

Coronavirus Disease 2019 (COVID-19), Comorbidities, and Clinical Manifestations

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SARS CoV-2, the novel coronavirus has created an unprecedented pandemic worldwide. Covid-19 a highly contagious illness, is caused by a coronavirus of the type, that was first identified by Dr. Almeida in 1964, at her laboratory in St Thomas Hospital in London. In a very interesting investigative report, titled, "Why weren't We Ready for the Coronavirus?" David Quammen describes the reasons, why the US has fared worse than other countries. (The New Yorker -05/05/2020). The author asks a former scientist of Center for Disease Control (CDC) Dr. Khan about the preparedness, what went so disastrously wrong? Dr Ali Khan replies, "This is lack of imagination". According to the latest disease prediction model, built by the researchers of Columbia University, if the country (USA) had locked down, two weeks earlier than it did on March 16th, it could have prevented 84% of deaths and 82% of cases (Pei: <https://doi.org/10.1101/202.05.15.20103655>). El Salvador's president closed the border and implemented mitigation efforts, before a single case was reported from his country. According to Johns Hopkins Covid-19 tracker (coronavirus.jhu.edu), there have been 1571 confirmed cases and 31 deaths in this country. Similarly, the Vietnam's success (324 confirmed cases and no deaths), is built on suppression of the virus, mitigation, and social distancing.

A Sri Lankan microbiologist Dr. Malik Peiris of the University of Hong Kong, isolated coronavirus from two patients as early as in 2003. Although earlier tradition was, to name the pathogens by geographical association, this novel virus was named SARS CoV, the name was further revised SARS CoV-1 and currently, it is called SARS CoV-2 and the disease is known as coronavirus disease 2019 (COVID-19). The new virus appeared gradually in humans last December (2019) in Wuhan, China, and in January of 2020 several Chinese laboratories sequenced wholly or partly, the genomes of the virus samples from different patients. The genetic sequence of the new coronavirus was made available, to the World Health Organization (WHO) on the 12th of January 2020. The WHO declared the novel coronavirus (COVID-19) outbreak, a global pandemic on March 11th, 2020. Dr. Bernardo Sebastian, the director, Amedeo literature service, has put together a comprehensive review of Covid-19 pandemic [1].

Over time, viruses mutate and evolve into new strains. Since the outbreak of SARS CoV-2, researchers have sequenced thousands of SARS CoV-2 genomes, and identified all the mutations that have occurred, Genome Wuhan-Hu-1, Genome WA2 of Seattle and the Genome NY1-PV08001 of New York, demonstrating, that most of the New York coronaviruses, links to the virus found in Europe than from Wuhan, China. Researchers from the USA and the UK, in a collaborative effort, have developed a real-time mutation tracking in SARS-CoV-2, focusing initially on the spike protein. The mutation Spike D614G seems to be the most dominant pandemic form in many countries [2]. Spike (S) proteins are of vital importance in terms of viral infectivity as well as antibody targets. Both the S-glycoprotein and ACE2 receptor are known to be extensively glycosylated. Spike protein has been shown to contain 66 glycosylation sites, suggesting the importance of understanding the role of glycosylation, for the development of new vaccines [3,4]. It has been reported that angiotensin-converting enzyme-2

is the main host cell receptor of human pathogenic coronavirus [5]. ACE2 is expressed by epithelial cells of the lung, intestine, kidney and blood vessels [6]. Circulating ACE2 enzyme seems to offer protection against influenza A(H7N9) virus-induced lung injury [7]. Viral entry is facilitated by the presence of ACE2 as well as TMPRSS2 protease activity. Sungnak and associates have co-detected these transcripts in specific respiratory and corneal epithelial cells, potentially explaining the high efficiency of SARS CoV-2 transmission [8,9].

MicroRNAs play a big role in our body, in controlling gene expression and as front-line defense, against viruses that invade. Studies have shown, that both virus and host-derived miRNAs, play a crucial role in the pathology of virus infection. Chinese researchers have found, that hsa-miR-4661-3p targets the S gene of SARS CoV-2 and a virus-encoded miRNA, MR147-3p, enhances the expression of TMPRSS2, with the function of strengthening SARS CoV-2 infection [10]. According to the researchers at the Center of Healthy Aging, Medical College of Georgia, with age, and some chronic conditions, the attacking microRNA dwindle, reducing ability to respond to viruses [11]. The naturally occurring miRNA, targets the 3'-UTR regions of the virus, the section of the messenger RNA, that contains regulatory regions, that influences the gene expression and protein function. Researchers from New Delhi, India, report, that of all the miRNA studied, hsa-miR-27b is a unique miRNA, specific to India SARS CoV-2 and had no complementarity-based nucleotide-binding, with the strain of SARS CoV-2 from other countries. They also describe a unique mutation in the spike surface glycoprotein (A930V: 24351 C > T), in the Indian sequence [12]. These researchers speculate, an important regulatory role of miR-27b in SARS CoV-2 infection. Studies are in progress in several laboratories, for using miRNA for neutralizing highly infectious pathogens [13].

Coronavirus can affect anyone, once infected the disease can cause symptoms from dry cough, to high fever and respiratory distress. Some individuals may have severe illness than others, because of preexisting conditions, such as hypertension, obesity, diabetes and vascular diseases. It appears that SARS CoV2, unlike other viruses, can be transmitted prior to the development of symptoms and throughout the course of illness. In view of this fact, transmission of this virus from asymptomatic individuals has been well documented [14]. However, detectable viral RNA does not always correlate, with the isolation of infectious virus. In a report from the Chinese Center for Disease Control and Prevention, which included 44,500 confirmed infections, disease severity was of the following order; mild (81%), severe disease with hypoxia (14%), critical case (5%) with overall case fatality rate of 2.3%; no deaths reported among non-critical cases [15]. Among hospitalized patients, the fatality is higher. In a study in New York City of 2634 Covid-19 patients, 14% received critical care and 12% received invasive mechanical ventilation, and mortality among those receiving ventilation was 88 percent [16].

In a study reported from New York City with 5700 patients with Covid-19, mean average age was 63 years. The authors found that 94% of the patients had a chronic health problem, and 88% had two or more comorbidities. The most common comorbidities were hypertension (56.6%), obesity (41.7%) and diabetes (33.8%). Seventeen percent had a respiratory rate greater than 24 breaths/minute and 28% received supplemental oxygen [16]. It is surprising to note, that although the World Health Organization (WHO) lists fever as common symptom (hence the worldwide temperature check), the study found, that around two-thirds of the patients did not have fever and yet, were sick enough to need to be hospitalized. The Scientist/News and Opinion (Apr 24, 2020), had an article titled, "Nearly all NYC-Area COVID-19 hospitalizations had comorbidities" stressing the role of underlying comorbidities in the severity of coronavirus disease. Unlike the pathogens causing pneumonia, which target the lungs, the SARS CoV-2 seem to target the blood vessels. In individuals with cardio-metabolic diseases, the blood vessels are already damaged and SARS CoV-2 infection, further aggravates the endothelial function, and dysregulates the vascular function.

The hospitalization rate for COVID-19 is 4.6% per 100,000 population, and almost 90% of the hospitalized patients have some type of underlying condition, according to the Centers for Disease Control and Prevention, USA. According to the Associated Hospitalization Surveillance Network (COVID-NET), which includes, laboratory confirmed cases in 99 counties in 14 states, hospitalization rate increased with patient age. Those aged 65 years and older, were admitted at a rate of 13.8%, with 50 - 64 year-olds at 7.4%, and 18-49-year-olds at 2.5%. Hypertension was the most common morbidity among the oldest patients, with a prevalence of 72%, followed by cardiovascular disease at 50.8% and obesity at 41%. Is this the common pattern of comorbidity in all the geographical areas? Not necessarily. In January

of 2020, Huang and associates reported, clinical features of 41 patients hospitalized with Covid-19 in Wuhan China [17]. The median age was 49 and all were male individuals. According to the authors, less than half had underlying diseases, including diabetes (20%), hypertension (15%) and cardiovascular disease (15%). Chen and associates from Wuhan's Jinyintan Hospital, reported a study of 99 covid-19 patients [18]. The average age was 55 years. Half of the patients had chronic diseases, including cardiovascular and cerebrovascular diseases. Wang and associates from Zhongnan Hospital, Wuhan, reported clinical characteristics of 138 hospitalized patients with 2019 coronavirus [19]. Of the 138 patients 64 (46.6%) had one or more of coexisting medical conditions. Hypertension (31.2%), Diabetes (10.1%). Cardiovascular disease (14.5%). Readers are urged to refer to the commentary on this work, by Adao and Guzik (Inside the Heart of COVID-19: Cardiovasc Res. (doi: 10.1093/cvr/cvaa086) for further information on this topic.

Chinese researchers, Wang and associates, did a meta-analysis of a total of 1558 patients with Covid-19 in 6 studies [20]. Hypertension (OR: 2.29, $P < 0.001$), diabetes (OR: 2.47, $P < 0.001$), chronic obstructive pulmonary disease (COPD) (OR: 5.97, $P < 0.001$), cardiovascular disease (OR: 2.93, $P < 0.001$) and cerebrovascular disease (OR:3.89, $P = 0.002$), were independent risk factors associated with COVID-19 patients. The meta-analysis showed a significant relationship, between patients with severe Covid-19 and cerebrovascular disease (Odds Ratio; OR: 3.89). The meta-analysis revealed, no correlation between increased risk of COVID-19 and liver disease, malignancy, or renal disease. Hypertension, diabetes, COPD, cardiovascular disease, and cerebrovascular disease are major risk factors for patients with COVID-19. Guan and associates on behalf of the China Medical Treatment Expert Group for COVID-19, analyzed the data from 1590 laboratory confirmed hospitalized patients in 575 hospitals in 13 provinces [20]. The mean age was 48.9 (much younger patients than in the USA). The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). The ranking of comorbidities seems to vary, according to the incidence and prevalence of cardiometabolic diseases, as well as the age group of the patients studied. In geographic areas like, China and India, with huge diabetes population, the ranking may be hypertension followed by diabetes. Whereas in the USA, with high incidence of obesity, the ranking will reflect the prevalence of metabolic diseases; hypertension followed by obesity as the major comorbidity.

The clinical manifestations of Covid-19, according to the latest reports seem to be heterogenous [21-26]. Researchers from academic hospitals from Wuhan, China, have reported that of the 416 covid-19 patients admitted, 20% had evidence of myocardial injury, evidenced by the presence of elevated levels of cardiac troponin-1 [27,28]. The authors speculated, that inflammation may be a potential mechanism, for myocardial injury and suggested aggressive treatment of patients 'at risk' for myocardial injury. The most common pattern of coagulopathy, observed in patients with Covid-19, is characterized by elevations in fibrinogen and D-dimer levels. These observations parallel rise in markers of inflammation, elevated levels of C-reactive protein, proinflammatory cytokines, IL1B, IFN λ , TNF α , IP10 and MCP1 [17]. Unlike sepsis mediated disseminated intravascular coagulation (DIC), the degree of activated partial thromboplastin (aPT) elevation is less than partial thromboplastin (PT) elevation. According to some researchers, a hallmark of severe COVID-19 coagulopathy, in 71.4% of patients who died of COVID-19 met ISTH criteria for DIC [29-32]. The observed coagulopathy, seems to be predominantly pro-thrombotic DIC, with high venous thromboembolism rates, pulmonary congestion, microvascular thrombosis, reduced capacity to cleave and remove fibrin, with high rates of central line thrombosis, and vascular occlusive events (ischemic limbs, strokes).

Researchers from the University of North Carolina demonstrated, that elevated levels of fibrin are the landmark of acute lung injury and in covid-19 infection, dysregulation of urokinase pathway, contributes to more severe lung pathology, and serpin-1 plays a protective role following infection [31]. Patients with severe coronavirus disease associated with ARDS, have increased pulmonary inflammation, thick mucus secretions in the airways, elevated levels of cytokines, extensive lung damage, and microthrombus. Neutrophilia seem to predict poor outcomes in patients with severe COVID-19 and neutrophil to lymphocyte ratio seems to be an independent risk factor for the severity of the disease [33]. Since Covid-19 mediated clinical manifestations are quite heterogenous, researchers are exploring the use of 'biomarkers' for developing combination therapies, to address the existing clinical manifestations. For instance, if the biomarker assays reveals a prothrombotic status, then clinicians should provide appropriate anti-thrombotic therapy.

On other hand, if it is a mild hypoxia, a Normobaric oxygen therapy should be appropriate. If the clinical manifestation indicates highly inflammatory condition, anti-inflammatory therapy should be sufficient. In those cases, where there is a definite indication of coagulopathy, treatment with low molecular weight heparins (LMWH), tissue plasminogen activator (tPA) or with antiproteases targeting plasmin, seems to be a better option. In a recent study, reported by Agnelli and associates in the NEJM (April 23, 2020), oral apixaban was found noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism [34].

Although survival rates vary from country to country, a report from London's Intensive Care National Audit and Research Center, found that 67% of reported COVID-19 patients from England, Wales, and Northern Ireland, receiving "advance respiratory support" died. A study in a similar patient group in China, found only 14% survived, after going on a ventilator. In New York City, an astronomical 80% of patients, who required ventilator at the height of this pandemic died, according to the city and state officials. According to the Chinese investigators, progressive hypoxia is a characteristic manifestation in the clinical course of severe and critically ill patients, with COVID-19 Pneumonia. Oxygen therapy plays an important role in the alleviation of respiratory distress. In a small pilot study of 250 Covid-19 cases, conducted by Dr Cosentini in Italy, half were found to have mild pneumonia-but their oxygen saturation was not yet compromised. All these patients were discharged from E.R., and they were sent home with pulse oximeters. None of these patients required a ventilator. We have several options, to help these patients who are suffering from an illness, which has no cure at the time of this writing. Having said that, we do have treatment options that include various noninvasive methods of delivering oxygen, patient positioning maneuvers, that open parts of lungs and close monitoring, treatment of inflammation and appropriate interventions for thromboembolic conditions.

Researchers from Harvard speculate, that successful results from on-going studies on hyperoxia trials, may ultimately yield a combined therapeutic approach for the treatment of stroke patients, where Normobaric Oxygen (NBO) is started in the field or in the ambulance and subsequently combined with Hyperbaric Oxygen (HBO), infusion of super-oxygenated solution or thrombolysis [35]. According to the Chinese investigators, progressive hypoxia is a characteristic manifestation, in the clinical course of severe and critically ill patients with COVID-19 Pneumonia [36]. Like the stroke patients, a timely delivery of oxygen either via NBO or HBO, may provide much needed oxygen, and protect the hypoxia-mediated tissue injury and loss of organs. Chinese researchers in Wuhan, China, performed HBO treatment in severe COVID-19 patients and concluded that, "HBO treatment can effectively correct systemic hypoxia, improve circulation, and immune function. Early HBO treatment may improve the total efficiency of systemic support treatments, reduce the use of mechanic ventilation and lower mortality rate of severe or critically ill patients with COVID-19". Prof. Paul Harch of Department of Medicine, Section of Emergency Hyperbaric Medicine, Louisiana State University, New Orleans, concluded, "With just 3-8 HBOTs the patients were bridged through the hypoxemic crisis phase of the infection and successfully discharged from the hospital". The author suggests that HBOT applied earlier in the disease process, would prevent the deterioration that leads to the significant morbidity and mortality of COVID-19 infection [38].

A meta-analysis of five studies by cardiologists of Shandong University, China, reported the presence of comorbidities in Covid-19 patients admitted to hospitals. The overall proportion of comorbidities were, hypertension (17.1%), cardia-cerebrovascular disease (16.4%), and diabetes (9.7%), respectively [39]. Severity and fatality seem to increase with comorbidities, hypertension, obesity, cardiovascular disease, diabetes and chronic pulmonary disease [40-42]. In a large study of 72314 patients from China, the authors reported that those who needed hospitalization had underlying conditions, especially hypertension, diabetes, and cardiovascular disease [43,44]. Early risk assessment, monitoring risk factors for hypoxia, neutrophil extracellular traps (NETs), blood vessel damage, lung injury, cardiac injury (cTn1 and proBNP), cytokine storm (IL-6, IL-7, IL-22, IL-17 etc.), activation of the coagulation cascade (fibrinogen, D-dimer, plasmin), will help the clinicians for making wise decision for appropriate interventions.

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