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#### \*CORRESPONDENCE Yuanshen Zhou ☑ yuanshenzhou@gzucm.edu.cn

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# Early long-term low-dosage colchicine and major adverse cardiovascular events in patients with acute myocardial infarction: a systematic review and meta-analysis

Yifang Zhou<sup>1</sup>, Yidan Liu<sup>1</sup>, Ruixiang Zeng<sup>1,2</sup>, Wenjie Qiu<sup>1</sup>, Yunhong Zhao<sup>3</sup> and Yuanshen Zhou<sup>1,2\*</sup>

<sup>1</sup>The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China, <sup>2</sup>Department of Critical Care Medicine, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China, <sup>3</sup>Department of Critical Care Medicine, Nanxiong City Hospital of Chinese Medicine, Shaoguan, China

**Background:** Current evidence on the efficacy and safety of colchicine after acute myocardial infarction (AMI) remains controversial. This study aims to clarify early low-dose long-term colchicine's exact efficacy and safety in AMI patients via more studies.

**Methods:** We searched PubMed, Web of Science, Embase, and Cochrane Library databases for randomized controlled trials assessing the efficacy of colchicine on major adverse cardiovascular events (MACE) in recent AMI patients from inception to January 29, 2023, without any restriction. Additionally, we conducted subgroup analyses to assess the impact of early ( $\leq$ 3 days) long-term ( $\geq$ 1 year) low-dosage (0.5 mg/d) colchicine. Summary estimates were computed using Mantel-Haenszel and reported as risk ratios (RRs) or standard mean differences (SMDs), mean differences (MDs) with 95% confidence intervals (Cls). Sensitivity analyses were performed to explore the potential sources of heterogeneity. Review Manager software was used for the meta-analysis.

**Results:** Eight studies identified from 564 screened records were analyzed, with 5,872 patients after AMI. The length of follow-up varied from five days to 22.7 months, and 0.5–1.0 mg colchicine was administered daily. In summary, compared to the control group, colchicine reduced the occurrence of MACE (RR, 0.56; 95% CI, 0.48–0.67) with 2.99-fold gastrointestinal adverse events in patients with recent AMI. Moreover, the relation referred to a gradual decrease in the occurrence of MACE with a longer follow-up duration (≥1 year) and lower dosage (0.5 mg/d) without leading more gastrointestinal adverse events. Colchicine decreased the follow-up levels of C-reactive protein (CRP) (MD −0.66, 95% CI, −0.98– −0.35) and neutrophils (SMD −0.22, 95% CI, −0.39– −0.55) when the follow-up period was 30 days.

**Conclusion:** Early long-term low-dose colchicine decreases the risk of MACE via anti-inflammation without leading more gastrointestinal adverse events in patients with AMI.

#### KEYWORDS

colchicine, myocardial infarction, major adverse cardiovascular events, CRP, inflammation

# 1. Introduction

Even with optimal medical therapy, post-acute myocardial infarction (AMI) patients continue to face a high risk of mortality and morbidity (1, 2). Hence, optimizing the current therapeutic strategies to improve cardiovascular outcomes after AMI is necessary and urgent.

Nearly all AMIs are triggered by thrombi associated with atherosclerosis (3). A critical contributor to atherosclerotic plaque progression and instability is inflammation (4), for example, the involvement of NLRP3 inflammasome (4). Additionally, the neutrophil-to-lymphocyte ratio (NLR) is positively correlated with Creactive protein (CRP) levels and is associated with in-hospital major adverse cardiovascular events (MACEs) (5). Furthermore, despite timely percutaneous coronary intervention (PCI), reperfussion injury also causes additional damage and inflammation (6, 7). Therefore, implementing the anti-inflammatory treatment makes sense.

Colchicine and canakinumab have been discovered to potentially reduce the incidence of MACEs in AMI settings (8). However, canakinumab is linked to a higher incidence of fatal infections (9). There is growing evidence that colchicine reduces the incidence of MACE in the secondary prevention of cardiovascular (CV) events (10, 11). Consequently, colchicine has gathered increasing interest as a tolerable and affordable antiinflammatory agent.

Colchicine may improve cardiovascular outcomes by suppressing activation of the NLRP3 inflammasome (12, 13). Animal experiments demonstrated that inhibition and disruption of major components of NLRP3 decline infarct size after ischemia-reperfusion (I/R), improve cardiac remodeling and fibrosis after AMI, and enhance cardiac contractile function (4).

Firstly, it remains controversial whether colchicine reduces the risk of MACE in patients with AMI (14-16). Secondly, the study population for meta-analyses of Diaz-Arocutipa et al. (15) and Mendoza et al. (17) included patients with unstable angina (UA), and UA patients were evenly and randomly distributed between the colchicine and control groups cannot be assured. Further, the inflammation levels were substantially higher in patients with AMI than UA (18). It may introduce biases. Thirdly, we included two more randomized controlled trials (RCTs) with 558 participants compared with previous analyses. Moreover, we excluded three RCTs, being included in the analysis of previous studies, of patients with acute coronary syndromes (ACS) from the study, as follows Akrami et al. 2021 (19) (AMI: UA = 65.5%: 34.5%), Raju et al. 2012 (20) (AMI: UA: stroke = 77.5%: 13.75%: 8.75%) and Tong et al. 2020 (21) (AMI: UA = 96.7%: 3.3%). Finally, we aimed to clarify early low-dose long-term colchicine's exact efficacy and safety in AMI patients by more RCTs.

# 2. Methods

## 2.1. Search strategy

RCTs were identified and selected from inception to January 29, 2023. A thorough search was conducted on Web of Science,

PubMed, Embase, and Cochrane Library databases without restriction(shown in **Supplementary document S1**).

### 2.2. Study selection and eligibility criteria

The search strategy used the following search terms: (Myocardial Infarction OR Infarction, Myocardial OR Infarctions, Myocardial OR Myocardial Infarctions OR Cardiovascular Stroke OR Cardiovascular Strokes OR Stroke, Cardiovascular OR Strokes, Cardiovascular OR Myocardial Infarct OR Infarct, Myocardial OR Infarcts, Myocardial OR Myocardial Infarcts OR Heart Attack OR Heart Attacks OR Acute Coronary Syndromes OR Coronary Syndrome, Acute OR Coronary Syndromes, Acute OR Syndrome, Acute Coronary OR Syndromes, Acute Coronary OR STEMI OR ST-Segment Elevation Myocardial Infarction OR ST Elevated Myocardial Infarction OR Non-ST Elevated Myocardial Infarction OR Non-ST-Elevation Myocardial Infarction OR Infarction, Non-ST-Elevation Myocardial OR Infarctions, Non-ST-Elevation Myocardial OR Myocardial Infarction, Non-ST-Elevation OR Myocardial Infarctions, Non-ST-Elevation OR Non-ST Elevation Myocardial Infarction OR Non-ST-Elevation Myocardial Infarctions)) AND (colchicine OR Colchicine, (R)-Isomer OR Colchicine, (+-)-Isomer)) AND (Randomized controlled trial OR randomized OR placebo). Additionally, potential missing RCTs were identified by searching the websites ClinicalTrials.gov and Chictr.org.cn.

Studies were eligible if they assessed the cardiovascular effect of colchicine and compared it with standard treatment or placebo in adult AMI patients (age  $\geq 18$  years). Moreover, studies were disqualified if they included (1) animal studies, observational studies, reviews, and meta-analyses, RCTs published only as letters or abstracts, as well as trials of unpublished data; (2) study populations with ACS and stable coronary artery disease; (3) they reported no relevant results.

Two investigators (YFZ and YL) independently filtered the titles and abstracts of the retrieved studies according to the inclusion and exclusion criteria, and subsequently excluded duplicates. Next, the full text of the selected studies was independently filtered.

After excluding duplicate studies, two investigators (YFZ and YL) independently screened the titles and abstracts of the retrieved studies based on the inclusion and exclusion criteria, after eliminating duplicate studies. Next, the full texts of the selected studies were screened independently. Finally, if disagreement between the investigators could not reach a consensus on including a particular survey, a third investigator (RZ) was invited to resolve it. Additionally, We hand-searched the reference lists of the final accepted articles for any related RCTs missed by the search strategy.

### 2.3. Data abstraction

Data abstraction was conducted separately from the selected studies by two researchers (YFZ and YL) and censored by a third

researcher (RZ). We contacted the corresponding author via e-mail if additional data were required.

The following data were taken: publication year, first author name, type of RCT, characteristics of the study population, age, sex, sample size, duration and dosage of colchicine, initiation of colchicine, time of follow-up, PCI, antiplatelet, statin, dyslipidemia, diabetes, hypertension, discontinuation of treatment.

# 2.4. Quality assessment and study risk of bias assessment

Two researchers (YFZ and YL) individually assessed quality and bias risk of selected RCTs. RCTs included were assessed for risk of bias with the use of the Cochrane Risk of Bias 2 Tool (22), which includes the following six domains: randomization, participant and personnel blinding, allocation concealment, selective reporting, incomplete outcome data, and other biases. In each RCT, three levels of bias were assessed: low, unclear, and high independently by two authors (YFZ and YL) and scrutinized by a third author (RZ).

### 2.5. Statistical analysis

All analyses were carried out using the Cochrane Review Manager (RevMan 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). We calculated the pooled risk ratios (RRs) , mean differences (MDs), or standard mean differences (SMDs) with 95% confidence intervals (CIs) for dichotomous and continuous data. The mean and standard deviation (SD) were estimated using the methods of Luo et al. and Wan et al. (23) if continuous data were reported as median  $\pm$  interquartile range (IQR). Heterogeneity in effect size was examined using the  $\chi^2$  test and  $I^2$  index. The  $\chi^2$  test (P < 0.05) or  $I^2$  index of  $\geq 50\%$  indicated significant heterogeneity among the included studies.

Possible publication bias was estimated upon visual inspection of the funnel plots. To assess the possible impact of the data from an individual trial on the overall results, sensitivity analysis was performed using sequential leave-one-out. We computed RRs and 95% CI using a random-effect model when studies had significant heterogeneity; otherwise, a fixed-effect model was selected.

The following variables were analyzed in the subgroup analyses: AMI period ( $\leq$ 3 days vs. >3 days), colchicine dosage (0.5 vs. 1 mg/d), and follow-up duration(<1 year vs.  $\geq$ 1 year). A two-tailed *P* < 0.05 was deemed statistically significant.

### 2.6. Outcomes

The primary outcome was MACE; the composite outcome included nonfatal myocardial infarction, heart failure (HF), nonfatal stroke, all-cause death, and urgent coronary revascularization. The secondary outcome consisted of the components of the primary outcome; a composite of UA, left ventricular ejection fraction (LVEF), CRP, leukocyte, and neutrophil. Safety and adverse events included gastrointestinal (GI) adverse events and diarrhea.

## 3. Results

#### 3.1. Study selection

Study selection process was shown in **Figure 1**. The initial search strategy identified 563 potential records. We retrieved and searched for an additional RCT (24) from other sources (15). After eliminating 237 duplicate records, 327 were retained. After reviewing the titles and abstracts of the 327 records, 23 potentially eligible full-text articles were retained. Eight RCTs that met the preset inclusion criteria were eventually selected for analyses, leading to the enrolment of 5,872 patients (colchicine group: control group = 2,938:2,934).

#### 3.2. Study characteristics

The key characteristics of the eight RCTs are shown in Table 1. Eight RCTs recruited 80.3% male participants with an average age of  $60.42 \pm 10.55$  years. The prevalence of hypertension was 49.6%, diabetes 21.6%, and dyslipidemia 32.9%. Moreover, 94.5% of patients underwent primary PCI, and 99.6% administered statins and antiplatelet drugs (99.9%). Between the two groups, baseline characteristics varied slightly across the included studies.

#### 3.3. Risk of bias in studies

Individual studies and overall bias summaries are shown in **Figure 2**. Seven (24, 26–31) of the eight RCTs (24–31) had a low risk of bias. The remaining (25) showed high risk or concern due to insufficient description of the information allocation concealment of patients and baseline imbalance. Funnel plots were constructed for the outcome indicators of concern. Since objective measures as treatment purposes, the selection bias was not considered high risk despite lacking double-blind in the two trials (24, 25).

### 3.4. Results of individual studies

The articles included were published between 2015 and 2022. The colchicine dosage and follow-up varied among the studies. In the colchicine groups, four trials (24, 28, 29, 31) were performed with oral colchicine (0.5 mg) daily, whereas two trials (25, 30) were conducted with 1 mg daily. The remaining two trials (26, 27) used 0.5 or 1 mg daily based on patients' weight. Additionally, two trials (29, 30) received an oral loading dosage of 1 or 2 mg. The length of follow-up varied from five days to 22.7 months.



#### 3.5. Primary outcomes

Our results indicated that colchicine was related to a substantially lower risk of MACE compared to the control group [RR 0.56, (95% CI, 0.48–0.67), P < 0.00001;  $I^2 = 0\%$ ; 5 RCTs, n =5,526] in a fix-effects model (shown in Figure 3). We found that colchicine diminished the incidence of MACE (RR 0.57, 95% CI, 0.48–0.67, P < 0.00001,  $I^2 = 7\%$ ) when the follow-up period was over one year, but it did not when the follow-up period was less than one year (RR 0.56, 95% CI, 0.31–1.03, P = 0.06,  $I^2 = 0\%$ ). Similarly, we noticed that a dosage of 0.5 mg colchicine reduced the incidence of MACE (RR 0.56, 95% CI, 0.47-0.67, P < 0.00001,  $I^2 = 0\%$ ), while 1 mg colchicine was ineffective (RR 0.60, 95% CI, 0.32–1.12, P = 0.11,  $I^2 = 0\%$ ) (shown in Figure 4). Early administration of low-dose colchicine significantly reduced the risk of MACE within the first three days (RR 0.58, 95% CI, 0.44-0.78, P = 0.002,  $I^2 = 0\%$ ) after the incidence of AMI, as compared to that between days 4 and 30 (RR 0.81, 95% CI, 0.64-1.02, P = 0.07) (shown in Figure 5).

#### 3.6. Secondary outcomes

Compared with the control group, the colchicine group had a lower risk of UA (RR 0.50, 95% CI, 0.31–0.80, P = 0.004,  $I^2 = 0\%$ ) and LVEF (RR 3.18, 95% CI, 0.10–6.27, P = 0.04,  $I^2 = 78\%$ ).

However, there were no significant differences in all-cause death (RR 0.98, 95% CI, 0.65–1.48, P = 0.93,  $I^2 = 0\%$ ), MI (RR 0.88, 95% CI, 0.67–1.15, P = 0.35,  $I^2 = 0\%$ ), HF (RR 0.54, 95% CI, 0.25–1.18, P = 0.12,  $I^2 = 0\%$ ), and stroke (RR 0.50, 95% CI, 0.09–2.95, P = 0.45,  $I^2 = 53\%$ ) between the colchicine and control groups (shown in **Figure 3**).

Moreover, colchicine did not reduce levels of inflammation, such as CRP [MD -0.21, (95% CI, -1.01-0.59), P = 0.61;  $I^2 = 86\%$ ; 8 RCTs, n = 1,319], leukocytes (SMD -0.05, 95% CI, -0.13-0.03, P = 0.24,  $I^2 = 0\%$ ) and neutrophils (SMD -0.07, 95% CI, -0.15-0.01, P = 0.09,  $I^2 = 47\%$ ) (shown in **Figure 6**). No differences in baseline CRP levels were observed. Subgroup analysis revealed colchicine decreased the follow-up levels of CRP by up to 66% when the follow-up period was 30 days [MD -0.66, (95% CI, -0.98- -0.35), P < 0.0001;  $I^2 = 34\%$ ]. However, different dosages (0.5 vs. 1 mg/d), and shorter-term or longer-term use of colchicine (5 days or over one year) did not affect CRP levels (shown in **Figure 4**).

#### 3.7. Safety and adverse events

Colchicine was significantly correlated with an increased risk of GI adverse events (RR 2.99, 95% CI, 1.14–7.82, P = 0.03;  $I^2 = 85\%$ , 5 RCTs, n = 5,290) in the colchicine group as compared to the control group, with diarrhea being the most common event (RR 3.26, 95% CI, 0.26–41.16, P = 0.36,  $I^2 = 85\%$ ) (shown in Figure 3).

Reference	Study design	Population	No(T/C)	Male	Age	DM	HTN	Dyslipidaemia	PCI	Stain	Antiplatelet
Akodad et al. (25)	Open label	STEMI patients ≤12 h successfully treated with PCI	44 (23/21)	78%	59.9	14%	43%	36%	100%	NR	100%
Deftereos et al. (26)	Double blind	STEMI patients ≤12 h from the onset of chest pain	151 (77/74)	69%	58	21%	40%	52%	100%	NR	NR
Gholoobi et al. (27)	Double blind	NSTEMI patients ≤12 h	150 (75/75)	52%	61.42	49%	NR	NR	NR	98%	100%
Hennessy et al. (28)	Double blind	a type 1 AMI patients within the prior 7 days	237 (119/118)	77%	61	22%	47%	NR	%06	96%	100%
Hosseini et al. (29)	Double blind	STEMI patients ≤12 h successfully treated with PCI	321 (161/160)	79%	59	0.36	0.4	0.21	100%	NR	NR
Mewton et al. (30)	Double blind	patients with a first episode of STEMI referred for PCI, chest pain ≤12 h	192 (101/91)	80%	61	13%	31%	33%	100%	98%	100%
Tardif et al. (31)	Double blind	MI patients within 30 days completed any planned PRPs	4,745 (2,366/2,379)	81%	60.55	20%	51%	NR	93%	%66	%66
Wasyanto (24)	Open label	AMI patients	32 (16/16)	88%	55.37	22%	47%	13%	NR	100%	NR
Reference	Colchicine	Initiation of colchicine	Duration of administration	Time of follow-up	Intervention(s)	Discontinuation (%)					
Akodad et al. (25)	1 mg QD	within first day of AMI	30 days	30 days	colchicine + conventional treatment vs. conventional treatment	13%					
Deftereos et al. (26)	0.5 mg BD or QD	within 3 days of MI	5 days	5 days	colchicine vs. placebo	15%					
Gholoobi et al. (27)	0.5 mg BD or QD	within 5 days of AMI	30 days	30 days	colchicine + routine medications vs. placebo + routine medications	NR					
Hennessy et al. (28)	0.5 mg QD	within 7 days of AMI	30 days	30 days	colchicine vs. placebo	5%					
Hosseini et al. (29)	1-mg oral loading dose, followed by 0.5 mg QD	the first day of MI	until discharge	l year	colchicine vs. placebo	8.6%					
Mewton et al. (30)	2-mg oral loading dose, followed by 0.5 mg BD	the first day of MI	5 days	3 months	colchicine vs. placebo	NR					
Tardif et al. (31)	0.5 mg QD	a mean of 13.5 days after MI	19.6 months (median)	22.6 months (median)	colchicine vs. placebo	18.6%					
Wasyanto (24)	0.5 mg QD	patients with AMI	5 days	5 days	colchicine vs. placebo	NR					
MI, myocardial ir of colchicine adr with <60 kg rece	nfarction; AMI, acute myocal ministration mostly coincide sived 0.5 mg QD for 5 days.	rdial infarction; DM, diabetes disease; HT sd with the follow-up period; if it did not, . Gholoobi, A. 2021: patients <75 kg, or o	N, hypertension; PC it has been indicated creatinine clearance	l, percutaneous - d in the table. De <50 ml/min: 0.5	coronary intervention; PRPs, percuta :ftereos, S 2015: 2 mg (1.5 mg initially 5 mg QD for 30 days and patients >;	neous revasculariz: / followed by 0.5 m 75 kg: 0.5 mg BD fe	ation pro g 1 h late or 30 day	cedures. QD, quaqu er) and continuing wi y.	ue die. B ith 0.5 r	D, bis in ng BD fo	die. The duration or 5 days; Patients



The incidence of GI adverse events decreased with an increase in treatment duration. Short-term colchicine use ( $\leq 5$  days) increased the instances of gastrointestinal adverse events (RR 5.89, 95% CI, 1.14–30.52, P = 0.03,  $I^2 = 63\%$ ). Interestingly, there was no difference in the follow-up duration of 30 days (RR 4.47, 95% CI, 0.46–43.64, P = 0.20,  $I^2 = 62\%$ ) and over 1 year (RR 0.99, 95% CI, 0.88–1.12, P = 0.90) between the colchicine and control groups (shown in **Figure 4**). Additionally, the risk of GI adverse events increased with increasing doses of colchicine. A colchicine dose of 0.5 mg daily had no significant effect on GI adverse events (RR 1.21, 95% CI, 0.64–2.28, P = 0.55,  $I^2 = 54\%$ )., whereas 1 mg (RR 4.88, 95% CI, 1.07–22.22, P = 0.04,  $I^2 = 38\%$ ) caused a 488% increase in RR for GI adverse events (shown in **Figure 4**).

Study or Subaroun	Events Total	Events Total	Weight	MLH Fixed 05% CI	M.H. Fiyod 05% Cl		Study or Subaroun	Events Total	Events Total V	Neiaht N	-H. Fixed, 95% CI	M-H, Fixed, 95% Cl	
Akodad M 2017	1 23	2 21	0.6%	0.46 10.04 4 691		_	Akodad M 2017	0 23	1 21	1.5%	0 31 10 01 7 121		_
Honnecey T 2010	0 111	2 113	0.0%				Honneev T 2010	0 111	2 112	2.200	0.01 0.01 / 101 4		
Hosepini G H 2012	27 161	30 160	8.6%	0.73 [0.44, 1.21]	-		Mewdon N 2021	2 101	4 01	1.00	0.20 (0.01, 4.13)		
Mavdon N 2021	13 101	10 01	5.7%	0.62 [0.44, 1.21]			Mewiuli, N. 2021	J 101 00 0000	4 31	4.070	0.00 [0.10, 2.34]		
Tardif, J. C 2019	162 2366	297 2379	84.4%	0.55 [0.46, 0.66]			Tardir, J. C 2019	89 2300	98 23/9	92.2%	0.91 (0.69, 1.21)		
Total (05% CI)	2762	2764	100.0%	0.5510.40.0.571	•		Total (95% CI)	2601	2604	100.0%	0.88 [0.67, 1.15]	•	
Total (95% CI)	100	2/04	100.0%	0.50 [0.40, 0.07]	•		Total events	92	105				
Total events	190	100		L			Heterogeneity: Chi <sup>2</sup> =	1.53, df = 3 (P = 0	0.68); I² = 0%		H	101 01 1 10	100
Test for overall effect	T.62, UT = 4 (P = 0. Z = 6.77 (P < 0.00	81), F= 0% 001)		0.0	1 0.1 1 10 Favours (colchicine) - Favours (control)	100	Test for overall effect	Z = 0.93 (P = 0.3	5)		U	Favours (colchicine) Favours (control)	100
C	Colchicine	Control		Risk Ratio	Risk Ratio		D	Colchicine	Control		Risk Ratio	Risk Ratio	
Study or Subaroup	Events Total	Events Total	Weiaht	M-H. Fixed. 95% Cl	M-H. Fixed. 95% Cl		Study or Subaroup	Events Total	Events Total	Neialıt M	-H. Randorn, 95% Cl	M-H. Random, 95% Cl	
Mewton N 2021	0 101	1 91	31%	0.30 0.01 7.291 -			Mewton N 2021	2 101	1 91	33.3%	1 80 10 17 19 54		
Tardif, J. C 2019	25 2366	50 2379	96.9%	0.50 [0.31, 0.81]	-		Tardif, J. C 2019	5 2330	19 2346	66.7%	0.26 [0.10, 0.71]	-	
Total (95% CI)	2467	2470	100.0%	0.50 (0.31, 0.80)	•		Total (95% CI)	2431	2437	100.0%	0.50 [0.09, 2.95]		
Total events	25	51					Total events	7	20				
Heterogeneity: Chi <sup>2</sup> = Test for overall effect	: 0.10, df = 1 (P = 0 : 7 = 2.91 (P = 0.0)	0.75); I² = 0% 14)		L.	1 1 1 01 0.1 1 10	100	Helerogeneity: Tau <sup>2</sup> Test for overall effect	= 0.97; Chi <sup>2</sup> = 2.12 t Z = 0.76 (P = 0.4	2, df = 1 (P = 0.15) 5)	( <b>P = 53%</b>		0.01 0.1 1 10	100
-				<b>B</b> : 1 B 4	Favours (colchicine) Favours (control)		÷ i i					ravours (control) ravours (control)	
=	Colchicine	Control		Risk Ratio	Risk Ratio		F	Colchicine	Control		Risk Ratio	Risk Ratio	
Study or Subgroup	Events lotal	Events Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl		Study or Subgrou	p Events Tota	al Events Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Dettereos, S 2015 Tardif, J. C 2019	1 // 43 2366	1 /4 44 2379	2.3% 97.7%	0.96 [0.06, 15.08] 0.98 [0.65, 1.49]	•		Akodad, M 2017 Mewton, N. 2021	1 2 8 10	3 1 21 1 14 91	6.6% 93.4%	0.91 (0.06, 13.69) 0.51 (0.23, 1.17)		
Total (95% CI)	2443	2453	100.0%	0.98 (0.65, 1.48)	•		Total (95% CI)	12	4 112	100.0%	0.54 (0.25, 1.18)	•	
Total events	44	45					Total events	q	15				
Heteronensity Chi?-	0 00 df = 1 /P = 0	199): P= 0%		÷			Heteroneneity Chi	P=016 df=1 (P	= 0 69) <sup>,</sup> P = 0%			H	
FICICIUUCIICIU VIII -	0.00.01 - 1.0 - 0			(	1.01 0.1 1 10	100		analar ite				0.01 0.1 1 10	100
Test for overall effect	Z = 0.09 (P = 0.9)	3)			Favours (colchicine) Favours (contro	) []	Test for overall effe	ect Z = 1.54 (P = 0	1.12)			Favours (colchicine) Favours (control)	100
Test for overall effect	Z = 0.09 (P = 0.9) Colchicine	3) Control		Mean Difference	Favours (colchicine) Favours (contro Mean Difference	)	Test for overall effe	ect Z = 1.54 (P = 0 Colchicine	l.12) Control		Risk Ratio	Favours (colchicine) Favours (control) Risk Ratio	100
Test for overall effect G Study or Subgroup	Z = 0.09 (P = 0.93 Colchicine <u>Mean SD Tota</u>	3) Control al Mean SD	Total We	Mean Difference eight IV, Random, 95% (	Favours (colchicine) Favours (contro Mean Difference Cl IV, Random, 95% Cl	[[[	Test for overall effe H Study or Subgrou	ect Z = 1.54 (P = 0 Colchicine D Events Tota	1.12) Control a <u>l Events Total</u>	Weight	Risk Ratio M-H, Random, 95%	Favours [colchicine] Favours [control] Risk Ratio CI M-H, Random, 95% CI	100
Telefogeneny, om – Test for overall effect G Study or Subgroup Deflereos, S 2015	Z = 0.09 (P = 0.9) Colchicine <u>Mean SD Tota</u> 51.94 11.11 7	3) Control <u>al Mean SD</u> 7 44.94 9.63	<u>Total We</u> 74 26	Mean Difference eight <u>IV, Random, 95% (</u> 9.9% 7.00 [3.69, 10.3	Favours (colchicine) Favours (contro Mean Difference Cl IV, Random, 95% Cl 1)	)]	Test for overall effe H <u>Study or Subgroup</u> Deflereos, S 2015	ect Z = 1.54 (P = 0 Colchicine <u>D Events Tota</u> 15 7	1.12) Control a <u>l Events Total</u> 7 1 74	Weight 42.5%	Risk Ratio <u>M-H, Random, 95%</u> 14.42 (1.95, 106.4	Favours (colchicine) Favours (control) Risk Ratio CI M-H, Random, 95% CI 10]	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
Test for overall effect Study or Subgroup 1 Deflereos, S 2015 Hosseini, S. H. 2022 Mewton, N. 2021	Z = 0.09 (P = 0.9) Colchicine <u>Mean SD Tota</u> 51.94 11.11 7 42.27 7.73 16 48 8.5 8	Control al <u>Mean SD</u> 7 44.94 9.63 1 40.96 8.29 0 46 8.6	<u>Total We</u> 74 28 160 38 81 33	Mean Difference           eight         V. Random, 95% (           8.9%         7.00 [3.69, 10.3           8.1%         1.31 [-0.44, 3.0           3.0%         2.00 [-0.64, 4.6	Favours (colchicine) Favours (contro Mean Difference CI IV, Random, 95% CI 1) 6) 4)	) ]	Test for overall effe <b>Study or Subgrou</b> Defiereos, S 2015 Tardif, J. C 2019	ect Z = 1.54 (P = 0 Colchicine <u>Events Tota</u> 15 7 225 233	1.12) Control a <u>l Events Total</u> 7 1 74 0 20B 2346	Weight 42.5% 57.5%	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (1.95, 106.4 1.09 (0.91, 1.3	CI M-H. Random, 95% CI CI M-H. Random, 95% CI CI M-H. Random, 95% CI CI DI	
Test for overall effect Study or Subgroup 1 Deflerees, S 2015 Hossein, S. H. 2022 Mewton, N. 2021 Total (95% CI)	Colchicine Colchicine <u>Mean</u> <u>SD</u> Tola 51.94 11.11 7 42.27 7.73 16 48 8.5 8	Control <u>al Mean SD</u> 7 44.94 9.63 1 40.96 8.29 0 46 8.6 8	Total We 74 28 160 38 81 33 315 100	Mean Difference           einint         N. Random, 95% (fragma and the second ando	Favours (colchicine) Favours (contro Mean Difference I N, Random, 95% Cl II II II II	)]	Test for overall effe H <u>Study or Subgroup</u> Deflereos, S 2015 Tardif, J. C 2019 Total (95% CI) Tarda exercis	ect Z = 1.54 (P = C Colchicine <u>5 Events Tota</u> 15 7 225 233 240	1.12) Control a <u>l Events Total</u> 7 1 74 0 20B 2346 7 2420 20D	Weight 42.5% 57.5% 100.0%	Risk Ratio <u>M-H, Random, 95%</u> 14.42 (1.95, 106.4 1.09 (0.91, 1.3 <b>3.26 (0.26, 41.1</b>	601 001 001 001 001 001 001 001 001 001	-
Test for overall effect Study or Subgroup 1 Deflereos, S 2015 Hossein, S. H. 2022 Mewton, N. 2021 Total (95% CI) Helerogeneity, Tau <sup>2</sup> = 5.6	Colchicine Colchicine <u>Mean</u> <u>SD</u> Tota 51.94 11.11 7 42.27 7.73 16 48 8.5 8 31 39; Chi <sup>2</sup> = 8.98, df =	Control <u>al Mean SD</u> 7 44.94 9.63 1 40.96 8.29 0 46 8.6 8 2 (P=0.01); P=	Total We 74 26 160 36 81 33 315 100 78%	Mean Difference           eight         IV. Random, 95%           8.9%         7.00 [369, 10.3           8.1%         1.31 [-0.44, 3.0           3.0%         2.00 [-0.64, 4.6]           0.0%         3.18 [0.10, 6.2]	Favours (colchicine) Favours (contro Mean Difference N. Random, 95% Cl 1) 0 0 1 1 1 0 0 1 0 0 0 0 0 0 0 0 0 0		Test for overall effe H Deflereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heteropaneity Tat	colchicine           colchicine <u>colchicine</u> <u>colchicine</u> 15           7           225           233           240           z-0           z-0	1.12) Control al <u>Events Total</u> 7 1 74 0 208 2346 7 2420 209 53 4f = 1 (P = 0.0	<u>Weight</u> 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (1.95, 106.4 1.09 (0.91, 1.3 <b>3.26 (0.26, 41.1</b>	Favours [colchicine] Favours [colchicine] Favours [colchicine] Favours [colchicine] Favours [colchicine] Favours [colchicine] Risk Ratio	
Testforoverall effect Study or Subgroup 11 Deflereos, S 2015 Helsseini, S H. 2022 Mewton, N. 2021 Total (95% C) Helerogeneity, Tau <sup>a</sup> = 5.6 Testfor overall effect Z =	0.00, 01 - 1 (1 - 0           Z = 0.09 (P = 0.9);           Colchicine           Mean         SD           51.94         11.11           7         7.73           48         8.5           8         5           30; ChiP = 8.96, df =           2.02 (P = 0.04)	Control <u>al Mean SD</u> 7 44.94 9.63 1 40.96 8.29 0 46 8.6 8 2 (P = 0.01); P =	Total We 74 26 160 36 81 33 315 100 78%	Mean Difference einit IV, Random, 95% ( 95% 7.00 (3.69, 10.3 8.1% 1.31 F.0.44, 30 30% 2.00 F.0.64, 46 0.0% 3.18 (0.10, 6.2)	Favours (colchicine) Favours (contro Mean Difference 1. N, Random, 95% CI 1	100 21] 100 100	Test for overall effe <b>H</b> <u>Study or Subgroup</u> Defereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity. Tau Test for overall effe	ect Z = 1.54 (P = C Colchicine <u>verits</u> Tota 15 7 225 233 240 240 p <sup>2</sup> = 2.90; Chi <sup>2</sup> = 6. ect Z = 0.91 (P = C	1.12) Control <u>al Events Total</u> 7 1 74 0 20B 2346 7 2420 209 53, df = 1 (P = 0.0 1.36)	<u>Weight</u> 42.5% 57.5% 100.0% 11); P= 85	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (1.95, 106 4 1.09 (0 91, 1.3 3.26 (0.26, 41.1	Favours (colchicine) Favours (control) Favours (colchicine) Favours (control) Risk Radio CI MH.Random, 95% CI 100 100 100 100 100 100 100 10	100
Testforoveral effect S Suby or Subgroup 1 Deflereos, 92015 Hosseini, S.H. 2022 Mewton, N. 2021 Total (95% CI) Heterogeneity, Tay"= 5 6 Test for overall effect Z =	0.00, 01-1 (1 - 0           Z = 0.09 (P = 0.9);           Colchicine           Mean         SD           51.94         11.11           7         7.73           48         8.5           31           59; Chi <sup>2</sup> = 8.90; df =           2.02 (P = 0.04)           Colchicine	Control <u>I Mean SD</u> 7 44.94 9.63 1 40.96 8.29 0 46 8.6 8 2 (P = 0.01); P= Control	Total We 74 28 160 38 81 33 315 100 78%	Mean Difference Einht IV. Random. 95% 89% 7.00 (36.9, 10.3) 81% 1.31 [-0.44, 3.0) 30% 2.00 [-0.64, 4.6] 0.0% 3.18 [0.10, 6.2] Risk Ratio	Favours (colchicine) Favours (contr Mean Difference I. N. Random, 95% Cl I	100 11	Test for overall effi Study or Subproup Defereos, 8 2015 Taratif, J. C 2019 Total (95% CI) Total events Heterogeneity, Tau Test for overall effic	$\frac{\text{Colchicine}}{\text{Colchicine}} = \frac{\text{Colchicine}}{15 - 7}$ $\frac{15 - 7}{225 - 233}$ $240$ $240$ $240$ $r^2 = 2.90; \text{Chi}^2 = 6.$ set $Z = 0.91$ (P = 0	1.12) Control al <u>Events Total</u> 7 1 74 0 208 2346 7 2420 209 53, df = 1 (P = 0.0 .36)	<u>Weight</u> 42.5% 57.5% 100.0% 11); P= 85	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (1.95, 106 4 1.09 (0.91, 1.3 3.26 (0.26, 41.1 %	Favours (colchicine) Favours (control) Favours (control) Risk Ratio CI MH. Random, 95% CI 101 101 101 101 101 101 101 10	100
Testforoverall effect Test for overall effect Study or Subgroup 1 Deflereos, S 2015 Hosseini, S H. 2022 Mewton, N. 2021 Total (95% CI) Heterogenehy, Tau"= 5 & Test for overall effect Z = Study or Subgroup E	0.05, 01 = 1 (1 = 0 Z = 0.09 (P = 0.9; Colchicine Mean <u>SD Totic</u> 51.94 11.11 7 42.27 7.73 16 48 8.5 8 31 39, Chi <sup>2</sup> = 8.98, df = 2.02 (P = 0.04) Colchicine <u>Vents Total Ev</u>	Control <u>al Mean SD</u> 7 44.94 9.63 1 40.96 8.29 0 46 8.6 8 2 (P=0.01); P= Control rents Total V	Total We 74 26 160 36 81 33 315 100 78%	Mean Difference Einht IV. Random, 95% 89% 7.00 [36,91.03 81% 1.31 [-0.44, 3.0 30% 2.00 [-0.64, 4.6 0.0% 3.18 [0.10, 6.27 Risk Ratio I-H. Random, 95% C1	Favours (colchicine) Favours (contro Mean Difference M. Random, 95% Cl M. Random, 95% Cl -20 -10 0 10 2 Favours (colchicine) Favours (contro Risk Ratio M-H, Random, 95% Cl	100 1] 1 10 10 10	Test for overall effi Study or Subprou Defereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity. Tau Test for overall effe	ext Z = 1.54 (P = C Colchicine <u>a</u> Events Totz 15 7 225 233 240 240 F = 2.90; ChP = 6 crt Z = 0.91 (P = C	L12) Control <u>1 Events Total</u> 7 1 74 0 208 2346 7 2420 209 53, df = 1 (P = 0 ( 336)	<u>Weight</u> 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (1.95, 106 4 1.09 (0.91, 1.3 3.26 (0.26, 41.1 %	Favours (colchicine] Favours (control) Favours (colchicine] Favours (control) Risk Radio CI MH. Random, 95% CI 100 101 101 101 101 101 101 10	100
Testforoverall effect Study or Subgroup 1 Deflereos, S 2015 Hosseini, S H. 2022 Newfon, N. 2021 Total (95% CI) Heterogeneity, Tau <sup>2</sup> = 5 & Test for overall effect Z = Study or Subgroup E Akodad, M. 2017	Colchicine Mean SD Totz 51.94 11.11 7 42.27 7.73 16 48 8.5 8 31 59, Ch7= 8.98, of= 2.02 (P = 0.04) Colchicine Vents Total Ex 10 23	Control           Il Mean         SD           7         44.94         96.3           1         40.96         8.29           0         46         8.6           8         2 (P=0.01); P=           Control         rents         Total V           0         21         2	<u>Total We</u> 74 26 160 36 81 33 <b>315 10</b> 0 78% <u>Neight M</u> 8.5%	Mean Difference           einht         IV, Random, 95%, 100 (56) (103)           98%         7.00 (156) (103)           13%         1.31 (54, 20)           30%         2.00 (-0.64, 46)           0.0%         3.18 (0.10, 6.27)           Risk Ratio           LH, Random, 95% (1           19.25 (1.20, 309 49)	Favours (colchicine) Favours (contro Mean Difference N. Random, 95% Cl 1 	100 100 100 100 100	Test for overall effi Study or Subgroup Deflereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity: Tau Test for overall effic	ext Z = 1.54 (P = C Colchicine <u>a Events Tota</u> 15 7 225 233 240 240 P <sup>2</sup> = 290; Ch <sup>2</sup> = 6 ext Z = 091 (P = C	1.12) Control <u>1 Events Total</u> 7 1 74 0 208 2346 7 2420 209 53, df=1 (P=0 ( 36)	Weight 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (1.95, 106.4 1.09 (0.91, 1.3 3.26 (0.26, 41.1	Favours [colchicine] Favours [control] Favours [colchicine] Favours [control] Favours [colchicine] Favours [control] Favours [colchicine] Favours [control]	100
Testoroveral effect Study or Subgroup 1 Deflereos, S 2015 9 Hosseini, S.H. 2022 - Mewton, N. 2021 Total (95% Ct) Helerogeneily, Tau <sup>2</sup> = 56 Testoroveral effect Z = Study or Subgroup 1 Study or Subgroup 2 Study or Subgroup 2 Study or Subgroup 2 Deflereos, S 2015	Colchicine Mean SD Toti 5194 11.11 7 42 27 7.73 16 48 85 8 31 19, Ch7=898, df= 2 02 (P = 0.04) Colchicine vents Total Ev 10 23 18 77	3) Control <u>I Mean SD</u> 7 44.94 9633 1 40.96 8.29 0 46 8.6 8 2 (P=0.01); P= Control Control 0 21 1 74	<u>Total We</u> 74 26 160 36 81 33 <b>315 10</b> 0 70% <u>Neight M</u> 8.5% 13.1%	Mean Difference eight V. Random, 95% ( 95% 7 000 [36,910.3 93% 2 00 [0 64, 46 0.0% 3.18 [0.10, 6.27 Risk Ratio LH. Random, 95% CI 19.25 [1.20, 930.49] 17.30 [2.37, 126.33]	Favours (colchicine) Favours (contro Mean Difference V. Random, 95% Cl II II II II II II II II II I		Test for overall effi Study or Subproup Defereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity. Tau Test for overall effe	et Z = 1.54 (P = C Colchicine <u>2 Events Totz</u> 15 7 225 233 240 240 P* = 290; Chi² = C et Z = 0.91 (P = C	1.12) <u>Control</u> <u>I Events Total</u> 7 1 74 0 20B 2346 7 2420 209 209 53, df=1 (P=0 ( 36)	Weight 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (195, 106, 4 1.09 (0.91, 1.3 3.26 (0.26, 41.1 %	Favours (colchicine) Favours (control) Risk Radio CI MH, Random, 95% CI GI 0.01 0.1 Favours (colchicine) Favours (control) Favours (colchicine) Favours (control)	100
Testforgenetik, Kill – Testforoverall effect S Study or Subgroup Hosseini, S.H. 2022 Hosseini, S.H. 2022 Mewton, N. 2021 Total (95% Ct) Heterogenetik, Tau <sup>2</sup> = 5.6 Testfor overall effect Z = I Study or Subgroup Extended Subgroup Extension, T. 2019	0.00,00         Colorbine           Colorbine         Mean           SD         Total           5194         11.11           7.73         16           48         8.5           99, Ch7=8.98, df=           2.02 (P=0.04)           Colchicine           Vents         Total           10         2.3           18         77           12         111	3) Control 1 Mean SD 7 44.94 963 1 40.96 82 0 46 86 8 2 (P=0 01); P= Control 0 21 1 74 6 113	Total         We           74         26           160         36           81         33           315         100           78%         9           Meight         M           8.5%         13.1%           23.1%         23.1%	Mean Difference eight // Random, 95% (/ 95% 7.00136,910.3 1% 1.31 [0.10,4.3 0 0.0% 3.18 [0.10,6.27 Risk Ratio <u>I.H. Random, 95% (1</u> 19.25 [/.20, 309.49] 17.30 [2.37,126.33] 2.04 [0.79,5.23]	Favours (colchicine) Favours (contro Mean Difference M. Random, 95% Cl H. H. H. H. H. H. H. H. H. H.	100 11 100 100 100 100 100 100	Test for overall effi Study or Subbrow Defereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity, Tar Test for overall effe	et Z = 1.54 (P = C Colchicine <u>2 Events Toto</u> 15 7 225 233 240 2 <sup>40</sup> P <sup>2</sup> = 290, ChP = 6 et t Z = 0.91 (P = C	1.12) Control al Events Total 7 1 74 0 208 2346 7 2420 209 53, df=1 (P=0 ( 36)	Weight 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.42 (1.95, 106, 4 1.09 (0.91, 13 3.26 (0.26, 41.1 %	Favours (colchicine) Favours (control) Risk Radio CI MH.Random, 95% CI 101 101 101 101 101 Favours (colchicine) Favours (control) Favours (colchicine) Favours (control)	100
Testforoveral effect Test for overall effect Study or Subgroup 1 Deflereos, S 2015 Hosseini, S H. 2022 Mewton, N. 2021 Total (95% CI) Heterogenetiy, Tau <sup>*</sup> = 56 Test for overall effect Z = Study or Subgroup E Study or Subgroup E Akodad, M. 2017 Deflereos, S 2015 Hennessy, T. 2019 Mewton, N. 2021	0.00,00         (P = 0.9)           Colchicine         Mean           Mean         SD Tot           51.94         11.11           7         7.73           48         8.5           99, Ch <sup>2</sup> = 8.96, df =           202 (P = 0.04)           Colchicine           vents         Total Ex           10         23           18         77           12         111           33         103	3) Control 1 Mean SD 7 44.94 9.63 1 40.96 82.9 0 46 86 8 2 (P=0.01); P= Control rents Total V 0 21 1 74 6 113 9 92	Total         We           74         26           160         36           81         33           315         100           :78%	Mean Difference einth IV, Rannon, 95%, // 95% 700 [2.68, 10.3 97% 7.00 [2.68, 10.3 97% 7.00 [2.68, 10.3 97% 7.00 [2.68, 10.3 97% 7.00 [2.68, 10.3 11, 20, 20, 20, 20, 20, 20, 20, 20, 20, 20	Favours (colchicine) Favours (contro Mean Difference M. Random, 95% Cl 		Test for overall effe	ett Z = 1.54 (P = C Colchicine <u>a</u> Events Tota 15 7 225 233 240 240 P <sup>2</sup> = 290; ChP = 6 ctt Z = 091 (P = C	1.12) Control <u>1 Events Total</u> 7 1 74 0 208 2346 7 2420 209 53, df=1 (P=0 ( 36)	Weight 42.5% 57.5% 100.0%	Risk Ratio <u>M-H. Random, 95%</u> 14.42 (1:95, 106, 4 1 09 (1) 91, 13 3.26 (0.26, 41, 1	Favours (colchicine) Favours (control) Risk Radio CI MHL Random, 95% CI 40 10 10 10 10 10 10 10 10 10 1	100
Testoroveral effect Testoroveral effect Study or Subgroup 1 Deflereos, S 2015 9 Hosseini, S H. 2022 9 Mewton, N. 2021 Total (9% Ct) Helerogeneity, Tau <sup>2</sup> = 5.6 Test for overall effect Z = Study or Subgroup E Study of X017 Deflereos, S 2015 Hennessy, T. 2019 Mewton, N. 2021 Taratí, J. C 2019	0.00, 0.0         (0.0, 0.0         (0.0, 0.0)         (0.0, 0.0	3) Control 1 Mean SD 7 44.94 9.63 1 40.96 8.29 0 46 86 8 2 (P=001); P= Control 0 21 1 74 6 113 9 92 414 2346	Total         Wee           74         26           160         32           81         32           315         100           70%	Nean Difference.           bifdt <i>I</i> , Random, <u>95%</u> (           9%         7.00136, 10.33           131         1.31           30%         2.001, 0.64, 26           0.0%         3.18           19.25         1.201, 0.623           19.25         1.20, 0.904, 91           19.25         1.20, 0.904, 91           17.30         2.37, 126, 233           2.04         10.75, 623           3.28         1.66, 647           0.99         0.88, 1.12	Favours (colchicine) Favours (contro Mean Difference N. Random, 95% Cl II II Favours (colchicine) Favours (contro Risk Ratio M-H, Random, 95% Cl		Test for overall effi Study or Subproup Defereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity, Tar Test for overall effe	ext Z = 1.54 (P = C Colchicine <u>a</u> Events Tota 15 7 225 233 240 240 P = 290; Chi <sup>2</sup> = 6 ext Z = 0.91 (P = C	1.12) Control <u>al Events Total</u> 7 1 74 0 208 2346 7 2420 209 53, of = 1 (P = 0.0 .36)	<u>Weight</u> 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.4 2 (195, 106, 4 1.09 (0.91, 13 3.26 (0.26, 41.1 %	Favours (colchicine) Favours (control) Risk Radio CI MH, Random, 95% CI 60 001 0,1 10 Favours (colchicine) Favours (control Favours (colchicine) Favours (control	, , , , , , , , , , , , , , , , , , , ,
Testforoverall effect           Stafforoverall effect           Stafforoverall effect           Deflereos, S 2015           Hossein, S.H. 2022           Mewfon, N. 2021           Total (95% CI)           Heleropenelly, Tarl=5 & CI           Study or Subgroup           Backada, M. 2017           Deflereos, S 2015           Hennessy, T. 2019           Mewton, N. 2021           Tarl (95% CI)           Tarlard, J.C. 2019           Total (95% CI)           Total (95% CI)	000, 01, 01, 01, 02, 00, 01, 01, 01, 02, 00, 01, 01, 02, 00, 01, 01, 01, 01, 01, 01, 01, 01, 01	3) Control al Mean SD 7 44.94 963 1 40.96 829 0 46 86 8 2 (P=0.01); P= Control Control 0 21 1 74 6 113 9 92 414 2346 2646 -	Total         We           74         25           160         36           81         33           315         100           78%         315           8.5%         13.1%           23.1%         25.8%           29.5%         100.0%	Mean Difference           111         IV, Random, 95%, 1           81%         7.00 [3.6 g, 10.3           81%         1.31 [0.44, 30           30%         2.00 [0.64, 46           0.0%         3.18 [0.10, 6.27           Risk Ratio           LH, Random, 95% (1           19.25 [1.20, 309 49]           17.30 [2.37, 126.33]           2.04 [0.79, 5.23]           3.28 [1.66, 6.47]           0.99 [0.88, 1.12]           2.99 [1.14,7.82]	Favours (colchicine) Favours (contri Mean Difference M. Random, 95% Cl 1 4 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7		Test for overall effi Study or Subgroup Deflereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity: Tau Test for overall effic	et Z = 1.54 (P = C Colchicine <u>a</u> Events Tota 15 7 225 233 240 P <sup>2</sup> = 2.90; Ch <sup>2</sup> = 6 et Z = 0.91 (P = C	Control           al         Events         Total           7         1         74           0         208         2346           7         2420         209           209         53, df=1 (P = 0.036)           336)         2	Weinlit 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.4 2 (195; 106.4 109 (0 91, 13 3.26 (0.26, 41.1 %	Favours (colchicine) Favours (control Favours (colchicine) Favours (control Risk Ratio CI MH, Random, 95% CI 00 00 00 01 01 01 01 01 01 01	100
Testforoverall effect           Testforoverall effect           Study or Subgroup           Deflereos, S 2015           Hosseini, S. H. 2022           Mewton, N. 2021           Total (95% Ct)           Helerogeneity, Tau*s 56           Study or Subgroup           Editoroverall effect           Z           Mewton, N. 2021           Total (95% Ct)           Helerogeneity, Tau*s 56           Deflereos, S 2015           Henenssy, T. 2019           Mewton, N. 2021           Tardif, J. C 2019           Total (95% Ct)           Total (95% Ct)           Total (95% Ct)	0.00, 0.1, 0.1, 0.2, 2         0.00, 0, P         0.03           Z = 0.09, 0, P         0.3         0.1           Colchicine         31         39, Ch7=8.09, 0f=         202           10         23         12         11.1         33         103           40         8.5         8         31         31         32         32           10         2.02 (P = 0.04)         Colchicine         23         13         7.12         111         33         103         408         2330         2644         481         48 <td>3) Control 1 Mean SD 7 4494 963 1 4096 829 0 46 86 8 2 (P=001); P= Control rents Total V 0 21 1 74 6 113 9 92 414 2346 266 - 430</td> <td>Total         We           74         26           160         36           81         32           315         101           76%         9           Weight         M           8.5%         13.1%           23.1%         25.8%           29.5%         100.0%</td> <td>Mean Difference einht IV, Random, 95%; ( 19% 7.001569,103 19% 2.001664,26 0.0% 3.18 [0.10,622] Risk Ratio LH, Random, 95% (1 19.25 [1.20,309.49] 17.30 [2.37,126.33] 2.04 [0.79,5.23] 3.28 [1.66,6.47] 0.99 [0.88,112] 2.99 [1.14,7.82]</td> <td>Favours (colchicine) Favours (contro Mean Difference N. Random, 95% Cl </td> <td>100 11</td> <td>Test for overall effi Study or Subproup Defereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity. Tar Test for overall effic</td> <td>ext Z = 1.54 (P = C Colchicine <u>a</u> Events Tota 15 7 225 233 240 240 P<sup>2</sup> = 2.90, Ch<sup>2</sup> = 6 0, Ch<sup>2</sup> = 6 0, Ch<sup>2</sup> = 6 0, Ch<sup>2</sup> = 6</td> <td>1.12) Control <u>al Events Total</u> 7 1 74 0 208 2346 7 2420 209 53, df = 1 (P = 0.0 .36)</td> <td>Weinlit 42.5% 57.5% 100.0%</td> <td>Risk Ratio <u>M.H. Random, 95%</u> 14.4 2 († 95, 106, 4 109 (109, 113 3.26 (10.26, 41.1 %</td> <td>Favours (colchicine) Favours (control) Risk Radio CI MH, Random, 95% CI 101 101 101 101 101 101 101 Favours (colchicine) Favours (control Favours (colchicine) Favours (control</td> <td>100</td>	3) Control 1 Mean SD 7 4494 963 1 4096 829 0 46 86 8 2 (P=001); P= Control rents Total V 0 21 1 74 6 113 9 92 414 2346 266 - 430	Total         We           74         26           160         36           81         32           315         101           76%         9           Weight         M           8.5%         13.1%           23.1%         25.8%           29.5%         100.0%	Mean Difference einht IV, Random, 95%; ( 19% 7.001569,103 19% 2.001664,26 0.0% 3.18 [0.10,622] Risk Ratio LH, Random, 95% (1 19.25 [1.20,309.49] 17.30 [2.37,126.33] 2.04 [0.79,5.23] 3.28 [1.66,6.47] 0.99 [0.88,112] 2.99 [1.14,7.82]	Favours (colchicine) Favours (contro Mean Difference N. Random, 95% Cl 	100 11	Test for overall effi Study or Subproup Defereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity. Tar Test for overall effic	ext Z = 1.54 (P = C Colchicine <u>a</u> Events Tota 15 7 225 233 240 240 P <sup>2</sup> = 2.90, Ch <sup>2</sup> = 6 0, Ch <sup>2</sup> = 6 0, Ch <sup>2</sup> = 6 0, Ch <sup>2</sup> = 6	1.12) Control <u>al Events Total</u> 7 1 74 0 208 2346 7 2420 209 53, df = 1 (P = 0.0 .36)	Weinlit 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.4 2 († 95, 106, 4 109 (109, 113 3.26 (10.26, 41.1 %	Favours (colchicine) Favours (control) Risk Radio CI MH, Random, 95% CI 101 101 101 101 101 101 101 Favours (colchicine) Favours (control Favours (colchicine) Favours (control	100
Intercogenetic, coline – Test for overall effect           Test for overall effect           Study or Subgroup           Intercogenetic, Flave           Hosseini, S.H. 2022           Mewton, N. 2021           Total (95% CI)           Heterogenetity, Tau*= 5 6           Test for overall effect Z =           Mewton, N. 2011           Study or Subgroup           Extudy or Subgroup           Mewton, N. 2011           Tardif, J. C. 2019           Total (95% CI)           Total events           Heterogenetity, Tau*= 0,           Test for overall effect Z =	0.00, 0.0         (V = 0.0)           Z = 0.09 (P = 0.9)         Colchicina           Mean         SD Tot           51.94         11.11         7           42.27         7.73         16           48         8.5         8           59, Chi <sup>2</sup> = 8.98, df =         2.02 (P = 0.04)           Colchicine         Vents         Total           Vents         Total         EV           10         23         18         77           12         110         23         103           408         2300         2644         481           81; Chi <sup>2</sup> = 25.98, e         22.92 (P = 0.03)         -	3) Control al Mean SD 7 4494 963 1 4096 8.29 0 46 86 8 2 (P = 0 01); P = Control 0 21 1 74 6 113 9 92 414 2346 2646 4 430 df = 4 (P < 0.01)	Total         We           74         26           160         36           81         33           315         100           70%         9           Neight         M           8.5%         13.1%           23.1%         25.8%           29.5%         100.0%           1001); P = 8         8	Mean Difference einth IV, Random, 95%, 1 93% 7 00 [3 68, 10.3 93% 7 00 [3 68, 10.3 93% 2 00 [-0 64, 4 6 0.0% 3.18 [0.10, 6.27 Risk Ratio <u>HH Random, 95% (1</u> 19.25 [1.20, 309 49] 17.30 [2.37, 126 33] 2.04 [0.79, 523] 3.28 [1.66, 64.7] 0.99 [0.88, 1.12] 2.99 [1.14, 7.82] 15%	Favours (colchicine) Favours (contro Mean Difference M. Random, 95% Cl -20 -10 0 10 2 Favours (colchicine) Favours (contro Risk Ratio M.H. Random, 95% Cl -20 -10 0 10 2 Favours (colchicine) Favours (contro Risk Ratio	100 10 10 10 100	Test for overall effi M Study of Submound Deflereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity: Tau Test for overall effo	et Z = 1.54 (P = C Colchicine <u>a</u> Events Tota 15 7 225 233 240 240 P <sup>2</sup> = 290, Ch <sup>2</sup> = 6. ct Z = 0 91 (P = C	Control           al Events Total           7         1           7         1           7         208           208         2346           7         2420           209         53, of =1 (P = 0 (f = 36))           36)         36)	Weight 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.4 2 (195; 106.4 109 (1091, 13 3.26 (10.26, 41.1 %	Favours [colchicine] Favours [control] Favours [colchicine] Favours [control] Risk Ratio CI MH, Random, 95% CI (0] 001 0.1 1 10 Favours [colchicine] Favours [control	100
Intercogenetic, with a test of overall effect           S           Study or Subgroup           Intercogenetic, S2015           Hosseini, S.H. 2022           Mewton, N. 2021           Total (95% CI)           Heterogenetic, Tau*= 5.6           Test for overall effect Z =           Akodad, M. 2017           Defferes, S 2015           Hennessy, T. 2019           Mewton, N. 2021           Tatal (95% CI)           Total events	0.00, 0.0         (0.0, 0.0         (0.0, 0.0)         (0.0, 0.0	3) Control 1 Mean SD 7 44,94 963 1 4096 829 0 46 86 8 2 (P = 0.01); P= Control 0 21 1 74 6 113 9 92 414 2346 2646 430 df= 4 (P < 0.01)	Total         We           74         25           81         33           315         101           78%         315           84         33           78%         315           80         35%           13.1%         23.1%           25.8%         29.5%           100.0%         301); P = 8	Mean Difference eind IV. Random. 95%, 1 93% 7 00 [3 68, 10.3 93% 7 00 [3 68, 10.3 93% 2 00 [-0 64, 4 6 0.0% 3.18 [0.10, 6.27 Risk Ratio <u>HL Random, 95% (1</u> 19.25 [1.20, 309 49] 17.30 [2.37, 126 33] 2.04 [0.79, 523] 3.28 [1 66, 6.47] 0.99 [0 88, 1.12] 2.99 [1.14, 7.82]	Favours (colchicine) Favours (control Mean Difference M. Random, 95% Cl Favours (colchicine) Favours (control Risk Ratio M.H. Random, 95% Cl Favours (colchicine) Favours (control Favours (colchicine) Favours (control Favours (colchicine) Favours (control Favours (colchicine) Favours (control Favours (colchicine) Favours (control)	100 10 10 10 10 100 100	Test for overall effi M Study of Subgroup Deflereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity. Tau Test for overall effe	ext Z = 1.54 (P = C Colchicine <u>a</u> Events Tota 15 7 225 233 240 P <sup>2</sup> = 2.90; Ch <sup>2</sup> = 6. ct Z = 0.91 (P = C	Control           al Events Total           7         1           7         1           7         2346           7         2420           209         53, off=1 (P = 0 (f 3)6)	Weight 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.4 2 (1.95, 106, 4 109 (0.91, 13 3.26 (0.26, 41,1 %	Favours [colchicine] Favours [control] Favours [colchicine] Favours [control] Risk Ratio CI MH, Random, 95% CI 101 101 101 101 Favours [colchicine] Favours [control	100
Testforoverall effect:           Stafforoverall effect:           Stafforoverall effect:           Deflereos, S 2015           Hosseini, S. H. 2022           Mewton, N. 2021           Total (95% CI)           Helerogeneity: Tau <sup>2</sup> 5 (6)           Study or Subgroup:           Isticky or Subgroup:           Isticky or Subgroup:           Study or Subgroup:           Isticky or Subgroup:           Test for overall effect:           Jeffereos, S 2015           Hennessy, T. 2019           Mewton, N. 2021           Total (95% CI)           Test for overall effect Z :	0.00, 0.1 (1 + 1 (1 + 2 2 = 0.09 (P = 0.9) Colchicine Mean SD Totic 51.94 11.11 7 42.27 7.73 16 48 8.5 8 31 39; Ch≠ 8.98, df = 202 (P = 0.04) Colchicine 10 23 20 2 (P = 0.04) Colchicine 10 23 18 77 12 111 33 103 408 2330 2644 481 81; Ch² = 25.98, - 2.23 (P = 0.03)	3) Control 1 Mean SD 7 4494 963 1 4096 829 0 46 86 8 2 (P = 0.01); P= Control 2 (P = 0.01); P= Control 1 74 6 113 9 92 414 2346 2646 - 430 df = 4 (P < 0.01)	Total         We           74         22           160         36           315         101           78%         315           81         33           78%         315           13.1%         23.1%           25.8%         29.5%           100.0%         101); P = 8	Mean Difference           birth         Nr. Random, 95%, 1           98%         7,00 [3,69,103           81%         1,31 [0,04,3.0           90%         2,00 [0,64,46           0.0%         3,18 [0,10,6.27           Risk Ratio           H.H. Random, 95% (T           19,25 [1,20,309,49]           17,30 [2,37,126,33]           2,04 [0,78,5,23]           3,28 [1,66,6,47]           0,99 [0,88,1,12]           2,99 [1,14,7,82]           L5%	Favours (colchicine) Favours (contro Mean Difference M. Random, 95% Cl Favours (colchicine) Favours (contro Risk Ratio M-H, Random, 95% Cl 0.01 0.1 1 10 Favours (colchicine) Favours (contro	100 10 10 10 10 10 100	Test for overall effi Study or Subproug Deflereos, S 2015 Tardif, J. C 2019 Total (95% CI) Total events Heterogeneity: Tau Test for overall effic	ext Z = 1.54 (P = C Colchicine <u>a Events Tota</u> 15 7 225 233 240 P = 290, Ch7 = 6. Ch7 = 6. Ch7 = 6. Ch7 = 6.	Control           al         Events         Total           7         1         74           0         208         2346           7         2420         209           53, df=1         (P = 0.0)           36)         36)	Weinht 42.5% 57.5% 100.0%	Risk Ratio <u>M.H. Random, 95%</u> 14.4 2 (195), 106, 4 109 (0 91, 13 3.26 (0.26, 41.1 %	Favours (colchicine) Favours (control) Favours (colchicine) Favours (control) Risk Ratio CI MH, Random, 95% CI IIII IIIIIIIIIIIIIIIIIIIIIIIIIIIII	100

## 3.8. Sensitivity analyses

The sensitivity analysis indicated no noticeable change in the overall effect of other outcomes by removing any individual study. In concrete regard, sensitivity analysis did not substantially impact the results, as followings, MACE (RR 0.66, 95% CI, 0.45–0.98, P = 0.04;  $I^2 = 0\%$ ), MI (RR 0.46, 95% CI, 0.14–1.52, P = 0.21,  $I^2 = 0\%$ ), CRP (MD -0.21, 95% CI, -1.01- 0.59, P = 0.61;  $I^2 = 86\%$ ) via eliminating COLCOT (**31**). Except GI adverse events showed a noticeably higher incidence (RR 4.14, 95% CI, 1.70–10.06, P = 0.002;  $I^2 = 49\%$ ) and neutrophils showed lower levels (SMD -0.22, 95% CI, -0.39- -0.55, P = 0.01;  $I^2 = 0\%$ ). Our meta-analysis exhibited high heterogeneity

and subgroup differences among CRP, LVEF, and GI adverse events ( $I^2 \ge 78\%$ ). Funnel plot analysis revealed symmetry (shown in Figure 7).

# 4. Discussion

### 4.1. Total effect of colchicine

The present analysis suggested that colchicine in patients with AMI reduced the risk of MACE by 0.56 times, accompanied by 2.99 times higher gastrointestinal risk. Subgroup analysis revealed that colchicine decreased the follow-up levels of CRP (MD

Study or Subgroup	Colchicine Events Total	Control Events Total V	Veight M-I	Risk Ratio 1, Fixed, 95% Cl	Risk M.H. Fixe	Ratio id, 95% Cl	Study or Subgroup	Colchicine Events Tota	Control <u>Events Total</u>	Weight_M-I	Kisk Ratio H, Fixed, 95% Cl	M-H.	usk Ratio Fixed, 95% Cl	
0.5 mg			0.70				< 1 year			0.07				
Hennessy, 1. 2019 Hosseini, S. H. 2022	22 161	30 160	8.6%	0.73 [0.44, 1.21]	·	-	Hennessy, T. 2019	0 111	3 2 21	0.7%	0.20 (0.01, 4.19)			
Tardif, J. C 2019	162 2366	297 2379	84.4%	0.55 [0.46, 0.66]			Mewton, N. 2021	13 10	1 19 91	5.7%	D.62 [0.32, 1.18]	-	-	
Subtotal (95% CI)	2638	2652	93.7% 0	.56 [0.47, 0.67]	•		Subtotal (95% CI)	235	5 225	7.0% 0	0.56 [0.31, 1.03]			
Heterogeneity: Chi <sup>2</sup> = 1	.52, df = 2 (P = 0.4	7); I <sup>#</sup> = 0%					Heterogeneity: Chi <sup>2</sup> =	0.54, df = 2 (P =	0.76); I <sup>2</sup> = 0%					
Test for overall effect Z	= 6.58 (P < 0.000	01)					Test for overall effect	Z = 1.86 (P = 0.0	16)					
1 mg							≥ 1 year							
Akodad, M 2017	1 23	2 21	0.6%	0.46 [0.04, 4.69]			Hosseini, S. H. 2022	22 16	1 30 160	8.6%	0.73 (0.44, 1.21)		-	
Subtotal (95% CI)	124	112	6.3% 0	.60 [0.32, 1.12]	•	-	Subtotal (95% CI)	162 2360	7 2539	93.0% (	0.55 [0.46, 0.66]		•	
Total events	14	21					Total events	184	327					
Test for overall effect 2	.06, df = 1 (P = 0.8 = 1.60 (P = 0.11)	1); 1*= 0%					Heterogeneity: Chi <sup>a</sup> = Test for overall effect	1.08, df = 1 (P = Z = 6.51 (P < 0.0	0.30); I <sup>2</sup> = 7% (0001)					
T-I-LOCK CD	2762	2764	00.01/ 0	5610 10 0 671					,					
Total events	198	350	100.0% 0	1.50 [0.48, 0.67]	•		Total (95% CI) Total events	198	2 2764	100.0% 0	0.56 [0.48, 0.67]		•	
Heterogeneity: Chi? = 1	.62, df = 4 (P = 0.8	1); F = 0%			0.01 0.1	1 10 1	00 Heterogeneity: Chi <sup>2</sup> =	1.62, df = 4 (P =	0.81); I <sup>2</sup> = 0%		E C	01 01	1 10	100
Test for overall effect 2 Test for subgroup diffe	:= 6.77 (P < 0.000 rences: Chi <sup>2</sup> = 0.0	01) 4. df=1 (P=0.84	4) I <sup>a</sup> = 0%		Favours (colchicine)	Favours [control]	Test for overall effect	Z = 6.77 (P < 0.0)	10001)	00) 8-00	0.	Favours [colchic	ien] Favours (control	1)
_								erences. on = c	5.00. di = 1 ti = 0	30).1 = 0.0				
C							D							
Study or Subaroup Mr	Colchicine Ian SD Total	Control Mean SD Te	tal Weight	Mean Difference	Mear CI M. Rar	Difference Idom, 95% Cl	Study of Subgroup	Colchicine Mean SD T	Control otal Mean SD	Total Weight	Mean Difference IV, Random, 95% (	a N.	Random, 95% CI	
0.5 mg	05 2.07		11 20.0~	0.371.0.05.0	211		5 days Akodad, M 2017	29.03 25.58	23 21.06 25.39	21 0.3%	7.17 [-7.90, 22.2	41		
Hennessy, T. 2019 1 Hosseini, S. H. 2022 17	.95 2.07 111 6.5 200.59 161	2.32 2.3 1 244.5 284.44 1	11 36.6% 60 0.1%	-0.37 [-0.95, 0 -68.00 [-121.88, -14	12	1	Deflereos, S 2015 Hosseini, S. H. 2022	43.57 20.82 176.5 200.59	77 67.5 50.89 161 244.5 284.44	71 0.4%	-23.93 [-36.65, -11.2 -68.00 [-121.88, -14.1]	2]		
Tardif, J. C 2019 1 Wasyanto 2019 3	37 1.02 99	1.6 1.3 1	08 38.7%	-0.23 (-0.55, 0	.09]	1-	Mewton, N. 2021 Wasyanto 2018	15.7 23.11 3.82 2.2	103 23.6 26 16 0.57 3.12	92 1.3% 16 11.5%	-7.90 (-14.84, -0.9) 3.25 (1.38, 5.1)	6] 2]	+	
Subtotal (95% CI)	387	3	95 96.3%	0.39 [-0.78, 1	57]	•	Subtotal (95% CI) Heterogeneity: Tau <sup>*</sup> =	126.13; Chi# = 32.44	380 4, df = 4 (P < 0 00001)	360 13.5% P=00%	-7.69 [-19.50, 4.1	1		
Heterogeneity: Tau <sup>#</sup> = 0.84; Test for overall effect Z = 0	Chi <sup>a</sup> = 19.51, df = 3 66 (P = 0.51)	P = 0.0002); P = 85	96				Test for overall effect.	2 = 1.28 (P = 0.20)						
1 mg							30 dyas Oholoobi, A 2021	3.10 0.52	75 3.93 0.61	75 30.4%	-0 75 [-0.93, -0 5]	η	-	
Akodad, M 2017 29	03 25 56 23	21.86 25.39	21 0.7%	7.17 - 7.90, 22	.24]	_	Hennessy, T. 2019 Subtotal (95% CI)	1.95 2.07	111 2.32 2.3 186	111 26.6% 106 57.0%	-0.37 [-0.95, 0.2 -0.66 [-0.98, -0.35	1] 5 <b>]</b>	1	
Subtotal (95% CI)	126	23.0 20	13 3.7%	-1.91 [-16.36, 12	54		Holorogeneity: Tau* = Test for overall effect	0.02, Chi* = 1.52, df = 4.13 (P < 0.0001)	= 1 (P = 0.22), P = 34 )	6				
Heterogeneity: Tau* = 77.7: Test for overall effect Z = 0.	3, Chi# = 3.17, df = 1 26 (P = 0.80)	P = 0.07), P = 68%					> 1 year							
Total (05% Ch	513	6	08 100 0%	0 231 102 1	401	•	Tardif, J. C 2019 Subtotal (95% CI)	1.37 1.02	99 16 1.3 99	108 29.4% 108 29.4%	-0 23 [-0 55, 0 0 -0.23 [-0.55, 0.05	a) 9)	1	
Heterogeneity: Tau <sup>a</sup> = 1.02;	Chi# = 25.17, df = 5	P = 0.0001); I# = 80	%	0.25111.02, 1	.20 .10	0 10 20	Heterogeneity: Not ap Test for overall effect.	dicable = 1.42 (P = 0.15)						
Test for overall effect Z = 0 Test for subgroup difference	37 (P = 0.71) es: ChP = 0.10. df =	(P = 0.76), P = 0%			Favours (experiment	al) Favours (control)	Total (95% CI)		665	654 100.0%	-0.21 (-1.01, 0.59	91	•	
							Heterogeneity: Tau* = Test for overall effect	0.54; Chi <sup>a</sup> = 48.92, d = 0.51 (P = 0.61)	ff = 7 (P ≺ 0 00001); P	= 86%		-20	10 0 10 20	
_							Test for subaroup dif	rences: Chi# = 5.05	df = 2 (P = 0.08) (P =	60.4%		Favours (orportio	nental Pavours (control)	
E	Colchicine	Control	R	isk Ratio	Risk R	atio	F	Colchicine	Control	Risk	Ratio	Risk Ra	tio	
Study or Subgroup	Events Total Ev	ents Total Wei	ight M-H, R	andom, 95% CI	M-H, Randor	n, 95% Cl	Study or Subgroup 5 days	Events Total	Events Total We	ight M-H, Bar	idom, 95% Cl	M-H, Random	. 95% CI	-
1 mg Akodad M 2017	10 23	0 21 8	2% 19.2	5 [1 20 309 49]			Deflereos, S 2015	18 77	1 74 13	1% 17.30	2 37, 126 33			
Mewton, N. 2021	33 103	9 92 30	0%	3.28 [1.66, 6.47]			Subtotal (95% CI)	180	166 3	.9% 5.89	[1.14, 30.52]	-		
Subtotal (95% CI) Total events	43	9 113 38	.2% 4.1	38 [1.07, 22.22]			Heterogeneity: Tau	51 = 0.97; Chi <sup>2</sup> = 2.68	, df = 1 (P = 0.10); l <sup>a</sup>	= 63%				
Heterogeneity: Tau <sup>a</sup> = 0	0.65; Chi <sup>2</sup> = 1.61, d	= 1 (P = 0.20); P	= 38%				Test for overall effe	t Z = 2.11 (P = 0.0)	3)					
rescior overall effect: 2	.= 2.05 (P = 0.04)						30 days Akodad, M 2017	10 23	0 21 F	5% 19.251	1 20, 309 49			
0.5 mg	12 111	6 110 00	000	0410 70 6 22		_	Hennessy, T. 2019 Subtotal (95% CD	12 111	6 113 23	1% 2.0	4 [0 79, 5 23]	-	•	
Tardif, J. C 2019	408 2330	414 2346 35.	.9% . .9% (	2.04 [0.79, 5.23]	•		Total events	22	6		[0.40, 45.04]			
Subtotal (95% CI)	2441	2459 61	.8% 1	.21 [0.64, 2.28]	-		Test for overall effe	= 1.85, Chi* = 2.85 t Z = 1.29 (P = 0.2)	, df = 1 (P = 0.10), P 0)	= 62%				
Heterogeneity: Tau <sup>2</sup> = 0	=20 0.14; Chi² = 2.19, d	= 1 (P = 0.14); P	= 54%				> 1 year							
Test for overall effect: 2	= 0.60 (P = 0.55)						Tardif, J. C 2019 Subtotal (95% CI)	408 2330 2330	414 2346 29 2346 29	.5% 0.9	9 (0.88, 1.12) 9 (0.88, 1.12)	1		
Total (95% CI)	2567	2572 100	.0% 2	.18 [0.88, 5.39]	+	•	Total events Heterogeneity Not	408 pplicable	414					
Total events Heterogeneity: Tau <sup>2</sup> = 0	463 0.59; Chi <sup>2</sup> = 17.83.	429 If = 3 (P = 0.0005	); I <sup>2</sup> = 83%	E.			Test for overall effe	t Z = 0.12 (P = 0.90	0)					
Test for overall effect: Z	= 1.69 (P = 0.09)	df= 1 /P = 0.17	R- 60.70	C	Favours [colchicine]	10 100 Favours (control)	Total (95% CI)	2644	2646 10	.0% 2.9	9 [1.14, 7.82]	-	•	
restfor subaroup diffe	rencês: Chir = 2.76	. or = 1 (P = 0.10)	. 1= 63.7%				Total events Heterogeneity: Tau	481 = 0.81; Chi <sup>a</sup> = 25.9	430 8, df = 4 (P < 0.000	), I*= 85%	0.01	01	10 100	
							Test for overall effe Test for suborouo o	t Z = 2.23 (P = 0.0) ferences: Chi <sup>a</sup> = 6	3) 13. df = 2 (P = 0.05	. I* = 67.4%	F	avours (colchicine) Fi	avours (control)	
4														

-0.66, 95% CI, -0.98- -0.35) and neutrophils (SMD -0.22, 95% CI, -0.39- -0.55) when the follow-up period was 30 days. Compared with other usages, early ( $\leq 3$  days) long-term ( $\geq 1$ year) low-dosage (0.5 mg/d) use of colchicine was more effective in reducing the risk of MACE (RR 0.57, 95% CI, 0.48-0.67) without causing more GI adverse events in AMI patients. Cardiovascular events after AMI are still common (32). Colchicine may contribute to changing the clincial status and enhancing the quality of life of AMI patients.

### 4.2. Analysis of the cardiovascular effect

An acute pro-inflammatory response is induced by the ischemia due to myocardial cell injury and death after AMI (33). Following AMI, the co-ordinated effect of activation of the complement cascade and NLRP inflammasomes, production of reactive oxygen species (ROS) et.al. release multiple pro-inflammatory mediators to induce the recruitment of inflammatory cells into the area of infarct, extending the ischemic injury (33).

Sensitive to ischemic and hypoxic injury, mitochondria can sensitively reflect cardiac cell injury and is closely correlated with the severity of myocardial injury in post-AMI (34). Zhang et al. found that oxidatively damaged mitochondria activate large numbers of NLRP3 inflammasomes in rats (34). Toldo et al. discovered that pharmacological inhibition of the NLRP3 inflammasome limits infarct size after AMI in mice, even within 60 min after myocardial ischemia-reperfusion (35).

Persistent and expanded pro-inflammatory response may exacerbate adverse left ventricle remodelling after AMI (33). Koichiro et al. showed that colchicine significantly improved survival, left ventricular end-diastolic diameter and LVEF at 4 weeks after MI in mice via attenuating the expression of proinflammatory cytokines and NLRP3 inflammasome, and inhibiting neutrophil and macrophage infiltration (36). Yan et al. (37) showed that activation of the NLRP3 inflammasome led to up-regulation of CRP levels, whereas blockade led to downregulation. So colchicine may ameliorate inflammation and improve cardiovascular outcomes via the NLRP3/CRP pathway (37). Notably, CRP can predict cardiovascular risk independent

	Colchie	line	Conti	01		RISK Ratio	RISK Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
$\leq$ 3 days							
Akodad, M 2017	1	23	2	21	0.8%	0.46 [0.04, 4.68]	
Hennessy, T. 2019	0	111	2	113	0.9%	0.20 [0.01, 4.19]	
Hosseini, S. H. 2022	22	161	30	160	11.4%	0.73 [0.44, 1.21]	
Mev/ton, N. 2021	13	101	19	91	7.6%	0.62 [0.32, 1.18]	
Tardif, J. C 2019	30	597	57	586	21.8%	0.52 [0.34, 0.79]	
Subtotal (95% CI)		993		971	42.4%	0.58 [0.44, 0.78]	•
Total events	66		110				
Heterogeneity: Chi# = 1	1.59, df = 4	(P = 0)	.81); I= =	0%			
Test for overall effect 2	Z = 3.68 (P	9 = 0.00	02)				
Zardif L C 2010	122	1775	150	1722	57 60	0.01 10 64 1 021	
Subtotal (05% CI)	125	1735	152	1733	57.6%	0.81 [0.64, 1.02]	
Total events	122	1755	150	1755	57.0 %	0.01[0.04, 1.02]	•
Hotorogonoity: Not an	licoblo		152				
Test for overall effect 2	Z = 1.83 (P	9 = 0.07	)				
Total (95% CI)		2728		2704	100.0%	0.71 [0.60, 0.85]	•
Total events	189		262				
Heterogeneity: Chi <sup>2</sup> = 4	1.35, df = 5	5(P = 0	.50); <b>I</b> <sup>2</sup> =	0%			
Test for overall effect 2	Z = 3.73 (P	9 = 0.00	02)				Eavours (colobicing) Eavours (control)
Test for subaroup diffe	rences: C	hi <sup>2</sup> = 3.	04. df = 1	(P = 0)	.08). I <sup>2</sup> = 6	i7.1%	

	Co	Ichicine			Control			Mean	Difference	9				Mean Diffe	erence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, R	andom, 95	5% CI				IV, Random	, 95% Cl
Akodad, M 2017	29.03	25.56	23	21.86	25.39	21	0.3%	7.1	7 [-7.90, 23	2.24]			_		
Deftereos, S 2015	43.57	20.82	77	67.5	50.89	71	0.4%	-23.93	[-36.65, -1]	1.21]	←				
Gholoobi, A. 2021	3.18	0.52	75	3.93	0.61	75	30.4%	-0.7	'5 <b>(</b> -0.93, -I	0.57]				-	
Hennessy, T. 2019	1.95	2.07	111	2.32	2.3	111	26.6%	-0.	37 [-0.95, 1	0.21]				-	
Hosseini, S. H. 2022	176.5	200.59	161	244.5	284.44	160	0.0%	-68.00 [-	121.88, -14	4.12]	←				
Mewton, N. 2021	15.7	23.11	103	23.6	26	92	1.3%	-7.90	) [-14.84, -1	0.96]	-	_			
Fardif, J. C 2019	1.37	1.02	99	1.6	1.3	108	29.4%	-0.	23 [-0.55, 1	0.09]					
Wasyanto 2018	3.82	2.2	16	0.57	3.12	16	11.5%	3	.25 [1.38, 9	5.12]					
(otal (95% Cl)			665			654	100.0%	-0.3	21 [-1.01. 0	0.591				•	
	,	,									1	avou	rs (ec	olchicinej F	- avours (control)
B Colchicine	Control	Std.	Mean Difference	e	Std. Mean E	ifference		<b>C</b>	Colchicine	•	Contro		5	Std. Mean Difference	Std. Mean Difference
B Colchicine <u>tudy or Subgroup Mean SD Total I</u>	Control <u>Mean SD To</u>	Std. t <u>al Weight</u>	Mean Differenc IV, Fixed, 95%	e Cl	Std. Mean D	ifference 95% Cl		C udy or Subgroup	Colchicine Mean SD	Total	Contro Mean	I <u>SD Total</u>	Weight	Std. Mean Difference IV, Fixed, 95% Cl	Std. Mean Difference IV, Fixed, 95% Cl
B Colchicine tudy or Subgroup Mean SD Total 1 iholoobi, A. 2021 8,843 1,935 75 8	Control <u>Mean SD Tol</u> 8,764 1,847	Std. I <u>al Weight</u> 75 6.4%	Mean Differenc <u>IV, Fixed, 95%</u> 0.04 (-0.28, 0.	e <u>CI</u> 36]	Std. Mean D IV, Fixed,	ifference 95% Cl	<u>s</u>	<b>udy or Subgroup</b> effereos, S 2015	Colchicine <u>Mean</u> <u>SD</u> 8,100.35 2,643.7	<b>Total</b> 77 9	Contro <u>Mean</u> 9,042.99 1,79	1 <u>SD Total</u> 7.8 71	5.8%	Std. Mean Difference <u>IV, Fixed, 95% C1</u> -0.41 (-0.74, -0.09) 0.431 (-0.40, 0.00)	Std. Mean Difference N. Fixed, 95% Cl
Colchicine           tudy or Subgroup         Mean         SD         Total         I           iholoobi, A 2021         8,843         1,935         75         8           lennessy, T. 2019         7.09         2.15         111	Control <u>Mean SD Tol</u> 8,764 1,847 7.38 2 1	<b>Std.</b> I <u>al Weight</u> 75 6.4% 11 9.5%	Mean Difference <u>IV, Fixed, 95%</u> 0.04 (-0.28, 0. -0.14 (-0.40, 0.	e CI 36] 12]	Std. Mean D IV, Fixed,	ifference 95% Cl	<u>\$</u>  	<b>udy or Subgroup</b> effereos, S 2015 toloobi, A 2021	Colchicine <u>Mean</u> <u>SD</u> 8,100.35 2,643.7 4,763 736 4,270 4,000	Total 77 9 75	Contro <u>Mean</u> 9,042.99 1,79 4,865	<b>SD Total</b> 7.8 71 956 75	S Weight 5.8% 6.0%	Std. Mean Difference N, Fixed, 95% C1 -0.41 (-0.74, -0.09) -0.12 (-0.44, 0.20) 0.454 (-0.40, 0.10)	Std. Mean Difference N. Fixed, 95% Cl
B         Colchicine           tudy or Subgroup         Mean         SD         Total 1           iholoobi, A 2021         8,843         1,935         75         6           lennessy, T. 2019         7.09         2.15         111         andr. J. C. 2019         6.95         1.71         192	Control Mean <u>SD Tol</u> 8,764 1,847 7.38 2 1 7.03 1.87 9	<b>Std.</b> Ial Weight 75 6.4% 11 9.5% 80 84.1%	Mean Difference IV. Fixed, 95% 0.04 (-0.28, 0.1 -0.14 (-0.40, 0.1 -0.04 (-0.13, 0.1	e Cl 36] 12] D4]	Std. Mean ( IV, Fixed, 	ifference <u>95% Cl</u> –	<b>S</b> D G H T	<b>udy or Subgroup</b> effereos, S 2015 toloobi, A. 2021 ennessy, T. 2019 trdif, J. C. 2019	Kolchicine           Mean         SD           8,100.35         2,643.7           4,763         736           4,370         1,480           3,950         1,340	<b>Total</b> 77 9 75 111 992	Contro <u>Mean</u> 9,042.99 1,79 4,865 4,620 1, 3,990 1,	1 <u>SD Total</u> 7.8 71 956 75 560 111 380 980	<b>Weight</b> 5.8% 6.0% 8.9% 79.3%	Std. Mean Difference N. Fixed, 95% Cl -0.41 [+0.74, -0.09] -0.12 [+0.44, 0.20] -0.16 [+0.43, 0.10] -0.03 [+0.12, 0.06]	Std. Mean Difference N. Fixed, 95% Cl
B Colchicine tudy or Subgroup Mean SD Total 1 holoobi, A 2021 8,843 1,935 75 6 enerssy, T. 2019 7.09 2.15 111 antif, J. C. 2019 6.95 1.71 992 oral (95% CI) 1178	Control Mean <u>SD Tol</u> 8,764 1,847 7.38 2 1 7.03 1.87 9 <b>11</b>	<b>Std.</b> 1al <u>Weight</u> 75 6.4% 11 9.5% 80 84.1% 66 <b>100.0</b> %	Mean Difference <u>IV. Fixed, 95%</u> 0.04 (-0.28, 0. -0.14 (-0.40, 0) -0.04 (-0.13, 0.) -0.05 (-0.13, 0.)	ie <u>Cl</u> 36] 12] 04]	Std. Mean I	ifference 95% Cl -	S D G H T T	ctudy or <u>Subgroup</u> effereos, S 2015 noloobi, A 2021 ennessy, T. 2019 rrdif, J. C 2019 <b>fal (95% Cl)</b>	Kolchicine           Mean         SD           8,100.35         2,643.7           4,763         736           4,370         1,480           3,950         1,340	Total 77 9 75 111 992 1255	Contro <u>Mean</u> 9,042.99 1,79 4,865 4,620 1, 3,990 1,	I <u>SD Total</u> 7.8 71 956 75 956 75 956 111 960 960 <b>1237</b>	5.8% 5.8% 6.0% 8.9% 79.3%	Std. Mean Difference N, Fixed, 95% C1 -0.41 [-0.74, -0.09] -0.12 [-0.44, 0.20] -0.16 [-0.43, 0.10] -0.03 [-0.12, 0.06] -0.07 [-0.15, 0.01]	Std. Mean Difference <u>N. Fixed</u> , 95% Cl
B Colchicine tauty or Subgroup Mean SD Total I http://sholodol.A.2021 8,843 1,935 75 6 enressy, T.2019 709 215 111 antif, J. C.2019 6,95 1,71 992 otal (95% CI) 1178 eleterogeneity. Chit™= 0.77, df = 2 (P = 0.66),P	Control Mean <u>SD Tol</u> 8,764 1,847 7.38 2 1 7.03 1.87 9 11/ *= 0%	<b>Std.</b> 14 <u>Weight</u> 75 6.4% 11 9.5% 80 84.1% 66 100.0%	Mean Difference <u>IV. Fixed, 95%</u> 0.04 (-0.28, 0.: -0.14 (-0.40, 0.: -0.04 (-0.13, 0.) -0.05 (-0.13, 0.)	e <u>CI</u> 36] [2] [4] [3]	Std. Mean I	ifference 95% Cl -	<u>s</u> D G H Т Т Т Н Н Н Н Н	C stereos, S 2015 toloobi, A 2021 toloobi, A 2021 tol	Colchicine           Mean         SD           8,100.35         2,643.7           4,763         736           4,370         1,460           3,950         1,340           5,61, df = 3 (P = 0.1)         2	Total 77 9 75 111 992 1255 3); F = 47	Contro <u>Mean</u> 9,042.99 1,79 4,865 4,620 1, 3,990 1,	<b>SD Total</b> 7.8 71 956 75 960 111 980 990 <b>1237</b>	5.8% 5.8% 6.0% 8.9% 79.3% 100.0%	Std. Mean Difference N. Fixed, 95% C1 -0.41 [+0.74, -0.09] -0.12 [+0.44, 0.20] -0.16 [+0.43, 0.10] -0.03 [+0.12, 0.06] -0.07 [-0.15, 0.01]	Std. Mean Difference M. Fixed, 95% CI
B         Colchicine           Rudy or Subgroup         Mean         SD         Total         1           fnoloodi, A. 2021         8,843         1,935         75         6           lennessy, T. 2019         7.09         2,15         111         andi, J. 2019         6,95         1,71         992           otal (95% CI)         1178         elerogeneity: Chi*= 0.77, df = 2 (P = 0.86); P. estfor overall effect Z = 1.16 (P = 0.24)         estfor overall effect Z = 1.16 (P = 0.24)	Control Mean <u>SD Tol</u> 8,764 1,847 7.38 2 1 7.03 1.87 9 11 '= 0%	Std. 1al Weight 75 6.4% 11 9.5% 80 84.1% 66 100.0%	Mean Difference <u>N. Fixed, 95%</u> 0.04   0.28, 0: -0.14   0.40, 0: -0.04   0.13, 01 -0.05 [-0.13, 0.1	e <u>C1</u> 12] 14] 13] Fav	Std. Mean I N. Fixed 	ifference 95% CI - 1 2 Favours [control	0 G G H T T O I T	C affereos, S 2015 noloobi, A 2021 annessy, T. 2019 rdif, J. C 2019 tal (95% CI) sterogeneity. Chi <sup>2</sup> = st for overall effect	Colchicine           Mean         SD           8,100.35         2,643.7           4,763         736           4,370         1,460           3,950         1,340           5.61, df = 3 (P = 0.1)         2           Z = 1.72 (P = 0.09)	<u>Total</u> 77 9 111 992 <b>1255</b> 3); <b>F</b> = 47	Contro Mean 3,042.99 1,75 4,865 1 4,620 1, 3,990 1, %	SD Total 7.8 71 956 75 950 111 980 990 1237	5.8% 6.0% 8.9% 79.3% 100.0%	Std. Mean Difference N. Fixed, 95% CI -0.41 [+0.74, -0.09] -0.12 [+0.44, 0.20] -0.16 [+0.43, 0.20] -0.03 [+0.12, 0.06] -0.03 [+0.15, 0.01]	Std. Mean Difference N. Fixed, 95% C1 
B         Colchicine           Rudy or Subgroup         Mean         SD         Total I           Wholoodi, A. 2021         8,843         1,935         75         6           Jernessy, T. 2019         7.09         2.15         111         ardif, J. C. 2019         6.95         1.71         992           ardal (95% CI)         1178         1178         estfor overall effect Z = 1.16 (P = 0.24)         estfor overall effect Z = 1.16 (P = 0.24)         5	Control Mean <u>SD Tol</u> 8,764 1,847 7.38 2 1 7.03 1.87 9 10 10 10	Std. 14 Weight 15 6.4% 11 9.5% 80 84.1% 66 100.0%	Mean Differenc IV. Fixed, 95% 0.04 (-0.28, 0): -0.14 (-0.40, 0): -0.04 (-0.13, 0) -0.05 (-0.13, 0)	e <u>C1</u> 36) 22] 34] 33] ——————————————————————————————	Std. Mean I N, Fixed, 	ifference 95% Cl - - 1 2 Favours (contr	<b>S</b> C G H T T H H H H U	Cudy or Subgroup thereas, S 2015 inloabil, A 2021 ennessy, T. 2019 rrdif, J. C 2019 tal (95% CI) terogeneity: Chi <sup>2</sup> = st for overall effect	Colchicine           Mean         SD           8,100.35         2,643.7           4,763         736           4,370         1,480           3,950         1,340           5,61, df = 3 (P = 0.1)         2 = 1.72 (P = 0.09)	Total 77 9 75 111 992 <b>1255</b> 3); F = 47	Contro Mean 3,042.99 1,759 4,865 4,620 1, 3,990 1, %	SD Total 7.8 71 956 75 560 111 360 980 1237	5.8% 5.8% 6.0% 8.9% 79.3%	Std. Mean Difference N. Fixed, 95% C1 -0.11 [-0.74,-0.09] -0.12 [-0.44, 0.10] -0.16 [-0.43, 0.10] -0.03 [-0.15, 0.01]	Std. Mean Difference M. Fixed, 95% Cl 

of other risk factors (4). This study observed that colchicine rapidly reduced neutrophils and CRP levels at the first month, suggesting a potential association with a later reduction in MACE.

Post-AMI cardiac healing is a complex process, initiated by intense inflammation lasting about 5 to 7 days, followed by resolution and repair with active resolution of inflammation, and finally entering the proliferation phase (4). CRP is a direct acute phase reactant of AMI (38). In post-AMI, neutrophils migrate into the injured myocardium and have a tendency to target the border zone of the infarct, an accumulation that is accentuated by reperfusion. With resolution of inflammation and myocardial repair, neutrophils undergo apoptosis and are subsequently eliminated from the infarct zone (33). We considered the reason why colchicine could not reduce levels of CRP and neutrophils in the first year after AMI can be explained by the fact that the anti-inflammatory effect of colchicine may gradually fail to reach



statistical significance with decreasing levels of inflammation in the late-stage cardiac repair. Indeed, late-stage cardiac remodeling results from the incomplete or damaged resolution of myocardial inflammation, accompanied by a greater degree of damage after AMI and amplified over time (4).

Atherosclerosis is a continuous inflammatory disorder within the arterial wall (3, 38). The persistence of lipid accumulation and vascular endothelium injury within coronary arteries and massive cardiomyocyte death, repair of inflammatory cells after AMI lead to ongoing inflammation (3, 4, 38). Disproportionate prolonged, excessive, or inadequate suppression of the inflammatory phase result in persistent tissue damage and improper repair, defective scar formation, increased cell loss, and systolic dysfunction, thereby promoting infarct enlargement, maladaptive remodeling, and ventricular dilation (4). Hence, timely, appropriate, and sufficiently lengthy long-term anti-inflammatory therapy has the potential to improve the prognosis of AMI.

Long-term treatment with colchicine has shown promise in reducing the risk of MACE, primarily by decreasing the incidence of UA and improving LVEF. Colchicine may interfere with neutrophil-platelet interactions for anti-thrombosis (6, 14, 39). Long-term colchicine treatment reduces plaque instability, particularly in low-intensity plaque volumes (6, 28). However, COVERT-MI reported an unexpected three-fold increase in the incidence of left ventricular thrombosis, possibly due to a proinflammatory rebound upon early cessation of colchicine therapy, leading to increase left ventricular injury and subsequent thrombosis (30). Additionally, LVEF showed prognostic value in predicting MACEs (40). Colchicine inhibition of post-AMI neutrophils extracellular traps may improve LVEF, attenuated ventricular remodeling, and enhance cardiac function (21, 41).

Our study aligned with a recent meta-analysis that low-dose colchicine decreased the risk of MACE, whereas 1 mg did not (14). Activated neutrophils may transform stable plaques into unstable ones (6). Interestingly, colchicine, highly concentrated in leukocytes, especially neutrophils, binds tubulin to inhibit neutrophil chemotaxis and recruitment (39). Additionally, inflammation facilitate appropriate changes in may cardioprotection (42). Early complete suppression of inflammation may result in the enlargement of the final MI size (42). Therefore, early administration of high-dose colchicine did not reduce myocardial injury and resulted in inflammation compared to the controls. Nevertheless, an excessive early inflammatory response or prolongation is also detrimental to cardiomyocyte repair (42).

Our analysis indicated that the early administration of lowdose colchicine significantly reduced the risk of MACE within the first three days after the incidence of AMI, compared to that between days 4 and 30. A current study observed that colchicine had achieved an 80% reduction in the incidence of MI in CAD settings (16). It suggests that early intervention with colchicine is beneficial for improving cardiovascular outcomes before inflammatory flare-ups cause MI.

The meta-Analyses of Diaz-Arocutipa et al. reported that subgroup analyses of colchicine's dose, follow-up duration, and treatment duration did not show a statistical difference (15). In contrast, our study included more trials (29, 30) with patients with MI occurring within 12 h and completely excluded UA patients. Moreover, the COPS trial included in the previous meta-analysis used colchicine 0.5 mg twice per day and then a dose of 0.5 mg daily for 11 months (21). Early use of high doses may delay the therapeutic time window, resulting in lower-thanexpected results. In the studied population, the rate of all-cause mortality was 1.78%, with cardiovascular deaths accounting for about half of the total causes. Our findings support previous studies on colchicine for coronary artery disease, showing no differences in all-cause mortality and cardiovascular mortality (6, 39).

## 4.3. Analysis of the adverse effect

As expected, the adverse effects of colchicine were mainly due to gastrointestinal symptoms (e.g., diarrhea and nausea), with rare adverse effects such as infection. Patients who cannot tolerate colchicine may discontinue the drug early because of more intense gastrointestinal reactions, even at low daily dosages, leading to higher-than-expected occurrences of MACE. However, 90% of the patients who did not develop early treatment intolerance were administered colchicine for long periods without notable long-term side effects (39, 43), resulting in lower occurrences of MACE. Additionally, long-term colchicine (0.5 mg) administration is difficult beyond safe serum levels despite moderate renal impairment or co-use with most medications. However, oral loading with 1–2 mg of colchicine quickly exceeds safe serum levels and may be fatal (39).

# 4.4. High heterogeneity among CRP, LVEF, and GI adverse events

Our study showed high heterogeneity among CRP, LVEF, and GI adverse events. We conducted analysis to explore the reasons behind this high heterogeneity.

#### 4.4.1. CRP

Colchicine administration for different lengths of time resulted in different anti-inflammatory effects during different stages of post-infarction healing. Due to being at the peak of postinfarction inflammation, the inhibition of inflammation with 5 days of colchicine use did not reach statistical significance. With 30 days of colchicine use, colchicine effectively reduced CRP levels during the resolution and repair stage. The lack of reduction in CRP levels during the first year after AMI can be attributed to the fact that the anti-inflammatory effect of colchicine may gradually fail to reach statistical significance with decreasing levels of inflammation in the late-stage cardiac repair.

#### 4.4.2. LVEF

Proper modulation of inflammation may facilitate cardioprotection (39). Early complete suppression of inflammation may result in an enlargement of the final MI size (39). Studies by Hosseini et al. 2022 and Mewton et al. 2021 were orally overloaded with colchicine. Early administration of high-dose colchicine did not reduce myocardial injury. On the contrary, it might result in inflammation and enlarged final MI size, thereby diminishing the optimal effect of colchicine in boosting LVEF.

#### 4.4.3. GI adverse events

Most participants in studies by Akodad et al. 2017 and Mewton et al. 2021, as well as Deftereos et al. 2015 received a daily oral dose of 1 mg of colchicine. The participants in Akodad et al. 2017 and Deftereos et al. 2015 had more missed visits. It was observed that the participants in Akodad et al. 2017 and Deftereos et al. 2015. On the other hand, patients taking 1 mg of colchicine daily experienced more GI adverse events than those taking 0.5 mg daily. Discontinued the colchicine due to more intense gastrointestinal reactions resulted in lower-than-expected results.

To sum up, combined with the results of the subgroup analysis, we concluded that the high heterogeneity among CRP, LVEF, and gastrointestinal adverse events had few impact on the final conclusion.

### 4.5. Research limitations and prospects

Our meta-analysis has several limitations: (1) The participants of studies existed heterogeneity with regards to the type and severity of diseases (NSTEMI and STEMI), colchicine duration, daily dosage, and loading dose. These factors can lead to misleading conclusions. However, we performed a subgroup analysis consistent with the leading results. (2) Different methodological qualities between open and double-blinded studies likely influence the reliability of results. (3) Since the present study was retrospective, the absence of CRP and neutrophil data in some of the cinical trials may induce bias in the results.

# 5. Conclusion

Our meta-analysis finds that colchicine can decrease the risk of MACE, including UA and LVEF, via anti-inflammation. Furthermore, colchicine is more effective and safe in the clinical setting, especially in early long-term low-dose. However, this meta-analysis still has some limitations. Future studies are desirable to validate our discovery and to provide further insights into the underlying mechanisms.

# Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

# Author contributions

YFZ was responsible for the conceptualization, methodology, acquisition, and analysis of data. YL was responsible for the acquisition and curation of the data and drafting of the manuscript. RZ supervised, analyzed, and interpreted the data. WQ performed constructive discussion, writing, reviewing, and editing. YHZ was responsible for the software, analysis, and interpretation of data. YSZ drafted the manuscript and revised it critically for important intellectual content and final approval of the version to be published.

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# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023. 1194605/full#supplementary-material

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