Remdesivir for COVID-19: real-time meta analysis of 81 studies

@CovidAnalysis, July 2025, Version 102
https://c19early.org/smeta.html

Abstract

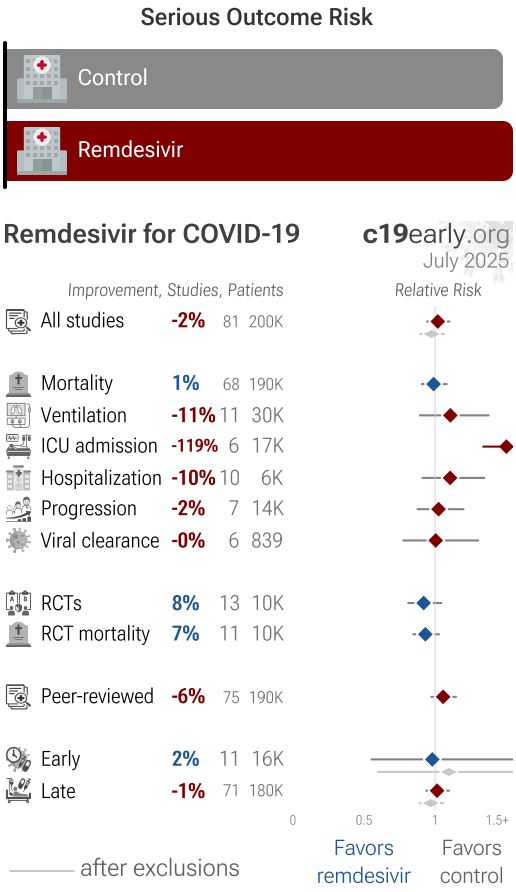
Meta analysis using the most serious outcome reported shows 2% [-6-11%] higher risk, without reaching statistical significance.

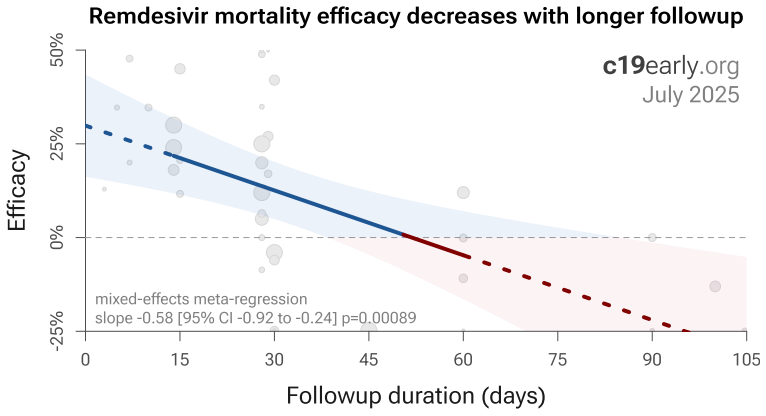
Meta regression with followup duration shows that mortality results are worse with longer followup. This may reflect antiviral efficacy being offset by side effects of treatment.

Studies show significantly increased risk of acute kidney injury [1-6], liver injury [7-10], and cardiac disorders [11]. Variants may be less susceptible to remdesivir [12-14].

Prescription treatments have been preferentially used by patients at lower risk [15]. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

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





REMDESIVIR FOR COVID-19 — HIGHLIGHTS

No significant improvements are seen. Meta regression with followup duration shows that mortality results are worse with longer followup. This may reflect antiviral efficacy being offset by side effects of treatment.

Studies show significantly increased risk of acute kidney injury, liver injury, and cardiac disorders.

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.

81 remdesivir COVID-19 studies

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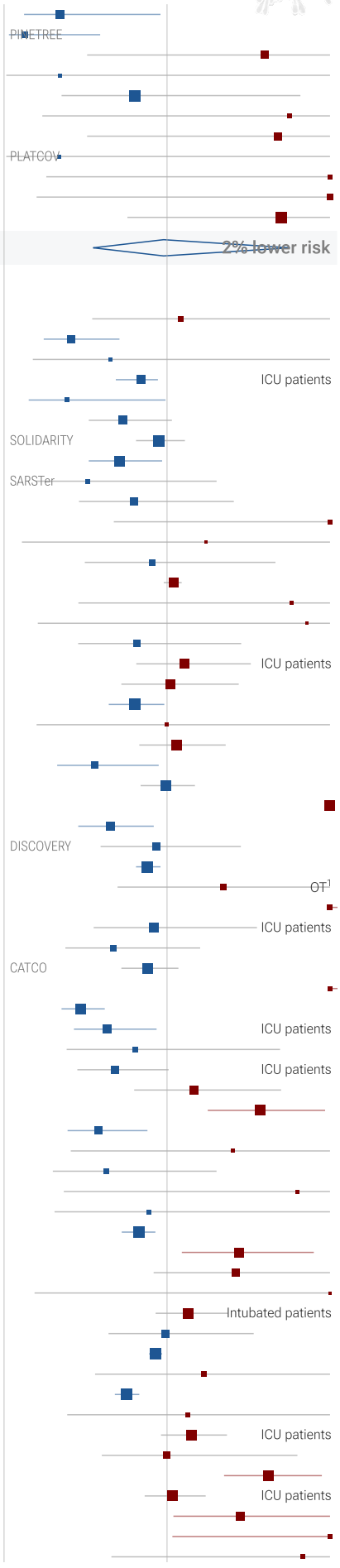
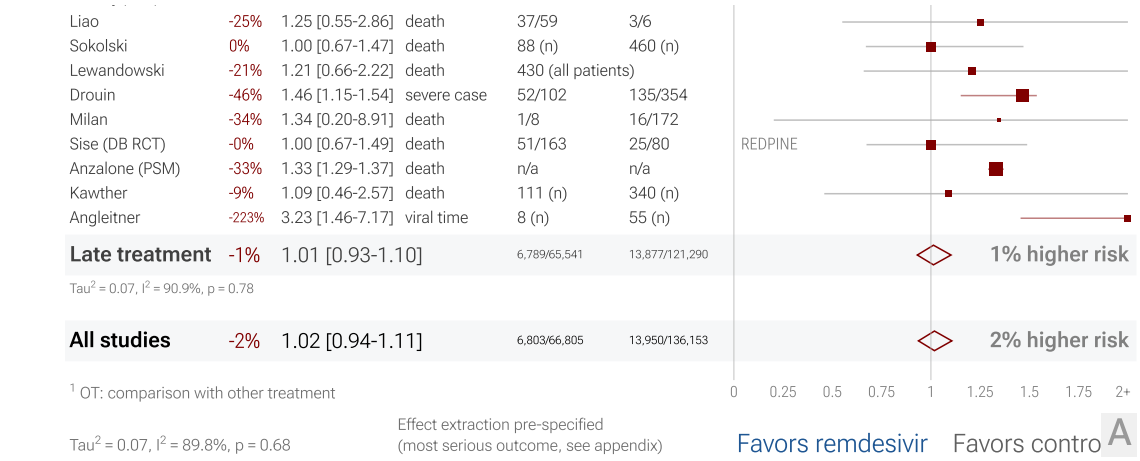
July 2025

	Improvement, RR [CI]			Treatment	Control
Madan (ES)	66%	0.34 [0.12-0.96]	death	4/112	27/260
Gottlieb (DB RCT)	87%	0.13 [0.03-0.59]	death/hosp.	2/279	15/283
Killingley	-60%	1.60 [0.51-5.03]	progression	6 (n)	12 (n)
Piccicacco	66%	0.34 [0.01-8.32]	death	0/82	1/90
Kneidinger	20%	0.80 [0.35-1.82]	severe case	6/46	28/172
Ong	-75%	1.75 [0.23-13.0]	recov. time	4 (n)	14 (n)
Chew	-68%	1.68 [0.51-5.58]	progression	12 (n)	151 (n)
Jittamala (RCT)	66%	0.34 [0.01-8.12]	hosp.	0/67	1/69
Seah	-129%	2.29 [0.26-20.1]	no recov.	2/7	1/8
Choi	-267%	3.67 [0.20-3.27]	death	308 (n)	13,656 (n)
Siami	-70%	1.70 [0.76-3.82]	hosp.	341 (n)	148 (n)
Early treatment	2%	0.98 [0.55-1.75]		14/1,264	73/14,863

Tau^2 = 0.43, I^2 = 50.0%, p = 0.95

	Improvement, RR [CI]			Treatment	Control
Wang (RCT)	-9%	1.09 [0.54-2.18]	death	22/158	10/78
Olender	59%	0.41 [0.24-0.71]	death	24/312	102/818
Spinner (RCT)	35%	0.65 [0.18-2.40]	death	5/384	4/200
Pasquini (ICU)	16%	0.84 [0.69-0.94]	death	14/25	24/26
Fried	61%	0.39 [0.15-0.99]	death	4/48	2,510/11,673
Beigel (RCT)	27%	0.73 [0.52-1.03]	death	541 (n)	521 (n)
SOLIDARITY .. (RCT)	5%	0.95 [0.81-1.11]	death	301/2,743	303/2,708
El-Solh	29%	0.71 [0.52-0.97]	death	63/219	202/424
Flisiak	49%	0.51 [0.19-1.30]	death	5/122	17/211
Garibaldi	20%	0.80 [0.46-1.41]	death	23/303	45/303
Ullah	-100%	2.00 [0.67-5.94]	death	8/30	4/30
Yeramaneni	-24%	1.24 [0.11-14.2]	death	32 (n)	7,126 (n)
Goldberg	9%	0.91 [0.50-1.67]	hosp. time	29 (n)	113 (n)
Tsuzuki	-4%	1.04 [0.98-1.09]	death	69/824	285/11,663
Mahajan (RCT)	-76%	1.76 [0.46-6.82]	death	5/34	3/36
Mulhem	-86%	1.86 [0.21-5.24]	death	1/8	515/3,211
Haji Aghajani	19%	0.81 [0.46-1.46]	death	46 (n)	945 (n)
Elhadi (ICU)	-11%	1.11 [0.81-1.51]	death	14/21	267/444
Pourhoseingholi	-2%	1.02 [0.72-1.44]	death	42/123	297/2,345
Arch (PSM)	20%	0.80 [0.64-0.98]	death	203/1,491	777/4,676
Barrat-Due (DB RCT)	0%	1.00 [0.20-4.60]	death	3/42	4/57
Ohl (PSM)	-6%	1.06 [0.83-1.36]	death	143/1,172	124/1,172
Madan	44%	0.56 [0.33-0.95]	death	23/398	27/260
Kuno (PSM)	1%	0.99 [0.84-1.17]	death	214/999	216/999
Elavarasi	-137%	2.37 [1.98-2.83]	death	146/403	207/1,352
Diaz	35%	0.65 [0.46-0.92]	death	33/286	173/852
Ader (RCT)	6%	0.94 [0.59-1.45]	death	34/414	37/418
Mozaffari	12%	0.88 [0.81-0.96]	death	4,441/28,855	5,499/28,855
Sarhan (RCT)	-35%	1.35 [0.70-2.60]	death	15/52	12/56
Schmidt (PSM)	-509%	6.09 [2.71-13.7]	severe case	43 (n)	434 (n)
Jamir (ICU)	8%	0.92 [0.55-1.55]	death	60/181	41/85
Mustafa	33%	0.67 [0.38-1.20]	death	16/200	29/244
Ali (RCT)	12%	0.88 [0.72-1.07]	death	127/634	152/647
Kurniyanto	-460%	5.60 [2.32-13.5]	death	7/45	12/432
Siraj	53%	0.47 [0.35-0.62]	death	108/413	197/587
Salehi (ICU)	37%	0.63 [0.43-0.94]	death	17/40	57/85
Elec	19%	0.81 [0.38-1.69]	death	7/38	29/127
Zangeneh (ICU)	32%	0.68 [0.45-1.01]	death	n/a	n/a
Malundo	-17%	1.17 [0.80-1.70]	death	24/115	197/1,100
Bowen	-57%	1.57 [1.25-1.97]	death	817 (n)	3,814 (n)
Raad	42%	0.58 [0.39-0.88]	death	n/a	n/a
Oku	-40%	1.40 [0.41-4.36]	death	3/46	8/172
Behboodikhah	38%	0.62 [0.30-1.30]	death	1,214 (n)	960 (n)
Cacho	-80%	1.80 [0.37-8.82]	death	5/57	2/41
Hartantri	11%	0.89 [0.31-2.53]	death	n/a	n/a
Alshamrani (PSM)	17%	0.83 [0.72-0.93]	death	137/246	725/1,078
Mitsushima	-44%	1.44 [1.09-1.90]	death	n/a	n/a
Punzalan	-42%	1.42 [0.92-2.20]	death	47/224	26/176
Kim	-1612%	17.12 [0.19-1565]	death	14/145	0/22
Aweimer	-13%	1.13 [0.93-1.37]	death	40/51	68/98
Arfijanto	1%	0.99 [0.64-1.53]	viral+	17/44	46/118
Bavaro (PSW)	7%	0.93 [0.89-0.97]	severe case	120 (n)	211 (n)
Shamsi	-23%	1.23 [0.56-2.69]	death	8/53	16/130
Mozaffari (PSM)	25%	0.75 [0.68-0.83]	death	14,169 (n)	5,341 (n)
Nadeem	-12%	1.12 [0.39-3.26]	death	12/96	4/36
Burhan (ICU)	-15%	1.15 [0.96-1.37]	death	33/43	345/516
Hagman	0%	1.00 [0.60-1.80]	death	105 (n)	213 (n)
Ho	-62%	1.62 [1.35-1.95]	death	5,294 (n)	21,151 (n)
Amirizadeh (ICU)	-3%	1.03 [0.86-1.24]	death	31/35	30/35
Muntean	-45%	1.45 [1.04-2.03]	death	71/287	45/264
Chang	-185%	2.85 [1.03-7.85]	death	81 (n)	81 (n)
Alsaraj (RCT)	-83%	1.83 [0.66-5.11]	death	9/52	5/53





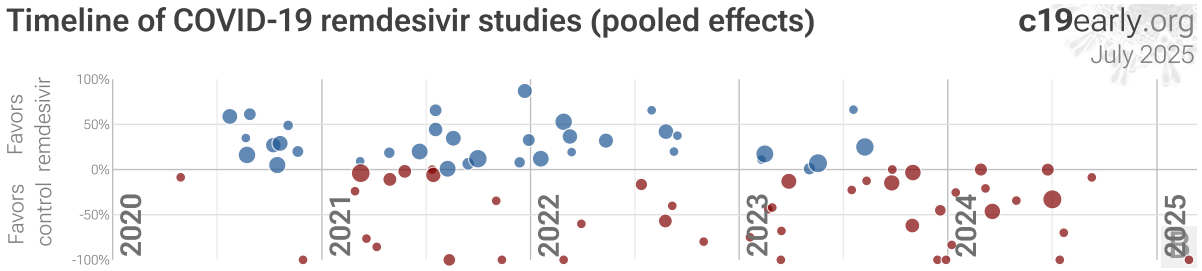


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in remdesivir 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[17-29] and cognitive deficits[20,25], cardiovascular complications[30-34], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[35]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

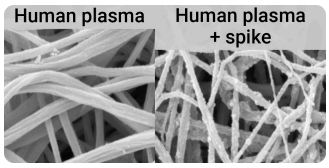


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[16].**

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,36-43], 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[44], 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 remdesivir 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, Randomized Controlled Trials (RCTs), and higher quality studies.

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.

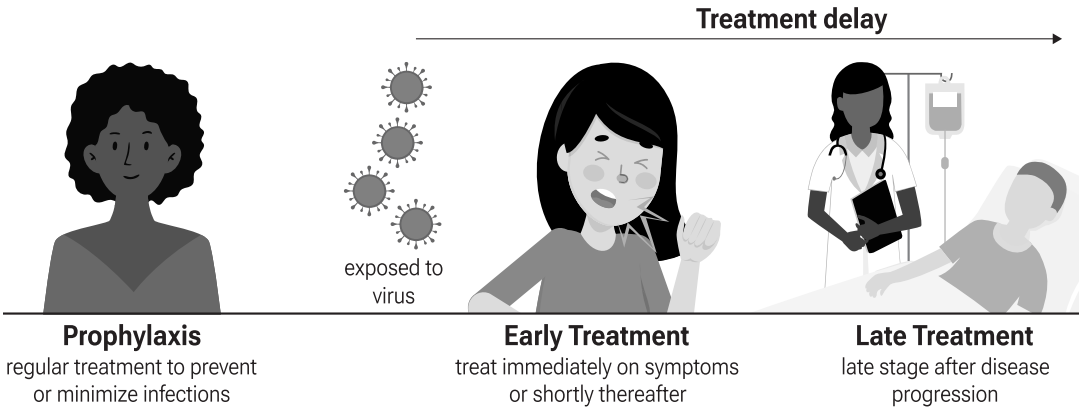


Figure 3. **Treatment stages.**

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, 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, and 12 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, viral clearance, and peer reviewed studies.

	Relative Risk	Studies	Patients
All studies	1.02 [0.94-1.11]	81	200K
After exclusions	0.97 [0.89-1.07]	58	170K
Peer-reviewed	1.06 [0.97-1.15]	75	190K
RCTs	0.92 [0.80-1.05]	13	10K
Mortality	0.99 [0.90-1.09]	67	190K
Ventilation	1.11 [0.89-1.38]	11	30K
ICU admission	2.19 [1.33-3.59] **	6	10K
Hospitalization	1.10 [0.90-1.35]	10	6,538
Viral	1.00 [0.77-1.31]	6	839
RCT mortality	0.93 [0.84-1.03]	11	10K
RCT hospitalization	0.58 [0.18-1.87]	3	1,979

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ **** $p<0.0001$.

	Early treatment	Late treatment
All studies	0.98 [0.55-1.75]	1.01 [0.93-1.10]
After exclusions	1.10 [0.59-2.03]	0.97 [0.88-1.06]
Peer-reviewed	1.15 [0.64-2.04]	1.05 [0.96-1.15]
RCTs	0.15 [0.04-0.58] **	0.93 [0.84-1.03]
Mortality	0.85 [0.14-5.18]	0.98 [0.90-1.08]
Ventilation		1.11 [0.89-1.38]
ICU admission	7.00 [4.00-11.50] ****	1.76 [1.15-2.70] **
Hospitalization	0.84 [0.40-1.76]	1.14 [0.94-1.39]
Viral	1.01 [0.46-2.22]	1.07 [0.75-1.52]
RCT mortality		0.93 [0.84-1.03]
RCT hospitalization	0.29 [0.11-0.73] **	1.11 [1.01-1.23] *

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * p<0.05 ** p<0.01 **** p<0.0001.

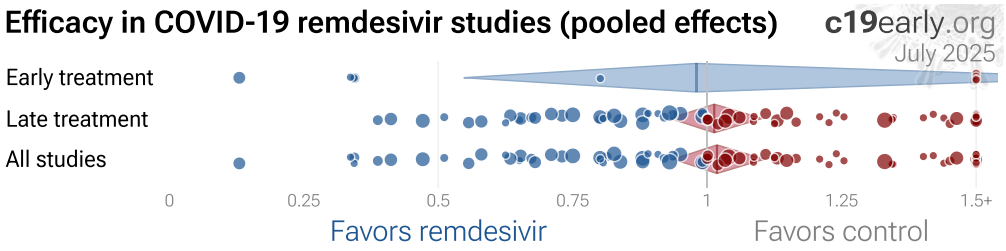


Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

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Cacho	-80%	1.80 [0.37-8.82]	death	5/57	2/41
Hartantri	11%	0.89 [0.31-2.53]	death	n/a	n/a
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Kim	-1612%	17.12 [0.19-1565]	death	14/145	0/22
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Muntean	-45%	1.45 [1.04-2.03]	death	71/287	45/264
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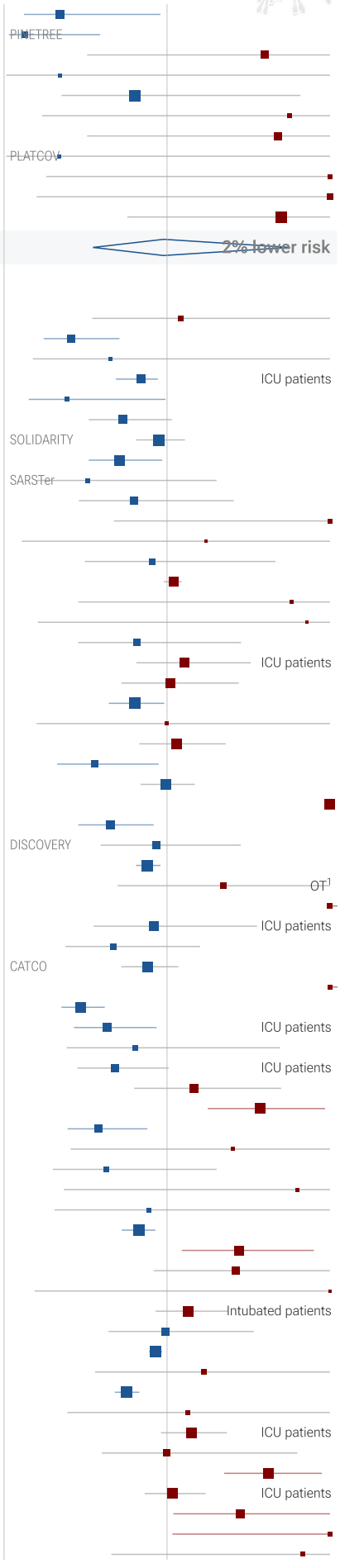
Alsaraj (RCT)	-83%	1.83 [0.66-5.11]	death	9/52	5/53



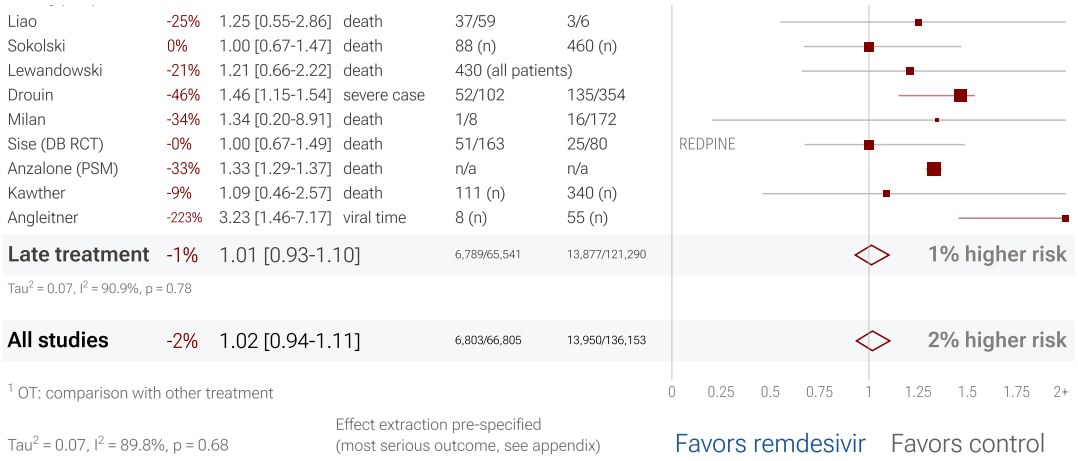


Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

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	Improvement	RR [CI]	Treatment	Control	
Madan (ES)	66%	0.34 [0.12-0.96]	4/112	27/260	
Piccicacco	66%	0.34 [0.01-8.32]	0/82	1/90	
Choi	-267%	3.67 [0.20-3.27]	308 (n)	13,656 (n)	
Early treatment	15%	0.85 [0.14-5.18]	4/502	28/14,006	15% lower risk
Tau^2 = 1.74, I^2 = 73.0%, p = 0.87					
	Improvement	RR [CI]	Treatment	Control	
Wang (RCT)	-9%	1.09 [0.54-2.18]	22/158	10/78	
Olender	59%	0.41 [0.24-0.71]	24/312	102/818	
Spinner (RCT)	35%	0.65 [0.18-2.40]	5/384	4/200	
Pasquini (ICU)	16%	0.84 [0.69-0.94]	14/25	24/26	ICU patients
Fried	61%	0.39 [0.15-0.99]	4/48	2,510/11,673	
Beigel (RCT)	27%	0.73 [0.52-1.03]	541 (n)	521 (n)	
SOLIDARITY .. (RCT)	5%	0.95 [0.81-1.11]	301/2,743	303/2,708	SOLIDARITY
El-Solh	29%	0.71 [0.52-0.97]	63/219	202/424	
Flisiak	49%	0.51 [0.19-1.30]	5/122	17/211	SARSTer
Garibaldi	20%	0.80 [0.46-1.41]	23/303	45/303	
Ullah	-100%	2.00 [0.67-5.94]	8/30	4/30	
Yeramaneni	-24%	1.24 [0.11-14.2]	32 (n)	7,126 (n)	
Tsuzuki	-4%	1.04 [0.98-1.09]	69/824	285/11,663	
Mahajan (RCT)	-76%	1.76 [0.46-6.82]	5/34	3/36	
Mulhem	-86%	1.86 [0.21-5.24]	1/8	515/3,211	
Haji Aghajani	19%	0.81 [0.46-1.46]	46 (n)	945 (n)	
Elhadi (ICU)	-11%	1.11 [0.81-1.51]	14/21	267/444	ICU patients
Pourhoseingholi	-2%	1.02 [0.72-1.44]	42/123	297/2,345	
Arch (PSM)	20%	0.80 [0.64-0.98]	203/1,491	777/4,676	
Barrat-Due (DB RCT)	0%	1.00 [0.20-4.60]	3/42	4/57	
Ohl (PSM)	-6%	1.06 [0.83-1.36]	143/1,172	124/1,172	
Madan	44%	0.56 [0.33-0.95]	23/398	27/260	
Kuno (PSM)	1%	0.99 [0.84-1.17]	214/999	216/999	
Elavarasi	-137%	2.37 [1.98-2.83]	146/403	207/1,352	
Diaz	35%	0.65 [0.46-0.92]	33/286	173/852	
Ader (RCT)	6%	0.94 [0.59-1.45]	34/414	37/418	DISCOVERY
Mozaffari	12%	0.88 [0.81-0.96]	4,441/28,855	5,499/28,855	
Sarhan (RCT)	-35%	1.35 [0.70-2.60]	15/52	12/56	OT[1]
Jamir (ICU)	8%	0.92 [0.55-1.55]	60/181	41/85	ICU patients
Mustafa	33%	0.67 [0.38-1.20]	16/200	29/244	
Ali (RCT)	12%	0.88 [0.72-1.07]	127/634	152/647	CATCO
Kurniyanto	-460%	5.60 [2.32-13.5]	7/45	12/432	
Siraj	53%	0.47 [0.35-0.62]	108/413	197/587	
Salehi (ICU)	37%	0.63 [0.43-0.94]	17/40	57/85	ICU patients
Elec	19%	0.81 [0.38-1.69]	7/38	29/127	
Zangeneh (ICU)	32%	0.68 [0.45-1.01]	n/a	n/a	ICU patients
Malundo	-17%	1.17 [0.80-1.70]	24/115	197/1,100	
Bowen	-57%	1.57 [1.25-1.97]	817 (n)	3,814 (n)	
Raad	42%	0.58 [0.39-0.88]	n/a	n/a	
Oku	-40%	1.40 [0.41-4.36]	3/46	8/172	
Behboodikhah	38%	0.62 [0.30-1.30]	1,214 (n)	960 (n)	
Cacho	-80%	1.80 [0.37-8.82]	5/57	2/41	
Hartantri	11%	0.89 [0.31-2.53]	n/a	n/a	
Alshamrani (PSM)	17%	0.83 [0.72-0.93]	137/246	725/1,078	
Mitsushima	-44%	1.44 [1.09-1.90]	n/a	n/a	
Punzalan	-42%	1.42 [0.92-2.20]	47/224	26/176	
Kim	-1612%	17.12 [0.19-1565]	14/145	0/22	
Aweimer	-13%	1.13 [0.93-1.37]	40/51	68/98	Intubated patients
Shamsi	-23%	1.23 [0.56-2.69]	8/53	16/130	
Mozaffari (PSM)	25%	0.75 [0.68-0.83]	14,169 (n)	5,341 (n)	
Nadeem	-12%	1.12 [0.39-3.26]	12/96	4/36	
Burhan (ICU)	-15%	1.15 [0.96-1.37]	33/43	345/516	ICU patients
Hagman	0%	1.00 [0.60-1.80]	105 (n)	213 (n)	
Ho	-62%	1.62 [1.35-1.95]	5,294 (n)	21,151 (n)	
Amirizadeh (ICU)	-3%	1.03 [0.86-1.24]	31/35	30/35	ICU patients
Muntean	-45%	1.45 [1.04-2.03]	71/287	45/264	
Chang	-185%	2.85 [1.03-7.85]	81 (n)	81 (n)	
Alsaraj (RCT)	-83%	1.83 [0.66-5.11]	9/52	5/53	
Liao	-25%	1.25 [0.55-2.86]	37/59	3/6	
Sokolski	0%	1.00 [0.67-1.47]	88 (n)	460 (n)	
Lewandowski	-21%	1.21 [0.66-2.22]	430 (all patients)		
Milan	-34%	1.34 [0.20-8.91]	1/8	16/172	
Sise (DB RCT)	-0%	1.00 [0.67-1.49]	51/163	25/80	REDPINE
Anzalone (PSM)	-33%	1.33 [1.29-1.37]	n/a	n/a	
Kawther	-9%	1.09 [0.46-2.57]	111 (n)	340 (n)	
Late treatment	2%	0.98 [0.90-1.08]	6,720/65,195	13,696/120,005	2% lower risk
Tau^2 = 0.09, I^2 = 90.9%, p = 0.76					
All studies	1%	0.99 [0.90-1.09]	6,724/65,697	13,724/134,011	1% lower risk

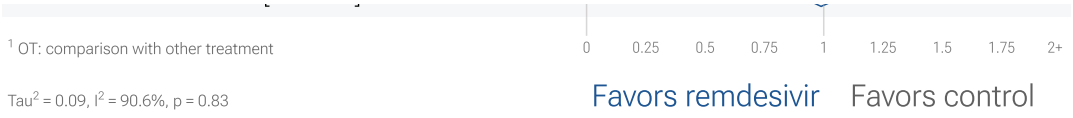

Figure 6. Random effects meta-analysis for mortality results.

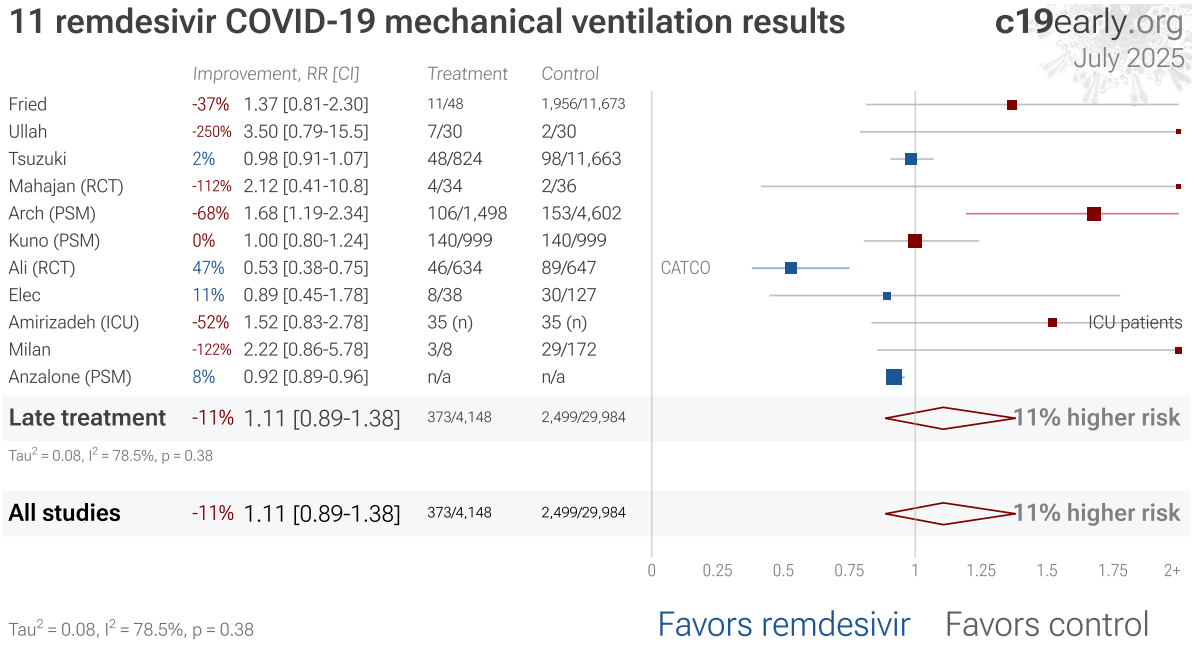

Figure 7. Random effects meta-analysis for ventilation.

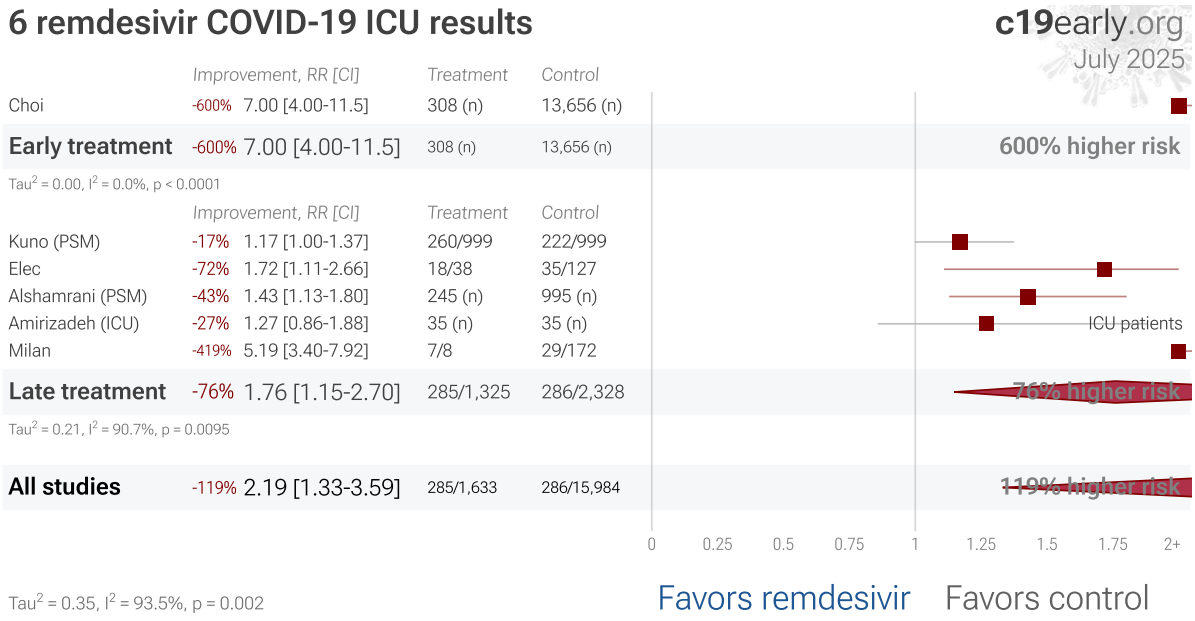

Figure 8. Random effects meta-analysis for ICU admission.

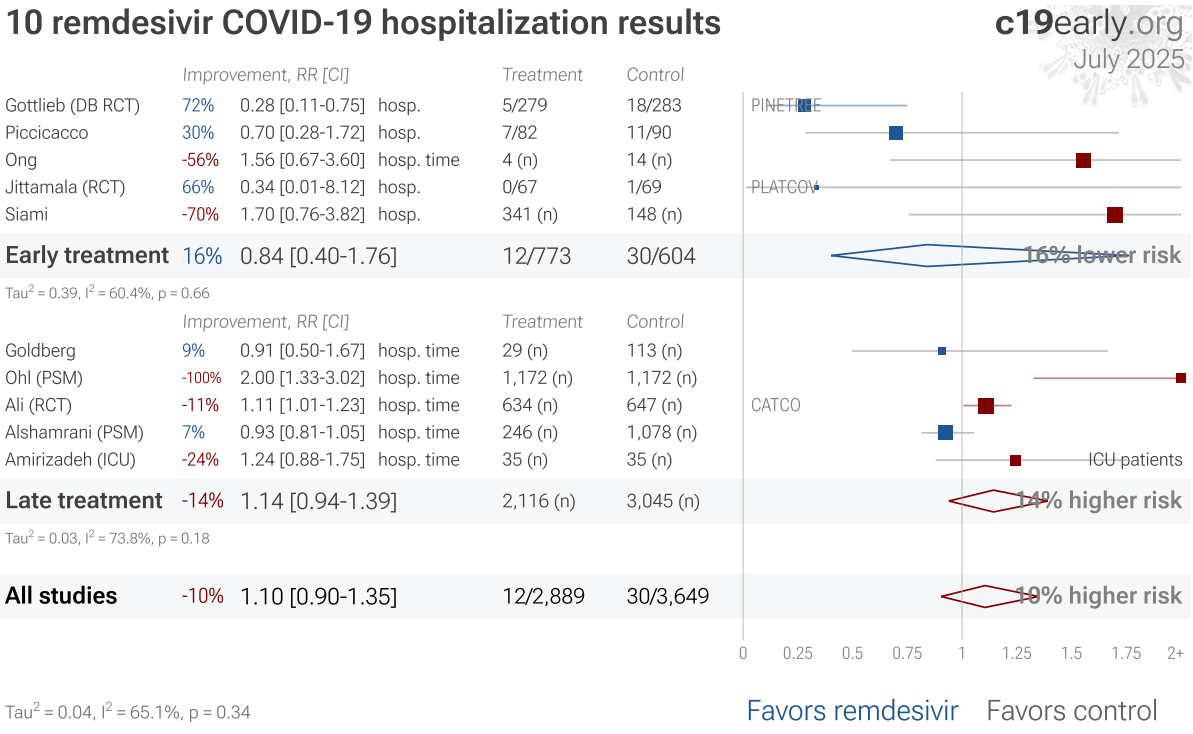

Figure 9. Random effects meta-analysis for hospitalization.

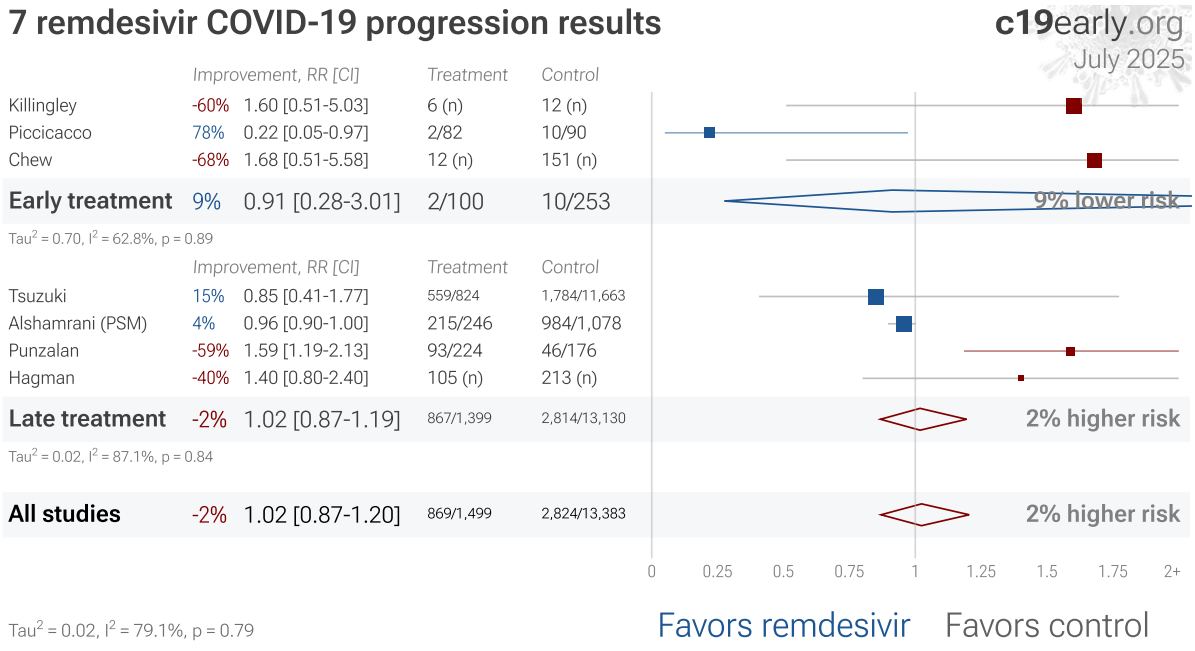

Figure 10. Random effects meta-analysis for progression.

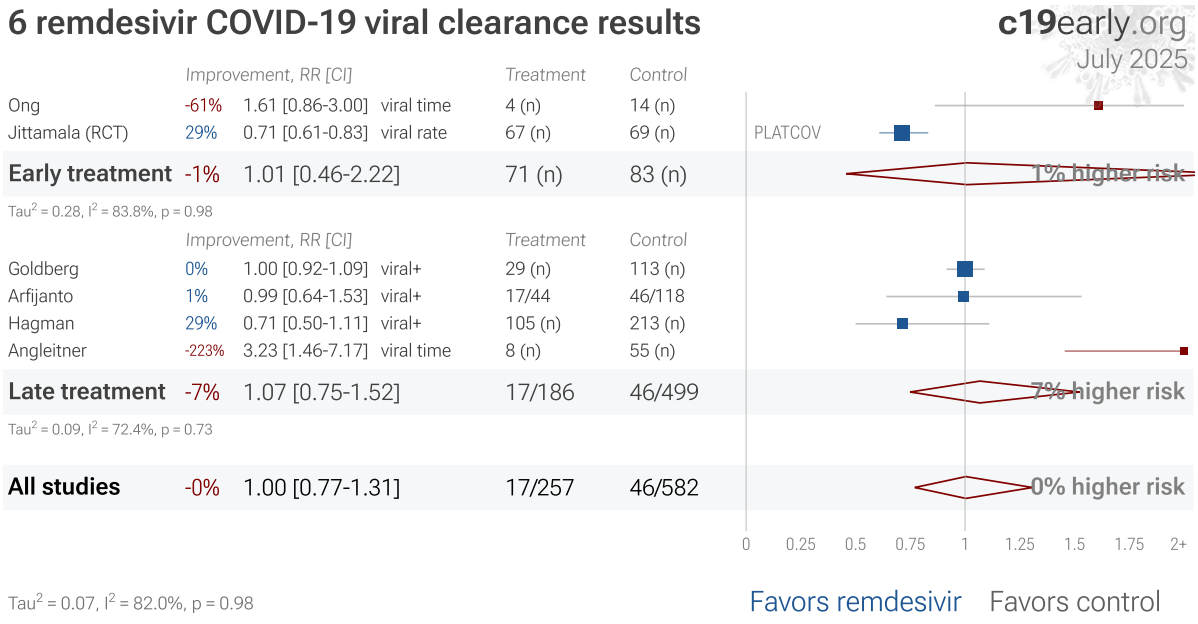

Figure 11. Random effects meta-analysis for viral clearance.

75 remdesivir COVID-19 peer reviewed studies

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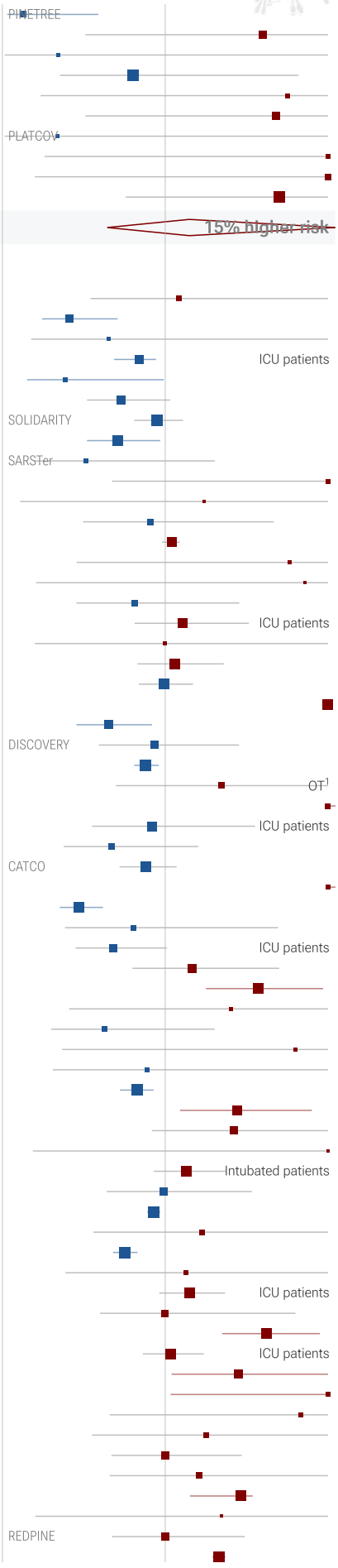
	Improvement, RR [CI]			Treatment	Control
Gottlieb (DB RCT)	87%	0.13 [0.03-0.59]	death/hosp.	2/279	15/283
Killingley	-60%	1.60 [0.51-5.03]	progression	6 (n)	12 (n)
Piccicacco	66%	0.34 [0.01-8.32]	death	0/82	1/90
Kneidinger	20%	0.80 [0.35-1.82]	severe case	6/46	28/172
Ong	-75%	1.75 [0.23-13.0]	recov. time	4 (n)	14 (n)
Chew	-68%	1.68 [0.51-5.58]	progression	12 (n)	151 (n)
Jittamala (RCT)	66%	0.34 [0.01-8.12]	hosp.	0/67	1/69
Seah	-129%	2.29 [0.26-20.1]	no recov.	2/7	1/8
Choi	-267%	3.67 [0.20-3.27]	death	308 (n)	13,656 (n)
Siami	-70%	1.70 [0.76-3.82]	hosp.	341 (n)	148 (n)
Early treatment	-15%	1.15 [0.64-2.04]		10/1,152	46/14,603

Tau^2 = 0.31, I^2 = 40.6%, p = 0.65

	Improvement, RR [CI]			Treatment	Control
Wang (RCT)	-9%	1.09 [0.54-2.18]	death	22/158	10/78
Olender	59%	0.41 [0.24-0.71]	death	24/312	102/818
Spinner (RCT)	35%	0.65 [0.18-2.40]	death	5/384	4/200
Pasquini (ICU)	16%	0.84 [0.69-0.94]	death	14/25	24/26
Fried	61%	0.39 [0.15-0.99]	death	4/48	2,510/11,673
Beigel (RCT)	27%	0.73 [0.52-1.03]	death	541 (n)	521 (n)
SOLIDARITY .. (RCT)	5%	0.95 [0.81-1.11]	death	301/2,743	303/2,708
El-Solh	29%	0.71 [0.52-0.97]	death	63/219	202/424
Flisiak	49%	0.51 [0.19-1.30]	death	5/122	17/211
Ullah	-100%	2.00 [0.67-5.94]	death	8/30	4/30
Yeramaneni	-24%	1.24 [0.11-14.2]	death	32 (n)	7,126 (n)
Goldberg	9%	0.91 [0.50-1.67]	hosp. time	29 (n)	113 (n)
Tsuzuki	-4%	1.04 [0.98-1.09]	death	69/824	285/11,663
Mahajan (RCT)	-76%	1.76 [0.46-6.82]	death	5/34	3/36
Mulhem	-86%	1.86 [0.21-5.24]	death	1/8	515/3,211
Haji Aghajani	19%	0.81 [0.46-1.46]	death	46 (n)	945 (n)
Elhadi (ICU)	-11%	1.11 [0.81-1.51]	death	14/21	267/444
Barrat-Due (DB RCT)	0%	1.00 [0.20-4.60]	death	3/42	4/57
Ohl (PSM)	-6%	1.06 [0.83-1.36]	death	143/1,172	124/1,172
Kuno (PSM)	1%	0.99 [0.84-1.17]	death	214/999	216/999
Elavarasi	-137%	2.37 [1.98-2.83]	death	146/403	207/1,352
Diaz	35%	0.65 [0.46-0.92]	death	33/286	173/852
Ader (RCT)	6%	0.94 [0.59-1.45]	death	34/414	37/418
Mozaffari	12%	0.88 [0.81-0.96]	death	4,441/28,855	5,499/28,855
Sarhan (RCT)	-35%	1.35 [0.70-2.60]	death	15/52	12/56
Schmidt (PSM)	-509%	6.09 [2.71-13.7]	severe case	43 (n)	434 (n)
Jamir (ICU)	8%	0.92 [0.55-1.55]	death	60/181	41/85
Mustafa	33%	0.67 [0.38-1.20]	death	16/200	29/244
Ali (RCT)	12%	0.88 [0.72-1.07]	death	127/634	152/647
Kurniyanto	-460%	5.60 [2.32-13.5]	death	7/45	12/432
Siraj	53%	0.47 [0.35-0.62]	death	108/413	197/587
Elec	19%	0.81 [0.38-1.69]	death	7/38	29/127
Zangeneh (ICU)	32%	0.68 [0.45-1.01]	death	n/a	n/a
Malundo	-17%	1.17 [0.80-1.70]	death	24/115	197/1,100
Bowen	-57%	1.57 [1.25-1.97]	death	817 (n)	3,814 (n)
Oku	-40%	1.40 [0.41-4.36]	death	3/46	8/172
Behboodikhah	38%	0.62 [0.30-1.30]	death	1,214 (n)	960 (n)
Cacho	-80%	1.80 [0.37-8.82]	death	5/57	2/41
Hartantri	11%	0.89 [0.31-2.53]	death	n/a	n/a
Alshamrani (PSM)	17%	0.83 [0.72-0.93]	death	137/246	725/1,078
Mitsushima	-44%	1.44 [1.09-1.90]	death	n/a	n/a
Punzalan	-42%	1.42 [0.92-2.20]	death	47/224	26/176
Kim	-1612%	17.12 [0.19-1565]	death	14/145	0/22
Aweimer	-13%	1.13 [0.93-1.37]	death	40/51	68/98
Arfijanto	1%	0.99 [0.64-1.53]	viral+	17/44	46/118
Bavaro (PSW)	7%	0.93 [0.89-0.97]	severe case	120 (n)	211 (n)
Shamsi	-23%	1.23 [0.56-2.69]	death	8/53	16/130
Mozaffari (PSM)	25%	0.75 [0.68-0.83]	death	14,169 (n)	5,341 (n)
Nadeem	-12%	1.12 [0.39-3.26]	death	12/96	4/36
Burhan (ICU)	-15%	1.15 [0.96-1.37]	death	33/43	345/516
Hagman	0%	1.00 [0.60-1.80]	death	105 (n)	213 (n)
Ho	-62%	1.62 [1.35-1.95]	death	5,294 (n)	21,151 (n)
Amirizadeh (ICU)	-3%	1.03 [0.86-1.24]	death	31/35	30/35
Muntean	-45%	1.45 [1.04-2.03]	death	71/287	45/264
Chang	-185%	2.85 [1.03-7.85]	death	81 (n)	81 (n)
Alsaraj (RCT)	-83%	1.83 [0.66-5.11]	death	9/52	5/53
Liao	-25%	1.25 [0.55-2.86]	death	37/59	3/6
Sokolski	0%	1.00 [0.67-1.47]	death	88 (n)	460 (n)
Lewandowski	-21%	1.21 [0.66-2.22]	death	430 (all patients)	
Drouin	-46%	1.46 [1.15-1.54]	severe case	52/102	135/354
Milan	-34%	1.34 [0.20-8.91]	death	1/8	16/172
Sise (DB RCT)	-0%	1.00 [0.67-1.49]	death	51/163	25/80
Anzalone (PSM)	-33%	1.33 [1.29-1.37]	death	n/a	n/a



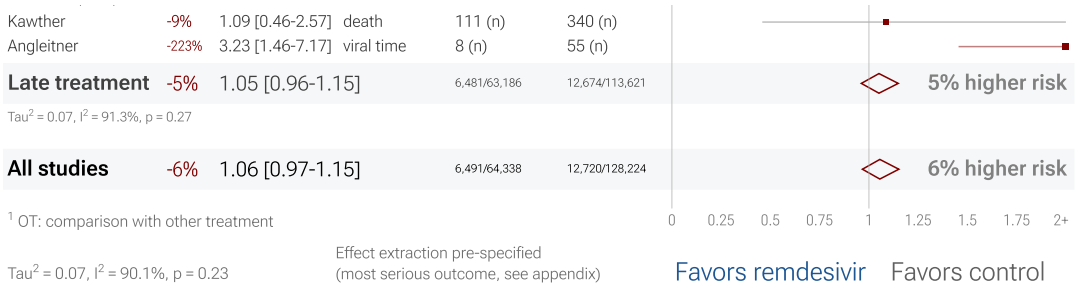


Figure 12. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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.

Randomized Controlled Trials (RCTs)

Figure 13 shows a comparison of results for RCTs and observational studies. Figure 14, 15, and 16 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.

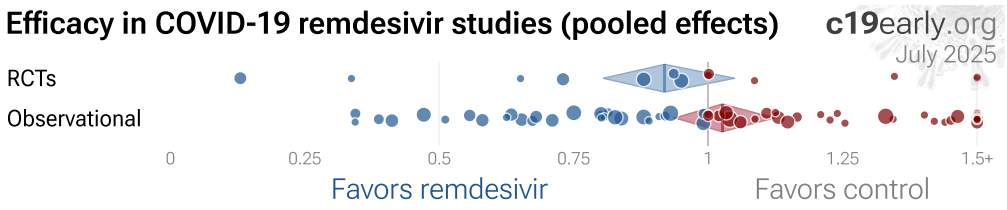


Figure 13. **Results for RCTs and observational studies.**

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[47], and analysis of double-blind RCTs has identified extreme levels of bias[48]. 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, 55 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, 58% have been confirmed in RCTs, with a mean delay of 7.7 months (64% 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.

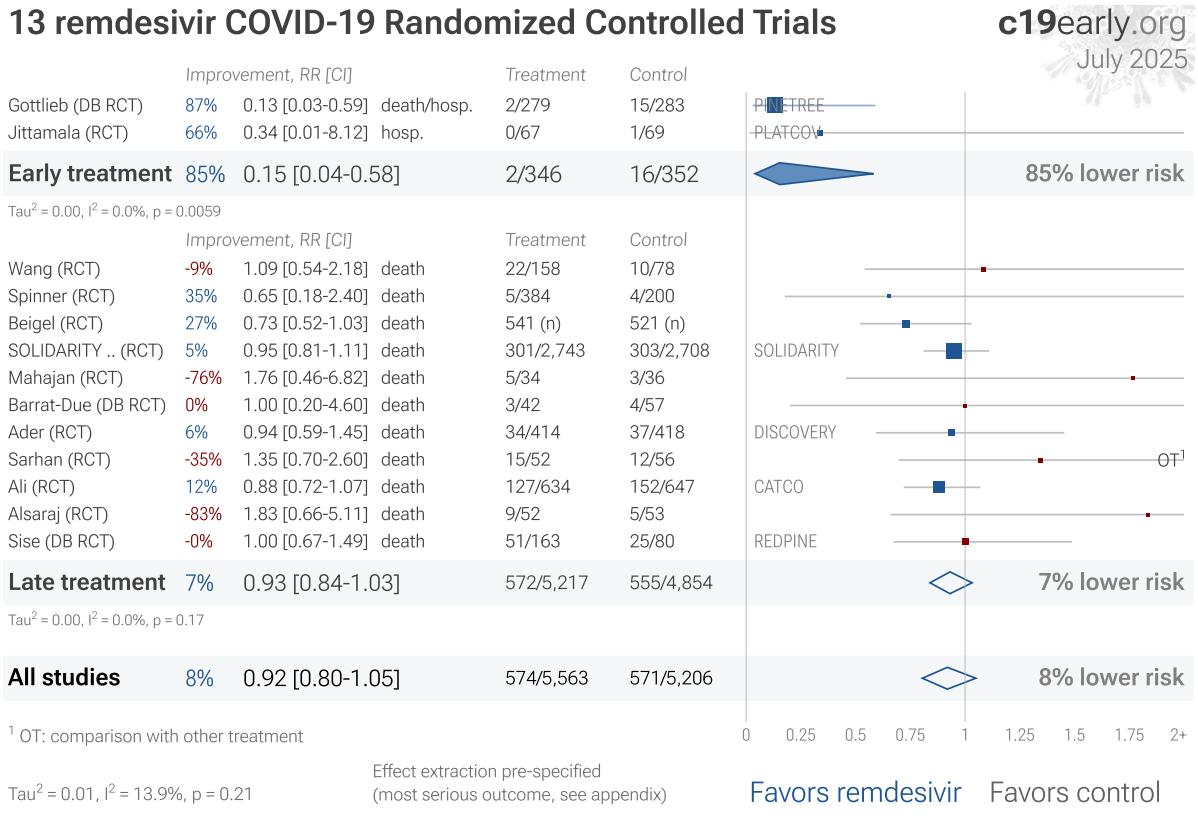


Figure 14. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

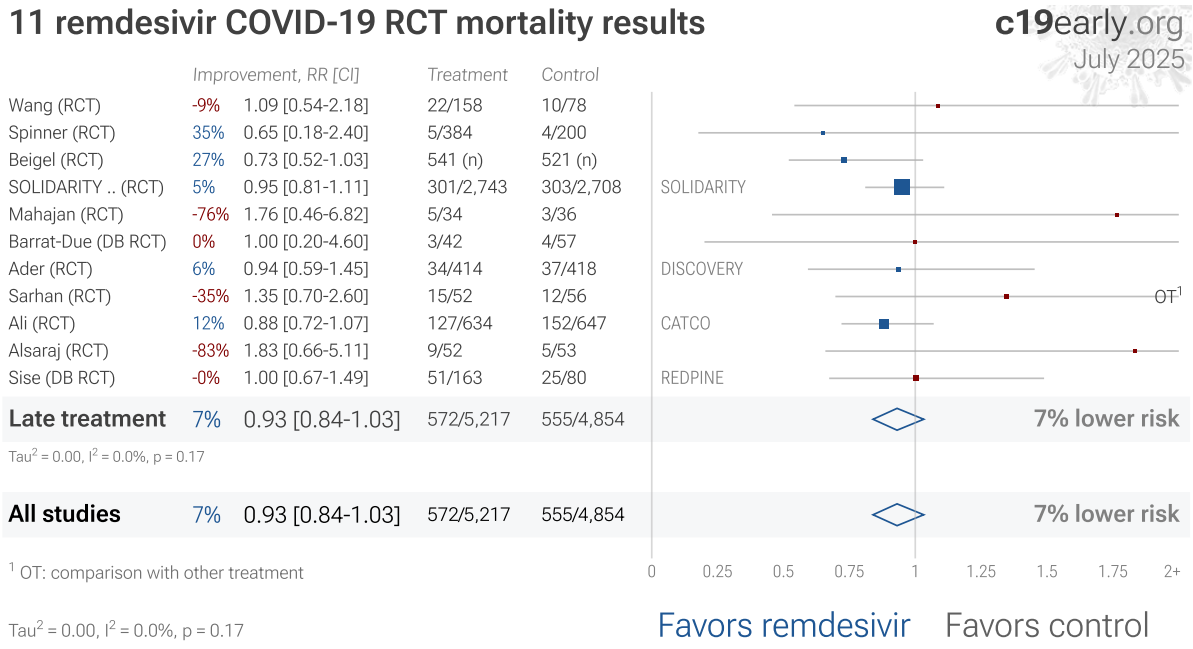


Figure 15. Random effects meta-analysis for RCT mortality results.

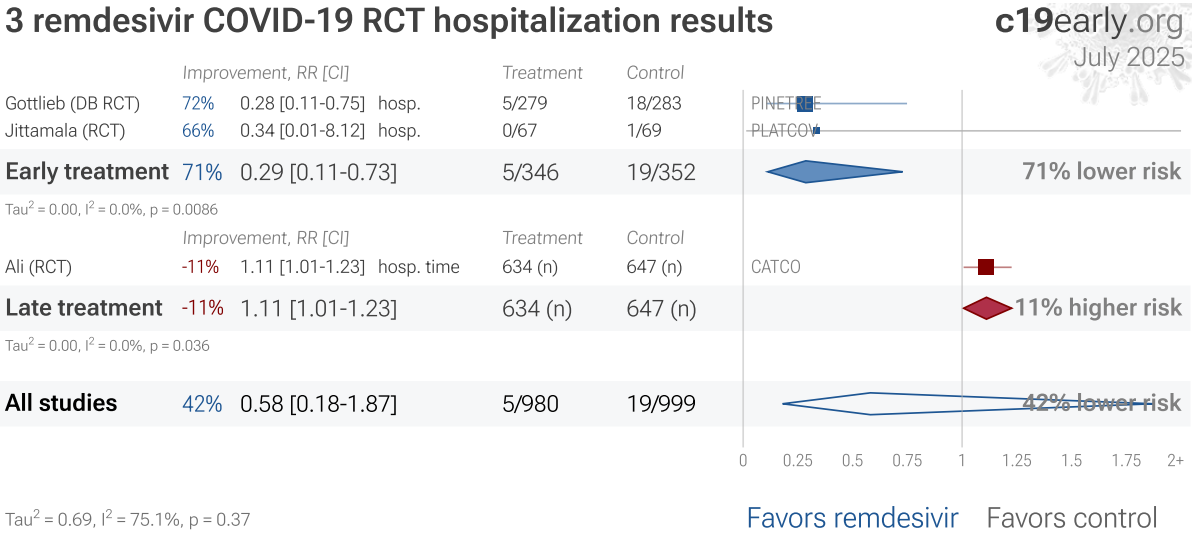


Figure 16. Random effects meta-analysis for RCT hospitalization results.

Exclusions

To avoid bias in the selection of studies, we analyze all non-retracted studies. Here we show the results after excluding studies with major issues likely to alter results, non-standard studies, and studies where very minimal detail is currently available. Our bias evaluation is based on analysis of each study and identifying when there is a significant chance that limitations will substantially change the outcome of the study. We believe this can be more valuable than checklist-based approaches such as Cochrane GRADE, which can be easily influenced by potential bias, may ignore or underemphasize serious issues not captured in the checklists, and may overemphasize issues unlikely to alter outcomes in specific cases (for example certain specifics of randomization with a very large effect size and well-matched baseline characteristics).

The studies excluded are as below. Figure 17 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Alsaraj, potential data issue.

Arfijanto, unadjusted results with no group details.

Drouin, substantial unadjusted confounding by indication likely.

El-Solh, very late stage, >50% on oxygen/ventilation at baseline; substantial unadjusted confounding by indication likely; significant confounding by contraindications possible.

Elavarasi, unadjusted results with no group details; substantial unadjusted confounding by indication likely.

Elec, substantial confounding by time possible due to significant changes in SOC and treatment propensity during the study period.

Elhadi, unadjusted results with no group details.

Fried, excessive unadjusted differences between groups; substantial unadjusted confounding by indication likely.

Kurniyanto, unadjusted results with no group details; substantial unadjusted confounding by indication likely.

Liao, unadjusted results with no group details.

Madan, unadjusted results with no group details.

Madan (B), excessive unadjusted differences between groups.

Malundo, unadjusted results with no group details.

Milan, unadjusted results with no group details.

Mulhem, substantial unadjusted confounding by indication likely; substantial confounding by time possible due to significant changes in SOC and treatment propensity during the study period.

Mustafa, unadjusted results with no group details.

Nadeem, unadjusted results with no group details.

Oku, unadjusted results with no group details.

Salehi, unadjusted results with no group details.

Sarhan, very late stage, >50% on oxygen/ventilation at baseline; significant unadjusted differences between groups.

Schmidt, confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.

Seah, unadjusted results with significant baseline differences.

Shamsi, unadjusted results with no group details.

Sokolski, unadjusted results with no group details.

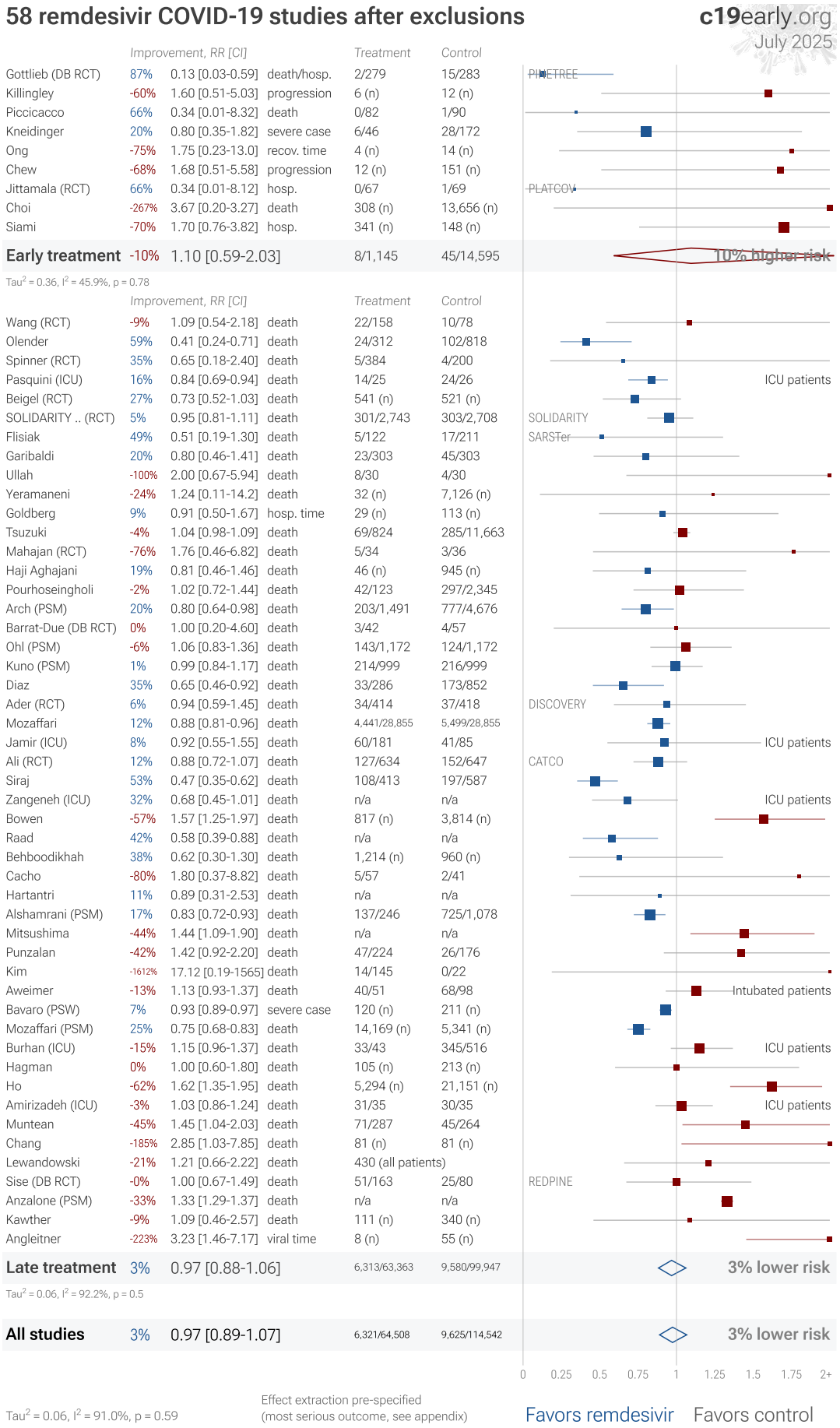


Figure 17. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the

appendix.

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[74,75]. 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[76]
<24 hours	-33 hours symptoms[77]
24-48 hours	-13 hours symptoms[77]
Inpatients	-2.5 hours to improvement[78]

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

Figure 18 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.

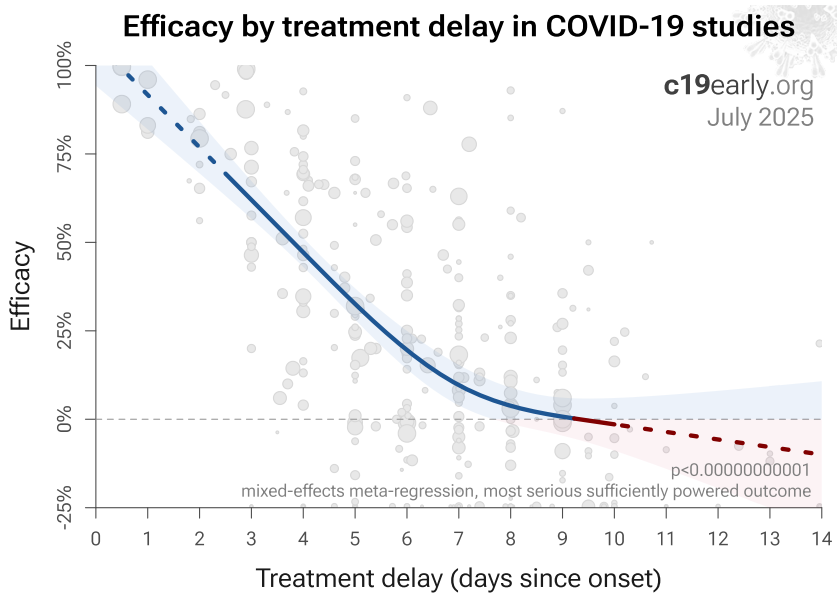


Figure 18. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

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 [80], for example the Gamma variant shows significantly different characteristics [81-84]. 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 [85,86].

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 [89-105], 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 19 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 20 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 21 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 $p = 0.000000082$ to $p = 0.0000000033$.

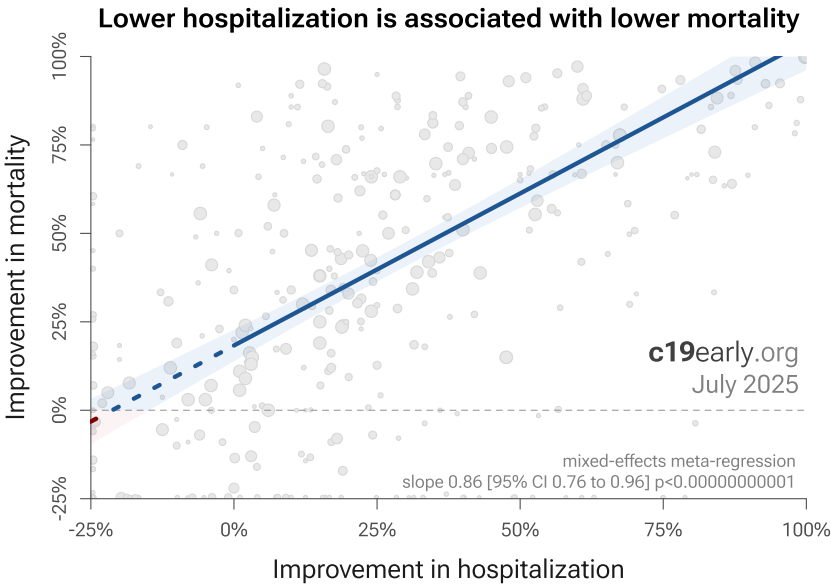


Figure 19. Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.

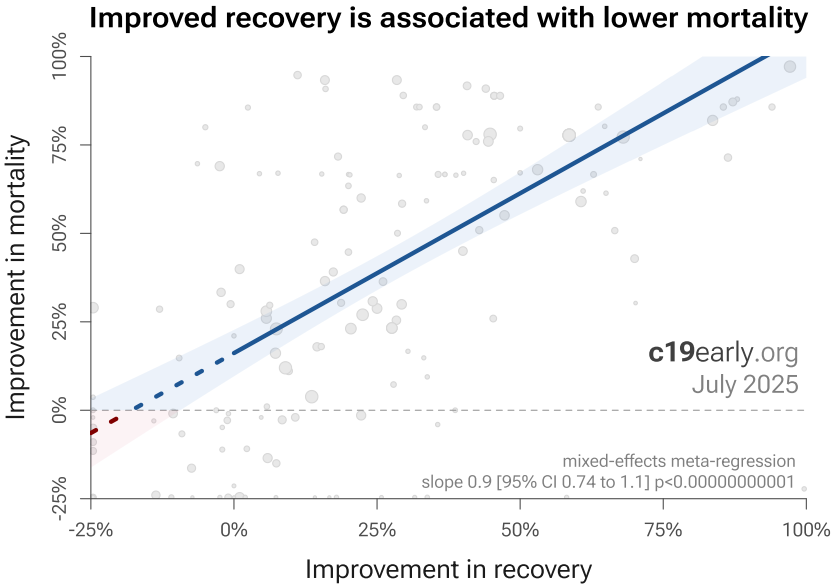


Figure 20. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

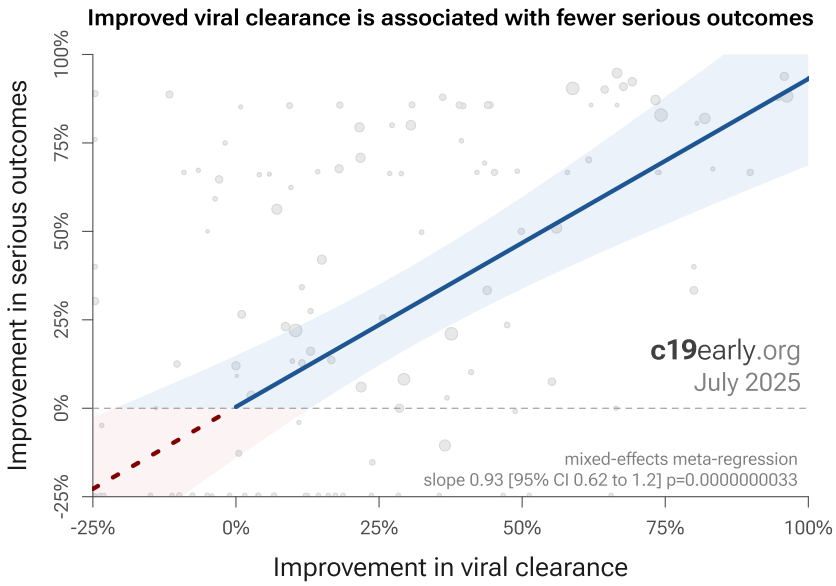


Figure 19. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

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

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% 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 22 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

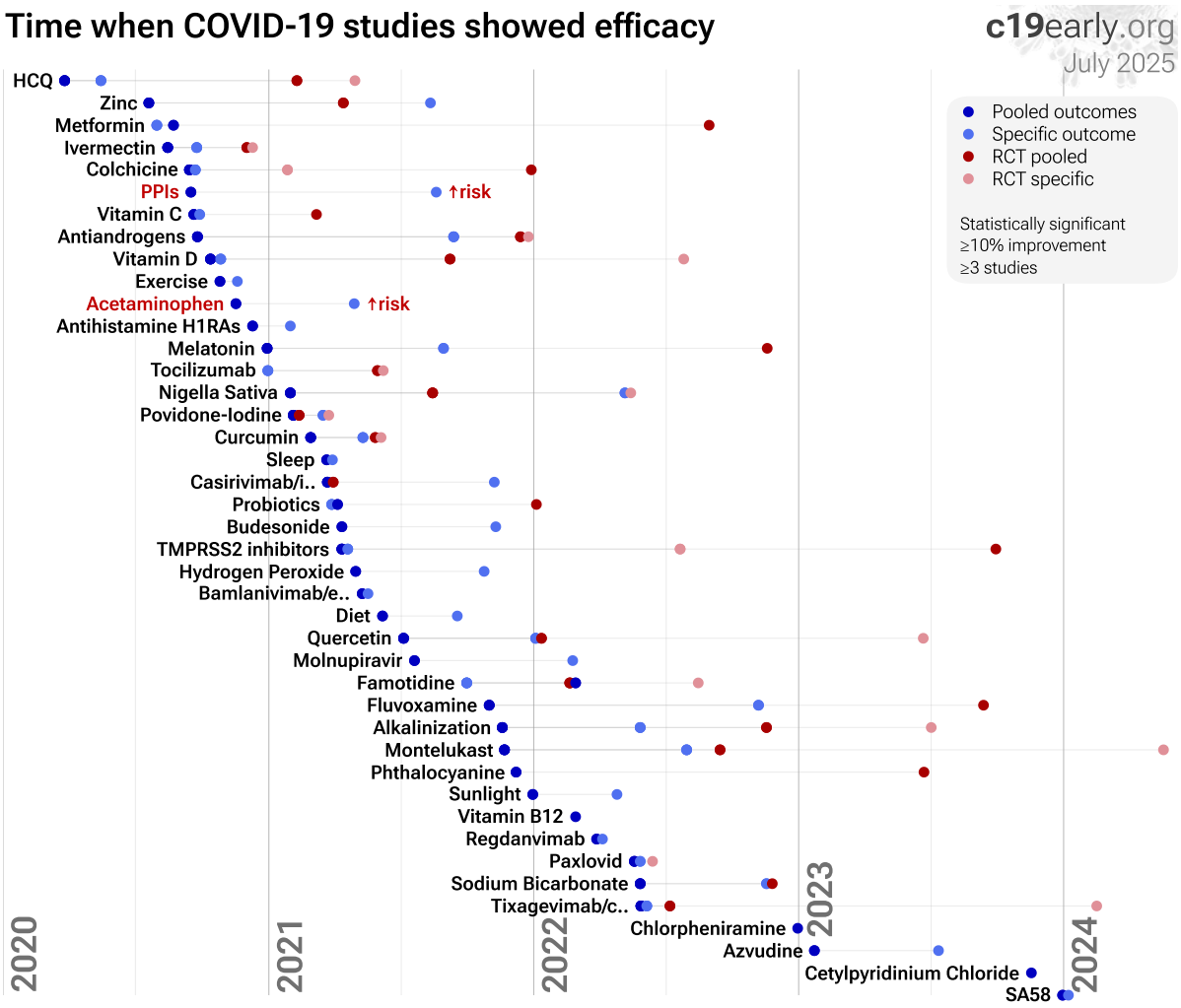


Figure 22. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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.

Efficacy decreases with longer followup

Figure 23 shows a mixed-effects meta-regression of mortality efficacy as a function of followup duration, which shows decreasing efficacy with longer followup. This may reflect antiviral efficacy being offset by side effects of treatment.

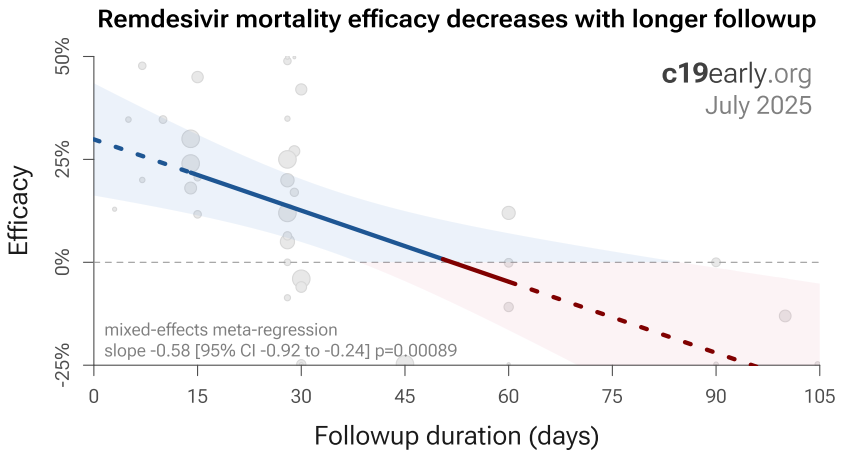


Figure 23. **Efficacy decreases with longer followup.** Meta-regression showing mortality efficacy as a function of followup duration in COVID-19 remdesivir studies.

Discussion

Retrospective studies may overestimate efficacy

Wilcock et al. show that COVID-19 prescription treatments have been preferentially used by patients at lower risk. Retrospective studies may overestimate efficacy, and data for accurate adjustment may not be available. For example, patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

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).

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 $p < 0.05$ [107-114]. 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.

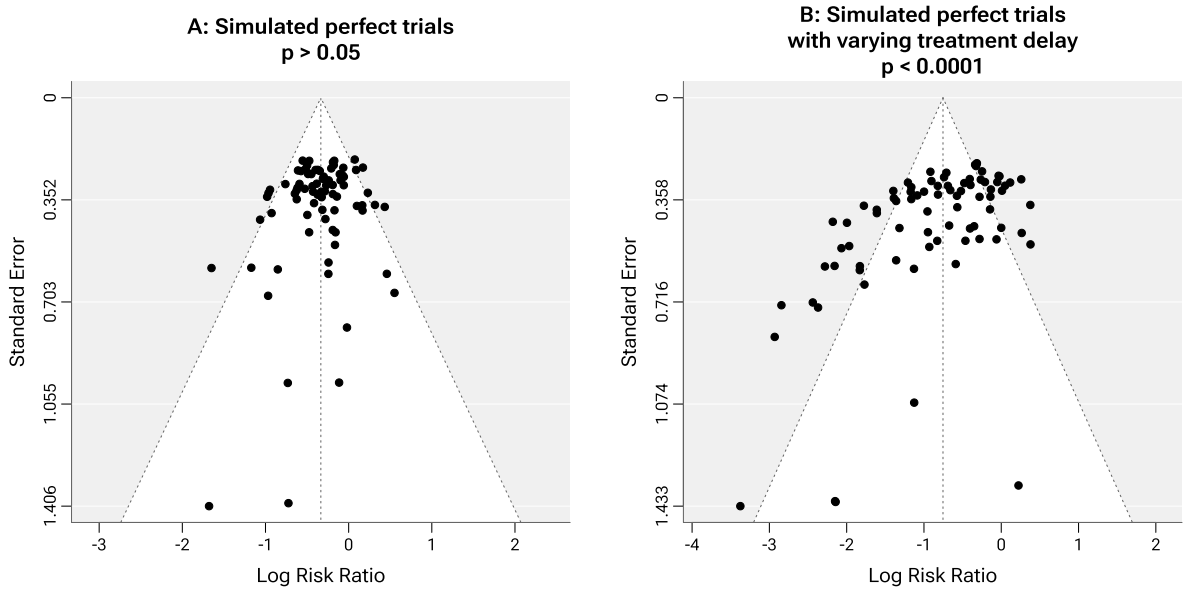


Figure 24. **Example funnel plot analysis for simulated perfect trials.**

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[89-105]. 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 81 studies compare against other treatments, which may reduce the effect seen.

Reviews

Multiple reviews cover remdesivir for COVID-19, presenting additional background on mechanisms and related results, including [12,13,115,116].

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 [36-43], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [44], 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 remdesivir in the context of multiple COVID-19 treatments, and Figure 26 shows a plot of efficacy vs. cost for COVID-19 treatments.

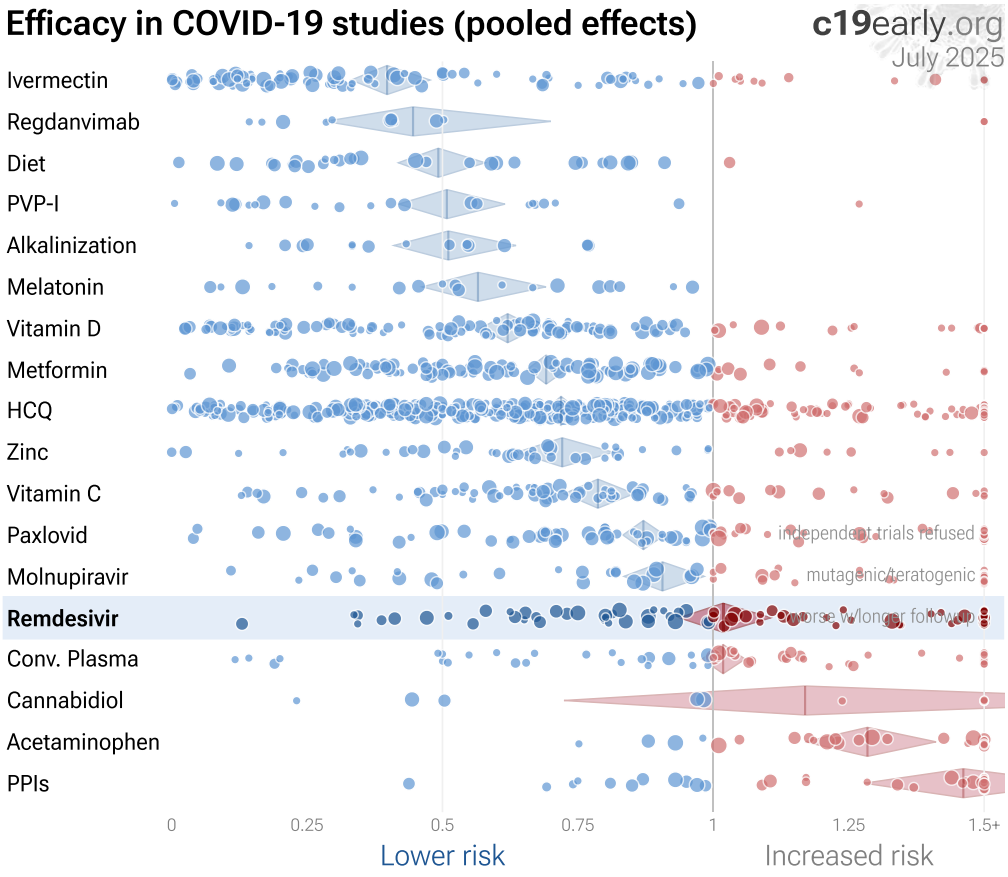


Figure 25. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy [117].

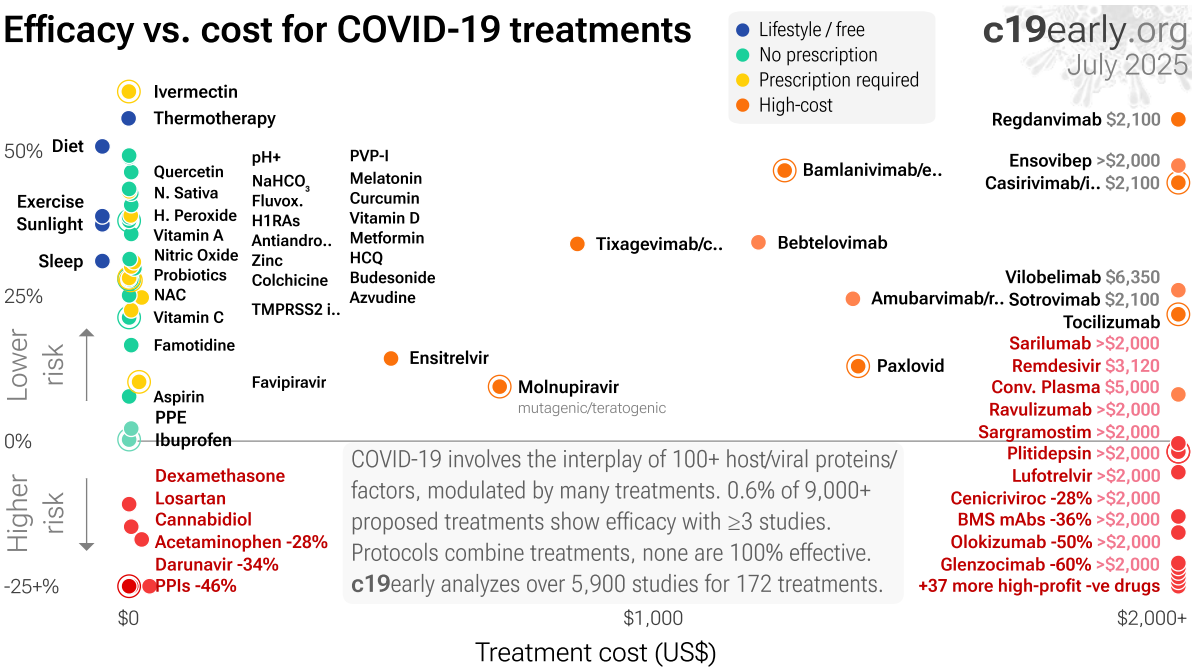


Figure 26. Efficacy vs. cost for COVID-19 treatments.

Conclusion

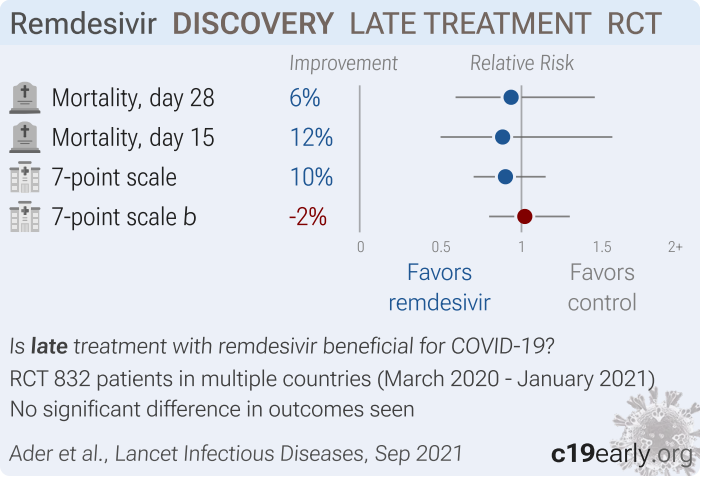
Meta analysis using the most serious outcome reported shows 2% [-6-11%] higher risk, without reaching statistical significance. Meta regression with followup duration shows that mortality results are worse with longer followup. This may reflect antiviral efficacy being offset by side effects of treatment.

Studies show significantly increased risk of acute kidney injury [1-6], liver injury [7-10], and cardiac disorders [11]. Variants may be less susceptible to remdesivir [12-14].

Prescription treatments have been preferentially used by patients at lower risk [15]. Retrospective studies may overestimate efficacy, for example patients with greater knowledge of effective treatments may be more likely to access prescription treatments but result in confounding because they are also more likely to use known beneficial non-prescription treatments.

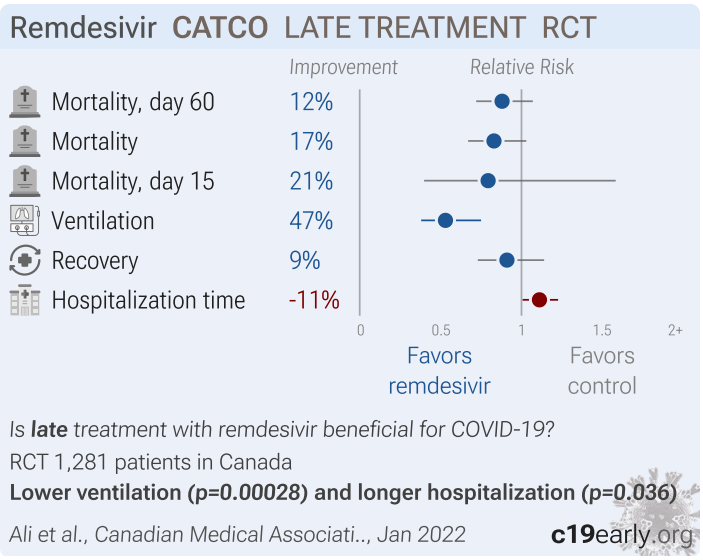
Study Notes

Ader



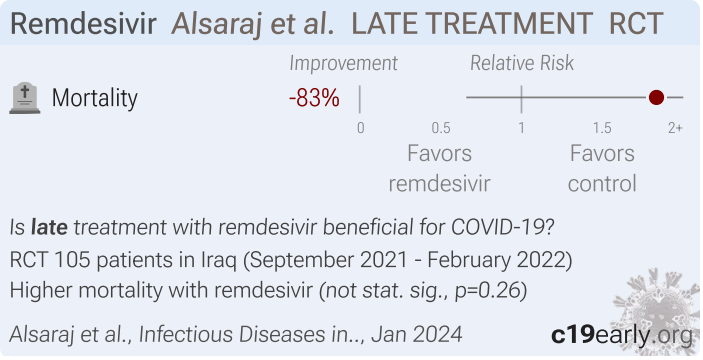
RCT 857 hospitalized patients, showing no significant differences with remdesivir treatment. EudraCT2020-000936-23.

Ali



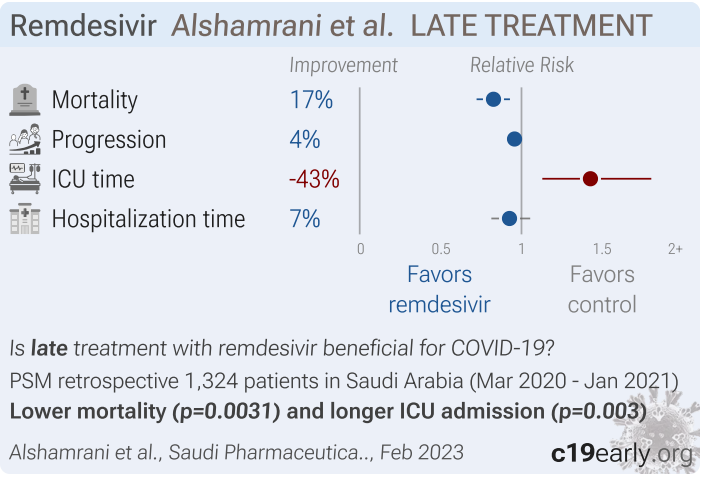
RCT 1,282 hospitalized patients in Canada showing lower mechanical ventilation with remdesivir treatment, but no significant difference for mortality.

Alsaraj



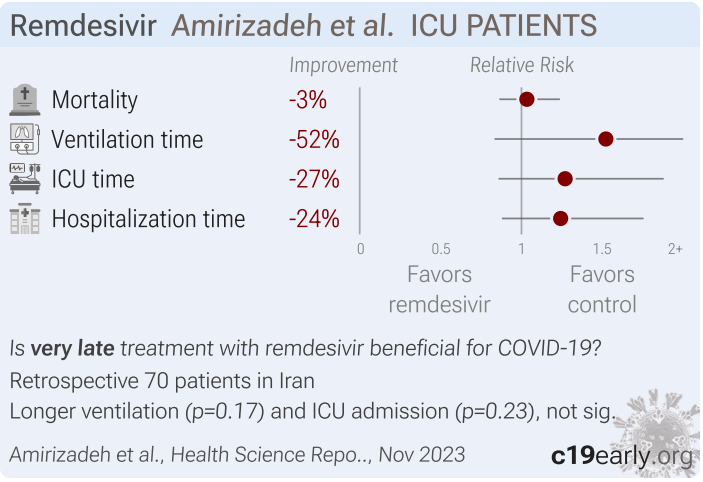
RCT 156 COVID-19 patients showing higher mortality with favipiravir and remdesivir overall. Favipiravir and remdesivir were more effective when started earlier, however note that Table 10 compares earlier favipiravir/remdesivir+standard care with standard care at any time, which will exaggerate the benefits/harms of earlier/later treatment. The confidence intervals for the Cox results are unusually narrow suggesting a possible error in calculation.

Alshamrani



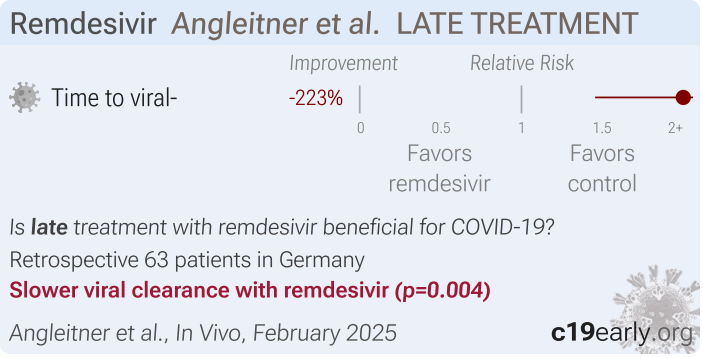
PSM retrospective 29 hospitals in Saudi Arabia, showing lower mortality with remdesivir treatment.

Amirizadeh



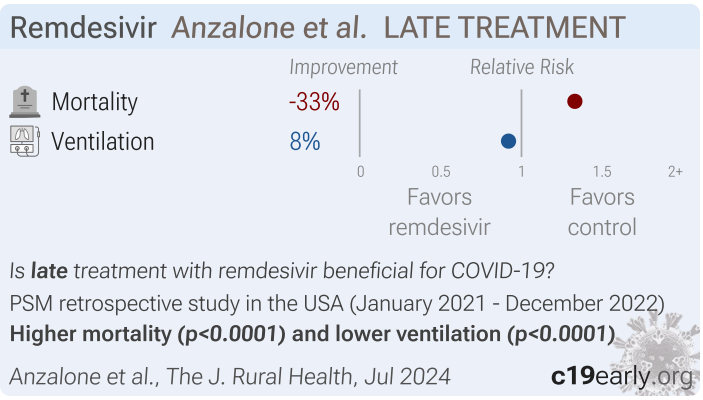
Retrospective 70 COVID-19 ICU patients, 35 receiving remdesivir plus standard treatment and 35 receiving standard treatment only. No significant differences were found for mortality, hospitalization time, ICU time, or ventilation time.

Angleitner



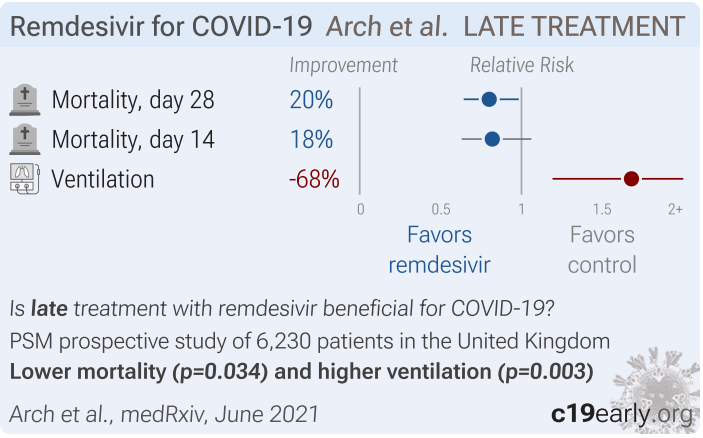
Analysis of 63 hematological malignancy patients showing prolonged SARS-CoV-2 viral shedding (average 47 days) associated with immunosuppression status and with remdesivir use.

Anzalone



Retrospective 3,018,646 COVID-19 patients in the US showing higher rates of hospitalization, inpatient death, acute kidney injury, major adverse cardiovascular events, and need for mechanical ventilation among rural patients compared to urban patients. The increased risk for rural patients persisted across pre-delta, delta, and omicron variant periods and after adjustments.

Arch

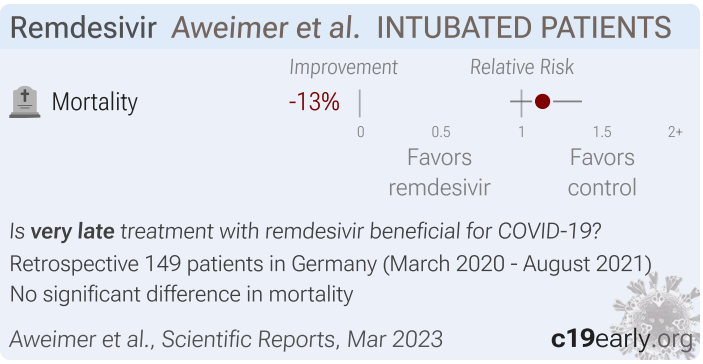


Prospective PSM analysis of remdesivir use in the UK showing statistically significantly lower mortality at 28 days. For unspecified reasons, the study prioritized short-term outcomes. Mortality at 14 days was also lower but not statistically significant. Confounding by indication is likely and may only be partially addressed by the variables included in the PSM.

Arfijanto

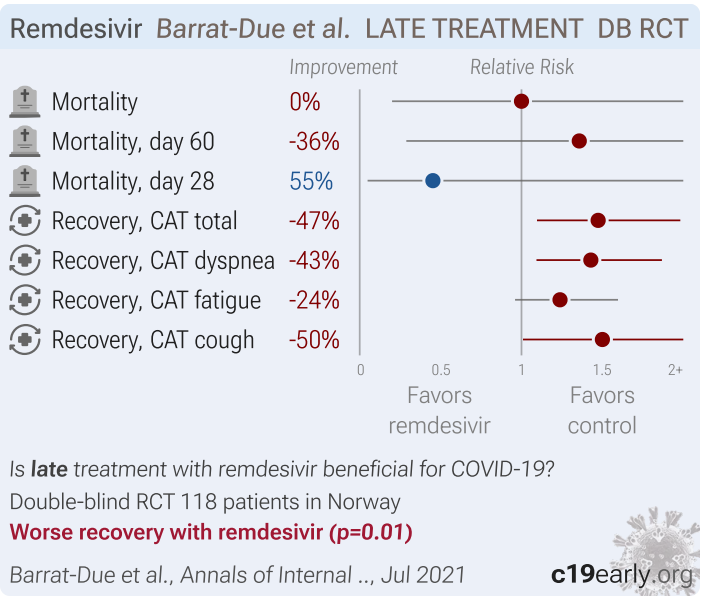
Retrospective 162 hospitalized COVID-19 patients in Indonesia, showing no significant difference in delayed viral clearance with remdesivir treatment in unadjusted results.

Aweimer



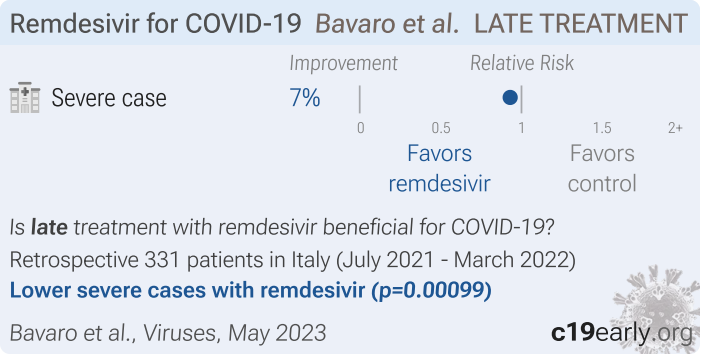
Retrospective 149 patients under invasive mechanical ventilation in Germany showing no significant difference in mortality with remdesivir in unadjusted results.

Barrat-Due



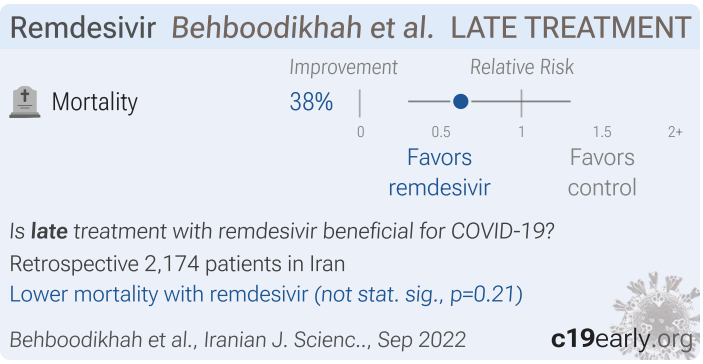
Small RCT in Norway showing no significant differences with remdesivir treatment. Add-on trial to WHO Solidarity. Longer term recovery results are from [118].

Bavaro



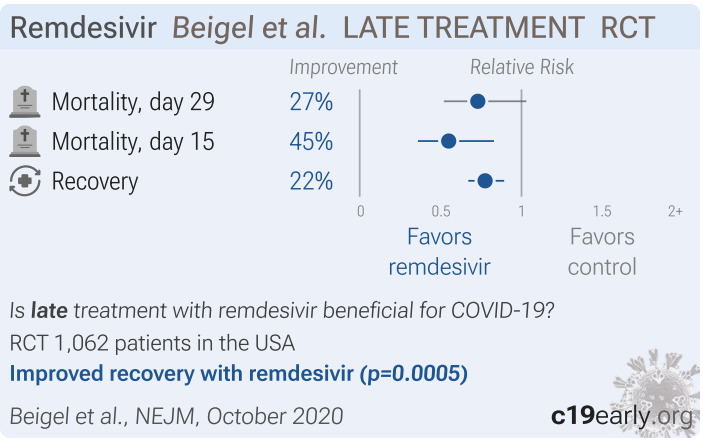
Retrospective 331 hospitalized COVID-19 patients in Italy, showing lower progression with remdesivir. Combination therapy with mAbs was more effective, and improved results were seen for immunocompromised patients.

Behboodikhah



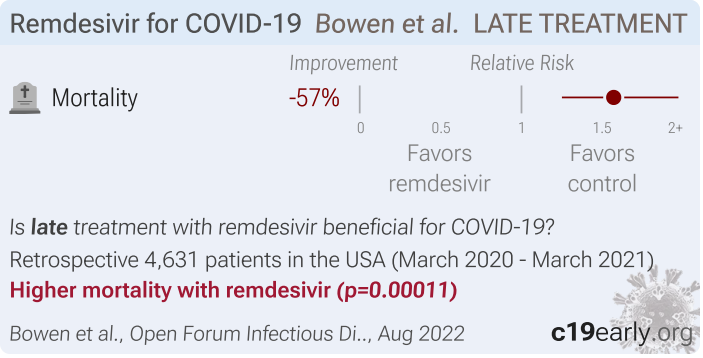
Retrospective 2,174 hospitalized patients showing no significant differences with remdesivir treatment.

Beigel



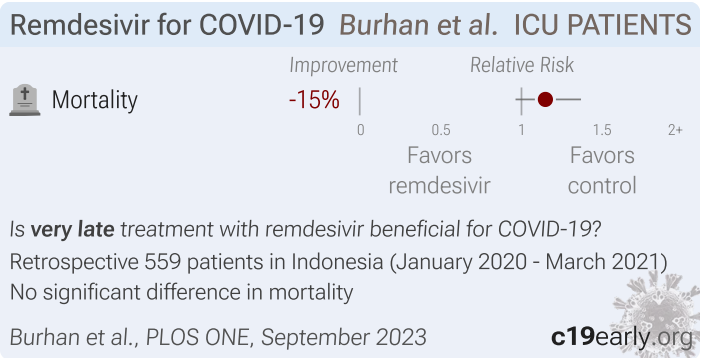
RCT 1,062 hospitalized patients showing faster recovery time with treatment, median 10 days vs. 15 days for placebo, rate ratio for recovery 1.29, p<0.001. Day 29 mortality was 11.4% with remdesivir and 15.2% with placebo, hazard ratio HR 0.73 [0.52-1.03].

Bowen



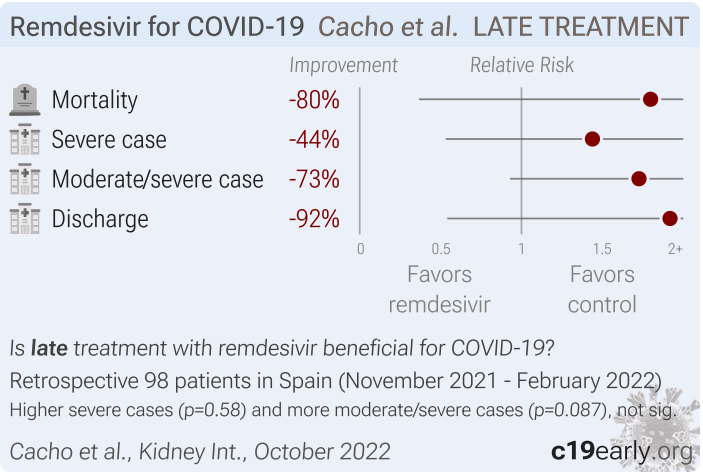
Retrospective 4,631 hospitalized patients in New York, showing higher mortality with remdesivir, and lower mortality with HCQ. Authors suggest that increased mortality during the first epidemic wave was partly due to strain on hospital resources.

Burhan



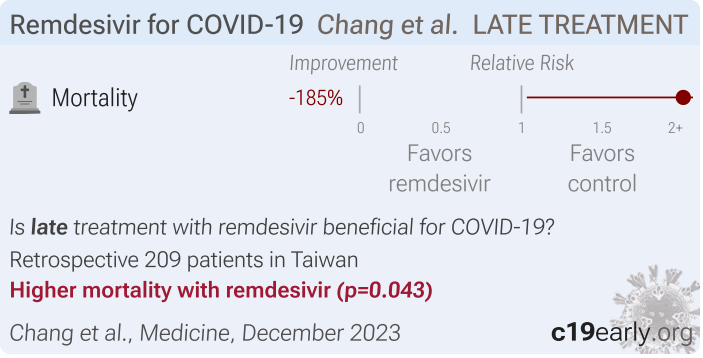
Retrospective 559 COVID-19 ICU patients in Indonesia, showing higher mortality with remdesivir in unadjusted results, without statistical significance. Note that confounding by indication should be less significant for ICU studies compared to studies of all hospitalized patients, because all patients are in critical condition.

Cacho



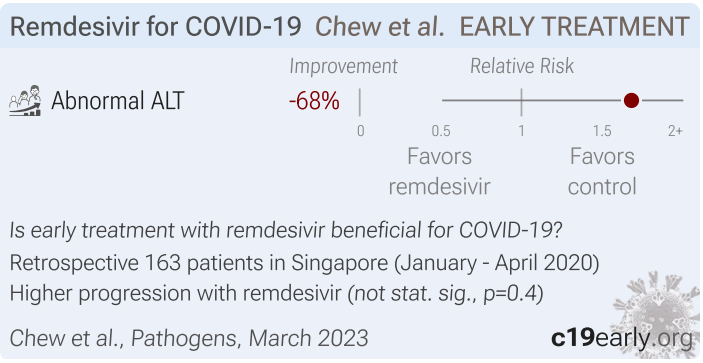
Retrospective 98 kidney transplant recipients with SARS-CoV-2 Omicron infection in Spain, showing no significant difference in mortality with remdesivir treatment. Earlier administration was associated with improved results, although this analysis is subject to survivorship/selection bias.

Chang



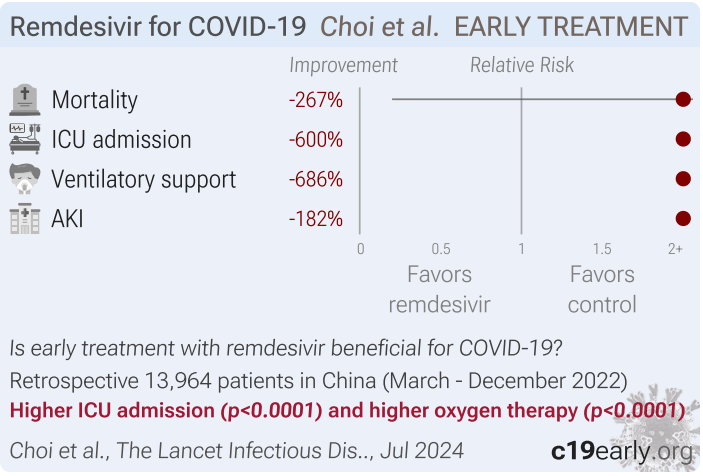
Retrospective 209 hospitalized COVID-19 patients in Taiwan showing higher mortality with a 5-day course of remdesivir compared to other antivirals or no antiviral treatment in multivariable analysis. Adjustments include qSOFA and CCI, with the adjusted result decreasing risk by 3x, however adjustment may not fully account for confounding by severity.

Chew



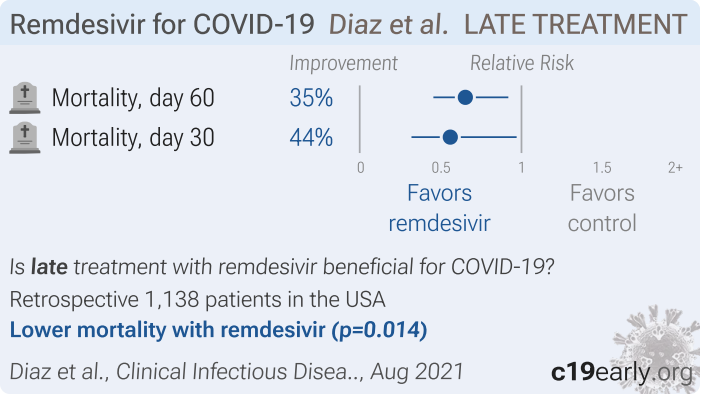
Retrospective 163 COVID-19 patients in Singapore, showing increased risk of liver injury (abnormal ALT) with acetaminophen in a dose-dependent manner, and with remdesivir, without statistical significance in both cases.

Choi



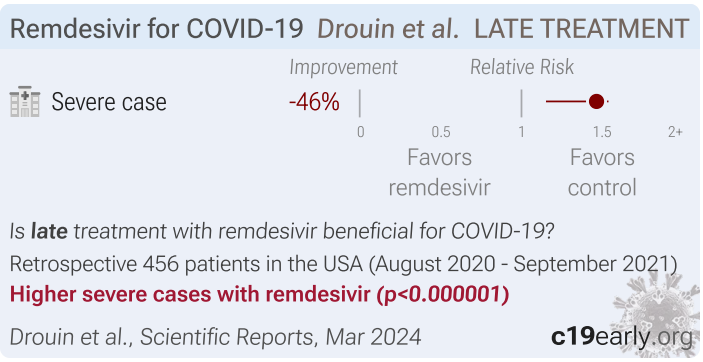
Target trial emulation study of 18,196 hospitalized COVID-19 patients in Hong Kong showing significantly higher ICU admission and AKI with remdesivir + paxlovid compared with paxlovid alone, and lower mortality and ventilatory support with remdesivir + paxlovid compared with remdesivir alone. Patients were treated within 5 days of diagnosis, however the time from onset is not known.

Diaz



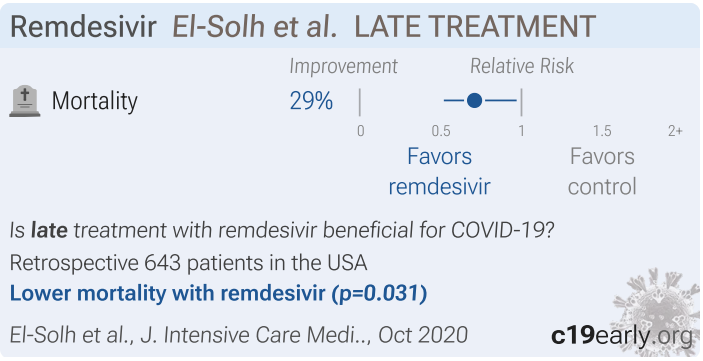
Retrospective 1,138 hospitalized patients in the USA, 286 treated with remdesivir, showing lower mortality with treatment. Age was not included in the adjustments (authors excluded variables that contributed to another score, in this case age is in Pneumonia Severity Index).

Drouin



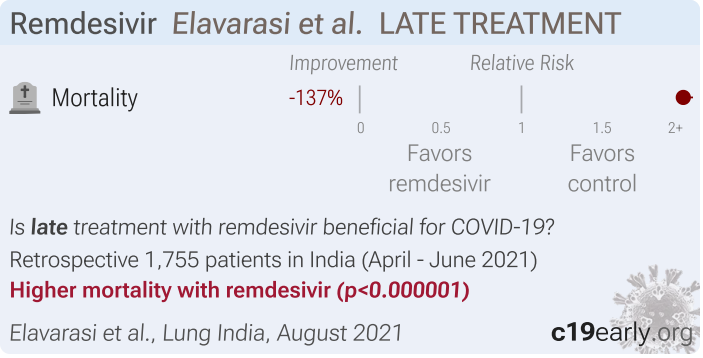
Retrospective 456 hospitalized patients in the USA showing an association between remdesivir treatment and increased COVID-19 severity in multivariable analysis, for remdesivir treatment within 7 days and when administered before meeting the severe case definition. Authors suggest this is due to remdesivir being preferentially used for more severe cases, citing Bhimraj et al., however that paper is from April 2020 before widespread use of remdesivir. During the period of the current study remdesivir was more widely recommended. However, there could still be significant residual confounding after adjustments.

El-Solh



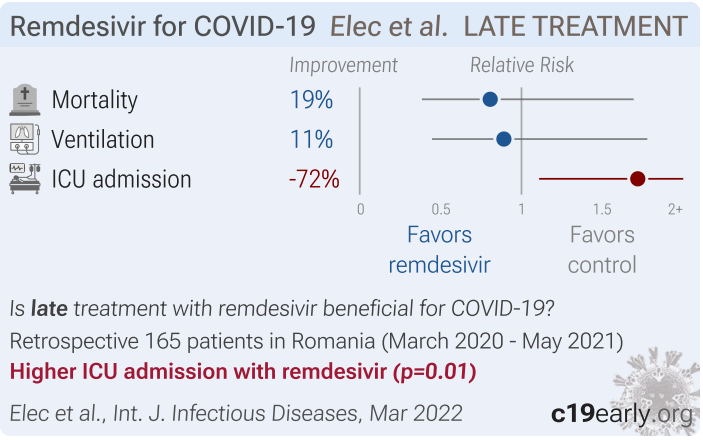
Retrospective 7,816 Veterans Affairs hospitalized patients showing lower mortality with remdesivir.

Elavarasi



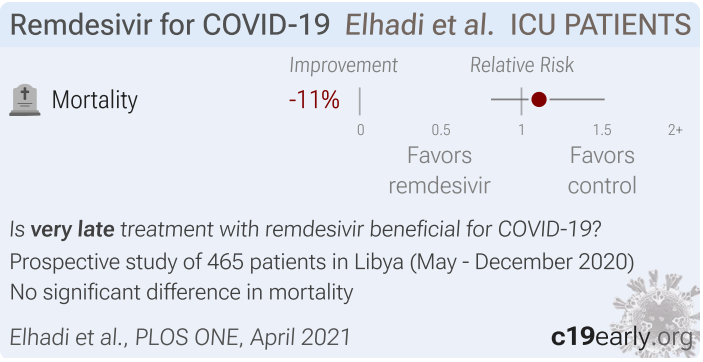
Retrospective 2017 hospitalized patients in India, showing higher mortality with remdesivir in unadjusted results, however no group details are provided and this result is subject to confounding by indication, with authors suggesting treatment was more likely for more severe patients.

Elec



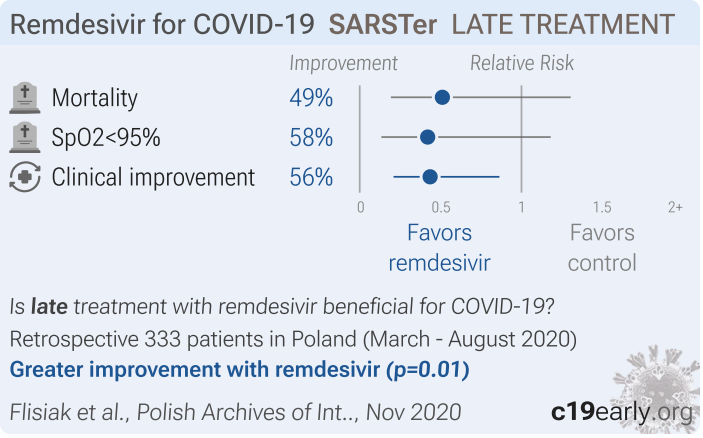
Retrospective 165 hospitalized COVID-19+ kidney transplant patients, 38 treated with remdesivir, showing no significant difference in mortality, higher ICU admission, and lower ICU mortality. Subject to confounding by time with significant changes to SOC and treatment propensity during the study period.

Elhadi



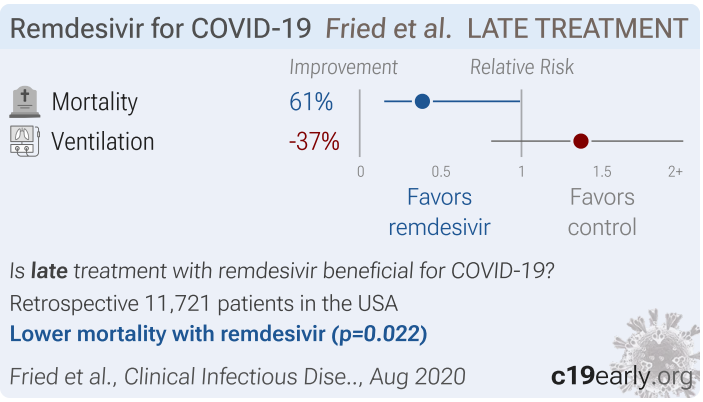
Prospective study of 465 COVID-19 ICU patients in Libya showing no significant differences with treatment.

Flisiak



Retrospective study comparing 122 remdesivir patients and 211 lopinavir/ritonavir patients, showing higher rates of clinical improvement with remdesivir and lower mortality (not statistically significant).

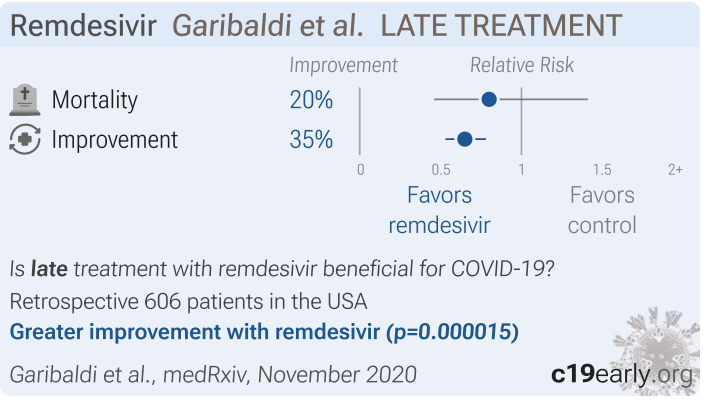
Fried



Database analysis of 11,721 hospitalized patients, 48 treated with remdesivir.

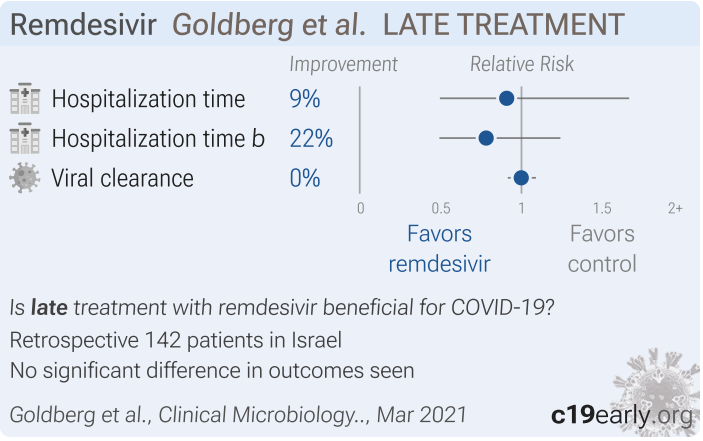
Data inconsistencies have been found in this study, for example 99.4% of patients treated with HCQ were treated in urban hospitals, compared to 65% of untreated patients (Supplemental Table 3), while patients are distributed in a more balanced manner between teaching or not-teaching hospitals, as well as in the most urbanized (Northeast) and less urbanized (Midwest) regions of the United States[119].

Garibaldi



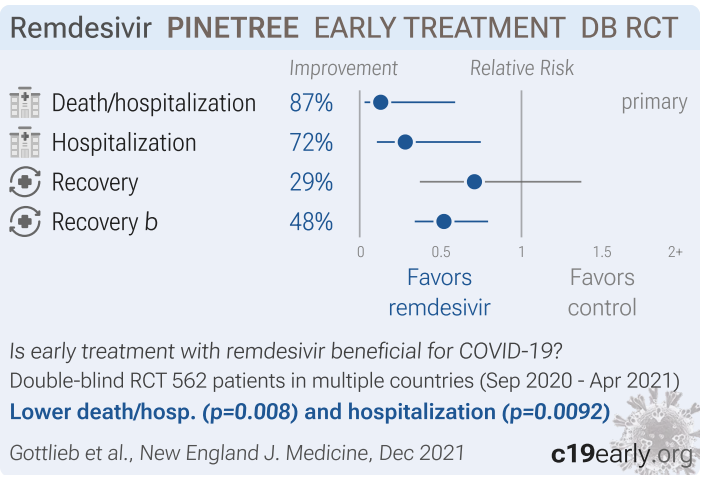
Retrospective 303 remdesivir patients and 303 matched controls showing significantly faster clinical improvement, and lower (but not statistically significant) mortality.

Goldberg



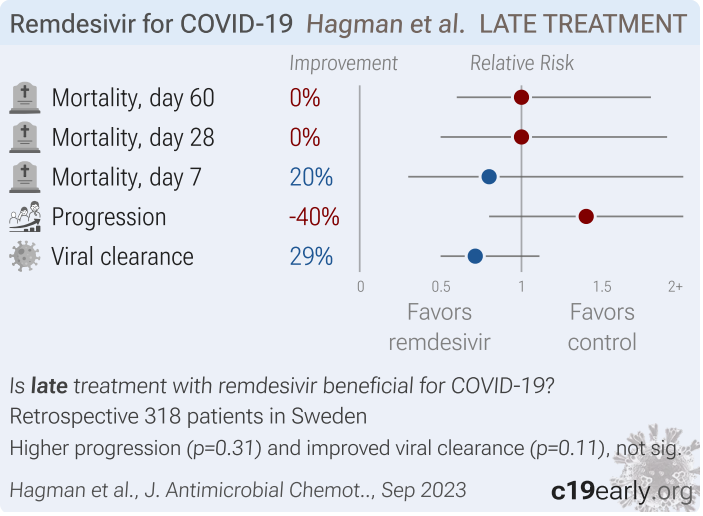
Retrospective 29 remdesivir patients and 113 controls, not finding a significant difference in nasopharyngeal viral load or hospitalization time. Hospitalization time was lower with treatment, with a larger reduction for non-intubated patients, although not statistically significant in both cases.

Gottlieb



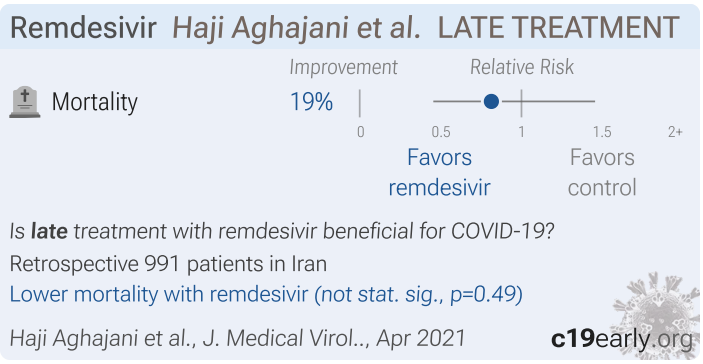
RCT high-risk outpatients, 279 treated with remdesivir and 283 control patients, median 5 days from symptoms, showing significantly lower hospitalization with treatment.

Hagman



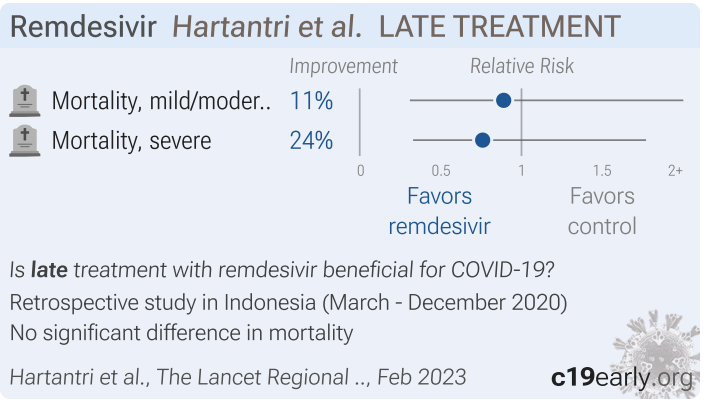
Retrospective 318 hospitalized COVID-19 patients in Sweden, showing improvements in viral clearance but no improvement for mortality with remdesivir treatment.

Haji Aghajani



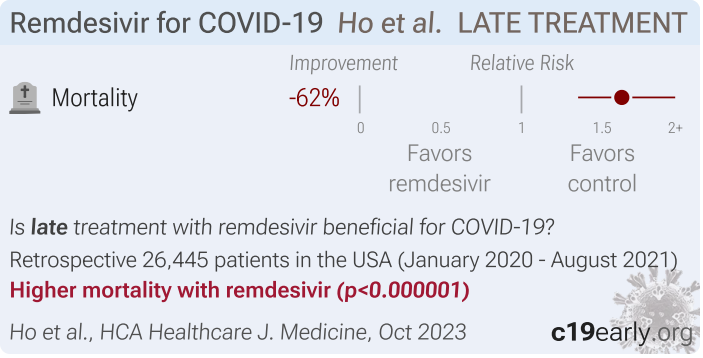
Retrospective 991 hospitalized patients in Iran focusing on aspirin use but also showing results for HCQ, remdesivir, and favipiravir.

Hartantri



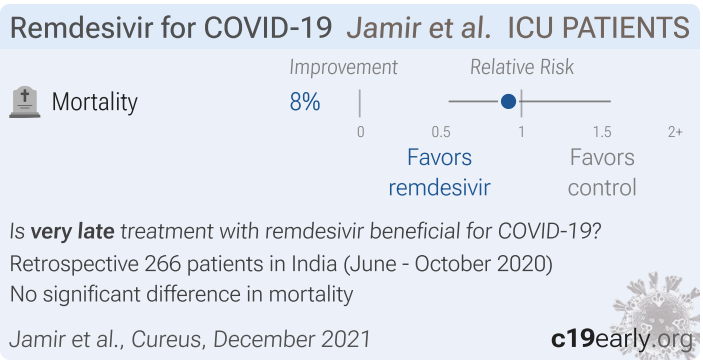
Retrospective 689 hospitalized patients in Indonesia, showing no significant difference in mortality with remdesivir treatment.

Ho



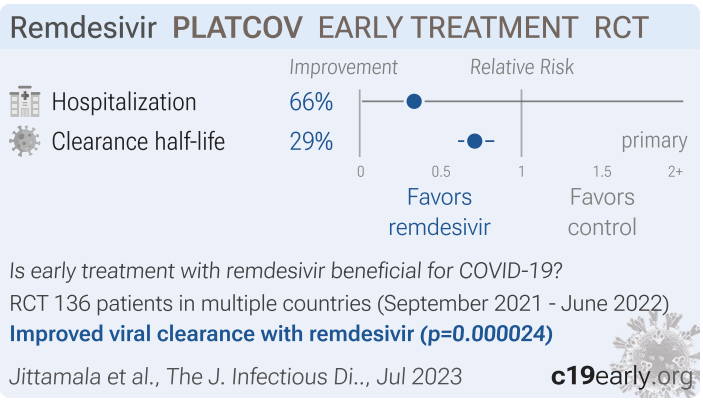
Retrospective 26,445 hospitalized COVID-19 patients in the USA, showing higher mortality with remdesivir.

Jamir



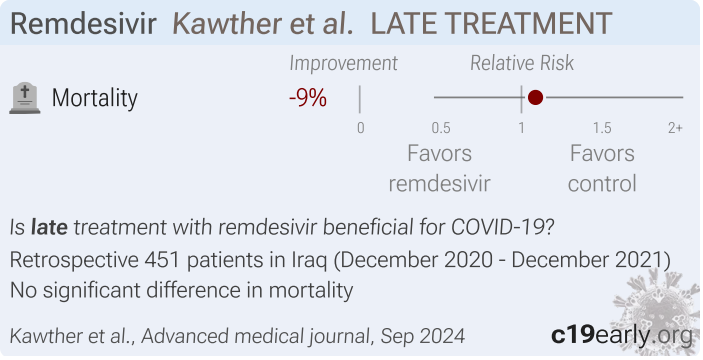
Retrospective 266 COVID-19 ICU patients in India, showing significantly lower mortality with PVP-I oral gargling and topical nasal use, and non-statistically significant higher mortality with ivermectin and lower mortality with remdesivir.

Jittamala



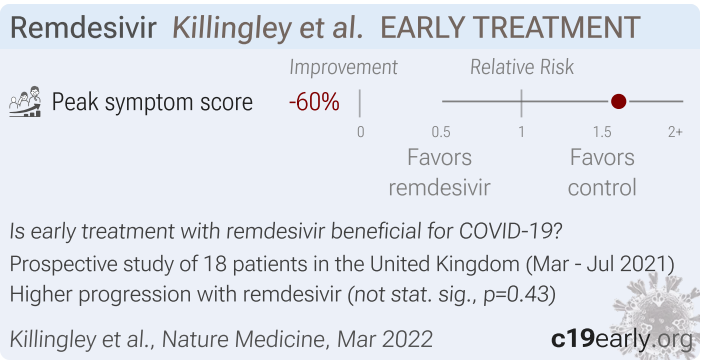
High conflict of interest RCT with very low risk patients with high existing immunity, showing faster viral clearance with remdesivir. The viral clearance half-life was very short in both arms. With rapid viral clearance and very low risk patients, the trial favors detecting an effect with intravenous treatments that have rapid onset of action.

Kawther



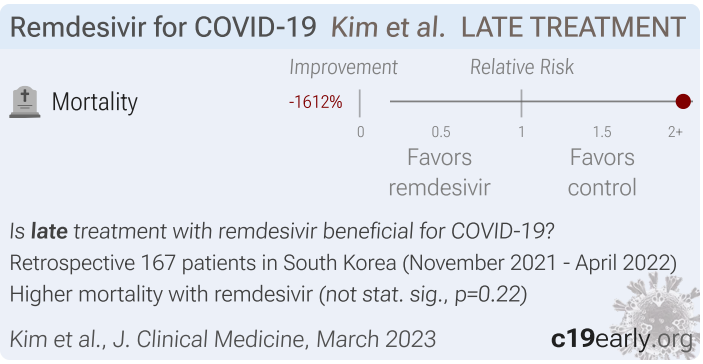
Retrospective 451 hospitalized COVID-19 patients in Iraq showing no significant difference in mortality with remdesivir treatment.

Killingley



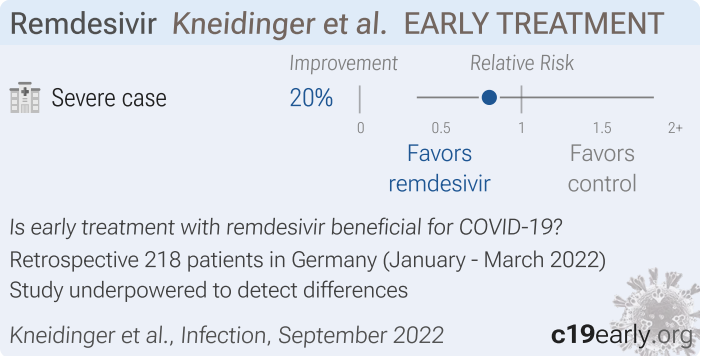
SARS-CoV-2 challenge study in 36 low-risk young adults. Infected participants had high viral loads peaking around 5 days post-exposure, mild-to-moderate upper respiratory symptoms, and anosmia, but no severe disease. Remdesivir had no significant effect on viral kinetics or symptoms. There was a 1-2 day delay before significant viral spread. A majority of patients reported symptoms prior to significant viral spread, supporting the use of early treatment targeted at the upper respiratory tract as a promising approach to limit progression of SARS-CoV-2.

Kim



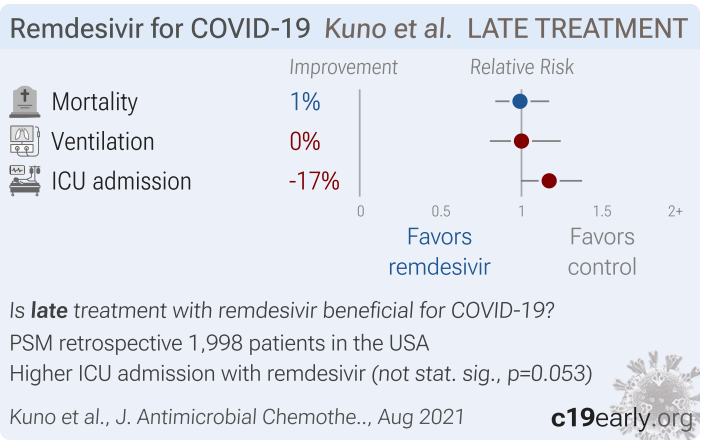
Retrospective 167 nosocomial COVID-19 patients in South Korea, showing higher mortality with remdesivir treatment, without statistical significance.

Kneidinger



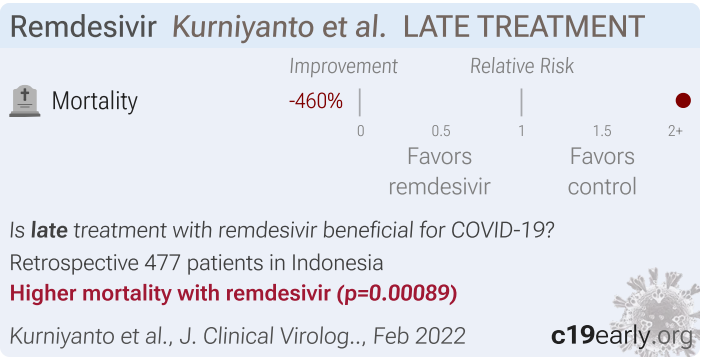
Retrospective 218 COVID+ lung transplant patients in Germany, showing no significant difference in severe cases with early remdesivir use.

Kuno



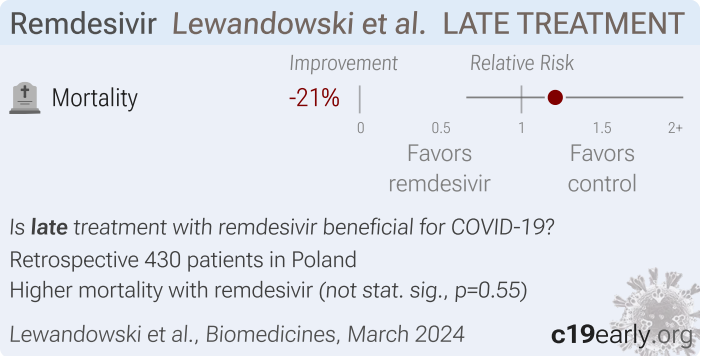
PSM retrospective 3,372 hospitalized patients in the USA treated with steroids, showing no significant difference in mortality with remdesivir, but a lower risk of acute kidney injury.

Kurniyanto



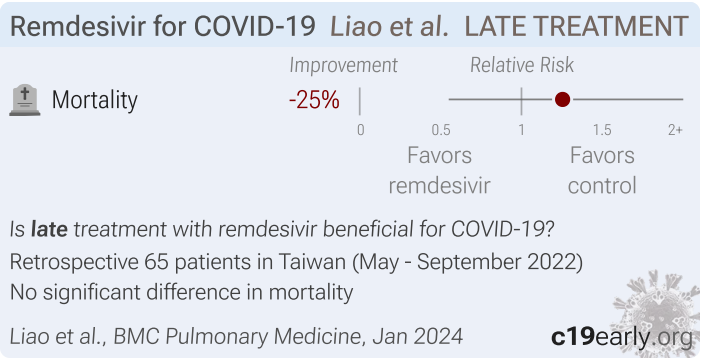
Retrospective 477 hospitalized patients in Indonesia, showing higher mortality with remdesivir in unadjusted results.

Lewandowski



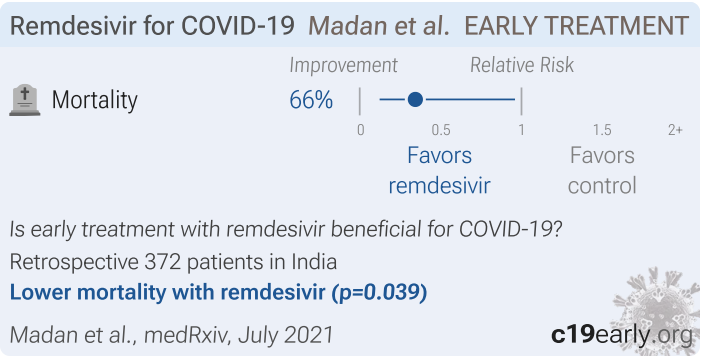
Retrospective 430 hospitalized COVID-19 patients with type 2 diabetes in Poland showing lower mortality with metformin and higher mortality with remdesivir, convalescent plasma, and aspirin in univariable analysis. These results were not statistically significant except for aspirin, and no baseline information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

Liao



Retrospective study of 215 critically ill COVID-19 patients with respiratory failure showing higher mortality for cancer patients. Remdesivir was used more for non-survivors, without statistical significance. Most patients received remdesivir, suggesting standard use for critically ill patients at the time, however it is not clear why some patients did not receive treatment, and baseline details per group are not provided.

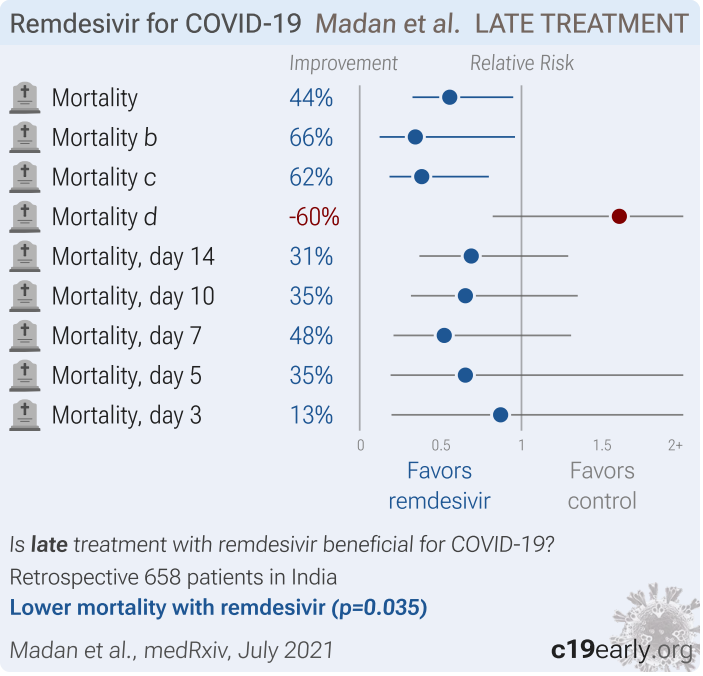
Madan



Retrospective 1,262 hospitalized patients, 398 treated with remdesivir, showing unadjusted lower mortality with treatment, and a treatment delay-response relationship.

Results for late treatment are listed separately[61].

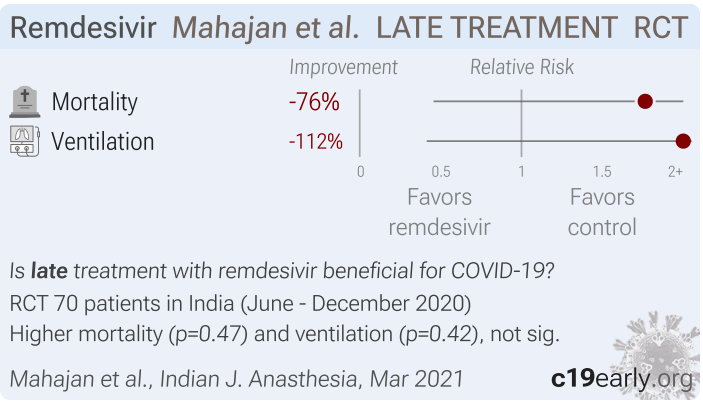
Madan



Retrospective 1,262 hospitalized patients, 398 treated with remdesivir, showing unadjusted lower mortality with treatment, and a treatment delay-response relationship.

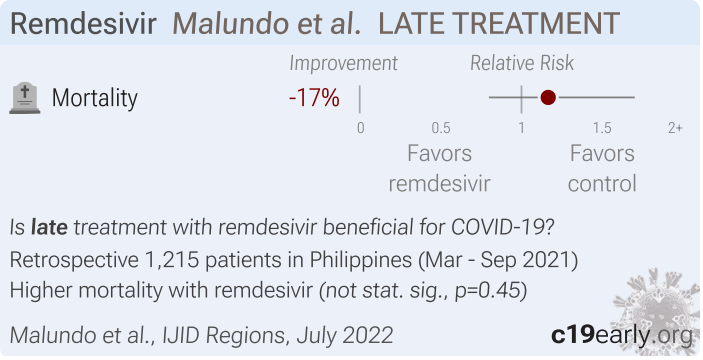
Results for early treatment are listed separately[60].

Mahajan



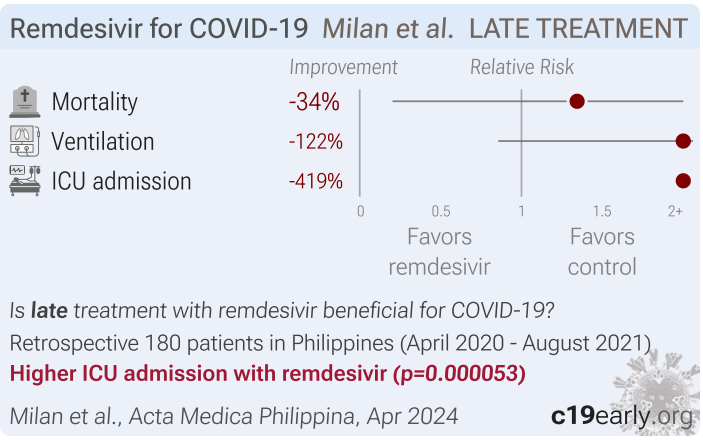
Small RCT with 34 remdesivir patients and 36 controls finding no significant difference in clinical outcomes.

Malundo



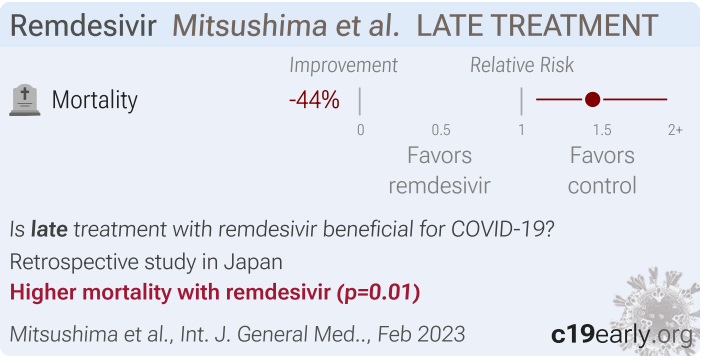
Retrospective 1,215 hospitalized patients in the Phillipines, showing no significant difference in outcomes with remdesivir or HCQ use in unadjusted results subject to confounding by indication.

Milan



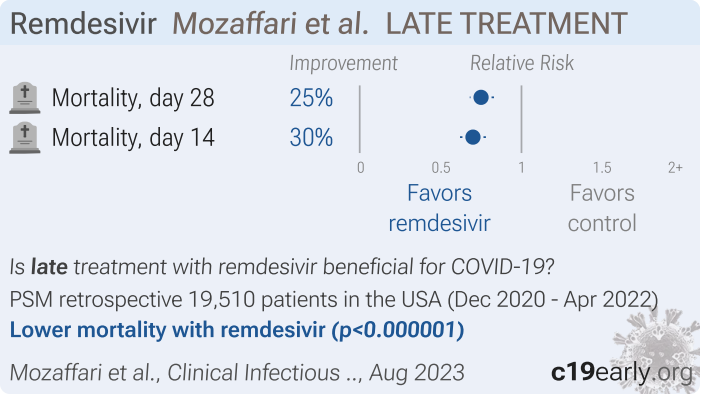
Retrospective 180 hospitalized pediatric COVID-19 patients in the Philippines showing lower mortality with vitamin D and zinc, and higher mortality with remdesivir, all without statistical significance. Remdesivir was given to few patients and authors do not provide information on the timing of treatment - confounding by indication may be significant.

Mitsushima



Retrospective 18,566 hospitalized patients in Japan, showing higher mortality with remdesivir treatment.

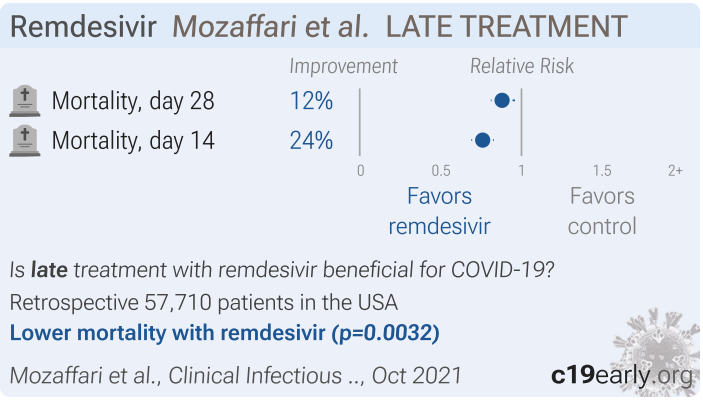
Mozaffari



Retrospective 19,184 immunocompromised patients treated with remdesivir and matched controls, showing lower mortality with treatment. Several authors work at Gilead and the study was funded by Gilead.

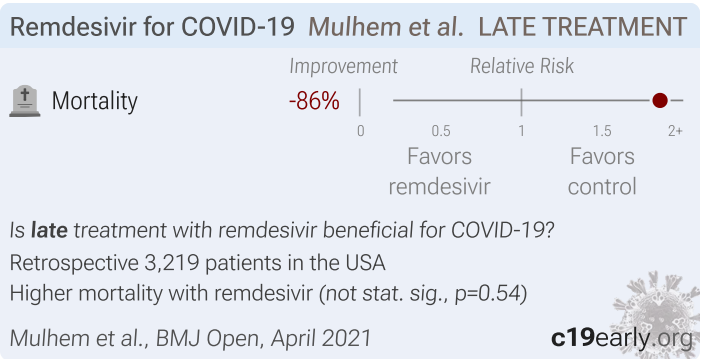
The majority of patients were treated with remdesivir. A significant fraction of non-remdesivir patients may have contraindications that also increase risk. Authors provide serum creatine for 26% of the cohort, but notably provide only median and IQR, not allowing comparison of the number of patients with high values. Authors state that "renal function was not significantly different" between remdesivir and non-remdesivir patients, but this does not seem realistic given the prevalence of renal impairment and the contraindictions for remdesivir.

Mozaffari



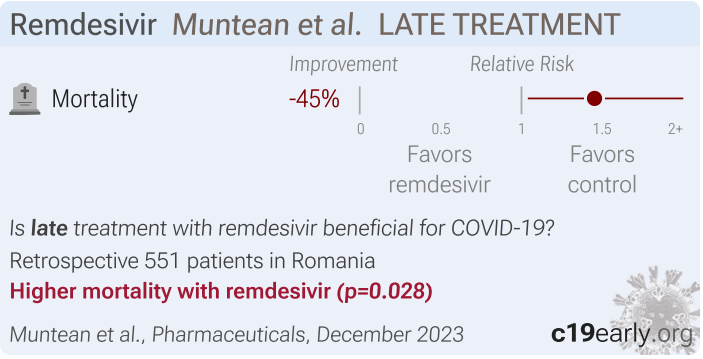
Retrospective 28,855 remdesivir patients with PSM matched controls, showing lower mortality with treatment.

Mulhem



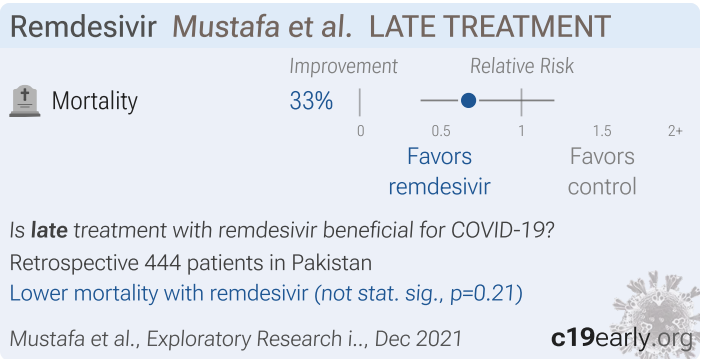
Retrospective database analysis of 3,219 hospitalized patients in the USA. Very different results in the time period analysis (Table S2), and results significantly different to other studies for the same medications (e.g., heparin OR 3.06 [2.44-3.83]) suggest significant confounding by indication and confounding by time.

Muntean



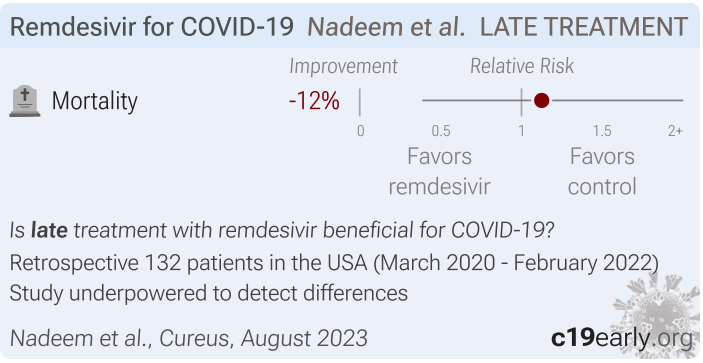
Retrospective 551 severe/critical COVID-19 patients showing higher mortality and higher risk of drug induced liver injury with remdesivir. Authors appear to have reversed the OR for remdesivir - use was more common in non-survivors (61% vs. 50%). Authors report 116 patients treated with HCQ but provide no results for HCQ.

Mustafa



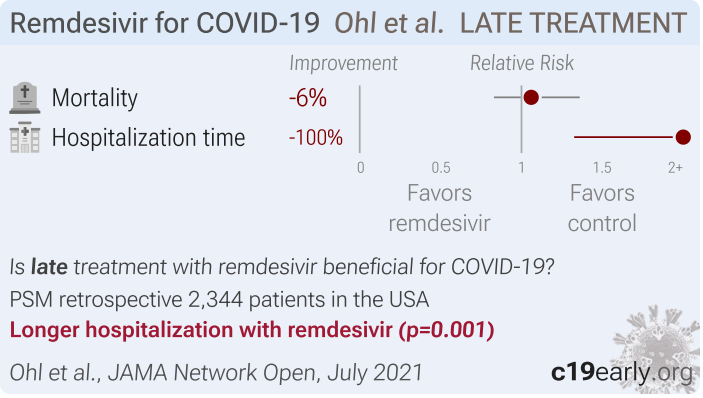
Retrospective 444 hospitalized patients in Pakistan, showing lower mortality with remdesivir treatment in unadjusted results, not reaching statistical significance.

Nadeem



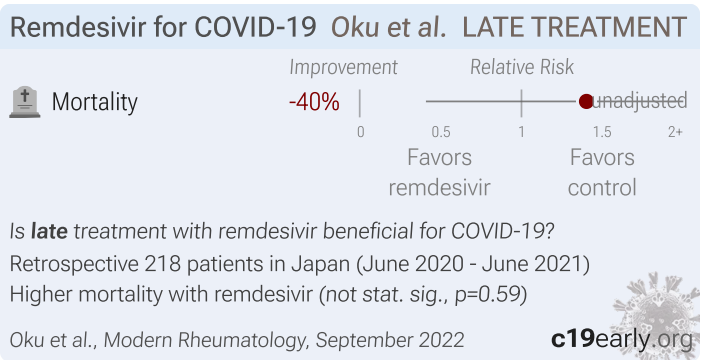
Retrospective 132 hospitalized COVID-19 patients in the USA, showing no significant difference in mortality with remdesivir in unadjusted results.

Ohl



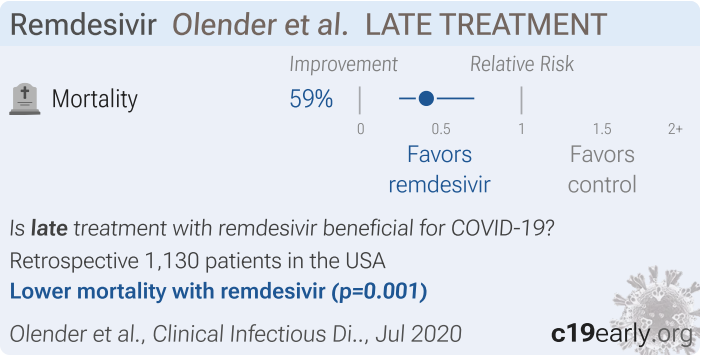
Retrospective 5,898 hospitalized patients in the USA, 2,374 receiving remdesivir treatment, showing no significant difference in mortality, and a longer time to hospital discharge with treatment.

Oku



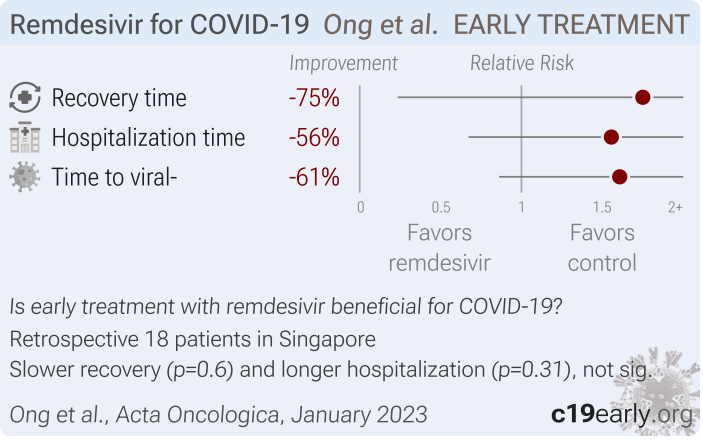
Retrospective 220 COVID-19 patients with rheumatic disease in Japan, showing no significant difference in mortality with remdesivir treatment.

Olender



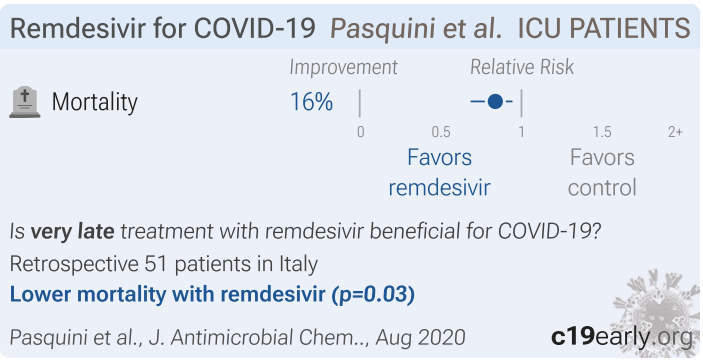
Comparative analysis between remdesivir trial GS-US-540–5773 and a retrospective SOC cohort with similar inclusion criteria, showing lower mortality and higher recovery at day 14 with remdesivir.

Ong



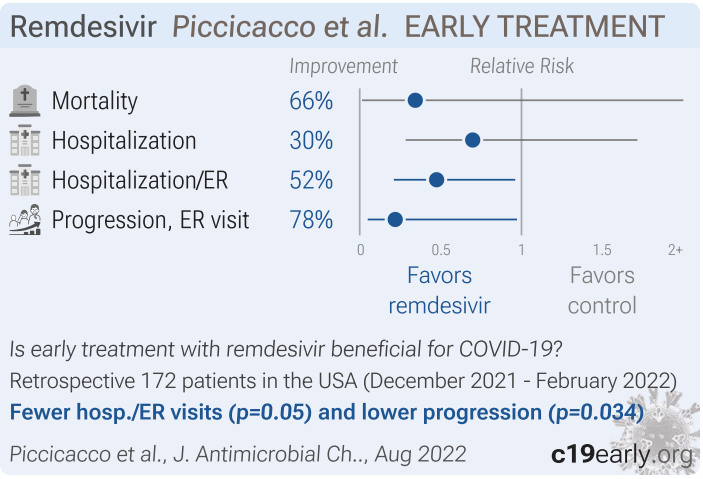
Retrospective 18 immunocompromised pediatric COVID-19 patients in Singapore, showing slower viral clearance with remdesivir, without statistical significance.

Pasquini



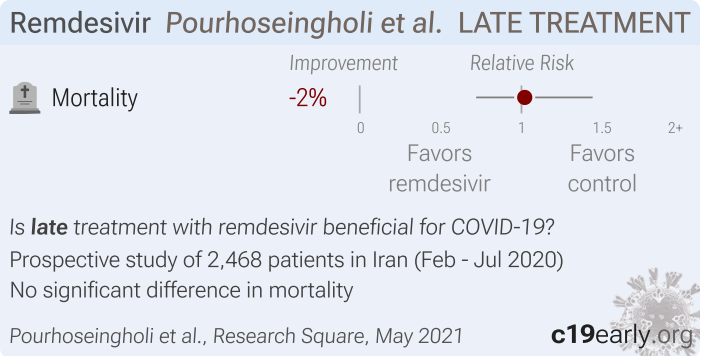
Retrospective 51 ICU patients under mechanical ventilation, 25 treated with remdesivir, showing lower mortality with treatment.

Piccicacco



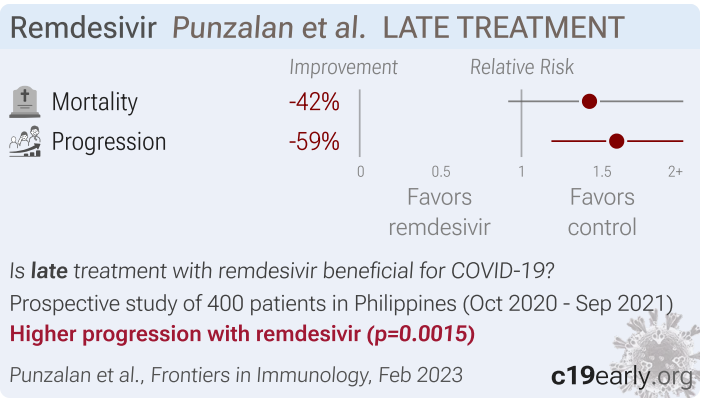
Retrospective high-risk outpatients in the USA, 82 treated with remdesivir, 88 with sotrovimab, and 90 control patients, showing significantly lower combined hospitalization/ER visits with both treatments in unadjusted results. The dominant variant was omicron B.1.1.529.

Pourhoseingholi



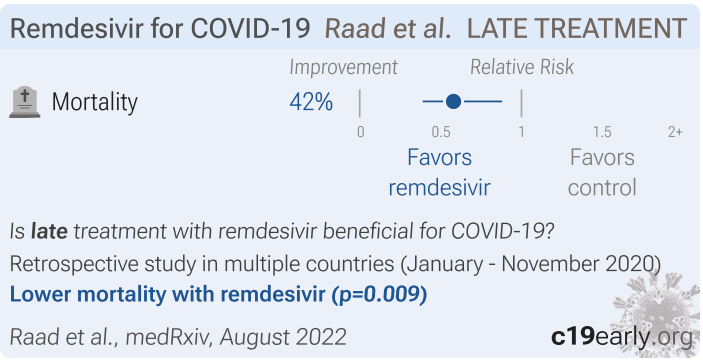
Prospective study of 2,468 hospitalized COVID-19 patients in Iran, showing no significant difference with remdesivir treatment. IR.MUQ.REC.1399.013.

Punzalan



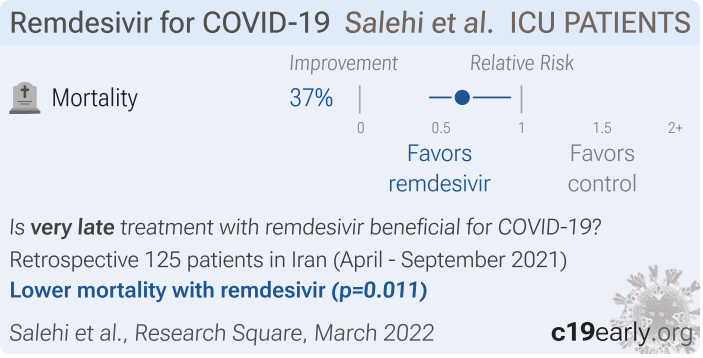
Prospective study of 400 hospitalized patients in the Philippines, showing higher progression with remdesivir in unadjusted results, without statistical significance.

Raad



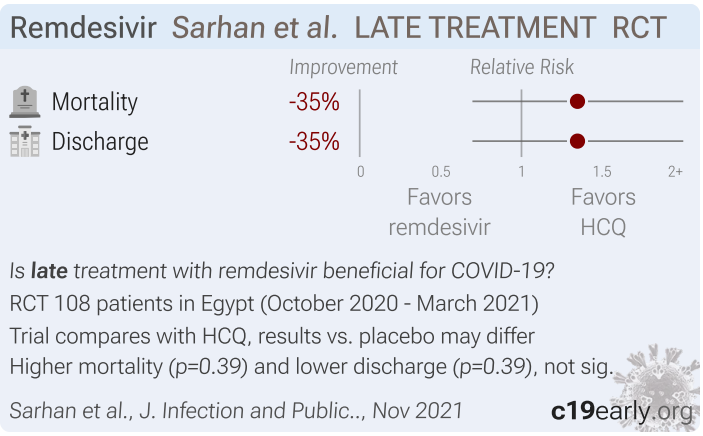
Retrospective 3,966 COVID-19 patients, 1,115 with cancer, showing lower mortality with remdesivir and higher mortality with convalescent plasma.

Salehi



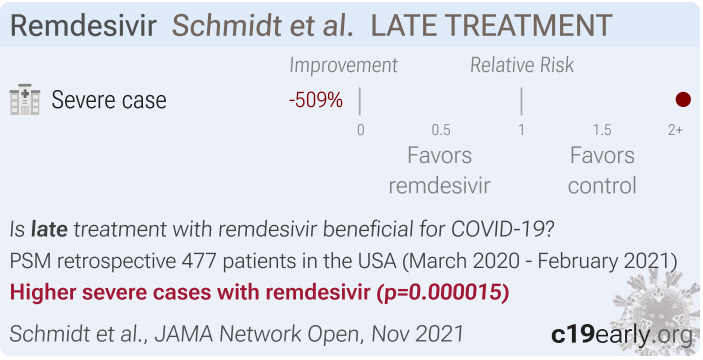
Retrospective 125 mechanically ventilated ICU patients in Iran, showing lower mortality with remdesivir treatment in unadjusted results.

Sarhan



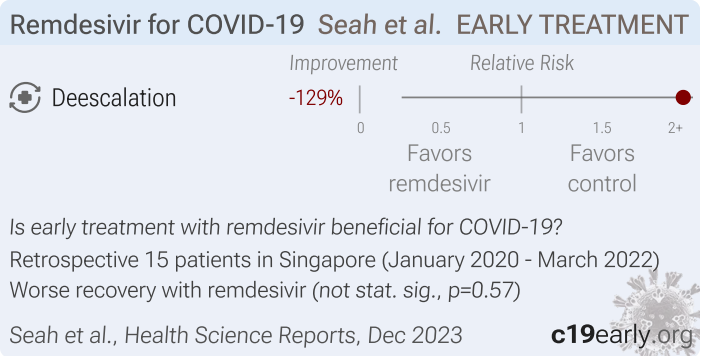
Small 108 patient RCT comparing HCQ vs. remdesivir in very late stage treatment. All patients received tocilizumab. There were significant unadjusted baseline differences in ventilation and ICU admission. REC-H-PhBSU-21011.

Schmidt



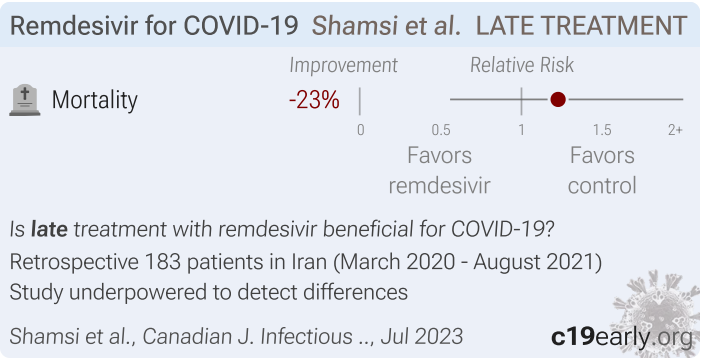
Retrospective 1,106 prostate cancer patients, showing higher mortality with remdesivir treatment.

Seah



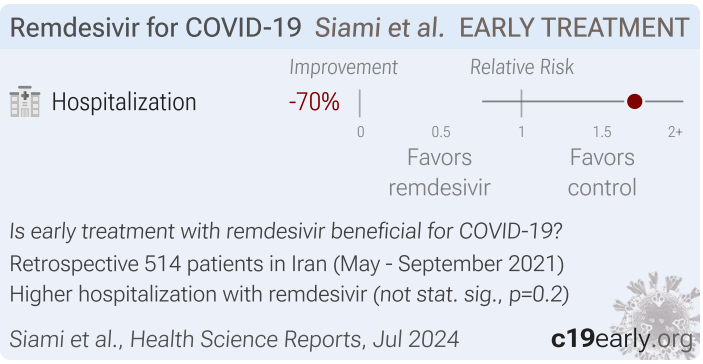
Retrospective 15 pediatric patients hospitalized for severe COVID-19 requiring oxygen and high dependency/intensive care unit (HD/ICU) admission in Singapore, showing no improvement in deescalation from HD/ICU care with remdesivir, however the remdesivir group had higher disease severity.

Shamsi



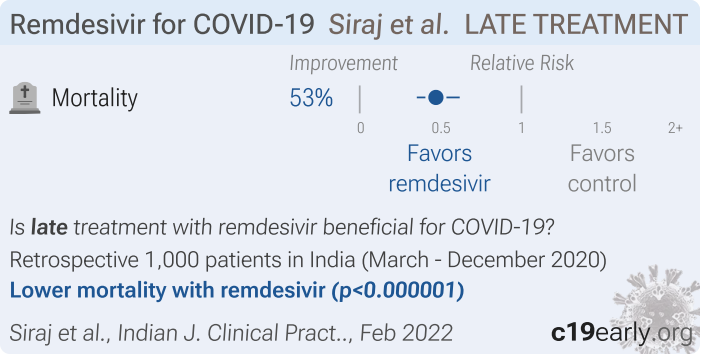
Retrospective 183 hospitalized pediatric COVID-19 patients in Iran, showing no significant difference in mortality with remdesivir in unadjusted results.

Siami



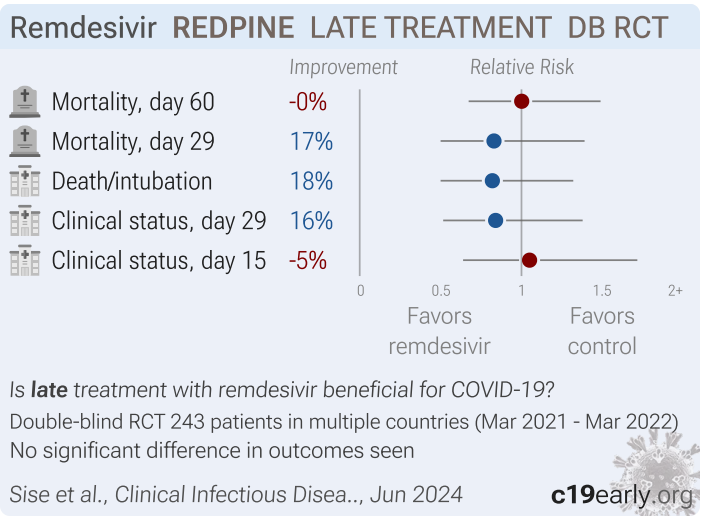
Retrospective 514 COVID-19 outpatients showing no significant benefit with remdesivir therapy.

Siraj



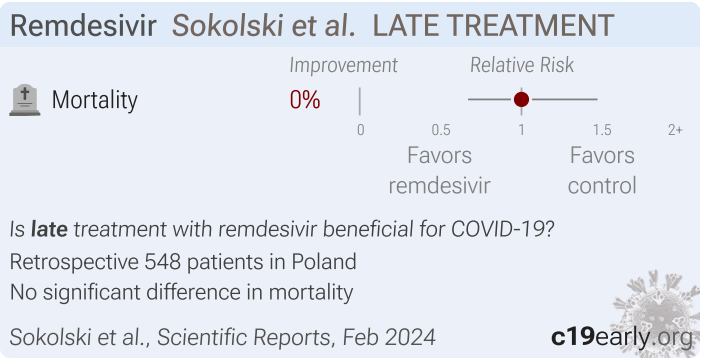
Retrospective 1,000 COVID+ hospitalized patients in India, showing lower mortality with famotidine and remdesivir in multivariable logistic regression.

Sise



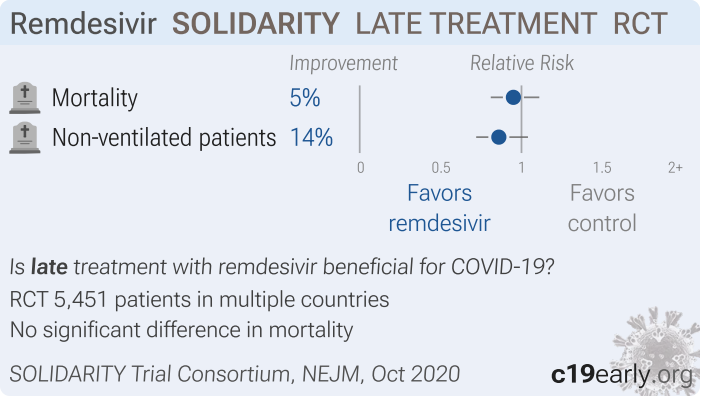
RCT 243 hospitalized COVID-19 patients with acute kidney injury, chronic kidney disease, or kidney failure showing no significant difference in all-cause mortality or invasive mechanical ventilation with remdesivir. The lower mortality at day 29 (without statistical significance) disappeared at day 60, consistent with remdesivir studies overall.

Sokolski



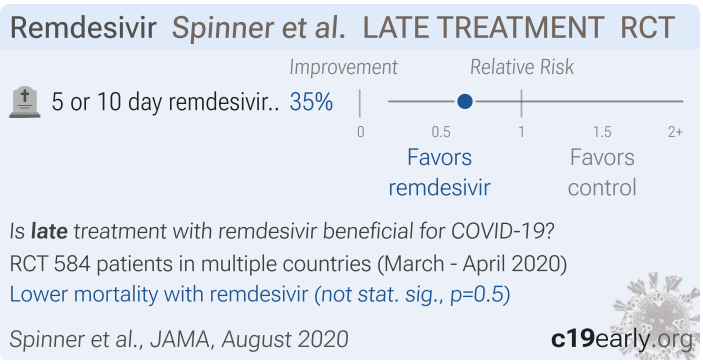
Retrospective 2,170 hospitalized COVID-19 patients showing no difference in mortality with remdesivir in unadjusted results.

SOLIDARITY Trial Consortium



WHO SOLIDARITY open-label RCT with 2,750 very late stage (76% on oxygen/ventilation) remdesivir patients, mortality relative risk RR 0.95 [0.81-1.11], p=0.50. Non-ventilated patients show a greater benefit, RR 0.86 [0.72-1.04], p = 0.13.

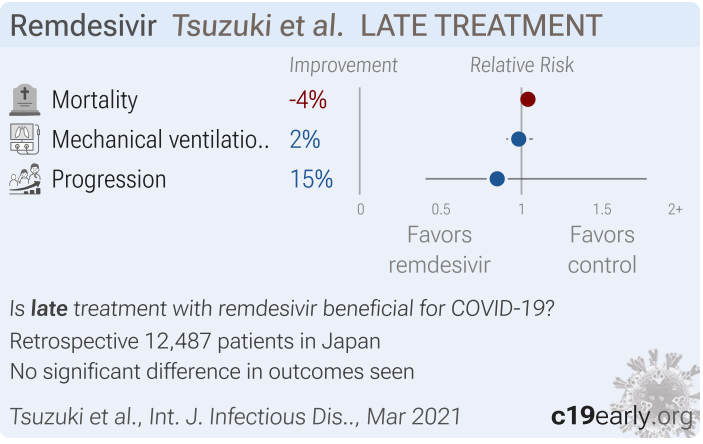
Spinner



Late stage (median 8 days from symptom onset) RCT 584 patients with moderate COVID-19 showing (non-statistically significant) lower mortality.

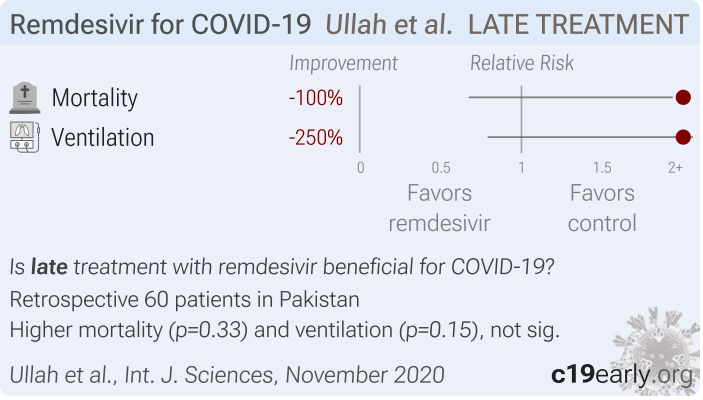
5-day remdesivir had significantly higher odds of a better clinical status distribution on the 7-point ordinal scale, odds ratio OR 1.65, p =0.02. The difference for 10-day remdesivir was not statistically significant, p=0.18.

Tsuzuki



Retrospective database analysis of 12,487 hospitalized patients in Japan, showing lower risk of oxygen requirement, but no significant difference in mortality or ventilation/ECMO.

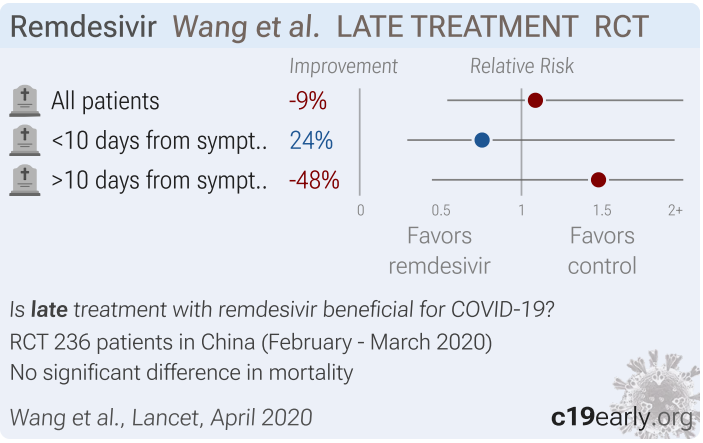
Ullah



Small late stage (hospitalized, <12 days symptoms) remdesivir study showing non-statistically significant higher mortality with treatment.

No adjustments were made for differences in the groups. Remdesivir mean age was 49 vs. control 57. Baseline oxygen requirement was 13.4 liters treatment vs. 10.8 control. Potential confounding by indication.

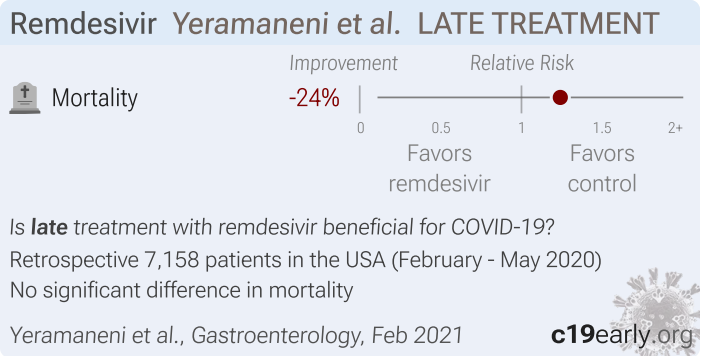
Wang



Small RCT with 237 hospitalized patients in China with severe COVID-19, not showing statistically significant benefits. 158 treatment patients and 79 control patients.

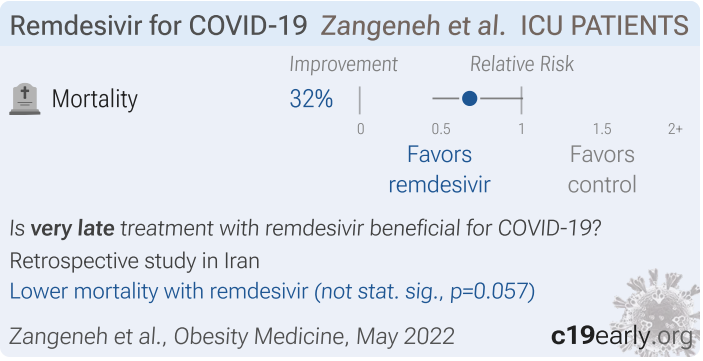
While too small for significance, the subgroup treated within 10 days showed reduced mortality RR 0.76, p = 0.58, and reduced median time to clinical improvement of 18 days vs. 23 days, hazard ratio 1.52 [0.95-2.43].

Yeramaneni



Retrospective 7,158 hospitalized COVID-19 patients in the USA analyzing famotidine treatment, showing no significant difference in mortality with associated remdesivir treatment.

Zangeneh



Retrospective 193 ICU patients in Iran, showing lower mortality with remdesivir treatment, not reaching statistical significance.

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 remdesivir 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 remdesivir for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. 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 [120]. 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.

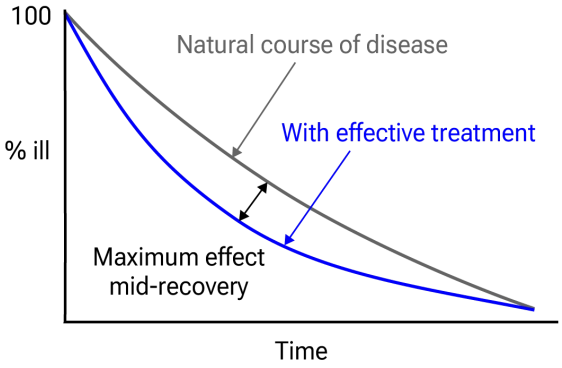


Figure 27. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 [124]. 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 (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta [125] 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 [74,75].

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/smeta.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.

Chew, 3/16/2023, retrospective, Singapore, peer-reviewed, median age 56.0, 7 authors, study period 23 January, 2020 - 15 April, 2020, average treatment delay 4.0 days.	abnormal ALT, 68.0% higher, OR 1.68, *p* = 0.40, treatment 12, control 151, adjusted per study, multivariable, RR approximated with OR.
Choi, 7/15/2024, retrospective, China, peer-reviewed, mean age 74.0, 8 authors, study period 16 March, 2022 - 31 December, 2022.	risk of death, 266.7% higher, HR 3.67, *p* = 0.07, treatment 308, control 13,656, remdesivir+paxlovid vs. paxlovid, day 90.
	risk of ICU admission, 600.0% higher, HR 7.00, *p* < 0.001, treatment 308, control 13,656, remdesivir+paxlovid vs. paxlovid, day 90.
	ventilatory support, 685.7% higher, HR 7.86, *p* < 0.001, treatment 308, control 13,656, remdesivir+paxlovid vs. paxlovid, day 90.
	AKI, 181.6% higher, HR 2.82, *p* < 0.001, treatment 308, control 13,656, remdesivir+paxlovid vs. paxlovid, day 90.
Gottlieb, 12/22/2021, Double Blind Randomized Controlled Trial, multiple countries, peer-reviewed, 30 authors, study period 18 September, 2020 - 8	risk of death/hospitalization, 87.0% lower, RR 0.13, *p* = 0.008, treatment 2 of 279 (0.7%), control 15 of 283 (5.3%), NNT 22, adjusted per study, COVID-19 related hospitalization or death

April, 2021, average treatment delay 5.0 days, trial NCT04501952 (history) (PINETREE).	from any cause @day 28, primary outcome.
	risk of hospitalization, 71.8% lower, RR 0.28, p = 0.009, treatment 5 of 279 (1.8%), control 18 of 283 (6.4%), NNT 22.
	risk of no recovery, 29.1% lower, RR 0.71, p = 0.31, treatment 43 of 66 (65.2%), control 45 of 60 (75.0%), adjusted per study, inverted to make RR<1 favor treatment, alleviation of symptoms @day 14.
	risk of no recovery, 47.9% lower, RR 0.52, p = 0.003, treatment 108 of 169 (63.9%), control 132 of 165 (80.0%), NNT 6.2, adjusted per study, inverted to make RR<1 favor treatment, post-hoc alleviation of symptoms @day 14.
Jittamala, 7/20/2023, Randomized Controlled Trial, multiple countries, peer-reviewed, median age 30.1, 42 authors, study period 30 September, 2021 - 10 June, 2022, trial NCT05041907 (history) (PLATCOV).	risk of hospitalization, 66.3% lower, RR 0.34, p = 1.00, treatment 0 of 67 (0.0%), control 1 of 69 (1.4%), NNT 69, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	relative clearance half-life, 28.9% better, RR 0.71, p < 0.001, treatment median 12.8 IQR 8.0 n=67, control median 18.0 IQR 10.5 n=69, primary outcome.
Killingley, 3/31/2022, prospective, United Kingdom, peer-reviewed, mean age 21.8, 31 authors, study period March 2021 - July 2021, trial NCT04865237 (history).	peak symptom score, 60.1% higher, RR 1.60, p = 0.43, treatment mean 8.48 (±8.1) n=6, control mean 5.3 (±7.7) n=12, relative peak symptom score.
Kneidinger, 9/9/2022, retrospective, Germany, peer-reviewed, 11 authors, study period 1 January, 2022 - 20 March, 2022, lung transplant patients.	risk of severe case, 19.9% lower, RR 0.80, p = 0.71, treatment 6 of 46 (13.0%), control 28 of 172 (16.3%), NNT 31.
Madan, 7/19/2021, retrospective, India, preprint, 22 authors, early treatment subset, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 65.6% lower, RR 0.34, p = 0.04, treatment 4 of 112 (3.6%), control 27 of 260 (10.4%), NNT 15, unadjusted, <5 days from onset.
Ong, 1/20/2023, retrospective, Singapore, peer-reviewed, 12 authors.	recovery time, 75.0% higher, relative time 1.75, p = 0.60, treatment 4, control 14, defervescence.
	hospitalization time, 55.6% higher, relative time 1.56, p = 0.31, treatment 4, control 14.
	time to viral-, 60.7% higher, relative time 1.61, p = 0.14, treatment 4, control 14.
Piccicacco, 8/1/2022, retrospective, USA, peer-reviewed, 7 authors, study period 27 December, 2021 - 4 February, 2022, average treatment delay 4.0 days, ER visit.	risk of death, 65.6% lower, RR 0.34, p = 1.00, treatment 0 of 82 (0.0%), control 1 of 90 (1.1%), NNT 90, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 29.
	risk of hospitalization, 30.2% lower, RR 0.70, p = 0.47, treatment 7 of 82 (8.5%), control 11 of 90 (12.2%), NNT 27, day 29.
	risk of hospitalization/ER, 52.5% lower, RR 0.48, p = 0.05, treatment 9 of 82 (11.0%), control 21 of 90 (23.3%), NNT 8.1, odds ratio converted to relative risk, day 29.
	risk of progression, 78.0% lower, RR 0.22, p = 0.03, treatment 2 of 82 (2.4%), control 10 of 90 (11.1%), NNT 12, day 29.

Seah, 12/14/2023, retrospective, Singapore, peer-reviewed, median age 2.5, 9 authors, study period 1 January, 2020 - 18 March, 2022, excluded in exclusion analyses: unadjusted results with significant baseline differences.	no deescalation, 128.6% higher, RR 2.29, $p = 0.57$, treatment 2 of 7 (28.6%), control 1 of 8 (12.5%), day 5.
Siami, 7/22/2024, retrospective, Iran, peer-reviewed, 5 authors, study period May 2021 - September 2021.	risk of hospitalization, 70.0% higher, OR 1.70, $p = 0.20$, treatment 341, control 148, adjusted per study, multivariable, RR approximated with OR.

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.

Ader, 9/14/2021, Randomized Controlled Trial, multiple countries, peer-reviewed, 17 authors, study period 22 March, 2020 - 21 January, 2021, average treatment delay 9.0 days, trial NCT04315948 (history) (DISCOVERY).	risk of death, 6.4% lower, RR 0.94, $p = 0.77$, treatment 34 of 414 (8.2%), control 37 of 418 (8.9%), NNT 156, adjusted per study, odds ratio converted to relative risk, day 28.
	risk of death, 11.7% lower, RR 0.88, $p = 0.76$, treatment 21 of 414 (5.1%), control 24 of 418 (5.7%), NNT 149, day 15.
	risk of 7-point scale, 9.9% lower, OR 0.90, $p = 0.39$, treatment 414, control 418, inverted to make OR<1 favor treatment, 28 days, RR approximated with OR.
	risk of 7-point scale, 2.0% higher, OR 1.02, $p = 0.85$, treatment 414, control 418, inverted to make OR<1 favor treatment, 15 days, RR approximated with OR.
Ali, 1/19/2022, Randomized Controlled Trial, Canada, peer-reviewed, 85 authors, average treatment delay 8.0 days, trial NCT04330690 (history) (CATCO).	risk of death, 12.0% lower, RR 0.88, $p = 0.21$, treatment 127 of 634 (20.0%), control 152 of 647 (23.5%), NNT 29, day 60.
	risk of death, 17.0% lower, RR 0.83, $p = 0.09$, treatment 117 of 634 (18.5%), control 145 of 647 (22.4%), NNT 25, in hospital.
	risk of death, 20.6% lower, RR 0.79, $p = 0.59$, treatment 14 of 634 (2.2%), control 18 of 647 (2.8%), NNT 174, day 15.
	risk of mechanical ventilation, 47.0% lower, RR 0.53, $p < 0.001$, treatment 46 of 634 (7.3%), control 89 of 647 (13.8%), NNT 15, day 60.
	risk of no recovery, 9.0% lower, RR 0.91, $p = 0.41$, treatment 634, control 647, clinical status, day 60.
	hospitalization time, 11.1% higher, relative time 1.11, $p = 0.04$, treatment median 10.0 IQR 12.0 n=634, control median 9.0 IQR 11.0 n=647.
Alsaraj, 1/8/2024, Randomized Controlled Trial, Iraq, peer-reviewed, 6 authors, study period September 2021 - February 2022, excluded in exclusion analyses: potential data issue.	risk of death, 83.5% higher, HR 1.83, $p = 0.26$, treatment 9 of 52 (17.3%), control 5 of 53 (9.4%), adjusted per study, multivariable, Cox proportional hazards, day 30.
Alshamrani, 2/15/2023, retrospective, Saudi Arabia, peer-reviewed, 3 authors, study period March 2020 - January 2021.	risk of death, 17.3% lower, RR 0.83, $p = 0.003$, treatment 137 of 246 (55.7%), control 725 of 1,078 (67.3%), NNT 8.6, adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable.

	risk of progression, 4.3% lower, RR 0.96, p = 0.12, treatment 215 of 246 (87.4%), control 984 of 1,078 (91.3%), NNT 26, 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 245, control 995, propensity score matching.
	hospitalization time, 7.4% lower, relative time 0.93, p = 0.25, treatment 246, control 1,078, propensity score matching.
Amirizadeh, 11/1/2023, retrospective, Iran, peer-reviewed, 5 authors, average treatment delay 8.04 (treatment) 7.45 (control) days.	**risk of death, 3.3% higher, RR 1.03, p = 1.00**, treatment 31 of 35 (88.6%), control 30 of 35 (85.7%).
	ventilation time, 52.2% higher, relative time 1.52, p = 0.17, treatment mean 7.03 (±8.92) n=35, control mean 4.62 (±5.24) n=35.
	ICU time, 27.0% higher, relative time 1.27, p = 0.23, treatment mean 14.03 (±11.55) n=35, control mean 11.05 (±9.1) n=35.
	hospitalization time, 24.2% higher, relative time 1.24, p = 0.22, treatment mean 16.11 (±11.52) n=35, control mean 12.97 (±9.65) n=35.
Angleitner, 2/26/2025, retrospective, Germany, peer-reviewed, mean age 60.0, 3 authors.	**time to viral-, 223.0% higher, relative time 3.23, p = 0.004**, treatment 8, control 55, Kaplan–Meier.
Anzalone, 7/2/2024, retrospective, USA, peer-reviewed, 18 authors, study period 1 January, 2021 - 31 December, 2022.	**risk of death, 33.0% higher, HR 1.33, p < 0.001**, adjusted per study, propensity score matching, multivariable, day 45.
	risk of mechanical ventilation, 8.0% lower, HR 0.92, p < 0.001, adjusted per study, propensity score matching, multivariable, day 45.
Arch, 6/21/2021, prospective, propensity score matching, United Kingdom, preprint, 10 authors, average treatment delay 6.0 days.	**risk of death, 19.9% lower, RR 0.80, p = 0.03**, treatment 203 of 1,491 (13.6%), control 777 of 4,676 (16.6%), NNT 33, odds ratio converted to relative risk, PSM, day 28.
	risk of death, 18.0% lower, RR 0.82, p = 0.12, treatment 140 of 1,502 (9.3%), control 565 of 4,728 (12.0%), NNT 38, odds ratio converted to relative risk, PSM, day 14.
	risk of mechanical ventilation, 68.0% higher, RR 1.68, p = 0.003, treatment 106 of 1,498 (7.1%), control 153 of 4,602 (3.3%), odds ratio converted to relative risk, PSM, day 28.
Arfijanto, 5/4/2023, retrospective, Indonesia, peer-reviewed, 8 authors, study period June 2021 - December 2021, excluded in exclusion analyses: unadjusted results with no group details.	**delayed viral clearance, 0.9% lower, RR 0.99, p = 1.00**, treatment 17 of 44 (38.6%), control 46 of 118 (39.0%), NNT 288.
Aweimer, 3/29/2023, retrospective, Germany, peer-reviewed, median age 67.0, 19 authors, study period 1 March, 2020 - 31 August, 2021.	**risk of death, 13.0% higher, RR 1.13, p = 0.33**, treatment 40 of 51 (78.4%), control 68 of 98 (69.4%), day 100.
Barrat-Due, 7/13/2021, Double Blind Randomized Controlled Trial, Norway, peer-reviewed, 43 authors, average treatment delay 8.0 days, trial NCT04321616 (history).	**risk of death, no change, RR 1.00, p = 1.00**, treatment 3 of 42 (7.1%), control 4 of 57 (7.0%), adjusted per study.
	risk of death, 35.7% higher, RR 1.36, p = 0.70, treatment 3 of 42 (7.1%), control 3 of 57 (5.3%), day 60.

	risk of death, 54.8% lower, RR 0.45, p = 0.63, treatment 1 of 42 (2.4%), control 3 of 57 (5.3%), NNT 35, day 28.
	risk of no recovery, 47.4% higher, RR 1.47, p = 0.01, treatment mean 16.8 (±11.4) n=42, control mean 11.4 (±10.4) n=76, relative CAT total score at 3 months.
	risk of no recovery, 42.9% higher, RR 1.43, p = 0.009, treatment mean 3.0 (±1.7) n=42, control mean 2.1 (±1.8) n=76, relative CAT dyspnea score at 3 months.
	risk of no recovery, 23.8% higher, RR 1.24, p = 0.10, treatment mean 2.6 (±1.5) n=42, control mean 2.1 (±1.6) n=76, relative CAT fatigue score at 3 months.
	risk of no recovery, 50.0% higher, RR 1.50, p = 0.04, treatment mean 1.8 (±1.6) n=42, control mean 1.2 (±1.5) n=76, relative CAT cough score at 3 months.
Bavaro, 5/19/2023, retrospective, Italy, peer-reviewed, median age 75.0, 27 authors, study period 1 July, 2021 - 15 March, 2022.	**risk of severe case, 7.0% lower, RR 0.93, p < 0.001**, treatment 120, control 211, propensity score weighting.
Behboodikhah, 9/15/2022, retrospective, Iran, peer-reviewed, 8 authors.	**risk of death, 37.5% lower, OR 0.62, p = 0.21**, treatment 1,214, control 960, adjusted per study, multivariable, RR approximated with OR.
Beigel, 10/8/2020, Randomized Controlled Trial, USA, peer-reviewed, 40 authors, average treatment delay 9.0 days.	**risk of death, 27.0% lower, HR 0.73, p = 0.07**, treatment 541, control 521, day 29.
	risk of death, 45.0% lower, HR 0.55, p = 0.005, treatment 541, control 521, day 15.
	risk of no recovery, 22.5% lower, RR 0.78, p < 0.001, treatment 541, control 521, inverted to make RR<1 favor treatment.
Bowen, 8/25/2022, retrospective, USA, peer-reviewed, 10 authors, study period 1 March, 2020 - 31 March, 2021.	**risk of death, 57.0% higher, HR 1.57, p < 0.001**, treatment 817, control 3,814, Table S2, Cox proportional hazards, day 30.
Burhan, 9/25/2023, retrospective, Indonesia, peer-reviewed, 26 authors, study period January 2020 - March 2021.	**risk of death, 14.8% higher, RR 1.15, p = 0.23**, treatment 33 of 43 (76.7%), control 345 of 516 (66.9%).
Cacho, 10/31/2022, retrospective, Spain, peer-reviewed, 15 authors, study period 1 November, 2021 - 28 February, 2022, average treatment delay 5.0 days.	**risk of death, 79.8% higher, RR 1.80, p = 0.70**, treatment 5 of 57 (8.8%), control 2 of 41 (4.9%).
	risk of severe case, 43.9% higher, RR 1.44, p = 0.58, treatment 10 of 57 (17.5%), control 5 of 41 (12.2%).
	risk of moderate/severe case, 72.6% higher, RR 1.73, p = 0.09, treatment 24 of 57 (42.1%), control 10 of 41 (24.4%).
	risk of no hospital discharge, 91.8% higher, RR 1.92, p = 0.35, treatment 8 of 57 (14.0%), control 3 of 41 (7.3%).
Chang, 12/29/2023, retrospective, Taiwan, peer-reviewed, 2 authors.	**risk of death, 184.7% higher, OR 2.85, p = 0.04**, treatment 81, control 81, adjusted per study, multivariable, RR approximated with OR.

Diaz, 8/19/2021, retrospective, USA, peer-reviewed, 45 authors.	risk of death, 34.7% lower, HR 0.65, $p = 0.01$, treatment 33 of 286 (11.5%), control 173 of 852 (20.3%), NNT 11, adjusted per study, odds ratio converted to relative risk, multivariable, Cox proportional hazards, day 60.
	risk of death, 44.0% lower, HR 0.56, $p = 0.04$, treatment 286, control 852, adjusted per study, multivariable, Cox proportional hazards, day 30, RR approximated with OR.
Drouin, 3/19/2024, retrospective, USA, peer-reviewed, median age 56.0, 13 authors, study period August 2020 - September 2021, excluded in exclusion analyses: substantial unadjusted confounding by indication likely.	risk of severe case, 46.4% higher, RR 1.46, $p < 0.001$, treatment 52 of 102 (51.0%), control 135 of 354 (38.1%), adjusted per study, odds ratio converted to relative risk, multivariable.
El-Solh, 10/20/2020, retrospective, database analysis, USA, peer-reviewed, 5 authors, excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline; substantial unadjusted confounding by indication likely; significant confounding by contraindications possible.	risk of death, 29.0% lower, HR 0.71, $p = 0.03$, treatment 63 of 219 (28.8%), control 202 of 424 (47.6%), NNT 5.3, adjusted per study, multivariable.
Elavarasi, 8/12/2021, retrospective, India, peer-reviewed, 31 authors, study period April 2021 - June 2021, excluded in exclusion analyses: unadjusted results with no group details; substantial unadjusted confounding by indication likely.	risk of death, 136.6% higher, RR 2.37, $p < 0.001$, treatment 146 of 403 (36.2%), control 207 of 1,352 (15.3%).
Elec, 3/14/2022, retrospective, Romania, peer-reviewed, 9 authors, study period 1 March, 2020 - 31 May, 2021, excluded in exclusion analyses: substantial confounding by time possible due to significant changes in SOC and treatment propensity during the study period.	risk of death, 19.3% lower, RR 0.81, $p = 0.66$, treatment 7 of 38 (18.4%), control 29 of 127 (22.8%), NNT 23.
	risk of mechanical ventilation, 10.9% lower, RR 0.89, $p = 0.73$, treatment 8 of 38 (21.1%), control 30 of 127 (23.6%), NNT 39.
	risk of ICU admission, 71.9% higher, RR 1.72, $p = 0.01$, treatment 18 of 38 (47.4%), control 35 of 127 (27.6%).
Elhadi, 4/30/2021, prospective, Libya, peer-reviewed, 21 authors, study period 29 May, 2020 - 30 December, 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 10.9% higher, RR 1.11, $p = 0.65$, treatment 14 of 21 (66.7%), control 267 of 444 (60.1%), day 60.
Flisiak, 11/3/2020, retrospective, Poland, peer-reviewed, 23 authors, study period 1 March, 2020 - 31 August, 2020, SARSTer trial.	risk of death, 48.9% lower, RR 0.51, $p = 0.18$, treatment 5 of 122 (4.1%), control 17 of 211 (8.1%), NNT 25, odds ratio converted to relative risk, all patients, day 28.
	no clinical improvement, 56.5% lower, RR 0.44, $p = 0.01$, treatment 9 of 122 (7.4%), control 36 of 211 (17.1%), NNT 10, odds ratio converted to relative risk.
Fried, 8/28/2020, retrospective, database analysis, USA, peer-reviewed, 11 authors, excluded in exclusion analyses: excessive unadjusted differences between groups; substantial unadjusted confounding by indication likely.	risk of death, 61.2% lower, RR 0.39, $p = 0.02$, treatment 4 of 48 (8.3%), control 2,510 of 11,673 (21.5%), NNT 7.6, remdesivir vs. non-remdesivir.
	risk of mechanical ventilation, 36.8% higher, RR 1.37, $p = 0.25$, treatment 11 of 48 (22.9%), control 1,956 of 11,673 (16.8%), remdesivir vs. non-remdesivir.
Garibaldi, 11/20/2020, retrospective, USA, preprint, 10 authors.	risk of death, 20.0% lower, HR 0.80, $p = 0.44$, treatment 23 of 303 (7.6%), control 45 of 303 (14.9%), adjusted per study, day 28.

	risk of no improvement, 35.0% better, RR 0.65, $p < 0.001$, treatment 52 of 303 (17.2%), control 80 of 303 (26.4%), NNT 11, adjusted per study, day 28.
Goldberg, 3/9/2021, retrospective, Israel, peer-reviewed, 7 authors.	**hospitalization time, 9.2% lower, relative time 0.91, $p = 0.77$**, treatment 29, control 113.
	risk of no viral clearance, 0.1% lower, RR 1.00, $p = 0.98$, treatment 29, control 113, relative change in Ct values.
Hagman, 9/26/2023, retrospective, Sweden, peer-reviewed, 9 authors, average treatment delay 6.0 days.	**risk of death, no change, HR 1.00, $p = 0.97$**, treatment 105, control 213, adjusted per study, multivariable, day 60.
	risk of death, no change, HR 1.00, $p = 0.99$, treatment 105, control 213, adjusted per study, multivariable, day 28.
	risk of death, 20.0% lower, HR 0.80, $p = 0.74$, treatment 105, control 213, adjusted per study, multivariable, day 7.
	risk of progression, 40.0% higher, OR 1.40, $p = 0.31$, treatment 105, control 213, adjusted per study, multivariable, Table S7, RR approximated with OR.
	risk of no viral clearance, 28.6% lower, HR 0.71, $p = 0.11$, treatment 105, control 213, adjusted per study, inverted to make HR<1 favor treatment, multivariable.
Haji Aghajani, 4/29/2021, retrospective, Iran, peer-reviewed, 7 authors.	**risk of death, 18.6% lower, HR 0.81, $p = 0.49$**, treatment 46, control 945, univariate Cox proportional regression.
Hartantri, 2/9/2023, retrospective, Indonesia, peer-reviewed, 10 authors, study period 1 March, 2020 - 31 December, 2020.	**risk of death, 11.0% lower, HR 0.89, $p = 0.84$**, adjusted per study, mild/moderate, multivariable, Cox proportional hazards.
	risk of death, 24.0% lower, HR 0.76, $p = 0.53$, adjusted per study, severe, multivariable, Cox proportional hazards.
Ho, 10/31/2023, retrospective, USA, peer-reviewed, 9 authors, study period 1 January, 2020 - 31 August, 2021.	**risk of death, 62.0% higher, OR 1.62, $p < 0.001$**, treatment 5,294, control 21,151, adjusted per study, multivariable, RR approximated with OR.
Jamir, 12/13/2021, retrospective, India, peer-reviewed, 6 authors, study period June 2020 - October 2020.	**risk of death, 8.0% lower, HR 0.92, $p = 0.77$**, treatment 60 of 181 (33.1%), control 41 of 85 (48.2%), NNT 6.6, adjusted per study, multivariable, Cox proportional hazards.
Kawther, 9/9/2024, retrospective, Iraq, peer-reviewed, 6 authors, study period December 2020 - December 2021.	**risk of death, 8.7% higher, OR 1.09, $p = 0.86$**, treatment 111, control 340, adjusted per study, RR approximated with OR.
Kim (B), 3/15/2023, retrospective, South Korea, peer-reviewed, 5 authors, study period 1 November, 2021 - 30 April, 2022.	**risk of death, 1612.4% higher, RR 17.12, $p = 0.22$**, treatment 14 of 145 (9.7%), control 0 of 22 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
Kuno, 8/9/2021, retrospective, propensity score matching, USA, peer-reviewed, 6 authors.	**risk of death, 0.9% lower, RR 0.99, $p = 0.96$**, treatment 214 of 999 (21.4%), control 216 of 999 (21.6%), NNT 499, PSM.
	risk of mechanical ventilation, no change, RR 1.00, $p = 1.00$, treatment 140 of 999 (14.0%), control 140 of 999 (14.0%), PSM.
	risk of ICU admission, 17.1% higher, RR 1.17, $p = 0.05$, treatment 260 of 999 (26.0%), control 222 of 999 (22.2%), PSM.
Kurniyanto, 2/28/2022, retrospective, Indonesia, peer-reviewed, 11 authors, excluded in exclusion analyses: unadjusted results with no group details;	**risk of death, 460.0% higher, RR 5.60, $p < 0.001$**, treatment 7 of 45 (15.6%), control 12 of 432 (2.8%).

substantial unadjusted confounding by indication likely.	
Lewandowski, 3/7/2024, retrospective, Poland, peer-reviewed, 15 authors.	**risk of death, 20.9% higher, OR 1.21, $p = 0.55$**, RR approximated with OR.
Liao, 1/15/2024, retrospective, Taiwan, peer-reviewed, median age 73.0, 10 authors, study period May 2022 - September 2022, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 25.4% higher, RR 1.25, $p = 0.67$**, treatment 37 of 59 (62.7%), control 3 of 6 (50.0%), day 120.
Madan (B), 7/19/2021, retrospective, India, preprint, 22 authors, excluded in exclusion analyses: excessive unadjusted differences between groups.	**risk of death, 44.4% lower, RR 0.56, $p = 0.03$**, treatment 23 of 398 (5.8%), control 27 of 260 (10.4%), NNT 22, unadjusted.
	risk of death, 65.6% lower, RR 0.34, $p = 0.04$, treatment 4 of 112 (3.6%), control 27 of 260 (10.4%), NNT 15, unadjusted, <5 days from onset.
	risk of death, 61.7% lower, RR 0.38, $p = 0.009$, treatment 9 of 226 (4.0%), control 27 of 260 (10.4%), NNT 16, unadjusted, 5-10 days from onset.
	risk of death, 60.5% higher, RR 1.60, $p = 0.18$, treatment 10 of 60 (16.7%), control 27 of 260 (10.4%), unadjusted, >10 days from onset.
	risk of death, 31.0% lower, RR 0.69, $p = 0.30$, treatment 19 of 398 (4.8%), control 18 of 260 (6.9%), NNT 47, day 14.
	risk of death, 34.7% lower, RR 0.65, $p = 0.32$, treatment 14 of 398 (3.5%), control 14 of 260 (5.4%), NNT 54, day 10.
	risk of death, 47.7% lower, RR 0.52, $p = 0.22$, treatment 8 of 398 (2.0%), control 10 of 260 (3.8%), NNT 54, day 7.
	risk of death, 34.7% lower, RR 0.65, $p = 0.53$, treatment 5 of 398 (1.3%), control 5 of 260 (1.9%), NNT 150, day 5.
	risk of death, 12.9% lower, RR 0.87, $p = 1.00$, treatment 4 of 398 (1.0%), control 3 of 260 (1.2%), NNT 672, day 3.
Mahajan, 3/20/2021, Randomized Controlled Trial, India, peer-reviewed, 3 authors, study period June 2020 - December 2020, average treatment delay 6.84 days.	**risk of death, 76.5% higher, RR 1.76, $p = 0.47$**, treatment 5 of 34 (14.7%), control 3 of 36 (8.3%).
	risk of mechanical ventilation, 111.8% higher, RR 2.12, $p = 0.42$, treatment 4 of 34 (11.8%), control 2 of 36 (5.6%).
Malundo, 7/14/2022, retrospective, Philippines, peer-reviewed, 16 authors, study period 12 March, 2021 - 9 September, 2021, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 16.5% higher, RR 1.17, $p = 0.45$**, treatment 24 of 115 (20.9%), control 197 of 1,100 (17.9%).
Milan, 4/30/2024, retrospective, Philippines, peer-reviewed, median age 11.0, 5 authors, study period 1 April, 2020 - 31 August, 2021, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 34.4% higher, RR 1.34, $p = 0.56$**, treatment 1 of 8 (12.5%), control 16 of 172 (9.3%), day 45.
	risk of mechanical ventilation, 122.4% higher, RR 2.22, $p = 0.15$, treatment 3 of 8 (37.5%), control 29 of 172 (16.9%), day 45.
	risk of ICU admission, 419.0% higher, RR 5.19, $p < 0.001$, treatment 7 of 8 (87.5%), control 29 of 172 (16.9%).
Mitsushima, 2/21/2023, retrospective, Japan, peer-reviewed, 3 authors.	**risk of death, 44.0% higher, OR 1.44, $p < 0.01$**, adjusted per study, multivariable, RR approximated with OR.

Mozaffari, 8/9/2023, retrospective, USA, peer-reviewed, 11 authors, study period 1 December, 2020 - 30 April, 2022.	risk of death, 25.0% lower, HR 0.75, $p < 0.001$, treatment 14,169, control 5,341, adjusted per study, propensity score matching, Cox proportional hazards, day 28.
	risk of death, 30.0% lower, HR 0.70, $p < 0.001$, treatment 14,169, control 5,341, adjusted per study, propensity score matching, Cox proportional hazards, day 14.
Mozaffari (B), 10/1/2021, retrospective, USA, peer-reviewed, 12 authors.	risk of death, 12.0% lower, HR 0.88, $p = 0.003$, treatment 4,441 of 28,855 (15.4%), control 5,499 of 28,855 (19.1%), NNT 27, adjusted per study, PSM, Cox proportional hazards, day 28.
	risk of death, 24.0% lower, HR 0.76, $p < 0.001$, treatment 3,057 of 28,855 (10.6%), control 4,437 of 28,855 (15.4%), NNT 21, adjusted per study, PSM, Cox proportional hazards, day 14.
Mulhem, 4/7/2021, retrospective, database analysis, USA, peer-reviewed, 3 authors, excluded in exclusion analyses: substantial unadjusted confounding by indication likely; substantial confounding by time possible due to significant changes in SOC and treatment propensity during the study period.	risk of death, 85.7% higher, RR 1.86, $p = 0.54$, treatment 1 of 8 (12.5%), control 515 of 3,211 (16.0%), adjusted per study, odds ratio converted to relative risk, logistic regression.
Muntean, 12/19/2023, retrospective, Romania, peer-reviewed, 8 authors.	risk of death, 45.1% higher, RR 1.45, $p = 0.03$, treatment 71 of 287 (24.7%), control 45 of 264 (17.0%).
Mustafa, 12/29/2021, retrospective, Pakistan, peer-reviewed, 7 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 32.7% lower, RR 0.67, $p = 0.21$, treatment 16 of 200 (8.0%), control 29 of 244 (11.9%), NNT 26.
Nadeem, 8/12/2023, retrospective, USA, peer-reviewed, mean age 59.0, 6 authors, study period 1 March, 2020 - 28 February, 2022, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 12.5% higher, RR 1.12, $p = 1.00$, treatment 12 of 96 (12.5%), control 4 of 36 (11.1%).
Ohl, 7/15/2021, retrospective, propensity score matching, USA, peer-reviewed, 9 authors.	risk of death, 6.0% higher, HR 1.06, $p = 0.66$, treatment 143 of 1,172 (12.2%), control 124 of 1,172 (10.6%), adjusted per study, PSM, Cox proportional hazards regression, day 30.
	hospitalization time, 100% higher, relative time 2.00, $p < 0.001$, treatment 1,172, control 1,172, PSM, Cox proportional hazards regression.
Oku, 9/6/2022, retrospective, Japan, peer-reviewed, 8 authors, study period 3 June, 2020 - 30 June, 2021, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 40.2% higher, RR 1.40, $p = 0.59$, treatment 3 of 46 (6.5%), control 8 of 172 (4.7%), unadjusted, odds ratio converted to relative risk.
Olender, 7/24/2020, retrospective, USA, peer-reviewed, 33 authors.	risk of death, 58.8% lower, RR 0.41, $p = 0.001$, treatment 24 of 312 (7.7%), control 102 of 818 (12.5%), odds ratio converted to relative risk, weighted multivariable logistic regression, day 14.
Pasquini, 8/23/2020, retrospective, Italy, peer-reviewed, 9 authors.	risk of death, 16.2% lower, RR 0.84, $p = 0.03$, treatment 14 of 25 (56.0%), control 24 of 26 (92.3%), NNT 2.8, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariate.
Pourhoseingholi, 5/26/2021, prospective, Iran, preprint, mean age 57.9, 11 authors, study period 2 February, 2020 - 20 July, 2020, average treatment delay 7.4 days.	risk of death, 2.0% higher, HR 1.02, $p = 0.92$, treatment 42 of 123 (34.1%), control 297 of 2,345 (12.7%), adjusted per study, multivariable, Cox proportional hazards.

Punzalan, 2/28/2023, prospective, Philippines, peer-reviewed, mean age 56.0, 17 authors, study period October 2020 - September 2021.	risk of death, 42.0% higher, RR 1.42, $p = 0.12$, treatment 47 of 224 (21.0%), control 26 of 176 (14.8%).
	risk of progression, 58.9% higher, RR 1.59, $p = 0.001$, treatment 93 of 224 (41.5%), control 46 of 176 (26.1%).
Raad, 8/26/2022, retrospective, multiple countries, preprint, 52 authors, study period January 2020 - November 2020.	risk of death, 42.0% lower, OR 0.58, $p = 0.009$, adjusted per study, multivariable, day 30, RR approximated with OR.
Salehi, 3/11/2022, retrospective, Iran, preprint, mean age 62.0, 11 authors, study period April 2021 - September 2021, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 36.6% lower, RR 0.63, $p = 0.01$, treatment 17 of 40 (42.5%), control 57 of 85 (67.1%), NNT 4.1.
Sarhan, 11/2/2021, Randomized Controlled Trial, Egypt, peer-reviewed, 8 authors, study period 1 October, 2020 - 10 March, 2021, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04779047 (history), excluded in exclusion analyses: very late stage, >50% on oxygen/ventilation at baseline; significant unadjusted differences between groups.	risk of death, 34.6% higher, RR 1.35, $p = 0.39$, treatment 15 of 52 (28.8%), control 12 of 56 (21.4%).
	risk of no hospital discharge, 34.6% higher, RR 1.35, $p = 0.39$, treatment 15 of 52 (28.8%), control 12 of 56 (21.4%).
Schmidt, 11/12/2021, retrospective, USA, peer-reviewed, 42 authors, study period 17 March, 2020 - 11 February, 2021, excluded in exclusion analyses: confounding by indication is likely and adjustments do not consider COVID-19 severity at baseline.	risk of severe case, 509.0% higher, OR 6.09, $p < 0.001$, treatment 43, control 434, adjusted per study, propensity score matching, multivariable, RR approximated with OR.
Shamsi, 7/17/2023, retrospective, Iran, peer-reviewed, 4 authors, study period 1 March, 2020 - 1 August, 2021, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 22.6% higher, RR 1.23, $p = 0.63$, treatment 8 of 53 (15.1%), control 16 of 130 (12.3%).
Siraj, 2/28/2022, retrospective, India, peer-reviewed, median age 56.0, 13 authors, study period March 2020 - December 2020.	risk of death, 52.9% lower, RR 0.47, $p < 0.001$, treatment 108 of 413 (26.2%), control 197 of 587 (33.6%), adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable.
Sise, 6/24/2024, Double Blind Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, mean age 69.0, 24 authors, study period March 2021 - March 2022, trial NCT04745351 (history) (REDPINE).	risk of death, 0.1% higher, RR 1.00, $p = 1.00$, treatment 51 of 163 (31.3%), control 25 of 80 (31.2%), day 60.
	risk of death, 17.0% lower, HR 0.83, $p = 0.39$, treatment 41 of 163 (25.2%), control 23 of 80 (28.7%), NNT 28, Cox proportional hazards, day 29.
	risk of death/intubation, 18.0% lower, HR 0.82, $p = 0.61$, treatment 48 of 163 (29.4%), control 26 of 80 (32.5%), NNT 33, Cox proportional hazards, day 29.
	clinical status, 16.0% lower, OR 0.84, $p = 0.50$, treatment 163, control 80, day 29, RR approximated with OR.
	clinical status, 5.0% higher, OR 1.05, $p = 0.85$, treatment 163, control 80, day 15, RR approximated with OR.
Sokolski, 2/28/2024, retrospective, Poland, peer-reviewed, 11 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, no change, HR 1.00, $p = 1.00$, treatment 88, control 460, Cox proportional hazards, day 90.

SOLIDARITY Trial Consortium, 10/15/2020, Randomized Controlled Trial, multiple countries, peer-reviewed, 15 authors, trial NCT04315948 (history) (SOLIDARITY).	risk of death, 5.0% lower, RR 0.95, $p = 0.53$, treatment 301 of 2,743 (11.0%), control 303 of 2,708 (11.2%), NNT 464, day 28.
Spinner, 8/21/2020, Randomized Controlled Trial, multiple countries, peer-reviewed, 30 authors, study period 15 March, 2020 - 18 April, 2020, average treatment delay 8.0 days.	5 or 10 day remdesivir vs. control 28 day mortality, 34.9% lower, RR 0.65, $p = 0.50$, treatment 5 of 384 (1.3%), control 4 of 200 (2.0%), NNT 143, day 28.
Tsuzuki, 3/10/2021, retrospective, Japan, peer-reviewed, 21 authors, average treatment delay 6.0 days.	risk of death, 4.0% higher, HR 1.04, $p = 0.21$, treatment 69 of 824 (8.4%), control 285 of 11,663 (2.4%), adjusted per study, day 30.
	risk of mechanical ventilation or ECMO, 1.7% lower, HR 0.98, $p = 0.68$, treatment 48 of 824 (5.8%), control 98 of 11,663 (0.8%), adjusted per study.
	risk of progression, 15.0% lower, HR 0.85, $p = 0.68$, treatment 559 of 824 (67.8%), control 1,784 of 11,663 (15.3%), adjusted per study.
Ullah, 11/29/2020, retrospective, Pakistan, peer-reviewed, 8 authors.	risk of death, 100% higher, RR 2.00, $p = 0.33$, treatment 8 of 30 (26.7%), control 4 of 30 (13.3%).
	risk of mechanical ventilation, 250.0% higher, RR 3.50, $p = 0.15$, treatment 7 of 30 (23.3%), control 2 of 30 (6.7%).
Wang (B), 4/29/2020, Randomized Controlled Trial, China, peer-reviewed, 46 authors, study period 6 February, 2020 - 12 March, 2020, average treatment delay 11.0 days.	all patients, 8.6% higher, RR 1.09, $p = 1.00$, treatment 22 of 158 (13.9%), control 10 of 78 (12.8%), day 28.
	<10 days from symptoms, 24.3% lower, RR 0.76, $p = 0.58$, treatment 8 of 71 (11.3%), control 7 of 47 (14.9%), NNT 28, day 28.
	>10 days from symptoms, 47.6% higher, RR 1.48, $p = 0.76$, treatment 12 of 84 (14.3%), control 3 of 31 (9.7%), day 28.
Yeramaneni, 2/28/2021, retrospective, USA, peer-reviewed, 6 authors, study period 11 February, 2020 - 8 May, 2020.	risk of death, 24.0% higher, OR 1.24, $p = 0.87$, treatment 32, control 7,126, adjusted per study, multivariable, day 30, RR approximated with OR.
Zangeneh, 5/13/2022, retrospective, Iran, peer-reviewed, 3 authors.	risk of death, 32.0% lower, HR 0.68, $p = 0.06$, Cox proportional hazards.

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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