

# Using Biomarkers to Inform COVID-19 Treatment

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# Disclosures

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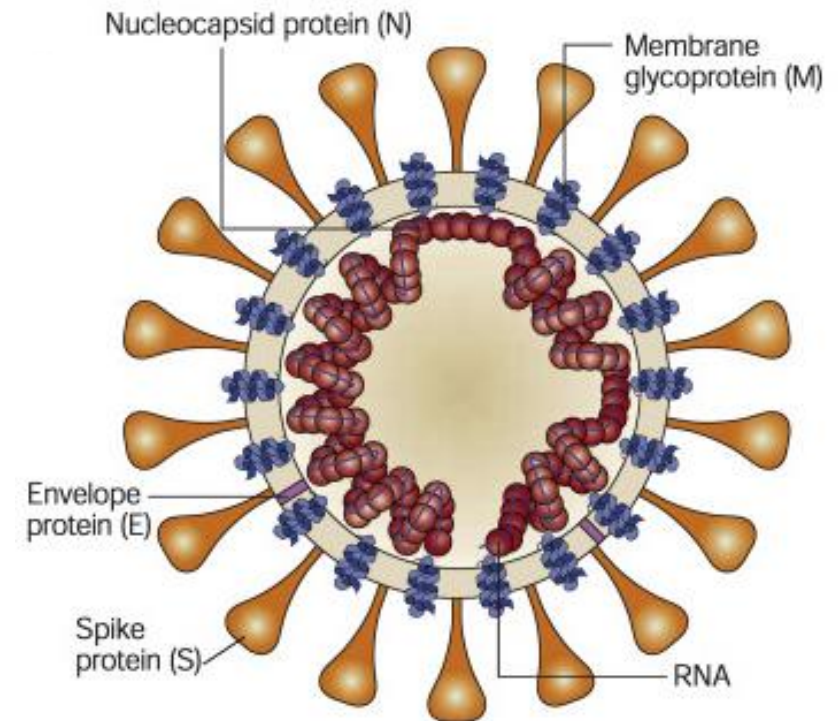
# Agenda

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- What is COVID19?
- How COVID19 affects the CV system and other complications
- How COVID19 affects patients with CV disease
- How biomarker testing may inform prognosis and management in COVID19

# What are coronaviruses?

- Coronaviruses are large (HBV – 3kbp; CoV – 30 kbp), enveloped RNA viruses
- Coronaviruses are zoonotic
- Animal reservoirs are ecologically diverse with the **widest variety seen in bats**, which are the **reservoirs for many of these viruses**
- Mammals may serve as **intermediate hosts**, facilitating **recombination and mutation events** with expansion of genetic diversity.
- Not all coronaviruses are pandemic strains - endemic human coronavirus are responsible for approximately **5–10% of all upper and lower respiratory tract infections.**
- Two previous outbreaks:
  - Severe acute respiratory syndrome - SARS-CoV (2002) - China
  - Middle East respiratory syndrome - MERS-CoV (2012) - Saudi Arabia



# Risk factors for/in COVID-19

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## Risk factors for infection

- Advanced age
- Race/ethnicity
- Male sex
- Medical conditions, including **cardiovascular disease**
- Poverty and crowding
- Congregate living
- Pregnancy

## Risk factors for adverse outcome

- **Cardiovascular disease**
- CKD
- COPD
- Immune compromise
- Obesity
- Diabetes

# COVID-19 Infection

## *Signs and Symptoms*



### Symptoms

Fever, respiratory symptoms, abdominal pain, diarrhea, vomiting, headache, myalgia



### Clinical presentation

Asymptomatic infection, mild illness, or fatal disease



### Transmission

Person-to-person via respiratory secretions



### Incubation

Range of 2-14 days (median – 5 days)

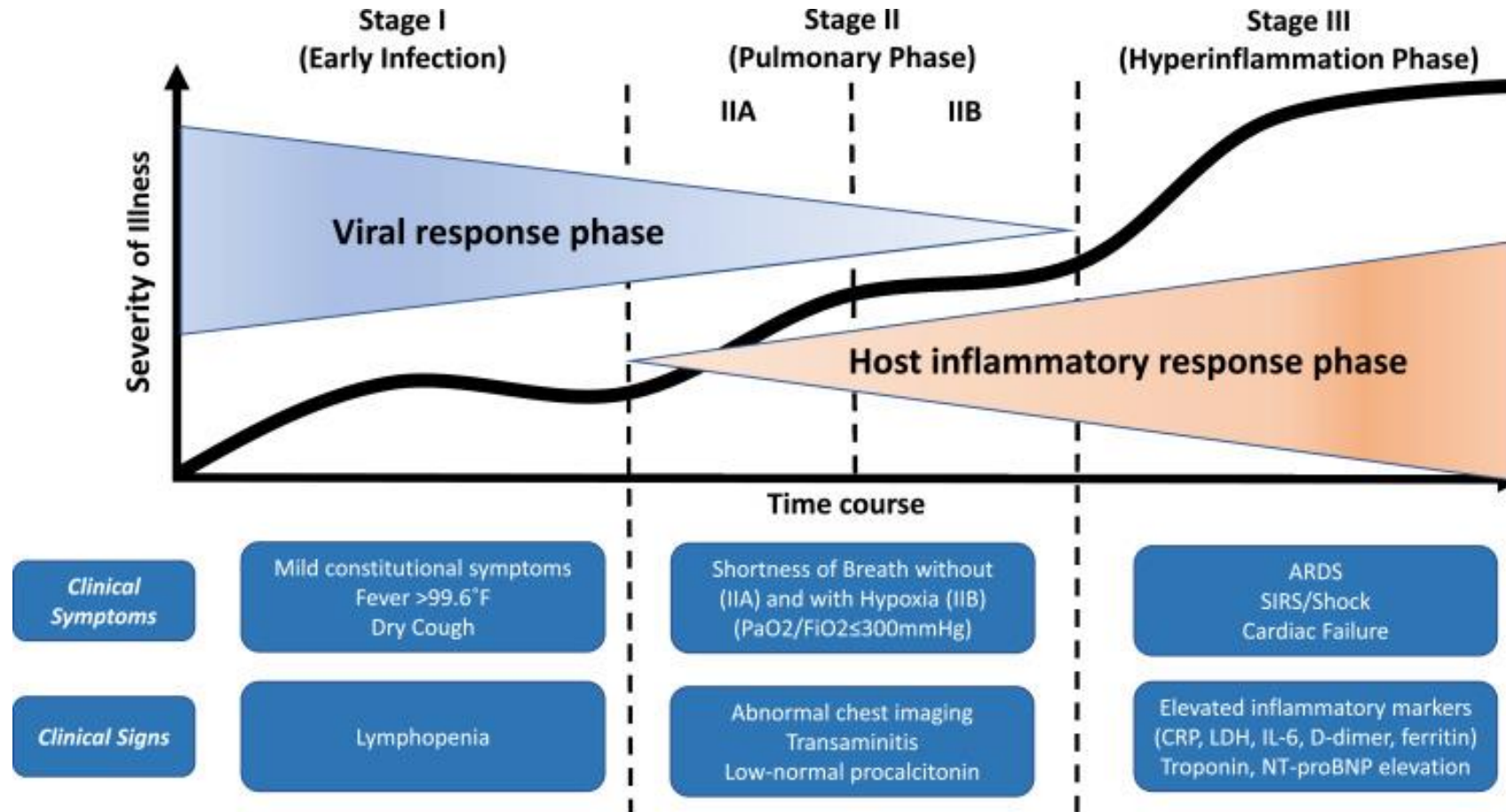


### Clinical progression

Can cause severe respiratory disease, especially in 65+ and multi-morbid patients

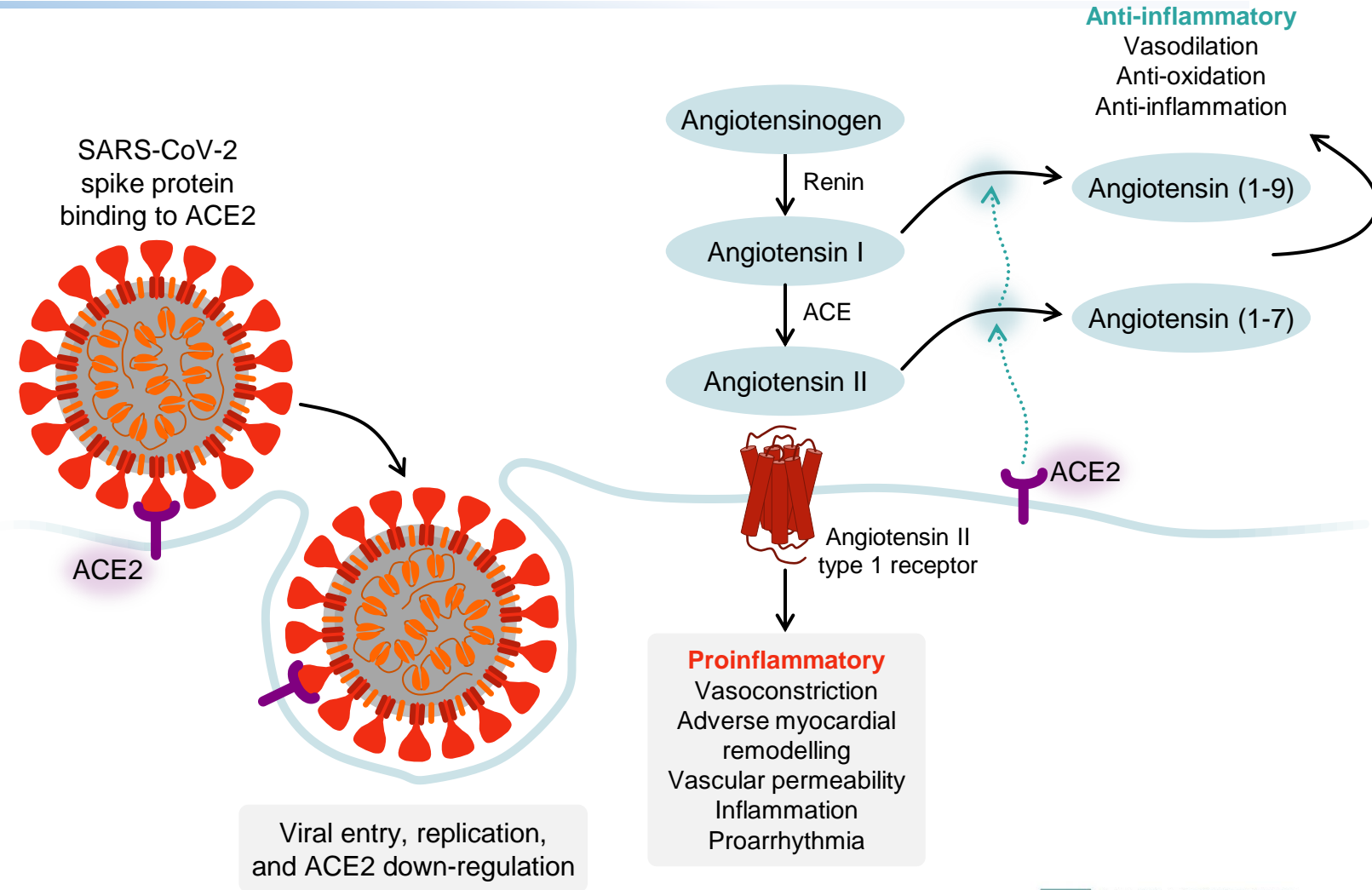
# Infectious Diseases Management

## Fundamental Parameters



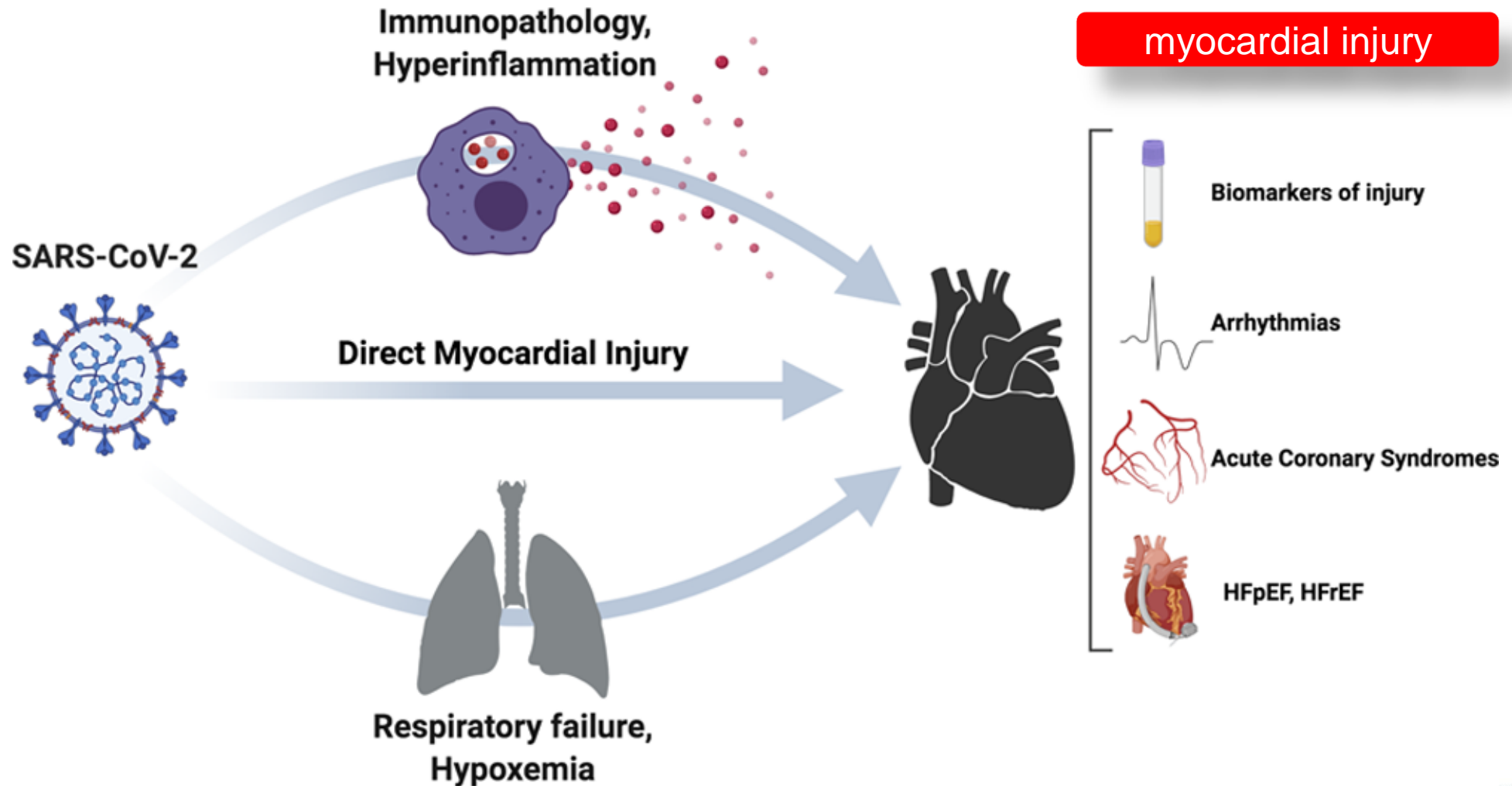
# SARS-CoV-2 and ACE2

- **SARS-CoV-2** enters lung epithelial cells through binding to its functional receptor, **ACE2**
- ACE2 is a key modulator in the **renin-angiotensin-aldosterone system**
- **ACE2** is expressed broadly, including in the lungs, heart and kidneys

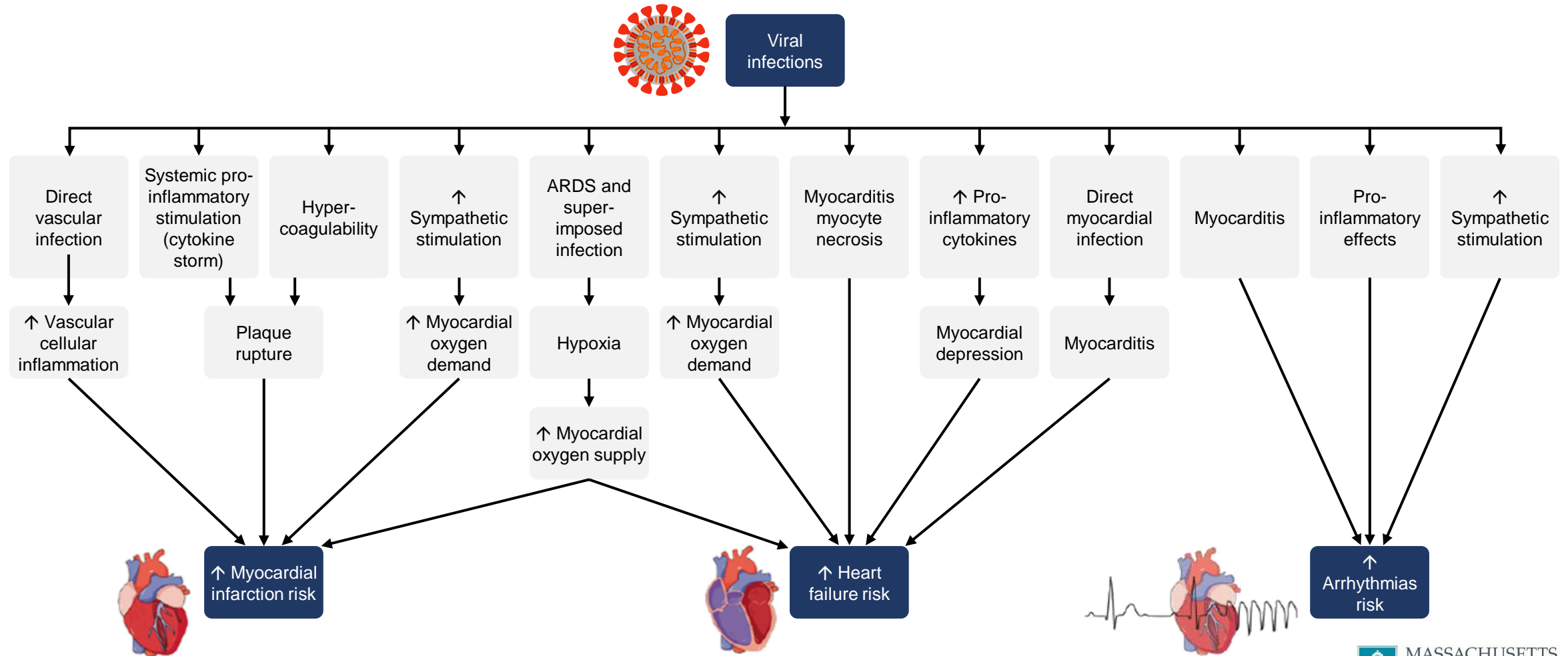




# Cardiac manifestation of COVID-19



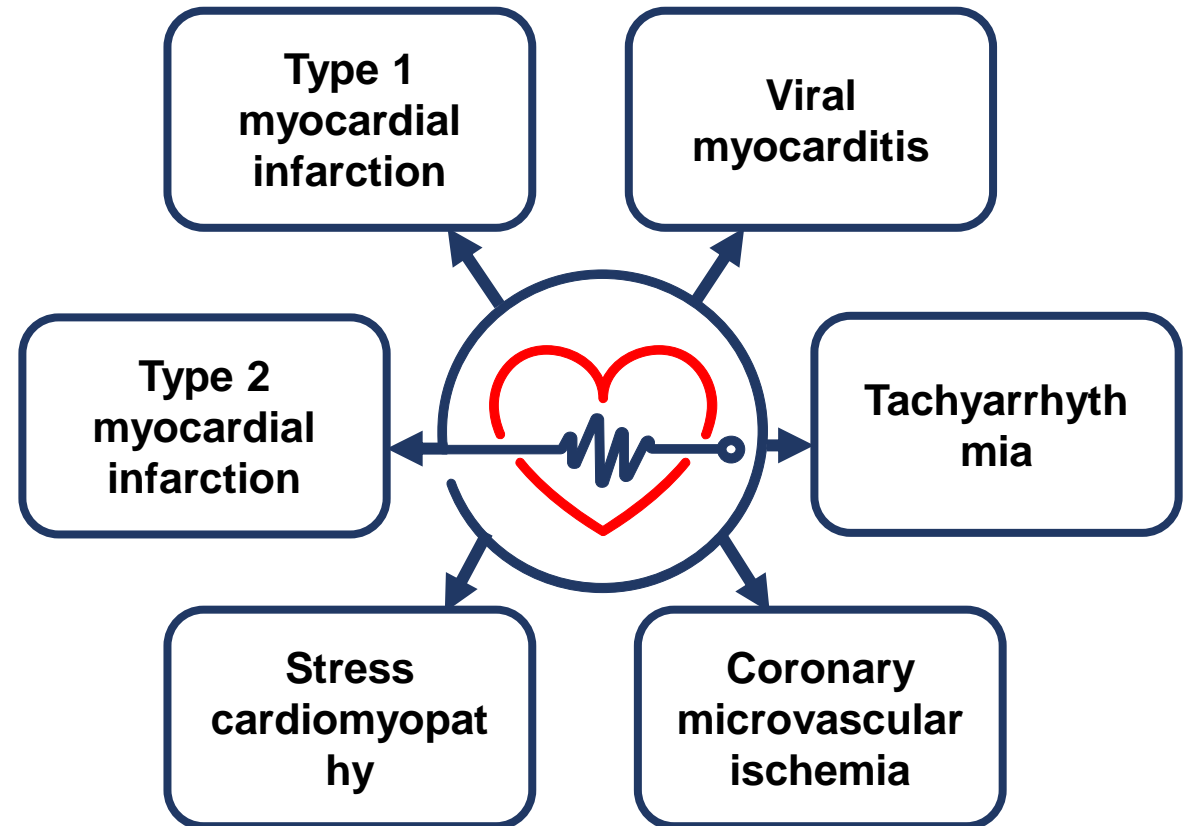
# Potential mechanisms for acute effects of viral infections on cardiovascular system



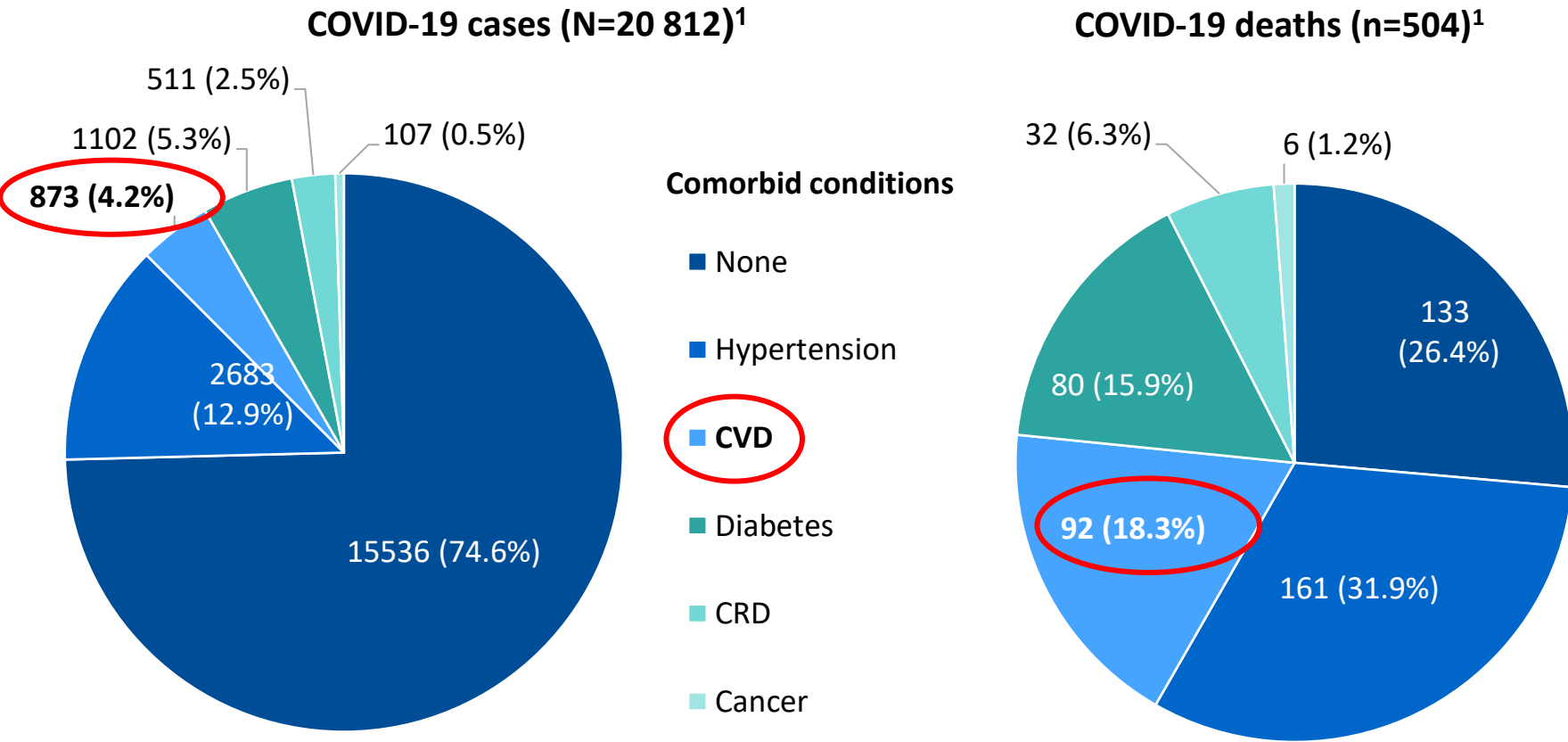
# Cardiac stress/injury in patients with COVID-19

- **Cardiac complications** are common in patients with severe respiratory disease, e.g. pneumonia<sup>1-3</sup>
- Acute cardiac injury has been reported in hospitalised patients with COVID-19<sup>4-7</sup>
- Initial findings suggest COVID-19-induced cardiac injury is more likely in **patients with underlying CVD**<sup>8</sup>
- Case reports of cardiac complications in CVD-naïve patients are emerging<sup>9,10</sup>

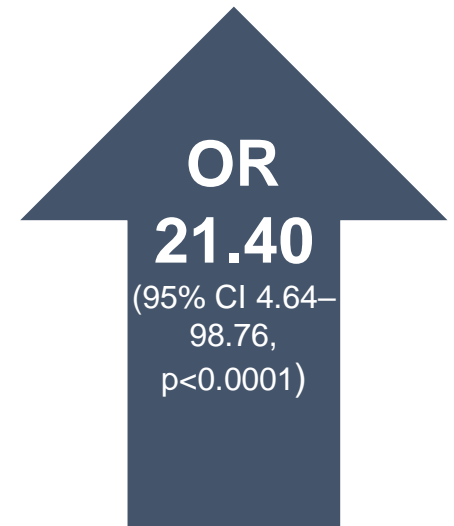
## Potential cardiac complications in COVID-19<sup>11</sup>



# COVID-19 in patients with cardiovascular disease



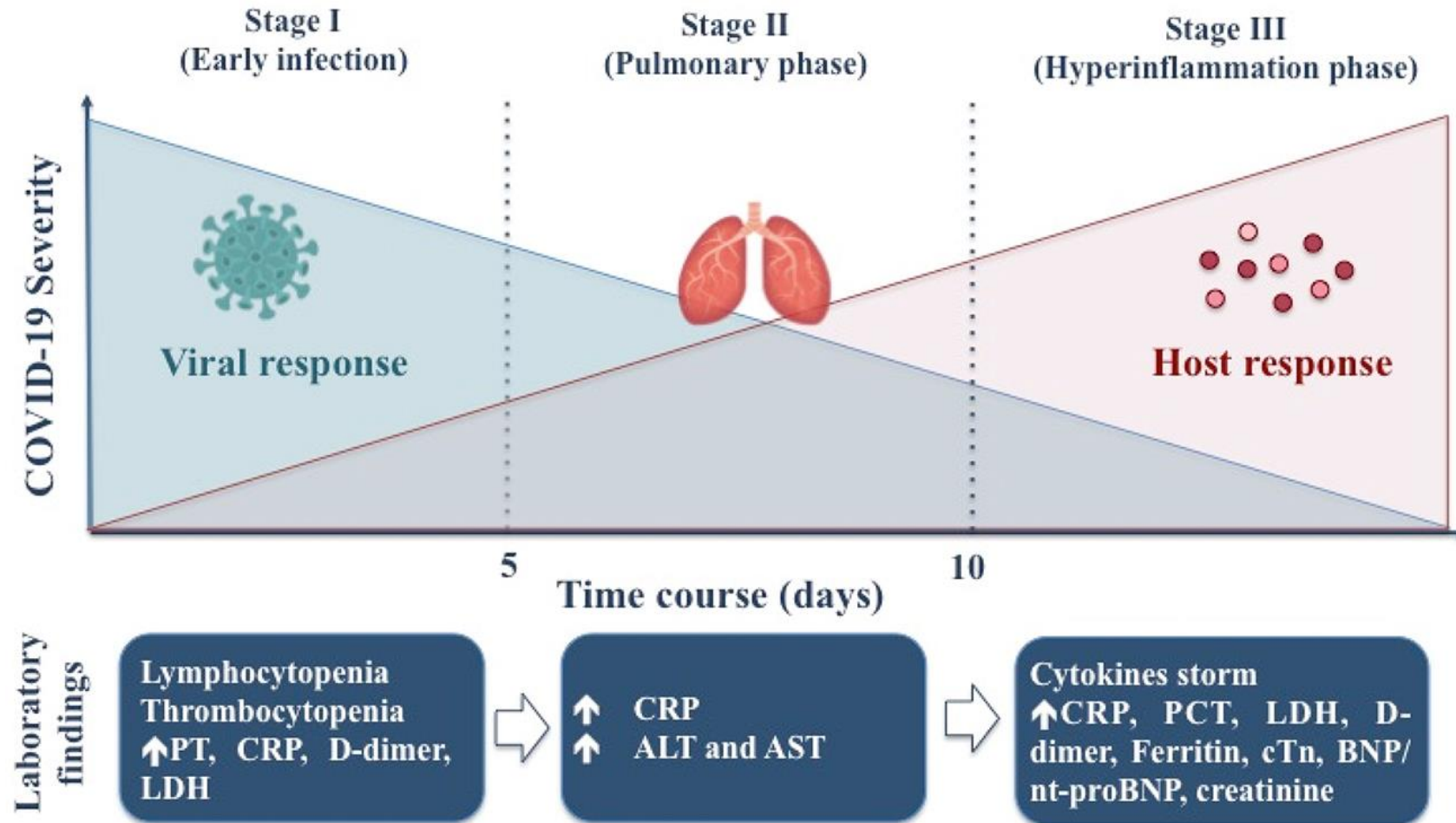
**Underlying CAD was associated with increased risk of mortality (univariate analysis, N=191)<sup>2</sup>**



**Patients with underlying cardiovascular disease accounted for 4.2% of COVID-19 cases, but 18.3% of COVID-19 deaths<sup>1</sup>**

# Cardiac Biomarkers in COVID-19





# Abnormal biomarkers in COVID-19 patients

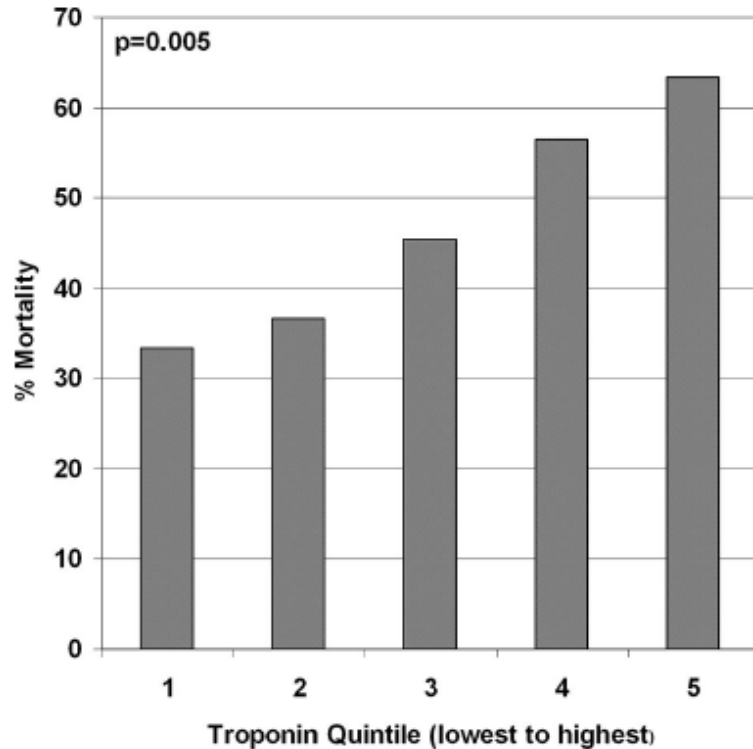
General chemistry	<ul style="list-style-type: none"><li>• Albumin</li><li>• Alanine/Aspartate aminotransferase</li><li>• Bilirubin</li><li>• Creatinine</li><li>• Lactate</li><li>• Lactic dehydrogenase</li></ul>
Cell counts	<ul style="list-style-type: none"><li>• Leukocyte count (leukocytosis with lymphopenia)</li><li>• Platelet count (thrombocytopenia)</li><li>• Red blood cell distribution width</li></ul>
Inflammatory/acute phase markers	<ul style="list-style-type: none"><li>• C-reactive protein</li><li>• Ferritin</li><li>• Interleukin-1</li><li>• Interleukin-2R</li><li>• Interleukin-6</li><li>• Interleukin-10</li><li>• Procalcitonin</li><li>• Tumor necrosis factor <math>\alpha</math></li></ul>
Thrombosis/hemostasis	<ul style="list-style-type: none"><li>• D-dimer</li></ul>
Cardiac markers	<ul style="list-style-type: none"><li>• B-type natriuretic peptide</li><li>• Creatine kinase-MB</li><li>• Myoglobin</li><li>• N-terminal pro-B type natriuretic peptide</li><li>• Troponin T</li><li>• Troponin I</li></ul>

- A large number of abnormal lab findings are present in those with COVID-19
- These findings are generally worse in those with more severe disease...
- Abnormal labs are associated with adverse outcome

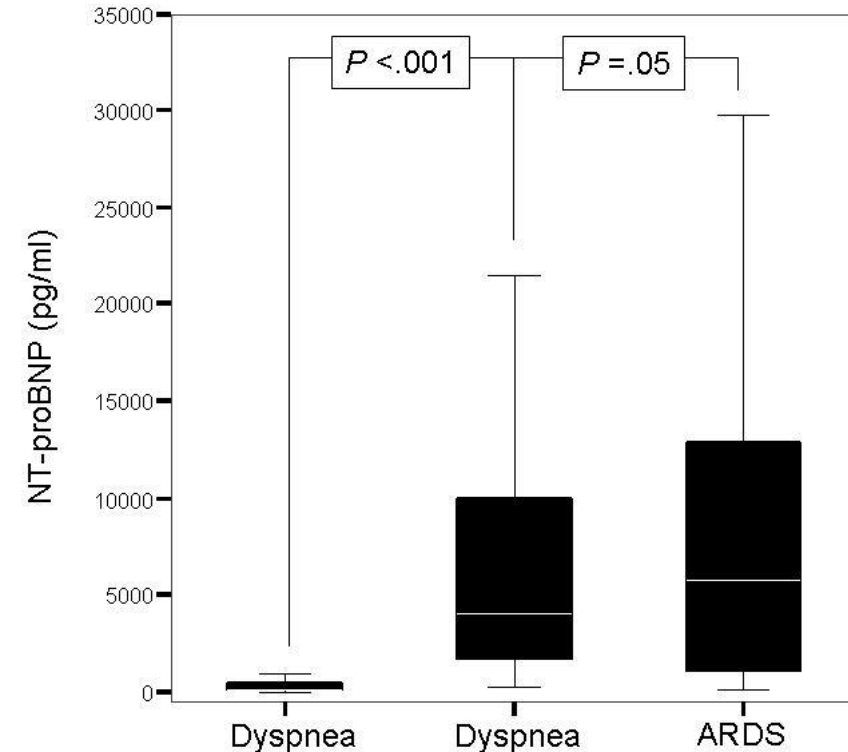
# Everything old is new again...

## Cardiac biomarkers in ARDS

### Troponin



### NT-proBNP

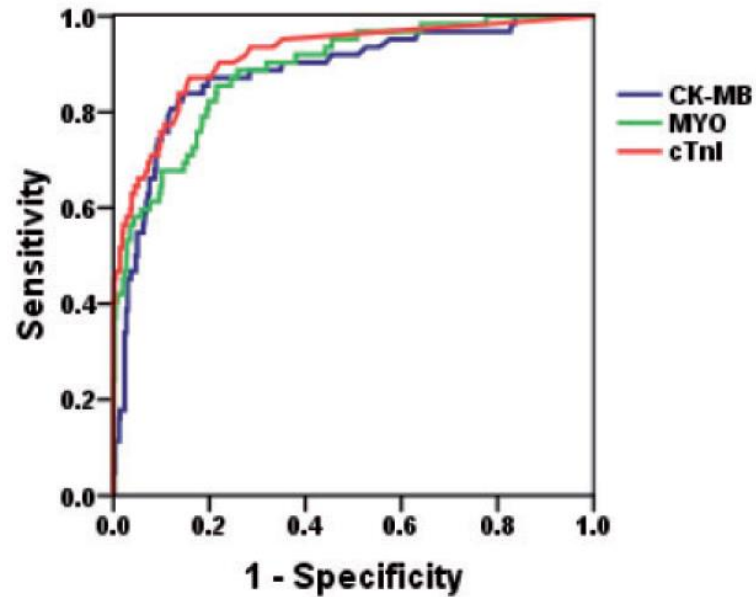


Hs-cTn and NT-proBNP powerful prognostic markers beyond primarily cardiac diseases

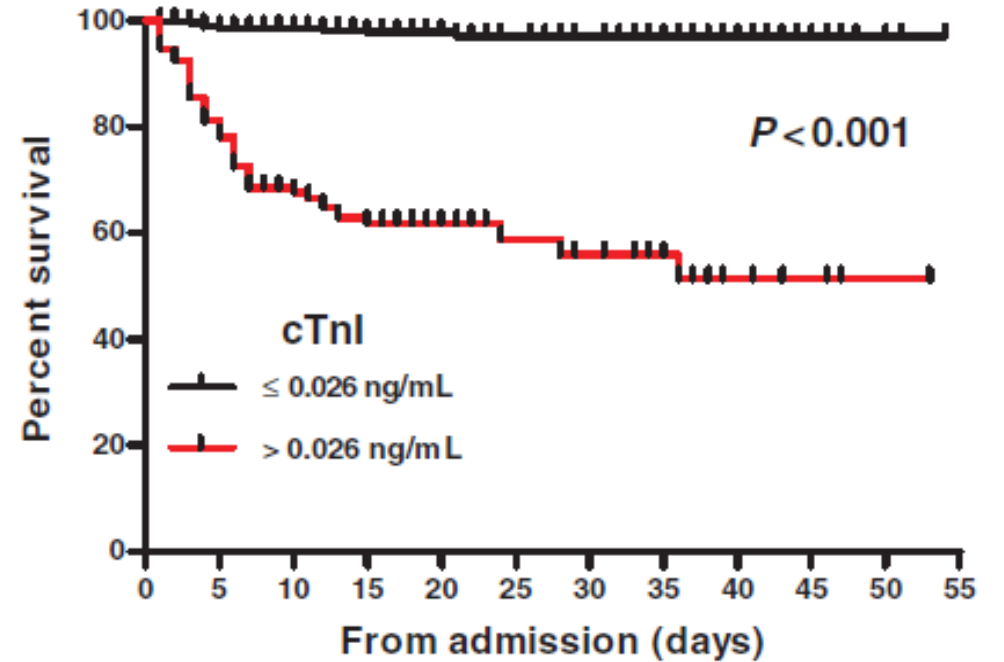


# Myocardial injury in COVID-19

*predictive value of troponin*



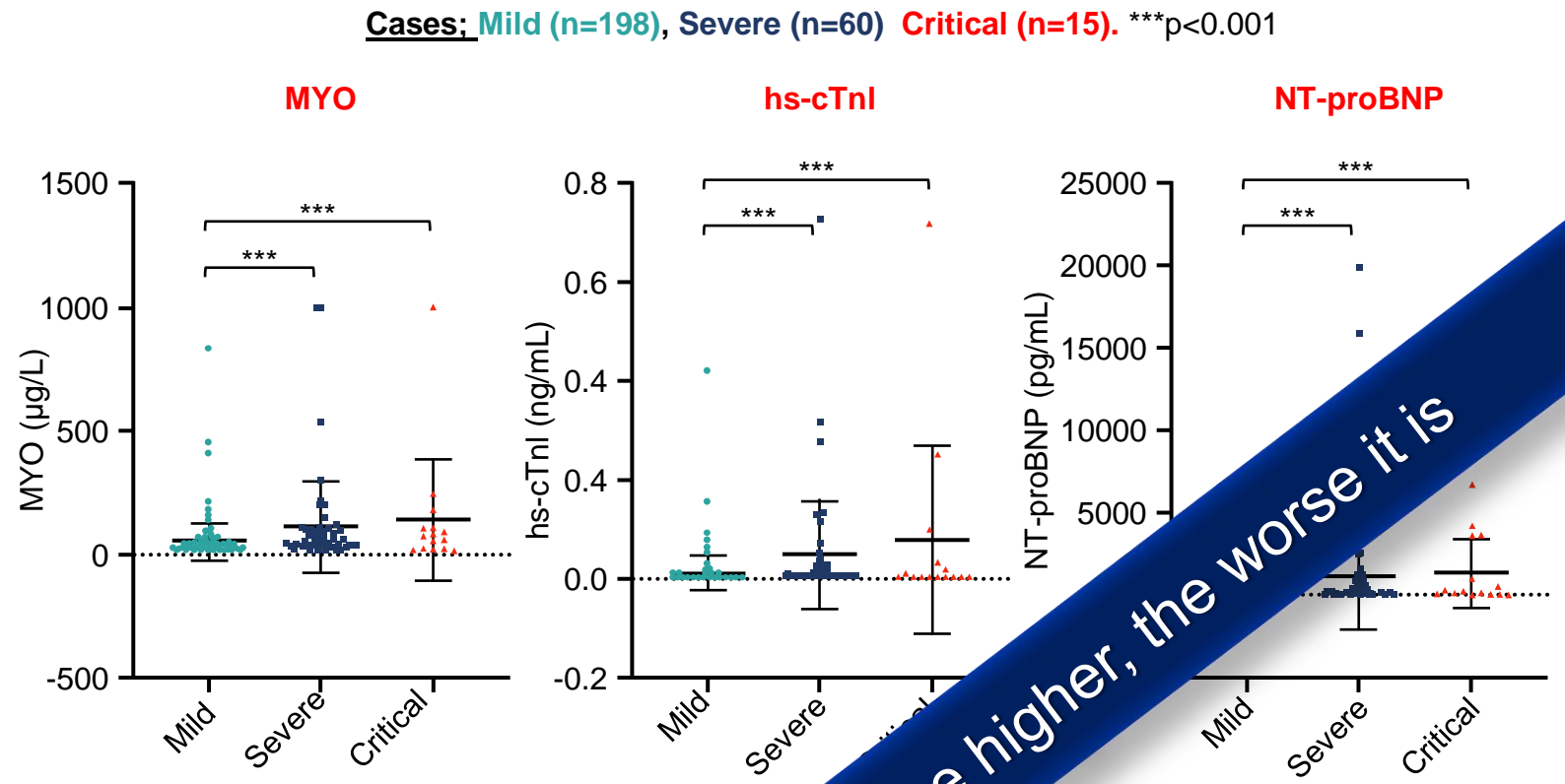
Variables	AUC	95% CI	Sensitivity	Specificity	P-value
CK-MB	0.87	0.81–0.93	0.81	0.87	<0.001
MYO	0.88	0.83–0.93	0.85	0.76	<0.001
cTnI	0.92	0.87–0.96	0.86	0.86	<0.001



# Predictive value of cardiac biomarkers in COVID-19

## Levels of biomarkers in patients with COVID-19 by severity

- **Concentrations** of cardiac biomarkers (myoglobin, hs-cTnI and NT-proBNP) were measured in 273 COVID-19+ patients
- Levels of cardiac biomarkers were **significantly higher** in severe/critical cases vs mild cases
- Data suggests cardiac biomarkers could have a **predictive role** in identifying more severe COVID-19 disease



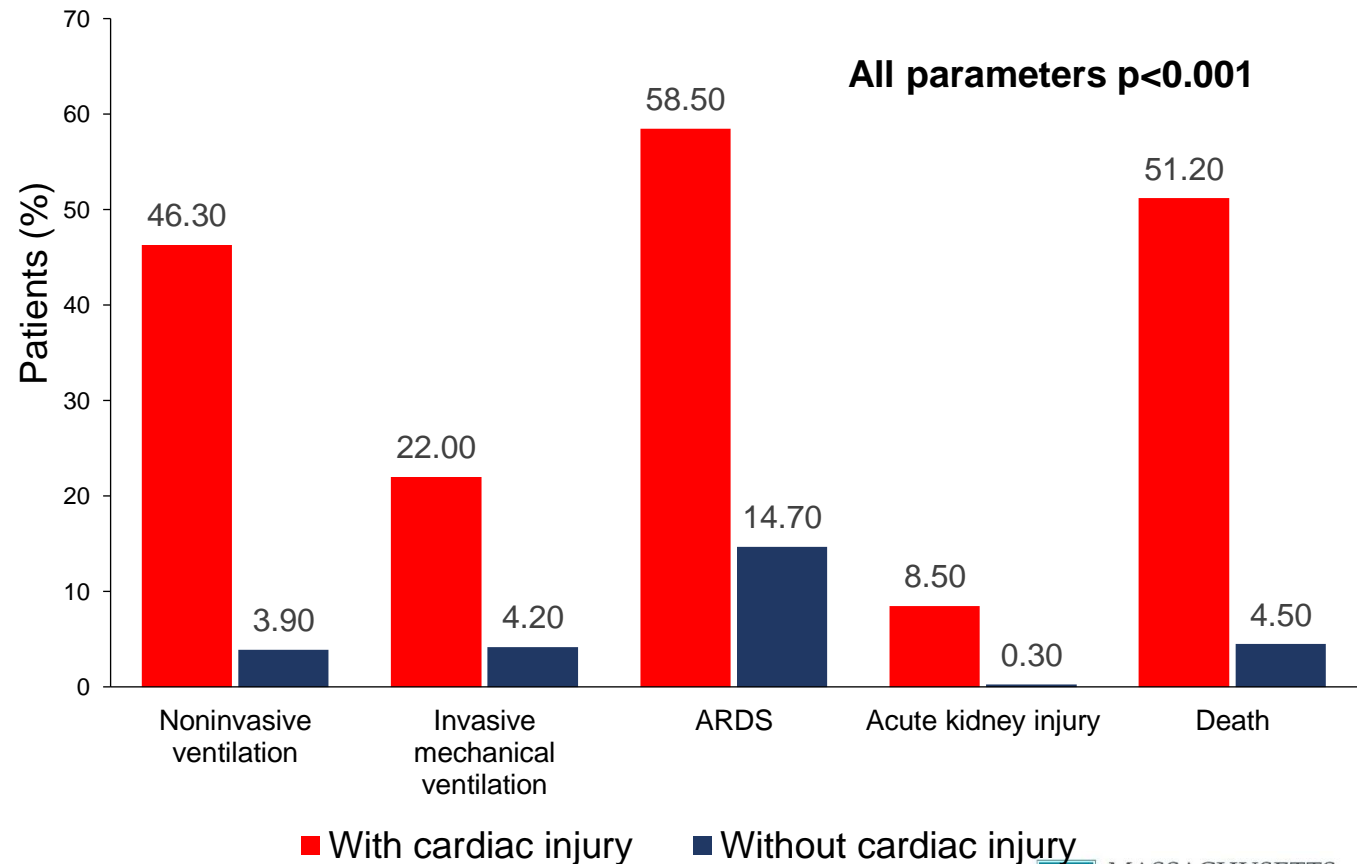
the higher, the worse it is

# Myocardial injury in COVID-19

*may predict disease progression*

- In a meta-analysis of 4 studies, patients with **severe COVID-19** had significantly higher cTn levels vs those with mild disease (mean  $\Delta$  25 ng/L)<sup>1</sup>
- In 416 COVID-19+ patients, **1 in 5** had myocardial injury when presenting to hospital<sup>2</sup>
- Patients with elevated hs-cTnI were more likely to need **invasive treatment**, develop **complications** and have **poorer clinical outcomes**<sup>2</sup>

Disease progression parameters for COVID-19 patients with or without myocardial injury<sup>2</sup>



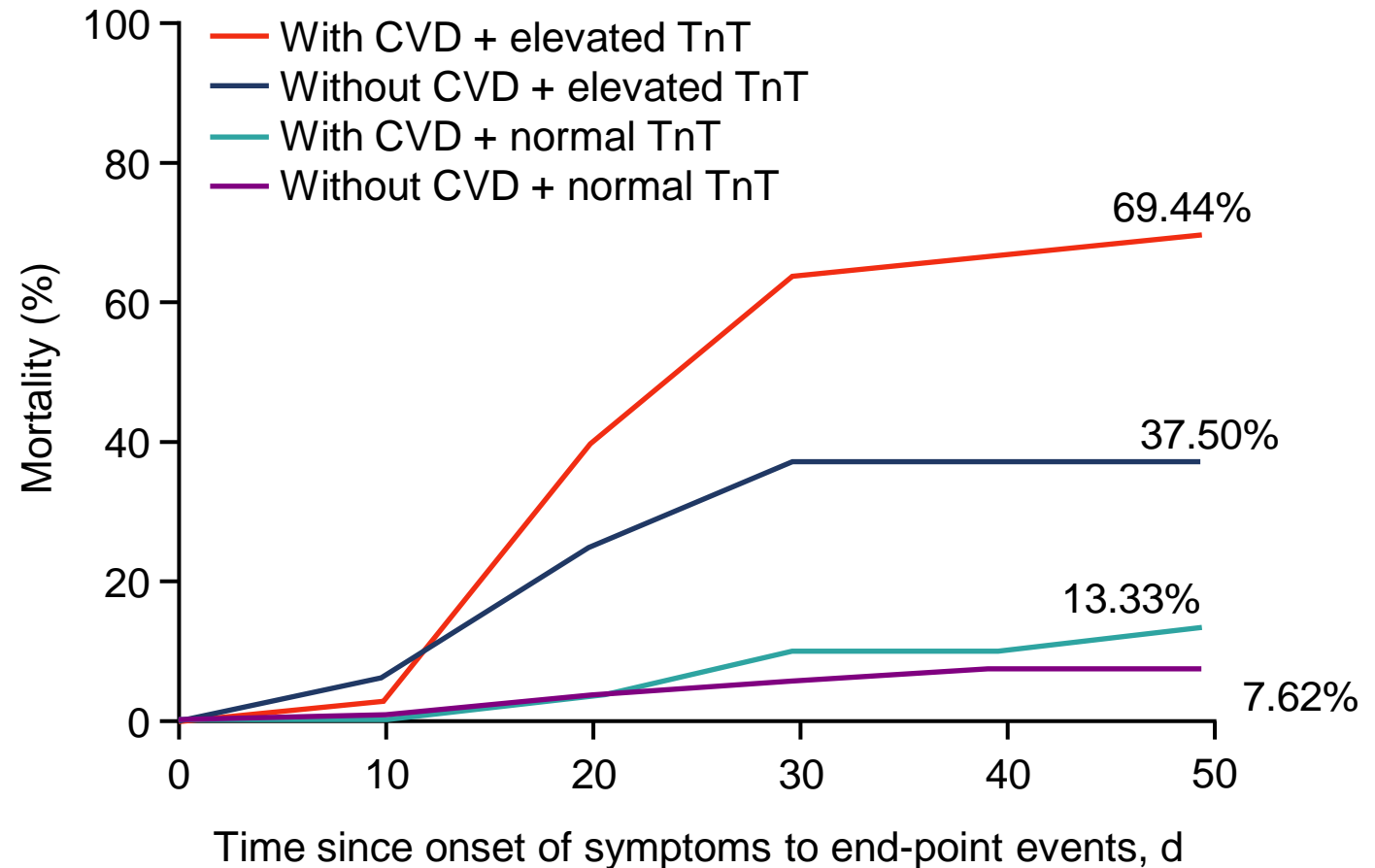
1. Lippi G et al. Prog Cardiovasc Dis. 2020; DOI:10.1016/j.pcad.2020.03.001

2. Shi S, et al. JAMA Cardiol 2020; DOI: 10.1001/jamacardio.2020.0950.

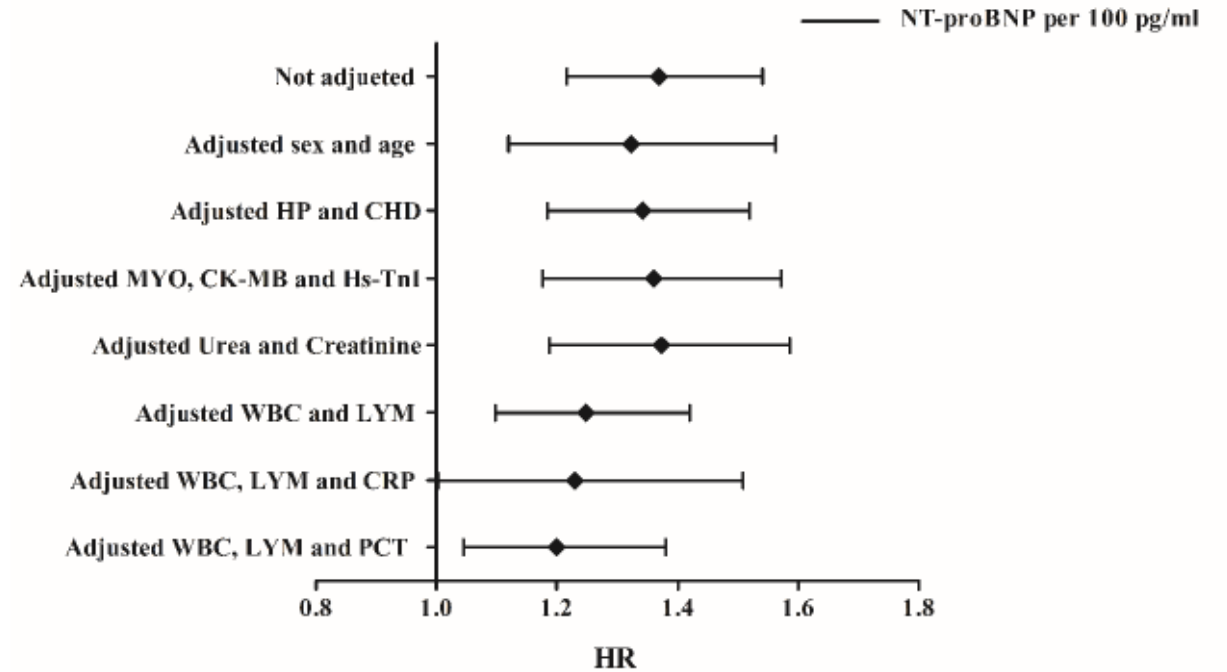
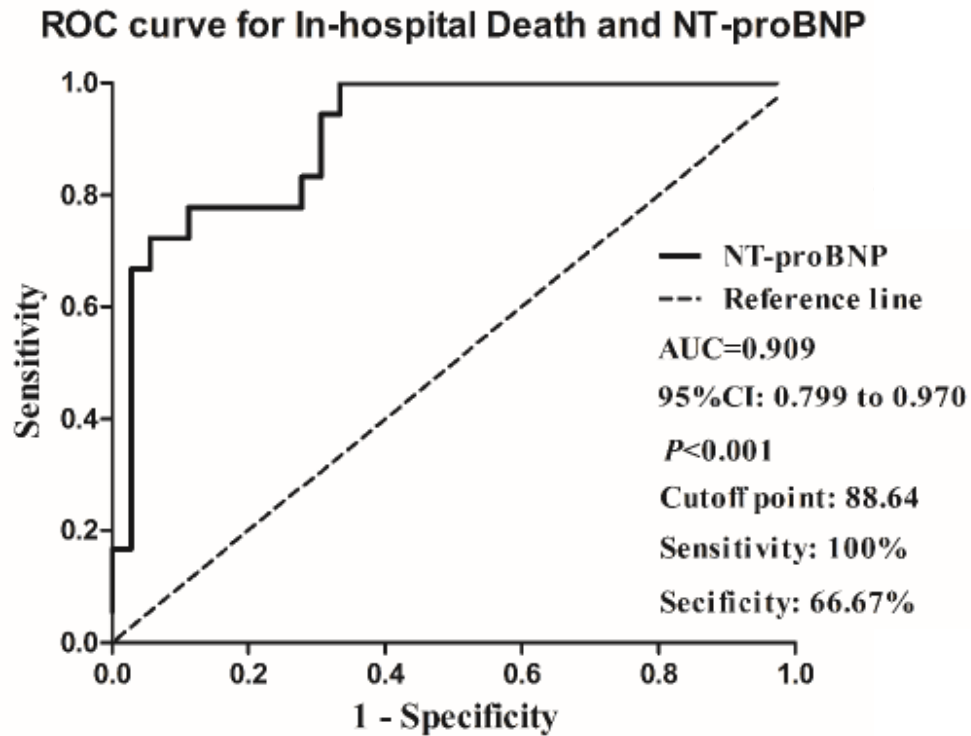


# Mortality rate was higher in COVID-19 patients with elevated cTnT and underlying CVD

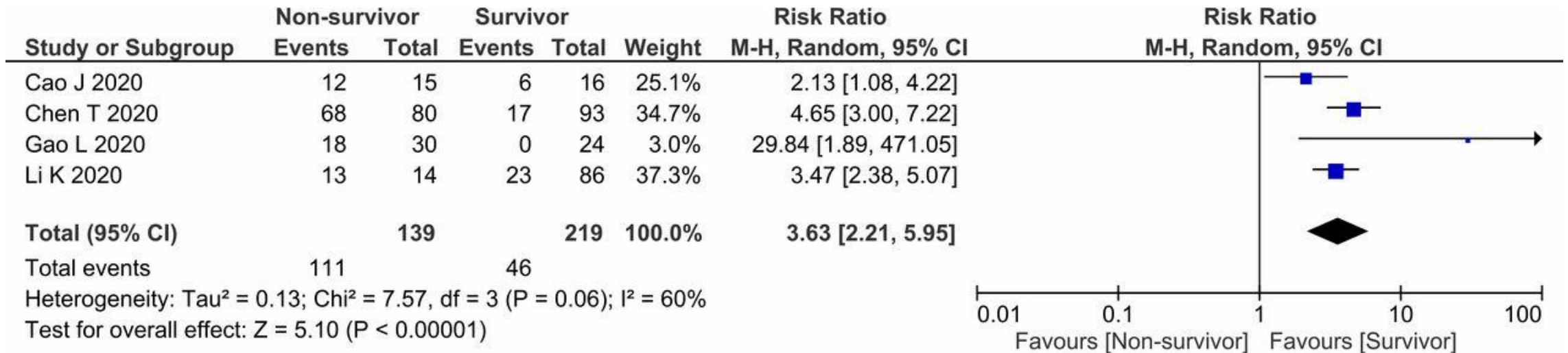
- In 187 hospitalised COVID-19+ patients, those with **underlying CVD** were more likely to have **cTnT elevation** (54.5%) versus those without CVD (13.2%)
- **Favorable prognosis** in patients with underlying CVD and normal cTnT levels (mortality rate **13.33%** vs. **69.44%** in patients with elevated cTnT and underlying CVD)
- Cardiac biomarkers may be useful in patients with CVD who develop COVID-19 for **risk stratification** and possible early and more aggressive interventions



# NT-proBNP and outcomes in COVID-19

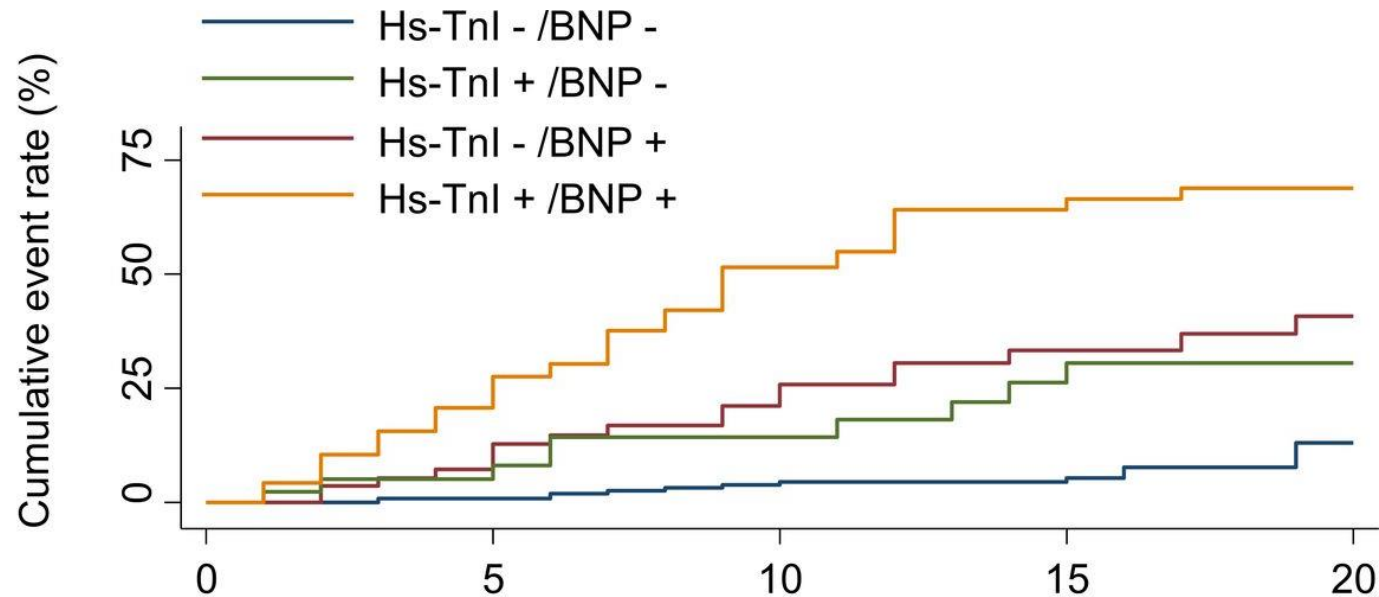


# Natriuretic peptides and outcomes in COVID19



# Additive value of hs-cTn and BNP

Cut-offs: hs-cTnI  $\geq 19.6$  ng/L, BNP  $\geq 100$  pg/mL



- **Elevated hs-cTnI and BNP were both predictive of mortality, particularly if rising**
- **Combination of both peptides was a superior method of prognostication compared to each alone**

# Should patients with COVID-19 undergo cardiac biomarker testing?

**Identify patients** with possible myocardial injury and help to predict severity of disease

Further develop understanding and knowledge of the **systemic consequences of COVID-19**

Facilitate appropriate **triage to critical care**

**Frequency** and **non-specific nature** of abnormal troponin or natriuretic peptide result

May increase need for **cardiologist consultation** and **downstream testing** on overstretched healthcare system





# Should patients with COVID-19 undergo cardiac biomarker testing?



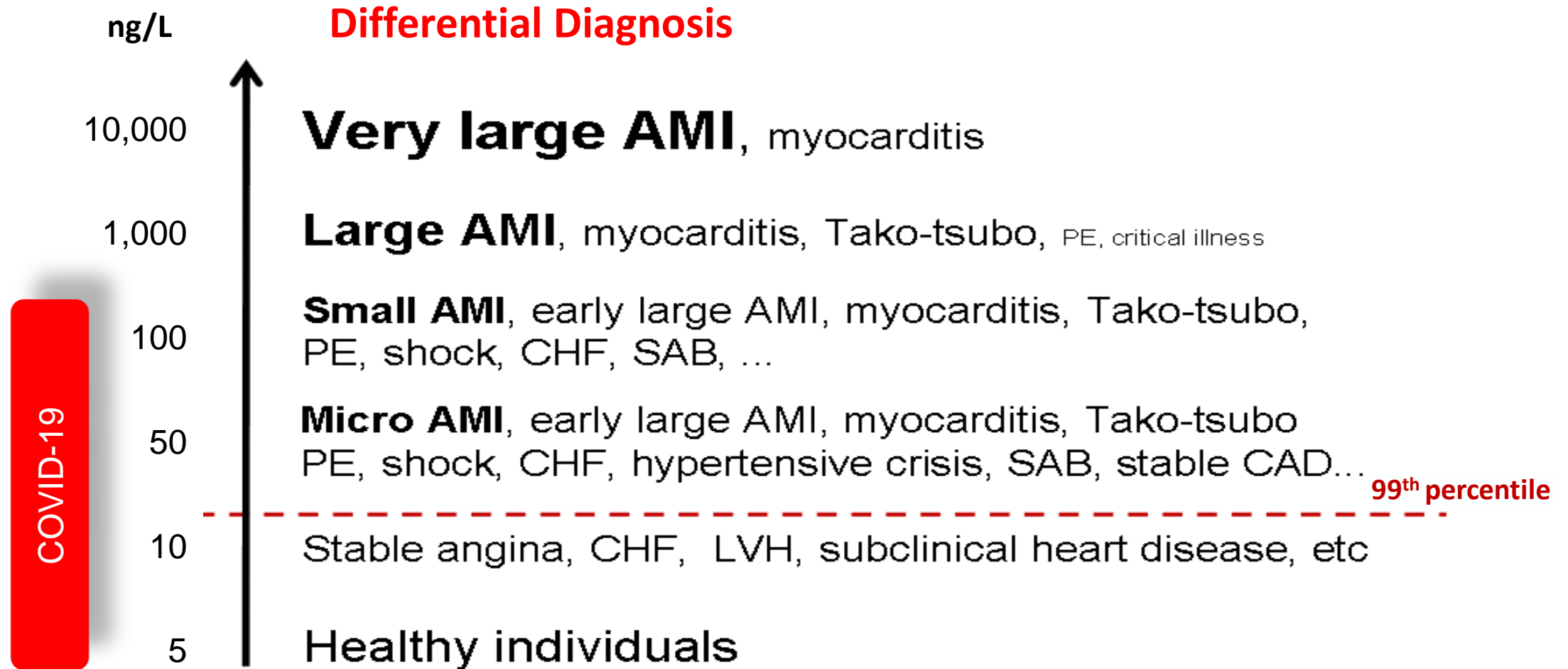
- Suggest to measure **cTn** only if the diagnosis of type 1 MI is being considered on **clinical grounds**, or in new onset LV dysfunction
- **Routine measurements** of cTn and/or NT-proBNP in patients with COVID-19 are **discouraged** given the **current limited evidence** of incremental value in clinical-decision making
- **cTn** should only be measured if **diagnosis of acute MI is being considered** on clinical grounds
- **BNP or NT-proBNP** elevation **should not necessarily trigger** evaluation or treatment for heart failure **unless** there is **clear clinical evidence** for the diagnosis

Context is everything

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; cTn, cardiac troponin; CVD, cardiovascular disease; LV, left ventricular; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ACC, American College of Cardiology; ESC, European Society of Cardiology; ACC statement, Troponin and BNP Use in COVID-19. 2020 Mar <https://www.acc.org/latest-in-cardiology/articles/2020/03/18/15/25/troponin-and-bnp-use-in-covid19>; <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/15/25/antagonists-addresses-concerns-re-using-raas-antagonists-in-covid-19>; [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang); ESC Guidance on the Use of Cardiac Biomarkers in COVID-19. 2020 Mar <https://www.escardio.org/Document/Esc-Guidance-on-the-Use-of-Cardiac-Biomarkers-in-COVID-19>; ACC and ESC Education/COVID-19 and Cardiology/ESC-COVID-19-Guidance#p07

# Myocardial injury

## How to interpret troponin in COVID-19



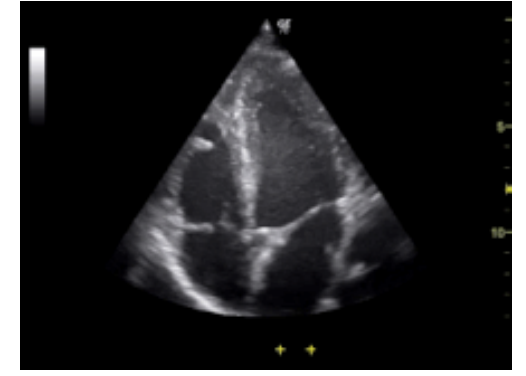
# Myocardial injury

*don't forget your standard tools*

If concern?

Standard evaluation

POCUS

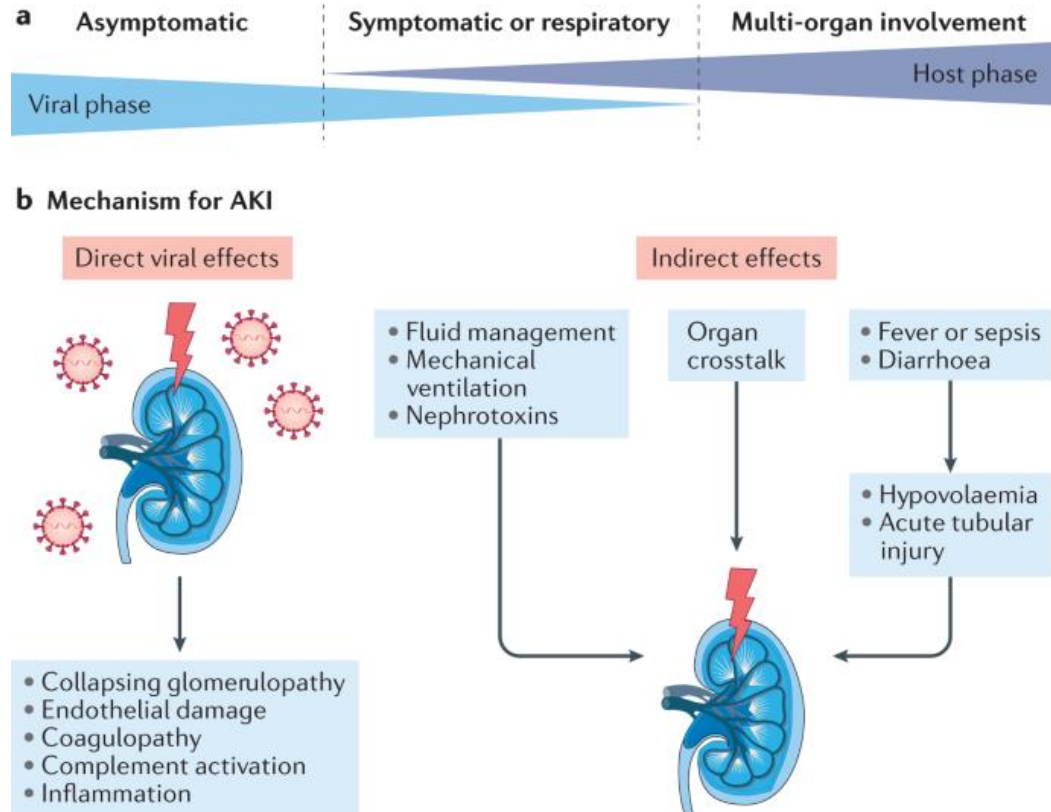


# Other complications of COVID19

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- Acute kidney injury
- Thrombosis, thromboembolic disease
- Secondary pneumonia
- Multisystem inflammatory syndrome in children (MIS-C)

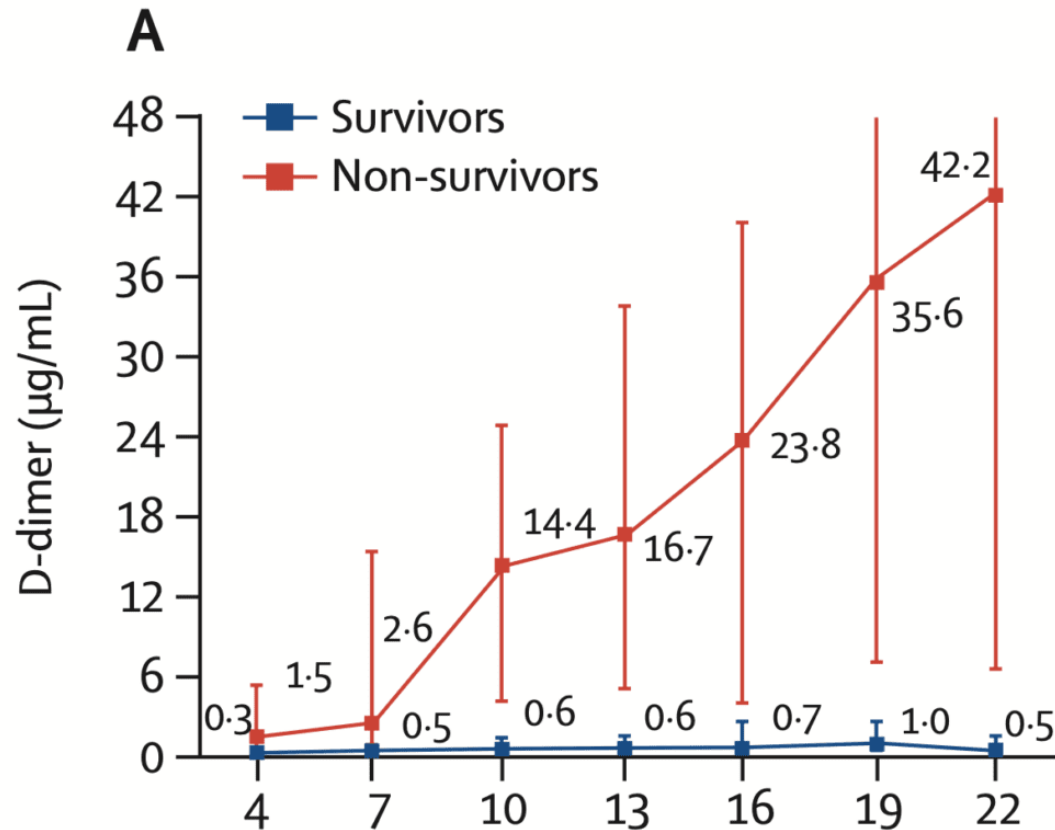
# COVID19 and AKI



## Predictors of AKI on admission

- **increased serum creatinine (14.4%)**
- **high serum urea (13.1%)**
- **proteinuria (43.9%)**
- **Hematuria (26.7%)**
  
- **The role of renal biomarkers such as NGAL or TIMP2/IGFBP7 ratio remains undetermined**

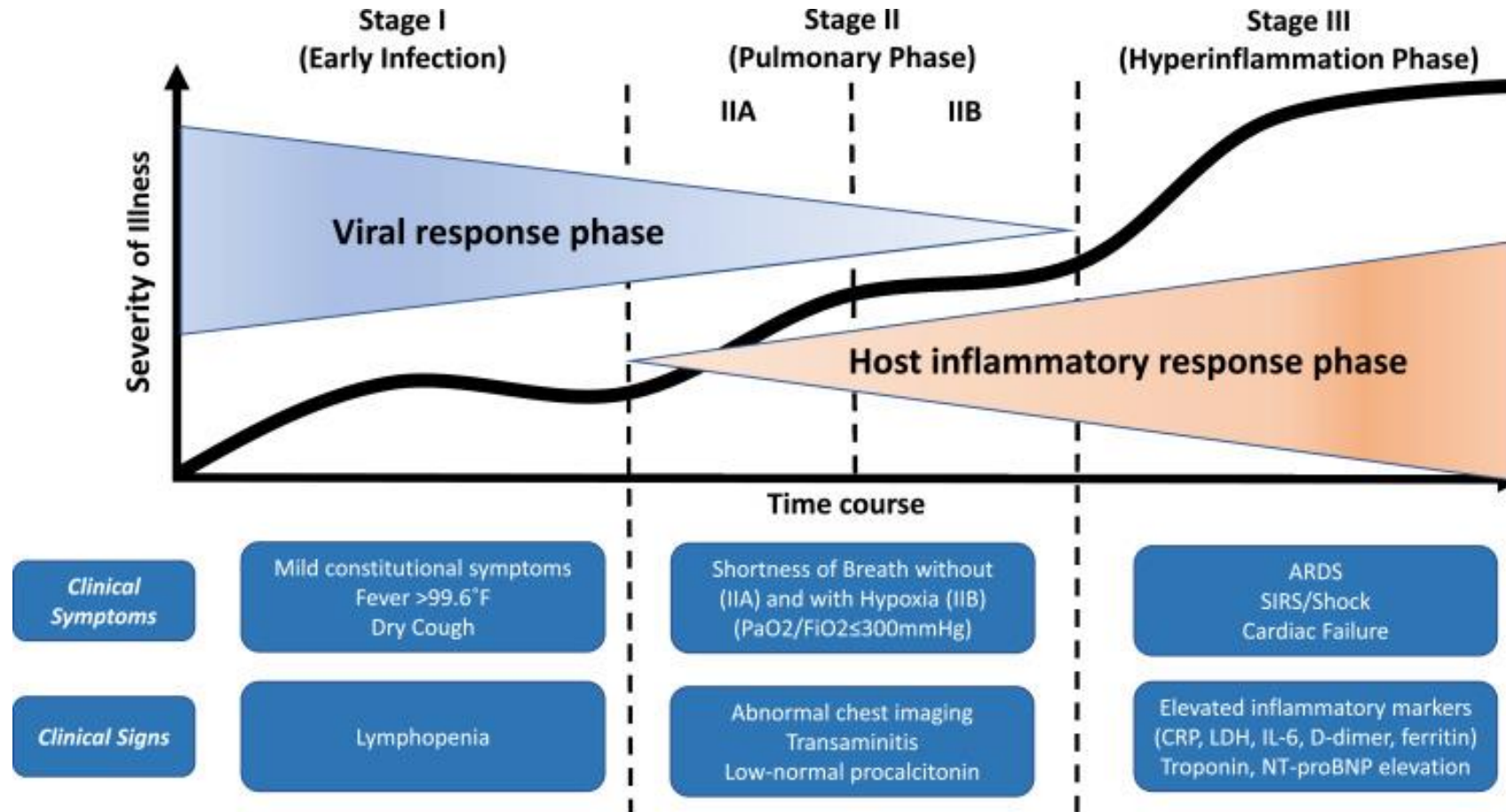
# COVID19 and activation of coagulation



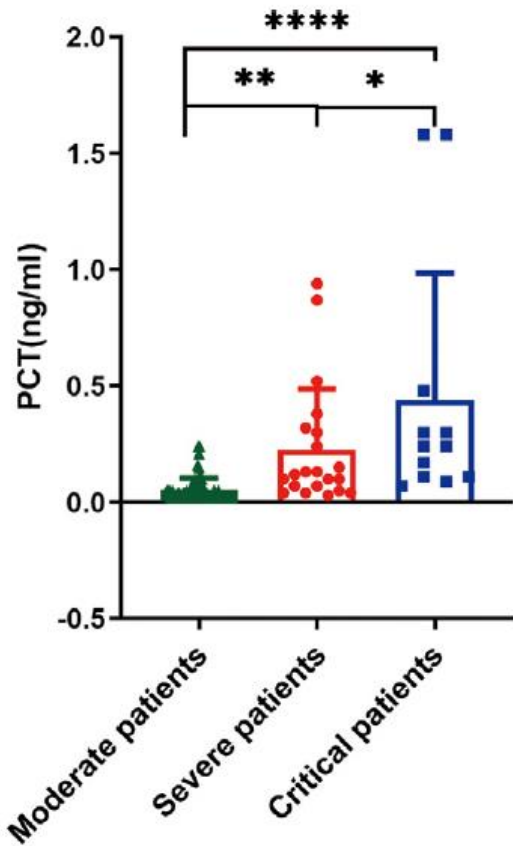
- **Thrombosis is common among patients with severe COVID19**
- **Elevated d-dimer is frequently noted among patients with COVID19**
- **Low d-dimer has excellent NPV for VTE while high d-dimer has lower PPV**
- **D-dimer is prognostic for adverse outcomes and when markedly elevated may be an indication for anticoagulation**

# Infectious Diseases Management

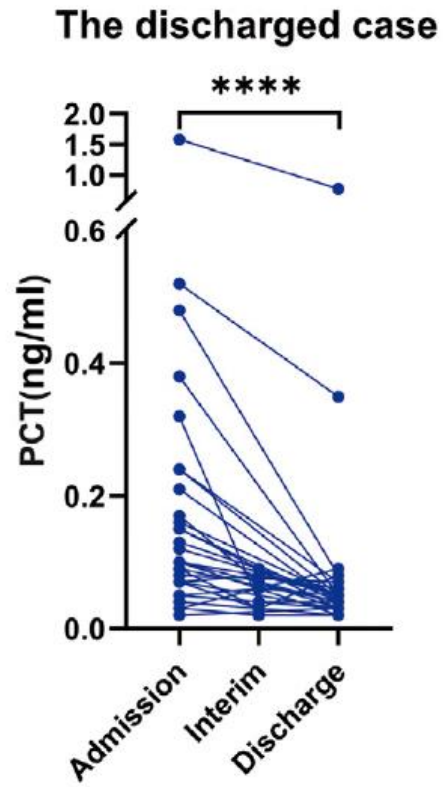
## Fundamental Parameters



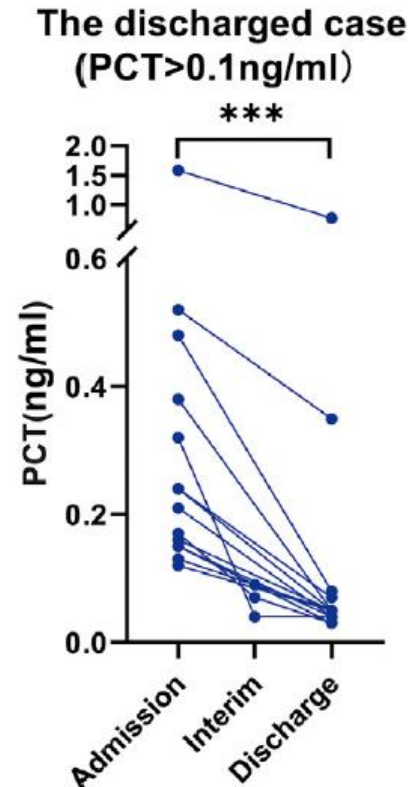
# COVID19 and the role of procalcitonin (PCT)



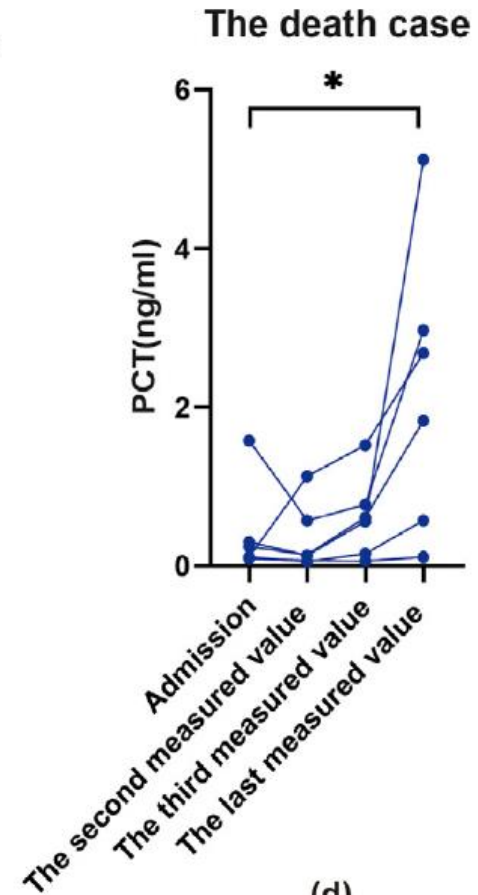
(a)



(b)



(c)



(d)



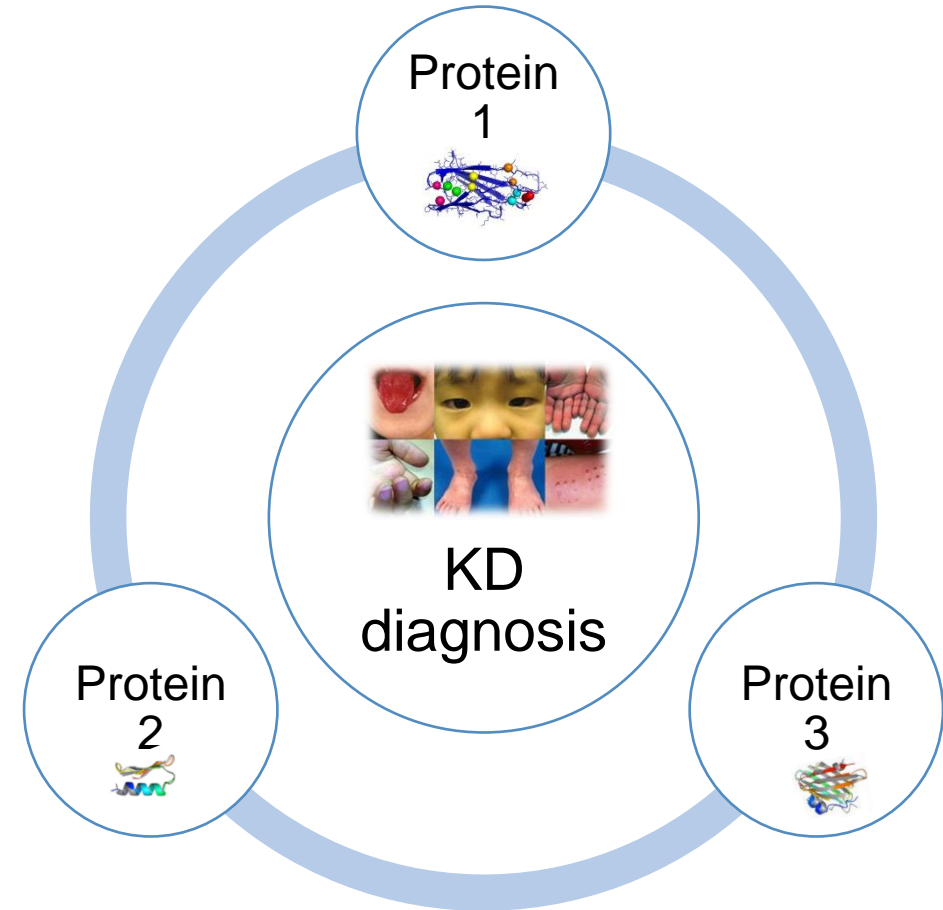
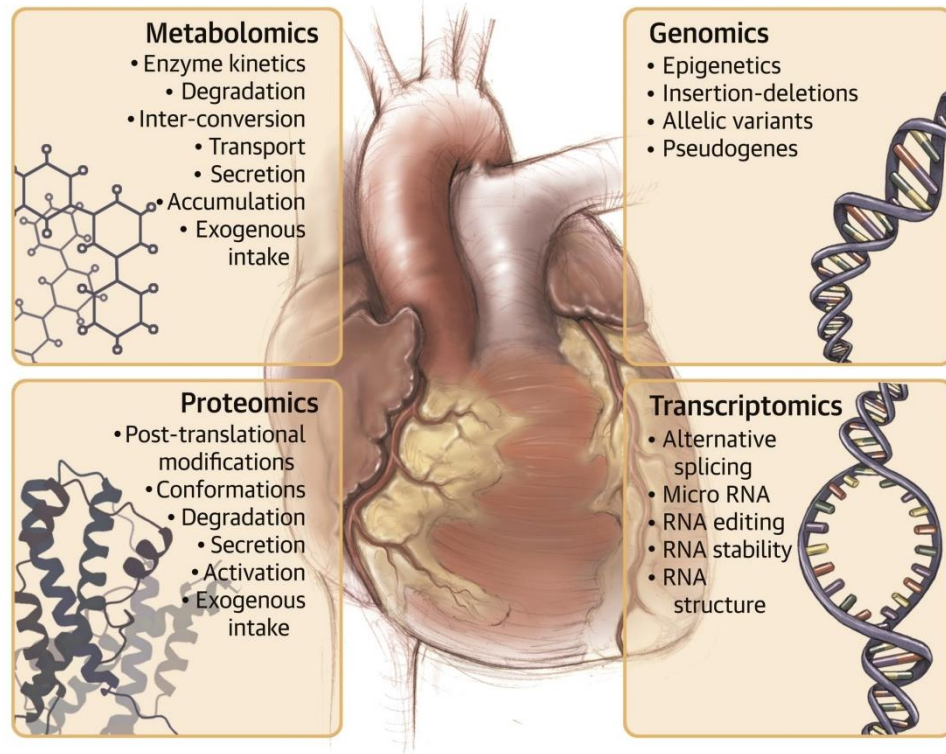
# MISC-C in COVID19

- Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe condition associated with COVID19
- Appears approximately 2–4 weeks after the onset of COVID19 in children and adolescents
- Shares many features with Kawasaki Disease
- Most cases have features of shock, with cardiac involvement, gastrointestinal symptoms, and significantly elevated markers of inflammation

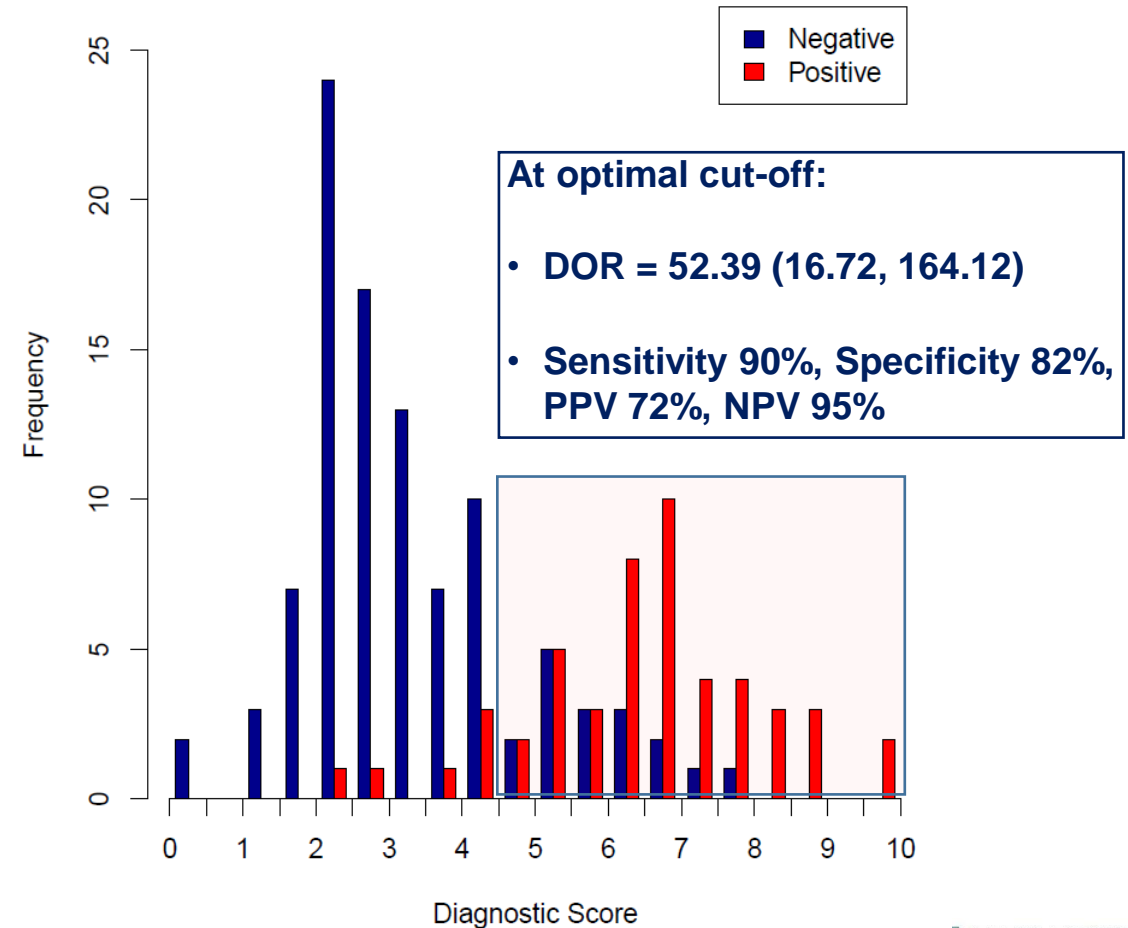
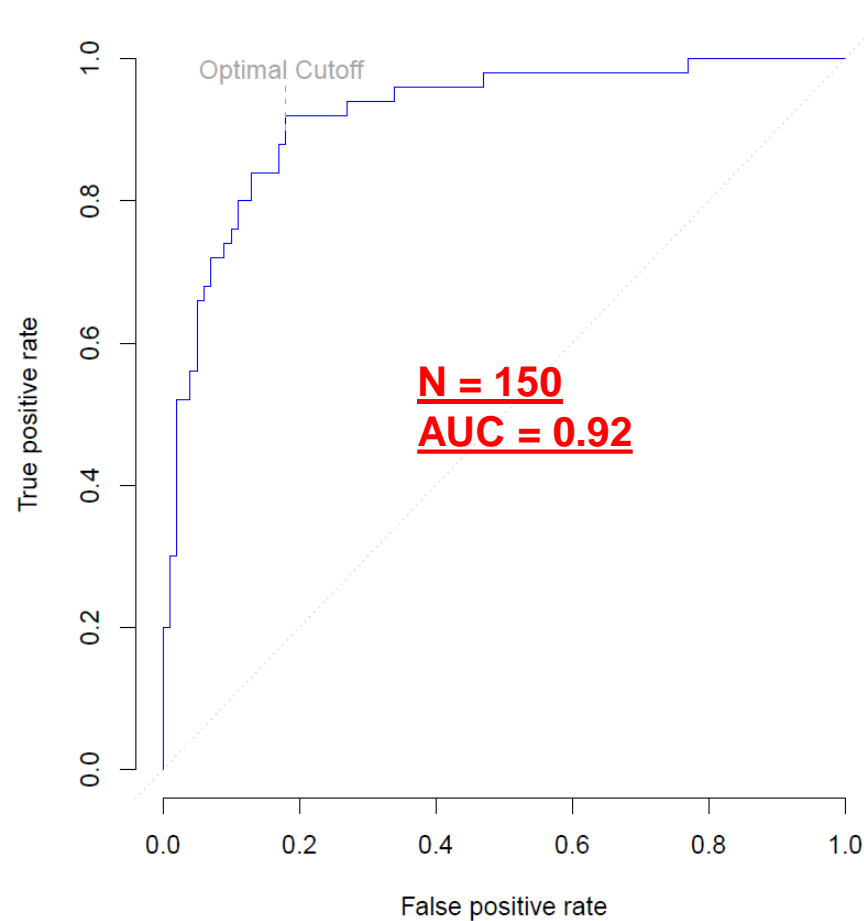
**N=570**

Signs/symptoms	Frequency
Abdominal pain	61.9%
Vomiting	61.8%
Rash	55.3%
Diarrhea	53.2%
Hypotension	49.5%
Conjunctival injection	48.4%
Cardiac dysfunction	40.6%
Shock	35.4%
Coronary aneurysm	18.6%
AKI	18.4%

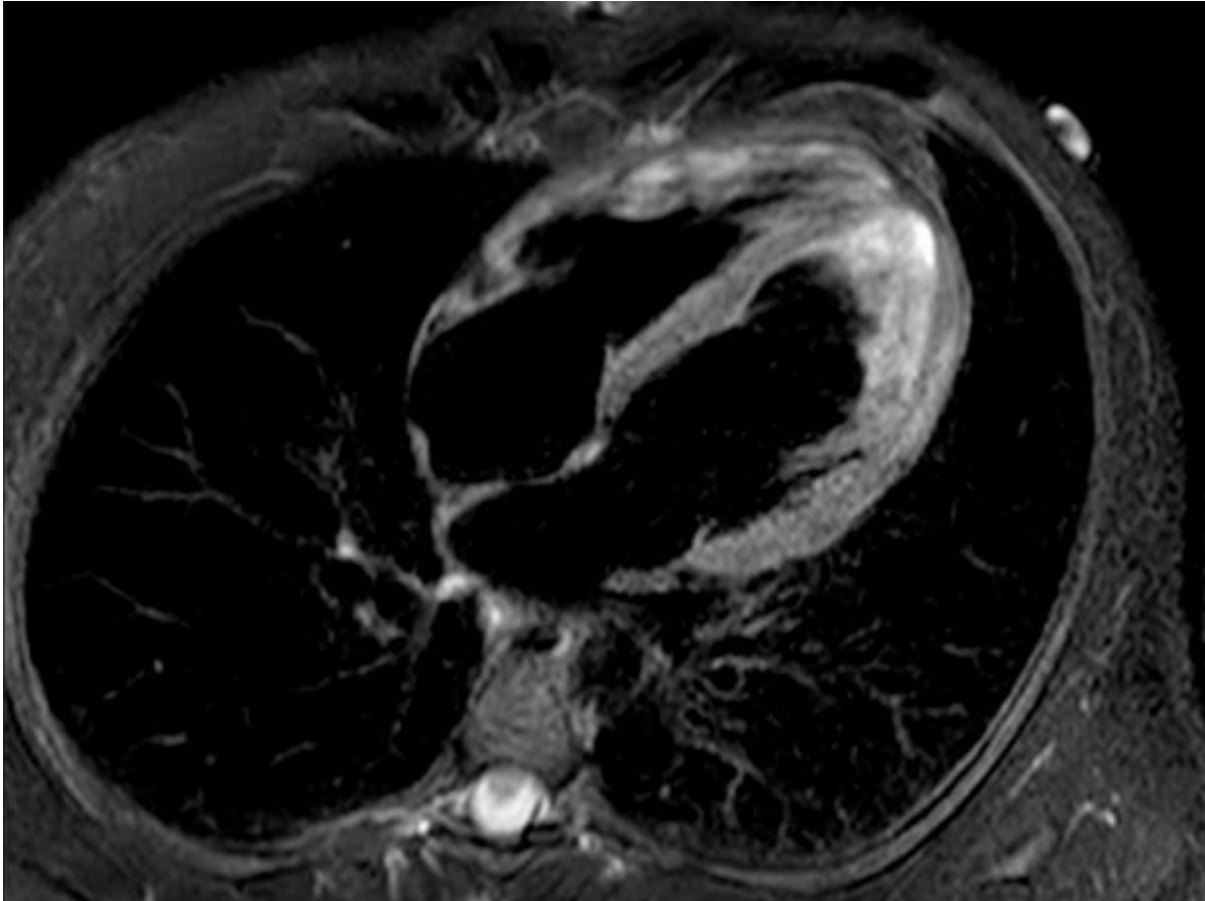
# OMICs and a biomarker-based diagnostic for KD



# Biomarker-based diagnosis of KD

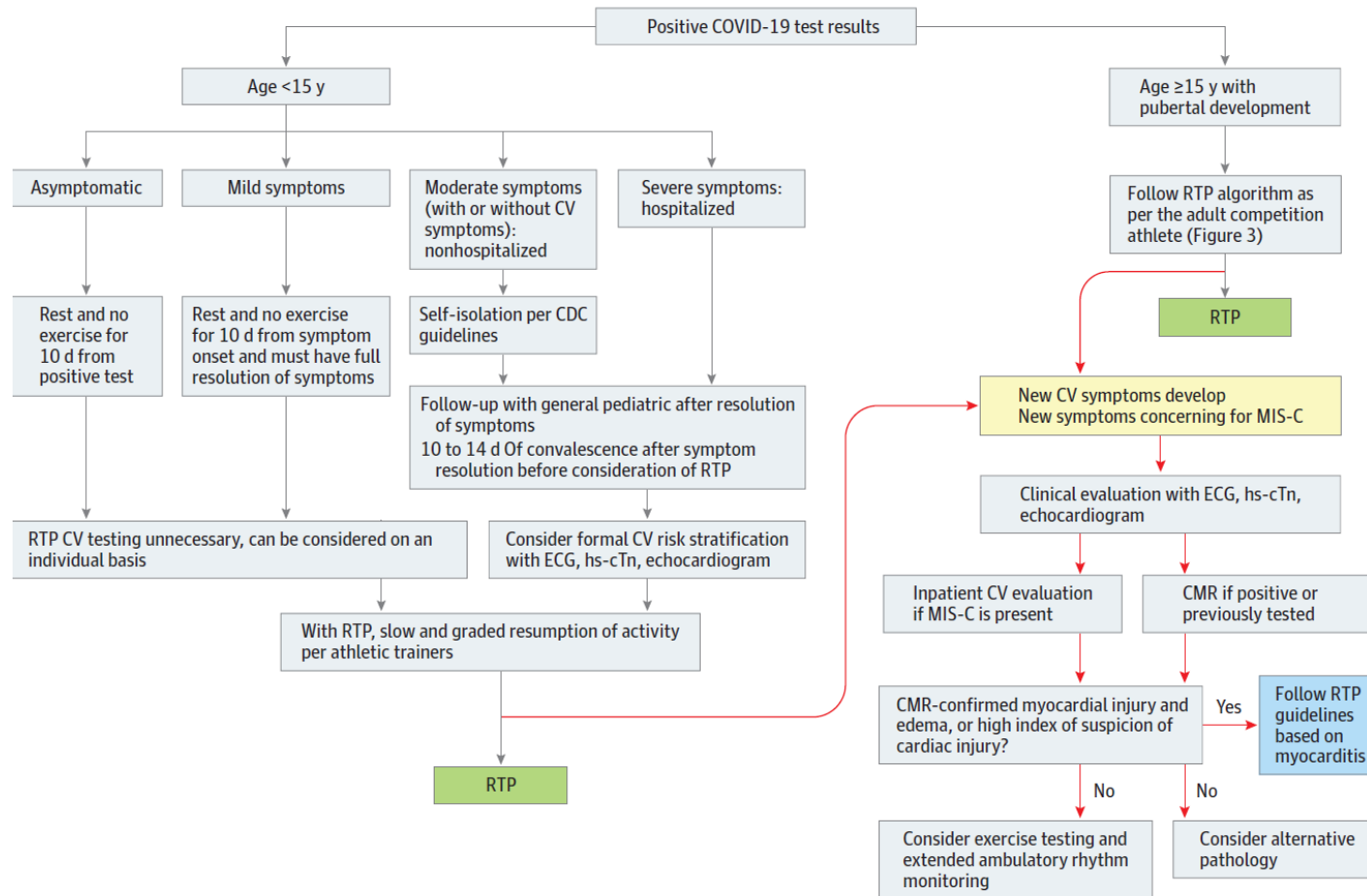


# Special topic: COVID19 in athletes



- Myocarditis is a common cause of sudden death in athletes with a mandatory 3-6 month suspension of strenuous activities
- Given potential for myocarditis associated with COVID19, the question of “return to play” has risen for recovered athletes
- Studies recent alerted to the presence of a higher-than-expected evidence of myocardial inflammation on cardiac MRI among young athletes with COVID19

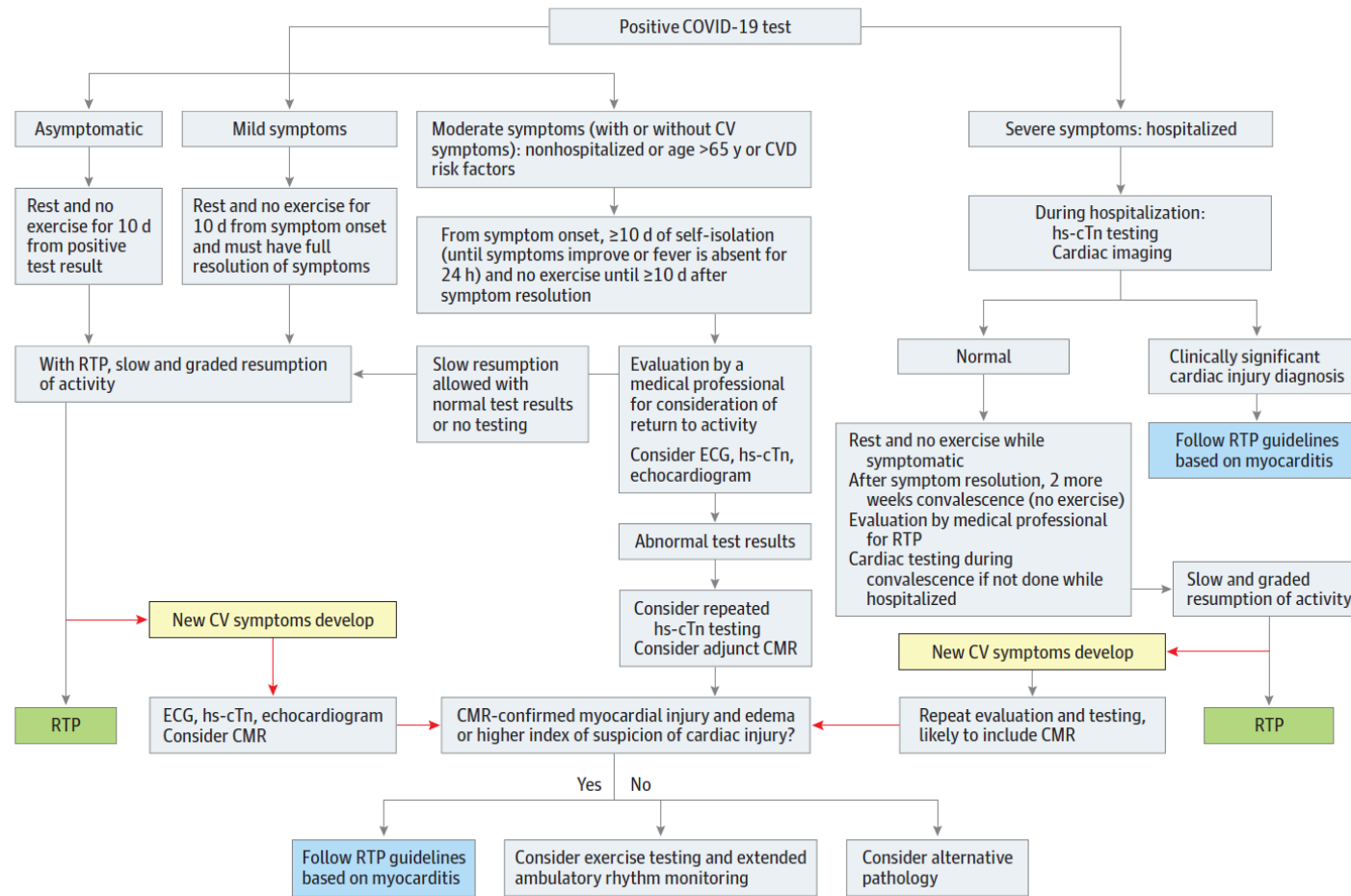
# Management for younger athletes



- Young kids with  $\leq$ mild sx: recover and RTP
- Young kids with  $>$ mild sx: consider formal evaluation (ECG, hs-cTn, echo)
- Older kids: treat as adults
- For both: monitor for MIS-C

# Management for older/elite athletes

- A much lower bar for biomarkers and imaging:
  - ❖ Any symptoms after recovery regardless of COVID severity
  - ❖  $\geq$ Moderate COVID
  - ❖ Severe COVID with elevated hs-cTn, managed as myocarditis
- Evaluation to include ECG, hs-cTn, and cMRI



# Long term follow up of recovered COVID-19

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- Following outbreaks of SARS-CoV-1 and MERS, longer term follow-up suggests that up to 30% of recovered patients have chronic organ dysfunction, including heart and lungs
- A routine follow up strategy for recovered patients with severe COVID-19 remains undefined but will likely require enhanced surveillance, particularly in those with CV disease
- The role of biomarker testing in recovered patients following COVID19 remains undefined

# Agenda

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- What is COVID19?
- How COVID19 affects the CV system and other complications
- How COVID19 affects patients with CV disease
- How biomarker testing may inform prognosis and management in COVID19



# Conclusion

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- The COVID-19 pandemic has reached every nation on earth
- Several biomarkers may have a role in the evaluation and management of patients with COVID19
- Remember: elevated hs-cTn or NP does not mean the patient has an acute MI or heart failure → clinical context matters!
- Means of long-term follow up of recovered COVID19 patients remains an open question