

Editorial

The future of COVID-19: May the uncertainty deepen or a glimpse of hope comes?

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Could there be any other infectious disease outbreak in the history of modern medicine that challenges the human intelligence in predicting the epidemiology and detecting the pathophysiology of COVID-19?

It was not in the best mind's thought that the top ten richest countries would be the most overwhelmed by the fast spreading SARS CoV-2, and contribute to three-fourths of COVID-19-related global mortality during the first wave of the current pandemic. Even in Europe and North America, the positive correlation of the caseload and deaths with the economic power of the respective countries is still unprecedented experience. It is not only the remarkable difference in caseload and deaths among rich and poor countries what makes this pandemic inscrutable, but also the lack of significant regional difference in the proportion of recovery.

Among others, the world mind people have publicly predicted as the worst of all to be in Africa. After four months since the first COVID-19 patient was reported in Africa, we have realized that the continent has contributed only about 1% to the global mortality figure, with the nearly global average proportion of recovery. The slow but ongoing increment of new infections with nearly equivalent recovery is a blessing in disguise, in a continent where health facilities and the health workforce are meager.

By extrapolating the accumulated knowledge from other viral infections, patients with autoimmune disease, pregnant women, and children were initially anticipated to have the highest morbidity and mortality. Because of the different degrees of immune modulation and immune suppression (partly due to the disease nature, and partly due to cytotoxic chemotherapy and high dose corticosteroid), it is known that patients with autoimmune disease are at higher risk of viral infection (Pope 2020).

However, as a global review of 110 rheumatoid arthritis patients, who also contracted COVID-19, showed that the mortality risk was not different from the general population (Gianfrancesco 2020). Furthermore, against earlier thought, anecdotal evidence from case series studies did not demonstrate an increased risk of COVID-19 in people with

autoimmune disease who were on immunosuppressive treatment. Initially, some patients were even advised to discontinue medications. The current recommendation, however, is not to discontinue immunosuppressive treatments for cancer, transplant, or autoimmune diseases, fearing increased risk of COVID-19 (Gianfrancesco 202; Monti 2020).

Similarly, many authors initially predicted the increased risk of COVID-19 among pregnant women and their babies by postulating an altered maternal immune response, and extrapolating the higher risk of viral infection and the physiologically increased expression of the ACE2 receptors in pregnant women (Liu 2020; Silasi 2015; Zhao 2020). The author has reviewed 841 pregnant women with COVID-19 from five studies and found that the maternal death risk was 0.6%, which was by 13-50 fold lower than hepatitis E virus, H1N1 influenza virus, SARS CoV and MERS CoV epidemics and pandemics in the last two decades (unpublished study).

There are a lot of immunological responses in which autoimmune diseases and pregnancy do share, which are attributed to be protective from worsening COVID-19. For instance, the bilateral activation of the immune system (the proinflammatory and anti-inflammatory cytokines and chemokines) in both systemic sclerosis and COVID-19 is a unique phenomenon, which has probably made both disease conditions have a benign course or more or less similar illness with the non-pregnant women. Of note, the increased risk of flares among patients with Th-1 and Th-17 autoimmune diseases in the postpartum period may signal that postpartum women with a significant drop in immune-modulating placental hormones, anti-inflammatory and antifibrotic cytokines could be at an increased risk of COVID-19.

Beyond the immunological distinctiveness of SARS Cov2 as compared with SARS CoV and MERS CoV, the pathological and hematological manifestations of COVID-19 have been as well creating a lot of confusion among experts in the field. Taking the experience of the Influenza virus and other

Coronaviruses, the imaging diagnosis of viral pneumonia was initially popular.

However, as the autopsy studies demonstrated, pulmonary microangiopathy (diffused pulmonary microthrombi) appearing as interstitial pneumonia is becoming evident (Kollias 2020, Belen-Apak 2020). The kind of adult respiratory syndrome (ARDS) developed in COVID-19 patients is also a bit bizarre from other causes; the lung compliance is preserved; alveolar-arterial oxygen gradient remains high. The very prominent finding is occlusion of the pulmonary microvasculature by the fibrin rich microthrombi (Wang 2020), which implies that the coagulopathy in pulmonary microvessels (in other organs too) progresses to occlusive microangiopathy.

In severely ill COVID-19 patients, disseminated intravascular coagulation (DIC) is not uncommon; however, unlike other causes, severe thrombocytopenia, hypofibrinogenemia, hemolytic anemia, bleeding tendency, markedly prolonged partial thromboplastin and prothrombin time are not prominent characteristics of COVID-19-related DIC, even in severe cases (Levi 2020). As one of the indicators of COVID-19 disease severity (most likely from non-erythrocyte cells source), lactate dehydrogenase (LDH) is markedly elevated. A meta-analysis has shown that elevated LDH levels were associated with about 6-fold increased risk of developing severe disease and about 16-fold increased risk of mortality (Henry 2020). High intravascular fibrin deposition with increased capillary leakage and significantly elevated serum D-dimer are consistent findings in severe COVID-19 patients, but not as such remarkable in other causes of DIC.

Luminal fibrin deposition (commonly in the pulmonary microvascular system) is probably initiated as a result of endothelial injury and dysregulated fibrinolysis leading to atypical disseminated coagulopathy and multiorgan failure (Whyte 2020; Ackermann 2020). This is again likely to be due to a significant increment in the major fibrogenic cytokines (IL-4, IL-6, TNF- α , and TGF- β 1). Interestingly, despite the subtle changes in coagulopathy indicators, the thromboembolic phenomenon can also occur in the veins and arteries (Thachil 2020; Tang 2020).

Overall, the accumulating evidence persuades to conclude atypical coagulopathy-microangiopathy (vascular disease) leading to respiratory and multiorgan failure. What is priming the coagulopathy/micro thrombosis is severe endothelial damage in the lung alveoli (Ackermann 2020). The extra respiratory failures (including stroke, renal and

cardiac failures) are also thought to be due to systemic microvasculitis and thrombosis.

Apart from the atypical nature in the pathophysiology and the confirmatory diagnostic challenge, the treatment modality is still limited to supportive therapy and treating secondary complications. When we look into the possible therapeutic and prophylactic research works on progress, there are a lot of uncertainties and a glimpse of hope. COVID-19 mobilizes the scientific society across the globe either to prevent its occurrence or cure it. As of 9 June 2020, the number of registered COVID-19 clinical trials worldwide is 1982.

Among several therapeutic clinical trials for the management of COVID-19, antivirals, anti-inflammatory agents (monoclonal antibodies, Bruton Tyrosine Kinase inhibitors, non-steroidal anti-inflammatory drugs, Vitamin D), anticoagulants, tissue plasminogen activators, and many more are on the frontline. Among the promising antivirals, the preliminary result has shown that Remdesivir was superior to placebo in shortening the time to recovery in hospitalized 1059 COVID-19 patients (Beigel 2020).

The second panel of basic science research and clinical trial is on vaccine development. Without going into the detail, as there are green lights, there are also anticipated challenges and uncertainties. The first challenge is the very long process to identify an effective vaccine, manufacture, and deliver to the beneficiaries. Although many are hoping in less than a year period, there are a lot of hurdles, which may let it pass the schedule.

The estimation of the spread using the mathematical model is still with very wide uncertainty. Nonetheless, will the virus infect most of the people before the vaccine is ready is a catching question. In other words, will the herd immunity be faster than the vaccine development and distribution? To date, nobody knows exactly how many asymptomatic infections are spreading in the community. As the purpose of the vaccine is for the COVID-19 naïve individuals, will it be a wastage of resources with the current ultrafast speed of spread?

SARS CoV-2 has the potential to infect anybody. It is also well noted that quite a fraction of the SARS CoV-2 carriers become symptomatic unless otherwise get tested and recognized as infected. Therefore, this will be another challenge in selecting the right candidates for the vaccination, as it will not be possible to blindly vaccinate close to eight billion people. Or else to go for vaccination after conducting the mass antibody screening, which is also damn

expensive and logistically burdensome. Whichever the approach is, there will be a wastage and disproportionate coverage while attempting the development of herd immunity by vaccinating a certain percentage of the population.

Secondly, COVID-19 is primarily a disease of aged people; however, as previous experiences and the immunogenicity studies showed, vaccinating aged people is not as successful as it is in children. Aged persons usually require repeated doses of vaccine to have an improved protection. Nevertheless, COVID-19 is likely to be a global endemic disease. Therefore, the future generation may benefit from being vaccinated early in childhood if an effective and safe vaccine is identified.

Thirdly, how long the vaccine can prevent reinfection (if not lifelong protection) is still unknown and unpredictable. Many of the viruses by their nature either do not reinfect or can cause milder disease in subsequent infection; a few exceptions (like human papillomavirus) are not in this domain. The lack of an approved vaccine for other coronaviruses (SARS CoV and MERS CoV, in particular) (Natalie 2020) may further widen the uncertainty.

One of the promising and groundbreaking vaccines under development is the RNA vaccine. However, it is not known whether this vaccine will have an exaggerated immune enhancement, probably similar to the SARS CoV-2 infection in susceptible individuals. Earlier, it was recognized that SARS CoV-2 susceptible individuals deteriorate because of the development of “cytokine storm” (Nile 2020), and the risk of immune enhancement with vaccines is still a serious concern (de Alwis 2020). One of the challenges in vaccine development for SARS CoV and MERS CoV in an animal model was that trial vaccines caused lung damage and peritonitis (Gretebeck 2015).

In general, with existing therapeutic interventions, the case fatality rate (CFR) of COVID-19 may continue being proportional in the developed and developing countries, but it is much lower than many other viral pandemics of the 21st century. However, the global lower CFR should not mask the overall deaths caused by or associated with this virus, which may reach about one million before the coming Christmas. As learnt from dozens of countries which are curbing the outbreak curve, the author is optimistic that the world is transiting from a state of uncertainty, confusion, and hopelessness to a glimpse of hope, primarily by taking the natural course of the disease as a learning curve. Though the vaccine development and equitable distribution seem unrealistic sooner or later, fairly effective therapeutic

agents are likely to be available within a year. As a result, COVID-19 is very unlikely to be the superbug of the 21st century.

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