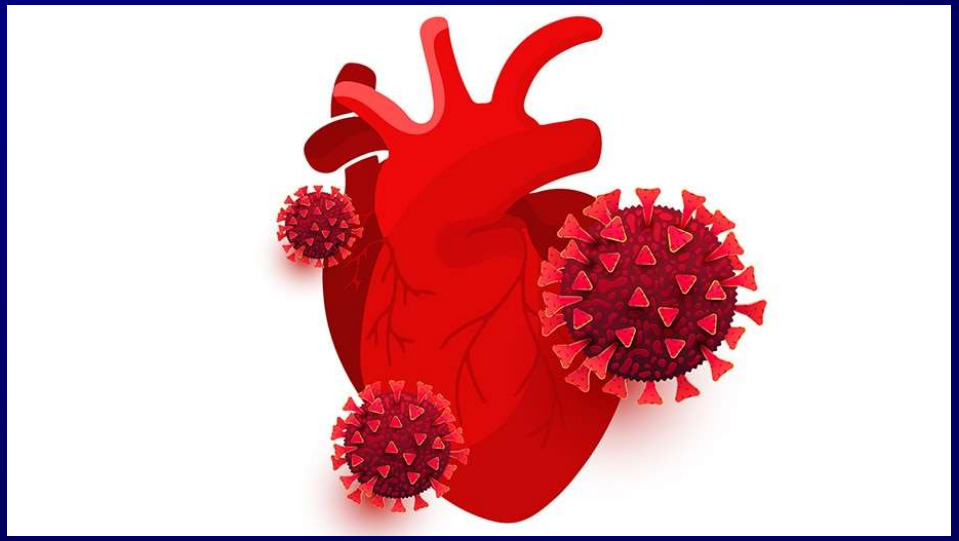
Post SARS-CoV-2- (COVID-19)
A Cardiology Perspective&



Project ECHO®

BC ECHO for **Post-COVID-19 Recovery**

Accredited by UBC CPD

UBC CONTINUING PROFESSIONAL DEVELOPMENT FACULTY OF MEDICINE

BRITISH COLUMBIA

doctors of bc

SharedCare Partners for Patients

DEPARTMENT OF FAMILY MEDICINE | Leaders in primary care, champions of community health

Krishnan Ramanathan MB, ChB, FRACP, FRCPC
Professor of Medicine, University of British Columbia
Medical Director Cardiac Intensive Care Unit St. Paul's Hospital

Conflict of Interest

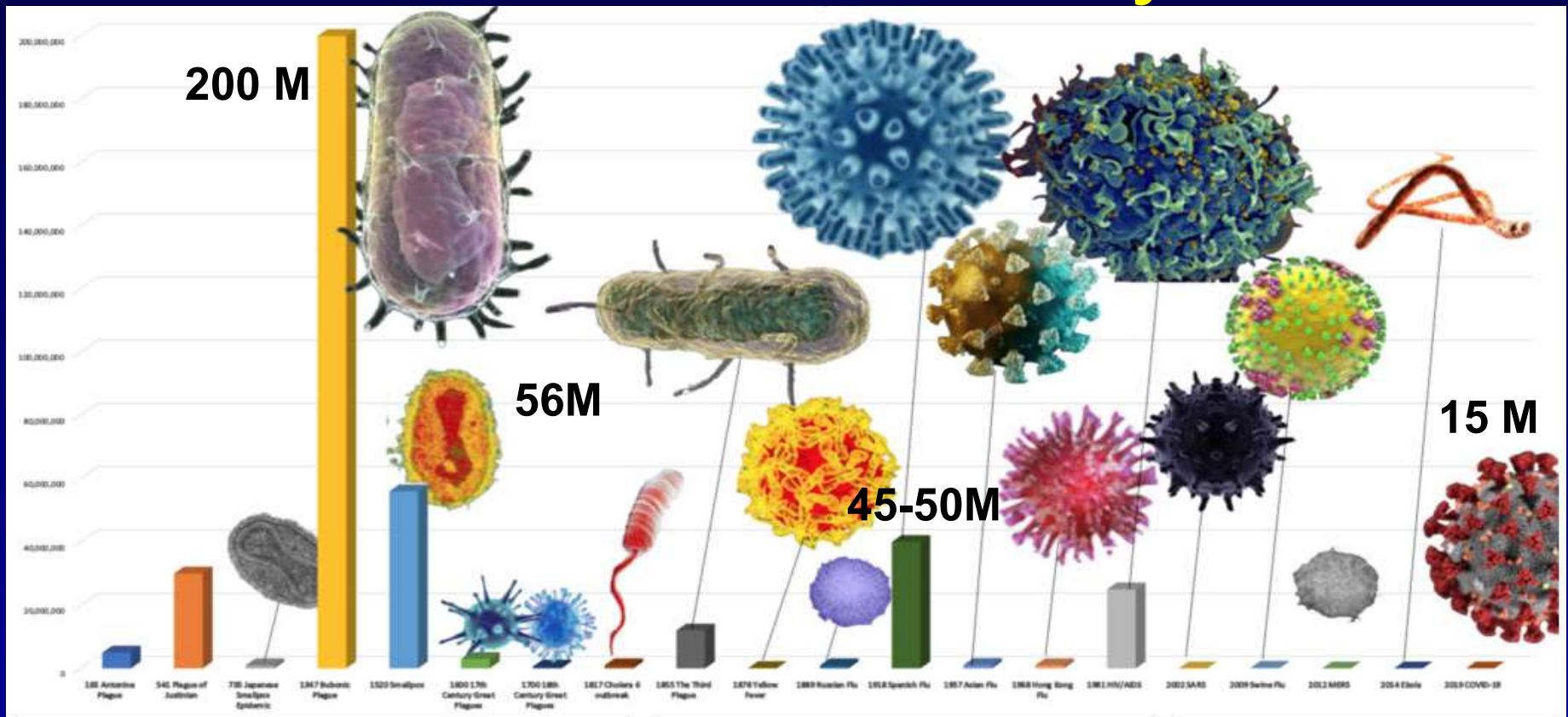
Name	Nature of Relationship	Company
K.Ramanathan	Speaking Honorarium	Pfizer/BMS, Bayer, Boehringer Ingelheim AstraZeneca, Amgen,
	Consultant/Advisor	Amgen, Bayer, BI, Novonordisk
	Research Grants	CIHR, CSBC

COVID-19 Clinic (Cardiology) VCH

The learning objectives for this session include:

- The learner will understand the cardiac manifestations of Post-COVID-19.
- The learner with be able to apply this knowledge to their clinical practice.
- The learner will better understand how to assess, treat and advise patients with cardiac conditions post-COVID-19.
- The learner will know where to access cardiology tools and resources to facilitate more effective clinical visits and optimize patient outcomes.

Pandemic History

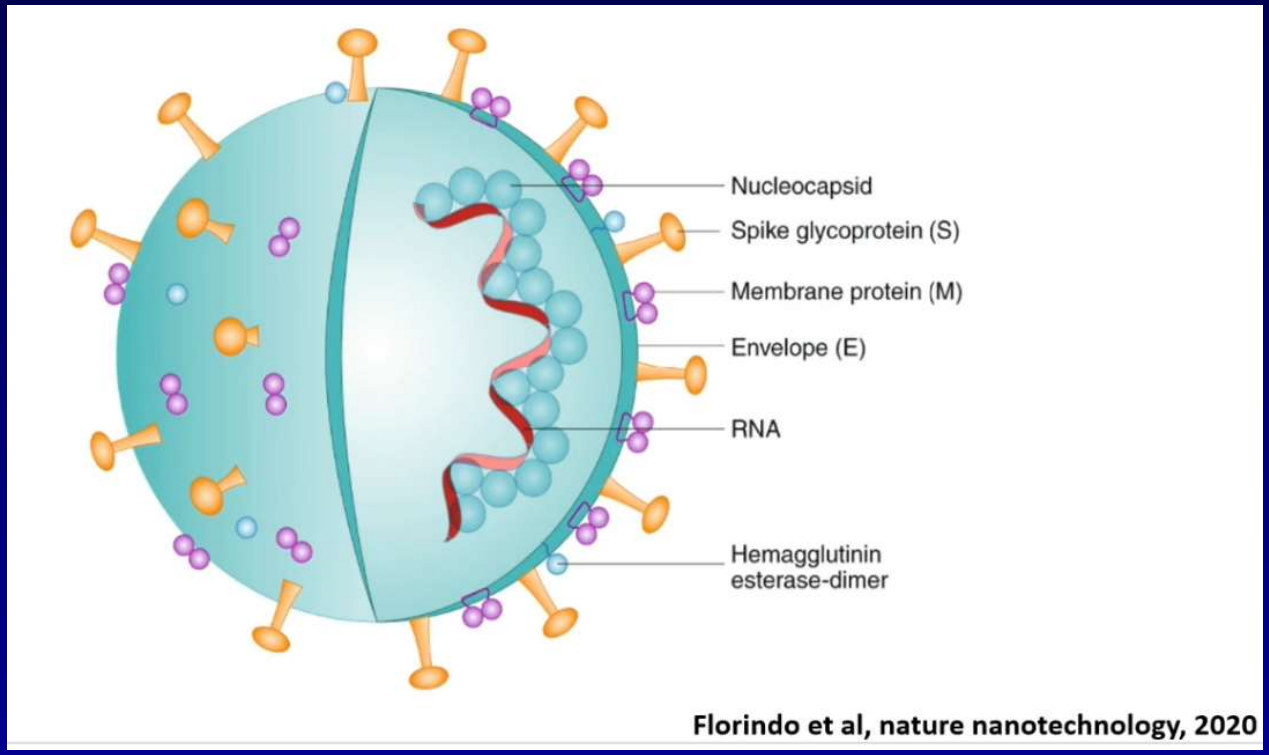


165 Antonine Plague
541 Plague of Justinian
735 Japanese Smallpox
1347 Bubonic Plague
1520 Smallpox
1600 17th Century Great Plagues

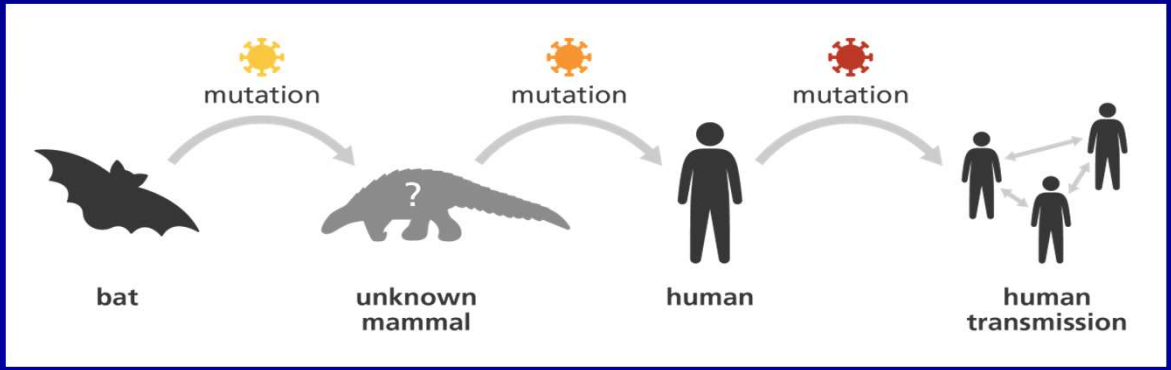
1817 Cholera 6 outbreak
1855 The Third Plague
1878 Yellow Fever
1889 Russian Flu
1918 Spanish Flu
1957 Asian Flu

1981 HIV/AIDS
2002 SARS
2009 Swine Flu
2012 MERS
2014 Ebola
2019 COVID-19

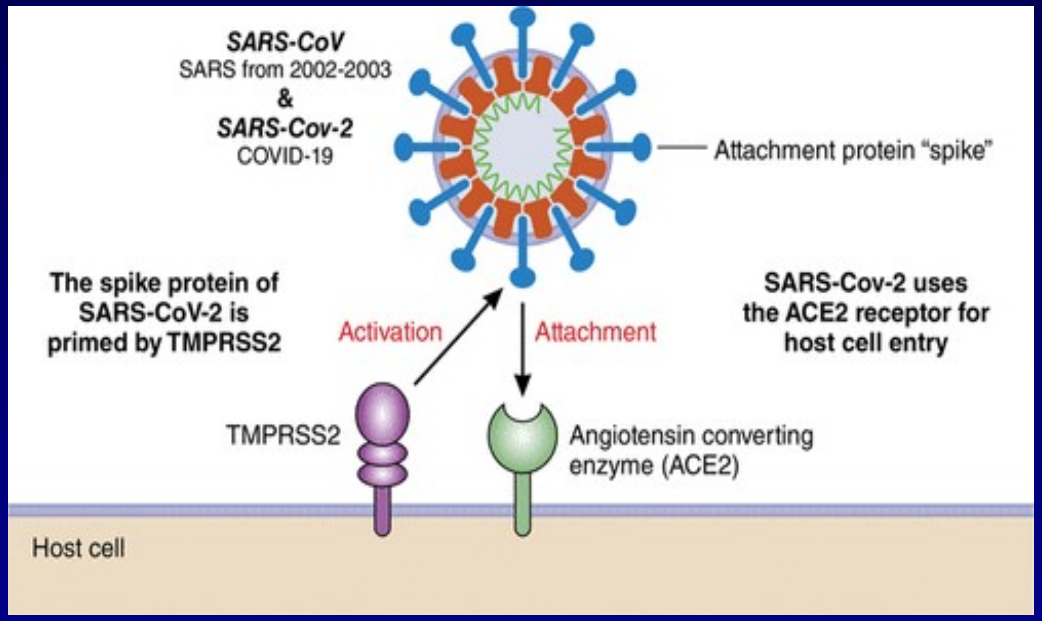
Coronavirus disease: SARS-CoV-2



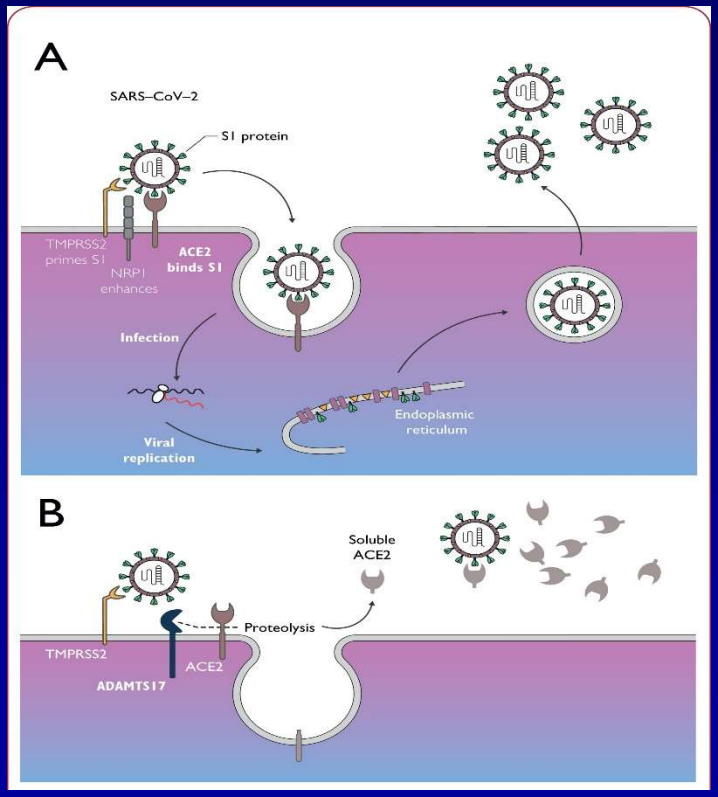
Florindo et al, nature nanotechnology, 2020



Critical role of ACE2 in the regulation of SARS-CoV-2 infection in ACE2-expressing cells



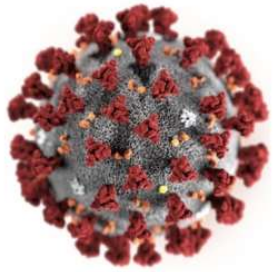
Heart > vascular > Body



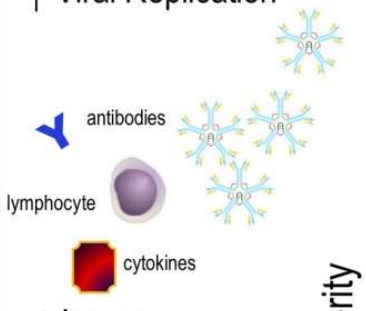
ACE2 receptors increase with age, suggesting that lower ACE2 levels may in part account for why children have less severe acute SARS-CoV-2 infections. Other studies have suggested that children have fewer ACE2 receptors in the nose, which decreases the ability for SARS-CoV-2 to bind, resulting in less severe disease

Eur Heart J, Volume 43, Issue 11, 14 March 2022, Pages 1033–1058,

COVID-19:
from viral aggression to systemic involvement



↑ Viral Replication



↓ Immune Response

Disease Severity

Early Stage

Flu-like symptoms development

Lung localization

Immune system activation
- *Altered lab findings*
- *Neurohormonal activation (e.g. Ang II)*
- *Thromboembolism*

Intermediate stage

Late Stage

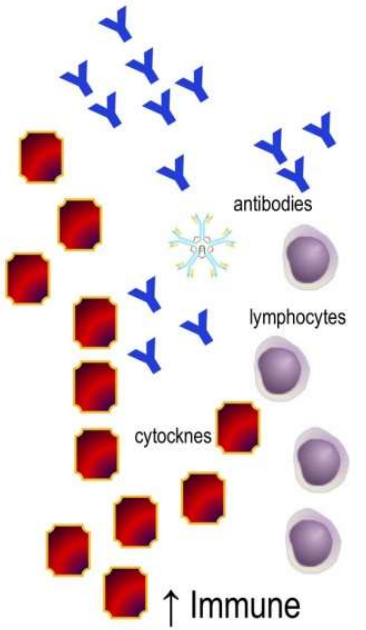
Healing

OR

Hyperinflammatory state
- *«Cytokine storm»*
- *Altered lab findings*
- *Multiorgan involvement*

Prothrombotic state
- *Altered lab findings*
- *DIC*

↓ Viral Replication



↑ Immune Response

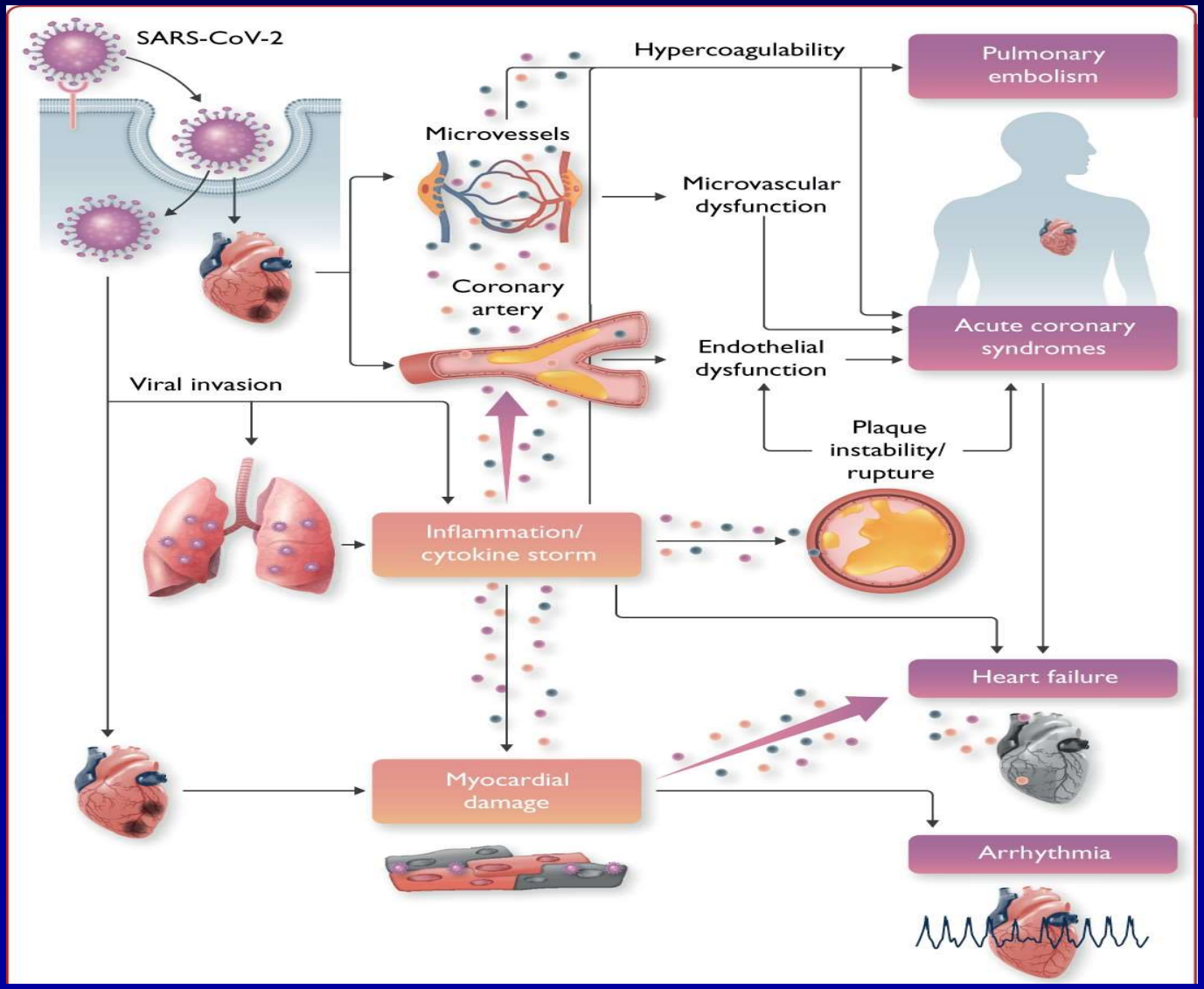
↑ Inflammation

Chloroquine, antiviral drugs and anticoagulants

Immunosuppressive drugs and anticoagulants

Time

Cardiovascular involvement in COVID-19—key manifestations & hypothetical mechanisms.



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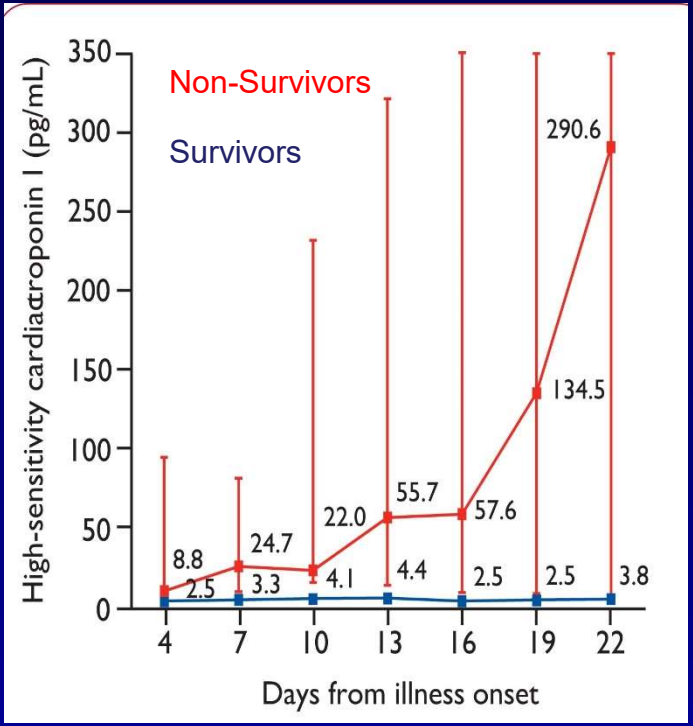
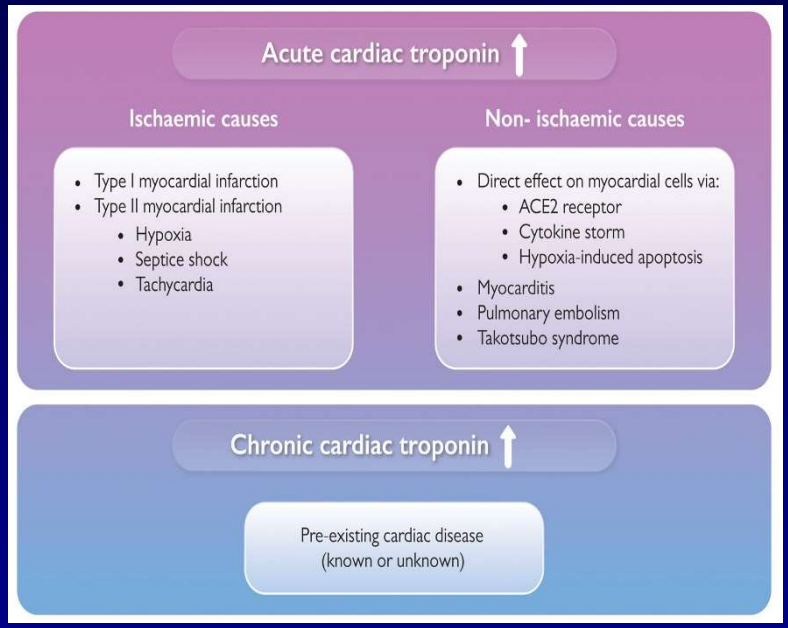
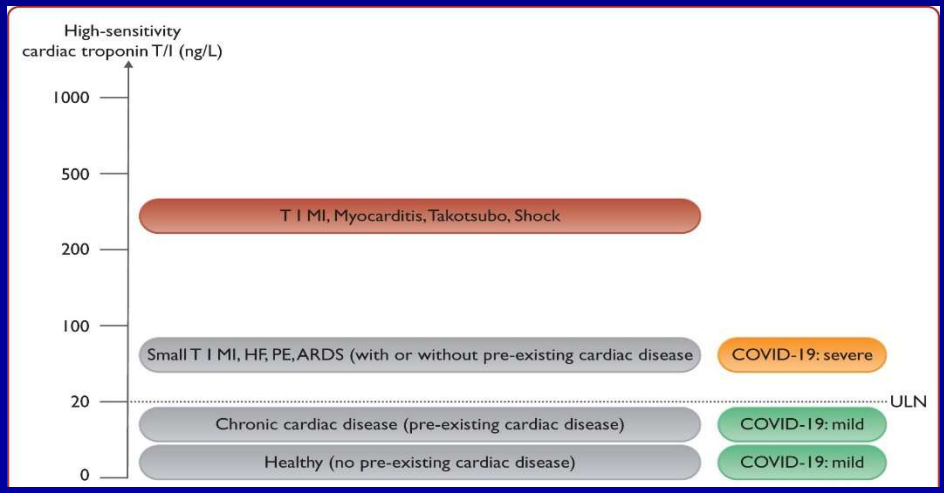
Temporal changes in high-sensitivity cardiac troponin I concentrations from illness onset in survivors vs. Non survivors

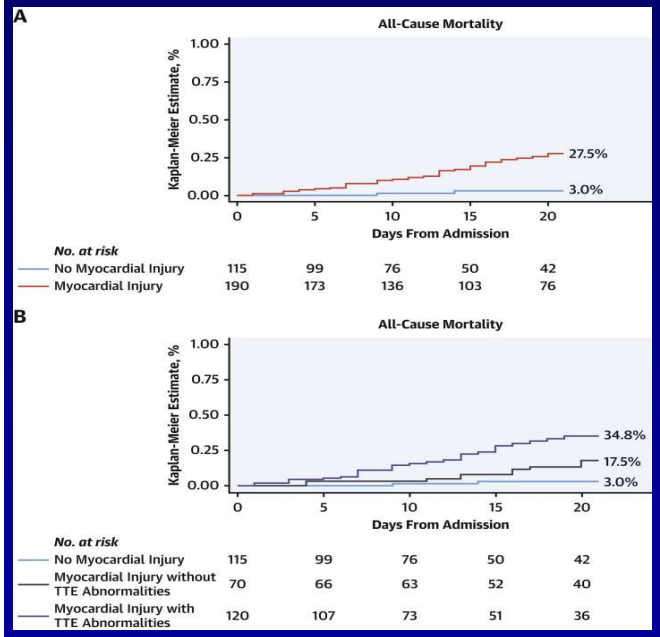


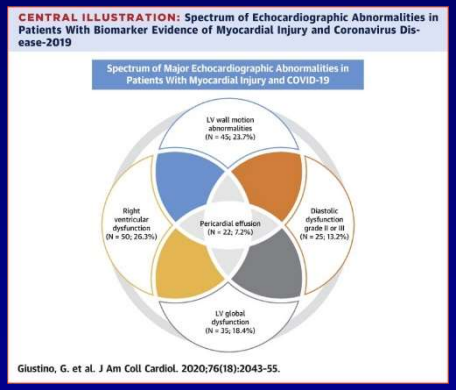
Potential mechanisms underlying elevations in cardiac troponin and myocardial injury in patients with C-19

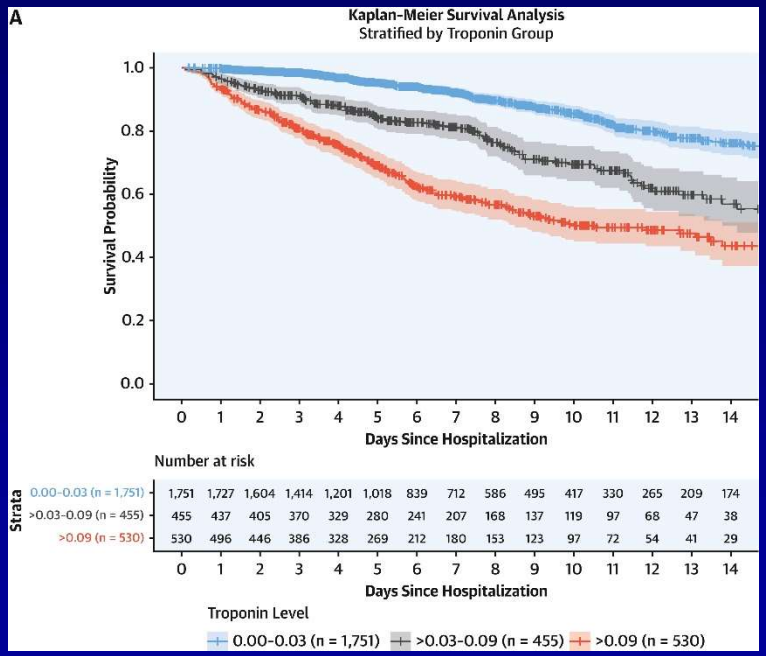




Myocardial injury is a predictor of mortality and more severe illness in COVID-19-confirmed patients





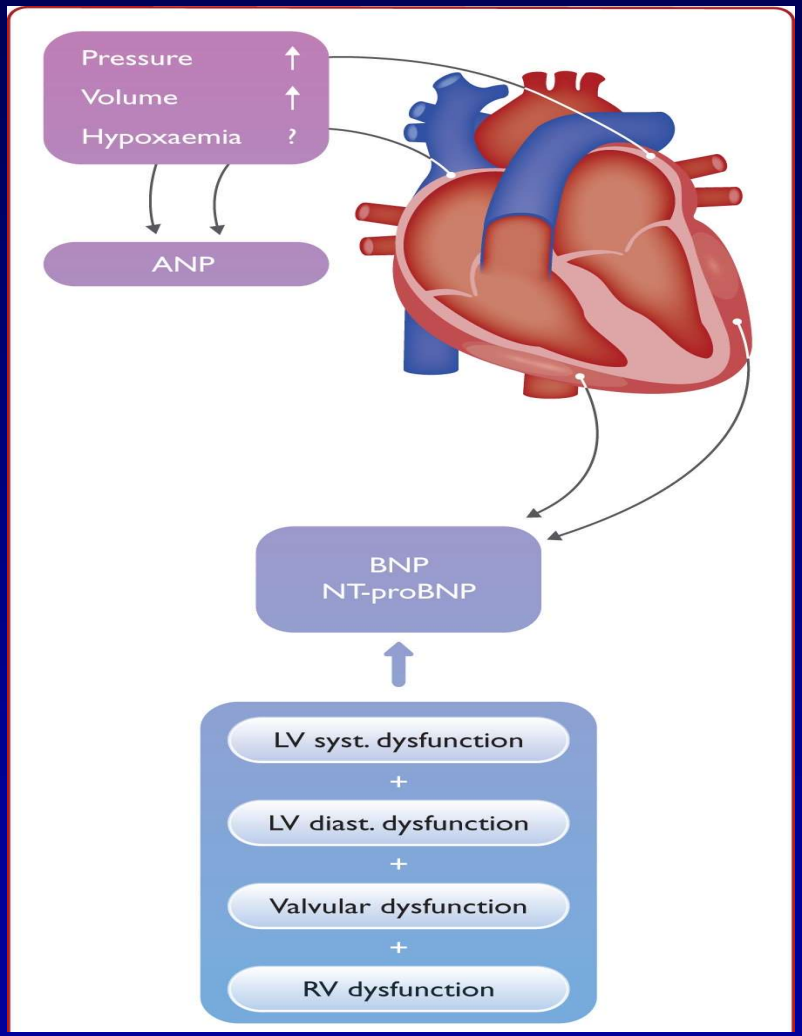


Glustino E et al JACC 2020 76(18) 2043

Lala A et al JACC 2020 76(5) 2020

Haemodynamic determinants of natriuretic peptides.

ANP, atrial natriuretic peptide; BNP, B-type natriuretic …



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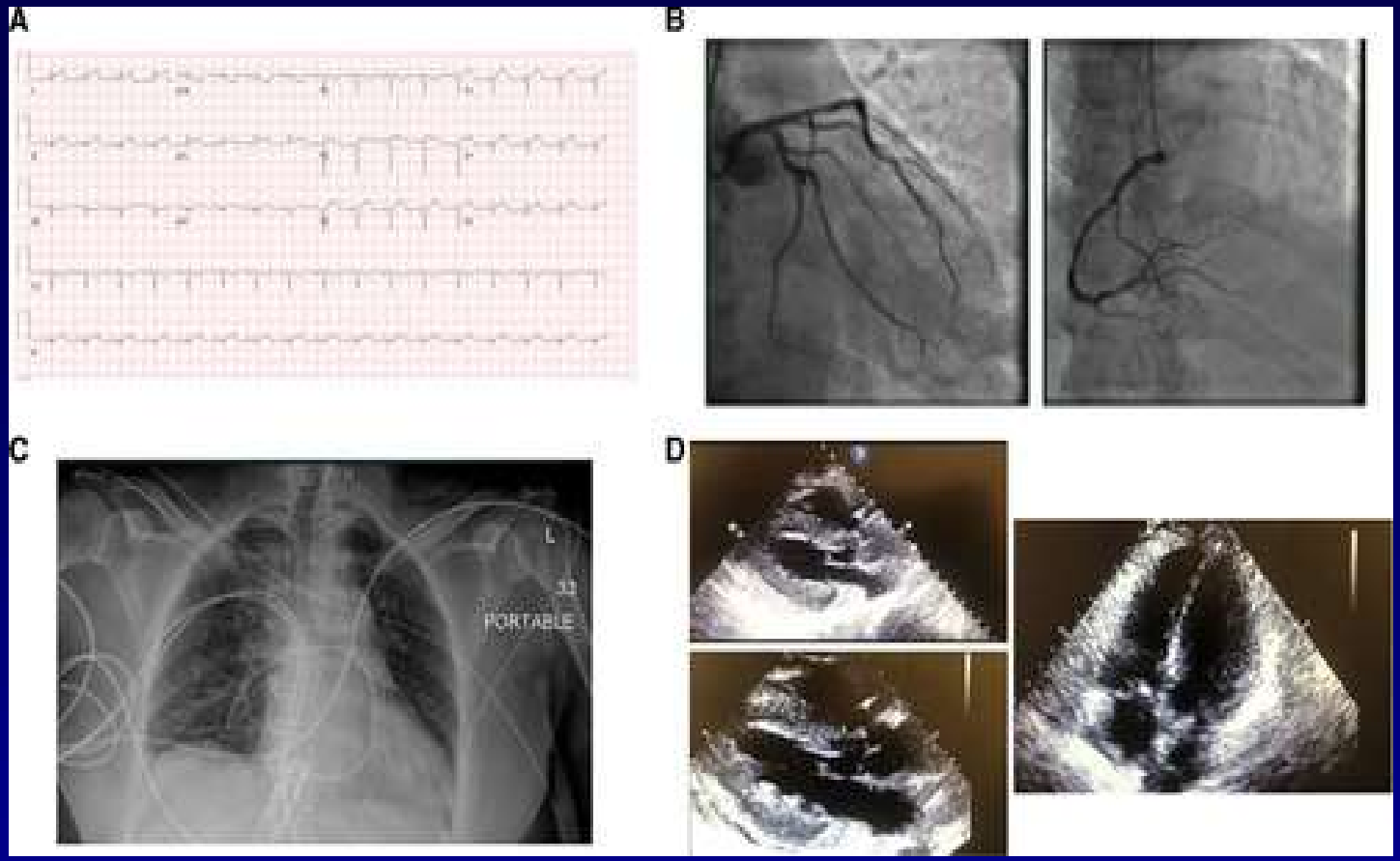
Summary 1

ACE-2 “gateway receptor”

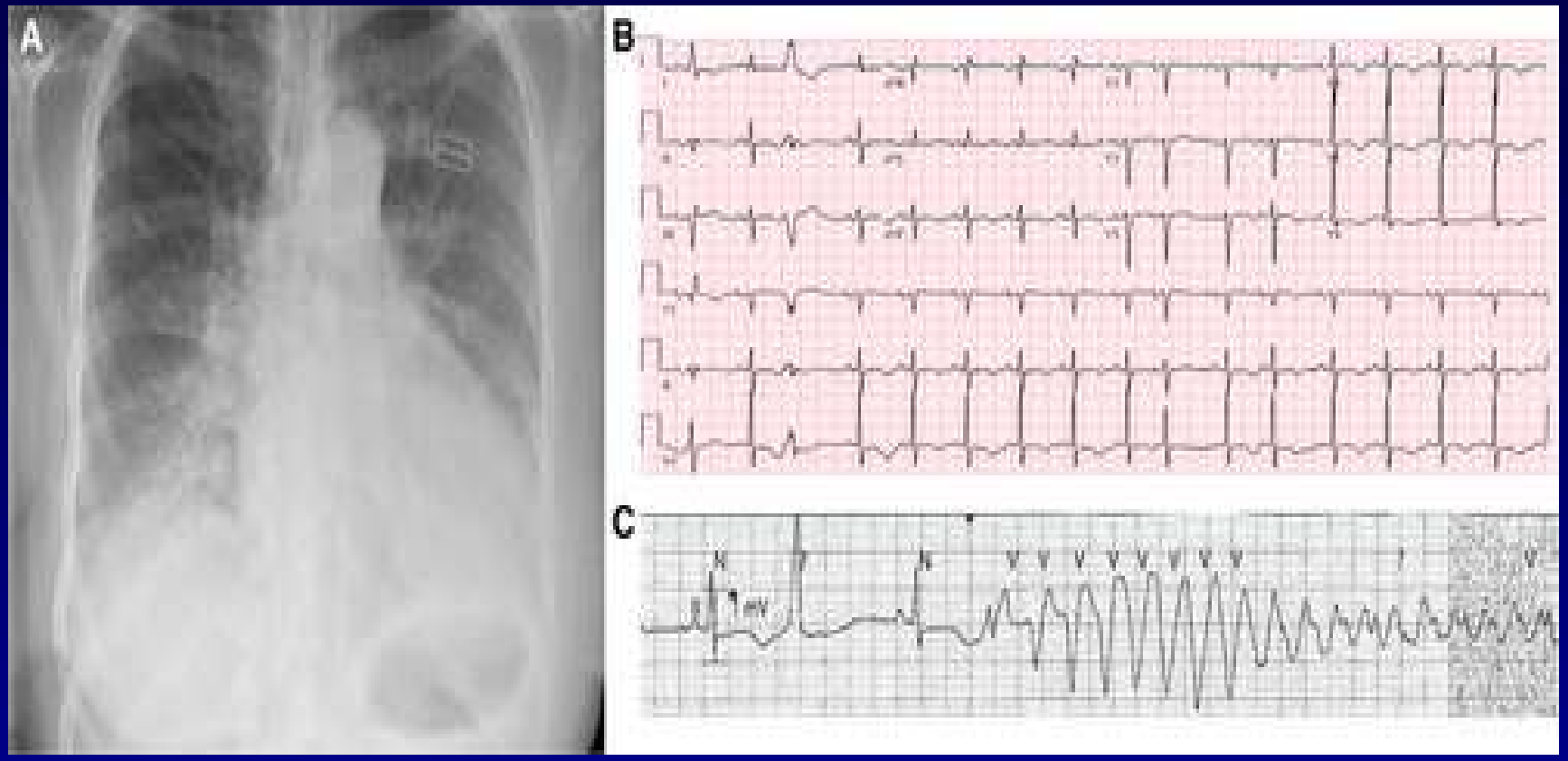
Immune system /Hyper inflammatory / Pro-thrombotic / Cytokine storm

Variety of effects on the CV system

Biomarkers important in acute phase



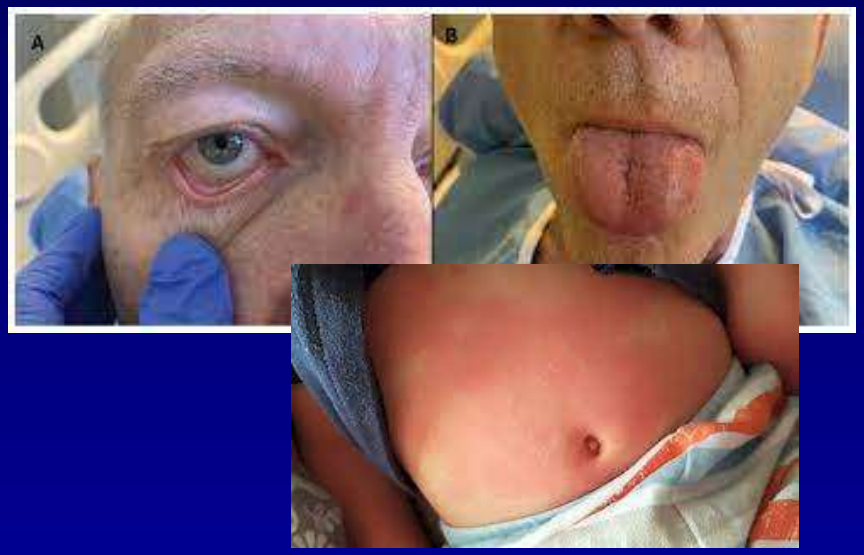
64Fwith HTN, DLp no known C-19 with 2/7 hy chest pain
No dyspnea, cough, fever, chills, diarrhea, recent travel, or sick contacts.
Afebrile, BP = 130/80 mmHg, 98 bpm, and O2 100% on 2 L of oxygen.
The ECG showed low voltage QRS complexes in the limb leads, ST segment elevations in leads I, II, aVL, V2–V6, and PR elevation and ST depressions in aVR
Troponin I on admission was 7.9 ng/mL.
BP fell to 72/43 mmHg, RA = 10mmmHg PA = 30/20 mmHg, PCWP =21 mmHg, and cardiac **index of 1.0 L·min-1·m-2,**

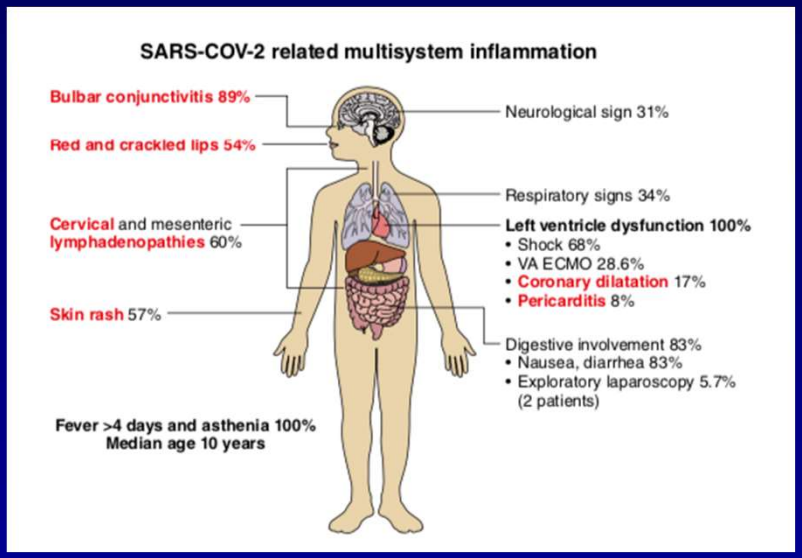


64 M NICMO (recent normalization of LVEF), AF, HTN & DM II
Non-productive cough & SOB for 2/7
Afebrile, BP 153/120 mmHg, HR 100 bpm, and O2 sat 88%.
CXR bibasilar predominant patchy airspace opacities, pulmonary vascular congestion & small bilateral pleural effusions. ECG – SR with PVC, lateral T wave inversions & QTc 528 ms.
WBC = 6.1 Create = 120 umol/L , elevated LFTs, cTnT 42 & BNP 6347
LVEF = 30% and CS and developed VT with dobutamine

Multisystem Inflammatory Syndrome in Young Adults

Age 17 Japanese UBC student several visits to the ED with fever



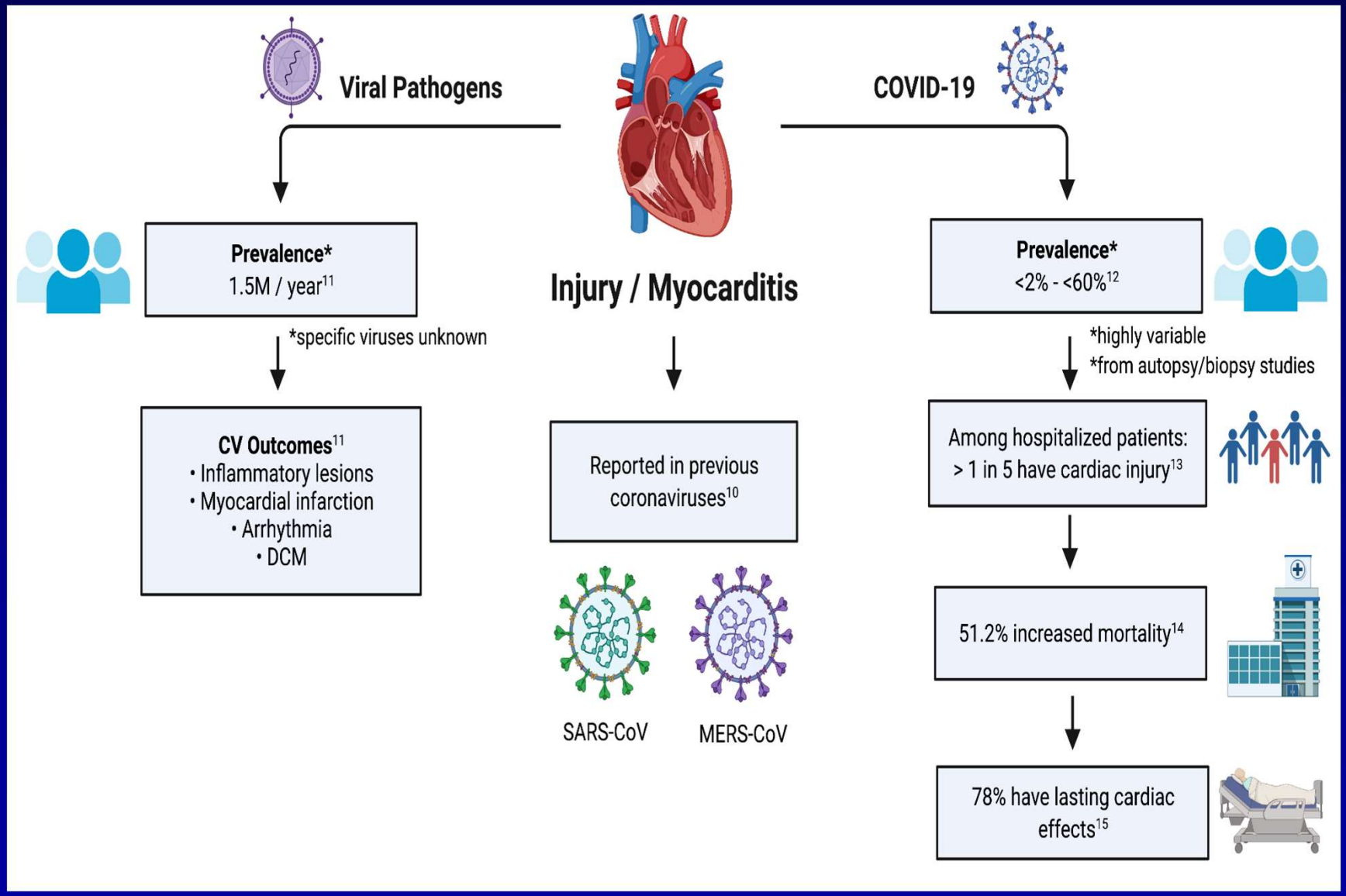


The differential diagnosis of MIS-A includes Kawasaki disease, adenovirus infection, bacterial infectious diseases (eg, enteritis, sepsis, or toxic shock syndrome), autoimmune and autoinflammatory disorders, and acute appendicitis.

LVEF 20% with dilated coronaries

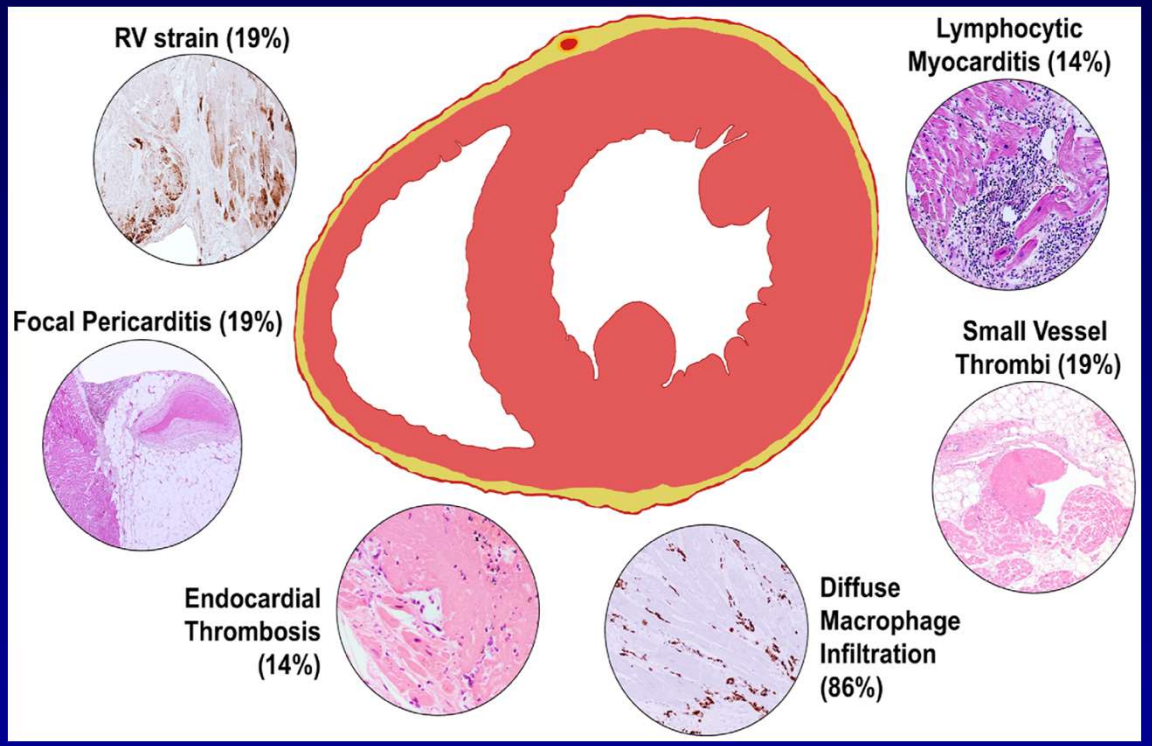
5 days of IVIG LVEF = 50%

COVID-19 *versus* Other Common Viral Pathogens



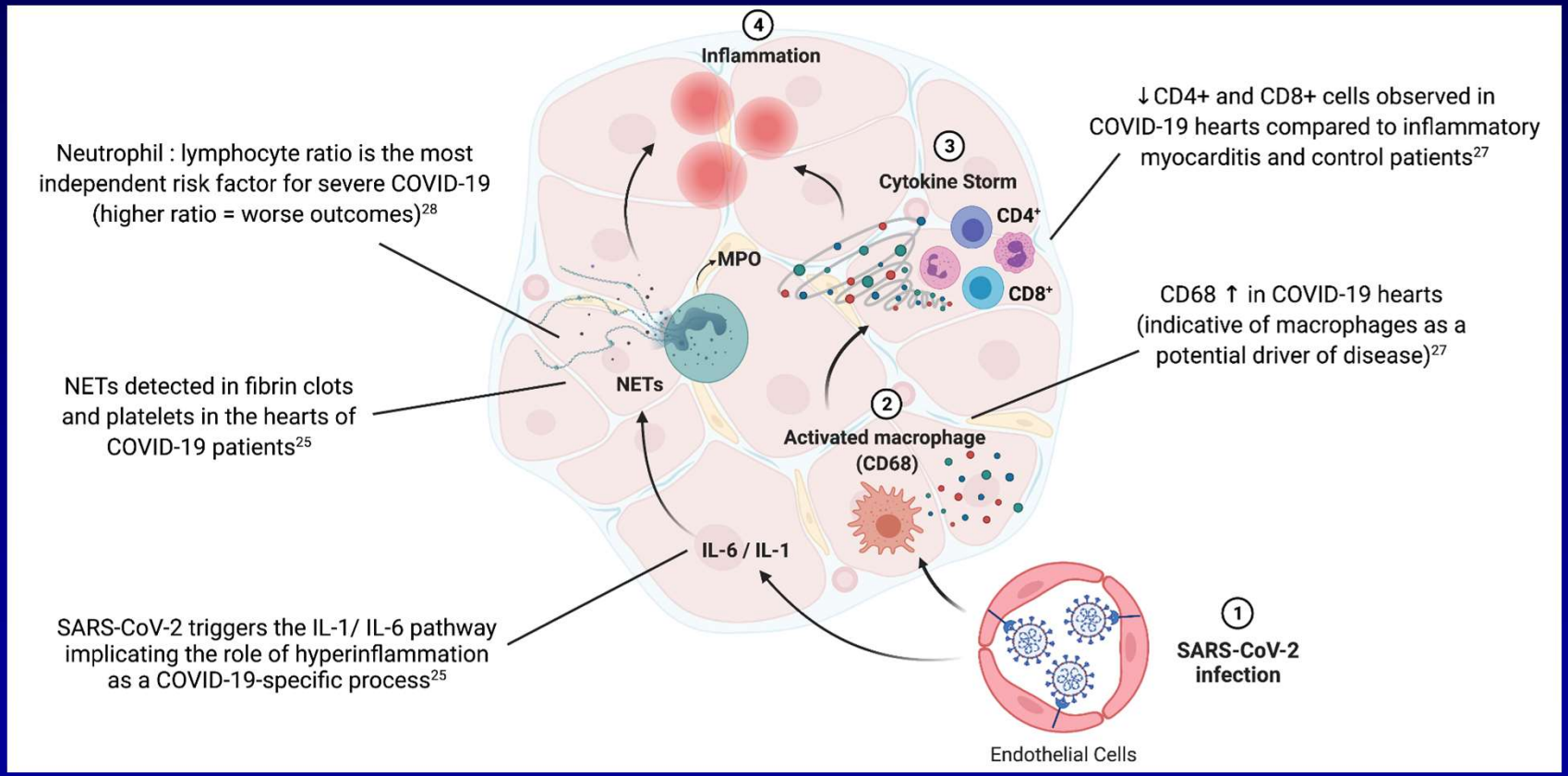
COVID-19-associated Heart Injury

- COVID-19 associated heart injury results from either cardiac viral infection or systemic inflammation and thrombosis[16].
- Manifestations of cardiac pathology, observed in COVID-19 autopsy patients, include microvascular thrombi, ischemic injury, right ventricular strain injury, pericarditis, myocardial inflammatory cellular infiltrates, and full myocarditis with myocyte destruction[17].
- While COVID-19 associated heart failure could be attributed to viral myocarditis, it is postulated that systemic inflammation which originates from lungs or blood vessels causes the majority of myocardial injury .



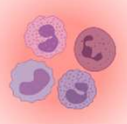
Basso et.al. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. European Heart Journal 2020.

Immune Over-activation by SARS-CoV-2

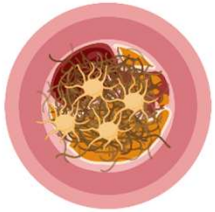


Knowledge Gaps: COVID-19-associated Myocarditis

Distinguishing between key immune cells/mediators involved in immune overactivation



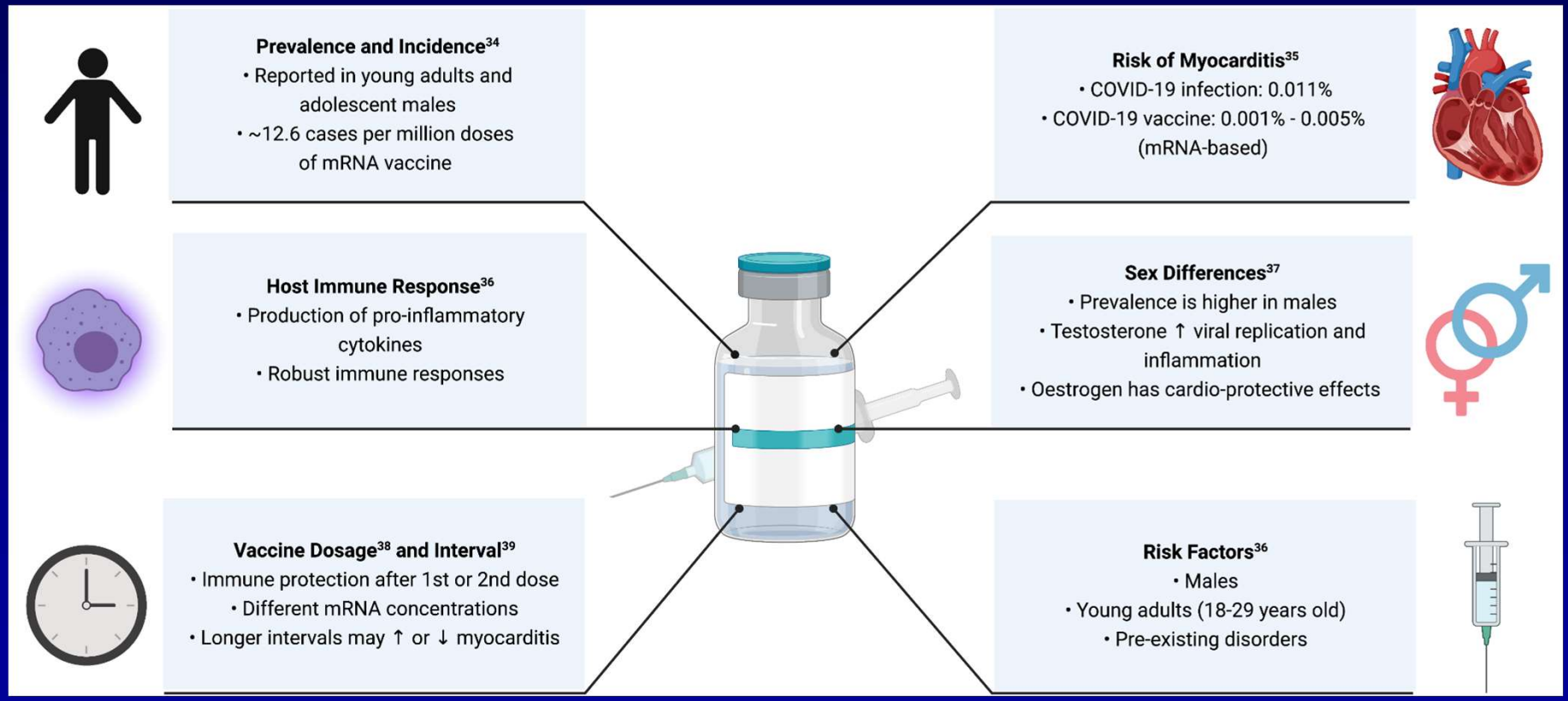
Understanding whether immune system works in conjunction with coagulation system to prevent spread of disease



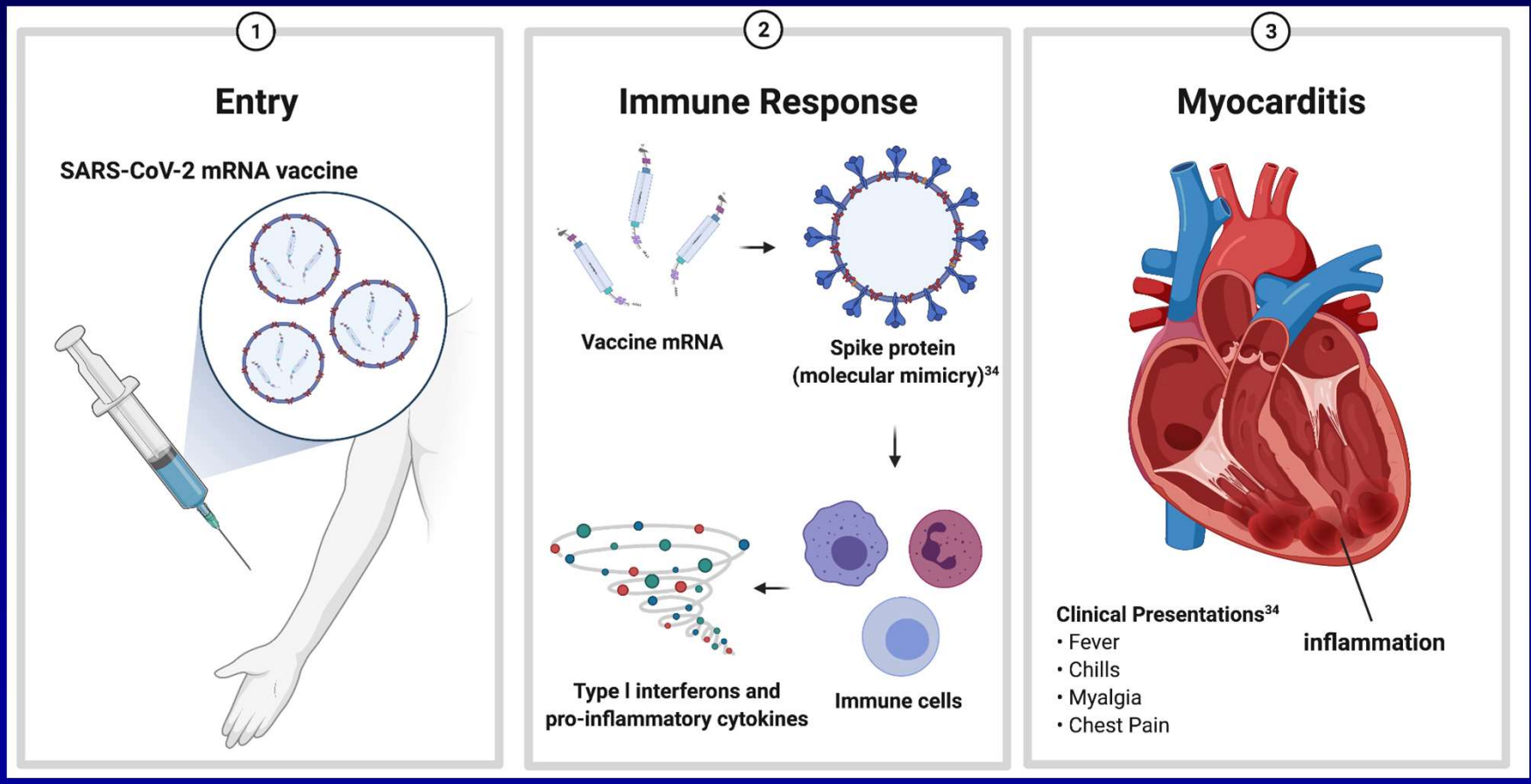
Understanding whether myocarditis is a result of expression of pro-inflammatory genes or immune overactivation

Identifying potential long term cardiovascular effects

COVID-19 Vaccine-associated Myocarditis



Mechanism of Vaccine-associated Myocarditis?



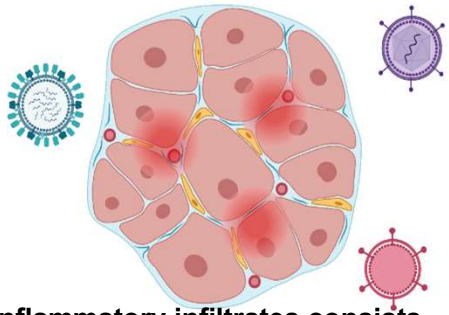
Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation. 2021;144(6):471-484.

Myocarditis

Viral Infection
0.01%

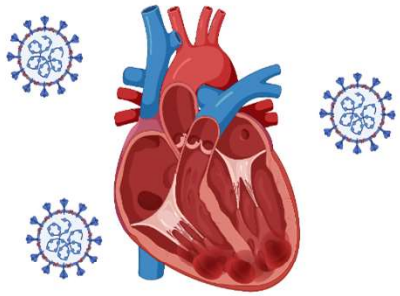
mRNA Vaccination
0.001-0.005%

Viral Myocarditis



- **Inflammatory infiltrates consists mostly of T-cells (CD4, CD8) and macrophages.**
- **Macrophages and T-cells play key roles in viral pathogen clearance – may contribute to autoimmunity in later stages.**

COVID-19-associated Myocarditis



- **Overactive immune response integrated with the coagulation system activation are the main driving factors.**
- **Significantly higher CD4:CD8 ratio relative to classical viral myocarditis**
- **Excessive neutrophil activation, platelet aggregation, and microthrombi were present.**

COVID-19 Vaccine-associated Myocarditis

- **Reported primarily in young adolescent males, although prevalence is rare.**
- **Myocarditis possibly induced by molecular mimicry mechanisms associated with mRNA vaccine.**

Summary 2

Spectrum of CV disease with C-19

Myocarditis is un-common and remains poorly understood

Vaccine induced myocarditis

Ongoing research

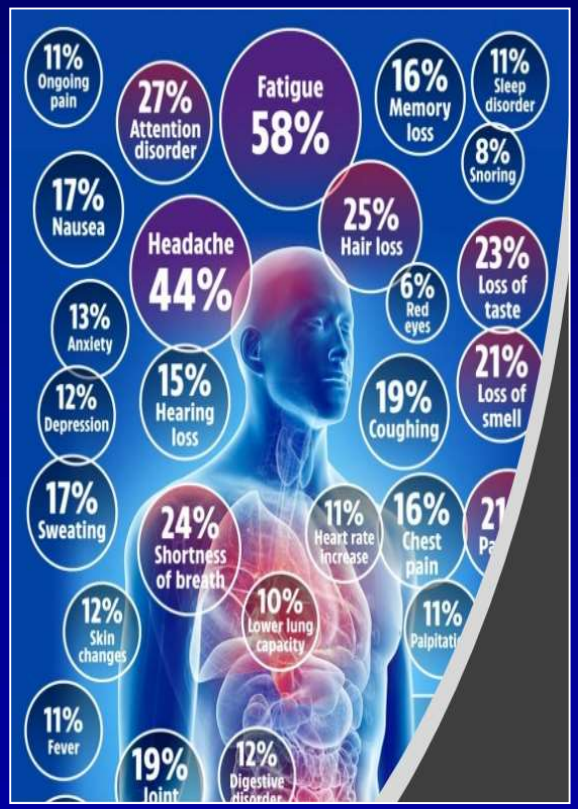
SARS CoV-2 (COVID-19) and Long Covid

Acute
COVID-19 +ve
> 3.9 M

1.1%

Greater than 4 weeks post acute illness

Figure. COVID-19-Related Symptoms



The Sun

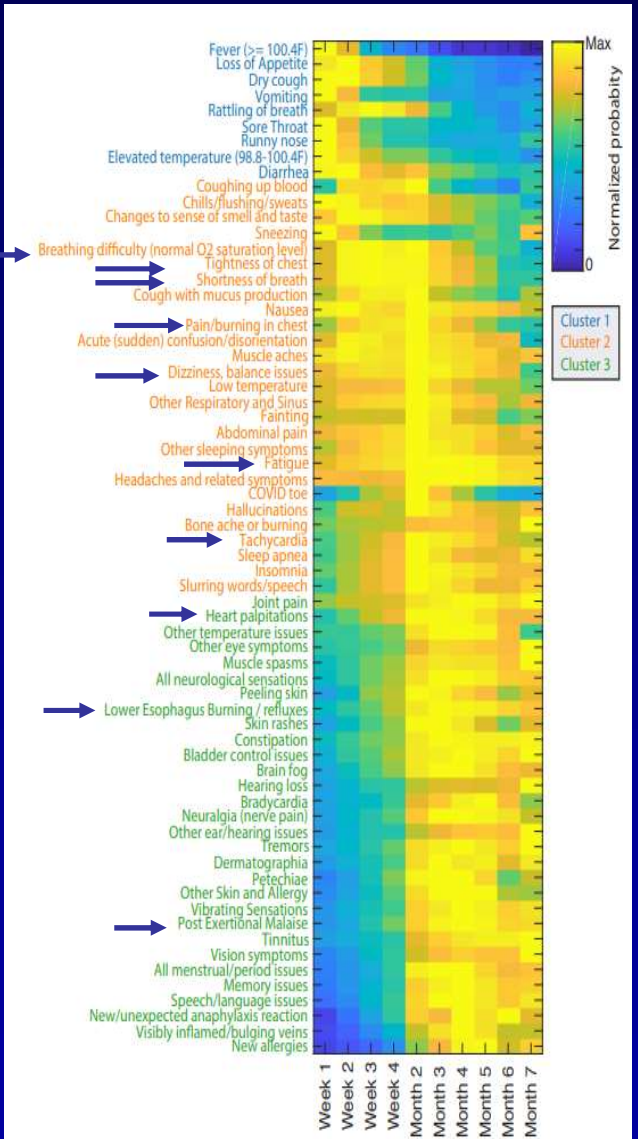
International Survey: More than 200 symptoms Reported
Web based n =3762 (56 Countries)

Women 79%

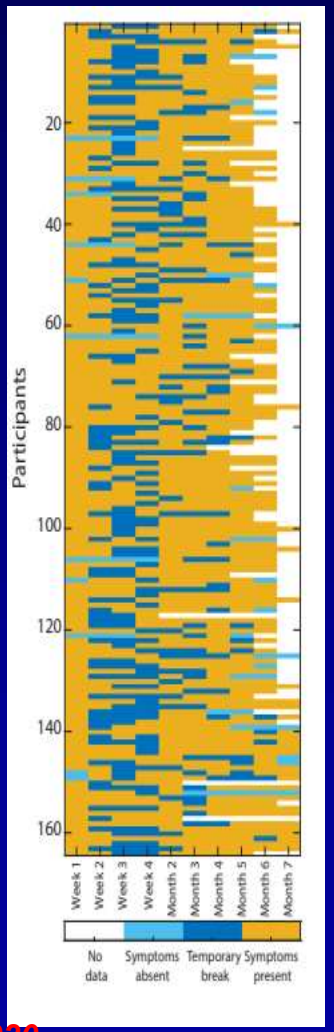
At 6 months

Fatigue = 77%
Post exertional malaise = 72%
Cognitive dysfunction = 58%

Arrow 10 cardiac symptoms



Saccadic symptoms n = 164



Davis Et al medRixiu 2020

Long COVID-19

Acute
COVID-19 +ve
~3.9 M

1.1%

Greater than 4 weeks post acute illness

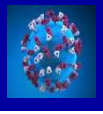
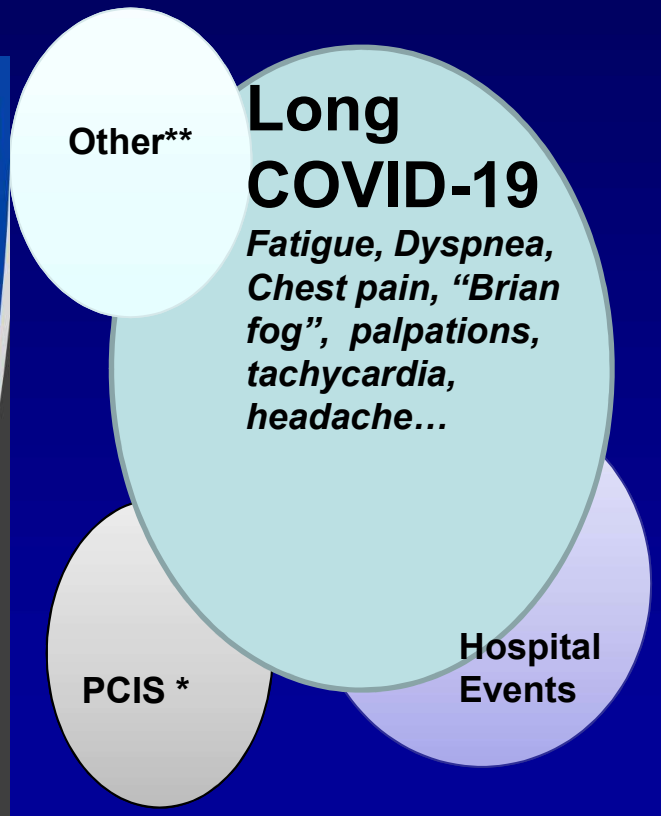


Figure. COVID-19-Related Symptoms

The Sun

Overlapping Conditions



* Post Critical Illness Syndrome
** M.I.D, GBS……

CDC COCA webinar 2021

Long COVID-19 Risk Factors

Acute COVID-19 +ve ~3.9 M

1.1%

Greater than 4 weeks post acute illness

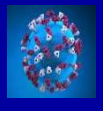


Figure. COVID-19-Related Symptoms

The Sun

Overlapping Conditions

Other**

Long COVID-19

Fatigue, Dyspnea, Chest pain, "Brian fog", palpations, tachycardia, headache…

PCIS *

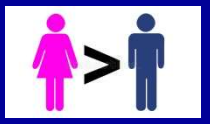
Hospital Events

Early C-19 RNA (viral load)

Presence of Antibodies SLE, RA

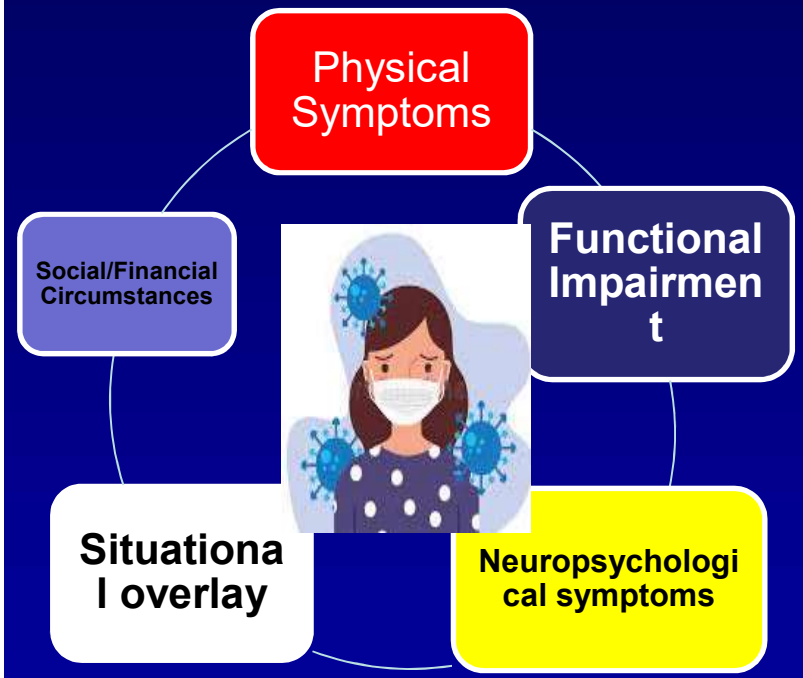
Reactivation of EB

DM II



* Post Critical Illness Syndrome
** M.I.D, GBS……

CDC COCA webinar 2021



Long COVID-19Patient "Multidimensional"

Health

- Persistent and fluctuating symptoms
- Debilitating impacts on health
- Ongoing rehabilitation needs

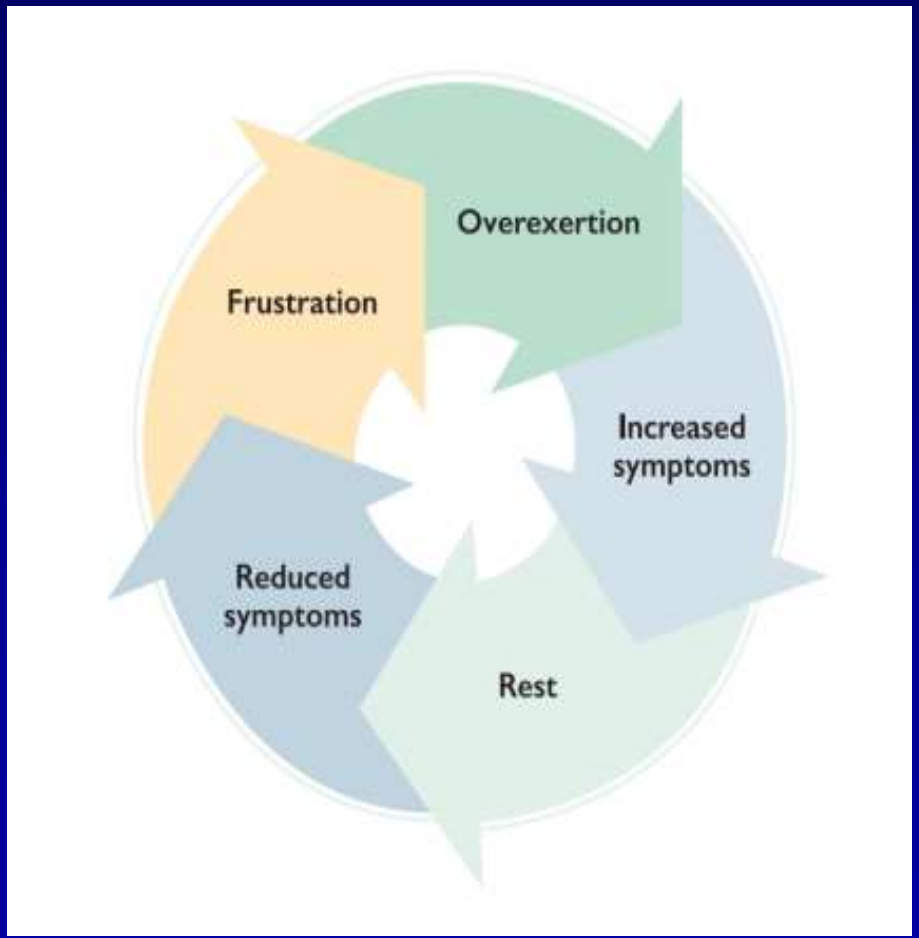
Work

- Ability to return to work (RTW) safely
- Linking abilities to work demands
- Managements attitude to accommodating RTW

Social and Economic

- Financial impact on individual / society
- Social attitudes to sufferers
- Social security systems

The Push and Crash Cycles Associated with Long COVID -19



Brain Fog Subjective Cognitive Decline

Physical Symptoms

Social/Financial Circumstances

Functional Impairment

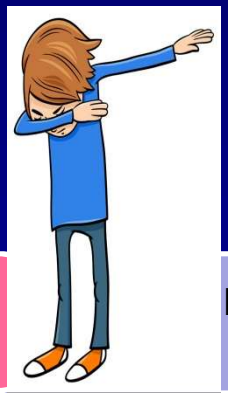
Situatio nal overlay

Neuropsych ological symptoms

Long COVID-19Patient "Multidimensional"

Interdisciplinary

Support Network



Allied health

Research

Physiatry/ Rehab

"Return Survivors to Health" Multidisciplinary Approach

Personalised Approach

Planned, supportive, coordinated RTW - Multi disciplinary approach (Mx, safety, health)

Case by case management (safety critical tasks)

Individualised risk based approach (fitness to work)

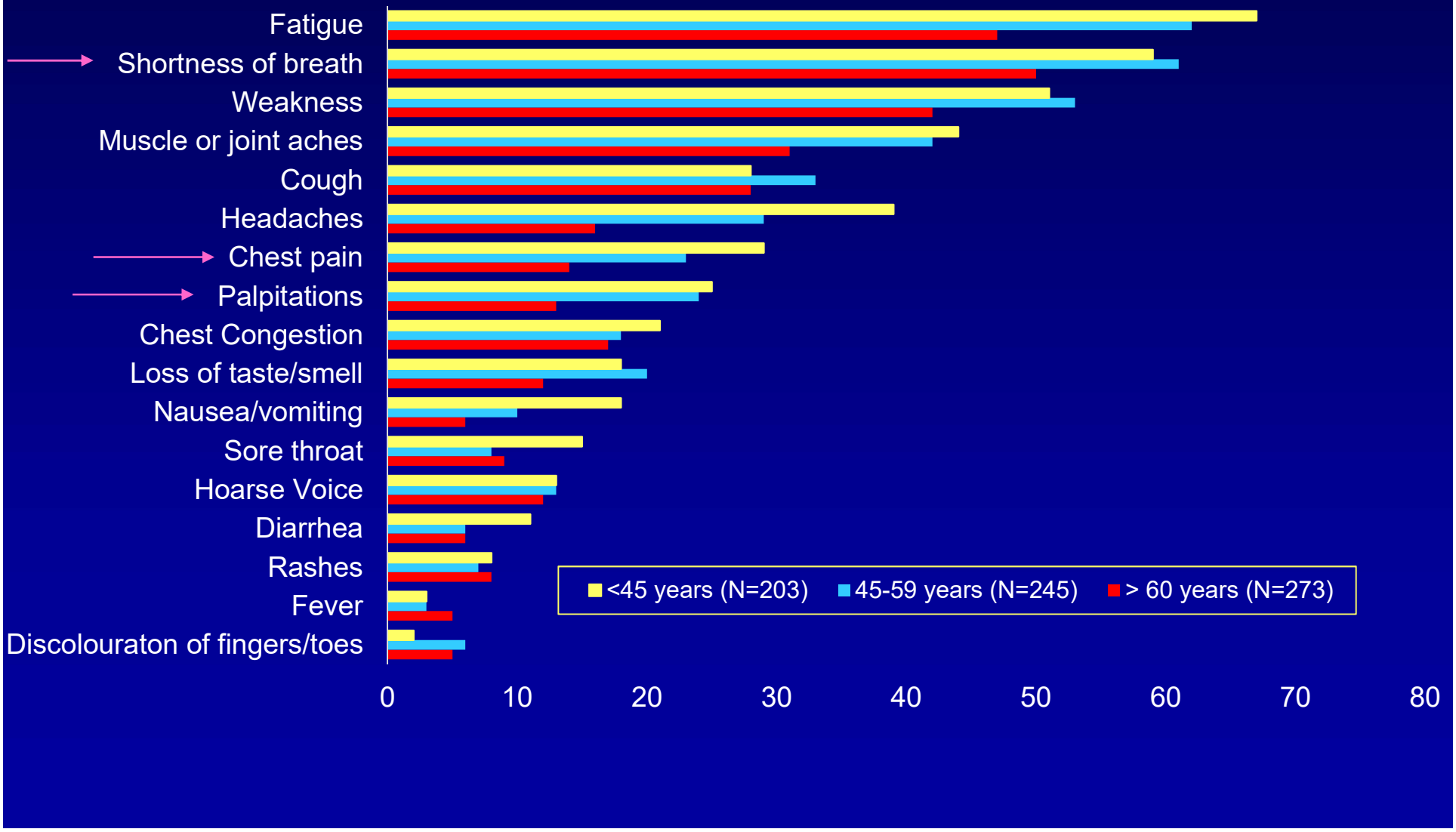
Phased approach to RTW (short days) - Flexibility, accommodation, hybrid working

Frequent reassessment and accommodation adjustments

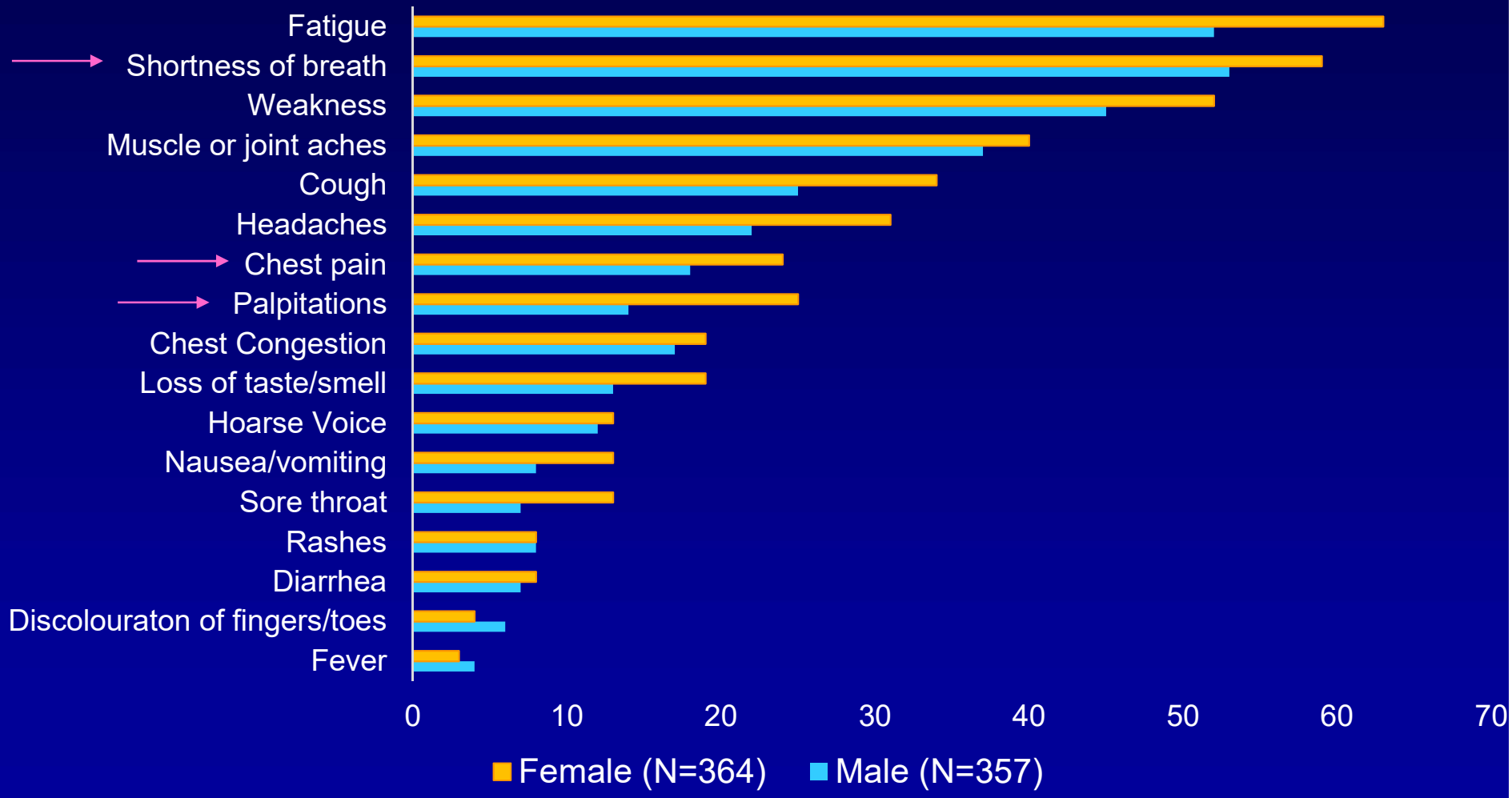
VCH Registry

Variable	Hospitalized (N=603)	Non-Hospitalized (N=233)
Median Age	59 (48,69)	45 (36,54)
Sex (% Female)	45.6%	62.7%
Ethnicity		
White	28.5%	44.2%
Asian	45.1%	29.2%
Other	11.6%	14.2%
No Answer	14.8%	12.5%
Work Status post COVID-19 Infection		
Full Time	28.4%	35.2%
Part-Time (>50% of regular hours)	3.2%	10.3%
Part-Time (<50% of regular hours)	4.5%	4.7%
Unable to Work	14.9%	24.5%
No Answer	49.1%	25.3%

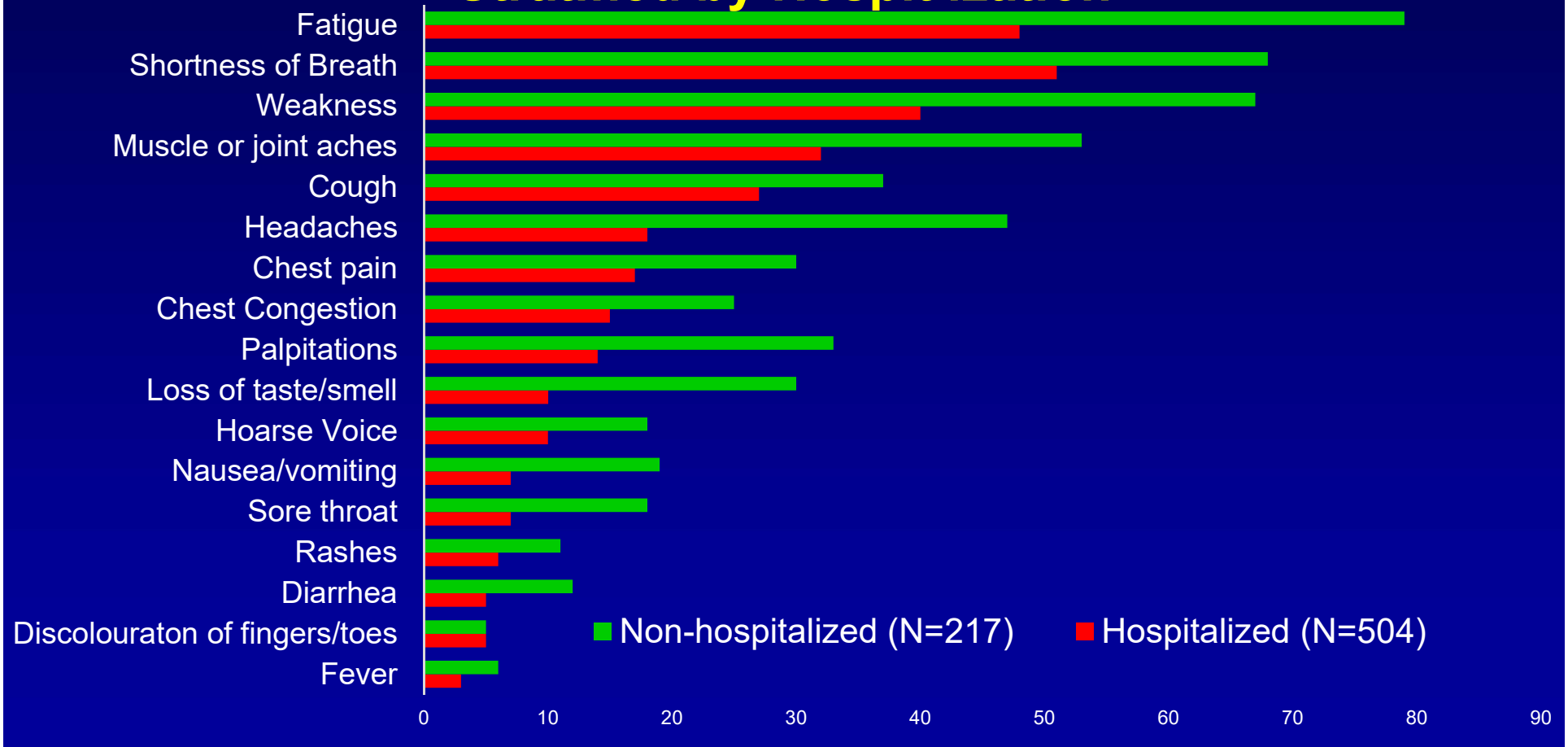
% Patiens with Persistent Symptoms at 3 months Stratifed by Age



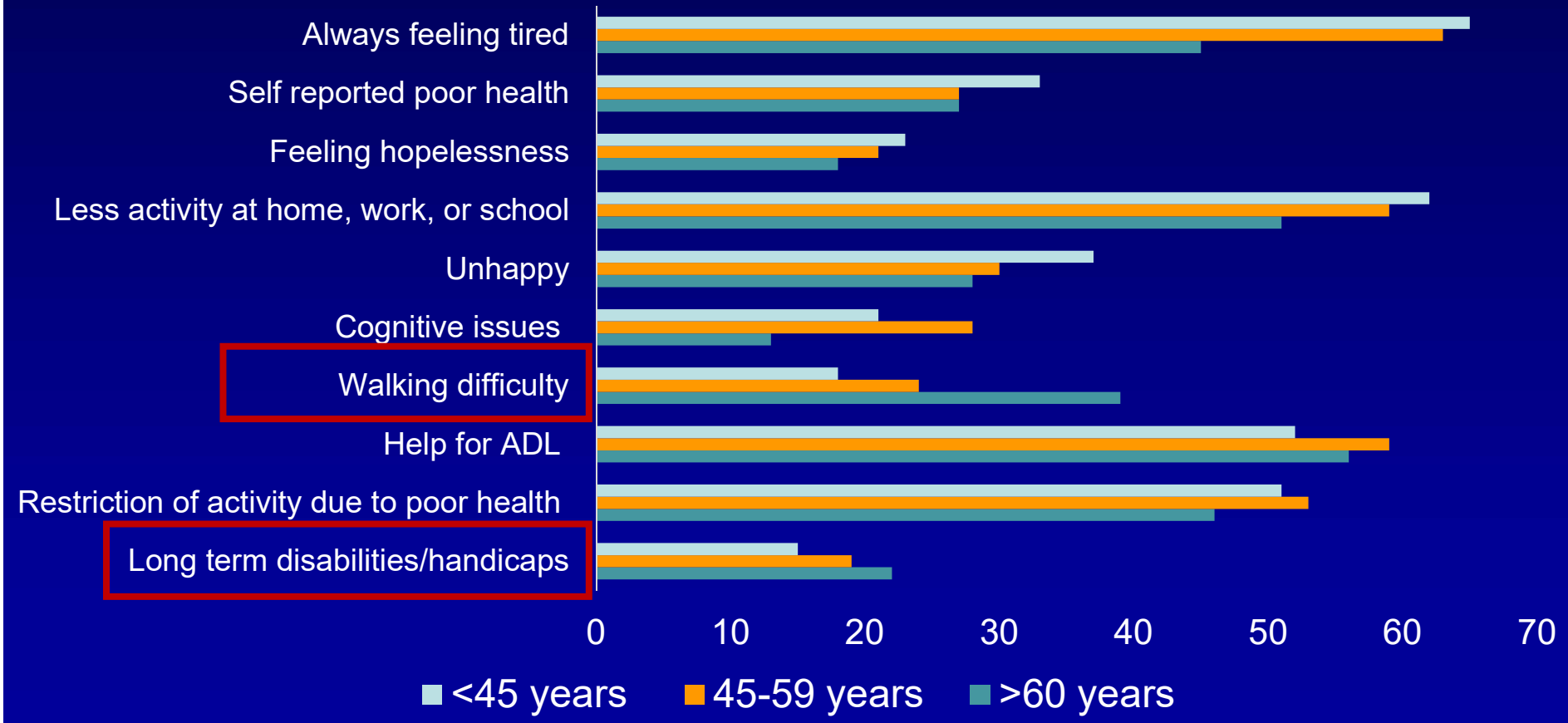
% Patients with Persistent Symptoms at 3 months Stratified by Sex



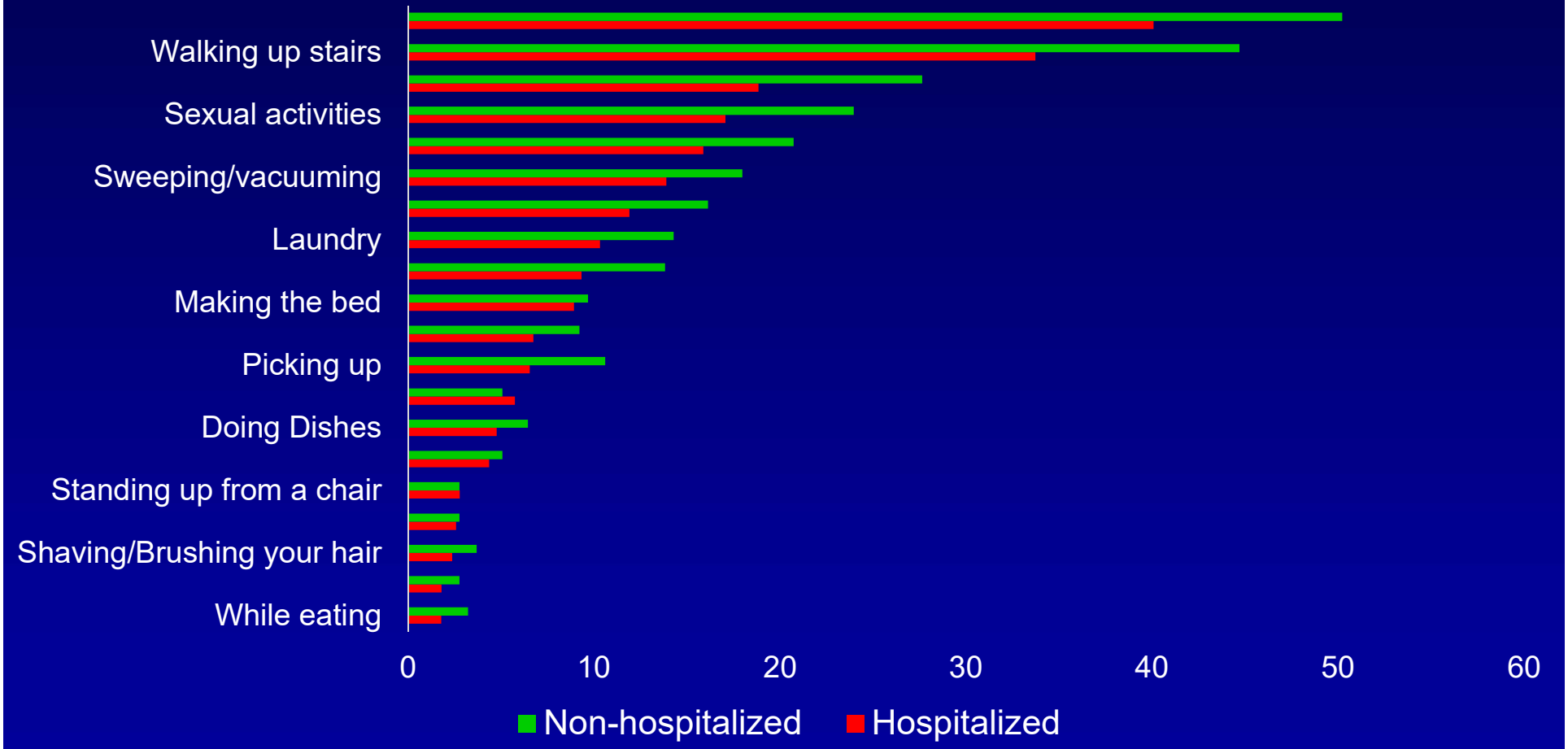
% Patients with Persistent Symptoms at 3 months Stratified by Hospitlization



MEDICAL STATUS AT 3 MONTHS STRATIFIED BY AGE



% of Patients who report moderate SOB



Summary 3

Chronic phase

Long COVID-19 – risk factors are now identified

No specific test but understanding is growing

Multidisciplinary approach

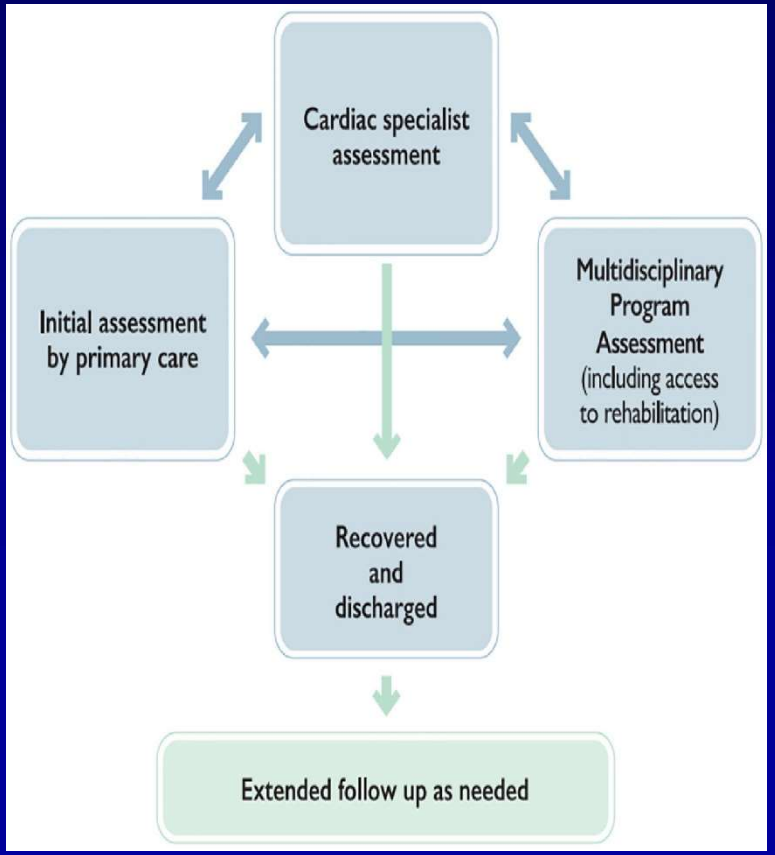
Cardiac features warranting further evaluation

Persistent or new unexplained chest pain.

Shortness of breath.

Frequent palpitations.

Orthostatic light headedness.



Canadian Journal of Cardiology 2021 371260-1262DOI: (10.1016/j.cjca.2021.05.011)

Paterson I, Ramanathan K et al CJC 2021:37;1260

Symptom	Suspected etiologies	Investigations	Treatment
Chest Pain	Ischemia (new* vs. existing)	ECG, cTn, Functional vs. Imaging	Guideline based goal directed
(rule of chest wall/GI)	Myo/pericarditis	ECG, cTn, Echo, CMR	Rest, NSAIDs, colchicine & other
	Thromboembolic disease	ECG, cTn, CT, V/Q	Anticoagulation

Pre-existing disease/ Risk factors

Severity of symptoms and quality- Hx is key

ACS – refer to acute management facility

ETT – New symptoms low yield

Emphasis on physical examination and non-invasive assessment utilising local expertise
*** Pre-existing RFs or multisystem disease**

Paterson I, Ramanathan K et al CJC 2021:37;1260

Symptom	Suspected etiologies	Investigations	Treatment
SOB	CHF	ECG, N.peptides, Echo, CMR, Cath	Guideline based goal directed
(anginal equivalent)	Thromboembolic disease	ECG, cTn, CT, V/Q	Anticoagulation
	Underlying lung disease	CXR, PFTs, CT	LABA/LAMA, Steroids
	Residual Lung disease/PH	CXR, PFTs, CT, R.heart cath	Specialized clinics referral
	Deconditioning	Pedometer, cardio/pul ETT	Rehabilitation

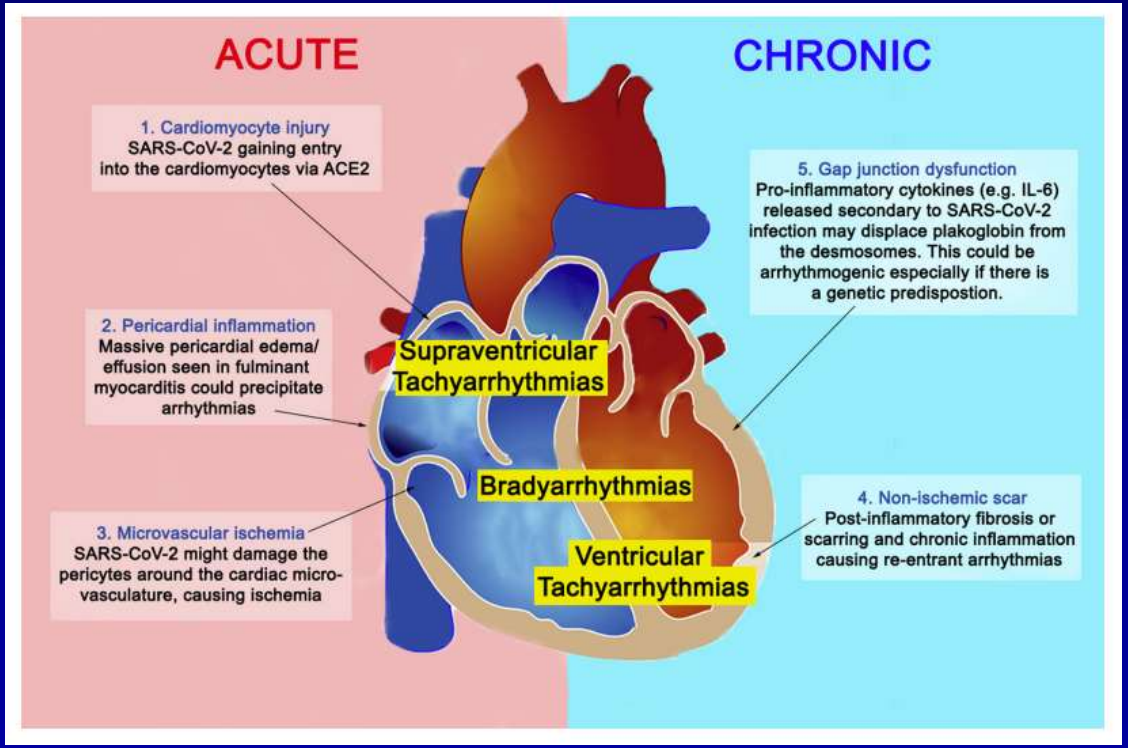
Pre-existing conditions- specialist referral
Difficult diagnosis
SOB alone was a poor predictor of PE
Similarly D-dimmer

Emphasis on physical examination and non-invasive assessment utilising local expertise

Paterson I, Ramanathan K et al CJC 2021:37;1260

Symptom	Suspected etiologies	Investigations	Treatment
Palpitations	Arrhythmias	ECG, Holter Monitor (Wearables)	As per usual care
	Inappropriate ST	ECG, ETT, active standing test	Beta blockers, Ivabradine

Severity / Frequency and duration
Genetic predisposition



Emphasis on physical examination and non-invasive assessment utilising local expertise

Paterson I, Ramanathan K et al CJC 2021:37;1260

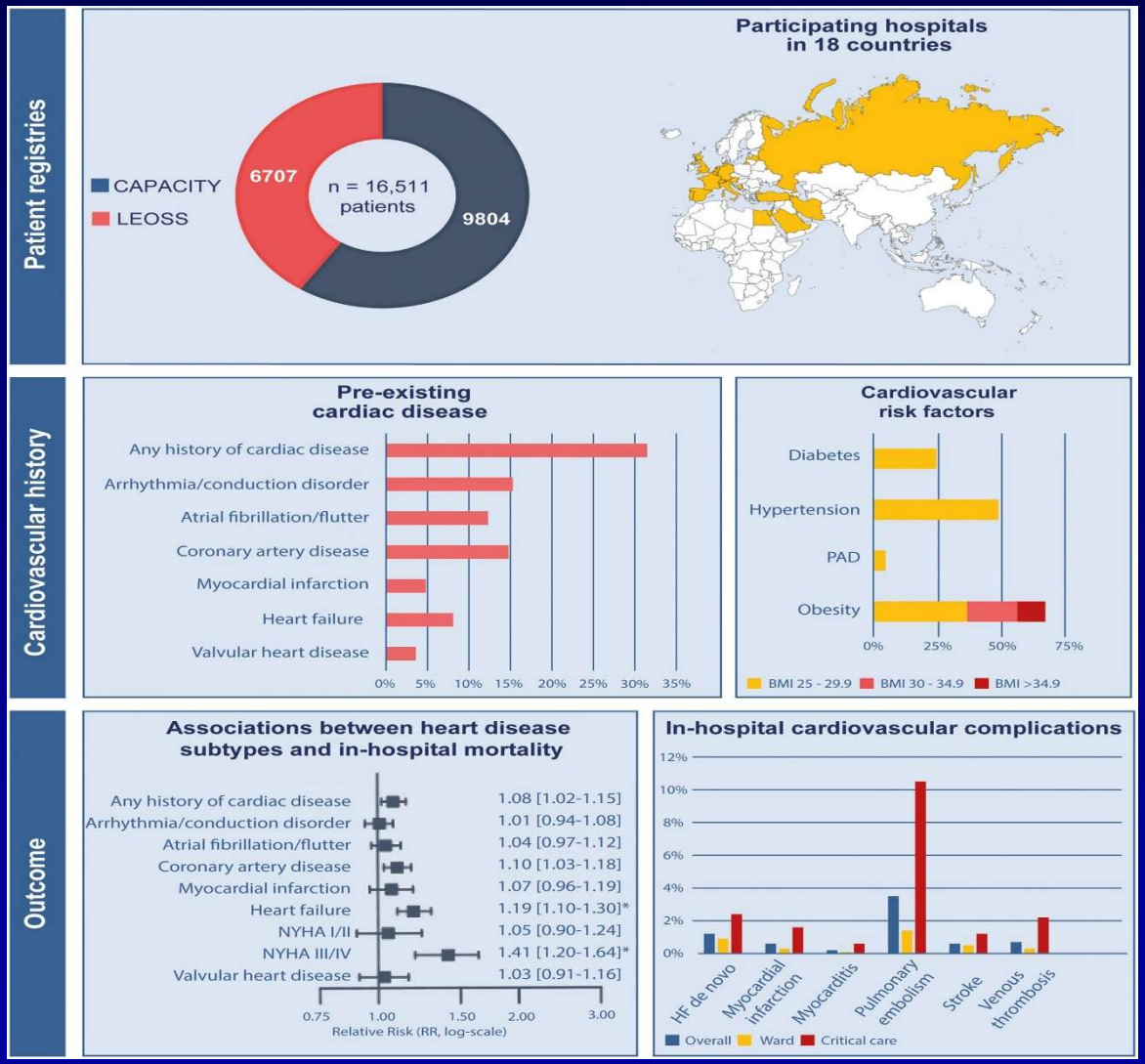
Symptom	Suspected etiologies	Investigations	Treatment
Postural /Orthostatic	Cardiac Dysautonomias POTS like	Postural Vital signs, Active Standing test	Hydration, Na supplementation, Compression garments. Midodrine. BB, Ivabradine

Specialist referral
Difficult diagnosis

Emphasis on physical examination and non-invasive assessment utilising local expertise

Paterson I, Ramanathan K et al CJC 2021:37;1260

Graphical Abstract After multivariable adjustment, the strongest association was found for heart failure and in-hospital ...



Eur Heart J, Volume 43, Issue 11, 14 March 2022, Pages 1104–1120

Summary 4

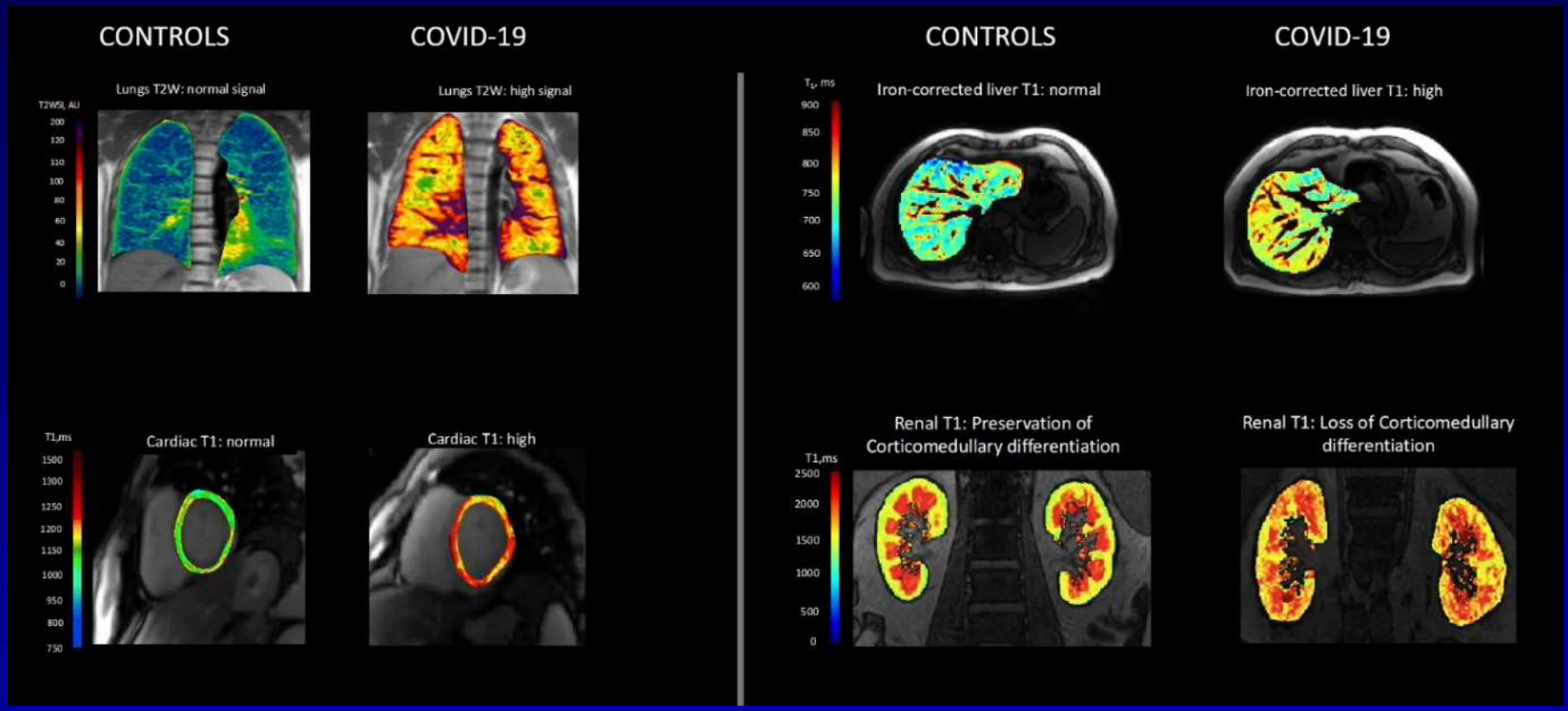
Specific symptoms for consideration

Pre-existing / genetic predisposing disease (CHF) is a key factor

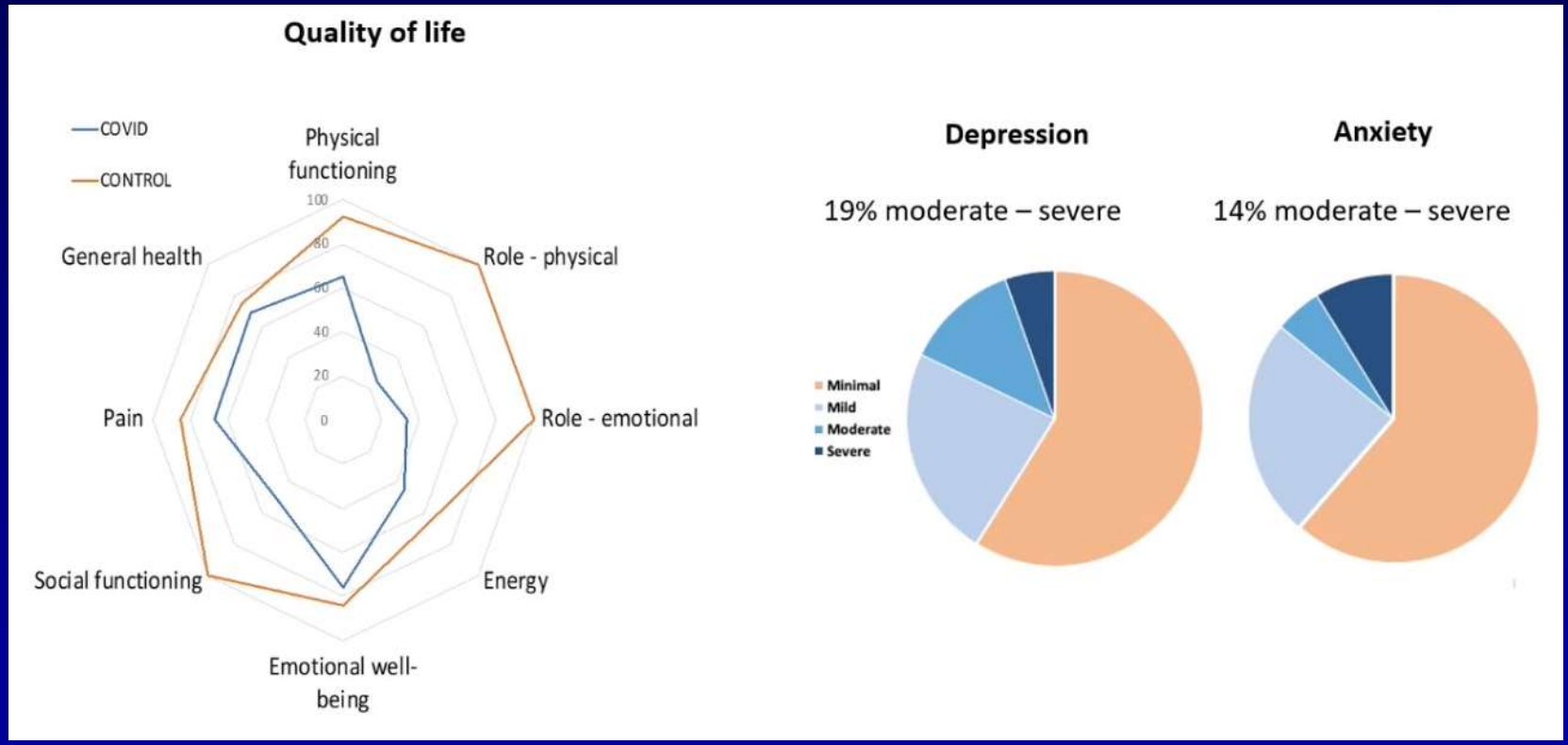
Very few investigations have been helpful in the chronic phase including 2D echo, CT, ETT, biomarkers

Investigations are best guided on the basis of a good history and clinical acumen

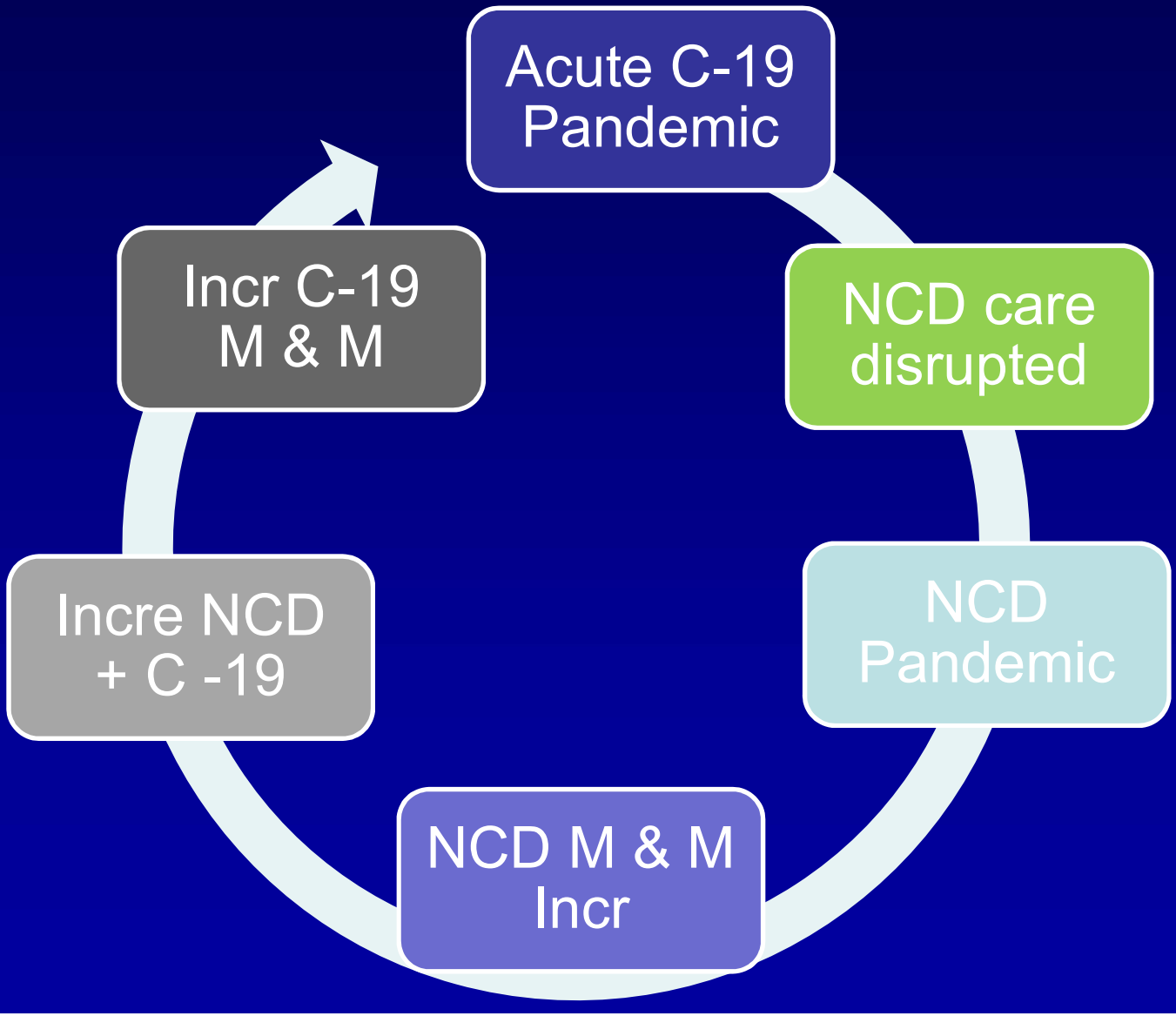
MRI Images Lung, Heart, Liver & Kidney

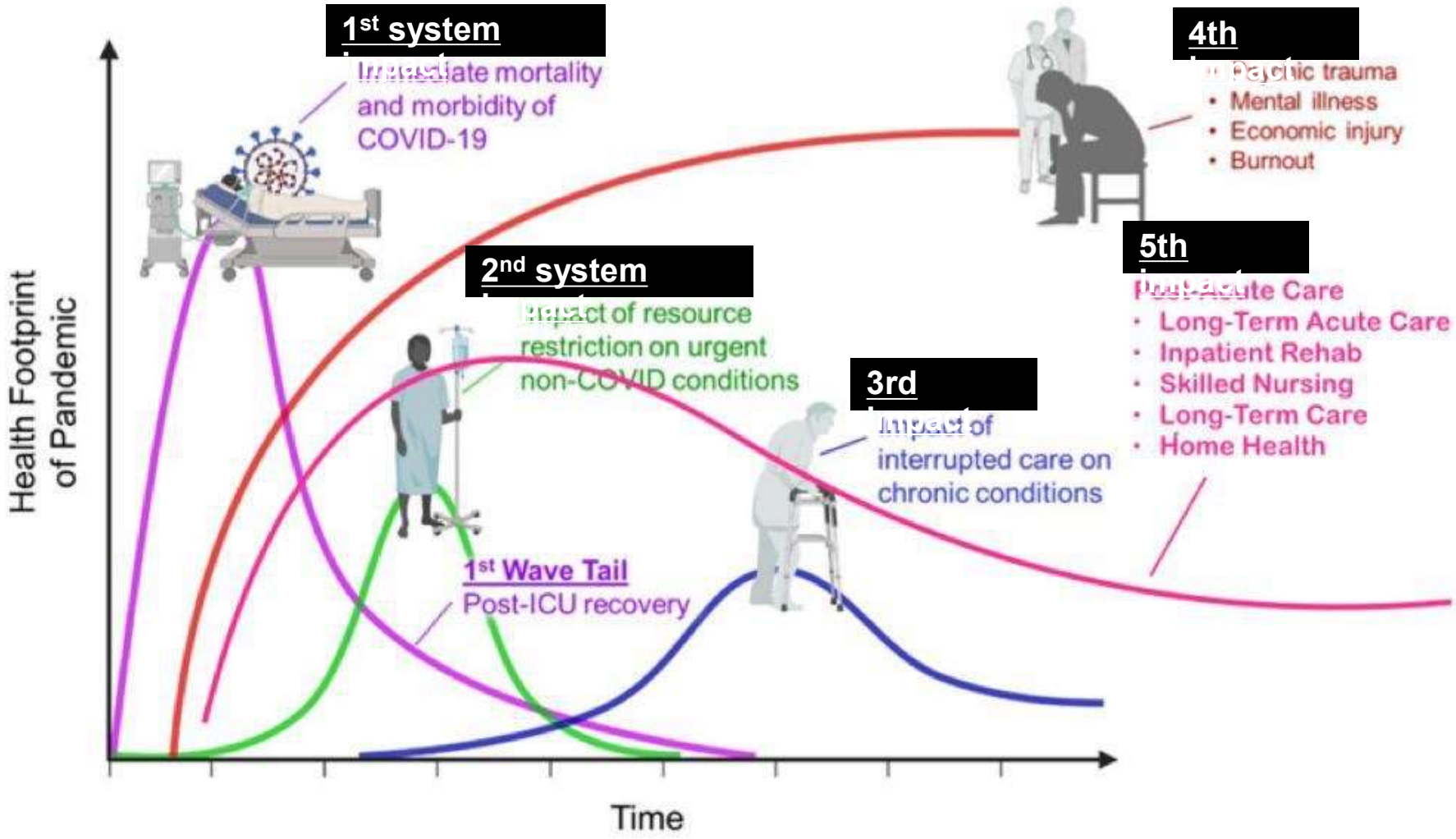


COVID-19 QoL & Mental Health



Inter-relationship between Acute COVID-19 & Non-Communicable Disease





Source: Twitter, Dr. Victor Tseng 2020, modified by Dr. Brian McMichael 2020, and Dr. Jill Calder 2022

Current variants of concern in Canada include:

Alpha (B.1.1.7)
Beta (B.1.351)
Gamma (P.1)
Delta (B.1.617.2)
Omicron (B.1.1.529)

Evidence demonstrates that Alpha and Delta variants are at least 50% easier to spread than the original version of the virus identified at the beginning of the pandemic.

The Gamma, Beta and Delta variants each have certain mutations that may have an impact on vaccine effectiveness.

Omicron is likely more transmissible than other variants of concern to date. Studies are underway to determine how much is due to:
Omicron's natural ability to spread, a reduction in immune protection following vaccination or previous infection

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Conclusion

- ACE-2 Receptor
- SARS-CoV-2 pandemic with estimated death > 15 million
- Acute illness (Inflammation / Pro thrombotic and cytokine storm)
- Variety of CV manifestations
- Biomarkers can be helpful with prognosis
- Unique " Myocarditis" manifestation but also with mRNA vaccine *(AZ vaccine thrombosis in women)*
- SARS-CoV-2 can result in prolonged "illness"
- Long COVID is a spectrum of physical, social, and psychological consequences.
- Cardiac symptoms are common along with fatigue and "brain fog"
- Mechanism unknown. Several triggers (physical /emotional /cognitive)
- Presently no laboratory test can definitively distinguish post-COVID conditions from other etiologies
- Therapy guided by careful assessment and often require a multidisciplinary approach in specialised clinics
- Increasing impact on NCD and overall health care and society
- **Resilience of the Health Care in Canada**

Acknowledgement

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Project Leader, Virtual Health & Shared Care

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