Comparing the efficacy of casirivimab and imdevimab, remdesivir, and favipiravir in reducing the need for invasive mechanical ventilation in hospitalized COVID-19 patients

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Short (running) title:

Casirivimab & imdevimab, Remdesivir, Favipiravir in COVID-19

the guidelines of the CONSORT 2010 Statement have been adopted

The research protocol was approved by

-IRB, faculty of medicine, Mansoura University, MS21.11.1737

-Research ethics committee, faculty of medicine, Tanta University, 35039/11/21

-Research ethics committee, ministry of health, Egypt, 10-2022/18

Consent to Participate:

-The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments

- All subjects provided informed consent to participate in the study

- Written informed consent was obtained from all participants

- Written informed consent was obtained from parent/guardian of each participant under 18 years of age.

Declaration of interests

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The authors have no relevant financial or non-financial interests to disclose

Abstract

Background

Corona Virus disease of 2019 (COVID-19) pandemic stimulates research works to find a solution to this crisis from starting 2020 year up to now. With ending of the 2021-year, various advances in pharmacotherapy against COVID-19 have emerged. Regarding antiviral therapy, Casirivimab and imdevimab antibody combination is a type of new immunotherapy against COVID-19. Standard antiviral therapy against COVID-19 includes Remdesivir and Favipiravir.

Aims

To evaluate the efficacy of antibodies cocktail (casirivimab and imdevimab) compared to standard antiviral therapy in reducing the need for invasive mechanical ventilation.

Methods

265 COVID-19 Polymerase Chain Reaction (PCR) confirmed patients with indication for antiviral therapy were included in this study and were divided into 3 groups (1:2:2): group A: REGN3048-3051(Antibodies cocktail (casirivimab and imdevimab)), group B: Remdesivir, group C: Favipiravir

The study design is a single-blind non-Randomized Controlled Trial (non-RCT) Mansoura University Hospital (MUH) owns the study's drugs. The duration of the study was about 6 months after ethical approval.

Results

Casirivimab and imdevimab achieve less need for O2 therapy and IMV, with less duration of this need than Remdesivir and Favipiravir.

Conclusion

Group A (Casirivimab and imdevimab) achieve better clinical outcomes than groups B (remdesivir) & C (Favipiravir) intervention groups.

Clinical Trial Registration: **NCT05502081,** 16/08/2022, Clinicaltrials.gov

Keywords – Antivirals; Casirivimab and imdevimab; COVID-19; Favipiravir; Remdesivir

Core tip

- This research can benefit the covid-19 patients by determining the most appropriate antiviral drug according to the case
- This study may change the protocol of treatment of COVID-19 patients
- Casirivimab and imdevimab achieve better clinical outcomes than Remdesivir and Favipiravir.

1. Introduction

1.1. Overview and classification of COVID-19

COVID-19 is an infectious viral disease caused by severe acute respiratory syndrome-coronavirus 2 (SARS CoV-2) that has killed a considerable number of individuals worldwide [1]. COVID-19 infection is graded as mild, moderate, severe, or critical [2]. From the beginning of the 2020 year until the present, the covid-19 pandemic pushes research efforts to discover a solution to this catastrophe. Various improvements in pharmacotherapy against COVID-19 have surfaced as the year 2021 draws to a close [3]

.1.2. Standard and controversial antivirals used in COVID-19 treatment (Remdesivir and Favipiravir)

Remdesivir is a conventional antiviral against COVID-19 that has been licensed by the Food and Drug Administration (FDA) for the treatment of mild, moderate, severe, and critical hospitalized COVID-19 patients [4]. Favipiravir, ivermectin, nitazoxanide, hydroxychloroquine, and ribavirin are among other medicines that have exhibited controversial antiviral activity. Favipiravir has become a routine antiviral treatment for mild and moderate COVID-19 outpatients [5]

1.3. Immunotherapy Advances for COVID-19 treatment

Immunotherapy to target virus antigens has just emerged, with a goal date of the end of 2020 [6]. Figure 1 depicts two types of immunotherapies: active immunotherapy and passive immunotherapy. Active immunotherapy, like vaccination, helps the body generate antibodies against viruses. Passive immunotherapy entails either the direct infusion of produced antibodies directed specifically at viruses or the administration of products containing antibodies, such as plasma [6].

Figure 1: COVID-19 immunization strategies [6].

These antibodies have three antiviral targets: antibodies that prevent virus attachment and entrance, antibodies that limit virus multiplication and transcription, and antibodies that inhibit various aspects of the immune system response.

Table 1 lists the many types of antibodies under research for COVID-19 therapy, as well as their targets [6]

1.4. Antibodies cocktail (Casirivimab and Imdevimab) against COVID-19.

This study focuses on an antibody cocktail that includes REGN3048-3051 (casirivimab and imdevimab). REGN3048 and REGN3051 are human monoclonal antibodies that target the spike glycoprotein on the surface of viral particles, preventing viral entry into human cells via the angiotensin-converting enzyme 2 (ACE2) receptor [7,8].

They have shown promising antiviral activity, but more research is needed to prove their benefit in COVID patients [9].

Previous research [9] on REGN3048-3051 has shown that the efficacy of this antibody cocktail is proven in COVID-19 outpatients' treatment in both low (2.4 g of REGN-COV2) and high (8.0 g of REGN-COV2) doses when compared to placebo. Time-weighted average change in viral load from baseline to day 7 (log10 scale) in patient, and Clinical Efficacy: Percentage of patients with one or more medically related visits and Symptoms offset on day 7.

According to a recent study [9], effectiveness is larger and more visible in seronegative outpatients (whose immune response has not yet matured to make antibodies against virus) and in outpatients with a high baseline viral load. Data [10] for these new antibody combinations are now available. The FDA has granted an Emergency Use Authorization (EUA) for the combination of casirivimab and imdevimab in the treatment and post-exposure prophylaxis of mild and moderate COVID-19 in adults and pediatric outpatients (over 12 years of age and weighing less than 40 kg) who have positive PCR results of direct SARS-CoV-2 viral testing and are at high risk of progressing to severe COVID-19 requiring hospitalization or causing death.

REGN3048 and REGN3051, on the other hand, are still not approved for use in patients [10] who are hospitalized due to COVID-19, require oxygen therapy due to COVID-19, or require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Casirivimab and imdevimab are now licensed experimental antibodies; however, serious and unexpected side events have been recorded with their use [10].

After a single intravenous injection, this antibody combination exhibits linear pharmacokinetics, with half-lives ranging from 25 to 37 days for both antibodies. This combination is not metabolized by liver cytochrome enzymes and is not eliminated by the kidneys [10]

The importance of this study came from that it is the only study that has discussed the use of casirivimab and imdevimab in COVID-19 patients

The gap of knowledge comes from the limitations of the previous studies including short duration of follow up, non-using much clinically relevant outcomes like mortality rate, non-studying the long-term effect of antiviral efficacy in lowering viral load on inflammatory markers, and these studies had been performed on non-

hospitalized patients only and not included hospitalized patients (trials were done only on outpatients and not inpatients).

This research is an extension of published paper that has written by the same authors [11].

2. Aim of the study

The purpose of this study is to compare the efficacy of a cocktail of antibodies (casirivimab and imdevimab) to standard antiviral medication (remdesivir and Favipiravir) in minimizing the requirement for invasive mechanical ventilation in hospitalized patients with moderate, severe, or critical COVID19.

3. Patients and population

265 COVID-19 PCR confirmed patients with indication for antiviral therapy were included in this study and were randomized (1:2:2) into 3 groups: group A: Antibodies cocktail (casirivimab and imdevimab), group B: Remdesivir, group C: Favipiravir [11]. A ratio of (1:2:2) was used as antibodies cocktail product was available for only about 50 COVID-19 patients, and also this ratio is the closest to reality according to number of patients who received each drug.

Population in this study was COVID-19 patients hospitalized in isolation hospital-Mansoura university [11].

A computer file containing a written informed consent from included patients was provided. Paper was not a tool for providing agreement by patients or their relatives to avoid transmission of infection [11].

Inclusion criteria

Patient should fulfill all these characteristics to be included: weight not less than 40 kg, age more than 12 years old, PCR- confirmed patients to be Positive before inclusion, and moderate, severe or critical COVID-19 disease as defined by WHO [11].

Exclusion criteria

Patient should not have any of the following to be included: prior use of standard antiviral therapy (remdesivir or Favipiravir), history of hypersensitivity or infusion related reactions after administration of monoclonal antibodies, patients expected to die within 48 hours, and current use of controversial antiviral therapy (hydroxychloroquine, ivermectin, nitazoxanide, oseltamivir, acyclovir, ribavirin, lopinavir/ritonavir, sofosbuvir, daclatasvir, semipirvir, azithromycin) [11].

4. Interventions

Population included in this study was assigned into 3 groups with 1:2:2 ratios to receive either casirivimab and imdevimab or standard antiviral therapy (remdesivir or Favipiravir) as shown figures 2,3 [11].

Figure 2: Assignment of the included COVID cases at their groups.

Figure 3: Frequency of interventions in included patients.

Group A patients received REGN3048-3051(Antibodies cocktail (casirivimab and imdevimab)) in low-dose regimen 1.2 gm (1200 mg of combined antibodies) diluted in 250 ml 0.9% sodium chloride solution as single I.V infusion over 30-60 minutes.

Group B patients received Remdesivir :

Day1 (loading dose): 200 mg (two 100mg vials) diluted in 500ml 0.9% sodium chloride solution infused I.V over 60 minutes

Day 2-5 or Day 2-10 (maintenance dose): 100 mg (one 100mg vial) in 250 ml 0.9% sodium chloride solution infused I.V over 30 minutes

Group C patients received Favipiravir :

Day 1 (loading dose): 1600 mg (8 tablets) or 1800 mg (9 tablets) orally or in Ryle tube / 12 hours

Day 2-5 or day 2-10 (maintenance dose): 600 mg (3 tablets) or 800 mg (4 tablets) orally or in Ryle tube / 12 hours.

Patients received standard of care as guided by Egyptian COVID-19 treatment protocol [11].

5. Materials and Methods

The type of this study is single blind non-RCT and is considered a Phase IV Clinical trial (post-marketing study) to report efficacy of new medicine [11].

Another resource used to obtain information about casirivimab and imdevimab is Fact Sheet for Health Care Providers- EUA OF casirivimab and imdevimab which provides clinical data about the use of this antibodies cocktail. Endnote citation software was used for references citation [11].

The research protocol was approved by IRB, faculty of medicine, Mansoura University, MS21.11.1737, Research ethics committee, faculty of medicine, Tanta University, 35039/11/21, and Research ethics committee, ministry of health, Egypt, 10-2022/18

Registry name and registration number: Clinicaltrials.gov, NCT05502081.

6. Outcomes

Outcomes include need for invasive mechanical ventilation (IMV), and Invasive mechanical ventilation and oxygen support duration (days).

In addition to clinical outcomes measured before and during intervention, patients' characteristics (age, gender) and relevant medical and medication history and current COVID-19 treatment drugs were recorded on admission.

Duration of research was about 6 months from November 2021 to April 2022.

7. Statistical analysis and Sample Size

Statistical analysis

Categorical variables were presented as proportion. Continuous variables were presented as mean (±standard deviation). Intention-to-treat strategy was used in this study. Statistical analysis was achieved with SPSS, version 26. ANOVA or Kruskal-Walli's test was used for comparison between groups, as comparison was performed between three groups. We reported the P-value for our statistical tests with level of statistical significance is P-value ≤ 0.05 [11].

Regarding baseline characteristics, Kruskal-Wallis or ANOVA test (depending on type of data and the continuous data distribution (normal or not)) was used to compare these characteristics between the study groups. We reported the P-value for our statistical tests. The level of statistical significance was P-value ≤ 0.05 [11].

In case of existing differences in some baseline characteristics, logistic regression was performed. This allowed studying the effect of these variables on the primary outcomes of the study to exclude the effect of these confounding variables and to ensure the effect on the outcomes is due to antiviral drugs [11].

Regarding the outcomes, we compared the need for invasive mechanical ventilation and duration of this need using the Kruskal-Walli's test with reporting the P-value.

Sample Size

A total sample sizes of 246 patients would achieve at least 80 % power to detect a risk difference of 0.2 (20%) in the need for invasive mechanical ventilation with a significance level (α) of 0.05 and 95% confidence level using the ANOVA or Kruskal-Walli's test of independent proportion in G*Power software. To compensate for the estimated loss-to-follow-up and to increase the study power, we increased the sample size to 53 patients in Antibodies cocktail Group compared to 106 patients in both remdesivir and Favipiravir groups. As antibodies

cocktail product was available for only about 50 COVID-19 patients, a ratio of (1:2:2) was used. In addition, the ratio (1:2:2) is the closest to reality according to number of patients who received each drug [11].

The online system had been used to obtain mortality rate in these three months [11].

The admission rate at Isolation Hospital-Mansoura University was 250 cases per month on average; our needed sample was about 250 cases [11].

8. Results

All continuous data revealed no normal distribution after statistical analysis with SPSS software. As a result, the Kruskal-Wallis Test is used to compare nonnormally distributed continuous, categorical, and nominal data between the three groups. Figure 4 represent a flow chart showing the flow of patients in the trial.

8.1. Baseline characteristics

Table 2 shows the statistical significance of the differences between the three groups, as well as a comparison of each two groups in baseline characteristics if there is a statistically significant difference between the three groups. Figures 1–9 show the distributions and frequencies of baseline characteristics in the three groups [11].

8.1.1. Age

A-C and B-C have a statistically significant difference, but A-B has a statistically non-significant difference [11].

8.1.2. Gender

There is a statistically significant difference between B and C, but not between A and B or A and C [11].

8.1.3. The total number of comorbidities

There is a statistically significant difference between B and C, but not between A and B or A and C [11].

8.1.4. Diagnosis method

The three groups differ in a statistically insignificant way [11].

8.1.5. COVID-19 Severity

The difference between A-B and A-C is statistically significant, whereas the difference between C-B is not. Group A has statistically considerably fewer severe cases than groups B and C [11].

8.1.6. Number of symptoms

There is a statistically significant difference between A-B & A-C and a statistically non-significant difference between C-B [11].

8.1.7. Antibiotics use

In general, there is no statistically significant difference in antibiotic use across the three groups. In the case of macrolides (azithromycin and clarithromycin), there is only a statistically significant difference between A and C.

8.1.8. Use of anticoagulants (enoxaparin, heparin, rivaroxaban)

In terms of anticoagulant use, whether preventive or therapeutic dose, there is a statistically insignificant difference between the three groups.

8.1.9. Antiplatelet therapy (aspirin, clopidogrel)

There is a statistically significant difference between A and C, but not between A and B and C and B.

8.1.10. Steroids (dexamethasone, prednisolone, and methylprednisolone) usage

There is a statistically significant difference between A and B, but not between A and C and C and B.

8.1.11 Uses of adjunct therapy (paracetamol, vitamin C, zinc, acetyl cysteine, lactoferrin)

In general, there is a statistically insignificant difference in additive treatment use between the three groups. There is only a statistically significant difference between A-C and A-B in paracetamol and zinc consumption.

8.1.12 Use of oxygen therapy

In general, the differences between A-B and A-C are statistically significant, while the difference between C-B is statistically non-significant. In terms of nasal prongs and HFNC use, there is a statistically insignificant difference between the three groups.

Regarding the use of a simple face mask (SFM), Continuous Positive Airway Pressure (CPAP), or Non-Invasive Ventilation (NIV), and IMV, there is a statistically significant difference between A-B and A-C.

In the use of mask reservoirs (MR), there is a statistically significant difference between B and C**.**

8.1.13. Use of vasopressors

In terms of vasopressor use, there is a statistically significant difference between A-B and A-C and a statistically non-significant difference between C-B. The use of vasopressors is statistically significantly lower in group A than in groups B and C.

8.1.14. Prone positioning

The three groups have a statistically insignificant difference in prone positioning.

8.1.15. Blood gases

There is a statistically significant difference in PaO2 between A-B and A-C, as well as A-B in PaO2/FiO2. In PaCO2, there is a statistically insignificant difference between the three groups.

8.2 Regression Analysis

Table 3 [11] shows how regression analysis was used to investigate the effect of baseline parameters (that reveal a statistically significant difference between the three groups) on study outcomes and the likelihood of confounding variables.

8.3 Outcomes following intervention in the three groups

Table 4 displays the significance of differences in clinical outcomes between the three groups and also includes a pairwise comparison of clinical outcomes between each two groups if there is a statistically significant difference between the three groups [11]. The distributions and frequency of these outcomes across the three groups are depicted in supplementary figures (S10-S16) in the Supporting Information.

8.3.1. Influence on blood oxygen pressure

On days 3, 7, and 14, there is a statistically significant difference in PaO2/FiO2 between A-B and A-C.

8.3.2. the requirement for IMV during hospitalization

Between A-B and A-C, there is a statistically significant difference in the demand for IMV.

8.3.3. influence on the number of days requiring IMV or O2 therapy

There is a statistically significant difference in number of days with need for IMV or oxygen therapy between A-B & A-C.

9. Discussion

In this study, casirivimab and imdevimab were compared to remdesivir and Favipiravir for treatment in COVID-19 hospitalized patients. There are no comparable treatment comparisons or relevant studies to compare this research to for similarities and differences [11]

3.1. Regarding bassline characteristics

The age difference between groups A and B is statistically significant. Group B has statistically considerably more females than Group C. The number of co-morbidities in Group C is statistically considerably higher than in Group B. Group A had statistically considerably less severe cases than groups B and C. Group A has a statistically significantly lower number of symptoms than groups B and C. PaO2 and PaO2/FiO2 values are statistically considerably higher in group A than in group B, and PaO2 values are statistically significantly higher in group A than in group C. In terms of antibiotic use, there is a statistically insignificant difference between the three

groups. Antiplatelet (aspirin) use is statistically significant higher in group A than in group C, while steroid use is statistically significant higher in group B than in group A. The use of O2 therapy in group A is statistically significant less than groups B & C and O2 therapy using SFM, NIV, IMV in group A is statistically significant less than Groups B & C, while the use of mask reservoir (MR) as O2 source is more in group B than group C. the use of vasopressors in group A is statistically significant less than groups B & C. Finally, There is statistically significant more cases in group A who not need O2 therapy with statistically significant higher O2 saturation on room air than groups B & C

9.2. Regression analysis

Following a statistical study of the baseline characteristics of the three groups' cases, it was discovered that statistically significant disparities in some baseline features exist between the three groups. Age, gender, number of symptoms, number of co-morbidities, severity of COVID, usage of antiplatelets and steroids, and zinc upon admission all differ [11].

As a result, it is vital to rule out the effect of these variables on the study's outcomes, which are indicated by the necessity for invasive mechanical breathing.

As a result, regression analysis was used to investigate the influence of these variables on the study's outcome (need for invasive mechanical ventilation). Following regression analysis, it was discovered that all baseline differences between the three groups had no effect on the research outcome (invasive mechanical ventilation need).

9.3. Regarding the outcomes after intervention in the three groups

9.3.1. effect on oxygen pressure in blood

PaO2/FiO2 value on day 3,7,14 is statistically significant higher in group A than groups B & C.

From these results, it is concluded that group A has more favorable oxygen level in blood than groups B & C.

9.3.2. need for invasive mechanical ventilation (IMV) during hospitalization

Group A has statistically significant lower need for IMV than groups B & C.

9.3.3. effect on number of days in which there is need for IMV or oxygen therapy

Group A has statistically significant less duration with need for O2 therapy or IMV than groups B & C.

The study's **limitations** include non-randomization of antiviral medicines among included patients, non-blinding of interventions to investigators, only relevant to hospitalized COVID-19 patients (no outpatients), and disparities in several baseline characteristics across the groups.

This study's **generalizability** is limited to hospitalized COVID-19 patients and does not include all COVID-19 patients.

10. Conclusion

Casirivimab and imdevimab achieve less need for O2 therapy and IMV, less duration of this need than Remdesivir and Favipiravir.

It is concluded that Casirivimab & imdevimab achieve better clinical outcomes than Remdesivir & Favipiravir.

11. Footnotes

Compliance with Ethics Guidelines:

The research protocol was approved by

-Research ethics committee, ministry of health, Egypt, 10-2022/18

-IRB, faculty of medicine, Mansoura University, MS21.11.1737

-Research ethics committee, faculty of medicine, Tanta University, 35039/11/21

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declaration of interests

The authors have no relevant financial or non-financial interests to disclose

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Authors contributions

Sahar K.Hegazy

Conceptualization; Project administration; Supervision

Samar Tharwat

Supervision

Ahmed H.Hassan

Conceptualization; Data curation; Methodology; Roles/Writing - original draft; Writing - review & editing

Data Availability

The datasets generated and/or analyzed during the current study are available in the Clinicaltrials.gov repository, https://clinicaltrials.gov/ct2/show/NCT05502081

For more statistical analysis that is performed on clinical data of this study, this is a link to a SPSS output file that contains all statistical analysis of the study. an excel data sheet and a SPSS data file containing all clinical data of the cases of the three groups can be found in this link in addition to an excel data sheet for included and excluded cases with date:

https://drive.google.com/drive/folders/1X1dDQwW9vBvusutwMbeebUjN8jJqYxsh?usp=sharing

Acknowledgment

This study is a part of big research that was divided into five parts to enable their publication as it discusses several outcomes (size limitations in journal publication), and one part of this research has been published which is Clinical Study to compare the efficacy and safety of casirivimab and imdevimab, remdesivir, and Favipiravir in hospitalized COVID-19 patients

https://doi.org/10.1016/j.jcvp.2023.100151

CONSORT 2010 statement

The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

12. Supplementary materials

Supplementary figures have been supported. Supplementary figures (S1-S9) represent the differences in distributions and frequencies of baseline characteristics between the three groups. While supplementary figures (S10-S15) in the Supporting Information show the differences in distributions and frequencies of these outcomes across the three groups.

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Figures

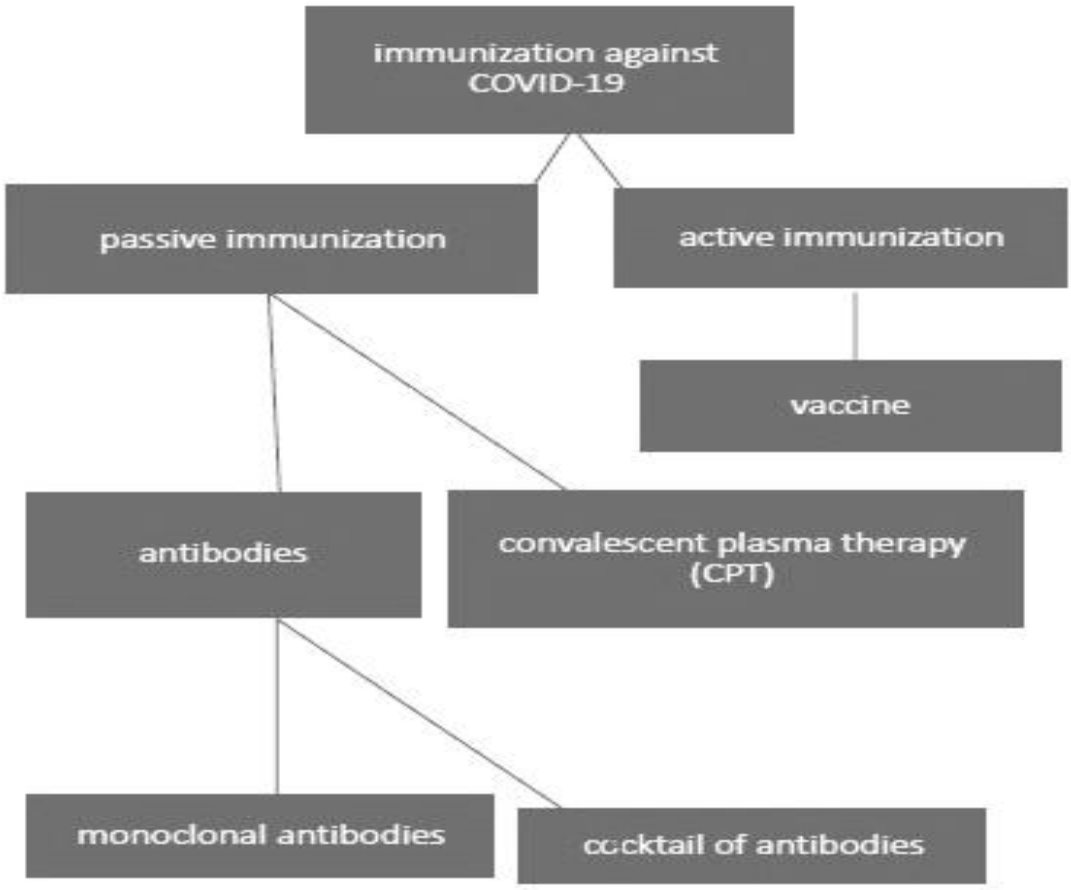

Figure 1: Immunization approaches against coronavirus disease of 2019,[6]

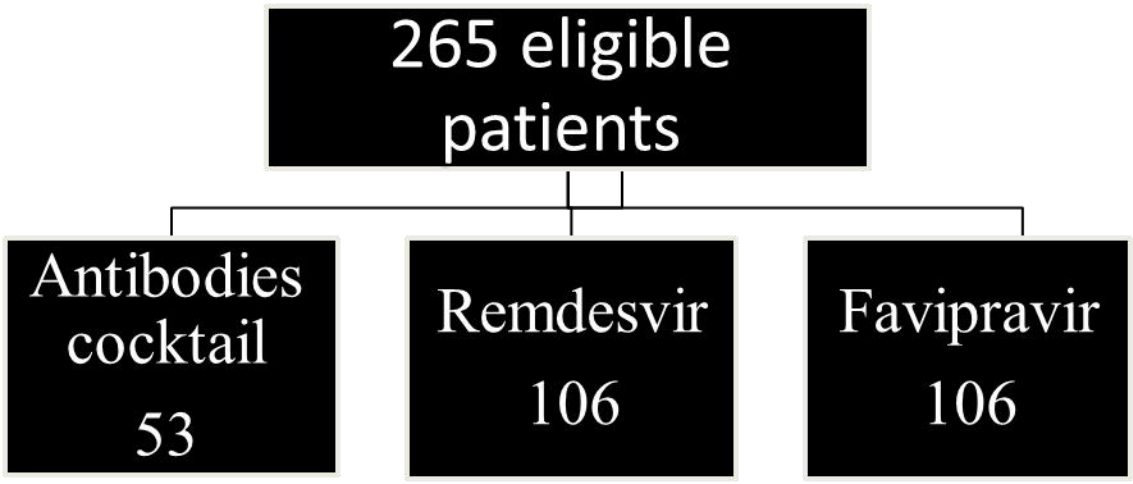

Figure 2: Assignment of the included coronavirus-infected cases at their groups.

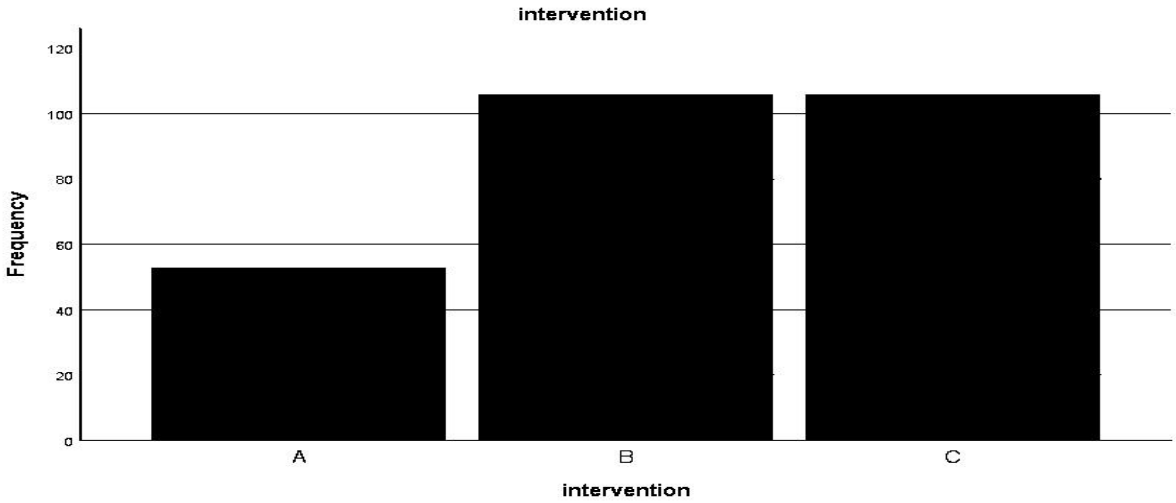

Figure 3: Frequency of interventions in included patients.

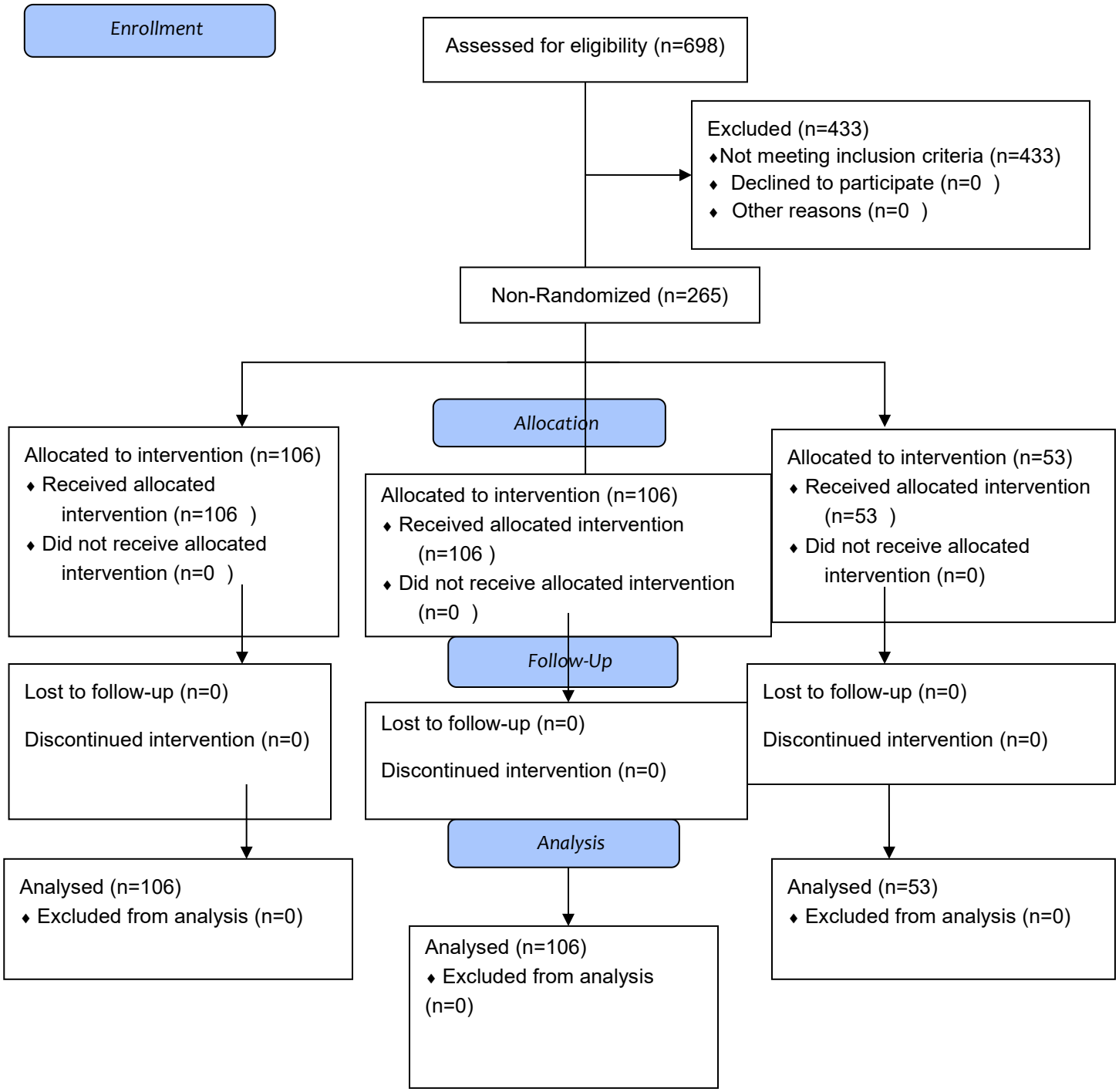

Figure 4: Flow chart of patients in the study

Figures legands

Fig 1: Immunization approaches against coronavirus disease of 2019,[6]

Fig 2: Assignment of the included coronavirus-infected cases at their groups.

Fig 3: Frequency of interventions in included patients.

Fig 4: Flow chart of patients in the study

A= Casirivimab/ Imdevimab

B= Remdesivir

C= Favipiravir

Table 1: antibodies candidate against SARS-CoV-2 under investigation by pharmaceutical companies [6].

Antibody	**Mechanism**	**Company**	**Stage of study/identification method**
Canakinumab (Ilaris®)	IL-1β inhibitor	Novartis	-In clinical stage for several inflammatory diseases including arthritis, periodic fever and lung cancer; -Repurposed by Novartis for COVID-19
Secukinumab (Cosentyx®)	IL-17 inhibitor	Novartis	In clinical stage for several autoimmune diseases including psoriasis; repurpose by Novartis for COVID-19
TZLS-501	Fully human monoclonal antibody targeting the receptor of IL-6, it binds to both membrane-bound and soluble forms of IL-6R, and rapidly depletes the circulating levels of IL-6 in blood.	Tiziana Life Sciences and Novimmune	Preclinical stage
Pritumumab	Fully human IgG antibody targeting vimentin	Nascent Biotech Inc.	-Received FDA approve for several carcinoma -Research began for COVID-19
COVID-HIG and COVID-EIG	Hyperimmune polyclonal antibody derived from human plasma or immunized horse	Emergent BioSolutions	Enter clinical trial within 4–5 months

Rcig	Recombinant anti SARS-CoV-2 hyperimmune gamma globulin, polyclonal antibodies	GigaGen	Preclinical stage- -Aimed for COVID19 hospitalized patients and prophylaxis in high-risk individuals
Antibody cocktail including REGN3048-3051	Fully human multivalent antibodies against the spike protein isolated from genetically modified mice or recovered COVID-19 patients	Regeneron	-Phase 1 clinical trial for Middle East Respiratory Syndrome (MERS) completed last year -Clinical trial for SARS-CoV-2 starts by early summer

Table 2: The Significance of differences in baseline characteristics between the three groups

Variables		intervention			
		Casirivimab /Imdevimab (A)	Remdesivir (B)	Favipiravir (C)	P-values*
Age		58.34±16.096	59.30±15.985	65.02±14.261	0.006
B & C					0.07
A & C					0.07
A & B					0.63
Gender	Male	24/53	42/106	61/106	0.03
	Female	29/53	64/106	45/106	
B & C					0.09
A & C					0.145
A & B					0.501
Number of co-morbidities	0	10/53	32/106	22/106	0.022
	1	16/53	27/106	19/106	
	2	14/53	28/106	33/106	
	3	11/53	16/106	18/106	
	4	2/53	2/106	10/106	
	5	0/53	1/106	3/106	
	6	0/53	0/106	1/106	
B & C					0.06

A & C					0.320
A & B					0.207
Method of diagnosis	**Symptoms only**	0/53	0/106	0/106	1
	Labs & Radiology	0/53	0/106	0/106	
	PCR confirmed	53/53	106/106	106/106	
B & C					NA
A & C					NA
A & B					NA
severity of COVID	**moderate**	18/53	20/106	20/106	0.024
	sever	27/53	60/106	53/106	
	critical	8/53	26/106	33/106	
B & C					0.475
A & C					0.07
A & B					0.035
Number of symptoms	**2**	4/53	2/106	2/106	0.001
	3	13/53	6/106	4/106	
	4	32/53	97/106	97/106	
	5	4/53	1/106	3/106	
B & C					0.482

A & C					0
A & B					0.003
Antibiotics use	**Yes**	53/53	106/106	106/106	1
	No	0/53	0/106	0/106	
B & C					0.102
A & C					0.002
A & B					0.075
Macrolide use	**Yes**	8/53	8/106	2/106	0.007
	No	45/53	98/106	104/106	
B & C					0.102
A & C					0.002
A & B					0.075
Fluroquinolones use	**Yes**	41/53	92/106	95/106	0.106
	No	12/53	14/106	11/106	
B & C					NA
A & C					NA
A & B					NA
3rd & 4th generation cephalosporin use	**Yes**	39/53	86/106	83/106	0.551
	No	14/53	20/106	23/106	
B & C					NA
A & C					NA
A & B					NA
Carbapenems use	**Yes**	.10/53	.32/106	.22/106	0.168

	No	43/53	74/106	84/106	
B & C					NA
A & C					NA
A & B					NA
Piperacillin /tazobactam use	**Yes**	0/53	0/106	0/106	1
	No	53/53	106/106	106/106	
B & C					NA
A & C					NA
A & B					NA
Amoxicillin /clavulanate use	**Yes**	0/53	0/106	0/106	0.472
	No	53/53	106/106	106/106	
B & C					NA
A & C					NA
A & B					NA
Cotrimoxazole use	**Yes**	0/53	0/106	0/106	1
	No	53/53	106/106	106/106	
B & C					NA
A & C					NA
A & B					NA
Linezolid use	**Yes**	5/53	12/106	4/106	0.115
	No	48/53	94/106	102/106	
B & C					NA
A & C					NA

A & B					NA
Teicoplanin use	**Yes**	1/53	0/106	2/106	0.365
	No	52/53	106/106	104/106	
B & C					NA
A & C					NA
A & B					NA
Anticoagulant use	**Yes**	49/53	101/106	96/106	0.411
	No	4/53	5/106	10/106	
B & C					NA
A & C					NA
A & B					NA
Dose of anticoagulant	**Prophylactic**	39/53	80/106	81/106	0.088
	Therapeutic	14/53	26/106	25/106	
B & C					NA
A & C					NA
A & B					NA
Antiplatelet use	**Yes**	5/53	6/106	0	0.012
	No	48/53	100/106	106/106	
B & C					0.039
A & C					0.005
A & B					0.262
Steroids use	**Yes**	45/53	105/106	98/106	0.002
	No	8/53	1/106	8/106	

B & C					0.50
A & C					0.068
A & B					0.001
additive-therapy use	Yes	51/53	106/106	105/106	0.104
	No	2/53	0/106	1/106	
B & C					NA
A & C					NA
A & B					NA
Paracetamol use	yes	50/53	105/106	106/106	0.019
	no	3/53	1/106	0/106	
B & C					0.574
A & C					0.006
A & B					0.022
Zinc use	Yes	4/53	0/106	1/106	0.003
	No	49/53	106/106	105/106	
B & C					0.614
A & C					0.004
A & B					0.001
Acetyl cysteine use	Yes	52/53	106/106	106/106	0.135
	No	1/53	0/106	0/106	
B & C					NA
A & C					NA
A & B					NA
Lactoferrin use	Yes	1/53	0/106	0/106	0.135

	No	52/53	106/106	106/106	
B & C					NA
A & C					NA
A & B					NA
vitamin C use	Yes	4/53	7/106	1/106	0.070
	No	49/53	99/106	105/106	
B & C					NA
A & C					NA
A & B					NA
O2 therapy use	Yes	37/53	99/106	102/106	0
	No	16/53	7/106	4/106	
B & C					0.497
A & C					0
A & B					0
NP[(1)] use	Yes	18/53	35/106	39/106	0.84
	No	35/53	71/106	67/106	
B & C					NA
A & C					NA
A & B					NA
SFM[(2)] use	Yes	30/53	82/106	87/106	0.002
	No	23/53	24/106	19/106	
B & C					0.428
A & C					0
A & B					0.004

MR[3] use	**Yes**	8/53	33/106	14/106	0.003
	No	45/53	73/106	92/106	
B & C					0.001
A & C					0.783
A & B					0.019
HFNC[4] use	**Yes**	5/53	22/106	18/106	0.202
	No	48/53	84/106	88/106	
B & C					NA
A & C					NA
A & B					NA
CPAP[5] use	**Yes**	4/53	39/106	36/106	0
	No	49/53	67/106	70/106	
B & C					0.635
A & C					0.001
A & B					0
IMV[6] use	Yes	1/53	29/106	29/106	0
	No	52/53	77/106	77/106	
B & C					1
A & C					0
A & B					0
Vasopressor use	Yes	0/53	23/106	18/106	0.002
	No	53/53	83/106	88/106	
B & C					1
A & C					0.016

A & B					0.001
Prone positioning	Yes	0/53	5/106	9/106	0.75
	No	53/53	101/106	97/106	
B & C					NA
A & C					NA
A & B					**NA**
O2 saturation on O2 therapy		96.26±2.391	95.86±3.795	96.01±3.130	0.942
B & C					NA
A & C					NA
A & B					NA
O2 saturation on RA[7]		92.36±4.816	87.62±7.171	88.35±7.006	0
B & C					0.448
A & C					0
A & B					0
PaO2[8]		77.868±41.79	56.432±35.30	63.294±39.45	0.005
B & C					0.252
A & C					0.20
A & B					0.001
PaCO2[9]		36.689±12.59	37.325±14.60	37.603±12.08	0.891
B & C					NA
A & C					NA
A & B					NA
PaO2/FiO2[10]		233.5057±207	156.7358±171	164.142±138	0.01
B & C					0.136

A & C				0.69
A & B				0.002

Table 3: The best regression model for studying effects of confounding variables on need for invasive mechanical ventilation

	Unstandardized Coefficients		Standardized Coefficients			
	B	Std. Error	Beta	Std. Error	t	P-value
(Constant)	.806	1.297			.621	.535
age	.003	.001	.098	.053	1.835	.068
gender	.029	.044	.038	.058	.652	.515
No of co-morbidities	-.002	.015	-.007	.048	-.144	.885
Severity of COVID	-.004	.036	-.007	.059	-.123	.903
No of symptoms	.029	.033	.049	.057	.854	.394
macrolide	-.030	.083	-.027	.074	-.362	.718
fluroquinolones	.001	.068	.001	.073	.020	.984
cephalosporin	.046	.071	.052	.081	.646	.519
carbapenems	.057	.070	.065	.080	.818	.415
Amox/calv	-.191	.398	-.019	.039	-.479	.632
linezolid	-.007	.072	-.006	.058	-.097	.923
teicoplanin	-.201	.316	-.028	.044	-.636	.526
Other Antibiotics	-.029	.105	-.012	.043	-.274	.784
Anticoagulant	-.102	.099	-.069	.067	-1.033	.303
Prophylaxis/therapeutic	-.014	.048	-.019	.063	-.298	.766
antiplatelet	-.028	.083	-.020	.060	-.340	.734
steroids	-.044	.078	-.036	.065	-.561	.576
Additive therapy	.096	.120	.041	.051	.803	.423
paracetamol	-.045	.095	-.024	.050	-.475	.635
zinc	-.101	.084	-.059	.049	-1.210	.228
acetylcysteine	-.027	.176	-.008	.052	-.151	.880
lactoferrin	.312	.237	.092	.070	1.315	.190

Vitamin C	.044	.072	.031	.050	.615	.539
Nasal prongs use	-.004	.043	-.005	.055	-.083	.934
FM use	.040	.053	.046	.060	.764	.446
MR use	-.027	.050	-.029	.054	-.538	.591
HFNC use	.004	.050	.003	.048	.071	.944
CPAP	.003	.092	.004	.101	.035	.972
vasopressor	.054	.093	.042	.072	.579	.563
Prone position	-.183	.105	-.080	.046	-1.740	.084
PaO2	-.002	.001	-.191	.067	-2.841	.005
PaCO2	-.005	.002	-.149	.052	-2.852	.005
PaO2/Fio2	.001	.000	.175	.065	2.695	.008

Table 4: The Significance of differences in outcomes between the three groups

Variables		intervention			
		Casirivimab /Imdevimab (A)	**Remdesivir (B)**	**Favipiravir (C)**	**P-values***
PaO2/FiO2 on day 3		298.57±211.3	154.14±138.9	166.96±130	0
B & C					0.478
A & C					0
A & B					0
PaO2/FiO2 on day 7		320.62±93.64	163.55±172.6	178.59±138	0
B & C					0.413
A & C					0
A & B					0
PaO2/FiO2 on day 14		389.75±51.93	154.67±174	165.2±98.87	0.005
B & C					0.155
A & C					0.022
A & B					0.001
PaO2/FiO2 on day 28			172.75±181	53±0	0.48
B & C					NA
Need for IMV	Yes	1/53	22/106	22/106	0.005
	No	52/53	84/106	84/106	
B & C					1
A & C					0.003
A & B					0.003

Duration of need for O2 therapy and IMV	3.72±3.527	9.2±7.107	7.46±5.077	0
B & C				0.119
A & C				0
A & B				0