

Unusual Extra Pulmonary Clinical Manifestation as Initial Presenting Feature of COVID-19 and its Management: A Systematic Review of Case Reports

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Abstract

Corona virus disease 2019 (COVID-19) is primarily an infectious disease of the respiratory system. COVID-19 might have unusual extra pulmonary clinical manifestations as initial symptoms. This systematic review included case reports published from January 2020 to June 2022 in English language that met the following criteria: unusual clinical manifestations as a sole or first initial manifestation of COVID-19, Confirmed positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) and real time RT-PCR COVID-19 patients, no history of pre-existing co morbidities or any family, past, personal history and complete details of patients with their management. All the case reports were identified in PubMed and Scencedirect database. The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A total of 14537 studies were screened and 46 case reports were included in this review. In 46 case reports, there were 49 patients (three case reports had two patients) in which 32 were males and 17 were females. Majority of the patients experienced neurological manifestations followed by gastrointestinal manifestations, haematological manifestations and ocular manifestations. Health care professionals should be aware and alert about unusual extra pulmonary clinical manifestations of COVID-19 patients; this would help in making timely diagnosis and accurate treatment of COVID-19 patients.

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Keywords: COVID-19; Case Reports; Extra Pulmonary

Introduction

The first corona virus was isolated from chicken embryos in the 1930 when infectious bronchitis virus caused an acute respiratory tract infection (1). In December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first isolated and identified in patients who were exposed at a seafood market in Wuhan City, Hubei Province, China and it was named 2019 novel corona virus (2). SARS-CoV-2 has been officially named by the International Committee on Taxonomy of Viruses. While World Health Organization named this disease as the corona virus disease 2019

SARS-CoV-2 is transmitted mainly through direct, indirect or close contact with infected persons or their respiratory droplets that are expelled during coughing, sneezing, talking. Corona virus gains entry into host cells through binding of SARS-CoV-2 S-protein to its cell surface receptor, angiotensin converting enzyme 2 (ACE2) initiates viral entry into type II pneumocytes in the human lung (1). The median incubation period for SARS-CoV-2 is estimated to be 5 days and majority of the patients develop symptoms within 2 to 14 days of infection (4). The most common symptoms of COVID-19 are fever (70%-90%), dry cough (60%-86%), shortness of breath (53%- 80%), fatigue (38%), myalgias (15%-44%), nausea/vomiting or diarrhoea

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(15%-39%), headache, weakness (25%), rhinorrhoea (7%) and anosmia or ageusia (3%) (5, 6). However, it is estimated that 17.9% to 33.3% of infected patients may remain asymptomatic (7).

According to The National Institute of Health guidelines, COVID-19 is categorized into five different types such as asymptomatic, pre-symptomatic infection (patients with positive SARS-CoV-2 test without any clinical symptoms), mild illness (patients with any symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, anosmia, or dysgeusia but without shortness of breath or abnormal chest imaging), moderate illness (patients with clinical symptoms or radiologic evidence of lower respiratory tract disease and oxygen saturation (SpO₂) ≥ 94% on room air), severe illness (SpO₂ ≤ 94% on room air with marked tachypnea with respiratory frequency >30 breaths/min or lung infiltrates >50%) and critical illness (patients with acute respiratory failure, septic shock, and/or multiple organ dysfunction) (8).

Although the respiratory system is the primary target for SARS-CoV-2 but initial clinical manifestations from other body systems such as neurological, cardiovascular, hepatobiliary, renal, endocrinological, dermatologic, ocular and gastrointestinal systems may also occur (9). Hence, it is essential for health care professionals to be aware about atypical extra pulmonary symptoms in COVID-19 patients as first presenting features to make the correct diagnosis of COVID-19 without any adjournment for the treatment. In this systematic review, we assessed the case reports of COVID-19 patients that presented with unusual extra pulmonary manifestations as initial presenting feature with the management.

Methods

We conducted a comprehensive literature search and constructed a systematic review. We selected case reports with detailed clinical information about patients regarding identification of COVID-19 and COVID-19 associated extra pulmonary unusual clinical manifestation with its clinical management. All the case reports that described the unusual clinical manifestations

as main clinical symptoms of COVID-19 were identified in PubMed and Scienedirect database.

The search terms included COVID-19, SARS- CoV-2, corona virus, unusual or rare or uncommon or initial, case reports, unusual clinical manifestation, unusual clinical symptoms, unusual clinical presentation. Case reports published from January 2020 to June 2022 and available in English language were assessed in this review.

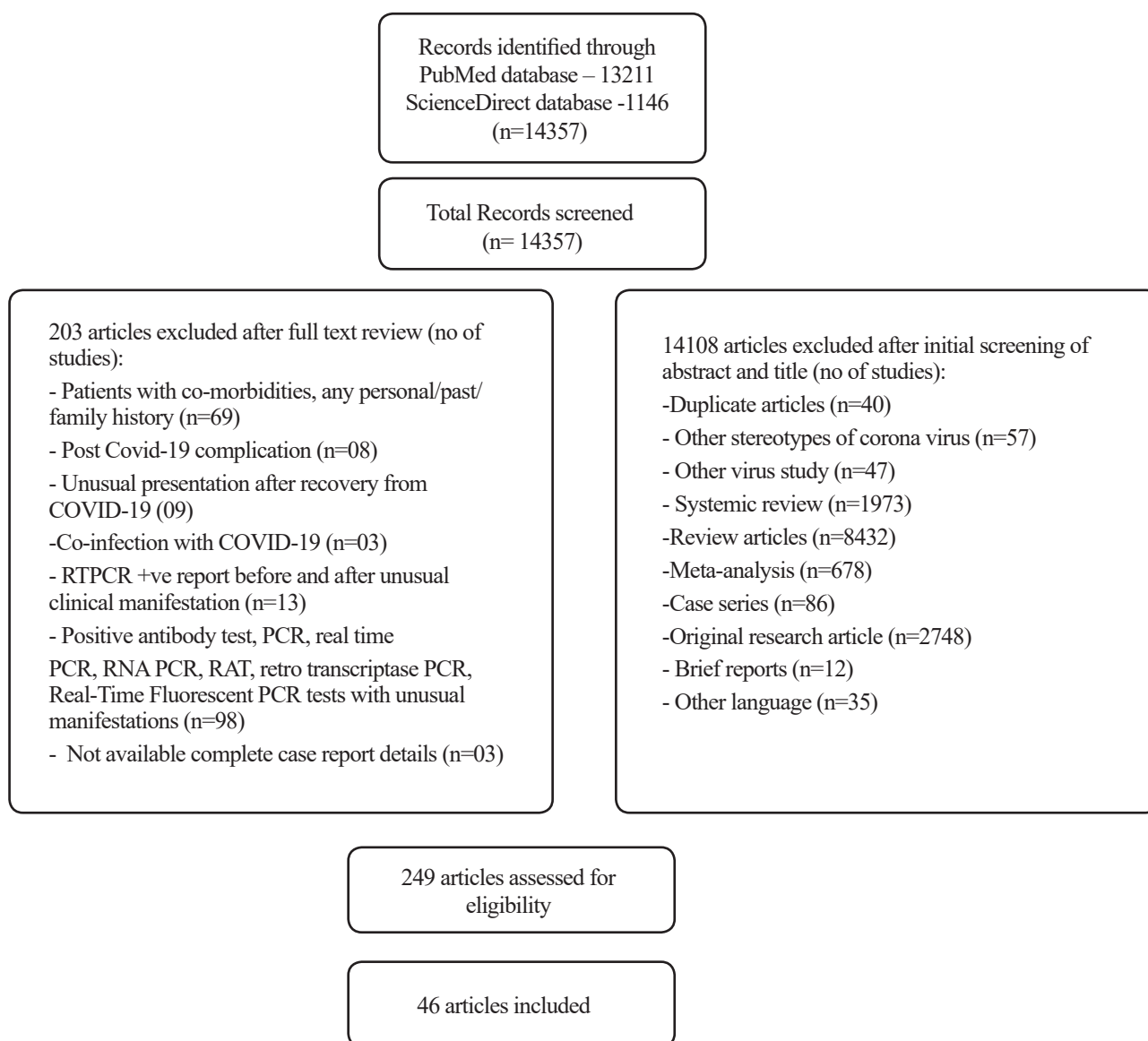
We included the case reports that met the following criteria: unusual clinical manifestations as a sole or first initial manifestation of COVID-19, Confirmed positive Reverse Transcription Polymerase Chain Reaction (RTPCR) and real time RTPCR positive COVID-19 patients, no history of pre-existing co morbidities or any family, past, personal history and complete case reports with demographic details of patients with the management. We excluded the case reports that did not meet our criteria. (figure.1)

The review was carried out by two researchers independently. Both the researchers independently read the full text to identify eligible case reports. After selecting eligible case reports, researchers created a datasheet. Selected case reports were entered by the first researcher and subsequently checked by the second researcher. The collection and analysis of the data was conducted by both the researchers independently. The results of the relevant case reports were summarized, scrutinised, and entered in a datasheet. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The detail of study selection flowchart is shown in Figure 1.

Results

Initially, we found a total of 14357 case reports from the PubMed and ScienceDirect databases. After initial screening, 14108 case reports were excluded as they did not meet our inclusion criteria and 249 case reports were found to be eligible for the systematic review (Figure 1). After reading of 249 case reports, 46 case reports were included in the systematic review.

Figure 1. PRISMA Flow Diagram outlining the process of study selection.



COVID- 19- Corona virus disease 2019, RTPCR-Reverse Transcription Polymerase Chain Reaction,PCR- Polymerase chain Reaction, RAT- Rapid Antigen Test.

Out of 46 case reports, we identified 19 case reports from India followed by 09 case reports from Iran, 04 case reports from USA, 01 case report from Brazil, 01 from Morocco, 01 from Israel, 01 from Italy, 01 from Mexico, 01 from Pakistan, 01 from Switzerland, 01 from Tunisia, 01 from Turkey, 01 from Ghana, 01 from china, 01 from Spain, 01 from Egypt and 01 from Indonesia. In 46 case reports, total number of patients were 49 (three case reports had two patients) in which 32 were males and 17 were females. Out of 49 patients, 34 were adults (19-59 year), 06 patients were senior adults (>60 year), 06 were children (0-12 year) and 03 were adolescent (13-18 year). All patients were confirmed positive cases of COVID-19 as in 37 case reports, diagnosis was confirmed by RT-PCR and in 09 case reports, real time RTPCR test was

performed to confirm COVID-19. Majority of the patients experienced neurological manifestations (n=14) followed by gastrointestinal manifestations (n=10), haematological manifestations (n=6), ocular manifestations (n=5) and other manifestations which are shown in Table 1. All the patients were hospitalized after developing these manifestations. More details regarding the symptoms of COVID-19 patients are mentioned in Table 2. All the patients were managed with respective pharmacological and surgical treatment with supportive care. Complete treatments details of all patients are shown in Table 3. After clinical management, 31 patients were recovered/ discharged, symptoms of five patients were improved, one patient became asymptomatic while seven patients died and five patient’s outcome were not clearly mentioned.

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Table 1. Demographic details of COVID-19 patients.

Out of 14357 studies, 46 case reports were included	
46 Case reports	49 patients (03 case reports had 02 patients)
Gender (n=49)	Males - 32 Females – 17
Age groups (n=49)	Adults (19-59 year) - 34 Senior adults (>60 year) - 06 Children (0-12 year) - 06 Adolescent (13-18 year) - 03
Diagnostic methods used to confirm SARV-CoV-2 infection	RTPCR- 40 real time RTPCR- 09
Extra pulmonary systemic manifestations (n=49)	Neurological -14 Gastrointestinal -10 Haematological - 06 Ocular – 05 Thromboembolic event -03 Cardiovascular - 02 Neuro-ophthalmological -02 Cutaneous -02 ENT -01 Psychiatric -01 Renal -01 Others -02
After clinical management (n=49)	Recovered – 31 Died-07 Improved -05 Outcome not mentioned-05 Asymptomatic -01

COVID- 19- Corona virus disease 2019, SARV-CoV-2 :Severe Acute Respiratory Syndrome Coronavirus 2.,RTPCR-Reverse Transcription Polymerase Chain Reaction, ENT-Ear Nose Throat

Table 2. Details of patient with initial unusual extrapulmonary clinical manifestation of COVID- 19 infection.

References							
Sr no	First author (ref.), country, year	No of patient	Patient details	Method to detect SARS-CoV-2 infection	COVID-19 symptoms	Unusual clinical presentation of COVID-19	Outcome
1	Amaravathi et al. (10), India 2021	1	45yr/M	RTPCR +ve	Acute abdominal pain in the epigastric and umbilical region.	Superior Mesenteric Arterial And Venous Thrombosis	Not reported
2	Davoodi et al (11), Iran 2020	1	57yr/F	RTPCR +ve	Swelling, pain, warmth, and redness in the left leg, mild dry cough	Deep Vein Thrombosis	Discharged
3	Sharma et al (12), India 2021	2	12yr/M	RTPCR +ve	Headache, altered mental status, fever, projectile vomiting.	Acute Fulminant Cerebellitis	Recovered
			10yr/M	RTPCR +ve	Severe occipital headache, non-projectile vomiting, mild left sided dysmetria, dysdiadochokinesia, gait ataxia.		Recovered
4	Fadakar et al (13),Iran 2020	1	47YrM	real-time RTPCR +ve	Body pain, progressive vertigo, headache, and ataxia	Acute Cerebellitis	Improved
5	Ghosh et al (14), India 2020	1	44yr/F	real-time RTPCR +ve	Confused, disorientated, and apractic and developed a memory and thought disorder	Acute hemorrhagic necrotizing encephalitis	Died
6	Esmacili et al (15), Iran 2022	1	67yr/M	RTPCR +ve	Decreased level of consciousness, drowsiness	Acute disseminated encephalitis	Died
7	Naz et al (16),Pakistan 2020	1	21yr/M	RTPCR +ve	Frontal headache and fever 2-days and 1-day history of neck stiffness.	Meningitis	Died
8	Kandasamy et al (17), India 2020	1	45yr/F	RTPCR +ve	Severe sharp epigastric pain radiating to back, nausea and vomiting.	Acute pancreatitis	Recovered
9	Bineshfaz et al (18),Iran 2021	1	14yr/M	RTPCR +ve	Abdominal pain in the epigastric region associated with anorexia, nausea, and vomiting	Acute Pancreatitis	Discharged
10	Mohammadi Arbati et al (19),Iran 2021	1	28yr/M	RTPCR +ve	Severe stabbing abdominal pain in the epigastric region with radiation to the back with frequent nausea and vomiting	Acute Necrotizing Pancreatitis	Discharged
11	Kenchappa et al (20), India 2020	1	10yr/ F	RTPCR +ve	Nausea, acute pain abdomen, tenderness in the right iliac fossa	Bowel Gangrene	Recovered
12	Tariverdi et al (21), Iran 2021	1	27m/F	RTPCR +ve	Fever, vomiting, and loose stool for 2 days	Dysentery	Discharged
13	Guotao et al (22),China 2022	1	83yr/M	real-time RTPCR +ve	Dark-red bloody stools 200 mL 2–3 times per day, fatigue, and poor appetite	Hematochezia	Not mentioned
14	Banerjee et al (23), India 2021	1	42yr/M	RTPCR +ve	Acute onset urinary retention, constipation, weakness of both legs, severe weakness of ankle dorsi and plantiflexion.	Conus Myelitis	Recovered
15	Natarajan et al (24), India 2020	1	13yr/F	RTPCR +ve	Febrile, irritable, altered sensorium, brisk deep tendon reflexes with an extensor plantar response.	Encephalitis	Recovered
16	Urso et al (25), Italy 2022	1	05Yr/F	RTPCR +ve	Painful tumefaction in the right latero-cervical area, with a large erythematous patch.	Encephalitis	Discharged

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Table 2. Continued

Sr no	First author (ref.), country, year	No of patient	Patient details	Method to detect SARS-CoV-2 infection	COVID-19 symptoms	Unusual clinical presentation of COVID-19	Outcome
17	Amarapurkar et al (26), India 2020	1	61yr/M	RTPCR +ve	Severe abdominal pain, vomiting.	Haemorrhagic enteritis	Not mentioned
18	Gupta et al (27), USA 2020	2	14yr/M	RTPCR +ve	Acute onset of severe epigastric and lower abdominal pain, nausea, and one episode of vomiting	Severe Enteritis	Discharged
			20yr/F	RTPCR +ve	Severe lower abdominal pain, vomiting, reduced appetite, and diarrhoea, with blood in stools for 1 day		Discharged
19	Singhavi et al (28), India 2020	1	20yr/M	RTPCR +ve	Flu-like symptoms	Hemolytic Anemia With Acute Myocarditis and Cardiogenic Shock	Discharged
20	Rehman et al (29), USA 2020	1	39yr/M	RTPCR +ve	Pain as a heaviness which felt sharp and lasted several hours long	Myocarditis	Discharged
21	Khan IA et al (30), India 2020	1	48yr/F	RTPCR +ve	Two tender necrotic indurated plaques with focal haemorrhagic bulla, peripheral retiform purpura	Purpura fulminant	Died
22	Kumar et al (31), India 2021	1	25yr/M	RTPCR +ve	Sudden diminution of vision in left eye associated with fever and myalgia	Unilateral submacular hemorrhage	Resolved
23	Sharma et al (32), India 2021	1	22yr/F	real-time RTPCR +ve	Acute-onset blurring of vision and perceiving an absolute scotoma in the inferior field of vision in the right eye.	Unilateral inferior altitudinal visual field defect	Discharged
24	Ben-David et al (33), Israel 2021	1	44yr/M	RTPCR +ve	fever, double vision, and headache, fatigue, generalized muscle weakness, and loss of appetite	Abducens nerve paresis	Discharged
25	Belghmaidi et al (34), Morocco 2020	1	24yr/F	RTPCR +ve	Scute onset of strabismus and diplopia of the left eye, fever, dry cough, and anosmia	Third Cranial Nerve Palsy	Recovered
26	Eleiwa et al (35), Egypt 2021	1	10yr/M	RTPCR +ve	Periorbital dull-ache swelling, drooping of upper eyelid, binocular horizontal diplopia on left gaze, painful eye movement, redness of the eye, low-grade fever, nausea, vomiting.	Orbital inflammatory disease	Improved
27	Georgy et al (36), India 2021	2	33yr/M	RTPCR +ve	Gum bleeding, black tarry stools, reddish spots on the skin, petechial lesions over the chest, legs, and oral mucosa.	Evans syndrome	Died
			54yr/M	RTPCR +ve	Low-grade intermittent fever and sore throat	Immune thrombocytopenia	Discharged
28	Sadr et al (37), Iran 2020	1	57 yr/F	RTPCR +ve	Headache and malaise	Isolated severe thrombocytopenia	Discharged
29	Kaushik et al (38), India 2021	1	56yr/M	RTPCR +ve	Fever, weakness in bilateral lower limbs.	Hypokalaemic Paralysis	Discharged
30	Vasanthapuram et al (39), India 2021	1	58yr/M	RTPCR +ve	Sudden onset of binocular diplopia.	Internuclear ophthalmoplegia	Discharged
31	Rodríguez-Rodríguez et al (40), Mexico 2021	1	55yr/F	real-time RTPCR +ve	persistent headache and left eye pain exacerbated with eye movements, unilateral & gradual visual loss, decreasing visual acuity, and chromatic impairment	Optic neuritis	Improved

Table 2. Continued

Sr no	First author (ref.), country, year	No of patient	Patient details	Method to detect SARS-CoV-2 infection	COVID-19 symptoms	Unusual clinical presentation of COVID-19	Outcome
32	Ghosh et al (41), India 2021	1	44yr/F	real-time RTPCR +ve	Severe headache, projectile vomiting, progressive asymmetric visual blurriness.	Pituitary Apoplexy	Discharged
33	Katti et al (42),India 2021	1	46yr/M	RTPCR +ve	Sudden loss of vision in both eyes.	Pituitary apoplexy	Discharged
34	Ramesh et al (43), India 2021	1	22yr/ F	real-time RTPCR +ve	Fever, headache, diplopia, recurrent episodes of transient loss of vision in both eyes.	Papilledema secondary to cerebral venous thrombosis	Discharged
35	Mehrabi Nasab et al (44),Iran 2021	1	83yr/M	RTPCR +ve	Sudden pallor, pain, and paresthesia in his left upper limb in the past 10 hrs.	Acute upper limb ischemia	Died
36	Singh et al (45),USA 2020	1	77yr/M	RTPCR +ve	Shortness of breath , pain, discoloration, and swelling of the left leg	Acute Limb Ischemia	Not Mentioned
37	Nasseh et al (46), Tunisia 2021	1	68yr/M	RTPCR +ve	Epigastric pain and diarrhea, hypogastric tenderness	Mesenteric Large vessel obstruction	Asymptomatic
38	Gupta et al (47), India 2021	1	49yr/F	RTPCR +ve	Subacute onset, gradually progressive, symmetric proximal muscle weakness of all four limbs	Myositis	Discharged
39	Fidan et al (48),Turkey 2020	1	35 yr/F	real-time RTPCR +ve	Otalgia and tinnitus.	Acute otitis media	Not mentioned
40	De Sene et al (49), Brazil 2021	1	29yr/M	real-time RTPCR +ve	Hiccups in the last 2 days.	Persistent hiccups	Discharged
41	Lovi et al (50), Ghana 2022	1	35yr/M	RTPCR +ve	Talkativeness, incoherent speech, visual hallucinations, auditory hallucinations, and insomnia for several days	Psychosis	Recovered
42	Suter et al (51), Switzerland 2020	1	42yr/M	RTPCR +ve	Painful tender violaceous lesions on both shins, fever, headache, severe fatigue and dry cough.	Erythema nodosum	Discharged
43	Danarti et al (52), Indonesia 2020	1	50yr/M	RTPCR +ve	Itchy skin lesions all over his body, extremities, neck and face, stinging feelings, with a burning sensation	Follicular eruption	Improved
44	Desai et al (53), USA 2021	1	21yr/M	RTPCR +ve	Right lower quadrant pain radiating to the right testicle for the past two days	Testicular Pain and Mesenteric Adenitis	Improved
45	Bozorgmehr et al (54),Iran 2021	1	21yr/M	RTPCR +ve	Fever, chills, haemoptysis	Haematuria	Died
46	Águila-Gordo et al(55), Spain 2020	1	50yr/M	RTPCR +ve	Dysesthesia at lower limbs and genital area, loss of strength and inability to maintain stable standing position and urinary incontinence	Acute myelitis	Recovered

Sr no- Serial no, COVID- 19- Corona virus disease 2019, SARV-CoV-2 -Severe Acute Respiratory Syndrome Coronavirus 2,RTPCR-Reverse Transcription Polymerase Chain Reaction.

Discussion

COVID-19 is primarily an infectious disease of the respiratory system. However, COVID-19 patients exhibit clinically diverse manifestations which range from asymptomatic to rapid progression to multiple organ failure and even death in severely ill patients (5). In addition, Patients of all age groups are at risk of SARS-CoV-2 infection but patients ≥ 60 years of age and with underlying medical co morbidities including obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung disease, cancer, solid organ or hematopoietic stem cell transplant have greater risk of developing severe COVID-19 infection. Stokes EK et al. (56) described that COVID-19 patients with co morbidities need hospitalization six times more as compared to patients without medical conditions (56). In present review, we selected the case reports of COVID-19 patients who had no pre-existing co morbidities to yield meticulous evidence regarding early extra pulmonary unusual clinical presentation associated with COVID-19 infection. Wiersinga et al., (6) stated that 74% to 86% hospitalized COVID-19 patients were aged at least 50 years. Similarly, in this review, we have observed that around 69% of the hospitalized COVID-19 patients (n=34) were in the adult age group. Gebhard et al., (57) reported that male COVID-19 patients are at higher risk of developing severe illness and mortality as compared to female COVID-19 patients (2,8). Likewise, we have noticed that 65% male COVID-19 patients (n=32) had unusual clinical symptoms.

COVID-19 is a complex infectious disease with varying clinical presentations and complications. In addition to respiratory symptoms, patients may present with extra pulmonary organ specific manifestations. Tsai et al., (5) reported that neurological symptoms has been reported in 36% of the severe COVID-19 patients (5). Hyposmia, hypogeusia, headache, seizures, stroke, sinus venous thrombosis, altered consciousness, demyelination, neuropathy, myalgia, dysautonomia and polyradiculitis are typical neurological presentations associated with SARS-CoV-2 infection (58-61). Whereas in this review, we have included the case reports of acute fulminant cerebellitis (12), acute cerebellitis (13), acute hemorrhagic necrotizing encephalitis (14), acute disseminated encephalitis (15), meningitis (16), conus myelitis (23), encephalitis (24,25), hypokalaemic paralysis (38), pituitary apoplexy (41,42), myositis (muscle weakness of all four limbs) (47) and acute myelitis (55) as sole atypical neurological manifestations in COVID-19. The aforementioned neurological manifestations could occur due to several mechanisms such as corona virus induced inflammation, neuronal damage secondary to cytokine storm with upregulation of inflammatory markers, post-acute respiratory distress syndrome or pneumonia induced

hypoxia, prothrombotic state due to endothelial damage, embolic events after SARS-CoV2 ACE2R mediated vascular damage and disruption of the blood-brain-barrier (62-64). Exact mechanism of COVID-19 related myositis is unknown but it could be due to deposition of virus antibody complexes on myocytes, muscle damage by circulating viral toxins, molecular mimicry between virus antigen and muscle protein, expression of muscle antigen on the cell membrane induced by the virus, and damage caused by a cytokine storm (65,66).

Gastrointestinal (GI) symptoms (incidence - 12% to 61%) in COVID-19 patients have been associated with a longer duration of illness (5). COVID-19 associated GI symptoms include anorexia, diarrhoea, nausea, vomiting and abdominal pain or discomfort (67). In the present review, we have included the case reports with uncommon GI manifestation of acute pancreatitis (17-19), bowel gangrene (20), dysentery (21), haematochezia (22), haemorrhagic enteritis (26) and severe enteritis (27) and mesenteric large vessel obstruction (46) as initial manifestations of COVID-19. Pancreatitis in COVID-19 could occur due to the direct cytopathic effect of local SARS-CoV-2 replication or indirectly by corona virus induced systemic immune response (68). Bowel gangrene may be explained by COVID-19 related inflammation and thrombosis present in the mesenteric vessels which might be responsible for bowel ischemia and strangulation of hypovascular area of the mesentery (20).

In COVID-19 patients, well known haematological common presentations related to the arterial or venous occlusion are stroke, myocardial infarction, deep venous thrombosis and pulmonary embolism (69). In this review, we have included case reports of superior mesenteric arterial and venous thrombosis (10), deep vein thrombosis (11), purpura fulminant (30), Evans syndrome (36), immune thrombocytopenia (36) and isolated severe thrombocytopenia (37) as first unusual haematological manifestations of COVID-19. Possible mechanisms of overall haematological manifestation associated with COVID-19 include hypoxia, inflammatory mediators, thrombocythemia, immobilization, and liver injury secondary to ACE2 receptor expression (70). Around 30% Intensive Care Unit COVID-19 patients have reported thromboembolic symptoms (5). In current review, we have found the case reports of papilledema (43) and acute limb ischemia (44,45) as main unusual thromboembolic presentation in COVID-19 patients. Mechanisms of the thromboembolic events associated with COVID-19 are dysfunction of endothelial cells caused by virus, leading to excess thrombin generation and inhibition of fibrinolysis with raised prothrombin levels (71). Moreover, hypoxemia is associated with an elevation of blood viscosity and activation of hypoxia related genes favouring the thrombotic events such as the

coagulation and fibrinolysis (72).

With regard to ocular manifestations, conjunctivitis, redness, episcleritis, vascular occlusions, dacryoadenitis, discharge, mucormycosis have been commonly reported in COVID-19 patients (73). In this review, we have included the case reports of unilateral submacular haemorrhage 31, unilateral inferior altitudinal visual field defect (32), abducens nerve paresis (33), third cranial nerve palsy (34) and orbital inflammatory disease (35) as rare ocular manifestations of COVID-19. The proposed mechanisms for unilateral inferior altitudinal visual field defect related to COVID-19 are direct viral involvement or a delayed immune response to the viral antigen (74) while unilateral submacular haemorrhage can occur due to endothelial damage involving retinal capillaries which results in microthrombi and microvascular dysfunction (75). In addition to above ocular symptoms, neuro-ophthalmological manifestations can also occur in COVID-19 patients such as acute transverse myelitis, viral encephalitis, toxic encephalopathy, leukoencephalopathy, acute disseminated encephalomyelitis, diffuse corticospinal tract signs and Miller Fisher syndrome (76, 77). In present review, we have quoted the case reports of internuclear ophthalmoplegia (39) and optic neuritis (40) as infrequent neuro-ophthalmological manifestations of COVID-19. Multiple mechanisms have been proposed for these manifestations which include post viral inflammatory syndrome, sequelae of a proinflammatory state or as a consequence of systemic conditions, such as cardiovascular disease or uncontrolled hypertension, haematological spread and direct viral invasion (77,78).

Around 20% to 30% critically ill hospitalized COVID-19 patients have been reported to have myocardial injury with higher degree of troponin elevations, biventricular cardiomyopathy, prolonged QTc, arrhythmias and cardiac arrest (79,5,80,81). We have included the case reports of haemolytic anaemia with acute myocarditis and cardiogenic shock (28) and myocarditis (29) as foremost manifestations of cardiovascular system associated with COVID-19. It is anticipated that high catecholamine, direct viral cytotoxicity, exaggerated inflammatory/immune-mediated response and consequent effects of acute anaemia may be possible mechanisms behind the presentation of haemolytic anaemia with acute myocarditis and cardiogenic shock in COVID-19 patients (28).

Additionally, COVID-19 patients may present with initial clinical manifestations of other body systems involvement such as Ear Nose Throat (ENT), psychiatric, dermatological and renal. The most common ENT manifestations in COVID-19 are sore throat (11.3%) and headache (10.7%) (82). We have included a case report of a COVID-19 patient who presented with acute otitis media (48) as an uncommon ENT manifestation. SARS-

CoV-2 affects long-term cognitive and neurological functions and may cause psychiatric illness. Common psychiatric illness observed in COVID-19 patients have been anxiety, depressed mood, fatigue, irritability, insomnia, and impairment of attention, concentration, and memory (83). In the present review, we have included a case report of psychosis as an unusual psychiatric illness in COVID-19 patient (50).

Common cutaneous manifestations associated with COVID-19 include morbilliform rash, acral lesions, urticarial, macular erythema, vesicular eruption, and retiform purpura. (84,85) We have included case reports of erythema nodosum (51) and follicular eruption (52) as dermatological manifestations in COVID-19 patients. Common renal symptoms in COVID-19 patients have been proteinuria, pyuria and acute kidney injury (86). We have included a case report of haematuria as an uncommon renal manifestation of COVID-19 patient (54). In addition, we have included the case reports of other nonspecific symptoms such as persistent hiccups (49) and testicular pain with mesenteric adenitis (53) as initial manifestations of COVID-19 infection.

In the systematic review, all the patients with unusual extra pulmonary presentation were hospitalized and treated with respective therapeutic strategies with 14% mortality. Richardson et al., (87) has reported overall 15 to 20 % mortality in hospitalized COVID-19 patients and 40% mortality in Intensive Care Unit patients (87).

There are several limitations in our systematic review. We did not include observational, original research, case series, retrospective, and systematic review or meta-analysis studies. The number of case reports included in this systematic review is low. We did not include the COVID-19 patients with common extra pulmonary symptoms, patients with any pre-existing disease and any family, past or personal history, unusual manifestations after recovery of infection, complications associated with COVID-19 pneumonia and patients with negative RTPCR test having unusual symptoms. We excluded the case reports in which other diagnostic methods were used to detect SARS-CoV2. In addition, we did not include SARS-CoV-2 loads in urine, sera and stool specimens associated with unusual manifestations of COVID-19 patients.

Conclusion

SARS-CoV-2 is a novel and typical respiratory virus disease which is highly contagious and subsequently can cause lethal consequences. COVID-19 patients may present with atypical extra pulmonary clinical manifestations as first symptom of the disease and it could be difficult to identify them as clinical symptoms

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of SARS-CoV-2 infection. Therefore, health care professionals should be aware and alert regarding the various organ systems affected and atypical extra pulmonary clinical manifestations in COVID-19 patients. This systematic review has categorized the possible

body systems involvement in COVID-19 infection with detailed case reports and the management that would facilitate an early diagnosis and accurate treatment of COVID-19 patients which would further help to stop the infection transmission chain in the community.

Table 3. Initial different systemic manifestation of COVID-19 infection and treatment.

Systemic manifestation of COVID-19 (no of patients)	Unusual Clinical Presentation Of COVID-19 (Ref)	Treatment
Neurological manifestations (n=14)	Acute Fulminant Cerebellitis (02 patients) (12)	External ventricular drain , steroids and acyclovir for 14 days External ventricular drain , steroids and acyclovir for 14 days
	Acute Cerebellitis (13)	lopinavir/ritonavir 400/100 mg twice daily for 14 days.
	Acute Hemorrhagic Necrotizing Encephalitis (14)	IV ceftriaxone (4 g/d), vancomycin (2 g/d), acyclovir (1.5 g/d), levetiracetam(1 g/d), saline 0.9% (1.5 l/d), mannitol (300 ml/d), IV methylprednisolone (1 g/d) for 5 days.
	Acute Disseminated Encephalitis (15)	Methylprednisolone 1 g IV daily for 5 days, IV Immunoglobulin 0.4 g/kg daily for 5 days after Methylprednisolone pulse therapy
	Meningitis (16)	Oxygen saturation
	Conus Myelitis (23)	IV pulse methylprednisolone (1G/day)
	Encephalitis (24)	Levetiracetam and ceftriaxone
	Encephalitis (25)	IV ceftriaxone (50 mg/kg/ day), vancomycin (15 mg/kg/day), acyclovir (0.8 mg/kg every 8 h), steroids (dexamethasone 0.6 mg/kg/day)
	Hypokalaemic Paralysis (38)	Oral potassium supplements, multivitamins, hydroxychloroquine, favipiravir and ivermectin.
	Pituitary Apoplexy(41)	IV dexamethasone (24 mg/day), clonazepam (2 mg/day), normal saline (0.9%), acetaminophen infusion and broad-spectrum β -lactam antibiotics.
	Pituitary Apoplexy (42)	IV antibiotics, multivitamin, lowmolecularweight heparin 40 mg once a day, oral zinc tablets, vitamin C, aspirin 75 mg, atorvastatin 20 mg, ivermectin 12 mg once a day, and doxycycline 100 mg twice a day.
	Myositis (47)	2 g/kg of intravenous immunoglobulin divided over 5 days and supportive care
	Acute Myelitis (55)	Hydroxychloroquine plus Lopinavir/Ritonavir, Dexamethasone and immunoglobulins
Haematological manifestations (n=06)	Superior Mesenteric Arterial And Venous Thrombosis (10)	IV unfractionated heparin, laparotomy with Superior Mesenteric Arterial thrombectomy.
	Deep Vein Thrombosis (11)	IV bolus heparin 80 units/kg then 18 units/kg/h, chloroquine 400 mg single dose, lopinavir/ritonavir 400 mg twice daily, rivaroxaban (10 mg per os daily)
	Purpura Fulminans (30)	Anticoagulation therapy
	Evans Syndrome (36)	Pulse dexamethasone 40 mg, platelet transfusions.
	Immune Thrombocytopenia (36)	Dexamethasone 6 mg
Isolated Severe Thrombocytopenia (37)	No treatment	

Table 3. Continued

Systemic manifestation of COVID-19 (no of patients)	Unusual Clinical Presentation Of COVID-19 (Ref)	Treatment
Ocular manifestations (n=05)	Unilateral Submacular Haemorrhage (31)	Intravitreal injection of ranibizumab
	Unilateral Inferior Altitudinal Visual Field Defect (32)	Injection methylprednisolone 1 g , oral prednisolone
	Abducens Nerve Paresis (33)	Azithromycin and hydroxychloroquine for 5 days
	Third Cranial Nerve Palsy (34)	Chloroquine 500 mg 2 times per day for 10 days, azithromycin 500 mg once a day the first day, then 250 mg every day for 6 days), vitamin C 1 g 2 times a day for 10 days and Zinc 90 mg 2 times a day for 10 days
	Orbital Inflammatory Disease (35)	Azithromycin 200 mg/5 ml suspension (5 ml once daily for 5 days , oral prednisone 1 mg/kg/ day for 2 weeks
Gastrointestinal manifestations (n=10)	Acute Pancreatitis (17)	Fluid replacement, optimization of electrolyte balance and empiric antibiotics
	Acute Pancreatitis (18)	Bowel rest, IV crystalloid fluid resuscitation, ondansetron, pantoprazole, ceftriaxone and metronidazole
	Acute Necrotizing Pancreatitis (19)	Supportive care (the nasogastric tube was fixed, resuscitation with intravenous crystalloid fluid, empiric antibiotic (vancomycin, cefepime), high-flow oxygen therapy, analgesia, and pantoprazole, oral treatment with oseltamivir, hydroxychloroquine, and ribavirin
	Bowel Gangrene (20)	Explorative laparotomy
	Dysentery (21)	Intravenous hydration and ceftriaxone
	Hematochezia (22)	oral pantoprazole, dexamethasone injection
	Haemorrhagic Enteritis (26)	Explorative laparotomy with resection of bowel segment and ileostomy
	Severe Enteritis (02 Patients) (27)	vitamin C, vitamin D, thiamine, zinc, melatonin, hydroxychloroquine, and famotidine For ileitis cefoxitin, metronidazole, and methylprednisolone 40 mg/day IV fluid, IV dexamethasone 6 mg/day, vancomycin and piperacillin/tazobactam
Mesenteric Large Vessel Obstruction (46)	Unfractionated heparin	
Cardiovascular manifestations (n=02)	Hemolytic Anemia With Acute Myocarditis And Cardiogenic Shock (28)	IV noradrenaline infusion, low molecular weight heparin, IV vitamin K, diuretics, injection methylprednisolone pulse therapy, cardiogenic shock
	Myocarditis (29)	Cardiac catheterization, acetaminophen
Neuro-ophthalmological manifestations (n=02)	Internuclear Ophthalmoplegia (39)	Vitamin B12 , oral doxycycline twice a day, ivermectin and vitamin C
	Optic Neuritis (40)	Supplementary oxygen and IV methylprednisolone 1 g/day for 5 days, followed by an oral prednisone taper
Thromboembolic event manifestation (n=03)	Papilledema Secondary To Cerebral Venous Thrombosis (43)	SC heparin, IV methylprednisolone and antibiotics
	Acute Upper Limb Ischemia (44)	Anticoagulation therapies
	Acute Limb Ischemia (45)	Ceftriaxone, azithromycin, hydroxychloroquine, and therapeutic anticoagulation with heparin, thrombectomy

Unusual Extra Pulmonary Clinical Manifestation as Initial Presenting Feature

Table 3. Continued

Systemic manifestation of COVID-19 (no of patients)	Unusual Clinical Presentation Of COVID-19 (Ref)	Treatment
ENT manifestations (n=01)	Acute Otitis Media (48)	Oseltamivir 75 mg orally every 12 h 7 days
Psychiatric manifestations (n=01)	Psychosis (50)	IM chlorpromazine, oral olanzapine 10 mg, oral carbamazepine 500 mg daily
Cutaneous manifestations (n=02)	Erythema Nodosum (51)	Betamethasone cream, paracetamol and tramadol
	Follicular Eruption (52)	Azithromycin 500 for 3days, hydroxychloroquine 200mg for 5days, oseltamivir 75mg for 5days, paracetamol when needed 500mg, Zegavit and Folavit.
Renal manifestation (n=01)	Hematuria (54)	Endotracheal intubation, anti-viral and antibiotic therapy
Others (n=02)	Persistent Hiccups (49)	Chlorpromazine
	Testicular Pain And Mesenteric Adenitis (53)	No treatment.

COVID- 19- Corona virus disease 2019, IV- Intravenous, IM- Intramuscular, SC- Subcutaneous, ENT-Ear Nose Throat

Conflict of Interest

The authors declare no conflict of interest.

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