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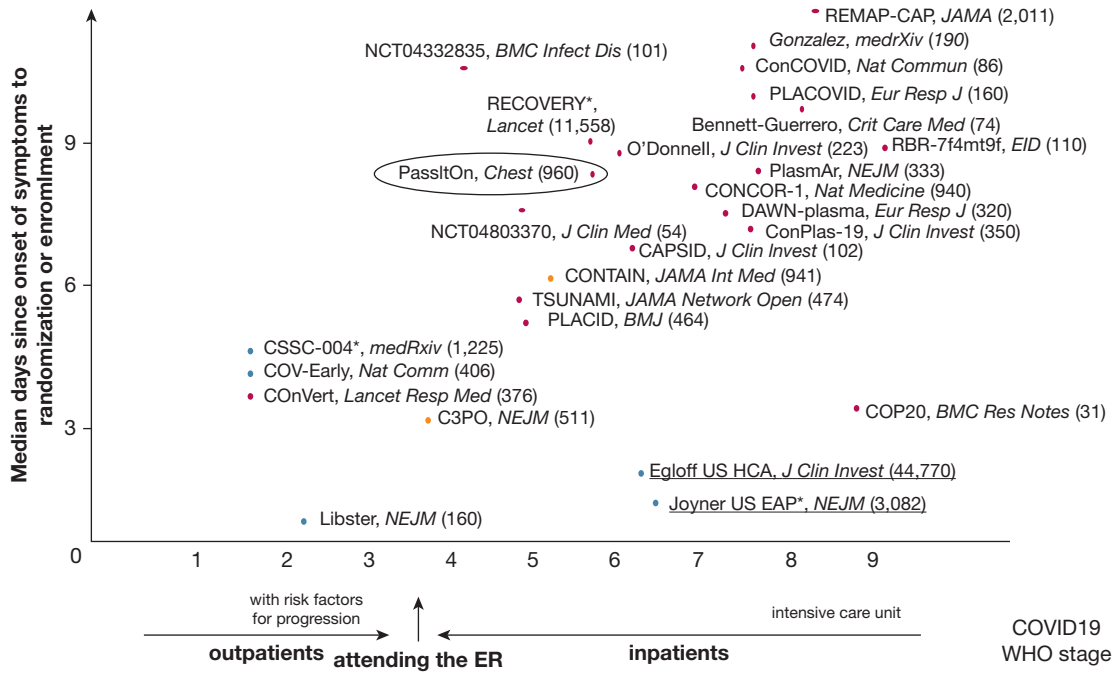

Figure 1 – *COVID-19 convalescent plasma randomized controlled trials and large uncontrolled trials reported as of July 17, 2022, are plotted according to timing of intervention and disease severity (according to World Health Organization 11-category ordinal scale)*[5]*: Blue represents trials that met the primary end point with statistical significance; orange represents trials that failed to meet the primary end point but showed trends in favor of COVID-19 convalescent plasma; red represents trials that failed to show benefit in the primary end point.*

viral stage of disease.[3,4] The negative outcome of PassItOn must be interpreted in that context.

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Late Treatment for COVID-19 With Convalescent Plasma

To the Editor:

We read with great interest the Passive Immunity Trial for Our Nation (PassITON) published in this issue of *CHEST* that reported no difference in a 28-day mortality rate or secondary outcomes between hospitalized

patients treated with COVID-19 convalescent plasma (CCP) and patients treated with placebo.[1]

Self et al[1] hypothesized that prior trials in hospitalized patients failed to show a benefit because of the wide variability in the neutralizing activity of CCP and the inclusion of patients with established immune responses to SARS-CoV-2. PassITON used plasma that has been shown to neutralize SARS-CoV-2 and did not benefit the 30% of participants who tested seronegative at baseline. Even under these ideal conditions (neutralizing plasma; seronegative patients), no evidence of CCP benefit emerged.

But the authors also noted that the premise of CCP is that it should be used in patients who are "in the early stages of infection." Although PassITON strove to enroll and treat early, random assignment took place at a median of 8 days after symptom onset, and up to 24 hours could pass before treatment was initiated. Additionally, at baseline, 13% of participants were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 22% of participants were receiving oxygen therapy or noninvasive ventilation, and 91% of participants were receiving oxygen. Thus, despite a strong motivation to do so, PassITON was unable to reach patients early enough during the disease course for the optimal use of CCP. The findings of PassITON are also consistent with the results of the Expanded Access Program, in which the dose-response benefit of high-antibody CCP in hospitalized patients who were found in the first 3 days of illness and in unventilated patients was not found in patients who were treated later in the disease course.[2]

CCP provides its greatest benefit in outpatients, as shown by the randomized controlled trials of Libster et al[3] and Sullivan et al[4] and in subsets of hospitalized patients with lower baseline World Health Organization scores.[5] An exception to this early treatment rule likely occurs among the patients who are immunocompromised, for whom evidence of CCP utility is found even late in disease.[6]

The dependence of the value of CCP on the use-case, which has been documented in all trials reported to date, indicate the critical need for a careful planning process to guide the deployment of convalescent plasma and other forms of antibody therapy in response to the inevitable outbreaks of novel infectious diseases of the future.

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COVID-19 Convalescent Plasma and Concomitant Therapies in PassITON

To the Editor:

The Passive Immunity Trial for Our Nation (PassITON) investigators concluded in this issue of *CHEST* that treatment with COVID-19 convalescent plasma (CCP) did not improve clinical outcomes.[1] However, this conclusion, which implies that CCP is ineffective, is