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INVITED REVIEW

Psychological and neuropsychiatric implications of COVID-19

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Abstract
COVID-19 infections have spread quickly, resulting in massive healthcare burden to societies worldwide. The most urgent interventions needed in the present climate include epidemiological measures to reduce the spread of infection, efficient treatment of patients with severe illness to reduce mortality rates, as well as development of diagnostic tests. Alongside this, the acute, medium, and long-term mental-health consequences of the COVID-19 outbreak for patients, their family members, medical professionals, and the public at large should not be underestimated. Here, we draw on evidence from previous coronavirus outbreaks (i.e., SARS, MERS) and emerging evidence from China, Europe, Asia and the US to synthesize the current knowledge regarding the psychological and neuropsychiatric implications of the COVID-19 pandemic.

Keywords Coronavirus, COVID-19 · Respiratory infection · Mental health · Liaison psychiatry

Introduction

Enormous progress in the medical sciences has not only extended the human lifespan but also contributed to the fact that living longer is frequently associated with chronic noncommunicable diseases (i.e., type 2 diabetes, cardiovascular and neurodegenerative diseases, and multiple types of cancer). Given that the main focus of contemporary medicine has been on these age-related noncommunicable diseases, it is not surprising that the current pandemics of COVID-19 took us largely unprepared and resulted in sudden and widespread anxieties. The rapid spread of COVID-19 over all continents has resulted in at least 23.5 million confirmed cases to date and claimed 843,000 lives (3rd September, 2020 [1]), with many unknowns remaining regarding the prevalence and extent of physical and mental health sequelae among the > 17 million recovered COVID-19 patients [2].

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The prolonged lockdown (now in its 7th month in parts of the UK), imposed quarantine and social isolation, shielding of immunocompromised and older people, the rise in unemployment (including furloughed workers) have all affected the global economy, with the pandemic now representing the most serious threat to persons and property. In this review, we discuss the impact of COVID-19 upon the psychological and neuropsychiatric symptoms among the adult population and reflect on the possible long-term sequelae post-COVID-19.

Psychological impact of COVID-19 on the general population

The outbreak of COVID-19 in China resulted in an almost instant increase in negative emotions (e.g. anxiety, depression, and indignation) in tandem with a decrease in positive emotions and life satisfaction among the general population [3]. Furthermore, the psychological distress in quarantine conditions appeared to be negatively associated with recommended health behaviours (e.g. ventilation of accommodation spaces, social distancing) to mitigate infection risk and positively with non-recommended behaviours (i.e. behaviours that provide little protection against infection such as ingesting vitamin pills or economic actions that contradict national guidelines for returning to normal activities once the pandemic risk is reduced) [4]. The

breakdown of calls to a psychological hotline, established at the peak of the pandemic in Wuhan (February 4–February 20, 2020) showed that the majority of users (70%) were from the general public, followed by people with mental disorders (18.5%), whereas medical workers accounted for only 2.2% of help seekers [5]. During the same period, deaths of medical workers quadrupled in comparison to the death rate in January and this was largely due to being overworked [5]. Furthermore, a recent online survey of people living in mainland China found that approximately 85% of respondents reported feeling "extremely" or "very nervous" regarding the COVID-19 outbreak [6], with younger adults (18–30 years) and older people (over the age of 60 years) reporting the highest levels of psychological distress [7]. In a recent Spanish survey, younger adults (18–35 years) were also found to be more psychologically vulnerable in terms of anxiety, depression, hostility and interpersonal sensitivity during the period of COVID-19 lockdown than their older counterparts (36–76 years) [8]. Interestingly, a nationwide representative survey conducted in the USA in March 2020 found that older adults had a more optimistic outlook and better mental health during the early stages of the pandemic [9]. A similar survey in 932 adults in the UK reported that self-isolating/social distancing females, younger age groups, those with a lower annual income, current smokers, and those with physical multimorbidity showed higher levels of poor mental health [10]. In contrast, a qualitative US study among 73 older adults with pre-existing depression reported a surprisingly high resilience among this group within the first 2 months of the COVID 19 pandemic, with participants being more concerned about the risks of contracting the virus than the risks of isolation [11].

Increased rates of suicide also have to be considered [12]. Suicide rates, particularly in low-income countries, e.g. Pakistan and India, appear to be associated with the consequences of the lockdown-related economic recession such as unemployment as well as fear of infection [13]. According to a recent model taking into account the unemployment figures arising from the COVID-19 pandemic worldwide (not including the furloughed staff) the suicide rate would increase from 4.936 to 5.644%, resulting in an increase in completed suicides from 2135 to 9570 per year [14]. This all suggests that the health, social, and economic consequences of the COVID-19 pandemic can lead to wider long-term complex problems that are not only confined to the SARS-CoV-2 viral infection.

Mental health and COVID-19

The major health threat posed by COVID-19 consists of respiratory failure, with people suffering from pre-existing conditions such as cardiopulmonary and metabolic health problems at the highest risk for severe adverse outcomes. Unsurprisingly, the severity of the physical problems caused by COVID-19 affects the mental health of the infected person, but, equally importantly, members of the medical teams providing the immediate health care and the community as a whole are also severely psychologically impacted. Some of the epidemiological measures that are widely employed such as swift identification and isolation of suspected cases, contact tracing, and collection of biological samples (e.g. nose and throat swabs) contribute significantly to increased anxiety and stress, and might even trigger new or augment pre-existing psychotic symptoms [15]. The National Health Commission of China rightly stresses the need for mental health care to be provided for COVID-19 patients (especially inpatients on infectious/medical wards), suspected cases (in self-isolation at home), their close contacts (i.e. families and friends), health professionals caring for COVID-19 patients, and the wider community (guidance issued on 26th January 2020 [16]).This strongly supports the role for liaison psychiatry and psychology services, and for them to be made available in a timely manner, as acute and emergency medicine are typically not equipped to deal with the direct (and indirect) mental health effects of COVID-19. Crucially, based on prior experience, this liaison support will have to be provided both during the acute and the convalescence phases of the illness [17].

Judging from reports from previous respiratory infections also caused by coronaviruses such as severe acute respiratory syndrome (SARS) and Middle East Respiratory syndrome (MERS) and the newly emerging evidence on COVID-19, the psychiatric presentation of the COVID-19 infection may well bear similarities to what has previously been described for SARS and MERS (reviewed in [18]). However, we acknowledge that although SARS-CoV-2 (the novel coronavirus causing the disease now designated as COVID-19) is genetically closely related to the SARS coronavirus (SARS-CoV), the two are dissimilar in important ways, resulting in differences in clinical presentation and outcomes of the acute respiratory syndromes caused by either virus [19]. Thus, we cannot yet exclude the possibility that the forthcoming reports may well describe a distinct psychological and neurologic profile of COVID-19 patients, either in the acute and/or in the convalescence stages of the respiratory illness, as a direct or delayed result of the attendant psychosocial experiences, or due to the neurotropic, neuroinvasive, and neurovirulent properties of the new virus (Table 1).

The first reports of the psychological impact of the COVID-19 epidemic are beginning to emerge. In a study of 1210 respondents from 194 cities in China, more than half confirmed a significant psychological impact of the outbreak, with around 1 in 6 reporting moderate to severe depressive symptoms and almost 1 in 3 reporting moderate to severe

Table 1 Summary of the psychological and neurological consequences of acute respiratory infections caused by CoVs due to their neurotropic, neuroinvasive, and neurovirulent properties

Health consequences	Acute phase	Convalescence phase
Psychological	Acute stress disorder Adjustment disorder Anxiety (including separation anxiety and generalised anxiety disorder) Depression and suicidality Dysphoria Acute manic episode Eating disorders (including increased restricting, binge eating, purging, and exercise behaviours) Insomnia Irritability Panic attacks Phobias Obsessive behaviour Acute psychosis (including reactive psychosis) Alcohol/drug withdrawal due to lockdown Medically unexplained symptoms[a]	Depression Psychosis Post-traumatic stress disorder (PTSD) Post-viral chronic fatigue syndrome[b]
Neurological	Delirium (due to well-known precipitating factors that occur during the course of a severe infection; also due to corticosteroid medication, sleep deprivation; also reported in an asymptomatic patient; also including catatonia) Cerebral vascular changes/stroke (i.e. ischaemic stroke, haemorrhage) Chemosensory dysfunction (hyposmia/anosmia and/or dysgeusia/ageusia) Absence of dyspnea Encephalitis (including unexplained fatal strain OC-43 of the human coronavirus, CT brain scans confirming presence of ischemia, necrosis and brain oedema, herpes simplex encephalitis, rhombencephalitis) Encephalomyelitis/Multiple sclerosis; autoimmune meningoencephalitis ? Complicated Kawasaki Disease (presenting with cerebral vasculitis, meningoencephalitis/encephalitis, systematic arteritis) Guillain-Barré syndrome (including atypical variants, i.e. facial diplegia) Leucoencephalopathy Febrile or afebrile seizures, status epilepticus, encephalopathies and encephalitis Cerebellar ataxia ? Secondary haemophagocytic lymphohistiocytosis (sHLH) Headache (including migraine) Syncope Stroke ? Limbic encephalitis Locked-in syndrome Muscular twitching, Acute polyradiculoneuritis Transient cortical blindness Ophthalmoparesis Miller Fisher syndrome Polyneuritis cranialis Spine demyelinating lesions Axial hypotonia in infants Rhabdomyolysis Myasthenia gravis Neuroleptic malignant syndrome	? Dementia (i.e. Alzheimer's disease, Vascular dementia, Lewy body disease such as Dementia with Lewy Bodies, Parkinson's Disease Dementia, post-encephalitic Parkinsonism) Encephalopathies Myalgic encephalomyelitis (ME) (post-viral chronic fatigue)[b] Locked-in syndrome (due to post-brain haemorrhage/stroke, such as, vertebrobasilar stroke; viral induced CNS/PNS demyelination[b], such as central pontine myelinolysis) Dysexecutive syndrome consisting of inattention, disorientation, or poorly organised movements in response to command

More than one-third of COVID-19 patients are reported to have neurological symptoms, usually occurring within the first few days of the overt clinical symptomatology [20] whereas strokes tend to appear 2–3 weeks later. The cerebral involvement appears to be associated with poor prognosis and worse disease course [21]. The summary based on PubMed, MEDLINE, EMBASE, Scopus, Google scholar and the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Cochrane Special Collections from inception to 31 August 2020

[a]A dysfunctional preoccupation with physical symptoms in a COVID-19+ person leading to excessive and unnecessary healthcare utilization. The neurological consequences derive from COVID-19 references, and also from reports on previous corona virus infections in humans and in animal models ([b])

anxiety [22]. Interestingly, women, students and those with poor self-assessed health reported much higher levels of anxiety, stress and depression, whereas provision of accurate heath information and implementation of precautionary measures had the inverse effect [22]. A systematic review based on 19 studies including 93,569 participants (64.1% females) conducted in 8 countries [China, Denmark, Spain, Italy ($n=2$), Iran, the US, Turkey and Nepal ($n=1$)] [23] reported relatively high rates of symptoms of anxiety (6.33–50.9%), depression (14.6–48.3%), post-traumatic stress disorder (7–53.8%), psychological distress (34.43–38%), and stress (8.1–81.9%). Risk factors associated with distress measures include female gender, younger age (≤40 years), presence of chronic/psychiatric illnesses, unemployment, student status and frequent exposure to social media/news concerning COVID-19.

Incorporation of COVID-19 related themes has also been observed in the delusional system of people with enduring mental health problems, with nearly one-third (31%) of patients admitted in a mental hospital during the COVID-19 period showing psychotic symptoms with COVID-19-related themes [24]. A systematic review on 43 studies included two studies on patients with confirmed COVID-19 infection, and 41 on the indirect effect of the pandemic (2 on patients with pre-existing psychiatric disorders, 20 on medical health care workers, and 19 on the general public) and reported high prevalence of post-traumatic stress symptoms (96.2%) and depression (29.2%) in COVID-19 patients, with significantly higher prevalence of depressive symptoms, worsening of psychiatric symptoms in those with pre-existing mental health disorders, whereas healthcare workers reported increases in depression, anxiety, psychological distress and poor sleep quality [25].

Long-term psychiatric consequences of COVID-19

The long-term psychiatric consequences of COVID-19 likely share similarities with those observed during the SARS outbreak where, following physical recovery, 50% and 20% of survivors continued to exhibit anxiety and depression, respectively, with people treated with antiviral and corticosteroid medications also exhibiting significant memory problems [26]. Moreover, roughly 50% of family members of SARS patients suffered from mental health problems, including experiencing depression and stigma [26]. During the convalescence phase, SARS patients also frequently suffered from post-traumatic stress disorder (PTSD), with the lowest level of blood oxygen saturation (SaO_2) during hospitalization being the most significant predictor for intrusion and avoidance symptoms in one study [27]. Finally, a web-based survey of 129 persons quarantined following epidemiological exposure to SARS during the SARS outbreaks in Toronto (Canada) found that approximately 1 in 3 suffered from symptoms of depression and/or PTSD in the aftermath of quarantine [26]. It appears that the length of time spent in quarantine as well as acquaintance with or direct exposure to someone with a diagnosis of SARS were associated with increased psychological burden [28]. Interestingly, in the case of MERS, it was anger and anxiety (3% and 6%, respectively), but not PTSD, that persisted 4–6 months post-quarantine, and they were related to inadequate access to food supplies, clothes, accommodation, social networking, history of psychiatric illnesses, and financial loss [29].

The latest reports on the long-term mental health sequelae in COVID-19 patients confirm some of the above findings. Namely, 12.2% had PTSD symptoms, 26.8% had anxiety and/or depression symptoms. In addition, 53.6% of patients reported chronic fatigue 3 months post-COVID-19 infection [30]. Relative to patients without chronic fatigue problems, those with fatigue problems had a lower perceived social support score. However, logistic regression analysis did not detect any association between clinical, psychological measures and the risk of fatigue problems in patients. Interestingly, fatigue appears to be one of the major issues in the general population that has not been affected directly by the infection, Thus, in a cross-sectional study conducted in Istanbul (Turkey) between March and June 2020, involving 3672 participants, 64.1% were categorised as psychologically fatigued as based on the Fatigue Assessment Scale. Level of education, avoiding going to crowded places, occupational status, as well as concerns regarding transmission, isolation, treatment and isolation variables were significantly associated with fatigue after adjusting for age, gender and income variables [31].

Mental wellbeing of health workers

The mental wellbeing of health workers appears to have been seriously compromised in previous coronavirus outbreaks (8096 probable SARS cases 2002–2003 and 1091 laboratory-confirmed cases of MERS 2012–2020) [17, 32], with up to 10% experiencing high levels of post-traumatic stress [33]. The same has now also been confirmed for COVID-19 in two recent reports. The first investigated 230 front-line medical staff tasked with caring for COVID-19 patients [34] and the second larger study surveyed 1257 health professionals working in 34 hospitals in China [35]. Another recent survey among frontline nursing staff found that 25.1% were psychologically distressed [36]. Multiple logistic regression analysis revealed that working in an emergency department, concern for family, being treated differently, negative coping style and COVID-19-related stress symptoms were all

positively related to psychological distress. The perception of higher levels of social support and effective precautionary measures were negatively associated with psychological distress [36]. Both studies revealed a high incidence of anxiety (45%), depression (50%), distress (72%) and altered sleep (i.e. insomnia; 34%) [35], especially among female nursing staff [34, 35]. Both in SARS and in MERS, direct exposure to someone with the infection was, similarly, associated with heightened psychological distress [28, 32]. Resilience appears to mediate, in part, the relationship between social support and mental health [37]. Interestingly, the high incidence of psychological distress occurred despite the fact that Chinese mental health services have significantly improved in response to recent major disasters (i.e. the Wenchuan and Lushan earthquakes). In particular, services have been developed that capitalize on recent advances in digital technologies and integrate stakeholders into internet platforms [38].

COVID-19 and neuro-psychiatric symptoms

COVID-19 and neurological symptoms

Although human coronaviruses usually affect the upper and, in vulnerable populations (i.e. newborns and infants, older people, and those who are immunocompromised), the lower respiratory tract, they are also neuroinvasive and neurotropic [39]. The first reports from the COVID-19 epidemic in China confirm this, with nearly half of the seriously ill patients showing some neurological symptoms [40], whereas in intensive care, this has been reported to reach 81% [41]. The most recent post-mortem study confirmed detectable cerebral viral load in 4 out of the 12 performed autopsies on COVID-19 patients [42]. This bears resemblance to the reported prevalence of neurological symptomatology in a large COVID study conducted in 214 patients, of which 78 (36.4%) had neurologic symptoms [40]. However, the incidence of neurological symptoms paralleled the severity of the illness, with up to 88% severely ill patients exhibiting neurological symptoms involving the central and peripheral nervous system, as well as the skeletal muscles [40]. This, alongside with the severity of the neurological symptoms, can explain the fact that the cerebrospinal fluid (CSF) of COVID-19 positive patients may not contain detectable viral particles, both in those with mild symptoms, and those with haemorrhages [43]. However, the RT-PCR methodology used in the detection of SARS-CoV-2 has certain limitations, with the RT-PCR targeting the N2 gene, having the highest sensitivity in the CSF in comparison to other investigated specimens [44]. Nevertheless, viral encephalitis may also present the first signs of the COVID-19 infection [45], indicating that SARS-CoV-2 can affect the central brain tissue both as a result of a direct invasion of the nervous system and its immune response to SARS-CoV-2. Current evidence suggests that the presence of SARS-CoV-2 in CSF may depend on disease severity and the degree of the virus' nervous tissue tropism.

The neurologic symptoms in the acute phase are usually mild and transient in nature, and may include headache, nausea, vomiting, and confusion, hyposmia/hypogeusia and musculoskeletal symptoms [40]. It is too early at this point to predict the long-term neurologic consequences of COVID-19 based on the symptomatology patients display during the acute phase. However, we should not exclude the possibility that more severely affected COVID-19 patients might be at an increased risk of cognitive impairment, which may be linked to cortical or subcortical neurodegeneration as well as to vascular mechanisms (Table 1). Comorbidities, which drive poor long-term outcomes in COVID-19 patients, are likely to be a key factor in the etiopathogenesis of the CNS manifestation of SARS-CoV-2 [46].

SARS-CoV-2 conceivably invades the brain via the olfactory nerve, spreading to the brainstem and to other areas in the brain as well as into the cerebrospinal fluid [47]. It is, thus, not surprising that hyposmia is one of the first neurologic symptoms noticed in COVID-19 [40]. The difficulties in spontaneous breathing characteristic of more severe cases are probably a result of the infection spreading to the brainstem [47]. Indeed, high viral loads of SARS-CoV and MERS-CoV have been detected in the brainstem of experimental animals infected with these viruses [48, 49]. Transsynaptic transmission of a number of CoVs is well established, so another potential route for brain entry is via initial invasion of peripheral nerve terminals [47].

COVID-19 and hypercytokinemia

A relatively small portion of COVID-19-infected patients will also exhibit a cytokine profile resembling secondary hemophagocytic lymphohistiocytosis (sHLH). This cytokine profile (i.e. 'hypercytokinemia') is associated with COVID-19 disease severity, multiorgan failure, and sepsis, as well as seizures and coma [50]. It consists of elevated interleukin (IL)-2, IL-7, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α [50]. In addition, this hyperinflammation syndrome is accompanied by hyperferritinemia [50]. Importantly, sHLH and elevated levels of ferritin alone can give rise to neurologic symptoms, e.g. seizures and coma [51, 52]. Of note, some of the above inflammatory markers are also altered in delirium, which frequently develops in more severe COVID-19 cases [53, 54]. Indeed, this cytokine storm is also often found in sepsis [55] and is relatively characteristic of other acute respiratory syndromes, largely due to hypoxemia and shock [56]. In addition, patients with such

severe illness may be treated with moderate-to-high doses of corticosteroids [56], which may exacerbate agitation, confusion, insomnia, and memory problems [57].

Delirium in COVID-19

The incidence of delirium in COVID-19 has been reported to range from 9 [51] to 14.8% [40], which is 1.5–twofold lower than the prevalence rate reported in two recent systematic reviews and meta-analyses for adults either treated in an intensive care unit (ICU) in general [58], or due to COVID-19 infection (64% [18]) on neurology wards (27% [59]) or those requiring end-of-life care/symptom control (24% [60]). Similarly, a bicentre French study reported very high incidence of delirium in their severely ill COVID-19 patents in the ICU [118/140 (84.3%)], with 88 patients (69.3%) exhibiting hyperactive delirium, despite high infusion rates of sedative treatments and neuroleptics [61]. The Brain MRI performed in 28 patients demonstrated enhancement of subarachnoid spaces in 17/28 patients (60.7%), intraparenchymal, predominantly white matter abnormalities in 8 patients, and perfusion abnormalities in 17/26 patients (65.4%). The 42 electroencephalograms mostly revealed unspecific abnormalities or diffuse, especially bifrontal, slow activity. Cerebrospinal fluid examination revealed inflammatory disturbances in 18/28 patients, including oligoclonal bands with mirror pattern and elevated IL-6. The CSF RT-PCR SARS-CoV-2 was positive in one patient [61].

Unfortunately, Mao and co-workers [40] and Chen and co-workers [53] did not report on the clinical criteria they used or types of delirium. Thus, their reported figures likely underestimate the extent of delirium in COVID-19, with a number of people, especially those with hypoactive and subsyndromal delirium, not being diagnosed. In support of this is the high number of COVID-19 patients who required ventilation. A most recent study, using the Confusion Assessment Method for the ICU, confirms this, reporting delirium to be present in 75.9% of COVID-19 patients admitted to intensive care unit [61], a figure similar (as high as 77%) to that of delirium prevalence among mechanically ventilated patients [62]. Based on the latter figure, we can speculate that as high as 32–44% of intensive mechanically ventilated COVID-19 patients may have had delirium (as per data available in Yang et al. and Zhao et al., respectively [63, 64]), which may not have been recognised or recorded, and only the most overt delirium symptomatology (i.e. anxiety, restlessness, hallucinations, and overt emotional disturbances, all characteristic of hyperactive delirium) noticed. Indeed, this figure is very similar to that reported in adults in intensive care units [58]. The mechanically ventilated group of patients had the most grave outcomes due to the severity and length of their illness, with a mortality rate of 79–86% for those who required non-invasive and invasive ventilation, respectively [64].

Although delirium onset does not appear to be related to gender, it is more frequent with older age, and male gender is an independent risk factor for poor outcome, including mortality [65]. Having said that, case reports also draw the attention to COVID-19 positive older people asymptomatic or with non-specific clinical features, who develop delirium as first clinical symptoms of the viral infection [66, 67] and in some instances related to leukoencephalopathy, as seen on CT brain scans [68]. This is in particular so for older people with dementia, among whom the onset of hypoactive delirium and worsening functional status may be considered as an early sign of possible COVID-19 infection, leading to emergency hospital admissions [69].

This heterogeneity of delirium clinical presentation calls for increased awareness and early recognition of COVID-19, to enable not only timely diagnosis but also preparedness for adequate specialised health care and avoidance of outbreaks of new clusters of infection in medical clinical setting. In addition, the long-term consequences of COVID-19 accompanying delirium may have a substantial impact on the currently available memory services for both younger and older people in terms of increase in cognitive changes associated either as a direct consequence of the prolong oxygen deprivation an inflammation, encephalopathy and/or psychological distress and mental health (reviewed in [70]).

Hypercoagulopathy and stroke

Another neurological consequence of viral infections is altered coagulation, as a result either of a direct viral infection, or an inflammatory response to it. As expected, majority of COVID-19 affected patients will develop a systemic coagulopathy and acquired thrombophilia, ranging from microangiopathy and local venous and arterial thrombus formation [71] to large vessel thrombosis, even in people younger than 50 years of age and with no previous health complications [72]. This hypercoagulopathy is due to the SARS-CoV-2 virus infecting the endothelial cells via the ACE2 receptors, resulting in release of cytokines that consequently lead to increase in blood coagulation markers and hyperfibrinolysis, i.e. fibrinogen degradation products. One of the contributing factors in increasing the susceptibility to SARS-CoV-2 infection in people with underlying medical conditions, such as hypertension, diabetes, cardiovascular disease, cerebrovascular disease and chronic renal illness, is the elevated plasminogen level, enhancing the virulence and infectivity of SARS-CoV-2 virus with the plasmin-associated hyperactive fibrinolysis. This results in highly increased D-dimer fibrin, which is now considered to be a risk factor of disease severity and mortality [73]. Indeed, COVID 19 patients with a previous history of cerebrovascular disease

have higher risk of severe COVID-19 than those without (RR 2.07] [74]) and 2.67 higher odds for poor outcome, including the need for intensive care admission and mechanical ventilation, as well as higher rate of mortality [75].

Although the incidence of symptomatic venous and arterial thromboembolism due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation in COVID 19 patients is high (up to 31% in intensive care unit [76], the latest studies from the U.S.A., Italy, China and Holland conducted in larger numbers of patients have reported substantially lower incidence of ischaemic stroke, ranging from 0.9% (32 out of 3556; [77]), 2.5% [78], 2.8% [38] to 3.7% (ICU patients [76]), whereas the composite thrombotic complication (i.e. symptomatic acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism in all COVID-19 patients admitted to the ICU) was 31% [76]. In addition, case reports on haemorrhagic strokes also have now started emerging [78–81], and may be attributable to either direct and indirect endothelial toxicity or disruption of the renin–angiotensin system as a result of the downregulation of ACE2 in COVID-19.

The systemic inflammatory response to COVID-19 may unmask previous asymptomatic cardiological and pulmonary conditions, leading to dissemination of embolisms and microthrombs outside the respiratory system. The thrombophilia appears to be associated with more severe forms of COVID-19 infection [82] and results in poorer outcomes, including mortality (RR 2.38 [1.92–2.96]) independent of gender, age, and comorbidities (i.e., hypertension, diabetes, and respiratory comorbidities [83]) and possibly leading to long-term disability. However, stroke has been described even in milder forms of COVID-19 [84], suggesting that COVID-19 patients are at increased risk of thrombus formation leading to stroke, and this may be largely due to viral caused damage to the blood vessel endothelium. Although the initial reports described the presence of antiphospholipid antibodies [85], these have not only not be consistently reported in COVID-19 stroke patients, but they are also not COVID-19 specific, since the antiphospholipid antibodies can arise transiently at the time of the acute infection, inflammation or thrombosis, and are not recommended for routine testing in COVID-19 patients [86].

Psychosis and viral infection

In the lack of firm data regarding the incidence rate and causative links of psychosis in COVID 19 patients, we can only speculate that the COVID-19 linked psychosis may arise as a direct brain response to the hypercytokinemia [87] and immune response or be either a secondary response to medication (i.e. corticosteroid-induced psychosis, similar to the leading cause for psychosis in SARS [88], or even a coincidental finding.

The incidence of psychosis among people with a viral infection ranges between 0.9 and 4.% [89] with only few reports having documented a direct link to the viral infection, i.e. psychotic symptoms significantly associated with coronavirus exposure, as determined by antibody levels and seroprevalence. Increased rates of immunoreactivity for certain coronavirus strains in the psychosis group [90] were due to recurrent influenza infections (H1N1) with co-occurring psychosis-like symptoms [91] with the rest attributing the psychotic episode to the SARS severity and higher doses of corticosteroids [17, 89]. The latest UK surveillance report in 153 COVID-19 patients with 91% confirmed SARS-CoV-2 infection, described altered mental state in 31% of the analysed sample, with the 23/39 cases having neuropsychiatric symptoms, with new onset psychosis occurring in all of the confirmed COVID-19 patients ($n = 10$) [92]. Although the study did not include iatrogenic factors that may have contributed to the altered mental state (i.e. corticosteroid medication, sedatives and antipsychotics) the young onset of the first onset psychosis and the severity of the viral infection are suggestive of an autoimmune precipitating factors leading to the altered mental state.

Although the majority of the reported psychotic episodes in COVID-19 patients are not supported by detailed laboratory [93] out of a number of antibodies linked to autoimmune encephalitis characterised with neuropsychiatric symptoms [i.e. Anti-Caspr2 (contactin-associated protein-like 2) antibodies; Anti-AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antibodies; Anti-GABA-A (γ-Aminobutyric acid A) receptor encephalitis; Anti-mGluR5 (metabotropic glutamate receptor 5) Dopamine-D2-receptor antibodies and Anti-*N*-Methyl-D aspartate (NMDA) receptor (anti-NMDAR) antibodies], there is emerging evidence that the NMDAR autoimmune response underlies the autoimmune psychosis in SARS-Cov-2 infection, either directly, as a result of NMDAR encephalitis and the psychosis occurring during symptomatic SARS-COV-2 infection [94, 95], or being a stressor precipitating autoimmune disorders, including autoimmune, anti-NMDA receptor psychosis [96].

Conclusions

It proves difficult, if not impossible, to keep pace with the growing torrent of new scientific papers about COVID-19 and the virus that causes the disease. Just to illustrate this point, within the last 5 months the number of publications in the public domain rapidly increased by more than 285-fold, from 140 (March 2020) to > 40,000 (end of August, 2020) publications. In addition, a number of preprint articles on

the > 50 known preprint servers have been withdrawn soon after their online appearance (EM-L and GK, observation).

Though the evidence of the COVID-19 neurological symptoms seems to have stabilised and is along the already known viral neurological symptoms, the mental health sequelae remain undefined. This is largely due to the number of 'confusables' introduced in the various case reports and consequent review papers, some based on limited clinical information, the same patients being repeatedly reported, inaccurate data and analyses that affect both the understanding of the disease and inappropriate changes in clinical care, including investigations, diagnosis, treatment [97] among many others. In particular, of concern are the poorly documented case reports and studies in relation to the temporal presentation of symptomatology (i.e. whether they are a consequence or a coincidence as a result of underlying mental health conditions, i.e. drug abuse), the tendency for syndromal description of the clinical psychiatric presentation, rather than putting it in the context of the known mental health classifications (Table 2), as well as the limited laboratory/biochemical and neuroimaging workup to accompany the clinical presentations. These all call for more stringent criteria to maintain the research integrity and reproducibility of findings especially when 'thru-hiking across the unknown(s)' of the COVID-19 [102].

Having said that, the current COVID-19 pandemic has already had significant effects on public health in Europe. Although firm data regarding the extent of mental health problems in the general population are still lacking for most Western countries, we can reasonably expect that they would paint a picture quite similar to what has been reported from China. Vulnerable individuals infected with SARS-CoV-2 and people in direct contact with patients (family/friends, and, in particular, medical staff) are those who will suffer from the highest burden of psychological distress. Social distancing measures (self-isolation and working alone) add to the increased need for mental health to be seriously considered in the current emergency state of affairs. Both children [103] and adults of all ages [104] can expect to experience various degrees of distress as a result of the quarantine measures, and these negative psychological consequences may include post-traumatic stress disorder symptoms, confusion, and anger due to prolonged duration of quarantine, fear of infection, tedium, inadequate supplies, inadequate information, financial loss, and stigma [104]. Importantly, these negative psychological effects can be either transient or long lasting.

As many as 48% of confirmed COVID-19 inpatients display overt psychological symptoms (i.e., depression, anxiety, phobia, and even panic attacks), and often express feelings of regret, resentment, loneliness, helplessness, and irritation, with age (21–30 years) but not gender influencing the level of anxiety and depression [105]. Again, these symptoms can occur during early admission but some may last well into the course of the disease [106] and over prolonged periods of time as reported recently [107]. Mental health problems alongside with problems in social functioning remain the highest self-reported heath issues among mild, moderate and severe SARS-COV-2 survivors at 3 months post-infection [107]. The possibility that some may even convert to full-blown longstanding mental health disorders should not be ruled out. The recommendations coming from Chinese colleagues are for patients' mental state to be monitored regularly following admission and before discharge, using self-administered scales for general health, depression, and anxiety through face-to-face or online assessments [106]. Similarly, the British Thoracic Society guidelines 'Post-COVID holistic assessment' advocate management of breathlessness and anxiety, that may need to be implemented even in those patients who have normal results at follow-up, and also be referred to the liaison services for further assessment and interventions [108]. In addition, the use of apps, internet and social media has now been acknowledged in sharing strategies for dealing with the psychological stress during the time of the pandemic and quarantine period, encouraging to keep social connections, chatting and communicating with family, friends, and co-workers, pet therapy for soothing emotions, and the introduction of online consultations) [106].

It is estimated that at least 15% of COVID-19 patients will require intensive care [109] largely due to their respiratory complications. Their associated complex heath needs, i.e., delirium, sepsis, hypoxia, hypotension, and glucose dysregulation require more specific treatments, such as sedation, mechanical ventilation, resulting in prolonged intensive care admission. They all both contribute and increase the risk for Post Intensive Care Syndrome (PICS), a complex syndrome that gives rise to secondary disabilities, including long-term consequences upon cognitive performance (i.e. memory and attention visuo-spatial ability), and mental health (i.e. anxiety depression and post-traumatic stress disorder) [110]. It is, thus, not surprising that nearly two-thirds of people who experience PICS fail to return back to work, whereas one-quarter have a drastic loss of independence, requiring assistance on activities of daily living [111] or worsening in their physical disabilities [112].

In most instances, medical staff has not been adequately trained to provide mental health care. Liaison psychiatry services have traditionally played an important role in easing the pressures on acute medical services. For example, the National Health Service in England aims for a 'Core 24' liaison mental health service model that emphasizes quick access for patients in a mental health crisis (e.g. patients who deliberately self-harm) [113]. In view of the current situation and the possibility of serious new viral outbreaks, liaison psychiatry needs to reassess its

Table 2 Differential diagnosis of primary and secondary psychosis

Primary psychosis	Organic (secondary psychosis)
Brief psychotic disorder: Brief Psychotic Disorder is a thought disorder in which a person will experience short term, gross deficits in reality testing, manifested with at least one of the following symptoms [98]: Delusions—strange beliefs and ideas resistant to rational/logical dispute or contradiction from others; Hallucinations—auditory, or visual; Disorganised Speech—incoherence, or irrational content; Disorganised or Catatonic behavior—repetitive, senseless movements, or adopting a pose which may be maintained for hours. The individual may be resistant to efforts to move into a different posture, or will assume a new posture they are placed in. To fulfil the diagnostic criteria for Brief Psychotic Disorder, the symptoms must persist for at least one day, but resolve in less than one month. The psychotic episode cannot be attributed to substance use (ethanol withdrawal, cocaine abuse) or a medical condition (fever and delirium) and the person does not fit the diagnostic criteria for Major Depressive disorder with psychotic features, Bipolar disorder with psychotic features, or Schizophrenia [98]	Delirium: Defined if criteria A–E are fulfilled [98]: A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). B. The disturbance develops over a short period of time (usually hours to a few days) represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day. C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception). D. The disturbances in criteria A and C are not explained by another pre-existing, established, or evolving neurocognitive disorder, and do not occur in the context of a severely reduced level of arousal, such as coma. E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e. because of a drug of abuse medication), or exposure to a toxin, or is because of multiple aetiologies
Acute and transient psychotic disorders (ICD-10: F23 [99]) are with an acute onset and a duration of psychotic symptoms not exceeding 1–3 months. The syndrome develops fully within 2 weeks. It is characterised with psychotic and polymorphic symptoms	Acute encephalopathy [100]: Refers to a rapidly developing (over less than 4 weeks, but usually within hours to a few days) pathobiological process in the brain. It can lead to a clinical presentation of subsyndromal delirium, delirium, or in case of a severely decreased level of consciousness, coma; all representing a change from baseline cognitive status.
Short-lived psychosis triggered by stress: Patients may spontaneously recover normal functioning within 2 weeks. In some instances, individuals may remain in a state of full-blown psychosis for many years, or have attenuated psychotic symptoms (i.e. low intensity hallucinations) present at most times	Poststroke psychosis: Slightly more frequent among males. Neurological presentation is typical for stroke, with lesions present typically in right hemisphere, especially frontal, temporal and parietal regions, and the right caudate nucleus. The most common psychosis appears to be a delusional disorder, followed by schizophrenia-like psychosis and mood disorder with psychotic features. In general, poststroke psychosis is associated with poor functional outcomes and high mortality
Reactive psychosis	Psychosis due to a general medical condition or medication: Symptoms can occur with other medical conditions such as cerebrovascular accident or traumatic brain injury, Wilson's disease, porphyria, or syphilis infection (also in HIV patients), as well as medications (e.g. steroids) and certain dietary supplements
Psychogenic psychosis: Evidence of incompatibility between the symptom and recognised neurological or medical conditions	Autoimmune psychosis [101]: Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status (to include lethargy, personality change, or cognitive deficits), or psychiatric symptoms. Also at least one of the following: new focal CNS findings; seizures not explained by a previously known seizure disorder; cerebrospinal fluid (CSF) pleocytosis (white blood cell count of > 5 cells/mm; MRI features suggestive of encephalitis. Reasonable exclusion of alternative causes

priorities. In particular, in a pandemic, liaison psychiatry services should consider extending their support beyond the individual service user to include families of patients and, crucially, medical staff. In this, the current multi-disciplinary liaison teams will have to be aided by dedicated health professionals who will directly be involved in the provision of the necessary immediate and long-term care. In addition to direct face-to-face interactions, novel routes of service provision via electronic means will have to be explored to mitigate the adverse psychological effects of social isolation.

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