Research Open

Journal of Cardiology and Clinical Practice
Volume 3 Issue 2

Review Article

SARS-CoV-2: It is Severe and Acute, but is it Only a Respiratory Syndrome?

Hannah Glanz[1] and Tyler Cymet[2]*

[1]Des Moines University, USA
[2]American Association of Colleges of Osteopathic Medicine, USA

***Corresponding author:** Tyler Cymet, 2102 Harmony Woods Road, Owings Mills, MD 21117, USA; **E-mail:** Tcymet@gmail.com

Received: October 06, 2020; **Accepted:** October 14, 2020; **Published:** October 21, 2020

Introduction

The first Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) endemic was identified in the Guangdong Province of southern China in November of 2002 [1]. SARS-CoV was found to spread from person-to-person via respiratory secretions. This virus was capable of causing severe respiratory symptoms and death [2]. In 2012 the CDC declared SARS-CoV a "select" agent that could pose a severe threat to public health and safety [3]. SARS-CoV and SARS-CoV-2 are classified as beta coronaviruses which contain an extended loop that varies between viruses and is considered a hypervariable region [4]. Beta coronaviruses have been responsible for more severe symptoms when compared to alpha coronaviruses. Symptoms of this SARS-CoV infection include fever, malaise, myalgia, headache, diarrhea, rigors, and respiratory distress. In severe cases, intubation of the infected person to maintain oxygenation was necessary [1]. In December 2019, the world saw the emergence of the novel SARS-CoV-2 (COVID-19) in the Hubei province in Wuhan, China. The World Health Organization (WHO) declared SARS-CoV-2 a global pandemic on March 11, 2020 [5]. This article aims to serve as a systemic review of COVID-19 symptoms during an infection and seeks to understand the role of viral testing and clearance, relapses, asymptomatic persons, and sequelae after recovery.

Virus Nomenclature

Viral respiratory infection (VRI) is the name for several types of lung infections. Viral infections enter the body through the upper respiratory tract and can cause an upper respiratory infection or lodge in the lower respiratory tract and cause infection. Infections can be classified by the causative virus (i.e. influenza) or by the syndrome they cause (i.e. pneumonia) [6]. SARS and Avian Influenza are not seen as classic respiratory infections but are often classified along with 8 viruses that demonstrate spread through person to person contact causing infection in the respiratory system.

Virus Transmission and Infection

Viral respiratory infections replicate in ciliated cells of the lung causing cytolysis of the respiratory mucosa. Respiratory viruses generally have two main modes of transmission, large particle aerosols of respiratory droplets transmitted directly from person-to-person by coughing or sneezing, or by fomites. Fomite transmission occurs indirectly when infected respiratory droplets are deposited on hands or on inanimate objects and surfaces with subsequent transfer of secretions to a susceptible subject's nose or conjunctiva.

In 2003, Li et al. determined that SARS entered human cells via the metallopeptidase, angiotensin-converting enzyme 2 (ACE2) [7]. Immunohistochemistry for localization of ACE2 was then performed by Hamming et al. in early 2004 [8]. Their research showed ACE2 was found in many human tissues including but not limited to the endothelial cells in arteries and veins, type 1 and type 2 alveolar epithelial cells, oral mucosa, nasal mucosa, the smooth muscle cells of the muscularis mucosae and muscularis propria of the stomach, small intestine, and colon. This wide distribution of ACE2 receptors in the body could be the reason for extensive symptoms of SARS-CoV-2 which has also been confirmed to enter the body via these receptors [9]. Analogous to SARS-CoV, SARS-CoV-2 stands for Severe Acute Respiratory Syndrome Coronavirus 2, which demonstrates fever, mild to severe respiratory symptoms, GI symptoms, and fatigue. As the virus continues to spread, many other symptoms and sequelae of this novel virus have been discovered.

The body often demonstrates a rapid and severe immune reaction to SARS-CoV-2 which leads to large amounts of cytokines released into the bloodstream. This release of cytokines leads to fever and has been dubbed a "cytokine storm". The rapid release of cytokines causes fever, swelling, fatigue, and nausea. IL-6 is a major proinflammatory cytokine cited to be responsible for the severe immune reaction to SARS-CoV-2 [10]. It has been theorized that individuals who are immunosuppressed may not exhibit as severe a reaction to the virus.

Symptomology of SARS-CoV-2

Fever

Fever is a typical physiologic response to infection and has a protective effect. Fever has also been shown to enhance the immune system during infectious disease states [11,12]. During the COVID-19 pandemic, fever has been used as one of the main criteria of determining whether or not a person qualifies for nasopharyngeal testing due to its high association with infection. In one study, researchers found that fever was present in 88.5% of persons infected (Table 1) [13].

Table 1: CDC recognized symptoms of COVID-19 [11].

Fever or chills
Cough
Shortness of breath or difficulty breathing
Fatigue
Muscle or body aches
Headache
New loss of taste or smell
Sore throat
Congestion or runny nose
Nausea or vomiting
Diarrhea

Anosmia and Ageusia

Anosmia (the loss of smell) and ageusia (the loss of taste) are also symptoms reported by COVID-19 positive patients. In Trubiano et al. they hypothesize the loss of sensory function is due to the invasion of the olfactory neuroepithelium and the olfactory bulb [14]. This hypothesis is based on research showing substantial amounts of ACE2 in the respiratory system.

GI: Nausea, Diarrhea

SARS-CoV-2 enters cells via angiotensin-converting enzyme 2 (ACE2) which is present in the lung, airway epithelia, blood vessels, and cells of the small intestine [15]. This could explain why GI symptoms have been accounted for in almost 50% of patients with COVID-19. These symptoms include nausea, vomiting, diarrhea, and abdominal pain. A subset of those infected have shown predominately GI symptoms with little to no respiratory involvement [16].

Headache

In a meta-analysis by Bolay et al. researchers describe the headache caused by COVID-19 as a "moderate-severe bilateral headache with pulsating or pressing quality, exacerbated by bending over, in the temporoparietal region or sometimes more anteriorly to the forehead, periorbital area, and sinuses." The study shows that 10% of patients reported headaches that were commonly unrelieved by common analgesics [17].

Hypercoagulability

COVID-19 associated hypercoagulability has been widely reported upon, although it has yet to be determined if the hypercoagulability is directly caused by SARS-CoV-2 infection or by the host immune response to the virus. Many markers of inflammation have been shown to be increased in patients with severe COVID-19 infections including increased d-dimer, PT, IL-6, CRP, ESR, and decreased levels of fibrinogen. Researchers have also discovered a COVID-19 endotheliopathy, likely due to viral entrance via ACE2 receptors, causing inflammation in host endothelial cells [18].

COVID Toes

Acrocyanotic lesions of the digits have been discovered in pediatric patients with suspected COVID-19 infections. Largely healthy appearing children have presented with reddish/purple lesions of the digits which then evolve to contain black crusts. The lesions have typically resolved within two weeks [19]. Dermatologists have noted pathology of the epidermis, dermis, and capillaries of the digits, including microthrombi in two cases [20]. It is hypothesized that the acrocyanotic lesions are due to microemboli associated with SARS-CoV-2 infection.

Cardiovascular

Although currently classified as a viral respiratory illness, SARS-CoV-2 has many devastating manifestations on the cardiovascular system. In some patients with severe COVID-19 infections, physicians are seeing an increase in troponin-I and troponin-T levels correlating to myocardial damage. Other cardiovascular complications include micro-infarctions, new-onset arrhythmias, myocarditis, and pericarditis [21]. It is still undetermined if damage to the myocardium is from the virus directly or from activated macrophages attempting to clear the virus.

Issues and Consequences of Infection

Relapse

There have been increasing reports of patients who test positive by reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 after having been deemed recovered and discharged from the hospital. The World Health Organization (WHO) published guidelines that state a patient is able to be discharged after two consecutive negative PCR results 24 hours apart [22]. In Li et al. the researchers discovered the median RNA shedding period to be 53 days with other patients shedding even longer [23]. It has not yet been determined if the positive RT-PCR is due to persistent infection with false negative testing, or reinfection after discharge.

Sequelae of Infection

Persons infected with SARS-CoV-2 are seeing long term symptoms that have yet to go away including fatigue, weakness, low-grade fevers, shortness of breath, and tachycardia [24]. Other research is investigating whether or not SARS-CoV-2 can predispose a person to cancer [25].

Viral Testing

The standard testing for SARS-CoV-2 has been RT-PCR based assays of respiratory specimens gathered by nasopharyngeal swab without swabbing the tonsils or oropharynx. The nasopharynx is the primary site for swabbing due to the presence of the virus on day one of symptoms [26]. However, RT-PCR may not be the appropriate method of testing for asymptomatic individuals who may be carriers or in the incubation phase of infection. There have been documented cases of asymptomatic persons testing positive via stool specimens after testing negative via nasopharyngeal swab [27]. In addition to missing the asymptomatic persons with SARS-CoV-2, there has been an unusually higher number of persons suffering from co-infection with other respiratory viruses. In one cohort, 80% of patients were

positive for co-infection with influenza A, influenza B, mycoplasma, or legionella pneumophila [28].

Other Biomarkers of Disease

Asymptomatic Carriers

A major complication of COVID-19 arises from those deemed "asymptomatic" after testing positive via RT-PCR and showing no symptoms of infection. Some of those asymptomatic patients go on to show signs and symptoms of the disease after a prolonged incubation period, but some never develop symptoms at all. In Kong et al. it is reported that 60% of all COVID-19 cases are potentially asymptomatic and 60% of those asymptomatic persons showed evidence of pneumonia on initial spiral CT (Table 2) [29-31].

Table 2: Testable markers in COVID-19 [18,29,30].

Increased	Decreased
C-Reactive Protein	Albumin
Lactate Dehydrogenase	Lymphocytes
Erythrocyte Sedimentation Rate	Leukocytes
Aspartate and Alanine Aminotransferases	
Creatine Kinase	
Bilirubin	
Creatinine	
Amyloid A	
Procalcitonin	

Discussion

SARS-CoV-2 affects more than the respiratory system; it appears to be a systemic illness. The wide variety and severity of symptoms may be attributed to SARS-CoV-2 beta coronavirus classification. Beta coronaviruses tend to act differently, with broader symptoms, more severe disease, and potential for entry of the virus through various modalities. There are also documented cases of SARS-CoV-2 where the respiratory system is spared. While the portal of entry can be the respiratory system, there are other ways in which people can become infected including GI and endothelial infection. The classic clinical picture of SARS-CoV-2 with cough, loss of taste, and fatigue may or may not be the most common presentation in the long term. As testing becomes more common, we will gain a better understanding of the range of illness. Until then, this respiratory syndrome could be considered part of a more severe acute systemic illness.

References

1. World Health Organization (2020) SARS (Severe Acute Respiratory Syndrome). *World Health Organization* https://www.who.int/ith/diseases/sars/en/.
2. Severe Acute Respiratory Syndrome (SARS) (2020) American Lung Association. https://www.lung.org/lung-health-diseases/lung-disease-lookup/severe-acute-respiratory-syndrome-sars
3. SARS (2020) Centers for Disease Control and Prevention. https://www.cdc.gov/sars/index.html
4. Betacoronavirus (2020) Betacoronavirus - an overview|ScienceDirect Topics. https://www.sciencedirect.com/topics/neuroscience/betacoronavirus
5. Coronavirus disease 2019 (COVID-19) Situation Report-51 (2020) World Health Organization.
6. Tesini B (2020) Overview of Viral Respiratory Infections - Infectious Diseases. https://www.merckmanuals.com/professional/infectious-diseases/respiratory-viruses/overview-of-viral-respiratory-infections
7. Li W, Moore M, Vasilieva N, Jianhua Sui, Swee Kee Wong, et al. (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 426: 450-454. [crossref]
8. Hamming I, Timens W, Bulthuis M, AT Lely, GJ Navis, et al. (2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology* 203: 631-637. [crossref]
9. Xiao L, Sakagami H, Miwa N (2020) ACE2: The key Molecule for Understanding the Pathophysiology of Severe and Critical Conditions of COVID-19: Demon or Angel? *Viruses* 12: 491. [crossref]
10. Moore JB, June CH (2020) Cytokine release syndrome in severe COVID-19. *Science* 368: 473-474. [crossref]
11. Symptoms of Coronavirus (2020) Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
12. Evans SS, Repasky EA, Fisher DT (2015) Fever and the thermal regulation of immunity: the immune system feels the heat. *Nature Reviews Immunology* 15: 335-349. [crossref]
13. Li LQ, Huang T, Wang YQ, Zheng-Ping Wang, Yuan Liang, et al. (2020) COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 92: 577-583. [crossref]
14. Jason A Trubiano, Sara Vogrin, Jason C Kwong, Natasha E Holmes (2020) Alterations in smell or taste – Classic COVID-19? *Clinical Infectious Diseases ciaa655. [crossref]*
15. Klopfenstein T, Kadiane-Oussou NDJ, Royer P-Y, Toko L, Gendrin V, et al. (2020) Diarrhea: An underestimated symptom in Coronavirus disease 2019. *Clinics and Research in Hepatology and Gastroenterology* 44: 282-283. [crossref]
16. Qureshi H (2020) The Digestive System and the COVID-19. *Journal of the Pakistan Medical Association* 70: 98-100.
17. Bolay H, Gül A, Baykan B (2020) COVID-19 is a Real Headache! *Headache: The Journal of Head and Face Pain*.
18. Connors JM, Levy JH (2020) COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 135: 2033-2040. [crossref]
19. https://www.fip-ifp.org/wp-content/uploads/2020/04/acroischemia-ENG.pdf Figure out how to Cite this one.
20. El Hachem M, Diociaiuti A, Concato C, R Carsetti, C Carnevale, et al. (2020) A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. *J Eur Acad Dermatol Venereol.*
21. Su Yen-Bo, Kuo Ming-Jen, Lin Ting-Yu, Chien Chian-Shiu, Yang Yi-Ping, et al. (2020) Cardiovascular Manifestation and Treatment in COVID-19. *Journal of the Chinese Medical* 83: 704-709. [crossref]
22. Hoang VT, Dao TL, Gautret P (2020) Recurrence of positive SARS-CoV-2 in patients recovered from COVID-19. *Journal of Medical Virology*.
23. Li N, Wang X, Lv T (2020) Prolonged SARS-CoV-2 RNA shedding: Not a rare phenomenon. *J Med Virol.* [crossref]
24. D'Ambrosio A (2020) COVID-19 Sequelae Can Linger for Weeks. Medical News and Free CME Online. https://www.medpagetoday.com/infectiousdisease/covid19/86482.
25. Hays P (2020) Clinical sequelae of the novel coronavirus: does COVID-19 infection predispose patients to cancer? *Future Oncology*. [crossref]
26. Sethuraman N, Jeremiah SS, Ryo A (2020) Interpreting Diagnostic Tests for SARS-CoV-2. *Jama* 323: 2249. [crossref]
27. Tang A, Tong Z-D, Wang H-L, Ya-Xin Dai, Ke-Feng Li, et al. (2020) Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. *Emerging Infectious Diseases* 26: 1337-1339. [crossref]
28. Xing Q, Li G, Xing Y, et al. (2020) Precautions are Needed for COVID-19 Patients with Coinfection of Common Respiratory Pathogens.

29. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Diagnostics.

30. Li H, Xiang X, Ren H, et al. (2020) Serum Amyloid A is a biomarker of severe Coronavirus Disease and poor prognosis. *Journal of Infection* 80: 646-655.

31. Kong W, Wang Y, Hu J, Chughtai A, Pu H (2020) Comparison of clinical and epidemiological characteristics of asymptomatic and symptomatic SARS-CoV-2 infection: A multi-center study in Sichuan Province, China. *Travel Medicine and Infectious Disease*.

Citation:

Hannah Glanz, Tyler Cymet (2020) SARS-CoV-2: It is Severe and Acute, but is it Only a Respiratory Syndrome? *J Cardiol Clin Pract* Volume 3(2): 1-4.