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Loneliness, internalizing symptoms, and inflammatory markers in adolescent COVID-19 survivors

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Abstract

Background: Concerns about the psychiatric sequelae after COVID-19 infection have increased as the pandemic spreads worldwide. The increase in self-isolation during this pandemic period has also revealed the importance of feelings of loneliness. This study aimed to examine the relationship between baseline inflammation levels, internalizing symptoms, and feelings of loneliness in adolescent COVID-19 survivors in the long term.

Methods: A total of 74 adolescents (41 girls, 55.4%, mean age 14.88) and their parents were included in the study. This cross-sectional study assessed internalizing symptoms via Revised Children's Anxiety and Depression Scale (RCADS) and feelings of loneliness using the UCLA-loneliness scale. Baseline inflammatory markers at COVID-19 diagnosis were collected. Logistic regression analysis was used to determine predictors for depression in adolescents.

Results: The most common disorder was Major Depressive Disorder (MDD) (25.7%), and 33.8% of the adolescents were in the clinical range in at least one internalizing domain. Baseline C-Reactive Protein (CRP) levels correlated weakly with MDD scores. Loneliness scores correlated with all internalizing symptoms, strong association with MDD scores. Loneliness, anxiety, and parental anxiety were associated with an increased likelihood of MDD. Baseline CRP positivity did not predict MDD in adolescent COVID-19 survivors.

Conclusions: This study indicates that anxiety, loneliness, and parental anxiety play an important role in adolescents' experience of depressive symptoms after COVID-19 infection. Thus, screening parental psychopathology and loneliness in COVID-19 survivors seems to be preventive for adolescent mental health problems.

KEYWORDS
adolescent, COVID-19, COVID-19 survivors, inflammation, internalizing symptoms, mental health

1 | INTRODUCTION

The novel coronavirus (COVID-19) outbreak has been declared a global pandemic by The World Health Organization (WHO) on 11 March 2020 (Cucinotta & Vanelli, 2020). As the pandemic spreads worldwide, concerns about the psychiatric sequelae after COVID-19 infection have increased (Rogers et al., 2020; Singh et al., 2020). Preliminary results have indicated that COVID-19 infection is associated with insomnia, delirium, depression, anxiety, post-traumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD) symptoms, fatigue, and cognitive dysfunction, notably at the early stages of the infection (Marques de Miranda et al., 2020; Mazza et al., 2020; Rogers et al., 2020; Taquet, Luciano, et al., 2021). In a large retrospective cohort study, anxiety and depression were the most common psychiatric diagnosis in COVID-19 patients (Taquet, Luciano, et al., 2021). Several studies have reported that patients with COVID-19 have high levels of depression and anxiety after COVID-19 infection (Mazza et al., 2020; Nalleballe et al., 2020). In a recent study, the risk of mood and anxiety disorders has continued at 6 months after COVID-19 infection (Taquet, Geddes, et al., 2021). In previous coronavirus outbreaks, several psychiatric symptoms, including internalizing symptoms, post-traumatic stress disorder (PTSD), suicide, and psychosis, were reported in patients with SARS (Severe Acute Respiratory Syndrome) at long-term follow-up (Cheng et al., 2004; Okusaga et al., 2011).

Loneliness refers to subjective and negative experiences of deficits in social relations (De Jong Gierveld et al., 2006). During the COVID-19 pandemic, social distancing and school closures can increase loneliness in children and adolescents whose usual social contacts are restricted by disease prevention measures (Loades et al., 2020). In the early stage of the pandemic, the prevalence of self-reported loneliness showed a significant increase relative to prepandemic levels (Killgore et al., 2020). Moreover, considering the isolation and hospitalization processes due to COVID-19 positivity and the strict restrictions in face-to-face social environments, transient feelings of loneliness may occur. Even these transient feelings of loneliness can have a negative impact on mental health (Luchetti et al., 2020; Martín-María et al., 2020). In a study with adolescents during COVID-19 quarantine, higher feelings of anxiety and loneliness were associated with lower feelings of happiness (Cauberghe et al., 2021). Additionally, loneliness was related to depression and anxiety in a recent web-based public survey study (Palgi et al., 2020).

To date, the relationship between loneliness, internalizing symptoms, and baseline inflammation markers in COVID-19 survivors is an area that has received little attention. Therefore, the primary aim of this study was to examine the prevalence and predictors of internalizing symptoms in an adolescent sample after COVID-19 infection. In addition, we intended to determine the relationships between baseline inflammation levels, loneliness, and internalizing symptoms of adolescents after COVID-19 infection.

Key Messages
- Major depressive disorder (MDD) was the most common internalizing symptom in adolescent COVID-19 survivors in the long term.
- The likelihood of experiencing MDD symptoms was higher when the adolescents' anxiety, loneliness, and parental anxiety were greater.
- Screening loneliness and parental psychopathology seems to be preventive for mental health problems in adolescent COVID-19 survivors.

2 | METHODS

We retrospectively screened 686 patient health records with COVID-19 infection from 1 April to 19 February 2021, in our Pediatric Infectious Diseases Unit. The survey data were collected from 20 February 2021 to 02 March 2021. A significant proportion of patients admitted with acute COVID-19 experience symptoms for at least 2 months (Carfi et al., 2020; Havervall et al., 2021). Thus, our study did not include the patients within the first 2 months of COVID-19 infection ($n = 182$). This study's inclusion criteria were as follows: Being 11 to 17 years old, having parent consent, and assent to participate in the online survey. We reached 128 patients (25.3%) via phone call, and of those participants, 34 (6.7%) patients and their parents refused to participate in the study. Thus, 94 patients agreed to participate in the survey. However, 20 participants (12 girls, eight boys, mean age 15.4 years) who agreed to participate were not included in this study because they did not fully complete the online survey forms. Eventually, a total of 74 adolescents (41 girls, 55.4%; mean age 14.8, age range from 11 to 17) and their parents (55 mothers, 74.3%) who agreed to participate in the study were assessed for psychiatric symptoms. There was no significant difference in age (U(Nresponders $= 74$, Nnon-responders $= 430$) $= 15\,035$, $z = -0.771$, $p = .441$), duration of hospitalization (U(Nresponders $= 74$, Nnon-responders$=430$) $= 15\,306$, $z = -0.525$, $p = .600$), and gender (χ^2(1, $N = 504$) $= 2.10$, $p = .147$) between responders and non-responders. The online survey included a self-reported questionnaire screening child internalizing symptoms along with sociodemographic variables. Additionally, parental depression, anxiety, and stress levels were collected from the parents by online survey. First, information was given verbally on the phone, and then the survey link was sent to those who agreed to participate in the study.

To evaluate internalizing symptoms in adolescents, we used the Turkish version of The Revised Child Anxiety and Depression Scale (RCADS) self-report questionnaire (Gormez et al., 2017). RCADS long version consist of 47 items are rated on a four-point scale (0–3), six subscales; social phobia (9 items), panic disorder (9 items), separation anxiety (7 items), generalized anxiety (6 items), obsessive–compulsive

disorder (6 items), and major depression (10 items). Raw scores are converted to gender- and age-standardized scores (T scores). The clinical cut-offs of six subscales' T scores are as follows: 65–69 (borderline clinical), ≥70 (clinical). Additionally, it consists of three summary scales: Total anxiety subscale (separation anxiety, social phobia, panic disorder, generalized anxiety, obsessive–compulsive disorder), depression subscale, and internalizing subscale (depression and total anxiety subscales). Higher scores indicate greater psychopathology in adolescents. The presence of fatigue symptoms was determined by the question verbally on the phone, "In the last month, have you felt tired for a great part of the day?" We used the UCLA Loneliness Scale (UCLA-LS) to assess adolescents' feelings of loneliness. The UCLA Loneliness Scale (UCLA-LS) was developed to measure individuals' general levels of loneliness (Russell, 1996). The Turkish version of the UCLA-LS has been used in this study, which consists of 20 (10 negatives and 10 positives) statements to which responses are given on a 4-point scale ranging from 1 (never) to 4 (often) (Demir, 1989). UCLA-LS scores range from 20 to 80, with higher scores indicating higher levels of loneliness. Depression Anxiety and Stress Scale (DASS-21) was used to determine the parents' current psychological status. It is a self-report questionnaire that consists of three subscales (Depression, Anxiety, and Stress) including seven items per subscale classify depression, anxiety, and stress according to cut-off scores (>9 points for depression; >7 points for anxiety; > 14 points for stress) (Lovibond & Lovibond, 1995). The reliability and validity of the DASS-21 were confirmed for the Turkish population (Sarıçam, 2018).

The psychiatric assessment was performed 7.12 ± 2.34 months (range from 2 to 11 months) after discharge. Inflammation markers showing the severity of COVID-19 inflammation (Feng et al., 2020) (C-reactive Protein [CRP], neutrophil/lymphocyte ratio [NLR], monocyte/lymphocyte ratio [MLR], and systemic immune-inflammation index [SII] [SII = platelets × neutrophils/lymphocytes]) at the time of COVID-19 diagnosis were determined retrospectively. According to our hospital's laboratory reference values, CRP levels above 0.005 mg/L were accepted as CRP positivity. Regardless of the severity of infection, all patients were hospitalized and isolated in the paediatric infectious diseases unit.

Online informed consent was obtained from parents, and assent was obtained from and adolescents. The institutional review board (ID-No: E2-21-19) approved the study by the principles in the Declaration of Helsinki.

2.1 | Data analyses

We used the Shapiro–Wilk test to analyse whether data were normally distributed for differences between gender groups and responders versus nonresponders. Mann–Whitney U test was used to compare continuous variables between gender groups and responders versus nonresponders. Descriptive statistics were presented as mean ± standard deviation and median (interquartile range). Differences in categorical variables in group comparisons were examined using Pearson's chi-squared and Fisher exact analysis. Reliability of the

RCADS, UCLA-LS, and DASS-21 scales' scores were assessed with Cronbach's α coefficients. Cronbach's α for the RCADS, UCLA-LS, and DASS-21 scales were .91, .87, and .90 in our sample, respectively. Spearman's correlation coefficient was calculated to investigate the association among the clinical variables. For the multivariate analysis, the possible factors identified with univariate analysis (p value < .25) were further entered into the multivariate logistic regression model (Bursac et al., 2008; Peng & So, 2002). The multivariate logistic regression was performed to ascertain the effects of duration of post-COVID-19 infection, CRP positivity, anxiety, loneliness, parental anxiety and parental depression on the likelihood of MDD (Table 5). The logistic regression model was statistically significant ($\chi^2(6) = 54.78$, $p < .001$). The model explained 76.9% (Nagelkerke R^2) of the variance in MDD and correctly classified 90.7% of cases. The data were analysed with SPSS version 23, and all statistical tests were two-tailed with the significance level set at $\alpha = .05$.

3 | RESULTS

Seventy-four adolescents (41 girls, 55.4%; mean age 14.88, age range from 11 to 17 years) and parents (55 mothers, 74.3%) were included in the study. The parents were all literate and at least a primary education graduate. The rate of mothers and fathers having COVID-19 at the same time as their adolescents were 55.4% and 54.1%, respectively. Before the COVID-19 infection, 11 adolescents (14.9%) had any psychiatric history. 17.6% of adolescents had an experience of their relatives' death due to COVID-19. 28.4% of the parents lost their jobs during the COVID-19 pandemic. Fatigue symptoms were determined in 37.8% of all adolescents (n = 28), particularly 48.8% of girl adolescents. Sociodemographic information of the whole sample, and gender differences are presented in Table 1.

A significant proportion of adolescents' self-reported symptoms were in the clinical range in at least one psychopathological domain: 33.8% (n = 25) in the whole sample, 39.4% (n = 13) in boys, and 29.3% (n = 12) in girls. There was no significant difference in the clinical range between boys and girls in at least one psychopathological domain ($\chi^2(1, N = 74) = .83$, $p = .360$). Furthermore, per cents of adolescents in the clinical range of RCADS all subscales were similar between the gender groups (p > .05). The three most common disorders were MDD (25.7%), separation anxiety disorder (24.3%), and panic disorder (24.3%) in adolescents, while anxiety was the most common symptom in parents (29.7%). Per cent of adolescents and parents in the clinical range of psychiatric symptoms and their comparisons of girls versus boys are shown in Table 2.

Measures of baseline inflammation marker levels and psychiatric symptoms scores in COVID-19 survivors are presented in Table 3. There was no significant difference in baseline inflammation marker levels and psychiatric symptoms scores between boys and girls (p > .05). CRP positivity rate was 40.5% in the adolescent sample. Baseline CRP levels had a positive correlation ($r = .258$, $p = .027$) with MDD scores. MDD scores had a strong positive correlation with loneliness ($r = .621$, $p < .001$) and weakly correlated with all parents'

TABLE 1 Sociodemographic and clinical information of the sample (n = 74)

	Total sample (n = 74)		Girls (n = 41)		Boys (n = 33)		Z or χ^2	p
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)		
Age (years)[a]	15 (2)	14.8 (1.8)	15 (3)	14.6 (1.7)	16 (3)	15.21 (1.9)	−1.38	.16
Duration after COVID-19 to psychiatric assessment (months)[a]	7 (4)	7.1 (2.3)	8 (4)	7.3 (2.4)	7 (4)	6.8 (2.1)	−0.86	.38
Duration of hospitalization (days)[a]	6 (4.2)	6.7 (4.1)	6 (5)	6.3 (3.5)	6 (5)	7.2 (4.8)	−0.28	.77
Psychiatric history prior to COVID-19 infection, n (%)[b]	11 (14.9)	-	3 (4.1)	-	8 (10.8)	-	-	.05
Monthly family income (TL)[a]	3000 (2700)	4083.7 (2756.5)	2850 (2500)	3577.6 (2392)	3600 (2929)	4712.5 (3073.3)	−2.14	.03
Presence of fatigue, n (%)[c]	28 (37.8)	-	20 (48.8)	-	8 (24.2)	-	4.6	.03
Duration of sleep (hours/day)[a]	8 (2)	8.3 (1.5)	8 (2)	8.7 (1.3)	8 (2)	7.94 (1.6)	−1.8	.06
Concurrent COVID-19 infection in family, n (%)[c]	51 (68.9)	-	29 (39.2)	-	22 (29.7)	-	0.14	.70
Relatives' death due to COVID-19 infection, n (%)[c]	13 (17.6)	-	6 (8.1)	-	7 (9.5)	-	0.54	.46
Parent reports (mother), n (%)[c]	55 (74.3)	-	31 (41.9)	-	24 (32.4)	-	0.08	.77
Parents' losing job, n (%)[c]	21 (28.4)	-	14 (18.9)	-	7 (9.5)	-	1.50	.22

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a]Mann–Whitney U test.
[b]Fisher exact test.
[c]Pearson chi-square test.

TABLE 2 Per cent of adolescents and parents at clinical psychiatric symptoms levels in the sample (n = 74)

	Total sample (n = 74)	Girls (n = 41)	Boys (n = 33)	χ^2	p
Adolescents' RCADS scores at the clinical range, n (%)					
Major depressive disorder[a]	19 (25.7)	11 (26.8)	8 (24.2)	0.06	.80
Obsessive–compulsive disorder[b]	7 (9.5)	4 (9.8)	3 (9.1)	-	1.0
Social phobia[b]	6 (8.1)	3 (7.3)	3 (9.1)	-	1.0
Separation anxiety disorder[a]	18 (24.3)	10 (24.4)	8 (24.2)	0.000	.98
Panic disorder[a]	18 (24.3)	8 (19.5)	10 (30.3)	1.15	.28
Generalized anxiety disorder[b]	7 (9.5)	2 (4.9)	5 (15.2)	-	.23
Total anxiety score[a]	12 (16.2)	6 (14.6)	6 (18.2)	0.16	.68
Total internalizing score[a]	14 (18.9)	8 (19.5)	6 (18.2)	0.02	.88
Parents' DASS-21 scores at the clinical range, n (%)					
Depression[a]	15 (20.3)	8 (19.5)	7 (21.2)	0.033	.85
Anxiety[a]	22 (29.7)	12 (29.3)	10 (30.3)	0.009	.92
Stress[a]	21 (28.4)	11 (26.8)	10 (30.3)	0.109	.74

Abbreviations: DASS-21, Depression and Anxiety Stress Scale; RCADS, Revised Children's Anxiety and Depression Scale.
[a]Pearson chi-square test.
[b]Fisher exact test.

DASS-21 scores. SAD symptoms had weak positive correlations with baseline CRP levels and all parent DASS-21 scores. There were weak positive correlations between OCD symptoms and parent anxiety, parent stress, and baseline NLR, SII. Loneliness scores correlated with all internalizing symptoms, strong association with major depressive disorder. Duration of post-COVID-19 infection to psychiatric assessment negatively correlated with age, MDD, SAD, GAD, total anxiety scores, and total internalizing scores. Duration of hospitalization did not correlate with all psychopathological scores of the adolescents and the parents (p > .05). The bivariate correlations between the

TABLE 3 Measures of current psychiatric symptoms and baseline inflammation in COVID-19 survivors

	Total sample (n = 74)		Girls (n = 41)		Boys (n = 33)		Z	p
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)		
Adolescents' RCADS scores								
Major depressive disorder	47 (32)	51.25 (16.5)	48 (33)	51.1 (17.3)	46 (27.5)	51.4 (15.8)	−1.16	.87
Obsessive–compulsive disorder	44 (17)	48.2 (12.0)	46 (16)	48.9 (11.1)	43 (18.5)	47.5 (13.1)	−1.01	.30
Social phobia	42 (20.5)	43.8 (13.2)	41 (20)	42.5 (12.8)	44 (21)	45.4 (13.6)	−0.99	.32
Separation anxiety disorder	50 (16.75)	54.6 (12.5)	51 (17.5)	54.9 (12.7)	50 (17)	54.24 (12.4)	−.371	.71
Panic disorder	47.5 (22.25)	51.9 (14.1)	45 (17.0)	49.8 (13.0)	51 (25.5)	54.5 (15.1)	−1.27	.20
Generalized anxiety disorder	45.5 (16)	46.9 (12.0)	42 (18.5)	44.4 (10.8)	49 (13.5)	50.0 (12.7)	−1.79	.07
Total anxiety score	45 (15.5)	48.2 (14.0)	43 (17.5)	46.9 (13.7)	46 (17.5)	49.8 (14.5)	−0.93	.34
Total internalizing score	45.5 (21.25)	48.8 (15.0)	44 (22.5)	47.7 (15.0)	48 (20.5)	50.21 (15.1)	−0.84	.39
Adolescents' UCLA loneliness scores	39.5 (17)	40.1 (11.4)	40 (17.5)	40.5 (10.9)	38 (17)	39.63 (12.0)	−0.23	.81
Parents' DASS-21 scores								
Depression	2 (8)	4.8 (6.71)	2 (7)	4.5 (5.9)	0.00 (8)	5.2 (7.6)	−.017	.98
Anxiety	2 (6.5)	5.02 (6.73)	2 (7)	4.9 (6.4)	2.0 (7)	5.1 (7.1)	−.151	.88
Stress	4 (10)	6.16 (7.12)	4.0 (11)	6.4 (7.7)	4 (10)	5.7 (6.3)	−.177	.85
C-reactive protein (mg/L)	0.00 (0.017)	0.015 (0.031)	0.00 (0.01)	0.01 (0.02)	0.00 (0.01)	0.020 (0.03)	−0.83	.40
Neutrophil/lymphocyte ratio	1.88 (2.68)	2.97 (2.44)	1.66 (2.25)	2.65 (2.32)	2.52 (4)	3.37 (2.55)	−1.37	.16
Monocyte/lymphocyte ratio	0.22 (0.22)	0.28 (0.18)	0.18 (0.21)	0.26 (0.18)	0.27 (0.26)	0.30 (0.18)	−1.26	.20
Systemic immune-inflammation index (SII)	498.05 (710.61)	754.44 (790.99)	390.4 (631.2)	748.4 (904.8)	643.6 (764.7)	761.9 (635.4)	−0.74	.45

Note: Mann–Whitney U test, IQR: Interquartile Range; RCADS: Revised Children's Anxiety and Depression Scale; DASS: Depression and Anxiety Stress Scale; Systemic immune-inflammation index (SII) (SII = platelets × neutrophils/lymphocytes).

current psychiatric symptoms and baseline inflammation markers are presented in Table 4.

The results of the univariate and multivariate logistic regression analysis of factors associated with depression at the clinical level in adolescents are presented in Table 5. In the logistic regression model, loneliness was a risk factor for the possibility of depression in the clinical range in COVID-19 patients (OR = 1.123, 95% CI = [1.009; 1.249]). Furthermore, the likelihood of experiencing depression at the clinical level was higher when the adolescents' anxiety (OR = 1.205, 95% CI = [1.080; 1.345]) and parental anxiety (OR = 1.314, 95% CI = [1.037; 1.665]) were greater.

4 | DISCUSSION

Our study showed that 33.8% of the sample was in the clinical range of at least one psychopathological domain, and MDD was the most common disorder in adolescents after COVID-19 infection in the long term. In the early stages of COVID-19 infection, patients may experience delirium, depression, anxiety, and insomnia (Rogers et al., 2020). Preliminary studies have shown that PTSD, depression, anxiety, obsessive–compulsive symptoms, fatigue, and insomnia were in

COVID-19 survivors after hospital treatment in the long term (Mazza et al., 2020; Rogers et al., 2020; Taquet, Geddes, et al., 2021; Taquet, Luciano, et al., 2021; Townsend et al., 2020). A recent study showed that patients are at increased risk of mood and anxiety disorders 3 months after COVID-19 infection (Taquet, Luciano, et al., 2021). According to previous studies, patients after viral infectious diseases are prone to mood and anxiety disorders (Wheaton et al., 2012; Wu et al., 2005). Approximately 39% of SARS survivors had depressive disorders in the long term after hospital discharge (Lam et al., 2009); 15.6% of the patients had depressive disorders even 30 months after SARS infection (Mak et al., 2009). Our findings align with the recent studies highlighting the risk for mood and anxiety disorders for COVID-19 survivors in the long term.

We found that depressive symptoms were weakly associated with baseline CRP levels in adolescents after COVID-19 infection. In a recent study, COVID-19 survivors featured by depressive symptoms showed higher CRP, higher rate of anxiety than those not having depressive symptoms (Liguori et al., 2021). Neuroinflammation is one of the research topics in the etiopathogenesis of psychiatric disorders, including MDD (Yuan et al., 2019). Some studies suggest that inflammation may have a causal effect on the development of depressive disorders (Bauer & Teixeira, 2019; Kuhlman et al., 2018),

TABLE 4 Spearman correlation analysis between clinical variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.
1. Age	1	-.322**	.084	.284*	.339**	.095	.171	.240*	.368**	.303**	.301**	.288*	-.054	-.093	.094	.123	.074	.096	-.003
2.		1	.283*	-.353**	-.190	-.133	-.287*	-.151	-.230*	-.247*	-.289*	-.171	-.087	-.052	-.099	-.396**	-.134	-.063	-.067
3.			1	-.038	-.049	-.013	-.068	.035	.041	.006	.004	.102	-.019	-.025	.011	-.113	.170	.046	.143
4.				1	.603**	.642**	.709**	.681**	.688**	.819**	.913**	.621**	.324**	.374**	.426**	.258**	.083	.137	.070
5.					1	.489**	.585**	.569**	.616**	.729**	.697**	.350**	.094	.059	.241*	.180	.248*	.203	.232*
6.						1	.605**	.583**	.692**	.849**	.812**	.385**	.289*	.245*	.363**	.165	.155	.116	.144
7.							1	.434**	.656**	.749**	.758**	.427**	.327**	.217	.256*	.346**	.047	.017	.044
8.								1	.645**	.794**	.795**	.487**	.266**	.295**	.446**	.142	.172	.153	.128
9.									1	.880**	.852**	.393**	.312**	.311**	.400**	.158	.141	.162	.131
10.										1	.977**	.506**	.311**	.314**	.468**	.245*	.180	.164	.155
11.											1	.569**	.343**	.356**	.472**	.259**	.153	.169	.129
12.												1	.285*	.224	.325**	.103	.015	.048	.016
13.													1	.685**	.698**	.158	-.204	-.177	-.176
14.														1	.708**	-.046	-.123	-.110	-.043
15.															1	.120	-.077	-.088	-.046
16.																1	.230*	.094	.160
17.																	1	.764**	.932**
18.																		1	.730**
19.																			1

Note: 2. Duration after COVID-19 infection to psychiatric assessment (month); 3. Duration of hospitalization (day); 4. Major depressive disorder; 5. Obsessive–compulsive disorder; 6. Social phobia; 7. Separation anxiety disorder; 8.Panic Disorder; 9. Generalized anxiety disorder; 10. Total anxiety score; 11. Total internalizing score; 12. UCLA loneliness scores; 13. Parents' DASS-21 Depression; 14. Parents' DASS-21 Anxiety; 15. Parents' DASS-21 Stress; 16. C-reactive Protein (mg/L); 17. Neutrophil/lymphocyte ratio; 18. Monocyte/lymphocyte ratio; 19. Systemic immune-inflammation index (SII) (SII = platelets × neutrophils/lymphocytes); DASS-21: Depression and Anxiety Stress Scale. *Systemic immune-inflammation index (SII) (SII = platelets × neutrophils/lymphocytes); DASS-21: Depression and Anxiety Stress Scale. analysis with rho coefficient; *$p < .05$. **$p < .01$; Systemic immune-inflammation index (SII); 18. Systemic immune-inflammation index (SII). Spearman correlation

TABLE 5 Factors associated with the clinical range of depression in adolescent COVID-19 survivors ($n = 74$)

	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Gender (girl)	1.146 (0.399–3.288)	.800	-	
Age (years)	1.148 (0.854–1542)	.361	-	
Duration of hospitalization (days)	1.041 (0.922–1.176)	.517	-	
Duration[a] (months)	0.863 (0.688–1.082)	.201	.754 (0.434–1.308)	.315
UCLA loneliness scores	1.141 (1.068–1.219)	<.001	1.123 (1.009–1.249)	**.033**
RCADS-total anxiety scores	1.193 (1.097–1.298)	<.001	1.205 (1.080–1.345)	**.001**
Parents' depression scores[b]	1.107 (1.024–1.196)	.010	.841 (0.664–1.065)	.152
Parents' anxiety scores[b]	1.103 (1.022–1.192)	.012	1.314 (1.037–1.665)	**.024**
CRP positivity	1.944 (0.677–5.584)	.217	1.212 (0.142–10.315)	.861
Neutrophil/lymphocyte ratio	1.037 (0.841–1.279)	.734	-	
Monocyte/lymphocyte ratio	4.369 (0.308–61.926)	.276	-	
Systemic immune-inflammation index	1.00 (0.99–1.001)	.999	-	

Abbreviations: CRP, C-reactive protein (mg/L); RCADS, Revised Children's Anxiety and Depression Scale. p-values <.05 are shown in bold type.
[a]After COVID-19 infection to psychiatric assessment.
[b]Depression and Anxiety Stress Scale. (DASS-21).

and CRP levels were associated with depressive symptoms (Howren et al., 2009; Valkanova et al., 2013). A recent retrospective cohort study reported that psychiatric symptoms 6 months after COVID-19 infection had a weaker association with the inflammation markers of COVID-19 than neurologic symptoms (Taquet, Geddes, et al., 2021). These results may refer to the psychosocial implications of the COVID-19 diagnosis rather than the severity and direct effects of the infection. In our study, depressive symptoms were weakly correlated with baseline CRP levels in adolescents after COVID-19 infection; however, baseline CRP positivity was not associated with the likelihood of MDD in COVID-19 survivors. Additionally, the duration after COVID-19 infection to psychiatric assessment had no impact on the likelihood of MDD. Our results may suggest that psychosocial factors had a more impact on MDD symptoms than direct effects of coronavirus infection.

Psychiatric sequels after COVID-19 infection can be caused by immune responses to the virus itself (Wu et al., 2020), as well as by psychosocial stressors, including social isolation, stigma, and the psychological impact of a novel severe disease (Kumar et al., 2021). Our findings indicated that loneliness is associated with all internalizing symptoms, particularly strongly associated with MDD, and was a risk factor for depressive symptoms in adolescents. The recent systematic review assessing the impact of loneliness on the mental health of children and adolescents reported that the strongest association was with depression (Loades et al., 2020). Two studies reported that lonely adolescents were more likely to score above clinical cut-offs for depression (Roberts & Chen, 1995; Stickley et al., 2016). During pandemic orders to stay at home, social isolation may be particularly difficult for adolescents, who require peer connections for emotional support and social development (Ellis & Zarbatany, 2017). Although social isolation is not necessarily synonymous with oneliness, preliminary results showed that approximately one third of adolescents had high levels of loneliness in the COVID-19

pandemic (Orgilés et al., 2020). Individuals with high levels of loneliness experience more stress and psychological difficulties in daily life, together with insufficient social support, leading to depression (Teo et al., 2018).

Parents are often the ones who interact the most with adolescents during the COVID-19 pandemic and form the adolescent's social environment. Our study showed that the likelihood of experiencing MDD symptoms was higher when the adolescents' and parents' anxiety was greater. Previous research examining the relationship between parent and child psychopathology indicated that parental anxiety was related to children's depression (Biederman et al., 1991; Burstein et al., 2010). Recent research suggests that parental mental health during COVID-19 affects child mental health (Orgilés et al., 2020; O'Sullivan et al., 2021; Xie et al., 2021). Parents who are anxious express more criticism towards their adolescents, indicating affective states of parents change parenting behaviour (Rueger et al., 2011). Thus, adolescents could be more likely to be exposed to parental anxiety and influenced by parenting due to home quarantine, social restrictions during the COVID-19 pandemic.

Our study had some limitations. First, our findings cannot be generalized to other populations due to a single-centre experience with a small sample. Second, this study is a cross-sectional design that does not allow interpretation for causality. Third, the pandemic period does not allow making the face-to-face evaluation of patients. Thus, an online survey was conducted to evaluate psychopathology. Although internalizing symptoms are the most psychopathology in COVID-19 survivors, psychopathologies other than internalizing symptoms, which may impact the results, could not be evaluated. However, there were data on previous psychiatric diagnoses, which diagnoses of adolescents were not reported in the online survey. Finally, our results may have been affected by other psychosocial factors like accessing peers, parenting features, and family stress during the COVID-19 pandemic not assessed in this study. In future studies, determining the

psychosocial factors affecting the long-term mental health of adolescents with COVID-19 seems to be necessary.

5 | CONCLUSION

This is the first study to investigate the relationships of baseline inflammatory markers, internalizing problems, feelings of loneliness in adolescent COVID-19 survivors. The tendency to experience loneliness in the COVID-19 pandemic may make adolescents particularly vulnerable to feelings of loneliness. Based on our results, loneliness, anxiety, and parental anxiety were associated with an increased likelihood of MDD in adolescents. However, baseline CRP positivity was not predictive of MDD in COVID-19 survivors. Our results highlighted the importance of psychosocial factors in the emergence of adolescent depression. Considering the effects of loneliness in adolescents, the closure of schools, strict protection measures that isolate young people, may need to be reviewed by politicians during the COVID-19 pandemic. Also, in this pandemic period, compulsory interaction with parents increases, screening parental psychopathology would be necessary for preventive adolescent mental health.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions." cd_value_code="text.

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