Operational definition of persistent COVID and its key elements in the CIBERPOSTCOVID project

TECHNICAL REPORT

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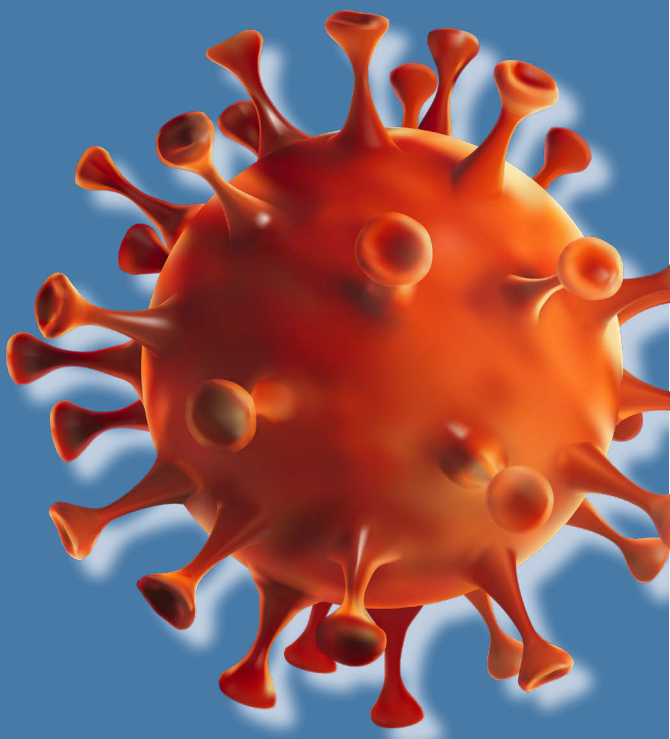
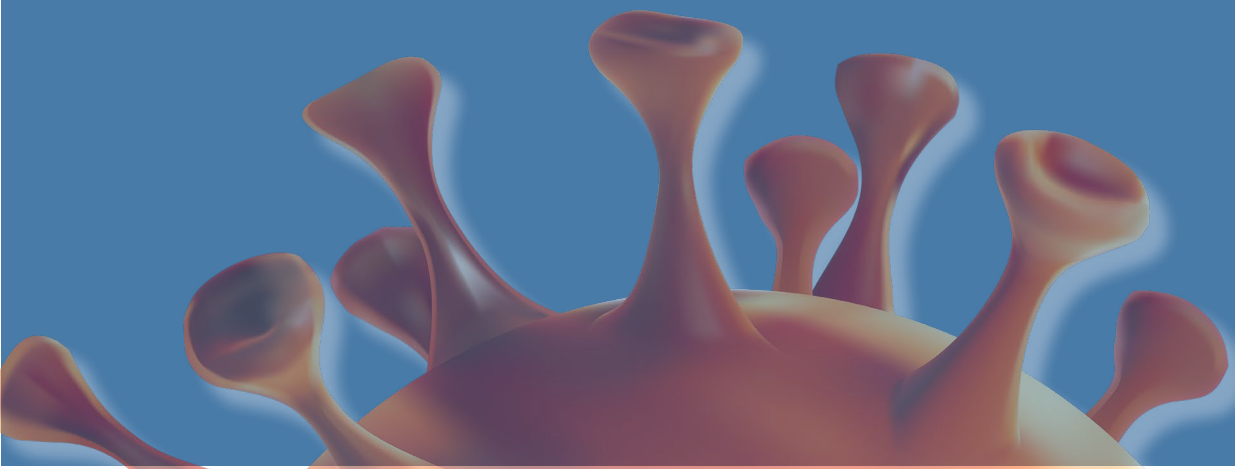
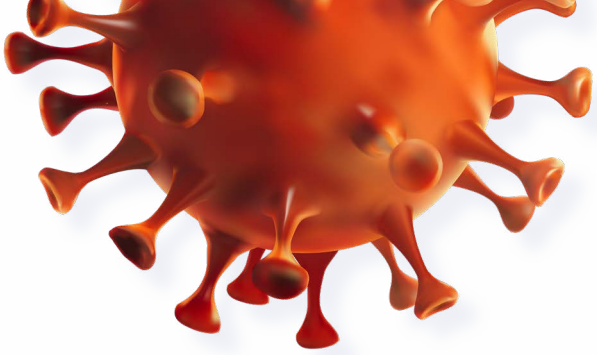
Instituto de Salud Carlos III
Salut/ Agència de Qualitat i Avaluació Sanitàries de Catalunya
SJD Parc Sanitari Sant Joan de Déu







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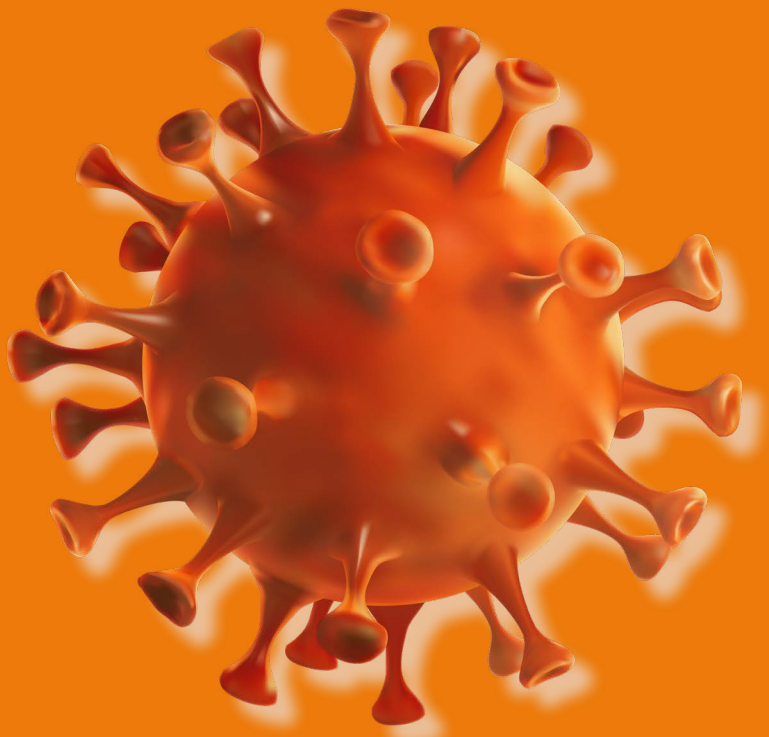


Operational definition of persistent COVID and its key elements in the CIBERPOSTCOVID project

Authors

Vicky Serra-Sutton (1,2), Antoni Serrano-Blanco (2,3), Marta Torres (1,2), Carla Montané (4,5), Ivan Solà (2,6), Alex Trejo (7,8), Mireia Espallargues (1,9)

On behalf of the CIBERPOSTCOVID steering group (*). Technical report prepared by the Consorcio de Investigación Biomédica en Red (CIBER). Instituto de Salud Carlos III. Ministry of Science and Innovation, 2022.

(1) Agency for Health Quality and Assessment of Catalonia, (2) CIBER of Epidemiology and Public Health, (3) Parc Sanitari Sant Joan de Déu, (4) independent consultant, (5) Elisava Design School, Universitat Pompeu Fabra, (6) Centro Cochrane Iberoamericano, (7) Onsanity Solutions SL, (8) Universitat Politècnica de Catalunya, (9) Red de Investigación Cooperativa Orientada al Resultado en Salud (RICORS).

(*) WP1 CIBERPOSTCOVID steering group

Ferrán Barbé and Marina Pollán (heads of the CIBERPOSTCOVID project), Jordi Alonso, Maria Arguimbau, Mireia Espallargues, Fernando García-Benavides, Montse Ferrer, Blanca Lumbreras, Javier Muñoz, Antoni Parada, Beatriz Pérez, José I. Pijoan, Vicky Serra-Sutton, Antoni Serrano-Blanco, Joan B. Soriano and Marta Torres.

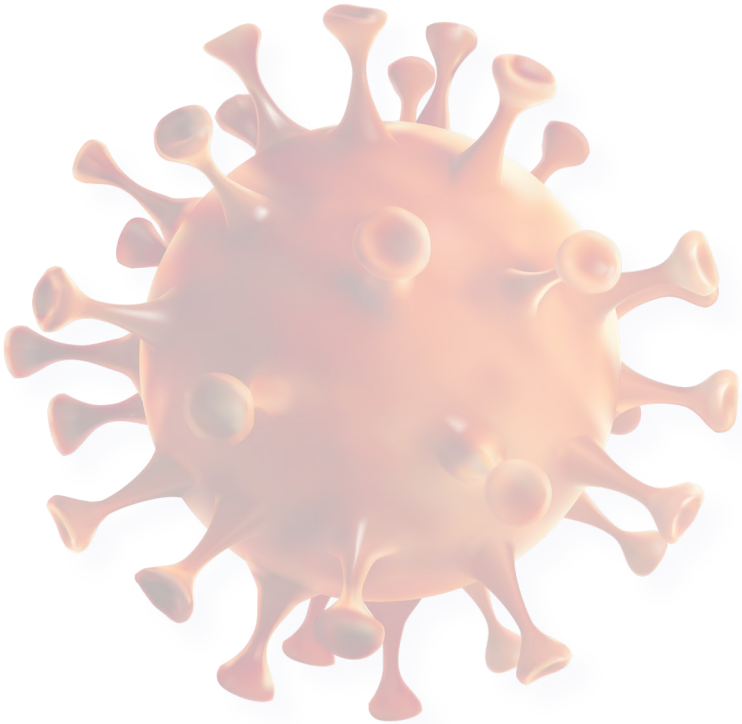
Vicky Serra-Sutton and Antoni Serrano-Blanco are the main joint researchers in the WP1 CIBERPOSTCOVID.

External collaborators

Qualitative study (Carla Montané), scoping review (Ivan Solà), Smart Delphi (Alex Trejo and Josep Mª Monguet), Communication (Cristina Juesas and Juan Carlos Durán).

Acknowledgements

Project partially financed by CIBER. We thank the key informants for their vital contributions to the CIBERPOSTCOVID project throughout the knowledge transfer process.



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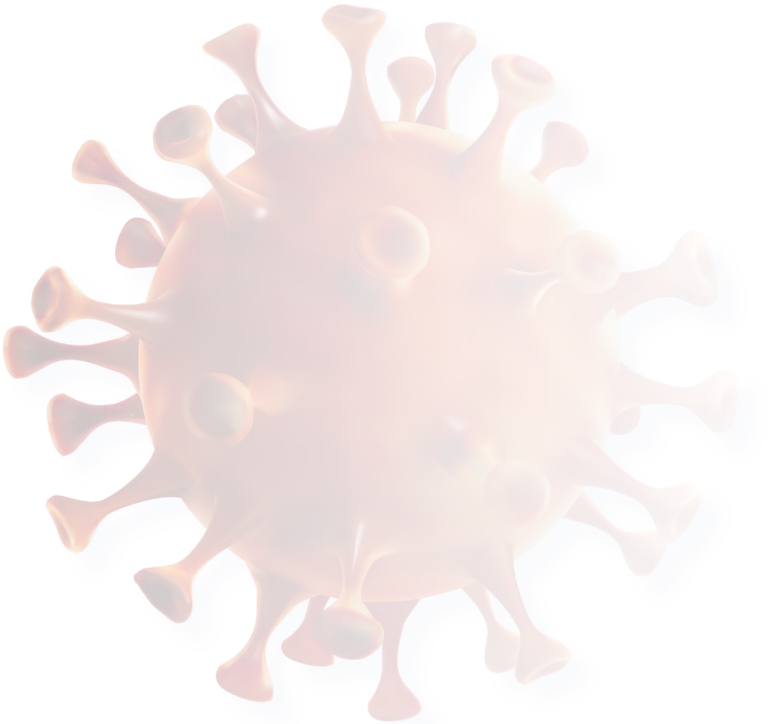


Executive summary

Background and context

In the Spanish National Health System, there is a general lack of agreement on what persistent COVID actually is and how its severity and predisposing profiles should be evaluated. This represents a major obstacle to the process of diagnosing this health problem and to the identification of profiles of high-risk patients with particular healthcare needs. It also complicates the definition of follow-up strategies, appropriate coding in information systems, and the implementation of interventions that apply a comprehensive, multidisciplinary approach. Consequently, there is a clear need for a better understanding of what persistent COVID really is.

In this first stage, the CIBERPOSTCOVID project proposes an operational definition of persistent COVID and its key elements.

Methodology

This definition was obtained via consensus between informants representing research institutions of reference such as the thematic areas of the Spanish network for biomedical research (CIBER), health professionals providing direct care to patients through Scientific societies, managers of clinical care and/or planning proposed by the public health authorities of Spain's autonomous communities, and representatives of patients receiving care in the Spanish national health service in collaboration with patients' associations. The project applied a mixed methodology that included:

1. a qualitative substudy (with semi-structured questionnaires and discussion groups)
2. a scoping review substudy of the evidence, and
3. a quantitative consensus substudy using the Smart Delphi platform.

More than 70 informants participated in the project to establish the operational definition and 71 published documents were consulted, including systematic reviews, clinical guidelines/ protocols and other consensus studies, as well as ongoing discussions with the project's steering group. The qualitative and scoping review substudies generated a set of statements that were then voted on in the quantitative consensus substudy. The aim was to obtain a definition of persistent COVID and its key elements based on a high level of agreement among the informants, supported by the literature consulted.

Results

The points that reached the highest level of agreement in the various sub-studies were the following (see Figure 1):

1. Persistent COVID is made up of a varied set of multiorgan manifestations and symptoms not attributable to other causes that persist, or fluctuate, for a minimum period of three months after the acute infection phase of COVID-19.

2. The most frequent manifestations and symptoms are systemic (e.g., fatigue), neurocognitive (e.g., brain fog or confusion) and respiratory or cardiovascular. Neurological, neuromuscular or psychological and psychiatric symptoms are also recorded.
3. The severity of these manifestations and symptoms should be measured using validated functional scales in order to interpret the profiles of patients and to cater for their needs.
4. Measuring the impact of manifestations and symptoms of persistent COVID on patients' everyday activities or social and working lives (i.e., on quality of life) was considered particularly important by the informants in both the qualitative and the consensus sub-studies, and reached a high level of agreement.
5. The responses highlighted the importance of the following points with regard to both the diagnostic process and the planning of future quantitative studies assessing the prevalence or incidence of the condition from clinical histories, records, or routine administrative clinical data:
   - the possibility that the manifestations and symptoms are due to other health problems must be considered, and ruled out;
   - the possible organ damage or sequelae caused by SARS-CoV-2 infection and its treatment should be borne in mind in the diagnostic assessment of persistent COVID;
   - a previous diagnosis of COVID-19 infection must be reported in the patient's medical history and/or clinical laboratory tests (confirmed by PCR or antigen test).

Despite reaching a high to moderate level of agreement on many of the items assessed, informants did not agree on how the operational definition of persistent COVID differs in the paediatric population. Nor was a consensus reached on how to measure patients' severity, although it was agreed that validated functional scales should be used and that the impact on different areas of daily life and on quality of life should be measured. Finally, the informants did not agree on a definition of patient profiles that might predispose to manifestations and symptoms of persistent COVID after COVID-19 infection.

Conclusions and final reflections

This study was carried out from various perspectives, including those of patients' representatives and professionals from different disciplines in order to further the understanding of persistent COVID and its characteristics.

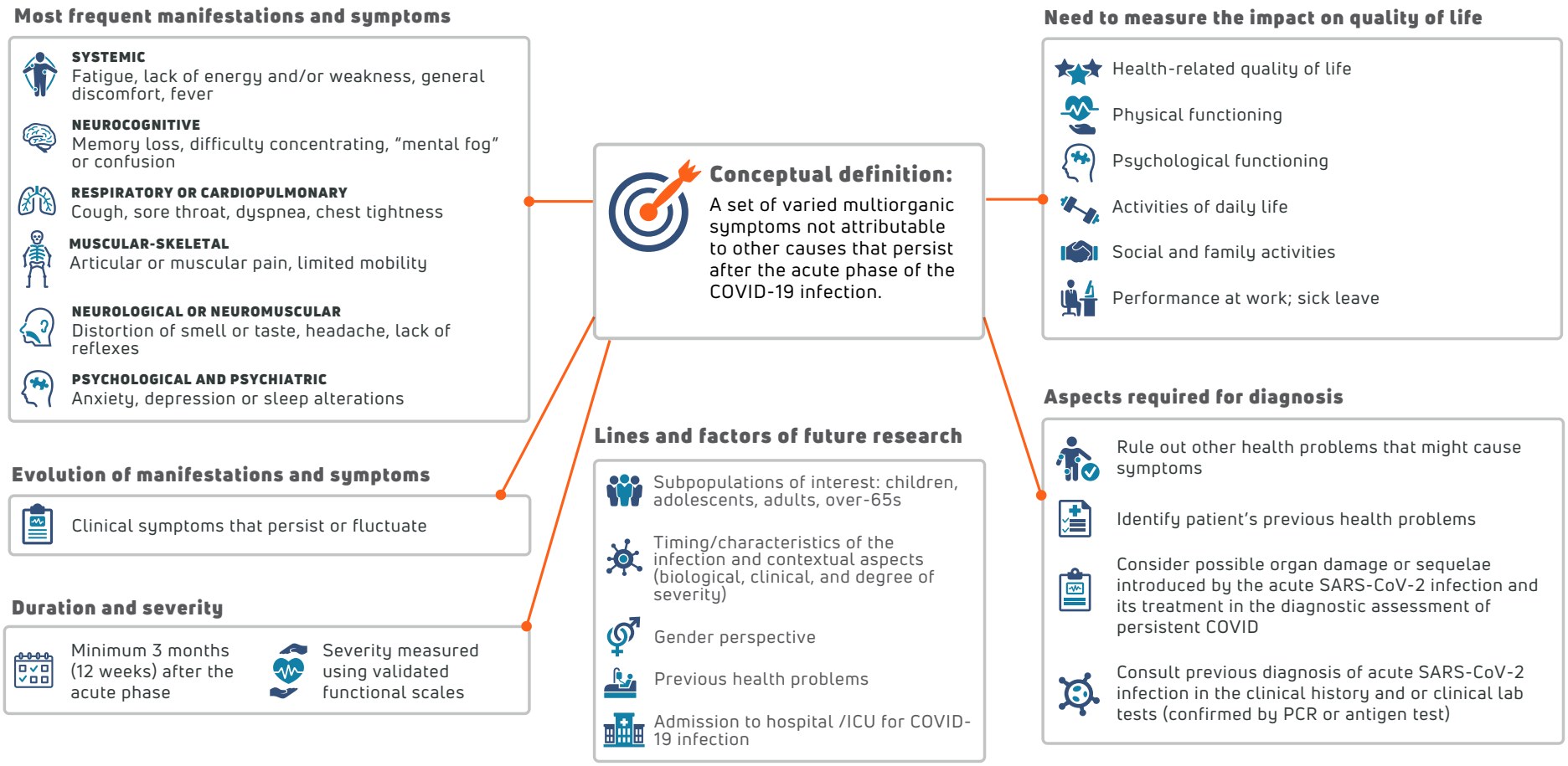
The CIBERPOSTCOVID project has fostered the generation of collective knowledge in a biomedical area where robust scientific evidence is lacking. The proposal is based on a participative, multidisciplinary and mixed methods process, widely used in the evaluation of health services and policies and above all in areas where only limited data are available.

An interesting finding of the study was the general agreement throughout the study regarding the impact that persistent COVID has on all areas of patients' lives – their everyday activities, their job performance, and their participation in society in general. The engagement of patients directly affected by persistent COVID is vital for heightening its visibility and recognition. They are taking an active part in the advances in the understanding of the condition and its definition.

To continue making progress, it is necessary to:

- Continue to listen carefully to patients (and their relatives) in the diagnosis and assessment of their needs.
- Search for predisposing factors using data from patients in routine clinical practice.
- Review and refine the proposal when new evidence becomes available, through its implementation in clinical practice and also through epidemiological studies.
- The proposed definition of persistent COVID is aligned with others published in this country and abroad, and can help to push forward the research being carried out within the framework of the Spanish national health system. It will be necessary to continue investigating the characteristics of persistent COVID in populations of interest (children, adolescents, adults, the over-65s) and the risk profiles and biological and clinical predisposing factors (for example, prior admission to hospital or intensive care, or variants in the immune system).

Figure 1. Operational definition of persistent COVID and key elements in the CIBERPOSTCOVID project.



Introduction and objectives

In the Spanish National Health System, there is a general lack of agreement on what persistent COVID actually is and how its severity should be evaluated. This represents a major obstacle to the process of diagnosing the condition and to the identification of profiles of high-risk patients with particular healthcare needs. It also complicates the definition of follow-up strategies, appropriate coding in information systems, and the implementation of interventions that apply a comprehensive, multidisciplinary approach. Consequently, there is a clear need for a better understanding of what persistent COVID really is and to identify patients' illness severity and risk profiles.

The CIBERPOSTCOVID project was set up in response to a request made by the Ministry of Health to the Carlos III Health Institute of the Ministry of Science and Innovation, and was carried out by two sections of the CIBER biomedical network consortium, Respiratory Disease (CIBERES) and Epidemiology and Public Health (CIBERESP). The overall aim of the project is to obtain a solid scientific grounding to deal with the health problem caused by persistent COVID, and includes a series of phases, ranging from its definition and consensus, the description of the barriers and facilitators in its diagnostic process, its clinical and biological predictors, to the burden of the manifestations and symptoms of the condition and the therapeutic options available. The project approaches the subject from the perspective of the Spanish national health system: it includes the testimonies of patients' representatives and health professionals and applies a multidisciplinary framework.

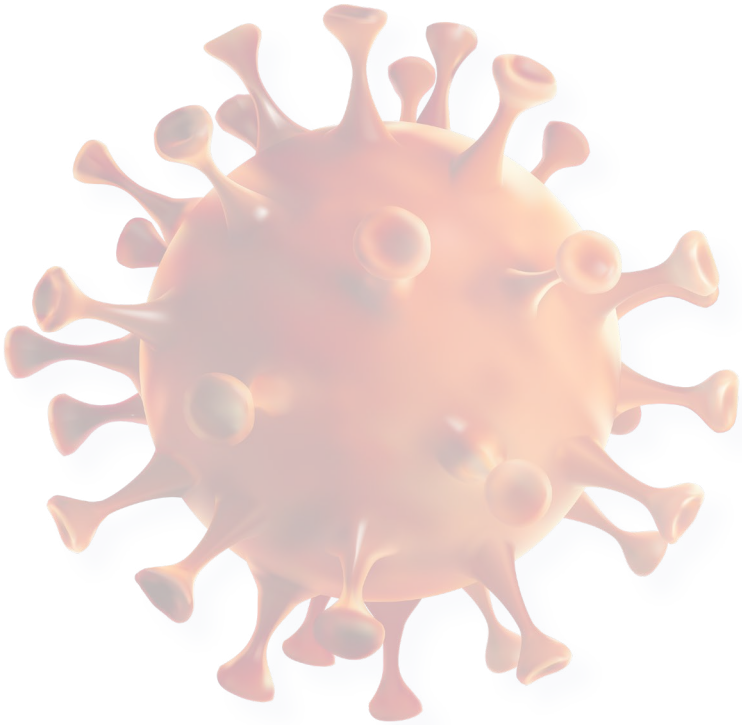
The first phase of the CIBERPOSTCOVID project (work package, WP1) consisted of establishing a consensus on the concept of persistent COVID in order to make a proposal for an operational definition and to update collective knowledge on its most important elements by examining the testimonies of key informants and literature review. This definition will be applied later to subsequent WPs focused on describing the prevalence and incidence of persistent COVID, the use of services, the costs, and its prognostic factors.

2.1. Principal objective

To propose an operational definition of persistent COVID based on consensus between key informants in the Spanish national health system.

2.2. Specific objectives

- To describe the opinions and positioning of informants on the concept of persistent COVID, and its possible classification within the framework of the health system.
- To describe the definition of persistent COVID and the specific standards based on existing and published consensus studies and clinical action protocols/guides.
- To describe the level of consensus on the definition and classification of persistent COVID in the Spanish health system.



3. Methodology

In order to obtain an operational definition within the framework of the CIBERPOSTCOVID project, a mixed methodology was proposed that included three sub-studies:

1. a qualitative sub-study with key informants,
2. a scoping review sub-study, and
3. a quantitative consensus sub-study using Smart Delphi.

Scientific quality standards were ensured through the application of the internal good practice guidelines of the Agency for Health Quality and Assessment of Catalonia (AQuAS) and the research protocol was implemented after approval by the IDIAP Jordi Gol Ethics Committee (Code CEIm: 21/244-PCV; 11/09/2021), thus guaranteeing confidentiality and data protection. The project had a steering group that met on several occasions throughout the project to discuss the results of the three sub-studies and the proposed operational definition of persistent COVID within the framework of the CIBERPOSTCOVID.

3.1. Qualitative sub-study with key informants

Study design

A phenomenological qualitative study was carried out to record the opinions of key informants in the Spanish national health system (namely researchers, health practitioners, patients' representatives and clinical managers/decision makers) who, due to their training and/or experience, were able to provide relevant information on persistent COVID, its definition, and the relevant elements.

Contents and field work

Each informant was asked what term they would use to refer to persistent COVID, what elements they thought should be taken into account in the operational definition, specific symptoms, potential risk factors, predisposing factors, as well as barriers and facilitators in the diagnostic process. They were also asked about severity profiles, ways to classify patients, the limiting impact of persistent COVID on daily life and quality of life, and future challenges.

Information was collected through a semi-structured questionnaire prepared from Microsoft Forms, which was sent by email to informants after they had provided their consent to participate in the study. A subgroup of these informants were invited to participate in one of the three discussion groups in which their opinions were examined in greater depth according to their profiles. The field work of the qualitative study was carried out between December and February 2022; the informants were contacted through reference institutions/organizations after AQuAs had sent them information on the study and requested their consent to participate and authorization to record the sessions for later analysis.

Sampling and participants

On the basis of the literature review and snowballing, the project's steering group worked to identify relevant organizations linked to the issue under study (i.e., persistent COVID and its terminological variants, and/or COVID-19). Intentional stratified sampling was carried out to contact managers at these organizations, who were asked to propose informants qualified to participate in the different stages of the project. These informants were:

1. Representatives of patients and relatives (through the following associations: FENAER, APEPOC, Long Covid ACTS-Long Covid Autonomous Communities Together Spain, Long COVID Aragón).
2. Researchers from CIBER thematic sections (Respiratory Diseases, Epidemiology and Public Health, Mental Health, Cardiovascular Diseases, Fragility and Aging, Liver and Digestive Diseases, Infectious Diseases) or other state-funded research networks such as REDISSEC and RICORS.
3. Health professionals involved in clinical practice, attached to 23 scientific societies from all over Spain.
4. Professionals in the field of clinical and health management, via the public health authorities of Spain's autonomous communities.

In all, 73 informants answered a semi-structured qualitative questionnaire (response rate: 60.3%). Of these, 35 also participated in three discussion groups (10-12 participants per group) in a virtual format via Zoom.

Data analysis

Content analysis was carried out of the semi-structured questionnaires, and, in the discussion groups, of the recorded sessions. The analyses were carried out by a senior qualitative analyst, reviewed by the core team and subsequently discussed with the project's steering group. The results of the semi-structured questionnaires and discussion groups were triangulated with the results of the literature review (described below) to propose the contents (i.e., statements and dimensions) to be included in the Smart Delphi platform for the quantitative consensus study (see below).

3.2. Scoping review sub-study

Study design

In parallel to the qualitative study, a scoping review of the literature was conducted to identify and describe the available definitions of persistent COVID published in the national and international biomedical literature. The main objective was to understand the phenomenon under study ("what is persistent COVID?") and to complement the information collected from the qualitative study in order to generate content for the Smart Delphi study (i.e., statements to be voted on and scored).

Criteria for the inclusion of documents

The following criteria were applied for the identification and inclusion of published documents:

- Concept: the studies and documents of interest had to provide an approach that would make it possible to define or delimit persistent COVID, both at the phenomenological level (i.e., obtaining definitions of the phenomenon in line with the approach of the person who formulated it), and at clinical and/or biological level (i.e., defining the entity, taking into account its characteristic signs and symptoms, risk factors and severity profiles) or at sociodemographic level.
- Population: the studies and documents of interest had to focus on people who had not fully recovered or had developed symptoms and/or other persistent clinical manifestations after acute infection by the SARS-CoV-2 virus.
- Context: documents aimed at health professionals of any speciality who have provided services to people affected by persistent COVID, as well as those responsible for planning health care, or members of the scientific community.

Bibliometric databases consulted

Various bibliographic databases and metasearch engines were consulted: MEDLINE (PubMed), EMBASE (embase.com), Science Citation Index (The Web of Science, Clarivate Analytics) and the COVID-19 collection of the L·OVE repository (Epistemonikos Foundation) until January 2022. To guarantee an exhaustive identification of guidelines, recommendation documents and other positions or statements and consensus studies, searches were carried out in the GIN International Guidelines Library (EBSCO), the eCOVID-19RecMap catalogue (covid19.recmap.org) and the COVID-19 Evidence Network to support Decision-making (COVID-END) website.

Documents describing conceptual definitions and key elements regarding persistent COVID were included. The protocol-specific part of the review was registered on the Open Science Framework platform (DOI 10.17605/OSF.IO/JMB3D). The initial searches were designed and led by the Agency for Health Quality and Assessment of Catalonia (CIBERESP Group 15) in September 2021. These searches were updated and implemented by the Ibero-American Cochrane Center until January 2022. The search strategies underwent external review using the PRESS tool (Sampson 2008, McGowan 2016). No time or language restrictions were applied to the searches. In the third stage, the reference lists of the relevant documents were reviewed and a follow-up was performed of the studies and relevant documents provided by the project's steering group identified ad hoc (from September 2021 to April 2022) or by the informants in the qualitative phase (December 2021 to February 2022).

Contents and data synthesis

An assessment of the overall quality of the documents (i.e., their methodological robustness) was carried out and the inclusion and exclusion criteria, defined in a new specific scoping review protocol registered on the public platform (doi:10.17605/OSF.IO/JMB3D), were applied. Two researchers from the Ibero-American Cochrane Center independently extracted the relevant information from each document included: namely, the terminology used to refer to long COVID, the conceptual/operational definition applied, symptomatology, duration, risk/predisposing factors, as well as the impact of long COVID on functionality and quality of life, the definition in the paediatric population, and the existing classifications of patients according to their severity.

A descriptive narrative synthesis, based on a content analysis, was carried out to understand the phenomenon under study. The results of the qualitative phase contributed to the scoping review of the evidence, and vice versa. The information of each thematic area defined in the qualitative study was triangulated in order to generate statements that could be included in the Smart Delphi quantitative consensus substudy.

Documents included in the scoping review

A total of 1024 references were obtained from the different information sources. After eliminating duplicates, 632 documents were submitted to the inclusion criteria. A total of 102 documents were evaluated in full, of which 31 were excluded (13 had an inappropriate design, eight had a scope or objectives different from that of this review, eight documents turned out to be duplicates of others already included, one study was only published as an abstract of a conference paper and did not provide enough information, and one reference ultimately turned out to be a primary study). The scoping review finally included a total of 71 documents (see Appendix 2). As the main objective of this study was to describe the published definitions and characteristics of persistent COVID in this country and abroad, neither the risk of bias nor the quality of the documents included was evaluated; given the novelty of the topic, the objective was to include all the potential evidence available that met the inclusion criteria. Most of the documents included were based on systematic reviews of the evidence (28 documents), scoping reviews, clinical practice guidelines or protocols (18), published consensus studies (nine), or other types of reference documents (16). All the systematic reviews included aimed to quantify symptomatology at different time points after acute SARS-CoV-2 virus infection.

3.3. Quantitative consensus sub-study. Smart Delphi

Study design

A modified Delphi consensus study was carried out to identify the elements on which there was quantitative agreement or disagreement regarding the concept of persistent COVID in the Spanish national health system. This quantitative consensus study was applied using the Smart Delphi platform that allows participants to vote virtually, asynchronously and in real time. As well as determining the degree of consensus on a topic, this methodology encourages the generation of collective knowledge among the participants and is thus a useful training exercise in areas where there is currently little agreement or little available scientific evidence.

Contents and field work

The results of the qualitative study and the scoping review were triangulated so as to generate statements to be included in the Smart Delphi CIBERPOSTCOVID quantitative consensus study. A total of 100 statements, classified in nine dimensions, were initially proposed by the project's core team. A pilot test was carried out to refine and reduce the number of statements, and a final figure of 67 was obtained, grouped under the following dimensions:

1. Terminology (four statements),
2. What characterizes "persistent COVID"? (12 statements)
3. Symptoms to take into account (nine statements),
4. Factors that may favor or predispose to greater risk (12 statements),

5. Impact on quality of life and working life (seven statements),
6. Severity profiles (four statements),
7. Identification and diagnosis process (six statements),
8. Different definition in the paediatric population? (eight statements),
9. Current challenges and progress (five statements).

Two waves were created in two consecutive rounds of the consensus. In the first wave, key informants (expert professionals and patients) proposed by the reference institutions/organizations described in the qualitative substudy were invited. Their votes in the first wave served to established the descriptive statistics of the central trend for the entire group for use in the second wave aimed at a broader group of professionals/patients' representatives. Smart Delphi allows for two consecutive rounds of voting in each wave. This implies that each participant votes for each proposed statement (first round) and scores it on a scale of 1 to 6 (1, totally disagree and 6, totally agree), without access to the opinions of the rest of the participants. Immediately after voting, the overall level of agreement of the participants up to that moment can be visualized through graphs and descriptive statistics of the trend of the entire group. Voting is then repeated in the second round. In both waves, informants were sent a link to allow them to participate directly in the Smart Delphi CIBERPOSTCOVID platform. The pilot test was carried out at the end of March 2022, and the first and second waves during April 2022.

Sampling and participants

A pilot test was carried out with 47 participants selected by the CIBERPOSTCOVID core group using convenience sampling. Participants were from the fields of research, clinical practice and clinical or health management, or were patients' representatives. In the first wave, the participation of 114 informants was requested; 96 informants scored some of the statements, and 71 scored all 67 statements (Table 1). A call for participation in the second wave with a more extensive consensus was launched through the web pages of the institutions described in the qualitative sub-study. This second wave, as well as being a broader virtual quantitative consensus exercise, was considered a training activity in this subject area of interest. The results of this second wave are not presented in this report, but they will appear in a scientific article currently in preparation. In total, between the first and second waves of the CIBERPOSTCOVID Smart Delphi study, 333 participants scored some of the statements and 242 scored all 67 statements.

Table 1. Participants in the first wave of quantitative consensus using Smart Delphi at CIBERPOSTCOVID*

	Participants 1st wave	%	Voted on some statements	%	Voted on all statement	%
Total	**114**	**100**	**96**	**84,6**	**71**	**62,3**
Patients' representatives	26	22,8	17	14,9	14	12,3
Clinical practice	36	31,6	39	34,2	33	28,9
Research in health-teaching	28	24,6	30	26,3	18	15,8
Health management-planning	24	21,0	10	8,8	6	5,3

(*) the first wave of Smart Delphi consensus included the participation of designated experts (professionals and patient representatives). The results of this first wave allowed the proposal of key elements of the operational definition of persistent COVID.

Data analysis

It was agreed that a statement included in Smart Delphi reached the threshold of consensus when 70% of the participants scored it either 5 or 6, or 1 or 2, with an interquartile range (IQR) between 0 and 1. The results of the qualitative study, the scoping review to propose statements and the pilot test underwent content analysis in order to eliminate repeated or lower priority content. In addition, descriptive statistical analyses were carried out: means, medians, standard deviations and IQRs. The results of the first wave were borne in mind to produce the proposed operational definition of persistent COVID and its key elements, since a more expert group of participants was included at this stage.

3.4. Proposed operational definition of persistent COVID

To construct the proposed operational definition of persistent COVID and the key elements that should be taken into account for its implementation in the future CIBERPOSTCOVID working groups (WPs), the results of the first wave of Smart Delphi quantitative consensus were assessed, together with the most salient results of the qualitative sub-study and the scoping review. As already noted, the results of the second wave (not presented here) will form part of another study currently underway. The results of each substudy were discussed with the members of the steering group throughout the CIBERPOSTCOVID project. The proposed operational definition of persistent COVID and its key elements is presented in Figure 1, at the beginning of this report.

Results

The results are presented below, structured according to the key elements included in the operational definition of persistent COVID in Figure 1, which presents a summary of the three CIBERPOSTCOVID sub-studies. Elements that reach a certain level of agreement among the informants in the qualitative phase are described, and also those with a lower degree of agreement. The results from each substudy are included, with regard to the following items:

- proposed operational definition and the elements to be included
- terminology and definitions
- most frequent manifestations and symptoms
- course of manifestations or symptoms
- duration
- severity profiles
- need to measure the impact on quality of life
- other elements to take into account in the diagnostic process
- definition in the paediatric population
- future lines and areas of research.

4.1. Proposed operational definition and the elements to be included

The results obtained from the qualitative study, the scoping review and the first wave of the Smart Delphi consensus gave rise to a proposal for an operational definition of persistent COVID and the elements that should be taken into account in the rest of the CIBERPOSTCOVID project (Figure 1, see summary section). These are the elements with the highest level of agreement in the qualitative phase, the scoping review, and the Smart Delphi quantitative consensus phase.

At the qualitative stage, informants agreed that the concept, the duration, and other key elements should be included in the proposed operational definition of persistent COVID. The most prominent concepts in the 35 informants' comments during the discussion groups in reference to persistent COVID and/or terminological variants (hereinafter "persistent COVID") were the existence of a set of varied symptoms, the permanence of symptoms beyond the acute

phase, and the persistence of these symptoms beyond three months. The following elements are highlighted:

The general and specific symptoms are the main elements of all the definitions proposed by the informants in the qualitative study:

- With regard to symptomatology, there was a tendency not to specify specific symptoms, but to speak of a set of varied and/or systemic signs or symptoms, and to express their types of manifestation under broad headings (for example, respiratory, neurological, etc.) and their clinical course as well (i.e., persistent, fluctuating or new).

The duration/time frame: Most informants agreed that the manifestations and symptoms should have a minimum duration of three months (12 weeks) after the acute infection of COVID-19 to be considered as persistent COVID. In many cases, this choice was justified because it was the time frame already established by the World Health Organization (WHO), but also because it was considered the minimum time necessary to rule out other pathologies and to respect a period of convalescence.

Functionality and impact on daily activities: The need to include functional alterations in various areas of patients' lives (everyday, family, work, and social activity) in the operational definition of persistent COVID was highlighted, as well as the impact on their quality of life. The need to refer to factors that hinder the return to the state of health pre-infection was also noted, especially in cases of greater functional involvement.

Reference to a laboratory diagnosis: There were two main positions on the diagnostic process: on the one hand, that SARS-Cov-2 infection had to be confirmed by a clinical laboratory test, to guarantee and document the acute episode; on the other, that the patient's clinical history had to record that there had been a probable and/or confirmed infection of COVID-19 (following the WHO definition) so as not to leave out patients who were infected in the first wave and who had no option of being diagnosed by a laboratory test due to its non-existence or unavailability.

Need to rule out symptoms attributed to other causes: -Among the proposed definitions, references to the symptomatology not being attributable or explainable by other causes were also very frequent – especially to avoid confusion, and to differentiate it clearly from other pathologies with similar symptoms or from previous comorbidities

4.2. Terminology and definitions

Results of the qualitative sub-study with key informants

The terms "persistent COVID" or "long COVID" were the ones that were mentioned the most by the informants in the qualitative substudy (Figure 2), especially among primary care health

Figure 2: Concept cloud of the terminology in the qualitative semi-structured questionnaires (n=72 informants)

staff, researchers and teachers, as well as representatives of patients' associations (48 of 72 participants). "Post-COVID syndrome" was the term mentioned by the rest of the health professionals (n=10), who represent a minority of specialists in the hospital setting. Although there was support for the term "persistent COVID", a variety of terminologies were described. An interesting point highlighted by the qualitative study was the description of the arguments for and against the different terminological variants that help to understand the phenomenon under study and its currents. The positions in favour or against different terminological variants are summarized in figures 3a and 3b.

The main reasons in favour of the term "persistent COVID" are the reinforcement of the concept of persistence and the arguments that: a) the symptoms last over time after the acute infection; b) the patients have not recovered, since the symptoms persist; and c) that there are already publications that speak of the persistence of the virus. Among the arguments against this term raised in the qualitative study were the lack of knowledge or evidence to confirm the persistence of the virus. The main reasons in favour of the term "long COVID" were its meaning of persistence, but also, and above all, because it was a term that was used by patients' representatives and reflected their demand for visibility and recognition. It is also widely used at international level.

In relation to the other concepts, the main reasons in favour of the term "post-COVID syndrome" (or "post-COVID symptoms") are: a) the lack of knowledge (there is still no evidence regarding the persistence of symptoms due to the virus); b) it is the term used by the WHO; c) there are already references to other viruses that also cause postviral syndromes; and d) in some cases the use of the term "persistent" may have negative consequences for the patient (i.e.,

iatrogenesis). Family and community medicine practitioners mainly rejected the term, as did the patients participating in the qualitative study; they hold that its use denies the persistence of the virus because the prefix "post-" implies that the previous state has disappeared. They feel that the term "post-COVID" suggests that a patient has overcome the disease and, therefore, refers to a different profile of patient; or, according to some informants, it might refer to a patient with severe acute COVID-19 who was admitted to the ICU and subsequently presents sequelae.

Figure 3a: Arguments for and against the use of the terms "persistent COVID" and "long COVID" (n=72 informants, semi-structured questionnaires)

PERSISTENT COVID/LONG COVID

Arguments in favour: PERSISTENT COVID

- The concept of persistence must appear, since these are symptoms that last over time after the acute infection.
- Patients have not recovered; they continue to have symptoms that persist after the acute infection.
- Some publications already talk about the persistence of the virus; they mention that viral persistence is one of the lines of research, and that there is no evidence to the contrary.

LONG COVID

- Several key informants (especially expert professionals and patients' representatives) note that the term was coined by the patients themselves to give it visibility, and that making use of it reinforces their recognition.
- In addition, the term is also used and applied internationally and in most of the investigations currently underway.

Arguments against (referring to "persistence"):

- The lack of knowledge/evidence ("we still know very little") means that we cannot speak of the persistence of the virus.
- In some cases, the inclusion of the term persistence may lead to iatrogenesis (by inducing patients to perpetuate something that is not yet known to be the case).

Profiles most engaged in the debate, for and against

- **In favour:** expert patients, family and community medicine practitioners, researchers and teachers.
- **Against:** neurologists, pulmonologists, internal medicine specialists, gastroenterologists, epidemiologists, planners.

Figure 3b: Arguments for and against the use of the term "post-COVID symptoms or syndrome" (n=72 informants, semi-structured questionnaires)

"POST-COVID" SYMPTOMS/SYNDROME

Arguments in favour: "WE KNOW VERY LITTLE", "THERE IS NO EVIDENCE OF THE VIRUS'S PERSISTENCE" AND "WE HAVE REFERENCES OF OTHER POST-VIRAL SYNDROMES"

- Some professionals note the lack of current knowledge to date ("we know very little"); they say that, at the moment, we can only speak of "post-COVID symptoms": "there is no evidence of viral persistence".
- It is also argued that it is a syndrome – a well-established medical term, which defines a series of symptoms that are associated with each other and reproduce, without having a clear etiology.
- It is also mentioned that there are already other viruses that also cause post-viral syndromes, with some similar symptoms, and that, therefore, the same criteria should be applied with regard to the name. Specifically, Chronic Fatigue Syndrome is mentioned as a reference.

"THE WORD IS "POST"; THAT'S WHAT THE WHO SAYS" (And if the WHO says so, we do too)

- It is considered important to apply the international terminology already in use: the WHO uses the term "post-COVID".
- It is also mentioned that the forthcoming ICD-11 classification refers to a "post-COVID" disease.

Arguments against: NOT POST

- "Post-" implies that the prior state has disappeared.
- Having "persistent COVID" means that you have not overcome the disease.
- "Post-COVID" is attributed to people who have had severe acute COVID with ICU admission and present sequelae.

NOT A SYNDROME

- The term "syndrome" fragments a disease, but the approach to it must be comprehensive.

Profiles most engaged in the debate, for and against

- **In favour:** neurologists, pulmonologists, internal medicine specialists, family, community and rural practitioners (1 case).
- **Against:** expert patients, family, community medicine practitioners, researchers and teachers.

Results of the scoping review sub-study

In the scoping review of the literature, 71 documents were included, of which 43 were literature reviews (see Appendix 2). Most of them contained information on the symptoms of COVID-19 at different times after acute infection with the SARS-CoV-2 virus.

In the literature, the terms used to refer to the concept of persistent COVID vary, although most documents associate it with a common phenomenon (namely, symptomatology that persists after acute infection by the SARS-CoV-2 virus). It was also observed that many documents take

as reference definitions already accepted by the scientific and academic community, but which appear only in a limited number of documents (principally from the action guide of the public body of the UK's National Institute for Health and Care Excellence; Callard 2021, Datta 2020, Greenhalgh 2020, NICE, SIGN, RCGP 2021). The scientific publications consulted refer to this phenomenon using terms such as "persistent COVID" (the most widely used in Spain) or others related to the immediate moment after the acute infection ("post-acute COVID", "post-acute sequelae of COVID-19" (PASC) or "post COVID-19", or "long COVID". Although these definitions fulfil an operational function, they were not formulated following a systematic and broad-ranging process of consensus such as the one conducted by the WHO in late 2021, where the concept of post-COVID-19 symptoms was proposed (Soriano 2021).

The reference documents included in the scoping review include definitions with different time frames (Figure 4). One of the first definitions of this concept was formulated in a document that offered guidelines for management in the context of primary care (Greenhalgh 2020). When it was published, it was recognized that there were no agreed definitions for persistent COVID and the proposal was made to differentiate between: i) "post-acute COVID-19" for manifestations and symptoms that extend up to three weeks from the onset of symptoms, and ii) "chronic COVID-19", in which symptoms extend beyond 12 weeks.

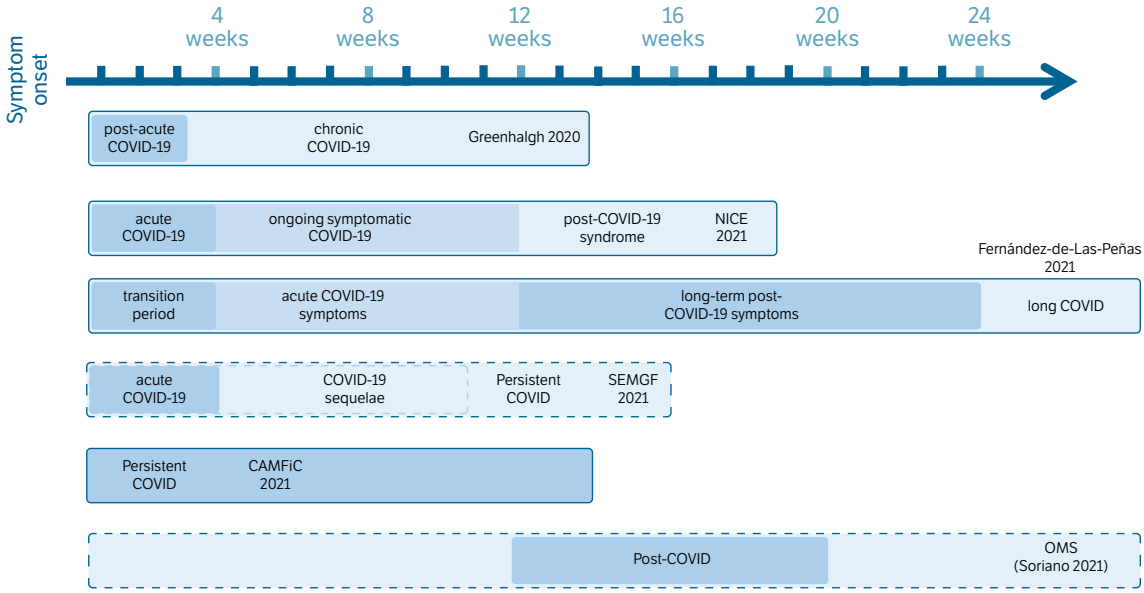
The intercollegiate clinical practice guidelines devised by NICE, SIGN and the RCGP (NICE, SIGN, RCGP 2021, Shah 2021) offered a working definition for the post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, present for more than 12 weeks, and not attributable to an alternative diagnosis. For its part, the WHO's definition of the concept was developed with a greater and more rigorous consensus on the basis of a Delphi study (Soriano 2021). This document defines a post-COVID patient as a person with a history of probable or confirmed SARS-CoV-2 infection, with a manifestation that generally occurs three months after the onset of COVID-19 and whose symptoms last at least two months and are not explained by an alternative diagnosis.

Another Spanish research group developed a classification of post-COVID-19 symptoms (Fernández de Las Peñas 2021), based on their evolution over the following time frame: i) a transition period, with symptoms potentially associated with acute infection four to five weeks after diagnosis, ii) appearance of acute post-COVID symptoms between five and 12 weeks after diagnosis of acute infection, iii) appearance of long-term post-COVID symptoms between 12 and 24 weeks after the diagnosis, and, finally, iv) appearance of symptoms of persistent COVID from 24 weeks after the diagnosis.

A multi-society clinical guide led by the Spanish Society of General and Family Physicians (SEMG, 2021) offers another operational definition based on the chronology of the symptoms:

i) manifestation of acute COVID-19 symptoms up to four weeks after infection, ii) sequelae of COVID-19 (frequently known as post-COVID-19) when there is a history of severe disease in the acute phase, frequently requiring admission to hospital, with symptoms derived from the sequelae of structural damage caused by the complications; and finally iii) persistent COVID-19 (or long COVID) defined as a set of multiorgan symptoms that affects people who suffered from COVID-19 (with or without confirmation by lab tests) with persistence of symptoms after four and even 12 weeks. The symptoms fluctuate and may manifest themselves in the form of outbreaks, and are not attributed to an alternative underlying disease.

Figure 4. Duration of symptoms and clinical manifestations of persistent COVID in some of the reference documents included in the scoping review of the literature.



Results of the Smart Delphi quantitative consensus sub-study

In the first wave of the CIBERPOSTCOVID Smart Delphi consensus study, 96 informants scored some of the statements and 71 scored all 67. Four statements were proposed to assess the approval of the terms "persistent COVID", "long COVID", "post-COVID syndrome" and "post-COVID symptoms". None of the terms reached the required level of consensus; the one with the highest agreement was "persistent COVID", which was scored 5 or 6 by 53.1% of the participants (mean: 4.38, SD: 1.5, IQR: 2).

In the first wave of the consensus study, the expert participants agreed on the following aspects of the conceptual definition of persistent COVID:

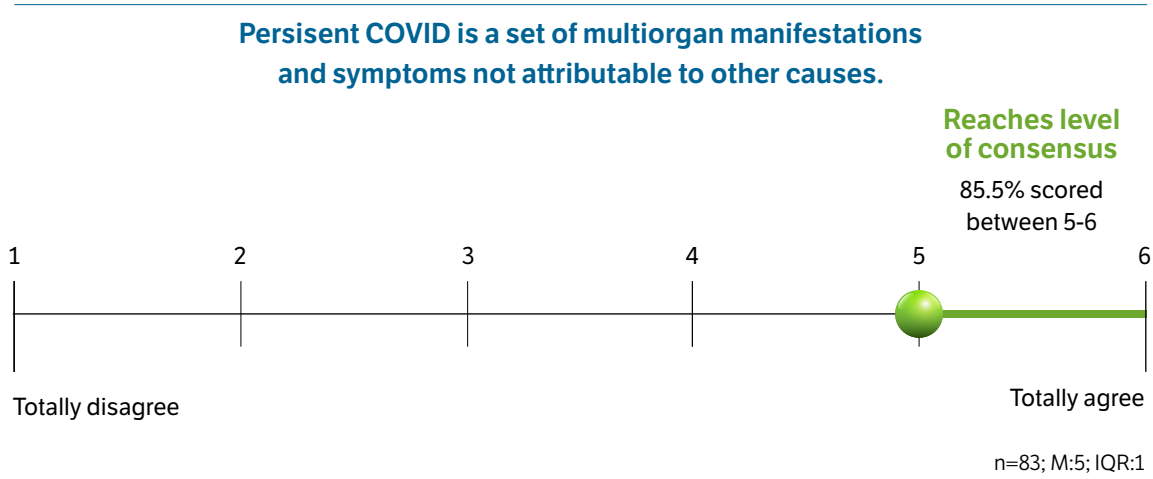
– “Persistent COVID” is a set of manifestations and symptoms that persist after acute COVID-19 infection [84.3% of participants gave scores between 5 and 6 (n=95), IQR, interquartile range: 1, mean: 4.9 and SD, standard deviation: 1.1].

– Clinical manifestations and symptoms of “persistent COVID” fluctuate over a period of time after acute COVID-19 infection [84.5% of participants gave scores between 5 and 6 (n=84), IQR: 1, mean: 5.1 and SD: 0.9].

– ”Persistent COVID” is a set of multi-organ manifestations and symptoms not attributable to other causes [85.5% gave scores between 5 and 6 (n=83), IQR: 1, mean: 5.1 and SD: 1.05; Figure 5].

– ”Persistent COVID” is considered when clinical manifestations and symptoms are present for at least three months (12 weeks) after acute COVID-19 infection [84.1% gave scores between 5 and 6 (n=83), IQR: 1, mean: 5.1 and SD: 1.04].

Figure 5. Level of agreement on the definition of persistent COVID in the first wave of the CIBERPOSTCOVID Smart Delphi consensus study

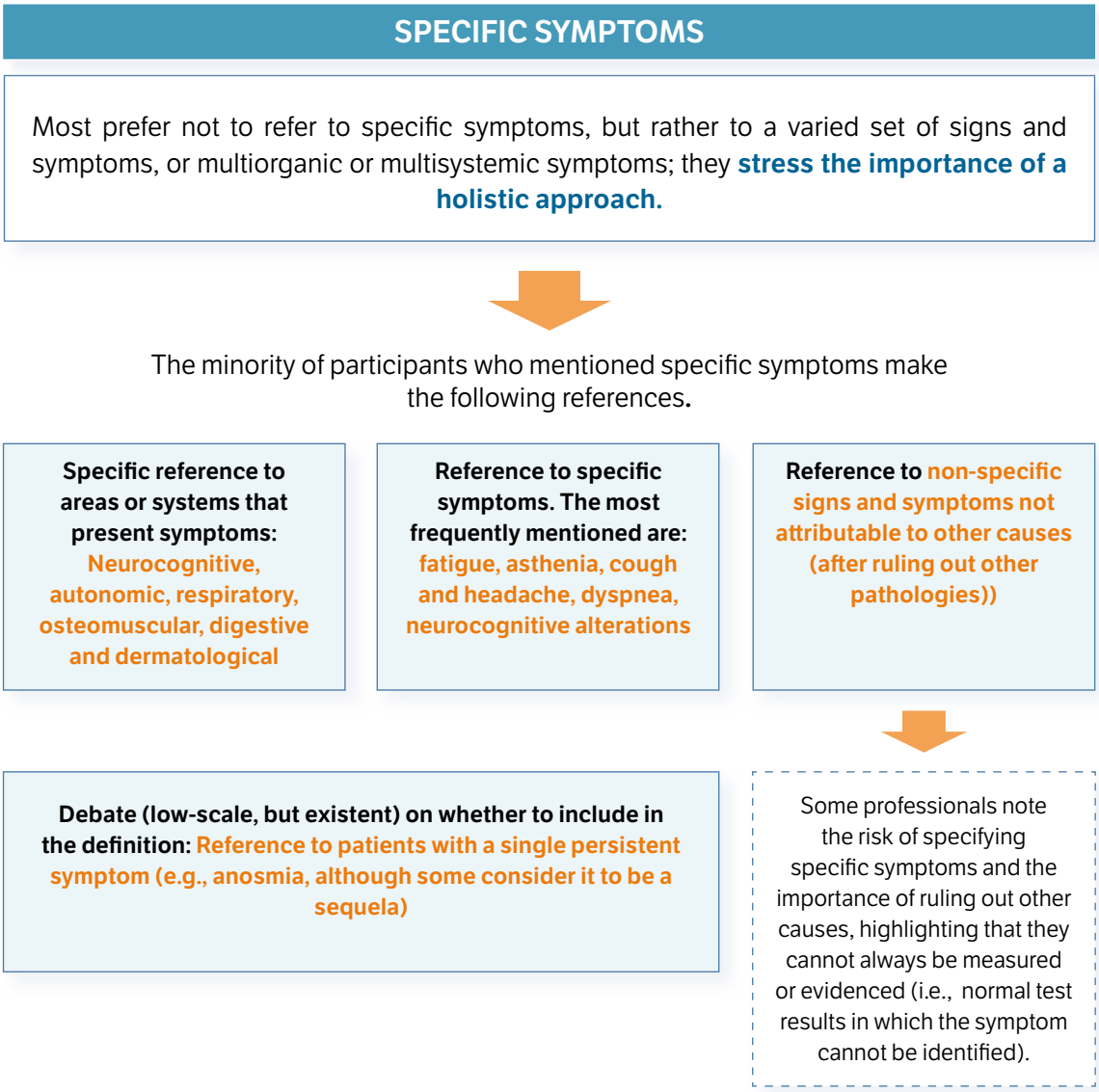


4.3. Most frequent manifestations and symptoms of persistent COVID

Results of the qualitative substudy with key informants

As previously mentioned, the debate generated in the three discussion groups involving 35 key informants underlined that, in the definition of persistent COVID, specific symptoms should not be listed but should be expressed as a set of varied manifestations, signs and symptoms. or as multiorgan or systemic symptoms. The emphasis is placed on addressing them as a whole and including in the operational definition the broad groups of manifestations and symptoms of “persistent COVID” (Figure 6). For this reason, both in the Smart Delphi study and in the operational definition in Figure 1, the manifestations and symptomatology are presented in broad groups.

Figure 6: Participants' views on the most frequent specific manifestations and symptoms in persistent COVID (n=35 informants, discussion groups)



Results of the scoping review sub-study

The consensus document published by the WHO (Soriano 2021) describes a set of manifestations and symptoms that includes fatigue, shortness of breath and cognitive dysfunction, but also other types of manifestations and symptoms that have an impact on daily functioning. There is no minimum number of defining symptoms. Symptoms may appear after initial recovery from an acute episode of COVID-19 or persist from the time of the initial illness; they may also fluctuate, and patients may relapse over time. The respondents agreed that a specific definition may be required for the paediatric population.

The most rigorous estimates of the prevalence of persistent overall manifestations and symptoms were extracted from a series of systematic reviews that included studies published up to the first semester of 2021. The following stand out:

- Fatigue is one of the most common systemic manifestations, found in between 31% and 58% of people who manifest persistent symptoms (Michelen 2021; López León 2021). People who required admission to hospital during the acute phase of the illness more often experience long-term illness (37%) than those who did not (24%) (Michelen 2021). Another review found a higher proportion of people with post-COVID symptoms in the long term (more than 12 weeks after the acute phase) (48%) than in the short term (37%) (Iqbal 2021). Symptoms such as lack of energy (Michelen 2021), general malaise or sweating (32%, Michelen 2021, Groff 2021) and, less frequently, fever, dizziness, tremors or a flu-like state were also reported.

- Headache was the main neurological symptom recorded, though its prevalence ranged widely, between 8% and 44% (Groff 2021, Iqbal 2021, López León 2021). Distortions of both taste (between 11% and 23%; Groff 2021, López León 2021) and smell (between 13% and 22.1%; Groff 2021; Michelen 2021) were also very common symptoms. About a quarter of patients with persistent symptoms reported concentration difficulties. Memory loss was also noted in all systematic reviews, in between 16% and 18% of cases; López León 2021; Groff 2021; Michelen 2021).

- A high proportion of respondents reported psychological symptoms, mainly in the form of anxiety (between 18% and 29%; Michelen 2021; Groff 2021, Iqbal 2021) and depression (between 15% and 20%; Nasserie 2021; Groff 2021, Iqbal 2021). Sleep disturbances were also frequent.

- Dyspnea or shortness of breath were the most frequent respiratory and cardiopulmonary symptoms, reported in between 24% and 39% of the responses; López León 2021; Iqbal 2021). They were more frequent in people hospitalized during the acute phase of COVID-19 (occurring in 28%). Chest pain and cough were two common symptoms identified in this subgroup. Other symptoms such as polypnea, increased need for oxygen or palpitations were also recorded.

Results of the Smart Delphi quantitative consensus sub-study

In the Smart Delphi consensus study, the following groups of clinical manifestations and symptoms reached the consensus threshold: neurocognitive, musculoskeletal, systemic, neurological or neuromuscular, and psychological or psychiatric (Figure 7).

The statement regarding respiratory or cardiopulmonary manifestations and symptoms just failed to reach the predefined consensus threshold (68.8% gave scores between 5 and 6 with an IQR of 2). In spite of this, they were added to the proposed operational definition of persistent COVID due to the agreement expressed in the qualitative phase and because they were conceptually relevant in the review of the scientific evidence.

Figure 7. Clinical manifestations and symptoms of persistent COVID reaching the consensus threshold in the first wave of the Smart Delphi consensus study

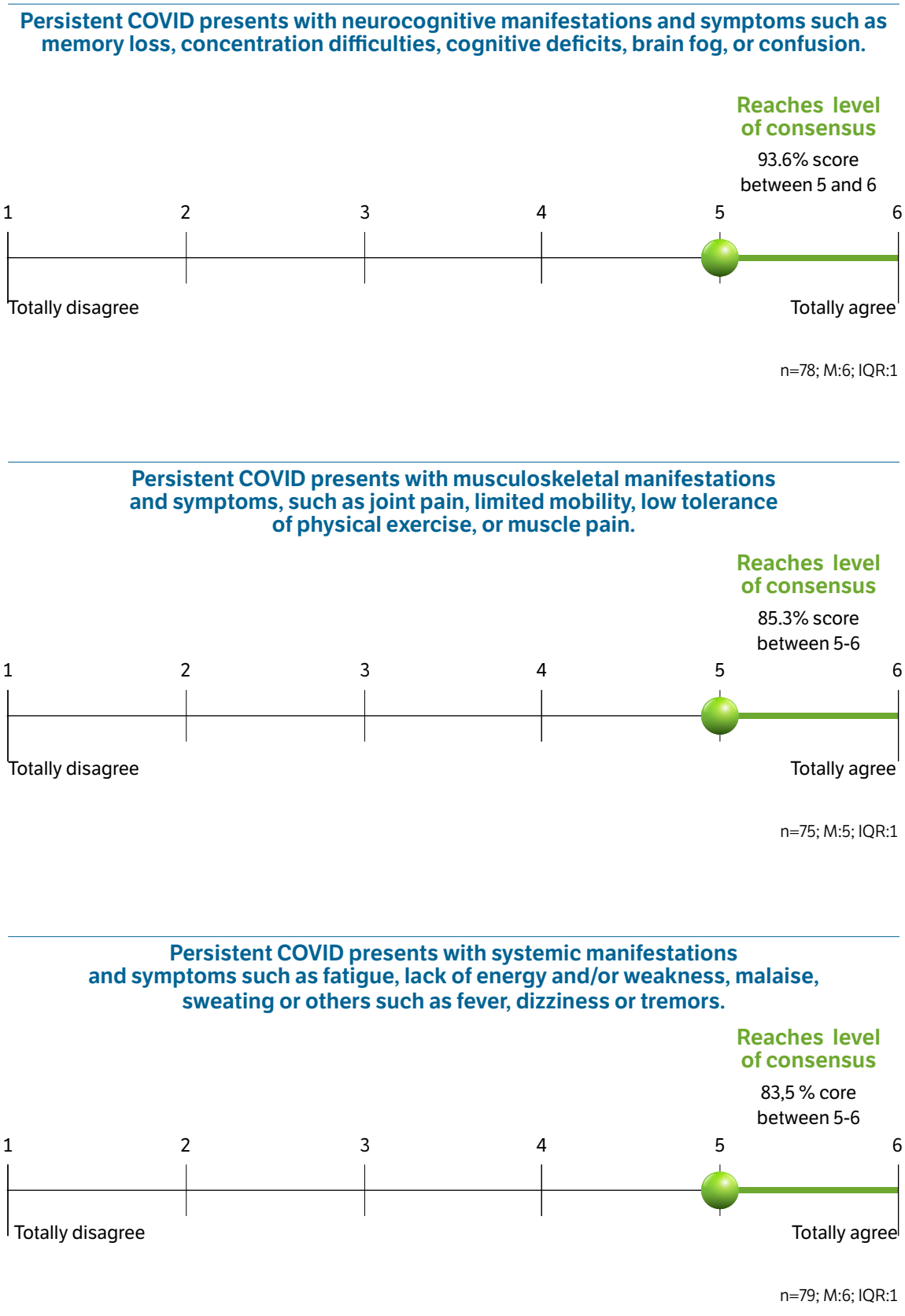
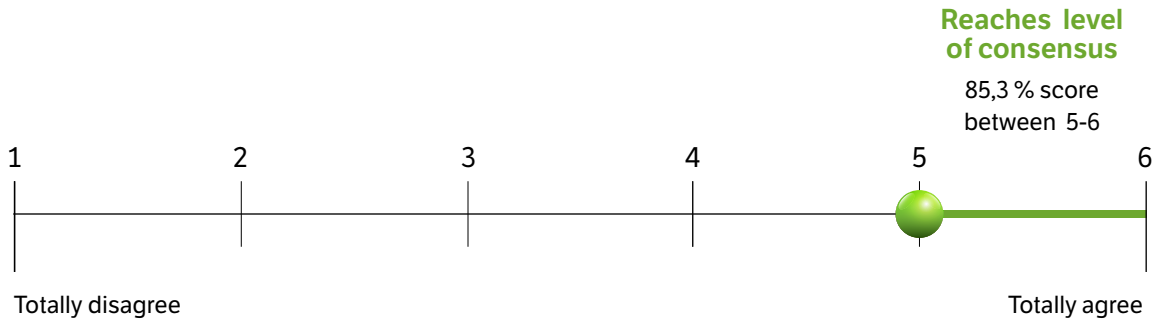


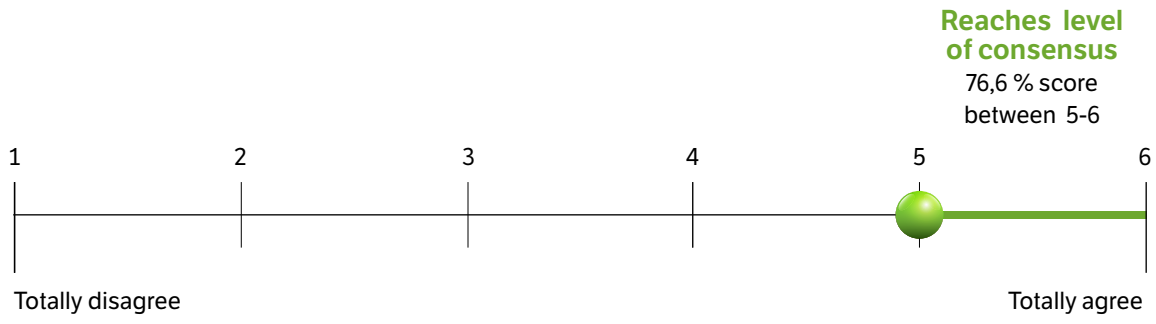
Figure 7 [continuation]. Clinical manifestations and symptoms of persistent COVID reaching the consensus threshold in the first wave of the Smart Delphi consensus study

Persistent COVID presents with neurological and neuromuscular manifestations and symptoms such as distortion of smell and/or taste, headache, lack of reflexes or hearing loss.



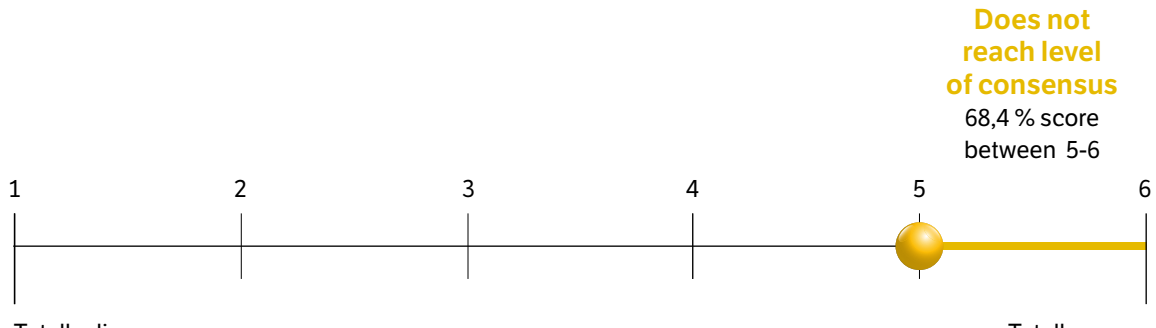
n=78; M:6; IQR:1

Persistent COVID presents with psychological and psychiatric manifestations and symptoms such as anxiety, depression or sleep disturbances.



n=77; M:5; IQR:1

Persistent COVID presents with respiratory or cardiopulmonary manifestations and symptoms such as cough, sore throat, dyspnea, polypnea, chest pain or pressure, increased oxygen requirement and others such as excess sputum.



n=76; M:5; IQR:2

.4.4. Impact of persistent COVID on quality of life

Results of the qualitative sub-study with key informants

The informants in the qualitative phase noted the importance of taking into account the impact of persistent COVID on the patient's quality of life and its social repercussions. Most respondents favored the inclusion of this impact in the definition, for three main reasons (Figure 8):

"The impact on people's quality of life is significant; it should be highlighted due to the need for recognition and support at social and occupational level; and functional alterations are also included in the definitions of other pathologies." Key informant in the CIBERPOSTCOVID qualitative study (semi-structured questionnaire).

Figure 8: Respondents' views on the impact on quality of life, functional alterations and limitations in daily life (n=35 informants, discussion groups).

Functional alteration in the fields of health, family, work and social life and the impact on patients' quality of life.

Impact on quality of life

- In the definition, the greatest weight should be given to clinical symptoms and the interference with functioning, the degree of disability produced by the presence of so many symptoms, and how they affect the patient's quality of life.
- The impact of the condition goes beyond the scope of health; it affects the social and occupational spheres as well.

Segments that highlight this point the most:
Family and community medicine, expert patients

Need for recognition and support at social and occupational level

- It is considered important to avoid shortfalls in the health system, which make patients feel abandoned and neglected.
- This is a very important social problem. It is the functional repercussion that will determine whether the condition will have legal repercussion in the long run with patients who have sick leave or face problems to continue their work or social life.

Segments that highlight this point the most:
Neurologists

The functional alteration is already included in other definitions of other pathologies

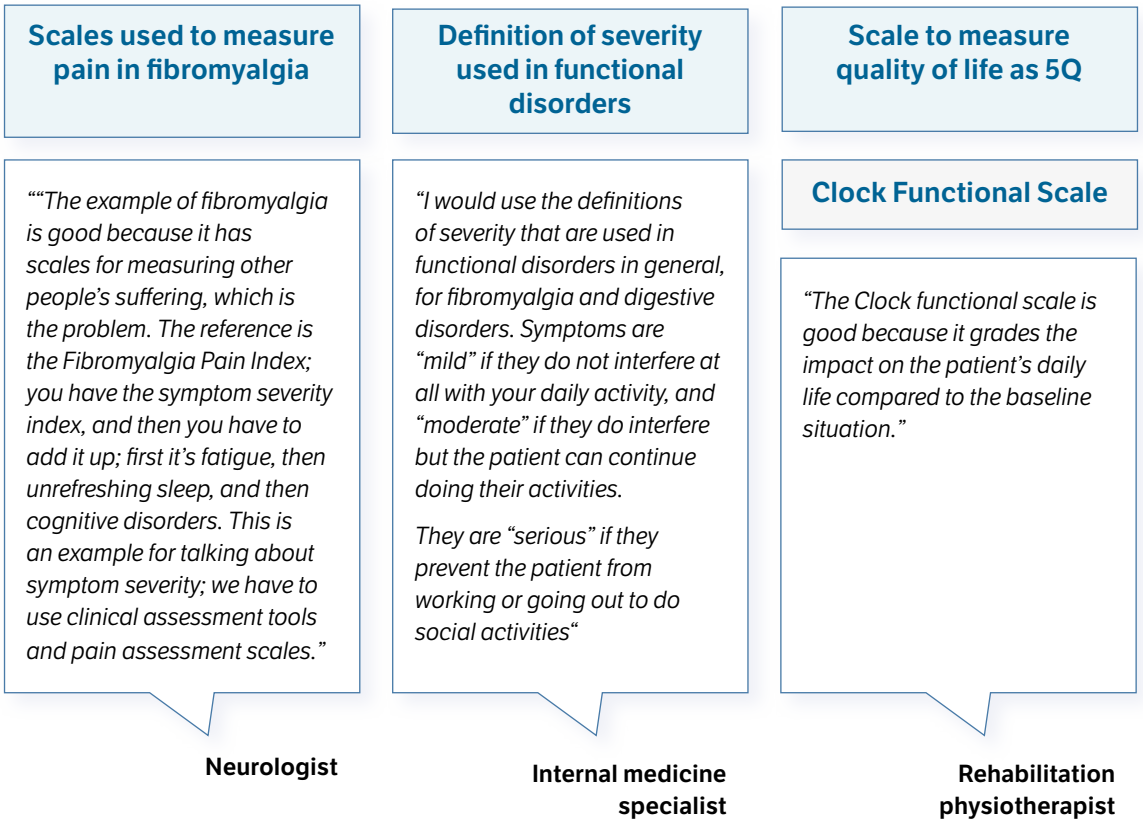
- The definition should recognize functionality, as in the case of other clinical conditions.
- In the definitions of mental disorders, it is always taken into account.

Segments that highlight this point the most:
Researchers, epidemiologists, mental health professionals

Some state that the functional alteration should be considered in the classification of severity, but that it need not be included in the definition: *It is considered important to establish what severe functional alteration represents for the patient (at a subjective level): it may be of little importance for some and very important for others.*

In the debate on the classification of severity of persistent COVID in the discussion groups (n=35), it emerged that it is unclear how this can be achieved, since the etiology and pathophysiology are not known. However, different profiles can be identified depending on the functional alteration of the patients. In this regard, it was mentioned that there is no specific validated scale for measuring the functional alteration caused by persistent COVID and that it will be necessary to build and validate one. Meanwhile, some professionals proposed taking other severity measurement scales from other similar pathologies as a reference, and mention the possibility of using scales to measure the impact on quality of life (Figure 9). On the other hand, when discussing how to classify the severity of persistent COVID in the discussion groups, some clinicians stressed the difficulty of creating an appropriate classification and highlighted the need to delegate the evaluation of the level of severity of the alteration caused by persistent COVID to specialists, due to the legal and economic repercussions.

Figure 9: Respondents' views and proposals for measuring the severity of persistent COVID based on other settings and classifications (n=35 informants, discussion groups).



Results of the scoping review sub-study

The scoping review of the literature shows that long COVID has an impact on the mental health of people who suffer symptoms weeks after the acute COVID-19. Between 14% and 35% of people manifest mental health symptoms or psychological distress (Malick 2021, Khraisat 2021, Bourmistrova 2022). Sleep disturbance, anxiety, depressive symptomatology (Renaud-Charest

2021) and even post-traumatic stress are the most frequent manifestations. Considering only studies that describe diagnoses of clinically significant depression and/or severe depressive symptoms (DSM-V criteria, BDI-13 score ≥9, PHQ-9 score >14, or HADS-D score >10), the estimated prevalence ranged from 3% to 12% (Renaud-Charest 2021). Long COVID also has an impact on people's quality of life, with up to 72% showing functional impairment or reduction in at least one dimension of quality of life included in validated instruments such as the EQ-5D-5L or the SF-36 (Ceban 2021; Malick 2021). The experience of fatigue or ICU admission in the acute phase of the disease have been shown to be predictors of an impact on quality of life in the longer term.

Results of the Smart Delphi quantitative consensus sub-study

The following statements regarding the impact of persistent COVID on different dimensions of quality of life reached the consensus threshold in the Smart Delphi study:

- persistent COVID impacts health-related quality of life [98.6% of scores between 5 and 6 (n=72); mean: 5.6 and SD: 0.56, IQR: 1].
- persistent COVID impacts physical function [97.2% of scores between 5 and 6 (n=72); mean: 5.6 and SD: 0.6, IQR: 1].
- persistent COVID impacts psychological function [93.1% of scores between 5 and 6 (n=72); mean: 5.4 and SD: 0.95, IQR: 1].
- persistent COVID limits everyday activities [90.3% of scores between 5 and 6 (n=72); mean: 5.4 and SD: 0.8, IQR: 1].
- persistent COVID impacts work activity and may cause patients to take sick leave [88.9% of scores between 5 and 6 (n=72); mean: 5.5 and SD: 0.9, IQR: 1].
- persistent COVID limits family and social activity [81.9% of scores between 5 and 6 (n=72); mean: 5.3 and SD: 0.9, IQR: 1].

4.5. Potential risk factors and predisposing profiles

Results of the qualitative sub-study with key informants

The most frequently mentioned risk profile in the summaries of the informants' opinions in the qualitative phase was that of a middle-aged woman. As regards the type of acute COVID-19 infection as a risk factor, two positions emerge:

- Those who believe that having had a severe acute COVID-19 infection/with hospital or ICU admission could be a potential risk factor for the subsequent development of a post-COVID syndrome or symptoms (mainly clinical specialists working in hospitals).
- Those who believe that having had a mild or even asymptomatic COVID-19 infection could be a potential risk factor for later developing persistent COVID (mainly family and community medicine practitioners and expert patients).

The health professionals consulted mentioned patients' medical histories and specifically alterations of the immune system and/or associated pathologies as potential risk factors. Among the conditions mentioned were: history of autoimmune diseases/fibromyalgia, immune system alterations, history of other central sensitization syndromes, immune-mediated disease, immunosuppression, genetic and immune-based factors, hormonal changes and immunity, fatigue and previous pain due to fibromyalgia and chronic fatigue.

Other potential risk factors noted by respondents included previous comorbidities and, to a lesser extent but also present, infection during the first epidemic wave.

As regards children and adolescents, the paediatricians consulted mentioned asthma, adolescence, female sex, and the existence of a family member with persistent COVID among the potential predisposing factors. Finally, some respondents felt that it is too early to define potential risk factors, due to the current lack of sufficient scientific evidence.

Results of the scoping review sub-study

The documents consulted in the scoping review provided little information on potential risk factors for developing long COVID. The main predictors of persistent symptomatology were female sex, middle age, the presence of comorbidities or hospital or ICU admission in the acute phase of infection (Michelen 2021, Ceban 2021, Igbal 2021). COVID-19). A few studies indicated that fatigue or dyspnea in the acute phase might be predictors of persistent symptoms.

In fact, the documents included in the literature review contain little information on previous comorbidities in people with COVID-19 who manifested persistent symptoms, although arterial hypertension, obesity and diabetes are the ones that appear most frequently. Eighty-five per cent of studies included in the review by Michelen 2021described participants' comorbidities, the most common being hypertension and diabetes. Nasserie 2021 also reported the most common comorbidity among participants in the studies included to be hypertension (median 35% IQR 21.8% to 41.0%) and diabetes (median 16.6%, IQR 10.0% to 23.0%). Almost half of the patients included in the studies providing data on persistent symptoms had at least pathology (one: 26.3%; two: 17.6%; ≥ three: 25.6%; Fernández de las Peñas 2021).

In general, the review by Fernández de las Peñas 2021 highlighted that pre-existing comorbidities were more prevalent among patients who had required hospitalization in the acute phase of the disease. These results were consistent with the review by these same authors that focused on the prevalence of pain; in that study, hypertension (23.8%, 95% CI: 17.6% to 31.2%) and obesity (22.2%, 95% CI: 13.7% to 34.0%) were the most prevalent comorbidities. Also, pre-existing comorbidities were for the most part more frequent among patients who had been hospitalized during the acute phase of the disease. The difference vis-à-vis non-hospitalized patients was statistically significant for obesity, hypertension, diabetes, and heart and kidney disease.

Results of the Smart Delphi quantitative consensus sub-study

In the first wave of the CIBERPOSTCOVID Smart Delphi study, the statement that there is insufficient scientific evidence to establish predisposing factors for persistent COVID reached the consensus threshold [74.6% of scores of 5 of 6 (n=71), mean: 4.8 and SD: 1.5; IQR:1]. None of the risk/predisposing factors for persistent COVID proposed in the Smart Delphi study reached the predefined threshold of agreement (Figure 10). However, given their presence in the qualitative study and the scoping review, it is important to take them into account in future research. This point is stressed in the considerations on the lines and factors of future research set out in the operational definition in Figure 1.

Figure 10. Examples of risk/predisposing factors for lpersistent COVID that did not reach the consensus threshold in the first wave of CIBERPOSTCOVID Smart Delphi.

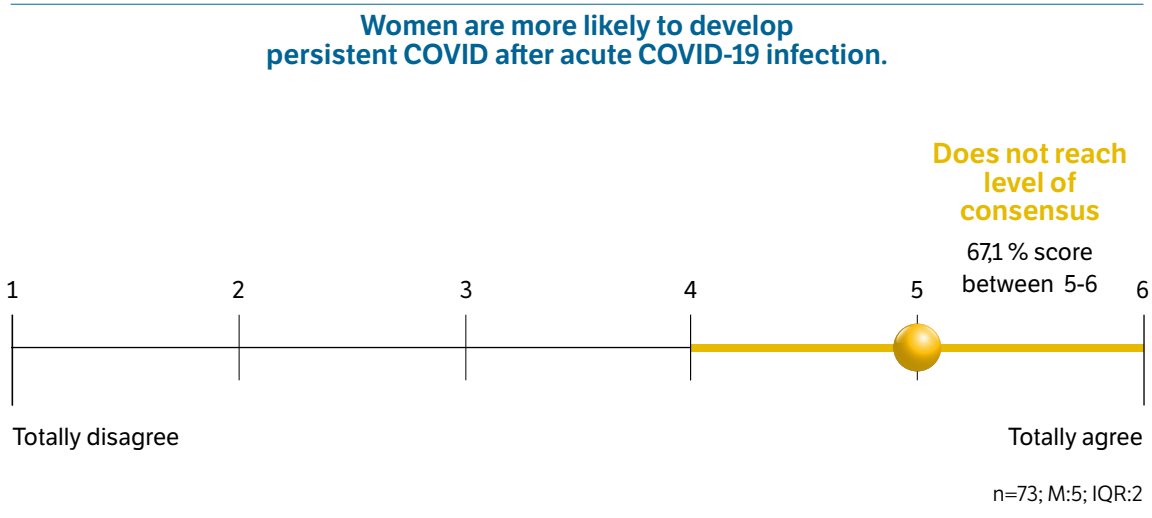
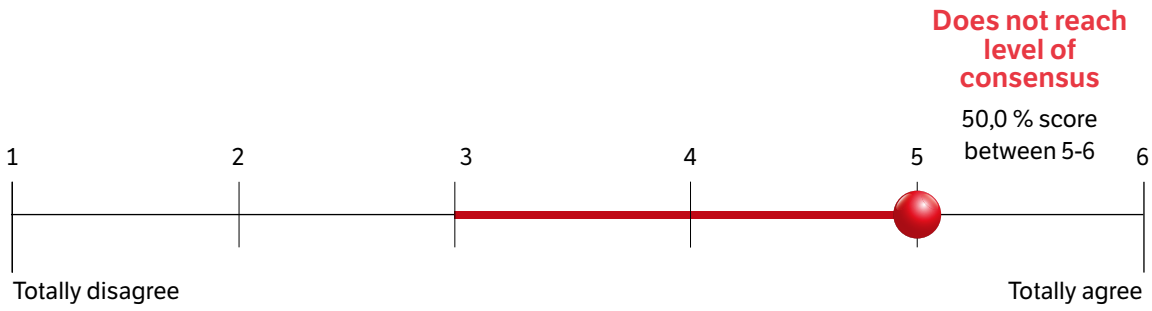


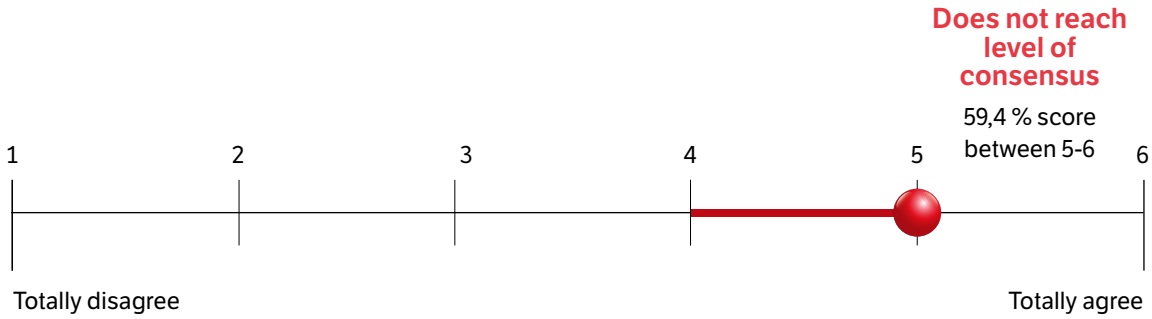
Figure 10 [continuation]. Examples of risk/predisposing factors for lpersistent COVID that did not reach the consensus threshold in the first wave of CIBERPOSTCOVID Smart Delphi.

Middle-aged people have a higher predisposition to develop persistent COVID after acute COVID-19 infection.



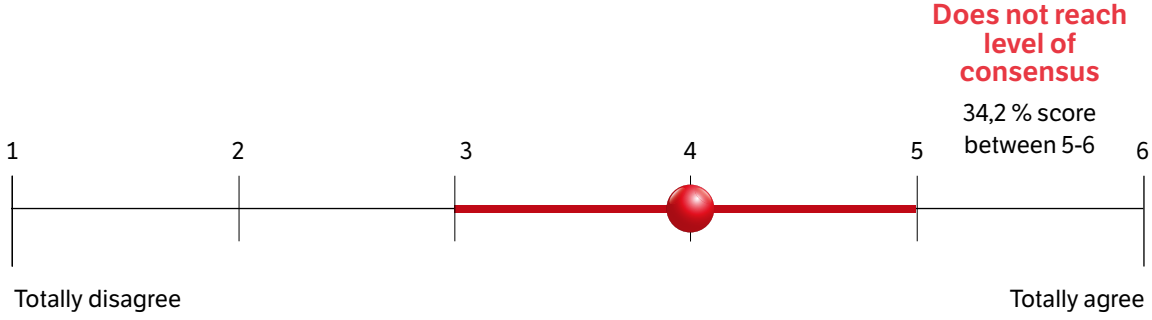
n=72; M:5; IQR:2

People infected with SARS-Cov-2 during the first wave (2020) have a greater predisposition to develop persistent COVID.



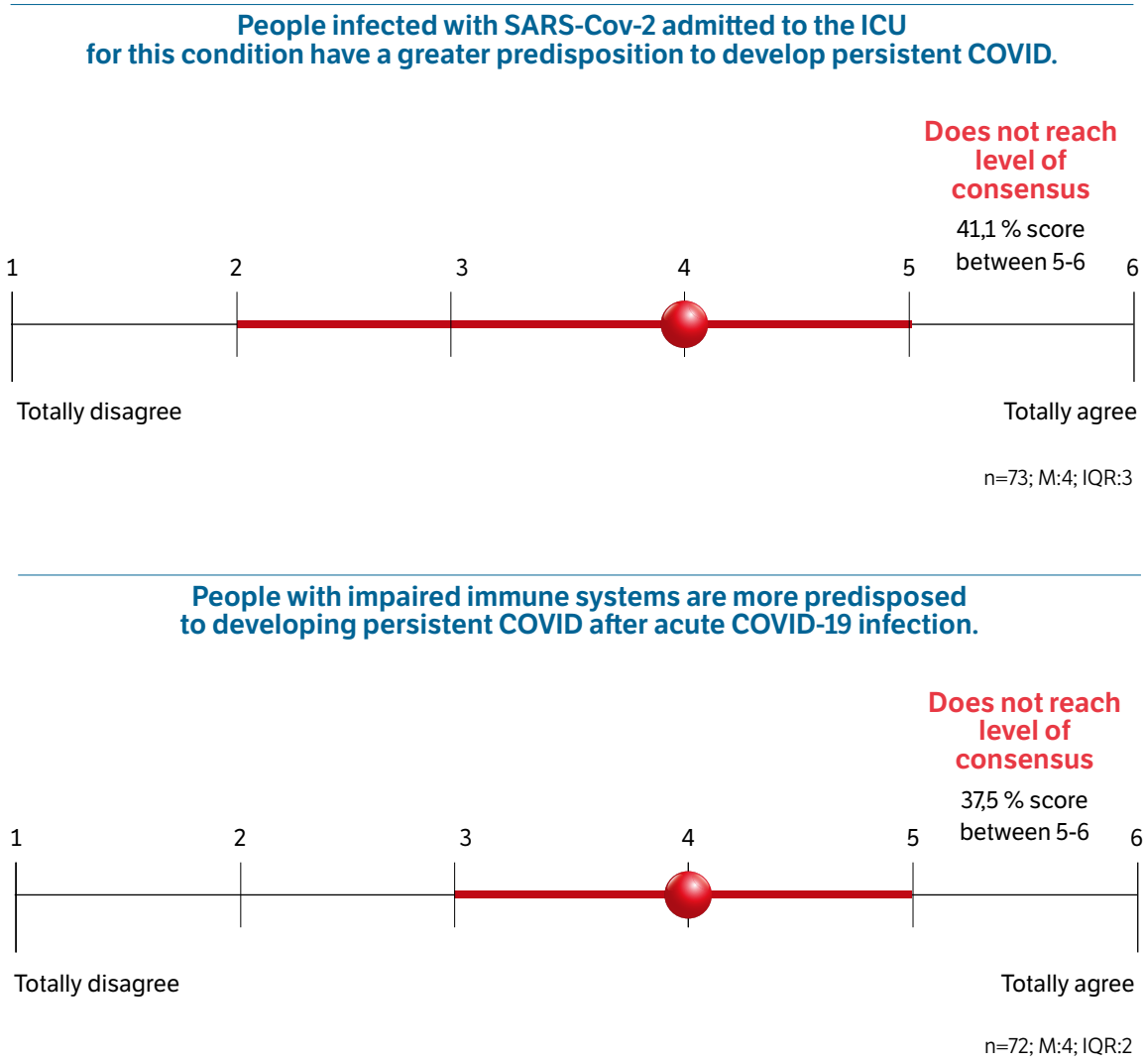
n=74; M:5; IQR:1

People infected with SARS-Cov-2 admitted to hospital for this condition have a greater predisposition to develop persistent COVID.



n=73; M:4; IQR:2

Figure 10 [continuation]. Examples of risk/predisposing factors for Ipersistent COVID that did not reach the consensus threshold in the first wave of CIBERPOSTCOVID Smart Delphi.



4.6. Definition of persistent COVID in the paediatric population

Results of the qualitative sub-study with key informants

In the group discussion in the qualitative phase regarding the need for a definition of persistent COVID in the paediatric setting, it was the paediatricians, neurologists and expert patients who spoke the most. A specific impact on the area of cognition was highlighted, but also the fact that the symptoms were different and less intense. Respondents also reported underdiagnosis due to the difficulties children have in expressing the symptoms and the persistence of a single symptom (Figure 11).

Figure 11: Respondents' views on the definition of persistent COVID in the paediatríc population (n=35 informants, 3 discussion groups)

The impact on cognitive function is very specific and requires attention.

- The impact on cognition in the paediatric population is important; it affects academic and psychoemotional performance. Patients' neurodevelopmental and maturational level should be borne in mind.
- Strong impact on mental health of the pandemic, confinement, and pressure on mental health services. These patients need attention.
- Stress on the importance of accompaniment and follow-up.

Segments that highlight this point the most
paediatricians + neurologists

The symptoms presented by children and adolescents are different from adults.

- The symptoms are less intense and the manifestation of the symptoms is different.
- Diagnosis in young children is difficult as they are unable to express what is happening to them and describe their symptoms.
- There are many asymptomatic cases in adolescents, and also cases with the persistence of a single symptom.

One paediatrician reported being against it, on the grounds that first a clear definition should be obtained in adults.

"We are not in a position to say whether it is different, if we do not have a clear definition in adults; with adolescents, the symptoms are similar to those described for adults. Right now I would not make a specific definition"

Results of the scoping review sub-study

At the time when the scoping review was conducted, little information of interest regarding the pediatric population was available. The Catalan Paediatrics Society has created an action protocol to standardize criteria and accepts the NICE definition, adding a brief specification for the age group of its target population: people under 18 years of age, diagnosed with COVID-19 (with or without microbiological confirmation) who, 12 weeks after the infection, continue to present symptoms without recovering their previous state of health (*Societat Catalana de Pediatria*, 2021).

One literature review (Zimmermann 2021) collected data from five studies with paediatric patients which showed that persistent symptomatology was more frequent in patients wo had suffered COVID-19 compared with controls after 12 weeks of follow-up. In that study the symptoms were varied and heterogeneous, the most frequent being fatigue (39%), headache (23%), dyspnea (23%), smell distortion (14%) and dizziness (14%). In the rest of the studies, the prevalence of symptoms ranged between 4% and 66% of participants (Table 2).

Table 2. Most frequently described manifestations and symptoms in the paediatric population in the review by Zimmerman et al. (2021)

SYSTEMIC	NEUROLOGICAL/ NEUROMUSCULAR	NEUROCOGNITIVE	PSYCHOLOGICAL
fatigue (3% to 87%	headache (3% to 80%) abdominal pain (1% to 76%) smell distortion (3% to 26%)	concentration difficulties (2% to 81%)	sleep alterations (2% to 63%)

RESPIRATORY	MUSCULOSKELETAL	GASTROINTESTINAL	DERMATOLOGICAL
nasal congestion (1% to 12%) cough (1% to 30%) chest pain (1% to 31%)	myalgia (1% to 61%)	loss of appetite or weight (2% to 50%)	skin rash (2% to 52%)

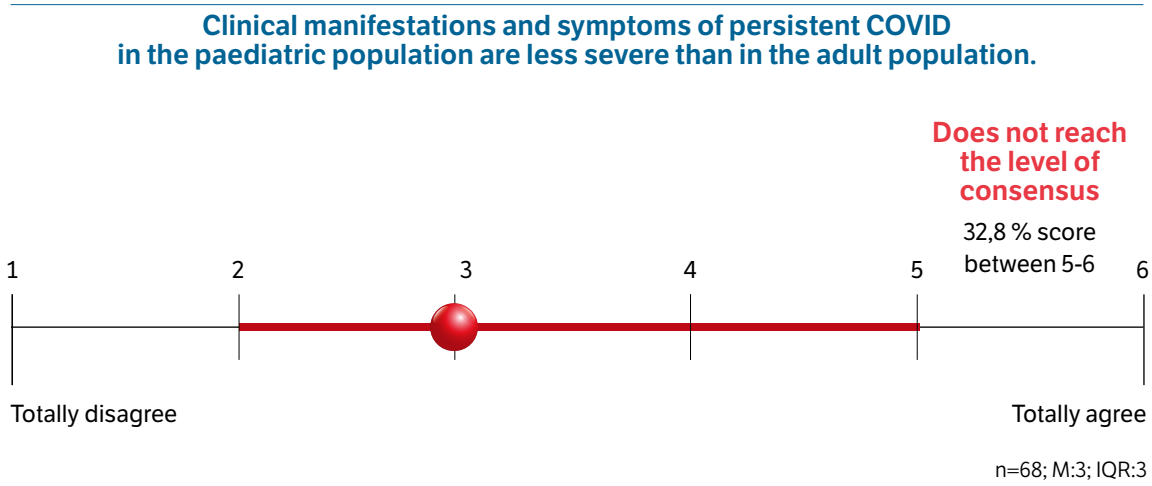
Results of the Smart Delphi quantitative consensus sub-study

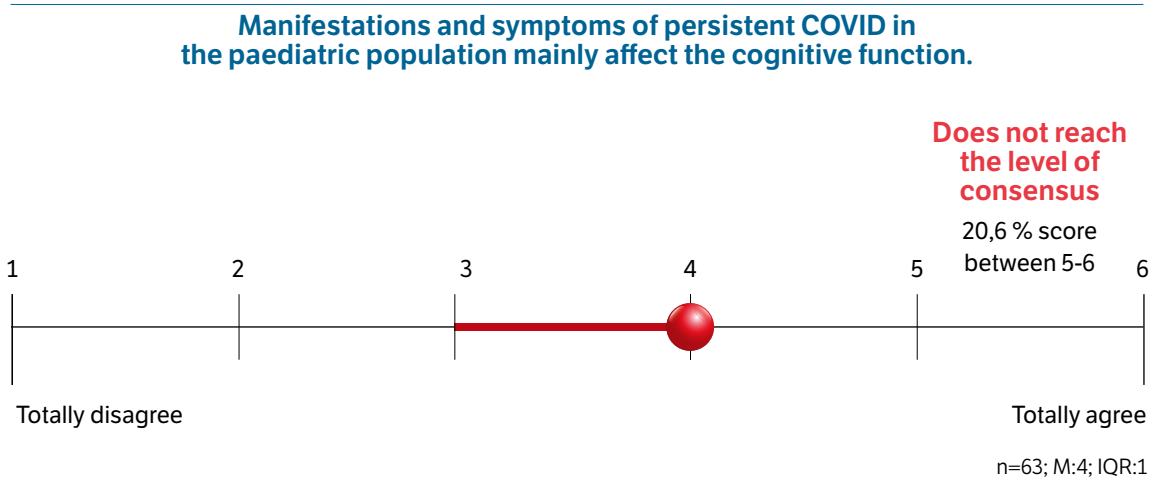
In the first wave of the CIBERPOSTCOVID Smart Delphi consensus study, the level of agreement on the need for a differentiated definition of persistent COVID in the paediatric population was low, although within the limit of the predefined threshold:

- A specific definition of persistent COVID is needed for the paediatric population [71.8% of scores between 5 and 6 (n=71), mean: 5.0, SD: 1.2, IQR: 2].
- There are differences in the clinical manifestations and symptoms of persistent COVID between the adult and the paediatric population [65.7% of scores between 5 and 6 (n=67), mean: 4.6, SD: 1.1, IQR: 1].

The statements related to specifying potential differences in the clinical manifestations and symptoms in the paediatric population did not reach the predefined consensus threshold. In fact, along with the predisposing factors of persistent COVID, these statements presented the lowest level of consensus of all the elements that might be included in the operational definition (Figure 12).

Figure 12. Potential differences in paediatric and adult populations in persistent COVID that did not reach the predefined consensus threshold in the first wave of the CIBERPOSTCOVID Smart Delphi study (n=79).





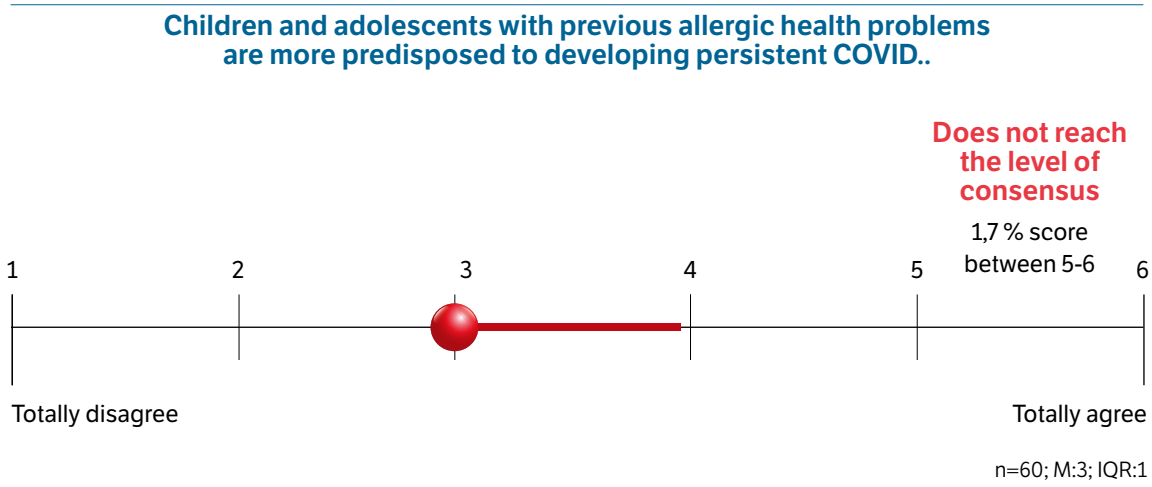
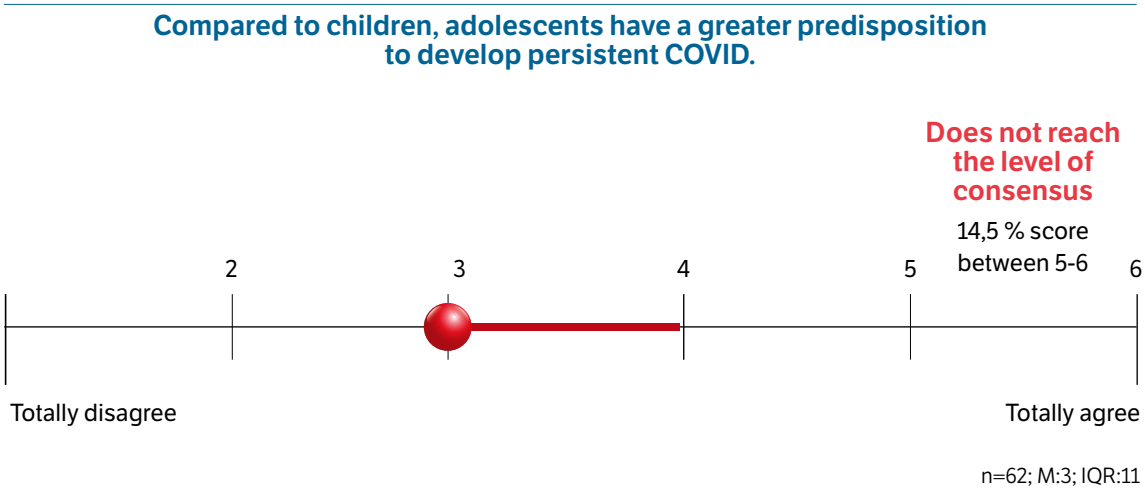


Figure 12 [continuation]. Potential differences in paediatric and adult populations in persistent COVID that did not reach the predefined consensus threshold in the first wave of the CIBER-POSTCOVID Smart Delphi study (n=79).



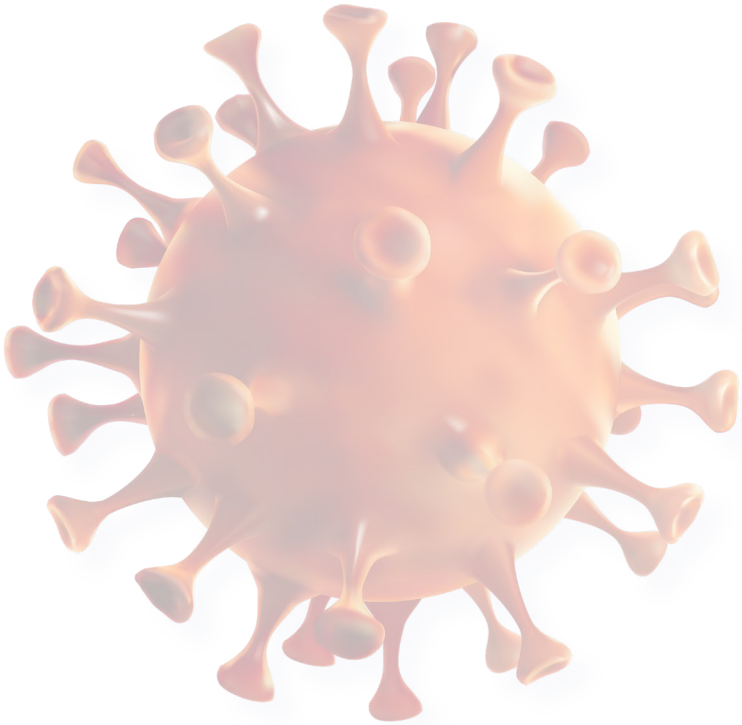
4.7. Other elements in the diagnostic process

In the Smart Delphi consensus study, some additional aspects were considered for inclusion in the diagnostic process of persistent COVID. The statements that reached the consensus threshold are presented below.

- To establish a diagnosis of persistent COVID, other health problems to which the symptoms might be attributed must be ruled out [90.3% of scores between 5 and 6 (n=72), mean: 5.5, SD: 0.8, IQR: 1].
- To establish a diagnosis of long COVID, it is necessary to bear in mind the patient's previous health problems [80.5% of scores between 5 and 6 (n=72), mean: 5.1, SD: 1.3, IQR:1].
- It is necessary to distinguish between organ damage or sequelae caused by acute SARS-Cov-2 infection and the symptoms attributed to long COVID [87.5% of scores between 5 and 6 (n=72), mean: 5.4, SD: 1.1, IQR:1].

In addition, the participants in the first wave of the Smart Delphi substudy presented moderate to high agreement on the following points:

- The severity of long COVID, understood as a functional alteration, should be measured using validated scales [93.1% of scores between 5 and 6 (n=72), mean: 5.43, SD: 0, 8, IQR: 1].
- The profiles and clinical, biological and demographic characteristics of groups of patients with persistent COVID should be studied [95.8% of scores between 5 and 6 (n=72), mean: 5.8, SD: 0 .5, IQR: 0].
- The definition of persistent COVID will need to be reviewed and refined as new information becomes available [95.8% of scores between 5 and 6 (n=72), mean: 5.7, SD: 0.7, IQR: 0].



5. Final reflections

The approach outlined here adds value to the proposed operational definition of persistent COVID, under the auspices of the CIBERPOSTCOVID project. It has made it possible to continue generating collective knowledge in a biomedical area in which, in the Spanish health system at least, the scientific evidence is not sufficiently robust. This participative, multidisciplinary project includes mixed methods that are widely used in the evaluation of health services and policies. The consensus definition of persistent COVID (and/or its terminological variants) is based on:

- the integration of the different points of view and experiences of informants designated by CIBER thematic sections, biomedical scientific societies, patients' associations, the public and occupational health authorities of Spain's autonomous communities, as well as reference institutions in the Spanish national health system.
- the areas where the agreement between informants has been notably high (both in the qualitative study and in the quantitative consensus study).
- the review of reference documents and the final positioning of the CIBERPOSTCOVID steering group.

As the results show, there is a diversity of opinions and positions expressed by researchers, clinical specialists in hospitals and in primary care, clinical care managers and health planners, as well as the patients (and especially expert patients).

The qualitative sub-study explored the opinions of these informants regarding persistent COVID and examined the reasons for their views. Like the scoping review of the scientific evidence, it served to generate the content (67 statements) to be scored in the Smart Delphi consensus substudy. In the latter case, there was a high level of agreement on some of the elements that define persistent COVID, which are reflected in the proposed definition summarized in Figure 1 and which will be implemented in the coming stages, based on clinical-administrative data and epidemiological studies. It will also be necessary to continue refining the definition to better understand the severity profiles of patients and their predisposing factors, since no agreement was reached on these issues at the different stages of the project.

Despite the value of the informants' opinions, some limitations of the qualitative and quantitative consensus substudies should be noted:

- Stratified sampling was carried out, seeking as wide a range of discourses as possible, and in an attempt to identify "expert" informants in the subject of study. However, even though informants were proposed by the health authorities and the managers of the reference institutions, it is possible that not all the key informants of the Spanish national health system were represented;

- Given the lack of available scientific evidence and the participants' recognition that they were still in the process of learning about persistent COVID, there may have been a bias in favor of factors that appear most frequently in published documents (for instance, the most common symptoms). However, the triangulation of the information obtained from the different sources and the open, participative discussion of the results make the proposal a robust operational definition for implementation in routine patient data (i.e., cohorts, registries or clinical-administrative data) within the framework of the CIBERPOSTCOVID project;
- The multidisciplinary nature of the study and the participation of respondents with different profiles have enriched the debate. However, the fact that the informants may have more than one profile (for example, an expert patient might also be a health professional) has made it difficult to identify the reasons why the participants do not agree on certain points. In some cases, the divergences are considered more philosophical than scientifically based (for example, the terminology used to refer to persistent COVID and its terminological variants such as long COVID or post-COVID syndrome);
- The analyses applied in the consensus study are descriptive. A global analysis of the level of consensus was carried out with the 67 statements but it was not stratified according to the profiles of the participants to discern whether the researchers, for example, had a different position from the patients. Further, because of the large number of statements, the first ones obtained a higher participation rate than the last. Despite these limitations, this exercise allows us to summarize the aspects in which a degree of quantitative agreement was reached, or was not reached, among the reference informants;
- The opinion of expert patients was obtained through collaboration with patient associations throughout the project. Nonetheless, the opinions of less expert patients treated in routine clinical practice should also be considered.

In summary, despite the progress made in generating and transferring scientific knowledge, the fact is that the majority of the informants consulted recognize that they have very little or no knowledge in the subareas under study. Projects such as the present one are essential in order to continue advancing in the collaborative construction of knowledge on persistent COVID.

The scoping review of the literature has made it possible to exhaustively identify and describe the way in which persistent COVID has been defined in published documents, but the results must be interpreted taking into account the following considerations:

- The results were obtained from summary documents or documents with guidelines and/or recommendations. This may have affected some of the results for different reasons. Among the most important is the fact that, having consulted the literature up to the first half of 2021, these reviews have not been able to incorporate the results of large cohorts of patient data published in recent months (this point is especially salient in the case of the paediatric population);

– The primary studies included in the summary documents are of variable quality. The definitions of persistent COVID have been developed by consensus with greater or lesser methodological rigour, but, in any case, they offer a definition of the problem that must incorporate empirical data to offer a more objective characterization. Future studies should precisely define aspects related to: i) the population of interest and its comorbidities, the symptoms in the acute phase and their severity, the objective determination of the presence of SARS-CoV-2 infection, as well as the incorporation in the studies of control groups of people without COVID-19; ii) exhaustive and systematic recruitment so as to avoid selection bias; iii) adequate follow-up (establishing whether it is short-, medium- or long-term follow-up, or measuring the results with homogeneous time intervals); or iv) an objective and homogeneous method of measurement to assess manifestations and symptoms;

– Given that the WHO's definition (Soriano 2021) was published relatively recently, it is possible that not enough time has elapsed for it to have been adequately disseminated in the scientific and academic community..

The definition of persistent COVID agreed upon in this study does not differ in essence from those published by reference institutions and organizations. Although no consensus has been reached regarding the term, "persistent COVID" appears as the most voted term to refer to this health problem in Spanish. Taking as a reference the publications of the WHO, SIGN, RCGP and NICE and the definition in the management guide published by the SEMG, coincidences are observed in the vast majority of areas. There is also a consensus on the idea of including in the operational definition a reference to the potential impact of persistent COVID on physical and psychological functioning, as well as on the limitation of daily activities.

In this proposal, and to some extent in contrast to other published studies, the most frequent symptoms associated with persistent COVID have been grouped together into large groups, as reflected by the positions taken by key informants in the qualitative phase.

Regarding the factors that may predispose to persistent COVID, no clear agreement has been reached on the role that age, severity or burden of symptoms may have during the acute phase, nor the role of previous comorbidities. Unlike the SEMG management guide, no agreement was reached on potential gender differences. However, the operational proposal of CIBERPOSTCOVID includes the need for future studies to delve more deeply into the differences caused by study populations, the gender perspective, the health profiles of patients with persistent COVID and other clinical, biological and sociodemographic characteristics, as well as in the use of services in the COVID-19 infection phase.

– No strong consensus was found in relation to elements of the diagnostic process. A high level of agreement was not reached as to whether a history of probable COVID-19 is necessary or the need to confirm diagnosis with laboratory tests, bearing in mind

their scarcity during the first epidemic wave. Agreement was reached on the need to take into account the previous state of health of the patients and to record the presence of comorbidities in the clinical history, and also on the sequelae and damage derived from the acute infection and the treatments received, in order to better understand the manifestations and symptoms of persistent COVID. In line with the WHO's definition, which indicates that a characterization of paediatric persistent COVID is probably necessary, various aspects of persistent COVID in the child and adolescent population were explored. However, no agreement on these aspects was reached in the present study, probably due to the low representation of specialists in this field and the lack of evidence regarding the differential characteristics between the paediatric and adult populations.

Conclusions and recommendations

- Persistent COVID represents a scenario in which professionals are faced with a new health problem for which little scientific evidence is available. This study was prepared from various perspectives, including that of the representatives involved in advancing research and increasing the understanding of persistent COVID and its characteristics.
- The problem of persistent COVID places professionals in a situation of uncertainty as they lack a solid grounding, and the necessary tools, to make an accurate diagnosis. Their response will depend, in most cases, on patients' accounts of their symptoms and, above all, on the impact it has on their functionality and quality of life.
- In this regard, the general agreement manifested throughout the study regarding the impact of persistent COVID on patients' lives is an important finding.
- The role of patients directly affected by persistent COVID is essential in order to heighten the visibility and recognition of this condition. Patients are taking an active part in the advances in the understanding of this condition and its definition.
- To continue making progress, it is necessary to:
  - Continue listening carefully to patients (and/or relatives) in the diagnosis and assessment of needs.
  - Search for predisposing factors using data taken from patients in routine clinical practice.
  - Review and refine the proposal when new evidence becomes available.

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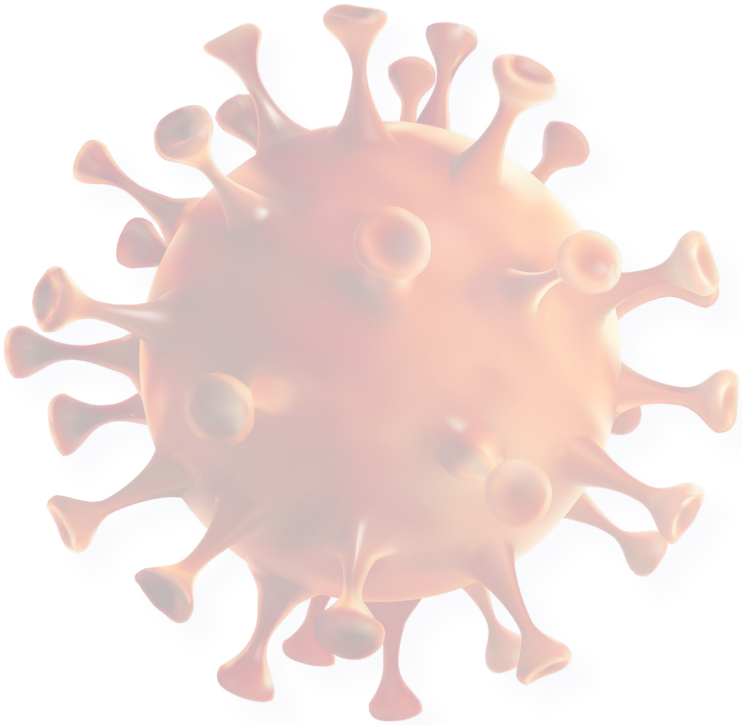
Appendices



7. Appendices

Appendix 1. Researchers and work team

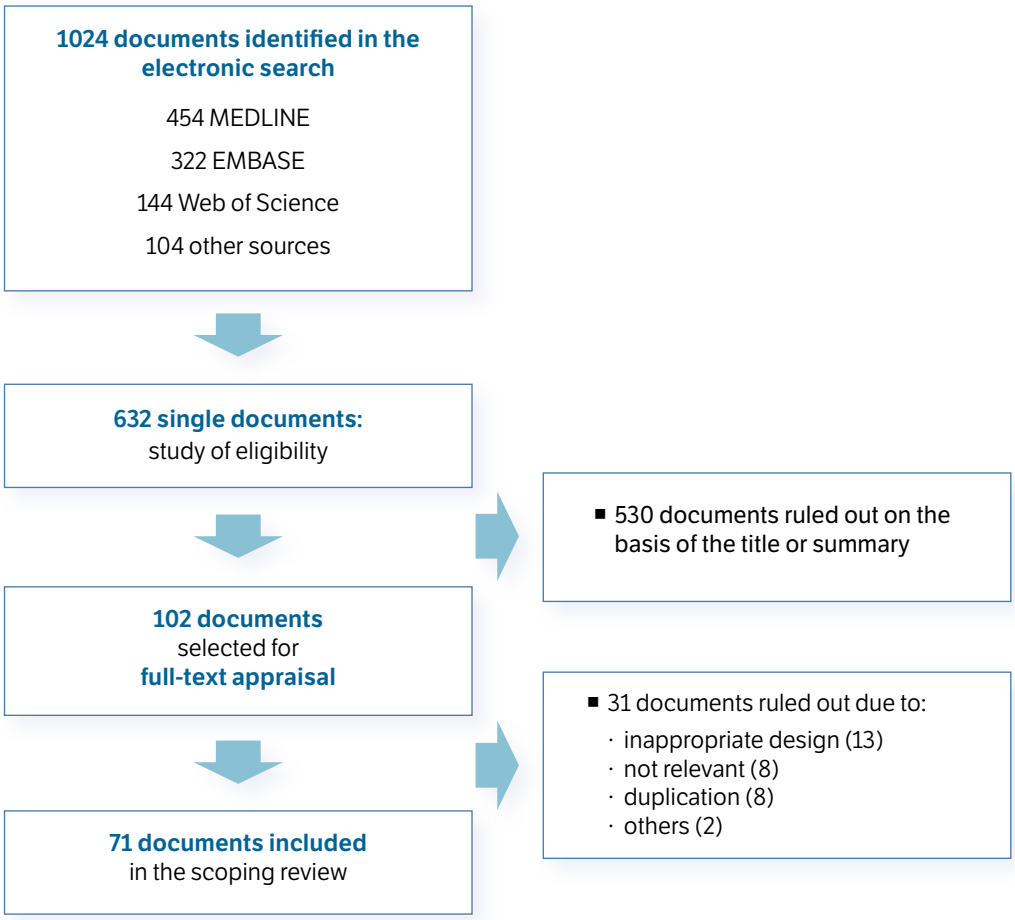
WP1 CIBERPOSTCOVID steering group: Ferran Barbé and Marina Pollán (CIBERPOSTCOVID project leaders), Jordi Alonso, Maria Arguimbau, Mireia Espallargues, Fernando García-Benavides, Montse Ferrer, Blanca Lumbreras, Javier Muñoz, Antoni Parada, Beatriz Pérez, José I. Pijoan, Vicky Serra-Sutton, Antoni Serrano-Blanco, Joan B. Soriano, Marta Torres.

Vicky Serra-Sutton and Antoni Serrano-Blanco are the principal researchers in the WP1 CIBERPOSTCOVID.

External collaborators: qualitative study (Carla Montané), scoping review (Ivan Solà), Smart Delphi (Álex Trejo and Josep Mª Monguet), communication (Cristina Juesas and Juan Carlos Durán).

Jordi Alonso joined this meeting of the CIBERPOSTCOVID steering group slightly later.

Appendix 2. Flow diagram of the appraisal of the documents obtained in the search carried out for the CIBERPOSTCOVID scoping review.



Appendix 3. Quotes indicating informants' opinions regarding the terminology used to refer to persistent/long COVID (n=35, 3 discussion groups).

Persistent/Long COVID

"I don't like the term "post", because viral persistence in tissue has been demonstrated many months later. The term "post" suggests that the virus is no longer there, and that this is just another response, but persistence or remnants of the virus, or sequencing of the complete virus, have been observed in infected tissues and cells more than a year later; so I prefer to talk about persistent or long COVID.

Researcher, family and community medicine

"We do not know the causes, but one of the theories is that the virus is persistent; post-COVID is a patient with acute COVID who has been admitted to the ICU and who has sequelae."

Researcher and teacher, family and community medicine

"From the patients' point of view we prefer the term LONG COVID; it gives a good description of how we live the disease, the symptoms have never gone away; we are not talking about sequelae, we are talking about LONG COVID and symptoms."

Expert patient, biologist

"I don't like "post" at all; "post" would be a sequela, meaning that you've overcome the disease and then you have organ damage; but we have not managed to overcome the disease, we continue to fight because there is an active infection in a reservoir, or because there is an inflammatory response sustained over time. It is a disease that has never become "post"; there are still many fluctuations; the symptoms of the acute phase persist or those that are a consequence come and go over time."

Expert patient, ICU specialist

Post-COVID symptoms/syndrome

"I think that calling this entity long COVID or persistent COVID when we still don't know exactly what it is is a gross error because it implies that the infection is chronic and that the virus is persistent; if we maintain this definition we are causing iatrogenesis."

Neurologist

"We don't know now whether we are dealing with a persistence of the virus, an altered immune response or some other factor, so from point of view of linguistic accuracy, "syndrome" would be the best term."

Internal medicine specialist

"Traditionally, more viruses cause postviral syndromes (.) Choosing the term "post" reflects this. What's more, the WHO used the term "POST-COVID condition" and it is important that we should use the same terminology; we shouldn't call it something different from the WHO; the WHO definition dates from December 21 and I think we should accept it.

Internal medicine specialist

"We have to follow the WHO; today it is a post-COVID condition and we must include what we know exists."

Pulmonologist

Appendix 4. Quotes indicating informants' opinions regarding the duration of symptoms/manifestations of persistent COVID in the qualitative study (n=35 informants, 3 discussion groups).

Time frame/duration

12 weeks or three months (the most popular)

"I would prefer 12 weeks; just as we should use the same definition, we should use the same time; if the WHO says 3 months, we should all follow the WHO's line."

Family and community medicine practitioner

"Three months seems right to me; the first month you think you are recovering, the second you're ok, but the third you see it clearly; the third month seems a good point to rule out sequelae and a longer convalescence phase; at that time you wonder if something is happening that perpetuates the disease."

Expert patient, ICU specialist

"12 weeks is the time frame we use here in Barcelona; After 12 weeks, the capacity for this symptom to disappear or for new ones to appear is already very low."

Researcher, family and community medicine practitioner

6 months

"It seems that, after 6 months, you have to start thinking that this is going to last longer. it is the term we use for other diseases, and I would continue to use it for this process which is still an infection."

Internal medicine specialist

"I think that at six months, you begin to think that it's lasting longer than it does normally. For other diseases it's a time frame we use and I would continue to use it for this process that is still an infection."

Paediatrician

"As a pulmonologist who treats COVID patients in the acute phase, we see a different profile of patients; there are no outbreaks and there is persistence of symptoms that improve over time, between 3 and 6 months; the ones that haven't improved at 6 months are very hard to get rid of."

Pulmonologist

12 months

"When you have time to explain things to patients and carry out the necessary tests, a 23-year-old with mental fog, or is sad, or has palpitations, you wouldn't expect them to have a malignant arrhythmia; you can't send them to cardiology, or to a multidisciplinary team, it is a mistake. My patients, if they're treated sensibly... in 3-6 months the majority improve; "persistent" should refer to 12 months."

Neurologist

"Talking about persistence after three months seems a bit premature, I think the time frame should be 6-12 months. I say this for post-COVID patients who are not hypermedicalized. We're all suffering pandemic fatigue that gives many similar symptoms, for the simple fact that it's lasted two years, and even vaccinated patients present post-COVID symptoms. In my experience, patients who are well informed about the psychological burden that this entails... it must be explained well."

Neurologist