Effectiveness of Convalescent Plasma Therapy in the Treatment of Moderate to Severe COVID-19 Patients: A Systematic Review and Meta-Analysis

Bikash Ranjan Meher¹, Biswa Mohan Padhy², Smita Das³, Rashmi Ranjan Mohanty⁴*, Kanhaiyalal Agrawal⁵

Abstract

Though Convalescent plasma therapy (CPT) is being used for management of COVID-19, the evidence is still equivocal. So, we carried out this study to evaluate the currently available data to provide evidence about CPT in COVID-19 patients. RCTs and observational studies with sample size with more than 5 were included in the analysis. Out of 196 studies, 12 studies were selected for systematic review and meta-analysis was carried out for 6 studies having a control arm. For dichotomous values, risk ratio (RR) and 95% confidence interval was expressed.

Main outcomes: All-cause mortality, clinical improvement by day 7 and viral detection by day 7 were the defined outcome measures before starting of data extraction.

Result: For 6 studies (2 RCTs and 4 observational studies) with 474 patients, the overall pooled RR for all-cause mortality was 0.61 (95% CI: 0.37 to 0.99, P = 0.04). Only RCTs and only observational studies for all-cause mortality showed pooled RR of 0.60 (95% CI: 0.33 to 1.0, P = 0.10) and 0.48 (95% CI: 0.17 to 1.36, P = 0.17) respectively. There was no bias in the studies due to randomization process and confounding. Sensitivity analysis was carried out only for observational studies. The overall pooled RR for clinical improvement by day 7 and viral detection by day 7 were 1.12 (95% CI: 0.96 to 1.31, P = 0.16) and 0.19 (95% CI: 0.09 to 0.60, P < 0.0001).

Conclusion and relevance: Though the review suggests modest utility of CPT in reducing all-cause mortality, improving clinical outcome, and early viral clearance, it should be interpreted cautiously.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global problem since its outbreak in December 2019 in China.¹ By mid-August, approximately 20 million people got infected and 0.7 million succumbed to death worldwide due to coronavirus disease-19 (COVID-19).² Although antimalarials chloroquine and hydroxychloroquine, antivirals remdesivir and favipiravir, and the antibiotic azithromycin are being repurposed for the treatment of COVID-19 no specific drug or treatment has yet proven effective.³⁻⁶ The current management is mostly limited to general supportive care and symptomatic treatment. Convalescent plasma (CP) is the liquid part of blood collected from patients who have recovered from an infection. It contains high level of antibodies and is usually considered safe for use. There are instances in the past where CP has been used in the treatment of infectious diseases like Severe Acute Respiratory Syndrome-1 (SARS -1), Middle East respiratory syndrome (MERS), and Ebola.⁶⁻⁹ A study of patients with severe pandemic influenza A (H1N1) revealed that those on convalescent plasma therapy (CPT) had low fatality as compared to patients not treated with CP.¹⁰ Similarly, shorter hospital stays and reduced mortality were observed in patients with SARS who received CP when compared with patients who received only methylprednisolone.¹¹

Due to these encouraging outcomes in respiratory infections, CPT is currently being explored as one of the treatment options in patients suffering from COVID-19. Although US-FDA has not yet formally granted approval for routine use of CP in COVID-19 patients, it has recently issued emergency use authorization.¹² Few randomised clinical trials (RCT) and observational studies have been performed to evaluate the efficacy and safety of CP in COVID-19.¹³⁻¹⁵ Based on this limited data, some systematic reviews and meta-analysis have been conducted.¹⁶⁻¹⁸ However, the evidence regarding the use of CPT is still equivocal. As the situation is evolving and newer studies are being reported across the world, we carried out this systematic review and meta-analysis to evaluate the currently available data and provide evidence on the effectiveness of CP in COVID-19 patients. This may help physicians and policymakers to make an informed decision for management of COVID-19 patients.

Materials and Methods

Development and registration of protocol

The PRISMA-P guidelines was followed for writing the protocol. It was registered in prospective register of systematic review (PROSPERO) with registration number CRD42020203901.
Types of studies

All types of studies including RCTs and observational studies with or without control arm with sample size more than 5 were included in the analysis. The systematic review was conducted for all studies whereas meta-analysis was performed only for studies with a control arm.

Types of Participants

Adult human subjects of both gender with a diagnosis of RT-PCR confirmed moderate to severe COVID 19 treated in hospital with CP along with other modes of treatment were included in the study.

Moderate COVID 19 was defined as any patients requiring oxygen therapy with pneumonia in X-RAY chest and/or HRCT thorax. Severe COVID 19 was defined as any patient with X-RAY chest and/or HRCT thorax finding of pneumonia requiring non-invasive/ invasive ventilation and/or requiring presser support/renal replacement therapy/ECMO.

Following are the exclusion criteria of our study:

1. The studies in which, the efficacy/outcome of CPT has not been measured or could not be extracted in terms of WHO ordinal score for clinical improvement in COVID 19.20

2. The studies with sample size less than 5.

Types of intervention

In all the included studies, the intervention was administration of CP in moderate to severe COVID 19 patients along with usual treatment irrespective of the dose, timing, and frequency of administration of CP.

Types of comparator

For RCTs and observational studies having control arm, the comparison was change in study outcomes between usual treatment with and without CPT.

Outcome measures

Primary outcome

1. All-cause mortality: Death in COVID 19 patients due to any cause during the available period of follow up in the studies.

Secondary outcomes

1. Clinical improvement in the form of change in WHO ordinal score for clinical improvement in COVID 19 patients within 7 days of CPT.20

2. Change in RT-PCR status of COVID 19 patients within 7 days of CPT.

Information source

The Cochrane Library, PubMed, EMBASE, and SCOPUS were searched for articles on CPT in moderate to severe COVID 19 from inception till 20th August 2020. We also searched the Pre-print servers medRxiv and bioRxiv. For unpublished data we checked the International Clinical Trials Registry Platform (ICTRP).

Search strategy

A combination of subject terms and keywords using the PICO method were employed. Medical Subject Headings (MeSH) as well as keyword variants of all relevant terms were used for the search. The algorithm was designed on a combination of keywords, and Boolean operators like: “Convalescent plasma therapy” OR “Plasma therapy” OR “Hyperimmune serum” AND “COVID 19” OR “Severe acute respiratory syndrome coronavirus 2”. The reference lists of retrieved articles were also checked for additional information.

Data extraction and management

Four review authors (RRM, BRM, SD, KA) independently extracted and assessed the quality of data according to the predesigned eligibility criteria following Cochrane Collaboration’s guidelines. Disagreements were resolved by discussion and in consultation with fifth review author (BMP). The extracted data was recorded in a pre-designed data extraction format which includes basic information, study design, patient characteristics, treatment details, and outcome measures.

Assessment of risk of bias in included studies

The risk of bias in studies included for meta-analysis was assessed by Cochrane risk of bias tool. We used version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) and Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) for RCTs and observational studies respectively.
Table 1: Characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study period</th>
<th>Study population</th>
<th>Primary outcome (all-cause mortality)</th>
<th>Secondary outcome (with in day 7)</th>
<th>Additional comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al 2020</td>
<td>China</td>
<td>February to April 2020</td>
<td>52</td>
<td>With CPT: n= 52; Median age- 70 Male-27 Female-25 Moderate disease- 23 Severe disease- 28 Without CPT: n=51; median age-69 male-33 female-18 moderate disease-22 severe disease-28</td>
<td>With CPT: 8/51 (One patient withdrew from the study) Without CPT: 12/50 (One patient received CPT after randomization)</td>
<td>With CPT: 5/52 5/51 6/47 25/40 CPT dose- 200ml 96% received single dose Median time of symptom onset to randomization-30 days Received all additional treatment CPT dose- median is 300ml. 3 patients received 2nd dose Median time to start CPT- 21.5 days Both group received all additional treatment CPT dose- 200 ml, single dose Median time to start CPT from symptom onset- 16.5 days. Received all additional treatment</td>
</tr>
<tr>
<td>Zeng et al 2020</td>
<td>China</td>
<td>April 2020</td>
<td>6</td>
<td>With CPT: n=6; Median age- 61.5 Male-5 Female-1 Moderate-0 Severe-6 Without CPT: n=15; Median age-73 Male-11 Female-4 Moderate-0 Severe-15</td>
<td>With CPT: 5/6 Without CPT: 14/15</td>
<td>With CPT: 1/6 Without CPT: 1/15</td>
</tr>
<tr>
<td>Duan et al 2020</td>
<td>China</td>
<td>January to February 2020</td>
<td>7 instead of 10</td>
<td>With CPT: n=7 instead of 10 (3 participants in treatment group were baseline RT PCR negative before intervention); Median age- 52.5 Male-6 Female-4 Moderate-4 Severe-3 Without CPT: n=10 (historic matched control)</td>
<td>With CPT: 0/7 Without CPT: 3/10</td>
<td>With CPT: 7/7 Without CPT: 7/10</td>
</tr>
<tr>
<td>Gharbharan et al 2020</td>
<td>Netherlands</td>
<td>April to June 2020</td>
<td>43</td>
<td>With CPT: n = 43; Median age- 63 Male-33 Female-10 Moderate-1 Severe-42 Without CPT: n=43</td>
<td>With CPT: 6/43 Without CPT: 11/43</td>
<td>Not available Not available Not available Not available</td>
</tr>
<tr>
<td>Rasheed et al 2020</td>
<td>Iraq</td>
<td>April to June 2020</td>
<td>21</td>
<td>With CPT: n=21; Moderate-0 Severe-21 Without CPT: n=28; Moderate-0 Severe-28</td>
<td>With CPT: 1/21 Without CPT: 8/28</td>
<td>Not available Not available Not available Not available</td>
</tr>
</tbody>
</table>

**Studies without control arm**

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study period</th>
<th>Study population</th>
<th>CPT dose-400 ml, Admission to CPT duration varies from 10 to 22 days</th>
<th>0 5(100) 2(40)</th>
<th>Received all additional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen et al 2020</td>
<td>China</td>
<td>January to March 2020</td>
<td>5</td>
<td>Median-age 60 Male-3 Female-2 Disease severity: Moderate-0 Severe-5</td>
<td>0 5(100) 2(40)</td>
<td>Received all additional treatment</td>
</tr>
</tbody>
</table>
### Data analysis

Cochrane Program Review Manager 5.3 software was used for the meta-analysis. For dichotomous values, risk ratio (RR) and 95% confidence interval was expressed in accordance with Cochrane Handbook for Systematic Reviews of Interventions. F statistic was used to check heterogeneity among eligible studies. The random-effect model was used for data synthesis.

#### Assessment of publication bias

Funnel plot was used to assess the presence of publication bias. We also used Egger’s test (Comprehensive meta-analysis software: Evaluation version) for quantifying the asymmetry due to publication bias.

#### Grade of evidence

GRADE profiler software (V 3.6.1) was used for quality assessment of the evidence.

#### Results

### Description of studies

The database search resulted in 196 studies. After screening and removal of duplicates, 20 studies were selected for evaluation of the full text, among those 12 studies were selected for systematic review and meta-analysis as per our inclusion criteria. Out of those, 12 studies, only 6 studies having a control arm (2 RCTs and 4 observational studies) were included in the meta-analysis. The PRISMA flowchart of study selection is depicted in Figure 1.

Out of 5546 patients in the 12 studies included in this review, 5243 patients had received CPT along with usual care. For the 6 studies included in the meta-analysis, the RCTs provided data about 189 patients. 95 patients were on usual treatment along with CPT and 94 were on usual treatment without CPT. In the study by Li et al, 2 patients were excluded from the final analysis because 1 patient withdrew consent and another patient in the usual treatment group received CPT after randomization. Four observational studies provided data about 285 patients. Among these, 2 studies (Rasheed et al, Zeng et al) had a total of 27 patients in the CPT group and 43 patients in the usual treatment group. The other 2 studies (Duan et al and Liu et al) had 10 and 39 patients respectively in the CPT group and used historical control groups for comparison. In the study by Duan et al, 3 patients were RT-PCR negative before starting of CPT, so they were excluded from final data analysis.

Among all the 6 studies, 44 cases were moderate COVID 19 and 125 cases were severe COVID 19 in the CPT group. Similarly, in the control group, 29 cases were moderate COVID 19 and 107 cases were severe COVID 19. The data regarding the severity of COVID 19 in the historical control group were not available. As the study by Liu et al had not reported the exact number of deaths, we calculated the numbers from the reported percentages (13% for CPT and 25% for the usual treatment group).

#### Risk of bias in included studies

The risk of bias assessment of all studies included in the meta-analysis was carried out for the primary outcome (all-cause mortality). The use of RoB-2 reported that both the RCTs had “some concerns” regarding the risk of bias. In the 4 observational studies included in the meta-analysis, there was “critical” risk of bias in all. The result of the risk of bias assessment of RCTs and observational studies is depicted in Figure 2.

#### Effects of intervention

In the 6 studies with control arm included in the meta-analysis, the effect of administration of CP in addition to usual therapy was assessed by measuring the pooled effect on the primary and secondary outcomes. The forest plots for primary and secondary outcomes are depicted in Figures 3, 4.

### Primary outcome (all-cause mortality)

All 6 studies in the meta-analysis had reported a reduction in all-cause mortality with the use of CP. Test for heterogeneity for the pooled studies

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**Table 1: Characteristics of included studies (Contd...)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population</th>
<th>CPT dose</th>
<th>Primary outcome (all-cause mortality)</th>
<th>Secondary outcome (within 7 days)</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erdogan et al 2020</td>
<td>n = 26</td>
<td>CPT dose - single dose</td>
<td>6(23)</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Turkey</td>
<td>Mean age: 67.4±15.5</td>
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<tr>
<td>Male-18</td>
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<tr>
<td>Female-8</td>
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<tr>
<td>Disease severity:</td>
<td></td>
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<tr>
<td>Moderate-9</td>
<td></td>
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<tr>
<td>Severe-17</td>
<td></td>
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<tr>
<td>Joyner et al 2020</td>
<td>n = 5000</td>
<td>CPT dose - 200ml to 500 ml.</td>
<td>602(12)</td>
<td>Not available</td>
<td>Not available</td>
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<tr>
<td>USA</td>
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<tr>
<td>April to May 2020</td>
<td>Median-67.2.3</td>
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<tr>
<td>Male-3153</td>
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<td>Female-1824</td>
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<td>Disease severity:</td>
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<tr>
<td>Moderate-949</td>
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<tr>
<td>Severe-4051</td>
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<tr>
<td>Jin et al 2020</td>
<td>n = 6</td>
<td>Single dose CPT</td>
<td>0</td>
<td>Not available</td>
<td>3(50)</td>
</tr>
<tr>
<td>China</td>
<td></td>
<td>Admission to CPT dose varies from 22 to 64 days</td>
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<tr>
<td>February to April 2020</td>
<td></td>
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<td>Male-4</td>
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<td>Female-2</td>
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<td>Disease severity:</td>
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<tr>
<td>Moderate- 3</td>
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<tr>
<td>Severe-3</td>
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</table>
among the studies and the pooled RR was 0.48 (95% CI: 0.17 to 1.36), which indicated a beneficial but statistically non-significant effect of adding CP (P=0.17). The study by Zeng et al., accounted for the heterogeneity and when it was removed in sensitivity analysis, the test for heterogeneity became non-significant (Chi² = 1.32, df=2, P=0.52, I²=0%). The RR did not change considerably and was 0.41 (95% CI: 0.14 to 0.87) and significantly favoured the addition of CP compared to usual therapy only (P=0.02).

Secondary outcomes

Clinical improvement by day 7

All the 4 studies included in the meta-analysis reported clinical improvement by day 7 and were analysed for this secondary outcome. The test of heterogeneity was not significant (Chi² = 1.38, df=3, P=0.71, I²=0%). The random effect model revealed that adding CP led to non-significant clinical improvement by day 7 compared to usual therapy only (RR=1.12, 95%CI: 0.96 to 1.31, P=0.16).

Virus detection by day 7 (RT-PCR)

Out of the 4 studies, only 2 studies that reported the detection of virus by RT-PCR by day 7 were included in the analysis. The test for heterogeneity was not significant (Chi² = 0.27, df=1, P=0.60, I²=0%) and the random effect model revealed that the RR for detectable viral load by day 7 was 0.19 (95%CI: 0.09 to 0.60). This implied that there is a statistically significant reduction in the detection of the virus with RT-PCR by day 7 in patients who were administered CP compared to patients on usual therapy only (P<0.0001).

Publication bias

Funnel plot suggested the presence of publication bias due to asymmetry. Egger’s test was statistically significant for publication bias for the primary outcome of all-cause mortality (Intercept -1.67, 95% CI: -2.31 to -1.02, P=0.001).

Grade of evidence

For all the outcomes (primary and secondary), the evidence was assessed using GRADE profiler. For all-cause mortality, in all the 6 studies included in the meta-analysis, there was moderate evidence for adding CP to usual therapy as the anticipated absolute effect was 112 fewer deaths per 1000 patients compared to usual therapy alone. However, the quality of evidence was very low. Even when data from only the two RCTs were considered, moderate evidence for the use of CP was found with 99 fewer deaths per 1000 patients compared to usual therapy alone. However, the quality of the evidence was still low.

Similarly, moderate evidence was found for the secondary outcomes of clinical improvement by day 7 and virus detection with RT-PCR by day 7 with the addition of CP with the anticipated absolute effect of 68 more showing improvement by day 7 and 538 fewer being RT-PCR positive by day 7 per 1000 patients compared to usual therapy alone. The quality of the evidence for these two outcomes was low and very low respectively.

In the 6 studies without control arm not included in the meta-analysis, all-cause mortality ranged from 0% to 23% suggesting a modest effect of adding CP to usual therapy.23-25 Clinical improvements by day 7 was reported to be 100% in 2 studies.24,25

The detailed analysis of the summary of evidence is depicted in Table 2.
Discussion

In this systematic review and meta-analysis, we have attempted to include all the contemporary evidence regarding the use of CP in COVID-19 patients. As there were only 2 published RCTs, we combined them with observational studies for estimating the pooled effect. Though there is a difference in methodology and substantial heterogeneity between RCTs and observational studies, there are many examples of meta-analysis combining them due to several reasons like an insufficient number of RCTs, lack of long-term outcomes in RCTs, evaluation of safety and efficacy in real-life scenarios. Moreover, the test of heterogeneity in the 6 pooled studies was not statistically significant. The
pooled estimate suggested a statistically significant reduction in all-cause mortality when CP was added to usual therapy with RR of 0.61 (P = 0.04). However, the significant effect should be considered cautiously as the upper limit of the 95% CI of the RR was 0.99 and quite close to 1. We also conducted subgroup analysis taking RCTs and observational studies separately into consideration and found that pooled effect from neither the RCTs nor the observational studies favoured the addition of CP in significantly reducing all-cause mortality. The observational study by Zeng et al, accounted for the heterogeneity and when it was removed in sensitivity analysis, the test for heterogeneity became non-significant. The RR of 0.41 (95% CI: 0.14 to 0.87) after the removal of Zeng et al, showed a significant reduction in all-cause mortality with the addition of CP in the pooled observational studies. This finding was also supported by the observational studies without control groups where all-cause mortality ranged from 0% to 23%. The possible reasons for the variability in the effect may be attributed to delay in initiating CPT (median duration 21 days), elderly patients (median age > 50 years), and presence of comorbidities like diabetes, hypertension, obesity, pre-existing lung diseases, and associated organ failure.

The RR of 1.12 for clinical improvement by day 7 suggested some benefit with CPT that was not statistically significant. Apart from the above-listed conditions, other possible contributors for limited clinical improvement might be the shorter duration of follow up (7 days), variability in dose, and timing of CP administration in the absence of well-defined guidelines. However, there was a significant decrease in virus detection by RT-PCR by day 7 when CP was added to usual treatment (RR 0.19, P < 0.0001). Early viral clearance may decrease the possibility of immune hyperactivity, cytokine storm and shorten the disease course, apart from limiting the transmission of infection. Though we have included a greater number of studies, our findings are broadly in concurrence with some of the systematic reviews on the efficacy of CPT in COVID-19.17,18 We have excluded the large observational study by Joyner et al from the meta-analysis as it was without a control arm.27 Additionally, we also excluded the study by Chen et al as it was not a primary study and was based on data compiled from 3 other observational studies.31 Inclusion of both these studies could have contributed to the significant reduction in all-cause mortality, greater clinical improvement, and higher viral clearance reported by a recent meta-analysis from India.19

Strength and Limitations

Our review has included a greater number of studies covering wide geographies and patients with different ethnicities. The WHO ordinal scale for clinical improvement was used for greater objectivity. Since we conducted the meta-analysis by pooling data from RCTs and observational studies, subgroup analysis and sensitivity analysis was carried out to confirm the robustness of our test.

Limitations of the study are the inclusion of studies with small sample sizes and high risk of bias. Other limitations include variations in patient profile, concomitant medications, dose and timing of CPT and follow up time.

Conclusion

This review suggests the modest utility of CPT in reducing all-cause mortality, improving clinical outcome, and early viral clearance in patients with COVID-19. However, in view of low to a very low quality of evidence currently available, clinicians should interpret our findings with caution. Currently, many clinical trials are ongoing, and clear recommendations
Table 2: Grade of evidence for included studies

Convalescent plasma compared to No convalescent plasma for COVID-19

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of Participants (studies) Follow up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (RR) (95% CI)</th>
<th>Anticipated absolute effects Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>472 (6 studies)</td>
<td>⚫⚫⚫⚫ VERY LOW²,³</td>
<td>RR 0.61 (0.37 to 0.99)</td>
<td>Study population 288 per 1000 (112 fewer to 181 fewer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'due to risk of bias, publication bias</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>187 (2 studies)</td>
<td>⚫⚫⚫ LOW²,³</td>
<td>RR 0.60 (0.33 to 1.10)</td>
<td>Study population 247 per 1000 (99 fewer to 25 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'due to risk of bias, publication bias</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>282 (4 observational studies)</td>
<td>⚫⚫⚫ VERY LOW²,³</td>
<td>RR 0.48 (0.17 to 1.36)</td>
<td>Study population 306 per 1000 (159 fewer to 110 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'due to risk of bias, publication bias</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical improvement by day 7</td>
<td>336 (4 studies)</td>
<td>⚫⚫⚫ LOW²,³</td>
<td>RR 1.12 (0.96 to 1.31)</td>
<td>Study population 565 per 1000 (68 more to 175 more)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'due to risk of bias, publication bias, large effect, plausible confounding would change the effect</td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td>Virus detection by day 7 (RT-PCR)</td>
<td>108 (2 studies)</td>
<td>⚫⚫⚫ VERY LOW²,³</td>
<td>RR 0.19 (0.09 to 0.41)</td>
<td>Study population 655 per 1000 (530 fewer to 596 fewer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'due to risk of bias, publication bias</td>
<td></td>
<td>Moderate</td>
</tr>
</tbody>
</table>

The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect.; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.; Very low quality: We are very uncertain about the estimate.

References


Author contribution

RRM developed the concept. Search, data extraction, and quality assessment was carried out by RRM, BRM, SD, KA. Resolution of disagreement was carried out by BMP. Statistical analysis, and statistical inferences was done by BRM and BMP. Manuscript was written by RRM, BMP, and BRM. The final version was approved by all authors for publication.

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