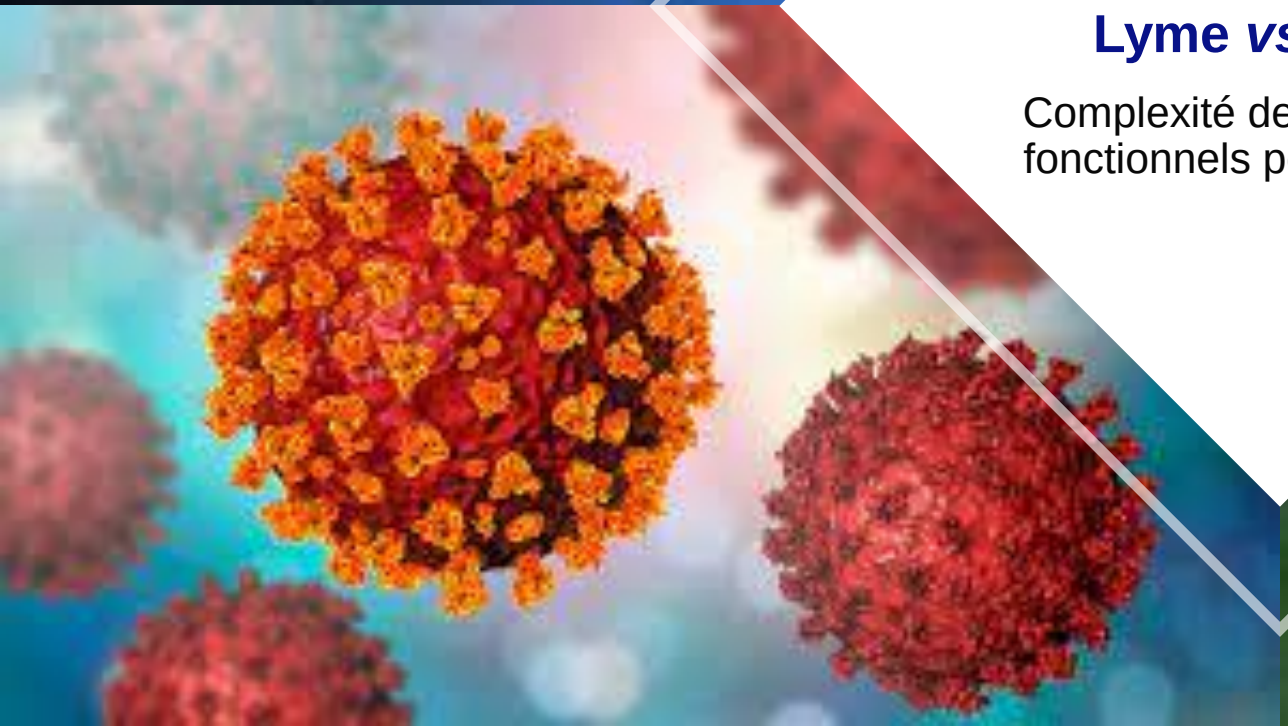
DIU Zoonose liées aux tiques

# Why is it taking so long?

## Lyme *vs* Covid

Complexité des syndromes fonctionnels post infectieux



Sophie Blanchi
Pauline Arias

# Syndromes fonctionnels post infectieux

- « Ensemble de symptômes causés par/associés à une infection et survenant après l'infection aiguë »
  - Construction sociale: entités nosologiques issues de l'expériences de patients,
  - Large spectre de symptômes médicalement inexpliqués ayant un impact sur la vie quotidienne des patients,
  - Bases physiopathologiques mal connues,
  - Difficultés de prise en charge pour le corps médical,
  - Conséquences socio-économiques.

- Multiples agents pathogènes avec syndrome post fonctionnels décrits:
  - EBV, HHV6, SARS-COV-1, MERS-COV, Ebola, C. jejuni, M. Pneumoniae…
  - Borrelia burgdorferi, SARS-COV-2

# Questions de recherche

1/Quelles définitions des syndromes post-Lyme et post-COVID-19?

2/ Existe-t-il des similitudes nosologiques entre ces deux syndromes?

# Axes de recherche

Physiopathologie

Symptômes et profil des patients

Imagerie Neurofonctionnelle

# Revue de la littérature: pubmed

| | Lyme | Covid |
|---|---|---|
| Mesch<br>Query box | Post-treatment Lyme Disease Syndrome<br>Post Lyme Disease Syndrome<br>Post-treatment Lyme disease syndrome[MeSH Terms]<br>Post-treatment Lyme disease symptoms[MeSH Terms]<br>(lyme disease[MeSH Terms]) AND (chronic disease[MeSH Terms] | Long-COVID<br>long-haul COVID<br>post-acute COVID syndrome<br>persistent COVID-19<br>long hauler COVID<br>post-acute sequelae of SARS-CoV-2 infection<br>chronic COVID syndrome<br><br>Query Box<br>"COVID-19" OR "SARS-CoV-2" AND "long-COVID" OR "post-acute COVID syndrome" OR "persistent COVID-19" OR "long-hauler COVID" OR « PASC » |
| Critères d'inclusion | Tout article<br>Diagnostic confirmé par sérologie ou clinique (EM) | Meta analyse, review, systematique review<br>Diagnostic confirmé par PCR |
| Critères exclusion | Population pédiatrique<br>Modèles animaux | Population pédiatrique<br>Symptômes post vaccinaux |
| Nombre d'articles | 546 | Query box 1,637<br>Query box AND « pathophysiology » 35<br>Query box AND « symptomes » 195 |

# Définitions multiples: « Lyme long »

- Avant 2006 : « **Chronic Lyme** » regroupant les BL disséminées tardives et les PTLDS.

- En 2006 : « **Post Treatment Lyme Disease Syndrome** » (PTLDS) définition de l'IDSA reprise par de nombreuses sociétés savantes dont la SPILF en 2006, l'European Federation of Neurological Societies 2010, les recommandations anglaises, suisses, allemandes, belges.

- En 2018 HAS : « **Symptomatologie/Syndrome persistant(e) polymorphe après une possible piqûre de tique** » (SPPT) => critiques

- En 2019 SPILF: « **Persistent symptoms after documented or suspected Lyme borreliosis** »

# Définitions multiples -> « PTLDS »

IDSA PTLDS (2006 Wormser)

**Inclusion criteria**

- An adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention.
- After treatment of the episode of Lyme there is resolution or stabilization of the objective manifestation(s) of Lyme disease.
- Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6 month period after completion of antibiotic therapy:
  - Fatigue
  - Widespread musculoskeletal pain
  - Complaints of cognitive difficulties
- Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities.

+ **Exclusion criteria** (fibromyalgia, chronic fatigue syndrome, sleep apnea … before LD

# Définitions multiples: Covid long

- Probable or confirmed SARS-CoV-2 infection (positive or negative SARS-CoV-2 test (PCR, Ag, serology)
- When none of these symptoms can be explained by another cause

- Mai 2020: NICE (British National Institute for Health and Care Excellence), CDC (center of disease control)
  - « …persistence of one or more initial symptoms **for at least 4 weeks** after onset…».

- Octobre 2021
  - NICE « …persistence of symptoms **for at least 12 weeks..**»
  - CDC: « The term "Post-COVID Conditions" is an umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present **four or more weeks** after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection »
  - WHO «… symptoms onset persist **at least two months**…».

# Définitions multiples: Covid long

OMS octobre 2021

- antécédents d'infection probable ou confirmée par le SARS-CoV-2,
- Généralement survenant dans les 3 mois après post-infection COVID-19 aiguë,
- symptômes persistant au moins 2 mois, ayant un impact sur le fonctionnement quotidien, et qui ne peuvent être expliqués par un autre diagnostic.
  - fatigue,
  - essoufflement,
  - dysfonctionnement cognitif,
  - autres symptômes
- d'apparition nouvelle après un rétablissement initial post infection COVID-19 aiguë,

OU persistant depuis la maladie initiale,

- fluctuant ou récidivant au fil du temps

| |
|---|
| Acouphènes et autres problèmes d'audition |
| Allergies nouvelles |
| Altération de l'odorat/du goût |
| Anxiété |
| Céphalées |
| Dépression |
| Douleurs abdominales |
| Douleurs articulaires |
| Douleurs thoraciques |
| Douleurs/spasmes musculaires |
| Étourdissements |
| Fièvre intermittente |
| Malaise après l'effort |
| Névralgies |
| Problèmes de menstruation et de règles |
| Problèmes gastro-intestinaux (diarrhée, constipation, reflux acide) |
| Sensations de piqûres d'épingles et d'aiguilles |
| Tachycardie/palpitations |
| Toux |
| Troubles de la mémoire |
| Troubles du sommeil |
| Vision trouble |

WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1

# Définitions multiples -> « PASC »

- Mars 2022: NICE Probable or confirmed SARS-CoV-2 infection (positive or negative SARS-CoV-2 test

Recommended

Use the following clinical case definitions to identify and diagnose the long-term effects of COVID-19:

**Acute COVID-19**

Signs and symptoms of COVID-19 for up to 4 weeks.

**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. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

In addition to the clinical case definitions, the term 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).

# Symptômes PTLDS

- Définition a priori des symptômes persistants :
  - Fatigue
  - Widespread musculoskeletal pain
  - Complaints of cognitive difficulties
- Subjectifs? Objectifs?
  - Quelles échelles?

NAME (or ID) ___ ___ ___ ___ ___ ___ Date: _____/_____/_____

**SYMPTOMS. During the past 2 weeks**, how much have you been **bothered** by any of the following?

| Rate "bother" for the past 2 weeks | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| 1. Shortness of breath | 0 | 1 | 2 | 3 | 4 |
| 2. Feeling feverish | 0 | 1 | 2 | 3 | 4 |
| 3. Sweats and/or chills | 0 | 1 | 2 | 3 | 4 |
| 4. Nausea and/or vomiting | 0 | 1 | 2 | 3 | 4 |
| 5. Back pain | 0 | 1 | 2 | 3 | 4 |
| 6. Headaches | 0 | 1 | 2 | 3 | 4 |
| 7. Stiff or painful neck | 0 | 1 | 2 | 3 | 4 |
| 8. Muscle aches or pains | 0 | 1 | 2 | 3 | 4 |
| 9. Joint pain or swelling | 0 | 1 | 2 | 3 | 4 |
| 10. Muscle weakness | 0 | 1 | 2 | 3 | 4 |
| 11. Feeling fatigued or having low energy | 0 | 1 | 2 | 3 | 4 |
| 12. Feeling worse after normal physical exertion | 0 | 1 | 2 | 3 | 4 |
| 13. Trouble falling or staying asleep | 0 | 1 | 2 | 3 | 4 |
| 14. Needing more sleep than usual | 0 | 1 | 2 | 3 | 4 |
| 15. Not feeling rested on awakening | 0 | 1 | 2 | 3 | 4 |
| 16. Numbness or tingling | 0 | 1 | 2 | 3 | 4 |
| 17. Shooting, stabbing or burning pains | 0 | 1 | 2 | 3 | 4 |
| 18. Skin or muscle twitching | 0 | 1 | 2 | 3 | 4 |
| 19. Discomfort with normal light or sound | 0 | 1 | 2 | 3 | 4 |
| 20. Balance problems or sense of room-spinning | 0 | 1 | 2 | 3 | 4 |
| 21. Change in visual clarity or trouble focusing | 0 | 1 | 2 | 3 | 4 |
| 22. Bladder discomfort or change in urination | 0 | 1 | 2 | 3 | 4 |
| 23. Light-headed or uncomfortable on standing | 0 | 1 | 2 | 3 | 4 |
| 24. Hot or cold sensations in extremities | 0 | 1 | 2 | 3 | 4 |
| 25. Irregular or rapid heart beats | 0 | 1 | 2 | 3 | 4 |
| 26. Feeling irritable, sad, or decreased pleasure | 0 | 1 | 2 | 3 | 4 |
| 27. Feeling panicky, anxious or worried | 0 | 1 | 2 | 3 | 4 |
| 28. Trouble finding words or retrieving names | 0 | 1 | 2 | 3 | 4 |
| 29. Trouble with memory | 0 | 1 | 2 | 3 | 4 |
| 30. Slower speed of thinking | 0 | 1 | 2 | 3 | 4 |

**Over the last 2 weeks, have any of the above impaired your work, social, or family functioning?** Yes No

**If Yes**, please indicate the number (#) of each of the most impairing symptoms below, **starting with the most impairing (#1)**, then list the next most impairing (#2) and continue listing in descending severity other impairing symptoms.

1. _____ 2. _____ 3_____ 4_____ 5_____ 6_____ 7_____

General Symptom Questionnaire (GSQ-30) Aucott, 2017

# Symptômes PTLDS

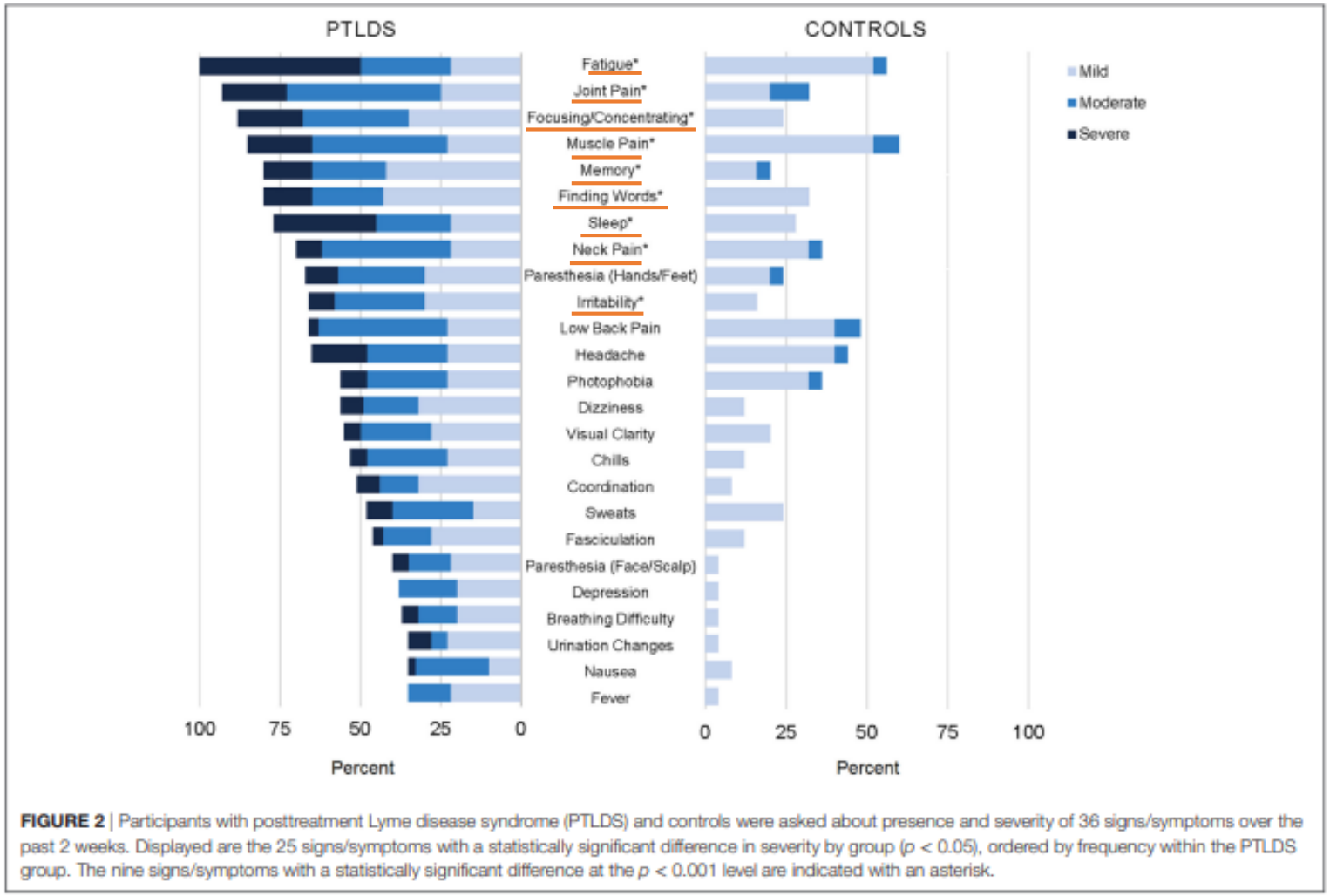
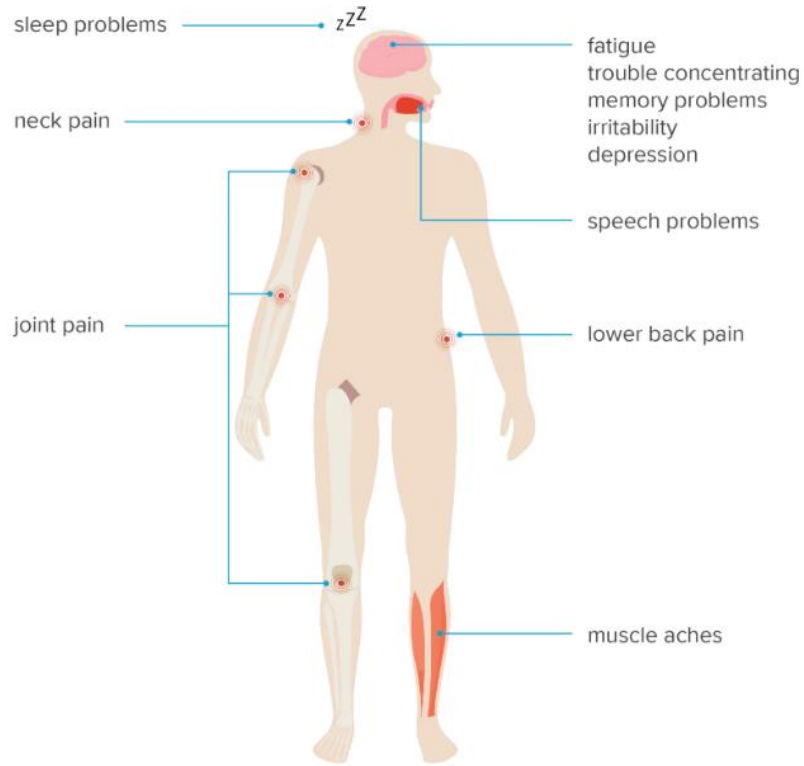



**FIGURE 2** | Participants with posttreatment Lyme disease syndrome (PTLDS) and controls were asked about presence and severity of 36 signs/symptoms over the past 2 weeks. Displayed are the 25 signs/symptoms with a statistically significant difference in severity by group ($p < 0.05$), ordered by frequency within the PTLDS group. The nine signs/symptoms with a statistically significant difference at the $p < 0.001$ level are indicated with an asterisk.

*(Rebman, 2017)*

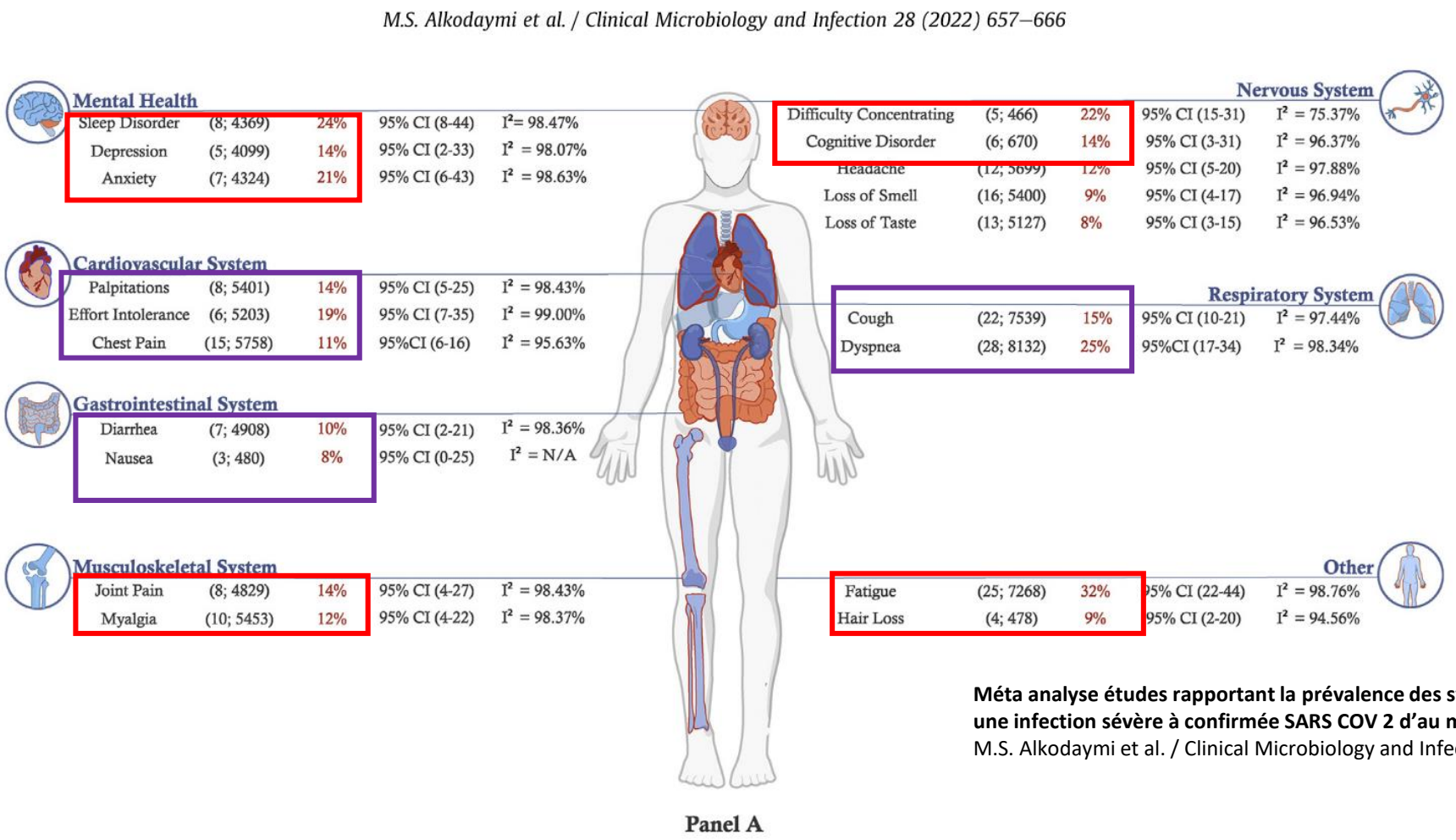
# Symptômes PTLDS

- Généraux
  - Fatigue : Symptôme le plus fréquent, sévère, différente du syndrome de fatigue chronique.
- Neurologiques
  - Troubles cognitifs : troubles de la mémoire, de la fluence verbale, de la concentration et de la formulation des idées.
  - Troubles sensitifs
  - Dépression
  - Troubles du sommeil
  - Cervicalgies
- Ostéo-articulaire
  - Myalgies
  - Arthralgies: migratrices, asymétriques et localisées dans les membres.




*(Bencke, 1995; Cairns, 2005; Berende, 2016; Turk, 2019; Cairns, 2020; Mac,2020; Rebman, 2021; Ursinus,2021; Aucott, 2022)*

# Symptômes PASC




**Méta analyse études rapportant la prévalence des symptômes persistant chez patients avec une infection sévère à confirmée SARS COV 2 d'au moins 50 patients suivis au moins 3 mois.**
M.S. Alkodaymi et al. / Clinical Microbiology and Infection 28 (2022) 657e666

*Dear et al, 10.1016/j.ebiom.2021.103722*

# Symptômes PASC

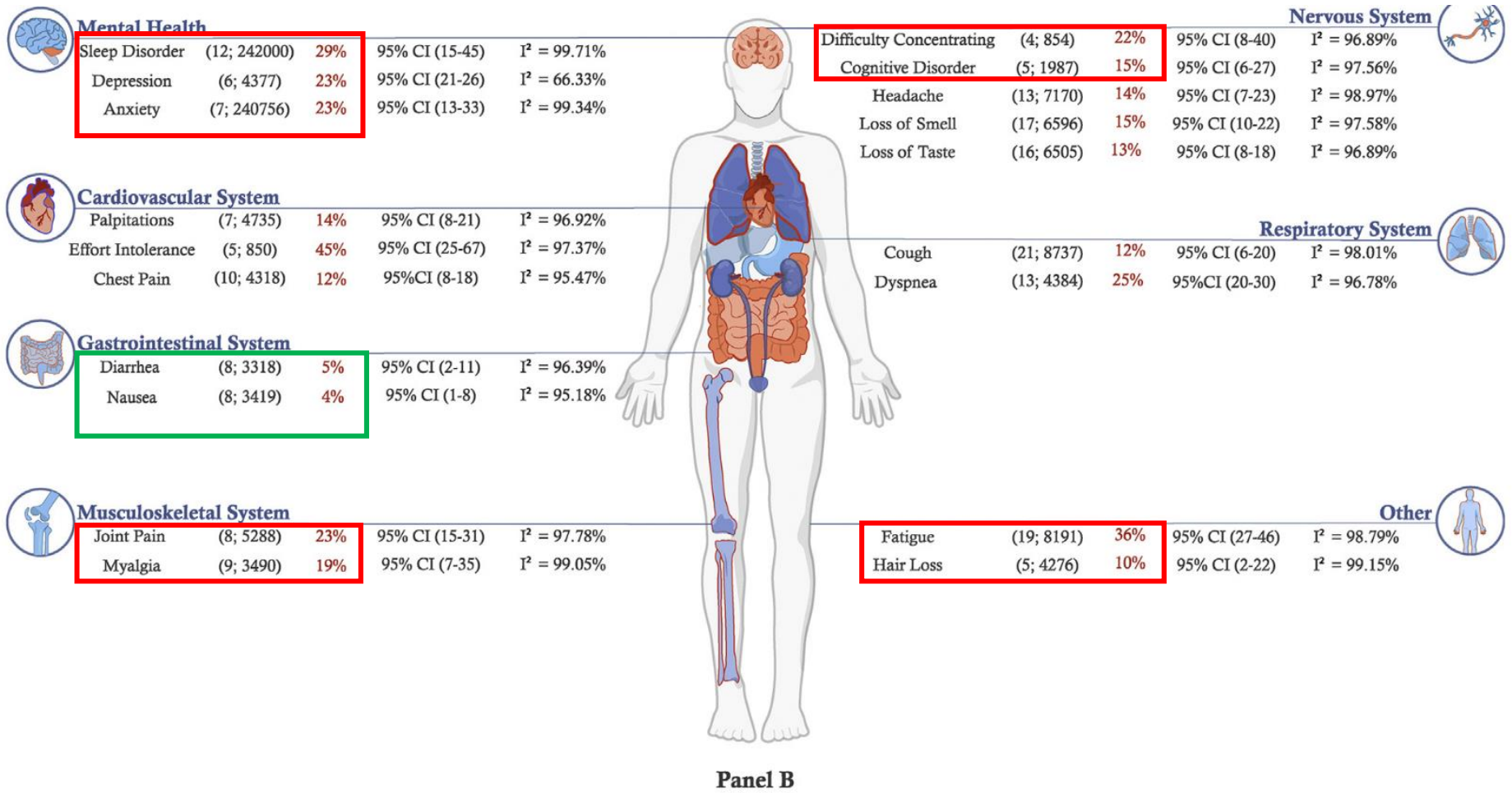



**Fig. 2.** Illustration of meta-analysis results with estimated prevalence of symptoms following acute COVID-19 infection across follow-up intervals of (A) 3 to <6 months and (B) 6 to <9 months (number of studies, size of population used to calculate point estimate).

# Symptômes PASC

- Pas de nombre limitant de symptômes
  - Fatigue,
  - Essoufflement,
  - Dysfonctionnement cognitif,
  - Autres symptômes

- Subjectifs? Objectifs?
  - Quelles échelles?

C19-YRS: 22-item patient-reported outcome measure designed to evaluate the long-term impact of COVID-19 across the domains of Activities and Participation of the International Classification of Functioning, Disability, and Health and evaluate the impact of PCS rehabilitation. O connor et al, 2022.

Post-COVID-19 Functional Status (PCFS) Scale :evaluation of PCFS Scale ability to detect functional limitations related to remaining symptoms and its correlation with quality of life using Short Form-36 (SF-36) and mental health and dyspnoea questionnaires in a cohort of patients 2–9 months after hospitalisation for COVID-19 hypoxemic pneumonia and analysed its

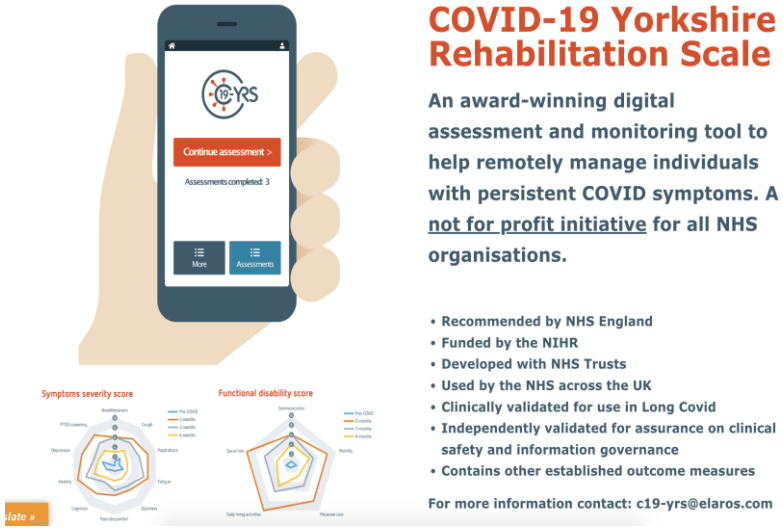
SBQ-LC Development and validation of the symptom burden questionnaire for long covid BMJ 2022 doi: https://doi.org/10.1136/bmj-2022-070230 (Published 27 April 2022)

WHO : Case report form for post covid condition

**Supplemental figure 1. French version of the PCFS scale**

| **A quel point la COVID-19 affecte-t-elle votre quotidien ?** **Veuillez indiquer laquelle de ces propositions se rapproche le plus de votre situation au cours de la dernière semaine.** *(Entourez le chiffre correspondant, si deux propositions vous semblent possibles, choisissez celle avec le chiffre le plus élevé)* | |
|---|---|
| Je n'ai pas de limitations dans ma vie de tous les jours, pas de **symptômes***, pas de douleurs, de signes d'anxiété ou de dépression en lien avec l'infection. | 0 |
| Je suis limité(e) de façon négligeable dans ma vie de tous les jours puisque je peux réaliser toutes mes tâches/activités habituelles, bien que persistent des **symptômes***, des douleurs, des signes d'anxiété ou de dépression. | 1 |
| Je suis limité(e) dans ma vie de tous les jours puisque je dois éviter ou réduire certaines activités/tâches quotidiennes, ou alors je suis obligé(e) de les répartir sur des périodes de temps plus longues en raison de **symptômes***, de douleurs, de signes d'anxiété ou de dépression. Je peux cependant réaliser toutes mes activités quotidiennes sans aucune aide. | 2 |
| Je suis limité(e) dans ma vie quotidienne puisque je ne peux pas réaliser les tâches et/ou activités habituelles en lien avec des **symptômes***, des douleurs, des signes d'anxiété ou de dépression. Je peux cependant prendre soin de moi-même sans aucune aide. | 3 |
| Je suis sévèrement limité(e) au quotidien : je ne suis pas capable seul(e) de prendre soin de moi, et je suis donc dépendant(e) de soins infirmier(e)s et/ou d'une tierce personne en raison de **symptômes***, de douleurs, de signes d'anxiété ou de dépression. | 4 |
| ***Les symptômes incluent, mais ne sont pas limités à : une dyspnée, une douleur, une fatigue, une faiblesse musculaire, une perte de mémoire.** | |

Benkalfate N, et al 2022




https://www.bsrm.org.uk/downloads/covid-19-yorkshire-rehabilitation-scale-jan2021-apbrochure-elaros-c19-yrs-brochure.pdf

World Health Organization

**Global COVID-19 Clinical Platform**

**Case Report Form (CRF) for Post COVID condition (Post COVID-19 CRF)**

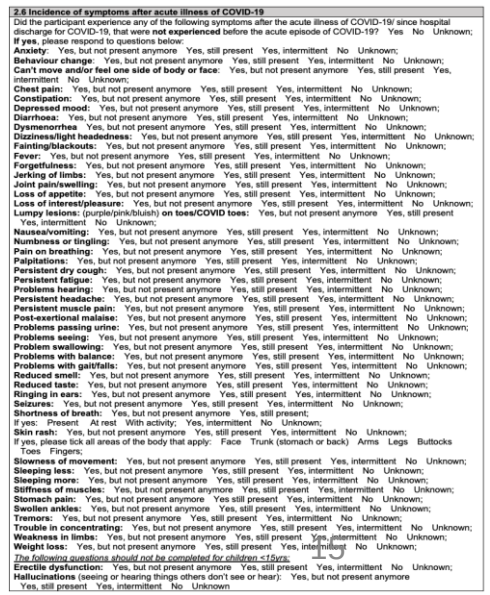
The WHO has established a Global Clinical Data Platform[1] of COVID-19 and invites all Member States and health facilities to report anonymised patient-level clinical information to the WHO platform using standardized Case Report Form (CRF):

- *Core CRF* captures clinical information of individuals hospitalized for COVID-19
- *Core-P CRF* has information of pregnant women hospitalized for COVID-19
- *MIS-CRF* has information related to multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19
- *Post COVID-19 CRF*, designed to build upon the Core CRF and assess the medium- and long-term sequelae of COVID-19

**The Post COVID-19 CRF includes 3 modules:**

**Module 1** includes background demographic and clinical information of the acute episode of COVID-19.
**Module 2** includes questions to help identifying patients who require further clinical evaluation.
**Module 3** includes medical assessment and results of examinations, tests, or diagnosis made during the follow up visit. Based on results, patients should be referred for clinical care, or rehabilitation as per national protocols.

https://cdn.who.int/media/docs/default-source/3rd-edl-submissions/who_crf_postcovid_feb9_2021.pdf?sfvrsn=76afd14_1&download=true


**2.6 Incidence of symptoms after acute illness of COVID-19**

Did the participant experience any of the following symptoms after the acute illness of COVID-19/ since hospital discharge for COVID-19, that were **not experienced** before the acute episode of COVID-19? Yes No Unknown;
**If yes,** please respond to questions below:
**Anxiety**: Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Behaviour change**: Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Can't move and/or feel one side of body or face**: Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Chest pain:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Constipation:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Depressed mood:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Diarrhoea:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Dysmenorrhea** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Dizziness/light headedness:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Fainting/blackouts:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Fever:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Forgetfulness:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Jerking of limbs:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Joint pain/swelling:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Loss of appetite:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Loss of interest/pleasure:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Lumpy lesions:** (purple/pink/bluish) **on toes/COVID toes:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Nausea/vomiting:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Numbness or tingling:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Pain on breathing:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Palpitations:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Persistent dry cough:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Persistent fatigue:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Problems hearing:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Persistent headache:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Persistent muscle pain:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Post-exertional malaise:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Problems passing urine:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Problems seeing:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Problem swallowing:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Problems with balance:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Problems with gait/falls:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Reduced smell:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Reduced taste:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Ringing in ears:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Seizures:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Shortness of breath:** Yes, but not present anymore Yes, still present;
If yes: Present At rest With activity; Yes, intermittent No Unknown;
**Skin rash:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
If yes, please tick all areas of the body that apply: Face Trunk (stomach or back) Arms Legs Buttocks Toes Fingers;
**Slowness of movement:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Sleeping less:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Sleeping more:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Stiffness of muscles:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Stomach pain:** Yes, but not present anymore Yes still present Yes, intermittent No Unknown;
**Swollen ankles:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Tremors:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Trouble in concentrating:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Weakness in limbs:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Weight loss:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
*The following questions should not be completed for children <15yrs:*
**Erectile dysfunction:** Yes, but not present anymore Yes, still present Yes, intermittent No Unknown;
**Hallucinations** (seeing or hearing things others don't see or hear): Yes, but not present anymore Yes, still present Yes, intermittent No Unknown

# Impact sur la qualité de vie


- PTLDS
  - SF-36 (short-form 36) *(Berende, 2016; Turk, 2019; Mac,2020; Rebman, 2021; Ursinus,2021; Aucott, 2022)*

  -> Significativement plus bas chez les patients PTLDS.

- PASC
  - SF-36/SF-12 Chen K-Y et al. (2020) doi: 10.3389/fpsyt.2020.00668, O Kelly et al 2022 doi: 10.1016/j.ijid.2022.03.013
  - EQ-5D-5L Preeti et al, 2021, doi: 10.1002/jmv.27309

  -> Significativement plus bas chez les patients PASC.

# Profils des patients PTLDS

**Facteurs de risque:**

- Démographiques
  - **Adultes versus enfants** *(Cairn, 2005)*
  - **Age**? plus jeune *(Aucott, 2016)* plus âgés *(Moon, 2019)*
  - **Sexe féminin** OR=3,218 *(Ljøstad, 2010)* OR= 4,17 *(Aucott, 2022)*
  - **Echelle des événements de vie** (+1) + 30% *(Aucott, 2022)*
  - **Comorbidités** *(Moon, 2019)*

- Maladie
  - **Forme disséminée précoce** *(Cairns, 2010)*
  - **NB** *(Cairns, 2005) (Cairns, 2010)*
  - **Symptômes>6 semaines** OR = 4,062 *(Ljøstad, 2010)* , retard de traitement *(Cairns, 2005) (Cairns, 2010)*

# Prévalence et profils des patients PASC

**Table 1** Patient characteristics according to their PCFS Scale Score

| | Post-COVID-19 Functional Status (PCFS) | | | |
|---|---|---|---|---|
| **PCFS n (%)** | **0 36 (30)** | **1 35 (29)** | **2 35 (29)** | **3–4* 15 (12)** |
| Age, years, mean±SD | 57±12 | 57±11 | 59±11 | 59±13 |
| Women, n (%) | 12 (33) | 13 (37) | 13 (37) | 7 (47) |
| Body mass index, kg/m$^2$, n (%) | | | | |
| 18–24 | 6 (17) | 11 (31) | 8 (23) | 3 (20) |
| 25–30 | 19 (53) | 15 (43) | 10 (29) | 6 (40) |
| >30 | 11 (31) | 9 (26) | 17 (49) | 6 (40) |
| Current or former smokers, n (%) | 20 (56) | 19 (54) | 16 (46) | 7 (47) |
| Comorbidities†, n (%) | 20 (56) | 20 (57) | 23 (47) | 7 (47) |
| Total duration of hospitalisation, days, median (IQR) | 11 (7; 15) | 9 (6; 16) | 13 (7; 29) | 14 (9; 25) |
| ICU stay, n (%) | 14 (39) | 17 (49) | 16 (46) | 10 (67) |
| Duration of ICU stay, days, median (IQR) | 10 (5; 19) (n=14) | 9 (6; 14) (n=17) | 18 (10; 29) (n=16) | 5 (2; 17)(n=10) |
| Mechanical ventilation, n (%) | 9 (25) | 9 (26) | 11 (31) | 4 (27) |
| Mechanical ventilation duration, days, median (IQR) | 13 (6; 15) (n=9) | 9 (7; 20) (n=9) | 18 (9; 24) (n=10) | 11 (7; 19) (n=4) |
| Total duration of oxygen therapy, days, median (IQR) | 9 (6; 19) | 9 (4; 16) | 12 (6; 25) | 13 (7; 21) |
| Corticosteroids, n (%) | 19 (53) | 21 (60) | 17 (49) | 9 (60) |
| Rehabilitation‡, n (%) | 8 (22) | 8 (23) | 11 (31) | 6 (40) |
| Weekly activity duration before COVID-19, min, median (IQR) | 60 (0; 120) (n=29) | 120 (60; 240) (n=25) | 60 (0; 180) (n=26) | 120 (0; 180) (n=11) |

The PCFS Scale assesses patient-relevant functional limitations: grade 0 reflects the absence of any functional limitation. Upward of grade 1, symptoms, pain or anxiety are present to an increasing degree. This has no effect on activities for patients in grade 1, whereas a lower intensity of the activities is required for those in grade 2. Grade 3 accounts for inability to perform certain activities, forcing patients to structurally modify these. Finally, grade 4 is reserved for those patients with severe functional limitations requiring assistance with activities of daily living.[6]

*Patients in categories # 3 (n=13) and 4 (n=2) were merged.

†History of chronic respiratory disease, chronic cardiac disease, arterial hypertension, diabetes, chronic kidney disease, immunodepression, psychiatric disease and thromboembolic disease.

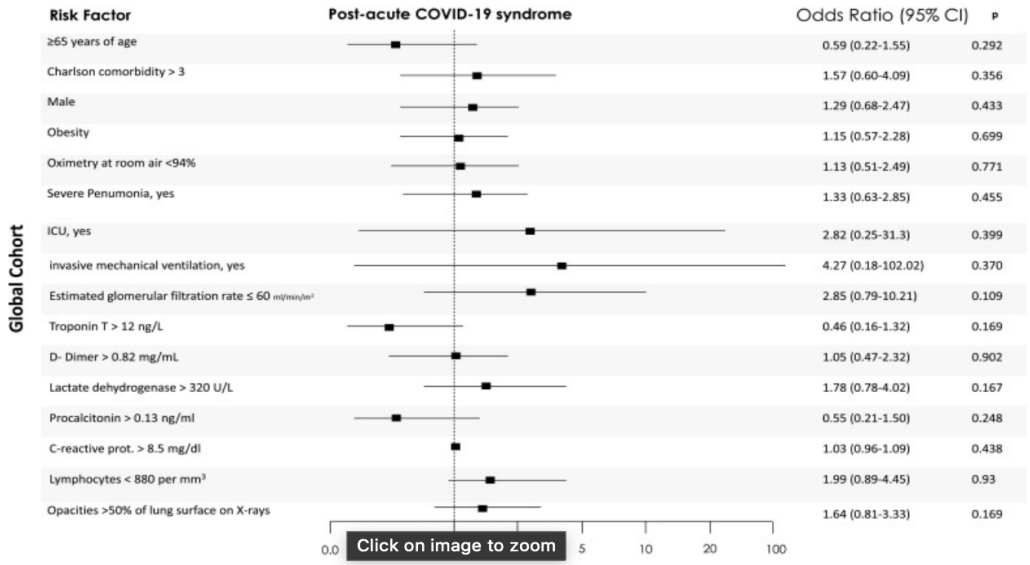
‡Includes patients who underwent respiratory rehabilitation as well as standard recovery centres following discharge.

ICU, intensive care unit; PCFS, Post-COVID-19 Functional Status.

Benkalfate N, et al 2022

As a proportion of the UK population, prevalence of self-reported long COVID was greatest in people aged 35 to 49 years, females, people living in more deprived areas, those working in social care, teaching and education or health care, and those with another activity-limiting health condition or disability.

https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/7april2022




Moreno et al. J Infect. 2021 Mar; 82(3): 378–383.
Published online 2021 Jan 12. doi: 10.1016/j.jinf.2021.01.004

# Prévalence et profils des patients PASC

**TABLE 3 |** Factors associated with Short-Form 36-item questionnaire (SF-36) among patients in the multivariate analysis.

| Dependent Variable | Independent Variable | *P* | Beta | 95%*CI* |
|---|---|---|---|---|
| **PF** | Age | <0.001 | −0.231 | −0.250, −0.097 |
| | Female | 0.033 | −0.107 | −3.999, −0.174 |
| | Clinical subtype | 0.001 | −0.175 | −9.198, −2.442 |
| **RP** | Chronic kidney disease | 0.005 | −0.147 | −118.331, −21.661 |
| | Length of stay (LOS) | 0.004 | −0.149 | −1.167, −0.221 |
| | Age | 0.038 | −0.107 | −0.571, −0.016 |
| **BP** | Female | 0.013 | −0.131 | −6.454, −0.773 |
| **GH** | Clinical subtype | 0.042 | −0.107 | −13.067, −0.233 |
| **VT** | Age | 0.004 | 0.128 | 0.032,0.289 |
| | Length of stay (LOS) | 0.040 | 0.113 | 0.023,0.461 |
| **SF** | NA | NA | NA | NA |
| **RE** | Length of stay (LOS) | 0.002 | −0.163 | −1.515, −0.357 |
| | Clinical subtype | 0.014 | −0.128 | −33.852, −3.920 |
| | Female | 0.043 | −0.105 | −17.774, −0.282 |
| | Smoking history | 0.022 | −0.119 | −1.515, −0.357 |
| **MH** | Clinical subtype | 0.022 | −0.120 | −13.045, −1.012 |
| | FVC | <0.001 | −0.223 | −0.052, −0.019 |

**TABLE 4 |** Logistic regression analysis of COVID-19 patients with a physical component summary (PCS) < 50.

| | | Multivariate logistic regression results | |
|---|---|---|---|
| | | OR [95% CI] | p value |
| **Age** | <45 | 1 | |
| | 45~60 | 2.22 [0.68, 7.17] | 0.184 |
| | >60 | 0.87 [0.34, 2.27] | 0.780 |
| **Sex** | Male | 1 | |
| | Female | 1.84 [0.87, 1.91] | 0.110 |
| **BMI** | Normal | 0.70 [0.16,2.99]. | 0.625 |
| | Overweight | 3.71 [1.42, 9.70] | 0.008 |
| | Obesity | 3.94 [1.47,10.52] | 0.006 |
| **Clinical subtype** | Mild | 1 | |
| | Server | 1.49 [0.55,4.00] | 0.434 |
| **LOS** | | 1.00 [0.96,1.04] | 0.911 |
| **FEV1** | | 0.68 [0.36,1.29] | 0.235 |
| **FVC** | | 1.00 [0.94,1.08] | 0.925 |
| **FEV1/FVC** | | 1.03 [0.99,1.06] | 0.132 |
| **Smoking** | No | 1 | |
| | Yes | 0.37 [0.05,2.60] | 0.319 |
| **Drinking** | No | 1 | |
| | Yes | 3.25 [0.74,14.28] | 0.118 |
| **Hypertension** | No | 1 | |
| | Yes | 1.08 [0.48,2.45] | 0.851 |
| **Diabetes** | No | 1 | |
| | Yes | 1.92[0.68,5.42] | 0.217 |

Chen K-Y et al. (2020) doi: 10.3389/fpsyt.2020.00668

**TABLE 5 |** Logistic regression analysis of COVID-19 patients with a mental component summary (MCS) < 50.

| | | Multivariate logistic regression results | |
|---|---|---|---|
| | | OR [95% CI] | p value |
| **Age** | <45 | 1 | |
| | 45~60 | 0.98 [0.44,2.20] | 0.957 |
| | >60 | 1.18 [0.58,2.41] | 0.641 |
| **Sex** | Male | 1 | |
| | Female | 2.22 [1.30,3.81] | 0.005 |
| **BMI** | Normal | 1 | |
| | Overweight | 1.14 [0.51,2.55] | 0.751 |
| | Obesity | 1.26 [0.56,2.87] | 0.579 |
| **Clinical subtype** | Mild | 1 | |
| | Severe | 1.70 [0.76,3.78] | 0.225 |
| **Length of stay (LOS)** | | 0.61 [0.27,1.36]. | 0.125 |
| **FEV1** | | 0.79 [0.53,1.27]. | 0.364 |
| **FVC** | | 1.00 [0.96,1.04] | 0.860 |
| **FEV1/FVC** | | 1.02 [0.99,1.05] | 0.276 |
| **Smoking** | No | 1 | |
| | Yes | 2.16 [0.67,6.89] | 0.195 |
| **Drinking** | No | 1 | |
| | Yes | 0.54 [0.16,1.85] | 0.329 |

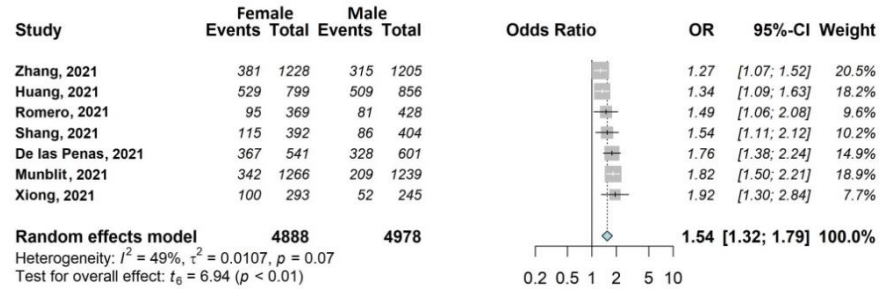



**Figure 6.** Forest plots of adjusted analyses for association between sex (female) and fatigue. HKSJ, Hartung-Knapp-Sidik-Jonkman.

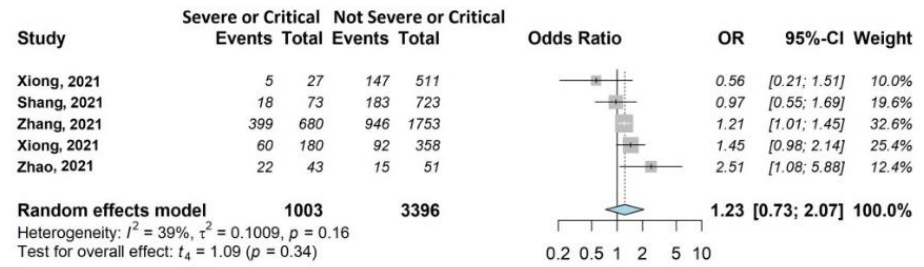



**Figure 7.** Forest plots of adjusted analyses for association between acute disease severity and fatigue. HKSJ, Hartung-Knapp-Sidik-Jonkman.

Maglietta et al J. Clin. Med. 2022, 11, 1541

# Prévalence PTLDS

**Etudes non contrôlées:**

- Suite à EM :
  - À 1 an **14,5%** *(Aucott, 2016)*
  - À 1 an **17%** *(Wormser, 2003)*
  - De 0,5% (étude chez des enfants) à **13,1%** *(Shapiro, 2005)*
  - **10,9%** à 6 mois et seuls **4,7%** avaient encore des symptômes entre 11 et 20 ans *(Weitzner, 2005)*

- Suite à NB :
  - **48%** ont des symptômes persistants à 1 ans dont 34% objectifs *(Eikeland, 2010)*
  - **28%** de symptômes persistants *(Dersh, 2015)*

# Prévalence PTLDS

**Etudes contrôlées:**

- EM : **2,2%** symptôme persistant à 1 an pas de différence avec groupe contrôle mais petits effectifs *(Cerar, 2010)*
- EM : 19% de PTLDS à 6 mois. A un an seuls **13%** avaient au moins un sp subjectif, problèmes de concentration et fatigue plus fréquents dans le groupe EM mais non significatif *(Wormser, 2020)*
- 27,2% des patients avec une BL ont des symptômes persistants à 6 mois (27,2% dans EM et 34,3% pour disséminée) versus 21,2% en population générale **+6%** *(Ursinus, 2021)*
- PTLD à 1 an plus fréquent chez les patients ayant un antécédent de BL (**13,7%** versus 4,1%) et plus de sp subjectifs (43,2% versus 24,5%) *(Aucott, 2022)*

# Bases physiopathologiques PTLDS

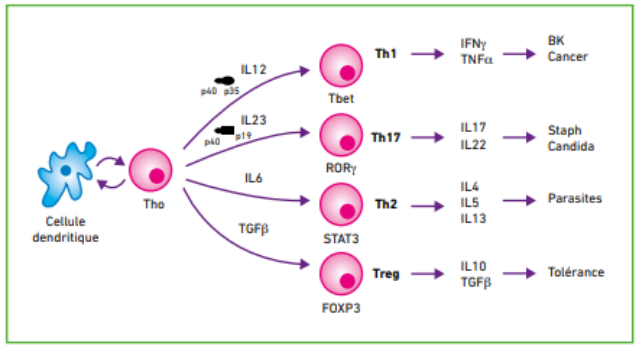
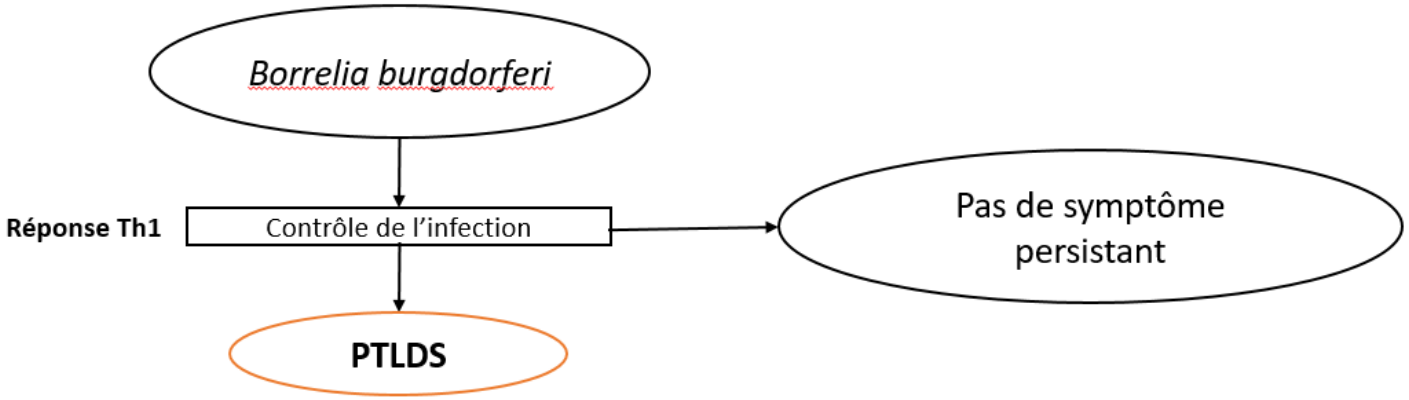



**Fig. 1 :** Polarisation des lymphocytes T *helper* (Th).




**Inflammation persistante ?**
*(Uhde, 2018) (Aucott, 2016)*

**Troubles neuropsychiatriques secondaires INFa ?**
*(Jacek, 2013)*

**Altération microbiote ?**
*(Morrissette, 2020)*

**Altération protéome ?**
*(Fitzgerald, 2021)*

**Rôle des effecteurs TH17 ?**
*(Aucott, 2016) (Strle, CID 2014)*

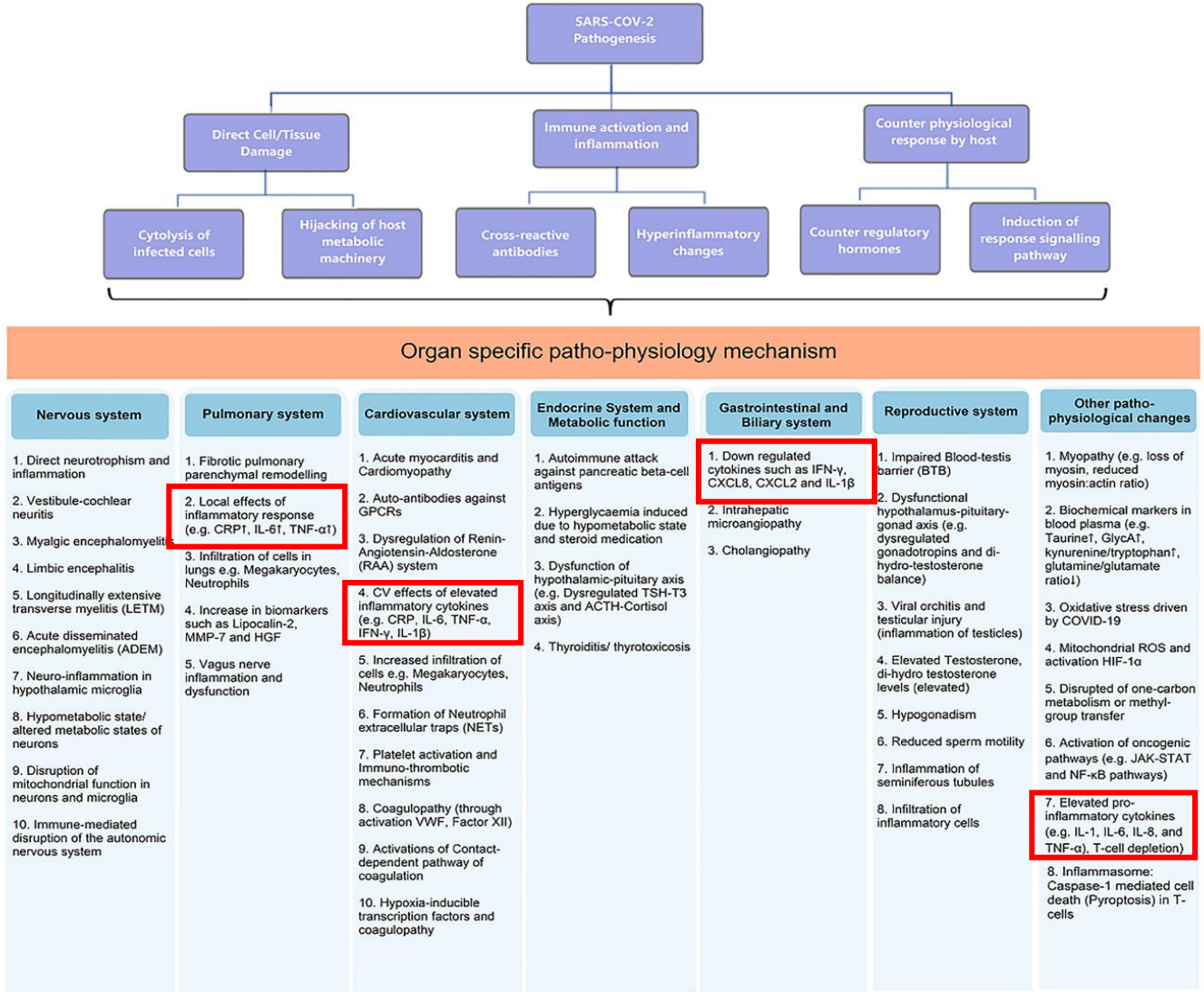
**Déséquilibre entre réponse Th1 et Threg?**
*(Jarefors,2006) (Widhe, 2002) (Ekerfelt, 2003) (Steere, 2020)*

**Autoimmunité?**
**Ac anti neuronaux, Ac anti phospholipides.**
*(Jacek, 2013)(Chandra, 2010)(Greco, 2011)*

***Mimétisme moléculaire?***
*(Steere, 2020)*

# Bases physiopathologiques PASC

Passage par la lame criblée pour atteindre le tronc cérébral neuro inflammation responsable d'une dysfonction prédominante au niveau du tronc cérébral



# Bases physiopathologiques PASC

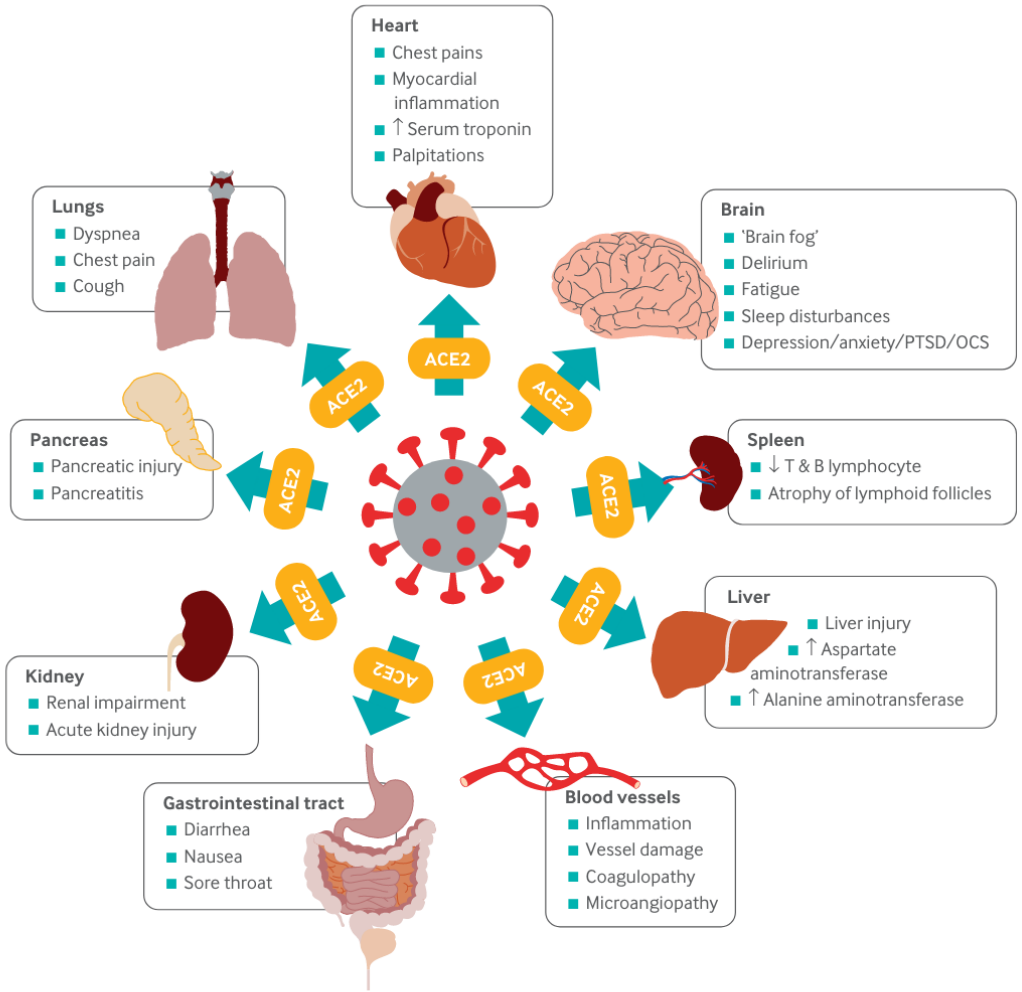



**Fig 1 | Multi-organ complications of covid-19 and long covid. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor. Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms, some of which are outlined here**

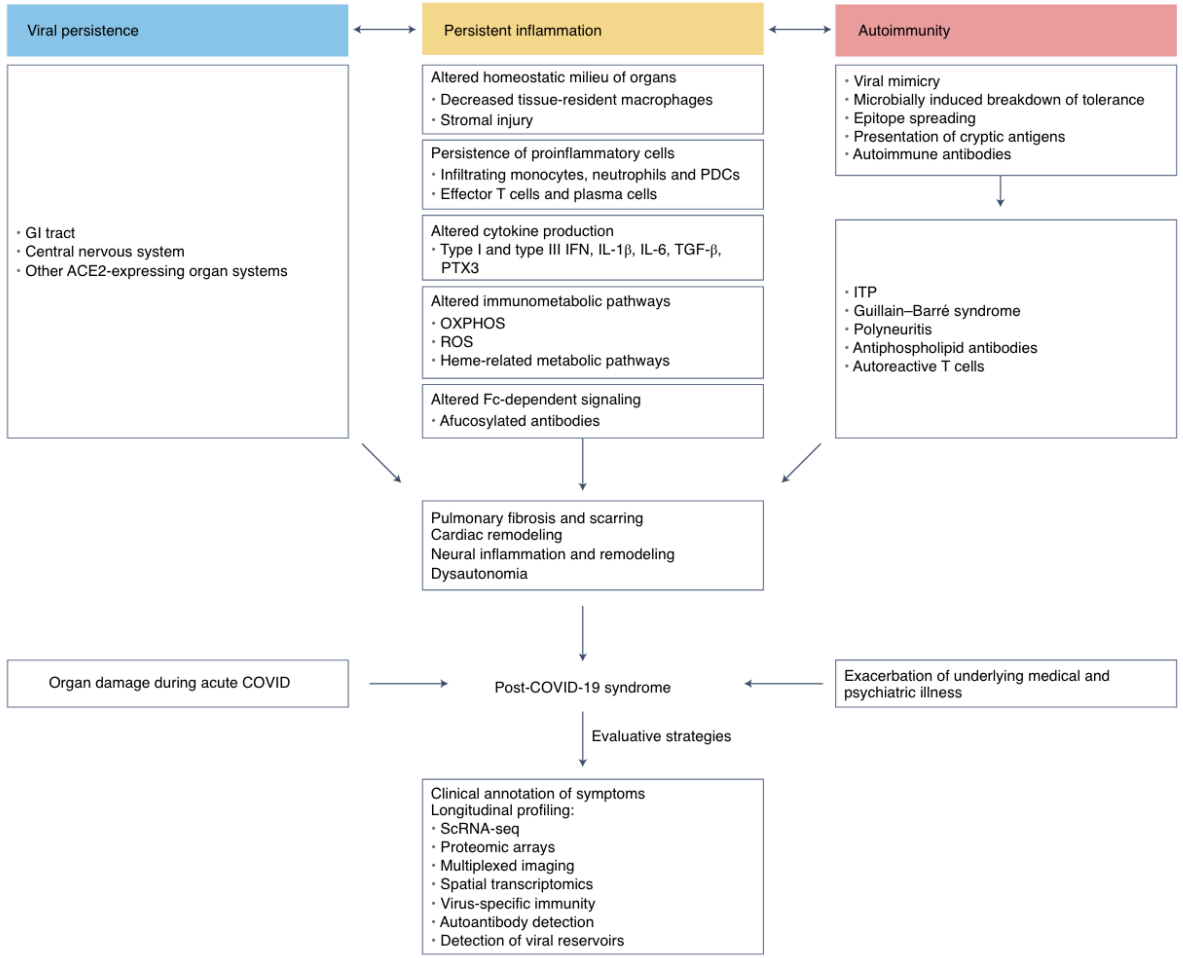
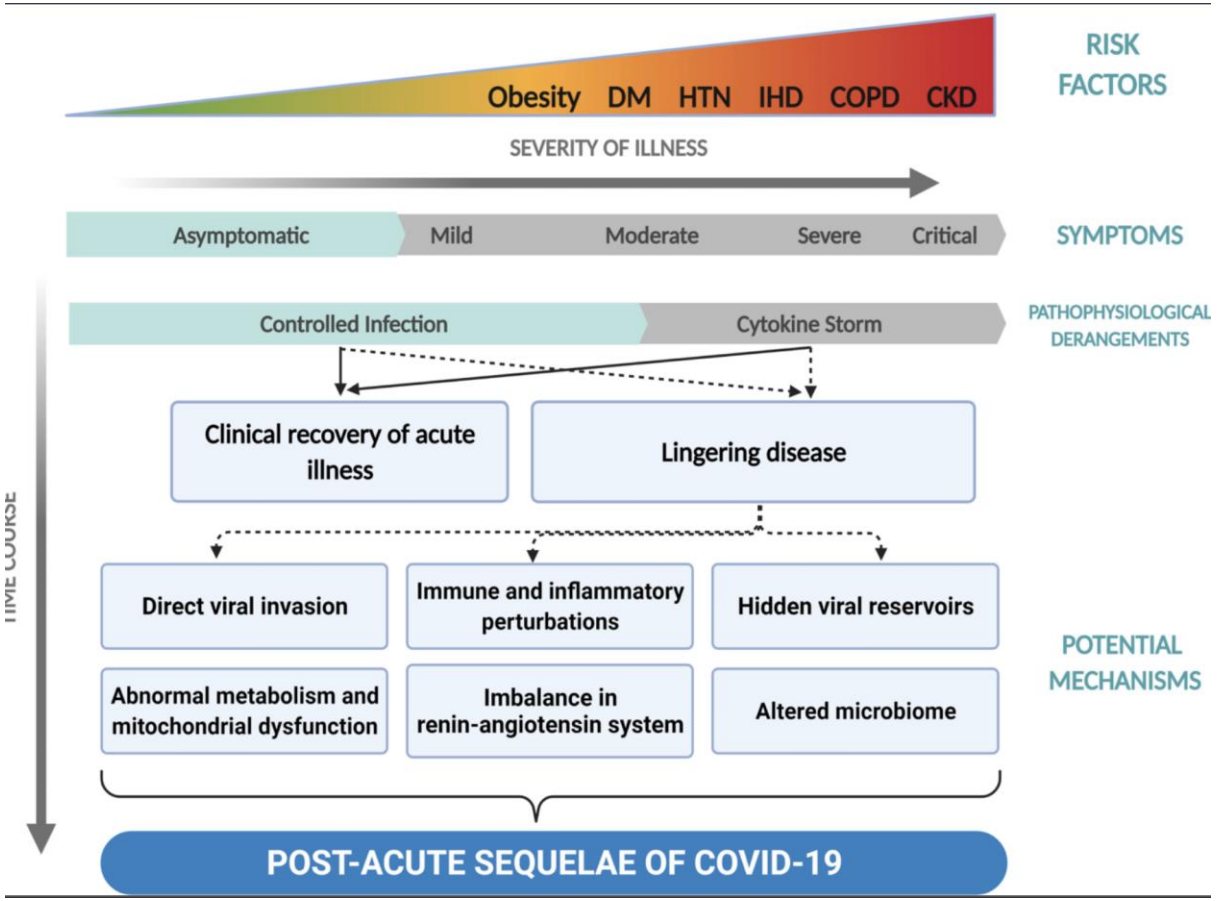



**Fig. 1 | Putative mechanisms and diagnostic strategies for patients with post-COVID-19 syndromes.** Delayed resolution of inflammation, autoimmunity and viral persistence represents overlapping mechanisms that may contribute to the pathogenesis of post-COVID-19 syndromes. Strategies to better characterize patients with post-COVID-19 syndromes are indicated. ITP, idiopathic thrombocytopenic purpura; OXPHOS, oxidative phosphorylation; PDCs, plasmacytoid dendritic cells; ROS, reactive oxygen species; TGF-β, transforming growth factor-β.

# Bases physiopathologiques PASC



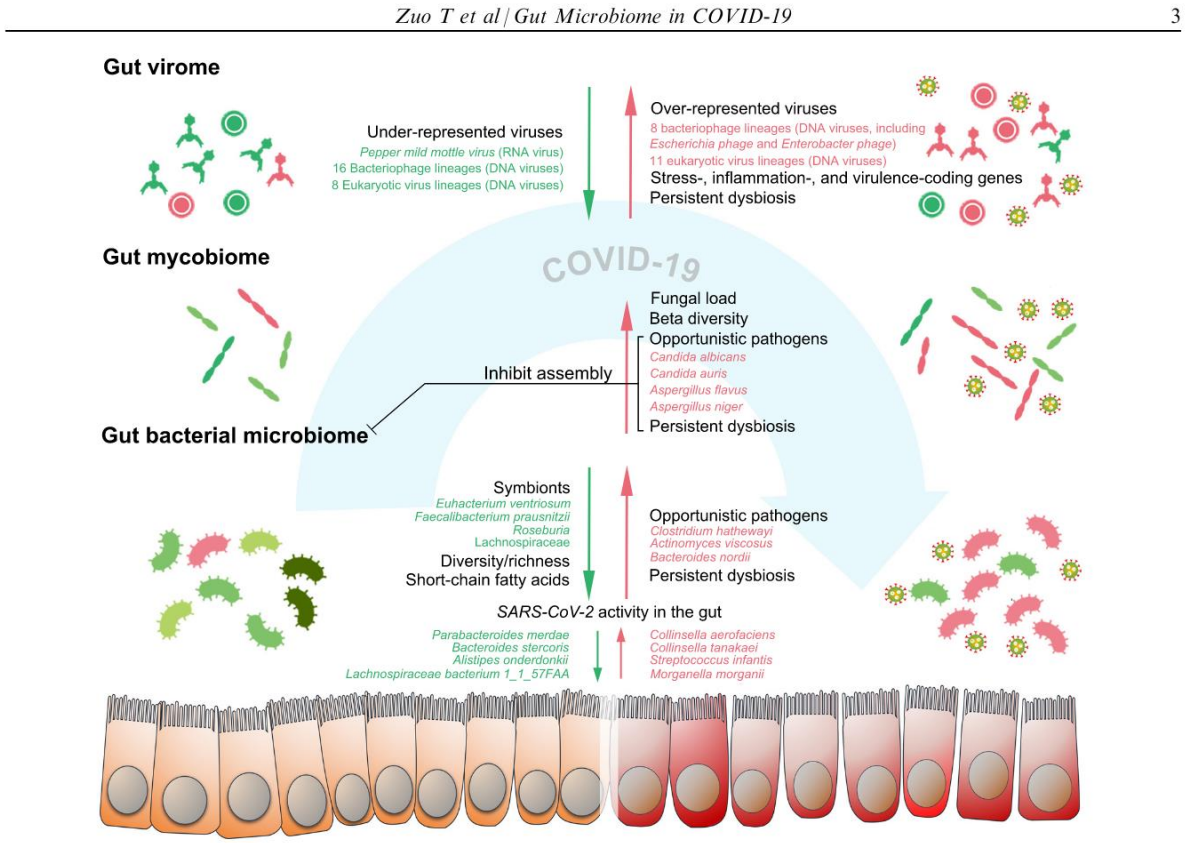
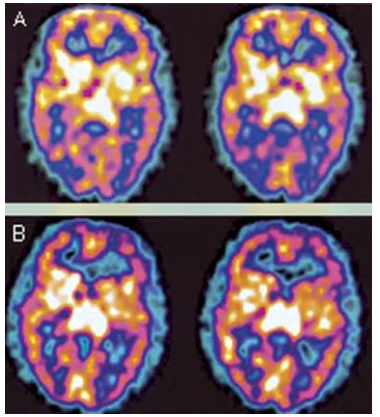
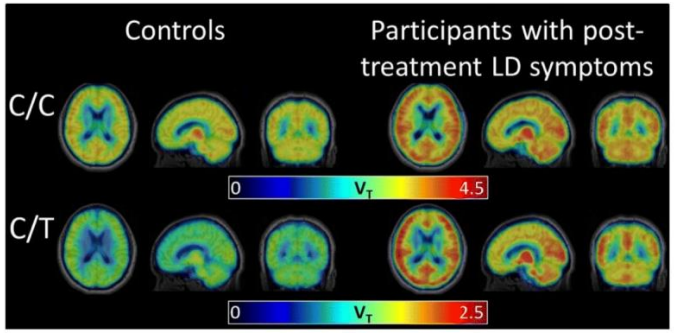




**Figure 1 Alterations in the gut bacterial, fungal, and viral microbiome in patients with COVID-19**
The gut bacterial microbiome in COVID-19 is characterized by decreased diversity and richness, and persistent bacterial microbiome dysbiosis even after disease resolution. The gut mycobiome in COVID-19 is characterized by increased fecal fungal load and increased beta-diversity (more heterogeneous), and it is unstable over time and also persistently altered after disease resolution. *SARS-CoV-2* shows infectivity in the gut. Delayed *SARS-CoV-2* viral shedding and persistent gut virome dysbiosis are both present after disease resolution. The gastrointestinal tract epithelial barrier is impaired in a subset of COVID-19 patients. The figure is created with BioRender.com.

# Neuro imagerie PTLDS

- **Enregistrement SPECT**
  - 75% au moins une anomalie (temporal, frontal, pariétal) *(Donta, 2012)*
- **IRM:**
  - 14% anormales : hypersignaux T2 à différentes localisations, certains avec une prédominance péri ventriculaire *(Donta, 2012)*
  - 43.5% lésions punctiformes et sous corticales en FLAIR ou T2 FSE. Nombre lésions corrélée à la durée des symptômes mais pas à la présence de troubles de la mémoire ou anomalies LCR. Pas de processus de démyélinisation *(Morgen, 2001)*
- **(11C)DPA-713 PET:**
  - Taux de TSPO plus élevé chez les patients PTLDS symptomatiques (inflammation). Pas d'atrophie corticale *(Coughlin, 2018)*



# Neuro imagerie PACS

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2823–2833
https://doi.org/10.1007/s00259-021-05215-4

ORIGINAL ARTICLE

## $^{18}$F-FDG brain PET hypometabolism in patients with long COVID

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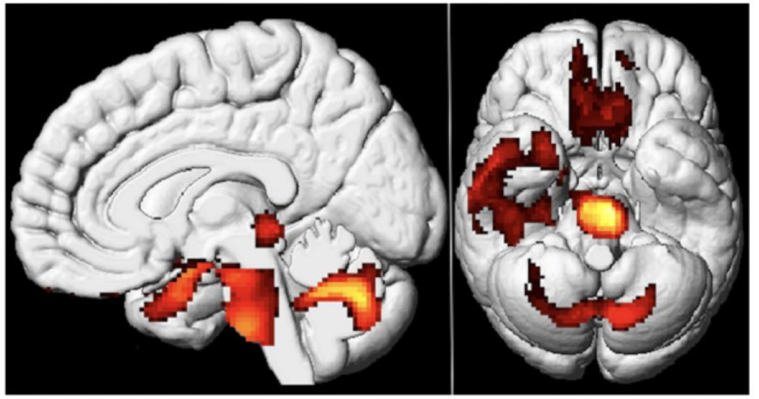

- $^{18}$F-FDG brain PET comparaison 35 PACS avec 44 patients sans PACS (recrutés avant le SARS COV 2), éval à S3 et +, patients avec anomalies IRM exclus
- Par rapport sujets sains, patients COVID long
  - hypométabolisme bilatéral dans le gyrus rectal/orbital bilatéral, gyrus olfactif ;
  - lobe temporal droit, amygdale et l'hippocampe, thalamus droit ;
  - le tronc cérébral bilatéral pons/medulla ;
  - cervelet bilatéral (p-voxel < 0,001 non corrigé, p-cluster < 0,05 corrigé par FWE).
- Ces clusters métaboliques étaient hautement discriminants pour distinguer les patients et les sujets sains (100% de classification correcte), significativement associés à des plaintes fonctionnelles plus nombreuses (clusters du tronc cérébral et du cervelet), et tous associés à la survenue de certains symptômes (hyposmie/anosmie, troubles de la mémoire/de la cognition, douleur et insomnie) (p < 0,05).

# Similitudes et différences

**Définitions évolutives et non consensuelles**

**Des bases physiopathologiques « commune »:**

- Peu d'études et discordances
- Persistance d'une inflammation prolongée avec des marqueurs variables entre les deux pathologies
- Imagerie?

**Des symptômes « communs » (double sens similarité et non spécifique)**

- Grande part de subjectivité, absence d'échelle standardisée
- Mais impact sur la qualité de vie majeur dans les deux cas

**Facteurs de risque similaires: sexe féminin**

- Discordance sur l'âge retrouvé dans les deux maladies

**Une prévalence similaire entre les deux maladies …et dans la population générale?**

- Merci pour votre attention