**COVID-19 Research Watch**

**December 7, 2020**

**CLINICAL PRESENTATION & MANAGEMENT**

**Delirium in Older Patients With COVID-19 Presenting to the Emergency Department**¹

This cohort study examined the frequency with which COVID-19 patients aged ≥65 years presented to seven US emergency departments (ED) with delirium. Of 817 patients, 226 (28%) had delirium at presentation at ED, and delirium was the sixth most common of all presenting symptoms and signs. Among patients with delirium, 37 (16%) presented with delirium as a primary symptom and 37% had no typical COVID-19 symptoms or signs, such as cough or fever. Delirium was often seen without other typical symptoms or signs and was associated with poor hospital outcomes and death. The findings suggest that older adults with COVID-19 commonly present to the ED with delirium. The authors emphasize the clinical importance of including delirium on checklists of presenting signs and symptoms of COVID-19 that guide screening, testing, and evaluation considering the burden of morbidity and mortality it has on elderly populations.

**Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis**²

A systematic review of 42 studies and 8,261 patients was conducted to evaluate the rates of venous and arterial thromboembolism (TE) and associated mortality risk among COVID-19 patients. Among all patients, the venous thromboembolism (VTE) rate was 21%, the deep vein thrombosis (DVT) rate was 20%, the pulmonary embolism (PE) rate was 13%, and the arterial thromboembolism (ATE) rate was 2%. These rates were higher among ICU patients where VTE rate was 31%, DVT rate was 28%, PE rate was 19%, and ATE rate was 5%. Furthermore, COVID-19 patients who developed TE had a 74% greater odds of mortality compared to those who did not develop TE. The results of ongoing clinical trials on thromboprophylaxis should inform its use in reducing the high risk of TE and its associated mortality in COVID-19 patients.

**Long COVID in the Faroe Islands – a longitudinal study among non-hospitalized patients**³

A longitudinal study was conducted to evaluate the persistence of symptoms beyond the initial, acute phase of confirmed COVID-19 cases. 180 COVID-19-recovered individuals from the Faroe Islands were interviewed and asked to retrospectively recall the presence or absence of COVID-19 symptoms in the acute and recovery phase of COVID-19. During the acute phase, 4.4% of participants were asymptomatic, 7.2% reported one or two symptoms, and over 30% reported nine or more symptoms. At the last follow up, 46.7% were asymptomatic, 33.3% reported one or two symptoms, and 19.4% reported 3 or more symptoms. More than half of the study population reported persistence of at least one symptom at an average of 125 days post-symptom onset, with the most persistent symptoms being fatigue, loss of smell and taste, and muscle and joint pain. Further monitoring is warranted to ensure proper quantification of persistent COVID-19 symptoms.

**MODELS AND FORECASTING**

**Assessment of risks associated with SARS-CoV-2 experimental human infection studies**⁴

Controlled human infection models (CHIs) are studies in which healthy human volunteers are experimentally infected with SARS-CoV-2 in order to identify the effectiveness of potential drug and
vaccine candidates. This analysis assessed the major risks of a CHI model as well as discussed potential mitigation strategies to address each identified risk. The primary risk of a CHI model is that a subject may develop severe disease; such a risk can be partly addressed by having rescue treatment options, selecting low-risk participants, and lowering the initial viral inoculum dose. These measures would also help decrease the risk of developing long-term sequelae, which are thought to be associated with severe disease. Nonetheless, adequate compensation mechanisms need to be implemented in the case that such events arise for the participant. Additionally, it is possible that the infected participant may trigger large-scale community transmission through infecting healthcare personnel or household contacts. Therefore, public health authorities must be alerted to trace potential transmission and subjects must adhere to a strict quarantine while they may be infectious. Lastly, isolated participants should initially undergo mental health screenings to minimize the impact of an unexpected lengthy quarantine. While risks of CHI models may be mitigated, the overall benefit of these studies should be weighed against the remaining risk.

NON-PHARMACEUTICAL/ PUBLIC HEALTH INTERVENTIONS

Trends in County-Level COVID-19 Incidence in Counties With and Without a Mask Mandate — Kansas, June 1–August 23, 2020

The governor of Kansas made an executive order on July 3rd, 2020 for a state mask mandate for public spaces, and by August 11th, 2020, 24 of Kansas’ 105 counties followed the mandate or adopted their own mandate while 81 counties opted out of the state mandate and did not adopt their own mandate. Segmented regression was used to analyze changes in COVID-19 incidence before and after the mask mandate among mandated and nonmandated counties. By August 17-23, COVID-19 incidence had decreased among mandated counties (net decrease of 6% from 17 to 16 cases per 100,000) and increased among nonmandated counties (net increase of 100% from 6 to 12 cases per 100,000). Countywide mask mandates may have contributed to the decrease in transmission in counties adopting the mask mandates; this study adds to the body of evidence that community-level mitigation strategies that emphasize wearing masks can help reduce the transmission of SARS-CoV-2.

PATHOPHYSIOLOGY

The potential role of serum angiotensin-converting enzyme in coronavirus disease 2019

In this study, researchers retrospectively evaluated the role of serum angiotensin-converting enzyme (ACE) activity in the progression of COVID-19 within 136 patients with confirmed COVID-19 and 60 age- and sex- matched normal controls. The COVID-19 patients were split into 16 severe cases and 120 non-severe cases, and the authors demonstrated a correlation between disease severity and older age (57.50 ± 11.70 years vs 49.19 ± 15.98 years), higher body mass index (BMI) (26.04 ± 5.63 kg/m² vs 23.60 ± 3.33 kg/m²), and higher proportion of hypertension (8 [50%] vs 25 [20.83%]). Hypertensive patients, older patients, and patients with a higher BMI exhibited lower baseline serum ACE activity. Overall, baseline serum ACE activity was much lower in patients with COVID-19 compared to controls, with severe COVID-19 patients expressing the lowest activity levels. Patients with COVID-19 also showed a large change in immune-inflammatory parameters— including fibrinogen, percentage of neutrophils, and lymphocyte count— compared to controls. After treatment and during recovery, serum ACE activity levels increased in the COVID-19 group. The authors suggest that since serum ACE activity can be used as a marker to monitor other respiratory illnesses, such as influenza and acute respiratory distress syndrome, it can similarly be used to monitor the progression of COVID-19.
Olfactory transmucosal SARS-CoV-2 invasions as a port of central nervous system entry in individuals with COVID-19

In this study, autopsy samples were obtained and analyzed from 33 individuals infected with SARS-CoV-2, which were either confirmed by RT-qPCR or strongly suggestive from clinical presentation. Clinical and post-mortem records indicated neurological alteration, including impaired consciousness, intraventricular hemorrhage, headache, behaviour change, acute cerebral ischemia, and acute infarcts. SARS-CoV-2 RNA and proteins were present in nasopharynx and brain samples. More specifically, viral RNA levels were highest in the olfactory mucosa, and neural-mucosal interface appeared to serve as an entry point to the central nervous system (CNS), which affects smell and taste. Other findings included inflammation in CNS due to upregulation of macrophages, histopathological evidence of cerebral micro-thrombosis and acute infarct in 18% of individuals, and thromboembolic ischemic infarction of CNS due to infection and SARS-CoV-2 neurotropism. The results of this study help explain COVID-19’s neurological consequences in cases that have resulted in death.

PEDIATRIC PRESENTATION

Assessment of 135,794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States

This retrospective cohort study examined the epidemiology of COVID-19 infection among 135,794 pediatric patients (<25 years old) undergoing diagnostic testing for the virus in seven US children’s health systems using electronic health records from January 1 through September 8, 2020. The study found that 96% of patients tested had negative results. Rates of severe cardiorespiratory presentation of COVID-19 illness were low and clinical manifestations were typically mild. Black, Hispanic, and Asian race/ethnicity; adolescence and young adulthood; and non-respiratory chronic medical conditions were associated with identified infection. Additionally, Kawasaki disease diagnosis was not an effective proxy for multisystem inflammatory syndrome of childhood. The authors concluded the findings will be critical not only in caring for severely ill patients, but also in constructing sustainable ways to minimize the disease burden caused by COVID-19; however further work is needed in both traditional medical research paradigms and in rapid and highly collaborative science to provide better care for pediatric patients across the spectrum of health.

REGIONAL LESSONS LEARNED

Effective control of SARS-CoV-2 transmission in Wanzhou, China

This study assessed data from 5 generations of transmission of SARS-CoV-2 in 183 confirmed COVID-19 cases and their contacts in Wanzhou, China. Among the cases, 67.2% were symptomatic and 32.8% were asymptomatic. Upon analysis, the reproductive number was calculated as 1.64 (95% CI: 1.16-2.40) from the first to the second generation of transmission. This number decreased in subsequent generations of transmission to 0.31-0.39; this decrease coincided with the implementation of strict control measures. There was evidence for higher risk of infection with the following factors: interaction with infected case within 5 days of being infected (OR: 2.88, 95% CI: 1.22-6.78), repeated contact with the case (OR: 2.89, 95% CI: 1.39-6.02), and greater than 8 hours of contact (OR: 6.08, 95% CI: 2.88-12.83). Understanding the key risk factors and implementing rigorous control measures are essential for the mitigation and prevention of COVID-19 resurgence.
TRANSMISSION PATTERNS

Serologic testing of U.S. blood donations to identify SARS-CoV-2-reactive antibodies: December 2019-January 2020

With the first known US COVID-19 case on January 19, 2020, this study sought to analyze blood samples donated to the American Red Cross from nine states from December 13, 2019 to January 17, 2020 in order to test for antibody presence against SARS-CoV-2 prior to the first recorded case. Out of the 7,389 samples, 106 samples showed reactivity against the SARS-CoV-2 spike protein. To probe whether this reactivity was due to cross-reactive antibodies or previous SARS-CoV-2 infection, these identified samples were further analyzed. Of the 90 samples available for further analysis, 39 contained both IgG and IgM SARS-CoV-2 antibodies, 84 neutralized the SARS-CoV-2 virus, and 1 contained antibodies specific to the S1 unit of the spike protein – an antigen more specific to the SARS-CoV-2 virus. Given the nature of this convenience sample, the authors do not extrapolate the results for regional or national representation, but rather suggest that the aforementioned findings provide support that SARS-CoV-2 virus was present in the US as early as December 2019.

Estimated SARS-CoV-2 seroprevalence in the US as of September 2020

The authors of this study evaluated the seroprevalence of SARS-CoV-2 antibodies in the US and in Puerto Rico. Residual sera from 177,919 samples were collected from two commercial laboratories over four collection periods, spanning from July 27 to September 24, 2020. Biweekly convenience samples were collected from every state and split evenly into four age groups (0-17 years, 18-49 years, 50-64 years, and ≥65 years). The researchers revealed that across almost all sampling jurisdictions, the seroprevalence of SARS-CoV-2 was less than 10%. The data in each jurisdiction were also stratified by sex, age group, and metropolitan status. While there was no significant difference in seroprevalences by sex or metropolitan status, seroprevalence in those >65 years was on average lower than in adults 18-49 years. The highest seroprevalence was recorded in New York at 23.3% during the first period of sera collection, and the lowest seroprevalence was recorded in South Dakota at 0.0% during the second collection period. The authors argue that their study area, as well as their sample inclusion criteria and characteristics, accurately reflect the demographics of the country as a whole and can be used to generate a better understanding of the true prevalence of COVID-19 in the United States.

No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2

van Dorp et al explored the hypothesis that SARS-CoV-2 may be evolving towards higher transmissibility as the virus has only recently become associated with humans and could still be adapting to human hosts. The authors tested if any homoplasies observed in SARS-CoV-2 were associated with increased viral transmission by creating a phylogenetic index called the Ratio of Homoplastic Offspring and applying the index to a set of recurrent mutations in a dataset of 46,723 SARS-CoV-2 genomes. No single recurrent mutation was found to be significantly associated with increased viral transmission and the recurrent mutations in circulation were identified to be evolutionary neutral and mainly induced by the human immune system. The authors did not find any evidence that the recurrent SARS-CoV-2 mutations were associated with significantly increased viral transmission and the genomic diversity of the SARS-CoV-2 population is currently limited.
ADDITIONAL RESOURCES
UCSF Library COVID-19 Research and Information Resources
UCSF Institute for Global Health Sciences COVID-19 Resources
UC Davis One Health Institute COVID-19 FAQs
Harvard Viswanath Lab Myths vs Facts

Note on this Document: This document was assembled by graduate and doctoral students attending the University of California, San Francisco with the intent of facilitating the rapid dissemination of information to the global community in order to help during this time. Masih Babagoli, Alyssa Bercasio, Mariam Carson, Sarah Gallalee, Graham Hinchcliffe, and Guntas Padda contributed to these summaries. This work is volunteer based.

References

3. Petersen, Maria Skaalum, et. Al. Long COVID in the Faroe Islands - a longitudinal study among non-hospitalized patients, Clinical Infectious Diseases, ciaa1792, https://doi.org/10.1093/cid/ciaa1792