Development of a patient-reported instrument to assess the symptoms of long-covid and their impact on patients' lives

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1. Résumé en français

Le « long covid » est défini par l'ensemble des manifestations tardives survenant après une infection par SARS-CoV 2. La prévalence du long covid est inconnue mais certains auteurs rapportent que jusqu'à 10% des patients ayant eu une infection confirmée par PCR continuent d'avoir des symptômes 3 semaines après. A ce jour, la nature précise des symptômes du « long covid » est encore mal connue, mais il existe potentiellement plusieurs phénotypes différents (symptômes respiratoires uniquement, manifestations neurologiques…). Un article récemment publié dans Nature appelle à impliquer les patients dans la définition du « long covid ».

Nous proposons d'impliquer un très grand nombre de patients ayant eu un COVID suspecté ou confirmé, via ComPaRe, pour :

- Identifier précisément les différentes manifestations du « long covid » (nature, timing…)
- Comprendre l'impact du « long covid » sur la vie des patients (vie sociale, professionnelle, moral…)
- Utiliser ces informations pour développer et valider un outil scientifique utilisable à la fois en pratique clinique pour le suivi des patients et en recherche comme critère de jugement.

2. Introduction

Post-acute covid-19 ("long covid") seems to be a multisystem disease, sometimes occurring after a relatively mild acute illness. There is no agreed definition for long covid [1 2], the most common one being the persistence of symptoms beyond 12 weeks. Symptoms of long covid are unknown, with potentially several phenotypes. Recent articles have called for involving patients in defining these symptoms[3].

Prevalence of long covid is also unknown, with some authors suggesting that around 10-15% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks, and a smaller proportion for months [1 4]. Finally, the impact of long COVID on patients' lives is unknown.

To draw reliable estimates on the prevalence and severity of the symptoms of long-covid and evaluate its impact on patients' lives to orient care and/or evaluate therapeutics, there is a need for reliable and valid clinimetrics [5].

3. Methods

We aim at developing a patient-reported instrument assessing both the symptoms of long covid and their impact on patients' lives. The instrument will serve as a clinimetric in both clinical practice and research. Development of the instrument will follow a multistep method[6].

The study will be nested within ComPaRe (Communauté de Patients pour la Recherche, www.compare.aphp.fr), an e-cohort of patients with chronic (i.e. lasting ≥ 6 months) conditions who volunteer to participate in research [7]. Patients in ComPaRe propose research ideas, answer Patient Reported Outcome Measurements (PROMs) and Patient Reported Experience Measurements (PREMs), or contributing to data analyses. All participants provide electronic consent before participating. ComPaRe approved by the Institutional Review Board of Hôtel-Dieu Hospital, Paris (IRB: 0008367).

3.1. Participants

Participants will be adult (≥18 years old) patients reporting a previous SARS-CoV 2 infection (either confirmed or suspected). They will be invited to join the project via a social media and general media campaign. Call for participation will be also issued by long covid-19 patient associations.

3.2. Step 1: generation of the items

The content of the patient-reported instrument will be developed from experiences of a large number of patients with COVID19.

- First, we will conduct a literature review of all articles referring to the terms 'post-acute', 'long', 'chronic' and "COVID-19" in the title or abstract. Any mention to symptoms occurring after the acute phase of COVID-19 will be extracted from articles. If the timing of symptoms is unclear, the symptom will still be extracted. Findings will be grouped by similarity and by organs by a group of physicians based on existing research [4 8 9].
- Second, we will conduct large survey with open-ended questions about patient reported symptoms of COVID in ComPaRe. All participants who reported a previous COVID-19 (confirmed or suspected) will be invited to participate. They will answer a series of open-ended questions asking them to describe the symptoms they experienced after infection (nature of the symptoms, notion of relapsing and remitting symptoms, timing, etc.). The survey will use broad questions to avoid directing patients towards known consequences of COVID.
- Third, to understand the impact of long covid on participants' lives, we will also ask participants involved in the survey about the impact of symptoms on their daily activities, professional life, social life, etc. Similar to the previous part, we will use open-ended questions.

Answers to all open-ended questions will be analyzed by content analysis by two investigators who will extract “in vivo codes”: literal terms used by participants to explain and describe the symptoms and impact of long-COVID on their lives. Answers related to the acute phase of COVID-19 (i.e. symptoms within the first three weeks of the disease) will be dropped from analysis. If no time frame is specified, data will be kept in the analysis. The investigators grouped the “in vivo codes” into a standardized set of symptoms and consequences of long COVID based on their medical knowledge and the literature [4 8].

3.3. Step 2: drafting an initial tool

From the results of the qualitative enquiry, we will draft a preliminary tool. Our aim is to design a tool to help clinicians monitor patients’ state and thus, our interest is in the symptoms currently experienced by participants.

Part 1: Symptoms of long COVID

The first part of the tool will consist of a checklist of all symptoms identified in the first part of the study.

- Have you ever experienced this symptom? (YES/NO)

Part 2: Impact of each symptom on patients’ lives

Impact score derived from items identified during the open-ended survey

This preliminary tool will be pilot-tested for clarity, wording and usability with a few patients in ComPaRe.

3.4. Step 3: Validation of the instrument

We aim to validate the tool among patients reporting a previous infection by SARS-CoV2 in ComPaRe. Participants may have participated in the previous steps of the study.

Global score of the instrument

The global score of the instrument will be the sum of items score. No weighting by life domain affected will be done.

Construct validity

We aim to compare patients' scores from our tool with measurements of:

- Quality of life, measured using the EQ-5D[10]
- The Post-COVID functional scale (PCFS)[11]
- MYMO2 scale

Reliability

We aim to assess the reliability of the instrument by a test-retest method. As symptoms are likely to evolve quickly, we plan a one-week interval between the two measurements. Agreement will be assessed using the intraclass correlation coefficient (ICC) for agreement and bland and Altman plots [12].

Patient Acceptable Symptom State

The PASS is the level of a continuous treatment outcome measure below which patients consider themselves well [13]. For example, most patients with knee osteoarthritis consider their pain acceptable when their score is less than 27 mm on a 0- to 100-mm visual analogue scale, thus defining a PASS of 27 mm for pain[14]. To determine the PASS for our instrument, we will match participants' answers to the instrument and their answers to an anchor question used to determine the PASS in rheumatology: *"Taking into account all the symptoms you have during your daily life and also your functional impairment, do you consider that your current state is satisfactory?"*

3.5. Analyses in subgroups

- Confirmed vs. Suspected COVID-19. Will be considered as confirmed, cases with a positive SARS-CoV2 PCR.

4. Planning for the study

Protocol	Planned number of participants	Timing
Set-up of the online questionnaire in ComPaRe / Public announcement of the study	-	Ready 13th of October 2020
Recruitment /data collection for step 1	500-1000	Until the 25th of October 2020
Data analysis for step 1		Until the 25th of November 2020
Recruitment / data collection for step 2	>1000	Until the 15th of December 2020
Data analysis for step 2		Until the 15th of January 2021

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