DOI 10.4149/BLL_2024_92

Bratisl Med J 2024; 125 (10):
589–596

CLINICAL STUDY

Investigation of the relationship between anxiety-depression, systemic immune-inflammation index and clinical progression in COVID-19

Begum Aygen GUMUS[1], Ali Emre SEVIK[2], Sevil ALKAN[3]

Canakkale Onsekiz Mart University Hospital, Psychiatry Department, Barbaros Mahallesi Prof. Dr. Sevim BULUC Sokak Terzioglu YerleSkesi, Canakkale, Turkey. **aliemresevik@gmail.com**

ABSTRACT

OBJECTIVE: Given the multisystem nature of COVID-19 and its potential neuro-psychiatric effects along with the recognized role of systemic inflammation in the prognosis of both COVID-19 and psychiatric disorders, it is imperative to assess psychiatric symptoms in COVID-19 patients. This study sought to investigate the value of systemic immune-inflammation index (SII) scores, levels of anxiety and depressive symptoms assessed within the initial 24 hours following COVID-19 diagnosis as potential predictors of the clinical trajectory of COVID-19.

METHODS: This study involved 64 patients admitted to our COVID-19 ward with mild-to-moderate COVID-19 pneumonia, all of whom underwent a psychiatric evaluation within 24 hours of admission. Upon admission, levels of c-reactive protein and inflammatory markers including leukocyte, neutrophil, thrombocyte, and lymphocyte counts were measured to calculate individual SII scores. Psychiatric evaluations were conducted using the State-Trait Anxiety Inventory (STAI), Hamilton Depression Rating Scale (HDRS), and Standardized Mini-Mental Test (SMMT).

RESULTS: The patients with clinical deterioration of COVID-19 exhibited higher STAI-Trait and STAI-State subscale scores measured upon admission compared to those without clinical deterioration. HDRS scores showed no significant correlation with clinical deterioration. STAI-State subscale scores correlated with SII scores and the duration of hospital stay. High baseline STAI scores and SII scores predicted COVID-19 clinical deterioration.

CONCLUSION: Our study demonstrated that the initial SII and STAI scores assessed within the initial 24 hours of hospitalization for COVID-19 significantly predicted the clinical progression of the disease during the hospital stay *(Tab. 5, Ref. 37)*. Text in PDF www.elis.sk

KEY WORDS: COVID-19, systemic inflammatory response index, disease severity, inflammation.

Introduction

The COVID-19 pandemic has increased the prevalence of psychiatric disorders by fusing societal and personal stressors with direct effects of SARS-CoV-2 on the central nervous system. This phenomenon is attributed to various factors, including the virus's direct impact on CNS, the neuropsychiatric consequences of systemic and CNS inflammation, and psychosocial elements like social isolation, illness anxiety, stigma, and functional impairment. Given the complexity of the COVID-19 virus and related research, identifying psychiatric symptoms in COVID-19-infected individuals stands as essential (1). The symptoms of COVID-19 might range from being completely absent to experiencing serious multi-organ failure and respiratory distress. About 50% of patients remain asymptomatic. Typical symptoms include fever, dry cough, difficulty breathing, back discomfort, exhaustion, diarrhea, and a loss of taste or smell. Additional symptoms may include headache, infrequent hemoptysis, conjunctivitis, gastrointestinal problems, or chest pain. Fatalities can result from complications such as pneumonia, organ failure, and cytokine storm. The severity of the disease is determined based on clinical, laboratory, radiographic, hemodynamic, and organ function assessment (2–5). It has been shown that inflammatory markers such as c-reactive protein (CRP), D-dimer, and ferritin correlate with the clinical severity of COVID-19. This condition leads to an increase in neutrophil-lymphocyte ratio (NLR), along with serum levels of various cytokines and chemokines (5, 6, 7) However, it is acknowledged that cytokine dysregulation is also associated with factors linked to psychiatric disorders (8–10). The exact cause of the altered inflammatory response remains uncertain. Extensive

[1]Psychiatry Department, Eyüpoglu Mahallesi, Sahinbey/Gaziantep, Turkey, [2]Canakkale Onsekiz Mart University Hospital, Psychiatry Department, Canakkale, Turkey, and [3]Department of Infectious Diseases and Clinical Microbiology, Canakkale Onsekiz Mart University, Faculty of Medicine, Canakkale, Turkey

Address for correspondence: Ali Emre Sevik, Ass Prof, MD, Canakkale Onsekiz Mart University Hospital, Psychiatry Department, Barbaros Mahallesi Prof. Dr. Sevim BULUC Sokak Terzioglu YerleSkesi A Blok No:2 B Blok No:4 17100 Canakkale, Turkey.
Phone: +905056588140

Acknowledgements: This study originates from the thesis of the first author, with the corresponding author serving as the mentor of this thesis.

research has been conducted on the connection between inflammation, anxiety disorders, and depression. Inflammatory markers like CRP and IL-6 cytokines, NLR, and leukocyte count have all been utilized to investigate how inflammation contributes to the development of anxiety disorders and depression (11, 12). In a thorough meta-analysis exploring the relationship between NLR and psychiatric disorders, NLR was found to be elevated across a wide range of psychiatric conditions. Another longitudinal meta-analysis examining the relationship between inflammatory markers and increased risk for depression found a small but significant link between elevated CRP levels and subsequent depressive symptoms. However, the available information failed to conclusively establish a clear risk factor or causal relationship (11). Another study revealed that individuals experiencing symptoms of depression without undergoing antidepressant therapy exhibited significantly higher NLR levels compared to healthy controls (13). Several studies have reported a correlation between the anxiety levels of individuals with COVID-19 and inflammatory markers (14, 15). The Systemic Immunity-Inflammation Index (SII), calculated as NLR value multiplied by platelet count, serves as a widely used quantitative indicator of the balance between systemic inflammation and immune response. This index evaluates the function of neutrophils, platelets, and lymphocytes, important players in various inflammatory pathways. The unpredictability of the pandemic has significantly raised the prevalence of depression and anxiety rates in society. Anxiety not only affects individuals with psychiatric disorders, it also has broader societal implications, presenting as significant challenges that need to be addressed (16).

Direct effects on the brain along with stress-induced effects are two categories used in classifying COVID-19's impact on the brain and mind. According to the stress-diathesis model, stress-mediated influences may lead to psychiatric disorders, exacerbate pre-existing conditions, or cause symptomatic stress reactions below diagnostic thresholds. The severity and prognosis of internal illnesses may be negatively impacted by anxiety and depressive symptoms, particularly those affecting the immune system. As our understanding of COVID-19 continues to evolve, we become increasingly aware of its prognosis and psychological effects. This study aims to investigate relationships between anxiety, the severity of depression symptoms, and COVID-19 prognosis. The study seeks to identify correlations and possible risk factors for symptoms of anxiety and depression using clinical methods and quantitative immune system assessments.

Methods

This single-center prospective study enrolled patients hospitalized with a diagnosis of COVID-19 between June 14, 2021, and September 14, 2021, at the COVID-19 clinic of University Hospital.

During this period, our center treated and followed up 141 patients diagnosed with COVID-19. Among these patients, 69 had mild-to-moderate pneumonia, 48 had severe pneumonia, 6 had communication-impairing hearing loss, 11 were receiving mental health treatment, 1 had a diagnosis of psychotic disorder, and 3 had an SSMT score below 23. A total of 77 patients were excluded from the study, including 8 who were unable to participate in interviews within the first 24 hours of admission. Subsequently, 64 patients were included in the final analysis.

Inclusion criteria were as follows: adult age over 18 years, mild-to-moderate pneumonia findings, follow-up in the setting of COVID-19 ward, absence of psychiatriCtreatment within the past one month, Standardized Mini-Mental Test (SMMT) score >23, and informed consent to participate in the study. Individuals were excluded from the study if their clinical state required intensive care unit follow-up at the beginning of hospital treatment, or if they had severe comorbid pneumonia or a respiratory system disease requiring continuous oxygen therapy before hospitalization due to COVID-19. Individuals with a known history of chronic psychiatric illness such as bipolar disorder, schizophrenia, or similar chronic psychiatric illnesses, those with current examination findings consistent with dementia or mental retardation, or elated diagnoses were also excluded. Similarly, prospective participants were excluded from the study if they had a hearing or visual impairment potentially preventing them from being interviewed, or if the SMMT score obtained during the psychiatric examination was below 23. After the psychiatric interview, the hospitalization process and clinical course of the patients were followed up through the hospital information system.

Throughout the follow-up period, the clinical progression of disease severity among patients with mild-to-moderate pneumonia was determined in accordance with the COVID-19 Adult Patient Treatment Guidelines (17).

Ethical consideration

The study obtained approval from the Ministry of Healthcare upon submission of an application to the Scientific Research Platform on May 8, 2021. Additionally, an approval was granted by the University Faculty of Medicine Clinical Research Ethics Committee, decision numbered 2021-06.

Data Collection Tools

Sociodemographic and Clinical Data: The first section of the survey form includes demographic variables such as age, gender, education, occupational, marital status, and income status. Additionally, it covers a brief history of current and lifetime psychiatric illnesses, alcohol and substance use, chronic illnesses, and family history of psychiatric illness. Details of succinct history of the COVID-19 disease and method of hospital admission were also collected.

The second part of the survey form captures clinical information, including initial symptoms related to the disease, duration from the onset of symptoms to hospital admission, vital signs, symptoms observed during follow-up, severity of the disease during clinical monitoring, requirement for oxygen therapy, clinical deterioration, intensive care unit admission, need for intubation, duration of hospitalization, and follow-up clinical data.

State-Trait Anxiety Inventory (STAI): STAI, developed by Spielberg et al. in 1970 and later translated into Turkish and validated by Oner and Le Compte (18), consists of 40 items

presented in a Likert format with four response options: "not at all," "somewhat," "a lot," and "totally." The inventory consists of two sets of twenty questions designed to measure anxiety levels. The value of the score directly correlates with the level of anxiety experienced by the individual.

Hamilton Depression Rating Scale (HDRS): HDRS**,** developed by Hamilton in 1960, is a tool used to assess the severity of depression and monitor its fluctuations based on responses to seventeen questions. This scale evaluates depressive symptoms experienced within the precedent fourteen days, assigning a score ranging from 0 to 4 for each item. A threshold score of 7 is regarded as indicative of depression. Akdemir et al evaluated the validity and reliability of the evaluation for Turkey (19).

Standardized Mini-Mental Test (SMMT): SMMT**,** introduced by Folstein et al. for the first time in 1975, is a rapid, practical, and standardized assessment tool designed to measure an individual's overall cognitive capacity. The test consists of eleven questions categorized into five domains: orientation, memory registration, attention, calculation, recall, and language. Scores range from 0 to 30, with higher scores indicating better cognitive function (20).

Statistical analysis

Data analysis was performed using the SPSS 22.0 software package. Descriptive statistics were utilized to present frequency and percentage values for categorical variables along with mean and standard deviation for continuous variables. For variables not following a normal distribution, the non-parametric Mann–Whitney U test was employed to compare continuous variables between two groups after the t-test had been used to evaluate the parametric assumptions. To compare categorical variables between the two groups, the chi-square test was performed. Correlation analyses were conducted to examine relationships between continuous variables. Spearman correlation analysis was used for variables with normal distribution, while Pearson correlation analysis was employed for those with a non-normal distribution.

The correlation coefficient (r) was interpreted as indicating weak (0.00-0.24), moderate (0.25–0.49), strong (0.50–0.74), or extremely strong (0.75–2.00) correlation. LogistiCregression analysis was used for several analyses. The threshold for statistical significance was set at $p<0.05$.

Results

The study included 64 inpatients with COVID-19, with a mean age of 56.5±16.0 years, with 64.1% (n=41) being male. The analysis of demographic characteristics revealed that 78.1% (n=50) of the participants were urban dwellers, 32.8% (n=21) were primary school graduates, and 76.6% (n=49) were married. The majority of them had a medium economic income (48.4%, n=31). Table 1 summarizes the demographic characteristics of the participants in detail.

In our sample, 15.6% (n=10) of the participants reported smoking and 34.4% (n=22) reported drinking alcohol. Additionally, 37.5% (n=24) reported to be exercising regularly (Tab. 2). There were no significant differences between the groups with and without clinical deterioration of COVID-19 in terms of age, gender, defined economic status, smoking, and alcohol use.

The examination of clinical data revealed that the duration of admission to the health center was 2.6±1.9 days, while the duration of hospitalization was 5.6±2.8 days. Additionally, 48.4% of patients (n=31) were newly admitted for follow-up. The most prevalent symptoms among patients were weakness (1.6%; n=1), myalgia (4.7%; n=3), loss of taste and smell (1.6%; n=1), headache (1.6%; n=1), cough (1.6%; n=1), shortness of breath (26.6%; n=17), gastrointestinal (GIS) symptoms (9.4%; n=6), fever (1.6% (n=1), and cough (1.6%; n=1). In line with the COVID-19 Guidelines issued by the Ministry of Healthcare, 56.3% (n=36) of patients with mild-to-moderate pneumonia exhibited a milder illness severity, characterized by oxygen saturation >93% in room air. During the hospital stay, the average SpO2 was 92.92±3.41. Notably, 39.1% of patients (n=25) experienced a progression

Tab. 1. Distribution of sociodemographic data of the patient.

		Mean±SD/n (%)
Age		5.50 ±16.02
Gender	Female	23 (35.9)
	Male	41 (64.1)
Place of residence	City center	50 (78.1)
	Village/Town	14 (21.9)
Education level	Uneducated	4 (6.3)
	Literate	5 (7.8)
	Primary school	21 (32.8)
	Secondary school	6 (9.4)
	High school	9 (14.1)
	College	7 (10.9)
	University	11 (17.2)
	Master's/Doctorate	1 (1.6)
Duration of education (years)		8.53±5.12
Marital status	Single	4 (6.3)
	Married	49 (76.6)
	Widowed	6 (9.4)
	Divorced	5 (7.8)
Working status	Working	28 (43.8)
	Not working	36 (56.3)
Defined economic status	Very good	1 (1.6)
	Good	5 (7.8)
	Moderate	31 (48.4)
	Poor	20 (31.3)
	Very poor	7 (10.9)
Smoking	Yes	10(15.6)
	Quit smoking	19(29.7)
	Never smoked	35(54.7)
Alcohol consumption	Yes	22(34.4)
	Used it for a while, then quit	5(7.8)
	Never used	37 (57.8)
Substance use	Used it for a while, then quit	1 (1.6)
	Never used	63 (98.4)
Regular exercise	Yes	24 (37.5)
	No	40 (62.5)

Mean±SS – mean±standard deviation

Tab. 2. Clinical data of COVID-19 inpatients.

		Mean±SD/n (%)
Time until hospital application (days)		2.61±1.94
Time to hospital admission (days)		5.67±2.88
Added symptom in follow-up	Yes +	31 (48.4)
	No –	33 (51.6)
Added symptom in follow-up	Fever	1 (1.6)
	Cough	1 (1.6)
	Dyspnea	17 (26.6)
	GIS symptoms	6 (9.4)
	Weakness	1 (1.6)
	Myalgia	3 (4.7)
	Inability to taste and smell	1 (1.6)
	Headache	1 (1.6)
Disease severity at admission	Mild-to-moderate pneumonia	64 (100.0)
Admission SpO_2 (%)		92.9±3.4
Increase in oxygen demand	Yes	28 (43.8)
	No	36 (56.3)
Deterioration of COVID-19 clinical manifestation	Yes	25 (39.1)
	No	39 (60.9)
Admission to the intensive care unit during hospital observation	Yes	13 (20.3)
	No	51 (79.7)
Need for intubation	Yes	7 (10.9)
	No	57 (89.1)
Death	Yes	7 (10.9)
	No	57 (89.1)
Follow-up duration in hospital (days)		10.84 ±7.34

indicative of condition deterioration, while 43.8% (n=28) experienced an increase in oxygen requirements (Tab. 2).

Analysis of psychometric assessment tools applied to patients according to cut-off scores

The mean STAI-State anxiety subscale score was 42.6±11.5, while the mean STAI-Trait anxiety subscale score was 37.0±9.1. Additionally, the mean HDRS score was 6.4±5.2, and the mean SMMT score was 28.6±1.7. Notably, the STAI-Trait and STAI-State anxiety subscale scores exceeded 40 points in 29.7% (n=19) and 48.4% (n=31) of patients, respectively, while 12.5% of the patients were assessed with a HDRS score above 7.

The relationship between clinical deterioration of COVID-19 and psychometric scale scores along with other variables

The mean STAI-Trait and STAI-State subscale scores of the patients experiencing clinical deterioration of COVID-19 were 41.1±8.5 (p=0.002) and 46.2±8.5 (p=0.026), respectively. In contrast, those without clinical deterioration had mean subscale scores of 34.5±8.7 and 40.4±11.5, respectively. The differences in these mean subscale scores between the two patient groups were statistically significant (p=0.002 and p=0.026, respectively).

Evaluation of anxiety and depression symptom levels

Upon examining the relationship between psychometric measurements and sociodemographic data, notable differences emerged. Specifically, STAI-Trait subscale scores were found to be significantly higher (p=0.001) in women (42.4±9.2) compared to men (34.1±7.6). Furthermore, individuals with a secondary school education level exhibited higher scores (39±9.2) than those with a high school education level and above (34.6±8.6) (p=0.028). Similarly, participants who rated their economic status as poor or very poor (40.1±9.8) were found to have significantly higher scores than others (34.9±8.1) (p=0.019). Moreover, HDRS scores were higher among participants with a secondary education level or below (7.8±5.6) compared to those with a high school or higher education level (4.6±3.9) (p=0.009). Likewise, those who described their economiCstatus as poor or very poor (8.1±6.2) had significantly higher HDRS scores than others (5.2±4.1) (p=0.044) (Tab. 3).

Correlation analysis of psychometric assessment tools

Significant correlations were found between distinct psychometric measurements. Specifically, there were statistically significant positive correlations across STAI-Trait subscale scores, STAI-State subscale scores (r=0.631; p<0.001) and HDRS scores (r=0.579; p<0.001). Conversely, a statistically significant negative correlation was observed between STAI-Trait subscale scores and SMMT scores (r=–0.268; p=0.032). Similarly, a significantly negative correlation was observed between STAI-State subscale scores and SMMT scores (r=–0.327; p=0.008), while a statistically significant positive correlation was found between HDRS and SMMT scores (r=0.589; p<0.001). Additionally, a statistically

Tab. 3. Relationship between sociodemographic data and anxiety and depression symptom levels.

		STAI-Trait		STAI-State		HDRS	
		Mean	SD	Mean	SD	Mean	SD
Age	>55 years old	38.12	10.23	43.42	12.43	6.66	5.54
	<56 years old	36.00	7.78	41.80	10.59	6.16	5.03
		p=0.35[a]		p=0.57[a]		p=0.70[a]	
Gender	Female	42.43	9.29	45.08	9.95	6.43	4.64
	Male	34.09	7.60	41.26	12.20	6.41	5.64
		p=0.001[b]		p=0.13[b]		p=0.61[b]	
Place of residence	City Center	37.36	9.54	42.50	11.65	6.16	5.34
	Village/Town	36.14	7.63	43.14	11.42	7.35	5.07
		p=0.78[b]		p=0.86[b]		p=0.20[b]	
Status of education	Secondary school or lower	39.00	9.17	44.30	12.28	7.83	5.77
	High School or Higher	34.64	8.59	40.50	10.26	4.60	3.93
		p=0.028[b]		p=0.86[b]		**p=0.009**[b]	
Marital status	Married	37.10	8.79	42.38	11.44	5.95	4.69
	Single	37.06	10.44	43.46	12.12	7.93	6.80
		P=0.66[b]		P=0.75[a]		P=0.54[b]	
Defined economic status	Poor	40.07	9.77	45.03	11.20	8.07	6.21
	Other	34.91	8.06	40.89	11.57	5.21	4.14
		p=0.019[b]		p=0.15[a]		**p=0.044**[b]	

a – t-test, b – Mann–Whitney U test

significant negative correlation was observed between HDRS and SMMT scores (r=0.431; p<0.001).

Furthermore, a statistically significant correlation was detected between SII (Systemic Immune-Inflammation Index, defined as platelet X neutrophil/lymphocyte) and STAI-State subscale scores (r=0.248; p=0.048) (Tab. 4).

Logistic regression analysis for predictors of clinical deterioration in COVID-19

The univariate logistic regression analysis was employed to evaluate the potential of variables (age, gender, hospitalization history, and STAI-Trait subscale score) to predict clinical deterioration in COVID-19. The results for age (p=0.040, OR=1.044, 95%CI 1.002–1.088), gender (p=0.238, OR=2.404, 95%CI 0.559–10.335), history of hospitalization (p=0.253, OR=2.141, 95%CI 0.580–7.910), STAI-Trait subscale score (p=0.013, OR=1.114, 95%CI 1.023–1.212) values are presented in Table 5.

Discussion

Data from psychiatric interviews, evaluation instruments, sociodemographic data, and SII results were collected for this study. Within 24 hours of admission, 64 patients with mild-to-moderate pneumonia were evaluated for anxiety and depressive symptoms at a COVID-19 clinic. The study investigated the relationship between these symptoms and clinical progression of COVID-19. Among the 64 participants admitted to COVID-19 clinic, no discernible differences were found between patients with and without clinical deterioration in terms of age, gender, economic status, smoking, or alcohol use.

Most studies investigating the psychological impact of COVID-19 on anxiety and depressive symptom levels found the effect to be higher in women than in men (21–24). Studies investigating anxiety and depression in patients hospitalized with COVID-19 infection also noted that anxiety and depressive symptom levels were higher in women (14, 25). Similarly, a comprehensive study comparing mental health during and prior to the pandemic reported that women were more affected by the pandemic process compared to men (24). In accordance with aforementioned studies, our results show that the STAI-Trait anxiety scores in hospitalized women were significantly higher than in hospitalized men. Similarly, STAI- State anxiety scores and depressive symptom levels were found to be higher in women, but the difference was not significant.

Tab. 4. Correlation of anxiety and depressive symptoms with inflammatory parameters.

		STAI-Trait Score	STAI- State Score	HDRS
CRP	r	0.073	–0.062	0.123
	p	0.567	0.627	0.334
NLR	r	0.02	0.103	0.055
	p	0.875	0.42	0.668
SII	r	0.094	**0.248**[a]	0.085
	p	0.459	**0.048**[a]	0.506

Tab. 5. Logistic regression analysis for predictors of clinical deterioration in COVID-19.

	Odds ratio (%95 confidence)	p
Age	1.044 (1.002–1.088)	**0.040**
Gender	2.404 (0.559–10.335)	0.238
History of re-hospitalization	2.141 (0.580–7.910)	0.253
STAI-Trait subscale	1.114 (1.023–1.212)	**0.013**

a – Spearman correlation analysis, CRP – c-reactive protein, NLR – neutrophil-to-lymphocyte ratio, SII – systemic immune-inflammation index (platelet neutrophil/lymphocyte counts

In a meta-analysis examining the data of 22 studies, the mean time from the onset of the disease to hospitalization was found to be 5.5 days (26). Similarly, the mean time to hospitalization in our study was found to be 5.67±2.88 days.

In our study, 20.3% (n=13) of the patients followed up in the COVID-19 ward were transferred to the intensive care unit. Several published studies state that 3–32% of hospitalized patients required a transfer to the intensive care unit due to complications that had emerged during their follow-up (28, 29). In previous studies, mortality rates ranged widely from 1.1% to 32.5%, with the severity of COVID-19 pneumonia during hospitalization being the determining factor (30–32). In a meta-analysis, the mortality rate in patients hospitalized with COVID-19 was 17.62% (33). The lower mortality rate in our study (10.9%; n=7) could have stemmed from the fact that individuals with a diagnosis of severe pneumonia had been excluded from the study due to their inability to undergo psychiatric evaluation. We assert that our study constitutes a significant contribution to ongoing research. In our study cohort, the STAI-Trait and STAI-State subscale anxiety scores, as well as HDRS scores exceeded the cut-off value in 29.7% (n=19), 48.4% (n=31) and 12.5% of patients evaluated within the first day of hospitalization, respectively.

These findings align with a meta-analysis encompassing 25 studies, which reported a 47% prevalence of anxiety in patients hospitalized for COVID-19 infection (34). However, unlike our study, those reviewed in this meta-analysis include all clinical severity stages of COVID-19 (35). In studies evaluating patients with a milder course of COVID-19, the prevalence rates of anxiety and depression were found to be 20.8% and 29.7%, respectively We posit that the our observed rates of patients surpassing cut-off scores established by symptom-screening tools are consistent with previously published findings.

The psychological ramifications of COVID-19 stem from an interplay of immunological reactions and stressors such as isolation, fear, and social stigma. Compared to other coronaviruses like SARS and MERS, COVID-19 induces higher levels of the cytokine T-helper-2, potentially exacerbating the symptoms. Elevated cytokines have been implicated in immune and mental health interactions, thereby potentially aggravating illness progression (23). Previous studies have established a correlation between the severity of COVID-19 disease and inflammatory markers such as CRP, D-dimer and ferritin, as well as increases in NLR and serum levels of various cytokines and chemokines (25). Several published studies have implicated systemic cytokine dysregulation as one of the factors associated with psychiatric disorders (8–10). Uncertainty remains regarding whether the systemic inflammatory response contributes to the onset of psychiatric disorders or arises as a consequence of these disorders. Among psychiatric illnesses with presumed immunological etiologies, anxiety disorders and depression have garnered the most research attention. Investigations have extensively scrutinized parameters such as leukocyte count, NLR, inflammatory markers like CRP, and cytokines like IL-6 to elucidate the involvement of inflammation in the pathophysiology of these conditions. A meta-analysis examining the relationship between NLR and psychiatric disorders revealed elevated NLR values found across a spectrum of mental diseases, suggesting a possible connection between inflammation and psychiatric pathology (11, 12). Similarly, in another meta-analysis aiming to examine the relationship between inflammatory markers and increased risk of depression, particularly through longitudinal studies, the findings indicated a modest yet significant correlation between elevated CRP levels and the development of symptoms of depression observed during follow-up. However, the available data did not suffice to establish a direct causal relationship (13).

Several published studies have reported a correlation between the anxiety levels of individuals with COVID-19 and inflammatory markers present in their peripheral blood (14, 15). Furthermore, an examination of additional data revealed that 23% of patients exhibited anxiety or depression symptoms six months after the onset of COVID-19 symptoms and subsequent hospital discharge. Notably, according to the study, the severity of COVID-19 was found to be associated with a higher likelihood of experiencing major anxiety or sadness during the post-recovery period. These psychological symptoms appeared to be linked to the severity of the disease, which in turn correlated with a heightened inflammatory response. However, despite these findings, the study did not provide detailed information on the relationship between inflammatory markers and psychiatric symptoms, particularly at the early symptoms (17). A study investigating post-discharge psychiatric symptoms in COVID-19 patients found no significant correlation between anxiety, depression, CRP, or NLR levels upon admission. However, anxiety and depression were found to be associated with SII scores. Notably, this investigation spanning the initial three days of hospitalization for COVID-19 patients found no significant correlation between CRP or NLR values and feelings of anxiety or depression (16). Consistent with these findings in the current literature, our study revealed no strong correlation of anxiety and depression symptom levels with c-reactive protein and NLR. However, a statistically significant correlation was found between the SII scores and the STAI-State subscale scores. Furthermore, our study identified a statistically significant correlation of the STAI-Trait and State subscale scores with clinical deterioration of patients hospitalized in the COVID-19 clinic during follow-up. In addition to this finding, it has been shown that there is a statistically significant correlation of the STAI-Trait subscale, STAI-State subscale, and HDRS scores assessed within the first 24 hours of hospitalization with the duration of hospitalization of the patients due to COVID-19. SII is recognized as an objective indicator reflecting the balance between systemic inflammation and immune response taking into account neutrophil, platelet and lymphocyte counts jointly involved in various immune and inflammatory response pathways (16). Given the significance of prognostic factors in COVID-19, inquiries into the influence of psychiatric comorbidities on the inflammatory response have been initiated. However, further research in this area is warranted. In our study, within the first 24 hours of admission, all patients underwent rapid assessments for signs of anxiety and sadness. Although this approach may seem limited, we assert that our research provides important insights

into predicting the clinical trajectories of COVID-19 individuals. Additionally, it establishes a quantifiable association between inflammation and the etiopathogenesis of anxiety symptoms, representing a significant advancement in this field. Previous studies examining psychiatric symptoms following COVID-19 infection have reported high rates of anxiety and depression symptom levels after inpatient treatment. However, there is a scarcity of literature correlating the psychiatric symptoms at the onset of the disease with the subsequent clinical course (36,37) Our study contributes to addressing this gap, shedding light on the early manifestation of psychiatriCsymptoms in COVID-19 patients and their potential implications for disease progression.

Limitations

The limitations of our study stem from the small sample size, absence of longitudinal follow-up of psychiatriCsymptoms, and lack of a control group comprising non-hospitalized patients. However, certain strengths merit acknowledgement. Notably, the uniformity in disease severity among patients at the initial assessment, limited to those with mild-to-moderate pneumonia, enhances the internal validity of our findings. Furthermore, the inclusion of patients without pre-existing diagnosis of psychiatriCdisease and drug use minimizes confounding variables, adding to the robustness of our study design.

Conclusion

In this study, we identified several predictors of the COVID-19 clinical course within 24 hours of hospitalization, including age, gender, recurrent hospitalizations for COVID-19, and the STAI-Trait subscale score. While to a lesser extent, SII also exhibited a capacity to predict clinical outcomes. The observed correlation between the STAI-Trait score and SII may shed light on the role of anxiety in COVID-19 prognosis. Early detection of psychiatric signs is essential for preventing post-infection complications. Addressing these symptoms promptly may mitigate anxiety and despair, potentially influencing the course of the infection and averting psychiatric sequalae. Given the impact of COVID-19 on the central nervous system and emergence of neuropsychiatric symptoms, further investigation is required. This study adds to our current understanding of the mental aspects of COVID-19, emphasizing the importance of comprehensive assessment and management of psychiatric symptoms in affected individuals.

References

1. Depression, Anxiety, and Acute Stress Disorder Among Patients Hospitalized With COVID-19: A Prospective Cohort Study. J Acad Consult Psychiatry 2020; (1): 19–21.

2. Hidayat M, Handayani D, Nurwidya F, Andarini SL. Hyperinflammation syndrome in covid-19 disease: Pathogenesis and potential immunomodulatory agents. Turkish J Immunol 2021; 9 (1): 1–11.

3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395 (10223): 497–506.

4. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382 (18): 1708–1720.

5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study | Elsevier Enhanced Reader. Lancet 2020; 395 (10229): 1054–1062.

6. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020; 130 (5): 2620–2629.

7. Gong J, Dong H, Xia QS, Huang Z yi, Wang D kun, Zhao Y et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19: a retrospective study. BMCInfect Dis 2020; 20 (1): 1–7.

8. Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand 2017; 135 (5): 373–387.

9. Renna ME, O'Toole MS, Spaeth PE, Lekander M, Mennin DS. The association between anxiety, traumatic stress, and obsessive–compulsive disorders and chronic inflammation: A systematic review and meta-analysis. Depress Anxiety 2018; 35 (11): 1081–1094.

10. Benedetti F, Aggio V, Pratesi ML, Greco G, Furlan R. Neuroinflammation in Bipolar Depression. Front Psychiatry 2020; 11 (2): 1–12.

11. Demir S, Atli A, Bulut M, İbiloglu AO, GgüneS M, Kaya MC et al. Neutrophil–lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. Neuropsychiatr Dis Treat 2015; 11: 2253–2258.

12. Parsons C, Roberts R, Mills NT. Review: Inflammation and anxiety-based disorders in children and adolescents – a systematic review and meta-analysis. Child Adolesc Ment Health 2021; 26 (2): 143–156.

13. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: A systematiCreview and meta-analysis of longitudinal studies. J Affect Disord 2013; 150 (3): 736–744.

14. Parker C, Shalev D, Hsu I, Shenoy A, Cheung S, Nash S et al. Depression, Anxiety, and Acute Stress Disorder Among Patients Hospitalized With Coronavirus Disease 2019: A Prospective Cohort Study. J Acad Consult Psychiatry 2021; 62 (2): 211–219.

15. Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L et al. Factors related to mental health of inpatients with COVID-19 in Wuhan, China. Brain Behav Immun 2020; 89 (5): 587–593.

16. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun 2020; 89: 594–600.

17. T.C. Saglik Bakanligi Halk Sagligi Genel Müdürlügü. COVID-19 (SARS-CoV-2 Enfeksiyonu) EriSkin Hasta Tedavisi. 2020. p. 6–14. https: // covid19.saglik.gov.tr/TR-66926/eriskin-hasta-tedavisi.html.

18. Büyüköztürk S. AraStirmaya Yönelik Kaygı Ölceginin GeliStirilmesi. Sener Büyüköztürk. Egitim Yönetimi 1997; 3 (4): 453–464.

19. Akdemir A, Örsel DS, Dag İ, TürkCapar MH, İScan N, Özbay H. Hamilton Depresyon Derecelendirme Ölcegi (HDDÖ)'nin gecerliligi-güvenilirligi ve klinikte kullanımı. Vol. 4, Psikiyatri Psikoloji Psikofarmakoloji Dergisi 1996: 251–259.

20. Güngen C, Ertan T, Eker E, YaSar R, Engin F. Standardize Mini Mental Test'in Türk Toplumunda Hafif Demans Tanısında Gecerlik ve Güvenilirligi. Turk Psikiyatri Derg 2002; 13 (4): 273–281.

21. Mazza C, Ricci E, Biondi S, Colasanti M, Ferracuti S, Napoli C et al. A nationwide survey of psychological distress among italian people during the covid-19 pandemic: Immediate psychological responses and associated factors. Int J Environ Res Public Health 2020; 17 (9): 1–14.

22. Özdin S, Bayrak Özdin S. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemiCin Turkish society: The importance of gender. Int J Soc Psychiatry 2020; 66 (5): 504–511.

23. Hacimusalar Y, Civan A, Burak A, Sinan M. Anxiety and hopelessness levels in COVID-19 pandemic: A comparative study of healthcare professionals and other community sample in Turkey. J Psychiatr Res 2020; (1). https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC7372275/.

24. Pierce M, Hope H, Ford T, Hatch S, Hotopf M, John A et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. Lancet Psychiatry 2020; 7 (10): 883–892. http: //dx.doi.org/10.1016/S2215-0366 (20)30308-4.

25. Kahve AC, Kaya H, Okuyucu M, Goka E, Barun S, Hacimusalar Y. Do anxiety and depression levels affect the inflammation response in patients hospitalized for COVID-19. Psychiatry Investig 2021; 18 (6): 505–512.

26. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F et al. Epidemiology of COVID-19: A systematiCreview and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol 2021; 93 (3): 1449–1458.

27. Nanshan Chen, Min Zhou, Xuan Dong et al. Epidemiological and clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive study. Lancet 2020; 395 (10223): 507–513.

28. Tsai PH, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK et al. Clinical manifestation and disease progression in COVID-19 infection. J. Chinese Med. Assoc 2021; 84 (1): 3–8.

29. Diez-Quevedo C, Iglesias-González M, Giralt-López M, Rangil T, Sanagustin D, Moreira M et al. Mental disorders, psychopharmacological treatments, and mortality in 2150 COVID-19 Spanish inpatients. Acta Psychiatr Scand 2021; 143 (6): 526–534.

30. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020; 146 (1): 110–118. https: //doi.org/10.1016/j.jaci 2020.04.006.

31. Poblador-Plou B, Carmona-Pírez J, Ioakeim-Skoufa I, Poncel-Falcó A, Bliek-Bueno K, Cano-Del Pozo M et al. Baseline chronic comorbidity and mortality in laboratory-confirmed COVID-19 cases: Results from the PRECOVID study in Spain. Int J Environ Res Public Health 2020; 17 (14): 1–14.

32. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematiCreview and meta-analysis of 42 studies and 423,117 patients. BMCInfect Dis 2021; 21 (1). https: //doi.org/10.1186/s12879-021-06536-3.

33. Deng J, Zhou F, Hou W, Silver Z, Wong CY, Chang O et al. The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. Ann N Y Acad Sci 2021; 1486 (1): 90–111.

34. Zhang J, Lu H, Zeng H, Zhang S, Du Q, Jiang T et al. The differential psychological distress of populations affected by the COVID-19 pandemic. Brain Behav Immun 2020; 87 (4): 49–50.

35. Liu D, Baumeister RF, Veilleux JC, Chen C, Liu W, Yue Y et al. Risk factors associated with mental illness in hospital discharged patients infected with COVID-19 in Wuhan, China. Psychiatry Res 2020; 292 (7): 113297.

36. Tomasoni D, Bai F, Castoldi R, Barbanotti D, Falcinella C, Mulè G et al. Anxiety and depression symptoms after virological clearance of COVID-19: A cross-sectional study in Milan, Italy. J Med Virol 2021; 93 (2): 1175–1179.

Received August 24, 2023.
Accepted April 14, 2024.