Intravenous Immunoglobulin Gamma for Severe Cases of Coronavirus Disease of 2019: A Randomized Placebo-Controlled Double-Blinded Clinical Trial

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Abstract

Background: Coronavirus disease of 2019 (COVID-19) with high-transmission power has infected people in many countries around the world. Discovering an effective medication for the treatment of this disease, especially in severe cases, has become the subject of intense scientific investigations. Therefore, the objective of this study was to evaluate the efficacy of intravenous immunoglobulin (IVIg) in patients with severe COVID-19 infection.

Methods: The study was conducted as a randomized placebo-controlled double-blinded clinical trial. Fifty-nine patients with severe COVID-19 infection who did not respond to initial treatment were randomly assigned into two groups. One group received IVIg (human) four vials every day for three days in addition to initial treatment, and the other group received placebo. Patients' demographic, clinical, and selected laboratory test results, as well as the occurrence of in-hospital mortality, were recorded.

Result: Among included patients, 30 patients received IVIg and 29 patients received placebo. Demographics, clinical characteristics and evaluated laboratory tests of two groups were not statistically different (P>0.05). The in-hospital mortality rate was significantly lower in the IVIg group as compared to the control group (6 [20.0%] vs 14 [48.3%], respectively, p = 0.022). Multivariate regression analysis demonstrated that administration of IVIg had a significant impact on mortality rate (aOR= 0.003 [95%CI: 0.001 - 0.815], p=0.042).

Conclusion: Our study was the first randomized double-blinded study that demonstrated that the administration of IVIg in patients with severe COVID-19 infection who did not respond to initial treatment could improve their clinical outcome and reduce the mortality rate. However, further multicenter studies with larger samples size are required to confirm the applicability of using this medication as the standard treatment.

Trial registration: The study protocol is registered at the Iranian Registry of Clinical Trials (www.IRCT.ir) with the registration number of IRCT20200501047259N1. Registered 17 May 2020. Retrospectively registered.

Background

Coronavirus disease of 2019 (COVID-19) outbreak has been announced as a pandemic by the World Health Organization on 11 March 2020 (1). The culprit virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly contagious and can spread mainly through respiratory droplets produced by coughing and sneezing (2). The mortality rate was reported to be about 2.5 percent at initial assessments; however, higher estimations were reported lately (3). Although a great deal of effort has been made to find a proper medication against this disease, no specific treatment has been established yet, and no vaccine is currently available. Therefore, the therapeutic strategies are mainly empirical and based on the experiences from treatment against other pathogens. Lopinavir/ritonavir, chloroquine phosphate, hydroxychloroquine, and alpha-interferon are of the most commonly used medications for

COVID-19 (4). Moreover, preclinical studies have proposed remdesivir (an RNA polymerase inhibitor with in vitro activity against multiple RNA viruses, including Ebola) and tocilizumab (humanized IgG1 monoclonal antibody, directed against the IL-6 receptor) (5).

Intravenous immunoglobulin (IVIg) is a blood product that is obtained from healthy donors and contains polyclonal immunoglobulin Gamma. Since its emergence about 30 years ago, it has been administered as an effective immunomodulatory therapy in autoimmune or inflammatory diseases (6). Moreover, significant positive outcomes have been observed by the administration of IVIg in patients with SARS and Middle East respiratory syndrome (MERS) (7-9). Considering the presence of overwhelming immune response in COIVD-19 (10, 11) as well as similarities between the pathogenesis of SARS and COVID-19, it seems that IVIg can be helpful to improve passive immunity and modulate the inflammation in patients with COIVD-19 (12). A case report in China described significant improvement of three patients with severe COVID-19 infection who received high dose IVIg (12). However, the lack of more inclusive studies still exists to propose this treatment as an effective therapeutic option for COVID-19. Therefore, the objective of this study was to evaluate the efficacy of IVIg in COVID-19 patients who did not respond to initial treatment.

Methods

This study was a randomized double-blinded placebo-controlled clinical trial on 59 patients with severe COVID-19 infection who did not respond to initial treatment. The study was conducted in accordance with the declaration of Helsinki protocol. Informed consent was obtained from the patients or their guardians after a short description of the study. The protocol of the study was approved by the medical ethics committee of the university (IR.UMSU.REC.1399.025). The study protocol is registered at the Iranian Registry of Clinical Trials with the registration number of IRCT20200501047259N1 (www.IRCT.ir).

Study Sample

The patients were consecutively included if they had developed acute respiratory syndrome and had a definite diagnosis of COVID-19 which was made based on real-time reverse transcription-polymerase chain reaction (rRT-PCR) test and the chest computed tomography scan findings from … (*hided for blinded peer review*) teaching hospital from May 9, 2020 to June 9, 2020. The inclusion criteria were age over 18 years, a definite diagnosis of COVID-19, on admission involvement of more than 30 percent of both lungs in high-resolution computed tomography (HRCT) (confirmed by two radiologists), O_2 saturation ($satO_2$) less than 90 percent, lack of adequate response to initial treatment including at least one antiviral and chloroquine drugs. Exclusion criteria were pregnancy, coagulation disorders, history of hypersensitivity for IVIg, advanced heart failure (left ventricular ejection fraction less than 35%), pulmonary fibrosis or history of lung surgery, sarcoidosis and tuberculosis that may interfere with an accurate estimation of the severity of pulmonary involvement by COVID-19. Inadequate response to initial treatment was defined as the lack of improvement of dyspnea and fever as well as hypoxemia ($satO_2$

less than 90%) and the need for oxygenation to maintain $satO_2$ above this level after 48 hours of starting the treatment.

Exposure

The included patients were randomly assigned into two groups of IVIg and control (1:1) using a computer-generated randomization schedule. IVIg group received IVIg (human) flebogamma 5% DIF GRIFOLS in addition to initial treatment. The patients received four vials every day for three days, and each vial had five-gram IVIg. Those patients who expired before 72 hours since the initiation of IVIg were excluded from our study due to the incomplete course of treatment. The control group continued to receive the initial treatment and received a placebo. Neither the patients nor the physicians nor whom responsible for data analysis were aware of the types of treatment allocated, and only the pharmacist of the center had knowledge about IVIg or placebo. Placebo and IVIg vials had similar appearance and were labeled as A and B. The placebo vials contained a similar volume of normal saline solution.

Outcome

The study primary outcome was in-hospital mortality.

Data analysis

The normal distribution of the variables was evaluated using the Kolmogorov-Smirnov test. The majority of the continuous variables had not a normal distribution; therefore, the median and interquartile range (IQR, 25 percentile – 75 percentile) of quantitative variables and frequency and percentage of qualitative variables were reported. Continuous variables were compared using the Mann Whitney U test. Qualitative variables were compared using Chi-square or Fischer exact test. Univariate logistic regression was used to model the mortality based on investigated variables. Significant variables in univariable logistic regression (p-value less than 0.2) were entered into multivariable logistic regression. The statistical analysis was conducted using Statistical Package for the Social Sciences version 22 (SPSS Inc., Chicago, IL).

Results

Among included patients, 30 patients received IVIg, and 29 patients received placebo. The investigated characteristics of the patients are described in Table 1. Demographics, clinical characteristics and evaluated laboratory tests of two groups did not have significant differences except for serum creatinine which was slightly higher in the control group (median [IQR] = 1.0 [0.8–1.1] vs 1.2 [1.0–1.4] in IVIg and control groups, respectively, P = 0.001) and white blood cells count (WBC) which was higher in the control group (median [IQR] = 5.05 [4.20- 7.00] vs 6.60 [5.00–10.90] in IVIg and control groups, respectively, P = 0.026). The in-hospital mortality rate was significantly lower in the IVIg group (6 [20.0%] vs 14 [48.3%], in IVIg and control groups, respectively, p = 0.022, Fig. 1). Duration of stay in ICU in the IVIg group was higher than control; however, this difference was not statistically significant (median [IQR] = 4 [3–6] vs 3

[2–4] days in IVIg and control groups, respectively, P = 0.101). However, the overall duration of hospitalization was longer in IVIg group (median [IQR] = 9 [7–13] vs 7 [6–9], days in IVIg and control groups, respectively, P = 0.014).

Table 1
Evaluated characteristics of included patients with severe COVID-19 infection in two study groups

		Total	IVIg	Control	P value
Age years*		56 (46 ,62)	55.5 (45 ,60)	56 (47 ,66)	0.375
Gender n (%)	**Male**	41 (69.4)	21 (70)	20 (68.9)	0.931
	Female	18 (30.5)	9 (30)	9 (31)	
HTN n (%)		13 (22)	7 (23.3)	6 (20.6)	0.807
DM n (%)		16 (27.1)	6 (20)	10 (34.4)	0.211
Chronic lung disease n (%)		2 (3.3)	2 (6.6)	0 (0)	0.157
HR /min		95 (89 ,105)	92.5 (89 ,100)	96 (90 ,108)	0.280
Systolic BP mmHg		120 (115 ,130)	120 (120 ,130)	120 (110 ,130)	0.428
Diastolic BP mmHg		80 (70 ,80)	80 (70 ,80)	80 (70 ,80)	0.542
RR /min		19 (18 ,22)	19.5 (18 ,22)	19 (18 ,21)	0.927
BT C°		37.1 (36.7 ,37.7)	37.05 (36.5 ,37.8)	37.1 (36.9 ,37.6)	0.772
O_2 saturation %		88 (85 ,89)	88 (85 ,89)	88 (85 ,89)	0.436
WBC 1000/mm^3		5.6 (4.6 ,8.7)	5.0 (4.2 ,7)	6.6 (5 ,10.9)	**0.026**
Neutrophil %		78 (70 ,83)	74 (70 ,80)	80 (74 ,87)	0.114
Lymphocyte %		18 (11 ,22)	19 (14 ,25)	16 (9 ,20)	0.085
Hb g/dl		13.9 (12.4 ,15)	13.7 (12.2 ,15)	14 (13.1 ,15.1)	0.309
Plt 1000/mm^3		190 (137,226)	186 (133 ,220)	191 (160 ,234)	0.457
LDH U/L		591 (444 ,742)	545.5 (473 ,705)	611 (421 ,800)	0.677
BUN mg/dl		34 (27 ,58)	30.5 (27 ,46)	50 (27 ,68)	0.082
Creatinine mg/dl		1.1 (1 ,1.3)	1 (0.8 ,1.1)	1.2 (1 ,1.4)	**0.001**

* Data are presented in median (IQR) unless determined otherwise. IVIg, Intravenous immunoglobulin; HR, Heart rate; BP, Blood pressure; RR, Respiratory rate; BT, Body temperature; WBC, White blood cells; Hb, Hemoglobin; Plt, Platelet; LDH, Lactate dehydrogenase; BUN, Blood urea nitrogen; K, Serum potassium; Na, Serum sodium; ESR, Erythrocyte sedimentation rate; AST, Enzymes aspartate transaminase; ALT, Aka alanine aminotransferase, ALP, Alkaline phosphatase; FBS, Fasting blood sugar; BS, Blood sugar; PaO_2, Partial pressure of oxygen, PCO_2, Partial pressure of carbon dioxide; HCO3, Bicarbonate; ICU, Intensive care unit.

	Total	IVIg	Control	P value
K mEq/L	4.1 (3.9 ,4.4)	4 (3.9 ,4.5)	4.1 (3.9 ,4.3)	0.813
Na mEq/L	138 (136 ,140)	138 (137 ,140)	138 (135 ,143)	0.728
ESR	29 (20 ,46)	28 (23 ,50)	31 (20 ,41)	0.808
AST U/L	31 (21 ,42)	34.5 (21 ,53)	29 (18 ,40)	0.271
ALT U/L	35 (27 ,45)	34 (27 ,42)	38 (24 ,47)	0.596
BS mg/dl	120 (106 ,174)	118 (105 ,141)	131 (109 ,229)	0.295
PH	7.3 (7.3 ,7.4)	7.4 (7.3 ,7.4)	7.3 (7.3 ,7.4)	0.210
PaO_2 mmHg	45 (38 ,49)	45 (40 ,49)	45 (37 ,50)	0.767
PCO_2 mmHg	39 (36 ,45)	38 (35 ,42)	39 (38 ,47)	0.084
HCO_3 mEq/L	24 (21 ,26)	24 (23 ,26)	24 (21 ,26)	0.522
Duration of stay in ICU days	3 (2 ,6)	4 (3 ,6)	3 (2 ,4)	0.101
Duration of hospitalization days	8 (6 ,11)	9 (7 ,13)	7 (6 ,9)	**0.014**

* Data are presented in median (IQR) unless determined otherwise. IVIg, Intravenous immunoglobulin; HR, Heart rate; BP, Blood pressure; RR, Respiratory rate; BT, Body temperature; WBC, White blood cells; Hb, Hemoglobin; Plt, Platelet; LDH, Lactate dehydrogenase; BUN, Blood urea nitrogen; K, Serum potassium; Na, Serum sodium; ESR, Erythrocyte sedimentation rate; AST, Enzymes aspartate transaminase; ALT, Aka alanine aminotransferase, ALP, Alkaline phosphatase; FBS, Fasting blood sugar; BS, Blood sugar; PaO_2, Partial pressure of oxygen, PCO_2, Partial pressure of carbon dioxide; HCO3, Bicarbonate; ICU, Intensive care unit.

Univariate regression analysis identified several related variables to the mortality of included patients (Table 2). By adjusting these variables, multivariate regression analysis demonstrated that the administration of IVIg had a significant impact on mortality and was an independent determinant of mortality (aOR = 0.003 [0.001–0.815], p = 0.042). Moreover, older age, lower diastolic blood pressure, and a higher level of serum lactate dehydrogenase (LDH) were other independent determinants of higher mortality in patients with severe COVID-19 infection (Table 3).

Table 2
The relationship between study variables and mortality of included patients with severe COVID-19 infection

		Mortality		Unadjusted OR (95% CI)	P value
		No	Yes		
IVIg **n (%)**	**No**	15 (38.4)	14 (70)	0.27 (0.08, 0.85)	**0.025#**
	Yes	24 (61.5)	6 (30)	Ref	
Age years		54 (44, 60)	60 (53.5, 70)	1.05 (1.01, 1.1)	**0.014**
Gender n (%)	**Male**	27 (70)	14 (70)	0.96 (0.3, 3.12)	0.951
	Female	12 (30)	6 (30)	Ref	
HTN n (%)		8 (23.3)	5 (25)	1.29 (0.36, 4.63)	0.694
DM n (%)		11 (20)	5 (25)	0.85 (0.25, 2.9)	0.793
Chronic lung disease n (%)		1 (6.6)	1 (5)	2 (0.12, 33.76)	0.630
HR /min		95 (90, 100)	95 (89, 108)	1.02 (0.96, 1.08)	0.543
Systolic BP mmHg		120 (120, 130)	120 (110, 130)	0.97 (0.93, 1.01)	**0.173**
Diastolic BP mmHg		80 (70, 80)	70 (70, 80)	0.95 (0.88, 1.01)	**0.120**
RR /min		19 (18, 22)	20 (18, 22)	0.98 (0.93, 1.04)	0.545
BT C°		37.1 (36.7, 37.7)	37.1 (36.75, 37.65)	1.26 (0.63, 2.52)	0.518
O_2 **saturation %**		89 (87, 89)	85 (80, 88)	0.84 (0.74, 0.97)	**0.015**
WBC 1000/mm^3		5.1 (4.6, 7.4)	7.2 (5.1, 11.2)	1.00 (1.00, 1.00)	0.743
Hb g/dl		13.9 (12.6, 15)	13.5 (12.05, 15.25)	0.95 (0.8, 1.13)	0.566
Plt 1000/mm^3		210 (135, 247)	172.5 (139.5, 193)	1.00 (1.00, 1.00)	**0.090**
LDH U/L		520 (400, 687)	761 (560.5, 1021)	1.00 (1.00, 1.00)	**0.003**
BUN mg/dl		29 (25, 39)	64 (50, 129.5)	1.06 (1.02, 1.09)	**0.001**

* Data are presented in median (IQR) unless determined otherwise. #variables with p value less than 0.2 were selected to enter multivariable regression analysis. IVIg, Intravenous immunoglobulin; HR, Heart rate; BP, Blood pressure; RR, Respiratory rate; BT, Body temperature; WBC, White blood cells; Hb, Hemoglobin; Plt, Platelet; LDH, Lactate dehydrogenase; BUN, Blood urea nitrogen; K, Serum potassium; Na, Serum sodium; ESR, Erythrocyte sedimentation rate; AST, Enzymes aspartate transaminase; ALT, Aka alanine aminotransferase, ALP, Alkaline phosphatase; FBS, Fasting blood sugar; BS, Blood sugar; PaO_2, Partial pressure of oxygen, PCO_2, Partial pressure of carbon dioxide; HCO3, Bicarbonate; ICU, Intensive care unit.

	Mortality		Unadjusted OR (95% CI)	P value
Creatinine mg/dl	1 (1, 1.2)	1.2 (1.1, 1.55)	3.63 (0.95, 13.87)	**0.059**
K mEq/L	4 (3.7, 4.4)	4.2 (4.1, 4.3)	0.95 (0.8, 1.14)	0.616
Na mEq/L	138 (137, 139)	138 (135, 143.5)	1.04 (0.95, 1.14)	0.344
ESR	28 (20, 41)	40 (26, 49.5)	1.01 (0.99, 1.03)	0.424
AST U/L	31 (21, 39)	29.5 (15.5, 52.5)	1.00 (0.97, 1.02)	0.735
ALT U/L	34.5 (25, 41)	38.5 (29.5, 48)	1.01 (0.99, 1.02)	0.306
BS mg/dl	119 (105, 174)	126 (109.5, 184)	1.00 (0.99, 1.01)	0.845
PaO_2 mmHg	46 (40, 50)	39.5 (34, 49)	0.92 (0.85, 0.99)	**0.035**
PCO_2 mmHg	40 (35, 46)	38 (36, 39.5)	0.99 (0.91, 1.08)	0.798
HCO_3 mEq/L	24 (22, 25)	24.5 (19.5, 26.5)	1.00 (0.89, 1.13)	0.946
PH	7.3 (7.3, 7.4)	7.3 (7.2, 7.4)	0.04 (0, 8.87)	0.243

* Data are presented in median (IQR) unless determined otherwise. #variables with p value less than 0.2 were selected to enter multivariable regression analysis. IVIg, Intravenous immunoglobulin; HR, Heart rate; BP, Blood pressure; RR, Respiratory rate; BT, Body temperature; WBC, White blood cells; Hb, Hemoglobin; Plt, Platelet; LDH, Lactate dehydrogenase; BUN, Blood urea nitrogen; K, Serum potassium; Na, Serum sodium; ESR, Erythrocyte sedimentation rate; AST, Enzymes aspartate transaminase; ALT, Aka alanine aminotransferase, ALP, Alkaline phosphatase; FBS, Fasting blood sugar; BS, Blood sugar; PaO_2, Partial pressure of oxygen, PCO_2, Partial pressure of carbon dioxide; HCO3, Bicarbonate; ICU, Intensive care unit.

Table 3
Multivariable regression analysis result for prediction of mortality of included patients with severe COVID-19 infection

	Adjusted OR (95% CI)	P value
IVIg	0.003 (0.001 ,0.815)	0.042
Age	1.485 (1.011, 2.181)	0.044
Systolic BP	1.078 (0.924 ,1.258)	0.336
Diastolic BP	0.543 (0.303 ,0.972)	0.040
O2 saturation	0.841 (0.621 ,1.138)	0.262
PLT	1.000 (0.999 ,1.000)	0.132
LDH	1.023 (1.000 ,1.046)	0.048
BUN	1.136 (0.990 ,1.304)	0.069
Creatinine	0.018 (0.001 ,6.085)	0.177
PaO2	0.834 (0.593 ,1.173)	0.298

IVIg, Intravenous immunoglobulin; BP, Blood pressure; LDH, Lactate dehydrogenase; BUN, Blood urea nitrogen; PaO2, Partial pressure of oxygen.

Discussion

Our results showed that IVIg could improve clinical outcomes in COVID-19 patients with severe respiratory system involvement. Previously, Prohaska et al. showed that IVIg could not reduce the mortality of patients with ARDS undergoing extracorporeal membrane oxygenation (ECMO) therapy. In this study, patients with bacterial and fungal infection also included, and only 54% of patients in the IVIg group and 28% of patients in the control group had viral infection (13). Recently, a randomized controlled trial studied the hyperimmune IVIg (hIVIg) effect on patients with confirmed influenza A or B infection. This study showed that hIVIg was not superior to placebo in treating patients with influenza A or B. In this study the mortality rates of patients in hIVIg and control groups were 4% and 3% respectively (14). The two mentioned studies have investigated IVIg effect in very high-risk and very low-risk patients for mortality, and it is possible that the effectiveness of IVIg in our study could be due to using the drug in patients with intermediate-risk of mortality.

Xie et al. studied the IVIg treatment's timing effect on mortality of patients with critical illness due to COVID-19 infection. In this study, 58 patients were included, and 28 patients died during 28 days of admission (total mortality = 48.2%). The mortality rate of patients who received IVIg during 48 hours of admission to ICU and those who received IVIg after 48 hours of admission were 23.3% vs 57.1%, respectively (p = 0.009) (15). The mortality rate of Xie et al. study is close to our results, which shows that early IVIg treatment could significantly reduce the mortality of critically ill COVID-19 patients. Cao et al. also reported desirable results in the treatment of 3 patients with COVID-19 and severe disease with IVIg 25 gr/day continued for five days (16). Our results showed that IVIg 20 g/day for three days could be effective and safe.

Very recently, a multicenter retrospective cohort study conducted on 325 patients including 222

(68%) patients with severe type and 103 (32%) with critical type of confirmed COVID-19. In 174 patients, IVIg was administered and 151 patients did not take IVIg. Two groups had significantly different bassline characteristics, and the IVIg group were in more severe condition. This study showed a 28 days mortality rate of 13% in both groups. The primary analysis showed no difference between the IVIg group and control group in reducing in-hospital mortality. However, after adjusting the outcomes of two groups with the severity of illness, results showed that administration of IVIg significantly decreased the 60-day mortality. This study also showed that IVIg dosage > 15 g/d and starting the drug ≤ 7 days could be more effective (17). A meta-analysis showed that IVIg could be effective in patients with severe sepsis or septic shock and its efficacy in mortality reduction could be better in patients with higher baseline risk and those with lower plasma immunoglobulins (18). Justel et al. studied patients admitted with severe pandemic influenza showed that lower level of IgG and IgM was associated with higher early mortality (19).

Our study showed that higher age, lower diastolic blood pressure, and higher LDH were also associated with higher mortality in COVID-19 patients with severe disease. Correspondingly, Du et al. also showed that age ≥ 65 years was associated with higher mortality in patients with COVID-19 pneumonia (20). Moreover, Henry et al. reported that elevated LDH was associated with 16 fold higher mortality among patients with COVID-19 infection (21).

To the best of our knowledge, our study is the first randomized double-blinded control trial that suggests the effectiveness of IVIg in reducing mortality in patients with severe COVID-19 pneumonia. However, some limitations existed in our study. The study was conducted as a pilot study and included a relatively small sample size. Therefore, further multicenter studies with larger samples size should be conducted in this regard. Moreover, it was better to follow the patients for evaluation of intermediate and long term effects of IVIg treatment. However, due to the pressing requirement of physicians and health care systems for providing evidence-based medications for patients with COVID-19, we decided to report the follow-up data in future updates of the study. Furthermore, it should be noted that the cost of IVIg treatment is relatively high, and it may not be widely available, particularly in low and middle-income countries.

Conclusion

The result of our study demonstrated that the administration of IVIg in patients with severe COVID-19 infection who did not respond to initial treatment could improve their clinical outcome and reduce the mortality rate. However, further multicenter studies with larger samples size are required to confirm the applicability of using this medication as the standard treatment of these patients.

Abbreviations

IVIg, Intravenous immunoglobulin;

HR, Heart rate;

BP, Blood pressure;

RR, Respiratory rate;

BT, Body temperature;

WBC, White blood cells;

Hb, Hemoglobin;

Plt, Platelet;

LDH, Lactate dehydrogenase;

BUN, Blood urea nitrogen;

K, Serum potassium;

Na, Serum sodium;

ESR, Erythrocyte sedimentation rate;

AST, Enzymes aspartate transaminase;

ALT, Aka alanine aminotransferase;

ALP, Alkaline phosphatase;

FBS, Fasting blood sugar;

BS, Blood sugar;

PaO2, Partial pressure of oxygen;

PCO2, Partial pressure of carbon dioxide;

HCO3, Bicarbonate;

ICU, Intensive care unit.

Declarations

Ethics approval: The protocol of this study was approved by medical ethics committee of the Urmia University of Medical Sciences (IR.UMSU.REC.1399.025).

Consent to participate: Informed consent was obtained from the participants.

Consent for publication: Consent for publication was granted.

Availability of data and materials: All Data and material collected during this study are available from the corresponding author upon reasonable request.

Conflicts of interest/Competing interests: None declared.

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Authors' contributions: Conceptualization: NG, RH, SRSE; Methodology: RH, SJM, RN, NG; Formal analysis and investigation: RH, SRSE; Writing - original draft preparation: SRSE, RH; Writing - review and editing: NG, RH, SJM, RN, SRSE; Funding acquisition: NG; Resources: NG, Supervision: NG, RH

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References

1. Ghebreyesus WD-GTA. WHO Director-General's opening remarks at the media briefing on COVID-19–11 March 2020 USA: World Health Organisation; 2020 [Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020.
2. Kucharski AJ, Russell TW, Diamond C, Liu Y, Edmunds J, Funk S, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. The lancet infectious diseases. 2020.
3. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. The Lancet infectious diseases. 2020.
4. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). StatPearls [Internet]: StatPearls Publishing; 2020.
5. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol

Chem. 2020;295(15):4773–9.
6. Galeotti C, Kaveri SV, Bayry J. IVIg-mediated effector functions in autoimmune and inflammatory diseases. Int Immunol. 2017;29(11):491–8.
7. Khanna N, Widmer AF, Decker M, Steffen I, Halter J, Heim D, et al. Respiratory syncytial virus infection in patients with hematological diseases: single-center study and review of the literature. Clin Infect Dis. 2008;46(3):402–12.
8. Wang J-T, Sheng W-H, Fang C-T, Chen Y-C, Wang J-L, Yu C-J, et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerg Infect Dis. 2004;10(5):818.
9. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med. 2014;160(6):389–97.
10. 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. The Lancet. 2020;395(10223):497–506.
11. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020.
12. Cao W, Liu X, Bai T, Fan H, Hong K, Song H et al, editors. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019. Open Forum Infectious Diseases; 2020.
13. Prohaska S, Schirner A, Bashota A, Körner A, Blumenstock G, Haeberle HA. Intravenous immunoglobulin fails to improve ARDS in patients undergoing ECMO therapy. J Intensive Care. 2018;6:11.
14. Davey RT Jr, Fernández-Cruz E, Markowitz N, Pett S, Babiker AG, Wentworth D, et al. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIg): a double-blind, randomized, placebo-controlled trial. The Lancet Respiratory medicine. 2019;7(11):951–63.
15. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. The Journal of infection. 2020:S0163-4453(20)30172-9..
16. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. Open forum infectious diseases. 2020;7(3):ofaa102.
17. Shao Z, Feng Y, Zhong L, Xie Q, Lei M, Liu Z, et al. Clinical Efficacy of Intravenous Immunoglobulin Therapy in Critical Patients with COVID-19: A multicenter retrospective cohort study. 2020.
18. Busani S, Damiani E, Cavazzuti I, Donati A, Girardis M. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. Minerva Anestesiol. 2016;82(5):559–72.
19. Justel M, Socias L, Almansa R, Ramírez P, Gallegos MC, Fernandez V, et al. IgM levels in plasma predict outcome in severe pandemic influenza. J Clin Virol. 2013;58(3):564–7.

20. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5):2000524.
21. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. The American Journal of Emergency Medicine. 2020.

Figures

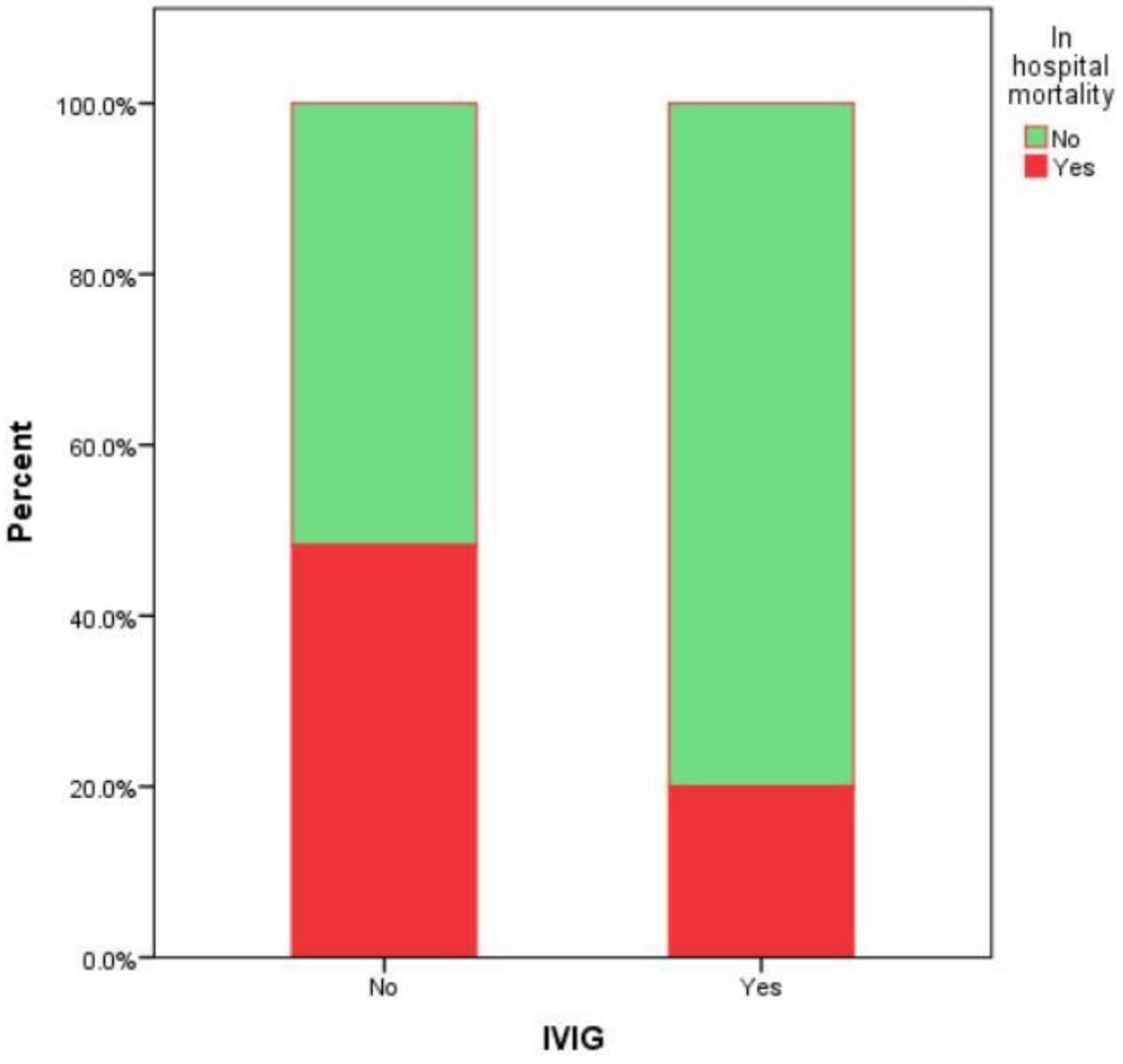

Figure 1

In hospital mortality rate in two study groups.

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