Chapter

Clinical Characteristics of COVID-19 Infection

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Abstract

The typical clinical symptoms of the patients who suffered from the novel viral pneumonia were fever, cough, and myalgia or fatigue with abnormal chest CT, and the less common symptoms were sputum production, headache, hemoptysis, and diarrhea. This new infectious agent is more likely to affect older males to cause severe respiratory diseases. Major risk factors for severe illness and mortality from COVID-19 are age, comorbidities such as: heart disease, hypertension, prior stroke, diabetes, chronic lung disease, and chronic kidney disease and associated with adverse outcomes. Loss of taste and smell preceding the onset of respiratory symptoms has been reported.

Keywords: COVID-19, Clinical, Coronavirus, SARS-CoV

1. Introduction

This chapter will discuss the clinical features of COVID-19. The epidemiology, virology, prevention, and diagnosis of COVID-19 are discussed elsewhere.

1.1 Asymptomatic infections

Asymptomatic infections have been well documented. One review estimated that 33 percent of people with SARS-CoV-2 infection never develop symptoms [1]. This estimate was based on four large population-based, cross-sectional surveys, among which the median proportion of individuals who had no symptoms at the time of a positive test was 46 percent (range 43 to 77 percent), and on 14 longitudinal studies, among which a median of 73 percent of initially asymptomatic individuals remained so on follow-up. However, there is still uncertainty around the proportion of asymptomatic infections, with a wide range reported across studies. Additionally, the definition of "asymptomatic" may vary across studies, depending on which specific symptoms were assessed.

Patients with asymptomatic infection may have objective clinical abnormalities. As an example, in a study of 24 patients with asymptomatic infection who all underwent chest computed tomography (CT), 50 percent had typical ground-glass opacities or patchy shadowing, and another 20 percent had atypical imaging abnormalities [2]. Five patients developed low-grade fever, with or without other typical symptoms, a few days after diagnosis. In another study of 55 patients with asymptomatic infection identified through contact tracing, 67 percent had CT evidence of pneumonia on admission; only two patients developed hypoxia, and all recovered [3].

As above, some individuals who are asymptomatic at the time of diagnosis go on to develop symptoms (ie, they were actually presymptomatic). In one study,

symptom onset occurred a median of four days (range of three to seven) after the initial positive RT-PCR test [4].

1.2 Severity of symptomatic infection

1.2.1 Spectrum of severity and case fatality rates

The spectrum of symptomatic infection ranges from mild to critical; most infections are not severe. Specifically, disease severity may be classified as:

- Mild disease (no or mild pneumonia) was reported in 81 percent of cases.
- Severe disease (eg, with dyspnea, hypoxia, or > 50 percent lung involvement on imaging within 24 to 48 hours) was reported in 14 percent.
- Critical disease (eg, with respiratory failure, shock, or multiorgan dysfunction) was reported in 5 percent.
- The overall case fatality rate was 2.3 percent; no deaths were reported among noncritical cases.

Since many severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are asymptomatic, the infection fatality rate (ie, the estimated mortality rate among all individuals with infection) is considerably lower and has been estimated by some analyses to be between 0.5 and 1 percent. Conversely, the reported case fatality rates are likely underestimates of the true case fatality rates, as many fatal infections are undiagnosed. Neither the case fatality rate nor the infection fatality rate account for the full burden of the pandemic, which includes excess mortality from other conditions because of delayed care, overburdened health care systems, and social determinants of health.

1.2.2 Risk factors for severe illness

Severe illness can occur in otherwise healthy individuals of any age, but it predominantly occurs in adults with advanced age or certain underlying medical comorbidities. Specific demographic features and laboratory abnormalities have also been associated with severe disease.

1.2.3 Increasing age

Individuals of any age can acquire SARS-CoV-2 infection, although adults of middle age and older are most commonly affected, and older adults are more likely to have severe disease.

In several cohorts of hospitalized patients with confirmed COVID-19, the median age ranged from 49 to 56 years.

Older age is also associated with increased mortality. In contrast, individuals aged 18 to 34 years accounted for only 5 percent of adults hospitalized for COVID-19 in a large health care database study and had a mortality rate of 2.7 percent; morbid obesity, hypertension, and male sex were associated with mortality in that age group.

Symptomatic infection in children and adolescents appears to be relatively uncommon; when it occurs, it is usually mild, although a small proportion experience severe and even fatal disease.

1.2.4 Comorbidities

Comorbidities and other conditions that have been associated with severe illness and mortality include Cardiovascular disease, Diabetes mellitus, Chronic obstructive pulmonary disease and other lung diseases, Cancer (in particular hematologic malignancies, lung cancer, and metastatic disease), Chronic kidney disease, Solid organ or hematopoietic stem cell transplantation, Obesity and Smoking.

1.2.5 Socioeconomic background and sex

Certain demographic features have also been associated with more severe illness. Males have comprised a disproportionately high number of critical cases and deaths in multiple cohorts worldwide. Black, Hispanic, and South Asian individuals comprise a disproportionately high number of infections and deaths due to COVID-19, likely related to underlying disparities in the social determinants of health.

1.2.6 Laboratory abnormalities

Particular laboratory features have also been associated with worse outcomes. These include, Lymphopenia, Thrombocytopenia, Elevated liver enzymes, Elevated lactate dehydrogenase (LDH), Elevated inflammatory markers (eg, C-reactive protein [CRP], ferritin) and inflammatory cytokines (ie, interleukin 6 [IL-6] and tumor necrosis factor [TNF]-alpha), Elevated D-dimer (>1 mcg/mL), Elevated prothrombin time (PT), Elevated troponin, Elevated creatine phosphokinase (CPK), Acute kidney injury. Deficiencies in certain micronutrients, in particular vitamin D, have been associated with more severe disease in observational studies.

1.2.7 Viral factors

Patients with severe disease have also been reported to have higher viral RNA levels in respiratory specimens than those with milder disease, although some studies have found no association between respiratory viral RNA levels and disease severity. Detection of viral RNA in the blood has been associated with severe disease, including organ damage (eg, lung, heart, and kidney), coagulopathy, and mortality.

1.2.8 Genetic factors

Host genetic factors are also being evaluated for associations with severe disease. One genome-wide association study identified a relationship between polymorphisms in the genes encoding the ABO blood group and respiratory failure from COVID-19 (type A associated with a higher risk) [5]. Type O has been associated with a lower risk of both infection and severe disease [6].

1.3 Incubation period

The incubation period for COVID-19 is generally within 14 days following exposure, with most cases occurring approximately four to five days after exposure. However, determinations of the incubation period can be imprecise and may differ by the method of assessing exposure and the specific calculations used for the estimate.

1.4 Initial presentation

Among patients with symptomatic COVID-19, cough, myalgias, and headache are the most commonly reported symptoms. Other features, including diarrhea, sore throat, and smell or taste abnormalities. Pneumonia is the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging. Although some clinical features (in particular smell or taste disorders) are more common with COVID-19 than with other viral respiratory infections, there are no specific symptoms or signs that can reliably distinguish COVID-19. However, development of dyspnea approximately one week after the onset of initial symptoms may be suggestive of COVID-19.

The range of associated symptoms includes; Cough in 50 percent, Fever in 43 percent, Myalgia in 36 percent, Headache in 34 percent, Dyspnea in 29 percent, Sore throat in 20 percent, Diarrhea in 19 percent, Nausea/vomiting in 12 percent, Loss of smell or taste, abdominal pain, and rhinorrhea in fewer than 10 percent each.

In a meta-analysis of observational studies, the pooled prevalence estimates for smell or taste abnormalities were 52 and 44 percent, respectively (although rates ranged from 5 to 98 percent across studies) [7]. However, the rate of objective smell or taste anomalies may be lower than the self-reported rates.

Most subjective smell and taste disorders associated with COVID-19 do not appear to be permanent; in a follow-up survey of the 202 patients with COVID-19, 89 percent of those who noted smell or taste alterations reported resolution or improvement by four weeks [8].

Although not noted in the majority of patients, gastrointestinal symptoms (eg, nausea and diarrhea) may be the presenting complaint in some patients. In a systematic review of studies reporting on gastrointestinal symptoms in patients with confirmed COVID-19, the pooled prevalence was 18 percent overall, with diarrhea, nausea/vomiting, or abdominal pain reported in 13, 10, and 9 percent, respectively [9].

Nonspecific signs and symptoms, such as falls, general health decline, and delirium, have been described in older adults, particularly those over 80 years old and those with underlying neurocognitive impairments.

Dermatologic findings in patients with COVID-19 are not well characterized. There have been reports of maculopapular, urticarial, and vesicular eruptions and transient livedo reticularis. Reddish-purple nodules on the distal digits similar in appearance to pernio have also been described, mainly in children and young adults with documented or suspected COVID-19.

1.5 Acute course and complications

Symptomatic infection can range from mild to critical. Some patients with initially non-severe symptoms may progress over the course of a week. In one study of 138 patients hospitalized in Wuhan for pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dyspnea developed after a median of five days since the onset of symptoms, and hospital admission occurred after a median of seven days of symptoms [10].

1.5.1 Recovery and long-term sequelae

The time to recovery from COVID-19 is highly variable and depends on age and pre-existing comorbidities in addition to illness severity. Individuals with mild infection are expected to recover relatively quickly (eg, within two weeks) whereas many individuals with severe disease have a longer time to recovery (eg, two to three months). The most common persistent symptoms include fatigue, dyspnea,

chest pain, cough, and cognitive deficits. Data also suggest the potential for ongoing respiratory impairment and cardiac sequelae. Some patients who have recovered from COVID-19 have persistently or recurrently positive nucleic acid amplification tests (NAATs) for SARS-CoV-2. Although recurrent infection or reinfection cannot be definitively ruled out in these settings, evidence suggests that these are unlikely.

2. Special populations

2.1 Pregnant and breastfeeding women

The general approach to prevention, evaluation, diagnosis, and treatment of pregnant women with suspected COVID-19 is largely similar to that in nonpregnant individuals.

2.2 Children

Symptomatic infection in children appears to be relatively uncommon; when it occurs, it is usually mild, although severe cases have been reported.

2.3 People with HIV

The impact of HIV infection on the natural history of COVID-19 is uncertain. The clinical features appear the same as in the general population. However, many of the comorbid conditions associated with severe COVID-19 (eg, cardiovascular disease) occur frequently among persons with HIV, and it is unclear whether these or other potential confounding features, rather than HIV infection itself, contribute to the risk. Low CD4 cell count may be associated with critical illness and death in patients with HIV and COVID-19.

3. Oral manifestations associated with COVID-19

Although many physicians continue to question the direct link between SARS-CoV-2 and oral disease, studies suggest that the mouth might be the most vulnerable area to this virus due to the abundance of the ACE2 (angiotensin converting enzyme) receptor in oral tissue.

The ACE2 receptor has been well-documented to be the target receptor of the SARS-CoV-2 virus and the portal of entry into the human cell. Compared with other oral tissues, cells of the salivary glands, tongue, and tonsils carry the most RNA linked to proteins that the SARS-CoV-2 virus needs to infect cells [11].

Oral manifestations associated with COVID-19 infection includes:

3.1 Gingival inflammation

Bleeding and inflammation in oral tissue have been suggested to be a result of a generalized increase in inflammation due to elevated levels of cytokines and interleukins initiated by the SARS CoV-2 virus. COVID-19 disease severity has been linked to an immune dysregulation, leading to a cytokine storm. Periodontal disease can increase levels of circulating cytokines, particularly interleukin-6 (IL-6), which has been implicated as one of the major interleukins leading to the cytokine storm [12] and periodontal disease is currently being examined as a possible contributing disease toward COVID-19 severity.

3.2 Xerostomia (dry mouth)

COVID-19 has been suggested to cause dry mouth for a variety of reasons. The most common is mouth breathing by an individual due to mask use. Mouth breathing can desiccate oral tissue especially without frequent hydration. Studies suggest that another biologic mechanism involves viral entry into the salivary glands, which are known to be abundant in the ACE2 receptor [13].

3.3 Oral ulcerations and gingival tissue breakdown

COVID-19 has been associated with vascular anomalies due to viral damage of blood vessels a process whereby the virus gains entry into the endothelial cells that line blood vessels via the ACE2 receptor and damages them. Tissue necrosis, including oral ulcerations, can be the result of vessel damage. Ulceration and tissue damage can be further exacerbated by increased inflammation and upregulation in inflammatory markers due to the SARS-CoV-2 virus [14].

3.4 Loss of taste and smell

A sudden onset in loss of taste (ageusia) and smell (anosmia) are two symptoms that can be the earliest indicators of COVID-19. An average of 47% (up to 80%) of individuals who test positive for COVID-19 can have subjective complaints of taste and smell loss, particularly in cases of asymptomatic or mild disease [15]. The mechanism behind this loss is suspected to be viral disruption of cranial nerves 1, 7, 9, and 10, as well as the supporting cells of neural transmission [16]. In addition, because the tongue has an abundance of ACE2 receptors, direct viral entry into tongue cells is possible.

4. Laboratory findings

Common laboratory findings among hospitalized patients with COVID-19 include lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase levels, elevated inflammatory markers (eg, ferritin, C-reactive protein, and erythrocyte sedimentation rate), and abnormalities in coagulation tests. Lymphopenia is especially common, even though the total white blood cell count can vary. On admission, many patients with pneumonia have normal serum procalcitonin levels; however, in those requiring ICU care, they are more likely to be elevated. Several laboratory features, including high D-dimer levels and more severe lymphopenia, have been associated with critical illness or mortality.

5. Imaging findings

5.1 Chest radiographs

Chest radiographs may be normal in early or mild disease. Common abnormal radiograph findings were consolidation and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions; lung involvement increased over the course of illness, with a peak in severity at 10 to 12 days after symptom onset.

Spontaneous pneumothorax has also been described, although it is relatively uncommon.

5.2 Chest CT

Although chest computed tomography (CT) may be more sensitive than chest radiograph and some chest CT findings may be characteristic of COVID-19, no finding can completely rule in or rule out the possibility of COVID-19. Chest CT in patients with COVID-19 most commonly demonstrates ground-glass opacification with or without consolidative abnormalities, consistent with viral pneumonia. In a systematic review of studies evaluating the chest CT findings in over 2700 patients with COVID-19, the following abnormalities were noted: Ground-glass opacifications, Ground-glass opacifications with mixed consolidation, adjacent pleural thickening, Interlobular septal thickening, Air bronchograms. Other less common findings were a crazy paving pattern (ground-glass opacifications with superimposed septal thickening), bronchiectasis, pleural effusion, pericardial effusion, and lymphadenopathy. Chest CT abnormalities in COVID-19 are often bilateral, have a peripheral distribution, and involve the lower lobes.

Although these findings are common in COVID-19, they are not unique to it and are frequently seen with other viral pneumonias.

As with chest radiographs, chest CT may be normal soon after the onset of symptoms, with abnormalities more likely to develop over the course of illness. However, chest CT abnormalities have also been identified in patients prior to the development of symptoms and even prior to the detection of viral RNA from upper respiratory specimens. Among patients who clinically improve, resolution of radiographic abnormalities may lag behind improvements in fever and hypoxia.

5.3 Lung ultrasound

Findings on lung ultrasound in patients with documented COVID-19 have included thickening, discontinuation, and interruption of the pleural line; B lines visible under the pleura that appear discrete, multifocal, or confluent; patchy, strip, and nodular consolidations; and air bronchogram signs in the consolidations.

6. Complications of COVID-19

Several complications of COVID-19 have been described:

6.1 Respiratory failure

Acute respiratory distress syndrome (ARDS) is the major complication in patients with severe disease and can manifest shortly after the onset of dyspnea.

6.2 Cardiac and cardiovascular complications

Other complications have included arrhythmias, myocardial injury, heart failure, and shock.

6.3 Thromboembolic complications

Venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in severely ill patients with COVID-19, particularly among patients in the intensive care unit (ICU), among whom reported rates have ranged from 10 to 40 percent. Arterial thrombotic

events, including acute stroke (even in patients younger than 50 years of age without risk factors) and limb ischemia, have also been reported.

6.4 Neurologic complications

Encephalopathy is a common complication of COVID-19, particularly among critically ill patients; Stroke, movement disorders, motor and sensory deficits, ataxia, and seizures occur less frequently.

6.5 Inflammatory complications

Some patients with severe COVID-19 have laboratory evidence of an exuberant inflammatory response, with persistent fevers, elevated inflammatory markers (eg, D-dimer, ferritin), and elevated proinflammatory cytokines; these laboratory abnormalities have been associated with critical and fatal illnesses. Although these features had been likened to cytokine release syndrome (eg, in response to T cell immunotherapy), the levels of proinflammatory cytokines in COVID-19 are substantially lower than those seen with cytokine release syndrome as well as with sepsis. Other inflammatory complications and auto-antibody-mediated manifestations have been described.

Guillain-Barré syndrome may occur, with onset 5 to 10 days after initial symptoms. A multisystem inflammatory syndrome with clinical features similar to those of Kawasaki disease and toxic shock syndrome has also been described in children with COVID-19. In the rare adults in whom it has been reported, this syndrome has been characterized by markedly elevated inflammatory markers and multiorgan dysfunction (in particular cardiac dysfunction), but minimal pulmonary involvement.

6.6 Secondary infections

Secondary infections do not appear to be common complications of COVID-19 overall, the reported rate of bacterial or fungal coinfections was 8 percent; these included mainly respiratory infections and bacteremia. Several reports have described presumptive invasive aspergillosis among immunocompetent patients with ARDS from COVID-19, although the frequency of this complication is uncertain.

Autopsy studies have noted detectable SARS-CoV-2 RNA (and, in some cases, antigen) in the kidneys, liver, heart, brain, and blood in addition to respiratory tract specimens, suggesting that the virus disseminates systemically in some cases; whether direct viral cytopathic effects at these sites contribute to the complications observed is uncertain.

7. Summary

The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection ranges from asymptomatic infection to critical and fatal illness. The proportion of infections that are asymptomatic is uncertain, as the definition of "asymptomatic" varies across studies and longitudinal follow-up to identify those who ultimately develop symptoms is often not performed. Nevertheless, some estimates suggest that up to 40 percent of infections are asymptomatic.

Most symptomatic infections are mild. Severe disease (eg, with hypoxia and pneumonia) has been reported in 15 to 20 percent of symptomatic infections; it

can occur in otherwise healthy individuals of any age, but predominantly occurs in adults with advanced age or certain underlying medical comorbidities.

Cough, myalgias, and headache are the most commonly reported symptoms. Other features, including diarrhea, sore throat, and smell or taste abnormalities, are also well described. Pneumonia, with fever, cough, dyspnea, and infiltrates on chest imaging, is the most frequent serious manifestation of infection. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections.

Certain laboratory features, such as lymphopenia, elevated D-dimer, and elevated inflammatory markers have been associated with severe COVID-19.

Acute respiratory distress syndrome (ARDS) is the major complication in patients with severe disease and can manifest shortly after the onset of dyspnea. Other complications of severe illness include thromboembolic events, acute cardiac injury, kidney injury, and inflammatory complications.

The possibility of COVID-19 should be considered primarily in patients with compatible symptoms, in particular fever and/or respiratory tract symptoms, who reside in or have traveled to areas with community transmission or who have had recent close contact with a confirmed or suspected individual with COVID-19. All symptomatic patients with suspected SARS-CoV-2 infection should undergo testing.

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