Convalescent Plasma in COVID-19: To what Degree should Clinicians Rely on Currently Available Data?

In this issue of the Saudi Journal of Medicine and Medical Sciences, AlShehry *et al.* report the interim findings of a phase II trial that describes the outcomes of 40 hospitalized adults with severe or critical coronavirus disease 2019 (COVID-19) who received convalescent plasma (CP), in comparison with 124 matched controls who did not receive CP. Authors found no difference in the intensive care unit or hospital length of stay. Although there was an association between the use of CP and lower risk of death, the upper limit of the confidence interval (CI) is consistent with the possibility of no benefit (hazard ratio: 0.55; 95% CI: 0.3 to 1.03). The absolute difference in the risk of death was reported by authors as 13%. The process of collecting and administering CP followed the standard safety protocols in Saudi Arabia. Overall, there were no reported adverse events in the cohort of patients receiving CP. Authors concluded that CP is safe, and that it may reduce risk of death in COVID-19.

While we congratulate the authors for their effort to explore this important area and for facilitating the complicated process of CP collection and administration, there are important concerns about the study design. Firstly, the lack of randomization limits the ability to generate prognostically balanced groups. Even though propensity matching was used, it does not completely account for selection bias and confounding factors, and should not be used as a substitute for randomization.[1] Secondly, the selection process of controls (prospective versus retrospective) could influence the validity of observations. Thirdly, authors presented the demographics with regards to matched variables, but other important prognostic variables such as more detailed severity of illness, other comorbidities, and the use of other interventions were not clear and will likely be explored in future publications of the trial. All those factors raise concerns about prognostically imbalanced groups (i.e., selection bias).

Considering the above, readers should interpret the results with caution, and avoid making definitive inferences about possible reduction in mortality. To date, 5 randomized clinical trials (n = 960) have examined the effect of CP, compared with controls not receiving CP, in hospitalized patients with COVID-19.[2-6] While CP appeared to be safe, none of these trials demonstrated a reduction in mortality with CP. Even the pooled estimate across trials for mortality outcome did not show definitive benefit or harm [Figure 1], challenging the results of the current trial and observational studies. Of note, the point estimate of mortality difference in the meta-analysis is 2.6% versus 13% observed by AlShehry *et al.* and neither of those differences was statistically significant.

In conclusion, the study by AlShehry *et al.* provides important information about the feasibility of using CP in Saudi Arabia and supports important clinical hypothesis. We congratulate authors on this accomplishment. It is our opinion, however, that further well-designed randomized clinical trials and their meta-analyses are urgently needed to determine the efficacy of CP in COVID-19 patients before widespread introduction of this intervention.

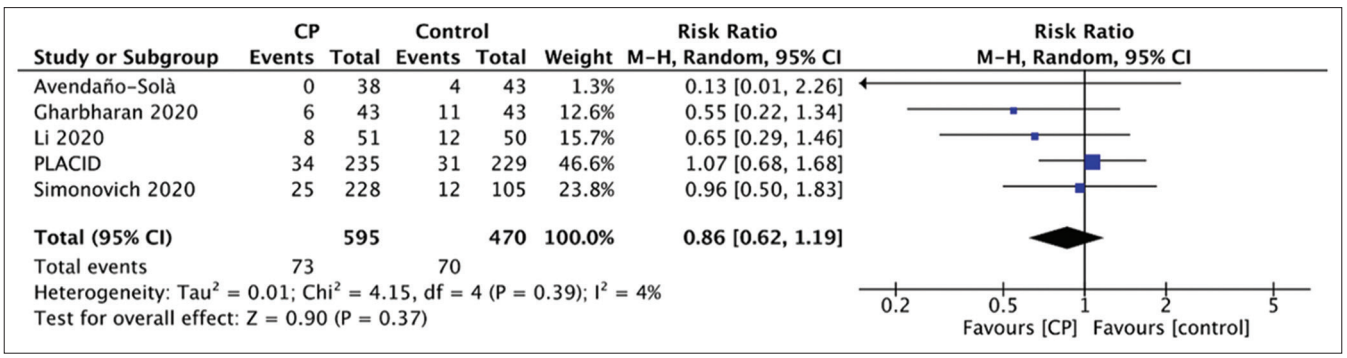

Figure 1: Pooled estimates of mortality outcome across five randomized control trials on convalescent plasma use in hospitalized COVID-19 adults using the Mantle–Haenszel Random-effects model. CP: Convalescent plasma, CI: Confidence interval

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