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Psychosis during the COVID-19 pandemic: A systematic review of case reports and case series

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ARTICLE INFO

Keywords:

COVID-19

SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2

2

Coronavirus disease 2019

Psychosis

Psychotic delusion

Hallucination

Paranoia

And schizophrenia

ABSTRACT

Background: Preliminary data suggest that patients with COVID-19 may experience psychiatric symptoms, including psychosis. We systematically reviewed the literature to evaluate the concurrence of new-onset psychosis or exacerbation of clinically stable psychosis through case reports and case series.

Methods: Six databases were searched, followed by an electronic and manual search of the relevant articles. Studies were identified using predetermined eligibility criteria. We evaluated the demographic characteristics, clinical history, course of illness, management, and prognosis of the patients in these studies.

Results: Case reports and case series, altogether consisting of 57 unique cases were included. The mean patient age for onset of psychotic symptoms was 43.4 years for men and 40.3 years for women. About 69% of patients had no prior history of psychiatric disorders. Most patients had mild COVID-19-related symptoms, with only 15 (26.3%) presenting with moderate to severe COVID-19-related disease and complications. The most commonly reported psychotic symptoms were delusions and hallucinations. Patients with psychotic symptoms were treated with antipsychotics, benzodiazepines, valproic acid, and electroconvulsive treatment. In 36 cases, psychotic symptoms resolved completely or improved significantly. Ten cases had partial improvement with residual psychotic symptoms, and one patient died due to cardiac arrest.

Conclusion: Most patients responded to a low-to-moderate dose of antipsychotics with a quick recovery. However, the residual psychiatric symptoms highlight the need for careful monitoring and longer follow-up. Clinicians should be mindful of the occurrence of psychosis due to COVID-19 infection in a subset of COVID-19 patients that can be misdiagnosed as a psychotic disorder alone.

1. Introduction

Coronaviruses are single-stranded RNA viruses, a member of the Coronavirinae family with several subtypes, most of which cause mild upper respiratory tract infections in immunocompetent individuals (Chen et al., 2020). In December 2019, the first case of atypical pneumonia was reported in Wuhan, China which was associated with a novel coronavirus, later termed severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) or more popularly as Coronavirus disease 2019 (COVID-19) (Lu et al., 2020). Since then, COVID-19 has disrupted the lives of millions worldwide (Nicola et al., 2020).

This virus is thought to enter human host cells by the angiotensin-converting enzyme 2 receptor, with little expression in the brain (Li et al., 2020). However, neurological symptoms have been observed in patients, ranging from headache and dizziness to acute cerebrovascular disease or impaired consciousness, encephalitis, anosmia, dysgeusia,

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<https://doi.org/10.1016/j.jpsychires.2022.06.041>

Received 5 November 2021; Received in revised form 15 June 2022; Accepted 24 June 2022

Available online 1 July 2022

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ataxia, and Guillain-Barre syndrome, etc. (Losy, 2021; Mao et al., 2020; Varatharaj et al., 2020). The reported prevalence of patients experiencing neurologic symptoms is variable across different studies. A study by Romero-Sánchez et al. reported that 57.4% of hospitalized COVID-19 patients experienced neurologic symptoms (Romero-Sánchez et al., 2020). Other symptoms experienced by COVID-19 patients include fever, myalgia, lethargy, dry cough, shortness of breath, abdominal pain, and diarrhea (Zhu et al., 2020).

Several possible mechanisms have demonstrated the neuropsychiatric effects exerted by COVID-19. It exerts a psychopathological sequela either by direct viral infection of the central nervous system (CNS) or by an indirect immune response (Wu et al., 2020). However, there have also been reports of viral RNA in the cerebrovascular fluid (CSF) (Watson et al., 2021). At the cellular level, the neurotropic effect of coronaviruses potentially results in neuronal injuries (Desforges et al., 2019). In animal models, the coronaviruses have been shown to proliferate in the limbic structure, which further supports the association of COVID-19 with psychiatric manifestations (Subbarao and Roberts, 2006). In addition, the immune-mediated cytokine storm that crosses the blood-brain barrier results in neuroinflammation and subsequent neuropsychiatric manifestations (Dantzer, 2018). Nevertheless, fear of illness, stigma and social isolation experienced by the COVID-19 patients are stressors that may contribute to the psychopathological outcomes (Brooks et al., 2020; Iqbal et al., 2020).

In the past, infectious disease outbreaks, including severe acute respiratory syndrome (SARS) in 2003 and the 2009 influenza A (H1N1), had long-lasting deleterious effects on public mental health (Ko et al., 2006; Yeung et al., 2017). In SARS infection, an increased antibody titer was associated with acute psychiatric manifestations (Cheng et al., 2004). The connection between locus ceruleus and influenza virus resulting in mood disorders has also been hypothesized (Manjunatha et al., 2011). Available data suggest that COVID-19 patients may experience anxiety, depression, and insomnia (Rogers et al., 2020). Case reports have reported acute psychotic disturbances in COVID-19 cases, indicating a possible relationship between psychosis and COVID-19 infection (Chacko et al., 2020). Not only this, patients with clinically stable schizophrenia have experienced worsening psychotic symptoms after contracting COVID-19 (Yao et al., 2020).

Recently published reviews have addressed the association of COVID-19 with psychosis (Smith et al., 2020; Tariku and Hajure, 2020; Watson et al., 2021). However, our study aims to systematically review the literature to evaluate the concurrence of psychosis with COVID-19 with a detailed review of demographics, past psychiatric history, current clinical presentation, a diagnostic workup for both COVID-19 and psychosis, as well as treatment, course of illness and prognosis for COVID-19 related psychosis which is unique for this review. By doing this, we hope to provide clinicians with valuable information regarding the symptomatology, course of illness, and treatment regimen that has shown significant benefit for psychosis in patients with COVID-19 patients.

2. Methods

Our systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009; Page et al., 2021). We developed the protocol in June 2021, which was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on September 6th, 2021 (CRD42021264491). [Supplementary Table 1](#) has the PRISMA checklist.

2.1. Eligibility criteria

The inclusion criteria were:

1. Clinical studies reporting new-onset of psychotic symptoms (patients with no previous psychiatric history and presenting to the emergency department with the first episode of psychosis) or worsening of psychosis (relapse of clinically stable symptoms of psychosis) in patients with COVID-19.
2. New-onset psychosis or worsening of clinical stable psychosis that cannot be explained by an underlying condition other than COVID-19.
3. The authors accepted the diagnoses of psychosis and COVID-19 described by case reports and case series.
4. Only case reports and case series were considered.
5. Editorial or letter to editors focusing on case reports or case series reporting onset of psychotic symptoms or worsening of psychotic symptoms in patients with COVID-19.
6. No restrictions on language, country, publication year, age, gender, or ethnicity of patients, geographic location, or year of publication of study were applied.

The exclusion criteria were:

1. Studies on patients with psychosis without COVID-19.
2. Patients with both delirium and psychosis or delirium alone.
3. Studies with psychotic symptoms overlapping with another multi-system disease, catatonia, encephalitis, substance abuse, and steroid use.
4. In vitro or animal studies.
5. Studies with unreliable and non-authentic data such as lack of details to ascertain diagnostic presentation.
6. Studies with the possibility of potential overlap (cases published in more than one paper with the same authors).
7. Non-peer-reviewed publications.
8. Cross-sectional, cohort, longitudinal study designs, abstract-only articles, conference papers, reviews, theses, posters, book chapters, editorials, letters, commentaries, and original articles were excluded.

2.2. Search strategy

On May 9th, 2021, we searched six electronic databases including PubMed, Scopus, Web of Science, PsycInfo, PsycArticles, and CINAHL, using the following search terms: (COVID-19 OR SARS-CoV-2* OR Severe Acute Respiratory Syndrome Coronavirus 2* OR Coronavirus Disease, 2019*) AND (Psychosis OR Psychotic OR delusion OR hallucination OR Paranoia* OR Schizophrenia). An updated search was completed on February 10th, 2022.

2.3. Study selection

Search results from six databases were imported to EndNote to remove any duplicates. Four independent reviewers (SS, SK, SJ, NBM) were split into two groups to perform title and abstract screening (when available) followed by the full-text screening of the included articles using the predetermined eligibility criteria. A manual search of the bibliography of the articles included in the electronic search was performed. Disagreements were resolved through discussion among reviewers or the guidance of the senior authors (SN or AMC).

2.4. Data extraction and management

Four independent reviewers (SJ, NBM, SS, SK) were split into two groups to extract the data using the Microsoft Excel table using a standardized template. This standardized template was developed after the initial extraction of three articles. The extracted data included: demographic characteristics of the patients including age, gender, and race, past personal and family psychiatric history, clinical features including neurological, psychiatric, and psychotic symptoms, methods of COVID-19 diagnosis, and other lab work including radiological

workup and neuroimaging, followed by clinical management, course of illness, and outcome. Non-English articles were translated into English by native speakers with experience in medical translation.

2.5. Risk of bias assessment

Four independent reviewers (SJ, NBM, SS, SK) were divided into two groups and assessed the risk of bias for all the included studies. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist was used to assess the quality of case reports and case series (Munn et al., 2020). The JBI critical appraisal checklist evaluates demographic characteristics and provides a clear description of the patient's history and timeline, current clinical condition, diagnostic tests or assessment methods, intervention(s) or treatment procedure(s), and post-intervention clinical condition. It also evaluates for reporting adverse events or unanticipated events and takeaway lessons in the case reports. These items are scored as yes, no, unclear, and not applicable.

3. Results

In this review, we identified 4132 studies using predetermined search terms. Fig. 1 elaborates the screening and selection process in the PRISMA flow diagram. Among the included studies, there were 40 case reports and seven case series, totaling 57 unique cases. In this review, we described the characteristics of patients presenting with a new-onset of psychosis or exacerbation of clinically stable psychosis in the context of COVID-19, their clinical presentation, management, course of illness,

and prognosis. Table 1 summarizes an overview of the included studies.

3.1. Demographic characteristics

In this review, the age range for men was 17–63 years with a mean age of 43.4 years. For women, the age range was 23–74 years with a mean age of 40.3 years. Age was not reported in four cases (Jaworowski et al., 2020; Wang et al., 2020). Of 57 cases, 34 were men (59.6%), and 23 were women (40.4%). Race was not reported for the majority of the patients. In case reports that mentioned race, there were seven Asian (Haddad et al., 2020; Javed and Shad, 2021; Kumar et al., 2021; Subramanyam et al., 2020; Wang et al., 2020), four Caucasian patients (Bakre et al., 2022; Ferrando et al., 2020; Lim et al., 2020; Makivic et al., 2020), three Black, all African-American (Baral et al., 2021; Gillett and Jordan, 2020; Smith et al., 2020), and one was from Eastern Europe (Kozato et al., 2021).

3.2. Past psychiatric history

Out of 57 cases, 38 (66.7%) patients did not have any past psychiatric history, whereas history was not mentioned in five patients. Substance use was the most commonly reported psychiatric disorder ($n = 7$) (15.9%) with a history of polysubstance use (Boulos et al., 2020; Lanier et al., 2020), opioid use disorder (Ferrando et al., 2020), alcohol use disorder (Skoneczny et al., 2020; Zhang et al., 2021), cannabis use disorder (Jaworowski et al., 2020; Mawhinney et al., 2020), and recreational occasional cocaine use (Correa-Palacio et al., 2020). Two (2.5%)

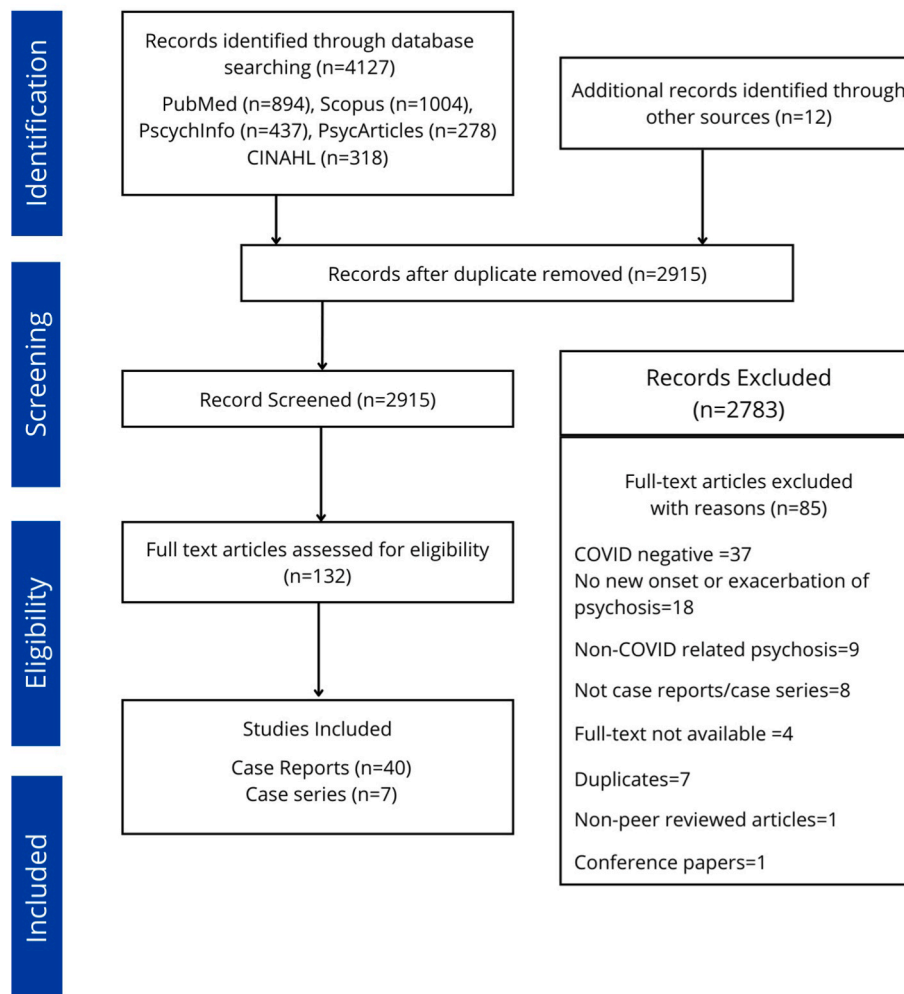


Fig. 1. PRISMA Flow Diagram.

Table 1
Summary of demographic characteristics, clinical features, laboratory work-up, neuroimaging, and psychopharmacological treatment.

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Al-Busaidi et al., 2021	46	M	None	None	Mental and psychomotor disturbances, agitation	Paranoid, grandiose, and religious delusions.	Full blood count, complete metabolic panel, and thyroid function were in the normal range.	CXR - Normal	CT head -Normal	Olanzapine 5 mg
Alba et al., 2021	40	M	None	Not mentioned	None	Disorganized behavior and speech, delusions of death, and mystical visual hallucinations in the form of angels and demons.	Unremarkable	CT scan of the chest - mild pulmonary infiltrates in both lungs	Not mentioned	Aripiprazole 5 mg and Diazepam 15 mg daily Diazepam was discontinued during hospitalization.
Alvarez-Cisneros et al., 2021	43	M	Hetero-aggressive episodes	Not mentioned	Restlessness, emotional liability, and aggression towards his mother	Delusions of grandeur	Hypokalemia - 3.3, elevation of hepatic enzymes (AST 53 U/L, ALT 69 U/L), indirect hyperbilirubinemia (total bilirubin 2.07 mg/dl, indirect bilirubin 1.73 mg/dl, direct bilirubin 0.34 mg/dl), and elevated ferritin levels (595 ng/mL).	Thoracic CT scan -Normal	Contrast brain MRI - Normal	Not mentioned
Austgen et al., 2022	52	F	None	Not mentioned	Insomnia, anxiety, worsening depression, suicidal thoughts, psychomotor slowing, catatonia, negativistic, mutism	Paranoia, nihilistic delusions	CRP, ESR, procalcitonin and fibrinogen - normal. The serum rheumatologic panel and CSF encephalitis panel were normal. CSF IgG was mildly elevated (4.15) as well as ferritin (238 ng/mL), CRP -1.35 mg/dL, ESR - 34 mm/h, and IL-6 -17 pg/mL.	Not mentioned	MRI with and without contrast of the brain - negative	Lack of improvement with Escitalopram to 10 mg for 3 days, sertraline to 100 mg for 5 days, risperidone to 3 mg for 8 days, aripiprazole to 15 mg for 10 days, olanzapine to 15 mg for 10 days. The patient responded to ECT treatment along with Lorazepam.
Bakre et al., 2022	29	F	None	None	Depressed, insomnia, low energy, poor concentration, and poor appetite	Disorganized thoughts such as being pregnant while she is not, having both husband and wife, visual	Urinalysis and urine culture: positive for Escherichia coli. WBC, Acetaminophen levels were normal.	Not done	Not done	Olanzapine 10 mg which was switched to aripiprazole 10 mg daily due to concerns regarding side effects.

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
						hallucinations of “black stuff” coming out of her mouth, and auditory hallucinations of Satan telling her to “fight” and telling her to “stay” at the hospital against her will, and paranoid delusions.				
Baral et al., 2021	53	M	None	Not mentioned	Agitation	Delusional thoughts of people plotting to kill him.	Mildly elevated ferritin The rest of the laboratory workup was unremarkable	None	CT head - Normal	Intramuscular haloperidol 5 mg once
Borovina et al., 2021	74	F	None	Not mentioned	Social isolation, insomnia, suicidal attempt.	Delusions of paranoia believing that her food is poisoned	Microcytic anemia with hemoglobin, mildly elevated neutrophils, mildly low lymphocytes The normal level of CRP, normal liver and renal function.	None	CT scan suggestive of vascular encephalomalacia and MRI indicative of chronic vascular lesions	Risperidone 6 mg daily and Diazepam 15 mg/day The sudden and unexpected death
Boulos et al., 2020	56	M	Recreational substance use as a teenager	None	None	New-onset psychosis with religious preoccupation, auditory hallucinations of God speaking to him, paranoia, loud speech, and tangential thought process. The patient believes that he is the miraculous transformation from death to life.	- CRP: 8.86 mg/dl, procalcitonin: 0.12 ng/mL, LAD total: 655 units/L, D-Dimer: 1.13 µg/mL FEU, Ferritin: 5697 ng/mL - CBC, chemistry, Thyroid, Bacterial and viral/parasite were unremarkable.	CXR on day 4: -Diffuse reticulonodular opacities throughout bilateral lung fields and increased airspace opacification in the lower lobes bilaterally.	Head CT, brain MRI with and without contrast - Normal	- Oral haloperidol 2.5 mg BID which was increased to 5 mg.
Chacko et al., 2020	52	M	None	Not mentioned	Mutism, anxiety, irritability, attempts to abscond, and an attempt to cut his wrist	- 1st admission: Mutism, altered mental status, the delusion that he caused the pandemic. - 2nd admission: Disorganization, selective mutism, irritability	Elevated liver transaminases along with acute inflammatory markers (ESR -40, CRP -1.5, and D-dimer = 1003). Urinalysis indicative of dehydration, with positive ketone and high specific gravity.	Chest CT-multifocal pneumonia.	Head CT and brain MRI with diffusion weight imaging -Normal	Olanzapine 2.5mg/PO QHS, sertraline 100mg/PO OD, clonazepam 0.25mg/PO BID, and trazadone 50mg/PO QHS.
Correa-Palacio et al., 2020	43	M	Recreational cocaine use	None	Irritability, psychomotor	Megalomaniac belief in communicating	Urine toxicology - negative	None	Head CT, brain MRI - Normal	Valproic acid 500 mg/8 h, paliperidone 15

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
					restlessness, aggression, anxiety	with God, persecutory delusions, visual/auditory hallucinations, insomnia, expansive mood, loud speech, and logorrhea	Mild renal failure that improved with intravenous hydration, mild leukocytosis possibly due to agitation			mg/day, olanzapine 5mg/day and lorazepam 1 mg as needed
Elkhaled Wu et al., 2020	23	M	None	Not mentioned	Restlessness and suicidal ideations for 2 days	Auditory hallucinations for two days	Leukocytosis, thrombocytopenia, and acute kidney injury. Elevated CRP, ferritin, interleukin-2, interleukin-6, D-dimer, procalcitonin, and liver enzymes. Day 9 - Drop-inn hemoglobin, severe thrombocytopenia, elevated prothrombin time and activated partial thromboplastin time, raised D-dimer, and low fibrinogen with a worsening clinical condition	Day 9 - Urgent CT abdomen revealed massive intraperitoneal hemorrhage	CT brain - Unremarkable. Brain MRI revealed an isolated oval-shaped lesion in the splenium of the corpus callosum, suggestive of a cytotoxic lesion of the corpus callosum.	None
Faisal et al., 2021	48	M	None	None	Anxious, restlessness, tremors, aggression	Auditory and visual hallucinations	Low hemoglobin, high CPR, high ferritin, activated partial thromboplastin time, prothrombin time, high D-dim, e,r, and high fibrinogen. Elevated CRP - 0.67 and ferritin - 421	CXR- multifocal bilateral ground-glass opacity, which dominated the periphery of the lung and improved on day 10. CXR - Normal	None	- PRN Haloperidol - Risperidone and lorazepam
Ferrando et al., 2020 Case I	30	M	None	Not mentioned	Anxiety, suicidal ideation, agitation, and decreased sleep	Bizarre behavior, auditory hallucinations of people who were chasing him, and drinking excessive amounts of water and Pedialyte	Elevated CRP - 0.67 and ferritin - 421	CXR - Normal	CT head -Normal	Quetiapine 25 mg for 4 days
Ferrando et al., 2020 Case II	34	F	Panic disorder	Not mentioned	Anxiety, suicidal ideation, inattention	Inattentive, pressured, agitated, disorganized, and suspicious, persisting on bizarre somatic sensations of "fire burning up inside" and migratory numbness and tingling	Low WBC	CXR - Normal	CT head -Normal	Fluoxetine 10 mg daily, clonazepam 0.5mg/BID and melatonin 3 mg at night. Aripiprazole 5 mg was added to the regimen.

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Ferrando et al., 2020 Case III	33	M	Opioid use	Not mentioned	None reported	Auditory hallucinations, paranoid and persecutory delusions, and severe agitation	Elevated CRP	CXR - Normal	CT head -Normal	Quetiapine 50 mg/ BID
Franchi M et al., 2020	36	F	Not mentioned	Not mentioned	None	Severe psychotic features and grandiose delusions	Not mentioned	None	None	Hospitalization with antipsychotics
Gillet et al., 2020	37	M	None	History of psychosis in sister, aunt, and grandfather.	Severe insomnia, worry, increasing confusion, bizarre actions, preoccupation with dying.	Paranoia, auditory hallucinations of the devil, and religious preoccupation	CBC - elevated WBC (24.18 × 10 ⁹ /L) with lymphopenia (0.51 × 10 ⁹ /L). CRP, electrolytes, toxicology for ethanol, paracetamol, salicylate, CSF studies, and serology tests - Unremarkable	CT neck/CT chest showed pneumomediastinum and surgical emphysema of the neck secondary to tracheal injury, and ground glass opacification and consolidation. -Fractures of the left radius, left ulna, left and right ankle,s and vertebral fracture at L1 on X-ray imaging.	CT Head - normal	Olanzapine with PRN diazepam
Haddad et al., 2020	30	M	Episodes of anxiety brought on by epistaxis	None	Agitation, insomnia, low mood, anxiety, and lack of interest.	Auditory hallucinations, delusions of paranoia	CBC = mild leukocytosis (14.0 × 10 ³ /μl). CPR = mildly elevated (12.3 mg/L). Ferritin = mildly elevated.	CXR - Normal	CT head - Normal	Lorazepam - 1 mg QID, mirtazapine 30mg/daily and risperidone 1mg/ BID
Hansen et al., 2020	42	M	Schizophrenia - catatonic type	Not mentioned	Insomnia, mood swings, uneasiness, and threatened his wife	Megalomaniacal delusions, erratic behavior, and incoherent speech.	Not mentioned	CXR - Bilateral infiltrates	Not mentioned	Olanzapine and lorazepam
Hassani et al., 2020	25	M	None	Not mentioned	Irritable mood, increased self-esteem, insomnia, talkativeness, agitation, suicidal attempt	Auditory and visual hallucinations. Delusion of grandiosity	Not mentioned	CT chest - pulmonary involvement suggestive of COVID-19. CXR -Normal	Not mentioned	Haloperidol, sodium valproate and bipyridine were prescribed.
Huarcaya-Victoria et al., 2020 Case I	23	F	None	Not mentioned	Decreased attention, anxiety, irritability	Religious delusions, delusions of damage, and reference with imperative, pejorative, and auditory hallucinations. Catatonic symptoms (stereotyped movements, catalepsy, verbigeration)	CBC with differential. -Unremarkable	Not reported	Not reported	Olanzapine 15 mg/ day

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Huarcaya-Victoria et al., 2020 Case II	38	F	Depressive episodes	Not mentioned	Psychomotor restlessness and insomnia	Auditory hallucinations, mystical religious delusions, euphoric mood, and bizarre behavior.	CBC with differential. -Unremarkable	Not reported	Not reported	Olanzapine 20 mg/day, valproic acid 1000 mg/day and clonazepam 1 mg/day.
Huarcaya-Victoria et al., 2020 Case III	47	F	None	Not mentioned	Guilt, sadness, suicidal attempt	Auditory hallucination, and delusions of harm	CBC with differential. -Unremarkable	Not reported	Not reported	Quetiapine 300 mg/day, sertraline 50 mg/day, and valproic acid 500 mg/day
Javed et al., 2021	17	M	None	Not mentioned	Severe agitation, aggression, emotional lability, insomnia, depressed mood with isolation	Bizarre behavior, paranoid delusions, auditory hallucinations, persecutory delusions	Urine drug screen - negative	Not reported	Not reported	Aripiprazole 2 mg/day which was increased to 5 mg/day
Jaworowski et al., 2020 Case I	Not mentioned	M	None	Not mentioned	None	Grandiose and religious delusions	Not mentioned	Not mentioned	Not mentioned	No discharge medication.
Jaworowski et al., 2020 Case II	Not mentioned	M	None	Not mentioned	None	Grandiose and religious delusions	Not mentioned	Not mentioned	Not mentioned	No discharge medication.
Jaworowski et al., 2020 Case III	Not mentioned	M	None	Not mentioned	Cannabis use	Paranoid, grandiose, and religious delusions.	Not mentioned	Not mentioned	Not mentioned	No discharge medication.
Kazi et al., 2021 Case 1	49	F	None	None	Suicidal ideations, not sleeping, agitation, lack of appetite and weight loss, feeling guilty and hopeless, cultism lasting for last than a minute, nightmares	Paranoia	CBC, CMP, and Thyroid function tests were unremarkable. Urinalysis showed moderate leucocytes, trace blood, and trace protein, positive for ketones and negative for nitrite and glucose. Urine microscopy showed few bacteria, 25–50 white cells, 5–10 red cells, moderate epithelial cells, and moderate mucus threads.	Chest X-ray - Unremarkable	CT Scan head - unremarkable	Olanzapine 25 mg, escitalopram 20 mg, and mirtazapine 15 mg Oral aripiprazole 2 mg was discontinued. However, the reason was not provided.
Kazi et al., 2021 Case 2	56	F	None	None	Altered mental status, agitation, mania-like symptoms with inflated self-esteem, easy distractibility, circumstantial thought process, rapid speech, racing thoughts, poor sleep at night, and despite	Paranoia, auditory and visual hallucinations, bizarre delusions	Prolonged QTc - 550 msec Urine drug screen, RPR test for syphilis, and HIV testing were negative. Two samples of blood culture showed no	Not reported	CT head - Normal	Oral aripiprazole 5 mg and intramuscular olanzapine 5 mg

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Khan et al., 2020	30	M	Not mentioned	Not mentioned	minimally sleeping, increased energy None	On 2nd hospital admission: visual and command auditory hallucinations (to kill himself), delusions of being in a different state	growth after five days of incubation Elevated lactic acid, D-dimers. EKG showed tachycardia. Cardiac enzymes were normal	On initial hospitalizations: CXR showed a right lower lobe patchy density with blunting of the left costophrenic angle suggesting early COVID-19 pneumonia. Chest CT angiography-suboptimal pulmonary arterial opacification for probable bilateral pulmonary embolism (PE)	Day 7 head CT without contrast -Near-complete bilateral opacification of the sphenoid sinuses and several ethmoid air cells consistent with a sinus infection and a mild hypodensity of the white matter surrounding the left basal ganglia and thalamus with apparent mass effect on the left lateral ventricle. MRI brain - Normal	Not mentioned
Kozato et al., 2021	In the fifties	M	None	Not mentioned	Insomnia, panic attacks, agitation, self-harm (biting himself), anhedonia	Auditory (male talking in a foreign language), tactile (something crawling on him), and visual hallucinations. Responding to internal stimuli	Normal except slightly elevated ALT	On previous admission, CXR: -Bilateral patchy consolidations. On day 8: (HRCT) scan of the chest: -Fibrosis and organizing pneumonia.		Risperidone was titrated from 2 mg to 4 mg after one week.
Kumar et al., 2021 Case C	62	F	Depression	Not mentioned	Fearfulness, suspiciousness, insomnia, agitation, violence, lacked insight and judgment	Persecutory delusions, auditory hallucinations	Routine investigations were normal	Not mentioned	Not mentioned	Risperidone 0.5 mg twice a day and lorazepam 1 mg at night
Lanier et al., 2020	58	M	Panic disorder, Anxiety, and Polysubstance abuse (including cocaine and alcohol).	Not mentioned	On day 2: Erratic behavior, throwing things	Hallucinations	WBC count of 2300 cells/ml lactate 1 mmol/dL, CRP 6.5 mg/L, Ferritin 110 ng/mL, creatinine kinase of 723 IU/L.	A liver ultrasound on day 2 demonstrated questionable hepatic cirrhosis, splenomegaly, and ascites.	CT head without contrast - normal	Haloperidol 2.5 mg at bedtime and lorazepam 1mg/8 h as needed for agitation.
Lim et al., 2020	55	F	None	None	None	Florid visual hallucinations of animals. Paranoid and persecutory delusions	Elevated CRP, Ferritin, D-dimer, and TNF-alpha	CXR: Bilateral lower zone and peripheral pulmonary infiltrates. Chest CT: Bilateral subpleural ill-defined ground-glass opacities and interlobular septal thickening	MRI Brain - normal	Haloperidol 0.5 mg BID that was switched to risperidone 0.5 mg
Los et al., 2021	39	F	None	Not mentioned	Aggression	Delusions of paranoia	Elevated levels of IL-6, CRP, CK, and slightly elevated AST, fibrinogen, D-dimers, and CK-MB	CT chest -COVID-19 pneumonia	Not done	Olanzapine 5 mg BID For aggression: the patient received Haloperidol (2 ×

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Lorenzo-Villalba et al., 2020	33	F	None	None	Changes in sleep and appetite	Auditory hallucinations, odd behavior (roaming naked), delusions	Elevated WBC, CRP	Chest CT - Right-sided ground-glass opacities in lower zones.	CT Head - Normal	2.5 mg, intramuscularly, i. m.), lorazepam (1 × 2.5 mg orally, and olanzapine 5 mg twice a day. Olanzapine 10 mg
Majadas et al., 2020	63	M	None	Not mentioned	None	Bizarre delusions and incoherent thought and speech	Elevated D-dimers	CT pulmonary angiography - low-risk pulmonary thromboembolism	MRI brain - Normal	Risperidone 2 mg/day which was titrated up to 6 mg/day
Makivic et al., 2021	46	M	Not mentioned	Not mentioned	Increased generalized fear	Auditory and visual hallucinations, gurgling with disinfectant, smearing marmalade around his eyes, responding to non-existing people, and delusions of paranoia, believing that metallic parts were implanted in his body.	ECG: Sinus-tachycardia, descending ST-segment depressions with negative T waves in leads II, III, and aVF and an incomplete right bundle branch block. High Troponin-T, D-Dimers, LDH, CRP	CT Chest -Right ventricle/left ventricle ratio was 1.6, which confirmed PE	Cranial CT and MRI - Normal	Medications as needed: 400 mg Valproate and 1 mg lorazepam for seizures. For generalized fear: lorazepam 2.5 mg (7.5 mg in total), risperidone 3 mg and quetiapine 25 mg, valproate 500 mg BD and risperidone 1 mg BD.
Mawhinney et al., 2021	41	M	Transient mood reactions with possible paranoia secondary to cannabis	Sister: postpartum psychosis and was diagnosed with bipolar disorder	Racing thoughts, agitation, restlessness. Confession of homosexual encounters and other sexual behavior not characteristic of the patient	Delusions of grandiosity and persecution, strong religious ideas with attempts to anoint other patients with water	Mildly elevated LFTs. CSF Analysis was normal	CXR -Consistent with COVID-19 pneumonitis. CT pulmonary angiogram -Covid-19 pneumonitis	CT and MRI brain -Normal	Olanzapine 7.5 mg and clonazepam 1 mg.
Mirza et al., 2020	53	M	None	Not mentioned	Suicidal attempt, confusion	Singing and chanting to himself. Command auditory hallucination	Elevated blood urea nitrogen and transaminases	CXR -An opacity in the upper lobe of the right lung, indicative of possible COVID19 pneumonia	CT head -Normal	None
Mollà Roig, P., 2021	43	M	None	None	Anxiety, insomnia, asthenia	Delusions of paranoia and reference	Unremarkable	Not done	Not done	Olanzapine 10 mg at night
Noone et al., 2020 Case I	49	M	None	None	Decreased appetite with insomnia- 1 week; followed by episodes of violence at home, crying spells, hopelessness, sadness, guilt,	Auditory hallucinations, delusions of grandiosity, and paranoia	Mild anemia	CXR - Lung volume low with increased interstitial markings	CT and MRI brain -Normal	Haloperidol 2 mg as needed for agitation and quetiapine up to 150 mg/day

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Noone et al., 2020 Case II	34	F	None	None	inattentiveness, restlessness, and passive suicidal ideations. Feeling unsafe, loud pressured speech, irritable mood, labile intense affect, and decreased attention and concentration.	Bizarre behavior includes disrobing in front of strangers, talkativeness, and persecutory ideas. Paranoid delusions.	Unremarkable	CXR -Normal	Brain MRI -Nonspecific T2 hyperintensities	Risperidone 1 mg BID
Parker et al., 2021	57	M	None	Not mentioned	Psychomotor agitation, fearfulness	Loud speech, disorganized thoughts, auditory and visual hallucinations (eg, erratic, darting eye contact, and audible self-talk), paranoid and persecutory delusions	Blood glucose 300 mg/dl. High creatinine and BUN, mildly high CRP	Not performed	CT head -Mild cerebral volume loss and chronic microvascular ischemic changes. MRI of the brain with and without contrast -Unremarkable, except for mild cerebral volume loss	Risperidone 3 mg/ BID
Saje et al., 2020	Middle age	M	Acute psychotic episodes and persistent depressive symptoms	Not mentioned	Anxiety, insomnia, emotional instability, severe irritability	Religious and grandiose delusions	None	None	None	None
Sanchez-Alonso et al., 2020	36	F	Schizoaffective disorder (stable on clozapine 250 mg)	Not mentioned	Irritability, aggression, insomnia	Disorganized behaviors	None	None	None	Clozapine increased to 350 mg/day and risperidone 6 mg/day
Santos et al., 2020	61	M	Not mentioned	None	None	Delusional jealousy, functional auditory hallucinations, psychosis	CBC, biochemical profile, urinalysis, serologic tests, Thyroid function tests, drug tests, and vitamin levels were normal	Not reported	CT head -Normal	Risperidone 3 mg at night, which was increased to 2 mg at breakfast and 3 mg at night. Lorazepam 0.5 mg 3 times/d was prescribed for anxiety management.
Sen et al., 2020	33	F	None	Not mentioned	Irritability decreased the need for sleep	Persecutory, derailment, mystic, and infidelity delusions without any insight	Increased WBC, CRP, D-dimer, fibrinogen	CT chest - bilateral ground-glass opacities	Cranial MRI -Hyperintense signal in the splenium of the corpus callosum with decreased apparent diffusion coefficient, which might indicate the presence of cytotoxic edema. Day 5: Follow up MRI of the brain -Complete resolution of cytotoxic edema in the corpus callosum.	Haloperidol 20 mg/day and olanzapine 20 mg/day

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Skoneczny et al., 2020	46	M	Alcohol use	Not mentioned	Aggression, sleep disturbance, slurred speech, insomnia, increased psychomotor activity	Delusion of grandiosity, sexual promiscuity, wandering in the neighborhood with a chainsaw and scattering pieces of paper	Unremarkable	CT chest -Interstitial lung inflammation, left lung tissue consolidation	Not mentioned	Valproate 2000 mg/day, olanzapine 20 mg/day and tiapride 400 mg/day
Smith et al., 2020	36	F	None	None	Decreased sleep, rapid speech, anxious mood	Persecutory delusions	Mild leukocytosis, elevated CRP	None	CT scan and MRI of the head -Normal	Risperidone 3 mg/day
Subramanyam et al., 2020 Case I	24	F	None	None	Decreased sleep, loss of appetite, severe fearfulness (drank two sips of methylated spirit in an attempt to commit suicide), agitation	Delusions of persecution and reference, agitated behavior, and auditory hallucinations	Unremarkable	CXR -Normal	Unremarkable	Not mentioned
Subramanyam et al., 2020 Case II	23	F	None	None	None	Aggression is the delusion of persecution.	Unremarkable	Unremarkable	Unremarkable	Not mentioned
Subramanyam et al., 2020 Case III	23	F	None	None	None	Delusions of reference and persecution	Unremarkable	Unremarkable	Unremarkable	Not mentioned
Tuna et al., 2020 Case II	52	F	None	None	Suicide attempt due to auditory hallucinations	Auditory hallucinations (voices commanding her to kill herself). Paranoid thoughts and persecutory delusions (people harming her and her family by infecting them with coronavirus and her grandchildren dying because of this) x 1 month	Not mentioned	CT chest -COVID-19 pneumonia	Unremarkable	Haloperidol 10 mg/day and biperiden 5 mg/day
Vepa et al., 2020	40	F	None	Not mentioned	Severe anxiety, aggression, wandering, agitation, derealization, depersonalization, followed by a suicide attempt.	Auditory hallucinations and delusions	Elevated WBC and RPR. The rest of the workup was unremarkable	CXR -Bilateral patchy consolidation. CT Chest -Multifocal, peripheral, bilateral ground-glass opacities and consolidation	CT head -Unremarkable	Haloperidol 5 mg
Wang et al., 2020 Case II	Not mentioned	M	Not mentioned	Not mentioned	Developed mood fluctuations, momentary excitement, and irritability post-intubation	Hallucinations	Not mentioned	Not mentioned	Not mentioned	Diazepam, olanzapine

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Table 1 (continued)

Authors, year	Age (Years)	Gender	Past Psychiatric History	Family Psychiatric Hx	Psychiatric presentation	Psychotic presentation	Lab workup	Radiological workup	Neuroimaging	Psychiatric treatment
Zhang et al., 2021	44	M	Alcohol use disorder. (Long history of auditory hallucinations and delusions, episodes of withdrawal, delirium tremens, and encephalopathy.)	None	Hopelessness, decreased energy, loss of appetite, insomnia, suicide attempt	Auditory hallucinations	Elevated CRP and D-dimer levels. Normal CBC and basic metabolic panel.	CT chest -Pan lobar ground-glass opacities (multifocal pneumonia). Hospital day 44 -New hazy opacity right lung	Not mentioned	Clozapine 250 mg/day, mirtazapine 45 mg/day, sertraline 175 mg/day

*ALT (Alanine transaminase), *AST (Aspartate aminotransferase), *BID (Twice a day), *BUN (Blood urea nitrogen), *CBC (Complete blood count), *CRP (C-reactive protein), *CSF (Cerebrospinal fluid), *CT (Computed tomography), *CXR (Chest X-ray), *EKG/ECG (Electrocardiogram), *ESR (Erythrocyte sedimentation rate), *HRCT (High-resolution computed tomography), *IAD (Left anterior descending artery), *LDH (Lactate dehydrogenase), *MRI (Magnetic resonance imaging), *OD (Once daily), *PRN (Taken as needed), *QHS (Every night at bedtime), *RPR (Rapid plasma reagin), *WBC (White blood cells).

patients had a history of panic disorder (Ferrando et al., 2020; Lanier et al., 2020) while two (2.5%) patients had unspecified anxiety (Haddad et al., 2020; Lanier et al., 2020). Two (2.5%) patients reported a history of psychotic disorder, including schizophrenia-catatonic type (Hansen et al., 2020) and schizoaffective disorder (Sanchez-Alonso et al., 2020). Two (3.5%) patients had a history of depressive episodes (Huarcaya-Victoria et al., 2020; Kumar et al., 2021) and another had a history of an acute psychotic episode and persistent depressive symptoms (Saje et al., 2021).

3.3. Family history of psychiatric disorders

Out of 57 cases, 20 (35.1%) patients had no history of psychiatric illness in the family. Thirty-five (61.4%) cases did not report a family history of psychiatric disorder. Only two (2.5%) patients (Gillett and Jordan, 2020; Mawhinney et al., 2020) had a family history of psychiatric disorders; one (2.3%) with psychotic episodes in his sister, aunt, and grandfather (Gillett and Jordan, 2020), and the other had a history of postpartum psychosis and bipolar disorder in his sister (Mawhinney et al., 2020).

3.4. Clinical features

This section summarizes clinical features such as a medical, neurological, psychiatric, and psychotic presentation.

3.4.1. General medical clinical features

Out of 57 cases, 11 (25%) patients presented with classic COVID-19 symptoms; fever, cough, malaise, headache, loss of taste and smell, myalgia, shortness of breath, and diarrhea (Boulos et al., 2020; Gillett and Jordan, 2020; Haddad et al., 2020; Hassani et al., 2020; Jaworowski et al., 2020; Kozato et al., 2021; Lim et al., 2020; Mawhinney et al., 2020; Parker et al., 2021; Skoneczny et al., 2020; Vepa et al., 2020; Zhang et al., 2021). Seventeen (28.1%) patients presented with fever and mild upper respiratory tract symptoms such as sore throat, nasal congestion, and cough. (Al-Busaidi et al., 2021; Austgen et al., 2022; Borovina et al., 2021; Faisal et al., 2021; Javed and Shad, 2021; Jaworowski et al., 2020; Lanier et al., 2020; Saje et al., 2021; Sanchez-Alonso et al., 2020; Santos et al., 2021; Sen et al., 2021; Smith et al., 2020). Two (3.5%) patients had bilateral pneumonia (Hansen et al., 2020; Majadas et al., 2020), and two developed hypoxic respiratory failure (Bachar et al., 2021; Mirza et al., 2020).

Five (8.8%) patients had a complicated course with death in one patient due to COVID-19 complications (Elkhaled et al., 2020). This patient developed acute respiratory distress syndrome requiring mechanical ventilation, acute renal injury, fulminant liver failure, severe myocarditis, and eventually had a cardiac arrest and died on the 15th day of hospitalization (Elkhaled et al., 2020). One patient presented with seizures, altered mental status, and COVID-19 pneumonia resulting in 21 days of hospitalization. This patient had 14 days of stay in the Intensive Care Unit (ICU) stay, followed by acute pulmonary embolism requiring placement of an Inferior Vena Cava Filter, and presented with psychiatric symptoms on the third day of hospital admission (Khan et al., 2020). One patient initially had classic COVID-19 symptoms with hemoptysis and left-sided chest pain followed by pain and swelling of the right calf 17 days after symptom onset (Makivic et al., 2021). Another patient developed bilateral lower extremity weakness (proximal > distal) and numbness of the right calf and left anterior thigh affecting his ability to ambulate (Noone et al., 2020). One patient died unexpectedly without a complicated course and any identifiable reasons. An autopsy was not performed for lack of permission from the family (Borovina et al., 2021).

Other symptoms in the remaining cases included; fever (Huarcaya-Victoria et al., 2020), shortness of breath (Freedman et al., 2020), tachycardia (Chacko et al., 2020), high blood pressure (Wang et al., 2020), mild respiratory insufficiency, and renal failure (Correa-Palacio

et al., 2020). One patient had persistent and severe signs of fetal distress at the 35th gestational week (Franchi et al., 2020). Fifteen (26.3%) had unremarkable medical presentations (Alvarez-Cisneros et al., 2021; Bakre et al., 2022; Ferrando et al., 2020; Huarcaya-Victoria et al., 2020; Jaworowski et al., 2020; Lorenzo-Villalba et al., 2020; Mollà Roig, 2021; Subramanyam et al., 2020; Tuna et al., 2020). About 52 (91.2%) patients had an uncomplicated medical course while five (9.8%) patients had a complicated course (defined by the presence of acute kidney injury requiring renal replacement, liver or respiratory failure, myocarditis, deep venous thrombosis (DVT), pulmonary embolism, etc.)

3.4.2. General neurological non-psychiatric clinical features

Twenty-eight (49.1%) patients did not have any neurological symptoms, whereas fourteen (24.5%) patients did not report any neurological symptoms. Nine cases (15.8%) reported altered mental status (Alvarez-Cisneros et al., 2021; Chacko et al., 2020; Elkhaled et al., 2020; Khan et al., 2020; Lanier et al., 2020; Lim et al., 2020; Noone et al., 2020), and one was diagnosed with delirium during a prior hospitalization (Majadas et al., 2020). Two patients were oriented but were unable to participate in bedside cognitive testing (Ferrando et al., 2020). Two cases presented with seizures (Khan et al., 2020; Makivic et al., 2021), and one had nystagmus (Mawhinney et al., 2020).

3.4.3. General psychiatric clinical features

Eleven (21.6%) patients presented with no additional psychiatric symptoms (other than psychosis). Table 1 provides a summary of psychiatric symptoms in addition to psychosis.

3.4.4. Clinical features of psychosis

Fifty-three (93%) patients had delusions, which included delusions of grandeur (n = 14), delusions of paranoia (n = 19), persecutory (n = 11), delusions of reference (n = 4), mystic and infidelity (n = 2), bizarre delusions (Kazi et al., 2021; Majadas et al., 2020), delusional jealousy (Santos et al., 2021), and unspecified delusions (n = 3). Thirty-five (72.7%) patients had auditory hallucinations, with command auditory hallucinations in four cases (Khan et al., 2020; Mirza et al., 2020; Tuna et al., 2020; Zhang et al., 2021). Visual hallucinations (n = 11), tactile hallucinations (n = 1) (Kozato et al., 2021), and unspecified hallucinations (n = 2) (Lanier et al., 2020; Wang et al., 2020) were also reported. Other psychotic symptoms are summarized in Table 1.

3.5. Diagnostic workup

3.5.1. Diagnostic work-up

Twenty-one (36.8%) patients had normal blood workup, whereas acute phase reactants (ferritin, C-reactive protein, D-Dimer, leukocytosis, thrombocytopenia) were elevated in 20 (35.1%) patients. Other lab abnormalities included elevated lactic acid (Khan et al., 2020), hypokalemia (Alvarez-Cisneros et al., 2021), and indirect hyperbilirubinemia (Alvarez-Cisneros et al., 2021). Abnormalities in complete blood count showed variations in six cases (Elkhaled et al., 2020; Faisal et al., 2021; Ferrando et al., 2020; Gillett and Jordan, 2020; Noone et al., 2020), whereas liver function tests were elevated in four cases (Alvarez-Cisneros et al., 2021; Chacko et al., 2020; Kozato et al., 2021; Mawhinney et al., 2020). In two cases, urinalysis showed signs of dehydration and mild acute renal failure (Correa-Palacio et al., 2020; Elkhaled et al., 2020). In one case, abnormal hematologic tests (drop in hemoglobin, elevated prothrombin time, and activated partial thromboplastin time) were associated with worsening of the clinical condition (Elkhaled et al., 2020). An electrocardiogram (ECG) showed sinus tachycardia in two patients whereas in others ECG showed descending ST-segment depressions with negative T-waves in leads II, III, and aVF, and an incomplete right bundle branch block with high Troponin-T (Khan et al., 2020; Makivic et al., 2021). For 14 patients, lab work was not mentioned. Reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 was positive in 38 (66.7%) patients with

reactive COVID-19 IgM/IgG antibodies reported in five patients. For ten patients, the diagnostic test used was not mentioned. Two patients were diagnosed with COVID-19 through computed tomography (CT) scan (Hassani et al., 2020; Sen et al., 2021). One patient was previously treated for COVID-19, but during the psychosis episode, his COVID-19 PCR was negative (Correa-Palacio et al., 2020).

3.5.2. Radiological imaging

Chest X-rays for eight (14%) patients showed diffuse reticulonodular opacities in bilateral lung fields, blunting of costophrenic angle, and increased airspace opacification in the bilateral lower lobes. Chest CT showed multifocal pneumonia, ground-glass opacities, and interlobular septal thickening with signs of COVID-19 in 14 (24.5%) patients. Thoracic CT was normal in one patient (Alvarez-Cisneros et al., 2021). In two patients, the MRI of the brain revealed an isolated oval-shaped lesion in the splenium of the corpus callosum, suggestive of a cytotoxic lesion of the corpus callosum (Elkhaled et al., 2020; Sen et al., 2021). Table 1 summarizes the findings for radiological imaging.

3.6. Management of medical presentation

Medical treatment was not reported for 15 (29.8%) patients. Supportive care or self-quarantine was advised in eight patients. Azithromycin was prescribed to nine patients, ceftriaxone in four, enoxaparin in four, lopinavir-ritonavir in three, remdesivir in three, oseltamivir in one, piperacillin-tazobactam in one, and acyclovir in one case. Tocilizumab was used in two and favipiravir in one patient. One patient was prescribed a combination of amoxicillin, clarithromycin, and tazocin (Kozato et al., 2021). Hydroxychloroquine (HCQ)/chloroquine was prescribed to 12 patients and methylprednisolone/dexamethasone was prescribed to seven patients. Mechanical Ventilation and/or oxygen were administered to seven patients. Two patients underwent surgeries for injuries sustained in suicide attempts; one for tracheal injury, and another for bone injuries from jumping in front of a train (Gillett and Jordan, 2020; Zhang et al., 2021).

3.7. Management of psychiatric presentation

For acute agitation, intramuscular (IM) haloperidol 2–10 mg was administered in nine (15.8%) patients with two (4.5%) patients prescribed 15 mg (Subramanyam et al., 2020) and 20 mg (Hassani et al., 2020), respectively. Olanzapine IM was used in three patients (Jaworowski et al., 2020; Mirza et al., 2020), and the dose was 5 mg in two patients (Kazi et al., 2021; Mirza et al., 2020). Other psychotropics for agitation included lorazepam 1–2 mg, diazepam, biperiden IM 10 mg, chlorpromazine 100 mg, and promethazine 50 mg.

For regular use, haloperidol was prescribed in nine (15.7%) patients; 0.5–5 mg in six patients, 10 mg in two patients, and 15 mg and 20 mg were prescribed in one patient each. Quetiapine was prescribed in five (8.8%) patients; whereby the dose was 25–100 mg in three patients and 300 mg/day in one patient (Ferrando et al., 2020; Huarcaya-Victoria et al., 2020; Makivic et al., 2021). In one patient, quetiapine 150 mg was switched to olanzapine due to ineffectiveness (Noone et al., 2020). Risperidone was prescribed in 14 (24.5%) patients; 0–2 mg in five patients, 2–4 mg in three patients, and 6 mg in four patients. Risperidone 0.5 mg was switched to haloperidol in one patient due to lack of efficacy (Lim et al., 2020). The dose was not mentioned in one patient (Zhang et al., 2021). Olanzapine was prescribed in 19 (33.3%) patients; eight patients at doses of 2–10 mg and six patients at 10–20 mg. One patient was administered at 25 mg and doses were not mentioned in four (9%) patients. It was ineffective in four patients. Ziprasidone was used in two patients at 20 mg and 40 mg at admission only (Huarcaya-Victoria et al., 2020). Aripiprazole was prescribed in eight patients at 5–30 mg with partial benefit in the patient receiving 10 mg (Ferrando et al., 2020; Parker et al., 2021; Zhang et al., 2021). Two patients reported improvement with aripiprazole 5 mg. Clozapine was dosed at 250 mg

and 350 mg (Sanchez-Alonso et al., 2020) with favorable outcomes in two patients along with risperidone 6 mg in one patient (Zhang et al., 2021). Other psychotropic medications are reported in Table 1. ECT treatment was administered in three patients with favorable effects (Austgen et al., 2022; Chacko et al., 2020).

3.8. Course of illness

Twenty-three (43.8%) patients presented with mild medical symptoms (e.g., gastrointestinal, cardiovascular, respiratory symptoms) initially followed by psychiatric and/or psychotic symptoms. Fifteen (26.3%) patients presented with moderate-severe medical illness (COVID-19 symptoms or COVID-19 pneumonia) followed by the gradual development of psychotic symptoms and/or psychiatric symptoms. In one case, the patient developed acute kidney failure after COVID-19 and psychosis followed by disseminated intravascular coagulation, resulting in cardiac arrest and death (Elkhaled et al., 2020). One patient died unexpectedly without a complicated course and any identifiable reasons. An autopsy was not performed for lack of permission from the family (Borovina et al., 2021). Eleven (19.3%) patients presented with neurological symptoms (e.g., tachylalia, altered mental status, catatonia, or other psychiatric symptoms (e.g., suicidal attempt, bizarre behaviors, insomnia, etc.) to the emergency department (ED) and later developed psychosis. Eight (14%) patients had psychiatric symptoms at the initial visit to ED.

3.9. Prognosis

Out of the total of 57 patients, psychotic symptoms improved significantly or resolved completely in 41 (72%) patients. Five (8.8%) patients have a resolution of psychosis with residual anxiety, depression, speech latency, and psychomotor retardation. One patient reported residual hallucinations and low mood. Three patients reported persistent altered mental status and psychosis. In six (10.5%) patients, no follow-up information was provided. One patient died from complications of COVID-19 (Elkhaled et al., 2020) and another due to unknown reasons (Borovina et al., 2021).

3.10. Risk of bias assessment

Fig. 2 and Table 2 show the quality assessment results using the JBI tool. None of our studies were scored unclear or not applicable. Of the 57 included studies, only 10 reported adverse or unanticipated events. The clinical condition of the patients was clearly described in all studies except one (Wang et al., 2020). 39 studies reported post-intervention

clinical conditions. A clear description of the intervention(s) or treatment procedure(s) was reported in 41 studies. 30 studies reported a clear description of the patient’s demographic characteristics, whereas 36 studies reported a clear timeline of the patient’s presentation and diagnostic tests/assessment methods.

4. Discussion

This review summarizes the demographic characteristics, clinical features, course of illness, treatment plan, and prognosis of patients presenting with COVID-19-associated psychosis. The mean age for onset of psychotic symptoms in patients with COVID was 43.4 years for men whereas it was 40.3 years for women, (with men constituting a higher proportion of patients in the included studies) which is similar to the mean age of 43.9 years in a previously published systematic review (Smith et al., 2021). Higher than the usual average age for patients with psychosis, signifies that age could be a potential risk factor for the development of psychosis in individuals with COVID-19. Gender distribution seems to be an insignificant factor in this patient population (Hu et al., 2021). Other studies also reported gender in all cases, but no association between gender and COVID-19 psychosis was considered (Iqbal et al., 2020). As there were more men in the study than females, more cases of psychosis were reported among men.

Only two patients had a past diagnosis of psychotic disorder. About 66.7% of patients had no prior history of psychiatric disorders, further strengthening the existing data regarding the increased incidence of new-onset psychosis in COVID-19 patients (Taquet et al., 2021). Among 22 patients with reported family history, only two patients had a family history of psychiatric disorders, which accounts for about 66.7% of patients with no prior psychiatric history, pointing towards secondary psychotic episodes, as suggested by Parra and colleagues (Parra et al., 2020). However, Smith and colleagues reported only 15% of patients with documented psychiatric history (Smith et al., 2021).

The estimated incidence of COVID-19-related new-onset psychosis is around 12.8% (Taquet et al., 2021), with a 25% higher risk of schizophrenia in January 2020 than in the previous year (Brown et al., 2020). The underlying mechanism is unknown and points towards a multifactorial etiology despite previously suggested theories. The role of iatrogenic factors, such as corticosteroids and hydroxychloroquine, is also critical in the development of psychosis (Parra et al., 2020). The immune and inflammatory changes, immunosuppressants used in COVID-19 treatment, and stress also explain elevated acute-phase reactants in COVID-19-related psychosis (Tripathy et al., 2021).

Of 57 patients, most patients had mild COVID-19-related respiratory illnesses, neurological, or psychotic symptoms, with only 15 patients

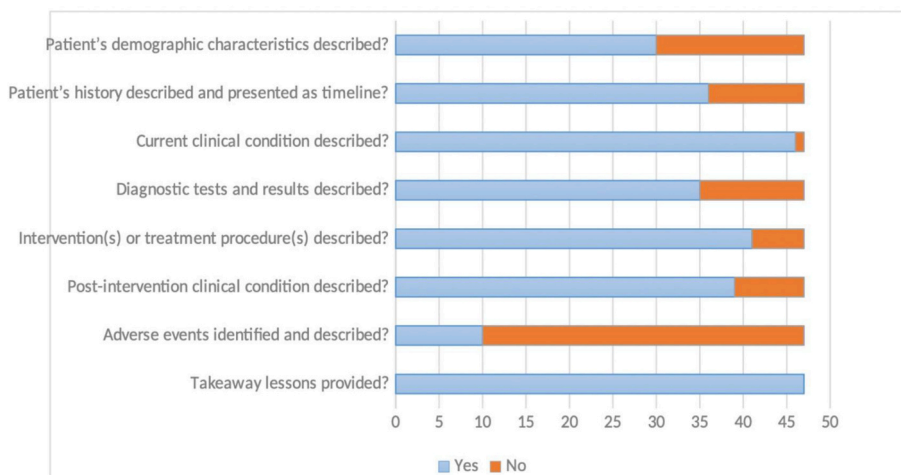


Fig. 2. Risk of Bias Assessment.

Table 2
Risk of bias assessment.

Author, year	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the postintervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?
Alba et al., 2021	1	1	1	1	1	1	0	1
Al Buseidi et al., 2021	0	1	1	1	1	1	0	1
Austgen et al., 2021	0	0	1	1	1	0	0	1
Alvarez-Cisneros et al., 2021	1	1	1	1	0	0	0	1
Bakre et al., 2021	0	1	1	1	1	1	1	1
Baral et al., 2021	1	1	1	1	1	1	0	1
Borovina et al., 2021	0	1	1	1	1	1	0	1
Boulos et al., 2020	1	1	1	1	1	1	0	1
Chacko et al., 2020	1	1	1	1	1	1	0	1
Correa-Palacio et al., 2020	1	1	1	1	1	1	0	1
Elkhaled et al., 2020	1	1	1	1	1	1	1	1
Faisal et al., 2021	0	1	1	1	0	1	0	1
Ferrando et al., 2020	1	0	1	1	1	1	1	1
Franchi et al., 2020	0	0	1	0	0	0	0	1
Gillet et al., 2020	1	1	1	1	1	1	1	1
Haddad et al., 2020	1	1	1	1	1	1	1	1
Hansen et al., 2020	1	0	1	0	0	0	0	1
Hassani et al., 2020	1	0	1	0	0	1	0	1
Huarcaya-Victoria et al., 2020	0	0	1	0	1	1	0	1
Javed et al., 2021	0	1	1	0	1	0	0	1
Jaworowski et al., 2020	0	0	1	0	1	1	0	1
Kazi et al., 2021	1	1	1	1	1	0	1	1
Khan et al., 2020	1	0	1	0	1	1	0	1
Kumar et al., 2021	0	0	1	0	1	0	0	1
Kozato et al., 2021	1	1	1	1	1	1	1	1
Lanier et al., 2020	1	1	1	1	1	1	0	1
Lim et al., 2020	1	1	1	1	1	1	1	1
Lorenzo-Villalba et al., 2020	1	1	1	1	1	1	0	1
Los et al., 2021	0	1	1	1	1	1	0	1
Majadas et al., 2020	1	1	1	1	1	1	0	1
Makivic et al., 2020	1	1	1	1	1	1	0	1
Mawhinney et al., 2020	1	1	1	1	1	1	0	1
Mirza et al., 2020	0	0	1	1	1	1	0	1
Mollà Roig, P. 2021	1	1	1	1	1	1	0	1
Noone et al., 2020	0	1	1	1	1	1	0	1
Parker et al., 2021	1	1	1	1	1	1	1	1
Saje et al., 2020	1	1	1	1	1	1	0	1
Sanchez-Alonso et al., 2020	0	1	1	0	1	0	0	1
Santos et al., 2021	0	1	1	0	1	1	0	1
Sen et al., 2021	1	1	1	1	1	1	0	1
Skoneczny et al., 2020	1	1	1	1	1	1	0	1
Smith et al., 2020	1	1	1	1	1	1	0	1
Subramanyam et al., 2020	1	1	1	0	1	1	0	1
Tuna et al., 2020	1	1	1	1	1	1	0	1
Vepa et al., 2020	0	1	1	1	1	1	0	1
Wang et al., 2020	0	0	0	0	0	1	0	1
Zhang et al., 2021	1	1	1	1	1	1	1	1

The following authors have no conflict of interest.

(26.3%) presenting with moderate to severe COVID-19-related disease and complications. In this review, the majority of patients presented with mild-moderate symptoms of COVID, neurological features, or psychiatric symptoms, with about one-third of patients presenting with the moderate-severe illness of COVID-19. In patients with moderate-

severe illness, prolonged immobilization, use of steroids, hypoxia, and cytokine storm can result in possible ischemic events and onset of neuropsychiatric symptoms (Kunal et al., 2020; Mehta et al., 2020).

Similar to the data reported by Smith et al. and Parra et al. delusions and hallucinations were common psychotic symptoms, that improved

with antipsychotics (Parra et al., 2020; Smith et al., 2021). Most patients responded to a low-to-moderate dose of antipsychotics with a quicker recovery. About 72% of patients had complete resolution, whereas the remaining patients had residual depression, anxiety, or psychosis symptoms. However, the residual depression, anxiety, or psychosis in a considerable percentage of patients highlights the need for careful monitoring and longer follow-up. Additionally, literature has pointed out the presence of confusion or delirium with psychosis in a subset of patients with COVID-19 that can be misdiagnosed as psychosis (Tripathy et al., 2021). In four pregnant patients with COVID-19, psychosis symptoms were reported that could be potentially due to either COVID-19 or postpartum psychosis.

This review has certain limitations, including a small sample size (57 patients in 47 studies). However, the sample size is higher compared to existing literature (Parra et al., 2020). The case reports/series do not suggest a cause-effect relationship (Hallab et al., 2018). Furthermore, case reports limit the ability to generalize while being affected by publication bias. It is also essential to be aware that 99.1% of published case reports only had positive outcomes and successful treatment, introducing publication bias (Oliveira and Leles, 2006). We excluded patients with delirium and psychosis in this review since patients with delirium can present with psychosis. However, it would facilitate understanding psychosis in patients with COVID-19 that did not present with delirium.

5. Conclusion

Undoubtedly, COVID-19 has disrupted the lives of millions of people worldwide. This review explores the surge in psychosis and highlights the demographics, clinical features, course of illness, treatment, and prognosis of COVID-19 patients developing neuro-psychiatric symptoms. Based on the results of our study, higher age can be potentially a risk factor for the development of psychosis. The psychosis resolved in most of the cases suggesting a favorable prognosis. The majority of patients responded to a low-to-moderate dose of antipsychotics with a quick recovery. However, the residual depression, anxiety, or psychosis in some patients highlights the need for vigilant monitoring and follow-up. Psychosis associated with COVID-19 infection should be one of the differential diagnoses when psychotic patients present to the emergency department. Clinicians should be on the outlook for transient psychosis, worsening of psychotic disorders, and the side effects of medications used to treat COVID-19 while screening for general mental well-being, especially of those with previously stable psychosis.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval

Not applicable.

Disclaimer statement

None to report.

Funding

None.

Acknowledgements

None to report.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpsychires.2022.06.041>.

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