

This paper represents a welcome attempt to study the use of high antibody-titer convalescent plasma (CP) early in the course of COVID-19, but it is unfortunately flawed in several key ways that render its negative conclusions very uncertain. In fact, hidden inside the data are several hints of CP efficacy, which are especially troubling in a trial halted early for futility. We will address here the design, the execution, and the findings of the study.

A. First are flaws in the **design** of the study

1. **Timing of the treatment.** The mean time of treatment was up till 7 days of self-reported illness. In the history of CP treatment, which emphasized treatment within 3 days of illness onset, this would generally not be viewed as early treatment. The only other outpatient CP trial- which showed a halving of COVID progression to severe disease with CP treatment – initiated treatment before 72 hours of symptoms in all patients, who were required to have no more than 48 hours of symptoms prior to treatment.¹
2. **Power.** Power was conditioned on the assumption that the outcome of interest would be halved by the treatment. Any finding smaller than that was not considered clinically important. It is hard to understand why reducing disease progression, by, say a third, would not be clinically important. Even that large difference would have required 600 participants, and, in a later planned re-estimation of sample size, that estimate was increased to 900, but the trial was stopped for futility – in our opinion far too soon - when only 531 participants had been enrolled.

This was precisely the error that Thomas Chalmers described in his classic paper on trials of anticoagulants in myocardial infarction.² Most trials found reductions in mortality of about 25-30%, which was generally not significant in these underpowered trials which declared the findings to be null, even though such a mortality reduction would clearly be of value. Chalmers' re-analysis of these data is credited with revitalizing the concept of anticoagulant use in myocardial infarction, leading to mounting larger and stronger trials showing the efficacy of this approach, now universally accepted as a component of treatment of this disorder.

3. **Number of Centers.** Fidelity to trial protocols is to a large extent dependent on the number of participating centers and the number of enrollments per center. This trial stretches this problem to an extreme, employing 48 emergency rooms to enroll 531 participants in 21 states, or just 11 participants per center, meaning that on average 5-6 treatments of CP were delivered in each center. Nineteen centers enrolled four or fewer subjects. The study does not say whether randomization was by center, which is ideal, or overall across all centers combined. No data were presented on any within-center differences in any aspect of the trial.
4. **Choice of the primary outcome.**
 - a. **Mixing heterogenous outcomes.** The primary outcome was *“a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization”*, with each of these disparate events having the same weight. Thus, a death in one treatment arm could be the equivalent of an emergency room visit in the other. Hospitalizations are clearly more significant than emergency room visits as an outcome.
 - b. **Non-objective outcomes.** Two of the three components of the primary outcome – admission to hospital or emergency care - are not objective assessments or measurements, but dependent on patient and physician choices made in the several different settings in which the trial took place.

- c. **Outcomes unrelated to the trial treatment.** Most troubling is the use of outcomes that may have had nothing to do with COVID, because all hospitalizations, emergency room visits and deaths were counted, not just those related to COVID. We are not provided with the reasons for ER visits and hospitalizations, but the patient population selected for this trial were required to have at least one serious medical condition, and half of them had three or more, so medical care for these other conditions could easily have occurred during the period of follow-up.
 - d. **Puzzling inclusion of hospitalizations on day of treatment in the primary outcome.** The authors note that although a criterion for admission to the trial was an expectation that the patient would be discharged from the emergency room, 25 hospitalizations occurred in the 531 patients (4.7%) on the same day as the visit. Especially troubling is that 19 of these early hospitalizations occurred in the CP treatment arm, just 6 in the control saline arm. This difference, by the way, is significant at $< .01$. In most trials these events would not have been considered trial outcomes. The authors acknowledge this problem by doing an analysis excluding them, described further below under suggestions of CP efficacy. Most of the 19 admissions in the CP arm were for “pneumonia” or “hypoxia” only 3 were for adverse plasma reactions.
 - e. **Inclusion of emergency room visits.** Emergency visits are especially troubling to include in the primary study outcome. If not followed by hospitalization, they do not represent substantial worsening of clinical status.
- B. Problems in the **execution** of the trial
1. **Differences in the two treatment groups after randomization.** The differences between most risk factors in the two treatment groups were generally modest. However, immunosuppressed individuals were nearly twice as common in the treatment group (12.8% vs 6.7%, $p < .05$). Among the 33 immunosuppressed participants in the CP arm were 5 organ transplant recipients, a group entirely unrepresented in the control arm. The treated arm had more people with three or more risk factors, and fewer with just one risk factor (19.8% vs 26%, $p = .09$). This factor may have been operative in the deaths found in the study. While the single control death had 2 risk factors, the five intervention arm deaths had an average of 4.2 risk factors each.
 2. **Difference in median day of treatment.** No further details are provided other than noting in a table that CP recipients’ median day of illness when treated was day 4, but for controls it was day 3. This difference did not achieve statistical significance but deserves explanation.
 3. **Distant CP donations.** Although not known at the time of trial design, it was recently reported that that CP obtained from locations near to the patient lowers mortality more than distantly sourced CP, possibly because of a better match of donated plasma antibody to patient virus type.³ But in this study in 21 states, 95% of the donor plasma was collected in either Chicago or Denver. Since only 4 of the 48 centers were in Illinois or Colorado, most CP usage had to be from remote sources. Remote plasma sourcing could have reduced CP efficacy, contributing to a lower than expected benefit, making the study underpowered for the effect observed (point 2 above) leading the DSMB to stop the trial for presumed futility.
- C. To turn to the **findings** of the study
1. The primary outcome was found in 30% of CP treated patients and in 31.9% of controls, a **reduction of 6%** in the treated. If the 25 participants hospitalized on the same day as their initial visit are excluded, the primary outcome occurred in 22.5% of the CP treated and in

29.5% of controls, a **24% reduction**, which is nearly significant ($p = .07$). The authors calculated that the first finding is compatible with **68% probability of the superiority of CP, the second with a 93% probability of superiority.**

If emergency room visits are excluded, and the focus is instead on hospitalizations after the day of treatment, we find that 33 of the CP treated (12.8%) and 50 of the controls (19.6%) were hospitalized, a **35% reduction, which is significant at the .035 level.**

2. The figure plotting differences by sub-group shows, that while the differences were generally small, the tilt was towards benefit from CP treatment, with 18 factors showing a more favorable outcome in the treatment arm, while this was true of just 6 factors in the control arm. In the 14% of patients of Asian or other ethnicity, the lowered outcome risk difference favoring the CP arm was sizable at 14%. Patients treated in the first three days also had more favorable responses to CP – a risk difference of 5%.
3. Two outcomes **improved significantly with CP**, and both were more objective measures than the decision to hospitalize or to visit the emergency room:
 - a. **Dyspnea** emerged nearly three times as often in controls as in the CP treated - 17 controls (6.7%) vs 6 treated (2.3%) $P < .05$.
 - b. **Symptom worsening** occurred in 39.7% of the treated, in 43.3% of controls, a 9% reduction. The number of participants whose symptoms worsened within a day of randomization was the same as the number hospitalized on the day of randomization – 19 in treated 6 in controls. If these 25 are removed (for the reason given above) and symptom worsening after day 1 from randomization is examined, the CP treated arm had **17% fewer participants experience symptom worsening (34.9% vs 41.9%, $p < .05$).**

In sum, despite some issues in the design and execution of this study, there were some very substantial signals of CP efficacy in this study. These signals should have been sufficient to permit the study to arrive at its pre-specified sample size, instead of terminating it when only 59% of the targeted population had been recruited. While these signals do not rise to the level of *proof* of CP efficacy, they constitute *real signals of efficacy*, that are difficult to ignore.

We disagree with the conclusion of the NIH press release on the study (<https://www.nih.gov/news-events/news-releases/nih-study-shows-no-significant-benefit-CP-covid-19-outpatients-early-symptoms>). This study cannot be used to demonstrate the ineffectiveness of CP. Rather, it suggests the potential value of an inexpensive, readily available, low risk intervention for a disease for which we still have few specific therapies.

¹ Libster et al NEJM

² Chalmers T NEJM 1977

³ Kundze K 2021