

Review Article

The Myriad of Clinical Presentations of COVID-19: a Short Review

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ABSTRACT

The ongoing pandemic of Coronavirus disease- 2019 is yet to be defeated. It is primarily a viral respiratory illness, with a myriad of clinical presentations being reported, since it was first identified towards the end of 2019 in China. Apart from the classical symptoms of fever, cough, and dyspnea, atypical presentations in COVID-19 patients, have puzzled healthcare workers worldwide. Patients with isolated non- respiratory complaints like diarrhea, vomiting, abdominal pain, skin rash, and confusion, have tested positive for severe acute respiratory syndrome coronavirus-2. The symptoms of olfactory and gustatory dysfunction have recently been added to the list for screening suspected cases after their prevalence was found to be high among COVID-19 patients. This article elaborates on the system-wise manifestations of COVID-19 and discusses the clinical implications of these aberrant presentations to healthcare workers.

Keywords: Coronavirus; COVID-19; Pandemic.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the ongoing pandemic that has challenged the global health system, destabilized human societies, and is taking a toll on the global economy.¹ The clinical presentations of COVID-19 have been not less than a Pandora's Box, with atypical presentations being reported worldwide. This article summarizes the clinical presentations of COVID-19 reported to date and tries to discuss the clinical implications of these myriads of phenotypes of COVID-19 patients.

COVID-19 CLINICAL FEATURES

Since COVID-19 was first identified in Wuhan, China; this novel disease has been found to have a wide clinical spectrum with classical involvement of the respiratory system to different other systems of the body. 50 to 88% of COVID-19 patients were asymptomatic at the time of testing in various studies, which is relevant because silent carriers are found to amplify viral dissemination to communities.^{2,3} The commonest clinical features that were seen in symptomatic COVID-19 patients in various studies from China⁴, United Kingdom⁵, Pakistan⁶, and

India⁷, have been listed in Table 1. In a study by Tambe et al. from Pune, Maharashtra, 57.4% of patients were afebrile at the time of presentation and 56.5% did not have cough.⁷

Table 1. Common clinical presentations in COVID-19 patients in different studies

Symptoms	Guan et al. ⁴	Docherty et al. ⁵	Asghar et al. ⁶	Tambe et al. ⁷
Fever	88.7%	69%	83%	42.6%
Dry cough	67.8%	70%	52%	43.5%
Sputum production	33.7%	25%	18%	5.6%
Fatigue	38.1%	37.5%	16%	5.1%
Dyspnea	18.7%	65%	43%	46.7%
Sore throat	13.9%	12%	16%	2%
Headache	13.6%	15%	8%	2.5%
Nausea/ vomiting	5%	18%	13%	5.1%
Diarrhea	5%	20%	17%	1%

Table 2 enlists the case fatality rate (CFR) of COVID-19 in different countries by 3rd June, 2020.⁸ Nepal has reported a total of 8 COVID-19 related deaths out of 2,099 patients by 3rd June, 2020.⁸ However, the CFR may be confounded by factors like the current stage of disease transmission in a specific country, the

magnitude of testing and reporting of deaths in that particular country.

Table 2: The case fatality rate of COVID-19 in different countries by 3rd June 2020

Country	France	Italy	UK	USA	China	Iran	Germany	India	Russia	Nepal
CFR (%)	19.52	14.35	14.16	5.83	5.49	5.04	4.68	2.80	1.20	0.0038

SYSTEM-WISE MANIFESTATIONS

The system-wise manifestations of COVID-19, with the reported atypical signs and symptoms, have been elaborated below:

Respiratory system

The disease may present as mild upper respiratory tract infection to lower respiratory tract involvement in the form of pneumonia and acute respiratory distress syndrome. COVID-19 pneumonia is a specific disease entity different from classical ARDS as despite severe hypoxemia in patients, lung compliance was surprisingly found to be near normal (unlike in cases of typical ARDS).⁹ Heterogeneous presentation of COVID-19 pneumonia has been observed with normal breathing (silent hypoxia) and very dyspneic phenotypes.⁹ Apart from cough and dyspnea, hemoptysis has been reported in 1 to 5% hospitalized COVID-19 patients and when present, it warrants evaluation for possible pulmonary embolism.¹⁰

Gastrointestinal system

Incidence of diarrhea in cases of COVID-19 ranged from 2% to 50%, which may precede or follow respiratory symptoms.¹¹ In a case series by Pan et al., from Hubei province, China; 18.6% of patients presented with a gastrointestinal specific symptom which included diarrhea, vomiting, or abdominal pain.¹² Around 2.9% of those patients, had digestive symptoms without respiratory symptoms. Likewise, a patient in France, with the only presenting complaint of acute abdominal pain, was reported to have COVID-19. A nasopharyngeal swab of that patient was sent for reverse transcriptase-polymerase chain reaction test, only after the abdominal computerized tomography revealed subpleural irregular lines and peribronchial opacities at lung bases leading to suspicion of COVID-19.¹³

Neurological system

COVID-19 can present with encephalopathy, more common in elderlies, and in critically ill patients.¹⁴ Encephalopathy may be specific to SARS-CoV-2 infection or may be secondary to multi-organ failure, cytokine storm, metabolic abnormalities or effect of drugs. Nearly one-fourth of patients had some form of neurological manifestations ranging from headache, agitation, and confusion to cerebrovascular events like cerebral hemorrhage and infarction.¹⁵ Clinical case reports of large vessel strokes and Guillain-Barre syndrome, being the presenting features in COVID-19 patients are reported, though the causal association is yet to be proved.^{16,17} With the demonstration of SARS-CoV-2 in CSF of COVID-19 patients with neurological symptoms, neuroinvasion by the virus seems to be a plausible hypothesis that needs further testing.¹⁸

Evidence suggests that olfactory and gustatory symptoms were common among mild to moderate COVID-19 patients. Hyposmia/anosmia and dysgeusia/ageusia were added to the list of symptoms, for the screening of potential COVID-19 infection, by World Health Organization on May 6th, 2020.¹⁹ SARS-CoV-2 is believed to invade olfactory bulb and epithelium, leading to impairment of smell sensation even without nasal obstruction.²⁰ An atypical case of sudden and complete loss of olfactory function has also been reported in a COVID-19 patient.¹⁹ In a study by Lechien et al., 85.6% of patients, had olfactory symptoms which were reported after, during, and even before other symptoms had appeared.²¹ High prevalence of these symptoms, with 11.8% cases, exhibiting olfactory dysfunction before the appearance of other complaints; is a relevant finding to aid for early detection of COVID-19.²¹

Cardiovascular system

The acute cardiac injury was present in 20% COVID-19 cases, which was associated to increased mortality.²² With myocardial localization of coronavirus, documented in a critically ill patient in Italy, the mechanism for acute cardiac injury is postulated to be either due to direct viral invasion or cytokine storm resulted from hyperimmune host response.²² In a case series from New York, 33% patients who presented with ST-segment elevation in ECG and symptomatology of chest pain, without fever or respiratory complaints; had non-obstructive coronaries in coronary angiography, and were positive for SARS-CoV-2.²³ Thus, the threshold for SARS-CoV-2 testing must be kept low, in patients presenting with features like myopericarditis and cardiogenic shock, even in absence of respiratory complaints, during the time of this pandemic. Another important fact, that needs to be emphasized, is the pro-arrhythmogenic potential of drugs like azithromycin, hydroxychloroquine, chloroquine, and antivirals, that are being compassionately used for COVID-19 patients, which if not monitored may lead to catastrophic cardiac events.

Hematopoietic system

On comparing hematological parameters between survivors and non-survivors of COVID-19, higher leukocyte counts, and lower platelet counts were found in non-survivors.²⁴ The increase in leucocyte count was largely driven by neutrophilia, whereas a decreasing trend was noted for lymphocytes, monocytes, and eosinophils.²⁵ Coagulopathy was common in patients of COVID-19, as reflected by the observation that criteria for disseminated intravascular coagulation, was met in 71.9% of non-survivors in study.²⁶ Despite the coagulopathy, COVID-19 primarily presented as a thrombotic entity, rather than bleeding diathesis. Incidence of arterial and venous thrombotic events ranged from 31 to 57% in critically ill patients in various studies, with pulmonary embolism being the commonest.²⁷ Elevated D- dimer levels, thrombocytopenia, prolonged prothrombin,

and activated partial thromboplastin time, were associated with greater mortality.²⁸ Except for this, lupus anticoagulant assays were positive in 91% of hospitalized COVID-19 patients with prolonged aPTT, which could explain the prothrombotic tendencies in these patients. However, this observation warrants further evaluation.²⁹

Renal system

Acute kidney injury, in COVID-19, may result from acute tubular necrosis due to dehydration, sepsis, cytokine storm, use of multiple drugs, hypoxia, or rhabdomyolysis.³⁰ 75.4% of hospitalized COVID-19 patients, had renal involvement in the form of abnormal urine dipstick tests, or AKI.³¹ Proteinuria and hematuria were found in 44% and 26% of hospitalized patients, respectively. The prognostic implication of kidney dysfunction is higher overall mortality among patients with renal involvement, as compared to those without renal involvement (11.2% versus 1.2%).³¹

Hepatic system

Aminotransferase levels were reported abnormal in 14 to 53% of hospitalized COVID-19 patients, with abnormal levels being more common in severe forms of the disease.³² However, clinically significant liver dysfunction was not present, even among the most severely ill patients.³³

Cutaneous manifestations

Macular, maculopapular or morbilliform rashes, urticarial, petechial, and ischemic acral lesions, have been documented in patients with COVID-19.³⁴ Chilblain like lesions, mostly on hands and feet, have been recently reported in COVID-19 patients, who had minimal other complaints.³⁵ Skin lesions may be due to direct viral invasion, systemic effects of infection, or secondary to use of drugs. Skin manifestations were present even before other

symptoms appear, yielding them useful for early detection of COVID-19. There have been reports, that in the background of fever, thrombocytopenia and petechial rash, cases of COVID-19 were mistaken for dengue fever, in endemic areas leading to delay in diagnosis of the disease proper.³⁶

Clinical implications

World Health Organization strongly recommends trace, isolate, test, and treat policy, for every suspected case to break the chains of COVID-19 transmission.³⁷ COVID-19 is reported to have various non-respiratory signs and symptoms, which may precede classical respiratory complaints. The absence of fever or cough, in any patient, should not be presumed as an exclusion criterion for COVID-19. The definition of clinical COVID-19 patient has been dynamically changing, with rapidly evolving research about this novel disease. Patients with typical cardiac events, isolated complaints of acute abdomen, encephalopathy, cutaneous manifestations, olfactory and gustatory dysfunction, are reported to have a positive SARS-CoV-2 test. These aberrant presentations can be grossly missed by healthcare workers, resulting in further dissemination of virus in the communities. Thus, healthcare workers must be updated of all possible ways, by which COVID-19 may present. Likewise, it is imperative that the threshold for testing for SARS-CoV-2 must be kept low during the time of pandemics like today, to diagnose patients with aberrant presentations.

CONCLUSIONS

COVID-19 has a myriad of clinical presentations, affecting different systems of the human body. Healthcare workers need to have a high degree of clinical suspicion for patients with atypical presentations so that they can be identified at the earliest, and necessary clinical and public health measures can be taken to contain the virus and beat this pandemic of COVID-19.

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