Cardiac effects of Covid-19

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Seminar for U of T Cardiology Residents

Mar 31, 2020

Disclosures:

- None for this topic

Key references:

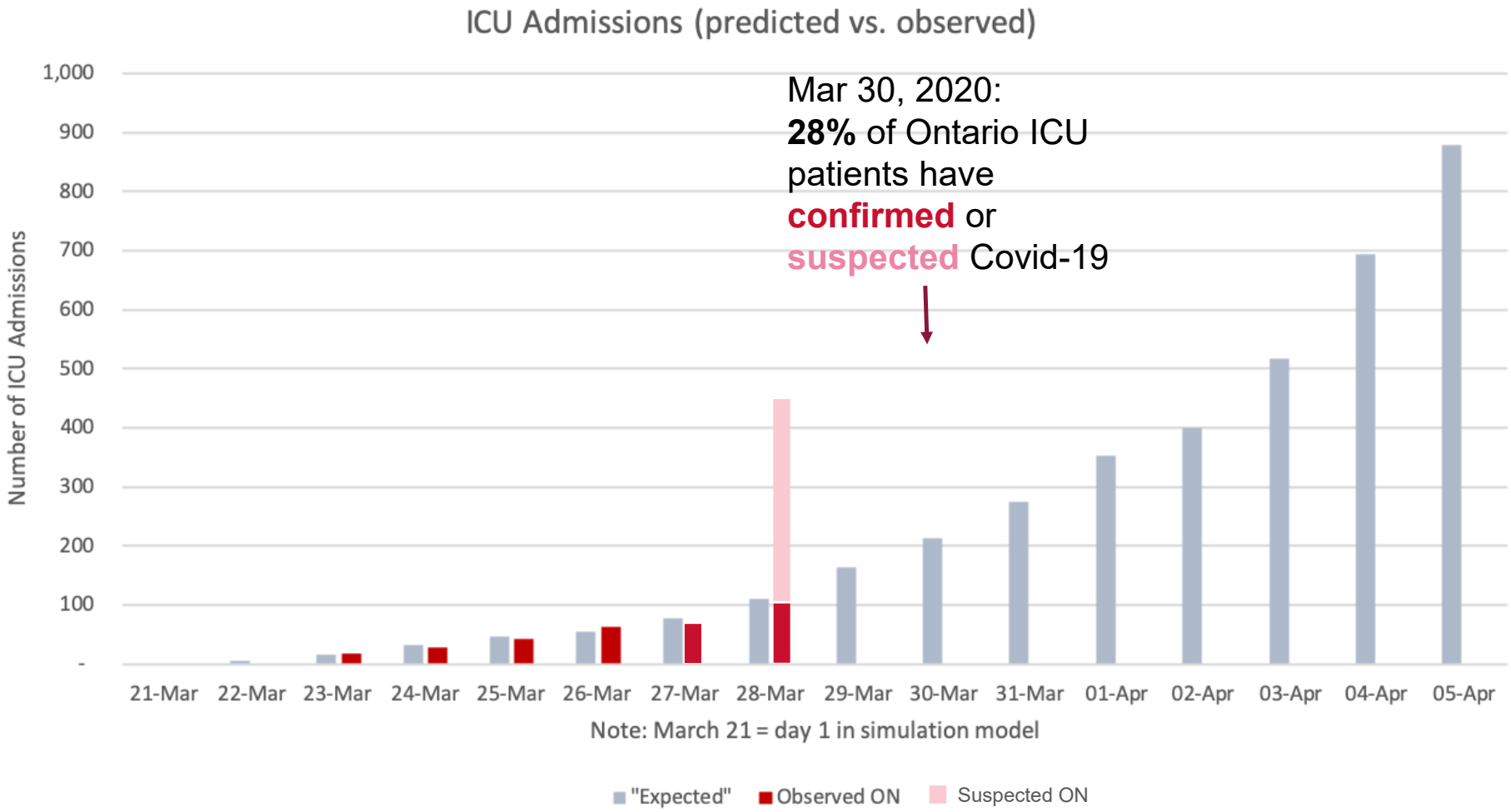
1. Shi *et al*. JAMA Cardiol doi:10.1001/jamacardio.2020.0950 [Published online Mar 25, 2020]
2. Guo *et al*. JAMA Cardiol doi:10.1001/jamacardio.2020.1017 [Published online Mar 27, 2020]
3. Driggin *et al*. J Am Coll Cardiol doi: 10.1016/j.jacc.2020.03.031 [Published online Mar 27, 2020]

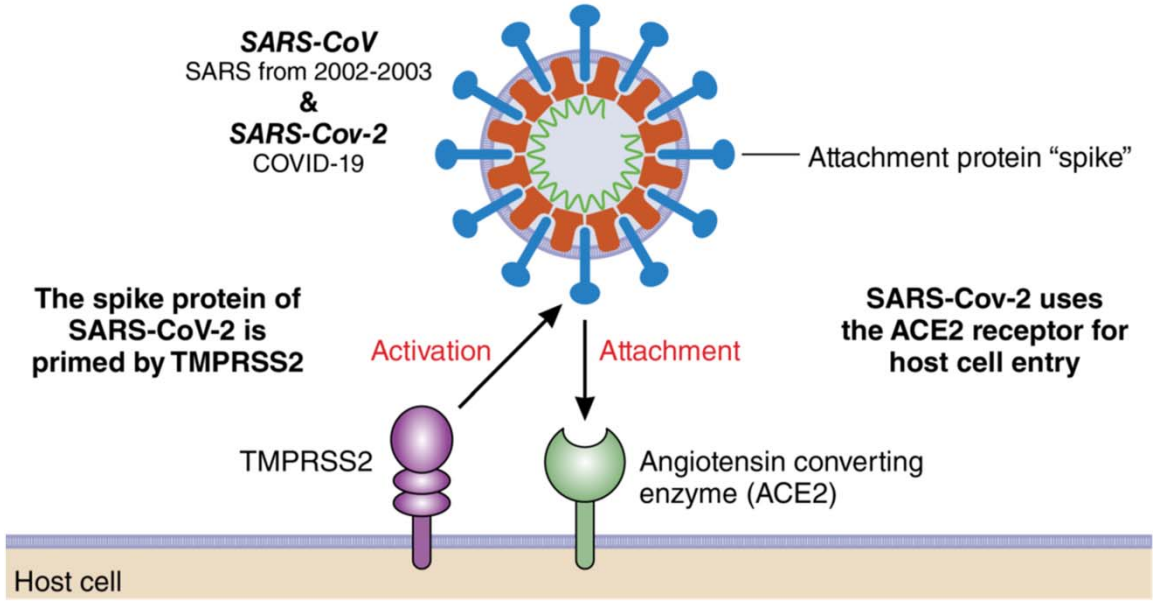
Learning Objectives

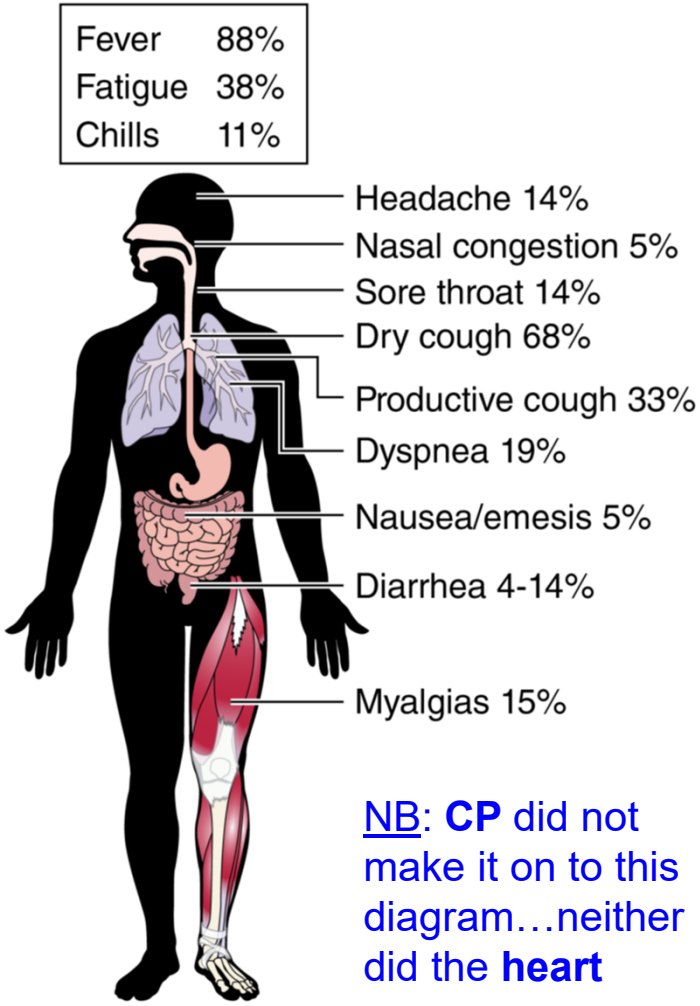
1. **Self care** enables better patient-, colleague-, family- & friend-care during Covid-19. **You are a role model**.

2. **Cardiovascular manifestations of Covid-19**

3. **Cardiovascular consequences of treatments for Covid-19**

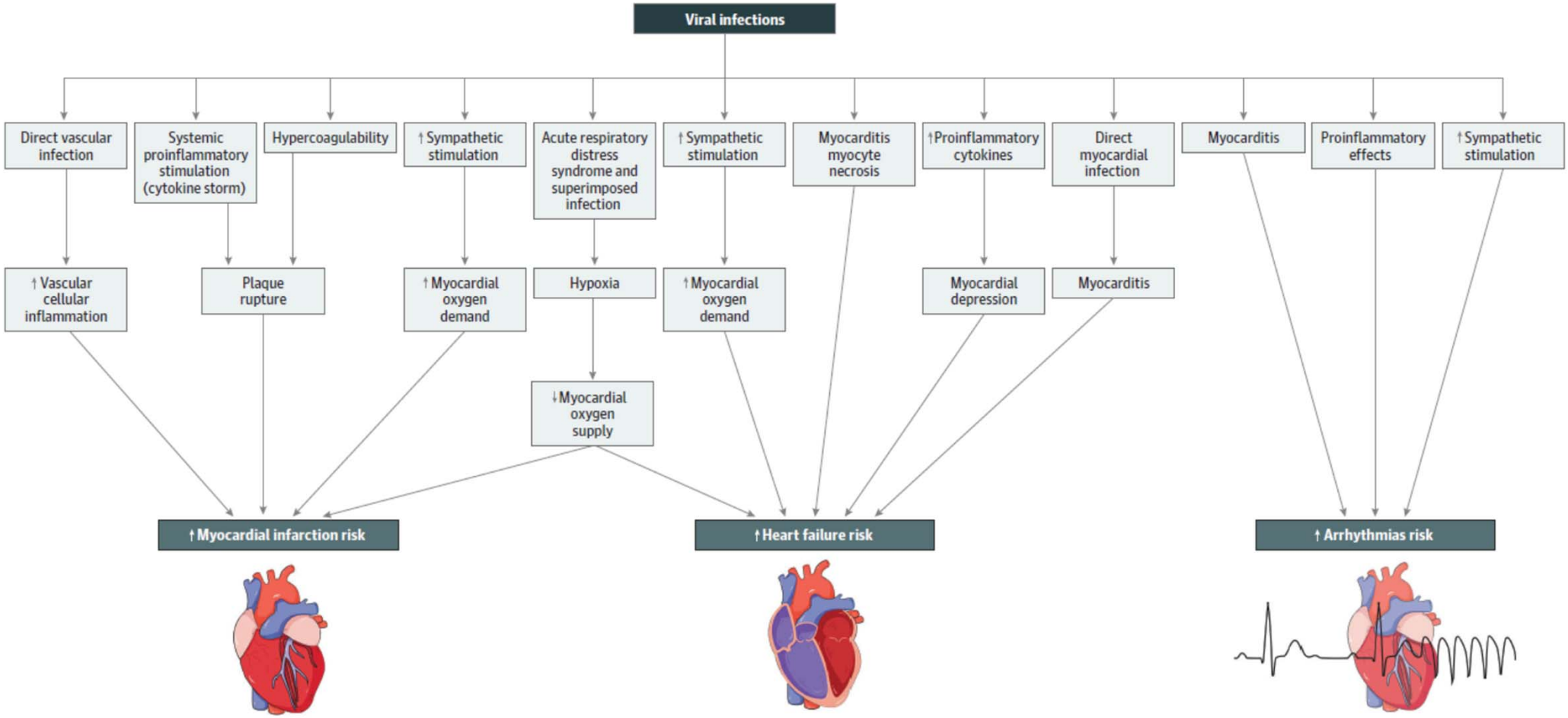

ICU Admissions (predicted vs. observed)
Mar 30, 2020:
28% of Ontario ICU patients have **confirmed** or **suspected** Covid-19
Number of ICU Admissions
1,000
900
800
700
600
500
400
300
200
100
-
21-Mar
22-Mar
23-Mar
24-Mar
25-Mar
26-Mar
27-Mar
28-Mar
29-Mar
30-Mar
31-Mar
01-Apr
02-Apr
03-Apr
04-Apr
05-Apr
Note: March 21 = day 1 in simulation model
"Expected"
Observed ON
Suspected ON





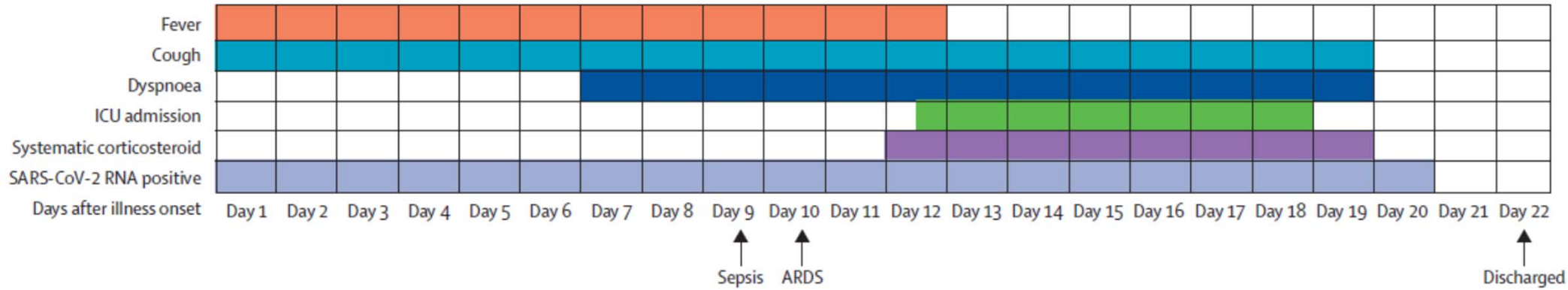
NB: **CP** did not make it on to this diagram…neither did the **heart**

Klerkin *et al*. 2020 10.1161/CIRCULATIONAHA.120.046941

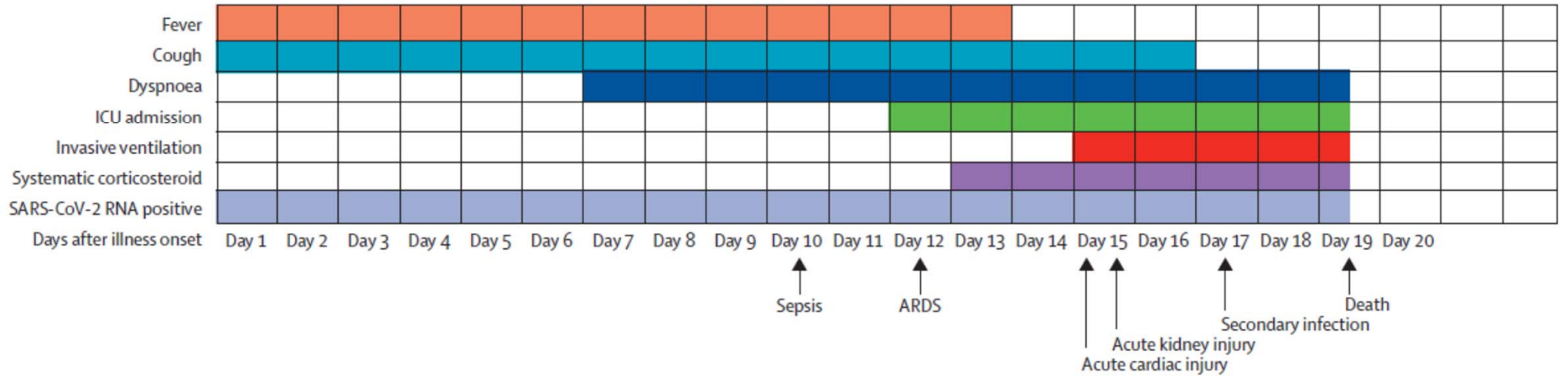


Madjid *et al*. JAMA Cardiol. doi:10.1001/jamacardio.2020.1286

N=137: Survivors **Age 52, M 59%, HTN 23%, T2D 14%, CAD 1%, Moderate 53%, Severe 39%, Critical 8%**



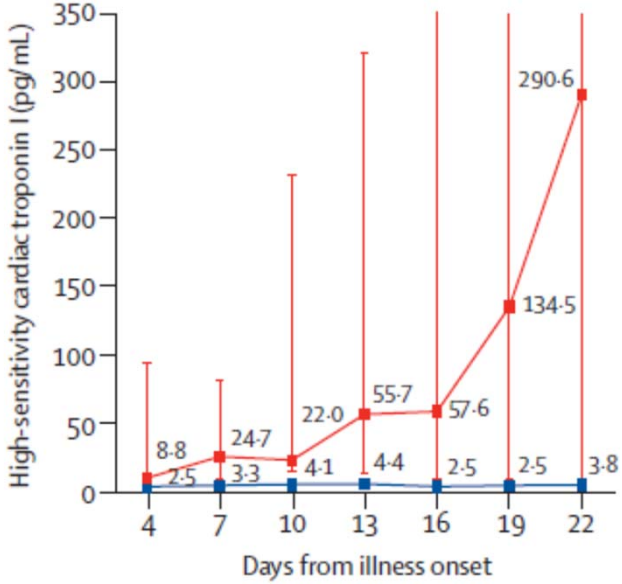
N=54: Non-survivors **Age 69, M 70%, HTN 48%, T2D, 31%, CAD 24%, Moderate 0%, Severe 22%, Critical 78%**

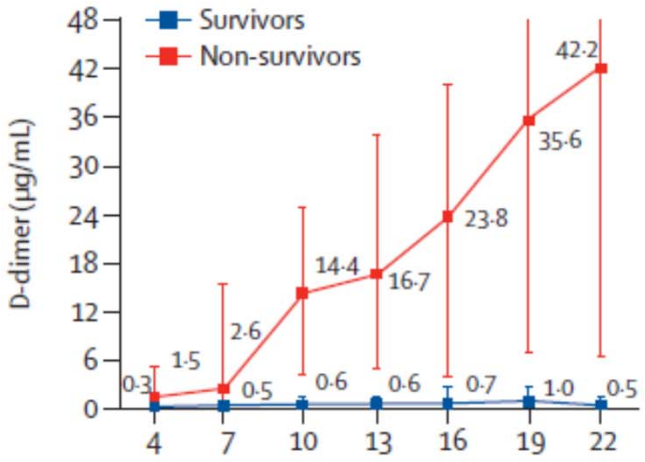


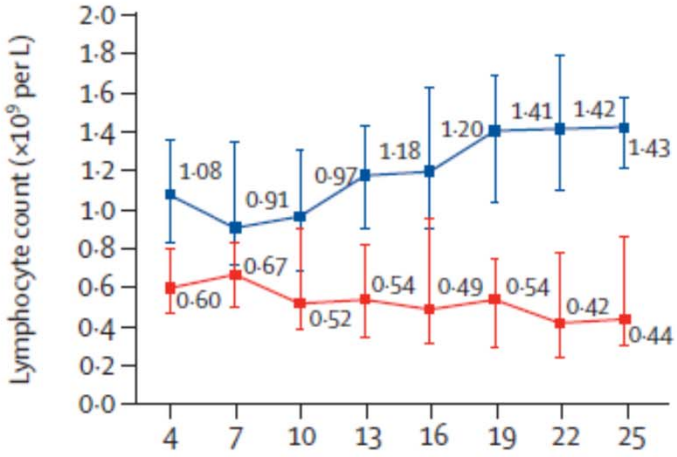
Zhou *et al*. Lancet 2020; 395:1054–62
doi.org/10.1016/ S0140-6736(20)30566-3

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

N=191, 137 discharged, 54 died; comorbidity (48%); HTN (30%), T2D (19%), CAD (8%)
Death was associated with age (OR 1.1/y; p=0.004), d-dimer >1µg/mL (OR 18; p=0.003)





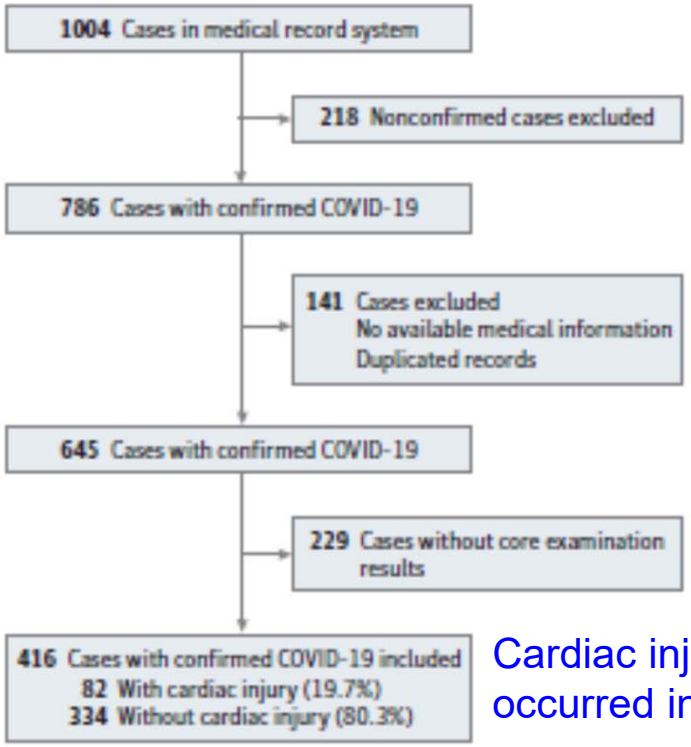


Covid-19 patients with **rising hs-troponin, rising d-dimer** & **persistent lymphopenia** had higher mortality

JAMA Cardiology | Original Investigation

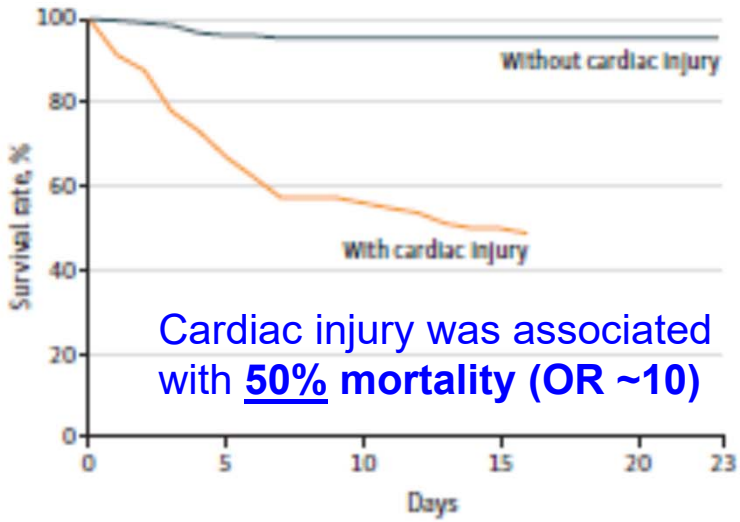
Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan

Figure 1. Flowchart of Patient Recruitment



Cardiac injury occurred in **20%**

B Time from admission



No. at risk						
With cardiac injury	82	55	46	41	0	0
Without cardiac injury	334	321	319	319	319	319

Cardiac injury was associated with **50% mortality (OR ~10)**

Mortal hazard: ~2 wk after sxs, ~1 wk after hospital admission

C Comparison of outcomes

	No. of events/ No. of patients	Time from symptom onset: Duration, mean (range), d	Time from symptom onset: P value log-rank	Time from admission: Duration, mean (range), d	Time from admission: P value log-rank
With cardiac injury	42/82	15.6 (1-37)	<.001	6.3 (1-16)	<.001
Without cardiac injury	15/334	16.9 (3-37)		7.8 (1-23)	

Table 1. Baseline Characteristics and Laboratory and Radiographic Findings of 416 Patients With COVID-19

Characteristic	Patients, No. (%)			
		Cardiac Injury		
	All (n = 416)	With (n = 82)	Without (n = 334)	*P* value
Age, median (range), y	64 (21-95)	74 (34-95)	60 (21-90)	<.001
Female	211 (50.7)	38 (46.3)	173 (51.8)	.39
Signs and symptoms at admission				
Fever	334 (80.3)	63 (76.8)	271 (81.1)	.44
Cough	144 (34.6)	28 (34.1)	116 (34.7)	>.99
Shortness of breath	117 (28.1)	26 (31.7)	91 (27.2)	.41
Fatigue	55 (13.2)	15 (18.3)	40 (12.0)	.15
Sputum production	23 (5.5)	3 (3.7)	20 (6.0)	.59
Muscle ache	19 (4.6)	5 (6.1)	14 (4.2)	.55
Diarrhea	16 (3.8)	1 (1.2)	15 (4.5)	.22
Chest pain	14 (3.4)	11 (13.4)	3 (0.9)	<.001
Sore throat	12 (2.9)	4 (4.9)	8 (2.4)	.26
Rhinorrhea	10 (2.4)	3 (3.7)	7 (2.1)	.42
Headache	9 (2.2)	2 (2.4)	7 (2.1)	.69

Patients with **Covid-19 cardiac injury** are **older** (mean age **74**) and present more often with **CP** (**13%**)

Table 1. Baseline Characteristics and Laboratory and Radiographic Findings of 416 Patients With COVID-19

Characteristic	Patients, No. (%)			
	All (n = 416)	Cardiac Injury		P value
		With (n = 82)	Without (n = 334)	
Chronic medical illness				
Hypertension	127 (30.5)	49 (59.8)	78 (23.4)	<.001
Diabetes	60 (14.4)	20 (24.4)	40 (12.0)	.008
Coronary heart disease	44 (10.6)	24 (29.3)	20 (6.0)	<.001
Cerebrovascular disease	22 (5.3)	13 (15.9)	9 (2.7)	<.001
Chronic heart failure	17 (4.1)	12 (14.6)	5 (1.5)	<.001
Chronic renal failure	14 (3.4)	5 (6.1)	9 (2.7)	.16
Chronic obstructive pulmonary disease	12 (2.9)	6 (7.3)	6 (1.8)	.02
Cancer	9 (2.2)	7 (8.5)	2 (0.6)	<.001
Pregnancy	7 (1.7)	0	7 (2.1)	.35
Hepatitis B infection	4 (1.0)	2 (2.4)	2 (0.6)	.18

Patients with **Covid-19 cardiac injury** tend to have **HTN** (**60%**), **T2D** (**25%**), **CAD** (**30%**) and **HF** (**15%**)

Hx/o **COPD** (7%) and **Cancer** (9%) are less common but have high OR (2-10 fold)

Table 1. Baseline Characteristics and Laboratory and Radiographic Findings of 416 Patients With COVID-19

Characteristic	Patients, No. (%)			
		Cardiac Injury		
	All (n = 416)	With (n = 82)	Without (n = 334)	*P* value
Laboratory findings at admission, median (IQR)				
Leukocytes/μL	5800 (4300-8300)	9400 (6900-13 800)	5500 (4200-7400)	<.001
Lymphocytes/μL	900 (600-1300)	600 (400-900)	1000 (800-1400)	<.001
Platelets $\times 10^3$/μL	207 (153-265)	172 (111-215)	216 (165-273)	<.001
Erythrocytes $\times 10^6$/μL	4.1 (3.6-4.4)	4.0 (3.4-4.3)	4.1 (3.6-4.4)	.01
Hemoglobin, g/dL	12.4 (11.1-13.4)	12.5 (10.8-13.2)	12.4 (11.2-13.5)	.34
C-reactive protein, mg/dL	4.5 (1.4-8.5)	10.2 (6.4-17.0)	3.7 (1.0-7.3)	<.001
Procalcitonin, ng/mL	0.07 (0.04-0.15)	0.27 (0.10-1.22)	0.06 (0.03-0.10)	<.001
Creatinine kinase-myocardial band, ng/mL	1.0 (0.7-2.0)	3.2 (1.8-6.2)	0.9 (0.6-1.3)	<.001
Myohemoglobin, μg/L	47 (28-93)	128 (68-305)	39 (27-65)	<.001
High-sensitivity troponin I, μg/L[a]	<0.006 (<0.006-0.02)	0.19 (0.08-1.12)	<0.006 (<0.006-0.009)	<.001
N-terminal pro-B-type natriuretic peptide, pg/mL	219 (73-699)	1689 (698-3327)	139 (51-335)	<.001
Alanine aminotransferase, U/L	28 (18-46)	29 (19-44)	28 (18-46)	.93
Aspartate aminotransferase, U/L	30 (22-43)	40 (27-60)	29 (21-40)	<.001
Albumin, g/dL	3.6 (3.2-3.8)	3.2 (2.9-3.4)	3.7 (3.3-3.9)	<.001
Creatinine, mg/dL	0.67 (0.55-0.81)	1.15 (0.72-1.92)	0.64 (0.54-0.78)	<.001
Potassium, mEq/L	4.0 (3.6-4.4)	4.0 (3.6-4.6)	4.0 (3.6-4.3)	.65
Sodium, mEq/L	140 (138-144)	141 (138-146)	140 (138-143)	.08
Chest radiography and computed tomography findings				
Pneumonia				
Unilateral	105 (25.2)	7 (8.5)	98 (29.3)	<.001
Bilateral	311 (74.8)	75 (91.5)	236 (70.7)	
Multiple mottling and ground-glass opacity	68 (16.3)	53 (64.6)	15 (4.5)	<.001

Patients with Covid-19 cardiac injury are more likely to manifest

Lymphopenia

Elevated troponin
Elevated BNP

AKI

Mottled glass CXR

Shi *et al*. JAMA Cardiol doi:10.1001/jamacardio.2020.0950

Table 2. Treatment, Complications, and Clinical Outcome of 416 Patients With COVID-19

Characteristic	Patients, No. (%)			
		Cardiac Injury		
	All (n = 416)	With (n = 82)	Without (n = 334)	P value
Time from symptom onset to admission, edian (range), d	10 (1-30)	10 (1-30)	10 (1-28)	.27
Treatment				
Oxygen inhalation	316 (76.0)	26 (31.7)	290 (86.8)	<.001
Noninvasive ventilation	51 (12.3)	38 (46.3)	13 (3.9)	<.001
Invasive mechanical ventilation	32 (7.7)	18 (22.0)	14 (4.2)	<.001
Continuous renal replacement therapy	2 (0.5)	2 (2.4)	0	.04
Antiviral treatment	403 (96.9)	82 (100)	321 (96.1)	.08
Glucocorticoids	304 (73.1)	72 (87.8)	232 (69.5)	<.001
Intravenous immunoglobulin therapy	259 (62.3)	68 (82.9)	191 (57.2)	<.001
Antibiotic treatment	235 (56.5)	68 (82.9)	167 (50)	<.001
Complications				
ARDS	97 (23.3)	48 (58.5)	49 (14.7)	<.001
Acute kidney injury	8 (1.9)	7 (8.5)	1 (0.3)	<.001
Electrolyte disturbance	30 (7.2)	13 (15.9)	17 (5.1)	.003
Hypoproteinemia	27 (6.5)	11 (13.4)	16 (4.8)	.01
Anemia	13 (3.1)	4 (4.9)	9 (2.7)	.30
Coagulation disorders	12 (2.9)	6 (7.3)	6 (1.8)	.02
Clinical outcome				
Remained in hospital	319 (76.7)	38 (46.3)	281 (72.2)	<.001
Discharged	40 (9.6)	2 (2.4)	38 (23.4)	
Died	57 (13.7)	42 (51.2)	15 (4.5)	<.001

Covid-19 cardiac injury is unlikely to be related to:

anti-viral Rx
steroids Rx
anti-microbial Rx

Patients with **Covid-19 cardiac injury** are more likely to have :

ARDS (60%)
[OR ~4]

Mortality (50%)
[OR ~10]

Shi *et al*. JAMA Cardiol doi:10.1001/jamacardio.2020.0950

JAMA Cardiology | Original Investigation

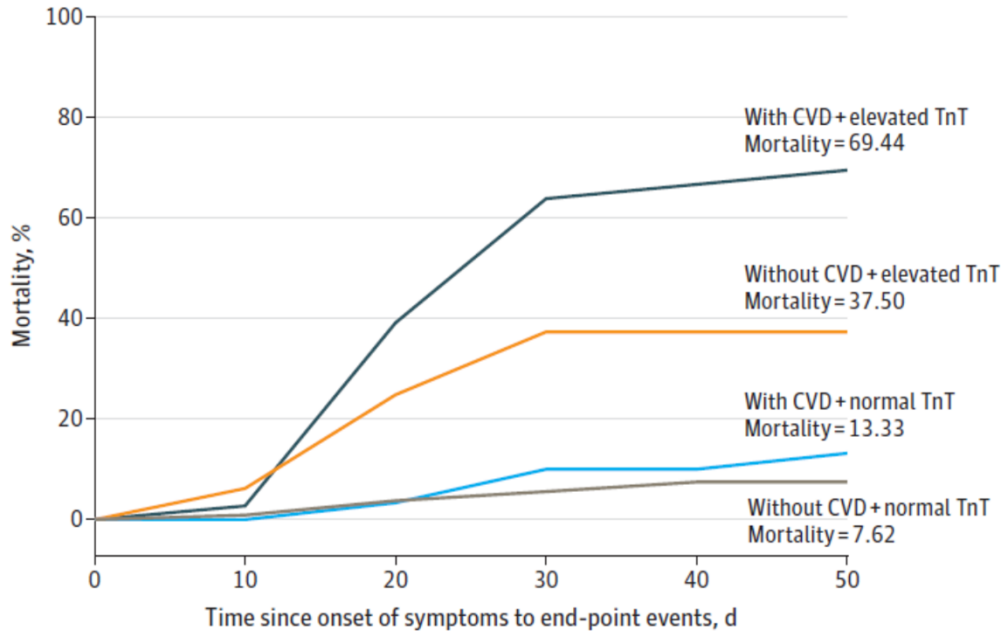
Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19)

OBJECTIVE To evaluate the association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19.

CONCLUSIONS AND RELEVANCE Myocardial injury is significantly associated with fatal outcome of COVID-19, while the prognosis of patients with underlying CVD but without myocardial injury is relatively favorable. Myocardial injury is associated with cardiac dysfunction and arrhythmias. Inflammation may be a potential mechanism for myocardial injury. Aggressive treatment may be considered for patients at high risk of myocardial injury.

Take away message: find Covid-19 patients with myocardial injury, consider them for more aggressive Rx, prepare to manage cardiac dysfunction and arrhythmias

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

Mortality in hospitalized Covid-19 patients:

CVD + cardiac injury: 70% [10X]

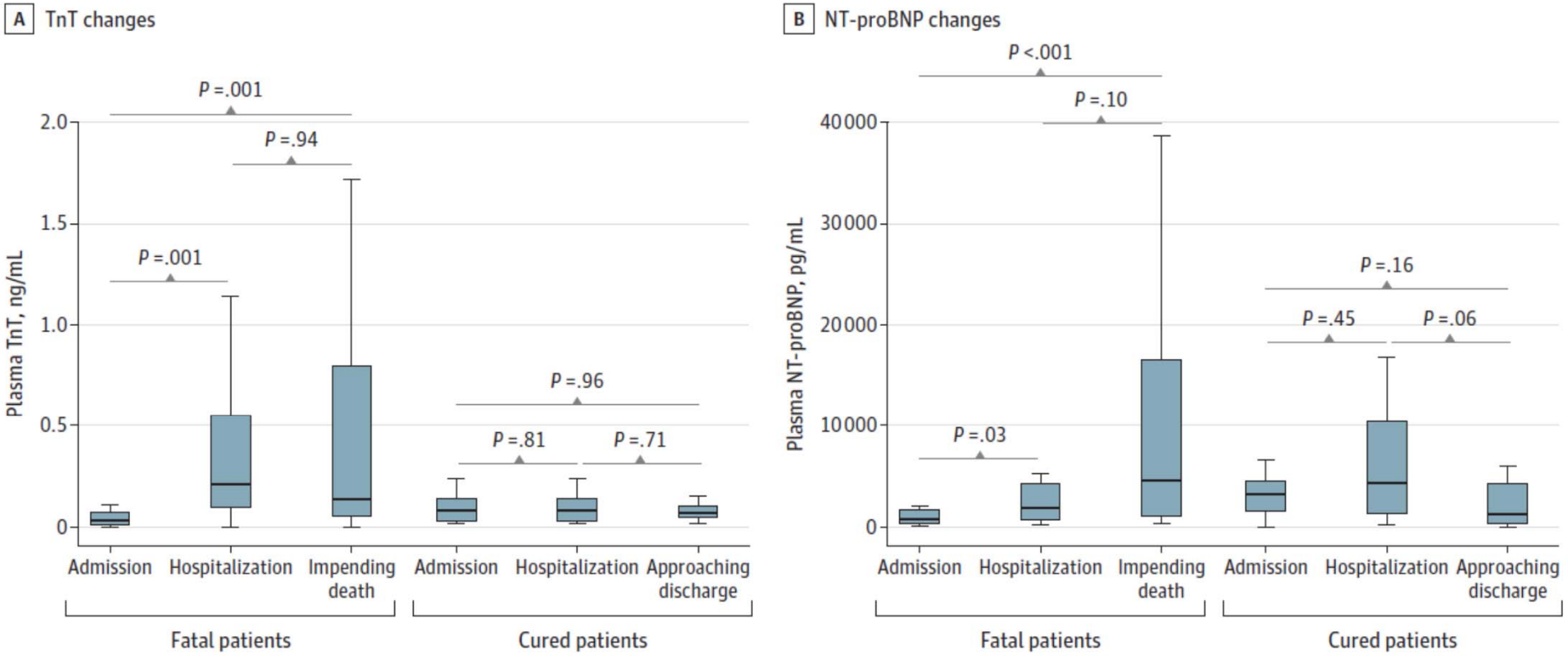
cardiac injury: ~35% [5X]

CVD: ~15% [2X]

Neither: ~7% [1X]

Guo *et al*. JAMA Cardiol. doi:10.1001/jamacardio.2020.1017

Figure 3. Dynamic Changes of TnT and NT-proBNP During Hospitalization



Rising cardiac biomarkers, specifically **TnT** and **NT-proBNP**, were identified in fatal cases

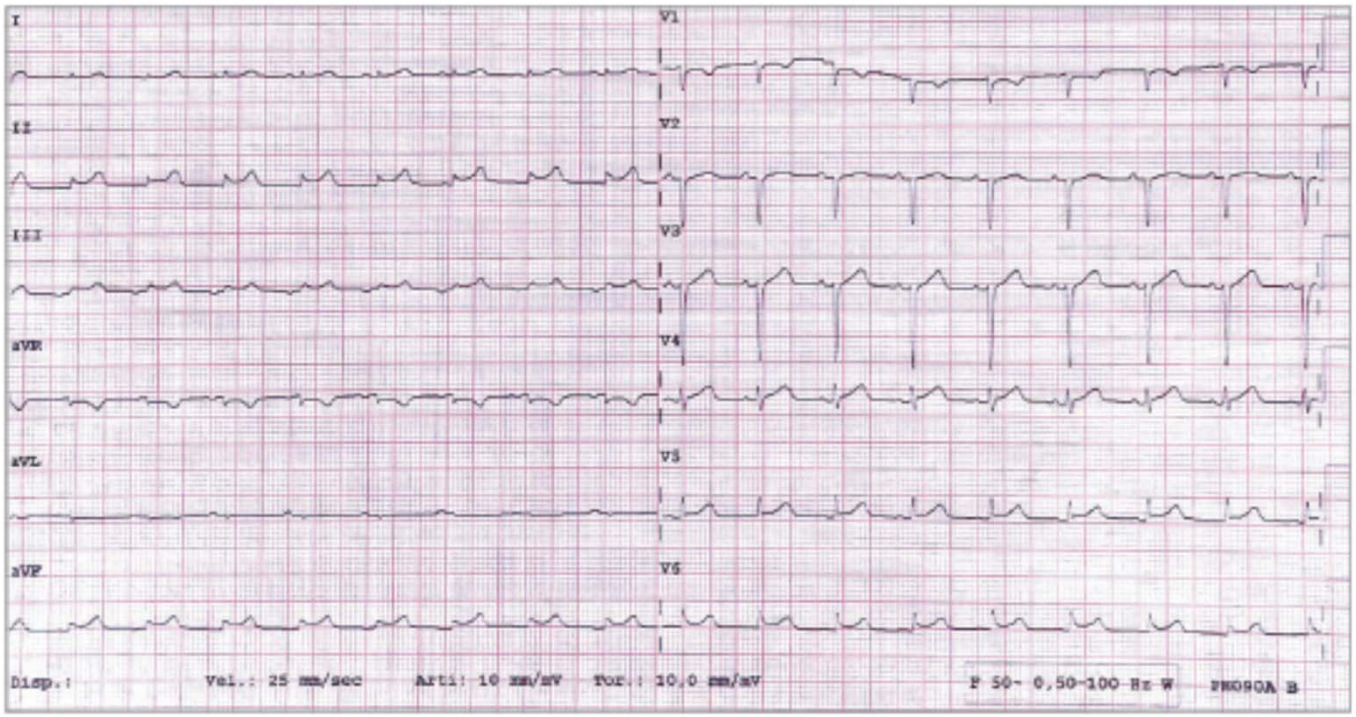
Guo *et al*. JAMA Cardiol. doi:10.1001/jamacardio.2020.1017

JAMA Cardiology | Brief Report

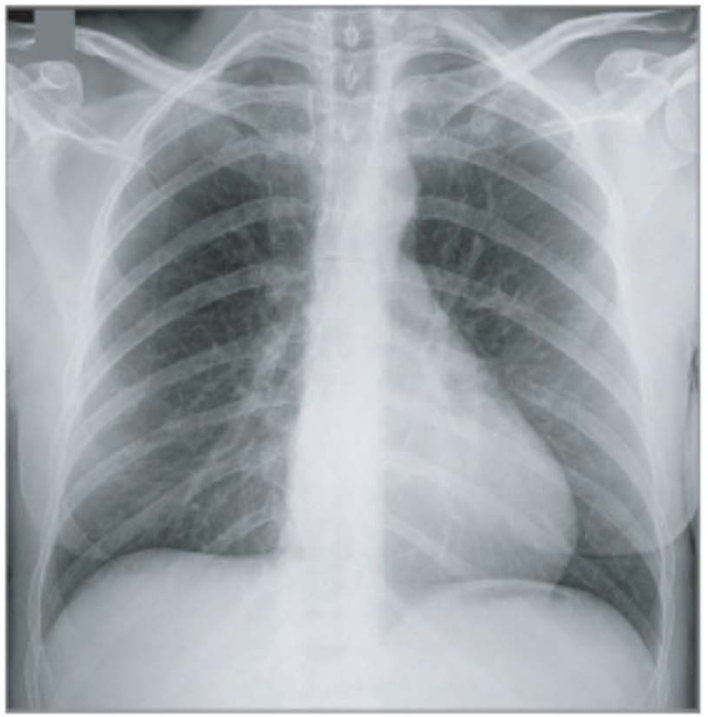
Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19)

Not every case has pneumonia!
Covid19 can present as a cardiac illness

A Electrocardiography



B Chest radiography



Inciardi *et al*. JAMA Cardiol. doi:10.1001/jamacardio.2020.1096

Findings In this case report, an otherwise healthy 53-year-old patient developed acute myopericarditis with systolic dysfunction confirmed on cardiac magnetic resonance imaging a week after onset of fever and dry cough due to COVID-19. The patient was treated with inotropic support, antiviral drugs, corticosteroids, and chloroquine, with progressive stabilization of the clinical course.

Meaning The emerging outbreak of COVID-19 can be associated with cardiac involvement, even after the resolution of the upper respiratory tract infection.

Case highlights possibility of **cardiac involvement** after resolution (i.e. **in the absence of) pneumonia**

COVID-19 Infection	Concern	Interpretation
Asymptomatic or early mild disease with constitutional symptoms (fever, dry cough, diarrhea and headache)	Should background cardiovascular medications be modified?	• There is no clear evidence that ACEi or ARB should be discontinued • NSAIDs should be avoided
Moderate disease with pulmonary complications and shortness of breath (including hypoxia)	Is there a cardiovascular contribution to the lung complications?	• Check troponin (evidence of myocardial injury and prognosis) • Check natriuretic peptides • Consider cardiac echocardiography to evaluate for evidence of underlying structural heart disease, high filling pressures • Avoid overuse of intravenous fluids which may worsen underlying pulmonary edema
Advanced stage disease with hypoxia, vasoplegia and shock	Is there evidence of cardiogenic contribution to shock and what therapy may be potentially curative?	• Check for evidence of hyperinflammation or a cytokine release storm (elevated troponin, natriuretic peptides, CRP and serum ferritin>1000 ng/ml (measure IL-6 levels if available) • If cardiac function is reduced (LVEF <0.50%), consider supportive care with inotropic therapy but move to consider anti-cytokine therapy with drugs such as tocilizumab and corticosteroids

My K.I.S.S. algorithm
Mild: No admission
No change in cardiac Rxs
Avoid NSAIDs

Moderate: Covid19 pneumonia
History or high likelihood of CVD?
Elevated cardiac biomarkers?
2-NOs: Ward admission [or discharge]
1-YES: Admit to ward for monitoring & care
2-YES: Telemetry and close supervision
No echo/POCUS *unless vitals are unstable*
Avoid excess fluid resuscitation

Severe: Covid19 sepsis/ARDS
Ventricular dysfunction on POCUS?
NO: serial biomarkers, needs ICU setting
YES: *Inotropes (vaso- & cardio-plegia)*
Consider anti-inflammatory Rx?

QUESTIONS YOU MAY BE ASKED (or may ask yourself):

1. Does this patient have an ACS (NSTEMI and STEMI)?

2. Is myocardial ischemia contributing to their shock?

3. Might their pulmonary edema be cardiogenic (even in part)?

All 3 of which can be condensed into:
(A) should we send this patient for coronary angiography?
Unless your patient has typical **ischemic-CP** and -**ECG** changes – the answer is **NO**.
Even with typical ischemic-CP and -ECG changes –angiography will show no occlusion.
Covid-19 myopericarditis can masquerade as ACS.
Consider POCUS to look for segmental WMA that matches ECG, and R/O pericardial effusion.

(B) will invasive hemodynamic monitoring (CVP, PA) help manage this patient?
Without a convincing history (or echo) of pre-existing structural heart disease – the answer is **NO**.
Even with known pre-existing LV dysfunction, valvular disease, *etc* – invasive monitoring to tailor inotropes may not change outcome – and may be too resource-intensive to warrant during crisis.

Table 1. Relative Frequency of Cardiovascular Risk Factors or Underlying Cardiovascular Conditions in Available COVID-19 Cohorts, and Representative Parent Populations

	Cardiovascular disease	Diabetes	Hypertension	Smoking	Coronary Artery Disease	Cerebrovascular Disease
Guan et al 2020 (28) (N=1099)	--	81 (7.3%)	165 (15.0%)	158 (14.4%)	27 (2.5%)	15 (1.4%)
Zhou et al 2020 (93) (N=191)	--	36 (18.8%)	58 (30.4%)	11 (5.8%)	15 (7.9%)	--
Wang et al 2020 (19) (N=138)	20 (14.5%)	14 (10.1%)	43 (31.2%)	--	--	7 (5.1%)
Huang et al 2020 (1) (N=41)	6 (14.6%)	8 (19.5%)	6 (14.6%)	3 (7.3%)	--	--
Ruan et al 2020 (21) (N=150)	13 (8.7%)	25 (16.7%)	52 (34.7%)	--	--	12 (8.0%)
Wu et al 2020 (27) (N=201)	8 (4.0%)	22 (10.9%)	39 (19.4%)	--	--	--
Wu et al 2020 (15)[C] (N=44,672)	4690 (10.5%)[B]	3261 (7.3%	2903 (6.5%)	--	--	--
Fang et al 2020[C, D] (N=2818)	233 (8.3%)^	206 (7.3%)	376 (13.3%)	--	--	--
Lu et. al. 2018 (94)[E] (N=12,654)	1455 (11.5%)	2125 (16.8%)	4884 (38.6%)	4985 (39.4%)		278 (2.2%)

[A] To date, no publications have described these statistics for COVID-19 patients from other areas including South Korea, Iran, Italy, Spain, and others. Therefore, the comparator parent population was chosen from China.

[B] Composite cardiovascular + cerebrovascular disease

[C] These studies by Wu et al and Fang et al include a large, population-based dataset and a meta-analysis, respectively, from China that are inclusive of the other displayed cohort studies

[D] Reference: Fang et al 2020. Clinical Characteristics of Coronavirus Pneumonia 2019 (COVID-19): An Updated Systematic Review. medRxiv doi: https://doi.org/10.1101/2020.03.07.20032573

[E] Chinese population prior to COVID-19 included for comparison. Please note that disease ascertainment has been different in this study compared with studies of patients with COVID-19.

Table 2. Association Between Underlying Cardiovascular Risk Factors (A), Known Cardiovascular Disease (B) and Outcomes in COVID-19[A]

		Outcome Variable	Guan et al 2020 (28)* N=1090	Zhou et al 2020 (93) N=191	Wang et al 2020 (19) N=138	Huang et al 2020 (1) N=41	Ruan et al 2020 (5) N=150	Wu et al 2020 (27)[B] N=201
A. Cardiovascular Risk Factors	Diabetes	ICU vs. non-ICU	--	--	8 (22.2%) vs. 6 (5.9%)	1 (7.7%) vs. 7 (25.0%)	--	--
		Severe vs. non-severe	28 (16.2%) vs. 53 (5.7%)	--	--	--	--	--
		Dead vs. alive	--	17 (31.4%) vs. 19 (13.9%)	--	--	12 (17.6%) vs. 13 (15.9%)	11 (25.0%) vs. 5 (12.5%)
	Hypertension	ICU vs. non-ICU	--	--	21 (58.3%) vs. 22 (21.6%)	2 (15.4%) vs. 4 (14.3%)	--	--
		Severe vs. non-severe	41 (23.7%) vs. 124 (13.4%)	--	--	--	--	--
		Dead vs. alive	--	26 (48.1%) vs. 32 (23.4%)	--	--	29 (42.6%) vs. 23 (28.0%)	16 (36.4%) vs. 7 (17.5%)
	Smoking	ICU vs. non-ICU	--	--	--	0 vs. 3 (10.7%)	--	--
		Severe vs. non-severe	38 (22.0%) vs. 130 (14.0%)	--	--	--	--	--
		Dead vs. alive	--	5 (9.3%) vs. 6 (4.4%)	--	--	--	--
B. Cardiovascular Disease	Coronary artery disease	ICU vs. non-ICU	--	--	9 (25.0%) vs. 11 (10.8%)	--	--	--
		Severe vs. non-severe	10 (5.8%) vs. 17 (1.8%)	--	--	--	--	--
		Dead vs. alive	--	4 (7.4%) vs. 2 (1.5%)	--	--	--	--
	Cerebrovascular disease	ICU vs. non-ICU	--	--	6 (16.7%) vs. 1 (1.0%)	--	--	--
		Severe vs. non-severe	4 (2.3%) vs. 11 (1.2%)	--	--	--	--	--
		Dead vs. alive	--	--	--	--	7 (10.3%) vs. 5 (6.1%)	--
	Cardiovascular disease	ICU vs. non-ICU	--	--	--	3 (23.0%) vs. 3 (10.7%)	--	--
		Severe vs. non-severe	--	--	--	--	--	--
		Dead vs. alive	--	--	--	--	13 (19.1%) vs. 0	4 (9.1%) vs. 4 (10.0%)

[A]Only a few studies, with single center experience have presented data to date, which limits the generalizability of the findings, and the confidence in the point estimates.
[B]This study used multivariable modeling for outcome of death for each CV risk factor for CVD

Table 3. Antiviral Therapies Currently being Studied for COVID-19: Potential Cardiovascular Interactions and Toxicities

Antiviral Therapy	ClinicalTrials.gov Identifiers	Mechanism of Action	CV Drug Class Interactions	CV Adverse Effects
Ribavirin	NCT04276688 NCT00578825	Inhibits replication of RNA and DNA viruses	Anticoagulants*	Unknown
Lopinavir/ Ritonavir	NCT04252885 NCT04275388 NCT04276688 NCT04286503 NCT02845843 NCT04307693 NCT04261907 NCT04295551 NCT00578825	Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A metabolism increasing levels of lopinavir	Antiplatelets* Anticoagulants* Statin* Antiarrhythmics*	-Altered cardiac conduction: QTc prolongation, high degree AV block, torsade de pointes
Remdesevir	NCT04302766 NCT04280705 NCT04292899 NCT04292730	Nucleotide-analog inhibitor of RNA-dependent RNA polymerases	Unknown	Unknown

*Indicates drug class interactions. Table 5 summarizes specific recommendations in the setting of medication interactions.

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Table 4. Other Therapies Being Studied for COVID-19: Potential Cardiovascular Interactions and Toxicities

Therapy	ClinicalTrials.gov Identifiers	Mechanism of Action	CV Drug Interactions	CV Adverse Effects
Bevacizumab	NCT04275414	Evidence has revealed higher VEGF levels in COVID-19 patients. By inhibiting VEGF, can decrease vascular permeability and pulmonary edema.	Unknown	-Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy -Severe hypertension -Thromboembolic events
Chloroquine/ Hydroxychloroquine	NCT04286503 NCT04303507 NCT04307693 NCT04261517 NCT04303299	Alters endosomal pH required for virus/cell fusion	Antiarrhythmics*	-Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy -Altered cardiac conduction: AV block, bundle branch block, torsade de pointes, ventricular tachycardia/fibrillation
Eculizumab	NCT04288713	Inhibits complement activation	Unknown	- Hypertension, tachycardia, peripheral edema
Fingolimod	NCT04280588	Inhibits lymphocytes through sphingosine-1 phosphate regulation	Antiarrhythmics	- Hypertension, first and second degree AV block, bradycardia, QTc prolongation -Contraindicated after myocardial infarction, unstable angina, CVA/TIA, ADHF - Contraindication with: high degree AV block, sick sinus syndrome, QTc $\geq$ 500 ms

Interferon	NCT04275388 NCT04273763 NCT04276688 NCT02845843 NCT04293887 NCT04251871 NCT04291729	Immune activation	Unknown	- Direct myocardial toxicity vs. exacerbation of underlying cardiomyopathy - Reports of: hypotension, arrhythmia, cardiomyopathy, myocardial infarction
Pirfenidone	NCT04282902	Antifibrotic ability, possible IL-1β and IL-4 inhibition to reduce cytokine storm and resultant pulmonary fibrosis	Unknown	Unknown
Methylprednisolone	NCT04273321 NCT04244591	Alters gene expression to reduce inflammation	Anticoagulants*	- Fluid retention, - Electrolyte disturbances - Hypertension
Tocilizumab	NCT04306705	Inhibits IL-6 receptor	Possibility of increasing metabolism of medications: Unknown effects	-Hypertension, increased serum cholesterol -No known effect on QTc interval

*Indicates drug class interactions. Table 5 summarizes specific recommendations in the setting of medication interactions. ADHF = acute decompensated heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack.

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Table 5. Recommendations Regarding Dosing and Adjustment in the Setting of Medication Interactions

Therapy	Specific Interaction	MOA of Drug Interaction and Specific Dose Adjustments	Other Notes
Ribavirin	**Anticoagulants** Warfarin	Unknown mechanism of action: No dosage adjustment recommended.	Monitor INR
Lopinavir/Ritonavir	**Anticoagulants** • Apixaban • Rivaroxaban	CYP3A4 inhibition: Apixaban should be administered at 50% of dose (do not administer if requirement 2.5 mg per day). Rivaroxaban should not be co-administered.	Dabigatran and warfarin can be administered with caution
	Antiplatelet • Clopidogrel • Ticagrelor	CYP3A4 inhibition: Diminished effect of clopidogrel. Do not co-administer. Increased effect of ticagrelor. Do not co-administer.	Consider prasugrel if no contraindications. If other agents used, consider a testing-guided approach (e.g. $P2Y_{12}$ platelet function assay).
	Statin • Atorvastatin • Rosuvastatin • Lovastatin • Simvastatin	OATTP1B1 and BCRP inhibition: Rosuvastatin should be adjusted to maximum dose 10 mg/day. CYP3A4 inhibition:	Start at lowest possible dose of rosuvastatin and atorvastatin and titrate up. Pravastatin and pitavastatin can also be considered.
Chloroquine / Hydroxychloroquine	**Beta Blockers** • metoprolol, carvedilol, propranolol, labetalol **Antiarrhythmics** • QT-prolonging agents • Digoxin	CYP 2D6 inhibition: Dose reduction for beta blockers may be required. P-glycoprotein inhibition: Monitor digoxin level for possible dose reduction.	Use cautiously with antiarrhythmics

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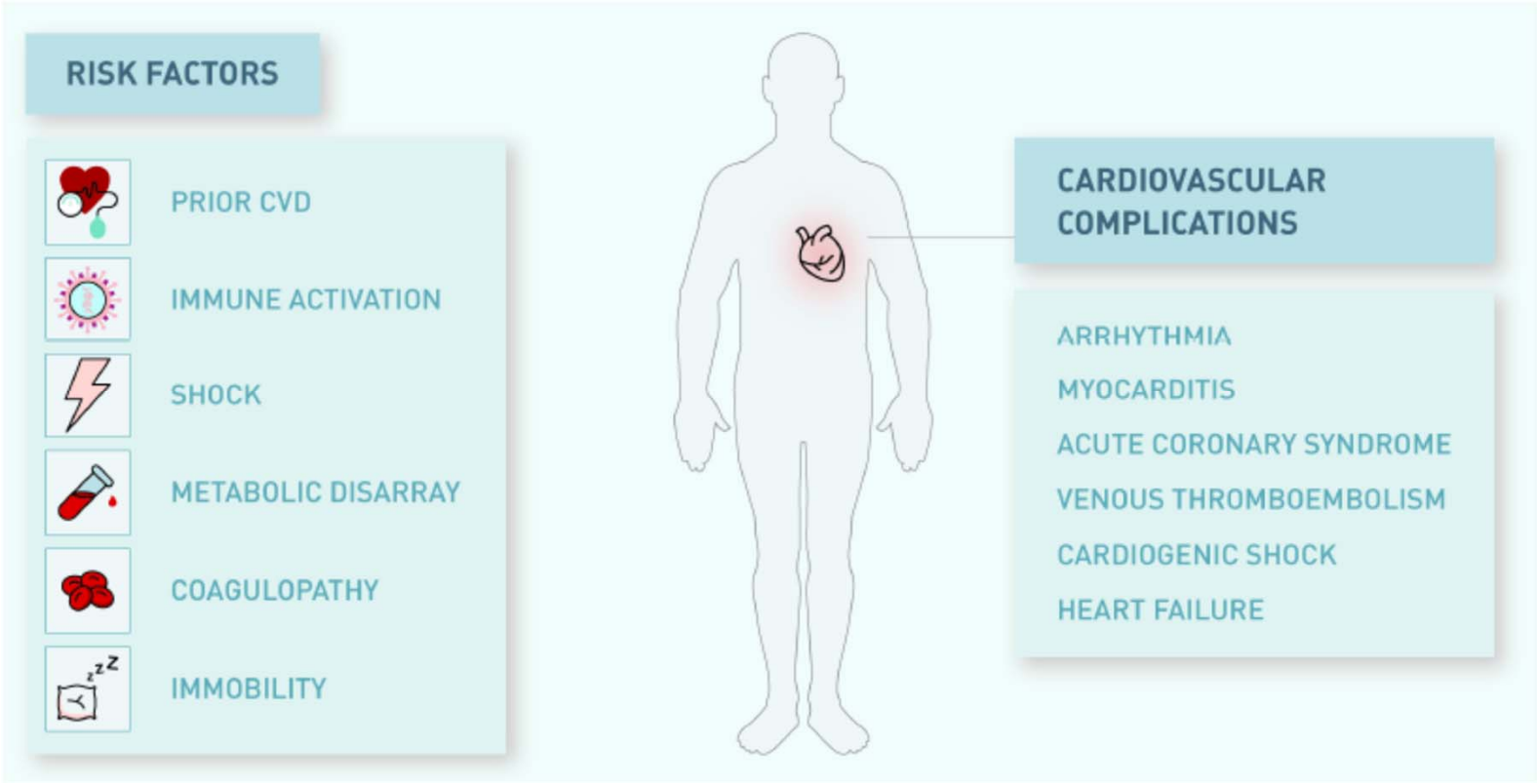

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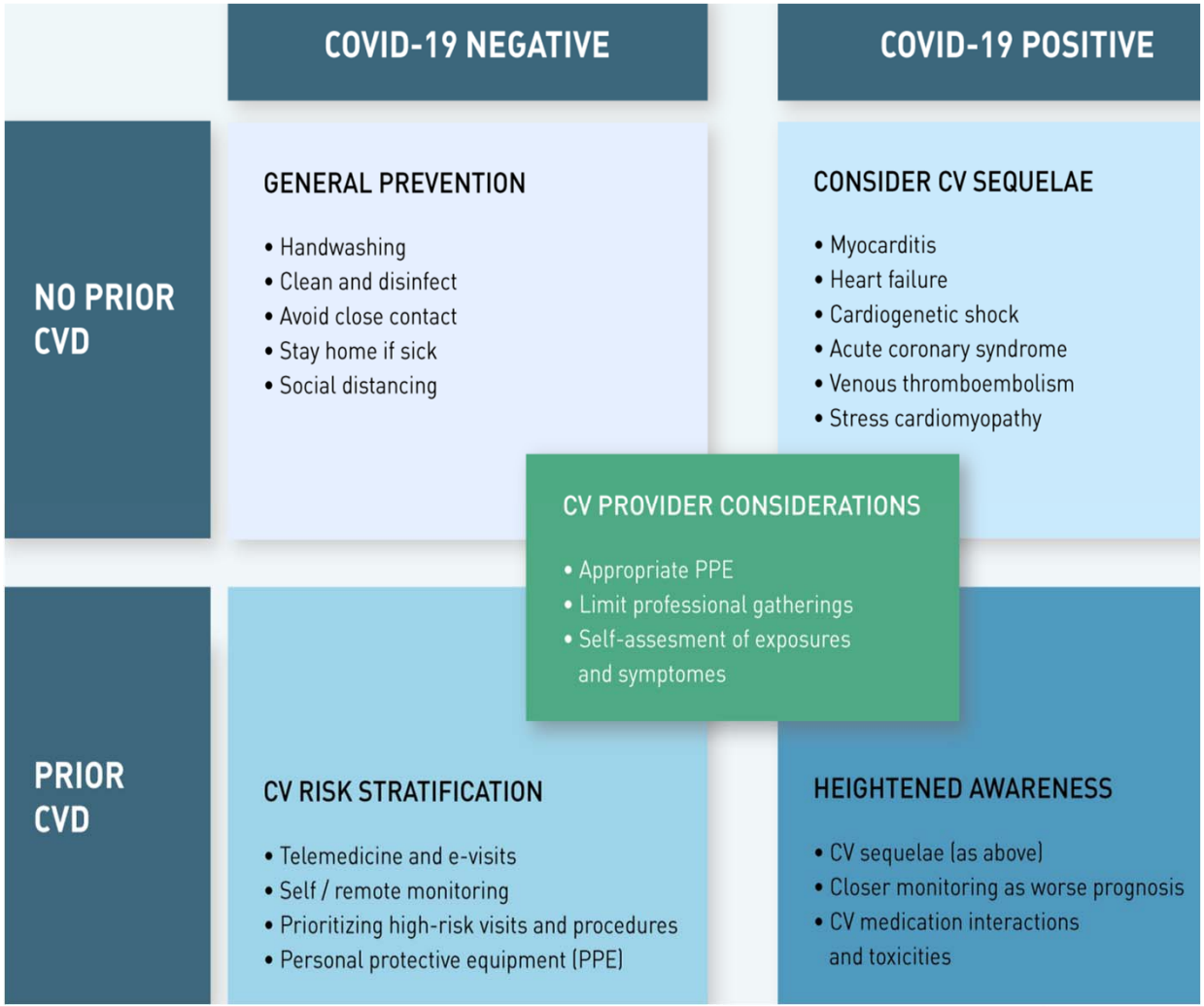

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