COVID 19 [SARS-COV-2] NON-PULMONARY SEQUELAE AND THEIR REHABILITATION
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LITERATURE BASE

- Pub Med searches: COVID 19 + [complications; cardiac; pulmonary; renal; neurological; rehab], long COVID
- Reference from review articles
- World wide studies: China, Italy, UK, US, … (English language based or English language cited)
- Extensive but much less for non-pulmonary and for rehab
- Studies also include experience with or extrapolation from SARS, MERS and ARDS (not completely the same diseases)
- Studies also extrapolate from non-COVID prior ICU studies
STUDIES ON SOCIAL ISOLATION AND HEALTH HABITS

• Staying at home (shift to school/work at home)
• Closing of gyms
• Restrictions at outpatient therapy programs
  • Increased sitting time (~3 hours)
  • Increased screen time (~5 hours)
  • Decreased sports/physical activity (~2 hours, 33.5%), decreased # steps/day
  • Switch to hyperpalatable, convenience foods-less protein, more carbs (46.1%)

• By extrapolation from prior known data, all off the above = less muscle (sarcopenia), more fat (obesity), decreased sleep (57.1% in COVID isolation), increased inflammation, “biostat reset” (increased appetite, want to exercise less, reset to maintain higher weight).
ISOLATION AND HEALTH HABITS (CONT’D)

- Sleep loss: drops leptin levels, increases ghrelin levels, increases hunger with preference for high carb foods.
- Decreased vitamin D exposure: non-COVID studies show deficiency leads to decrease muscle strength. No COVID specific studies reported.
- By extrapolation from non-COVID data-these changes in health habits increase risk for cardiovascular disease, HTN, DM, immunosuppression, decreased QoL scores and increased mortality. Changes in health habits increase chances for developing the risk factors that lead to more severe COVID 19 infection.
CONSIDERATION FOR GERIATRIC PATIENTS

• Pre-existing age-related sarcopenia
• Food-insecurity
• Pre-morbid insulin resistance
• Hormonal and skeletal muscle capillary changes making it harder to make muscle
• Pre-existing osteopenia, osteoporosis
• Sarcopenia may increase risk of falls, fractures from osteopenia.
PREVENTION WITH REHAB MEASURES

- Home resistive exercises (free weights, resistance bands, ZOOM Telemedicine PT)
  - Telehealth exercise over 12 weeks in sarcopenic patients led to increased muscle mass and function
  - Lower intensity, higher reps but to muscle exhaustion, heavy to lighter load, diversity of exercises, short-term goal setting (compliance)
  - Clearance from cardiac, co-morbidity and patient education
- Aerobic exercises (counting steps, smart device programs, videos)
- Vit D if needed, multiple vitamin with minerals
- High protein diet (small frequent meals, high in leucine and creatin-meat, fish dairy, eggs)
  - 0.75 g protein/kg body weight/day
  - Older adults 1.2-1.5 g/kg/d-safe if renal function okay, may need adjust if not
DISEASE DIRECT VS ICU/IMMOBILIZATION RELATED

DISEASE DIRECT

- Affinity of COVID 19 for ACE1 and ACE 2 receptors (heart, kidneys, liver ...)
- Invasion of virus into organ tissues through hematological or neuronal retrograde routes (brain)
- Triggers cytokines/cytokine storm
- Effects of hypoxia

ICU

- Prone positioning
- Prolonged bedrest
- Isolation
- Loss of time concepts
- Medication related (steroid, pain meds)
ICU

Early

• ARDS
• Sepsis/Septic shock
• Multi-organ failure
• Acute kidney injury
• Cardiac injury
• Myofascial pain in neck/shoulders

Late

• Critical illness polyneuropathy (CIP)
• Critical illness myopathy (CIM)
• Post-intensive care syndrome (PICS)
• Dysphagia
• Muscle weakness
• Loss of ROM
• Impaired standing, balance, ADL’s
• Disorders of consciousness.
## ICU CONDITION DIFFERENCES

### CIP
- Symmetrical distal > proximal weakness
- Distal sensory loss
- Muscle atrophy
- Decreased or absent DTR
- Difficult vent weaning due to diaphragm weakness
- Can also see dysphagia and incontinence
- Recovery up to 2 years
- Secondary effects are depression, anxiety, loss of ROM, stress disorders

### CIM
- Non-necrotizing myopathy with fiber atrophy and fibrosis
- Proximal > distal weakness
- Sensation preserved
- CN preserved
- May recover better than CIP

### PICS
- Reduced pulmonary function (restrictive pattern)
- Reduced inspiratory muscle strength
- Poor knee extension
- Impaired UE and grip strength
- Recovery over 1 year
SYSTEMS INVOLVED

- Cardiac
- Renal
- Musculoskeletal
- Psychological and Mental Health
- Neurological
- Endocrine

- Gastrointestinal
- Hepatic
- Dermatological
- Hematological
- Rheumatological
SOME REHAB/EXERCISE BASICS

AVOID in:
• Tachycardia
• Hypo- or Hypertension
• Desaturating despite oxygen
• Co-morbidities in which exercise is contraindicated

STOP if:
• Sudden rise/drop in temperature
• Respiratory status/fatigue worsen and symptoms do not go away with rest breaks
• Chest pain/tightness, dizziness, palpitations, sudden headache/blurred vision
ICU REHABILITATION

• Early mobilization and respiratory therapy in the ICU at bedside
  • Improves long term recovery and functional independence, reduces time on ventilator, LOS in hospital
• Caution as being too aggressive with therapies/activity can lead to a decline
• Encourage: ROM, positioning/splinting. Once not sedated, OOB to chair, active strengthening, breathing exercises, secretion management
• Early psychological support (SW, clergy, psychology, psychiatry)
ICU REHAB AND DISORDERS OF CONSCIOUSNESS

- Subset patients remain unresponsive after removal of sedation.
- Multidisciplinary team: Critical care medicine, Neurology, PM&R, PT, OT, SLP
- >=18 yrs old, no prior DOC prior to COVID 19
- Multimodal sensory stimulation (auditory, visual, tactile), upright positioning, stretching, ROM, oral care, music.
- 57% emerged to minimally conscious state or better.
- Improvement did not relate to MRI or EEG findings.
- Improvement did relate to earlier wean of fentanyl, longer use of oxycodone (neuroprotective), lower BMI, lower CRP, higher minimum partial arterial pressure of oxygen, earlier use of amantadine or modafinil. (did not account if those more critically ill did not get oxy or neurostimulants sooner)
Fig. 1 Feature-based common data element findings on brain MRI [32], by percentage of patients (N=21). The asterisk denotes the percentage of patients who received contrast (n = 8). DWI diffusion-weighted imaging, MCS minimally conscious state, MRI magnetic resonance imaging, SWI susceptibility-weighted imaging, UWS/VS unresponsive wakefulness state/vegetative state.
Fig. 2  EEG findings, by percentage of patients ($n = 18$). EEG, FIRDA frontal intermittent rhythmic delta activity, GPED generalized periodic epileptiform discharges, GRDA generalized rhythmic delta activity, LRDA lateralized rhythmic delta activity, MCS minimally conscious state, UWS/VS unresponsive wakefulness state/vegetative state.
CHALLENGES FOR INPATIENT REHAB

- Isolation needs:
  - Space-treating patient in rooms or isolation areas
  - Equipment-single use, cleaning
- Inability to do group therapy
- Inability to discharge to SNF facilities, group homes
- Limited ability to bring family in for training (adapting with telemedicine while maintaining privacy issues)
- PPE needs
CHALLENGES FOR HOME / OUTPATIENT REHAB

- Limited number of staff
- Clothing/PPE changes
- Telemedicine
- Equipment issues
POST-ACUTE SEQUELAE OF COVID-19 INFECTION (PASC)

• AKA: post-COVID-19 syndrome, Long-haulers, and Long COVID-19 (over 32-87% those hospitalized, data ltd for minimally symptomatic)

• No consensus definition. Ongoing symptoms 3-4 weeks or longer after initial SARS-CoV-2 diagnosis or symptom onset.

• Increased risk for those requiring hospitalization and were critically ill

• Some evidence that it may be more common in women (2x)

• Increased risk if more than 5 symptoms initially

• Etiologies: likely multifactorial: ongoing organ dysfunction, persistent hyper-inflammatory state, sequelae of cerebral hypoxia, late effects due to VTE or CVA, medication side effects, deconditioning, comorbidities, altered immunity, re-infection and psychological effects.
• 87% hospitalized had symptoms at 60 days
  • 32% 1-2 symptoms
  • 55% 3 or more symptoms

• Risk by age group
  • 26% 18-34 yrs
  • 32% 35-49 yrs
  • 47% 50 or older

• Symptoms can be continuous or relapsing/remitting
• Can be continuation of initial symptoms or onset of new symptoms
• Post-acute COVID more than 3 but less than 12 weeks
• Chronic COVID more than 12 weeks
PASC

• Co-morbidities that are risk factors for severe COVID-19.
  • HTN
  • Obesity
  • CAD
  • DM

• More severe COVID-19 is higher risk for PASC
• Above co-morbidities for COVID-19 are more common in patients with PASC
• Higher risk for PASC if 3 or co-morbidities
PASC PATTERNS

• Most common presentations in 2 types:
  1. Fatigue, headaches, shortness of breath, cough, loss of smell, sore throat
  2. Multiple-system symptoms including fever and GI

• Categorized by most common symptom:
  1. Post COVID cardio-respiratory syndrome
  2. Post COVID fatigue syndrome
  3. Post COVID neuro-psychiatric syndrome
Fatigue (chronic, overwhelming) is most common (53.1%).
  - Rehab: start with sleep hygiene/meds if needed, eval sleep apneas, more to follow with psychological aspects.

Dyspnea also common (22-43%)

Other common symptoms:
  - Joint pain
  - Chest pain
  - Muscle weakness/myalgias
  - “Brain fog” (impairments in attention, memory)
  - Headaches
  - Cough
  - Impaired sleep
  - Anxiety/depression

Can also see:
  - Dizziness
  - Stress disorders
  - Abdominal pain, nausea, vomiting
  - Peripheral neuropathy
  - Palpitations
  - Chronic pain
  - Poor quality of Life
RENAL EFFECTS

• Acute renal failure second in incidence after respiratory symptoms
• 0.5-19% of COVID-19 patients, 20-30% hospitalized/critically ill. But 27-64% requiring RRT did not need dialysis at ICU discharge or 28 days
• Causes: virus-induced renal endothelial damage, hypoxia induced renal damage, cardiorenal syndrome due to right heart strain, cytokine release, rhabdomyolysis, microemboli/microthrombi due to inflammatory hypercoagulability.
• Decreased eGFR persisted in 35% at 6 months
• 13% developed reduced eGFR after normal renal function during acute COVID phase.
• Increased risk for contrast induced nephropathy
• Higher risk if premorbid renal issues or renal transplant, transplant patients at higher risk for more severe COVID infection.
• Avoid nephrotoxic meds or adjust dosing.
RENAL-ACUTE SETTING

• Avoid volume overload (pulmonary edema, right heart failure) or volume depletion (impaired renal perfusion)
• RRT helpful for volume overload
• CRRT helpful for hemodynamically unstable patients
• CVVHD helpful for removal of cytokines
• Use IJ in prone patients (catheter visible and less likely to dislodge)
• Lung protective ventilation
  • Lowers risk of ventilation induced hemodynamic effects and cytokine burden
  • Could cause hypercapnia, respiratory acidosis, hypotension and AKI.
• Cardiorenal syndrome may need ECMO
GASTROINTESTINAL TRACT

• Can be only symptom in some COVID-19 patients
• Can include diarrhea, malabsorption, constipation to ileus, vomiting, anorexia, abdominal pain, melena
• Increased permeability of GI wall to foreign pathogens
• May be a risk for fecal-oral transmission
• Those with chronic GI conditions are at higher risk
• Rehab: anti-emetics, ensuring hydration status, early involvement of dietician, monitoring nutritional panels, vitamin/trace mineral replacement
LIVER

• Transaminitis (may be septic response, hepatic congestion related to ventilation, meds in addition to direct effects of virus
• Steatosis and inflammatory activity seen on biopsy. CT and US can show steatosis.
• Caution with hepatically metabolized meds.
• Higher risk in patients with chronic liver disease.
• Acute injury is usually self resolves. May need specialist referral is does not. Avoid hepatotoxic meds, adjust med doses for any hepatic impairment.
• 8-12% of COVID patients had acute cardiac injury
• Presence of cardiac injury increased risk of mortality
• Presence of tissue necrosis and interstitial macrophage and monocyte infiltration on biopsies.
CARDIAC

• Myocardial injury (Myocarditis, STEMI and NSTEMI). (up to 77% of COVID patients that had died)

• Associated with increased mortality.
  • Risk factors: more severe COVID-19 infection, male gender, pre-existing coronary artery disease and/or HTN, advanced age, DM, history of CVA, and with presence of MI, rapid heart failure or myocarditis.
  • Associated with increased risk of dysrhythmias.

• Cardiomegaly
• Pericardial effusion
• Heart failure (23-49%)
• Prolonged sinus tachycardia
• Atrial and ventricular arrhythmias more common in those with myocarditis and/or elevated troponins.
• Elevations of NT-proBMP, troponin, plasma IL-6 levels
• ECHO screening not recommended for all COVID 19 patients, but any with cardiac symptoms and abnormal ECG and blood work should get (right more than left ventricular failure tends to be seen)
• Cardiac CTA with delayed myocardial imaging-looking for diffuse biventricular hypokinesis, late gad uptake=acute myopericarditis
• Changes in HRCT (High-resolution CT) in up to 34%
• Cardiac MRI with inflammation in up to 60% more than 2 months out
• Cardiac MRI in mild to asymptomatic college athletes: Myocarditis 15%, prior myocardial injury in 31%.
• Serial clinical exam, ECG, ECHO at 4 and 12 weeks recommended.
CARDIAC

• Cardiac telemetry
• Implantable defibrillators
• Despite inflammatory basis, steroid use not effective for cardiac issues (is effective for lung issues)
• HTN/Cardiac meds:
  • In patients with HTN, continuing ACEI/ARB will lower morbidity and mortality risk
  • No evidence starting this if not already on is beneficial
  • No increased risk of ACEI, ARB, beta-blockers, calcium-channel blockers, or thiazide diuretics.
  • Tocilizumab (recombinant humanized monoclonal anti-IL-6 receptor antibody) approved in China for COVID 19 with elevated IL-6, data pending on effect.
• Caution with exercise in myocarditis and very low EF on ECHO. Cardiology involvement recommended.

• Cardiac rehab improves: exercise capacity, Quality of Life scores, psychological well being, reduce mortality and morbidity, reduce unplanned hospital readmissions. Can reduce post-myocarditis cardiac failure

• Can begin in ICU with healthy lifestyle education, reassurance, mobilization. Level 5 evidence for individualized therapy based on tolerance, cardiac impairment.

• Level 2b evidence for “complete rest” for 3-6 months after myocarditis, resume if LVEF normal, serum biomarkers of myocardial injury are normal and no significant arrhythmias on exercise testing. Level 2 a evidence for periodic cardiac reassessment after return to sports/physically demanding job for 2 years.
• Begin with light activity $\leq 3$ METS, avoid excessive sedentary periods. Avoid exhaustive or high intensity exercise, increase rest periods for increase in symptoms.

• Mild beta-blocker can be considered for patients with tachycardia.
• Orthostatic hypotension
  • OOB to recliner even on vent, compression stockings, abdominal binders, midodrine or florinef.

• Difficulty with temperature regulation
  • Blankets, fans
LYMPHATICS

• Mediastinal lymphadenopathy - common in more critical ill COVID-19 patients
Impaired cognition/brain fog (executive function, memory, attention, resolving delirium)
Headache (due to high cytokine levels)
Loss of taste and smell (up to 1/10th patients at 6 months)
Meningitis and encephalitis
  • Altered mental status, altered behavior or speech, focal motor deficits, seizures
Intracranial hemorrhage
  • Thalami, medial temporal lobes, sub-insular regions
Acute hemorrhagic necrotizing encephalopathy
Dizziness
Peripheral neuropathies, CN impairment (anosmia, ophthalmoplegia)
Neuralgia
Seizure
Post-infectious myelitis, some evidence for AIDP/GBS and CIDP (COVID-19 vs. Vaccine)
Ischemic stroke
• All patients should be followed progressively for neurological symptoms. Level 2b.

• Consider a cognitive screen. Level 2 b.

• Symptoms of headache, dizziness, hyponosmia are likely to improve with minimal intervention. Level 4.

• Education should be provided that mild to moderate neurological symptoms are likely to have full recovery. Level 3b

• Inpatient multidisciplinary rehab is recommended for patients with moderate to severe neurological symptoms to maximize recovery. Level 5.

• Physical, cognitive and functional assessments should be considered prior to returning to work. Level 5.
MUSCULOSKELETAL

• Diffuse weakness and muscle fatigue
  • Atrophy/loss of muscle mass begins in 1st week. Worse with multi-organ failure, sepsis, increased ICU LOS.
  • Data for SARS is 9-18% weight loss

• Steroid induced myopathy
• Dysphagia
• Falls
• Heterotopic ossification
In COVID-19 patients employed at time of illness, occupational goal-based rehab shown to have greater functional improvements to traditional rehab.

Exercise-based rehab suggested. Stretching, ROM, strengthening

Multidisciplinary/bundled approach focusing on physical, psychological and cognitive aspects simultaneously. Level 5.

Individualized. Inpatient, outpatient, home telehealth, patient directed according to patient needs. Level 5.
PSYCHOLOGICAL

• ICU psychosis, depression (29%), anxiety, acute stress disorder. Depression and anxiety can persist to become more chronic. Later can see PTSD.

• Increased risk as LOS in ICU/hospital gets longer
PSYCHOLOGICAL

• Communication/reassurance, social contact (in-person or remote), information/education helps. Level 5 evidence
• Active and ongoing monitoring should be undertaken for those with subthreshold symptoms. Level 1a.
• Health care workers that contract COVID-19 should be considered high risk. Level 5.
• Referral for psychological services for cognitive behavioral therapy, cognitive processing therapy, eye movement desensitization and reprocessing is appropriate for those with moderate to severe symptoms. Level 1a.
• Hyperactive immune response/Cytokine storm can lead to multi-organ system failure
• Lymphopenia
• Thrombocytopenia
• Coagulation dysfunction
  • Disseminated intravascular coagulation (seen in 74% of those that died)
• Luminal dilation of pulmonary vessels with mural thickening
• Increased risk of VTE
• Highest risk in acute phase (20-30%) and those critically ill (30-40%) but is less in post-acute (2.5%)
• Mean onset in post-acute was about 23 days-PPX for 45 days to 6 weeks post ICU d/c being done (little data about ideal time frame)
Diabetic ketoacidosis has been seen in patients without known DM in weeks to months after resolution of COVID 19 symptoms

Sick euthyroid

Clinical thyrotoxicosis weeks after resolution of respiratory symptoms

New onset auto-immune Hashimoto’s thyroiditis or Graves’ disease

Osteopenia and osteoporosis

Monitoring of BG, thyroid studies in COVID recovery patients is suggested.
Hair loss (20%)-most common (viral + stress)
Pressure sores
Erythematous rash
Urticaria
Vesicular rash
Main region is on trunk
Usually only minimal itching
Secondary drug rashes
Prevention: emollient barrier creams, turn/position, skin inspections
REPRODUCTIVE SYSTEM

• Orchitis
• Pregnancy increases risk to contract COVID-19 and have more severe symptoms
• Perinatal maternal infection can lead to: fetal distress, premature labor, newborn respiratory distress, prenatal death, thrombocytopenia associated with abnormal liver function.
OPHTHALMOLOGICAL

• Rare: chemosis, conjunctivitis
NUTRITIONAL

- Malnutrition in 26-45%.
- Monitoring, dietician, SW, access to food.
OUTPATIENT PASC PROGRAMS

• Vary substantially
• Therapy only, single specialty, multi-disciplinary
• Led by: PM&R, Internal Medicine, Pulmonology, Infectious Disease
• Patients may have been in acute rehab, SNF rehab or no rehab prior to program
• Referral patterns: Pulmonology, Cardiology, Neurology, IM, Family Medicine, ID, PM&R, PT, OT.
### Post-COVID 19 Functional Status Scale

<table>
<thead>
<tr>
<th>Statement</th>
<th>Corresponding PCFS scale grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no limitations in my everyday life and no symptoms, pain, depression or anxiety related to the infection.</td>
<td>0</td>
</tr>
<tr>
<td>I have negligible limitations in my everyday life as I can perform all usual duties/activities, although I still have persistent symptoms, pain, depression or anxiety.</td>
<td>1</td>
</tr>
<tr>
<td>I suffer from limitations in my everyday life as I occasionally need to avoid or reduce usual duties/activities or need to spread these over time due to symptoms, pain, depression or anxiety. I am, however, able to perform all activities without any assistance.</td>
<td>2</td>
</tr>
<tr>
<td>I suffer from limitations in my everyday life as I am not able to perform all usual duties/activities due to symptoms, pain, depression or anxiety. I am, however, able to take care of myself without any assistance.</td>
<td>3</td>
</tr>
<tr>
<td>I suffer from severe limitations in my everyday life: I am not able to take care of myself and therefore I am dependent on nursing care and/or assistance from another person due to symptoms, pain, depression or anxiety.</td>
<td>4</td>
</tr>
</tbody>
</table>
OTHER TRACKING OPTION

• Patient self assessment score for each symptom: 0 no improvement to 10 full recovery.
PATIENT ADVOCACY GROUPS

• Advocacy Exchange https://www.covidadvocacyexchange.com
• National Patient Advocate Foundation COVID Care Resource Center https://www.patientadvocate.org/covidcare
• Long-haul COVID fighter Facebook groups
• The Body Politic COVID-19 Support Group https://www.wearebodypolitico.com/covid19
• Survivor Corps https://www.survivorcorps.com


