

Efficacy of Various Treatment Therapies on Patient related Outcome in Hospitalized COVID-19 Patients - A Retrospective Study

Farhana Siraj^{1*}, Nazia Mehfooz², Syed Mudasir Qadri¹, Suhail Mantoo¹, Afshan Shabir³, Tajamul Hussain², Umar Hafiz³, Ajaz Nabi Koul¹, Muzaffar Bindroo⁴, Mushtaq Dangroo⁴, Fayaz Sofi⁴, Sanaullah Shah², Rafi Jan²

¹Department of Internal Medicine, ²Pulmonary Medicine, ³Geriatrics, ⁴Rheumatology SKIMS, Soura.

ABSTRACT

Background: In December 2019, coronavirus disease (2019), with the causative organism being novel severe acute respiratory syndrome coronavirus 2 (SARS CoV 2), was first reported and declared a pandemic by WHO on March 11, 2020. The treatment is evolving and is primarily supportive. Corticosteroids are considered one of the standards of care in managing COVID-19 patients with severe illness with respiratory failure.

Objectives: This retrospective study was undertaken to assess the effect of various treatment modalities on patient-related outcomes in hospitalized COVID-19 patients.

Material and methods: Single-center retrospective study that included confirmed COVID-19 cases treated at our institute (a tertiary care hospital in Jammu and Kashmir, India) between March 2020 and December 2020. Patients with age more than 18 years were included in the study.

Results: Our study included a total of 1,000 COVID-19 positive patients. The median age of the study population was 56 years, and males outnumbered females. The majority of the patients (n = 658, 65.8%) had a severe illness at presentation. On assessing the effect of various drugs used in managing COVID-19 patients of all severity, the use of remdesivir and famotidine was associated with significantly higher survival. In a subgroup of patients with severe disease, systemic steroids were associated with substantially higher survival chances in addition to remdesivir and famotidine. The likelihood of survival was significantly higher in patients with severe COVID 19 illness who received a combination of systemic steroids plus remdesivir compared to steroids and remdesivir alone.

Conclusion: Steroids were effective in severe COVID-19 illness, and the combination of steroids and remdesivir was more effective in severe disease. There is a need to undertake more large scale prospective randomized trials to determine the most effective drug therapies to treat sick patients and prevent the worsening of mild cases.

Keywords: Pandemic, COVID-19 illness, SARS CoV 2, severe COVID-19

JMS: 2022; 25(2):15-22 DOI: <https://doi.org/10.33883/jms.v25i2.1177>

BACKGROUND

First reports of novel severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) caused an outbreak of coronavirus disease 2019 in the city of Wuhan, China, in December 2019 and spread to the whole world in a short period and got designated as a pandemic by the World Health Organization (WHO) on March 11, 2020^{1,2} The coronavirus disease can present as an asymptomatic

infection, but mild respiratory tract illness, severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure and death has also been the reported manifestations³. Several clinical trials have evaluated different treatment modalities in the management of

Access this article online



Website:
www.jmsskims.org

DOI:
<https://doi.org/10.33883/jms.v25i2.1177>

Correspondence:

Dr. Farhana Siraj, MD
Assistant Professor,
Department of Internal Medicine, SKIMS
Email: bagdadifarhana6@gmail.com

How to cite this article: Siraj F, Mehfooz N, Qadri SM, Mantoo S, Shabir A, Hussain T, Khan UH, Koul AN, Bindroo M, Dangroo M, Sofi F, Shah S, Jan RA. Efficacy of Various Treatment Therapies on Patient related Outcome in Hospitalized COVID-19 Patients- A Retrospective Study. JMS 2022; 25 (2) 15-22

Received: 2022-03-10 Accepted: 2022-04-13



This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

COVID-19 illness, and many more are underway, primarily assessing the clinical results in terms of accelerating the clearance of the virus, reduction in duration of symptoms, progression of the disease, need for mechanical ventilation and mortality^{4,5}. Only a few of these treatment interventions have shown significant clinical benefit. Corticosteroid use has been one of the standards of care in managing COVID-19 patients with respiratory failure. Multiple randomized controlled trials (RCTs) and observational studies on corticosteroid use in hospitalized COVID-19 patients have shown a reduction in mortality and a decrease in the progression of the disease^{6,7}. Based on trial results, remdesivir was approved to treat hospitalized COVID-19 patients⁸. However, recent evidence suggested little or no benefit in reducing hospital stay, need for mechanical ventilation and reduction in mortality⁹. Results from initial RCTs that evaluated the use of tocilizumab (anti-interleukin [IL-6] receptor antibody) in COVID-19 produced conflicting results¹⁰⁻¹². Two large RCTs reported a reduction in mortality in a group of COVID-19 patients with severe and critical illnesses^{12,13}. Several studies have compared the efficacy of various treatment modalities, either alone or in combination, in COVID-19 patients and reported a beneficial effect of drugs like corticosteroids, tocilizumab and remdesivir on clinical outcomes¹⁴. Our institute is the only tertiary care centre in Jammu and Kashmir (J&K) to manage severe to critical COVID-19 patients. To evaluate the effect of various treatment modalities on patient-related outcomes (survival and mortality) in hospitalized COVID-19 patients, a retrospective study was planned.

MATERIAL AND METHODS

A single-centre retrospective study included confirmed COVID-19 patients treated at our institute (a tertiary care hospital in J&K UT) between March 2020 and December 2020. The Institutional Ethical Committee approved the study. Our study included patients with positive nasopharyngeal swabs by reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 for more than 18 years. Patients with incomplete medical records, especially with no known outcome, those who died within 24 hours of admission and pregnant/lactating women were excluded.

Classification of Patients into Nonsevere and Severe Category

For analysis, patients were grouped into two categories, nonsevere and severe. Those with mild and moderate diseases were included in a nonsevere category, whereas those with severe and critical COVID-19 illnesses were included in the severe category. The classification of patients into various grades of severity was based on the definitions provided by the Indian Council of Medical Research/ICMR¹⁵. The severity of illness was established on various clinical and radiological parameters. The mild group included those having upper respiratory tract symptoms and oxygen saturation $\geq 94\%$ with routine radiology. The moderate group included lower airway involvement during a clinical examination or imaging with $\text{SpO}_2 \leq 94\%$ on room air. The severe group included patients with $\text{SpO}_2 < 90\%$ on room air, a respiratory rate of > 30 breaths/min, $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg or lung infiltrates $> 50\%$, and the critical group included patients having ARDS, septic shock or multiorgan dysfunction. Patients were managed in areas of a hospital dedicated to COVID-19. Severe or critically ill patients were handled in a high-dependency unit and dedicated COVID intensive care units (ICUs). All patients received treatment based on the national and international available guidelines as per the institutional protocol.

OUTCOME

The primary outcome studied was to assess the outcome of various drugs used to manage COVID-19 illness on all-cause mortality and survival.

Data Extraction

Patient data was extracted from medical record files available in the medical record-keeping department. Data regarding the patient's demographic profile, clinical presentation, the severity of illness, laboratory parameters, treatment received and outcome in terms of mortality was recorded and entered on a preformed proforma. The data was then transferred and maintained on an excel spreadsheet.

Statistical Analysis

Frequencies and percentages described categorical variables, whereas mean, median and interquartile range (IQR) values described the continuous variables. The difference in means of continuous variables was compared using independent 't'-tests in the case of normally distributed

data, and a nonparametric test (Mann-Whitney test) was used in non-normally distributed data. The χ^2 test or Fisher's exact test was used to find the difference between categorical variables. A 'p-value of <0.05 was considered statistically significant. Multivariate logistic regression was done, including medications that significantly affected the primary outcome of univariate analysis. The statistical analyses were performed using SPSS version 26.0 software.

RESULTS

Our study included 1,000 RT-PCR COVID-19 positive patients admitted to our institute. The median age (IQR) of the study population was 56 years (45-65), with the majority of them being males, with the nonsurvivor category having a significantly higher median (IQR) age (median age 62[55-70] vs 53 [40-65], p0.001). In addition, males outnumbered females (64.6% vs 35.4%, p 0.67); however, no gender difference was observed between the two categories.

The most common comorbid illness observed was hypertension (50.9%), followed by diabetes mellitus (29.8%), chronic kidney disease (8.2%) and malignancy

(8.1%). Among nonsurvivors, a significantly higher proportion of patients had hypertension, chronic kidney disease, chronic lung disease and chronic liver disease (Table 1).

Patients in the nonsurvivor group demonstrated increased median (IQR) heart rate (100 [84.75-112], p 0.001) and increased respiratory rate (24 [20-30], p 0.001) compared to the survivor group at the time of presentation. The majority of the study participants (n=658, 65.8%) had a severe illness at admission to the hospital. The likelihood of survival was significantly lower in patients belonging to the severe category (88.9% vs 56.7%, p 0.001). Among various laboratory parameters, nonsurvivors had substantially lower haemoglobin, elevated total leukocyte count, higher creatinine, lower albumin, higher international normalized ratio (INR) and higher lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), ferritin and IL-6 levels (Table 2).

TLC = Total leukocyte count; SD = Standard deviation; IQR = Interquartile range; NL ratio = Neutrophil-to-lymphocyte

Table 1: Demography and Clinical Profile of study participants

Variables	Total (N=1,000)	Survivors (N=695)	Non Survivors (N=305)	P value
Age, median (IQR), years	56(45-65)	53(40-65)	62(55-70)	0.001
Gender, no. (%)				
Male	646(64.6)	446(64.2)	200(65.6)	0.670
Female	354(35.4)	249(35.8)	105(34.4)	
Comorbid illnesses, no. (%)				
Hypertension	509(50.9)	324(46.6)	185(60.7)	0.001
Diabetes mellitus	298(29.8)	194(27.9)	104(34.1)	0.049
Chronic kidney disease	82(8.2)	37(5.3)	45(14.8)	0.001
Malignancies	81(8.1)	50(7.2)	31(10.2)	0.113
Chronic lung disease	52(5.2)	28(4)	24(8)	0.012
Chronic liver disease	24(2.4)	10(1.4)	14(4.6)	0.003
Cardiovascular disease	23(2.3)	14(2)	9(3)	0.363
Cerebrovascular disease	21(2.1)	14(2)	7(2.3)	0.776
Post-transplant	10 (1.0)	6(0.9)	4(1.3)	0.512
Vital signs				
Systolic blood pressure (mmHg), median (IQR)	120(110-130)	120(110-130)	120(107-132)	0.628
Respiratory rate/min, median (IQR)	21 (21-26)	20(18-24)	24(20-30)	0.001

Table 2: Laboratory investigations of study participants

Laboratory parameters	Total (n=1,000)	Survivors (n=695)	Non survivors (n=305)	P value
Hemoglobin(g/dL), mean (SD)	11.9(2.5)	12.19 (2.43)	11.12 (2.66)	0.001
TLC ($\times 10^9/L$), mean (SD)	8.35 (4.46)	7.69 (3.68)	10.21 (5.71)	0.001
NL ratio, median (IQR)	6.3(2.8-12.6)	4.81(2.29-9.22)	11.86(6.22-22.63)	0.001
Platelets ($\times 10^9/L$), mean (SD)	158.3(85.95)	157.8 (80.95)	137.74 (83.91)	0.001
Serum Creatinine (mg/dL), median (IQR)	1.03(0.8-1.51)	0.72(0.53-1.03)	1.44(0.96-2.51)	0.001
Serum bilirubin (mg/dL), median (IQR)	0.63(0.5-0.88)	0.61(0.5-0.8)	0.96(0.78-1.27)	0.001
Alanine transaminase(U/L),median(IQR)	36(23-61)	38(23-61)	33.5(22-59.75)	0.291
Aspartate transaminase(U/L),median(IQR)	38.5(23-51.75)	35(22.5-48.5)	43(37-60)	0.05
Alkaline phosphatase (U/L), median (IQR)	94(74-123)	92(72-118)	102(77.5-141.5)	0.004
Serum albumin (g/dL), median (IQR)	3.2(3.0-3.8)	3.4(3.03-3.9)	3(3-3)	0.001
Lactate dehydrogenase (U/L),median (IQR)	384(267.75-525.25)	345(262-482)	481(393.25-694)	0.001
Creatinine phosphokinase (U/L), median (IQR)	96(44.25-212)	90(39-184)	151(66-310)	0.002
Serum ferritin (ng/mL), median (IQR)	480(289.5-933)	446(259-885)	654(388-1039)	0.011
Interleukin-6 levels (pg/mL),median (IQR)	34(12.6-80.94)	26(9-69)	61(29-148)	0.001
INR, median (IQR)	1.14(1.05-1.3)	1.13(1.04-1.27)	1.19(1.09-1.33)	0.001
APTT (seconds), median (IQR)	32.8(30.5-36.8)	33(30.5-37)	32(30-37)	0.638
Prothrombin time(seconds), median (IQR)	15(13.8-16.5)	15(14-16)	15(14-17.5)	0.003
Lactate dehydrogenase (U/L),median (IQR)	384(267.75-525.25)	345(262-482)	481(393.25-694)	0.001
Creatinine phosphokinase (U/L), median (IQR)	96(44.25-212)	90(39-184)	151(66-310)	0.002
D-dimer (ng/mL), median (IQR)	636(239-1853)	584(211-1455)	1053(376-2451.5)	0.009

ratio; INR = International normalized ratio; APTT = Activated partial thromboplastin time.

Oxygen supplementation was provided to a total of 780 patients using nasal cannula (10.6%), facemask (22.3%), nonrebreathing mask (61.15%) and high flow nasal oxygen (5.8%). Mechanical ventilation was provided to 10.6% (n=106) patients. Noninvasive ventilation was the most common mode of mechanical ventilation provided to 6.7% of patients while invasive mechanical ventilation was used in 3.9% of cases (Table 3).

On evaluating the effect of various drug therapies used in

managing COVID-19 patients of all severity, the use of remdesivir and famotidine was associated with significantly higher survival. In addition, in a subgroup of patients with severe disease, systemic steroids were associated with significantly higher odds of survival in addition to remdesivir and famotidine (Table 4).

In patients with severe COVID-19 illness, likelihood of survival was statistically significant in those who received combination of systemic steroids plus remdesivir compared to steroids and remdesivir alone (Table 5).

On multivariate regression analysis adjusted for age and

Table 3: Effect of Various Treatment Therapies on Survival in Study Participants

Treatment	Survivors (n=695)	Nonsurvivors(n=305)	OR*(95%CI)	P value
Oxygen supplementation	482 (69.3)	298 (97.7)	0.05 (0.02-0.11)	0.001
Remdesivir	305 (43.9)	108 (35.4)	1.42 (1.08-1.88)	0.012
Steroids	466 (67.1)	209 (68.5)	0.98 (0.69-1.24)	0.64
Antibiotics	613 (88.2)	266 (87.2)	1.09 (0.73-1.65)	0.65
Plasma therapy	57 (8.2)	31 (10.2)	0.79 (0.50-1.27)	0.31
Tocilizumab	15 (2.2)	11 (3.6)	0.59 (0.26-1.35)	0.18
Famotidine	528 (76)	183 (60)	2.10 (1.57-2.81)	0.001
Anticoagulants	410 (59)	224 (73.4)	0.52 (0.39-0.70)	0.001
Noninvasive ventilation	16 (2.3)	51 (16.7)	0.12 (0.07-0.21)	0.001
Invasive ventilation	3 (0.4)	36 (11.8)	0.03 (0.01-0.10)	0.001

*Odds ratio and 95% confidence interval for survival.

Table 4: Effect of Various Treatment Therapies on Survival in Severe COVID-19 Patients

Treatment	Survivors (n=387)	Nonsurvivors(n=271)	OR* (95%CI)	P value
Remdesivir	249(64.3)	101(37.3)	3.03(2.20-4.17)	0.001
Steroids	344(88.9)	191(70.5)	3.35(2.24-5.07)	0.001
Antibiotics	349(90.2)	237(87.5)	1.32(0.81-2.13)	0.27
Plasma therapy	55(14.2)	29(10.7)	1.38(0.85-2.24)	0.18
Tocilizumab	15(3.9)	10(3.7)	0.59(0.26-1.35)	0.18
Famotidine	313(80.9)	166(61.3)	2.67(1.88-3.77)	0.001
Anticoagulants	303(78.3)	204(75.3)	0.84(0.58-1.22)	0.36
Noninvasive ventilation	14(3.6)	41(15.1)	0.21(0.11-0.39)	0.001
Invasive ventilation	3(0.7)	35(13)	0.052(0.01-0.15)	0.001

*Odds ratio and 95% confidence interval for survival.

Table 5: Treatment vs. Survival in Severe COVID-19

Treatment	Survivors (n=387)	Nonsurvivors (n=271)	OR (95%CI)	P value
Steroids only	121	109	0.67(0.48-0.93)	0.017
Remdesivir only	26	19	0.95(0.51-1.8)	0.88
Steroids plus remdesivir	223	82	3.13(2.25-4.36)	0.001
None	17	60	0.16(0.09-0.28)	0.001

severity of disease, use of remdesivir, systemic steroids and famotidine in management of COVID-19 illness was associated with significantly better survival (Table 6).

Table 6: Multivariant Logistic Regression Analysis Adjusted for Age and Severity of Illness

Treatment	OR (95%CI)	P value
Remdesivir	2.69(1.93-3.76)	0.000
Steroids	2.45(1.57-3.82)	0.000
Famotidine	1.98(1.35-2.90)	0.000

DISCUSSION

This retrospective study evaluated the effect of various therapies used to treat COVID-19 patients on survival. The use of remdesivir, steroids and famotidine was significantly observed to improve the survival of hospitalized COVID-19 patients. In addition, a combination of remdesivir and steroids was better than remdesivir and steroids alone in improving survival.

Different modalities of treatment are under evaluation for

different severities of COVID-19 illness. Symptomatic treatment is given for mild-to-moderate COVID-19 illness, and inpatient supportive treatment plays a vital role in moderate-to-severe illness. Many the clinical trials have tried different treatment modalities for better management of COVID-19 patients, and many more are underway for assessing the clinical outcome in terms of accelerating the clearance of the virus, reducing in the duration of symptoms, halting the progression of the disease, decreasing the need for mechanical ventilation and reducing mortality. The RCT by Wang et al. failed to show any difference in time to improve clinically with remdesivir compared to placebo(hazard ratio [HR] 1.23 [95% CI 0.87-1.75]), had enrolled only 237 patients, which makes it underpowered(16). A subsequent RCT - Adaptive COVID-19 Treatment Trial (ACTT-1) inferred

usage of remdesivir shortens the time of clinical improvement in hospitalized patients with no mortality benefit¹⁷. One more RCT revealed that standard treatment

and five-day remdesivir in patients with moderate COVID-19 had higher odds of a better clinical status than standard care with a 10-day remdesivir; however, there was no mortality benefit¹⁸. But the most extensive trial for remdesivir, the SOLIDARITY trial, demonstrated little or no benefit on ventilation, hospital stay in days and overall survival with the use of this drug (9). Our study observed that the use of antiviral drug remdesivir in the management of moderate and severe COVID-19 hospitalized patients was associated with significantly higher odds of survival. Our findings are supported by a Bayesian re-analysis of 4 clinical trials of remdesivir, including 7,322 COVID-19 patients, demonstrating better survival in patients with oxygen but without requiring invasive ventilation (probability of >1% absolute decrease in mortality 81%) than patients on oxygen with invasive ventilation (probability of >1% absolute decrease in mortality 4%)¹⁹.

Steroids have been the mainstay in managing moderate and severe COVID illness. However, early use of corticosteroids in the first week of viral pneumonia can lead to higher subsequent plasma viral load or prolonged SARS-CoV-2 virus shedding^{20,21}. The use of steroids in COVID pneumonia in the second week has been efficacious in improving the clinical outcome, especially for those with high inflammatory markers and worsening oxygenation²². Earlier use of steroids in moderate and severe COVID-19 ARDS, as reported by Villar et al., demonstrated an increase in ventilator-free days and a reduction in overall mortality²³. The RECOVERY trial showed lower 28-day mortality in hospitalized COVID-19 patients on oxygen or invasive ventilation, but this advantage was not seen in patients not receiving oxygen⁶. A systemic review and meta-analysis, including 44 studies, assessed the efficacy and safety of steroids and reported them to have a beneficial effect on short-term mortality and reduced the use of invasive ventilation⁷. Our study observed that the use of steroids in the subgroup of patients with severe COVID-19 illness was associated with significantly higher survival chances. The additive effect of steroids and remdesivir on the outcome of COVID-19 patients has not been discussed much. A comparison study of remdesivir, with or without corticosteroids, by Garibaldi et al., has reported that concomitant use of these drugs does not reduce the time to death²⁴.

Although remdesivir is linked with faster clinical improvement, in the SOLIDARITY trial, there was no corroboration of effect modification of remdesivir on patients (approximately 50%) who also were treated with corticosteroids⁹. However, the present study demonstrated better survival in patients receiving steroids and remdesivir.

The histamine H2-receptor antagonist famotidine mainly decreases gastric acid formation and likely inhibits 3-chymotrypsin-like protease (3CLpro), a protein essential for viral replication²⁵. Although literature regarding the famotidine usage in the therapeutic armamentarium of COVID-19 is sparse, results from few retrospective studies, including hospitalized patients, have demonstrated a reduced risk of in-hospital mortality and need for invasive ventilation²⁶⁻²⁸. In our study, famotidine was related to high odds of survival in patients with all grades of severity and was an independent predictor for better survival.

The IL-6 receptor monoclonal antibody tocilizumab works by inhibiting soluble IL-6 receptor and membrane IL-6. Initially, many randomized clinical trials and meta-analyses had demonstrated a reduced likelihood of progression to invasive ventilation, but the overall-cause mortality was not affected. Initial trials results were conflicting; however, in the RECOVERY trial, tocilizumab increased the chances of discharge from the hospital by 28 days, reduced chances of invasive ventilation and improved survival^{10,11,13}. The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial exhibited the addition of tocilizumab use in critically ill patients and the standard of care decreased time to show a better clinical outcome and reduced mortality²⁹. The effect of tocilizumab on survival outcome could not be well-determined in our study because of use in only 36 patients, either because of unavailability or unaffordability.

RELEVANCE

The COVID-19 pandemic is the most significant public health crisis the world has faced recently since the Spanish flu outbreak of 1918. The pace and the number of clinical trials undertaken to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence, even in the middle of a pandemic. Most drug therapies, except a few, have not shown desired therapeutic efficacy.

LIMITATIONS

This retrospective analysis has a few limitations:

The research and recommendations are evolving with every passing day.

The published treatment data up to this date is derived exclusively from observational data or small clinical trials, introducing a greater degree of bias or imprecision regarding the magnitude of treatment effect size.

Our study included adult patients only; no pediatric or pregnant patients were included.

CONCLUSIONS

Our study concluded that remdesivir, steroids and famotidine were significantly associated with better survival of hospitalized COVID-19 patients. However, the combination of remdesivir and steroids was much better than remdesivir and steroids alone in terms of the survival of such patients. There is still a need to undertake more large scale prospective randomized trials to determine the most effective drug therapies to treat sick patients and prevent the worsening of mild cases.

ACKNOWLEDGEMENT

We thank the departments of Microbiology, Radiodiagnosis and Imaging, Hospital Administration and Medical Records Section at SKIMS for being very helpful and cooperative.

Conflict of Interest: None

Funding: None

Written informed consent: Taken

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March, 2020. Available from: <https://www.who.int/director-general/speeches/details/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19,11th-March,2020>.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-20.
4. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med*. 2020;383(21):2041-52.
5. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;383(21):2030-40.
6. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.
7. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. *Crit Care*. 2020;24(1):696.
8. FDA emergency use authorization for remdesivir. Available from: <https://www.fda.gov/media/137564/download>. Accessed May 5, 2020.
9. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511.
10. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 Pneumonia. *N Engl J Med*. 2021;384(1):20-30.
11. Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. *Lancet Respir Med*. 2021;9:511-21.
12. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P; CORIMUNO-19 Collaborative Group. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern*

Med. 2021;181(1):32-40.

13. RECOVERY Collaborative Group, Horby PW, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, Thomas K, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY). *Med Rxiv* 2021.02.11.21249258.
14. Misra S, Nath M, Hadda V, Vibha D. Efficacy of various treatment modalities for nCoV-2019: a systematic review and meta-analysis. *Eur J Clin Invest.* 2020;50(11):e13383.
15. Clinical management protocol for COVID 19 (in adults); Govt.of India Ministry of Health and Family Welfare . Version 6 : 24.05.2021, <https://www.mohfw.gov.in>
16. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2020;395: 1569-78.
17. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - Final report. *N Engl J Med.* 2020;383(19):1813-26.
18. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al; GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA.* 2020;324(11):1048-57.
19. Lee TC, McDonald EG, Butler-Laporte G, Harrison LB, Cheng MP, Brophy JM. Remdesivir and systemic corticosteroids for the treatment of COVID-19: a Bayesian re-analysis. *Int J Infect Dis.* 2021;104:671-6.
20. Lee N, Allen Chan KC, Hui DS, Ng EK, Wu A, Chiu RW, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol.* 2004;31(4):304-9.
21. Tang X, Feng YM, Ni JX, Zhang JY, Liu LM, Hu K, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. *Respiration.* 2021;100(2):116-26.
22. Ruiz-Irastorza G, Pijoan JI, Bereciartua E, Dunder S, Dominguez J, Garcia-Escudero P, et al; Cruces COVID Study Group. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: an observational comparative study using routine care data. *PLoS One.* 2020;15(9):e0239401.
23. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al; Dexamethasone in ARDS Network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med.* 2020;8(3):267-76.
24. Garibaldi BT, Wang K, Robinson ML, Zeger SL, Bandeen-Roche K, Wang MC, et al. Comparison of time to clinical improvement with vs without remdesivir treatment in hospitalized patients with COVID-19. *JAMA Netw Open.* 2021;4(3):e213071.
25. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sin B.* 2020;10(5):766-88.
26. Freedberg DE, Conigliaro J, Wang TC, Tracey KJ, Callahan MV, Abrams JA; Famotidine Research Group. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: a propensity score matched retrospective cohort study. *Gastroenterology.* 2020;159(3):1129-1131.e3.
27. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. *Am J Gastroenterol.* 2020;115(10):1617-23.
28. Janowitz T, Gablenz E, Pattinson D, Wang TC, Conigliaro J, Tracey K, et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series. *Gut.* 2020;69(9):1592-7.
29. Rubin EJ, Longo DL, Baden LR. Interleukin-6 receptor inhibition in Covid-19 - Cooling the inflammatory soup. *N Engl J Med.* 2021;384(16):1564-5.