I hope everyone had a wonderful weekend.

Today I have chosen a review on vaccine response in pregnant and lactating women followed by biomarkers and risk stratification. The third and fourth articles are on remdesivir and the last is an article on combination therapy with steroids and tocilizumab in the elderly.

Have a great week

Ed

COVID-19 Vaccine Response in Pregnant and Lactating Women: A Cohort Study
AJOG published online March 26, 2021
doi.org/10.1016/j.ajog.2021.03.023
Because pregnant and lactating women were excluded from initial COVID-19 vaccine trials, data are lacking regarding vaccine efficacy and infant humoral protection in this population. The objective was to evaluate the immunogenicity and reactogenicity of COVID-19 mRNA vaccination in pregnant and lactating women compared to: (1) non-pregnant controls and (2) natural COVID-19 infection in pregnancy.

131 reproductive-age vaccine recipients (84 pregnant, 31 lactating, and 16 non- pregnant) were enrolled in a prospective cohort study at two academic medical centers. Titers of SARS-CoV-2 Spike and RBD IgG, IgA and IgM were quantified in participant sera (N=131) and breastmilk (N=31) at baseline, second vaccine dose, 2-6 weeks post second vaccine, and at delivery by Luminex. Umbilical cord sera (N=10) titers were assessed at delivery. Titers were compared to those of pregnant women 4-12 weeks from natural infection (N=37) by ELISA. A pseudovirus neutralization assay was used to quantify neutralizing antibody titers for the subset of women who delivered during the study period. Post-vaccination symptoms were assessed via questionnaire.

Vaccine-induced antibody titers were equivalent in pregnant and lactating compared to non-pregnant women (median [IQR] 5.59 [4.68-5.89] pregnant, 5.74 [5.06-6.22] lactating, 5.62 [4.77-5.98] non-pregnant, $p = 0.24$). All titers were significantly higher than those induced by SARS-CoV-2 infection during pregnancy ($p < 0.0001$). Vaccine-generated antibodies were present in all umbilical cord blood and breastmilk samples. Neutralizing antibody titers were lower in umbilical cord compared to maternal sera, although this finding did not achieve statistical significance. The second vaccine dose increased SARS-CoV-2-specific IgG, but not IgA, in maternal blood and breastmilk. No differences were noted in reactogenicity across the groups.

Comment: mRNA vaccines generated robust humoral immunity in pregnant and lactating women, with immunogenicity and reactogenicity similar to that observed in non-pregnant women. In addition, as has been reported by others, vaccine-induced immune responses were significantly greater than the response to natural infection which is why ACIP recommends persons who have recovered from natural SARS-CoV-2 infection should still be immunized. Future work examining T cells and other immune functions may provide additional insights on mRNA vaccine-induced immunity in pregnancy and lactation.

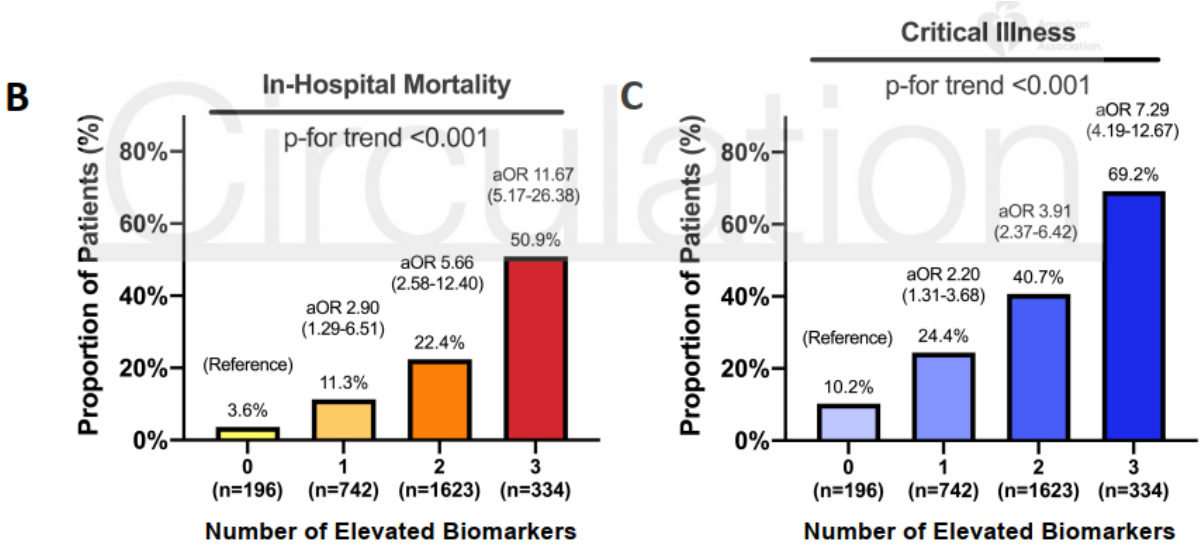
Multiple Biomarker Approach to Risk Stratification in COVID-19
Circulation published online February 15, 2021
Doi:10.1161/CIRCULATIONAHA.120.053311

Myocardial injury, thrombosis, and a systemic inflammatory response to SARS CoV-2 are common features of COVID-19, and biomarkers of each these processes (cardiac troponin [cTn], D-dimer and CRP, respectively) has been associated with disease severity and mortality. The aim of this study was to determine whether a constellation of biomarkers at admission would predict in-hospital clinical outcomes in patients with COVID-19.

Consecutive adults age ≥18 years with COVID-19 admitted to the NYU Langone Health (NYULH) system between March 1st and April 16th, 2020 were identified and included if cTn, D-dimer, and CRP were measured. Routine multi-marker surveillance was standard of care for patients with COVID-19; electronic admission order sets included cTn, D-Dimer, and CRP laboratory tests. Myocardial injury was defined as an initial cTn above the site-specific upper limit of normal (ULN). An elevated D-Dimer was defined based on the assay ULN (>230 ng/mL). Given that 98.5% of our hospitalized patients with COVID-19 had an initial CRP concentration above the ULN, we defined increased inflammation as a CRP >50 mg/L. This threshold was prognostically important in other studies. Demographics, comorbidities, medications, clinical presentation, and laboratory data were abstracted from the electronic health record. Comorbidities were defined by ICD-10 codes. All-cause, in-hospital mortality was recorded. Critical illness was defined by receipt of intensive care, mechanical ventilation, transfer to hospice, or death.

A total of 3,281 consecutive adults with COVID-19 were identified and 2,895 (88.2%) had measurement of all 3 biomarkers (cTn: median 0.015 ng/mL, D-Dimer: median 403 ng/mL, and CRP: median 113 mg/L) at admission. Myocardial injury was present in 486 (16.8%) patients, D-Dimer level was elevated in 2,243 (77.5%), and CRP was >50 mg/L in 2,261 (78.1%). Only 196 (6.8%) patients had normal cTn, D-dimer, and had CRP<50 mg/L ("no elevated biomarkers"). Elevations of all 3 biomarkers were present in only 334 (11.5%). Patients with no elevated biomarkers were at low risk of critical illness and in-hospital mortality. Continuous CRP (C-statistic 0.611, 95% CI 0.587-0.634), D-dimer (C-statistic 0.639, 95% CI 0.615-0.664), and troponin (C-statistic 0.680, 95% CI 0.655- 0.705) concentrations were each separately associated with mortality.

Patients with 1, 2, and 3 elevated biomarkers had 3-fold, 6-fold, and 11-fold higher adjusted odds of death compared to COVID-19 patients with no elevated biomarkers at presentation.



Comment: These findings support prior observations on the prognostic nature of these biomarkers in COVID-19 and provide a framework for estimating risk. This study was retrospective and selection bias cannot be excluded. Only in-hospital events were recorded.

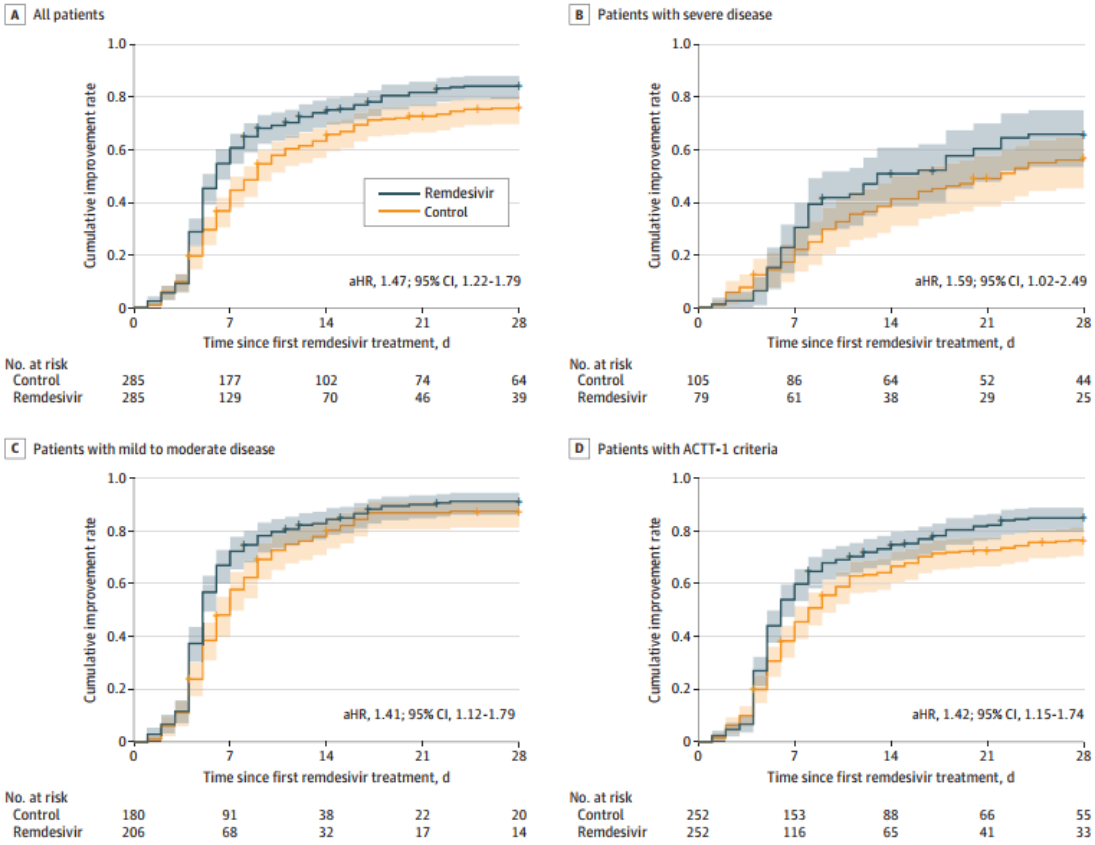
Comparison of Time to Clinical Improvement With vs Without Remdesivir Treatment in Hospitalized Patients with COVID-19

JAMA Netw Open published online March 24, 2021
doi:10.1001/jamanetworkopen.2021.3071

This retrospective comparative effectiveness research study was conducted from March 4 to August 29, 2020, in a 5-hospital health system. Of 2483 individuals with confirmed SARS-CoV-2 infection assessed by PCR, those who received remdesivir were matched to infected individuals who did not receive remdesivir using time invariant covariates (age, sex, race/ethnicity, Charlson Comorbidity Index, body mass index, and do-not-resuscitate or do-not-intubate orders) and time-dependent covariates (ratio of peripheral blood oxygen saturation to fraction of inspired oxygen, blood pressure, pulse, temperature, respiratory rate, CRP level, complete white blood cell count, lymphocyte count, albumin level, alanine aminotransferase level, glomerular filtration rate, D-dimer level, and oxygen device. The primary outcome was rate of clinical improvement (hospital discharge or decrease of 2 points on the World Health Organization severity score), and the secondary outcome, mortality at 28 days. An additional outcome was clinical improvement and time to death associated with combined remdesivir and corticosteroid treatment. Patients prescribed remdesivir were required to have significant illness (oxygen saturation 94% breathing ambient air or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation) and have an alanine aminotransferase level less than 5 times the upper reference limit.

Of 2483 consecutive admissions, 342 individuals received remdesivir, 184 of whom also received corticosteroids and 158 of whom received remdesivir alone. For these 342 patients, the median age was 60 years (interquartile range, 46-69 years), 189 (55.3%) were men, and 276 (80.7%) self-identified as non-White race/ethnicity. Remdesivir recipients had a shorter time to clinical improvement than matched controls without remdesivir treatment (median, 5.0 days [interquartile range, 4.0-8.0 days] vs 7.0 days [interquartile range, 4.0-10.0 days]; adjusted hazard ratio, 1.47 [95% CI, 1.22-1.79]). Remdesivir recipients had a 28-day mortality rate of 7.7% (22 deaths) compared with 14.0% (40 deaths) among matched controls, but this difference was not statistically significant in the time-to-death analysis (adjusted hazard ratio, 0.70; 95% CI, 0.38-1.28). The addition of corticosteroids to remdesivir was not associated with a reduced hazard of death at 28 days (adjusted hazard ratio, 1.94; 95% CI, 0.67-5.57).

Figure 2. Time to Clinical Improvement



Comment: The FDA approved the use of remdesivir for the treatment of hospitalized patients with COVID-19 based mostly on the results of the ACTT-1 trial, whereas WHO recommended against the use of remdesivir based on results from the Solidarity trial. Both of these trials were RCTs. This trial was a retrospective analysis using a time-dependent propensity score method to produce matched sets in which patients were very similar on measured confounders. However, as with any retrospective propensity analysis there can be unmeasured variables that biased treatment effect estimates. Although there was no significant reduction in the hazard of death for patients who received both remdesivir and corticosteroids, the small numbers of events may have prevented the investigators from detecting a benefit. The increased median time to death and the higher number of severely ill patients in the combination group suggest that the combination group was in fact more severely ill and may have derived some benefit from the addition of corticosteroids that was not accounted for in the marginal structural model. A deeper dive indicates Remdesivir recipients who breathed ambient air initially or received oxygen via nasal cannula reached clinical improvement after a median of 5 days, compared with 6 days in controls (aHR, 1.41). Likewise, severely ill patients needing a higher level of respiratory support achieved clinical improvement after a median of 8 days, versus 9 days in controls (aHR, 1.59). Rates of death by 28 days were not significantly different between the two groups. Duration of symptoms were not included. The number of patients in this analysis was modest. An interesting aspect of the study was that 276 (80.7%) self-identified as non-White race/ethnicity a much higher percentage than other studies. In the end the authors believe patients with milder disease are likely to benefit the most. See below.

Clinical Efficacy and Safety of Remdesivir in Patients with COVID-19: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

J Antimicrob Chemother published online a March 2021
doi:10.1093/jac/dkab093

Five RCTs, including 13,544 patients, were included in this meta-analysis. Among them, 3839 and 391 patients were assigned to the 10-day and 5-day remdesivir regimens, respectively. Patients receiving 5-day remdesivir therapy presented greater clinical improvement than those in the control group [OR = 1.68 (95% CI 1.18–2.40)], with no significant difference observed between the 10-day and placebo groups [OR = 1.23 (95% CI 0.90–1.68)]. Patients receiving remdesivir revealed a greater likelihood of discharge [10-day remdesivir versus control: OR = 1.32 (95% CI 1.09–1.60); 5-day remdesivir versus control: OR = 1.73 (95% CI 1.28–2.35)] and recovery [10-day remdesivir versus control: OR = 1.29 (95% CI 1.03–1.60); 5-day remdesivir versus control: OR = 1.80 (95% CI 1.31–2.48)] than those in the control group. In contrast, no mortality benefit was observed following remdesivir therapy. Furthermore, no significant association was observed between remdesivir treatment and an increased risk of adverse events.

Comment: Remdesivir can help improve the clinical outcome of hospitalized patients with COVID-19 and a 5-day regimen, instead of a 10-day regimen, may be sufficient for treatment. This review demonstrated a positive impact of remdesivir treatment on clinical outcomes of hospitalized COVID-19 patients. The consistent finding was a shorter time to clinical improvement and recovery was observed in patients receiving remdesivir than in the control group, although patients receiving remdesivir treatment were associated with a lower risk of mortality than the control group, the difference was not statistically significant. I think the ACTT-1 post hoc analysis probably is the best guidance on where remdesivir is likely to make a difference:

- The benefit of remdesivir for reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 435; recovery rate ratio 1.45; 95% CI, 1.18–1.79). In a post hoc analysis of deaths by Day 15, remdesivir appeared to confer a survival benefit in this subgroup (HR for death 0.28; 95% CI, 0.12–0.66).
- In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 193), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09, 95% CI, 0.76–1.57). In a post hoc analysis of deaths by Day 15, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 0.82; 95% CI, 0.40–1.69).
- Among the patients who were on mechanical ventilation or ECMO at study enrollment (ordinal scale 7, n = 285), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.98; 95% CI, 0.70–1.36). In a post hoc analysis of deaths by Day 15, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 0.76; 95% CI, 0.39–1.50).

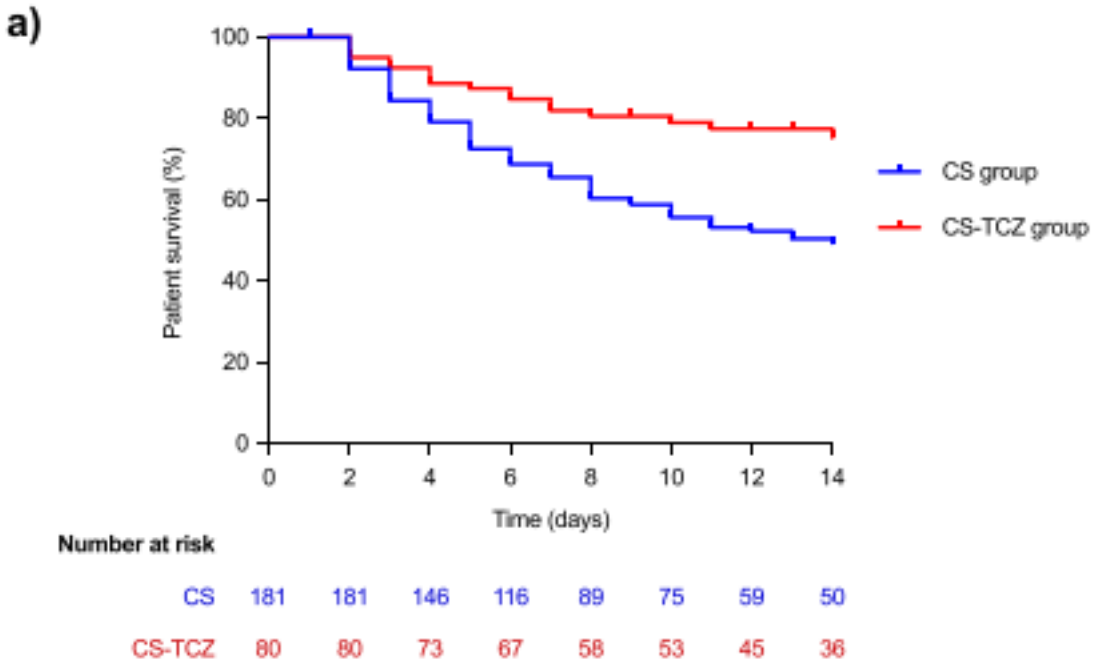
The ACP said remdesivir should not be started in hospitalized COVID-19 patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) since these patients have likely moved from the viral to the inflammatory stage of the disease. IDSA also states remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.

Combination Therapy with Tocilizumab and Corticosteroids for Aged Patients with Severe COVID-19 Pneumonia: A Single-Center Retrospective Study

Int J Infect Dis 2021; 105:476-494
doi.org/10.1016/j.ijid.2021.02.099

This retrospective single-center study was conducted on consecutive patients aged 65 years who developed severe COVID-19 between 03 March and 01 May 2020 and were treated with corticosteroids at various doses (methylprednisolone 0.5 mg/kg/12 h to 250 mg/24 h), either alone (CS group) or associated with intravenous tocilizumab (400–600 mg, one to three doses) (CS-TCZ group). The primary outcome was all-cause mortality by day +14, whereas secondary outcomes included mortality by day +28 and clinical improvement (discharge and/or a 2-point decrease on a 6-point ordinal scale) by day +14. Propensity score (PS)-based adjustment and inverse probability of treatment weights (IPTW) were used for statistical analysis.

Totals of 181 and 80 patients were included in the CS and CS-TCZ groups, respectively. All-cause 14-day mortality was lower in the CS-TCZ group, both in the PS-adjusted (hazard ratio [HR]: 0.34; 95% confidence interval [CI]: 0.17–0.68; P = 0.002) and IPTW-weighted models (odds ratio [OR]: 0.38; 95% CI: 0.21–0.68; P = 0.001). This protective effect was also observed for 28-day mortality (PS-adjusted HR: 0.38; 95% CI: 0.21–0.72; P = 0.003). Clinical improvement by day +14 was higher in the CS-TCZ group with IPTW analysis only (OR: 2.26; 95% CI: 1.49–3.41; P < 0.001). The occurrence of secondary infection was similar between both groups.



Comment: This study had a number of limitations. First, AS WITH ANY retrospective observational design, the impact of unmeasured confounders cannot be completely ruled out, despite PS-based and IPTW adjustments. There were baseline imbalances since patients in the CS group were older and had a higher burden of comorbidities (including chronic lung disease and dementia), whereas those in the CS-TCZ group showed increased disease severity by day 0 (as suggested by lower SpO2/ FiO2 ratio and lymphocyte counts and higher LDH levels). More patients were admitted to the ICU in the CS-TCZ group

than in the CS group, likely reflecting their younger age. However, no significant differences in mortality rates were found between patients admitted to the ICU and those staying in a hospital ward. Most of the patients were treated before publication of the results from the RECOVERY Trial on use of dexamethasone and therefore low-to-intermediate-dose dexamethasone was less commonly used than methylprednisolone boluses. Very few patients were on remdesivir and overall number of patients were moderate. They also dosed TCZ in 3 doses. However, their experience suggests that the use of IV TCZ on top of corticosteroid therapy may be more useful than corticosteroids alone to improve outcomes in patients aged 65 years with hyperinflammatory status triggered by SARS-CoV-2 infection.

With the REMAP CAP and RECOVERY trials (RCTs) reviewed in the Briefing several weeks ago, both the NIH and IDSA now recommend the use of tocilizumab (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) in combination with dexamethasone within the prior 24 hours who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO_2/30 L/min of oxygen flow).