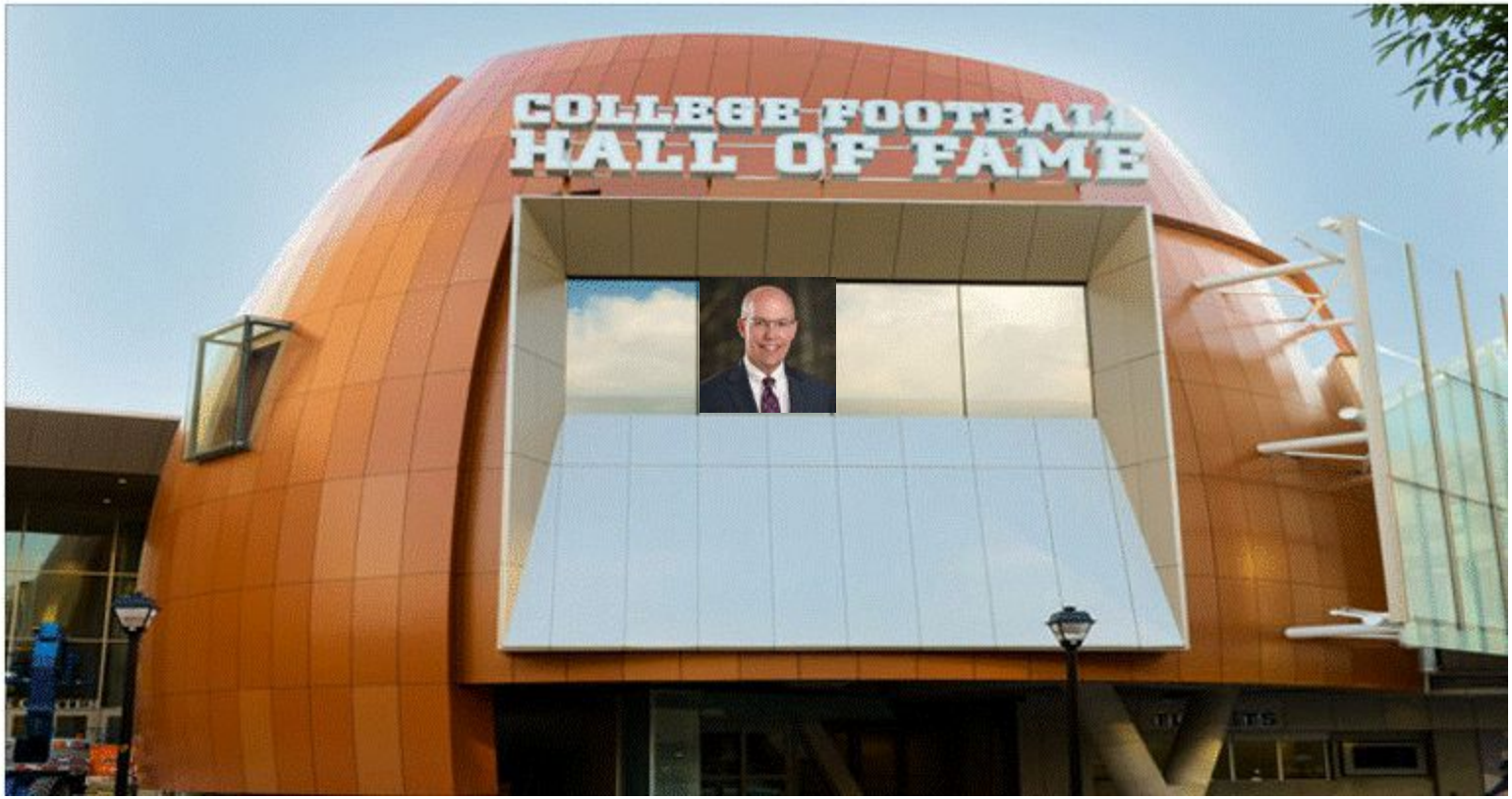
The cardiologist who saved college football

“if we have college football this fall, Dr. Ackerman will be one of the reasons why.”

“The Minnesota-based cardiologist leads the Windland Smith Rice Sudden Death Genomics Lab which studies, among other things, sudden death in young athletes. He explained to the Big 12's leaders that a new myocarditis study in the Journal of American Medical Association that sparked panic across college sports didn't have the 'bandwidth' to be transferable in a useful way.”

John Talty AL.com 8/19/20

“Ackerman said it'd be a 'scientific foul' to infer that those findings are relevant for 18 to 24-year old athletes.“



UAB MEDICINE

Knowledge that will change your world

CMR in Competitive Athletes After COVID-19

College Sports

Big Ten football reverses decision, will return to play in late October

Washington Post By **Emily Giambalvo**
September 16, 2020 at 4:52 p.m. CDT

- CMR exam of a
  clinic Jun-Aug
- None hospitaliz
- ECG, troponin
- 12/26 athletes
  - 8 without elevated T2

•LIFE & ARTS SPORTS COLLEGE FOOTBALL

Big Ten Considers Resuming Fall Football

Coronavirus concerns prompted conference leaders to postpone the season until 2021, but improved testing could bring it back

By Rachel Bachman, Laine Higgins and Louise Radnofsky Wall Street Journal
Sept. 14, 2020 7:00 am ET

rditis (increased T2

?

  - Significance and risk of low level asymptomatic myocarditis is unknown

Big Ten announces plan to resume football the weekend of Oct. 23-24

By **Megan Ryan** Star Tribune

SEPTEMBER 17, 2020 — 12:34AM

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JAMA Cardiology Published online Sept 11, 2020

Big 10 Plan to Protect Athletes

- Daily antigen testing
- Positive antigen test confirmed with rPCR
- Athletes testing positive prohibited from competition for minimum 21 days
  - Troponin, echo and cardiac MRI in all
  - Clearance from a cardiologist
- Whether CMR is necessary in asymptomatic athletes in order to safely resume high level atheletics is controversial

ACC Guidelines: Return to Sports in Adults after COVID-19[1]

- COVID-19 negative and asymptomatic: Exercise training OK
- **ALL COVID-19 positive: 2 weeks asymptomatic before considering return to participation**
  - Asymptomatic:
    - Slow resumption of activity after 2 weeks asymptomatic
  - Mild-moderate symptoms
    - CV exam, echo, troponin after 2 weeks asymptomatic
    - CMR, exercise testing, ambulatory rhythm monitoring based on clinical course and initial testing
  - Hospitalized, normal imaging / troponin in hospital:
    - CV exam, consider cardiac retesting before resumption of exercise, after minimum 2 weeks asymptomatic
  - Hospitalized, myocardial dysfunction or injury in hospital, follow myocarditis guidelines[2]:
    - Exercise restriction for 3 – 6 months prior to retesting for resolution (ventricular function and troponin normal, no arrhythmia on Holter or GXT)
    - Athletes with probable or definite myocarditis should not participate in competitive sports while active inflammation is present.

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1. JAMA Cardiol. Published online May 13, 2020. doi:10.1001/jamacardio.2020.2136
2. Circulation. 2015;132(22):e273-e280.

ACC Guidelines Return to Sports: Kids

- ALL COVID-19 positive: 2 weeks asymptomatic before considering return to play
  - Asymptomatic or mildly symptomatic (no fever, < 3 days symptoms):
    - OK to participate 2 weeks after symptom resolution
  - Moderate symptoms (prolonged fevers / bedrest, no hospitalization)
    - Age < 12: OK to participate 2 weeks after symptom resolution
    - Age > 12: ECG prior to resumption exercise 2 weeks after symptom resolution
      - Normal ECG: OK to participate
      - Abnormal ECG: evaluation by pediatric cardiologist, consider troponin, imaging
  - Severe symptoms: (hospitalized, abnormal cardiac testing, multisystem inflammatory syndrome in children)
    - Follow myocarditis guidelines
      - Exercise restriction for 3 – 6 months
      - ECG, echo, 24 hour Holter, exercise stress test, +/- MRI prior to resumption of exercise

1. https://www.acc.org/latest-in-cardiology/articles/2020/07/01/12/42/returning-to-play-after-coronavirus-infection-a-perspective-from-pediatric-cardiologists

Acute CV Complications: Arrhythmias

- Case series China 5.9% malignant arrhythmias
  - 17.3% in patients with myocardial injury vs 1.5% without[1] **JAMA Cardiol**. 2020. doi: 10.1001/jamacardio.2020.1017
  - Most in-hospital arrests involve non-shockable rhythms (asystolic, PEA)[2]
- Increased risk of out of hospital arrest in Italy during pandemic[3]
- In hospital arrests mostly due to non-shockable rhythms (asystolic 89,7%, PEA 4.4%, shockable 5.9%)[4]
- Hypokalemia due to increased urinary potassium excretion from excessive Ang-II availability due to SARS-CoV-2 binding to ACE2 may predispose to arrhythmia
- Recent study demonstrated 0% survival to hospital discharge in patients suffering in-hospital cardiac arrest
- Atrial fibrillation reported in 19% of patients in Italy and it Mt Sinai, more frequent in ICU patients.

[1]JAMA Cardiol. 2020. doi:10.1001/jamacardio.2020.1017
[2]Resuscitation. 2020;151:1823.doi:10.1016/j.resuscitation.2020.04.005
[3]N Engl J Med. 2020. doi: 10.1056/NEJMc2010418
[4]Resucitation 2020;151-18-23

COVID-19 Coagulopathy

- Elevated D-dimer and INR common in hospitalized COVID-19 patients, especially in ICU
  - DIC vs complement mediated microangiopathy
  - Thrombotic microangiopathy of lungs and less commonly other tissues has been reported in autopsy series
- 49% incidence of thrombotic event in Dutch study of ICU patients despite thromboprophylaxis
  - 65/75 events were pulmonary embolism
  - 5 strokes and 2 systemic arterial embolisms
- 1.6% of COVID-19 patients in NYC study presented with or developed stroke, compared with 0.2% of influenza patients
  - Mostly older patients with stroke risk factors
  - Stroke may be presenting symptom in young patients
- Rate of post-discharge pulmonary embolism was 4.8 / 1000 hospital discharges in UK study, not different from historical rate for medical discharges
  - Routine post discharge anti-coagulation not recommended
  - High risk groups not identified, only 11% of the study group was in the ICU

Nature Reviews Rheum 2020; 16:581-9
Thromb Res 2020; 191:148-50
https://doi.org/10.1182/blood.2020008086
JAMA Neurol. Published online July 2, 2020. doi:10.1001/jamaneurol.2020.2730

Livedo racemosa: skin manifestation reported in 4 ICU patients.
Biopsy revealed thrombogenic vasculopathy
All 4 patients had PTE despite prophylactic level anti-coagulation

JAMA Dermatol. 2020;156(9):1-3. doi:10.1001/jamadermatol.2020.2800

Cardiac Medications and COVID-19

- Cardiac Medications and COVID
  - ACEI / ARB
    - Concern: Upregulation of ACE2 receptor might increase risk or severity of infection
    - Potential benefit: Upregulation of ACE2 decreases severity of ARDS in animal models by offsetting Ang II vasoconstriction
    - Data: Retrospective data finds no effect of ACEI/ARB on outcomes
  - Anti-coagulants: prophylactic dose heparin recommended in hospitalized patients
  - Statins: Retrospective studies suggest improved outcomes
  - Colchicine: anti-inflammatory, might mitigate cytokine storm
    - One small open label randomized trial showed faster recovery and lower biochemical endpoints
    - Larger studies in progress
    - Newer data has questioned if cytokine storm is a feature of severe COVID-19 (instead: bradykinin storm > excess hyaluronic acid in the lungs?)

Conclusions

- Primary or secondary cardiac complications are common in hospitalized patients with COVID-19
- Myocardial injury is highly prevalent in hospitalized patients
  - Ischemic and non-ischemic mechanisms
  - Takotsubo has been reported
  - SARS-CoV-2 mRNA has been demonstrated in the heart by biopsy and at autopsy, but by EM viral particles mostly in non-cardiomyocyte cell lines (macrophages, pericytes)
  - RV failure and dilation common in autopsy series and may account for many cases of myocardial injury in severely ill patients
- MRI studies have shown concerning prevalence of abnormalities after recovery from COVID, including outpatients with few symptoms, but clinical significance of these findings is uncertain at present
- Long term consequences of COVID-19 on cardiopulmonary function is currently unknown, but so far no epidemic of cardiomyopathy…
- Thrombotic complications are a prominent feature of COVID-19