Metformin reduces COVID-19 risk: real-time meta analysis of 105 studies

@CovidAnalysis, July 2025, Version 92
https://c19early.org/mfmeta.html

Abstract

Significantly lower risk is seen for mortality, ventilation, ICU admission, hospitalization, progression, and recovery. 69 studies from 63 independent teams in 22 countries show significant benefit.

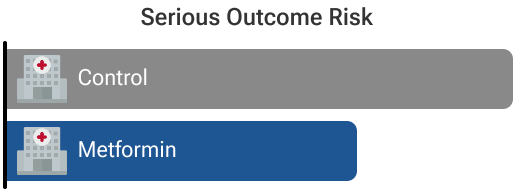
Meta analysis using the most serious outcome reported shows 31% [27-34%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies.

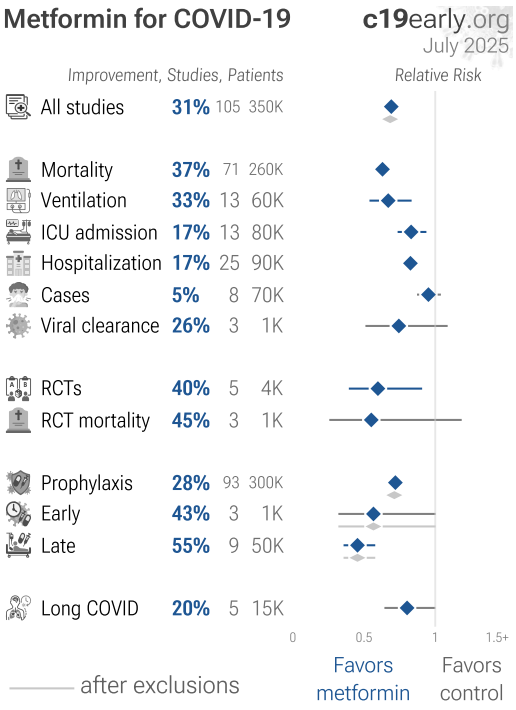
Results are very robust — in exclusion sensitivity analysis 83 of 105 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

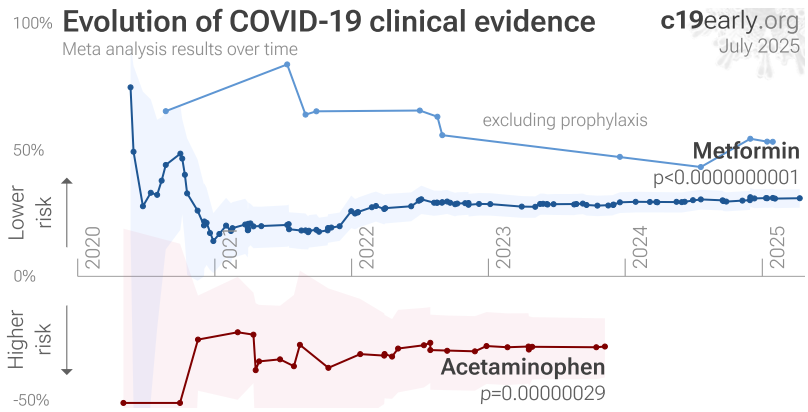
Most studies analyze existing use with diabetic patients. Prophylaxis results typically include continuing use after infection and hospitalization, and greater benefit is seen for more serious outcomes. The TOGETHER RCT shows 27% lower mortality. While not statistically significant, $p = 0.53$, this is consistent with the mortality results from all studies, 37% [33-41%].

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. Other treatments are more effective. All data and sources to reproduce this analysis are in the appendix.

23 other meta analyses show significant improvements with metformin for mortality [1-22], hospitalization [7,13], progression [1], and severity [8,9,13].







METFORMIN FOR COVID-19 — HIGHLIGHTS

Metformin reduces risk with very high confidence for mortality, ventilation, ICU admission, hospitalization, progression, and in pooled analysis, high confidence for recovery, and very low confidence for viral clearance.

3rd treatment shown effective in July 2020, now with $p < 0.00000000001$ from 105 studies.

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

105 metformin COVID-19 studies

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	Improvement, RR [CI]			Treatment	Control	
Reis (DB RCT)	27%	0.73 [0.28-1.94]	death	7/215	9/203	TOGETHER — impossible data, see notes
Bramante (DB RCT)	3%	0.97 [0.06-15.5]	death	1/408	1/396	COVID-OUT — OT[1]
Bramante	53%	0.47 [0.25-0.89]	PASC	10/248	21/248	
Early treatment	43%	0.57 [0.32-1.00]		18/871	31/847	**43% lower risk**
$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.051$						
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Abu-Jamous	65%	0.35 [0.11-0.84]	death	4/23	94/168	
Tamura	97%	0.03 [0.00-0.58]	death	115 (n)	73 (n)	
Li	76%	0.24 [0.06-0.98]	death	2/37	21/94	
Shaseb (RCT)	74%	0.26 [0.06-1.06]	death	85 (n)	104 (n)	
Ventura-.. (DB RCT)	44%	0.56 [0.33-0.95]	oxygen time	10 (n)	10 (n)	
Mehrizi	44%	0.56 [0.53-0.60]	death	population-based cohort		
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He	74%	0.26 [0.20-0.34]	death	53,030 (all patients)		
Bramante (DB RCT)	-43%	1.43 [0.32-6.38]	hosp.	4/1,443	3/1,548	ACTIV-6
Late treatment	55%	0.45 [0.36-0.58]		10/1,713	118/1,997	**55% lower risk**
$Tau^2 = 0.06$, $I^2 = 81.0\%$, $p < 0.0001$						
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Wang	12%	0.88 [0.81-0.97]	ICU	6,504 (n)	10,000 (n)	
Ando	39%	0.61 [0.38-0.99]	hosp.			
Wander	15%	0.85 [0.80-0.90]	death			
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)	
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169	
Bliden	60%	0.40 [0.12-1.37]	death	3/34	9/41	
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50	
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970	
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556	
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31	OT[1]
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41	
Wong	51%	0.49 [0.43-0.57]	death			
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)	
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a	
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995	
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a	
Hunt	67%	0.33 [0.25-0.43]	death	73/3,956	1,539/22,552	
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)	
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort		
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)	
Chan	59%	0.41 [0.12-1.44]	death	400 (n)	2,736 (n)	
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort		
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)	
Ouchi	10%	0.90 [0.77-1.05]	death	6,168 (n)	9,875 (n)	
Morrison (PSM)	41%	0.59 [0.41-0.84]	death	2,684 (n)	2,684 (n)	
Mannucci	38%	0.62 [0.41-0.93]	death	n/a	n/a	

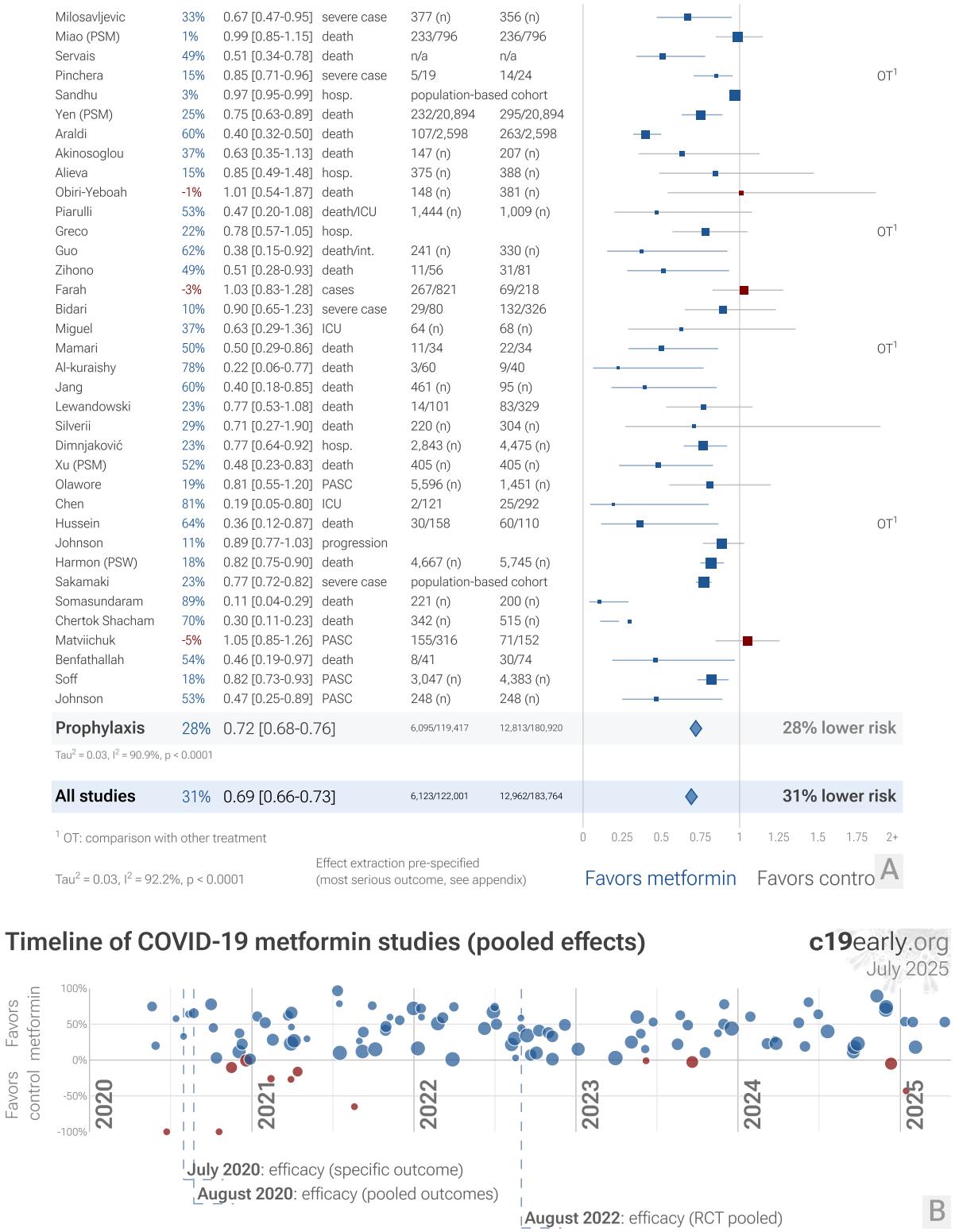

***Figure 1.* A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in metformin studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes, one or more specific outcome, and pooled outcomes in RCTs. Efficacy based on RCTs only was delayed by 25.0 months, compared to using all studies.

Introduction

Immediate treatment recommended

SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological injury[24-36] and cognitive deficits[27,32], cardiovascular complications[37-41], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[42]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Minimizing replication as early as possible is recommended.

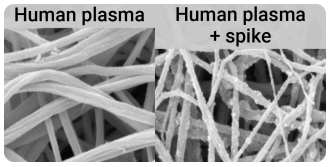

Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from[23].**

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,43-50], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[51], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Extensive supporting research

A systematic review and meta-analysis of 15 non-COVID-19 preclinical studies showed that metformin inhibits pulmonary inflammation and oxidative stress, minimizes lung injury, and improves survival in animal models of acute respiratory distress syndrome (ARDS) or acute lung injury (ALI)[52]. Metformin inhibits SARS-CoV-2 *in vitro*[53,54], minimizes LPS-induced cytokine storm in a mouse model[55], minimizes lung damage and fibrosis in a mouse model of LPS-induced ARDS[56], may protect against SARS-CoV-2-induced neurological disorders[25], may be beneficial via inhibitory effects on ORF3a-mediated inflammasome activation[57], reduces UUO and FAN-induced kidney fibrosis[56], increases mitochondrial function and decreases TGF-β-induced fibrosis, apoptosis, and inflammation markers in lung epithelial cells[56], may reduce inflammation, oxidative stress, and thrombosis via regulating glucose metabolism[58], attenuates spike protein S1-induced inflammatory response and α-synuclein aggregation[59], may reduce COVID-19 severity and long COVID by inhibiting NETosis via suppression of protein kinase C activation[60], enhances interferon responses and reduces SARS-CoV-2 infection and inflammation in diabetic models by suppressing HIF-1α signaling[61], reduces hyperglycemia-induced hepatic ACE2/TMPRSS2 up-regulation and SARS-CoV-2 entry[62], and may improve outcomes via modulation of immune responses with increased anti-inflammatory T lymphocyte gene expression and via enhanced gut microbiota diversity[63].

Other infections

Efficacy with metformin has been shown for influenza A[64].

Analysis

We analyze all significant controlled studies of metformin for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, Randomized Controlled Trials (RCTs), and higher quality studies.

Treatment timing

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

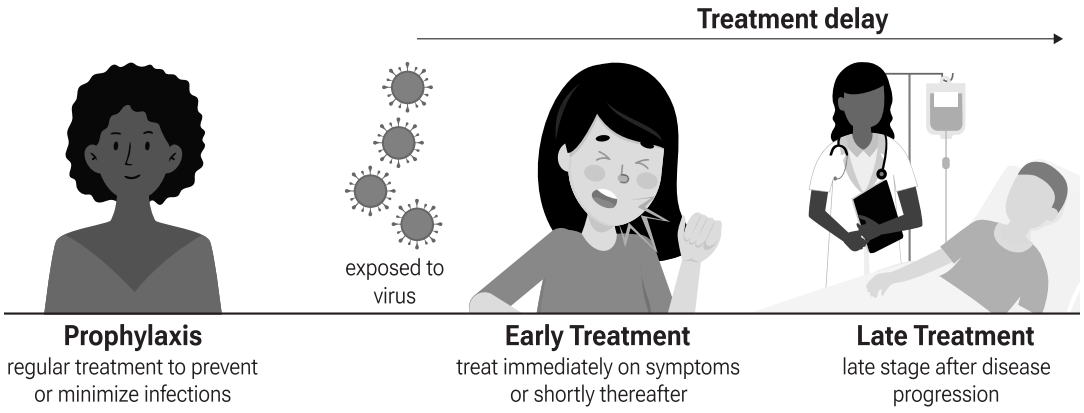

Figure 3. Treatment stages.

Preclinical Research

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4 *In Silico* studies support the efficacy of metformin[58,65-67].

8 *In Vitro* studies support the efficacy of metformin[25,53,54,56,58,59,61,62].

4 *In Vivo* animal studies support the efficacy of metformin[55,56,59,61].

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 4 plots individual results by treatment stage. Figure 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, and 15 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, progression, recovery, cases, viral clearance, peer reviewed studies, and long COVID.

	Relative Risk	Studies	Patients
All studies	0.69 [0.66-0.73] ****	105	350K
After exclusions	0.68 [0.65-0.72] ****	97	340K
Peer-reviewed	0.70 [0.66-0.74] ****	97	320K
RCTs	0.60 [0.39-0.91] *	5	4,422
Mortality	0.63 [0.59-0.67] ****	71	260K
Ventilation	0.67 [0.54-0.83] ***	13	60K
ICU admission	0.83 [0.74-0.94] **	13	80K
Hospitalization	0.83 [0.77-0.89] ****	25	90K
Recovery	0.68 [0.50-0.93] *	5	7,167
Cases	0.95 [0.87-1.04]	8	70K
Viral	0.74 [0.51-1.09]	3	1,437
RCT mortality	0.55 [0.26-1.19]	3	1,411
RCT hospitalization	0.94 [0.83-1.06]	4	3,618

Table 1. **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, after exclusions, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

	Early treatment	Late treatment	Prophylaxis
All studies	0.57 [0.32-1.00]	0.45 [0.36-0.58] ****	0.72 [0.68-0.76] ****
After exclusions	0.57 [0.32-1.00]	0.45 [0.36-0.58] ****	0.71 [0.68-0.75] ****
Peer-reviewed	0.57 [0.32-1.00]	0.36 [0.22-0.60] ****	0.72 [0.69-0.76] ****
RCTs	0.76 [0.30-1.89]	0.57 [0.29-1.10]	
Mortality	0.76 [0.30-1.89]	0.43 [0.33-0.56] ****	0.66 [0.62-0.70] ****
Ventilation		0.21 [0.04-0.99] *	0.69 [0.55-0.85] ***
ICU admission		0.37 [0.13-1.09]	0.84 [0.75-0.95] **
Hospitalization	0.94 [0.55-1.61]	0.94 [0.83-1.06]	0.81 [0.75-0.88] ****
Recovery		1.04 [0.97-1.12]	0.59 [0.40-0.87] **
Cases			0.95 [0.87-1.04]
Viral	0.81 [0.52-1.25]	0.59 [0.37-0.95] *	
RCT mortality	0.76 [0.30-1.89]	0.26 [0.06-1.06]	
RCT hospitalization	0.94 [0.55-1.61]	0.94 [0.83-1.06]	

Table 2. **Random effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$ ** $p<0.01$ *** $p<0.001$ **** $p<0.0001$.

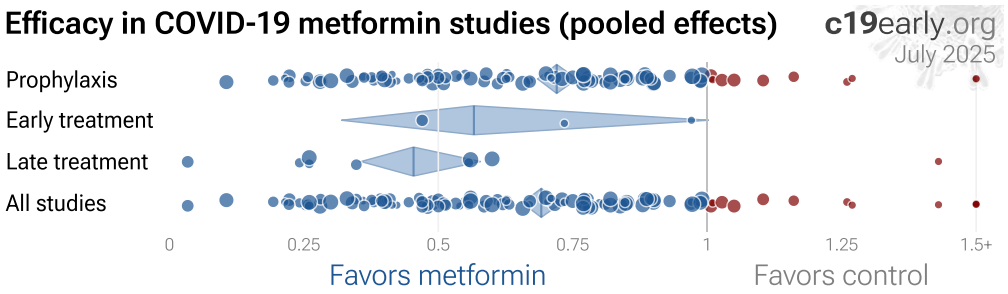

Figure 4. **Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

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Ando	39%	0.61 [0.38-0.99]	hosp.			
Wander	15%	0.85 [0.80-0.90]	death			
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)	
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169	
Bliden	60%	0.40 [0.12-1.37]	death	3/34	9/41	
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50	
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970	
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556	
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31	OT[1]
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41	
Wong	51%	0.49 [0.43-0.57]	death			
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)	
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a	
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995	
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a	
Hunt	67%	0.33 [0.25-0.43]	death	73/3,956	1,539/22,552	
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)	
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort		
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)	
Chan	59%	0.41 [0.12-1.44]	death	400 (n)	2,736 (n)	
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort		
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)	
Ouchi	10%	0.90 [0.77-1.05]	death	6,168 (n)	9,875 (n)	
Morrison (PSM)	41%	0.59 [0.41-0.84]	death	2,684 (n)	2,684 (n)	
Mannucci	38%	0.62 [0.41-0.93]	death	n/a	n/a	

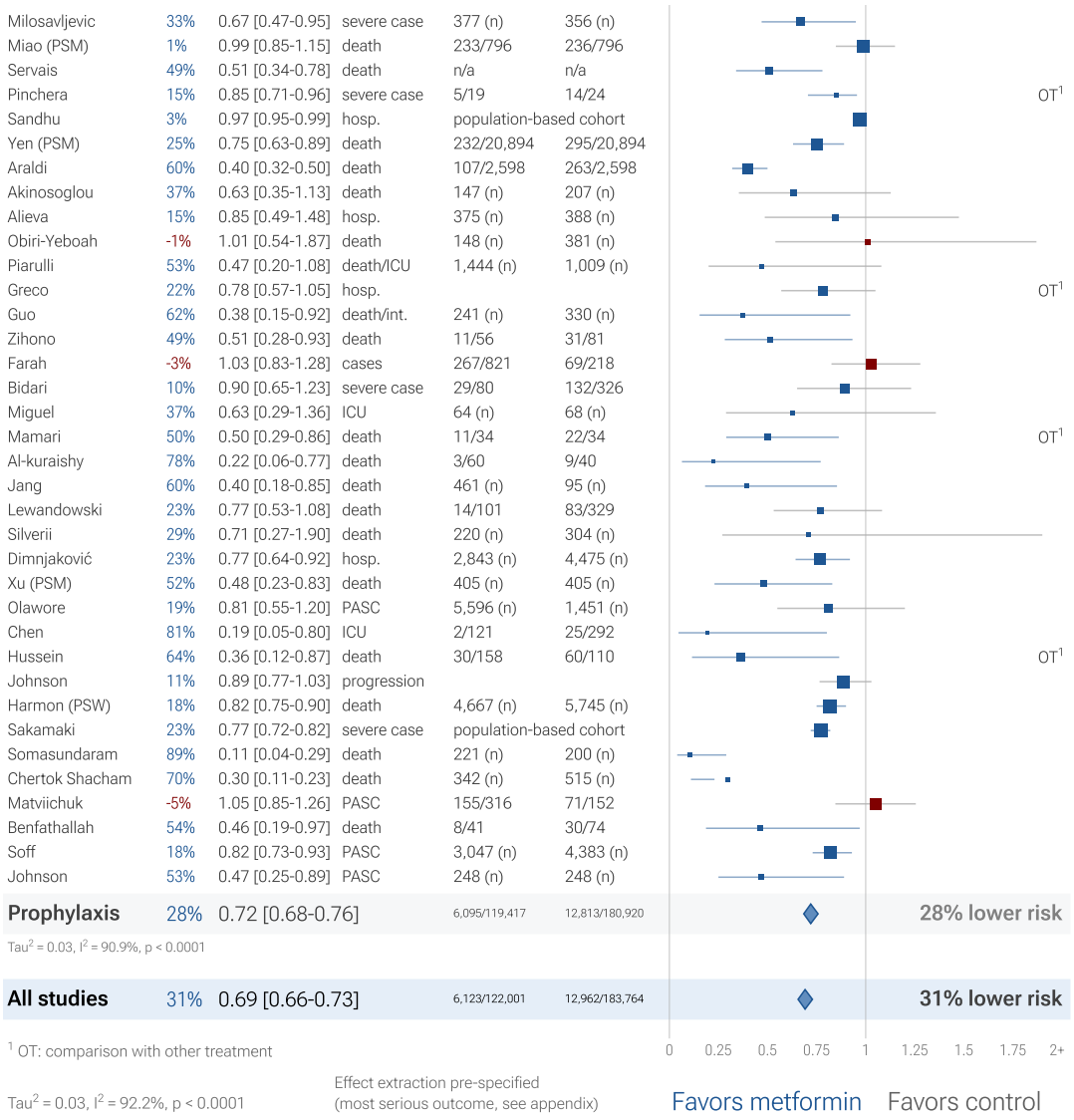

Figure 5. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For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

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	Improvement, RR [CI]	Treatment	Control	
Reis (DB RCT)	27% 0.73 [0.28-1.94]	7/215	9/203	TOGETHER impossible data, see notes
Bramante (DB RCT)	3% 0.97 [0.06-15.5]	1/408	1/396	COVID-OUT OT[1]
Early treatment	24% 0.76 [0.30-1.89]	8/623	10/599	~~24% lower risk~~
$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.56$				
	Improvement, RR [CI]	*Treatment*	*Control*	
Abu-Jamous	65% 0.35 [0.11-0.84]	4/23	94/168	
Tamura	97% 0.03 [0.00-0.58]	115 (n)	73 (n)	
Li	76% 0.24 [0.06-0.98]	2/37	21/94	
Shaseb (RCT)	74% 0.26 [0.06-1.06]	85 (n)	104 (n)	
Mehrizi	44% 0.56 [0.53-0.60]	population-based cohort		
Sugimoto	40% 0.60 [0.53-0.66]	population-based cohort		
He	74% 0.26 [0.20-0.34]	53,030 (all patients)		
Late treatment	57% 0.43 [0.33-0.56]	6/260	115/439	57% lower risk
$Tau^2 = 0.06$, $I^2 = 85.2\%$, $p < 0.0001$				
	Improvement, RR [CI]	*Treatment*	*Control*	
Luo	75% 0.25 [0.07-0.84]	3/104	22/179	
Cariou	20% 0.80 [0.45-1.43]	746 (n)	571 (n)	CORONADO
Wang	58% 0.42 [0.01-1.98]	1/9	13/49	
Chen	33% 0.67 [0.20-1.78]	4/43	15/77	
Kim	64% 0.36 [0.10-1.23]	113 (n)	122 (n)	
Li	78% 0.22 [0.09-0.54]	2/37	21/94	
Mirani	45% 0.55 [0.27-1.11]	25/69	13/21	
Goodall	3% 0.97 [0.75-1.25]	74/210	280/771	
Pérez-Bel.. (PSM)	-10% 1.10 [0.84-1.40]	79/249	79/249	
Bramante	12% 0.88 [0.78-1.00]	394/2,333	791/3,923	
Sourij	37% 0.63 [0.33-1.10]	14/77	44/161	
Lalau (PSM)	22% 0.78 [0.55-1.10]	671 (n)	419 (n)	
Ramos-Rincón	1% 0.99 [0.77-1.29]	206/420	179/370	
Crouse	61% 0.39 [0.16-0.87]	8/76	34/144	
Lally	52% 0.48 [0.28-0.84]	16/127	144/648	
Oh	-26% 1.26 [0.81-1.95]	5,946 (n)	5,946 (n)	
Wargny	28% 0.72 [0.53-0.95]	247/1,553	330/1,241	CORONADO
Bramante (PSM)	62% 0.38 [0.16-0.91]	342 (n)	342 (n)	
Khunti	23% 0.77 [0.73-0.81]	population-based cohort		
Jiang (PSM)	46% 0.54 [0.13-2.26]	3/74	10/74	
Ghany	66% 0.34 [0.19-0.59]	392 (n)	747 (n)	
Alamgir	27% 0.73 [0.63-0.84]	11,062 (n)	11,062 (n)	
Gálvez-Barrón	-16% 1.16 [0.73-1.49]	20 (n)	83 (n)	
Ravindra	30% 0.70 [0.28-1.56]	5/53	57/313	
Blanc	79% 0.21 [0.03-1.46]	1/14	25/75	
Cheng (PSM)	-65% 1.65 [0.71-3.86]	678 (n)	535 (n)	
Wander	15% 0.85 [0.80-0.90]			
Saygili (PSM)	42% 0.58 [0.37-0.92]	120 (n)	120 (n)	
Ong	47% 0.53 [0.31-0.87]	33/186	57/169	
Bliden	60% 0.40 [0.12-1.37]	3/34	9/41	
Wallace (PSW)	72% 0.28 [0.21-0.37]	103/1,203	1,536/6,970	
Ojeda-Fern.. (PSM)	16% 0.84 [0.79-0.89]	1,476/6,556	1,787/6,556	
Usman	60% 0.40 [0.12-1.37]	3/34	9/41	
Wong	51% 0.49 [0.43-0.57]			
Wong (PSW)	59% 0.41 [0.22-0.80]	786 (n)	428 (n)	
Ma (PSW)	74% 0.26 [0.07-0.89]	3/361	40/995	
Hunt	67% 0.33 [0.25-0.43]	73/3,956	1,539/22,552	
Shestakova	22% 0.78 [0.67-0.91]	population-based cohort		
Loucera	30% 0.70 [0.61-0.80]	1,896 (n)	14,072 (n)	
Chan	59% 0.41 [0.12-1.44]	400 (n)	2,736 (n)	
Zaccardi	34% 0.66 [0.60-0.72]	population-based cohort		
Ouchi	10% 0.90 [0.77-1.05]	6,168 (n)	9,875 (n)	
Morrison (PSM)	41% 0.59 [0.41-0.84]	2,684 (n)	2,684 (n)	
Mannucci	38% 0.62 [0.41-0.93]	n/a	n/a	
Miao (PSM)	1% 0.99 [0.85-1.15]	233/796	236/796	
Servais	49% 0.51 [0.34-0.78]	n/a	n/a	
Yen (PSM)	25% 0.75 [0.63-0.89]	232/20,894	295/20,894	
Araldi	60% 0.40 [0.32-0.50]	107/2,598	263/2,598	
Akinosoglou	37% 0.63 [0.35-1.13]	147 (n)	207 (n)	
Obiri-Yeboah	-1% 1.01 [0.54-1.87]	148 (n)	381 (n)	
Zihono	49% 0.51 [0.28-0.93]	11/56	31/81	
Mamari	50% 0.50 [0.29-0.86]	11/34	22/34	OT[1]
Al-kuraishy	78% 0.22 [0.06-0.77]	3/60	9/40	
Jang	60% 0.40 [0.18-0.85]	461 (n)	95 (n)	
Lewandowski	23% 0.77 [0.53-1.08]	14/101	83/329	
Silverii	29% 0.71 [0.27-1.90]	220 (n)	304 (n)	
Xu (PSM)	52% 0.48 [0.23-0.83]	405 (n)	405 (n)	
Hussein	64% 0.36 [0.12-0.87]	30/158	60/110	OT[1]
Harmon (PSW)	18% 0.82 [0.75-0.90]	4,667 (n)	5,745 (n)	
Somasundaram	89% 0.11 [0.04-0.29]	221 (n)	200 (n)	

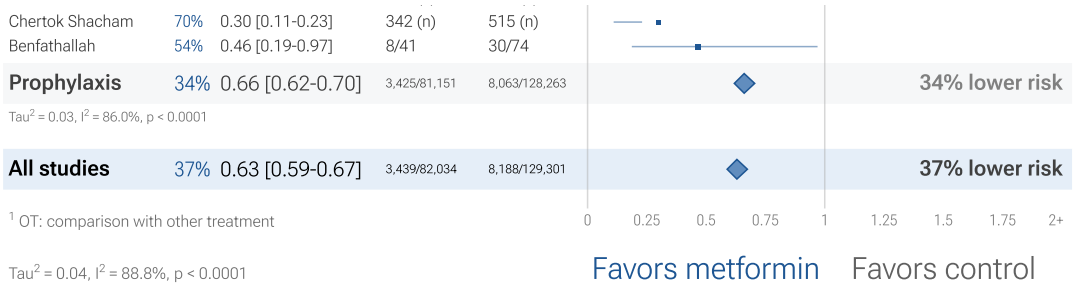

Figure 6. Random effects meta-analysis for mortality results.

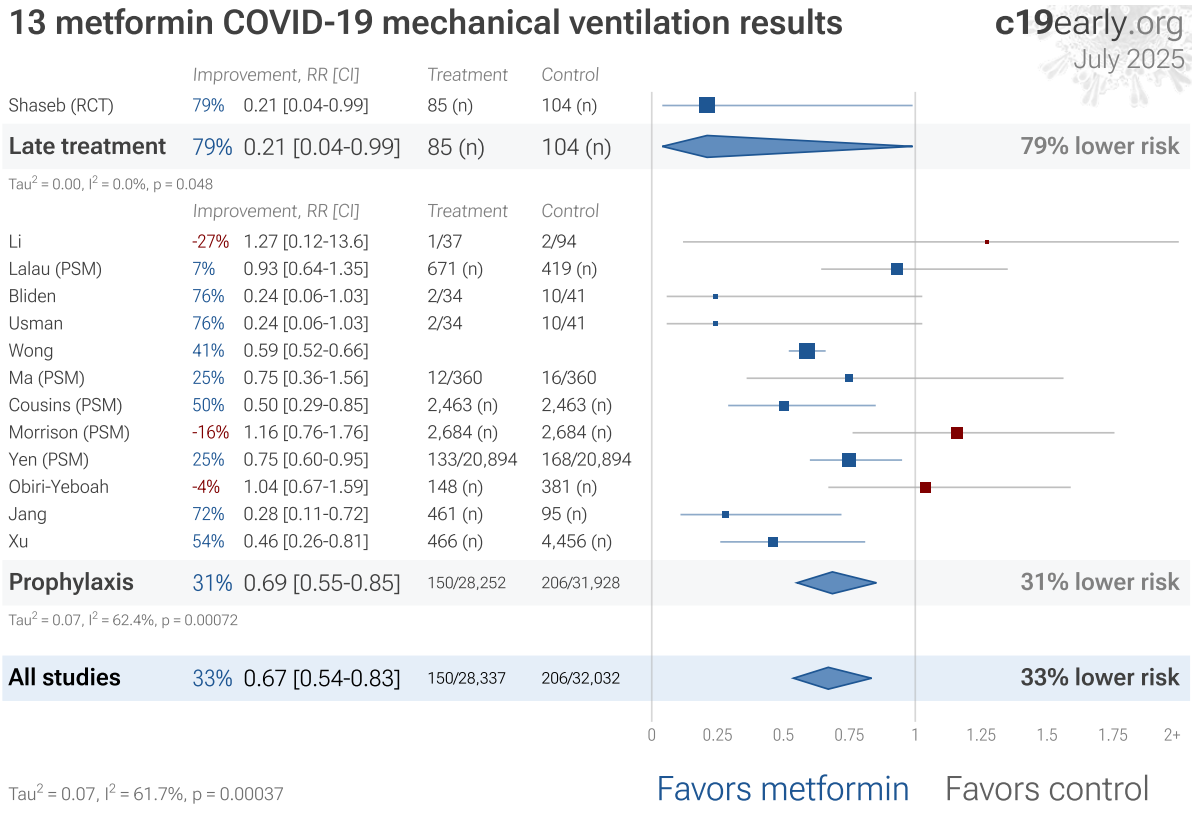

Figure 7. Random effects meta-analysis for ventilation.

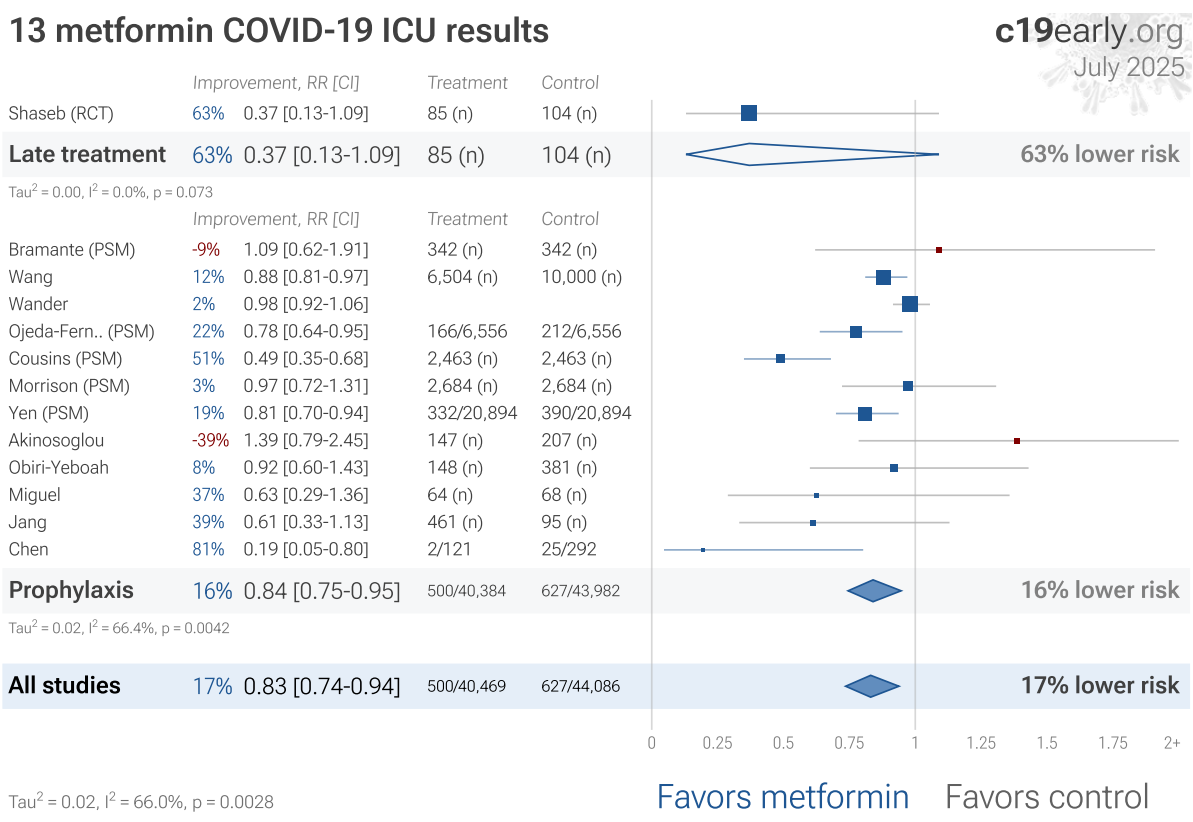

Figure 8. Random effects meta-analysis for ICU admission.

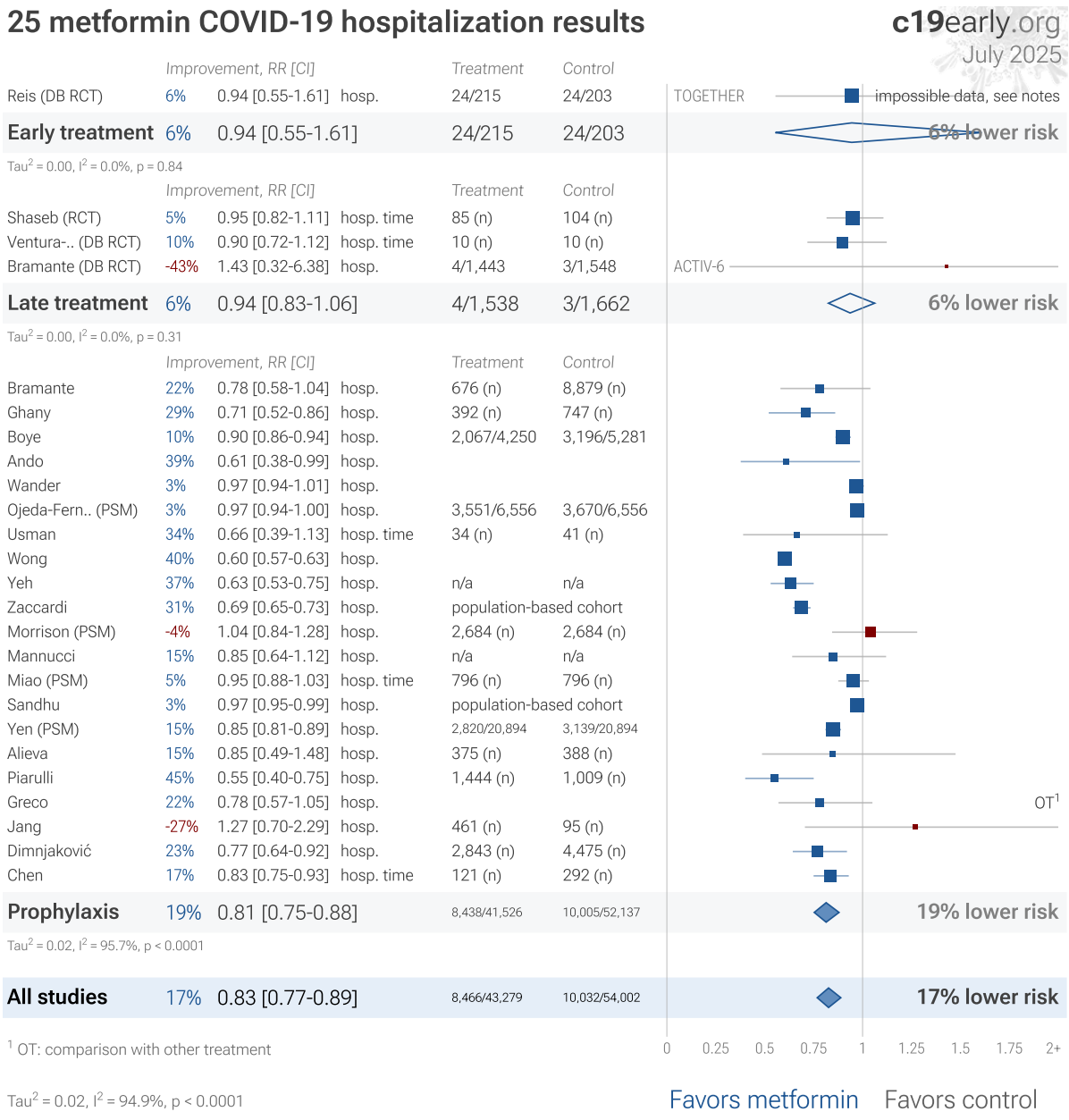

Figure 9. Random effects meta-analysis for hospitalization.

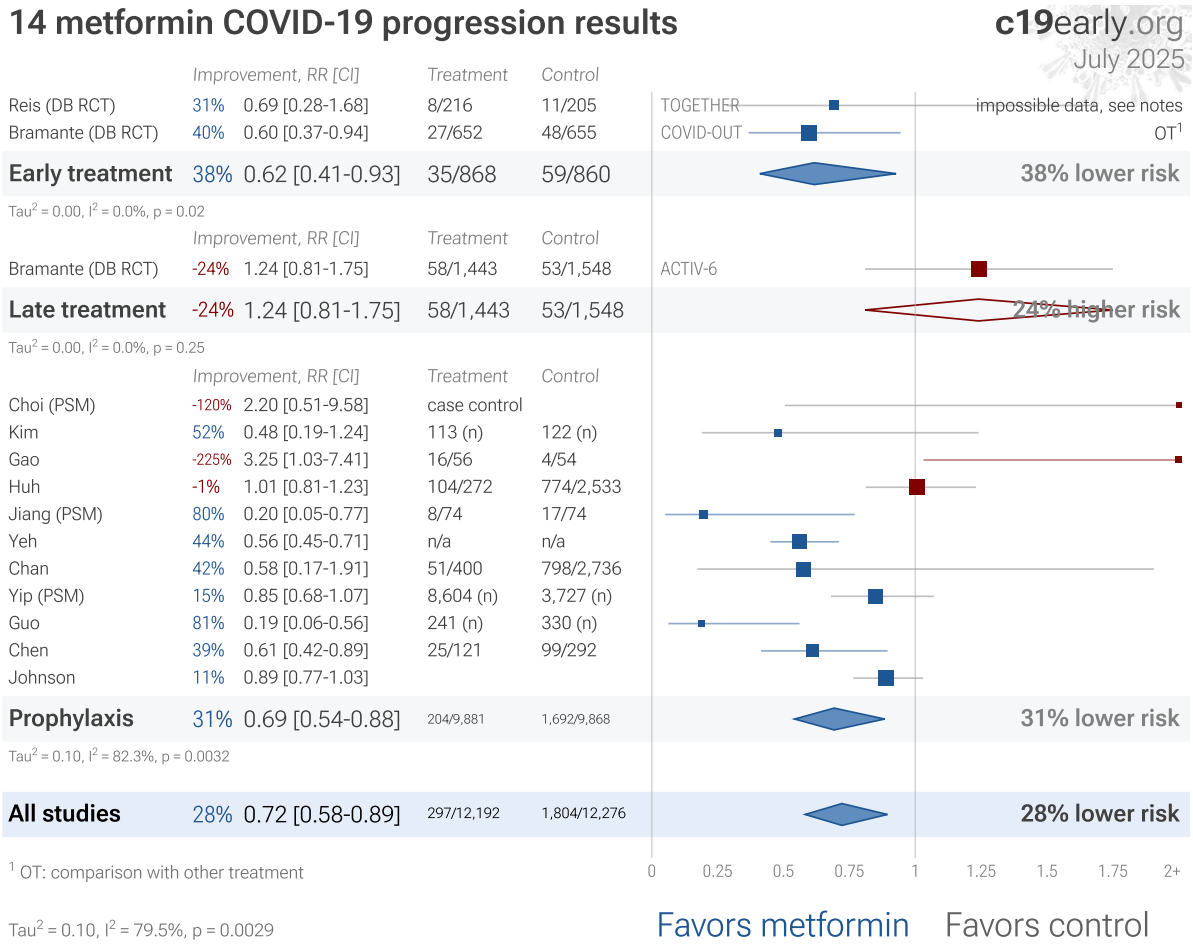

Figure 10. Random effects meta-analysis for progression.

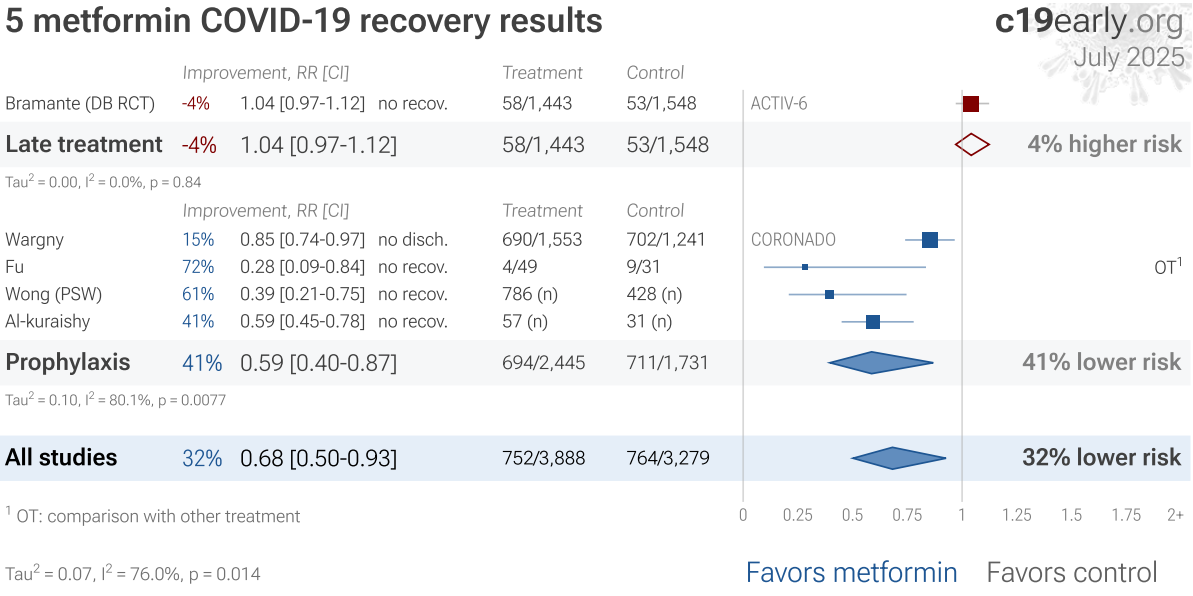

Figure 11. Random effects meta-analysis for recovery.

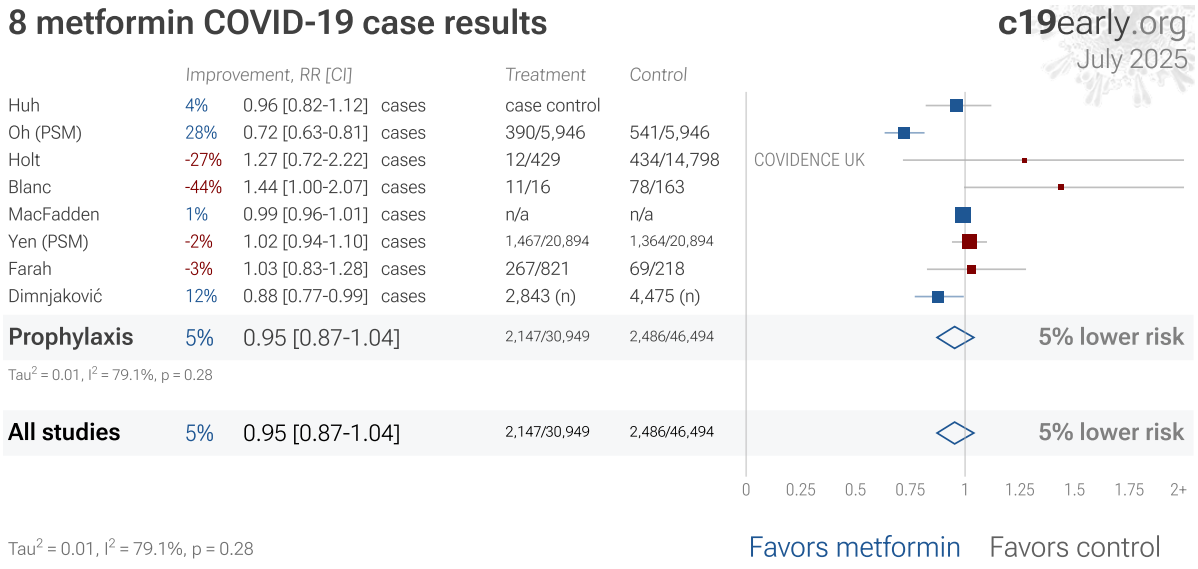

Figure 12. Random effects meta-analysis for cases.

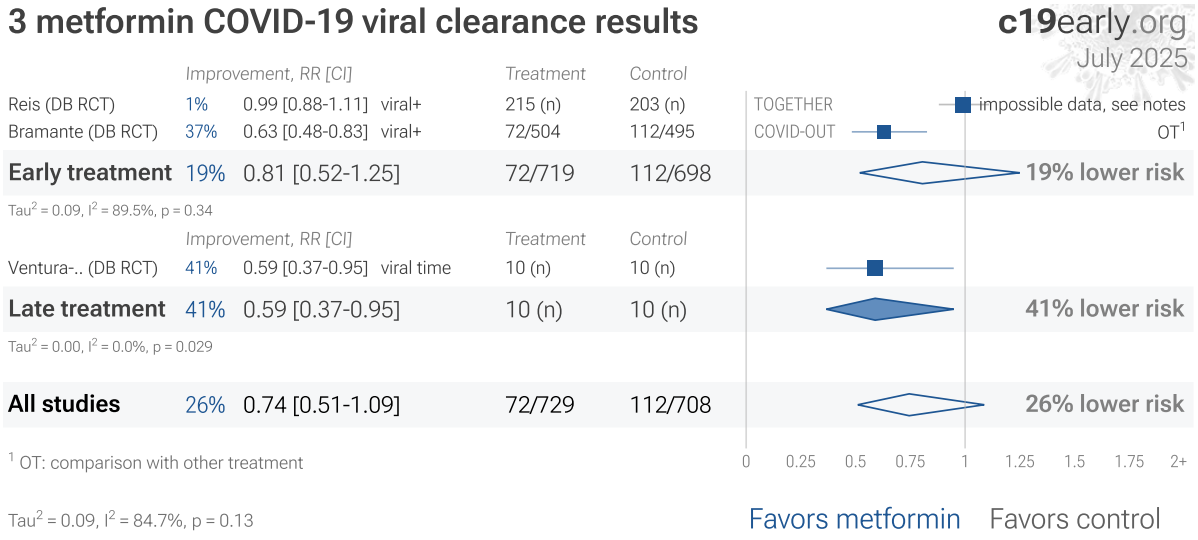

Figure 13. Random effects meta-analysis for viral clearance.

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	Improvement, RR [CI]			Treatment	Control	
Reis (DB RCT)	27%	0.73 [0.28-1.94]	death	7/215	9/203	TOGETHER
Bramante (DB RCT)	3%	0.97 [0.06-15.5]	death	1/408	1/396	COVID-OUT
Bramante	53%	0.47 [0.25-0.89]	PASC	10/248	21/248	
Early treatment	43%	0.57 [0.32-1.00]		18/871	31/847	**43% lower risk**

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.051$

	Improvement, RR [CI]			Treatment	Control	
Tamura	97%	0.03 [0.00-0.58]	death	115 (n)	73 (n)	
Li	76%	0.24 [0.06-0.98]	death	2/37	21/94	
Shaseb (RCT)	74%	0.26 [0.06-1.06]	death	85 (n)	104 (n)	
Ventura-.. (DB RCT)	44%	0.56 [0.33-0.95]	oxygen time	10 (n)	10 (n)	
Mehrizi	44%	0.56 [0.53-0.60]	death	population-based cohort		
He	74%	0.26 [0.20-0.34]	death	53,030 (all patients)		
Late treatment	64%	0.36 [0.22-0.60]		2/247	21/281	**64% lower risk**

$Tau^2 = 0.23$, $I^2 = 86.3\%$, $p < 0.0001$

	Improvement, RR [CI]			Treatment	Control	
Luo	75%	0.25 [0.07-0.84]	death	3/104	22/179	
Cariou	20%	0.80 [0.45-1.43]	death	746 (n)	571 (n)	CORONADO
Choi (PSM)	-120%	2.20 [0.51-9.58]	progression	case control		
Wang	58%	0.42 [0.01-1.98]	death	1/9	13/49	
Chen	33%	0.67 [0.20-1.78]	death	4/43	15/77	
Kim	64%	0.36 [0.10-1.23]	death	113 (n)	122 (n)	
Li	78%	0.22 [0.09-0.54]	death	2/37	21/94	
Mirani	45%	0.55 [0.27-1.11]	death	25/69	13/21	
Goodall	3%	0.97 [0.75-1.25]	death	74/210	280/771	
Gao	-225%	3.25 [1.03-7.41]	progression	16/56	4/54	
Pérez-Bel.. (PSM)	-10%	1.10 [0.84-1.40]	death	79/249	79/249	
Bramante	12%	0.88 [0.78-1.00]	death	394/2,333	791/3,923	
Sourij	37%	0.63 [0.33-1.10]	death	14/77	44/161	
Lalau (PSM)	22%	0.78 [0.55-1.10]	death	671 (n)	419 (n)	
Huh	-1%	1.01 [0.81-1.23]	progression	104/272	774/2,533	
Crouse	61%	0.39 [0.16-0.87]	death	8/76	34/144	
Lally	52%	0.48 [0.28-0.84]	death	16/127	144/648	
Oh	-26%	1.26 [0.81-1.95]	death	5,946 (n)	5,946 (n)	
Wargny	28%	0.72 [0.53-0.95]	death	247/1,553	330/1,241	CORONADO
Bramante (PSM)	62%	0.38 [0.16-0.91]	death	342 (n)	342 (n)	
Holt	-27%	1.27 [0.72-2.22]	cases	12/429	434/14,798	COVIDENCE UK
Khunti	23%	0.77 [0.73-0.81]	death	population-based cohort		
Jiang (PSM)	46%	0.54 [0.13-2.26]	death	3/74	10/74	
Ghany	66%	0.34 [0.19-0.59]	death	392 (n)	747 (n)	
Gálvez-Barrón	-16%	1.16 [0.73-1.49]	death	20 (n)	83 (n)	
Ravindra	30%	0.70 [0.28-1.56]	death	5/53	57/313	
Blanc	79%	0.21 [0.03-1.46]	death	1/14	25/75	
Boye	10%	0.90 [0.86-0.94]	hosp.	2,067/4,250	3,196/5,281	
Cheng (PSM)	-65%	1.65 [0.71-3.86]	death	678 (n)	535 (n)	
Wang	12%	0.88 [0.81-0.97]	ICU	6,504 (n)	10,000 (n)	
Ando	39%	0.61 [0.38-0.99]	hosp.			
Wander	15%	0.85 [0.80-0.90]	death			
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)	
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169	
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50	
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970	
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556	
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31	OT[1]
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41	
Wong	51%	0.49 [0.43-0.57]	death			
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)	
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a	
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995	
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a	
Hunt	67%	0.33 [0.25-0.43]	death	73/3,956	1,539/22,552	
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)	
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort		
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)	
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort		
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)	
Ouchi	10%	0.90 [0.77-1.05]	death	6,168 (n)	9,875 (n)	
Morrison (PSM)	41%	0.59 [0.41-0.84]	death	2,684 (n)	2,684 (n)	
Mannucci	38%	0.62 [0.41-0.93]	death	n/a	n/a	
Milosavljevic	33%	0.67 [0.47-0.95]	severe case	377 (n)	356 (n)	
Miao (PSM)	1%	0.99 [0.85-1.15]	death	233/796	236/796	
Servais	49%	0.51 [0.34-0.78]	death	n/a	n/a	
Pinchera	15%	0.85 [0.71-0.96]	severe case	5/19	14/24	OT[1]
Sandhu	3%	0.97 [0.95-0.99]	hosp.	population-based cohort		
Yen (PSM)	25%	0.75 [0.63-0.89]	death	232/20,894	295/20,894	
Akinosoglou	37%	0.63 [0.35-1.13]	death	147 (n)	207 (n)	

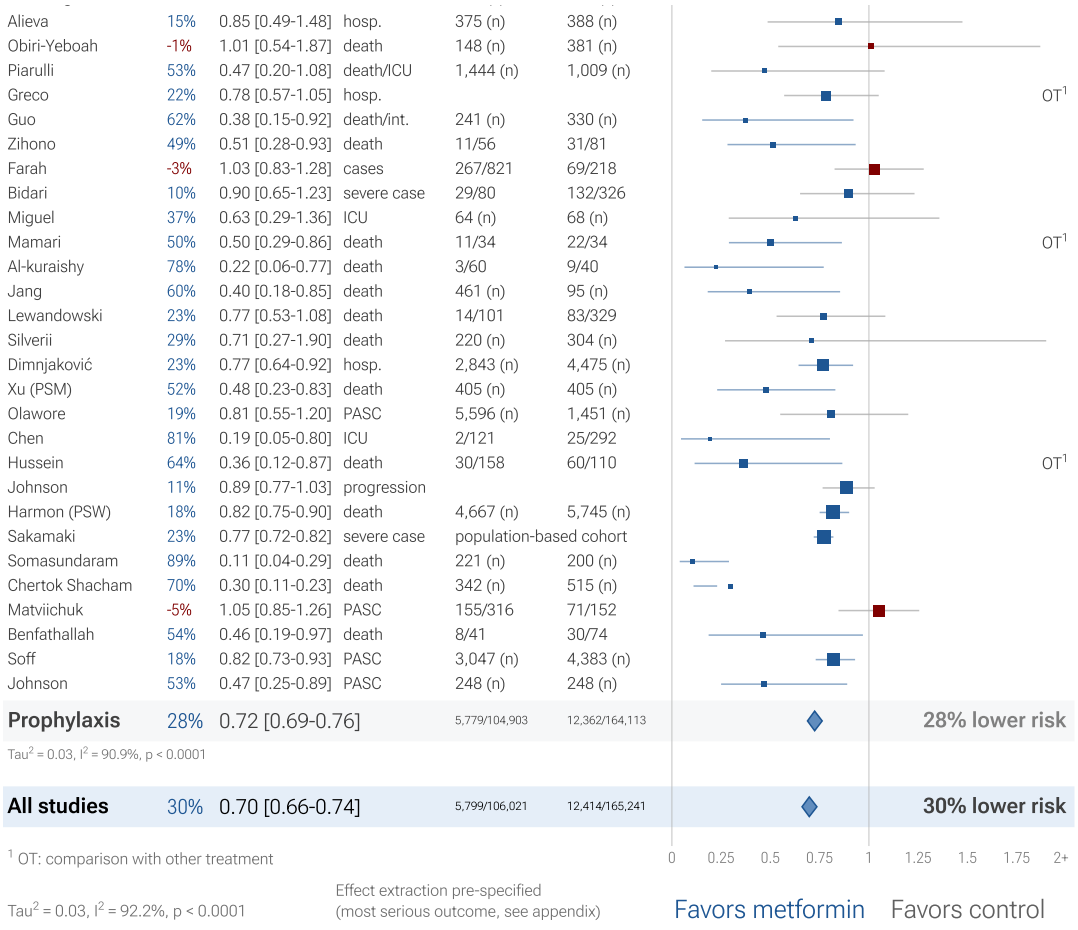


Figure 14. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

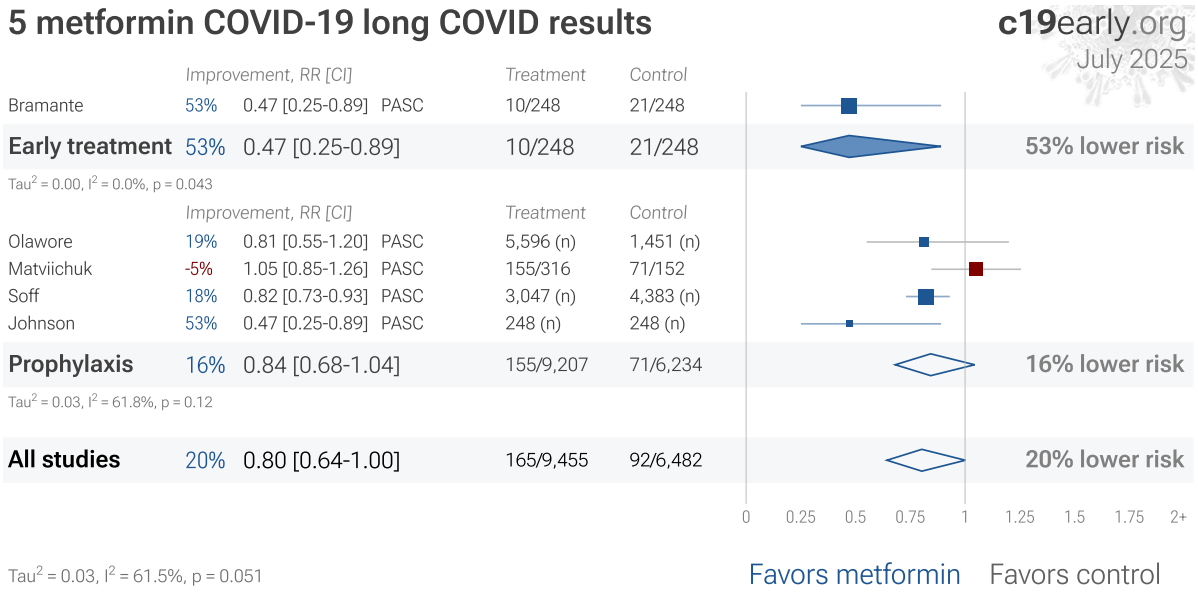


Figure 15. **Random effects meta-analysis for long COVID.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below.

Randomized Controlled Trials (RCTs)

Figure 16 shows a comparison of results for RCTs and observational studies. Random effects meta analysis of RCTs shows 40% improvement, compared to 31% for other studies. Figure 17, 18, and 19 show forest plots for random effects meta-analysis of all Randomized Controlled Trials, RCT mortality results, and RCT hospitalization results. RCT results are included in Table 1 and Table 2.

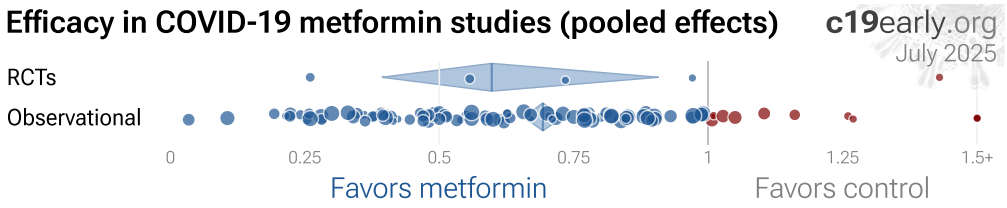


Figure 16. **Results for RCTs and observational studies.**

RCTs have many potential biases

RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases [70], and analysis of double-blind RCTs has identified extreme levels of bias [71]. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, reporting, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs

RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be

significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment

High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 172 treatments we have analyzed, 67% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments. They may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration.

Observational studies have been shown to be reliable

Evidence shows that observational studies 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.* analyzed reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. We performed a similar analysis across the 172 treatments we cover, showing no significant difference in the results of RCTs compared to observational studies, RR 0.98 [0.92-1.05][76]. Similar results are found for all low-cost treatments, RR 1.00 [0.91-1.09]. High-cost treatments show a non-significant trend towards RCTs showing greater efficacy, RR 0.92 [0.84-1.02]. Details can be found in the supplementary data. *Lee (B) 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 remote survey bias may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see[78,79].

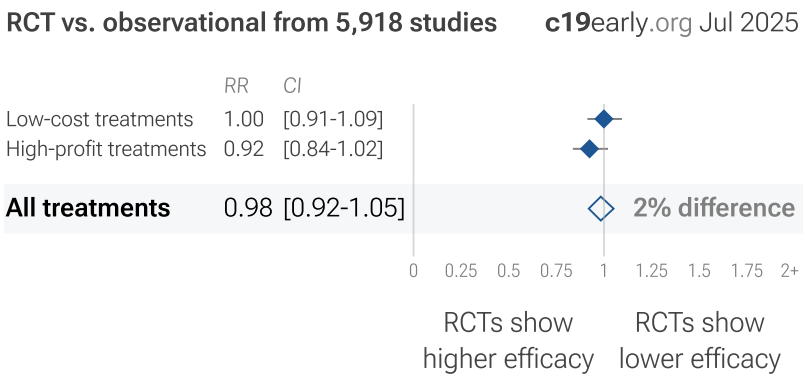


Figure 20. **For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[73].**

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

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of these, 58% have been confirmed in RCTs, with a mean delay of 7.7 months (64% with 8.9 months delay for low-cost treatments). The remaining treatments either have no RCTs, or the point estimate is consistent.

Summary

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

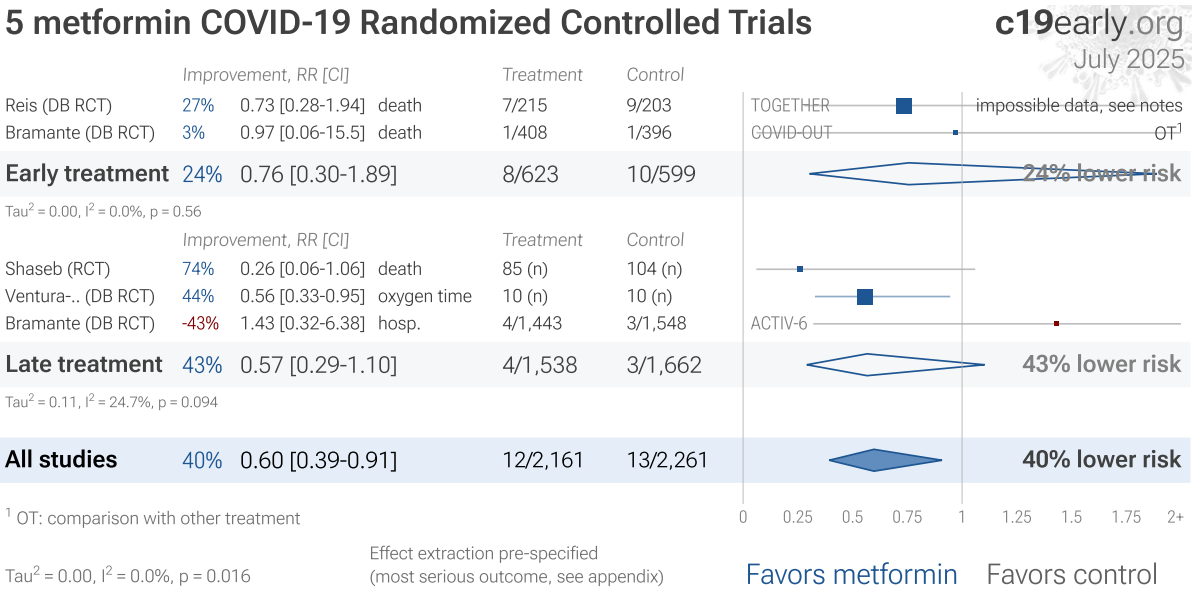


Figure 17. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious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

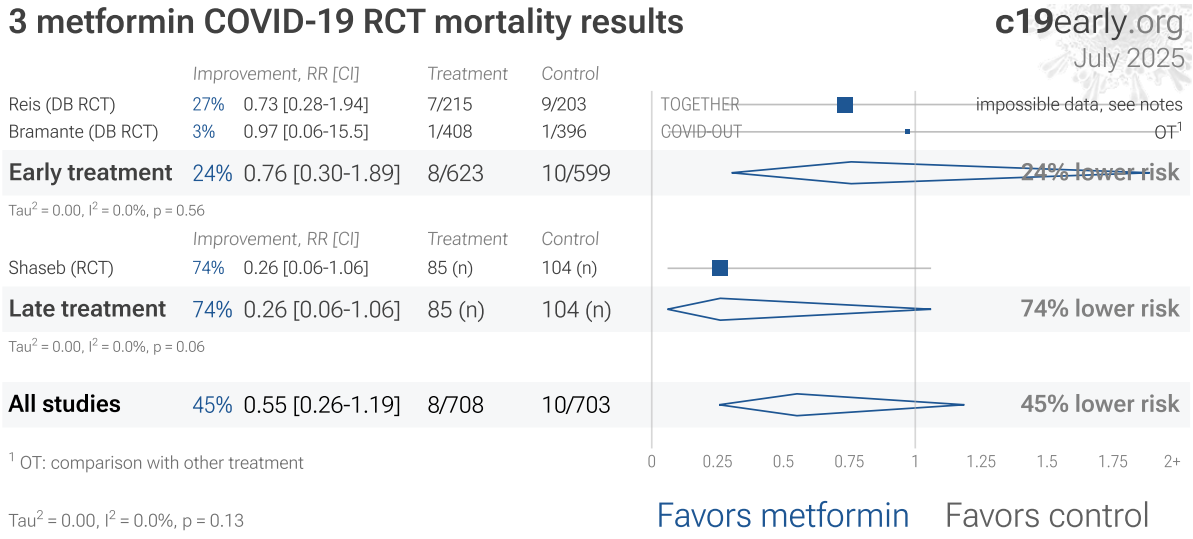


Figure 18. **Random effects meta-analysis for RCT mortality results.**

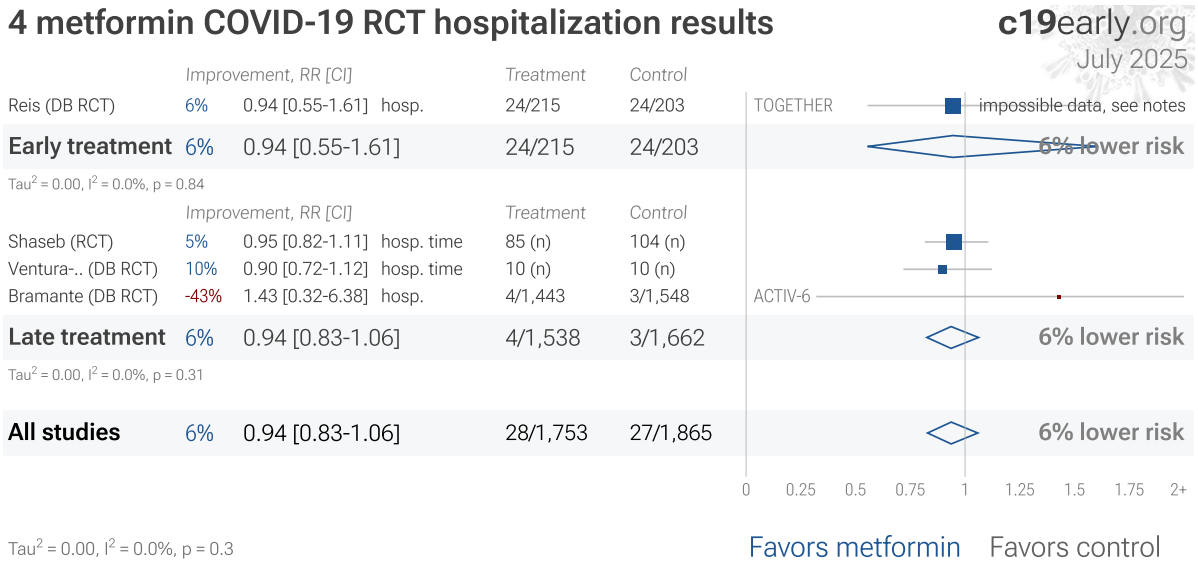


Figure 19. Random effects meta-analysis for RCT hospitalization results.

NIH

NIH provides an analysis of metformin for COVID-19[80], concluding that there is insufficient evidence to recommend for or against use. However, they appear to have only examined a fraction of the evidence. For example, considering RCTs providing clinical results for COVID-19 and metformin, they reference only[81,82], and appear not to know about 3 other RCTs[54,83,84] as shown in Figure 21. Authors reference only one of the 100 observational studies. For COVID-19, observational study results do not systematically differ from RCTs, RR 0.98 [0.92-1.05] across 172 treatments[73].

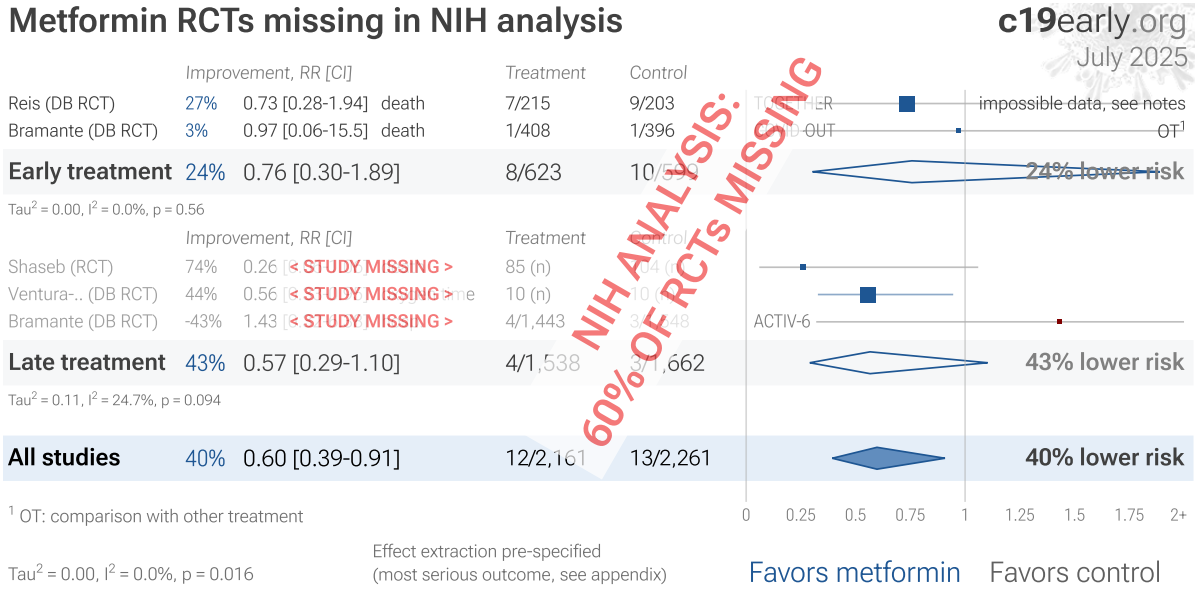


Figure 21. Analysis by NIH is missing 3 RCTs.

Exclusions

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

The studies excluded are as below. Figure 22 shows a forest plot for random effects meta-analysis of all studies after exclusions.

Akinosoglou, unadjusted results with no group details.

Al-kuraishy, unadjusted results with significant baseline differences.

Alieva, unadjusted results with no group details.

Bidari, unadjusted results with no group details.

Bliden, unadjusted results with minimal group details.

Farah, unadjusted results with no group details.

Holt, significant unadjusted confounding possible.

Ravindra, minimal details provided.

97 metformin COVID-19 studies after exclusions

c19early.org
July 2025

	Improvement, RR [CI]			Treatment	Control	
Reis (DB RCT)	27%	0.73 [0.28-1.94]	death	7/215	9/203	TOGETHER
Bramante (DB RCT)	3%	0.97 [0.06-15.5]	death	1/408	1/396	COVID-OUT
Bramante	53%	0.47 [0.25-0.89]	PASC	10/248	21/248	
Early treatment	43%	0.57 [0.32-1.00]		18/871	31/847	**43% lower risk**

$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.051$

	Improvement, RR [CI]			Treatment	Control	
Abu-Jamous	65%	0.35 [0.11-0.84]	death	4/23	94/168	
Tamura	97%	0.03 [0.00-0.58]	death	115 (n)	73 (n)	
Li	76%	0.24 [0.06-0.98]	death	2/37	21/94	
Shaseb (RCT)	74%	0.26 [0.06-1.06]	death	85 (n)	104 (n)	
Ventura-.. (DB RCT)	44%	0.56 [0.33-0.95]	oxygen time	10 (n)	10 (n)	
Mehrizi	44%	0.56 [0.53-0.60]	death	population-based cohort		
Sugimoto	40%	0.60 [0.53-0.66]	death	population-based cohort		
He	74%	0.26 [0.20-0.34]	death	53,030 (all patients)		
Bramante (DB RCT)	-43%	1.43 [0.32-6.38]	hosp.	4/1,443	3/1,548	ACTIV-6
Late treatment	55%	0.45 [0.36-0.58]		10/1,713	118/1,997	**55% lower risk**

$Tau^2 = 0.06$, $I^2 = 81.0\%$, $p < 0.0001$

	Improvement, RR [CI]			Treatment	Control	
Luo	75%	0.25 [0.07-0.84]	death	3/104	22/179	
Cariou	20%	0.80 [0.45-1.43]	death	746 (n)	571 (n)	CORONADO
Choi (PSM)	-120%	2.20 [0.51-9.58]	progression	case control		
Wang	58%	0.42 [0.01-1.98]	death	1/9	13/49	
Chen	33%	0.67 [0.20-1.78]	death	4/43	15/77	
Kim	64%	0.36 [0.10-1.23]	death	113 (n)	122 (n)	
Li	78%	0.22 [0.09-0.54]	death	2/37	21/94	
Mirani	45%	0.55 [0.27-1.11]	death	25/69	13/21	
Goodall	3%	0.97 [0.75-1.25]	death	74/210	280/771	
Gao	-225%	3.25 [1.03-7.41]	progression	16/56	4/54	
Pérez-Bel.. (PSM)	-10%	1.10 [0.84-1.40]	death	79/249	79/249	
Bramante	12%	0.88 [0.78-1.00]	death	394/2,333	791/3,923	
Sourij	37%	0.63 [0.33-1.10]	death	14/77	44/161	
Lalau (PSM)	22%	0.78 [0.55-1.10]	death	671 (n)	419 (n)	
Huh	-1%	1.01 [0.81-1.23]	progression	104/272	774/2,533	
Ramos-Rincón	1%	0.99 [0.77-1.29]	death	206/420	179/370	
Crouse	61%	0.39 [0.16-0.87]	death	8/76	34/144	
Lally	52%	0.48 [0.28-0.84]	death	16/127	144/648	
Oh	-26%	1.26 [0.81-1.95]	death	5,946 (n)	5,946 (n)	
Wargny	28%	0.72 [0.53-0.95]	death	247/1,553	330/1,241	CORONADO
Bramante (PSM)	62%	0.38 [0.16-0.91]	death	342 (n)	342 (n)	
Khunti	23%	0.77 [0.73-0.81]	death	population-based cohort		
Jiang (PSM)	46%	0.54 [0.13-2.26]	death	3/74	10/74	
Ghany	66%	0.34 [0.19-0.59]	death	392 (n)	747 (n)	
Alamgir	27%	0.73 [0.63-0.84]	death	11,062 (n)	11,062 (n)	
Gálvez-Barrón	-16%	1.16 [0.73-1.49]	death	20 (n)	83 (n)	
Blanc	79%	0.21 [0.03-1.46]	death	1/14	25/75	
Boye	10%	0.90 [0.86-0.94]	hosp.	2,067/4,250	3,196/5,281	
Cheng (PSM)	-65%	1.65 [0.71-3.86]	death	678 (n)	535 (n)	
Wang	12%	0.88 [0.81-0.97]	ICU	6,504 (n)	10,000 (n)	
Ando	39%	0.61 [0.38-0.99]	hosp.			
Wander	15%	0.85 [0.80-0.90]	death			
Saygili (PSM)	42%	0.58 [0.37-0.92]	death	120 (n)	120 (n)	
Ong	47%	0.53 [0.31-0.87]	death	33/186	57/169	
Al-Salameh	55%	0.45 [0.17-0.94]	death/ICU	9/47	22/50	
Wallace (PSW)	72%	0.28 [0.21-0.37]	death	103/1,203	1,536/6,970	
Ojeda-Fern.. (PSM)	16%	0.84 [0.79-0.89]	death	1,476/6,556	1,787/6,556	
Fu	72%	0.28 [0.09-0.84]	no recov.	4/49	9/31	OT[1]
Usman	60%	0.40 [0.12-1.37]	death	3/34	9/41	
Wong	51%	0.49 [0.43-0.57]	death			
Wong (PSW)	59%	0.41 [0.22-0.80]	death	786 (n)	428 (n)	
MacFadden	1%	0.99 [0.96-1.01]	cases	n/a	n/a	
Ma (PSW)	74%	0.26 [0.07-0.89]	death	3/361	40/995	
Yeh	44%	0.56 [0.45-0.71]	progression	n/a	n/a	
Hunt	67%	0.33 [0.25-0.43]	death	73/3,956	1,539/22,552	
Cousins (PSM)	50%	0.50 [0.29-0.85]	ventilation	2,463 (n)	2,463 (n)	
Shestakova	22%	0.78 [0.67-0.91]	death	population-based cohort		
Loucera	30%	0.70 [0.61-0.80]	death	1,896 (n)	14,072 (n)	
Chan	59%	0.41 [0.12-1.44]	death	400 (n)	2,736 (n)	
Zaccardi	34%	0.66 [0.60-0.72]	death	population-based cohort		
Yip (PSM)	7%	0.93 [0.72-1.22]	death/hosp.	8,604 (n)	3,727 (n)	
Ouchi	10%	0.90 [0.77-1.05]	death	6,168 (n)	9,875 (n)	
Morrison (PSM)	41%	0.59 [0.41-0.84]	death	2,684 (n)	2,684 (n)	
Mannucci	38%	0.62 [0.41-0.93]	death	n/a	n/a	
Milosavljevic	33%	0.67 [0.47-0.95]	severe case	377 (n)	356 (n)	
Miao (PSM)	1%	0.99 [0.85-1.15]	death	233/796	236/796	
Servais	49%	0.51 [0.34-0.78]	death	n/a	n/a	

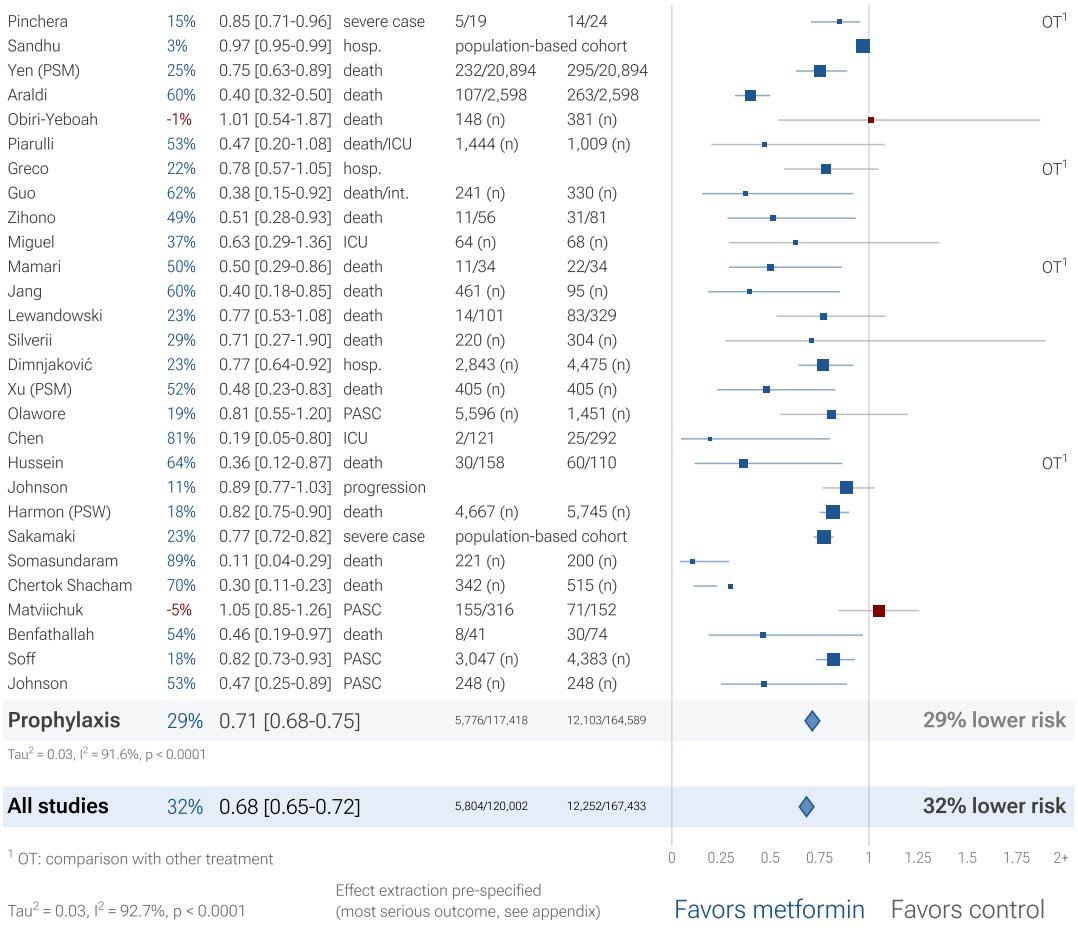


Figure 22. **Random effects meta-analysis for all studies after exclusions.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Heterogeneity

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

Treatment delay

The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours[93,94]. Baloxavir marboxil studies for influenza also show that treatment delay is critical — *Ikematsu et al.* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden et al.* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar et al.* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	Result
Post-exposure prophylaxis	86% fewer cases [95]
<24 hours	-33 hours symptoms [96]
24-48 hours	-13 hours symptoms [96]
Inpatients	-2.5 hours to improvement [97]

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

Figure 23 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

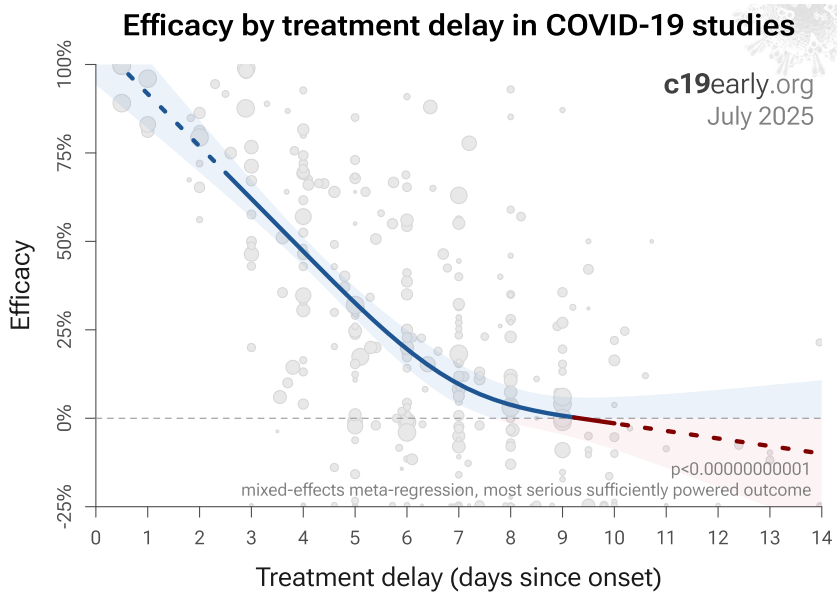


Figure 23. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

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

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [99], for example the Gamma variant shows significantly different characteristics [100-103]. Different mechanisms of action may be more or less effective depending on variants, for example the degree to which TMPRSS2 contributes to viral entry can differ across variants [104,105].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

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

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic [108-124], therefore efficacy may depend strongly on combined treatments.

Effect measured

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

Meta analysis

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

Pooled Effects

Pooled effects are no longer required to show efficacy as of July 2020

This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however pooled effects are no longer required for metformin as of July 2020. Efficacy is now known based on specific outcomes.

Combining studies is required

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

Specific outcome and pooled analyses

We present both specific outcome and pooled analyses. In order to combine the results of studies reporting different outcomes we use the most serious outcome reported in each study, based on the thesis that improvement in the most serious outcome provides comparable measures of efficacy for a treatment. A critical advantage of this

approach is simplicity and transparency. There are many other ways to combine evidence for different outcomes, along with additional evidence such as dose-response relationships, however these increase complexity.

Ethical and practical issues limit high-risk trials

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

Validating pooled outcome analysis for COVID-19

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

Analysis of the the association between different outcomes across studies from all 172 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 24 shows that lower hospitalization is very strongly associated with lower mortality ($p < 0.000000000001$). Similarly, Figure 25 shows that improved recovery is very strongly associated with lower mortality ($p < 0.000000000001$). Considering the extremes, *Singh et al.* show an association between viral clearance and hospitalization or death, with $p = 0.003$ after excluding one large outlier from a mutagenic treatment, and based on 44 RCTs including 52,384 patients. Figure 26 shows that improved viral clearance is strongly associated with fewer serious outcomes. The association is very similar to *Singh et al.*, with higher confidence due to the larger number of studies. As with *Singh et al.*, the confidence increases when excluding the outlier treatment, from $p = 0.000000082$ to $p = 0.0000000033$.

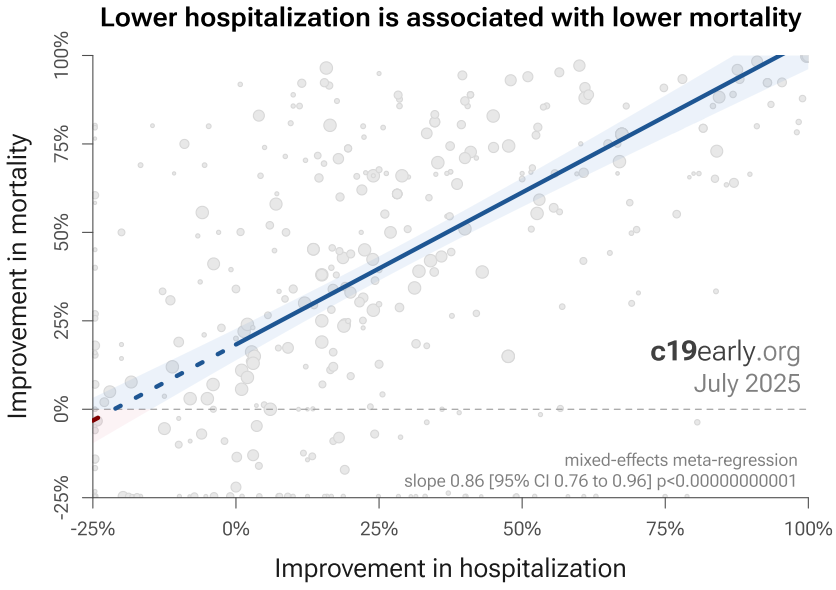


Figure 24. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

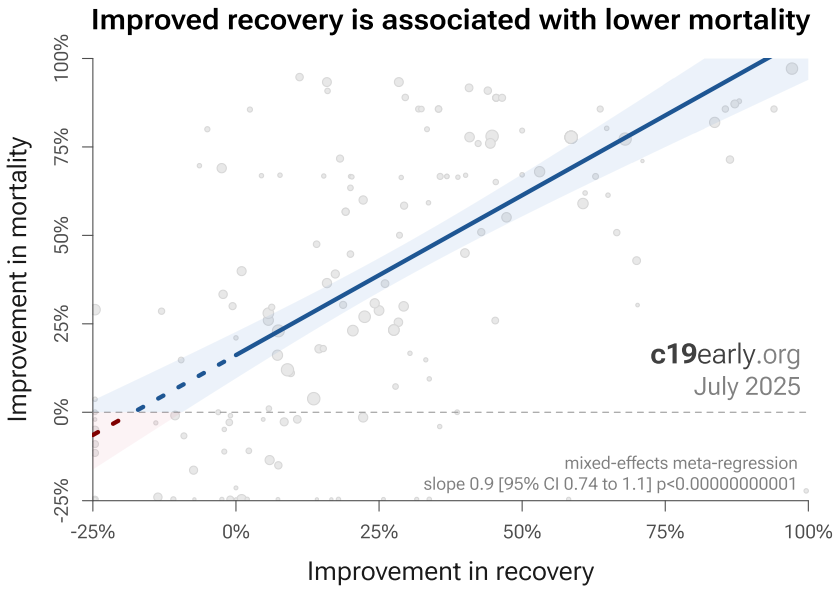


Figure 25. Improved recovery is associated with lower mortality, supporting pooled outcome analysis.

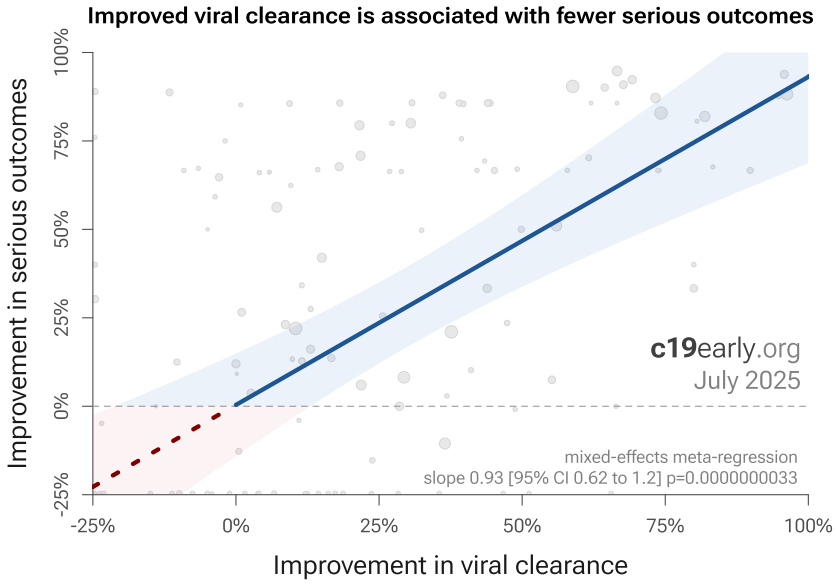


Figure 24. Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.

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

Currently, 55 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of these have been confirmed with one or more specific outcomes, with a mean delay of 4.9 months. When restricting to RCTs only, 57% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 7.3 months. Figure 27 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

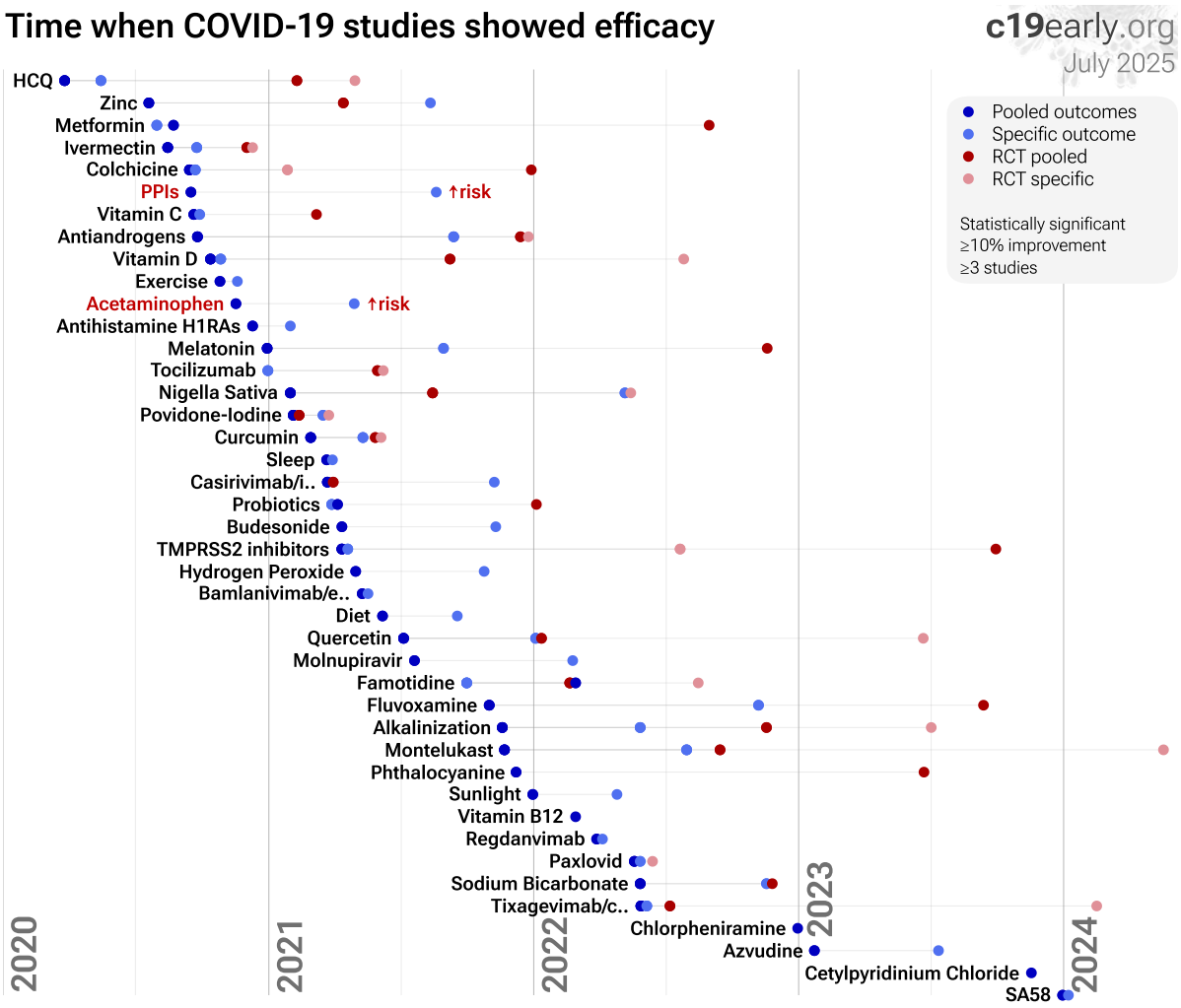


Figure 27. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Limitations

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

Summary

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

Discussion

Results for other infections

Efficacy with metformin has also been shown for influenza A [64].

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 [126-129]. For metformin, there is currently not enough data to evaluate publication bias with high confidence.

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 28 shows a scatter plot of results for prospective and retrospective studies. 66% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 62% of prospective studies, showing similar results. The median effect size for retrospective studies is 38% improvement, compared to 32% for prospective studies, suggesting a potential bias towards publishing results showing higher efficacy.

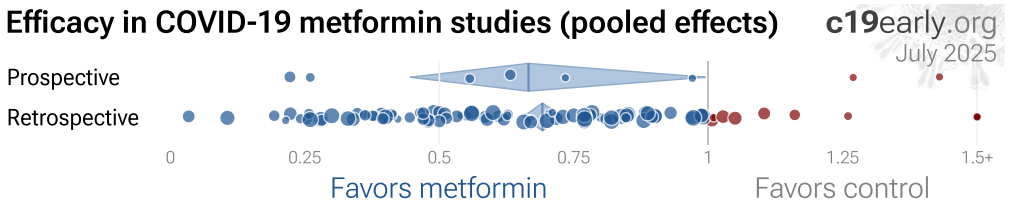


Figure 28. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 29 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 $p < 0.05$ [130-137]. 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.

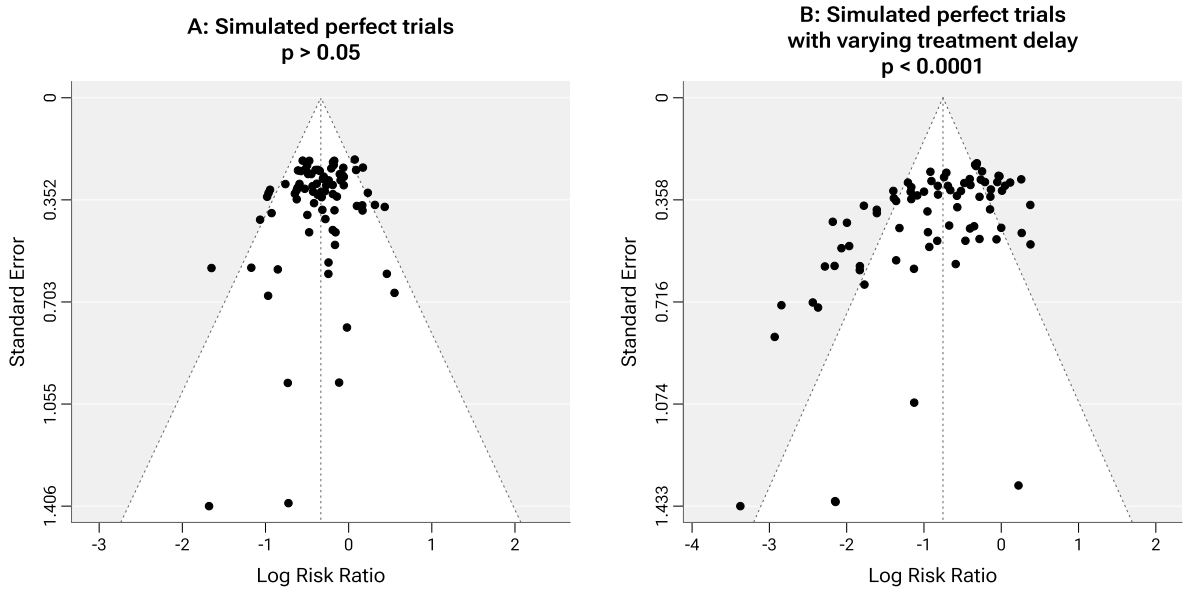


Figure 29. **Example funnel plot analysis for simulated perfect trials.**

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. Metformin for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 metformin 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 metformin 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 for specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

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

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

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

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

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone [108-124]. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

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

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

Notes

6 of the 105 studies compare against other treatments, which may reduce the effect seen. 23 other meta analyses show significant improvements with metformin for mortality [1-22], hospitalization [7,13], progression [1], and severity [8,9,13].

Reviews

Many reviews cover metformin for COVID-19, presenting additional background on mechanisms and related results, including [57,60,138-144].

Other studies

Additional preclinical or review papers suggesting potential benefits of metformin for COVID-19 include [236-258]. We have not reviewed these studies in detail.

Perspective

Results compared with other treatments

SARS-CoV-2 infection and replication involves a complex interplay of 100+ host and viral proteins and other factors [43-50], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk [51], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 30 shows an overview of the results for metformin in the context of multiple COVID-19 treatments, and Figure 31 shows a plot of efficacy vs. cost for COVID-19 treatments.

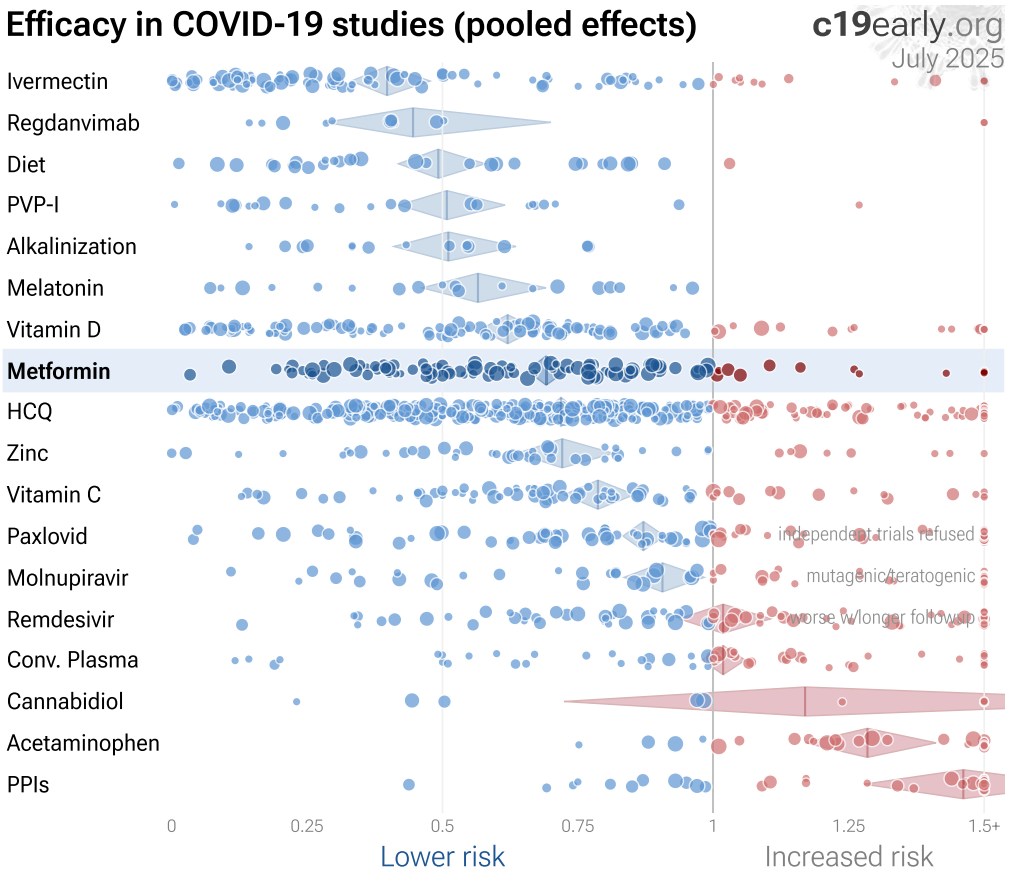


Figure 30. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy[259].

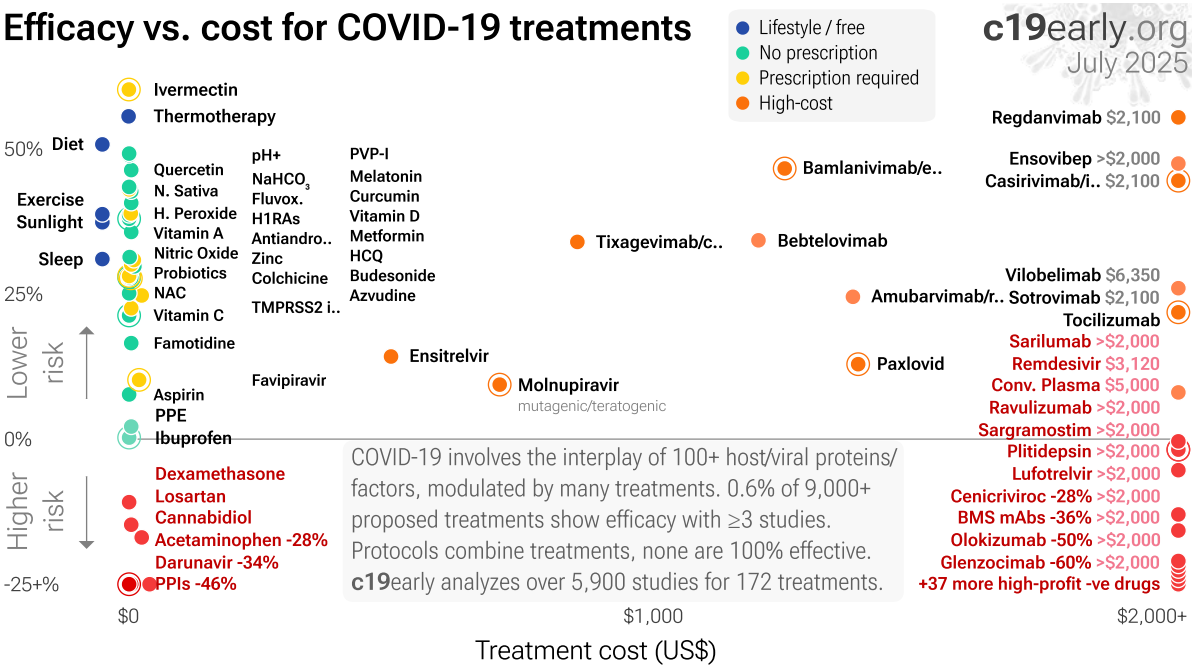


Figure 31. **Efficacy vs. cost for COVID-19 treatments.**

Conclusion

Significantly lower risk is seen for mortality, ventilation, ICU admission, hospitalization, progression, and recovery. 69 studies from 63 independent teams in 22 countries show significant benefit. Meta analysis using the most serious outcome reported shows 31% [27-34%] lower risk. Results are similar for Randomized Controlled Trials, higher quality studies, and peer-reviewed studies. Results are very robust — in exclusion sensitivity analysis 83 of 105 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

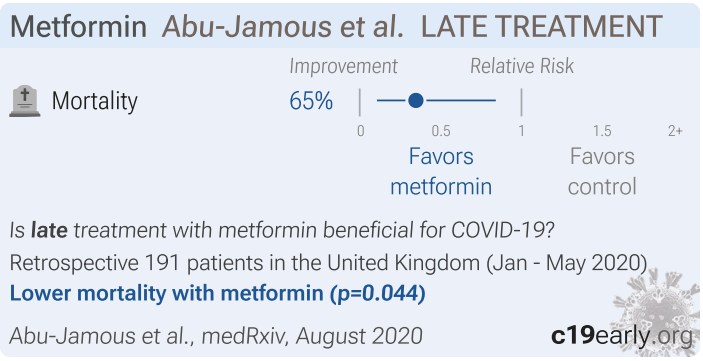
Most studies analyze existing use with diabetic patients. Prophylaxis results typically include continuing use after infection and hospitalization, and greater benefit is seen for more serious outcomes. The TOGETHER RCT shows 27% lower mortality. While not statistically significant, $p = 0.53$, this is consistent with the mortality results from all studies, 37% [33-41%].

23 other meta analyses show significant improvements with metformin for mortality [1-22], hospitalization [7,13], progression [1], and severity [8,9,13].

Efficacy with metformin has also been shown for influenza A [64].

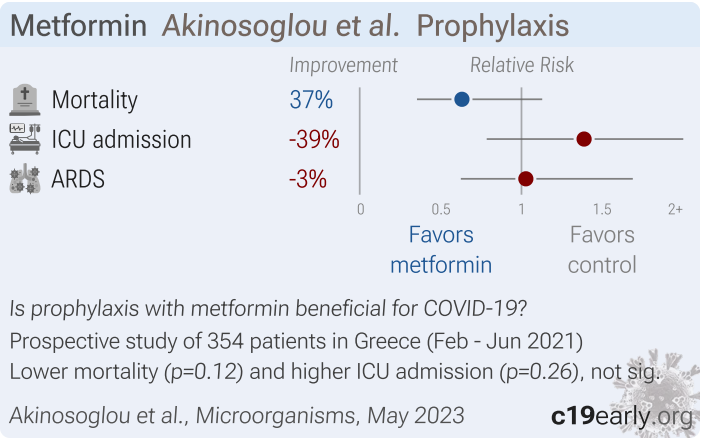
Study Notes

Abu-Jamous



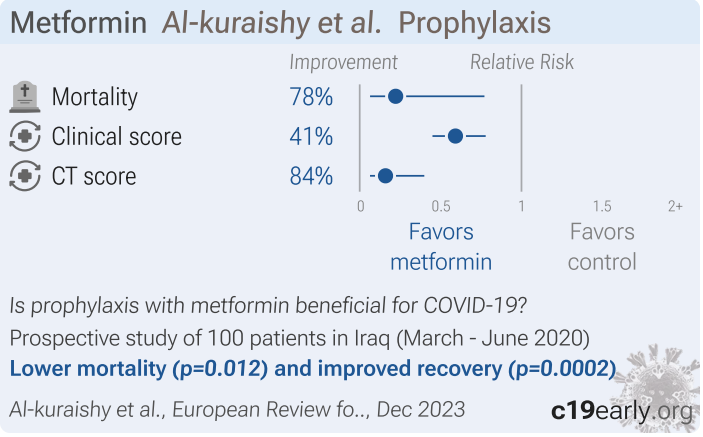
Retrospective diabetes patients in the UK, showing lower mortality for metformin treatment (administered within 21 days after a positive PCR test).

Akinosoglou



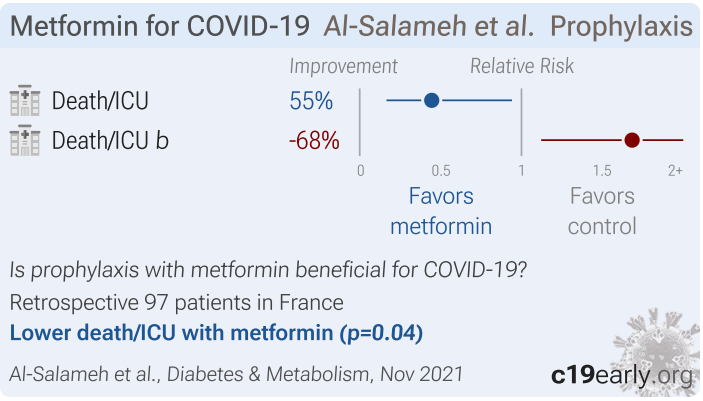
Prospective multicenter study of 354 hospitalized type 2 diabetes patients with COVID-19 in Greece showing increased risk with DPP4 inhibitor use as part of chronic diabetes treatment. There was no significant difference with metformin use in unadjusted results. Results do not account for differences in the risk of hospitalization.

Al-kuraishy



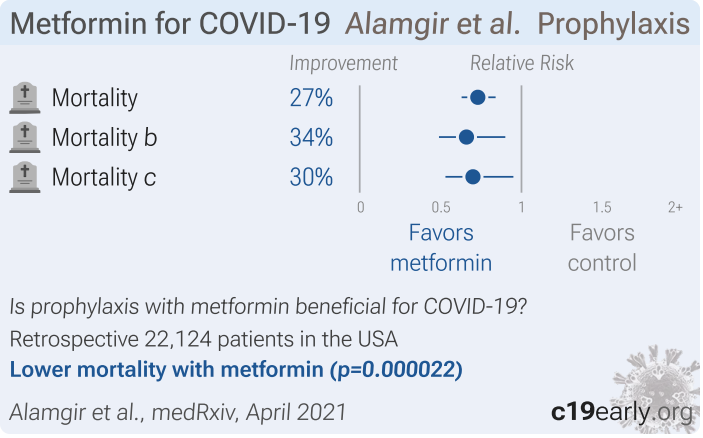
Prospective study of 60 hospitalized type 2 diabetes patients with COVID-19 on metformin monotherapy compared to 40 patients on other diabetes treatments, showing significantly lower inflammatory biomarkers, oxidative stress, and mortality, and improvements in radiological and clinical outcomes with metformin. Confounding due to differences in baseline characteristics may be significant.

Al-Salameh



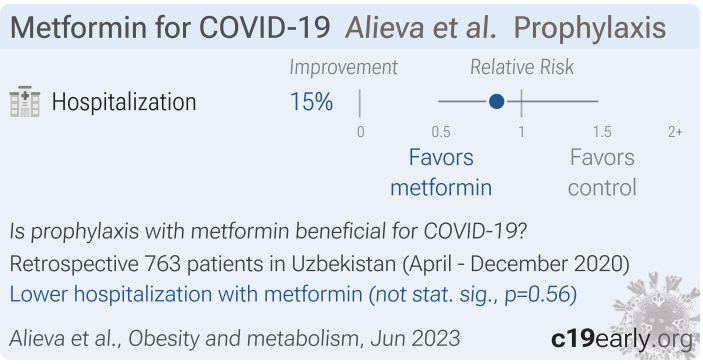
Retrospective 140 diabetic patients in France, showing lower mortality for patients where metformin use was continued after hospitalization.

Alamgir



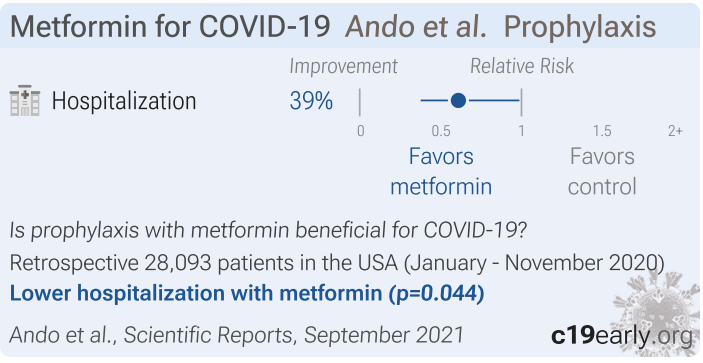
In Silico study followed by PSM analysis of the National COVID Cohort Collaborative data in the USA, showing 27% lower mortality with metformin use.

Alieva



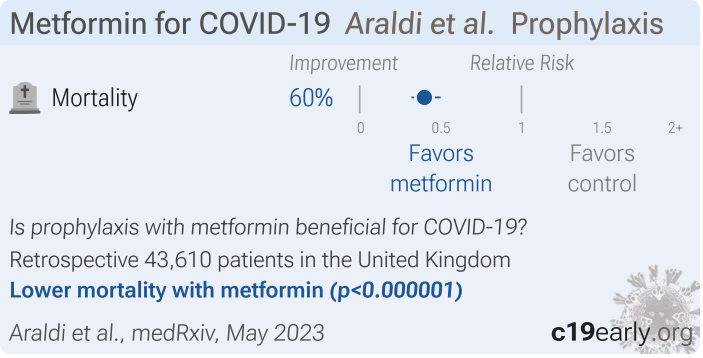
Retrospective 763 COVID-19 patients with type 2 diabetes in Uzbekistan, showing lower hospitalization with metformin use in unadjusted results, without statistical significance.

Ando



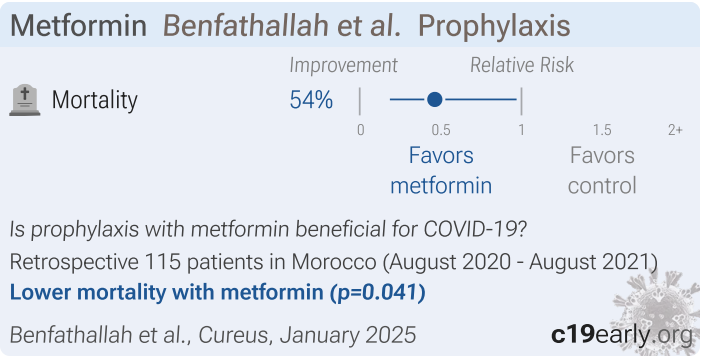
Retrospective 28,093 COVID+ patients in the USA, showing lower risk of hospitalization with metformin use.

Araldi



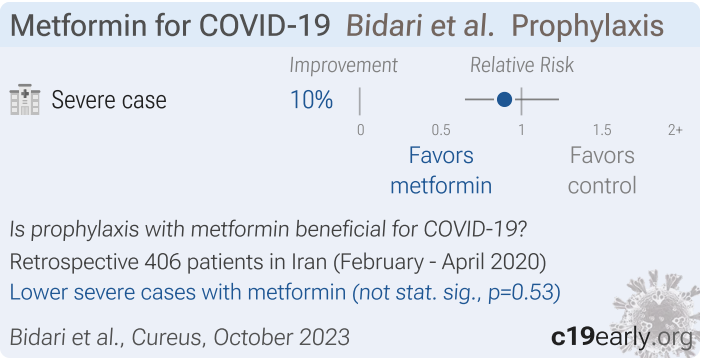
UK Biobank retrospective including 43,610 type 2 diabetes patients, showing lower mortality with metformin use within matched type 2 diabetes patients.

Benfathallah



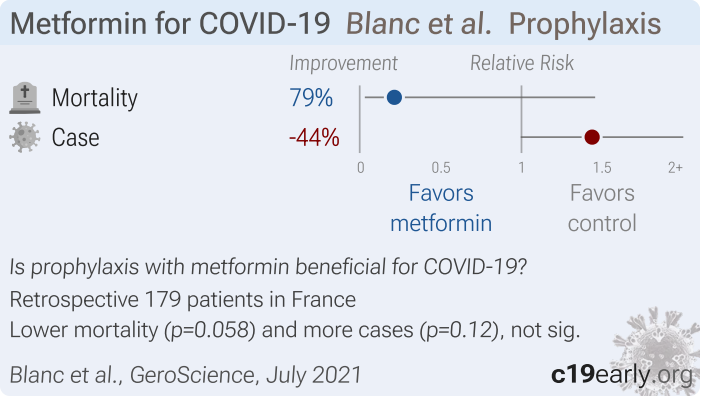
Retrospective 115 hospitalized type 2 diabetes patients in Morocco showing significantly lower mortality with metformin use.

Bidari



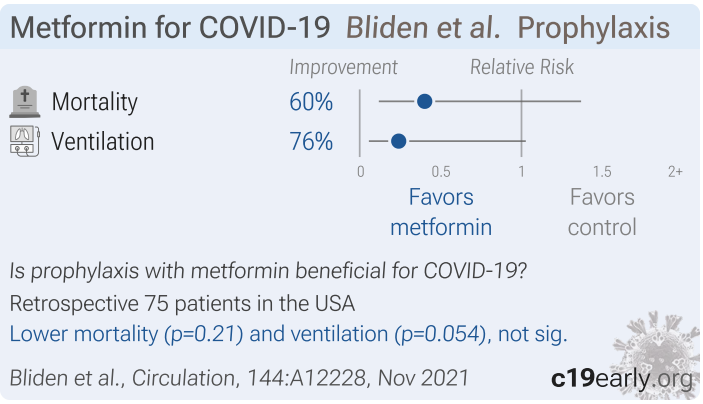
Retrospective 406 COVID-19 patients in Iran, showing lower risk of severe cases with metformin use in unadjusted results, without statistical significance.

Blanc



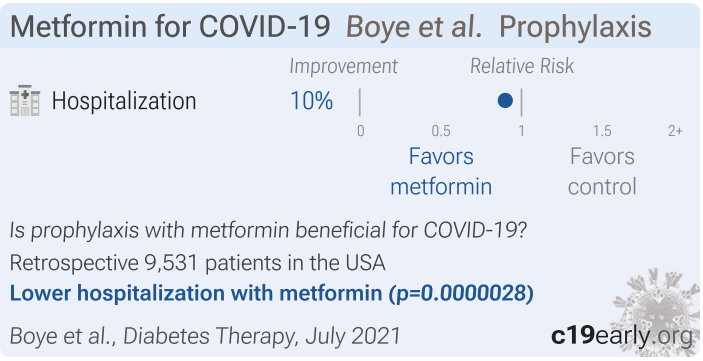
Retrospective 179 patients in France exposed to COVID-19 showing, without statistical significance, a higher risk of cases, and a lower risk of mortality among cases with existing metformin treatment.

Bliden



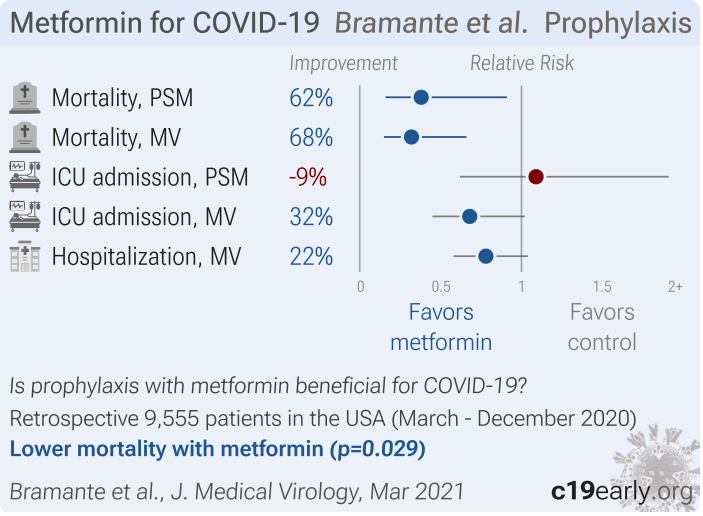
Retrospective 75 diabetes patients, 34 on metformin, showing lower mortality with treatment in unadjusted results with minimal group details.

Boye



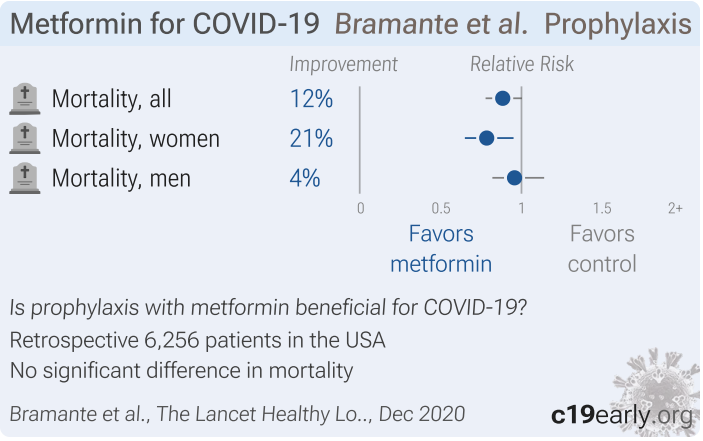
Retrospective 9531 COVID+ diabetes patients in the USA, showing lower risk of hospitalization with existing biguanides treatment (defined as mainly metformin in the abstract and entirely metformin in the text).

Bramante



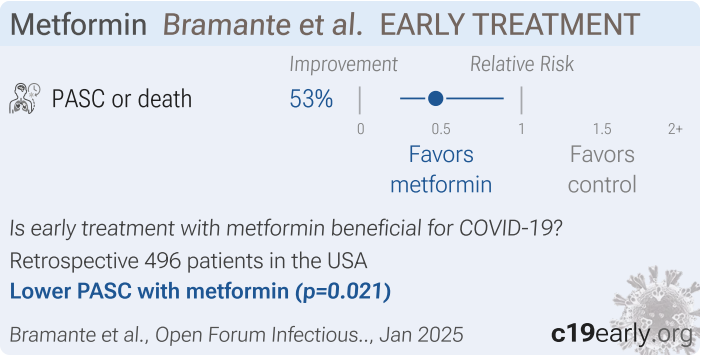
Retrospective 17,396 PCR+ patients in the USA, showing lower mortality with metformin use.

Bramante



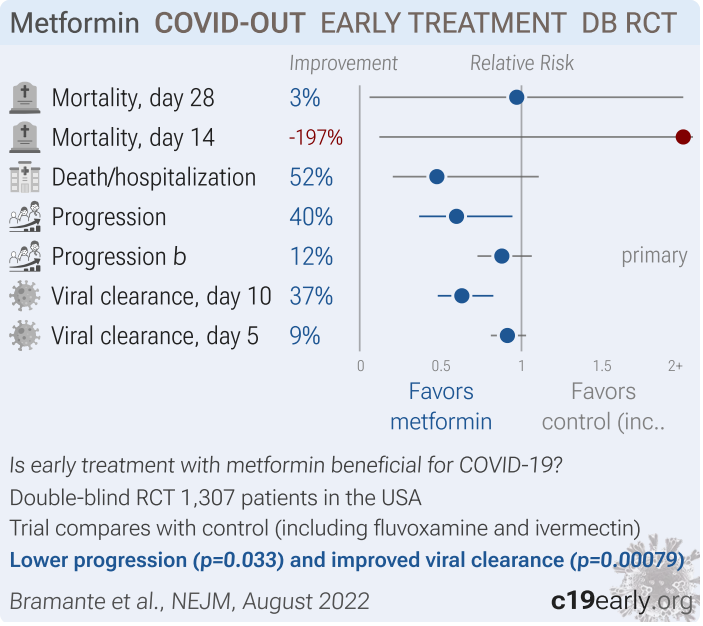
Retrospective 6,256 COVID-19+ diabetes patients in the USA, showing lower mortality with existing metformin treatment, statistically significant only for women.

Bramante



Emulated target trial of Omicron-infected outpatients without diabetes or prediabetes, showing significantly lower long COVID or death with metformin treatment.

Bramante



COVID-OUT remotely operated RCT, showing lower combined ER/hospitalization/death with metformin. Results for other treatments are listed separately - ivermectin, fluvoxamine.

The "control" group includes patients receiving active treatments fluvoxamine and ivermectin.

Control arm results are very different between treatments, for example considering hospitalization/death, this was 1.0% for ivermectin vs. 2.7% for overall control, however it was 1.3% for the ivermectin-specific control. 394 control patients are shared. The rate for the non-shared 261 metformin control patients is 5%, compared to 1.3% for ivermectin control patients. The metformin arm started earlier, however it is unclear why the difference in outcomes is so large.

Results were delayed for 6 months with no explanation, with followup ending Feb 14, 2022.

Adherence was very low, with 77% overall reporting 70+% adherence. Numbers for 100% adherence are not provided.

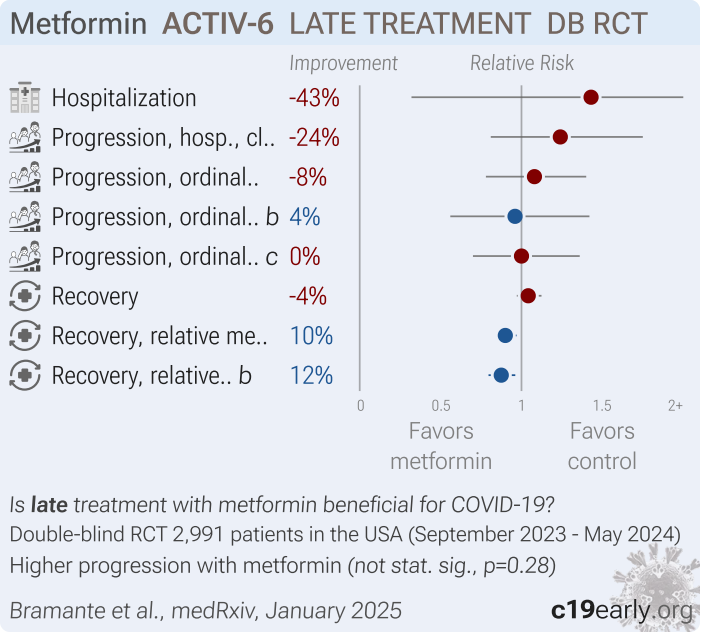
Multiple outcomes are missing, for example time to recovery (where ACTIV-6 showed superiority of ivermectin).

Treatment was 14 days for metformin and fluvoxamine, but only 3 days for ivermectin.

Trial outcomes were changed on January 20, 2022[260], and again on March 2, 2022[261]. COVIDOUT.

Medication delivery varied significantly over the trial. In this presentation[262], author indicates that delivery was initially local, later via FedEx, was much slower in August, there were delays due to team bandwidth issues, and they only realized they could use FedEx same day delivery in September.

Bramante



RCT 2,991 outpatient adults with mild to moderate COVID-19 showing no significant difference in time to sustained recovery with metformin compared to placebo. Median days to symptom resolution was 9 days vs. 10 days for placebo, without statistical significance. There was a median 5 day delay for drug receipt (treatment delay is unspecified but may be greater).

eFigure 5 shows HR 0.40 [0.28-0.58], p = 0.000001, for patients that had recovered by the time of drug receipt and had no symptoms on that day. This result suggests a major confounding factor or flaw in the study leading to very unreliable results and a strong bias towards the placebo group. A likely possible cause is the inclusion of metformin side effects as COVID-19 symptoms. Authors include many side effects of metformin as COVID-19 symptoms: diarrhea: a common side effect of metformin, especially in the initial days of treatment; nausea: frequently reported with metformin use, vomiting: less common but a documented side effect of metformin; fatigue: metformin may cause mild fatigue or malaise in some individuals, and headache: rare but also a possible side effect of metformin. Authors do a sensitivity analysis using day 1 vs. baseline symptoms, however they do not provide details of this analysis. The text suggests authors only used diarrhea, and the day 1 focus would also result in only partial correction.

Note that it would be simple for authors to perform an analysis focusing on more COVID-19 specific and/or serious symptoms.

Trial designs favoring placebo/no effect were likely done to minimize efficacy of an earlier treatment in the trial - for example the wide inclusion of non-COVID-19 specific symptoms, inclusion of typical side-effect symptoms, use of the last of 3 days instead of the first of 3 days for sustained recovery, very slow shipping, and inclusion of patients up to 12 days from onset.

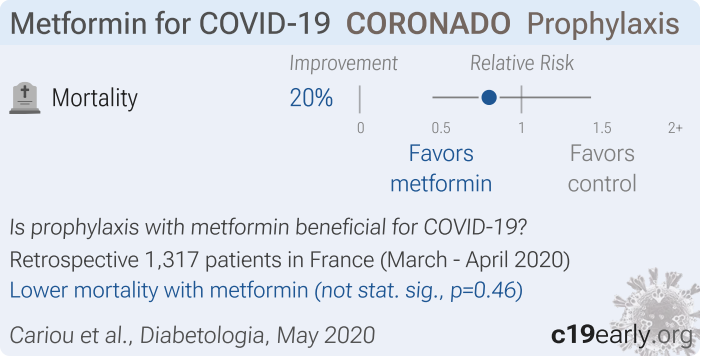
Patients with symptoms ≤7 days from onset were eligible, however eFigure 1 shows there were patients with up to 12 days from symptoms to drug receipt, suggesting up to 5 days shipping delay. Trial operation is not logical for an acute condition like COVID-19. Table 1 shows 48 hours delay between enrollment and receipt of medication (treatment time is not reported and may be even later - patients may not be at the location at delivery time). It is unclear why authors would not use overnight shipping as a worst case, widely available for the study population, for <24 hours delivery (other than designing the trial to favor finding no effect).

The study period was September 2023 - May 2024, by which time SARS-CoV-2 variants resulted in signficantly fewer serious outcomes, reducing the potential for a treatment to show a significant affect on serious outcomes.

There is an extensive list of major conflicts of interest reported (any many unreported).

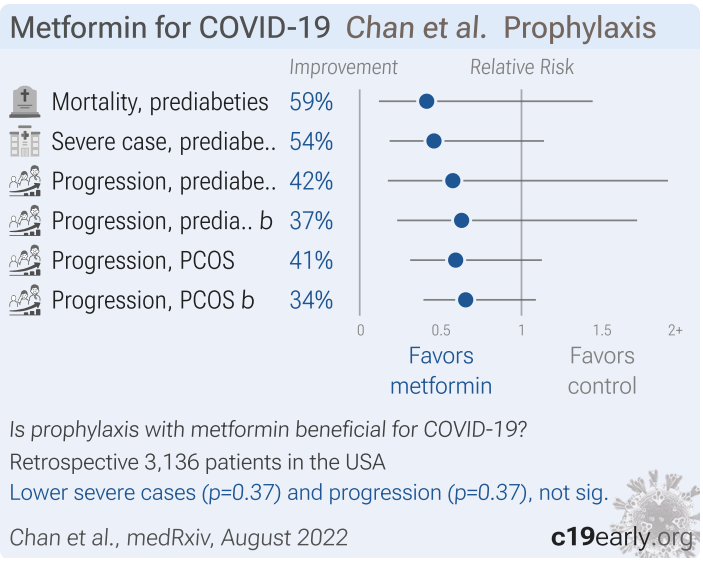
ACTIV trial authors have reported a number of issues that may affect the reliability of the results in ACTIV trials including participant fraud[263], biased participant demographics[264], resource issues that may have led to protocol deviations[264], differences in trial design including inconsistent inclusion/exclusion criteria[264], participant self-selection bias[263,264], underrepresentation of older patients due to web-based recruitment[264], changes in treatment and public health policies during trials[264], treatment delay determination from shipping logs and delivery that may not be directly to the patient[263], variable placebo responses (e.g., oral vs. inhaled)[265], logistical challenges maintaining blinding[265], errors from complex data collection systems[265], unplanned design changes including endpoint changes[265], and inconsistent SoC across trial sites and time periods[265].

Cariou



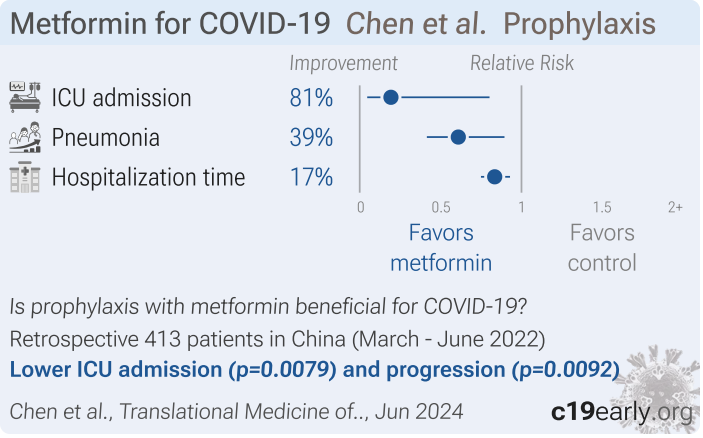
Analysis of 1,317 hospitalized COVID-19 patients with diabetes showing lower mortality with metformin use, without statistical significance.

Chan



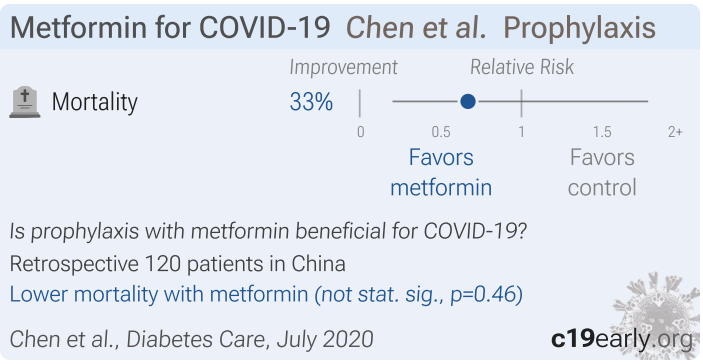
Retrospective 3,136 patients with prediabetes and 282 with PCOS, showing metformin associated with reduced COVID-19 severity.

Chen



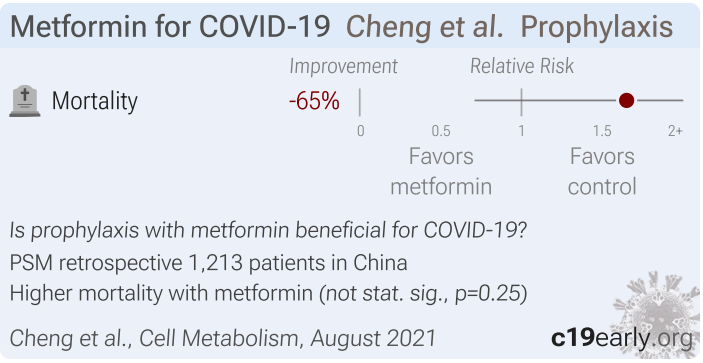
Retrospective 413 hospitalized COVID-19 patients with type 2 diabetes in China showing lower ICU admission, lower pneumonia incidence, and shorter hospital stay with metformin use.

Chen



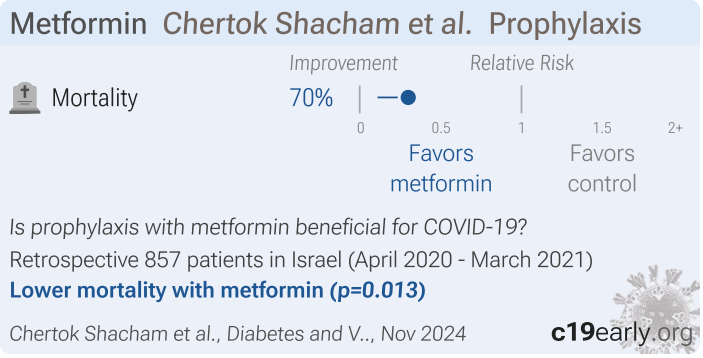
Retrospective 120 COVID-19 diabetes patients, showing non-statistically significantly lower mortality with existing metformin treatment.

Cheng



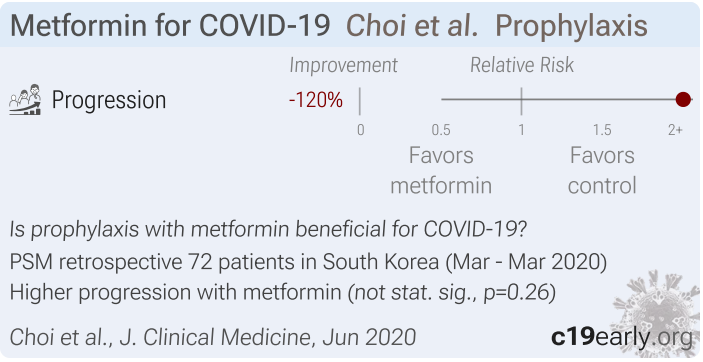
Retrospective 1,213 hospitalized diabetic COVID-19 patients in China, showing no significant difference in mortality with pre-existing metformin use.

Chertok Shacham



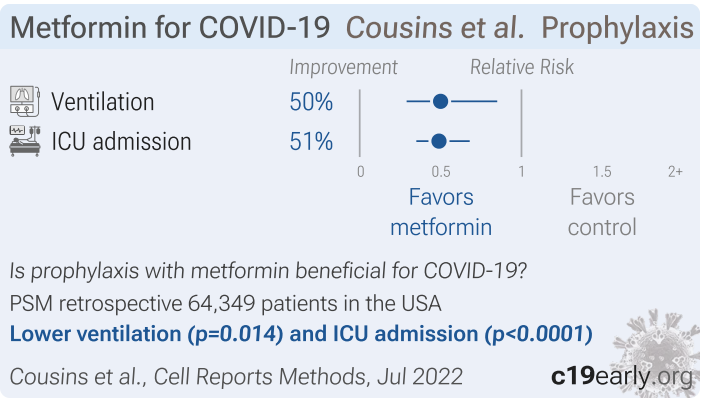
Retrospective 857 hospitalized type 2 diabetes patients showing lower mortality with pre-admission metformin use. Authors report no significant difference in mortality with in-hospital metformin use, but do not report the actual result.

Choi



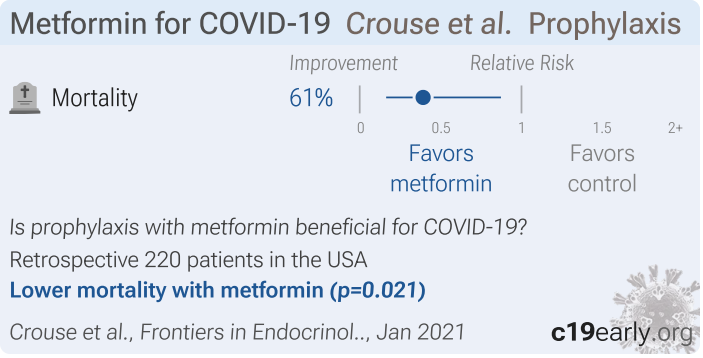
Retrospective 293 patients in South Korea, showing higher risk of progression with metformin use, without statistical significance.

Cousins



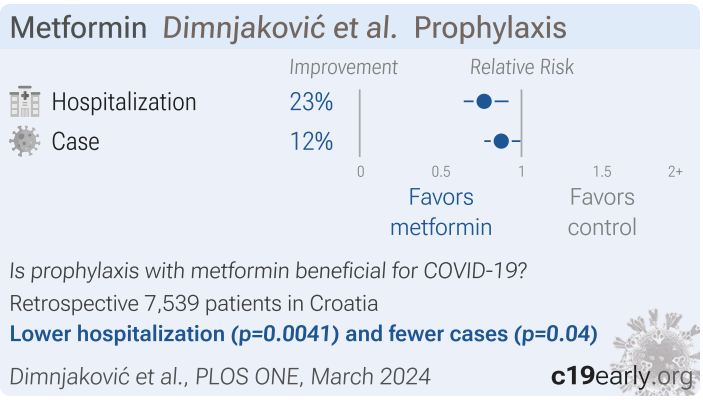
PSM retrospective 64,349 COVID-19 patients in the USA, showing metformin associated with lower ICU admission and mechanical ventilation.

Crouse



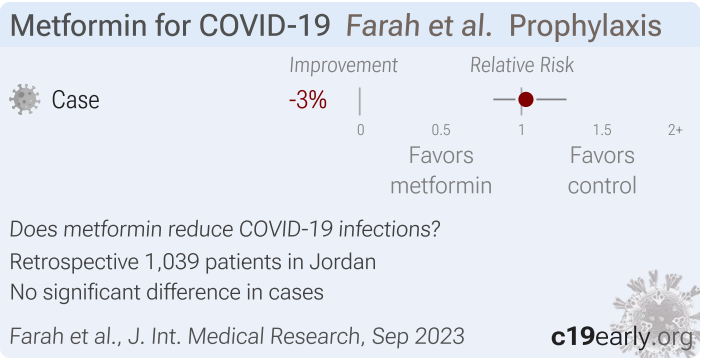
Retrospective 219 COVID-19+ diabetes patients in the USA, showing lower mortality with existing metformin treatment.

Dimnjaković



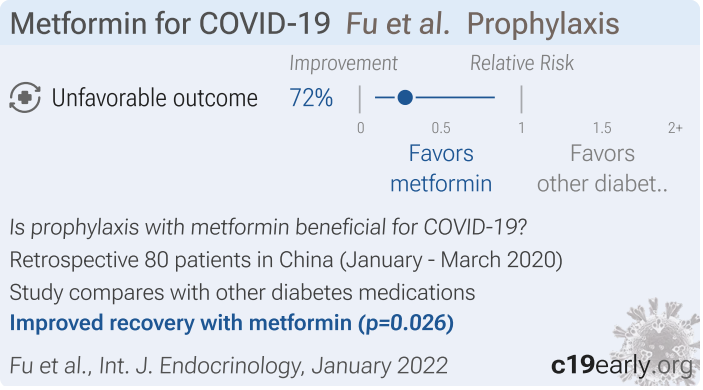
Retrospective 7,539 patients with diabetes mellitus type 2 and chronic kidney disease in Croatia showing lower risk of SARS-CoV-2 infection with SGLT-2 inhibitors, metformin, and repaglinide use, and lower risk of COVID-19 hospitalization with SGLT-2 inhibitors and metformin use.

Farah



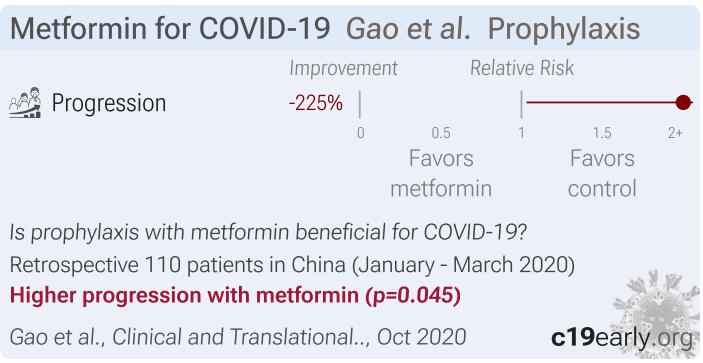
Retrospective 1,039 diabetes patients in Jordan, showing no significant difference in COVID-19 cases with metformin use in unadjusted results. Severity outcomes are not provided for metformin.

Fu



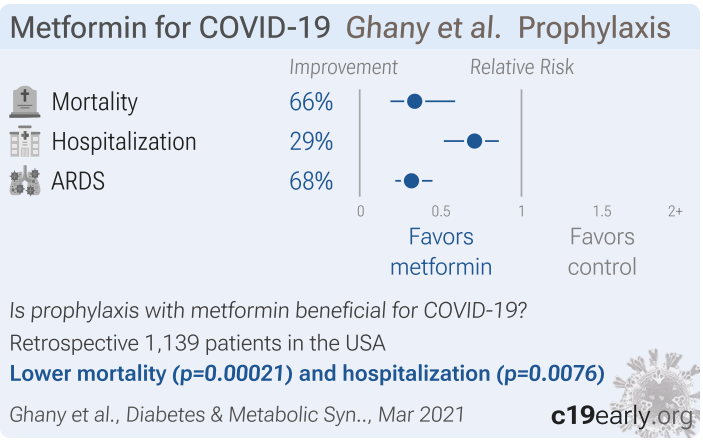
Retrospective 108 T2D patients hospitalized with COVID-19, showing lower risk of unfavorable outcomes with metformin use vs. other diabetic medications.

Gao



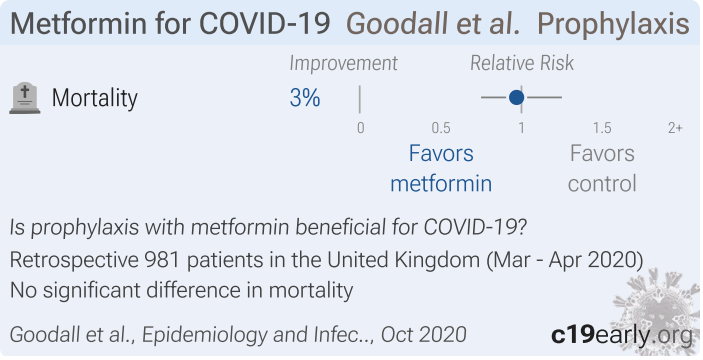
Retrospective 110 hospitalized COVID-19 patients with diabetes in China, showing increased risk of severity with metformin.

Ghany



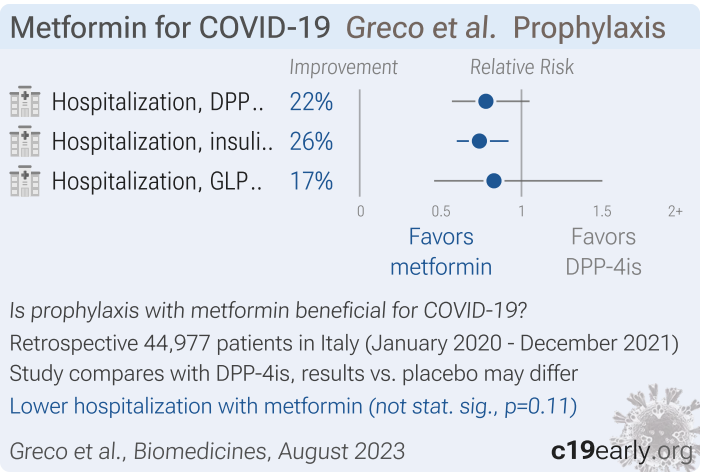
Retrospective 1,139 elderly COVID+ patients in the USA, 392 with pre-existing metformin use, showing significantly lower mortality, hospitalization, and ARDS with treatment.

Goodall



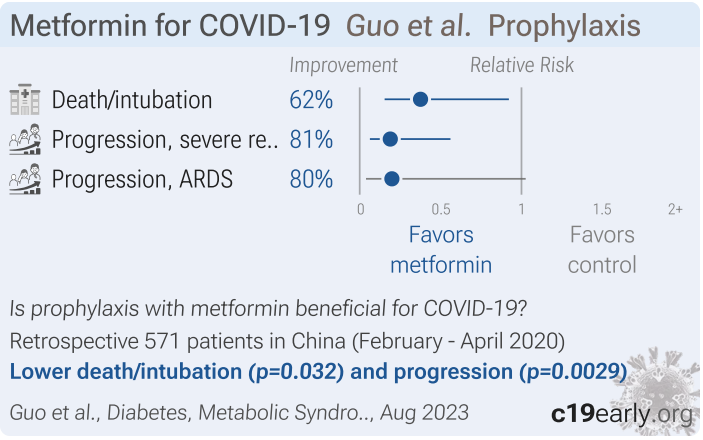
Retrospective 981 hospitalized patients in the UK, showing no significant difference with metformin use.

Greco



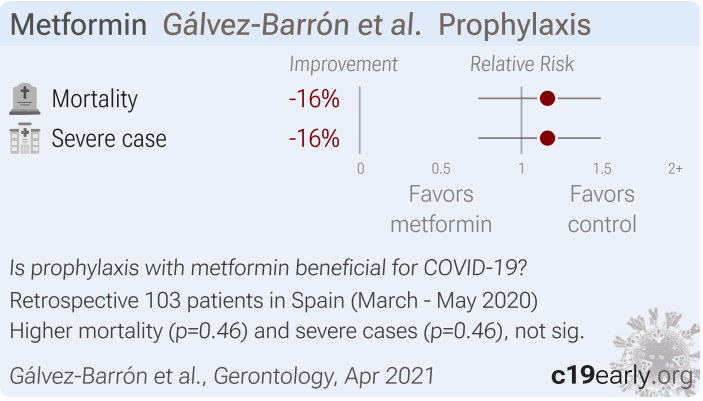
Retrospective 76,764 diabetes patients in Italy, showing that patients on metformin had lower rates of COVID-19 hospitalization compared to those on insulin/insulin secretagogues, GLP-1 receptor agonists, and DPP-4 inhibitors. Metformin vs. no metformin results are not provided. The most relevant result for COVID-19 and metformin may be the DPP-4i comparison, based on the DPP-4i group being the most similar to the metformin group in terms of baseline COVID-19 risk and confounders. Patients on insulin/secretagogues may have more severe or advanced diabetes.

Guo



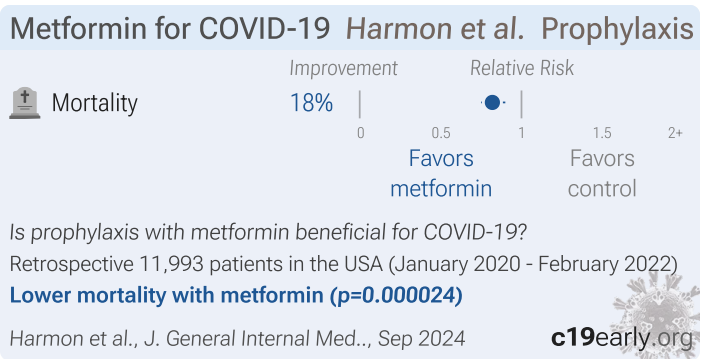
Retrospective 571 type 2 diabetes patients with COVID-19 in China, showing lower combined mortality/mechanical ventilation with metformin.

Gálvez-Barrón



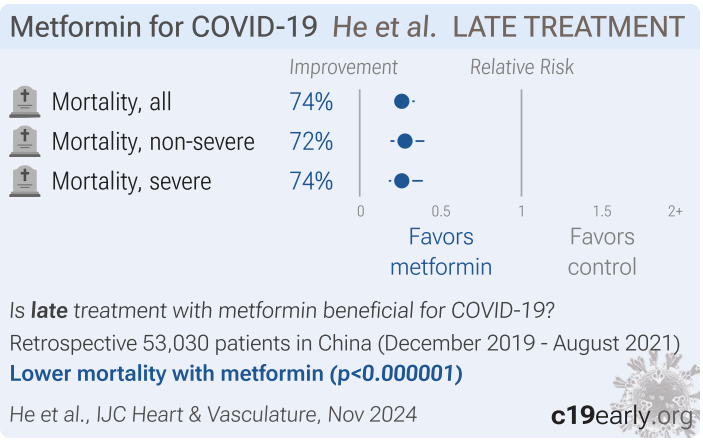
Analysis of 103 elderly hospitalized COVID-19 patients in Spain, showing higher mortality with metformin, without statistical significance.

Harmon



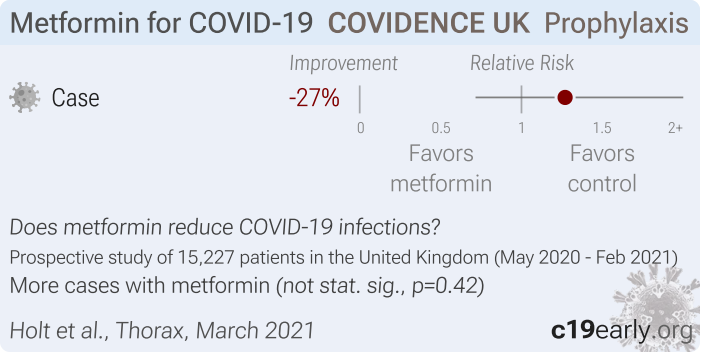
Retrospective 11,993 hospitalized COVID-19 patients with diabetes mellitus but without chronic kidney disease or need for hemodialysis, showing lower mortality with metformin use.

He



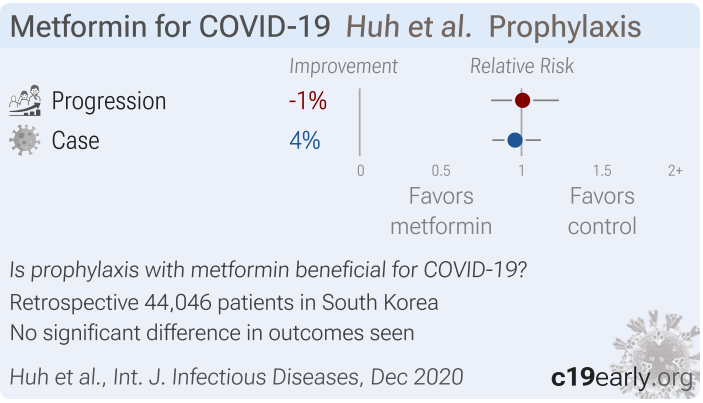
Retrospective 53,030 COVID-19 patients from 138 hospitals in Hubei, China showing lower mortality with metformin.

Holt



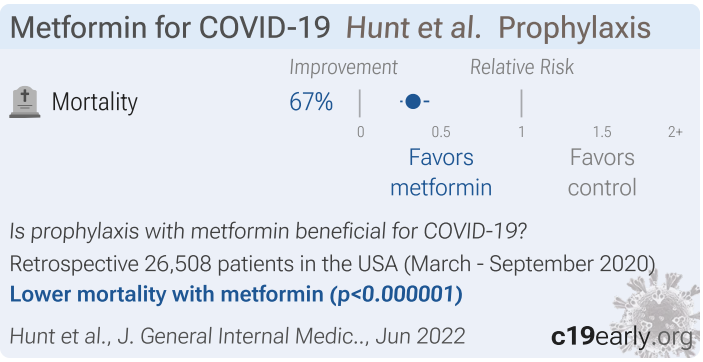
Prospective survey-based study with 15,227 people in the UK, showing lower risk of COVID-19 cases with vitamin A, vitamin D, zinc, selenium, probiotics, and inhaled corticosteroids; and higher risk with metformin and vitamin C. Statistical significance was not reached for any of these. Except for vitamin D, the results for treatments we follow were only adjusted for age, sex, duration of participation, and test frequency.

Huh



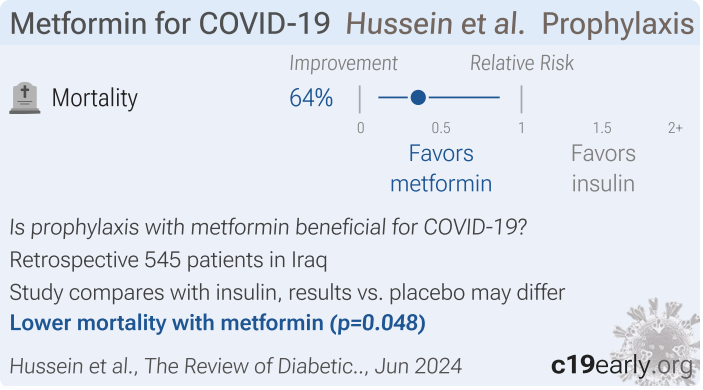
Retrospective database analysis showing no significant differences with pre-existing metformin use.

Hunt



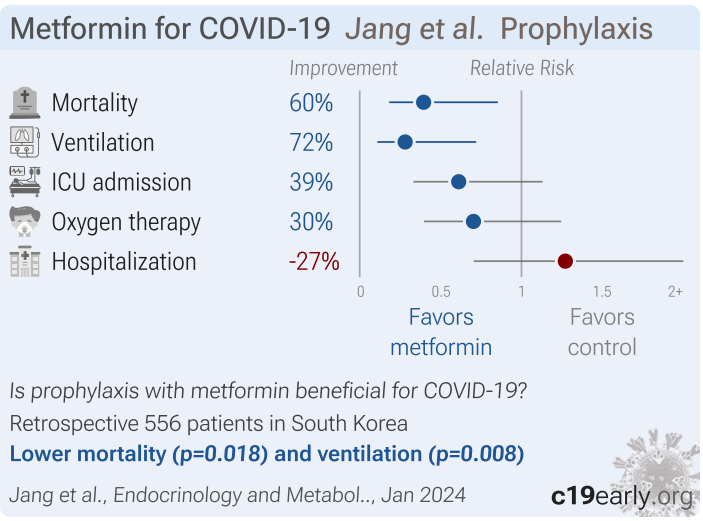
Retrospective 26,508 consecutive COVID+ veterans in the USA, showing lower mortality with multiple treatments including metformin. Treatment was defined as drugs administered ≥50% of the time within 2 weeks post-COVID+, and may be a continuation of prophylactic treatment in some cases, and may be early or late treatment in other cases. Further reduction in mortality was seen with combinations of treatments.

Hussein



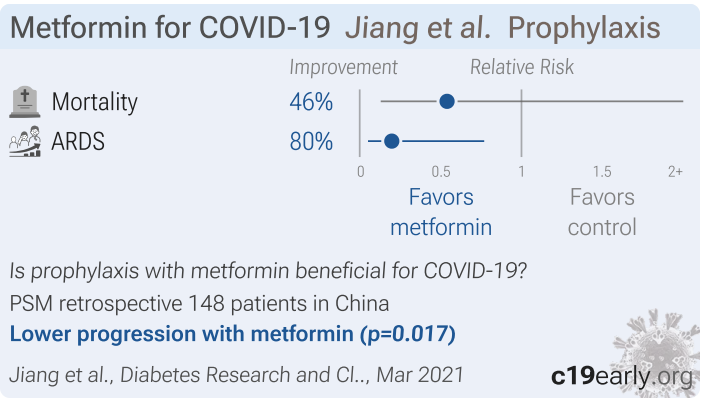
Retrospective 545 hospitalized COVID-19 patients with diabetes showing high mortality (33%). Metformin, SGLT inhibitors, and DPP4 inhibitors were associated with lower mortality compared with insulin.

Jang



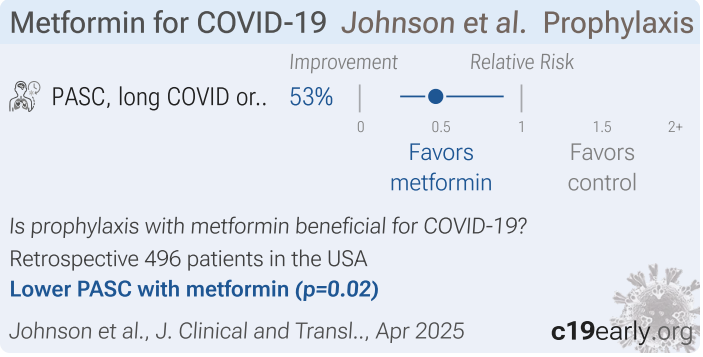
Retrospective 556 diabetic patients in South Korea with COVID-19 showing lower risk of mechanical ventilation and death with metformin, lower risks of oxygen treatment and death with DPP-4 inhibitors, and increased risk of mechanical ventilation with sulfonylureas. The study used nationwide data to analyze the impact of common antidiabetic medications on COVID-19 outcomes. Authors note that South Korea had a policy early in the pandemic of hospitalizing nearly all confirmed COVID-19 patients regardless of severity.

Jiang



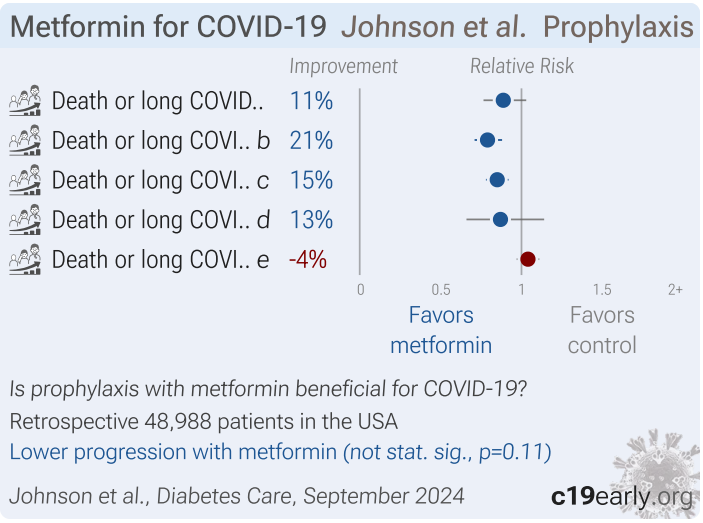
Retrospective 328 COVID-19 patients with type 2 diabetes in China, showing significantly lower risk of ARDS with existing metformin use.

Johnson



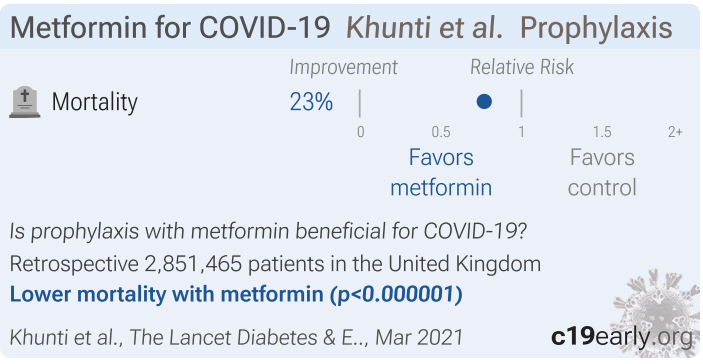
N3C target trial emulation study with 9,660 adult COVID-19 patients, showing metformin associated with lower risk of long COVID or death.

Johnson



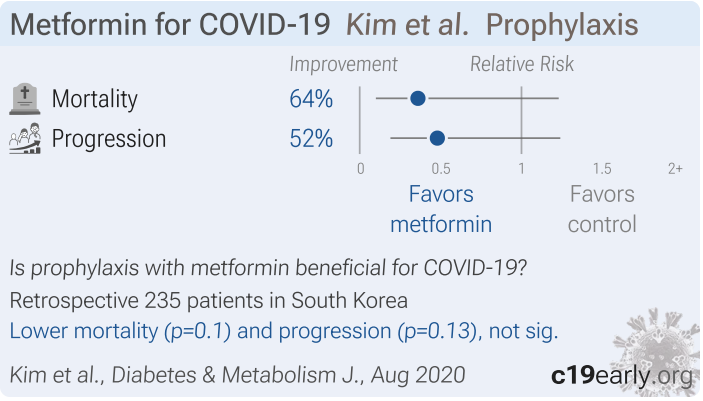
N3C/PCORnet retrospective adults with type 2 diabetes in the USA showing lower incidence of mortality or long COVID with metformin use.

Khunti



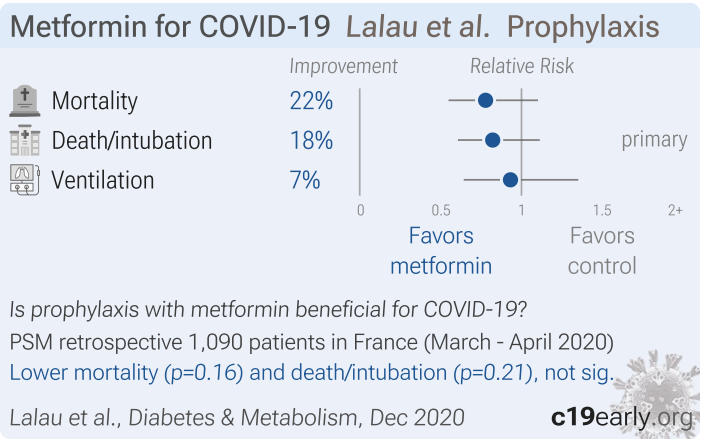
Retrospective 2,851,465 people with type 2 diabetes in the UK, showing lower mortality with existing metformin use. Results are subject to confounding by indication because metformin is typically used early in the progression of type 2 diabetes.

Kim



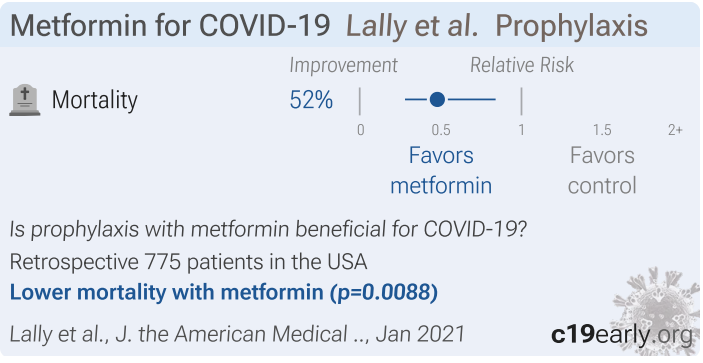
Retrospective 235 hospitalized diabetes patients in South Korea, showing lower mortality and lower progression to severe disease with metformin.

Lalau



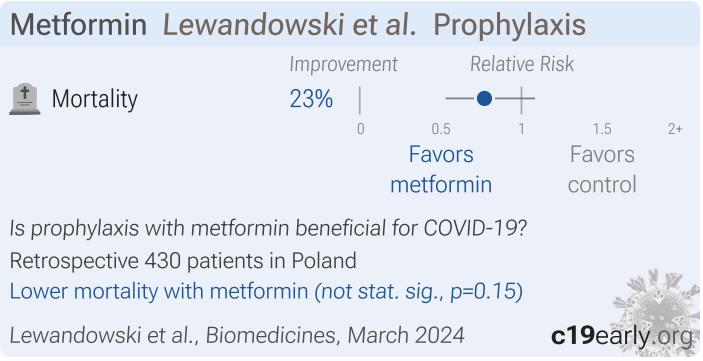
Retrospective 2,449 hospitalized COVID-19 diabetes patients in France, 1,496 with existing metformin use, showing lower mortality with treatment. Statistical significance was reached in model 1 but not in models 2-4 which also adjust for HbA1c, eGFR, and diabetes duration, but have a lower number of patients. CORONADO (Coronavirus SARS-CoV-2 and Diabetes Outcomes).

Lally



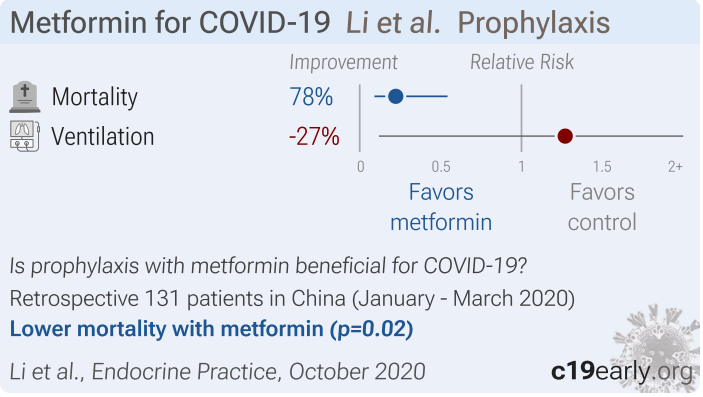
Retrospective 775 nursing home residents in the USA, showing lower mortality with existing metformin use.

Lewandowski



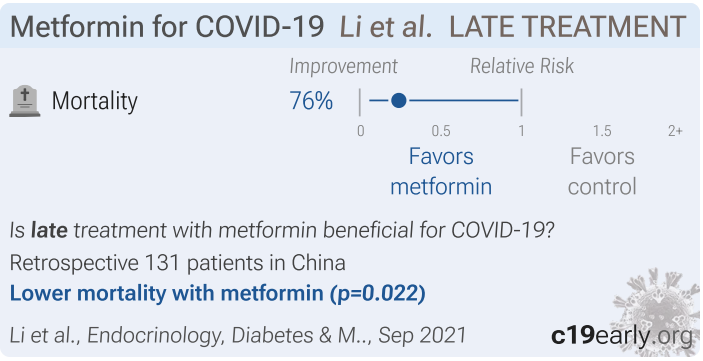
Retrospective 430 hospitalized COVID-19 patients with type 2 diabetes in Poland showing lower mortality with metformin and higher mortality with remdesivir, convalescent plasma, and aspirin in univariable analysis. These results were not statistically significant except for aspirin, and no baseline information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

Li



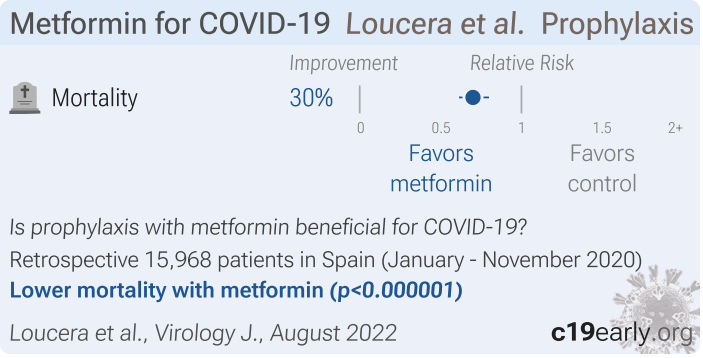
Retrospective 131 type II diabetes patients with COVID pneumonia, showing lower mortality with existing metformin use. Acarbose (commonly used in China as an initial therapy for diabetes) did not have a similar association with mortality, suggesting that the result may not be explained by metformin being used early in type II diabetes.

Li



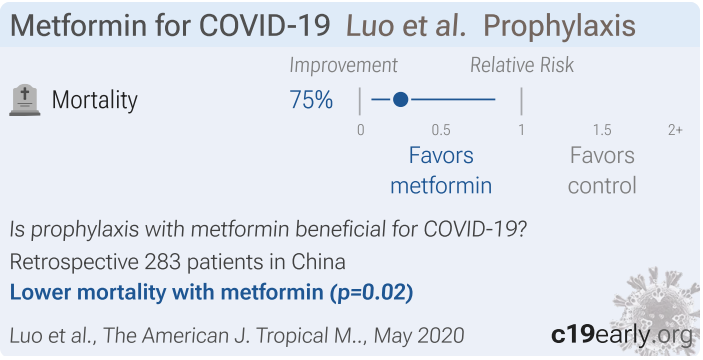
Retrospective 131 hospitalized COVID-19 patients with type 2 diabetes, showing lower mortality with metformin treatment and acarbose treatment.

Loucera



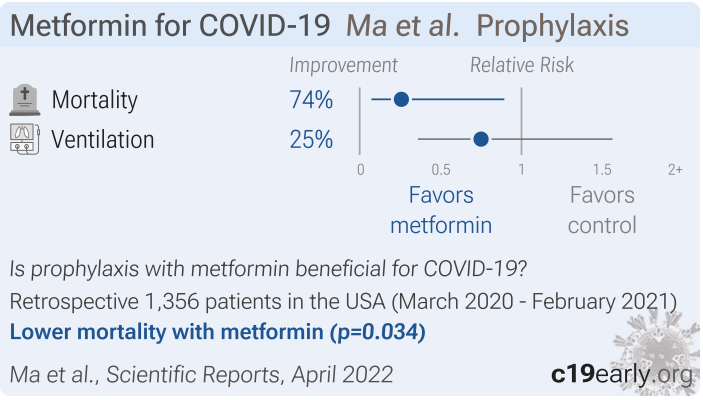
Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with existing use of several medications including metformin, HCQ, azithromycin, aspirin, vitamin D, vitamin C, and budesonide. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

Luo



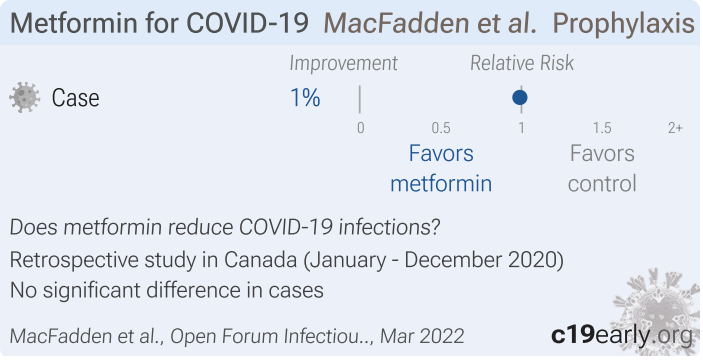
Retrospective 283 COVID-19+ diabetes patients in China, showing lower mortality with existing metformin treatment.

Ma



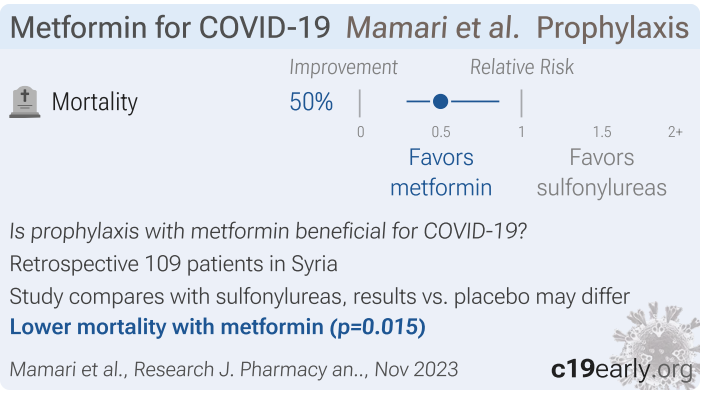
PSM/IPTW retrospective 1,356 hospitalized COVID-19 patients with type 2 diabetes in China, showing lower mortality/hospice with metformin use.

MacFadden



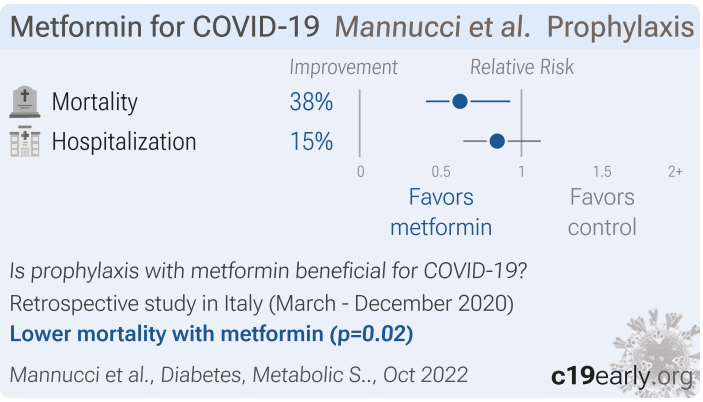
Retrospective 26,121 cases and 2,369,020 controls ≥65yo in Canada, showing no significant difference in cases with chronic use of metformin.

Mamari



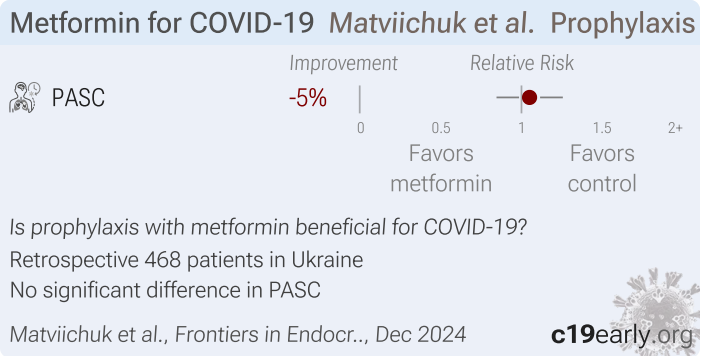
Retrospective 109 hospitalized COVID-19 patients in Syria, 68 with diabetes, showing significantly lower mortality with metformin vs. sulfonylureas, and significantly higher mortality with discontinuation of metformin.

Mannucci



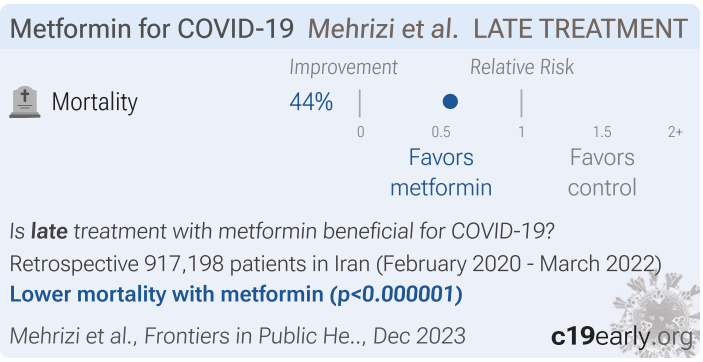
Retrospective 54,009 diabetes patients in Italy, showing lower mortality with metformin use.

Matviichuk



Retrospective 469 patients with type 2 diabetes in Ukraine showing no significant difference in post-COVID-19 syndrome (PCS) with metformin. There was higher risk with insulin analogs, but lower risk with human insulin.

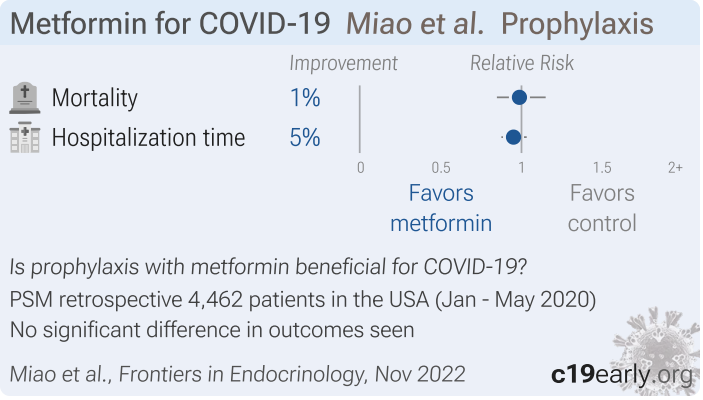
Mehrizi



Retrospective study of 917,198 hospitalized COVID-19 cases covered by the Iran Health Insurance Organization over 26 months showing that antithrombotics, corticosteroids, and antivirals reduced mortality while diuretics, antibiotics, and antidiabetics increased it. Confounding makes some results very unreliable. For example, diuretics like furosemide are often used to treat fluid overload, which is more likely in ICU or advanced disease requiring aggressive fluid resuscitation. Hospitalization length has increased risk of significant confounding, for example longer hospitalization increases the chance of receiving a medication, and death may result in shorter hospitalization. Mortality results may be more reliable.

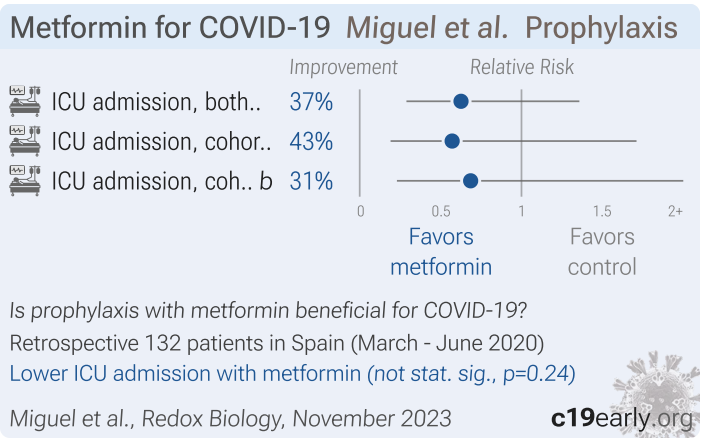
Confounding by indication is likely to be significant for many medications. Authors adjustments have very limited severity information (admission type refers to ward vs. ER department on initial arrival). We can estimate the impact of confounding from typical usage patterns, the prescription frequency, and attenuation or increase of risk for ICU vs. all patients.

Miao



Retrospective 4,462 COVID+ diabetes patients in the USA, showing no significant difference in outcomes with metformin use.

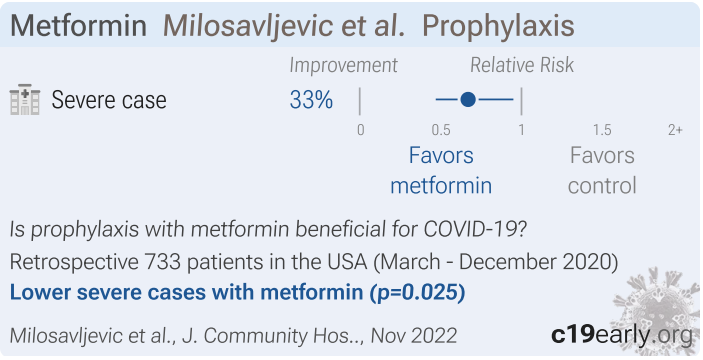
Miguel



Mouse models showing reduced lung and kidney injury with metformin. Metformin minimized lung damage and fibrosis in a mouse model of LPS-induced ARDS, and reduced UUO and FAN-induced kidney fibrosis. In Vitro study showing that metformin increased mitochondrial function and decreased TGF-β-induced fibrosis, apoptosis, and inflammation markers in lung epithelial cells.

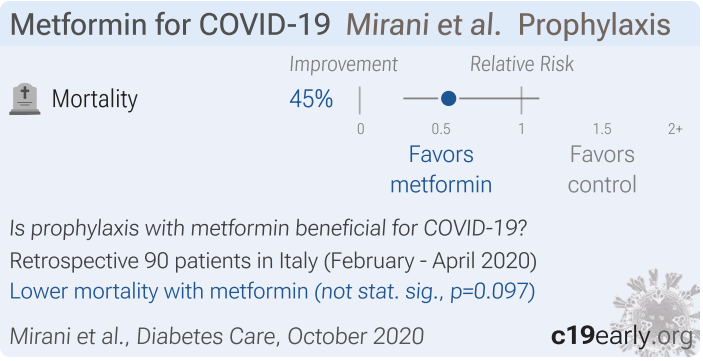
Authors also include a retrospective study showing lower ICU admission with metformin without statistical significance.

Milosavljevic



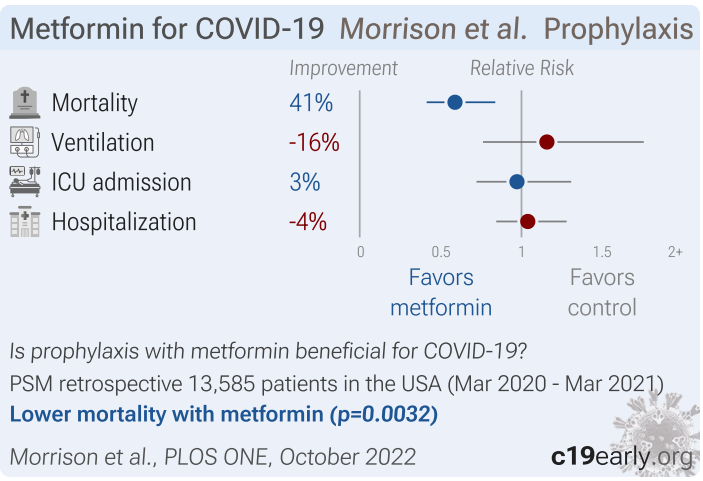
Retrospective 733 hospitalized COVID-19 patients with diabetes in the USA, showing lower risk of severity with metformin use.

Mirani



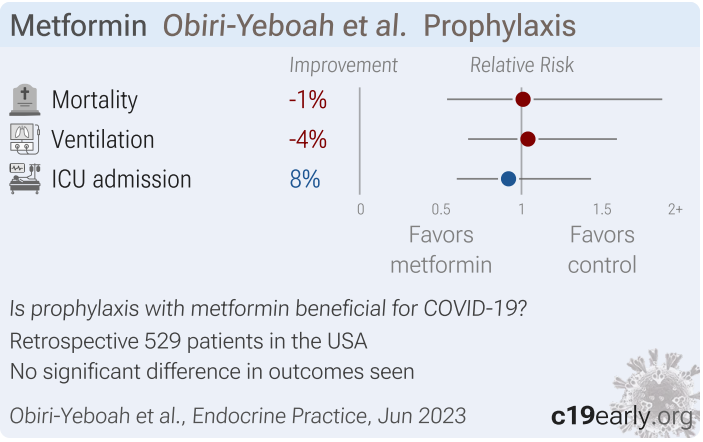
Retrospective 90 hospitalized COVID-19 patients with diabetes in Italy, showing lower mortality with metformin use, without statistical significance.

Morrison



Retrospective 13,585 COVID+ patients in the USA, showing lower mortality with metformin use, but no significant difference for ventilation, ICU admission, and hospitalization.

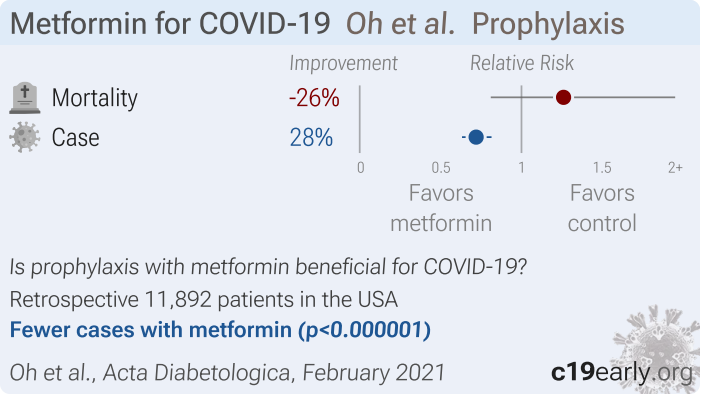
Obiri-Yeboah



Retrospective 529 hospitalized COVID-19 patients with type 2 diabetes, showing no significant difference in outcomes with metformin use. This does not account for the different risk of being hospitalized based on metformin use.

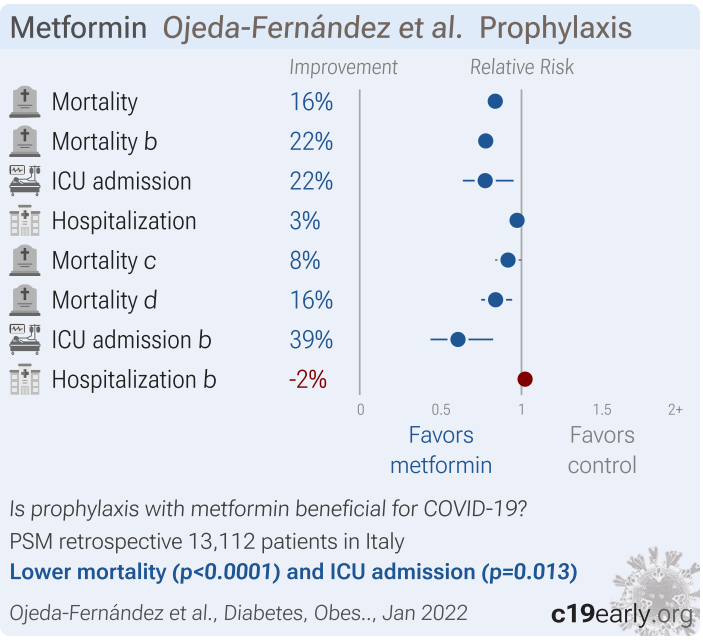
Authors note that *"there is a lower-than-expected proportion of metformin prescription in our population (28%) compared to the general US population"*, without noting that this may reflect the lower risk of being hospitalized for metformin patients, as shown in other studies[266].

Oh



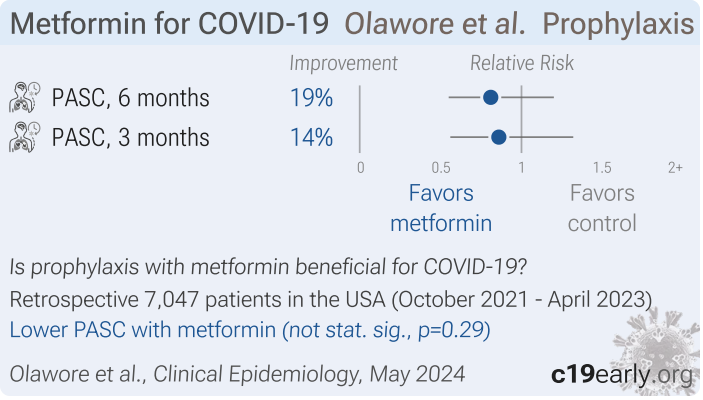
Retrospective 27,493 type II diabetes patients in the USA, 7,204 on metformin, showing significantly lower COVID-19 cases, but no significant difference in mortality.

Ojeda-Fernández



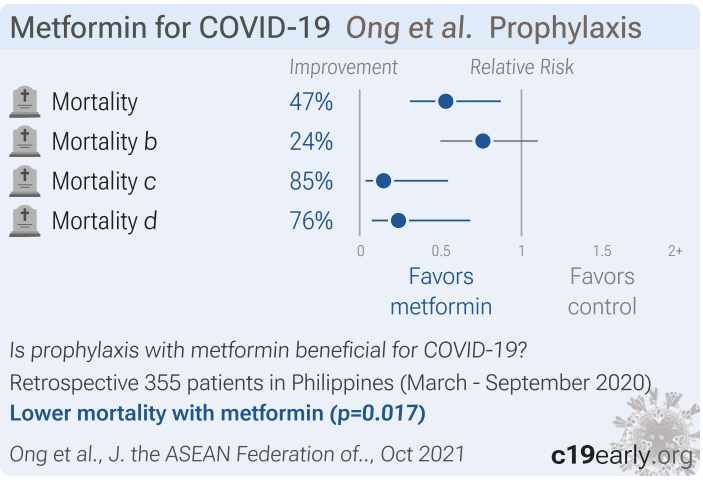
Retrospective 31,966 COVID+ patients using anti-hyperglycemic drugs in Italy, showing lower mortality and ICU admission with metformin use.

Olawore



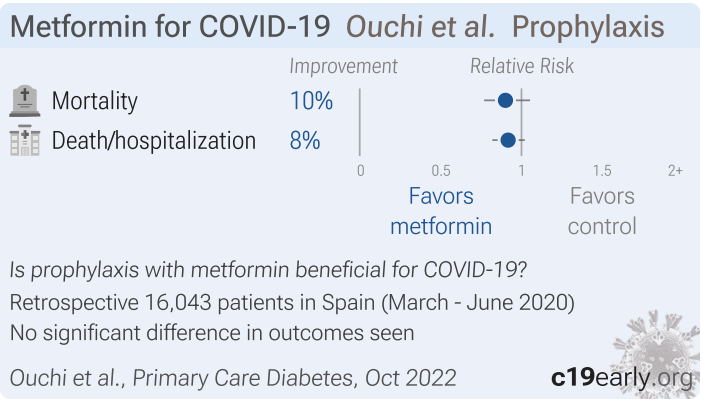
Retrospective 7,047 outpatients with type 2 diabetes showing a lower risk of PASC (long COVID) with metformin compared to sulfonylurea or DPP-4 inhibitor use, without statistical significance.

Ong



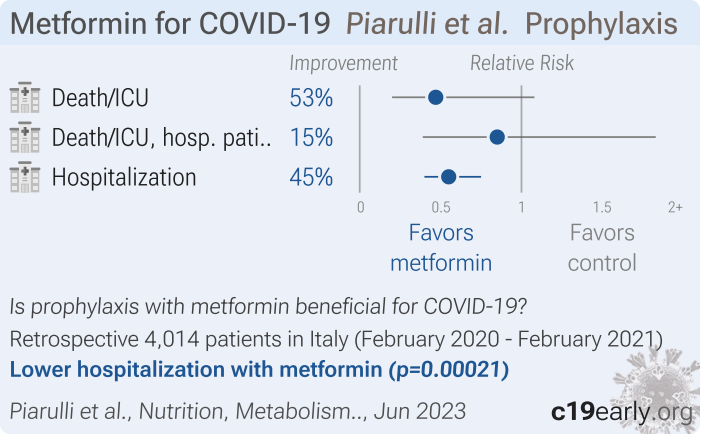
Retrospective 355 diabetic hospitalized COVID-19 patients in the Philippines, showing lower mortality with metformin use.

Ouchi



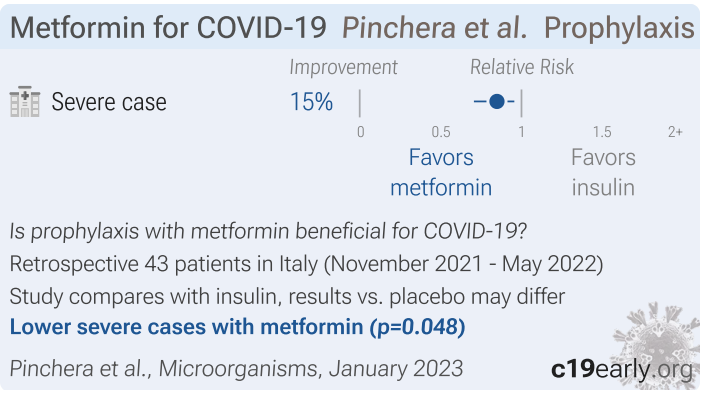
Retrospective 31,006 diabetic COVID-19 patients in Spain, showing lower mortality with metformin treatment, without statistical significance. Authors provide results for metformin compared with untreated patients rather than all non-metformin patients, which may increase confounding due to higher prevalence for treatment of patients with more severe disease.

Piarulli



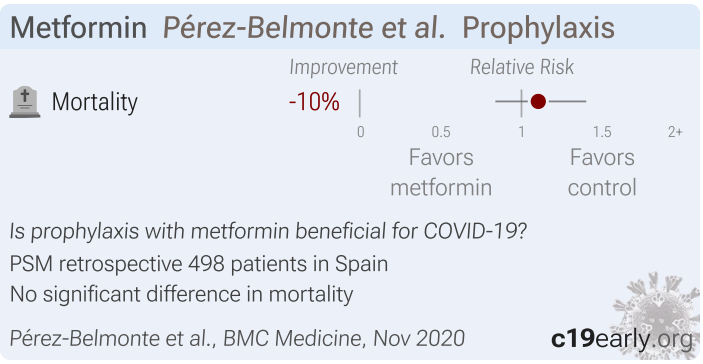
Retrospective diabetic COVID-19 patients in Italy, showing lower risk of hospitalization with metformin use.

Pinchera



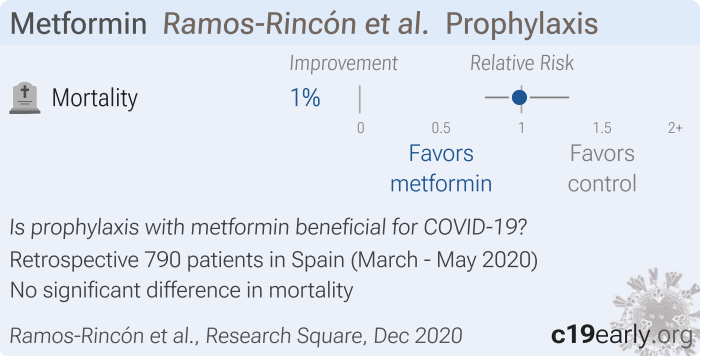
Retrospective 43 diabetes patients hospitalized for COVID-19 in Italy, showing lower risk of severe cases with metformin vs. insulin.

Pérez-Belmonte



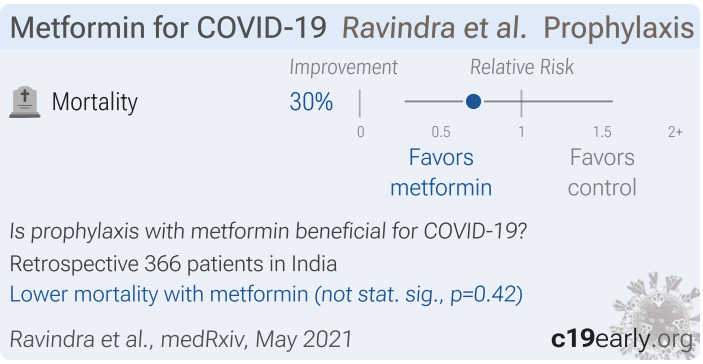
Retrospective 2,666 type 2 diabetes COVID-19 patients in Spain, showing higher mortality with existing metformin use (not statistically significant).

Ramos-Rincón



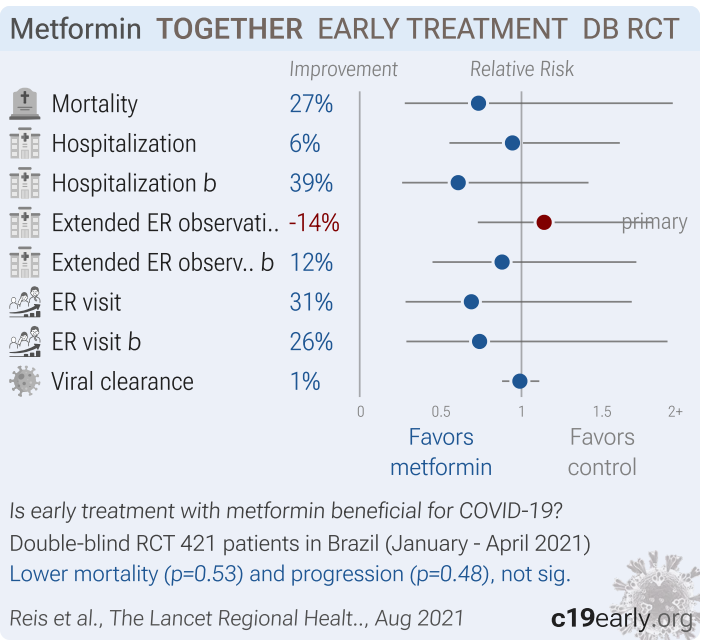
Retrospective 790 hospitalized type 2 diabetes patients ≥80 years old in Spain, showing no significant difference in mortality with existing metformin use.

Ravindra



Retrospective 1,035 hospitalized patients in India. Of 366 diabetic patients, there was lower mortality for the 53 that were on metformin.

Reis



SEE ALSO

TOGETHER Trial: Doin' Metformin Dirty
TOGETHER Trial & The Negative Number of Metformin Patients
TOGETHER Trial: Doin' Metformin Dirty, Part 3

Data for the primary outcome in this trial appears to be impossible[267]. For example, considering the metformin arm and the ITT population: 24 were hospitalized and 8 had an ER visit (tables S2/S3), therefore the number for combined ER or hospitalization must be between 24 and 32. However, authors report 34 events for ER/hospitalization.

RCT with 215 patients treated with metformin and 203 controls, showing no significant difference with treatment.

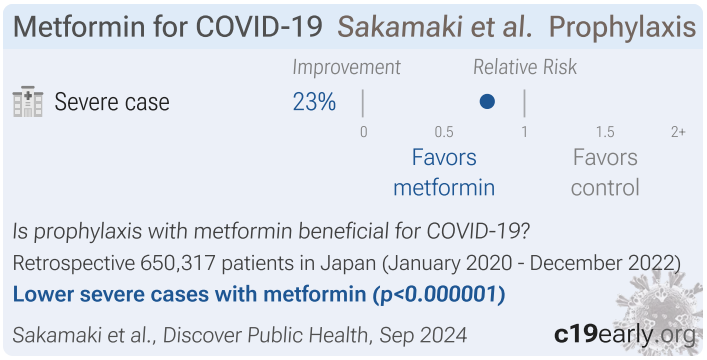
For multiple major issues with this trial see[267,268]. An expression of concern was posted in 2024[269].

The hospitalization risk for off-protocol patients was several times higher in both arms, resulting in Simpson's paradox when combining per-protocol and off-protocol patients[270].

750mg twice daily for 10 days.

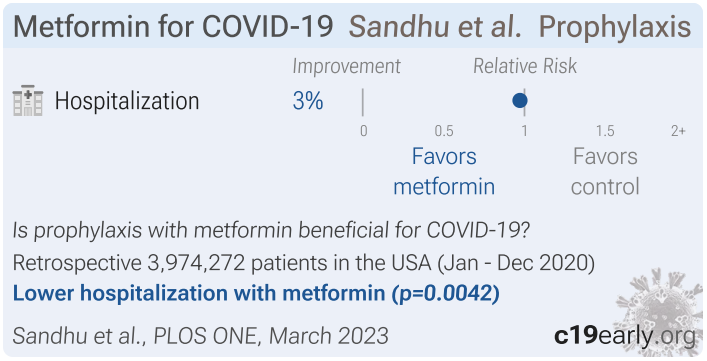
The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see[271-275].

Sakamaki



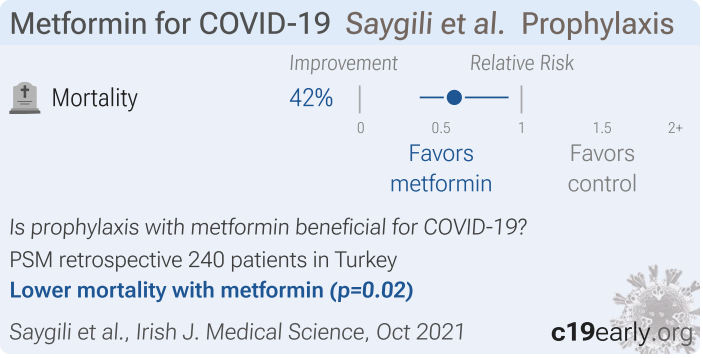
Retrospective 650,317 COVID-19 patients in Japan showing lower risk of severe COVID-19 with metformin use.

Sandhu



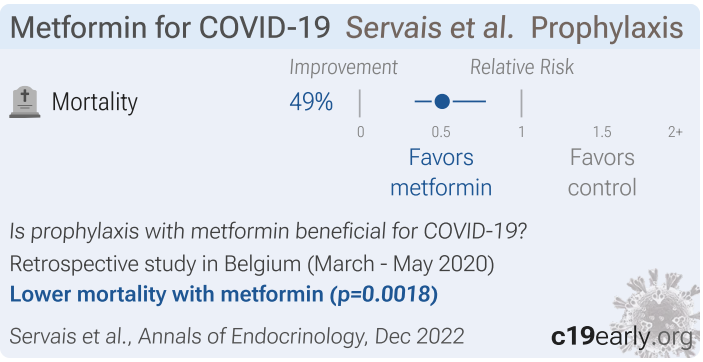
Retrospective 3,974,272 COVID-19 patients in the USA, showing 3% lower risk of hospitalization with pre-existing metformin use.

Saygili



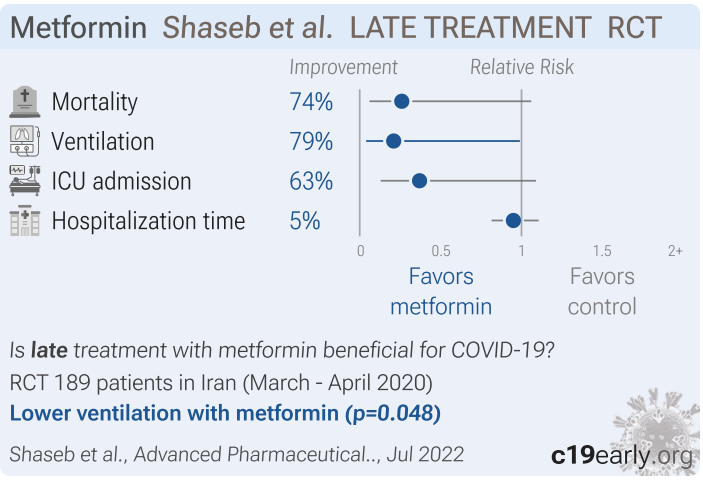
Retrospective 586 diabetic hospitalized COVID-19 patients in Turkey, showing lower mortality with existing metformin use.

Servais



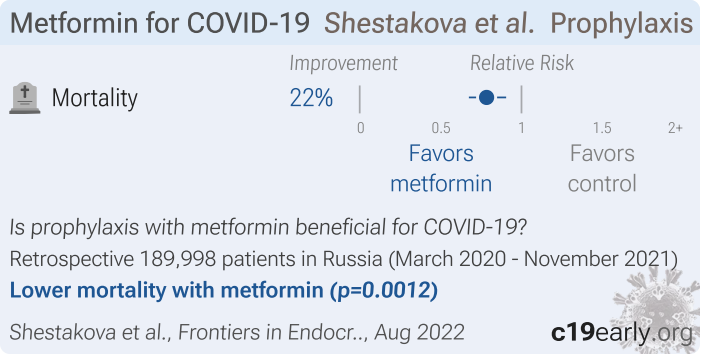
Retrospective 375 hospitalized diabetes patients in Belgium, showing lower risk of COVID-19 mortality with metformin use.

Shaseb



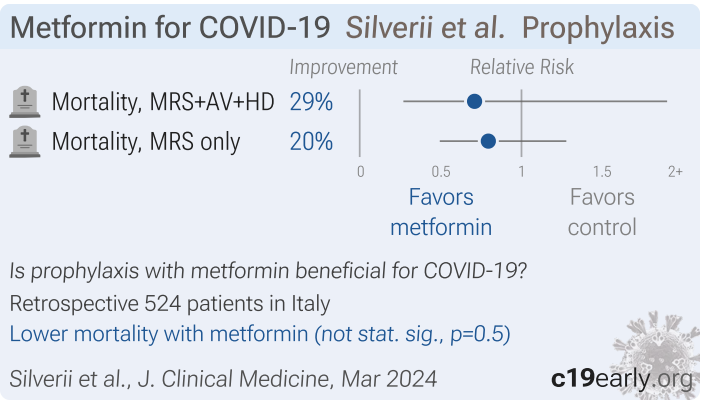
RCT 189 hospitalized patients showing lower mortality, ICU admission, and intubation with metformin, statistically significant only for intubation. Treatment patients may have also taken metformin prior to admission. Authors note that patients receiving metformin prior to the study were not matched, and diabetes and hyperlipidemia differed between groups.

Shestakova



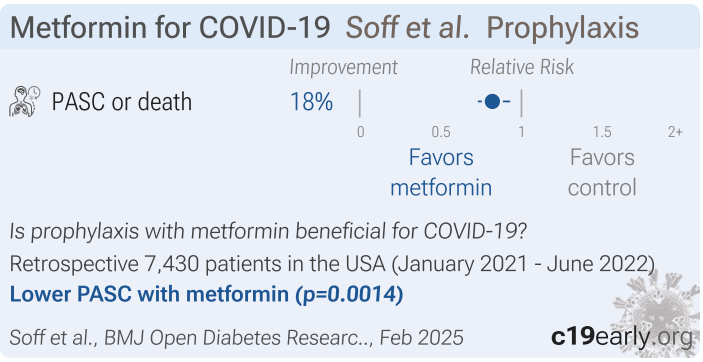
Retrospective 224,190 type 2 diabetes patients in Russia, showing lower mortality with metformin use.

Silverii



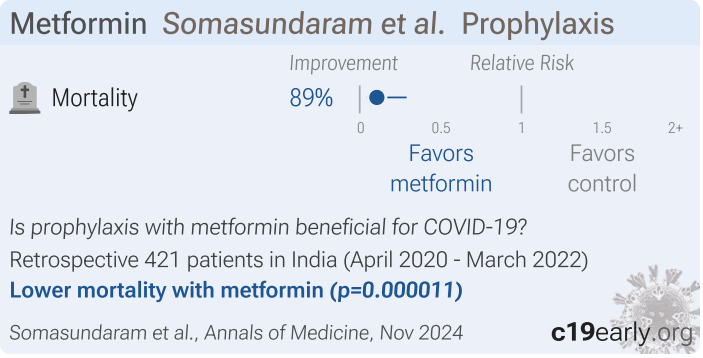
Retrospective 524 hospitalized COVID-19 patients with diabetes in Italy, showing lower risk of mortality with metformin use, without statistical significance. The results adjusted only for COVID-19 MRS differ between the text and Figure 2.

Soff



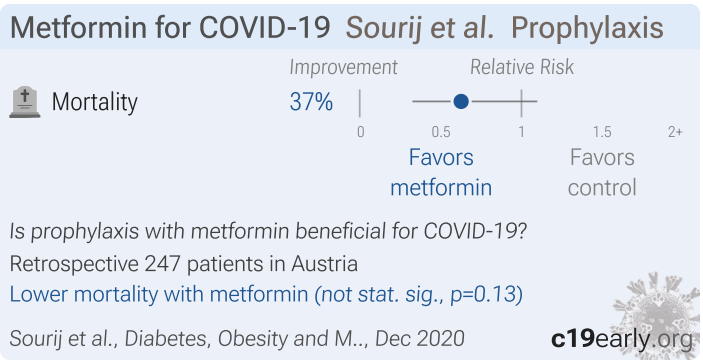
Retrospective 7,430 COVID-positive patients with type 2 diabetes showing lower risk of long COVID or death with metformin use, and higher risk with insulin use.

Somasundaram



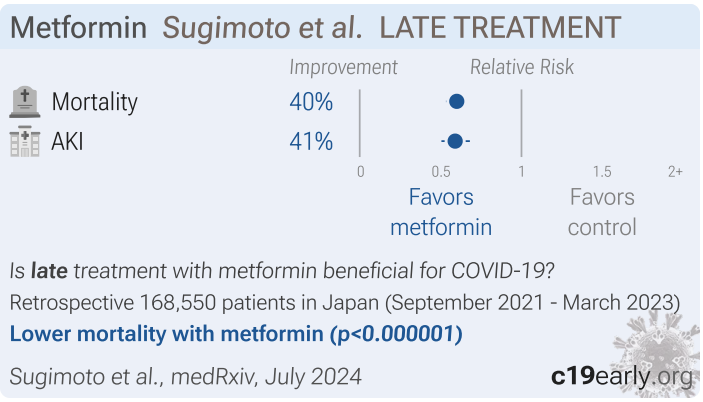
Retrospective 421 hospitalized COVID-19 patients with type 2 diabetes in India, showing significantly lower mortality with metformin use compared to other antidiabetic medications.

Sourij



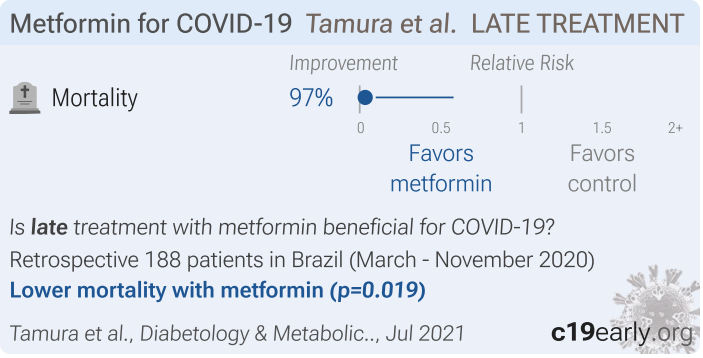
Retrospective 247 hospitalized COVID-19 diabetes patients, showing lower mortality with metformin use in unadjusted results.

Sugimoto



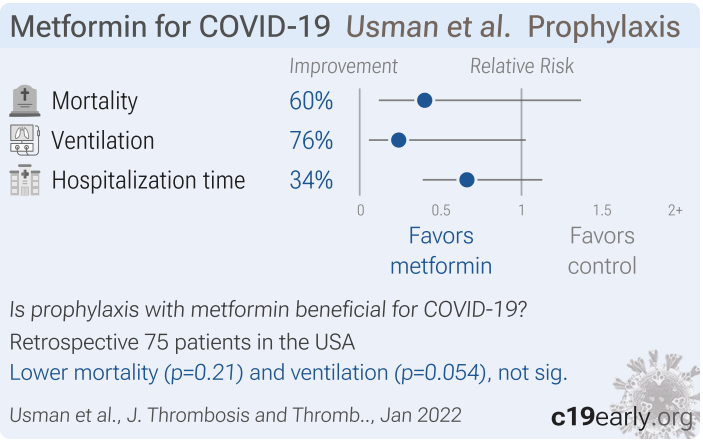
Retrospective 168,370 hospitalized COVID-19 patients with diabetes in Japan showing lower mortality and reduced risk of acute kidney injury with biguanide (likely primarily or only metformin) use. Authors hypothesize that metformin's activation of AMPK in renal tubular epithelium may provide a protective effect against COVID-19-induced kidney damage.

Tamura



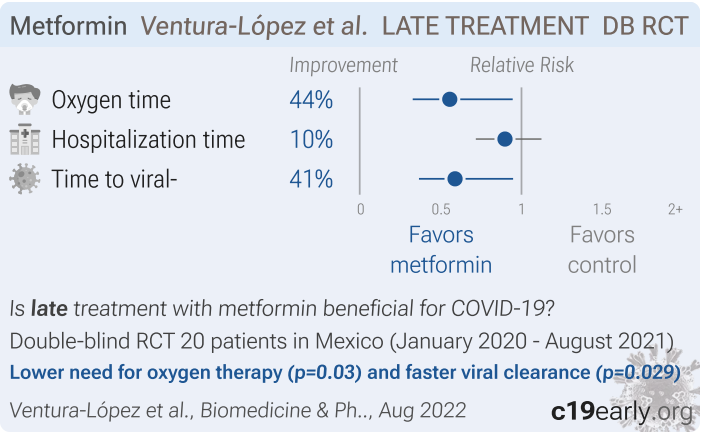
Retrospective 188 hospitalized patients in Brazil, showing lower risk of mortality with metformin use. Authors note that, although pre-hospital metformin use improved clinical parameters at admission, continuous use during hospitalization is essential. Patients that used pre-hospital metformin therapy but interrupted the treatment during hospitalization showed higher mortality than those that continued metformin therapy.

Usman



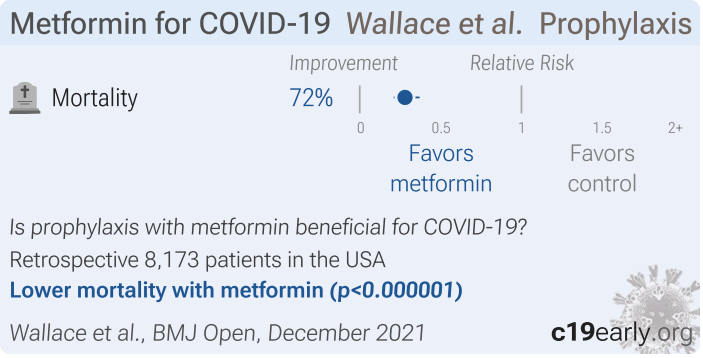
Retrospective 75 diabetes patients, 34 on metformin, showing improved clinical outcomes with treatment, without statistical significance.

Ventura-López



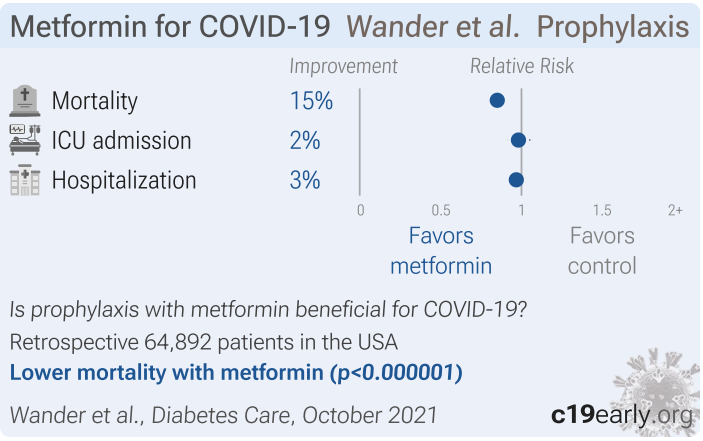
RCT 20 hospitalized COVID-19 patients showing faster viral load reduction and lower oxygen use with metformin glycinate 620mg twice daily for 14 days compared to placebo. The in vitro portion demonstrated inhibition of viral replication and cytopathic effects with metformin glycinate pretreatment.

Wallace



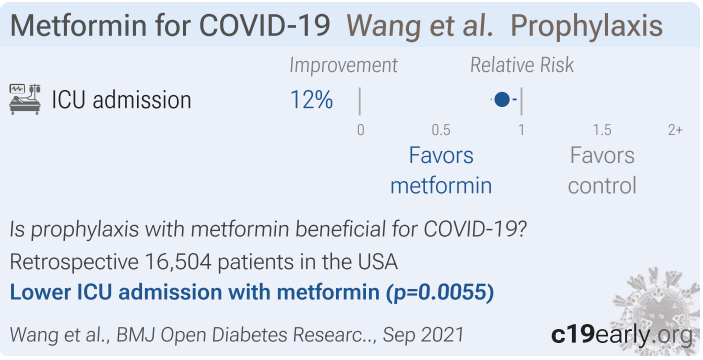
Retrospective 9,532 hospitalized COVID+ veterans in the USA, showing lower mortality with metformin use. The study provides results for use before, after, and before+after. Before+after should more accurately represent prophylaxis up to COVID-19 infection (and continued use). Before included use up to 2 years before, and after included use up to 60 days later.

Wander



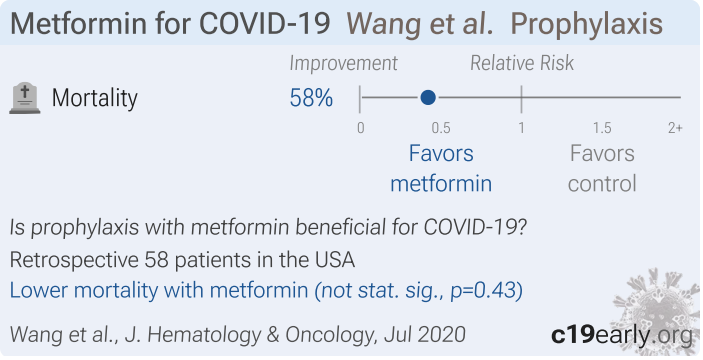
Retrospective 64,892 veterans with diabetes in the USA, showing lower mortality with existing metformin use.

Wang



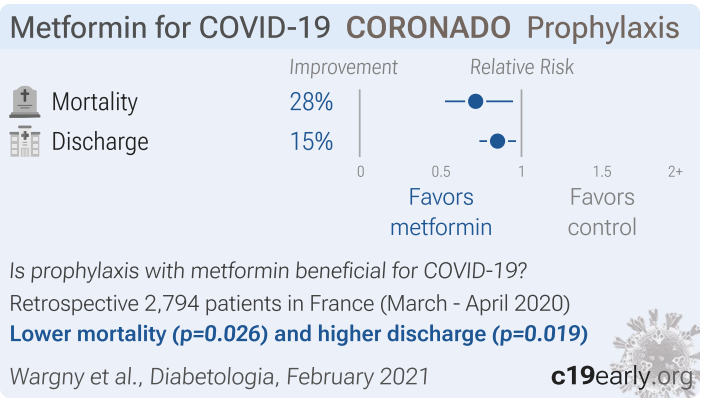
Retrospective 16,504 COVID-19 type 2 diabetes patients, showing lower risk of ICU admission with existing metformin use.

Wang



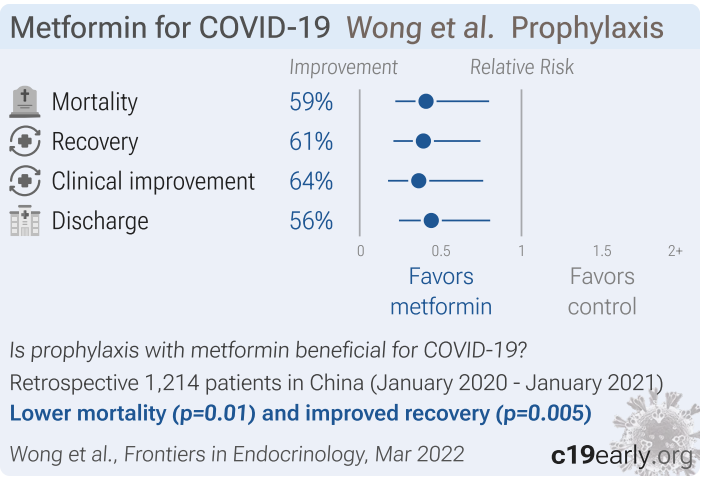
Retrospective 58 multiple myeloma COVID-19 patients in the USA, showing non-statistically significant lower mortality with metformin treatment.

Wargny



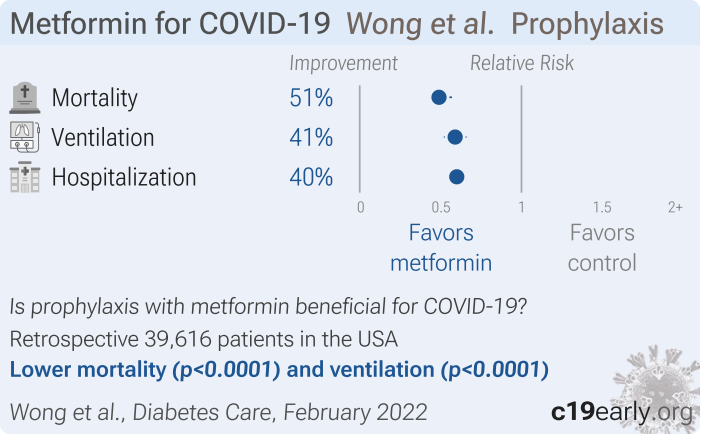
Retrospective 2,796 hospitalized diabetes patients with COVID-19 in France, showing lower mortality with metformin use.

Wong



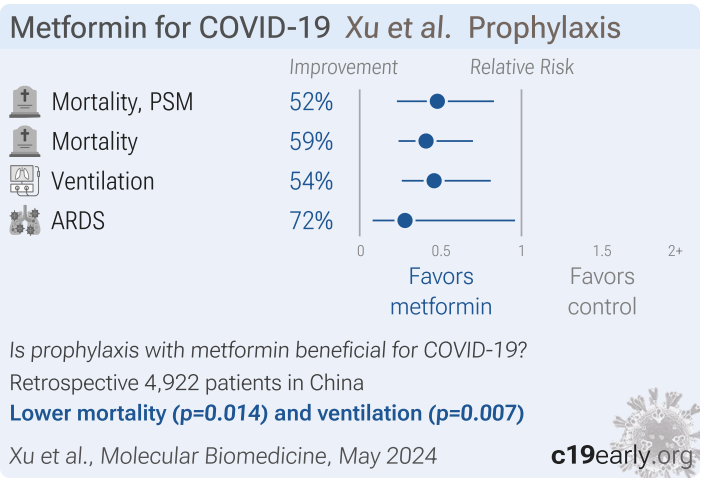
Retrospective 1,214 COVID+ type 2 diabetes patients in Hong Kong, showing lower mortality and improved recovery with metformin use.

Wong



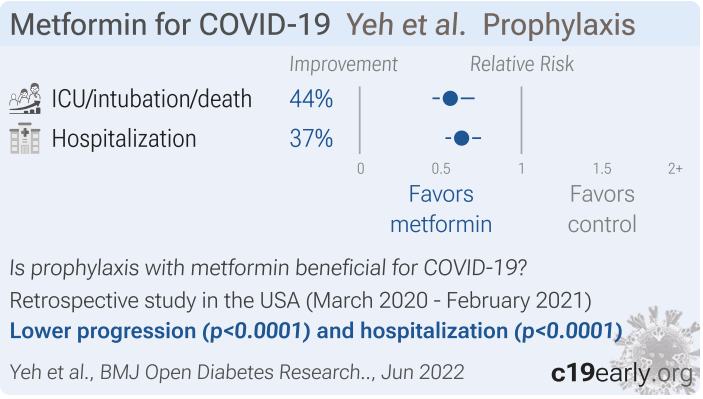
N3C retrospective 39,616 COVID-19 patients with diabetes in the USA, showing lower mortality, ventilation, and hospitalization with metformin use.

Xu



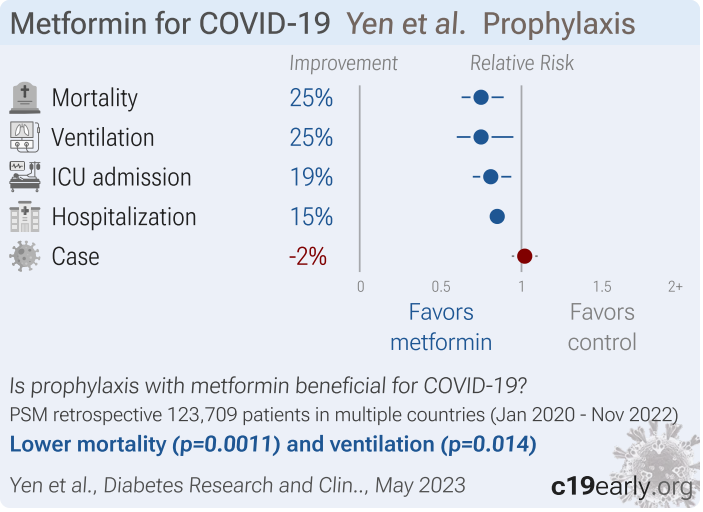
Retrospective 4,922 COVID-19 patients with type 2 diabetes in China, showing lower mortality with metformin and alpha-glucosidase inhibitor treatment and higher mortality with insulin treatment.

Yeh



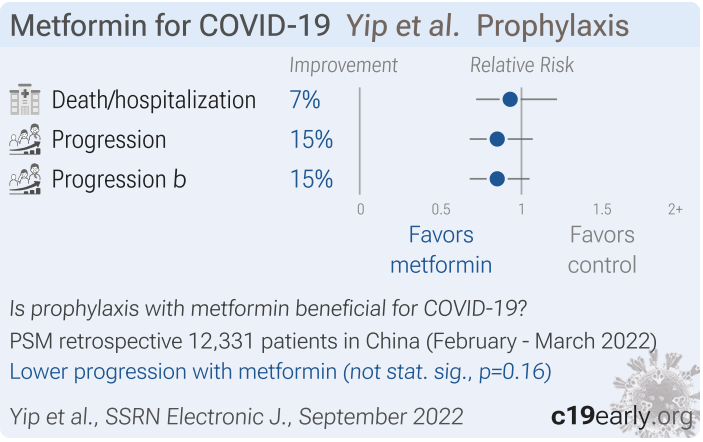
Retrospective 4,944 COVID-19 patients with type 2 diabetes in the USA, showing lower risk of hospitalization and combined ICU/intubation/death with metformin use.

Yen



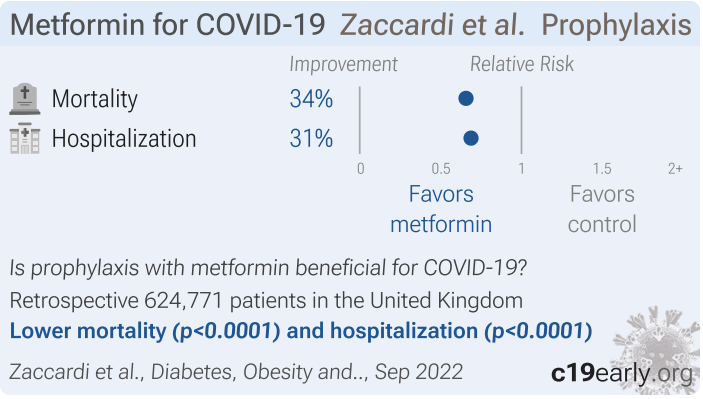
TriNetX retrospective 123,709 vaccinated patients with type 2 diabetes, showing significantly lower risk of COVID-19 mortality, mechanical ventilation, and hospitalization with metformin use. There was no significant difference for cases. The increasing benefit for more serious outcomes matches the results of studies to date.

Yip



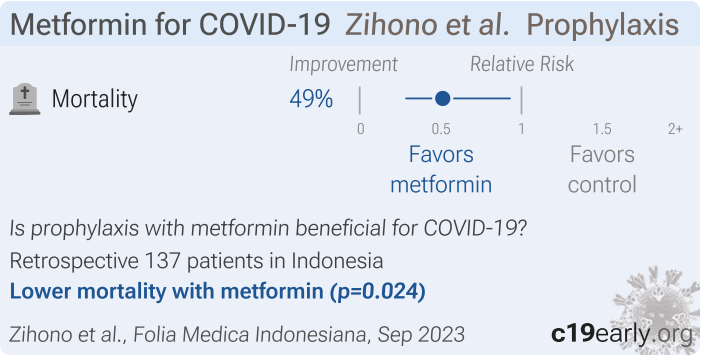
Retrospective 12,331 diabetes patients in Hong Kong, showing no significant difference in outcomes with metformin use.

Zaccardi



Retrospective 624,771 people with type 2 diabetes in the UK, showing lower COVID-19 mortality and hospitalization with metformin use.

Zihono



Retrospective 137 hospitalized mild to moderate COVID-19 patients with type 2 diabetes in Indonesia, showing a significantly lower mortality with metformin 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 metformin 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 metformin for COVID-19 that report a comparison with a control group are included in the main analysis. Sensitivity analysis is performed, excluding studies with major issues, epidemiological studies, and studies with minimal available information. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

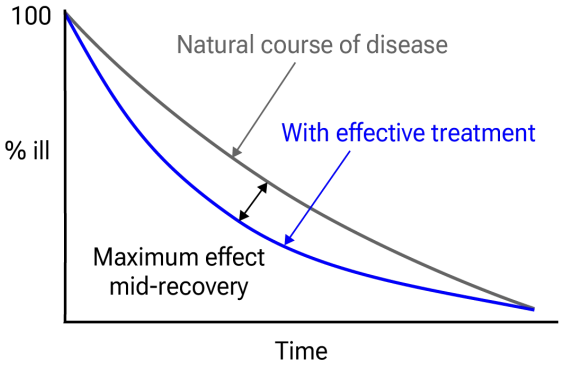


Figure 32. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral outcomes. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction[276]. 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 (B) et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used when

provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported *p*-values and confidence intervals followed *Altman, Altman (B)*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 [280]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.5) with scipy (1.16.0), pythonmeta (1.26), numpy (2.3.1), statsmodels (0.14.4), and plotly (6.2.0).

Forest plots are computed using PythonMeta [281] with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.4.0) using the metafor (4.6-0) and rms (6.8-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant. Grobid 0.8.2 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective [93,94].

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/mfmeta.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.

Bramante (C), 1/29/2025, retrospective, USA, peer-reviewed, 10 authors.	PASC or death, 53.0% lower, HR 0.47, *p* = 0.02, treatment 10 of 248 (4.0%), control 21 of 248 (8.5%), NNT 23.
Bramante, 8/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 37 authors, average treatment delay 4.8 days, this trial compares with another treatment - results may be better when compared to placebo, trial NCT04510194 (history) (COVID-OUT).	risk of death, 2.9% lower, RR 0.97, *p* = 1.00, treatment 1 of 408 (0.2%), control 1 of 396 (0.3%), NNT 13464, day 28.
	risk of death, 197.1% higher, RR 2.97, *p* = 1.00, treatment 1 of 408 (0.2%), control 0 of 396 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), day 14.
	risk of death/hospitalization, 52.3% lower, RR 0.48, *p* = 0.09, treatment 8 of 652 (1.2%), control 18 of 655 (2.7%), NNT 66, odds ratio converted to relative risk.
	risk of progression, 40.2% lower, RR 0.60, *p* = 0.03, treatment 27 of 652 (4.1%), control 48 of 655 (7.3%), NNT 31, odds ratio converted to relative risk, combined ER, hospitalization, death.
	risk of progression, 12.1% lower, RR 0.88, *p* = 0.18, treatment 154 of 652 (23.6%), control 179 of 653 (27.4%), NNT 26, odds ratio converted to relative risk, combined hypoxemia, ER,

	hospitalization, death, primary outcome.
	risk of no viral clearance, 36.9% lower, RR 0.63, $p < 0.001$, treatment 72 of 504 (14.3%), control 112 of 495 (22.6%), NNT 12, day 10.
	risk of no viral clearance, 8.7% lower, RR 0.91, $p = 0.15$, treatment 251 of 504 (49.8%), control 270 of 495 (54.5%), NNT 21, day 5.
Reis, 8/31/2021, Double Blind Randomized Controlled Trial, Brazil, peer-reviewed, 23 authors, study period 15 January, 2021 - 3 April, 2021, impossible data, see notes, trial NCT04727424 (history) (TOGETHER).	**risk of death, 26.6% lower, RR 0.73, $p = 0.53$**, treatment 7 of 215 (3.3%), control 9 of 203 (4.4%), NNT 85, day 28.
	risk of hospitalization, 5.6% lower, RR 0.94, $p = 0.88$, treatment 24 of 215 (11.2%), control 24 of 203 (11.8%), NNT 152, ITT.
	risk of hospitalization, 39.1% lower, RR 0.61, $p = 0.28$, treatment 8 of 168 (4.8%), control 14 of 179 (7.8%), NNT 33, PP.
	risk of extended ER observation or hospitalization, 14.0% higher, RR 1.14, $p = 0.58$, treatment 34 of 215 (15.8%), control 28 of 203 (13.8%), ITT, primary outcome.
	risk of extended ER observation or hospitalization, 12.0% lower, RR 0.88, $p = 0.72$, treatment 14 of 168 (8.3%), control 17 of 179 (9.5%), NNT 86, PP.
	risk of ER visit, 31.0% lower, RR 0.69, $p = 0.48$, treatment 8 of 216 (3.7%), control 11 of 205 (5.4%), NNT 60, ITT.
	risk of ER visit, 25.9% lower, RR 0.74, $p = 0.62$, treatment 7 of 171 (4.1%), control 10 of 181 (5.5%), NNT 70, PP.
	risk of no viral clearance, 1.0% lower, RR 0.99, $p = 0.85$, treatment 215, control 203, adjusted per study.

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.

Abu-Jamous, 8/23/2020, retrospective, United Kingdom, preprint, 7 authors, study period 1 January, 2020 - 27 May, 2020.	**risk of death, 65.3% lower, RR 0.35, $p = 0.04$**, treatment 4 of 23 (17.4%), control 94 of 168 (56.0%), NNT 2.6, odds ratio converted to relative risk.
Bramante (B), 1/14/2025, Double Blind Randomized Controlled Trial, placebo-controlled, USA, preprint, median age 47.0, 28 authors, study period 19 September, 2023 - 1 May, 2024, trial NCT04885530 (history) (ACTIV-6).	**risk of hospitalization, 43.0% higher, HR 1.43, $p = 0.65$**, treatment 4 of 1,443 (0.3%), control 3 of 1,548 (0.2%), day 28.
	risk of progression, 24.0% higher, HR 1.24, $p = 0.28$, treatment 58 of 1,443 (4.0%), control 53 of 1,548 (3.4%), adjusted per study, hospitalization, clinic visit, ER visit, or death, day 28.
	risk of progression, 8.0% higher, HR 1.08, $p = 0.62$, treatment 1,443, control 1,548, adjusted per study, ordinal scale, day 28.
	risk of progression, 4.0% lower, HR 0.96, $p = 0.87$, treatment 1,443, control 1,548, adjusted per study, ordinal scale, day 14.
	risk of progression, no change, HR 1.00, $p = 1.00$, treatment 1,443, control 1,548, adjusted per study, ordinal scale, day 7.

	risk of no recovery, 4.2% higher, HR 1.04, p = 0.28, treatment 58 of 1,443 (4.0%), control 53 of 1,548 (3.4%), adjusted per study, inverted to make HR<1 favor treatment, skeptical prior.
	risk of no recovery, 10.0% lower, RR 0.90, p = 0.006, treatment mean 9.0 (±9.69) n=1,443, control mean 10.0 (±10.0) n=1,548, relative median days to sustained recovery, last of three days.
	risk of no recovery, 12.5% lower, RR 0.88, p = 0.006, treatment mean 7.0 (±9.69) n=1,443, control mean 8.0 (±10.0) n=1,548, relative median days to sustained recovery, first of three days.
He, 11/30/2024, retrospective, China, peer-reviewed, median age 59.0, 10 authors, study period 29 December, 2019 - 31 August, 2021.	**risk of death, 74.0% lower, HR 0.26, p < 0.001**, adjusted per study, all, multivariable, Cox proportional hazards.
	risk of death, 72.0% lower, HR 0.28, p < 0.001, adjusted per study, non-severe, multivariable, Cox proportional hazards.
	risk of death, 74.0% lower, HR 0.26, p < 0.001, adjusted per study, severe, multivariable, Cox proportional hazards.
Li (B), 9/29/2021, retrospective, China, peer-reviewed, 13 authors.	**risk of death, 75.8% lower, RR 0.24, p = 0.02**, treatment 2 of 37 (5.4%), control 21 of 94 (22.3%), NNT 5.9.
Mehrizi, 12/18/2023, retrospective, Iran, peer-reviewed, 10 authors, study period 1 February, 2020 - 20 March, 2022.	**risk of death, 44.0% lower, OR 0.56, p < 0.001**, RR approximated with OR.
Shaseb, 7/2/2022, Randomized Controlled Trial, Iran, peer-reviewed, 26 authors, study period 20 March, 2020 - 5 April, 2020, trial IRCT20160310026998N10.	**risk of death, 74.0% lower, OR 0.26, p = 0.06**, treatment 85, control 104, RR approximated with OR.
	risk of mechanical ventilation, 79.0% lower, OR 0.21, p = 0.048, treatment 85, control 104, RR approximated with OR.
	risk of ICU admission, 63.0% lower, OR 0.37, p = 0.07, treatment 85, control 104, RR approximated with OR.
	hospitalization time, 5.0% lower, relative time 0.95, p = 0.52, treatment 85, control 104.
Sugimoto, 7/21/2024, retrospective, Japan, preprint, 12 authors, study period September 2021 - March 2023.	**risk of death, 40.0% lower, HR 0.60, p < 0.001**, treatment 30,908, control 137,642, adjusted per study, multivariable, day 100, model 2.
	AKI, 41.0% lower, HR 0.59, p < 0.001, treatment 30,908, control 137,642, adjusted per study, multivariable, model 2.
Tamura, 7/13/2021, retrospective, Brazil, peer-reviewed, 4 authors, study period 10 March, 2020 - 13 November, 2020.	**risk of death, 96.6% lower, OR 0.03, p = 0.02**, treatment 115, control 73, adjusted per study, in-hospital use, multivariable, RR approximated with OR.
Ventura-López, 8/31/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, peer-reviewed, mean age 47.5, 14 authors, study period January 2020 - August 2021.	**oxygen time, 44.3% lower, relative time 0.56, p = 0.03**, treatment mean 5.9 (±4.6) n=10, control mean 10.6 (±6.2) n=10.
	hospitalization time, 10.2% lower, relative time 0.90, p = 0.35, treatment mean 8.8 (±6.1) n=10, control mean 9.8 (±5.4) n=10.
	time to viral-, 41.1% lower, relative time 0.59, p = 0.03, treatment mean 3.3 (±2.16) n=10, control mean 5.6 (±0.89) n=10.

Prophylaxis

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

Akinosoglou, 5/27/2023, prospective, Greece, peer-reviewed, median age 70.0, 23 authors, study period February 2021 - June 2021, excluded in exclusion analyses: unadjusted results with no group details.	**risk of death, 36.8% lower, OR 0.63, $p = 0.12$**, treatment 147, control 207, RR approximated with OR.
	risk of ICU admission, 38.7% higher, OR 1.39, $p = 0.26$, treatment 147, control 207, RR approximated with OR.
	risk of ARDS, 2.7% higher, OR 1.03, $p = 0.92$, treatment 147, control 207, RR approximated with OR.
Al-kuraishy, 12/1/2023, prospective, Iraq, peer-reviewed, 10 authors, study period March 2020 - June 2020, excluded in exclusion analyses: unadjusted results with significant baseline differences.	**risk of death, 77.8% lower, RR 0.22, $p = 0.01$**, treatment 3 of 60 (5.0%), control 9 of 40 (22.5%), NNT 5.7.
	relative clinical score, 40.8% better, RR 0.59, $p < 0.001$, treatment 57, control 31.
	relative CT score, 84.0% better, RR 0.16, $p < 0.001$, treatment 57, control 31.
Al-Salameh, 11/30/2021, retrospective, France, peer-reviewed, 4 authors.	**risk of death/ICU, 55.5% lower, RR 0.45, $p = 0.04$**, treatment 9 of 47 (19.1%), control 22 of 50 (44.0%), NNT 4.0, adjusted per study, odds ratio converted to relative risk, metformin continued, multivariable.
	risk of death/ICU, 68.4% higher, RR 1.68, $p = 0.02$, treatment 34 of 43 (79.1%), control 22 of 50 (44.0%), adjusted per study, odds ratio converted to relative risk, metformin discontinued, multivariable.
Alamgir, 4/6/2021, retrospective, database analysis, USA, preprint, 11 authors.	**risk of death, 27.0% lower, OR 0.73, $p < 0.001$**, treatment 11,062, control 11,062, all patients, RR approximated with OR.
	risk of death, 34.0% lower, OR 0.66, $p = 0.007$, treatment 5,369, control 5,369, diabetic patients with CCI≤3, RR approximated with OR.
	risk of death, 30.0% lower, OR 0.70, $p = 0.02$, treatment 2,525, control 2,525, non-diabetic patients with CCI≤3, RR approximated with OR.
Alieva, 6/6/2023, retrospective, Uzbekistan, peer-reviewed, 9 authors, study period April 2020 - December 2020, excluded in exclusion analyses: unadjusted results with no group details.	**risk of hospitalization, 15.3% lower, OR 0.85, $p = 0.56$**, treatment 375, control 388, RR approximated with OR.
Ando, 9/9/2021, retrospective, USA, peer-reviewed, 6 authors, study period 1 January, 2020 - 30 November, 2020.	**risk of hospitalization, 39.0% lower, HR 0.61, $p = 0.04$**, treatment 19 of 663 (2.9%), control 1,056 of 27,430 (3.8%), adjusted per study, multivariable, Cox proportional hazards.
Araldi, 5/19/2023, retrospective, United Kingdom, preprint, 3 authors.	**risk of death, 60.0% lower, HR 0.40, $p < 0.001$**, treatment 107 of 2,598 (4.1%), control 263 of 2,598 (10.1%), NNT 17, adjusted per study, type 2 diabetes patients, matched cohort, multivariable, Cox proportional hazards.
Benfathallah, 1/11/2025, retrospective, Morocco, peer-reviewed, mean age 65.5, 5 authors, study period 1 August, 2020 - 1 August, 2021.	**risk of death, 53.6% lower, RR 0.46, $p = 0.04$**, treatment 8 of 41 (19.5%), control 30 of 74 (40.5%), NNT 4.8, adjusted per study, odds ratio converted to relative risk, multivariable.

Bidari, 10/19/2023, retrospective, Iran, peer-reviewed, 8 authors, study period February 2020 - April 2020, excluded in exclusion analyses: unadjusted results with no group details.	risk of severe case, 10.5% lower, RR 0.90, $p = 0.53$, treatment 29 of 80 (36.2%), control 132 of 326 (40.5%), NNT 24.
Blanc, 7/17/2021, retrospective, France, peer-reviewed, 22 authors.	risk of death, 78.6% lower, RR 0.21, $p = 0.06$, treatment 1 of 14 (7.1%), control 25 of 75 (33.3%), NNT 3.8, COVID+.
	risk of case, 43.7% higher, RR 1.44, $p = 0.12$, treatment 11 of 16 (68.8%), control 78 of 163 (47.9%).
Bliden, 11/8/2021, retrospective, USA, preprint, 9 authors, excluded in exclusion analyses: unadjusted results with minimal group details.	risk of death, 59.8% lower, RR 0.40, $p = 0.21$, treatment 3 of 34 (8.8%), control 9 of 41 (22.0%), NNT 7.6.
	risk of mechanical ventilation, 75.9% lower, RR 0.24, $p = 0.05$, treatment 2 of 34 (5.9%), control 10 of 41 (24.4%), NNT 5.4.
Boye, 7/18/2021, retrospective, USA, peer-reviewed, 14 authors.	risk of hospitalization, 10.0% lower, RR 0.90, $p < 0.001$, treatment 2,067 of 4,250 (48.6%), control 3,196 of 5,281 (60.5%), NNT 8.4, odds ratio converted to relative risk.
Bramante (D), 3/23/2021, retrospective, USA, peer-reviewed, 18 authors, study period 4 March, 2020 - 4 December, 2020.	risk of death, 62.0% lower, OR 0.38, $p = 0.03$, treatment 342, control 342, propensity score matching, RR approximated with OR.
	risk of death, 68.0% lower, OR 0.32, $p = 0.003$, treatment 676, control 8,879, adjusted per study, multivariable, RR approximated with OR.
	risk of ICU admission, 9.0% higher, OR 1.09, $p = 0.78$, treatment 342, control 342, propensity score matching, RR approximated with OR.
	risk of ICU admission, 32.0% lower, OR 0.68, $p = 0.06$, treatment 676, control 8,879, adjusted per study, multivariable, RR approximated with OR.
	risk of hospitalization, 22.0% lower, OR 0.78, $p = 0.10$, treatment 676, control 8,879, adjusted per study, multivariable, RR approximated with OR.
Bramante (E), 12/3/2020, retrospective, database analysis, USA, peer-reviewed, 17 authors.	risk of death, 11.6% lower, HR 0.88, $p = 0.65$, treatment 394 of 2,333 (16.9%), control 791 of 3,923 (20.2%), NNT 31, adjusted per study, multivariable, Cox proportional hazards.
	risk of death, 21.5% lower, HR 0.79, $p = 0.01$, treatment 1,129, control 2,173, adjusted per study, women, multivariable, Cox proportional hazards.
	risk of death, 4.3% lower, HR 0.96, $p = 0.69$, treatment 1,204, control 1,750, adjusted per study, men, multivariable, Cox proportional hazards.
Cariou, 5/29/2020, retrospective, France, peer-reviewed, mean age 69.8, 41 authors, study period 10 March, 2020 - 10 April, 2020, trial NCT04324736 (history) (CORONADO).	risk of death, 20.0% lower, OR 0.80, $p = 0.46$, treatment 746, control 571, adjusted per study, multivariable, RR approximated with OR.
Chan, 8/30/2022, retrospective, USA, preprint, 15 authors.	risk of death, 58.6% lower, OR 0.41, $p = 0.66$, treatment 400, control 2,736, adjusted per study, mortality/hospice, multivariable, prediabeties, RR approximated with OR.

	risk of severe case, 54.1% lower, OR 0.46, p = 0.37, treatment 400, control 2,736, adjusted per study, multivariable, prediabeties, RR approximated with OR.
	risk of progression, 42.4% lower, RR 0.58, p = 0.37, treatment 51 of 400 (12.8%), control 798 of 2,736 (29.2%), NNT 6.1, adjusted per study, odds ratio converted to relative risk, moderate, multivariable, prediabeties.
	risk of progression, 37.0% lower, OR 0.63, p = 0.37, treatment 400, control 2,736, adjusted per study, mild ER, multivariable, prediabeties, RR approximated with OR.
	risk of progression, 40.7% lower, OR 0.59, p = 0.22, treatment 196, control 86, adjusted per study, moderate, multivariable, PCOS, RR approximated with OR.
	risk of progression, 34.5% lower, OR 0.66, p = 0.20, treatment 196, control 86, adjusted per study, mild ER, multivariable, PCOS, RR approximated with OR.
Chen (C), 6/8/2024, retrospective, China, peer-reviewed, mean age 66.3, 11 authors, study period 20 March, 2022 - 18 June, 2022.	risk of ICU admission, 80.7% lower, RR 0.19, p = 0.008, treatment 2 of 121 (1.7%), control 25 of 292 (8.6%), NNT 14.
	pneumonia, 39.1% lower, RR 0.61, p = 0.009, treatment 25 of 121 (20.7%), control 99 of 292 (33.9%), NNT 7.6.
	hospitalization time, 16.6% lower, relative time 0.83, p = 0.001, treatment 121, control 292.
Chen (D), 7/31/2020, retrospective, China, peer-reviewed, 12 authors.	risk of death, 33.0% lower, RR 0.67, p = 0.46, treatment 4 of 43 (9.3%), control 15 of 77 (19.5%), NNT 9.8, adjusted per study, odds ratio converted to relative risk.
Cheng, 8/20/2021, retrospective, propensity score matching, China, peer-reviewed, 35 authors.	risk of death, 65.0% higher, HR 1.65, p = 0.25, treatment 678, control 535, after PSM.
Chertok Shacham, 11/29/2024, retrospective, Israel, peer-reviewed, mean age 71.3, 3 authors, study period 1 April, 2020 - 31 March, 2021.	risk of death, 70.0% lower, OR 0.30, p = 0.01, treatment 342, control 515, adjusted per study, multivariable, RR approximated with OR.
Choi, 6/23/2020, retrospective, South Korea, peer-reviewed, median age 29.0, 8 authors, study period 5 March, 2020 - 18 March, 2020.	risk of progression, 120.0% higher, OR 2.20, p = 0.26, treatment 6 of 36 (16.7%) cases, 3 of 36 (8.3%) controls, case control OR, propensity score matching.
Cousins, 7/6/2022, retrospective, propensity score matching, USA, peer-reviewed, 10 authors.	risk of mechanical ventilation, 50.0% lower, OR 0.50, p = 0.01, treatment 2,463, control 2,463, propensity score matching, RR approximated with OR.
	risk of ICU admission, 51.0% lower, OR 0.49, p < 0.001, treatment 2,463, control 2,463, propensity score matching, RR approximated with OR.
Crouse, 1/13/2021, retrospective, USA, peer-reviewed, 6 authors.	risk of death, 60.8% lower, RR 0.39, p = 0.02, treatment 8 of 76 (10.5%), control 34 of 144 (23.6%), NNT 7.6, adjusted per study, odds ratio converted to relative risk, multiple logistic regression.
Dimnjaković, 3/27/2024, retrospective, Croatia, peer-reviewed, 7 authors.	risk of hospitalization, 23.1% lower, OR 0.77, p = 0.004, treatment 2,843, control 4,475, adjusted per study, multivariable, RR approximated with OR.

	risk of case, 12.5% lower, OR 0.88, p = 0.04, treatment 2,843, control 4,475, adjusted per study, multivariable, RR approximated with OR.
Farah, 9/20/2023, retrospective, Jordan, peer-reviewed, mean age 59.5, 10 authors, excluded in exclusion analyses: unadjusted results with no group details.	risk of case, 2.7% higher, RR 1.03, p = 0.87, treatment 267 of 821 (32.5%), control 69 of 218 (31.7%).
Fu, 1/17/2022, retrospective, China, peer-reviewed, median age 63.0, 14 authors, study period 8 January, 2020 - 7 March, 2020, this trial compares with another treatment - results may be better when compared to placebo.	risk of unfavorable outcome, 71.9% lower, RR 0.28, p = 0.03, treatment 4 of 49 (8.2%), control 9 of 31 (29.0%), NNT 4.8, unfavorable outcome, metformin vs. other treatments.
Gao, 10/19/2020, retrospective, China, peer-reviewed, 7 authors, study period 31 January, 2020 - 20 March, 2020.	risk of progression, 225.0% higher, RR 3.25, p = 0.045, treatment 16 of 56 (28.6%), control 4 of 54 (7.4%), odds ratio converted to relative risk, progression to life threatening complications.
Ghany, 3/31/2021, retrospective, USA, peer-reviewed, 8 authors.	risk of death, 66.0% lower, HR 0.34, p < 0.001, treatment 392, control 747, adjusted per study, multivariable, Cox proportional hazards.
	risk of hospitalization, 29.0% lower, HR 0.71, p = 0.008, treatment 392, control 747, adjusted per study, multivariable, Cox proportional hazards.
	risk of ARDS, 68.0% lower, HR 0.32, p < 0.001, treatment 392, control 747, adjusted per study, multivariable, Cox proportional hazards.
Goodall, 10/13/2020, retrospective, United Kingdom, peer-reviewed, 7 authors, study period 12 March, 2020 - 15 April, 2020.	risk of death, 3.0% lower, HR 0.97, p = 0.81, treatment 74 of 210 (35.2%), control 280 of 771 (36.3%), NNT 93.
Greco, 8/18/2023, retrospective, Italy, peer-reviewed, 8 authors, study period January 2020 - December 2021, this trial compares with another treatment - results may be better when compared to placebo.	risk of hospitalization, 22.0% lower, OR 0.78, p = 0.11, treatment 30,238, control 2,264, DPP-4is, RR approximated with OR.
	risk of hospitalization, 26.0% lower, OR 0.74, p = 0.006, treatment 30,238, control 14,739, insulin or insulin secretagogues, RR approximated with OR.
	risk of hospitalization, 17.0% lower, OR 0.83, p = 0.54, treatment 30,238, control 317, GLP-1 RAs, RR approximated with OR.
Guo, 8/24/2023, retrospective, China, peer-reviewed, median age 65.0, 8 authors, study period 4 February, 2020 - 11 April, 2020.	risk of death/intubation, 62.4% lower, HR 0.38, p = 0.03, treatment 241, control 330, adjusted per study, multivariable, Cox proportional hazards.
	risk of progression, 81.1% lower, HR 0.19, p = 0.003, treatment 241, control 330, adjusted per study, severe respiratory failure, multivariable, Cox proportional hazards.
	risk of progression, 80.1% lower, HR 0.20, p = 0.05, treatment 241, control 330, adjusted per study, ARDS, multivariable, Cox proportional hazards.
Gálvez-Barrón, 4/14/2021, retrospective, Spain, peer-reviewed, mean age 86.8, 13 authors, study period 12 March, 2020 - 2 May, 2020.	risk of death, 16.1% higher, RR 1.16, p = 0.46, treatment 20, control 83, odds ratio converted to relative risk, control prevalance approximated with overall prevalence.

	risk of severe case, 16.1% higher, RR 1.16, $p = 0.46$, treatment 20, control 83, odds ratio converted to relative risk, control prevalance approximated with overall prevalence.
Harmon, 9/19/2024, retrospective, USA, peer-reviewed, 6 authors, study period 25 January, 2020 - 9 February, 2022.	**risk of death, 18.0% lower, RR 0.82, $p < 0.001$**, treatment 4,667, control 5,745, propensity score weighting.
Holt, 3/30/2021, prospective, United Kingdom, peer-reviewed, 34 authors, study period 1 May, 2020 - 5 February, 2021, trial NCT04330599 (history) (COVIDENCE UK), excluded in exclusion analyses: significant unadjusted confounding possible.	**risk of case, 27.0% higher, RR 1.27, $p = 0.42$**, treatment 12 of 429 (2.8%), control 434 of 14,798 (2.9%), adjusted per study, odds ratio converted to relative risk, minimally adjusted, group sizes approximated.
Huh, 12/19/2020, retrospective, database analysis, South Korea, peer-reviewed, 8 authors.	**risk of progression, 0.7% higher, RR 1.01, $p = 0.11$**, treatment 104 of 272 (38.2%), control 774 of 2,533 (30.6%), adjusted per study, odds ratio converted to relative risk, multivariable.
	risk of case, 4.0% lower, OR 0.96, $p = 0.82$, treatment 329 of 7,341 (4.5%) cases, 1,545 of 36,705 (4.2%) controls, adjusted per study, case control OR, multivariable.
Hunt, 6/29/2022, retrospective, USA, peer-reviewed, 8 authors, study period 1 March, 2020 - 10 September, 2020.	**risk of death, 67.0% lower, RR 0.33, $p < 0.001$**, treatment 73 of 3,956 (1.8%), control 1,539 of 22,552 (6.8%), NNT 20, adjusted per study, day 30.
Hussein, 6/30/2024, retrospective, Iraq, peer-reviewed, 4 authors, this trial compares with another treatment - results may be better when compared to placebo.	**risk of death, 63.8% lower, RR 0.36, $p = 0.048$**, treatment 30 of 158 (19.0%), control 60 of 110 (54.5%), NNT 2.8, adjusted per study, odds ratio converted to relative risk, multivariable.
Jang, 1/29/2024, retrospective, South Korea, peer-reviewed, 6 authors.	**risk of death, 60.5% lower, OR 0.40, $p = 0.02$**, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of mechanical ventilation, 71.9% lower, OR 0.28, $p = 0.008$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of ICU admission, 38.8% lower, OR 0.61, $p = 0.12$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of oxygen therapy, 29.7% lower, OR 0.70, $p = 0.23$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
	risk of hospitalization, 27.1% higher, OR 1.27, $p = 0.42$, treatment 461, control 95, adjusted per study, multivariable, RR approximated with OR.
Jiang, 3/31/2021, retrospective, China, peer-reviewed, 12 authors.	**risk of death, 46.0% lower, HR 0.54, $p = 0.40$**, treatment 3 of 74 (4.1%), control 10 of 74 (13.5%), adjusted per study, mixed effect Cox, propensity score matching.
	risk of ARDS, 80.2% lower, RR 0.20, $p = 0.02$, treatment 8 of 74 (10.8%), control 17 of 74 (23.0%), NNT 8.2, adjusted per study, odds ratio converted to relative risk, mixed effect Cox, propensity score matching.
Johnson, 4/11/2025, retrospective, USA, peer-reviewed, 7 authors.	**risk of PASC, 53.0% lower, RR 0.47, $p = 0.02$**, treatment 248, control 248, adjusted per study, long COVID or death, day 180.

Johnson (B), 9/17/2024, retrospective, USA, peer-reviewed, 19 authors.	**death or long COVID, 11.3% lower, HR 0.89, *p* = 0.11**, treatment 42,275, control 6,713, combined.
	death or long COVID, 21.0% lower, HR 0.79, *p* < 0.001, treatment 42,275, control 6,713, N3C, EHR code.
	death or long COVID, 15.0% lower, HR 0.85, *p* < 0.001, treatment 42,275, control 6,713, N3C, phenotype.
	death or long COVID, 13.0% lower, HR 0.87, *p* = 0.32, treatment 30,748, control 5,933, PCORnet, EHR code.
	death or long COVID, 4.0% higher, HR 1.04, *p* = 0.26, treatment 30,748, control 5,933, PCORnet, phenotype.
Khunti, 3/30/2021, retrospective, population-based cohort, United Kingdom, peer-reviewed, 15 authors.	**risk of death, 23.0% lower, HR 0.77, *p* < 0.001**, adjusted per study.
Kim, 8/12/2020, retrospective, South Korea, peer-reviewed, 32 authors.	**risk of death, 64.0% lower, OR 0.36, *p* = 0.10**, treatment 113, control 122, adjusted per study, multivariable, RR approximated with OR.
	risk of progression, 52.0% lower, OR 0.48, *p* = 0.13, treatment 113, control 122, adjusted per study, multivariable, RR approximated with OR.
Lalau, 12/10/2020, retrospective, France, peer-reviewed, 33 authors, study period 10 March, 2020 - 10 April, 2020.	**risk of death, 22.2% lower, OR 0.78, *p* = 0.16**, treatment 671, control 419, day 28, model 2, propensity score matching, RR approximated with OR.
	risk of death/intubation, 17.8% lower, OR 0.82, *p* = 0.21, treatment 671, control 419, day 28, model 2, propensity score matching, primary outcome, RR approximated with OR.
	risk of mechanical ventilation, 6.8% lower, OR 0.93, *p* = 0.72, treatment 671, control 419, day 28, model 2, propensity score matching, RR approximated with OR.
Lally, 1/31/2021, retrospective, USA, peer-reviewed, 6 authors.	**risk of death, 52.0% lower, HR 0.48, *p* = 0.009**, treatment 16 of 127 (12.6%), control 144 of 648 (22.2%), NNT 10, adjusted per study, multivariable regression.
Lewandowski, 3/7/2024, retrospective, Poland, peer-reviewed, 15 authors.	**risk of death, 22.9% lower, RR 0.77, *p* = 0.15**, treatment 14 of 101 (13.9%), control 83 of 329 (25.2%), NNT 8.8, odds ratio converted to relative risk.
Li (C), 10/1/2020, retrospective, China, peer-reviewed, 16 authors, study period 23 January, 2020 - 19 March, 2020.	**risk of death, 77.7% lower, HR 0.22, *p* = 0.02**, treatment 2 of 37 (5.4%), control 21 of 94 (22.3%), NNT 5.9, adjusted per study, multivariable.
	risk of mechanical ventilation, 27.0% higher, RR 1.27, *p* = 1.00, treatment 1 of 37 (2.7%), control 2 of 94 (2.1%).
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	**risk of death, 30.0% lower, HR 0.70, *p* < 0.001**, treatment 1,896, control 14,072, Cox proportional hazards, day 30.
Luo, 5/21/2020, retrospective, China, peer-reviewed, 9 authors.	**risk of death, 74.7% lower, RR 0.25, *p* = 0.02**, treatment 3 of 104 (2.9%), control 22 of 179 (12.3%), NNT 11, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariate.

Ma (B), 4/1/2022, retrospective, USA, peer-reviewed, 4 authors, study period 16 March, 2020 - 15 February, 2021.	risk of death, 74.2% lower, RR 0.26, $p = 0.03$, treatment 3 of 361 (0.8%), control 40 of 995 (4.0%), NNT 31, odds ratio converted to relative risk, in-hospital death or hospice, propensity score weighting.
	risk of mechanical ventilation, 25.0% lower, RR 0.75, $p = 0.44$, treatment 12 of 360 (3.3%), control 16 of 360 (4.4%), NNT 90, propensity score matching.
MacFadden, 3/29/2022, retrospective, Canada, peer-reviewed, 9 authors, study period 15 January, 2020 - 31 December, 2020.	risk of case, 1.0% lower, OR 0.99, $p = 0.45$, RR approximated with OR.
Mamari, 11/30/2023, retrospective, Syria, peer-reviewed, 2 authors, this trial compares with another treatment - results may be better when compared to placebo.	risk of death, 50.0% lower, RR 0.50, $p = 0.01$, treatment 11 of 34 (32.4%), control 22 of 34 (64.7%), NNT 3.1.
Mannucci, 10/31/2022, retrospective, Italy, peer-reviewed, 10 authors, study period 1 March, 2020 - 31 December, 2020.	risk of death, 38.0% lower, OR 0.62, $p = 0.02$, RR approximated with OR.
	risk of hospitalization, 15.0% lower, OR 0.85, $p = 0.25$, RR approximated with OR.
Matviichuk, 12/11/2024, retrospective, Ukraine, peer-reviewed, 9 authors.	risk of PASC, 5.0% higher, RR 1.05, $p = 0.64$, treatment 155 of 316 (49.1%), control 71 of 152 (46.7%), odds ratio converted to relative risk.
Miao, 11/9/2022, retrospective, USA, peer-reviewed, 6 authors, study period 1 January, 2020 - 7 May, 2020.	risk of death, 1.3% lower, RR 0.99, $p = 0.91$, treatment 233 of 796 (29.3%), control 236 of 796 (29.6%), NNT 265, propensity score matching.
	hospitalization time, 4.9% lower, relative time 0.95, $p = 0.23$, treatment 796, control 796, propensity score matching.
Miguel, 11/17/2023, retrospective, Spain, peer-reviewed, 19 authors, study period March 2020 - June 2020.	risk of ICU admission, 37.4% lower, RR 0.63, $p = 0.24$, treatment 64, control 68, both cohorts combined.
	risk of ICU admission, 42.9% lower, RR 0.57, $p = 0.34$, treatment 3 of 15 (20.0%), control 14 of 40 (35.0%), NNT 6.7.
	risk of ICU admission, 31.4% lower, RR 0.69, $p = 0.52$, treatment 6 of 49 (12.2%), control 5 of 28 (17.9%), NNT 18.
Milosavljevic, 11/9/2022, retrospective, USA, peer-reviewed, mean age 67.4, 7 authors, study period 1 March, 2020 - 31 December, 2020.	risk of severe case, 33.0% lower, OR 0.67, $p = 0.03$, treatment 377, control 356, RR approximated with OR.
Mirani, 10/6/2020, retrospective, Italy, peer-reviewed, median age 66.0, 8 authors, study period 20 February, 2020 - 9 April, 2020.	risk of death, 45.0% lower, HR 0.55, $p = 0.10$, treatment 25 of 69 (36.2%), control 13 of 21 (61.9%), NNT 3.9, adjusted per study, Cox proportional hazards.
Morrison, 10/10/2022, retrospective, USA, peer-reviewed, mean age 62.5, 3 authors, study period March 2020 - March 2021.	risk of death, 41.1% lower, OR 0.59, $p = 0.003$, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.
	risk of mechanical ventilation, 15.7% higher, OR 1.16, $p = 0.49$, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.
	risk of ICU admission, 2.8% lower, OR 0.97, $p = 0.85$, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.

	risk of hospitalization, 3.9% higher, OR 1.04, p = 0.72, treatment 2,684, control 2,684, propensity score matching, RR approximated with OR.
Obiri-Yeboah, 6/8/2023, retrospective, USA, peer-reviewed, mean age 67.0, 8 authors.	**risk of death, 1.0% higher, OR 1.01, p = 0.98**, treatment 148, control 381, RR approximated with OR.
	risk of mechanical ventilation, 4.0% higher, OR 1.04, p = 0.87, treatment 148, control 381, RR approximated with OR.
	risk of ICU admission, 8.0% lower, OR 0.92, p = 0.72, treatment 148, control 381, RR approximated with OR.
Oh, 2/13/2021, retrospective, USA, peer-reviewed, 2 authors.	**risk of death, 26.0% higher, OR 1.26, p = 0.30**, treatment 5,946, control 5,946, adjusted per study, multivariable, RR approximated with OR.
	risk of case, 28.0% lower, RR 0.72, p < 0.001, treatment 390 of 5,946 (6.6%), control 541 of 5,946 (9.1%), NNT 39, adjusted per study, odds ratio converted to relative risk, propensity score matching.
Ojeda-Fernández, 1/10/2022, retrospective, Italy, peer-reviewed, 11 authors.	**risk of death, 16.2% lower, RR 0.84, p < 0.001**, treatment 1,476 of 6,556 (22.5%), control 1,787 of 6,556 (27.3%), NNT 21, odds ratio converted to relative risk, propensity score matching.
	risk of death, 22.1% lower, RR 0.78, p < 0.001, treatment 968 of 6,556 (14.8%), control 1,261 of 6,556 (19.2%), NNT 22, odds ratio converted to relative risk, in-hospital mortality, propensity score matching.
	risk of ICU admission, 22.4% lower, RR 0.78, p = 0.01, treatment 166 of 6,556 (2.5%), control 212 of 6,556 (3.2%), NNT 143, odds ratio converted to relative risk, propensity score matching.
	risk of hospitalization, 2.7% lower, RR 0.97, p = 0.11, treatment 3,551 of 6,556 (54.2%), control 3,670 of 6,556 (56.0%), NNT 55, odds ratio converted to relative risk, propensity score matching.
	risk of death, 8.3% lower, RR 0.92, p = 0.06, treatment 793 of 3,297 (24.1%), control 876 of 3,297 (26.6%), NNT 40, odds ratio converted to relative risk, excluding patients previously treated with insulin, propensity score matching.
	risk of death, 16.0% lower, RR 0.84, p = 0.003, treatment 512 of 3,297 (15.5%), control 618 of 3,297 (18.7%), NNT 31, odds ratio converted to relative risk, excluding patients previously treated with insulin, in-hospital mortality, propensity score matching.
	risk of ICU admission, 39.2% lower, RR 0.61, p = 0.002, treatment 64 of 3,297 (1.9%), control 102 of 3,297 (3.1%), NNT 87, odds ratio converted to relative risk, excluding patients previously treated with insulin, propensity score matching.
	risk of hospitalization, 2.2% higher, RR 1.02, p = 0.36, treatment 1,822 of 3,297 (55.3%), control 1,792 of 3,297 (54.4%), odds ratio converted to relative risk, excluding patients previously treated with insulin, propensity score matching.
Olawore, 5/31/2024, retrospective, USA, peer-reviewed, 8 authors, study period October 2021 - April 2023.	**risk of PASC, 19.0% lower, RR 0.81, p = 0.29**, treatment 5,596, control 1,451, 6 months.

	risk of PASC, 14.0% lower, RR 0.86, *p* = 0.50, treatment 5,596, control 1,451, 3 months.
Ong, 10/30/2021, retrospective, Philippines, peer-reviewed, 6 authors, study period 1 March, 2020 - 30 September, 2020.	**risk of death, 46.8% lower, RR 0.53, *p* = 0.02**, treatment 33 of 186 (17.7%), control 57 of 169 (33.7%), NNT 6.3, adjusted per study, odds ratio converted to relative risk, combined pre-existing and in-hospital use.
	risk of death, 23.9% lower, RR 0.76, *p* = 0.16, treatment 28 of 109 (25.7%), control 57 of 169 (33.7%), NNT 12, odds ratio converted to relative risk, pre-existing use, unadjusted.
	risk of death, 85.2% lower, RR 0.15, *p* = 0.002, treatment 2 of 40 (5.0%), control 57 of 169 (33.7%), NNT 3.5, odds ratio converted to relative risk, in-hospital use, unadjusted.
	risk of death, 76.0% lower, RR 0.24, *p* = 0.005, treatment 3 of 37 (8.1%), control 57 of 169 (33.7%), NNT 3.9, odds ratio converted to relative risk, mixed pre-existing/in-hospital use, unadjusted.
Ouchi, 10/4/2022, retrospective, Spain, peer-reviewed, mean age 71.5, 5 authors, study period March 2020 - June 2020.	**risk of death, 9.9% lower, OR 0.90, *p* = 0.19**, treatment 6,168, control 9,875, inverted to make OR<1 favor treatment, metformin monotherapy vs. untreated, RR approximated with OR.
	risk of death/hospitalization, 8.3% lower, OR 0.92, *p* = 0.12, treatment 6,168, control 9,875, inverted to make OR<1 favor treatment, metformin monotherapy vs. untreated, RR approximated with OR.
Piarulli, 6/24/2023, retrospective, Italy, peer-reviewed, 7 authors, study period February 2020 - February 2021.	**risk of death/ICU, 53.0% lower, OR 0.47, *p* = 0.08**, treatment 1,444, control 1,009, adjusted per study, for all patients, combined odds of hospitalization and ICU/death for hospitalized patients, multivariable, RR approximated with OR.
	risk of death/ICU, 15.0% lower, OR 0.85, *p* = 0.68, treatment 209, control 180, adjusted per study, among hospitalized patients, multivariable, RR approximated with OR.
	risk of hospitalization, 45.0% lower, OR 0.55, *p* < 0.001, treatment 1,444, control 1,009, adjusted per study, multivariable, RR approximated with OR.
Pinchera, 1/6/2023, retrospective, Italy, peer-reviewed, 9 authors, study period November 2021 - May 2022, this trial compares with another treatment - results may be better when compared to placebo.	**risk of severe case, 15.2% lower, RR 0.85, *p* = 0.048**, treatment 5 of 19 (26.3%), control 14 of 24 (58.3%), NNT 3.1, adjusted per study, odds ratio converted to relative risk, multivariable.
Pérez-Belmonte, 11/16/2020, retrospective, propensity score matching, Spain, peer-reviewed, 26 authors.	**risk of death, 10.4% higher, RR 1.10, *p* = 0.48**, treatment 79 of 249 (31.7%), control 79 of 249 (31.7%), adjusted per study, odds ratio converted to relative risk, mixed effect logistic regression, propensity score matching.
Ramos-Rincón, 12/28/2020, retrospective, Spain, preprint, 25 authors, study period 1 March, 2020 - 29 May, 2020.	**risk of death, 1.3% lower, RR 0.99, *p* = 0.78**, treatment 206 of 420 (49.0%), control 179 of 370 (48.4%), adjusted per study, odds ratio converted to relative risk, multivariable.
Ravindra, 5/5/2021, retrospective, India, peer-reviewed, 14 authors, excluded in exclusion analyses: minimal details provided.	**risk of death, 29.6% lower, RR 0.70, *p* = 0.42**, treatment 5 of 53 (9.4%), control 57 of 313 (18.2%), adjusted per study, odds ratio converted to relative risk.

Sakamaki, 9/27/2024, retrospective, Japan, peer-reviewed, mean age 52.1, 3 authors, study period 15 January, 2020 - 31 December, 2022.	risk of severe case, 23.0% lower, OR 0.77, $p < 0.001$, adjusted per study, multivariable, RR approximated with OR.
Sandhu, 3/31/2023, retrospective, USA, peer-reviewed, mean age 50.7, 7 authors, study period 1 January, 2020 - 31 December, 2020.	risk of hospitalization, 2.8% lower, OR 0.97, $p = 0.004$, RR approximated with OR.
Saygili, 10/29/2021, retrospective, Turkey, peer-reviewed, 5 authors.	risk of death, 41.5% lower, RR 0.58, $p = 0.02$, treatment 120, control 120, overall mortality, Cox regression in matched group, propensity score matching.
Servais, 12/7/2022, retrospective, Belgium, peer-reviewed, median age 73.0, 21 authors, study period 1 March, 2020 - 6 May, 2020.	risk of death, 49.0% lower, HR 0.51, $p = 0.002$, adjusted per study, multivariable.
Shestakova, 8/9/2022, retrospective, Russia, peer-reviewed, 6 authors, study period 20 March, 2020 - 25 November, 2021.	risk of death, 21.6% lower, RR 0.78, $p = 0.001$, treatment 21,471 of 139,637 (15.4%), control 12,721 of 50,361 (25.3%), adjusted per study, odds ratio converted to relative risk, Table S2, multivariable.
Silverii, 3/24/2024, retrospective, Italy, peer-reviewed, 6 authors.	risk of death, 29.0% lower, OR 0.71, $p = 0.50$, treatment 220, control 304, adjusted for COVID-19 MRS, antivirals, heart disease, RR approximated with OR.
	risk of death, 20.5% lower, OR 0.80, $p = 0.34$, treatment 220, control 304, adjusted for COVID-19 MRS only, RR approximated with OR.
Soff, 2/4/2025, retrospective, USA, peer-reviewed, mean age 62.0, 11 authors, study period 1 January, 2021 - 30 June, 2022.	PASC or death, 18.0% lower, OR 0.82, $p = 0.001$, treatment 3,047, control 4,383, adjusted per study, multivariable, RR approximated with OR.
Somasundaram, 11/9/2024, retrospective, India, peer-reviewed, mean age 53.3, 13 authors, study period 1 April, 2020 - 31 March, 2022, trial CTRI/2022/02/040064.	risk of death, 89.4% lower, OR 0.11, $p < 0.001$, treatment 221, control 200, adjusted per study, multivariable, RR approximated with OR.
Sourij, 12/4/2020, retrospective, Austria, peer-reviewed, mean age 71.1, 24 authors.	risk of death, 37.3% lower, RR 0.63, $p = 0.13$, treatment 14 of 77 (18.2%), control 44 of 161 (27.3%), NNT 11, odds ratio converted to relative risk.
Usman, 1/18/2022, retrospective, USA, peer-reviewed, 10 authors.	risk of death, 59.8% lower, RR 0.40, $p = 0.21$, treatment 3 of 34 (8.8%), control 9 of 41 (22.0%), NNT 7.6.
	risk of mechanical ventilation, 75.9% lower, RR 0.24, $p = 0.05$, treatment 2 of 34 (5.9%), control 10 of 41 (24.4%), NNT 5.4.
	hospitalization time, 33.7% lower, relative time 0.66, $p = 0.13$, treatment 34, control 41.
Wallace, 12/31/2021, retrospective, database analysis, USA, peer-reviewed, 6 authors.	risk of death, 72.0% lower, HR 0.28, $p < 0.001$, treatment 103 of 1,203 (8.6%), control 1,536 of 6,970 (22.0%), NNT 7.4, adjusted per study, before+after, propensity score weighting, Cox proportional hazards.
Wander, 10/6/2021, retrospective, database analysis, USA, peer-reviewed, 8 authors.	risk of death, 15.0% lower, RR 0.85, $p < 0.001$, treatment 29,685, control 35,207, odds ratio converted to relative risk, logistic regression, within 30 days of diagnosis, control prevalance approximated with overall prevalence.

	risk of ICU admission, 1.9% lower, RR 0.98, p = 0.62, treatment 29,685, control 35,207, odds ratio converted to relative risk, logistic regression, within 30 days of diagnosis, control prevalance approximated with overall prevalence.
	risk of hospitalization, 3.2% lower, RR 0.97, p = 0.09, treatment 29,685, control 35,207, odds ratio converted to relative risk, logistic regression, within 30 days of diagnosis, control prevalance approximated with overall prevalence.
Wang (C), 9/7/2021, retrospective, USA, peer-reviewed, 4 authors.	**risk of ICU admission, 12.0% lower, RR 0.88, p = 0.005**, treatment 6,504, control 10,000, Cox proportional hazards.
Wang (D), 7/14/2020, retrospective, USA, peer-reviewed, 13 authors.	**risk of death, 57.7% lower, RR 0.42, p = 0.43**, treatment 1 of 9 (11.1%), control 13 of 49 (26.5%), NNT 6.5, odds ratio converted to relative risk.
Wargny, 2/17/2021, retrospective, France, peer-reviewed, 43 authors, study period 10 March, 2020 - 10 April, 2020, trial NCT04324736 (history) (CORONADO).	**risk of death, 28.3% lower, RR 0.72, p = 0.03**, treatment 247 of 1,553 (15.9%), control 330 of 1,241 (26.6%), NNT 9.4, adjusted per study, odds ratio converted to relative risk, multivariable, day 28.
	risk of no hospital discharge, 14.8% lower, RR 0.85, p = 0.02, treatment 690 of 1,553 (44.4%), control 702 of 1,241 (56.6%), NNT 8.2, adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, multivariable, day 28.
Wong, 3/7/2022, retrospective, China, peer-reviewed, 11 authors, study period 21 January, 2020 - 31 January, 2021.	**risk of death, 59.0% lower, OR 0.41, p = 0.01**, treatment 786, control 428, adjusted per study, propensity score weighting, multivariable, RR approximated with OR.
	risk of no recovery, 60.6% lower, OR 0.39, p = 0.005, treatment 786, control 428, adjusted per study, inverted to make OR<1 favor treatment, propensity score weighting, multivariable, RR approximated with OR.
	clinical improvement, 63.5% better, OR 0.36, p = 0.009, treatment 786, control 428, adjusted per study, inverted to make OR<1 favor treatment, propensity score weighting, multivariable, RR approximated with OR.
	risk of no hospital discharge, 55.8% lower, OR 0.44, p = 0.009, treatment 786, control 428, adjusted per study, inverted to make OR<1 favor treatment, propensity score weighting, multivariable, RR approximated with OR.
Wong (B), 2/24/2022, retrospective, USA, peer-reviewed, 15 authors.	**risk of death, 51.0% lower, HR 0.49, p < 0.001**, treatment 10,408, control 29,208, Cox proportional hazards.
	risk of mechanical ventilation, 41.0% lower, OR 0.59, p < 0.001, treatment 10,408, control 29,208, adjusted per study, multivariable, RR approximated with OR.
	risk of hospitalization, 40.0% lower, OR 0.60, p < 0.001, treatment 10,408, control 29,208, adjusted per study, multivariable, RR approximated with OR.
Xu (B), 5/17/2024, retrospective, China, peer-reviewed, 6 authors.	**risk of death, 52.0% lower, HR 0.48, p = 0.01**, treatment 405, control 405, adjusted per study, propensity score matching, multivariable, Cox proportional hazards.

	risk of death, 59.0% lower, HR 0.41, p = 0.001, treatment 466, control 4,456, adjusted per study, multivariable, Cox proportional hazards.
	risk of mechanical ventilation, 54.0% lower, HR 0.46, p = 0.007, treatment 466, control 4,456, adjusted per study, multivariable, Cox proportional hazards, Table S7.
	risk of ARDS, 72.0% lower, HR 0.28, p = 0.04, treatment 466, control 4,456, adjusted per study, multivariable, Cox proportional hazards, Table S7.
Yeh, 6/9/2022, retrospective, USA, peer-reviewed, mean age 62.3, 9 authors, study period 1 March, 2020 - 28 February, 2021, trial NCT02788903 (history).	**ICU/intubation/death, 44.0% lower, OR 0.56, p < 0.001**, RR approximated with OR.
	risk of hospitalization, 37.0% lower, OR 0.63, p < 0.001, RR approximated with OR.
Yen, 5/6/2023, retrospective, multiple countries, peer-reviewed, 4 authors, study period 1 January, 2020 - 22 November, 2022.	**risk of death, 25.0% lower, HR 0.75, p = 0.001**, treatment 232 of 20,894 (1.1%), control 295 of 20,894 (1.4%), NNT 332, propensity score matching, Kaplan–Meier.
	risk of mechanical ventilation, 25.0% lower, HR 0.75, p = 0.01, treatment 133 of 20,894 (0.6%), control 168 of 20,894 (0.8%), NNT 597, propensity score matching, Kaplan–Meier.
	risk of ICU admission, 19.0% lower, HR 0.81, p = 0.005, treatment 332 of 20,894 (1.6%), control 390 of 20,894 (1.9%), NNT 360, propensity score matching, Kaplan–Meier.
	risk of hospitalization, 15.0% lower, HR 0.85, p < 0.001, treatment 2,820 of 20,894 (13.5%), control 3,139 of 20,894 (15.0%), NNT 65, propensity score matching, Kaplan–Meier.
	risk of case, 2.0% higher, HR 1.02, p = 0.63, treatment 1,467 of 20,894 (7.0%), control 1,364 of 20,894 (6.5%), propensity score matching, Kaplan–Meier.
Yip, 9/21/2022, retrospective, China, peer-reviewed, mean age 69.0, 10 authors, study period 16 February, 2022 - 31 March, 2022.	**risk of death/hospitalization, 7.0% lower, HR 0.93, p = 0.61**, treatment 8,604, control 3,727, propensity score matching, Cox proportional hazards.
	risk of progression, 15.0% lower, HR 0.85, p = 0.16, treatment 8,604, control 3,727, ER/hosp./death, propensity score matching, Cox proportional hazards.
	risk of progression, 15.0% lower, HR 0.85, p = 0.13, treatment 8,604, control 3,727, hypoxemia/ER/hosp./death, propensity score matching, Cox proportional hazards.
Zaccardi, 9/13/2022, retrospective, United Kingdom, peer-reviewed, 11 authors.	**risk of death, 34.3% lower, RR 0.66, p < 0.001**, meta analysis of 6 groups reported.
	risk of hospitalization, 31.2% lower, RR 0.69, p < 0.001, meta analysis of 6 groups reported.
Zihono, 9/10/2023, retrospective, Indonesia, peer-reviewed, 6 authors.	**risk of death, 48.7% lower, RR 0.51, p = 0.02**, treatment 11 of 56 (19.6%), control 31 of 81 (38.3%), NNT 5.4.

Supplementary Data

Supplementary Data

Footnotes

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

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