Using Biomarkers to Inform COVID-19 Treatment

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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 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**

- **Stage I (Early Infection)**
  - Viral response phase
  - Clinically: Mild constitutional symptoms, Fever >99.6°F, Dry Cough

- **Stage II (Pulmonary Phase)**
  - Host inflammatory response phase
  - Clinically: Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FiO2 ≤ 300 mmHg)

- **Stage III (Hyperinflammation Phase)**
  - ARDS
  - SIRS/Shock
  - Cardiac Failure
  - Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
  - Troponin, NT-proBNP elevation

**Clinical Symptoms**
- Mild constitutional symptoms
- Fever >99.6°F
- Dry Cough

**Clinical Signs**
- Lymphopenia
- Abnormal chest imaging
- Transaminits
- Low-normal procalcitonin
**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

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**Angiotensin Converting Enzyme (ACE) System**

- Angiotensinogen $\rightarrow$ Renin $\rightarrow$ Angiotensin I $\rightarrow$ ACE $\rightarrow$ Angiotensin II

**SARS-CoV-2 Spike Protein Binding to ACE2**

**Viral entry, replication, and ACE2 down-regulation**

**Proinflammatory**
- Vasoconstriction
- Adverse myocardial remodelling
- Vascular permeability
- Inflammation
- Proarrhythmia

**Anti-inflammatory**
- Vasodilation
- Anti-oxidation
- Anti-inflammation

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ACE, angiotensin converting enzyme; COVID-19, coronavirus disease 2019; CV, cardiovascular; SARS-CoV, severe acute respiratory syndrome coronavirus.

Cardiac manifestation of COVID-19

- Immunopathology, Hyperinflammation
- Direct Myocardial Injury
- Respiratory failure, Hypoxemia

SARS-CoV-2

myocardial injury

- Biomarkers of injury
- Arrhythmias
- Acute Coronary Syndromes
- HFpEF, HFrEF

Akhmerov and Marban, Circ Res 2020
Potential mechanisms for acute effects of viral infections on cardiovascular system

- Direct vascular infection
  - Systemic pro-inflammatory stimulation (cytokine storm)
  - Hyper-coagulability
  - ARDS and super-imposed infection
  - Sympathetic stimulation
  - Myocarditis
  - Myocyte necrosis
  - Pro-inflammatory cytokines

- Myocardial oxygen demand
  - Hypoxia
  - Myocardial depression
  - Myocardial oxygen supply

- Myocardial infarction risk
  - Myocardial oxygen demand
  - Myocardial oxygen supply

- Heart failure risk
  - Myocardial depression
  - Myocardial oxygen supply

- Arrhythmias risk
  - Myocarditis
  - Pro-inflammatory effects

Cardiac stress/injury in patients with COVID-19

- **Cardiac complications** are common in patients with severe respiratory disease, e.g. pneumonia

- Acute cardiac injury has been reported in hospitalised patients with COVID-19

- Initial findings suggest COVID-19-induced cardiac injury is more likely in patients with underlying CVD

- Case reports of cardiac complications in CVD-naïve patients are emerging
COVID-19 in patients with cardiovascular disease

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

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

\[
\text{OR} = 21.40 \\
(95\% \text{ CI 4.64–98.76, } p<0.0001)
\]

Comorbid conditions
- None
- Hypertension
- CVD
- Diabetes
- CRD
- Cancer

COVID-19 cases (N=20 812)
- 15536 (74.6%)
- 2683 (12.9%)
- 107 (0.5%)
- 511 (2.5%)
- 1102 (5.3%)
- 873 (4.2%)

COVID-19 deaths (n=504)
- 161 (31.9%)
- 80 (15.9%)
- 32 (6.3%)
- 133 (26.4%)
- 6 (1.2%)
- 92 (18.3%)

CAD, coronary artery disease; CI, confidence interval; COVID-19, coronavirus disease 2019; CRD, chronic respiratory disease; CVD, cardiovascular disease; OR, odds ratio

Cardiac Biomarkers in COVID-19
**Stage I** (Early infection)  
Viral response

**Stage II** (Pulmonary phase)

**Stage III** (Hyperinflammation phase)

**COVID-19 Severity**

**Time course (days)**
5  
10

**Laboratory findings**
Lymphocytopenia  
Thrombocytopenia  
PT, CRP, D-dimer, LDH

CRP  
ALT and AST

Cytokines storm  
CRP, PCT, LDH, D-dimer, Ferritin, cTn, BNP/nt-proBNP, creatinine
## Abnormal biomarkers in COVID-19 patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Biomarkers</th>
</tr>
</thead>
</table>
| **General chemistry**           | • Albumin  
• Alanine/Aspartate aminotransferase  
• Bilirubin  
• Creatinine  
• Lactate  
• Lactic dehydrogenase |
| **Cell counts**                 | • Leukocyte count (leukocytosis with lymphopenia)  
• Platelet count (thrombocytopenia)  
• Red blood cell distribution width |
| **Inflammatory/acute phase markers** | • C-reactive protein  
• Ferritin  
• Interleukin-1  
• Interleukin-2R  
• Interleukin-6  
• Interleukin-10  
• Procalcitonin  
• Tumor necrosis factor α |
| **Thrombosis/hemostasis**       | • D-dimer |
| **Cardiac markers**             | • 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*

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

*Bajwa, et al, Crit Care Med, 2008*
Myocardial injury in COVID-19
predictive value of troponin

Predictive value of cardiac biomarkers in COVID-19

- **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

Levels of biomarkers in patients with COVID-19 by severity

**Cases:** Mild (n=198), Severe (n=60) Critical (n=15). ***p<0.001

COVID-19, coronavirus disease 2019; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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 hospital\(^2\)

- Patients with elevated hs-cTnI were more likely to need invasive treatment, develop complications and have poorer clinical outcomes\(^2\)

<table>
<thead>
<tr>
<th>Disease Progression Parameters</th>
<th>With Cardiac Injury</th>
<th>Without Cardiac Injury</th>
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</thead>
<tbody>
<tr>
<td>Noninvasive ventilation</td>
<td>46.30</td>
<td>3.90</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>22.00</td>
<td>4.20</td>
</tr>
<tr>
<td>ARDS</td>
<td>58.50</td>
<td>14.70</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>8.50</td>
<td>0.30</td>
</tr>
<tr>
<td>Death</td>
<td>51.20</td>
<td>4.50</td>
</tr>
</tbody>
</table>

All parameters p<0.001

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

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NT-proBNP and outcomes in COVID-19

Gao, et al; medRxiv https://doi.org/10.1101/2020.03.07.20031575
# Natriuretic peptides and outcomes in COVID19

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Non-survivor</th>
<th>Survivor</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Cao J 2020</td>
<td>12</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Chen T 2020</td>
<td>68</td>
<td>80</td>
<td>17</td>
</tr>
<tr>
<td>Gao L 2020</td>
<td>18</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Li K 2020</td>
<td>13</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>139</td>
<td>219</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>111</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 7.57$, df = 3 ($P = 0.06$); $I^2 = 60$

Test for overall effect: $Z = 5.10$ ($P < 0.00001$)

Pranata R, et al, BMJ 2020; http://dx.doi.org/10.1136/postgradmedj-2020-137884
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

*Chapman AR, et al. Circulation. 2020; DOI: 10.1161/CIRCULATIONAHA.120.047008.*
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

Myocardial injury
How to interpret troponin in COVID-19

Differential Diagnosis

Very large AMI, myocarditis

Large AMI, myocarditis, Tako-tsubo, PE, critical illness

Small AMI, early large AMI, myocarditis, Tako-tsubo, PE, shock, CHF, SAB, ...

Micro AMI, early large AMI, myocarditis, Tako-tsubo, PE, shock, CHF, hypertensive crisis, SAB, stable CAD...

Stable angina, CHF, LVH, subclinical heart disease, etc

Healthy individuals

Myocardial injury

don’t forget your standard tools

If concern?

Standard evaluation

POCUS
Other complications of COVID-19

• 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

Stage I (Early Infection)
- Viral response phase
  - Clinical Symptoms: Mild constitutional symptoms, Fever >99.6°F, Dry Cough
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Stage II (Pulmonary Phase)
- Host inflammatory response phase
  - IIA: Shortness of Breath without Hypoxia (IIA) and with Hypoxia (IIB) (PaO2/FiO₂ ≤ 300 mmHg)
  - IIB: ARDS, SIRS/Shock, Cardiac Failure

Stage III (Hyperinflammation Phase)
- Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin, Troponin, NT-proBNP elevation)
COVID19 and the role of procalcitonin (PCT)

- **(a)**
  - Moderate patients
  - Severe patients
  - Critical patients

- **(b)**
  - The discharged case
  - PCT (ng/mL)
  - Admission
  - Interim
  - Discharge
  - **(PCT > 0.1 ng/mL)**

- **(c)**
  - The discharged case
  - PCT (ng/mL)
  - Admission
  - Interim
  - Discharge
  - ***

- **(d)**
  - The death case
  - PCT (ng/mL)
  - Admission
  - Interim
  - Discharge
  - The second measured value
  - The third measured value
  - The last measured value

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

<table>
<thead>
<tr>
<th>Signs/symptoms</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>61.9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>61.8%</td>
</tr>
<tr>
<td>Rash</td>
<td>55.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53.2%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>49.5%</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>48.4%</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>40.6%</td>
</tr>
<tr>
<td>Shock</td>
<td>35.4%</td>
</tr>
<tr>
<td>Coronary aneurysm</td>
<td>18.6%</td>
</tr>
<tr>
<td>AKI</td>
<td>18.4%</td>
</tr>
</tbody>
</table>

OMICs and a biomarker-based diagnostic for KD

**Results not published, internal data, Prevencio Inc.**
Biomarker-based diagnosis of KD

Results not published, internal data, Prevencio Inc.

N = 150
AUC = 0.92

At optimal cut-off:
- DOR = 52.39 (16.72, 164.12)
- Sensitivity 90%, Specificity 82%, PPV 72%, NPV 95%
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 \( \leq \text{mild sx} \): recover and RTP
- Young kids with \( > \text{mild sx} \): 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
  - 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 COVID-19 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