New-onset neuropsychiatric sequelae and 'long-COVID' syndrome (Review)

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Abstract. The ongoing coronavirus disease 2019 (COVID-19) pandemic has had a widespread impact on individuals' mental health through indirect psychological and social mechanisms, related to factors such as fear of infection or death, social isolation, lack of social support and financial instability. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has also been associated with the development or recurrence of neuropsychiatric symptoms, both during the acute phase, as well as during the post-acute 'long-COVID' phase. In addition to the COVID-19 survivors with a mental health history that are at a high risk of experiencing a range of neuropsychiatric symptoms following resolution of acute COVID-19, there is accumulating evidence that a diagnosis of COVID-19 may also be associated with new-onset neuropsychiatric morbidity among survivors without pre-existing mental health disorders. In particular, studies investigating the incidence of post-acute neuropsychiatric sequelae, based mostly on retrospective cohort study designs and data from national health registries, have reported the development of new-onset manifestations, including depression, anxiety, psychotic symptoms, sleep disturbances and fatigue. Nevertheless, when COVID-19 survivors were compared with SARS-CoV-2-negative controls and especially survivors of other disorders (such as influenza), the findings regarding the risk of incident neuropsychiatric manifestations varied among studies. While there is evidence of an association between SARS-CoV-2 infection and the subsequent occurrence of new-onset neuropsychiatric symptoms, especially among patients with increased disease severity, further research using methodological approaches less susceptible to confounding bias is required to establish causal relationships.

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Contents

1. Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic has had significant repercussions on health systems globally, as well as a profound impact on individuals' mental health (1-5). Furthermore, there is evidence to suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

may be associated with the presence of neuropsychiatric manifestations during the acute phase of COVID-19, and a number of individuals may experience a range of new, recurring or ongoing symptoms, including neuropsychiatric manifestations, that persist beyond the acute illness and comprise a condition that is colloquially referred to as 'long-COVID' syndrome (6-10). In particular, neuropsychiatric symptoms associated with 'long-COVID' may include depression, anxiety, post-traumatic stress symptoms, sleep disturbances, fatigue, cognitive impairment/deficits and psychotic features, which can potentially become debilitating and have a disconcerting impact on the well-being of COVID-19 survivors (10,11).

Previous studies have reviewed neuropsychiatric symptoms associated with 'long-COVID' syndrome and their correlates, highlighting the long-term effects of COVID-19 on the mental health of individuals, especially among vulnerable groups (i.e. patients with mental health history) (10-15).

Nevertheless, as researchers strive to identify the mechanisms implicated in the neuropsychiatric manifestations of 'long-COVID', it is of crucial importance to better understand the potential new-onset mental health symptoms that may follow initial recovery from an acute COVID-19 infection or persist beyond the acute illness. The aim of the present review was to provide a comprehensive overview of the published literature on new-onset neuropsychiatric sequelae of COVID-19 and to provide insight into the putative underlying pathophysiological mechanisms.

2. New-onset neuropsychiatric sequelae in COVID-19 survivors

Studies attempting to investigate the association of long COVID with new-onset neuropsychiatric manifestations have mainly used retrospective cohort study designs and data from national health registries (16-25). In most of these studies, which have attempted to investigate the incidence of neuropsychiatric symptoms among COVID-19 survivors, individuals with pre-existing psychiatric problems were excluded (specific criteria vary within each study design). Moreover, in order to explore whether COVID-19 survivors experience a higher risk of presenting neuropsychiatric manifestations, most studies have included as control group individuals without COVID-19 or survivors of other disorders, usually influenza, while sub-analyses of hospitalized or non-hospitalized patients have also been applied (Table I).

A population-based cohort study by Lund *et al* (18) using Danish registry data comprised 8,983 patients who tested positive for SARS-CoV-2 infection (follow-up was from 2 weeks after a positive test to 6 months) during the first wave of the COVID-19 pandemic (February-May 2020), who were alive and not admitted to hospital 2 weeks after their positive test. This previous study also included 1,310 patients who tested positive for SARS-CoV-2 and were admitted to hospital within 2 weeks of their test, along with a matched SARS-CoV-2-negative reference population of 80,894 individuals. Notably, non-hospitalized patients positive for SARS-CoV-2 [27 out of 8,586 (0.3%)] presented a statistically significantly lower risk [adjusted risk ratio (aRR), 0.62; 95% confidence interval (CI), 0.42-0.91] for first-ever psychiatric diagnosis compared with their SARS-CoV-2-negative counterparts [429 out of 74,641 (0.6%)]. Among patients positive for SARS-CoV-2, regarding first-ever diagnosis of psychiatric illnesses, no differences emerged with respect to hospital admission status (no vs. yes; RR, 0.63; 95% CI, 0.26-1.52). Notably, in comparison with SARS-CoV-2-negative individuals, patients positive for SARS-CoV-2 were not at an increased risk of initiating psychiatric drugs, including antidepressants (aRR, 0.84; 95% CI, 0.62-1.13), benzodiazepines and Z-drugs (aRR, 1.03; 95% CI, 0.75-1.41) or antipsychotics (aRR, 0.93; 95% CI, 0.61-1.42).

In another cohort study by Abel *et al* (21), the risk of incident mental health symptoms occurring following SARS-CoV-2 infection (follow-up was from 1 week to 10 months) was investigated using data from a UK primary care registry (February-December 2020), including 86,922 patients positive for SARS-CoV-2 and 345,764 matched controls with a negative SARS-CoV-2 test result (without mental distress, sleep problems or fatigue in the preceding 5 years). In this previous study, having a positive result on a SARS-CoV-2 test was associated with an increased risk of any psychiatric morbidity [adjusted hazard ratio (aHR), 1.83; 95% CI, 1.66-2.02] and of being prescribed psychotropic medication (aHR, 2.24; 95% CI, 2.09-2.40). The association between SARS-CoV-2 infection and psychiatric morbidity was greater for older adults, while women with a positive SARS-CoV-2 test had a higher incidence for all outcomes compared with men, albeit the relative increase associated with a positive test result was larger for men than for women based on tests for equivalence of aHRs. Notably, a higher risk of psychiatric manifestations was also found for individuals with influenza compared with control individuals (aHR, 2.98; 95% CI, 1.55-5.75). Crucially, the results of a further analysis of that study to explore confounding bias (using a negative exposure control) were, according to the authors, suggestive of unobserved confounding.

In a nationwide cohort study in South Korea (data extracted, January-June 2020; follow-up until December 2020), Park *et al* (26) used data from the National Health Insurance Service COVID-19 database, and compared 6,148 COVID-19 survivors with 254,735 individuals without a COVID-19 diagnosis, after excluding individuals with mental health history prior to 2020. Newly diagnosed mental disorders were significantly more frequent in the COVID-19 cohort [738 out of 6,148 (12.0%)] compared with the control group [19,524 out of 254,357 (7.7%); P<0.001].

In accordance with the results of the previous study, Taquet *et al* (20) performed a retrospective cohort study (January-December 2020) using electronic health records in the USA. This previous study investigated the incidence of first neurological/psychiatric diagnoses (i.e. excluding those diagnosed before the index event) among 236,379 COVID-19 survivors in the 6 months post-infection (i.e. 1-180 days post-index event) and compared associated risks with two propensity score-matched control cohorts of 105,579 patients diagnosed with influenza and of 236,038 patients with any respiratory tract infection (RTI), including influenza, during the same period. According to the findings of this study, 8.63% (95% CI, 8.28-8.98) of the survivors received a first diagnosis of any psychiatric disorder (either anxiety disorder, mood disorder or psychotic disorder) in the 6 months after COVID-19 diagnosis, whereas the estimated incidence was higher for patients with intensive care unit (ICU) admission (12.96; 95% CI,

Table I. Studies reporting neuropsychiatric sequelae following SARS-CoV-2 infection.

First author, year	Study design	Country	Participants	Age	Time since acute COVID-19/Follow-up period	Inclusion criteria	Exclusion criteria	Main findings	(Refs.)
Lund, 2021	Population-based cohort study	Denmark	• 8,983 individuals positive for SARS-CoV-2 who were not admitted to hospital 2 weeks after their positive test along with 80,894 eligible SARS-CoV-2-negative individuals • 1,310 patients who tested positive for SARS-CoV-2 and were admitted to hospital within 2 weeks of their test	Median (IQR) • 43 (30-56) years in SARS-CoV-2-positive non-hospitalized individuals • 43 (29-56) years in SARS-CoV-2-negative individuals • 64 (52-76) years in SARS-CoV-2-positive hospitalized individuals	2 weeks post-positive test to 6 months	• Individuals with a positive or negative SARS-CoV-2 test in Denmark between February 27 and May 31, 2020 • Patients who were alive 2 weeks after their positive test	• Less than 1 year of residency in Denmark • Inconclusive test results • Patient death in the 2 weeks after their test • Prescription drug use and medical history (any time to day 13)	• Lower risk of first ever anxiety diagnosis in non-hospitalized patients with SARS-CoV-2-positive compared with negative controls. No differences in first ever depression or first ever fatigue-related disorder diagnosis • No differences in first ever psychiatric diagnosis among patients positive for SARS-CoV-2, with respect to hospital admission status	(18)
Abel, 2021	Retrospective cohort study	United Kingdom	• 86,922 SARS-CoV-2-positive patients • 345,764 matched controls with negative SARS-CoV-2 test result	Median (IQR) • 44 (30-61) years in the eligible cohort of 11,923,105 individuals	Follow-up for up to 10 months, from February 1 to December 9, 2020	• Individuals aged 16 years or older during 2020 • Individuals registered at the Clinical Practice Research Datalink Aurum participating clinical practice from February 1 to December 8, 2020	• Individuals with less than 2 years of historical data or less than 1 week follow-up were excluded • In the incident cohort, individuals with recorded histories of psychiatric morbidity, fatigue, sleep problems, or psychotropic medications in the 5 years prior to their index date	• Individuals with a SARS-CoV-2-positive test had increased risk of any psychiatric morbidity (i.e., new-onset anxiety, depression, self-harm, fatigue and sleep disorders), as well as of being prescribed psychotropic medication compared with negative individuals • Higher risk of psychiatric manifestations for individuals with influenza compared with negative individuals	(21)
Park, 2021	Nationwide retrospective cohort study	Korea	• 6,148 COVID-19 survivors • 254,735 individuals without a COVID-19 diagnosis	• In total sample, most individuals (24.5%) were between 20-29 and between 30-39 (17.5%) years of age • Statistically significant differences between the groups	Data were extracted from January 1 to June 4, 2020 and development of mental illness was determined from January 1 to December 1, 2020	Individuals included in the National Health Insurance Service COVID-19 data base in South Korea (from January 1 to June 4, 2020)	• Individuals under the age of 20 • Individuals who had a previous history of mental illness up until December 31, 2019 • For COVID-19 patients: Patients who died from the infection during their hospital admission	• Anxiety and stress-related disorder, as well as mood disorders without psychotic features, were significantly more frequent in the COVID-19 cohort as compared with the control group • No differences emerged regarding alcohol or drug misuse, eating disorders, personality disorders, non-affective psychotic disorders or affective psychotic disorders	(26)

Table I. Continued.

First author, year	Study design	Country	Participants	Age	Time since acute COVID-19/Follow-up period	Inclusion criteria	Exclusion criteria	Main findings	(Refs.)
Taquet, 2021	Retrospective cohort study	USA	• 236,379 patients who had a COVID-19 diagnosis • 105,579 matched controls diagnosed with influenza • 236,038 matched controls diagnosed with any RTI, including influenza	Mean (SD) • 46 (19.7) years in patients with COVID-19 • 38.6 (19.7) years in propensity score-matched patients with influenza • 46.0 (20.4) years in propensity score-matched patients with any RTI	Follow-up, 1-180 days after the index event	All cohorts included patients older than 10 years who had an index event on or after January 20, 2020 (the date of the first recorded COVID-19 case in the USA), and who were still alive at the time of the main analysis (December 13, 2020), from the TriNetX electronic health records network	Individuals with a psychiatric diagnosis before the index event (excluded when estimating first diagnoses incidence)	• Psychiatric disorders' first diagnosis (mood disorder, anxiety disorder, psychotic disorder, insomnia) was more common in COVID-19 survivors in comparison with patients with influenza or RTI • Patients with COVID-19 experienced a higher risk of new-onset substance use disorder compared with patients with influenza, but lower compared with patients with RTI • Higher incidences in patients with more severe COVID-19	(20)
Taquet, 2021	Retrospective cohort study	USA	44,779 COVID-19 survivors without pre-existing psychiatric illness, compared with propensity score-matched control cohorts presenting other health events (i.e., including influenza, other RTI, skin infection, cholelithiasis, urolithiasis and fracture of a large bone)	Mean (SD) • 49.3 (19.7) years in patients with COVID-19 • 41.8 (19.8) years in patients with influenza, 47.2 (19.9) years in patients with other RTI, 46.7 (20.9) years in patients with skin infection, 53.2 (19.3) years in patients with cholelithiasis, 50.2 (18) years in patients with urolithiasis and 48 (23.6) years in patients with fracture of a large bone	Follow-up, 14-90 days after COVID-19 diagnosis	• Patients diagnosed with COVID-19 between January 20 and August 1, 2020, from the TriNetX electronic health records network • All seven cohorts (COVID-19 and six control health events) included all patients older than 10 years who had the corresponding health event on or after January 20, 2020	• Patients who had died by the time of the analyses (August 1, 2020) • In the primary analysis, patients who had a psychiatric diagnosis recorded before the health event (COVID-19 or control health event)	• In patients with no psychiatric history, a diagnosis of COVID-19 was associated with increased incidence of a first psychiatric diagnosis in the following 14 to 90 days compared with the six other health event cohorts • Greatest incidences noted for anxiety disorders • When diagnoses were considered separately (i.e. for anxiety disorder, mood disorder, psychotic disorder, insomnia) incidences were greater in patients with COVID-19 compared with patients with influenza, as well as patients with other RTI (except psychotic disorder); differences also emerged when comparing with the other health events.	(16)
Patel, 2022	Retrospective cohort study	USA	778,738 veterans, who were tested for COVID-19. Among	Mean (SD) age of the total cohort was 61 (15.4) years	Follow-up 7 days to 3 months after the index date (i.e., date	Veterans, who were tested for COVID-19 at VA facilities between	• Patients defined as employees and others, keeping only veterans	• COVID-19 survivors and particularly those who required hospitalization, developed	(22)

Table I. Continued.

First author, year	Study design	Country	Participants	Age	Time since acute COVID-19/Follow-up period	Inclusion criteria	Exclusion criteria	Main findings	(Refs.)
			them, 123,757 (15.9%) were diagnosed with COVID-19		of the earliest positive test or negative test. If the patient had been admitted to a VA hospital during the preceding 15 days, the date of admission served as the index date)	February 20, 2020 and March 27, 2021, for any indication, and who had at least one primary care follow-up in the previous 18 months	with proven established care at the VA healthcare system • Patients who died within 3 months of the index date or who did not have a minimum of 3 months of follow-up after the index date • Patients who had the respective physical and mental health conditions as prevalent conditions before the index date • Patients with an index date later than December 27, 2020	new-onset depressive episode, adjustment disorder, insomnia and dementia at a significantly higher rate than those without • Hospitalization was associated with a significantly higher incidence and odds of developing mental health conditions	
Chen, 2022	Retrospective cohort study	USA	3,158 veteran patient who were hospitalized for COVID-19, between March and August 2020	Mean (SD) age of total sample was 64.33 (14.78) years	Follow-up, up to 6-months following COVID-19 hospitalization	All veterans hospitalized at Veterans Health Administration hospitals for COVID- 19 from March through August of 2020	• Patients who died during hospitalization or within 6 months of discharge, or were missing covariate information • Patients who had been diagnosed with the respective psychiatric condition within 2 years prior to hospitalization	• 277 (7.9%) patients developed a new mental health diagnosis following hospitalization with the most common being depressive, anxiety, and adjustment disorders • Patients with mental health history were not excluded and thus among patients with a new mental health diagnosis, 64% had an existing comorbid diagnosis	(23)
Xie, 2022	Retrospective cohort study	USA	153,848 individuals who survived the first 30 days of SARS-CoV-2 infection, and two control groups: A contemporary group (n=5,637,840) with no evidence of SARS-CoV-2, and a	Mean (SD) after weighting • 63.06 (16.18) years in the COVID-19-positive cohort • 63.40 (16.22) years in the contemporary control group • 63.32 (16.30) years in the historic control	• For the COVID-19-positive cohort: Follow-up from the date of the positive test result up to November 30, 2021 (median follow-up days, IQR: 377, 347-469). • Contemporary	• For the COVID-19-positive cohort: individuals who had used the Veterans Health Administration in 2019 and had at least one positive COVID-19 test result between March 1, 2020 and January 15, 2021, and	Individuals with mental health history (from 2 years before the positive SARS-CoV-2 test up to 30 days after the test)	• Compared to their contemporary SARS-CoV-2 negative counterparts, COVID-19 survivors presented an increased risk of incidence of any mental health diagnosis, any mental health-related drug prescription and any mental health diagnosis or prescription, even among non-hospitalized individuals	(25)

Table I. Continued.

First author, year	Study design	Country	Participants	Age	Time since acute COVID-19/Follow-up period	Inclusion criteria	Exclusion criteria	Main findings	(Refs.)
			historic control group (n=5,859,251) that predated the COVID-19 pandemic	group	control group had a similar distribution of follow-up time (median, IQR: 378, 348-471), while similar methods were applied with respect to the historic group (median, IQR: 378, 347-470)	also were alive 30 days after the positive test result • For the contemporary control group: Individuals who used the Veterans Health Administration in 2019 and that were alive by 1 March 2020 and not in the COVID-19 group • For the historic control group: Individuals who used the Veterans Health Administration in 2017, were alive on March 1, 2018 and were not in the COVID-19 group		• Findings were also consistent in comparisons using the historic control group • Risk of new-onset mental health disorders was higher in patients with COVID-19 compared with both patients with seasonal influenza and individuals admitted to hospital for any other cause	
Iosifescu, 2022	Retrospective cohort study	USA	• 388 patients with COVID-19 with new-onset neurological/ neuropsychiatric symptoms • 18,423 patients with COVID-19 without neurological/ neuropsychiatric symptoms • 149 patients with influenza with new-onset neurological/ neuropsychiatric symptoms	Mean (SD) • 57.2 (19.3) years in patients with COVID-19 with new-onset neurological/ neuropsychiatric symptoms • 55.2 (20.8) years in patients with COVID-19 without neurological/ neuropsychiatric symptoms • 40.0 (24.0) years in patients with influenza with new-onset neurological/ neuropsychiatric symptoms	Individuals were retrospectively screened between January 1, 2020 and June 9, 2021	• Patients of the Montefiore Health System, one of the largest healthcare systems in New York City (data between January 1, 2020 and June 9, 2021) • For the COVID-19 cohort, all individuals who tested positive for SARS-CoV-2 infection • For the influenza cohort individuals: Diagnosed with influenza in the same hospital system and within the same timeframe, but without a COVID-19 diagnosis	• Individuals not screened • Having neurological/ neuropsychiatric symptoms prior to diagnosis • Developed symptoms <2 weeks after the diagnosis	• New-onset neuropsychiatric symptoms were recorded in 2.06% of COVID-19 survivors and in 2.58% of patients with influenza • Patients with influenza presented similar neuropsychiatric manifestations to COVID-19 survivors, apart from a lower incidence in altered mental status	(17)
Clift, 2022	Retrospective cohort study	UK	• 32,525 COVID-19 hospital admission survivors	Mean (SD) • 65.40 (18.42) years in COVID-19 admission	• Follow-up time was calculated from the discharge date	• Adults alive and registered with a contributing general	For each outcome, the authors excluded individuals with	• Both SARI survivors and COVID-19 survivors displayed higher risk for new-onset	(24)

Table I. Continued.

First author, year	Study design	Country	Participants	Age	Time since acute COVID-19/Follow-up period	Inclusion criteria	Exclusion criteria	Main findings	(Refs.)
			• 16,679 SARI admission survivors • 8,330,986 adults in the reference population	survivors • 69.34 (18.70) years in SARI admission survivors • 49.07 (18.40) years in adults of the reference population	for those surviving a COVID-19 or SARI-related hospital admission and for the remaining population from January 24, 2020 • Patient follow-up was until the earliest date of outcome of interest or censoring (left practice, died for any reason, or reached the end of follow-up alive) • Follow-up was truncated to 1 year for analysis	practice from January 24, 2020 (date of first COVID-19 case in England), until the data extract date (July 7, 2021) • In historic cohort: Adults aged 18 years and older entering the cohort from January 24, 2015 to January 23, 2020	previously recorded records of the outcome of interest	neuropsychiatric diagnosis post discharge for all studied outcomes compared with the general population • No significant differences between COVID-19 survivors and SARI survivors	
Coleman, 2022	Retrospective cohort study	USA	• 46,610 COVID-19-positive individuals • 46,610 propensity score-matched controls with RTI diagnosis	Not included in the paper	• Follow-up 21 to 365 days after initial presentation (cutoff date, October 20, 2021)	• Individuals included in National COVID Cohort Collaborative electronic health record repository (January 2020-October 2021) • For COVID-19 cohort: SARS-CoV-2 positive test after January 1, 2020 • For control cohort: Patients with a diagnosis of a RTI other than COVID-19	• Patients with a history of any mental illness prior to 21 days after COVID-19 diagnosis • Patients without a medical record extending back to a year prior to COVID-19	• New-onset anxiety disorder diagnosis was higher in patients with COVID-19 compared to in patients with RTI in the early post-acute phase (from 21 to 120 days), but not during the late post-acute phase (from 121 to 365 days) • No differences in new-onset mood disorders, neither in the early post-acute phase nor in the late post-acute phase	(19)
Rivera-Izquierdo, 2022	Prospective, multicenter, cohort study	Spain	• 453 patients hospitalized due to COVID-19 • 453 patients hospitalized due to other causes	Mean (SD) • 61.2 (14.3) years in patients hospitalized due to COVID-19 • 55.9 (17.8) years in patients hospitalized due to other causes	Patients were consulted by telephone 12 months after discharge	• Adults hospitalized and discharged alive from March 1 to April 15, 2020, in four hospitals in Andalusia, Spain • For COVID-19 cohort: SARS-CoV-2 positive test	• Patients lost to follow-up • Symptoms that were present prior to hospital admission	• Higher incidences in anxiety symptoms and confusion/memory loss in COVID-19 survivors compared with individuals hospitalized due to other causes • No significant differences in depressive symptoms, sleep disturbances, fatigue, or headache	(27)

Table I. Continued.

First author, year	Study design	Country	Participants	Age	Time since acute COVID-19/Follow-up period	Inclusion criteria	Exclusion criteria	Main findings	(Refs.)
Jacob, 2022	Retrospective cohort study	Germany	• 56,350 patients with COVID-19 • 56,350 propensity score-matched controls with AURI	Mean (SD) • 43.6 (19.2) years in patients with COVID-19 • 43.6 (19.2) years in AURI controls	Up to 14 months follow-up; patients were diagnosed between March 2020 and May 2021	• Adults with at least one visit to one of 1,198 general practices in Germany between March 2020 and May 2021 • Patients diagnosed with COVID-19 or AURI	• COVID-19 diagnosis within the preceding year • Depression or anxiety disorder history within the preceding year	No significant difference in incidence of depression or anxiety disorder between patients with COVID-19 and AURI	(28)

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IQR, interquartile range; AURI, acute upper respiratory infection; RTI, respiratory tract infection; SARI, severe acute respiratory infections; VA, Veteran Affairs.

12.28-14.24). Notably, a first diagnosis of a psychiatric disorder was more common in COVID-19 survivors in comparison to both patients with influenza (HR, 1.81; 95% CI, 1.69-1.94) and those presenting other RTIs (HR, 1.48; 95% CI, 1.42-1.55).

It should be noted that a previous retrospective cohort study (16), which was performed by the same research group using USA electronic health records (January-August 2020), assessed the incidence of first psychiatric diagnoses in 44,779 COVID-19 survivors, without pre-existing psychiatric illness, at 14-90 days post-COVID-19 diagnosis and also compared associated risks with matched control cohorts presenting with other health events (including influenza, other RTIs, skin infection, cholelithiasis, urolithiasis and fracture of a large bone). Among the COVID-19 survivors, 5.8% (95% CI, 5.2-6.4) had their first recorded diagnosis of psychiatric illness in comparison to 2.5-3.4% of patients in the aforementioned control cohorts.

In accordance with the findings of previous studies suggesting an increased risk for new-onset psychiatric disease in the post-COVID-19 period, a propensity score-matched retrospective cohort study was conducted to compare US veterans who were tested for COVID-19 between February 2020 and March 2021 vs. patients with negative SARS-CoV-2 test results (22). Incident conditions were defined as conditions that developed during a follow-up period of 7 days to 3 months post-index date in patients without such pre-existing conditions. COVID-19 survivors (15.9% out of 778,738 veterans), particularly those who required hospitalization, developed new-onset neuropsychiatric symptoms at a significantly higher rate than those without COVID-19. In the outpatient setting, the results were more perplexing. Although the incidence of mental health conditions was overall rather low (0.2-1.5%), patients with COVID-19 presented a significantly lower incidence of mental health conditions than patients negative for COVID-19. When comparing the incidence of mental health conditions between COVID-19-positive matched patients who were hospitalized to those treated as outpatients, it emerged that hospitalization was associated with a significantly higher incidence and odds of developing mental health conditions.

Another study in veteran patients (n=3,518), who were all hospitalized for COVID-19, between March and August 2020, revealed that 277 (7.9%) patients developed a new mental health diagnosis following hospitalization (i.e. having not been diagnosed with the specific condition within 2 years prior to hospitalization) (23). Younger patients and those residing in rural areas were more likely to develop new mental health diagnoses, whereas women and patients with more comorbidities were less likely to develop new diagnoses.

Furthermore, a recent cohort study of US veterans (March 2020-November 2021) estimated the risks of incident mental health disorders in COVID-19 survivors (i.e. without a history of the mental health outcome in the 2 years prior to the beginning of follow-up) (25). This previous study included 153,848 individuals who survived the first 30 days of SARS-CoV-2 infection, 5,637,840 individuals as a contemporary control group with no evidence of SARS-CoV-2 and 5,859,251 individuals as a historic pre-pandemic control group (totalling 13,052,788 person-years of follow-up). The results of this study showed that compared with their contemporary SARS-CoV-2-negative counterparts, COVID-19 survivors

presented an increased risk of any incident mental health diagnosis (HR,1.46; 95% CI, 1.40-1.52), any incident mental health-related drug prescription (HR, 1.86; 95% CI, 1.78-1.95), and any incident mental health diagnosis or prescription (HR, 1.60; 95% CI, 1.55-1.66). The risks of examined outcomes were found to be increased even among non-hospitalized individuals but were the highest among patients hospitalized during the acute phase of COVID-19. Findings were also consistent in comparisons performed using the historic control group. Furthermore, the risk of incident mental health disorders was higher in patients with COVID-19 compared with both patients with seasonal influenza and individuals admitted to hospital for any other cause.

Iosifescu *et al* (17), in a retrospective cohort study performed in a large healthcare network in New York City, USA, screened patients with COVID-19 and influenza (January 2020-June 2021) for the presence of new-onset neurological/neuropsychiatric symptoms persisting ≥2 weeks past COVID-19 or influenza diagnosis, respectively. Notably, those with pre-existing neurological/neuropsychiatric symptoms were excluded. New-onset neuropsychiatric symptoms were recorded in 2.05% (388 out of 18,881) of COVID-19 survivors and in 2.58% (149 out of 5,772) of patients with influenza. It should be noted that patients with influenza presented neuropsychiatric manifestations similar to COVID-19 survivors, apart from a lower incidence of altered mental status and a non-significantly lower incidence of fatigue. The mean onset of neurological/neuropsychiatric symptoms among COVID-19 survivors was 138 days post-diagnosis, with inpatients experiencing symptoms significantly earlier than outpatients (120 vs. 146 days, respectively). Conversely, patients with influenza displayed a significant delay in symptom onset (mean onset, 238 days) compared with COVID-19 survivors. These findings could indicate that COVID-19, in comparison to other respiratory viruses, may induce early neurological/neuropsychiatric manifestations, whereas severe and mild COVID-19 infection may be potentially associated with earlier symptom onset or more gradual development of neurological/neuropsychiatric manifestations, respectively. Furthermore, compared with patients with COVID-19 without neurological/neuropsychiatric symptoms, patients with COVID-19 with such symptoms were older, more likely female and had lower levels of laboratory parameters, such as lactate dehydrogenase, C-reactive protein (CRP) and D-dimer. Conversely, race, ethnicity, hospitalization status, body mass index (BMI), blood urea nitrogen (BUN), lymphocytes, leukocytes and comorbidities were not significantly associated with neurological/neuropsychiatric symptoms among COVID-19 survivors. Among patients with new-onset neurological/neuropsychiatric symptoms, COVID-19 survivors compared with patients with influenza, were significantly older, prevalently male and presented higher hospitalization rate, BMI, as well as laboratory values (i.e. CRP, D-dimer and BUN).

One of the largest published studies on the incidence of neuropsychiatric disorders post-COVID thus far is an English cohort study (24). This previous study comprised data from 8.38 million adults (January 2020-July 2021), including 16,679 (0.20%) individuals surviving hospitalization for severe acute respiratory infections (SARI) other than COVID-19 and 32,525 (0.39%) individuals surviving hospitalization for COVID-19. These patient groups were compared with the remaining general population regarding new-onset diagnoses of neuropsychiatric conditions (individuals with previous records of the outcome of interest were excluded) or first psychiatric medication prescription during 12 months of follow-up from hospital discharge. Both SARI survivors and COVID-19 survivors displayed a higher risk for new-onset neuropsychiatric diagnosis post-discharge for all studied outcomes compared with the general population. Nevertheless, no significant differences were observed when COVID-19 survivors were compared with SARI survivors regarding new-onset neuropsychiatric symptoms. Regarding the first recorded neuropsychiatric prescription after hospital discharge, the risks were significantly higher in survivors of SARI and hospitalized patients with COVID-19 compared with the remaining population for all medications analysed (i.e. antidepressants, hypnotics/anxiolytics and antipsychotics). Conversely, no significant differences emerged between the COVID-19 and the SARI cohort, except for a lower risk of antipsychotic prescriptions in COVID-19 survivors (aHR, 0.80; 95% CI, 0.69-0.92).

Similar results suggesting an excess risk for new-onset neuropsychiatric diagnoses during the post-COVID period were found in a retrospective electronic health record cohort study (January 2020-October 2021) by Coleman *et al* (19), including 46,610 propensity score-matched patient pairs of individuals positive for COVID-19 and comparable controls with RTI diagnosis. This previous study investigated the incidence of new-onset mental illness from day 21 to 1 year following initial presentation (patients with any psychiatric diagnosis during COVID-19 infection, i.e. first 21 days after diagnosis or prior to COVID-19 infection, were excluded). A statistically significant difference was identified in the hazard rate of new-onset psychiatric sequelae between COVID-19 and control groups in the early post-acute phase (from 21 to 120 days), but not in the late post-acute phase (from 121 to 365 days). In particular, the estimated incidence proportion of a new-onset psychiatric diagnosis in the early post-acute phase for the COVID-19 group was 3.8% (95% CI, 3.6-4.0), which was significantly higher than the 3.0% (95% CI, 2.8-3.2) for the RTI group (HR, 1.3; 95% CI, 1.2-1.4).

From the previous evidence, new-onset neuropsychiatric morbidity seems strongly associated with respiratory infections, particularly SARS-CoV-2. Nevertheless, the findings regarding increased neuropsychiatric incidence in survivors of COVID-19 in comparison with other respiratory infections vary among studies. Since most studies suffer from methodological limitations and biases, future well-designed cohorts, basic research studies and focused meta-analyses are required to evaluate the true extent of the association between 'long-COVID' and new-onset neuropsychiatric disorders.

New-onset affective and anxiety symptoms and 'long-COVID'. In studies investigating new-onset neuropsychiatric manifestations in COVID-19 survivors without pre-existing mental health problems, depression and anxiety emerge among the most commonly reported symptoms.

In particular, Taquet *et al* (20) found in a retrospective cohort study of 236,379 COVID-19 survivors that 1-180 days post-COVID-19 diagnosis, 7.11% (95% CI, 6.82-7.41; ICU

admission, 9.79; 95% CI, 8.65-11.06) received a first diagnosis of an anxiety disorder, whereas 4.22% (95% CI, 3.99-4.47; ICU admission, 5.82; 95% CI, 4.86-6.97) received a first diagnosis of a mood disorder. When compared with patients with influenza and patients with other RTIs, COVID-19 survivors had higher probabilities of new-onset anxiety (HR 1.78 and 1.48, respectively) and mood disorder (HR 1.79 and 1.41, respectively). In a previous retrospective cohort study (16) from the same research group, including 44,779 COVID-19 survivors, it emerged that 14-90 days post-COVID-19 diagnosis, 2.0% (95% CI, 1.7-2.4) received their first recorded diagnosis of a mood disorder (depressive episode, 1.7; 95% CI, 1.4-2.1; mania/bipolar, 0.1; 95% CI, 0.04-0.25), whereas 4.7% (95% CI, 4.2-5.3) received their first diagnosis of a anxiety disorder; both were found to present more commonly in the COVID-19 cohort compared with the influenza and other RTI matched cohorts. When anxiety disorders were analysed individually, adjustment disorder (0.94; 95% CI, 0.74-1.2) and generalized anxiety disorder (0.85; 95% CI, 0.66-1.1) were the most frequent, followed by post-traumatic stress disorder (PTSD; 0.25; 95% CI, 0.16-0.4) and panic disorder (0.26; 95% CI, 0.17-0.4), whereas obsessive-compulsive disorder (OCD) presented rarely (0.04; 95% CI, 0.008-0.17).

Furthermore, Park *et al* (26) in a South Korean nationwide cohort study, compared 6,148 COVID-19 survivors with 254,735 individuals without a COVID-19 diagnosis and found that significantly more COVID-19 survivors presented anxiety and stress-related disorder (8.0 vs. 5.2%, P<0.001), as well as mood disorders without psychotic features (5.6 vs. 3%, P<0.001).

A prospective cohort study by Rivera-Izquierdo *et al* (27) in Spain investigated the incidence (symptoms that were present prior to hospital admission were excluded) of sequelae or persistent symptoms 12 months after discharge in 453 individuals hospitalized due to COVID-19 compared with an equal number of individuals hospitalized due to other causes (March-April 2020) and discharged alive. According to the findings of this study, a higher incidence of anxiety symptoms was noted in COVID-19 survivors compared with in individuals hospitalized due to other causes (7.3 vs. 3.1%; RR, 2.36; 95% CI, 1.28-4.34), while no differences emerged in depressive symptoms (4.0 vs. 3.5%; RR, 1.13; 95% CI, 0.58-2.18).

Consistent with the aforementioned findings, Coleman *et al* (19), in a retrospective cohort study of 46,610 propensity score-matched patient pairs of individuals positive for COVID-19 and comparable controls with a RTI diagnosis indicated that new-onset anxiety disorder diagnosis was significantly increased for patients with COVID-19 compared with patients with RTI in the early post-acute phase (HR, 1.3; 95% CI, 1.1-1.4), but not during the interval of 121-365 days following initial presentation (HR, 1.0, 95% CI, 0.91-1.1). However, regarding new-onset mood disorders, no differences emerged in the early post-acute phase (21-120 days) or in the late post-acute phase (121-365 days).

Conversely, Patel *et al* (22), in a retrospective cohort study of US veterans, found that COVID-19 survivors that required hospitalization, compared with propensity-matched hospitalized patients negative for COVID-19, displayed significantly higher incidences of a depressive episode (6.6 vs. 4.3%; P<0.001) and adjustment disorder (2.5 vs. 1.7%, P<0.001), whereas no statistically significant differences emerged regarding the incidence of panic disorder, generalized anxiety and PTSD. With respect to admission to hospital, hospitalized patients with COVID-19 compared with those treated as outpatients demonstrated higher incidences of depressive episodes (6.6 vs. 1.2%; P<0.001), panic disorder (0.3 vs. 0.1%; P<0.001), generalized anxiety (0.7 vs. 0.3%; P<0.001), PTSD (1.4 vs. 0.5%; P<0.001) and adjustment disorder (2.4 vs. 0.9%; P<0.001). Accordingly, Chen *et al* (23) found that among the 277 (7.9% of 3,518) veteran hospitalized COVID-19 survivors with new-onset mental health manifestations, the most common new diagnoses included depression (28%), anxiety (28%), adjustment disorders (24%) and PTSD (17%), whereas in another US veteran cohort study, Xie *et al* (25) found that COVID-19 survivors compared with individuals without COVID-19 presented increased risks of anxiety, depression, stress and adjustment disorders.

In a cohort study by Clift *et al* (24), SARI and COVID-19 survivors compared with the general population displayed higher levels of new-onset anxiety (SARI aHR, 1.86; 95% CI, 1.56-2.21; COVID-19 aHR, 2.36; 95% CI, 2.03-2.74), depression (SARI aHR, 3.46; 95% CI, 2.21-5.40; COVID-19 aHR, 1.95; 95% CI, 1.05-3.65) and bipolar disorder (SARI aHR, 2.26; 95% CI, 1.25-4.08; COVID-19 aHR, 2.26; 95% CI, 1.25-4.07). No differences were found between the COVID-19 and the SARI cohort (reference group) regarding new-onset anxiety disorder (aHR, 1.00; 95% CI, 0.79-1.27), depression (aHR, 0.63; 95% CI, 0.25-1.58) or bipolar affective disorder (aHR, 0.74; 95% CI, 0.32-1.69).

Similar were the findings in a retrospective cohort study by Jacob *et al* (28) (March 2020-May 2021) including patients without a history of depression or anxiety disorder within the preceding year, which were followed in general practices in Germany. In this study, 56,350 patients with COVID-19 were compared with an equal sample of patients with acute upper respiratory infection matched using propensity scores based on sex, age, index month and Charlson comorbidity index. According to the findings, COVID-19 diagnosis was not significantly associated with an increase in the incidence of depression [incidence rate ratio (IRR), 1.02; 95% CI, 0.95-1.10] or anxiety disorder (IRR, 0.94; 95% CI, 0.83-1.07) in comparison to a diagnosis of acute upper respiratory infection. No significant association emerged between COVID-19 diagnosis and the incidence of either depression or anxiety in all sex and age subgroups.

In accordance with the previous studies, in a retrospective cohort study by Iosifescu *et al* (17), among 388 patients with COVID-19 with neurological/neuropsychiatric sequalae (out of 18,811 patients with COVID-19), 30% reported anxiety disorders and 27% depression, albeit no differences were found with respect to the flu cohort.

Lund *et al* (18) in a population-based cohort study, found that non-hospitalized individuals positive for SARS-CoV-2 [9 out of 8,884 (0.1%)], compared with negative individuals [107 out of 79,616 (0.1%)], did not present a significantly different risk of first ever depression diagnosis (aRR, 0.91; 95% CI, 0.46-1.80). However, patients with COVID-19 had a significantly lower risk [15 out of 8,786 (0.2%)] of first anxiety diagnosis compared with SARS-CoV-2-negative individuals [293 out of 77,654 (0.4%); aRR, 0.54; 95% CI, 0.32-0.90].

In a cohort study by Abel *et al* (21), patients with SARS-CoV-2 infection compared with individuals with SARS-CoV-2 negative test results, presented increases in new-onset anxiety (aHR, 1.93; 95% CI, 1.71-2.18), depression (aHR, 1.74; 95% CI, 1.52-2.00) and self-harm risks (aHR, 2.21; 95% CI, 1.11-4.39). Regarding psychiatric medications, the largest increases included receipt of nonbenzodiazepine hypnotics (aHR, 4.90; 95% CI, 4.00-5.99), mood stabilizers (aHR, 3.55; 95% CI, 2.74-4.61), benzodiazepines (aHR, 3.50; 95% CI, 2.95-4.15) and antidepressants (aHR, 1.72; 95% CI, 1.57-1.88). However, these findings should be interpreted with caution considering that the results of a further analysis performed in the same study using a negative exposure control to explore confounding bias were suggestive of unobserved confounding.

Despite evidence of an association between COVID-19 and new-onset anxiety and depression symptoms, especially among patients with increased disease severity, further research is required using methodological approaches less susceptible to confounding bias given the inconsistent findings regarding the comparison of COVID-19 survivors with other respiratory infections.

New-onset psychotic symptoms, insomnia, other neuropsychiatric symptoms and 'long-COVID'. Individual cases of putative COVID-19-associated neuropsychiatric disorders (e.g. psychosis, OCD, etc.) (29,30) have been reported since the COVID-19 pandemic outbreak; more recently, studies using large sets of health record data have attempted to investigate if this association is significant considering possible confounding factors (16,29). Research regarding the possible association of 'long-COVID' syndrome with new-onset neuropsychiatric symptoms has aimed to estimate incidences and risks regarding psychotic disorders, sleep disturbances, fatigue, substance use disorders and other mental health manifestations among COVID-19 survivors, in comparison, usually, either with individuals without SARS-CoV-2 infection or with patients who had other illnesses, such as influenza and other RTIs (20-22).

Taquet *et al* (20), in a retrospective cohort study, found that in the 6 months succeeding COVID-19 diagnosis, the first psychotic disorder diagnosis was recorded in 0.42% (95% CI, 0.36-0.49; ICU admission, 0.70; 95% CI, 0.46-1.06), first substance use disorder diagnosis in 1.92% (95% CI, 1.77-2.07; ICU admission, 3.15; 95% CI, 2.60-3.82) and first insomnia diagnosis in 2.53% (95% CI, 2.37-2.71; ICU admission, 4.24; 95% CI, 3.55-5.07) of COVID-19 survivors, with higher incidences observed among those admitted to the ICU. When compared with patients with influenza, COVID-19 survivors had higher probabilities of a new-onset psychotic disorder (HR, 2.16), newly diagnosed substance use disorder (HR, 1.22) and new-onset insomnia (HR, 1.92). Similar were the results when compared with patients with RTI, with the exception that new-onset substance use disorder was less common in patients with COVID-19 (HR, 0.92). In a previous retrospective cohort study by Taquet *et al* (16), 14-90 days after COVID-19 diagnosis, 0.1% of COVID-19 survivors (95% CI, 0.08-0.2) had their first recorded diagnosis of psychotic disorder and 1.9% (95% CI, 1.6-2.2) had their first diagnosis of insomnia, while both diagnoses were more frequently recorded in the COVID-19 cohort as compared with a matched cohort of individuals who had influenza.

Park *et al* (26), in a nationwide cohort study in South Korea, compared 6,148 COVID-19 survivors with 254,735 individuals without a COVID-19 diagnosis regarding the development of neuropsychiatric manifestations following recovery. Although they found differences related to COVID-19 diagnosis, these were potentially explained by increases in anxiety and mood disorders since when individual diagnoses were explored no differences emerged regarding alcohol or drug misuse (0.2 vs. 0.3; P=0.612), eating disorders (0.0 vs. 0.1; P=0.315), personality (0.0 vs. 0.0%; P=0.601) non-affective (0.2 vs. 0.3%; P=0.224) and affective psychotic (1.1 vs. 1.1%, P=0.968) disorders.

Abel *et al* (21), in a cohort study comparing patients with SARS-CoV-2 infection with individuals with SARS-CoV-2 negative test results, found that COVID-19 was related to increases in fatigue (aHR, 5.98; 95% CI, 5.33-6.71) and sleep disorders (aHR, 3.16; 95% CI, 2.64-3.78), while an initially recorded increase in psychosis lost statistical significance after adjusting for confounders (HR, 2.34; 95% CI, 1.48-3.70; aHR, 1.84; 95% CI, 0.93-3.64). Regarding psychiatric medications, the largest increases were for receipt of antipsychotics (aHR, 7.61; 95% CI, 5.00-11.60).

Patel *et al* (22) found that, among hospitalized US veteran patients, COVID-19 was associated with significantly higher incidences of insomnia (4.9 vs. 3.2%; P<0.001) and dementia (3.0 vs. 1.9%; P<0.001) compared with propensity-matched hospitalized patients negative for COVID-19, while in outpatient settings patients with COVID-19 presented a significantly higher incidence of dementia (0.3 vs. 0.2%; P=0.03). Additionally, when comparing hospitalized and non-hospitalized patients with COVID-19, it emerged that hospitalized patients presented significantly increased rates of insomnia (4.9 vs. 1.1%; P<0.001) and dementia (3.0 vs. 0.6%; P<0.001). In another US veteran cohort study, Xie *et al* (25) found that COVID-19 survivors compared with individuals without COVID-19 presented increased risks of incident opioid and other (non-opioid) substance use disorders, as well as neurocognitive decline and sleep disorders.

According to the findings of a Spanish prospective cohort study by Rivera-Izquierdo *et al* (27), incidence was higher for hospitalized COVID-19 survivors compared with individuals hospitalized due to other causes regarding confusion or memory loss (3.1 vs. 0.9%; RR, 3.50; 95% CI, 1.16-10.55), while no differences emerged for sleep disturbances (2.2 vs. 1.5%; RR, 1.43; 95% CI, 0.55-3.81), fatigue (7.7 vs. 8.8%; RR, 0.88; 95% CI, 0.57-1.35) or headache (2.0 vs. 2.0%; RR, 1.00; 95% CI, 0.40-2.50). In line with the aforementioned non-significant results concerning fatigue, in a Danish population-based cohort study (18), individuals positive for COVID-19 but not hospitalized (18 of 8,809 individuals, 0.2%) did not present a statistically significantly different risk of first-ever fatigue-related disorder diagnosis compared with negative individuals (175 of 78,543 individuals, 0.2%; aRR, 0.97; 95% CI, 0.60-1.59).

In an English cohort study (24), SARI and COVID-19 survivors (both requiring hospitalization), when compared with the general population, displayed higher first recorded new-onset diagnosis of dementia (SARI aHR, 2.55; 95%

CI, 2.17-3.00; COVID-19 aHR, 2.63; 95% CI, 2.21-3.14) and psychotic disorder (SARI aHR, 3.63; 95% CI, 1.88-7.00; COVID-19 aHR, 3.05; 95% CI, 1.58-5.90). No differences in new-onset psychiatric morbidity emerged between the two patient groups, whereas regarding the first recorded neuropsychiatric prescription only significantly lower risk of antipsychotic prescriptions was noted among COVID-19 survivors (aHR, 0.80; 95% CI, 0.69-0.92).

Findings of a systematic review of 40 case reports regarding the incidence of COVID-19-associated psychosis suggested that clinical presentations often lacked clinically relevant information, such as whether a delirium diagnosis was excluded (29). Thus, an appropriate differential diagnosis between non-delirious psychosis and delirium is crucial in order to prevent the risk of overreporting psychotic disorders by misdiagnosing cases of delirium, especially among patients hospitalized for COVID-19 and older patients. In addition, distinguishing psychotic features as part of a broader syndrome, such as delirium, from a distinct clinical psychotic disorder related to COVID-19 infection is also of paramount importance (29,31,32).

3. Pathophysiological mechanisms and 'long-COVID' neuropsychiatric symptoms

Putative pathophysiological mechanisms involved in newly diagnosed neuropsychiatric manifestations in patients without a history of mental illness following the acute phase of COVID-19 are multifactorial, resulting either from long-term damage to the brain as a consequence of direct viral effects, persistent systemic inflammation or the psychosocial negative impact of the pandemic, including social isolation, financial instability, fear of infection, lockdowns and lack of family support (Fig. 1) (33-36).

OCD was described in case reports as occurring in the weeks following the resolution of COVID-19 infection. In these cases, OCD was associated with inflammatory factors, in particular autoantibodies produced in response to the virus and targeting the basal ganglia, causing neuronal injury that was seen as abnormalities in cortico-basal ganglia-thalamocortical loops using functional neuroimaging analyses (37-39). These patients had no previous personal or family history of mental illness, indicating that autoimmunity triggered by the virus against convergent surface epitopes in the central nervous system (CNS) was partly responsible for their symptoms. Moreover, dysregulated microglial activation by SARS-CoV-2 outlasts the initial immune host response, ensuing pathological synaptic pruning, and leading to altered behaviour and cognition (40,41). Psychological factors are also involved in the disease process, as high-stress levels during the COVID-19 pandemic are linked with high cortisol levels in the serum, which correlate with obsessive symptoms, but are not related to compulsive behaviours (42).

Newly reported cognitive symptoms and attention complaints by patients were found to be independent of disease severity, suggesting conspicuous vulnerability of the CNS to SARS-CoV-2 infection, as a consequence of high inflammatory response and prolonged hospitalization (43). The dysregulated inflammatory process in SARS-CoV-2 infection is due to high levels of proinflammatory cytokines (IL-6 and TNF-α) secreted by activated macrophages (44,45). Sleep disorders are also accompanied by high IL-6 levels in the serum, indicating this as a possible underlying mechanism in poor sleep quality in patients during the 'long-COVID' phase (46,47). This so called 'cytokine storm' is shown to be caused by the S1 subunit of the SARS-CoV-2 spike protein and contributes to disruption of the blood-brain barrier (BBB), therefore facilitating the entry of the virus in the CNS (48,49) and organ damage and/or failure (50-52). Another factor initiating the cytokine release is activation of the NLR family pyrin domain-containing 3 inflammasome leading to dissemination of inflammatory precursors and pyroptosis, a form of cell death (53,54).

The hypometabolic state of different important brain areas in the frontal and temporal lobes, due to cytokine and neurotropism-related encephalopathy (55), contributes to the brain pathology and is evident as diffuse slowing in electroencephalography and bilateral frontotemporal hypoperfusion in arterial spin labelling MRI (56,57). Neuroinvasion of the virus is suspected to occur either through cranial nerves that innervate the respiratory tract (particularly the olfactory nerve), or through hematogenous spread by crossing the BBB or the blood-cerebrospinal fluid barrier (58-60). Once inside the CNS, the virus enters the cells expressing angiotensin-converting enzyme 2, such as neurons, astrocytes, oligodendrocytes and choroid plexus cells, with the choroidal epithelial cells being distinctly susceptive to SARS-CoV-2 infection as suggested by a number of studies (61-66).

SARS-CoV-2 also induces infection-associated thrombosis by platelet activation and endothelial damage, leading to cerebrovascular events and subsequent ischemia (56,67). The procoagulant effect of the virus is exerted by endothelial damage of the infected organs, activation of the complement system and NETs release through neutrophil recruitment (48,68,69). This hypoxia-induced injury results in neuronal apoptosis and disrupted brain function, impeding distal brain connectivity (70).

Neuronal autoantibodies in the CSF have been detected in a number of patients presenting with psychosis in the post-COVID-19 context. A patient in May 2020 with SARS-CoV-2 infection and consequent anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis was admitted with a number of psychiatric symptoms, including psychomotor agitation, auditory hallucinations, dyskinesias and anxiety, and had a background of substance abuse but no past psychiatric history (71). NMDA-R antibodies were seen in a CSF sample of this patient, while increased levels of CSF autoantibodies have also been reported to be present in 11 patients with SARS-CoV-2 infection and concomitant neurological symptoms (72). This case, along with the case of a previously healthy man with COVID-19-associated catatonia and IgG autoantibodies against several murine proteins detected in immunohistochemistry (with marked staining in neuronal cells in the hippocampus, somatosensory cortex, and thalamus, the ependymal cells of the ventricles and choroid plexus, along with the neuropil of the caudate putamen), suggests a form of psychopathology arising from autoimmune encephalitis attributed to COVID-19 infection (73-75).

Further research in these areas is needed, as well as close monitoring of neuropsychological function in patients with

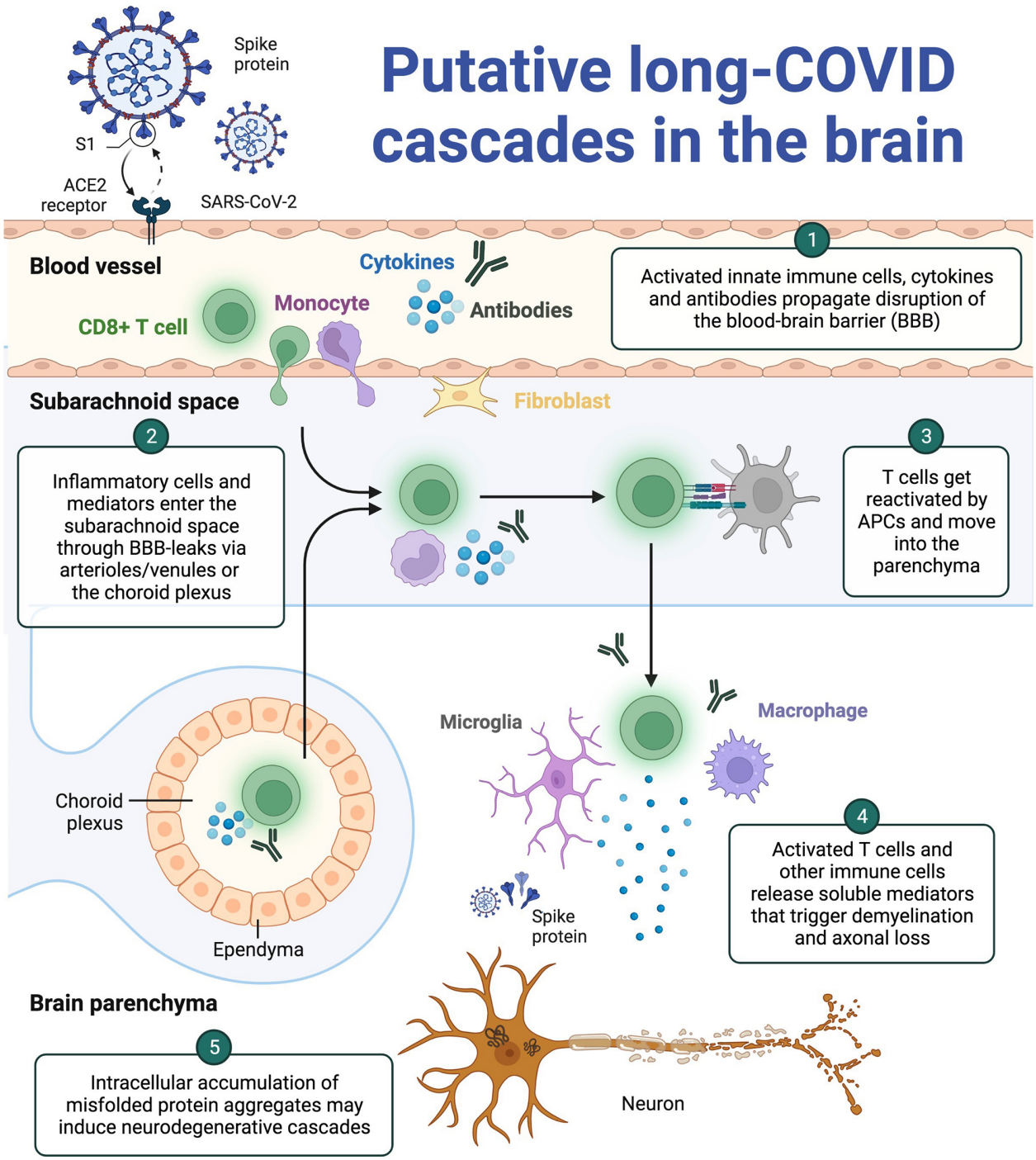

Figure 1. Putative 'long-COVID' cascades in the brain. Following the acute phase of SARS-CoV-2 infection, circulating (auto)antibodies, cytokines and activated innate immune cells (including $CD8^+$ T cells and monocytes) may persist for several months during the post-COVID period, potentially propagating LCS symptoms via a disruption of the BBB (77). Activated fibroblasts and endothelial cells at the BBB lining are also implicated in BBB disruption, causing increased BBB permeability and permitting the transmigration of (auto)antibodies, cytokines and activated immune cells in the subarachnoid space. Within the subarachnoid space, T cells can be reactivated by antigen-presenting cells (78). Within the brain tissue, a limited presence of SARS-CoV-2 spike protein or viral particles is hypothesized in LCS; thus, neurovirulence is probably not strongly associated with LCS pathophysiology (79). Conversely, autoantibodies, cytokines and immune cells are considered the main orchestrators of LCS, precipitating microglial activation and overt immune reactions, which lead to demyelination and neuronal loss. At the neuronal level, it is hypothesized that in LCS, the ongoing neuroinflammatory processes may lead to accumulation of misfolded protein aggregates, which could further induce metabolic stress and neurodegenerative cascades (80). This image was created with BioRender (https://biorender.com). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; BBB, blood-brain barrier; APCs, antigen-presenting cells; LCS, long-COVID syndrome.

COVID-19 months after disease recovery. New COVID-19 variants are rapidly emerging across the world and it remains unclear how individuals infected with these strains will be impacted in the long term (76).

4. Conclusions

The present review provided a comprehensive overview of the currently published epidemiological data on new-onset

neuropsychiatric manifestations associated with 'long COVID' syndrome, as well as insights into the underlying putative pathophysiological mechanisms implicated in the development of new-onset neuropsychiatric symptoms in COVID-19 survivors. While there is evidence of an association between SARS-CoV-2 infection and subsequent occurrence of neuropsychiatric symptoms, considering possible unobserved confounding0, further research using approaches less susceptible to bias is required with a view to establishing causal relationships. Furthermore, follow-up of patients recovering from COVID-19 by interdisciplinary health care teams and the application of well-documented diagnostic criteria of neuropsychiatric disorders are essential to ensure the correct differential diagnosis of 'long-COVID' syndrome in clinical practice.

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Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating the final decision, for this article. The other authors declare that they have no competing interests.

References

1. Zoumpourlis V, Goulielmaki M, Rizos E, Baliou S and Spandidos DA: [Comment] The COVID-19 pandemic as a scientific and social challenge in the 21st century. Mol Med Rep 22: 3035-3048, 2020.
2. Tsamakis K, Tsiptsios D, Ouranidis A, Mueller C, Schizas D, Terniotis C, Nikolakakis N, Tyros G, Kympouropoulos S, Lazaris A, *et al*: COVID-19 and its consequences on mental health (Review). Exp Ther Med 21: 244, 2021.
3. Tsamakis K, Triantafyllis AS, Tsiptsios D, Spartalis E, Mueller C, Tsamakis C, Chaidou S, Spandidos DA, Fotis L, Economou M and Rizos E: COVID-19 related stress exacerbates common physical and mental pathologies and affects treatment (Review). Exp Ther Med 20: 159-162, 2020.
4. Efstathiou V, Stefanou MI, Siafakas N, Makris M, Tsivgoulis G, Zoumpourlis V, Spandidos DA, Smyrnis N and Rizos E: Suicidality and COVID-19: Suicidal ideation, suicidal behaviors and completed suicides amidst the COVID-19 pandemic (Review). Exp Ther Med 23: 107, 2022.
5. Giannopoulou I, Galinaki S, Kollintza E, Adamaki M, Kympouropoulos S, Alevyzakis E, Tsamakis K, Tsangaris I, Spandidos DA, Siafakas N, *et al*: COVID-19 and post-traumatic stress disorder: The perfect 'storm' for mental health (Review). Exp Ther Med 22: 1162, 2021.
6. Centers for Disease Control and Prevention (CDC): Post-COVID conditions: Information for healthcare providers, 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html.
7. Deer RR, Rock MA, Vasilevsky N, Carmody L, Rando H, Anzalone AJ, Basson MD, Bennett TD, Bergquist T, Boudreau EA, *et al*: Characterizing long COVID: Deep phenotype of a complex condition. EBioMedicine 74: 103722, 2021.
8. Brodin P: Immune determinants of COVID-19 disease presentation and severity. Nat Med 27: 28-33, 2021.
9. Stefanou MI, Palaiodimou L, Bakola E, Smyrnis N, Papadopoulou M, Paraskevas GP, Rizos E, Boutati E, Grigoriadis N, Krogias C, *et al*: Neurological manifestations of long-COVID syndrome: A narrative review. Ther Adv Chronic Dis 13: 20406223221076890, 2022.
10. Efstathiou V, Stefanou MI, Demetriou M, Siafakas N, Makris M, Tsivgoulis G, Zoumpourlis V, Kympouropoulos SP, Tsoporis JN, Spandidos DA, *et al*: Long COVID and neuropsychiatric manifestations (Review). Exp Ther Med 23: 363, 2022.
11. Schou TM, Joca S, Wegener G and Bay-Richter C: Psychiatric and neuropsychiatric sequelae of COVID-19-A systematic review. Brain Behav Immun 97: 328-348, 2021.
12. Bourmistrova NW, Solomon T, Braude P, Strawbridge R and Carter B: Long-term effects of COVID-19 on mental health: A systematic review. J Affect Disord 299: 118-125, 2022.
13. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD, Cao B, *et al*: Fatigue and cognitive impairment in post-COVID-19 syndrome: A systematic review and meta-analysis. Brain Behav Immun 101: 93-135, 2021.
14. Renaud-Charest O, Lui LMW, Eskander S, Ceban F, Ho R, Di Vincenzo JD, Rosenblat JD, Lee Y, Subramaniapillai M and McIntyre RS: Onset and frequency of depression in post-COVID-19 syndrome: A systematic review. J Psychiatr Res 144: 129-137, 2021.
15. Shanbehzadeh S, Tavahomi M, Zanjari N, Ebrahimi-Takamjani I and Amiri-arimi S: Physical and mental health complications post-COVID-19: Scoping review. J Psychosom Res 147: 110525, 2021.
16. Taquet M, Luciano S, Geddes JR and Harrison PJ: Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 8: 130-140, 2021.
17. Iosifescu AL, Hoogenboom WS, Buczek AJ, Fleysher R and Duong TQ: New-onset and persistent neurological and psychiatric sequelae of COVID-19 compared to influenza: A retrospective cohort study in a large New York City healthcare network. Int J Methods Psychiatr Res 31: e1914, 2022.
18. Lund LC, Hallas J, Nielsen H, Koch A, Mogensen SH, Brun NC, Christiansen CF, Thomsen RW and Pottegård A: Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: A Danish population-based cohort study. Lancet Infect Dis 21: 1373-1382, 2021.
19. Coleman B, Casiraghi E, Blau H, Chan L, Haendel MA, Laraway B, Callahan TJ, Deer RR, Wilkins KJ, Reese J and Robinson PN: Risk of new-onset psychiatric sequelae of COVID-19 in the early and late post-acute phase. World Psychiatry 21: 319-320, 2022.
20. Taquet M, Geddes JR, Husain M, Luciano S and Harrison PJ: 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: A retrospective cohort study using electronic health records. Lancet Psychiatry 8: 416-427, 2021.
21. Abel KM, Carr MJ, Ashcroft DM, Chalder T, Chew-Graham CA, Hope H, Kapur N, McManus S, Steeg S, Webb RT and Pierce M: Association of SARS-CoV-2 infection with psychological distress, psychotropic prescribing, fatigue, and sleep problems among UK primary care patients. JAMA Netw Open 4: e2134803, 2021.

22. Patel N, Dahman B and Bajaj JS: Development of new mental and physical health sequelae among US veterans after COVID-19. J Clin Med 11: 3390, 2022.
23. Chen JI, Hickok A, O'Neill AC, Niederhausen M, Laliberte AZ, Govier DJ, Edwards ST, Gordon HS, Slatore CG, Weaver FM, *et al*: Psychiatric disorders newly diagnosed among veterans subsequent to hospitalization for COVID-19. Psychiatry Res 312: 114570, 2022.
24. Clift AK, Ranger TA, Patone M, Coupland CAC, Hatch R, Thomas K, Hippisley-Cox J and Watkinson P: Neuropsychiatric ramifications of severe COVID-19 and other severe acute respiratory infections. JAMA Psychiatry 79: 690-698, 2022.
25. Xie Y, Xu E and Al-Aly Z: Risks of mental health outcomes in people with covid-19: Cohort study. BMJ 376: e068993, 2022.
26. Park HY, Song IA, Lee SH, Sim MY, Oh HS, Song KH, Yu ES, Park HY and Oh TK: Prevalence of mental illness among COVID-19 survivors in South Korea: Nationwide cohort. BJPsych Open 7: e183, 2021.
27. Rivera-Izquierdo M, Láinez-Ramos-Bossini AJ, de Alba IG, Ortiz-González-Serna R, Serrano-Ortiz Á, Fernández-Martínez NF, Ruiz-Montero R and Cervilla JA: Long COVID 12 months after discharge: Persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised due to other causes-a multicentre cohort study. BMC Med 20: 92, 2022.
28. Jacob L, Koyanagi A, Smith L, Bohlken J, Haro JM and Kostev K: No significant association between COVID-19 diagnosis and the incidence of depression and anxiety disorder? A retrospective cohort study conducted in Germany. J Psychiatr Res 147: 79-84, 2022.
29. Smith CM, Gilbert EB, Riordan PA, Helmke N, von Isenburg M, Kincaid BR and Shirey KG: COVID-19-associated psychosis: A systematic review of case reports. Gen Hosp Psychiatry 73: 84-100, 2021.
30. Alkhamees AA: Obsessive-compulsive disorder post-COVID-19: A case presentation. Egypt J Neurol Psychiatr Neurosurg 57: 150, 2021.
31. Webster R and Holroyd S: Prevalence of psychotic symptoms in delirium. Psychosomatics 41: 519-522, 2000.
32. Rogers JP and David AS: A longer look at COVID-19 and neuropsychiatric outcomes. Lancet Psychiatry 8: 351-352, 2021.
33. Yang CP, Chang CM, Yang CC, Pariante CM and Su KP: Long COVID and long chain fatty acids (LCFAs): Psychoneuroimmunity implication of omega-3 LCFAs in delayed consequences of COVID-19. Brain Behav Immun 103: 19-27, 2022.
34. Druss BG: Addressing the COVID-19 pandemic in populations with serious mental illness. JAMA Psychiatry 77: 891-892, 2020.
35. Moreno C, Wykes T, Galderisi S, Nordentoft M, Crossley N, Jones N, Cannon M, Correll CU, Byrne L, Carr S, *et al*: How mental health care should change as a consequence of the COVID-19 pandemic. Lancet Psychiatry 7: 813-824, 2020.
36. Kola L: Global mental health and COVID-19. Lancet Psychiatry 7: 655-657, 2020.
37. Gerentes M, Pelissolo A, Rajagopal K, Tamouza R and Hamdani N: Obsessive-compulsive disorder: Autoimmunity and neuroinflammation. Curr Psychiatry Rep 21: 78, 2019.
38. Maia TV, Cooney RE and Peterson BS: The neural bases of obsessive-compulsive disorder in children and adults. Dev Psychopathol 20: 1251-1283, 2008.
39. Uvais NA: Obsessive-compulsive disorder following COVID-19 infection. Prim Care Companion CNS Disord 23: 21cr03063, 2021.
40. Frick L and Pittenger C: Microglial dysregulation in OCD, tourette syndrome and PANDAS. J Immunol Res 2016: 8606057, 2016.
41. Awogbindin IO, Ben-Azu B, Olusola BA, Akinluyi ET, Adeniyi PA, Di Paolo T and Tremblay MÈ: Microglial implications in SARS-CoV-2 infection and COVID-19: Lessons from viral RNA neurotropism and possible relevance to Parkinson's disease. Front Cell Neurosci 15: 670298, 2021.
42. Morgado P, Freitas D, Bessa JM, Sousa N and Cerqueira JJ: Perceived stress in obsessive-compulsive disorder is related with obsessive but not compulsive symptoms. Front Psychiatry 4: 21, 2013.
43. Pilotto A, Cristillo V, Cotti Piccinelli S, Zoppi N, Bonzi G, Sattin D, Schiavolin S, Raggi A, Canale A, Gipponi S, *et al*: Long-term neurological manifestations of COVID-19: Prevalence and predictive factors. Neurol Sci 42: 4903-4907, 2021.
44. Park MD: Macrophages: A Trojan horse in COVID-19? Nat Rev Immunol 20: 351, 2020.
45. Tizenberg BN, Brenner LA, Lowry CA, Okusaga OO, Benavides DR, Hoisington AJ, Benros ME, Stiller JW, Kessler RC and Postolache TT: Biological and psychological factors determining neuropsychiatric outcomes in COVID-19. Curr Psychiatry Rep 23: 68, 2021.
46. Titze-de-Almeida R, da Cunha TR, dos Santos Silva LD, Ferreira CS, Silva CP, Ribeiro AP, de Castro Moreira Santos Júnior A, de Paula Brandão PR, Silva APB, da Rocha MCO, *et al*: Persistent, new-onset symptoms and mental health complaints in long COVID in a Brazilian cohort of non-hospitalized patients. BMC Infect Dis 22: 133, 2022.
47. Hong S, Mills PJ, Loredo JS, Adler KA and Dimsdale JE: The association between interleukin-6, sleep and demographic characteristics. Brain Behav Immun 19: 165-172, 2005.
48. Iadecola C, Anrather J and Kamel H: Effects of COVID-19 on the nervous system. Cell 183: 16-27.e1, 2020.
49. Erickson MA and Banks WA: Neuroimmune axes of the blood-brain barriers and blood-brain interfaces: Bases for physiological regulation, disease states and pharmacological interventions. Pharmacol Rev 70: 278-314, 2018.
50. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, *et al*: Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 27: 992-1000.e3, 2020.
51. Cheon SY and Koo BN: Inflammatory response in COVID-19 patients resulting from the interaction of the inflammasome and SARS-CoV-2. Int J Mol Sci 22: 7914, 2021.
52. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO, *et al*: Cytokine elevation in severe and critical COVID-19: A rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med 8: 1233-1244, 2020.
53. Liu X, Zhang Z, Ruan J, Pan Y, Magupalli VG, Wu H and Lieberman J: Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature 535: 153-158, 2016.
54. Zhao N, Di B and Xu LL: The NLRP3 inflammasome and COVID-19: Activation, pathogenesis and therapeutic strategies. Cytokine Growth Factor Rev 61: 2-15, 2021.
55. Shah P, Patel J, Soror NN and Kartan R: Encephalopathy in COVID-19 patients. Cureus 13: e16620, 2021.
56. Moore P, Esmail F, Qin S, Nand S and Berg S: Hypercoagulability of COVID-19 and neurological complications: A review. J Stroke Cerebrovasc Dis 31: 106163, 2022.
57. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, *et al*: Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 382: 2268-2270, 2020.
58. Bauer L, Laksono BM, de Vrij FMS, Kushner SA, Harschnitz O and van Riel D: The neuroinvasiveness, neurotropism, and neurovirulence of SARS-CoV-2. Trends Neurosci 45: 358-368, 2022.
59. Ludlow M, Kortekaas J, Herden C, Hoffmann B, Tappe D, Trebst C, Griffin DE, Brindle HE, Solomon T, Brown AS, *et al*: Neurotropic virus infections as the cause of immediate and delayed neuropathology. Acta Neuropathol 131: 159-184, 2016.
60. Koyuncu OO, Hogue IB and Enquist LW: Virus infections in the nervous system. Cell Host Microbe 13: 379-393, 2013.
61. Fodoulian L, Tuberosa J, Rossier D, Boillat M, Kan C, Pauli V, Egervari K, Lobrinus JA, Landis BN, Carleton A and Rodriguez I: SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain. iScience 23: 101839, 2020.
62. Lukiw WJ, Pogue A and Hill JM: SARS-CoV-2 infectivity and neurological targets in the brain. Cell Mol Neurobiol 42: 217-224, 2022.
63. Jacob F, Pather SR, Huang WK, Zhang F, Wong SZH, Zhou H, Cubitt B, Fan W, Chen CZ, Xu M, *et al*: Human pluripotent stem cell-derived neural cells and brain organoids reveal SARS-CoV-2 neurotropism predominates in choroid plexus epithelium. Cell Stem Cell 27: 937-950.e9, 2020.
64. Pellegrini L, Albecka A, Mallery DL, Kellner MJ, Paul D, Carter AP, James LC and Lancaster MA: SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF barrier in human brain organoids. Cell Stem Cell 27: 951-961.e5, 2020.
65. McMahon CL, Staples H, Gazi M, Carrion R and Hsieh J: SARS-CoV-2 targets glial cells in human cortical organoids. Stem Cell Reports 16: 1156-1164, 2021.

66. Zhang BZ, Chu H, Han S, Shuai H, Deng J, Hu YF, Gong HR, Lee AC, Zou Z, Yau T, *et al*: SARS-CoV-2 infects human neural progenitor cells and brain organoids. Cell Res 30: 928-931, 2020.
67. Beristain-Covarrubias N, Perez-Toledo M, Thomas MR, Henderson IR, Watson SP and Cunningham AF: Understanding infection-induced thrombosis: Lessons learned from animal models. Front Immunol 10: 2569, 2019.
68. Goshua G, Pine AB, Meizlish ML, Chang CH, Zhang H, Bahel P, Baluha A, Bar N, Bona RD, Burns AJ, *et al*: Endotheliopathy in COVID-19-associated coagulopathy: Evidence from a single-centre, cross-sectional study. Lancet Haematol 7: e575-e582, 2020.
69. Ramlall V, Thangaraj PM, Meydan C, Foox J, Butler D, Kim J, May B, De Freitas JK, Glicksberg BS, Mason CE, *et al*: Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection. Nat Med 26: 1609-1615, 2020.
70. Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, Lekoubou A, Oh JS, Ericson JE, Ssentongo P and Chinchilli VM: Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: A systematic review. JAMA Netw Open 4: e2128568, 2021.
71. Panariello A, Bassetti R, Radice A, Rossotti R, Puoti M, Corradin M, Moreno M and Percudani M: Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: A case report. Brain Behav Immun 87: 179-181, 2020.
72. Franke C, Ferse C, Kreye J, Reincke SM, Sanchez-Sendin E, Rocco A, Steinbrenner M, Angermair S, Treskatsch S, Zickler D, *et al*: High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. Brain Behav Immun 93: 415-419, 2021.
73. Mulder J, Feresiadou A, Fällmar D, Frithiof R, Virhammar J, Rasmusson A, Rostami E, Kumlien E and Cunningham JL: Autoimmune encephalitis presenting with malignant catatonia in a 40-year-old male patient with COVID-19. Am J Psychiatry 178: 485-489, 2021.
74. Endres D, Maier V, Leypoldt F, Wandinger KP, Lennox B, Pollak TA, Nickel K, Maier S, Feige B, Domschke K, *et al*: Autoantibody-associated psychiatric syndromes: A systematic literature review resulting in 145 cases. Psychol Med 52: 1-12, 2020 (Epub ahead of print).
75. Watson CJ, Thomas RH, Solomon T, Michael BD, Nicholson TR and Pollak TA: COVID-19 and psychosis risk: Real or delusional concern? Neurosci Lett 741: 135491, 2021.
76. Desai AD, Lavelle M, Boursiquot BC and Wan EY: Long-term complications of COVID-19. Am J Physiol Cell Physiol 322: C1-C11, 2022.
77. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, Juno JA, Burrell LM, Kent SJ, Dore GJ, *et al*: Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol 23: 210-216, 2022.
78. Farzi R, Aghbash PS, Eslami N, Azadi A, Shamekh A, Hemmat N, Entezari-Maleki T and Baghi HB: The role of antigen-presenting cells in the pathogenesis of COVID-19. Pathol Res Pract 233: 153848, 2022.
79. Spudich S and Nath A: Nervous system consequences of COVID-19. Science 375: 267-269, 2022.
80. Sulzer D, Antonini A, Leta V, Nordvig A, Smeyne RJ, Goldman JE, Al-Dalahmah O, Zecca L, Sette A, Bubacco L, *et al*: COVID-19 and possible links with Parkinson's disease and parkinsonism: From bench to bedside. NPJ Parkinsons Dis 6: 18, 2020.