

Using Biomarkers to Inform COVID-19 Treatment

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Disclosures

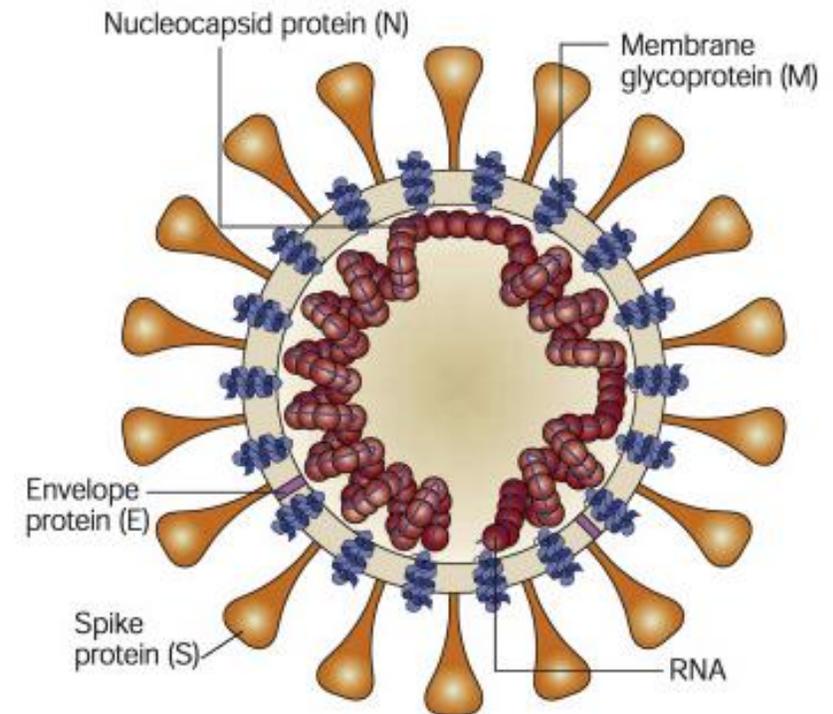
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Agenda

- 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

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)

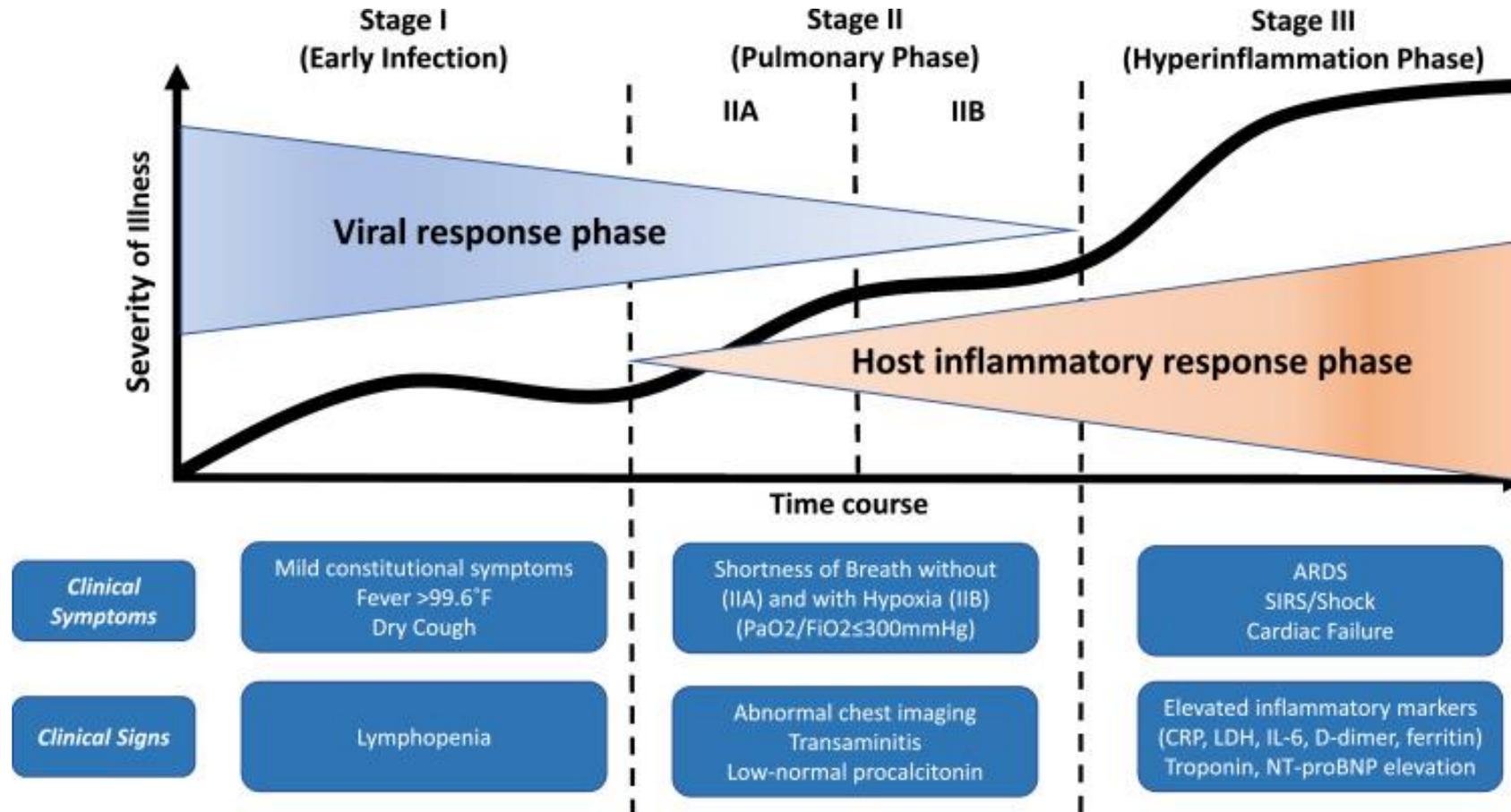


Clinical progression

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

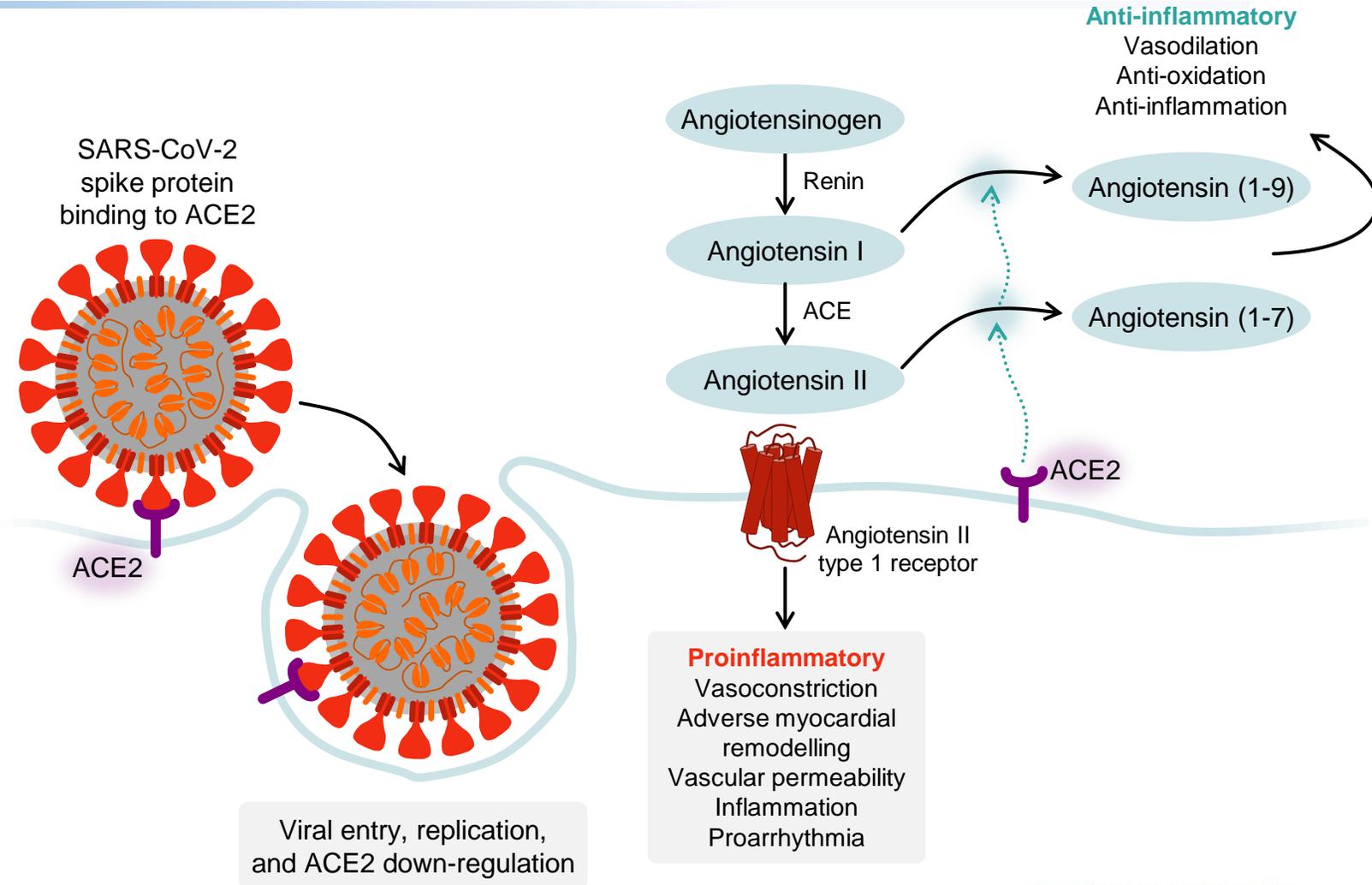
Infectious Diseases Management

Fundamental Parameters

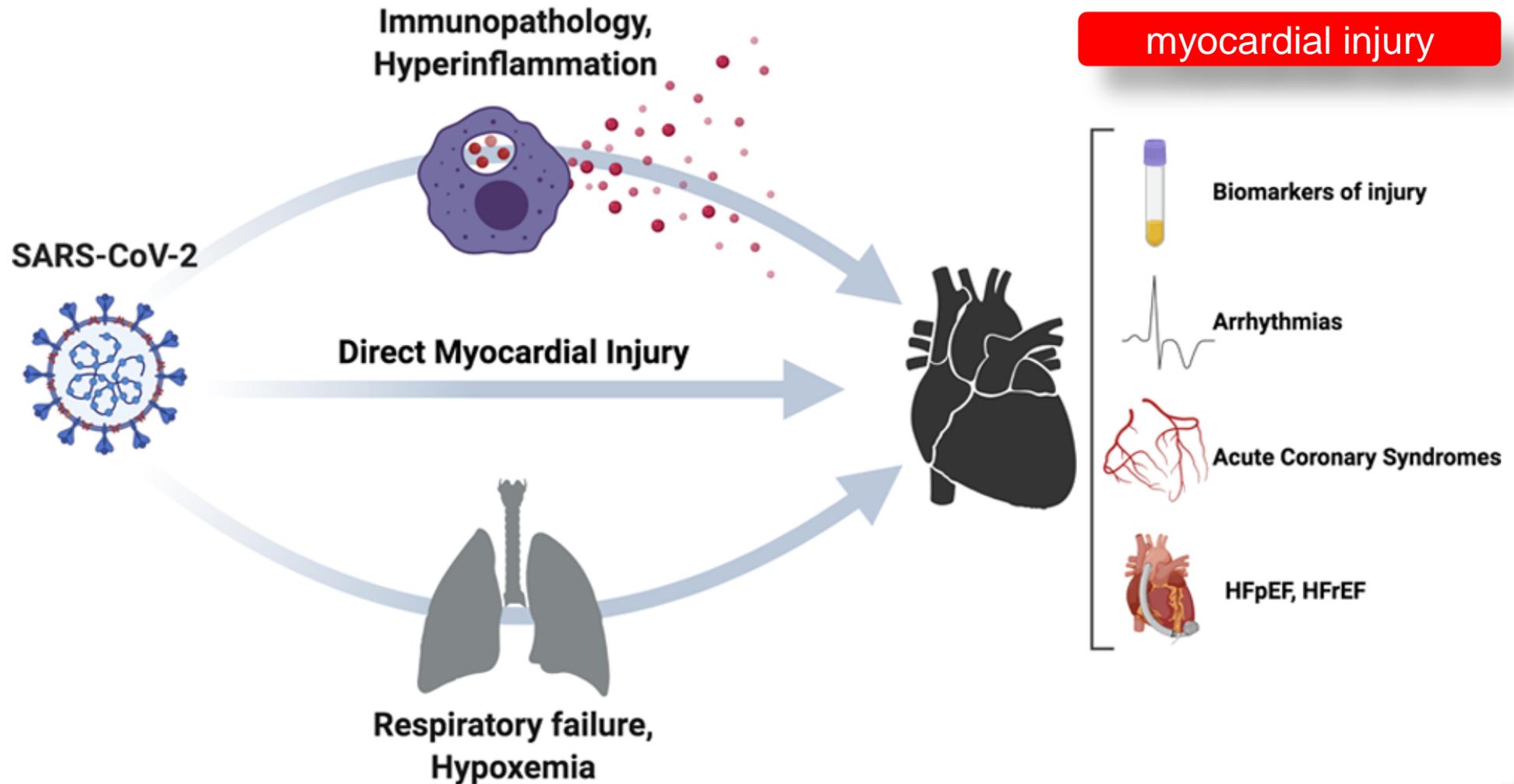


SARS-CoV-2 and ACE2

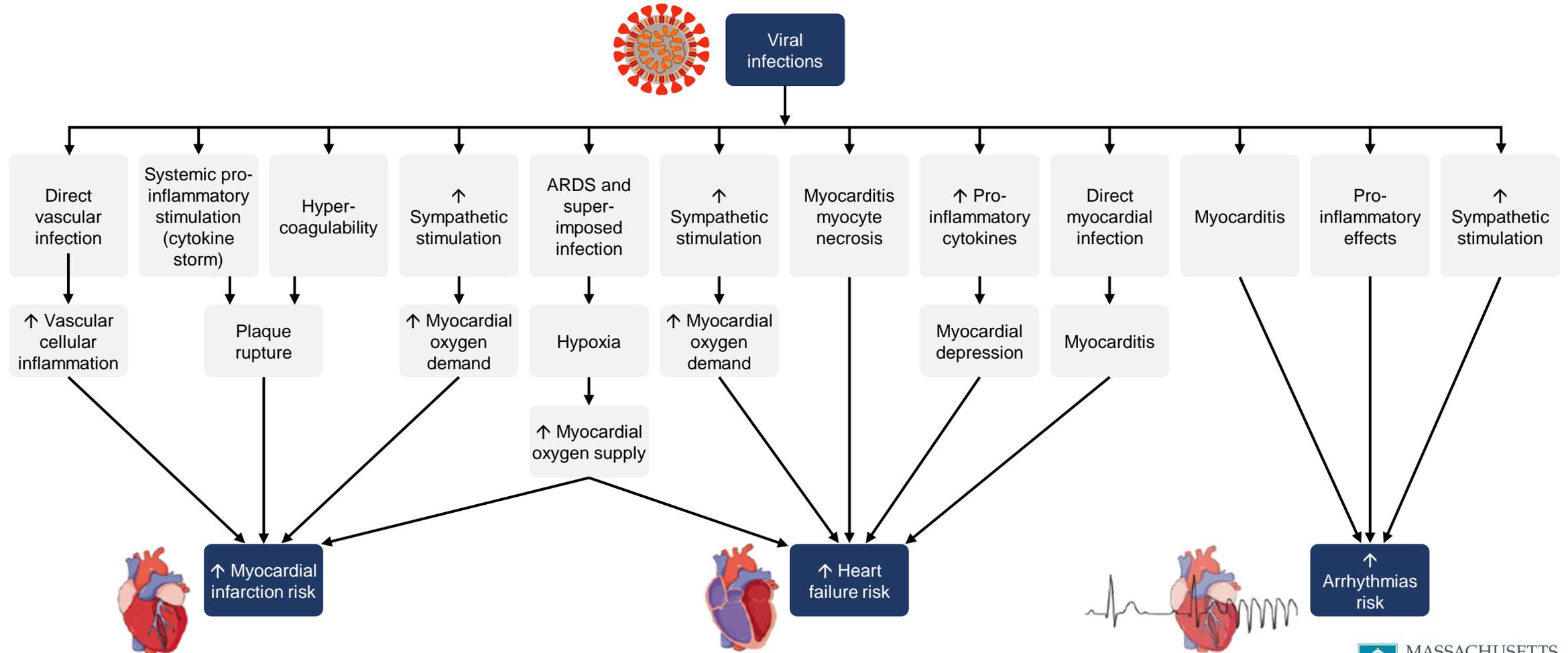
- **SARS-CoV-2** enters lung epithelial cells through binding to its functional receptor, **ACE2**
- ACE2 is a key modulator in the **renin-angiotensin-aldosterone system**
- **ACE2** is expressed broadly, including in the lungs, heart and kidneys



Cardiac manifestation of COVID-19



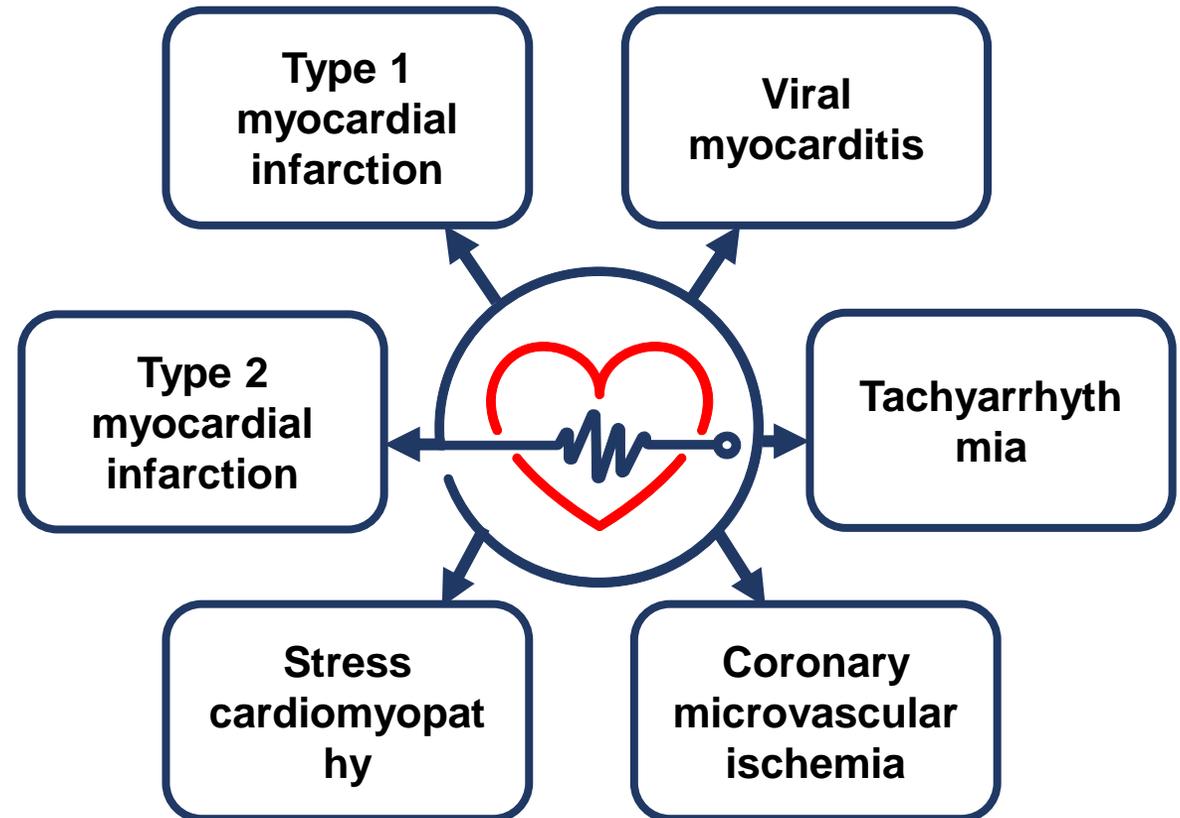
Potential mechanisms for acute effects of viral infections on cardiovascular system



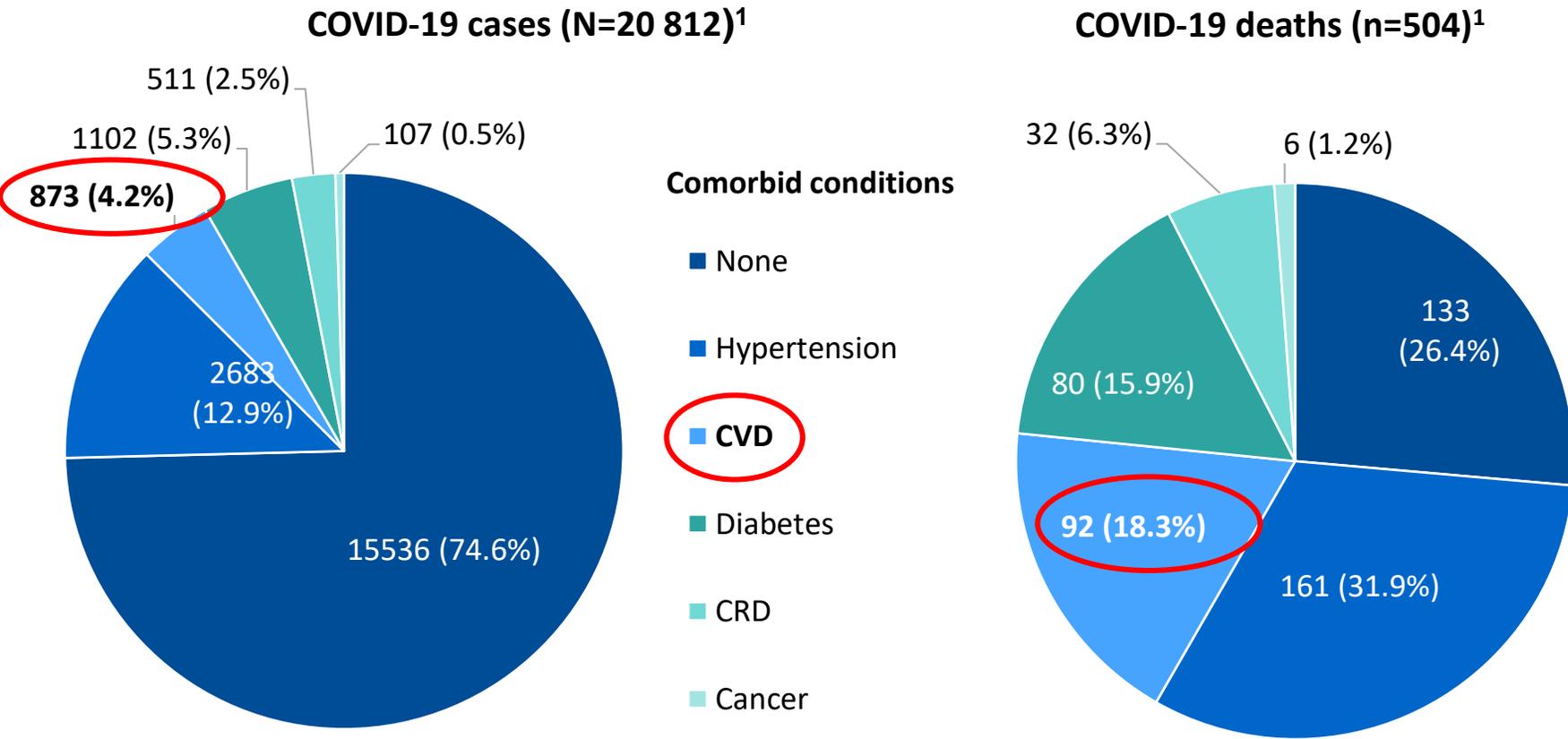
Cardiac stress/injury in patients with COVID-19

- **Cardiac complications** are common in patients with severe respiratory disease, e.g. pneumonia¹⁻³
- Acute cardiac injury has been reported in hospitalised patients with COVID-19⁴⁻⁷
- Initial findings suggest COVID-19-induced cardiac injury is more likely in **patients with underlying CVD**⁸
- Case reports of cardiac complications in CVD-naïve patients are emerging^{9,10}

Potential cardiac complications in COVID-19¹¹



COVID-19 in patients with cardiovascular disease



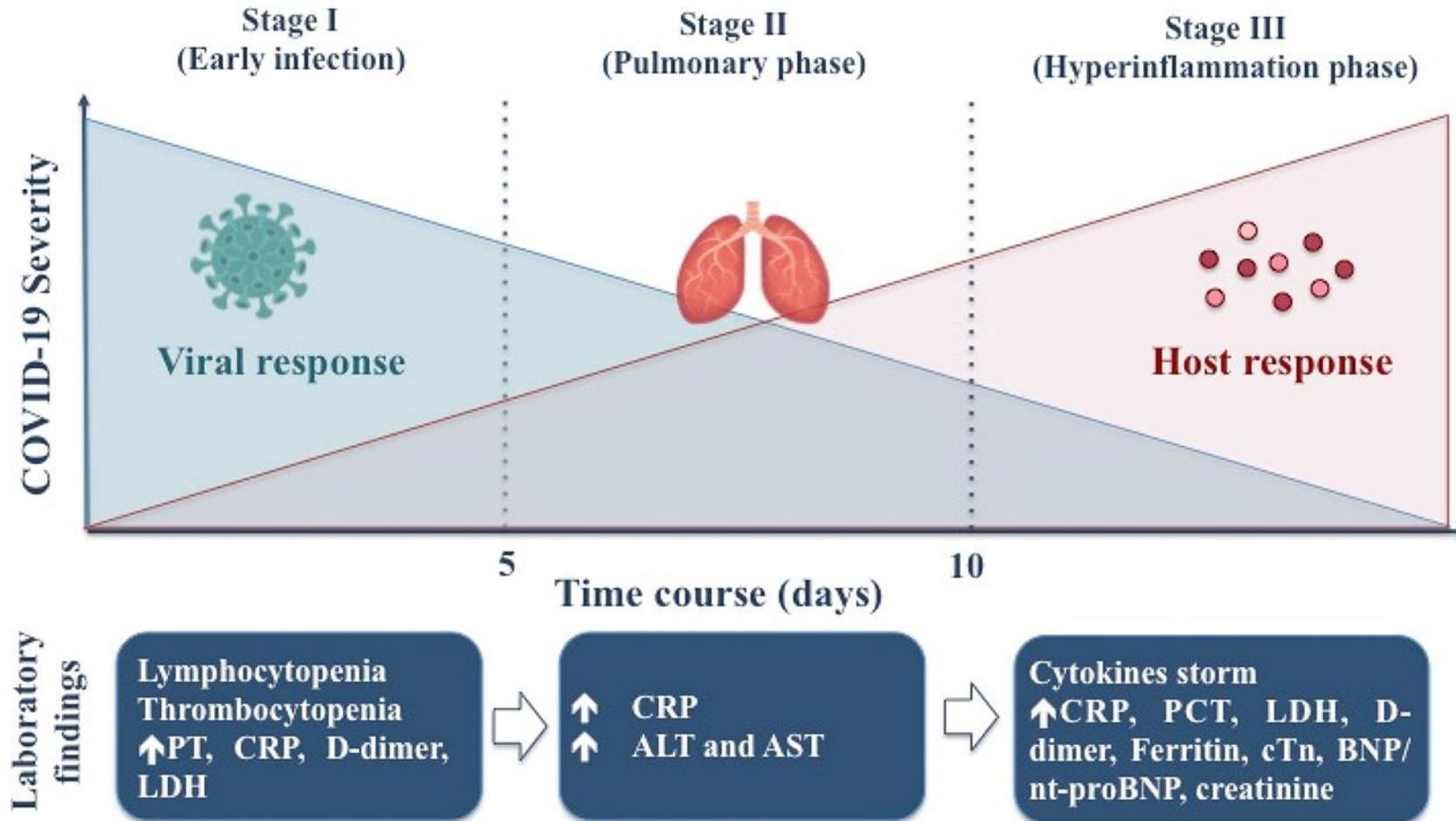
Underlying CAD was associated with increased risk of mortality (univariate analysis, N=191)²



Patients with underlying cardiovascular disease accounted for 4.2% of COVID-19 cases, but 18.3% of COVID-19 deaths¹

Cardiac Biomarkers in COVID-19





Abnormal biomarkers in COVID-19 patients

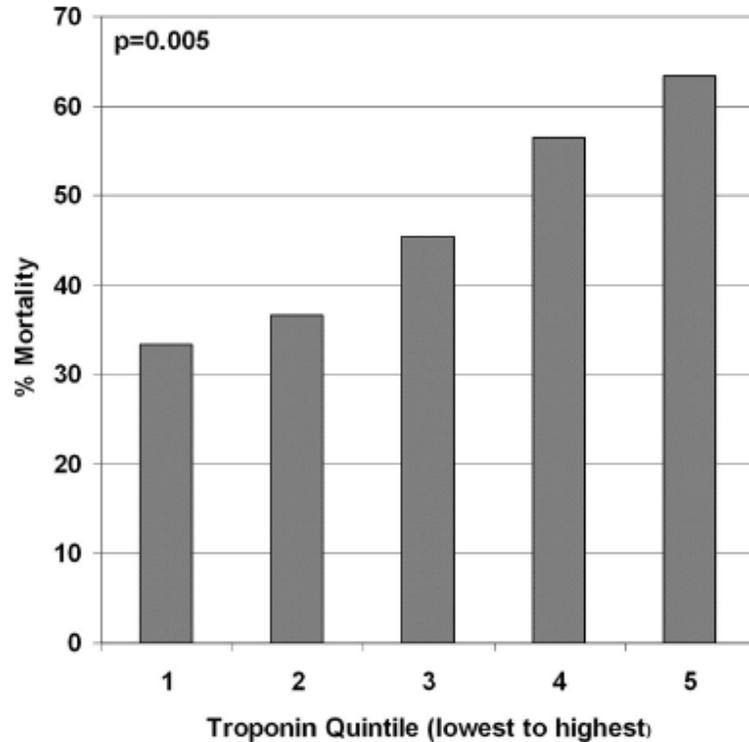
General chemistry	<ul style="list-style-type: none">• Albumin• Alanine/Aspartate aminotransferase• Bilirubin• Creatinine• Lactate• Lactic dehydrogenase
Cell counts	<ul style="list-style-type: none">• Leukocyte count (leukocytosis with lymphopenia)• Platelet count (thrombocytopenia)• Red blood cell distribution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

- 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

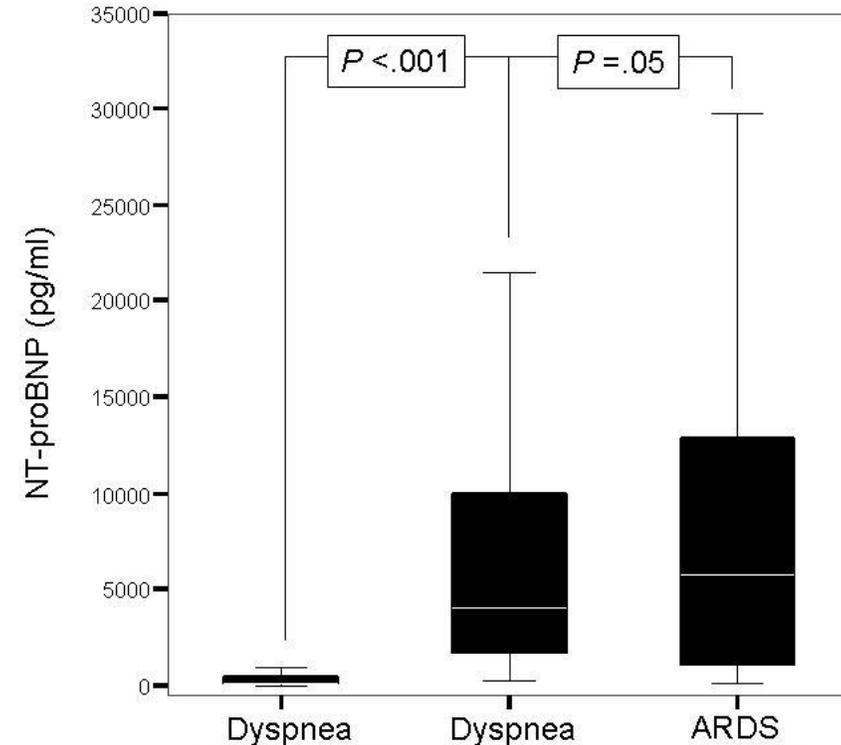
Everything old is new again...

Cardiac biomarkers in ARDS

Troponin



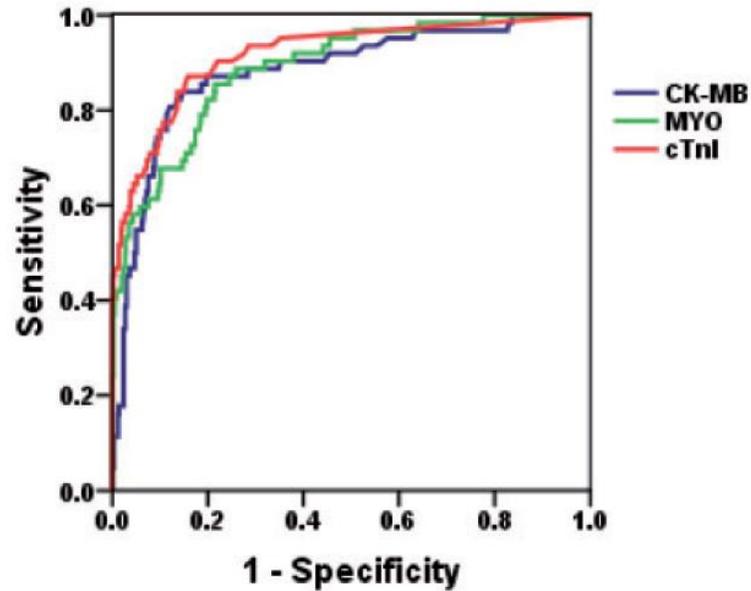
NT-proBNP



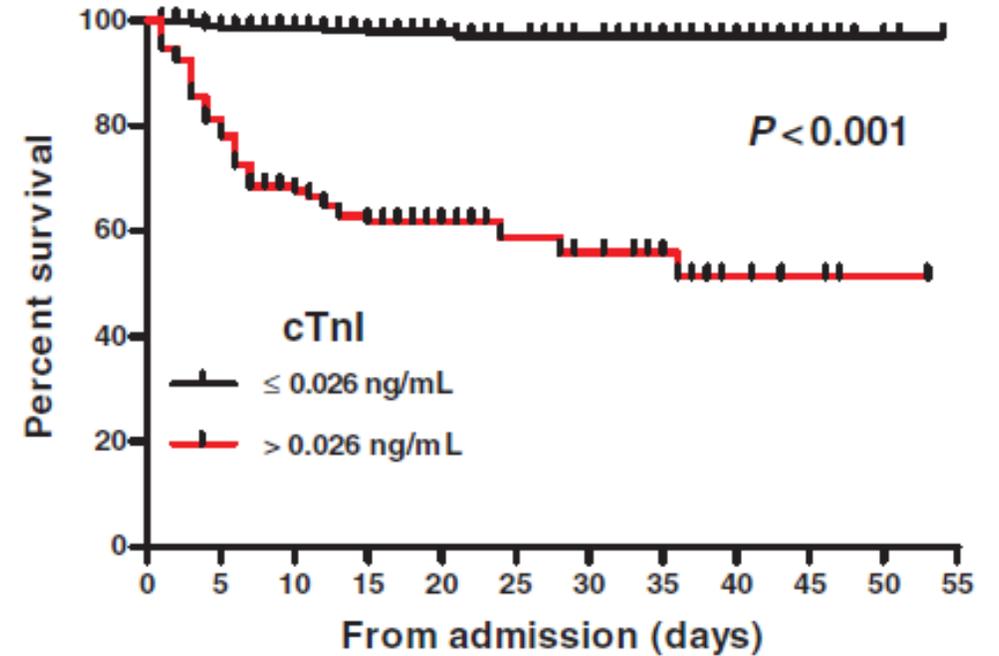
Hs-cTn and NT-proBNP powerful prognostic markers beyond primarily cardiac diseases

Myocardial injury in COVID-19

predictive value of troponin



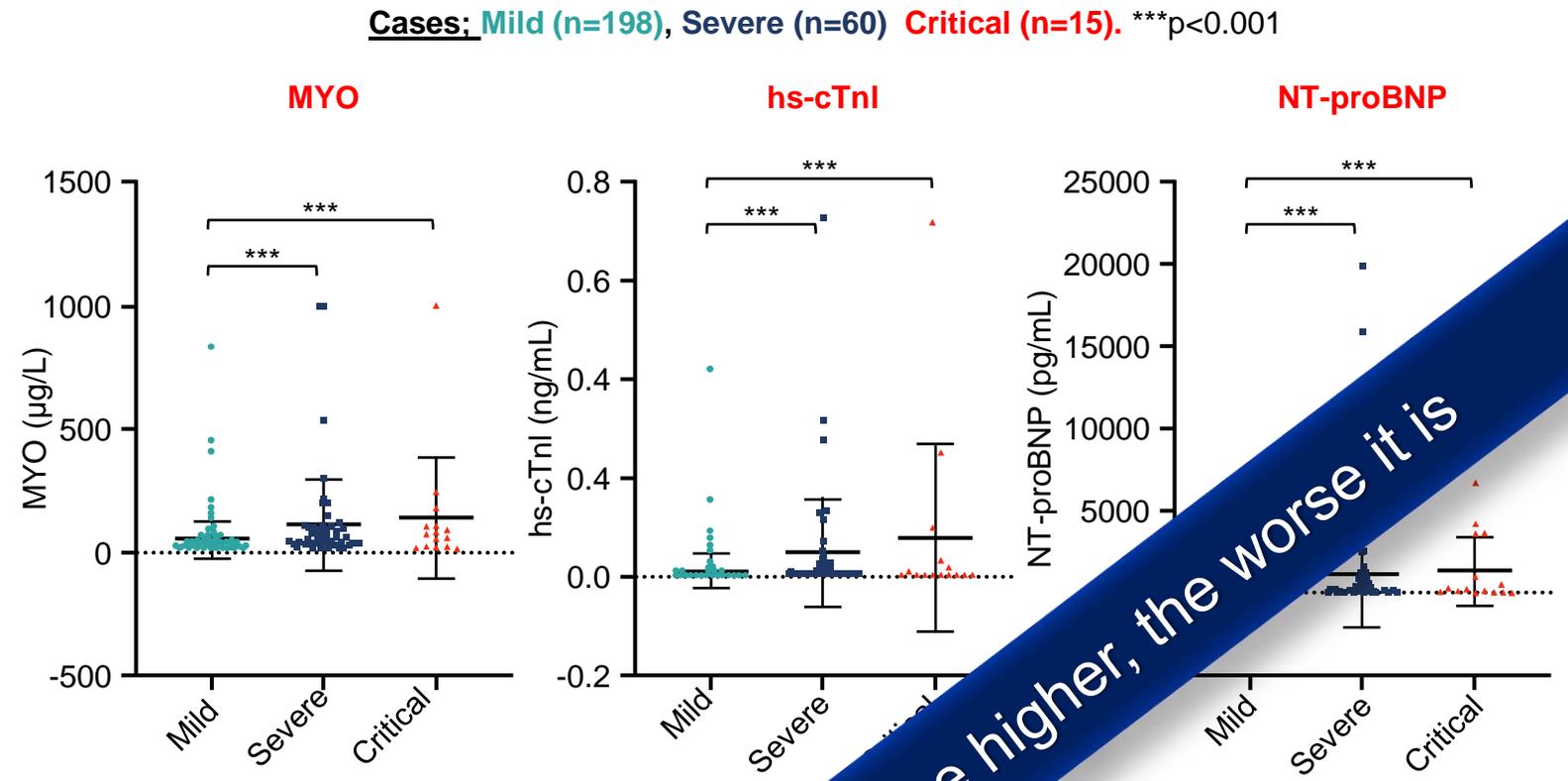
Variables	AUC	95% CI	Sensitivity	Specificity	P-value
CK-MB	0.87	0.81–0.93	0.81	0.87	<0.001
MYO	0.88	0.83–0.93	0.85	0.76	<0.001
cTnI	0.92	0.87–0.96	0.86	0.86	<0.001



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



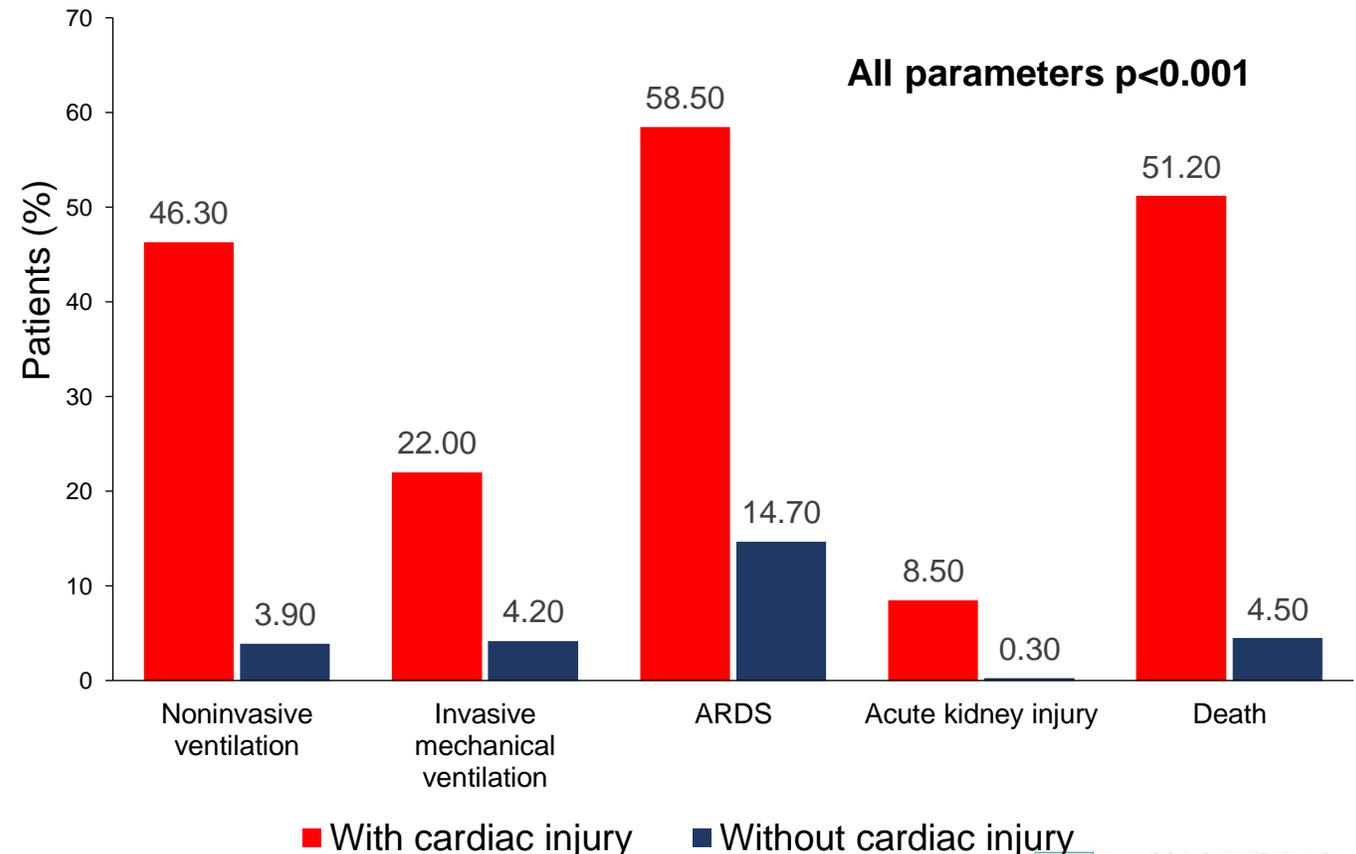
the higher, the worse it is

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 Δ 25 ng/L)¹
- In 416 COVID-19+ patients, **1 in 5** had myocardial injury when presenting to hospital²
- Patients with elevated hs-cTnI were more likely to need **invasive treatment**, develop **complications** and have **poorer clinical outcomes**²

Disease progression parameters for COVID-19 patients with or without myocardial injury²



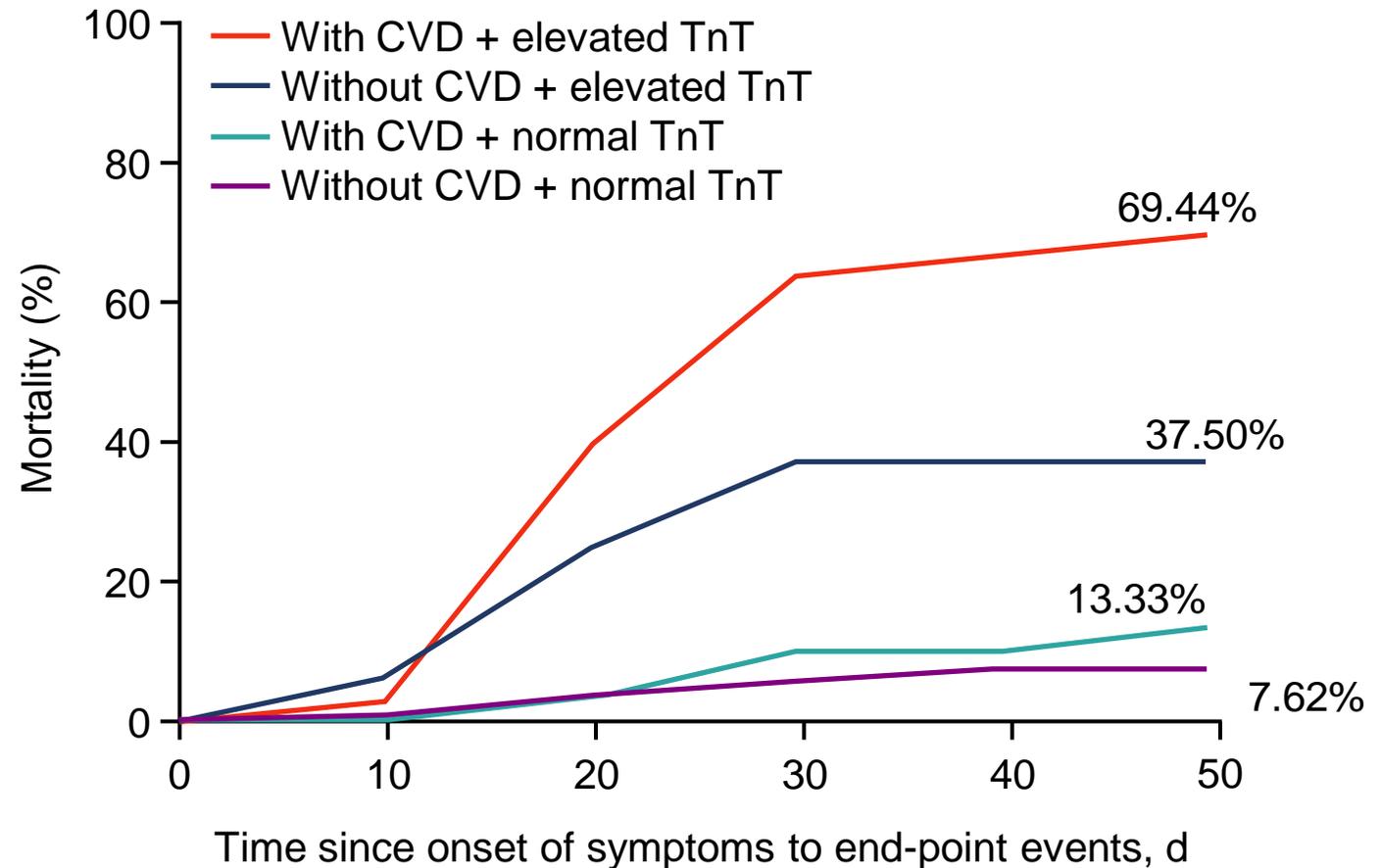
1. Lippi G et al. Prog Cardiovasc Dis. 2020; DOI:10.1016/j.pcad.2020.03.001

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

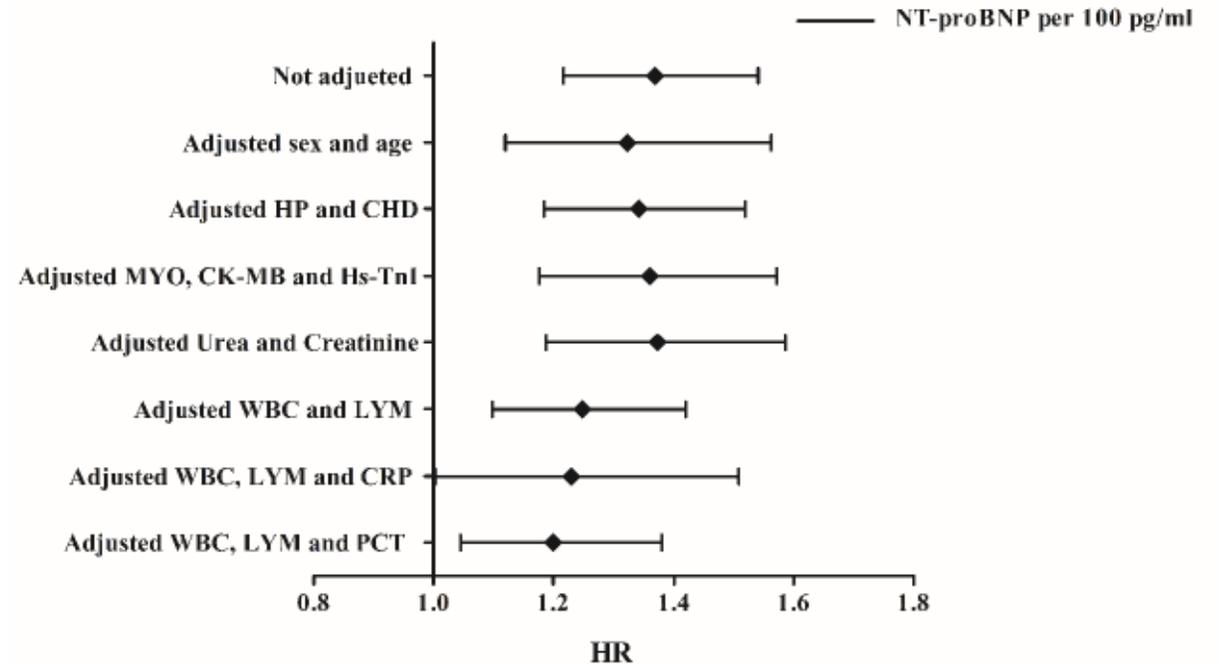
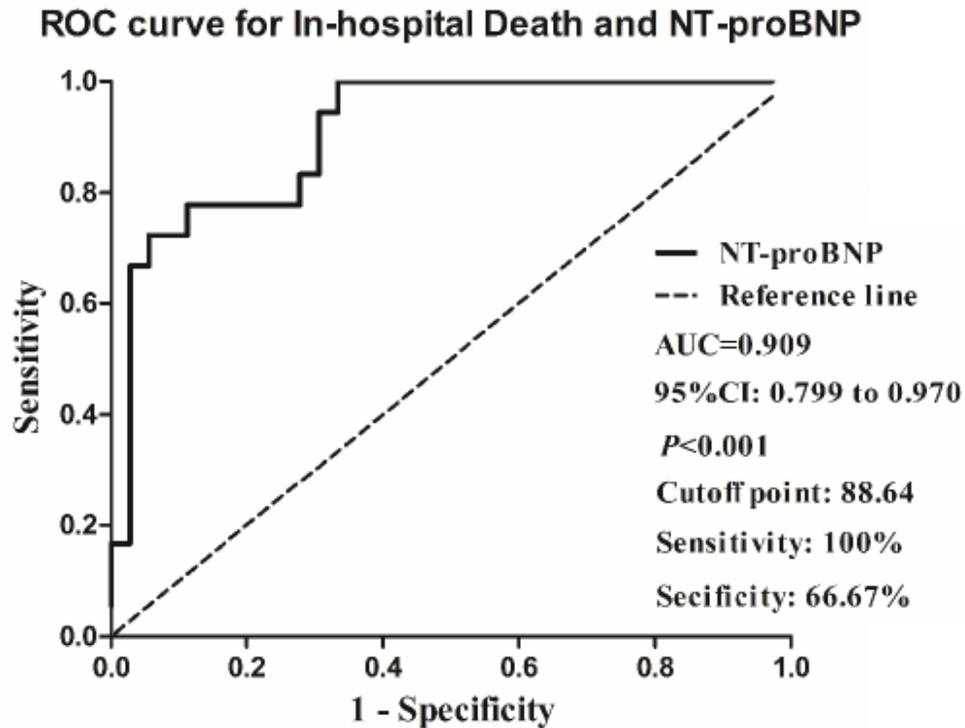


Mortality rate was higher in COVID-19 patients with elevated cTnT and underlying CVD

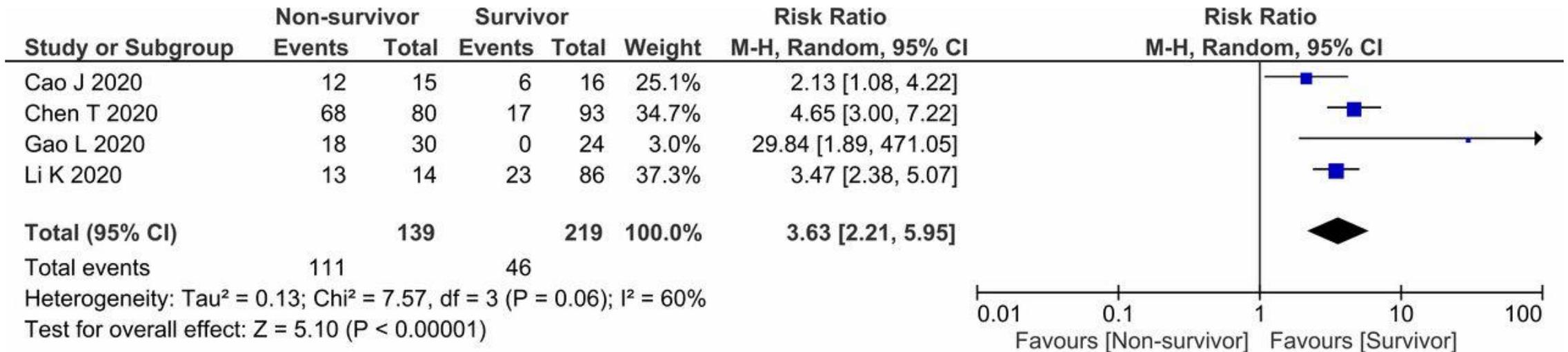
- In 187 hospitalised COVID-19+ patients, those with **underlying CVD** were more likely to have **cTnT elevation** (54.5%) versus those without CVD (13.2%)
- **Favorable prognosis** in patients with underlying CVD and normal cTnT levels (mortality rate **13.33%** vs. **69.44%** in patients with elevated 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

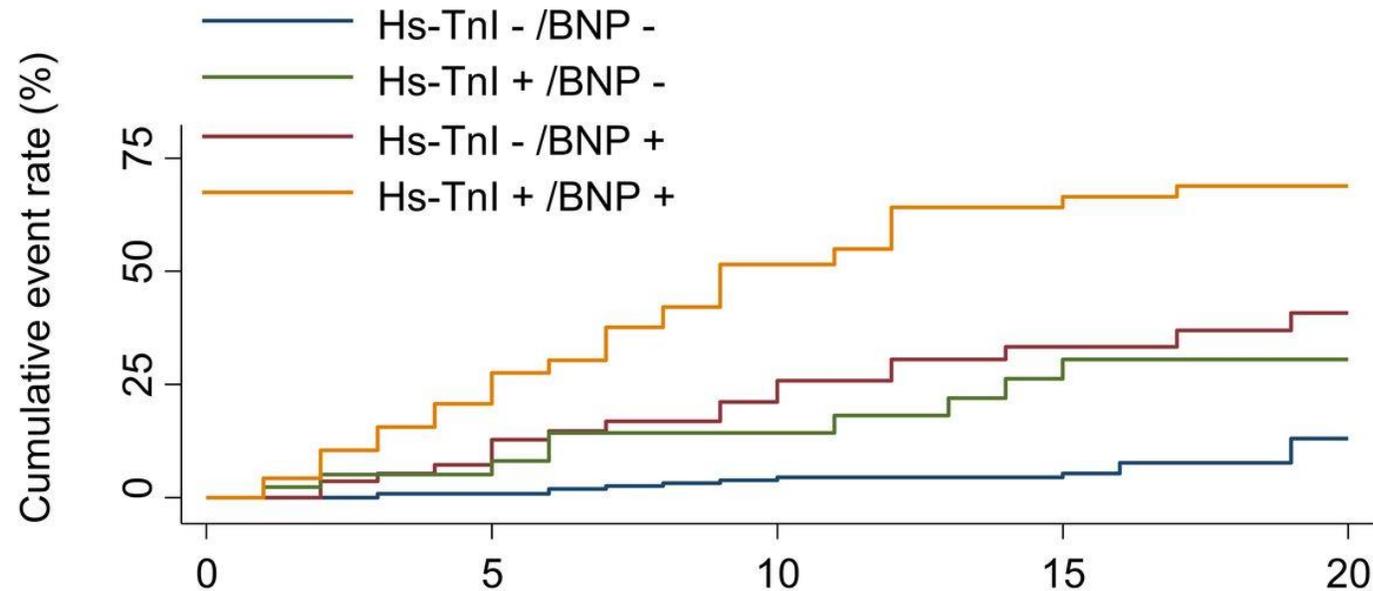


Natriuretic peptides and outcomes in COVID19



Additive value of hs-cTn and BNP

Cut-offs: hs-cTnI ≥ 19.6 ng/L, BNP ≥ 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**

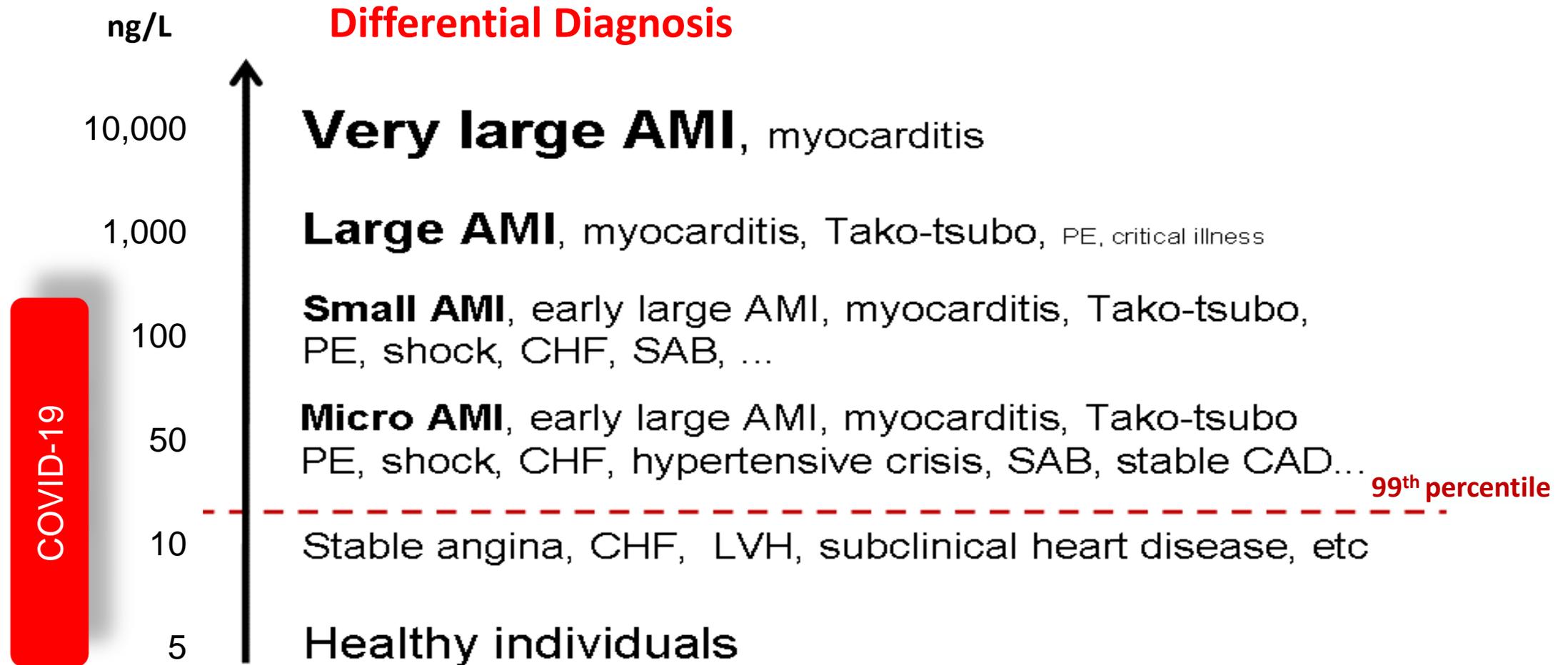
Frequency and **non-specific nature** of abnormal troponin or natriuretic peptide result

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



Myocardial injury

How to interpret troponin in COVID-19



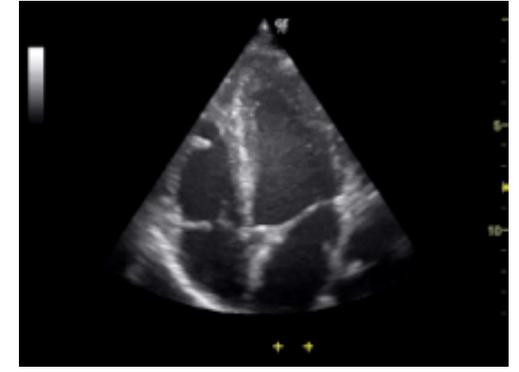
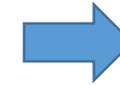
Myocardial injury

don't forget your standard tools

If concern?

Standard evaluation

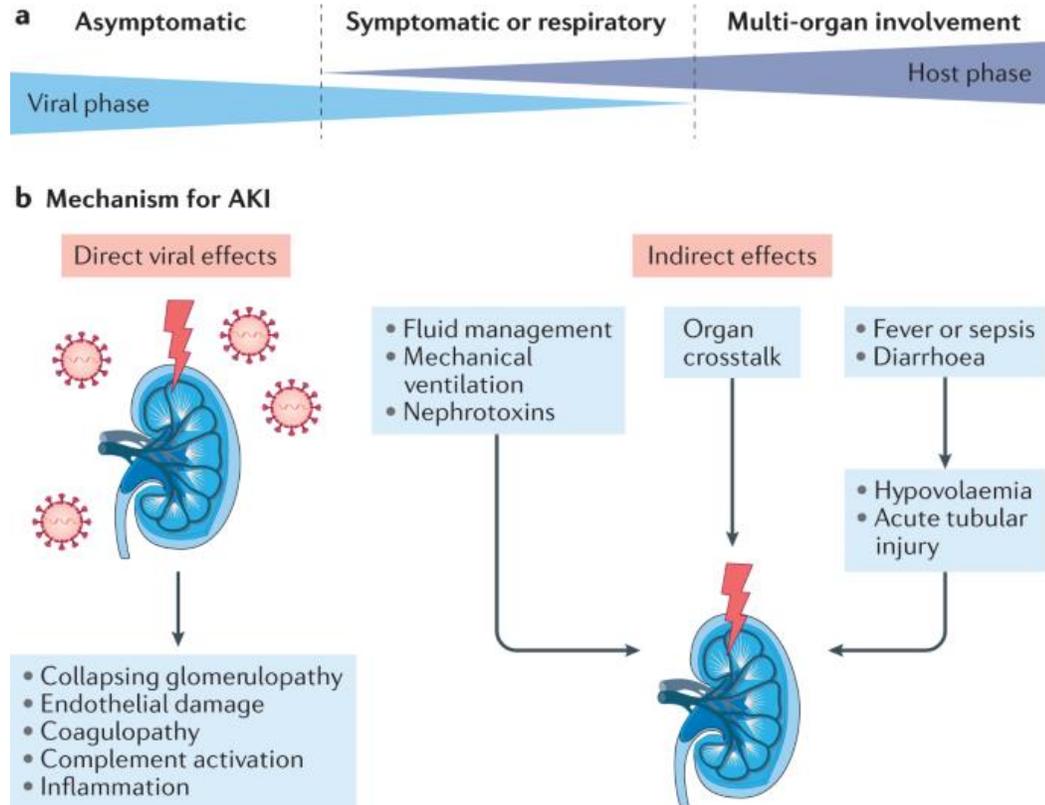
POCUS



Other complications of COVID19

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

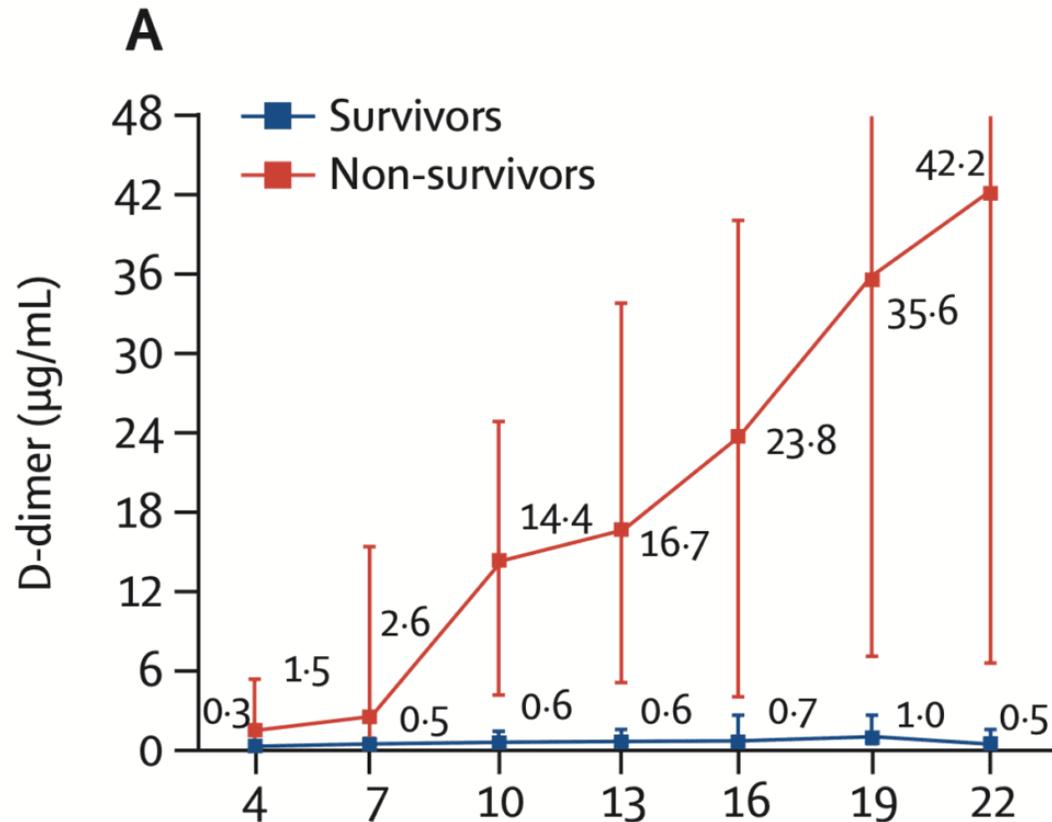
COVID19 and AKI



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**

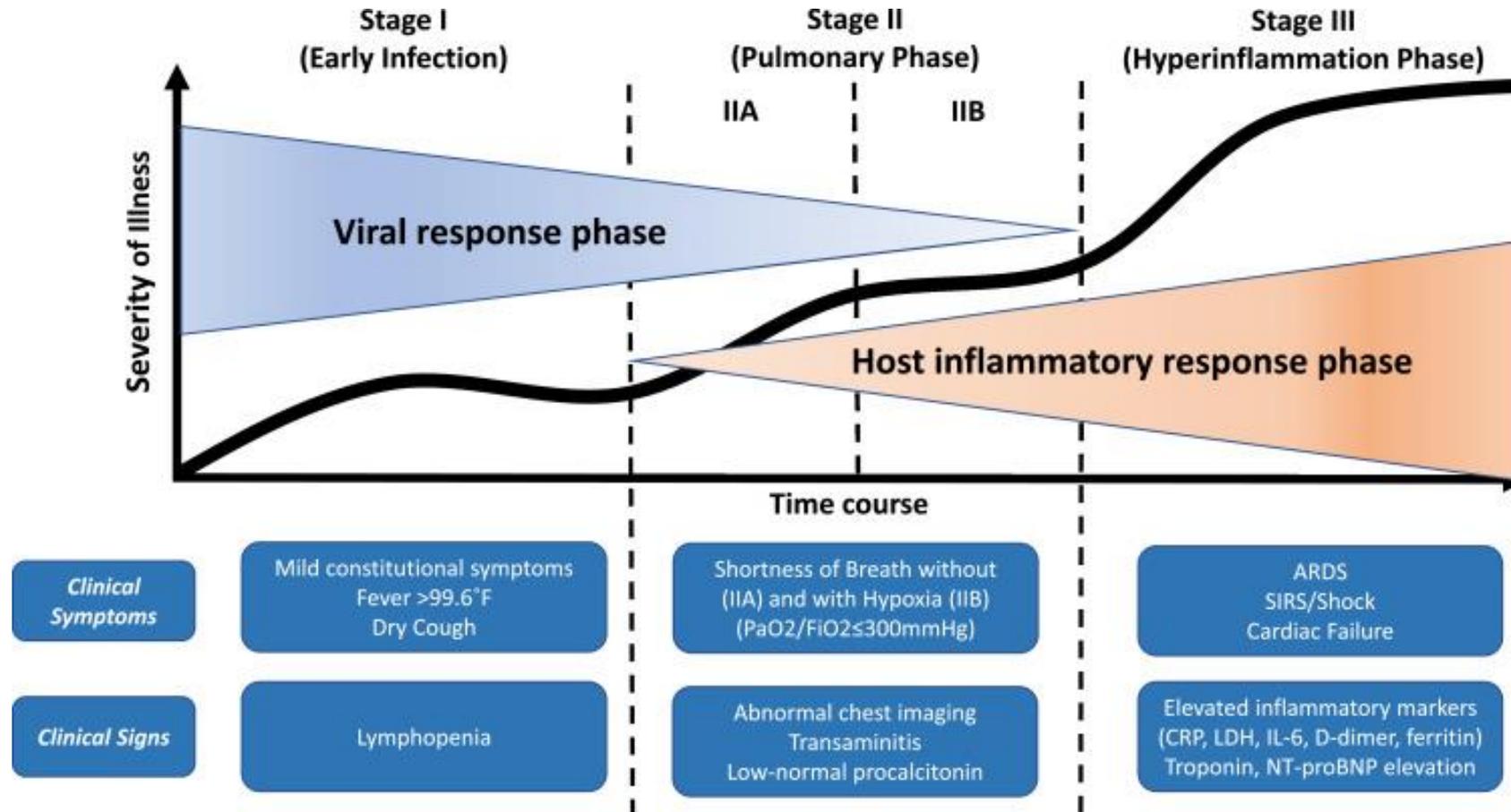
COVID19 and activation of coagulation



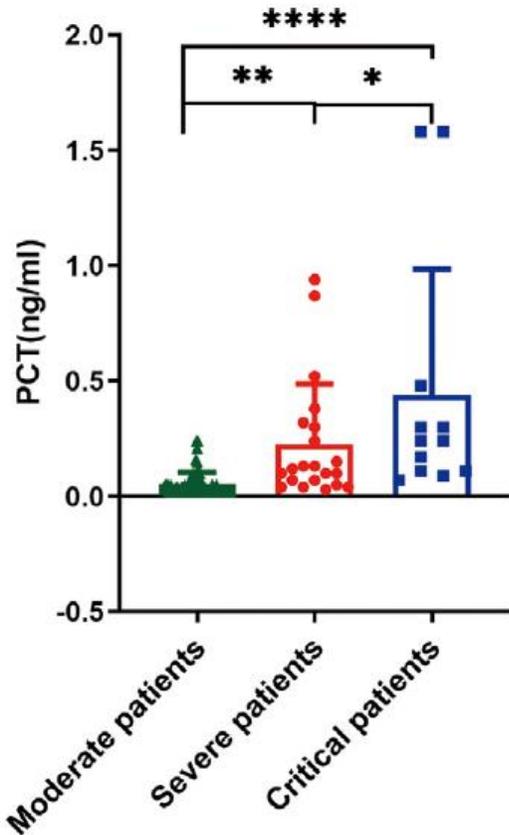
- **Thrombosis is common among patients with severe COVID19**
- **Elevated d-dimer is frequently noted among patients with COVID19**
- **Low d-dimer has excellent NPV for VTE while high d-dimer has lower PPV**
- **D-dimer is prognostic for adverse outcomes and when markedly elevated may be an indication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

Infectious Diseases Management

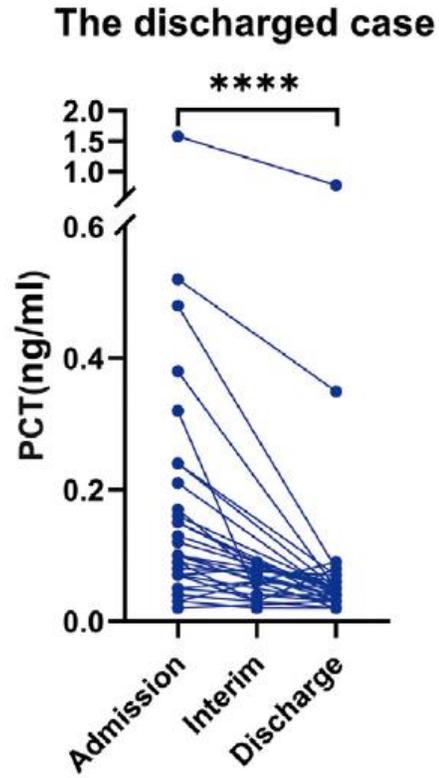
Fundamental Parameters



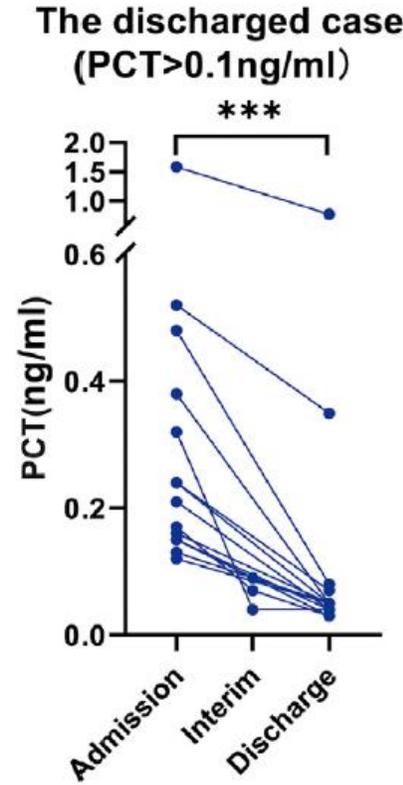
COVID19 and the role of procalcitonin (PCT)



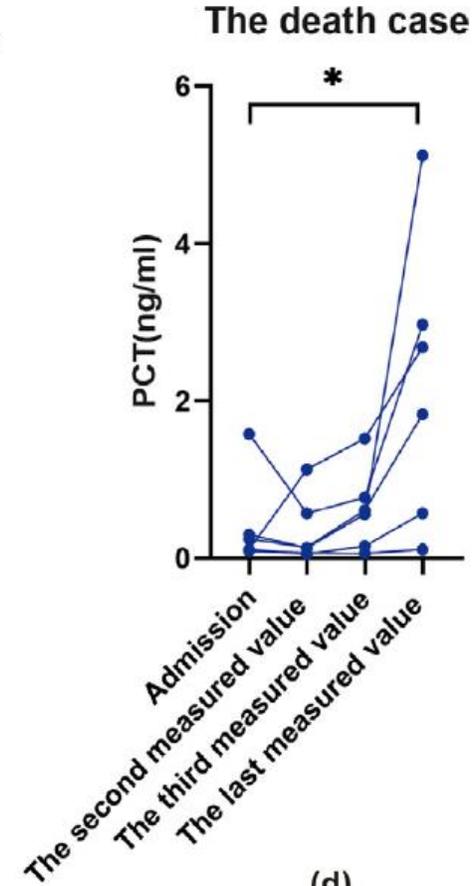
(a)



(b)



(c)



(d)

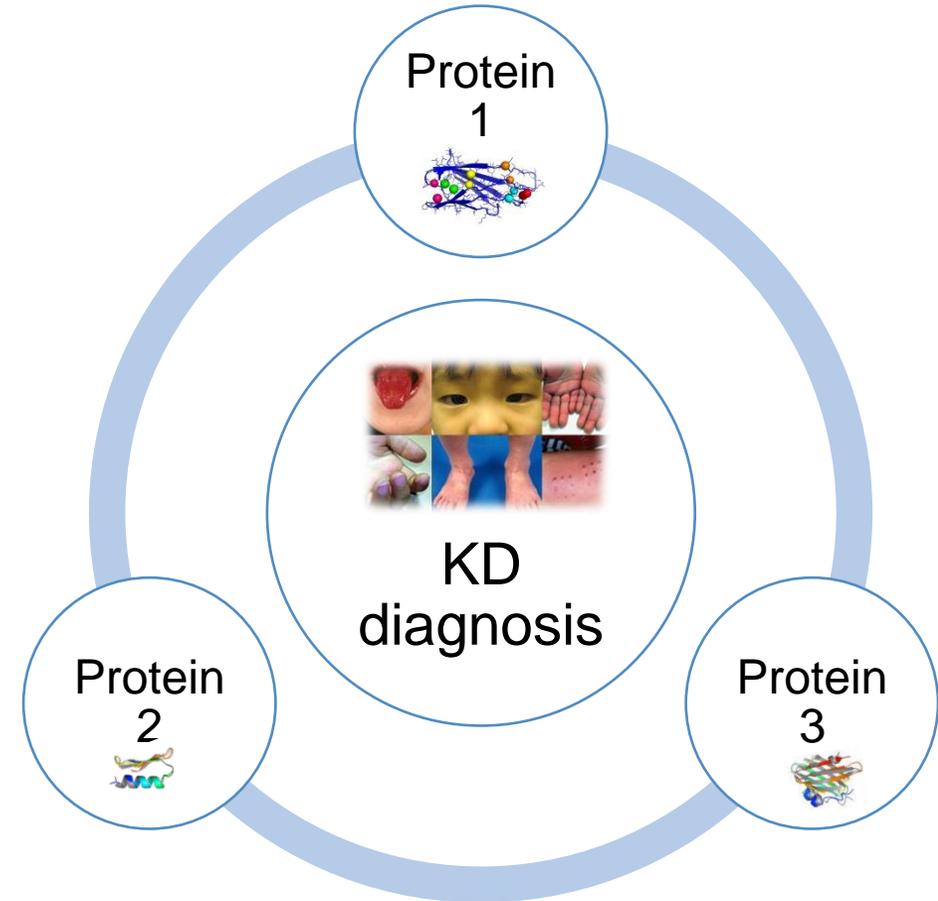
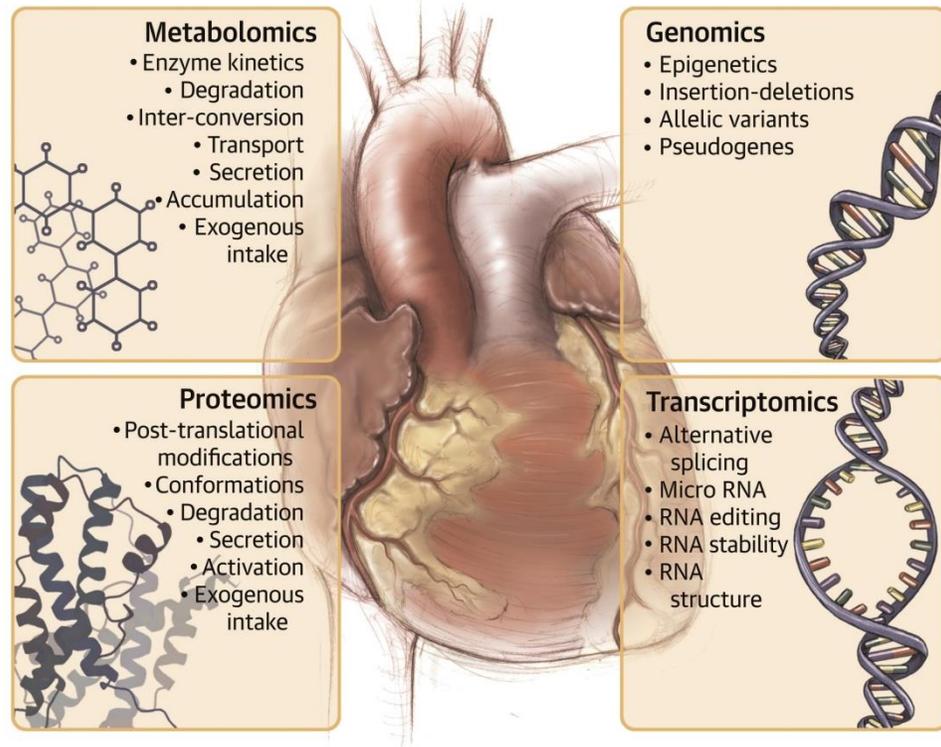
MISC-C in COVID19

- 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

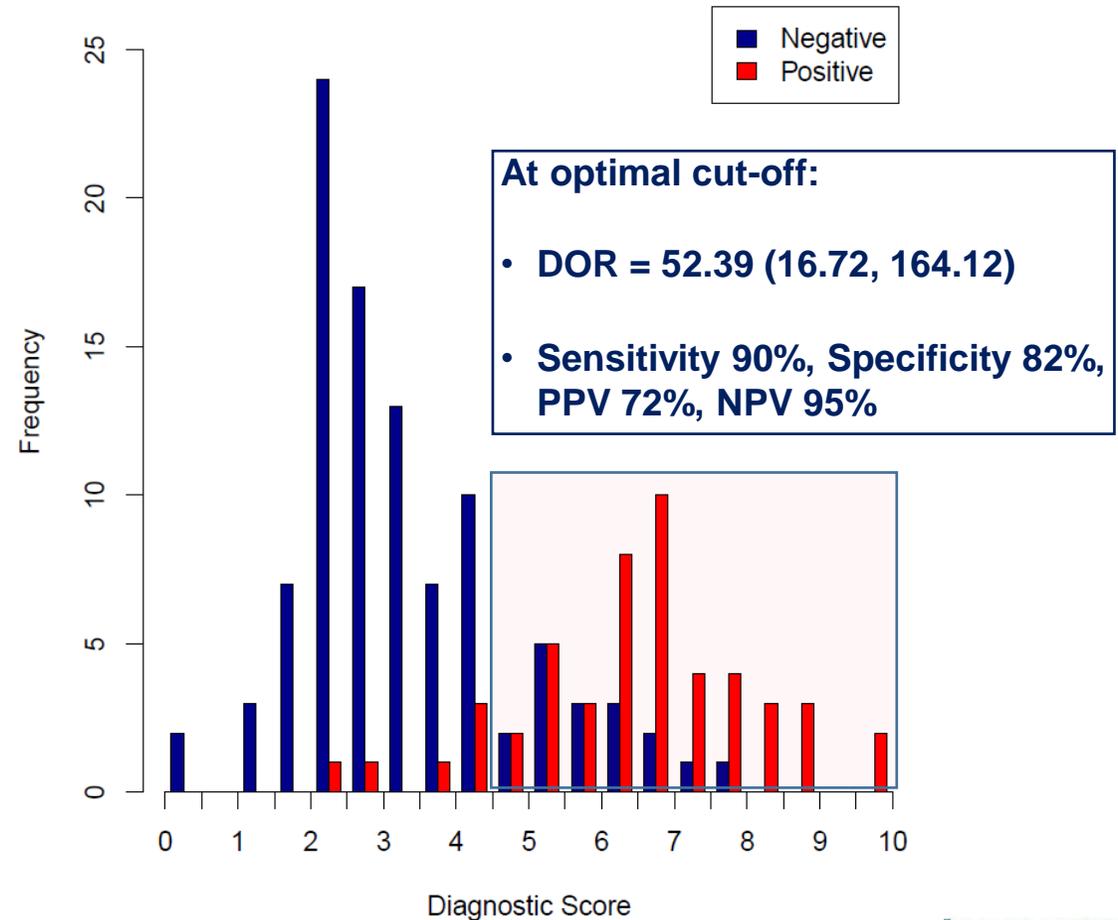
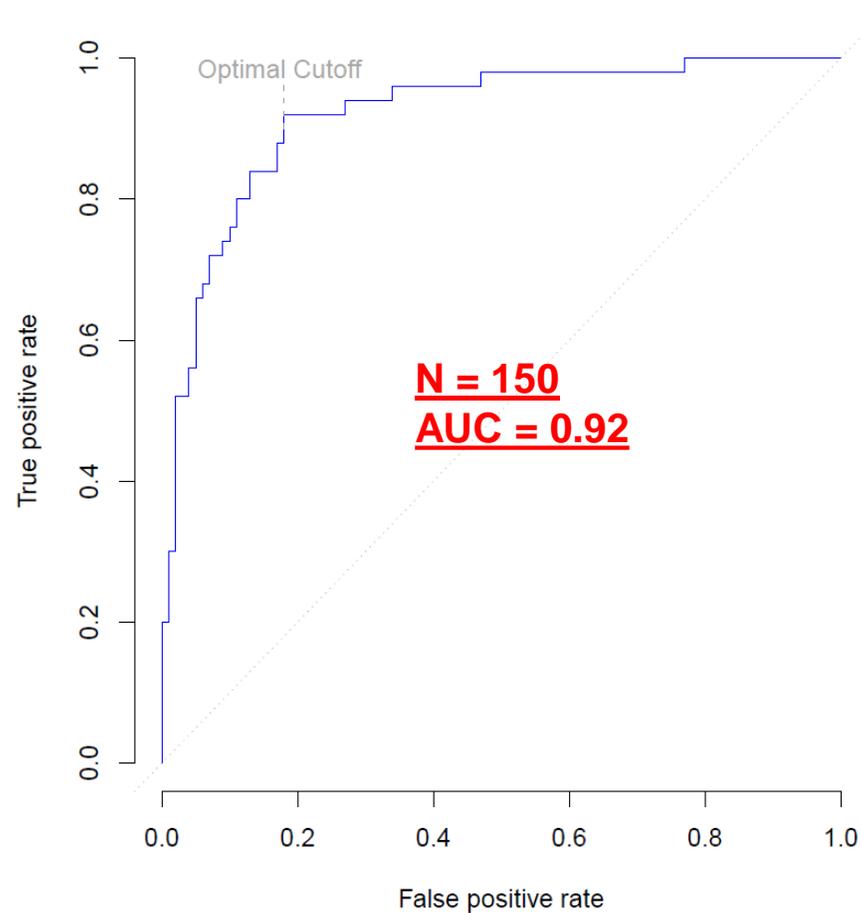
N=570

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%

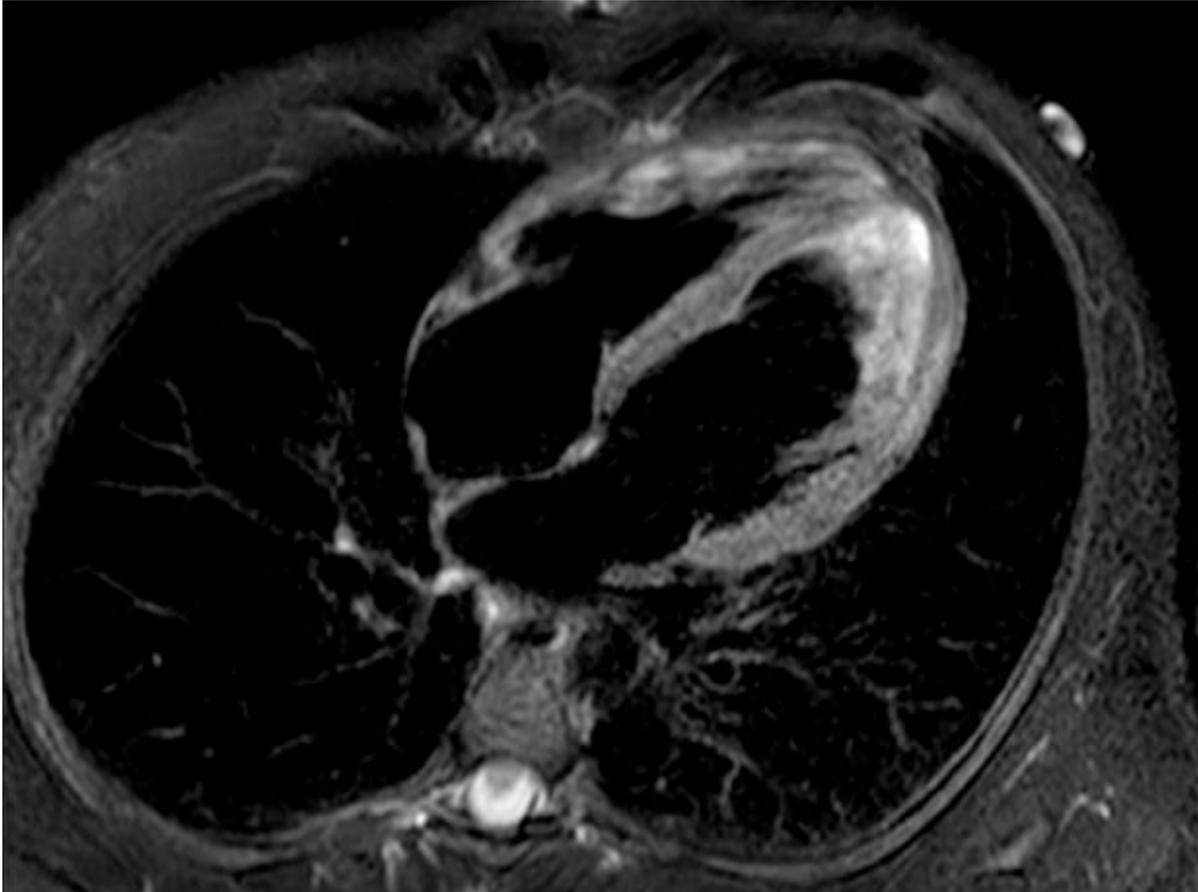
OMICs and a biomarker-based diagnostic for KD



Biomarker-based diagnosis of KD

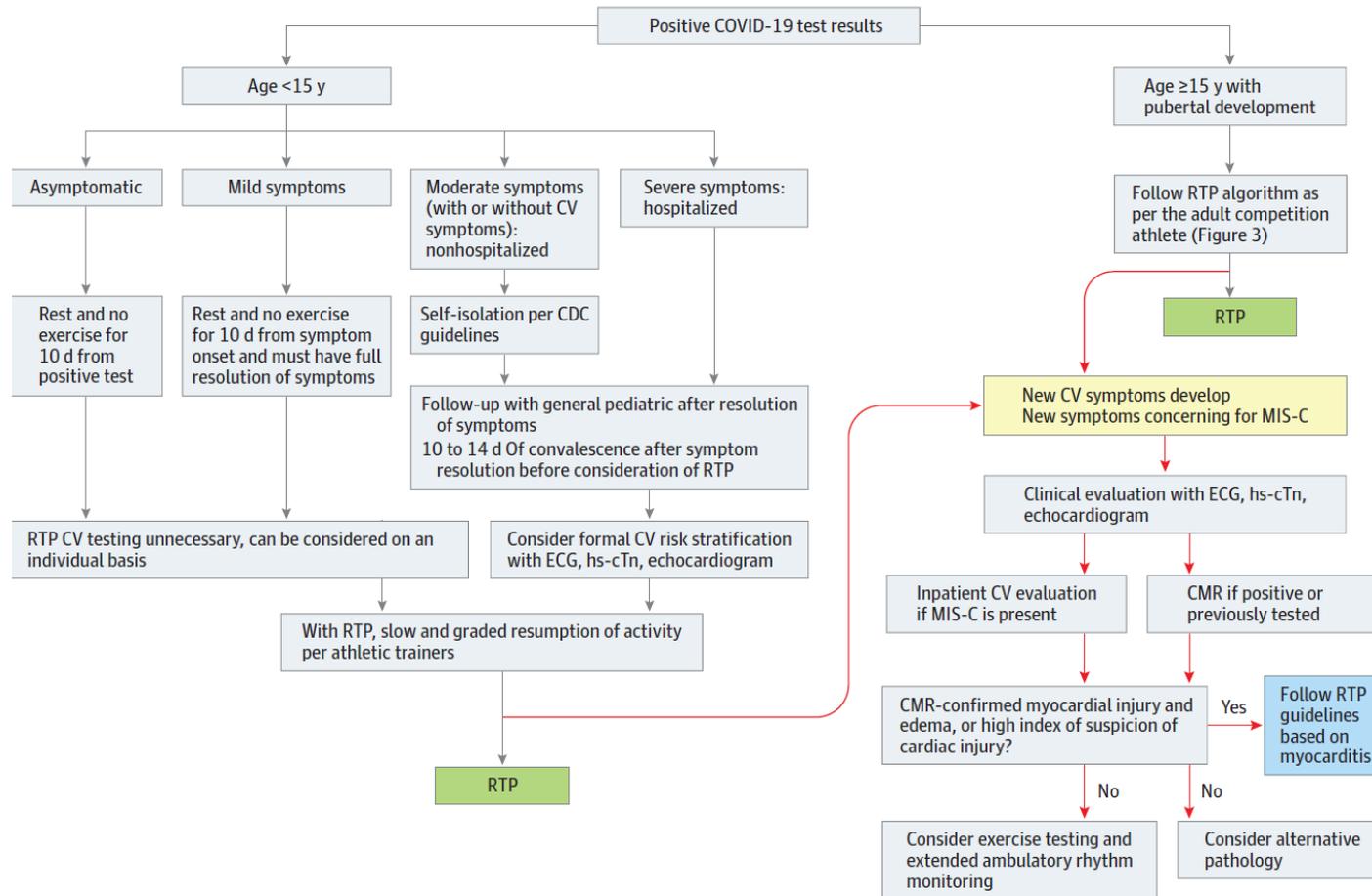


Special topic: COVID19 in athletes



- 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

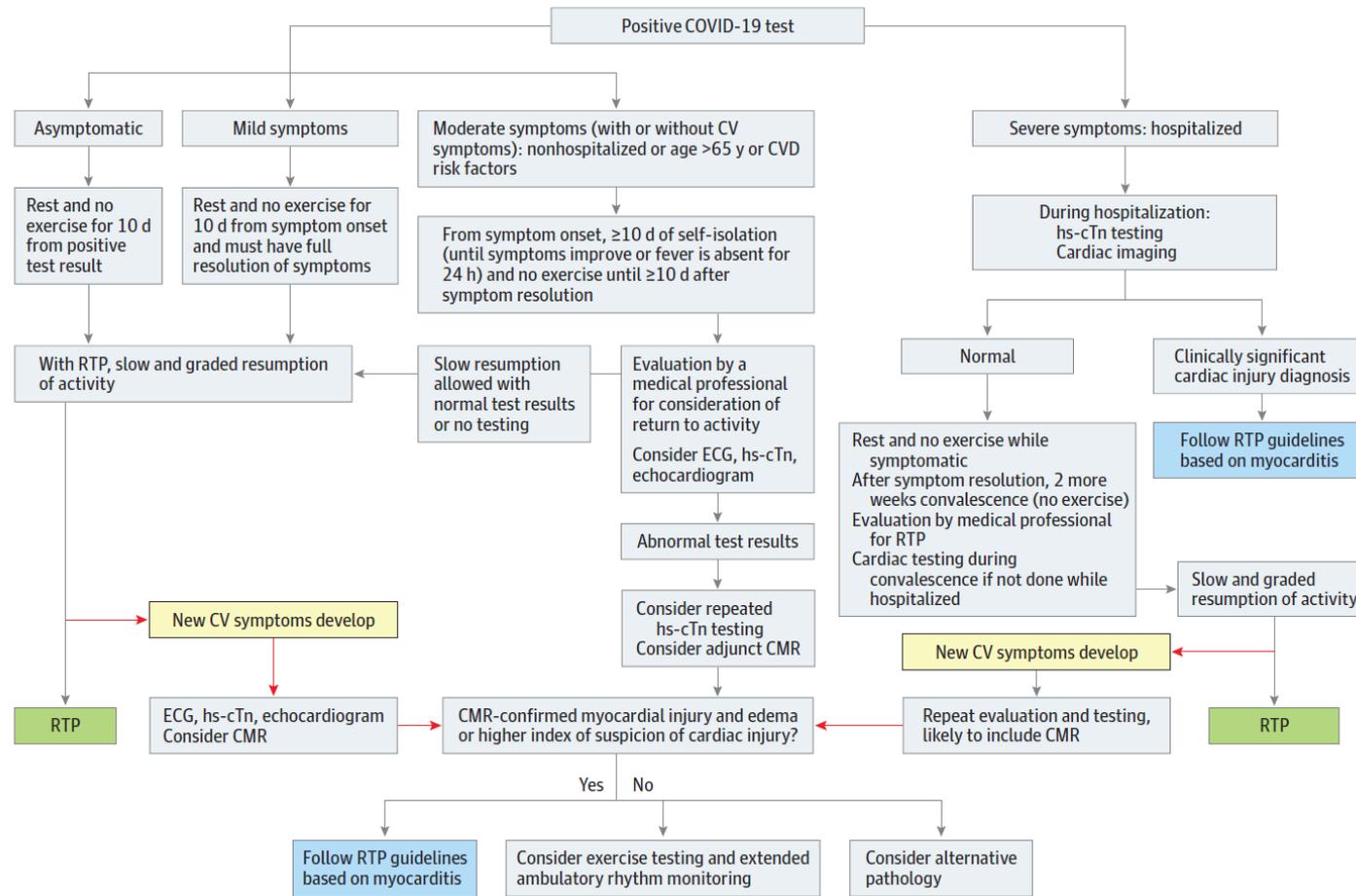
Management for younger athletes



- 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

- 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

- 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

- 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