Pairwise and Network Meta-Analysis of Antiviral and other Treatment Efficacy in Covid-19 Patients

Singh P[1], Upadhyay A. K[2], Karthikeyan R[3], Vinodh Kumar O.R[4]

[1]Ph. D. Student, [2]Professor and Head, Department of Veterinary Public Health and Epidemiology, College of Veterinary and Animal Sciences GBPUAT, Pantnagar, India, [3]Ph. D. Student and [4]Senior Scientist, India Division of Epidemiology, ICAR-Indian Veterinary Research Institute, Izatnagar, India.

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Abstract

A total of 77 literatures till November 2020 were screened regarding various interventions to treat COVID-19 patients, among which 16 and 15 studies fulfilling predefined exclusion and inclusion criteria were subjected to Pairwise and Network meta-analysis respectively. In Pairwise meta-analysis, the recovery rate of *treatment with* Lopinavir/Ritonavir versus other antiviral (OR= 0. 0381, CI= 0.0021-0.6870), placebo (OR= 0.6592, CI= 0.4207-1. 0329), Remdesivir (OR= 0.5286, CI= 0.3915-0.7137) and standard care (OR= 0.9787, CI= 0.8523-1.1238) in fixed and random effect model with 95% confidence limit found statistically significant protection than those of all other treatment. In Network meta-analysis, recovery estimates sizes of treatment, in reference with other antivirals 1.0000 (0.9917, 1.0000) shows less risk with treatment Standard care 0.7811 (0.6696, 0.8417), Remdesivir 0.7717 (0.6491, 0.8144), Lopinavir/ Ritonavir 0.7801 (0.6701, 0.8473), Placebo 0.7219 (0.6178, 0.7836).

Keywords: *COVID-19,* treatment efficacy, Network meta-analysis, Pairwise meta-analysis, worldwide.

Introduction

To date seven coronavirus have been identified that can infect humans. The newly-identified SARS-CoV-2 are highly pathogenic, causing severe lower respiratory tract infection in relatively more patients with a higher chance to develop acute respiratory distress syndrome (ARDS) and extrapulmonary manifestations[1].

In December, 2019, Wuhan City of Hubei Province of China reported cluster of cases of pneumonia of unknown etiology associated with the Huanan seafood market in Wuhan and causative agent was identified as severe acute respiratory syndrome coronavirus 2(SARS CoV-2 previously 2019-nCoV) with use of next-generation sequencing[2,3].

A few medicines are as of now being tried around the world. Viral contaminations are the most incessant irresistible sicknesses and are normal triggers for comprising major organic, clinical, and financial issues around the world[4,5]. Therefore therapeutic management of COVID-19 cases will play a vital role in prevention and halt the spread of disease[6].

There are dearth of FDA approved antiviral drugs and other interventions capable of combating

Corresponding Author: A. K. Upadhyay, Professor and Head, Department of Veterinary Public Health and Epidemiology, College of Veterinary and Animal Sciences GBPUAT, Pantnagar-263145, India.

E-mail: ajay.akup@gmail.com

COVID-19 infections, which has led to great difficulty in limiting morbidity and case fatality rate caused by this pandemic[7]. The World Health Organization's International Clinical Trials Registry Platform stated that presently more than 590 clinical trials are identifying effective therapeutics interventions to treat COVID-19 patients[8,9]. There are several candidate medications such as Arbidol, Azithromycin, Favipiravir, Hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir and Tocilizumab have been evaluated to treat COVID-19 but none of the drugs has been approved so far[10]. Despite sincere efforts worldwide to identify potential treatments for COVID-19 patients, there is no promising evidence for drugs that specifically targeting SARS-CoV-2[11].

Methods

The recommended approach to developing the research question is the **PICO** (i.e., participants, intervention, comparator, and outcome) framework. Pairwise meta-analysis and network meta-analysis can be used to answer comparative effectiveness research questions in which multiple interventions are available, or can be used for a given condition. The studies had patients with lab confirmed COVID-19 of any age which were enrolled either in *remdesivir and lopinavir/ritonavir* compared to standard care, placebo and other antiviral *treatment.* Remdesivir and lopinavir/ritonavir were taken in the treatment arm and placebo, standard care and other antiviral in the control arm. We performed a comprehensive published article search regarding treatment of COVID-19 patients and its recovery worldwide from all peer-reviewed articles. All the individual studies were reviewed and screened manually by two investigators independently based on the pre-define inclusion and exclusion criteria (Supplementary Table 1) and the third investigator resolved the discrepancy between the two review investigators. All peer-reviewed articles documenting the treatment efficacy of COVID-19 worldwide till November 2020 were selected for review from electronic databases like PubMed, Science Direct, Scopus, Indianjournals.com, J-Gate@ Consortium of e-Resources in Agriculture (CeRA), Google Scholar, and Springer publications. The keywords used for the search were COVID-19, SARS-CoV-2 treatment, worldwide, efficacy, clinical trial, remdesivir and lopinavir/ritonavir**.** Screening at title and abstract level followed by full-text screening, data extraction, and quality assessment, were also carried out before starting the review of full papers. A total of 77 literatures till November 2020 were screened regarding various interventions to treat COVID-19 patients among which 16 and 15 publications (Supplementary Table 2 and 3) were extracted into the author's name, year of publication, article title, sample size, recovery and death were incorporated for pairwise and network meta-analysis respectively. The PRISMA flowchart summarizing screening and selection process is depicted.

Data analysis

Analysis of pairwise meta-analysis within frequentist framework using "netmeta" and random-effects network meta-analysis within a Bayesian framework using "pcnetmeta", Arm-based model for binary outcomes were performed in R studio software (version 3.6.3)[12].

model = "het_cor",

link = "probit",

prior.type = "chol",

a = 0.001, b = 0.001, c=5,

n.adapt = 5000, n.iter = 10000,

n.thin=1, n.chains = 3.

Results

A meta-analysis of these studies showed significant variability/heterogeneity between the studies, and the between-study variance, I^2 = 0. 0 % and Tau^2 =51.4%. In meta-analysis, network plot setup visualized the network among treatment. Each node represents a treatment, and the edges indicate the direct comparisons between the two treatments and the thickness of the line corresponds to the number of trials in the comparison and size of the node corresponds to the number of studies that involve the intervention. Direct comparison between lopinavir/ ritonavir-standard care, remdesivir-standard care, lopinavir/ritonavir-placebo, remdesivir-placebo whereas indirect comparison between lopinavir/ ritonavir-other antivirals was created in 'netmeta".

Meta-analysis outcome measured in treatment effect size which reflects the magnitude and direction of the treatment effect of each study. The treatment effect size of every treatment was lower than that of treatment between *l*opinavir/ritonavir and other antivirals (3.2669) (Supplementary Table 4). The recovery rate of *treatment with* lopinavir/ritonavir versus other antiviral (Odds Ratio (OR)= 0.0381, CI= 0.0021-0.6870), placebo (OR= 0.6592, CI= 0.4207-1. 0329), remdesivir (OR= 0.5286, CI= 0.3915-0.7137) and standard care (OR= 0.9787, CI= 0.8523-1.1238) in fixed and random effect model with 95% confidence limit found statistically significant protection than those of all other treatment including other antivirals, remdesivir, placebo and standard care (Table 1 and 2) which revealed that lopinavir/ritonavir had better efficacy among the interventions for COVID-19 patients' treatment.

One of the most useful tools used in meta-analysis is forest plot which provides a visual summary of analysis and findings. The reference treatment remdesivir passes through a line of no effect and OR of lopinavir/ritonavir was significantly lower compared to all other treatments viz. standard care, placebo and other antiviral. The reference treatment other antivirals passed through the line of no effect and OR of lopinavir/ritonavir and standard care were significantly lower compared to placebo and remdesivir and the reference treatment standard care passes through line of no effect and OR of lopinavir/ ritonavir was border line significantly lower compared to those of all other treatment placebo, other antiviral and remdesivir revealed that lopinavir/ritonavir had significantly protective effect among COVID-19 patients treatment. One of the most important functions of meta-analysis is that the comparative advantage of treatment can be determined through rank probability. Rank probability (Table 3) showed that lopinavir/ritonavir (0.8930) was the best treatment followed by standard care (0.8319), placebo (0.4794), remdesivir (0.2723) and other antiviral (0.0234).

The net heat plot is a matrix visualization that highlights hot spots of inconsistency between specific direct evidence in the whole network and renders transparent possible drivers[13]. In this plot the area of a grey square displays the contribution of the direct estimate of one design in the column to a network estimate in a row. In combination, the colors show the detailed change in inconsistency when relaxing the assumption of consistency for the effects of single designs. The colors on the diagonal represent the inconsistency contribution of the corresponding design. The colors on the off-diagonal are associated with the change in inconsistency between direct and indirect evidence in a network estimate in the row after relaxing the consistency assumption for the effect of one design in the column. Cool colors indicate an increase and warm colors a decrease: the stronger the intensity of the color, the greater the difference between the inconsistency before and after the detachment. So, a blue colored element indicates that the evidence of the design in the column supports the evidence in the row. A clustering procedure is applied to the heat matrix in order to find warm colored hot spots of inconsistency. In the case that the colors of a column corresponding to design d are identical to the colors on the diagonal, the detaching of the effect of design d dissolves the total inconsistency in the network.

Network meta-analysis of COVID-19 treatment efficacy by Remdesivir and Lopinavir/ Ritonavir.

The network meta-analysis was carried out to evaluate the comparative efficacy and safety of treatment used in treating COVID-19 by R package "pcnetmeta". *The treatment reference number has been designated as A (*Standard care*), B(*Remdesivir*), C (*Lopinavir/ Ritonavir*), D (*Other antivirals*), and E (*Placebo*).* The direct comparison between A to B, A to C, B to E and indirect between A to E, E to C and no comparison between E and D was created in "pcnetmeta".

Recovery effect estimates in network meta-analysis are presented in absolute plot, showed that the treatment-specific effect sizes in reference with treatment D (Other antiviral) shows less risk with treatment A (Standard care), B(Remdesivir), C (Lopinavir/ Ritonavir), E (Placebo). Contrast plot indicated the comparison among reference D (Other antiviral) with other treatments showing significant failure and density plot displaying posterior density of estimates of absolute risk, here D (Other antiviral)

showed high density of risk among other treatments of COVID-19.

In rank plot each vertical bar represents probabilities of ranks for a specific treatment, a dark area indicates the probability of a higher rank and the black area indicates the probability of the best treatment. Rank probabilities of treatments outcomes from first to last were placebo (0.8031), remdesivir (0.4072), standard care (0.4834), lopinavir/ ritonavir (0.4073), other antiviral (1.0000) (Table 4). This indicated that placebo have better role in recovery of COVID-19 than other treatments.

Table 1: Treatment estimate (sm = 'OR'): Fixed effect model with 95%-confidence limit

Treatment	Antivirals	Lopinavir–ritonavir	Placebo	Remdesivir	Standard care
Antivirals	–	26.2308 (1.4557-472.6701)	17.2905 (0.9268-322.5623)	13.8653(0.7576-253.7646)	25.6722 (1.4200-464.1354)
Lopinavir–Ritonavir	0.0381 (0.0021-0.6870)	–	0.6592 (0.4207-1.0329)	0.5286(0.3915-0.7137)	0.9787 (0.8523-1.1238)
Placebo	0.0578 (0.0031-1.0789)	1.5171 (0.9682-2.3771)	–	0.8019 (0.5485-1.1725)	1.4848 (0.9580-2.3011)
Remdesivir	0.0721 (0.0039 -1.3200)	1.8918 (1.4011-2.5545)	1.2470 (0.8529-1.8233)	–	1.8515 (1.4104-2.4306)
Standard care	0.0390 (0.0022-0.7042)	1.0218 (0.8898-1.1732)	0.6735 (0.4346-1.0438)	0.5401 (0.4114-0.7090)	–

Table 2: Treatment estimate (sm = 'OR'): Random effect model with 95%-confidence limit

Treatment	Antivirals	Lopinavir–ritonavir	Placebo	Remdesivir	Standard care
Antivirals	–	26.2308 (1.4557-472.6701)	17.2905 (0.9268-322.5623)	13.8653 (0.7576-253.7646)	25.6722 (1.4200-464.1354)
Lopinavir–ritonavir	0.0381 (0.0021-0.6870)	–	0.6592 (0.4207-1.0329)	0.5286 (0.3915-0.7137)	0.9787 (0.8523-1.1238)
Placebo	0.0578 (0.0031-1.0789)	1.5171 (0.9682-2.3771)	–	0.8019 (0.5485-1.1725)	1.4848 (0.9580-2.3011)
Remdesivir	0.0721 (0.0039 -1.3200)	1.8918 (1.4011-2.5545)	1.2470 (0.8529-1.8233)	–	1.8515 (1.4104-2.4306)
Standard care	0.0390 (0.0022-0.7042)	1.0218 (0.8898-1.1732)	0.6735 (0.4346-1.0438)	0.5401 (0.4114-0.7090)	–

Table 3: Estimated rank P-score of fixed and random model of treatments from the COVID-19 dataset obtained from the "netmeta" R package.

S. No	Treatment	P-score (fixed)	P-score (random)
1	Antivirals	0.0234	0.0234
2	Lopinavir–ritonavir	0.8930	0.8930
3	Placebo	0.4794	0.4794
4	Remdesivir	0.2723	0.2723
5	Standard care	0.8319	0.8319

Table 4: Estimated rank probabilities of treatments from the COVID-19 dataset obtained from the "pcnetmeta" R package

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5
A	0.0498	0.2451	0.4834	0.2216	0.0000
B	0.0788	0.4072	0.1067	0.3181	0.0000
C	0.0682	0.2418	0.3719	0.4073	0.0000
D	0.0000	0.0000	0.0000	0.0000	1.0000
E	0.8031	0.1059	0.0380	0.0530	0.0000

Discussion

Coronavirus disease caused unprecedented challenges to the healthcare[14]. The result of Pairwise meta-analysis shown that lopinavir–ritonavir (0.8319) is the best intervention for treating COVID-19 patients followed by standard care (0.8319), placebo (0.4794), remdesivir (0.2723) and other antivirals (0.0234). During the SARS outbreak, treatment with lopinavir in combination with ritonavir, was explored with some success in nonrandomized clinical trials[15]. Patients with SARS-CoV treated with lopinavir/ritonavir showed a progressive decrease of viral load[16].

Lopinavir–ritonavir combination is a protease inhibitor that has in vitro antiviral activity against SARS-CoV and Middle East Respiratory Syndrome (MERS) coronaviruses[10]. In an earlier study, the clinical efficacy of lopinavir/ritonavir was evaluated in the treatment of 47 COVID-19 patients from Ruian people's hospital China[1]. The results shown that 42 patients who received lopinavir/ritonavir has significant and speedy recovery to normal body temperature than control group who received standard adjuvant therapy (test group: 4.8±194 days vs control group: 73±1.53 days, *p*=.0364). In a systematic review and meta-analysis of COVID-19 clinical features and/or treatment found that treatment with lopinavir-ritonavir showed no significant benefit in mortality and ARDS (acute respiratory distress syndrome) rates while corticosteroids were associated with a higher rate of ARDS (P = .0003)[16]. Similarly, a randomized clinical trial was conducted in 199 patients and found that patients who received lopinavir-ritonavir have no significant clinical improvement compared to control group with a standard of care[18].

Remdesivir is a prodrug of nucleoside analogue and viral RNA-dependent RNA polymerase competitive inhibitor that has antiviral activity against broad spectrum of RNA viruses including MERS and SARS-CoV[19, 20]. A randomized clinical trial involving 596 COVID-19 patients, revealed that patients received 10 days course of remdesivir has no significant improvement in health status compared to the control group randomized with standard care[21]. On the other hand, those who received a 5-day course had better outcome than standard care with uncertain clinical effect.

A systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy of remdesivir versus placebo or standard of care and found that placebo group had a higher risk of mortality as compared to the intervention group with significant odds ratio (OR=0.61; 95% CI 0.45- 0.82; P=0.001), findings suggested that remdesivir extends

clinical benefits by reducing mortality, adverse events and oxygen support in moderate to severely ill COVID-19 patients[22].

Favipiravir is a purine nucleotide analogue that inhibits the viral RNA-dependent RNA polymerase also has potential to combat several viral diseases including COVID-19[10]. The efficacy and safety of the drug favipiravir was estimated and found that there was a significant clinical improvement in the favipiravir group on the 14th day compared to the control group (RR=1.29, 1.08–1.54). There was no significant differences between the two groups on viral clearance (day 14: RR=1.06, 95% CI= 0.84–1.33), non-invasive ventilation or oxygen requirement (OR=0.76, 95% CI=0.42–1.39), and adverse effects (OR=0.69, 95% CI=0.13–3.57).

The result revealed that placebo (0.8031) has better role in recovery of *COVID-19* than other treatments followed by remdesivir (0.4072), standard care (0.4834), lopinavir/ ritonavir (0.4073) and other antiviral (1.0000). In contrary to our study a study found that both 10-day and 5-day remdesivir regimens were associated with higher odds of clinical improvement (OR of 10-day regimen: 1.35, 95% CI=1.09-1.67); OR of 5-day regimen: 1.81, 95% CI=1.32-2.45, and higher probabilities of clinical recovery (RR of 10-day regimen: 1.24, 95% CI=1.07-1.43; RR of 5-day regimen: 1.47, 95% CI=1.16-1.87 compared with placebo[24].

The standard care and glucocorticoids probably reduce death, mechanical ventilation and duration of hospitalization and the clinical impact of remdesivir on mortality, mechanical ventilation, and length of hospital stay is uncertain, but it probably reduces duration of symptoms[11]. Remdesivir improves the recovery rate in both moderate and severe patients[26]. The result outcome of remdesivir treatment for 10 days increased the recovery rate on day 14 by 50% among severe COVID-19 patients (RR = 1.5, 95%CI = 1.33–1.7), while on day 28 it was increased by 14% among moderate and severe COVID-19 patients (RR = 1.14, 95% CI = 1.06–1.22). Additionally, remdesivir decreased the mortality rate, when treatment started on day 14 by 36% among all patients (RR = 0.64, 95%CI = 0.45–0.92) but not when treatment started on day 28 (RR = 1.05, 95%CI = 0.56–1.97). None of the mechanically ventilated COVID-19 patients showed better response to remdesivir in the recovery (RR = 0.3, 95%CI = 0.13–0.7) and mortality (RR = 2.33, 95%CI = 1.24–4.4) rates on day 14.

Conclusion

The result of pairwise and network meta-analysis suggests that remdesivir, other antiviral and standard care found marginal clinical benefit in COVID-19 patients while placebo and lopinavir/ritonavir may safely and effectively improve clinical outcomes of COVID-19. This analysis may help in further improvement in the treatment of COVID–19 patients. Consequently, further large scale randomized clinical trial are wanted to refine the outcomes of this intervention on the treatment of patients with COVID-19.

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