COVID-19 Resource Desk

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Prepared by System Library Services   Retraction Watch

New Research

*note, **PREPRINTS** have not undergone formal peer review

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

Clinical Syndrome

1. The Incidence and Mortality Ratio of Ischemic Cerebrovascular Accidents in COVID-19 Cases: A Systematic Review and Meta-Analysis. Parsay S, Vosoughi A, Khabbaz A, Sadigh-Eteghad S. J Stroke Cerebrovasc Dis. 2020 Dec 17;30(3):105552. doi: 10.1016/j.jstrokecerebrovasdis.2020.105552. Online ahead of print.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7746086/

MATERIALS AND METHODS: Our search databases included Google Scholar, MEDLINE via PubMed, and Scopus. We searched the databases up to July 22, 2020. The primary outcome was the incidence of ischemic CVA in COVID-19 cases, while the secondary outcomes were the ratio of mortality in these cases. Standard meta-analysis methods used to measure the pooled incidence and mortality rates of ischemic CVA in COVID-19 cases.

RESULTS: After excluding studies with reasons, only 20 articles were eligible to be included in our qualitative synthesis, and 17 studies were evaluated quantitatively in our meta-analysis. Included studies reported a pooled average incidence of 1.7% for ischemic CVA, ranging from 1.3% to 2.3%. Mortality in patients of ischemic CVA to all COVID-19 cases was 0.5%, ranging from 0.4% to 0.6%. The mortality rate of patients with CVA to those who suffered from COVID-19 infection and ischemic CVA simultaneously was 29.2% ranging from 21.6% to 38.2%. Overall, the heterogeneity of the studies was high.

CONCLUSIONS: Our analysis revealed a pooled incidence of 1.7% for ischemic CVA in the setting of COVID-19 infection, with a mortality rate of 29.2% amongst the COVID-19 patients who are suffering ischemic CVA.

Diagnostics & Screening

2. Field performance and public health response using the BinaxNOW TM Rapid SARS-CoV-2 antigen detection assay during community-based testing. Pilarowski G, Marquez C, Rubio L,et al. Clin Infect Dis. 2020 Dec 26:ciaa1890. doi: 10.1093/cid/ciaa1890. Online ahead of print.

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1890/6052342

Among 3,302 persons tested for SARS-CoV-2 by BinaxNOW TM and RT-PCR in a community setting, rapid assay sensitivity was 100%/98.5%/89% using RT-PCR Ct thresholds of 30, 35 and none. The

specificity was 99.9%. Performance was high across ages and those with and without symptoms. Rapid resulting permitted immediate public health action.

3. Multi-organ point-of-care ultrasound for COVID-19 (PoCUS4COVID): international expert consensus. Hussain A, Via G, Melniker L, et al. Crit Care. 2020 Dec 24;24(1):702. doi: 10.1186/s13054-020-03369-5.
https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03369-5
COVID-19 has caused great devastation in the past year. Multi-organ point-of-care ultrasound (PoCUS) including lung ultrasound (LUS) and focused cardiac ultrasound (FoCUS) as a clinical adjunct has played a significant role in triaging, diagnosis and medical management of COVID-19 patients. The expert panel from 27 countries and 6 continents with considerable experience of direct application of PoCUS on COVID-19 patients presents evidence-based consensus using GRADE methodology for the quality of evidence and an expedited, modified-Delphi process for the strength of expert consensus. The use of ultrasound is suggested in many clinical situations related to respiratory, cardiovascular and thromboembolic aspects of COVID-19, comparing well with other imaging modalities. The limitations due to insufficient data are highlighted as opportunities for future research.

Epidemiology & Public Health

4. Variation in US Hospital Mortality Rates for Patients Admitted With COVID-19 During the First 6 Months of the Pandemic. Asch DA, Sheils NE, Islam MN, Chen Y, Werner RM, Buresh J, Doshi JA. JAMA Intern Med. 2020 Dec 22. doi: 10.1001/jamainternmed.2020.8193. Online ahead of print.
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2774572
MAIN OUTCOMES AND MEASURES: The primary outcome was the hospital's risk-standardized event rate (RSER) of 30-day in-hospital mortality or referral to hospice adjusted for patient-level characteristics, including demographic data, comorbidities, community or nursing facility admission source, and time since January 1, 2020. We examined whether hospital characteristics were associated with RSERs or their change over time.
RESULTS: The mean (SD) age among participants (18 888 men [49.0%]) was 70.2 (15.5) years. The mean (SD) hospital-level RSER for the 955 hospitals was 11.8% (2.5%). The mean RSER in the worst-performing quintile of hospitals was 15.65% compared with 9.06% in the best-performing quintile (absolute difference, 6.59 percentage points; 95% CI, 6.38%-6.80%; P < .001). Mean RSERs in all but 1 of the 398 hospitals improved; 376 (94%) improved by at least 25%. The overall mean (SD) RSER declined from 16.6% (4.0%) to 9.3% (2.1%). The absolute difference in rates of mortality or referral to hospice between the worst- and best-performing quintiles of hospitals decreased from 10.54 percentage points (95% CI, 10.03%-11.05%; P < .001) to 5.59 percentage points (95% CI, 5.33%-5.86%; P < .001). Higher county-level COVID-19 case rates were associated with worse RSERs, and case rate declines were associated with improvement in RSERs.
CONCLUSIONS AND RELEVANCE: Over the first months of the pandemic, COVID-19 mortality rates in this cohort of US hospitals declined. Hospitals did better when the prevalence of COVID-19 in their surrounding communities was lower.

Healthcare Delivery & Healthcare Workers

5. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, et al., Oxford University Hospitals Staff Testing Group. N Engl J Med. 2020 Dec 23. doi: 10.1056/NEJMoa2034545. Online ahead of print.
https://www.nejm.org/doi/full/10.1056/NEJMoa2034545
RESULTS: A total of 12,541 health care workers participated and had anti-spike IgG measured; 11,364 were followed up after negative antibody results and 1265 after positive results, including 88 in whom seroconversion occurred during follow-up. A total of 223 anti-spike-seronegative health care workers had a positive PCR test (1.09 per 10,000 days at risk), 100 during screening while they were asymptomatic and 123 while symptomatic, whereas 2 anti-spike-seropositive health care workers had a positive PCR test (0.13 per 10,000 days at risk), and both workers were asymptomatic when tested (adjusted incidence rate ratio, 0.11; 95% confidence interval, 0.03 to 0.44; P = 0.002). There were no symptomatic infections in workers with anti-spike antibodies. Rate ratios were similar when the anti-nucleocapsid IgG assay was used alone or in combination with the anti-spike IgG assay to determine baseline status.
CONCLUSIONS: The presence of positive anti-spike or anti-nucleocapsid IgG antibodies was associated with a substantially reduced risk of SARS-CoV-2 reinfection in the ensuing 6 months..

6. Racial Bias in Pulse Oximetry Measurement. Michael W. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. NEJM 2020 Dec 17. DOI: 10.1056/NEJMc2029240
https://www.nejm.org/doi/full/10.1056/NEJMc2029240
Oxygen is among the most frequently administered medical therapies, with a level that is commonly adjusted according to the reading on a pulse oximeter that measures patients' oxygen saturation. Questions about pulse oximeter technology have been raised, given its original development in populations that were not racially diverse.[1,2] The clinical significance of potential racial bias in pulse oximetry measurement is unknown.
Our study involved adult inpatients who were receiving supplemental oxygen at the University of Michigan Hospital (from January through July 2020) and patients in intensive care units at 178 hospitals (from 2014 through 2015).[3] We analyzed paired pulse oximetry measures of oxygen saturation and measures of arterial oxygen saturation in arterial blood gas, with all evaluations performed within 10 minutes of each other. To ensure that the arterial oxygen saturation was directly measured by co-oximetry, we limited analyses to measures of arterial blood gas that included carboxyhemoglobin and methemoglobin saturations.

Laboratory Results

7. Antibody Responses 8 Months after Asymptomatic or Mild SARS-CoV-2 Infection. Choe PG, Kim KH, Kang CK, Suh HJ, Kang E, Lee SY, Kim NJ, Yi J, Park WB, Oh MD. Emerg Infect Dis. 2020 Dec 22;27(3). doi: 10.3201/eid2703.204543. Online ahead of print.
https://wwwnc.cdc.gov/eid/article/27/3/20-4543_article
Waning humoral immunity in coronavirus disease patients has raised concern over usefulness of serologic testing. We investigated antibody responses of 58 persons 8 months after asymptomatic or mildly symptomatic infection with severe acute respiratory syndrome coronavirus 2. For 3 of 4 immunoassays used, seropositivity rates were high (69.0%-91.4%).

8. Rapid generation of durable B cell memory to SARS-CoV-2 spike and nucleocapsid proteins in COVID-19 and convalescence. Hartley GE, Edwards ESJ, et al. Sci Immunol. 2020 Dec 22. DOI: 10.1126/sciimmunol.abf8891

https://immunology.sciencemag.org/content/5/54/eabf8891

Lasting immunity following SARS-CoV-2 infection is questioned because serum antibodies decline in convalescence. However, functional immunity is mediated by long-lived memory T and B (Bmem) cells. Therefore, we generated fluorescently-labeled tetramers of the spike receptor binding domain (RBD) and nucleocapsid protein (NCP) to determine the longevity and immunophenotype of SARS-CoV-2-specific Bmem cells in COVID-19 patients. A total of 36 blood samples were obtained from 25 COVID-19 patients between 4 and 242 days post-symptom onset including 11 paired samples. While serum IgG to RBD and NCP was identified in all patients, antibody levels began declining at 20 days post-symptom onset. RBD- and NCP-specific Bmem cells predominantly expressed IgM+ or IgG1+ and continued to rise until 150 days. RBD-specific IgG+ Bmem were predominantly CD27+, and numbers significantly correlated with circulating follicular helper T cell numbers. Thus, the SARS-CoV-2 antibody response contracts in convalescence with persistence of RBD- and NCP-specific Bmem cells. Flow cytometric detection of SARS-CoV-2-specific Bmem cells enables detection of long-term immune memory following infection or vaccination for COVID-19.

9. Role of IgM and IgA Antibodies in the Neutralization of SARS-CoV-2. Klingler J, Weiss S, Itri V, Liu X, Oguntuyo KY, Stevens C, et al. J Infect Dis. 2020 Dec 24:jiaa784. doi: 10.1093/infdis/jiaa784. Online ahead of print.

https://tinyurl.com/yb7nfqjj

METHODS: We studied spike- and RBD-specific Ig isotypes in convalescent and acute plasma/sera using a multiplex bead assay. We also determined virus neutralization activities in plasma, sera, and purified Ig fractions using a VSV pseudovirus assay.
RESULTS: Spike- and RBD-specific IgM, IgG1, and IgA1 were produced by all or nearly all subjects at variable levels and detected early after infection. All samples displayed neutralizing activity. Regression analyses revealed that IgM and IgG1 contributed most to neutralization, consistent with IgM and IgG fractions' neutralization potency. IgA also exhibited neutralizing activity, but with lower potency.
CONCLUSION: IgG, IgM and IgA are critical components of convalescent plasma used for COVID-19 treatment.

10. Discordant neutralizing antibody and T cell responses in asymptomatic and mild SARS-CoV-2 infection. Reynolds CJ, Swadling L, et al. Sci Immunol. 2020 Dec 23;5(54):eabf3698. doi: 10.1126/sciimmunol.abf3698.

https://immunology.sciencemag.org/content/5/54/eabf3698

Understanding the nature of immunity following mild/asymptomatic infection with SARS-CoV-2 is crucial to controlling the pandemic. We analyzed T cell and neutralizing antibody responses in 136 healthcare workers (HCW) 16-18 weeks after United Kingdom lockdown, 76 of whom had mild/asymptomatic SARS-CoV-2 infection captured by serial sampling. Neutralizing antibodies (nAb) were present in 89% of previously infected HCW. T cell responses tended to be lower following asymptomatic infection than in those reporting case-definition symptoms of COVID-19, while nAb titers were maintained irrespective of symptoms. T cell and antibody responses were sometimes discordant. Eleven percent lacked nAb and had undetectable T cell responses to spike protein but had

T cells reactive with other SARS-CoV-2 antigens. Our findings suggest that the majority of individuals with mild or asymptomatic SARS-CoV-2 infection carry nAb complemented by multispecific T cell responses at 16-18 weeks after mild or asymptomatic SARS-CoV-2 infection.

Prognosis

11. Development and external validation of a COVID-19 mortality risk prediction algorithm: a multicentre retrospective cohort study. Mei J, Hu W, Chen Q, Li C, Chen Z, Fan Y, Tian S, Zhang Z, Li B, Ye Q, Yue J, Wang QL. BMJ Open. 2020 Dec 24;10(12):e044028. doi: 10.1136/bmjopen-2020-044028. https://bmjopen.bmj.com/content/10/12/e044028
METHODS: The model discrimination was assessed by the area under the receiver operating characteristic curve (AUC) and Somers' D test, and calibration was examined by the calibration plot. Decision curve analysis was conducted.
MAIN OUTCOME MEASURES: The primary outcome was all-cause mortality within 60 days after the diagnosis of COVID-19.
RESULTS: The full model included seven predictors of age, respiratory failure, white cell count, lymphocytes, platelets, D-dimer and lactate dehydrogenase. The simple model contained five indicators of age, respiratory failure, coronary heart disease, renal failure and heart failure. After cross-validation, the AUC statistics based on derivation cohort were 0.96 (95% CI, 0.96 to 0.97) for the full model and 0.92 (95% CI, 0.89 to 0.95) for the simple model. The AUC statistics based on the external validation cohort were 0.97 (95% CI, 0.96 to 0.98) for the full model and 0.88 (95% CI, 0.80 to 0.96) for the simple model. Good calibration accuracy of these two models was found in the derivation and validation cohort.
CONCLUSION: The prediction models showed good model performance in identifying patients with COVID-19 with a high risk of death in 60 days. It may be useful for acute risk classification.
WEB CALCULATOR: We provided a freely accessible web calculator (https://www.whuyijia.com/).

12. Prospective Latin American cohort evaluating outcomes of patients with COVID-19 and abnormal liver tests on admission. Mendizabal M, Piñero F, et al. Ann Hepatol. 2020 Dec 21:100298. doi: 10.1016/j.aohep.2020.100298. Online ahead of print.
https://www.clinicalkey.com/#!/content/journal/1-s2.0-S1665268120302234
MATERIALS & METHODS: We performed a prospective cohort study including 1611 hospitalized patients with confirmed SARS-CoV-2 infection from April 15, 2020 through July 31, 2020 in 38 different Hospitals from 11 Latin American countries. We registered clinical and laboratory parameters, including liver function tests, on admission and during hospitalization. All patients were followed until discharge or death. We fit multivariable logistic regression models, further post-estimation effect through margins and inverse probability weighting.
RESULTS: Overall, 57.8% of the patients were male with a mean age of 52.3 years, 8.5% had chronic liver disease and 3.4% had cirrhosis. Abnormal liver tests on admission were present on 45.2% (CI 42.7-47.7) of the cohort (n = 726). Overall, 15.1% (CI 13.4-16.9) of patients died (n = 244). Patients with abnormal liver tests on admission presented higher mortality 18.7% (CI 15.9-21.7), compared to those with normal liver biochemistries 12.2% (CI 10.1-14.6); P < .0001. After excluding patients with history of chronic liver disease, abnormal liver tests on admission were independently associated with death

[OR 1.5 (CI 1.1-2.0); P = 0.01], and severe COVID-19 (2.6 [2.0-3.3], P < .0001), both adjusted by age, gender, diabetes, pneumonia and body mass index >30.
CONCLUSIONS: The presence of abnormal liver tests on admission is independently associated with mortality and severe COVID-19 in hospitalized patients with COVID-19 infection and may be used as surrogate marker of inflammation.
CLINICALTRIALS.GOV: NCT04358380.

13. Association of frailty and mortality in patients with COVID-19: a meta-analysis. Kow CS, Hasan SS, Thiruchelvam K, Aldeyab M. Br J Anaesth. 2020 Dec 5:S0007-0912(20)30962-4. doi: 10.1016/j.bja.2020.12.002. Online ahead of print.
https://bjanaesthesia.org/article/S0007-0912(20)30962-4/fulltext
Studies that were not included in meta-analyses also demonstrated a significant association between frailty status (regardless of degrees of frailty) and higher odds of mortality, and significant association between increasing level of frailty and a higher hazard of mortality. Our findings indicate that increased risk of mortality spanned the continuum of frailty in patients with COVID-19, and hence Clinical Frailty Scale or other validated frailty assessment tools can be useful in prioritising allocation of critical care resources for patients with COVID-19.

14. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. McGurnaghan SJ, Weir A, et al. Lancet Diabetes Endocrinol. 2020 Dec 23:S2213-8587(20)30405-8. doi: 10.1016/S2213-8587(20)30405-8. Online ahead of print.
https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30405-8/fulltext
FINDINGS: Of the total Scottish population on March 1, 2020 (n=5 463 300), the population with diabetes was 319 349 (5·8%), 1082 (0·3%) of whom developed fatal or critical care unit-treated COVID-19 by July 31, 2020, of whom 972 (89·8%) were aged 60 years or older. In the population without diabetes, 4081 (0·1%) of 5 143 951 people developed fatal or critical care unit-treated COVID-19. As of July 31, the overall odds ratio (OR) for diabetes, adjusted for age and sex, was 1·395 (95% CI 1·304-1·494; p<0·0001, compared with the risk in those without diabetes. The OR was 2·396 (1·815-3·163; p<0·0001) in type 1 diabetes and 1·369 (1·276-1·468; p<0·0001) in type 2 diabetes. Among people with diabetes, adjusted for age, sex, and diabetes duration and type, those who developed fatal or critical care unit-treated COVID-19 were more likely to be male, live in residential care or a more deprived area, have a COVID-19 risk condition, retinopathy, reduced renal function, or worse glycaemic control, have had a diabetic ketoacidosis or hypoglycaemia hospitalisation in the past 5 years, be on more anti-diabetic and other medication (all p<0·0001), and have been a smoker (p=0·0011). The cross-validated predictive model of fatal or critical care unit-treated COVID-19 in people with diabetes had a C-statistic of 0·85 (0·83-0·86).
INTERPRETATION: Overall risks of fatal or critical care unit-treated COVID-19 were substantially elevated in those with type 1 and type 2 diabetes compared with the background population. The risk of fatal or critical care unit-treated COVID-19, and therefore the need for special protective measures, varies widely among those with diabetes but can be predicted reasonably well using previous clinical history.

15. Evaluating a Widely Implemented Proprietary Deterioration Index Model among Hospitalized COVID-19 Patients. Singh K, Valley TS, Tang S, Li BY, Kamran F, Sjoding MW, Wiens J, Otles E, Donnelly JP, Wei MY, McBride JP, Cao J, Penoza C, Ayanian JZ, Nallamothu BK. Ann Am Thorac Soc. 2020 Dec 24. doi: 10.1513/AnnalsATS.202006-698OC. Online ahead of print.
https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.202006-698OC

METHODS: We studied adult patients admitted with COVID-19 to non-ICU care at a large academic medical center from March 9 through May 20, 2020. We used the EDI, calculated at 15-minute intervals, to predict a composite outcome of ICU-level care, mechanical ventilation, or in-hospital death. In a subset of patients hospitalized for at least 48 hours, we also evaluated the ability of the EDI to identify patients at low risk of experiencing this composite outcome during their remaining hospitalization.

RESULTS: Among 392 COVID-19 hospitalizations meeting inclusion criteria, 103 (26%) met the composite outcome. Median age of the cohort was 64 (IQR 53-75) with 168 (43%) Black patients and 169 (43%) women. Area under the receiver-operating-characteristic curve (AUC) of the EDI was 0.79 (95% CI 0.74-0.84). EDI predictions did not differ by race or sex. When exploring clinically-relevant thresholds of the EDI, we found patients who met or exceeded an EDI of 68.8 made up 14% of the study cohort and had a 74% probability of experiencing the composite outcome during their hospitalization with a sensitivity of 39% and a median lead time of 24 hours from when this threshold was first exceeded. Among the 286 patients hospitalized for at least 48 hours who had not experienced the composite outcome, 14 (13%) never exceeded an EDI of 37.9, with a negative predictive value of 90% and a sensitivity above this threshold of 91%.

CONCLUSIONS: We found the EDI identifies small subsets of high- and low-risk COVID-19 patients with good discrimination although its clinical utility as an early warning system is limited by low sensitivity. These findings highlight the importance of independent evaluation of proprietary models before widespread operational use among COVID-19 patients.

Therapeutics

16. Effect of a Lower vs Higher Positive End-Expiratory Pressure Strategy on Ventilator-Free Days in ICU Patients Without ARDS: A Randomized Clinical Trial. Writing Committee and Steering Committee for the RELAx Collaborative Group, Algera AG, Pisani L, Serpa Neto A, den Boer SS, Bosch FFH, Bruin K, Klooster PM, Van der Meer NJM, Nowitzky RO, Purmer IM, Slabbekoorn M, Spronk PE, van Vliet J, Weenink JJ, Gama de Abreu M, Pelosi P, Schultz MJ, Paulus F. JAMA. 2020 Dec 22;324(24):2509-2520.
https://jamanetwork.com/journals/jama/fullarticle/2774078

Abstract: Noninferiority randomized clinical trial conducted from October 26, 2017, through December 17, 2019, in 8 intensive care units (ICUs) in the Netherlands among 980 patients without ARDS expected not to be extubated within 24 hours after start of ventilation. Final follow-up was conducted in March 2020. Participants were randomized to receive invasive ventilation using either lower PEEP, consisting of the lowest PEEP level between 0 and 5 cm H2O (n = 476), or higher PEEP, consisting of a PEEP level of 8 cm H2O (n = 493). The primary outcome was the number of ventilator-free days at day 28, with a noninferiority margin for the difference in ventilator-free days at day 28 of -10%. Secondary outcomes included ICU and hospital lengths of stay; ICU, hospital, and 28- and 90-day mortality; development of ARDS, pneumonia, pneumothorax, severe atelectasis, severe hypoxemia, or need for rescue therapies for hypoxemia; and days with use of vasopressors or sedation.

Results: Among 980 patients who were randomized, 969 (99%) completed the trial (median age, 66 [interquartile range {IQR}, 56-74] years; 246 [36%] women). At day 28, 476 patients in the lower PEEP group had a median of 18 ventilator-free days (IQR, 0-27 days) and 493 patients in the higher PEEP group had a median of 17 ventilator-free days (IQR, 0-27 days) (mean ratio, 1.04; 95% CI, 0.95-∞; P = .007 for noninferiority), and the lower boundary of the 95% CI was within the noninferiority margin. Occurrence of severe hypoxemia was 20.6% vs 17.6% (risk ratio, 1.17; 95% CI, 0.90-1.51; P = .99) and need for rescue strategy was 19.7% vs 14.6% (risk ratio, 1.35; 95% CI, 1.02-1.79; adjusted P = .54) in patients in the lower and higher PEEP groups, respectively. Mortality at 28 days was 38.4% vs 42.0% (hazard ratio, 0.89; 95% CI, 0.73-1.09; P = .99) in patients in the lower and higher PEEP groups, respectively. There were no statistically significant differences in other secondary outcomes.

Conclusions and relevance: Among patients in the ICU without ARDS who were expected not to be extubated within 24 hours, a lower PEEP strategy was noninferior to a higher PEEP strategy with regard to the number of ventilator-free days at day 28. These findings support the use of lower PEEP in patients without ARDS.

17. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. Rentsch CT, DeVito NJ, MacKenna B, et al. Lancet Rheumatol. 2020 Nov 5. doi: 10.1016/S2665-9913(20)30378-7. Online ahead of print.
https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30378-7/fulltext
FINDINGS: Between Sept 1, 2019, and March 1, 2020, of 194 637 people with rheumatoid arthritis or systemic lupus erythematosus, 30 569 (15·7%) received two or more prescriptions of hydroxychloroquine. Between March 1 and July 13, 2020, there were 547 COVID-19 deaths, 70 among hydroxychloroquine users. Estimated standardised cumulative COVID-19 mortality was 0·23% (95% CI 0·18 to 0·29) among users and 0·22% (0·20 to 0·25) among non-users; an absolute difference of 0·008% (-0·051 to 0·066). After accounting for age, sex, ethnicity, use of other immunosuppressive drugs, and geographical region, no association with COVID-19 mortality was observed (HR 1·03, 95% CI 0·80 to 1·33). We found no evidence of interactions with age or other immunosuppressive drugs. Quantitative bias analyses indicated that our observed associations were robust to missing information for additional biologic treatments for rheumatological disease. We observed similar associations with the negative control outcome of non-COVID-19 mortality.
INTERPRETATION: We found no evidence of a difference in COVID-19 mortality among people who received hydroxychloroquine for treatment of rheumatological disease before the COVID-19 outbreak in England. Therefore, completion of randomised trials investigating pre-exposure prophylactic use of hydroxychloroquine for prevention of severe outcomes from COVID-19 are warranted.

18. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. ACTIV-3/TICO LY-CoV555 Study Group. NEJM 2020 Dec 22. DOI: 10.1056/NEJMoa2033130
https://www.nejm.org/doi/full/10.1056/NEJMoa2033130
METHODS In this platform trial of therapeutic agents, we randomly assigned hospitalized patients who had Covid-19 without end-organ failure in a 1:1 ratio to receive either LY-CoV555 or matching placebo. In addition, all the patients received high-quality supportive care as background therapy, including the

antiviral drug remdesivir and, when indicated, supplemental oxygen and glucocorticoids. LY-CoV555 (at a dose of 7000 mg) or placebo was administered as a single intravenous infusion over a 1-hour period. The primary outcome was a sustained recovery during a 90-day period, as assessed in a time-to-event analysis. An interim futility assessment was performed on the basis of a seven-category ordinal scale for pulmonary function on day 5.

RESULTS On October 26, 2020, the data and safety monitoring board recommended stopping enrollment for futility after 314 patients (163 in the LY-CoV555 group and 151 in the placebo group) had undergone randomization and infusion. The median interval since the onset of symptoms was 7 days (interquartile range, 5 to 9). At day 5, a total of 81 patients (50%) in the LY-CoV555 group and 81 (54%) in the placebo group were in one of the two most favorable categories of the pulmonary outcome. Across the seven categories, the odds ratio of being in a more favorable category in the LY-CoV555 group than in the placebo group was 0.85 (95% confidence interval [CI], 0.56 to 1.29; P=0.45). The percentage of patients with the primary safety outcome (a composite of death, serious adverse events, or clinical grade 3 or 4 adverse events through day 5) was similar in the LY-CoV555 group and the placebo group (19% and 14%, respectively; odds ratio, 1.56; 95% CI, 0.78 to 3.10; P=0.20). The rate ratio for a sustained recovery was 1.06 (95% CI, 0.77 to 1.47).

CONCLUSIONS Monoclonal antibody LY-CoV555, when coadministered with remdesivir, did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure. (Funded by Operation Warp Speed and others; TICO ClinicalTrials.gov number, NCT04501978. opens in new tab.)

19. Role of Low-Molecular-Weight Heparin in Hospitalized Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia: A Prospective Observational Study. Falcone M, Tiseo G, et al. Open Forum Infect Dis. 2020 Nov 19;7(12):ofaa563. doi: 10.1093/ofid/ofaa563. eCollection 2020 Dec. https://academic.oup.com/ofid/article/7/12/ofaa563/5992463

BACKGROUND: This study was conducted to evaluate the impact of low-molecular-weight heparin (LMWH) on the outcome of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia.

METHODS: This is a prospective observational study including consecutive patients with laboratory-confirmed SARS-CoV-2 pneumonia admitted to the University Hospital of Pisa (March 4-April 30, 2020). Demographic, clinical, and outcome data were collected. The primary endpoint was 30-day mortality. The secondary endpoint was a composite of death or severe acute respiratory distress syndrome (ARDS). Low-molecular-weight heparin, hydroxychloroquine, doxycycline, macrolides, antiretrovirals, remdesivir, baricitinib, tocilizumab, and steroids were evaluated as treatment exposures of interest. First, a Cox regression analysis, in which treatments were introduced as time-dependent variables, was performed to evaluate the association of exposures and outcomes. Then, a time-dependent propensity score (PS) was calculated and a PS matching was performed for each treatment variable.

RESULTS: Among 315 patients with SARS-CoV-2 pneumonia, 70 (22.2%) died during hospital stay. The composite endpoint was achieved by 114 (36.2%) patients. Overall, 244 (77.5%) patients received LMWH, 238 (75.5%) received hydroxychloroquine, 201 (63.8%) received proteases inhibitors, 150 (47.6%) received doxycycline, 141 (44.8%) received steroids, 42 (13.3%) received macrolides, 40 (12.7%) received baricitinib, 13 (4.1%) received tocilizumab, and 13 (4.1%) received remdesivir. At multivariate analysis, LMWH was associated with a reduced risk of 30-day mortality (hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.21-0.6; P < .001) and composite endpoint (HR, 0.61; 95% CI, 0.39-

0.95; P = .029). The PS-matched cohort of 55 couples confirmed the same results for both primary and secondary endpoint.

CONCLUSIONS: This study suggests that LMWH might reduce the risk of in-hospital mortality and severe ARDS in coronavirus disease 2019. Randomized controlled trials are warranted to confirm these preliminary findings.

20. Real-world prevalence and consequences of potential drug-drug interactions in the first-wave COVID-19 treatments. Martínez-López-de-Castro N, Samartín-Ucha M, Paradela-Carreiro A, Pérez-Landeiro A, et al. J Clin Pharm Ther. 2020 Dec 23. doi: 10.1111/jcpt.13337. Online ahead of print.
https://onlinelibrary.wiley.com/doi/full/10.1111/jcpt.13337

METHODS: Cohort, retrospective and single-centre study carried out in a third-level hospital. Adult patients, admitted with suspected COVID-19, that received at least one dose of hydroxychloroquine, lopinavir/ritonavir, interferon beta 1-b or tocilizumab and with any pDDIs according to "Liverpool Drug Interaction Group" between March and May 2020 were included. The possible consequences of pDDIs at the QTc interval level or any other adverse event according to the patient's medical record were analysed. A descriptive analysis was carried out to assess possible factors that may affect the QTc interval prolongation.

RESULTS AND DISCUSSION: Two hundred and eighteen (62.3%) patients of a total of 350 patients admitted with COVID-19 had at least one pDDI. There were 598 pDDIs. Thirty-eight pDDIs (6.3%) were categorized as not recommended or contraindicated. The mean value difference between baseline and pDDI posterior ECG was 412.3 ms ± 25.8 ms vs. 426.3 ms ± 26.7 ms; p < 0.001. Seven patients (5.7%) had a clinically significant alteration of QTc. A total of 44 non-cardiological events (7.3%) with a possible connection to a pDDI were detected.

WHAT IS NEW AND CONCLUSION: The number of pDDIs in patients admitted for COVID-19 in the first pandemic wave was remarkably high. However, clinical consequences occurred in a low percentage of patients. Interactions involving medications that would be contraindicated for concomitant administration are rare. Knowledge of these pDDIs and their consequences could help to establish appropriate therapeutic strategies in patients with COVID-19 or other diseases with these treatments.

21. Early use of nitazoxanide in mild Covid-19 disease: randomised, placebo-controlled trial. Rocco PRM, Silva PL, Cruz FF, Junior MACM, et al. Eur Respir J. 2020 Dec 24:2003725. doi: 10.1183/13993003.03725-2020. Online ahead of print.
https://erj.ersjournals.com/content/early/2020/12/17/13993003.03725-2020

Nitazoxanide is widely available and exerts broad-spectrum antiviral activity in vitro However, there is no evidence of its impact on SARS-CoV-2 infection. In a multicenter, randomised, double-blind, placebo-controlled trial, adult patients presenting up to 3 days after onset of Covid-19 symptoms (dry cough, fever, and/or fatigue) were enrolled. After confirmation of SARS-CoV2 infection by RT-PCR on a nasopharyngeal swab, patients were randomised 1:1 to receive either nitazoxanide (500 mg) or placebo, TID, for 5 days. The primary outcome was complete resolution of symptoms. Secondary outcomes were viral load, laboratory tests, serum biomarkers of inflammation, and hospitalisation rate. Adverse events were also assessed.From June 8 to August 20, 2020, 1575 patients were screened. Of these, 392 (198 placebo, 194 nitazoxanide) were analysed. Median time from symptom onset to first dose of study drug was 5 (4-5) days. At the 5-day study visit, symptom resolution did not differ between the nitazoxanide and placebo arms. Swabs collected were negative for SARS-CoV-2 in 29.9%

of patients in the nitazoxanide arm versus 18.2% in the placebo arm (p=0.009). Viral load was also reduced after nitazoxanide compared to placebo (p=0.006). The percent viral load reduction from onset to end of therapy was higher with nitazoxanide (55%) than placebo (45%) (p=0.013). Other secondary outcomes were not significantly different. No serious adverse events were observed.In patients with mild Covid-19, symptom resolution did not differ between nitazoxanide and placebo groups after 5 days of therapy. However, early nitazoxanide therapy was safe and reduced viral load significantly.

22. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, et al. N Engl J Med. 2020 Dec 22. doi: 10.1056/NEJMoa2033130. Online ahead of print.
https://www.nejm.org/doi/full/10.1056/NEJMoa2033130
RESULTS: On October 26, 2020, the data and safety monitoring board recommended stopping enrollment for futility after 314 patients (163 in the LY-CoV555 group and 151 in the placebo group) had undergone randomization and infusion. The median interval since the onset of symptoms was 7 days (interquartile range, 5 to 9). At day 5, a total of 81 patients (50%) in the LY-CoV555 group and 81 (54%) in the placebo group were in one of the two most favorable categories of the pulmonary outcome. Across the seven categories, the odds ratio of being in a more favorable category in the LY-CoV555 group than in the placebo group was 0.85 (95% confidence interval [CI], 0.56 to 1.29; P = 0.45). The percentage of patients with the primary safety outcome (a composite of death, serious adverse events, or clinical grade 3 or 4 adverse events through day 5) was similar in the LY-CoV555 group and the placebo group (19% and 14%, respectively; odds ratio, 1.56; 95% CI, 0.78 to 3.10; P = 0.20). The rate ratio for a sustained recovery was 1.06 (95% CI, 0.77 to 1.47).
CONCLUSIONS: Monoclonal antibody LY-CoV555, when coadministered with remdesivir, did not demonstrate efficacy among hospitalized patients who had Covid-19 without end-organ failure. (Funded by Operation Warp Speed and others; TICO ClinicalTrials.gov number, NCT04501978.).

Transmission / Infection Control

23. Assessment of Air Contamination by SARS-CoV-2 in Hospital Settings. Birgand G, Peiffer-Smadja N, Fournier S, Kerneis S, Lescure FX, Lucet JC. JAMA Netw Open. 2020 Dec 1;3(12):e2033232. doi: 10.1001/jamanetworkopen.2020.33232.
https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2774463
FINDINGS: Among 2284 records identified, 24 cross-sectional observational studies were included in the review. Overall, 82 of 471 air samples (17.4%) from close patient environments were positive for SARS-CoV-2 RNA, with a significantly higher positivity rate in intensive care unit settings (intensive care unit, 27 of 107 [25.2%] vs non-intensive care unit, 39 of 364 [10.7%]; P < .001). There was no difference according to the distance from patients (≤1 m, 3 of 118 [2.5%] vs >1-5 m, 13 of 236 [5.5%]; P = .22). The positivity rate was 5 of 21 air samples (23.8%) in toilets, 20 of 242 (8.3%) in clinical areas, 15 of 122 (12.3%) in staff areas, and 14 of 42 (33.3%) in public areas. A total of 81 viral cultures were performed across 5 studies, and 7 (8.6%) from 2 studies were positive, all from close patient environments. The median (interquartile range) SARS-CoV-2 RNA concentrations varied from 1.0×10^3 copies/m3 (0.4×10^3 to 3.1×10^3 copies/m3) in clinical areas to 9.7×10^3 copies/m3 (5.1×10^3 to 14.3×10^3

copies/m3) in the air of toilets or bathrooms. Protective equipment removal and patient rooms had high concentrations per titer of SARS-CoV-2 (varying from 0.9 × 103 to 40 × 103 copies/m3 and 3.8 × 103 to 7.2 × 103 TCID50/m3), with aerosol size distributions that showed peaks in the region of particle size less than 1 μm; staff offices had peaks in the region of particle size greater than 4 μm. CONCLUSIONS AND RELEVANCE: In this systematic review, the air close to and distant from patients with coronavirus disease 2019 was frequently contaminated with SARS-CoV-2 RNA; however, few of these samples contained viable viruses. High viral loads found in toilets and bathrooms, staff areas, and public hallways suggest that these areas should be carefully considered.

Vaccine

24. Covid-19 Vaccine Distribution: Work on Your Listening System. Andrews, S. & Seth Mohta, N. **[PSJH Author]** NEJM Catalyst. 2020 Dec. https://catalyst.nejm.org/doi/full/10.1056/CAT.20.0686
Sandra Andrews, the Senior Vice President and Chief Operating Officer of Clinical Care at Providence describes the strategy that Providence developed to prepare for their first round of Covid-19 vaccines, their teams of teams approach, learning their way forward by doing, and the importance of strong two-way communication to build trust in the health system.

25. National Trends in the US Public's Likelihood of Getting a COVID-19 Vaccine—April 1 to December 8, 2020. Szilagyi PG, Thomas K, Shah MD, et al.. JAMA. Published online December 29, 2020. doi:10.1001/jama.2020.26419
https://jamanetwork.com/journals/jama/fullarticle/2774711
Results: Between April 1-14 and November 25-December 8, the percentage who stated they were somewhat or very likely to get vaccinated declined from 74% to 56% (difference: 18 percentage points [95% CI, 16-20]) (Figure). Significant declines over time in the likelihood of seeking vaccination were observed for both women and men and in all age, racial/ethnic, and educational subgroups.

Women & Children

26. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatin AA, Gray KJ, Bordt EA, Shook LL, et al. JAMA Netw Open. 2020 Dec 1;3(12):e2030455. doi: 10.1001/jamanetworkopen.2020.30455.
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2774428
MAIN OUTCOMES AND MEASURES: The main outcomes were SARS-CoV-2 viral load in maternal plasma or respiratory fluids and umbilical cord plasma, quantification of anti-SARS-CoV-2 antibodies in maternal and cord plasma, and presence of SARS-CoV-2 RNA in the placenta.
RESULTS: Among 127 pregnant women enrolled, 64 with RT-PCR results positive for SARS-CoV-2 (mean [SD] age, 31.6 [5.6] years) and 63 with RT-PCR results negative for SARS-CoV-2 (mean [SD] age, 33.9 [5.4] years) provided samples for analysis. Of women with SARS-CoV-2 infection, 23 (36%) were asymptomatic, 22 (34%) had mild disease, 7 (11%) had moderate disease, 10 (16%) had severe disease, and 2 (3%) had critical disease. In viral load analyses among 107 women, there was no detectable viremia in maternal or cord blood and no evidence of vertical transmission. Among 77 neonates tested in whom SARS-CoV-2 antibodies were quantified in cord blood, 1 had detectable immunoglobuilin M to

nucleocapsid. Among 88 placentas tested, SARS-CoV-2 RNA was not detected in any. In antibody analyses among 37 women with SARS-CoV-2 infection, anti-receptor binding domain immunoglobin G was detected in 24 women (65%) and anti-nucleocapsid was detected in 26 women (70%). Mother-to-neonate transfer of anti-SARS-CoV-2 antibodies was significantly lower than transfer of anti-influenza hemagglutinin A antibodies (mean [SD] cord-to-maternal ratio: anti-receptor binding domain immunoglobin G, 0.72 [0.57]; anti-nucleocapsid, 0.74 [0.44]; anti-influenza, 1.44 [0.80]; P < .001). Nonoverlapping placental expression of SARS-CoV-2 receptors angiotensin-converting enzyme 2 and transmembrane serine protease 2 was noted.

CONCLUSIONS AND RELEVANCE: In this cohort study, there was no evidence of placental infection or definitive vertical transmission of SARS-CoV-2. Transplacental transfer of anti-SARS-CoV-2 antibodies was inefficient. Lack of viremia and reduced coexpression and colocalization of placental angiotensin-converting enzyme 2 and transmembrane serine protease 2 may serve as protective mechanisms against vertical transmission.

FDA / CDC / NIH/ WHO Updates

CDC - The Advisory Committee on Immunization Practices' Updated Interim Recommendation for Allocation of COVID-19 Vaccine — United States, December 2020

WHO - SARS-CoV-2 Variant – United Kingdom of Great Britain and Northern Ireland

WHO - Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages

Commentary & News

Covid-19: What have we learnt about the new variant in the UK? Mahase E. BMJ. 2020 Dec 23;371:m4944. doi: 10.1136/bmj.m4944.

More Than 2,900 Health Care Workers Died This Year — And the Government Barely Kept Track Kaiser Health News.

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