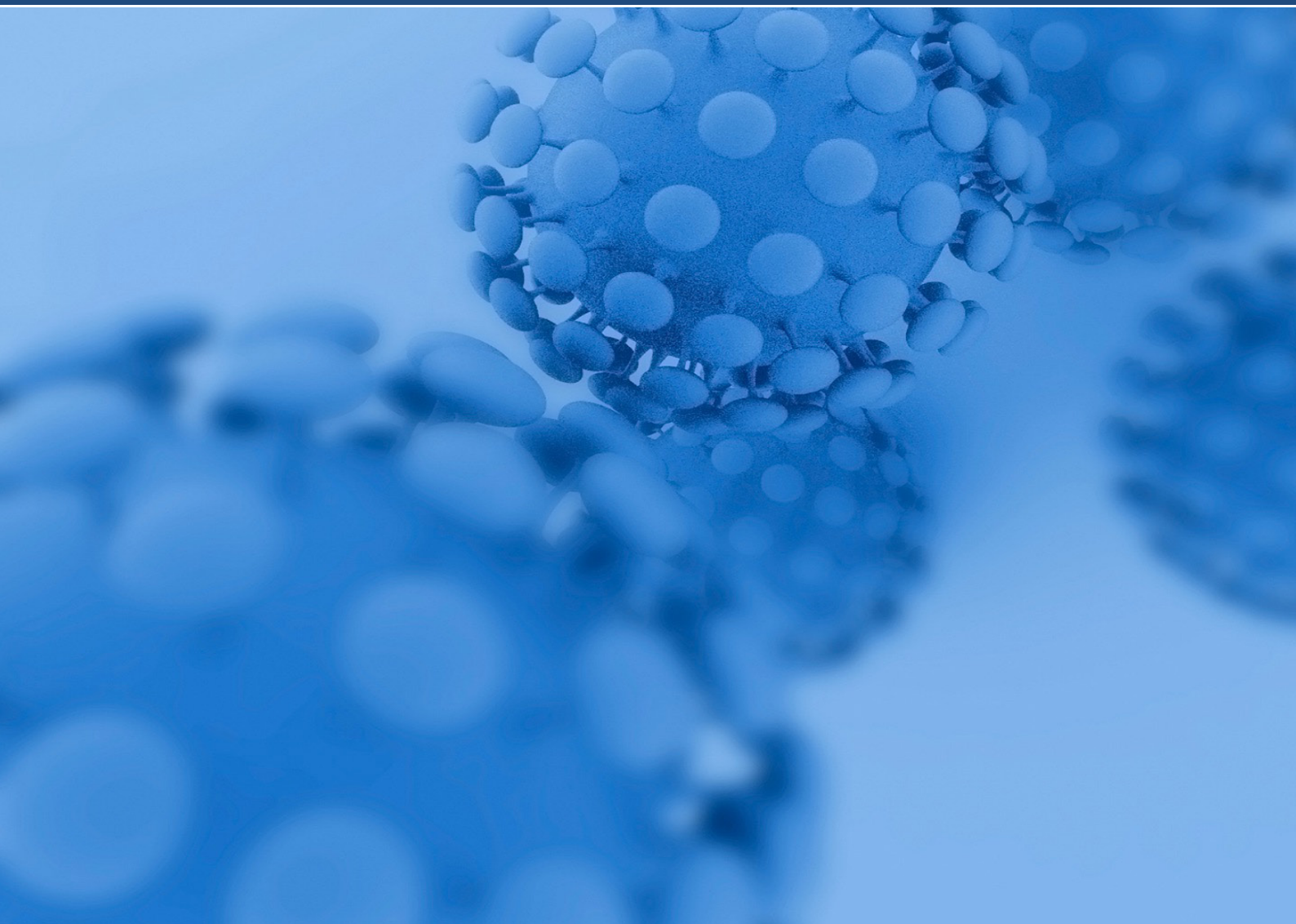
# Post-Acute COVID Syndrome (PACS): Definition, Impact and Management

## A Report of the Multidisciplinary Collaborative Group for the Scientific Monitoring of COVID-19 (GCMSC)

June 2021



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# Post-Acute COVID Syndrome (PACS): Definition, Impact and Management


## Summary

A variety of studies suggest that **up to 10-15% of all patients with COVID-19** may present persistent symptomatology weeks or even months after the original infection. Given the accumulated burden of COVID-19 in Catalonia, Spain, we speculate that over 90,000 patients could have been or are currently affected by **persistent symptoms or sequelae.**

Several definitions of Post COVID-19 have been suggested. In the present document, we support use of the term **Post-Acute COVID syndrome (PACS)** as an entity comprising two sub-groups:

**1. Long-COVID**: persistence of symptoms (present or not at the onset of the infection) after 4 weeks of infection, with a permanent, relapsing / remitting or progressive improvement course.

**2. Sequelae:** irreversible tissue damage after 12 weeks that could trigger different degrees of permanent dysfunction and associated symptomatology.

Although the exact **causes of PACS** remain unknown, virus-specific pathophysiologic changes and immunologic aberrations and inflammatory damage in response to the acute infection have been proposed as possible underlying mechanisms. In the case of the younger population, in which the prevalence of PACS decreases down to 8%, the multisystemic inflammatory syndrome in children (MIS-C) would be the consequence of an aberrant immune response and, although rare, it can be potentially serious, requiring early diagnosis and treatment.

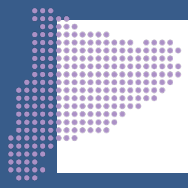
There is wide **heterogeneity in the prevalence and clinical presentation** of PACS, although fatigue (52%), cardio-respiratory (30-42%) and neurological symptoms (40%) are those most frequently reported.

We propose **a clear set of case definitions of PACS and its clinical scenarios**. We recommend standardization and adequate coding of these case definitions to foster comparability, better estimates of the magnitude of the problem at the international level, and the establishment of national disease registries. We also recommend a **comprehensive medical examination** to characterise the clinical features and complications when assessing PACS. Data on the evolution and resolution dynamics of PACS remain scarce to date. Clear and functional referral circuits connecting primary care and hospitals are necessary to guarantee adequate management of these patients, with the development of multidisciplinary units that could offer a comprehensive and complete management of the patient.

Persistent COVID symptoms can have a **serious impact** on people's ability to return to work, with significant psychological, social and economic consequences for themselves, their families and society. **It is now time to establish the appropriate strategies** to tackle this second added burden of COVID in order to minimise its impact.

# Key Messages

1. An estimated 10-15% of people suffer from persistent symptoms after SARS-CoV-2 infection.



2. In Catalonia, around 90,000 people are or have been affected by persistent symptoms.

3. We propose that the term Post-Acute COVID-19 Syndrome (PACS) includes two non-mutually exclusive scenarios:
   - Long-COVID: symptoms appearing or persisting beyond 4 weeks after infection.
   - Sequelae: irreversible organ damage beyond 12 weeks after infection.

4. A clear and adequate definition of this syndrome is key to establish patient registries and conduct research studies.

5. A specific ICD code for this syndrome and its sub-entities is needed to facilitate its identification, allow comparisons, and better evaluate its impact worldwide.

6. There is a great variety of PACS symptoms, but the most frequent are fatigue, respiratory symptoms and neurological alterations.

7. The mechanisms underlying PACS are not clearly understood but could involve cytopathic damage, immune dysregulation, and inflammatory tissue damage.

8. An adequate clinical management requires clear circuits to refer these patients from primary care to the hospital.

9. We also recommend the creation of multidisciplinary units for an effective and holistic follow-up of these patients.

10. Health authorities need to allocate adequate resources to address this emerging situation and optimize health outcomes.

# Síndrome de COVID postagudo (PACS): Definición, impacto y manejo


## Resumen

Varios estudios sugieren que hasta un **10-15% de todos los pacientes con COVID-19** pueden presentar sintomatología persistente semanas o incluso meses después de la infección inicial. Dada la carga de enfermedad por COVID-19 acumulada en Cataluña (España), calculamos que más de 90.000 pacientes podrían haber sufrido o estar sufriendo actualmente **síntomas o secuelas persistentes**.

Se han propuesto varias definiciones de Post COVID-19. En el presente documento, abogamos por el uso del término **Síndrome de COVID postagudo (PACS**, por sus siglas en inglés) como una entidad que incluye dos subgrupos:

**1. COVID-prolongado**: persistencia de síntomas (presentes o no al inicio de la infección) después de 4 semanas de infección, con curso permanente, recurrente/remitente o de mejora progresiva.

**2. Secuelas:** daños irreversible a los tejidos después de 12 semanas, que pueden desencadenar distintos grados de disfunción permanente y la correspondiente sintomatología.

Aunque siguen sin conocerse las **causas exactas** del PACS, se han propuesto como posibles mecanismos subyacentes los cambios fisiopatológicos generados por el virus, las alteraciones inmunológicas secundarias a la interacción virus-huésped y el daño inflamatorio como respuesta a la infección aguda. En la población más joven, en quienes la prevalencia del PACS se reduce hasta un 8%, el síndrome inflamatorio multisistémico en niños y niñas (MIS-C, por sus siglas en inglés) sería la consecuencia de una respuesta inmunológica aberrante, y aunque poco frecuente, puede ser potencialmente grave, por lo que requiere un diagnóstico y tratamiento precoces.

La prevalencia y la presentación clínica del PACS son **muy heterogéneas**, aunque con mayor frecuencia aparecen fatiga (52%), síntomas cardiorrespiratorios (30-42%) y síntomas neurológicos (40%).

Proponemos como **definición** de caso "PACS" y sus distintos escenarios clínicos. Recomendamos **la estandarización y una codificación adecuada** de esta definición de caso para fomentar la comparabilidad, mejores estimaciones de la magnitud del problema a nivel internacional y el establecimiento de registros nacionales de la enfermedad. También recomendamos una **exploración médica integral** para caracterizar las características clínicas y las complicaciones al evaluar el PACS. En la actualidad, sigue habiendo pocos datos sobre la dinámica de evolución y de resolución del PACS. Se necesitan circuitos de derivación claros y funcionales que conecten la atención primaria y los hospitales para garantizar una gestión adecuada de estos pacientes, con el desarrollo de unidades multidisciplinares que puedan ofrecer un manejo integral y completo del paciente.

Los síntomas prolongados de COVID pueden tener **graves repercusiones** sobre la capacidad de las personas para incorporarse al trabajo, con consecuencias significativas a nivel psicológico, social y económico, tanto para ellas mismas como para sus familias y para la sociedad. **Ahora es el momento de establecer las estrategias apropiadas** para abordar esta segunda carga adicional de COVID con el objetivo de minimizar su impacto.

# Mensajes clave

1. Según las estimaciones, 10-15% de las personas sufren síntomas persistentes después de la infección con SARS-CoV-2.

2. En Cataluña, cerca de 90.000 personas sufren o han sufrido síntomas persistentes.

3. Proponemos que el término Síndrome de COVID-19 postagudo (PACS) incluya dos escenarios que no son mutuamente excluyentes:
   - COVID-prolongado: los síntomas aparecen o persisten más allá de 4 semanas después de la infección.
   - Secuelas: daño orgánico irreversible más allá de 12 semanas después de la infección.

4. Es fundamental disponer de una definición clara y apropiada de este síndrome para establecer registros de pacientes y llevar a cabo estudios de investigación.

5. Se necesita un código CIE específico para este síndrome y sus fenotipos clínicos, para facilitar su identificación, permitir las comparaciones y evaluar mejor su impacto a nivel mundial.

6. Existe una gran variedad de síntomas de PACS, pero los más frecuentes son fatiga, síntomas respiratorios y alteraciones neurológicas.

7. Los mecanismos subyacentes en el PACS no se conocen con claridad, pero podrían implicar daño citopático, desregulación inmunológica y daño inflamatorio como respuesta a la infección aguda.

8. Para una gestión clínica adecuada se requieren circuitos claros para derivar a estos pacientes desde la atención primaria al hospital.

9. También recomendamos la creación de unidades multidisciplinarias para un seguimiento efectivo y holístico de estos pacientes.

10. Las autoridades sanitarias deben asignar los recursos apropiados para abordar esta situación emergente y optimizar los resultados en salud.

# Síndrome de COVID postaguda (PACS): Definició, impacte i gestió

## Resum


Diversos estudis suggereixen que al voltant d'un **10-15% de tots els pacients amb COVID-19** poden presentar simptomatologia persistent setmanes o fins i tot mesos després de la infecció original. Donada la càrrega de malaltia per COVID-19 acumulada a Catalunya (Espanya), calculem que més de 90.000 pacients podrien haver patit o estar patint actualment **símptomes o seqüeles persistents**.

S'han proposat diverses definicions de la Post COVID-19. En aquest document, advoquem per l'ús del terme **Síndrome de COVID postaguda** (**PACS**, per les seves sigles en anglès) com una entitat que inclou dos sub-grups:

**1. COVID perllongada**: persistència de símptomes (que podien o no ser presents a l'inici de la infecció) al cap de 4 setmanes de la infecció, amb un curs permanent, recurrent/remitent o de millora progressiva.

**2. Seqüeles**: danys irreversibles als teixits al cap de 12 setmanes, que poden desencadenar diferents graus de disfunció permanent i la simptomatologia corresponent.

Tot i que encara no es coneixen les **causes exactes** de la PACS, s'han proposat com a possibles mecanismes subjacents els canvis fisiopatològics generats pel virus, les alteracions immunològiques secundàries a la interacció virus-hoste i el dany inflamatori com a resposta a la infecció aguda. Entre la població més jove, en la qual la prevalença de la PACS es redueix fins a un 8%, la síndrome inflamatòria multisistèmica en nens i nenes (MIS-C, per les seves sigles en anglès) seria la conseqüència d'una resposta immunitària aberrant i, tot i que poc freqüent, pot esdevenir greu, per la qual cosa requereix diagnòstic i tractament precoços.

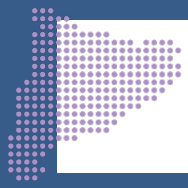
La prevalença i la presentació clínica de la PACS són **molt heterogènies**, tot i que els símptomes més freqüents són la fatiga (52%), els símptomes cardiorespiratoris (30-42%) i els símptomes neurològics (40%).

Proposem com a definició de cas "PACS" i els seus diferents escenaris clínics. Recomanem **l'estandardització i una codificació adequada** d'aquesta definició de cas per tal de fomentar la comparabilitat, fer millors estimacions de la magnitud del problema a nivell internacional i establir registres nacionals de la malaltia. També recomanem una **exploració mèdica exhaustiva** per identificar les característiques clíniques i les complicacions quan s'avaluï la PACS. Actualment, encara hi ha poques dades sobre la dinàmica d'evolució i de resolució de la PACS. Calen circuits de derivació clars i funcionals que connectin l'atenció primària i els hospitals, per tal de garantir una gestió apropiada d'aquests pacients, amb el desenvolupament d'unitats multidisciplinàries que puguin oferir una gestió integral i completa del pacient.

Els símptomes perllongats de COVID poden tenir **greus repercussions** sobre la capacitat de les persones de reincorporar-se a la feina, cosa que comporta conseqüències significatives a nivell mental, social i econòmic, tant per a elles mateixes com per a les seves famílies i per a la societat. **Ara és el moment d'establir les estratègies apropiades** per abordar aquesta segona càrrega addicional de COVID per tal de minimitzar-ne l'impacte.

# Missatges clau

1. Segons les estimacions, **10-15% de les persones** pateixen símptomes persistents després de la infecció amb SARS-CoV-2.



2. A **Catalunya**, prop de **90.000 persones** pateixen o han patit símptomes persistents.

3. Proposem que el terme **Síndrome de COVID-19 postaguda (PACS)** inclogui dos escenaris que no són mútuament excloents:
   - **COVID perllongada**: els símptomes apareixen o persisteixen més de 4 setmanes després de la infecció.
   - **Seqüeles**: dany orgànic irreversible més de 12 setmanes després de la infecció.

4. És essencial disposar d'una **definició clara i adequada** d'aquesta síndrome per tal d'establir registres de pacients i dur a terme estudis de recerca.

5. Cal un **codi CIE específic** per a aquesta síndrome i els seus fenotips clínics, per tal de facilitar-ne la identificació, permetre les comparacions i avaluar-ne millor l'impacte a nivell mundial.

6. Els **símptomes de la PACS són molt variables**, però els més freqüents són la fatiga, els símptomes respiratoris i les alteracions neurològiques.

7. Els **mecanismes subjacents en la PACS no es coneixen amb claredat**, però podrien implicar dany citopàtic, desregulació immunològica i dany inflamatori com a resposta a la infecció aguda.

8. Per a una gestió clínica adequada, són necessaris **circuits clars per tal de derivar aquests pacients** des de l'atenció primària a l'hospital.

9. També recomanem la creació d'**unitats multidisciplinàries** per tal d'assolir un seguiment efectiu i holístic d'aquests pacients.

10. És necessari que les autoritats sanitàries destinin els **recursos necessaris** per a l'abordatge d'aquesta situació emergent i per optimitzar els resultats en salut.

# Index

# 01 Introduction

At the outset of the COVID-19 pandemic, it was natural to focus first on patients with severe disease who required the prioritization of potentially scarce resources in the hospital and intensive care units. However, for the **long-term management** of COVID-19, we need to understand and optimize care beyond the acute infection or hospitalization event. It is time to expand the research focus to studies on **living with long-term symptoms** of this disease[1].

Primary care physicians and specialists at hospitals increasingly attend patients who suffer from **persistent and cyclical symptoms** after their initial infection, independent of its severity. People have started colloquially to term this phenomenon as '**long COVID**" and those struggling with persistent symptoms are calling themselves '**long haulers**', which in fact include two groups of people: those who experience **sequelae of organ damage** (such as acute lung and kidney injury resulting in pulmonary fibrosis and chronic kidney disease, respectively), and those who continue to experience **debilitating symptoms despite no detectable damage** to these organs[2].

In an online, voluntary, self-completed, anonymized survey carried out in Spain between 13 July and 14 October 2020, **201 distinct symptoms were described**, being 95.9% general, 86.5% neurological, 86.2% psychological/emotional, 82.8% musculoskeletal, 79.3% respiratory, and 70.8% digestive[3].

# 02 Definition

## Terms and definitions

No consensus has yet been reached on the definition and chronology associated with persistent COVID-19 symptoms. The terms "prolonged COVID-19", "prolonged sequelae", "post-acute COVID-19", "post-acute COVID-19 Syndrome (PACS)[4]" "persistent COVID-19 symptoms", "post-COVID-19 manifestations", "long-term COVID-19 effects", "post-COVID-19 syndrome", "post-acute COVID-19 sequelae", "chronic COVID syndrome", among others, have been used by different authors[5]. Also, different definitions of these terms are shown in *Annex 1, Box 1*.

## Case definition

We support the term of *(Figures 1,2)*:

**Post-acute COVID-19** syndrome when symptoms persist beyond 4 weeks, differentiating the terms:

• **Long COVID** for persistent symptoms beyond 4 weeks present during acute COVID or appearing later in the case of asymptomatic subjects. The symptoms are not the result of irreversible organic damage.

• **Sequelae** refers to irreversible tissue damage after 12 weeks that could represent different degrees of permanent dysfunction and symptoms.

**Figure 1 Situations Leading to Post-Acute COVID-19.**

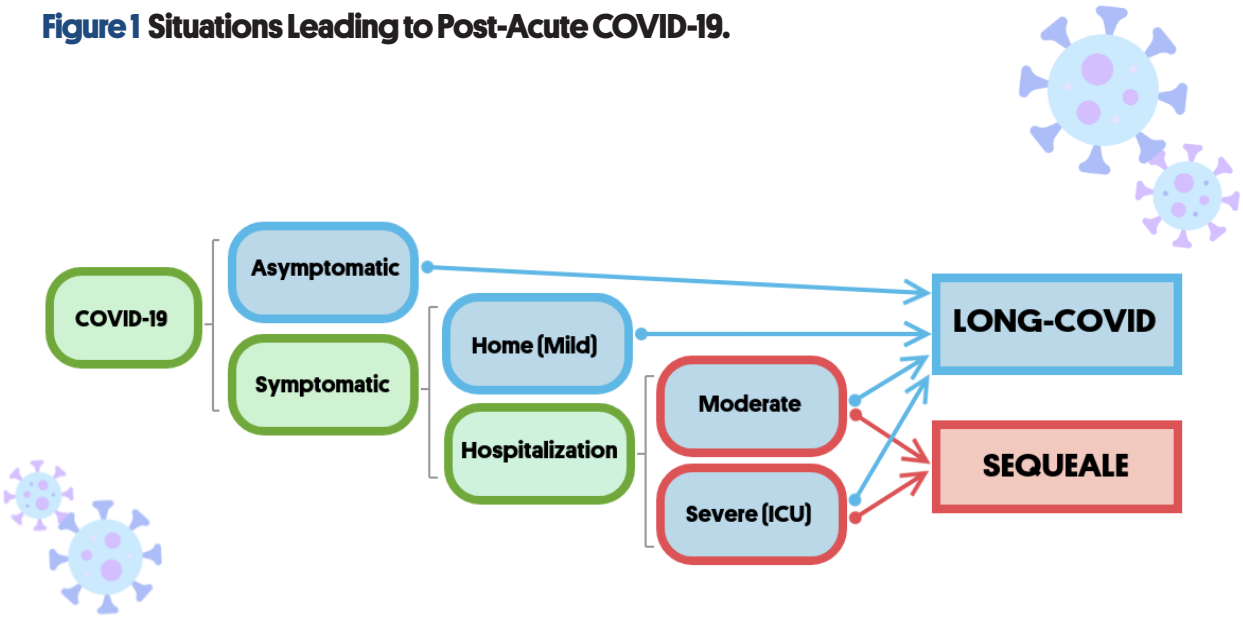
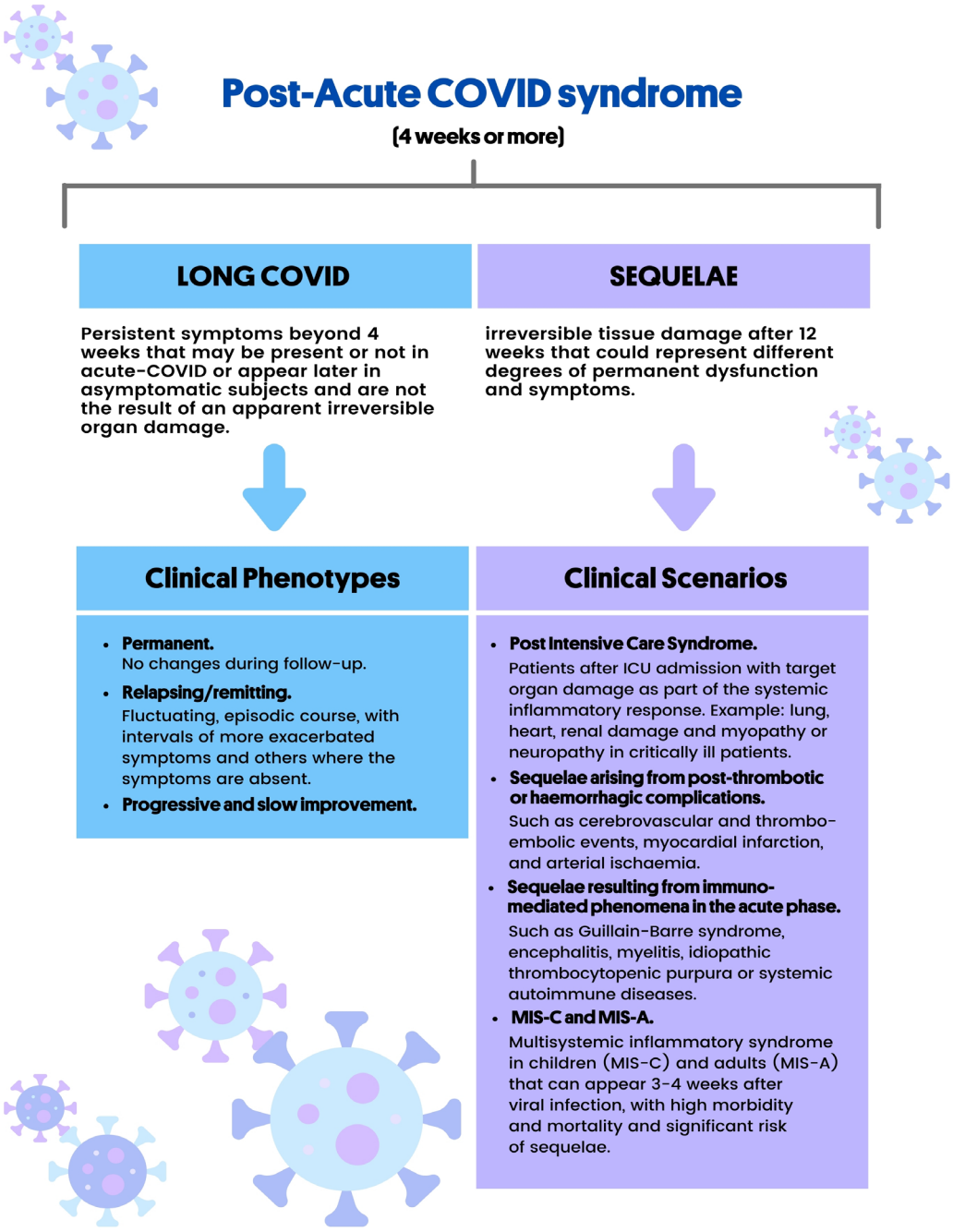


**Figure 2** **Differences between Long COVID and sequelaes.**



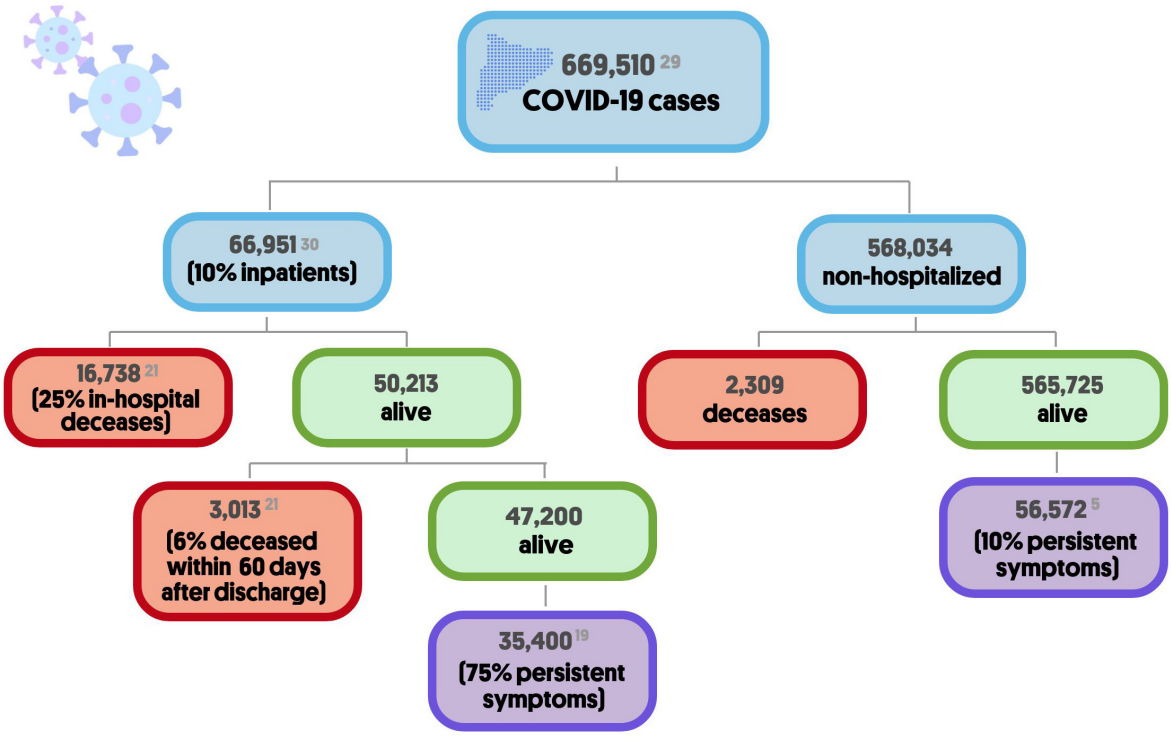
# 03 Magnitude of the problem

Post COVID-19 condition occurs in **many different sets of patients**, such as those hospitalized with COVID-19 illness of varying severity, those who have not been hospitalized or those having recovered from a pauci-or asymptomatic acute illness[6].

Several studies have been published with data on the **prevalence** of patients with persistent symptoms or long COVID in hospitalized or non-hospitalized patients[7-13,14-21,22-30] *(Table 1, Annex 1)*. Estimating prevalence of persistent symptoms **is not easy due to differences** in populations and methods used, and some studies reporting mixed data from hospitalized and non-hospitalized patients. Therefore, estimates **vary greatly** among different studies.

In Catalonia, Spain, with a population of about 7,5 million, 669,510 confirmed cases and 22,060 deaths have been reported as of 15 May[31]. 25% of patients died during hospitalization and further 6% died 60 days after being discharged[23]. Assuming that 10% of confirmed cases are hospitalized[32], that 75% of hospitalized patients[21] and 10% of non-hospitalized patients[7] have persistent symptoms, we speculate that over **90,000 COVID-19-confirmed patients** might have had or still have **persistent symptoms or sequelae** *(Figure 3)*.

**Figure 3. Estimation of total number of cases with post-acute COVID-19 Syndrome in Catalonia.**



Little is known regarding long-COVID among **pediatric patients**, given the paucity of severe COVID-19 cases affecting children. It is important however to **monitor the persistence of symptomatology** in this specific population, irrespective of the initial presence or absence and severity of symptoms. In addition, the advent of a rare complication known as the Multisystem inflammatory syndrome in children (MIS-C), could be considered a persistent complication per se given that it usually occurs 3-4 weeks after the documented SARS-CoV-2 infection, or could lead to longer-term problems that would also qualify as "long-covid".

## Impact of Post-Acute COVID-19 Syndrome on working life

Medical leave, also called temporary inability or sick leave, is the official recognition that a worker who contributes to Social Security cannot do his/her usual job due to a health problem. It generally entitles the patient to an economic benefit.

The doctor who examines the person who is unwell has information tables from the National Social Security Institute about the conditions that can lead to work disabilities. These tables include the standard duration of sick leave for each condition.

In the specific case of persistent COVID-19 symptoms of, there are **no specific protocols or actions**, which means that returning to work is based on the type and intensity of symptoms, as well as the type of work activity of each person. There is no specific inability diagnosis, and it is limited to the specific symptoms at individual basis[33,34].

It will be the responsibility of the primary care team to monitor and justify the continuity of the leave or the assessment of the return to work (asymptomatic, adaptation of work within the company or a gradual return to work).

The truth is that PACS has a **serious impact on people's ability to return to work**, affecting the mental, social sphere and with economic consequences for them, their families and society.

According to data from the INSS 2021[35], the average duration of sick leave due to infection is **short**- around 21 days- and 90% of cases are resolved within 60 days, although 10% extend beyond two months and some to even one year. It is important to further investigate the long-term impact of COVID-19 on peoples' working capacity.

# 04 Mechanisms contributing to the pathophysiology of post-acute COVID-19

**Mechanisms** contributing to the pathophysiology of post-acute COVID-19 include: first, virus-specific pathophysiologic changes and immunologic aberrations and inflammatory damage in response to the acute infection; second, other potential mechanisms, and third, expected sequelae of post-critical illness[36].

## 4.1. Virus-specific pathophysiologic changes and immunologic aberrations and inflammatory damage by organ

### 4.1.1. Pulmonary

**Viral-dependent mechanisms** (including invasion of alveolar epithelial and endothelial cells by SARS-CoV-2) and **viral-independent mechanisms** (such as immunological damage, including perivascular inflammation) contribute to the breakdown of the endothelial–epithelial barrier with invasion of monocytes and neutrophils and extravasation of a protein-rich exudate into the alveolar space, consistent with other forms of acute respiratory distress syndrome. After the acute infection, lung fibrosis may be developed. This fibrotic state may be provoked by cytokines such as interleukin-6 (IL-6) and transforming growth factor-, which have been implicated in the development of pulmonary fibrosis of other origin.

### 4.1.2. Hematological

Mechanisms of **thromboinflammation** that provoke a **hypercoagulable state** include endothelial injury, complement activation, platelet activation and platelet–leukocyte interactions, neutrophil extracellular traps, release of pro-inflammatory cytokines, disruption of normal coagulant. Pathways and hypoxia, similar to the pathophysiology of thrombotic microangiopathy syndromes.

### 4.1.3. Cardiovascular

Mechanisms perpetuating **cardiovascular sequelae** in post-acute COVID-19 include direct viral invasion, downregulation of ACE2, inflammation and the immunologic response affecting the structural integrity of the myocardium, pericardium and conduction system. COVID-19 may also perpetuate arrhythmias due to a heightened catecholaminergic state due to cytokines such as IL-6, IL-1 and tumor necrosis factor-, which can prolong ventricular action potentials by modulating cardiomyocyte ion channel expression. Autonomic dysfunction after viral illness, resulting in postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia, has previously been reported as a result of adrenergic modulation.

### 4.1.4. Neuropsychiatric

The mechanisms contributing to **neuropathology** in COVID-19 can be grouped into overlapping categories of direct viral infection, severe systemic inflammation, neuroinflammation, microvascular thrombosis and neurodegeneration.

Furthermore, levels of immune activation directly correlate with cognitive–behavioral changes. Inflammaging (a chronic low-level brain inflammation that characterizes aging), along with the reduced ability to respond to new antigens and an accumulation of memory T cells (hallmarks of immunosenescence in aging and tissue injury), may play a role in persistent effects of COVID-19. Other proposed mechanisms include dysfunctional lymphatic drainage from circumventricular organs, as well as viral invasion in the extracellular spaces of olfactory epithelium and passive diffusion and axonal transport through the olfactory complex. Biomarkers of cerebral injury, such as elevated peripheral blood levels of neurofilament light chain, have been found in patients with COVID-19 with a more sustained increase in severe infections, suggesting the possibility of more chronic neuronal injury.

Post-COVID brain fog in critically ill patients with COVID19 may evolve from mechanisms such as deconditioning or PTSD. However, reports of COVID-19 brain fog after mild COVID-19 suggest that dysautonomia may contribute as well. Finally, long-term cognitive impairment is well recognized in the post-critical illness setting, occurring in 20–40% of patients discharged from an ICU.

### 4.1.5. Endocrine

**Endocrine manifestations** in the post-acute COVID-19 setting may be consequences of direct viral injury, immunological and inflammatory damage, as well as iatrogenic complications.

COVID-19 also presents risk factors for **bone demineralization** related to systemic inflammation, immobilization, exposure to corticosteroids, vitamin D insufficiency and interruption of antiresorptive or anabolic agents for osteoporosis.

### 4.1.6. Gastrointestinal and hepatobiliary

COVID-19 has the potential to **alter the gut microbiome**, including enrichment of opportunistic infectious organisms and depletion of beneficial commensals.

### 4.1.7. Dermatologic

The predominant dermatologic complaint after the acute infection of COVID-19 was **hair loss**, which was noted in approximately 20% of patients. Hair loss can possibly be attributed to telogen effluvium resulting from viral infection or a resultant stress response.

### 4.1.8. Multisystem inflammatory syndrome in children (MIS-C)

The **Multisystem inflammatory syndrome in children (MIS-C)** is a condition where different body parts can become **inflamed** (including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs) and that often leads to severe and potentially life-threatening symptoms[37]. MIS-C is defined by the presence of the following symptoms in people < 21 years old (< 19 years old per the World Health Organization definition): fever; elevated inflammatory markers; multiple organ dysfunction; current or recent SARS-CoV-2 infection; and exclusion of other plausible diagnosis. MIS-C may result from an aberrant acquired immune response rather than acute viral infection. MIS-C could be considered a persistent complication per se given that it usually occurs 3-4 weeks after the documented SARS-CoV-2 infection, or could lead to longer-term problems". Importantly, recovery from the MIS-C clinical episode appears to be -if adequately managed- rapid and satisfactory, leaving no significant longer-term sequelae.

## 4.2. Other potential mechanisms contributing to the pathophysiology

Knowledge of SARS-CoV-2 **neurotropism** and its **gastrointestinal distribution** is key to better understanding of COVID-19 diagnosis and may explain Long-COVID. J. Meinhardt et al[38] were able to demonstrate that at least two-thirds of 33 post-mortem subjects had viral particles in the olfactory mucosa after a median of 31 days (from 4 to 79 days) from the onset of infection. Results were verified by real-time quantitative PCR (rt-qPCR) and in-situ hybridization to detect SARS-CoV-2 RNA, as well as by immunohistochemistry and electron microscopy to detect proteins. In the case of bowel, C. Gaebler et al[39] found the persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel of 7 out of 14 asymptomatic individuals 4 months after COVID-19 diagnosis by Immunofluorescence and PCR analyses of intestinal biopsies.

A recent study done in the USA and China[40] investigated **how autoantibodies could mediate neutrophil extracellular traps** (NET)s during a COVID-19 infection. Extensive damage to the body from NETs after infection may be contributing to thromboinflammation and the symptoms experienced by COVID-19 'long-haulers'. These data reveal high levels of anti-NET antibodies in individuals hospitalized with COVID-19, where they likely impair NET clearance and thereby potentiate SARS-CoV-2 mediated thromboinflammation.

Another study[41] indicates that similar to many other viruses, SARS-CoV-2 utilizes **exosomal like extracellular vesicle cellular transport avenues** for reproduction and intra-host spreading as a mode of systemic virus dissemination. Releasing of the SARS-CoV-2-loaded exosomes or EDMVs represent a reasonable explanation for the appearance of the viral RNA in the recovered COVID-19 patients 7–14 day post discharge.

Another hypothesis recently published described how mast cell activation might cause a propensity for severe acute Covid-19 infection and chronic post-Covid-19 illnesses[42].

## 4.3. Sequelae of post-critical illness

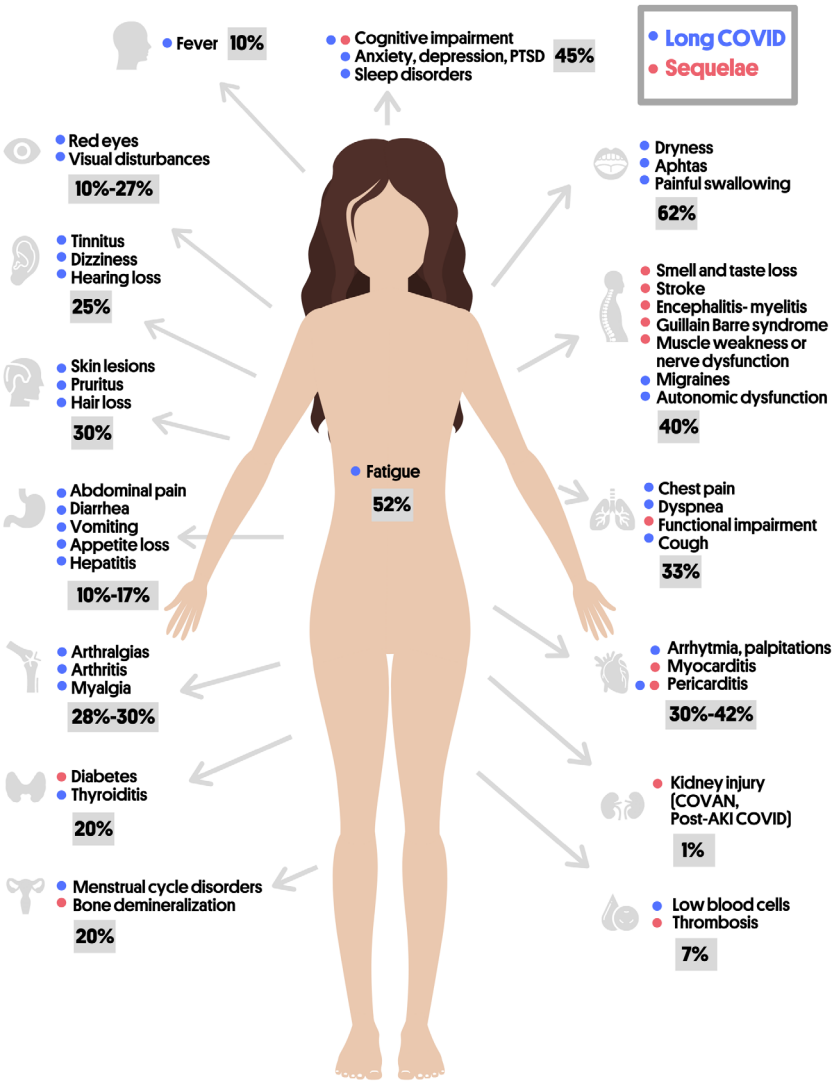
The pathophysiology of post-intensive care syndrome is **multifactorial** and has been proposed to involve microvascular ischemia and injury, immobility and metabolic alterations during **critical illness**. Additionally, survivors of acute COVID-19 may be at increased risk of infections with bacterial, fungal (pulmonary aspergillosis) or other pathogens. However, these secondary infections do not explain the persistent and prolonged sequelae of post-acute COVID-19.

# 05 Clinical Manifestations

## 5.1. Prevalence of symptoms in adults

There is wide heterogeneity in the prevalence of symptoms after COVID19, although the presence of fatigue (52%), cardio-respiratory (30-42%) and neurological symptoms (40%) are the most frequently reported. Dryness, not always reported, could be as prevalent as the previous ones, although more studies are needed to confirm this suspicion *(Figure 4 and Annex 1, Table 2)*.

**Figure 4** Post-Acute COVID: Clinical Manifestations.



## 5.2. Pulmonary complications in adults

### 5.2.1. Pulmonary symptoms after COVID infection

The **lung** is the **organ primary affected by COVID-19 infection**, and consequently, respiratory symptoms and limitations to exercise are prevalent after severe COVID infection. The most frequent pulmonary symptoms that patients could present after a COVID infection is dyspnea, cough and chest pain[14,19,20,22]. In Table 2, we have estimated the prevalence of these symptoms after COVID-19 infection: dyspnea (33%), cough (22%) and chest pain (30%). Additionally, exercise limitation is frequent. The median 6-min walking distance could be lower than normal reference values in approximately one-quarter of patients at 6 months[21]. The proportion of symptoms that are clearly associated with pulmonary sequelae and those in absence of lung persistent damage is unknown.

### 5.2.2. Pulmonary sequelae

**Different strategies** have been recommended to **detect pulmonary sequelae**[43]. CT scan is a basic test used in these approaches, as it could describe the extension and characteristics of these sequelae. Approximately 50% of 349 patients who underwent high-resolution computed tomography of the chest at six months had at least one abnormal pattern in the post-acute COVID-19 Chinese study[21].

**Fibrotic changes** on computed tomography scans of the chest are frequently observed. Although the definition of fibrosis is not currently clear, one proposed definition is the presence of reticulation or traction bronchiectasis[44]. Fibrotic changes were observed three months after hospital discharge in approximately 25% and 65% of survivors in cohort studies of mild-to-moderate cases[45] and mostly severe cases[46]. However, more studies are necessary to really establish the real incidence and definition of lung fibrosis after COVID19 infection. Preliminary data suggest that there is an association of the severity of COVID pneumonia with persistent diffusion impairment[47] and pulmonary fibrosis[48].

Finally, although pulmonary embolism risk is incremented in COVID19 infection, the long-term risks of chronic pulmonary embolism and consequent pulmonary hypertension are unknown at this time.

## 5.3. Extra-pulmonary symptoms in adults

### 5.3.1. General Symptoms

**Fatigue and exercise intolerance** are the most prevalent and, depending on the study, may be present in almost 50-80% of patients *(Table 2)*, resembling the scenario of Myalgic

Encephalomyelitis/Chronic Fatigue Syndrome[5,7,8,10–14,16–22,29,45,49–54]. However, it is very important to be cautious when fatigue and exercise intolerance are also associated with weight and appetite loss, because it could be a warning sign that requires detection of a malignant origin. If fever and sweating are also present, a possible lymphoproliferative syndrome or inflammatory disease must be ruled out[55].

### 5.3.2. Skin and Mucosa lesions

**Hair loss** (often transitory as a telogen effluvium), **oral aphthae**, as well as **skin lesions** and **dryness** may appear after infection in almost one-third of patients. In the case of dryness, there are not many studies reporting this symptom but both Carfi and the Spanish Registry from primary care reveal that it could be present in 15-60%. These should be evaluated in case they are related to an endocrinological or immunological etiology.

### 5.3.3. Musculoskeletal symptoms

**Arthralgias** are very common (10-50%) and may be disabling. It is always necessary to identify the number and type of joint, pattern of presentation (inflammatory or mechanical) and especially if they are associated with other inflammatory symptoms. It should be kept in mind that a previous infection such as SARS-CoV-2 may precipitate the onset of immunological disease. Likewise, between 20-30% of patients report **myalgias**. It is important to check for weakness and elevation of muscle biomarkers and try to exclude inflammatory disease or sequelae after severe COVID19.

### 5.3.4. Cardiological signs

**Chest pain** (30%) always requires that coronary heart disease be ruled out first, especially in patients with cardiovascular risk factors. Identifying how and when it begins and recognizing other warning symptoms such as **dyspnea**, **sweating** and **signs of heart failure**, need urgent management, preferably in hospital. In case of **pleuritic pain**, the possibility of serositis should be considered. If **recurrent palpitations** (10-60%) occur, the possibility of an inappropriate sinus tachycardia should be considered, as well as a POTS if it is associated with orthostatic symptoms. It is recommended in this case to include a holter and a specific dysautonomia study.

### 5.3.5. Digestive manifestations

Digestive symptoms, like in acute infection, may be frequent (10-17%) and remain in the form of "flares" with days of **abdominal discomfort** and **diarrhoea** and others of complete normality. As mentioned above, part of the symptomatology is likely to be due to a **change in the microbiota**. However, the presence of alterations in the **stool** (mucus or blood) should always be ruled out and if this appears together with abdominal pain and fever, referral to a gastroenterologist should be preferred.

## 5.3.6. Ear, Nose and Throat complaints

**Odynophagia** is a recurrent symptom (18%) and is also described in **chronic fatigue syndrome associated with fatigue**. It is rarely associated with dysphagia and in that case further investigation is recommended. On the other hand, **hearing disturbances** (5%), **tinnitus** (25%) or **episodic peripheral vertigo** could appear after infection. If these symptoms do not improve and become disabling, treatment and referral to a specialist is recommended.

## 5.3.7. Ophthalmological complaints

Most frequent mild changes in **visual acuity** or **even blurred vision** (27%). Less frequently described are sudden or severe disturbances that could be associated with other disorders such as photopsia, myodesopsia or metamorphopsia. In this case, a serious complication should be suspected and an early referral to an ophthalmologist should be made.

## 5.3.8. Vascular and haematological disorders

**Thrombosis** is a very common complication during acute infection, around 31.3% venous thromboembolism and include 19.8% deep venous thrombosis and 18.9% pulmonary thrombosis[56,57]. However, **after discharge, prevalence is low**, around 0.8-2.5%[58,59]. Patients with sequelae and secondarily limited mobility have a high risk of thrombosis and should be monitored during follow-up. Besides that, **arterial thrombosis is a quite rare** complication, between 1-3.6%[60,61]. Respect to haematological aspect, COVID-19 is associated with **lymphopenia**, as well as **thrombopenia**, but in the vast majority of cases these subsequently resolve (7%). Therefore, if they persist or appear later, they should be studied and an immune-mediated, haemolytic or thrombotic origin should be excluded.

## 5.3.9. Neurological symptoms

**Loss of smell and taste are very common and prolonged** (16-22%). The chemosensory deficits are often the earliest, and sometimes the only signs in otherwise asymptomatic carriers of the SARS-CoV-2 virus. The reasons for the surprisingly early and specific chemosensory dysfunction in COVID-19 are now beginning to be elucidated[62]. Respect to olfactory dysfunction (OD), at 60 days and 6 months, 15.3% and 4.7% of anosmic/hyposmic patients did not objectively recover olfaction, respectively. The higher baseline severity of objective olfactory evaluations was strongly predictive of persistent OD.

**Headache**, also frequent (33%), predominantly fronto-parietal and often controlled with standard analgesia. However, there are some cases that may be refractory or associated with "red flags" (presence of vomiting, fever or interruption of sleep) and should be ex-

amined preferentially to rule out serious problems. Physical strength and sensitivity should always be explored, as well as other common findings such as those related to dysautonomia (inappropriate tachycardia, changes in sweating, orthostasis)[64–66] that may appear around 16%, and possible neurocognitive impairment (short-term memory, concentration/attention problems, orientation)[21,67] or sleep disorders in almost 40%.

### 5.3.10. Psychological area

Many studies reveal a **high prevalence of anxiety, depression, mood disorders** (40%) and there are several cases of post-traumatic stress syndrome. Patients should always be asked about them and if some of them are already known and have been exacerbated after infection. For holistic patient management, it is useful to know if mental health disorders are present and may require early referral to a support team[68–73].

### 5.3.11. Autoimmune disorders

COVID-19 patients exhibit increases in **autoantibody reactivities** compared to uninfected controls, with a high prevalence of autoantibodies against immunomodulatory proteins including cytokines, chemokines, complement components, and cell surface proteins (the "exoproteome")[74]. Some autoantibodies, particularly neutralizing antibodies against IFN-I, contribute to COVID-19 pathophysiology by antagonizing innate antiviral response and may contribute to disease severity in COVID-19[75]. Furthermore, case report and series of autoimmune disorders have been described, not only with single organ involvement (thyroiditis, diabetes, etc) but also with systemic manifestations (vasculitis, inflammatory myopathy or lupus). Therefore it may be important in the presence of symptoms such as arthralgias, skin lesions, dryness or other recurrent or persistent findings to rule out the onset of an autoimmune disease triggered by the infection, especially in the light of possible underlying immune dysregulation in Long-COVID[76–80].

## 5.4. Post-acute COVID-19 in children

The clinical expression of SARS-CoV-2 infections in children is strikingly milder than that of adults, with the majority of pediatric infections being **mild or directly asymptomatic**[81,82]. When present, symptoms tend to be **short-lasting**. Similarly to adults, however, but probably less noticeable given the milder nature of COVID-19 in the pediatric population, children may experience persistent symptoms that merit attention and an adequate follow-up. Beyond MIS-C, there is now increasing evidence of the longer-term persistence of symptoms of COVID-19 in this population group. A cohort of 171 SARS-CoV-2 infected children (with or without symptoms, median age 3 years) was followed in Melbourne, Australia, to document outcomes 3–6 months after diagnosis[83]. They described a prevalence of **8% of persistent symptoms** (mild cough, fatigue, etc.) typically mild in nature, and

self-limited. An Italian cohort of older pediatric patients (n=129, mean age 11)[84], followed 60-120 days post their original infection (irrespective of the presence or absence of symptoms) detected a much higher prevalence of persistent symptomatology (66% with at least one symptom), or various degrees of severity and duration. Importantly, authors highlighted that, unexpectedly, children with an asymptomatic or paucisymptomatic COVID-19 episode could also develop chronic, persisting symptoms. Other symptoms reported in the literature[85] include insomnia, fatigue, dyspnea, heart palpitations or chest pain, headaches, difficulties concentrating, muscle weakness, dizziness and sore throats as persisting weeks or even months after the original infection. **Increasing age** seems to be associated with a h**igher risk of occurrence and duration of persistent symptomatology**.

## 5.5. Post-acute COVID-19 in pregnancy

There are currently **no studies** on persistent symptoms in this group of patients, although there are prospective studies and even systematic reviews on pregnancy and COVID-19 which report data on complications (gestational hypertension, pre-eclampsia and premature rupture of membranes) as well as a higher rate of caesarean sections compared to the usual prevalence (more than 50%). It should be **a priority to follow up** these patients beyond pregnancy to find out whether or not they have prolonged symptoms, as well as other psychological comorbidities due to the complications described above[86–88].

# 06 Management and Follow-up

When prolonged symptoms are detected beyond 4 weeks of infection (or 12 weeks in the case of sequelae) it is necessary to **perform a complete work-up** to characterize the clinical features and, above all, to rule out complications or other severe etiologies that may explain the prolonged symptoms.

Comprehensive guidelines has been published by the Catalan and Spanish Society of Family and Community Medicine[89], by the Spanish Society of General and Family physicians[90] and by the Catalan Health Services[33], with the intention to **improve the quality of care of COVID-19 patient** with persistent symptoms or sequelae.

In this regard, we provide **recommendations on diagnostic tests** that could be ordered and when a referral should be made from primary care to the hospital for further investigation *(Tables 3, 4, 5, Annex 2)*.

Overall, there is a trend towards improvement of symptoms *(Table 6, Annex 2)*. In this sense, whereas fatigue may be one of the most long-lasting symptoms, other symptoms may decrease in intensity or even disappear completely. However, it is difficult to confirm the percentage of patients who improve and the time to achieve this goal due to the great heterogeneity of the studies published to date. There are case reports and a few prospective studies that demonstrated that **vaccination could produce a significant improvement** in symptoms, although more data are needed to confirm this approach[91].

# 07 Conclusion

**Around 10-15%** of people are estimated to present **persistent symptomatology** during weeks or even months after an initial infection with SARS-CoV-2. In **Catalonia**, with a total of 669,150 cases diagnosed as of 15 May 2021, and excluding deaths, we estimate that **at least 90,000 people** are or have been affected by persistent symptoms. In this report, we highlight the need to establish **a clear and common definition for Post-Acute COVID-19 syndrome**, which englobes two non-mutually exclusive scenarios:

i) **Long-COVID** refers to symptoms that persist or appear beyond 4 weeks after infection, and which may be permanent, recurrent or progressively improve

ii) **Sequelae** refers to irreversible damage to organs 12 weeks after the infection, leading to different grades of permanent dysfunction and symptoms.

A clear definition of Post-acute COVID-19 Syndrome is **key** to establishing prospective patient registries and conducting research projects. This involves defining a **specific code** for the syndrome and its sub-entities, according to the International Classification of Diseases (ICD), which will allow its correct identification at the international level, facilitate comparisons between and within countries, and better evaluate its impact.

The mechanisms underlying PACS are **not clearly understood**, but could involve cytopathic damage, immune dysregulation, and inflammatory damage to organs. A great variety of PACS symptoms have been reported, but the most frequent are fatigue, respiratory symptoms and neurological alterations.

**Clear circuits to derive** these patients from primary care to hospital care need to be agreed upon, to guarantee their adequate clinical management. Accordingly, we insist on the importance of creating multidisciplinary units with the involvement of different specialists, in order to achieve an effective and holistic follow-up of these patients.

Given the projected health, economic and societal **impact** of PACS, health authorities must allocate **sufficient resources** to address this issue and optimize health and research outcomes.

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# Annex 1. Definitions and Symptoms

## Box 1. Definitions and Symptoms.

**Chronic COVID Syndrome:** Prolonged status of symptomatic disease after a period of three weeks of the acute COVID disease.

**Long COVID:** It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).

> **Ongoing symptomatic COVID-19**: Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.
> **Post-COVID-19 syndrome**: Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

**Post-acute COVID-19**: symptoms from 3 to 12 weeks.

**Chronic COVID-19**: symptoms extending beyond 12 weeks.

**Persistant COVID-19 symptons**
Specifies three criteria to identify patients suffering from: having presented with a symptomatic form of Covid-19; presenting with one or more initial symptoms 4 weeks after the start of the disease; and none of these symptoms can be explained by another diagnosis.

**Post-acute COVID-19**
Persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms. It is further divided into two categories:

- subacute or ongoing symptomatic COVID-19, symptoms and abnormalities present from 4–12 weeks beyond acute COVID-19.
- chronic or post-COVID-19 syndrome, symptoms and abnormalities persisting or present beyond 12weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses.

# Annex 1

## Table 1. Summary of selected studies on the prevalence of Long COVID in non-hospitalized and hospitalized patients.

| COUNTRY | STUDY | SETTING | NUMBER OF CASES INCLUDED | STUDY PERIOD | TIME WINDOW | AGE (YEARS) FEMALES % | RESULTS |
|---|---|---|---|---|---|---|---|
| **United Kingdom** | Office for National Statistics (2020)[5] | Population representative Non hospitalized patients | 8 193 | 27/04t-22/11/2020 | 5 and 12 weeks | - | • 21% had symptoms 5 weeks after infection<br>• 10% had symptoms 12 weeks after infection |
| | Sudre et al. (2020)[6] | COVID Symptom App users (out of which 14% were hospitalized) | 4 182 | - | >=28 days >=8 weeks >=12 weeks | 42 years (median) 71.5% female | • 13.3% of cases had symptoms lasting 28 days after symptom onset (14.9% women, 9.5% men). 97.7% fatigue, 91.2% headache<br>• 4.5% of cases had symptoms for over 8 weeks and 2.3% for over 12 weeks after |
| | Townsend et al. 2020)[7] | Hospital outpatients (out of which 56% were hospitalized) | 128 | - | 72 days (IQR: 62–87) | 49.5 years 54% female | • 52% reported persistent fatigue at 10 weeks after symptom onset |
| | Cruz et al. (2021)[8] | Hospitalized patients | 119 | 3rd June to 2nd July 2020 | 4-6 weeks post-discharge median (IQR) 61 (51-67) | 58.7% years 38% female | • 68% reported persistent fatigue, 57% sleep disturbance and 32% breathlessness at 60 days after discharge |
| | Arnold et al. (2020)[9] | Hospitalized patients | 110 | 30 March to 3 June 2020 | 8–12 weeks after hospital admission median of 83 days (IQR 74–88 days) | 60 years (median) 38.2% female | • 81 (74%) patients reported at least one ongoing symptom: 39% breathlessness, 39% fatigue and 24% insomnia |
| | Sykes et al. (2021)[10] | Hospitalized patients | 134 (pneumonia) | - | median of 113 days (range = 46–167) post-discharge. | 58 years (median) 34.3% female | • 86% of patients reporting at least 1 symptom at follow-up. 60% of people experiencing increased breathlessness, myalgia (reported by 51.5% of patients), anxiety (47.8%), extreme fatigue (39.6%), low mood (37.3%), and sleep disturbance (35.1%) |
| | Mandal et al. (2020)[11] | Hospitalized patients | 384 | April to June 2020 | 54 days | 59,9 days 38% female | • 71.9% Symptoms persistence<br>• 53% reported persistent breathlessness, 34% cough and 69% fatigue |

# Annex 1

| COUNTRY | STUDY | SETTING | NUMBER OF CASES INCLUDED | STUDY PERIOD | TIME WINDOW | AGE (YEARS) FEMALES % | RESULTS |
|---|---|---|---|---|---|---|---|
| | Halpin et al (2020)[12] | Hospitalized patients (Ward, ICU patients) | 100 | - | 4 to 8 weeks after dis-charge by | 70.5 years (ward patients) 58.5 years (ICU patients) 46% female | • 72% fatigue<br>• 40% Breathlessness<br>• 31% posttraumatic stress disorder |
| | Andrews et al. (2020)[13] | COVID-19 positive health care workers (UK and Italy) | 114 | May 26 to June 10, 2020 | 52 days | 38 years 75.4% female | • 9.6% anosmia<br>• 7% ageusia |
| | Evans et al. (2021)[14] | Hospitalized patients | 1,077 | March 2020 to 30th November 2020 | 5 months | 58 years 36% female 69% white ethnicity | 92.8 % had at least one persistent symptom with a median number of 9. Factors associated with failure to recover were female, middleage, white ethnicity, two or more co-morbidities, and more severe acute illness |
| **Switzer-land** | Nehme et al. (2020)[15] | Hospital outpatients | 669 | 18 March to 15 May 2020 | 30 to 45 days after diagnosis. | 42.8 years 60% women | • About 33% of cases had symptoms 30–45 days after diagnosis |
| **France** | Carvalho -Schneider et al. (2020)[16] | Hospitalized patients | 150 | 17 March to 3 June 2020 | Day 7, 30 and 60 | 49 years 56% female | • 66.1% One or more persisting symptom at day 60<br>• The most frequent symptom reported at D30 and D60 was anos-mia/ageusia |
| | Garrigues et al. (2020)[17] | Hospitalized patients | 120 | March 15th and April 14th, 2020 | 110.9 days | 63.2 years 37.5% female | • Most patients had per-sistent symptoms<br>• The most frequent-ly reported persistent symptoms were fatigue (55%), dyspnea (42%), loss of memory (34%), concentration and sleep disorders (28% and 30.8%, respectively |
| **Italy** | Carfi, Bernabei & Landi (2020)[18] | Hospitalized patients | 143 | April 21 to May 29, 2020 | Mean of 60.3 (SD, 13.6) days after | 56.5 years 37.1% female | • 87% had symptoms, 55% had three or more symptoms at 60 days after discharge |
| **China** | Huang et al. (2021)[19] | Hospitalized patients | 1,733 | Jan 7, 2020, and May 29, 2020 | Median follow-up time was 186·0 (175·0 –199·0) days | 57 years (median) 48% female | • 76% reported persistent symptoms, Fatigue or muscle weakness (63%) and sleep difficulties (26%) and anxiety or de-pression (23%) were the most common symptoms |
| | Xiong et al. (2020)[20] | Hospitalized patients | 538 | Discharged before 1 March 2020 | 3 months after dis-charge from hospital | 52 years 54.5% female | • 49.6% one or more general symptoms<br>• 28.3% reporting physi-cal decline or fatigue |

# Annex 1

| COUNTRY | STUDY | SETTING | NUMBER OF CASES INCLUDED | STUDY PERIOD | TIME WINDOW | AGE (YEARS) FEMALES % | RESULTS |
|---|---|---|---|---|---|---|---|
| **United States** | Chopra et al. (2020)[21] | Hospitalized patients | 488 | 16 March and 1 July 2020 | Patients alive 60 days after discharge | 62 years 48.2% female | • 32.6% Cardiopulmonary symptoms (such as cough and dyspnea) |
| | Tenforde et al. (2020)[22] | Hospital outpatients (out of which 7% were hospitalized) | 292 | April 15–June 25, 2020 | 14–21 days after the test date | 18-50 years 52% female | • 35% had symptoms after a median of 16 days after testing positively for SARS-CoV-2 infection<br>• 26% of interviewees aged 18–34 years,<br>• 32% aged 35–49 years,<br>• 47% aged ≥50 years • fatigue (71%), cough (61%), and headache (61%) |
| | Taquet el al (2020)[23] | Global federated network that captures anonymised data from electronic health records | 44 779 no previous psychiatric illness and who were alive | Jan 20, and Aug 1, 2020 | First 14 to 90 days after a diagnosis of COVID-19 | 49.3 years 54.9% female | • 18.1% Psychiatric illness<br>• The most common psychiatric diagnosis after COVID-19 diagnosis was anxiety disorder (12.8%, 95% CI 12.4–13.3), followed by mood disorders (9.9%, 9.5–10.3)<br>• This finding appears robust, being observed in all age strata and in both sexes |
| **Egipt** | Kamal et al. (2020)[24] | Hospital outpatients | 287 | - | - | 32.3 years 64.1% female | 89.2% post Covid-19 manifestations (72.8% fatigue, 38% anxiety, 31.4% joints pain) |
| **Mexico** | Galvan -Tejada et al. (2020)[25] | General population | 141 | 25 July to 20 September 2020 | 25 July to 20 September 2020 | 39 years 51% female | 98.4% have at least one symptom |
| **Australia** | Horvath et al. (2020)[26] | General population | 102 | February and April 2020 | February and April 2020 | 45 years 60% female | • 11% hiposmia and anosmia<br>• 17.6% dysgeusia |
| **Spain** | Moreno -Pérez et al. (2020)[27] | Hospital outpatients (out of which 58% were hospitalized) | 277 | 27th February to 29th April 2020 | 27th February to 29th April 2020 | 56 years (median) 47.3% female | • 50.9% Post-acute COVID-19 syndrome<br>• 34.8% fatigue<br>• 34.4% Dyspnea, Persistence<br>• 21.4% Anosmia-dysgeusia<br>• 21.3% Cough, Persistence<br>• 19.6% Myalgias-arthralgias |
| **US, UK, Australia, Austria, Italy, France, Ireland, Egypt, China, Mexico** | López-León et al (2021) Meta-Analysis[28] | | 47,910 patients were included (15 publications) | | | | It was estimated that 80% (95% CI 65-92) of the patients that were infected with SARS-CoV-2 developed one or more long-term symptoms |

# Annex 1

## Table 2. Symptoms prevalence in different prospective and retrospective studies.

| Article | Prospective/retrospective cohorts (percentage values of different symptoms) | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Fatigue Weight Lack of appetite | Fever | Chest Pain | Dyspnea Cough | Arrhythmia [palpitations] Myocarditis Pericarditis | Arthralgia Arthritis Myalgia | Scl Sicca | Skin lesions Aphtas Hair loss | Abd dyscomf Diarrhea | Cytopenia Thrombos | Endocrino disorders | Anosmia Disgeusia | Headache dizziness Paresthes | Sore throat Hearing loss tinnitus | Visual Impairment Red eyes | Brain Fog Sleep D | Dysauto nomia | Mental Health Psyq morb |
| Carfì [18] N143 | 50/-/<10 | | 25 | 40/18 | | 25/-/<10 | 15 | | -/<5 | | | 15/10 | 10/5/- | <10/-/- | -/10 | | | |
| Zhao [43] N 55 | 16.4/-/- | | | 15/2 | | | | | 30.9/- | | | | 18/-/- | | | | | |
| D ' Cruz [8] N 119 | 68/-/- | | 23 | 32/7 | | 50 (general) | | | | | | | | | | -/57 | | 18-24 |
| Garrigues [17] N 120 | 55/-/- | | 11 | 42/17 | | | | -/-/20 | | | | 13/11 | | | | 34/31 | | |
| Helpin [12] N 100 | 66/-/- | | | 54/18 | | ~25 (pain) | | | | | | | | ~10/-/- | | ~25/- | 3 (continence) | ~25 |
| Carvalho Schneider [16] N 150 D30 | 36/16 | 3.6 | 18 | 11/- | -(6.5)/-/- | 10/-/36 | | 15.4/-/- | 17.3/8.7 | | | 28 (both) | 36/-/- | | | | | |
| Carvalho Schneider [16] N 150 D60 | 21.5/17 | 0 | 13 | 8/- | -(11)/-/- | 16/-/21.5 | | 11.5/-/- | 11.5/4 | | | 23 (both) | 21.5/-/- | | | | | |
| Goërtz (47) N 2113 | 95/18.4 | 43 | 61 | 90/68 | -(55)/-/- | 38.2/-/65 | | 5.6/-/- | -/41.1 | | | 40/42.3 | 76/52/- | 62/-/- | 25.7 (general) | | 26 | |
| Huang [19] N 1733 | 63/-/8 | <1 | 5 | 26 (mMRC≥ 1) | -(9)/-/- | 9/-/2 | | 3/-/22 | -/5 | | | 11/7 | 2/6/- | 4/-/- | | -/26 | | 23 |
| Davis [48] N 3762 | 80/-/14 | <1 | 33 | 38/20 | -(43)/-/- | 35/-/44 | | 10/-/- | 20/20.5 | | 20 (menstrual disorders) | 25.2(both) | 50/38/20 | 20/<5/26.2 | 15/- | 58/45 | 10 (continence) | >50 |
| Dennis [49] N 201 | 98/-/- | 75 | 73 | 87/74 | -/11/- | 78/-/88 | | | 54/60 | | | | 83/40/- | 71/-/- | | | | |
| Petersen [50] N 180 | 28/-/3 | 0 | 5 | 8/10 | | 10/-/8 | | 3/-/- | -/3 | | | 23/15 | 8/-/- | 3/-/- | | | | 23 (global) |
| Xiong [20] N 538 | 28/-/- | | 12.3 | 21.4/7.1 | 11.2/-/- | 7.6/-/4.5 | | -/-/29 | | 7.3 (lymphopenia) | | | -/2.6/- | 3.2/-/- | | -/18 | 23.6(sweat | 4.3 depressi, 6.5 anxiety |
| Mandal [11] N 384 | 69/-/- | | | 53/34 | | | | | | | | | | | | -/61-93 | | |
| Rauch [51] N127 | 25/-/- | | 2 | 30/6 | | | | | -/4 | | | 19 (global) | 9/8/4 | | | 16/15 | 6 | 10 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Logue (52) N177 | 14/-/- | <1 | | 10/<5 | | 10 (global) | | <1/-/- | -/<5 | | | 13.6 (global) | 5/-/- | | | | <5 (sweat) | |
| Arnold (9) N110 | 40/-/- | 1 | 15 | 40/10 | | 5/-/25 | | | 2/1 | | | 10/- | 2/-/- | | | -/30 | | |
| Moreno-Perez (27) N 277 | 35/-/- | 0 | | 34/21 | | 20 (global) | | 8 | -/11 | | | 21.4 (global) | 18/-/- | | 5.4/- | 15.2/- | | |
| Evans (14) N1077 | 56.2/-/- | | | 48.1/- | | 38.7 pain (global) | | | | | | | | | | 17/41.8 | | 25/12 |
| Nehme (15) N 669 | 15/-/- | 0 | | 10/5 | | | | | 2 (global) | | | 10 (global) | 2/-/- | | | | | |
| Sykes (10) N 134 | 39.6/-/- | 10.4 | 17.9 | 59.7/35.1 | | -/-/51.5 | | 8.2/-/- | | | | 9.7/9 | | 12.7/-/- | | 9.7/35.1 | | 39.6/47.8 |
| Sudre (6) N 4182 | 68/-/13 | 12 | 23 | 37/27 | | -/-/20 | | | 15/15 | | | 39/- | 40/-/- | 27/-/- | | | | |
| ONS (5) N 8193 | 11.5/-/- | 6.7 | | 4.6/11.4 | | -/-/7.9 | | | 2.2/2.7 | | | 7.9/8.2 | 10.1/-/- | 6.7/-/- | | | | |
| SEMG (3) N 1834 | 95.9/-/- | | 49 | 79.3/- | 69.9/-/- | 57/-/82.8 | 65.8 | -/-56.2 | -/70.8 | 38.4 (haematoma) | | 40/- | 86.5/43/42 | | 56.8 (pruritus | 48/- | | 57/- |
| Media ponderada | 51.63/14.08/11.52 | 10.0 | 30.07 | 33.18/22.37 | 42.33/11.00/- | 33.60/-/27.95 | 62.13 | 7.15/-/37.68 | 9.97/17.10 | 33.02 | 20.00 | 22.23/16.41 | 33.27/33.80/26.70 | 18.88/5/26.20 | 27.10/45.25 | 44.78/39.37 | 15.73 | 40.67/15.96 |

# Annex 2. Follow-up and clinical management

## Table 3. Recommended Diagnostic Tests.

| | Fatigue | Fever | Chest pain Palpitation | Dyspnea Cough | Arthralgia Arthritis | Myalgia | Abdominal Pain Diarrhoea Jaundice | Skin Lesion Aphtous Sd Sicca | Cytopenia | Thrombosis | Headache | Neurocg | Mental Health |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blood Pres<br>Heart Rate<br>Sat O2 | X | X | X | X | | | X | | | X | X | | |
| CRP/ESD | X | X | X | X | X | X | X | X | X | X | X | X | |
| Renal, Electrolytes | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hepatic(H)<br>Pancreatic (P) ; amilase, lipase | H | H | H | H | H | H | H & P | H | H | H | H | H | H |
| TSH/T4<br>Vit D | X | | X | X | X | X | X | X | X | | X | X | X |
| Cortisol | X | | | | | X | | | | | | | |
| Tni, NTproBNP | X | | X | X | | | | | | X | | | |
| CPK, Aldolase | X | | X | | | X | | | | | | | |
| Protein, Albumin, Proteinogr | X | | | | X | X | | X | X | X | X | X | X |
| Folic, B12, iron | X | | | | X | X | X | X | X | X | X | X | X |
| Haemogram | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Coagulation (D dimer) | X | X | X | X | | | X | | X | X | X | | |
| AI profile | ANA | Depend | | | ANA/FR/CCP | ANA/FR | Anti transglut | ANA/FR | ANA/FR | | | | |
| Urinary sediment<br>Prot/Creat (Q) | X | X | | | X (Q) | X (Q) | | X (Q) | X (Q) | | | | |
| Stool<br>- Stool cultural (SC)<br>- Clostridioides (Cx)<br>- Parasites (P)<br>- Fecal occult Blood (FOB) | | | | | | | SC, Cx (if ATB), P, FOB | | | | | | |
| ECG | X | | X | X | | | | | | X | X | | |
| Radiography | Tx | Tx | Tx | Tx | Hands, Feet | | | | | | | | |
| US | | | PoCUS | BLUE | Joint | | Abdominal (pain) | | | Lower Limb (DVT) | Temporal | | |
| CT | | | CT angiography | Angiography CT<br>High resolution CT | | | | | | | Head | Head | |
| Spirometry | | | | X | | | | | | | | | |
| Endoscopy | | | | | | | X | | | | | | |

Highly recommended
Moderately recommended

# Annex 2

## Table 4. Pulmonary algorithms.

### Respiratory symptoms

| DYSPNEA (33%) |
|---|
| **DEFINITION**: Persistence of lack of breath > 4 weeks after COVID19 infection |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Vital signs AND auscultation: crackles, SaO2<br>• Characteristics of dyspnea<br>• Associated Symp: chest pain, fatigue, cough |
| **INITIAL TESTS**<br>• Blood test: CRP, electrolytes, renal function, Haemogram. Coagulation<br>• Chest X-ray<br>• Forced Espirometry |
| CONSIDER:<br>- Complete pulmonary function tests<br>- Thoracic HRCT scan and/or angio-CT scan<br>- Exercise test<br>- Ecocardiography |

**WHEN to refer for HOSPITAL assessment**

- Respiratory failure defined as SaO2 < 93%
- Restrictive pattern
- Interstitial Lung disease
- Persistence of dyspnea with unclear origin

**Emergency**
**Respiratory Medicine**
**Internal Medicine**

## Table 5. Extra-pulmonary algorithms

### Fatigue

| FATIGUE 51.6% |
|---|
| **DEFINITION**: Prolonged tiredness or exhaustion for no justifiable reason |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Vital signs (blood pressure, heart-rate, Tª) and oxygen saturation<br>• Weight and appetite<br>• Adenopathies, visceromegaly and other data suggestive of tumoural etiology<br>• Chest pain, dyspnoea<br>• Neurologic symptoms<br>• PCFS: Post-COVID19 Functional Status Scale |
| **BLOOD TESTS**<br>• CRP, ERD<br>• Biochemistry: electrolytes, renal function, liver profile, TSH/T4, cortisol, Vit D<br>• Nutritional and muscle profile: Prot, Alb, CPK, LDH, Aldolasa, proteinogram, folic, B12, iron metabolism<br>• Haemogram |
| **RULE OUT** chronic fatigue syndrome (CFS) and fibromyalgia (FM) and, cardio-pulmonary or neurologic etiology |

**WHEN to refer for HOSPITAL assessment**

- CFS +/- FM diagnosis
- Fatigue + **RED FLAGS**: ***hyporexia, weight loss, fever, adenopathies+/- visceromegaly, chest pain, dyspnoea, focal neurologic déficits, swealling of joints***

!

- **Internal Medicine**
- **CFS/FM Unit**
- **Chronic Pain Unit**
- **Rehabilitation**

# Annex 2

## Musculo-skeletal symptoms

| ARTHRALGIAS AND ARTHRITIS 33.2% |
|---|
| **DEFINITION**: Pain (arthralgia) or swelling (arthritis) that may affect one or more joints, leading to functional limitation |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Number of joints: mono, oligo, polyarthralgias<br>• Which joints, symmetry<br>• Inflammatory signs: edema, joint pain or heat |
| **BLOOD TESTS**<br>• CRP, ERD<br>• Biochemistry: electrolytes, renal function, liver profile, uric, TSH/T4<br>• Haemogram. Coagulation<br>• Immunological P: ANA (IFI Hep2), RF/CCP, dsDNA-Ab/C<br>• Urinary sediment. Prot/Creat |
| **RADIOLOGICAL STUDIES**<br>• Rx hands, feet, and other depends on symptoms<br>• Ultrasonography |
| **RULE OUT** chronic fatigue syndrome (CFS), fibromyalgia (FM) or possible autoimmune systemic disease |

| MYALGIAS 40.5% |
|---|
| **DEFINITION**: Muscle pain that may be associated with a feeling of weakness |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Distribution: proximal and/or distal<br>• Muscular strength<br>• ICU previous (severe COVID19)<br>• Physical deconditioning |
| **BLOOD TESTS**<br>• CRP, ERD<br>• Biochemistry: electrolytes, renal function, liver profile, TSH/T4<br>• Nutritional and muscle profile: Prot, Alb, CPK, LDH, Aldolasa, proteinogram, folic, B12, iron metabolism<br>• Haemogram. Coagulation<br>• Immunological P: ANA (IFI Hep2)<br>• Urinary sediment. Prot/Creat |
| **EMG**: In case of weakness and/or increase of CPK/Ald |
| **RULE OUT** CFS/FM, drugs (statins, antibiotics, etc), physical deconditioning or probably myopathy of the critically ill patient |

**WHEN to refer for HOSPITAL assessment**

- CFS and FM Diagnosis
- Recurrent swealling joints
- Myalgia + weakness + CPK/Ald high
- Gout
- ANA≥ 80, FR/CCP positive

- **Internal Medicine (Systemic Autoimmune Diseases (SAD) Unit)**
- **Rheumatology**
- **Chronic Pain Unit**
- **Rehabilitation Unit**

ANA: antinuclear antibodies, RF: rheumatoid factor, CCP: anti-cyclic citrullinated peptide, dsDNA-Ab: Anti-DNA antibody, C: Complement

## Skin & Mucosa Lesions, Hair Loss

| SKIN & MUCOSA LESIONS 7.1% |
|---|
| **DEFINITION**: Some patients may present skin lesions after acute COVID19 such as rashes (erythema, urticaria, purpura, etc.) as well as oral mucosal lesions (aphthae) |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Skin and mucosal exploration. Associated adenopathies<br>• Sicca syndrome: xerostomia, xerophthalmia, xeroderma<br>• Pruritus<br>• When?: before, during and/or after COVID19 (recurrent aphthous stomatitis) |
| **BLOOD TESTS**<br>• CRP, ERD<br>• Biochemistry: electrolytes, renal function, liver profile, TSH/T4<br>• Nutritional profile: Prot, Alb, folic, B12, iron metabolism<br>• Haemogram<br>• Immunological P: ANA (IFI Hep2), dsDNA/C, RF, anti-tissue transglutaminase antibodies<br>• Serology: HIV, syphilis, HBV, HCV, HSV, CMV, EBV, Parvovirus-B19 |
| **RULE OUT** vitamin deficiency, other infection, immune-mediated conditions, drugs |

| HAIR LOSS 23.5% |
|---|
| **DEFINITION**: Many people have a hair loss as part of the stress of the infectious event, so-called telogenic effluvium. |
| **PHYSICAL EXPLORATION**<br>• Distribution: diffuse, localized<br>• Other symptoms: pruritus, dermatitis |
| **BLOOD TESTS**<br>• Biochemistry: electrolytes, renal function, liver profile, TSH/T4<br>• Nutritional profile: Prot, Alb, folic, B12, iron<br>• Haemogram |
| **RULE OUT** hormonal disorder. |

**WHEN to refer for HOSPITAL assessment**

- Recurrent/persistent skin lesions or aphthous stomatitis
- Hair loss that not improve
- Infectious or probably AI disease

**Dermatology**
**Internal Medicine**
***Infectious diseases unit (HIV, Lues)**
***SAD unit (sicca, aphtous, rash, etc)**

# Annex 2

## Cardiovascular Signs & Symptoms

| CHEST PAIN 34.1% |
|---|
| **DEFINITION**: Chest complaints for longer than 4 weeks. |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Vital signs (blood pressure, heart-rate, Tª and oxygen saturation)<br>• Characteristics of chest pain: oppressive, pleuritic, irradiated<br>• Associated symptoms: dyspnoea, sweating, dizziness, pale skin, cough, fever<br>• Cardiopulmonary auscultation: Heart sounds, crackles<br>• Other signs: venous ingurgitation, lower limbs oedema |
| **BLOOD TESTS**<br>• CRP, ERD<br>• Biochemistry: electrolytes, renal function, liver profile<br>• Cardiological parameters: TnI, CPK, NT-proBNP<br>• Haemogram. Coagulation (D Dimer)<br>• Immunological Parameters (ONLY SEROSITIS): ANA (IFI Hep2) |
| **ECG:** repolarization changes, heart blocks, hypertrophy, arrhythmias. |
| **THORAX RADIOGRAPHY (US):** Interstitial pattern, vascular redistribution (heart failure), pleural or pericardial effusion, pulmonary mass |
| **RULE OUT:** myocardial infarction, heart failure, pulmonary hypertension, pulmonary embolism or serositis |

| ARRHYTHMIA (or palpitations) 35% |
|---|
| **DEFINITION**: perception of fast or slow heartbeat. |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Vital signs (blood pressure, heart-rate, Tª and oxygen sat)<br>• Frequency, triggering factor (effort, orthostatism)<br>• CP auscultation: murmurs, premature complexes |
| **BLOOD TESTS**<br>• Biochemistry: electrolytes, renal function, liver profile, TSH/T4<br>• Cardiological parameters: TnI, CPK, NT-proBNP<br>• Haemogram. Coagulation (D Dimer in case of tachycardia) |
| **ECG:** repolarization changes, heart blocks, hypertrophy, arrhythmias, premature complexes |
| **THORAX RADIOGRAPHY (US):** Interstitial pattern, vascular redistribution (heart failure), pleural or pericardial effusion, pulmonary mass/nodule |
| **HOLTER**: heart rate variability |
| **RULE OUT:** extreme bradycardia (BC), frequent supraventricular or ventricular extrasystole, atrial fibrillation (AF) or flutter, ventricular tachycardia (VT) or fibrillation (VF) |

**WHEN to refer for HOSPITAL assessment**

- Myocardial infarction
- Heart failure
- Suspicion of Pulmonary hypertension
- Suspicion of Pulmonary embolism
- Serositis
- Extreme BC, AF or flutter, VT, VF

**Emergency**
**Cardiology**
**Pneumologist**
**Internal Medicine**

## Gastroenterological and Hepatic symptoms

| DIARRHOEA (+/- abdominal pain and vomiting) 24.5% |
|---|
| **DEFINITION**: Intestinal disorder characterized by frequent and loose bowel movements. |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Vital signs (arterial pressure, fever)<br>• Characteristics of diarrhea: episodic, blood or mucus in stools<br>• Associated Symp: abdominal pain, alternating with constipation, weigh loss<br>• Symptoms suggestive of food intolerances or malabsorption |
| **BLOOD TESTS**<br>• CRP, ERD<br>• Biochemistry: electrolytes, renal function, liver profile, amylase and lipase<br>• Nutritional profile: Prot, Alb, folic, B12, iron<br>• Haemogram. Coagulation<br>• Immunological Parameters: anti-tissue transglutaminase antibodies |
| **STOOLS:** stool culture, parasites, *clostridioides difficile* toxin, blood test |
| **COLONOSCOPY** |
| **RULE OUT:** food intolerances, celiac disease, malabsorption syndrome, inflammatory bowel disease, infectious colitis or parasitosis, drugs (dysbacteriosis) |

| HEPATITIS |
|---|
| **DEFINITION**: inflammation of the liver, characterized by jaundice, elevated transaminase levels and weakness |
| **ANAMNESIS AND PHYSICAL EXPLORATION**<br>• Risky sexual behaviors, travels, drugs (antibiotics, anti-inflammatory drugs, etc), alcohol abuse, tick bite, etc<br>• Jaundice, hepatomegaly, choluria, acholia, pruritus, encephalopathy |
| **BLOOD TESTS**<br>• CRP<br>• Biochemistry: electrolytes, renal function, liver profile (cytolysis +/- cholestasis), Prot, Alb, LDH, TSH/T4<br>• Haemogram. Coagulation<br>• Serology: HIV, HBV, HCV, HAV, HEV, syphilis, CMV, EBV, HSV<br>• Immunological: ANA. Proteinogram (gammaglobulins) |
| **Abdominal US:** biliary tract disorders, spleno-portal axis, hepatic nodule(s), ascites |
| **RULE OUT:** other viral hepatitis, autoinmune liver diseases, DILI, biliary tract disease |

DILI: Drug-induced Liver Injury

**WHEN to refer for HOSPITAL assessment**

- Chronic Diarrhoea ( ≧ 4 weeks) or inflammatory ≧ 2weeks
- Blood or mucus in stools
- Oral intolerance
- Abdominal pain that disturbs sleep
- AST or ALT > 3x ULN (persistent) +/- coagulopathy
- HIV, HBC, HCV, syphilis verified
- Data suggesting autoimmune hepatitis
- Biliary tract complications

**Emergency**
**Gastroenterologist**
**Hepatologist**
**Surgeon**
**Internal Medicine**

# Annex 2

## Smell and Taste Loss, Headache

**SMELL DISTURBANCES 27.5%**

**DEFINITION**: Smell disturbances are very frequent not only at the onset of infection, but may also persist in the long-term.

**ANAMNESIS AND PHYSICAL EXPLORATION**

- Chronology
- Changes in follow-up
- **RULE OUT:** Drugs (cocaine), traumatism, allergic rinitis, polips, previous nasal surgery, smoking, brain tumour.

**TASTE DISTURBANCES 24.7%**

**DEFINITION**: Taste disturbances are very frequent not only at the onset of infection, but may also persist in the long-term.

**ANAMNESIS AND PHYSICAL EXPLORATION**

- Chronology
- Changes in follow-up
- RULE OUT: tongue lesions, smoking.

**HEADACHE 44.9%**

**DEFINITION**: A pain located in the head, as over the eyes, at the temples, or at the base of the skull.

**PHYSICAL EXPLORATION**

- Chronology and pain location
- Other symptoms: vomiting, fever, loss of strength and sensitivity, seizures, sleep-disrupting headache, pulse and pain temporal arteries, temporo-mandibular joint pain

**BLOOD TESTS**

- CRP, ERD if > 50 years (Giant Cell Arteritis)
- Biochemistry: electrolytes, renal function, liver profile, TSH/T4
- Nutritional profile: Prot, Alb, folic, B12, iron
- Haemogram

**CRANIAL CT**

**RULE OUT** meningeal signs, neurologic manifestations, visual acuity changes, sleep apnea, Giant Cell Arteritis

**WHEN to refer for HOSPITAL assessment**

- Severe or recurrent headache that does not improve with analgesics or disturbs sleep
- Neurological symptoms associated
- Suspicion of Giant Cell Arteritis

**Emergency**
**Neurology**
**Internal Medicine**

## Neurocognitive, dysautonomia and Neuropsychiatric dysfunction

**NEUROCOGNITIVE DYSFUNCTION 49.9 (50%)**

**ANAMNESIS AND PHYSICAL EXPLORATION**
Concentration and memory disorders, language impairment, troubles in routine tasks.

**BLOOD TESTS:**

- Biochemistry: electrolytes, renal function, liver profile, TSH/T4
- Nutritional profile: Prot, Alb, folic, B12, iron, proteinogram
- Haemogram
- Serology: HIV, syphilis, HBV, HCV, HSV

**DYSAUTONOMIA 15.7%**

**ANAMNESIS AND PHYSICAL EXPLORATION**
POTS, inappropriate sinusal tachycardia, hyperhidrosis and sphincter dysfunction.

**EMG, HOLTER AND TILT TABLE TEST**

**NEUROPSYCHIATRIC DYSFUNCTION 42.4%**

**ANAMNESIS AND PHYSICAL EXPLORATION**
Dysthymia/depression, anxiety, emotional lability, psychotic disorder, post-traumatic stress syndrome.

**BLOOD TESTS: Same studies**

**WHEN to refer for HOSPITAL assessment**

Severe or moderate neurocognitive dysfunction that affecting quality of life → **Neurologist**, **Internal Medicine (in case of infectious disease)**

Suspicion of dysautonomia and compatible EMG → **Neurologist**

Severe or moderate neuropsychiatric disorders that affecting quality of life → **Emergency**, **Psychology and psychiatry**

# Annex 2

## Miscellany

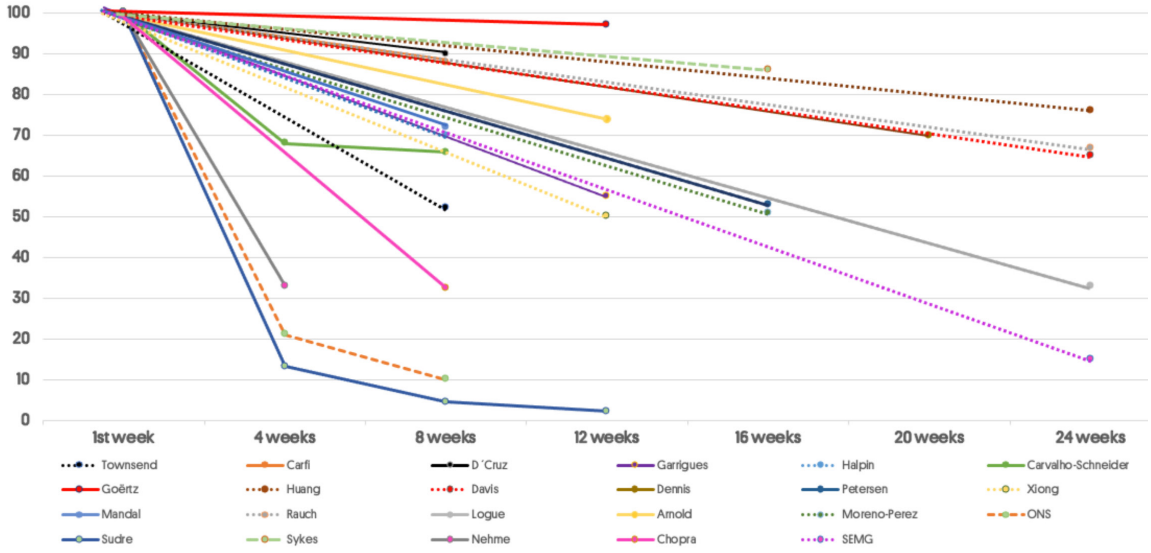
| | WHEN to refer for HOSPITAL assessment | |
|---|---|---|
| **EYE SYMPTOMS AND VISION 10-18.2%**<br>**Red eye, photopsias, myodesopsias, loss of visual acuity, metamorphopsia** | • Severe or acute visual loss<br>• Metamorphopsia<br>• Acute and recurrent photopsias | • **Emergency (amaurosis)**<br>• **Ophthalmologist** |
| **HEARING LOSS AND VESTIBULAR SYMPTOMS 5-26.1%**<br>**Hypoacusia, tinnitus, dizziness, nistagmus**<br>**Odynophagia, dysphagia, dysphonia, dyspnea** | • Severe or acute hearing loss<br>• Severe or recurrent dizziness<br>• Dysphagia, Dysphonia, dyspnea | • **Emergency**<br>• **ENT specialist** |
| **HAEMATOLOGICAL/THROMBOSIS 7.3/2.5**<br>**Cytopenias: anaemia, leukopenia, thrombopenia**<br>**Deep vein thrombosis, pulmonary embolism, arterial ischemia** | • AHAI, Leuko <3.000, PLat <100.000<br>• Venous thromboembolism<br>• Acute arterial Ischemia | • **Emergency**<br>• **Haematologist**<br>• **Internal Medicine/Pneumologist** |
| **ENDOCRINOLOGICAL DISORDERS**<br>**Diabetes mellitus, thyroiditis, menstrual cycle disorders, erectile dysfunctions, bone demineralization** | • Thyrotoxic storm<br>• Menstrual cycle disorders<br>• Erectile dysfunctions<br>• Bone demineralization | • **Emergency**<br>• **Gynaecologist**<br>• **Urologist**<br>• **Rheumatologist** |

## Sequelae

| | | |
|---|---|---|
| **POST SEVERE COVID**<br>Patients after hospital admission with target organ damage as part of the systemic inflammatory response. | • Persistent interstitial lung disease, bronchiectasis<br>• Myocarditis<br>• Chronic Renal Disease<br>• Myopathy & Neuropathy (critically ill patient) | • **Pneumologist**<br>• **Cardiologist**<br>• **Nephrologist**<br>• **Rehabilitation** |
| **THROMBOTIC OR HAEMORRHAGIC COMPLICATIONS**<br>Sequelae arising from post-thrombotic or haemorrhagic complications occurring within the acute phase or at least within 4 weeks. | • Stroke<br>• Myocardial infarction<br>• Arterial ischaemia<br>• Thromboembolic events | • **Neurologist**<br>• **Cardiologist**<br>• **Haematologist (thrombophilia)**<br>• **Internal Medicine**<br>• **Pneumologist**<br>• **Rehabilitation** |
| **IMMUNE-MEDIATED PHENOMENA**<br>Sequelae resulting from immune-mediated phenomena during the acute or post-acute phase. | • Acute polyradiculoneuritis (Guillain-Barre)<br>• Encephalitis<br>• Myelitis<br>• Systemic autoimmune diseases | • **Neurologist**<br>• **Rehabilitation**<br>• **SAD unit**<br>• **Rheumatologist** |
| **MIS-C and MIS-A**<br>Multisystemic inflammatory syndrome in children (MIS-C) and adults (MIS-A) characterised by hyperinflammation that can appear 3-4 weeks after viral infection, with high morbidity and mortality and significant risk of subsequent sequelae. | • Fever, increase acute inflammatory parameters<br>• Skin rash, mucocutaneous lesions<br>• Coronary disease<br>• Neurological symptoms<br>• Gastroenteric disease | • **Emergency**<br>• **Paediatrician**<br>• **Rheumatologist**<br>• **Internal Medicine (SAD unit)** |

# Annex 2

## Table 6. Follow up studies.



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