An insight into the Transmission Dynamics and Atypical Clinical Manifestations of COVID-19

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ABSTRACT

SARS-CoV-2 belongs to the Coronaviridae family, a zoonotic group of viruses that have caused global worry. The main mode of transmission is established to be droplet spread, however, airborne transmission has not been ruled out. The median incubation period has been reported to be 5.0 days and the median duration of viral shedding as 20 days. According to the World Health Organization (WHO), the reproductive number of SARS-CoV-2 is between 2.0 to 2.5, a value dependent on social distancing measures. The atypical manifestations of Coronavirus Disease 2019 (COVID-19) include venous and arterial thromboembolisms, myocarditis, arrhythmias, demyelinating disorders, encephalopathy, acute kidney injury, and varying ocular and dermatological manifestations. The transmission dynamics of the virus and the atypical clinical manifestations have made combating this pandemic a global challenge. This review aims to provide an overview of the above to raise awareness among the health care workers, public health officials, and the public.

Keywords: COVID-19, Coronavirus, Epidemiology, Transmission mechanics, Clinical Presentation, Atypical presentation, Complications

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INTRODUCTION

Towards the end of 2019 numerous atypical cases of pneumonia were reported in Wuhan, a city in the Hubei province, China[1]. Most patients presented with symptoms of dry cough, shortness of breath, and fever. Lung imaging of these patients showed bilateral lung infiltrates. Throat swab samples revealed a previously unknown causative agent which was later termed as "Severe Acute Respiratory Syndrome Coronavirus-2" (SARS-CoV-2)[2]. The disease caused by this virus has officially been named "Coronavirus Disease 2019" (COVID-19) and has over 3 million confirmed cases globally. The SARS-CoV-2 belongs to the Coronaviridae family, members of which were responsible for causing Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012, both of which have left a mark in the history of mankind[1].

As of 28th April 2020, more than 3 million confirmed cases of COVID-19 have been reported worldwide. The initial cases appeared only in Wuhan, China, and later spread all over the world. Currently, the country with the highest number of reported cases is the United States of America with a total of more than one million with the majority localized in New York State. Other countries that have taken a great hit include Italy and Spain with more than 200,000 confirmed cases each. France has also reported more than 160,000 confirmed cases of COVID-19. MERS on the other hand was initially reported in Saudi Arabia in September 2012 and later spread to 27 countries. To date, WHO has reported 2,519 MERS confirmed cases and 866 deaths. Whereas, SARS made its initial appearance in Asia in February 2003 and rapidly spread to 26 countries. It affected around 8,000 people and 774 deaths were reported. Since 2004, there have been no reported SARS cases[3].

The most common clinical manifestations of COVID-19 include fever, cough, fatigue, and dyspnea[4]. Recently multiple studies have also reported atypical symptoms in patients with COVID-19. Though primarily considered a respiratory disease, clinical manifestations, and complications involving the central nervous system and cardiovascular system have been reported. Furthermore, hematological, renal, ocular, and cutaneous manifestations have also surfaced. Due to the novelty of this disease, there is little information on the transmission dynamics and atypical clinical manifestations of COVID-19 that have now become a worldwide threat not only to public health, but also to the global economy. This review aims to consolidate the information available regarding the transmission dynamics and the atypical manifestations of COVID-19 in an attempt to enhance our understanding of the pandemic and effective measures to control it.

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Search Methodology

For this review article, a literature search was conducted from 5th April 2020 to 20th April 2020 using the search engines PubMed and Google Scholar. Key terms used for the search were "SARS-COV-2", "COVID-19", "complications", "presentations", "epidemiology", and "transmission dynamics". All studies on COVID-19 including case reports, case series, cohort studies, case-control studies, systematic reviews, and narrative reviews were included. The exclusion criteria were limited to articles that were not available in the English language. Thirty four relevant articles were shortlisted, studied, and included in the final narrative review.

Origin and Mode of Transmission

Initially, most of the cases that were reported were linked to the Huanan seafood market in Wuhan. The link to the seafood market and the typical characteristics of this zoonotic virus indicates a possible spillover phenomenon from an animal to a human[1]. The exact animal vector has not yet been identified but scientists are closely looking into bats and pangolins as the most likely culprits. Soon after its emergence, all reported cases were associated with direct person-person transmission primarily via respiratory droplets[1]. Some studies have even claimed transmission by asymptomatic carriers, which if proven correct, will pose a greater challenge for public health personnel[1]. Studies have also detected the prolonged presence of COVID-19 RNA in fecal samples of infected patients, therefore the feco-oral route is also being suggested as a possible route[5]. MERS-related coronavirus and SARS coronavirus are also zoonotic viruses that are suspected to have originated in bats. The spread of the former was believed to be from infected dromedary camels to humans via direct or indirect contact[6]. However, human to human spread of MERS has been documented in hospital settings[7]. SARS coronavirus, unlike MERS, has a similar mode of transmission as SARS-CoV-2.

Transmission Dynamics

The emergence and transmission of infectious diseases are determined by factors that can be used to develop transmission dynamic models that can predict the outcome and magnitude of a pandemic. The infectious period of COVID-19 is usually linked to the viral shedding[8]. Multiple studies have shown that the viral load of SARS-CoV-2 saliva samples from patients with COVID-19 is high in the early phases of the disease[8]. The viral shedding is reported to continue for 8 to 37 days with a median of 20 days[9]. These findings help explain the increased transmissibility of the disease and the necessity of early diagnosis and isolation of the infected individuals.

The incubation period is the time between the exposures to a pathogen to the development of clinical symptoms. Most studies show the average incubation period for COVID 19 is four to five days. A study conducted to see the initial transmission dynamics showed that the mean incubation period was 5.2 days (95% CI 4.1 to 7.0 days) and the 95th percentile of the distribution was 12.5 days[10]. An estimate of the publicly reported cases in China stated that the incubation period was 5.1 days (95% CI 4.5 to 5.8 days) and that more than 97 percent developed symptoms within 11.5 days (95% CI 8.2-15.6 days)[11]. The data, however, is limited as research is still being done around the world. The incubation period for SARS was reported to be 4.0 days (95% CI 3.6-4.4 days), whereas for MERS it was 5.2 days, both of which are very close to the incubation period reported for COVID 19[12,13].

The reproductive number indicates the transmissibility of the virus and is defined as "the average number of secondary cases produced by one infected individual introduced into a population of susceptible individuals, where an infected individual has acquired the disease, and susceptible individuals are healthy but can acquire the disease"[14]. The average R_o for SARS-CoV-2 has been reported to have a mean of 3.28 and a median of 2.79[15]. WHO reported it to be 2.0 to 2.5 in their situation report released in March 2020[16]. However, due to a lack of sufficient data, this estimate may be over or under-evaluated. In comparison, the basic reproductive number of SARS and MERS has been reported to range between 2 and 3 and <1, respectively[13].

Another factor to be considered in understanding the transmissibility of the virus, or specifically the rapidity with which new cases are appearing, is the serial interval. This is the time taken from the onset of the illness in the primary case (infector) to the onset in the secondary case (infectee). Li et al. calculated it to be 7.5 days[10]. However, another study calculated a median serial interval of 4.0 days (95% CI 3.1-4.9 days)[17]. This difference between the reported serial intervals could have important consequences, as an accurate estimate of serial intervals is essential for determining the basic reproduction number (R_0) and the extent of interventions required to control the pandemic. Comparatively, the serial interval was reported to be 7.6 days for MERS and 8.4 days for SARS[13].

Doubling Time, which is the time taken for the number of cases of a specific disease to double, is an important epidemiological parameter to consider. If there is a fixed exponential growth, the number of cases double in a fixed time. One study in Wuhan recognized it to be 7.4 days (95% CI 4.8-17.0 days), whereas, a modeling study calculated it to be 6.4 days[10,18]. Today, all public health efforts are directed towards "flattening the curve" which essentially means to increase this doubling time to match the health care facilities that are available.

In light of the above discussion, it can be summarized that the epidemiology of COVID 19 closely resembles that of SARS and MERS. However, the SARS-CoV-2 is less virulent but more infective than its SARS-coronavirus and MERS-related coronavirus.

Clinical Manifestations and Atypical Presentations

SARS-CoV-2 has developed a worldwide notorious reputation for primarily causing respiratory symptoms, however, people infected by this virus are presenting with a wide variety of typical and atypical symptoms. The most common presenting symptoms include fever, dry cough, fatigue, and dyspnea[4,19–21]. Table-I summarizes the common clinical signs and symptoms mentioned in multiple studies.

Table-I: Clinical Signs and Symptoms of COVID-19

Signs and Symptoms	Results by Dawei Wang et al. [4]	Results by Wei-jie Guan et al.[19]	Results by Nanshan Chen et al. [20]	Results by Kui Liu et. al [21]
Fever	98.6%	88.7%	83%	81.8%
Fatigue	69.6%	38.1%	Not studied	32.1%**
Cough	59.4%	67.8%	82%	48.2%
Anorexia	39.9%	Not studied	Not studied	Not studied
Myalgia	34.8%	14.9%	11%	32.1%**
Dyspnea	31.2%	18.7%	31%	19.0%
Expectoration	26.8%	33.7%	Not studied	4.4%
Pharyngalgia	17.4%	13.9%	5%	Not studied
Diarrhea	10.1%	3.8%	2%	8.0%
Nausea	10.1%	5.0%*	1%*	Not studied
Dizziness	9.4%	Not studied	Not studied	Not studied
Headache	6.5%	13.6%	8%	9.5%
Vomiting	3.6%	5.0%*	1%*	Not studied
Abdominal pain	2.2%	Not studied	Not studied	Not studied
*Nausea or vomiting , **Myalgia or Fatigue				

Other less frequent clinical symptoms being reported are anosmia and dysgeusia[22]. These symptoms are thought to be prominent in the early stages of the disease. In response, to such reports from multiple sources, the Center for Disease Control, America has added "new loss of taste and smell" to the list of symptoms of COVID-19[23].

A major complication associated with COVID-19 is acute respiratory distress syndrome, however, complications involving multiple organ systems are also surfacing all over the world[24]. Physicians have reported the association of this infection with neurological manifestations such as headache, confusion, agitation, encephalopathy, cerebrovascular disease, and cortico spinal tract involvement in patients admitted with respiratory distress due to COVID-19[25]. Guillain-Barre syndrome, a post-infectious demyelinating disease, has also been reported in relation to COVID-19[26].

Complications related to the myocardium that have been reported include cardiac arrhythmias, acute cardiac injury, cardiomyopathy, and heart failure[27]. Acute cardiac injury has been observed in approximately 8–12% of all patients[28]. In another study, myocarditis and acute myocardial injury were observed in one-fifth of the patients with severe respiratory symptoms of COVID-19. Due to this correlation, some clinicians are recommending the routine measurement of troponin levels in COVID-19 patients with ECG changes. Some studies are even reporting cardiac involvement as an associated complication even in the absence of respiratory signs and symptoms.

Additionally, acute renal failure and proteinuria have been observed in some critically ill patients with COVID-19. Clusters of SARS-CoV-2 have been identified in podocytes from kidneys in autopsies of patients who died of respiratory failure associated with multiorgan failure. Immunostaining with the SARS-CoV-2 nucleoprotein antibody was positive in tubules thus providing direct evidence of the invasion of SARS-CoV-2 into kidney tissue. Patients who develop acute kidney injury have a higher incidence of mortality, hence, it is being recommended that clinicians should keep a close eye on renal functions in patients with severe COVID-19[29].

In a study conducted in Wuhan, a few patients of COVID-19 were observed to have signs of acro-ischemia including finger/toe cyanosis, skin bullae, and dry gangrene. Elevated levels of D-dimers, fibrinogen, fibrinogen degradation products (FDP), prothrombin time (PT) were seen in some of these patients and it was further observed that D-dimer and FDP levels increased progressively when COVID-19 exacerbated[9]. Evidence of complications such as pulmonary embolism, bilateral lower limb ischemia, and bilateral cerebral infarcts in multiple territories have also been observed[30,31]. Further investigation is required to establish an association between hyper-coagulable states and COVID-19 and the subsequent use of anticoagulation therapy as a potential treatment. Immune thrombocytopenic purpura has also been shown to have a temporal sequence with COVID-19 but needs to be further studied[32].

Although the number of cases and severity of COVID-19 in children is lesser than in older adults, the Pediatric Intensive Care Society UK has indicated a possible involvement of multisystem inflammatory disease in SARS-CoV-2 positive children with overlapping features of toxic shock syndrome and atypical Kawasaki disease[33].

Previous data suggests that other related coronaviruses can produce a broad spectrum of ocular manifestations, therefore studies are in progress regarding the association of ocular pathologies in patients with COVID-19[34]. However, due to insufficient data, a definite correlation is yet to be established. Like many viral infections, COVID-19 also presents with skin manifestations including erythematous rash, widespread urticaria, and chickenpox-like vesicles[35].

Case Fatality Rate

There is some controversy regarding the calculation of the case fatality rate (CFR) which is defined as the proportion of people dying from a certain disease compared to the number of people infected by the same disease. Some epidemiologists suggest that the rate might be overestimated initially keeping in mind its definition. The denominator includes both active and closed cases, which are low during the initial stages of the disease[36]. This has been contradicted by another study that indicates that CFR may be underestimated due to a "time-lag bias associated with diagnosing and reporting cases". One method to eliminate this is to divide the total number of deaths on a day by the total number of cases 14 days prior. As of 1st March 2020, it was calculated to be 5.6% (95% CI 5.4-5.8%) for China and 15.2% (95% CI 12.5-17.9) outside of China[37]. A report comprising of 45,500 patients, calculated the overall case fatality rate as 2.3% in China. A huge discrepancy can be seen in the case fatality rates being reported. This could partly be due to the different calculation methods and the different levels of healthcare system available from country to country. The case fatality rate is calculated to be 9.6% for SARS and 40% for MERS[13].

CONCLUSION

The transmission dynamics of the disease, the varying degrees of severity, and atypical presentations ranging from minor

symptoms of conjunctivitis to life threatening venous and arterial thromboembolisms pose a global health care challenge.

Recommendations: The data on COVID-19 from studies conducted across the world varies from each other, thus suggesting an evolving epidemiology. This may in part be due to strict movement restrictions, containment measures, and increased campaigns of public awareness which are being implemented in all the hard-hit areas. Even though the knowledge and perception regarding SARS-COV-2 and COVID-19 may be considered adequate in the local setting of Pakistan,[38] it is recommended that:

1. The population adhere to effective preventative measures and social distancing.
2. The clinicians be well versed with the signs and symptoms unrelated to the respiratory system, the infrequent manifestations, and the associated complications of COVID-19 while treating patients during the pandemic.

The trajectory of this pandemic will ultimately depend on the effectiveness of social distancing policies and human behavior in the coming months.

AUTHOR'S CONTRIBUTION

Ali R: Conceived idea, Designed research methodology, Literature search, Data collection, Literature review, Data interpretation, Statistical analysis, Manuscript writing, Manuscript final reading and approval.
Mirza TM: Designed research methodology, Literature search, Data collection, Literature review, Data interpretation, Manuscript writing, Manuscript final reading and approval.

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