Colchicine

Section last reviewed and updated 6/30/2022

Last literature search conducted 5/31/2022

Recommendation 1: In hospitalized patients with COVID-19, the IDSA panel recommends against colchicine for treatment of COVID-19. (Strong recommendation, Moderate certainty of evidence)

Recommendation 2: In ambulatory persons with COVID-19, the IDSA panel suggests against colchicine for treatment of COVID-19. (Conditional recommendation, Moderate certainty of evidence)

Why is colchicine considered for treatment?

Colchicine has been used in various inflammatory conditions, such as gouty arthritis, pericarditis, and familial Mediterranean fever for its anti-inflammatory properties. The anti-inflammatory mechanisms of colchicine are broad [1, 2] and include disruption of microtubules resulting in downregulation of pro-inflammatory cytokines [3, 4] and by reducing recruitment of inflammatory cells to endothelial cells [5]. Colchicine is widely available and relatively cheap, making it an attractive therapeutic to mitigate the inflammatory phase of COVID-19. This has resulted in numerous randomized controlled trials of colchicine in the management of COVID-19.

Summary of the evidence

Our search identified 12 comparative randomized controlled trials in persons with COVID-19 treated with colchicine or an inactive comparison (e.g., standard of care with or without placebo). Ten studies [6-15] informed the recommendations for hospitalized patients and reported on the outcomes of mortality, need for mechanical ventilation, length of hospital stay, and adverse events. The three studies [15-17] identified to inform the recommendation for ambulatory persons reported on the outcomes of mortality, hospitalization, need for mechanical ventilation, and serious adverse events.

Benefits

<u>Hospitalized</u>

In hospitalized patients, treatment with colchicine for COVID-19 rather than no colchicine failed to show or exclude a beneficial effect on mortality (risk ratio [RR]; 95%

confidence interval [CI]: 0.99; 0.92, 1.06; moderate certainty of evidence [CoE]). Treatment with colchicine rather than no colchicine for the purpose of COVID-19 does not reduce need for mechanical ventilation (RR: 1.02; 95% CI: 0.90, 1.16; high CoE). Hospitalized patients receiving colchicine experienced a trend toward reduced hospital stay (mean difference [MD]: -1.77 days; 95% CI: -3.69, 0.15; very low CoE); however, there are concerns about risk of bias, inconsistency and imprecision.

Ambulatory

Treatment with colchicine likely does not reduce mortality or need for mechanical ventilation compared to no colchicine among ambulatory persons with COVID-19 (RR: 0.50; 95% CI: 0.19, 1.33; moderate CoE and RR: 0.50; 95% CI: 0.24, 1.07, moderate CoE, respectively). The evidence could not exclude no meaningful reduction in hospitalization (RR: 0.82; 95% CI: 0.64, 1.05; moderate CoE).

Harms

Hospitalized

We were unable to exclude the potential for adverse events in hospitalized patients receiving treatment with colchicine rather than no colchicine for COVID-19 (RR: 2.04; 95% CI: 1.07, 3.91; low CoE).

Ambulatory

One study reported on serious adverse events among persons treated with colchicine rather than no colchicine for COVID-19. Serious adverse events may be less frequent among ambulatory persons receiving treatment with colchicine rather than no colchicine; however, this may not be meaningfully different from those not receiving colchicine (RR: 0.78; 95% CI: 0.61, 1.00; moderate CoE).

Other considerations

The panel determined the certainty of the evidence of treatment of colchicine for hospitalized patients to be moderate due to imprecision. The guideline panel made a strong recommendation against treatment of COVID-19 with colchicine for hospitalized patients with COVID-19.

The panel determined the certainty of the evidence of treatment of colchicine for ambulatory persons to be moderate due to imprecision. The guideline panel made a conditional recommendation against treatment of COVID-19 with colchicine for ambulatory persons.

Conclusions and research needs for this recommendation

The guideline panel recommends against colchicine for the treatment of hospitalized patients with COVID-19. The guideline panel suggests against colchicine for the treatment of ambulatory persons with COVID-19.

Table 1. GRADE evidence profile, Recommendation 1
Question: Colchicine compared to no colchicine for hospitalized patients with COVID-19
Last reviewed and updated 6/13/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	colchicine	no colchicine	Relative (95% CI)	Absolute (95% CI)		
Mortality												
10 [1-10]	randomized trials	not serious	not serious	not serious	serious [a]	none	1335/6684 (20.0%)	1385/6810 (20.3%)	**RR 0.99** (0.92 to 1.06)	**2 fewer per 1,000** (from 16 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mechanical ventilation												
5 [4-8]	randomized trials	not serious [b]	not serious	not serious	not serious	none	652/6242 (10.4%)	651/6370 (10.2%)	**RR 1.02** (0.90 to 1.16)	**2 more per 1,000** (from 10 fewer to 16 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Length of hospital stay												
4 [1-3,9]	randomized trials	serious [c]	serious [d]	not serious	serious [a,e]	none	134	132	-	MD **1.77 days fewer** (3.69 fewer to 0.15 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events												
3 [8-10]	randomized trials	serious [c]	not serious	not serious	serious [e,f]	none	41/148 (27.7%)	20/151 (13.2%)	**RR 2.04** (1.07 to 3.91)	**138 more per 1,000** (from 9 more to 385 more)	⨁⨁◯◯ LOW	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. 95% CI cannot exclude the potential for both meaningful benefit or harm.
b. Largest trial was not blinded.
c. Subjectively measured outcome with >50% of studies in analysis with unclear or unreported methods for randomization and lack of blinding.
d. High I2 (97%). One study had an imbalance of patients receiving dexamethasone (23% vs 45% in intervention vs placebo arm) possibly contributing to shorter duration of hospitalization in placebo arm.
e. Few events suggest fragility of the estimate.
f. 95% CI cannot exclude the potential for no meaningful harm.

References

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10. Gorial FI, Maulood MF, Abdulamir AS, Alnuaimi AS, Abdulrrazaq MK, Bonyan FA. Randomized controlled trial of colchicine add on to the standard therapy in moderate and severe corona virus Disease-19 infection. Ann Med Surg (Lond) **2022**; 77: 103593.

Table 2. GRADE evidence profile, Recommendation 2
Question: Colchicine compared to no colchicine for ambulatory persons with mild-to-moderate COVID-19
Last reviewed and updated 6/13/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	colchicine	no colchicine	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3 [1-3]	randomized trials	not serious [a]	not serious	not serious	serious [b]	none	5/2431 (0.2%)	11/2426 (0.5%)	**RR 0.50** (0.19 to 1.33)	**2 fewer per 1,000** (from 4 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalization												
2 [1,3]	randomized trials	not serious [a]	not serious	not serious [c]	serious [d]	none	107/2391 (4.5%)	131/2386 (5.5%)	**RR 0.82** (0.64 to 1.05)	**10 fewer per 1,000** (from 20 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [b]	none	10/2230 (0.4%)	20/2204 (0.9%)	**RR 0.50** (0.24 to 1.07)	**5 fewer per 1,000** (from 7 fewer to 1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events												
1 [1]	randomized trials	not serious	not serious	not serious	serious [b,e]	none	108/2195 (4.9%)	139/2217 (6.3%)	**RR 0.78** (0.61 to 1.00)	**14 fewer per 1,000** (from 24 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Potential bias due to unclear or unreported details of randomization or deviations from intended interventions; however, low risk of bias for these domains within the study carrying the largest weight in the analysis and findings are not inconsistent.
b. Few events suggests fragility of the estimate.
c. Hospital admission is an intermediary outcome for morbidity, ICU admission, and need for ventilation. Not rated down.
d. 95% CI cannot exclude no meaningful benefit.
e. 95% CI cannot exclude no meaningful difference.

References

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Supplementary Materials

Study characteristics

- **Table s1.** Should patients (hospitalized and ambulatory) with COVID-19 receive colchicine vs. no colchicine?

Forest plots

- **Figure s1a.** Outcome of mortality for colchicine vs. no colchicine
- **Figure s1b.** Outcome of duration of hospitalization for colchicine vs. no colchicine (hospitalized patients)
- **Figure s1c.** Outcome of hospitalization for colchicine vs. no colchicine (ambulatory persons)
- **Figure s1d.** Outcome of mechanical ventilation for colchicine vs. no colchicine
- **Figure s1e.** Outcome of adverse events for colchicine vs. no colchicine (hospitalized patients)

Risk of bias

- **Table s2.** Randomized controlled studies (colchicine vs. no colchicine)

Table s1. Should patients (hospitalized and ambulatory) with COVID-19 receive colchicine vs. no colchicine?

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Absalón-Aguilar 2022 [1]	Mexico/ Instituto Nacional de Ciencias Médicas y Nutrición Salva-dor Zubirán and at Instituto Nacional de Cardiología Ignacio Chávez	RCT	116 (56/60)	34.4	Median (IQR): 53 (44–62)	Hospitalized with severe disease (SpO_2 ≤93%)	(1) Colchicine 1.5 mg PO at baseline (day of recruitment) and then 0.5 mg PO BID for 10 days	(2) Placebo	N/A	Death or progression to critical disease (multiple organ failure, shock, or need for invasive mechanical ventilation) Length of hospital admission Adverse events	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
Asultan 2021 [2]	Syria/ Al Assad University Hospital	RCT	49 (14/14/21)	61.2	N/A	Hospitalized with severe disease (SpO_2 ≤93%)	(1) Supportive care plus colchicine (colchicine 1.5 mg PO followed by 0.5 mg after hour in day 1,then 0.5 mg BID for the next 4 days)	(2) Supportive care plus budesonide inhaler (200 mcg BID for 5 days in an inhalation chamber) (3) Supportive care only	All patients received appropriate supportive care with oxygen supplementation, vitamins, anticoagulants, dexamethasone, prone position, noninvasive ventilation (CPAP or BIPAP), antibiotics, and fluids. Vitamins consist of vitamin C,	Hospitalization days ICU/Death	N/A

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
									vitamin D, and zinc. All patients had taken anticoagulants		
Deftereos 2020 [3]	Greece/ 16 tertiary care hospitals	RCT	105 (55/50)	41.9	Median (IQR): 64 (54-76)	Hospitalized with mild to moderate disease (WHO scale 3/4)	(1) Loading dose of colchicine 1.5 mg PO followed by 0.5 mg colchicine 60 minutes later if no adverse gastrointestinal effects were observed, 0.5 mg colchicine BID (reduced to QD among patients with body weight <60 kg) until hospital discharge or a maximum of 21 days In the case of azithromycin coadministration, a single 1.0 mg loading dose of colchicine was administered	(2) Medical treatment for COVID-19 per local protocols	Chloroquine or hydroxychloroquine, azithromycin, lopinavir or ritonavir, tocilizumab	2-grade increase on WHO ordinal clinical scale Requiring mechanical ventilation All-cause mortality Adverse events	ELPEN Pharmaceuticals Acarpia Pharmaceuticals Karian Pharmaceuticals

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Diaz 2021 [4]	Argentina/ 42 centers	RCT	1279 (640/639)	35.1	Mean (SD): 61.8 (14.6)	Hospitalized with severe disease (SpO_2 ≤93%)	(1) Colchicine loading dose of 1.5 mg PO, followed by 0.5 mg PO within 2 hours of the initial dose, and subsequently 0.5 mg BID for 14 days or discharge, whichever occurred first The colchicine dose was reduced in patients with kidney or liver dysfunction or if drugs that could interact were used concomitantly	(2) usual care	Corticosteroids, anticoagulant drugs, convalescent plasma, ivermectin, antiplatelet drugs, oseltamivir, hydroxychloroquine, lopinavir/ritonavir	Intubation for mechanical ventilation 28-day mortality Adverse events	Population Health Research Institute Fundacion ECLA
Dorward 2021 [5]	UK/ multicentre	RCT	314 (174/140)	53.5	N/A	Ambulatory care	(1) Colchicine 500 µg daily for 14 days	(2) SoC largely focused on managing symptoms with antipyretics and inhaled budesonide on an off-label, case-by-case basis for people aged ≥65 years or 50-65 with comorbidities	SoC	Death Hospitalization Duration of hospitalization Mechanical ventilation	UK Research and Innovation Department of Health and Social Care through the National Institute for Health Research

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Gaitán-Duarte 2021 [6]	Colombia/ 6 referral hospitals	RCT	633 (160/153/ 159/161)	32.0	Mean (SD): 55.4 (12.8)	Hospitalized with severe disease (with pneumonia; 85% of patients on non-invasive support or no oxygen, 15% on high-flow cannula or mechanical ventilation)	(1) Emtricitabine/ Tenofovir (200/300 mg PO for 10 days) (2) Colchicine + Rosuvastatin (0.5 mg and 40 mg PO for 14 days) (3) Emtricitabine/ Tenofovir + Colchicine + Rostuvastin (200/300 mg, 0.5 mg and 40 mg PO)	(4) SoC based on the recommendations of the Colombian consensus for hospitalized patients with COVID-19 that included the use of dexamethasone, ivermectin or albendazole as prophylaxis for *Strongyloides* infection, enoxaparin, acetaminophen, oxygen as needed, and mechanical ventilation, or dialysis, if required	SoC	All-cause mortality within 28 days Mechanical ventilation Adverse events	Colombian Ministry of Science and Technology
Gorial 2022 [7]	Iraq/ Alkarkh hospital	RCT	160 (80/80)	46.9	Median (IQR): 49 (37-60.5)	Ambulatory and hospitalized with moderate to severe COVID-19 (WHO classification)	(1) Colchicine 0.5 mg tablet BID for 1 week followed by 0.5 mg tablet QD for another week	(2) SoC with acetaminophen 500 mg on need, vitamin c 1000 mg BID, zing 75-125 mg/day, vitamin d3 5000IU/day, azithromycin 250 mg/day for 5 days, oxygen therapy/C-pap if needed,	SoC	Death Adverse events	None

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
								dexamethasone 6 mg/day or methylprednisolone 40 mg BID, if needed, and mechanical ventilation, if needed			
Lopes 2021 [8]	Brazil	RCT	72 (36/36)	54.2	N/A	Hospitalized with severe disease (SpO_2 ≤92%)	(1) Colchicine 0.5 mg PO TID for 5 days, then 0.5 mg BID for 5 days; if body weight ≥80kg, the first dose was 1.0 mg Whether a patient had chronic kidney disease, with glomerular filtration rate under 30mL/min/1.73m2, colchicine dose was reduced to 0.25 mg TID for 5 days, then 0.25 mg BID for 5 days, no matter the body weight	(2) Institutional treatment with azithromycin 500 mg QD for up to 7 days, hydroxychloroquine 400 mg BID for 2 days, then 400 mg QD for up to 8 days and unfractionated heparin 5000 UI TID until the end of hospitalization	Institutional treatment	Time of hospitalization Death rate Adverse events	Fundação de Amparo à Pesquisa do Estado de São Paulo

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Mareev 2021 [9]	Russia	RCT	43 (21/22)	30.2	N/A	Hospitalized with severe disease (pneumonia + elevated CRP >60 mg/l + fever >37.5°C; persistent cough; dyspnea with the respiratory rate (RR) >20 brpm and / or SaO2 <94% when breathing atmospheric air)	(1) Colchicine 1 mg during first 1-3 days followed by 0.5 mg/day	(2) Control	N/A	Change in SHOCS-COVID score Death Hospitalization duration	MSU Medical Research and Educational Center
Pascual-Figal 2021 [10]	Spain	RCT	103 (52/51)	47.6	Mean (SD): 51.0 (12.0)	Hospitalized with mild to moderate disease (WHO scale 3/4)	(1) Initial load dose of colchicine 1.5 mg PO (1 mg and 0.5 mg two hours after), followed by 0.5 mg every 12 hours during the next 7 days and 0.5 mg every 24 hours until the completion of 28	(2) SoC: • dexamethasone (6 mg QD for 10 days) for patients who required supplemental oxygen (WHO scale ≥4) • remdesivir for 5 days (time from	SoC	WHO 7-points ordinal clinical scale Death Mechanical ventilation Adverse events	"Cardiology Research group" at the IMIB-Arrixaca and the University of Murcia, Murcia, Spain Centro

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
							days of total treatment The dose was reduced by half in patients receiving ritonavir or lopinavir or with at least one of the following: reduced renal clearance (<50 mL/min/ 1.37m2), weight <70 kg or age >75 years old	symptoms onset <7 days; two or more measurements of oxygen saturation below 94% on room air, respiratory rate >24 breaths/min without supplemental oxygen or Pa02/Fi02<30 • tocilizumab single dose of 600 mg and baricitinib at 4 mg/day for 14 days (need for tocilizumab or baricitinib established according to physician on care criteria)			Nacional de Investigaciones Cardiovasculares Spanish Ministry of Economy and Competitiveness (MINECO) Pro-CNIC Foundation
RECOVERY Collaborative Group 2021 [11]	177 hospitals in UK, 2 hospitals in Indonesia,	RCT	11 340 (5610/5730)	30.3	Mean (SD): 63.4 (13.8)	Hospitalized with severe disease (68% of patients on non or simple oxygen, 27%	(1) Colchicine 1 mg followed by 500 µg 12 h later and then 500 µg BID orally or by nasogastric tube for 10 days in total or until	(2) SoC	Corticosteroids, remedesivir	28-day mortality Median time to being	UK Research and Innovation (Medical Research Council)

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
	2 hospitals in Nepal					on non-invasive ventilation, and 5% on invasive mechanical ventilation)	discharge, whichever occurred first Dose frequency was halved for patients receiving a moderate CYP3A4 inhibitor (eg, diltiazem), those who had renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m2), and patients with an estimated body weight of less than 70 kg			discharged alive Discharged from hospital within 28 days Invasive mechanical ventilation Adverse events	National Institute of HEalth Research Wellcome Trust
Tardif 2021 [12]	Canada/ led by the Montreal Heart Institute	RCT	4488 (2235/2253)	53.9	N/A	Ambulatory care with at least one high risk characteristic	(1) 0.5 mg BID for the first 3 days and then QD for 27 days thereafter	(2) Placebo	N/A	Composite of death or hospital admission for COVID-19 Need for mechanical ventilation	The Government of Quebec, the Bill & Melinda Gates Foundation, the National Heart, Lung, and Blood Institute of the US National Institutes of Health, the

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Serious adverse events	Montreal Heart Institute Foundation, the NYU Grossman School of Medicine, the Rudin Family Foundation, and philanthropist Sophie Desmarais.

Figure s1a. Forest plot for the outcome of mortality for colchicine vs. no colchicine

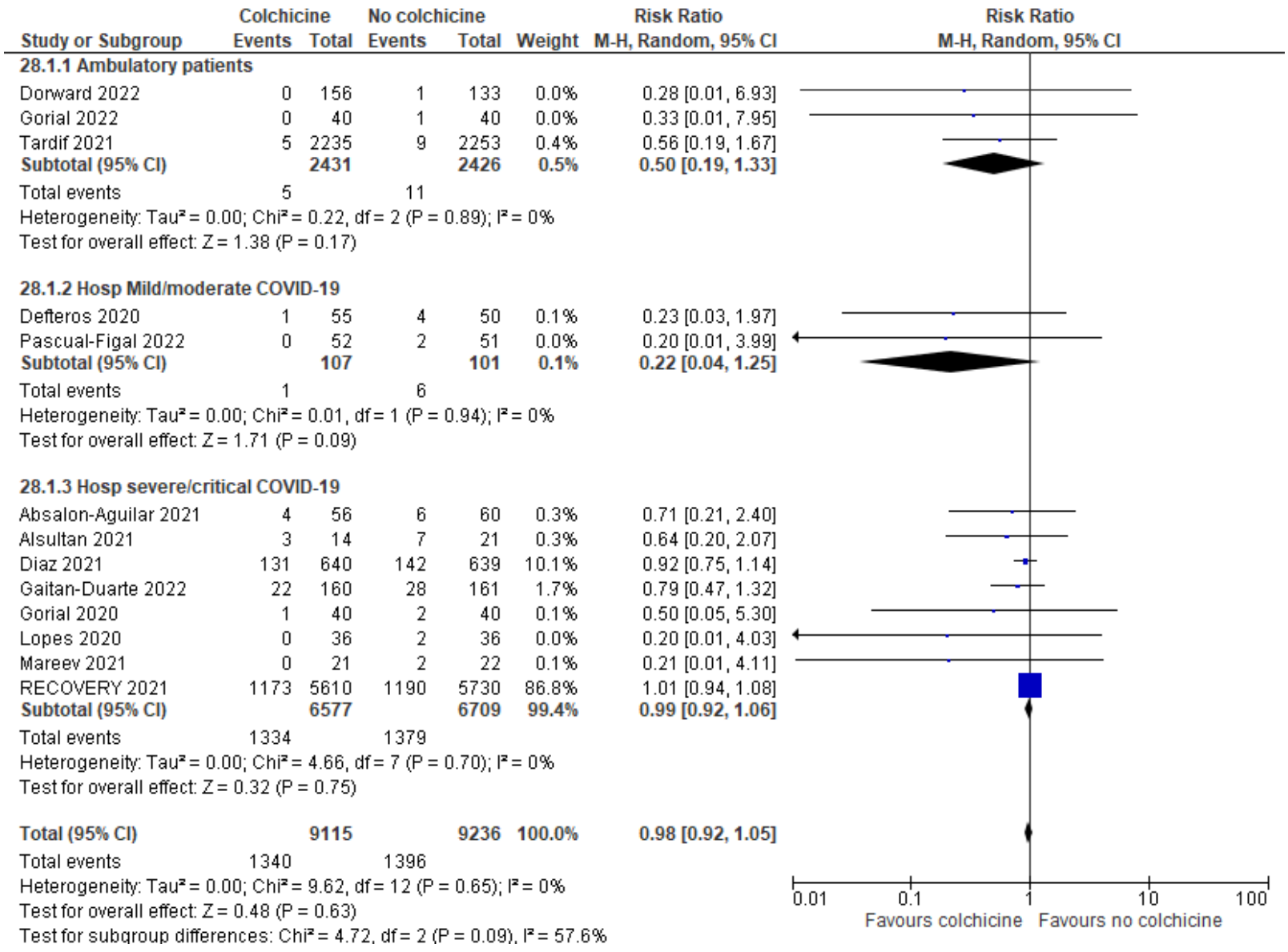

Figure s1b. Forest plot for the outcome of duration of hospitalization for colchicine vs. no colchicine (hospitalized patients)

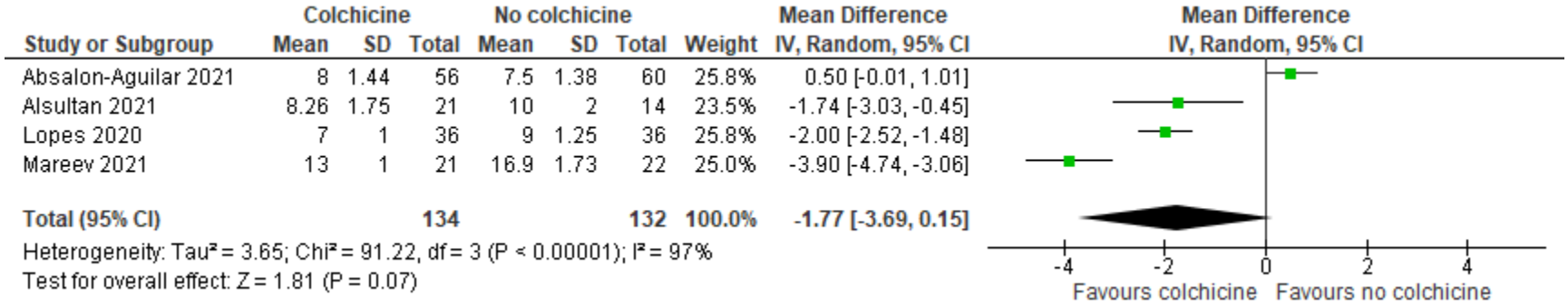

Figure s1c. Forest plot for the outcome of hospitalization for colchicine vs. no colchicine (ambulatory persons)

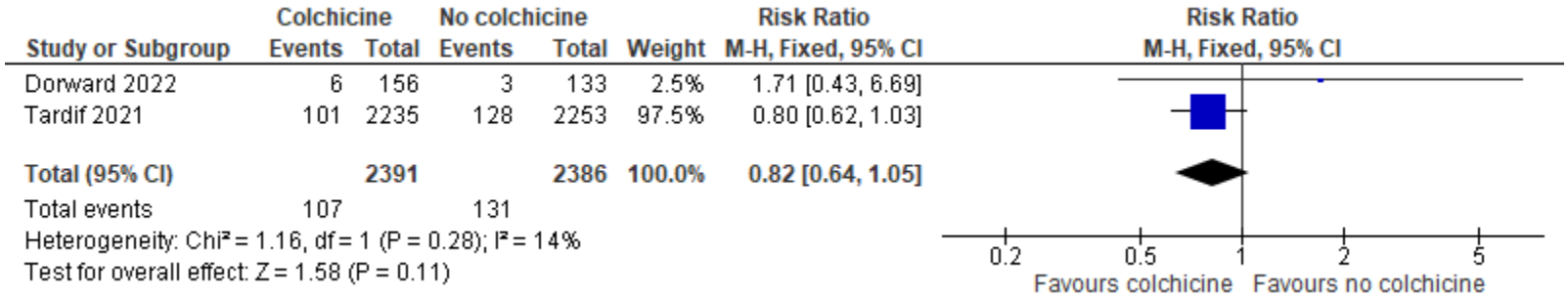

Figure s1d. Forest plot for the outcome of mechanical ventilation for colchicine vs. no colchicine

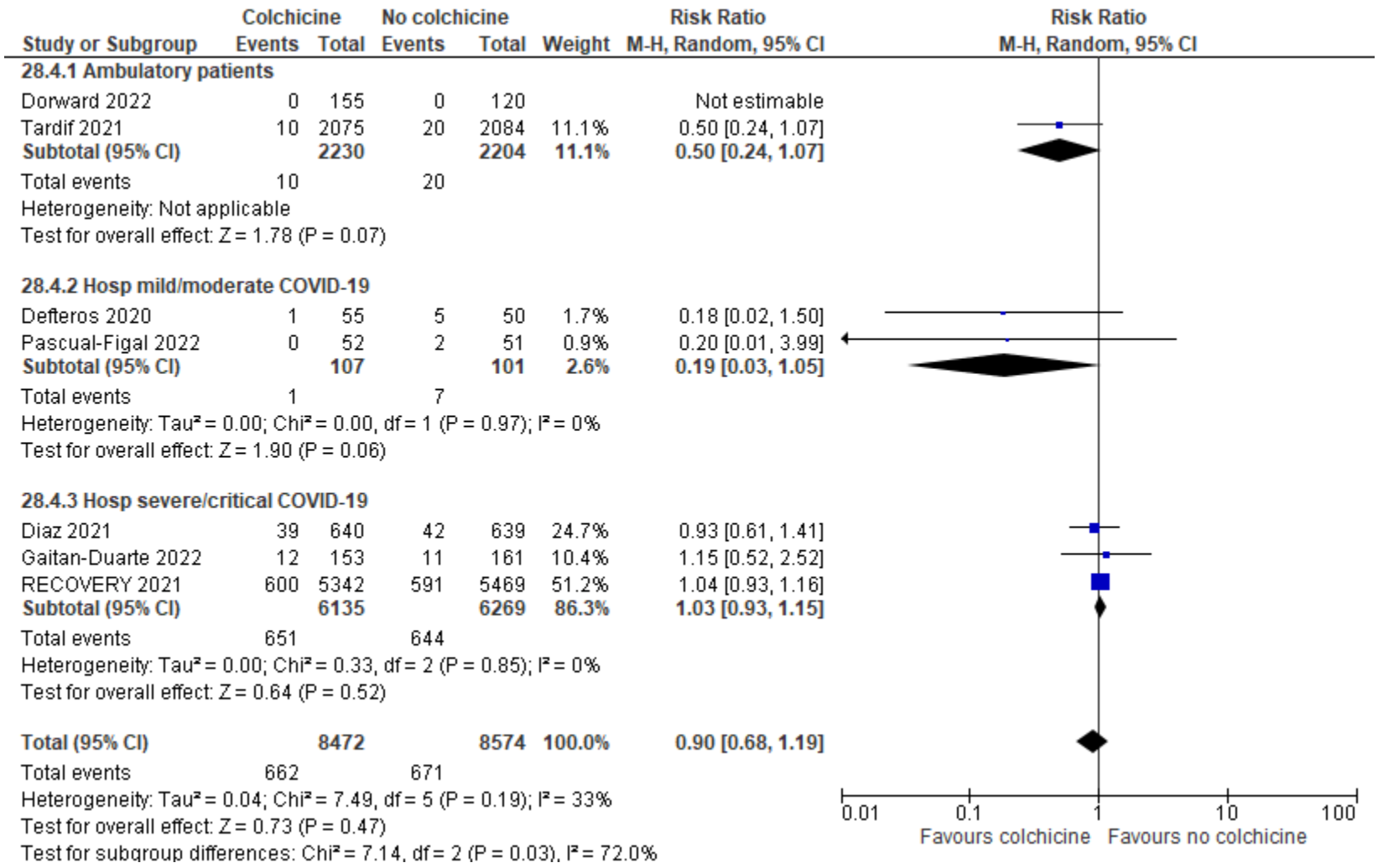

Figure s1e. Forest plot for the outcome of adverse events for colchicine vs. no colchicine (hospitalized patients)

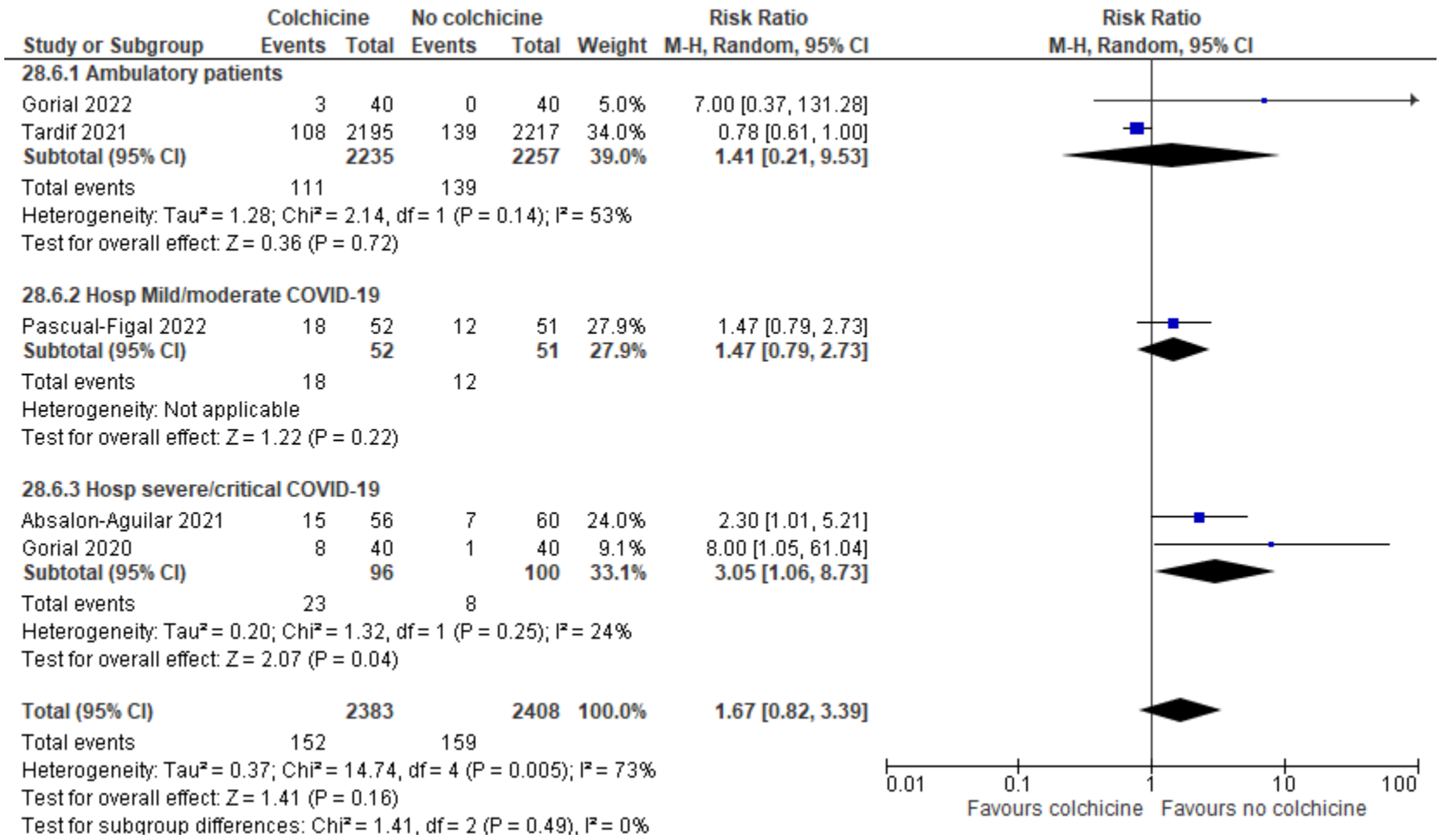

Table s2. Risk of bias for randomized controlled studies (colchicine vs. no colchicine)

Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result
Abalsón-Aguila 2022 [1]					
Alsultan 2021 [2]					
Deftereos 2020 [3]					
Diaz 2021 [4]					
Dorward 2021 [5]					
Gaitan-Duarte 2021 [6]					
Gorial 2022 [7]					
Lopes 2021 [8]					
Mareev 2021 [9]					
Pascual-Figal 2021 [10]					
RECOVERY Collaborative Group 2021 [11]					
Tardif 2021 [12]					

Low Risk	Some Concerns	High Risk

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