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Efficacy of various treatment modalities for nCOV-2019: a systematic review and meta-analysis

Running title: Treatment modalities in nCOV-2019

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Abstract

Background: Several therapeutic agents have been investigated for treatment of novel Coronavirus-2019 (nCOV-2019). We conducted a systematic review and meta-analysis to assess the efficacy of various treatment modalities in nCOV-2019 patients.

Methods: A literature search was conducted before 29 June 2020 in PubMed, Google Scholar, Cochrane library databases. A fixed-effect model was applied if I^2 <50%, else results were combined using random-effect model. Risk Ratio (RR) or Standardized Mean Difference (SMD) along-with 95% Confidence Interval (95%CI) were used to pool the results. Between-study heterogeneity was explored using influence and sensitivity analyses and publication bias was assessed using funnel plots. Entire statistical analysis was conducted in R version 3.6.2.

Results: Fifty studies involving 15 *in-vitro* and 35 clinical studies including 9170 nCOV-2019 patients were included. Lopinavir-Ritonavir was significantly associated with shorter mean time to clinical recovery (SMD -0.32; 95%CI -0.57 to -0.06), Remdesivir was significantly associated with better overall clinical recovery (RR 1.17; 95%CI 1.07 to 1.29) and Tocilizumab was associated with less all-cause mortality (RR 0.38; 95%CI 0.16 to 0.93). Hydroxychloroquine was associated with longer time to clinical recovery and less overall clinical recovery. It additionally had higher all-cause mortality and more total adverse events.

Conclusion: Our meta-analysis suggests that except *in vitro* studies, no treatment has shown overall favorable outcomes in nCOV-2019 patients. Lopinavir-Ritonavir, Remdesivir and Tocilizumab may have some benefits while Hydroxychloroquine administration may cause harm in nCOV-2019 patients. Results from upcoming large clinical trials may further clarify role of these drugs.

Keywords: Novel Coronavirus-2019; nCOV-2019; Treatments; Interventions; Humans

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Abbreviations: novel-Coronavirus 2019= nCOV-2019; Randomized controlled trials= RCTs; Standard Deviation= SD; Risk Ratio= RR; Standardized Mean Difference= SMD; 95% Confidence Interval= 95% CI; Multiplicity of Infection= MOI; Inhibitory concentration= IC; Cytotoxic concentration= CC; Selectivity Index= SI; Effective concentration= EC; United States of America= USA; United Kingdom= UK, Figure= Fig.

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Introduction:

The novel Coronavirus-2019 (nCOV-2019) has now encompassed more than 200 countries since a cluster of cases were initially reported in Wuhan, China on 31st December 2019.[1] As of 5th July 2020, 11,388,558 people have been infected globally from nCOV-2019 while 533,638 have died of this severe infection.[2] The nCOV-2019 belongs to the Coronaviridae family and has structural similarities to the betacoronavirus that has caused two epidemics in the past 18 years; Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-Cov).[3]

No drug or therapeutic agent has yet been approved by the United States- Food and Drug Administration (US-FDA) for treating nCOV-2019 pneumonia patients. Based on the initial results obtained from certain *in vitro* studies,[4,5] non-randomized trials[6] and interim analysis of some randomized controlled trials (RCTs)[7] Hydroxychloroquine and Remdesivir received FDA emergency use authorization for nCOV-2019.[8,9] However, recent RCTs published on these respective drugs need evidence synthesis for their usage in nCOV-2019 patients.[10,11] FDA cautioned against the use of Chloroquine or Hydroxychloroquine outside clinical trial settings due to high risk of associated adverse events.[12] With more than 500 trials already registered in clinicaltrials.gov on the treatment of nCOV-2019, it is imperative to investigate the available evidence till date and assess each treatment in terms of benefit or harm to the nCOV-2019 patients.

The aim of this systematic review and meta-analysis was to pool the initial evidence available from RCTs, non-RCTs, observational and *in vitro* studies for analyzing the benefit/harm of various treatment modalities including anti-viral, corticosteroid treatment, plasma therapy and traditional medicines administered to nCOV-2019 pneumonia patients. The results of this systematic review and meta-analysis might be useful in designing future clinical trials and providing guidelines.

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Methods

Electronic search

Electronic databases including, PubMed, EMBASE, Medline, Google Scholar, Cochrane library and clinicaltrials.gov were searched till 29 June 2020. The following MeSH terms or free text terms were used: "2019 novel coronavirus", "2019 nCOV", "COVID19", "SARS-CoV-2", "drug therapy", "anti-viral therapy", "symptomatic treatment", "immunotherapy". The detailed search criteria are given in the supplementary file 1. Furthermore, the reference list of all the relevant identified articles were thoroughly searched. Only those articles were included whose full texts were available in English language. Studies published on human subjects after 31st December 2019 since the nCOV-2019 outbreak initiated, were only searched. The protocol for this systematic review and meta-analysis was registered in PROSPERO (ID: CRD42020175792) and there were no major deviations from the published protocol in PROSPERO.

Population

Subjects diagnosed with pneumonia caused by new Coronavirus 2019 infection (nCOV-2019) confirmed positive on high throughput sequencing or real-time reverse-transcription polymerase chain reaction analysis of throat swab specimens, serology or culture.

Intervention

Various specific, preventive and immune treatments administered to the nCOV-2019 patients.

Comparator

nCOV-2019 patients receiving standard care only or placebo treatment or standard care with a comparator drug.

Outcome

Outcome for *in vitro* studies

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Average half-maximal inhibitory concentration (IC_{50}), Average half maximal effective concentration (EC_{50}), Average cytotoxic concentration (CC_{50}) and Average selectivity Index (SI) of the various drugs included in the systematic review.

Outcome for clinical studies

(1) All-cause mortality; (2) total adverse events; (3) overall clinical recovery defined as the number of patients becoming negative for nCOV-2019 or significant improvement on chest CT and getting discharged from the hospital; (4) time to clinical recovery defined as the time taken in number of days for the negative conversion of nCOV-2019 or significant improvement on chest CT and getting discharged from the hospital.

Inclusion and exclusion criteria

The criteria for the inclusion of studies in our systematic review and meta-analysis was:

For inclusion of *in vitro* studies: (1) studies aimed at evaluating the efficacy of multiple drugs/treatment choices for nCOV-2019, (2) studies should have reported data on inhibitory effect and cytotoxicity of the drug; (3) only published studies.

For inclusion of clinical studies: (1) randomized controlled trials (RCTs), non-RCTs, cohort studies, case-control studies; (2) studies aimed at evaluating multiple therapeutic choices for nCOV-2019; (3) studies must have a control group comparing the primary treatment drug to either standard care/control or placebo or studies assessing the primary treatment drug with a comparator drug; (4) conducted on human subjects only; (5) only published studies.

The following clinical and *in vitro* studies were excluded from our systematic review and meta-analysis: (1) conducted on animal models; (2) unpublished studies; (3) ongoing registered clinical trials; (4) desired outcome data not reported; (5) single arm studies/trials where the primary treatment drug is not compared to either standard care alone, placebo or standard care with a comparator drug (criteria for clinical studies). This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) 2015 guidelines.[13]

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Data extraction

All titles and abstracts retrieved by searching available literature were screened independently by two authors (SM and MN) against the eligibility criteria. The information extracted from each eligible study included the first author, year of publication, study design, sample size, interventions (including type of treatment administered), outcome measures, main results. Any disagreement was resolved by mutual consensus among all the authors (DV, VH, SM, MN).

Risk of bias assessment

The quality assessment was done for only the clinical studies included in our systematic review and meta-analysis by two independent authors (SM and MN) using the new Cochrane risk of bias tool for randomized controlled trials (ROB-2) for RCTs and Newcastle-Ottawa Scale (NOS) for non-RCTs, cohort and case-control studies.[14,15] Any disagreement was resolved by consulting with the remaining authors of the review.

The risk of publication bias was assessed by using Funnel plots and the asymmetry of the funnel plot was investigated using the Egger's regression test.[16]

Statistical analysis

Dichotomous variables were represented by number (percentage) and the continuous variables were represented by mean and standard deviation (SD). If median, ranges and/or interquartile range were reported, then they were converted to mean and SD using the formula depending upon the sample size given by Wan et al. 2014.[17] A meta-analysis was performed only for clinical studies and for those treatments in which required outcome data could be pooled from two or more studies. For dichotomous variables, the data was pooled using Risk ratio (RR) and 95% Confidence Interval (95% CI) while for continuous variables, the data was pooled using Standardized Mean Difference (SMD) and 95%CI. Heterogeneity among the included studies was investigated using Cochran's Q statistic, I^2 metric tests and by using prediction intervals. A fixed-effect model was applied if I^2 was less than 50%, else a random-effect model was used to pool the results. Labbé plots were used to determine the trend and between-study heterogeneity present in the binary outcome meta-analysis. The source of heterogeneity was further assessed by using the influence diagnostic tools and by

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conducting the sensitivity analyses and meta-regression analyses. All the statistical analysis was conducted using R version 3.6.2.

Results:

Initial search yielded 1490 articles by searching various databases for published and preprint articles. After screening 928 articles, 377 full text articles were reviewed for eligibility and finally 50 studies were included in our systematic review and meta-analysis. Further, out of the 50 included studies, 15 were *in vitro* studies and 35 were clinical studies. The meta-analysis was finally conducted on 23 clinical studies. Fig. 1 represents the PRISMA flow diagram for the inclusion of studies in our systematic review and meta-analysis. The PRISMA checklist is available in the supplementary file 3.

Results from the systematic review of *in vitro* studies

Overall, 15 *in vitro* published studies were included in the systematic review, which comprised majorly of treatments done on Vero E6 cells for viral titration, drug inhibition and cytotoxicity analyses. Nine studies were included from China,[5,18–25] three from United States of America (USA),[26–28] one each from Germany,[29] Netherlands[30] and Australia.[31]

There were two studies[5,20] involving the anti-malarial drug on Hydroxychloroquine which had chloroquine as a positive control in both the studies. The studies had a wide range of multiplicity of infection (MOI) from 0.01 to 0.8 and an average half-maximal effective concentration (EC_{50}) of 6.84μM [0.72 – 12.96] in the treatment arm as compared to 6.415μM [5.47–7.36] in the control arm. The two studies showed potency in inhibiting nCOV-2019 *in vitro* in Vero cells. While the cytotoxic concentration (CC_{50}) of 249.50μM and selectivity index (SI) of 61.45 at an MOI of 0.01 in one study[20] were lower compared to the positive control, the EC_{50} value of hydroxychloroquine was higher than chloroquine. These studies depicted that hydroxychloroquine had better efficacy and lesser cytotoxicity in inhibiting nCOV-2019 than Chloroquine *in vitro* but a higher dosage might be required for effectiveness, which could have adverse consequences.

Two studies [23,24] involving the broad-spectrum antiviral Remdesivir with MOI in the range of 0.02 to 0.05 exhibited average EC_{50} of 11.96μM, CC_{50} greater than 100μM and SI greater than

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129.87. Remdesivir showed promising results *in vitro* and depicted potency inhibiting viral proliferation in Vero E6 cell line. Not only Remdesivir was able to block nCOV-2019 infection at lower concentrations it also had higher selectivity towards the viral cells that meant it had lower toxicity towards the host cells.

One study each involving 47D11 H2L2 antibody,[30] Arbidol,[18] Auranofin,[28] Beta-d-N4-hydroxycytidine,[26] Darunavir,[29] Antibodies n3086/n3113,[25] Interferon-α/ Interferon –β,[27] Ivermectin,[31] Lianhuaqingwen,[21] Chloroquine,[23] Lopinavir,[24] Ementine Hydrochloride,[24] Homoharringtonine[24] and Pudilan Xiaoyan Oral Liquid[22] had a wide range of EC_{50} [0.15–100μM] or IC_{50} [0.08–411.2μM] values for MOI of [0.05 – 2]. However, each of these compounds demonstrated the potential to stall the process of viral replication and growth through inhibiting viral titre in Vero, Calu3 and Huh7 cell lines.

There was one *in vitro* study[19] on the phytochemical extracts from six Chinese traditional medicinal plants viz. *Cimicifuga rhizoma, Meliae cortex, Coptidis rhizoma, Phellodendron cortex, Sophora subprostrata radix* and *Mountan cortex radicis*. Extracts from five of the six plants showed potential as herbal medicine by inhibiting nCOV-2019 infection in both A59 and Vero cells with significant EC_{50} [2.0±0.5–27.5±1.1μg/mL], CC_{50} [71.3 ± 7.2–334.3 ± 7.0μg/mL] and SI [11.1–34.9] values.

All the studies had an incubation time (hours post infection) of treatment ranging from 24 to 72 hours on average with a median of 48 hours. Table-1 depicts the baseline characteristics of *in vitro* studies included in our systematic review.

Results from clinical studies

A total of 35 clinical studies with 9170 nCOV-2019 pneumonia patients were included in the systematic review out of which 5563 (60.67%) patients were male. The overall mean age of the subjects present in the included studies was 56.34 ± 14.33 years. We included 12 RCTs, 3 non-RCTs and 20 observational (including retrospective/prospective cohort, case-control) studies. Eighteen studies were from China [10,11,32–47], six from USA [48–53], five from Italy [54–58], two from France [6,59] and one each from Brazil [60], Hong Kong [61], Spain [62] and Greece [63].

There was no significant difference in the mean age and sex distribution between any of the treatment and comparator groups included in our meta-analysis. Table-2 depicts the baseline characteristics of clinical studies included in the systematic review and meta-

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analysis. Since only limited clinical trials and observational studies have been published till date, the data from several studies could not be pooled together to assess any of the four outcome measures. Fig S2.1 in the supplementary file 2 illustrates the effect of various treatment modalities in individual studies in terms of all-cause mortality, total adverse events, overall clinical recovery and time to clinical recovery.

Results from the meta-analyses of clinical studies

Hydroxychloroquine Versus Control groups

Eight studies [6,10,32,33,48–50,59] consisting of 3400 nCOV-2019 cases were included in the meta-analysis and were divided into two groups: 1522 subjects to Hydroxychloroquine group and 1878 subjects to control group. Compared to the control group, Hydroxychloroquine had an increased risk of having total adverse events (RR 1.82; 95% CI 1.57 to 2.12) and was associated with a longer time to clinical recovery (SMD 0.55; 95% CI 0.21 to 0.89). However, Hydroxychloroquine was not found to be significantly associated with all-cause mortality (RR 1.22; 95%CI 0.76 to 1.95) and overall clinical recovery (RR 0.93; 95%CI 0.84 to 1.04) (Fig. 2(a-d)). Although, through the Labbé plots, we did observe a trend that all-cause mortality was more towards the Hydroxychloroquine group (supplementary file 2) while overall clinical recovery was more in the control group (Fig. 8(a)).

Lopinavir-Ritonavir Versus Control groups

Four studies [36–39] consisting of 397 nCOV-2019 cases were included in the meta-analysis and were divided into two groups: 227 subjects to Lopinavir-Ritonavir group and 170 subjects control group. There was no significant association between the two groups in terms of total adverse events (RR 1.73; 95%CI 0.57 to 5.26) and overall clinical recovery (RR 1.08; 95%CI 0.94 to 1.24). Labbé plot observed a trend of having more adverse events towards the Lopinavir-Ritonavir group (supplementary file 2). A borderline association was observed depicting a trend in terms of a shorter mean time (in days) to clinical recovery in the Lopinavir-Ritonavir group compared to the control group (SMD -0.47; 95%CI -1.00 to 0.07) (Fig. 3 (a-c)). Due to less number of available studies, a meta-analysis could not be performed for assessing the all-cause mortality between the two groups.

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Lopinavir-Ritonavir Versus Arbidol groups

The benefit/harm of Lopinavir-Ritonavir treatment over Arbidol treatment was assessed in two studies [38,39] consisting of 155 nCOV-2019 cases; 86 in the lopinavir-ritonavir treatment group and 69 in Arbidol treatment group. Lopinavir-Ritonavir treatment group was significantly associated with higher total adverse events as compared to the Arbidol treatment group (RR 2.25; 95%CI 1.07 to 4.74). None of the two treatment groups were found to be associated with an increase in the overall clinical recovery of nCOV-2019 patients (RR 0.95; 95%CI 0.78 to 1.15) (Fig. 3 (d-e)). The findings were concurrent when analysed using the Labbé plots (supplementary file 2). A meta-analysis could not be performed for all-cause mortality and time to clinical recovery because of less number of studies.

Arbidol Versus Control groups

Two studies [38,39] consisting of 134 nCOV-2019 cases were included in the meta-analysis and were divided into two groups: 69 subjects to Arbidol group and 65 subjects to control group. When compared to the control group, treatment with Arbidol was not found to be associated with incidence of the total adverse events (RR 1.80; 95%CI 0.52 to 6.19) or overall clinical recovery (RR 1.08; 95%CI 0.85 to 1.38) (Fig. 4 (a, b)). The findings were concurrent when analysed using the Labbé plots (supplementary file 2). A meta-analysis could not be performed for the remaining outcome measures of all-cause mortality and time to clinical recovery due to fewer number of studies.

Remdesivir Versus Placebo group

The effect of Remdesivir treatment over placebo was assessed in two RCTs [11,52] consisting of 1295 nCOV-2019 patients; 696 in Remdesivir group while 599 in placebo group. Compared to placebo group, Remdesivir was not associated with either all-cause mortality (RR 0.74; 95%CI 0.40 to 1.37), total adverse events (RR 0.91; 95%CI 0.79 to 1.05) or time to clinical recovery (SMD -0.78; 95%CI -2.05 to 0.50). However, a significant association was observed with better overall clinical recovery (RR 1.17; 95%CI 1.07 to 1.29) in Remdesivir group

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compared to placebo group (Fig. 5 (a-d)). Similar findings were observed in Labbé plot analysis as well (supplementary file 2).

Corticosteroids Versus Control groups

Five studies [42–45,62] consisting of 674 nCOV-2019 cases were included in the meta-analysis and were divided into two groups: 515 subjects to Corticosteroid group and 159 subjects to control group. Administration of Corticosteroid treatment was found to have no significant association with all-cause mortality (RR. 1.17; 95%CI 0.37 to 3.65) or the average time to clinical recovery (SMD 0.16; 95%CI -0.26 to 0.58) compared to the control group (Fig. 6 (a, b)). Since enough studies could not be pooled, no meta-analysis was performed to assess the effect of Corticosteroid treatment on the total adverse events and overall clinical recovery.

Tocilizumab Versus Control groups

Four studies [55–58] consisting of 806 nCOV-2019 cases were included in the meta-analysis and were classified into two groups: 294 subjects to Tocilizumab and 512 subjects in control groups. Tocilizumab was found to have significantly less all-cause mortality compared to the control group (RR 0.38; 95%CI 0.16 to 0.93). However, there was no significant difference between the two groups in terms of overall clinical recovery (RR 1.11; 95%CI 0.80 to 1.54). Due to less number of studies, a meta-analysis was not possible for the other two outcomes of interest.

Combination therapy

The combination of Hydroxychloroquine and Azithromycin was tested in three studies [6,49,50] including 1253 nCOV-2019 cases wherein, 854 cases were allocated to the Hydroxychloroquine + Azithromycin treatment group and the rest 399 cases to the control group. The combination of Hydroxychloroquine + Azithromycin was significantly associated with a higher risk of all-cause mortality compared to the control group (RR 2.01; 95%CI 1.47 to 2.73) while no association was observed between the two in terms of overall clinical recovery (RR 0.94; 95%CI 0.72 to 1.23) (Fig. 7 (a, b)). However, we did observe a slight trend in a lesser overall clinical recovery towards the Hydroxychloroquine + Azithromycin

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treatment group using the Labbé plot (supplementary file 2). The total adverse events and time to clinical recovery outcomes could not be assessed due to limited number of studies.

Publication bias

The publication bias was assessed using funnel plot analysis for all those treatment modalities wherein data from more than two studies could be pooled together. The shape of the funnel plots did not show any evidence of significant publication bias except for two instances wherein Hydroxychloroquine was compared with control group to assess the overall clinical recovery outcome (P-value: 0.003) and Lopinavir-Ritonavir treatment was compared with control group to assess the total adverse event outcome (P-value: 0.02). This was confirmed by the significant p-values obtained from the Egger's regression test. The p-value of Egger's regression test was not significant for the presence of any publication bias for the rest of the funnel plots. Fig. 8(b) represents the funnel plot analysis carried out for hydroxychloroquine vs. control group for assessing the overall clinical recovery outcome. The remaining funnel plots have been depicted in the Table S2.1 of supplementary file 2.

Meta-regression analysis

A meta-regression analysis was conducted to determine if the risk of bias and ethnicity of each study were associated with the overall effect size difference. A meta-regression analysis was performed only for those treatments where data from more than two studies was pooled. The two predictor variables used in the meta-regression analysis were categorized as: risk of bias (low, some concerns, high); and ethnicity (Asian, Caucasian). The "ethnicity" variable as a predictor, was found to be significantly associated with the overall effect size difference while assessing the time to clinical recovery outcome between Hydroxychloroquine and control group (P-value: 0.02) and assessing the all-cause mortality outcome between Hydroxychloroquine and control group (P-value<0.001) ((Fig. 8(c)) and similar outcome between Corticosteroid and control group (P-value: 0.007). The "risk of bias" variable as a predictor was also found to be significantly associated with the overall effect size difference while assessing the all-cause mortality outcome between Corticosteroid and control group (P-value: 0.009) and while assessing the time to clinical recovery outcome between Hydroxychloroquine and control group (P-value: 0.02). Risk of bias and ethnicity

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did not have any association with the overall effect size difference for assessing the remaining outcomes between other treatment groups.

Quality (Risk of bias) assessment

The risk of bias was assessed using ROB-2 tool for RCTs and NOS for non-RCTs, cohort and case-control studies. For NOS, the total score was divided into three categories: (1) 1-3 (High risk of bias); (2) 4-6 (Some concerns); 7-9 (Low risk of bias). Overall, 9 (25.71%) studies included in our review had an overall low risk of bias, 22 (62.86%) studies had some concerns related to the risk of bias while four studies (11.43%) had high risk of bias. All the four studies[10,32,34,61] with a high risk of bias belonged to the RCT sub-group (Fig. 9 (a, b)). The individual items for the quality scale are depicted in supplementary file 1.

Influence diagnostics and sensitivity analysis

Influence diagnostics tools and sensitivity analysis were used to further explain the heterogeneity observed in our results and to identify the outlier studies which could be significantly affecting the overall pooled effect estimates. The influence diagnostics and sensitivity analysis were performed for treatments in which data from more than two studies was pooled. The influence diagnostic tools generated two plots including 1) Baujat plots; 2) Influence analysis plots; and two plots for sensitivity analysis including 3) leave-one-out analysis ordered by heterogeneity and 4) leave-one-out analysis ordered by effect size.

The Baujat and influence analysis plots identified one potential outlier namely, Yu B, 2020[33] while assessing the all-cause mortality outcome in Hydroxychloroquine vs. control group analysis. After conducting the sensitivity analysis by omitting a single study in each turn (ordered by both effect size and I^2), the overall effect size and amount of heterogeneity changed significantly by omitting the Yu B, 2020 study. Hydroxychloroquine was found to be significantly associated with the risk of having more all-cause mortality compared to control group (RR 1.57; 95%CI 1.30 to 1.90; I^2= 0%) (Fig. 10). A borderline association was observed between Hydroxychloroquine and less overall clinical recovery when Gautret P, 2020[6] outlier study was omitted in the sensitivity analysis (RR 0.92; 95%CI 0.84 to 1.00; I^2= 67%).

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The influence diagnostic tools identified Ye XT, 2020[37] study as a potential outlier while assessing the time to clinical recovery outcome between Lopinavir-Ritonavir and control groups; and after omitting this study in the sensitivity analysis we observed that Lopinavir-Ritonavir was significantly associated with a shorter mean time to clinical recovery than the control group (SMD -0.32; 95%CI -0.57 to -0.06, I^2= 0%).

While assessing the all-cause mortality outcome between Corticosteroid and control groups, we observed Lu X, 2020[44] as a potential outlier study. After removing the outlier, a significant association was observed between less all-cause mortality and Corticosteroid treatment with reduced heterogeneity (RR 0.61; 95%CI 0.37 to 0.98, I^2= 0%).

The significant association between less all-cause mortality and Tocilizumab treatment was lost when Capra R, 2020,[58] Guaraldi G, 2020[55] and Campochiaro C, 2020[56] were omitted sequentially in the sensitivity analysis.

Discussion:

Our systematic review and meta-analysis summarized the *in-vitro* and clinical studies so far regarding the effect of various treatment modalities administered to nCOV-2019 pneumonia patients. *In vitro* studies observed significant inhibitory effects of Remdesivir and Hydroxychloroquine on nCOV-2019. Hydroxychloroquine was found to have a better efficacy and less cytotoxicity than Chloroquine in inhibiting nCOV-2019 while Remdesivir had significant potency in blocking the viral infection. However, the clinical translation of promising *in vitro* results in some of these drugs has not been successful. In 35 clinical studies consisting of 9170 nCOV-2019 patients, we assessed the potential of several treatments against their comparators in terms of harm which included all-cause mortality and total adverse events and in terms of benefit which included overall clinical recovery and time to clinical recovery. While assessing the benefits of administered treatments, Lopinavir-Ritonavir treatment had a borderline association with shorter mean time to clinical recovery compared to the control group, Remdesivir treatment had significant association with better overall clinical recovery compared to placebo group and Tocilizumab was associated with less all-cause mortality compared to controls. However, the present evidence stems from only a few of trials/studies conducted on these drugs and the clinical usefulness of these results will only be determined once further large RCTs are published on the same. In terms

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of harm, our meta-analysis suggests that Hydroxychloroquine treatment compared to control group and Lopinavir-Ritonavir treatment compared to Arbidol treatment were significantly associated with more total adverse events in nCOV-2019 patients. Hydroxychloroquine was also associated with a longer time to clinical recovery compared to control group. Hydroxychloroquine combined with Azithromycin was associated with higher all-cause mortality compared to control group. We did not observe any significant association in terms of either benefit or harm for the remaining treatments administered to nCOV-2019 patients when analysed against their respective comparator groups. Although our systematic review of individual studies observed several treatments associated with benefit few including Favipiravir, Chloroquine, Baricitinib, 5-day Remdesivir treatment; and certain treatments associated with harm including colchicine, corticosteroids and combination therapy of Hydroxychloroquine + Azithromycine in nCOV-2019 patients (supplementary file 2); the results were reported only from single studies and thus lacked sufficient statistical power to draw any profound conclusions. Around 62.86% of the studies included in our review had moderate/some concerns related to the risk of bias.

When we conducted the influence and sensitivity analysis, we observed that Hydroxychloroquine was associated with a higher all-cause mortality and less overall clinical recovery (borderline association) in nCOV-2019 patients compared to the control group. The borderline association of Lopinavir-Ritonavir treatment having a shorter mean time to clinical recovery compared to control group was confirmed to be statistically significant after the sensitivity analysis. Further, Tocilizumab was no longer associated with less all-cause mortality while Corticosteroid treatment had a significant association with less all-cause mortality compared to control group. Our findings are in concordance with a review published in April 2020 by Sanders JM et al. which reviewed the initial pharmacological treatments available for nCOV-2019 and concluded that no available therapy was found to be effective for treating this infection.[64]

Initial evidence from *in vitro* and observational studies suggested that Hydroxychloroquine has comparatively faster viral clearance and results in better clinical improvement of nCOV-2019 patients in contrast to control groups.[5,33] Further, the combination of Hydroxychloroquine and Azithromycin resulted in 100% clinical recovery in a small open label non-RCT published by Gautret P et al. 2020.[6] However, when early results from few

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RCTs were reported, Hydroxychloroquine no longer had any benefit over standard care and instead was associated with more adverse events and higher mortality rate.[10,32] We also conducted a subgroup analysis based on study design which further strengthened this notion. Hydroxychloroquine compared to control group was found to be associated with a longer time to clinical recovery in both non-RCTs/cohort study subgroup as well as in the RCT subgroup (Fig S2.2 in supplementary file 2). Two recent meta-analyses conducted by Ren L et al. 2020 and Wang J et al. 2020 found that patients taking Chloroquine or Hydroxychloroquine had more adverse events compared to patients assigned to placebo group.[65,66] Another meta-analysis published a couple of months ago by Sarma et al. 2020 found no association of Hydroxychloroquine with virological cure, death or clinical worsening and safety in nCOV-2019 patients.[67] Similar findings on Hydroxychloroquine with or without azithromycin were observed from another meta-analysis of five trials which although did observe a trend but the results were not found to be statistically significant in terms of negative conversion of nCOV-2019 (Odds Ratio [OR] 1.95; 95%CI 0.19 to 19.73) and reduction in progression rate (OR 0.89 95%CI 0.58 to 1.37).[68] Our meta-analysis along with the subgroup and sensitivity analyses further corroborates these findings.

The effectiveness and safety of corticosteroid treatment in nCOV-2019, SARS and MERS have been investigated in several meta-analyses. Use of corticosteroid treatment was found to be associated with higher mortality (RR 2.11; 95%CI 1.13 to 3.94) in nCOV-2019 and SARS patients in a meta-analysis of 15 studies conducted by Yang Z et al. 2020.[69] While three meta-analyses found that corticosteroid use did not worsen/improve mortality in patients with nCOV-2019, SARS-Cov and MERS-Cov.[70–72] Further, the meta-analysis by Li H et al. 2020 also observed a delayed time to virus clearance in the corticosteroid group compared to controls (MD 3.78; 95%CI 1.16 to 6.41).[71] The findings of our meta-analysis are also in line with the previously published meta-analyses on corticosteroids. We did not observe any significant association between corticosteroid treatment and all-cause mortality and time to clinical recovery, but after conducting the sensitivity analysis, we observed a significant association between less all-cause mortality and Corticosteroid treatment after removing the outlier study. However, the result stems from a pooled synthesis of only a couple of trials and further large RCTs are required to confirm/refute our findings.

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Use of Convalescent Plasma has been shown to be extremely promising in some recently published case-series.[73,74] Only one RCT was available on determining the effectiveness of Convalescent plasma compared to controls,[47] thus we could not conduct a meta-analysis. However, we systematically reviewed the trial and observed that convalescent plasma was neither associated with more/less adverse events nor with more/less overall clinical recovery compared to control group (supplementary file 2). Although, we observed a trend of more overall clinical recovery towards the Convalescent plasma arm (RR 1.20; 95% CI 0.80 to 1.81). A recently published systematic review of five studies by Rajendran K et al. 2020 concluded that plasma therapy in nCOV-2019 patients was safe, clinically effective and was associated with a reduced mortality.[75] Results from ongoing clinical trials on plasma therapy are awaited and will give us a better insight into the effectiveness of Convalescent Plasma in treating nCOV-2019 patients.

Limitations

Although we made sure that our systematic review and meta-analysis was conducted very comprehensively, certain inherent and obvious limitations cannot be ignored. Firstly, due to the limited number of studies, our meta-analysis pooled the data from RCTs and non-RCTs/cohort/case-control studies together which is generally not advisable. However, we did conduct a subgroup analysis based on study design wherever possible to separate the RCTs from non-RCTs/cohort/case-control studies. Secondly, all outcome measures could not be assessed for all the potential treatments due to scarcity of literature. Lastly, since several clinical trials on nCOV-2019 treatments are currently ongoing, the results of our meta-analysis might change significantly owing to the findings published in near future.

Nonetheless, our meta-analysis presents preliminary evidence of benefit/harm of the possible treatments being administered to nCOV-2019 patients and these preliminary results could be used for conducting and planning large clinical trials and prospective multicentric cohort studies.

Conclusion:

The result of this systematic review and meta-analysis suggest that Hydroxychloroquine and Remdesivir have shown promising results in the *in vitro* studies. However, based on the

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current clinical evidence, our meta-analysis did not observe significant beneficial effect of any treatment on nCOV-2019 patients apart from a significant association in better overall clinical recovery of Remdesivir compared to placebo, less all-cause mortality in Tocilizumab arm compared to controls and a borderline association in time to clinical recovery of Lopinavir-Ritonavir treatment compared to control group. Hydroxychloroquine with or without azithromycin might be associated with higher all-cause mortality, more total adverse events, less overall clinical recovery and a longer mean time to clinical recovery. Results from further large clinical trials are warranted.

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Table 1: Baseline characteristics of *in vitro studies* on the inhibition and potential treatment of nCOV-2019

S. No.	Author, Year	Country	Sample type	Assay Used	Treatment	Control	EC_{50} or IC_{50}	Incubation time (h)
1.	Wang C, 2020[30]	Netherlands	Vero E6	VNA	47D11 H2L2 antibody	Isotype	0.15ug/ml	24
2.	Wang X, 2020[18]	China	Vero E6	CCK8	Arbidol	-	4.11[3.55-4.73]uM	48
3.	Rothan H, 2020[28]	USA	Huh7	q-RT-PCR	Auranofin	DMSO	1.4uM	24, 48
4.	Sheahan T, 2020[26]	USA	Calu 3, Vero E6	CTG; Plaque	NHC	-	Vero: 0.3, Calu3: 0.08uM	48, 72
5.	Kim HY, 2020[19]	China	MHV-A59; Vero	MTT	CIrh; MEco; COrh; PHco; Ssr; Mcr	No extract	CIrh = 19.4±7.0, MEco = 13.0±1.4, COrh = 2.0±0.5, PHco = 10.4±2.2, Ssr = 27.5±1.1, Mcr = 61.9 ± 6.1 ug/ml	
6.	Meyer S, 2020[29]	Germany, USA, Belgium	Caco-2	MTT; CPE	Darunavir	RDV	>100uM	48
7.	Wu Y,	China	Vero E6	CPE	Group E antibodies:	-	n3086 = 26.6, n3113 =	3

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	2020[25]				n3086, n3113		18.9 ug/ml	
8.	Yao X, 2020[5]	China	Vero	96 Well	HCQ	CQ	0.72uM	24, 48
9.	Liu J, 2020[20]	China	Vero E6	CCK8	HCQ	CQ	12.96uM	48
10.	Mantlo E, 2020[27]	USA	Vero E6	CPE	IFN-α, IFN-β	-	IFN-α = 1.35, IFN-β = 0.76 IU/ml	22
11.	Caly L, 2020[31]	Australia	Vero/hSLAM	12-well; Taqman RT-PCR	Ivermectin	Viral DNA	2uM	0, 72
12.	Runfeng L, 2020[21]	China	Vero E6	MTT; CPE; Plaque	Lianhuaqingwen	RDV	411.2 μg/mL	72
13.	Deng W, 2020[22]	China	Vero E6	CPE	PDL	-	1.078 mg/mL	-
14.	Wang M, 2020[23]	China	Vero E6	CCK8	RDV, CQ	NA	RDV- 0.77uM, CQ - 1.13uM	48
15.	Choy KT, 2020[24]	China	Vero E6	TCID50; qRT-PCR; CTG; LCVA	RDV, LPV, EH, HH	-	RDV = 23.15uM, LPV = 26.63, EH = 0.46, HH = 2.55	48

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Abbreviations: Virus Neutralization assay (VNA); Cell counting kit 8 (CCK8); CellTiter-Glo (CTG); Methyl Thiazolyl Tetrazolium (MTT); Cytopathic effect (CPE) inhibition assay; Luminescent Cell Viability Assay (LCVA); Cell Viability Assay (CVA); Qualitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR); Dimethyl Sulfoxide (DMSO); Chloroquine (CQ); Remdesivir (RDV); Beta-d-N4-hydroxycytidine (NHC); Cimicifuga rhizome (CIrh), Meliae cortex (MEco), Coptidis rhizome (Corh), Phellodendron cortex (PHco), Sophora subprostrata radix (Ssr), Mountan cortex radices (Mcr); Hydroxychloroquine (HCQ); Lopinavir (LPV); Pudilan Xiaoyan Oral Liquid (PDL); Ementine Hydrochloride (EH); Homoharringtonine (HH); N-Nonyldeoxynojirimycin (NN-DNJ); Interferon-α/ Interferon –β (IFN α/ β)

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Table 2: Baseline characteristics of clinical studies included in the systematic review and meta-analysis

S. No	Author, Year (Country)	Study design (Single/ Multicentre)	Total sample size	Overall age, Mean (SD)	Total males, n (%)	Treatment	Comparator	Risk of Bias
1	Tang W, 2020 [10] (China)	Phase-4, Open label RCT (Multicentre)	150	46.1 (14.7)	82	HCQ	Control	High
2	Chen J, 2020 [32] (China)	Phase-3, Open label RCT (Single)	30	48.6 (3.7)	21	HCQ	Control	High
3	Gautret P, 2020 [6] (France)	Open label non-RCT (Multicentre)	36	45.1 (22)	15	HCQ, HCQ + Azithromycin	Control	Some concerns
4	Geleris J, 2020 [48] (USA)	Observational study (Single)	1376	.	781	HCQ	Control	Low
5	Yu B, 2020 [33] (China)	Retrospective cohort study (Single)	550	68 (13.38)	344	HCQ	Control	Some concerns
6	Magagnoli J, 2020 [49] (USA)	Retrospective cohort study (Single)	807	68.53 (12.49)	772	HCQ, HCQ + Azithromycin	Control	Some concerns
7	Mahévas M, 2020 [59]	Retrospective observational study	173	60 (11.96)	125	HCQ	Control	Some concerns

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	(France)	(Multicentre)						
8	Rosenberg ES, 2020 [50] (USA)	Retrospective cohort study (Multicentre)	1227	63	724	HCQ, HCQ + Azithromycin	Control	Low
9	Borba MGS, 2020 [60] (Brazil)	Phase-2b, Parallel, double-blind RCT (Single)	81	51.1 (13.9)	61	Low dose CQ	High dose CQ	Low
10	Huang M, 2020 (a) [35](China)	Prospective Observational study (Multicentre)	373	44.65 (13.29)	175	CQ	Control	Some concerns
11	Huang M, 2020 (b) [34] (China)	Open label RCT (Single)	22	46 (16.64)	13	CQ	Lopinavir-Ritonavir	High
12	Cao B, 2020 [36] (China)	Open label RCT (Single)	199	58.33 (14.19)	120	Lopinavir–Ritonavir	Control	Some concerns
13	Ye XT, 2020 [37] (China)	Retrospective observational study (Single)	47	.	22	Lopinavir–Ritonavir	Control	Some concerns
14	Jun C, 2020 [38] (China)	Retrospective observational study (Single)	134	48.25 (5.19)	69	Lopinavir–Ritonavir + Arbidol	Control	Low
15	Li Y, 2020 [39]	Phase-4, Open label	86	49.4 (14.7)	24	Lopinavir–Ritonavir +	Control	Some concerns

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	(China)	RCT (Single)				Arbidol		
16	Wang Y (a), 2020 [11] (China)	Phase-3, Double-blind, Placebo-controlled RCT (Multicentre)	236	64 (11.19)	140	Remdesivir	Placebo	Low
17	Beigel JH. 2020 [52] (USA)	Phase-3, Double-blind, Placebo-controlled RCT (Multicentre)	1059	58.9 (15)	684	Remdesivir	Placebo	Low
18	Goldman JD, 2020 (USA) [53]	Open label RCT (Multicentre)	397	60.5 (14.93)	253	Remdesivir 5-day	Remdesivir 10-day	Some concerns
19	Cai Q, 2020 [40] (China)	Open label non-RCT (Single)	80	47.92 (19.06)	35	Favipiravir	Lopinavir-Ritonavir	Some concerns
20	Cantini F, 2020 [54] (Italy)	Open label non-RCT (Single)	24	63.57 (11.95)	20	Baricitinib	Control	Low
21	Hung IFN, 2020 [61] (Hong Kong)	Phase-2, Open label RCT (Multicentre)	127	48.67 (22.5)	68	Lopinavir/ Ritonavir, Ribavirin, IFN-B1	Lopinavir-Ritonavir	High
22	Deng L, 2020 [41] (China)	Retrospective cohort study (Single)	33	44.56 (15.73)	17	Lopinavir/ Ritonavir, Arbidol	Lopinavir-Ritonavir	Some concerns
23	Fadel R, 2020 [51] (USA)	Quasi Experimental study (Multicentre)	213	61.96 (16.07)	109	Early-corticosteroid group	Late-corticosteroid group	Some concerns

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24	Wang Y (b), 2020 [42] (China)	Retrospective cohort study (Single)	46	55.33 (12.24)	26	Corticosteroid	Control	Some concerns
25	Zha L, 2020 [43] (China)	Retrospective cohort study (Multicentre)	31	41.67 (17.1)	20	Corticosteroid	Control	Some concerns
26	Lu X, 2020 [44] (China)	Case-Control study (Single)	62	58.66 (13.6)	32	Corticosteroid	Control	Low
27	Qin N, 2020 [45] (China)	Retrospective observational study (Single)	72	49.33 (15.89)	41	Corticosteroid	Control	Some concerns
28	Cruz AF, 2020 (Spain) [62]	Retrospective cohort study (Single)	463	65.79 (13.3)	73	Corticosteroid	Control	Some concerns
29	Liu X, 2020 [46] (China)	Retrospective cohort study (Single)	22	55.27 (12.27)	15	Dipyridamole	Control	Some concerns
30	Li L, 2020 (China) [47]	Open label RCT (Multicentre)	103	70 (12.03)	60	Convalescent Plasma	Control	Some concerns
31	Guaraldi G, 2020 (Italy) [55]	Retrospective cohort study (Multicentre)	544	66.67 (15.61)	359	Tocilizumab	Control	Some concerns
32	Campochiaro C, 2020 (Italy) [56]	Retrospective cohort study (Single)	65	63.75 (16.47)	56	Tocilizumab	Control	Low

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33	Colaneri M, 2020 (Italy) [57]	Retrospective cohort study (Single)	112	63.55 (16.95)	82	Tocilizumab	Control	Some concerns
34	Capra R, 2020 (Italy) [58]	Retrospective observational study (Single)	85	64.17 (13.95)	64	Tocilizumab	Control	Some concerns
35	Deftereos SG, 2020 [63] (Greece)	Open label RCT (Multicentre)	105	64.67 (16.54)	61	Colchicine	Control	Some concerns

Abbreviations: HCQ- Hydroxychloroquine; CQ- Chloroquine; IFN- Interferon; USA- United States of America

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Figure legends

Figure 1: PRISMA flow diagram for the systematic review and meta-analysis

Figure 2(a-d): Meta-analysis of hydroxychloroquine vs. control groups to assess (a) all-cause mortality, (b) total adverse events, (c) overall clinical recovery, (d) time to clinical recovery.

Figure 3(a-c): Meta-analysis of lopinavir-ritonavir vs. control groups to assess (a) total adverse events, (b) overall clinical recovery, (c) time to clinical recovery.
Figure 3(d, e): Meta-analysis of lopinavir-ritonavir vs. arbidol groups to assess (d) total adverse events, (e) overall clinical recovery.

Figure 4(a, b): Meta-analysis of arbidol vs. control groups to assess (a) total adverse events, (b) overall clinical recovery.

Figure 5(a-d): Meta-analysis of Remdesivir vs. Control groups to assess (a) all-cause mortality, (b) total adverse events, (c) overall clinical recovery, (d) time to clinical recovery.

Figure 6(a, b): Meta-analysis of Corticosteroid vs. Control groups to assess (a) all-cause mortality, (b) time to clinical recovery.
Figure 6(c, d): Meta-analysis of Tocilizumab vs. Control groups to assess (c) all-cause mortality, (d) overall clinical recovery.

Figure 7(a-b): Meta-analysis of combination therapy. Meta-analysis of Hydroxychloroquine + Azithromycin vs. Control groups to assess (a) all-cause mortality, (b) overall clinical recovery.

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Figure 8(a): Labbé plot analysis for observing the trend and between-study heterogeneity in meta-analysis between Hydroxychloroquine and Control group for assessing the overall clinical recovery outcome. Figure 8(b): Funnel plot for publication bias analysis of Hydroxychloroquine Vs. Control group assessing the overall clinical recovery (Egger's P-value: 0.003). Figure 8(c): Meta-regression analysis for assessing the all-cause mortality outcome between Hydroxychloroquine and Control group using "ethnicity" as predictor variable (P-value: <0.001).

Figure 9(a, b): Risk of bias assessment of the included studies in the systematic review using the (a) new Cochrane risk of bias tool for randomized controlled trials (ROB-2) and (b) Newcastle Ottawa Scale for non-RCTs, cohort and case-control studies.

Figure 10: Influence diagnostic tools and sensitivity analysis plots for identifying the potential outlier studies and assessing the heterogeneity in the pooled effect size for assessing the all-cause mortality outcome between hydroxychloroquine treatment and control group.

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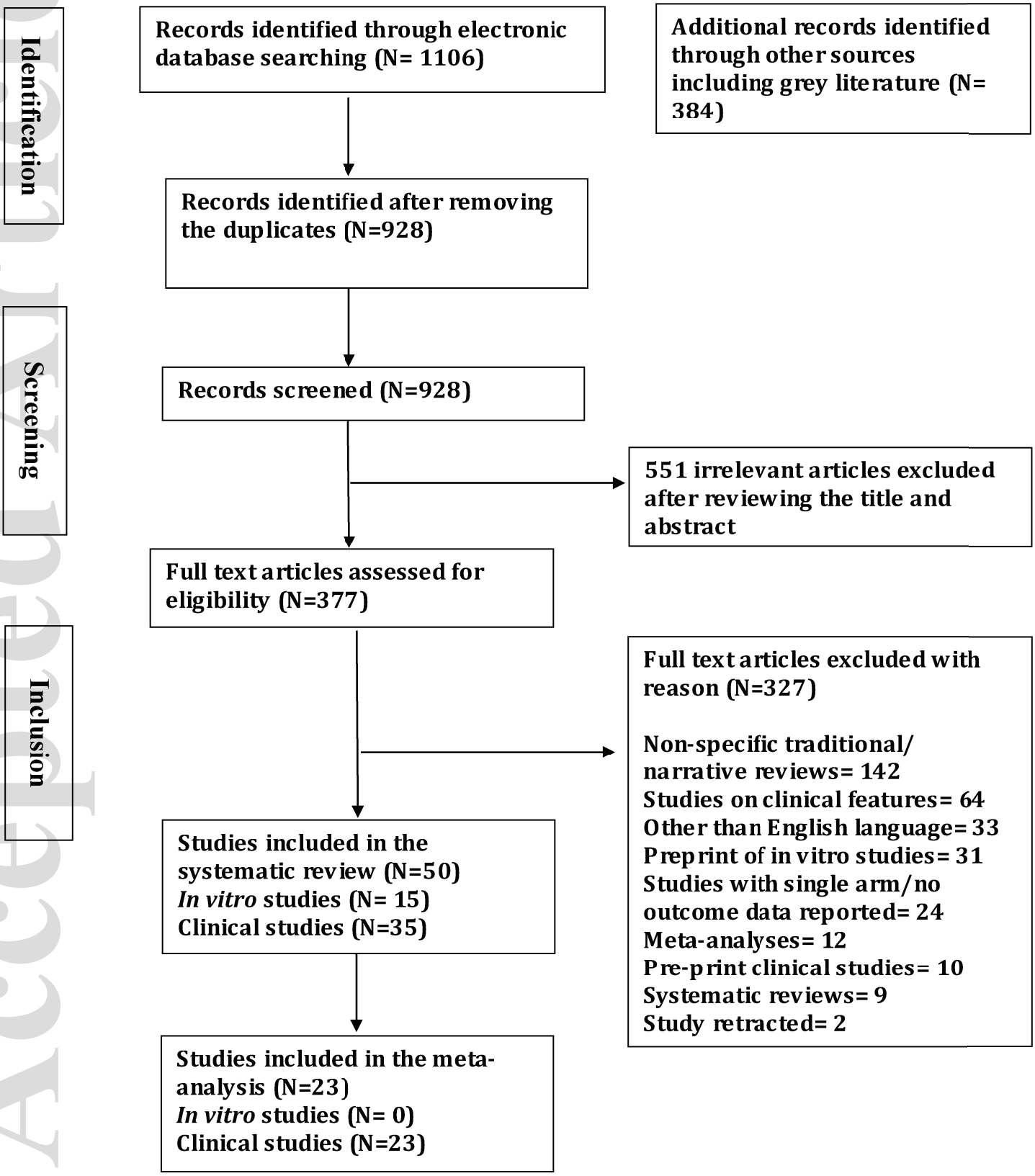

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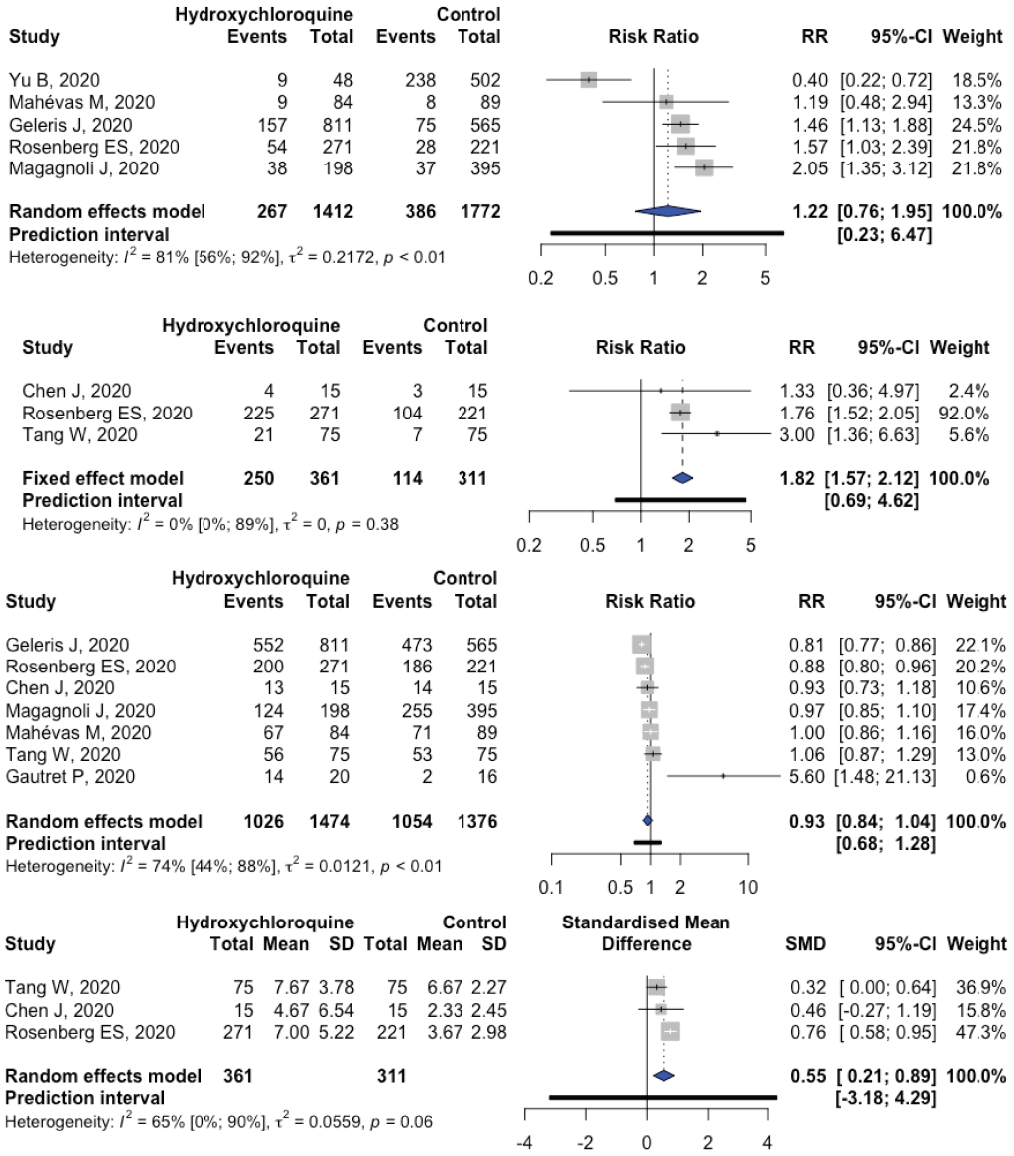

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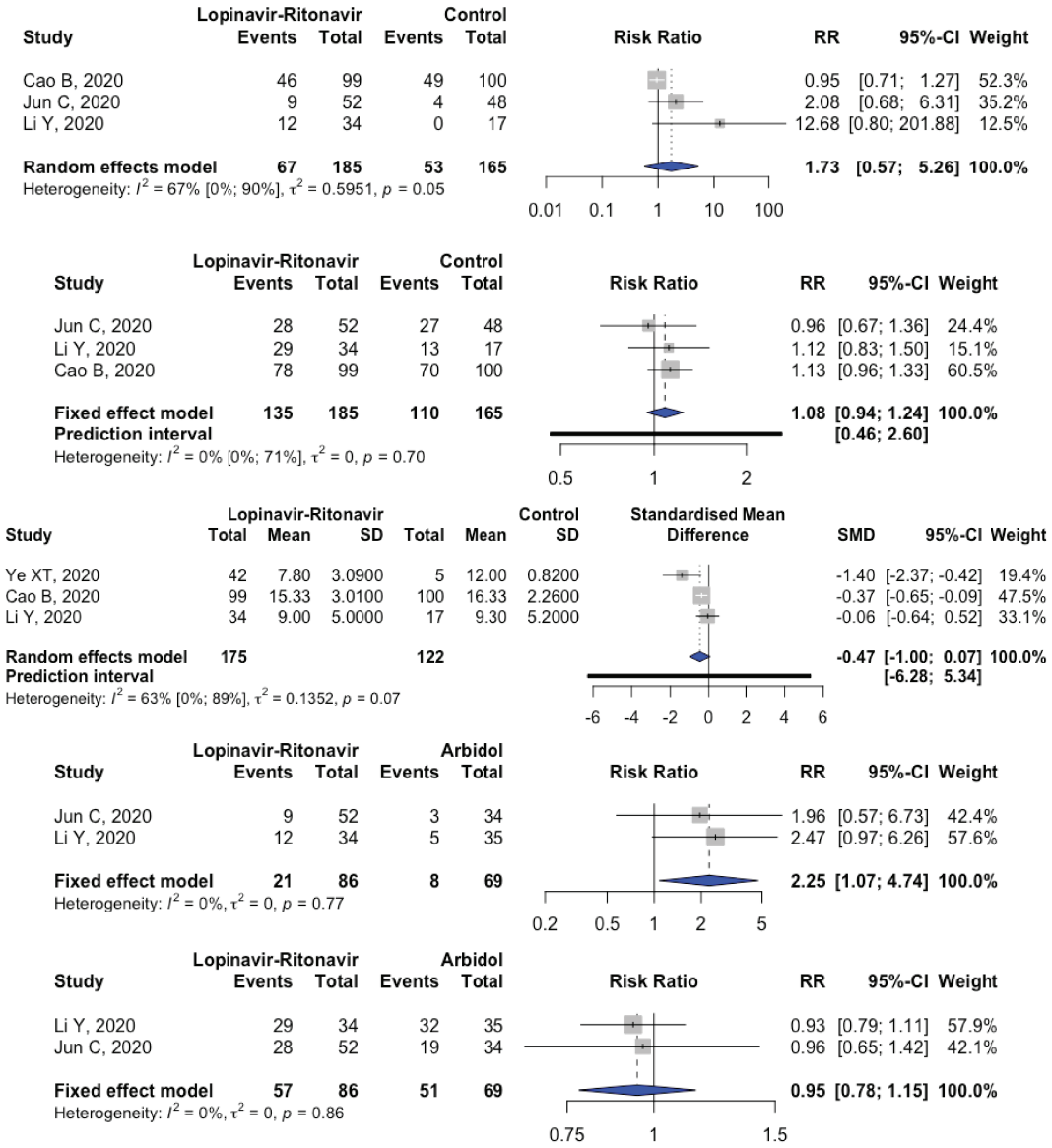

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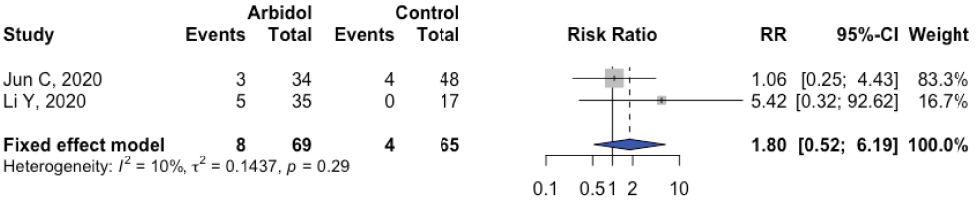

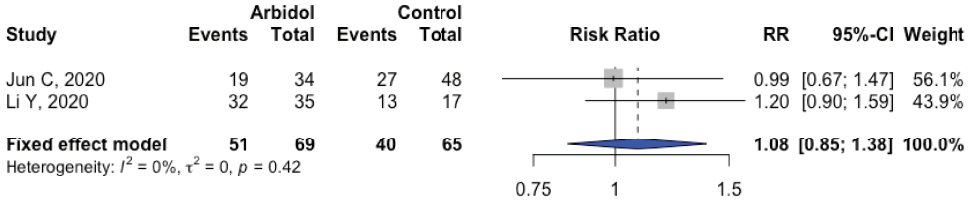

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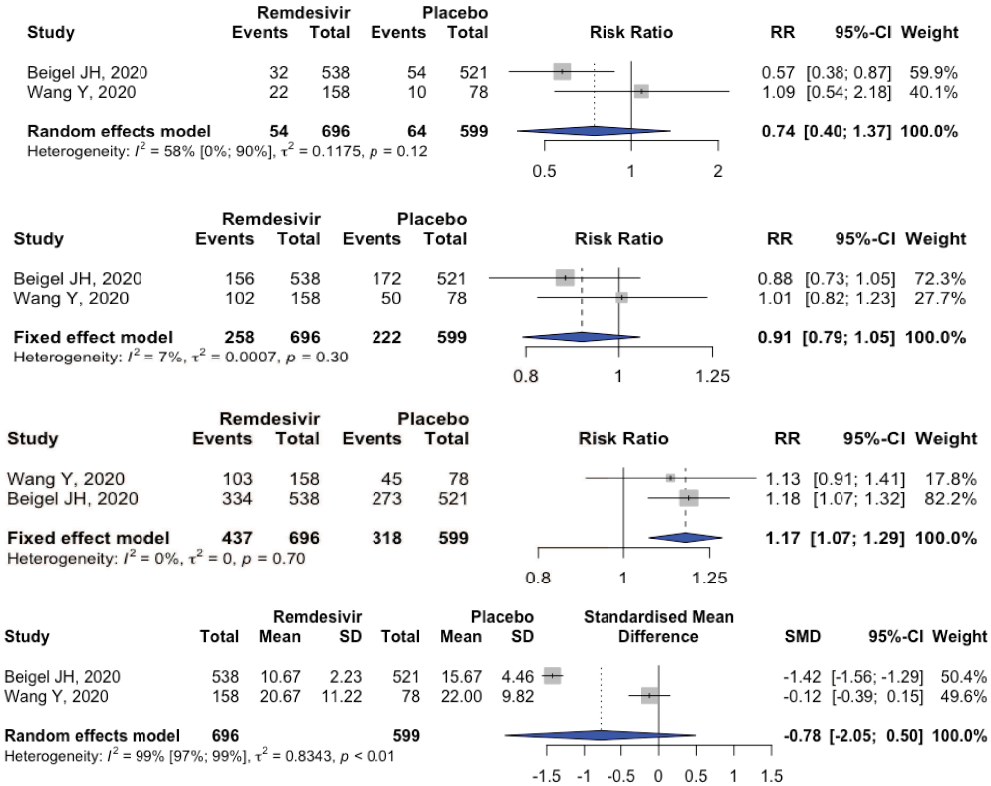

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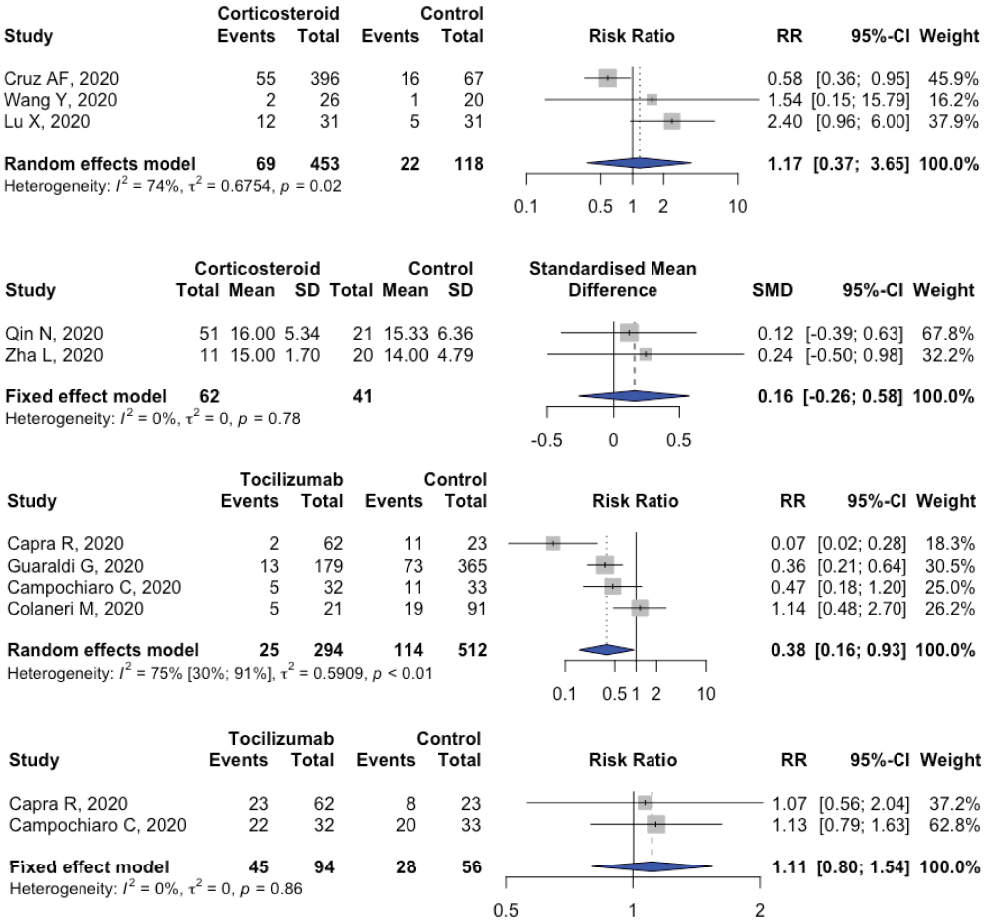

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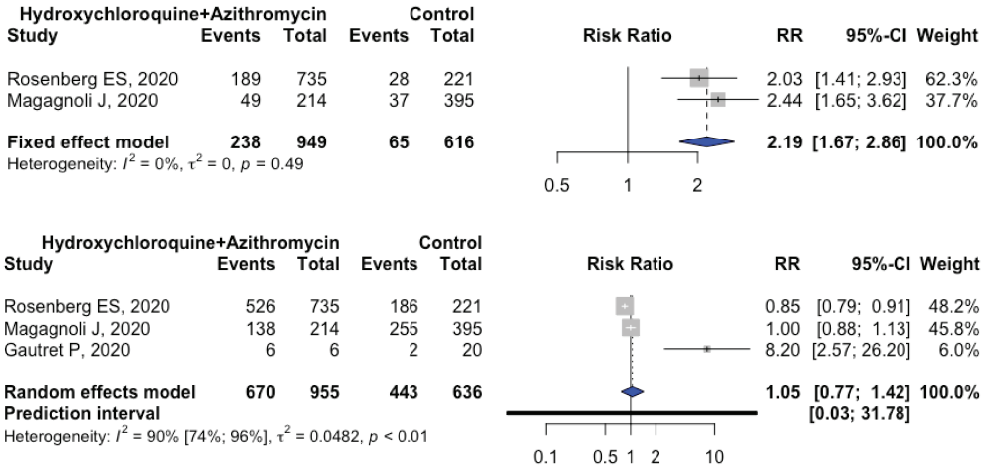

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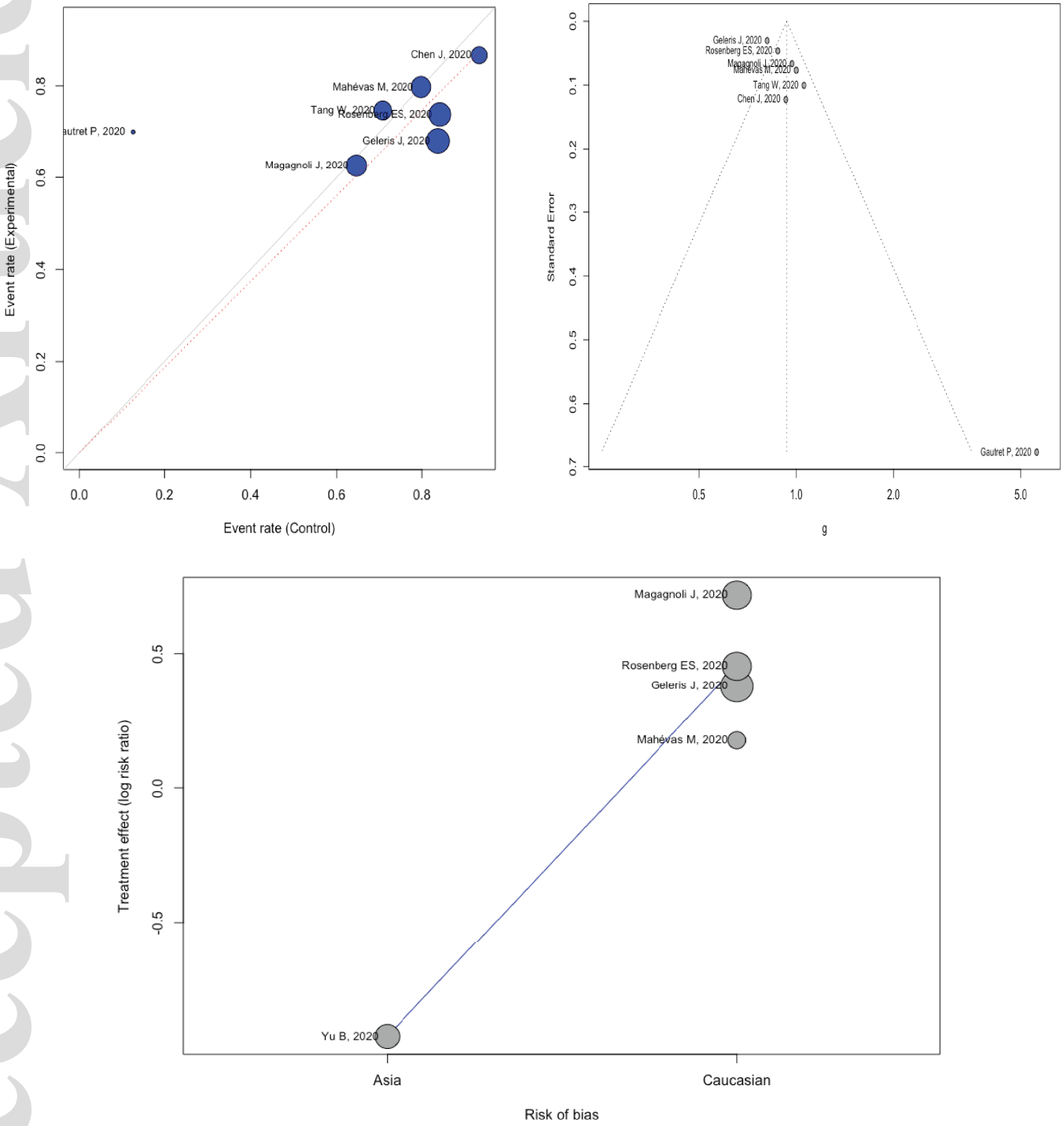

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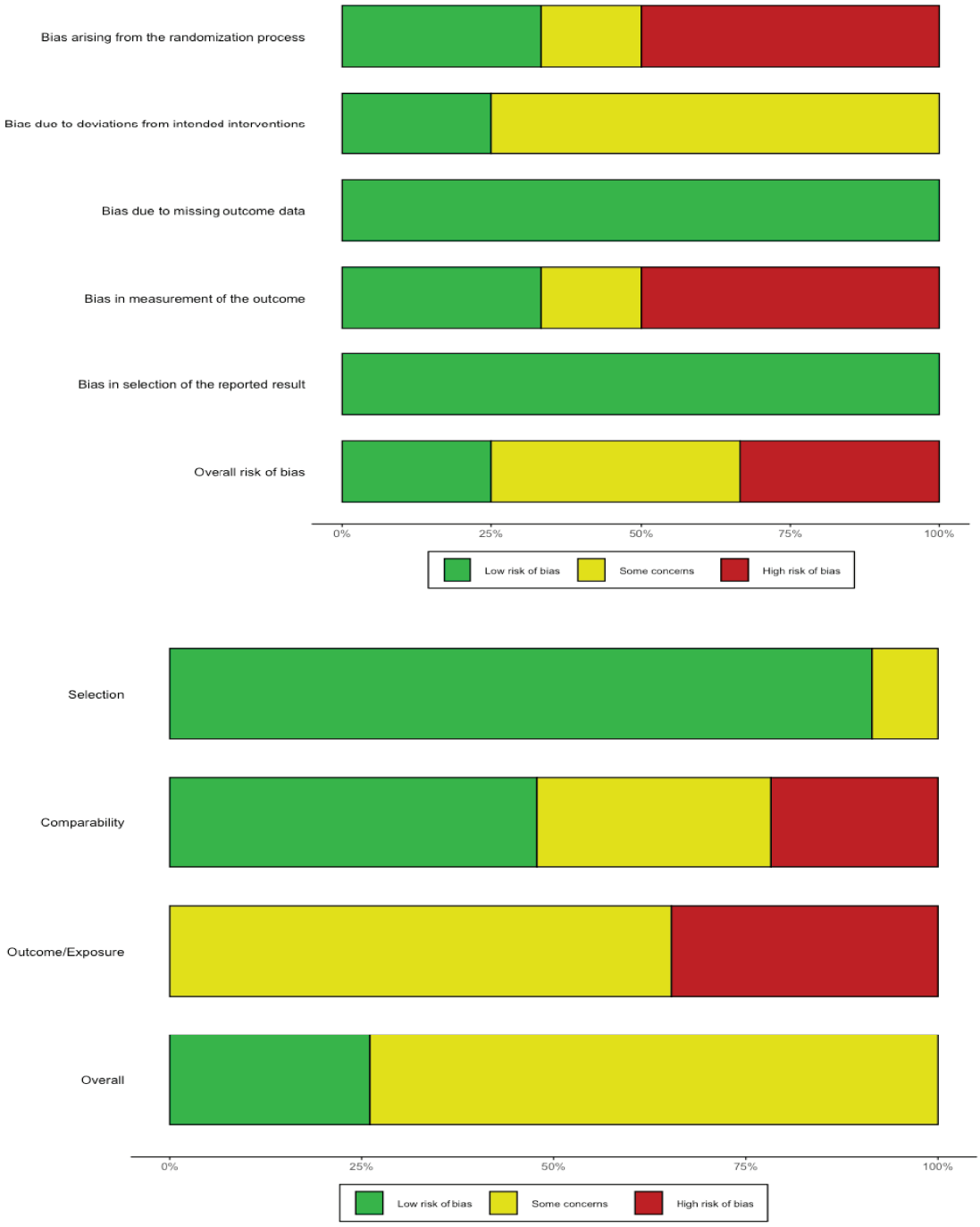

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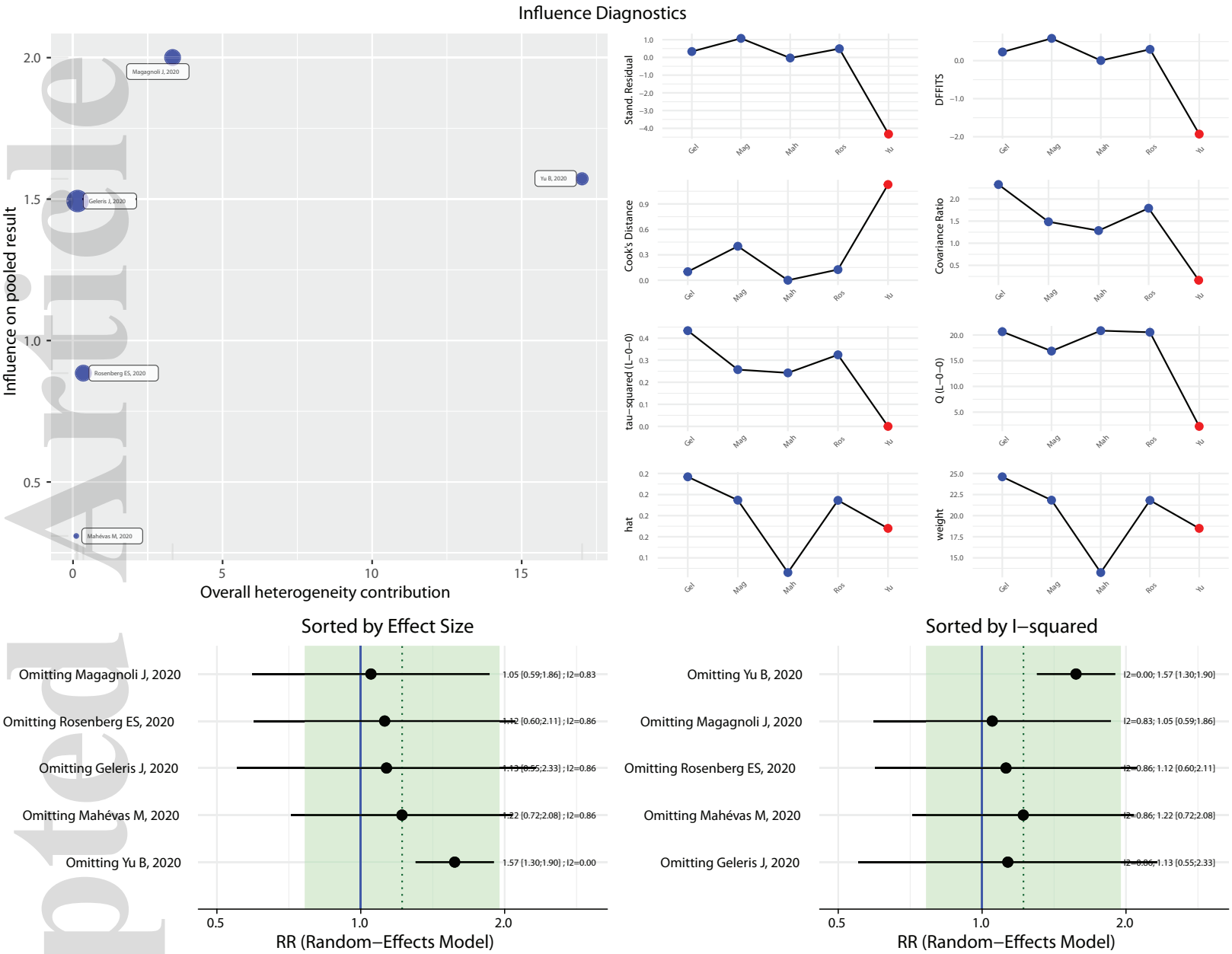

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