

Factors contributing to cognitive dysfunction in patients suffering from COVID-19

Xi Mei, Chengying Zheng, Yuanyuan Zhang, Dongsheng Zhou (✉), and Guolin Bian (✉)

Ningbo Kangning Hospital, Ningbo Key Laboratory of Sleep Medicine, Affiliated Tongyi Hospital of Medical College of Ningbo University, Ningbo 315201, China

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KEYWORDS

corona virus disease 2019 (COVID-19), cognitive impairment, risk factors, evaluation methods, potential mechanism.

ABSTRACT

The corona virus disease 2019 (COVID-19) is an epidemic pneumonia caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In addition to pulmonary symptoms and a variety of physical symptoms, patients also experience symptoms of cognitive impairment. Previous studies have shown that many patients will experience varying degrees of cognitive decline in the subacute and prognostic stages after having COVID-19. Then, what are the factors that lead to cognitive decline? This article reviews and analyzes the inherent factors before the onset of the disease, the factors directly related to the disease, and the factors of hospital admission. In addition, this paper also summarizes the evaluation methods of cognitive decline and the possible mechanisms of the pathogenesis, thus providing corresponding clinical intervention ideas for inhibiting or regulating related factors.

1 Introduction

The corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a serious global public health problem [1]. Growing evidence shows that aside from respiratory system, COVID-19 can affect multiple systems including the central nervous system [2]. Nonspecific clinical symptoms such as headache can be related with viral infection syndrome [3]. Furthermore, anosmia and dysgeusia are symptoms seen in early phases of infection [4]. The patients suffering from

COVID-19 complained the neurological and cognitive sequelae including the presence of cognitive impairment [5].

There are many subtypes of cognitive impairment. According to the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [6], in terms of cognitive dimensions, cognitive decline can be classified as a decline in (1) complex attention (continuity, distributivity and selectivity attention, processing speed), (2) executive function (make decision, plan, and response), (3) learning and memory (implicit learning, transient, and long-term memory), (4)

Address correspondence to Dongsheng Zhou, wyzhouds@sina.com; Guolin Bian, 2584086@qq.com

linguistic functions (expressive language and perceptual language), (5) perceptual-motor (ability to describe, visual perception, visual construction, and perceptual movement), and (6) social cognition (emotional awareness and mental state). In terms of the degree of disease, cognitive impairment can be divided into mild cognitive impairment and severe cognitive impairment. In patients with COVID-19, the cognitive impairments were assessed by cross-sectional studies and cohort studies, and mild cognitive impairment was a common subtype [7, 8].

The mechanisms of cognitive impairment due to COVID-19 are not clear. Various hypotheses were presented including direct viral invasion of neurons, infection of vascular endothelium, inflammation, and other potential relevant etiological factors [9, 10]. Previous studies revealed many features both in Alzheimer's disease (AD) and COVID-19 including type 4 allele of the gene for apolipoprotein E [11, 12]. COVID-19 causes neurocognitive impairment, fatigue, anxiety and depression symptoms, and impairment of neurogenesis in hippocampus [13]. Although the mechanisms are not clear, elucidation of risk factors on cognitive impairment can be valuable for suppressing the cognitive decline. In the present review, we will analyze the main factors including premorbid factors, post-admission factors, and factors related to presenting illness. We also briefly discussed evaluation methods and potential mechanisms associated with cognitive impairment caused by mental health.

2 Prevalence and clinical manifestation

In a cross-sectional clinical study, the clinical manifestation of cognitive impairment and its proportion in 135 adult patients was noticed as follows: memory recollection (22%), recognition (23%), encoding (24%), processing speed (16%), executive functioning (19%), verbal fluency (17%),

and category fluency (17%) [14]. In a retrospective study, 24% of 50 hospitalized patients had short-term memory loss [15]. In an observational study on 58 adults, patients showed inattention, disorientation, and unreasonable response to commands [16]. Cognitive deficits, particularly mental retardation, and memory loss have been observed in both children and adults [17]. In a retrospective cohort study, more than six million older adults with COVID-19 were at significantly increased risk for suffering from AD within one year after initial COVID-19 diagnosis [18]. The prevalence of decline of cognitive domain after COVID-19 infection included attention and working memory (10%), processing speed (18%), executive functioning (16%), phonemic fluency (15%), category fluency (20%), encoding (24%), recollection (23%), and memory recognition (10%) [19].

3 Risk factors

3.1 Predisposing factors

Predisposing factors include advanced age, frailty, dementia, low educational level, delirium, et al., as shown in Fig. 1. Although population of all ages can be affected by COVID-19, cognitive decline rates of elderly population significantly increase after 65 years old [20]. COVID-19 further increased the vulnerability of patients with delirium and cognitive dysfunction [21]. Delirium is a premorbid factor as well as a clinical manifestation [22]. Hospitalized patients with dementia often have atypical presentations of COVID-19, and changes in mental status complicate early identification of cases [23]. Behavioral, cognitive, and functional decline of patients with mild cognitive impairment were more negatively affected by COVID-19 [24]. Low education level, hypertension, and chronic obstructive pulmonary disease (COPD) were also

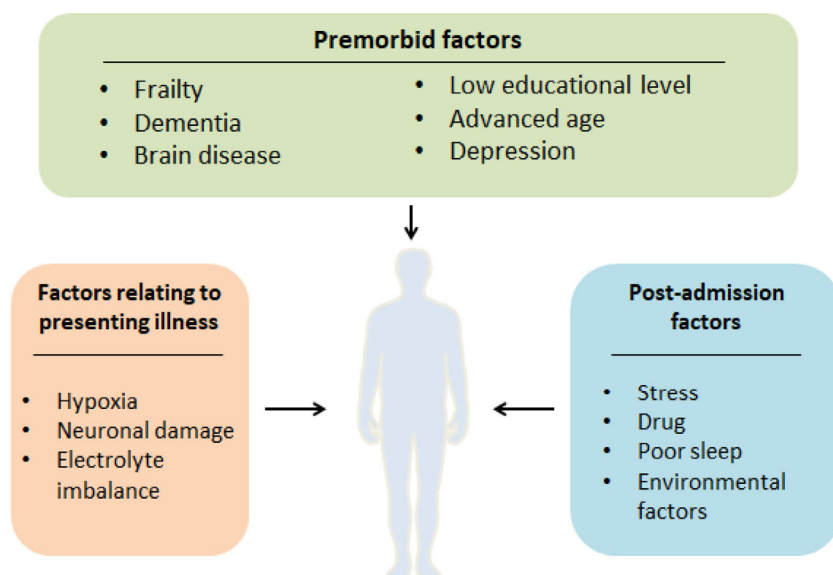


Figure 1 Risk factors for cognitive decline relate to COVID-19 infection.

premorbid risk factors of longitudinal cognitive decline [25].

3.2 Factors related to presenting illness

Hypoxia, neuronal damage, and electrolyte imbalance are common factors related to presenting illness. Hypoxia as a secondary effect of respiratory insufficiency is considered one of the main causal mechanisms leading to transient or permanent cognitive deficits [26]. Viral influences can induce chronic inflammatory and immune reaction in neuronal tissues, leading to long-term neuropsychiatric syndromes, including cognitive, emotional, and behavioral symptoms [27]. The brain microvascular injury caused by COVID-19 infection can also lead to dementia-like cognitive impairment [28]. In clinical, patients with COVID-19 could experience decreased appetite, impaired kidney function, and pulmonary hypoxia, all of which can lead to electrolyte imbalance. Electrolyte imbalance can also affect brain homeostasis, leading to acute cognitive dysfunction [29]. COVID-19 severity was associated with the degree of cognitive decline [25].

3.3 Post-admission factors

Post-traumatic stress disorder, usually caused

by acute illness and critical care admission, among patients with COVID-19 infection was clinically significant symptoms [30]. Patients had reductions in cognitive function [31]. In addition, specific healthcare environment-related factors, such as the mechanical ventilation, are risk contributors to hospital-acquired delirium and cognitive fluctuations [32]. Drug use and withdraw, poor sleep, and environmental factors such as social isolation can cause cognitive decline by changing in hippocampal neuroplasticity [33, 34].

3.4 Evaluation methods

Cognitive evaluation as well as magnetic resonance imaging (MRI) and electroencephalogram (EEG) detections are common methods used to evaluate cognitive levels as shown in Fig. 2. Cognitive assessments usually included neuropsychological scales and neuropsychological measures. However, mini-mental state examination (MMSE) did not present significant difference between patients and health subjects [5]. Montreal cognitive assessment (MoCA) can be adopted to assess the cognitive performance in a longitudinal prospective study [35]. In mild cognitive impairment (MCI) screening, the sensitivity of

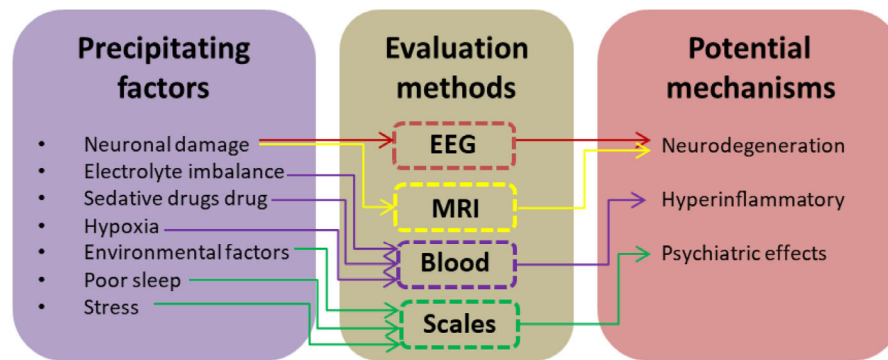


Figure 2 Precipitating factors and evaluation methods for potential mechanism of cognitive impairments.

MoCA was higher than that of MMSE; while in dementia diagnosis, the sensitivity of MoCA and MMSE were comparable [36]. Because large amount of the patients with COVID-19 belonged to MCI, the MoCA may be the proper method to evaluate the cognitive state.

Five cognitive domains were extensively focused on, including attention, working memory, executive function, visuospatial function, and language function. The following tasks were used to test each of them: (1) attention: Number Span Forward, flanker task, and Trail Making Test Part A; (2) working memory: Number Span Backward; (3) executive function: stroop color word interference, Hopkins Verbal Learning Test-Revised, Trail Making Test Part B; (4) visuospatial function: Clock drawing test, line segment orientation judgment; (5) verbal function: phonemic and category fluency, Boston Naming [19].

EEG recording of encephalopathy associated with severe COVID-19 is essential for acute care and management of chronic neurocognitive sequelae [37, 38]. Some evidence suggested that COVID-19 may predominantly target frontal lobes, as revealed by behavioral symptoms, MRI, and EEG signals from fronto-temporal regions, and hypometabolism on ^{18}F -FDG-PET of frontal lobes [39, 40].

3.5 Potential mechanisms

Several potential mechanisms may explain the

effect of COVID-19 on cognition including both biological and psychological components. COVID-19 evokes a powerful inflammatory response which is characterized by a hyperinflammatory condition with significant amounts of inflammatory factors [41]. Direct influence of viruses and indirect effects of immune activation and dysregulation are factors contributing to cognitive decline [42, 43]. Experimental findings suggest that increased inflammatory reactions to viruses, featuring elevated concentrations of cytokines, such as interleukin-6 (IL-6), IL-10, and tumor necrosis factor (TNF), may have a critical role in the early stages of cognitive impairment [44].

The underlying mechanisms of cognitive deficits are not completely understood but may be multi-factorial, related to the direct neurotrophic impact of viral infections, the aftereffects of prolonged hospitalization in the intensive care unit, the administration of mechanical ventilation and tranquilizing drugs, cerebral hypoxia, inflammation, the subsequent influence of drugs, and the impairment of the peripheral organs [45–47]. Moreover, cognitive impairments may be related to long-term olfactory deficits after suffering from COVID-19 [48]. The SARS-CoV-2 entered the nervous system and causes encephalitis, which can lead to synapsis damage and thus affect cognitive decline [49]. The process by which synaptic connections are essential in enhancing cognitive functions is important for

information processing in the brain [50]. Acquisition of immediate and delayed effects of glucocorticoids on cognitive control functions is initiated by exposure to acute stress [51].

4 Discussion

Cognitive performances of COVID-19 patients are consistent with usual cognitive performance; both of them are defined by uniform criteria of DSM-5 [52]. The transition from cognitive decline to cognitive impairment needs to be determined by long-term follow-up, usually over six months, and compare the differences between pre- and post-infection. Not all patients with COVID-19 meet the criterion of cognitive impairment; some just have cognitive decline, and the symptoms are reversible, such as transient dizziness caused by the common cold, which can also result in decreased attention and problem-solving skills [53].

The impact of COVID-19 on cognition has been confirmed by many studies. Many risk factors directly or indirectly lead to cognitive decline. Therefore, the control of risk factors can effectively alleviate cognitive decline. In the case that the inherent risk factors cannot be changed, many factors associated with presenting illness and post-admission risk factors can be found through assessment or evaluation methods. Meanwhile, the inducing mechanism can also be found and prevented or intervened, as shown in Fig. 2.

Most of the studies are focused on the assessment methods, including EEG, MRI, blood biomarkers, and neuropsychological scales. In the future, it is important to carry out clinical research using cerebrospinalfluid (CSF) biomarkers for neurodegenerative diseases to investigate specific pathophysiological processes caused by SARS-CoV-2 [7]. Worsening of depression and anxiety was associated with COVID-19 restriction. Poor

mental status affects cognitive function, but it is usually reversible. Research for understanding the underlying mechanisms of COVID-19 on AD or other dementia need to be conducted intensively.

In regard to clinical response to patients with AD in the ward, many pre-arranged planning were arranged [54]. COVID-19 invades the lungs at an early stage, which causes fever, and if secondary organ damage occurs, it is easily detected clinically at this time. In this case, it is necessary to pay attention to (1) the subsequent development of high fever, and (2) maybe there is virus invasion of parenchymal organs, including heart, brain, and kidney. Virus reproduction in parenchymal organs reached the pathogenic virus load; it is difficult to be detected clinically in time [55, 56]. Current management principles include: (1) in the heart, review of ECG, attention to arrhythmia, cardiac enzyme profile, troponin, electrolytes, and hypotension; (2) in the nervous system, attention to mental status, seizures, or positive neurological signs; (3) in the kidneys, attention to sudden hypertension, sudden decrease in urine volume; (4) in the lungs, attention to asphyxia caused by sputum and oxygen saturation; (5) in the hepatic side, concern for sudden impairment of liver function [57]. COVID-19-induced depressive symptoms or depressed mood may also affect cognitive levels and lead to pseudo cognitive decline. In this case, non-pharmacological treatment options may be more appropriate, including cognitive behavior therapy (CBT), physical therapy, etc. [58, 59].

When this review was being written, as well as with the development of COVID-19, there are new changes in the prevention and treatment of COVID-19 [60]. In this paragraph, we will focus on the novel prevention and treatment methods, including drug and non-drug treatment methods.

Cognitive function is a multidimensional feature that mainly includes attention, working memory, executive function, et al. Patients with COVID-19 exhibited reduced capacity on tests assessing attention and executive function [61]. In terms of memory improvement, medications can be used to help improve memory in patients with COVID-19, such as Anlisin, a cholinesterase inhibitor [62]. Non-pharmacological methods such as transcranial magnetic stimulation, transcranial electrical stimulation, hyperbaric oxygen therapy can also be used and have effects in improving memory [63].

Cognitive levels are associated with anxiety and depression condition, sleep quality, and olfactory function. Cognitive complaints in patients with COVID-19 were related to anxiety and depression [64]. Regarding anxiety and depression related cognitive decline, bright light therapy was a non-drug method which can produce good results [65]. Treatment of post traumatic stress disorder, delirium, and sleep difficulties were investigated in recent studies [66, 67]. Meanwhile, confinement associated with COVID-19 has significant impacts on social and cognitive domains and worsens the neuropsychiatric profile of patients with mild cognitive decline and dementia [68]. Symptomatic treatment is the usual clinical treatment option.

This review emphasizes the high incidence of cognitive deficits following infection of COVID-19. Although we express the precipitating factors and evaluation methods for potential mechanism of cognitive impairments, the clinical interventions, which is one objective of future investigations to be studied on this topic, could be most important to improve the cognitive condition.

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Declaration of conflicting interests

The authors declare there are no conflicting interests regarding the content of this article.

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Xi Mei received her Ph.D. degree from Xi'an Jiaotong University, China (2012), and then received his postdoctoral training in Capital Medical University (2012–2015). Now, she is an associate researcher in Ningbo Kangning Hospital, China. Her current research interests are focused on the early diagnosis of Alzheimer's disease, investigation on brain cognitive function using noninvasive brain detection including high density electroencephalogram, functional near infrared imaging technology, magnetic resonance imaging and optical coherence tomography, and sleep disorders

in patients with Alzheimer's disease. E-mail: meixi18401856@163.com.