**New Research**

*note, PREPRINTS have not undergone formal peer review

**COVID-19 related publications by Providence caregivers – see Digital Commons**

**Clinical Syndrome**


   Latent class analysis identified four subphenotypes (SP) with consistent characteristics. SP1 was characterized by shock, acidemia, and multi-organ dysfunction, including acute kidney injury treated with renal replacement therapy. SP2 was characterized by high C-reactive protein, early need for mechanical ventilation, and the highest rate of ARDS. SP3 had the highest burden of chronic diseases, while SP4 had limited chronic disease burden and mild physiologic abnormalities. 28-day mortality in the Discovery cohort ranged from 20.6% (SP4) to 52.9% (SP1). Mortality across subphenotypes remained different after adjustment for demographics, comorbidities, organ dysfunction and illness severity, regional and hospital factors.


   In this multicohort study, neurological manifestations were prevalent among patients hospitalized with COVID-19 and were associated with higher in-hospital mortality. Preexisting neurological disorders were associated with increased risk of developing neurological signs and/or syndromes in COVID-19.

**Diagnostics & Screening**

The Quidel Sofia 2 SARS Antigen Fluorescent Immunoassay positive percentage agreement against an RT-PCR test result is 96.7%, and the negative percentage agreement is 100.0% in symptomatic patients. Data collected during June 30-August 31, 2020, were analyzed to compare antigen test performance with that of RT-PCR in a hospital setting. Among 1,732 paired samples from asymptomatic patients, the antigen test sensitivity was 60.5%, and specificity was 99.5% when compared with RT-PCR. Among 307 symptomatic persons, sensitivity and specificity were 72.1% and 98.7%, respectively. Health care providers must remain aware of the lower sensitivity of this test among asymptomatic and symptomatic persons and consider confirmatory NAAT testing in high-prevalence settings because a false-negative result might lead to failures in infection control and prevention practices and cause delays in diagnosis, isolation, and treatment.

**Epidemiology & Public Health**

4. **Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study.** Romero-Brufau S, et al. *BMJ.* 2021 May 12;373:n1087. doi: 10.1136/bmj.n1087. [https://www.bmj.com/content/bmj/373/bmj.n1087.full.pdf](https://www.bmj.com/content/bmj/373/bmj.n1087.full.pdf)

   A delayed second dose strategy was optimal for vaccine efficacies at or above 80% and vaccination rates at or below 0.3% of the population per day, resulting in absolute cumulative mortality reductions between 26 and 47 per 100 000. The delayed second dose strategy for people under 65 performed consistently well under all vaccination rates tested. A delayed second dose vaccination strategy, at least for people aged under 65, could result in reduced cumulative mortality under certain conditions.


   We found that SARS-CoV-2 seroprevalence was higher among cats (16.2%) than dogs (2.3%). In addition, seroprevalence was higher among animals living in close contact with SARS-CoV-2-positive owners.


   Most adults hospitalized with COVID-19 were those recommended to be prioritized for vaccination based on risk for developing severe COVID-19. These findings highlight the urgency to vaccinate patients at high risk for severe COVID-19 and monitor vaccination impact on hospitalizations and outcomes.

7. **Are Patients with Inflammatory Bowel Disease at an Increased Risk of Developing SARS-CoV-2 than Patients Without Inflammatory Bowel Disease? Results from a Nationwide Veterans' Affairs Cohort Study.** Khan N, et al. *Am J Gastroenterol.* 2021 Apr;116(4):808-810. doi:
Among 38,378 patients with IBD and 67,433 patients without IBD, 87 (0.23%) and 132 (0.20%) patients developed incident SARS-CoV-2 infection, respectively. Patients with IBD are not at a significantly increased risk of developing SARS-CoV-2 infection when compared with patients without IBD.

Healthcare Delivery & Healthcare Workers


After shutting down elective surgeries beginning in March of 2020, NorthShore University Health System set a recovery goal to achieve 80% of our historical volumes by October 1, 2020. Using the Data Coronavirus Analytics Research Team, our operational and clinical teams were able to achieve 89% of our historical volumes a month ahead of schedule, allowing rapid recovery of surgical volume and financial stability. The Data Coronavirus Analytics Research Team also was used to demonstrate that the accelerated recovery period had no negative impact with regard to iatrogenic COVID-19 infection and did not result in increased deep vein thrombosis, pulmonary embolisms, or cerebrovascular accident. These achievements demonstrate how a coordinated and transparent data-driven effort that was built upon a robust laboratory testing capability was essential to the operational response and recovery from the COVID-19 crisis.


Home-based hospital care is an attractive innovation that may extend critical hospital resources during the COVID-19 pandemic. We found that most patients did not require care escalation, with approximately 1 in 5 admitted within 14 days. We observed more severe respiratory involvement among transferred patients, particularly those requiring immediate care escalation. In addition, overall comorbidity burden was associated with transfer, similar to previous studies describing underlying conditions as important risk factors for severe COVID-19 illness.

Prognosis

In critically ill COVID-19 patients, we observed a linear association between BMI and the need for IMV, independent of other metabolic risk factors, and a non-linear association between BMI and mortality risk.


Ten articles were included in the systematic review and meta-analysis, for a total of 1179 COVID-19 patients after IHCA with attempted CPR. The estimated overall mortality rate (in-hospital or at 30 days) was 89.9%. The estimated rate of non-shockable presenting rhythms was 89%, and the estimated rate of ROSC was 32.9%. Although one of three COVID-19 patients undergoing IHCA may achieve ROSC, almost 90% may not survive at 30 days or to hospital discharge.


Between Jan 17 and Aug 10, 2020, we enrolled 78 674 patients across 255 health-care facilities in England, Scotland, and Wales. NSAID use is not associated with higher mortality or increased severity of COVID-19. Policy makers should consider reviewing issued advice around NSAID prescribing and COVID-19 severity.

**Survivorship & Rehabilitation**


This study describes the multidisciplinary COVID-19 Activity Rehabilitation Program (CARP), and reports the clinical characteristics of the first 100 patients. The cohort consisted of 100 patients (mean age 45 years, 68% women, BMI 30.2, presenting a mean of 93 days after infection). Common pre-existing conditions were respiratory and mental health, including depression and/or anxiety. The majority (75%) had not been hospitalized for COVID-19. Common presenting symptoms were fatigue (80%), respirator complaints (59%), and neurologic complaints (59%) followed by subjective cognitive impairment, sleep disturbance, and mental health symptoms. More than one-third of the patients (34%) reported difficulties with performing basic activities of daily living. Only 1 in 3 patients had returned to unrestricted work duty at the time of the analysis. For most patients, laboratory and imaging studies were normal or non-diagnostic despite debilitating symptoms. Most patients required physical therapy, occupational therapy, or brain rehabilitation.

In most patients who recovered from severe COVID-19, dyspnoea scores and exercise capacity improved over time; however, in a subgroup of patients at 12 months we found evidence of persistent physiological and radiographic change. A unified pathway for the respiratory follow-up of patients with COVID-19 is required.


Readmission and mortality rates for COVID-19 following discharge are low. Most readmissions occur early and are due to respiratory causes and may reflect the prolonged acute disease course.


SARS-CoV-2-specific immune memory response persists in over 70% of patients nearly one year after infection, which provides a promising sign for prevention from reinfection and vaccination strategy.


The absolute risk of severe post-acute complications after SARS-CoV-2 infection not requiring hospital admission is low. However, increases in visits to general practitioners and outpatient hospital visits could indicate COVID-19 sequelae.

**Therapeutics**


Multiple drugs were used in the first few months of the covid-19 pandemic, with substantial geographical and temporal variation. Hydroxychloroquine, azithromycin, lopinavir-ritonavir, and umifenovir (in China only) were the most prescribed repurposed drugs. Antithrombotics, antibiotics, H2 receptor antagonists, and corticosteroids were often used as adjunctive treatments. Research is needed on the comparative risk and benefit of these treatments in the management of covid-19.

AF is a prevalent and severe condition in older COVID-19 patients. Advanced age, dependency and relevant clinical manifestations of disease characterized a worse prognosis. Pre-admission and in-hospital anticoagulant therapy were positively associated with survival.


Our sample included 51,169 inpatients from every region of the United States. Males and females were equally represented, and most patients were white and non-Hispanic. The largest proportion of patients were older than 45 years. Corticosteroids were used the most among all patients (56.5%), followed by hydroxychloroquine (17.4%), tocilizumab (3.1%), and lopinavir/ritonavir (1.1%). We found substantial variation in medication use by region, race, ethnicity, sex, age, and insurance status. Variations in medication use are likely attributable to multiple factors, including the timing of the pandemic by region in the United States and processes by which medications are introduced and disseminated.


NSAID use is not associated with higher mortality or increased severity of COVID-19. Policy makers should consider reviewing issued advice around NSAID prescribing and COVID-19 severity.


A total of 40 participants were enrolled to receive a single intravenous dose of either etesevimab or a placebo in one of four sequential ascending intravenous dose cohorts. All 40 participants completed the study. Seventeen (42.5%) participants experienced 22 treatment emergent adverse events (TEAEs) that were drug-related. Etesevimab was well tolerated after administration of a single dose at a range of 2.5 mg/kg to 50 mg/kg in healthy Chinese adults. The PK profiles of etesevimab in healthy volunteers showed typical monoclonal antibody distribution and elimination characteristics.

The frequency of adverse events among HCWs due to PPE use is very high. Healthcare facilities should take the necessary precautions and change the working conditions during the COVID-19 pandemic to prevent adverse events associated with PPE use and minimize harm to HCWs.


In a prospective cohort study in The Lancet Respiratory Medicine, we identified 19 cases of reinfection in people who at study entry were seropositive for both SARS-CoV-2 receptor binding domain and full-length spike protein, tested negative on three nasal swab PCR tests over a 2-week quarantine period, and subsequently developed a positive PCR test at least 2 weeks after leaving quarantine. Our findings suggest that about a quarter of young healthy individuals with subsequent SARS-CoV-2 reinfection shed viable virus. Some of these individuals were asymptomatic and could unknowingly transmit SARS-CoV-2 to others.


Two doses of BNT162b2 are highly effective across all age groups (≥16 years, including older adults aged ≥85 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalisations, severe disease, and death, including those caused by the B.1.1.7 SARS-CoV-2 variant. There were marked and sustained declines in SARS-CoV-2 incidence corresponding to increasing vaccine coverage. These findings suggest that COVID-19 vaccination can help to control the pandemic.


Vaccination responses from 84 patients with IMID and 182 controls were analysed. While all controls developed anti-SARS-CoV-2 IgG, five patients with IMID failed to develop a response. Moreover, 99.5% of controls but only 90.5% of patients with IMID developed neutralising antibody activity. Overall responses were delayed and reduced in patients compared with
controls. Immune responses against the SARS-CoV-2 are delayed and reduced in patients with IMID. This effect is based on the disease itself rather than concomitant treatment.


BNT162b2 is 95% effective against Covid-19. In addition, we reported that recombinant SARS-CoV-2 bearing S genes from the B.1.1.7 variant, first identified in South Africa (B.1.351 lineage), and the variant first identified in Brazil (P.1 lineage) remained susceptible to BNT162b2 vaccine–elicited serum neutralization, although at a reduced level for the B.1.351 variant. The newly emerged B.1.526, B.1.429, and B.1.1.7+E484K variants also remain susceptible.


In this study, all patients who did not demonstrate a positive serological response had been treated with rituximab, except one patient that was treated with belimumab. Longer duration from most recent rituximab exposure was associated with a greater likelihood of response. The results suggest that time from last rituximab exposure is an important consideration in maximising the likelihood of a serological response, but this likely is related to the substantial variation in the period of B-cell depletion following rituximab. Confirming B-cell reconstitution before vaccination may increase the likelihood of a positive serological response.


The first U.S. multisite test-negative design vaccine effectiveness study among HCP found a single dose of Pfizer-BioNTech or Moderna COVID-19 vaccines to be 82% effective against symptomatic COVID-19 and 2 doses to be 94% effective.


In this interim safety analysis, we found an increase in systemic reactogenicity after the boost dose reported by participants in heterologous vaccine schedules in comparison to homologous vaccine schedules, and this was accompanied by increased paracetamol usage. Of note, these data were obtained in participants aged 50 years and older, and reactogenicity might be higher in younger age groups for whom a mixed vaccination schedule is being advocated in Germany, France, Sweden, Norway, and Denmark. Pending availability of a more complete safety dataset and immunogenicity results for heterologous prime-boost schedules (to be reported shortly), these data suggest that the two heterologous vaccine schedules in this trial might have some
short-term disadvantages. Routine prophylactic use of paracetamol after immunisation could help mitigate these.

**Whole Person Care**


Seven studies, documenting the care of 493 patients met the inclusion criteria. Approximately two thirds of patients required a continuous subcutaneous infusion with median doses of 15 mg morphine and 10 mg midazolam in the last 24 h of life. A higher proportion of patients required continuous subcutaneous infusion than is typically encountered in palliative care. Doses of medications required to manage symptoms were generally modest. There was no evidence of a standardised yet holistic approach to measure effectiveness of these medications and this needs to be urgently addressed.

**Women & Children**


In this cohort study involving 103 women who received a COVID-19 mRNA vaccine, 30 of whom were pregnant and 16 of whom were lactating, immunogenicity was demonstrated in all, and vaccine-elicited antibodies were found in infant cord blood and breast milk. Pregnant and nonpregnant vaccinated women developed cross-reactive immune responses against SARS-CoV-2 variants of concern.


Of 394 patients, 171 (43.4%) had multisystem inflammatory syndrome in children. Children with multisystem inflammatory syndrome in children were more likely younger, Black, present with fever/abdominal pain than cough/dyspnea, and less likely to have comorbidities compared with those without multisystem inflammatory syndrome in children. Among nonmultisystem inflammatory syndrome in children patients, the presence of greater than or equal to two comorbidities was associated with greater odds of critical illness. This study delineates significant clinically relevant differences in presentation, explanatory factors, and outcomes among children admitted to PICU with severe acute respiratory syndrome coronavirus 2-related illness stratified by multisystem inflammatory syndrome in children.

Overall and within multiple subgroups, we found a substantially lower rate of in-hospital mortality in pregnant patients than nonpregnant patients hospitalized with COVID-19 and viral pneumonia. The rates found in this study are consistent with results of multiple other studies (3, 4). A cohort study including all symptomatic patients with COVID-19 aged 20 to 39 years hospitalized throughout the United Kingdom reported mortality of 0.8% in pregnant and 3.1% in nonpregnant persons.

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**GUIDELINES & CONSENSUS STATEMENTS**


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**FDA / CDC / NIH / WHO Updates**

CDC - *Interim Public Health Recommendations for Fully Vaccinated People*, updated May 13, 2021 to say *fully vaccinated people no longer need to wear a mask or physically distance in any setting, except where required by federal, state, local, tribal, or territorial laws, rules, and regulations, including local business and workplace guidance*. *Also can refrain from testing following a known exposure unless they are residents or employees of a correctional or detention facility or a homeless shelter.*


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