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Efficacy of high-dose intravenous immunoglobulin in severe and critical COVID-19: A retrospective cohort study

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ABSTRACT

Background: Various immunomodulatory therapies have been explored to manage the dysregulated immune response seen in severe COVID-19 infection. The objective of this study was to evaluate the efficacy of intravenous immunoglobulin (IVIG) in severe and critical COVID-19 disease.

Methods: This retrospective study included 535 patients with severe and critical COVID-19 admitted to the intensive care unit (ICU) of a tertiary care hospital, from May 2020 to December 2020. Primary outcome was the percentage of patients requiring mechanical ventilation. Secondary outcomes were a) in-hospital mortality, b) 28-day mortality, c) ICU-length of stay (ICU-LOS), d) days to discontinuation of supplemental oxygen, and e) days to COVID-PCR negativity. Logistic regression and linear regression were performed using the adjusted and unadjusted analyses.

Results: We analyzed a total of 535 patients out of which 255 (47.7%) received IVIG along with standard treatment and 280 (52.3%) received only standard treatment. Two groups were similar in terms of COVID-19 severity, APACHE II score, oxygen requirements, and initial management. The requirement of invasive ventilation was significantly less in the IVIG group compared to the Non-IVIG group (32.2% vs 40.4%, $p < 0.05$). In-hospital mortality, 28-day mortality, and ICU-LOS were also significantly less in the IVIG group (all $p < 0.05$). Subgroup analysis within the IVIG group showed that early administration of IVIG (≤ 7 days from ICU admission), old age (≥ 65 years), and obesity were associated with better outcomes (need for mechanical ventilation and in-hospital mortality) (all $p < 0.05$). IVIG administration in patients with chronic respiratory disease was associated with a reduced requirement for mechanical ventilation ($p < 0.05$), but there was an insignificant improvement in mortality.

Conclusion: High-dose IVIG improves outcomes in severe and critical COVID-19 patients. The study also underscores the importance of timing and patient selection when administering IVIG.

1. Introduction

COVID-19 has become a global medical challenge with over 300 million confirmed cases and 5.5 million deaths involving 222 countries globally [1]. The estimates of COVID-19 mortality rate in patients with severe and critical COVID-19 vary from 30 to 60% in various studies [2–4]. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection primarily involves the lungs leading to hypoxic respiratory failure. The percentage of COVID-19 patients admitted to ICU requiring invasive mechanical ventilation (IMV) ranges from 29% to 90% [5–6].

Dysregulated immune response to SARS-CoV-2 infection leading to excessive inflammation is the primary pathology in severe COVID-19

disease. Targeting this inflammatory response is the key strategy behind the use of various immunosuppressants like IL-1 inhibitors (e.g., Anakinra), IL-6 inhibitors (e.g., Tocilizumab), and Bruton's tyrosine kinase inhibitors (e.g., Acalabrutinib) [7–8]. Several studies investigating these immunosuppressive agents have, however, failed to show any clinically meaningful improvement in outcomes in COVID-19 patients [9–11]. Human immune response to infection is a complex biological system and blocking a single targeted pathway is not likely to control the whole inflammatory 'storm' that occurs in severe disease. Moreover, potent immunosuppression comes at a price of increased risk of opportunistic infections [12–14]. Hence, there is an active interest in the role of various immune-modulation therapies, like intravenous

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immunoglobulin (IVIG) [15].

Recent studies on pathophysiology of Covid-19 have highlighted the role of endothelial dysfunction as the principal mechanism of injury by the virus [16]. Predominant involvement of the respiratory system in Covid-19 is explained by the fact that SARS CoV-2 virus accesses the host cells via ACE-2 (Angiotensin Converting Enzyme 2) which is abundant in the lungs. However, ACE-2 is also expressed by endothelial cells elsewhere. In fact, various complications seen in Covid-19 like hypertension, thrombosis, pulmonary embolism, acute kidney injury, and brain stroke indicate that endothelium is the prime target for the virus [17]. This is because, in physiology, endothelium has an important role in promoting vasodilation, fibrinolysis, and anti-aggregation. The increased incidence of Kawasaki disease in young Covid-19 patients also points towards systemic vasculitis caused by SARS CoV-2 virus. These newer insights into the pathophysiology of Covid-19 have given directions for further research into therapeutic options for the management of the severe Covid-19 disease. Several studies have shown that various treatment options used for Covid-19 like hydroxychloroquine, tocilizumab, and azithromycin improve endothelial dysfunction [18]. In-vitro studies have shown that high-dose IVIG offers a protective effect on virus-induced endothelial damage [19–20].

Human immunoglobulin for intravenous injection (IVIG) is a blood product that is prepared from pooled serum of normal humans. It contains polyclonal immunoglobulin G (IgG) antibodies and has been used in a variety of primary and secondary immunodeficiencies, autoimmune and inflammatory conditions. IVIG has also shown broad-spectrum antiviral properties [15].

The antibody-mediated humoral response is an important strategic tool to treat viral infections. Certain antibodies bind to the external surface of viral particles and block the entry of the virus into human cells and virus multiplication, thus reducing viral load [15]. Besides directly neutralizing the exogenous viral antigens, IVIG also improves immune functions of lymphocytes and has anti-complement effects [21]. Human cell studies have shown that IVIG inhibits proinflammatory T(H) 17 cells, thereby reducing pro-inflammatory cytokines like IL-17 and IL-21. Simultaneously, IVIG upregulates regulatory T-cells [22]. This 'immunomodulatory' action of IVIG can pathophysiologically explain its potential benefit in SARS-CoV-2 infection. Few recent studies have also shown that currently available IVIG preparations have antibodies with significant in-vitro cross-neutralizing activity against SARS-CoV-2 [23,24]. This is because common human coronaviruses (HCoV) account for a large proportion of mild respiratory infections; and thus, antibodies against these human coronaviruses are present in the normal population.

Although the principal antibody in IVIG is IgG, there are some available preparations of IVIG that are enriched with IgA or IgM (pentaglobin). There is some evidence suggesting the role of these two immunoglobulins in immunomodulation of inflammatory response in sepsis and septic shock [25,26]. But there is no evidence to support the role of IgA or IgM enriched IVIG preparations in managing hyper-inflammatory response in Covid-19.

In order to evaluate the clinical efficacy of IVIG in severe and critical COVID-19 patients, we retrospectively collected the clinical and outcome data of COVID-19 patients admitted to our ICU. In addition, we tried to explore the emplacement of IVIG in the management of COVID-19 patients, in terms of patient selection and timing of administration.

2. Material and methods

2.1. Study design

We performed a single-center retrospective cohort study that was conducted in a tertiary care hospital. The study was approved by the Institutional Ethics committee. The need for informed consent was waived owing to the retrospective nature of the study.

2.2. Patient selection and data collection

Data was collected retrospectively for severe and critical COVID-19 patients who were admitted to the ICU from May 2020 to December 2020.

Inclusion criteria were as follows: 1) Adults ≥ 18 years 2) RT-PCR confirmed COVID-19 infection on throat swab or sputum 3) Severe or Critical COVID-19 disease (as per WHO classification) [27], except those who were already on invasive mechanical ventilation. 4) Worsening oxygenation despite initial management.

Exclusion criteria were as follows: 1) Patients on invasive mechanical ventilation 2) Patients who received anti-interleukin agents (like Tocilizumab) or thymosin alpha-1 or high-dose steroids (>1 mg/kg body weight of methylprednisolone) any time before requiring invasive mechanical ventilation 3) Patients who received convalescent plasma after administering IVIG 4) culture-positive sepsis at the time of admission. We captured patients' data from Electronic Health Records and ICU monitoring charts. All details (demographic, clinical, Lab parameters, treatment, and outcomes) were entered in a predesigned proforma. The severity of illness was measured using Acute Physiology And Chronic Health Evaluation II (APACHE II). CT severity score (CTSS) was used to report the severity of COVID-19 on high-resolution CT scan (HRCT) of the lungs [28], with the score ranging from 0 (no involvement) to 25 (maximum involvement).

Detailed clinical data, including daily oxygen requirements and follow-up RT-PCR results were collected in all patients.

2.3. Patient management protocol

Only those patients were included in the study who were managed as per the standard hospital protocol for severe/critical COVID-19 disease. This included Remdesivir, low-dose steroids (≤ 1 mg/kg methylprednisolone), convalescent plasma, low molecular weight heparin, and empiric antibiotics. IVIG was considered if patients' oxygenation worsened (defined as one-category deterioration on WHO ordinal scale [29]) despite the above line of management, and there was no contraindication. It was administered after informed consent from the patient's family. The dose of IVIG was 0.5 g/kg body weight/day as a continuous infusion for 3 days. The actual body weight of the patient was taken for calculating the dose. All patients received a uniform dose and uniform duration of IVIG treatment.

2.4. Outcome measures

Primary outcome of the study was percentage of patients requiring mechanical ventilation. Secondary outcome measures included in-hospital mortality, 28-day mortality, ICU-length of stay (ICU-LOS), days to discontinuation of supplemental oxygen, and days to COVID RT-PCR negativity. Days to COVID negativity were defined from the day of first positive RT-PCR to twice continuous negative RT-PCR done at least 24 h apart.

2.5. Statistical analysis

Demographic data was summarized with descriptive statistics. Continuous data was represented as mean (Standard deviation) or Median (Interquartile Range, IQR) and categorical data was reported in counts (percentage) respectively. Shapiro Wilk test was used to determine the normality of the test data distribution.

Demographic, clinical, laboratory, treatment, and outcome parameters were compared between the IVIG and non-IVIG groups using the Mann-Whitney test (non-parametric test) and Pearson's or Fisher's exact chi-square test. Logistic regression and linear regression were performed using adjusted and unadjusted analysis. Unadjusted logistic regression model was performed without controlling confounding factors. In the multivariate logistic regression model, age (<65 , ≥ 65 years), gender

(male or female), obesity (yes and no), and comorbidities (Yes and No) were controlled. Backward stepwise deletion based on the Wald test was applied. All reported p-values are 2-tailed and $p < 0.05$ is defined as statistically significant. Statistical analyses were performed using the statistical software R (version 4.0.3 - R Core Team [2019]; R: A language and environment for statistical computing) and SPSS (the statistical package for social sciences) IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0.

3. Results

3.1. Patient characteristics

In total, 1186 patients of severe and critical COVID-19 disease were assessed for eligibility from May 2020 to December 2020. Out of these, 535 patients were included in the study, and 651 patients were excluded due to various reasons (Fig. 1). Among the included patients, 255 (47.7%) received IVIG (IVIG group) and 280 (52.3%) did not receive IVIG (Non-IVIG group).

Detailed demographic and clinical profile of patients is summarized in Table 1. Subjects were comparable in the two groups with respect to baseline characteristics. Median age of patients in the study was 64 (55–71) years, and 401 (75%) patients were male. Most of the patients (85.1%) had one or more underlying co-morbidities. The profile of comorbidities in the two groups was similar except for Diabetes (57.3% vs 47.9%, $p = 0.03$) and Hypertension (64.7% vs 47.1%, $p < 0.0001$) which were significantly more in those in the IVIG group.

COVID-19 disease severity was similar in IVIG and Non-IVIG groups (Table 1, Fig. 2). There was no significant difference in the number of severe COVID-19 patients (68.6% vs 66.4%, $p > 0.05$) and critical COVID-19 patients (29% vs 31.4%, $p > 0.05$) between the two groups. Median CT score was 17(14.25–19.75) in the IVIG group and 18 (15–20) in the Non-IVIG group ($p > 0.05$). Median APACHE II score was 9 (6–12) in the IVIG group and 10(6–15) in the Non-IVIG group ($P > 0.05$). At the time of ICU admission, the initial oxygen requirements were similar in the two groups. Of the enrolled patients, 12 (2.2%) patients required oxygen by nasal prongs (flow rates 2–4 L/min), 148(27.7%) face mask (flow rates 4–8 L/min), 241 (45%) Non-rebreathing mask (flow rates

10–15 L/min) and 124 (23.2%) Non-invasive ventilation/High-flow nasal cannula. Among laboratory parameters, WBC count (11.4 [7.6–14.5] vs 9.0 [6.0–13.0], $p < 0.0001$) and C-reactive protein (CRP) (87.04[19.00–145.00] vs 23.30[10.07–90.67], $p < 0.0001$) were higher in the IVIG group, while serum creatinine (80.0[62.0–106.0] vs 88.0 [71.0–124.0], $p < 0.0001$) was higher in the Non-IVIG group. There was no significant difference in other laboratory parameters, as shown in Table 1.

Concerning the IVIG group, the median time of ICU admission to IVIG administration was 5 (3–8) days.

3.2. Outcomes

Analysis of primary outcome in 2 groups showed that 82 (32.2%) patients required invasive ventilation in the IVIG group compared to 113 (40.4%) in the Non-IVIG group which is statistically significant ($P < 0.05$) (Table 2). Analysis of secondary outcomes showed that in-hospital mortality (20.5% vs 30.7%, $p < 0.05$), 28-day mortality (23.6% vs 32.5%, $p < 0.05$), and ICU-LOS (10 vs 11, $p < 0.05$) were lower in the IVIG group compared to the Non-IVIG group. The difference in requirement of invasive ventilation, in-hospital mortality and 28-day mortality, and ICU-LOS was significant even after adjusting for age, gender, obesity, and comorbidities (Table 2). However, days to discontinuation of oxygen (11[9–16] vs 11[8.0–14.5], $p = 0.23$) and days to COVID PCR negativity in 2 groups (9[7–11] vs 9[7–11.250], $p = 0.148$) did not display significant differences across the two groups.

3.3. Subgroup analysis for primary and secondary outcomes

Multivariate analysis within the IVIG group showed that early administration of IVIG (≤ 7 days from ICU admission) (adjusted OR,0.05; 95% CI,0.02–0.12; $p < 0.001$), older age (≥ 65 years), (adjusted OR,0.08; 95% CI,0.03–0.19; $p = 0.000$), presence of obesity (adjusted OR,0.38; 95% CI,0.16–0.88; $p = 0.025$), and presence of chronic respiratory disease (adjusted OR,0.20; 95% CI,0.05–0.85; $p = 0.029$) were associated with significantly improved primary outcome (need for invasive ventilation) (Table 3, Fig. 3). In other words, those receiving an early administration of IVIG, individuals from the older age group, and

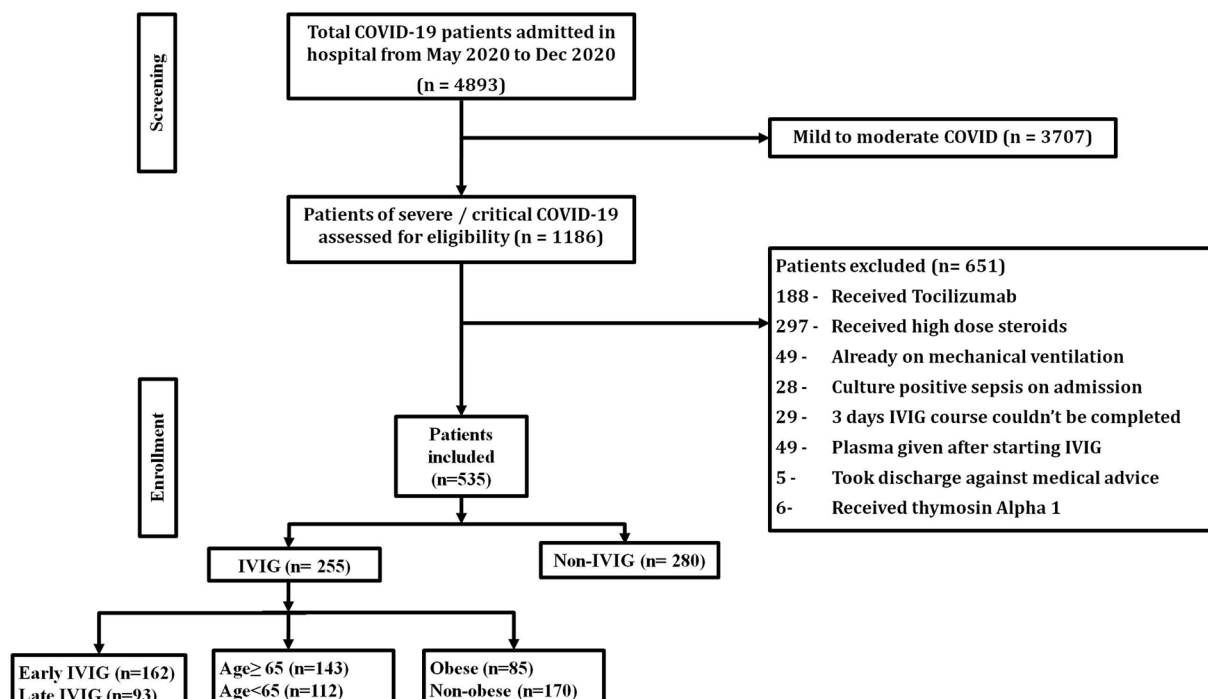


Fig. 1.

Table 1
Patient characteristics.

	Total (n = 535)	IVIG (n = 255)	Non-IVIG (n = 280)	p-value
Median Age (IQR), years	64 (55–71)	67 (57–71)	62 (55–71)	0.074 [‡]
Sex, Male N (%)	401(75.0%)	182(71.4%)	219(78.2%)	0.068*
Comorbidities, n (%)	458(85.1%)	230(90.2%)	228(81.4%)	0.003*
Obesity (BMI ≥ 30 Kg/m ²)	154(28.8%)	83(32.5%)	71(25.4%)	0.066*
Hypertension	297(55.5%)	165(64.7%)	132(47.1%)	<0.0001*
Diabetes Mellitus	280(52.3%)	146(57.3%)	134(47.9%)	0.030*
Coronary Artery Disease	92(17.2%)	39(15.3%)	53(18.9%)	0.266*
Chronic Respiratory Disease	65(12.1%)	37(14.5%)	28(10.0%)	0.111*
Chronic Kidney Disease	98(18.3%)	41(16.1%)	57(20.4%)	0.201*
Chronic Liver Disease	22(4.1%)	10(3.9%)	12(4.3%)	0.832*
Other	71(14.7%)	25(12.3%)	46(16.4%)	0.208*
APACHE II Score, Median (IQR)	9(6–13)	9(6–12)	10(6–15)	0.079 [‡]
COVID-19 Severity classification, n (%)				
Severe COVID-19	361(67.5%)	175(68.6%)	186(66.4%)	0.588*
Critical COVID-19	162(30.3%)	74(29.0%)	88(31.4%)	0.545*
CT Severity Score[‡], Median (IQR)	17.0 (15.0–20.0)	17.0 (14.2–19.7)	18.0 (15.0–20.0)	0.104 [‡]
Oxygen requirements, n (%)				
Nasal Prongs, (2–4 L/min)	12 (2.2%)	6 (2.4%)	6 (2.1%)	0.870*
Face Mask, (4–8 L/min)	148 (27.7%)	65 (25.5%)	83 (29.6%)	0.284*
Non-rebreathing mask (10–15 L/min)	241 (45.0%)	115 (45.1%)	126 (45.0%)	0.982*
NIV/ HFNC	124 (23.2%)	65 (25.5%)	59 (21.1%)	0.226*
Laboratory parameters, Median (IQR)				
Hb (g/L)	125.0 (111.0–138.0)	125.0 (111.0–138.0)	128.0 (112.3–141.0)	0.005 [‡]
WBC COUNT (1x 10 ⁹ /L)	10.3 (6.5–13.9)	11.4 (7.6–14.5)	9.0 (6.0–13.0)	<0.0001 [‡]
Creatinine (μmol/L)	80.0 (62.0–106.0)	80.0 (62.0–106.0)	88.0(71.0–124.0)	<0.0001 [‡]
Urea (mmol/L)	6.5(4.8–10.2)	6.4 (4.8–9.4)	6.9(11.2–4.8)	0.306 [‡]
ALT (U/L)	54.0 (37.0–73.0)	54.0 (40.0–70.0)	52.0 (34.0–78.0)	0.675 [‡]
AST (U/L)	38.0 (26.0–60.0)	36.0 (27.0–55.0)	40.0 (24.0–66.7)	0.623 [‡]
Total Serum Bilirubin (μmol/L)	12.0 (9.0–16.0)	13.0 (9.0–17.0)	11.0 (8.0–16.0)	0.007 [‡]
LDH (U/L)	393.0 (274.0–530.0)	384.0 (257.0–509.0)	396.0 (299.2–555.7)	0.084 [‡]
Ferritin (pmol/L)	902.6 (494.3–1441.4)	874.1 (514.0–1447.1)	1004.4 (443.2–2107.7)	0.294 [‡]
D-Dimer (ng/ml)	409.0 (241.0–797.0)	356.0 (221.0–716.0)	482.5 (251.0–851.9)	0.009 [‡]
C-Reactive Protein (mg/L)	46.8 (13.2–124.0)	87.0 (19.0–145.0)	23.3 (10.1–90.7)	<0.0001 [‡]
Procalcitonin (ng/ml)	0.1 (0.1–0.3)	0.1 (0.1–0.3)	0.2 (0.1–0.4)	0.147 [‡]
HbA1c (%)	6.6 (6.0–8.1)	6.7 (6.1–7.9)	6.6 (6.0–8.3)	0.871 [‡]

IVIG: Intravenous Immunoglobulin, Hb: Hemoglobin, WBC: White Blood Cells, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, LDH: Lactate Dehydrogenase, APACHE II: Acute Physiology And Chronic Health Evaluation II, IQR: Interquartile range.

The p-values signify exact 2-sided Chi-Square test (*) results for binary outcomes and Mann-Whitney U test (‡) results for continuous outcomes.

[‡] CT Scan was done in 232 patients in IVIG group, and 261 patients in Non-IVIG group.

those with obesity or chronic respiratory diseases were less likely to need invasive ventilation.

In multivariate analysis for in-hospital mortality, the factors which remained associated with better outcome were early administration of IVIG (≤ 7 days from ICU admission) (adjusted OR,0.08; 95% CI,0.03–0.17; $p < 0.001$), older age (≥ 65 years), (adjusted OR,0.26; 95% CI,0.12–0.57; $p = 0.001$) and obesity (adjusted OR,0.45; 95% CI,0.22–0.86; $p = 0.039$) (Fig. 3).

4. Discussion

The role of IVIG has been explored in several viral infections like Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), Ebola virus, and Zika virus infections. While some studies have established the clinical efficacy of this strategy in these infections [30–31], others have failed to prove any significant benefit [32–33]. Hence, the role of intravenous immunoglobulin in respiratory viral infections is still controversial. Compared to MERS and SARS, COVID-19 is distinct in its prolonged course of the disease, severe lung injury, and silent progressive hypoxemia. Thus, there is a need to explore the role of IVIG in COVID-19. Few studies have evaluated the effect of IVIG on patient outcomes in COVID-19 disease [34–38], with a majority of them being small sampled with inconsistent methodology and results.

This study was aimed at retrospectively evaluating the efficacy of IVIG in severe and critical COVID-19 patients. To our knowledge, this is the largest study yet, to assess the efficacy of IVIG treatment in severe and critical COVID-19 patients. Notably, this study is important because

the two groups were comparable not only in their baseline clinical parameters but also with respect to the initial treatment received.

Our results show that the use of IVIG prevents further worsening of respiratory failure and reduces the need for invasive mechanical ventilation in a significant number of severe/critical COVID-19 patients. We also found a significant improvement in mortality (both in-hospital and 28-day mortality) with the use of IVIG.

Sakoulas et al did a randomized controlled trial of 33 patients of moderate to severe COVID-19, where patients in the IVIG arm ($n = 16$) received high-dose IVIG (0.5 g/kg/day) for 3 days. No difference was observed in the need for mechanical ventilation in the IVIG group. However, they found a significantly reduced ventilation rate among the subset of patients with severe hypoxia (A-a gradient > 200 mmHg), suggesting a benefit in severe disease [39]. Tabarsi et al did a randomized controlled trial comparing 52 critically ill Covid 19 patients who received IVIG (0.4 g/kg/day for 3 days) along with the standard of care to a control group of 32 patients receiving standard of care (hydroxychloroquine and lopinavir/ritonavir). They did not find any significant difference between the two groups with respect to the need for mechanical ventilation ($p = 0.39$). However, they found that early use of IVIG was associated with a shorter hospital and ICU length of stay [40].

Our results showed that IVIG treatment reduced in-hospital mortality by 10.2% and 28-day mortality by 8.9%, which was statistically significant (Table 2). Shao et al reported a multi-center retrospective study of 325 patients with severe/critical COVID-19 disease in which IVIG was given to 174 patients, while 151 patients did not receive IVIG (control group). Their primary analysis showed no significant reduction in 28-day mortality (13% in both groups) with the use of IVIG [41]. In their

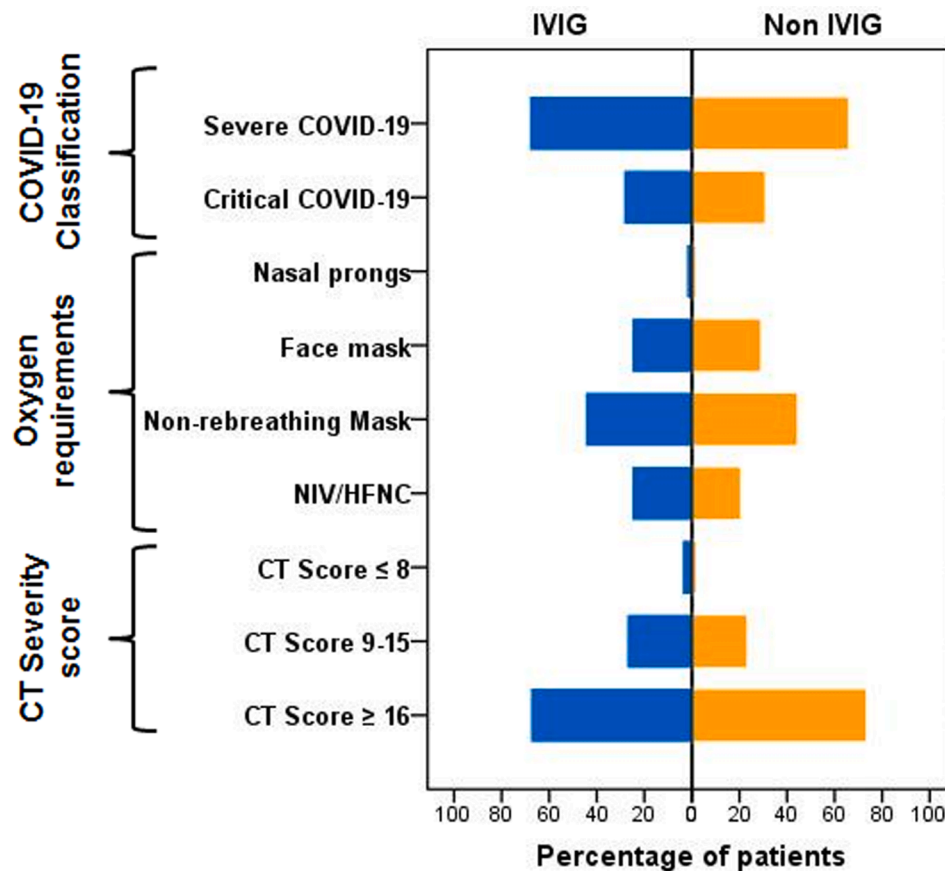


Fig. 2.

Table 2
Effect of IVIG treatment on the primary and secondary outcomes in all patients.

	Total (n = 535)	IVIG (n = 255)	Non-IVIG (n = 280)	p-value
Primary outcome				
Number (%) of patients requiring mechanical ventilation	195 (36.4%)	82 (32.2%)	113 (40.4%)	0.049*
Secondary Outcomes				
In-hospital mortality	138 (25.8%)	52 (20.5%)	86 (30.7%)	0.007*
28-day mortality	151 (28.3%)	60 (23.6%)	91 (32.5%)	0.023*
Days to COVID Negativity from admission, Median (IQR)	9.0 (7.0–11.0)	9.0 (7.0–11.0)	9.0 (7.0–11.2)	0.148 [‡]
Days to Discontinuation of Oxygen, Median (IQR)	11.0 (9.0–15.0)	11.0 (9.0–16.0)	11.0 (8.0–14.5)	0.230 [‡]
Length of stay in ICU (ICU-LOS), Median (IQR)	10.0 (8.0–13.0)	10.0 (8.0–12.2)	11.0 (8.0–14.0)	0.002 [‡]

The p-values signify exact 2-sided Chi-Square test (*) results for binary outcomes and Mann-Whitney U test ([‡]) results for continuous outcomes.

study, the two groups had significantly different baseline characteristics. After adjusting the confounding variables in the overall cohort, they found a significant reduction in mortality in the IVIG group. However, in their study, variable dose (0.1–0.5 g/kg/day), duration (5 to 15 days), and schedule of IVIG administration were used at 4 participating hospitals. Moreover, clinicians were free to use other therapies. These factors could have altered the outcomes. Gharebaghi et al did a randomized

control trial, where 30 patients were given IVIG in a dose of 20 g/day for 3 days, while 29 patients received a placebo. Two groups were similar in their baseline characteristics. They found that in-hospital mortality was significantly lower in the IVIG group compared to the control group (20.0% vs 48.3%, $p = 0.022$) [42]. In a recent single-center retrospective study, Esen et al. demonstrated improved ICU mortality in 51 severe Covid 19 patients who received IVIG compared to 42 controls (OR:2.2, 95% CI: 0.9–5.4, $p = 0.014$) [43]. However, the baseline disease severity was different in the IVIG vs non-IVIG arm. Secondly, a few patients in both arms received Tocilizumab or Anakinra, based on the levels of inflammatory markers. Thirdly, the dose of steroids used as the standard of care in both groups was very high (IV methylprednisolone 200 mg/day). All of these factors could have confounded the results of the study. A recent meta-analysis of 4 clinical trials and 3 cohort studies including 825 hospitalized patients showed that IVIG use was associated with a significant reduction in mortality in the critical subgroup of Covid 19 patients, but not in the non-severe subgroups [44].

In our study, all patients in the IVIG group received a uniform high-dose (1.5 g/kg over 3 days) of IVIG. The median dose of IVIG was 35 (35–40) g/day. This can be a significant factor responsible for the improvement in oxygenation and mortality in the IVIG group. Studies comparing various doses of IVIG have shown better outcomes with higher doses. In the study by Shao et al, 74 patients received IVIG at a higher dose (>15 g/day) and 100 patients received IVIG at a lower dose (≤15 g/day). They found better 28-day mortality (7% vs 17%, $p < 0.05$) and 60-day mortality (12% vs 24%, $p < 0.05$) in the high-dose subgroup [41]. Raman et al reported a multi-center randomized study in non-severe Covid-19 patients, where patients in the IVIG group received a dose of 0.4 g/kg/day for 5 days [45]. In this study, IVIG use was associated with a lesser need for mechanical ventilation and shorter ICU and hospital stay. This “dose-effect” relationship of IVIG has also been

Table 3
Subgroup analysis: Efficacy of IVIG on outcomes in various subgroups.

Factors	Need for mechanical ventilation				In-hospital mortality			
	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Early IVIG	0.09(0.50–0.17)	<0.001	0.05(0.02–0.12)	<0.001	0.08(0.04–0.17)	<0.001	0.08(0.03–0.17)	<0.001
Age ≥ 65	1.09(0.77–1.56)	0.618	0.08(0.03–0.19)	0.000	2.87(1.91–4.32)	<0.001	0.26(0.12–0.57)	0.001
Obesity	1.12(0.76–1.65)	0.569	0.38(0.16–0.88)	0.025	1.01(0.66–1.55)	0.965	0.45(0.22–0.86)	0.039
Hypertension	1.69(1.18–2.42)	0.005	1.09(0.51–2.33)	0.818	1.51(1.02–2.25)	0.042	0.75(0.35–1.63)	0.469
Diabetes	1.25(0.88–1.78)	0.212	1.29(0.61–2.72)	0.500	0.96(0.65–1.41)	0.828	0.72(0.34–1.51)	0.379
Chronic Resp. Disease	0.69(0.39–1.220)	0.199	0.20(0.05–0.85)	0.029	0.69(0.36–1.310)	0.253	0.25(0.05–1.22)	0.086

Early IVIG: ≤ 7 days of ICU admission.

* Adjusted for Age, Sex, Obesity and comorbidities.

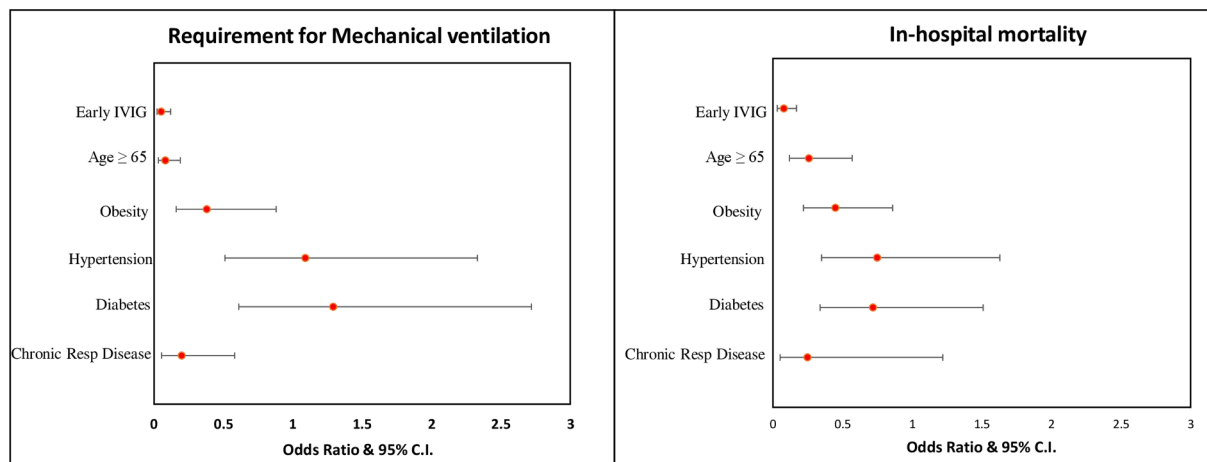


Fig. 3.

shown in multiple studies in sepsis, where it has been used for its therapeutic potential. Based on these studies, the recommended dose for IVIG is 1.5–2 g/kg body weight [46–47].

The results of logistic regression analysis in our study suggest that early administration of IVIG improves outcomes significantly (Table 3, Fig. 3). The likely reason for better outcomes with early IVIG administration lies in the fact that viremia develops within 1st week of infection. Subsequently, the primary immune response develops in 2nd week. Cytokine storm and hyperinflammatory shock usually occur in the 2nd or 3rd week [48]. Studies have shown that the worsening of respiratory failure in COVID-19 correlates with the beginning of cytokine storm, and this stage of the disease is best managed by combining potentiation of serum immunity along with anti-inflammatory therapy [49–50]. Since IVIG has both these actions [51], it is optimally suited for administration at this stage. Our findings are consistent with the findings of Shao et al who also found that patients who received IVIG within 7 days of admission had better outcomes than those who received it later [41]. Xie et al reported a single-center retrospective study from Wuhan where 58 patients with severe/critical COVID-19 were administered IVIG at a dose of 20 g/day. Their results showed that the mortality rate in patients who received IVIG during the first 48 h of admission was 23.3% compared to 57.1% in patients who received IVIG after 48 h [35]. However, in this study, the total duration of IVIG treatment was not uniform. Also, few patients received high-dose steroids and few others received thymosin alpha-1 along with IVIG, which could affect the outcomes.

We also observed that IVIG had better outcomes in patients with advanced age (≥65 years). To our knowledge, no study to date has reported IVIG outcomes in advanced age patients with severe COVID-19 disease. The improved outcomes in geriatric patients may be because there is a diminution of endogenous antibody function with age [52]. Elderly subjects with even apparently normal IgG titers may have a

reduced innate response [53]. IVIG can, thus, improve outcomes in older patients by strengthening their immune response.

An important observation in our subgroup analysis was that obese patients (BMI > 30) in the IVIG group had better outcomes than non-obese patients. Obesity has been shown to alter immune function. Elevated circulating pro-inflammatory cytokines, reduced adiponectin levels, and impaired B and T cell responses can result in a delayed resolution of viral infections [54]. In fact, obesity is considered a risk factor for severe COVID-19 disease [55]. IVIG can, thus, improve the altered immune responses in obese patients, thus improving their outcomes. Alternatively, the better outcomes in obese patients can be due to the higher dose of IVIG used in these patients. In our study, the median dose used in obese patients was 45 (45–50) g/day, which was higher than the median dose in the overall group (35 [35–40] g/day). Does this mean that the observed effect in obesity is just an expression of the “dose–effect” relationship of IVIG? And does this imply that we need to use still higher doses of IVIG in all patients to improve outcomes? The pharmacokinetics of IVIG in obesity is complex, and some studies suggest a lower dose of IVIG (less than as per actual body weight) in obese patients [56]. The consensus, however, is to start with recommended dose for the disease, and then titrate it up or down as per clinical outcomes. Perhaps, we need larger prospective studies on IVIG dosing in obesity to answer these questions.

Patients suffering from chronic respiratory diseases like bronchial asthma, chronic obstructive lung disease (COPD), interstitial lung disease (ILD), sarcoidosis, cystic fibrosis, etc. are considered to be at high risk for severe Covid-19 [57]. This is due to alteration in local and systemic immune response, increased levels of ACE-2, excessive mucous production, and poor pulmonary reserve. They are more likely to need intensive care, mechanical ventilation, and organ support [58]. A meta-analysis of 7 studies including 1592 COPD patients showed up to five-

times increased risk of severe Covid-19 in these patients [59]. Our study showed that the use of IVIG in these patients led to a significant reduction in the requirement of mechanical ventilation (Table 3, Fig. 3). The benefit in in-hospital mortality was not statistically significant. However, these results should be interpreted with caution owing to a limited number of patients with chronic respiratory diseases (12.1%) in our study cohort.

In our study, we did not find any difference in days to discontinuation of oxygen or ICU length of stay between the two groups (Table 2). This was mainly due to lesser mortality in the IVIG group. Those who improved in the IVIG group took a longer time to come off oxygen supplementation. This is consistent with the trend observed clinically during the recovery of severe and critical COVID-19 patients.

Also, we did not find any difference in days to COVID-19 RT-PCR negativity in the two groups. To our knowledge, no study has reported the effect of IVIG on the time taken for the RT-PCR test to become negative. Some studies have shown that the use of steroids delays virus clearance and hence prolongs time to COVID-PCR negativity [60–61]. A possible explanation why IVIG has not delayed virus clearance is because IVIG has antiviral properties, as suggested by some studies [62].

The present study has several limitations. First, being a retrospective study, it is prone to bias and we were not able to compare the results with a placebo-control group. Second, we did not compare inflammatory markers (like interleukin-6, C-reactive protein, ferritin, D-dimer, etc.) and T cells subgroup analysis before and after giving IVIG which could have given more insights into the subgroup of patients who benefitted from IVIG. High-dose IVIG has been shown to inhibit cytokine production by Th1 and Th17 cells in several studies [22,63]. Third, we did not have data on baseline immunoglobulin levels of the enrolled patients, which could have affected the response to IVIG in some patients. Fourth, we could not do CT scans in all our patients. A follow-up CT scan could have given additional objective evidence on the impact of IVIG in reducing long-term lung sequelae. Fifth, the number of years of smoking was not evaluated in our study. Finally, we followed up our patients till 28 days only. Extending the follow-up to 60 days could have given better information regarding secondary infections and thrombotic events related to IVIG treatment.

Despite these limitations, we would like to highlight a few important aspects of this study. All the subjects in both study groups received uniform initial management for COVID-19. Since IVIG is a costly therapy, it was only considered when patients had worsening oxygenation despite initial treatment. We excluded subjects who received any confounding treatment like tocilizumab, thymosin alpha 1, or high-dose steroids. Moreover, all patients received IVIG as per a standard high-dose protocol.

5. Conclusion

This single-center retrospective cohort study demonstrated that high-dose IVIG improves outcomes in the severe and critical type of COVID-19 patients. The study also highlights the importance of selecting appropriate timing (early use) and patient selection when administering IVIG.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

The study was approved by the Institutional Ethics committee of Max Hospital (Ref. No. BHR/RS/MSSSH/GMHRCMS/MHEC/CCM/21-01). The requirement for informed consent was waived by the Ethics committee.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author (Ritesh Aggarwal) on a reasonable request.

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