

NMCB consensus document Long-COVID

Background

The Long COVID Foundation seeks to establish a consensus on case criteria for Long-COVID (LC), encompassing both inclusion and exclusion criteria and methodology. This is done with a view to potentially combining data or creating a larger cohort. The NMCB consortium plans to incorporate approximately 500-600 LC adult patients from various cohorts for standardized follow-up assessments. This initiative will enhance data comparability and generate new, standardized longitudinal data across different cohorts. The NMCB assessments also cover ME/CFS, other Post-Acute Infection Syndromes (PAIS) like Lyme and Q-fever, and HC. All University Medical Centers (UMCs) participate in the NMCB consortium, and data sharing is governed by the ELSI-HealthRI Joint Data Registry Agreement.

The current consensus centers on adult patients. We plan to extend our efforts to include children and adolescents. This document also aids in the standardization of our Case Report Forms (CRF) and primary evaluations. The NMCB database and biobank intend to integrate or amalgamate the CRFs from the various associated cohorts, facilitating longitudinal comparisons.

Aim

To record the consensus regarding case-inclusion procedures and related methodology.

Committee

5.1.2e

1. Inclusion criteria

- a) Persisting symptoms, feeling unrecovered for ≥ 6 months since (re-)infection with COVID-19
- b) COVID-19 (re-)infection is confirmed by a positive PCR for SARS-CoV-2, positive SARS-CoV-2 serology, or CO-RADS (COVID-19 Reporting and Data System), or antigen rapid test.

Elaboration and implementation:

Ad a:

- 1) **Subtyping based on symptom duration and number:**
 - a. **6 months:** Consensus was adopted for ≥ 6 months as a criterium (WHO guidelines use ≥ 3 months).
 - b. **Record onset:** Duration/onset of symptoms (relative to infection) and preferably also course/triggering events should be recorded.
 - c. **Minimum symptom number:** Some argued that a lower-bound should be considered for symptom number, whereas others noted that also a single symptom could be sufficient (e.g., loss of smell). A consensus solution is to distinguish between "LC" (≥ 3 symptoms) vs "LC with limited symptoms" (1 or 2 symptoms). The latter is expected to pertain to a smaller subgroup and will be relatively undersampled.
 - d. **Fatigue:** consensus emerged that fatigue is not required, however caseness is probable to involve at least one the following core symptoms: brain fog, fatigue, PEM, POTS/dysautonomia. To allow comparison with other PAIS and ME/CFS the CCC, ICC and IOM criteria will be determined.
- 2) **Standardized checklist:** the RECOVER symptom checklist can be taken as a basis (<https://jamanetwork.com/journals/jama/fullarticle/2805540>), updated with additional symptoms based on emerging data and insights.
- 3) **Symptom severity:** in consideration of the ubiquitous nature of some LC symptoms (e.g., fatigue), symptom checklists should preferably include a severity rating. A 'symptom' qualifies when moderate to severe.
- 4) **Optional additional scales:** simple checklists are preferably appended with more fine-grained assessments using normed scales, e.g., DSQ-PEM (5-item PEM checklist), brain fog (e.g., CIS subscale), fatigue (e.g., CIS, FSS, MFI), POTS and other autonomic dysfunctions (e.g., DSQ-2 items), assessment of related/sequential comorbidities (e.g., ME/CFS, IBS, depression), and QoL. Obviously mindful of patient burden.

2. Exclusion

- a) Somatic or psychiatric condition pre-COVID infection, or condition developed post-COVID, that may provide an alternative explanation for the symptoms:
 - Inflammatory, metabolic/endocrine/genetic or cardiovascular disorder, cancer (remission < 5 yrs)
 - Moderate to severe psychiatric disorder (mainly anxiety, depression, drug and alcohol abuse)
- b) Pregnancy or breast feeding
- c) BMI>40
- d) Age <18 or >70

Elaboration and implementation:

Ad a:

1. **Pre-existing conditions:** Patients with pre-existing conditions are typically excluded, unless there is very high confidence that the post-COVID symptoms cannot be attributed to the pre-existing condition (e.g., relapse, exacerbation). An alternative scenario is when patients with preexisting conditions are intentionally included as a subsample for defined research purposes, e.g.; 1) Studying the role of COVID in exacerbation or relapse of the primary condition; 2) Studying pre-existing conditions as a risk factor for post-COVID.
2. **Conditions developed post-COVID:** see section 3 below on common comorbidities
3. **Clinical data:** Consensus was that it is sufficient to confirm exclusion criteria based on self-report (see RECOVER check list) and medical status.
4. There was no consensus on exclusion of secondary depression. Given the diagnostic criteria (e.g., persistent fatigue or loss of energy, diminished ability to think or concentrate) depression will be difficult to discern from, and thus confound reporting of, somatic and (other) cognitive impairments. Proposal is to; 1) exclude if threshold value exceeds 'moderately-severe' (e.g., PHQ9 ≥ 15), and/or; 2) *temporary* exclude until (partial) remission due to treatment or spontaneous recovery (the 3 month spontaneous recovery rate is 50%).

Hospitalized patients: Studies often exclude patients hospitalized for COVID-19 to eliminate confounding, in particular post-IC sequela. For consensus it was proposed to allow inclusion as a smaller subgroup (comparable to *ad a*, point 1) accompanied with careful registration of received in-hospital treatment, e.g., RECOVER check list as an example.

3. Non-excluding post-COVID comorbidities / symptoms

With emerging conditions like post-COVID, it may not be immediately apparent whether post-COVID symptoms or syndromes are coincidental or directly related. "Coincidental" means that although the symptoms or conditions manifest after COVID-19, there is no known or probable consequential link between the two. This acts as an exclusion criterium on the grounds that the co-morbidity may be regarded as an alternative explanation of the symptoms. In contrast, "related" syndromes have a likely connection to the infection even if this reflects, through lack of mechanistic understanding, a mere statistical/epidemiological association. A such syndrome would then be an inclusion criterion. Judgement hinges on expert consensus and emerging research. As more data becomes available, these relationships will be more clearly defined. The consensus, considering our current knowledge, was that it is best to take an inclusive approach; a conservative stance might obstruct the emergence of vital insights.

At present there is data to consider the following conditions/syndromes as possibly COVID related sequela

	Include	Conditional	Exclude	Comments
POTS / orthostatic intolerance	X			
Other dysautonomia	X			
ME/CFS	X			
Fibromyalgia	X			doi.org/10.1371/journal.pone.0281593 doi: 10.1097/j.pain.0000000000002711
Irritable bowel syndrome (IBS)	X			dx.doi.org/10.1136/gutjnl-2022-328483
Interstitial cystitis				doi: 10.1007/s11255-021-03030-2
Overactive bladder	X			doi: 10.1007/s11255-021-03030-2 (COVID-19-associated cystitis)
Raynaud's phenomenon	X			
Migraine	X			doi.org/10.1101/2023.03.06.531302

Multiple chemical sensitivities	X			
Hashimoto's thyroiditis			X	Exclude for research: COVID-19 may cause autoimmune thyroid disease or exacerbate underlying thyroid disease that was silent/undetected or in remission. doi: 10.1016/j.tmaid.2022.102314
Sicca syndrome / xerostomia		X		doi: 10.1111/odi.14159 Exclude possible/unrelated auto-immune cause
Secondary depression		X		See section 2
Mast cell Activation Syndrome (MACS)		X		doi:10.1016/j.ijid.2021.09.043; DOI: 10.12968/hmed.2022.0123
Small fiber peripheral neuropathy		X		doi: 10.1002/mus.27458; DOI:10.1212/NXI.0000000000001146 Exclude diabetic neuropathy. Add questions to differentiate mono and polyneuropathies
Disordered sleep (e.g., restless leg syndrome, etc.)		X		