Convalescent Plasma for COVID-19: real-time meta analysis of 57 studies

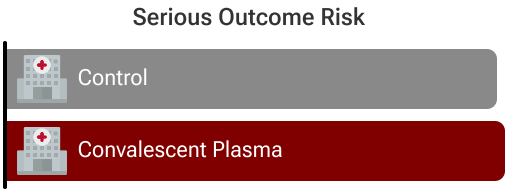
@CovidAnalysis, June 2025, Version 44
https://c19early.org/cpmeta.html

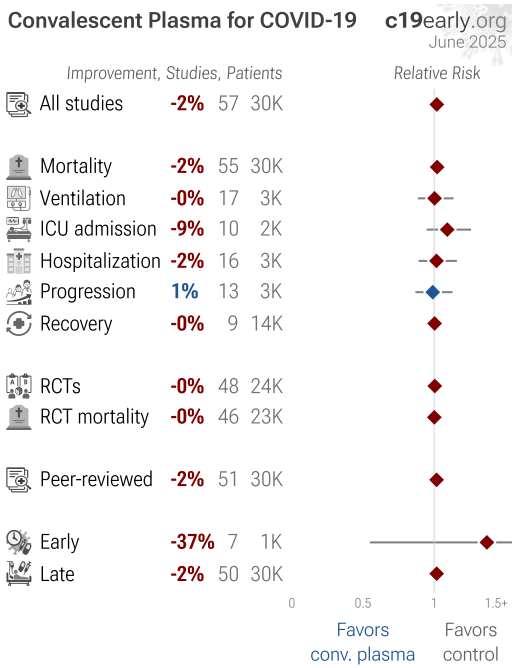
Abstract

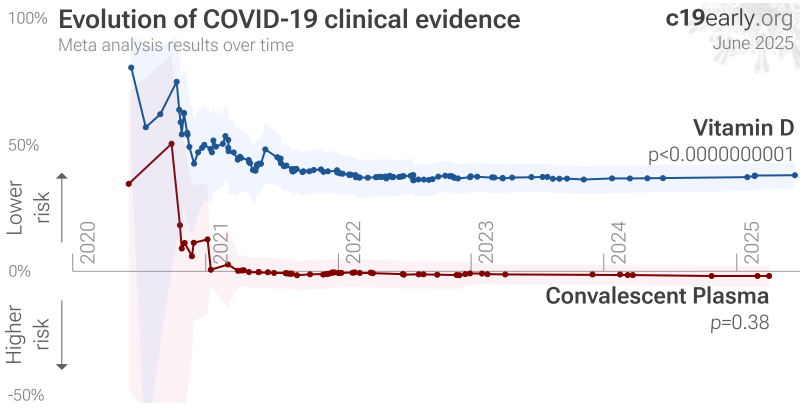
Meta analysis using the most serious outcome reported shows 2% [-2-6%] higher risk, without reaching statistical significance.

29 RCTs with 3,534 patients have not reported results (up to 4 years late).

All data and sources to reproduce this analysis are in the appendix.







CONVALESCENT PLASMA FOR COVID-19 — HIGHLIGHTS

Meta analysis of studies to date shows no significant improvements with convalescent plasma.

Real-time updates and corrections with a consistent protocol for 172 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

57 convalescent plasma COVID-19 studies (+29 unreported RCTs)

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June 2025

	Improvement, RR [CI]			Treatment	Control
Libster (DB RCT)	50%	0.50 [0.09-2.65]	death	2/80	4/80
Balcells (RCT)	-247%	3.47 [0.35-11.9]	death	5/28	2/30
Van Hise (RCT)	-441%	5.41 [0.29-101]	hosp.	3/49	0/23
Korley (RCT)	-396%	4.96 [0.58-42.2]	death	5/250	1/248
Alemany (DB RCT)	80%	0.20 [0.01-4.14]	death	0/188	2/188
Gharbharan (DB RCT)	-1%	1.01 [0.06-16.0]	death	1/207	1/209
Hoffmann (RCT)	51%	0.49 [0.05-5.27]	death	1/59	2/58
Keitel-A.. (DB RCT)	unknown, >3 years late			22 (total)	
Early treatment	**-37%**	**1.37 [0.55-3.42]**		**17/861**	**12/836**

$Tau^2 = 0.28$, $I^2 = 18.0\%$, $p = 0.51$

	Improvement, RR [CI]			Treatment	Control
Li (RCT)	35%	0.65 [0.27-1.39]	death	8/51	12/50
Avendaño-Solà (RCT)	88%	0.12 [0.01-2.11]	death	0/38	4/43
Agarwal (RCT)	-7%	1.07 [0.73-1.58]	death	34/235	31/229
Bajpai (RCT)	-323%	4.23 [0.43-41.6]	death	3/14	1/15
AlQahtani (RCT)	50%	0.50 [0.05-5.08]	death	1/20	2/20
Simonovich (RCT)	4%	0.96 [0.50-1.83]	death	25/228	12/105
Ray (RCT)	33%	0.67 [0.30-1.50]	death	10/40	14/40
Recovery Co.. (RCT)	0%	1.00 [0.93-1.07]	death	1,399/5,795	1,408/5,763
Gonzalez	-7%	1.07 [0.76-1.50]	death	60/130	26/60
Pouladza.. (SB RCT)	40%	0.60 [0.16-2.29]	death	3/30	5/30
Bennett-.. (DB RCT)	19%	0.81 [0.36-1.86]	death	16/59	5/15
Elhadi (ICU)	-16%	1.16 [0.88-1.54]	death	16/23	265/442
Teofili (RCT)	-100%	2.00 [0.16-24.3]	death	1/4	1/8
Gharbharan (RCT)	4%	0.96 [0.25-2.41]	death	6/43	11/43
Cho	-4%	1.04 [0.64-1.62]	death	402 (n)	4,642 (n)
Sekine (RCT)	-38%	1.38 [0.73-2.63]	death	18/80	13/80
Kirenga (RCT)	-21%	1.21 [0.51-2.89]	death	10/69	8/67
Hsue (DB RCT)	-212%	3.12 [0.14-71.7]	death	1/16	0/18
Devos (RCT)	1%	0.99 [0.52-1.88]	death	320 (n)	163 (n)
Bégin (RCT)	-13%	1.13 [0.88-1.45]	death	156/625	69/313
Körper (RCT)	37%	0.63 [0.33-1.22]	death	11/53	17/52
Abayomi (DB RCT)	-17%	1.17 [0.58-2.35]	death	7/11	6/11
Menichetti (RCT)	23%	0.77 [0.39-1.49]	death	14/231	19/240
Holm (RCT)	45%	0.55 [0.11-2.84]	death	2/17	3/14
Ortigoza (DB RCT)	12%	0.88 [0.63-1.20]	death	59/462	71/462
Bar (RCT)	81%	0.19 [0.04-0.84]	death	40 (n)	39 (n)
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van den Berg (RCT)	17%	0.83 [0.41-1.68]	death	11/52	13/51
Mesina	-29%	1.29 [0.70-2.36]	death	18/65	14/65
De Santis (RCT)	13%	0.87 [0.48-1.56]	death	11/36	25/71
Bajpai (RCT)	-14%	1.14 [0.76-1.69]	death	42/200	37/200
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Song (RCT)	-52%	1.52 [0.70-3.27]	death	22/87	7/42
Lacombe (RCT)	49%	0.51 [0.20-1.32]	death	7/60	12/60
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Iasella (PSM)	-26%	1.26 [0.93-1.71]	death	73/290	58/290
Shaheen (RCT)	0%	1.00 [0.43-2.31]	death	8/30	8/30
Sevdi (DB RCT)	unknown, >4 years late			60 (total)	
Averyanov (RCT)	unknown, >4 years late			60 (total)	
Torres (DB RCT)	unknown, >4 years late			150 (total)	
Chowdhury (RCT)	unknown, >4 years late			60 (est. total)	
Lubis (RCT)	unknown, >4 years late			60 (est. total)	
Cardesa Gil (RCT)	unknown, >4 years late			72 (total)	
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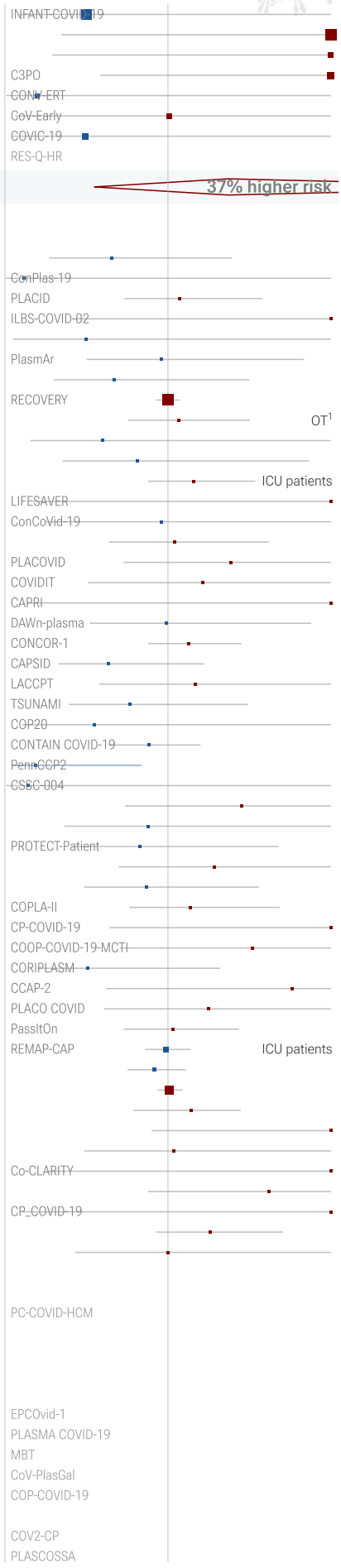
Torres (RCT)	unknown, >4 years late			200 (total)	
Fundacin B.. (RCT)	unknown, >4 years late			61 (total)	
Camacho.. (DB RCT)	unknown, >4 years late			31 (total)	
Herrick (DB RCT)	unknown, >4 years late			50 (est. total)	
Talarico (RCT)	unknown, >4 years late			400 (est. total)	
Martinaud (DB RCT)	unknown, >4 years late			18 (total)	



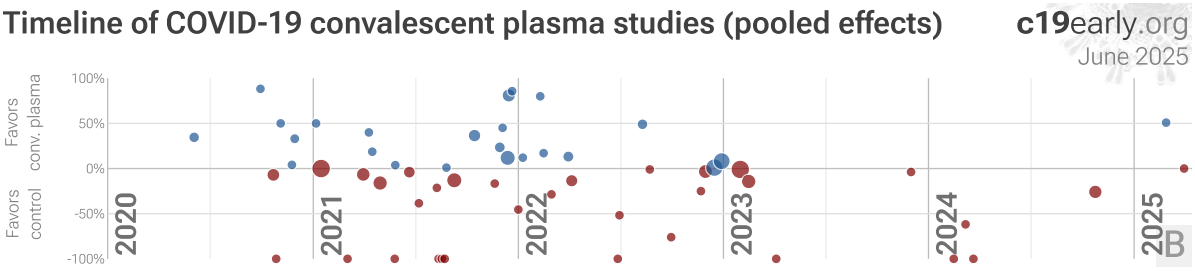


***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in convalescent plasma studies.**

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[2-14] and cognitive deficits[5,10], cardiovascular complications[15-19], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[20]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

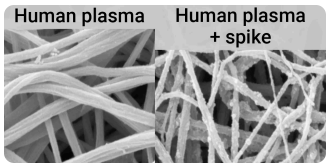


***Figure 2.* SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[1].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,21-28], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[29], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis

We analyze all significant controlled studies of convalescent plasma for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies,

studies within each treatment stage, individual outcomes, peer-reviewed studies, and Randomized Controlled Trials (RCTs).

Treatment timing

Figure 3 shows stages of possible treatment for COVID-19. Prophylaxis refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

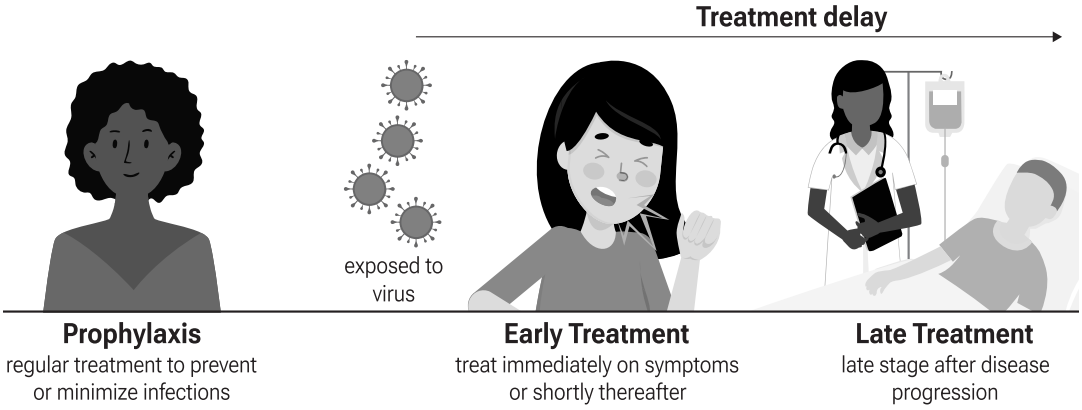


Figure 3. **Treatment stages.**

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Table 2 shows results by treatment stage. Figure 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, viral clearance, peer reviewed studies, and long COVID.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**-2%** [-6-2%]	57	31,852	1,960
Peer-reviewed studies	**-2%** [-6-2%]	51	31,294	1,900
Randomized Controlled Trials	**-0%** [-5-4%]	48	24,717	1,782
Mortality	**-2%** [-7-3%]	55	30,710	1,933
Ventilation	**-0%** [-14-11%]	17	3,663	559
ICU admission	**-9%** [-26-5%]	10	2,893	290
Hospitalization	**-2%** [-16-11%]	16	3,936	448
Recovery	**-0%** [-4-4%]	9	14,198	386
Viral	**4%** [-7-15%]	8	1,541	317
RCT mortality	**-0%** [-5-5%]	46	23,575	1,755
RCT hospitalization	**4%** [-9-16%]	14	3,560	438

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval.

	Early treatment	Late treatment
All studies	-37% [-242-45%]	-2% [-6-2%]
Peer-reviewed studies	-19% [-218-55%]	-2% [-6-2%]
Randomized Controlled Trials	-37% [-242-45%]	-0% [-5-4%]
Mortality	-19% [-218-55%]	-2% [-7-3%]
Ventilation	0% [-254-72%]	-0% [-14-12%]
ICU admission	67% [-35-92%]	-10% [-25-3%]
Hospitalization	10% [-18-31%]	-4% [-20-11%]
Recovery	-2% [-15-9%]	0% [-4-4%]
Viral	-4% [-11-3%]	13% [-12-33%]
RCT mortality	-19% [-218-55%]	-0% [-5-5%]
RCT hospitalization	10% [-18-31%]	3% [-13-17%]

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage.

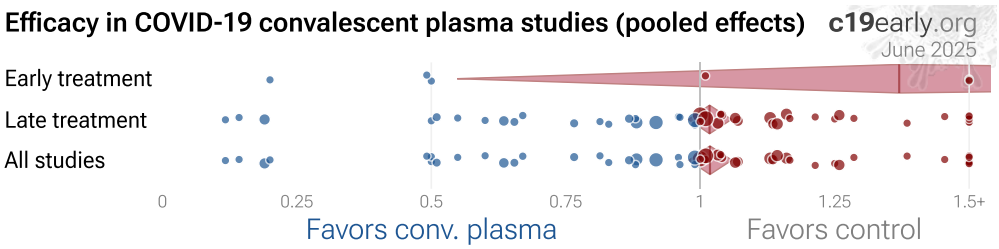


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

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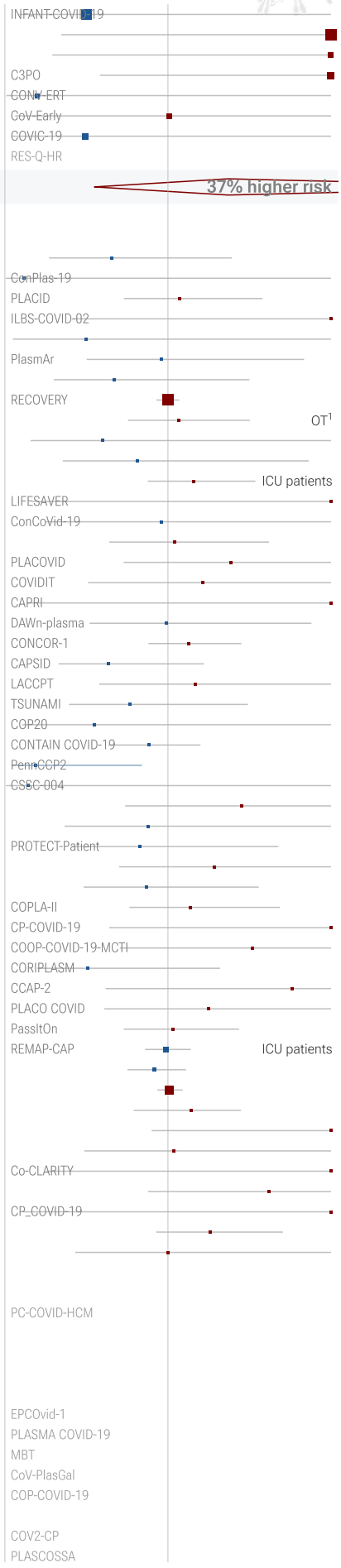

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55 convalescent plasma COVID-19 mortality results

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	Improvement	RR [CI]	Treatment	Control
Li (RCT)	35%	0.65 [0.27-1.39]	8/51	12/50
Avendaño-Solà (RCT)	88%	0.12 [0.01-2.11]	0/38	4/43
Agarwal (RCT)	-7%	1.07 [0.73-1.58]	34/235	31/229
Bajpai (RCT)	-323%	4.23 [0.43-41.6]	3/14	1/15
AlQahtani (RCT)	50%	0.50 [0.05-5.08]	1/20	2/20
Simonovich (RCT)	4%	0.96 [0.50-1.83]	25/228	12/105
Ray (RCT)	33%	0.67 [0.30-1.50]	10/40	14/40
Recovery Co.. (RCT)	0%	1.00 [0.93-1.07]	1,399/5,795	1,408/5,763
Gonzalez	-7%	1.07 [0.76-1.50]	60/130	26/60
Pouladza.. (SB RCT)	40%	0.60 [0.16-2.29]	3/30	5/30
Bennett-.. (DB RCT)	19%	0.81 [0.36-1.86]	16/59	5/15
Elhadi (ICU)	-16%	1.16 [0.88-1.54]	16/23	265/442
Teofili (RCT)	-100%	2.00 [0.16-24.3]	1/4	1/8
Gharbharan (RCT)	4%	0.96 [0.25-2.41]	6/43	11/43
Cho	-4%	1.04 [0.64-1.62]	402 (n)	4,642 (n)
Sekine (RCT)	-38%	1.38 [0.73-2.63]	18/80	13/80
Kirenga (RCT)	-21%	1.21 [0.51-2.89]	10/69	8/67
Hsue (DB RCT)	-212%	3.12 [0.14-71.7]	1/16	0/18
Devos (RCT)	1%	0.99 [0.52-1.88]	320 (n)	163 (n)
Bégin (RCT)	-13%	1.13 [0.88-1.45]	156/625	69/313
Körper (RCT)	37%	0.63 [0.33-1.22]	11/53	17/52
Abayomi (DB RCT)	-17%	1.17 [0.58-2.35]	7/11	6/11
Menichetti (RCT)	23%	0.77 [0.39-1.49]	14/231	19/240
Holm (RCT)	45%	0.55 [0.11-2.84]	2/17	3/14
Ortigoza (DB RCT)	12%	0.88 [0.63-1.20]	59/462	71/462
Bar (RCT)	81%	0.19 [0.04-0.84]	40 (n)	39 (n)
Sullivan (DB RCT)	86%	0.14 [0.01-2.75]	0/592	3/589
Jalili (RCT)	-45%	1.45 [0.74-2.87]	16/60	11/60
Baldeón (DB RCT)	12%	0.88 [0.37-2.11]	7/63	12/95
van den Berg (RCT)	17%	0.83 [0.41-1.68]	11/52	13/51
Mesina	-29%	1.29 [0.70-2.36]	18/65	14/65
De Santis (RCT)	13%	0.87 [0.48-1.56]	11/36	25/71
Bajpai (RCT)	-14%	1.14 [0.76-1.69]	42/200	37/200
Rojas (SB RCT)	-220%	3.20 [0.64-16.0]	46 (n)	45 (n)
Song (RCT)	-52%	1.52 [0.70-3.27]	22/87	7/42
Lacombe (RCT)	49%	0.51 [0.20-1.32]	7/60	12/60
Thorlaci.. (DB RCT)	-76%	1.76 [0.62-5.01]	15/98	4/46
Manzini (DB RCT)	-25%	1.25 [0.61-2.57]	14/60	12/60
Self (DB RCT)	-3%	1.03 [0.73-1.44]	89/482	80/465
Higgins (RCT)	1%	0.99 [0.86-1.14]	370/944	324/790
Denkinger (RCT)	8%	0.92 [0.75-1.11]	68 (n)	66 (n)
Alshamrani (PSM)	-14%	1.14 [0.79-1.45]	24/41	108/205
Krishnan	-270%	3.70 [0.90-15.8]	case control	
Kasten	-4%	1.04 [0.49-2.21]	7/19	11/31
Gauiran (RCT)	-400%	5.00 [0.25-98.5]	2/22	0/22
Lewandowski	-62%	1.62 [0.88-2.98]	430 (all patients)	
Khawaja (DB RCT)	-154%	2.54 [0.11-59.6]	1/37	0/20
Iasella (PSM)	-26%	1.26 [0.93-1.71]	73/290	58/290
Shaheen (RCT)	0%	1.00 [0.43-2.31]	8/30	8/30
Late treatment	-2%	1.02 [0.97-1.07]	2,597/12,388	2,742/16,267

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.4$

All studies	-2%	1.02 [0.97-1.07]	2,611/13,200	2,754/17,080

[1] OT: comparison with other treatment

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.39$

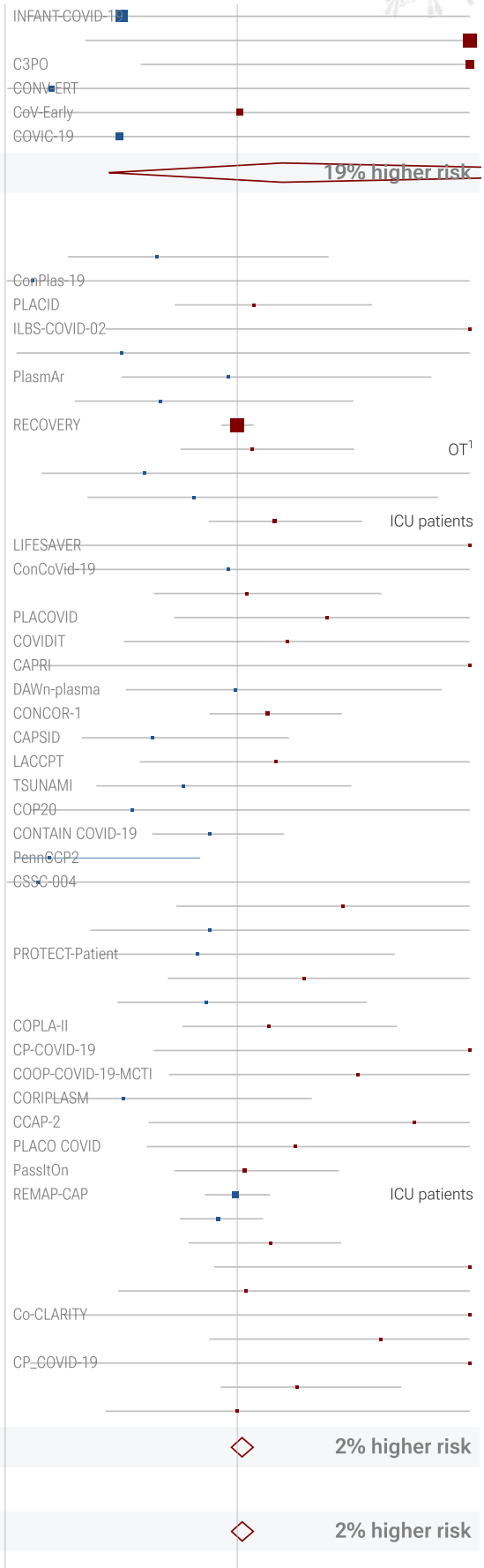

Figure 6. Random effects meta-analysis for mortality results.

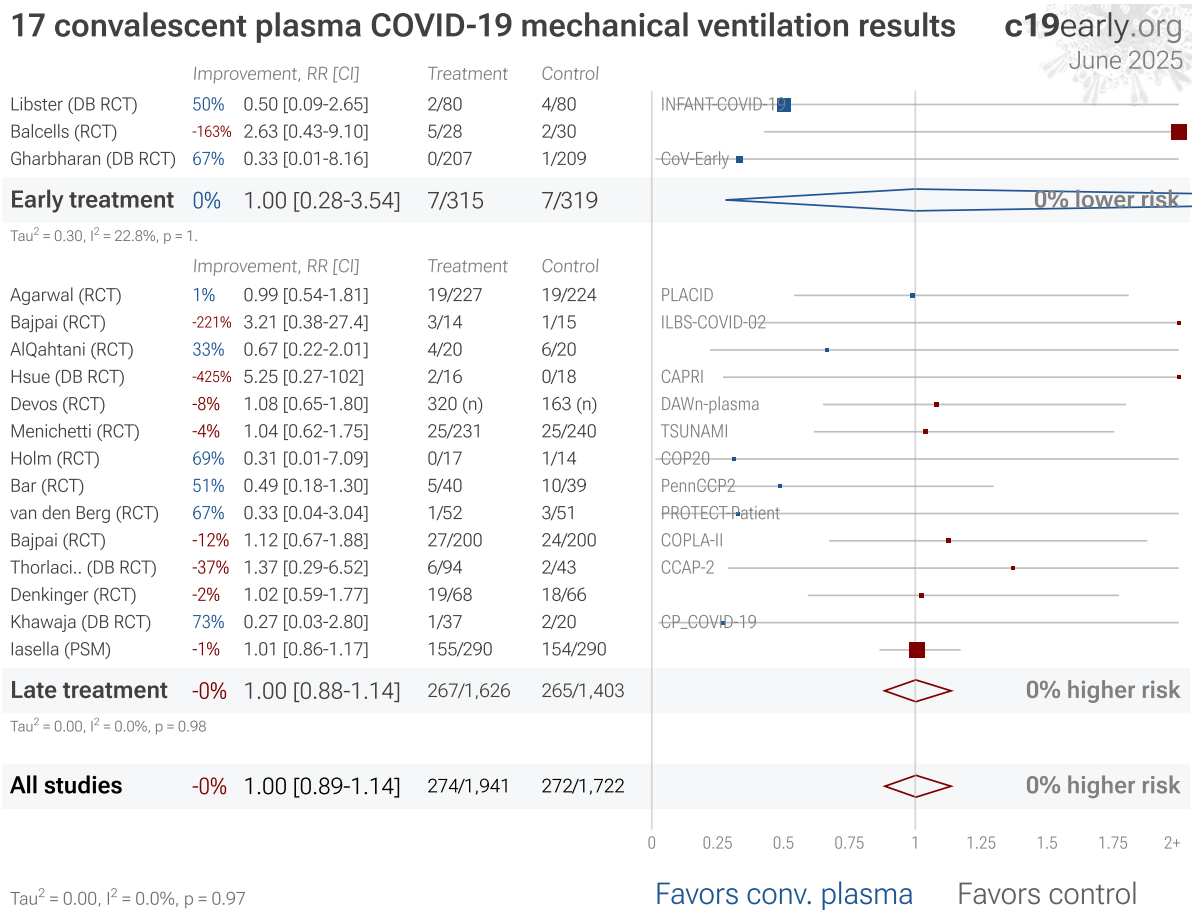

Figure 7. Random effects meta-analysis for ventilation.

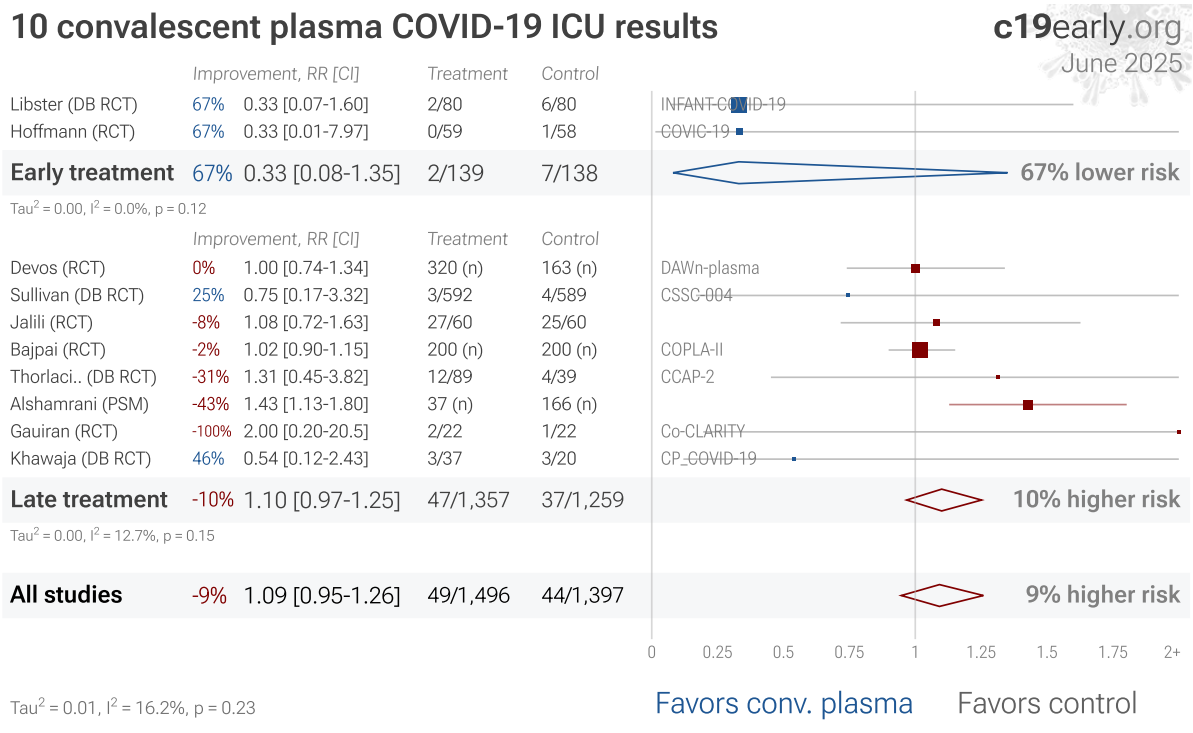

Figure 8. Random effects meta-analysis for ICU admission.

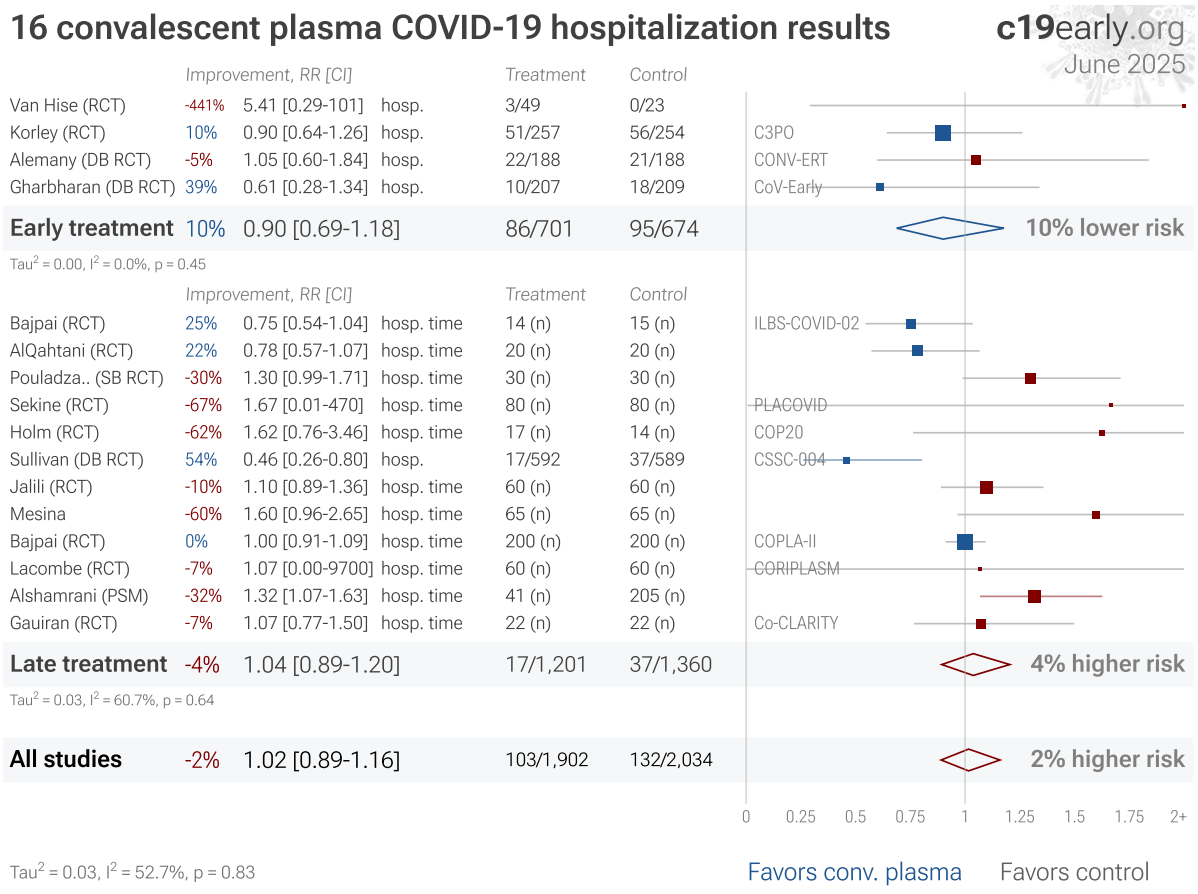

Figure 9. Random effects meta-analysis for hospitalization.

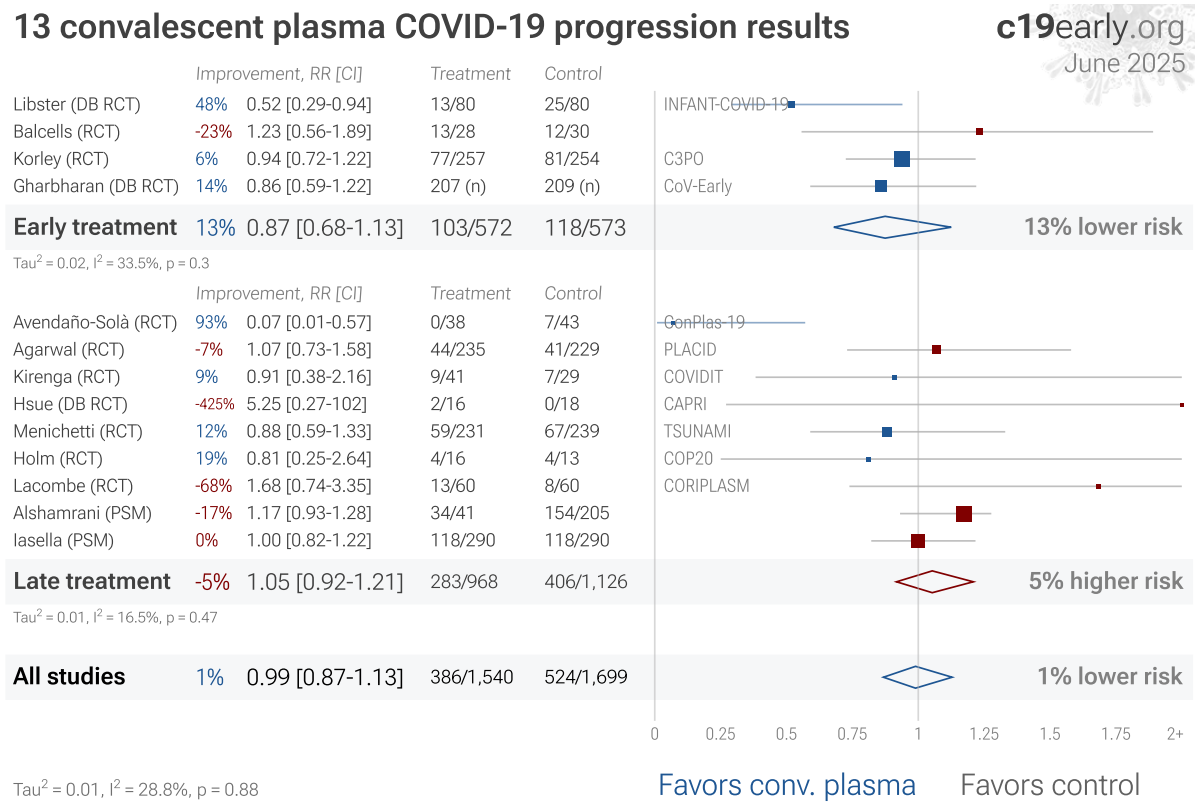

Figure 10. Random effects meta-analysis for progression.

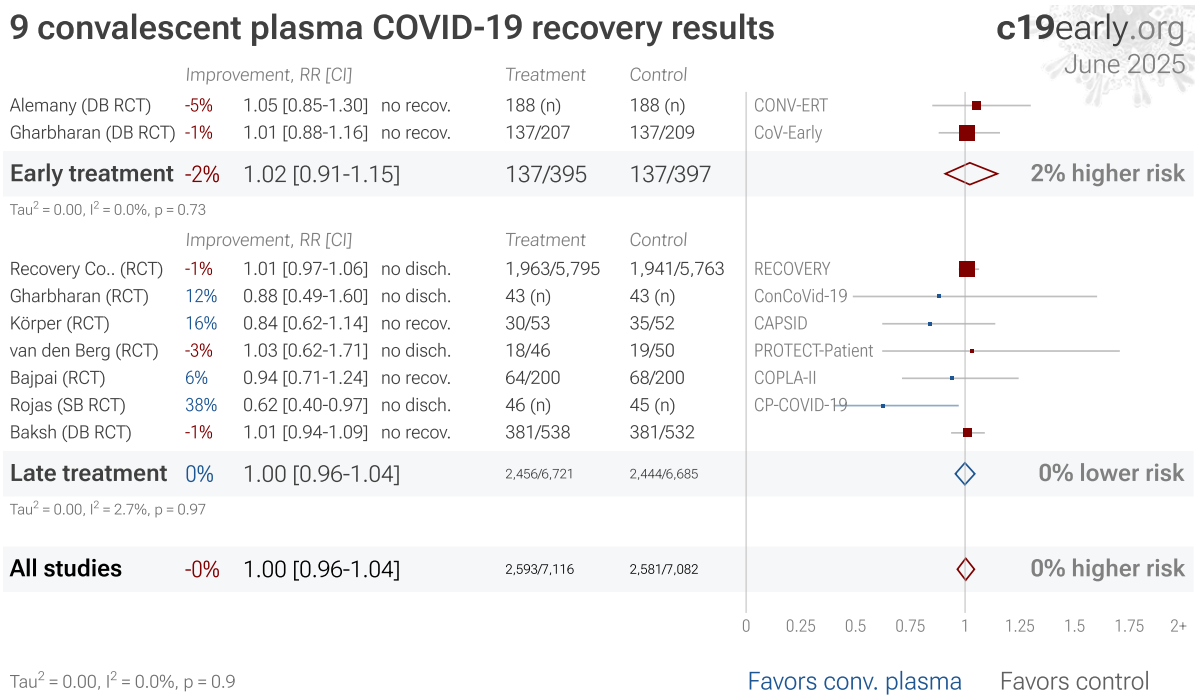

Figure 11. Random effects meta-analysis for recovery.

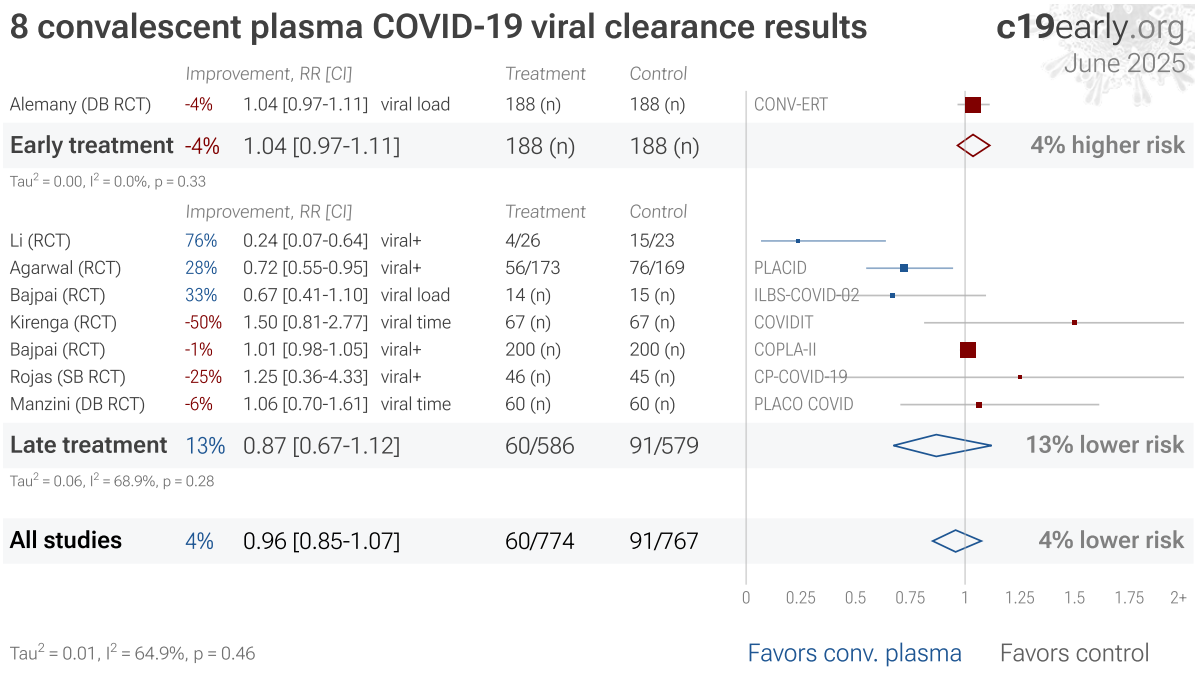

Figure 12. Random effects meta-analysis for viral clearance.

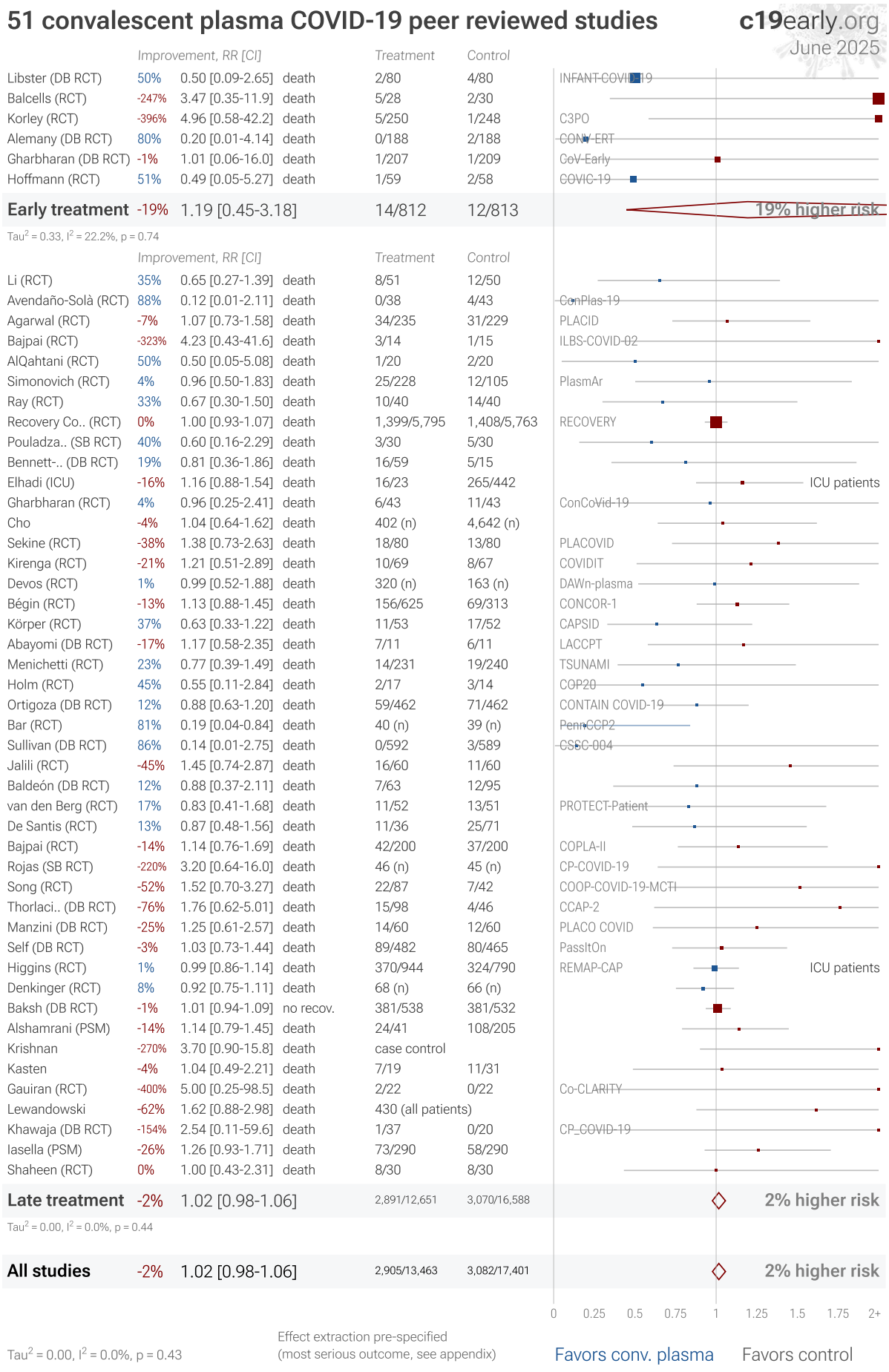

Figure 13. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found

below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

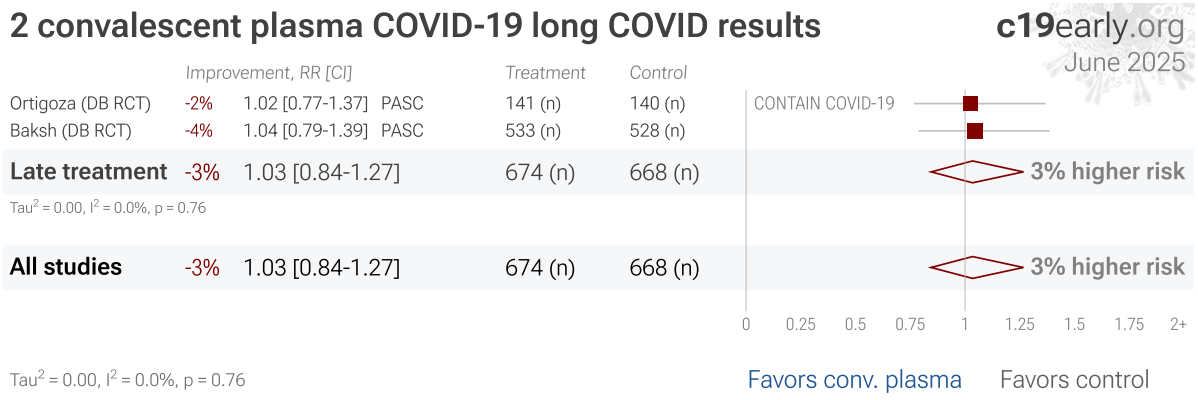

Figure 14. **Random effects meta-analysis for long COVID.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Figure 15 shows a comparison of results for RCTs and non-RCT studies. Figure 16, 17, and 18 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

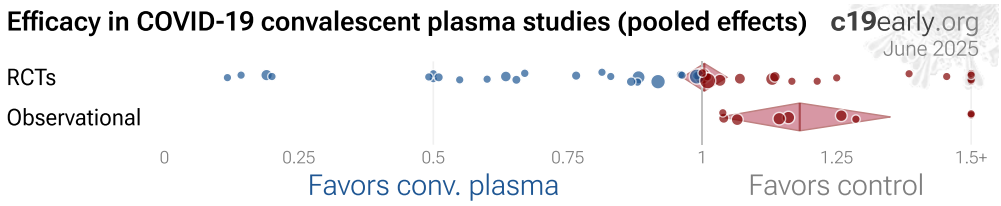

Figure 15. **Results for RCTs and non-RCT studies.**

48 convalescent plasma COVID-19 Randomized Controlled Trials

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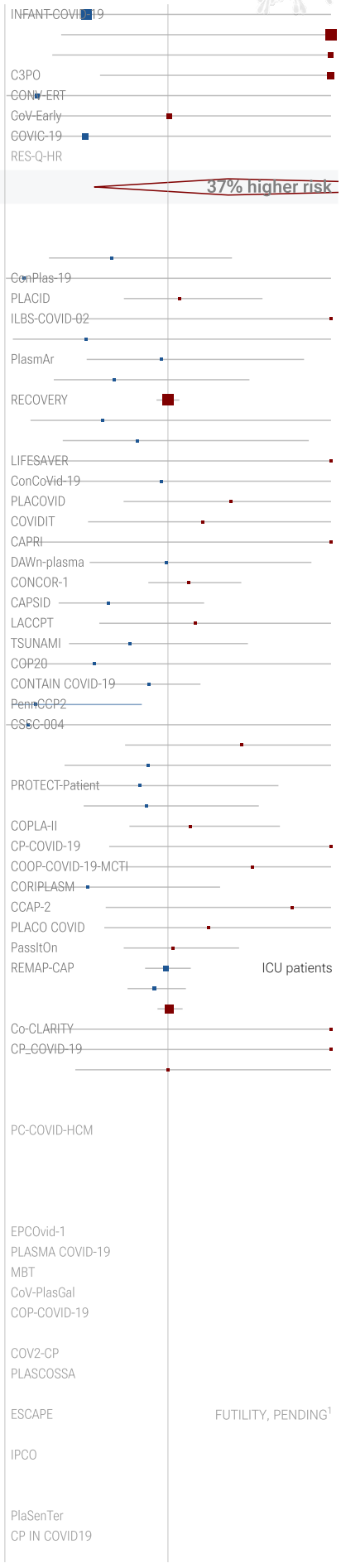
	Improvement, RR [CI]			Treatment	Control
Libster (DB RCT)	50%	0.50 [0.09-2.65]	death	2/80	4/80
Balcells (RCT)	-247%	3.47 [0.35-11.9]	death	5/28	2/30
Van Hise (RCT)	-441%	5.41 [0.29-101]	hosp.	3/49	0/23
Korley (RCT)	-396%	4.96 [0.58-42.2]	death	5/250	1/248
Alemany (DB RCT)	80%	0.20 [0.01-4.14]	death	0/188	2/188
Gharbharan (DB RCT)	-1%	1.01 [0.06-16.0]	death	1/207	1/209
Hoffmann (RCT)	51%	0.49 [0.05-5.27]	death	1/59	2/58
Keitel-A.. (DB RCT)	unknown, >3 years late			22 (total)	
Early treatment	**-37%**	**1.37 [0.55-3.42]**		**17/861**	**12/836**

$Tau^2 = 0.28$, $I^2 = 18.0\%$, $p = 0.51$

	Improvement, RR [CI]			Treatment	Control
Li (RCT)	35%	0.65 [0.27-1.39]	death	8/51	12/50
Avendaño-Solà (RCT)	88%	0.12 [0.01-2.11]	death	0/38	4/43
Agarwal (RCT)	-7%	1.07 [0.73-1.58]	death	34/235	31/229
Bajpai (RCT)	-323%	4.23 [0.43-41.6]	death	3/14	1/15
AlQahtani (RCT)	50%	0.50 [0.05-5.08]	death	1/20	2/20
Simonovich (RCT)	4%	0.96 [0.50-1.83]	death	25/228	12/105
Ray (RCT)	33%	0.67 [0.30-1.50]	death	10/40	14/40
Recovery Co.. (RCT)	0%	1.00 [0.93-1.07]	death	1,399/5,795	1,408/5,763
Pouladza.. (SB RCT)	40%	0.60 [0.16-2.29]	death	3/30	5/30
Bennett-.. (DB RCT)	19%	0.81 [0.36-1.86]	death	16/59	5/15
Teofili (RCT)	-100%	2.00 [0.16-24.3]	death	1/4	1/8
Gharbharan (RCT)	4%	0.96 [0.25-2.41]	death	6/43	11/43
Sekine (RCT)	-38%	1.38 [0.73-2.63]	death	18/80	13/80
Kirenga (RCT)	-21%	1.21 [0.51-2.89]	death	10/69	8/67
Hsue (DB RCT)	-212%	3.12 [0.14-71.7]	death	1/16	0/18
Devos (RCT)	1%	0.99 [0.52-1.88]	death	320 (n)	163 (n)
Bégin (RCT)	-13%	1.13 [0.88-1.45]	death	156/625	69/313
Körper (RCT)	37%	0.63 [0.33-1.22]	death	11/53	17/52
Abayomi (DB RCT)	-17%	1.17 [0.58-2.35]	death	7/11	6/11
Menichetti (RCT)	23%	0.77 [0.39-1.49]	death	14/231	19/240
Holm (RCT)	45%	0.55 [0.11-2.84]	death	2/17	3/14
Ortigoza (DB RCT)	12%	0.88 [0.63-1.20]	death	59/462	71/462
Bar (RCT)	81%	0.19 [0.04-0.84]	death	40 (n)	39 (n)
Sullivan (DB RCT)	86%	0.14 [0.01-2.75]	death	0/592	3/589
Jalili (RCT)	-45%	1.45 [0.74-2.87]	death	16/60	11/60
Baldeón (DB RCT)	12%	0.88 [0.37-2.11]	death	7/63	12/95
van den Berg (RCT)	17%	0.83 [0.41-1.68]	death	11/52	13/51
De Santis (RCT)	13%	0.87 [0.48-1.56]	death	11/36	25/71
Bajpai (RCT)	-14%	1.14 [0.76-1.69]	death	42/200	37/200
Rojas (SB RCT)	-220%	3.20 [0.64-16.0]	death	46 (n)	45 (n)
Song (RCT)	-52%	1.52 [0.70-3.27]	death	22/87	7/42
Lacombe (RCT)	49%	0.51 [0.20-1.32]	death	7/60	12/60
Thorlaci.. (DB RCT)	-76%	1.76 [0.62-5.01]	death	15/98	4/46
Manzini (DB RCT)	-25%	1.25 [0.61-2.57]	death	14/60	12/60
Self (DB RCT)	-3%	1.03 [0.73-1.44]	death	89/482	80/465
Higgins (RCT)	1%	0.99 [0.86-1.14]	death	370/944	324/790
Denkinger (RCT)	8%	0.92 [0.75-1.11]	death	68 (n)	66 (n)
Baksh (DB RCT)	-1%	1.01 [0.94-1.09]	no recov.	381/538	381/532
Gauiran (RCT)	-400%	5.00 [0.25-98.5]	death	2/22	0/22
Khawaja (DB RCT)	-154%	2.54 [0.11-59.6]	death	1/37	0/20
Shaheen (RCT)	0%	1.00 [0.43-2.31]	death	8/30	8/30
Sevdi (DB RCT)	unknown, >4 years late			60 (total)	
Averyanov (RCT)	unknown, >4 years late			60 (total)	
Torres (DB RCT)	unknown, >4 years late			150 (total)	
Chowdhury (RCT)	unknown, >4 years late			60 (est. total)	
Lubis (RCT)	unknown, >4 years late			60 (est. total)	
Cardesa Gil (RCT)	unknown, >4 years late			72 (total)	
Zuluaga (SB RCT)	unknown, >4 years late			60 (est. total)	
Sierra-M.. (DB RCT)	unknown, >4 years late			410 (est. total)	
Quintero.. (SB RCT)	unknown, >4 years late			236 (est. total)	
Torres (RCT)	unknown, >4 years late			200 (total)	
Fundacin B.. (RCT)	unknown, >4 years late			61 (total)	
Camacho.. (DB RCT)	unknown, >4 years late			31 (total)	
Herrick (DB RCT)	unknown, >4 years late			50 (est. total)	
Talarico (RCT)	unknown, >4 years late			400 (est. total)	
Martinaud (DB RCT)	unknown, >4 years late			18 (total)	
Gonzalez (RCT)	unknown, >3 years late			134 (total)	
Kaufman (DB RCT)	unknown, >3 years late			45 (total)	
Pathak (RCT)	unknown, >3 years late			100 (total)	
Schiffer (RCT)	unknown, >3 years late			58 (est. total)	
Perilla (RCT)	unknown, >3 years late			231 (est. total)	
de la Pu.. (DB RCT)	unknown, >3 years late			93 (total)	
Karyana (RCT)	unknown, >3 years late			364 (est. total)	
ElDesouky (RCT)	unknown, >3 years late			67 (est. total)	
Dillner (RCT)	unknown, >3 years late			59 (total)	



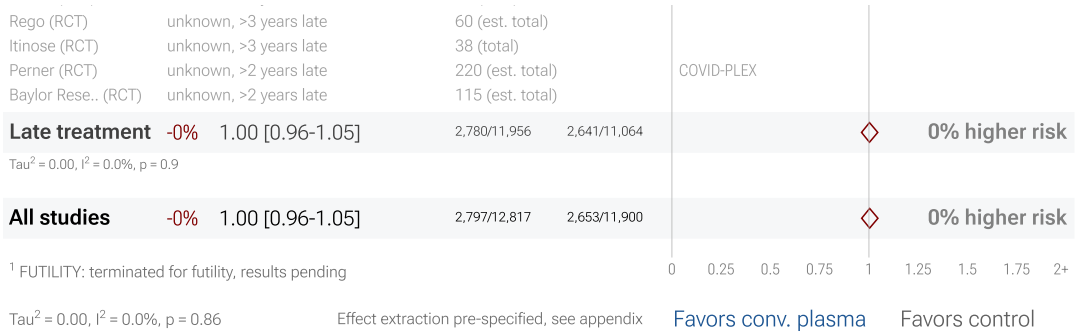


Figure 16. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

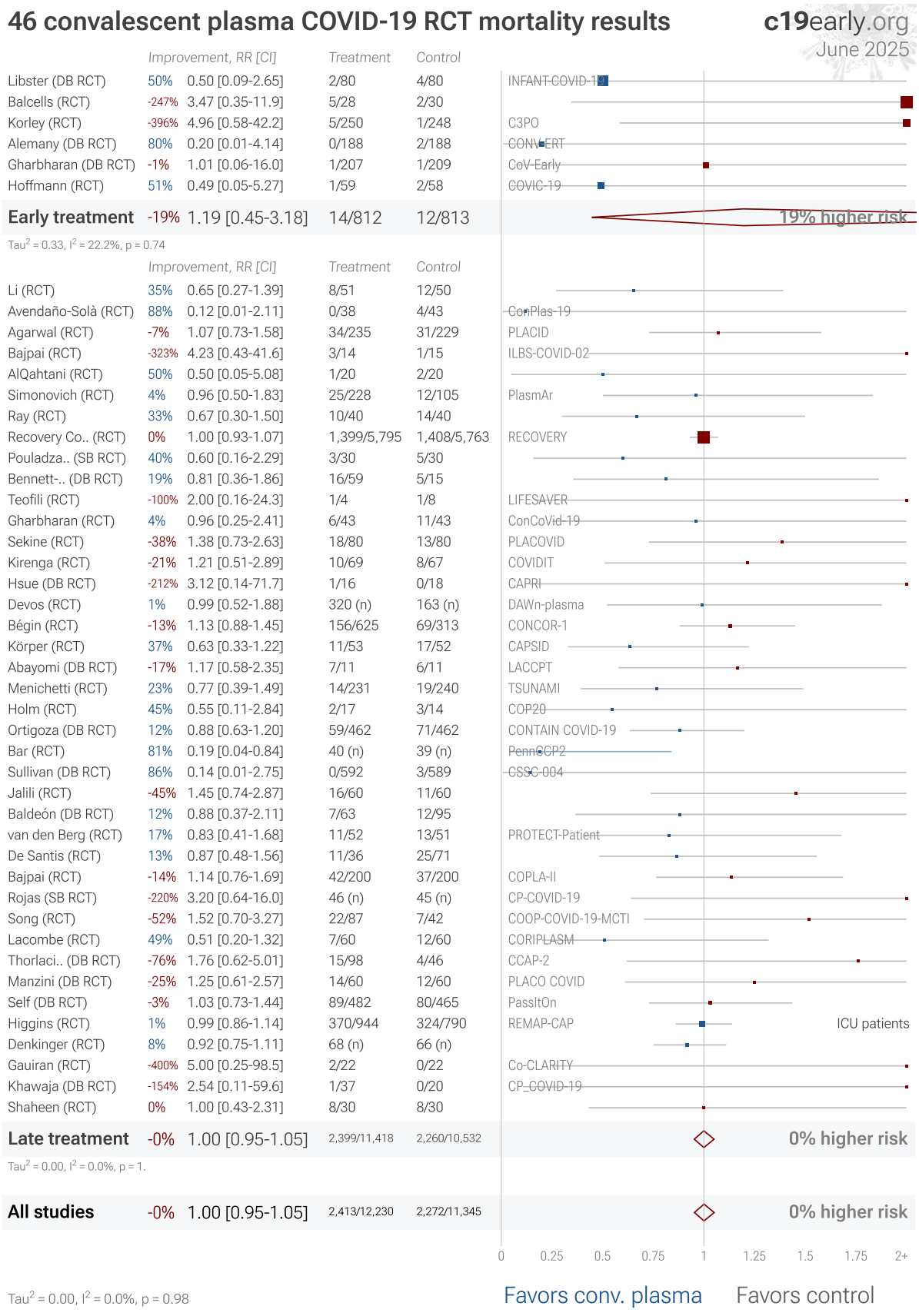


Figure 17. Random effects meta-analysis for RCT mortality results.

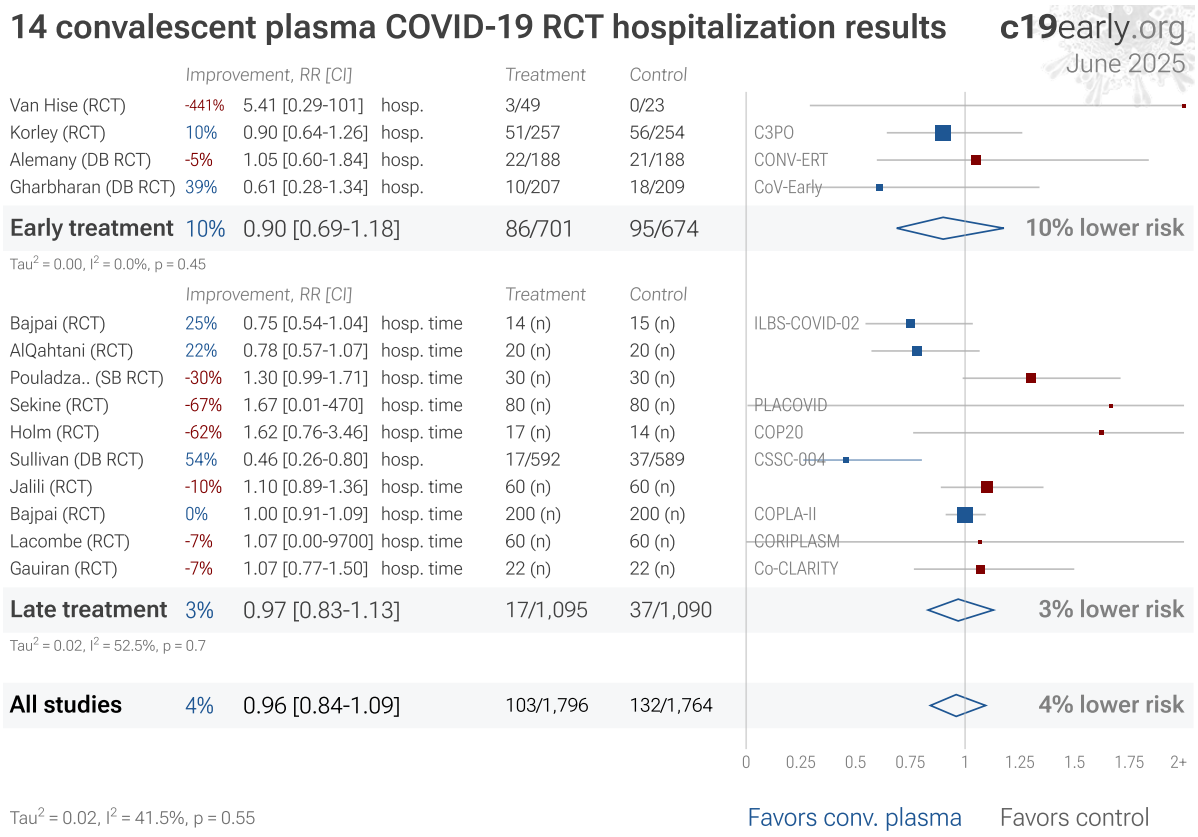


Figure 18. **Random effects meta-analysis for RCT hospitalization results.**

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases[32], and analysis of double-blind RCTs has identified extreme levels of bias[33]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way.

Every treatment RCT to date involves delayed treatment. Among the 172 treatments we have analyzed, 67% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

Using all studies identifies efficacy 8+ months faster (9+ months for low-cost treatments)

Currently, 54 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 59% have been confirmed in RCTs, with a mean delay of 7.7 months (66% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

Summary

We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

Unreported RCTs

29 convalescent plasma RCTs have not reported results[35-63]. The trials report a total of 3,534 patients, with 15 trials having actual enrollment of 1,143, and the remainder estimated. The results are delayed from 2 years to over 4 years.

Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours[64,65]. Baloxavir marboxil studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post-exposure prophylaxis	86% fewer cases[66]
<24 hours	-33 hours symptoms[67]
24-48 hours	-13 hours symptoms[67]
Inpatients	-2.5 hours to improvement[68]

Table 3. **Studies of baloxavir marboxil for influenza show that early treatment is more effective.**

Figure 19 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

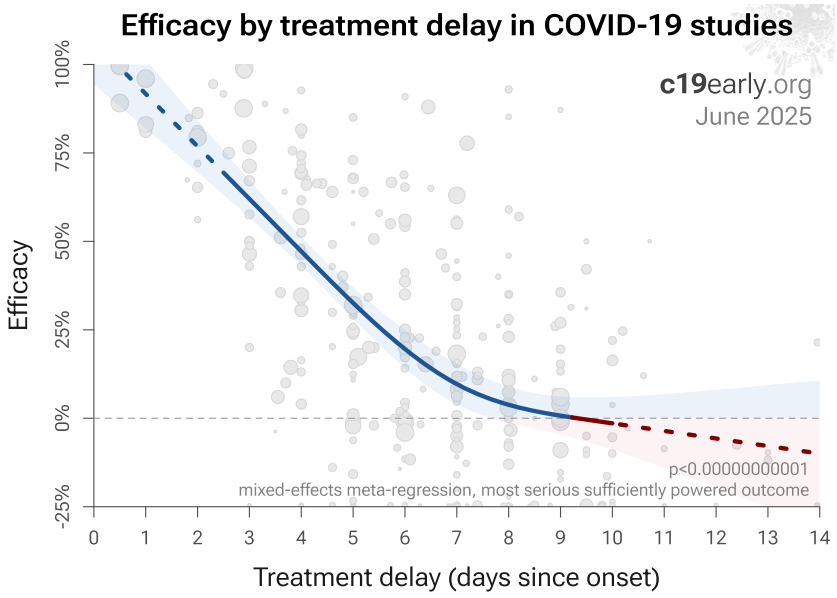


Figure 19. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results, for example as in *López-Medina et al.*

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [70], for example the Gamma variant shows significantly different characteristics [71-74]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants [75,76].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams et al.* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu et al.* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic [79-95], therefore efficacy may depend strongly on combined treatments.

Effect measured

Across all studies there is a strong association between different outcomes, for example improved recovery is strongly associated with lower mortality. However, efficacy may differ depending on the effect measured, for example a treatment may be more effective against secondary complications and have minimal effect on viral clearance.

Meta analysis

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though early treatment is very effective. All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Pooled Effects

Combining studies is required

For COVID-19, delay in clinical results translates into additional death and morbidity, as well as additional economic and societal damage. Combining the results of studies reporting different outcomes is required. There may be no mortality in a trial with low-risk patients, however a reduction in severity or improved viral clearance may translate into lower mortality in a high-risk population. Different studies may report lower severity, improved recovery, and lower mortality, and the significance may be very high when combining the results. "*The studies reported different outcomes*" is not a good reason for disregarding results. Pooling the results of studies reporting different outcomes allows us to use more of the available information. Logically we should, and do, use additional information when evaluating treatments—for example dose-response and treatment delay-response relationships provide additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

Trials with high-risk patients may be restricted due to ethics for treatments that are known or expected to be effective, and they increase difficulty for recruiting. Using less severe outcomes as a proxy for more serious outcomes allows faster and safer collection of evidence.

Validating pooled outcome analysis for COVID-19

For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, which follows from a reduction in PCR positivity. We can directly test this for COVID-19.

Analysis of the the association between different outcomes across studies from all 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 20 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 21 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an

association between viral clearance and hospitalization or death, with *p = 0.003* after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 22 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from *p = 0.00000009* to *p = 0.0000000039*.

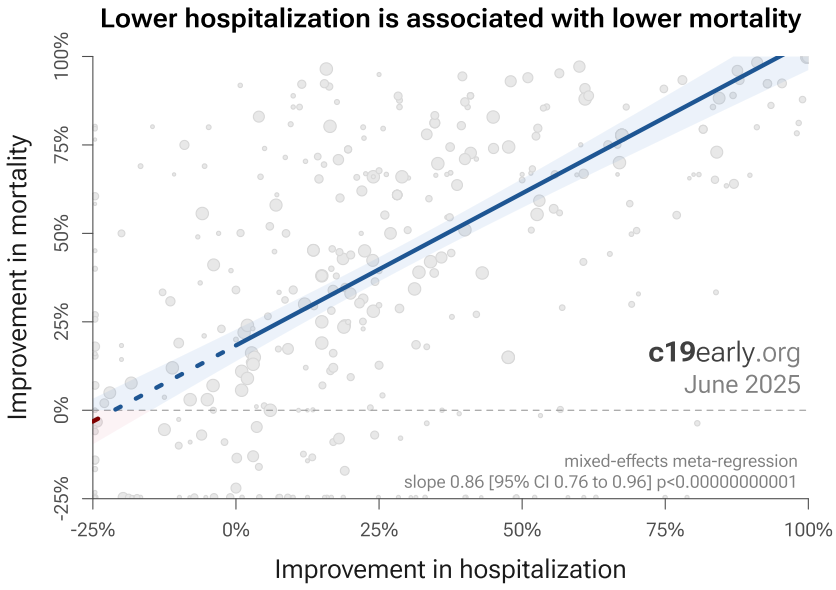


Figure 20. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

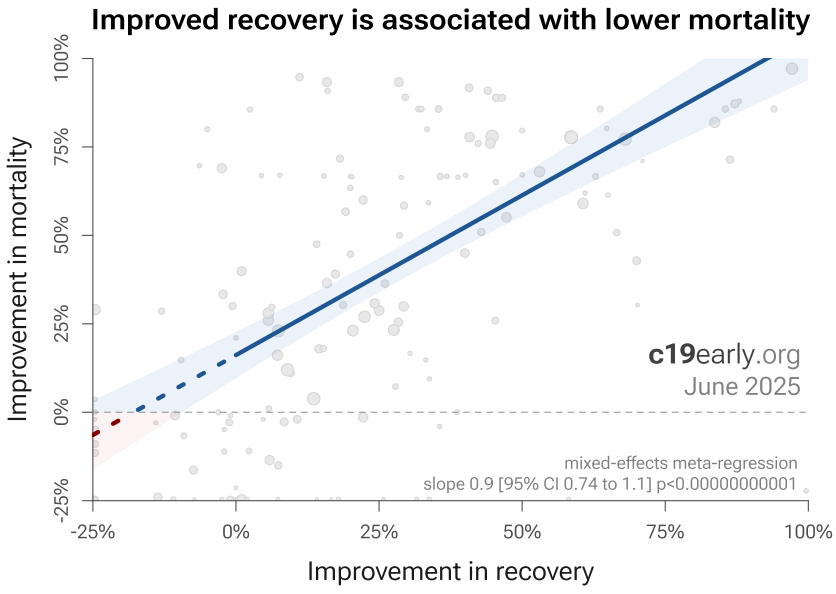


Figure 21. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

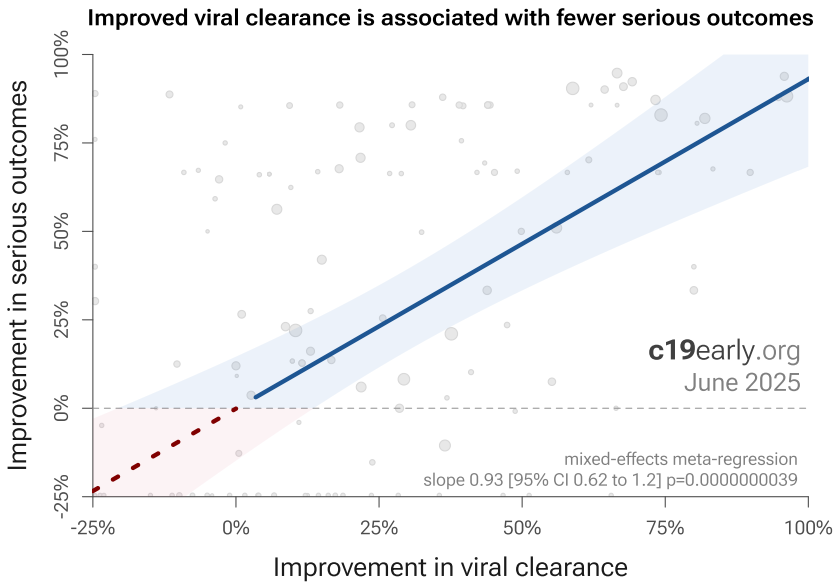


Figure 20. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (7 months for RCTs)

Currently, 54 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 90% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 23 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

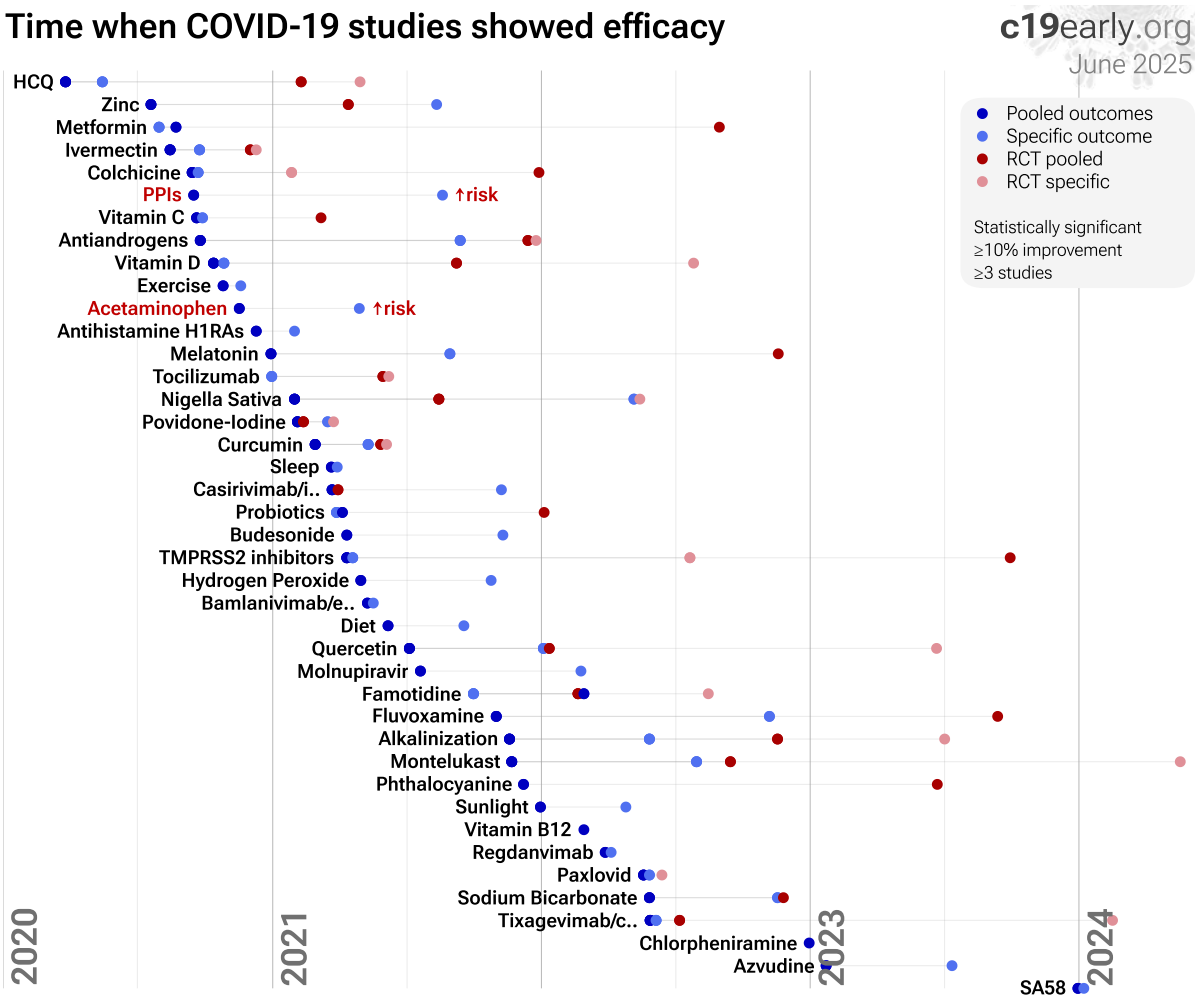


Figure 23. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

Pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral clearance may show no efficacy if most studies only examine viral clearance. In practice, it is rare for a non-antiviral treatment to report viral clearance and to not report clinical outcomes; and in practice other sources of heterogeneity such as difference in treatment delay is more likely to hide efficacy.

Summary

Analysis validates the use of pooled effects and shows significantly faster detection of efficacy on average. However, as with all meta analyses, it is important to review the different studies included. We also present individual outcome analyses, which may be more informative for specific use cases.

Discussion

Publication bias

Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and

CTRI/2021/08/0354242). For convalescent plasma, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis

Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 24 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry ($p > 0.05$). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, $p < 0.0001$, with six variants of Egger's test all showing $p < 0.05$ [97-104]. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.

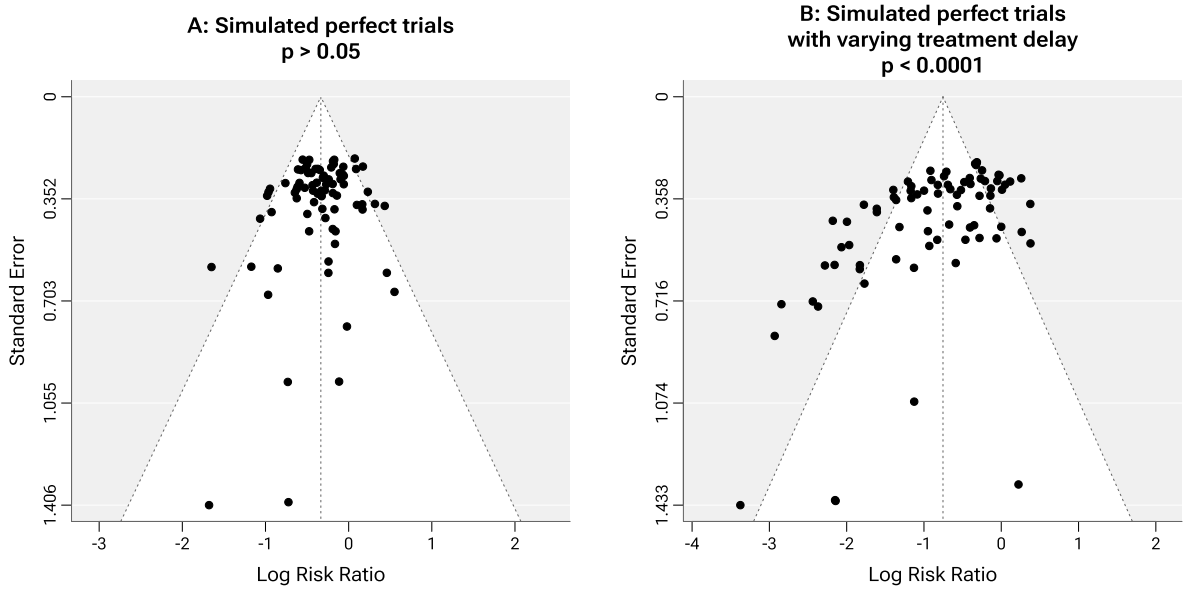


Figure 24. **Example funnel plot analysis for simulated perfect trials.**

Limitations

Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials with conflicts of interest may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone [79-95]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Notes

1 of the 57 studies compare against other treatments, which may reduce the effect seen.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors [21-28], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [29], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 25 shows an overview of the results for convalescent plasma in the context of multiple COVID-19 treatments, and Figure 26 shows a plot of efficacy vs. cost for COVID-19 treatments.

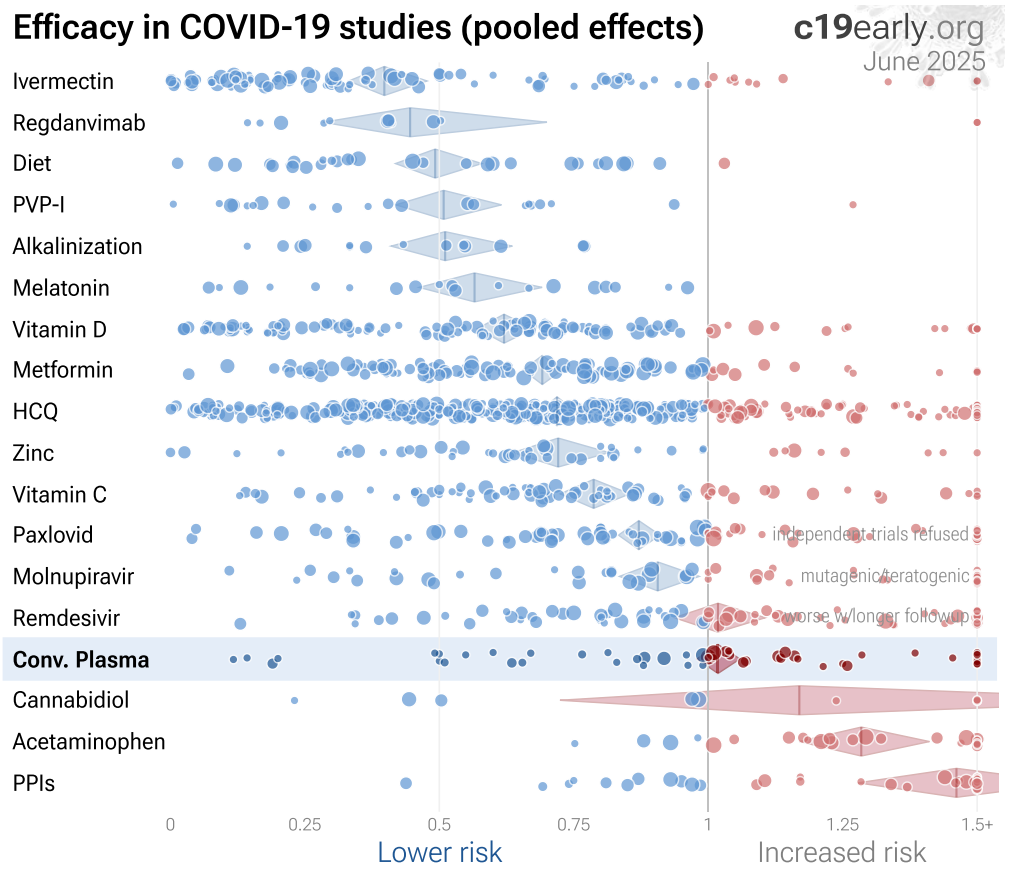


Figure 25. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [105].

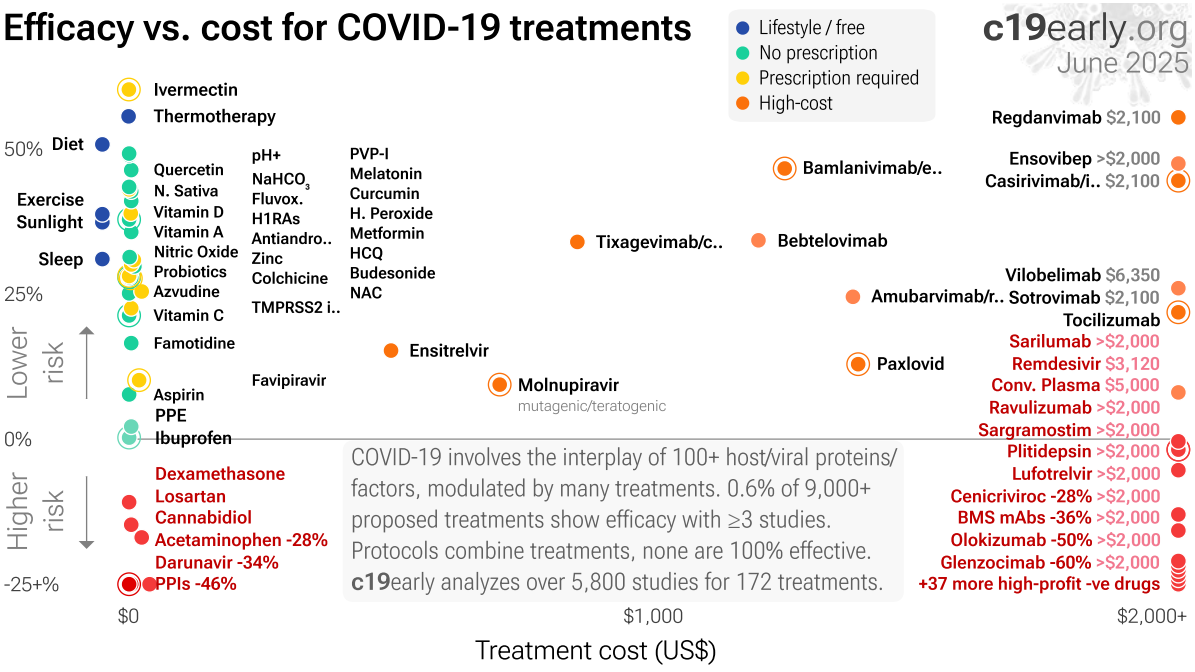


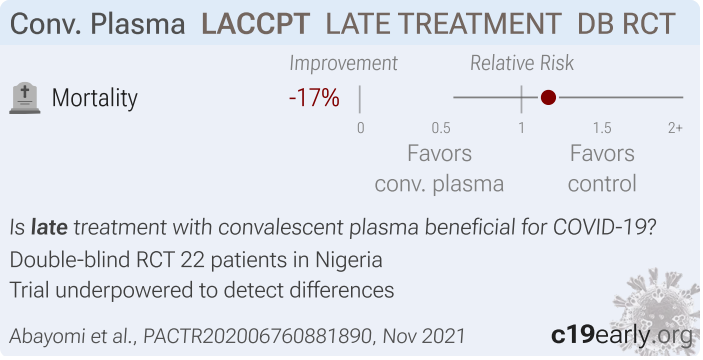
Figure 26. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

Meta analysis using the most serious outcome reported shows 2% [-2-6%] higher risk, without reaching statistical significance.

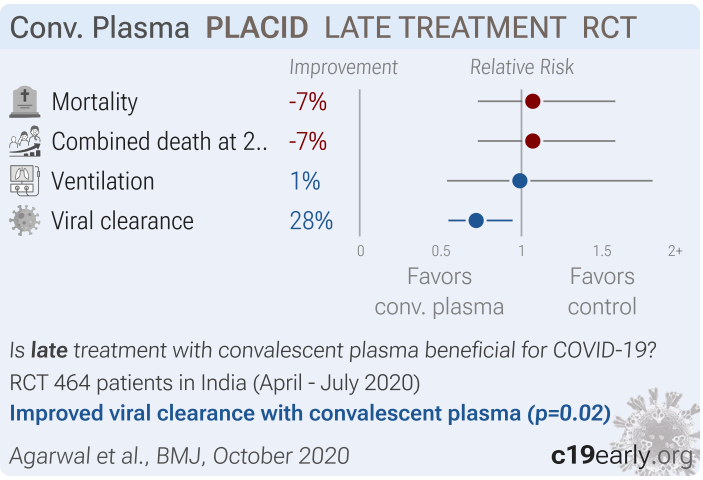
Study Notes

Abayomi



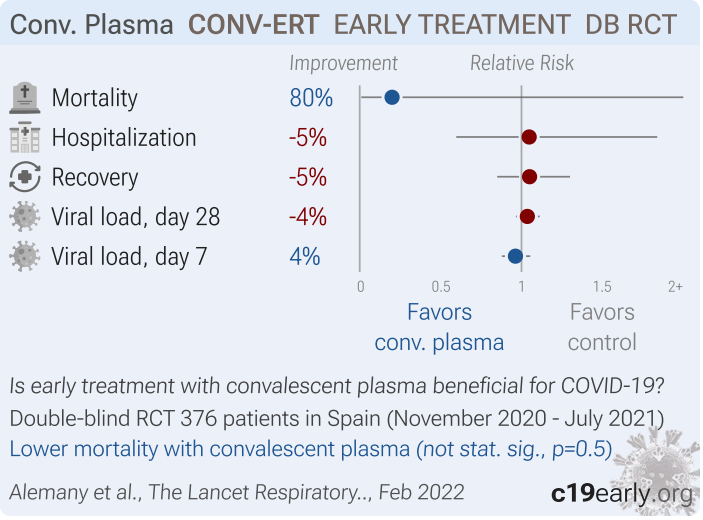
RCT 22 hospitalized patients, show no significant difference in mortality with convalescent plasma. Results are from *Axfors et al.*.

Agarwal



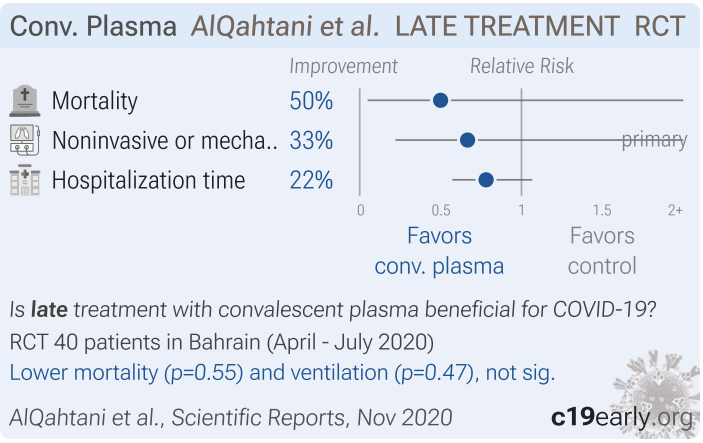
RCT 464 hospitalized patients in India, 235 treated with convalescent plasma, showing no improvement in combined death at 28 days or progression to severe disease.

Alemany



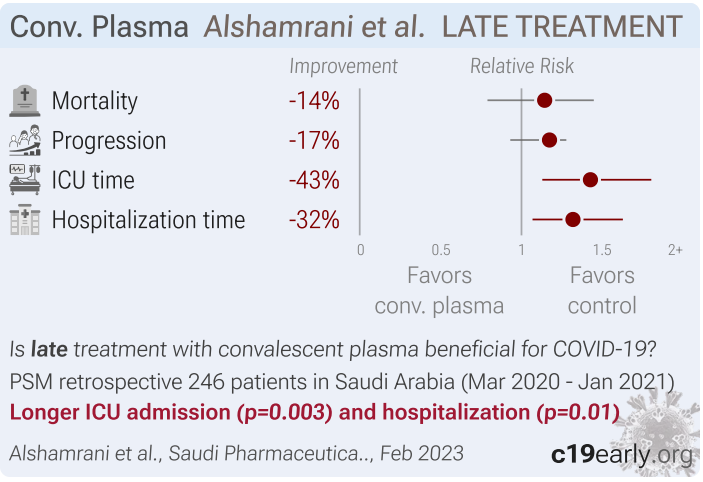
RCT 188 convalescent plasma and 188 control patients, showing no significant difference in outcomes.

AlQahtani



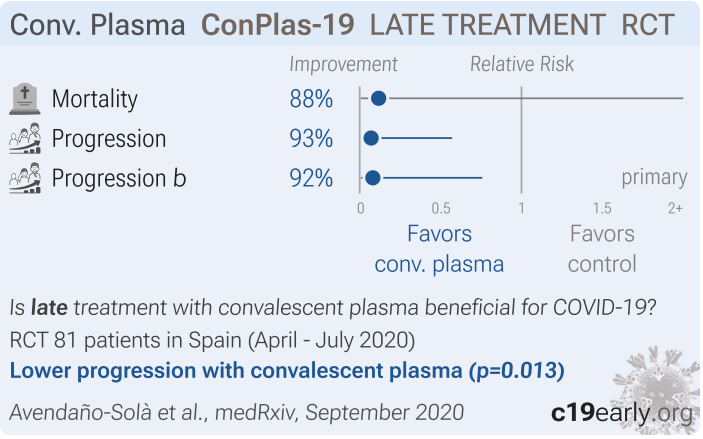
Small RCT with 40 hospitalized patients in Bahrain, 20 treated with convalescent plasma, not showing significant differences.

Alshamrani



PSM retrospective 29 hospitals in Saudi Arabia, showing longer ICU and hospitalization time with convalescent plasma, but no significant difference in mortality.

Avendaño-Solà

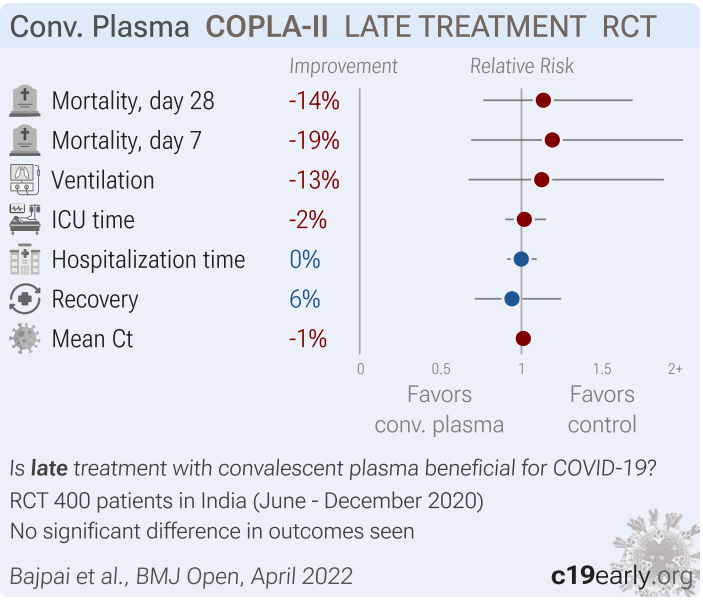


Early terminated RCT with 81 hospitalized patients, 38 treated with convalescent plasma, showing lower progression with treatment.

Averyanov

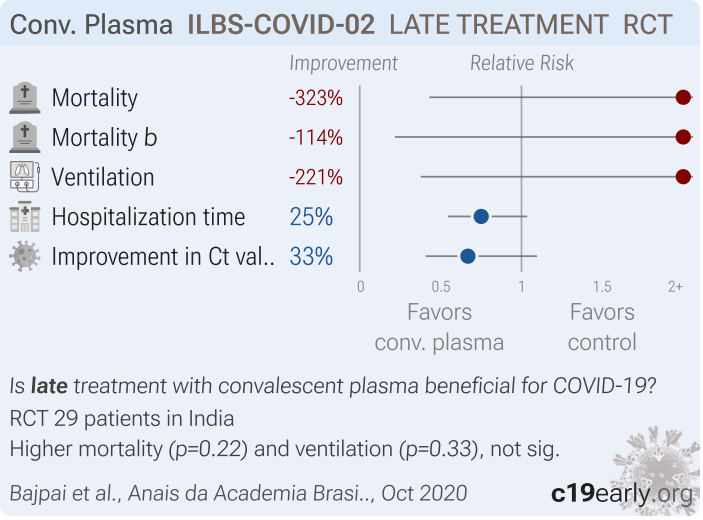
60 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

Bajpai



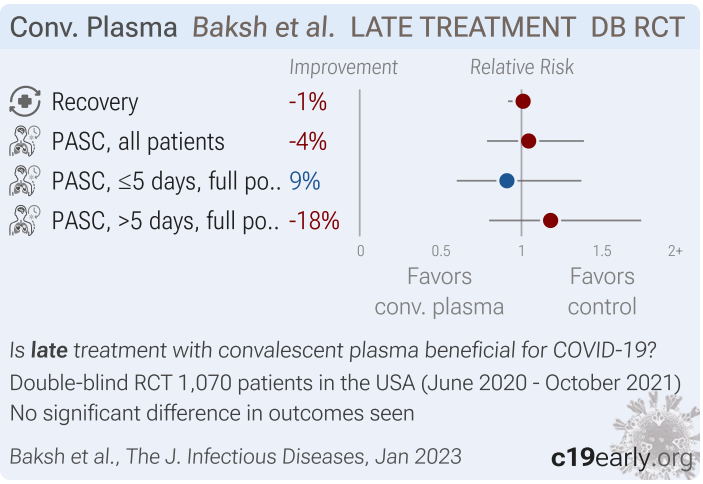
RCT 400 hospitalized severe COVID-19 patients in India showing no significant difference in time to clinical improvement, mortality, or other outcomes with convalescent plasma compared to standard treatment. In a subgroup analysis, results were better for patients receiving plasma within 3 days of admission. There was no difference in outcomes based on patient baseline antibody levels.

Bajpai



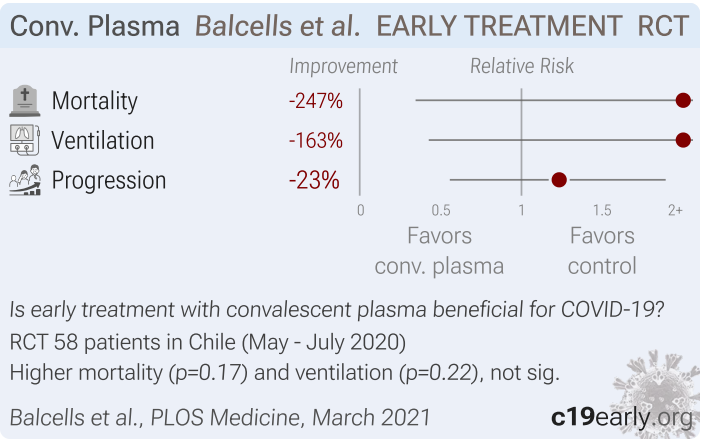
RCT 29 severe COVID-19 patients showing no significant differences with convalescent plasma compared to fresh frozen plasma.

Baksh



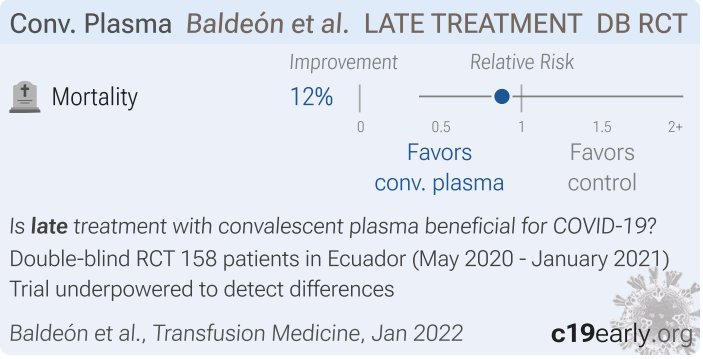
RCT 1,070 outpatients in the USA, showing no significant difference in recovery with convalescent plasma treatment. Long COVID results are from *Gebo et al.*

Balcells



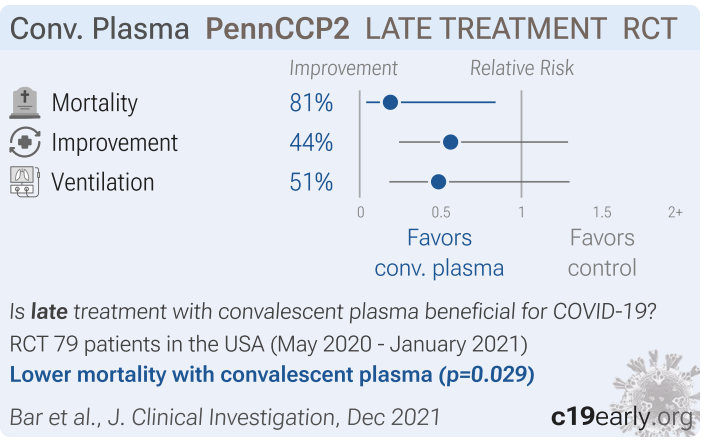
Small RCT with 28 early and 30 deferred (treated according to prespecified deterioration criteria) convalescent plasma patients, not showing significant differences. "Early" is relative, with a median of 5 days from symptom onset. 13 patients in the deferred group received plasma.

Baldeón



RCT 158 patients in Ecuador, showing no significant difference in mortality with convalescent plasma. Authors note indications of improved results for earlier treatment.

Bar

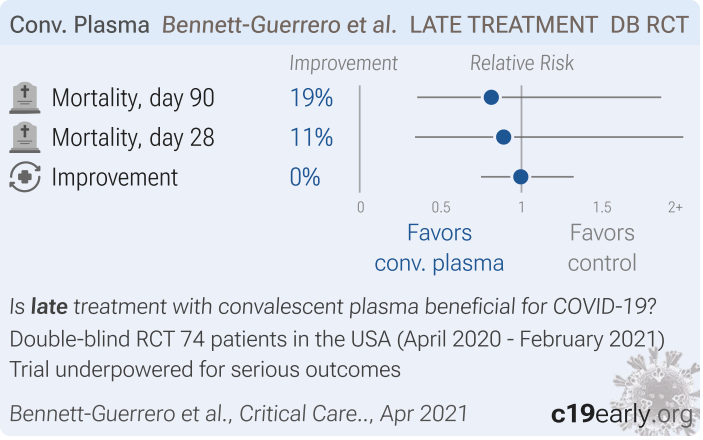


RCT 79 hospitalized patients in the USA, showing significant benefit in clinical severity score and 28-day mortality with convalescent plasma treatment.

Baylor Research Institute

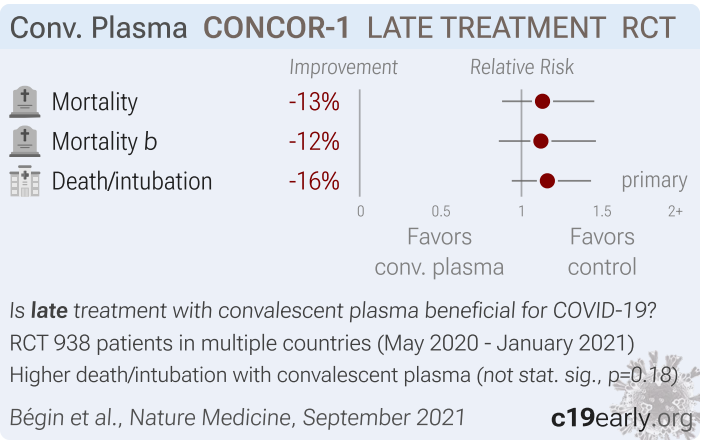
Estimated 115 patient convalescent plasma late treatment RCT with results not reported over 2 years after estimated completion.

Bennett-Guerrero



RCT 74 hospitalized patients in the USA, showing no significant difference with convalescent plasma treatment.

Bégin



RCT 940 hospitalized patients, 614 assigned to convalescent plasma, showing no significant differences.

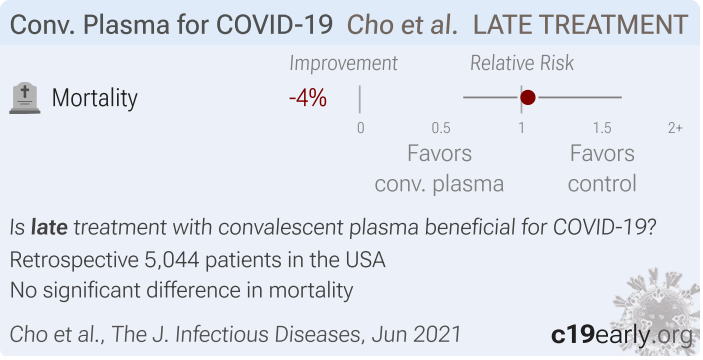
Camacho-Ortiz

31 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

Cardesa Gil

72 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

Cho



Target trial emulation with 4,755 patients showing no significant difference in 30-day mortality with convalescent plasma.

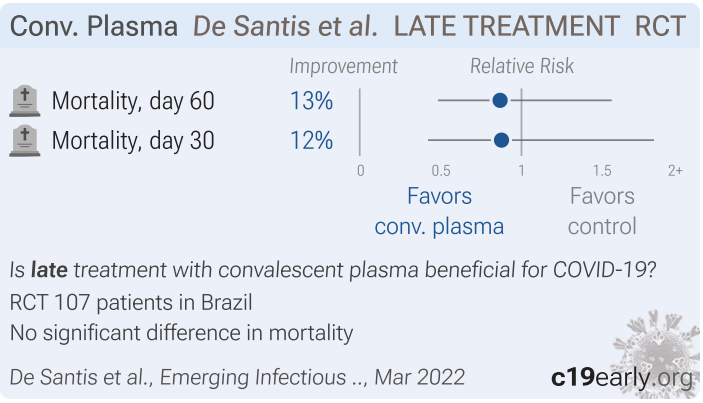
Chowdhury

Estimated 60 patient convalescent plasma late treatment RCT with results not reported over 4 years after estimated completion.

de la Puerta Rueda

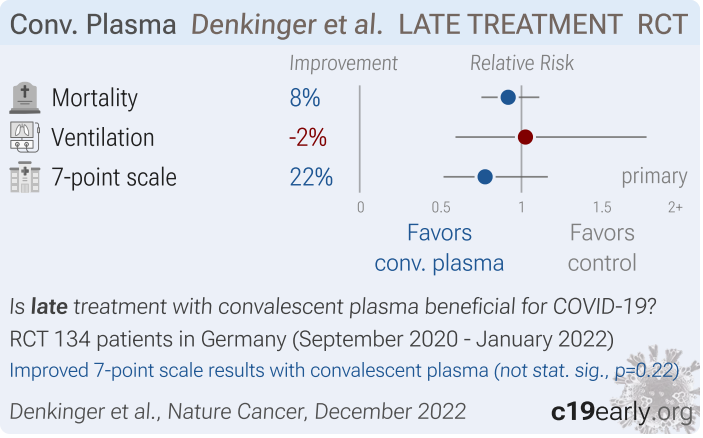
93 patient convalescent plasma late treatment RCT with results not reported over 3 years after completion.

De Santis



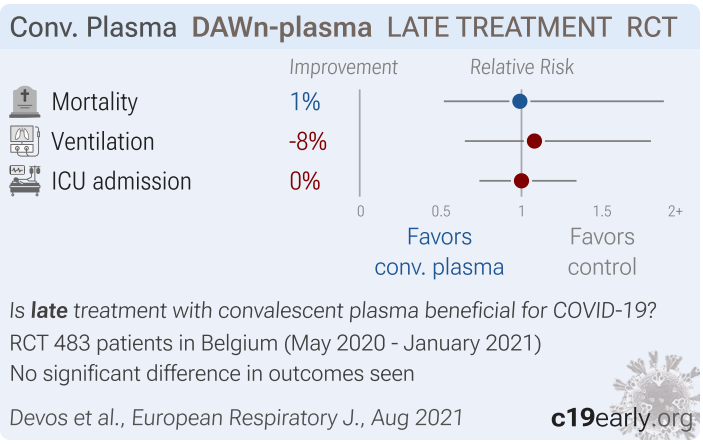
RCT 110 hospitalized patients in Brazil, showing no significant difference in outcomes with high-dose convalescent plasma.

Denkinger



RCT 134 hospitalized patients showing no significant difference in outcomes with convalescent plasma for all patients, however significantly improved mortality and time to improvement was seen for patients with cancer.

Devos



RCT 489 hospitalized COVID-19 patients in Belgium, showing no significant difference in outcomes with convalescent plasma.

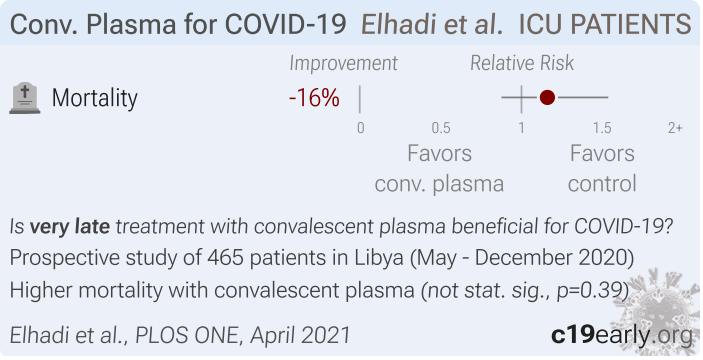
Dillner

59 patient convalescent plasma late treatment RCT with results not reported over 3 years after completion.

ElDesouky

Estimated 67 patient convalescent plasma late treatment RCT with results not reported over 3 years after estimated completion.

Elhadi

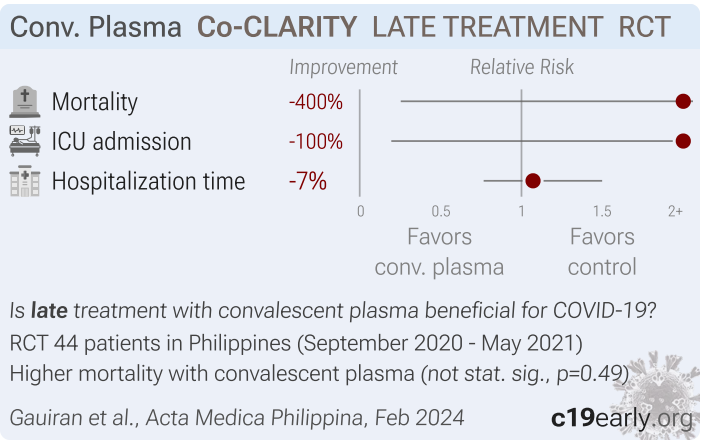


Prospective study of 465 COVID-19 ICU patients in Libya showing no significant differences with treatment.

Fundacin Biomedica Galicia Sur

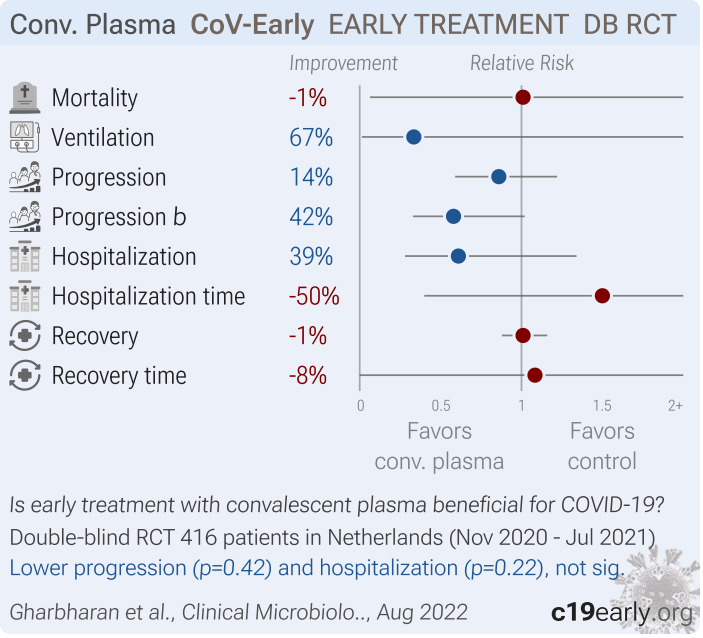
61 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

Gauiran



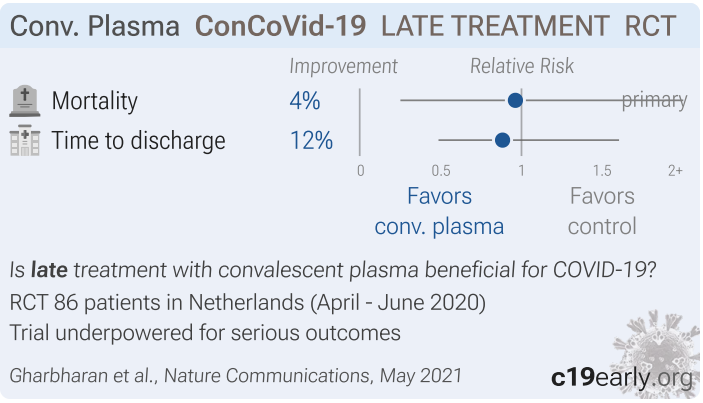
Early terminated RCT 44 hospitalized COVID-19 patients showing no significant differences with convalescent plasma treatment.

Gharbharan



RCT 416 outpatients in the Netherlands, showing no significant difference with convalesent plasma treatment. Hospitalization was lower, and improved results were seen with ≤5 days of symptoms, without statistical significance.

Gharbharan

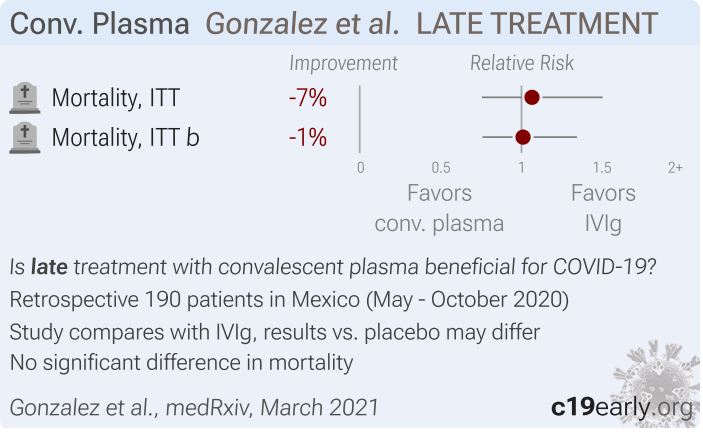


RCT 86 hospitalized patients, 43 treated with convalescent plasma, showing no significant differences with treatment. Authors conclude that the most likely explanation was already high antibody titers on the day of inclusion, and they recommend treating patients early.

Gonzalez

134 patient convalescent plasma late treatment RCT with results not reported over 3 years after completion.

Gonzalez

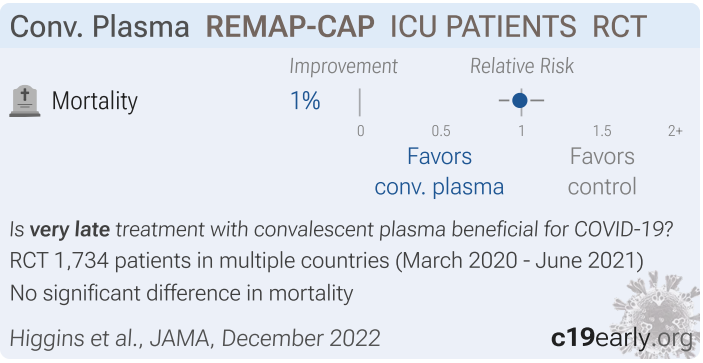


RCT 190 hospitalized severe condition patients in Mexico, showing no significant difference between convalescent plasma and human immunoglobulin treatment.

Herrick

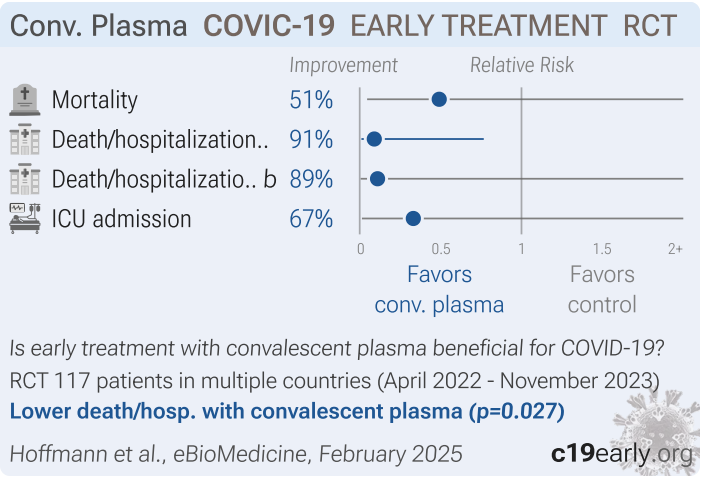
Estimated 50 patient convalescent plasma late treatment RCT with results not reported over 4 years after estimated completion.

Higgins



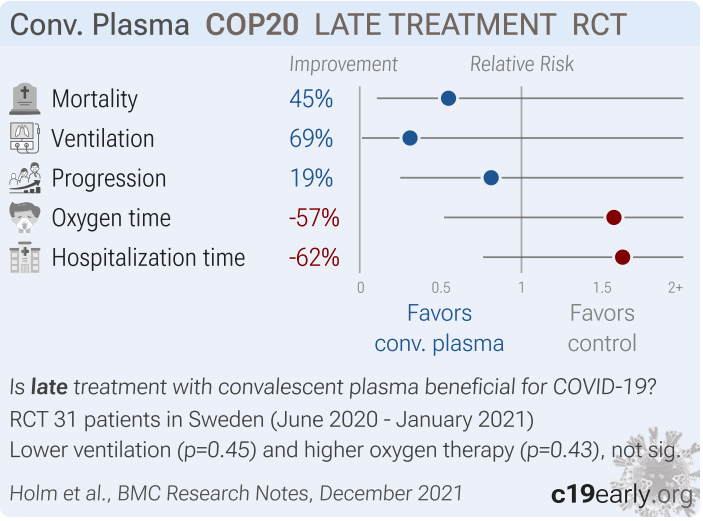
Long-term followup for the REMAP-CAP very late stage ICU trial, showing no significant difference with convalescent plasma treatment.

Hoffmann



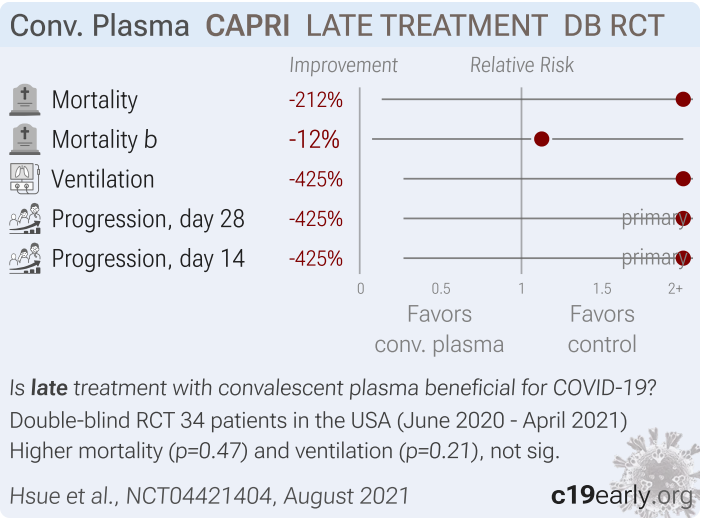
RCT 117 immunocompromised patients with mild COVID-19 showing lower hospitalization or death with early administration of very high-titre COVID-19 convalescent plasma (CCP). The trial was terminated early due to declining enrollment.

Holm



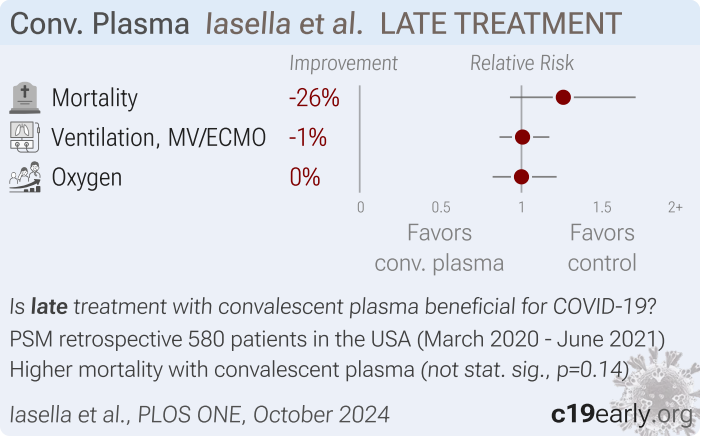
RCT 31 hospitalized patients requiring supplemental oxygen in Sweden, showing no significant difference in outcomes with convalescent plasma.

Hsue



RCT 34 hospitalized patients in the USA, showing no significant difference with convalescent plasma treatment.

Iasella

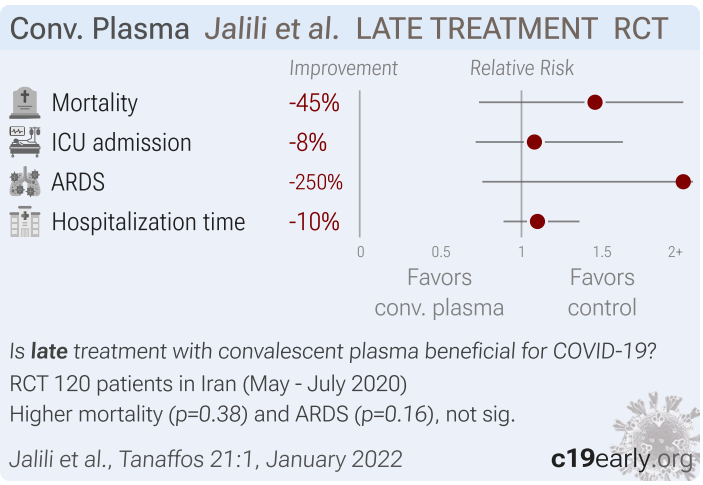


Retrospective propensity-matched analysis of 290 hospitalized COVID-19 patients who received convalescent plasma (CCP) compared to 290 controls, showing no significant difference in 30-day mortality, ECMO/mechanical ventilation, or hospital length of stay.

Itinose

38 patient convalescent plasma late treatment RCT with results not reported over 3 years after completion.

Jalili



RCT 120 hospitalized patients in Iran, showing no significant differences with convalescent plasma treatment.

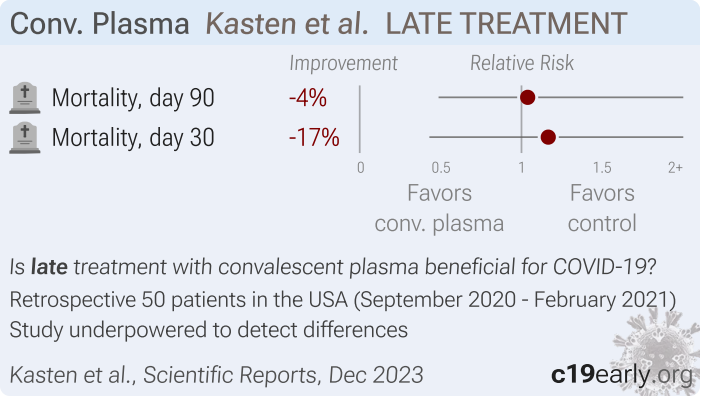
Jiang

Estimated 72 participant convalescent plasma prophylaxis RCT with results expected soon (estimated completion over 5 months ago).

Karyana

Estimated 364 patient convalescent plasma late treatment RCT with results not reported over 3 years after estimated completion.

Kasten



Retrospective 144 immunocompromised patients treated with anti-CD20 therapy prior to contracting COVID-19. Among 50 patients hospitalized within 14 days, administration of high-titer convalescent plasma in the first 14 days was not associated with improved outcomes.

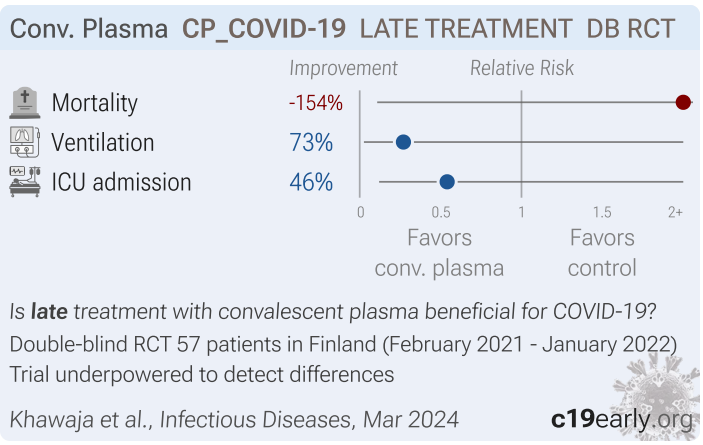
Kaufman

45 patient convalescent plasma late treatment RCT with results not reported over 3 years after completion.

Keitel-Anselmino

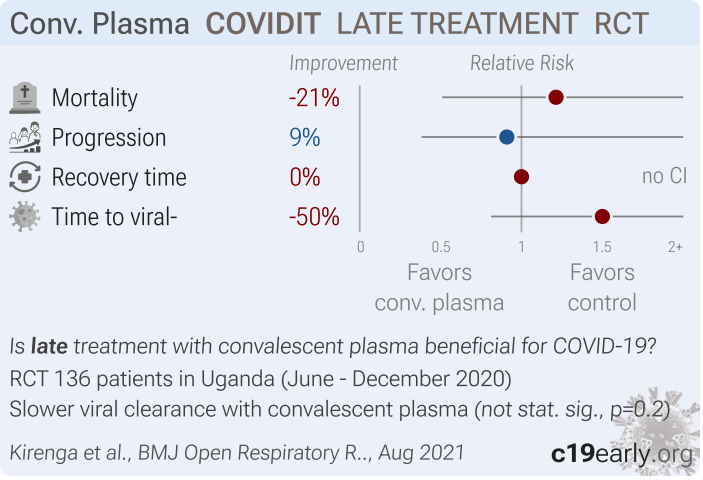
22 patient convalescent plasma early treatment RCT with results not reported over 3 years after completion.

Khawaja



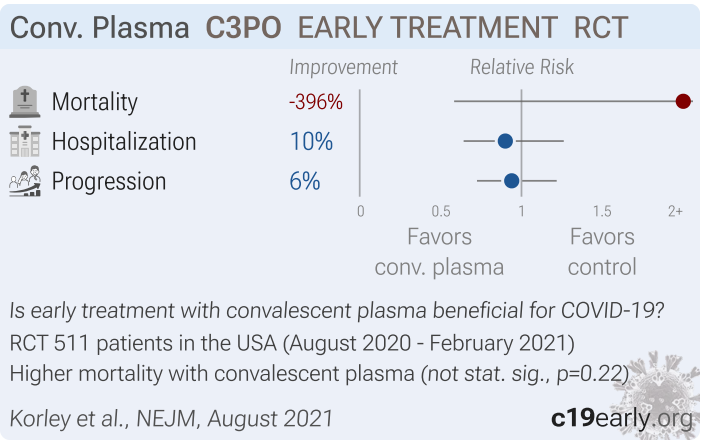
RCT 57 hospitalized COVID-19 patients showing no significant difference in outcomes with convalescent plasma treatment.

Kirenga



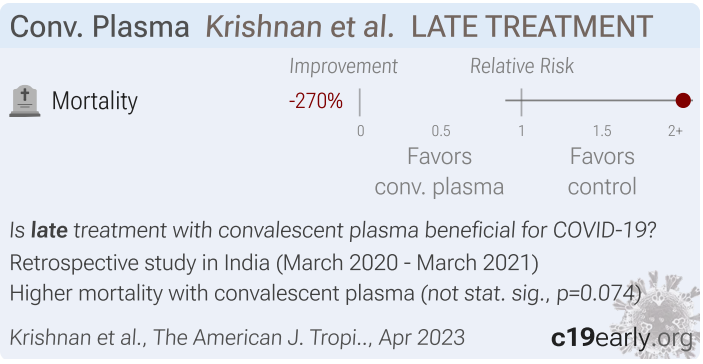
RCT 136 hospitalized COVID-19 patients in Uganda, showing no significant benefit with convalescent plasma treatment.

Korley



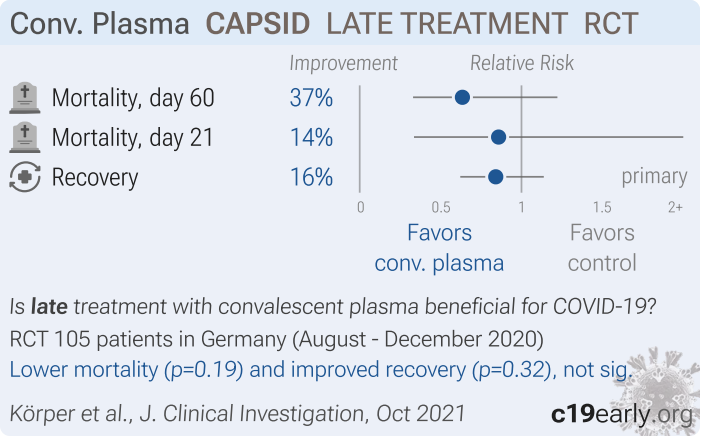
RCT 511 emergency department patients, 257 assigned to convalescent plasma, showing no significant difference in outcomes.

Krishnan



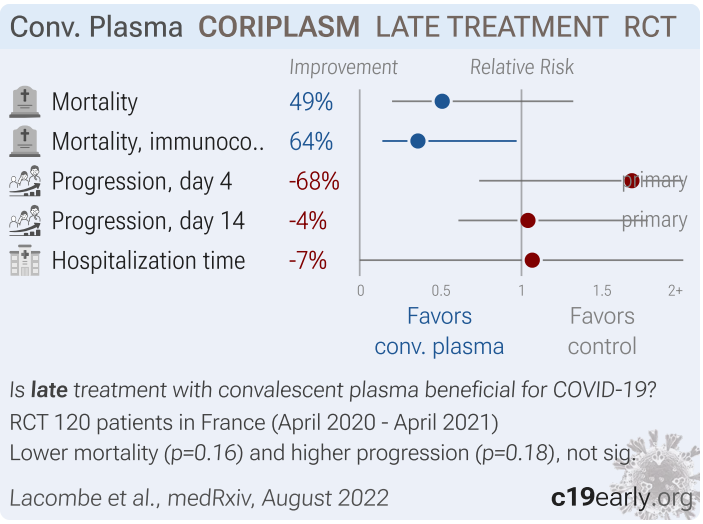
Case control study with 2,431 hospitalized COVID-19 patients in India, showing higher mortality with convalescent plasma treatment, without statistical significance.

Körper



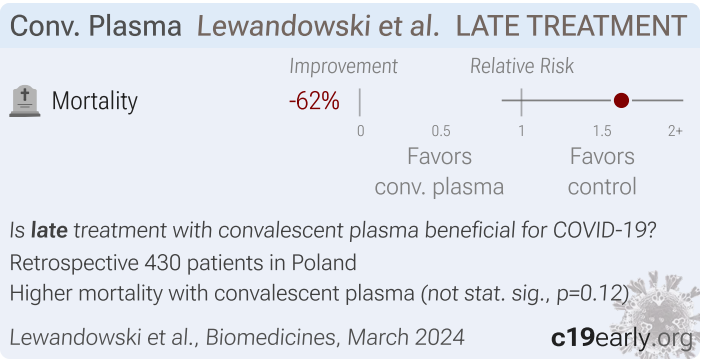
RCT 105 hospitalized patients in Germany, 53 treated with convalescent plasma, showing no significant difference in mortality or the primary composite outcome of survival and no longer fulfilling criteria for severe COVID-19 on day 21.

Lacombe



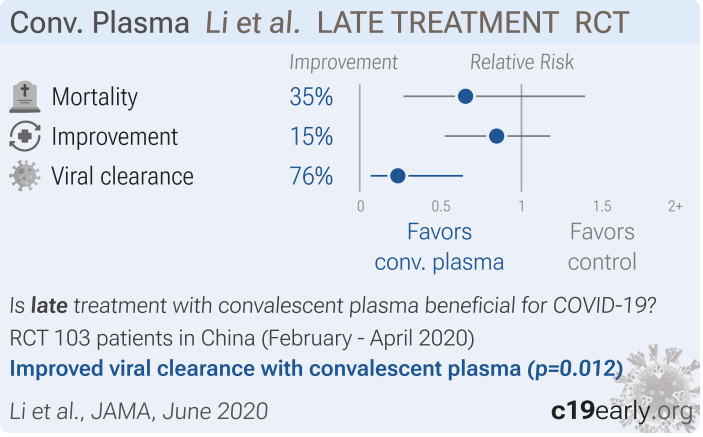
RCT 120 hospitalized patients in France, showing no significant difference in outcomes with convalescent plasma treatment, with the exception of lower mortality in the subgroup of immunosuppressed patients.

Lewandowski



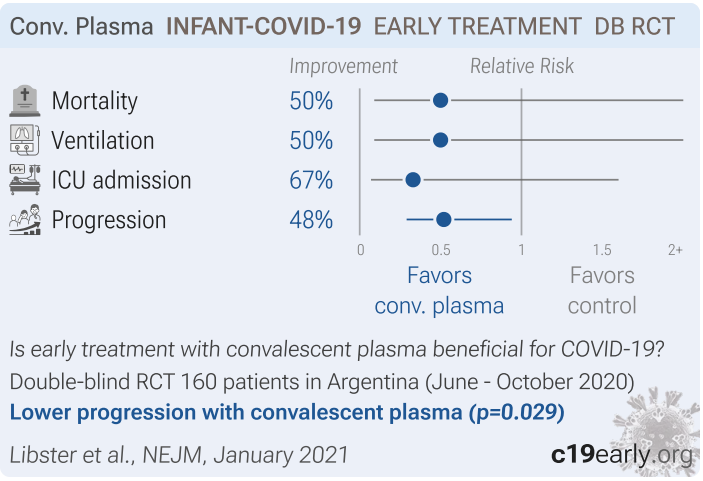
Retrospective 430 hospitalized COVID-19 patients with type 2 diabetes in Poland showing lower mortality with metformin and higher mortality with remdesivir, convalescent plasma, and aspirin in univariable analysis. These results were not statistically significant except for aspirin, and no baseline information per treatment is provided to assess confounding.

Li



Small RCT 103 severe condition patients, 52 treated with convalescent plasma, showing improved viral clearance but no statistically significant improvements in mortality or clinical improvement. ChiCTR2000029757.

Libster

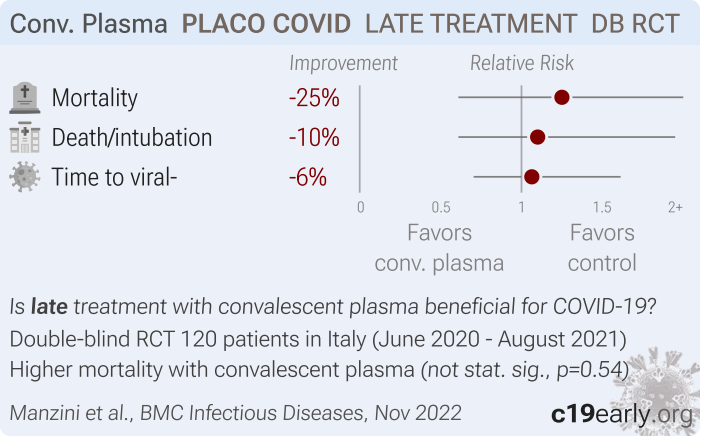


RCT 160 patients >=65 with symptom onset <72 hours, 80 treated with convalescent plasma, showing lower progression to severe disease with treatment.

Lubis

Estimated 60 patient convalescent plasma late treatment RCT with results not reported over 4 years after estimated completion.

Manzini



RCT 180 hospitalized COVID-19 patients with respiratory impairment in Italy showing no significant improvement in mortality or mechanical ventilation with either standard plasma or COVID-19 convalescent plasma compared to standard of care.

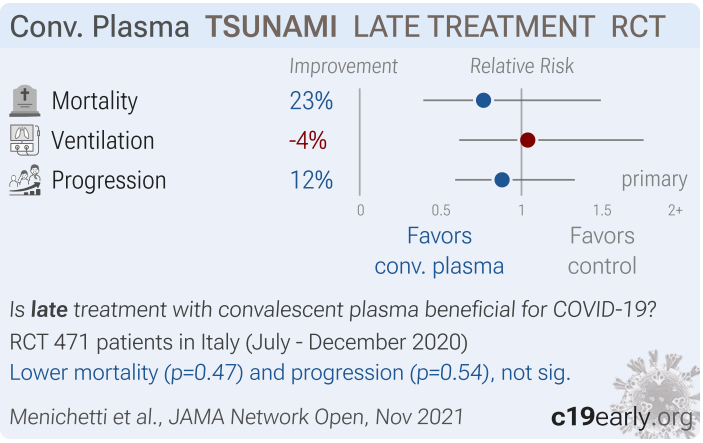
Marshall

86 patient convalescent plasma late treatment study with results not reported over 2 years after completion.

Martinaud

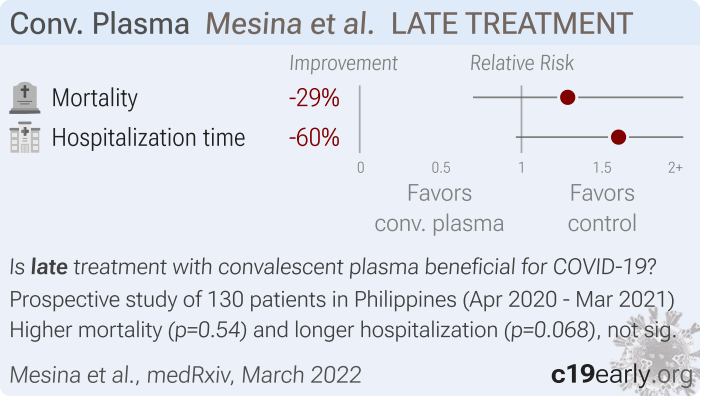
18 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

Menichetti



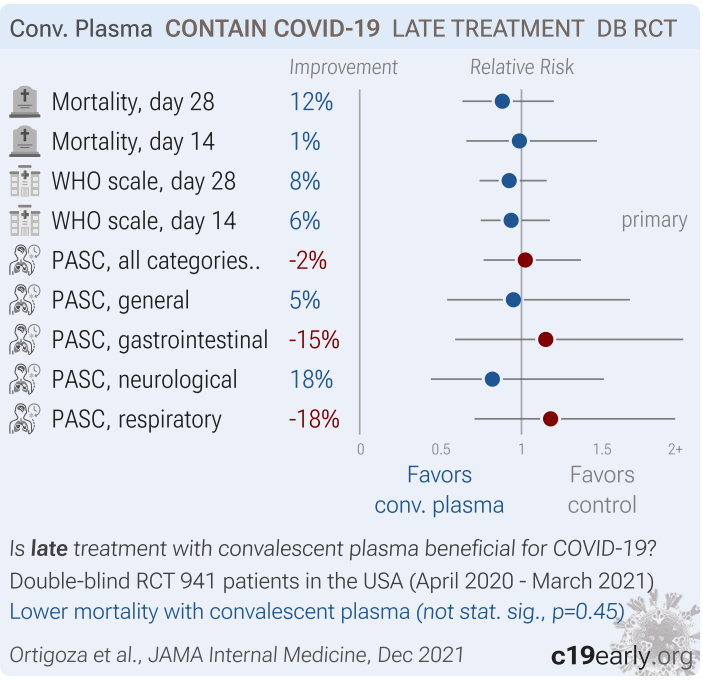
RCT 487 patients in Italy, showing no significant difference in outcomes with convalescent plasma.

Mesina



Prospective study of 65 hospitalized COVID-19 patients in the Philippines treated with convalescent plasma and 65 matched controls showing no significant difference in mortality and longer hospitalization with treatment.

Ortigoza



RCT 941 hospitalized patients in the USA, showing no significant difference with convalescent plasma treatment. PASC results are from *Yoon et al.*

Pathak

100 patient convalescent plasma late treatment RCT with results not reported over 3 years after completion.

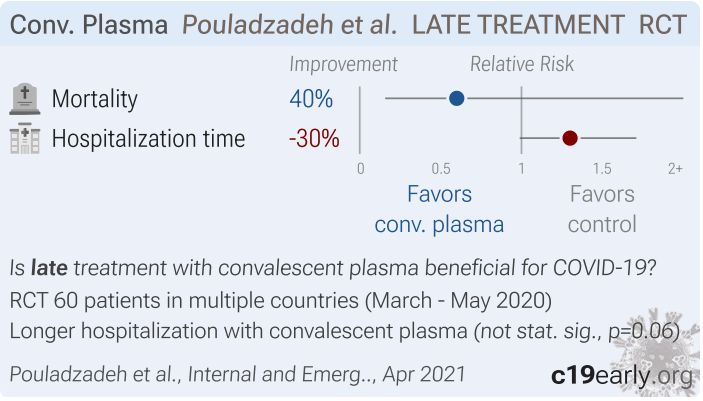
Perilla

Estimated 231 patient convalescent plasma late treatment RCT with results not reported over 3 years after estimated completion.

Perner

Estimated 220 patient convalescent plasma late treatment RCT with results not reported over 2 years after estimated completion.

Pouladzadeh

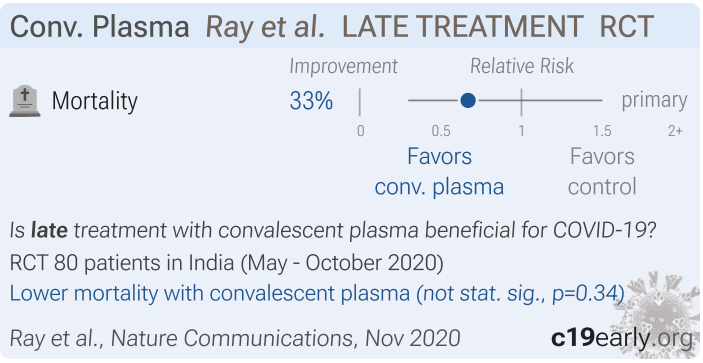


RCT 62 hospitalized patients in Iran, showing no significant difference in mortality and length of stay with convalescent plasma.

Quintero-Vega

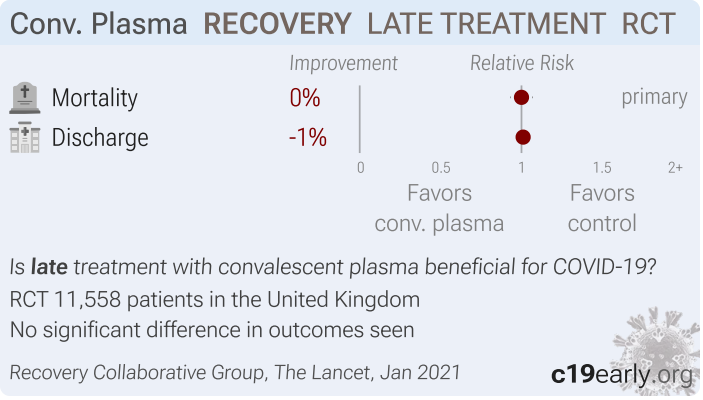
Estimated 236 patient convalescent plasma late treatment RCT with results not reported over 4 years after estimated completion.

Ray



RCT 80 severe COVID-19 patients in India showing no significant difference in 30-day mortality with convalescent plasma therapy (CPT). Patients receiving CPT had greater reduction in inflammatory cytokines, but this did not translate to clinical benefit in terms of survival or duration of hospital stay.

Recovery Collaborative Group

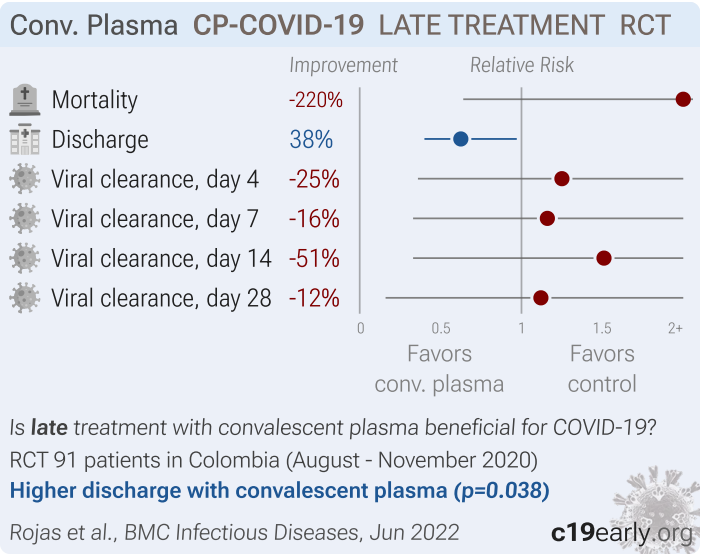


RCT 16,287 hospitalized patients in the UK, showing no significant differences with convalescent plasma treatment. Subgroup analysis shows better results for those treated <= 7 days from symptom onset.

Rego

Estimated 60 patient convalescent plasma late treatment RCT with results not reported over 3 years after estimated completion.

Rojas

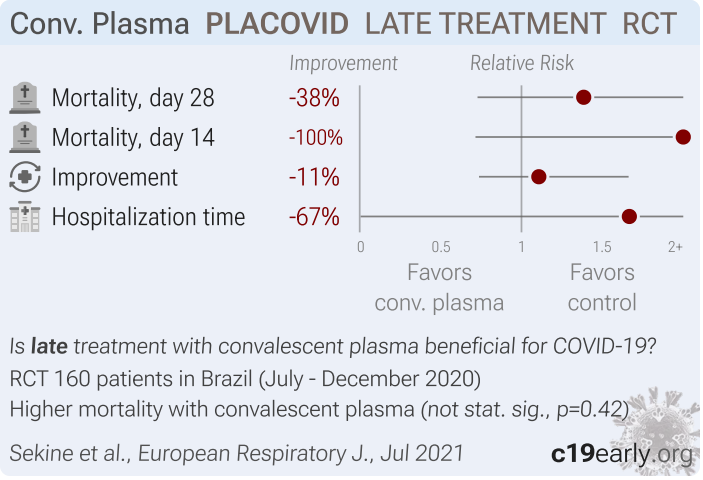


RCT 91 hospitalized patients in Colombia showing shorter time to discharge with convalescent plasma, but higher mortality (without statistical significance).

Schiffer

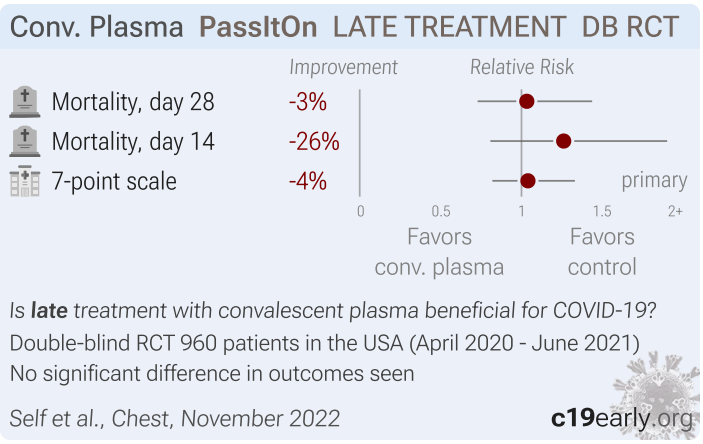
Estimated 58 patient convalescent plasma late treatment RCT with results not reported over 3 years after estimated completion.

Sekine



RCT 160 hospitalized patients in Brazil, showing no significant difference in outcomes with convalescent plasma.

Self

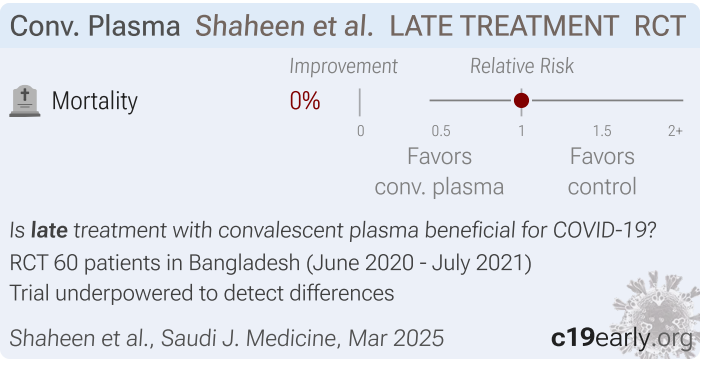


RCT 947 hospitalized patients in the USA, showing no signficant difference with convalescent plasma treatment.

Sevdi

60 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

Shaheen

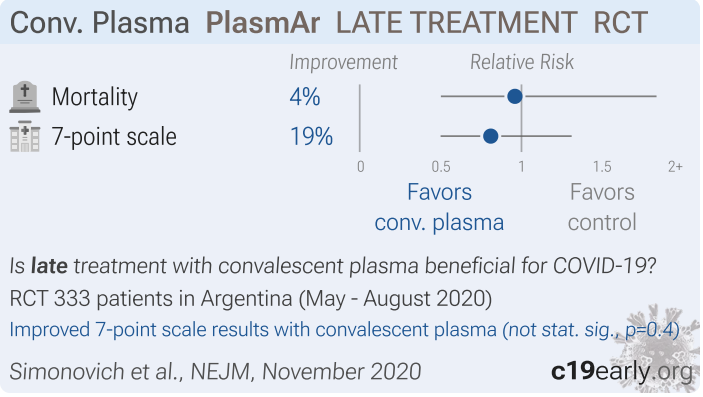


RCT 60 severe COVID-19 patients showing no benefit with convalescent plasma.

Sierra-Madero

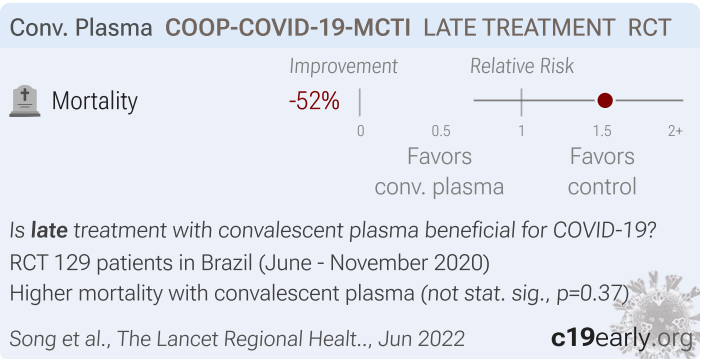
Estimated 410 patient convalescent plasma late treatment RCT with results not reported over 4 years after estimated completion.

Simonovich



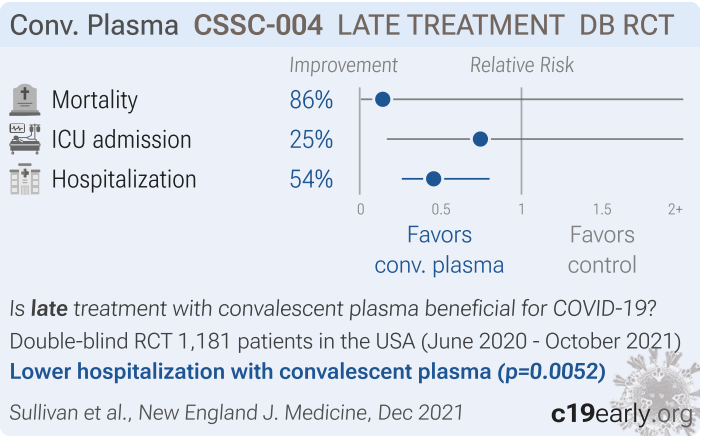
RCT 333 hospitalized patients in Argentina, 228 treated with convalescent plasma, showing no significant differences in clinical status or mortality.

Song



RCT 129 severe COVID-19 patients in Brazil, showing no significant difference in outcomes with convalescent plasma.

Sullivan

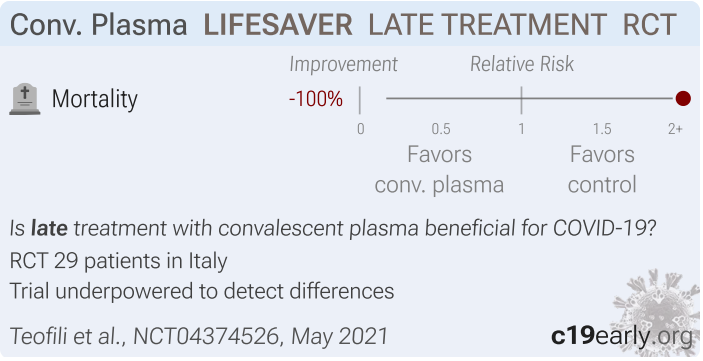


RCT 1,181 outpatients in the USA, mean 6 days from symptom onset, showing lower hospitalization with treatment.

Talarico

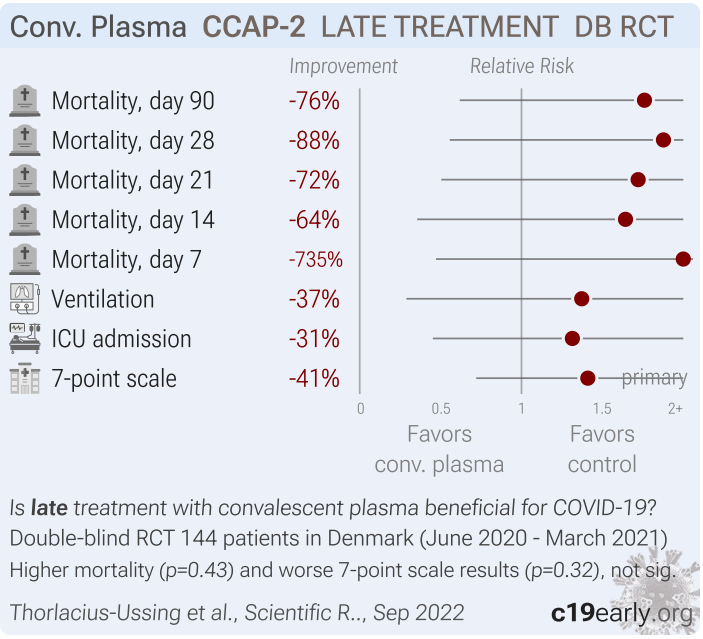
Estimated 400 patient convalescent plasma late treatment RCT with results not reported over 4 years after estimated completion.

Teofili



RCT 12 patients in Italy, showing no significant difference with convalescent plasma treatment. Results are from *Axfors et al.*.

Thorlacius-Ussing



RCT 147 patients in Denmark, showing no significant difference in outcomes with convalescent plasma. The trial was terminated due to futility.

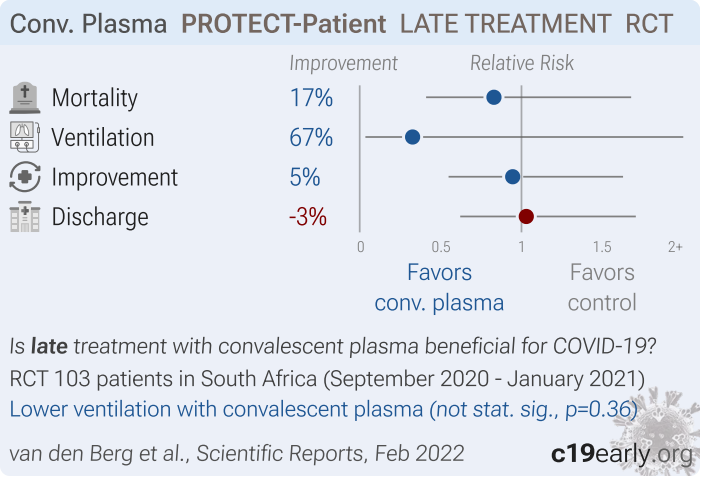
Torres

200 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

Torres

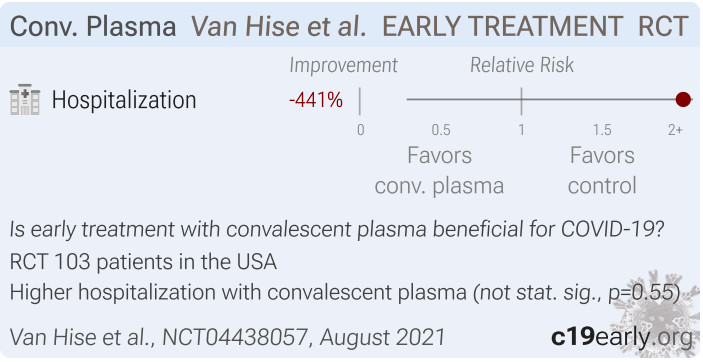
150 patient convalescent plasma late treatment RCT with results not reported over 4 years after completion.

van den Berg



RCT 103 hospitalized patients in South Africa, showing no significant difference in outcomes with convalescent plasma.

Van Hise



RCT 72 outpatients in the USA showing no significant difference with convalescent plasma treatment.

Zuluaga

Estimated 60 patient convalescent plasma late treatment RCT with results not reported over 4 years after estimated completion.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are convalescent plasma and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of convalescent plasma for COVID-19 that report a comparison with a control group are included in the main analysis. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for

example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [109]. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to *Zhang et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [113]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.4) with scipy (1.15.3), pythonmeta (1.26), numpy (2.3.0), statsmodels (0.14.4), and plotly (6.1.2).

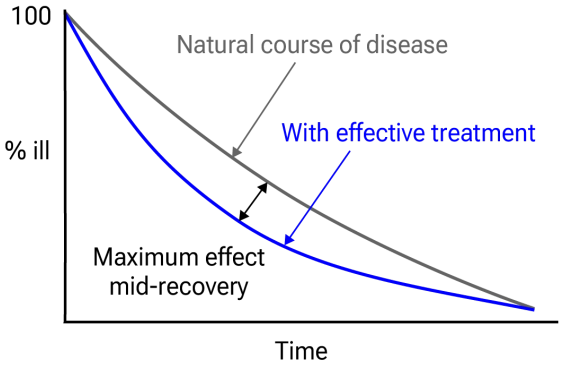


Figure 27. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

Forest plots are computed using PythonMeta [114] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective [64,65].

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/cpmeta.html.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Alemany, 2/9/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Spain, peer-reviewed, median age 56.0, 108 authors, study period 10 November, 2020 - 28 July, 2021, trial NCT04621123 (history) (CONV-ERT).	risk of death, 80.0% lower, RR 0.20, $p = 0.50$, treatment 0 of 188 (0.0%), control 2 of 188 (1.1%), NNT 94, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of hospitalization, 4.8% higher, RR 1.05, $p = 1.00$, treatment 22 of 188 (11.7%), control 21 of 188 (11.2%).
	risk of no recovery, 5.0% higher, HR 1.05, $p = 0.67$, treatment 188, control 188, time to symptom resolution.
	viral load, 3.6% higher, relative load 1.04, $p = 0.33$, treatment 188, control 188, relative change in viral load, day 28.
	viral load, 3.7% lower, relative load 0.96, $p = 0.42$, treatment 188, control 188, relative change in viral load, day 7.
Balcells, 3/3/2021, Randomized Controlled Trial, Chile, peer-reviewed, 32 authors, study period 10 May, 2020 - 18 July, 2020, average treatment delay 5.0 days, trial NCT04375098 (history).	risk of death, 247.4% higher, RR 3.47, $p = 0.17$, treatment 5 of 28 (17.9%), control 2 of 30 (6.7%), adjusted per study, odds ratio converted to relative risk, logistic regression, early vs. deferred.
	risk of mechanical ventilation, 163.3% higher, RR 2.63, $p = 0.22$, treatment 5 of 28 (17.9%), control 2 of 30 (6.7%), adjusted per study, odds ratio converted to relative risk, logistic regression, early vs. deferred.
	risk of progression, 23.3% higher, RR 1.23, $p = 0.51$, treatment 13 of 28 (46.4%), control 12 of 30 (40.0%), adjusted per study, odds ratio converted to relative risk, logistic regression, early vs. deferred.
Gharbharan, 8/23/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Netherlands, peer-reviewed, 59 authors, study period November 2020 - July 2021, average treatment delay 5.0 days, trial NCT04589949 (history) (CoV-Early).	risk of death, 1.0% higher, RR 1.01, $p = 1.00$, treatment 1 of 207 (0.5%), control 1 of 209 (0.5%), day 28.
	risk of mechanical ventilation, 66.6% lower, RR 0.33, $p = 1.00$, treatment 0 of 207 (0.0%), control 1 of 209 (0.5%), NNT 209, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of progression, 14.0% lower, OR 0.86, $p = 0.42$, treatment 207, control 209, adjusted per study, improved severity score, RR approximated with OR.
	risk of progression, 42.0% lower, OR 0.58, $p = 0.06$, treatment 123, control 103, adjusted per study, improved severity score, ≤5 days, RR approximated with OR.
	risk of hospitalization, 39.0% lower, HR 0.61, $p = 0.22$, treatment 10 of 207 (4.8%), control 18 of 209 (8.6%), NNT 26, adjusted per study, day 28.
	hospitalization time, 50.0% higher, relative time 1.50, $p = 0.56$, treatment 207, control 209.
	risk of no recovery, 1.0% higher, RR 1.01, $p = 0.92$, treatment 137 of 207 (66.2%), control 137 of 209 (65.6%), continued COVID-19 symptoms, day 27.
	recovery time, 8.3% higher, relative time 1.08, $p = 0.99$, treatment 207, control 209.

Hoffmann, 2/27/2025, Randomized Controlled Trial, multiple countries, peer-reviewed, median age 57.0, 33 authors, study period 11 April, 2022 - 27 November, 2023, trial NCT05271929 (history) (COVIC-19).	risk of death, 50.8% lower, RR 0.49, *p* = 0.62, treatment 1 of 59 (1.7%), control 2 of 58 (3.4%), NNT 57, day 180.
	risk of death/hospitalization, 91.0% lower, RR 0.09, *p* = 0.03, treatment 0 of 59 (0.0%), control 5 of 58 (8.6%), NNT 12, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of death/hospitalization, 89.0% lower, RR 0.11, *p* = 0.06, treatment 0 of 59 (0.0%), control 4 of 58 (6.9%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of ICU admission, 66.9% lower, RR 0.33, *p* = 0.50, treatment 0 of 59 (0.0%), control 1 of 58 (1.7%), NNT 58, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
Keitel-Anselmino, 10/29/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Germany, trial NCT04681430 (history) (RES-Q-HR).	22 patient RCT with results unknown and over 3 years late.
Korley, 8/18/2021, Randomized Controlled Trial, USA, peer-reviewed, 28 authors, study period August 2020 - February 2021, average treatment delay 3.7 days, trial NCT04355767 (history) (C3PO).	risk of death, 396.0% higher, RR 4.96, *p* = 0.22, treatment 5 of 250 (2.0%), control 1 of 248 (0.4%).
	risk of hospitalization, 10.0% lower, RR 0.90, *p* = 0.59, treatment 51 of 257 (19.8%), control 56 of 254 (22.0%), NNT 45.
	risk of progression, 6.0% lower, RR 0.94, *p* = 0.70, treatment 77 of 257 (30.0%), control 81 of 254 (31.9%), NNT 52.
Libster, 1/6/2021, Double Blind Randomized Controlled Trial, Argentina, peer-reviewed, 56 authors, study period 4 June, 2020 - 25 October, 2020, trial NCT04479163 (history) (INFANT-COVID-19).	risk of death, 50.0% lower, RR 0.50, *p* = 0.43, treatment 2 of 80 (2.5%), control 4 of 80 (5.0%), NNT 40.
	risk of mechanical ventilation, 50.0% lower, RR 0.50, *p* = 0.43, treatment 2 of 80 (2.5%), control 4 of 80 (5.0%), NNT 40.
	risk of ICU admission, 67.0% lower, RR 0.33, *p* = 0.17, treatment 2 of 80 (2.5%), control 6 of 80 (7.5%), NNT 20.
	risk of progression, 48.0% lower, RR 0.52, *p* = 0.03, treatment 13 of 80 (16.2%), control 25 of 80 (31.2%), NNT 6.7.
Van Hise, 8/12/2021, Randomized Controlled Trial, USA, preprint, 1 author, trial NCT04438057 (history).	risk of hospitalization, 440.8% higher, RR 5.41, *p* = 0.55, treatment 3 of 49 (6.1%), control 0 of 23 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Abayomi, 11/20/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Nigeria, peer-reviewed, 1 author, trial PACTR202006760881890 (LACCPT).	risk of death, 16.7% higher, RR 1.17, *p* = 1.00, treatment 7 of 11 (63.6%), control 6 of 11 (54.5%).

Agarwal, 10/22/2020, Randomized Controlled Trial, India, peer-reviewed, 6 authors, study period 22 April, 2020 - 14 July, 2020, average treatment delay 8.0 days, trial CTRI/2020/04/024775 (PLACID).	**risk of death, 7.0% higher, RR 1.07, *p* = 0.74**, treatment 34 of 235 (14.5%), control 31 of 229 (13.5%).
	combined death at 28 days or progression to severe disease, 7.0% higher, RR 1.07, *p* = 0.74, treatment 44 of 235 (18.7%), control 41 of 229 (17.9%).
	risk of mechanical ventilation, 1.0% lower, RR 0.99, *p* = 0.98, treatment 19 of 227 (8.4%), control 19 of 224 (8.5%), NNT 892.
	risk of no viral clearance, 28.0% lower, RR 0.72, *p* = 0.02, treatment 56 of 173 (32.4%), control 76 of 169 (45.0%), NNT 7.9, day 7.
AlQahtani, 11/4/2020, Randomized Controlled Trial, Bahrain, peer-reviewed, 11 authors, study period 19 April, 2020 - 9 July, 2020, trial NCT04356534 (history).	**risk of death, 50.0% lower, RR 0.50, *p* = 0.55**, treatment 1 of 20 (5.0%), control 2 of 20 (10.0%), NNT 20.
	noninvasive or mechanical ventilation, 33.3% lower, RR 0.67, *p* = 0.47, treatment 4 of 20 (20.0%), control 6 of 20 (30.0%), NNT 10, primary outcome.
	hospitalization time, 21.9% lower, relative time 0.78, *p* = 0.12, treatment 20, control 20.
Alshamrani, 2/15/2023, retrospective, Saudi Arabia, peer-reviewed, 3 authors, study period March 2020 - January 2021.	**risk of death, 14.3% higher, RR 1.14, *p* = 0.39**, treatment 24 of 41 (58.5%), control 108 of 205 (52.7%), adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable.
	risk of progression, 17.3% higher, RR 1.17, *p* = 0.047, treatment 34 of 41 (82.9%), control 154 of 205 (75.1%), adjusted per study, odds ratio converted to relative risk, AKI, ARDS, multi-organ failure, or mortality, propensity score matching, multivariable.
	ICU time, 42.6% higher, relative time 1.43, *p* = 0.003, treatment 37, control 166, propensity score matching.
	hospitalization time, 31.8% higher, relative time 1.32, *p* = 0.01, treatment 41, control 205, propensity score matching.
Avendaño-Solà, 9/29/2020, Randomized Controlled Trial, Spain, peer-reviewed, 38 authors, study period 4 April, 2020 - 10 July, 2020, average treatment delay 8.0 days, trial NCT04345523 (history) (ConPlas-19).	**risk of death, 88.3% lower, RR 0.12, *p* = 0.12**, treatment 0 of 38 (0.0%), control 4 of 43 (9.3%), NNT 11, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 29.
	risk of progression, 93.0% lower, RR 0.07, *p* = 0.01, treatment 0 of 38 (0.0%), control 7 of 43 (16.3%), NNT 6.1, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 29, progression to categories 5-7.
	risk of progression, 91.9% lower, RR 0.08, *p* = 0.03, treatment 0 of 38 (0.0%), control 6 of 43 (14.0%), NNT 7.2, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 15, progression to categories 5-7, primary outcome.
Averyanov, 9/23/2020, Randomized Controlled Trial, placebo-controlled, Russia, trial NCT04392414 (history).	60 patient RCT with results unknown and over 4 years late.

Bajpai, 4/6/2022, Randomized Controlled Trial, India, peer-reviewed, mean age 55.5, 23 authors, study period June 2020 - December 2020, trial NCT04425915 (history) (COPLA-II).	risk of death, 13.5% higher, RR 1.14, *p* = 0.62, treatment 42 of 200 (21.0%), control 37 of 200 (18.5%), day 28.
	risk of death, 19.0% higher, RR 1.19, *p* = 0.64, treatment 25 of 200 (12.5%), control 21 of 200 (10.5%), day 7.
	risk of mechanical ventilation, 12.5% higher, RR 1.13, *p* = 0.76, treatment 27 of 200 (13.5%), control 24 of 200 (12.0%), day 7.
	ICU time, 1.7% higher, relative time 1.02, *p* = 0.80, treatment mean 11.1 (±7.77) n=200, control mean 10.91 (±6.96) n=200.
	hospitalization time, 0.1% lower, relative time 1.00, *p* = 0.98, treatment mean 13.8 (±7.03) n=200, control mean 13.82 (±7.19) n=200.
	risk of no recovery, 5.9% lower, RR 0.94, *p* = 0.75, treatment 64 of 200 (32.0%), control 68 of 200 (34.0%), NNT 50, day 28.
	relative mean Ct, 1.1% worse, RR 1.01, *p* = 0.54, treatment mean 34.31 (±6.61) n=200, control mean 34.7 (±6.2) n=200, day 7.
Bajpai (B), 10/27/2020, Randomized Controlled Trial, India, peer-reviewed, mean age 48.2, 17 authors, trial NCT04346446 (history) (ILBS-COVID-02).	risk of death, 323.0% higher, HR 4.23, *p* = 0.22, treatment 3 of 14 (21.4%), control 1 of 15 (6.7%), adjusted per study, 28 days, Cox proportional hazards.
	risk of death, 114.3% higher, RR 2.14, *p* = 0.60, treatment 2 of 14 (14.3%), control 1 of 15 (6.7%), 7 days.
	risk of mechanical ventilation, 221.4% higher, RR 3.21, *p* = 0.33, treatment 3 of 14 (21.4%), control 1 of 15 (6.7%), 7 days.
	hospitalization time, 24.9% lower, relative time 0.75, *p* = 0.08, treatment 14, control 15.
	relative improvement in Ct value, 33.1% better, RR 0.67, *p* = 0.11, treatment 14, control 15.
Baksh, 1/31/2023, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 26 authors, study period 3 June, 2020 - 1 October, 2021, average treatment delay 6.0 days, trial NCT04373460 (history).	risk of no recovery, 1.0% higher, RR 1.01, *p* = 0.62, treatment 381 of 538 (70.8%), control 381 of 532 (71.6%), NNT 125, inverted to make RR<1 favor treatment, day 14.
	risk of PASC, 4.4% higher, RR 1.04, *p* = 0.78, treatment 533, control 528, all patients.
	risk of PASC, 9.0% lower, OR 0.91, *p* = 0.67, treatment 232, control 234, ≤5 days, full population, RR approximated with OR.
	risk of PASC, 18.0% higher, OR 1.18, *p* = 0.41, treatment 301, control 294, >5 days, full population, RR approximated with OR.
Baldeón, 1/9/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Ecuador, peer-reviewed, 17 authors, study period May 2020 - January 2021, average treatment delay 10.6 days.	risk of death, 12.0% lower, RR 0.88, *p* = 1.00, treatment 7 of 63 (11.1%), control 12 of 95 (12.6%), NNT 66.
Bar, 12/15/2021, Randomized Controlled Trial, USA, peer-reviewed, median age 63.0, 40 authors, study period 18 May, 2020 - 8 January, 2021, trial NCT04397757 (history) (PennCCP2).	risk of death, 81.0% lower, HR 0.19, *p* = 0.03, treatment 40, control 39, Cox proportional hazards, day 28.
	risk of no improvement, 43.8% lower, OR 0.56, *p* = 0.18, treatment 40, control 39, WHO8 score, day 28, RR approximated with OR.

	risk of mechanical ventilation, 51.2% lower, RR 0.49, p = 0.16, treatment 5 of 40 (12.5%), control 10 of 39 (25.6%), NNT 7.6.
Baylor Research Institute, 12/31/2022, Randomized Controlled Trial, placebo-controlled, USA, trial NCT04333251 (history).	Estimated 115 patient RCT with results unknown and over 2 years late.
Bennett-Guerrero, 4/16/2021, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 18 authors, study period 8 April, 2020 - 1 February, 2021, average treatment delay 9.0 days, trial NCT04344535 (history).	**risk of death, 18.6% lower, RR 0.81, p = 0.75**, treatment 16 of 59 (27.1%), control 5 of 15 (33.3%), NNT 16, day 90.
	risk of death, 11.0% lower, RR 0.89, p = 1.00, treatment 14 of 59 (23.7%), control 4 of 15 (26.7%), NNT 34, day 28.
	risk of no improvement, 0.4% lower, RR 1.00, p = 1.00, treatment 47 of 59 (79.7%), control 12 of 15 (80.0%), NNT 295.
Bégin, 9/9/2021, Randomized Controlled Trial, multiple countries, peer-reviewed, 33 authors, study period 14 May, 2020 - 29 January, 2021, average treatment delay 8.0 days, trial NCT04348656 (history) (CONCOR-1).	**risk of death, 13.0% higher, RR 1.13, p = 0.33**, treatment 156 of 625 (25.0%), control 69 of 313 (22.0%), day 90.
	risk of death, 12.0% higher, RR 1.12, p = 0.40, treatment 141 of 614 (23.0%), control 63 of 307 (20.5%), day 30.
	risk of death/intubation, 16.0% higher, RR 1.16, p = 0.18, treatment 199 of 614 (32.4%), control 86 of 307 (28.0%), primary outcome.
Camacho-Ortiz, 5/1/2021, Double Blind Randomized Controlled Trial, Mexico, trial NCT04358783 (history) (COP-COVID-19).	31 patient RCT with results unknown and over 4 years late.
Cardesa Gil, 12/30/2020, Randomized Controlled Trial, Spain, trial NCT04366245 (history).	72 patient RCT with results unknown and over 4 years late.
Cho, 6/21/2021, retrospective, USA, peer-reviewed, 24 authors, trial NCT04545047 (history).	**risk of death, 4.0% higher, HR 1.04, p = 0.88**, treatment 402, control 4,642.
Chowdhury, 10/30/2020, Randomized Controlled Trial, Bangladesh, trial NCT04403477 (history).	Estimated 60 patient RCT with results unknown and over 4 years late.
de la Puerta Rueda, 12/31/2021, Double Blind Randomized Controlled Trial, Spain, trial NCT05247307 (history).	93 patient RCT with results unknown and over 3 years late.
De Santis, 3/31/2022, Randomized Controlled Trial, Brazil, peer-reviewed, 23 authors, average treatment delay 9.0 days.	**risk of death, 13.2% lower, RR 0.87, p = 0.67**, treatment 11 of 36 (30.6%), control 25 of 71 (35.2%), NNT 21, day 60.
	risk of death, 12.3% lower, RR 0.88, p = 0.81, treatment 8 of 36 (22.2%), control 18 of 71 (25.4%), NNT 32, day 30.
Denkinger, 12/29/2022, Randomized Controlled Trial, Germany, peer-reviewed, 54 authors, study period 3 September, 2020 - 20 January, 2022, average treatment delay 7.0 days.	**risk of death, 8.2% lower, RR 0.92, p = 0.39**, treatment 68, control 66, inverted to make RR<1 favor treatment, day 84.
	risk of mechanical ventilation, 2.5% higher, RR 1.02, p = 1.00, treatment 19 of 68 (27.9%), control 18 of 66 (27.3%).
	risk of 7-point scale, 22.5% lower, HR 0.78, p = 0.22, treatment 68, control 66, inverted to make HR<1 favor treatment, primary outcome.
Devos, 8/26/2021, Randomized Controlled Trial, Belgium, peer-reviewed, 26 authors, study period 2 May, 2020 - 26 January, 2021, average treatment delay 7.0 days, trial NCT04429854 (history) (DAWn-plasma).	**risk of death, 1.0% lower, HR 0.99, p = 0.98**, treatment 320, control 163.
	risk of mechanical ventilation, 8.0% higher, HR 1.08, p = 0.78, treatment 320, control 163.

	risk of ICU admission, no change, HR 1.00, p = 1.00, treatment 320, control 163.
Dillner, 1/26/2022, Randomized Controlled Trial, Sweden, trial NCT04649879 (history).	59 patient RCT with results unknown and over 3 years late.
ElDesouky, 12/31/2021, Randomized Controlled Trial, Egypt, trial NCT04438694 (history) (CP IN COVID19).	Estimated 67 patient RCT with results unknown and over 3 years late.
Elhadi, 4/30/2021, prospective, Libya, peer-reviewed, 21 authors, study period 29 May, 2020 - 30 December, 2020.	risk of death, 16.0% higher, RR 1.16, p = 0.39, treatment 16 of 23 (69.6%), control 265 of 442 (60.0%).
Fundacin Biomedica Galicia Sur, 3/31/2021, Randomized Controlled Trial, Spain, trial NCT05578391 (history) (CoV-PlasGal).	61 patient RCT with results unknown and over 4 years late.
Gauiran, 2/15/2024, Randomized Controlled Trial, Philippines, peer-reviewed, median age 60.0, 26 authors, study period 28 September, 2020 - 31 May, 2021, average treatment delay 8.0 days, trial NCT04567173 (history) (Co-CLARITY).	risk of death, 400.0% higher, RR 5.00, p = 0.49, treatment 2 of 22 (9.1%), control 0 of 22 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 100% higher, RR 2.00, p = 1.00, treatment 2 of 22 (9.1%), control 1 of 22 (4.5%).
	hospitalization time, 7.1% higher, relative time 1.07, p = 0.70, treatment 22, control 22.
Gharbharan (B), 5/27/2021, Randomized Controlled Trial, Netherlands, peer-reviewed, 32 authors, study period 8 April, 2020 - 14 June, 2020, average treatment delay 10.0 days, trial NCT04342182 (history) (ConCoVid-19).	risk of death, 3.8% lower, RR 0.96, p = 0.95, treatment 6 of 43 (14.0%), control 11 of 43 (25.6%), NNT 8.6, adjusted per study, odds ratio converted to relative risk, multivariable logistic regression, primary outcome.
	time to discharge, 11.7% lower, relative time 0.88, p = 0.68, treatment 43, control 43, adjusted per study, multivariable Fine and Gray regression.
Gonzalez, 6/19/2021, Randomized Controlled Trial, Argentina, trial NCT04468009 (history).	134 patient RCT with results unknown and over 3 years late.
Gonzalez (B), 3/31/2021, retrospective, Mexico, preprint, 17 authors, study period 5 May, 2020 - 17 October, 2020, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04381858 (history).	risk of death, 6.5% higher, RR 1.07, p = 0.76, treatment 60 of 130 (46.2%), control 26 of 60 (43.3%), day 28, intention-to-treat.
	risk of death, 1.0% higher, RR 1.01, p = 1.00, treatment 70 of 130 (53.8%), control 32 of 60 (53.3%), followup, day 28, intention-to-treat.
Herrick, 5/5/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, trial NCT04442191 (history).	Estimated 50 patient RCT with results unknown and over 4 years late.
Higgins, 12/16/2022, Randomized Controlled Trial, multiple countries, peer-reviewed, 66 authors, study period 9 March, 2020 - 22 June, 2021, trial NCT02735707 (history) (REMAP-CAP).	risk of death, 1.0% lower, HR 0.99, p = 0.90, treatment 370 of 944 (39.2%), control 324 of 790 (41.0%), NNT 55, adjusted per study, day 180.
Holm, 12/4/2021, Randomized Controlled Trial, Sweden, peer-reviewed, 14 authors, study period June 2020 - January 2021, average treatment delay 7.0 days, trial NCT04600440 (history) (COP20).	risk of death, 45.1% lower, RR 0.55, p = 0.64, treatment 2 of 17 (11.8%), control 3 of 14 (21.4%), NNT 10.

	risk of mechanical ventilation, 68.9% lower, RR 0.31, *p* = 0.45, treatment 0 of 17 (0.0%), control 1 of 14 (7.1%), NNT 14, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of progression, 18.8% lower, RR 0.81, *p* = 1.00, treatment 4 of 16 (25.0%), control 4 of 13 (30.8%), NNT 17, progression to HFNC.
	oxygen time, 57.1% higher, relative time 1.57, *p* = 0.43, treatment 17, control 14.
	hospitalization time, 62.5% higher, relative time 1.62, *p* = 0.21, treatment 17, control 14.
Hsue, 8/23/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, 1 author, study period 9 June, 2020 - 30 April, 2021, trial NCT04421404 (history) (CAPRI).	**risk of death, 212.5% higher, RR 3.12, *p* = 0.47**, treatment 1 of 16 (6.2%), control 0 of 18 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 28.
	risk of death, 12.5% higher, RR 1.12, *p* = 1.00, treatment 1 of 16 (6.2%), control 1 of 18 (5.6%), all cause, day 28.
	risk of mechanical ventilation, 425.0% higher, RR 5.25, *p* = 0.21, treatment 2 of 16 (12.5%), control 0 of 18 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 28.
	risk of progression, 425.0% higher, RR 5.25, *p* = 0.21, treatment 2 of 16 (12.5%), control 0 of 18 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), death or mechanical ventilation, day 28, primary outcome.
	risk of progression, 425.0% higher, RR 5.25, *p* = 0.21, treatment 2 of 16 (12.5%), control 0 of 18 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), death or mechanical ventilation, day 14, primary outcome.
Iasella, 10/24/2024, retrospective, USA, peer-reviewed, 30 authors, study period March 2020 - June 2021.	**risk of death, 25.9% higher, RR 1.26, *p* = 0.14**, treatment 73 of 290 (25.2%), control 58 of 290 (20.0%), propensity score matching, day 30.
	risk of mechanical ventilation, 0.6% higher, RR 1.01, *p* = 1.00, treatment 155 of 290 (53.4%), control 154 of 290 (53.1%), MV/ECMO, propensity score matching, day 30.
	oxygen, no change, RR 1.00, *p* = 1.00, treatment 118 of 290 (40.7%), control 118 of 290 (40.7%), propensity score matching, day 30.
Itinose, 4/7/2022, Randomized Controlled Trial, Brazil, trial NCT05077930 (history).	38 patient RCT with results unknown and over 3 years late.
Jalili, 1/1/2022, Randomized Controlled Trial, Iran, peer-reviewed, 15 authors, study period May 2020 - July 2020.	**risk of death, 45.5% higher, RR 1.45, *p* = 0.38**, treatment 16 of 60 (26.7%), control 11 of 60 (18.3%).
	risk of ICU admission, 8.0% higher, RR 1.08, *p* = 0.85, treatment 27 of 60 (45.0%), control 25 of 60 (41.7%).
	risk of ARDS, 250.0% higher, RR 3.50, *p* = 0.16, treatment 7 of 60 (11.7%), control 2 of 60 (3.3%).
	hospitalization time, 9.9% higher, relative time 1.10, *p* = 0.39, treatment 60, control 60.

Karyana, 12/31/2021, Randomized Controlled Trial, Indonesia, trial NCT04873414 (history) (PlaSenTer).	Estimated 364 patient RCT with results unknown and over 3 years late.
Kasten, 12/1/2023, retrospective, USA, peer-reviewed, median age 63.6, 13 authors, study period 1 September, 2020 - 28 February, 2021, trial NCT04884477 (history).	risk of death, 3.8% higher, RR 1.04, *p* = 1.00, treatment 7 of 19 (36.8%), control 11 of 31 (35.5%), day 90.
	risk of death, 16.5% higher, RR 1.17, *p* = 1.00, treatment 5 of 19 (26.3%), control 7 of 31 (22.6%), day 30.
Kaufman, 6/30/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, trial NCT04361253 (history) (ESCAPE).	45 patient RCT with results unknown and over 3 years late.
Khawaja, 3/21/2024, Double Blind Randomized Controlled Trial, placebo-controlled, Finland, peer-reviewed, mean age 51.7, 23 authors, study period 2 February, 2021 - 19 January, 2022, average treatment delay 8.0 days, trial NCT04730401 (history) (CP_COVID-19).	risk of death, 154.1% higher, RR 2.54, *p* = 1.00, treatment 1 of 37 (2.7%), control 0 of 20 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 73.0% lower, RR 0.27, *p* = 0.28, treatment 1 of 37 (2.7%), control 2 of 20 (10.0%), NNT 14.
	risk of ICU admission, 45.9% lower, RR 0.54, *p* = 0.65, treatment 3 of 37 (8.1%), control 3 of 20 (15.0%), NNT 15.
Kirenga, 8/9/2021, Randomized Controlled Trial, Uganda, peer-reviewed, median age 50.0, 30 authors, study period 16 June, 2020 - 31 December, 2020, average treatment delay 7.0 days, trial NCT04542941 (history) (COVIDIT).	risk of death, 21.4% higher, RR 1.21, *p* = 0.80, treatment 10 of 69 (14.5%), control 8 of 67 (11.9%).
	risk of progression, 9.1% lower, RR 0.91, *p* = 1.00, treatment 9 of 41 (22.0%), control 7 of 29 (24.1%), NNT 46.
	time to viral-, 50.0% higher, relative time 1.50, *p* = 0.20, treatment 67, control 67.
Krishnan, 4/5/2023, retrospective, India, peer-reviewed, mean age 52.8, 48 authors, study period March 2020 - March 2021.	risk of death, 270.0% higher, OR 3.70, *p* = 0.07, adjusted per study, case control OR, multivariable.
Körper, 10/15/2021, Randomized Controlled Trial, Germany, peer-reviewed, median age 60.0, 27 authors, study period 30 August, 2020 - 24 December, 2020, trial NCT04433910 (history) (CAPSID).	risk of death, 36.5% lower, RR 0.63, *p* = 0.19, treatment 11 of 53 (20.8%), control 17 of 52 (32.7%), NNT 8.4, day 60.
	risk of death, 14.2% lower, RR 0.86, *p* = 0.79, treatment 7 of 53 (13.2%), control 8 of 52 (15.4%), NNT 46, day 21.
	risk of no recovery, 15.9% lower, RR 0.84, *p* = 0.32, treatment 30 of 53 (56.6%), control 35 of 52 (67.3%), NNT 9.3, composite outcome of survival and no longer fulfilling criteria for severe COVID-19, day 21, primary outcome.
Lacombe, 8/10/2022, Randomized Controlled Trial, France, preprint, 33 authors, study period 16 April, 2020 - 21 April, 2021, average treatment delay 7.0 days, trial NCT04345991 (history) (CORIPLASM).	risk of death, 49.0% lower, HR 0.51, *p* = 0.16, treatment 7 of 60 (11.7%), control 12 of 60 (20.0%), NNT 12, adjusted per study, day 28.
	risk of death, 64.0% lower, HR 0.36, *p* = 0.04, treatment 4 of 22 (18.2%), control 11 of 27 (40.7%), NNT 4.4, adjusted per study, day 28, immunocompromised.
	risk of progression, 68.3% higher, RR 1.68, *p* = 0.18, treatment 13 of 60 (21.7%), control 8 of 60 (13.3%), adjusted per study, odds ratio converted to relative risk, WHO-CPS ≥6, day 4, primary outcome.

	risk of progression, 4.0% higher, HR 1.04, p = 0.89, treatment 19 of 60 (31.7%), control 20 of 60 (33.3%), NNT 60, adjusted per study, ventilation, additional immunomodulators, or death, day 14, primary outcome.
	hospitalization time, 6.7% higher, relative time 1.07, p = 0.99, treatment 60, control 60.
Lewandowski, 3/7/2024, retrospective, Poland, peer-reviewed, 15 authors.	**risk of death, 61.8% higher, OR 1.62, p = 0.12**, RR approximated with OR.
Li, 6/3/2020, Randomized Controlled Trial, China, peer-reviewed, 34 authors, study period 14 February, 2020 - 1 April, 2020.	**risk of death, 34.6% lower, RR 0.65, p = 0.30**, treatment 8 of 51 (15.7%), control 12 of 50 (24.0%), NNT 12, odds ratio converted to relative risk, 28 days.
	risk of no improvement, 15.3% lower, RR 0.85, p = 0.37, treatment 25 of 52 (48.1%), control 29 of 51 (56.9%), NNT 11, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, 28 days.
	risk of no viral clearance, 76.4% lower, RR 0.24, p = 0.01, treatment 4 of 26 (15.4%), control 15 of 23 (65.2%), NNT 2.0, inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
Lubis, 10/31/2020, Randomized Controlled Trial, Indonesia, trial NCT04380935 (history).	Estimated 60 patient RCT with results unknown and over 4 years late.
Manzini, 11/22/2022, Double Blind Randomized Controlled Trial, Italy, peer-reviewed, median age 66.6, 54 authors, study period June 2020 - August 2021, trial NCT04428021 (history) (PLACO COVID).	**risk of death, 25.0% higher, RR 1.25, p = 0.54**, treatment 14 of 60 (23.3%), control 12 of 60 (20.0%), adjusted per study, day 30.
	risk of death/intubation, 10.0% higher, RR 1.10, p = 0.76, treatment 17 of 59 (28.8%), control 14 of 56 (25.0%), day 30.
	time to viral-, 6.4% higher, relative time 1.06, p = 0.76, treatment 60, control 60, inverted to make RR<1 favor treatment.
Marshall, 3/23/2023, USA, trial NCT04412486 (history).	86 patient study with results unknown and over 2 years late.
Martinaud, 6/1/2021, Double Blind Randomized Controlled Trial, France, trial NCT04372979 (history) (PLASCOSSA).	18 patient RCT with results unknown and over 4 years late.
Menichetti, 11/29/2021, Randomized Controlled Trial, Italy, peer-reviewed, 110 authors, study period 15 July, 2020 - 8 December, 2020, average treatment delay 7.0 days, trial NCT04716556 (history) (TSUNAMI).	**risk of death, 23.4% lower, RR 0.77, p = 0.47**, treatment 14 of 231 (6.1%), control 19 of 240 (7.9%), NNT 54.
	risk of mechanical ventilation, 3.9% higher, RR 1.04, p = 1.00, treatment 25 of 231 (10.8%), control 25 of 240 (10.4%), mechanical ventilation or death.
	risk of progression, 12.0% lower, RR 0.88, p = 0.54, treatment 59 of 231 (25.5%), control 67 of 239 (28.0%), NNT 40, PaO2/FiO2 <150 mm Hg or death, primary outcome.
Mesina, 3/1/2022, prospective, Philippines, preprint, median age 60.0, 7 authors, study period April 2020 - March 2021.	**risk of death, 28.6% higher, RR 1.29, p = 0.54**, treatment 18 of 65 (27.7%), control 14 of 65 (21.5%).
	hospitalization time, 60.0% higher, relative time 1.60, p = 0.07, treatment mean 16.0 (±25.08) n=65, control mean 10.0 (±7.87) n=65.

Ortigoza, 12/13/2021, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, median age 63.0, 268 authors, study period 17 April, 2020 - 15 March, 2021, average treatment delay 7.0 days, trial NCT04364737 (history) (CONTAIN COVID-19).	**risk of death, 11.8% lower, RR 0.88, $p = 0.45$**, treatment 59 of 462 (12.8%), control 71 of 462 (15.4%), NNT 39, odds ratio converted to relative risk, day 28.
	risk of death, 1.3% lower, RR 0.99, $p = 0.95$, treatment 35 of 463 (7.6%), control 39 of 463 (8.4%), NNT 116, odds ratio converted to relative risk, day 14.
	WHO scale, 7.6% lower, OR 0.92, $p = 0.50$, treatment 468, control 473, day 28, RR approximated with OR.
	WHO scale, 6.4% lower, OR 0.94, $p = 0.58$, treatment 468, control 473, day 14, primary outcome, RR approximated with OR.
	risk of PASC, 2.4% higher, RR 1.02, $p = 0.88$, treatment 141, control 140, all categories combined.
	risk of PASC, 5.0% lower, OR 0.95, $p = 0.87$, treatment 141, control 140, general, RR approximated with OR.
	risk of PASC, 15.0% higher, OR 1.15, $p = 0.70$, treatment 141, control 140, gastrointestinal, RR approximated with OR.
	risk of PASC, 18.0% lower, OR 0.82, $p = 0.54$, treatment 141, control 140, neurological, RR approximated with OR.
	risk of PASC, 18.0% higher, OR 1.18, $p = 0.53$, treatment 141, control 140, respiratory, RR approximated with OR.
Pathak, 8/9/2021, Randomized Controlled Trial, India, trial NCT04374487 (history).	100 patient RCT with results unknown and over 3 years late.
Perilla, 12/1/2021, Randomized Controlled Trial, Colombia, trial NCT04391101 (history).	Estimated 231 patient RCT with results unknown and over 3 years late.
Perner, 6/30/2022, Randomized Controlled Trial, Denmark, trial NCT04634422 (history) (COVID-PLEX).	Estimated 220 patient RCT with results unknown and over 2 years late.
Pouladzadeh, 4/10/2021, Single Blind Randomized Controlled Trial, multiple countries, peer-reviewed, mean age 53.5, 17 authors, study period March 2020 - May 2020, trial IRCT20200310046736N1.	**risk of death, 40.0% lower, RR 0.60, $p = 0.71$**, treatment 3 of 30 (10.0%), control 5 of 30 (16.7%), NNT 15.
	hospitalization time, 30.0% higher, relative time 1.30, $p = 0.06$, treatment 30, control 30.
Quintero-Vega, 2/1/2021, Single Blind Randomized Controlled Trial, Colombia, trial NCT04425837 (history) (PLASMA COVID-19).	Estimated 236 patient RCT with results unknown and over 4 years late.
Ray, 11/29/2020, Randomized Controlled Trial, India, peer-reviewed, mean age 26.0, 38 authors, study period 31 May, 2020 - 12 October, 2020, trial CTRI/2020/05/025209.	**risk of death, 33.0% lower, HR 0.67, $p = 0.34$**, treatment 10 of 40 (25.0%), control 14 of 40 (35.0%), NNT 10, adjusted per study, Mantel-Haenszel, primary outcome.
Recovery Collaborative Group, 1/15/2021, Randomized Controlled Trial, United Kingdom, peer-reviewed, 36 authors, average treatment delay 9.0 days, trial NCT04381936 (history) (RECOVERY).	**risk of death, no change, RR 1.00, $p = 0.95$**, treatment 1,399 of 5,795 (24.1%), control 1,408 of 5,763 (24.4%), NNT 345, day 28, primary outcome.
	risk of no hospital discharge, 1.0% higher, RR 1.01, $p = 0.57$, treatment 1,963 of 5,795 (33.9%), control 1,941 of 5,763 (33.7%), inverted to make RR<1 favor treatment, day 28.

Rego, 1/30/2022, Randomized Controlled Trial, Brazil, trial NCT04528368 (history).	Estimated 60 patient RCT with results unknown and over 3 years late.
Rojas, 6/27/2022, Single Blind Randomized Controlled Trial, Colombia, peer-reviewed, 45 authors, study period 8 August, 2020 - 13 November, 2020, average treatment delay 11.0 days, trial NCT04332835 (history) (CP-COVID-19).	**risk of death, 220.0% higher, HR 3.20, $p = 0.16$**, treatment 46, control 45, Cox proportional hazards.
	risk of no hospital discharge, 37.5% lower, HR 0.62, $p = 0.04$, treatment 46, control 45, inverted to make HR<1 favor treatment, Cox proportional hazards.
	risk of no viral clearance, 25.0% higher, OR 1.25, $p = 0.72$, treatment 46, control 45, adjusted per study, mid-recovery, day 4, RR approximated with OR.
	risk of no viral clearance, 16.0% higher, OR 1.16, $p = 0.82$, treatment 46, control 45, adjusted per study, day 7, RR approximated with OR.
	risk of no viral clearance, 51.0% higher, OR 1.51, $p = 0.60$, treatment 46, control 45, adjusted per study, day 14, RR approximated with OR.
	risk of no viral clearance, 12.0% higher, OR 1.12, $p = 0.91$, treatment 46, control 45, adjusted per study, day 28, RR approximated with OR.
Schiffer, 9/1/2021, Randomized Controlled Trial, Germany, trial NCT04712344 (history) (IPCO).	Estimated 58 patient RCT with results unknown and over 3 years late.
Sekine, 7/8/2021, Randomized Controlled Trial, Brazil, peer-reviewed, 28 authors, study period 15 July, 2020 - 10 December, 2020, average treatment delay 10.0 days, trial NCT04547660 (history) (PLACOVID).	**risk of death, 38.5% higher, RR 1.38, $p = 0.42$**, treatment 18 of 80 (22.5%), control 13 of 80 (16.2%), day 28.
	risk of death, 100% higher, RR 2.00, $p = 0.28$, treatment 10 of 80 (12.5%), control 5 of 80 (6.2%), day 14.
	risk of no improvement, 10.7% higher, RR 1.11, $p = 0.74$, treatment 31 of 80 (38.8%), control 28 of 80 (35.0%), day 28.
	hospitalization time, 66.7% higher, relative time 1.67, $p = 0.87$, treatment 80, control 80.
Self, 11/30/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 51 authors, study period 28 April, 2020 - 1 June, 2021, average treatment delay 8.0 days, trial NCT04362176 (history) (PassItOn).	**risk of death, 3.3% higher, RR 1.03, $p = 0.86$**, treatment 89 of 482 (18.5%), control 80 of 465 (17.2%), odds ratio converted to relative risk, day 28.
	risk of death, 26.1% higher, RR 1.26, $p = 0.29$, treatment 63 of 482 (13.1%), control 48 of 465 (10.3%), odds ratio converted to relative risk, day 14.
	risk of 7-point scale, 4.0% higher, OR 1.04, $p = 0.76$, treatment 487, control 473, day 14, primary outcome, RR approximated with OR.
Sevdi, 6/17/2020, Double Blind Randomized Controlled Trial, Turkey, trial NCT04442958 (history).	60 patient RCT with results unknown and over 4 years late.
Shaheen, 3/31/2025, Randomized Controlled Trial, Bangladesh, peer-reviewed, mean age 51.7, 9 authors, study period June 2020 - July 2021.	**risk of death, no change, RR 1.00, $p = 1.00$**, treatment 8 of 30 (26.7%), control 8 of 30 (26.7%).

Sierra-Madero, 12/31/2020, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, trial NCT04388410 (history) (EPCOvid-1).	Estimated 410 patient RCT with results unknown and over 4 years late.
Simonovich, 11/24/2020, Randomized Controlled Trial, Argentina, peer-reviewed, 39 authors, study period 28 May, 2020 - 27 August, 2020, average treatment delay 8.0 days, trial NCT04383535 (history) (PlasmAr).	risk of death, 4.1% lower, RR 0.96, $p = 1.00$, treatment 25 of 228 (11.0%), control 12 of 105 (11.4%), NNT 216.
	risk of 7-point scale, 19.0% lower, OR 0.81, $p = 0.40$, treatment 228, control 105, RR approximated with OR.
Song, 6/30/2022, Randomized Controlled Trial, Brazil, peer-reviewed, median age 61.0, 20 authors, study period 2 June, 2020 - 18 November, 2020, average treatment delay 8.0 days, trial NCT04415086 (history) (COOP-COVID-19-MCTI).	risk of death, 51.7% higher, RR 1.52, $p = 0.37$, treatment 22 of 87 (25.3%), control 7 of 42 (16.7%).
Sullivan, 12/21/2021, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 58 authors, study period 3 June, 2020 - 1 October, 2021, average treatment delay 6.0 days, trial NCT04373460 (history) (CSSC-004).	risk of death, 85.7% lower, RR 0.14, $p = 0.12$, treatment 0 of 592 (0.0%), control 3 of 589 (0.5%), NNT 196, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ICU admission, 25.4% lower, RR 0.75, $p = 0.73$, treatment 3 of 592 (0.5%), control 4 of 589 (0.7%), NNT 580.
	risk of hospitalization, 54.3% lower, RR 0.46, $p = 0.005$, treatment 17 of 592 (2.9%), control 37 of 589 (6.3%), NNT 29.
Talarico, 5/15/2021, Randomized Controlled Trial, Italy, trial NCT04385043 (history) (COV2-CP).	Estimated 400 patient RCT with results unknown and over 4 years late.
Teofili, 5/26/2021, Randomized Controlled Trial, Italy, preprint, 1 author, trial NCT04374526 (history) (LIFESAVER).	risk of death, 100% higher, RR 2.00, $p = 1.00$, treatment 1 of 4 (25.0%), control 1 of 8 (12.5%).
Thorlacius-Ussing, 9/30/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Denmark, peer-reviewed, 27 authors, study period 13 June, 2020 - 16 March, 2021, average treatment delay 11.0 days, trial NCT04345289 (history) (CCAP-2).	risk of death, 76.0% higher, RR 1.76, $p = 0.43$, treatment 15 of 98 (15.3%), control 4 of 46 (8.7%), day 90.
	risk of death, 87.8% higher, RR 1.88, $p = 0.39$, treatment 12 of 98 (12.2%), control 3 of 46 (6.5%), day 28.
	risk of death, 72.1% higher, RR 1.72, $p = 0.55$, treatment 11 of 98 (11.2%), control 3 of 46 (6.5%), day 21.
	risk of death, 64.3% higher, RR 1.64, $p = 0.72$, treatment 7 of 98 (7.1%), control 2 of 46 (4.3%), day 14.
	risk of death, 734.7% higher, RR 8.35, $p = 0.18$, treatment 5 of 98 (5.1%), control 0 of 46 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 7.
	risk of mechanical ventilation, 37.2% higher, RR 1.37, $p = 1.00$, treatment 6 of 94 (6.4%), control 2 of 43 (4.7%), day 28.
	risk of ICU admission, 31.5% higher, RR 1.31, $p = 0.77$, treatment 12 of 89 (13.5%), control 4 of 39 (10.3%), day 28.
	risk of 7-point scale, 41.0% higher, OR 1.41, $p = 0.32$, treatment 98, control 46, day 14, primary outcome, RR approximated with OR.
Torres, 2/4/2021, Randomized Controlled Trial, Spain, trial NCT04547127 (history) (MBT).	200 patient RCT with results unknown and over 4 years late.

Torres (B), 9/30/2020, Double Blind Randomized Controlled Trial, Mexico, trial NCT04542967 (history) (PC-COVID-HCM).	150 patient RCT with results unknown and over 4 years late.
van den Berg, 2/15/2022, Randomized Controlled Trial, placebo-controlled, South Africa, peer-reviewed, 30 authors, study period 30 September, 2020 - 14 January, 2021, average treatment delay 9.0 days, trial NCT04516811 (history) (PROTECT-Patient).	risk of death, 17.0% lower, RR 0.83, $p = 0.65$, treatment 11 of 52 (21.2%), control 13 of 51 (25.5%), NNT 23, day 28.
	risk of mechanical ventilation, 67.3% lower, RR 0.33, $p = 0.36$, treatment 1 of 52 (1.9%), control 3 of 51 (5.9%), NNT 25.
	risk of no improvement, 5.4% lower, RR 0.95, $p = 1.00$, treatment 16 of 47 (34.0%), control 18 of 50 (36.0%), NNT 51, day 28.
	risk of no hospital discharge, 3.0% higher, RR 1.03, $p = 1.00$, treatment 18 of 46 (39.1%), control 19 of 50 (38.0%), day 28.
Zuluaga, 12/30/2020, Single Blind Randomized Controlled Trial, Colombia, trial NCT04385186 (history).	Estimated 60 patient RCT with results unknown and over 4 years late.

Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Jiang, 1/1/2025, Randomized Controlled Trial, China, trial NCT05904067 (history).	Estimated 72 patient RCT with results unknown and over 5 months late.

Supplementary Data

Supplementary Data

Footnotes

a. Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

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