Psychological outcomes of COVID-19 survivors at sixth months after diagnose: the role of kynurenine pathway metabolites in depression, anxiety, and stress

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Abstract

Coronavirus disease 2019 (COVID-19) has resulted in long-term psychiatric symptoms because of the immunologic response to the virus itself as well as fundamental life changes related to the pandemic. This immune response leads to altered tryptophan (TRP)–kynurenine (KYN) pathway (TKP) metabolism, which plays an essential role in the pathophysiology of mental illnesses. We aimed to define TKP changes as a potential underlying mechanism of psychiatric disorders in post-COVID-19 patients. We measured plasma levels of several TKP markers, including KYN, TRP, kynurenic acid (KYNA), 3-hydroxykynurenine (3-HK), and quinolinic acid (QUIN), as well as the TRP/KYN, KYNA/3-HK, and KYNA/QUIN ratios, in 90 post-COVID-19 patients (on the first day of hospitalization) and 59 healthy controls (on the first admission to the Check-Up Center). An online questionnaire that included the Depression, Anxiety and Stress Scale-21 (DASS-21) was used 6 months after the initial assessment in both groups. A total of 32.2% of participants with COVID-19 showed depressive symptoms, 21.1% exhibited anxiety, and 33.3% had signs of stress at follow-up, while 6.6% of healthy controls exhibited depressive and anxiety symptoms and 18.6% had signs of stress. TRP and 3-HK were negative predictors of anxiety and stress, but KYN positively predicted anxiety and stress. Moreover, TRP negatively predicted depression, while KYNA/3-HK was a negative predictor of anxiety. The correlation between depression, anxiety, and stress and TKP activation in COVID-19 could provide prospective biomarkers, especially the reduction in TRP and 3HK levels and the increase in KYN. Our results suggest that the alteration of TKP is not only a potential biomarker of viral infection-related long-term psychiatric disorders but also that the therapy targets future viral infections related to depression and anxiety.

Keywords Anxiety · Depression · COVID-19 · Inflammation · Kynurenine · Tryptophan · Kynurenic acid

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Introduction

The coronavirus disease 2019 (COVID-19) virus that first emerged in Wuhan Province, China, in December 2019 quickly spread all over the world and became a pandemic. Since then, it has caused the death of nearly 5.8 million people worldwide by January 2022 (WHO 2022). There is considerable concern about the burden of psychiatric disorders after the pandemic. Apart from its enormous impact on the psychological state of people by changing everything that people are accustomed to Li et al. (2020), it has been suggested that there may be outcomes due to the direct effect of the virus on the human nervous system as well as its impact on neuroimmunology (Troyer et al. 2020). Past viral pandemics indicated that neuropsychiatric manifestations during viral pandemics are common (Manjunatha et al. 2011) and the COVID-19 pandemic is not an exception.

Considering that the pandemic has been a source of fear of illness, death, obscurity of the future, and major changes in our lives, such as social isolation and lockdowns, it has led to traumatization to some extent for almost everyone (Carvalho et al. 2020). According to the literature, the degree of influence on individuals is related to biopsychological and psychosocial factors, such as a good stress response and positive appraisal of the coronavirus crisis, that are associated with the psychological and biological consequences of the COVID-19 pandemic (Berezina and Rybtsov 2021; Veer et al. 2021). However, short- and long-term immunologic responses to viruses as well as the direct impact of the virus on emerging psychiatric symptoms appear to have received less attention.

The tryptophan–kynurenine (TKP) pathway plays a pivotal role in regulating the immune response. Activated TKP has been found to be linked to a wide variety of clinical conditions, such as inflammatory reactions, infection, cancer, neurodegenerative disorders, and psychiatric disorders (Tanaka et al. 2020, 2021). SARS-CoV-2 infection is also associated with altered tryptophan–kynurenine metabolism, which is increased neurotoxic metabolites such as quinolinic acid (QA) and 3-hydroxykynurenine (3-HK) and decreased neuroprotective metabolites such as kynurenic acid (KA), as an early inflammation marker (Lawler et al. 2021). Furthermore, the metabolites of TKP were shown to indicate the severity of the infection and predict mortality (Mangge et al. 2021; Michaelis et al. 2022). On the other hand, the TKP is an emerging research interest in terms of its involvement in the pathophysiology of mental disorders (Myint 2012; Pu et al. 2020). Existing literature suggests that dysregulation of this pathway may be implicated in a range of psychiatric disorders, including major depressive disorder (Pu et al. 2020), schizophrenia,

(Noyan et al. 2021), and anxiety disorders (Butler et al. 2022). Regarding the association between TKP and psychiatric disorders, the literature shows decreased tryptophan (Ogawa et al. 2014), kynurenine, and kynurenic acid in patients with MDD (Ogyu et al. 2018), and increased plasma kynurenine levels in patients with endogenous anxiety (Orlikov et al. 1994). Moreover, a recent study indicated that reduced kynurenine levels were associated with major depressive disorder as well as better treatment response to escitalopram in this patient group (Erabi et al. 2020).

Although the neuroendocrine-immune changes in the acute phase of SARS-CoV-2 infection have been investigated, research on possible pathways for the long-term (neuro)psychiatric effects of SARS-CoV-2 infection has still suffered obscurity. Thus, in a sample of patients infected with SARS-CoV-2, we evaluated plasma levels of numerous TKP indicators in the blood sample that patients gave shortly after they tested positive in the PCR test. These TKP indicators were kynurenine, kynurenic acid, 3-hydroxykynurenine, quinolinic acid, and tryptophan, as well as the kynurenic acid/quinolinic acid rate, kynurenic acid/3-hydroxykynurenine, and kynurenine/tryptophan ratios. Post-COVID conditions are an umbrella term referring to the health consequences that present 4 or more weeks after infection with SARS-CoV-2 (Greenhalgh et al. 2020). Although the post-acute or long-COVID terms have not yet been well defined, we used the acute-COVID term for the first 3 weeks of SARS-CoV-2 infection and long-term (post-acute) COVID for outcomes after 3 weeks of infection. To examine the long-term psychiatric effects of SARS-CoV-2 infection, we evaluated the patients 6 months later regarding psychiatric symptomatology. We hypothesized that TKP alterations may be a possible causal factor for psychiatric manifestations after infection with SARS-CoV-2. While little is known about TKP's role in psychiatric manifestations, there are no studies investigating the effect of TKP in SARS-CoV-2-infected patients in terms of psychiatric manifestations. We intend to shed light on TKP alterations as a possible underlying mechanism of psychiatric disorders in post-COVID-19 patients and perhaps other future viral infections. Furthermore, our study might contribute to the limited knowledge for treating psychiatric ramifications of SARS-CoV-2 infection by revealing the underlying mechanism. We hypothesize that TKP metabolites differ significantly in SARS-CoV-2-infected patients with psychiatric symptoms from those without psychiatric symptoms and healthy controls.

Methods

Study design and participants

This study was a prospective cohort study. Individuals who presented to Gazi University Medical Faculty Hospital between April and November 2020 were examined. Individuals who have been diagnosed with COVID-19 by fully meeting the World Health Organization COVID-19 criteria (World Health Organization 2022), as well as those who have not been diagnosed with COVID-19 or vaccinated against COVID-19, were included in the study. SARS-CoV-2 RT-PCR positivity in oropharyngeal and nasopharyngeal samples confirmed COVID-19 infection in all patients. Patients were admitted to the hospital if they had a fever, cough, dyspnea, or rapid breathing and met at least one of the following criteria: respiratory rate > 30 breaths per minute; severe respiratory distress; or $SpO_2 \leq 90\%$ on room air (World Health Organization 2022). Healthy controls with no history of psychiatric illness, as well as COVID-19 infection and vaccination, enrolled in the study at Gazi University Hospital's Check-Up Center.

The study's exclusion criteria were being under 18 years of age; having any psychiatric diagnosis and serious medical conditions affecting immunological function, such as respiratory, cardiovascular, endocrine, or neurological diseases or medications; being pregnant; and having a disease that causes communication problems, such as deafness, mental retardation, or dementia.

A total of 606 individuals have been invited to participate in the study since July 2020. However, 115 patients with COVID-19 and 59 uninfected and unvaccinated against COVID-19 healthy controls participated in the study. After 6 months of the first assessment, 25 individuals were excluded from the study, because they refused to agree to the online interview.

The following assessments were performed to determine the risk factors and biomarkers that may lead to the development of depression and anxiety disorders:

A data extraction form was used to collect sociodemographic and clinical data, such as age, sex, healthcare worker, chronic disease history, length of hospitalization, length of stay in the intensive care unit, and baseline kynurenine metabolite levels.

Blood sampling and tryptophan–kynurenine pathway metabolite measurement

Blood samples from the patient group were taken on the first day of hospitalization, while blood samples from the healthy control group were collected on the first admission to the XXX University Hospital's Check-Up Center from 9:00 to 11:00 a.m. Then, 5 ml of blood that was drawn from each person was transferred to a vacuum tube. Finally, after 1 h of waiting at room temperature, blood was centrifuged at 3000×g for 10 min at 4 °C. Serum samples were stored at − 80 °C until analysis. The levels of tryptophan (TRP), kynurenine (KYN), kynurenic acid (KYNA), 3-hydroxykynurenie (3HK), and quinolinic acid (QA) in serum specimens and validated *Jasem Serum/Plasma Tryptophan and Its Kynurenine Pathway Metabolites LC–MS/MS Analysis Kit* were used (Sem Laboratuar Cihazları Pazarlama San. ve Tic. Inc., Istanbul, Turkey). The LC–MS/MS platform used for chromatographic and mass spectral analysis of these TRYP–KYN pathway metabolites consisted of an Agilent HPLC system (Agilent Technologies, Santa Clara, CA, USA) involving a flexible pump (G7104A), column compartment (G7116B) and autosampler (G7129C) coupled to an Agilent Ultivo triple quadrupole LC/MS (6465B, Agilent Technologies, Santa Clara, CA, USA) with an electrospray ionization (ESI) source. The limit of quantitation concentrations of QA, 3HKYN, KYN, KYNA, and TRP were 0.906 ng/mL, 0.696 ng/mL, 2.436 ng/mL, 0.708 ng/mL, and 45.011 ng/mL, respectively.

Clinical assessment

Our study psychiatrists used the Turkish version of the structured clinical interview for DSM-5 (SCID-5) after receiving standard training in its use. The validity in Turkey Reliability has been investigated (Elbïr et al. 2019) (Kappa coefficient: 0.74, the percentage of diagnostic harmony between interviewers: 99%). The interviews were conducted at the beginning of the study during the hospital stay, and patients diagnosed with psychiatric diagnoses were excluded. This interview was only conducted face to face with the patients who agreed to the examination voluntarily 6 months after the first interview.

The following scale was completed in online interviews with patients 6 months after the first interview:

Depression–Anxiety Stress Scale (DASS-21): Lovibond created the Depression–Anxiety Stress Scale (DASS-21) by selecting DASS-42 items to shorten the application time (Lovibond and Lovibond 1995). It is a valid and reliable scale to measure depression, anxiety, and stress levels. Each subscale evaluates negative emotions and consists of seven items. The Likert four-level rating system is used on the scale, with 0 to 3 points reflecting nonconformity (0) to extremely consistency (3). The higher the score, the more negative feelings there are (Lovibond 2014). The following are the recommended cut-off scores for conventional severity labels (normal, mild, moderate, and severe, extremely severe): For depression, scores ranging

from 0 to 4 would be considered normal, 5 to 6 mild, 7 to 10 moderate, 11 to 13 severe and 14 + extremely severe. For anxiety, scores were considered to range from 0 to 3 normal, 4 to 5 mild, 6 to 7 moderate, 8 to 9 severe, and 10 + extremely severe. For stress, scores would be considered to range from 0 to 7 normal, 8 to 9 mild, 10 to 12 moderate, 13 to 16 severe, and 17 + extremely severe moderate stress (Sarıçam 2018). The DASS-21 distinguishes patients (depression average score = 10.83; anxiety average score = 10.39; stress mean score = 11.85) from healthy controls (depression average score = 5.88; anxiety mean points = 5.37; stress mean points = 7.90) ($U = 5310.50$; 4748.50; 5562.50, $p = 0.00$) at a good level in a Turkish society (Sarıçam 2018). As a result, each total was divided into two categories to distinguish patients with psychiatric symptoms from healthy controls in the current study. The first contained the 'normal to moderate' groups, while the second contained the 'severe to extremely severe' groups. The first group was accepted as normal, and the second group of patients was accepted as patients with depression/anxiety/stress. A Turkish validity and reliability study was conducted (Cronbach's α ranges from 0.87 to 0.90, with intercorrelations ranging from 0.82 to 0.93) (Yıldırım et al. 2018). In this study, Cronbach's alpha was used to assess the validity of the questionnaire, and it was found to be 0.952.

Statistical analysis

SPSS software version 22 was used to analyze the data. First, descriptive statistics were applied to summarize the sample's characteristics. Second, outliers were identified visually using box plots, and those lying more than three times the interquartile range (IQR) below the first quartile or above the third quartile were removed. Visual inspection of histograms, as well as skewness and the Shapiro–Wilk statistic, were used to determine data normality. Because variables, except for TRP level, are not normally distributed, they were converted to the log natural for an approximately normal distribution. The independent samples t test and Mann–Whitney U tests were then performed to determine whether there were any significant differences between groups of outpatients and inpatients with COVID-19. Data are provided as the mean ± SD and the median and sum of the ranks where needed. Additionally, Pearson correlation tests were used between quantitative variables (functional scales and mood assessment vs. serum kynurenines). Based on DASS-21 subscale scores, multiple linear regression analysis was performed to determine the components linked with depression, anxiety, and stress. The significance values were set at $p < 0.05$.

Results

The sociodemographic characteristics of the 149 participants are presented in Table 1. Patients with COVID-19 (44.58 ± 15.36) were older than the healthy controls (30.58 ± 7.43) ($p < 0.001$). However, there was no statistically significant difference based on sex, education level, being a health worker, or smoking status between these two groups. A total of 26.17% of the 90 post-COVID-19 patients ($N = 39$, length of hospital stay = 10.72 ± 6.22) were admitted to the hospital with pneumonia caused by COVID-19, and 10% of patients with COVID-19 required intensive care. At the end of the sixth month, 6.6% of post-COVID-19 participants applied to the post-COVID-19 outpatient clinic. According to the SCID-5, 66.6% of those (4.4% of post-COVID-19 participants) were diagnosed with generalized anxiety disorder, and 33.3% of those (2.2% of post-COVID-19 participants) were diagnosed with major depressive disorder.

According to the Mann–Whitney U test results, in terms of DASS-21 total scores ($p < 0.001$), depression level ($p < 0.001$), anxiety level ($p < 0.001$), and stress level ($p < 0.001$), there was a noteworthy difference between the two groups. Additionally, in terms of severe and extremely severe depression ($p < 0.001$), anxiety ($p = 0.018$), and stress ($p = 0.05$), there was also a considerable difference between the groups. A total of 32.2% of participants with COVID-19 showed severe and extremely severe depressive symptoms, 21.1% exhibited severe and extremely severe anxiety and 33.3% showed signs of severe and extremely severe stress at follow-up, while 6.6% participants exhibited severe and extremely severe depressive and anxiety symptoms and 18.6% had signs of severe and extremely severe stress. The mean scores, median, and sum of ranks of the scale and its subscales are summarized in Table 1.

The mean TRP level in post-COVID-19 patients was considerably higher (11.73 ± 3.41 µg/ml) than that in the control group (1.53 ± 2.69 µg/ml) (t (147) = 6.792, $p < 0.001$). The mean KYN level in post-COVID-19 patients was substantially different (6.29 ± 0.58 ng/ml) from that in the control group (6.08 ± 0.24 ng/ml), (t (147) = − 3.037 $p = 0.003$). Additionally, the mean TRP/KYN ratio in post-COVID-19 patients was considerably different (1.87 ± 0.54) from that in the control group (2.52 ± 0.44), (t (147) = 7.928 $p < 0.001$). The mean KYNA level in post-COVID-19 patients was significantly different (2.61 ± 0.80 ng/ml) from that in the control group (2.08 ± 0.37 ng/ml), (t (147) = − 5.376 $p < 0.001$), as was the mean 3HK level in post-COVID-19 patients (2.04 ± 0.97 ng/ml) compared with that in the control group (2.45 ± 0.30 ng/ml), (t (147) = 3.749 $p < 0.001$). Post-COVID-19 patients had a significantly higher mean

Table 1 Demographic characteristics of participants, DASS-21, and kynurenine pathway metabolites

	COVID-19 positive ($n=90$)	Control ($n=59$)	P value	df (X^2) or $U(z)$ or df (t)
Age (years); mean (SD)	44.58 (15.36)	30.58 (7.43)	**< 0.001**	147 (-6.515)[c]
Sex; % female (n)	54.80 (51)	45.20 (42)	0.074	1 (3.203)[a]
Education level; % less than 12 years (n)	62.50 (30)	37.50 (18)	0.718	1 (0.130)[a]
Healthcare-worker; % yes (n)	44.60 (25)	36.60 (34)	0.328	1 (0.955)[a]
Smoking status; % smokers (n)	66.70 (28)	33.30 (14)	0.327	1 (0.959)[a]
Inpatient; % (n)	26.17 (39)	None		
Comorbidity; % (n)	COPD: 3.33 (3)	None		
	HT: 5.6 (5)			
	CAD: 4.4 (4)			
	Asthma: 7.8 (7)			
	DM: 7.8 (7)			
Length of stay; mean (SD)	10.72 (6.22); Min=4, Max=27	None		
Staying intensive care; % (n)	6 (9)	None		
DASS scores; mean, (median; sum of ranks)				
DASS-21 total	34.8 (90.23, 8121)	14.8 (51.76, 3054)	**< 0.001**	1284 (-5.361)[b]
DASS-21 depression	5.83 (89.07, 8016.5)	2.39 (53.53, 3158.5)	**< 0.001**	1388.5 (-5.013)[b]
DASS-21 anxiety	5.08 (88.28, 7945)	2.17 (54.75, 3230)	**< 0.001**	1460 (-4.723)[b]
DASS-21 stress	6.4 (89.43, 8049)	2.83 (52.98, 3126)	**< 0.001**	1356 (-5.125)[b]
Distribution of groups according to DASS-21 subscale severity level; people who have severe-to-very severe symptoms, % (n)				
Depression	Outpatient:48.5 (16)	12.1 (4)	**< 0.001**	1 (13.379)[a]
	Inpatient: 39.4 (13)			
Anxiety	Outpatient:43.5 (10)	17.4 (4)	**0.018**	1 (5.607)[a]
	Inpatient:39.1 (9)			
Stress	Outpatient:46.3 (19)	26.8 (11)	**0.05**	1 (3.855)[a]
	Inpatient:26.8 (11)			
Diagnosis at 6. months	MDD: 2.2 (2)	None		
	GAD: 4.4 (4)			
The level of the TKP metabolites; Mean (SD)				
TRP (microgram/ml)	11.73 (3.41)	15.32 (2.69)	**< 0.001**	147 (6.792)[c]
KYN (ng/ml)	6.29 (0.58)	6.08 (0.24)	**0.003**	147 (−3.037)[c]
TRP/KYN	1.87 (0.54)	2.52 (0.44)	**< 0.001**	147 (7.928)[c]
KYNA (ng/ml)	2.61 (0.80)	2.08 (0.37)	**< 0.001**	147 (−5.376)[c]
3-HK (ng/ml)	2.04 (0.97)	2.45 (0.30)	**< 0.001**	147 (3.749)[c]
QUIN (ng/ml)	4.86 (1.03)	4.10 (0.34)	**< 0.001**	147 (−6.423)[c]
KYNA/3-OHKYN	1.52 (3.35)	0.85 (0.13)	0.13	147 (− 1.523)[c]
KYNA /QUI	0.54 (0.12)	0.51 (0.08)	0.09	147 (−1.705)[c]

COPD chronic obstructive pulmonary disease, *HT* hypertension, *CAD* coronary artery disease, *DM* diabetes mellitus, *DASS-21* The Depression, Anxiety and Stress Scale-21, *TKP* tryptophan kynurenine pathway, *KYN* kynurenine, *TRP* tryptophan, *KYNA* kynurenic acid, *3-HK* 3-hydroxykynurenine, *QUIN* quinolinic acid

[a] df (X^2); Chi-square test

[b] $U(z)$; Mann–Whitney U test

[c] $df(t)$; independent samples t test

QUIN level (4.86 ± 1.03 ng/ml) than the control group (4.10 ± 0.34 ng/ml), (t (147) $= − 6.423$ $p < 0.001$). The mean KYNA/3-HK ratio level in post-COVID-19 patients was not significantly different (1.52 ± 3.35) from that in the control group (0.85 ± 0.13), (t (147) $= − 1.523$ $p = 0.13$), whereas the mean KYNA/QUIN ratio in post-COVID-19 patients was not different (0.54 ± 0.12) from that in the control group (0.51 ± 0.08), (t (147) $= − 1.705$ $p = 0.09$).

Table 1 displays the mean value and standard deviation of TKP metabolites. In addition, the mean values of TKP metabolites in the control and post-COVID-19 groups are illustrated in Fig. 1.

Moreover, Fig. 2 illustrates the difference between the mean TKP metabolite levels according to the severity of depression, anxiety, and stress. The mean TRP level in the low depression level was significantly higher
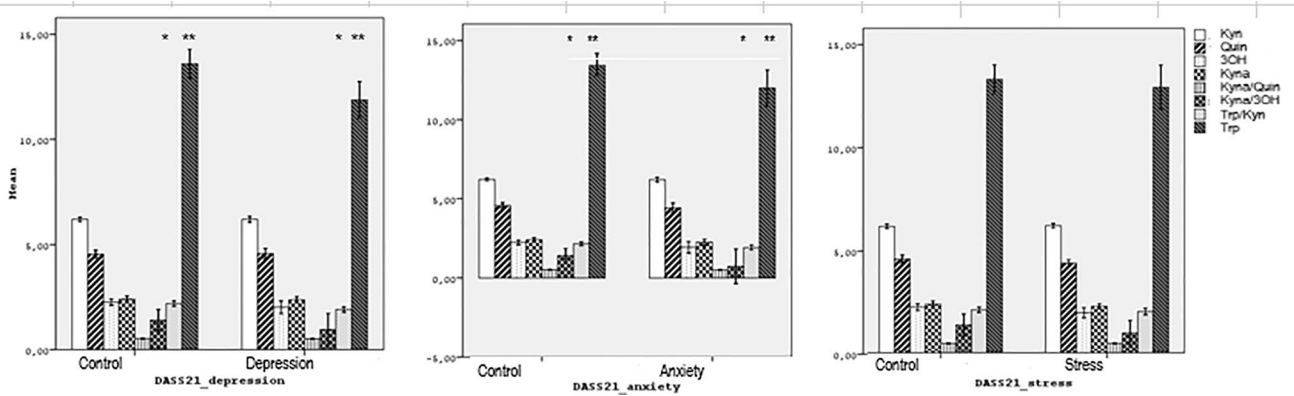
Fig. 1 Comparison of the mean values of TKP metabolites in the control and post-COVID-19 groups
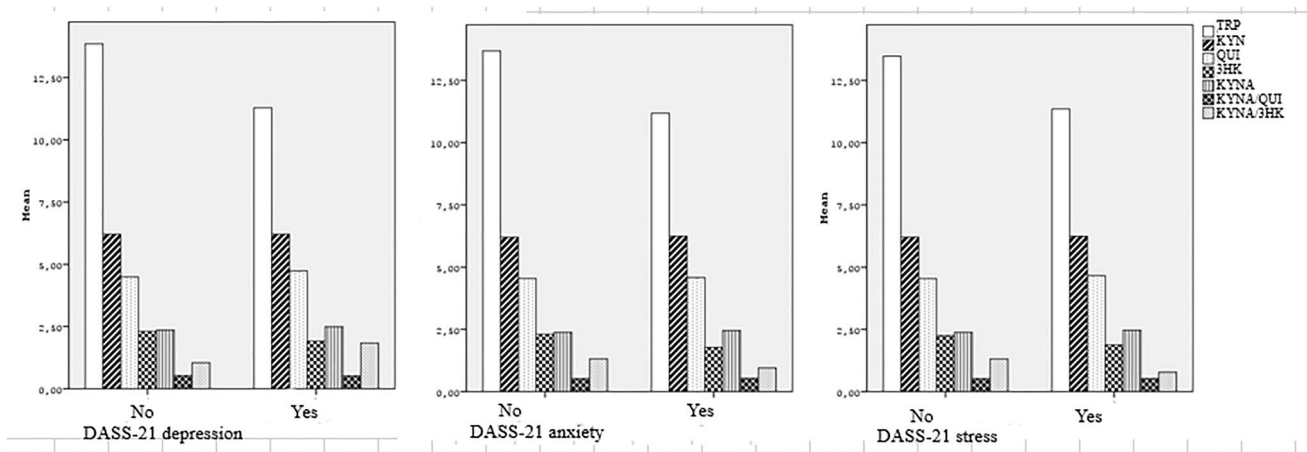

Fig. 2 The TKP metabolite levels according to depression, anxiety, and stress severity

(13.18 ± 3.58 μg/ml) than that in the high depression level (11.29 ± 2.980 μg/ml) (t (147) = 3.860, p < 0.001). In addition, the TRP level was significantly higher both at low anxiety levels (13.65 ± 3.63) compared to high anxiety levels (11.18 ± 2.67), (t (147) = 3.380, p < 0.001) and at low stress levels (13.41 ± 3.68) compared to high stress levels (11.35 ± 2.28), (t (147) = 2.327, p = 0.02). 3HK levels were significantly higher in participants with low depression (p = 0.02) and anxiety levels (p = 0.02). The mean values and standard deviations of the TKP metabolites according to the symptom levels shown in Fig. 2 are provided in Supplementary Material 1.

KYN, KYNA, 3-HK, QUIN, and TRP levels and the KYNA/QUIN, KYNA/3-HK, and KYN/TRP ratios and their correlation with DASS-21 scores were explored. Depression (r = − 0.332, p = 0.01; r = − 0.568, p = 0.01), anxiety (r = − 0.311, p = 0.01; r = − 0.256, p = 0.01), and stress levels (r = − 0.308, p = 0.01; r = − 0.240, p = 0.01) were all negatively related to the TRP level and TRP/KYN ratio,

respectively, whereas depression (r = 0.267, p = 0.01), anxiety (r = 0.205, p = 0.01), and stress levels (r = 0.269, p = 0.01) were positively related to the KYNA/3-HK ratio. In other words, whereas TRP/KYN exhibited a moderate relationship with depression symptom scores, TRP and KYNA/3HK had a low-level relationship with depression, anxiety, and stress symptom scores. Hospitalization length was positively and weakly associated with QUIN (r = 0.459, p = 0.01), KYN (r = 0.370, p = 0.01), and KYNA (r = 0.322, p = 0.01), but negatively associated with TRP level (r = − 0.174, p = 0.01) and TRP/KYN ratio (r = − 0.430, p = 0.01). While the correlation level of hospital stay was very weak with TRP, it was weak with TRP/KYN. Table 2 demonstrates the correlations between kynurenine pathway markers and DASS-21 total score, DASS-21 depression, DASS-21 anxiety, DASS-21 stress, age, and length of hospitalization.

Male sex was a negative predictor for depression (B = − 2.05, CI − 3.79, − 0.31, p = 0.02), anxiety (B = − 1.79, CI − 3.29, − 0.28, p = 0.02), and stress (B = − 2.31, CI

Table 2 Bivariate correlation analysis between DASS-21 subscales and kynurenine pathway metabolites

	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Age													
2 Length of stay	0.679[b]												
3 DASS-21 depression	0.034	0.211[b]											
4 DASS-21 stress	0.023	0.188[a]	0.813[b]										
5 DASS-21 anxiety	0.136	0.244[b]	0.802[b]	0.869[b]									
6 DASS-21 total	0.077	0.241[b]	0.919[b]	0.953[b]	0.936[b]								
7 TRP	−0.174[a]	−0.332[b]	−0.284[b]	−0.308[b]	−0.311[b]	−0.322[b]							
8 KYN	0.370[b]	0.453[b]	0.064	0.107	0.098	0.102	−0.088						
9 TP/KYN	−0.430[b]	−0.568[b]	−0.206[a]	−0.240[b]	−0.256[b]	−0.254[b]	0.597[b]	−0.794[b]					
10 KYNA	0.322[b]	0.325[b]	0.154	0.117	0.088	0.132	−0.097	0.644[b]	−0.558[b]				
11 3-HK	0.014	−0.087	−0.197[a]	−0.245[b]	−0.229[b]	−0.238[b]	0.280[b]	0.284[b]	-0.046	0.264[b]			
12 QUIN	0.459[b]	0.496[b]	0.125	0.123	0.136	0.14	−0.266[b]	0.696[b]	−0.663[b]	0.634[b]	0.115		
13 KYNA/QUI	0.051	0.029	0.071	0.016	−0.039	0.017	0.059	0.291[b]	−0.197[a]	0.738[b]	0.213[b]	0.039	
14 KYNA/3-HK	0.157	0.222[b]	0.267[b]	0.269[b]	0.205[a]	0.273[b]	−0.386[b]	0.192[a]	−0.372[b]	0.424[b]	−0.523[b]	0.285[b]	0.368[b]

DASS-21 The Depression, Anxiety and Stress Scale- 21, *KYN* kynurenine, *TRP* tryptophan, *KYNA* kynurenic acid, *3-HK* 3-hydroxykynurenine, *QUIN* quinolinic acid

[a]Correlation is significant at the 0.05 level (two-tailed)

[b]Correlation is significant at the 0.01 level (two-tailed)

Table 3 The predictors for DASS-21 subscales

DASS-21 depression	DASS-21 anxiety				DASS-21 stress				DASS-21 depression			
	B	SE	95% CI	p	B	SE	95% CI	p	B	SE	95% CI	p
Age	− 0.03	0.04	− 0.10; 0.05	0.53	− 0.01	0.03	− 0.07; 0.06	0.84	− 0.07	0.04	− 0.15; 0.01	**0.09**
Sex	− 2.05	0.88	− 3.79; − 0.31	**0.02**	− 1.79	0.76	− 3.29; − 0.28	**0.02**	− 2.31	0.89	− 4.08; 0.55	**0.01**
Length of stay	0.18	0.10	− 0.01; 0.38	**0.07**	0.10	0.09	− 0.07; 0.27	0.24	0.15	0.10	− 0.05; 0.34	0.15
TRP	− 0.51	0.19	− 0.89; − 0.13	**0.01**	− 0.36	0.17	− 0.69; − 0.04	**0.03**	− 0.37	0.20	− 0.76; 0.01	**0.06**
KYN	1.65	1.20	− 0.73; 4.03	0.17	1.86	1.04	− 0.20; 3.92	**0.08**	2.46	1.22	0.04; 4.87	**0.05**
QUIN	− 1.31	2.84	− 6.93; 4.30	0.64	− 0.75	2.46	− 5.62; 4.11	0.76	− 0.76	2.88	− 6.46; 4.95	0.79
3-HK	− 0.90	0.55	− 2.00; 0.19	0.11	− 1.27	0.48	− 2.22; − 0.32	**0.01**	− 1.58	0.56	− 2.69; 0.47	**0.01**
KYNA	2.05	4.30	− 6.45; 10.54	0.64	0.48	3.72	− 6.88; 7.85	0.90	0.47	4.36	− 8.16; 9.10	0.91
KYNA/QUIN	− 1.69	17.18	− 35.67; 32.28	0.92	0.63	14.88	− 28.81; 30.07	0.97	1.25	17.44	− 33.25; 35.75	0.94
KYNA/3-HK	− 0.13	0.16	− 0.44; 0.18	0.41	− 0.30	0.14	− 0.56; − 0.03	**0.03**	− 0.25	0.16	− 0.57; 0.06	0.12
TRP/KYN	2.15	1.43	− 0.68; 4.98	0.14	0.84	1.24	− 1.61; 3.29	0.50	0.31	1.45	− 2.56; 3.19	0.83

DASS-21 depression; $R^2 = 0.163$, DASS-21 anxiety; $R^2 = 0.185$, DASS-21 stress; $R^2 = 0.195$

CI confidence interval, *SE* = standard error, *DASS-21* The Depression, Anxiety and Stress Scale- 21, *KYN* kynurenine, *TRP* tryptophan, *KYNA* kynurenic acid, *3-HK* 3-hydroxykynurenine, *QUIN* quinolinic acid

− 4.08, 0.55, $p = 0.01$). The TRP level was negatively associated with depression ($B = - 0.51$, CI − 0.89, − 0.13, $p = 0.01$), anxiety ($B = - 0.36$, CI − 0.69, − 0.04, $p = 0.03$), and stress ($B = - 0.37$, CI − 0.76, 0.01, $p = 0.06$), while the KYN level was positively associated with anxiety ($B = 1.86$, CI − 0.20, 3.92, $p = 0.08$) and stress levels ($B = 2.46$, CI 0.04, 4.87, $p = 0.05$). 3HK was a negative predictor of anxiety ($B = - 1.27$, CI − 2.22, -0.32, $p = 0.01$) and stress ($B = - 1.58$, CI − 2.69, 0.47, $p = 0.01$). KYNA/3-HK was negatively related to anxiety ($B = - 0.30$, CI − 0.56, -0.03, $p = 0.03$). Table 3 shows the predictors of depression, anxiety, and stress.

Discussion

This is the first long-term study to explore the relationship between TKP metabolites and depression and anxiety symptoms linked to the COVID-19 pandemic. These results were based on post-COVID-19 outpatients and inpatients and COVID-19-negative, unvaccinated controls. Depression, anxiety, and stress levels were all negatively related to the TRP/KYN ratio and the TRP level, whereas the KYNA/3-HK ratio was positively related. However, when compared to TRP, the relationship between DASS-21 scores and other metabolite levels was modest. TRP and 3HK were negative predictors of anxiety and stress, but KYN was a positive predictor of anxiety and stress. Moreover, TRP was a negative predictor of depression. Finally, we revealed that hospitalization length was positively associated with QUIN, KYN, and KYNA, but negatively associated with TRP levels and the TRP/KYN ratio. Long-term hospitalization was also linked to increased DASS-21 scores.

According to a Chinese study on 1210 Chinese people who completed the DASS 21 questionnaire, 28.8% had anxiety, 8.8% had stress, and 16.5% experienced depression at least moderate levels (Wang et al. 2020). In another study, 23% of surviving participants from COVID-19 reported depression or anxiety symptoms at follow-up in a cohort study conducted in the early period of the pandemic (Huang et al. 2021). While one study did reveal no differences in depression and anxiety scores between healthy controls and patients with COVID-19 (Frontera et al. 2021), our data support that there is a growing concern and that individuals infected with SARS-COV-2 have increased depression, anxiety, and stress symptoms when compared to noninfected individuals based on the current literature (Thye et al. 2022). Furthermore, whereas the levels of anxiety and depression were higher in individuals even if they were not infected with SARS-COV-2 in the first months of the pandemic (Özdin and Bayrak Özdin 2020), our findings suggest that these proportions have declined.

Psychosocial and biological conditions created by the COVID-19 pandemic are thought to interact with preexisting conditions, increasing a person's susceptibility to harm or worsening health outcomes (Cândido and Gonçalves Júnior 2021). Thus, there might be many reasons for psychiatric consequences related to the COVID-19 pandemic. Several studies have found that the COVID-19 pandemic response and associated quarantine periods triggered and exacerbated a slew of personal, social, medical, political, and economic difficulties (Shrestha et al. 2020; Xiang et al. 2021). These changes have had an impact on both clinical and general population mental health (Brasso et al. 2022). While a good stress response and a positive appraisal are the best resistance factors (Rolin et al. 2021), it has been

established that the steps taken to inhibit the spread of the virus impact brain activation as well as social behavior (Candini et al. 2021; Ellena et al. 2020). In summary, the direct effects or indirect effects of the virus in the brain due to inflammation or deprivation of social interaction and individual characteristics may affect each other synergistically and determine the emotional and behavioral responses to the pandemic. However, we focused mainly on the biologic part of the pandemic (Horton 2020), especially on the relationship between SARS-CoV-2 infection and TKP. TKP is induced following immunological activation and plays critical roles in the immune response to SARS-COV-2, such as other viral infections (Atlas et al. 2013; Bipath et al. 2015; Larrea et al. 2007). In the studies, the TRP level and 3HK decreased (Thomas et al. 2020), while KYN (Thomas et al. 2020), KYNA (Shen et al. 2020; Thomas et al. 2020), and QUIN (Shen et al. 2020; Thomas et al. 2020), the KYNA/KYN ratio (Cai et al. 2020) and the ratio of KYN/TRP (Kimhofer et al. 2020) increased in patients with COVID-19 compared to the control group. Consistent with these studies, we revealed that TRP and 3HK levels and the TRP/KYN ratio were lower in post-COVID-19 patients than in the control group, whereas KYN, KYNA, and QUIN levels and the KYNA/QUIN ratio were higher in post-COVID-19 patients than in the control group. However, there was no difference in the KYNA/3HK ratio between the groups. In post-COVID-19 patients, peripheral KYN passes the blood–brain barrier, increases KYNA synthesis in the CNS, and thus blocks glutamate neurotransmission (Miller et al. 1994), and increased QUIN contributes to oxidative stress (Varatharaj et al. 2020) and can lead to cognitive disturbances. The alteration of TKP by increasing the transformation of TRP to KYN has been shown to reduce serotonin levels in post-COVID-19 patients (Thomas et al. 2020). Even though depression and anxiety disorders are reported to be sensitive in post-COVID-19 patients (Mazza et al. 2020), whether the vulnerability of psychiatric symptoms in these patients is associated with decreased serotonin due to increased TRP to KYN conversion remains to be determined (Collier et al. 2021). We believe that the current study is significant in terms of revealing the link between TKP and depression/anxiety/stress.

The literature focuses mainly on the depression–TKP associated with (Marx et al. 2020), while data on the anxiety–TKP interaction are limited (Kim and Jeon 2018). TRP, the primary precursor of TKP, is reduced in depression (Anderson et al. 1990; Cho et al. 2017) and anxiety (Miller et al. 2000), whereas a few studies revealed that there is no difference in TRP levels between controls and patients with depression (Hennings et al. 2013; Sublette et al. 2011). Parallel with the literature, we revealed that the decrease in TRP levels was not only negatively related to depression, anxiety, and stress levels but also a negative predictor of depression

in patients with COVID-19. A study involving social anxiety disorder suggested that there was an increase in KYN and KYN/TRP in those with a social anxiety disorder who had a history of suicidal ideation (Butler et al. 2022) and pharmacologically induced anxiety caused an increase in plasma KYN concentration (Orlikov and Ryzov 1991). Moreover, a meta-analysis revealed that individuals who had an increased KYN/TRP ratio exhibited depressive symptoms. The KYN level in COVID-19 patients was greater than that in the control group, and we found that KYN is a positive predictor of depression and anxiety, which is consistent with the previous studies. KYN, 3-HK, and QUIN are excitatory tryptophan catabolites with anxiogenic activity in anxiety animal models (Lapin 1998; Lapin et al. 1996). Meanwhile, KYNA has been shown to have anxiolytic properties and to be an anti-excitatory tryptophan catabolite (Lapin 1998). Additionally, KYNA, KYNA/QUIN, and the KYNA/3-HK ratio are decreased in depressive patients following comprehensive metanalysis results (Marx et al. 2020), and unlike animal studies related to anxiety, the 3-HK level was found to be nonsignificantly different between depressive patients and the control group (Cho et al. 2017; Meier et al. 2016). Unlike these studies on anxiety and depression, we determined that the 3-HK level was negatively correlated with depression, anxiety, and stress scores, whereas the KYNA/3-HK ratio was positively correlated, and the QUIN level was not. Furthermore, we determined that 3-HK was a negative predictor of stress and anxiety, while KYNA/3-HK was a negative predictor of anxiety. In summary, the levels of TKP metabolites were like those in current studies related to COVID-19, but there were some differences from the studies investigating the relationship between depression/anxiety and TKP.

When earlier findings of TKP in COVID-19 patients and TKP in mental disorders are considered, our findings show that the switch in tryptophan metabolism from the serotonin pathway to TKP in post-COVID-19 patients is also associated with depression, anxiety, and stress symptoms. Furthermore, these findings may contribute to the limited research on anxiety–KNY pathway associations. Additionally, studies that focus on the relationship between TKP and depression/anxiety in unmedicated people with depression or anxiety disorders focused mostly on the plasma or serum blood level of TKP metabolites at the time of diagnosis. As a result, our study varies from similar studies in that it investigates the long-term impact of the immune reaction in the presence of a viral infection affecting the CNS.

There were some limitations and strengths related to our study. We assessed TKP metabolites in peripheral blood rather than cerebrospinal fluid. However, recent research has shown that kynurenine metabolites in cerebrospinal fluid are correlated with plasma kynurenine metabolites (Haroon et al. 2020), and peripheral kynurenine markers may be

associated with a central mechanism (Chiappelli et al. 2016). While we excluded patients taking psychotropic medication or having a psychiatric diagnosis at the beginning of the study and evaluated those who came to the outpatient clinic voluntarily in terms of psychiatric diagnosis, the amount of TKP metabolites might be evaluated not only upon hospital admission but also at the sixth month of diagnosis to see the change in TKP metabolites. Since vaccination or medication against COVID-19 could cause a change in the inflammatory response that affects TKP (Wang et al. 2021), blood samples were not repeated 6 months after admission. Low albumin levels are linked to inflammation (Don and Kaysen 2004). An increase in the free TRP component, combined with increased tissue uptake and quick equilibration of free and albumin bound TRP, results in a decrease in total [TRP] (Nazzari et al. 2020). Under these settings, the [KYN]/ [TRP] ratio might be raised merely by directing plasma-free TRP down the KYN route, with no need for TDO or IDO induction. Future research should examine the free-circulating form of the metabolites. The last important limitation of our study is that various psychosocial problems associated with the COVID-19 pandemic and individual characteristics such as genetic factors (Oxenkrug 2011), gut microbiota (Gheorghe et al. 2019), or inflammatory indicators (Nazzari et al. 2020) that may impact TKP during infection were not investigated. Long-term observational studies with larger samples are required in this field to evaluate all these aspects.

Conclusions

Consistent with previous research, the levels of anxiety and depression in COVID-19 survivors have risen over time during the pandemic. Furthermore, we determined that the metabolites of the kynurenine pathway, specifically KYN, TRP, 3-HK, and the KYN/TRP ratio, have a strong relationship with the symptoms of depression and anxiety that emerge in post-COVID-19 individuals. TRP and 3-HK were found to be negative predictors of anxiety and stress, and KYNA/3-HK was a negative predictor of anxiety. However, KYN positively predicted anxiety and stress. Moreover, TRP was a negative predictor of depression. In addition, we determined that despite a greater rate of anxiety and depression in the online survey, only a small number of patients were referred to the post-COVID-19 outpatient clinic. TRP, 3-HK, KYNA/3-HK, and TRP/KYN can be evaluated as biomarkers to determine depression and anxiety problems reported in COVID-19 patients in the long term. This study may contribute to the limited information on the association between anxiety and TKP. This association, we hope, will be important in the development of medications for COVID-19 treatment, the selection of appropriate drugs for the treatment of

depression and anxiety symptoms that arise in COVID-19 patients, and future pandemic research. However, we are aware that a biologically based approach alone is not sufficient to combat the pandemic. Despite our concentration on the biological side, we believe that the psychological consequences of pandemics such as COVID-19 cannot be understood apart from the social environments under which they spread. As a result, it should be encouraged to investigate the synergistic effects of direct and indirect SARS-CoV-2 damage on mental health in a larger sample size using proper techniques. Based on a greater understanding of these consequences and data from longer follow-up periods, it will be possible to provide effective and targeted therapies to reduce the direct and indirect damage caused by SARS-CoV-2 infection.

Declarations

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