

Long COVID—

Present Understanding

**Limits of Prediction & How to Use Long COVID Information
in Morbidity and Mortality Prediction**

By: Nicholas C. Bellos, MD FIDSA FACP

01/23/2023



Quest
Diagnostics™

Nicholaos C. Bellos, MD FIDSA FACP

- Boarded Infectious Disease
- Graduate of Baylor College of Medicine Houston, TX
- Completed Internal Medicine training and Chief Residency at Tulane Affiliated Hospitals in New Orleans, LA
- Fellowship in Infectious Diseases at the University of Miami where he subsequently joined the Faculty and subsequently moved to Dallas and entered private practice.
- Extensive Hospital experience including transplant patients and HIV
- Active Clinical practice
- ExamOne focus on clinical utility, analytic validity test portfolio
- Interests are in Infectious Diseases in Immunocompromised and Transplant patients
- Physician Chair Quest Pandemic Preparedness Committee
- Over 65 articles as a leading author in major medical journals regarding HIV therapeutics.
- Also serves as medical director for Quest Diagnostics Outpatient Services. Involved on the payer provider side of health care and currently continues to see patients one day a week.

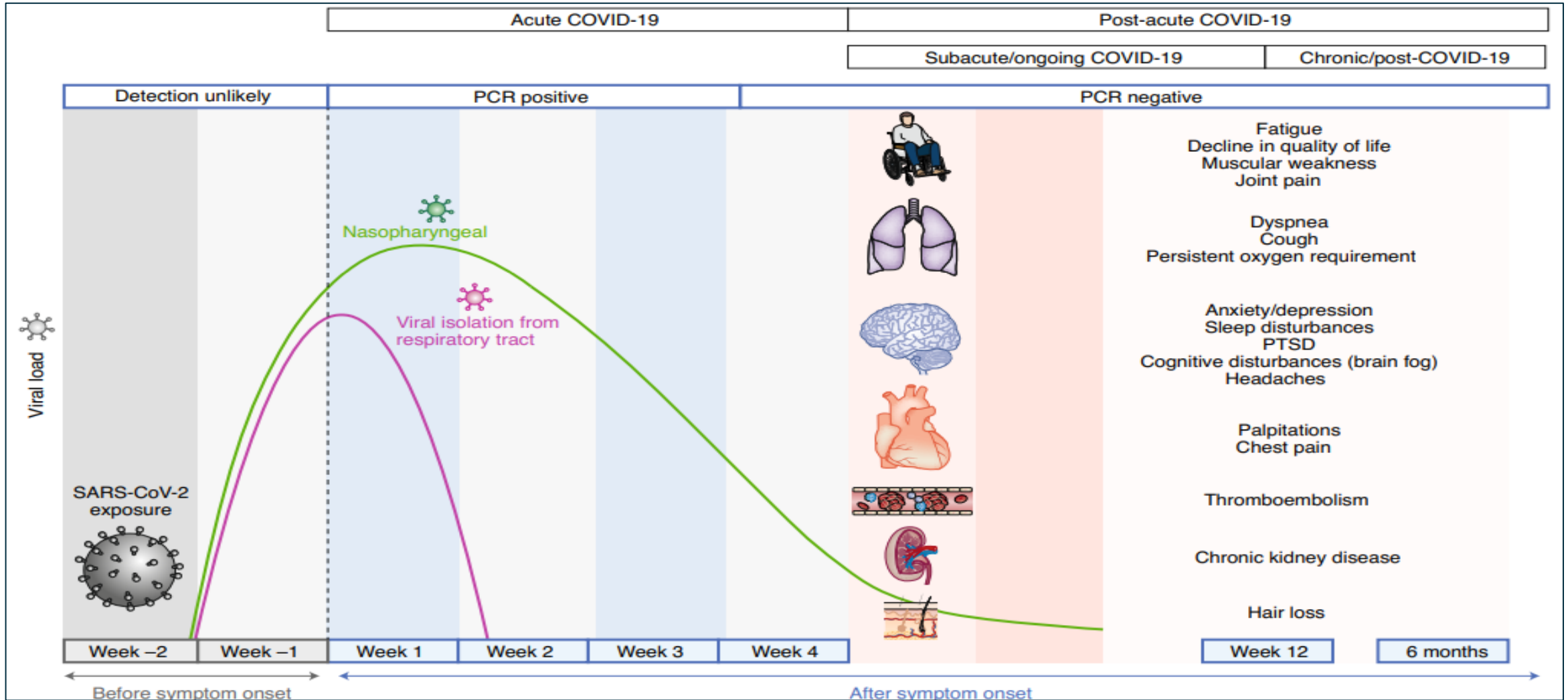
Agenda

- What is Long COVID?
 - Approach to evaluating patients in the clinic or hospital
 - Necessary criteria to give someone the diagnosis of Long COVID
 - Prevalence in different populations
 - Morbidity & Mortality
 - on morbidity and mortality
 - Summary
- Treatment
 - Surveillance
 - Resolution
 - Information for actuaries and underwriters who are active in making morbidity and mortality determinations
 - Areas of research on morbidity and mortality
 - Summary

High-rate of multi-organ disease in patients with Long COVID-19 Syndrome

- **COVID-19** is now recognized as a multi-organ disease with a broad spectrum of manifestations.
- There are increasing reports of **persistent and prolonged effects** after acute COVID-19.
- Long COVID-19 is a syndrome **characterized by persistent symptoms and/or delayed or long-term complications** beyond 4 weeks from the onset of symptoms.
- **Hospitalization, ICU admission and care, as well as ventilation** support are highly associated with the development of long COVID.
- **Severity of outpatient illness** also correlates with the development of long term COVID.

Timeline of Long COVID-19 Syndrome



Epidemiology of Long COVID-19 Syndrome

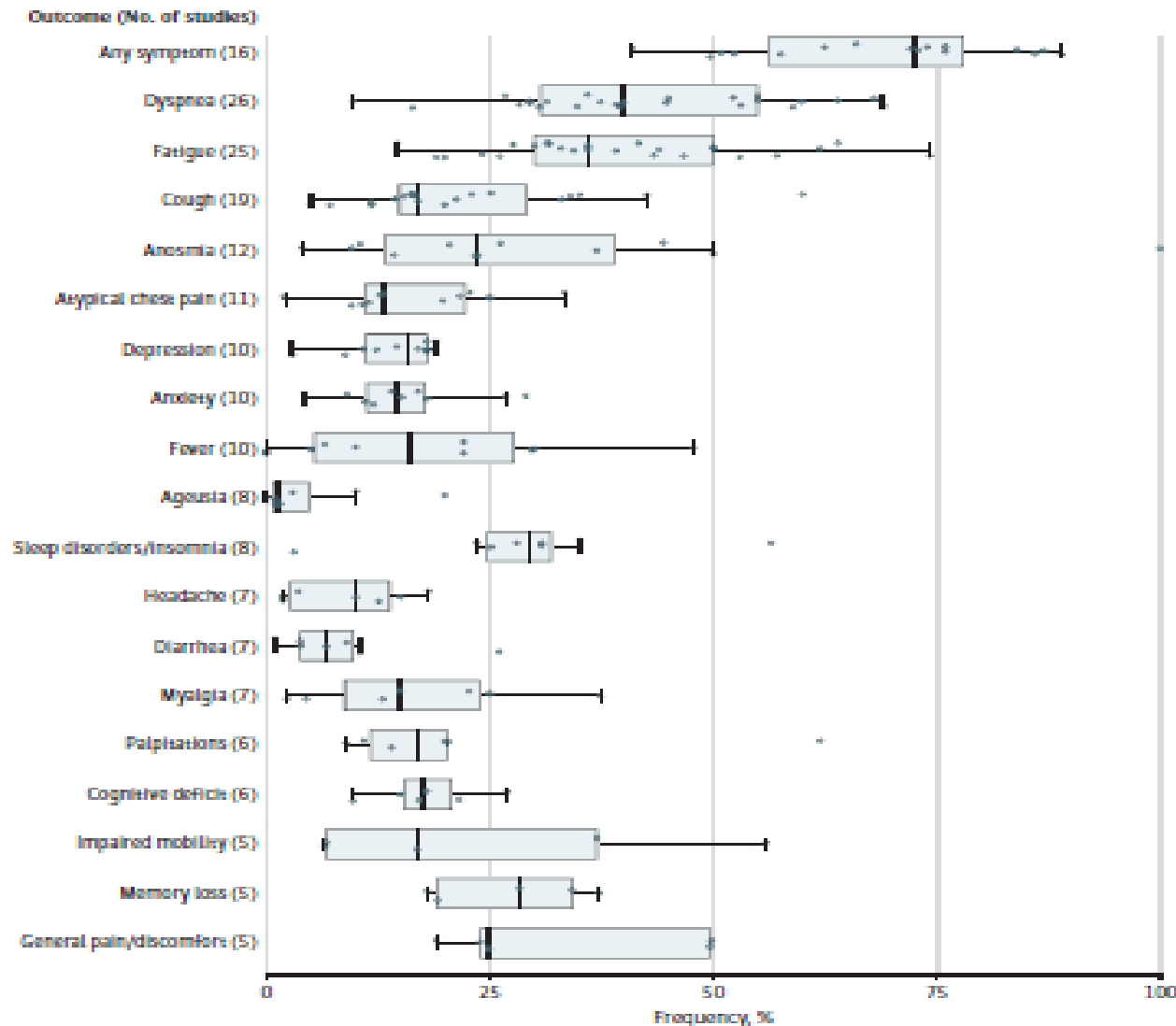
Observational cohort studies from 38 hospitals in Michigan, US, similar studies from Europe (Italy, Spain and France) UK, and China reported that among patients at least 60 days long discharge

- **6.7% died** while **15.1% required re-admission.**
- **32.6%-87% reported persistent symptoms** including 18.9% of new or worsened symptoms
- **21.7%** had chest pain - Patients experiencing persistent cardiac complications may be monitored with serial clinical, echocardiogram and electrocardiogram
- **23%** had anxiety or depression
- **55%** experienced 3 or more symptoms
- **Decline in quality of life**, as measured by EuroQol visual analog scale was identified in **44.1% of patients**

- 23- 43% had shortness of breath while walking up the stairs
- 27.3% joint pain
- 53% had fatigue
- 23% had anxiety or depression
- 26% had sleep difficulties

Epidemiology of Long COVID-19 Syndrome (continued)





Figure 1. Reported Frequencies of Symptoms Examined by 5 or More Studies



- 9751 participants, 54% male
- 45 studies reporting 84 symptoms of long COVID
- Symptoms persistent at least 60 days after diagnosis, symptoms onset or hospitalization
- The median proportion of participants with at least persistent symptom was **72.5%**
 - Shortness of breath or dyspnea - **36%**
 - Fatigue or exhaustion – **40%**
 - Sleep disorder or insomnia – **29.4%**

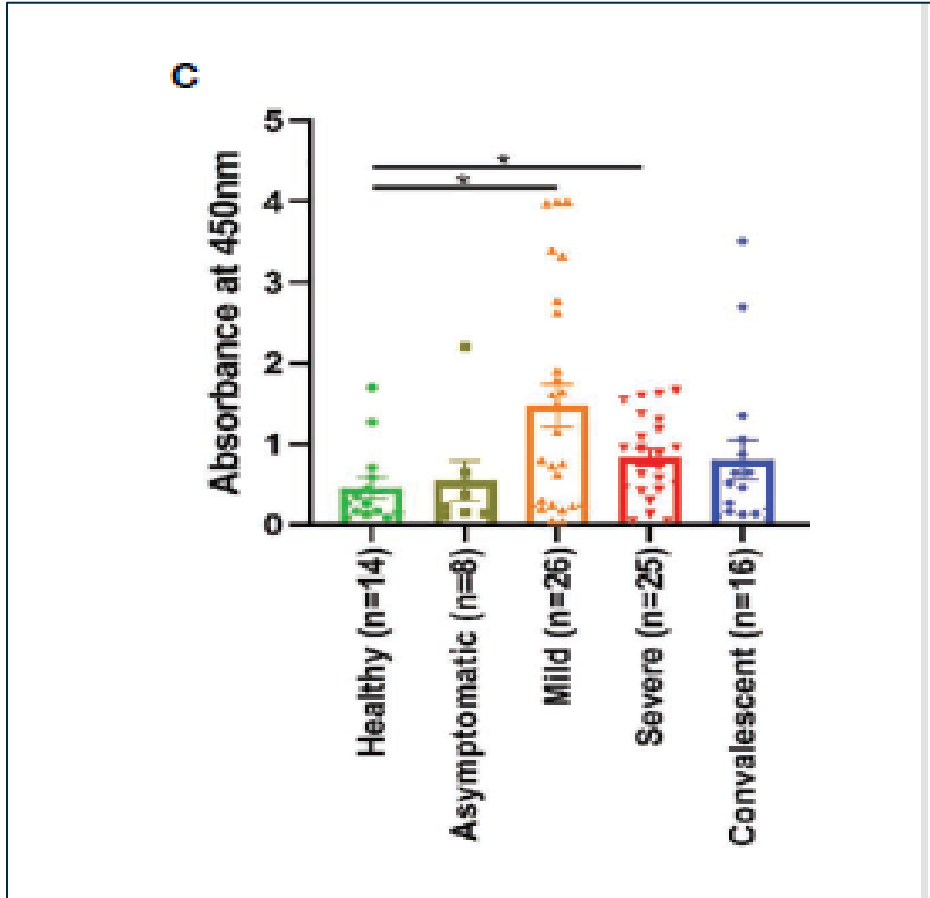
What Actuaries and Underwriters Should Consider in Clinical Records and Lab Results that Should Inform Mortality and Morbidity

- Hs CRP
- ProBNP
- Cardiac troponin
- Pulmonary function tests
- Hbg A1c
- Serum Creatinine

Secondary Disease	Analyte & Ratio
 Cardiovascular Disorders	ApoA1 ApoB ApoB/ApoA1 TG Chol, LDL-Chol, HDL-Chol, LDL-Phos, HDL-Phos
 Prediabetes or Diabetes Type II	Glucose
 Kidney Disorders	Creatinine
 Inflammation (NMR only analytes)	GlycA GlycB Glyc SPC* Glyc/SPC

MPO: marker of inflammation and oxidative stress for CVD and neuro-affective symptoms in PACS

MPO is elevated in patients with COVID-19



⁵Shrivastava et al., Frantiers in cel an dmol biol; 2021.

- Associated with cardiovascular events in landmark prospective studies (e.g., EPIC) ^{1,2}
- Associated with kidney and liver impairment ^{3,4}
- CVD Risk in high MPO patients is reduced by statins and fenofibrates
- MPO is elevated in patients with severe COVID-19⁵

¹Meuwese et al, J Am Coll Cardiol.; 2007;50:159-65

²Brennan al.,N Engl J Med. 2003;349:1595-604

³Correa S. Am J Kidney Dis. 2020;76(1):32-41.

⁴Rensen et al., Am J Pathol.; 2009;175:1473.

⁵Shrivastava et al., Frantiers in cel an dmol biol; 2022;175:.

⁶Kadhem Al-Hakeim, RxMed Pre-print, April 2022

Long COVID-19 by organ systems: Pulmonary

- Shortness of breath, decreased exercise capacity and low oxygen
- **Reduced diffusion capacity, restrictive pulmonary physiology, and ground-glass opacities and fibrotic changes on imaging**
 - CT scans can reveal scarring of the lungs observed 3 months after hospital discharge in approximately 25% and 65% of survivors in cohort studies of mild-to-moderate cases
 - Pulmonary vascular clots have been observed in 20–30% of patients with COVID-19 , which is higher than in other critically ill patient populations (1–10%)
- **Management** : Assessment of progression or recovery of pulmonary disease and function may include as clinically appropriate
 - Home pulse oximetry
 - 6 MWTs (6 minutes walk test)
 - Other pulmonary function tests (PFTs): e.g., spirometry, lung volume testing)
 - Serial PFTs and 6MWTs for those with persistent dyspnea, as well as high-resolution computed tomography of the chest at 6 and 12 months
 - Lung transplantation
 - Clinical trials of antifibrotic therapies to prevent pulmonary fibrosis after COVID-19 are underway

Long COVID-19 by organ systems: Cardiovascular

- Persistent symptoms may include **palpitations, shortness of breath and chest pain**
- Long term sequelae may include **increased cardiometabolic demand, myocardial fibrosis or scarring** (detectable via cardiac MRI), **arrhythmias, tachycardia** and **autonomic dysfunction**
- **Management:** Patients experiencing persistent cardiac complications may be monitored with serial clinical, echocardiogram and electrocardiogram
 - Serial clinical and imaging evaluation with electrocardiogram and echocardiogram at 4–12 weeks may be considered. Current evidence does not support the routine utilization of advanced cardiac imaging, and this should be considered on a case-by-case basis.
 - Recommendations for competitive athletes with cardiovascular complications related to COVID-19 include abstinence from competitive sports or aerobic activity for 3–6 months until resolution of myocardial inflammation by cardiac MRI or troponin normalization

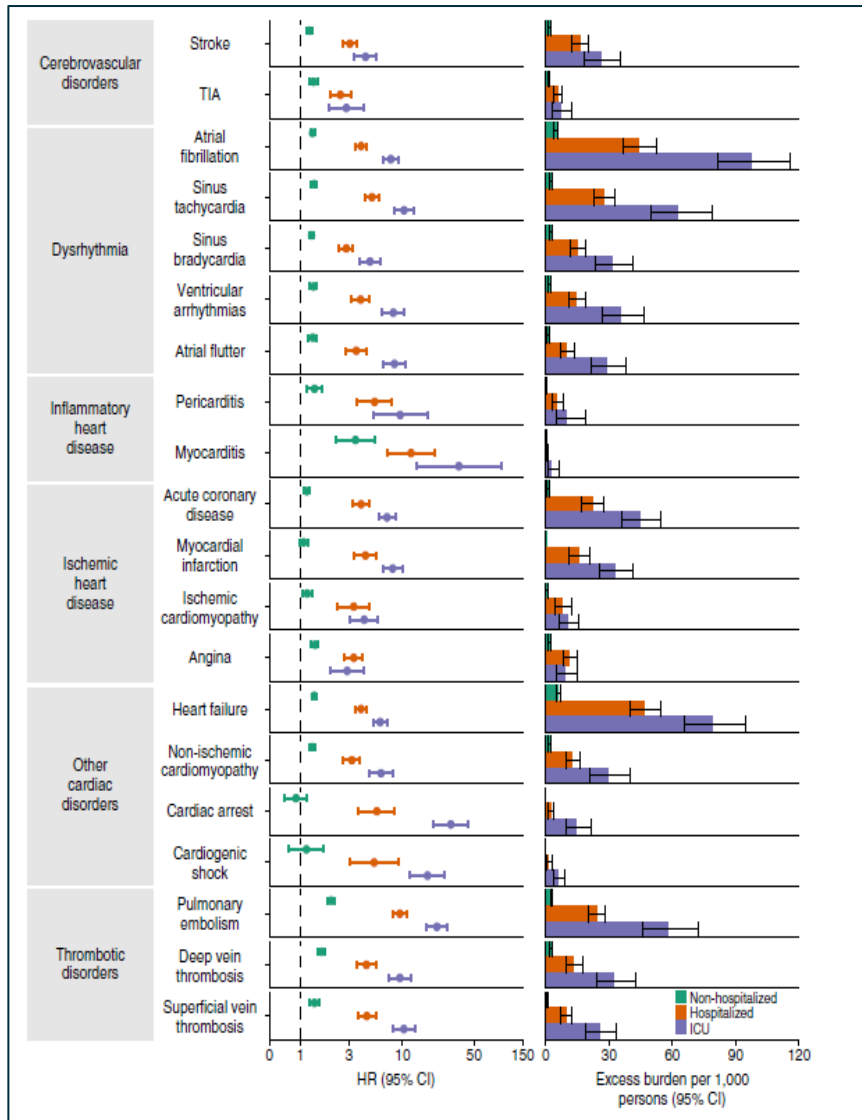
Elevated Troponin and BNP Predict Abnormal Echocardiogram in Long COVID-19

International prospective echocardiographic study in patients after COVID-19

- A total of 1216 patients 52-71 years, 70% males from 69 countries across six continents
- Overall, 667 (55%) patients had an abnormal echocardiogram.
- Left and right ventricular abnormalities were reported in 479 (39%) and 397 (33%) patients
- Severe cardiac disease (severe ventricular dysfunction or tamponade) was observed in 182 (15%) patients.
- In those without prior cardiac disease (n = 901), the echocardiogram was abnormal in 46%, and 13% had severe disease.
- Independent predictors of left and right ventricular abnormalities were elevated:
 - Natriuretic peptides (BNP or NT-proBNP): OR 2.96, 95% CI 1.75-5.05
 - Cardiac troponin: OR 1.69, 95% CI 1.13-2.53
- Echocardiography changed management in 45% of patients with abnormal echocardiogram including initiating disease-specific therapy.
- Changes in therapy were greater in those with elevated biomarkers vs. the rest of the population: 39% vs. 31%, p<0.001

Elevated NT-proBNP and hs-Tn levels were predictors of the abnormal echocardiogram findings that results in optimization of the disease management

Risks and 12-month burdens of incident Long COVID-19 cardiovascular outcomes, compared with the contemporary control cohort



- Those with a history of COVID19 infection were **more likely to have the following 12 months later (risks for each of these varied):**
 - Strokes
 - Dysrhythmias
 - Myocardial infarction
 - Heart Failure
 - Deep vein thrombosis and pulmonary embolism
- Heart attack risk was 63% higher
- Myocarditis risk was 538% higher.
- **Heart outcomes** were elevated regardless of age, race, sex, obesity, smoking, high blood pressure, diabetes, high cholesterol, or having a pre-existing heart problem and risk was far higher among hospitalized patients versus those who were not hospitalized.
- Risk for **stroke** among non-hospitalized cases was 23% higher compared to controls, but the risk of stroke among ICU patients was 435% higher than controls.

Long COVID-19 by Organ Systems: Hematologic, Renal and Endocrine

- **Hematologic sequelae:**

- Thromboembolic events have been noted to be <5% in Long COVID-19 in retrospective studies

- **Management:** Direct oral anticoagulants and low-molecular-weight heparin may be considered for extended thromboprophylaxis in patients with predisposing risk factors for immobility, persistently elevated d-dimer levels (greater than twice the upper limit of normal) and other high-risk comorbidities such as cancer

- **Renal sequelae:**

- Reduced eGFR has been reported at 6 months follow-up
- COVID-19 survivors with persistent impaired renal function may benefit from early and close follow-up with a nephrologist as supported by its previous association with improved outcomes

- **Endocrine sequelae:**

- New or worsening control of existing diabetes mellitus, subacute thyroiditis and bone demineralization
- Patients with newly diagnosed diabetes in the absence of traditional risk factors for type 2 diabetes, or hyperthyroidism should **undergo the appropriate laboratory testing** and should be referred to endocrinology

Risk and Burdens of Incident Diabetes in Long COVID-19: Cohort Study

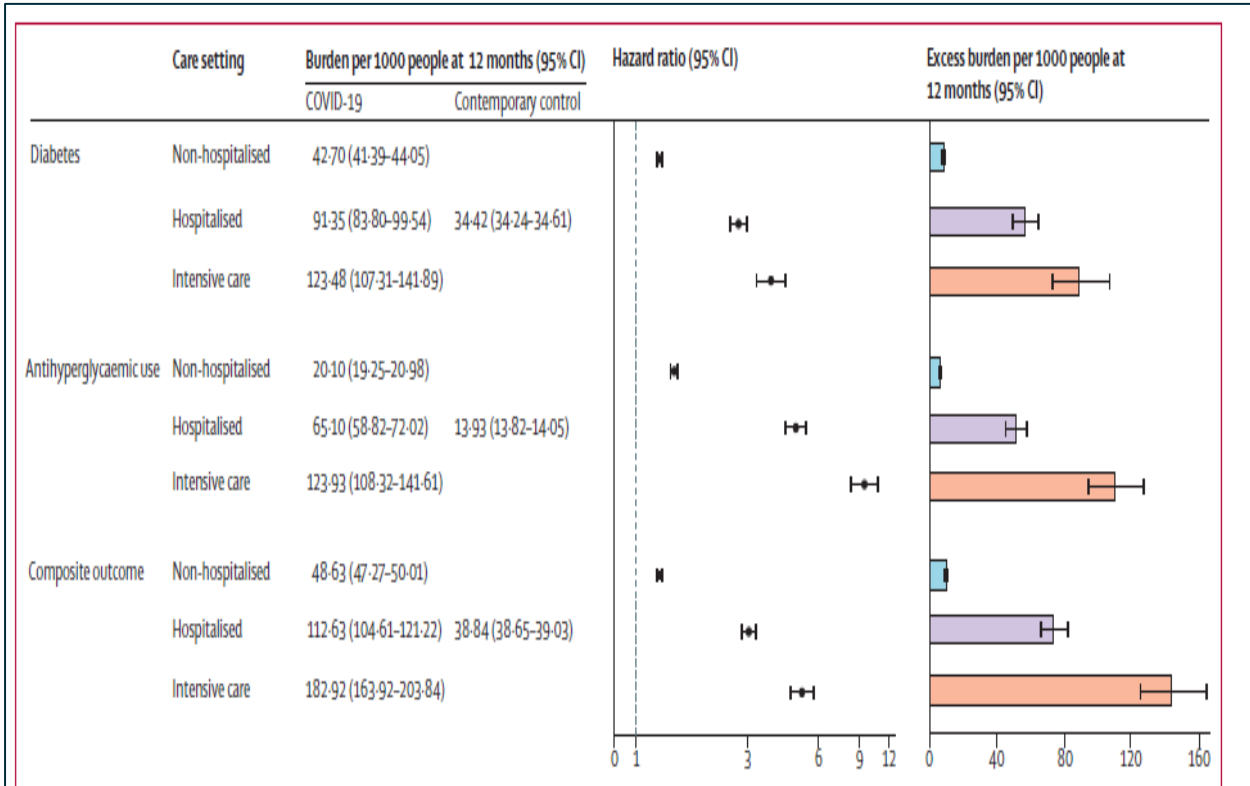


Figure 2: Risks and burdens of post-acute COVID-19 diabetes outcomes by severity of the acute infection compared with the contemporary control group
 Severity of the acute infection was defined as non-hospitalised (blue), hospitalised (purple), and admitted to intensive care (orange). The outcomes were ascertained from day 30 after COVID-19 infection until the end of follow-up. Adjusted hazard ratios and 95% CIs are presented in a base 10 logarithmic scale. Adjusted event rates per 1000 people at 12 months for each care setting during the acute infection, contemporary control group, and excess burden per 1000 people at 12 months and related 95% CIs are also presented.

- Higher Diabetes risk score
- Increased risk of incident diabetes in all patients and up to 5-fold greater risk in those after intensive care
- Excess burden of incident diabetes: 13.66 per 1000 people at 12 months

Long COVID-19 by organ systems: Neuropsychiatric

- **Neuropsychiatric.** Persistent abnormalities may include:
 - Fatigue
 - Myalgia
 - Headache
 - Cognitive impairment (brain fog)
 - Anxiety, depression, sleep disturbances and PTSD have been reported in 30–40% of COVID-19 survivors
 - A real-world, dataset analysis of 62,354 COVID-19 survivors from 54 healthcare organizations in the United States estimated the incidence of first and recurrent psychiatric illness between 14 and 90d of diagnosis to be 18.1%
 - The pathophysiology of neuropsychiatric complications is mechanistically diverse and entails immune dysregulation
- **Management consideration:**
 - Standard therapies should be implemented for neurologic complications such as headaches, with imaging evaluation and referral to a specialist reserved for refractory headache
 - Further neuropsychological evaluation should be considered in the long acute illness setting in patients with cognitive impairment
 - Standard screening tools should be used to identify patients with anxiety, depression, sleep disturbances, PTSD, dysautonomia and fatigue

Long COVID-19 : Multisystem Inflammatory Syndrome in Children (MIS-C)

- **Diagnostic criteria: CDC reports 6400 cases 55 deaths**

- Typically affects children >7 years and disproportionately of African, Afro-Caribbean or Hispanic origin 3-6 weeks post-acute illness
- Fever
- Elevated inflammatory markers;
- Current or recent SARS-CoV-2 infection; and exclusion of other plausible diagnoses
- Clinical presentations of MIS-C include abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions, hypotension and cardiovascular and neurologic compromise
- Cardiovascular complications: coronary artery aneurysm
- Neurologic complications: headache, encephalopathy, stroke and seizures

- **Management considerations**

- **Immunomodulatory therapy** with intravenous immunoglobulin, adjunctive glucocorticoids and low-dose aspirin until coronary arteries are confirmed normal at least 4 weeks after diagnosis
- **Therapeutic anticoagulation** with enoxaparin or warfarin and low-dose aspirin is recommended in those with a coronary artery z score ≥ 10 , documented thrombosis or an ejection fraction $< 35\%$
- **Serial echocardiographic assessment** is recommended at intervals of 1–2 and 4–6 weeks after presentation. Cardiac MRI may be indicated 2–6 months after diagnosis in those presenting with significant transient left ventricular dysfunction (ejection fraction $< 50\%$)

Long COVID-19 by Organ Systems: Interdisciplinary Management

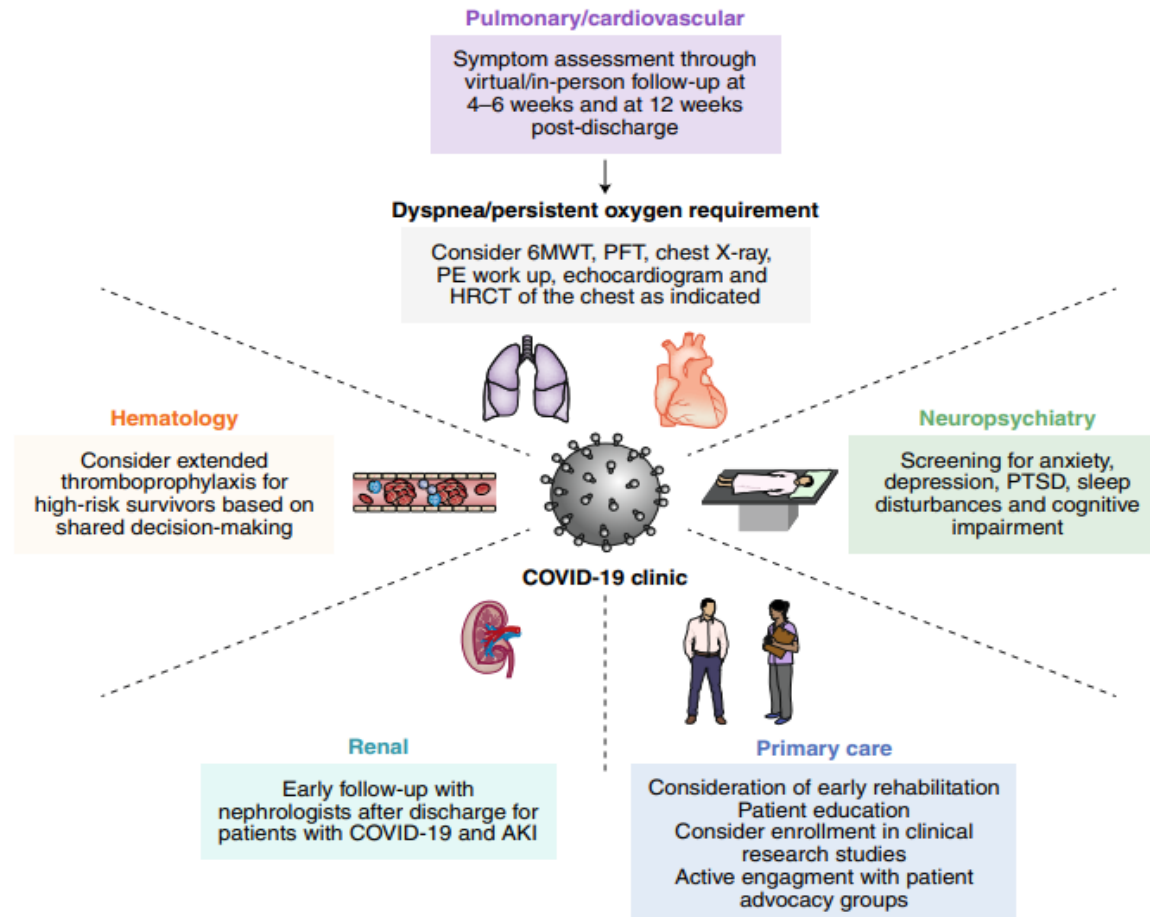


Fig. 2 | Interdisciplinary management in COVID-19 clinics. Multidisciplinary collaboration is essential to provide integrated outpatient care to survivors of acute COVID-19 in COVID-19 clinics. Depending on resources, prioritization may be considered for those at high risk for post-acute COVID-19, defined as those with severe illness during acute COVID-19 and/or requirement for care in an ICU, advanced age and the presence of organ comorbidities (pre-existing respiratory disease, obesity, diabetes, hypertension, chronic cardiovascular disease, chronic kidney disease, post-organ transplant or active cancer). The pulmonary/cardiovascular management plan was adapted from a guidance document for patients hospitalized with COVID-19 pneumonia⁷⁶. HRCT, high-resolution computed tomography; PE, pulmonary embolism.

Medication Therapies

- Oral therapies Paxlovid, Lageviro are available and should be initiated within 5 days of symptom development or positive Covid test.
- Veklury (remdesivir) IV infusion therapy may be provided either in the inpatient or outpatient setting.
- Initiation of therapy early (within 5 days) reduces the severity of acute COVID and thus the risk for development of long COVID.
- Vaccination has also been shown to reduce severity of acute COVID as well as hospitalizations. This has also been associated with a decreased risk of long COVID.

Long COVID-19 - GOING FORWARD

- There is **no syndromic definition** for Long COVID
- Estimations are **1/5 individuals who have had previous COVID infection will develop long term COVID** and there are individuals who are predicting this could be the next "pandemic"
- Biomarkers- **currently no specific biomarkers exist for LONG TERM COVID**. The diagnosis is made based on a syndromic approach with evaluation and treatment based on specific organ system involvement.
- **Mortality risk is based on the specific system involved, degree of severity** of presenting symptoms (i.e., CHF secondary to Covid myocarditis, clot based on increased coagulability etc.) and standard rates based on the severity.
- **Recurrent COVID 19 infections increase the risk of long term COVID development** and potential development of disability depending on severity of symptoms.
- Long Term COVID is considered a diagnosis for long-term disability. **Disability will be based on the organ system involved**. The determination, however, may be based on Long Term COVID, or related to the organ system involved (neurologic, cardiac, pulmonary etc.)