Comments and Critique of CONCOR-1 Study by Begin *et al*. (1).

We read with interest the results of the CONCOR-1 study. The analysis showing a relationship between plasma titer and outcome is an important contribution to the emerging literature on the characteristics of effective COVID-19 convalescent plasma (CCP). However, we are concerned that the conclusion that low titer plasma can cause harm is not supported by the data on the paper. Of the more than 20 randomized controlled trials of CCP efficacy reported to date CONCOR-1 is the only one that reports a hint of potential harm. As detailed below, we think this conclusion is faulty and could have arisen from a combination of chance and flawed data analysis. Furthermore, we note that CONCOR-1 dates from the early days of the pandemic when many patients were treated with CCP late in disease, which differs from current practices and recommendations to use CCP early in hospitalization. We are worried that the overall negative tone of the report may give physicians pause when considering whether to use CCP in circumstances where it could prove helpful. Early in the course of hospitalization and in immunocompromised patients. Using plasma with adequate concentration of antibodies.

Precis. The results of Begin *et al* (1) are irrelevant to current clinical practice in the United States on the use of CCP, since the Food and Drug Administration (FDA) modified Emergency Use Authorization of February 2021(2), which requires early use of high titer plasma.

We detail our concerns below

1. The CCP study arm may have been sicker. Randomization ideally results in equivalent experimental and control cohorts but sometimes the groups can differ through no fault of the investigators. There is a suggestion that the CCP arm may have been sicker than the control arm, having a higher prevalence of abnormal CXRs (90.0% vs 85.0%, $p < .05$) and more participants in the ICU at randomization (19.2% vs. 16.9 %). A small difference in the severity of illness in the CCP group could have accounted for the small plurality in deaths among CP treated individuals.

2. Control group selection. The control group was standard of care, which must surely have varied in the 72 centers in 3 countries involved in CONCOR-1. Location-dependent differences in standard of care treatment that define the control group may been driven enrollment choice. Choice of who to approach for enrollment might have differed if control had been placebo controlled and not standard of care.

3. Use of a composite primary analysis. We note that there was no difference in mortality or intubation between CCP and control groups when these endpoints were considered separately and that a statistically significant difference emerges only after these endpoints are combined. Adding endpoints that were not significant individually to produce borderline significance ($p = 0.03$) weakens the conclusion of any harm from CCP.

4. The harmful effect of Anti-S IgG appears only in multivariate analysis. The univariate analysis (Supplement table 10) and in Figure 4 shows no deleterious effect for Anti-S IgG.

    UNIVARIATE OR 1·005 (0·821, 1·231)

    MULTIVARIATE OR 1·528 (1·140, 2·049), p=0·0046

A deleterious result for Anti-S IgG emerged only after the introduction of adjustment factors such as plasma supplier and other antibodies. Outcomes varied by CCP supplier, with an OR of

0.95 among Supplier 1 CP and OR of 1.42 for the other three suppliers (see Figure 5 in(1)). CCP from Supplier 1 also had the highest levels of all antibodies including the putatively dangerous Anti-S IgG. What this analysis shows is that for recipients of 'weak plasma' (shown by adjusting for the higher levels of plasma and better mortality in Supplier 1) a negative effect of anti-S IgG emerges. However, this adjustment is entirely theoretical because the circumstance (high Anti-S with weak other antibodies) did not actually occur. The proper analysis would be to adjust for the other antibodies *within strata* of the 4 suppliers, although there would only be power for the first 2 suppliers, who accounted for 85% of the units used (Supplementary table 9).

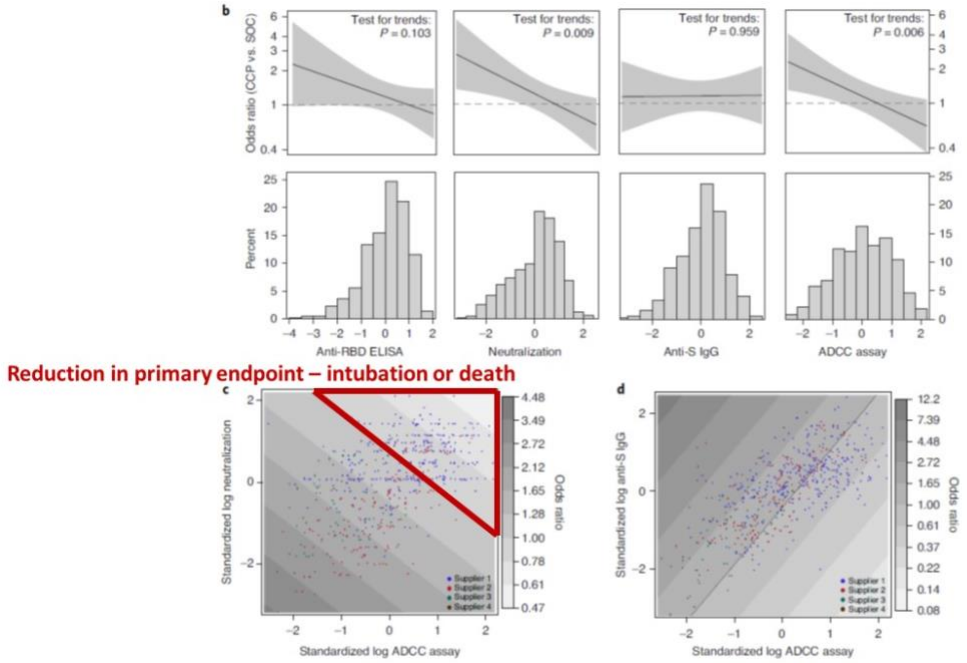

Figure 1. This is Figure 4 in the paper (1). Panel B shows statistically significant trends for high titer CCP reducing intubation or death. Panel C has a red triangle added in the section where the plot shows CCP efficacy in reducing primary endpoint.

5. <u>Trial focuses on Late and severe COVID-19 disease.</u> CONCOR-1 trial design criteria for enrollment required that patients were hypoxemic. The mean overall FiO2 for study participants was 49 mm and 88% had abnormal chest X-rays. Hypoxemia and radiographic findings imply that the majority had pneumonia with sufficient pulmonary inflammation to impair gas exchange. CCP is believed to work primarily as an antiviral and its efficacy is maximal when it is given early, neutralizes SARS-CoV-2 and thus avoids life threatening inflammation. A key subgroup, comprising of subjects requiring minimal or no supplemental oxygen and who received high titer CCP was not included in the study. This is the scenario where CCP is most likely to have a positive impact. Hence, the trial design tested CCP in patients where it was unlikely to be effective. Remarkably, CONCOR-1 observed signals of efficacy in patients treated with high titer CCP suggesting that high antibody amounts may confer therapeutic benefit even in a patient cohort with severe disease, which is unexpected and warrants further clinical investigation.

6. <u>Evidence for efficacy of CCP in CONCOR-1.</u> In our opinion CONCOR-1 provides additional evidence for CCP efficacy against COVID-19. Importantly, there was a strong dose response whereby units with high titer and functional activity were associated with benefit relative to

usual care. The purported harmful effect of low titer sera is not rigorously established and is not noted with high titer CCP, which conferred a benefit. It is noteworthy that current recommendations of the CCP usage (in the US based on the FDA EUA) mandate the use of only high titer CCP. This renders the concern cited in the article immaterial. Unfortunately, it is a distraction from what should be viewed by clinicians as further support for the use of high titer CCP for treatment of patients with COVID-19.

1. Bégin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, Zeller MP, Beaudoin-Bussières G, Amorim L, Bazin R, Loftsgard KC, Carl R, Chassé M, Cushing MM, Daneman N, Devine DV, Dumaresq J, Fergusson DA, Gabe C, Glesby MJ, Li N, Liu Y, McGeer A, Robitaille N, Sachais BS, Scales DC, Schwartz L, Shehata N, Turgeon AF, Wood H, Zarychanski R, Finzi A, Arnold DM. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nature medicine. 2021. Epub 2021/09/11. doi: 10.1038/s41591-021-01488-2. PubMed PMID: 34504336.

2. Anonymous. Investigational COVID-19 Convalescent Plasma. Guidance for Industry2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma.