Review on Identification of Major Infection Site and Disease Progression Pathway for Early Detection of Novel Corona Virus (Covid-19)

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Abstract

The Novel Coronavirus disease, COVID-19, is a new highly contagious infection, transmitted from human to human of pandemic proportion. The number affected is increasing dramatically, without specific therapy nor vaccination available. The major challenges for its epidemiological control include the prolonged incubation period without symptoms and its ability to transmit the disease by both symptomatic and asymptomatic. This review is to bring an awareness to the scientific and medical community a major route of infection during incubation period, suggesting a new diagnostic approach to be adopted. Exploration of this study may unfold a unique approach to the early detection and clinical management well before its progression to severe disease manifestation. We highlight the importance of evaluating pancreatic function, hepatocellular changes and gastrointestinal lining to enable early diagnosis of the disease.

1. Introduction

In December 2019, a cluster of acute respiratory illness, now known as novel coronavirus (2019 nCoV)–infected pneumonia (NCIP) occurred in Wuhan, China [1-5] In January 2020, and China National Health Commission confirmed human to human transmission of Covid-19 [6, 7]. The disease has rapidly spread from Wuhan to other areas of the globe as a highly infectious disease and recorded in more than 183 countries. As of 8th April 2020, total of 1,464,852 have been infected, 85,397 deaths recorded and 351,105 has recovered according to the Systems Science and Engineering at John Hopkins University, USA.

The main concern is where the Covit-19 propagates inside the human body before it expresses symptoms in the respiratory tract. This review highlights a major site of disease proliferation leading to biochemical changes that cause internal tissue damages. We highlight the importance of investigating the pancreatic enzyme profiles, hepatocellular and gastrointestinal changes, based on organ dysfunction observed within the first 10 days of infection during the first phase of the incubation period.

The demographic, clinical and biological characteristics abnormalities associated with COVID-19 have been described. More specifically, we have reports on the sequence of symptoms, incubation period, biological and CT abnormalities and some treatment outcomes [8, 9, 10,14,15].

Additionally, there are reports of data on virus shedding, with studies on the dynamics of viral load in sputum, urine, throat swab and stool samples in symptomatic and asymptomatic individuals. Viral shedding in patients who recovered is also described [8,9,14,15].

According to the World Health Organization (WHO), the most common symptoms of Covid-19 are fever, tiredness and a dry cough. Some patients may also have a runny nose, sore throat, nasal congestion and dyspnea at a median of 8 days after symptom onset [28]. Many patients reported gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain [8,10, 23]. Studies have identified the SARS-CoV-2 RNA in stool specimens of infected patients, and its viral receptor angiotensin converting enzyme 2 (ACE2) was found to be highly expressed in gastrointestinal epithelial cells [9,23]. Faeces of Covid-19 patients were found to be highly infectious [27].

Some reported losing the sense of taste and/or smell [19]. About 80% who contracted Covid-19 experienced a mild infection and recovered without needing any special treatment [14,15]. Those who have a serious form of Covid-19 may rapidly progress to acute respiratory distress syndrome, coagulation dysfunction and septic shock [35].

The main challenge to disease control globally is the increasingly reported asymptomatic individuals who can transmit SARS-CoV-2 infection [16, 17].

Assessment of the viral loads in symptomatic patients have shown this peaks within the first few days of symptoms, and also that individuals can have a similarly high viral load without showing any symptoms [18].

Eight strains of the Corona Covid-19 virus are currently identified circulating around the globe, which scientists are tracking by their genetic footprints [25]. Laboratories around the world are rapidly sequencing the genomes of virus samples taken from people infected with COVID-19. The information is uploaded to NextStrain.org website, that shows how the virus is migrating and splitting into similar but new subtypes. Genetic sequence reveals the virus as unique microscopic fragments to the origins of its original strain, how it behaves as it mutates and which strains are turning into conflagrations while others are dying due to quarantine measures [25].

a. Implications of the available evidence

Most commonly cited issue of Covid-19 is based with the status of bilateral lung abnormalities and pneumonia, where the disease process appears to start as its first site of Covid-19 virus invasion that subsequently progresses into a severe condition. This observation has hindered identifying true nature of the disease.

Study related to the first case of Coronavirus in the United States reported, no evidence of infiltrates or abnormalities in the chest radiography until the 8th day of symptoms [35]. At this stage the total number of days including incubation period approximately 18-21 and patient suffered leukopenia, mild thrombocytopenia, elevated creatinine and altered hepatic functions [35].

Some observations indicate its full grown status occurs within 14-18 days and that the silent incubation period alters the biochemical function of the vital internal organs of the host. Cohort studies conducted in China have observed few common issues among the Covid-19 infected patients.

Major clinical and biochemical observations include evidence of systemic virus dissemination beyond the respiratory tract, with virus detection reported in plasma and pleural effusion fluid, stools, urine and tears; with bacterial and fungal super infections. The other features reported include impaired interferon pathways, pancreatitis and hepatitis. Severe dehydration due to third space fluid loss and impaired immune response are also reported [10, 11,14,15,18, 26, 28].

a. Pathway of Covid-19 infection and disease progression

The main entry point of the Covid-19 is the respiratory tract, where it first attaches to the mucus membrane of the nasal passage and sinus cavity. Covid-19 has a longer prodromal period of 14-18 days until lung invasion and a very slow phase of expression of symptoms compared with other coronaviruses infectious respiratory diseases [16, 26].

Once it reaches the lungs it enters the blood [28] stream and infects the most preferable sites in the human body. The coronaviruses are the common infection source of upper respiratory, gastrointestinal and central nervous system in humans and other mammals [31]. Coronaviruses are enveloped positive-stranded RNA viruses that replicate in the cytoplasm. To deliver their nucleocapsid into the host cell, they rely on the fusion of their envelope with the host cell membrane [34].

Human cell surface receptor, angiotensin converting enzyme 2 (ACE2), is recognized by the new coronavirus and serves as the access point into human cells [30]. The SARS-CoV-2 mediates entry in to human host cell using angiotensin-converting enzyme (ACE2) as a functional receptor [12]. The SARS-related coronaviruses are covered by spike glycoproteins that contain a variable

receptor-binding domain (RBD). The 'spike glycoprotein S' of Covid-19 not only attach to the host cell surface but also fuse the viral and host cell membranes to allow the infection to start [30,34].

Virus Receptor Binding domain(RBD) binds to angiotensin-converting enzyme-2 (ACE-2) receptor found in the heart, lungs, kidneys, pancreas and gastrointestinal tract [13] thus facilitating viral entry into target cells. Other than the esophagus and the upper and stratified epithelial cells of the respiratory tract, ACE2 is also highly expressed in the digestive system. The intestinal epithelial cells and the absorptive enterocytes from ileum to colon are the most vulnerable sites [33].

It is also reported that ACE2 receptor is highly expressed on the cell membrane of pancreatic tissues [33]. Once the Viral RNA is released and enters the cytoplasm of the host cell, ACE2 receptor on the cell membrane becomes inactive and down regulated. This causes severe inflammation and vascular permeability. (Fig 1)

Fig 1: Receptor mediation between SARS-COV2 and ACE2 receptor of the host cell and replication process of the Covid-19 inside the human cell [36].

Evidently, absence of cough and dyspnea during first 14 days and detection of Covid-19 in stools [10] of patients with atypical abdominal symptoms [8,9] indicates SARS COV-2 Virus first site of major infection is not in the lungs. As it enters the blood stream Covid-19 immediately invade the host cell in the intestinal lining [9,10,23] hepatocellular and pancreatic tissues. As the infection proceeds it creates a hemorrhagic condition within the internal muscular lining of the intestine. This alters three major digestive enzymes secretions from the pancreas namely amylase, peptidase and lipase indicating the changes to pancreatic functions. At this stage the liver develops hepatocellular changes.

This hypothesis is based on the fact that Covid-19 virus has a long incubation period of 1-14 days without any pathophysiological or symptomatic change of reaction in the lungs. The disease gradually progresses into lungs, kidney and heart after completing the 14-18 days of silent incubation. Globally, pancreatitis and hepatitis are clinically identified in Covid-19 infected patients. The severe dehydration and third space fluid loss becomes life threatening with sudden multiple organ failure [26].

Considering the above facts, attempts at early detection of Covid-19 should focus on the status of the gastrointestinal lining, profile of the pancreas and levels of the pancreatic enzymes. Hepatic change indicates the advance stages of the disease.

Clinical observation of the change in smell and taste of Covid-19 infected patients [19] during first 1-4 days suggest involvement of the vagal nerve and changes in the gastrointestinal secretions. Vagal nerve afferents control pancreatic enzyme secretion that results from the sight, smell, and taste of food. This suggest clear indication of alteration of pancreatic functions due the Covid-19 infection.

b. Suggested biochemical and pathophysiological investigations for early detection

The three enzymes that contribute to further damage are pancreatic amylase, lipases and trypsinogen secreted by the pancreas. Change in serum amylase levels could lead to thick mucus build up and ground-glass opacity that commonly seen in the lungs of Covid-19 infected patients [37, 38]. Proteases digest proteins in the body, leading to destruction of red blood cells and blood profile.

Certain parameters such as measurement of Mean Platelet Volume (MPV) can be an early detection criteria as many Covid-19 infected patients exhibit thrombocytosis [8, 9] or thrombocytopenia at the time no abnormalities present in the chest X-Ray. (MPV) can be used as an indicator of platelet functions for thrombolytic inflammatory diseases [20]. Increased or decreased values of MPV is an indication of inflammatory condition of the pancreas [21, 22].

Serum Angiotensin level [24] is another marker for early detection. Angiotensin-converting enzyme-2 (ACE-2) and its effector peptide angiotensin II (Ang II) has been implicated in the pathogenesis of pancreatitis. This indicate of Covid-19 impact on the pancreas pointing damage and destruction of pancreatic cellular functions that leads to disease progression.

c. Covid-19 disease progression and recommendations

This reveals the importance of investigating the clinical and biochemical changes to identify Covid-19 infection before disease progression. These changes are associated with the probable damage to the pancreatic function due to gastrointestinal cellular changes as a major site of Covid-19 infection. Cohort studies also revealed that the longest observed duration of viral shedding in a survivor is 37 days. Table 1

Table 1: clinical changes for early detection [4, 6, 7, 8, 9,15,16, 26, 27,39]

No of Days	Symptoms	Covid-19 infection site & damage
1-3	Dry eyes Glossy eyes with a yellow tint (closed observation)	Enter blood via respiration or eyes. Virus occupy nasal cavity, sinus, lungs and saliva.
1-14	No specific symptoms. No fever or cough	Slight enlargement of pancreas due to over production of pancreatic enzymes. Inflammation of the lungs and gastrointestinal tract. Virus appears in stools
1-14	Thrombocytosis observed Thrombopenia observed Lung X ray no abnormality	No indication or symptoms of a respiratory infection
1-14	Some experience the losing of smell and taste	Impact on the Vagal nerve afferents control pancreatic enzyme secretion that results from the sight, smell, and taste of food. Also indicate upper respiratory tract infection.
14 -18 days Symptomatic period	Fever average 38.5C Sore throat Dry cough Shortness of breath, Nasal congestion Headache Stomach pain and diarrhea Severe dehydration	As a protective mechanism mucus production increases in the lungs. Disease progressed rapidly indicating bleeding in the inner muscle intestinal wall, reduction in bicarbonates secretion from the pancreas unable to neutralize digestion enzymes.
23 -25 days	Sepsis Acute respiratory distress syndrome (ARDS)	Impact liver, kidneys and heart functions Virus present in all the excretory organs and blood
23 - 25 days	Disease progression varies according the severity of the condition based with age, underlying other health condition. Acute cardiac injury Acute kidney injury Secondary infections	Covid-19 present in Urine, Blood, Stool, Saliva, mucus, organs, breath

25 - 31 days	Death or Survival	Covid -19 continued to be contagious
37 days	If Survived	Covid-19 completes the life cycle. Possibility of detecting in the hair follicle and sweat. Viral shedding lasts in stools for more than 1 month after recovery [27].

d. Recommendations

The following biochemical and physical investigations can be suggested to identify the early onset of the disease

Table 2: List of biochemical tests suggested to identify early onset [20,21,22,24,29]

Mean Platelet Volume (MPV)	Indicator of thrombocytic activity, has been investigated in various proinflammatory and prothrombotic clinical states. Positive correlation between MPV and liver and pancreatic enzymes.
Platelet Activation Factor (PAF)	Serves as a primary mediator of inflammation in the pathogenesis pancreas and PAF contributes to local tissue damage and bleeding.
Serum Amylase	Inflammatory process associated with tissue damage of pancreas
Serum Lipase	Inflammatory process associated with tissue damage of pancreas
Trypsin Activation Peptide (TAP)	TAP activity increases early in the course of the pancreatic changes and attains maximal value within 24–48 hours.
Pancreatic Bicarbonate	Pancreatic secretion for acid balancing. May indicate cellular changes in pancreas.
Vasodilator Intestinal Peptide (VIP)	Concentration of this peptide (VIP) of ACE2 pathway determine specially with diarrhea patients for intestinal cellular damage.
Serum Angiotensin Level	Effector peptide of Angiotensin II for pathogenesis of pancreas
Abdominal Investigations 1. contrast enhanced computed tomography (CECT) 2. magnetic resonance imaging (MRI)	Observation of pancreatic, spleen and gastrointestinal tissue changes specifically hemorrhage within the tissues.

Early identification of Covid-19 asymptomatic individuals is the biggest challenge faced globally. This study recommends a longer quarantine period of 18 – 21 days instead of 14 days. Furthermore due to further viral shedding of survived individuals, actual full recovery period should extend up to 37 days. Shedding can be further monitored by testing stools, sweat and hair follicles. Another major way of disease spread is via excretion of urine and faeces. Proper hygiene practice and sanitary issues in poor countries need attention as Covid-19 virus indicates prolong survival period in the human excretory system.

Above biochemical investigations first should focus on families with infected individuals. Individuals with underline health issues and older generation need priority of testing.

Conclusion

We believe that these findings will contribute to a better understanding of the actual process of the disease progression and will contribute to advances in the implementation of more efficient clinical treatment and infection control strategies.

This review has compiled many data reported in literature and highlighted the alternative diagnostic pathways to identify the Covid-19 infection. Suggested clinical and biochemical parameters would be useful for early diagnosis of both asymptomatic and symptomatic individuals infected with SAR CoV-2 virus.

The main organ effected by Covid-19 are identified as pancreas and Intestine. We believe investigation of the pancreatic functions are the fastest and shortest way to identify the Covid-19 deadly virus.

Due to unavailability of actual sample testing with infected patients, we present this argument as an awareness of possible approach for a cure. This opens doors with a new concept to tackle the New Corona Covid-19 virus before full grown level of the disease for easy management and to stop the spread in the worldwide scale.

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