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

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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, Bacward 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 examination results 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

Characteristics	(n = 40), n (%)
Age (years), median (minimum–maximum)	39.5 (19–65)
≤ 29	7 (17.5)
30–39	13 (32.5)
40–49	4 (10.0)
50–59	13 (37.5)
60–69	3 (2.5)
Sex	
Male	13 (32.5)
Female	27 (67.5)
Occupation	
Unemployed	13 (32.5)
Government employee	12 (30.0)
Private employee	9 (22.5)
Entrepreneur	5 (12.5)
Farmer	1 (2.5)
Education	
Senior high school	25 (62.5)
Bachelor degree	15 (37.5)
Ethnic	
Karonese	14 (35.0)
Batak	13 (32.5)
Javanesse	11 (27.5)
Aceh	2 (5.0)
NLR, median (minimum–maximum)	3.4 (1.4–9.3)
CRP (mg/L), median (minimum–maximum)	12.6 (1.4–17.2)
D-dimer (ng/ml), median (minimum–maximum)	227 (126–1600)
Ferritin serum (ng/ml), median (minimum–maximum)	308.5 (17.3–1789)

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).

Table 2: Association between inflammatory markers and cognitive function

Cognitive test	NLR		CRP		D-dimer		Ferritin serum	
	r	p	*r*	p	*r*	p	*r*	p
FDS	−0.165	0.308	−0.059	0.718	−0.274	0.088	−0.365	0.020
BDS	−0.177	0.273	−0.114	0.485	−0.369	0.019	−0.408	0.009
TMT-A	0.126	0.438	0.084	0.606	0.296	0.064	0.438	0.005
TMT-B	0.116	0.474	0.111	0.495	0.363	0.022	0.433	0.005

Spearman correlation test. NLR: Neutrophil to lymphocyte ratio, CRP: C-reactive protein, FDS: Forward digit span, BDS: Backward digit span, TMT: Trail making tests.

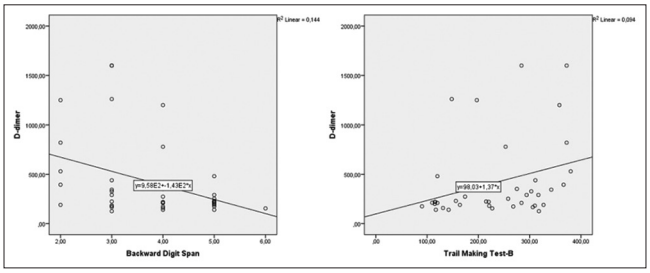

Figure 1: Correlation between D-dimer and BDS and TMT-B

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

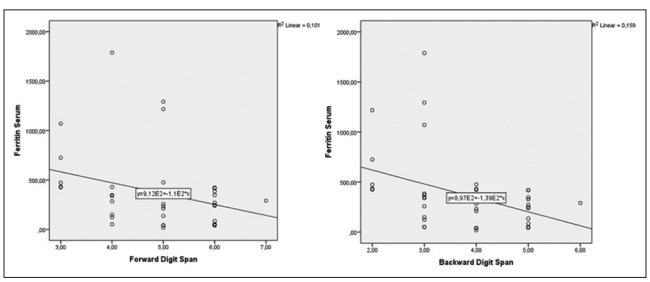

Figure 2: Correlation between Ferritin Serum and FDS and BDS

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].

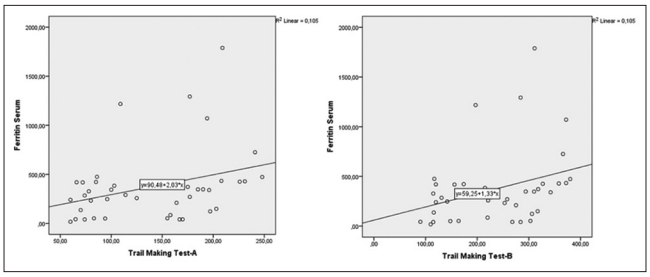

Figure 3: Correlation between Ferritin Serum and Trail Making Test A and B

As we know that increasing evidence suggests that infection with Sars-CoV-2 causes neurological deficits in a substantial proportion of affected patients. While these symptoms arise acutely during the course of infection, less is known about the possible long-term consequences for the brain. Severely affected COVID-19 cases experience high levels of inflammatory cytokines and acute respiratory dysfunction and often require assisted ventilation. According to Heneka *et al*. in 2020, all these factors are the mechanism those have been suggested to cause cognitive decline [22].

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 tempral 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 ferroscenescence 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 coagulation 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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References

1. Li Z, Liu T, Yang N, Han D, Mi X, Li Y, *et al*. Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the pheriphery to the brain. Front Med. 2020;14(5):533-41. https://doi.org/10.1007/s11684-020-0786-5
   PMid:32367431
2. Situasi Terkini Perkembangan Coronavirus Disease (COVID-19); 2021. Available from: https://infeksiemerging.kemkes.go.id. [Last accessed on 2022 Jan 21].
3. Wildwing T, Holt N. The neurological symptoms of COVID-19: A systematic overview of systematic reviews, comparison with other neurological conditions and implications for healthcare services. Ther Adv Chronic Dis. 2021;12:76979. https://doi.org/10.1177/2040622320976979
   PMid:33796241
4. Ermis U, Rust MI, Bungenberg J, Costa A, Dreher M, Balfanz P, *et al*. Neurological symptoms in COVID-19: A cross-sectional monocentric study of hospitalized patients. Neurol Res Pract. 2021;3(1):17. https://doi.org/10.1186/s42466-021-00116-1
   PMid:33712089
5. Vyas A, Panwar VR, Mathur V, Patel P, Mathur S, Sharma A, *et al*. Mild cognitive impairment in COVID-19 survivors: Measuring the brain fog. Int J Ment Health. 2021;20:1-12.
6. Garcia-Grimshaw M, Chirino-Perez A, Flores-Silva FD,

Valdes-Ferrer SI, Vargas-Martinez MD, Jimenez-Avila AI, *et al*. Critical role of acute hypoxemia on the cognitive impairment after severe COVID-19 pneumonia: A multivariate causality model analysis. Neurol Sci. 2021:43(2):2217-29. https://doi.org/10.1007/s10072-021-05798-8
PMid:35022935

7. Susilawathi NM, Tini K, Wijayanti IA, Rahmawati PL, Wardhana DP, Samatra DP, *et al*. Neurological manifestations of CVID-19: A clinical approach. Med J Indonesia. 2021;30(2):157-65.
8. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. Am J Pathol. 2021;191(1):4-17. https://doi.org/10.1016/j.ajpath.2020.08.009
PMid:32919977
9. Ren AL, Digby RJ, Needham EJ. Neurological update: COVID-19. J Neurol. 2021;268:4379-87. https://doi.org/10.1007/s00415-021-10581-y
PMid:33929617
10. Nalbant A, Kaya T, Varim C, Yaylaci S, Tamer A, Cinemre H. Can the neutrophil/lymphocyte ratio (NLR) have a role in the diagnosis of coronavirus 2019 disease (COVID-19)? Rev Assoc Med Bras. 2020;66(6):746-51. https://doi.org/10.1590/1806-9282.66.6.746
PMid:32696861
11. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther Adv Respir Dis. 2020;14:1-14. https://doi.org/10.1177/1753466620937175
PMid:32615866
12. Miskowiak KW, Johnsen S, Sattler SM, Nielsen S, Kunalan K, Rungby J. *et al*. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. Eur Neuropsychopharmacol. 2021;46:39-48. https://doi.org/10.1016/j.euroneuro.2021.03.019
PMid:33823427
13. Putzu I, Robert CD. White blood cells identification and counting from microscopic blood image. World Acad Sci Eng Technol. 2013;73:363-70.
14. Sproston NR, Asworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol. 2018;9:754. https://doi.org/10.3389/fimmu.2018.00754
PMid:29706967
15. Natalya MA, Diana VK, Shima M, Saenkoa EL. Intrinsic pathway of blood coagulation contributes to thrombogenicity of atherosclerotic plaque. Blood. 2002;99(12):4475-85. https://doi.org/10.1182/blood-2001-11-0140
PMid:12036878
16. Fei F, Smith JA, Cao L. Clinical laboratory characteristics in patients with suspected COVID-19: One single-institution experience. J Med Virol. 2020;93(3):1665-71. https://doi.org/10.1002/jmv.26527
PMid:32946118
17. Cao P, Wu Y, Wu S, Wu T, Zhang Q, Zhang R, *et al*. Elevated serum ferritin level effectively discriminates severity illness and predicts prognosis of COVID-19 patients. Res Sq. 2020;26:1-12.
18. Tombaugh NT. Trail making test A and B: Normative data stratified by age and education. Arch Clin Neuropsychol. 2004;19:203-14.
19. Centers for Disease Control and Prevention; 2021. Available from: https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm. [Last accessed on 2021 Nov 25].
20. Li, Y, Wang C, Peng M. Aging immune system and its correlation with liability to severe lung complications. Front Public Health. 2021;9: 735151. https://doi.org/10.3389/fpubh.2021.735151
PMid:34888279
21. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of sex, age, and comorbidities with mortality in COVID-19 patients: A systematic review and meta-analysis. Intervirology. 2021;64:36-47. https://doi.org/10.1159/000512592
PMid:33296901
22. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther. 2020;12(1):69. https://doi.org/10.1186/s13195-020-00640-3
PMid:32498691
23. Pranata H, Batubara CA, dan Sinurat PP. Hubungan rasio neutrofil dan high sensitivity C-reactive protein dengan Keparahan dan outcome pada Psien Stroke Iskemik Akut. [Tesis]. Medan: Universitas Sumatera Utara, Program Magister (S-2) Ilmu Kedokteran; 2020.
24. Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic values of serum ferritin and D-dimer trajectory in patients with COVID-19. Viruses. 2021;13(3):491. https://doi.org/10.3390/v13030419
PMid:33807920
25. Aykut DS, Arslan FC, Karaguzel EO, Aral G, Karakullukcu S. The relationship between neutrophil-lymphocyte, platelet-lymphocyte ratio and cognitive function in bipolar disorder. Nord J Psychiatry. 2018;72(2):119-23. https://doi.org/10.1080/08039488.2017.1397192
PMid:29108448
26. Renteria MA, Gillet SR, McCLure LA, Wadley VG, Glasser SP, Howard VJ, *et al*. C-reactive protein and risk of cognitive decline: The REGARDS study. PLoS One. 2020;15(12):e0244612. https://doi.org/10.1371/journal.pone.0244612
PMid:33382815
27. Frontera JA, Boutajangout A, Masurkar AV, Betensky RA, Ge Y, Vedvyas A, *et al*. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. Alzheimers Dement. 2022;18:12556. https://doi.org/10.1002/alz.12556
PMid:35023610
28. Turana T, Nathaniel M, Shen R, Ali S, Aparasu RR. Citicoline and COVID-19-related cognitive and other neurologic complications. Brain Sci. 2022;12(1):59. https://doi.org/10.3390/brainsci12010059
PMid:35053804
29. Xu J, Sun W, and Yang L. Association between iron metabolism and cognitive impairment in older non-alcoholic fatty liver disease individuals: A cross-sectional study in patients from a Chinese center. Medicine (Baltimore). 2019;98(48):e18189. https://doi.org/10.1097/MD.0000000000018189
PMid:31770275
30. Sfera A, Osorio C, Maguire G, Rahman L, Afzaal J, Cummings M, *et al*. COVID-19, ferrosenescence and neurodegeneration, a mini-review. Prog Neuropsychopharmacol Biol Psychiatry. 2021;109:110230. https://doi.org/10.1016/j.pnpbp.2020.110230
PMid:33373681
31. Pyne JD, Brickman AM. The impact of the COVID-19 pandemic on dementia risk: Potential pathways to cognitive decline. Neurodegener Dis. 2021;21(1-2):1-23. https://doi.org/10.1159/000518581
PMid:34348321