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ORIGINAL ARTICLE

Comparison of inflammation markers and severity of illness among patients with COVID-19, acute psychiatric disorders and comorbidity

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KEYWORDS
COVID-19;
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Abstract
Background and objectives: Neutrophil, lymphocyte counts, lactate dehydrogenase (LDH), D-dimer, fibrinogen, and comorbid illness are associated with the course and prognosis of COVID-19. However, the course of acute severe psychiatric disorders overlapping with COVID-19 infection was not investigated and remained as an unclarified research area. This study aimed to demonstrate inflammatory markers and the course of patients suffering from both conditions.
Methods: Thirty-eight inpatients with COVID-19 and comorbid acute psychiatric disorders (COVID-19+PD), 31 inpatients with COVID-19, and 38 inpatients with an acute psychiatric disorder (PD) were included in the study. Neutrophil, lymphocyte counts, serum ferritin, lactate dehydrogenase (LDH), D-dimer, fibrinogen, Systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR), and C-reactive protein (CRP) were compared to evaluate inflammation levels.
Results: Patients with SARS-CoV-2 infection had older age compared to the PD group. CALL (Comorbidity, age, lymphocyte, lactate dehydrogenase) scores which predict the progression risk in patients with COVID-19 pneumonia, of both COVID-19 groups were found similar. The COVID-19+PD had higher SII in the study sample. Additionally, the COVID-19+PD group had higher NLR, ferritin, and CRP levels than those of the PD group.
Conclusions: The prognosis of COVID-19 is not worse when accompanied by a psychiatric disorder. Laboratory assessment can guide clinicians to distinguish those infected with SARS-CoV-2 within psychiatric inpatient units. The biochemical assessment did not robustly support higher

Abbreviations: Absolute neutrophil count, ANC; Alanine aminotransferase, ALT; Comorbidity, age, lymphocyte, lactate dehydrogenase, CALL; COVID-19 and psychiatric disorder group, COVID-19+PD; C-reactive protein, CRP; Interleukin, IL; Lactate dehydrogenase, LDH; Neutrophil/lymphocyte ratio, NLR; Polymerase Chain Reaction, PCR; Psychiatric disorder group, PD; Systemic immune-inflammation index, SII.

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inflammatory levels in the comorbid COVID-19 and psychiatric disorder group compared to the COVID-19 group.

Introduction

The COVID-19 outbreak caused by SARS-CoV-2 continues, with more than 200 million people getting infected and more than 5 million deaths as of December 2021.[1] People infected with SARS-CoV-2 experience the infection with different severity levels.[2] Studies have shown that factors such as advanced age, presence of comorbidities, severe dyspnea, fever, abnormalities in biochemical measurements are related to disease severity.[3] In the previous studies, it has been reported that high levels of alanine aminotransferase (ALT), creatinine, lactate dehydrogenase (LDH), C − reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), D-dimer, and fibrinogen indicate higher severity of COVID-19.[2-5]

Another interesting issue is the question of whether the prognosis of COVID-19 would be poorer among individuals with mental disorders. In the study conducted by Nemani et al. (2021) to investigate COVID-19-related mortality, 7348 patients with a positive SARS-CoV-2 Polymerase Chain Reaction (PCR) test result were re-evaluated after 45 days. Results showed that mortality is associated with schizophrenia spectrum diagnoses but not with anxiety disorders and mood disorders.[6] Lee et al (2020) also reported patients with a severe mental illness had a worse prognosis of COVID-19 when compared with patients without a history of mental illness.[7]

Cytokines increased by inflammatory stimuli or infections may cause systemic symptoms, especially during acute inflammation.[8] This acute phase response includes some clinical and pathological changes such as fever and elevated acute-phase proteins (CRP, fibrinogen, ferritin, serum amyloid A protein, procalcitonin, etc.) as well as an increase in neutrophils, platelets, and NLR).[8,9] These inflammation markers increase in those having infections such as MERS, SARS, SARS-CoV-2.[4,10,11] On the other hand, the increase in inflammation markers also has been shown in those with severe mental illnesses such as schizophrenia and bipolar disorder.[10,12-14] As seen in the previous pandemics, increased rates of acute psychiatric conditions and acute exacerbations of remitted patients have been reported in the COVID-19 epidemic.[15-17] These reports attract the attention of researchers, giving rise to further efforts to investigate the relationship between mental disorders and pandemics. It is known that both psychosocial and immune factors play a role in the etiopathogenesis of psychiatric illness.[18,19]

According to the hypothesis of Raony et al. (2020), changes in cytokine levels can be considered as a link between immune system alterations and mental health disorders during COVID-19 infection, as they play a possible role in disrupting neurotransmitter metabolism, leading to behavioral changes.[10] A meta-analysis of 16 studies by Wang et al. (2018) reported that Cerebrospinal fluid levels of several interleukins (IL) such as IL-1β, IL-6, and IL-8 were significantly increased in patients with schizophrenia compared to controls.[20] It is also assumed that Human Coronaviruses (HCoVs) enter the central nervous system by retrograde neuronal routes (via the olfactory nerve and enteric nervous system) and hematogenous spread (via infected leukocytes that cross the blood-brain barrier, carrying the virus to the brain and/or by the direct infection of angiotensin-converting enzyme 2 expressing brain microvascular endothelial cells).[10] Severance et al. (2011) also suggested that immunoglobulin G response against human coronavirus (NL63) is associated with psychotic symptoms, and exposure to coronaviruses may be a comorbid risk factor in people with severe mental disorders.[21]

Although the SARS-CoV-2 infection and associated immune alterations could lead to psychotic exacerbations, the laboratory assessment of COVID-19 patients treated for a mental disorder was not investigated, especially considering cardiovascular or metabolic burden and morbidity of psychiatric disorders. Moreover, given the immune system disturbances shown in COVID-19 infection might have mental health outcomes, the laboratory assessments of individuals treated for both COVID-19 and having a severe psychiatric disorder were not compared with those suffering from COVID-19. Most clinicians need further knowledge about complications and the treatment of patients having both COVID-19 and a severe mental disorder. These acutely-ill individuals suffering from dual health conditions could be at risk for more severe complications than seen in COVID-19 itself. Therefore, in this study, we aimed to evaluate the inflammatory markers and the rates of complications among inpatients treated for a severe mental disorder along with COVID-19 by comparing with other inpatients with COVID-19 and without a psychiatric disorder. Secondly, we assessed the inflammatory markers of peripheral blood within inpatients with COVID-19 and a psychiatric disorder. Finally, we aimed to demonstrate the clinical outcomes of COVID-19 and the blood markers of the inflammation in an acutely-ill psychiatric population treated in the psychiatric ward for COVID-19 (for those having both clinical conditions) by comparing with patients treated in the regular psychiatry services and regular COVID-19 inpatient units.

Materials and methods

Study design

As a response to the hospitalization needs of patients with acute psychiatric conditions accompanying COVID-19, a special ward was designed at Kanuni Sultan Süleyman Training and research hospital in April 2020. The hospital was also declared as the main treatment center for COVID-19.

The study was designed as a retrospective cohort study. Three patient groups aged between 18-65 years from different units were consecutively included in the study: i) COVID-19 and psychiatric disorder group (COVID-19+PD): The group was composed of patients hospitalized in the COVID-19 special psychiatry unit. These patients were having acute

psychiatric disorders together with COVID-19. The diagnosis of COVID-19 was confirmed by PCR testing. ii) COVID-19 group: The group was composed of patients hospitalized in the COVID-19 unit. They were diagnosed with COVID-19 and had no psychiatric diagnoses. The diagnosis of COVID-19 was confirmed by PCR testing. iii) Psychiatric disorder group (PD): The group involved patients hospitalized with an acute psychiatric disorder in the psychiatric ward of the hospital. They didn't have COVID-19. These patients had no COVID-19 related symptoms and it's confirmed by PCR testing that patients do not have COVID-19.

All participants were inpatients from the same hospital at the same time interval. By screening electronic patient files between May-August 2020, sociodemographic information, inflammation- and COVID-19-related inflammation markers, clinical diagnoses, treatments, and complications were collected.

All patients were admitted to both psychiatry and COVID-19 wards from the emergency room. The diagnosis of COVID-19 was confirmed by PCR testing. The COVID-19 treatment was determined in line with the national treatment guideline available at that time.[22] Patients in psychiatry wards were hospitalized for suicide risk, aggression, exacerbation of existing psychotic disorder, non-compliance with oral or intramuscular treatment. Participants recruited from psychiatric wards suffered from a diagnosis of schizophrenia, bipolar disorder, major depression, psychosis spectrum disorders, or severe anxiety disorder, and were hospitalized for a median of 3 weeks. Psychiatric diagnoses and treatments were organized by experienced psychiatry consultants according to their best choices. All psychiatric disorders were treated with psychotropic medications and electroconvulsive therapy was not used. Most patients were treated with first- or second-generation antipsychotics and mood stabilizers. For all study groups, patients with autoimmune diseases, immune deficiency, autoinflammatory illnesses, active malignancy, treated with oral corticosteroids, immunosuppressive drugs, or biological agents were excluded. Likewise, mental retardation, autism spectrum disorders, were not included in the study. The complications were periodically recorded during the clinical follow-up.

The official approval of the study was received from the Institutional Review Board and Ministry of Health (COVID-19 Scientific Research Platform). Also, the Local Ethics Committee reviewed and approved the study protocol and waived the requirement of obtaining informed consent due to the retrospective nature of the study.

Laboratory procedures

On the first day of the hospitalization, blood samples were routinely collected at 7 am after overnight fasting. Absolute neutrophil count (ANC), CRP, platelet counts, lymphocyte counts, ALT, creatinine, ferritin, NLR parameters are measured as indicators of the inflammatory response.[4,8,9] D-dimer, fibrinogen, LDH, CRP, lymphocyte counts, ALT, NLR values have been previously shown as values indicating the prognosis of COVID-19.[2-5,23] Electrocardiograms in the patient files were used to calculate the corrected QT interval of hospitalized subjects.

CALL score (C = co-morbidity, A = age, L = lymphocyte count, L= LDH) was determined by Ji et al. (2020) to predict the progression risk in patients with COVID-19 pneumonia.[2] The CALL score ranges between 4-13 points and is calculated as using (Comorbidity = 1-4 points, Age = 1 - 3 points, Lymphocyte counts= 1 - 3 points, LDH= 1 -3 points). Systemic Immune-Inflammation Index (SII) was defined by Hu et al. (2014) to reflect the degree of systemic inflammation and immune response.[24] It was calculated based on peripheral lymphocyte, neutrophil, and platelet counts (SII = Platelet counts x Neutrophil counts / Lymphocyte counts).[24]

Statistical analysis

Continuous variables were demonstrated as means and standard deviations and categorical variables were shown as frequencies. Continuous variables were compared using the independent sample t-test and the one-way ANOVA test as per the number of groups involved in the analysis. Categorical variables were compared by the chi-square test. When cell size was equal to or less than 5, Fisher's exact test was applied.

To compare laboratory parameters, ANCOVA models controlled for age and gender effects were implemented. Laboratory values were the dependent outcomes of ANCOVA models. The significance levels were obtained from posthoc tests. In posthoc analyses, the Bonferroni test was preferred to reduce the likelihood of type-I error. The alpha level was set at 0.05 for each comparison. The Statistical Package for Social Sciences version 24 (IBM Corporation, Armonk, NY) was used for data analyses,

Results

Sociodemographic characteristics and medical comorbidities

Sociodemographic, clinic, and treatment characteristics of the study groups were shown in Table 1. The study groups differed significantly for the mean age (F=24.6, $p<0.001$). There were no significant differences regarding gender and the duration of education. CALL scores of both COVID-19 groups were similar. Additionally, smoking status significantly differed among study groups (X^2= 20.7, $p<0.001$). Smoking was less common in the COVID-19 group than those found in the COVID-19+PD and PD groups. Other medical comorbidities were similar across study groups.

Laboratory paratmeters & inflammation markers

The comparison of laboratory parameters of the three groups was demonstrated in Table 2. ALT and creatinine levels were similar across study groups. Both COVID-19 groups also had similar D-dimer levels. SII values were significantly higher in the COVID-19+PD group compared to the other two groups (F=5.3, p=0.007). Besides, LDH values were found to be lower in the COVID-19+PD group compared to the COVID-19 group and lower in the PD group compared to both groups (F=15.9, $p< 0.001$).

The COVID-19+PD group had higher ANC levels than the COVID-19 group (F=7.4, $p<0.001$). Although the ANC value in PD group was between both groups, it was not significantly different from the two groups. NLR ratio was higher in COVID-19+PD group than PD group (F=9.8, $p<0.001$). Finally,

Table 1 Sociodemographic, clinic, and treatment characteristics of study participants.

Variables	COVID-19+PD, n =38	COVID-19, n=31	PD, n=38	Statistics	*P*
Age, years, mean ± SD	45.7 ± 13.6 [A]	50.8 ± 10.2 [A]	32.8 ± 8.8 [B]	F=24.6	**<0.001**
Gender, female n (%)	11 (28.9)	14 (45.2)	15 (39.5)	X^2 =2.0	0.363
Education, years, mean ± SD	7.4 ± 4.0	7.6 ± 4.4	9.1 ± 4.2	F=2.1	0.125
Current smoker	20 (52.6) [A]	2 (6.5) [B]	21 (55.3) [A]	X^2= 20.7	**<0.001**
Medical comorbidities, n (%)					
Hypertension	4 (10.5) [AB]	7 (22.6) [A]	0 (0.0) [B]	X^2 = 9.4	**0.009**
COPD	1 (2.6)	0 (0.0)	0 (0.0)	X^2 = 1.8	0.400
Diabetes	5 (13.2)	5 (16.7)	1 (2.6)	X^2 = 4.0	0.132
Hypothyroidism	4 (10.5)	2 (6.5)	4 (10.5)	X^2 = 0.4	0.806
Hyperlipidemia	0 (0.0)	2 (6.5)	3 (7.9)	X^2 = 3.0	0.227
Asthma	2 (5.3)	3 (9.7)	0 (0.0)	X^2 = 3.6	0.162
CHD or CVD	2 (5.3)	1 (3.2)	0 (0.0)	X^2 = 2.0	0.375
Cardiac illness	3 (7.9)	3 (9.7)	0 (0.0)	X^2 = 3.6	0.165
HBV infection	0 (0.0)	1 (3.2)	1 (2.6)	X^2= 1.2	0.561
Epilepsy	2 (5.3)	0 (0.0)	1 (2.6)	X^2 = 1.7	0.419
CALL score [a], mean ± SD	6.6 ± 2.1	7.2 ± 2.3	N/A	t=1.2 [b]	0.233
Total N° of AP, mean ± SD	2.1 ± 0.8	N/A	2.5 ± 1.3	t= 1.8 [b]	0.074

CHD: Coronary heart disease, COPD: Chronic obstructive pulmonary disease, COVID-19=Coronavirus disease-19, COVID-19+PD=Coronavirus disease-19 and psychiatric disorder, CVD: Cardiovascular disease, HBV: Hepatitis B virus, N/A= not applicable, PD=psychiatric disorder, SD=standard deviation.

[a] CALL scores were calculated for patients with COVID-19, abiding by Ji et al (2020).

[b] Independent sample t-test

*Different superscripts indicate statistical differences between two groups at p<0.05/3 level.

ferritin and CRP levels were found higher in both COVID-19 groups than the PD group (for ferritin, F=6.3, p=0.003; for CRP, F=8.5, p< 0.001).

Prognosis and complications

Table 3 provides the cardiovascular complications of the COVID-19 during their hospitalizations. Study groups did not statistically differ for a particular complication. When all cardiovascular complications were assessed together, the COVID-19+PD group more frequently showed a cardiovascular incident than that of the COVID-19 group (21.1% vs. 3.2%, p=0.035). Cardiovascular arrest, respiratory failure, and death were not observed in the study population.

Finally, Table S1 shows that the COVID-19 group more commonly received favipiravir treatment than the COVID-19 +PD group and other medical treatments were similar between COVID-19 inpatient groups.

Table 2 Comparison of laboratory values using ANCOVA models.

Variables at admission (mean ± SD)	COVID-19+PD, n =38	COVID-19, n=31	PD, n=38	F [a]	*P*
ALT, U/L	23.3 ± 18.2	26.2 ± 12.5	30.8 ± 41.9	0.4	0.664
LDH, U/L	263 ± 96 [A]	324 ± 92 [B]	184 ± 41 [C]	15.9	**< 0.001**
Creatinine, mg/dL	0.9 ± 0.4	0.8 ± 0.2	0.8 ± 0.2	0.9	0.419
Ferritin, ng/mL [b]	241 ± 204 [A]	319 ± 245 [A]	76 ± 60 [B]	6.3	**0.003**
D-dimer, mg/L [c]	1.3 ± 1.4	0.8 ± 0.7	N/A	3.4	0.071
Fibrinogen, mg/dL [c]	387 ± 135	471 ± 161	N/A	6.1	**0.016**
ANC, $10^3/\mu$L	6.0 ± 2.9 [A]	3.7 ± 1.6 [B]	5.3 ± 1.8 [AB]	7.4	**0.001**
Lymphocyte, $10^3/\mu$L	1.7 ± 0.7 [A]	1.6 ± 0.7 [A]	2.7 ± 0.6 [B]	18.0	**< 0.001**
Platelets, $10^3/\mu$L	230 ± 83 [AB]	217 ± 77 [A]	273 ± 63 [B]	3.8	**0.025**
NLR ratio	4.3 ± 3.4 [A]	3.0 ± 1.8 [AB]	2.1 ± 1.0 [B]	9.8	**< 0.001**
CRP, mg/L [d]	32.4 ± 51.0 [A]	46.6 ± 52.1 [A]	4.6 ± 6.5 [B]	8.5	**< 0.001**
QTc interval, ms	420.6 ± 23.5	421.0 ± 27.6	424.7 ± 29.7	0.4	0.648
SII, $10^3/\mu$L	1047.4 ± 176.1[A]	607.2 ± 85.8[B]	572.0 ±271.1[B]	5.3	**0.007**

ALT: Alanine transaminase, ANC: Absolute neutrophil count, COVID-19=Coronavirus disease-19, COVID-19+ PD = Coronavirus disease-19 and psychiatric disorder, CRP: C − reactive protein, LDH: Lactate dehydrogenase, NLR: Neutrophil to lymphocyte ratio, PD=psychiatric disorder, QTc: corrected QT interval, SD: standard deviation, SII: Systemic Immune-Inflammation Index.

[a] Results were compared using ANCOVA models, adjusted by age and gender.

[b] Values of 13 cases are missing in the PD group

[c] Values of the PD group are missing.

[d] Values of 5 cases are missing in the PD group

*Different superscripts indicate statistical differences between two groups at p<0.05/3 level.

Table 3 Cardiovascular complications of patient with COVID-19 during hospitalization.

Cardiovascular complications, n (%)	COVID-19+PD,n =38	COVID-19,n=31	Statistics	*p*
Bradycardia (symptomatic)	1 (2.6)	0 (0.0)	Fisher's	1.0
Tachycardia (symptomatic)	3 (7.9)	1 (3.2)	Fisher's	0.622
QTc prolongation	2 (5.3)	0 (0.0)	Fisher's	0.498
Acute coronary syndrome	1 (2.6)	0 (0.0)	Fisher's	1.0
Arrhythmia [a]	1 (2.6)	0 (0.0)	Fisher's	1.0
Any cardiovascular complication	8 (21.1)	1 (3.2)	Fisher's	**0.035**

COVID-19=Coronavirus disease-19, COVID-19+ PD = Coronavirus disease-19 and psychiatric disorder, PD=psychiatric disorder, QTc: corrected QT interval.
[a] One patient had atrial fibrillation during treatment

Discussion

The results of our study showed that the severity of COVID-19, assessed by the CALL score was similar between study groups with COVID-19. Results also showed ANC and SII levels were higher and LDH and fibrinogen levels were lower in the COVID-19+PD patient group compared to the COVID-19 inpatients. Third, when compared to psychiatric inpatients without COVID-19, the COVID-19+PD group had higher SII, NLR, ferritin, and CRP levels.

Prognostic factors of COVID-19 in the psychiatric sample

In the previous literature, D-dimer, fibrinogen, NLR, LDH, CRP, and low lymphocyte count were found as poor prognostic factors in COVID-19.[2,4,23] In our study, fibrinogen and LDH values were found to be lower in the COVID-19+PD group compared to the COVID-19 group. Also, there was no significant difference was found between COVID-19 groups in terms of D-dimer, NLR, CRP, and lymphocyte counts. These results of our study suggested the COVID-19+PD group did not have a higher illness severity and a worse prognosis than the COVID-19 inpatients without a psychiatric disorder. Besides, the total CALL scores of the COVID-19 groups were similar, indicating similar infection severity in both groups.[2] Cardiac complication rates were also similar and other severe complications of COVID-19 (e.g intensive care unit admission, respiratory failure, and so on) were not seen in our sample. While these results indicate a favorable prognosis of the COVID-19 in our study compared to previous literature with higher mortality and morbidity rates, our results could suggest that the presence of exacerbated psychiatric disorders does not adversely affect the course of COVID-19. On the other hand, it should be taken into account that patients with severe mental disorders have disadvantages and difficulties in reaching health services during pandemic periods, leading to low treatment compliance, and are susceptible to drug interactions, especially when receiving both neuroleptic drugs and the treatment of the infection. These disadvantageous situations should be kept in mind while interpreting these results related to mental disorders.[18,25]

Inflammation markers

In our study, ANC and SII were found higher in the COVID-19 +PD group compared to the COVID-19 patient group. Neutrophil, NLR, SII are the markers that can be obtained via routine blood work, showing systemic inflammatory response.[4,24,26] This result somewhat supported the notion that there was a more systemic inflammatory response to SARS-CoV-2 in acutely-ill patients with severe psychiatric disorders. Epidemiological studies conducted during epidemic periods have shown that infections could also trigger psychiatric diseases.[15,17,18] Debates over the role of inflammatory responses as a trigger of severe psychiatric disorder remained inconclusive and the exact etiopathogenesis of such effect has not been elucidated yet.[21,27,28]

Several mechanisms explain the neural effects of the inflammatory response. A current hypothesis suggests that the activation of brain microglial cells causes the increased production of pro-inflammatory cytokines and free radicals. This may lead to neuronal degeneration, white matter abnormalities, and decreased neurogenesis, which are associated with the pathophysiology of schizophrenia.[29] Cytokines can also directly alter the activity of enzymes involved in tryptophan catabolism. Induction of the enzyme indoleamine 2,3-dioxygenase by pro-inflammatory cytokines results in the increased production of kynurenine, which is also converted to kynurenic acid and quinolinic that modulate glutamatergic N-methyl D-aspartate receptors in the brain.[20] Although there are several links between the development of mental disorders triggered by immunologic responses, the underlying effects of immune mechanisms on neurochemical processes of the brain still require further exploration.

On the other hand, ANC in the PD group did not differ from those of the other study groups and SII in the PD group was significantly lower compared to the COVID-19+PD group. Moreover, higher SII values in the COVID+PD group suggest that patients with psychiatric disorders might be prone to an excessive inflammatory response to COVID-19. The similarity between COVID-19 and PD groups in terms of ANC and SII values was also somewhat surprising. Accordingly, patients with psychiatric disorders seem to have some similarities in inflammatory markers to those seen in individuals with COVID-19. However, these preliminary results should be further investigated and tested by larger studies.

The relationship between COVID-19 and psychiatric disorders

During the COVID-19 pandemic, clinicians reported serious cases with exacerbated mental illness such as first-episode psychosis, mood swings, and suicide attempts.[15,16,30] In a

study including patients with COVID-19, NLR was positively related to patients' self-perceived illness severity.[31] In the same study, IL levels such as IL-1β, IL-6, IL-8, IL-10, tumor necrosis factor-α, high-sensitive CRP, and blood cell counts (e.g white blood cells, neutrophils, lymphocytes) were also related to mental health.[31] Our results extended previous findings by demonstrating the increase in ANC and SII in the COVID-19+PD group.

In a recent study conducted in Italy, results have shown that neutrophil counts and NLR in patients with COVID-19 are associated with self-reported depression levels.[32] Previous literature also reported higher NLR in COVID-19 cases who developed psychosis.[16] Mazza et al. (2020) re-evaluated the depression and anxiety levels of 402 patients hospitalized for COVID-19 at the first month of the hospital discharge.[33] Their findings showed that SII measured during hospitalization was positively associated with depression and anxiety scores during the follow-up.[33] According to the results of our study, the higher levels of SII and ANC in the COVID-19+PD group compared to the COVID-19 group contributed to our current understanding of the potential immunological mechanisms of acute infections, which might have a possible role in the newly emerging mental disorders. Considering cytokines in the blood cannot be measured in clinical practice, SII and ANC could be cheap, accessible, and quick tools that can be used in clinical practice. Therefore, both laboratory measurements could be indicative of future psychopathology. patients with COVID-19 with elevated SII and ANC may be more likely to develop psychiatric disorders. Clinicians should be careful about mental disorders that can be triggered by the infection.

Prognosis and complications

In our study, there was no significant difference between the COVID-19 groups regarding cardiac complications such as arrhythmias, QT prolongation, and acute coronary syndrome. Besides, taken together, total rates of cardiac complications were higher in the COVID-19+PD group. It has been reported that drugs used in the treatment of COVID-19 can prolong the QT interval on EKG and could pose a risk for sudden cardiac death.[34] Neuroleptic drugs use in patients with severe mental disorders may cause similar changes in electrocardiograms and cause serious cardiac events.[35,36] Although this information raises suspicion over the potential cardiac risks of the coexistence of COVID-19 and severe mental illness, in the study sample, no life-threatening outcome or mortality was observed. Nevertheless, multi-center and larger cohorts are needed to predict cardiac risks of patients suffering from both health conditions.

Clinical implications

In our study, the COVID-19+PD group differed from the other two groups regarding increased SII. Also, the COVID-19+PD group had higher NLR, CRP, ferritin, and lower lymphocyte counts than acute psychiatric inpatients without COVID-19. Increased SII seems to be a marker of SARS-CoV-2 infection in psychiatric wards. The inpatient units of mental health hospitals are at risk for the spread of infection.[18] Many cases with COVID-19 were diagnosed in the inpatient units of mental health hospitals throughout the pandemic and it was emphasized that almost all patients rapidly caught COVID-19 after the detection of the first cases in psychiatric wards.[19,37] Many cases with COVID-19 could be asymptomatic or showed no apparent severe symptoms.[38] Likewise, many cases can transmit the disease to others during the prodromal stage when they are asymptomatic.[39] In this context, screening the biochemical alterations of these patients and the early recognition of asymptomatic patients in psychiatric wards could be life-saving in many aspects. Considering that COVID-19 PCR tests do not seem feasible to be routinely performed for screening within inpatient psychiatric units with limited sources; blood count measurements can be a cheaper and easier way to detect those requiring gold-standard PCR tests especially for asymptomatic cases. Elevated SII could alert the clinician for COVID-19 like elevated NLR, CRP, and ferritin. Similarly, despite being nonspecific, these inflammatory markers could be considered to rule out a possible infection in psychiatric wards, especially when a negative PCR test result could not exclude possible COVID-19 cases in psychiatry services.

Limitations and strengths

The limitations of the study have to be considered. The age difference among study groups might affect the results. This finding was consistent with the previous literature regarding the effect of age on the severity of COVID-19, especially when considering that patients were consecutively included in the study.[2,3] To keep this variable constant, we implemented ANCOVA models adjusted for age and gender. Second, the small sample size was associated with lower rates of severe complications. The cross-sectional assessment of biochemical parameters was not able to show the changes during the clinical course. Additionally, COVID-19 treatments were administered according to the guidelines of the period in which the study was conducted and the treatments of that period became outdated. Finally, favipiravir use was different between COVID-19 groups, which could play a confounding role in study results. Given that the patients with psychiatric comorbidities using multiple psychotropic medications are susceptible to drug interactions, we assume clinicians could be hesitant about using favipiravir for the treatment of COVID-19, which ultimately may have had an impact on the study results. Despite all these limitations, our research provided a unique contribution to existing knowledge and demonstrated the clinical severity, prognosis, and outcomes of patients with COVID-19 together with an acute psychiatric disorder.

Conclusions

Patients with both an acute severe mental disorder and COVID-19 are a special group to be treated carefully in clinical practice. In our study, the global severity of the illness, inflammatory markers, and clinical outcomes of these patients were not markedly worse than those suffering from COVID-19. NLR, SII, CRP, ferritin, and lower lymphocyte counts could be helpful for clinicians in the early diagnosis of possible COVID-19 infection to prevent the spread of infection in psychiatric wards. Future studies should focus

on specific diagnostic categories as well as medications used in the treatment of affective and psychotic disorders.

Conflict of Interest

The authors have no conflict of interest to declare.

Ethical statement

Ethics approval of the original study had been obtained from the İstanbul Kanuni Sultan Suleyman Training and Research Hospital Research Ethics Committee before collecting the data.

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