Favipiravir for COVID-19: real-time meta analysis of 68 studies

@CovidAnalysis, March 2024, Version 79
https://c19early.org/ameta.html

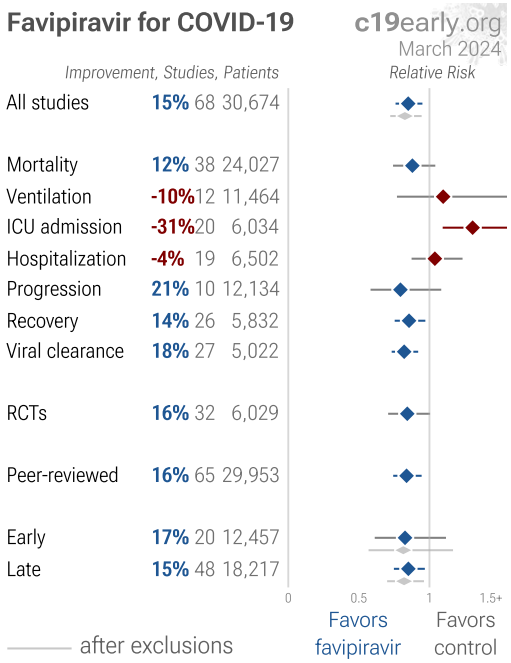
Abstract

Statistically significant lower risk is seen for recovery and viral clearance. 30 studies from 30 independent teams in 16 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 15% [5-24%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies.

Studies to date show no significant difference for mortality. A small mortality improvement is seen, without statistical significance, however meta regression with followup duration shows decreasing efficacy with longer followup. There is also no benefit seen for mechanical ventilation, ICU admission, or hospitalization. This may reflect antiviral efficacy being offset by side effects of treatment.

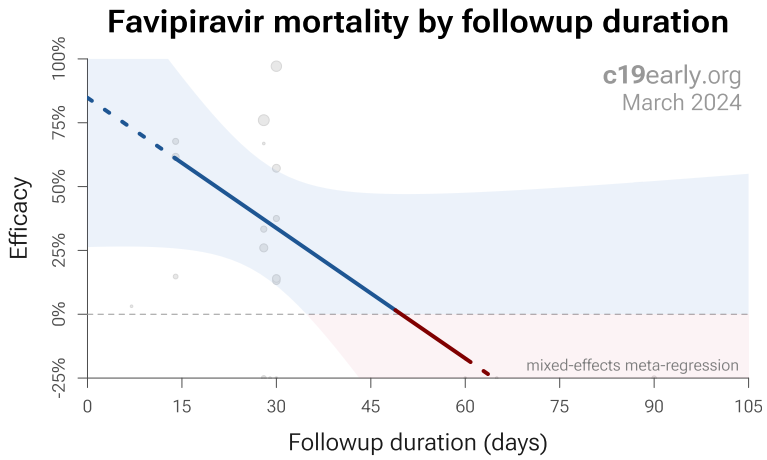
1 RCT with 1,008 patients has not reported results (2 years late) *Kara*.



Potential risks of the mechanism of action include the creation of dangerous variants, and mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity *Hadj Hassine, Waters, Zhirnov*. Favipiravir may impair clotting *Gül*.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments are significantly more effective.

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



HIGHLIGHTS

Favipiravir reduces risk for COVID-19 with very high confidence for viral clearance and in pooled analysis, high confidence for recovery, and very low confidence for mortality and progression, however increased risk is seen with very high confidence for ICU admission. Potential risks include the creation of dangerous variants, carcinogenicity, and genotoxicity.

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.

68 favipiravir COVID-19 studies

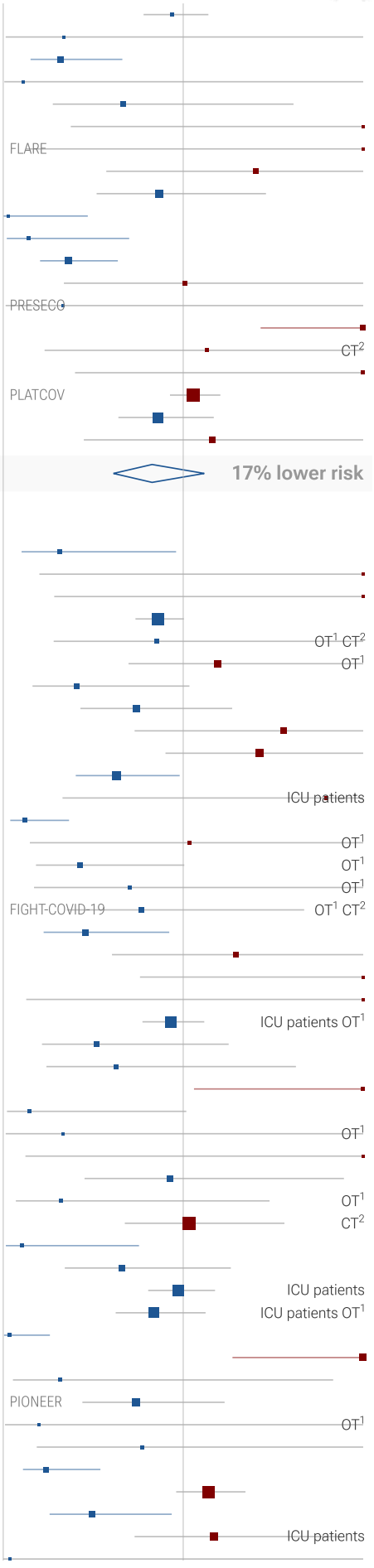
c19early.org
March 2024

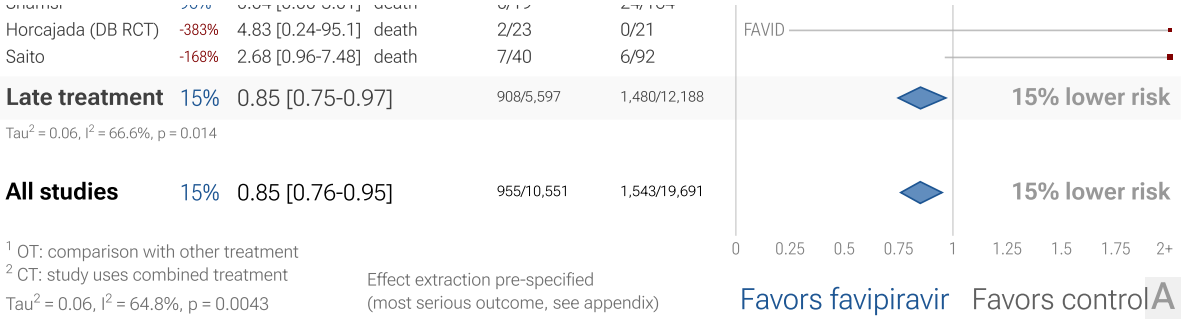
	Improvement	RR [CI]		Treatment	Control
Ruzhentsova (RCT)	6%	0.94 [0.78-1.14]	hosp.	3/112	2/56
Udwadia (RCT)	66%	0.34 [0.01-8.12]	death	0/73	1/75
Sawanpanyalert	68%	0.32 [0.15-0.66]	progression	n/a	n/a
Holubar (DB RCT)	89%	0.11 [0.01-2.02]	hosp.	0/75	4/74
Alattar (PSM)	33%	0.67 [0.28-1.61]	death	8/387	12/387
Bosaeed (DB RCT)	-619%	7.19 [0.38-138]	ICU	3/112	0/119
Lowe (DB RCT)	-202%	3.02 [0.13-72.6]	ICU	1/59	0/60
Adhikari (RCT)	-40%	1.40 [0.57-3.44]	no improv.	10/38	6/32
Tsuzuki	13%	0.87 [0.52-1.46]	death	2,532 (n)	5,122 (n)
Qadir	97%	0.03 [0.00-0.47]	death	0/125	17/125
Usanma Koban	86%	0.14 [0.02-0.70]	viral+	47 (n)	79 (n)
Sirijatuphat (RCT)	64%	0.36 [0.20-0.64]	improv.	62 (n)	31 (n)
McMahon (RCT)	-1%	1.01 [0.34-3.03]	oxygen	6/99	6/100
Golan (DB RCT)	67%	0.33 [0.01-8.12]	death	0/599	1/588
Bruminhent	-227%	3.27 [1.43-7.50]	progression	n/a	n/a
Chandiwana (RCT)	-13%	1.13 [0.23-5.46]	progression	37 (n)	39 (n)
Vaezi (DB RCT)	-105%	2.05 [0.40-10.6]	hosp.	4/38	2/39
Luvira (RCT)	-6%	1.06 [0.93-1.21]	viral rate	116 (n)	132 (n)
Lokanuwatsatien	14%	0.86 [0.64-1.17]	PASC	400 (n)	402 (n)
Iwata (DB RCT)	-16%	1.16 [0.45-2.21]	oxygen	12/43	12/43
Early treatment	17%	0.83 [0.61-1.12]		47/4,954	63/7,503

$Tau^2 = 0.17$, $I^2 = 61.3\%$, $p = 0.22$

17% lower risk

	Improvement	RR [CI]		Treatment	Control
Cai	69%	0.31 [0.10-0.96]	pneumonia	35 (n)	45 (n)
Ivashchenko (RCT)	-300%	4.00 [0.20-79.6]	death	2/40	0/20
Lou (RCT)	-422%	5.22 [0.28-96.2]	ICU	2/9	0/10
Pushkar (RCT)	14%	0.86 [0.73-1.00]	no recov.	73/100	85/100
Khamis (RCT)	15%	0.85 [0.28-2.59]	death	5/44	6/45
Solaymani.. (RCT)	-19%	1.19 [0.70-2.04]	death	26/190	21/183
Zhao (RCT)	59%	0.41 [0.16-1.03]	viral+	7/36	9/19
Aghajani	26%	0.74 [0.43-1.27]	death	40 (n)	951 (n)
Alamer	-56%	1.56 [0.73-3.36]	death	12/233	21/223
Almoosa	-42%	1.42 [0.90-2.25]	death	33/110	24/116
Shinkai (SB RCT)	37%	0.63 [0.40-0.98]	imp. time	107 (n)	49 (n)
Assiri (ICU)	-79%	1.79 [0.33-8.02]	death	11/67	3/51
Kulzhanova	88%	0.12 [0.04-0.37]	no improv.	3/40	25/40
Chen (RCT)	-3%	1.03 [0.15-7.22]	ICU	2/116	2/120
Alotaibi	57%	0.43 [0.18-1.01]	death	244 (n)	193 (n)
Tabarsi (RCT)	30%	0.70 [0.17-2.88]	death	3/32	4/30
Atipornwa.. (RCT)	23%	0.77 [0.35-1.67]	death	10/100	13/100
Damayanti	54%	0.46 [0.22-0.92]	no recov.	96 (n)	96 (n)
Shenoy (DB RCT)	-29%	1.29 [0.60-2.77]	death	14/175	11/178
Chuah (RCT)	-1154%	12.54 [0.76-208]	death	5/250	0/250
Finberg (RCT)	-200%	3.00 [0.13-70.3]	death	1/25	0/25
Al Mutair (ICU)	7%	0.93 [0.77-1.12]	death	119/269	128/269
Kurniyanto	48%	0.52 [0.22-1.25]	death	10/325	9/152
Cilli	38%	0.62 [0.24-1.63]	death	5/23	8/23
Al-Muhsen	-263%	3.63 [1.06-12.4]	death	156 (n)	442 (n)
Yulia	85%	0.15 [0.02-1.02]	death	432 (all patients)	
Uyaroğlu (PSM)	67%	0.33 [0.01-7.96]	death	0/42	1/42
AlQahtani (RCT)	-196%	2.96 [0.12-71.1]	death	1/54	0/52
Shinada	7%	0.93 [0.45-1.89]	hosp.	17 (n)	17 (n)
Hassaniazad (RCT)	68%	0.32 [0.07-1.48]	death	2/32	6/31
Hafez	-3%	1.03 [0.68-1.56]	viral+	59 (n)	1,446 (n)
Rahman (DB RCT)	89%	0.11 [0.01-0.75]	no improv.	1/19	8/16
Tehrani (RCT)	34%	0.66 [0.34-1.26]	hosp.	10/38	16/40
Abdulrahman (ICU)	3%	0.97 [0.81-1.18]	death	74/193	593/1,506
Acar Sevinc (ICU)	16%	0.84 [0.62-1.12]	death	57/85	12/15
Tawfik	96%	0.04 [0.00-0.26]	death	1/103	17/62
Babayigit	-184%	2.84 [1.27-6.14]	ventilation	47/325	17/977
Behboodikhah	68%	0.32 [0.05-1.83]	death	95 (n)	2,079 (n)
Shah (RCT)	26%	0.74 [0.44-1.23]	death	26/251	34/248
Alosaimi (PSM)	80%	0.20 [0.01-4.03]	death	0/37	2/37
Delen	23%	0.77 [0.19-3.20]	ICU	3/34	4/35
Hartantri	76%	0.24 [0.11-0.54]	death	n/a	n/a
Alshamrani (PSM)	-14%	1.14 [0.96-1.35]	death	326/1,159	316/1,380
Arfijanto	51%	0.49 [0.26-0.94]	viral+	8/37	55/125
Sulaiman (ICU)	-17%	1.17 [0.73-1.87]	death	73 (n)	73 (n)
Shamsi	96%	0.04 [0.00-3.01]	death	0/19	24/164

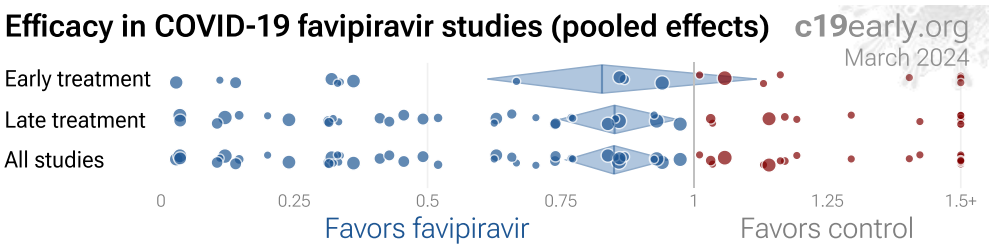




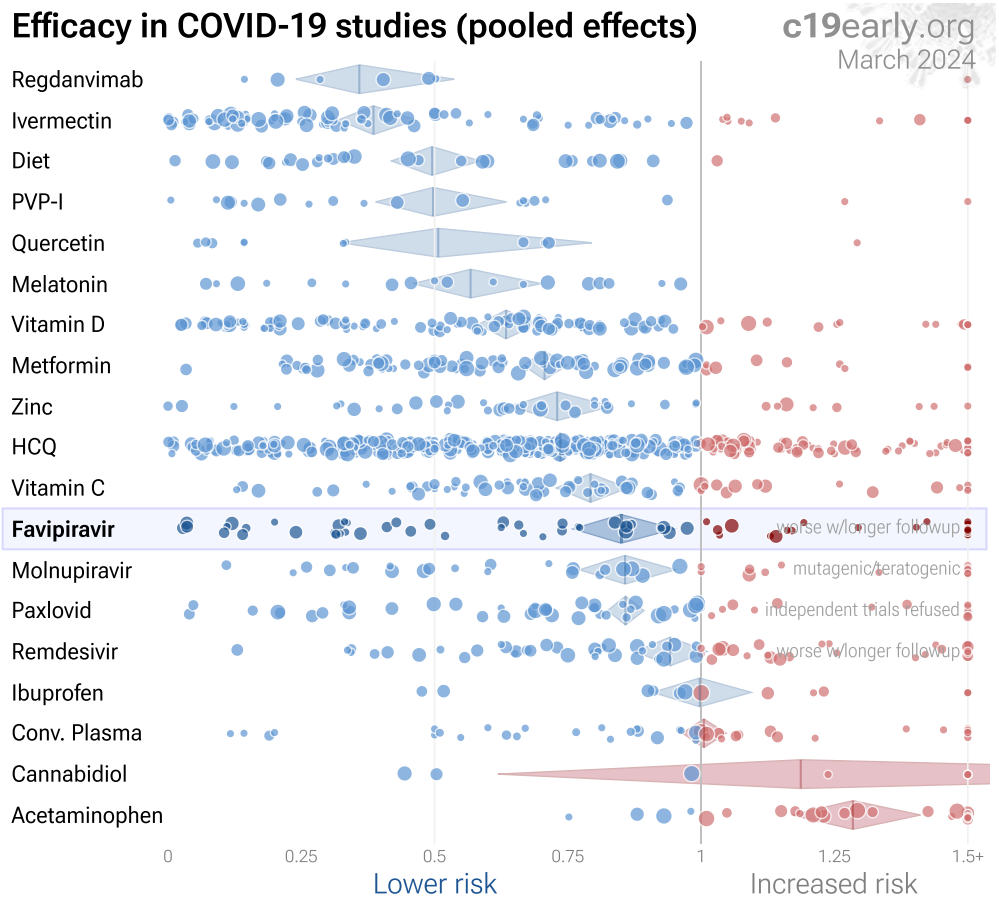
[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau² = 0.06, I² = 64.8%, p = 0.0043

Effect extraction pre-specified
(most serious outcome, see appendix)

A



B



C

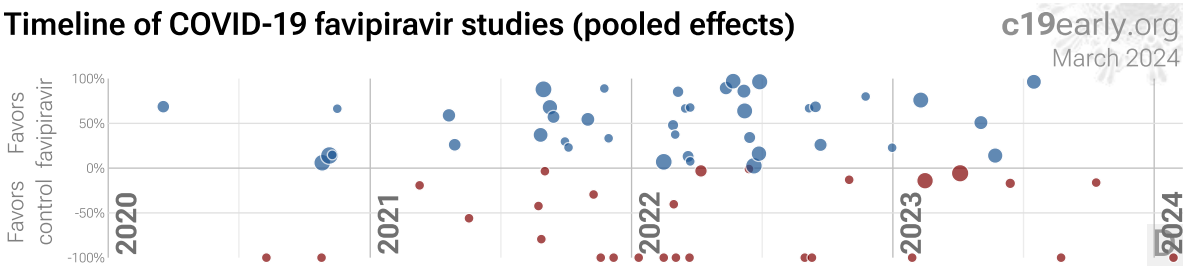


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. 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. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in favipiravir 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 issues *Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors *Note A, Malone, Murigneux, Lv, Lui*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk *c19early.org (B)*, 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 favipiravir 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 2 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.

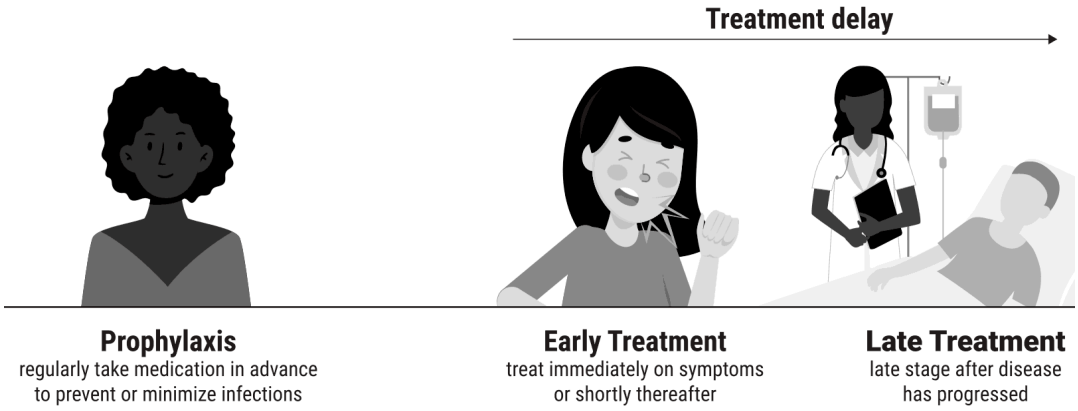


Figure 2. Treatment stages.

Preclinical Research

An *In Silico* study supports the efficacy of favipiravir [Unal].

2 *In Vitro* studies support the efficacy of favipiravir [Unal, Yildiz Pekoz].

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

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 3, 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, viral clearance, and peer reviewed studies.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**15%** [5-24%] **	68	30,674	1,108
After exclusions	**17%** [6-28%] **	53	24,523	913
Peer-reviewed studies	**16%** [6-26%] **	65	29,953	1,068
Randomized Controlled Trials	**16%** [-0-29%]	32	6,029	683
Mortality	**12%** [-4-26%]	38	24,027	602
Ventilation	**-10%** [-56-23%]	12	11,464	379
ICU admission	**-31%** [-56--9%] **	20	6,034	366
Hospitalization	**-4%** [-23-13%]	19	6,502	329
Recovery	**14%** [3-25%] *	26	5,832	520
Viral	**18%** [8-27%] ***	27	5,022	435
RCT mortality	**6%** [-23-28%]	14	3,734	345
RCT hospitalization	**15%** [-12-36%]	9	1,145	184

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 percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

	Early treatment	*Late treatment*
All studies	**17%** [-12-39%]	**15%** [3-25%] *
After exclusions	**19%** [-17-43%]	**18%** [4-30%] *
Peer-reviewed studies	**18%** [-12-39%]	**17%** [4-28%] *
Randomized Controlled Trials	**8%** [-33-37%]	**20%** [1-35%] *
Mortality	**42%** [-22-72%]	**10%** [-8-24%]
Ventilation	**-2%** [-60-35%]	**-10%** [-66-27%]
ICU admission	**-381%** [-4086-45%]	**-29%** [-55--8%] **
Hospitalization	**-4%** [-137-54%]	**-7%** [-27-11%]
Recovery	**9%** [-16-28%]	**17%** [3-29%] *
Viral	**8%** [-9-21%]	**40%** [22-53%] ***
RCT mortality	**67%** [-219-97%]	**5%** [-25-27%]
RCT hospitalization	**-55%** [-177-14%]	**26%** [9-40%] **

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. * $p<0.05$ ** $p<0.01$ *** $p<0.001$.

68 favipiravir COVID-19 studies

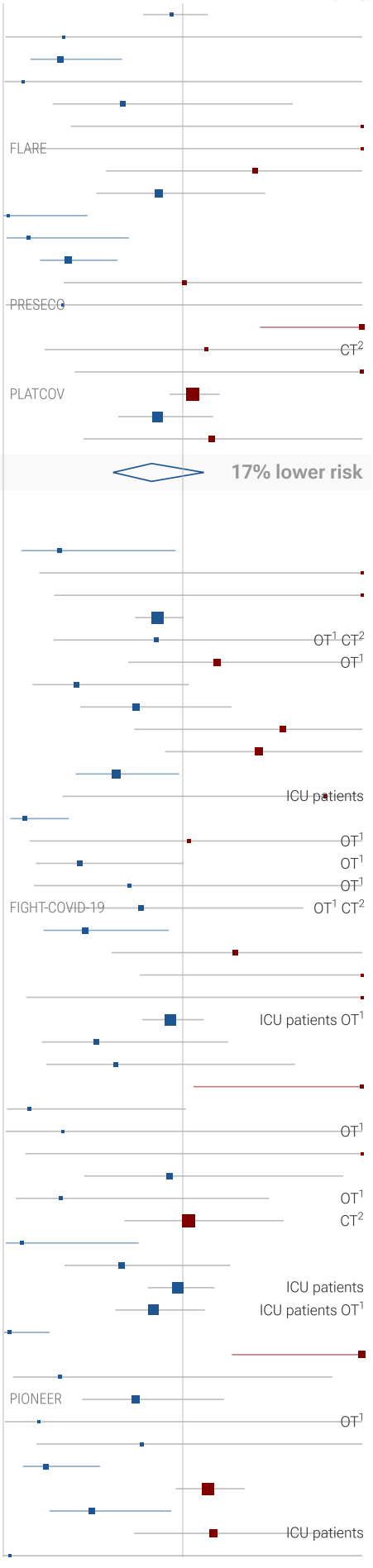
c19early.org
March 2024

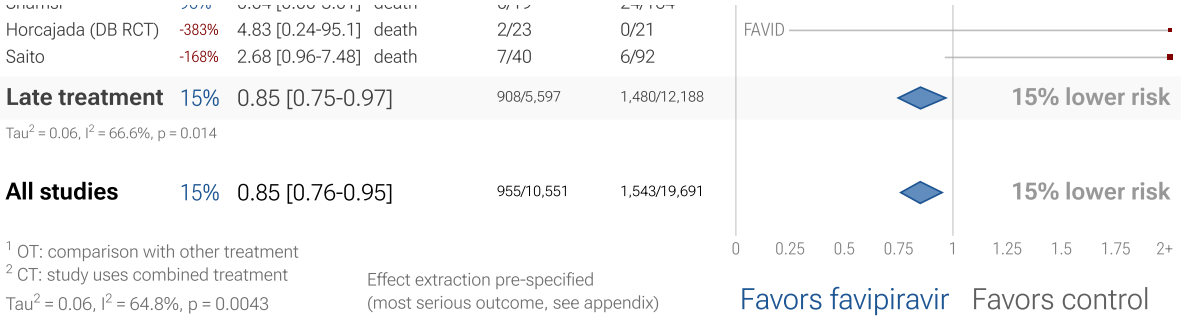
	Improvement	RR [CI]		Treatment	Control
Ruzhentsova (RCT)	6%	0.94 [0.78-1.14]	hosp.	3/112	2/56
Udwadia (RCT)	66%	0.34 [0.01-8.12]	death	0/73	1/75
Sawanpanyalert	68%	0.32 [0.15-0.66]	progression	n/a	n/a
Holubar (DB RCT)	89%	0.11 [0.01-2.02]	hosp.	0/75	4/74
Alattar (PSM)	33%	0.67 [0.28-1.61]	death	8/387	12/387
Bosaeed (DB RCT)	-619%	7.19 [0.38-138]	ICU	3/112	0/119
Lowe (DB RCT)	-202%	3.02 [0.13-72.6]	ICU	1/59	0/60
Adhikari (RCT)	-40%	1.40 [0.57-3.44]	no improv.	10/38	6/32
Tsuzuki	13%	0.87 [0.52-1.46]	death	2,532 (n)	5,122 (n)
Qadir	97%	0.03 [0.00-0.47]	death	0/125	17/125
Usanma Koban	86%	0.14 [0.02-0.70]	viral+	47 (n)	79 (n)
Sirijatuphat (RCT)	64%	0.36 [0.20-0.64]	improv.	62 (n)	31 (n)
McMahon (RCT)	-1%	1.01 [0.34-3.03]	oxygen	6/99	6/100
Golan (DB RCT)	67%	0.33 [0.01-8.12]	death	0/599	1/588
Bruminhent	-227%	3.27 [1.43-7.50]	progression	n/a	n/a
Chandiwana (RCT)	-13%	1.13 [0.23-5.46]	progression	37 (n)	39 (n)
Vaezi (DB RCT)	-105%	2.05 [0.40-10.6]	hosp.	4/38	2/39
Luvira (RCT)	-6%	1.06 [0.93-1.21]	viral rate	116 (n)	132 (n)
Lokanuwatsatien	14%	0.86 [0.64-1.17]	PASC	400 (n)	402 (n)
Iwata (DB RCT)	-16%	1.16 [0.45-2.21]	oxygen	12/43	12/43
Early treatment	17%	0.83 [0.61-1.12]		47/4,954	63/7,503

$Tau^2 = 0.17$, $I^2 = 61.3\%$, $p = 0.22$

17% lower risk

	Improvement	RR [CI]		Treatment	Control
Cai	69%	0.31 [0.10-0.96]	pneumonia	35 (n)	45 (n)
Ivashchenko (RCT)	-300%	4.00 [0.20-79.6]	death	2/40	0/20
Lou (RCT)	-422%	5.22 [0.28-96.2]	ICU	2/9	0/10
Pushkar (RCT)	14%	0.86 [0.73-1.00]	no recov.	73/100	85/100
Khamis (RCT)	15%	0.85 [0.28-2.59]	death	5/44	6/45
Solaymani.. (RCT)	-19%	1.19 [0.70-2.04]	death	26/190	21/183
Zhao (RCT)	59%	0.41 [0.16-1.03]	viral+	7/36	9/19
Aghajani	26%	0.74 [0.43-1.27]	death	40 (n)	951 (n)
Alamer	-56%	1.56 [0.73-3.36]	death	12/233	21/223
Almoosa	-42%	1.42 [0.90-2.25]	death	33/110	24/116
Shinkai (SB RCT)	37%	0.63 [0.40-0.98]	imp. time	107 (n)	49 (n)
Assiri (ICU)	-79%	1.79 [0.33-8.02]	death	11/67	3/51
Kulzhanova	88%	0.12 [0.04-0.37]	no improv.	3/40	25/40
Chen (RCT)	-3%	1.03 [0.15-7.22]	ICU	2/116	2/120
Alotaibi	57%	0.43 [0.18-1.01]	death	244 (n)	193 (n)
Tabarsi (RCT)	30%	0.70 [0.17-2.88]	death	3/32	4/30
Atipornwa.. (RCT)	23%	0.77 [0.35-1.67]	death	10/100	13/100
Damayanti	54%	0.46 [0.22-0.92]	no recov.	96 (n)	96 (n)
Shenoy (DB RCT)	-29%	1.29 [0.60-2.77]	death	14/175	11/178
Chuah (RCT)	-1154%	12.54 [0.76-208]	death	5/250	0/250
Finberg (RCT)	-200%	3.00 [0.13-70.3]	death	1/25	0/25
Al Mutair (ICU)	7%	0.93 [0.77-1.12]	death	119/269	128/269
Kurniyanto	48%	0.52 [0.22-1.25]	death	10/325	9/152
Cilli	38%	0.62 [0.24-1.63]	death	5/23	8/23
Al-Muhsen	-263%	3.63 [1.06-12.4]	death	156 (n)	442 (n)
Yulia	85%	0.15 [0.02-1.02]	death	432 (all patients)	
Uyaroğlu (PSM)	67%	0.33 [0.01-7.96]	death	0/42	1/42
AlQahtani (RCT)	-196%	2.96 [0.12-71.1]	death	1/54	0/52
Shinada	7%	0.93 [0.45-1.89]	hosp.	17 (n)	17 (n)
Hassaniazad (RCT)	68%	0.32 [0.07-1.48]	death	2/32	6/31
Hafez	-3%	1.03 [0.68-1.56]	viral+	59 (n)	1,446 (n)
Rahman (DB RCT)	89%	0.11 [0.01-0.75]	no improv.	1/19	8/16
Tehrani (RCT)	34%	0.66 [0.34-1.26]	hosp.	10/38	16/40
Abdulrahman (ICU)	3%	0.97 [0.81-1.18]	death	74/193	593/1,506
Acar Sevinc (ICU)	16%	0.84 [0.62-1.12]	death	57/85	12/15
Tawfik	96%	0.04 [0.00-0.26]	death	1/103	17/62
Babayigit	-184%	2.84 [1.27-6.14]	ventilation	47/325	17/977
Behboodikhah	68%	0.32 [0.05-1.83]	death	95 (n)	2,079 (n)
Shah (RCT)	26%	0.74 [0.44-1.23]	death	26/251	34/248
Alosaimi (PSM)	80%	0.20 [0.01-4.03]	death	0/37	2/37
Delen	23%	0.77 [0.19-3.20]	ICU	3/34	4/35
Hartantri	76%	0.24 [0.11-0.54]	death	n/a	n/a
Alshamrani (PSM)	-14%	1.14 [0.96-1.35]	death	326/1,159	316/1,380
Arfijanto	51%	0.49 [0.26-0.94]	viral+	8/37	55/125
Sulaiman (ICU)	-17%	1.17 [0.73-1.87]	death	73 (n)	73 (n)
Shamsi	96%	0.04 [0.00-3.01]	death	0/19	24/164





[1] OT: comparison with other treatment
[2] CT: study uses combined treatment
Tau² = 0.06, I² = 64.8%, p = 0.0043

Effect extraction pre-specified
(most serious outcome, see appendix)

Figure 3. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

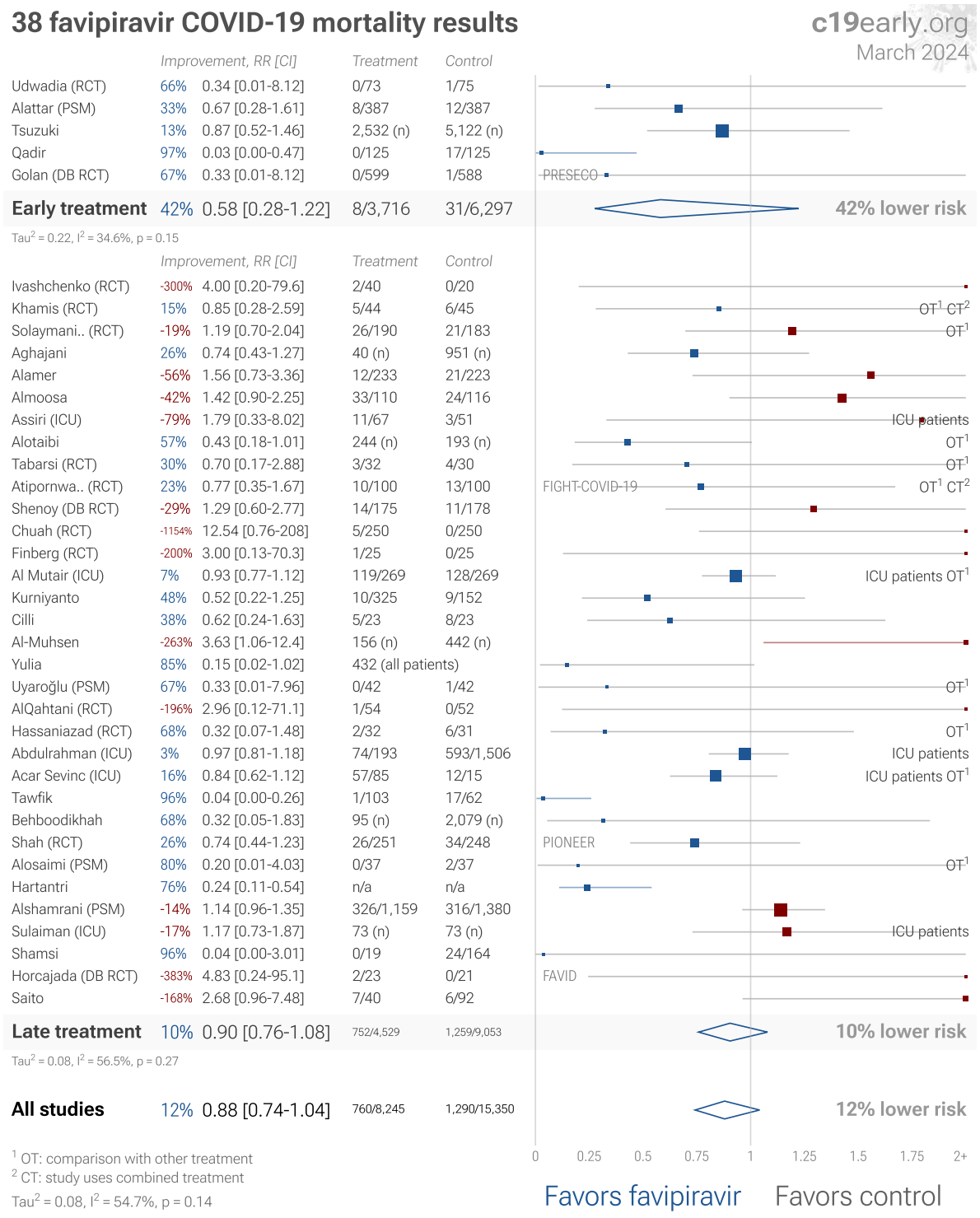


Figure 4. Random effects meta-analysis for mortality results.

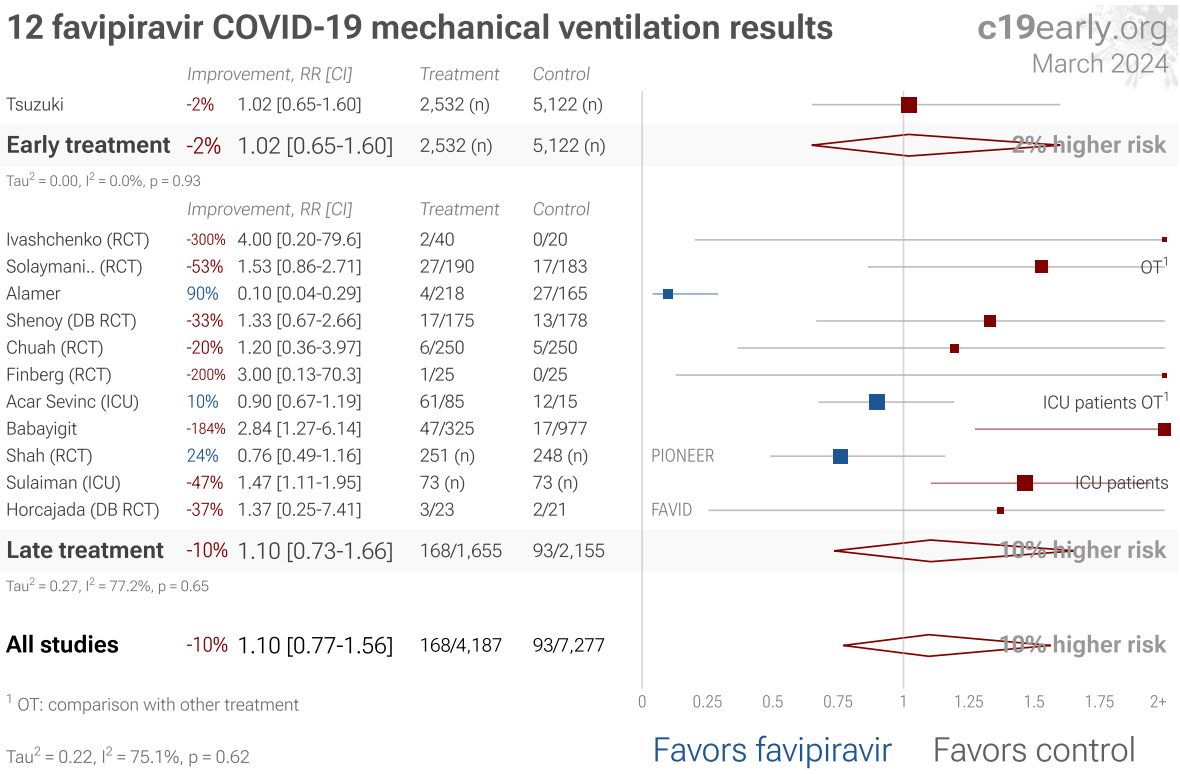


Figure 5. Random effects meta-analysis for ventilation.

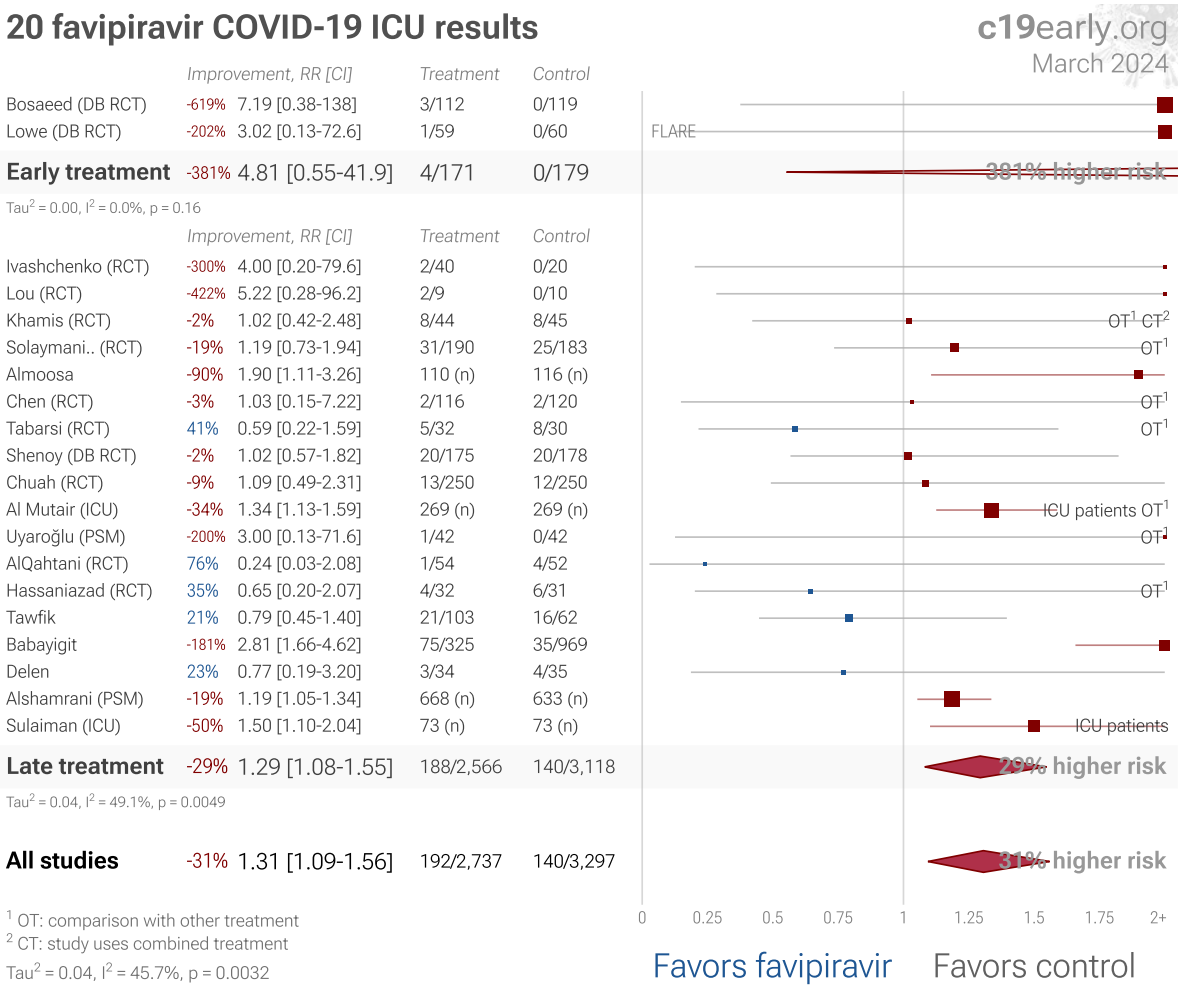


Figure 6. Random effects meta-analysis for ICU admission.

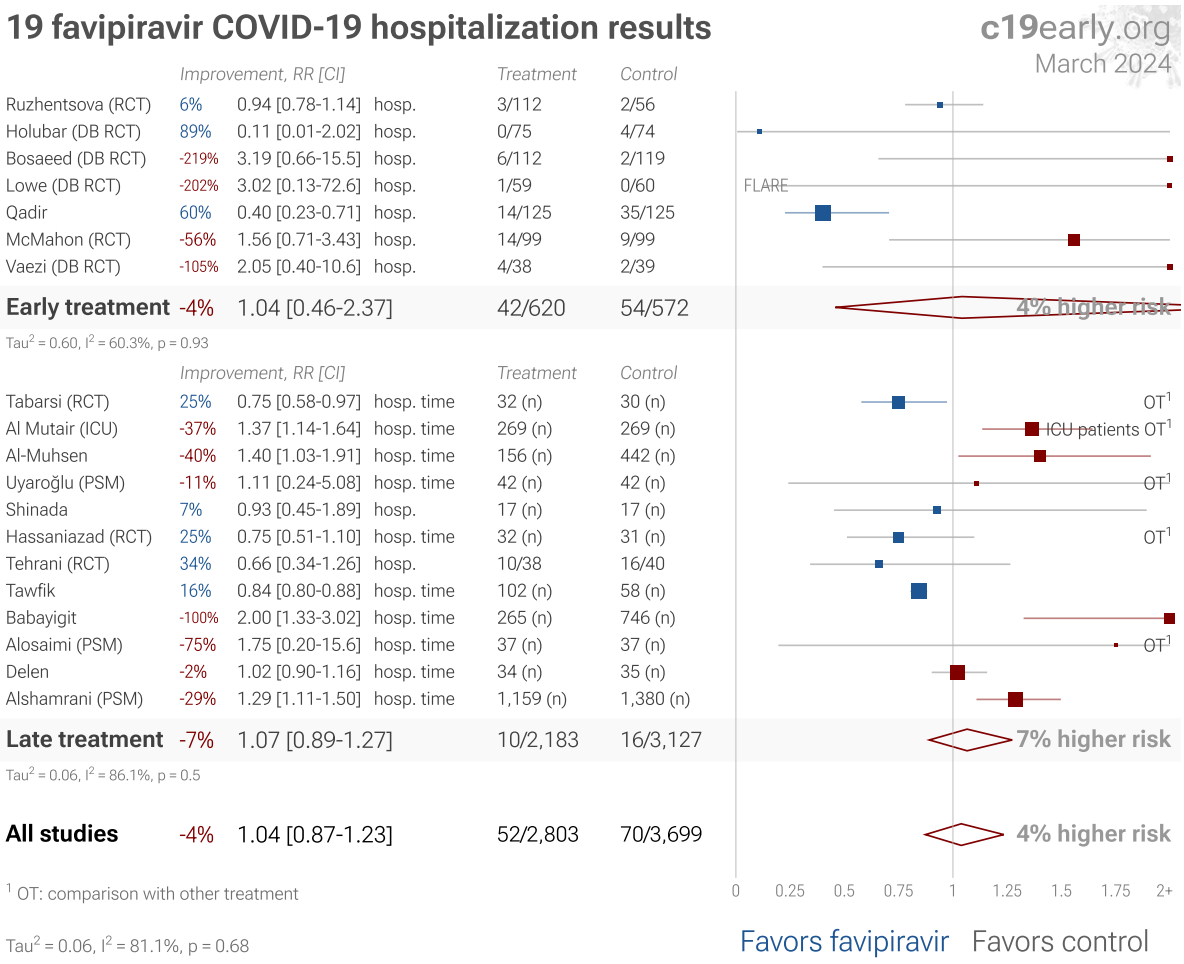


Figure 7. Random effects meta-analysis for hospitalization.

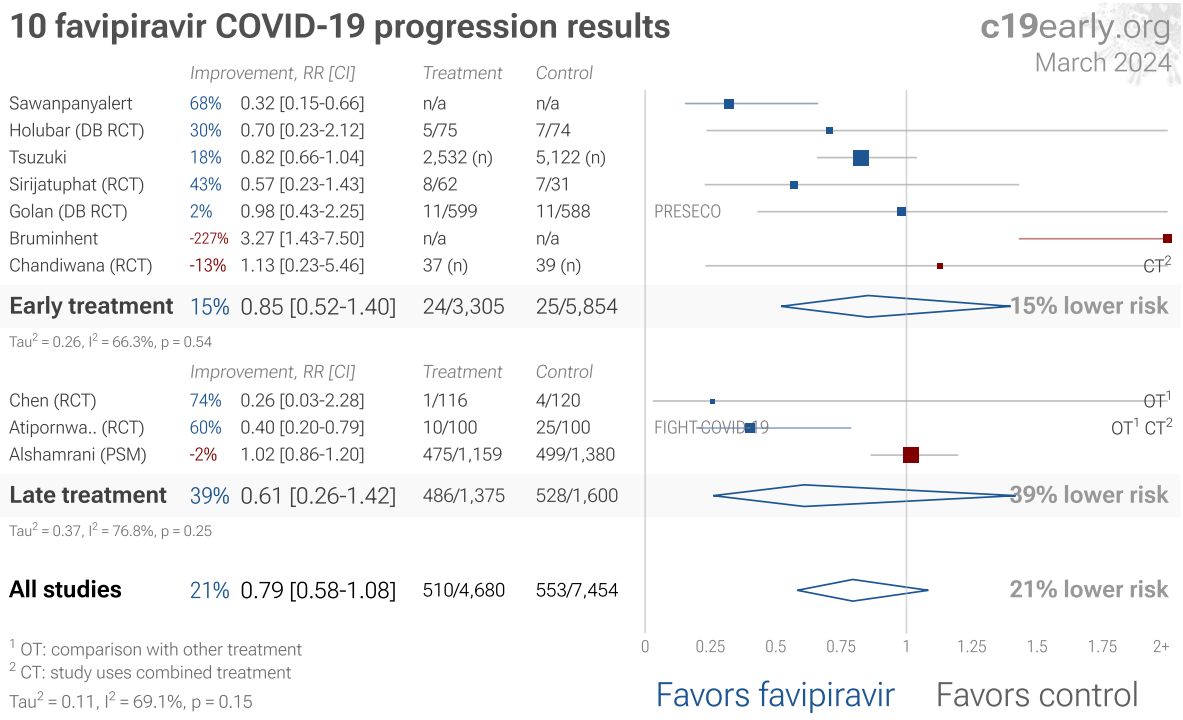


Figure 8. Random effects meta-analysis for progression.

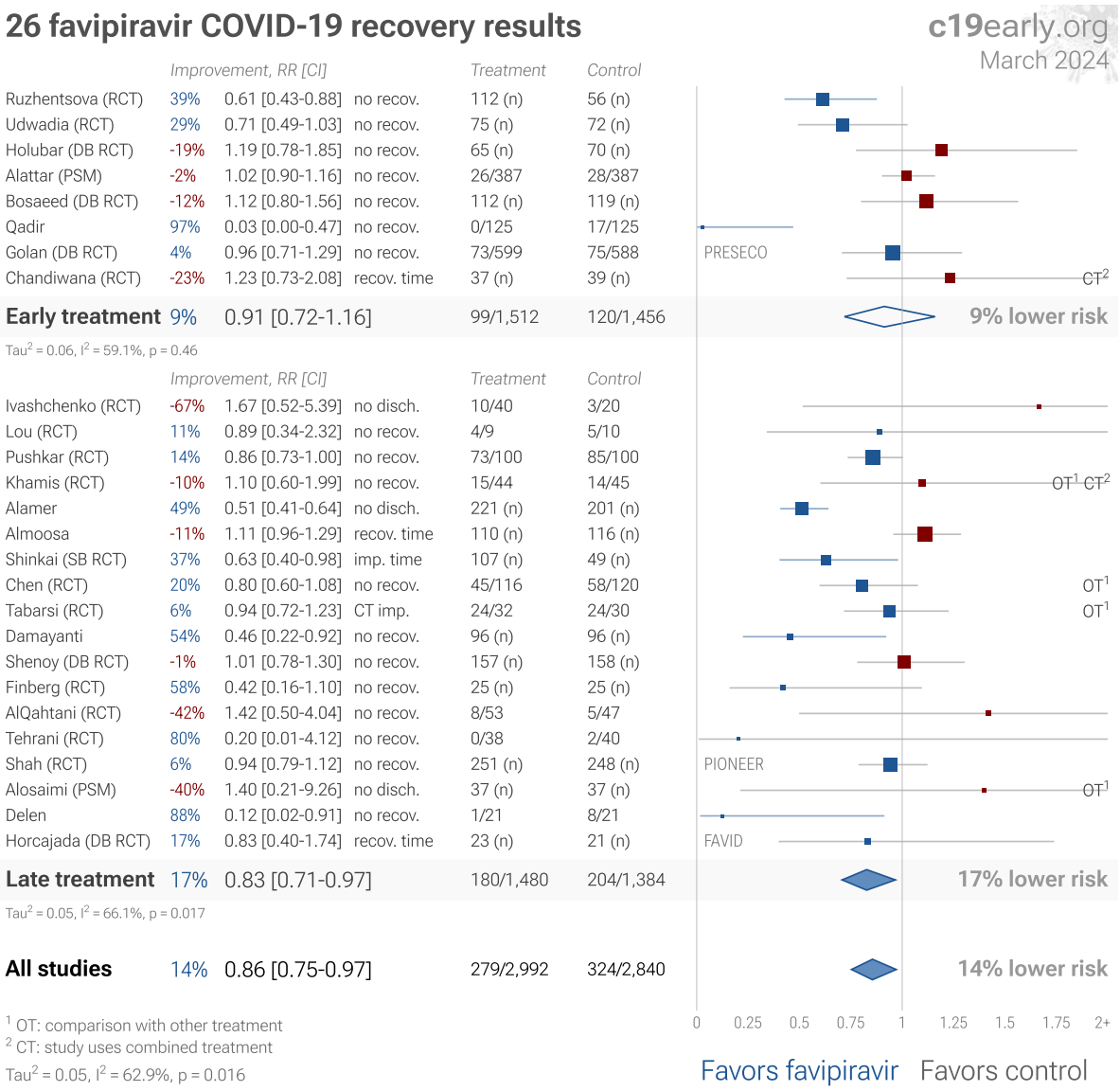


Figure 9. Random effects meta-analysis for recovery.

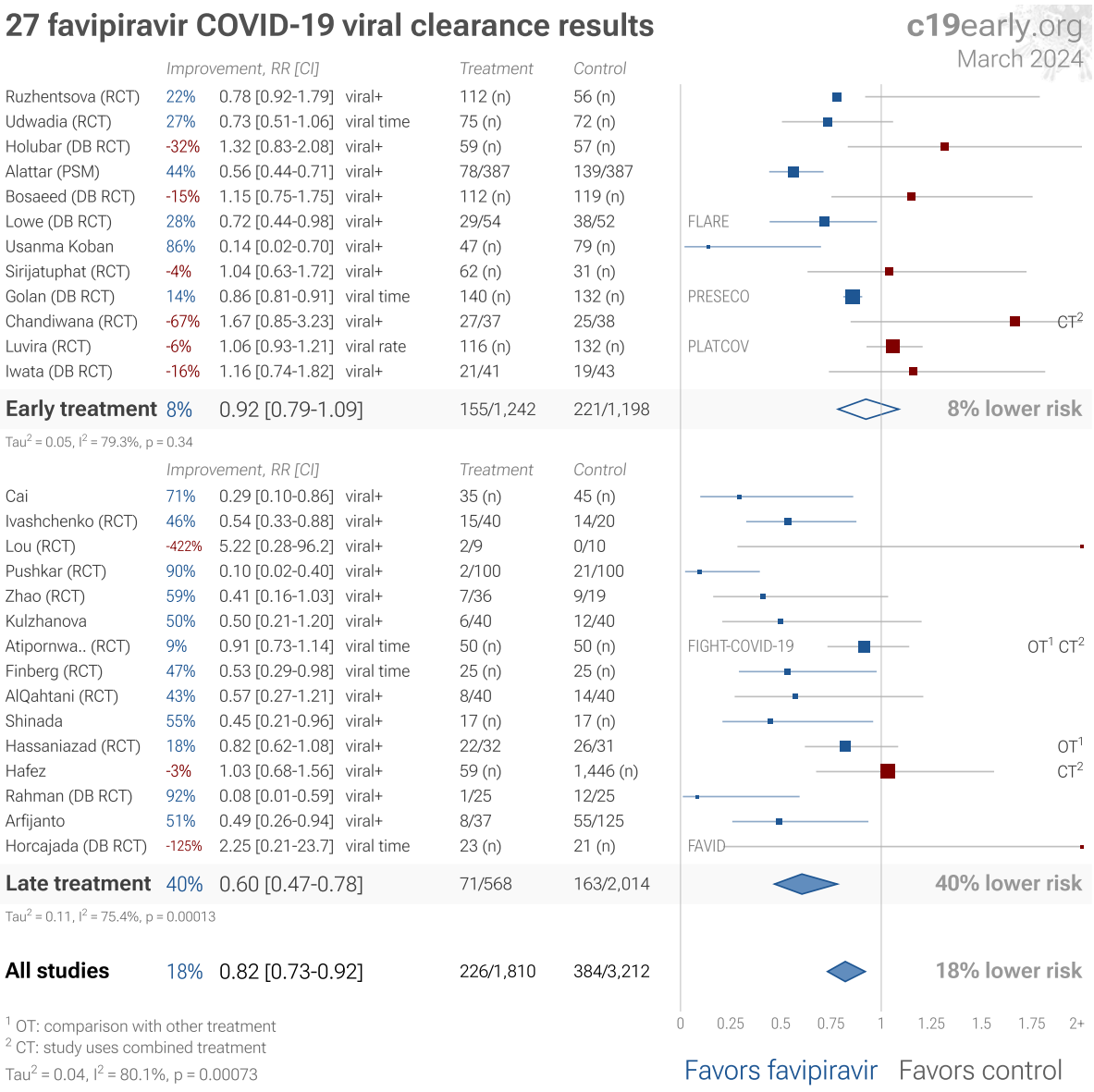


Figure 10. Random effects meta-analysis for viral clearance.

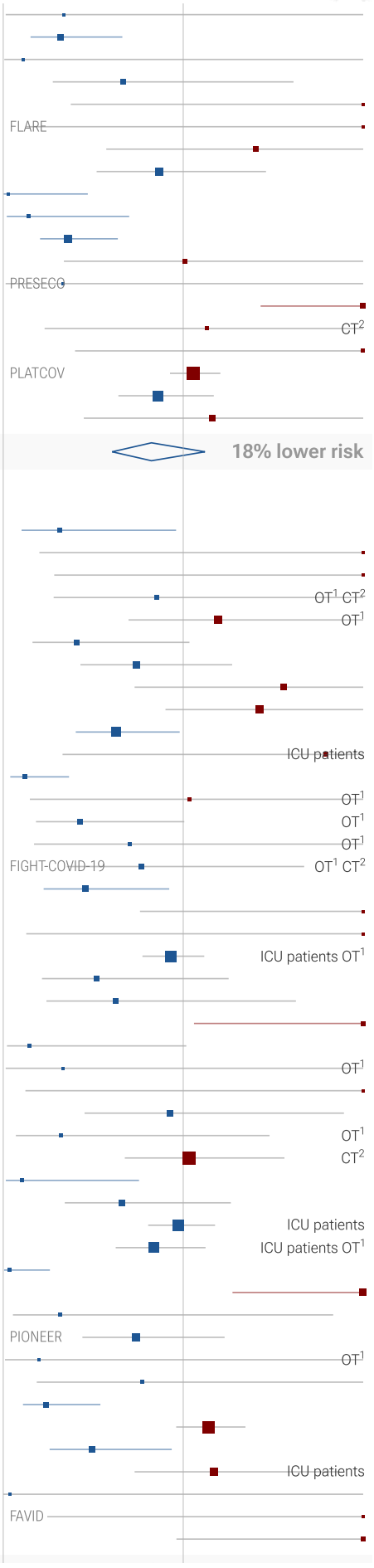
65 favipiravir COVID-19 peer reviewed studies

c19early.org
March 2024

	Improvement	RR [CI]		Treatment	Control
Udwadia (RCT)	66%	0.34 [0.01-8.12]	death	0/73	1/75
Sawanpanyalert	68%	0.32 [0.15-0.66]	progression	n/a	n/a
Holubar (DB RCT)	89%	0.11 [0.01-2.02]	hosp.	0/75	4/74
Alattar (PSM)	33%	0.67 [0.28-1.61]	death	8/387	12/387
Bosaeed (DB RCT)	-619%	7.19 [0.38-138]	ICU	3/112	0/119
Lowe (DB RCT)	-202%	3.02 [0.13-72.6]	ICU	1/59	0/60
Adhikari (RCT)	-40%	1.40 [0.57-3.44]	no improv.	10/38	6/32
Tsuzuki	13%	0.87 [0.52-1.46]	death	2,532 (n)	5,122 (n)
Qadir	97%	0.03 [0.00-0.47]	death	0/125	17/125
Usanma Koban	86%	0.14 [0.02-0.70]	viral+	47 (n)	79 (n)
Sirijatuphat (RCT)	64%	0.36 [0.20-0.64]	improv.	62 (n)	31 (n)
McMahon (RCT)	-1%	1.01 [0.34-3.03]	oxygen	6/99	6/100
Golan (DB RCT)	67%	0.33 [0.01-8.12]	death	0/599	1/588
Bruminhent	-227%	3.27 [1.43-7.50]	progression	n/a	n/a
Chandiwana (RCT)	-13%	1.13 [0.23-5.46]	progression	37 (n)	39 (n)
Vaezi (DB RCT)	-105%	2.05 [0.40-10.6]	hosp.	4/38	2/39
Luvira (RCT)	-6%	1.06 [0.93-1.21]	viral rate	116 (n)	132 (n)
Lokanuwatsatien	14%	0.86 [0.64-1.17]	PASC	400 (n)	402 (n)
Iwata (DB RCT)	-16%	1.16 [0.45-2.21]	oxygen	12/43	12/43
Early treatment	18%	0.82 [0.61-1.12]		44/4,842	61/7,447

$Tau^2 = 0.18$, $I^2 = 63.4\%$, $p = 0.22$

	Improvement	RR [CI]		Treatment	Control
Cai	69%	0.31 [0.10-0.96]	pneumonia	35 (n)	45 (n)
Ivashchenko (RCT)	-300%	4.00 [0.20-79.6]	death	2/40	0/20
Lou (RCT)	-422%	5.22 [0.28-96.2]	ICU	2/9	0/10
Khamis (RCT)	15%	0.85 [0.28-2.59]	death	5/44	6/45
Solaymani.. (RCT)	-19%	1.19 [0.70-2.04]	death	26/190	21/183
Zhao (RCT)	59%	0.41 [0.16-1.03]	viral+	7/36	9/19
Aghajani	26%	0.74 [0.43-1.27]	death	40 (n)	951 (n)
Alamer	-56%	1.56 [0.73-3.36]	death	12/233	21/223
Almoosa	-42%	1.42 [0.90-2.25]	death	33/110	24/116
Shinkai (SB RCT)	37%	0.63 [0.40-0.98]	imp. time	107 (n)	49 (n)
Assiri (ICU)	-79%	1.79 [0.33-8.02]	death	11/67	3/51
Kulzhanova	88%	0.12 [0.04-0.37]	no improv.	3/40	25/40
Chen (RCT)	-3%	1.03 [0.15-7.22]	ICU	2/116	2/120
Alotaibi	57%	0.43 [0.18-1.01]	death	244 (n)	193 (n)
Tabarsi (RCT)	30%	0.70 [0.17-2.88]	death	3/32	4/30
Atipornwa.. (RCT)	23%	0.77 [0.35-1.67]	death	10/100	13/100
Damayanti	54%	0.46 [0.22-0.92]	no recov.	96 (n)	96 (n)
Chuah (RCT)	-1154%	12.54 [0.76-208]	death	5/250	0/250
Finberg (RCT)	-200%	3.00 [0.13-70.3]	death	1/25	0/25
Al Mutair (ICU)	7%	0.93 [0.77-1.12]	death	119/269	128/269
Kurniyanto	48%	0.52 [0.22-1.25]	death	10/325	9/152
Cilli	38%	0.62 [0.24-1.63]	death	5/23	8/23
Al-Muhsen	-263%	3.63 [1.06-12.4]	death	156 (n)	442 (n)
Yulia	85%	0.15 [0.02-1.02]	death	432 (all patients)	
Uyaroğlu (PSM)	67%	0.33 [0.01-7.96]	death	0/42	1/42
AlQahtani (RCT)	-196%	2.96 [0.12-71.1]	death	1/54	0/52
Shinada	7%	0.93 [0.45-1.89]	hosp.	17 (n)	17 (n)
Hassaniazad (RCT)	68%	0.32 [0.07-1.48]	death	2/32	6/31
Hafez	-3%	1.03 [0.68-1.56]	viral+	59 (n)	1,446 (n)
Rahman (DB RCT)	89%	0.11 [0.01-0.75]	no improv.	1/19	8/16
Tehrani (RCT)	34%	0.66 [0.34-1.26]	hosp.	10/38	16/40
Abdulrahman (ICU)	3%	0.97 [0.81-1.18]	death	74/193	593/1,506
Acar Sevinc (ICU)	16%	0.84 [0.62-1.12]	death	57/85	12/15
Tawfik	96%	0.04 [0.00-0.26]	death	1/103	17/62
Babayigit	-184%	2.84 [1.27-6.14]	ventilation	47/325	17/977
Behboodikhah	68%	0.32 [0.05-1.83]	death	95 (n)	2,079 (n)
Shah (RCT)	26%	0.74 [0.44-1.23]	death	26/251	34/248
Alosaimi (PSM)	80%	0.20 [0.01-4.03]	death	0/37	2/37
Delen	23%	0.77 [0.19-3.20]	ICU	3/34	4/35
Hartantri	76%	0.24 [0.11-0.54]	death	n/a	n/a
Alshamrani (PSM)	-14%	1.14 [0.96-1.35]	death	326/1,159	316/1,380
Arfijanto	51%	0.49 [0.26-0.94]	viral+	8/37	55/125
Sulaiman (ICU)	-17%	1.17 [0.73-1.87]	death	73 (n)	73 (n)
Shamsi	96%	0.04 [0.00-3.01]	death	0/19	24/164
Horcajada (DB RCT)	-383%	4.83 [0.24-95.1]	death	2/23	0/21
Saito	-168%	2.68 [0.96-7.48]	death	7/40	6/92



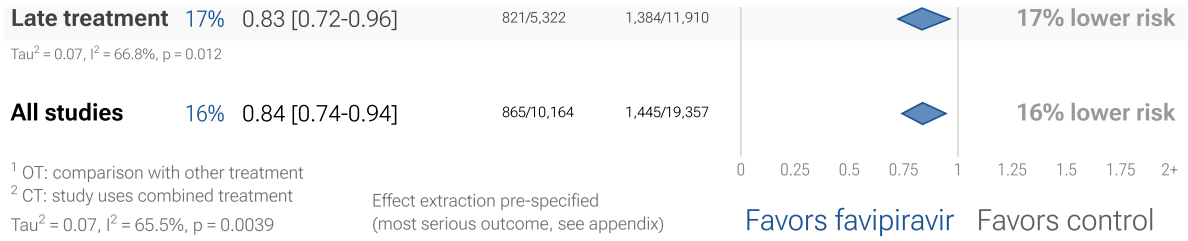


Figure 11. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with 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 12 shows a comparison of results for RCTs and non-RCT studies. Figure 13, 14, and 15 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.

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases *Jadad*, and analysis of double-blind RCTs has identified extreme levels of bias *Gøtzsche*. 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, 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 66 treatments we have analyzed, 63% 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).

RCT bias for widely available treatments. RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for favipiravir are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see *Deaton, Nichol*.

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

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.

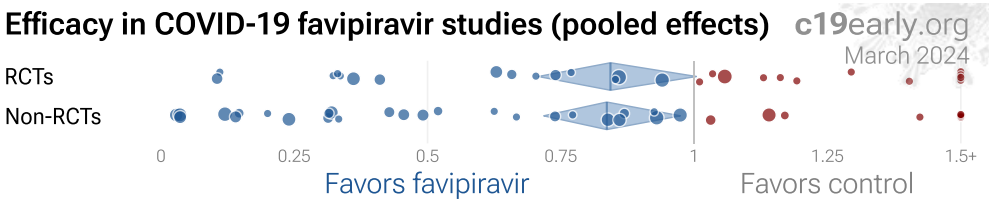


Figure 12. **Results for RCTs and non-RCT studies.**

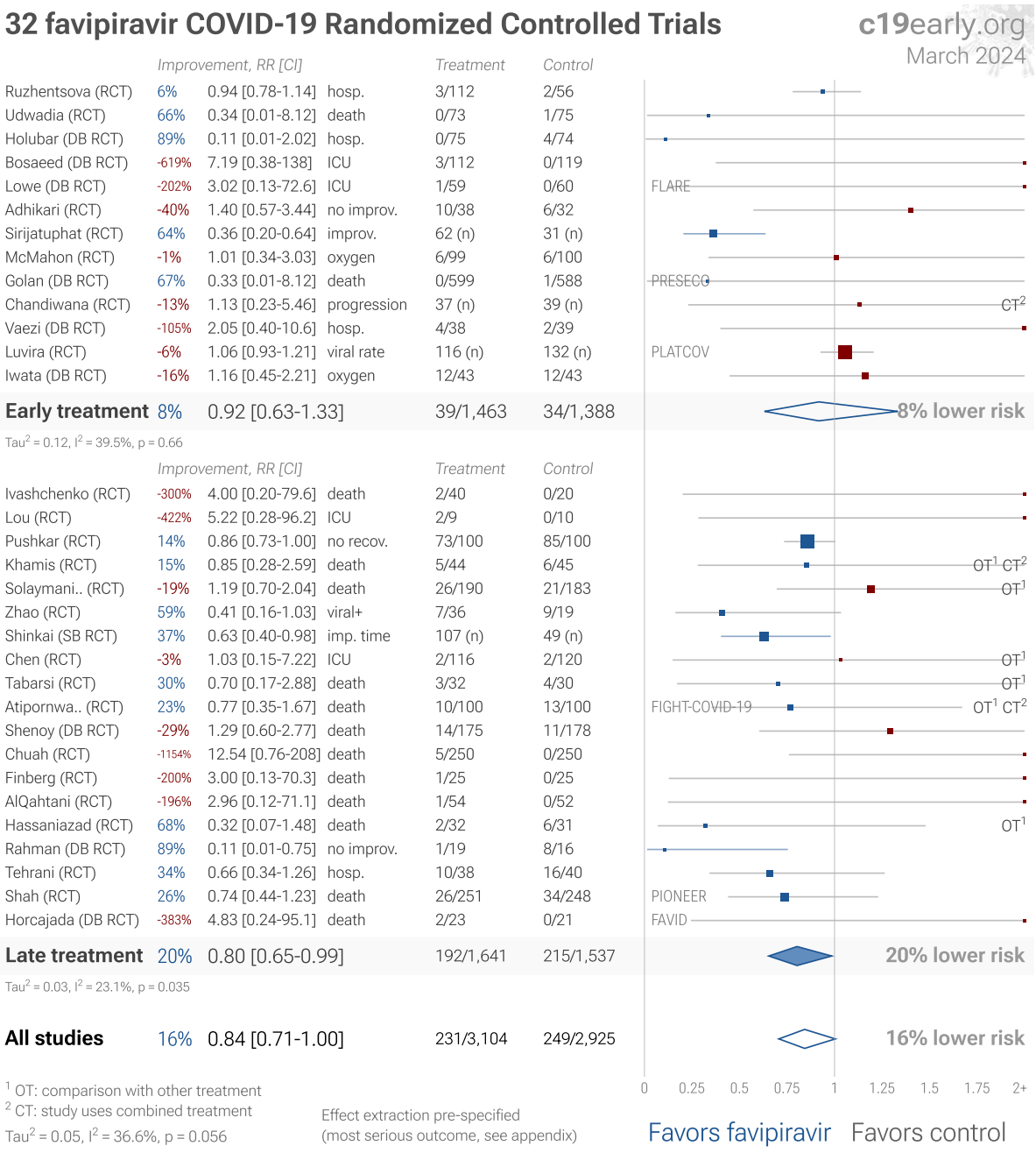


Figure 13. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

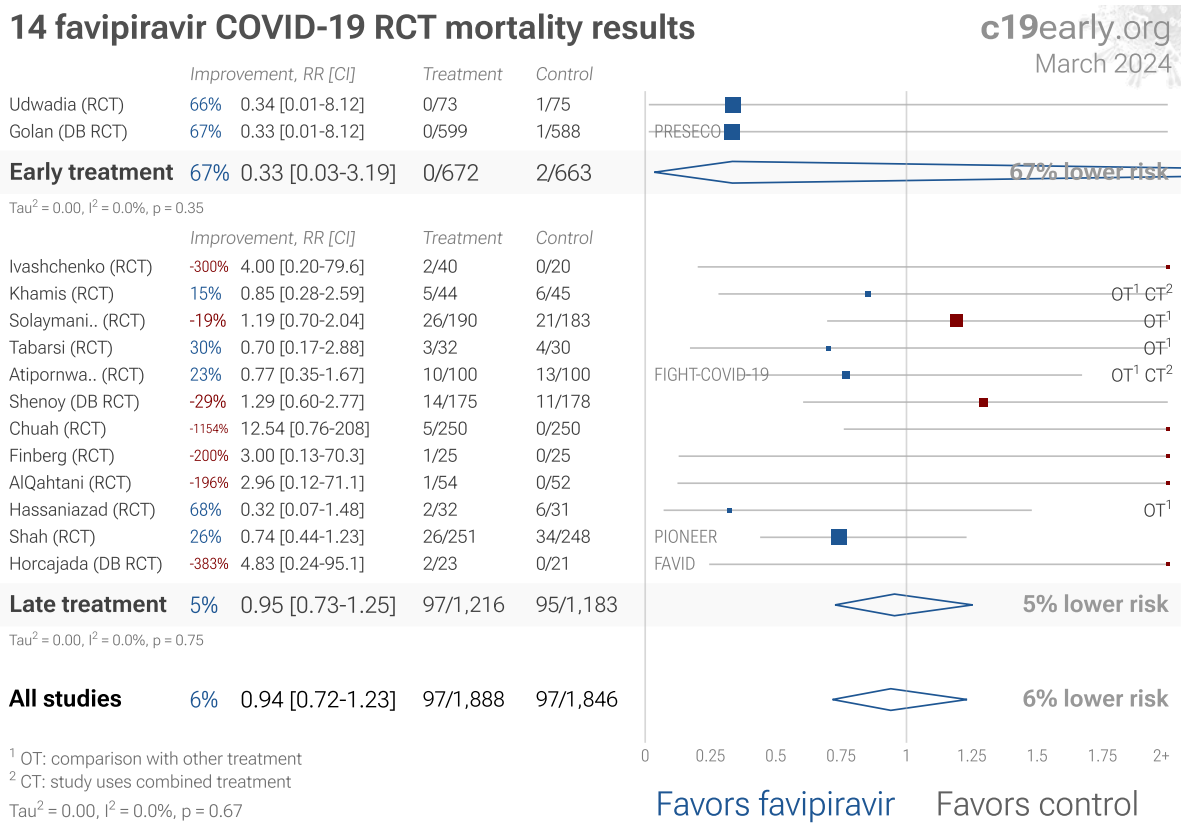


Figure 14. Random effects meta-analysis for RCT mortality results.

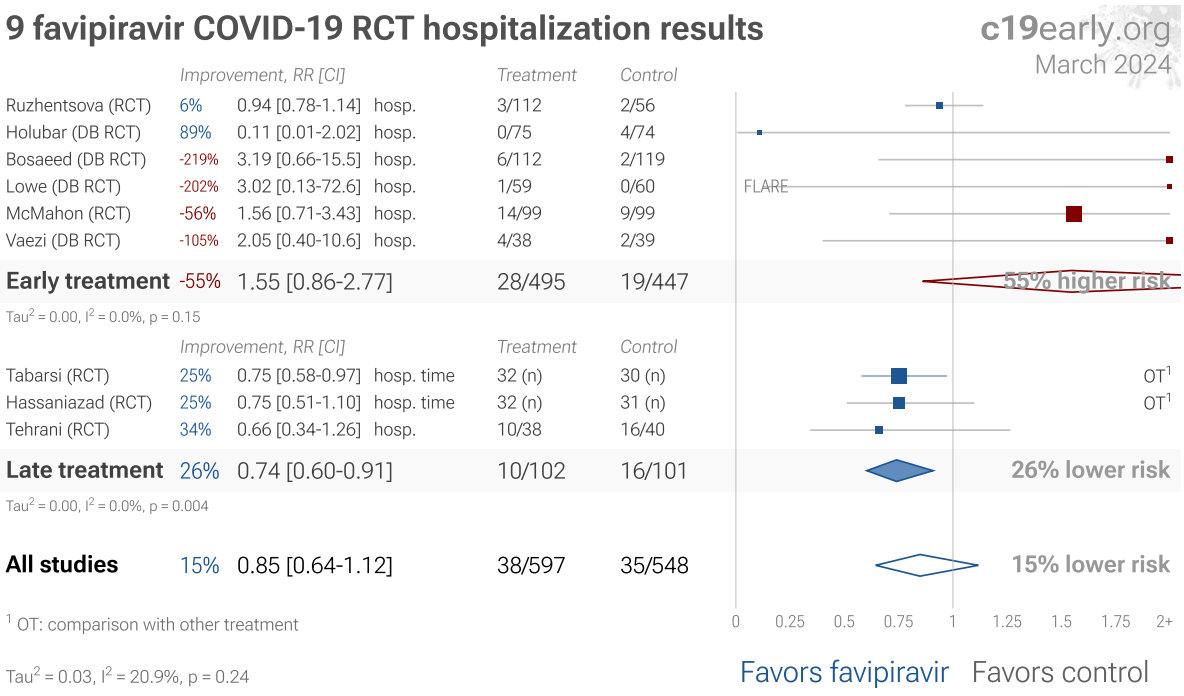


Figure 15. Random effects meta-analysis for RCT hospitalization results.

Unreported RCTs

1 favipiravir RCT has not reported results [Kara]. The trial reports total actual enrollment of 1,008 patients. The result is delayed over 2 years.

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 may underemphasize serious issues not captured in the checklists, overemphasize issues unlikely to alter outcomes in specific cases (for example, lack of blinding for an objective mortality outcome, or certain specifics of randomization with a very large effect size), and can be easily influenced by potential bias.

The studies excluded are as below. Figure 16 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Abdulrahman, very late stage, ICU patients.

Acar Sevinc, very late stage, ICU patients.

Al Mutair, very late stage, ICU patients.

Arfijanto, unadjusted results with no group details.

Assiri, unadjusted results with no group details; very late stage, ICU patients.

Babayigit, substantial unadjusted confounding by indication possible.

Cilli, unadjusted results with no group details.

Damayanti, minimal details provided.

Khamis, study compares against another treatment showing significant efficacy.

Kurniyanto, unadjusted results with no group details.

Lokanuwatsatien, unadjusted results with no group details.

Saito, unadjusted results with no group details.

Shamsi, unadjusted results with no group details.

Sulaiman, very late stage, ICU patients.

Tawfik, unadjusted results with minimal group details.

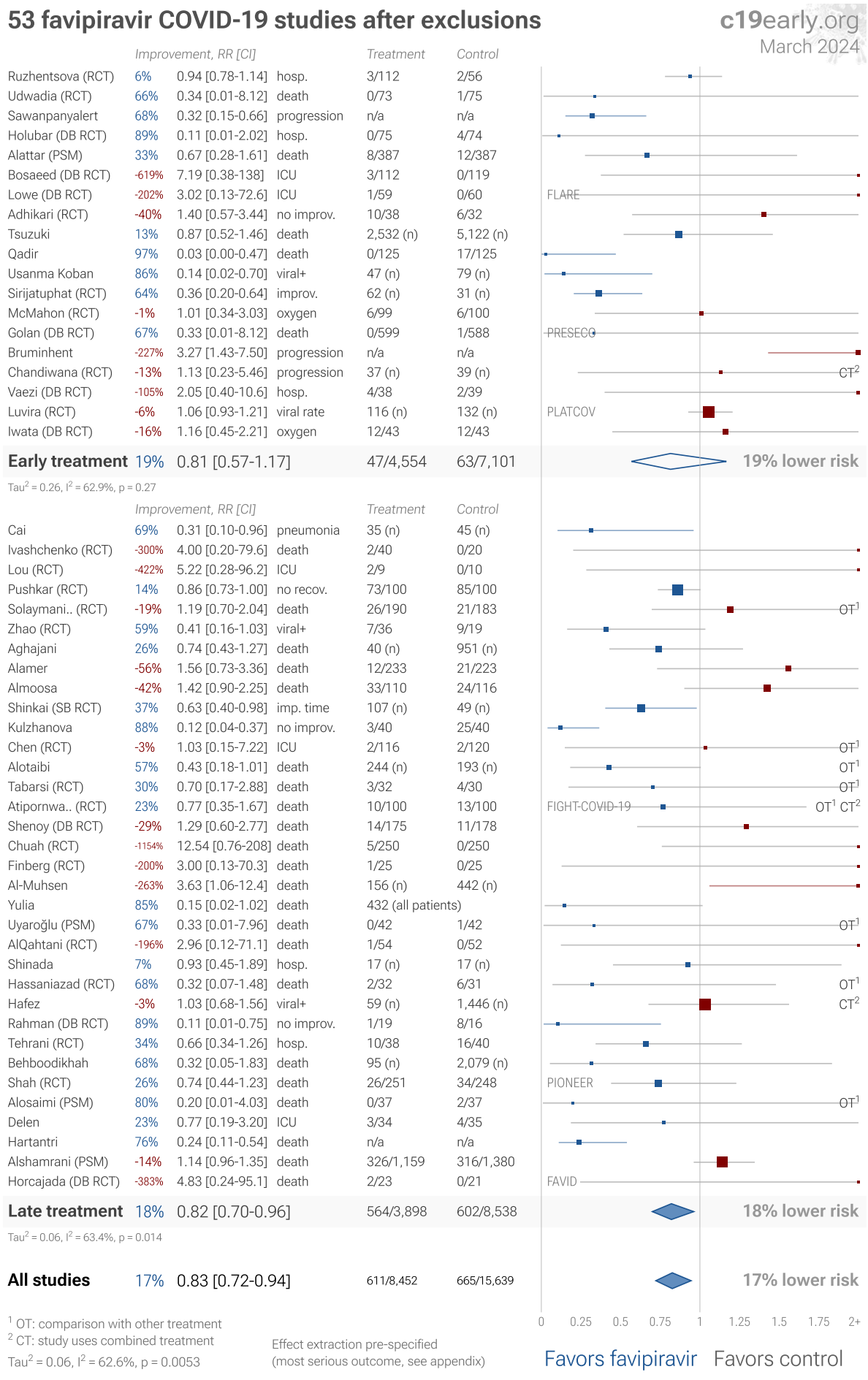


Figure 16. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific

outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction 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 *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* 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* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	*Result*
Post exposure prophylaxis	86% fewer cases *Ikematsu*
<24 hours	-33 hours symptoms *Hayden*
24-48 hours	-13 hours symptoms *Hayden*
Inpatients	-2.5 hours to improvement *Kumar*

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

Figure 17 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

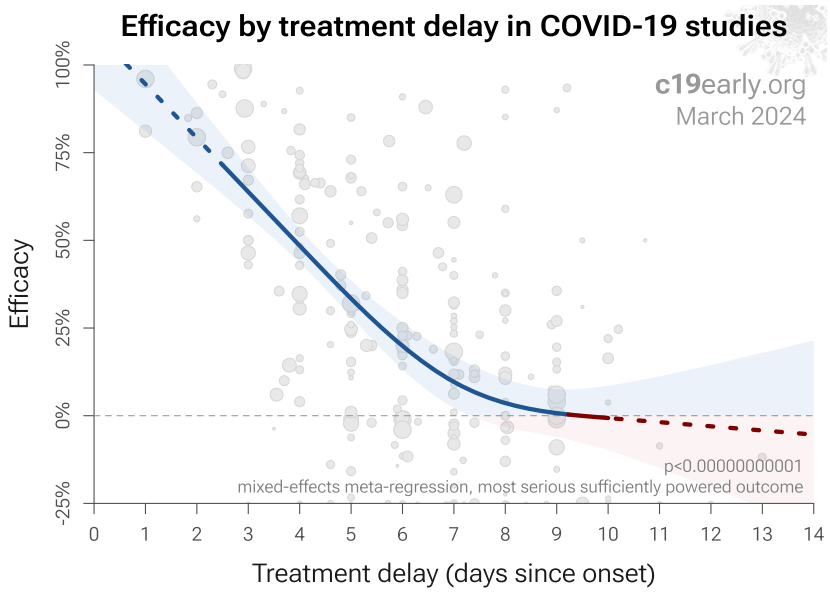


Figure 17. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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 (as in *López-Medina*).

Effect measured. Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

Variants. There are many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics *Faria, Karita, Nonaka, Zavascki*. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective *Peacock, Willett*.

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

Other treatments. The use of other treatments may significantly affect outcomes, including anything from supplements, other medications, or other kinds of treatment such as prone positioning.

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

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 18. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

Pooled outcomes identify efficacy faster. Currently, 44 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 treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

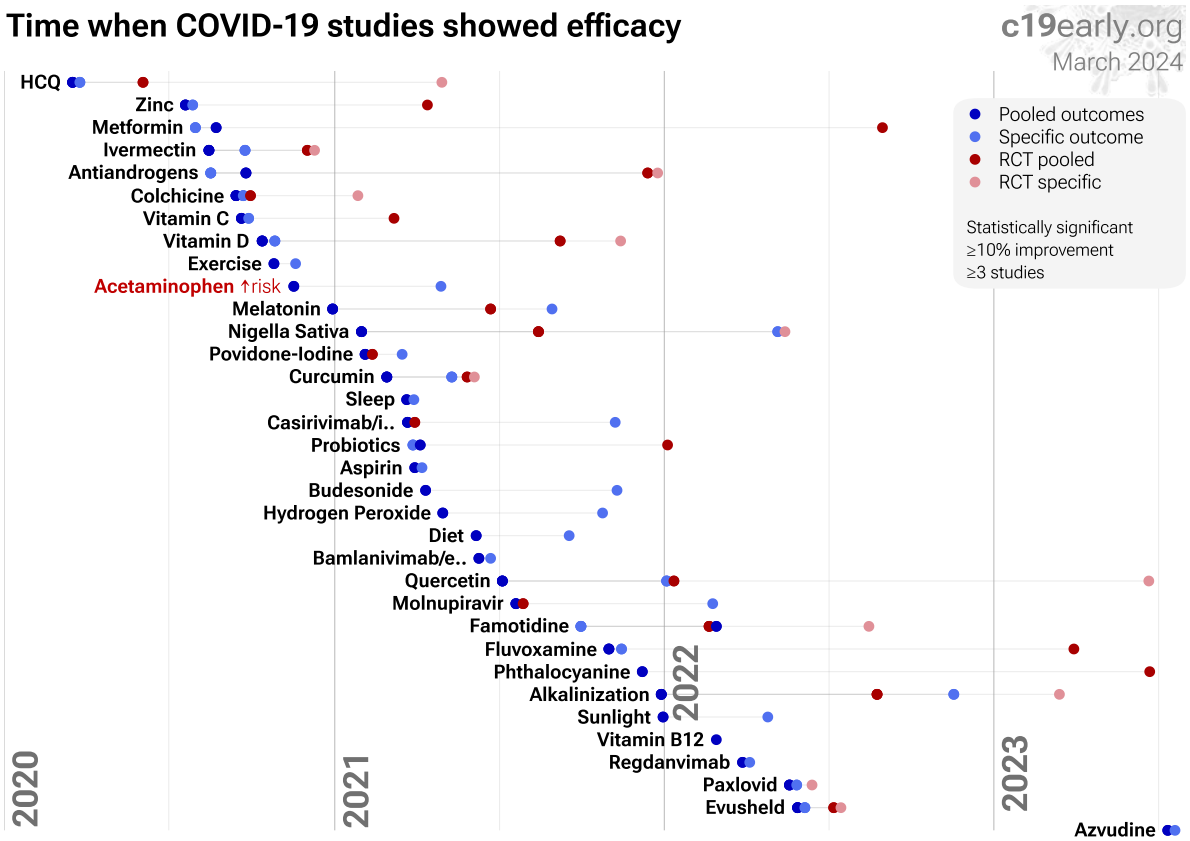


Figure 18. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

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. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

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.

Discussion

Publication bias. Publishing is often biased towards positive results, however evidence suggests that there may be a negative bias for inexpensive treatments for COVID-19. Both negative and positive results are very important for COVID-19, media in many countries prioritizes negative results for inexpensive treatments (inverting the typical incentive for scientists that value media recognition), and there are many reports of difficulty publishing positive results *Boulware, Meeus, Meneguesso*.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 19 shows a scatter plot of results for prospective and retrospective studies. 36% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 51% of prospective studies, consistent with a bias toward publishing negative results.

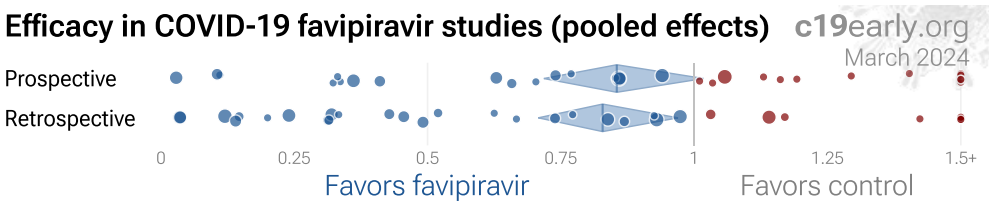


Figure 19. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 20 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 $p < 0.05$ *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. 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.

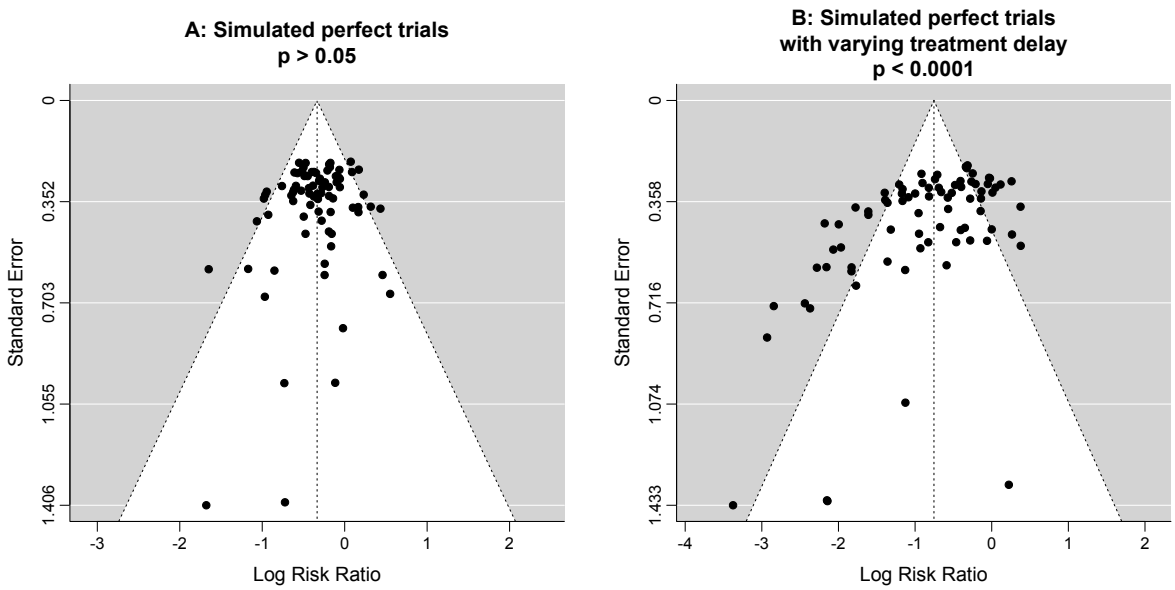


Figure 20. Example funnel plot analysis for simulated perfect trials.

Conflicts of interest. Pharmaceutical drug trials often have conflicts of interest whereby sponsors or trial staff have a financial interest in the outcome being positive. Favipiravir for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 favipiravir trials have been run by physicians on the front lines with the primary goal of finding the best methods to save human lives and minimize the collateral damage caused by COVID-19. While pharmaceutical companies are careful to run trials under optimal conditions (for example, restricting patients to those most likely to benefit, only including patients that can be treated soon after onset when necessary, and ensuring accurate dosing), not all favipiravir trials represent the optimal conditions for efficacy.

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 by 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 affiliated with special interests 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 *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. 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, vaccine, 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. 11 of the 68 studies compare against other treatments, which may reduce the effect seen. 4 of 68 studies combine treatments. The results of favipiravir alone may differ. 3 of 32 RCTs use combined treatment.

Reviews. Multiple reviews cover favipiravir for COVID-19, presenting additional background on mechanisms and related results, including *Bacigalupo, Hadj Hassine, Waters, Zhirnov*.

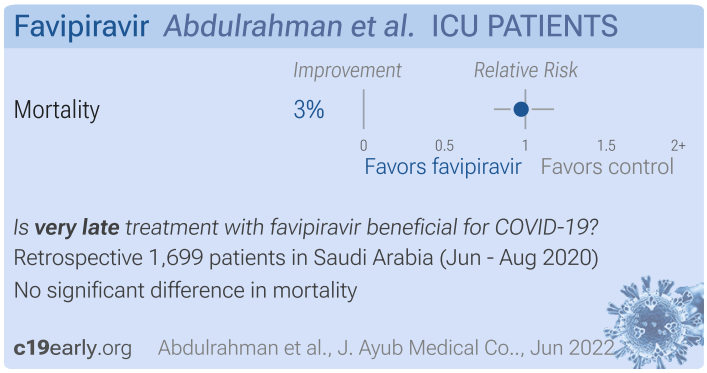
Conclusion

Statistically significant lower risk is seen for recovery and viral clearance. 30 studies from 30 independent teams in 16 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 15% [5-24%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Studies to date show no significant difference for mortality. A small mortality improvement is seen, without statistical significance, however meta regression with followup duration shows decreasing efficacy with longer followup. There is also no benefit seen for mechanical ventilation, ICU admission, or hospitalization. This may reflect antiviral efficacy being offset by side effects of treatment.

Potential risks of the mechanism of action include the creation of dangerous variants, and mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity *Hadj Hassine, Waters, Zhirnov*. Favipiravir may impair clotting *Gül*.

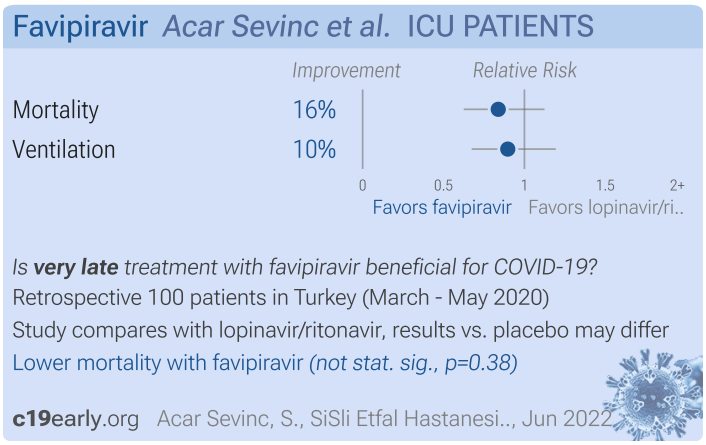
Study Notes

Abdulrahman



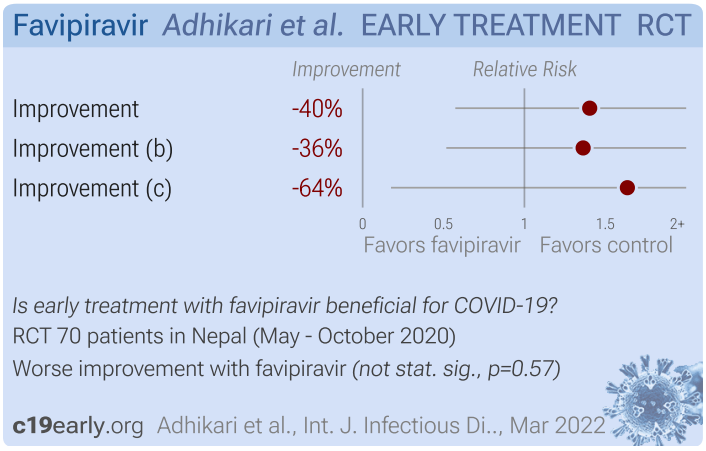
Abdulrahman: Retrospective 1,699 ICU patients in Saudi Arabia, 193 treated with favipiravir, showing no significant difference in mortality.

Acar Sevinc



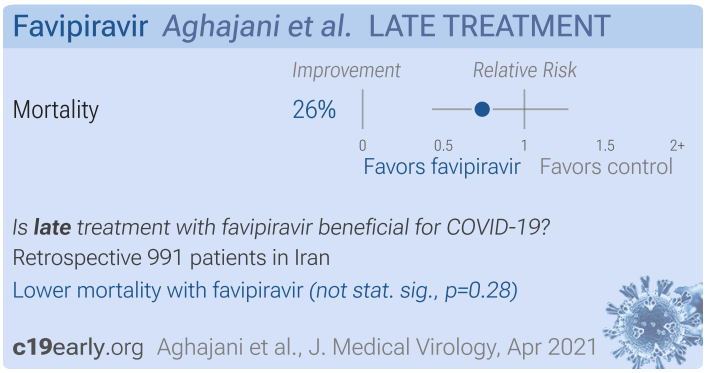
Acar Sevinc: Retrospective 100 ICU patients in Turkey, showing improved survival with favipiravir vs. lopinavir/ritonavir.

Adhikari



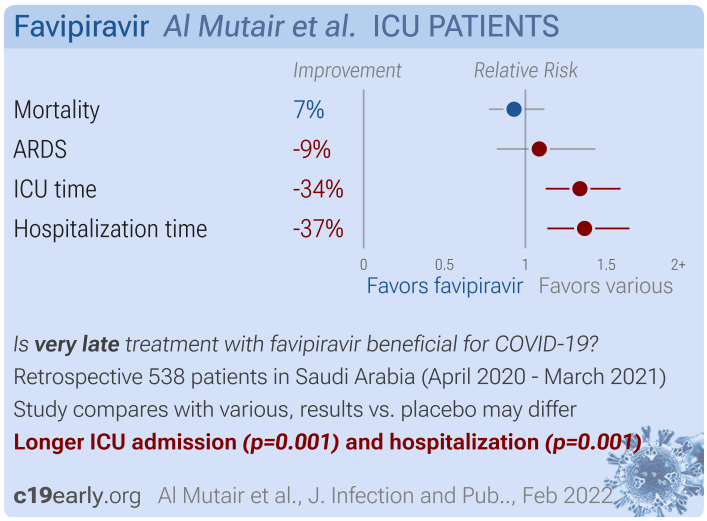
Adhikari: Preliminary report for an RCT in Nepal with 38 favipiravir patients and 32 control patients, showing no significant differences. There were no serious side effects.

Aghajani



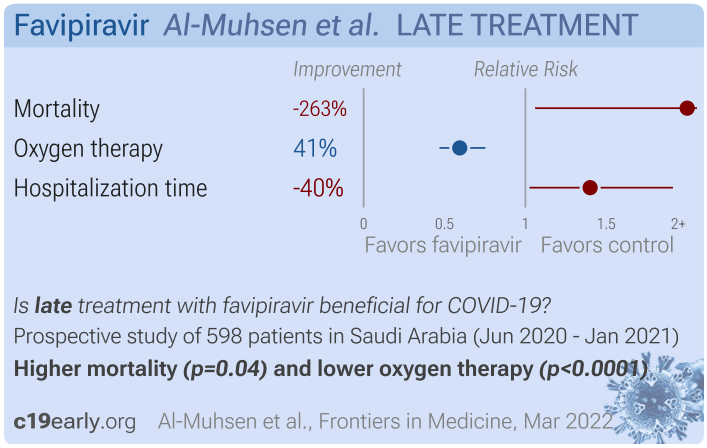
Aghajani: Retrospective 991 hospitalized patients in Iran focusing on aspirin use but also showing results for HCQ, remdesivir, and favipiravir.

Al Mutair



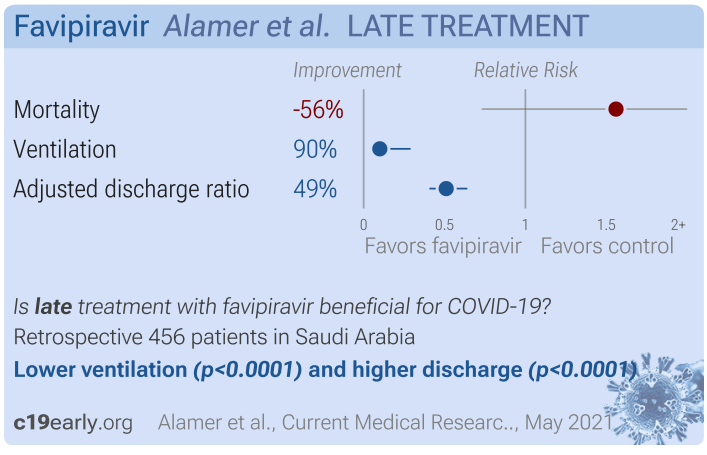
Al Mutair: Retrospective 269 favipiravir ICU patients in Saudi Arabia and 269 matched controls receiving different treatments, showing no significant difference.

Al-Muhsen



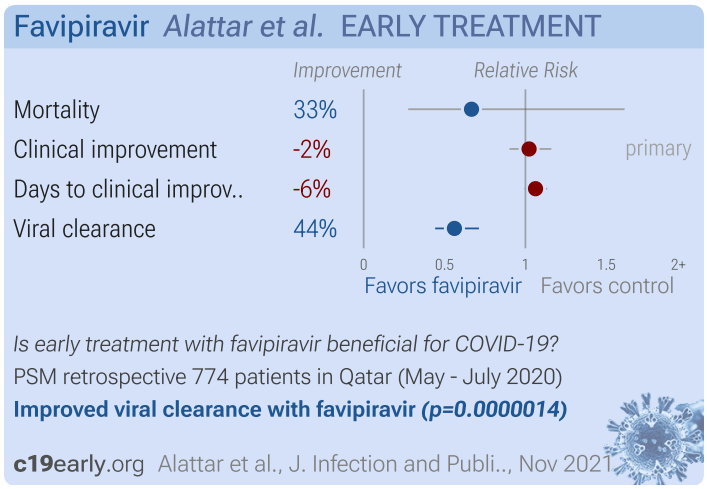
Al-Muhsen: Prospective observational study of 598 hospitalized patients in Saudi Arabia, showing higher risk of mortality and longer hospitalization time with favipiravir.

Alamer



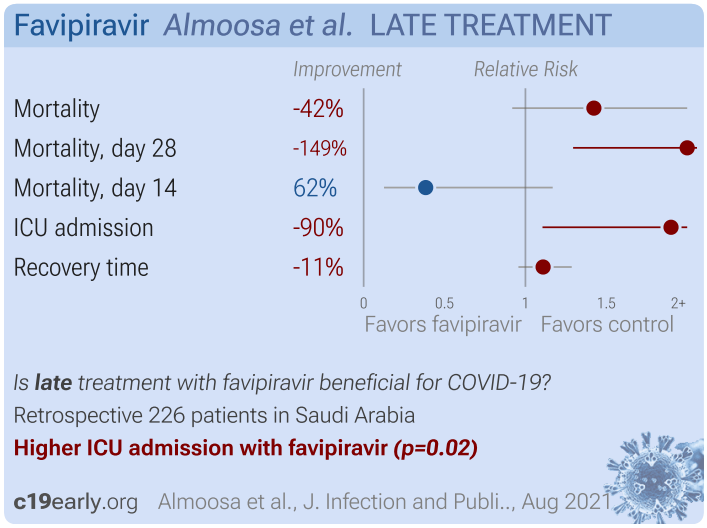
Alamer: Retrospective 234 favipiravir and 223 control patients in Saudi Arabia, showing shorter time to discharge and lower progression to ventilation, but no significant difference in mortality.

Alattar



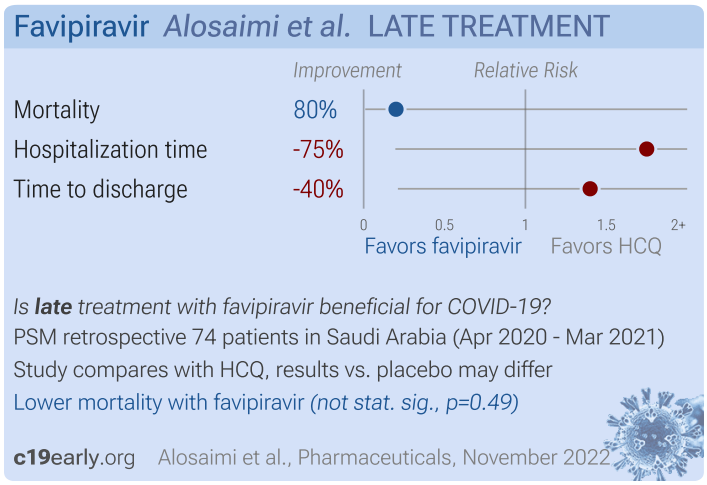
Alattar: PSM retrospective with 1,493 patients, showing significantly improved viral clearance with favipiravir. There were no significant differences in clinical improvement or mortality. Mortality was lower (2.1% vs 3.1%), without statistical significance with the small number of events.

Almoosa



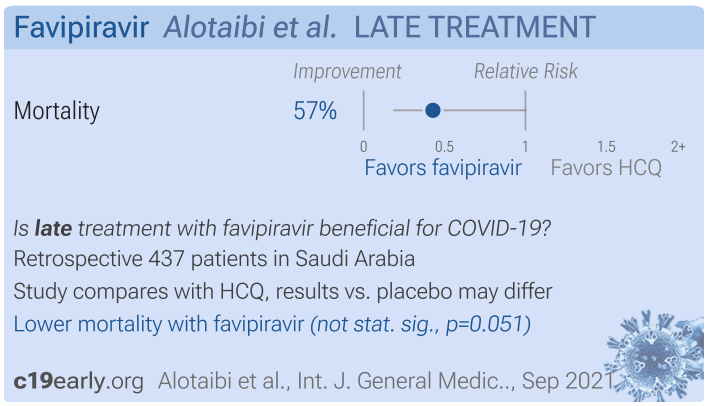
Almoosa: Retrospective 226 COVID-19 pneumonia patients, 110 treated with favipiravir, showing higher mortality (p=0.1) and ICU admission (p=0.02) with treatment in multivariate analysis.

Alosaimi



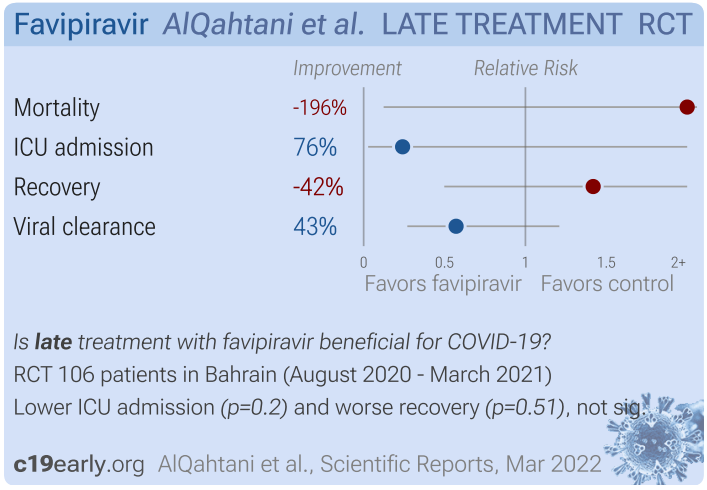
Alosaimi: Retrospective 200 hospitalized COVID-19 patients in Saudi Arabia, showing no significant difference in outcomes between HCQ and favipiravir.

Alotaibi



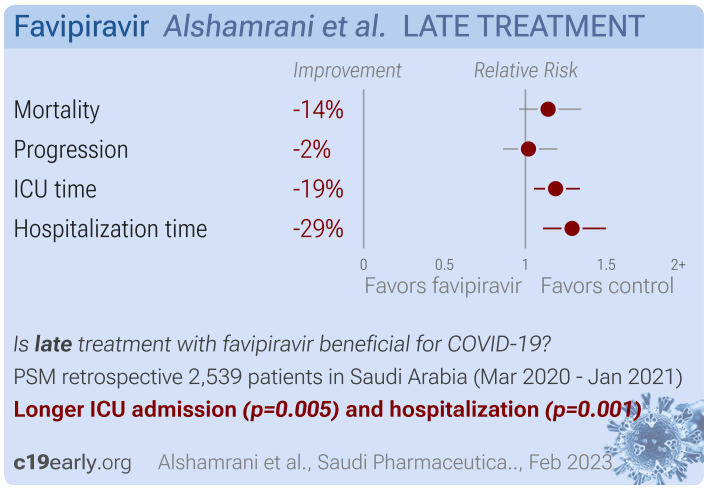
Alotaibi: Retrospective hospitalized patients in Saudi Arabia, showing lower mortality with favipiravir compared to HCQ, not quite reaching statistical significance. Authors do not indicate the factors behind which therapy was chosen. May be subject to significant confounding by indication and confounding by time.

AlQahtani



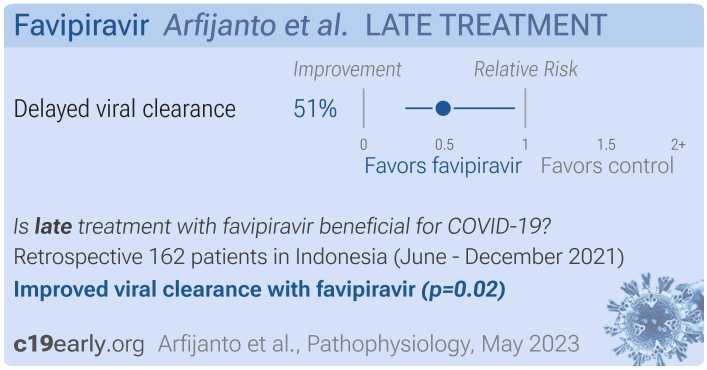
AlQahtani: RCT with 54 favipiravir, 51 HCQ, and 52 SOC hospitalized patients in Bahrain, showing no significant differences. Viral clearance improved with both treatments, but did not reach statistical significance with the small sample size.

Alshamrani



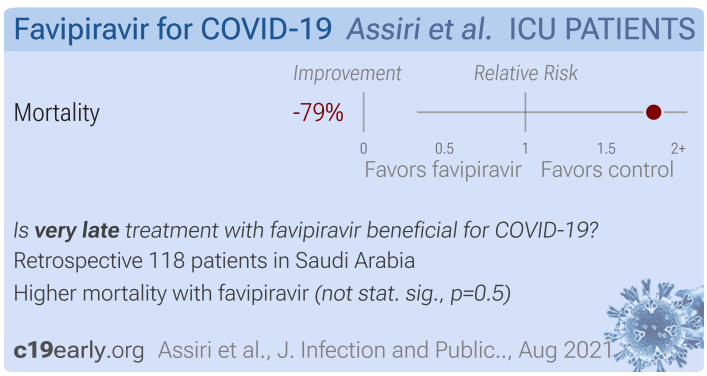
Alshamrani: PSM retrospective 29 hospitals in Saudi Arabia, showing higher mortality with favipiravir treatment, without statistical significance.

Arfijanto



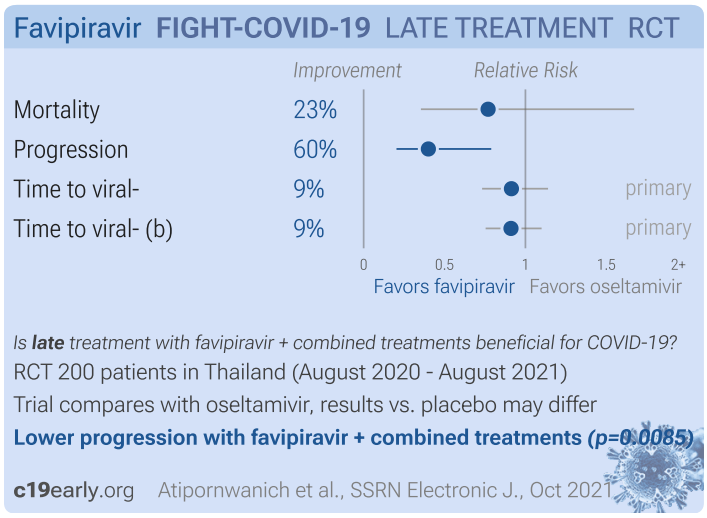
Arfijanto: Retrospective 162 hospitalized COVID-19 patients in Indonesia, showing lower incidence of delayed viral clearance with favipiravir treatment in unadjusted results.

Assiri



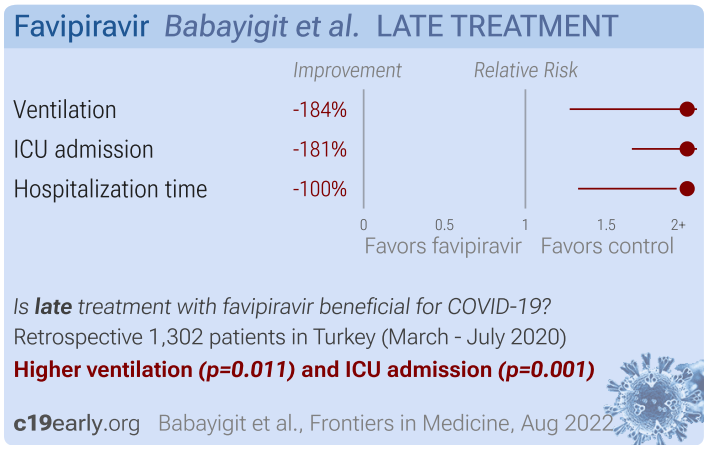
Assiri: Retrospective 118 ICU patients in Saudi Arabia showing no significant differences in unadjusted results with zinc, vitamin D, and favipiravir treatment.

Atipornwanich



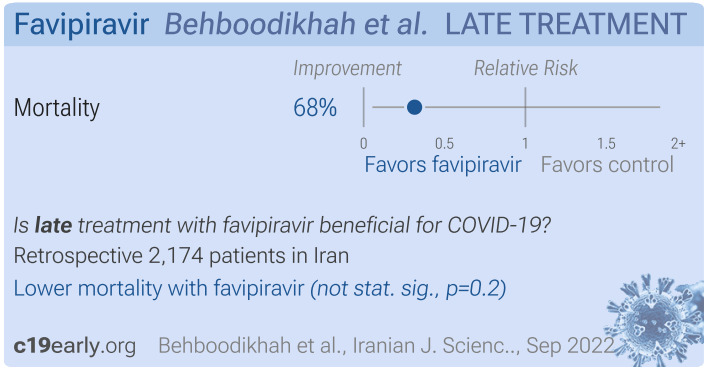
Atipornwanich: RCT 200 moderate/severe patients in Thailand, showing significantly lower progression with favipiravir vs. oseltamivir. NCT04303299.

Babayigit



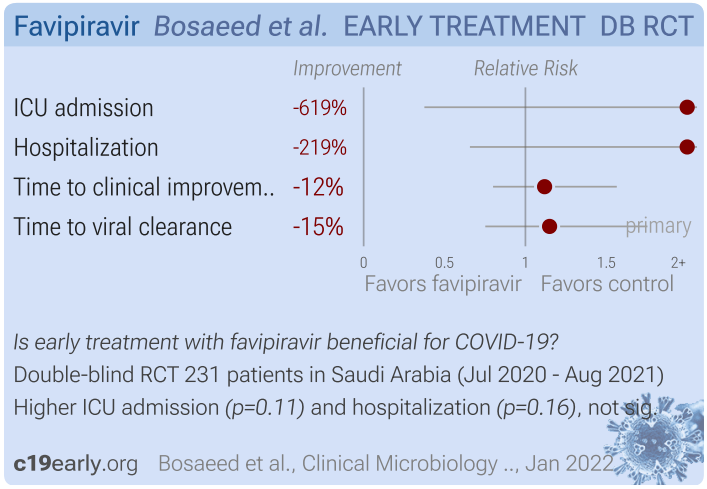
Babayigit: Retrospective 1,472 hospitalized patients in Turkey, showing a higher ICU admission and ventilation with favipiravir. Results may be subject to confounding by indication.

Behboodikhah



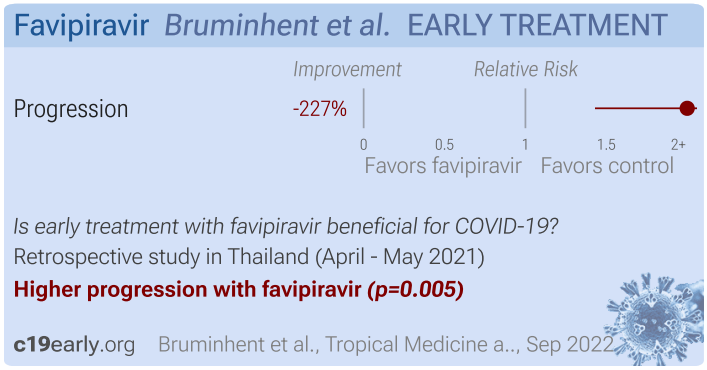
Behboodikhah: Retrospective 2,174 hospitalized patients showing significantly shorter length of stay with favipiravir treatment.

Bosaeed



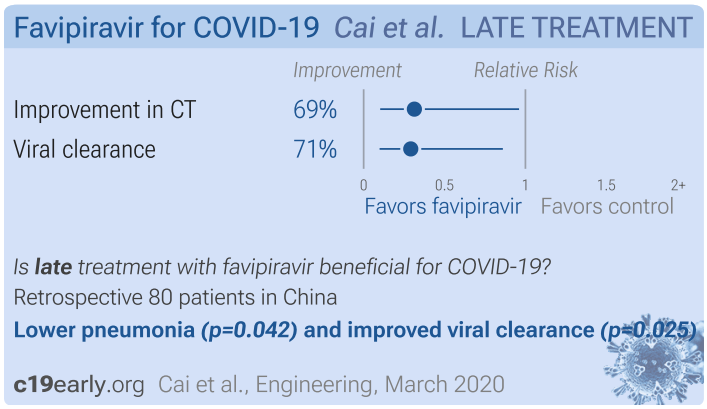
Bosaeed: RCT with 112 favipiravir and 119 control patients showing no significant differences in outcomes. Viral clearance and clinical recovery for patients treated within 48 hours was better than those treated later. NCT04464408.

Bruminhent



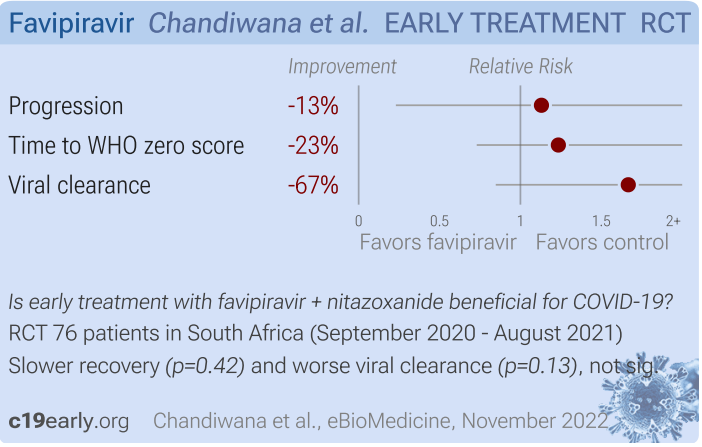
Bruminhent: Retrospective 514 patients in Thailand, showing higher risk of progression with favipiravir treatment.

Cai



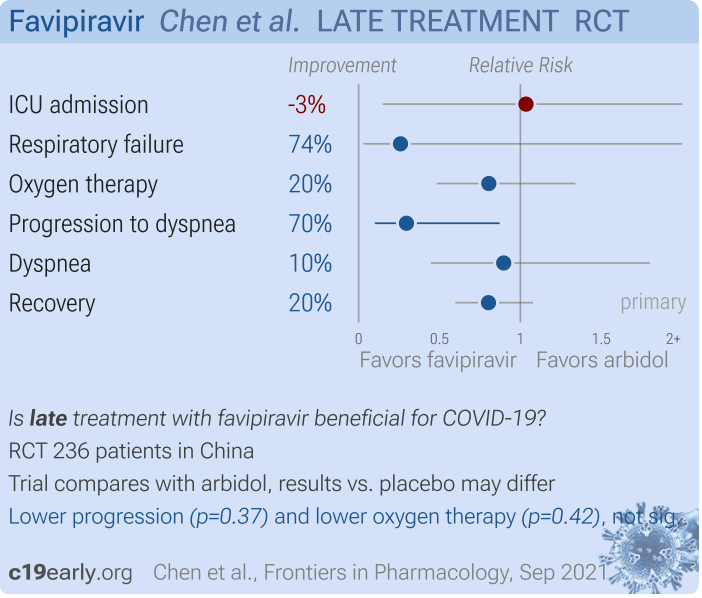
Cai: Comparison of 35 FPV patients and 35 LPV/RTV patients, showing significant improvements in chest CT and faster viral clearance with FPV.

Chandiwana



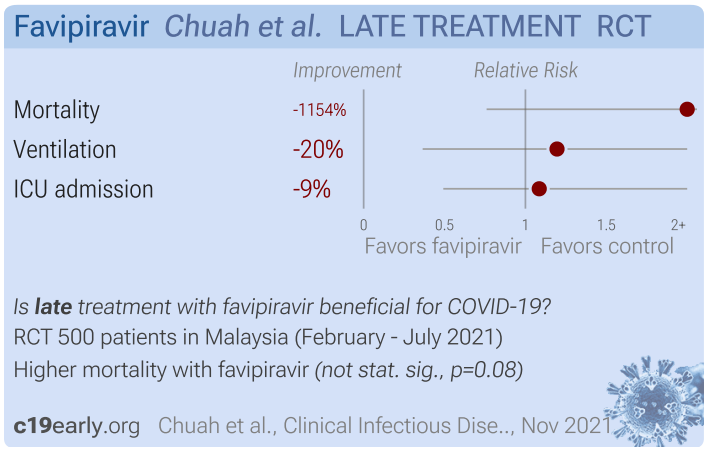
Chandiwana: Very high COI low-risk patient RCT in South Africa, showing no significant differences with favipiravir plus nitazoxanide. There were no deaths and no COVID-19 hospitalizations for favipiravir plus nitazoxanide. More patients were seropositive at baseline in the treatment arm (28% vs 22%). Favipiravir 1600mg 12-hourly for 1 day, then 600mg 12-hourly for 6 days. Nitazoxanide 1000mg 12-hourly for 7 days.

Chen



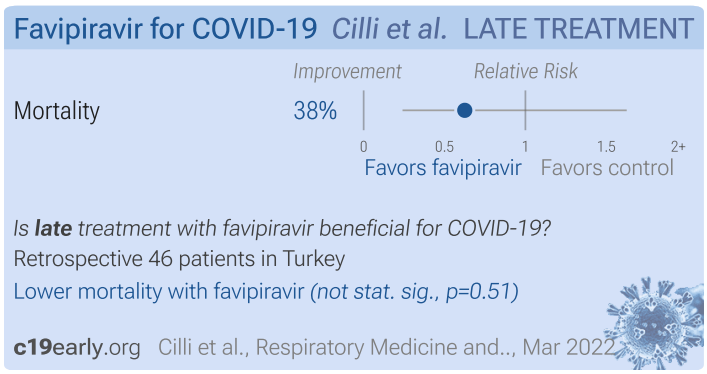
Chen: Very late stage (9 days from symptom onset) RCT with 116 favipiravir patients and 120 arbidol patients in China, showing no significant difference in clinical recovery (relief of fever and cough, respiratory frequency ≤24 times/min, and oxygen saturation ≥98%), however the time to resolution of fever and cough was significantly lower with favipiravir. ChiCTR2000030254.

Chuah



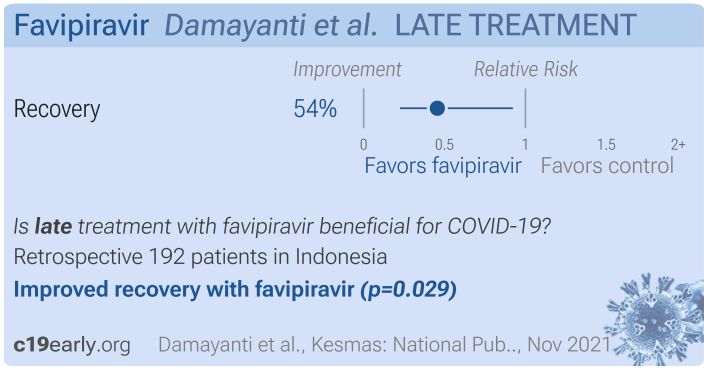
Chuah: RCT 500 hospitalized patients in Malaysia, showing no significant differences with favipiravir treatment.

Cilli



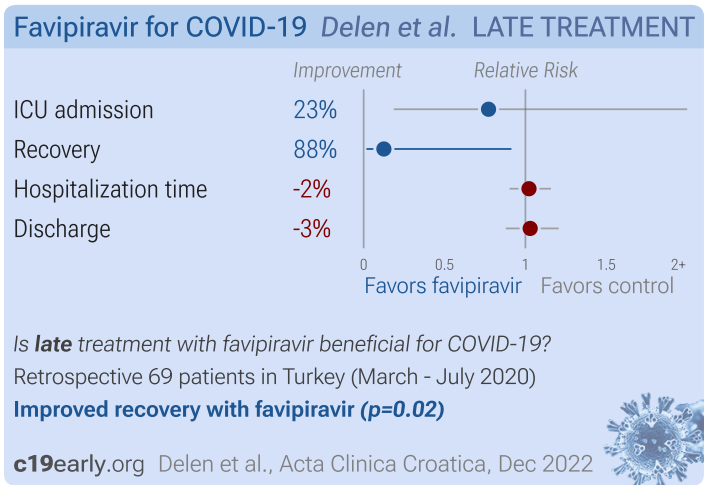
Cilli: Retrospective 46 idiopathic pulmonary fibrosis patients with COVID-19 in Turkey, showing lower mortality with favipiravir in unadjusted results, without statistical significance.

Damayanti



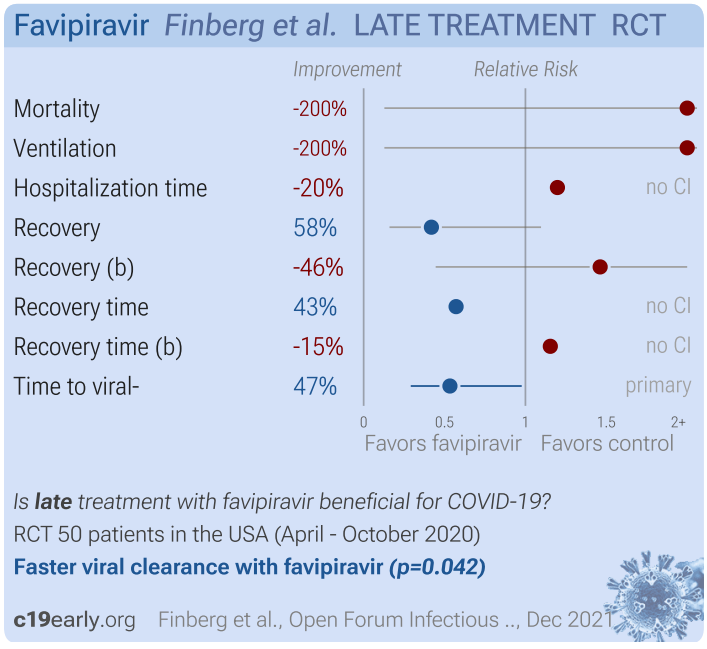
Damayanti: Retrospective 192 hospitalized patients in Indonesia, 96 patients treated with favipiravir, showing improved recovery with treatment. Only the abstract is currently available.

Delen



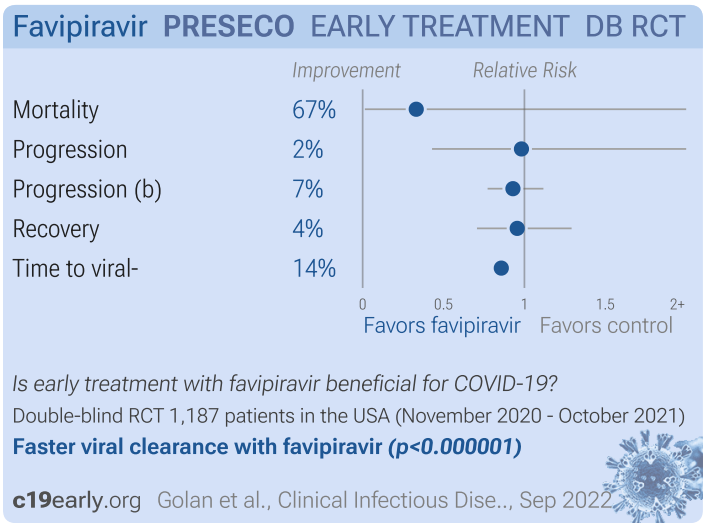
Delen: Retrospective 69 COVID-19 patients in Turkey, showing improved fever recovery with the addition of favipiravir to HCQ, but no significant difference in discharge, ICU admission, or hospitalization time.

Finberg



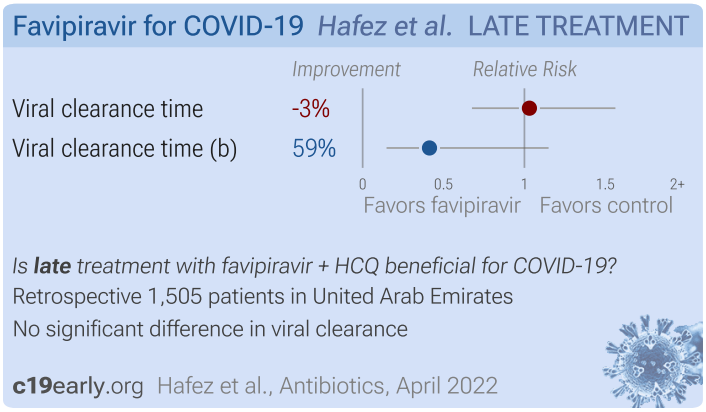
Finberg: Small very late treatment RCT in the USA, with 25 favipiravir and 25 control patients, showing faster viral clearance with treatment. The benefit was only seen in patients <8 days from symptom onset. There were no significant differences in clinical outcomes. The death in the favipiravir group occurred after discharge and was believed to be unrelated to COVID-19 or favipiravir.

Golan



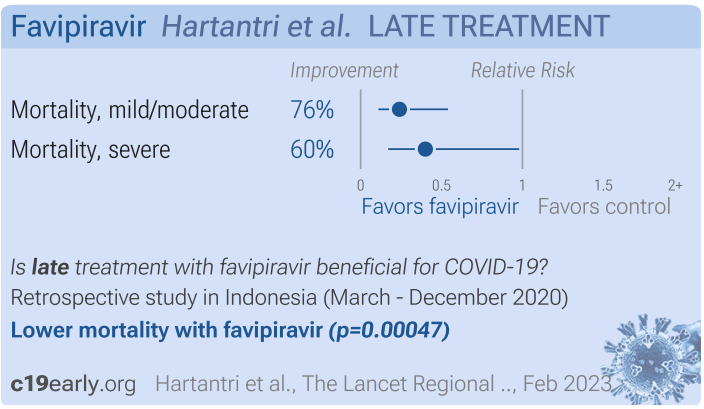
Golan: RCT low-risk (1 death in the control arm) patients in the USA, showing no significant differences with favipiravir. A majority of trial outcomes were modified after completion: *clinicaltrials.gov*. 44% of patients had no detectable viral load at baseline in the viral shedding sub-study. The primary outcome required 4 days of sustained clinical recovery and occurred after a median of 7 days, suggesting there was limited room for improvement in the population studied. The percentages for viral clearance at day 10 do not match any number of the reported group sizes. Authors write "of the six RCTs conducted", however there has been at least 24 other RCTs at the time of publication *c19favipiravir.com*. 1800mg bid day 1, 800mg bid days 2-10.

Hafez



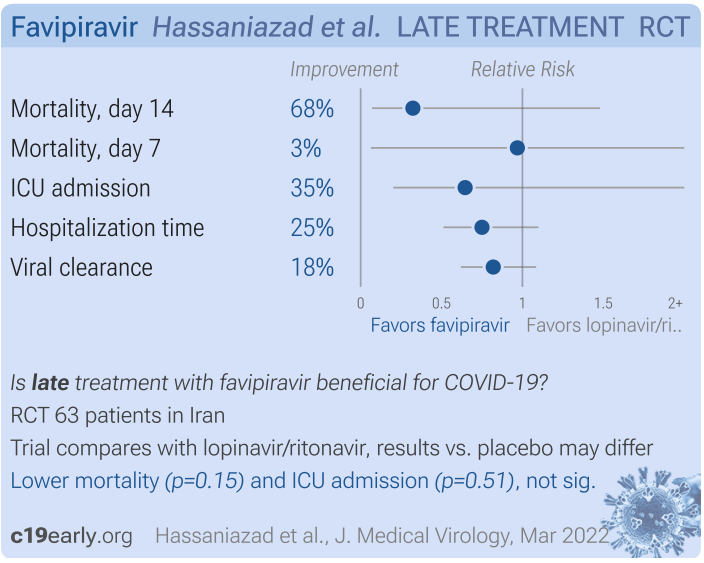
Hafez: Retrospective hospitalized patients in the United Arab Emirates, showing no significant difference in viral clearance with different combinations of HCQ, AZ, favipiravir, and lopinavir/ritonavir.

Hartantri



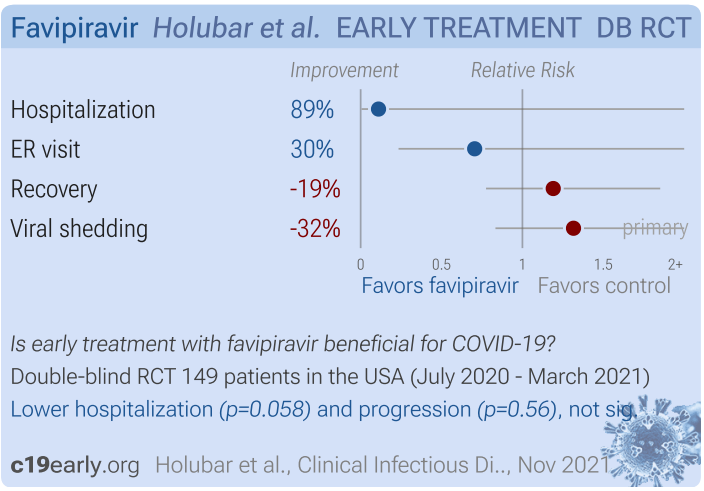
Hartantri: Retrospective 689 hospitalized patients in Indonesia, showing lower mortality with favipiravir treatment.

Hassaniazad



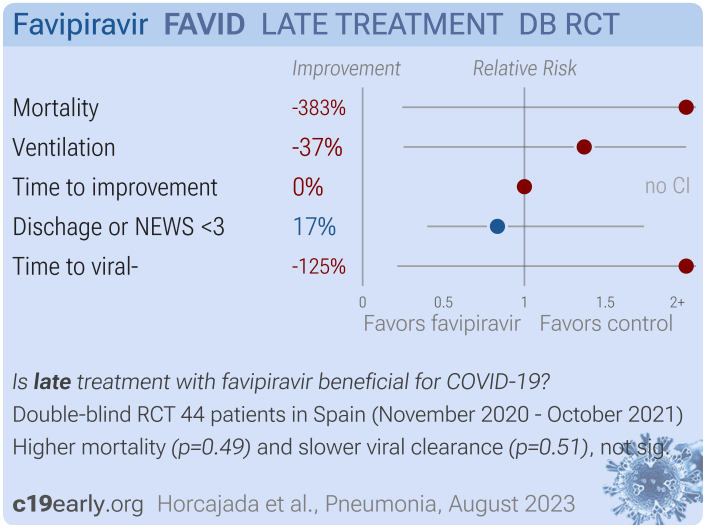
Hassaniazad: RCT comparing favipiravir and lopinavir/ritonavir, showing no significant differences. All patients received interferon-beta. Favipiravir 1600mg bid for the first day and 600mg bid for the following 4 days.

Holubar



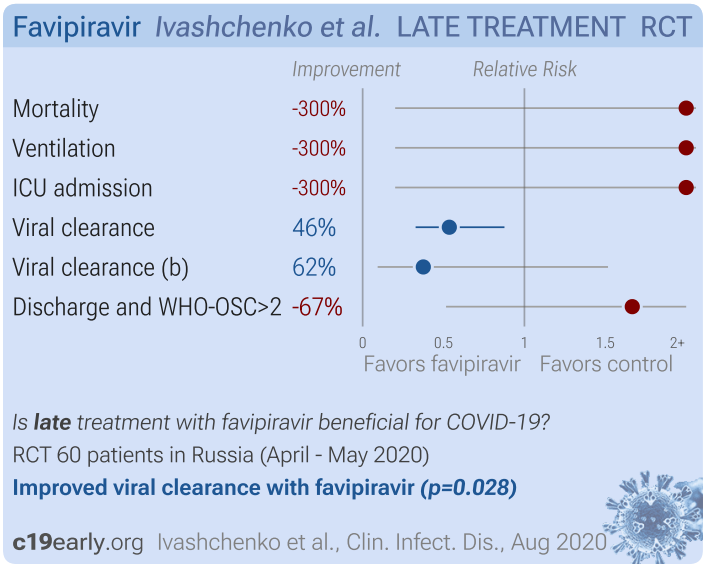
Holubar: Small RCT 116 mITT patients in the USA, 59 treated with favipiravir, showing no significant differences with treatment.

Horcajada



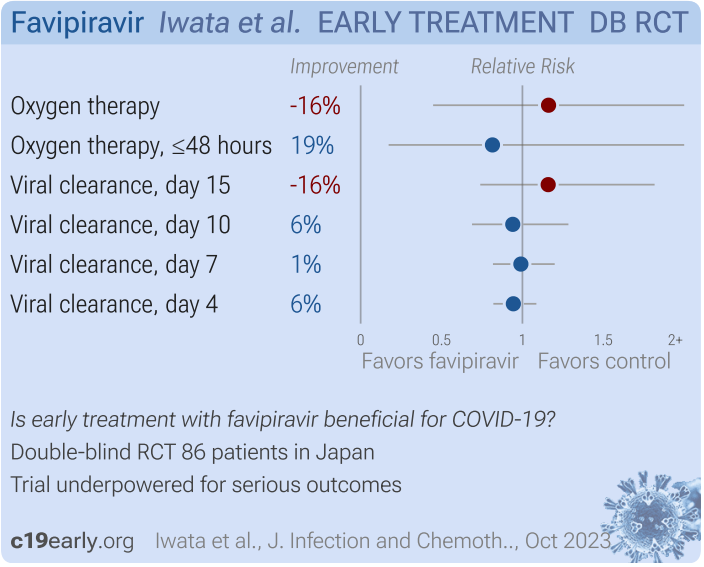
Horcajada: Underpowered RCT with 44 hospitalized patients in Spain, showing no significant difference with favipiravir treatment in the primary outcome of time to clinical improvement, or in the secondary efficacy outcomes. Adverse events were more frequent in the favipiravir group (68%) compared to placebo (32%), but most were mild.

Ivashchenko



Ivashchenko: Interim results for a small RCT with 40 favipiravir and 20 control patients showing faster viral clearance with favipiravir. There is limited data in this report to evaluate the results. 75% of the control group received HCQ/CQ.

Iwata

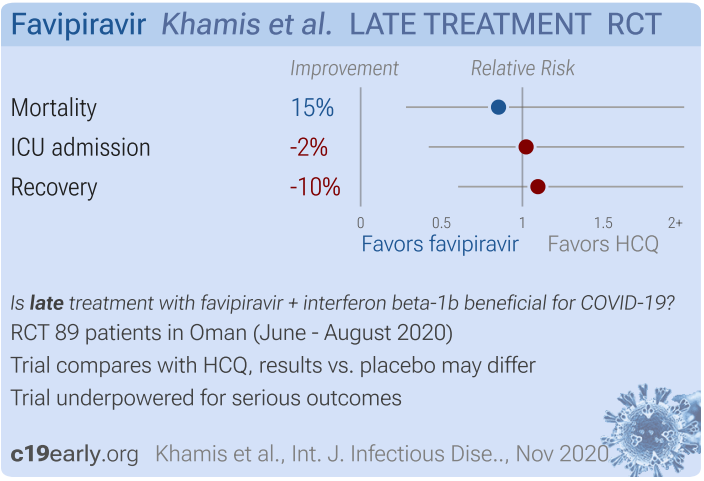


Iwata: Early terminated RCT 84 patients in Japan, showing no significant difference in outcomes with favipiravir treatment. There was a trend for improved efficacy for patients enrolled within 48 hours of symptom onset.

Kara

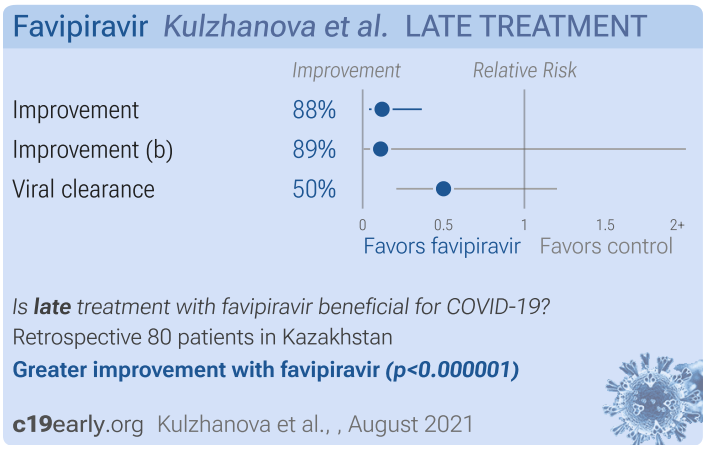
Kara: 1,008 patient favipiravir early treatment RCT with results not reported over 2 years after completion.

Khamis



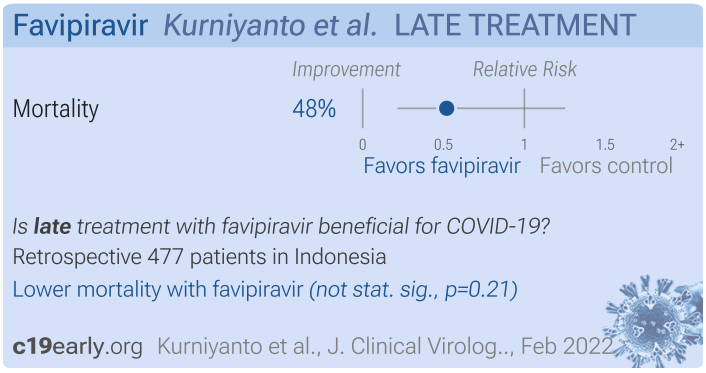
Khamis: Small 89 patient RCT comparing favipiravir and inhaled interferon with HCQ for moderate to severe COVID-19 pneumonia, not finding significant differences. There was no control group.

Kulzhanova



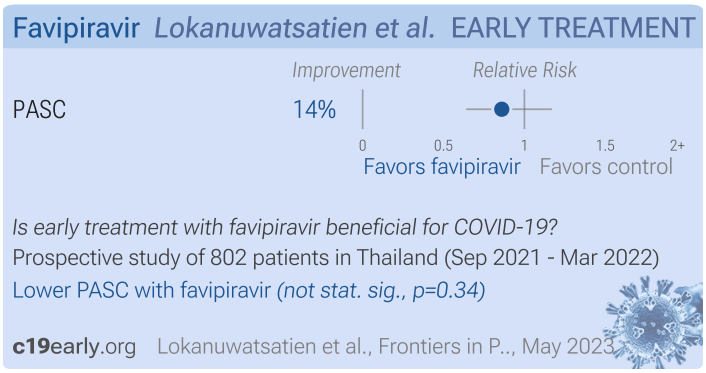
Kulzhanova: Retrospective 40 favipiravir patients in Kazakhstan and 40 controls, showing faster recovery and viral clearance with treatment.

Kurniyanto



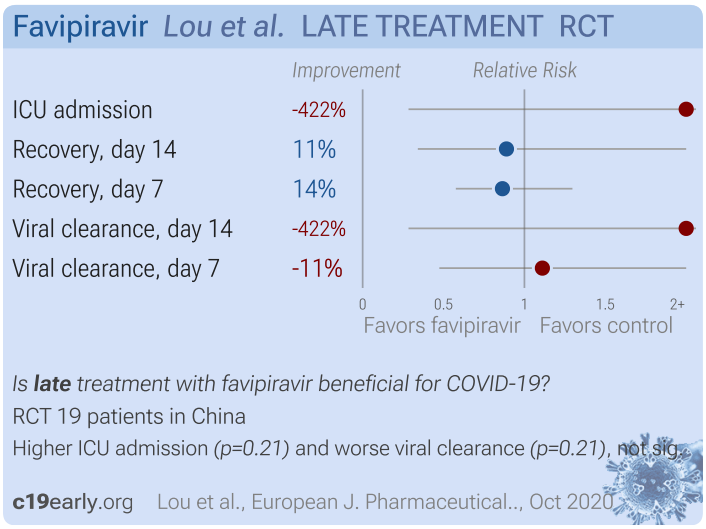
Kurniyanto: Retrospective 477 hospitalized patients in Indonesia, showing lower mortality with favipiravir in unadjusted results, not reaching statistical significance.

Lokanuwatsatien



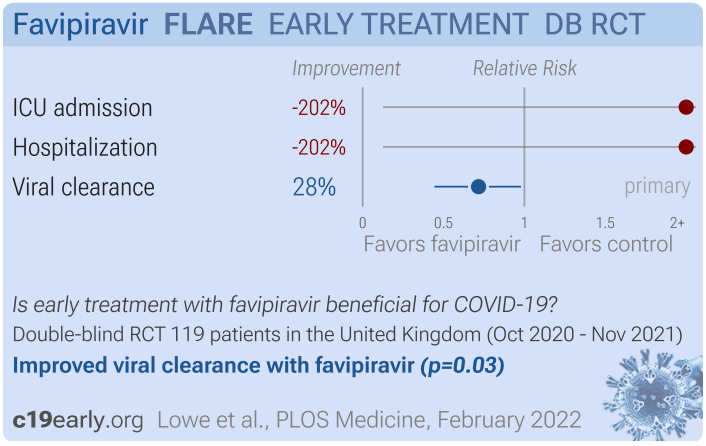
Lokanuwatsatien: Prospective analysis of 802 COVID-19 pediatric patients in Thailand, showing no significant difference in long COVID with favipiravir treatment in unadjusted results.

Lou



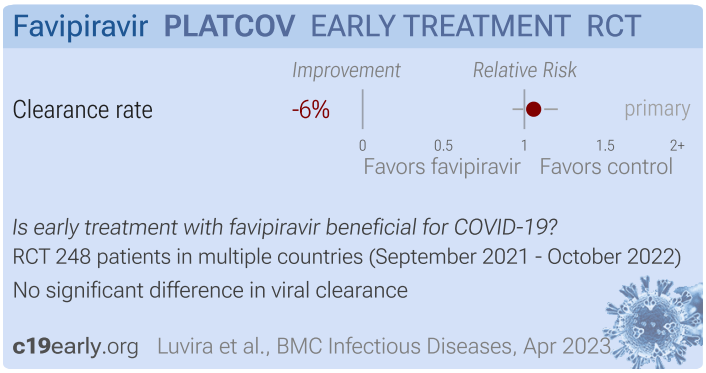
Lou: Small late stage RCT with 10 favipiravir, 10 baloxavir marboxil, and 10 control patients in China, showing no significant differences.

Lowe



Lowe: 240 patient RCT comparing favipiravir, favipiravir + LPV/r, LPV/r, and placebo, showing improved viral clearance with favipiravir. Efficacy was lower in the combined favipiravir + LPV/r arm, where plasma levels of favipiravir were lower. Favipiravir 1800mg twice daily on day 1 followed by 400mg four times daily on days 2-7.

Luvira



Luvira: High conflict of interest RCT with very low risk patients, high existing immunity, and a post-hoc change to exclude patients more likely to benefit. There was no significant difference in viral clearance with favipiravir among patients with high viral load at baseline. Patients in both arms had very short viral clearance half-life times.

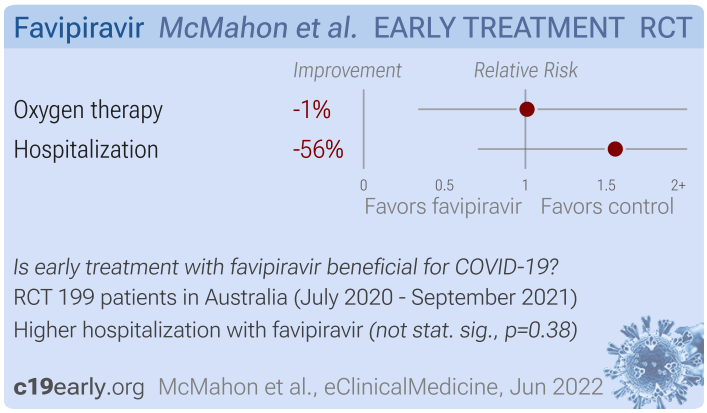
With rapid viral clearance and very low risk patients, infection is less likely to spread to other tissues. Systemic treatment is less applicable, and has less time to reach therapeutic concentrations before self-recovery.

Treatment administered directly to the respiratory tract, e.g. as in *Yildiz Pekoz*, may be more effective for COVID-19 in general, and extend applicability to fast-resolving cases with infection primarily localized to the respiratory tract.

Authors note that "all-cause hospitalisation for clinical deterioration (until day 28) was a secondary endpoint", but do not provide the result.

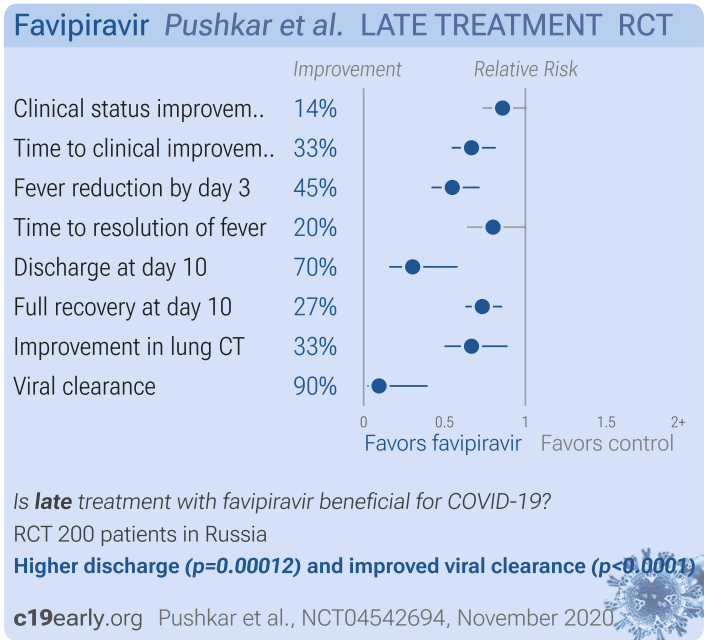
For more discussion of the post-hoc change and other issues see *Schilling*.

McMahon



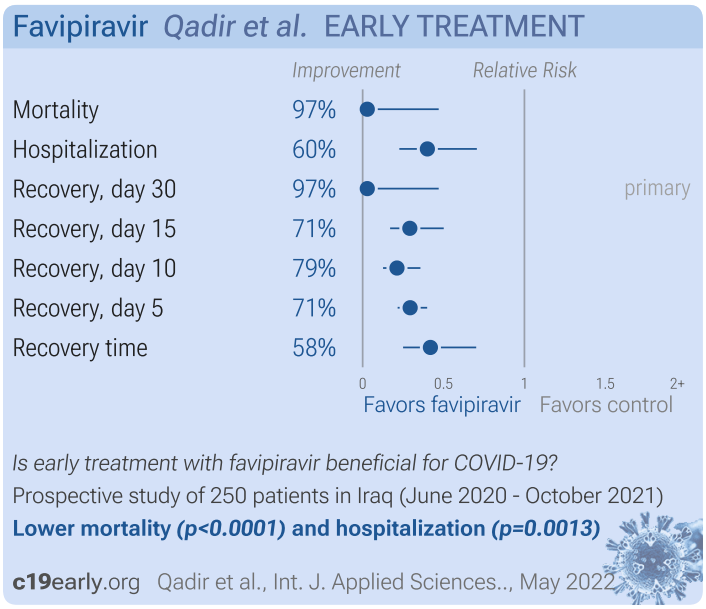
McMahon: RCT with 99 favipiravir and 100 placebo patients in Australia, all except one being outpatients, showing no significant differences with treatment.

Pushkar



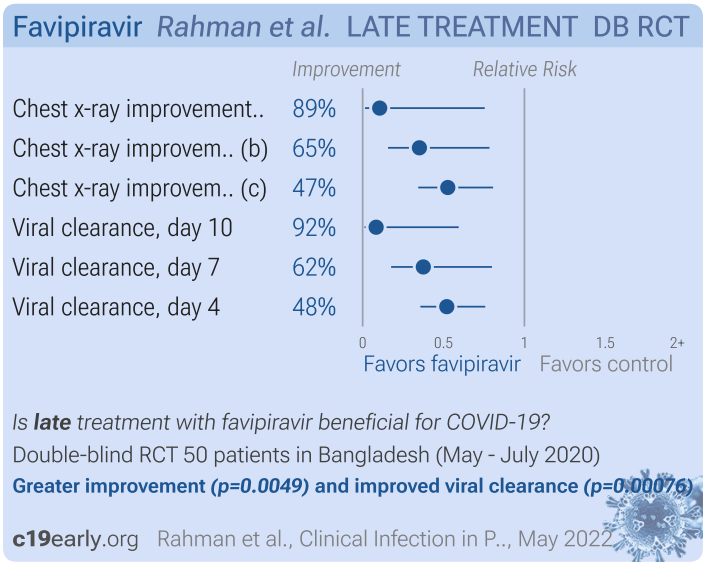
Pushkar: RCT 200 patients showing improvements in clinical recovery and viral clearance with favipiravir. There is no paper available but results are posted in clinicaltrials.gov.

Qadir



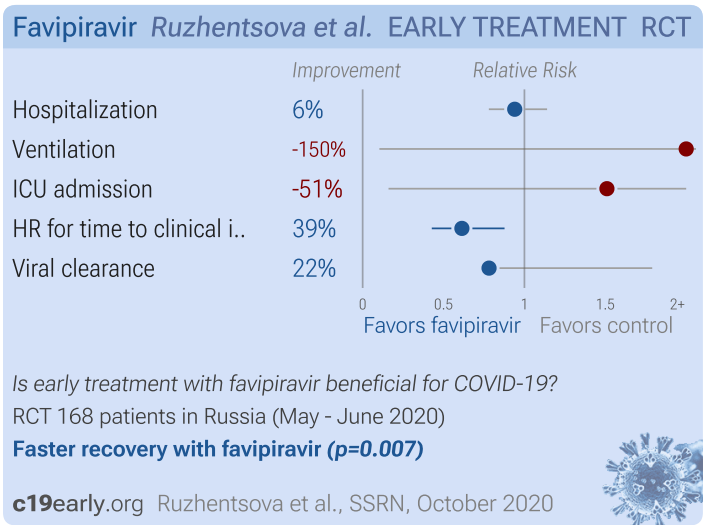
Qadir: Prospective study with 125 favipiravir patients and 125 patients declining favipiravir treatment, showing lower mortality and improved recovery with treatment. All patients received vitamin C, D, and zinc. Favipiravir 3200mg day 1, followed by 600mg bid days 2-10.

Rahman



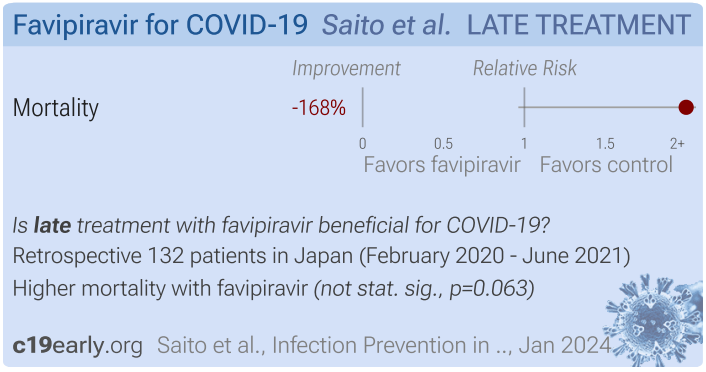
Rahman: RCT hospitalized patients in Bangladesh, showing faster recovery and viral clearance with favipiravir treatment.

Ruzhentsova



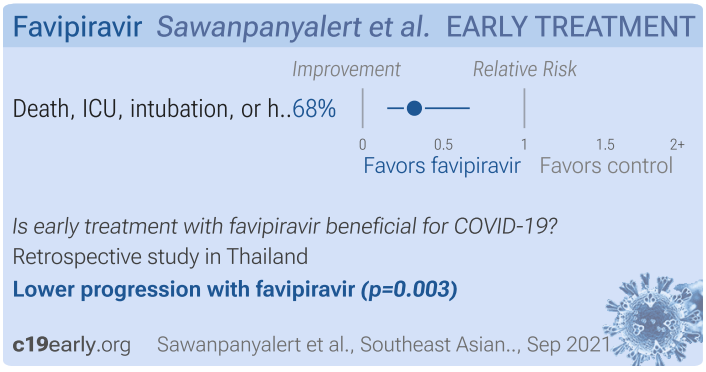
Ruzhentsova: RCT 168 patients, 112 receiving favipiravir and 56 SOC, showing shorter time to clinical improvement and faster viral clearance with favipiravir.

Saito



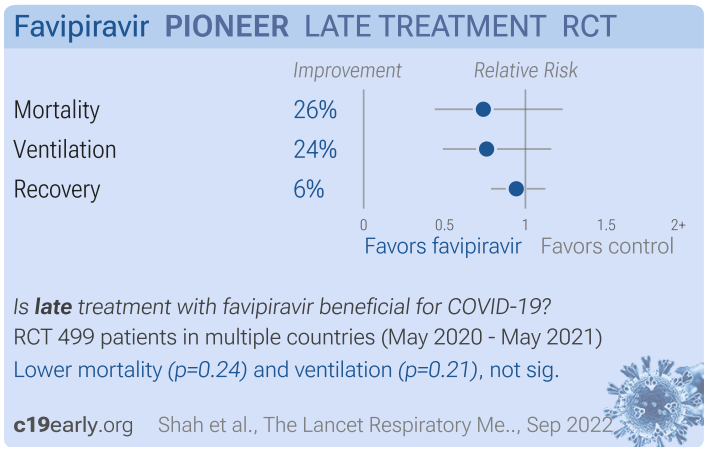
Saito: Retrospective 132 hospitalized COVID-19 patients over age 65 in Japan during the Alpha variant surge, showing higher mortality with favipiravir in unadjusted results, without statistical significance.

Sawanpanyalert



Sawanpanyalert: Retrospective 744 hospitalized patients in Thailand, showing lower risk of a poor outcome for favipiravir treatment within 4 days of symptom onset. Early treatment with CQ/HCQ and lopinavir/ritonavir or darunavir/ritonavir also showed lower risk, but without statistical significance. Sample sizes for the number of patients treated within 4 days of symptom onset are not provided.

Shah

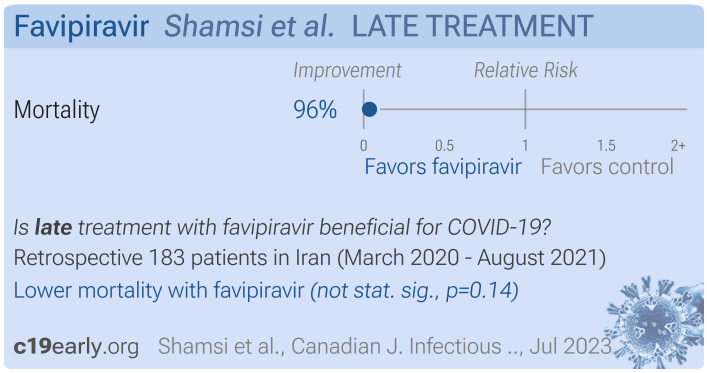


Shah: PIONEER very late treatment RCT showing lower mortality and mechanical ventilation with favipiravir, without statistical significance.

The conclusion "favipiravir is not efficacious in treating hospitalised adult patients with COVID-19" is incorrect. Authors show 26% and 24% lower mortality and mechanical ventilation. While these results are not statistically significant, they predict efficacy, and cannot be used to rule out efficacy.

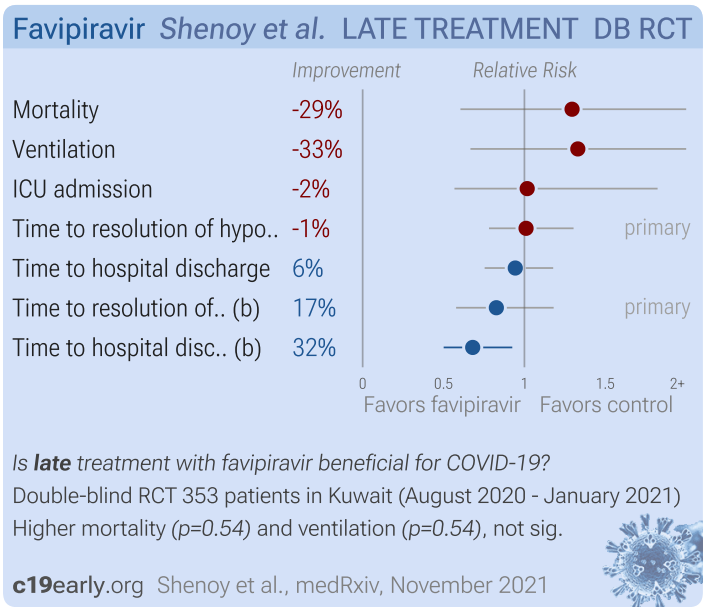
Favipiravir 1,800mg bid day 1, 800mg bid days 2-10.

Shamsi



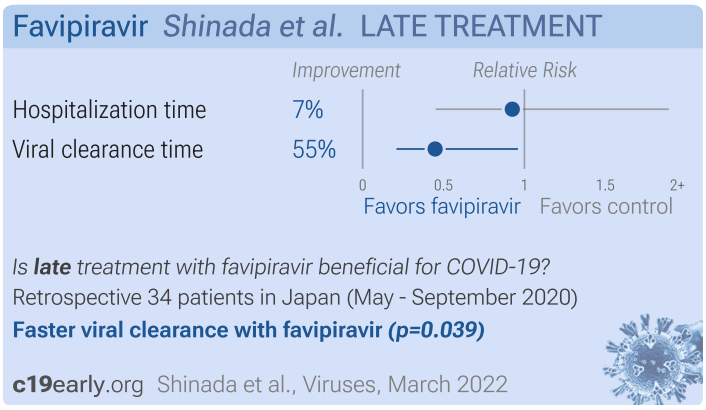
Shamsi: Retrospective 183 hospitalized pediatric COVID-19 patients in Iran, showing no significant difference in mortality with favipiravir in unadjusted results.

Shenoy



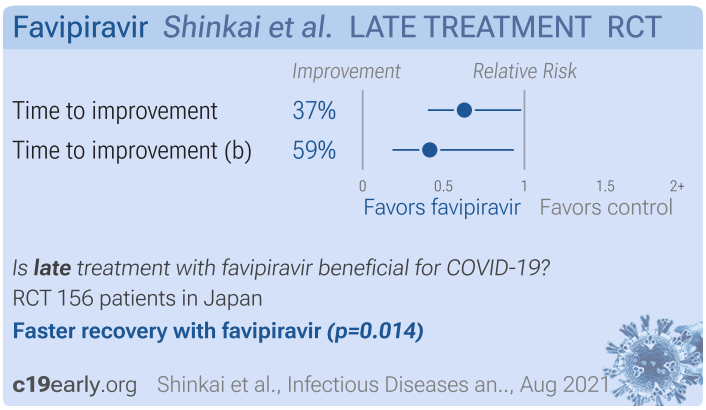
Shenoy: Late stage RCT with 353 hospitalized patients, showing no significant differences with favipiravir treatment overall, however a trend towards benefit was seen within patients treated relatively early, including a statistically significant shorter time to discharge with treatment.

Shinada



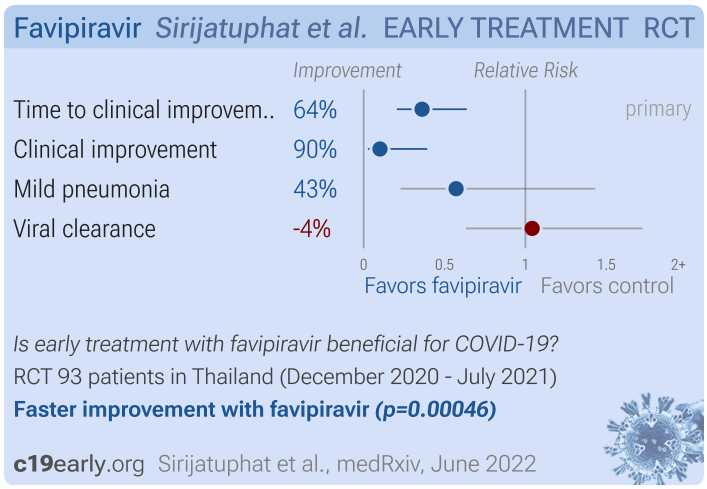
Shinada: Retrospective 17 COVID+ patients treated with favipiravir and 17 matched controls in Japan, showing faster viral clearance with treatment. Favipiravir 3600mg day one, 1600mg per day for up to 14 days.

Shinkai



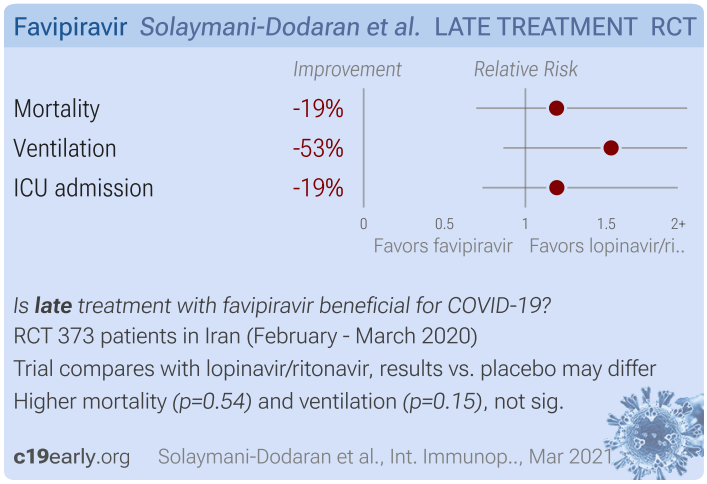
Shinkai: RCT 156 patients in Japan, 107 treated with favipiravir, showing significant improvement in a composite outcome defined as the time to improvement in temperature, SpO2, CT findings, and recovery to PCR-.

Sirijatuphat



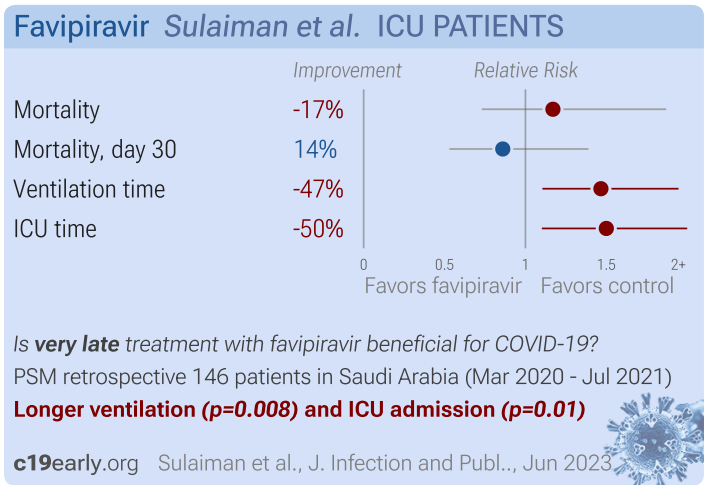
Sirijatuphat: RCT 93 patients in Thailand showing significantly faster clinical improvement with favipiravir treatment. 1800mg favipiravir bid day 1, 800mg bid 5-14 days until PCR-.

Solaymani-Dodaran



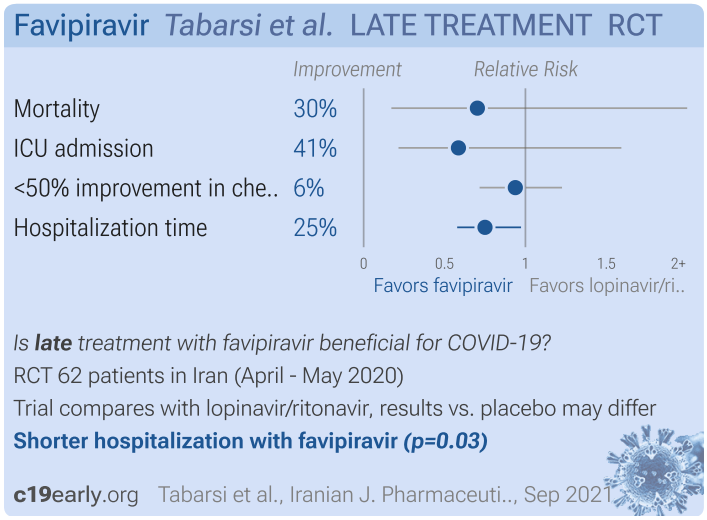
Solaymani-Dodaran: RCT late stage patients (median SpO2 89), 193 treated with favipiravir, 187 with lopinavir/ritonavir, showing no significant differences in mortality, intubation, or ICU admission.

Sulaiman



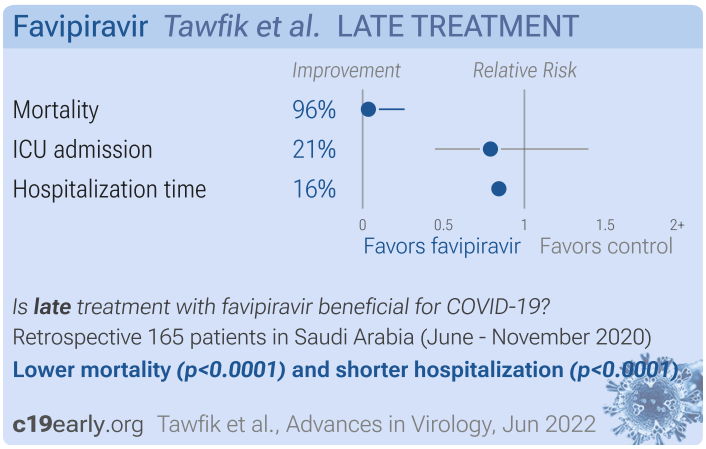
Sulaiman: PSM retrospective 1,218 COVID-19 ICU patients in Saudi Arabia, showing no significant difference in mortality, and longer ICU/MV time with favipiravir treatment.

Tabarsi



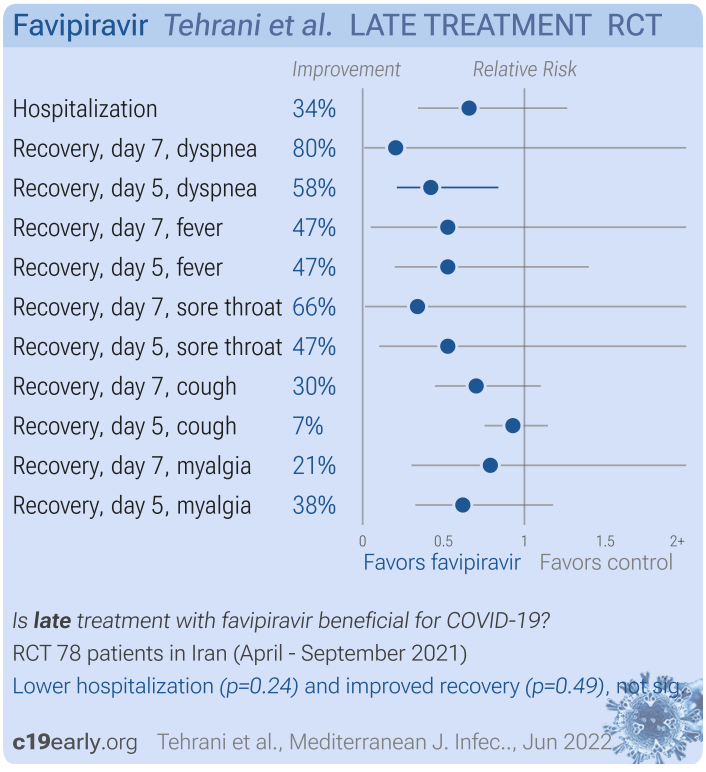
Tabarsi: Small 62 patient late stage RCT in Iran comparing favipiravir and lopinavir/ritonavir, showing significant improvement in fever, cough, and dyspnea with favipiravir on day 5. There was no significant difference in mortality, ICU admission, or chest CT improvement. IRCT20151227025726N14.

Tawfik



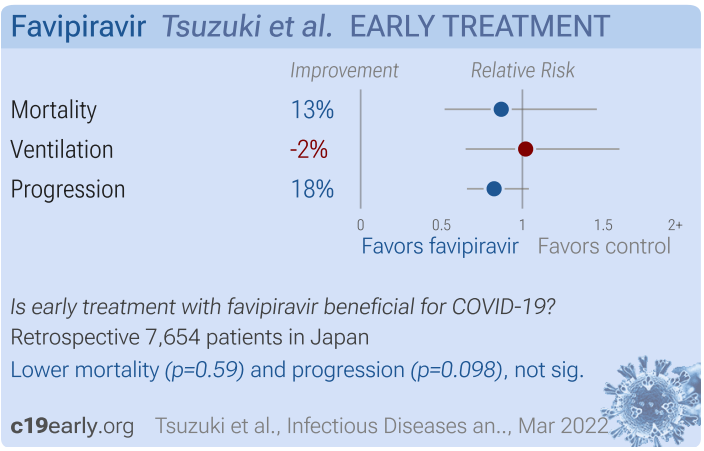
Tawfik: Retrospective 103 hospitalized patients in Saudi Arabia, showing lower mortality with favipiravir in unadjusted results, and greater efficacy for treatment within 3 days of admission.

Tehrani



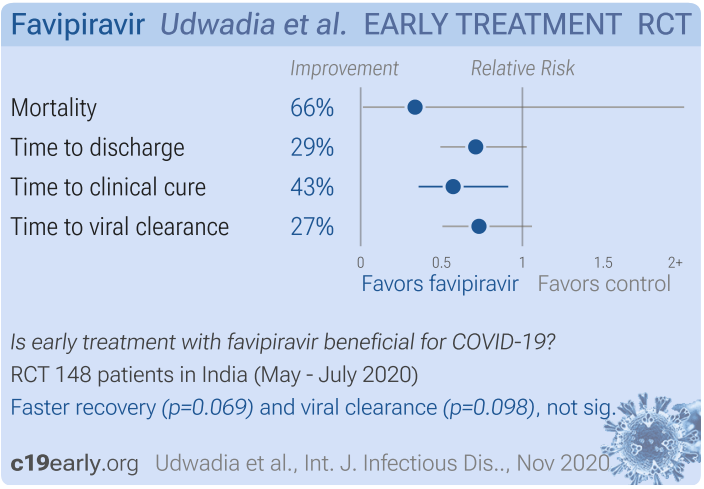
Tehrani: RCT 78 patients in Iran, showing improved recovery with favipiravir treatment.

Tsuzuki



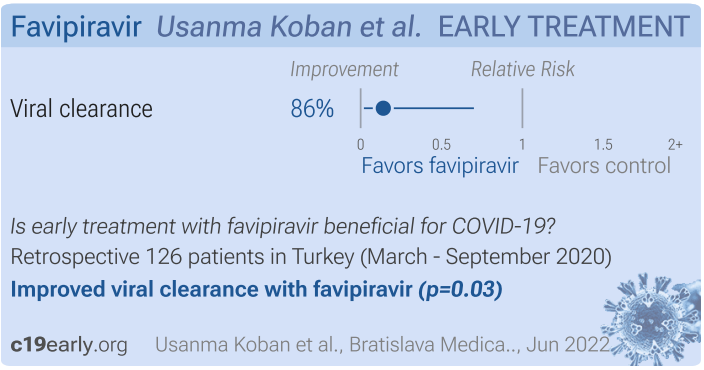
Tsuzuki: Retrospective database analysis of 7,654 hospitalized patients in Japan, showing no significant differences with favipiravir treatment. NCGM-G-003494-0.

Udwadia



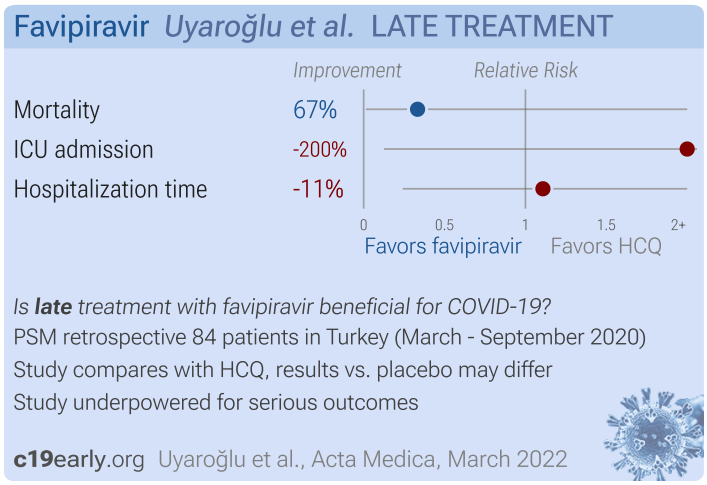
Udwadia: RCT with 75 favipiravir patients and 75 control patients showing improved recovery with treatment.

Usanma Koban



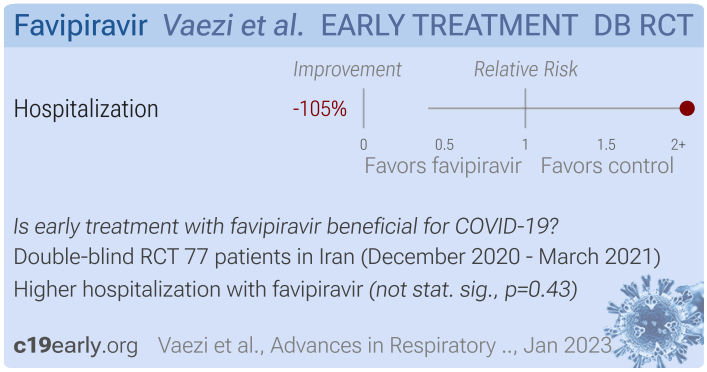
Usanma Koban: Retrospective 126 patients in Turkey, showing lower risk of PCR+ at day 14 with favipiravir treatment.

Uyaroğlu



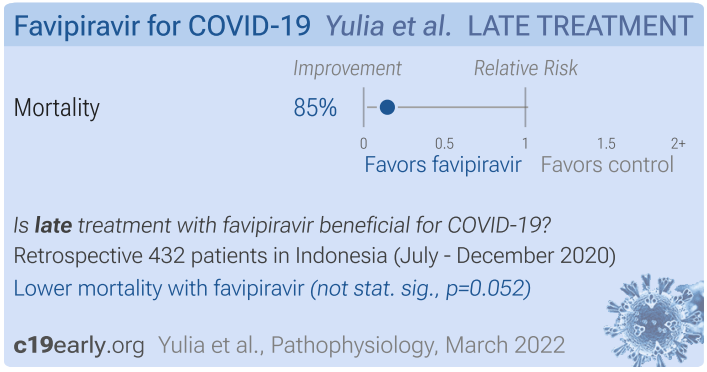
Uyaroğlu: PSM retrospective 260 late stage hospitalized COVID-19 pneumonia patients in Turkey, showing no significant difference between favipiravir and HCQ.

Vaezi



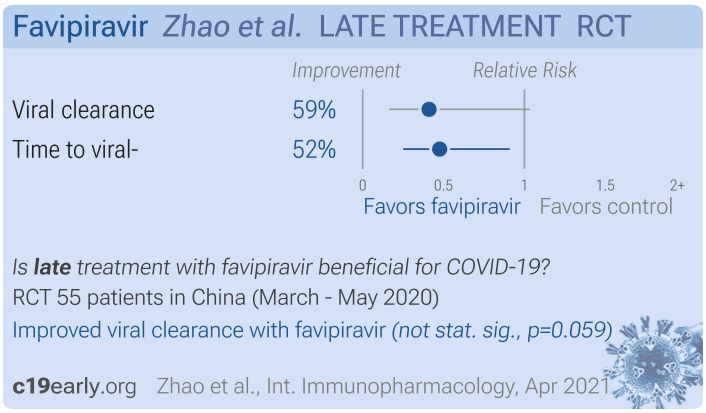
Vaezi: RCT 77 outpatients in Iran, showing increased hospitalization with treatment, without statistical significance. Favipiravir 1600mg daily for five days. 21% of favipiravir patients did not complete treatment.

Yulia



Yulia: Retrospective hospitalized patients in Indonesia, showing lower mortality and shorter hospitalization with favipiravir.

Zhao



Zhao: RCT with 55 patients (36 favipiravir, 19 control) who were PCR+ after recovery, showing improved viral clearance with treatment.

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 favipiravir 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 favipiravir 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. 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 both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used 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 test status. 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. 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*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *Sweeting*. 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 (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta [Deng] 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 (4.1.2) using the metafor (3.0-2) and rms (6.2-0) 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 0.8.0 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 [McLean, Treanor].

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/ameta.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.

Adhikari, 3/1/2022, Randomized Controlled Trial, Nepal, peer-reviewed, 12 authors, study period May 2020 - October 2020.	risk of no improvement, 40.4% higher, RR 1.40, $p = 0.57$, treatment 10 of 38 (26.3%), control 6 of 32 (18.8%), all.
	risk of no improvement, 36.3% higher, RR 1.36, $p = 0.75$, treatment 8 of 27 (29.6%), control 5 of 23 (21.7%), mild cases.
	risk of no improvement, 63.6% higher, RR 1.64, $p = 1.00$, treatment 2 of 11 (18.2%), control 1 of 9 (11.1%), moderate cases.
Alattar, 11/30/2021, retrospective, Qatar, peer-reviewed, median age 46.0, 25 authors, study period 23 May, 2020 - 18 July, 2020, average treatment delay 5.0 days.	risk of death, 33.3% lower, RR 0.67, $p = 0.50$, treatment 8 of 387 (2.1%), control 12 of 387 (3.1%), NNT 97, propensity score matching, day 28.
	risk of no clinical improvement, 2.2% higher, RR 1.02, $p = 0.73$, treatment 26 of 387 (6.7%), control 28 of 387 (7.2%), NNT 194, adjusted per study, inverted to make RR<1 favor treatment, day 28, Cox proportional hazards, propensity score matching, primary outcome.
	days to clinical improvement, 6.2% higher, relative time 1.06, $p = 0.07$, treatment 387, control 387, propensity score matching.
	risk of no viral clearance, 43.9% lower, RR 0.56, $p < 0.001$, treatment 78 of 387 (20.2%), control 139 of 387 (35.9%), NNT 6.3, propensity score matching.
Bosaeed, 1/11/2022, Double Blind Randomized Controlled Trial, Saudi Arabia, peer-reviewed, 31 authors, study period 23 July, 2020 - 4 August,	risk of ICU admission, 618.8% higher, RR 7.19, $p = 0.11$, treatment 3 of 112 (2.7%), control 0 of 119 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting

2021, average treatment delay 3.0 days, trial NCT04464408 (history).	arm).
	risk of hospitalization, 218.8% higher, RR 3.19, p = 0.16, treatment 6 of 112 (5.4%), control 2 of 119 (1.7%).
	time to clinical improvement, 11.9% higher, HR 1.12, p = 0.51, treatment 112, control 119, adjusted per study, inverted to make HR<1 favor treatment.
	time to viral clearance, 14.9% higher, HR 1.15, p = 0.51, treatment 112, control 119, adjusted per study, inverted to make HR<1 favor treatment, primary outcome.
Bruminhent, 9/10/2022, retrospective, Thailand, peer-reviewed, 6 authors, study period 26 April, 2021 - 27 May, 2021.	risk of progression, 227.0% higher, OR 3.27, p = 0.005, adjusted per study, multivariable, RR approximated with OR.
Chandiwana, 11/1/2022, Randomized Controlled Trial, South Africa, peer-reviewed, mean age 34.9, 16 authors, study period 3 September, 2020 - 23 August, 2021, this trial uses multiple treatments in the treatment arm (combined with nitazoxanide) - results of individual treatments may vary, trial NCT04532931 (history).	risk of progression, 13.0% higher, OR 1.13, p = 0.89, treatment 37, control 39, adjusted per study, day 28, Table S9, RR approximated with OR.
	time to WHO zero score, 23.5% higher, HR 1.23, p = 0.42, treatment 37, control 39, inverted to make HR<1 favor treatment, Cox proportional hazards, Table S10.
	risk of no viral clearance, 66.7% higher, RR 1.67, p = 0.13, treatment 27 of 37 (73.0%), control 25 of 38 (65.8%), adjusted per study, inverted to make RR<1 favor treatment.
Golan, 9/6/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 9 authors, study period November 2020 - October 2021, trial NCT04600895 (history) (PRESECO).	risk of death, 66.9% lower, RR 0.33, p = 0.50, treatment 0 of 599 (0.0%), control 1 of 588 (0.2%), NNT 588, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 28.
	risk of progression, 1.8% lower, RR 0.98, p = 1.00, treatment 11 of 599 (1.8%), control 11 of 588 (1.9%), NNT 2911, narrow definition.
	risk of progression, 7.1% lower, RR 0.93, p = 0.44, treatment 159 of 599 (26.5%), control 168 of 588 (28.6%), NNT 49, broad definition.
	risk of no recovery, 4.5% lower, RR 0.96, p = 0.79, treatment 73 of 599 (12.2%), control 75 of 588 (12.8%), NNT 176.
	time to viral-, 14.3% lower, relative time 0.86, p < 0.001, treatment median 6.0 IQR 2.0 n=140, control median 7.0 IQR 2.0 n=132, 50% conversion.
Holubar, 11/24/2021, Double Blind Randomized Controlled Trial, USA, peer-reviewed, 26 authors, study period 8 July, 2020 - 23 March, 2021, average treatment delay 5.0 days, conflicts of interest: Pfizer, Gates Foundation, Gilead, Regeneron, Janssen.	risk of hospitalization, 89.0% lower, RR 0.11, p = 0.06, treatment 0 of 75 (0.0%), control 4 of 74 (5.4%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	risk of ER visit, 29.5% lower, RR 0.70, p = 0.56, treatment 5 of 75 (6.7%), control 7 of 74 (9.5%), NNT 36.

	risk of no recovery, 19.0% higher, RR 1.19, *p* = 0.43, treatment 65, control 70, inverted to make RR<1 favor treatment, initial resolution of symptoms.
	viral shedding, 31.6% higher, RR 1.32, *p* = 0.24, treatment 59, control 57, inverted to make RR<1 favor treatment, primary outcome.
Iwata, 10/12/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Japan, peer-reviewed, 13 authors, trial jRCT2041210004.	risk of oxygen therapy, 16.2% higher, RR 1.16, *p* = 0.73, treatment 12 of 43 (27.9%), control 12 of 43 (27.9%), adjusted per study, odds ratio converted to relative risk, multivariable, day 28.
	risk of oxygen therapy, 18.5% lower, RR 0.81, *p* = 0.77, treatment 5 of 24 (20.8%), control 6 of 22 (27.3%), NNT 16, adjusted per study, odds ratio converted to relative risk, patients with onset ≤48 hours, multivariable, day 28.
	risk of no viral clearance, 15.9% higher, RR 1.16, *p* = 0.66, treatment 21 of 41 (51.2%), control 19 of 43 (44.2%), day 15.
	risk of no viral clearance, 6.0% lower, RR 0.94, *p* = 0.82, treatment 26 of 41 (63.4%), control 29 of 43 (67.4%), NNT 25, day 10.
	risk of no viral clearance, 0.9% lower, RR 0.99, *p* = 1.00, treatment 34 of 41 (82.9%), control 36 of 43 (83.7%), NNT 126, day 7.
	risk of no viral clearance, 5.6% lower, RR 0.94, *p* = 0.48, treatment 36 of 41 (87.8%), control 40 of 43 (93.0%), NNT 19, day 4.
Kara, 6/1/2021, Randomized Controlled Trial, Turkey, peer-reviewed, trial NCT04411433 (history).	1,008 patient RCT with results unknown and over 2 years late.
Lokanuwatsatien, 5/24/2023, prospective, Thailand, peer-reviewed, 8 authors, study period September 2021 - March 2022, excluded in exclusion analyses: unadjusted results with no group details.	risk of PASC, 14.0% lower, OR 0.86, *p* = 0.34, treatment 400, control 402, RR approximated with OR.
Lowe, 2/15/2022, Double Blind Randomized Controlled Trial, placebo-controlled, United Kingdom, peer-reviewed, 18 authors, study period 6 October, 2020 - 4 November, 2021, trial NCT04499677 (history) (FLARE).	risk of ICU admission, 201.7% higher, RR 3.02, *p* = 0.50, treatment 1 of 59 (1.7%), control 0 of 60 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of hospitalization, 201.7% higher, RR 3.02, *p* = 0.50, treatment 1 of 59 (1.7%), control 0 of 60 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of no viral clearance, 28.4% lower, RR 0.72, *p* = 0.03, treatment 29 of 54 (53.7%), control 38 of 52 (73.1%), NNT 5.2, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, day 5, primary outcome.

Luvira, 4/5/2023, Randomized Controlled Trial, multiple countries, peer-reviewed, median age 30.1, 36 authors, study period 30 September, 2021 - 31 October, 2022, trial NCT05041907 (history) (PLATCOV).	relative clearance rate, 5.7% worse, RR 1.06, $p = 0.42$, treatment median 16.6 IQR 10.0 n=116, control median 15.7 IQR 13.0 n=132, primary outcome.
McMahon, 6/14/2022, Randomized Controlled Trial, placebo-controlled, Australia, peer-reviewed, median age 36.0, 33 authors, study period 31 July, 2020 - 19 September, 2021, trial NCT04445467 (history).	risk of oxygen therapy, 1.0% higher, RR 1.01, $p = 1.00$, treatment 6 of 99 (6.1%), control 6 of 100 (6.0%).
	risk of hospitalization, 55.6% higher, RR 1.56, $p = 0.38$, treatment 14 of 99 (14.1%), control 9 of 99 (9.1%).
Qadir, 5/23/2022, prospective, Iraq, peer-reviewed, 3 authors, study period 22 June, 2020 - 25 October, 2021.	risk of death, 97.1% lower, RR 0.03, $p < 0.001$, treatment 0 of 125 (0.0%), control 17 of 125 (13.6%), NNT 7.4, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 30.
	risk of hospitalization, 60.0% lower, RR 0.40, $p = 0.001$, treatment 14 of 125 (11.2%), control 35 of 125 (28.0%), NNT 6.0.
	risk of no recovery, 97.1% lower, RR 0.03, $p < 0.001$, treatment 0 of 125 (0.0%), control 17 of 125 (13.6%), NNT 7.4, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 30, primary outcome.
	risk of no recovery, 70.8% lower, RR 0.29, $p < 0.001$, treatment 14 of 125 (11.2%), control 48 of 125 (38.4%), NNT 3.7, day 15.
	risk of no recovery, 78.8% lower, RR 0.21, $p < 0.001$, treatment 14 of 125 (11.2%), control 66 of 125 (52.8%), NNT 2.4, day 10.
	risk of no recovery, 70.6% lower, RR 0.29, $p < 0.001$, treatment 32 of 125 (25.6%), control 109 of 125 (87.2%), NNT 1.6, day 5.
	recovery time, 58.1% lower, relative time 0.42, $p < 0.001$, treatment 125, control 125.
Ruzhentsova, 10/26/2020, Randomized Controlled Trial, Russia, preprint, 31 authors, study period 23 May, 2020 - 30 June, 2020, average treatment delay 3.55 days.	risk of hospitalization, 6.0% lower, RR 0.94, $p = 0.49$, treatment 3 of 112 (2.7%), control 2 of 56 (3.6%), adjusted per study.
	HR for time to clinical improvement, 38.7% lower, HR 0.61, $p = 0.007$, treatment 112, control 56, inverted to make HR<1 favor treatment.
	risk of no viral clearance, 21.9% lower, RR 0.78, $p = 0.16$, treatment 112, control 56, inverted to make RR<1 favor treatment, day 5 mid-recovery.
Sawanpanyalert, 9/9/2021, retrospective, Thailand, peer-reviewed, 11 authors.	risk of death, ICU, intubation, or high-flow oxygen, 68.0% lower, OR 0.32, $p = 0.003$, within 4 days of symptom onset, RR approximated with OR.

Sirijatuphat, 6/8/2022, Randomized Controlled Trial, Thailand, peer-reviewed, 9 authors, study period December 2020 - July 2021, trial TCTR20200514001.	time to clinical improvement, 63.9% lower, HR 0.36, $p < 0.001$, treatment 62, control 31, inverted to make HR<1 favor treatment, primary outcome.
	clinical improvement, 89.9% lower, OR 0.10, $p < 0.001$, treatment 62, control 31, inverted to make OR<1 favor treatment, logistic regression, day 14, RR approximated with OR.
	risk of mild pneumonia, 42.9% lower, RR 0.57, $p = 0.25$, treatment 8 of 62 (12.9%), control 7 of 31 (22.6%), NNT 10.
	risk of no viral clearance, 4.2% higher, HR 1.04, $p = 0.87$, treatment 62, control 31, adjusted per study, inverted to make HR<1 favor treatment.
Tsuzuki, 3/21/2022, retrospective, Japan, peer-reviewed, 21 authors, average treatment delay 4.0 days.	risk of death, 13.1% lower, HR 0.87, $p = 0.59$, treatment 2,532, control 5,122, adjusted per study, day 30.
	risk of mechanical ventilation, 2.0% higher, HR 1.02, $p = 0.93$, treatment 2,532, control 5,122, adjusted per study, IMV/ECMO.
	risk of progression, 17.5% lower, HR 0.82, $p = 0.10$, treatment 2,532, control 5,122, adjusted per study, oxygen requirement.
Udwadia, 11/16/2020, Randomized Controlled Trial, India, peer-reviewed, 11 authors, study period 14 May, 2020 - 3 July, 2020, trial CTRI/2020/05/025114.	risk of death, 66.4% lower, RR 0.34, $p = 1.00$, treatment 0 of 73 (0.0%), control 1 of 75 (1.3%), NNT 75, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	time to discharge, 28.9% lower, HR 0.71, $p = 0.07$, treatment 75, control 72, inverted to make HR<1 favor treatment.
	time to clinical cure, 42.8% lower, HR 0.57, $p = 0.02$, treatment 75, control 72, inverted to make HR<1 favor treatment.
	time to viral clearance, 26.8% lower, HR 0.73, $p = 0.10$, treatment 75, control 72, inverted to make HR<1 favor treatment.
Usanma Koban, 6/7/2022, retrospective, Turkey, peer-reviewed, 3 authors, study period 1 March, 2020 - 30 September, 2020.	risk of no viral clearance, 86.0% lower, OR 0.14, $p = 0.03$, treatment 47, control 79, adjusted per study, multivariable, day 14, RR approximated with OR.
Vaezi, 1/28/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Iran, peer-reviewed, 6 authors, study period 5 December, 2020 - 31 March, 2021, trial IRCT20171219037964N3.	risk of hospitalization, 105.3% higher, RR 2.05, $p = 0.43$, treatment 4 of 38 (10.5%), control 2 of 39 (5.1%), day 28.

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.

Abdulrahman, 6/21/2022, retrospective, Saudi Arabia, peer-reviewed, 15 authors, study period June 2020 - August 2020, excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 2.6% lower, RR 0.97, $p = 0.81$, treatment 74 of 193 (38.3%), control 593 of 1,506 (39.4%), NNT 97.
Acar Sevinc, 6/28/2022, retrospective, Turkey, peer-reviewed, mean age 65.6, 1 author, study period 10 March, 2020 - 10 May, 2020, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04645433 (history), excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 16.2% lower, RR 0.84, $p = 0.38$, treatment 57 of 85 (67.1%), control 12 of 15 (80.0%), NNT 7.7.
	risk of mechanical ventilation, 10.3% lower, RR 0.90, $p = 0.75$, treatment 61 of 85 (71.8%), control 12 of 15 (80.0%), NNT 12.
Aghajani, 4/29/2021, retrospective, Iran, peer-reviewed, 7 authors.	risk of death, 26.1% lower, HR 0.74, $p = 0.28$, treatment 40, control 951, univariate Cox proportional regression.
Al Mutair, 2/15/2022, retrospective, Saudi Arabia, peer-reviewed, 14 authors, study period April 2020 - March 2021, this trial compares with another treatment - results may be better when compared to placebo, excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 7.0% lower, RR 0.93, $p = 0.49$, treatment 119 of 269 (44.2%), control 128 of 269 (47.6%), NNT 30.
	risk of ARDS, 8.6% higher, RR 1.09, $p = 0.63$, treatment 76 of 269 (28.3%), control 70 of 269 (26.0%), severe ARDS.
	ICU time, 33.7% higher, relative time 1.34, $p = 0.001$, treatment 269, control 269.
	hospitalization time, 36.6% higher, relative time 1.37, $p = 0.001$, treatment 269, control 269.
Al-Muhsen, 3/4/2022, prospective, Saudi Arabia, peer-reviewed, 11 authors, study period June 2020 - January 2021.	risk of death, 263.0% higher, HR 3.63, $p = 0.04$, treatment 156, control 442, Cox proportional hazards, day 65.
	risk of oxygen therapy, 40.6% lower, RR 0.59, $p < 0.001$, treatment 52 of 156 (33.3%), control 248 of 442 (56.1%), NNT 4.4.
	hospitalization time, 40.0% higher, relative time 1.40, $p = 0.03$, treatment 156, control 442.
Alamer, 5/19/2021, retrospective, Saudi Arabia, peer-reviewed, 18 authors.	risk of death, 56.0% higher, HR 1.56, $p = 0.26$, treatment 12 of 233 (5.2%), control 21 of 223 (9.4%), adjusted per study, day 90.
	risk of mechanical ventilation, 90.0% lower, HR 0.10, $p < 0.001$, treatment 4 of 218 (1.8%), control 27 of 165 (16.4%), NNT 6.9, adjusted per study.
	adjusted discharge ratio, 49.0% lower, RR 0.51, $p < 0.001$, treatment 221, control 201, adjusted per study, inverted to make RR<1 favor treatment.
Almoosa, 8/24/2021, retrospective, Saudi Arabia, peer-reviewed, 14 authors.	risk of death, 42.3% higher, RR 1.42, $p = 0.10$, treatment 33 of 110 (30.0%), control 24 of 116 (20.7%), adjusted per study, odds ratio converted to relative risk, overall mortality, multivariate binary logistic regression.
	risk of death, 149.3% higher, RR 2.49, $p = 0.006$, treatment 26 of

	110 (23.6%), control 11 of 116 (9.5%), day 28.
	risk of death, 61.7% lower, RR 0.38, $p = 0.11$, treatment 4 of 110 (3.6%), control 11 of 116 (9.5%), NNT 17, day 14.
	risk of ICU admission, 90.0% higher, OR 1.90, $p = 0.02$, treatment 110, control 116, adjusted per study, multivariate binary logistic regression, RR approximated with OR.
	recovery time, 10.9% higher, relative time 1.11, $p = 0.17$, treatment 110, control 116.
Alosaimi, 11/24/2022, retrospective, Saudi Arabia, peer-reviewed, 13 authors, study period April 2020 - March 2021, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 80.0% lower, RR 0.20, $p = 0.49$**, treatment 0 of 37 (0.0%), control 2 of 37 (5.4%), NNT 18, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), propensity score matching.
	hospitalization time, 75.0% higher, relative time 1.75, $p = 0.63$, treatment 37, control 37, propensity score matching.
	time to discharge, 40.0% higher, relative time 1.40, $p = 0.74$, treatment 37, control 37, propensity score matching.
Alotaibi, 9/14/2021, retrospective, Saudi Arabia, peer-reviewed, 11 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 57.2% lower, RR 0.43, $p = 0.05$**, treatment 244, control 193, inverted to make RR<1 favor treatment, multivariate, day 30.
AlQahtani, 3/23/2022, Randomized Controlled Trial, Bahrain, peer-reviewed, 13 authors, study period August 2020 - March 2021, trial NCT04387760 (history).	**risk of death, 196.3% higher, RR 2.96, $p = 1.00$**, treatment 1 of 54 (1.9%), control 0 of 52 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 30.
	risk of ICU admission, 75.9% lower, RR 0.24, $p = 0.20$, treatment 1 of 54 (1.9%), control 4 of 52 (7.7%), NNT 17.
	risk of no recovery, 41.9% higher, RR 1.42, $p = 0.51$, treatment 8 of 53 (15.1%), control 5 of 47 (10.6%).
	risk of no viral clearance, 42.9% lower, RR 0.57, $p = 0.21$, treatment 8 of 40 (20.0%), control 14 of 40 (35.0%), NNT 6.7.
Alshamrani, 2/15/2023, retrospective, Saudi Arabia, peer-reviewed, 3 authors, study period March 2020 - January 2021.	**risk of death, 14.0% higher, RR 1.14, $p = 0.13$**, treatment 326 of 1,159 (28.1%), control 316 of 1,380 (22.9%), adjusted per study, odds ratio converted to relative risk, propensity score matching, multivariable.
	risk of progression, 1.9% higher, RR 1.02, $p = 0.83$, treatment 475 of 1,159 (41.0%), control 499 of 1,380 (36.2%), adjusted per study, odds ratio converted to relative risk, AKI, ARDS, multi-organ failure, or mortality, propensity score matching, multivariable.
	ICU time, 18.6% higher, relative time 1.19, $p = 0.005$, treatment 668, control 633, propensity score matching.
	hospitalization time, 28.8% higher, relative time 1.29, $p < 0.001$, treatment 1,159, control 1,380, propensity score matching.

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, 50.9% lower, RR 0.49, $p = 0.02$, treatment 8 of 37 (21.6%), control 55 of 125 (44.0%), NNT 4.5.
Assiri, 8/28/2021, retrospective, Saudi Arabia, peer-reviewed, 8 authors, excluded in exclusion analyses: unadjusted results with no group details; very late stage, ICU patients.	risk of death, 79.3% higher, RR 1.79, $p = 0.50$, treatment 11 of 67 (16.4%), control 3 of 51 (5.9%), inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
Atipornwanich, 10/5/2021, Randomized Controlled Trial, Thailand, peer-reviewed, 16 authors, study period 19 August, 2020 - 28 August, 2021, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with lopinavir/ritonavir or duranivir/ritonavir/HCQ) - results of individual treatments may vary, trial NCT04303299 (history) (FIGHT-COVID-19).	risk of death, 23.1% lower, RR 0.77, $p = 0.66$, treatment 10 of 100 (10.0%), control 13 of 100 (13.0%), NNT 33, favipiravir arms vs. oseltamivir arms.
	risk of progression, 60.0% lower, RR 0.40, $p = 0.009$, treatment 10 of 100 (10.0%), control 25 of 100 (25.0%), NNT 6.7, favipiravir arms vs. oseltamivir arms.
	time to viral-, 8.7% lower, relative time 0.91, $p = 0.43$, treatment mean 9.5 (±5.0) n=50, control mean 10.4 (±6.3) n=50, HCQ arms, primary outcome.
	time to viral-, 8.9% lower, relative time 0.91, $p = 0.34$, treatment mean 10.2 (±4.6) n=50, control mean 11.2 (±5.7) n=50, non-HCQ arms, primary outcome.
Babayigit, 8/31/2022, retrospective, Turkey, peer-reviewed, mean age 51.9, 68 authors, study period 11 March, 2020 - 18 July, 2020, excluded in exclusion analyses: substantial unadjusted confounding by indication possible.	risk of mechanical ventilation, 184.4% higher, RR 2.84, $p = 0.01$, treatment 47 of 325 (14.5%), control 17 of 977 (1.7%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of ICU admission, 181.5% higher, RR 2.81, $p = 0.001$, treatment 75 of 325 (23.1%), control 35 of 969 (3.6%), adjusted per study, odds ratio converted to relative risk, multivariable.
	hospitalization time, 100% higher, relative time 2.00, $p = 0.001$, treatment 265, control 746.
Behboodikhah, 9/15/2022, retrospective, Iran, peer-reviewed, 8 authors.	risk of death, 68.5% lower, OR 0.32, $p = 0.20$, treatment 95, control 2,079, adjusted per study, multivariable, RR approximated with OR.
Cai, 3/18/2020, retrospective, China, peer-reviewed, 26 authors.	risk of no improvement in CT, 68.7% lower, OR 0.31, $p = 0.04$, treatment 35, control 45, inverted to make OR<1 favor treatment, multivariate, RR approximated with OR.
	risk of no viral clearance, 70.9% lower, HR 0.29, $p = 0.03$, treatment 35, control 45, inverted to make HR<1 favor treatment, multivariate.
Chen, 9/2/2021, Randomized Controlled Trial, China, peer-reviewed, 14 authors, average treatment delay 9.0 days, this trial compares with another treatment - results may be better when compared to placebo.	risk of ICU admission, 3.4% higher, RR 1.03, $p = 1.00$, treatment 2 of 116 (1.7%), control 2 of 120 (1.7%).
	risk of respiratory failure, 74.1% lower, RR 0.26, $p = 0.37$, treatment 1 of 116 (0.9%), control 4 of 120 (3.3%), NNT 40.

	risk of oxygen therapy, 19.5% lower, RR 0.80, p = 0.42, treatment 21 of 116 (18.1%), control 27 of 120 (22.5%), NNT 23.
	risk of progression to dyspnea, 70.4% lower, RR 0.30, p = 0.03, treatment 4 of 116 (3.4%), control 14 of 120 (11.7%), NNT 12.
	risk of dyspnea, 10.3% lower, RR 0.90, p = 0.84, treatment 13 of 116 (11.2%), control 15 of 120 (12.5%), NNT 77.
	risk of no recovery, 19.7% lower, RR 0.80, p = 0.15, treatment 45 of 116 (38.8%), control 58 of 120 (48.3%), NNT 10, day 7, primary outcome.
Chuah, 11/19/2021, Randomized Controlled Trial, Malaysia, peer-reviewed, 18 authors, study period February 2021 - July 2021.	risk of death, 1154.0% higher, RR 12.54, p = 0.08, treatment 5 of 250 (2.0%), control 0 of 250 (0.0%), odds ratio converted to relative risk, continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of mechanical ventilation, 19.5% higher, RR 1.20, p = 0.76, treatment 6 of 250 (2.4%), control 5 of 250 (2.0%), odds ratio converted to relative risk.
	risk of ICU admission, 8.5% higher, RR 1.09, p = 0.84, treatment 13 of 250 (5.2%), control 12 of 250 (4.8%), odds ratio converted to relative risk.
Cilli, 3/3/2022, retrospective, Turkey, peer-reviewed, 10 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 37.5% lower, RR 0.62, p = 0.51, treatment 5 of 23 (21.7%), control 8 of 23 (34.8%), NNT 7.7, day 30.
Damayanti, 11/1/2021, retrospective, Indonesia, peer-reviewed, 3 authors, excluded in exclusion analyses: minimal details provided.	risk of no recovery, 54.5% lower, RR 0.46, p = 0.03, treatment 96, control 96, adjusted per study, inverted to make RR<1 favor treatment.
Delen, 12/31/2022, retrospective, Turkey, peer-reviewed, mean age 60.1, 8 authors, study period March 2020 - July 2020.	risk of ICU admission, 22.8% lower, RR 0.77, p = 1.00, treatment 3 of 34 (8.8%), control 4 of 35 (11.4%), NNT 38.
	risk of no recovery, 87.5% lower, RR 0.12, p = 0.02, treatment 1 of 21 (4.8%), control 8 of 21 (38.1%), NNT 3.0, day 5, fever.
	hospitalization time, 2.2% higher, relative time 1.02, p = 0.74, treatment 34, control 35.
	risk of no hospital discharge, 2.9% higher, RR 1.03, p = 1.00, treatment 31 of 34 (91.2%), control 31 of 35 (88.6%).
Finberg, 12/7/2021, Randomized Controlled Trial, USA, peer-reviewed, 10 authors, study period 17 April, 2020 - 30 October, 2020, average treatment delay 8.4 days, trial NCT04358549 (history).	risk of death, 200.0% higher, RR 3.00, p = 1.00, treatment 1 of 25 (4.0%), control 0 of 25 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 60.
	risk of mechanical ventilation, 200.0% higher, RR 3.00, p = 1.00, treatment 1 of 25 (4.0%), control 0 of 25 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).

	risk of no recovery, 58.1% lower, OR 0.42, *p* = 0.08, treatment 25, control 25, inverted to make OR<1 favor treatment, day 8 mid-recovery, 6-point ordinal scale, RR approximated with OR.
	risk of no recovery, 46.2% higher, OR 1.46, *p* = 0.54, treatment 25, control 25, inverted to make OR<1 favor treatment, day 15, 6-point ordinal scale, RR approximated with OR.
	time to viral-, 46.7% lower, relative time 0.53, *p* = 0.04, treatment 25, control 25, primary outcome.
Hafez, 4/8/2022, retrospective, United Arab Emirates, peer-reviewed, 6 authors, this trial uses multiple treatments in the treatment arm (combined with HCQ) - results of individual treatments may vary.	**viral clearance time, 3.1% higher, HR 1.03, *p* = 0.09**, treatment 59, control 1,446, inverted to make HR<1 favor treatment, HCQ + favipiravir, Cox proportional hazards.
	viral clearance time, 58.7% lower, HR 0.41, *p* = 0.09, treatment 4, control 1,446, inverted to make HR<1 favor treatment, HCQ + favipiravir + lopinavir/ritonavir, Cox proportional hazards.
Hartantri, 2/9/2023, retrospective, Indonesia, peer-reviewed, 10 authors, study period 1 March, 2020 - 31 December, 2020.	**risk of death, 76.0% lower, HR 0.24, *p* < 0.001**, adjusted per study, mild/moderate, multivariable, Cox proportional hazards, day 28.
	risk of death, 60.0% lower, HR 0.40, *p* = 0.04, adjusted per study, severe, multivariable, Cox proportional hazards, day 28.
Hassaniazad, 3/24/2022, Randomized Controlled Trial, Iran, peer-reviewed, mean age 53.8, 7 authors, this trial compares with another treatment - results may be better when compared to placebo, trial IRCT20200506047323N3.	**risk of death, 67.7% lower, RR 0.32, *p* = 0.15**, treatment 2 of 32 (6.2%), control 6 of 31 (19.4%), NNT 7.6, day 14.
	risk of death, 3.1% lower, RR 0.97, *p* = 1.00, treatment 1 of 32 (3.1%), control 1 of 31 (3.2%), NNT 992, day 7.
	risk of ICU admission, 35.4% lower, RR 0.65, *p* = 0.51, treatment 4 of 32 (12.5%), control 6 of 31 (19.4%), NNT 15, day 14.
	hospitalization time, 25.0% lower, relative time 0.75, *p* = 0.14, treatment 32, control 31.
	risk of no viral clearance, 18.0% lower, RR 0.82, *p* = 0.24, treatment 22 of 32 (68.8%), control 26 of 31 (83.9%), NNT 6.6, day 7.
Horcajada, 8/24/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Spain, peer-reviewed, 30 authors, study period November 2020 - October 2021, trial EudraCT2020-002753-22 (FAVID).	**risk of death, 382.6% higher, RR 4.83, *p* = 0.49**, treatment 2 of 23 (8.7%), control 0 of 21 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 28.
	risk of mechanical ventilation, 37.0% higher, RR 1.37, *p* = 1.00, treatment 3 of 23 (13.0%), control 2 of 21 (9.5%), day 28.
	dischage or NEWS <3, 16.7% lower, relative time 0.83, *p* = 0.64, treatment 23, control 21.
	time to viral-, 125.0% higher, relative time 2.25, *p* = 0.51, treatment 23, control 21.

Ivashchenko, 8/9/2020, Randomized Controlled Trial, Russia, peer-reviewed, 21 authors, study period April 2020 - May 2020, average treatment delay 6.7 days.	risk of death, 300.0% higher, RR 4.00, $p = 0.55$, treatment 2 of 40 (5.0%), control 0 of 20 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 29.
	risk of mechanical ventilation, 300.0% higher, RR 4.00, $p = 0.55$, treatment 2 of 40 (5.0%), control 0 of 20 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of ICU admission, 300.0% higher, RR 4.00, $p = 0.55$, treatment 2 of 40 (5.0%), control 0 of 20 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	risk of no viral clearance, 46.4% lower, RR 0.54, $p = 0.03$, treatment 15 of 40 (37.5%), control 14 of 20 (70.0%), NNT 3.1, mid-recovery day 5.
	risk of no viral clearance, 62.5% lower, RR 0.37, $p = 0.21$, treatment 3 of 40 (7.5%), control 4 of 20 (20.0%), NNT 8.0, day 10.
	risk of no discharge and WHO-OSC>2, 66.7% higher, RR 1.67, $p = 0.51$, treatment 10 of 40 (25.0%), control 3 of 20 (15.0%).
Khamis, 11/9/2020, Randomized Controlled Trial, Oman, peer-reviewed, 11 authors, study period 22 June, 2020 - 13 August, 2020, this trial compares with another treatment - results may be better when compared to placebo, this trial uses multiple treatments in the treatment arm (combined with interferon beta-1b) - results of individual treatments may vary, excluded in exclusion analyses: study compares against another treatment showing significant efficacy.	risk of death, 14.8% lower, RR 0.85, $p = 1.00$, treatment 5 of 44 (11.4%), control 6 of 45 (13.3%), NNT 51, day 14.
	risk of ICU admission, 2.3% higher, RR 1.02, $p = 1.00$, treatment 8 of 44 (18.2%), control 8 of 45 (17.8%).
	risk of no recovery, 9.6% higher, RR 1.10, $p = 0.82$, treatment 15 of 44 (34.1%), control 14 of 45 (31.1%).
Kulzhanova, 8/31/2021, retrospective, Kazakhstan, peer-reviewed, 10 authors, average treatment delay 6.45 days.	risk of no improvement, 88.0% lower, RR 0.12, $p < 0.001$, treatment 3 of 40 (7.5%), control 25 of 40 (62.5%), NNT 1.8, mid-recovery day 7.
	risk of no improvement, 88.9% lower, RR 0.11, $p = 0.12$, treatment 0 of 40 (0.0%), control 4 of 40 (10.0%), NNT 10.0, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 14.
	risk of no viral clearance, 50.0% lower, RR 0.50, $p = 0.18$, treatment 6 of 40 (15.0%), control 12 of 40 (30.0%), NNT 6.7.
Kurniyanto, 2/28/2022, retrospective, Indonesia, peer-reviewed, 11 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 48.0% lower, RR 0.52, $p = 0.21$, treatment 10 of 325 (3.1%), control 9 of 152 (5.9%), NNT 35.
Lou, 10/25/2020, Randomized Controlled Trial, China, peer-reviewed, 13 authors, average treatment delay 8.5 days, trial ChiCTR2000029544.	risk of ICU admission, 422.2% higher, RR 5.22, $p = 0.21$, treatment 2 of 9 (22.2%), control 0 of 10 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).

	risk of no recovery, 11.1% lower, RR 0.89, p = 1.00, treatment 4 of 9 (44.4%), control 5 of 10 (50.0%), NNT 18, day 14.
	risk of no recovery, 13.6% lower, RR 0.86, p = 0.58, treatment 7 of 9 (77.8%), control 9 of 10 (90.0%), NNT 8.2, day 7.
	risk of no viral clearance, 422.2% higher, RR 5.22, p = 0.21, treatment 2 of 9 (22.2%), control 0 of 10 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 14.
	risk of no viral clearance, 11.1% higher, RR 1.11, p = 1.00, treatment 5 of 9 (55.6%), control 5 of 10 (50.0%), day 7.
Pushkar, 11/5/2020, Randomized Controlled Trial, Russia, preprint, mean age 50.0, 1 author.	risk of no clinical status improvement of 2+ WHO-OSCI at ~10 days, 14.1% lower, RR 0.86, p = 0.06, treatment 73 of 100 (73.0%), control 85 of 100 (85.0%), NNT 8.3.
	relative time to clinical improvement, 33.3% lower, relative time 0.67, p < 0.001, treatment 100, control 100.
	risk of no fever reduction by day 3, 45.2% lower, RR 0.55, p < 0.001, treatment 40 of 100 (40.0%), control 73 of 100 (73.0%), NNT 3.0.
	relative time to resolution of fever, 20.0% lower, relative time 0.80, p = 0.05, treatment 100, control 100.
	risk of no discharge at day 10, 69.7% lower, RR 0.30, p < 0.001, treatment 10 of 100 (10.0%), control 33 of 100 (33.0%), NNT 4.3.
	risk of no full recovery at day 10, 26.7% lower, RR 0.73, p < 0.001, treatment 66 of 100 (66.0%), control 90 of 100 (90.0%), NNT 4.2.
	risk of no improvement in lung CT, 33.3% lower, RR 0.67, p = 0.007, treatment 40 of 100 (40.0%), control 60 of 100 (60.0%), NNT 5.0.
	risk of no viral clearance, 90.5% lower, RR 0.10, p < 0.001, treatment 2 of 100 (2.0%), control 21 of 100 (21.0%), NNT 5.3.
Rahman, 5/13/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Bangladesh, peer-reviewed, mean age 37.8, 10 authors, study period May 2020 - July 2020, trial NCT04402203 (history).	risk of no chest x-ray improvement, 89.5% lower, RR 0.11, p = 0.005, treatment 1 of 19 (5.3%), control 8 of 16 (50.0%), NNT 2.2, day 10.
	risk of no chest x-ray improvement, 64.9% lower, RR 0.35, p = 0.007, treatment 5 of 19 (26.3%), control 12 of 16 (75.0%), NNT 2.1, day 7.
	risk of no chest x-ray improvement, 47.4% lower, RR 0.53, p = 0.001, treatment 10 of 19 (52.6%), control 16 of 16 (100.0%), NNT 2.1, day 4.

	risk of no viral clearance, 91.7% lower, RR 0.08, $p < 0.001$, treatment 1 of 25 (4.0%), control 12 of 25 (48.0%), NNT 2.3, day 10.
	risk of no viral clearance, 62.5% lower, RR 0.38, $p = 0.010$, treatment 6 of 25 (24.0%), control 16 of 25 (64.0%), NNT 2.5, day 7.
	risk of no viral clearance, 48.0% lower, RR 0.52, $p < 0.001$, treatment 13 of 25 (52.0%), control 25 of 25 (100.0%), NNT 2.1, day 4.
Saito, 1/28/2024, retrospective, Japan, peer-reviewed, 6 authors, study period February 2020 - June 2021, average treatment delay 6.9 days, excluded in exclusion analyses: unadjusted results with no group details.	risk of death, 168.3% higher, RR 2.68, $p = 0.06$, treatment 7 of 40 (17.5%), control 6 of 92 (6.5%).
Shah, 9/22/2022, Randomized Controlled Trial, placebo-controlled, multiple countries, peer-reviewed, median age 58.9, 120 authors, study period 5 May, 2020 - 26 May, 2021, average treatment delay 8.9 days, trial NCT04373733 (history) (PIONEER).	risk of death, 26.0% lower, HR 0.74, $p = 0.24$, treatment 26 of 251 (10.4%), control 34 of 248 (13.7%), NNT 30, day 28.
	risk of mechanical ventilation, 24.0% lower, HR 0.76, $p = 0.21$, treatment 251, control 248.
	risk of no recovery, 5.7% lower, HR 0.94, $p = 0.53$, treatment 251, control 248, inverted to make HR<1 favor treatment.
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, 96.4% lower, RR 0.04, $p = 0.14$, treatment 0 of 19 (0.0%), control 24 of 164 (14.6%), NNT 6.8, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Shenoy, 11/9/2021, Double Blind Randomized Controlled Trial, Kuwait, preprint, 8 authors, study period 22 August, 2020 - 27 January, 2021, average treatment delay 6.3 days, trial NCT04529499 (history).	risk of death, 29.5% higher, RR 1.29, $p = 0.54$, treatment 14 of 175 (8.0%), control 11 of 178 (6.2%), day 28.
	risk of mechanical ventilation, 33.0% higher, RR 1.33, $p = 0.54$, treatment 17 of 175 (9.7%), control 13 of 178 (7.3%).
	risk of ICU admission, 1.7% higher, RR 1.02, $p = 0.54$, treatment 20 of 175 (11.4%), control 20 of 178 (11.2%).
	time to resolution of hypoxia, 1.0% higher, HR 1.01, $p = 0.94$, treatment 157, control 158, inverted to make HR<1 favor treatment, primary outcome.
	time to hospital discharge, 5.7% lower, HR 0.94, $p = 0.60$, treatment 175, control 178, inverted to make HR<1 favor treatment.
	time to resolution of hypoxia, 17.4% lower, HR 0.83, $p = 0.29$, treatment 157, control 158, inverted to make HR<1 favor treatment, earlier treatment subgroup, primary outcome.
	time to hospital discharge, 32.0% lower, HR 0.68, $p = 0.01$, treatment 175, control 178, inverted to make HR<1 favor treatment, earlier treatment subgroup.

Shinada, 3/24/2022, retrospective, Japan, peer-reviewed, 11 authors, study period 28 May, 2020 - 26 September, 2020, average treatment delay 8.9 days.	hospitalization time, 7.5% lower, HR 0.93, $p = 0.84$, treatment 17, control 17.
	viral clearance time, 55.2% lower, HR 0.45, $p = 0.04$, treatment 17, control 17.
Shinkai, 8/27/2021, Single Blind Randomized Controlled Trial, Japan, peer-reviewed, 39 authors, average treatment delay 4.8 days.	time to improvement, 37.1% lower, HR 0.63, $p = 0.01$, treatment 107, control 49, adjusted per study, inverted to make HR<1 favor treatment, Cox proportional hazards, composite time to improvement in temperature, SpO2, CT findings, and recovery to PCR-.
	time to improvement, 58.5% lower, HR 0.41, $p = 0.01$, treatment 47, control 13, adjusted per study, inverted to make HR<1 favor treatment, <5 days from onset of fever, Cox proportional hazards, composite time to improvement in temperature, SpO2, CT findings, and recovery to PCR-.
Solaymani-Dodaran, 3/11/2021, Randomized Controlled Trial, Iran, peer-reviewed, 44 authors, study period 4 February, 2020 - 8 March, 2020, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 19.2% higher, RR 1.19, $p = 0.54$, treatment 26 of 190 (13.7%), control 21 of 183 (11.5%).
	risk of mechanical ventilation, 53.0% higher, RR 1.53, $p = 0.15$, treatment 27 of 190 (14.2%), control 17 of 183 (9.3%).
	risk of ICU admission, 19.4% higher, RR 1.19, $p = 0.56$, treatment 31 of 190 (16.3%), control 25 of 183 (13.7%).
Sulaiman, 6/14/2023, retrospective, Saudi Arabia, peer-reviewed, mean age 60.1, 20 authors, study period 1 March, 2020 - 31 July, 2021, excluded in exclusion analyses: very late stage, ICU patients.	risk of death, 17.0% higher, HR 1.17, $p = 0.51$, treatment 73, control 73, in-hospital, propensity score matching.
	risk of death, 14.0% lower, HR 0.86, $p = 0.53$, treatment 73, control 73, propensity score matching, day 30.
	ventilation time, 46.7% higher, relative time 1.47, $p = 0.008$, treatment 73, control 73, propensity score matching.
	ICU time, 50.0% higher, relative time 1.50, $p = 0.01$, treatment 73, control 73, propensity score matching.
Tabarsi, 9/30/2021, Randomized Controlled Trial, Iran, peer-reviewed, 27 authors, study period 4 April, 2020 - 7 May, 2020, average treatment delay 7.0 days, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 29.7% lower, RR 0.70, $p = 0.70$, treatment 3 of 32 (9.4%), control 4 of 30 (13.3%), NNT 25.
	risk of ICU admission, 41.4% lower, RR 0.59, $p = 0.36$, treatment 5 of 32 (15.6%), control 8 of 30 (26.7%), NNT 9.1.
	risk of <50% improvement in chest CT, 6.2% lower, RR 0.94, $p = 0.76$, treatment 24 of 32 (75.0%), control 24 of 30 (80.0%), NNT 20.
	hospitalization time, 25.0% lower, relative time 0.75, $p = 0.03$, treatment 32, control 30.

Tawfik, 6/29/2022, retrospective, Saudi Arabia, peer-reviewed, mean age 60.1, 8 authors, study period 3 June, 2020 - 3 November, 2020, excluded in exclusion analyses: unadjusted results with minimal group details.	risk of death, 96.5% lower, RR 0.04, $p < 0.001$, treatment 1 of 103 (1.0%), control 17 of 62 (27.4%), NNT 3.8.
	risk of ICU admission, 21.0% lower, RR 0.79, $p = 0.45$, treatment 21 of 103 (20.4%), control 16 of 62 (25.8%), NNT 18.
	hospitalization time, 15.8% lower, relative time 0.84, $p < 0.001$, treatment mean 9.6 (±1.2) n=102, control mean 11.4 (±1.7) n=58.
Tehrani, 6/15/2022, Randomized Controlled Trial, Iran, peer-reviewed, mean age 52.5, 5 authors, study period April 2021 - September 2021, average treatment delay 5.29 days, trial IRCT20211004052664N1.	risk of hospitalization, 34.2% lower, RR 0.66, $p = 0.24$, treatment 10 of 38 (26.3%), control 16 of 40 (40.0%), NNT 7.3.
	risk of no recovery, 79.6% lower, RR 0.20, $p = 0.49$, treatment 0 of 38 (0.0%), control 2 of 40 (5.0%), NNT 20, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7, dyspnea.
	risk of no recovery, 57.9% lower, RR 0.42, $p = 0.010$, treatment 8 of 38 (21.1%), control 20 of 40 (50.0%), NNT 3.5, day 5, dyspnea.
	risk of no recovery, 47.4% lower, RR 0.53, $p = 1.00$, treatment 1 of 38 (2.6%), control 2 of 40 (5.0%), NNT 42, day 7, fever.
	risk of no recovery, 47.4% lower, RR 0.53, $p = 0.25$, treatment 5 of 38 (13.2%), control 10 of 40 (25.0%), NNT 8.4, day 5, fever.
	risk of no recovery, 66.1% lower, RR 0.34, $p = 1.00$, treatment 0 of 38 (0.0%), control 1 of 40 (2.5%), NNT 40, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm), day 7, sore throat.
	risk of no recovery, 47.4% lower, RR 0.53, $p = 0.68$, treatment 2 of 38 (5.3%), control 4 of 40 (10.0%), NNT 21, day 5, sore throat.
	risk of no recovery, 29.8% lower, RR 0.70, $p = 0.17$, treatment 16 of 38 (42.1%), control 24 of 40 (60.0%), NNT 5.6, day 7, cough.
	risk of no recovery, 7.1% lower, RR 0.93, $p = 0.56$, treatment 30 of 38 (78.9%), control 34 of 40 (85.0%), NNT 17, day 5, cough.
	risk of no recovery, 21.1% lower, RR 0.79, $p = 0.77$, treatment 6 of 38 (15.8%), control 8 of 40 (20.0%), NNT 24, day 7, myalgia.
	risk of no recovery, 38.1% lower, RR 0.62, $p = 0.16$, treatment 10 of 38 (26.3%), control 17 of 40 (42.5%), NNT 6.2, day 5, myalgia.
Uyaroğlu, 3/17/2022, retrospective, propensity score matching, Turkey, peer-reviewed, 6 authors, study period 20 March, 2020 - 30 September, 2020, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 66.7% lower, RR 0.33, $p = 1.00$, treatment 0 of 42 (0.0%), control 1 of 42 (2.4%), NNT 42, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).

	risk of ICU admission, 200.0% higher, RR 3.00, p = 1.00, treatment 1 of 42 (2.4%), control 0 of 42 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	hospitalization time, 10.8% higher, relative time 1.11, p = 0.90, treatment 42, control 42.
Yulia, 3/7/2022, retrospective, Indonesia, peer-reviewed, median age 46.0, 10 authors, study period July 2020 - December 2020.	**risk of death, 85.3% lower, OR 0.15, p = 0.05**, inverted to make OR<1 favor treatment, RR approximated with OR.
Zhao, 4/21/2021, Randomized Controlled Trial, China, peer-reviewed, 25 authors, study period 27 March, 2020 - 9 May, 2020.	**risk of no viral clearance, 59.0% lower, RR 0.41, p = 0.06**, treatment 7 of 36 (19.4%), control 9 of 19 (47.4%), NNT 3.6.
	time to viral-, 52.4% lower, relative time 0.48, p = 0.04, treatment 36, control 19, inverted to make RR<1 favor treatment.

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.

References

1. **Abdulrahman** et al., *Favipiravir efficacy and safety for the treatment of severe coronavirus 2019: a retrospective study*, Journal of Ayub Medical College Abbottabad, doi:10.55519/JAMC-03-10305.
2. **Acar Sevinc**, S., *Favipiravir Experience in COVID-19 Patients at a Tertiary Center Intensive Care Unit*, SiSli Etfal Hastanesi Tip Bulteni / The Medical Bulletin of Sisli Hospital, doi:10.14744/SEMB.2021.35902.
3. **Adhikari** et al., *Efficacy of Favipiravir in treatment of mild & moderate COVID-19 infection in Nepal: a multi-center, randomized, open-labelled, phase III clinical trial*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.12.109.
4. **Aghajani** et al., *Decreased In-Hospital Mortality Associated with Aspirin Administration in Hospitalized Patients Due to Severe COVID-19*, Journal of Medical Virology, doi:10.1002/jmv.27053.
5. **Al Mutair** et al., *Overview of Clinical Outcome and Therapeutic Effectiveness of Favipiravir in Patients with COVID-19 Admitted to Intensive Care Unit, Riyadh, Saudi Arabia*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2022.01.013.
6. **Al-Muhsen** et al., *Favipiravir Effectiveness and Safety in Hospitalized Moderate-Severe COVID-19 Patients: Observational Prospective Multicenter Investigation in Saudi Arabia*, Frontiers in Medicine, doi:10.3389/fmed.2022.826247.
7. **Alamer** et al., *Effectiveness and safety of favipiravir compared to supportive care in moderately to critically ill COVID-19 patients: a retrospective study with propensity score matching sensitivity analysis*, Current Medical Research and Opinion, doi:10.1080/03007995.2021.1920900.
8. **Alattar** et al., *Favipiravir for the Treatment of Coronavirus Disease 2019 Pneumonia; a Propensity Score-matched Cohort Study*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2022.08.011.

9. **Almoosa** et al., *Favipiravir versus Standard of Care in Patients with Severe COVID-19 Infections: A Retrospective Comparative Study*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2021.08.022.

10. **Alosaimi** et al., *Analyzing the Difference in the Length of Stay (LOS) in Moderate to Severe COVID-19 Patients Receiving Hydroxychloroquine or Favipiravir*, Pharmaceuticals, doi:10.3390/ph15121456.

11. **Alotaibi** et al., *Effectiveness and Safety of Favipiravir Compared to Hydroxychloroquine for Management of Covid-19: A Retrospective Study*, International Journal of General Medicine, 2021:14, www.dovepress.com/getfile.php?fileID=73585.

12. **AlQahtani** et al., *Randomized controlled trial of favipiravir, hydroxychloroquine, and standard care in patients with mild/moderate COVID-19 disease*, Scientific Reports, doi:10.1038/s41598-022-08794-w.

13. **Als-Nielsen** et al., *Association of Funding and Conclusions in Randomized Drug Trials*, JAMA, doi:10.1001/jama.290.7.921.

14. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.

15. **Alshamrani** et al., *Comprehensive evaluation of six interventions for hospitalized patients with COVID-19: A propensity score matching study*, Saudi Pharmaceutical Journal, doi:10.1016/j.jsps.2023.02.004.

16. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.

17. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.

18. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:/10.1016/j.micpath.2020.104228.

19. **Anglemyer** et al., *Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials*, Cochrane Database of Systematic Reviews 2014, Issue 4, doi:10.1002/14651858.MR000034.pub2.

20. **Arfijanto** et al., *Duration of SARS-CoV-2 RNA Shedding Is Significantly Influenced by Disease Severity, Bilateral Pulmonary Infiltrates, Antibiotic Treatment, and Diabetic Status: Consideration for Isolation Period*, Pathophysiology, doi:10.3390/pathophysiology30020016.

21. **Assiri** et al., *COVID-19 related treatment and outcomes among COVID-19 ICU patients: A retrospective cohort study*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2021.08.030.

22. **Atipornwanich** et al., *Various Combinations of Favipiravir, Lopinavir-Ritonavir, Darunavir-Ritonavir, High-Dose Oseltamivir, and Hydroxychloroquine for the Treatment of COVID-19: A Randomized Controlled Trial (FIGHT-COVID-19 Study)*, SSRN Electronic Journal, doi:10.2139/ssrn.3936499.

23. **Babayigit** et al., *The association of antiviral drugs with COVID-19 morbidity: The retrospective analysis of a nationwide COVID-19 cohort*, Frontiers in Medicine, doi:10.3389/fmed.2022.894126.

24. **Bacigalupo** et al., *Unveiling patenting strategies of therapeutics and vaccines: evergreening in the context of COVID-19 pandemic*, Frontiers in Medicine, doi:10.3389/fmed.2023.1287542.

25. **Behboodikhah** et al., *Evaluation of the Costs and Outcomes of COVID-19 Therapeutic Regimens in Hospitalized Patients in Shiraz*, Iranian Journal of Science and Technology, Transactions A: Science, doi:10.1007/s40995-022-01351-0.

26. **Bosaeed** et al., *Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicenter, placebo-controlled trial clinical trial*, Clinical Microbiology and Infection, doi:10.1016/j.cmi.2021.12.026.

27. **Boulware**, D., *Comments regarding paper rejection*, twitter.com/boulware_dr/status/1311331372884205570.

28. **Bruminhent** et al., *Clinical Course and Outcomes among COVID-19 Patients at the Hospitel in Bangkok: A Retrospective Study*, Tropical Medicine and Infectious Disease, doi:10.3390/tropicalmed7090238.

29. ***c19early.org***, c19early.org/timeline.html.

30. ***c19early.org (B)***, c19early.org/treatments.html.

31. ***c19favipiravir.com***, c19favipiravir.com/meta.html#fig_fpr.

32. **Cai** et al., *Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study*, Engineering, doi:10.1016/j.eng.2020.03.007.

33. **Chandiwana** et al., *Safety and efficacy of four drug regimens versus standard-of-care for the treatment of symptomatic outpatients with COVID-19: A randomised, open-label, multi-arm, phase 2 clinical trial*, eBioMedicine, doi:10.1016/j.ebiom.2022.104322.

34. **Chen** et al., *Favipiravir Versus Arbidol for Clinical Recovery Rate in Moderate and Severe Adult COVID-19 Patients: A Prospective, Multicenter, Open-Label, Randomized Controlled Clinical Trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2021.683296.

35. **Chuah** et al., *Efficacy of Early Treatment with Favipiravir on Disease Progression among High Risk COVID-19 Patients: A Randomized, Open-Label Clinical Trial*, Clinical Infectious Diseases, doi:10.1093/cid/ciab962.

36. **Cilli** et al., *Characteristics and outcomes of COVID-19 patients with IPF: A multi-center retrospective study*, Respiratory Medicine and Research, doi:10.1016/j.resmer.2022.100900.

37. ***clinicaltrials.gov***, clinicaltrials.gov/ct2/history/NCT04600895?A=6&B=7&C=merged#StudyPageTop.

38. **Concato** et al., NEJM, 342:1887-1892, doi:10.1056/NEJM200006223422507.

39. **Damayanti** et al., *The Effectiveness and Safety of Favipiravir in COVID-19 Hospitalized Patients in Bali, Indonesia*, Kesmas: National Public Health Journal, doi:10.21109/kesmas.v16i4.5433.

40. **Davidson** et al., *No evidence of important difference in summary treatment effects between COVID-19 preprints and peer-reviewed publications: a meta-epidemiological study*, Journal of Clinical Epidemiology, doi:10.1016/j.jclinepi.2023.08.011.

41. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.

42. **Deaton** et al., *Understanding and misunderstanding randomized controlled trials*, Social Science & Medicine, 210, doi:10.1016/j.socscimed.2017.12.005.

43. **Delen** et al., *Effects of Hydroxychloroquine Plus Favipiravir Treatment on the Clinical Course and Biomarkers in Hospitalized COVID-19 Patients with Pneumonia*, Acta Clinica Croatica, doi:10.20471/acc.2022.61.03.05.

44. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.

45. **Eberhardt** et al., *SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels*, Nature Cardiovascular Research, doi:10.1038/s44161-023-00336-5.

46. **Egger** et al., *Bias in meta-analysis detected by a simple, graphical test*, BMJ, doi:10.1136/bmj.315.7109.629.

47. **Faria** et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil*, Science, doi:10.1126/science.abh2644.

48. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.

49. **Finberg** et al., *US201 Study: A Phase 2, Randomized Proof-of-Concept Trial of Favipiravir for the Treatment of COVID-19*, Open Forum Infectious Diseases, doi:10.1093/ofid/ofab56310.

50. **Golan** et al., *Favipiravir in patients with early mild-to-moderate COVID-19: a randomized controlled trial*, Clinical Infectious Diseases, doi:10.1093/cid/ciac712.

51. **Gøtzsche**, P., *Bias in double-blind trials*, Doctoral Thesis, University of Copenhagen, www.scientificfreedom.dk/2023/05/16/bias-in-double-blind-trials-doctoral-thesis/.

52. **Gül** et al., *Effect of favipiravir use on INR, PT, aPTT tests of COVID-19 patients*, Sabuncuoglu Serefeddin Health Sciences, doi:10.55895/sshs.1213382.

53. **Hadj Hassine** et al., *Lethal Mutagenesis of RNA Viruses and Approved Drugs with Antiviral Mutagenic Activity*, Viruses, doi:10.3390/v14040841.

54. **Hafez** et al., *Antiviral Used among Non-Severe COVID-19 Cases in Relation to Time till Viral Clearance: A Retrospective Cohort Study*, Antibiotics, doi:10.3390/antibiotics11040498.

55. **Harbord** et al., *A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints*, Statistics in Medicine, doi:10.1002/sim.2380.

56. **Hartantri** et al., *Clinical and treatment factors associated with the mortality of COVID-19 patients admitted to a referral hospital in Indonesia*, The Lancet Regional Health - Southeast Asia, doi:10.1016/j.lansea.2023.100167.

57. **Hassaniazad** et al., *Efficacy and safety of favipiravir plus interferon-beta versus lopinavir/ritonavir plus interferon-beta in moderately ill patients with COVID-19: A randomized clinical trial*, Journal of Medical Virology, doi:10.1002/jmv.27724.

58. **Hayden** et al., *Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents*, New England Journal of Medicine, doi:10.1056/NEJMoa1716197.

59. **Holubar** et al., *Favipiravir for treatment of outpatients with asymptomatic or uncomplicated COVID-19: a double-blind randomized, placebo-controlled, phase 2 trial*, Clinical Infectious Diseases, doi:10.1093/cid/ciac312.

60. **Horcajada** et al., *Safety and efficacy of favipiravir in COVID-19 patients with pneumonia. A randomized, double-blind, placebo-controlled study (FAVID)*, Pneumonia, doi:10.1186/s41479-023-00124-6.

61. **Ikematsu** et al., *Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts*, New England Journal of Medicine, doi:10.1056/NEJMoa1915341.

62. **Ivashchenko** et al., *AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial*, Clin. Infect. Dis., doi:10.1093/cid/ciaa1176.

63. **Iwata** et al., *Findings from a discontinued clinical trial of favipiravir in high-risk patients with early-onset COVID-19*, Journal of Infection and Chemotherapy, doi:10.1016/j.jiac.2023.10.010.

64. **Jadad** et al., *Randomized Controlled Trials: Questions, Answers, and Musings, Second Edition*, doi:10.1002/9780470691922.

65. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.

66. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.

67. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.

68. **Kara** et al., *Efficacy and Safety of Hydroxychloroquine and Favipiravir in the Treatment of Mild to Moderate COVID-19*, NCT04411433, clinicaltrials.gov/study/NCT04411433.

69. **Karita** et al., *Trajectory of viral load in a prospective population-based cohort with incident SARS-CoV-2 G614 infection*, medRxiv, doi:10.1101/2021.08.27.21262754.

70. **Khamis** et al., *Randomized Controlled Open Label Trial on the Use of Favipiravir Combined with Inhaled Interferon beta-1b in Hospitalized Patients with Moderate to Severe COVID-19 Pneumonia*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2020.11.008.

71. **Kulzhanova** et al., *Clinical efficacy of the antiviral drug favipiravir in the complex treatment of patients with COVID-19 coronavirus infection*, , newjournal.ssmu.kz/upload/iblock/026/6_15_4_23_2021.pdf.

72. **Kumar** et al., *Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial*, The Lancet Infectious Diseases, doi:10.1016/S1473-3099(21)00469-2.

73. **Kurniyanto** et al., *Factors Associated with Death and ICU Referral among COVID-19 Patients Hospitalized in the Secondary Referral Academic Hospital in East Jakarta, Indonesia*, Journal of Clinical Virology Plus, doi:10.1016/j.jcvp.2022.100068.

74. **Lee** et al., *Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines*, Arch Intern Med., 2011, 171:1, 18-22, doi:10.1001/archinternmed.2010.482.

75. **Lokanuwatsatien** et al., *Prevalence and associating factors of long COVID in pediatric patients during the Delta and the Omicron variants*, Frontiers in Pediatrics, doi:10.3389/fped.2023.1127582.

76. **López-Medina** et al., *Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial*, JAMA, doi:10.1001/jama.2021.3071.

77. **Lou** et al., *Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial*, European Journal of Pharmaceutical Sciences, doi:10.1016/j.ejps.2020.105631.

78. **Lowe** et al., *Favipiravir, lopinavir-ritonavir, or combination therapy (FLARE): A randomised, double-blind, 2 × 2 factorial placebo-controlled trial of early antiviral therapy in COVID-19*, PLOS Medicine, doi:10.1371/journal.pmed.1004120.

79. **Lui** et al., *Nsp1 facilitates SARS-CoV-2 replication through calcineurin-NFAT signaling*, Virology, doi:10.1128/mbio.00392-24.

80. **Luvira** et al., *Clinical antiviral efficacy of favipiravir in early COVID-19 (PLATCOV): an open-label, randomised, controlled, adaptive platform trial*, BMC Infectious Diseases, doi:10.1186/s12879-023-08835-3.

81. **Lv** et al., *Host proviral and antiviral factors for SARS-CoV-2*, Virus Genes, doi:10.1007/s11262-021-01869-2.

82. **Macaskill** et al., *A comparison of methods to detect publication bias in meta-analysis*, Statistics in Medicine, doi:10.1002/sim.698.

83. **Malone** et al., *Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design*, Nature Reviews Molecular Cell Biology, doi:10.1038/s41580-021-00432-z.

84. **McLean** et al., *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100.

85. **McMahon** et al., *Favipiravir in early symptomatic COVID-19, a randomised placebo-controlled trial*, eClinicalMedicine, doi:10.1016/j.eclinm.2022.101703.

86. **Meeus**, G., *Online Comment*, twitter.com/gertmeeus_MD/status/1386636373889781761.

87. **Meneguesso**, A., *Médica defende tratamento precoce da Covid-19*, www.youtube.com/watch?v=X5FCrIm_19U.

88. **Moreno** et al., *Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study*, BMC Medical Research Methodology, doi:10.1186/1471-2288-9-2.

89. **Murigneux** et al., *Proteomic analysis of SARS-CoV-2 particles unveils a key role of G3BP proteins in viral assembly*, Nature Communications, doi:10.1038/s41467-024-44958-0.

90. **Nichol** et al., *Challenging issues in randomised controlled trials*, Injury, 2010, doi: 10.1016/j.injury.2010.03.033, www.injuryjournal.com/article/S0020-1383(10)00233-0/fulltext.

91. **Nonaka** et al., *SARS-CoV-2 variant of concern P.1 (Gamma) infection in young and middle-aged patients admitted to the intensive care units of a single hospital in Salvador, Northeast Brazil, February 2021*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2021.08.003.

92. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.

93. **Peacock** et al., *The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry*, bioRxiv, doi:10.1101/2021.12.31.474653.

94. **Peters**, J., *Comparison of Two Methods to Detect Publication Bias in Meta-analysis*, JAMA, doi:10.1001/jama.295.6.676.

95. **Pushkar** et al., *Study of Favipiravir Compared to Standard of Care in Hospitalized Patients With COVID-19*, NCT04542694, clinicaltrials.gov/ct2/show/results/NCT04542694?view=results.

96. **Qadir** et al., *Efficacy of Favipiravir in the Treatment of Mild to Moderate COVID-19 Patients in Erbil: A Controlled Clinical Trial*, International Journal of Applied Sciences: Current and Future Research Trends, 13:1, ijascfrtjournal.isrra.org/index.php/Applied_Sciences_Journal/article/view/1235.

97. **Rahman** et al., *Safety and Efficacy of Favipiravir for the management of COVID-19 Patients: A Randomized Control Trial*, Clinical Infection in Practice, doi:10.1016/j.clinpr.2022.100145.

98. **Rothstein**, H., *Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments*, www.wiley.com/en-ae/Publication+Bias+in+Meta+Analysis:+Prevention,+Assessment+and+Adjustments-p-9780470870143.

99. **Rücker** et al., *Arcsine test for publication bias in meta-analyses with binary outcomes*, Statistics in Medicine, doi:10.1002/sim.2971.

100. **Ruzhentsova** et al., *Phase 3 Trial of Coronavir (Favipiravir) in Patients with Mild to Moderate COVID-19*, SSRN, doi:10.2139/ssrn.3696907.

101. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.

102. **Saito** et al., *Predictors of in-hospital mortality in elderly unvaccinated patients during SARS-CoV-2 Alpha variants epidemic*, Infection Prevention in Practice, doi:10.1016/j.infpip.2024.100341.

103. **Sawanpanyalert** et al., *Assessment of outcomes following implementation of antiviral treatment guidelines for COVID-19 during the first wave in Thailand*, Southeast Asian Journal of Tropical Medicine and Public Health, 52:4, journal.seameotropmednetwork.org/index.php/jtropmed/article/view/490.

104. **Scardua-Silva** et al., *Microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19*, Scientific Reports, doi:10.1038/s41598-024-52005-7.

105. **Schilling** et al., *Pharmacometrics of high dose ivermectin in early COVID-19: an open label, randomized, controlled adaptive platform trial (PLATCOV)*, eLife, doi:10.7554/eLife.83201.

106. **Shah** et al., *Favipiravir in patients hospitalised with COVID-19 (PIONEER trial): a multicentre, open-label, phase 3, randomised controlled trial of early intervention versus standard care*, The Lancet Respiratory Medicine, doi:10.1016/S2213-2600(22)00412-X.

107. **Shamsi** et al., *Survival and Mortality in Hospitalized Children with COVID-19: A Referral Center Experience in Yazd, Iran*, Canadian Journal of Infectious Diseases and Medical Microbiology, doi:10.1155/2023/5205188.

108. **Shenoy** et al., *Favipiravir In Adults with Moderate to Severe COVID-19: A Phase 3 Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial*, medRxiv, doi:10.1101/2021.11.08.21265884.

109. **Shinada** et al., *Longitudinal Analysis of Neutralizing Potency against SARS-CoV-2 in the Recovered Patients after Treatment with or without Favipiravir*, Viruses, doi:10.3390/v14040670.

110. **Shinkai** et al., *Efficacy and Safety of Favipiravir in Moderate COVID-19 Pneumonia Patients without Oxygen Therapy: A Randomized, Phase III Clinical Trial*, Infectious Diseases and Therapy, doi:10.1007/s40121-021-00517-4.

111. **Sirijatuphat** et al., *Early Treatment of Favipiravir in COVID-19 Patients Without Pneumonia: A Multicentre, Open-Labelled, Randomized Control Study*, medRxiv, doi:10.1101/2022.06.06.22275902.

112. **Solaymani-Dodaran** et al., *Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia*, International Immunopharmacology, doi:10.1016/j.intimp.2021.107522.

113. **Stanley** et al., *Meta-regression approximations to reduce publication selection bias*, Research Synthesis Methods, doi:10.1002/jrsm.1095.

114. **Sulaiman** et al., *When Antivirals Backfire: An Evaluation of Favipiravir's Clinical Outcomes in Critically Ill Patients with COVID-19: A Multicenter Cohort Study*, Journal of Infection and Public Health, doi:10.1016/j.jiph.2023.06.011.

115. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

116. **Tabarsi** et al., *Favipiravir Effects on the Control of Clinical Symptoms of Hospitalized COVID-19 Cases: An Experience with Iranian Formulated Dosage Form*, Iranian Journal of Pharmaceutical Research, doi:10.22037/ijpr.2021.115510.15401.

117. **Tawfik** et al., *Effectiveness of Early Favipiravir Therapy in Hospitalised COVID-19 Patients*, Advances in Virology, doi:10.1155/2022/9240941.

118. **Tehrani** et al., *Efficacy of Favipiravir in the Treatment of Moderate COVID-19 Patients: A Randomized, Open-label, Controlled Clinical Trial*, Mediterranean Journal of Infection Microbes and Antimicrobials, doi:10.4274/mjima.galenos.2022.2022.30.

119. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.

120. **Treanor** et al., *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016.

121. **Tsuzuki** et al., *Effectiveness of Favipiravir on Nonsevere, Early-Stage COVID-19 in Japan: A Large Observational Study Using the COVID-19 Registry Japan*, Infectious Diseases and Therapy, doi:10.1007/s40121-022-00617-9.

122. **Udwadia** et al., *Efficacy and Safety of Favipiravir, an Oral RNA-Dependent RNA Polymerase Inhibitor, in Mild-to-Moderate COVID-19: A Randomized, Comparative, Open-Label, Multicenter, Phase 3 Clinical Trial*, International Journal of Infectious Diseases, doi:10.1016/j.ijid.2020.11.142.

123. **Unal** et al., *Favipiravir, umifenovir and camostat mesylate: a comparative study against SARS-CoV-2*, bioRxiv, doi:10.1101/2022.01.11.475889.

124. **Usanma Koban** et al., *The factors affecting the prolonged PCR positivity in COVID-19 patients*, Bratislava Medical Journal, doi:10.4149/BLL_2022_082.

125. **Uyaroğlu** et al., *Comparison of Favipiravir to Hydroxychloroquine Plus Azithromycin in the Treatment of Patients with Non-critical COVID-19: A Single-center, Retrospective, Propensity Score-matched Study*, Acta Medica, doi:10.32552/2022.ActaMedica.719.

126. **Vaezi** et al., *Favipiravir in the Treatment of Outpatient COVID-19: A Multicenter, Randomized, Triple-Blind, Placebo-Controlled Clinical Trial*, Advances in Respiratory Medicine, doi:10.3390/arm91010004.

127. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.

128. **Waters** et al., *Human genetic risk of treatment with antiviral nucleoside analog drugs that induce lethal mutagenesis: the special case of molnupiravir*, Environmental and Molecular Mutagenesis, doi:10.1002/em.22471.

129. **Willett** et al., *The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism*, medRxiv, doi:10.1101/2022.01.03.21268111.

130. **Williams**, T., *Not All Ivermectin Is Created Equal: Comparing The Quality of 11 Different Ivermectin Sources*, Do Your Own Research, doyourownresearch.substack.com/p/not-all-ivermectin-is-created-equal.

131. **Xu** et al., *A study of impurities in the repurposed COVID-19 drug hydroxychloroquine sulfate by UHPLC-Q/TOF-MS and LC-SPE-NMR*, Rapid Communications in Mass Spectrometry, doi:10.1002/rcm.9358.

132. **Yang** et al., *SARS-CoV-2 infection causes dopaminergic neuron senescence*, Cell Stem Cell, doi:10.1016/j.stem.2023.12.012.

133. **Yildiz Pekoz** et al., *Pulmonary delivery of favipiravir inhalation solution for COVID-19 treatment: in vitro characterization, stability, in vitro cytotoxicity, and antiviral activity using real time cell analysis*, Drug Delivery, doi:10.1080/10717544.2022.2118398.

134. **Yulia** et al., *Evaluation of Antibacterial and Antiviral Drug Effectiveness in COVID-19 Therapy: A Data-Driven Retrospective Approach*, Pathophysiology, doi:10.3390/pathophysiology29010009.

135. **Zavascki** et al., *Advanced ventilatory support and mortality in hospitalized patients with COVID-19 caused by Gamma (P.1) variant of concern compared to other lineages: cohort study at a reference center in Brazil*, Research Square, doi:10.21203/rs.3.rs-910467/v1.

136. **Zeraatkar** et al., *Consistency of covid-19 trial preprints with published reports and impact for decision making: retrospective review*, BMJ Medicine, doi:10.1136/bmjmed-2022-0003091.

137. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.

138. **Zhao** et al., *Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: a multicenter, open-label, randomized trial*, International Immunopharmacology, doi:10.1016/j.intimp.2021.107702.

139. ***Zhirnov*** et al., *Favipiravir: the hidden threat of mutagenic action*, Journal of microbiology, epidemiology and immunobiology, doi:10.36233/0372-9311-114.