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REVIEW

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Post-traumatic stress disorder, anxiety and depression in post-COVID19 patients: integrative review

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ABSTRACT

Background: Global estimates point to high prevalence of neuropsychiatric disorders in individuals hospitalized for COVID-19. In Brazil, anxiety and depression rates resulting from SARS-CoV-2 infection range from 29.7% to 68%, respectively, being more prevalent in young women, with lower educational level, with comorbidities and psychological problems. previous. **Objective:** Identify possible causes, verify prevalence and identify risk factors for anxiety, depression and post-traumatic stress disorder (PTSD) in patients hospitalized for COVID-19. **Methods:** An integrative literature review was carried out involving retrospective and/or prospective cohort studies and population-based clinical trials published in the last three years. The main evidence on the relationship between neuropsychiatric disorders and intrinsic changes in neuroimmunomodulation parameters was also raised. **Results:** Twenty-one studies were included that addressed the presence of symptoms of PTSD, anxiety, depression, fatigue in sleep disorders in COVID19 survivors. **Conclusion:** With this literature review, it can be concluded that PTSD, anxiety, depression, fatigue and sleep disturbances are highly prevalent symptoms in COVID-19 survivors, being persistent for up to one-year post-infection.

Keywords: Post-traumatic stress disorder, Anxiety, Depression, Fatigue, Sleep disorders, SARS-CoV-2.

BACKGROUND

Global estimates point to a prevalence of 17.9% of neuropsychiatric disorders in individuals hospitalized for COVID-19[(1)]. These rates are similar to those reported in survivors of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), whose psychiatric disorders were persistent for a period of up to twelve months[(2,3)]. In Brazil, anxiety and depression rates resulting from SARS-CoV-2 infection range from 29.7% to 68%, respectively[(4,5)], which are more prevalent in young females with a lower educational level, with comorbidities and previous psychological problems[(6,7)].

Excessive cytokine activation and a compromised cellular immune response caused by direct infection or indirect CNS involvement by SARS-CoV-2 can cause neurological complications at different levels of severity[(8,9)]. Regarding the neuropsychiatric manifestations in these patients, anxiety, depression, sleep disorders and post-traumatic stress disorder (PTSD) stand out as the most frequent[(10,11)].

In view of the above, the objective of the present study was to analyze the possible causes, raise the prevalence and identify risk factors for anxiety, depression and PTSD in patients hospitalized for COVID-19 through an integrative literature review.

METHODS

Manuscript search and selection strategy

This study is characterized as an integrative literature review. The search for articles was carried out in the MEDLINE/PubMed, SciELO and LILACS databases from January to April 2022. The search strategy is shown in Figure 1.

Eligibility Criteria

Prospective and retrospective cross-sectional and cohort observational studies and randomized clinical trials involving adult patients (≥ 18 years), of both sexes and regardless of ethnicity, with a previous diagnosis confirmed positive for COVID-19 through laboratory tests were eligible. The final sample consisted of complete scientific articles published in English, which evaluated PTSD through scales and psychological tests with validation described in the literature. Editorials, consensus reports, comments, letters to the editor and research protocols were excluded.

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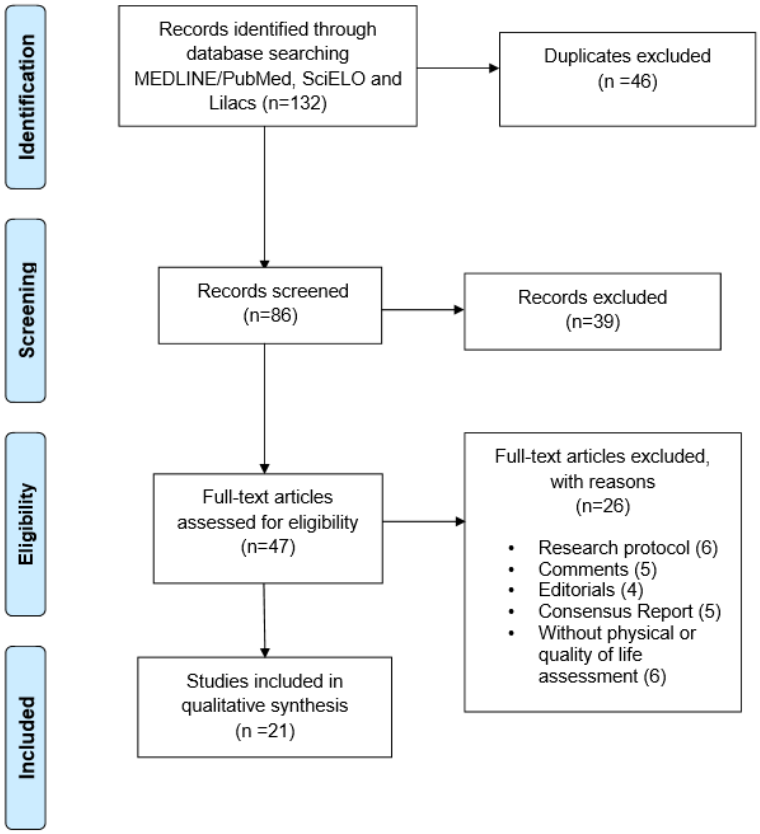

Figure 1. Prisma Flowchart - Selection of studies.

Table 1. Search strategy of PubMed

Search	Query
#1	“COVID-19”[Mesh Terms]
#2	“SARS-CoV-2”[Mesh Terms]
#3	“COVID-19”[Title/Abstract] OR “SARS-CoV-2”[Title/Abstract
#4	#1 OR #2 OR #3
#5	“critical care”[Mesh Terms]
#6	“Intensive Care Units”[Mesh Terms]
#7	“post-acute COVID-19 syndrome”[Supplementary Concept]
#8	“follow-up”[Title/Abstract] OR “intensive care unit”[Title/Abstract] OR “ICU”[Title/Abstract] OR “critical illness”[Title/Abstract] OR “Intensive care center”[Title/Abstract] OR “Mechanical ventilation”[Title/Abstract] OR “intensive care unit acquired weakness”[Title/Abstract] OR “post-intensive care syndrome”[Title/Abstract] OR "Hospital”[Title/Abstract] OR “Hospitalization”[Title/Abstract] OR "Hospital internment”[Title/Abstract] OR “Hospital Admission”[Title/Abstract] OR “Nursery”[Title/Abstract]
#9	#5 OR #6 OR #7 OR #8
#10	“psychological assessment”[Title/Abstract] OR "psychological evaluation”[Title/Abstract] OR “psychological disorders”[Title/Abstract] OR “Psychiatric disorders” [Title/Abstract] OR “psychotherapy”[Title/Abstract] OR “psychological measurements”[Title/Abstract] OR “post traumatic stress disorder” [Title/Abstract OR “PTSD”[Title/Abstract] OR “anxiety”[Title/Abstract] OR “depression”[Title/Abstract] OR “health-related quality of life” [Title/Abstract]
#11	#4 AND #9 AND #10

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RESULTS

The studies that were included in this review are shown in Table II. Articles were stratified according to authors, year and country of publication, sample size, mean age of participants, psychiatric disorders, comorbidities, follow-up time, instruments used in the assessment, and main outcomes.

Table 2. Incidence of psychiatric disorders in survivors of COVID-19 infection.

Author, Year, Country	Sample size	Average age	Psychiatric disorders	Comorbidities	Post COVID-19 follow-up	Instrument	Outcome
Albu et al., 2021[37]; Spain	30	54	47%	SAH; DM	> 3 months	MFIS, PSQI, WHOQOL-BREF	Cognitive deficit and fatigue were the most frequent symptoms in rehabilitation
Bellan et al., 2021[20], Italy	238	61	17,20%	DM (15,1%); SAH (41,2%); Obesity (10,5%)	3-4 months	IES-R	Male sex was an independent risk factor for psychiatric disorders
D'Cruz et al., 2021[36]; England	119	59	25%	SAH (45%); DM (34,5%)	61 days	TSQ; GAD-7; PHQ-9	Psychiatric disorders were associated with functional disability
Iqbal et al., 2021[29]; Pakistan	158	40	53%	SAH (13,3%); asthma (10,1%); DM (9,5%)	80-101 days	EQ-5D-5L	There was no association between disease recovery time and psychiatric symptoms.
DeLorenzo et al., 2020[18]; Italy	185	57	22,20%	SAH (37,8%); DM (11,4%)	20-29 days	STAI; WHIIRS; BREF; MoCA	Female sex was an independent predictor for PTSD; Hospitalization was a protective factor for PTSD
Mazza et al., 2021[25]; Italy	226	58	9%	SAH (45,3%); DM (38,2%); Obesity (47,1%)	3 months	IES; BDI; STAI; WHIIRS	PTSD symptoms and anxiety reduced after 3 months of follow-up
Matalon et al., 2021[23]; Israel	64	47,1	19%	NR	1 month	PROMIS	There was a reduction in anxiety and depression levels after one month
Huang et al., 2021[30]; China	1733	57	23%	SAH (27,2%); DM (14,6%); CVD (6,4%)	175-199 days	EQ-5D-5L; PCL-C; GAD-7	After one year of follow-up, there was improvement in physical and functional capacity.

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Mazza et al., 2020[24]; Italy	402	57,8	28%	NR	31 days	IES-R; PCL-5; BDI-13; STAI; WHHIRS; GAD-7	Systemic inflammation was significantly associated with PTSD
Maley et al., 2022[44]; USA	60	59	33%	SAH (28,3%); DM (26,7%)	182 days	HADS; IES-6	Mental disorders were associated with sedation and time on IMV
Méndez et al., 2021[32]; Spain	179	57	25,10%	SAH (32,4%); DM (16,2%)	2 months	GAD-7; PHQ-2; DTS	Patients with psychiatric disorders had a higher prevalence of neurocognitive impairment
Morin et al., 2021[34]; France	478	61	7%	SAH (47,1%); DM (26,8%); Obesity (37%)	4 months	Q3PC	Psychiatric disorders were less frequent in patients who stayed in the ICU
Poyraz et al., 2021[19]; Turkey	284	39,7	34,50%	NR	50 days	IES-R; HADS; PSQI	Female sex was an independent predictor for PTSD; Hospitalization was a protective factor for PTSD
Romero-Duarte et al., 2021[22]; Spain	789	63	6,80%	SAH (51,3%); DM (20,8%); CVD (20,6%)	6 months	Clinical intervention	Depressive symptoms were more prevalent in women
Sami et al., 2020[35]; Iran	490	56,5	8%	SAH (35%); DM (28%)	1 months	PHQ-9, DASS-21	10-13% had fatigue and 8% had sleep disturbances. These factors were independent of disease severity.
Sykes et al., 2021[39]; USA	134	58	47,80%	DM (22%); HAS (41%); Asthma (14,2%)	46-167 days	EQ-5D-5L	After 100 days of follow-up, 43% of patients had anxiety and 35% had sleep disturbances.
Taquet et al., 2021[12]; USA	57,476	46	17,39%	SAH (30%); DM (15,5%); Obesity (18,1%)	6 months	ICD-10	Mood and anxiety disorders were prevalent after 3 months of disease resolution
Venturelli et al., 2021[43]; Italy	767	63	11,00%	SAH (21,7%); DM (7,4%)	81 days	IES-R, HADS, RSA, MoCA	COVID-19 survivors have a wide range of psychiatric disorders

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Xiong et al., 2021[40]; China	538	52	22,70%	SAH (15,2%); DM (7,4%)	91-116 days	Self report	Psychiatric disorders and functional sequelae were associated with disease severity
Tarsitani et al, 2021[42]; Italy	115	57	10,40%	DPOC (13%)	3 months	PCL5	Male sex was protective for PTSD
Damiano et al., 2022[38]; Brazil	425	55,7	13,60%	NR	6 – 9 months	HAD; ASQ; PCL-C	There was no association between infection severity and psychiatric symptoms.

***Note:** ASQ: Ask Suicide-Screening Questions; BDI: Beck Depression Inventory; BREF: DM: diabetes mellitus; DASS: Depression Anxiety Stress Scales; CVD: cardiovascular disease; EQ-5D-5L: Euro Quality of life - five dimensions - five levels; GAD-7: Generalized Anxiety Disorder 7; HADS: Hospital Anxiety and Depression Scale; SAH: systemic arterial hypertension; HRQL: IES-R: Impact of Events Scale-Revised; MoCA: Montreal Cognitive Assessment; NR: not reported; PCL-5: PTSD Checklist for DSM-5; PHQ-9: Patient Health Questionnaire 9; PROMIS: Patient-Reported Outcomes Measurement Information System; PSQI: Pittsburgh Sleep Quality Index; Q3PC: Cognitive Screening Questionnaire; RSA: Resilience Scale for Adults; STAI: State-Trait Anxiety Inventory; PTSD: traumatic stress disorder; TSQ: Trauma Screening Questionnaire; ICU: intensive care unit; IMV: invasive mechanical ventilation; WHIIRS: Women's Health Initiative Insomnia Rating Scale.

DISCUSSION

Incidence of neuropsychiatric manifestations resulting from COVID-19

A population-based study involving 62.354 COVID-19 survivors found that the onset of psychiatric disorders was greater in individuals with no prior history of mental illness in the first 90 days after illness diagnosis[12]. According to other authors, these conditions vary in intensity and duration[13], and generally occur during and/or after the resolution of the infection[14,15]. According to Rogers et al. (2020), 32.2% of critically ill patients who survived COVID-19 had PTSD symptoms[16] and in the study by Marvaldi et al. (2021), it was observed that 14.9% of patients had anxiety and depression[17].

According to some recent studies, the main risk factors for developing PTSD post-COVID-19 include female gender[18,19], disease severity, presence of comorbidities, and pre-existing anxiety and depression disorders[20-22]. Neuroplastic changes, invasive clinical procedures, limited communication skills, high drug requirements, and long hospital stays can exacerbate or consolidate PTSD-associated symptoms[23].

In an interesting retrospective study conducted by Mazza et al. in 2020 involving 402 COVID-19 survivors, 56% of patients were observed to have at least one psychiatric disorder[24]. In another study published in 2021 by Mazza et al., it was found that PTSD-associated symptoms persisted for more than three months after disease resolution[25]. According to several studies, no differences were observed between levels of anxiety and depression with disease severity and length of hospital stay[21,26,27]. These findings suggest that the psychological implications may not be directly related to COVID-19[18,28,29]. In a cohort of 1276 individuals hospitalized for COVID-19, it was shown that during the one-year follow-up, there was a significant increase in mood disorders (30). Two other studies found that short and medium-term outcomes after hospitalization for COVID-19 had a negative impact on functional capacity and quality of life[31,32]. Naidu et al., observed that post-COVID19 patients who had prolonged stress were more likely to present, after hospital discharge, conditions of dyspnea, myalgia, anorexia and mental confusion[33].

In a multicenter study involving 22,330 patients compromised by COVID-19, it was evidenced that high levels of anxiety and depression were associated with the presence of sleep disorders[34]. In other studies, the association of anxiety and depression with high levels of fatigue[35], cognitive impairment[36,37], and a significant portion of patients who presented a significant reduction in the capacity of executive function, attention, and memory, compromise the performing daily activities[32,38,39,40].

The study conducted by Bellan et al. in 2021, showed that neuropsychiatric symptoms, particularly COVID-19-related PTSD, can persist for more than twelve months, after disease resolution in up to 20% of cases[41]. On the other hand, in a cohort conducted with Italian post-COVID19 patients, 10.4% of the sample had PTSD during hospitalization[42].

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It was also observed that many patients had persistent dyspnea associated with anxiety and PTSD, negatively impacting recovery and quality of life[43]. Recent data point to abnormalities in different neurochemical systems resulting from SARS-CoV-2 infection[44,45]. Therefore, these findings should be further investigated as the complex result of multiple interactions between various brain networks.

Instruments for the assessment of neuropsychiatric disorders associated with COVID-19.

Most of the instruments used to assess neuropsychiatric disorders are composed of questionnaires, scales, and self-applied psychometric inventories. These are used by clinicians and researchers due to the ease of administration, low cost, and the possibility of obtaining accurate information from the respondent's point of view. Among the studies analyzed, several scales were used in combination for psychological/psychiatric assessment of patients infected with SARS-CoV-2. The categories/classes of instruments that emerged from the results show a multifaceted character of the anxiety and PTSD constructs.

This diversity of approaches in the evaluation of neuropsychiatric manifestations brings the benefit of a greater number of valid alternatives for researchers and clinicians, depending on the purpose of the evaluation (specific clinical diagnosis of a disorder, the severity of the disorder, global assessment in a specific context. However, the adoption of specific scales in the verification of these symptoms associated with viral infection can be of great value, since it would allow comparisons and groupings of several clinical studies.

Role of the neuroendocrine-immune axis in psychiatric disorders

The entry of SARS-CoV-2 into the host cell occurs via the interaction of the spike protein (S) with the cellular receptor for angiotensin-converting enzyme 2 (ACE2). The binding of SARS-CoV-2 S protein with ACE2 receptors on the cell surface is responsible for activating intracellular signaling pathways, which result in the formation of endosomal vesicles containing the virus[46-48]. SARS-CoV-2 can reach the CNS via the anterograde neuronal circuit through the olfactory nerves and blood circulation[49]. In the first case, the virus spreads in a retrograde way, through trans-synaptic transfer, with subsequent axonal transport to the bodies of neuronal cells[9]. Through the blood-brain barrier, the infection can occur by vascular endothelium cells, which express ACE2 receptors, with the virus being transported through the endothelium to neurons and glial cells, or by infection of leukocytes, whose secretion of cytokines and macrophages secondarily promotes neurological cell injury[50]. The higher rate of systemic immuno-inflammation, characterized by the count of circulating neutrophils, lymphocytes, and platelets, was significantly associated with the severity of psychopathological symptoms[25].

An expressive relationship between COVID-19-related neurological symptoms and immune markers was evidenced by the high level of circulating cytokines, including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF-α). These findings indicate that persistent inflammation and hypoxic injury can trigger severe neuropsychiatric impairments[51-53].

Benedetti et al., using functional magnetic resonance imaging, found that the severity of depressive symptoms was associated with a reduction in gray matter volumes in the anterior cingulate cortex[54]. Consistent with these results, post-mortem examinations of brains from COVID-19 patients revealed homeostatic changes in astrocytes and microglia, consistent with morphological changes found in major psychiatric disorders[55]. According to the study by Chaudhury et al (2021), direct and indirect pathways of brain dysfunction may also explain the short- and long-term impacts of COVID-19, even in asymptomatic patients[56].

Some studies performed with functional genomics have revealed that different types of viral infections, including SARS-CoV-2 lead to dysfunction of the hypothalamic-pituitary-adrenocortical (HPA) axis[57-59]. The “cytokine storm” triggered by COVID-19 may contribute to the activation of this neuroendocrine axis, increasing the production of glucocorticoids[60]. Therefore, the neuropathological mechanisms of the psychiatric sequelae associated with COVID-19 need to be better elucidated.

The depletion of ACE2 by SARS-CoV-2 can directly interrupt or inhibit the activation of psychoneuroendocrine pathways related to PTSD, anxiety, and depression. This process occurs by the massive secretion at the systemic level and in the CNS, of several pro-inflammatory cytokines, such as IL-2, IL-6, TNF-α, and interferon-gamma (IFN-γ), which compromise the synthesis, release, and the reuptake of some neurotransmitters, including dopamine, norepinephrine, and serotonin[61,62].

Different cytokines act on the hypothalamus, pituitary, and adrenal cortex contributing to the suppression of cortisol concentrations and sympathetic-adrenal hyperactivation associated with secondary hypofunction of the HPA axis[59,63-65]. In critically ill patients with COVID-19, plasma cortisol levels were

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significantly lower, both in the acute phase and after disease resolution, relative to those with moderate symptoms[14]. On the other hand, low cortisol levels have also been identified in mild or asymptomatic cases of COVID-19[66]. In light of this scenario, further research is needed to assess how changes in cortisol levels relate to the intensity of mental disorders.

According to the state of the art regarding the significant presence of PTSD, anxiety, depression, and sleep disorders in post-COVID19 patients, the implementation of psychological intervention in the multi-professional rehabilitation team can be recommended[45].

CONCLUSION

With this literature review, it can be concluded that PTSD, anxiety, depression, fatigue, and sleep disorders are highly prevalent symptoms in COVID-19 survivors, being persistent for up to one-year post-infection.

Authors' contribution: MMC and LVFO contributed to the elaboration of the design of the study; MMC, MCO, ACO, MEML, SKAS, JPRA, RSM, DRPF, ALF, RSRT, RKP, RPV, SSF, LVFO development of the study and data acquisition. MMC, MCO, ACO, MEML, SKAS, JPRA, RSM, DRPF, ALF, RSRT, RKP, RPV, SSF, LVFO contributed to article design and data tabulation. MMC, MCO, ACO, MEML, SKAS, LVFO contributed to the critical review, correction and approval of the final version.

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