Clinical Manifestations of Corona Virus Disease

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3.1 Introduction

COVID-19, formerly called “2019 novel coronavirus” or “2019-nCoV,” is the name given to the disease caused by a new strain of coronavirus, called severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2. SARS-CoV-2 belongs to the family of highly contagious β-coronaviruses, including the fatal severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). However, compared to its predecessors, SARS-CoV-2 is less fatal, with a greater number of asymptomatic cases, thereby resulting in extensive spread of COVID-19 in significantly larger number of individuals worldwide.

As per the latest World Health Organization (WHO) situation report, SARS-CoV-2 has an overall case fatality rate of 1.4%, with the documented rates varying widely from <1% to >7%, depending on the study population demographics [1]. However, the results of recently conducted seroprevalence studies from across the world have demonstrated that that the actual number of infected cases is much higher than the cumulative number of confirmed infections, probably due to lack of screening of asymptomatic or mildly symptomatic (paucisymptomatic) individuals [2, 3]. Hence, the reported fatality rates based on confirmed cases may be higher than rates based on number of infections, falsely elevating the rates of hospitalization, critical condition, and disease fatality. Nevertheless, SARS-CoV-2 appears to have a complex and unpredictable disease course and needs further elucidation. The enormous wealth of data generated on SARS-CoV-2 to date suggests that it can
affect anyone—from infants to the elderly, male and female, newborn and pregnant women—resulting in a wide variety of clinical signs and symptoms, with varying disease severity.

### 3.2 Clinical Manifestations of COVID-19

COVID-19 has indeed baffled the healthcare professionals worldwide with its widespread symptomatology, multiorgan involvement, and a wide spectrum of disease severity ranging from asymptomatic to symptomatic but mild or moderate, to severe requiring intensive care management, and to the disease being fatal (Table 3.1). As per WHO, approximately 80% of infections in COVID-19 are mild-to-moderate or asymptomatic; 15% develop severe disease that requires supplemental oxygen; and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, acute kidney injury, thromboembolism, and/or multiorgan failure [4]. Other acute and life-threatening conditions that have been described in COVID-19 patients include acute pulmonary embolism, acute coronary syndrome, delirium, and acute stroke.

Symptomatic cases often develop a wide spectrum of clinical manifestations on an average of 5–6 days (can be up to 14 days) after exposure to the virus (Table 3.2).

| Disease severity | Clinical criteria |
|------------------|-------------------|
| Asymptomatic     | No clinical symptoms  |
|                  | No findings on chest imaging |
| Mild disease     | Symptomatic patients with minimal symptoms |
|                  | No hypoxia |
|                  | No evidence of viral pneumonia in chest imaging studies |
| Moderate         |  |
| disease          | Pneumonia |
|                  | Presence of fever, cough, dyspnea, and fast breathing but no signs of severe pneumonia |
|                  | SpO$_2$ ≥ 90% on room air |
|                  | Multiple limited patchy shadows and interstitial changes in chest imaging |
| Severe disease   | Severe pneumonia |
|                  | Presence of fever, cough, dyspnea, and fast breathing with either respiratory rate of >30 breaths per minute or severe respiratory distress or SpO$_2$ < 90% on room air or PaO$_2$/FiO$_2$ ≤ 300 mmHg |
|                  | Multilobular disease or lesion progression of >50% within 48 h |
|                  | Sequential organ failure assessment of ≥2 points and/or other clinical conditions requiring hospitalization |
| Critical         | Acute respiratory distress syndrome with chest imaging showing bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules |
| disease          | Sepsis |
|                  | Septic shock |
|                  | Multiorgan dysfunction |

$SpO_2$ blood oxygen saturation level, $PaO_2$ arterial blood partial pressure of oxygen, $FiO_2$ fraction of inspired oxygen
In addition, COVID-19 is characterized by a high proportion of asymptomatic cases, who despite being infected [i.e., detected positive for nucleic acid of SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR)] does not develop any typical clinical symptoms or signs and no apparent abnormalities in images, including lung computed tomography (CT). Al-Sadeq et al. performed a systematic review of 63 studies from around the world to estimate the incidence of asymptomatic COVID-19 cases [5]. Authors found a great heterogeneity in the reported data, with studies having a large sample size (n > 1000 cases), showing a lower incidence, ranging from 1.2 to 12.9%, while studies with a smaller sample size (n < 1000) reported a much higher incidence of up to 87.9%. Apparently, the term “asymptomatic cases” in literature has been broadly applied to include all those cases who are either completely asymptomatic, have mild symptoms or CT chest
findings, and do not seek medical advice (paucisymptomatic), or develop symptoms beyond the incubation period (presymptomatic). A follow-up study of 24 asymptomatic RT-PCR-positive patients done in China showed that 60% of them were presymptomatic and showed COVID-19 symptoms after a period of 1–3 weeks [6]. Similarly, in a meta-analysis of 38 studies with 506 asymptomatic cases, abnormal chest CT imaging was found in approximately 62% of cases, with ground-glass opacity being the most frequently observed abnormality (43.09%) [7]. Of note, patients with normal CT scan findings were younger than patients with abnormal CT. However, irrespective of the terminology applied for these asymptomatic cases in general, recent virologic, epidemiologic, and modeling reports have supported the possibility of SARS-CoV-2 transmission from either of them, therefore reinforcing the adoption of isolation measures by everyone infected with this virus [8].

SARS-CoV-2 apparently infects mostly adults, with the average age of hospitalized patients being 49–56 years [9–12]. Children account for approximately 1–5% of diagnosed COVID-19 cases and appear to have a mild course of disease with an overall good prognosis [13]. Very old people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, absence of fever or low-grade fever, reduced alertness, reduced mobility, diarrhea, loss of appetite, and delirium [14, 15]. Available literature also reveals a slight male predominance (54–73%) in the incidence of COVID-19, suggesting that males are more susceptible to SARS-CoV-2 infection than females [12]. However, this observed gender difference could be the result of differences in susceptibility and exposure to the virus, along with bias in reporting or diagnosis of infection. Elderly male patients (over 60 years), smokers, and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, cerebrovascular disease, chronic kidney disease, immunosuppression, and cancer are at the highest risk of getting severe disease and death, probably due to the attenuated early immune response [16, 17].

3.2.1 General Systemic Manifestations

To date, fever, cough, and/or shortness of breath have been described as the three most prevalent and typical clinical manifestations in COVID-19 patients, which are similar to any other respiratory viral illness [9–11]. In a systematic literature review with meta-analysis on clinical findings of COVID-19, fever (88.7%), cough (57.6%), and dyspnea (45.6%) were identified as the most common presenting symptom in 632 hospitalized patients with confirmed COVID-19 [10]. In another recent meta-analysis of 80 studies, fever (87%) and cough (68%) were the most commonly reported symptoms by a bigger cohort of 61,742 patients infected with SARS-CoV-2 [11].

Apparently, most initial studies on COVID-19 clinical manifestations highlighted only fever and cough as the common symptom, since in the initial stages of the pandemic the diagnostic testing was limited to only severe symptomatic cases [18]. However, the clinical data collected after the expansion of the number and
types of patients eligible for diagnostic testing reflects a more complete COVID-19 symptom profile, including symptoms such as new changes in taste and smell (anosmia/hyposmia and ageusia/hypogeusia), anorexia, soreness in throat, rhinorrhea, nasal stuffiness or congestion, dyspnea, chest tightness or heaviness, cough with excessive mucus production and expectoration, hemoptysis, headache, dizziness, fever with chills, fatigue or myalgia, arthralgia, nausea, vomiting, abdominal pain, and diarrhea [19]. In addition, some patients may report even nonspecific or vague symptom such as chills and a “tickle in throat,” without cough and normal chest radiograph.

3.2.2 Respiratory Manifestations

Lung involvement is the most common manifestation of COVID-19, ranging from mild pneumonia to severe disease associated with hypoxia and finally critical disease associated with ARDS and death. [9, 12, 14, 16–18, 20] The most common clinical manifestations of pneumonia cases associated with COVID-19 include fever, non-productive cough, and dyspnea, which are consistent with the manifestation of lower respiratory tract infections. Compared with moderate cases, severe cases more frequently report chest tightness along with tachypnea and dyspnea (with oxygen saturation level (SpO2) of 90% or lower and showing no improvement even with high-flow nasal cannula [12]. Out of 82 patients admitted at a single institution in India with confirmed COVID-19, up to 75% patients were admitted with severe pneumonia, with a mortality rate as high as 28% [20].

Hypoxia is frequently a presenting feature of COVID-19 pneumonia [21]. However, one atypical presentation is the occurrence of extremely low SpO2 levels along with normal breathing, commonly being referred to as “silent hypoxemia” or “apathetic hypoxia” or “happy hypoxia.” [22] Though it is insidious in onset and initially well tolerated by patients, it can be a harbinger of sudden clinical deterioration with rapid progression to severe hypoxia and respiratory failure [21, 23]. Elucidating the different clinical findings of severe hypoxemia,Gattinoni et al. have identified two distinct phenotypes of COVID-19 pneumonia [24]. At the beginning, COVID-19 pneumonia presents with Type L phenotype characterized by low elastance (i.e., high compliance), low ventilation-to-perfusion ratio, low lung weight with only ground-glass densities present on CT scan (primarily located subpleurally and along the lung fissures), and very little amount of non-aerated recruitable tissue. The near-normal lung compliance and increased respiratory drive explains absence of dyspnea with hypoxemia. As the disease progresses, Type L may evolve into Type H COVID-19 pneumonia in nearly 20–30% of patients. It is characterized by severe hypoxemia, decreased respiratory system compliance, increased lung weight with bilateral infiltrates on chest CT scan, and potential for lung recruitment. Serial CT chest imaging of patients thus could help to continuously monitor the disease changes and establish the basis for appropriate treatment.

In chest radiological findings, chest X-ray are usually normal in mild to moderate cases. However, in patients with severe pneumonia, bilateral patchy nodular or
interstitial infiltration is seen in more than 90% of cases. (Fig. 3.1) Ground-glass haziness or opacification, with or without subsegmental areas of consolidation, are the most common chest CT scan findings, seen in approximately 50% and 44% cases, respectively [25]. Most of these lesions are bilateral (seen in >80% patients), located peripherally or subpleural, and posterior with a lower lobe predominance [9–11, 25] (Figs. 3.2 and 3.3). Other common findings include pulmonary vascular

**Fig. 3.1** A 62-year-old male, known case of hypothyroidism, presented with fever, cough, dyspnea, anorexia, and diarrhea. Chest X ray shows bilateral heterogenous chest infiltrates consistent with severe pneumonia

**Fig. 3.2** A 30-year-old female presented with mild COVID-19 symptoms including fever, cough, sore throat, fatigue and anosmia. CT scan chest (a, axial view and b, coronal view) shows near-normal findings with a documented small patchy area of ground glass opacity in postero-basal segment of right lower lobe
A 72-year-old male, known case of multiple myeloma on chemotherapy, presented with mild fever, cough, and myalgia. CT scan chest (a, axial view and b, coronal view) shows a peripheral ground glass opacity with consolidation in right lower lobe and few pure ground-glass opacities in left lower lobe, with fibrous stripes.
enlargement (64%), intralobular septal thickening (60%), adjacent pleural thickening (41.7%), air bronchograms (41.2%), subpleural lines, crazy paving, bronchus distortion, bronchiectasis, and interlobular septal thickening (Figs. 3.4 and 3.5). In severe and critically ill patients, chest CT scan may demonstrate extensive multilobular and diffuse infiltrates which can rapidly evolve into full lung consolidation (Fig. 3.5).

### 3.2.3 Neurological Manifestations

There has been a consistently growing literature regarding the neurological manifestations of SARS-CoV-2 virus, which share structural homology to other known neurotropic coronaviruses, such as the SARS-CoV and MERS [26–28]. However, the neurotropism and neuropathogenicity of SARS-CoV-2 is complex and not yet fully elucidated [29]. Direct entry of virus to the nervous system could plausibly be achieved via the transcribrial route infecting the olfactory nerve, axonal transport, and trans-synaptic transfer across infected neurons, hematogenous and/or lymphatic spread leading to infection of vascular endothelium, or leukocyte migration across the inflamed blood-brain barrier. In addition, various indirect mechanisms such as hypoxia, coagulation dysfunction, cytokine storm, immune-mediated neuroinflammation, altered lung-brain and gut-brain crosstalk, and presence of cardiovascular comorbidities, like hypertension or diabetes (especially in elderly population), may contribute to the neuropathogenesis of severe neurological manifestations.

The most common neurological manifestations of SARS-CoV-2 include headache, myalgia, dizziness, new onset smell and taste dysfunction, and impaired consciousness. In an initial investigational study of neurologic manifestations of 214 COVID-19 patients from Wuhan, China; a total of 78 patients (36.4%) manifested

![Fig. 3.4 A 57-year-old male, known hypertensive, diabetic and asthmatic, presented with fever, productive cough, and chest pain. CT scan chest (a, axial view and b, coronal view) shows bilateral interlobular septal thickening with ground glass opacities and traction bronchiectasis](image-url)
Fig. 3.5 A 59-year-old male, known case of hypertension and diabetes, presented with complaints of fever, dry cough, and headache. CT scan chest (a, axial view and b, coronal view) shows peripheral patchy areas of ground-glass opacities with consolidation and fibrosis in both lungs.
neurological symptoms including central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system manifestations (new changes in smell or taste, vision impairment, and nerve pain), and skeletal muscular injury manifestations [27]. Compared to patients with mild to moderate disease, patients with severe COVID-19 were found to have a higher incidence of neurologic symptoms, including acute cerebrovascular diseases (5.7% vs. 0.8%), impaired consciousness (14.8% vs. 2.4%), and skeletal muscle injury (19.3% vs. 4.8%).

A recent systematic review of 92 studies on neurological symptoms of COVID-19 revealed headache [(observed in 3308 patients out of total 16,446 of patients (3308/16,446; 20.1%)], dizziness (151/2236; 6.8%), headache or dizziness as a combined manifestation (79/654; 12.1%), taste and smell dysfunctions (536/906; 59.2% and 430/846; 50.8%, respectively), and impaired consciousness (146/2890; 5.1%, ranging from 1.4 to as high as 69.0% in different studies) as the most frequently described neurological symptoms of SARS-CoV-2 infection [28]. New onset of smell and taste dysfunction and headache were more commonly reported by patients with mild or moderate COVID-19 (65.0% and 66.0%; and 10.8% respectively), as compared to patients who were serious or critically ill (3.4% and 8.3%, respectively). On the other hand, impaired consciousness (also described as confusion or agitation in certain studies) was more frequently observed among seriously ill patients (11.9%) in comparison with patients who presented with either mild or moderate COVID-19 (3.2%). Dizziness has been described as a vague symptom in majority of studies with no clear difference between vertigo and dizziness. Furthermore, the exact etiology of dizziness, such as generalized weakness, myalgia, stroke, or eight cranial nerve involvement, remains undisclosed. COVID-19 infection has been shown to have a significant independent association with acute ischemic stroke secondary to pathophysiologic mechanisms such as the proinflammatory prothrombotic state and cytokine storm [30]. Hence, COVID-19 patients without any other comorbidities may present in neurological emergency with an acute stroke.

Recent literature has revealed that new-onset smell and taste dysfunction (anosmia/hyposmia and ageusia/ hypogeusia) are well-established symptoms of COVID-19, with a reported prevalence of 52.73% (29.64–75.23%) and 43.93% (20.46–68.95%) [31]. These symptoms are more prevalent early in the clinical course of infection, with a large study of 417 patients with mild to moderate SARS-CoV-2 infection showing smell dysfunction in 85.6% and taste dysfunction in 88.8% of patients [32]. This high prevalence of olfactory and gustatory dysfunction indicates neurotropism of SARS-CoV-2, resulting in direct damage to the olfactory receptor neurons. For many patients with COVID-19, especially in paucisymptomatic patients, olfactory dysfunction may be the first or the only presenting symptom [33, 34]. Though most patients gradually regain their sense of taste and smell as they recover, some may have persistent symptoms even after complete recovery from SARS-COV-2 infection.

The complete spectrum of neuropsychiatric manifestations of COVID-19 is still unclear. Delirium is now recognized as one of the potential neurological
manifestations of COVID-19 and may be the sole presenting feature in absence of any respiratory symptom [35]. Other common neuropsychiatric manifestations reported in COVID-19 patients include anxiety, depression, mood swings, insomnia, psychosis, and suicidal ideation [36, 37].

Several other severe neurological manifestations observed in serious or critically ill COVID-19 patients reported in literature include acute cerebrovascular complications including stroke, acute cerebral hemorrhage, and cerebral venous sinus thrombosis; generalized seizures; meningitis/encephalitis; acute disseminated encephalomyelitis; acute hemorrhagic necrotizing encephalopathy; acute flaccid myelitis; Guillain–Barre syndrome and its variants (Miller Fisher syndrome, polyneuritis cranialis); and CNS demyelination [38–45].

### 3.2.4 Cardiovascular Manifestations

Cardiac involvement in COVID-19 patients is the commonest associated comorbidity in the form of hypertension and the commonest complication associated with mortality in the form of acute myocardial injury as a result of acute coronary syndrome, new or worsening heart failure, myocarditis, stress cardiomyopathy, arrhythmias, cardiogenic shock, and cardiac arrest [46]. Furthermore, cardiac involvement has been shown to occur both in the presence as well as absence of respiratory involvement [47].

The most plausible causative mechanisms of cardiac manifestations include direct viral invasion of myocardium, hypoxemia, unstable hemodynamic status with hypoperfusion, instability of coronary plaque, enhanced systematic inflammation, ACE2 receptor downregulation, cytokine storm, increased catecholamine production, and concurrent medication toxicity [48]. COVID-19 patients may present with acute myopericarditis with typical chest pain and pericardial effusion and/or cardiac tamponade, myocarditis, acute myocardial injury, and de novo arrhythmias [47, 49–51]. Arterial and venous thromboembolic events, presenting either as aortic thrombosis, deep vein thrombosis, acute pulmonary embolism, ischemic stroke, or myocardial infarction, secondary to COVID-19-associated coagulopathy, are common cardiovascular manifestation among severe COVID-19 patients [52, 53].

Laboratory testing, including serial cardiac troponin and d-dimer levels, electrocardiography (ECG), echocardiography, and CT coronary angiography, in suspected individuals with recent symptoms of an acute cardiac illness helps in early identification and prompt treatment of COVID-19-related cardiovascular manifestations. An analysis of ECGs from 50 patients with proven COVID-19 pneumonia showed ST-T abnormalities in 30% of patients and left ventricular hypertrophy in 33% of patients at baseline [54]. During hospitalization, 26% of patients developed new ECG abnormalities which included atrial fibrillation, ST-T changes, tachy-brady syndrome, and changes consistent with acute pericarditis. Pavri et al. have demonstrated that abnormal PR interval behavior (paradoxical prolongation or lack of shortening) with an increasing heart rate is associated with increased severity of disease and mortality [55].
Cardiac injuries have more frequently been observed in patients with severe disease and leads to the higher mortality rate (10.5%) than those without cardiac injuries [48]. In a cohort of 54 patients with COVID-19, troponin I (TnI) elevation was found in 42.6% of all the 39 severe and 15 critical patients [56]. Sinus tachycardia was the most common type of arrhythmia, present in all critical patients and 23 severely ill patients. Atrioventricular block and ventricular tachycardia were observed in critically ill patients at end stage, while bradycardia and atrial fibrillation were less common. Of note, persistent hypotension during treatment, presence of pericardial effusion, and severe myocardial injury have been found as independent risk predictors for severity of COVID-19 [46–48, 56].

3.2.5 Gastrointestinal and Hepatic Manifestations

Though initially overlooked in the course of pandemic, the frequent involvement of the gastrointestinal (GI) tract and the hepatic system by SARS-CoV-2 is now being increasingly recognized in the literature. SARS-CoV-2 infects the GI tract via its viral angiotensin-converting enzyme II receptor, which is found to be highly expressed both in GI epithelial cells and in liver [57, 58].

GI symptoms can manifest with a frequency as high as 39.6–50% in COVID-19 patients [58]. The most common GI presentation in patients with COVID-19 includes anorexia (1.0–78.64% %), diarrhea (3.8–34%), nausea and/or vomiting (3.9–10.1%), and abdominal pain (1.1–5%) [11, 58–60]. These GI symptoms may either coexist, occur prior to the onset of, or may even manifest in the complete lack of respiratory manifestations of COVID-19. It is important for gastroenterologist to recognize that diarrhea may be the only presenting feature of COVID-19. Most cases of diarrhea are mild and present as nondehydrating loose stools. In a cross-sectional multicentric study focusing on the prevalence of digestive symptoms of COVID-19, Pan et al. found that nearly 50% patients presented with one or more digestive symptom, including lack of appetite (78.6% of cases), diarrhea (35% of cases), vomiting (3.9% of cases), and abdominal pain (1.9% of cases). Of the total 103 patients, 97 had developed respiratory symptoms along with digestive symptoms, while 6 presented with only digestive symptoms in the absence of respiratory symptoms [59]. Authors also found that patients with digestive symptoms were more likely to exhibit elevated liver enzymes and prolonged coagulation on laboratory testing.

Mao et al. performed a systematic review and meta-analysis of 35 studies, comprising 6686 patients, to determine the prevalence and prognosis of digestive system involvement, including gastrointestinal symptoms and liver injury, in patients with COVID-19 [60]. Authors found that the pooled prevalence of all GI symptoms was 15%, with nausea and/or vomiting, diarrhea, and loss of appetite being the three most common symptoms, while the pooled prevalence of abnormal liver functions was 19%. Of concern, patients with GI symptoms were found to have a delayed diagnosis, severe course of disease, and a higher prevalence of complications. Recent literature also confirms fecal–oral transmission of COVID-19, indicating
that the virus can replicate in both respiratory and digestive tract [61]. Mao et al. demonstrated a pooled estimate of 54% for SARS-CoV-2 viral RNA positivity in fecal samples, with positivity persisting for up to 47 days after symptom onset [60]. However, isolating virus from stool samples does not necessarily equate to virus infectivity, and more research is needed to establish the direct role of feco-oral route in disease transmission.

In addition to the GI manifestations, the SARS-CoV-2 infection may also lead to a broad spectrum of liver impairment, secondary to hepatocyte invasion, hepatotoxic potential of drugs used for COVID-19 treatment, or immune-mediated liver injury. The reported incidence of liver function abnormalities in patients with COVID-19 ranges from 1% to 53% [59, 60, 62]. These abnormalities commonly include increased levels of hepatocyte-related enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) along with total bilirubin concentrations, with greater elevations seen in severe cases compared with moderate cases [12]. Cholangiocyte-related enzymes, such as alkaline phosphatase and γ-glutamyl transpeptidase, have also been reported to be slightly increased in a few patients [62]. Hypoalbuminemia (<35 g/L) is seen in severe cases and may predict the outcome of COVID-19 independent of age and comorbidity [12, 63]. Most patients only have mild elevation of liver enzymes levels, which resolves as the patient improves clinically. However, the risk of hepatic injury increases with the increasing severity of COVID-19, with a noted pooled prevalence of 22.8% (11.7–39.8%) among 288 death cases [64].

### 3.2.6 Hematological and Biochemical Manifestations

COVID-19 cases commonly present with wide variation in white blood cell (WBC) counts, ranging from leukopenia or normal WBC count, leukocytosis, and lymphopenia. Lymphopenia is the most common WBC derangement (noted in approximately 35–75% of patients) and is believed to represent a defective immune response to the virus [9, 10, 65]. SARS-CoV-2 primarily affects T lymphocytes, in particular CD4+ and CD8+ T cells, causing lymphopenia and a decrease in interferon γ (IFN-γ) production by CD4+ T cells. Since the production of IFN-γ is essential for the resistance against infection of various pathogens including viruses, the suppression of IFN-γ production in severe cases seems to correlate with disease severity of COVID-19 [12].

Compared to leukopenia, leukocytosis (either neutrophilia, lymphocytosis, or both) is noted in a minority of COVID-19-infected patients and may represent a superimposed bacterial infection or the hyperinflammatory state associated with cytokine storm (particularly neutrophilia). Thrombocytopenia is more frequently found in severe cases and is associated with nearly fivefold increased risk of mortality [66]. Recent laboratory findings analysis of 61,742 patients with SARS-CoV-2 infection revealed thrombocytosis in 61%, lymphopenia in 57.5%, leukopenia in 28%, leukocytosis in 18.3%, and thrombocytopenia in only 13% of patients [11].
The evaluation of serum cytokines on admission reveal significantly increased levels of macrophage-related proinflammatory cytokines [interleukin (IL) 2R, IL-6, IL-10, and tumor necrosis factor α (TNF-α)], particularly in severe COVID-19 cases [12]. Neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio can be used as independent prognostic markers in determining disease severity [67]. Coagulation parameters, particularly the values of prothrombin time and activated partial thromboplastin time, D-dimer, fibrin, and fibrin/fibrinogen degradation products, are more frequently deranged in patients with severe or critical COVID-19 and are suggestive of onset of consumptive coagulopathy [68].

In association with hematological markers, multiple biochemical markers of systemic inflammation, and organ injury, including serum levels of ferritin, lactate dehydrogenase, C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, and cortisol, liver enzymes (ALT and AST), serum creatinine, and cardiac-specific troponin levels tend to be higher in severe cases compared to mild and moderate cases and denotes poor prognosis [9–12, 69].

### 3.2.7 Ophthalmic Manifestations

The ophthalmic manifestations of COVID-19 may develop in the form of conjunctivitis, epiphora, anterior uveitis, retinitis, or optic neuritis [70–72]. Conjunctivitis may even manifest as the sole symptom, with either redness, irritation, foreign body sensation, or tearing in eyes, thus predisposing the ophthalmologists to the risk of contracting the virus in undiagnosed or unsuspected cases [73]. Examination findings are consistent with clinical diagnosis of mild follicular conjunctivitis and may include unilateral or bilateral bulbar conjunctival hyperemia, follicular reaction of the palpebral conjunctiva, watery discharge, and mild eyelid edema. Bilateral chemosis alone may represent third-spacing in a critically ill patient rather than a true ocular manifestation of the virus.

In a retrospective analysis of 38 patients with clinically confirmed COVID-19, 12 patients (31.6%) had ocular manifestations suggestive of conjunctivitis [71]. Patients with ocular symptoms were found to have higher values of WBC and neutrophil counts procalcitonin, CRP, and LDH. While 11 of 12 patients (91.7%) had positive RT-PCR test results from nasopharyngeal swabs, only two (16.7%) tested positive for SARS-CoV-2 from both nasopharyngeal and conjunctival swabs. Conjunctival specimens usually demonstrate the presence of viral RNA during the middle phase of illness and may not be useful in early diagnosis [72, 74]. Nonetheless, despite the low prevalence and rapid regression of viral presence in the conjunctiva, SARS-CoV-2 transmission through tears may be possible, even in patients without apparent ocular involvement [75].
3.2.8 Dermatological Manifestations

SARS-CoV-2 infection can affect skin like any other organ system. The patterns of dermatological manifestations associated with SARS-CoV-2 could be classified into four main categories: exanthema (varicella-like, papulovesicular, and morbilliform rash), vesicular (chilblain-like, purpuric/petechial, and livedoid lesions), urticarial, and acro-papular eruption [76]. In addition, one should also consider the cutaneous adverse drug reactions to the prescribed drugs for the treatment of COVID-19 in the differential diagnosis of skin lesions [77]. Rare occurrence of oral ulceration and blistering has also been described as one of the dermatological manifestations of COVID-19 [78].

Highlighting the wide spectrum of cutaneous manifestations associated with COVID-19, Freeman et al. demonstrated morphologies such as morbilliform (22%), pernio-like (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%) in 171 patients from an international registry from the American Academy of Dermatology [79]. In a nationwide study from Spain, Casas C et al. have described five cutaneous clinical patterns and several subpatterns associated with COVID-19 in the form of pseudo-chilblain (19%), vesicular eruptions (9%), urticarial lesions (19%), maculo-papules (47%), and livedo or necrosis (6%) [80]. They also showed that the large groups appear at different times in the disease and are associated with different duration, severity, and probably prognosis. Hence, accurate diagnosis of the varied skin lesions seen in COVID-19 may help in early diagnosis and categorization of the disease.

3.3 Summary

SARS-CoV-2 viral infection has been shown to infect people across all the ages and range in severity from completely asymptomatic, to symptomatic with multisystemic manifestations, to being lethal with dramatic complications. As our knowledge about COVID-19 is rapidly evolving, new and atypical symptoms are being added to the existing broad list of clinical manifestations. It is important that public healthcare professionals and clinicians are aware of the entire clinical spectrum of SARS-CoV-2 infection so as to aid prompt recognition of infected cases. Timely diagnosis can lead to appropriate isolation and treatment measures, thus helping to curb the growing menace of this global pandemic.

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Clinical Manifestations of Corona Virus Disease

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