PINNACLECARE

Medical Intelligence Report

Date: June 9, 2020

Topic: Weekly Update for COVID-19

Effect of COVID-19 on People with Cancer

Information from initial reports in China suggested that people with cancer were more susceptible to infection by SARS-CoV-2 and had poorer outcomes compared to the general public. A report published in the *Lancet* from the COVID-19 and Cancer Consortium (CCC19) describes the outcomes for individuals with active or previous malignancy, aged 18 years and older, with confirmed SARS-CoV-2 infection from the USA, Canada, and Spain between March 17 and April 16 (Kuderer et al., 2020). At the time of the analysis, there were 1035 individuals registered in the CCC19, and 928 were included in this study.

The researchers found an association between an increased risk of death during the 30 days of the study and the following characteristics: increased age, male sex, smoking status (former smoker vs never smoked), number of comorbidities (two vs none), Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, active cancer (progressing vs remission), and receipt of azithromycin plus hydroxychloroquine.

Characteristics of Individuals in the CCC19 Study:

- The most prevalent malignancies were breast cancer (21%) and prostate cancer (16%).
- 39% patients were on active anticancer treatment.
- 43% had active (measurable) cancer.
- As of May 7, 13% patients had died.

Based on the results of the analysis, the authors conclude that "**patients with cancer appear to be at increased risk of mortality and severe illness due to SARS-CoV-2 infection, regardless of whether they have active cancer, are on anticancer treatment, or both.**" They suggest that individuals with cancer, and those who have had cancer, should be included in increased surveillance and testing for SARS-CoV-2, should minimize their exposure to the healthcare system, and doctors and patients should reconsider which procedures and treatments are warranted. For example, in those with poor health status, as measured by ECOG performance status, careful conversations will be needed about the risks and benefits of

continuing anticancer therapy as well as about the use of aggressive interventions for the treatment of COVID-19. Another notable finding from the study was that there was no association between surgery and mortality during the 30 days of the study, suggesting that **elective surgery for cancer control is feasible when the delay of surgery may compromise cancer treatment**.

The UK Coronavirus Cancer Monitoring Project (UKCCMP) is another group made up of patients with active cancer being treated at a network of 55 cancer centers in the United Kingdom. A report on the outcomes of those enrolled in the UKCCMP between March 18 and April 26 was published in the *Lancet* (Lee et al., 2020). Based on their analysis of 800 people from the project, the researchers found that **recent chemotherapy use before severe infection with SARS-CoV-2 was not associated with an increased rate of mortality**. Based on this information they conclude that the increased rate of mortality from COVID-19 in people with cancer is due to advancing age and the presence of other chronic conditions. **In agreement with the results of Kuderer and colleagues, chemotherapy or anticancer treatments do not seem to increase the risk of mortality from COVID-19**.

A study of all adult patients with any type of malignant solid tumor or hematological malignancy who were admitted to nine hospitals in Wuhan, China with laboratory-confirmed COVID-19 between January 13 and March 18 was published in the *Lancet* (Tian et al., 2020). Comparisons were made between the outcome of individuals with COVID-19 who had cancer (232 people) or did not have cancer (512 people). The researchers found that people with cancer were more likely to have severe symptoms of COVID-19. Individuals in both groups with the following characteristics had a higher risk of severe disease: older age, elevated inflammatory molecules (interleukin 6, procalcitonin, and D-dimer), and reduced blood cells called lymphocytes. There were additional characteristics that were associated with poor outcome in people with cancer, including advanced tumor stage, elevated levels of tumor necrosis factor α, elevated levels of N-terminal pro-B-type natriuretic peptide, reduced levels of a type of white blood cell called CD4+ T cells, and reduced albumin–globulin ratio, which is indicative of several disease states.

Outcome of Surgery with Active COVID-19

A study on the outcome of people with COVID-19 who underwent surgery at 235 hospitals in 24 countries was published in the *Lancet* (COVIDSurg, 2020). Based on their analysis, the authors conclude that 50% of people who have surgery while infected with SARS-CoV-2 have postoperative pulmonary complications. These types of complications were associated with a high rate of mortality. The rates of complications and mortality are higher than those reported for high-risk surgical candidates before the pandemic. People with the following risk factors had a higher mortality: male sex, age 70 years or older, those with more severe disease based on an American Society of Anesthesiologists grade between 3 and 5, surgery for malignant disease, emergency surgery, and major surgery. Based on these results, the authors conclude that "**thresholds for surgery during the SARS-CoV-2 pandemic should be higher than during normal practice, and men aged 70 years and older who have emergency or major elective surgery are at particularly high risk of mortality**."

Lethality of COVID-19

A doctor in Italy has suggested that COVID-19 is becoming less lethal, but researchers and physicians from the WHO and other organizations disputed the claim by Dr. Alberto Zangrillo, the head of San Raffaele Hospital in Milan (Achenbach et al., 2020). The *Washington Post* reported several experts who instead feel the changes in the number of deaths occurring in Italy are due to a reduction in transmission compared to the peak of the outbreak, which means that there is less virus in circulation, and people may be less likely to be exposed to high doses of it. **At this point, there has been no evidence of different strains of SARS-CoV-2 with different infection properties, and the mutation rate of the virus has been relatively low**.

COVID-19 Transmission

Researchers reported in the journal *Cell* on the characteristics of human lung cells that likely contribute to the variability in SARS-CoV-2 infection between different people (Hou et al, 2020). The researchers investigated lung tissue from multiple different donors, and they observed a striking variation in the level of infectivity of the cells and the amount of viral replication between different people. There was less variation in the cells in the upper respiratory tract than in those in the lower respiratory tract, suggesting a basis for why only a subset of people progress to severe disease. They also found that there are larger amounts of the ACE2 receptor produced on the surface of cells in the nasal region of the respiratory tract. ACE2 is the protein on the surface of human cells that the virus interacts with to start infection of the cell**. The increased production of ACE2 was correlated to a high level of infectivity by SARS-CoV-2 in the nasal tract**, with a decreasing gradient of infectivity moving down into the lungs. Compared to cells in the nasal tract, **there was a much lower level of infectivity in the bronchioles and alveoli** of the lower respiratory tract. Based on their experiments, **the researchers speculate that nasal surfaces might be the dominant initial site for SARS-CoV-2 respiratory tract infection.** A combination of a large amount of virus exposure in the nose from the environment and a high level of ACE2 receptors would lead to a high level of infectivity. Changing the exposure of cells in the nose from variations in the amount of virus present may be enough to cause a variation in the clinical response to the virus. This has been supported by other studies that observed more severe clinical symptoms after exposure to high levels of SARS-CoV-2 (Mandavilli, 2020).

Because there is a low level of ACE2 receptors in the cells in the lower parts of the lung, direct infection from nasal cells to the lower lung is thought to be unlikely. Instead, Hou and colleagues suggest that nasal secretions with large amounts of virus are aspirated into the lungs, especially at night during sleep. Previous research indicates that this type of viral spread causes patchy sites of infection, which have been observed in CT scans and autopsies of people with COVID-19. This type of infection pathway is also supported by the timeline observed for progression of upper respiratory symptoms to infection of the lung over a period of around five days. Older people and those who are characterized with obesity have been found to have decreased lung function that increases the possibility of aspiration of fluids into the lungs, and could explain the increased susceptibility of these populations. Based on their results, the researchers conclude that if the nasal cavity is confirmed as the initial site of infection that leads to seeding of the lung through aspiration of nasal fluids, the widespread use of masks could help slow transmission by preventing exposure of virus to the nasal passages.

Rate of Symptomatic COVID-19 in Healthcare Workers

Two recent papers have described the infection rate of healthcare workers in the Netherlands and in Wuhan, China (Cheng et al., 2020, Kluytmans-van den Bergh et al., 2020, and Lai et al., 2020). In the study from China, it was found that workers who had direct interaction with people with COVID-19 had an infection rate of 0.55% for SARS-CoV-2. However, the rate of infection was higher (1.65%) for workers who were caring for people not known to be infected. The authors found these rates encouraging as they suggest that when personal protective equipment is available in ample supply, its use will protect healthcare workers. The increased rate of infection in people not knowingly caring for patients with COVID-19 may suggest that insufficient measures were taken due to a perceived reduction in the level of risk. Testing in two hospitals in the Netherlands indicated a 0.89% overall infection rate. Based on further investigation of those who tested positive, it was determined that most had probably been exposed in the community rather than at work in the hospital. In both studies, only around half of those who tested positive reported experiencing a fever.

Pre-Symptomatic and Asymptomatic Transmission in China

Based on the available evidence, it is estimated that 30% to 59% of COVID-19 cases are asymptomatic. Chinese officials were able to implement contact tracing, quarantine for key populations, medical observation, and curtailed social activities during the original outbreak in China, which has allowed for a determination of the extent of transmission that occurs from people without symptoms (Zhang et al., 2020). The information covers people who were evaluated between January 28 and March 15. The evaluation indicates that 23% of the confirmed cases in Guangzhou, China were asymptomatic at diagnosis, and 86% later developed symptoms. When the contacts of pre-symptomatic individuals were investigated, it was found that the rate of infection was 3.3% overall. When only household contacts were evaluated, the rate of infection was much higher at 16.1%. Social contacts had a rate of infection of 1.1%, and there was no workplace transmission from the people who were pre-symptomatic. **Based on the study, the authors conclude that there is evidence for transmission from people with pre-symptomatic COVID-19 infections, and those in close contact have a higher risk than other types of contact**.

Monitoring the Outbreak

Methods that can quickly detect increased transmission of SARS-CoV-2 are helpful for controlling new surges in cases, but there is a lag between the time when infections begin to rise and the time people begin to notice symptoms and seek out testing. This lag means that the number of infections begins to increase before there is a noticeable difference in the results from diagnostic testing or monitoring of hospital admissions. Researchers also can monitor the amount of viral genetic material in the environment, and because viral RNA has been found to be present in the fecal matter of those who are infected**, analysis of the amount of RNA in sewage allowed researchers to identify an outbreak seven days before it was observable from testing or hospital admissions**. The results of the study of the solids from wastewater

produced in New Haven, Connecticut were published in a preprint (Peccia et al., 2020). The researchers collected daily samples from the wastewater treatment facility and quantified the amount of SARS-CoV-2 RNA between the March 19 and May 1. The amount of RNA was compared to the hospital admissions and data from community-based testing. Based on the results, the researchers found that monitoring wastewater can accurately track an outbreak in the community and that the start and end of an outbreak is apparent earlier from the analysis of wastewater compared to testing or hospital admissions. A similar study was published as a preprint in April where researchers sampled wastewater from Paris, France (Lesté-Lasserre, 2020). The French researchers also found that the changes in the levels of viral RNA was detectable before other monitoring methods such as the number of deaths in hospitals and diagnosis of new cases.

Effects of Social Distancing on Transmission

Several reports have been published that indicate the social distancing measures put into place helped to reduce the transmission of COVID-19.

In one of the studies, the researchers investigated whether the restrictions put in place by governments in the United States were more effective than if they had only provided information and recommendations (Courtemanche et al., 2020). In the study, they evaluated four types of social distancing measures put into place between March 1 and April 27. The four measures were stay-in-place orders, public-school closures, bans on large social gatherings, and closures of entertainment-related businesses. At the start of the time-period for the study (March 1), no jurisdiction had implemented all four measures. As of March 22, all four measures were being enforced for 25% of the United States population. This proportion grew to approximately 65% by March 29, and the last stay-in-place order took effect April 7 so that 95% of the population were under all four levels. The researchers determined that stay-in-place orders lead to a 3% reduction in the growth rate of COVID-19 cases on top of the effects from the other measures after 6 to 10 days. There was a 4.5% reduction after 11 to 15 days and a 5.9% reduction after 16 to 20 days. The rate of COVID-19 cases leveled off from day 21 onward with a decrease of 8.6% in the growth rate of cases compared to at the start of the government orders. The closing of entertainment facilities and gyms also lead to a reduction in the growth rate of COVID-19 cases of 4.4% reduction after 1 to 5 days, a 4.7% reduction after 6 to 10 days, a 6.1% reduction after 11 to 15 days, a 5.6% reduction after 16 to 20 days, and a 5.2% reduction after 21 or more days. On the other hand, the researchers found that implementation of **a ban on large social gatherings and closure of schools did not have an effect on the reduction in COVID-19 cases**. They theorize that this lack of effect may mean that the socialization was simply moved to other venues, leading to continued exposure to the virus. When the effects of all four measures together were determined, the researchers found that after 1 to 5 days, the growth rate of COVID-19 cases was reduced by 5.4%. There were further reductions with increased time under the restrictions as observed in the other evaluations. When all four measures were implemented for 6 to 10 days, a 6.8% reduction in COVID-19 cases was observed with an 8.2% reduction after 11 to 15 days, a 9.1% reduction after 16 to 20 days, and a 12.0% reduction after 21 days or more. Courtemanche and colleagues also determined that the mean growth rate in COVID-19 cases would have been 16.2% without any interventions and 11% with all of the measures except stay-in-place orders. The actual growth rate was 3% during the time-period used for the calculations. **Based on their comparisons, the authors determined that by the**

end of the sample period, the model predicts that cases would have been 10 times higher without SIPOs [stay-in-place orders] and 35 times higher without any government-mandated social distancing restrictions. The timing of the evaluations can make a large difference in the calculated impacts because of the exponential characteristics of viral transmission. About a month after the earliest interventions were put into place (April 6), the number of cases would only have increased two-fold compared to the number of cases if nothing had been done. However, by the second week in April, the outbreak had entered the exponential phase of transmission where an "explosion" in the number of cases becomes evident if there are no interventions in place. At this point, changes in social distancing measures would no longer be able to reduce the growth rate.

A similar study that involved the response of governments from around the world also indicates that the social distancing measures have been effective (Hsiang et al., 2020). In the report, published in the journal *Nature*, 1,717 local, regional, and national interventions implemented across China, South Korea, Italy, Iran, France, and the United States were evaluated. If no interventions had been put into place, the authors estimate that there would have been a growth rate of 38% per day in the infection rate of COVID-19, which corresponds to having the number of new cases double every two days. **The reduction in the growth of new cases with implementation of social distancing throughout the world is estimated to have prevented or delayed 62 million confirmed cases, which averts 530 million total infections.** Because of the exponential growth observed with viral transmission, the authors determined that small delays in policy deployment produce dramatically different health outcomes.

An assessment of the effect of lockdowns in eleven European countries (France, Italy, Spain, the United Kingdom, Belgium, Germany, Sweden, Switzerland, Austria, Denmark, and Norway) was also published in the journal *Nature* (Flaxman et al., 2020). Based on the researchers' assessment, the restrictive interventions have led to a reduction in the reproduction number (an estimate of how many people a sick individual infects) to below one and allowed for control of the current outbreak. The initial reproduction number averaged between the countries before social distancing restrictions was estimated to be 3.8, and at the time of the study, the reproduction number was estimated to be 0.66 for the eleven countries in the study. **The calculations suggest that as of May 4, between 12 and 15 million people in in the eleven European countries have been infected, which is between 3.2% and 4.0% of the population**. The researchers were also able to estimate the number of deaths that were avoided due to the implementation of social distancing. Based on their calculations beginning at the start of the epidemic, **3,100,000 deaths have been averted due to interventions across the eleven countries**.

Outcomes of COVID-19 Cases in California and Washington State

Kaiser Permanente is an integrated healthcare delivery system used in a similar way to traditional health insurance, but because of the way it is organized, the company has access to patient medical records in a manner that is similar to that of national health programs in England and Sweden. Researchers can more easily use this group to investigate health trends because the full medical records, with identifying information removed, are available. Using the Kaiser Permanente group, researchers at the University of California, Berkeley have been able to determine the incidence, clinical outcomes, and transmission dynamics of severe COVID-19 in

California and Washington state. Based on the available data, 1840 people were admitted to the hospital with COVID-19 by April 22 out of a total of 9,596,321 people enrolled in the program (Lewnard et al., 2020). The peak of hospital admission rates was on March 23 in northern California, April 1 in southern California, and April 4 in Washington. As seen in other studies, the incidence of hospital admission increased with increasing age. The median duration of the stay in the hospital for survivors was 9.3 days with a range between 0.8 and 32.9 days while the median duration of the hospital stay for non-survivors was 12.7 days with a range between 1.6 and 37.7 days. The probability of being admitted to the intensive care unit was 48.5% for men and 32.0% for women. The median duration of the stay in the intensive care unit was 10.6 days with a range from 1.3 to 30.8 days. The case fatality ratio was 23.5% for men and 14.9% for women, and 18.4% of the total group had died as of April 22. **Based on this information, people who were admitted to hospital with COVID-19 had a high probability of being admitted to the intensive care unit, of a long hospital stay, and of death from COVID-19**. As of March 1, it was calculated that infected individuals were responsible for 2.06 secondary infections in the northern California region, 2.49 secondary infections in the southern California region, and between 1.31 and 1.53 in the Washington region. Importantly, the transmission declined in response to social distancing interventions and was reported to be between 0.81 and 0.90 in the northern California region, between 0.78 and 0.87 in the southern California region, and between 0.78 and 0.86 in the Washington region as of April 1. The estimated number of secondary infections cannot be directly applied to the general public as the population included in the study are of a high enough socioeconomic status to qualify for healthcare. Individuals without access to healthcare might be expected to have a higher rate of transmission due to the increased employment in so-called essential jobs. **The authors emphasize the extended length of stay in the hospital and in the intensive care unit and the potential contribution to hospital capacity if high numbers of people become ill.**

Coronavirus Response in Sweden

Officials in Sweden have opted to pursue a less restrictive social distancing structure than other countries in the region. The thought process behind the different strategy is to try and protect vulnerable groups, such as the elderly, while allowing less vulnerable individuals to continue interacting with the community thereby producing a slow and steady rate of infection among younger, healthier people in order to better weather a potential second wave of infections (Birnbaum, 2020). This strategy has led to criticism from public health experts and has resulted in an increased number of deaths in Sweden from COVID-19 compared to neighboring countries (8 times larger than Denmark and 19 times higher than Norway). Studies of the number of people with antibodies to SARS-CoV-2 are not much higher than seen in other countries with more restrictive measures in place (around 7%), but the number of deaths in Sweden is much higher. Part of the rationale behind the decision was to mitigate the effect on the economy by allowing those of working age to continue to do their jobs. However, this benefit has not materialized, in part due to the interconnectedness of the economy in Europe and the rest of the world. At this time, the Swedish economy is expected to shrink by 7% this year, which is the worst contraction since World War II. **One of the officials involved in implementing the more relaxed approach, Anders Tegnell, publically stated that he now feels that stricter interventions should have been implemented based on the high level of deaths that have occurred in the country**.

Chloroquine

The role of chloroquine for the treatment of COVID-19 has fluctuated wildly since the start of the pandemic. Initial reports suggested that it may have antiviral effects that would be useful for treatment or prevention of infection, but proof either for or against these proposed functions has not been established. An early study from France by Gautret and colleagues reported promising results for the use of chloroquine combined with azithromycin, leading to multiple heads-of-state and other officials endorsing the drug. However, soon after publishing the results, numerous researchers published questions about the very small number of participants, the unclear dosing decisions, and questionable control group of patients. The paper was later disavowed by the society that publishes the journal. Other small studies have been published that suggested little effect on COVID-19 by chloroquine, but these studies did not have control groups for comparison, making it difficult to interpret the results. Then a paper was released from the Veterans Administration reporting no benefit from the drug, but an increase in the negative cardiac side effects that seemed to cause an increased mortality compared to those who were not taking chloroquine. In May, another study was published that reported similar results, suggesting no benefit from chloroquine and an increased rate of mortality due to cardiac side effects. This study, published in the peer-reviewed journal the *Lancet* by Mehra and colleagues at Brigham and Women's Hospital and Harvard University, did not use medical data that they had directly collected from the participants in the study. Instead, the researchers utilized a company that collects medical records, with the patient's permission, so that a large and diverse database is available for researchers to analyze. The company used is called Surgisphere, and the paper in the *Lancet* reported that hydrochloroquine and chloroquine had no beneficial effect on COVID-19 and was associated with a higher mortality rate due to cardiac toxicity. After the publication of the paper investigating the effect of chloroquine, and release of multiple other papers using data from Surgisphere, researchers began to question the validity of the medical information that was reported (Servick and Enserink, 2020a and Servick and Enserink, 2020b). The questions were based on an "astonishing number" of patients' information that had been collected in such a short timeframe, inconsistent details about the patients' demographics, and implausible dosing schedules. All together the inconsistencies discovered suggest that the patient data was falsified. The article has since been retracted (Mehra et al., 2020).

Two other studies have also been affected that used the same patient database from Surgisphere. The first was published in the *New England Journal of Medicine* and investigates the effect of angiotensin-converting enzyme (ACE) inhibitors (a treatment for high blood pressure) on the risks of severe symptoms or infection from SARS-CoV-2. The second was a preprint investigating the effect of an anti-parasitic drug called ivermectin on the mortality of people with COVID-19. Dr. Mehra was also the lead author on the ACE-inhibitor study, which was retracted from the *New England Journal of Medicine* on June 4 (Rubin, 2020 and Mehra et al., 2020). The WHO had halted its section of the SOLIDARITY trial investigating the effects of chloroquine based on the results of the *Lancet* study, and officials are unsure if it is safe to restart the trial or not. Ivermectin is being used for COVID-19 in some South American countries where the parasite it treats is found. Specifically, the Peruvian Ministry of Health modified its COVID-19 treatment protocol to include ivermectin (as well as hydroxychloroquine) for mild and severe cases of COVID-19. The city government in Trinidad, Bolivia has distributed 350,000 free doses of ivermectin after the country's Ministry of Health authorized its use against COVID-19.

While the studies involving data obtained from Surgisphere are not valid, there were several other recently released publications that suggest that **chloroquine is not effective in treating or preventing COVID-19**. In the first study, the researchers investigated if use of chloroquine could prevent COVID-19 after a high-risk exposure to a confirmed case (Boulware, et al., 2020). The study followed 821 participants directly, and the researchers reported that there was not a statistically significant difference in the incidence of new illness between participants receiving hydroxychloroquine (11.8% became ill) and those receiving placebo (14.3% became ill). There were more side effects reported with use of hydroxychloroquine, but there were no serious adverse events during the trial. **Overall the authors report that hydroxychloroquine did not prevent COVID-like illness or prevent confirmed infection after exposure to someone with COVID-19 when used within 4 days after exposure**. The second clinical trial from the United Kingdom, which was called RECOVERY, investigated 1,542 participants who received hydroxychloroquine and 3,132 who received usual care during hospitalization for COVID-19 (Herper, 2020). It was reported that after 28 days of treatment, 25.7% of those on hydroxychloroquine and 23.5% of those received usual care had died, and the difference between the two groups was not statistically significant. **There was no beneficial effect from the use of chloroquine on how long individuals with COVID-19 stayed in the hospital or with other measured outcomes**.

Anakinra

Anakinra is an anti-inflammatory agent that is used to treat a number of autoimmune disorders and targets interleukin-1beta, IL6, and other cytokines that have been shown to be involved in the cytokine storm that leads to poor outcomes for people with severe COVID-19. A study from a hospital in Paris, France, published in the *Lancet Rheumatology*, investigated the effect of anakinra in 52 people with severe forms of COVID-19 whose symptoms were indicative of worsening respiratory function (Huet et al., 2020). Participants were given smaller doses of anakinra with subcutaneous injections rather than IV infusion as has been utilized in some other studies. The outcomes of the people who were given anakinra were compared to previous patients treated earlier in the same hospital. In the group given anakinra, 25% were admitted to the intensive care unit or died during the study compared to 73% of patients who received standard care. The treatment was found to be safe and without serious side effects compared to those not taking anakinra. **Based on their investigation, the researchers report that anakinra reduced the need for invasive mechanical ventilation in the intensive care unit and mortality among patients with severe forms of COVID-19 without serious side-effects**.

References

Achenbach J, Cha AE, Guarino B, Janes C. Experts dispute reports that coronavirus is becoming less lethal. *The Washington Post*. Published on June 1, 2020. Accessed on June 2, 2020 at https://www.washingtonpost.com/health/experts-dispute-reports-coronavirus-is-becoming-less-lethal/2020/06/01/8f8ace7c-a432-11ea-b619-3f9133bbb482_story.html

Birnbaum M. Scientist behind Sweden's covid-19 strategy suggests it allowed too many deaths. *The Washington Post*. Published on June 4, 2020. Accessed on June 6, 2020 at

https://www.washingtonpost.com/world/europe/sweden-epidemiologist-anders-tegnell/2020/06/03/063b20e4-a5a0-11ea-b619-3f9133bbb482_story.html

Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 [published online ahead of print, 2020 Jun 3*]. N Engl J Med*. 2020;10.1056/NEJMoa2016638. doi:10.1056/NEJMoa2016638

Cheng VC, Wong SC, Yuen KY. Estimating Coronavirus Disease 2019 Infection Risk in Health Care Workers. *JAMA Netw Open*. 2020;3(5):e209687. Published 2020 May 1. doi:10.1001/jamanetworkopen.2020.9687

Courtemanche C, Garuccio J, Le A, Pinkston J, Yelowitz A. Strong Social Distancing Measures In The United States Reduced The COVID-19 Growth Rate [published online ahead of print, 2020 May 14]. *Health Aff (Millwood*). 2020;101377hlthaff202000608. doi:10.1377/hlthaff.2020.00608

COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study [published online ahead of print, 2020 May 29]. *Lancet*. 2020;S0140-6736(20)31182-X. doi:10.1016/S0140-6736(20)31182-X

Flaxman S. et al. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. *Nature*. Published June 8, 2020. Accessed on June 8, 2020 at https://www.nature.com/articles/s41586-020-2405-7

Herper M. Study: Hydroxychloroquine had no benefit for hospitalized Covid-19 patients, possibly closing door to use of drug. *STAT News.* Published on June 5, 2020. Accessed on June 8, 2020 at https://www.statnews.com/2020/06/05/hydroxychloroquine-had-no-benefit-for-hospitalized-covid-19-patients-possibly-closing-door-to-use-of-drug/

Hou et al., SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract, *Cell* (2020), https://doi.org/10.1016/j.cell.2020.05.042

Hsiang S et al. The effect of large-scale anti-contagion policies on the COVID-19 pandemic. *Nature*. Published June 8, 2020. Accessed on June 8, 2020 at https://www.nature.com/articles/s41586-020-2404-8

Huet T et al. Anakinra for severe forms of COVID-19: a cohort study. *The Lancet Rheumatology*. Published May 29, 2020. Accessed on https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30164-8/fulltext

Hopkins JS. Hydroxychloroquine Doesn't Help Hospitalized Covid-19 Patients, New Research Finds. *The Wall Street Journal*. Published June 5, 2020. Accessed on June 8, 2020 at https://www.wsj.com/articles/hydroxychloroquine-doesnt-help-hospitalized-covid-19-patients-new-research-

Kluytmans-van den Bergh MFQ, Buiting AGM, Pas SD, et al. Prevalence and Clinical Presentation of Health Care Workers With Symptoms of Coronavirus Disease 2019 in 2 Dutch

Hospitals During an Early Phase of the Pandemic. *JAMA Netw Open*. 2020;3(5):e209673. Published 2020 May 1. doi:10.1001/jamanetworkopen.2020.9673

Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study [published online ahead of print, 2020 May 28]. *Lancet*. 2020;S0140-6736(20)31187-9. doi:10.1016/S0140-6736(20)31187-9

Lai X, Wang M, Qin C, et al. Coronavirus Disease 2019 (COVID-2019) Infection Among Health Care Workers and Implications for Prevention Measures in a Tertiary Hospital in Wuhan, China. *JAMA Netw Open*. 2020;3(5):e209666. Published 2020 May 1. doi:10.1001/jamanetworkopen.2020.9666

The Lancet Editors. Expression of concern: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis [published online ahead of print, 2020 Jun 3]. *Lancet*. 2020;S0140-6736(20)31290-3. doi:10.1016/S0140-6736(20)31290-3

Lee LYW, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study [published online ahead of print, 2020 May 28]. *Lancet*. 2020;S0140-6736(20)31173-9. doi:10.1016/S0140-6736(20)31173-9

Lesté-Lasserre C. Coronavirus found in Paris sewage points to early warning system. *Science*. Published April 21, 2020. Accessed June 9, 2020 at https://www.sciencemag.org/news/2020/04/coronavirus-found-paris-sewage-points-early-warning-system

Lewnard JA, Liu VX, Jackson ML, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study [published correction appears in BMJ. 2020 Jun 4;369:m2205]. *BMJ*. 2020;369:m1923. Published 2020 May 22. doi:10.1136/bmj.m1923

Louisiana State University Health Sciences Center. 1ST COVID autopsy series by LSUHealthNO pathologists reveals new cardiopulmonary findings. Published May 27, 2020. Accessed on June 4, 2020 at https://www.eurekalert.org/pub_releases/2020-05/lsuh-1ca052620.php

Mandavilli A. It's Not Whether You Were Exposed to the Virus. It's How Much. *The New York Times.* Published on May 29, 2020. Accessed on June 2, 2020 at https://www.nytimes.com/2020/05/29/health/coronavirus-transmission-dose.html

Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621 [published online ahead of print, 2020 Jun 4] [retraction of: N Engl J Med. 2020 May 1;:]. *N Engl J Med*. 2020;10.1056/NEJMc2021225. doi:10.1056/NEJMc2021225

Mehra MR, Ruschitzka F, Patel AN. Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The *Lancet*.

Published June 5, 2020. Accessed June 6, 2020 at https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31324-6/fulltext

Peccia J. et al. SARS-CoV-2 RNA concentrations in primary municipal sewage sludge as a leading indicator of COVID-19 outbreak dynamics. *medRxiv*. Published on May 22, 2020. Accessed on May 28, 2020 at https://www.medrxiv.org/content/10.1101/2020.05.19.20105999v1

Rabin RC. Scientists Question Medical Data Used in Second Coronavirus Study. *The New York Times*. Published June 2, 2020. Accessed on June 2, 2020 at https://www.nytimes.com/2020/06/02/health/virus-study.html

Rubin EJ. Expression of Concern: Mehra MR et al. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621 [published online ahead of print, 2020 Jun 2]. *N Engl J Med.* 2020;NEJMe2020822. doi:10.1056/NEJMe2020822

Servick K, Enserink M. A mysterious company's coronavirus papers in top medical journals may be unraveling. *Science*. Published June 2, 2020. Accessed on June 3, 2020 at https://www.sciencemag.org/news/2020/06/mysterious-company-s-coronavirus-papers-top-medical-journals-may-be-unraveling

Servick K, Enserink M. The pandemic's first major research scandal erupts. *Science*. Published on June 4, 2020. Accessed on June 6, 2020 at https://science.sciencemag.org/content/368/6495/1041

Thebault R, Tran AB, Williams V. The coronavirus is infecting and killing black Americans at an alarmingly high rate. *The Washington Post.* Published on April 7, 2020. Accessed on June 6, 2020 at https://www.washingtonpost.com/nation/2020/04/07/coronavirus-is-infecting-killing-black-americans-an-alarmingly-high-rate-post-analysis-shows/?arc404=true

Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study [published online ahead of print, 2020 May 29]. *Lancet Oncol*. 2020;S1470-2045(20)30309-0. doi:10.1016/S1470-2045(20)30309-0

Zhang W, Cheng W, Luo L, Ma Y, Xu C, Qin P, et al. Secondary transmission of coronavirus disease from presymptomatic persons, China. *Emerg Infect Dis.* 2020 Aug. Accessed on June 4, 2020 at https://doi.org/10.3201/eid2608.201142