Higher Inflammatory Markers are correlated with Worse Cognitive Function in Coronavirus Disease-2019 Patients

Fasihah Irfani Fitrif, Winda Rahmah Darman, Kiking Ritarwan

Department of Neurology, Faculty of Medicine, Universitas Sumatera Utara, Adam Malik General Hospital Medan Indonesia, Medan, Indonesia

Abstract

AIM: This study aimed to determine the correlation between inflammation with cognitive function in COVID-19 patients.

METHODS: We recruited COVID-19 patients using consecutive sampling methods in Adam Malik General Hospital Medan, Indonesia. The neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), D-dimer, and ferritin serum levels were measured as inflammatory markers. Cognitive function was assessed in several cognitive domains using Forward Digit Span for attention, Backward Digit Span for working memory, and Trail Making Test parts A and B for executive function. The correlation between inflammatory markers and cognitive function was analyzed using Spearman correlation test.

RESULTS: This study involved 40 COVID-19 patients consisting of 13 (32.5%) males and 27 (67.5%) females; the median age of the patients was 39.5 (19–65) years. We found that higher D-dimer and ferritin levels were significantly correlated with worse BDS scores ($r = -0.369 \ p = 0.019$ and $r = -0.408 \ p = 0.009$, respectively) and higher ferritin level was also correlated with worse FDS score ($r = -0.365 \ p = 0.020$ and). Higher D-dimer and ferritin levels were also significantly correlated with a longer time of completion of TMT-B ($r = 0.363 \ p = 0.022$ and $r = 0.433 \ p = 0.005$) and higher ferritin level was also correlated with a longer time of completion of TMT-A ($r = 0.438 \ p = 0.005$). There were no significant correlations between NLR and CRP levels with cognitive function.

CONCLUSION: Higher inflammatory markers are correlated with worse attention, working memory, and executive function in COVID-19 patients.

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared by the World Health Organization (WHO) as a global pandemic in January 2020, only after 3 months after the first case was confirmed and soon became a major health problem [1]. The number of cases of COVID-19 in Indonesia has continued to rise until 4,254,443 confirmed cases and has caused 143,766 deaths by the end of November 2021 [2]. Although COVID-19 mainly affects the respiratory system, its manifestation in other organs, including the nervous system has been increasingly recognized. The manifestations range from mild symptoms such as headache, ageusia, anosmia, fatigue, and myalgia to more serious symptoms, such as Guillain-Barre Syndrome (GBS) and encephalitis. As COVID-19 is a new disease, the potential similarities with other neurological conditions have not yet been explored in the literature. Several researchers identified that many of the neurological symptoms of COVID-19 appear similar to the symptoms of functional neurological disorder. In addition, recent articles discussed the similarities between so-called “Long Covid” and chronic fatigue syndrome, as it has become increasingly noticeable that symptoms are similar [3]. According to Ermis et al., major clinical features of hospitalized COVID-19 patients found were coordination deficits (74%), cognitive impairment (61.5%), paresis (47%), abnormal reflex status (45%), sensory abnormalities (45%), general muscle weakness and pain (32%), hyposmia (26%), and headache (21%) [4].

There is also a growing body of evidence about the association between cognitive impairment with COVID-19 that may persist after several months or longer after infection. A growing contingent of recovered COVID-19 patients are reportedly facing neurological symptoms described as slow thinking, difficulty in focusing, confusion, lack of concentration, forgetfulness, or haziness in thought process. This perception and experience of mental fatigue that is associated with and related to mild cognitive impairments may be conceptually defined as “brain fog.” The impairment is not fully understood but often affects working memory, information processing, attention, and reaction time [5]. Cognitive deficits mainly affected executive function, attention, language, and delayed memory recall [4]. Mechanisms underlying
cognitive impairment in COVID-19 include hypoxemia, the hyperinflammatory and hypercoagulable states that are promoted by SARS-CoV-2 thus playing a crucial role in developing cognitive deficits [6]. In the central nervous system (CNS), SARS-CoV-2 may also infect the microglia and astrocyte and induce an inflammatory response. Immune cell activation damages the BBB and prolongs a proinflammatory state inducing neurodegenerative problems in individuals at risk [7].

The natural history of COVID-19 includes an initial stage of viral replication that can be followed by the second stage of immunopathology driven by a hyperinflammatory response to SARS-CoV-2 infection [8]. The importance of inflammation as a pathogenesis mechanism in COVID-19 has also been shown in several previous studies. Inflammatory markers are associated with disease severity and mortality. A number of neuropathological studies of COVID-19 patients, even without a distinct neurological syndrome, have demonstrated CNS inflammatory changes, with microglial activation, astrocytosis, and perivascular T-cell cuffing [9]. There have been a lot of studies that found the association between the hyperinflammatory state in COVID-19, but studies about its association with cognitive impairment are still limited, especially during patient admission.

Several inflammatory markers that have been commonly measured during the acute period of COVID-19 include white blood cell count and neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), D-dimer, and ferritin serum which are proved to be useful, rapid and reliable markers for systemic inflammation. Increased NLR and fever were frequently found in COVID-19 [10]. A meta-analysis showed that elevated CRP, D-dimer, and ferritin serum levels were associated with an increased worsening of the prognosis and mortality from severe COVID-19, acute respiratory infection distress syndrome (ARDS), as well as the need for ICU care [11]. Higher D-dimer and ferritin levels also correlated with poorer verbal recall and psychomotor speed [12]. We aimed to determine the correlation between these inflammatory markers with cognitive function in COVID-19 patients.

**Methods**

**Study design and participants**

This was an analytic and cross-sectional study including COVID-19 patients who were treated in the isolation ward of H. Adam Malik General Hospital, Medan, from July 2021 to October 2021. The inclusion criteria were confirmed cases of COVID-19, aged more than 18 years old, were fully cooperative, able to speak Bahasa Indonesia, able to read and write. We excluded patients that had aphasia and a history of cognitive impairment before SARS-CoV-2 infection. We recruited patients using non-random consecutive sampling method, and written informed consent was obtained for every patient.

**Laboratory test**

All patients underwent laboratory examination to measure the NLR, CRP, D-dimer, and serum ferritin levels. NLR is the ratio of absolute neutrophil count to absolute lymphocyte count. The normal cut off value of NLR was 2.4, thus the value of NLR above 2.4 was considered to be abnormal [13]. CRP is an acute-phase protein, the plasma concentration of CRP deviates by at least 25% during inflammatory disorders [14]. The normal CRP level in this study was 0–10.90 mg/L [15]. D-dimer is a fibrin degeneration product that is useful for detecting abnormal clot formation or thrombotic events and for assessing the presence of clot rupturing or fibrinolytic processes [16]. The normal D-dimer level in this study was 0–240 ng/ml.15 Ferritin is the primary tissue iron-storage protein in the liver, and it is also an acute-phase protein that can be induced in the setting of systemic inflammation [17]. The normal ferritin level in this study was 23.9–336.2 ng/ml [15]. Laboratory tests were performed during patients’ admission. We recorded the value of each marker as continuous variable.

**Cognitive assessments**

Cognitive assessments included Forward and Backward Digit Span (FDS and BDS) and Trail Making Tests A and B (TMT-A and TMT-B) to assess attention, working memory, and executive function, respectively. FDS and BDS are among the oldest neuropsychology tests and are the most frequently used to assess verbal memory. The sequence of digits presented starts with two digits long and will get longer. The patients were asked to repeat the number correctly, FDS in order and BDS in reverse order. Test was terminated when the patients failed to accurately report the sequence either on a sequence of length or when the maximum length had been reached (nine digits forward, eight backward).

The TMTs are pencil and paper tests and are believed to measure visual-motor function, symbol recognition, the ability to scan pages, flexible integration of information and the alphabet under time pressure, as well as executive function such as sequencing and mental flexibility. Both parts of the TMT consisted of 25 circles distributed over a sheet of paper. In part A, the circles were numbered 1 – 25, and the patients were asked to draw lines to connect the numbers in ascending order. In part B, the circles included both numbers (1 – 13) and letters (A – L); as in part A, the patients were asked to draw lines to connect the
circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patients were instructed to connect the circles as quickly as possible without lifting the pen or pencil from the paper. The time of completion was recorded. It was unnecessary to continue the test if the patient had not completed TMT-A or TMT-B after three or five minutes had elapsed, respectively [18].

**Statistic analysis and ethical clearance**

The data were analyzed using the Windows Statistical Product and Science Service computer program version 22.0. The Spearman correlation test was used to determine the correlation between NLR, CRP, D-dimer, serum ferritin, and cognitive function, with \( P < 0.05 \) was considered statistically significant. This study was approved by the Faculty of Medicine Universitas Sumatera Utara/Haji Adam Malik General Hospital Ethical Committee.

**Results**

We included 40 COVID-19 patients with a median age of 39.5 (19–65) years. There were 27 females (67.5%) and 13 males (32.5%). The median value of NLR, CRP, D-dimer, and ferritin were 3.4 (1.4–9.3), 12.6 mg/L (1.4–17.2), 227 ng/ml (126–1600), and 308.5 ng/mL (17.3–1789), respectively. All values showed higher than normal levels [Table 1].

**Table 1: Demographic and clinical characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (minimum–maximum)</td>
<td>39.5 (19–65)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>≤ 29</td>
<td>13 (32.5)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>30–39</td>
<td>13 (32.5)</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td>40–49</td>
<td>1 (2.5)</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>50–59</td>
<td>1 (2.5)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>60–69</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Sex</td>
<td>27 (67.5)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>13 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Government employee</td>
<td>12 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Private employee</td>
<td>9 (22.5)</td>
<td></td>
</tr>
<tr>
<td>Entrepreneur</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>25 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Senior high school</td>
<td>11 (27.5)</td>
<td></td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>15 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Ethnic</td>
<td>14 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Karonese</td>
<td>13 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Batak</td>
<td>11 (27.5)</td>
<td></td>
</tr>
<tr>
<td>Javanese</td>
<td>2 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Aceh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLR, median (minimum–maximum)</td>
<td>3.4 (1.4–9.3)</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>CRP (mg/L), median (minimum–maximum)</td>
<td>12.6 (1.4–17.2)</td>
<td>127 (126–1600)</td>
</tr>
<tr>
<td>D-dimer (ng/ml), median (minimum–maximum)</td>
<td>227 (126–1600)</td>
<td></td>
</tr>
<tr>
<td>Ferritin serum (ng/ml), median (minimum–maximum)</td>
<td>308.5 (17.3–1789)</td>
<td></td>
</tr>
</tbody>
</table>

NLR: Neutrophil to lymphocyte ratio; CRP: C-reactive protein.

There were no significant correlations between NLR and CRP with cognitive function. We found that higher D-dimer and ferritin levels were significantly correlated with worse BDS scores (\( r = -0.369 \) \( P = 0.019 \) and \( r = -0.408 \) \( P = 0.009 \), respectively) and higher ferritin level was also correlated with worse FDS score (\( r = -0.365 \) \( P = 0.020 \) and). Higher D-dimer and ferritin levels were also significantly correlated with longer time of completion of TMT-B (\( r = 0.363 \) \( P = 0.022 \) and \( r = 0.433 \) \( P = 0.005 \)) and higher ferritin level was also correlated with longer time of completion of TMT-A (\( r = 0.438 \) \( P = 0.005 \)) (Table 2 and Figures 1-3).

**Spearman correlation test**

Spearman correlation test --> this is a description for the Figure 1-3.

**Discussion**

This study aimed to determine the correlation between inflammation and cognitive function in admitted COVID-19 patients. Most of the patients were female (67.5%). The age ranged from 19 to 65 years old. The Centers for Disease Control and Prevention (CDC) used the age group of 18–29 years as a reference group because in this age range, there is the largest cumulative number of COVID-19 cases compared to other age groups. The results of this study show that the highest percentage of people with COVID-19 is in the age group of 30–39 years and 50–59 years. The results of this study are in accordance with data from the CDC, which showed that the age group of 50–64 years compared to the age group of 18–29 years had a four
times higher number of COVID-19 patients [19]. The correlation between aging and declined innate immunity generally explained the more susceptibility of older persons to infection [20]. Biswas et al. (2020) found that male patients with COVID-19 were associated with a significantly increased risk of death by 1.86 times compared to female patients, but we did not study the association between age and gender with the severity of the disease [21].

A meta-analysis showed that elevated serum CRP, procalcitonin, D-dimer, and serum ferritin levels were associated with an increased worsening of the prognosis and mortality from severe COVID-19, ARDS and COVID-19 patients requiring ICU care [11]. Our study found increased levels of all these markers in our patients. Several previous studies have found similar findings. Nalbant et al. found that increased NLR and fever were found to be high in COVID-19 cases. There was no difference in the increase in NLR values for differences in age and sex [10]. Under certain conditions with an inflammatory reaction or tissue damage caused by infection or non-infection, CRP levels increased to 100 times or more [23]. Recent evidence suggests that CRP levels can also be used to monitor the progression and repair of COVID-19 patients [24].

We found no correlation between NLR and CRP with cognitive function. Aykut et al. (2017), in their study about the relationship between neutrophil-lymphocyte, platelet-lymphocyte ratio, and cognitive functions in bipolar disorder, observed some improvement in the attention function as subjects NLR values increased. No significant correlation was determined between platelet-lymphocyte ratio and neurocognitive tests [25]. According to Renteria et al., race did not modify the association between CRP and cognition. Findings suggest that levels of CRP at age 45+, are a marker of cognitive impairment but may not be suitable for risk prediction for cognitive decline [26]. There are a few possible explanations for the nonsignificant result of the association NLR and CRP with cognitive function in our study. First, prior studies that reported an association between NLR and CRP with cognitive decline had different cognitive assessments and longer follow-up periods. Second, previous studies generally accounted for few potentially confounding demographic and health variables. For instance, most studies would only include basic demographic, a few others controlled for relevant health behavior or medical comorbidities. These are several possible explanations for some inflammatory markers, such as NLR and CRP were not correlated with cognition impairment in our study. Meanwhile, some inflammatory markers such as D-dimer and ferritin serum were found correlated with cognition impairment in our study.

This study found that a higher D-dimer level was correlated with poorer attention, working memory, and executive function. This finding provides another possible underlying mechanism for cognitive impairment in COVID-19 patients and is a similar study from Frontera et al., which found a significant correlation between neurodegenerative biomarkers and the inflammatory marker D-dimer, which may provide some insight into the mechanism of acute brain injury after SARS-CoV-2 infection. Hypoxia and hyperinflammation, both hallmarks of acute COVID-19, have been linked to the development of Alzheimer’s disease type pathology in non-COVID population via upregulation of enzymes in the amyloidogenic pathway and downregulation of protein that break down Aβ [27]. Miskowiak et al. examined objective performance-based and subjectively rated cognitive functions in 29 COVID-19 patients 3-4 months after their hospital discharge. The percentage of patients with clinically significant objective cognitive impairment ranged from 59% to 65%, with verbal learning and executive functions being most affected. More than 80% of patients reported experiencing severe cognitive difficulties in daily life. Greater objective cognitive impairments were associated with more subjective cognitive difficulties, absenteeism, and poorer quality of life. Poorer pulmonary function and more respiratory symptoms after recovery were associated with more cognitive impairments. Among acute illness severity markers, higher maximum D-dimer levels correlated with poorer verbal recall and psychomotor speed [12]. According to Turana et al. (2021), further investigations found that cognitive impairment was associated with the degree of pulmonary dysfunction and D-dimer levels during acute illness, suggesting restriction of oxygen delivery to the brain [28].

This study found a significant correlation between higher ferritin levels with poorer performance on all cognitive examinations. Ferritin may contribute to worse cognition in COVID-19 patients by the accumulation of iron molecules that can deposit in the
brain which could be due to the passing through of ferri-
ions in blood circulation to the blood-cerebrospinal fluid
barrier by transferrin/transferrin receptor and endosome,
then iron overload in the peripheral circulation can lead
to iron deposition in the CNS [29]. As viruses replicate
more efficiently in iron-rich senescent cells, they may
have developed the ability to induce this phenotype in
host tissues, predisposing to both immune dysfunction
and neurodegenerative disorders [30].

According to Xu et al. in 2019, iron molecules can
deposit in microglia and astrocytes of the endothelium,
cerebellum, substantia nigra, hippocampus, which may
lead to cognitive impairment in severe cases. Their
autopsy study showed that patients with cognitive
impairment had 15 to 20 times higher iron deposit in the
superior temporal gyrus compared to the control group.
This pathological change was closely related to gender
and iron metabolism genes. Their previous study also
found that the abnormal expression of iron metabolism
genes occurred before the decline of learning and
memory ability in animals, suggesting that the molecular
biological changes in the brain tissues may occur
earlier than behavioral abnormalities. In addition, iron
deposition in neurons caused by abnormal expression
of iron metabolism genes, the peripheral iron load is
also a cause of cognitive impairment [29].

The causative agent of COVID-19 disease
was associated with hyperferritinemia and unfavorable
prognosis in older individuals, suggesting virus-induced
ferrosenescence. Ferrosenescence is an iron-associated
disruption of both the human genome and its repair
mechanisms, leading to premature cellular senescence
and neurodegeneration. As viruses replicate more
efficiently in iron-rich senescent cells, they may have
developed the ability to induce this phenotype in host
tissues, predisposing them to both immune dysfunction
and neurodegenerative disorders. The association
of unfavorable COVID-19 prognosis with advanced
chronological age, hyperferritinemia, and lymphopenia
suggests that SARS-CoV-2, like other viruses, maybe
iron-dependent; it likely promotes ferrosenescence to
acquire this metal and disable host natural killer cells [30].

Pyne et al. in 2021 found that overall, SARS-
CoV-2 infection, moderated in severity by age-, sex-, and race/ethnicity-dependent factors, initiates a disease
progression that has the potential to promote cognitive
decline and exacerbate pre-existing dementia. The
damage cascade of COVID-19 is multifaceted and
interdependent, with multiple pathways that could
lead to cognitive hazard mechanisms. One such
cognitive hazard mechanism, cerebral direct infection,
is possible with the SARS-CoV-2 virus exhibiting
neuroinvasive and neurotropic characteristics with
neurovirulent potential. The greatest cognitive risk may
be derived from immune-mediated damage originating
as cytokine storms and detrimental immune response
across the disease progression of COVID-19, which
may affect cognition via cerebral ischemia, hypoxia/
acidosis, and neuroinflammation, the initiation of the
cogulation cascade, excessive immune response,
that can generate micro/macro thromboemboli. While
long-term cognitive outcomes have not been fully
evaluated, emerging reports indicate high rates of long-
term symptoms and cognitive alterations in recovered
COVID-19 patients. For those at higher baseline
dementia risk, older adults, those with cardiovascular
risk factors, and people of color, COVID-19 may not only
increase the risk of cognitive decline but also interact in
a synergistic way with pre-existing dementia risk factors
to disproportionately increase this dementia risk [31].

Conclusion

This study provides evidence that higher
inflammatory markers are correlated with worse
cognitive function in COVID-19 patients. Based on our
findings, NLR, CRP, D-dimer, and ferritin serum may
be used as a marker of cognitive impairment among
COVID-19 patients. Further investigations are required
to disentangle the association of inflammatory markers
and cognitive decline.

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