Original Research

An early Bayesian Network Meta-analysis of Coronavirus Diseases 2019 (COVID-19) clinical trials

Farshid Javdani[1], Mohammad Hashem Abdi[2], Samaneh Abiri[3], Marzieh Haghbeen[3], Ahmad Rastgarian[4], Mohammad Hasan Damshenas[4], Pouyan Keshavarz[1], Mohammad Amin Akbarnejad[1], Naser Hatami[1], Sayyed Reza Ahmadi[5], Seyed Reza Habibzadeh[5], Neema John Mehramiz[6], Mahdi Foroughian[5], Navid Kalani[3*]

1. Student Research Committee, Jahrom University of Medical Sciences, Jahrom, Iran.
2. Department of Nursing, Jahrom University of Medical Sciences, Jahrom, Iran.
3. Research center for social Determinants of Health, Jahrom University of Medical Sciences, Jahrom, Iran.
4. Anesthesiology, Critical care and pain management research center, Jahrom University of Medical Sciences, Jahrom, Iran.
5. Department of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
6. Department of Psychiatry Neurology. Banner university medical center, Tucson, AZ, USA.

Corresponding Author: Navid Kalani. Research center for social Determinants of Health, Jahrom University of Medical Sciences, Jahrom, Iran. Email: navidkalani@ymail.com. https://orcid.org/0000-0003-1900-4215

Abstract

In this paper, we conducted a Bayesian Network Meta-analysis of the latest COVID-19 clinical trials including 5 studies on 591 patients receiving 4 different agents of Arbidol, Favipiravir, lopinavir-ritonavir, and Hydroxychloroquine and standard treatment protocol. We ranked the best agent based on patient improvement using Markov-Monte-Carlo-Chain. Hydroxychloroquine showed the best efficiency following the Favipiravir, Arbidol, lopinavir-ritonavir, and standard regimen in the first week of treatment. In the second week, with excluding Hydroxychloroquine arm (as some reporting studies hadn't addressed its efficacy in the second week), Favipiravir was the best treatment following by lopinavir-ritonavir, standard care, and Arbidol. As we saw a huge change in the ranking of the drugs by evaluating outcomes in the second week of treatment, we think that COVID-19 randomized clinical trials should be performed based on a standard study protocol worldwide, that could help policy makers to make a decision on the treatment protocol.

Keywords: Network Meta-analysis, Favipiravir, SARS-CoV-2, COVID-19, lopinavir-ritonavir.

Submitted: 13 April 2020, Revised: 29 May 2020, Acepted: 5 June 2020

Introduction

In late 2019, a new coronavirus, also called SARS-CoV-2, was identified as the cause of the emergence of an unknown acute respiratory disease in Wuhan, China. An increasing number of infections have been reported in other countries around the world, and the number of new cases outside China has surpassed China itself (1). Due to severe pulmonary damages caused by novel coronavirus infection, the mortality rate has been very high in some patients; while, there is no specific treatment for the SARS-CoV-2 infection and the main solution is supportive care such as preserving vital signs, regulating oxygen levels and blood pressure, and preventing secondary infections or organ failures (2). With the worldwide

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[DOR: 20.1001.1.23222913.2020.9.3.8.9]

spread of the disease, researchers are struggling to find an effective therapy for the disease. Several clinical trials have been launched, testing different candidate agents for the treatment of COVID-19 (3).

In the present study, we investigated the rank of different agents studied in randomized controlled trials (RCTs) for patients with COVID-19 with a comprehensive, pre-specified method (4). To obtain relevant studies, Scopus, PubMed, Science Direct, and MEDRIX databases were searched with keywords of “CPVID-19”, “Coronavirus Diseases”, “SARS-CoV-2”, “trial”, “clinical trial” in 2020 (till 23 March). After selecting articles, a network meta-analysis of treatment improvement outcome was carried out using a hierarchical Bayesian network for dichotomous variables. Analyzes were conducted employing Bayesian Markov Monte Carlo Chain by NetMetaXL 1.6.1 and WinBUGS 1.4.3 software for ranking treatments based on odds ratios (ORs), shown as “Rankograms" with the surface under the cumulative ranking curve (SUCRA) probabilities.

Finally, 5 studies (5-9) with 591 patients were included in our study, comprising 4 different agents of Arbidol, Favipiravir (FPV), lopinavir-ritonavir (LPV/RPV), and Hydroxychloroquine along with standard treatment protocol. The study outcome was considered as COVID-19 clinical recovery or positive-to-negative conversion of the SARS-CoV-2 rate at 7 and 14 days of treatment initiation. Improved patients to the total number of patients ratio was 79/151 (52.32%) for FPV, 23/165 (13.94%) for LPV/RTV, 14/20 (70%) for Hydroxychloroquine, 72/136 (52.94%) for Arbidol, and 9/123 (7.32%) for Control patients, at the first week. At second week, the ratio was 10/15 (66.67%) for Arbidol, 32/35 (91.43%) for FPV, 89/163 (54.6%) for LPV/RTV, and 36/106 (33.96%) for control patients.

All 5 studies had reported the improvement rate of patients within first 7 days, and the ranking probability based on SUCRA showed that Hydroxychloroquine had the highest possibility of being the best therapy to reach the COVID-19 improvement (SUCRA=0.9901), followed by FPV (SUCRA=0.6749), Arbidol (SUCRA=0.3735), LPV/RPV (SUCRA=0.2754), and control (SUCRA=0.1861), where higher SUCRA indicates better efficiency of treatment, as shown in Figure 1.a. Study of Gautret et al. and Chen et al. were excluded in the analysis of recovery rate till 14th day of treatment, cause of lack of follow up after the first week. Results of analysis of 3 studies of Cao et al., Cai et al., and Yueping et al. revealed that FPV had the highest possibility of being the best therapy to reach the COVID-19 improvement within 2 weeks (SUCRA=0.9996), followed by LPV/RPV (SUCRA=0.6564), Control (SUCRA=0.3168), and Arbidol (SUCRA=0.02722), where higher SUCRA indicates better efficiency of treatment (Figure 1.b).

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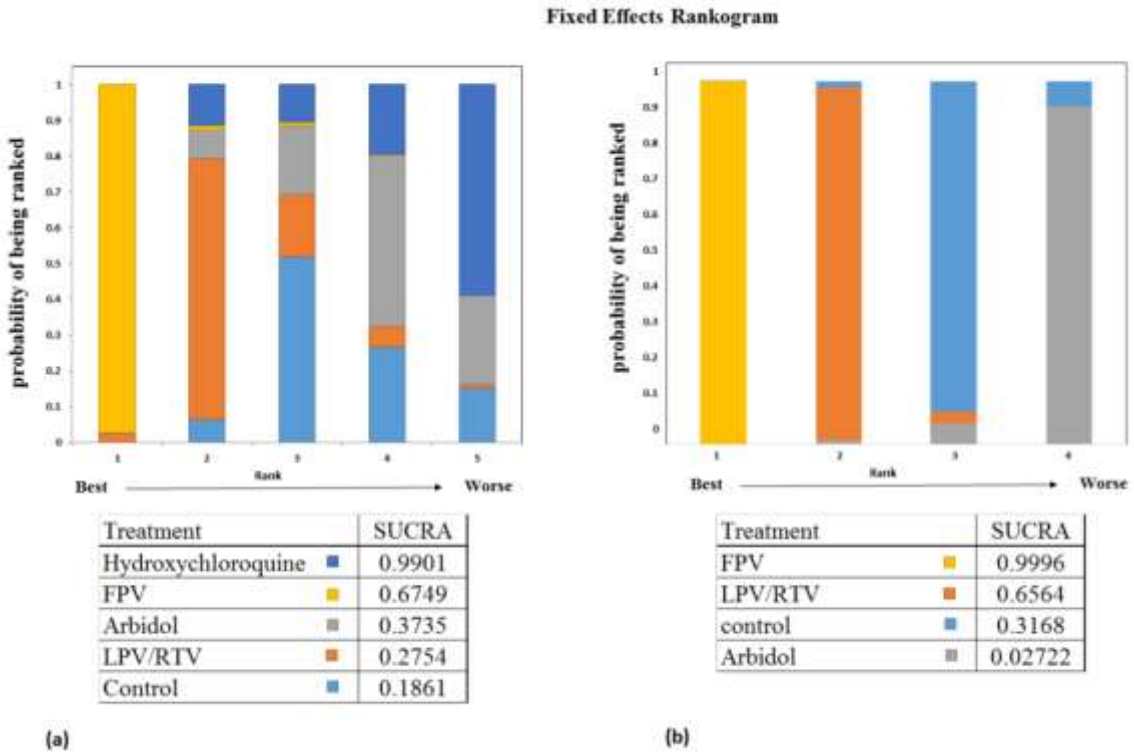


Figure 1. Rankograms of COVID-19 clinical trials. (a) Patient recovery within the first 7 days. (b) Patient recovery within the first 14 days.

While the Cao et al. study didn't reveal any significant effect of LPV/RTV in comparison of the control standard treatment regimen, in the pooled analysis of our study, there was a significant difference between LPV/RTV and standard regimens in the second week based on OR of 5.71, CI (1.29 – 31.30) for the comparison. While in the first week of treatment, no significant difference was observed as the OR of comparison was 1.26, CI (0.43 – 4.16), as shown as the supplementary figure 1.

We saw a huge change in the ranking of the rest of the drugs. LPV / RPV upgraded to second place on the 14th day. The observed effect of arbidol was also reduced and moved to the last rank in the second week of treatment. Also, a clear definition of the patient's condition improvement would be necessary for standardizing further studies. Serial PCR studies may not be available in all clinical settings and we propose researchers report the clinical condition of patients along with biochemical evaluations.

Given that many trials are being conducted globally about the COVID-19 treatment, the importance of our results, in addition to ranking the best available treatment regimen is to emphasize the need for standardizing methodology for clinical trials.

Acknowledgement:

We would like to thank the Clinical Research Development Unit of Peymanieh Educational and Research and Therapeutic Center of Jahrom

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University of Medical Sciences for providing facilities to this work.

Competing Interest: None

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