Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Role of colchicine in the management of COVID-19 patients: A meta-analysis of cohort and randomized controlled trials

Avinash Kumar Singh [a], Arya Vidyadhari [b], Harmandeep Singh [c], Kashif Haider [d], Anoop Kumar [e,**], Manju Sharma [f,*]

[a] Department of Pharmaceutical Medicine (Division of Pharmacology) School of Pharmaceutical Education & Research, Jamia Hamdard, New Delhi, 110062, India
[b] Department of Pharmaceutics, School of Pharmaceutical Education & Research, Jamia Hamdard, New Delhi, 110062, India
[c] Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysore, Karnataka, 570015, India
[d] Department of Pharmaceutical Chemistry, School of Pharmaceutical Education & Research, Jamia Hamdard, New Delhi, 110062, India
[e] Department of Pharmacology & Clinical Research, Delhi Pharmaceutical Sciences & Research University (DPSRU), New Delhi, 110017, India
[f] Department of Pharmacology, School of Pharmaceutical Education & Research, Jamia Hamdard, New Delhi, 110062, India

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ABSTRACT

Background: Colchicine is well known drug for the treatment of acute gout. Recently, it has also been used in the management of COVID-19 patients.
Aim: The aim of current study is to find out the role of colchicine in COVID-19 patients.
Material & methods: The relevant studies were searched in PubMed/Medline, Google scholar and clinical trail.gov.com till inception and sorted based on the inclusion and exclusion criteria. The quality assessment of studies were done using Newcastle Ottawa Quality Assessment Scale. The pooled estimate was calculated as odd ratio and pooled prevalence with 95% confidence interval. A random effect model was used and publication bias was assessed qualitatively by trim and fill method.
Results: Out of 38 studies, a total of 6 studies were found relevant for the analysis containing 1146 patients (705 males and 441 females). The pooled odd ratio was found to be 0.35 [0.23, 0.53] which indicate significance reduction of mortality in colchicine group as compared to non-colchicine group. The pooled prevalence of the patients treated with colchicine were found to be significant [0.11(0.03, 0.24)]. The heterogeneity among studies was also found to be low (I2 = 11%). However, funnel plot has indicated the involvement of publication bias [Egger: bias = 10.168291 (95% CI = 5.042044 to 15.294537) P = 0.0053].
Conclusion: Colchicine might be helpful in reduction of mortality in the management of COVID-19 patients. However, further studies are required to confirm its exact role.

1. Introduction

Coronavirus disease 2019 (COVID-19) infection announced a global pandemic by WHO on 11th march 2020. The exact pathophysiology of Coronavirus is yet to be disclose. The exposure of coronavirus has enormous health burdens with morbidity and mortality causing in millions of people covering globes [1]. The COVID-19 pandemic is still underway. Various classes of Drugs such as anti-inflammatory, anti--viral, antihelmintics and steroids etc. have been used in the management of COVID-19 patients. Colchicine is also one of the dug which is used in the management of COVID-19.[2] The abnormal inflammatory response or hyper inflammatory state is responsible to cause the sudden release of inflammatory mediators like cytokine in to the circulation known to be cytokine storm and Clinical manifestation and biochemistry data implies the excessive inflammation resulted in organ damage during COVID-19, indicating the potential role of colchicine. The stimulation of inflammasome and cytokine storm is a way of advancing and aggravating the COVID-19 respiratory infection [3–4]. Colchicine is a well-known drug in the market used in the treatment of acute gout due to its anti-inflammatory activity. Recent studies have also shown the

* Corresponding author. Department of Pharmacology, School of Pharmaceutical Education & Research, Jamia Hamdard, New Delhi, 110062, India.
** Corresponding author. Department of Pharmacology & Clinical Research, Delhi Pharmaceutical Sciences & Research University (DPSRU), New Delhi, 110017, India.
E-mail address: msharma@jamiahamdard.ac.in (M. Sharma).

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anti-viral properties of colchicine due to its inhibitory microtubules polymerization action. [5]. **Fatih Haslak et al. 2020** have reported the protective role of colchicine in the management of COVID-19 infection however **Omer Gendelman et al. 2020** have shown no effect of colchicine in the management of COVID-19. Thus, in the current investigation, we have performed a meta-analysis of available clinical trials data on use of colchicine in the management of COVID-19.

2. Materials and methods

The study was done as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines and Protocol was registered **(CRD42021249337)** at International Prospective Register of Systematic Reviews (PROSPERO).

2.1. Search strategy

The relevant studies were searched in PubMed/Medline, Google scholar and Clinical trial. gov.in up to 31th November 2021 with suitable MeSH (Medical Sub Headings) terms. The MeSH terms used for search is mentioned as follows;- (Colchicine, isomer [MeSH Terms]) AND (COVID19; Coronavirus Disease 19; Coronavirus Disease-19; 2019-nCoV Disease; 2019-nCoV Diseases; COVID 19; 2019-nCoV Infection; Coronavirus Disease 2019; SARS CoV 2 Infection; COVID-19 Virus Infection; COVID 19 Virus Disease; 2019 Novel Coronavirus Disease; Disease 2019, Coronavirus; Infection, SARS-CoV-2; COVID-19 Virus Disease; 2019 nCoV Disease; Virus Infection, COVID-19; SARS Coronavirus 2 Infection; Virus Disease, COVID-19; Disease, COVID-19 Virus; Disease, 2019-nCoV; COVID-19 Virus Diseases; SARS-CoV-2 Infection; COVID 19 Virus Infection; SARS-CoV-2 Infections; COVID-19 Virus Infections; 2019 Novel Coronavirus Infection; Infection, 2019-nCoV; Infection, COVID-19 Virus; 2019-nCoV Infections; 2019 nCoV Infection; COVID-19 Pandemic; COVID-19 Pandemics; Pandemic, COVID-19; COVID 19 Pandemic [MeSH Terms]). The reference of the included studies were screened to boost the search.

2.2. Inclusion and exclusion criteria

The inclusion criteria was as follows- The Cohort and RCT studies in which at least one of the drug is colchicine. The full-text and English language published articles were only included. Articles were first screened by examining title and abstract followed by assessing and retrieving full-text potentially relevant studies for inclusion by two reviewers (AKS and AV) separately. Any conflicts about the inclusion were rescreened by fifth and sixth reviewer (AK and MS). The final decision was made by third and fourth reviewer consultation (HS and KH). The exclusion criteria was as follows- Case-series, case reports, reviews, correspondence and letter to the editor were excluded. The basic criteria for study selection were mentioned in Table 1.

2.3. Data extraction

Data was extracted independently by two reviewers (AKS and AV) from the included study in predesigned data collection sheet which include following column (1). Author name and publication year, (2). Study design (3). Place where the study has been conducted. (4). Sample size with gender distribution. (5).Adverse drug reaction/adverse drug event or complications associated with colchicine treatment. (6). Intervention given with dose (7). Comparator and length of the treatment (8). The outcome of the study. Any conflicts in the data collection were first tried to resolve by discussion, if not the third and fourth reviewer consulted.

Table 1
PICOST criteria for study selection.

S. No	Parameter	Inclusion Criteria
01	Participants	Patients had COVID-19 infection and admitted in the hospital
02	Intervention	Colchicine
03	Comparators	Placebo, SoC (Standard of Care), Hydroxyurea,
04	Outcome	Mortality
05	Study designs	Cohort and RCT
06	Time Periods	Inception to 31 Nov. 2021

2.4. Assessment of risk of bias

The risk of bias was assessed on the basis of selection, comparability and outcome measures between the selected articles by two reviewers (AKS and KH) independently using Newcastle – Ottawa Quality Assessment Scale.[6] The selection, comparability and outcomes were assessed as Good, Fair and Poor on the basis of score. Each study can have maximum of 0–9 points, based on the score on NOS scale. The study can be classified as Good quality (8–9 points), Fair quality (6–7 points), and poor quality (<6 points). Out of 6 included studies, 5 studies were of Good quality whereas only one study was found to be of fair quality after the assessment with NOS scale.

2.5. Statistical analysis

The primary outcome was to calculate the pooled odd ratio for categorical data of all the included studies with 95% CI. The test for overall effect were also calculated with Z value. The heterogeneity was calculated using Cochrane Q and I square statistics. The random-effects model was used due to variation among studies concerning study design, study population and study place. The pooled prevalence of patients treated with colchicine was calculated. Publication bias were assessed using funnel plots by trim and fill method. All statistical analysis were done using Review Manager (Rev Man) v5.3, Comprehensive meta-analysis (CMA) software version 3 and StatsDirect software.

3. Result

Of the 38 articles retrieved and were screened in the first pass (title and abstract screening) after checking the duplicated. Remaining 6 articles were qualified for the inclusion criteria in the meta-analysis after full-text screening in the second pass. List of excluded study is presented in supplementary file. The selection of study screening is presented as PRISMA diagram (Fig. 1).

3.1. Study characteristics

A total of 6 studies (2 RCT and 4 cohort) with 1146 patients in which male and females were 705 and 441 qualified for the inclusion in this study. The cohort studies were prospective and conducted in USA, Italy and New York respectively. The length of stay in hospital were 28 days and 30 days where as the length of intervention is same for the first cohort and less for the second cohort study (21 days). The mean dose of colchicine was found to be 0.8 mg/day. The RCT were conducted in Brazil and Greece. The length of hospital stay for first RCT were not mentioned in the study. Detailed study characteristics were mentioned in Table 2.

3.2. Quality assessment

All the included studies were found to have low risk of bias as per score attained on the NOS scale. We found a low risk of bias in selection, comparability and outcome measures in the included cohort and RCT studies. Similarly, low risk of bias was seen in selection, comparability and exposure measures of the Newcastle-Ottawa scale (NOS) thus resulted high quality among majority of the included studies (Table 3).

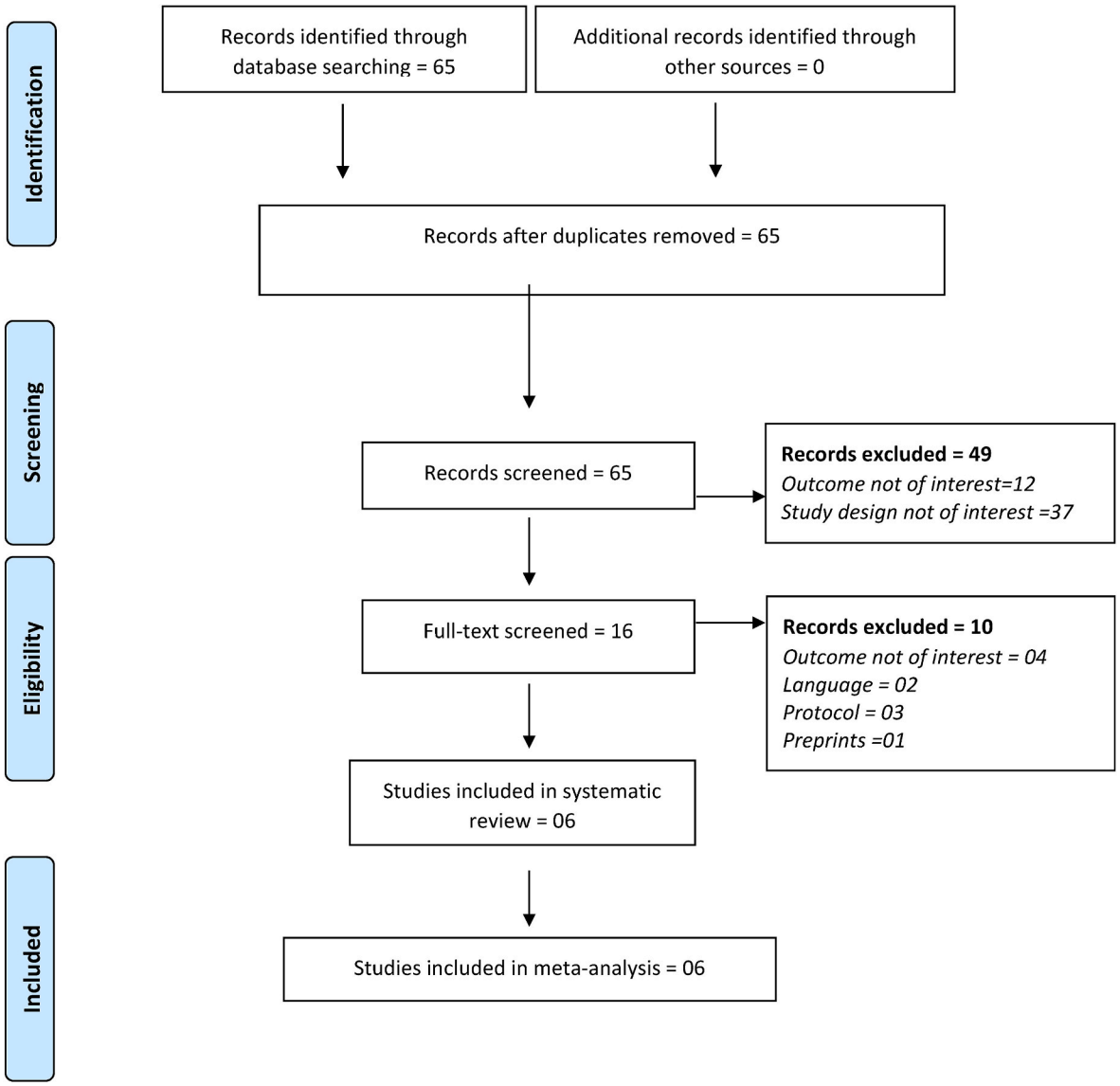

Fig. 1. PRISMA flow-diagram showing study selection process.

3.3. Colchicine use and risk of enter in to seriousness

The odd ratio of the included studies were 0.35 [0.23, 0.53] showed the reduction in mortality rate and the colchicine treatment were favors the COVID-19 infected patients to do not enter in to serious condition. The pooled meta-analysis of 6 studies showed COVID-19 infected patients with and without the use of colchicine with an overall test effect of Z = 4.96 with 95% CI (P < 0.00001) (Fig. 2). The pooled prevalence of patients treated with colchicine were found to be significant with 11% (95% CI = 3%–24%). The forest plot is presented in Fig. 3. The heterogeneity among the studies were found to be low (I2 = 11%). This findings were based on adjusted analysis or pooled analysis.

3.4. Colchicine use and adverse event during COVID-19

The most frequent adverse event was diarrhea among the COVID-19 patients treated with colchicine and the least effected adverse event was headache and vomiting. The only one study has been reported the gastrointestinal effect as adverse event during the colchicine treatment. All the reported adverse drug reaction/adverse event and associated complications during the colchicine treatment were mentioned in Table 2.

3.5. Publication bias

The visual inspection of funnel plots indicates the involvement of publication bias among the included studies (Figs. 4 and 5), which was further confirmed by Eaggers test (Egger: bias = 10.168291 (95% CI = 5.042044 to 15.294537) P = 0.0053. The asymmetry of the funnel plot was supported by trim and fill method. The power of this method is to identify and correct the asymmetry of bias in funnel plot. StatsDirect provides this bias indicator method for all meta-analysis study. The Duval and Tweedie's trim and fill method was applied over random effect model and the upper limit was found to be 0.52799 with Q Value 5.62978 (Fig. 6).

4. Discussion

Colchicine is being indicated for gout, pericarditis and coronary disease as an anti-inflammatory agents. Currently, there are no

Table 2
(Baseline parameter of the included study).

Study author & Year	Country	Study design	Median Age (Years)	Sample Size (N)	Male/ Female	ADR/ADE /Complications	Daily dose of Colchicine (mg/day)	Intervention	Comparator	C-Reactive Protein (Baseline VS After therapy with Colchicine) mg/dl)	C-Reactive Protein (Baseline VS After therapy with Placebo mg/dl)	Length of Intervention	Mortality	Length of Hospital stay (Days)	Result
Luigi Brunetti_2020	USA	Cohort	Colchicine-61.2 ± 13.0 Placebo-63.0 ± 16.4	369	M-230 F-139	Gastrointestinal Effect Common	1.2 mg	Colchicine-74	Standard-295	CRP-15.0 ± 9.0 VS 14.9 ± 8.9	CRP-10.9 ± 6.6 Vs 14.4 ± 8.8	28 days	Cochicine-3 Standard-9	28 days	Treatment with colchicine was associated with a higher rate of discharge and was associated with a decrease in mortality in patients with severe COVID-19 by day 28.
Maria Isabel Lopes_2020	Brazil	RCT	55 years	72	M-33 F-39	Fever- 32 Cough- 36 Fatigue- 19 Myalgia- 19 Diarrhea- 11	0.5 mg	Colchicine-36	Placebo-36	CRP-9.4 ± 1.7	CRP-9.8 ± 2.6	10 days	Colchicine-0 Placebo-2	Colchicine-23 Placebo-26	Colchicine reduced the length of both, supplemental oxygen therapy & hospitalization.
Mirko Scarsi_2020	Italy	Cohort	69.9 years	262	M-167 F-95	Diarrhea- 9	1 mg	Colchicine-122	SoC-140	CRP-15.9 ± 9.2 VS 17.8 ± 8.6	CRP-11.2 ± 8.26 Vs 12.1 ± 8.7	21 days	Colchine-20 SoC-51	30 days	The study were supporting the possible use of colchicine in the treatment of the early phase of COVID-19 with the purpose of preventing the host's auto inflammatory response.
Spyridon G. Deftereos_2020	Greece	RCT	64 years	105	M-61 F-44	Vomiting- 1 Diarrhea- 25 Nausea- 2 Abdominal Pain-5 Muscle Spasm- 1 Headache- 1 Others- 6	1 mg	Colchicine-50	Control-55	CRP-3.6 Vs CRP-4.2 ± 2.6	CRP-4.0 Vs CRP-4.8 ± 2.1	21 days	Colchicine-2 Control-9	Colchicine-22 Control-18	Participants who received colchicine had statistically significantly improved time to clinical deterioration
Lucio Manenti_2021	Italy	Retrospective Cohort	60.5 years	141	M-100 F-41	Fever- 68 Dyspnea- 26 Cough- 50 Arthro-myalgias-6 Diarrhea- 5	1 mg	Colchicine-70	Control-71	116.6	115.2	21 days	Colchicine-5 Control-20	21 days	This study evidence that colchicine may be safe and effective drug for the treatment of COVID-19.

(*continued on next page*)

Table 2 (*continued*)

Study author & Year	Country	Study design	Median Age (Years)	Sample Size (N)	Male/ Female	ADR/ADE /Complications	Daily dose of Colchicine (mg/day)	Intervention	Comparator	C-Reactive Protein (Baseline VS After therapy with Colchicine) mg/dl)	C-Reactive Protein (Baseline VS After therapy with Placebo mg/dl)	Length of Intervention	Mortality	Length of Hospital stay (Days)	Result
Tegveer Sandhu_2021	New York	Prospective Cohort	70 years	197	M-114 F-83	Asthma COPD Hypothyroidism CAD	1.2 mg for 3 days & 0.6 mg for 12 days	Colchicine-53	Control-144	−33	15	15 days	Colchicine-26 Control group-105	42 days	Colchicine given to the patients admitted in the hospital with COVID-19 may improve the outcome and lower the levels of inflammatory markers.

Randomized controlled trial (RCT), Not Reported (NR), Male (M), Female (F), Adverse Drug Reaction (ADR), Adverse Drug Event (ADE), Chronic Obstructive Pulmonary Disease (COPD), Coronary Artery disease (CAD), C-reactive protein (CRP), Standard of Care (SoC).

approved anti-inflammatory agents to manage the COVID-19 patients.[7] The use of colchicine in the management of COVID-19 infection is limited and still doubtful. The beneficiary effect of colchicine were high in the subgroup of diabetic men with COVID-19 infection.[8,9] Mohamed Nabil Elshafei et al., _2021 performed the meta-analysis on the benefitted role of colchicine in COVID-19 infection. The another meta-analysis were conducted by Timotius Ivan Hariyanto et al., 2021 to conclude the colchicine treatment outcome in COVID-19 infection. Colchicine is also responsible to shift the neutrophils to inflamed tissues as well as inhibition of inflammasome or preventing the endothelial damage resulted to be beneficial for the treatment of hospitalized COVID-19 patients.[10–12] Colchicine has anti-inflammatory or anti-viral properties because it forms a complex with tubulin, including neutrophils migration and inhibition of inflammasome with tumor necrosis factor.[13–15] Lopes MI. et al., _2021 conducted RCT that colchicine reduces the length of hospitalization and cost of treatment for COVID-19 patients. The study also reveals that significant clinical output from colchicine in patients hospitalized with COVID-19 infections. However very few RCT has conducted to best of knowledge for the management of COVID-19 infections. This study utilizes the "real-world data" to explain the association of COVID-19 infected patients and colchicine treatment. The pooled odd ratio between colchicine and non-colchicine groups were 0.35 [0.23, 0.53] at 95% CI ascertain the random effect model. The overall effect for the test was found to be significant Z = 4.96 (p=.00001) which indicate the result of the conducted study for the management of COVID-19 patients. The pooled prevalence of patients treated with colchicine was found to be significant. The funnel plots indicate the publication bias of the included study. The Low heterogeneity among the colchicine and non-colchicine group were indicated as Chi2 = 5.64 (p = 0.34), I2 = 11%. The trim and fill method was opted to identify and correct the asymmetry of bias in funnel plot. The most frequent adverse event was diarrhea among colchicine treatment group. The rationale of colchicine treatment is based on experimental evidence and extended involvement in the control of auto inflammatory diseases.[16,17] Prior colchicine administration may alter physiological immune response in Covid-19 patients [18]. Colchicine might reducing the crowd on emergency departments and also lower the hospitalizations of COVID-19 patients [19]. Some of the study concluded that treatment with Immunosuppressive agents like colchicine has no any association with SARS-CoV-2 infection [20]. The safety parameter of colchicine was satisfactory, as no patients had to stop the colchicine for severe adverse events and the patients treated with colchicine had a good survival rate as compared to standard of care (SoC) treatment [21].

The restricted evidence on the use of colchicine treatment on COVID-19 infections may alter the result. The dose variability is also a major concern for this study. The safety and efficacy parameters were not assessed or reported properly. The sample size of the included studies were small and proper inflammatory markers were not available in the majority of the study, making it difficult to signify the impact of colchicine in management of COVID-19 patients.

5. Conclusion

In conclusion, Colchicine might be helpful in reduction of mortality in the management of COVID-19 patients. However, further studies may warranted the role of colchicine in COVID-19 patients to enter into serious condition.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical clearance

This study did not need any ethical approval, or informed consent on

Table 3
(Newcastle – ottawa quality assessment).

Study & Year	Selection	Comparability	Outcome	Total Score	Quality of the Study
Maria Isabel Lopes_2020	***	**	**	7	Good
Mirko Scarsi_2020	**	**	**	6	Fair
Spyridon G. Deftereos_2020	***	**	**	7	Good
Luigi Brunetti_2020	***	**	***	8	Good
Lucio Manenti_2020	***	**	***	8	Good
T. Sandhu_2021	***	**	***	8	Good

Assessment of the Cohort and Randomized Control Trial (RCT) Study types.

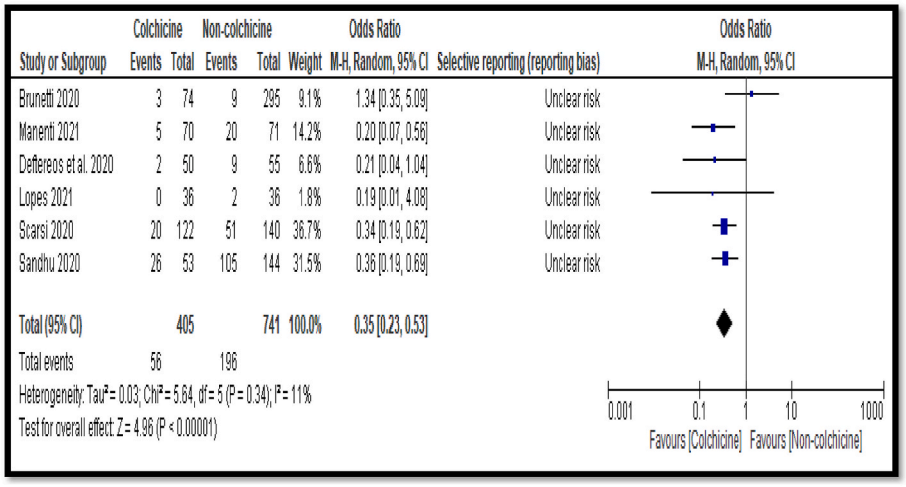

Fig. 2. Forest plot.

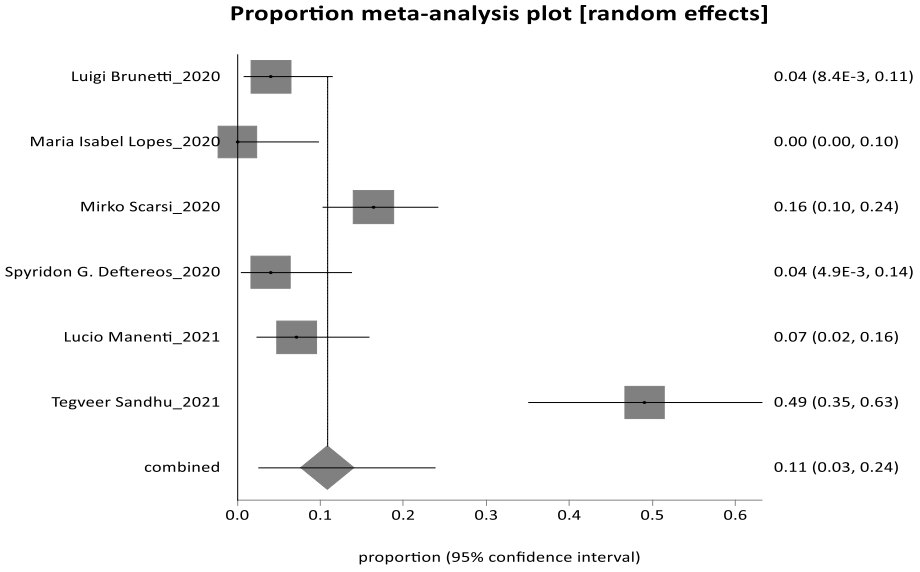

Fig. 3. Pooled Prevalence of patients treated with Colchicine.

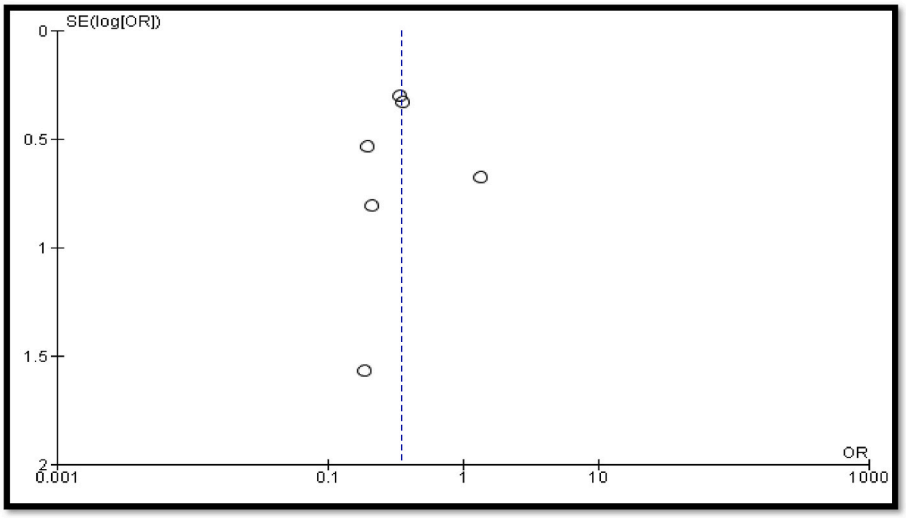

Fig. 4. Funnel Plot (Bias assessment plot).

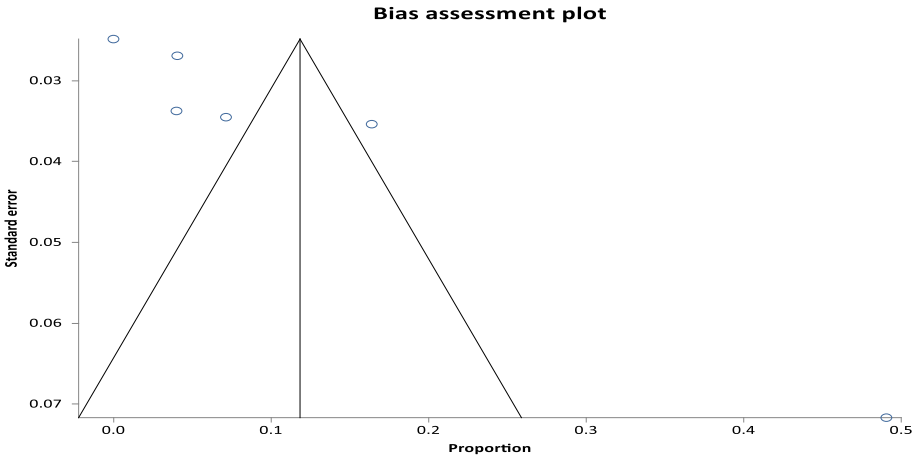

Fig. 5. Funnel plots.

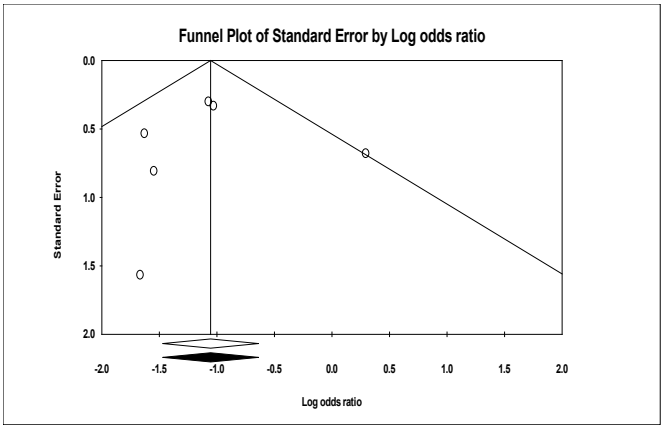

Fig. 6. Funnel Plot (Trim and fill method).

studies with human or Title Page animal subjects because this study uses the published and pooled population only.

Author contribution

First and Second author- AKS and AV did primary and secondary screening and manuscript writing Third and fourth author – HS and KH has draft the manuscript and table redrafting. Fifth and Sixth author – AKand MS has resolve the query and draft the methodology and manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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