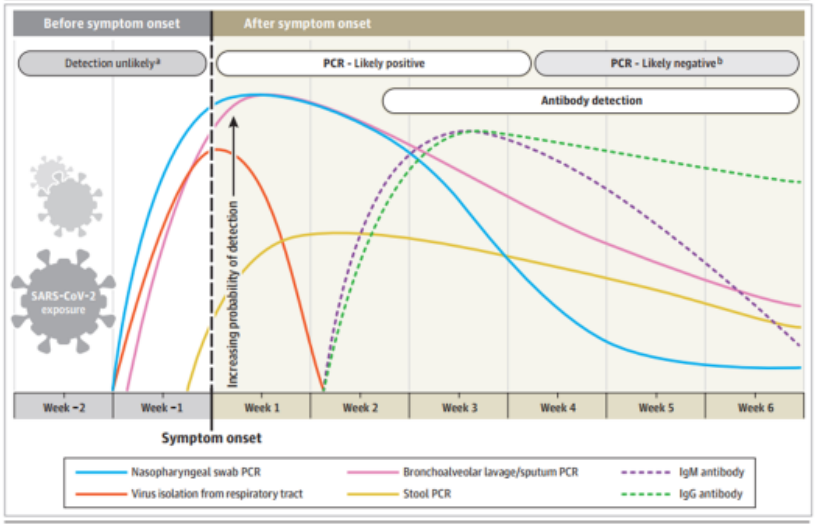
VIIs editorial on Convalescent Plasma: (see article below) This rush to treat with plasma has inadvertently undermined research which could provide clear evidence in well-designed RCTs. The push to distribute plasma to seriously ill patients as quickly as possible has come at a cost of enrolling and completing well designed clinical trials. This past weekend the FDA heard testimony from researches running a large national study. (Mayo Clinic) They reported hospitalized Covid-19 patients who received plasma reduced their mortality rate by about 50%. The researchers said they saw signs that the treatment might be working in patients who received plasma early in the course of their illness. They based their conclusions on an analysis of about 3,000 patients. Patients who at three days or less after diagnosis received plasma containing high levels of antibodies against the coronavirus had a mortality rate of 6.6% at seven days after the transfusion. That compared with a mortality rate of 13.3% for patients who got plasma at four days or more after diagnosis. At 30 days after transfusion, the mortality rate was reduced by about 36%, investigators reported. Although this is an observational trial, there is a positive signal for patients who received high tittered plasma early rather than late which confirms other observational trials. RCTs are underway. Although plasma may have a role, the development of monoclonal antibodies may be a much better interim solution until a vaccine is available.

Convalescent Plasma for COVID-19. A randomized clinical trial

MedRxiv published online July 3, 2020, article provided by Malar Narayanan

This study was a randomized trial comparing convalescent plasma with standard of care therapy in patients hospitalized for COVID-19. Patients were randomized 1:1 and received 300ml of plasma with anti-SARS CoV-2 neutralizing antibody titers of at least 1:80. The primary endpoint was day-60 mortality and key secondary endpoints were hospital stay and WHO 8-point disease severity scale improvement on day 15. Patients with a documented IgA deficiency or on mechanical ventilation for >96 hours were excluded. The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline.[almost all SARS-CoV-2 infected patients have antibodies by day 14-see figure below] A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40). These observations caused concerns about the potential benefit of convalescent plasma in the study population and after discussion with the data safety monitoring board, the study was discontinued. No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.58) was observed between plasma treated patients and patients on standard of care.

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset



JAMA published online May 6, 2020

Comment: Most COVID-19 patients already have high neutralizing antibody titers at hospital admission. Looking at the timeline for infected patients who require hospitalization they are usually in the second week from time of infection. Trials to date suggest plasma more likely to be effective when given early in the course of disease. NIH guidelines state there is insufficient clinical data to recommend either for or against use of convalescent plasma. Today in JAMA the article reviewed in the Daily Briefing when posted online in June 2020 was officially published. (JAMA 2020; 324:460-470) To refresh readers memory, among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation was limited by early termination of the trial due to drop in cases, which may have been underpowered to detect a clinically important difference.

Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study

FEBS published online July 28, 2020

The study population included the 14,000 members of Leumit Health Services who were tested for COVID-19 infection from February 1st to April 30th, 2020, and who had at least one previous blood test for plasma 25(OH)D level. Suboptimal" or "low" plasma 25(OH)D level was defined as plasma 25-hydroxyvitamin D, or 25(OH)D, concentration below the level of 30 ng/mL.

Of 7,807 individuals, 782 (10.1%) were COVID-19-positive, and 7,025 (89.9%) COVID-19-negative. The mean plasma vitamin D level was significantly lower among those who tested positive than negative for COVID-19 [19.00 ng/mL (95% confidence interval [CI] 18.41-19.59) *vs.* 20.55 (95% CI 20.32-20.78)]. In Multivariate analyses that controlled for demographic variables, and psychiatric and somatic disorders, the adjusted OR of COVID-19 infection [1.45 (95% CI 1.08-1.95, p<0.001)], and of hospitalization due to the SARS-CoV-2 virus [1.95 (95% CI 0.98-4.845, p=0.061)] were preserved. In the multivariate analyses, age over 50 years, male gender and low-medium socioeconomic status were also

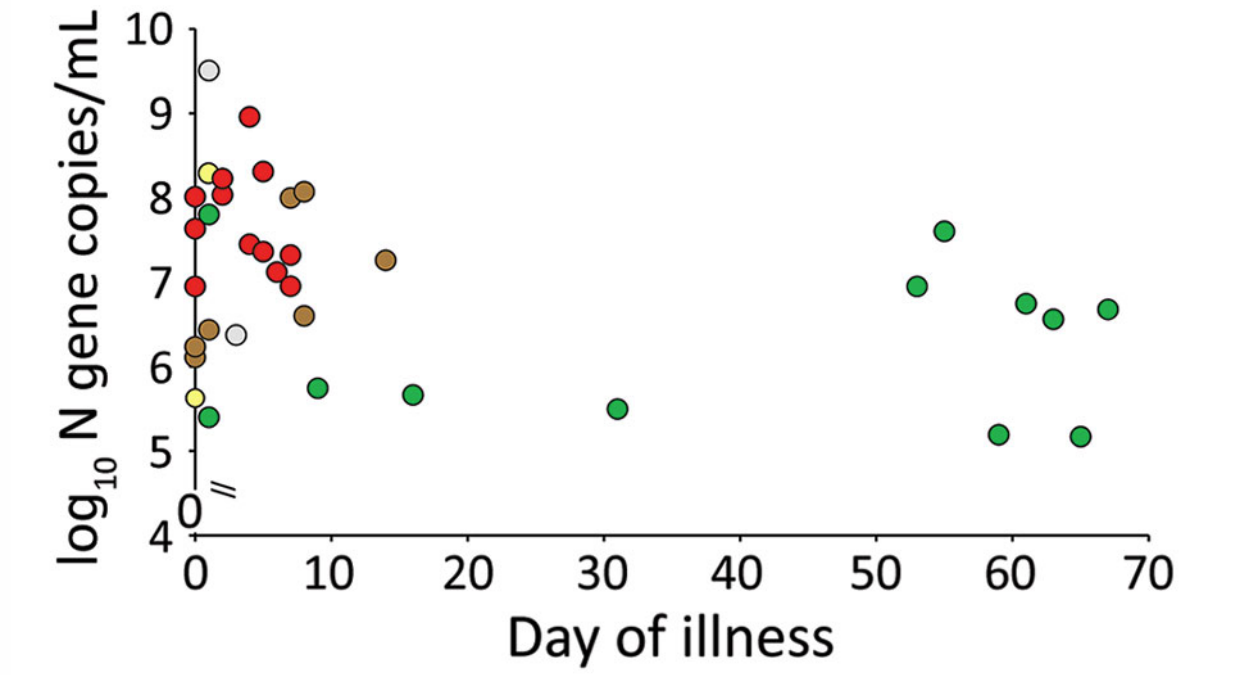
positively associated with the risk of COVID-19 infection; age over 50 years was positively associated with the likelihood of hospitalization due to COVID-19.

Comment: The impact of vitamin D metabolites on the immune system response, and on the development of COVID-19 infection has been described. Limited observational studies suggest an association between vitamin D levels and severity of SARS-CoV-2 infection with people with vitamin D deficiency at higher risk for severe disease. (MedRxiv April 30, 2020). A recent randomized double-blind trial of critically ill non-Covid-19 patients found no significant effect of vitamin D administration on 90-day mortality versus placebo. (N Engl J Med 2019; 381:2529) The NIH and NICE guidelines state there is insufficient evidence to support the use of vitamin D.

SARS-CoV-2 Virus Culture and Subgenomic RNA for Respiratory Specimens from Patients with Mild Coronavirus Disease

Emerg Infect Dis published online August 3, 2020

The investigators tested 68 respiratory specimens from 35 COVID-19 patients, of whom 32 had mild illness, found that live virus and evidence of viral replication were rarely detectable beyond 8 days after symptom onset, but that viral RNA was detectable for many weeks using RT-PCR. In addition to virus culture, specimens with a moderate to high viral load were also assessed for sgRNA to detect viral replication. Twelve of the 33 specimens (36.4%) were positive on both tests, while 12 were negative on both. Seven of 33 (21.2%) were positive for sgRNA but negative on culture, and 2 (6.1%) were positive on culture but negative for sgRNA. The researchers detected virus sgRNA in 18 of 22 specimens (81.8%) collected within 8 days after symptom onset and in 1 of 11 (9.1%) collected 9 or more days after illness onset.

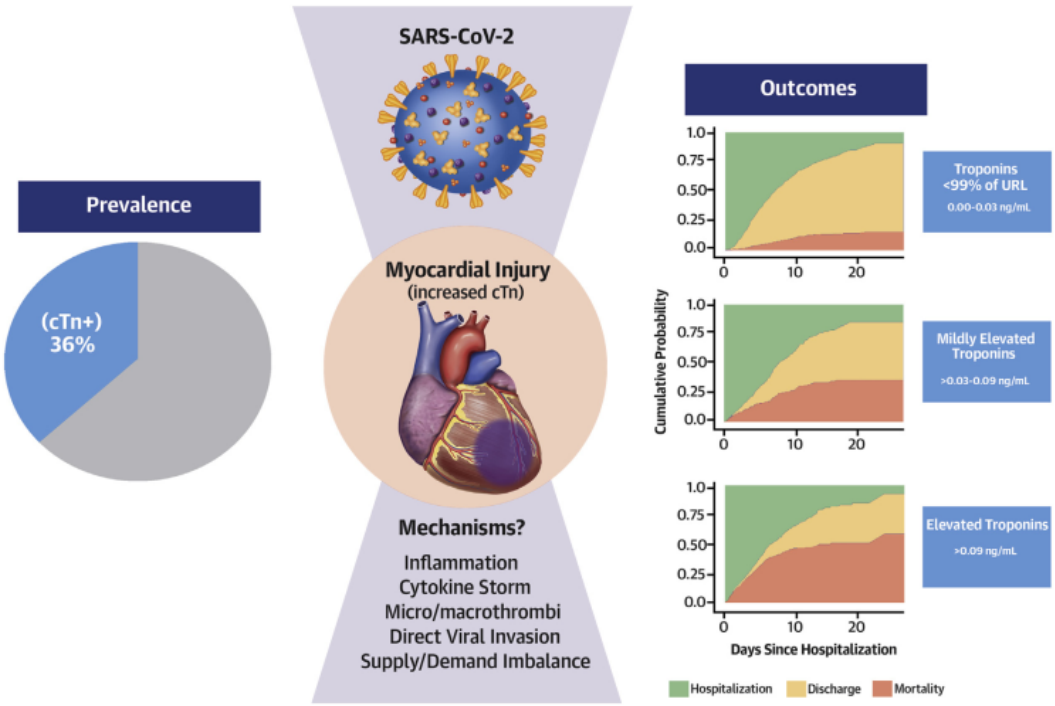


Severe acute respiratory syndrome coronavirus 2 viral RNA load, virus culture, and subgenomic virus RNA (sgRNA) in relation to days after onset of illness for patients with mild coronavirus disease, Hong Kong. Red indicates culture and sgRNA positive, green indicates culture and sgRNA negative, yellow indicates culture positive and sgRNA negative, brown indicates culture negative and sgRNA positive, and gray indicates culture positive and no sgRNA data (because of insufficient specimen).

Comment: The findings suggest that virus isolation and sgRNA detection were positive within the first 8 days after onset of illness and mainly for specimens with ≥6 $\log_{10}$ virus N gene copies/mL of clinical specimen. Two other studies of virus culture for mildly ill or moderately ill patients showed virus culture was only successful within the first 9 days after onset of illness (Nature. 2020; 581:465–9. Clin Infect Dis. Published online May 22, 2020) Patients who are severely ill and immunocompromised might shed infectious virus for much longer periods, and this shedding might also be prolonged by corticosteroid therapy. The CDC has now shifted to recommending a symptom-based approach over test based for releasing COVOID-19 patients from isolation based on these studies and others. For most patients, they can be released after 10 days from first symptom (and symptoms resolving) or if asymptomatic and test +, 10 days from the + test.

Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection
J Am Coll Cardiol 2020; 76:533-546
Patients with COVID-19 admitted to 1 of 5 Mount Sinai Health System hospitals in New York City between February 27, 2020, and April 12, 2020, with troponin-I (normal value <0.03 ng/ml) measured within 24 h of admission were included (n = 2,736). Demographics, medical histories, admission laboratory results, and outcomes were captured from the hospitals' electronic health records.

The median age was 66.4 years, with 59.6% men. Cardiovascular disease (CVD), including coronary artery disease, atrial fibrillation, and heart failure, was more prevalent in patients with higher troponin concentrations, as were hypertension and diabetes. A total of 506 (18.5%) patients died during hospitalization. In all, 985 (36%) patients had elevated troponin concentrations. After adjusting for disease severity and relevant clinical factors, even small amounts of myocardial injury (e.g., troponin I >0.03 to 0.09 ng/ml; n = 455; 16.6%) were significantly associated with death (adjusted hazard ratio: 1.75; 95% CI: 1.37 to 2.24; p < 0.001) while greater amounts (e.g., troponin I >0.09 ng/dl; n = 530; 19.4%) were significantly associated with higher risk (adjusted HR: 3.03; 95% CI: 2.42 to 3.80; p < 0.001)



Comment: Surprisingly, troponin levels were generally present at low levels. Although present as low-level concentrations, troponin elevation to >3 times the URL was associated with a 3-fold increased risk of mortality despite adjustment for clinically relevant factors. Patients with CVD are more likely to have myocardial injury than patients without CVD. Troponin elevation among patients hospitalized with COVID-19 is associated with higher risk of mortality. EHR for patient-level data was not verified by manual chart review. Use of anticoagulation and antiviral therapy was not included in part due to patient participation in clinical trials leading to incomplete data. Lastly, BNP levels were not available for more than two-thirds of the study cohort within 24 h of admission, and therefore, patterns in the context of myocardial injury could not be described.