UNDINE	
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Executive Summary

COVID-19 is frequently associated with a wide range of long-term symptoms, referred to as 'post-COVID-19 condition' or 'long COVID'. The World Health Organization defines long COVID as a condition that persists usually 3 months from the acute onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include, but are not limited to, fatigue, shortness of breath, and cognitive dysfunction, and generally have an impact on everyday functioning.

Considering the long COVID condition so defined as too vague for identifying the genetic immunological determinants of the disease, we decided to restrict the recruitment of long COVID patients within the UNDINE project to the more severe cases characterized as here described. The first step required towards studying long COVID cases which have been achieved by the consortium are: 1) the definition of long COVID and 2) creation of a suitable layout of the case report form (CRF) for data collection.

Abbreviations

CRF	Case report form
D	Deliverable
DECT	Dual-energy CT
EC	European Commission
POTS	Postural orthostatic tachycardia syndrome
WP	Work Package
WT	Work Task

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Definition and description of clinical presentation of mild to severe long-COVID

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is the cause of coronavirus disease 2019 (COVID-19). The clinical practice describes COVID-19 as frequently associated with a wide range of long-term symptoms, referred to as 'post-COVID-19 condition' or 'long COVID'.

The World Health Organization has reached a final consensus definition for post-COVID-19 condition in adults describing it as occurring in individuals with a history of SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis (Soriano et al. 2022). Common symptoms include, but are not limited to, fatigue, shortness of breath, and cognitive dysfunction, and generally have an impact on everyday functioning. Additional sequelae of symptoms that have been associated to long COVID are anosmia, hair loss, tremors, paraesthesia, diarrhea, conjunctivitis, dysgeusia, fever, cough, rhinorrhea, pharyngodynia, ear pain, chest pain, myalgia, arthralgia, asthenia, dyspnoea, syncope, headache, confusion, abdominal pain, nausea/vomiting, ejaculation difficulty/reduced libido. It is unclear if and how long COVID symptoms cluster together and whether the condition can be subclassified into distinct symptom-based phenotypes.

Considering the long COVID condition so defined as too vague for identifying the genetic immunological determinants of the disease, the first important goal of WP7, Task 7.1, was to identify the suitable enrolment criteria to restrict the recruitment of long COVID patients to the more severe cases characterized by Brodin et al. (2022, Fig.1).

UNDINE long COVID patients should present:

❖ Persistent signs and symptoms after PCR-verified SARS-CoV2 infection for over three months, not present before the infection and not explained by the severity of the acute phase and by its treatments,

❖ Severe organ damage or dysfunction verified by imaging (e.g. air-trapping/mosaic pattern in lung Dual energy CT (DECT) imaging) or biochemical/molecular test,

❖ Postural orthostatic tachycardia syndrome (POTS) (Jamal et al., 2022),

❖ Deficient oxygen saturation (SpO_2) during the six-minute walking test.

The second goal was to create an appropriate layout for a case report form (CRF), allowing to file the relevant anamnestic and clinical data for long COVID patients. The CRF has been prepared as an excel file, and its format is shown as Table 1. Several UNDINE partners (KI, UNITOV, OSR, KUL) have already identified long COVID patients in their patients cohort and have planned to send samples to KI for centralised immunological analyses.

2   Conclusion

Considering the broad range of symptoms, mostly elusive and self-reported, which characterized long COVID patients, we choose a strict and objectively specified definition of the syndrome for maximizing the chances to more reliably identify the genetic and immunological causes of this heterogeneous condition. The UNDINE participating centers will be informed about the definition of long COVID cases and will receive the CRF in order to start the data collection.

3   References

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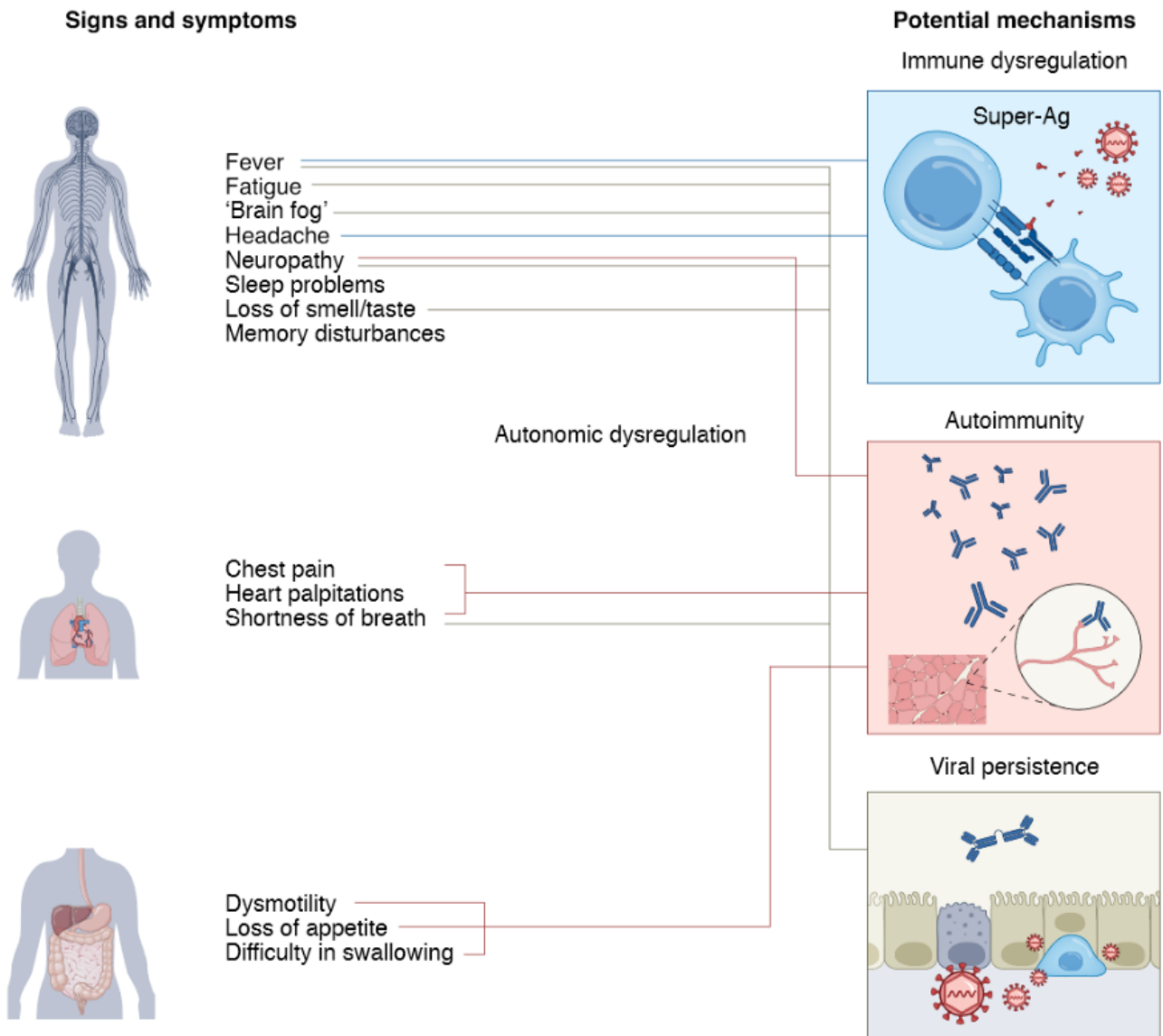
Figure 1. Common signs and symptoms and possible causes of long COVID. a, Signs and symptoms frequently present or reported in patients with long COVID. **b**, Hypothetical mechanisms that could explain key signs and symptoms targeted for further investigation. Super-Ag, superantigen. (taken from Brodin et al. 2022).

Table 1. Case report form (CRF) for long-COVID data collection.

Patient				Comorbidities								Acute COVID-19											Long COVID						
Code Patient	Gender	Age	Ethnicity (country of origin)	Obesity	Chronic diseases* (cardiologic, kidney, pulmonary, ..)	Autoimmune disease?	Prior post-infectious disease (Guillain barré, IgA nephritis, Sydenham's chorea, ME/CFS etc)*	Hypertension	Immunodeficiencies* (Primary, HIV, organ transplantation/immunosuppressive treatment)	PCR+ (when?)	Hospitalization (Yes/No)	Pneumonia	Oxygeno-dependant (<6L O2)	Oxygeno-dependant (>6L O2)*	ICU	ARDS	ECMO	Encephalitis	Kawasaki - MIS-C	Diagnosis date	Hospitalization (Yes/No)	Objective signs fo organ dysfunction*	POTS?	Persistent fever?	Seropositive (date?)	Able to work/study?	Loss of smell?
XCW001	Female	52 years	Caucasian	N	N		N	N	No		Yes	N	Y	N	N	N	N	Y	Y		Yes	N	Y	N	N	N	N