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Neuropsychiatric symptoms of patients two years after experiencing severe COVID-19: A mixed observational study

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ABSTRACT

Background: The impact of SARS-CoV-2 infection (COVID-19) on mental health has not been extensively studied in the medium and long term. This study assessed how clinical, biological, and social factors affect mental health in patients who recovered from severe COVID-19. The evaluation was done 90 days after hospital discharge and followed up at 12 and 24 months.

Methods: A retrospective-prospective cohort mixed observational study was conducted on patients over 18 years of age who required hospitalization in Internal Medicine or ICU for severe COVID-19 pneumonia during 2020 and 2021. Demographic information, clinical variables, and data for the scales were obtained from electronic medical records and telephone interviews. For comparisons of the different variables in each clinical variable (insomnia, depression, anxiety), the Student's *t*-test for independent samples has been used (normal distribution); otherwise, the Mann–Whitney test will be used. All tests and intervals will be performed with a confidence level of 95. Fisher's exact or Pearson's Chi-square test has been used as appropriate for qualitative variables.

Results: 201 patients were recruited. 37.3% presented insomnia, 22.4% anxiety, and 21.4% depressive symptoms. A direct association was established between female sex and depressive symptoms. Psychotropic history, fatigue, and C-reactive protein levels (CRP) were correlated with depression. Anosmia and ageusia, CRP, cognitive symptoms, and dyspnea predicted insomnia. Sex, orotracheal intubation (OTI), pain, fatigue, mental health history, and academic level were independent predictors of anxiety. High percentages of depressive, anxiety, and insomnia symptoms were detected in the second month after discharge and persisted at 12 and 24 months. The fatigue variable maintained a significant relationship with depressive symptoms at 2, 12 and 24 months. A possible limitation could be recall bias in retrospective data collection.

Conclusions: This is a novel study to follow up on mental health for two years in patients with severe COVID-19. Clinical, biological, and psychosocial variables could be predictors of depressive symptoms, anxiety, and insomnia. The psychiatric symptoms persisted throughout the 2-year follow-up. These findings are critical for the follow-up of these patients and open the possibility of further studies in the medium and long term.

Síntomas neuropsiquiátricos de los pacientes 2 años después de sufrir COVID-19 grave. Estudio observacional mixto

Palabras clave:
COVID-19
Clínica psiquiátrica
Depresión
Insomnio

RESUMEN

Antecedentes: El impacto de la infección por SARS-CoV-2 (COVID-19) en la salud mental no se ha estudiado ampliamente a medio y largo plazo. Este estudio evaluó cómo los factores clínicos, biológicos y sociales afectan a la salud mental en los pacientes que se recuperaron de una COVID-19 grave. La evaluación se desarrolló 90 días después del alta hospitalaria y se realizó un seguimiento a los 12 y 24 meses.

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Métodos: Se realizó un estudio observacional mixto de cohortes retrospectivo/prospectivo en los pacientes mayores de 18 años que requirieron hospitalización en medicina interna o en la UCI por neumonía grave por COVID-19 durante 2020 y 2021. La información demográfica, las variables clínicas y los datos para las escalas se obtuvieron de las historias clínicas electrónicas y de las entrevistas telefónicas. Para las comparaciones de las distintas variables en cada variable clínica (insomnio, depresión, ansiedad), se ha utilizado la prueba t de Student para muestras independientes (distribución normal); en caso contrario, se utilizará la prueba de Mann-Whitney. Todas las pruebas e intervalos se realizarán con un nivel de confianza del 95%. Para las variables cualitativas se ha utilizado la prueba exacta de Fisher o la prueba Chi-cuadrado de Pearson, según proceda.
Resultados: Se reclutaron 201 pacientes. El 37,3% presentaba insomnio, el 22,4% ansiedad y el 21,4% síntomas depresivos. Se estableció una asociación directa entre el sexo femenino y los síntomas depresivos. Los antecedentes psicotrópicos, la fatiga y los niveles de proteína C reactiva (PCR) se correlacionaron con la depresión. La anosmia y la ageusia, la PCR, los síntomas cognitivos y la disnea predijeron el insomnio. El sexo, la intubación orotraqueal (IOT), el dolor, la fatiga, los antecedentes de salud mental y el nivel académico fueron predictores independientes de la ansiedad. Los altos porcentajes de síntomas depresivos, de ansiedad y de insomnio se detectaron en el segundo mes tras el alta y persistieron a los 12 y 24 meses. La variable fatiga mantuvo una relación significativa con los síntomas depresivos a los 2, 12 y 24 meses. Una posible limitación podría ser el sesgo de recuerdo en la recogida retrospectiva de datos.
Conclusiones: Se trata de un estudio novedoso de seguimiento de la salud mental durante 2 años en los pacientes con COVID-19 grave. Las variables clínicas, biológicas y psicosociales podrían ser predictores de síntomas depresivos, ansiedad e insomnio. Los síntomas psiquiátricos persistieron durante los 2 años de seguimiento. Estos hallazgos son críticos para el seguimiento de estos pacientes y abren la posibilidad de nuevos estudios a medio y largo plazo.

Introduction

The World Health Organization (WHO) declared the outbreak of coronavirus disease (COVID-19) as an international public health emergency on January 2020.[1] Throughout the initial two years of the pandemic, the general public experienced a range of unprecedented limitations and isolation protocols.[2] This infectious disease is highly contagious and has led to global awareness with a significant psychological impact. Humanity faced a critical challenge[3] that was widely discussed in the media and social networks. However, there was a risk of misinformation, inaccurate data, and sensationalism due to the abundance of information available.[4]

SARS-Cov-2 is one of the seven coronaviruses (CoV) that is infective in humans.[5] Previously, two epidemics in this millennium occurred before the current SARS-Cov-2 pandemic. Coronaviruses that affect humans have been found to cause respiratory and overall health issues, including psychiatric and neurological disorders.[6] A similar situation has been noticed during the present pandemic. Even though the World Health Organization (WHO) stopped categorizing the illness as a global health emergency in May 2023, they caution that it is still not fully contained and suggest that healthcare authorities should still view it as a potential threat.[7] The global impact of SARS-CoV-2 infection has had noticeable effects on people's mental health. While the biopsychosocial model can explain some of its causes, it may need adjustments.[8] Studies have shown higher rates of mental disorders in several population samples.[9,10]

Many COVID-19 patients have exhibited neuropsychiatric symptoms, both in the acute phase of the illness and in the medium to long term.[6,11,12] The presence of psychopathology has been attributed to multiple causes. In this sense, mental illness has been attributed to psychosocial stress and biological factors. The virus can trigger a cytokine storm and inflammatory response in the body and brain[13] and could affect the nervous system.[14] This is consistent with the idea that mental illness is associated with inflammation in the brain.[15] To date, hardly any studies collect information at 12 and 24 months, such as pooling clinical and social predictors behind prevalent psychiatric symptomatology with repercussions at the socioeconomic and health levels.

Therefore, the main objective of this study was to analyze which clinical, biological, or social factors could be associated with the presence of psychiatric symptoms, as well as their persistence over 24 months of follow-up. The aim is to respond to the growing interest in studying this possible multifactorial origin of psychiatric symptoms and their evolution in the medium and long term after acute infection by COVID-19 due to the potential future consequences on morbidity and mortality, public health, and socioeconomic level.

Material and methods

Study population and data collection

A mixed observational, retrospective study with a prospective component was conducted on 201 patients from the Poniente area of Almería and attended at the Poniente University Hospital in southeastern Spain, with a reference population of 265,000 inhabitants. The entire study population was included. The patients were selected in outpatient clinics for first assistance after hospital discharge in the second month. Medical and demographic data were retrospectively collected from a checklist of psychiatric and physical symptoms at the second month of discharge. Subsequent telephone follow-up was made to assess the clinical situation at 12 and 24 months. For the patients admitted in 2021, the 12-month clinical information was obtained prospectively. In the 2020 sample, the 12-month information had to be obtained retrospectively as these patients were in their second year of evolution. The 24-month evolution data were obtained prospectively from the 2020 sample. The study included patients over 18 who survived severe COVID-19 pneumonia from March 2020 to August 2021 and were hospitalized in Internal Medicine or the Intensive Care Unit (ICU) and were scheduled for outpatient consultation for medical review. Patients with severe pluripathology, encephalopathy, and pre-infection dementia were excluded.

The study was conducted following the Declaration of Helsinki and following the provisions of articles 12 of Law 14/2007 of July 3 on biomedical research and 60 of Royal Legislative Decree1/2015 of July 24, and Organic Law 3/2018 of December 5, on the Protection of Personal Data and Guarantee of Digital Rights. The data were collected anonymized, with no direct intervention with the subjects

included in the study. The Provincial Research Ethics Committee of Almería approved the study with reference PI_22_09.

Study variables

The data were obtained through the electronic medical record registered in the digital platform of the Andalusian Health System (SAS). The variables included were: age, sex, residents' origin country, obesity, psychiatric symptoms (depressive symptoms and insomnia, manic clinic, psychosis), other persistent symptoms (headache, odynophagia, anosmia, ageusia, pain, dyspnea, diarrhea, vomiting, fatigue, dermatitis, alopecia, distal tremor), previous work, days of stay in Internal Medicine ward and/ICU, orotracheal intubation (OTI) during ICU stay, C-reactive protein one month after hospital discharge, history of anxiety/depression, previous psychotropic drug use, psychotropic drug initiation, corticosteroid use at discharge, toxic use, having a severe mental disorder (bipolar disorder, schizophrenia, personality disorders, eating disorder), delirium in ICU, and medical comorbidity. Additionally, depressive, anxious, and insomnia symptoms and fatigue at 2, 12, and 24 months, Hamilton depression, Hamilton anxiety, and Insomnia Severity Index (ISI) scales at 12 and 24 months to evaluate depressive, anxiety and insomnia symptoms.

Statistical analysis

The collected data were entered into an anonymized database. A descriptive analysis of the demographic variables of the study population was performed. For this purpose, qualitative variables were expressed as frequencies and percentages. Quantitative variables were defined as measures of central tendency and dispersion (arithmetic means, standard deviation). For comparisons of the different variables in each clinical variable (insomnia, depression, anxiety) of the patients, the Student's *t*-test for independent samples will be used if these are distributed according to a normal distribution otherwise the Mann–Whitney test. All tests and intervals will be performed with a confidence level of 95. Fisher's exact or Pearson's Chi-square test will be used to compare qualitative variables.

Possible risk factors associated with presenting the clinical variable of interest were evaluated using multivariate analysis. A binary logistic regression model was used to analyze the possible risk factors associated with psychiatric problems in patients hospitalized for COVID-19 in 2020/2021 in the second month after hospital discharge. The handling of missing data was carried out using the hot-deck method. The analysis was performed using SPSS version 26 software (IBM Inc., Armonk, NY, USA), establishing a confidence level of 0.05.

Results

A total of 201 patients were recruited. The sociodemographic and clinical variables of the study population are shown in Table 1. The mean age was 57.5 ± 13.3 years, with the youngest 26 and the oldest 86 years old. 67.2% of the sample were men, with a predominance of Spanish nationality (72.1%), and 50.2% were in the active labor force. Of those admitted, 43.3% required admission to the ICU. IMV with OTI was accurate in 17.9% of patients, with ICU delirium recorded in 7.5% of the total sample. Blood C-reactive protein (CRP) levels were greater than or equal to 0.5 mg/dl in 33.6%. Persistent somatic symptoms were detected in 69.7% of patients. Neuropsychiatric clinic (depressive symptomatology, anxiety, insomnia, cognitive deficits) was present in 55.7% of the sample, with insomnia in 37.3%, anxiety in 22.4%, and depressive clinic in 21.4%. The proportion of patients who passed the pre-specified cutoffs of these scales that had clinically relevant depression/anxiety/insomnia at 12 months were 13.5%,39.6%, and

Table 1
Sociodemographic variables and clinical conditions at 60 days.

	Frequency	%
Sex		
Male	135	67.0
Female	66	33.0
Age (years)		
25–40	22	11.0
41–50	43	21.0
51–60	51	25.0
61–74	59	29.0
75–90	26	13.0
Country group		
Northafricans	34	17.0
Subsaharans	2	1.0
Hispanics	11	5.5
Spanish	145	72.0
East Europeans	8	4.0
Arabian	1	0.5
Academic level		
without studies	45	22.4
Basic studies	80	39.8
Medium studies	32	15.9
Superior studies	22	10.9
N/A	22	10.9
Job		
Pensioner	70	35.0
Employee	101	50.0
Unemployed	16	8.0
N/A	14	7.0
Psychotropics history		
No	167	83.0
Yes	34	17.0
Mental health history		
No	166	83.0
Yes	35	17.0
Overweight/obesity		
No	45	24.7
Yes	137	75.3
Comorbidity		
No	107	53.2
Yes	94	46.8
Diabetes mellitus/hypertension de novo		
No	194	96.5
Yes	7	3.5
Toxics		
No	175	87.1
Yes	26	12.9
ICU		
No	114	57.0
Yes	87	43.0
OTI		
No	51	25.0
Yes	36	18.0
No ICU	114	57.0
Corticosteroids		
No	68	33.8
Yes	133	66.2
Psychotropics de novo		
No	155	77.1
Yes	46	22.9
Neuropsychiatric symptoms		
No	89	44.0
Yes	112	56.0
Depressive symptoms		
No	158	79.0
Yes	43	21.0

Table 1
(*Continued*)

	Frequency	%
Anxiety		
No	156	78.0
Yes	45	22.0
Insomnia		
No	126	63.0
Yes	75	37.0
Manic		
No	200	99.5
Yes	1	0.5
Psychosis		
No	200	99.5
Yes	1	0.5
ICU delirium		
No	186	92.5
Yes	15	7.5
Cognitive impairment		
No	143	71.0
Yes	58	29.0
Non psychiatric symptoms persistent		
No	61	30.3
Yes	140	69.7
Fatigue		
No	116	57.7
Yes	85	42.3
Pain		
No	144	71.6
Yes	48	23.9
Distal tremor		
No	174	86.6
Yes	27	13.4
Dyspnea		
No	139	69.2
Yes	62	30.8
Alopecia		
No	158	78.6
Yes	43	21.4
Polyneuropathy		
No	173	86.1
Yes	28	13.9
C reactive protein		
<0.5	113	66.5
0.6–1.5	43	25.3
1.6–2.5	8	4.7
2.6–3.5	3	1.8
>3.5	3	1.8

24%, respectively, for Hamilton depression, Hamilton anxiety, and ISI scales. At 24 months, the proportion was 9.2%, 29.9%, and 23% respectively.

Depressive, anxiety, and insomnia symptoms are shown in bivariate Tables S1–S3. Depressive and anxiety symptoms were significantly associated with the female sex. Significant differences were also obtained with other variables and insomnia, such as persistent somatic symptoms, pain, dyspnea, fatigue, mental health history, and psychopharmacological treatment before infection. Statistical significance was established for the inflammatory parameter CRP with depressive symptoms.

When analyzing the evolution of the clinical variables over time (Tables 2–4), it was observed that there were no significant differences between the percentages of depressive symptoms, insomnia, and anxiety at 2, 12, and 24 months. There were differences in the case of the fatigue variable. Depressive symptoms have a higher average score on the Hamilton depressive scales than not; when applying the Mann–Whitney test, statistically significant differences are found. We obtain the same findings in the case of anxiety and the Hamilton anxiety scale and insomnia with the ISI scale. The scale mean score exceed the cutoff point for depressive, anxious, and insomnia symptoms. The variable fatigue was significantly associated with depression at 12 and 24 months. Variable insomnia and anxiety maintained a significant relationship at 12 months but not at 24 months.

The results of the multilevel analysis are shown in Table 5. The variables with the most significant capacity to predict the clinical variable depression are female gender, presence of fatigue, having previously consumed psychotropic drugs, and C-reactive protein > 3.6. The multivariate model showed significant differences in anxiety when associated with the female sex, presenting pain, fatigue, insomnia, having a history of anxiety and depression, and ICU admission with orotracheal intubation. Having higher education was correlated with anxiety. Logistic regression offered statistically significant differences in the case of insomnia in the association of anosmia and ageusia anxiety, cognitive complaints, dyspnea, and with C-reactive protein > 2.6.

Discussion

This study analyzed psychosocial, clinical, and biological variables as possible predictors of a medium- and long-term psychiatric clinic in patients who passed moderate or severe COVID-19. WHO in 2017 found the prevalence of depression in the general population to be 4.4% and 3.6% for anxiety.[16] Following the pandemic, there was an overall increase in mental health symptoms during the first two months, subsequently decreasing and becoming comparable to previous levels for most symptoms by the mid-20s.[17]

The prevalence of psychiatric symptoms in the general population was estimated to be 4.4% in 2017. The prevalence of psychiatric symptoms in our sample revealed high percentages of depressive symptoms, anxiety, and insomnia at mid-term (2nd month),[6,18] persisting elevated at 12 and 24 months.[19] There were no significant differences in the percentages of psychiatric symptoms throughout the follow-up period. Not all the studies reviewed observed this persistence of symptoms beyond the medium term.[20] Having depressive symptoms has a higher average score on the Hamilton depressive scales than not; when applying Mann–Whitney test, statistically significant differences are found. We obtain the same findings in the case of anxiety and the Hamilton anxiety scale and insomnia with the ISI scale.

The multilevel analysis revealed the existence of a group of variables significantly associated with the development of psychiatric symptoms in the medium term. The CRP variable, considered a systemic proinflammatory marker,[21] was shown to be a clinical predictor in our study, being significantly associated with suffering from depressive symptoms and in line with the inflammatory hypothesis of depression.[22] The general population has a higher prevalence of clinical depression or anxiety in the female sex.[23] As expected, the female sex showed a high association, presenting the male sex as a protective effect.

Some studies have suggested that a pre-existing psychiatric disorder increases susceptibility to SARS-CoV-2 infection, which could mean a more significant presence of a history of mental health in this population.[24,25] Our study detected no record of severe mental illness, although a history of anxiety and depression, and psychotropic drug use was detected. In turn, they were significantly associated with the persistence of anxious and depressive symptoms, respectively, a circumstance that could be expected from an additional predisposition.

Table 2
Monitoring of fatigue, anxiety, depression, and insomnia at different evaluation periods.

	2nd month		12th month		24th month		Chi-squared[a]	*p*-Value[a]
	Frequency	%	Frequency	%	Frequency	%		
Fatigue								
No	116	57.7	141	77.9	70	34.8	26.02	0.001
Yes	85	42.3	40	22.1	15	7.5		
Anxiety								
No	156	77.6	140	76.5	67	77.9	0.09	0.950
Yes	45	22.4	43	23.5	19	7.5		
Depression								
No	158	78.6	142	77.6	71	82.6	0.68	0.640
Yes	43	21.4	41	22.4	15	17.4		
Insomnia								
No	126	63.0	117	64.0	60	70.0	1.38	0.490
Yes	75	37.0	67	36.0	26	30.0		

[a] Chi-squared test.

Table 3
Relationship between depression, anxiety and insomnia symptoms and scales at different evaluation periods.

	n	Mean	SD	*p*-Value[a]
Depression				
HDRS (12th month)				
No	71	0.56	1.33	<0.001
Yes	25	8.92	4.78	
HDRS (24th month)				
No	71	0.46	1.07	<0.001
Yes	15	9.40	6.69	
Anxiety				
HARS (12th month)				
No	74	0.96	2.01	<0.001
Yes	22	13.41	8.39	
HARS (24th month)				
No	67	0.37	1.14	<0.001
Yes	19	11.84	8.33	
Insomnia				
ISI (12th month)				
No	58	0.16	0.49	<0.001
Yes	38	9.89	5.82	
ISI (24th month)				
No	60	0.27	1.10	<0.001
Yes	26	12.08	6.46	

[a] *U* de Mann–Whitney.

According to the published literature, older age, male sex, and medical comorbidity were associated with greater severity.[26] There was no statistical significance between psychopathology and age. Male sex could be a protective factor. Medical comorbidity is a factor that generates neuropsychiatric symptoms in COVID-19 in the medium and long term.[27] In our study, medical comorbidity in COVID-19 patients who recovered from the acute phase was associated with a higher probability of presenting anxiety in the medium term. The greater severity in our patients was determined by the stay in the ICU or the presence of invasive mechanical ventilation with orotracheal intubation (IOT). According to our findings, despite the implicit severity of the disease, being hospitalized patients, the ICU factor and the IOT factor were not associated with any psychiatric symptoms in the medium term in the multivariate. Indeed, the OTI factor was associated with anxiety in the medium term in the multivariate, a circumstance not extensible to the subgroup of patients with delirium in the ICU, in which an association with anxiety was observed.[11,12] Analyzing longer-term results (16 months), a large prospective observational study, severity, determined by days of bed rest, was associated with persistent mental health symptoms.[28] It is well known that post-ICU syndrome symptoms (PICS) and post-COVID-19 syndrome symptoms (in ICU patients) might overlap, so the prevalence of psychiatric symptoms might be overestimated in this maximum severity subgroup.[29]

Persistent physical symptoms (1–3 months) and abnormality in the HADS anxiety and depression scales were previously associated.[30] Our study found this association in the bivariate but was not sustained in the multivariate. However, we did obtain a significant association in the multilevel analysis when analyzing persistent physical symptoms separately for the variables dyspnea, pain, and fatigue. Low FEV1 levels have been associated with mild to severe levels of depression.[11] An association has been suggested between persistent dyspnea and depression and anxiety.[12] Our results established an association in the bivariate analysis for dyspnea in all the models analyzed, but it was only sustained for insomnia in the multilevel analysis.

Pain is usually related to a more significant presence of anxious and depressive symptoms,[31] compatible with the high level of significance found in the multivariate analysis with anxiety. There is not much literature associating fatigue with the presence of psychiatric symptoms in the context of COVID-19 infection. It has been suggested that psychopathology was associated with persistent fatigue after acute infection and independently of clinical severity.[32]

Fatigue persisted at 12 and 24 months, although the percentage of patients presenting fatigue decreased from the second month to two years of follow-up, these differences being statistically significant. Fatigue was significantly associated with patients with depressive and anxious symptoms, even in patients evaluated at 24 months.

The upper nasal transcriptional pathway and neurotropism of coronaviruses and SARS-CoV-2 have been hypothesized.[33,34] The association observed between anosmia and psychiatric symptoms, in our case insomnia, is described in several studies, surpassing this association with more worrisome symptoms such as fever, cough, and respiratory distress.[35,36] Certain drugs may have affected the central nervous system. The literature relates the use of corticoids with affective, psychotic, cognitive, or sleep symptoms.[37] In our study, no association was observed with any of the psychiatric disorders analyzed.

Psychosocial factors are influential factors in the presence of psychiatric symptoms. Having superior studies represents a 7-fold increased risk of anxiety compared to not having education in our sample. No bibliography has been found to corroborate these findings, so these results could be considered noteworthy when evaluating this patient profile. Having a family, among other factors, was not associated with this patient profile. This aspect provides value regarding physical and mental health.[38]

Table 4
Relationship between psychiatric symptoms and fatigue in the twelfth and twenty-fourth months.

	Fatigue 12th/24th months			Chi-squared	*p*-Value
	No	Yes	Total		
Depression (12th month)					
No	51	12	63	15.22	<0.001
Yes	6	12	18		
Total	57	24	81		
Depression (24th month)					
No	21	4	25	4.11[a]	0.043
Yes	2	4	6		
Total	23	8	31		
Anxiety (12th month)					
No	50	12	62	13.38	<0.001
Yes	7	12	19		
Total	57	24	81		
Anxiety (24th month)					
No	20	4	24	2.76[a]	0.096
Yes	3	4	7		
Total	23	8	31		
Insomnia (12th month)					
No	40	9	49	7.54	0.006
Yes	17	15	32		
Total	57	24	81		
Insomnia (24th month)					
No	17	3	20	2.03[a]	0.154
Yes	6	5	11		
Total	23	8	31		

[a] Yates correction.

Table 5
Multiple regression analysis of the risk of suffering depressive symptoms, insomnia or anxiety adjusted for several potential risk factors.

		95% C.I. for OR		
	OR	Lower	Upper	*p*-Value
Binary logistic regression for depressive clinic				
Sex	0.16	0.05	0.50	0.001
Fatigue	17.23	4.42	67.18	<0.001
Psychotropic history	7.08	1.76	28.47	0.006
CPR[a] (≤0.5)	Ref.			0.019
CPR (0.6–1.5)	1.62	0.48	5.47	0.435
CPR (1.6–2.5)	0.38	0.02	5.39	0.481
CPR (2.6–3.5)	11.05	0.92	132.23	0.058
CPR (>3.6)	83.10	4.44	1555.59	0.003
Binary logistic regression for insomnia				
Cognitive impairment	3.94	1.77	8.76	<0.001
Anosmia ageusia	3.40	1.46	7.95	0.005
Dyspnea	3.56	1.66	7.63	0.001
CPR (≤0.5)	Ref.			0.014
CPR (0.6–1.5)	0.54	0.23	1.28	0.165
CPR (1.6–2.5)	1.69	0.33	8.64	0.525
CPR (2.6–3.5)	16.99	1.56	185.19	0.020
CPR (>3.6)	14.60	1.22	174.92	0.034
Binary logistic regression for anxiety				
Sex	0.21	0.07	0.56	0.002
OTI[b]	1.85	1.00	3.42	0.049
Mental health history	11.10	3.58	34.35	<0.001
Fatigue	3.11	1.09	8.86	0.033
Pain	3.81	1.41	10.31	0.008
Academic level (no studies)	Ref.			0.094
Academic level (basics)	1.95	0.49	7.76	0.341
Academic level (medium)	1.14	0.21	6.11	0.870
Academic level (superior)	7.18	1.29	39.95	0.024

Dependent variables: Depressive symptoms. Insomnia. Anxiety. Independent variables: Sex. Age. Country. OTI. UCI delirium. Cognitive impairment 2nd month. Mental health history. Fatigue. Pain. Anosmia/ageusia. Dyspnea. Diabetes mellitus/Hypertension de Novo. Non Psychiatric Symptoms Persistent. Psychotropic History. Job. Corticosteroids. PCR. Academic level.

[a] CPR: C-reactive protein.

[b] OTI: orotracheal intubation.

This study has some limitations. Although the selected hospital covers a wide population area and the patients were selected based on their availability when attending outpatient clinics, a selection bias should be considered when assessing the conclusions' validity. Another possible limitation is the potential recall bias regarding patients recruited 24 months after acute infection and asked about their clinical status at 12 months. Using prospective methods to collect data on psychiatric symptoms would have been interesting. It could reduce the risk of recall bias and improve data quality. It is important to emphasize that the data collected on psychiatric symptoms were obtained from post-discharge review clinical interviews by COVID-19, not being on-demand consultations by psychiatric clinics, in which the patients were asked about those symptoms and being able to detect milder symptoms, which otherwise would have gone unnoticed by the health system, for descriptive purposes of the actual dimension of the problem. The 24-month follow-up was only obtained from patients who became ill in 2020. This study also has some strengths. Its main interest lies in bringing together a wide range of psychosocial, clinical, and biological variables to determine hypothetical predictors that may intervene in the presence of increased psychiatric symptoms in the medium and long term in patients with moderate and severe COVID-19. The two-year follow-up gives the study added value due to the scarcity of existing literature that assesses the clinical situation in such a long term.

Conclusions

This research unveils factors that can predict psychiatric symptoms in patients at mid-term. These factors include being female, experiencing fatigue, having a history of anxiety or depression, taking psychotropic drugs, having high levels of C-reactive protein in the depressive clinic, and having a history of delirium in the ICU. Regarding psychosocial factors, having superior studies represents a greater risk of anxiety. The persistence of psychiatric symptoms in the two years of follow-up shows us novel and interesting information for providing adequate clinical care and allocating mental health resources for patients affected by COVID-19. This research additionally emphasizes the importance of studying the long-term consequences of this disease.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Provincial Research Ethics Committee of Almería (reference PI_22_09).

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.medcli.2024.05.002.

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