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Disease Activity is Associated with Depression and Anxiety in Cushing's Syndrome During COVID-19 Pandemic

COVID-19 Pandemisi Sırasında Cushing's Sendromunda Depresyon ve Anksiyetenin Hastalık Aktivitesi ile İlişkisi

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Abstract

Objective: To assess the depression and anxiety and their relationship with disease activity in patients with Cushing's syndrome (CS) in the coronavirus disease-2019 (COVID-19) pandemic. **Material and Methods:** This cross-sectional study included 54 patients with CS (48 females, 6 males). Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI)-State, STAI-Trait were used to evaluate scores and severity of depression, the current state of anxiety, and general anxiety, respectively. Patients with active CS (n=10) were recorded as group 1, those who were still receiving glucocorticoid replacement therapy after surgery (n=14) as group 2, and those in remission (n=30) as group 3. The groups were compared in terms of parameters that could affect anxiety and depression scores. Correlation analyses were also performed. **Results:** BDI-II scores were higher in group 1 than group 3 (p=0.002), and STAI-State scores were higher in group 1 than group 2 (p=0.03) while STAI-Trait scores and the other parameters were similar between the groups. Moderate and severe depression were detected in 60% of group 1, 25% of group 2, and 16% of group 3 patients. High state anxiety was seen in 70% of patients in group 1, 50% of group 2, and 57% of group 3 patients. Positive correlations between BDI-II scores and disease activity (r=0.438, p=0.001) and STAI-State scores and disease activity (r=0.297, p=0.029) were observed. **Conclusion:** Increased depression and state anxiety during the pandemic in patients with active CS suggests that psychiatric disorders may increase in those with a higher risk of severe COVID-19 disease.

Keywords: Cushing's syndrome; mental disorders; depression; anxiety; COVID-19 pandemic

Özet

Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] pandemisinde, Cushing sendromlu (CS) hastalarda depresyon ve anksiyete durumunu ve bunların hastalık aktivitesiyle ilişkisini değerlendirmek. **Gereç ve Yöntemler:** Bu kesitsel çalışma, 54 (48 kadın, 6 erkek) CS'li hastayı içermektedir. Beck Depresyon Envanteri-II (BDI-II), Durumluk Anksiyete Ölçeği [State-Trait Anxiety Inventory (STAI)]-State, Sürekli Anksiyete Ölçeği State-Trait (STAI) testleri; sırasıyla depresyon ciddiyeti, mevcut anksiyete durumu ve genel anksiyeteyi değerlendirmek için kullanılmıştır. Aktif CS'li hastalar (n=10) grup 1, operasyon sonrası hâlen glukokortikoid replasman tedavisi alanlar (n=14) grup 2 ve remisyonda olanlar (n=30) grup 3 olarak kaydedildi. Gruplar, anksiyete ve depresyon puanlarını etkileyebilecek parametreler açısından karşılaştırıldı. Aynı zamanda korelasyon analizleri de yapıldı. **Bulgular:** BDI-II skorları grup 1'de grup 3'e göre daha yüksek (p=0,002) ve STAI-State skorları grup 1'de grup 2'ye göre daha yüksek (p=0,03) iken, STAI-Trait skorları ve diğer parametreler gruplar arasında benzer saptandı. Grup 1'deki hastaların %60'ında, grup 2'de %25'inde ve grup 3'te %16'sında orta ve şiddetli depresyon saptandı. Grup 1'de hastaların %70'inde, grup 2'de %50 ve grup 3'te %57'sinde yüksek durumluk anksiyete saptandı. BDI-II skorları ile hastalık aktivitesi (r=0,438, p=0,001) ve STAI-State skorları ile hastalık aktivitesi (r=0,297, p=0,029) arasında pozitif korelasyon saptandı. **Sonuç:** Aktif CS'li hastalarda pandemi sırasında artan depresyon ve durumluk anksiyetesi, şiddetli COVID-19 hastalık riski yüksek olanlarda psikiyatrik bozuklukların artabileceğini düşündürmektedir.

Anahtar kelimeler: Cushing sendromu; mental hastalıklar; depresyon; anksiyete; COVID-19 pandemisi

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Introduction

Coronavirus disease-2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2, which was first evidenced in China and spread rapidly to the entire world (1). Disease-related mortality rates increase with additional risk factors such as advanced age, obesity, diabetes mellitus (DM), and hypertension (HT) (2-4). In addition to increased mortality, it may cause respiratory, neurological, and cardiac complications (5-8). Besides this, it has been reported that chronic stress, social isolation, and economic difficulties during the pandemic have also caused many psychiatric disorders, especially depression and anxiety (9).

Cushing's syndrome (CS), a rare endocrinologic disorder with increased morbidity and mortality, is caused by glucocorticoid excess (10). Patients have an increased risk for infections and complications, including metabolic syndrome, visceral obesity, glucose metabolism disorders, HT, and musculoskeletal disorders caused by hypercortisolemia (11,12). Additionally, CS may cause neuropsychiatric disorders. Although depression is the most common accompanying psychiatric disorder, anxiety and bipolar disorders can also be seen (13). Psychiatric disorders have been associated with female gender, advanced age, and severely active disease (14,15). However, it has been reported that psychiatric disorders may persist even in remission (16-18).

Although it has not been a long time since the beginning of the COVID-19 pandemic, its effects on mental health have been evaluated in different populations, especially pregnant women and healthcare workers most affected by the pandemic (9,19-22). On the other hand, studies conducted in patients with DM, HT, malignancy, and cardiovascular disease associated with severe COVID-19 disease are relatively few (22,23). No study evaluating the psychiatric effects was assessed during the pandemic period in patients with active CS who are susceptible to psychiatric disorders. Active CS may be at risk for COVID-19 due to the immunosuppression caused by hypercortisolemia. Therefore, this study aimed to demonstrate depression and anxiety in patients with CS during the pandemic and its relationship with disease activity.

Material and Methods

The study was designed as a cross-sectional one involving patients with CS. In all, 54 patients diagnosed with pituitary CS (n=27), adrenal CS (n=26), and ectopic ACTH syndrome (n=1) in the clinic the last three years who were still undergoing follow-ups were included in this study. Patients whose final CS diagnosis was yet to be established and could not answer questions on psychiatric assessment tests were excluded.

The first COVID-19 case was reported on 11 March 2020 in Turkey, and then strict precautionary measures were applied in the country. Later, with a decreasing number of cases, the normalization process started in June 2020. Anxiety and depression status were evaluated in CS patients followed up in the clinic, who were admitted for four months from the normalization date. The patients and the people they were in contact with were also questioned about having COVID-19 disease.

Beck Depression Inventory-II (BDI-II) and State-Trait Anxiety Inventory (STAI) tests were performed under the supervision of an experienced psychiatrist (KO). This test score ranges between 0-63, consisting of 21 items ranging from 0 to 3 (24). Scores can be interpreted as minimal depression (0-12), mild depression (13-18), moderate depression (19-28), and severe depression (29-63) (25).

STAI is also a self-reported questionnaire with two subscales having 20 items for assessing trait anxiety and 20 items for state anxiety. While the STAI-State scale evaluates the current state of anxiety, the STAI-Trait scale evaluates the general state of anxiety and personal characteristics. Total scores in both scales range from 0 to 80 (26-28). The patients were categorized according to the severity of anxiety STAI-State and STAI-Trait scores. Scores ≥40 were considered high anxiety, and scores <40 were regarded as low anxiety (29).

Ten patients with active CS in the study time were classified as group 1. Fourteen patients whose hypothalamic-pituitary-adrenal (HPA) axis was not improved after surgical treatment and were still receiving glucocorticoid replacement therapy as group 2, and 30 patients in remission as group 3. Current age, age at diagnosis, gender, the origin of CS,

marital status, educational status, smoking, alcohol use, psychiatric drug use, body mass index (BMI), comorbidities (obesity, DM, HT, osteoporosis, hyperlipidemia) were recorded, and the groups were compared in terms of these parameters. Total BDI-II and STAI scores and frequencies of moderate-severe depression and high anxiety were also compared. Correlation analyzes were performed between BDI-II score, STAI-State, STAI-Trait scores and age, age at diagnosis, frequency of female patients, the origin of CS, marital status, educational status, frequency of obesity, DM, HT, and disease activity.

The study was approved by the Clinical Ethics Committee, and written informed consent was obtained from all patients. This study was performed following the Helsinki Declaration. Statistical analyses were performed using SPSS version 22.0. Categorical variables were defined as frequency and percentage rate, and numerical variables were determined as mean±standard deviation (SD). The Kolmogorov-Smirnov test assessed the normality of the distribution of the quantitative variables. A one-way ANOVA test was performed for normally distributed numeric variables in an independent group comparison, and the Kruskal-Wallis test was performed for non-normally distributed data. Categorical variables were compared using the Chi-square test. Spearman's correlation analysis was used for correlation analysis. Statistically significant results were defined with a p value of <0.05.Our study was approved by Bakırköy Dr. Sadi Konuk Training and Research Hospital ethics committee unit at 22.06.2020 with the protocol number 2020/271.The name of our study was "the progress of the patients with thyroid, bone and metabolism, acromegaly, prolactinoma and cushing syndrome during the pandemic"

Results

In this study, 48 of 54 patients were females. The mean present age was 48.4±11.9 (22-75) years. History for COVID-19 disease and any contact revealed that none of them had COVID-19, and only one patient had a history of contact.

The current age and age at diagnosis were similar in the groups. Groups were similar in terms of gender, the origin of CS, marital status, smoking, alcohol use, psychiatric drug use, BMI, and the frequency of comorbidities such as DM, HT, osteoporosis, and hyperlipidemia. The educational level in group 3 was statistically higher than group 1 (p=0.01). All comparisons of the groups have been given in Table 1.

BDI-II scores were higher in group 1 than in group 3 (p=0.002), STAI-State scores were higher in group 1 than group 2 (p=0.03), while the STAI-Trait scores were similar between the groups. According to BDI-II scores, moderate to severe depression was detected in 60% of group 1, 25% of group 2, and 16% of group 3 patients. The moderate to severe depression rate was significantly higher in group 1 than in group 3 (p=0.014). According to STAI-State scores, increased anxiety was detected in 70% of group 1, 50% of group 2, and 57% of group 3 patients. There was no significant difference between the groups in terms of high state anxiety. According to STAI-Trait scores, increased anxiety was detected in 90% of group 1, 93% of group 2, and 83% of group 3 patients. There was no significant difference between the groups in terms of high trait anxiety. Neuropsychiatry testing of the patients with CS between the groups has been depicted in Table 2.

In correlations analysis, positive correlations of BDI-II with female gender and disease activity (r=0.380, p=0.005; r=0.438, p=0.001, respectively) were found. A positive correlation was also detected between disease activity and STAI-State (r=0.297, p=0.029). No statistically significant correlation of STAI-Trait with clinical-laboratory parameters were observed. The correlations between BDI-II score, STAI-State, and STAI-Trait with clinical-laboratory parameters in all participants are given in Table 3.

Discussion

This study evaluated depression and anxiety during the pandemic period in CS patients and showed that depression and anxiety scores were increased in patients with active disease. According to the authors' best knowledge, this is the first report evaluating mental health in CS during the COVID-19 pandemic. The literature reports several studies on the psychological effects of the pandemic (20-22). On the other hand, CS is a disease that has a negative impact on

Table 1. Clinical comparison of the patients with Cushing's syndromes grouped according to disease activity.

N=54	Patients with active disease (Group 1) (n=10)	Patients on steroid replacement therapy (Group 2) (n=14)	Patients in remission (Group 3) (n=30)	p value
Current age (years)				
Mean±SD	50.8±11.7	52.6±10.1	45.9±12.5	NS
Age at diagnosis (years)				
Mean±SD	47.6±11	51.4±10	43.0±12.6	NS
Female (n)/male (n)				
Mean±SD	10/0	14/0	24/6	NS
Origin of CS				
pituitary (n)/surrenal (n)/ectopic (n)	7/2/1	5/9/0	15/15/0	NS
Education level (years)				
Mean±SD	6.2±2	8.5±3.7	10.3±4	0.01[a]
Marital status				
married (n)/unmarried (n)	9/1	14/0	20/10	NS
Smoking (n, %)	5 (50)	4 (29)	11 (37)	NS
Alcohol use (n; %)	1 (10)	0	1 (11%)	NS
Psychiatric medication use (n, %)	2 (20)	4 (29)	5 (17)	NS
BMI (kg/m^2)				
Mean±SD	36.2±8.3	31.1±8.5	29.1±7.2	NS
Obesity (n, %)	8 (80)	7 (50)	14 (47)	NS
Diabetes Mellitus (n, %)	5 (50)	5 (36)	10 (33)	NS
Hypertension (n, %)	5 (50)	7 (50)	9 (30)	NS
Osteoporosis (n, %)	3 (30)	2 (14)	1 (3)	NS
Hyperlipidemia (n, %)	7 (70)	5 (36)	12 (40)	NS
History of COVID-19 disease/ contact history of a patient with COVID-19	0/0	0/0	0/1	NS

a: Difference between groups 1 and 3; p<0.05 statistically significant, significant p-values are shown in bold; SD: Standard deviation; CS: Cushing's syndrome; BMI: Body mass index; NS: Not significant.

mental health and could be affected due to the psychology during the pandemic (13). High depression and anxiety scores were found, especially in active CS patients, suggesting that they were psychologically affected in this process.

The increase in depression and anxiety has been previously reported, especially in high-risk groups for COVID-19 (20-22). Mainly DM, HT, obesity, and cardiovascular diseases, which CS frequently accompanies, increase the risk of COVID-19 morbidity and mortality (11,30,31). Besides, immunosuppression caused by hypercortisolemia increases the risk of infection in CS, especially during the active disease period (12). Although there are no studies evaluating the course of COVID-19 in CS, these patients are actually at high risk for the reasons mentioned above. Patients also noticed that both immunosuppression status and comorbidities of CS might increase the risk of COVID-19. So, it was observed that anxiety and depression increased significantly in CS with active disease.

It is known that CS is often associated with psychiatric disorders (13). Although the etiopathogenesis of neuropsychiatric diseases observed in CS is unclear, it is thought to be associated with decreased glucose uptake in the brain, increased excitatory amino acids, decreased neurotrophic factors, and suppression of neurogenesis. Psychiatric complications such as depression, mania, and anxiety are frequently found in active CS, primarily due to hypercortisolemia. Although there was no control group in this study, the active patient group was com-

Table 2. Neuropsychiatry testing of the patients with Cushing syndrome grouped according to disease activity.

N=54	Patients with active disease (Group 1) (n=10)	Patients on steroid replacement therapy (Group 2) (n=14)	Patients in remission (Group 3) (n=30)	p value
BDI-II				
Mean±SD	20.6±12	11.1±10.2	8.8±8.5	0.002[a]
STAI-State				
Mean±SD	46.2±7.5	37.2±8.1	41.5±5.9	0.03[b]
STAI-Trait				
Mean±SD	48.3±5.5	44.9±5.0	46.1±7.1	NS
Severity of depression using BDI-II scores				
Minimal-mild (n, %)	4 (30)	11 (75)	11 (75)	0.014[a]
Moderate-severe (n, %)	6 (60)	3 (25)	5 (16)	
Severity of anxiety using STAI-State scores				
Low state anxiety (n, %)	3 (30)	7 (50)	13 (43)	NS
High state anxiety (n, %)	7 (70)	7 (50)	17 (57)	
Severity of anxiety using STAI-Trait scores				
Low trait anxiety (n, %)	1 (10)	1 (7)	5 (17)	NS
High trait anxiety (n, %)	9 (90)	13 (93)	25 (83)	

a: Difference between group 1 and 3; b: Difference between group 1 and 2; p<0.05 statistically significant, significant p-values are shown in bold; BDI-II: Beck Depression Inventory II; STAI: State-Trait Anxiety Inventory; NS: Not significant; BDI-II scores: Minimal depression, 0-12 points; mild depression, 13-18 points; moderate depression, 19-28 points; severe depression, 29-63 points. STAI-State scores: Low state anxiety, <40 points; High state anxiety, ≥40 points.
STAI-Trait scores: Low trait anxiety, <40 points; High trait anxiety, ≥40 points.

Table 3. Correlation between BDI-II, STAI-State and STAI-Trait scores and clinical and laboratory parameters in the entire study group.

	BDI-II		STAI-State		STAI-Trait	
N=54	r value	p value	r value	p value	r value	p value
Age (years)	0.094	0.500	0.020	0.886	0.011	0.937
Age at diagnosis (years)	0.101	0.467	-0.008	0.955	0.024	0.865
Female gender	0.380	0.005	0.243	0.077	0.243	0.077
Origin of CS	-0.250	0.071	-0.158	0.258	-0.053	0.705
Education levels (years)	-0.254	0.064	-0.203	0.141	-0.224	0.103
Marital status	-0.114	0.411	0.092	0.510	0.096	0.489
Obesity	0.232	0.092	0.055	0.694	0.054	0.700
Diabetes mellitus	0.160	0.248	0.201	0.145	0.053	0.702
Hypertension	0.118	0.397	-0.029	0.833	0.117	0.398
Disease activity	0.438	0.001	0.297	0.029	0.233	0.09

p<0.05 statistically significant, significant, p-values are shown in bold; BDI-II: Beck Depression Inventory-II; STAI: State-Trait Anxiety Inventory CS: Cushing's syndrome.

pared with patients in remission to evaluate the effect of hypercortisolemia. Simultaneously, the patients in remission whose HPA did not improve and still received steroid replacement therapy as a separate group were assessed because the patients in remission have normal physiological cortisol rhythm. In contrast, patients who still receive steroid replacement have not reached normal physiology yet (32).

The most common psychiatric disorder in CS is depression, and the frequency of depres-

sion in patients with the active disease has been reported to be a wide range of 51-80% (15,33-35). In this case series, moderate to severe depression rate was detected in about 60% of patients with active CS, consistent with the literature (13). Depression scores were higher in active patients than those in remission. However, comorbidities were similar in groups of active disease and remission. Both the low depression scores and the lower frequency of moderate to severe depression in the remission group suggested that disease activity was the primary determinant of depression in CS. Several studies showed that symptoms of psychiatric diseases improved with decreasing cortisol levels in remission (16,36-38).

On the other hand, it has been reported that the severity of depression did not reduce with remission (39,40). In addition to disease activity, female gender and advanced age have also been observed to be associated with increased depression in CS (15). However, in the present study, correlations were found between depression scores, disease activity, and female gender. Although it did not reach statistical significance, depression scores and moderate to severe depression rates were low in patients on steroid replacement therapy than in those with active disease. This situation suggested that although the HPA has not improved yet, the reduction of hypercortisolemia and surgical treatment for CS led to the partial improvement in depression symptoms, even if patients were not in remission.

Although less common than depression, anxiety disorders are frequent in active CS patients, and their frequency has been reported to be 63-79% (11,14,41). In the present study, high state anxiety was detected in 70% of the active disease group, and high trait anxiety was found in 90%, and these rates were higher than in the literature (13). The STAI-State scale shows the anxiety status. The STAI-Trait scale shows the general state of anxiety and personal characteristic, so STAI-State scores were significant for this study, especially to evaluate the effects of a pandemic on patients (27). Although the trait anxiety scores were higher in this series, they were similarly high in all patient groups, whereas the state anxiety scores were higher in the active disease group. This situation suggests that the pandemic process affects active CS patients more. Simultaneously, it was found that STAI-State scores correlated only with disease activity in the correlation analysis. In patients with CS, prospective studies on an extensive study sample could support the relationship between anxiety scores and disease activity.

The most important limitation of this study is the absence of a control group. Yet, the active patients were evaluated separately and compared with patients in remission. Another limitation is having a small number of patients. However, CS is already a rare endocrinopathy. This study group consisted of a small number of patients. The patients could be evaluated by a single psychiatrist in the same center in the short term.

Conclusion

In conclusion, the authors have shown that depression and the current state of anxiety scores increased during the pandemic, especially in active CS patients. These results have shown that psychiatric disorders may also increase during the pandemic period in CS patients, who have an increased risk of severe COVID-19. Therefore, it is crucial to evaluate especially active CS patients for psychiatric complications during stressful and risky conditions such as pandemics.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Sema Çiftçi Doğanşen, Hamide Pişkinpaşa; Design: Hamide

Pişkinpaşa, Özlem Karaarslan; Control/Supervision: Sema Çiftçi Doğanşen, Hamide Pişkinpaşa, Seda Turgut; Data Collection and/or Processing: İlkay Çakır, Meral Mert, Ayşe Esen, Hamide Pişkinpaşa, Sema Çiftçi Doğanşen, Naim Pamuk, Evin Bozkur, Özlem Karaarslan; Analysis and/or Interpretation:İlkay Çakır, Meral Mert, Sema Çiftçi, Doğanşen; Literature Review: Hamide Pişkinpaşa; Writing the Article: Hamide Pişkinpaşa; Critical Review: Sema Çiftçi Doğanşen, Seda Turgut.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-1720. [Crossref] [Pubmed] [PMC]
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323:1239-1242. [Crossref] [Pubmed]
3. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323:2052-2059. Erratum in: JAMA. 2020;323:2098. [Crossref] [Pubmed] [PMC]
4. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323:1775-1776. Erratum in: JAMA. 2020;323:1619. [Crossref] [Pubmed]
5. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020;31:1003-1008. [Crossref] [Pubmed] [PMC]
6. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75:2950-2973. [Crossref] [Pubmed] [PMC]
7. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. J Clin Neurosci. 2020;77:8-12. [Crossref] [Pubmed] [PMC]
8. Lee IC, Huo TI, Huang YH. Gastrointestinal and liver manifestations in patients with COVID-19. J Chin Med Assoc. 2020;83:521-523. [Crossref] [Pubmed] [PMC]
9. Dubey S, Biswas P, Ghosh R, Chatterjee S, Dubey MJ, Chatterjee S, Lahiri D, Lavie CJ. Psychosocial impact of COVID-19. Diabetes Metab Syndr. 2020;14:779-788. [Crossref] [Pubmed] [PMC]
10. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93:1526-1540. [Pubmed] [PMC]
11. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A. Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol. 2016;4:611-629. [Crossref] [Pubmed]
12. Fareau GG, Vassilopoulou-Sellin R. Hypercortisolemia and infection. Infect Dis Clin North Am. 2007;21:639-657, viii. [Crossref] [Pubmed]
13. Pivonello R, Simeoli C, De Martino MC, Cozzolino A, De Leo M, Iacuaniello D, Pivonello C, Negri M, Pellecchia MT, Iasevoli F, Colao A. Neuropsychiatric disorders in Cushing's syndrome. Front Neurosci. 2015;9:129. [Crossref] [Pubmed] [PMC]
14. Starkman MN, Schteingart DE, Schork MA. Depressed mood and other psychiatric manifestations of Cushing's syndrome: relationship to hormone levels. Psychosom Med. 1981;43:3-18. [Crossref] [Pubmed]
15. Sonino N, Fava GA, Raffi AR, Boscaro M, Fallo F. Clinical correlates of major depression in Cushing's disease. Psychopathology. 1998;31:302-306. [Crossref] [Pubmed]
16. Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW, Chrousos GP. The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. J Clin Endocrinol Metab. 1997;82:912-919. [Crossref] [Pubmed]
17. Ragnarsson O, Johannsson G. Cushing's syndrome: a structured short- and long-term management plan for patients in remission. Eur J Endocrinol. 2013;169:R139-52. [Crossref] [Pubmed]
18. Forget H, Lacroix A, Cohen H. Persistent cognitive impairment following surgical treatment of Cushing's syndrome. Psychoneuroendocrinology. 2002;27:367-383. [Crossref] [Pubmed]
19. Bäuerle A, Teufel M, Musche V, Weismüller B, Kohler H, Hetkamp M, Dörrie N, Schweda A, Skoda EM. Increased generalized anxiety, depression and distress during the COVID-19 pandemic: a cross-sectional study in Germany. J Public Health (Oxf). 2020;42:672-678. [Crossref] [Pubmed] [PMC]

20. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. Brain Behav Immun. 2020;88:901-907. Erratum in: Brain Behav Immun. 2021;92:245. [Crossref] [Pubmed] [PMC]
21. Lebel C, MacKinnon A, Bagshawe M, Tomfohr-Madsen L, Giesbrecht G. Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic. J Affect Disord. 2020;277:5-13. Erratum in: J Affect Disord. 2021;279:377-379. [Crossref] [Pubmed] [PMC]
22. Wang Y, Duan Z, Ma Z, Mao Y, Li X, Wilson A, Qin H, Ou J, Peng K, Zhou F, Li C, Liu Z, Chen R. Epidemiology of mental health problems among patients with cancer during COVID-19 pandemic. Transl Psychiatry. 2020;10:263. [Crossref] [Pubmed] [PMC]
23. Alessi J, de Oliveira GB, Franco DW, Brino do Amaral B, Becker AS, Knijnik CP, Kobe GL, de Carvalho TR, Telo GH, Schaan BD, Telo GH. Mental health in the era of COVID-19: prevalence of psychiatric disorders in a cohort of patients with type 1 and type 2 diabetes during the social distancing. Diabetol Metab Syndr. 2020;12:76. [Crossref] [Pubmed] [PMC]
24. Beck AT, Steer RA, Brown GK. BDI-II, Beck Depression Inventory: Manual. (2nd ed.) Boston: Harcourt Brace; 1996. [Crossref]
25. Kapci EG, Uslu R, Turkcapar H, Karaoglan A. Beck Depression Inventory II: Evaluation of the psychometric properties and cut-off points in a Turkish adult population. Depress Anxiety. 2008;25:E104-10. [Crossref] [Pubmed]
26. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory (Self-Evaluation Questionnaire) Palo Alto, CA, USA; 7 Consultant Psychologists Press; 1970. [Link]
27. Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. Br J Clin Psychol. 1983;22:245-249. [Crossref] [Pubmed]
28. Öner N, Compte AL. Süreksiz Durumluluk/Sürekli Kaygı Envanteri El Kitabı. (2. Baskı). İstanbul; Boğaziçi Üniversitesi Yayınevi; 1998. [Link]
29. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S467-72. [Crossref] [Pubmed] [PMC]
30. Hasenmajer V, Sbardella E, Sciarra F, Minnetti M, Isidori AM, Venneri MA. The immune system in Cushing's Syndrome. Trends Endocrinol Metab. 2020;31:655-669. [Crossref] [Pubmed]
31. Kakodkar P, Kaka N, Baig MN. A Comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). Cureus. 2020;12:e7560. [Crossref] [Pubmed] [PMC]
32. Hochberg Z, Pacak K, Chrousos GP. Endocrine withdrawal syndromes. Endocr Rev. 2003;24:523-538. [Crossref] [Pubmed]
33. Dorn LD, Burgess ES, Dubbert B, Simpson SE, Friedman T, Kling M, Gold PW, Chrousos GP. Psychopathology in patients with endogenous Cushing's syndrome: 'atypical' or melancholic features. Clin Endocrinol (Oxf). 1995;43:433-442. [Crossref] [Pubmed]
34. Haskett RF. Diagnostic categorization of psychiatric disturbance in Cushing's syndrome. Am J Psychiatry. 1985;142:911-916. [Crossref] [Pubmed]
35. Kelly WF. Psychiatric aspects of Cushing's syndrome. QJM. 1996;89:543-551. [Crossref] [Pubmed]
36. Cohen SI. Cushing's syndrome: A psychiatric study of 29 patients. Br J Psychiatry. 1980;136:120-124. [Crossref] [Pubmed]
37. Kelly WF, Kelly MJ, Faragher B. A prospective study of psychiatric and psychological aspects of Cushing's syndrome. Clin Endocrinol (Oxf). 1996;45:715-720. [Crossref] [Pubmed]
38. Rasmussen SA, Rosebush PI, Smyth HS, Mazurek MF. Cushing disease presenting as primary psychiatric illness: A case report and literature review. J Psychiatr Pract. 2015;21:449-457. [Crossref] [Pubmed]
39. Santos A, Granell E, Gómez-Ansón B, Crespo I, Pires P, Vives-Gilabert Y, Valassi E, Webb SM, Resmini E. Depression and anxiety scores are associated with amygdala volume in cushing's syndrome: preliminary study. Biomed Res Int. 2017;2017:2061935. [Crossref] [Pubmed] [PMC]
40. Sonino N, Fallo F, Fava GA. Psychosomatic aspects of Cushing's syndrome. Rev Endocr Metab Disord. 2010;11:95-104. [Crossref] [Pubmed]
41. Loosen PT, Chambliss B, DeBold CR, Shelton R, Orth DN. Psychiatric phenomenology in Cushing's disease. Pharmacopsychiatry. 1992;25:192-198. [Crossref] [Pubmed]