Neurological implications of Long COVID

Brain Summit 2022: Current Trends in Neurology

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The magnitude

- 651,881,708 cases worldwide
- 6,652,850 deaths worldwide
- 101,104,275 cases in US
- 1,108,815 deaths in US
- 8,097,377 cases in TX
- 97,764 deaths in TX

as of 12/8/22

Source- https://www.worldometers.info/coronavirus/country/us/

Manifestations

- Pulmonary - hypoxia, cough, SOB, respiratory failure
- Cardiac - Myocarditis, Heart failure, cardiogenic shock, acute cardiac events
- Neuro - smell and taste abnormalities, confusion, headache, dizziness, CVA, ICU delirium, altered consciousness
- MSK/general - Debility, weakness, some cases of rhabdomyolysis
- GI – diarrhea, liver damage, pancreatic injury
- Psychological – Anxiety, Depression, PTSD, stress, Isolation……

Lopez M, Bell K, Annaswamy T, Juengst S, Ifejika N. COVID-19 Guide for the Rehabilitation Clinician: A Review of Nonpulmonary Manifestations and Complications. Am J Phys Med Rehabil. 2020 Aug;99(8):669-673. doi: 10.1097/PHM.0000000000001479. PMID: 32467492; PMCID: PMC7299122.

Long-COVID, PASC, Post COVID Conditions

- The World Health Organization (WHO) defines it as a condition characterized by symptoms impacting everyday life, such as fatigue, shortness of breath and cognitive dysfunction, which occur after a history of probable or confirmed SARS-CoV-2 infection
- Symptoms usually occur 3 months from the onset of acute COVID-19 symptoms, last for at least 2 months and cannot be explained by an alternative diagnosis
- The UK National Institute for Health and Care Excellence (NICE) makes a distinction between disease occurring from 4 to 12 weeks after infection (ongoing symptomatic COVID-19) and symptoms persisting beyond 12 weeks (post-acute COVID-19 syndrome

WHO. A clinical case definition of post-COVID-19 condition by a Delphi consensus. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (2021).
NICE. *COVID-19 Rapid Guideline: Managing the Long-term Effects of COVID-19*. (NICE, 2020).

Long-COVID, PASC, Post COVID Conditions

- Depending on studies anywhere between 10-30% of patients may report chronic symptoms.
- One Italian study reported that 87.4% reported at least 1 symptom at 60days
- 1 in 13 (7.5%) Americans, 3.1% of people in UK and 4.6% of Canadians have long COVID symptoms
- 31,486 symptomatic infections,1,856 (6%) had not recovered and 13,350 (42%) only partially

https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm

https://www150.statcan.gc.ca/n1/daily-quotidien/221017/dq221017b-eng.htm

Hastie, C.E., Lowe, D.J., McAuley, A. *et al.* Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study. *Nat Commun* **13**, 5663 (2022). https://doi.org/10.1038/s41467-022-33415-5

https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1september2022

Carfì A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA.* 2020;324(6):603–605. doi:10.1001/jama.2020.12603

Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in Adults at 6 Months After COVID-19 Infection. *JAMA Netw Open.* 2021;4(2):e210830. doi:10.1001/jamanetworkopen.2021.0830

Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220-232. doi: 10.1016/S0140-6736(20)32656-8. Epub 2021 Jan 8. PMID: 33428867; PMCID: PMC7833295.

PASC symptoms

- fatigue (79.0%),
- headache (55.3%),
- shortness of breath (55.3%),
- difficulty concentrating (53.6%),
- cough (49.0%),
- changed sense of taste (44.9%),
- diarrhea (43.9%),
- muscle or body aches (43.5%).

COVID-19 Survivors' Reports of the Timing, Duration, and Health Impacts of Post-Acute Sequelae of SARS-CoV-2 (PASC) Infection

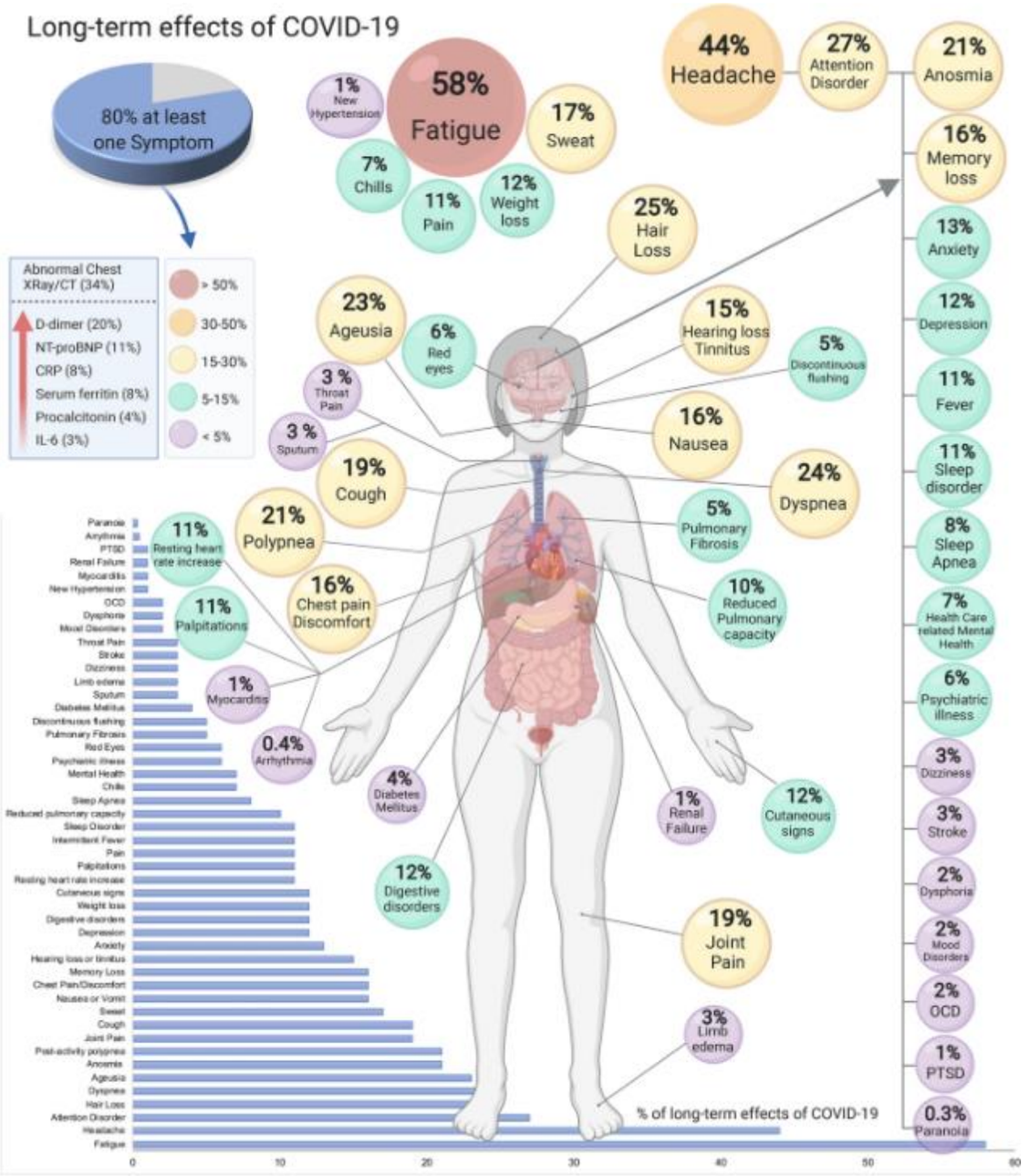
Natalie Lambert, Survivor Corps, Sarah A. El-Azab, Nathan S. Ramrakhiani, Anthony Barisano, Lu Yu, Kaitlyn Taylor, Alvaro Esperanca, Charles A. Downs, Heather L. Abrahim, Amir M. Rahmani, Jessica L. Borelli, Rana Chakraborty, Melissa D. Pinto

medRxiv 2021.03.22.21254026; doi: https://doi.org/10.1101/2021.03.22.21254026

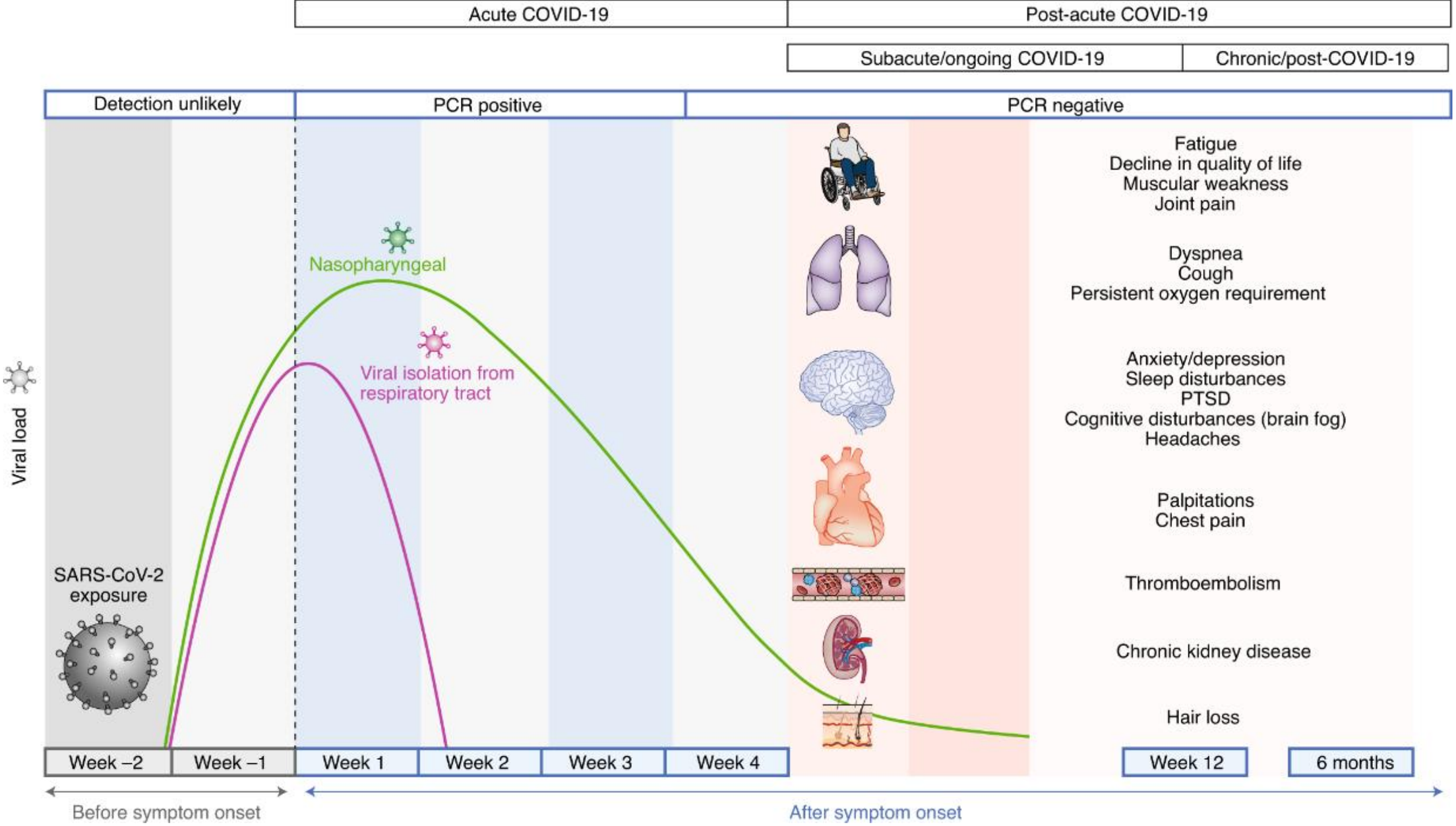
PASC symptoms

- Most common symptoms were Fatigue (77.7%), post exertional malaise (72.2%), cognitive dysfunction (55.4%)
- They noted 205 symptoms across 10 organ systems
- 45.2% patients required reduced work schedule
- 22.3% patients were not working at the time of the survey

Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact Hannah E. Davis, Gina S. Assaf, Lisa McCorkell, Hannah Wei, Ryan J. Low, Yochai Re'em, Signe Redfield, Jared P. Austin, Athena Akrami medRxiv 2020.12.24.20248802; doi: https://doi.org/10.1101/2020.12.24.20248802



Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C. *et al.* More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* **11**, 16144 (2021). https://doi.org/10.1038/s41598-021-95565-8



Nalbandian, A., Sehgal, K., Gupta, A. *et al.* Post-acute COVID-19 syndrome. *Nat Med* **27,** 601–615 (2021). https://doi.org/10.1038/s41591-021-01283-z

Pathophysiology

- Virus specific pathophysiologic changes
- Immunologic aberrations and inflammatory damage in response to acute infection
- Expected sequalae of post-critical illness
- Post intensive care syndrome: microvascular ischemia and injury (blockage of smaller blood vessels), metabolic alternations and immobility
- Microclots
- Vagal nerve damage

Nalbandian, A., Sehgal, K., Gupta, A. *et al.* Post-acute COVID-19 syndrome. *Nat Med* **27,** 601–615 (2021). https://doi.org/10.1038/s41591-021-01283-z

Pretorius E, Vlok M, Venter C, Bezuidenhout JA, Laubscher GJ, Steenkamp J, Kell DB. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovasc Diabetol. 2021 Aug 23;20(1):172. doi: 10.1186/s12933-021-01359-

https://www.theguardian.com/commentisfree/2022/jan/05/long-covid-research-microclots?CMP=Share_iOSApp_Other

Neurologic pathophysiology

- Susceptibility weighted imaging (SWI) MRI results showed that patients who recovered from COVID-19 had significantly higher susceptibility values in the frontal lobe and brain stem compared to healthy controls. The clusters obtained in the frontal lobe primarily show differences in the white matter.
- These brain regions are linked with fatigue, insomnia, anxiety, depression, headaches and cognitive problems
- exhibited diffuse hypometabolism predominantly involving right frontal and temporal lobes including the orbito-frontal cortex and internal temporal areas.

Brain Alterations in COVID Recovered Revealed by Susceptibility-Weighted Magnetic Resonance Imaging. Sapna S Mishra, Rakibul Hafiz, Rohit Misra, Tapan K. Gandhi, Alok Prasad, Vidur Mahajan, Bharat B. Biswal medRxiv 2022.11.21.22282600; doi: https://doi.org/10.1101/2022.11.21.22282600

Goehringer, F., Bruyere, A., Doyen, M. *et al.* Brain ^{18}F-FDG PET imaging in outpatients with post-COVID-19 conditions: findings and associations with clinical characteristics. *Eur J Nucl Med Mol Imaging* (2022). https://doi.org/10.1007/s00259-022-06013-2

Etter, M.M., Martins, T.A., Kulsvehagen, L. *et al.* Severe Neuro-COVID is associated with peripheral immune signatures, autoimmunity and neurodegeneration: a prospective cross-sectional study. *Nat Commun* **13**, 6777 (2022). https://doi.org/10.1038/s41467-022-34068-0

Neurologic pathophysiology

- Respiratory COVID induces CSF cytokine elevation and microglial reactivity (mice)
- CCL11 activates hippocampal microglia and impairs neurogenesis
- Respiratory COVID causes persistent loss of oligodendrocytes and myelinated axons
- prominent signs of severe Neuro-COVID are blood-brain barrier (BBB) impairment, elevated microglia activation markers and a polyclonal B cell response targeting self-antigens and non-self-antigens. COVID-19 patients show decreased regional brain volumes associating with specific CSF parameters

Etter, M.M., Martins, T.A., Kulsvehagen, L. *et al.* Severe Neuro-COVID is associated with peripheral immune signatures, autoimmunity and neurodegeneration: a prospective cross-sectional study. *Nat Commun* **13**, 6777 (2022). https://doi.org/10.1038/s41467-022-34068-0

Fernández-Castañeda A, Lu P, Geraghty AC, Song E, Lee MH, Wood J, O'Dea MR, Dutton S, Shamardani K, Nwangwu K, Mancusi R, Yalçın B, Taylor KR, Acosta-Alvarez L, Malacon K, Keough MB, Ni L, Woo PJ, Contreras-Esquivel D, Toland AMS, Gehlhausen JR, Klein J, Takahashi T, Silva J, Israelow B, Lucas C, Mao T, Peña-Hernández MA, Tabachnikova A, Homer RJ, Tabacof L, Tosto-Mancuso J, Breyman E, Kontorovich A, McCarthy D, Quezado M, Vogel H, Hefti MM, Perl DP, Liddelow S, Folkerth R, Putrino D, Nath A, Iwasaki A, Monje M. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell. 2022 Jul 7;185(14):2452-2468.e16. doi: 10.1016/j.cell.2022.06.008. Epub 2022 Jun 13. PMID: 35768006; PMCID: PMC9189143.

Neurological sequalae

- The risks of cognitive deficit (known as brain fog), dementia, psychotic disorders, and epilepsy or seizures were still increased at the end of the 2-year follow-up period.
- Children did have an increased risk of cognitive deficit, insomnia, intracranial hemorrhage, ischemic stroke, nerve, nerve root, and plexus disorders, psychotic disorders, and epilepsy or seizures

Taquet M, Sillett R, Zhu L, Mendel J, Camplisson I, Dercon Q, Harrison PJ. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. Lancet Psychiatry. 2022 Oct;9(10):815-827. doi: 10.1016/S2215-0366(22)00260-7. Epub 2022 Aug 17. PMID: 35987197; PMCID: PMC9385200.

Fatigue

- Most common symptom reported by almost 3/4th patients
- Physical, Cognitive/mental or combined
- Poor exercise tolerance, inability to perform day to day activities
- Assessing sleep, mood, diet, fluid intake is important
- Overall prevalence of chronic fatigue syndrome as a long COVID symptom is 45.2%.
- ?CFS/ Myalgic-encephalomyelitis type presentation – the 4P used are Prioritizing, pacing, positioning, planning. Use of stimulant type of medications not proven, but still used.

Salari, N., Khodayari, Y., Hosseinian-Far, A. *et al.* Global prevalence of chronic fatigue syndrome among long COVID-19 patients: A systematic review and meta-analysis. *BioPsychoSocial Med* **16**, 21 (2022). https://doi.org/10.1186/s13030-022-00250-5

AAPMR PASC Fatigue Consensus recommendations- Assessment

- Patients' **physical functioning and endurance** should be assessed to inform activity and therapy recommendations. (Examples of tests that can be chosen based on an individual's activity tolerance: 30 s sit to stand, 2-min step (seated or standing), 6 min walk test, 10 m walk test
- **Exacerbating conditions** like- sleep, mood, anxiety, depression, PTSD, Cardiopulmonary, autoimmune and endocrine issues should be evaluated.
- A **medication review** should be conducted to investigate medications that may be contributing to fatigue. Of note, antihistamine, anticholinergic, and antidepressant/anxiolytic medications can contribute to fatigue in patients with PASC.
- The following **basic lab workup** should be considered in new patients or those without lab workup in the 3 months before visit including complete blood count with differential, chemistries including renal and hepatic function tests, thyroid stimulating hormone, c-reactive protein or erythrocyte sedimentation rate, and creatinine kinase.

Herrera, JE, Niehaus, WN, Whiteson, J, et al. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. *PM&R*. 2021; 13(9): 1027- 1043. https://doi.org/10.1002/pmrj.12684

AAPMR PASC Fatigue Consensus recommendations- Treatment

- Begin an individualized and structured, titrated return to activity program.
- Discuss energy conservation strategies.
- Encourage a healthy dietary pattern and hydration.
- Treat, in collaboration with appropriate specialists, underlying medical conditions, such as pain, insomnia/sleep disorders (including poor sleep hygiene), and mood issues that may be contributing to fatigue.

Cognitive fog

- Inability to focus or concentrate
- Impaired memory (most commonly short term)
- Impaired receptive language
- Difficulty with multi-tasking
- Impaired executive functioning
- Could either be subjective cognitive issues without objective evidence or mild cognitive impairment.

AAPMR PASC Cognitive Symptoms Consensus recommendations- Assessment

- The following basic lab work-up should be considered to screen for reversible factors contributing to cognitive symptoms. The initial lab work-up in new patients or those without lab work-up in the 3 months prior to visit including: complete blood count, vitamin B12, thiamine, folate, homocysteine, 1,25- dihydroxy vitamin D, magnesium, liver function tests, comprehensive metabolic panel thyroid function tests (thyroid stimulating hormone, free T3, free T4). In high-risk patients, one may consider syphilis rapid plasma regain and human immunodeficiency virus testing.
- Clinicians should conduct a full patient history with review of pre-existing conditions and comprehensive medication and supplement review for those that may contribute to cognitive symptoms. Of note, patients with PASC often present on antihistamine, anticholinergic, and antidepressant/anxiolytic medications which can contribute to cognitive symptoms.

Fine, J.S., Ambrose, A.F., Didehbani, N., Fleming, T.K., Glashan, L., Longo, M., Merlino, A., Ng, R., Nora, G., Rolin, S., Silver, J.K., Terzic, C.M., Verduzco Gutierrez, M. and Sampsel, S. (2022), Multi-Disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Cognitive Symptoms in Patients with Post-Acute Sequelae of SARS-CoV-2 infection (PASC). PM&R: The Journal of Injury, Function and Rehabilitation. Accepted Author Manuscript. https://doi.org/10.1002/pmrj.12745

AAPMR PASC Cognitive Symptoms Consensus recommendations- Treatment

- For patients that screen positive for cognitive symptoms, refer to a specialist (i.e. Speech-Language Pathologist, Occupational Therapist, Neuropsychologist) with expertise in formal cognitive assessment and remediation.
- Reinforce sleep hygiene techniques including non-pharmacologic approaches as first line of sleep remediation.
- For patients who achieve a return to their normal, daily activities, regular exercise (at least 2-3 times/week of aerobic exercise) may be effective in improving cognition and also contribute to improved sleep patterns.

Fine, J.S., Ambrose, A.F., Didehbani, N., Fleming, T.K., Glashan, L., Longo, M., Merlino, A., Ng, R., Nora, G., Rolin, S., Silver, J.K., Terzic, C.M., Verduzco Gutierrez, M. and Sampsel, S. (2022), Multi-Disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Cognitive Symptoms in Patients with Post-Acute Sequelae of SARS-CoV-2 infection (PASC). PM&R: The Journal of Injury, Function and Rehabilitation. Accepted Author Manuscript. https://doi.org/10.1002/pmrj.12745

Cognitive fog

- Mechanisms- deconditioning, PTSD, dysautonomia, post critical illness, ?myelin disruption
- Detailed in clinic cognitive assessment if possible, or referral to speech therapy and or neuropsych should be considered
- Cognitive therapy by a SLP is the mainstay of treatment, after improving sleep, nutrition and other medical issues.
- Supplements can be tried.
- Stimulants can be used but without any evidence behind it.
- A case series reported that patients who took guanfacine+NAC reported improved working memory, concentration, and executive functions, including a resumption of normal workloads.

Fesharaki-Zadeh A, Lowe N, Arnsten AFT. Clinical experience with the α2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in "Long-COVID19". Neuroimmunology Reports. 2023;3:100154. doi: 10.1016/j.nerep.2022.100154. Epub 2022 Nov 25. PMCID: PMC9691274.

Autonomic dysfunction

- Heart rate variability, drop in blood pressure, orthostatic intolerance, POTS, NCS
- Possible mechanism- defects in adrenergic modulation
- Incidence varies: one online survey reports 19% patients receiving diagnosis of POTS, another study reports 25% had dysautonomia
- Can manifest with variety of symptoms.

Review of systems	Clinical features
Cardiovascular	• Orthostatic intolerance • Postural tachycardia • Orthostatic hypotension • Postprandial hypotension • Exercise intolerance • Syncope • Presyncope • Palpitations • Chest pain, pressure or discomfort
Neurologic	• Dizziness or lightheadedness • Cognitive dysfunction (a.k.a. "brain fog") • Paresthesia • Generalized weakness • Neuropathic pain • Headache, including migraine
Respiratory	• Shortness of breath • Hyperventilation
Gastrointestinal	• Nausea • Dysphagia • Acid reflux • Early satiety • Abdominal fullness, distension or pain • Gastric and intestinal dysmotility • Diarrhea or constipation
Genitourinary	• Urinary frequency, urgency or hesitancy • Incomplete bladder emptying • Urinary retention • Overactive bladder • Polyuria • Nocturia • Interstitial cystitis • Erectile dysfunction • Vaginal dryness • Pelvic pain
Thermoregulatory	• Hypohydrosis • Hyperhidrosis • Anhidrosis • Gustatory sweating • Heat intolerance • Cold intolerance
Pupillomotor	• Blurred vision • Light sensitivity • Dilated pupils
Secretomotor	• Dry eyes • Dry mouth
Constitutional	• Fatigue • Sleep disturbance • Loss of appetite • Weight loss or gain • Pallor • Flushing • Diaphoresis • Myalgia

Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med (Lond)*. 2021;21(1):e63-e67. doi:10.7861/clinmed.2020-0896

Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;**38**:101019.

POTS[20]	1. Sustained HR increase ≥30 bpm within 10 min for adults (≥40 bpm for adolescents 12–19 years of age) of standing or on TTT 2. Absence of OH 3. Symptoms of orthostatic intolerance for ≥6 months 4. Exclusion of other causes of postural tachycardia, such as dehydration, medication side effect, and other medical conditions
NCS[20]	1. Transient loss of consciousness typically preceded by prodromal symptoms and signs, such as pallor, diaphoresis, nausea, abdominal discomfort, yawning, sighing, and hyperventilation. That may occur up to 60 s prior to loss of consciousness. 2. A sudden fall in blood pressure, heart rate, and cerebral hypoperfusion on standing or on TTT
OH[21]	Sustained drop in blood pressure ≥20/10 mm Hg within 3 min of standing or on TTT
IST[22]	1. Average sinus HR exceeding 90 bpm over 24 hours or HR while awake and at rest ≥100 bpm 2. Palpitations and other distressing symptoms associated with sinus tachycardia

POTS

- The study is based on a large series of approximately 300,000 vaccinated individuals from one geographic territory in the USA (Los Angeles County), with 0.27% new post-vaccination POTS diagnoses compared with 0.18% in the pre-vaccination period, giving an odds ratio of 1.52 for post-vaccination POTS diagnoses
- The pre-infection incidence of POTS was 1.73%, compared with 3.42% after infection.
- This suggests that those with symptomatic COVID-19 infection were more likely to develop POTS in general, and that the risk of post-infection POTS is much higher than post-vaccination POTS in this cohort
- the rate of new-onset POTS diagnoses is more than five times higher following natural SARS-CoV-2 infection than after COVID-19 vaccination

Kwan, A.C., Ebinger, J.E., Wei, J. *et al.* Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. *Nat Cardiovasc Res* (2022). https://doi.org/10.1038/s44161-022-00177-8

AAPMR PASC Autonomic Symptoms Consensus recommendations- Assessment

- **Medication history:** evaluate for medications that may impact symptoms, signs or assessment parameters (i.e., medications with side effects, such as orthostatic intolerance, orthostatic hypotension, or resting or postural tachycardia; these may include anti-hypertensive, anti-cholinergic, and stimulant medications)
- Clinicians should conduct a neurologic exam, including sensory exam to look for signs of small fiber neuropathy (particularly the loss of pinprick or temperature sensation)
- To evaluate for autonomic dysfunction, clinicians should perform a 10-min stand test recording heart rate and blood pressure while patients is supine and after standing 3, 5, 7 and 10 min. Consider obtaining a tilt table test in symptomatic individuals with a negative 10-min stand test
- Recommended initial laboratory tests in individuals with suspected autonomic dysfunction including: CBC, CMP, TFT, vitamin B12, ferritin, morning cortisol, ANA, ESR, CRP.
- Where diagnosis is uncertain or symptoms are progressing, consider a referral to an autonomic specialist for more detailed assessment including autonomic function tests such as Valsalva maneuver, deep breathing test, quantitative sudomotor axon reflex test (QSART), and a skin biopsy for evaluation of small fiber neuropathy

AAPMR PASC Autonomic Symptoms Consensus recommendations- Treatment

- Increased fluid/salt intake: >3 L of fluid and >10 g of salt (4 mg of sodium) daily
- Compression garments (waist-high stockings and/or abdominal binder)
- Lifestyle management to include recognizing and avoiding symptom triggers and physical counterpressure maneuvers to mitigate orthostatic intolerance
- For individuals with severe or persistent symptoms after a trial of non-pharmacologic measures, consider pharmacologic interventions. First-line medications: low-dose beta blockers (e.g. propranolol or atenolol); fludrocortisone; midodrine
- Second-line medications: pyridostigmine; ivabradine; clonidine; methyldopa; modafinil, methylphenidate; selective serotonin reuptake inhibitors (SSRIs); serotonin and norepinephrine reuptake inhibitors (SNRIs); bupropion; droxidopa
- personalized autonomic rehabilitation program interventions to reduce fatigue and gradually improve exertional tolerance

Headache

- Very common symptom seen in about 60% of patients in one study
- In a follow-up study of 100 patients, approximately 38% had ongoing headaches after 6weeks.
- Commonly presents as non-specific initially but usually will change to some of the common phenotypes like tension, migraine, neuropathic etc.
- Commonly used medications are same like in other causes – Gabapentin, Duloxetine, Amitriptyline, Propranolol, Topiramate.

Tabacof, Laura MD; Tosto-Mancuso, Jenna PT, DPT; Wood, Jamie PT, PhD; Cortes, Mar MD; Kontorovich, Amy MD, PhD; McCarthy, Dayna DO; Rizk, Dahlia MD; Rozanski, Gabriela PT, PhD; Breyman, Erica BS; Nasr, Leila BS; Kellner, Christopher MD; Herrera, Joseph E. DO, FAAPMR; Putrino, David PT, PhD Post-acute COVID-19 Syndrome Negatively Impacts Physical Function, Cognitive Function, Health-Related Quality of Life, and Participation, American Journal of Physical Medicine & Rehabilitation: January 2022 - Volume 101 - Issue 1 - p 48-52 doi: 10.1097/PHM.0000000000001910

Loss of smell and taste

- The analysis of new daily cases of COVID-19, acute incidence of OD, and rates of recovery suggest that more than 700 000, and possibly as many as 1.6 million, US individuals experience COD because of SARS-CoV-2.
- A study of 110 patients, 16 patients (14.5%) anosmia/hyposmia was unchanged .
- persistent OD was self-reported in 40 patients (36.5%).
- Olfactory dysfunction was associated with lower tissue perfusion in the orbital and medial frontal regions in the arterial spin labeling sequence
- Treatment- Olfactory retraining: abscent.org , intranasal Theophylline

Khan AM, Kallogjeri D, Piccirillo JF. Growing Public Health Concern of COVID-19 Chronic Olfactory Dysfunction. *JAMA Otolaryngol Head Neck Surg.* Published online November 18, 2021. doi:10.1001/jamaoto.2021.3379
Lucidi D, Molinari G, Silvestri M, De Corso E, Guaraldi G, Mussini C, Presutti L, Fernandez IJ. Patient-reported olfactory recovery after SARS-CoV-2 infection: A 6-month follow-up study. Int Forum Allergy Rhinol. 2021 Aug;11(8):1249-1252. doi: 10.1002/alr.22775. Epub 2021 Feb 4. PMID: 33539667.
Henkin RI, Schultz M, Minnick-Poppe L. Intranasal Theophylline Treatment of Hyposmia and Hypogeusia: A Pilot Study. *Arch Otolaryngol Head Neck Surg.* 2012;138(11):1064–1070. doi:10.1001/2013.jamaoto.342
Yus M, Matias-Guiu JA, Gil-Martínez L, Gómez-Ruiz N, Polidura C, Jorquera M, Delgado-Alonso C, Díez-Cirarda M, Matías-Guiu J, Arrazola J. Persistent olfactory dysfunction after COVID-19 is associated with reduced perfusion in the frontal lobe. Acta Neurol Scand. 2022 Aug;146(2):194-198. doi: 10.1111/ane.13627. Epub 2022 Apr 25. PMID: 35467007; PMCID: PMC9111206.

Neurological sequalae

- Among 17 patients (mean age 43.3 years, 69% female, 94% Caucasian, and 19% Latino), 59% had ≥1 test interpretation confirming neuropathy.
- A total of 1556 participants were included: 542 CV+ patients and 1014 control subjects. CV+ patients reported a higher occurrence of peripheral neuropathy symptoms in the extremities anytime within 90 days post infection (28.8% vs 12.9%, odds ratio [OR] [95% confidence interval] = 2.72 [2.10-3.54]), as well as such symptoms persisting up to 90 days after infection (6.1% vs 1.9%, OR = 3.39 [1.91-6.03]).
- The complications of acute COVID-19, such as ischemic or hemorrhagic stroke, hypoxic– anoxic damage, posterior reversible encephalopathy syndrome and acute disseminated myelitis, may lead to lingering or permanent neurological deficits

Anne Louise Oaklander, Alexander J. Mills, Mary Kelley, Lisa S. Toran, Bryan Smith, Marinos C. Dalakas, Avindra Nath. Neurol Neuroimmunol Neuroinflamm May 2022, 9 (3) e1146; DOI: 10.1212/NXI.0000000000001146

Odozor CU, Kannampallil T, Ben Abdallah A, Roles K, Burk C, Warner BC, Alaverdyan H, Clifford DB, Piccirillo JF, Haroutounian S. Post-acute sensory neurological sequelae in patients with severe acute respiratory syndrome coronavirus 2 infection: the COVID-PN observational cohort study. Pain. 2022 Dec 1;163(12):2398-2410. doi: 10.1097/j.pain.0000000000002639. Epub 2022 Mar 24. PMID: 35324536.

Psychiatric Sequalae

- 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 90 days of diagnosis to be 18.1%
- In a cohort of 402 COVID-19 survivors in Italy 1month after hospitalization, approximately 56% screened positive in at least one of the domains evaluated for psychiatric sequelae (PTSD, depression, anxiety, insomnia and obsessive-compulsive symptomatology)

Taquet, M., Luciano, S., Geddes, J. R. & Harrison, P. J. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62354 COVID-19 cases in the USA. *Lancet Psychiatry* **8**, 130–140 (2021).

Psychiatric symptoms

- Symptoms range from adjustment disorder, anxiety, depression and PTSD
- Main reasons: uncertainty, fear of unknown, isolation, lack of normalcy, medical complications
- Insomnia and lack of physical activity also contribute
- Group or Individual counseling
- Anti-depressants – choice depends on physician prescribing and side effect profile.
- Fluvoxamine? Some benefit seen in acute COVID. PASC benefit unknown
- Consider referral to psychiatry/psychology as deemed appropriate

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Thank you!

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