

November 19,2021

Without a Crystal Ball...What is Long COVID?

Regina Rosace, MD SCOR Global Life Americas rrosace@scor.com



A Rose by any Other Name...

Post-Acute Sequelae of SARS-CoV-2 (PASC)

Post Acute COVID-19

Ongoing symptomatic COVID-19

Post-COVID-19 Syndrome

Long COVID

"long haulers"











Different types of critical illnesses can happen post-ICU

- Chronic Critical Illness (CCI)
 - Secondary to prolonged ventilation because of primary reason for ICU stay

• Persistent Critical Illness

- Issues no longer directly attributable to the reason one entered the ICU in the first place
 - Poor nutrition
 - Endocrinopathies
 - \circ Infections
 - o Neuromuscular weaknesses
 - Cognitive issues/ brain dysfunction
 - Mood/ anxiety/ PTSD





The first medical condition identified on social media

A Few Symptoms

| Persistent fatigue | Arthralgias |
|--|-----------------------|
| Brain fog (mild subjective cognitive impairment) | Sleeping difficulties |
| Headaches | Smell disorders |
| Dyspnea | Anxiety |
| Chest pain/palpitations | Depression |

Social Media Support Groups





Find Us on





Table 3. A definition of post COVID-19 condition

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others* and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

A separate definition may be applicable for children.

Notes:

There is no minimal number of symptoms required for the diagnosis; though symptoms involving different organs systems and clusters have been described.

*A full list of described symptoms included in the surveys can be found in Annexes 2 .

Definitions:

Fluctuate – a change from time to time in quantity or quality.

Relapse - return of disease manifestations after period of improvement.

Cluster – two or more symptoms that are related to each other and that occur together. They are composed of stable groups of symptoms, are relatively independent of other clusters, and may reveal specific underlying dimensions of symptoms (32).





Annex 1. Repository of published/available definitions of post COVID-19 condition

| Source | Text |
|--|---|
| Wellcome | Symptoms persisting beyond 4 weeks after symptom onset suggestive of COVID-19 (33). |
| Lancet | Multiorgan symptoms after COVID-19 are being reported by increasing numbers of patients. They range from cough and shortness of breath, to fatigue, headache, palpitations, chest pain, joint pain, physical limitations, depression, and insomnia, and affect people of varying ages. At the Lancet–Chinese Academy of Medical Sciences conference on 23 November 2020, Bin Cao presented data (in press at the Lancet) on the long-term consequences of COVID-19 for patients in Wuhan, and warned that dysfunctions and complications could persist in some discharged patients for at least 6 months. So-called long COVID is a burgeoning health concern and action is needed now to address it (<i>34</i>). |
| NICE | 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 (35). |
| Scientific American | Individuals whose symptoms persist or develop outside the initial viral infection, but the duration and pathogenesis are unknown (36). |
| Royal Society | The onset of persistent or recurrent episodes of one or more of the following symptoms, within x* weeks of infection with SARS-CoV-2 and continuing for y* weeks or more: severe fatigue, reduced exercise capacity, chest pain or heaviness, fever, palpitations, cogintive impairment, anosomia or ageusia, vertigo and tinnitus, headache, peripheral neuropathy, metallic or bitter taste, skin rash joint pain or swelling (3). |
| | * Maximum period between acquisition of the infection (if known) and the onset of symptoms, and the minimum duration of symptoms, should be specified in the definition. |
| Haute Autorité de santé, France | Three criteria: 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 (37). |
| CDC | Long COVID: While most persons with COVID-19 recover and return to normal health, some patients can have symptoms that can last for weeks or even months after recovery from acute illness. Even people who are not hospitalized and who have mild illness can experience persistent or late symptoms (38). |
| Wikipedia | Condition characterized by long-term sequelae – persisting after the typical convalescence period – of coronavirus disease 2019 (COVID-19) (39). |
| Nature | Post-acute COVID-19 as persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms (40). |







Guidelines should not pool evidence from uncomplicated and severe COVID-19. *Nicholas J White, Nathalie Strub-Wourgaft, Abul Faiz, Philippe J Guerin



 Supplement to: White NJ, Strub-Wourgaft N, Faiz A, Guerin PJ. Guidelines should not pool evidence from uncomplicated and severe COVID-19. Lancet 2021; published online March 22. <u>http://dx.doi.org/10.1016/S0140-6736(21)00469-4</u>





Fig. 1 | Timeline of post-acute COVID-19. Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated. Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. The common symptoms observed in post-acute COVID-19 are summarized.





| Table 1 Findings from clinical studies on the prevalence of post-acute COVID-19 syndrome | | | | | | | | | |
|--|-----------------------------------|----------------------------------|---|-----------------------------|--------------------------------|--------------------------------------|--------------------------------------|--------------------------------|---------------------------------|
| | Carfi et al. ³ | Halpin et al. ²⁴ | Carvalho- Schneider et al. ²¹ | Chopra et al. ²⁰ | Arnold et al. ²² | Moreno-Pérez et al. ²³ | Moreno-Pérez et al. ²³ | Garrigues et al. ³⁶ | Huang et al. ⁵ |
| Site | Italy | United Kingdom | France | United States | United Kingdom | Spain | Spain | France | China |
| Number of participants | 143 | 100 | 150 | 488 | 110 | 277 | 277 | 120 | 1,733 |
| Follow-up | | | | | | | | | |
| Duration | 2 months post-symptom onset | 1-2 months post-discharge | 2 months post-symptom onset | 2 months post-discharge | 3 months post-symptom onset | 2-3 months post-COVID-19 onset | 4 months post-COVID-19 onset | 3-4 months post-admission | 6 months post- symptom onset |
| Mode of follow-up evaluation | In person | Telephone survey | Telephone survey | Telephone survey | In person | In person | In person | Telephone survey | In person |
| Baseline characteristics | | | | | | | | | |
| Age (years) | Mean (s.d.) = 56.5 (14.6) | Median (ward/ ICU)= 70.5/58.5 | Mean (s.d.) = 45 (15) | NR | Median (IQR)=60 (44-76) | Median (IQR) = 56 (42-67.5) | Median (IQR) = 56 (42-67.5) | Mean (s.d.)=63.2 (15.7) | Median (IQR)= 57 (47-65) |
| Female (%) | 37.1 | 46 | 56 | NR | 38.2 | 47.3 | 47.3 | 37.5 | 48 |
| Acute COVID-19 features | | | | | | | | | |
| Oxygen therapy requirement (%) | 53.8 | 78 | | | 75.4 | | | | 75 |
| Non-invasive ventilation (%) | 14,7 | 30 | | | | | | | 6 |
| Invasive ventilation (%) | 4.9 | 1 | | | | | | | 1 |
| ICU care (%) | 12.6 | 32 | 0 | | 16.4 | 8.7 | 8.7 | 20 | 4 |
| Post-acute COVID-19 | | | | | | | | | |
| ≥1 symptom (%) | 87.4 | | 66 | 32.6 | 74 | 50.9 | | | 76 |
| ≥3 symptoms (%) | 55.2 | | | | | | | | |
| General sequelae | | | | | | | | | |
| Fatigue (%) | 53.1 | 64 | 40 | | 39 | 34.8 | | 55 | 63 |
| Joint pain (%) | 27.3 | | 16.3 | | 4.5 | 19.6 | | | 9 |
| Muscular pain (%) | | | | | | 19.6 | | | 2 |
| Fever (%) | 0 | | 0 | | 0.9 | 0 | | | 0.1 |
| Respiratory sequelae | | | | | | | | | |
| Dyspnea (%) | 43.4 | 40 | 30 | 22.9 | 39 | 34.4 | 11.1 | 41.7 | 23 |
| Cough (96) | -15 | | | 15.4 | 11.8 | 21.3 | 2.1 | 16.7 | |
| Cardiovascular sequelae | 200 | | 222 | | 121 | | | COLOR. | |
| Chest pain (%) | 21.7 | | 13.1 | | 12.7 | | | 10.8 | 5 |
| Palpitations (%) | | | 10.9 | | | | | | 9 |
| Neuropsychiatric sequelae | | | | | | | | | |
| Anxlety/depression (%) | | | | | | | | | 23 |
| Sleep disturbances (%) | | | | | 24 | | | 30.8 | 26 |
| PISD (%) | 1.00 | 31 | 22.4 | | | ~ | | -0.0 -0.0 | 22 |
| Loss of taste/smell (%) | -15 | | 22.7 | 13.1 | 11.8 | 21.4 | ~ . | 10.8-13.3 | 7-11 |
| Headache (%) | -10 | | | | 1.0 | 17.8 | 5.4 | | 2 |
| Gastrointestinal sequeiae | | | | | | -0 | | | 12 |
| Diarmea (%) | | | | | 0.9 | 10.5 | | | -5 |
| Dermatologic sequelae | | | | | | | | 20 | 22 |
| Hairioss (%) | | | | | | | | 20 | 22 |
| Skin rash (%) | | | | | | | | | 2 |
| Crade | Euro/Deluteuri | FO FD FI | | | 55.26 | | | EO ED EL | EuroOal street |
| | analog scale | rg-su-st | | | JP-20 | scale | | rQ-DD-DL | analog scale |
| Decline (percentage of patients reporting or yes/no) | 44.1 | Yes | | | Yes | Yes | | Yes | Yes |





| | Carfi et al. ³ | Halpin et al. ³⁴ | Carvalho- Schneider et al. ²⁸ | Chopra et al.20 | Arnold et al.22 |
|--------------------------------|-----------------------------------|---------------------------------|---|----------------------------|------------------------------|
| Site | Italy | United Kingdom | France | United States | United Kingdom |
| Number of participants | 143 | 100 | 150 | 488 | 110 |
| Follow-up | | | | | |
| Duration | 2 months post-symptom onset | 1-2months post-discharge | 2 months post-symptom onset | 2 months post-discharge | 3 months post-symptom on: |
| Mode of follow-up evaluation | In person | Telephone survey | Telephone survey | Telephone survey | In person |
| Baseline characteristics | | | | | |
| Age (years) | Mean (s.d.) = 56.5 (14.6) | Median (ward/ ICU)=70.5/58.5 | Mean (s.d.) = 45 (15) | NR | Median (IQR)=6((44-76) |
| Female (%) | 37.1 | 46 | 56 | NR | 38.2 |
| Acute COVID-19 features | | | | | |
| Oxygen therapy requirement (%) | 53.8 | 78 | | | 75.4 |
| Non-Invasive ventilation (%) | 14.7 | 30 | | | |
| Invasive ventilation (%) | 4.9 | 1 | | | |
| ICU care (%) | 12.6 | 32 | 0 | | 16.4 |
| Post-acute COVID-19 | | | | | |
| ≥1 symptom (%) | 87.4 | | 66 | 32.6 | 74 |
| ≥3 symptoms (%) | 55.2 | | | | |
| General sequelae | | | | | |
| Fatigue (%) | 531 | 64 | 40 | | 39 |
| Joint pain (%) | 27.3 | | 16.3 | | 4.5 |
| Muscular pain (%) | | | | | |
| Fever (%) | 0 | | 0 | | 0.9 |
| Respiratory sequelae | | | | | |
| Dyspnea (%) | 43.4 | 40 | 30 | 22.9 | 39 |
| | | | | | |

Table 1 | Findings from clinical studies on the prevalence of post-acute COVID-19 syndrome

The Art & Science of Risk



Statistical bulletin

Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 April 2021

Estimates of the prevalence of self-reported "long COVID", and the duration of ongoing symptoms following confirmed coronavirus infection, using UK Coronavirus (COVID-19) Infection Survey data to 6 March 2021.

| Symptom | 5 weeks post | 12 weeks post |
|----------|--------------|---------------|
| fatigue | 11.8% | 8.3% |
| cough | 10.9% | 7.2% |
| headache | 10.1% | 7.0% |
| myalgia | 7.7% | 5.6% |





13.7% with symptoms at 12 weeks

Table 2: Percentage of study participants reporting any symptom at 12 weeks by sex and age group UK, 26 April 2020 to 6 March 2021

| Estimate | Lower 95% confidence limit | Upper 95% confidence limit |
|----------|--|--|
| 12.7 | 9.8 | 16.4 |
| 14.7 | 10.7 | 20.3 |
| 7.4 | 5.3 | 10.5 |
| 8.2 | 5.7 | 11.8 |
| 11.5 | 7.8 | 16.8 |
| 18.2 | 14.1 | 23.4 |
| 16.1 | 11.8 | 22.0 |
| 16.4 | 12.0 | 22,4 |
| 11.2 | 8.4 | 14.8 |
| | Estimate 12.7 14.7 7.4 8.2 11.5 18.2 16.1 16.4 11.2 | EstimateLower 95% confidence limit12.79.814.710.77.45.38.25.711.57.818.214.116.111.816.412.011.28.4 |

Source: Office for National Statistics





Data ending October 2, 2021



Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA Maxime Taquet,

18.1% overall

16

| | COVID-19 | /ID-19 Influenza in matched cohort (n= 26 497) | | Other respiratory tract Infection in matched cohort (n=44775) | | Skin infection in matched cohort (n=38 977) | | Cholelithiasis in matched cohort (n=19733) | | Urolithiasis in matched cohort (n=28 827) | | Fracture in matched cohort (n=37 841) | |
|-----------------------------------|---------------------|--|---------|---|---------|--|---------|--|---------|--|---------|---------------------------------------|---------|
| | % (95% CI) | % (95% CI) | p value | % (95% CI) | pvalue | % (95% Cl) | pvalue | % (95% CI) | p value | % (95% CI) | pvalue | % (95% CI) | p value |
| Psychilatric illness | 5-8 (5-2 6-4) | 2-8 (2-5-3-1) | <0.0001 | 3-4 (3-1-3-7) | <0-0001 | 3·3 (3-3-7) | <0-0001 | 3-2 (2-8-3-7) | <0-0001 | 2-5 (2-2-2-8) | <0-0001 | 2-5 (2-2-2-7) | <0-0001 |
| Psychotic disorder | 0-1 (0-08-0-2) | 0-04 (0-010-10) | 0-019 | 0-1 (0-06-0-16) | 0-23 | 0-15 (0-096-0-24) | 0-83 | 0-11 (0-054-0-24) | 0-21 | 0-044 (0-016-0-12) | 0-0051 | 0-16 (0-11-0-24) | 0-77 |
| Mood disorder | (1-2-2-4) | 1-1 (0-9-1-3) | <0-0001 | 15 (1-3-17) | 0-0054 | 17 (15-1-9) | 0-55 | 1-6 (1-3-1-9) | 0-14 | 1-2 (1-1-4) | 0-00011 | 1-4 (1-2-1-6) | 0-0050 |
| Anxiety disorder | (4-7 (4-2-5-3) | 2·2 (1·9-2·5) | «0-0001 | 2-5 (2-2-2-8) | <0.0001 | 2-4 (2-1-2-7) | <0-0001 | 2-6 (2-2-3) | <0-0001 | 1-8 (1-6-2-1) | <0-0001 | 1-6 (1-4-1-8) | <0-0001 |
| Insomnia | (1-9)(1-0-2-2) | 0-6 (0-5-0-8) | «0-0001 | 0-8 (0-7-1-0) | <0.0001 | 0-89 (0-73-1-1) | <0.0001 | 1-1 (0-88-1-4) | <0-0001 | 0-57 (0-43-0-74) | <0-0001 | 0-7 (0-570-85) | <0-0001 |
| Dementia in all participants | 0-44 (0-33-0-60) | 0-11 (0-06-0-20) | 0-00044 | 0-25 (0-18-0-35) | 0-00063 | 0-28 (0-20-0-39) | 0-13 | 0-24 (0-14-0-38) | <0-0001 | 0-16 (0-09-0-28) | <0-0001 | 0-34 (0-25-0-44) | 0-14 |
| Dementia (among those > 65 years) | (1-6)(1-2-1) | 0-66 (0-41-1-1) | 0-0043 | 0-84 (0-61-1-1) | 0-00071 | 0-70 (0-49-1-0) | 0-00069 | 0-58 (0-36-0-94) | <0-0001 | 0-60 (0-38-0-95) | <0-0001 | 0-94 (0-68-1-3) | 0-0036 |





6-month neurological and psychiatric outcomes in 236379 survivors of COVID-19: a retrospective cohort study using electronic health records Maxime Taquet, John R Geddes, Masud Husain, Sierra Luciano, Paul J Harrison

236,379 patients with COVID-19.

| | All patients | Patients without hospitalisation | Patients with hospitalisation | Patients with ITU admission | Patients with encephalopathy |
|--|-------------------------|--|----------------------------------|--------------------------------|---------------------------------|
| Mood, anxiety, or psychotic disorder (any) | 23·98% (23·58–24·38) | 23·59% (23·12-24·07) | 24·50% (23·76–25·26) | 27·78% (26·33–29·29) | 36-25% (34-16-38-43) |
| Mood, anxiety, or psychotic disorder (first) | 8-63% (8-28-8-98) | 8-15% (7-75-8-57) | 8-85% (8-22-9-52) | 12.68% (11.28–14.24) | 12·96% (11·13-15·07) |
| Any outcome | 33·62% (33·17-34·07) | 31·74% (31·22-32·27) | 38·73% (37·87-39·60) | 46-42% (44-78-48-09) | 62-34% (60-14-64-55) |
| Any first outcome | 12·84% (12·36–13·33) | 11.51% (10.98–12.07) | 15·29% (14·32-16·33) | 25·79% (23·50–28·25) | 31·13% (27·29-35·36) |



1) Taquet, Maxime, et al. "6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records." *The Lancet Psychiatry* 8.5 (2021): 416-427.



High-dimensional characterization of Ziyad Al-Aly post-acute sequalae of COVID-19

- 73,435 COVID-19 positive non-hospitalized VHA users
- Compared to 4,990,835 VHA users without COVID-19, non-hospitalized
- Beyond the first 30 days of illness, COVID-19 survivors had an increased risk of death (HR 1.59) by 6 months (8 excess deaths per 1000 patients)
- Increased incidence in 6 months of respiratory conditions, with a high burden of bronchodilator use, nervous system disorders including HA, and neurocognitive disorders, mental health issues, metabolic disorders, cardiovascular conditions including dysrhythmias and chest pain, abdominal discomfort and elevated LFTs, blood clots, arthralgias, arthritis, malaise and fatigue.





High-dimensional characterization of Ziyad Al-Aly post-acute sequalae of COVID-19

- 13,654 COVID-19 positive hospitalized VHA users
- Compared to 13,997 patients hospitalized with seasonal flu.
- All patients had to survive 30 days, and the analysis included 6 months of follow up data
- COVID-19 survivors had a 50% increased risk of death compared to flu survivors. The risks increased with increasing severity of disease.
- Of those patients ill enough to be hospitalized with COVID who survived the first 30 days, there were 29 excess deaths per 1000 patients over 6 months.





Ziyad Al-Aly

One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID



Al-Aly, Ziyad, preprint One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID







Al-Aly, Ziyad, preprint One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID



One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID

Ziyad Al-Aly





Al-Aly, Ziyad, preprint One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID







One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID



Ziyad Al-Aly



Al-Aly, Ziyad, preprint One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID



Possible Mechanisms of PASC

- Organ dysfunction that persists after acute infection
- Residual inflammation from a dysregulated immune response
 - Cytokine imbalance
 - Mast Cell Activation Syndrome
 - Autonomic dysregulation
 - Unwelcome immune cells in the CNS
- Lingering virus may be "hidden" in a privileged site, as replicationcompetent virus is rarely recovered beyond 20 days of symptom onset
- Possible neuro-invasion leading to neuropsychiatric symptom
- Endothelial injury along with diffuse thrombosis with microangiopathy
- Coinfection or reactivation of another virus







Any Questions?





