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Original article

# Intravenous immunoglobulin treatment for patients with severe COVID-19: a retrospective multicentre study

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ABSTRACT

*Objectives:* Intravenous immunoglobulin (IVIG) is commonly used to treat severe COVID-19, although the clinical outcome of such treatment remains unclear. This study evaluated the effectiveness of IVIG treatment in severe COVID-19 patients.
*Methods:* This retrospective multicentre study evaluated 28-day mortality in severe COVID-19 patients with or without IVIG treatment. Each patient treated with IVIG was matched with one untreated patient. Logistic regression and inverse probability weighting (IPW) were used to control confounding factors.
*Results:* The study included 850 patients (421 IVIG-treated patients and 429 non-IVIG-treated patients). After matching, 406 patients per group remained. No significant difference in 28-day mortality was observed after IPW analysis (average treatment effect (ATE) = 0.008, 95% CI −0.081 to 0.097, p 0.863). There were no significant differences between the IVIG group and non-IVIG group for acute respiratory distress syndrome, diffuse intravascular coagulation, myocardial injury, acute hepatic injury, shock, acute kidney injury, non-invasive mechanical ventilation, invasive mechanical ventilation, continuous renal replacement therapy and extracorporeal membrane oxygenation except for prone position ventilation (ATE = −0.022, 95% CI −0.041 to −0.002, p 0.028).
*Discussion:* IVIG treatment was not associated with significant changes in 28-day mortality in severe COVID-19 patients. The effectiveness of IVIG in treating patients with severe COVID-19 needs to be further investigated through future studies. **Jiao Liu, Clin Microbiol Infect 2021;27:1488**


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## Introduction

The first outbreak of coronavirus disease (COVID-19) was reported in Wuhan (Hubei, China) in December 2019 [1]. This outbreak has progressed into a global pandemic that has become a serious threat to global public health [2–5]. Most patients exhibit mild symptoms, although approximately 15% of cases progress to severe disease depending on age, ethnicity and comorbidities [6–8]. Although current studies have shown that dexamethasone or remdesivir may be helpful in severe COVID-19 patients, novel therapies and vaccines are being developed, and exploration of pre-existing therapeutic strategies is urgently needed [9–11].

Since immunoglobulin (IG) has been widely used for treating autoimmune diseases and serious viral infections [12,13], intravenous IG (IVIG) as the blood product purified from the plasma of healthy people has been considered for the treatment of COVID-19 patients.

IG is rich in antibodies and provides passive immune protection against a broad range of pathogens. The rationale for use of IVIG is its ability to modulate immunity. The presence of the Fc portion of IG may interact with activating Fc$\gamma$Rs on innate immune cells, thereby modulating the function of these cells [14]. Additionally, IVIG inhibits human T-cell proliferation and cytokine production [15,16]. Therefore, although the underlying mechanisms of IVIG administration to treat viral infection are not fully understood, IVIG may lead to a multitude of immune responses via multiple pathways. Besides, continuous infusion of IG can effectively increase the serum level of immunoglobulin, neutralize pathogens in patients and enhance the immunity of the patients, thereby shortening the course of the disease and promoting recovery [17,18]. IVIG has been most recently used to treat patients with severe COVID-19 [19,20], but available data are still limited outside the clinical trial setting. This retrospective multicentre study of patients hospitalized with severe COVID-19 aimed to explore the clinical benefits as well as potential harm of IVIG use.

## Materials and methods

### *Study setting and design*

This multicentre retrospective study evaluated outcomes among patients with severe COVID-19 according to the use or non-use of IVIG treatment. The retrospective study protocol was approved by each hospital's institutional review board, which waived the requirement for informed consent.

Adults with confirmed COVID-19, presence of a respiratory rate higher than 30 breaths/min, oxygen saturation less than 93% at rest, $PaO_2/FiO_2 \leq 300$ mmHg and lung imaging showing that the lesions had progressed more than 50% within a period of 24–48 hr were included. Patients presenting the following conditions were excluded: pregnancy or lactating, brain dead, allergy to IVIG therapy or immunoglobulin deficiency.

In order to avoid immortal time bias, we matched each patient treated with IVIG with an untreated patient, according to the day of admission for treatment (or lack of treatment). Patients were sorted ascendingly by days spent in the hospital. The following step was to match each IVIG treated patient to an untreated patient who had been in the hospital at least as many days as the time to IVIG of the treated patient. In case of multiple matching patients, one untreated matching patient was thus randomly selected.

### *Definitions*

Nasal and pharyngeal swab specimens were collected from patients with an epidemiological history and chest imaging (computed tomography or radiography) that suggested viral pneumonia. The nasopharyngeal swab specimens were subjected to high-throughput sequencing or real-time reverse transcription polymerase chain reaction to confirm the diagnosis of COVID-19. The clarification of COVID-19 was based on the Chinese management guidelines for COVID-19 (sixth version) [21]. Briefly, patients were diagnosed as severe when respiratory rate was higher than 30 breaths/min, oxygen saturation less than 93% at rest, $PaO_2/FiO_2 \leq 300$ mmHg.

Diagnosis of acute respiratory distress syndrome (ARDS) was based on the Berlin definition, with a $PaO_2/FIO_2 < 300$ mmHg, a positive end-expiratory pressure $\geq 5$ $cmH_2O$, a decreased light transmittance of both lungs that could not be explained completely by pleural effusion, atelectasis or nodules, and a respiratory failure that could not be explained by heart failure or fluid overload [22]. The definition of diffuse intravascular coagulation (DIC) was based on underlying diseases facilitating its occurrence and clinical symptoms, as well as laboratory indicators [23].

Immunosuppression status was identified on the basis of the presence of malignancy, liver cirrhosis or chronic renal failure as well as the use of immunosuppressive therapy. Immunosuppressive therapy refers to the use of immunosuppressive drugs, such as cytotoxic drugs administered to patients with active tumour, organ transplantation or HIV, as well as cumulative use of corticosteroids for over three months [24].

Myocardial injury was defined as an increase in troponin concentration above the 99th percentile upper reference limit (>0.4 ng/mL) [25,26].

### *Data collection*

Patients' medical records were reviewed for the collection of the following variables: age, sex, comorbidities, blood test results, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, imaging findings, IVIG treatment characteristics (maximum daily dose, duration of treatment) and respiratory support (oxygen therapy, non-invasive mechanical ventilation, invasive mechanical ventilation, prone position ventilation and extracorporeal membrane oxygenation (ECMO)). Laboratory parameters as well as APACHE II and SOFA scores were assessed upon hospital admission.

### *Outcomes*

The primary outcome was defined as 28-day all-cause mortality after propensity matching analysis. The start of the 28 days was defined as day of admission to the hospital. The secondary outcomes were defined as ARDS, DIC, myocardial injury, acute hepatic injury, shock, acute kidney injury (AKI), non-invasive mechanical ventilation, invasive mechanical ventilation, prone position ventilation, continuous renal replacement therapy and ECMO between the two groups (treated versus untreated patients).

### *Statistical analysis*

Continuous variables were expressed as median (interquartile range (IQR)) and were compared using the Mann–Whitney U test. Categorical variables were expressed as numbers (%) and compared using Fisher's exact test or the chi-squared test. Missing data were not imputed in this study. Univariate logistic regression analysis was conducted and applied to evaluate possible predictors of 28-day mortality in the matched sample. We included variables associated with the dependent variable in bivariate analysis ($p < 0.1$) as well as what made clinical sense, without missing data for multivariate analysis. We estimated the predictors for 28-day

mortality by fitting multivariate logistic regression with random intercepts to account for clustering of the inpatient hospitals. Model fit was evaluated by Hosmer–Lemeshow goodness of fit test.

The propensity score method was conducted to evaluate the relationship between IVIG and 28-day mortality. The following variables were included in the propensity score: fever, hypertension, corticosteroids (methylprednisolone, dexamethasone, hydrocortisone and prednisolone), SOFA score, tumour, chronic obstructive pulmonary disease, chronic cardiac disease, antiviral, chronic liver disease, diabetes, gender, stroke, immunosuppression, age, systolic pressure, chronic kidney disease, APACHE II and respiratory support. A propensity score density plot was used to illustrate the distribution of propensity score in both groups. Standardized mean difference (SMD) was used to examine the balance of covariate distribution between treatment groups after the propensity score. IPW was performed to adjust the baseline characteristics in the IVIG and non-IVIG groups. Differences were considered statistically significant at $p < 0.05$, and all analyses were performed using SPSS software (version 22.0) and Stata software (version 16.0).

## Results

### *Patient characteristics*

Mild or moderate disease was observed in 1496 of the 2346 patients hospitalized with confirmed COVID-19. The remaining 850 patients were enrolled. Table 1 shows the patients' characteristics and laboratory parameters upon admission. Treatment of IVIG was provided to 421 patients (49.5%) and was not provided to 429 patients (50.5%). The median age was 63 years (IQR 55–73 years) and

**Table 1**
Characteristics and physiological parameters of patients with severe COVID-19 on admission

| Variables | All patients ($n = 850$) | Non-IVIG group ($n = 429$) | IVIG group ($n = 421$) |
|---|---|---|---|
| Age, years | | | |
| Median (IQR) | 63 (55–73) | 64 (54–74) | 63 (55–73) |
| Sex, *n* (%) | | | |
| Male | 501 (58.9) | 258 (60.1) | 243 (57.7) |
| Female | 349 (41.1) | 171 (39.9) | 178 (42.3) |
| Smoking, *n* (%) | 30 (3.5) | 14 (3.3) | 16 (3.8) |
| Comorbidities, *n* (%) | | | |
| Chronic obstructive pulmonary disease | 31 (3.6) | 10 (2.3) | 21 (5.0) |
| Diabetes mellitus | 127 (14.9) | 59 (13.8) | 68 (16.2) |
| Hypertension | 285 (33.5) | 102 (23.8) | 183 (43.5) |
| Chronic cardiac disease | 109 (112.8) | 42 (9.8) | 67 (15.9) |
| Chronic kidney disease | 30 (3.5) | 20 (4.7) | 10 (2.4) |
| Chronic liver disease | 27 (3.2) | 10 (2.3) | 17 (4.0) |
| Stroke | 54 (6.4) | 27 (6.3) | 27 (6.4) |
| Malignancy | 29 (3.4) | 6 (1.4) | 23 (5.5) |
| Immunosuppression | 30 (3.5) | 13 (3.0) | 17 (4.0) |
| Tuberculosis | 12 (1.4) | 5 (1.2) | 7 (1.7) |
| Signs and symptoms at admission, *n* (%) | | | |
| Fever | 653 (76.8) | 267 (62.2) | 386 (91.7) |
| Cough | 645 (75.9) | 308 (71.8) | 337 (80.0) |
| Sputum production | 363 (42.7) | 195 (45.5) | 168 (39.9) |
| Dyspnoea | 569 (66.9) | 277 (64.6) | 292 (69.4) |
| SOFA score | 2 (2–3) | 2 (2–3) | 3 (2–4) |
| APACHE II score | 8 (5–9) | 8 (6–10) | 7 (5–9) |
| Laboratory findings, median (IQR) | | | |
| Leucocytes (/$10^9$/L) | 8.1 (4.6–10.8) | 9.3 (6.2–12.0) | 6.9 (3.9–8.5) |
| Lymphocytes (/$10^9$/L) | 0.9 (0.5–1.1) | 1.0 (0.4–1.3) | 0.7 (0.5–0.9) |
| CD3 (/μL) | 475 (319–609) | 538 (368–630) | 399 (253–579) |
| CD4 (/μL) | 273 (149–367) | 323 (214–440) | 212 (144–289) |
| CD8 (/μL) | 184 (105–240) | 185 (106–250) | 182 (80–240) |
| Haemoglobin (g/L) | 123 (113–135) | 121 (111–130) | 126 (115–139) |
| Platelets ($10^9$/L) | 182 (128–224) | 193 (138–231) | 172 (123–214) |
| Prothrombin time (s) | 12 (11.0–13.1) | 13 (11.2–14.2) | 12 (10.8–12.3) |
| Activated partial thromboplastin time (s) | 30.7 (25.6–35.3) | 32.4 (26.0–38.1) | 29.1 (25.0–32.5) |
| Thrombin time (s) | 17.4 (15.7–18.0) | 17.6 (15.3–18.2) | 17.2 (16.1–18.0) |
| D-dimer (μg/mL) | 5.1 (0.6–3.2) | 5.5 (0.5–3.4) | 4.9 (0.6–3.1) |
| Total bilirubin (μmol/L) | 14.1 (9.6–16.8) | 14.1 (9.8–16.9) | 14.1 (9.6–16.6) |
| Alanine aminotransferase (U/L) | 39.2 (20.0–43.0) | 40.2 (19.0–42.0) | 38.4 (20.0–45.0) |
| Aspartate aminotransferase (U/L) | 48.2 (27.0–51.0) | 47.6 (24.0–45.5) | 48.7 (31.0–55.0) |
| Albumin (g/L) | 32.7 (28.8–36.0) | 31.7 (28.2–34.6) | 33.2 (29.1–37.0) |
| Serum creatinine (μmol/L) | 97.5 (59.0–91.7) | 119.7 (56.6–91.0) | 85.7 (60.0–91.7) |
| Creatine kinase (U/L) | 218.3 (62.0–217.0) | 196.1 (52.0–163.0) | 227.1 (66.0–235.0) |
| Creatine kinase isoenzyme MB (U/L) | 18.8 (11.0–20.0) | 17.47 (11.0–19.0) | 19.4 (11.0–20.0) |
| C-reactive protein (mg/L) | 71.1 (30.2–108.2) | 69.0 (22.6–106.9) | 72.1 (33.5–108.2) |
| Interleukin-6 (pg/mL) | 12.1 (7.2–13.2) | 12.5 (7.0–13.1) | 11.8 (7.2–13.2) |
| Procalcitonin (ng/mL) | 0.1 (0.05–0.25) | 0.08 (0.05–0.25) | 0.11 (0.05–0.24) |
| Radiological findings, *n* (%) | | | |
| Abnormalities | | | |
| Ground-glass opacity | 460 (54.1) | 281 (65.5) | 179 (42.5) |
| Pulmonary consolidation | 98 (11.5) | 65 (15.2) | 33 (7.8) |
| Pulmonary interstitial abnormalities | 275 (32.4) | 106 (24.7) | 169 (40.1) |
| Pneumothorax | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pleural effusion | 22 (2.6) | 11 (2.6) | 11 (2.6) |

IVIG, intravenous immunoglobulin; IQR, interquartile range; APACHEII, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

58.9% of the patients were male. The median SOFA score was 2 (IQR 2–3) and the median APACHE II score was 8 (IQR 5–9). Four hundred and six patients in both groups were matched (see methods).

*IVIG treatment*

The median duration of IVIG treatment was 9.5 days for all patients (IQR 4–12 days), 11 days for survivors (IQR 6–15 days) and 7 days for non-survivors (IQR 3–10 days). The median doses of IVIG were 9.85 g/day for survivors and 10.42 g/day for non-survivors. The median time interval from hospital admission to initiation of IVIG treatment among all patients was 2.8 days (IQR 1–3 days) (Table S1, Fig. S1).

*Mortality*

Table 2 shows the preliminary comparison between deaths and survivors at 28 days after matching, as well as the univariable and multivariable analysis of 28-day mortality with logistic regression. The results of IPW analysis are shown in Fig. S2. The common support is shown in Fig. S2A and SMD is shown in Fig. S2B. The majority of the SMD was within −10 and 10, indicating that the patients for IPW analysis were well matched. As shown in Table 3, after IPW analysis, 28-day mortality between patients in the IVIG and non-IVIG groups was not significantly different. The average treatment effect (ATE) was 0.008 (95% CI −0.081 to 0.097, p 0.863). Moreover, logistic regression analysis suggested that the other independent risk factors for 28-day mortality among patients with severe COVID-19 were APACHE II score (OR 1.16, 95% CI 1.05–1.18, $p < 0.001$), age (OR 1.05, 95% CI 1.03–1.06, $p < 0.001$), diabetes (OR 1.98, 95% CI 1.21–3.25, p 0.003), use of glucocorticoids (OR 3.00, 95% CI 1.91–4.70, $p < 0.001$) and SOFA score (OR 1.54, 95% CI 1.31–1.81, $p < 0.001$). In addition, the risk factors for death at 28 days associated with IVIG treatment were consistent across subgroups except for patients with white blood cells ≥10 (OR 2.21, p 0.007), with activated partial thromboplastin time ≥37 (OR 2.75, p 0.015) and with prothrombin time ≥13.5 (OR 3.61, p 0.002) (Fig. S3).

*Secondary outcomes*

As shown in Table 3, after IPW analysis, except for prone position ventilation (ATE = −0.022, 95% CI −0.041 to −0.002, p 0.028), there were no significant differences between the IVIG group and non-IVIG group for ARDS, DIC, myocardial injury, acute hepatic injury, shock, AKI, non-invasive mechanical ventilation, invasive mechanical ventilation, continuous renal replacement therapy and ECMO.

## Discussion

This is the first large cohort retrospective study evaluating the association between IVIG treatment and mortality among a well-defined cohort of patients with severe COVID-19. The results suggest that use of IVIG treatment was not associated with 28-day mortality.

The use of IVIG as an adjunctive treatment for sepsis and septic shock has been studied for decades. Rodríguez et al. reported that IVIG treatment plus adequate antibiotic treatment improved survival among surgical ICU patients with intra-abdominal sepsis [27]. Lizuka et al. found that IVIG (5 g/day for 3 days) did not reduce mortality among patients with sepsis and septic shock [28]. Tagami et al. reported that IVIG treatment (5 g/day for 3 days) was not significantly associated with survival among mechanically ventilated patients with pneumonia and septic shock [17], or among ventilated patients with septic shock after emergency laparotomy [29]. What must be noted is that the dose used in the above-mentioned studies was lower than the IVIG dose used in other studies and may be insufficient for patients with severe sepsis [30,31]. Moreover, IVIG treatment carries a risk of complications, which include thromboembolic events, renal dysfunction, aseptic meningoencephalitis and anaphylaxis [32]. It is possible that these complications may counterbalance the effectiveness of IVIG treatment.

The use of IVIG has also been reported in the treatment of several coronavirus-induced infections. Studies of SARS and MERS infection have suggested that IVIG led to a significant improvement in leucocyte and platelet counts, although the lack of control group precludes any definitive conclusions [33,34]. In Wuhan, China, the use of high-dose IVIG treatment (25 g/day for 5 days) plus antivirals (lopinavir/ritonavir) and methylprednisolone for severe COVID-19 has resulted in increased lymphocyte counts, lower concentrations of inflammatory markers, partial/complete resolution of specific lung findings, and negative nasal and oropharyngeal swab test results within a few days of starting treatment [35].

Another treatment of COVID-19 is convalescent plasma. It has been reported that no significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo [36]. In addition, the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial has shown no effect of convalescent plasma treatment for patients hospitalized with COVID-19 [36].

The present study involved a large and well-defined group of patients with severe COVID-19. However, several limitations should be considered. First, retrospective studies are prone to bias and we were unable to compare the results to those from a placebo control group. We cannot clearly indicate why some patients received IVIG and other did not since the decision was left to the discretion of the physician in charge of the patient. Second, there was some heterogeneity in the patient population since some critically ill patients were treated outside the ICU due to a shortage of ICU beds. Third, data collection for the baseline immunoglobulin levels, which may be associated with the efficacy of IVIG, was not available in frontline efforts to fight the pandemic. Fourth, we did not have access to long-term follow-up data or information regarding secondary infections and thrombotic events that were related to the IVIG treatment. Fifth, patients receiving other medical treatments have not been included in our study, probably reducing our estimates of IVIG effect. Sixth, early in the COVID-19 pandemic, much laboratory data were missing and unsuitable for imputation. Seventh, we cannot exclude the efficacy of IVIG in COVID-19 patients in general since our results were based on data of some severe COVID-19 patients. Eighth, due to the unclear reason for the IVIG use in the clinic, Directed Acyclic Graph (DAG) was not used for the selection of relevant variables in the multivariable analysis. We only selected variables with $p < 0.1$ that are also important factors in the clinic for the multivariable analyses. This is a limitation of our study. Nineth, different IVIG dosages were not studied due to the difficulty to ascertain the effect of low-vs. high-dose IVIG. Tenth, this study is a retrospective study and survival bias exist in our study. The marginal structural model might be a promising tool to address this bias. However, the data in this study were collected during the early pandemic. There were no medication guidelines, and clinicians prescribed treatment based on their own decisions. Therefore, it is hard to find variables that might prompt patient selection into IVIG treatment, and we matched each patient treated with IVIG with one untreated patient according to the number of days from admission to treatment (or lack of treatment). Eleventh, the lack of

**Table 2**
Characteristics and physiological parameters of survivors and non-survivors with severe COVID-19 on admission (after matching)

| Variables | Survivors ($n = 296$) | Non-survivors ($n = 516$) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | p | OR (95% CI) | p | OR (95% CI) |
| Age, years | | | | | | |
| Median (IQR) | 70 (62–78) | 61 (51–70) | <0.001 | 1.05 (1.04, 1.07) | <0.001 | 1.05 (1.03, 1.06) |
| Sex, n (%) | | | | | | |
| Male | 187 (63.2) | 293 (56.8) | 0.075 | 0.77 (0.57, 1.03) | 0.307 | 0.83 (0.57, 1.19) |
| Female | 109 (36.8) | 223 (43.2) | | | | |
| Smoking, *n* (%) | 7 (2.4) | 20 (3.9) | 0.248 | 0.60 (0.25, 1.44) | | |
| Comorbidities, *n* (%) | | | | | | |
| Chronic obstructive pulmonary disease | 13 (4.4) | 14 (2.7) | 0.179 | 1.69 (0.78, 3.64) | 0.981 | 1.01 (0.39, 2.62) |
| Diabetes mellitus | 62 (20.9) | 60 (11.6) | <0.001 | 2.05 (1.39, 3.02) | 0.003 | 1.98 (1.21, 3.25) |
| Hypertension | 115 (38.9) | 155 (30.0) | 0.007 | 1.51 (1.12, 2.05) | 0.258 | 0.78 (0.51, 1.20) |
| Chronic cardiac disease | 46 (15.5) | 56 (10.9) | 0.044 | 1.54 (1.01, 2.34) | 0.322 | 0.75 (0.43, 1.32) |
| Chronic kidney disease | 10 (3.4) | 15 (2.9) | 0.684 | 1.18 (0.53, 2.67) | 0.615 | 0.73 (0.22, 2.47) |
| Chronic liver disease | 8 (2.7) | 17 (3.3) | 0.668 | 0.83 (0.35, 1.95) | 0.212 | 0.49 (0.16, 1.50) |
| Stroke | 22 (7.4) | 26 (5.0) | 0.150 | 1.54 (0.85, 2.76) | 0.386 | 1.13 (0.53, 2.41) |
| Malignancy | 15 (5.1) | 12 (2.3) | 0.033 | 2.27 (1.05, 4.93) | 0.361 | 1.63 (0.57, 4.64) |
| Immunosuppression | 12 (4.1) | 16 (3.1) | 0.447 | 1.34 (0.63, 2.88) | 0.764 | 0.85 (0.29, 2.46) |
| Tuberculosis | 6 (2.0) | 5 (1.0) | 0.333 | 2.15 (0.65, 7.11) | | |
| Signs and symptoms at admission, *n* (%) | | | | | | |
| Fever | 236 (79.7) | 387 (75.0) | 0.053 | 1.42 (0.99, 2.02) | 0.072 | 1.57 (0.96, 2.57) |
| Cough | 229 (77.4) | 387 (75.0) | 0.308 | 1.23 (0.87, 1.74) | | |
| Sputum production | 134 (45.3) | 210 (40.7) | 0.140 | 1.24 (0.93, 1.66) | | |
| Dyspnoea | 214 (72.3) | 330 (64.0) | 0.006 | 1.56 (1.14, 2.14) | | |
| Oxygen therapy, *n* (%) | | | | | | |
| None | 85(28.7) | 111 (21.5) | <0.001 | 1.12 (1.01, 1.43) | 0.036 | 0.77 (0.60, 0.98) |
| Nasal cannula | 145 (50.0) | 373 (72.3) | | | | |
| High-flow nasal cannula | 33 (11.1) | 12 (2.3) | | | | |
| Non-invasive mechanical ventilation | 18 (6.1) | 10 (1.9) | | | | |
| Invasive mechanical ventilation | 6 (2.0) | 6 (1.2) | | | | |
| ECMO | 0 (0.00) | 0 (0.00) | | | | |
| SOFA score | 3 (2–5) | 2 (2–3) | <0.001 | 1.64 (1.46, 1.84) | <0.001 | 1.54 (1.31, 1.81) |
| APACHE II score | 9 (7–13) | 6 (4–8) | <0.001 | 1.23 (1.18, 1.28) | <0.001 | 1.16 (1.05, 1.18) |
| Laboratory findings, median (IQR) | | | | | | |
| Systolic pressure | 131 (120, 144) | 128 (119, 140) | 0.046 | 1.01 (1.00, 1.01) | 0.431 | 1.00 (1.00, 1.01) |
| Leucocytes (/$10^9$/L) | 8.6 (5.8–12.9) | 6.2 (4.3–9.8) | <0.001 | 1.14 (1.09, 1.18) | | |
| Lymphocytes (/$10^9$/L) | 0.6 (0.4–0.9) | 0.8 (0.5–1.1) | <0.001 | 0.69 (0.52, 0.91) | | |
| CD3 (/μL) | 353 (244–370) | 510 (345–655) | 0.034 | 0.99 (0.99, 1.00) | | |
| CD4 (/μL) | 207 (145–243) | 282 (166–409) | 0.067 | 0.99 (0.99, 1.00) | | |
| CD8 (/μL) | 124 (78–218) | 157 (113–250) | 0.077 | 0.99 (0.98, 1.00) | | |
| Haemoglobin (g/L) | 126 (115–135) | 124 (113–134) | 0.463 | 1.00 (0.99, 1.01) | | |
| Platelets ($10^9$/L) | 166 (114–226) | 174 (134–224) | 0.064 | 1.00 (1.00, 1.00) | | |
| Prothrombin time (s) | 12.0 (11.3–13.3) | 11.5 (10.9–12.8) | <0.001 | 1.10 (1.03, 1.18) | | |
| Activated partial thromboplastin time (s) | 29.2 (24.6–35.4) | 30.3 (26.2–35.3) | 0.145 | 1.00 (0.98, 1.01) | | |
| Thrombin time (s) | 16.8 (15.7–18.2) | 16.6 (15.7–17.9) | 0.380 | 1.02 (0.97, 1.06) | | |
| D-dimer (μg/mL) | 2.1 (0.8–11.4) | 0.7 (0.5–1.6) | <0.001 | 1.08 (1.05, 1.10) | | |
| Total bilirubin (μmol/L) | 14.0 (10.6–18.5) | 12.7 (9.4–16.1) | 0.007 | 1.03 (1.00, 1.06) | | |
| Alanine aminotransferase (U/L) | 32.0 (21.0–48.0) | 29.0 (19.0–42.0) | 0.074 | 1.00 (1.00, 1.00) | | |
| Aspartate aminotransferase (U/L) | 43.0 (31.0–58.0) | 35.0 (25.0–48.0) | <0.001 | 1.00 (1.00, 1.00) | | |
| Albumin (g/L) | 29.8 (26.9–32.6) | 34.1 (30.4–37.7) | <0.001 | 0.87 (0.84, 0.9) | | |
| Serum creatinine (μmol/L) | 76.7 (63.0–99.9) | 68.0 (56.4–87.0) | <0.001 | 1.00 (1.00, 1.00) | | |
| Creatine kinase (U/L) | 151.0 (82.0–330.0) | 97.0 (54.0–174.0) | <0.001 | 1.00 (1.00, 1.00) | | |
| Creatine kinase isoenzyme MB (U/L) | 16.9 (12.0–22.0) | 13.0 (10.0–17.0) | <0.001 | 1.03 (1.01, 1.04) | | |
| C-reactive protein (mg/L) | 93.8 (53.1–145.6) | 43.7 (18.2–73.2) | <0.001 | 1.02 (1.01, 1.02) | | |
| Interleukin-6 (pg/mL) | 10.7 (8.0–13.9) | 9.0 (7.0–11.5) | 0.872 | 1.00 (0.98, 1.03) | | |
| Procalcitonin (ng/mL) | 0.16 (0.09–0.44) | 0.07 (0.05–0.14) | <0.001 | 1.08 (1.00, 1.18) | | |
| Radiological findings, *n* (%) | | | | | | |
| Abnormalities | | | | | | |
| Ground-glass opacity | 95 (32.1) | 354 (68.6) | 0.501 | 1.78 (0.52, 6.15) | | |
| Pulmonary consolidation | 50 (16.9) | 46 (8.9) | <0.001 | 7.43 (4.50, 12.27) | | |
| Pulmonary interstitial abnormalities | 50 (16.9) | 220 (42.6) | 0.165 | 0.73 (0.47, 1.14) | | |
| Pneumothorax | 0 (0.0) | 0 (0.0) | 1.000 | | | |
| Pleural effusion | 5 (1.7) | 15 (2.9) | 0.845 | 1.29 (0.46, 3.63) | | |
| Treatment | | | | | | |
| Antiviral treatment | 167 (56.4) | 396 (76.7) | <0.001 | 0.39 (0.29, 0.53) | <0.001 | 0.31 (0.21-0.48) |
| Intravenous immunoglobulin | 153 (51.7) | 253 (49.0) | 0.466 | 1.11 (0.84, 1.48) | 0.481 | 0.85 (0.54, 1.34) |
| Glucocorticoid treatment | 195 (65.9) | 282 (54.7) | 0.002 | 1.60 (1.19, 2.15) | <0.001 | 3.00 (1.91, 4.70) |

IVIG, intravenous immunoglobulin; IQR, interquartile range; APACHEII, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation.

**Table 3**
The main and secondary outcomes of IVIG and non-IVIG groups after IPW analysis

| Outcome | ATE | 95% CI | p |
|---|---|---|---|
| 28-day mortality | 0.008 | −0.081, 0.097 | 0.863 |
| Acute respiratory distress syndrome | 0.329 | −1.901, 2.559 | 0.772 |
| Diffuse intravascular coagulation | 0.027 | −0.025, 0.078 | 0.311 |
| Myocardial injury | 0.061 | −0.008, 0.129 | 0.081 |
| Acute hepatic injury | 0.074 | −0.003, 0.152 | 0.060 |
| Shock | −0.014 | −0.078, 0.050 | 0.666 |
| Acute kidney injury | 0.030 | −0.035, 0.096 | 0.363 |
| Non-invasive mechanical ventilation | 0.044 | −0.044, 0.132 | 0.325 |
| Invasive mechanical ventilation | −0.008 | −0.074, 0.057 | 0.801 |
| Prone position ventilation | −0.022 | −0.041, −0.002 | 0.028 |
| Continuous renal replacement therapy | −0.012 | −0.039, 0.015 | 0.395 |
| Extracorporeal membrane oxygenation | −0.003 | −0.013, 0.006 | 0.507 |

information on the weight-adjusted doses given to each patient may lead to suboptimal treatment in most patients reported herein, which should be taken into account in future RCT studies.

In conclusion, the present study revealed that IVIG treatment was not associated with significant improvements in 28-day mortality in severe COVID-19 patients. In the future, a larger, possibly randomized, study is needed to further investigate the effects of different IVIG dosages in severe COVID-19.

## Transparency declaration

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## Author contributions

J.L., Y.Z.C. and R.R.L. drafted the manuscript. Z.X.W., Y.Z.L. and Q.H.X. collected the clinical data. Y.X.F. conducted statistical analysis. H.B.F., S.S.H., J.G., L.D.Z., W.Z., H.X.D., Y.A.L., T.W., L.M.C. and Z.L.W. summarized all data collected. J.L.T. and D.C.C revised the manuscript.

## Appendix A. Supplementary data

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