Review
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The Clinical Observation of Inflammation Theory for Depression: The Initiative of the Formosa Long COVID Multicenter Study (FOCuS)

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There is growing evidence that the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with increased risks of psychiatric sequelae. Depression, anxiety, cognitive impairments, sleep disturbance, and fatigue during and after the acute phase of COVID-19 are prevalent, long-lasting, and exerting negative consequences on well-being and imposing a huge burden on healthcare systems and society. This current review presented timely updates of clinical research findings, particularly focusing on the pathogenetic mechanisms underlying the neuropsychiatric sequelae, and identified potential key targets for developing effective treatment strategies for long COVID. In addition, we introduced the Formosa Long COVID Multicenter Study (FOCuS), which aims to apply the inflammation theory to the pathogenesis and the psychosocial and nutrition treatments of post-COVID depression and anxiety.

KEY WORDS: COVID-19; Depression; Neuropsychiatric sequelae; Inflammation; Long COVID; Post-acute COVID-19 syndrome.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a global health crisis. As the COVID pandemic progresses, there is emerging evidence and a growing health concern that a considerable proportion (approximately 10−20%) of patients surviving acute COVID-19 infection can experience persistent symptoms and complications. This post-COVID condition is commonly denoted as "long COVID". The UK National Institute for Health and Care Excellence (NICE) defines long COVID as "signs and symptoms that continue or develop after acute COVID-19", including [1] ongoing symptomatic COVID-19 (symptoms lasting from 4 up to 12 weeks after acute COVID-19 infection) and [2] post-COVID-19 syndrome (symptoms lasting 12 weeks or more after the start of acute COVID-19 [1,2]. In order to establish a globally agreed definition, the World Health Organization (WHO) has developed a consensus clinical case definition for adults: "Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis." [3].

Long COVID can involve multiple organs and systems,

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including the immune system, pulmonary system, cardiovascular system, gastrointestinal system, liver, kidney, pancreas, spleen, and the brain [4-7]. The clinical manifestations of long COVID encompass a multitude of symptoms with the symptom severity and duration varying substantially. The heterogeneous clinical manifestations represent a challenge for early diagnosis and treatment of long COVID. The main features of long COVID symptoms include depression, anxiety, fatigue, sleep disturbances, cognitive impairments of attention and memory, breathlessness, chronic pain, and myalgia [5]. Long COVID symptoms may fluctuate or relapse over time and are commonly long-lasting [8,9]. A significant minority of patients with long COVID could suffer from symptoms lasting even longer than one year [10-12]. Long COVID symptoms are generally debilitating and exert a devasting impact on daily functioning and well-being. which causes huge healthcare, economic, and mental health burdens to the whole society [13-16].

CLINICAL MANIFESTATIONS OF LONG COVID PSYCHIATRIC SEQUELAE

Numerous surveys and meta-analyses have highlighted psychiatric symptoms as one of the most common complications in COVID-19 survivors [5,17-19]. The most frequently long COVID psychiatric symptoms are depression, heightened anxiety and psychological distress, sleep difficulties, posttraumatic stress symptoms, and cognitive disturbances (difficulties with memory and concentration and impaired executive functions; also commonly termed as "brain frog") [20,21]. Although the prevalence of the long COVID psychiatric symptoms and disorders varied depending on the measuring tools and time points during the COVID-19 disease course, the prevalence of major depressive disorder (MDD) and anxiety disorder in COVID-19 survivors were found to be around 20−40% [21-23].

Several longitudinal studies on the trajectories of long COVID psychiatric symptoms have shown that some symptoms, such as anxiety, could recover naturally, but some symptoms, particularly depression and cognitive impairments, tend to be chronic [8-10,12,24,25]. Chronic psychiatric sequelae of long COVID are disabling, exerting a long-lasting destructive impact on well-being, quality of life, and educational and occupational functioning, and causing morbidity [23,26,27].

Notably, the relationship between psychiatric disorders/symptoms and the COVID-19 disease is bidirectional. Patients with a pre-pandemic existing psychiatric disorder were found to be at increased risk for long COVID psychiatric sequelae [24,28]. Life changes and disruptions, restrictions, social isolations, economic loss, and threats of death during the COVID pandemic also create a huge and compound stressful environment where risk factors for psychiatric disorders are exacerbated [29,30]. In addition to COVID-19 infection-associated psychiatric sequelae, exacerbated existing mental health problems, and multiple stressors along with the pandemic can contribute to mental health problems in COVID-19 survivors [15,16]. This creates a great challenge for researchers and clinicians to identify the mechanisms and treatment targets for addressing mental health problems in COVID-19 survivors.

DEPRESSION AS A CENTRAL SYMPTOM OF LONG COVID

Among the neuropsychiatric and physical symptoms of long COVID, depression plays a central role, serving as a risk factor for persistent fatigue, pain, and cognitive impairments in COVID-19 survivors [31-33]. The links between post-COVID depression and other long COVID sequelae may be underpinned by their shared pathogenic inflammatory mechanisms and pathways.

In a follow-up study in hospitalized patients with the COVID-19 disease, rather than other demographic variables and acute COVID-19 severity, post-COVID depression at one-month follow-up was found to be the only and most robust predictor of the severity of long-term fatigue (at 6- and 12- month post-COVID) [31]. In addition, the severity of depressive symptoms one month after hospitalization for COVID-19 was found to be positively associated with persistent pain and dyspnea at the 3-month follow-up [32]. The development of post-COVID fatigue may be related to immune dysregulation and inflammation. In some patients who showed persistent heightened inflammation after recovery from acute COVID-19 disease, the severity of post-COVID fatigue was found to be associated with the level of pro-inflammatory markers [34]. There is some emerging evidence suggesting that depression and fatigue may share a common pathogenic pathway that involves systemic and neuro-inflammation [35]. Therefore, the link between post-COVID depression

and fatigue may be due to common pathogenic inflammatory mechanisms.

Post-COVID depression was found to have a cross-sectional and longitudinal association with cognitive impairments in patients who had ever been hospitalized for severe acute COVID-19 [35]. In this study, depression severity one month after discharge was negatively associated with verbal fluency and information processing and predicted poor attention and executive functions at a 3-month follow-up. Moreover, systemic inflammation at admission for acute COVID-19 predicted both depression severity and cognitive impairments at 3-month follow-up after discharge. Furthermore, for patients who showed reductions in systemic inflammation, the reduction in systemic inflammation could also predict the reduction in their depression severity over time. In contrast, patients who experiences no or few changes in systemic inflammation had persistent severe depression. Taken together, the results suggested that the association between depression and cognitive impairments might be due to a shared underpinned pathogenetic mechanism, unsolved systemic inflammation. This also led us to ask whether we could reduce post-COVID depression and other inflammation-associated long COVID symptoms, such as cognitive impairments, fatigue, and sleep [36] by addressing inflammation processes.

COULD THE INFLAMMATION THEORY OF DEPRESSION APPLY TO LONG COVID SEQUELAE?

The neuropsychiatric sequelae of long COVID are multifactorial. The development of depression and other psychiatric symptoms of long COVID may involve several different mechanisms, including direct brain infection and neuro-injury by SARS-CoV-2, unresolved systemic inflammation and ensuing increased inflammation in the brain through compromised blood-brain barrier (BBB), and oxidative stress [7,35,37,38]. They may operate alone or together, leading to the development of depression, cognitive impairments, and other psychiatric sequelae (sleep disturbances, fatigue) in COVID-19 survivors.

The inflammation theory of depression has proposed inflammation as a key pathogenic mechanism for MDD. Evidence supporting the inflammation theory of depression comes from (a) The association between systemic peripheral inflammation and depression is well documented with the blood level of inflammatory biomarkers, particularly pro-inflammatory cytokines (e.g., interleukin [IL]-6) and C-reactive protein (CRP), positively associated with severity of depression [39-44]. (b) Infection, like psychosocial stress, can activate systemic inflammation, and then induced "sickness behaviors" – cognitive-affective behavioral changes like the core symptoms of depression [45,46]. (c) Increased neuroinflammation in patients with MDD, evidenced by increased cytokines found in cerebrospinal fluid and positron emission tomography brain imaging studies showing upregulation of translocator protein by active microglia, in patients with MDD [47-50].

As the inflammation theory of depression suggests, it is hypothesized that immune dysregulation with systemic and neuro-inflammation is one of the key pathogenic mechanisms linking SARS-CoV-2 infection and post-COVID depression. There are two hypothesized immune pathways by which SARS-CoV-2 infection can lead to the development of enduring depression (see Fig. 1): (a) SARS-CoV-2 infection can induce cytokine dysregulation by activating the mounting release of pro-inflammatory cytokines (e.g., IL-1 β, IL-6, and tumor necrosis factor) and inhibiting anti-inflammatory type-I interferons responses, causing "the cytokine storm". Cytokine dysregulation drives systemic peripheral inflammatory responses [51-53]. Cytokine dysregulation can compromise the function of the BBB, leading to pro-inflammatory cytokines passing the leaky BBB and activating microglia. Chronic activation of microglia enhances the synthesis and release of pro-inflammatory cytokines, driving neuro-inflammation. Cytokine dysregulation can also disrupt the mechanisms of glutamate and monoamine neurotransmission, alter glucocorticoid receptor resistance and reduce hippocampal neuroplasticity, subsequently impairing cognitive functions and leading to the development of depression. (b) SARS-CoV-2 can directly invade the brain. The neuro-invasion pathway may involve direct brain damage by SARS-CoV-2 and/or the persistence of the coronavirus activating long-lasting inflammation in the brain to cause depression [54,55]. As previously mentioned, depression and other long COVID neuropsychiatric sequelae may share common pathogenic pathways that involve both systemic inflammation and neuroinflammation.

Notably, not all patients with depression have increased inflammation and the relationship between inflammation

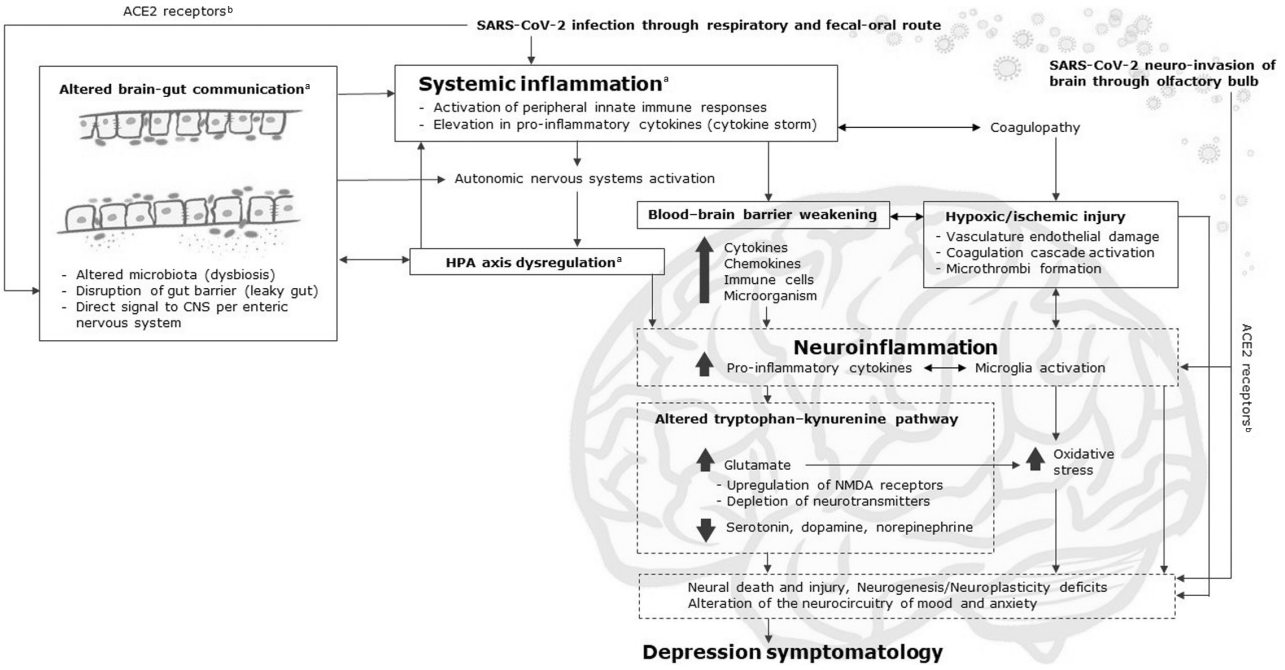

Fig. 1. Immune/inflammatory pathways linking COVID-19 infection and depression.
ACE2 receptors, angiotensin-converting enzyme 2 receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CNS, central nervous system; HPA, hypothalamic–pituitary–adrenal; NMDA, N-methyl D-aspartate.
[a]Stress exacerbation.
[b]SARS-CoV-2 invades organs by binding to angiotensin-converting enzyme type 2 receptors on epithelial and endothelial cells of the gastrointestinal system, respiratory system, blood vessels, central nerve system, *et al.*

and depression is evident only for special subsets of depressive patients (e.g., refractory depression) [56]. This implies that inflammatory biomarkers could help to precisely identify COVID-19 survivors who follow the immune/inflammatory pathways leading to depression and can benefit most from interventions for depression that addresses immune dysregulation and inflammation.

ADDRESSING INFLAMMATION AS A TREATMENT TARGET FOR POST-COVID DEPRESSION

To the best of our knowledge, there are no evidence-based effective interventions available for post-COVID depression or other psychiatric sequelae. Informed by the emerging evidence regarding the mediating role of inflammation in the relationship between SARS-CoV-2 infection and the development of enduring depression [57], it is reasonable to address inflammation as the target of treatment modalities for post-COVID depression [29,58]. Considering the possible adverse effects of immune suppressants, evidence-based psychosocial and nutrition intervention that can address both inflammation and depression seems to be a safe, compelling treatment choice.

Literature on psychosocial interventions has documented that cognitive behavior therapy, mindfulness meditation, and mind-body interventions (e.g., Yoga, Tai-chi) can reduce depression, anxiety and stress as well as improve immune dysregulation [59-62]. The association between psychosocial intervention and decreases in pro-inflammatory cytokines and CRP are most consistent and evident for interventions for depression that incorporate cognitive-based treatment and multiple interventions. Furthermore, the intervention effect on reducing hyper-inflammatory status can predict the intervention effect on improving depression [59].

Nutrition science provides another intervention option that can alleviate depression by reducing systemic inflammatory status. Long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs) are a promising choice with solid empirical evidence established for their effects on improving major depressive disorder, anxiety, and antenatal and postnatal depression [63-67]. In addition, there is emerging evidence on the effect of omega-3 PUFAs in

addressing immune dysregulation induced by SARS-CoV-2 infection as well as post-COVID depression, anxiety, and other psychological distress [38,68]. Further research is needed using an experimental design (randomized controlled trial) to test the effect of nutrition interventions with omega-3 PUFAs on post-COVID depression as well as to test decreased inflammation as the mediating mechanism of the intervention effect. Beyond omega-3 PUFAs, potential nutrition interventions for long COVID include a nutrition supply with vitamin C, polyphenols, probiotics, and vitamin D and keeping a healthy diet to reduce inflammation and oxidative stress [69-71]. However, these

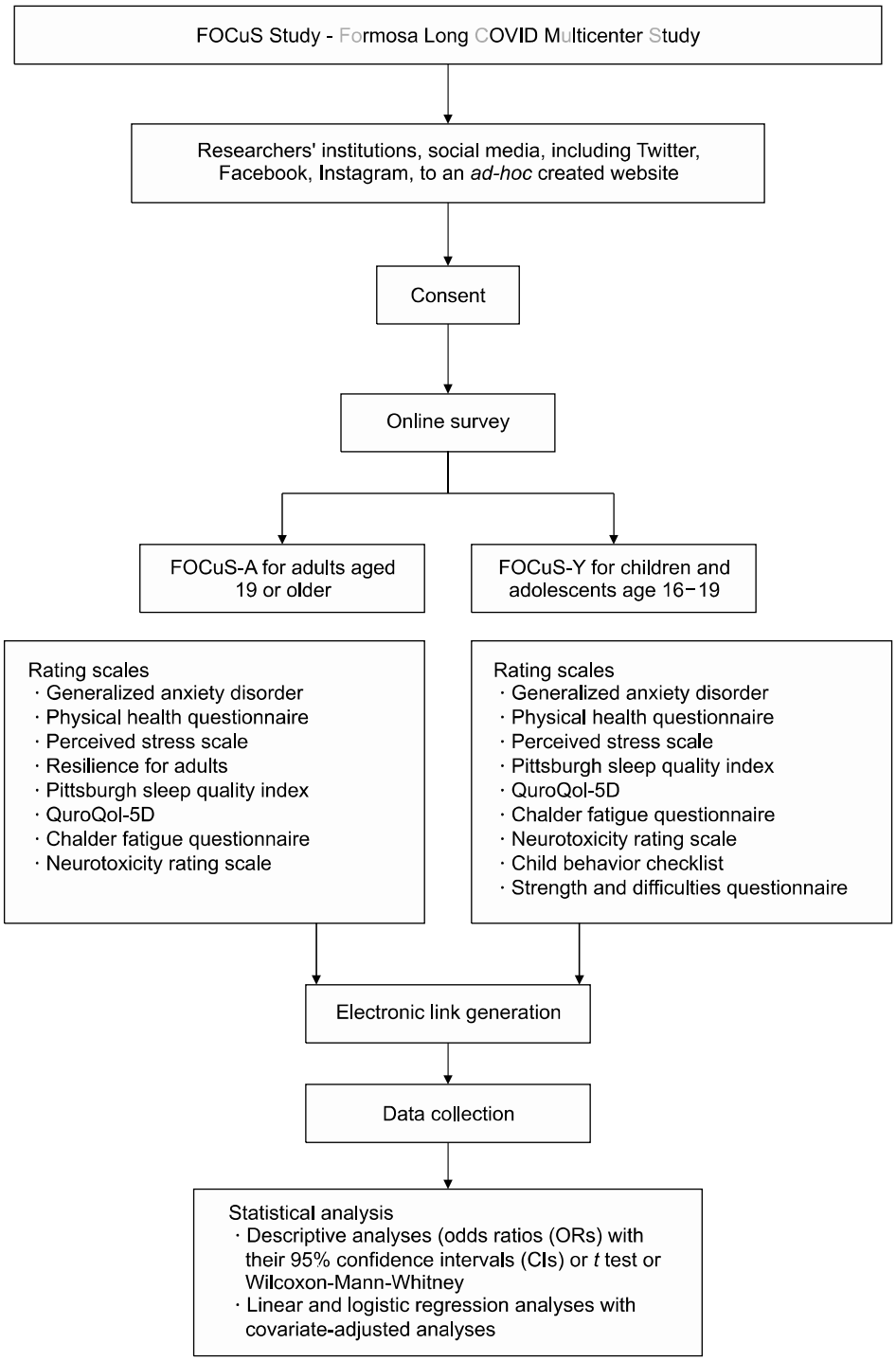

Fig. 2. The flow chart of the initial cohort of the Formosa Long COVID Multicenter Study (FOCuS).

nutrition interventions generally lack solid empirical evidence to support their effects on improving post-COVID depression as well as inflammatory dysregulation.

POST-COVID CLINICAL OBSERVATION TO TEST THE INFLAMMATION THEORY OF DEPRESSION: THE FOCUS

WHO estimates up to one-tenth of the world population has already been infected with COVID-19. The high prevalence of long COVID, therefore, makes it a globe-wide cohort to test the inflammation theory of depression. However, many questions remain: (1) What are the key inflammatory mechanisms and pathways responsible for the susceptibility of COVID survivors to develop persistent depression, and their biomarkers? How do the inflammatory biomarkers in post-COVID patients link to the molecular biology of depression? (2) How can we treat/prevent post-COVID depression optimally? Till now, there has been neither approved intervention nor treatment consensus for long COVID.

Therefore, we establish a multi-center research group to investigate depression, anxiety, and common neuropsychiatric syndromes of long COVID in COVID survivors in Taiwan, the Formosa Long COVID Multicenter Study (FOCuS). The FOCuS will start with the construction and validation of two questionnaire measures of neuropsychiatric and physical symptoms of long COVID for the adults (FOCuS-A) and for the youths (FOCuS-Y). The initial step of the FOCuS aims to examine the psychometric properties of the FOCuS-A and FOCuS-Y as well as to investigate the prevalence, clinical manifestations, and risk factors of long COVID physical and neuropsychiatric symptoms in Taiwanese COVID patients. Figure 2 shows the flow chart of the proposed procedure of the initial step of the FOCuS to validate FOCuS-A and FoCuS-Y.

The FOCuS study aims to test the inflammation theory of post-COVID depression. This will be done by the prospective study examining the relationship between inflammatory biomarkers and symptom severity of depression. We believe the FOCuS study will help provide a foundation to conduct future clinical trials to test whether we could treat post-COVID depression with an intervention that is evidence-based to improve depressive symptoms through reducing systemic and neuroinflammation.

CONCLUSION

This review highlights the high prevalence and burden of long COVID depression and suggests systemic and neuro-inflammation as the key mechanisms leading to the development of long COVID depression based on available evidence. Future epidemiological and experimental research is needed to test, validate, and translate the hypothesized causal role of inflammation in the pathogenesis of long COVID depression. The information presented in this review would serve as a starting point for further exploration in the FOCuS study.

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■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Conceptualization: All authors contributed to the study conceptualization and design, including Shu-Tsen Liu, Sheng-Che Lin, Jane Pei-Chen Chang, Chia-Chun Yang, Ching-Fang Sun, Che-Sheng Chu, Chih-Sung Liang, Kai-Jie Yang, Senthil Kumaran Satyanarayanan, Shao-Cheng

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