### Table 7. GRADE evidence profile, PICO 7

**Question**: Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19

<table>
<thead>
<tr>
<th>Nr of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Certainty assessment</th>
<th>Nr of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (RCT) (follow up: range 15 days to 60 days)</strong></td>
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<tr>
<td>2 (^{1,2}) randomized trials</td>
<td>serious a,b</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious c</td>
<td>none</td>
<td>14/95 (14.7%)</td>
<td>23/94 (24.5%)</td>
<td>RR 0.60 (0.33 to 1.10)</td>
<td>98 fewer per 1,000 (from 164 fewer to 24 more)</td>
<td>□□□□</td>
<td>VERY LOW</td>
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<tr>
<td><strong>Mortality at 30 days (NRS)</strong></td>
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<tr>
<td>1 (^{3}) observational studies</td>
<td>serious d,e</td>
<td>not serious</td>
<td>not serious e</td>
<td>not serious</td>
<td>none f</td>
<td>115/515 (22.3%) g</td>
<td>166/561 (29.6%)</td>
<td>RR 0.75 (0.61 to 0.93) e,h</td>
<td>74 fewer per 1,000 (from 115 fewer to 21 fewer)</td>
<td>□□□□</td>
<td>MODERATE</td>
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<td><strong>Mortality at 7 days (NRS)</strong></td>
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<tr>
<td>1 (^{3}) observational studies</td>
<td>serious d,e</td>
<td>not serious</td>
<td>not serious e</td>
<td>not serious</td>
<td>none f</td>
<td>46/515 (8.9%) g</td>
<td>77/561 (13.7%)</td>
<td>RR 0.65 (0.46 to 0.92) e,h</td>
<td>48 fewer per 1,000 (from 74 fewer to 11 fewer)</td>
<td>□□□□</td>
<td>MODERATE</td>
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<tr>
<td><strong>Worsening oxygenation (follow up: 14 days)</strong></td>
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<tr>
<td>1 (^{4}) observational studies</td>
<td>very serious j</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious k</td>
<td>none</td>
<td>7/39 (17.9%)</td>
<td>38/156 (24.4%)</td>
<td>OR 0.86 (0.75 to 0.98)</td>
<td>27 fewer per 1,000 (from 49 fewer to 4 fewer)</td>
<td>□□□□</td>
<td>VERY LOW</td>
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<tr>
<td><strong>SAEs (transfusion-associated circulatory overload, transfusion-related acute lung injury, severe allergic transfusion reaction) (follow up: 4 hours)</strong></td>
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<tr>
<td>1 (^{5}) observational studies</td>
<td>extremely serious l</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>SAEs from 20,000 transfused patients: Within first 4 hours, of the SAEs, 63 deaths were reported (0.3% of all transfusions) and 13 of those deaths were judged as possibly or probably related to the transfusion of COVID-19 convalescent plasma. There were 83 non-death SAEs reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion-related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction.</td>
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<td>□□□□</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>
SAEs (mortality, cardiac, thrombotic, sustained hypotensive events requiring intervention) (follow up: 7 days)

<table>
<thead>
<tr>
<th>1</th>
<th>observational studies</th>
<th>extremely serious 1</th>
<th>not serious</th>
<th>not serious</th>
<th>not serious</th>
<th>none</th>
</tr>
</thead>
</table>

SAEs from 20,000 transfused patients: Within 7 days of transfusion, 1,711 deaths (8.56%) and 1,136 serious adverse events (5.68%) were reported. Non-mortality SAEs included: 643 cardiac events (569 judged as unrelated to the transfusion); 406 sustained hypotensive events requiring intravenous pressor support; and 87 thromboembolic or thrombotic events (55 judged as unrelated to the transfusion).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio; OR: Odds ratio

Explanations

a. Li 2020 time between symptom onset and randomization was over 14 days for >90% (median 30 days), no adjustment for co-interventions, allocation concealment methods not reported and participants and healthcare professionals not blinded.
b. Gharbharan 2020 was an open-label trial, allocation concealment not reported, and no adjustments for co-interventions.
c. The 95% CI includes the potential for appreciable benefit; however, cannot exclude the potential for harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.
d. Joyner 2020 adjusted for time epoch, gender, race, age at enrollment (as categories), and indicator variables having already developed one or more severe COVID-19 conditions, being on a ventilator, use of hydroxychloroquine, use of remdesivir, and use of steroids prior to transfusion.
e. Comparator arm received low titer convalescent plasma, not no convalescent plasma, which was postulated to be less effective than the high titer. The directionality, since the comparator group did not receive placebo, may have underestimated the effectiveness of convalescent plasma (biased toward the null).
f. Mortality analyses suggests a decreasing trend of mortality between low, moderate, and high IgG groups.
g. Additional analysis included a timing comparison between transfusing at <= to 3 days from diagnosis (not symptoms) and 4+ days: 7 day mortality: 1,340/15,407 (8.7%) vs. 2,366/19,915 (11.9%) - RR 0.73 (95% CI 0.69 - 0.78); 30 day mortality: 3,329/15,407 (21.6%) vs. 5,323/19,915 (26.7%) - RR 0.81 (95% CI 0.78 - 0.84). Low certainty evidence. Overall, the adjusted 30-day mortality in patients treated within 3 days of diagnosis with high antibody levels (20%) compared favorably to those treated beyond 3 days with low antibody level plasma (30%) - RR 0.77.
h. Crude relative risk. Adjusted inverse relative risk = 1.18 (95% CI: 0.99, 1.41).
i. Crude relative risk. Adjusted inverse relative risk = 1.45 (95% CI: 1.00, 2.03).
j. Liu 2020 propensity score matching was enforced on the administration of hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion; however, there may be some residual confounding.

k. The 95% CI includes the potential for appreciable benefit; however, may not include a clinically meaningful benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

l. No comparative effects available. Some subjectivity in classification of outcomes as transfusion related.

References