Official title:

Neuropsychiatric 'long-COVID' in adult patients (Phase 1)

Public title:

Long-term mental and brain health effects of COVID among adult patients

Protocol version 1.1 dated 31 August 2022

Sponsor: Department of Psychiatry, The Chinese University of Hong Kong

Collaborators: The University of Hong Kong, Castle Peak Hospital, Kwai Chung Hospital, United Christian Hospital, Pamela Youde Nethersole Eastern Hospital

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Brief Summary: This is a cross-sectional observational case-control study (i) investigate the clinical patterns and clustering of self-reported, prolonged neuropsychiatric morbidities among patients infected by the pre-omicron SARS-CoV-2 virus more than 1 year ago; (ii) investigate the health-related quality of life (HRQoL) of these patients; (iii) explore the relationship between the clinical parameters of the acute COVID-19 episode, socioeconomical factors and prolonged neuropsychiatric symptoms of these patients; and (iv) to investigate any structural differences of the brain among patients with neuropsychiatric long-COVID using multimodal MRI

Study type: observational

Study design: Cross-sectional case control

Follow up duration: nil

Sampling method: convenient sample

Study population: COVID patients

Condition: COVID-19

Intervention: nil

Study Groups: We will recruit 2 groups of subjects – a COVID patients group and a non-COVID control group.

Estimated recruitment: 500 COVID group and 250 non-COVID control. 90 subjects will be recruited for MRI brain imaging sub-study.

Inclusion and exclusion criteria: Inclusion criteria for COVID patients group: (i) history of confirmed SARS-CoV-2 infection of any level of severity; (ii) SARS-CoV-2 infection occurred more than 1 year ago,before Omicron variant prevailed in Hong Kong in Feburary 2022; (iii) aged between 18-65 years; and Inclusion criteria for non-COVID control group: (i) no history of SARS-CoV-2 infection confirmed by lateral-flow test or PCR; and (ii) matched with COVID patients group in terms of the following 5 characteristics: age, gender, ethnicity, pre-COVID medical and psychiatric comorbidities, and socioeconomic status. Exclusion criteria for both groups: unable to give informed consent.

Sex: All

Ages: 18 to 65

Accepts healthy volunteers: Yes

Primary outcome measure:
Core neuropsychiatric symptom cluster(s) among COVID patients measured using self-reported questionnaires one year after initial infection.

Secondary outcome measures:

1. Grey matter volume differences between COVID patients who suffer from core

neuropsychiatric symptom cluster(s) and those who do not as measured by MRI, particularly in

the olfactory cortex, limbic cortex, frontal cortex, and the brainstem one year after initial

infection.

2. Differences in white matter integrity between COVID patients who suffers from core

neuropsychiatric symptom cluster(s) and those who do not as measured by MRI, particularly in

the olfactory cortex, limbic cortex, frontal cortex, and the brainstem one year after initial

infection.

3. Differences in frequency of neuropsychiatric symptoms between COVID patients one year

after initial infection and controls who have never been infected as measured by self-reported

questionnaires.

4. Differences in HRQoL between COVID patients one year after initial infection and controls

who have never been infected measured using self-reported questionnaires.

5. Correlation of clinical characteristics of acute COVID, as retrieved from electronic health record, with core neuropsychiatric symptom clusters, as measured by self-reporting questionnaire.

6. Correlation of socioeconomic factors with core neuropsychiatric symptom cluster(s) as measured by self reporting questionnaires.

7. Correlation of vaccination status (type/number of doses) with core neuropsychiatric symptom cluster(s) as measured by self reporting questionnaires.

cluster(s).

8. Differences in diffusivity and the index along the perivascular space (ALPS index) between

COVID patients one year after initial infection who suffers from core neuropsychiatric symptom cluster(s) and those who do not as measured by MRI.

9. Differences in perfusion between COVID patients one year after initial infection who suffers from core neuropsychiatric symptom cluster(s) and those who do not as measured by MRI.

Detailed description of assessment:

The method of assessment will be an online survey, supplemented by subject's electronic health record. The following data will be collected via the online survey: (i) demographic data; (ii) pre-COVID physical and mental health status; (iii) socioeconomic profile and social impact of COVID-19, including level of social deprivation and health behaviour (iv) clinical parameters of acute COVID-19 episode; (v) self reported symptoms checklist for 'long-COVID', which include items of neuropsychiatric dimensions e.g. cognitive complaint, fatigue, depression, anxiety, insomnia; (iv)neuropsychiatric symptoms scales of mood, anxiety, post-traumatic stress, sleep and fatigue symptoms (vii) brief online cognitive tests with focuses on attention and memory(a. One-back memory test: subjects will be presented with sequence of letters, and they are asked to decide whether the letter they see is the same as the last letter presented; b. Psychomotor vigilance test: the subjects are asked to press the button as quickly as possible when they see the display turn red; c. Digit symbol substitution test : subjects will be presented with symbols, and they are asked to search for the correct symbol-digit pairing from a list, and respond by choosing the paired digit); d. finger tap test.

Separately, we will ask for COVID group's subjects' consent to access their clinical data in relation to their clinical characteristics and treatment of COVID in the premises run by the Hospital Authority via the electronic Clinical Management System (CMS), or CDARS and the Hospital Authority Data Sharing Portal. Specifically, we will ask for permission to access the following details of consented subjects:

1. The dates of admissions and discharges; 2. The progress of the subject during the admission period(s), including any intensive care unit admission record; 3. All of the

investigation results and reports, including but not limited to haematological, biochemical, microbiological and radiological investigations, during the admission period(s); 4. The treatment record, including medication and other therapeutic intervention e.g. oxygen therapy, during the admission periods. 5. All medical diagnoses the subject were given at all-time until the end of the research project. No control group's subjects' medical record will be retrieved.

The MRI brain imaging sub-study is a nested case control study of under the main study. We will recruit 2 groups of subjects – a COVID patients group suffering from core neuropsychiatric symptoms cluster and a matched COVID patients control group which do not have core neuropsychiatric symptom. The sample of the MRI subpart will be recruited from the subject pool of the main study.

MRI brain examinations will be performed using a 3.0 Tesla scanner (MAGNETOM Prisma; Siemens AG, Munich, Germany) equipped with high-performance gradients. A standard 64-channel head coil with parallel imaging capability will be used for signal reception. The scanning sequences will include 1. T1W Multi-echo MPRAGE; 2.T2W ; 3. Multi shell DWI: 2shells (b=1500/3000s/mm2) 92-93 directions per shell, MB = 4, TR = 3.23s, 1.5mm voxels, and 4. Arterial spin labelling.

Planned statistical analysis strategies:

1. T-test and Chi-sqaure test (or non-parametic equvient if applicable) to test the difference in the demographics and socioecomic characteristics between the COVID group and control group sample.

2. Summary statistics of frequency of neuropsychiatric complaints among patients infected with COVID.

3. T-test and Chi-square test (or non-parametric equivalent if applicable) to test the difference in level of mood, anxiety, post-traumatic stress, insomnia, fatigue and HRQoL as measured by respective questionnaires between the COVID group and control group sample.

4. Network analysis to explore the structure of neuropsychiatric symptoms and uncover any symptoms clustering.

5. Univariate t-test (or ANOVA if more than 3 groups) and Chi-square test (or non-parametric equivalent if applicable) to test the differences in demographics, pre-COVID physical and mental health problems, clinical characteristics of acute COVID (e.g. symptoms severity, use of antiviral medication), pre-infection vaccination status, socioeconomic status (especially deprivation index, severe illness or death in close social circle, quarantine durations, being healthcare workers) between patients classified as suffering from neurpsychiatic symptom cluster(s) and those who do not.

6. Generalised estimating equation in testing adjusted regression coefficients of potential predictors above in predicting the presence of neuro. Factors to be included into the GEE will have to achieve a $p < 0.15$ threshold in the univariate analyses.

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