Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Clinical study to compare the efficacy and safety of casirivimab & imdevimab, remdesivir, and favipravir in hospitalized COVID-19 patients

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ABSTRACT

Background: Corona Virus disease - 2019 (COVID-19) disease induces scientific research to find a control to this pandemic from 2020 year up to now. Recently, various advances in pharmacotherapy against COVID-19 have emerged.

Objectives: To compare the efficacy and safety of antibodies cocktail (casirivimab and imdevimab), Remdesivir, and Favipravir in the COVID-19 patients

Study design: This study is a single-blind non-Randomized Controlled Trial (non-RCT). The drugs of the study are prescribed by lectures on chest diseases, faculty of medicine-Mansoura University. The duration of the study is about six months after ethical approval.

265 hospitalized COVID-19 patients were used to represent the COVID-19 population and were assigned into three groups in a ratio of (1:2:2) respectively, Group (A) received REGN3048–3051(Antibodies cocktail (casirivimab and imdevimab)), group (B) received remdesivir, and group (C) received favipravir.

Results: Casirivimab and imdevimab achieve less 28-day mortality rate, and less mortality at hospital discharge than Remdesivir, and Favipravir.

Conclusion: From all of these results, it is concluded that Group A (Casirivimab & imdevimab) achieves more favorable outcomes than B (Remdesivir) & C (Favipravir) intervention groups.

Clinical trial registration: NCT05502081, 16/08/2022, Clinicaltrials.gov

1. Background

1.1. COVID-19 overview and classification

COVID-19 is an infectious viral disease caused by SARS CoV-2 (sever acute respiratory syndrome-corona virus 2) that has affected large number of people all over the world with high mortality rate [1]. COVID-19 infection has been classified [2] as mild, moderate, severe, and critical disease. Mild disease in which symptoms of COVID-19 exist (e.g., cough, sore throat, fever, headache, loss of taste and smell muscle pain, vomiting, diarrhea) but without abnormal chest imaging, shortness of breath, or dyspnea. Moderate disease in which lower respiratory tract is affected with an arterial oxygen saturation (SpO2) on room air ≥94%. Severe disease in which on room air SpO2 <94%, lung infiltrates >50%, respiratory rate >30 breaths/min, or a ratio of partial arterial pressure of O2 to inspired oxygen fraction (PaO2/FiO2) <300 mm Hg. Critical disease in which respiratory failure, septic shock, and/or multiple organ dysfunctions may occur.

Covid-19 pandemic stimulates research works to find a solution to this crisis from the start of year 2020 until now. With the end of the year 2021, various advances in pharmacotherapy against COVID-19 have emerged [3].

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

Regarding antiviral drugs used in the treatment of COVID-19, remdesivir has been approved by Food and drug administration (FDA) [4]. Other drugs that have shown controversial antiviral activity include: favipravir, ivermectin, nitazoxanide, hydroxychloroquine, ribavirin. Favipravir became a standard antiviral which has been used for the treatment of mild and moderate COVID-19 outpatients [5].

1.3. Advances in immunotherapy for treatment of COVID-19

Recently, with the end of 2020, immunotherapy to target virus antigen has been developed [6]. Fig. 1 shows two types of immunotherapies

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

Antibody	Mechanism	Company	Stage of study/identification method
VIR-7832/ VIR-7831	bind to highly conserved epitope in s protein -Induce NK-mediated antibody-dependent cell cytotoxicity	GSK and VIR biotechnology	isolated from SARS-Cov patients
SAB	Anti SARS-CoV-2 fully human poly clonal antibodies	SAB Biotherapeutics	produced by genetically engineered cattle it may enter clinical trial -SAB-301 against MERS passes phase 1 of clinical trial and entered phase II/III
–	Target multiple viral S epitope	ImmunoPrecise	Using B cell Select® and Deep Display® technology
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

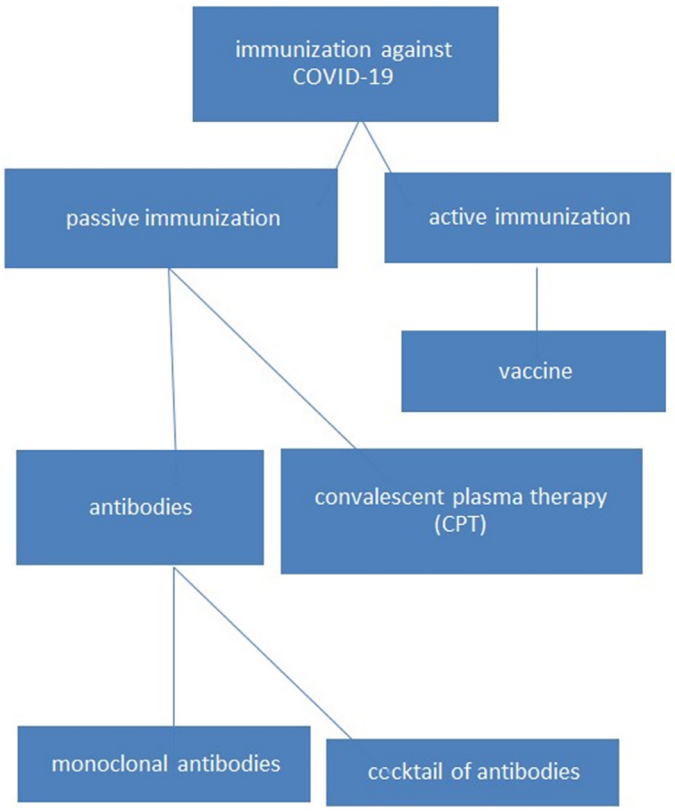

Fig. 1. Immunization approaches against COVID-19. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

include active and passive immunotherapy. Active immunotherapy is to enhance body to produce antibodies against virus as by vaccination. Passive immunotherapy involves direct administration of prepared antibodies acting specifically against viruses or administration of products containing antibodies like plasma [6].

In this study, the point of research is antibodies cocktail including REGN3048–3051(**casirivimab and imdevimab)**. There are three targets for these antibodies to work as antiviral including: antibodies that prevent the virus attachment and entry, antibodies that decrease transcription and replication of virus, and antibodies that block the response of immune system.

Table 1 includes various types of antibodies under investigation for treatment of COVID-19 and their targets [6].

1.4. Casirivimab and imdevimab as antibodies cocktail against COVID-19

Antibodies cocktail including REGN3048–3051(**casirivimab and imdevimab)** are human monoclonal antibodies targeting the spike glycoprotein on surface of viral particles thereby preventing viral entry into human cells through the angiotensin-converting enzyme 2(ACE2) receptor, [7,8], and have shown antiviral activity and needs for further investigation to prove their efficacy in COVID patients [9].

Previous study [9] on REGN3048–3051 has concluded that both the efficacy and the safety of these antibodies cocktail are proved in COVID-19 outpatients in both low (2.4 g of REGN–COV2), or high (8.0 g of REGN–COV2) dose when compared to placebo, Efficacy and safety are measured as shown below.

Efficacy is measured as virologic efficacy that is time-based average change from baseline in viral load through day 7 (log10 scale) in the patients, and clinical efficacy that is percentage of patients with one or more medically attended visits and Symptoms offset at day 7.

Safety is measured as Percentage of treated patients who experience infusion-related and hypersensitivity reactions and incidence of any serious and unexpected adverse effect.

This previous study [9] concluded that efficacy is greater and more obvious in seronegative outpatients (whose immune response is not developed yet to produce antibodies against virus) and with high baseline viral load outpatients.

Now, data [10] is available for these new antibodies' cocktails. The U.S. Food and Drug Administration (FDA) has allowed an emergency use authorization (EUA) for casirivimab and imdevimab combination in the treatment and post-exposure prophylaxis of mild to moderate COVID-19 in adults and pediatric outpatients (more than12 years of age and not less than 40 kg) with positive Polymerase Chain Reaction (PCR) results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19 requiring hospitalization or causing death.

In contrast, REGN3048 and REGN3051 are still not authorized for use in patients, who are hospitalized due to COVID-19, who require oxygen therapy due to COVID-19, who 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 [10].

Now, casirivimab and imdevimab are approved investigational antibodies, Serious and unexpected adverse effects can occur that were not previously reported with their use [10].

Confirmed adverse effects include hypersensitivity and infusion-related reactions and the study has shown that there is no difference in safety profile between intravenous (I.V) infusion and subcutaneous (S.C) injection. Data about the use during pregnancy and breastfeeding mothers is insufficient yet. Also, Data does not support any dosage adjustment in hepatic and renal patients [10].

After single intravenous administration of these antibodies, they follow linear pharmacokinetics with a half-life of about 25 to 37 days for both antibodies. Regarding elimination, this combination is not metabolized in liver, and not excreted by kidneys [10].

Limitations of the previous study performed on antibody cocktail include short duration of follow up (7 days), not used many clinically relevant outcomes like mortality rate, not studied the long-term effect of antiviral in lowering viral load and inflammatory markers, and study performed on non-hospitalized patients only and not included hospitalized patients (trial is done only on outpatients and not inpatients)

2. Objectives

To evaluate the efficacy of antibodies cocktail (casirivimab and imdevimab) compared to standard antiviral therapy in reducing 28-day mortality in hospitalized patients with moderate, severe or critical COVID19, as well to examine its safety by monitoring infusion related reactions, hypersensitivity or other significant adverse effects.

3. Patients and population

265 hospitalized COVID-19 patients are used to represent COVID-19 population and was assigned into 3 groups in a ratio of (1:2:2) respectively, group (A) received REGN3048–3051(Antibodies cocktail (casirivimab and imdevimab)), group (B) received remdesivir, and group (C) received favipravir.

Populations in this study are the COVID-19 patients admitted to isolation hospital-Mansoura University. Paper will not be a tool for providing agreement by the patients or their relatives to avoid transmission of infection.

Inclusion criteria include age more than 12 years old, weight not less than 40 kg, moderate, severe or critical COVID-19 disease as defined by WHO, and PCR- confirmed patients to be Positive before inclusion.

Exclusion criteria include history of hypersensitivity or infusion related reactions after administration of monoclonal antibodies, prior use of standard antiviral therapy (remdesivir or favipravir), Current use of controversial antiviral therapy (ivermectin, hydroxychloroquine, oseltamivir, nitazoxanide, ribavirin, lopinavir/ritonavir, daclatasvir, sofosbuvir, semipirvir, acyclovir, azithromycin), and patients expected to die within 48 h.

4. Interventions

Population included in this study will be assigned to three different antiviral drugs with 1:2:2 ratios to receive antibodies cocktail, remdesivir or favipravir as shown in Figs. 2 and 3.

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 500 ml 0.9% sodium chloride solution as single I.V infusion over 30–60 min.

Group B patients will receive Remdesivir :

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

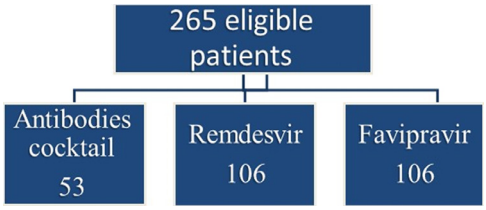

Fig. 2. Assignment of the included COVID cases at their groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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

Group C patients will receive Favipravir:

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

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

Patients will be received standard of care by Physicians, Clinical pharmacists, and Nurses and guided by Egyptian COVID-19 treatment protocol.

5. Study design

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

The research protocol was approved by IRB, faculty of medicine, Mansoura University, MS21.11.1737, Research ethics committee, faculty of medicine, Tanta University, 35,039/11/21, and Research ethics committee, ministry of health, Egypt, 10–2022/18

Registry name and registration number: Clinicaltrials.gov, NCT05502081

6. Outcomes

Parameters that were assessed during hospitalization on day 0(baseline), 3, 7, 14, and 28 include:

C-reactive protein (CRP),ferritin, lactate dehydrogenase (LDH), and D-dimer

Clinical outcomes measured after intervention:

Primary outcomes include 28-day mortality rate (efficacy), and percentage of the patients who developed infusion-related or hypersensitivity reactions during and after the end of drug infusion and reporting any Serious and unexpected adverse events that may occur and have not been previously reported with REGEN–COV use that may cause drug discontinuation (Safety).

Secondary outcomes include inflammatory markers including CRP, ferritin, LDH

In addition to clinical outcomes measured before and during the intervention, vital signs and patient characteristics (age, gender) will be recorded on admission

The duration of research will be about six months from November 2021 to April 2022.

7. Statistical analysis and sample size

7.1. Statistical analysis

Intention-to-treat strategy is used in this study. Statistical analysis is achieved with SPSS, version 26. Categorical variables are presented as proportion. Continuous variables are presented as mean (± standard deviation). As the comparison is conducted between three groups, the Kruskal-Wallis or ANOVA test is used for such comparison. the P-value

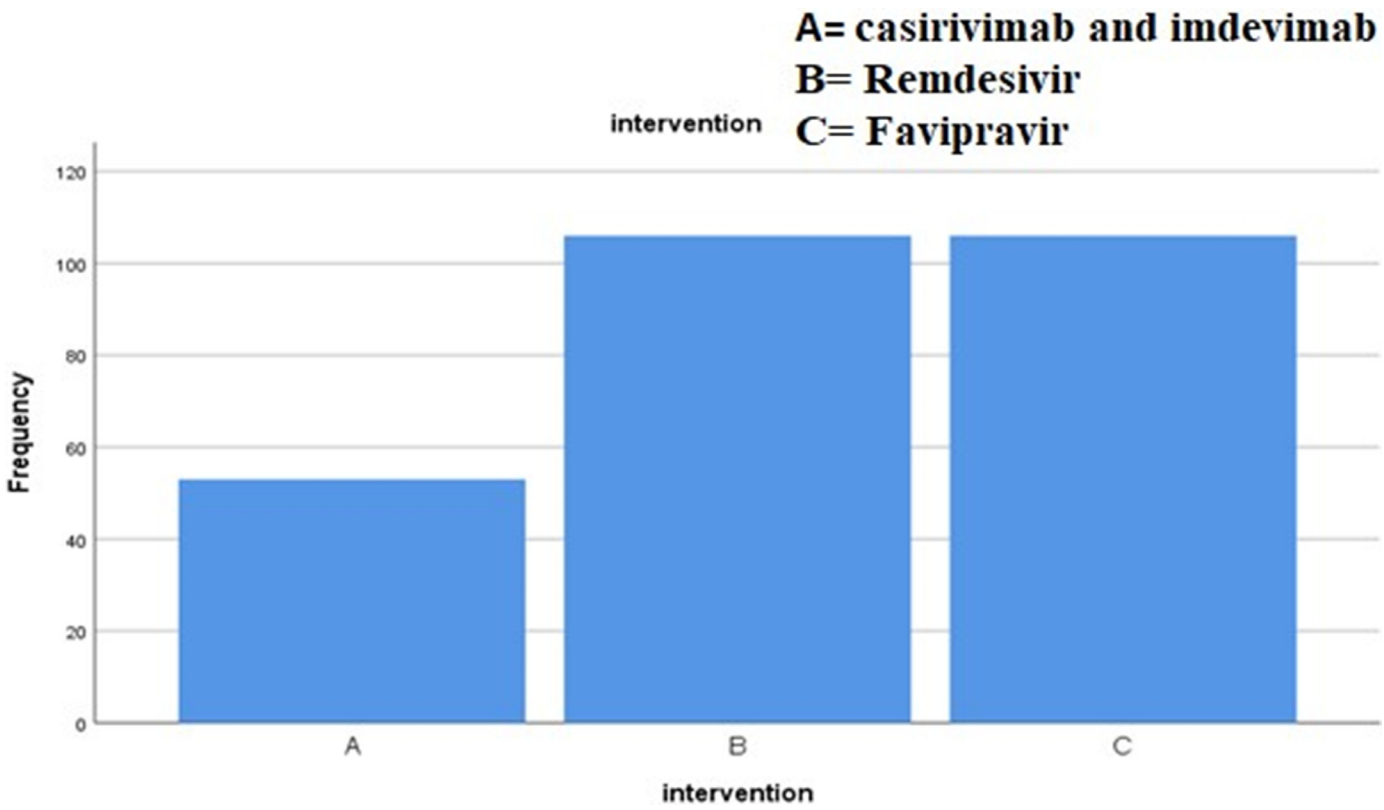

Fig. 3. Frequency of interventions in included patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for statistical tests with a value ≤ 0.05 will be statistically significant difference.

Regarding baseline characteristics, the Kruskal-Wallis or ANOVA test (depending on the type of data and data distribution (normal or not)) will be used to compare these characteristics between the study groups.

In case of existing differences in some baseline characteristics, regression analysis will be performed. This allows studying the effect of these baseline characteristics on the primary outcomes to exclude the effect of these confounding variables and to ensure the effect on the outcomes is due to interventions.

Regarding the outcomes, we will compare the 28-day all-cause mortality rate, result of PCR test at hospital discharge, and incidence of infusion-related or hypersensitivity reactions during and after the end of drug infusion (primary outcome) using the Kruskal-Wallis test with reporting the P-value.

While the secondary outcomes (hospital stay duration, ICU stay duration and others) are compared using the Kruskal-Wallis or ANOVA test depending on type of data and the distribution of continuous data (normal or not).

7.2. 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 28-day mortality (primary outcome) with a significance level (α) of 0.05 and 95% confidence level using the ANOVA or Kruskal-Wallis test of independent proportion in G*Power software. To compensate for the estimated loss-to-follow-up and increase the study power, we will increase the sample size in both remdesivir and favipravir groups to 106 patients compared to 53 patients in Antibodies cocktail Group. A ratio of (1:2:2) is used as Antibodies cocktail product is available for only about 50 COVID-19 patients. Also, according to number of patients who receive each drug, the ratio (1:2:2) is the closest to reality.

The mortality data was estimated from the average mortality rate in August, September, and October 2021 at Isolation Hospital of Mansoura University among all hospitalized patients. Mortality rate is found to be about 360 cases in these three months

(120 cases / month). The online system has been used to obtain mortality rate in these three months.

The current admission rate at Isolation Hospital of Mansoura University is 250 cases per month; our needed sample is about 250 cases.

8. Results

After statistical analysis is performed by SPSS software, all continuous data shows no normal distribution. So, the Kruskal-Wallis Test is used to compare non-normally distributed continuous, categorical and nominal variables between the three groups.

8.1. Regarding baseline characteristics

Table 2 represents the significance of difference between the three groups and also includes a comparison between every two groups in baseline characteristics if they show statistically significant difference between the three groups. Supplementary figures (S1-S9) represent distributions and frequencies of baseline characteristics between the three groups.

8.1.1. Age

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

8.1.2. Gender

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

Table 2
The significance of differences in baseline characteristics between the three groups.

Variables		Intervention			
		Casirivimab/ Imdevimab (A) (intravenous)	Remdesivir (B) (intravenous)	Favipravir (C) (enteral)	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

(*continued on next page*)

Table 2 (*continued*)

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
WHO clinical progression score	3	0/53	1/106	0/106	0.004
	4	15/53	5/106	10/106	
	5	35/53	100/106	96/106	
	6	3/53	0/106	0/106	
B & C					0.305
A & C					0.014
A & B					0.001
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
Heart rate		82.40±12.443	85.70±16.072	87.02±16.798	0.345
B & C					NA
A & C					NA
A & B					NA
Respiratory rate		24.25±3.246	25.40±5.580	24.72±5.012	0.652
B & C					NA
A & C					NA
A & B					NA
Body temperature		36.951±0.492	36.938±0.456	36.906±1.183	0.288

(*continued on next page*)

Table 2 (*continued*)

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*	92.36±4.816	87.62±7.171	88.35±7.006	0
B & C				0.448
A & C				0
A & B				0
LDH†	413.06±294.784	389.81±222.668	378.50±250.183	0.466
B &C				NA
A & C				NA
A & B				NA
CK‡	185.96±207.6	228.07±367.1	232.75±287	0.109
B & C				NA
A & C				NA
A & B				NA
D-dimer	0.6189±0.493	0.1433±0.227	0.2915±0.385	0
B & C				0.005
A & C				0
A & B				0
CRP§	61.566±39.71	61.292±35.3	95.513±157.8	0.114
B & C				NA
A & C				NA
A & B				NA
Ferritin	442.34±190.4	418.06±193.8	1158.4±6953	0.230
B & C				NA
A & C				NA
A & B				NA

* Room air, † Lactate dehydrogenase, ‡ Creatine kinase, § C-reactive protein.

Table 3
The best regression model for studying effects of confounding variables on 28-day mortality.

	Unstandardized Coefficients		Standardized Coefficients		t	P-value
	B	Std. Error	Beta	Std. Error		
(Constant)	.806	1.297			.621	.535
Age	.003	.001	.098	.053	1.835	.068
Gender	.029	.044	.038	.058	.652	.515
Number of co-morbidities	−0.002	.015	−0.007	.048	−0.144	.885
Severity of COVID	−0.004	.036	−0.007	.059	−0.123	.903
Number of symptoms	.029	.033	.049	.057	.854	.394
D-dimer	.064	.047	.083	.061	1.356	.177

8.1.3. Number of comorbidities

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

8.1.4. Method of diagnosis

There is a statistically non-significant difference between the three groups

8.1.5. Severity of COVID-19

There is a statistically significant difference between A-B &A-C and a statistically non-significant difference between C-B. There are statistically significantly less severe cases in group A than in groups B & C.

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.

8.1.7. Inflammatory markers

There is a statistically non-significant difference between the three groups in CK, LDH, Ferritin and CRP levels. There is a statistically significant difference between the three groups in D-dimer.

8.2. Regression analysis

Regression analysis is performed to explore the effect of baseline characteristics (that show a statistically significant difference between the three groups) on the outcomes of the study and the possibility of existence of confounding variables as shown in Table 3.

8.3. Regarding outcomes of the study after intervention in the three groups

Table 4 shows the significance of difference between clinical outcomes in the three groups and also includes a pairwise comparison between every two groups in clinical outcomes if they show statistically significant difference between the three groups. Supplementary figures (S10-S25) in the Supporting Information show the distributions and frequencies of these outcomes across the three groups.

8.3.1. Effect on inflammatory markers (CRP, D-dimer, CK, LDH, ferritin)

There is only a statistically significant difference in CRP on day 3,7, D-dimer, LDH and ferritin on day 7 between A-B & A-C, LDH on day 3 between A-B.

8.3.2. Effect on 28-day mortality (primary outcome)

There is a statistically significant difference in 28-day mortality between A-B & A-C.

8.3.3. Mortality at discharge

There is a statistically significant difference in death at discharge between A-B & A-C.

8.3.4. Incidence of any serious adverse effect leading to drug discontinuation (primary outcome)

There is a statistically non-significant difference between the three groups in causing of any serious adverse effect.

8.3.5. Incidence of acute kidney injury (AKI) and acute liver damage (ALD)

There is a statistically non-significant difference between the three groups in causing any deterioration on kidneys or liver functions.

9. Discussion

This study compared casirivimab and imdevimab with remdesivir and favipravir for use in COVID-19 hospitalized patients. There is no similar treatment comparison or related studies to be compared with this research for similarity and differences.

9.1. Regarding baseline characteristics

The age in groups A & B is statistically significantly lower than that in group C. there is statistically significantly more female in group B group than group C. Number of co-morbidities is statistically significantly more in group C than Group B. There are statistically significantly less severe cases in group A than groups B & C. There is a statistically significantly a smaller number of symptoms in group A than groups B & C.

9.2. Regression analysis

After statistical analysis of baseline characteristics in the three groups and finding that statistically significant differences in some baseline characteristics exist between the three groups. Differences exist between age, gender, number of symptoms, number of co-morbidities, and severity of COVID.

So, it is necessary to exclude the effect of these variables on the outcomes of the study which represented by the primary outcome and mainly 28-day mortality.

For this reason, regression analysis is performed to explore the effects of these variables on the primary outcome of the study (28-day mortality).

After regression analysis, it is found that all baseline characteristics that differ between the three groups have no effect on the study outcome.

9.3. Regarding outcomes of the study after intervention in the three groups

9.3.1. Effect on inflammatory markers (CRP, D-dimer, CK, LDH, ferritin)

CRP at day 3,7 and D-dimer LDH & ferritin at day 7 are statistically significantly lower in group A than groups B & C. LDH at day 3 is statistically significantly lower in group A than group B.

From these results, it is concluded that inflammatory marker levels have been lowered by A than B & C interventions.

Table 4
The significance of differences in baseline characteristics between the three groups.

Variables	Intervention			
	Casirivimab/ Imdevimab (A) (intravenous)	Remdesivir (B) (intravenous)	Favipravir (C) (enteral)	P-values
CRP* at day 3	33.87±31.44	52.61±37.719	64.1±63.035	0.002
B & C				0.557
A & C				0.001
A & B				0.004
CRP at day 7	14.06±14.548	47.43±52.631	65.73±90.34	0
B & C				0.891
A & C				0
A & B				0
CRP at day 14	7.5±5.745	37.05±55.395	39.31±54.77	0.516
B & C				NA
A & C				NA
A & B				NA
CRP at day 28		39±38.419	96±0	0.264
B & C				NA
D-dimer at day 3	0.244±0.2211	0.23±0.3321	0.29±0.3845	0.219
B & C				NA
A & C				NA
A & B				NA
D-dimer at day 7	0.109±0.1483	0.319±0.5017	0.425±0.5678	0.015
B & C				0.223
A & C				0.004
A & B				0.05
D-dimer at day 14	0.05±0.10	0.41±0.5999	0.313±0.461	0.423
B & C				NA
A & C				NA
A & B				NA
D-dimer at day 28		0.40±0.80	0.40±0	0.429
B & C				NA
CK† at day 3	142.2±135.12	197.94±342.1	181.45±166	0.089
B & C				NA

(*continued on next page*)

Table 4 (*continued*)

A & C				NA
A & B				NA
CK at day 7	126.743±112	211.9±420.23	175.99±155	0.222
B & C				NA
A & C				NA
A & B				NA
CK at day 14	49.5±30.116	122.89±93.259	142.75±176	0.252
B & C				NA
A & C				NA
A & B				NA
CK at day 28		119.22±88.21	134.25±113	0.157
B & C				NA
LDH‡ at day 3	351.27±258.57	404.45±214.92	354.7±204.2	0.01
B & C				0.06
A & C				0.156
A & B				0.003
LDH at day 7	271.4±165.99	371.37±196.2	349.68±201	0.007
B & C				0.382
A & C				0.017
A & B				0.002
LDH at day 14	379.75±313.9	360.89±244.8	306.88±266	0.457
B & C				NA
A & C				NA
A & B				NA
LDH at day 28		314.5±108.99	270±0	0.48
B & C				NA
Ferritin at day 3	393.04±170.2	427.25±194.8	1110±6784.6	0.106
B & C				NA
A & C				NA
A & B				NA
Ferritin at day 7	368.42±167.8	450.37±247.6	1433±8174	0.01

(*continued on next page*)

Table 4 (*continued*)

	B & C				0.605
	A & C				0.003
	A & B				0.01
Ferritin at day 14		398.5±131.43	637.37±436	519.88±431	0.293
	B & C				NA
	A & C				NA
	A & B				NA
Ferritin at day 28			1355±896.3	410±0	0.157
	B & C				NA
28-day mortality	Dead	1/53	34/106	43/106	0
	Alive	52/53	72/106	63/106	
	B & C				0.176
	A & C				0
	A & B				0
Day of death		0.19±1.061	12.57±6.22	10.13±6.530	0
	B & C				0.234
	A & C				0
	A & B				0
Mortality at discharge	Dead	1/53	33/106	41/106	0
	Alive	52/53	73/106	65/106	
	B & C				0.223
	A & C				0
	A & B				0
Incidence of serious adverse effect	Yes	0/53	0/106	0/106	1
	No	53/53	106/106	106/106	
	B & C				NA
	A & C				NA
	A & B				NA

∗ C-reactive protein.
† Creatine kinase.
‡ Lactate dehydrogenase.

9.3.2. Effect on mortality at day 28 (primary outcome)

Group A has a statistically significantly lower 28-day mortality rate than groups B & C.

9.3.3. Mortality at discharge

In addition to lowering 28-day mortality, a statistically significantly lower mortality rate at hospital discharge with group A than groups B & C.

9.3.4. Incidence of any serious adverse effect leading to drug discontinuation (primary outcome)

All three interventions have no significant adverse effect that proves their safety.

Limitations of this study includes non-randomization of antiviral drugs among included patients, non- blinding of interventions to investigators, applicable only on hospitalized COVID-19 patients (not include outpatients), and the differences in some baseline characteristics between the groups

Generalizations of this study

This study can be generalized on hospitalized COVID-19 patients only and not involve all COVID-19 patients.

10. Conclusion

Casirivimab and imdevimab group achieves less 28-day mortality rate & less mortality at hospital discharge than Remdesivir and Favipravir groups.

It is concluded that group A (Casirivimab & imdevimab) has more favorable clinical outcomes than groups B (remdesivir) & C (favipravir).

Statements and declarations

Compliance with Ethics Guidelines

The research protocol was approved by

- IRB, faculty of medicine, Mansoura University, MS21.11.1737
- Research ethics committee, faculty of medicine, Tanta University, 35,039/11/21
- Research ethics committee, ministry of health, Egypt, 10–2022/18

Registry name and registration number: Clinicaltrials.gov, NCT05502081

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.

Funding

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

Thanking patient participants

The authors thank study participants for their involvement in the study.

Declaration of Competing Interest

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

CRediT authorship contribution statement

Sahar K. Hegazy: Conceptualization, Project administration, Supervision. **Samar Tharwat:** Supervision, Validation, Visualization. **Ahmed H. Hassan:** Conceptualization, Data curation, Methodology, 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

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Preprints for this study are available at 2 websites.

Clinical Study to Evaluate the Possible Efficacy and Safety of Antibodies Combination (casirivimab and imdevimab) versus standard antiviral therapy as antiviral agent against Corona virus 2 infection in hospitalized COVID-19 patients. https://www.medrxiv.org/content/10.1101/2022.08.20.22279020v2.full.pdf https://www.researchsquare.com/article/rs-1991618/v2.

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.

Additional outcomes of this research are collected and will be analyzed to be published soon.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcvp.2023.100151.

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