Original Article

Relationship between sleep quality and the psychological status of patients hospitalised with COVID-19

Tuba Akıncı [a, *], H. Melek Başar [b]

[a] Department of Neurology, Beylikduzu State Hospital, Istanbul, Turkey
[b] Department of Psychiatry, Beylikduzu State Hospital, Istanbul, Turkey

A B S T R A C T

Aim: We explored the sleep quality of patients who required mental health and clinical interventions in our hospital after being diagnosed with COVID-19.
Method: We enrolled 189 patients hospitalised with COVID-19 in April and May of 2020, of whom 78 were female and 111 male. We evaluated sleep quality and related factors in terms of demographic characteristics, the duration of hospitalisation, and Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety-Depression Scale scores.
Results: All participants were divided into two groups according to PSQI score: n = 102 (54%) patients with PSQI scores ≥5 and n = 87 (46%) patients with PSQI scores <5. No significant between-group difference was evident in terms of age, gender, marital status, educational level, or chronic disease history. The duration of hospitalisation (p = 0.002) and the depression rate (p = 0.010) were higher in the group exhibiting poor sleep quality (PSQI score ≥5).
Conclusion: The duration of hospitalisation was longer in patients experiencing poor sleep quality. Therefore, improvement in sleep quality will reduce the length of hospital and intensive care unit stays.

© 2021 Elsevier B.V. All rights reserved.

1. Introduction

In December 2019, pneumonia caused by a novel coronavirus that came from Wuhan, China, developed into a worldwide pandemic [1]. The World Health Organisation (WHO) has termed the virus SARS-CoV-2 and the disease coronavirus disease-19 (COVID-19) [2]. The virus spread rapidly within China and many other countries, and soon became a global health issue [3]. On March 11, 2020, the WHO described COVID-19 as a pandemic [4]. Outbreaks of contagious diseases affect both physical and psychological health. New contagious diseases such as severe acute respiratory syndrome (SARS) increase the incidences of anxiety, depression, and stress [5] as well as compromise sleep [6]. No specific treatment for, or vaccine against, the virus is yet available; timely diagnosis and treatment, and patient isolation, are important [7]. The virus is transmitted via droplets from close contacts [8]. Even if isolated individuals remain physically well, they are often psychologically challenged by the necessary procedures and investigations as well as the unfamiliar caregivers and hospital environment [9,10]. Psychological and sleep status affect immunity [11], with good sleep quality enhancing immunity to viral infections [12]. The mental health and sleep quality of patients isolated because of a possible COVID-19 infection require attention. Most patients infected with SARS-CoV-2 recover without mental illness, as do patients with SARS-CoV or MERS-CoV. A significant proportion of patients with acute SARS-CoV-2 infection become delirious. Clinicians must be aware of the risks of depression, anxiety, fatigue, post-traumatic stress disorder and (rare) long-term neuropsychiatric syndromes [13]. In one study, hospitalised COVID-19 patients experienced significant psychological distress, the extent of which was related to the levels of inflammatory markers. The association between depression symptom severity and C-reactive protein (CRP) level indicates that the virus may trigger inflammation that affects the central nervous system and induces neuropsychiatric symptoms [14].

COVID-19 patients frequently exhibit sleep impairment [15], perhaps because of isolation (the absence of a family member), physical discomfort or a psychological factor (fear, anxiety, helplessness and/or depression) [14]. Poor sleep quality in

* Corresponding author. Department of Neurology, Beylikduzu State Hospital, Pinartepe Mah. Yavuz Sultan Selim Bulv. 253 Sok. No:8, Pınartepe, Büyükçekmece, 34500, Istanbul, Turkey. GSM : +90 531 6966269, Fax: +90 212 8562740.
E-mail addresses: tubaags@yahoo.com (T. Akıncı), hmelekbasar@gmail.com (H. Melek Başar).

COVID-19 patients with lymphopenia is associated with slow recovery and an increased need for intensive care unit (ICU) care [16].

We used the Hospital Anxiety-Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI) (both of which are commonly employed clinically) to measure anxiety, depression, and sleep quality in patients hospitalised with COVID-19. We analysed physical and mental health status, sleep quality and clinical outcomes. We hope that our results will facilitate targeted interventions to treat psychological health and sleep disturbances in patients hospitalised with COVID-19.

2. Materials and methods

The study complied with all relevant tenets of the Declaration of Helsinki and was approved by the Ministry of Health Scientific Research Board (no. 2020-05-05T21_19_07) and the Kanuni Training and Research Hospital Ethics Committee (no. KAEK/ 2020.05.31). Patients were diagnosed and treated in accordance with the guidelines of the Turkish Ministry of Health [17], and only those who agreed to participate were included. All gave written informed consent. All were aged at least 18 years. Patients on medication to treat a sleep disorder or any other psychiatric disorder were excluded. A semi-structured questionnaire was used to collect socio-demographic data (age, gender, educational level and/ or a history of any chronic illness). The PSQI was used to evaluate sleep quality over the previous month and the HADS to review emotional status. The assessment forms were completed within the first three days of hospitalisation. The participants were split into two groups based on their PSQI scores. Patients with PSQI scores <5 were assigned to the good-sleep group and those with scores ≥5 to the poor-sleep group. The results of blood tests performed during hospitalisation (assays of CRP, leukocyte, ferritin and D-dimer levels) and treatment modalities were recorded. All patients were treated in accordance with the Ministry of Health protocol [17]. The duration of hospitalisation was recorded. The discharge criteria were the absence of fever, recovery from symptoms, and significant clinical and radiological improvements evident on at least one day.

3. Assessment criteria

3.1. Socio-demographic information

We recorded information on patient age, gender, marital status, educational level and any history of chronic illness. Laboratory results were obtained from the electronic medical records and information on treatments from patient files.

3.2. Pittsburgh Sleep Quality Index

The PSQI is consistent, reliable and repeatable, and was used to determine sleep quality within the previous month ($\alpha = 0.77$) [18]. The 19 questions evaluate sleep quality and amount as well as the status and severity of sleep disturbances. All evaluations were performed by the same physician via one-on-one interviews. The PSQI explores subjective sleep quality, latency, duration and efficiency; the use of sleep medication; and any deterioration in daily work performance. All answers are scored from 0 to 3. The maximum score is 21; higher scores indicate poorer sleep and higher levels of disturbance. A global score ≥5 indicates significantly poor sleep quality. The diagnostic sensitivity is 89.6%, and the specificity is 86.5% [18,19]. The PSQI was translated into Turkish by Agargun et al. [20].

3.3. Hospital Anxiety-Depression Scale

The HADS was developed by Zigmond and Snaith [21], and the validity and reliability of the Turkish version has been confirmed by Aydemir et al. [22]. There are 14 questions. Seven (odd-numbered) questions measure anxiety and seven depression. The answers are scored on a four-point Likert scale (0–3). The maximum score is 21. The Turkish thresholds are 10 for the anxiety subscale (HAD-A) and seven for the depression subscale (HAD-D) [22]. Those who score higher are considered to be at risk.

3.4. Statistics

We used SPSS ver. 17.0 software. The normal distribution of data for each group of individuals was assessed with histograms and the Kolmogorov–Smirnov test. Descriptive analyses are presented as median and 25th-75th percentil values. Continuous variables are presented as the means ± standard deviations and categorical variables as numbers with percentages. The Mann–Whitney U-test was used to compare between-two groups data, and the Kruskal Wallis Test was used when evaluating more than two groups. Data on continuous variables were subjected to Spearman correlation analysis, and differences between categorical variables were analysed using the Chi-Squared test. Factors affecting hospitalisation period were analysed with the help of linear regression analysis. A p-value <0.05 was taken to indicate statistical significance.

4. Results

A total of 207 patients, of whom 189 answered all questions, hospitalised with COVID-19 in April and May of 2020 were included. The average age was 46.27 ± 13.26 years (range 19—79 years); 78 (41%) were female and 111 (59%) were male; 17.5% (n = 33) were single and the rest were married; 15.5% (n = 29) were university graduates, 19% (n = 35) were high-school graduates, and the others had been educated only to the primary level or lower; 62% (n = 117) had no history of chronic illness. Patients were divided into two groups: those with PSQI scores ≥5 (n = 102; 54%) and those with PSQI scores <5 (n = 87; 46%). No significant between-group difference was evident in terms of age, gender, marital status, educational level or history of chronic illness (p = 0.717, 0.572, 0.220, 0.696, 0.655, respectively). Patients with poor sleep quality were hospitalised for a significantly longer

Table 1
Patient demographic characteristics.

	PSQI <5 N = 87	PSQI ≥5 N = 102	p-value
Age (years)	46.05 ± 14.46	45.91 ± 14.10	0.717[a]
Gender			
Female	34 (39%)	44 (43%)	0.572[b]
Male	53 (61%)	58 (57%)	
Educational level			
University	13 (15%)	16 (15%)	0.696[b]
High school	14 (16%)	21 (21%)	
Primary school and lower	60 (69%)	65 (64%)	
Marital status			
Married	75 (86%)	81 (79%)	0.220[b]
Single	12 (14%)	21 (21%)	
Chronic illness			
Yes	32 (37%)	40 (39%)	0.655[b]
No	55 (63%)	62 (61%)	
Hospitalisation period			
Days (mean ± SD)	6.18 ± 3.78	8.23 ± 5.79	**0.002**[a]

[a] Mann–Whitney *U* Test.
[b] Chi-Squared Test.

period than were those with good sleep quality (p = 0.002) (Table 1). The admission levels of CRP, leukocytes, ferritin and D-dimers did not differ between the groups (p = 0.471, 0.039, 0.184, 0.501, respectively). Seventeen (17%) patients with anxiety levels above the HAD-A threshold suffered from poor sleep (PSQI $\geq$5). Fifty-three (52%) patients with above-HAD-D threshold depression suffered from poor sleep (PSQI $\geq$5). The depression rate amongst those with poor sleep quality was significantly higher than in those with good sleep quality (p = 0.010). No significant between-group difference in anxiety was evident (p = 0.131). The HADS anxiety and depression scores and PSQI data are summarised in Table 2.

5. Discussion

Of 189 patients evaluated in the first three days of hospitalisation, 102 suffered from poor sleep. No demographic feature or blood parameter differed between the two groups. Patients with poor sleep quality were hospitalised for longer than the others and had a higher incidence of depression.

An epidemic/pandemic affects both physical and mental health [23,24]. During the SARS outbreak, stress, anxiety and depression increased and sleep was affected in the general population [5,25]. Both good mental health and sleep enhance immunity. Declines in sleep duration and quality increase the risk of viral infection [12,23], whereas stress compromises sleep quality [26]. Sleep is impaired by stress-mediated activation of the hypothalamic-pituitary-adrenal (HPA) axis; changes to sleep increase such activation, creating a vicious cycle between stress and insomnia [27]. The increase in cortisol secretion after HPA activation supresses proinflammatory and antiviral immune responses. Insomnia is associated with increased levels of norepinephrine, which plays a role in antitumour responses, and reduced levels of natural killer cells [28]. Insomnia triggers abnormal cortisol synthesis and reduces the number and activity of NK cells, compromising immune system function [29,30].

A circadian rhythm facilitates daytime wakefulness and night-time sleep. The principal regulator of this circadian rhythm is bright light, but mealtimes and daytime exercise also play roles [31]. Exposure to bright light during the day increases night-time melatonin levels [32]. Melatonin is a hormone secreted by the pineal gland and exhibits anti-inflammatory, antioxidant and immunomodulatory properties. Night-time melatonin levels are highest during childhood and decrease with age. It has been suggested that elderly individuals may be more sensitive to COVID-19 because melatonin levels have decreased with age [33].

The immune system also follows a rhythm. The peak proliferation of progenitor cells that will differentiate into granulocytes and macrophages and that of cells that will secret melatonin at night are synchronised. A disruption in circadian rhythm increases susceptibility to infection. Chronic stress and sleep deprivation stimulate proinflammatory responses and decrease the levels and activities of protective immune cells [34,35]. After sleep deprivation, levels of receptors for the proinflammatory cytokines interleukin (IL)-1-beta, IL-6 and tumour necrosis factor-alpha increase, whereas those for anti-inflammatory cytokines such as IL-10 fall. Increased proinflammatory gene expression triggers inflammatory diseases, and a decrease in antiviral gene expression causes infectious illnesses [36,37]. Long-term sleep deprivation elicits oxidative stress by decreasing antioxidant enzyme activities [38].

In a study in which 164 healthy individuals were followed-up for five days after exposure to rhinovirus, brief sleep was associated with a risk of infection. Irrespective of all other risk factors, those with sleep durations <5 h were at higher risk [39]. Sleep duration, activity and efficiency were evaluated in a prospective study of 125 adults who received three standard doses of hepatitis B vaccine. Vaccination outcomes were poorer for those who slept for <6 h/night [40]. Too-brief sleep may compromise antibody formation and enhance susceptibility to infectious diseases. In a study evaluating immunological memory in 27 adults, the T helper 1 cell count was higher in those who slept soon after the injection of hepatitis A vaccine [41]. Good sleep quality enhances the immune system. We found that the duration of hospitalisation increased in those with poor sleep quality and most clinical deteriorations occurred in that group. Sleep-related history-taking is always relevant.

The pandemic has imposed significant burdens on mental health. Anxiety, depression and anger have increased, whereas positive emotions and life satisfaction have fallen, with these phenomena associated with sleep disturbances and suicidal tendencies [42]. The most affected groups are women, those with histories of psychiatric disorders, urban inhabitants and those with chronic comorbid illnesses [43]. Anxiety-related symptoms increase during major disease outbreaks, with younger individuals (<35 years of age) and women more at risk [43,44]. However, we found no significant difference in anxiety between the groups with good and poor sleep quality (p = 0.131). This might have been because the mean age exceeded 35 years and the male proportion was high.

Quarantine markedly changes sleep-wake rhythms and (paradoxically) reduces sleep quality despite more time in bed. Such decreases were more prominent in those with high levels of depression, anxiety and stress [45]. Studies in many countries have shown that sleep is negatively affected in urban females who had become depressed and intolerant of uncertainty [46]. In a study on the psychopathology of COVID-19 survivors at the one-month follow-up after hospital discharge, the elevations in post-traumatic stress disorder and depression, anxiety, insomnia, obsessive-compulsive, and psychiatric morbidities, ranged from 10% to 35%. The baseline Systemic Immune Inflammation Index (platelets $\times$ neutrophils/lymphocytes) [47], which reflects peripheral lymphocyte-, neutrophil- and platelet-based immune responses and systemic inflammation, was positively associated with the depression and anxiety scores at follow-up [48].

Although patients diagnosed with or treated for psychiatric illnesses were excluded from our study, our work supports previous findings that significant differences in depression rates could be found between groups with and without poor sleep quality. Worldwide uncertainty about the disease aside, the urban location and quarantine might have impacted our results. It is important to improve the sleep of patients hospitalised with COVID-19; this enhances immune system function and reduces the burden placed on ICUs. It is essential to continuously monitor the psychological consequences of epidemics and engage in mental health interventions.

Our study was a single-centre work with a small sample size. Studies with larger patient groups are required. We used the PSQI

Table 2
HADS and PSQI scores.

	PSQI <5 N = 87	PSQI $\geq$5 N = 102	p-value
HAD-A (1, 3, 5, 7, 9, 11, 13)			0.131[a]
Below threshold (0−10 points)	79 (91%)	85 (83%)	
Above threshold (11−21 points)	8 (9%)	17 (17%)	
HAD-D (2, 4, 6, 8, 10, 12, 14)			**0.010**[a]
Below threshold (0−7 points)	58 (67%)	49 (48%)	
Above threshold (8−21 points)	29 (33%)	53 (52%)	

[a] Chi-Squared Test.

to measure sleep quality, but the answers were not objectively verified. Some causal relationships might thus have been missed. Non-subjective sleep evaluation methods such as polysomnography are required. Additionally, stress can be objectively measured using serum cortisol levels.

Credit author statement

Tuba Akıncı: Conceptualization, Methodology, Software, Data curation, Writing- Original draft, Visualization, Investigation, Supervision, Validation, Writing- Reviewing and Editing. **H. Melek Başar:** Writing - Review & Editing.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.01.034.

References

[1] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.
[2] WHO. Coronavirus disease (COVID-19) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports; 2020.
[3] Bao Y, Sun Y, Meng S, et al. 2019-nCoV epidemic: address mental health care to empower society. Lancet 2020;22:37–8.
[4] WHO. Current novel coronavirus (2019-nCoV) outbreak. 2020. . [Accessed 30 January 2020].
[5] Wu KK, Chan SK, Ma T. Posttraumatic stress, anxiety, and depression in survivors of severe acute respiratory syndrome (SARS). J Trauma Stress 2005;18:39–42.
[6] Shen L, Schie J, Ditchburn G, et al. Positive and negative emotions: differential associations with sleep duration and quality in adolescents. J Youth Adolesc 2018;47:2584–95.
[7] WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance. 2020.
[8] Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle. J Med Virol 2020;92:401–2.
[9] Silverstone P. Prevalence of psychiatric disorders in medical inpatients. J Nerv Ment Dis 1996;184:43–51.
[10] Wilkinson MJB, Barczak R. Psychiatric screening in general practice: comparison of the general health questionnaire and the hospital anxiety depression scale. J Roy Coll Gen Pract 1988;38:311–3.
[11] Irwin M. Effects of sleep and sleep loss on immunity and cytokines. Brain Behav Immun 2002;16:503–12.
[12] Gamaldo CE, Shaikh AK, McArthur JC. The sleep-immunity relationship. Neurol Clin 2012;30:1313–43.
[13] Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiat 2020;7:611–27.
[14] Guo Q, Zheng Y, Shi J, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. Brain Behav Immun 2020;88:17–27.
[15] Liguori C, Pierantozzi M, Spanetta M, et al. Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection. Brain Behav Immun 2020;88:11–6.
[16] Zhang J, Xu D, Xie B, et al. Poor-sleep is associated with slow recovery from lymphopenia and an increased need for ICU care in hospitalized patients with COVID-19: a retrospective cohort study. Brain Behav Immun 2020;88:50–8.
[17] Sağlık Bakanlığı TC. COVID-19 Erişkin Hasta Yönetimi ve Tedavisi Rehberi. 22.03.2020.
[18] Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28:193–213.
[19] Buysse DJ, Reynolds CF, Monk TH, et al. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 1991;14:331–8.
[20] Agargün MY, Kara H, Anlar O. Pittsburgh Uyku Kalitesi İndeksinin geçerliği ve güvenirliği. Türk Psikiyatri Derg 1996;7:107–15.
[21] Zigmond AS, Snaith PR. The hospital anxiety and depression scale. Acta Psyciat Scand 1983;67:361–70.
[22] Aydemir Ö, Güvenir T, Kuey L, et al. Hastane anksiyete ve depresyon ölçeği Türkçe formunun geçerlilik ve güvenilirliği. Türk Psikiyatri Derg 1997;8:280–7.
[23] Xiao H, Zhang Y, Kong D, et al. Social Capital and sleep quality in individuals who self-isolated for 14 days during the coronavirus disease 2019 (COVID-19) outbreak in January 2020 in China. Med Sci Monit 2020;26:921–3.
[24] Xue Z, Lin L, Zhang S, et al. Sleep problems and medical isolation during the SARS-CoV-2 outbreak. Sleep Med 2020;70:112–5.
[25] Altena E, Baglioni C, Espie CA, et al. Dealing with sleep problems during home confinement due to the COVID-19 outbreak: practical recommendations from a task force of the European CBT-I Academy. J Sleep Res 2020:e13052.
[26] Reeth OV, Weibel L, Spiegel K, et al. Interactions between stress and sleep: from basic research to clinical situations. Sleep Med Rev 2000;4:201–19.
[27] Akerstedt T. Psychosocial stress and impaired sleep. Scand J Work Environ Health 2006;32:493–501.
[28] Irwin M, Clark C, Kennedy B, et al. Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. Brain Behav Immun 2003;17:365–72.
[29] Vgontzas AN, Chrousos GP. Sleep, the hypothalamicpituitary- adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinol Metab Clin North Am 2002;31:15–36.
[30] Sephton SE, Sapolsky RM, Kraemer HC, et al. Diurnal cortisol rhythm as a predictor of breast cancer survival. J Natl Cancer Inst 2000;92:994–1000.
[31] Mayda Domaç F. Etiopathogenesis of circadian sleep-wake rhythm disoreders. In: Watson RR, Preedy PR, editors. Neurological Modulation of sleep: mechanisms and function of sleep health. United States: Elsevier; 2020. p. 87–94.
[32] Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wakecycle: sleeparchitecture, circadianregulation, andregu-latory feedback. J Biol Rhythm 2006;21:482–93.
[33] Shneider A, Kudriavtsev A, Vakhrusheva A. Can melatonin reduce the severity of COVID- 19 pandemic? Int Rev Immunol 2020;39:153–62.
[34] Dhabhar FS. Enhancing versus suppressive effects of stres on immune function: implications for immunoprotection and immunpathology. Neuroimmunomodulation 2009;16:300–17.
[35] Akbulut H, içli F, Büyükçelik A, et al. The role of granulocyte-macrophage-colony stimulating factor, cortisol,and melatoninin the regulation of circadian rhythms of peripheral blood cells in healthy volunteers and patients with breast cancer. J Pineal Res 1999;26:1–8.
[36] Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. Ann NY Acad Sci 2010;1193:48–59.
[37] Mackiewicz M, Sollars PJ, Ogilvie MD, et al. Modulation of IL-1beta gene expression in the rat CNS during sleep deprivation. Neuroreport 1996;7:529–33.
[38] Teixeira KRC, Santos CPD, Medeiros LAD, et al. Night workers have lower levels of antioxidant defenses and higher levels of oxidative stres damage when compared to day workers. Sci Rep 2019;9:1–11.
[39] Prather AA, Janicki-Deverts D, Hall MH, et al. Behaviorally assessed sleep and susceptibility to the common cold. Sleep 2015;38:1353–9.
[40] Prather AA, Hall M, Fury JM, et al. Sleep and · antibody response to hepatitis B vaccination. Sleep 2012;35:1063–9.
[41] Langet T, Dimitrov S, Bollinger T, et al. Sleep after vaccination boosts immunological memory. J Immunol 2011;187:283–90.
[42] Sher L. COVID-19, anxiety, sleep disturbances and suicide. Sleep Med 2020;70:124.
[43] Özdin S, Bayrak Özdin Ş. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: the importance of gender. Int J Soc Psychiatr 2020;66:504–11.
[44] Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatr Res 2020;288:112954.
[45] Cellini N, Canale N, Mioni G, et al. Changes in sleep pattern, sense of time and digital media use during COVID-19 lockdown in Italy. J Sleep Res 2020:e13074.
[46] Voitsidis P, Gliatas I, Bairachtari V, et al. Insomnia during the COVID-19 pandemic in a Greek population. Psychiatr Res 2020:e113076.
[47] Feng X, Li S, Sun Q, et al. Immune-inflammatory parameters in COVID-19 cases: a systematic review and meta-analysis. Front Med (Lausanne) 2020;7:301.
[48] Mazzaa MG, Lorenzo RD, Conteb C, et al. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav Immun 2020;89:594–600.