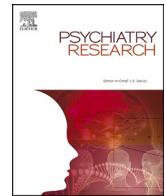




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Neuropsychiatric symptoms in the psychiatric counseling of patients admitted with COVID-19 infection

Mohammad Reza Shegarf Nakhaei^{a,*}, Ahmad Ali Noorbala^b, Atieh Sadeghniaat Haghighi^c,
Mohammad Arbabi^{d,e}

^a Assistant Professor of Psychiatry, Fellowship in Psychosomatics, Sabzevar University of Medical Sciences, Sabzevar, Iran

^b Professor of Psychiatry, Tehran University of Medical Sciences, Tehran, Iran

^c Resident of Psychiatry, Tehran University of Medical Sciences, Tehran, Iran

^d Psychosomatic Medicine Research Center, Department of Psychiatry, Tehran University of Medical Sciences, Tehran, Iran

^e Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Background: Covid-19 patients suffer from psychiatric disorders too. The present study was designed to investigate the rate of psychiatric consultation requests in a general hospital. Reasons for consultation requests, types of psychiatric diagnoses, and factors in consultation requests were also investigated.

Methods: This cross-sectional study included all patients admitted with Covid-19 and referred to psychiatric consultation service in a major Covid-19 center in Tehran, Iran (2020). After accessing patients' electronic files, records of patients' demographic information, positive psychiatric symptoms, past psychiatric history and DSM5 diagnoses were made. Statistical analyses were done in SPSS 26 using descriptive statistics and chi-square and Fisher's exact test ($p < 0.05$).

Results: Out of 1791 Covid-19 hospitalized patients, 132 patients (7.3%) had been referred to psychiatric consultation service. The most common reason for requests were restlessness and aggression (23.5%). Meanwhile, 92.4% of the patients were diagnosed to suffer from at least one psychiatric disorder including insomnia (64%), delirium (30.3%), anxiety due to hypoxia (15.3%) and generalized anxiety disorder (10.6%).

Conclusion: Although studies report a high prevalence of psychiatric disorders in Covid-19 patients, requests for psychiatric consultations and consideration of psychiatric disorders are still remarkably low. The most common disorders appeared to be insomnia, delirium and anxiety.

1. Introduction

In December 2019, several cases of pneumonia with unknown causes were recorded in Wuhan, China. In January 2020, the cause of this unexplained pneumonia was found to be the new enveloped RNA corona virus, isolated from the broncho-alveolar lavage fluid of a Chinese patient (Hosseini et al., 2020). The virus was named SARS-CoV2 and introduced as the pathogen of the COVID-19 disease. The incubation period ranged somewhere between 3 and 14 days after exposure, and the most common symptoms were fever, cough, fatigue, headache, hemoptysis and apnea (Noorbala et al., 2010). In many of its extreme cases, such comorbidities as severe acute respiratory syndrome (SARS), digestive disorders, acute cardiac problems, multi-organ deficiency (affecting kidney, liver and heart) and neuropsychiatric symptoms

appeared (Noorbala et al., 2010; Arbabi et al., 2012). Although most symptoms of the Covid-19 disease are respiratory symptoms, and medical centers rely on such symptoms for the primary screening and while the first reports of the Covid-19 concentrated mainly on the respiratory symptoms, reports of other clinical manifestations including neuropsychiatric symptoms are on the rise (Funk et al., 2020; Mirfazeli et al., 2020).

Neuropsychiatric involvement emerges when severe respiratory symptoms occur (Noorbala et al., 2010; Aarabi et al., 2017). It is estimated that about one-third of the Covid-19 patients suffer from neuropsychiatric symptoms (Mirfazeli et al., 2020). Earlier studies list hypertension, coronary heart disease, diabetes mellitus, renal disorders, smoking, and COPD as predisposing diseases, which tend to increase the mortality rate (Rogers et al., 2020). Despite frequent updates on the

* Corresponding author.

E-mail address: rezashegarf@yahoo.com (M.R.S. Nakhaei).

Covid-19 disease, many aspects of the disease are still unknown (Hosseini et al., 2020). Viral respiratory diseases come along with acute and long-term psychopathologic outcomes in survivors. For instance, several neuropsychiatric disorders were reported with MERS and SARS epidemics (Iqbal et al., 2020).

Evidence shows that such complications as delirium, depression, anxiety, insomnia and psychosis may occur in Covid-19 patients (Iqbal et al., 2020; Kong et al., 2020). Zandifar et al. reported a high percentage of anxiety, depression and stress even in clinically stable Covid-19 patients (Zarghami et al., 2020). Present findings indicate that in the acute phase of the disease (Liu et al., 2020), delirium is a serious complication and the most common neuropsychiatric symptom (Iqbal et al., 2020). Even in the absence of respiratory symptoms, delirium may occur in Covid-19 patients (Arbabi et al., 2012). Psychiatric disorders are closely associated with physical health diseases and affect their prognosis; this fact is also true with the Covid-19 disease. Nevertheless, there are research reports of few psychiatric consultation requests in general hospitals despite frequent comorbidity of psychiatric and physical health diseases. A 2017 study reported a low rate of psychiatric consultation requests (3.5%) in Brazil, where requests from medical and surgical wards were 71.2% and 28.8%, respectively (Deng et al., 2020). The main reason for consultation requests was depression (49.1%), and 52.5% of the patients were female with an average age of 45.9 years (Deng et al., 2020).

Considering the high prevalence of psychiatric disorders in medical patients, their effects on the prognosis of the diseases, the urgency to manage psychiatric problems, on the one hand, and considering the psychiatric effects of the Covid-19 disease by increasing stressors and/or direct/indirect harm to the central nervous system on the other hand, the researchers decided to investigate the current rate of psychiatric consultation requests in a referral hospital for Covid-19 patients. The researchers also aimed to investigate the reasons of consultation requests, different types of psychiatric diagnoses, and relevant factors in consultation requests.

2. Methods

This cross-sectional study was conducted on 132 Covid-19 patients at Imam Khomeini Hospital (the referral hospital for Covid-19 patients) in Tehran, Iran, from February 2019 through July 2020. Out of 1791 Covid-19 hospitalized patients, all patients for whom psychiatric consultations had been requested were included in the study via a census sampling method. Permission was obtained to access the patients' electronic files so as to track the records of requests. Consultations were done by senior residents of psychiatry.

The residents were instructed with relevant guidelines for doing and recording the consultations properly, to obtain a consistent record of the patients' demographic information, disease and medical condition, positive psychiatric symptoms, psychiatric history if any, mental state examination (MSE), the diagnosis based on DSM5 criteria and necessary medical advice.

Statistical analyses were run in SPSS 26, using descriptive statistics such as frequency (for qualitative variables), and mean (\pm SD) (for quantitative variables). Also, chi-square and Fisher's exact test were used for investigating the relationship between qualitative variables and disorders. $P < 0.05$ was considered statistically significant.

3. Results

Out of 1791 Covid-19 patients hospitalized in Imam Khomeini Hospital, Tehran, Iran, from February 2019 to July 2020, 132 patients were referred to the psychiatric consultation service. In other words, psychiatric consultation was requested for only 7.3% of the hospitalized patients, of whom 54.4% were male and 45.6% female. On average, psychiatric consultation was requested for the patients 5.95(\pm 7.94) days after hospitalization.

The patients' mean age was 55.73 \pm 18.90 years. As for marital status, 79.5% were married, and 20.5% were single. Meanwhile, 17.9% were illiterate, 34.5% did not finish high school, 28.2% had high school diploma, and 19.2% had university degrees. Covid-19 symptoms were assessed upon hospitalization. The most common reported symptoms were dyspnea (59.8%), coughing (59.1%) and fever (56.8%).

Different reasons for psychiatric consultation requests were evaluated, and the most common reasons were history of a psychiatric disorder (50%), restlessness and aggression (23.5%), anxiety (22.1%), ignoring the treatment plan (21%), and depression (19.7%). Other reasons for requesting psychiatric consultations included insomnia (7.6%), expressing irrelevant words (3.8%), elevated mood (0.8%), disorientation (9.8%), and hallucination and delusion (9.1%). Of all requested psychiatric consultations, 92.4% of the patients were diagnosed with at least one psychiatric disorder. As shown in Fig. 1, insomnia was the most common problem (64%), followed by delirium (30.3%), anxiety due to hypoxia (15.3%), generalized anxiety disorder (10.6%), major depressive disorder (9.8%), and adjustment disorder (9.1%). Therefore, placed after delirium, complaints of anxiety and depression accounted for the most common symptoms in the patients. The least common disorder was the psychotic disorder (0.3%).

The psychiatric disorders were studied in relation with age, gender, education and marital status. As shown in Table 1, no significant difference was found between male and female gender across different age groups. But a significant difference was observed with patients' marital status, as 84% of the patients with a psychiatric disorder were married while only 30% of the patients without a disorder were single. Odds ratio of having a psychiatric disorder in married patients was 10.46 times more than single patients ($p = 0.004$) but no significant differences existed between single and divorced/widowed individuals ($p = 0.71$).

The prevalence of various psychiatric disorders was also considered by age and gender but no significant relationships were observed. As shown in Table 2, a significant difference was found between O₂ saturation level and 'having or not having' a psychiatric disorder; O₂ saturation level was more than 90% in 64% of the patients with a psychiatric disorder, while O₂ saturation level above 90% was seen in all patients without a disorder. In fact, O₂ saturation level below 90% predisposed the patient to psychiatric disorders.

Medical conditions were also studied. The following conditions were observed in the consulted patients: diabetes (27%), hypertension (34%), hyperlipidemia (5.3%), ischemic heart disease (19.62%), chronic obstructive pulmonary disease (12%), pulmonary embolism (3.33%), CVA (4.54%), endocrine and metabolic disorders (9%), malignancy (7.57%), liver diseases (5.32%), kidney diseases (5.57%), neurologic diseases (5.3%), and rheumatoid (2.27%). However, no significant relationship existed between these conditions and an increased risk for psychiatric disorders.

Medications were prescribed for 78.8% of the consulted cases; the most common prescribed drugs were olanzapine (20.6%), haloperidol (17.4%) and gabapentin (16.7%) (Fig. 2).

Finally, the relationship between the present psychiatric disorders diagnosed and previous diagnoses was studied. Of all, 64 patients (97%) with a history of psychiatric disorder were also diagnosed to have a psychiatric disorder after consultation. Of those without a previous psychiatric disorder, 58 patients (87.9%) were then diagnosed to suffer from a psychiatric disorder. As shown in Table 3, patients with delirium (15%) had a history of dementia more than those without delirium (3.3%) ($p = 0.02$). Also, patients with substance use disorder (20%) had a history of personality disorder compared with those without the substance use disorder (1.6%) ($p = 0.03$). A significantly higher percentage of patients without delirium (17.4%) had a history of generalized anxiety disorder in comparison with patients with delirium (2.5%) ($p = 0.02$).

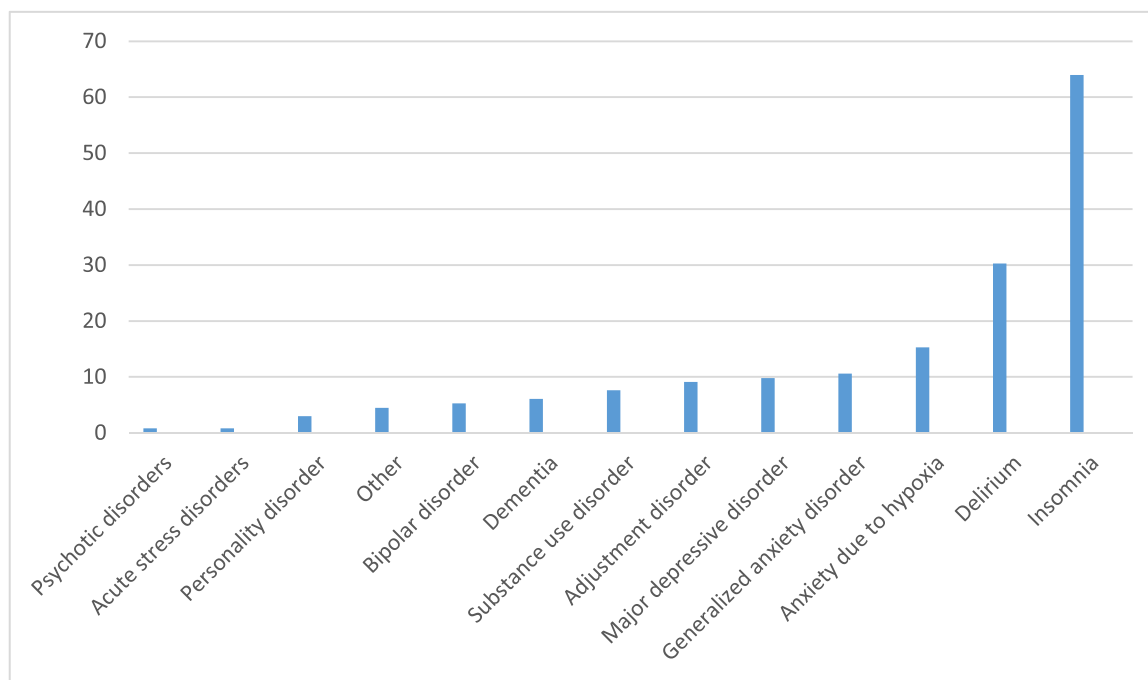


Fig. 1. Prevalence of different types of psychiatric disorders.

Table 1
Prevalence of psychiatric disorders by age, gender, education and marital status.

	Subgroup	Without a disorder	With a disorder	p-value	OR (95% CI)
Gender	Female	7 (70.0)	53 (43.4)	0.18	3.04 (0.75–12.31)
	Male	3 (30.0)	69 (56.6)		
Age median	<56	6 (60.0)	60 (49.2)	0.51	1.55 (0.42–5.77)
	>56	4 (40.0)	62 (50.8)		
Marital status	Single	4 (40.0)	13 (10.7)	0.004	10.46 (2.10–52.04)
	Married	3 (30.0)	102 (83.6)		
	Widowed/divorced	3 (30.0)	7 (5.7)		
	0.72 (0.12–4.16)				
Education	Less than diploma	5 (55.6)	36 (52.2)	0.99	1.15 (0.28–4.63)
	Diploma and more	4 (44.4)	33 (47.8)		

4. Discussion

The present study was conducted to evaluate the reasons of consultation requests, different types of psychiatric diagnoses, and relevant factors in consultation requests. The results showed that 7.3% of the Covid-19 patients received psychiatric consultations; furthermore, the consultations were requested within 5.95 days after hospitalization on average. The most frequent reasons for consultation requests were restlessness and aggression. However, dyspnea, coughing and fever were the most prevalent symptoms in Covid-19 patients. In 92.4% of the consultations, a psychiatric diagnosis was confirmed, with insomnia, delirium and anxiety being the most common symptoms. Psychiatric disorders were significantly more frequent in married patients. Underlying medical conditions mostly included diabetes, hypertension and ischemic heart diseases. All patients without psychiatric disorders had O₂ saturation level above 90%.

Rate of consultation requests may vary from context to context. In the present study, this rate amounted to 7.3% of the hospitalized Covid-19 patients. In a systematic review, Hosseini et al. analyzed 22 studies

published from 1977 to 2019, and found that consultation requests varied from 0.08% in a study by Gala in the US to 22.6% in a study by Krantgartner in Australia. In two Iranian studies, Arbabi (2007) and Elyasi (2018) reported the consultation requests to be 1.19% and 5.4%, respectively (Hosseini et al., 2020). Noorbala et al. (2009) found that 58.1% of patients hospitalized in a general hospital (i.e. Imam Khomeini Hospital, Tehran, Iran) suffered from psychiatric problems (Noorbala et al., 2010). Other studies have found that the prevalence of psychiatric disorders in hospitalized patients varied from 30% to 60% (Noorbala et al., 2010). Therefore, while 30 to 60 percent of patients hospitalized in general hospitals suffer from at least one psychiatric disorder, few of them receive psychiatric consultation services. Although the results of the present study revealed that the rate of consultation requests increased from 1.19% in earlier studies to 7.3% in the present study, most hospitalized patients in need of psychiatric consultation services are neglected.

One reason behind this increase may be the establishment of a psychosomatic ward in the research setting (i.e. Imam Khomeini Hospital, Tehran, Iran) since 2010, and provision of efficient psychiatric consultations, which has encouraged other specialist wards to place requests for psychiatric consultations. However, we are still behind our expectations. We are certain that prevalent psychiatric disorders can exacerbate the course of medical conditions. Such comorbidities induce further symptoms, more serious dysfunctions, unhealthy lifestyle, increased medical expenses, lowered response to treatment, longer duration of hospitalization, and higher mortality rates (Hosseini et al., 2020). Prompt and early psychiatric consultation has remarkable effects on patients' recovery from medical conditions, and reduces medical expenses (Hosseini et al., 2020; Arbabi et al., 2012).

Consultation-Liaison Psychiatry lies at the convergence juncture of psychiatry and the rest of medicine. Hospital managers consider consultation-liaison psychiatrists as providers of mental health services but they are unfortunately unaware of most services psychiatrists can provide at all levels. Therefore, information about what the psychiatry team can provide for general hospitals becomes essential. The team needs to adopt a step-by-step, flexible, balanced and informative approach (Funk et al., 2020).

In this study, the time between hospitalization and consultation

Table 2
Prevalence of psychiatric disorders by O2 saturation and existing comorbidity.

	Subgroup	Without a disorder	With a disorder	p-value	OR (95% CI)
O ₂ saturation	90 and less	0 (0.0)	36 (35.3)	0.03	
	More than 90	10 (100.0)	66 (64.7)		
Comorbidity					
DM	No	7 (70.0)	89 (73.0)	0.99	0.87 (0.21–3.55)
	Yes	3 (30.0)	33 (27.0)		
HTN	No	7 (70.0)	80 (65.6)	0.99	1.23 (0.30–4.98)
	Yes	3 (30.0)	42 (34.4)		
Hyperlipidemia	No	10 (0.0)	115 (94.3)	0.99	–
	Yes	0 (0.0)	7 (5.7)		
IHD-MI	No	8 (80.0)	98 (80.3)	0.99	0.98(0.20–4.91)
	Yes	2 (20.0)	24 (19.7)		
COPD-AsThma	No	10 (100.0)	106 (86.9)	0.61	–
	Yes	0 (0.0)	16 (13.1)		
Pulmonary embolism	No	10 (100.0)	118 (96.7)	0.99	–
	Yes	0 (0.00)	4 (3.3)		
CVA	No	10 (100.0)	116 (95.1)	0.99	–
	Yes	0 (0.00)	6 (4.9)		
Metabolic or endocrinological	No	10 (100.0)	110 (90.2)	0.60	–
	Yes	0 (0.00)	12(9.8)		
Malignancy	No	10 (100.0)	112 (91.8)	0.99	
	Yes	0 (0.00)	10 (8.2)		
Liver disease	No	7 (70.0)	118 (96.7)	0.01	0.08 (0.02–0.42)
	Yes	3 (30.0)	4 (3.3)		
Kidney disease	No	9 (90.0)	113 (92.6)	0.56	0.72 (0.08–6.31)
	Yes	1 (10.0)	9 (7.4)		
Neurologic disease	No	9 (90.0)	116 (95.1)	0.43	0.47 (0.05–4.30)
	Yes	1 (10.0)	6 (4.9)		
Rheumatoid	No	10 (100.0)	119 (97.5)	0.99	–
	Yes	0 (0.0)	3 (2.5)		
Other	No	8 (80.0)	103 (84.4)	0.66	0.74 (0.15–3.75)
	Yes	2 (20.0)	19 (15.6)		

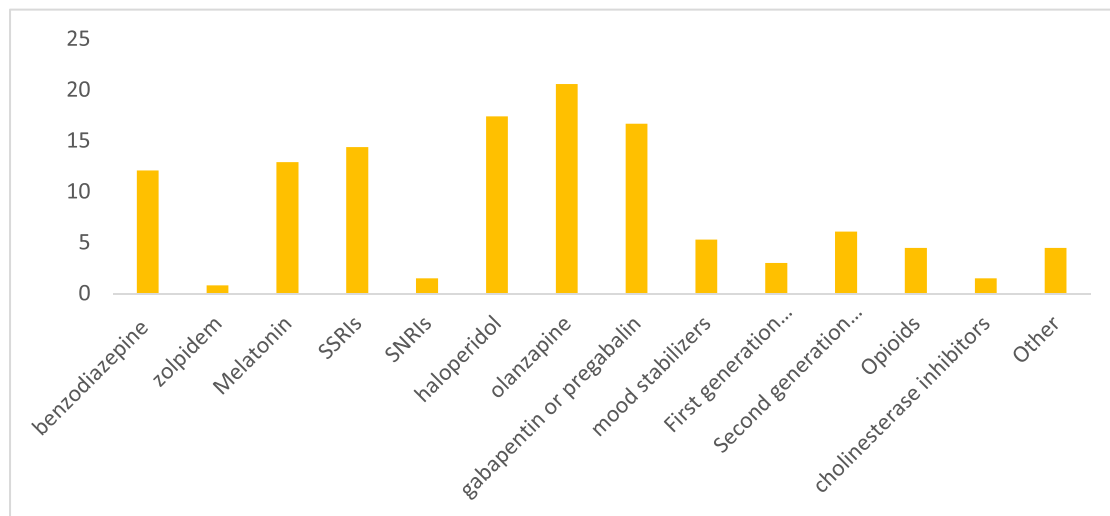


Fig. 2. Prescribed medications after psychiatric consultation.

request was 5.95 days. Arbabi (2007) found that patients stayed hospitalized 12.56 days before the consultation request (Arbabi et al., 2012). The reasons for the shortened request time in our study may be attributed to patients’ clinically aggravated state, incidence of anxiety due to hypoxia and delirium leading to restlessness, which altogether prompted requests for psychiatric consultation.

Another aspect considered in the present study was identifying the symptoms which encouraged other specialists to request psychiatric consultation, and we found that restlessness and aggression (23.5%), anxiety (22.1%), and depression (19.7%) were the most common symptoms; in fact, these symptoms accounted for 65.3% of the consultation requests.

In an earlier study (Arbabi, 2007), 61% of the consultation requests

were due to anxiety, depression and aggression, which is similar to the present study (Arbabi et al., 2012). In another study, 49.1% of consultation requests were due to depression (Deng et al., 2020). Indeed, it seems that consultation requests originate in patients’ objective signs such as aggression and restlessness, which may disturb the ward discipline and quiet.

In the present study, the most common symptoms in Covid-19 patients included dyspnea (59.8%), coughing (59.1%), and fever (56.8%). Similarly, Mirfazeli et al. found similar results (dyspnea 59.8%, coughing 59.1%, and fever 56.8%) which are in line with our findings (Mirfazeli et al., 2020). Out of all consultation requests in the present study, 92.4% of cases suffered from at least one psychiatric disorder. Similarly, Arbabi (2007) found at least one psychiatric disorder in 90.1% of the

Table 3
Relationship between pre-existing disorders and the present diagnosed disorder.

		Adjustment disorder	Major depressive disorder	Generalized anxiety	Dementia	Bipolar	Substance use disorder	Personality disorder	Illness anxiety	Schizophrenia	Obsessive	Other
Anxiety disorder due to other medical condition	N = 18	5.6%	0.0%	5.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	5.6%	16.7%*
Hypoxia												
Insomnia	N = 2	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Adjustment disorder	N = 12	0.0%	0.0%	8.3	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	8.3
Major depressive disorder	N = 13	0.0%	100.0*	7.7	7.7	0.0%	7.7	0.0%	0.0%	0.0%	0.0%	0.0%
Generalized anxiety disorder	N = 14	0.0%	7.1	100.0*	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Bipolar disorder	N = 7	0.0%	0.0%	0.0%	14.3	100.0*	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Delirium	N = 40	2.5	7.5	2.5*	15.0*	2.5	0.0%	0.0%	0.0%	0.0%	2.5	0.0%
Dementia	N = 8	0.0%	12.5	0.0%	100.0*	12.5	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Substance use disorder	N = 10	0.0%	0.0%	0.0%	10.0	0.0%	60.0*	20.0*	0.0%	0.0%	0.0%	0.0%
Personality disorder	N = 4	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0*	0.0%	0.0%	0.0%	0.0%
Psychotic disorder	N = 1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Acute stress disorder	N = 1	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Other	N = 6	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	16.7*	16.7	0.0%	16.7

consultation requests.

The most common symptoms included insomnia (64%), delirium (30.3%), anxiety due to hypoxia (15.3%), generalized anxiety disorder (10.6%), major depressive disorder (9.8%), and adjustment disorder (9.1%). Therefore, followed by insomnia and delirium, complaints of anxiety and depression accounted for the most disturbing symptoms,

In a 2017 study in an Iranian setting (i.e. Imam Khomeini Hospital, Tehran, Iran), the most common psychiatric diagnoses were reported to be mood disorders (37.91%), delirium (13.6%), and anxiety (12.64%) (Aarabi et al., 2017). Arbabi et al. (2007) reported the prevalence of psychiatric disorders as follows: major depressive disorder (23.8%), bipolar disorder (5.8%), mood disorder due to a medical condition (0.8%), mixed anxiety-depressive disorder (13.1%), adjustment disorder (9.1%), dementia (0.6%), delirium (7%), anxiety disorder (8.6%), somatoform (8.4%), psychotic disorder (2.4%), substance misuse disorder (6.1%), and other disorders (7.1%) (Arbabi et al., 2012).

As shown, before the Covid-19 pandemic, the most common diagnosis was the mood disorders, while after the pandemic, diagnoses of insomnia, delirium and anxiety became more prevalent in psychiatric consultations. Similar findings are reported by Rogers et al. on the prevalence of psychiatric disorders during SARS and MERS outbreaks (Rogers et al., 2020), and by Iqbal et al. in Qatar (Iqbal et al., 2020). Studies not taking 'delirium' into account also reported similar results, where the most common disorders were insomnia and depression (Kong

et al., 2020; Zarghami et al., 2020; Liu et al., 2020; Deng et al., 2020).

As stated earlier, in the present study, no significant differences were found between various psychiatric disorders and variables such as gender and age groups. However, a significant relationship was found between marital status and incidence of a psychiatric disorder, so that the chances of psychiatric disorder in married patients was 10.46 times more than single patients ($p = 0.004$); but no significant difference was observed between single and divorced/widowed patients ($p = 0.71$). This may be explained by the fact that the quarantine of Covid-19 patients leads married patients to a distance from their spouse, while in single individuals there is already adjustment to the absence of a supportive spouse. Kong et al. (2020) studied 144 Covid-19 patients in Wuhan, China, and found that high rates of depression and anxiety were statically related to patients with older age, lower education, and lower social support (Kong et al., 2020). Ma et al. (2020) reported a positive correlation between depression and the female gender (Ma et al., 2020).

In patients referred to psychiatric consultation services, the following conditions and disorders were observed: diabetes (27%), hypertension (34%), hyperlipidemia (5.3%), ischemic heart disease (19.62%), chronic obstructive pulmonary disease (12%), pulmonary embolism (3.33%), CVA (4.54%), endocrine and metabolic disorders (9%), malignancy (7.57%), liver diseases (5.32%), kidney diseases (5.57%), neurologic diseases (5.3%), and rheumatic diseases (2.27%). No significant relationship was found between medical conditions and

increased risk for psychiatric disorders. In earlier studies, the most common underlying medical conditions were diabetes, hypertension and heart diseases (Mahammedi et al., 2020; Zandifar et al., 2020; Khateri et al., 2020).

In the present study, O₂ saturation level above 90% was observed in only 64% of the patients with a psychiatric disorder; however, all patients without a disorder had an O₂ saturation level above 90%, and the difference between the two groups was significant ($p = 0.03$). In fact, O₂ saturation level below 90% predisposed the patient to psychiatric disorders. Kong et al. (2020) who studied 144 Covid-19 patients in Wuhan, China, found that the O₂ saturation level was equal to or below 93% in 11.1% of the patients, and that low O₂ saturation level was statistically related with depression and anxiety (Kong et al., 2020). It was also shown that hypoxia can lead to neuropsychiatric and degenerative disorders by oxidative stress (Zhao et al., 2017).

History of dementia was higher in patients with delirium compared to those without delirium (15% vs. 3.3%, respectively) ($p = 0.02$). Since pre-existing cognitive problems give rise to the prevalence of delirium, such a finding is expected and confirms the findings of earlier studies (Jackson et al., 2017). In short, as psychiatric disorders may persist even months after treating a viral disease, it is our hope that patients are followed up after treatment for assessing the course of their psychiatric disorders. While this study attempted to reflect a real picture, it had limitations as well. For instance, obtaining a history and mental state examination were difficult in some critically ill patients, but spending enough time visiting patients, taking a telephone history from the family, and talking to the primary care physician helped us to collect the required and reliable information. The future course of disorders and their persistence after discharge were not included in this study and we hope additional studies deal with them in future.

Author statement

We really appreciate the reviewers' constructive comments, and sincerely apologize we were unable to return the revised manuscript in due time. Temporarily we couldn't enter the submission system, and it took a bit longer to respond to the comments. However, we are pleased to inform you that the revision is almost completed. We will be grateful if you kindly have the manuscript examined for the revised sections.

Conflict of interest

The authors declare that there is no conflict of interest.

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