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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 29, 2020. Originating from Wuhan, Hubei province, China, the virus has spread so rapidly throughout the world and has already claimed 218,000 lives and is currently afflicting 3.14 million people. The US has over 1.03 million confirmed cases of COVID-19, followed by Spain, Italy, France, UK, Germany, Turkey, Russia, Iran, and China. On careful inspection of the COVID-19 statistics, a peculiar unsettling trend becomes apparent. Western European countries and the US appear to have difficulties in overcoming the catastrophe. In contrast, countries in East Asia, Middle East and mid-Europe have sorted out the situation. Here, we 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. More detailed evaluation may also identify more susceptible populations. Such differences are due to variations in structure or tissue-specific expression (alternate splicing and accessibility) of the target receptors. So, we will highlight mere 12-fold lower affinity is insufficient to ignore CD147, as interactions occur between tens of spike proteins and equal number of cell surface ACE2 and/or CD147. Similar to pharmacogenomics to drug development and precision medicine, Sankramikogenomics will become an important field in other infectious diseases and pathogenicity.

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 F et al., 2020). Coronavirus disease (COVID-19) started by the end of 2019 in China and

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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 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, we 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, we 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. We, therefore, propose to evaluate infection-genomics (sankramikogenomics), in understanding the susceptibility to COVID-19 and the severity of disease progress.

Disease statistics and methods

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

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

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

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

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

Results and Discussion

In the first wave, COVID-19 infections started in and affected mostly China. Then people 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 (Figure 1). 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

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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 99.22% out of 82,858 cases resolved, the IDR is decreased to 5.64% (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 recovery (Figure 2). 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 2.68% (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 (1.23% and 0.49%, 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 2.42% except for Japan (17.18%) (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 COVID-19 infections and death (Figure 2).

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 84.59% out of 92,584 cases resolved, the IDR is decreased to 7.50% (Table 2). All 11 Middle East countries have low IDRs ranging between 0.61-7.50% with Bahrain at the lowest IDR. Thus, despite more than 162,000 COVID-19

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infections, Middle East countries have done extremely well in their fight against COVID-19 (Figure 2).

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 Z 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 to 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 98.44% IDR followed by Netherlands, Norway, Sweden, Portugal, Belgium, France and Italy (all above 28%; 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 (4.33-6.99%) (Table 3). Iceland has the lowest IDR of 0.61%. 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 (Figure 3).

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 (Figure 1). 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). Nineteen states have been successfully defending the infections keeping the IDRs below 10%. South Dakota with IDR (1.12%) leads the country, followed by Wyoming, Hawaii, Tennessee, Alaska, Montana, North Dakota, Arkansas, Utah, South Carolina, Idaho, Texas, Iowa, New Hampshire, West Virginia, Nevada, Maine, Oklahoma and Louisiana (Table 4). These states have done extremely well in fighting COVID-19 infections and related deaths. Next four states, Delaware, Wisconsin, New Mexico, and Minnesota have IDRs range between 11.11 and 13.60%, immediately followed by five states with IDRs below 25%. These nine states have done well in avoiding extreme impact of COVID-19 infections. The next eight states have IDR range from 25-50%. Unfortunately, 15 states have poor record in fighting COVID-19. They are grouped states into

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one with 51-79% IDRs and the other above 80% IDRs (Table 4). These 23 states, particularly the last 10, need substantial measures to slow down the devastations caused by COVID-19.

Angiotensin-converting enzyme 2 (ACE2), ACE1 and COVID-19

The novel coronavirus causing COVID-19 is closely related to SARS virus (Wu F et al., 2020) and binds to host receptor angiotensin-converting enzyme 2 (ACE2) through its spike protein receptor-binding domain (RBD) to gain entry into the cell (Lu F et al., 2020; Wan et al., 2020; Wrapp et al., 2020). ACE2 was identified as a Captopril-insensitive homolog of ACE1 (Tipnis et al., 2000). This paralog converts angiotensin II to angiotensin 1-9 (Donoghue et al., 2000). ACE2 removes one amino acid residue, while ACE1 is a carboxydipeptidase and removes dipeptides from the C-terminal from various peptide substrates. Further, classical ACE inhibitors do not inhibit ACE2 activity. ACE1 inhibitors that prevent the conversion of angiotensin I into angiotensin II, and angiotensin II receptor antagonists reduce cardiac fibrosis, left ventricular enlargement and remodelling (Re, 2004). Hence, ACE1 contributes to the development of cardiovascular disease through the generation of angiotensin II. In contrast, ACE2 plays a cardioprotective role and eliminates many of the negative consequences of angiotensin II (For details, see Ussher and Lopaschuk, 2012; Turner, 2015). Thus, primarily ACE2 acts as a counterbalance to ACE1.

Tissue-specific expression of ACE2 and associated proteases: After the completion of human genome project, there have been a number of efforts to systematically annotate the protein-coding parts and to identify their tissue specific expression. Using quantitative transcriptomics analyses combined with antibody-based profiling, Fagerberg et al. (2014) created a comprehensive, integrative expression map of 27 major organs and tissues. Accordingly, highest expression of ACE2 (average FPKM in parentheses) occurs in small intestine (93.7), followed by duodenum (69), gall bladder (32.6), kidney (30.8), testes (26.9) and heart (12.3). Interestingly, the main target of SARS-CoV2, the lung has extremely low expression (0.3 from 5 samples). In contrast, ACE1 is highly expressed in the lung (32.6) (Table S1). Human proteome data also suggests ACE1 is expressed in the adult lung but ACE2 is not (Kim et al., 2014; Wilhelm et al., 2014; Schmidt et al., 2018). Single cell RNA-seq data also suggests that ACE2 is expressed in a small number (1-2%) of type II alveolar cells (AT2) of the lungs (Zou et al., 2020). Similarly, almost no nasal and bronchial cells express high levels of ACE2. However, the epithelial cells from the respiratory track has ~2% ACE2 positive cells (Zou et al., 2020). Single cell RNA-seq data indeed suggests the expression of ACE2 in myocardial

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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). Recent immunohistochemistry studies of 24 human tissues showed that highest ACE2 expression was in microvilli of the intestinal tract and renal proximal tubules, in membranes of gall bladder epithelium, testicular Sertoli cells and Leydig cells, a subset of glandular cells in seminal vesicle, and in cytoplasm cardiomyocytes (Hikmet et al., 2020). ACE2 protein expression was not detected in lung, bronchus, nasopharynx, esophagus, stomach, endometrium, smooth muscle tissue, spleen, cerebral cortex, adipose tissue or different structures of the skin. Based on these findings, the authors questioned the role of ACE2 for infection of human lungs (Hikmet et al., 2020). In immunostaining techniques, it is difficult to identify 1% cells (finding one cell in a hundred) that express ACE2, particularly when the expression levels are not astronomically high. Such limitation can be overcome by robust single-cell RNA-seq data. Single-cell RNA-seq studies in 13 tissues showed that ACE2 is expressed in lung AT2, liver cholangiocyte, colon colonocytes, esophagus keratinocytes, ileum endothelial cells, rectum endothelial cells, stomach epithelial cells, and kidney proximal tubules (Qi et al., 2020). Lukassen et al. investigated the expression of ACE2 and the transmembrane protease serine 2 (TMPRSS2; thought to play important role in infection (Hoffman et al., 2020)) in lung tissue and in cells derived from subsegmental bronchial branches (Lukassen et al., 2020). Their data suggest that ACE2 as well as TMPRSS2 are predominantly expressed in a transient secretory cell type in the subsegmental bronchial branches. These cells show an enrichment for pathways related to RHO GTPase function and viral processes suggesting their increased vulnerability for infection (Lukassen et al., 2020). ACE2 and TMPRSS2 are co-expressed in nasal epithelial cells, specifically goblet and ciliated cells (Sungnak et al., 2020). Muus et al. provide the most comprehensive and integrated analyses of cell type-specific expression of mediators of SARS-CoV-2 viral entry – ACE2, TMPRSS2 and Cathepsin L (CTSL) (Muus et al., 2020). As expected, secretory goblet and multiciliated cells in the proximal airways and AT2 cells in the distal lung are $ACE2^{+}TMPRSS2^{+}$ dual-positive cells. In addition, enterocytes, pancreatic ductal cells, prostate luminal epithelial cells, cholangiocytes, oligodendrocytes in the brain, inhibitory enteric neurons, and fibroblasts and pericytes from heart and other tissues are also dual-positive ($ACE2^{+}TMPRSS2^{+}$). Among them, such cells are most prevalent in ileum followed by liver, lung, nasal mucosa, bladder, testis, prostate and kidney (Muus et al., 2020). Single-cell assay for transposase-accessible chromatin sequencing (Chen et al., 2018) data indicates that chromatin at both the ACE2 and TMPRSS2 loci are accessible in epithelial cells, especially

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AT2 cells (Muus et al., 2020). Further, $ACE2^{+}CTSL^{+}$ cells are found in the olfactory epithelium, ventricular cardiomyocytes, heart macrophages, and pericytes in multiple tissues, including the heart, lung, and kidney. In addition, several other proteases have been shown to be co-expressed with ACE2 and they may play a role in COVID-19 infections (Muus et al., 2020). The epithelial cells of the oral mucosa and tongue (Xu et al., 2020) and cornea and conjunctiva (Xia et al., 2020) have high ACE2 expression.

ACE2, a gateway in COVID-19 infections: SARS-CoV2 enters an individual through the ACE2 receptors found in the respiratory track (Muus et al., 2020 and several other references). Nature has a number of physical barriers to protect us from such infections including nose hairs, curved and mucous protected nasal passages, and ciliated mucous membrane. These barriers provide excellent protection considering an average adult breathes 11,000 liters of air/day. Despite the number of particles, viruses and bacteria among other pathogens that enter our system daily, most of us remain healthy unaffected by the plethora of "attacks". Most of these living or dead particles are trapped in the mucus and slowly pushed out of the nose or mouth through cilia, the microscopic hairs. About 1.4 liters of mucus/day keeps the nasal cavity and airways moist, and "captures" all particulate matter for disposal. Mucus gets diluted with serous fluid and swallowed twice a minute. When an individual is dehydrated due to low water intake, cold and dry winters, air conditioners/ heaters or smoking, the volume of serous fluid is reduced. This in turn leads to thick and sticky mucus, which makes people more susceptible to illness, allergies and other respiratory problems (D'Amato et al., 2018). Such dry nasal and upper respiratory track provide SARS-CoV2 access to epithelial cells and their ACE2 resulting in potential infection. Thus, preventing dehydration by ample water intake will reduce the transmission.

Alternatively, the virus could enter through mouth and eyes as the epithelial cells of the oral mucosa and tongue (Xu et al., 2020) and cornea and conjunctiva (Xia et al., 2020) also have high ACE2 expression. Entry or secondary site infection through the mouth probably leads to frequent olfactory and taste disorders in the patients before the onset of full-blown disease (Giacomelli et al., 2020). These routes are accessible through frequent touching of the face and rubbing of eyes. Surprisingly, individuals touch their face 23 times/hour (Kwok et al., 2015). Among these face touches, 44% contact with a mucous membrane (mouth, nose and eyes, one third times each), whereas 56% contact nonmucosal areas. Thus, hand hygiene is an essential and inexpensive preventive method to break transmission associated with self-inoculation.

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Key covariates associated with COVID-19 severity: The clinical consequences of COVID-19 infection ranges from asymptomatic carrier status to death. Three key covariates, age, sex and smoking, define COVID-19 severity. The initial evaluation indicates that the disease severity and mortality rates show a significant rise with age (<0.1% for patients under 30 years old to >10% for patients over 70) (Wang et al., 2020; Hauser et al., 2020). Children are less likely to develop severe disease compared to adults (Lu X et al., 2020). There is also a slightly higher incidence and mortality in men compared to women (del Rio and Malani, 2020; Guan et al., 2020). Earlier studies using bulk transcriptomics and analysis of single-cell RNA-seq data failed to find significant differences between age groups (>60 vs <60) or gender groups (male vs female) (Cai G., 2020). Muus et al. correlated ACE2 expression in double positive $ACE2^{+}TMPRSS2^{+}$ cells such as airway epithelial cells (basal, multiciliated, and secretory cells), alveolar AT2 cells, and submucosal gland secretory cells (Muus et al., 2020). The expression of ACE2 increases with age in basal and multiciliated cells, while it is elevated in males in airway secretory cells and AT2 cells.

Preliminary analyses indicate that more adverse events occur in smokers (Vardavas and Nikitara, 2020). Interestingly, ACE2 gene expression in Asian current smokers is higher compared to non-smokers but not in Caucasian current smokers (Cai, G., 2020). ACE2 is expressed in remodelled AT2 cells of former smokers and in goblet cells and club cells of current smokers and non-smokers, respectively. Thus, smokers especially former smokers may be more susceptible to SARS-CoV2 (Cai, G., 2020). The sex predisposition may be due to the much higher smoking rate in men than in women in China (Cai, H., 2020). ACE2 expression in multiciliated cells is elevated in former or current smokers (Muus et al., 2020). Further, in AT2 cells, there is joint up-regulation of ACE2 and TMPRSS2 with age and ACE2 and CTSL down-regulation in smokers. Overall, there is increased ACE2 expression in airway epithelial cells and reduced expression in AT2 cells of smokers. In the mouse model data also suggested the increased expression levels of ACE2 in airway secretory cells, but not in AT2 cells (For details, see Muus et al., 2020). Thus, expression of ACE2 and associated proteases support the impact of covariates on COVID-19 severity.

CD147, the other receptor, may be as important as ACE2

Recently, a second receptor for SARS-CoV2, namely CD147 (also known as Basigin or EMMPRIN) was identified to play important role in COVID-19 infection (Wang et al., 2020). It is a transmembrane protein of the immunoglobulin super family and is the main upstream

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stimulator of matrix metalloproteinases. CD147 may be upregulated during asthmatic and diabetic complications. CD147 acts as receptor for the invasion on red blood cells by Malaria parasite *Plasmodium falciparum* (Muramatsu, 2012). Azithromycin, a classical antibiotic, prevents this invasion and used as a prophylactic against Malaria (Kain et al., 2001). It also exhibits anti-viral responses in epithelial cells through increased levels of interferons and interferon-stimulated proteins leading to decreased viral replication and virus release (Gielen et al., 2010; Tran et al., 2019). According to anecdotal reports, azithromycin in combination with hydroxychloroquine or chloroquine is used for treatment of COVID-19 (Damle et al., 2020). Hydroxychloroquine and chloroquine also exhibit direct in vitro antiviral activity (Liu et al., 2020). The open-label non-randomized clinical trial suggested the use of azithromycin and hydroxychloroquine for COVID-19 therapy (Gautret et al., 2020). In this trial, 26 patients treated daily with hydroxychloroquine (600 mg) show a significant decrease in viral load after six days compared to untreated controls. Among them, all six patients who received azithromycin (500 mg on the first day followed by 250 mg daily) show negative PCR results in nasopharyngeal samples. In comparison, 57.1% patients treated with hydroxychloroquine only, and 12.5% of untreated individuals were virus-free (Gautret et al., 2020). Although further clinical studies are essential to validate these findings, it appears that CD147 could be a target for COVID-19 treatment (Ulrich and Pillat, 2020).

Most studies suggest that the severe devastation due to directly related to two key structural features of SARS-CoV2; its increased affinity and enhanced protease access. The changes in the receptor binding domain (RBD) of spike protein leads to increased binding affinity to ACE2 compared to SARS virus (Wrapp et al., 2020; Walls et al., 2020). 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). The binding affinity of the spike protein to CD147 is weak (Kd, 0.185 µM compared to human ACE2, ~15 nM) (Wang et al., 2020). Although the affinity difference between individual molecules of spike protein and the two target receptors are ~12-fold, it may not have a significant impact on the interaction between the virus particles and the target cell. These affinities are determined by the surface density and accessibility of these receptors to the virus particles. Each virus particle binds to several ACE2 and/or CD147 receptor molecules on the surface of the target cell through multiple spike proteins, similar to hooks and loops in a Velcro strip. Thus, not only individual affinities but also how many such interactions contribute together to binding determines the overall effectiveness of the interaction. Time and again we

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have seen how low affinity binding interactions in biology leads to high affinity, precision binding (For example, see Crocker et al., 2015). Considering such cooperative binding interactions, we propose that CD147 is also an important receptor to be considered in our war on COVID-19 infections. It may help us resolve some of the symptoms or complications observed during the disease.

Infection-genomics (Sankramikogenomics)

It is difficult to imagine or comprehend such high IDRs in most of the European countries and the US 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 cities, such as New York, 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 F 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 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.

Some communities appear to be resistant to COVID-19 infection and 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 (Figure 3), (b) East Asian countries (Figure 2), and (b) Middle East countries (Figure 2). 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, we 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

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(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 states with low and high IDRs. Of the 25 US states with low IDRs have six-out-of-seven states have high proportion of population belonging to German ethnicity; South Dakota (38.8%), North Dakota (41.4%), Iowa (35.1%), Wisconsin (40.5%), Minnesota (33.8%) and Kansas (27.2%) (Table 4). Only Nebraska (36.1%) has high IDR and is in the bottom 13th position. 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). In contrast, 6-out-of-10 states that have less than 11% German population have high IDRs (>80%). 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 large number 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 (Figure 1). 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 (discussed above) (Table 4).

COVID-19 infections were also rapidly brought under control in Middle East countries; they have an average of 41.1% Closed cases with low IDRs (Table 2). The people from this region are of distinct ethnicity than both German and Oriental people. Therefore, we 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 ethnic backgrounds. With more interracial (or inter-ethnic) marriages, these distinguishing features will be blurred

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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. We would like to coin the term "Sankramikogenomics" for such susceptibility/resistance studies of other infectious 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. Pharmacogenomics helps us to understand how the genetic makeup of an individual affects his/her response to drugs and paves way to precision medicine. Sankramikogenomics, on the flip side, helps us to understand how the genetic makeup of an individual affects his/her response (susceptibility, resistance and altered symptoms) to pathogenic infections and severity of the diseases.

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 with significant depth could be used evaluate ACE2 and CD147 expression along with relevant proteases and other accessory proteins in specific cell types of major organs will help us clarify details (Muus 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 and ethnic variations (Oliveira-Paula et al., 2019) and the D allele is associated with a reduced ACE2 expression. D-allele frequency is inversely proportional to COVID-19 infections

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(Delanghe et al., 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 and CD147 receptors 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 COVID-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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Tables and Figures

Table 1. COVID-19 infections in the East Asian countries (April 29, 2020)‡

	Total	Death	IDR (%)	Recovered cases	Recovered cases (%)	Active cases	Closed cases	Closed cases (%)
Japan	13,736	394	17.18	1,899	82.82	11,443	2,293	16.69
China	82,858	4,633	5.64	77,578	94.36	647	82,211	99.22
South Korea	10,761	246	2.68	8,922	97.32	1,593	9,168	85.20
Malaysia	5,851	100	2.42	4,032	97.58	1,719	4,132	70.62
Thailand	2,938	54	2.00	2,652	98.00	232	2,706	92.10
Taiwan	429	6	1.92	307	98.08	116	313	72.96
Singapore	14,951	14	1.23	1,128	98.77	13,809	1,142	7.64
Hong Kong	1,038	4	0.49	811	99.51	223	815	78.52
Vietnam	270		0.00	222	100.00	48	222	82.22

Various countries with COVID-19 infections are sorted in descending order of their Interim Death Rates (%). Based on the IDRs various countries are grouped into two groups: 11-24% IDRs, greenish yellow; and below 10% IDRs, green.

‡Updated data was obtained from https://www.worldometers.info/coronavirus/.

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Table 2. COVID-19 infections in the Middle East countries (April 29, 2020)‡

	Total	Death	IDR (%)	Recovered cases	Recovered cases (%)	Active cases	Closed cases	Closed cases (%)
Iran	92,584	5,877	7.50	72,439	92.50	14,268	78,316	84.59
Iraq	1,928	90	6.39	1,319	93.61	519	1,409	73.08
Saudi Arabia	20,077	152	5.18	2,784	94.82	17,141	2,936	14.62
UAE	11,380	89	3.92	2,181	96.08	9,110	2,270	19.95
Palestine	343	2	2.74	71	97.26	270	73	21.28
Oman	2,131	10	2.67	364	97.33	1,757	374	17.55
Israel	15,728	210	2.64	7,746	97.36	7,772	7,956	50.58
Jordan	449	8	2.25	348	97.75	93	356	79.29
Kuwait	3,440	23	1.92	1,176	98.08	2,241	1,199	34.85
Qatar	11,921	10	0.87	1,134	99.13	10,777	1,144	9.60
Bahrain	2,811	8	0.61	1,310	99.39	1,493	1,318	46.89

Various countries with COVID-19 infections are sorted in descending order of their Interim Death Rates (%). Based on the IDRs all countries are grouped in one group of below 10% IDRs, green.

‡Updated data was obtained from https://www.worldometers.info/coronavirus/.

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Table 3. COVID-19 infections in the Western Europe (April 29, 2020)‡

	Total	Death	IDR (%)	Recovered cases	Recovered cases (%)	Active cases	Closed cases	Closed cases (%)
UK	161,145	21,678	98.44	344	1.56	139,123	22,022	13.67
Netherlands	38,416	4,566	94.81	250	5.19	33,600	4,816	12.54
Norway	7,660	206	86.55	32	13.45	7,422	238	3.11
Sweden	19,621	2,355	70.09	1,005	29.91	16,261	3,360	17.12
Portugal	24,322	948	40.56	1,389	59.44	21,985	2,337	9.61
Belgium	47,334	7,331	40.12	10,943	59.88	29,060	18,274	38.61
France	165,911	23,660	33.54	46,886	66.46	95,365	70,546	42.52
Italy	201,505	27,359	28.41	68,941	71.59	105,205	96,300	47.79
Spain	232,128	23,822	16.13	123,903	83.87	84,403	147,725	63.64
Ireland	19,877	1,159	11.15	9,233	88.85	9,485	10,392	52.28
Switzerland	29,264	1,699	6.99	22,600	93.01	4,965	24,299	83.03
Finland	4,740	199	6.64	2,800	93.36	1,741	2,999	63.27
Denmark	8,851	434	6.62	6,121	93.38	2,296	6,555	74.06
Germany	159,912	6,314	5.10	117,400	94.90	36,198	123,714	77.36
Austria	15,357	569	4.33	12,580	95.67	2,208	13,149	85.62
Iceland	1,795	10	0.61	1,636	99.39	149	1,646	91.70

Various countries with COVID-19 infections are sorted in descending order of their Interim Death Rates (%). Based on the IDRs various countries are grouped into five groups: higher than 80% IDRs, red; 51-79% IDRs, brown; 25-50% IDRs, dark yellow; 11-24% IDRs, greenish yellow; and below 10% IDRs, green.

‡Updated data was obtained from https://www.worldometers.info/coronavirus/.

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Table 4. COVID-19 infections in the US (April 17, 2020)‡

	Total	Death	IDR (%)	Recovered cases	Recovered cases (%)	Active cases	Closed cases	Closed cases (%)	German Ancestry*
USA	1,035,765	59,266	29.41	142,238	70.59	834,261	201,504	19.45	
States									
Mississippi	6,342	239	100.00	0	0.00	6,103	239	3.77	5.3
Oregon	2,385	99	100.00	0	0.00	2,286	99	4.15	19.1
Vermont	862	47	100.00	0	0.00	815	47	5.45	10.5
Indiana	16,588	992	98.61	14	1.39	15,582	1,006	6.06	23.0
Georgia	24,854	1,036	97.09	31	2.91	23,787	1,067	4.29	7.0
Connecticut	26,312	2,089	96.98	65	3.02	24,158	2,154	8.19	9.0
Alabama	6,750	242	92.37	20	7.63	6,488	262	3.88	6.8
Ohio	16,769	799	86.94	120	13.06	15,850	919	5.48	25.6
New Jersey	113,856	6,442	83.52	1,271	16.48	106,143	7,713	6.77	10.6
Arizona	6,948	293	80.72	70	19.28	6,585	363	5.22	13.7
Illinois	48,102	2,125	77.81	606	22.19	45,371	2,731	5.68	18.6
Pennsylvania	45,016	2,060	72.92	765	27.08	42,191	2,825	6.28	25.1
Nebraska	3,374	55	71.43	22	28.57	3,297	77	2.28	**36.1**
Florida	32,846	1,171	63.06	686	36.94	30,989	1,857	5.65	10.0
Colorado	14,316	736	56.83	559	43.17	13,021	1,295	9.05	20.3
Maryland	20,113	1,016	44.58	1,263	55.42	17,834	2,279	11.33	13.8
Rhode Island	7,926	239	41.14	342	58.86	7,345	581	7.33	5.4
Missouri	7,376	327	37.41	547	62.59	6,502	874	11.85	24.2
California	46,163	1,862	35.81	3,337	64.19	40,964	5,199	11.26	8.1
New York	301,450	23,144	33.01	46,963	66.99	231,343	70,107	23.26	11.1
Michigan	39,262	3,567	29.95	8,342	70.05	27,353	11,909	30.33	20.3
Washington	13,842	786	29.81	1,851	70.19	11,205	2,637	19.05	17.8
Massachusetts	58,302	3,153	27.97	8,118	72.03	47,031	11,271	19.33	6.0
District of Columbia	3,994	190	22.35	660	77.65	3,144	850	21.28	ND

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North Carolina	9,739	361	21.71	1,302	78.29	8,076	1,663	17.08	10.4
Virginia	14,339	492	21.33	1,815	78.67	12,032	2,307	16.09	11.5
Kansas	3,577	127	20.16	503	79.84	2,947	630	17.61	27.2
Kentucky	4,375	225	16.70	1,122	83.30	3,028	1,347	30.79	14.4
Minnesota	4,181	301	13.60	1,912	86.40	1,968	2,213	52.93	33.8
New Mexico	2,974	110	13.50	705	86.50	2,159	815	27.40	8.8
Wisconsin	6,289	300	11.48	2,313	88.52	3,676	2,613	41.55	40.5
Delaware	4,575	137	11.11	1,096	88.89	3,342	1,233	26.95	13.5
Louisiana	27,286	1,801	9.43	17,303	90.57	8,182	19,104	70.01	7.5
Oklahoma	3,410	207	8.39	2,260	91.61	943	2,467	72.35	13.7
Maine	1,040	51	8.02	585	91.98	404	636	61.15	8.1
Nevada	4,805	225	7.83	2,647	92.17	1,933	2,872	59.77	11.3
West Virginia	1,095	38	7.32	481	92.68	576	519	47.40	17.6
New Hampshire	2,010	60	6.02	936	93.98	1,014	996	49.55	9.0
Iowa	6,376	136	5.91	2,164	94.09	4,076	2,300	36.07	35.1
Texas	26,171	690	5.82	11,170	94.18	14,311	11,860	45.32	9.6
Idaho	1,952	60	5.23	1,087	94.77	805	1,147	58.76	17.5
South Carolina	5,735	192	4.93	3,701	95.07	1,842	3,893	67.88	10.0
Utah	4,343	45	4.82	888	95.18	3,410	933	21.48	11.2
Arkansas	3,127	57	4.48	1,216	95.52	1,854	1,273	40.71	10.7
North Dakota	991	19	4.44	409	95.56	563	428	43.19	41.4
Montana	451	15	4.04	356	95.96	80	371	82.26	26.0
Alaska	351	9	3.80	228	96.20	114	237	67.52	15.6
Tennessee	10,052	188	3.68	4,921	96.32	4,943	5,109	50.83	9.7
Hawaii	609	16	3.07	505	96.93	88	521	85.55	5.9
Wyoming	536	7	2.00	343	98.00	186	350	65.30	23.6
South Dakota	2,313	11	0.78	1,392	99.22	910	1,403	60.66	38.8

Various US states with COVID-19 infections in descending order of their Interim Death Rates (%). Based on the IDRs various states are grouped into five groups: higher than 80% IDRs,

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red; 51-79% IDRs, brown; 25-50% IDRs, dark yellow; 11-24% IDRs, greenish yellow; and below 10% IDRs, green.

‡Updated data was obtained from https://www.worldometers.info/coronavirus/.

*The data on German and East Asian (not shown) ancestry of population in various US states were obtained from https://statisticalatlas.com/state/STATE/Ancestry.

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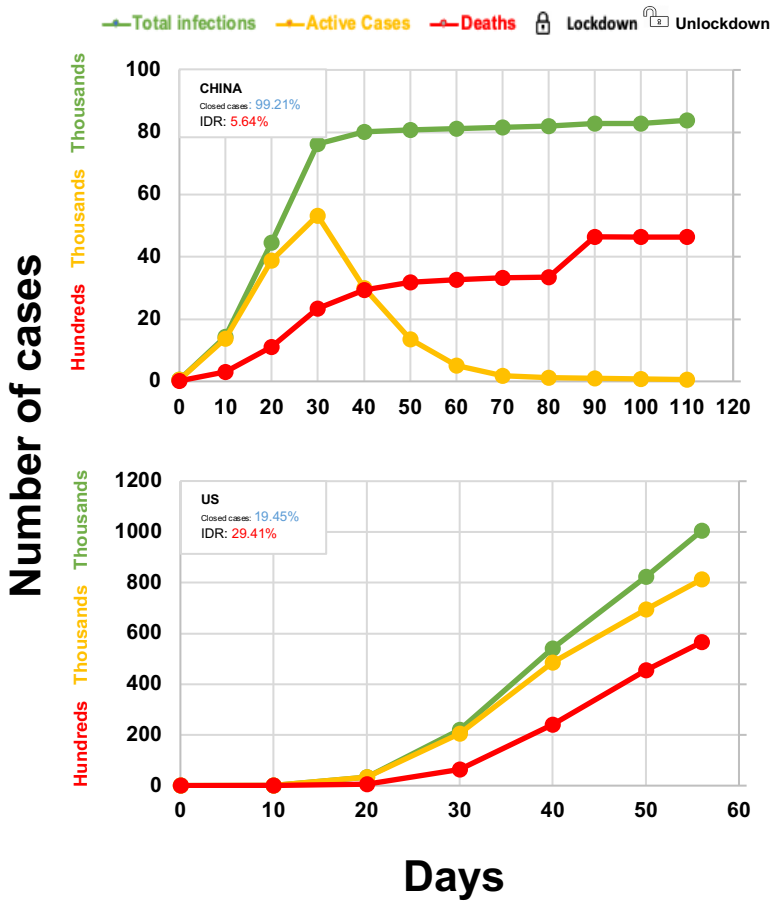

Figure 1. Impact of COVID-19 infections in China and the US‡.

The day when the number of total cases reached 100 was considered as Day 0

‡Data was obtained from https://www.worldometers.info/coronavirus/.

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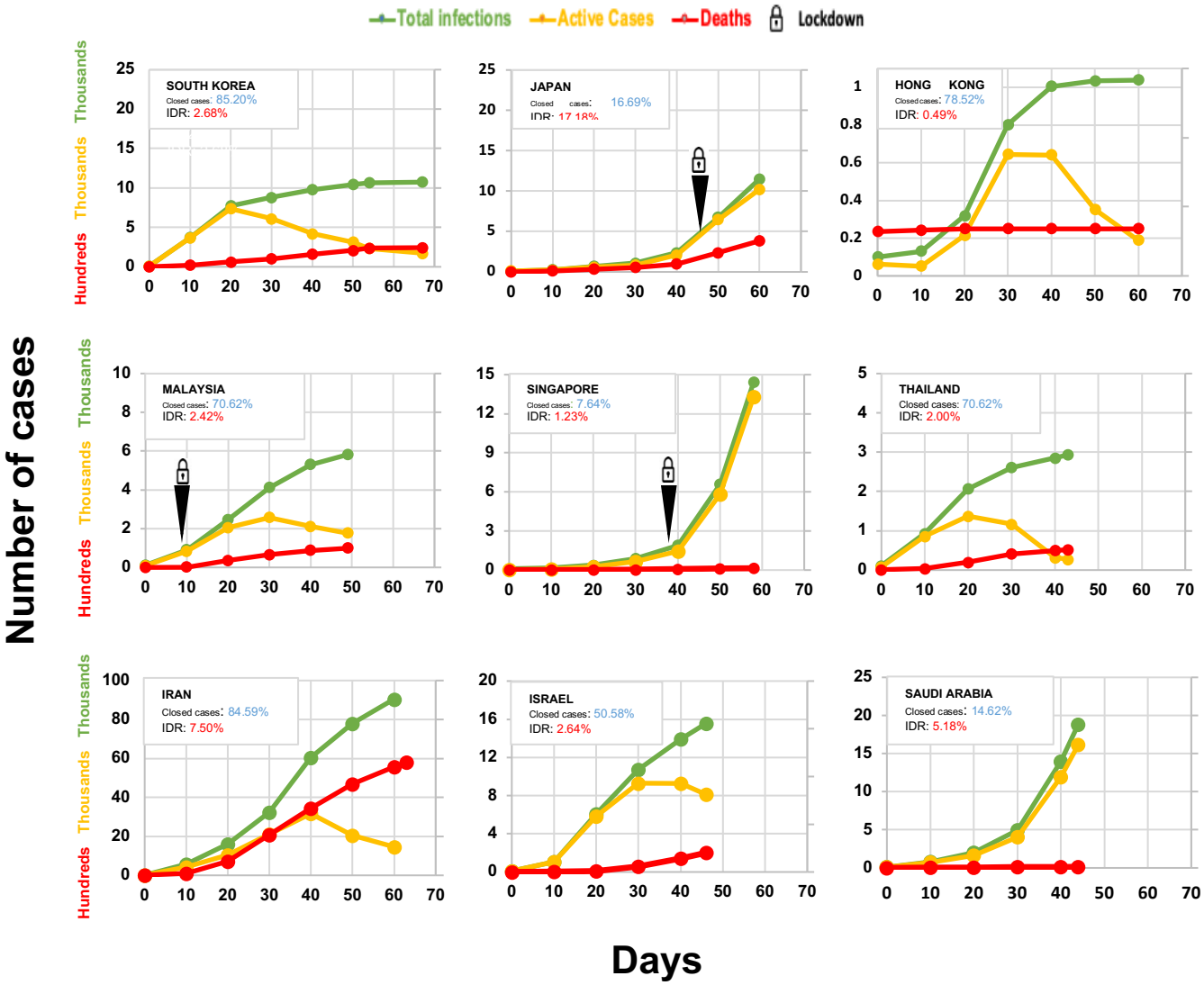

Figure 2. Impact of COVID-19 infections in East Asian countries and Middle East countries ‡.

The day when the number of total cases reached 100 was considered as Day 0.

‡Updated data was obtained from https://www.worldometers.info/coronavirus/.

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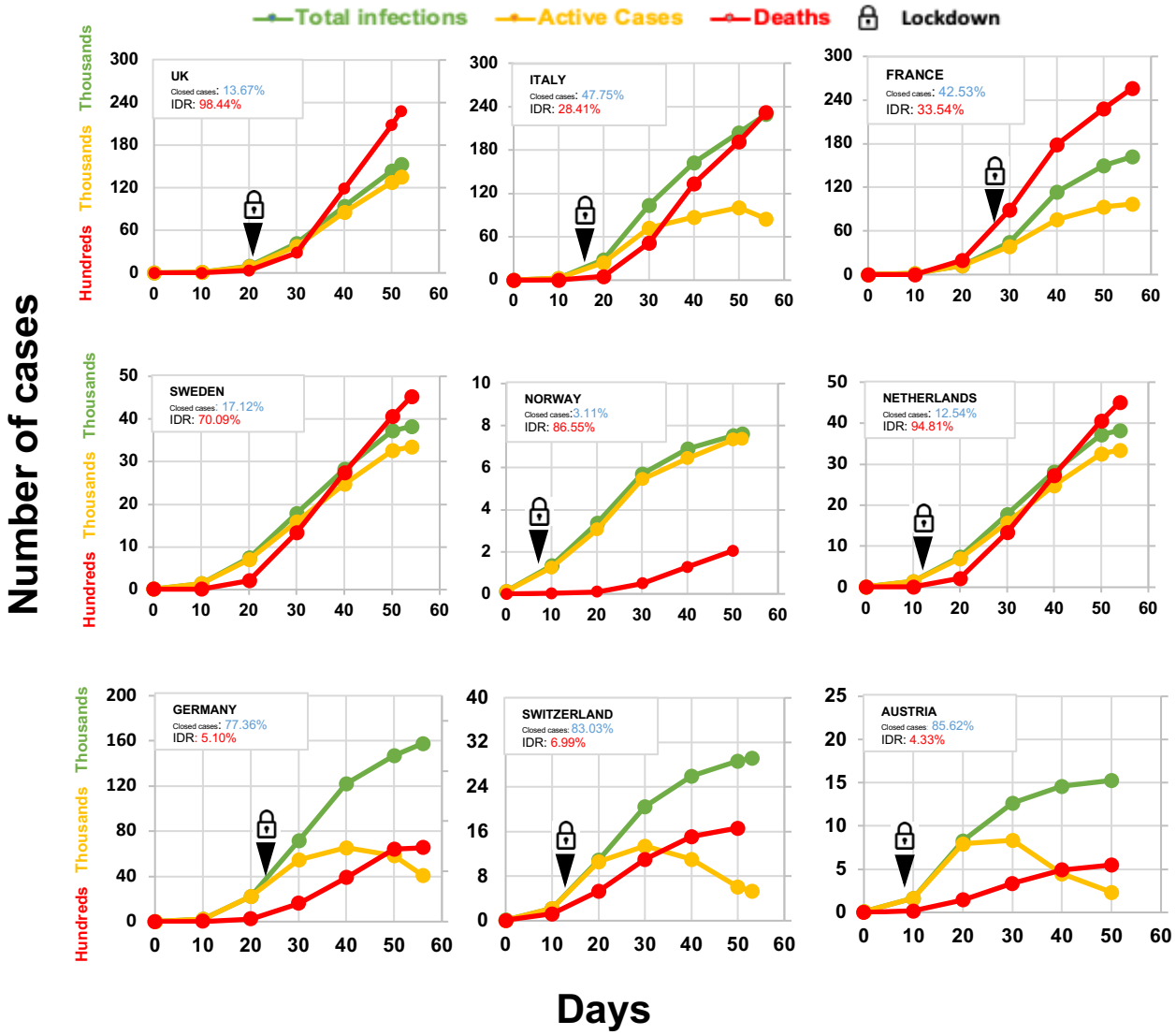

Figure 3. COVID-19 infections in Western European countries‡

The day when the number of total cases reached 100 was considered as Day 0.

‡Updated data was obtained from https://www.worldometers.info/coronavirus/