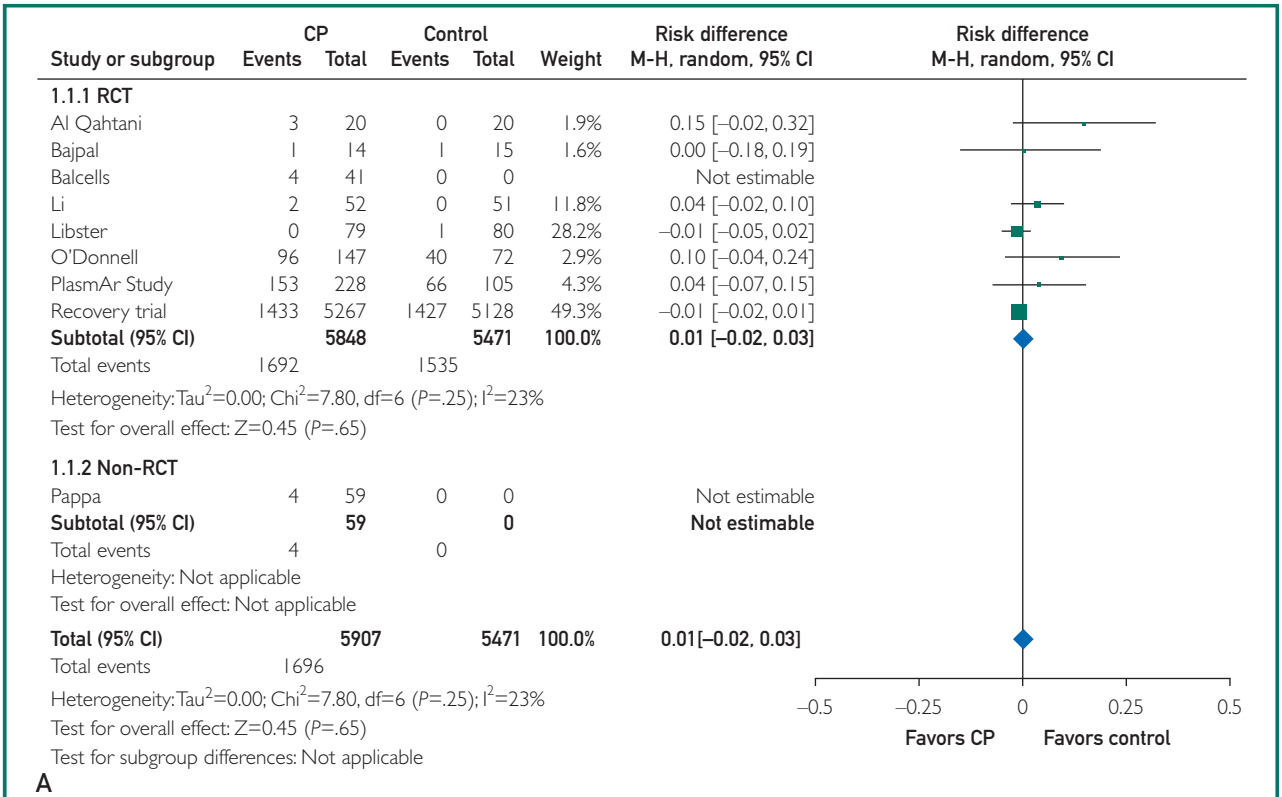
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

How Safe Is COVID-19 Convalescent Plasma?

To the Editor: We read with interest the systematic review and meta-analysis by Klassen and colleagues,[1] recently published in *Mayo Clinic Proceedings*. The investigators included in their analysis 30 randomized clinical trials (RCTs) and matched control studies, documenting that COVID-19 convalescent plasma (CP) transfusion, especially when it is given within 3 days of hospital admission, is associated with lower mortality of patients with COVID-19 compared with standard treatment. Adverse events analysis, in combination with benefits analysis, is essential to make an informed decision about health intervention. For this reason, we would like to add safety data to the analysis of Klassen and coworkers.[1]

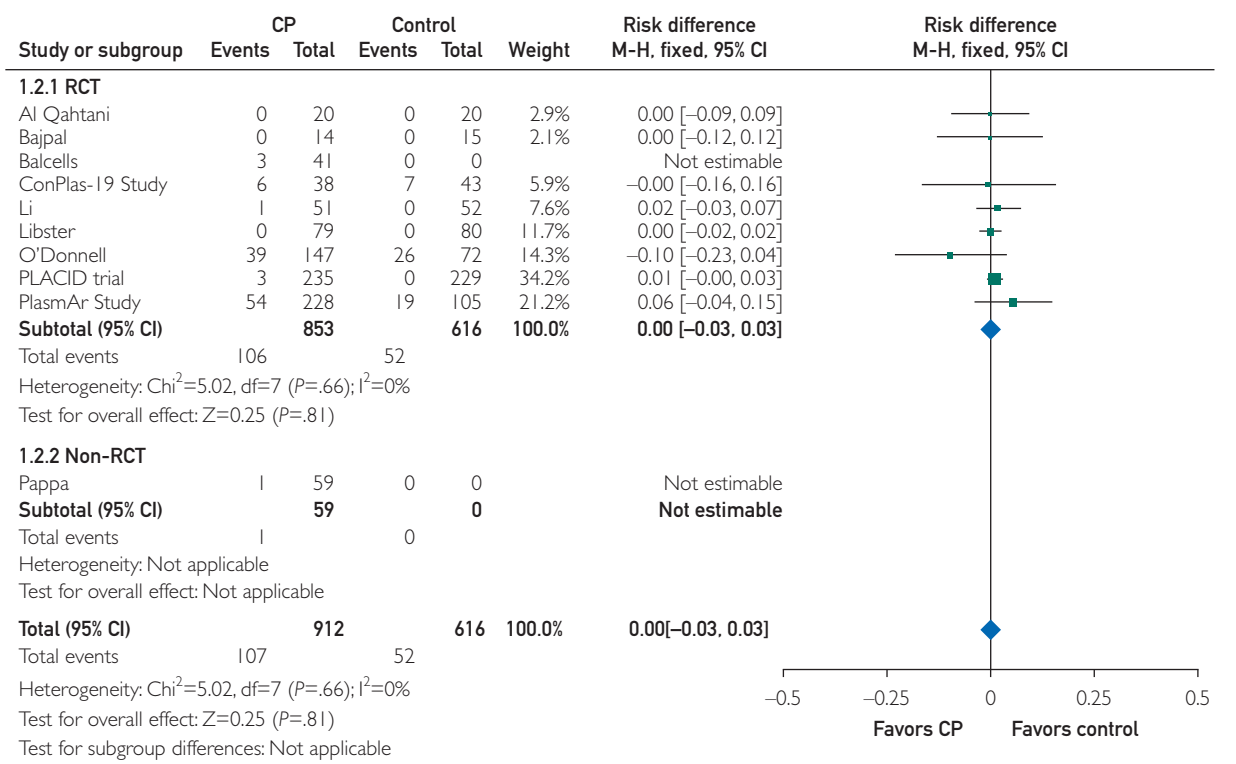
Through an online systematic search on PubMed and MEDLINE (range, January 1, 2020, to May 15, 2021), we identified 30 studies (14 RCTs and 16 non-RCTs with matched control group) that were downloaded and analyzed for safety data (Supplemental Table, available online at http://www.mayoclinicproceedings.org). Overall, severe (serious and grade 3-4) and thromboembolic adverse reactions were recorded and analyzed. In addition, we collected and evaluated the prevalence of overall and severe adverse reactions to CP transfusion in the selected studies. The study weight was calculated using the Mantel-Haenszel method, and statistical heterogeneity was assessed using the I^2 statistic. Measures of treatment effect were risk difference (RD) together with 95% CI. All calculations were conducted using Review Manager, version 5.4 software (Cochrane Collaboration).

The mean prevalence (standard deviation) of all and severe CP infusion–related adverse events was 2.1% (2.6%) and 0.7% (1.4%), respectively. As reported in



A

FIGURE. Forest plots of comparison of convalescent plasma (CP) vs standard treatment. A, Outcome: all adverse reactions. Data are from 8 randomized clinical trials (RCTs) and 1 non-RCT. B, Outcome: severe adverse reactions. Data are from 9 RCTs and 1 non-RCT. C, Outcome: thromboembolic adverse reactions. Data are from 7 RCTs and 2 non-RCTs. MH, Mantel-Haenszel. *Figure continued on next page.*



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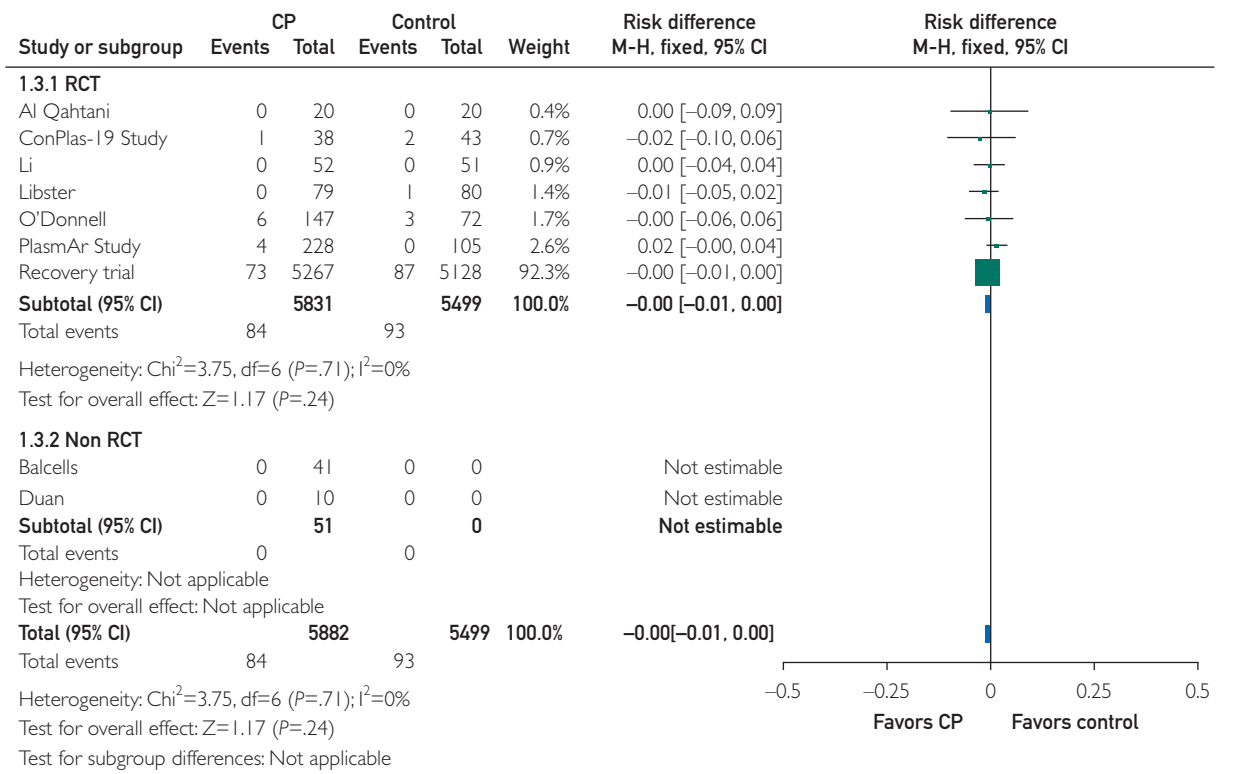

C

FIGURE. (*continued*).

Figure A and B, treatment with CP did not increase the risk of overall adverse events (RD, 0.01; 95% CI, −0.02 to 0.03; P=.65) and severe adverse events (RD, 0.00; 95% CI, −0.03 to 0.03; P=.81) compared with standard treatment. Similarly, the rate of thromboembolic events did not differ between the study groups (1.4% in the CP arm vs 1.7% in the control arm; RD, 0.00; 95% CI, −0.01 to 0.00; P=.24; Figure C). In addition, the funnel plot of comparison of all 3 outcomes (all, severe, and thromboembolic adverse reactions; Supplemental Figure, available online at http://www.mayoclinicproceedings.org) appeared to be symmetric, suggesting a substantial homogeneity among the included studies and the lack of publication bias.

In conclusion, the results of this updated meta-analysis confirm the safety of CP transfusion and, in particular, document the very low rate (0.7%) of CP transfusion−related serious adverse reactions, similar to that reported in the large US Expanded Access Program.[2] Differing from the previous systematic reviews, we have focused our analysis on the CP-related thromboembolic risk, considering the particular critical setting of COVID-19, with a hyperinflammatory and hypercoagulative state, and the concerns from some clinicians.[3] After a careful analysis of the published literature, we can conclude that the addition of CP to the COVID-19 treatment does not increase the patients' thromboembolic risk. Finally, we personally think that considering the lack of valid anti−COVID-19 therapies, the relatively low costs, and the high safety profile, CP collection and use should be endorsed and implemented by governments of developing and developed countries, without waiting for conclusive evidence of its efficacy.[4]

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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Potential Competing Interests: The authors report no competing interests.

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https://doi.org/10.1016/j.mayocp.2021.06.011

In Reply—How Safe Is COVID-19 Convalescent Plasma?

To the Editor: We would like to thank Franchini and Cruciani for their letter in response to our systematic review and meta-analysis studying the effect of convalescent plasma therapy on the mortality of patients diagnosed with coronavirus disease 2019 (COVID-19).[1] This letter highlights important new meta-analytical data based on 30 controlled studies (including 14 randomized clinical trials) demonstrating that convalescent plasma transfusion does not increase the risk of adverse events, including thromboembolic events, compared with patients diagnosed with COVID-19 who either were not transfused or were transfused with standard fresh frozen plasma. This new safety analysis supports the viewpoint that human convalescent plasma has a favorable risk-benefit ratio, particularly when it is reviewed in the context of the mosaic of evidence supporting some degree of effectiveness of convalescent plasma therapy for COVID-19.[2] Taken as a whole, these data support the continued use of convalescent plasma as the COVID-19 pandemic endures, especially in regions with limited vaccine access and in immunocompromised patients who cannot mount effective immune responses to vaccines.[3]

At the onset of the COVID-19 pandemic, several theoretical safety risks regarding convalescent plasma therapy were raised, including the potentiation of COVID-19 respiratory deterioration through antibody-dependent enhancement or cytokine storms, transfusion-associated circulatory overload, and enhanced thromboembolic risk.[4] However, the meta-analytical safety data presented in the letter by Franchini and Cruciani along with the consistent signatures of safety emerging from worldwide use of convalescent plasma, including in the United States under the Expanded Access Program and Emergency Use Authorization, have generally allayed these safety concerns.[5,6] Convalescent plasma safety can