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Infection-Genomics of COVID-19: Are some communities resistant?

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Abstract

The 2019-Novel Coronavirus has currently gripped the world in terror, affecting 210 countries and territories as of April 17, 2020. Originating from Wuhan, Hubei province, China, the virus has spread so rapidly throughout the world and has already claimed 144,700 lives and is currently afflicting 2.17 million people. The US has over 677,000 confirmed cases of COVID-19, followed by Spain, Italy, France, Germany, UK and China. On careful inspection of the COVID-19 statistics, a peculiar unsettling trend becomes apparent. Here, I will highlight this trend and propose the importance of infection-genomics (sankramikogenomics), in understanding the susceptibility to COVID-19 and the severity of disease progress.

Introduction

Currently, the whole world is put on hold by a novel corona virus, SARS-CoV2, that is closely related to the Severe Acute Respiratory Syndrome (SARS) virus that caused havoc in 2013 (Wu et al., 2020). Coronavirus disease (COVID-19) started by the end of 2019 in China and spread in many Asian countries by February 2020. By end of March, COVID-19 infected ~200 countries, claimed ~30,000 lives and afflicted over 450,000 people. Within the last two weeks, it has spread to 2.1 million people and claimed 134,600 lives. In many parts of the world, COVID-19 is still marching through the communities unabated.

Over the last several decades, several infectious diseases have emerged to infect the mankind. These diseases, depending on their severity, caused serious disruptions to either a small region of the world or spread throughout the world with significant number of human deaths and devastation. In 2018, malaria infected 228 million people worldwide claiming 405,000 lives. African Region had a disproportionately high share of 93% of malaria cases and 94% of malaria deaths (World Malaria Report, 2019). Nearly all malaria deaths are caused by *Plasmodium*

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falciparum, the deadliest malaria parasite. *P. falciparum* accounted for 99.7% of cases in the African Region, while other regions are affected by less virulent species (World Malaria Report 2008). In contrast, 70% dengue infection burden is in Asia, although 129 countries are at risk (Bhatt et al., 2013). Similarly, seasonal influenza, avian flu and other air borne diseases also affect certain regions of the world but has little or no impact elsewhere. With these factors in mind, I evaluated COVID-19 disease data.

The COVID-19 infection data (https://www.worldometers.info/coronavirus/) shows the total number of confirmed cases in each country along with Active cases and Closed cases defining patients still undergoing medical treatment or the cases closed as the patients have either recovered or died. These 'Closed cases' could be considered as the completion of the battle between COVID-19 and us with two outcomes – discharge from the hospital or death. From these data, one can calculate the interim death rate (IDR); IDR is the percent of cases ending in death among all 'Closed cases' at any given time. IDR is distinct from case fatality rate that can be evaluated after the complete resolution of COVID-19. The IDR data will alert all relevant government agencies, clinical institutions, pharma industry as well as common man regarding COVID-19 outcome.

Here, I have used IDRs to understand the impact of COVID-19 in various countries and regions in the world. The data suggests that, as with any of the vector- or air-borne infectious diseases, COVID-19 also shows differential impact on various regions of the world. I, therefore, propose to evaluate infection-genomics (sankramikogenomics), in understanding the susceptibility to COVID-19 and the severity of disease progress.

Disease statistics and methods

All COVID-19 data were obtained from https://www.worldometers.info/coronavirus/ Worldometer website. As the data is dynamic and changes rapidly, I have used the latest data obtained on April 17, 2020, 8 am (Singapore time). The IDR (%) was calculated as follows:

$$\text{IDR} = \frac{\text{Number of deaths}}{\text{Total closed cases}} \text{ X } 100$$

I also calculated Recovered case (%) and Closed case (%) as follows:

$$\text{Recovered case (\%)} = \frac{\text{Number of recovered cases}}{\text{Total number of cases}} \text{ X } 100$$

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$$\text{Closed case (\%)} = \frac{\text{Number of closed cases}}{\text{Total number of cases}} \quad X\ 100$$

Results and Discussion

In the first wave, COVID-19 infections started in and affected mostly China. Then peoples in surrounding East Asian countries were infected. In the second wave, these infections affected Middle East countries, particularly Iran was most affected. In the third wave, COVID-19 infections affected Western European countries and the US. In the fourth and final wave, it has spread to remaining parts of the world. There is no clear separation or breaks between these waves. These waves are considered only to keep the discussions simple.

The first wave of COVID-19

COVID-19 in Eastern Asian countries: The first COVID-19 infection in China is thought to be on November 17, 2019, it was first identified as the disease caused by a new coronavirus by Zhang Jixian on December 27, 2019 (Ma, 2020). The first death was recorded on January 9 and on January 22 had 571 total confirmed cases, 554 active cases and all 17 closed cases ended in death, 100% IDR. This is understandable considering the doctors and paramedical people were not fully aware of the symptoms as they were witnessing nature's new drama unfold. By January 31, total confirmed cases increased to 11,791 but there were 502 resolved cases including 259 death and 243 recovered. With this the IDR plummeted to 51.5%. By February 10, there were 42,638 confirmed cases with 5012 resolved cases and 20.2% IDR. By February 15, within 24 days, they cut to the IDR to 15%. All these reductions in IDRs were during the upswing of COVID-19 infections. Currently, with 98.66% out of 82,341 cases resolved, the IDR is decreased to 4.11% (Table 1). About 80% of deaths were in patients older than 60 years, and 75% patients had pre-existing health conditions including cardiovascular diseases and diabetes. China to a great extent has overcome COVID-19 infections. Although there are a small number of cases trickling in daily, they probably have blunted the peak impact through lockdown and other drastic measures. The data suggest that the clinical institutions and the government with people's cooperation, restricted the COVID-19 related IDR (Table 1).

In South Korea, the first case was recorded on January 20, 2020. The IDR reached the peak of 51.5% (32 deaths) on March 3 and since then declined to 24.1% on March 6 on much improved

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recovery. With aggressive measures, they controlled the spread without shutting everything down through testing most of the population (Beaubien, 2020) and reduced the IDR to current rate of 2.87% (Table 1). Similarly, by adopting different measures Singapore (daily monitoring of temperature and symptoms, quarantine and stay-home-notice, contact tracing, business continuity plan, social distancing and work from home) and Hong Kong reined COVID-19 infections and IDRs (1.44% and 0.82%, respectively). Japan (investigating flare-ups of cases, identifying the infected and then monitoring their contacts) also controlled COVID-19 infection and IDR (Table 1). Taiwan, Thailand, Vietnam and Malaysia also have IDRs range between 0 to 4.11% except for Japan (16.5%) (Table 1). The battle-readiness was enhanced probably through the experience gained from SARS-2013 and MERV-2015 infections that swept this region. Thus, most of the East Asian countries, in many ways able to control COVIS-19 infections and death.

The second wave of COVID-19

COVID-19 in Middle East countries: This wave started in Iran on February 19 with two COVID-19 infections and showed steady increase until March 30 to reach 44,605 infections. From March 30 onwards, they cut the number of infections in half from 3200 to 1500 on April 15. From March 16 to April 11, Iran had 125 or more COVID-19 deaths and the death rate is also slowly coming down. Currently, with 73.21% out of 77,995 cases resolved, the IDR is decreased to 8.53% (Table 2). All 11 Middle East countries have low IDRs ranging between 0.99-8.55% with Bahrain with the lowest IDR. Thus, despite more than 110,000 COVID-19 infections, Middle East countries have done extremely well in their fight against COVID-19.

Alarming IDRs in the first world

COVID-19 in Western European countries: In contrast, COVID-19 has left a significant track of death and devastation in many Western European countries (Table 3). On January 31, France and Germany had 6 and 7 COVID-19 cases, respectively, lower than Japan (15), Singapore (13) and South Korea (11) cases (Wu and McGoogan, 2020). On February 15, Germany, Italy, Spain and UK had 16, 3, 2 and 9 cases, compared with Japan (259), Singapore (65) and South Korea (28) cases. Then, something changed – confirmed COVID-19 cases increased almost uncontrolled proportions in the coming weeks in Germany, Italy, Spain and UK; even after 49 days the number of confirmed cases is increasing ~8%-14% each day compared to the previous day. What is more worrisome is that the IDRs in many European countries are alarmingly high. The UK tops the chart with 97.6% IDR followed by Netherlands, Ireland, Norway, Sweden,

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Portugal, Belgium, Italy, France and Spain (all above 35%, except for Spain, 20.37%; Table 3). Some of these initial high IDRs were due to herd-immunity approach in solving COVID-19 (Kwok et al., 2020). In stark contrast, Germany, Switzerland and Austria have low IDRS (4.36-7.46%) (Table 3). Thus, most Western European countries were exposed to very severe outcomes with COVID-19 infections. Only a small number of countries have regained control over COVID-19.

COVID-19 in the US: On February 15, the US had 15 cases, the number reached 100 cases on March 2 and 6,346 cases on March 17. COVID-19 cases swell 100-times to 677,056 in about a month. Since April 2, the number is increasing ~30,000 new cases on an average every day. We evaluated the data from all 50 US states (Table 4). Fifteen states have been successfully defending the infections keeping the IDRs below 10%. Wyoming with IDR (1.12%) leads the country, followed by South Dakota, Hawaii, Montana, North Dakota, Tennessee, Arkansas, Iowa, Maine, West Virginia, Alaska, New Hampshire, Minnesota, Utah and Texas (Table 4). These states have done extremely well in fighting COVID-19 infections and related deaths. Next seven states, Oklahoma, Nevada, New Mexico, Delaware, Washington DC, Massachusetts and North Carolina have IDRs range between 10.19 and 13.60%, immediately followed by Virginia with an IDR of 17.95%. These eight states have done well in avoiding extreme impact of COVID-19 infections. The next 11 states have IDR range from 25-50%. Unfortunately, 18 states have poor record in fighting COVID-19. They are grouped states into one with 51-79% IDRs and the other above 80% IDRs (Table 4). These 29 states, particularly the last 11, need substantial measures to slow down the devastations caused by COVID-19.

Infection-genomics (Sankramikogenomics)

It is difficult to imagine such high IDRs in most of the above countries with optimal numbers of doctors, top class expertise and facilities. The knowledge and experience in handling COVID-19 or similar catastrophes may not be the key limiting factor. The total number of cases are yet to reach the total capacity of their healthcare systems, although some may have. It is also hard to believe that the high IDRs are due to old age and confounding comorbidity such as, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer (Wu and McGoogan, 2020; Guan et al., 2020; Yang et al., 2020). Therefore, we hypothesize that additional factors contributing to high IDRs could be (a) delay in seeking medical help and/or (b) susceptibility of patients of certain ethnicities. The delay in reaching clinics and hospitals could be due to milder, apparently ‘innocuous’ symptoms associated with the early

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stages of COVID-19 infection. The lack of proper medical insurance cover, particularly in the US, may prevent some patients from seeking medical help in a timely fashion. However, this may not be a concern in Europe where most countries have accessible healthcare systems. The novel coronavirus causing COVID-19 is closely related to SARS virus (Wu et al., 2020) and binds to host receptor angiotensin-converting enzyme 2 (ACE2) through its spike protein receptor-binding domain (RBD) (Lu et al., 2020; Wan et al., 2020; Wrapp et al., 2020). Interestingly, the changes in the RBD leads to 10-fold increase compared to SARS virus in the binding affinity to ACE2 (Wrapp et al., 2020). All three monoclonal antibodies that bind to SARS virus RBD failed to bind to COVID-19 virus RBD indicating the antibody epitopes are distinct. Further, insertion of "RRAR" furin recognition site (with improved host protease processing (Hoffmann et al., 2020; Walls et al., 2020)) may make it more virulent, akin to avian and human influenza viruses (Chen et al., 1998). Thus, within a short time the scientific and medical community, have identified how subtle changes in structure in the virus may be responsible for this devastation. This is further compounded by the higher basic reproduction number (R_0, ~3.28 with a median of 2.79) of COVID-19 compared to SARS coronavirus (Liu et al., 2020).

Structural variation of ACE2 and COVID-19 severity: It is also important to evaluate the human receptor and associated factors to complete the picture of this present pandemic. Considering all things and circumstances are equal, which they are not, three distinct groups of countries have been able to control COVID-19 calamity. They are (a) Germany, Austria and Switzerland in Western Europe, (b) East Asian countries, and (b) Middle East countries. They have been successful in defending against the COVID-19 catastrophe with low IDRs (Tables 1-3). Without trying to take the credit away from the medical and paramedical services and their innovative methods as well as the efforts of their government and the community, and putting 'political correctness' aside, I considered the demographic ethnicity of these countries. Germany has 87.2% of the population belonging to German ethnicity (2017 estimate), while more than 70% of the populations of Austria and Switzerland are closely related to Germanic lineage (https://www.indexmundi.com/COUNTRY/demographics_profile.html). Interestingly, the 'first four German patients' who were positively confirmed to have the virus recovered from COVID-19 without hospitalization (Rothe et al., 2020). Taking these and other factors into account, we propose the possibility that people of this ethnic background may be 'somewhat resistant' to COVID-19. To test this hypothesis, we considered the demographic ethnicities, with specific focus on ancestral history and percent of Germans, of various US

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states with low and high IDRs. Of the 15 US states with low IDRs have four states have high proportion of population belonging to German ethnicity; Minnesota (33.8%), Iowa (35.1%), North Dakota (41.4%) and South Dakota (38.8%) (Table 4). Hawaii, although has only 5.9% population belonging to German ethnicity, shows low IDR of 1.84%. The low IDR could be due to its 19.2% East Asian population (the highest among the US states) (see discussions below). However, ten other states have low IDRs, but their German populations are also low. In contrast, 8-out-of-12 states that have less than 11% German population have high IDRs (>80%). Wisconsin (40.5%) and Nebraska (36.1%) with high proportion of population belonging to German ethnicity buck the trend with high IDRs. Although it is crystal clear that COVID-19 infections and outcomes depend on innumerable factors including (but not limited to population) density, healthcare facility and personnel, access to healthcare insurance, and total COVID-19 infections and capacity, we observed that 50% of the states follow the 'German factor'.

As the first country to face the unknown enemy, only China had an explosion of COVID-19 infections. The high rate of infection was also due to unexpected viral transmission by asymptomatic patients through their natural day-to-day interactions. Despite this initial onslaught, China along with eight countries including South Korea, Hong Kong, Japan and Singapore reined COVID-19-associated death and devastation compared to the rest of the world (Table 1). In addition to enforced social discipline and other measures, it is also possible that there could be an 'Oriental factor' responsible for the resistance factor. Hawaii has high proportion of Oriental Asian population and low IDR (Table 4).

COVID-19 infections were also rapidly brought under control in Middle East countries; they have an average of 33.3% Closed cases with low IDRs (Table 2). The people from this region are distinct ethnicity than both German and Oriental people. Therefore, I propose the third "Middle East factor" that reduces the severity of COVID-19 infections. Thus, the differential susceptibilities are probably due to three distinct factors identified here. Further, detailed studies will expose additional 'resistance' and/or 'susceptible' factors responsible for determining the impact of COVID-19 infections on people from different backgrounds. With more interracial (or inter-ethnic) marriages, these distinguishing features will be burred with time. The search and identification of such differences between people belonging to distinct ethnicities could be related to structure, splice forms and expression regulation of ACE2 and other associated genes; we propose to name such studies as Infection-genomics of COVID-19. I would like to coin the term "Sankramikogenomics" for such susceptibility/resistance studies

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of other infections diseases. In the Indian language Hindi, the word "Sankramik" means infections. Sankramikogenomics is conceptually similar to pharmacogenomics where we identify genes that affect an individual's response to drugs and avoids "one size fits all" concept with a move towards precision medicine. As three resistance phenotypes have evolved independently, a common mechanism may not be able to explain the resistance in these three distinct communities.

ACE2 expression and vulnerability

ACE2 the target receptor, which plays a crucial role in the entry of virus into the cell, has been the focus for the Infection-genomics of COVID-19 infection and disease progress. Several groups have analyzed human genome and single-cell RNA-seq databases for ACE2 variants, allele frequency and expression in various tissues to understand the susceptibility and mechanism of pathophysiology of COVID-19 infection (Cao et al., 2020; Delanghe et al., 2020; Zhao et al., 2020; Zou et al., 2020). In a recent study, Asian male (55 y) was reported to have an extremely large number of ACE2-expressing cell clusters, including type II alveolar cells (AT2), in the lung compared to five African American and two white individuals (Zhao et al., 2020). Single cell RNA-seq data suggests that ACE2 is expressed in specific cell types of major organs such as AT2 (lung, 1-2% cells), myocardial cells (heart, 7.5%), proximal tubule cells (kidney, 4%), urothelial cells (urinary bladder, 2.4%), digestive track epithelial cells (esophagus, >1%; and ileum, ~30%), and make them vulnerable to this infection (Zou et al., 2020). Analyses of coding-region variants in ACE2 and the expression quantitative trait loci (eQTL) variants among different populations show that none of the ACE2 mutants are resistant to binding to the virus (Cao et al., 2020). Variations in allele frequencies in the eQTL variants along with varied ACE2 expression may suggest distinct susceptibility from different populations (Cao et al., 2020). The deletion/insertion (D/I) polymorphism in intron 16 of ACE1 shows geographical variation and the D allele is associated with a reduced ACE2 expression. D-allele frequency is inversely proportional to COVID-19 infections (Delanghe et al., 2020). The lung with >1% AT2 cells expressing ACE2 is thought to be susceptible to the infection. Interestingly, the nasal and bronchial cells do not express high levels of ACE2 (Zou et al., 2020). On the other hand, epithelial cells of the oral mucosa and tongue have high ACE2 expression (Xu et al., 2020) and hence, the patients frequently exhibit olfactory and taste disorders that may precede the onset of full-blown disease (Giacomelli et al., 2020). As aerosolized viruses have access to lungs, they will infect AT2 cells and replicate. Although it is not clear whether smoking or nicotine increases ACE2 expression, preliminary analyses

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indicates that more adverse events occur in smokers (Vardavas and Nikitara, 2020). Viruses will reach heart, kidney and ileum through blood, most likely at later stages, which is the leading cause of death through comorbidities. Patients with preexisting hypertension and cardiovascular diseases, particularly who are taking ACE inhibitors or angiotensin II receptor antagonists and have increased ACE2 expression (Ferrario et al., 2005; Huang et al., 2010), have an increased risk of severe disease and death (Driggin et al., 2020; Zheng et al., 2020). Thus, ACE2 is critical for initial infection followed by disease progression.

ACE2 structure and vulnerability

Minor sequence changes in ACE2 may alter the interaction between SARS-Cov2 virus with human cells and thus, the entry of the virus and infectivity. In a recent study, Stawiski et al. analyzed the polymorphisms of ACE2 with specific emphasis on its interaction with Spike protein. The authors analyzed large datasets (over 290,000 samples representing >400 population groups) and identified nine and 17 rare ACE2 variants that probably increase or decrease binding to virus spike protein (Stawiski et al., 2020). Such variations in ACE2, the target receptor that plays a crucial role in the entry of virus, probably explains the varied sankramikogenomics of COVID-19 in distinct ethnic people.

Conclusions and future prospects

CoVID-19 disrupted the most sophisticated systems and brought them to their knees. The unusual high IDRs in the US and major Western European countries compared to East Asian and Middle East countries could be due to differential susceptibilities of people belonging to distinct ethnicities. We hypothesized that Germanic, oriental and Middle East people may have enhanced resistance to COVID-19-induced death. These factors could be related to structure, splice forms and expression regulation of ACE2 receptor or secondary mechanisms leading to death through comorbidities. We have initiated the search for such factors through sankramikogenomics. These mechanistic studies will help in developing strategies to reduce COBID-induced mortality. We urgently need to find therapeutic solutions to resolve this coronavirus gauntlet (Li and De Clercq, 2020; Rayner et al., 2020). These approaches along with better recovery protocols used in the some of the key healthcare centers will help reduce the death. COVID-19 is our warning siren; a strong cooperative, multi-pronged approach is needed overcome this catastrophe.

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