Intravenous immunoglobulin treatment for patients with severe COVID-19: a retrospective multi-center study

Jiao Liu
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Yizhu Chen
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Ranran Li
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Xuan Dong
Wuhan Jinyintan Hospital
Yizhong Li
Wuhan Number 9 Hospital
Qianghong Xu
Zhejiang hospital
Huibin Feng
Huangshi Central hospital
Sisi Huang
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Jun Guo
huazhong university of science and technology union jiangbei hospital
Lidi Zhang
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Xiaofei Ye
Second Military Medical UNIVERSITY
Wei Zhu
Tianyou hospital affiliated to wuhan university of science and technology
Hangxiang Du
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Yong'an Liu
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Tao Wang
Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital
Limin Chen

Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital

Zhenliang Wen

Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital

Jean-Louis Teboul (✉ jean-louis.teboul@aphp.fr)

Hopital Bicetre

Dechang Chen (✉ chendechangsh@hotmail.com)

Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital

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Research

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Abstract

Background: Intravenous immunoglobulin (IVIG) is commonly used to treat severe COVID-19, although the clinical outcomes remain unclear. This study evaluated the effectiveness of IVIG treatment for severe COVID-19.

Methods: This retrospective multi-center study evaluated 28-day mortality and time for SARS-CoV-2 RNA clearance in severe COVID-19 patients with or without IVIG treatment. Propensity score matching was used to control confounding factors. Logistic regression and competing risk analyses were performed.

Results: The study included 850 patients (421 patients received IVIG). No significant differences in 28-day mortality or time for SARS-CoV-2 RNA clearance were observed (p=0.357 and p=0.123, respectively). High-dose of IVIG treatment (>10 g/day) (n=27) was associated with decreased 28-day mortality (OR: 0.33, 95% CI: 0.14–0.77; p=0.011). The IVIG group had prolonged median hospitalization, less shock, and higher incidences of acute respiratory distress syndrome, myocardial injury. Furthermore, IVIG-treated patients were more likely to require non-invasive mechanical ventilation and less likely to require invasive mechanical ventilation.

Conclusions: IVIG treatment for severe COVID-19 patients was not associated with significant improvements in 28-day mortality or time for SARS-CoV-2 RNA clearance. However, some improvements in 28-day survival were observed for high-dose IVIG treatment (>10 g/day).

Background

The first outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease (COVID-19) was reported in Wuhan (Hubei, China) during December 2019. This outbreak has progressed to a global pandemic that has become a serious threat to global public health (1–3). Most patients exhibit mild symptoms, although approximately 15% of cases progress to severe disease (4–6). Unfortunately, there is no single effective treatment for COVID-19, and patients with severe COVID-19 have a poor response to medical management and a dismal prognosis (7, 8).

Immunoglobulin (IG) is the blood product purified from the plasma of healthy people, and is rich in antibodies that target bacterial and viral components. Continuous infusion of IG can increase the serum level of immunoglobulin G (IgG) and effectively neutralize respiratory pathogens in patients, which can shorten the course of the disease and promote their recovery (9). Intravenous IG (IVIG) downregulates proinflammatory mediators (10) and has been widely used for treating autoimmune diseases and serious viral, bacterial, and fungal infections (11). Hyperimmune IVIG (h-IVIG) can, when used within 5 days after the onset of symptoms, also reduce the viral load and mortality for patients with severe H1N1 infection (12). Although IVIG has been used to treat Middle East respiratory syndrome (MERS), there are no clear data regarding its anti-MERS activity and specific efficacy (13). Similarly, IVIG has been widely used by physicians to treat patients with severe COVID-19 during the current pandemic, although the benefits of this treatment remain unclear. Therefore, we performed a retrospective multi-center study of hospitalized

patients with severe COVID-19 to evaluate whether the use of IVIG treatment improved their clinical outcomes.

Methods

Study setting and design

This multicenter 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 the institutional review board at each hospital, which waived the requirement for informed consent.

A total of 2,346 adults with confirmed COVID-19 were treated at the four tertiary Chinese hospitals between December 2019 and March 2020. We excluded 1,496 patients with non-severe disease. The 850 eligible patients with severe COVID-19 were grouped according to the use of IVIG (421 patients) or the non-use of IVIG (429 patients). The effects on 28-day mortality were also evaluated for various IVIG treatment parameters: high-dose treatment (≥ 10 g/day), low-dose treatment (< 10 g/day), long-course treatment (≥ 8 days), short-course treatment (< 8 days), early treatment (≤ 48 h after hospitalization), and late treatment (> 48 h after hospitalization).

Definitions

The diagnosis of COVID-19 was based on the World Health Organization's interim guidelines (14). Nasal and pharyngeal swab specimens were collected ≥ 24 h apart 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, and its severity was judged based on the World Health Organization's interim guidelines and the Chinese management guidelines for COVID-19 (sixth version) (15). Immunosuppression status was identified based on the presence of malignancy, liver cirrhosis, or chronic renal failure, as well as the use of immunosuppressive therapy.

Data collection

The patients' medical records were reviewed to collect the following variables: age, sex, comorbidities, blood test results, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, imaging findings, IVIG treatment parameters (maximum daily dose, duration of treatment), and respiratory support (oxygen therapy, noninvasive mechanical ventilation, invasive mechanical ventilation, prone position ventilation, and extracorporeal membrane oxygenation).

Outcomes

The primary outcome was defined as 28-day all-cause mortality. The secondary outcomes were defined as the time from symptoms onset to SARS-CoV-2 RNA clearance from respiratory secretions, in-hospital mortality, and lengths of intensive care unit (ICU) and hospital stays.

Statistical analysis

Continuous variables were expressed as median (interquartile range, IQR) and were compared using the Kruskal-Wallis H test or the *t* test. Categorical variables were expressed as number (%) and compared using Fisher's exact test or the chi-squared test. The Kaplan-Meier method was used to estimate the curves for survival and time to SARS-CoV-2 RNA clearance, and differences were evaluated using the log-rank test. Relationships between IVIG treatment and 28-day mortality were evaluated using logistic rank test. The relationships between IVIG treatment and 28-day all-cause mortality were also evaluated for various subgroups: age (≥ 65 years *vs.* <65 years), APACHE II score (≥ 11 *vs.* <11), chronic obstructive pulmonary disease (COPD, yes *vs.* no), SOFA score (≥ 7 *vs.* <7), comorbid chronic diseases (yes *vs.* no), invasive mechanical ventilation (yes *vs.* no), white blood cell count (≥ 10×10^9L *vs.* <10×10^9/L), C-reactive protein (CRP, ≥ 6.9 mg/L *vs.* <6.9 mg/L), activated partial thromboplastin time (APTT, ≥ 37 s *vs.* <37 s), and prothrombin time (PT, ≥ 13.5 s *vs.* <13.5 s). The median values for our patient population were used as the cut-off values for continuous variables. Propensity score matching (PSM) was estimated by logistic regression using 1:1 caliper matching (caliper 0.02),without replacement. The Matching variables included: sex, age, COPD, diabetes, chronic cardiac disease, hypertension, stroke, malignancy, immunosuppression, chronic kidney disease, chronic liver disease, APACHE II, SOFA, fever and systolic blood pressure at admission, therapy included corticosteroids, antiviral drugs. Differences were considered statistically significant at *p*-values less than 0.05 and all analyses were performed using SPSS software (version 22.0) and R software (version 3.6.2).

Results

Patient characteristics

Among the 2,346 hospitalized patients with confirmed COVID-19, mild or moderate disease was observed for 1,496 patients. Thus, 850 patients with severe COVID-19 were considered eligible for this study (Fig. 1). Table 1 shows the patients' characteristics and laboratory parameters from their admission. Treatment using 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 59% 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).

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)	*p*-value
Age, years				
Median (IQR)	63 (55–73)	64 (54–74)	63 (55–73)	0.577
Sex, n (%)				
Male	501 (58.9)	258 (60.1)	243 (57.7)	0.473
Female	349 (41.1)	171 (39.9)	178 (42.3)	
Smoking, n (%)	30 (3.5)	14 (3.3)	16 (3.8)	0.671
Comorbidities, n (%)				
Chronic obstructive pulmonary disease	31 (3.8)	10 (2.4)	21 (5.2)	0.032
Diabetes mellitus	127 (15.1)	59 (13.9)	68 (16.2)	0.348
Hypertension	285 (33.8)	102 (24.1)	183 (43.7)	< 0.0001
Chronic cardiac disease	109 (12.9)	42 (9.9)	67 (16.0)	0.009
Chronic kidney disease	30 (3.6)	20 (4.7)	10 (2.4)	0.068
Chronic liver disease	27 (3.2)	10 (2.4)	17 (4.1)	0.161
Stroke	54 (6.4)	27 (6.4)	27 (6.4)	0.964
Malignancy	29 (3.4)	6 (1.4)	23 (5.5)	0.001
Immunosuppression	30 (3.6)	13 (3.1)	17 (4.1)	0.441
Tuberculosis	12 (1.4)	5 (1.2)	7 (1.7)	0.550
Signs and symptoms at admission, n (%)				
Fever	653 (77.4)	267 (63.1)	386 (91.7)	< 0.0001
Cough	645 (76.3)	308 (72.6)	337 (80.1)	0.011
Sputum production	363 (43.0)	195 (46.0)	168 (39.9)	0.074
Dyspnea	569 (67.4)	277 (65.3)	292 (69.5)	0.194
SOFA score	2 (2–3)	2 (2–3)	3 (2–4)	< 0.001

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

Variables	All patients (n = 850)	Non-IVIG group (n = 429)	IVIG group (n = 421)	*p*-value
APACHE □ score	8 (5–9)	8 (6–10)	7 (5–9)	0.0002
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)	< 0.0001
Lymphocytes (/10^9/L)	0.9 (0.5–1.1)	1.0 (0.4–1.3)	0.7 (0.5–0.9)	0.007
CD3 (/μL)	475 (319–609)	538 (368–630)	399 (253–579)	0.087
CD4 (/μL)	273 (149–367)	323 (214–440)	212 (144–289)	0.026
CD8 (/μL)	184 (105–240)	185 (106–250)	182 (80–240)	0.505
Hemoglobin (g/L)	123 (113–135)	121 (111–130)	126 (115–139)	< 0.0001
Platelets (10^9/L)	182 (128–224)	193 (138–231)	172 (123–214)	0.002
Prothrombin time (s)	12 (11.0–13.1)	13 (11.2–14.2)	12 (10.8–12.3)	< 0.0001
Activated partial thromboplastin time (s)	30.7 (25.6–35.3)	32.4 (26.0–38.1)	29.1 (25.0–32.5)	< 0.0001
Thrombin time (s)	17.4 (15.7–18.0)	17.6 (15.3–18.2)	17.2 (16.1–18.0)	0.009
D-dimer (μg/mL)	5.1 (0.6–3.2)	5.5 (0.5–3.4)	4.9 (0.6–3.1)	0.574
Total bilirubin (μmol/L)	14.1 (9.6–16.8)	14.1 (9.8–16.9)	14.1 (9.6–16.6)	0.258
Alanine aminotransferase (U/L)	39.2 (20.0–43.0)	40.2 (19.0–42.0)	38.4 (20.0–45.0)	0.247
Aspartate aminotransferase (U/L)	48.2 (27.0–51.0)	47.6 (24.0–45.5)	48.7 (31.0–55.0)	< 0.0001
Albumin (g/L)	32.7 (28.8–36.0)	31.7 (28.2–34.6)	33.2 (29.1–37.0)	0.004
Serum creatinine (μmol/L)	97.5 (59.0–91.7)	119.7 (56.6–91.0)	85.7 (60.0–91.7)	0.400

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

Variables	All patients (n = 850)	Non-IVIG group (n = 429)	IVIG group (n = 421)	*p*-value
Creatine kinase (U/L)	218.3 (62.0–217.0)	196.1 (52.0–163.0)	227.1 (66.0–235.0)	0.016
Creatine kinase isoenzyme MB (U/L)	18.8 (11.0–20.0)	17.47 (11.0–19.0)	19.4 (11.0–20.0)	0.342
C-reactive protein (mg/L)	71.1 (30.2–108.2)	69.0 (22.6–106.9)	72.1 (33.5–108.2)	0.377
Interleukin-6 (pg/mL)	12.1 (7.2–13.2)	12.5 (7.0–13.1)	11.8 (7.2–13.2)	0.926
Procalcitonin (ng/mL)	0.1 (0.05–0.25)	0.08 (0.05–0.25)	0.11 (0.05–0.24)	0.078
Radiological findings, n (%)				
Abnormalities				
Ground-glass opacity	460 (95.2)	281 (98.3)	179 (90.9)	0.0002
Pulmonary consolidation	98 (20.3)	65 (22.7)	33 (16.8)	0.109
Pulmonary interstitial abnormalities	275 (56.9)	106 (37.1)	169 (85.8)	< 0.0001
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)	1
Pleural effusion	22 (4.6)	11 (3.9)	11 (5.6)	0.368

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

IVIG treatment

The median time from hospital admission to the initiation of IVIG treatment among all patients was 2.8 days (IQR: 1–3 days), and this time was shorter for survivors (2.6 days) than for non-survivors (3.2 days). The median duration of IVIG treatment for all patients was 9 days (IQR: 4–12 days), and the treatment duration was longer for survivors (median: 11 days, IQR: 6–15 days) than for non-survivors (median: 7 days, IQR: 3–10 days). The median doses of IVIG were 9.9 g/day for survivors and 10.4 g/day for non-survivors (**Supplementary Table 1, Supplementary Fig. 1**).

Mortality

Death within 28 days was observed for 164 patients in the IVIG group (39%) and for 154 patients in the non-IVIG group (36%) (Table 2). In-hospital death was observed for 166 patients in the IVIG group (39%) and for 158 patients in the non-IVIG group (36%). The overall 28-day mortality between IVIG and non-IVIG group was not significantly different (p = 0.357). The cumulative 28-day survival rate was also not significantly different between IVIG and non-IVIG groups ($p = 0.710$, Fig. 2A). After propensity score

matching, the 28-day mortality rates were also not significantly different in most IVIG treatment subgroups (**Table 3**). However, the logistic regression model suggested that high-dose IVIG treatment (> 10 g/day, n = 27[15.5%]) was associated with reduced 28-day mortality (odds ratio: 0.33, 95% confidence interval: 0.14–0.77; $p = 0.011$).

Table 2
Clinical outcomes and courses of severe COVID-19 patients with or without IVIG treatment

	Non-IVIG group (n = 429)	IVIG group (n = 421)	*p*-value
28-day mortality, n (%)	154 (35.9)	164 (39.0)	0.357
In-hospital mortality, n (%)	158 (36.3)	166 (39.4)	0.609
Length of hospitalization, median (IQR)	14 (8–19)	15 (10–22)	0.005
Acute respiratory distress syndrome, n (%)	215 (50.5)	272 (64.6)	< 0.001
Diffuse intravascular coagulation, n (%)	9 (2.1)	13 (3.1)	0.372
Myocardial injury, n (%)	50 (11.7)	73 (17.3)	0.021
Acute hepatic injury, n (%)	47 (11.0)	91 (21.6)	< 0.001
Shock, n (%)	96 (22.5)	56 (13.3)	0.001
Acute kidney injury, n (%)	38 (8.9)	48 (11.4)	0.232
High-flow oxygen therapy, n (%)	103 (24.0)	92 (21.9)	0.455
Non-invasive mechanical ventilation, n (%)	49 (11.4)	129 (30.6)	< 0.001
Invasive mechanical ventilation, n (%)	66 (15.4)	45 (10.7)	0.042
Prone position ventilation, n (%)	18 (4.2)	7 (1.7)	0.029
Continuous renal replacement therapy, n (%)	16 (3.8)	16 (3.8)	0.973
Extracorporeal membrane oxygenation, n (%)	5 (1.2)	3 (0.7)	0.488

IQR: interquartile range.

Logistic regression analysis suggested that the other independent risk factors for 28-day mortality among patients with severe COVID-19 were APACHE II score, age, antiviral treatment, diabetes, use of glucocorticoids, and SOFA score (**Supplementary Table 2**).

The multivariate analysis suggested that the use of IVIG treatment was related to the APACHE II score, APTT, lymphocyte count, platelet count, leukocyte count, and SOFA score (**Supplementary Table 3**). The relationships between 28-day mortality and IVIG treatment were consistent across most subgroups

described in the methods section, except for patients with a SOFA score of ≥ 7, COPD, or with invasive mechanical ventilation (**Supplementary Fig. 2**).

Secondary outcomes

Patients in the IVIG group had a longer median hospitalization than the non-IVIG group (15 days [IQR: 10–22 days] vs. 14 days [IQR: 8–19 days], $p = 0.005$) (Table 2). During hospitalization, patients in the IVIG group had a lower incidence of shock (13.3% vs. 22.5%, $p = 0.001$) but were more likely to develop acute respiratory distress syndrome (64.6% vs. 50.5%, $p < 0.001$), myocardial injury (17.3% vs. 11.7%, $p = 0.021$), and acute hepatic injury (21.6% vs. 11.0%, $p < 0.001$). Furthermore, patients in the IVIG group had greater use of non-invasive mechanical ventilation (30.6% vs. 11.4%, $p < 0.001$) but less use of invasive mechanical ventilation (10.7% vs. 15.4%, $p = 0.042$) and prone position ventilation (1.7% vs. 4.2%, $p = 0.029$).

Relative to patients in the non-IVIG group, patients in the IVIG group were more likely to receive anticoagulation treatment (9.3% vs. 5.4%, $p = 0.029$), glucocorticoid treatment (71.0% vs. 46.2%, $p < 0.001$), antibiotic treatment (95.7% vs. 79.0%, $p < 0.001$), antifungal treatment (13.5% vs. 2.3%, $p < 0.001$), and antiviral treatment (73.9% vs. 64.6%, $p = 0.003$) (**Supplementary Table 4**). Patients who received IVIG were less likely to receive ganciclovir (21.4% vs. 28.4%, $p = 0.017$) and ribavirin (27.8% vs. 40.1%, $p < 0.001$), but more likely to receive arbidol hydrochloride (35.4% vs. 11.2%, $p < 0.001$) and lopinavir plus ritonavir (3.8% vs. 1.4%, $p = 0.028$) (**Supplementary Table 4**). The two groups had similar times for SARS-CoV-2 RNA clearance ($p = 0.123$) (Fig. 2B). Comparison of the laboratory parameters on admission (day 1) and during treatment (day 3) revealed several significant inter-group differences (**Supplementary Table 5**). Patients in the IVIG group had significantly higher values for leukocyte count ($p < 0.001$), neutrophil count ($p < 0.001$), lymphocyte count ($p = 0.003$), platelet count ($p < 0.001$), and PT ($p = 0.030$) at day 3 posttreatment compared to the values on admission. In addition, patients in the IVIG group had significantly lower values for APTT ($p = 0.003$) and CRP concentration ($p < 0.001$).

Table 3.

Twenty-eight-day mortality among severe COVID-19 patients using various adjustment methodologies after

propensity score matching.

	Logistic regression model			
Variables	N (%)	OR	95% CI	*p*-value
All patients treated with IVIG *vs.* not treated with IVIG	174(50.0)	0.95	0.62–1.47	0.824
Patients treated with IVIG (≤10 g/d) *vs.* not treated with IVIG	147(84.5)	1.17	0.74–1.86	0.505
Patients treated with IVIG (>10 g/d) *vs.* not treated with IVIG	27(15.5)	0.33	0.14–0.77	0.011
Patients treated with IVIG (≤48 h) *vs.* not treated with IVIG	101(58.0)	1.28	0.76–2.16	0.353
Patients treated with IVIG (>48 h) *vs.* not treated with IVIG	73(42.0)	0.65	0.37–1.13	0.129
Patients treated with IVIG (≤8 days) *vs.* not treated with IVIG	87(50.0)	0.67	0.40–1.13	0.129
Patients treated with IVIG (>8 days) *vs.* not treated with IVIG	87(50.0)	1.41	0.81–2.46	0.230
IVIG: intravenous immunoglobulin; OR, odds ratio; CI, confidence interval.				

Discussion

This is the first large cohort study to evaluate 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 or the time to SARS-CoV-2 RNA clearance from respiratory specimens. However, after propensity score matching, the logistic regression suggested that high-dose IVIG treatment (> 10 g/day) was associated with reduced 28-day mortality among patients with severe COVID-19. Moreover, use of IVIG treatment was independently associated with the APACHE II score, APTT, lymphocyte count, platelet count, leukocyte count, and SOFA score.

The use of IVIG has been reported in the treatment of other coronaviruses. Studies of SARS and MERS infection have suggested that IVIG led to significant improvement in leukocyte and platelet counts although the lack of control group and patient's overall clinical course (16, 17). The present study revealed that although IVIG treatment overall was not associated with a significant reduction in 28-day mortality in severe COVID-19 patients, patients who received IVIG were less likely to experience shock or to require invasive mechanical ventilation and prone position ventilation, suggesting that IVIG treatment may provide some clinical benefits for treating severe COVID-19. 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 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 the treatment (18). Moreover, Rodriguez et al reported that IVIG

treatment plus adequate antibiotic treatment improved survival among surgical ICU patients with intra-abdominal sepsis (19). Therefore, until a vaccine or other specific treatment is available, IVIG plus antiviral drugs may be an alternative therapeutic strategy for COVID-19.

The use of IVIG as an adjunctive treatment for sepsis and septic shock has been studied for decades. Lizuka et al. found that low-dose IVIG (5 g/day for 3 days) did not reduce mortality among patients with sepsis and septic shock (20). Tagami et al. reported that IVIG treatment (5 g/day for 3 days) was not significantly associated with the survival among mechanically ventilated patients with pneumonia and septic shock (9), or among ventilated patients with septic shock after emergency laparotomy (21). Moreover, Davey Jr. et al. reported that h-IVIG was not superior to placebo for adults who were hospitalized because of influenza A and B viral infections (22). The lack of a relationship between use of IVIG treatment and reduced mortality may be related to the use of only a low dose that was approved by the Japanese Ministry of Health, Labor, and Welfare (20). This dose was lower than the IVIG dose that used in international studies and may be insufficient for patients with severe sepsis (23, 24). We found in the present study that high-dose (> 10 g/day) IVIG treatment may help reduce the 28-day mortality rate. Consistently, a meta-analysis of IVIG treatment for sepsis revealed survival benefits at a total dose of ≥ 1 g/kg or at a treatment duration of ≥ 2 days (25), indicating the beneficial effects of high dose IVIG treatment.

IVIG treatment carries a risk of complications, which include thromboembolic events, renal dysfunction, aseptic meningoencephalitis, and anaphylaxis (26). It is possible that these complications might compromise the effectiveness of IVIG treatment in critically ill patients. Nevertheless, IVIG remains widely used for patients with sepsis, despite a lack of strong evidence supporting this application (26–28). The use of high dose of IVIG is effective in the treatment of COVID-19, possibly through immune modulation, saturating Fcγ receptor, and reducing antibody-dependent enhancement of inflammatory response (29). Therefore, well controlled studies are needed to confirm the clinical and survival benefits of IVIG treatment.

Our study revealed that IVIG treatment influenced immune cell counts (leukocytes, neutrophils, and lymphocytes) and CRP concentrations in patients with severe COVID-19. These results may reflect the ability of IVIG to regulate the inflammatory response by modulating complement and cytokine production, as well as neutralizing superantigens and antibodies (30). These mechanisms are used to justify the widespread use of IVIG for treating inflammatory and autoimmune diseases. We also found that IVIG treatment was associated with increased platelet counts, which suggests an improvement in coagulation function. In consistent with our finding, Ishikura et al. have reported that IVIG treatment significantly decreased the disseminated intravascular coagulation score for septic patients (31). In this context, IVIG treatment ameliorates hemostatic abnormalities via the intrinsic and extrinsic coagulation pathways, and IVIG treatment induces anti-inflammatory and anti-coagulation effects which may benefit the hemostasis in patients.

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. The decision was left at the discretion of the physician in charge of the patient. Second, there was some heterogeneity in the patient population, such as critically ill patients who were treated outside the ICU due to a shortage of ICU beds. Third, we did not have access to long-term follow-up data or information regarding secondary infections that were related to the IVIG treatment.

Conclusions

The present study revealed that IVIG treatment was not associated with significant improvements in 28-day mortality or time to SARS-CoV-2 RNA clearance in patients with severe COVID-19. However, some improvements in 28-day mortality were observed for high-dose IVIG treatment (> 10 g/day). These regimens may be worthy of consideration until a more effective treatment is identified.

Declarations

Acknowledgements

None

Authors’ contributions

JL, YZC and RRL drafted the manuscript. XD, YZL and QHX collected the clinical data. YXF did statistical analysis. HBF, SSH, JG, LDZ, WZ, HXD, YAL, TW, LMC, and ZLW summarized all the collected data. JLT and DCC revised the manuscript.

Authors’ information

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Availability of data and materials

The patients’ medical records were collected from hospitals' electronic medical records.

Ethics approval and consent to participate

The retrospective study protocol was approved by the institutional review board at each hospital, which waived the requirement for informed consent.

Consent for publication

Not applicable

Competing interests

None

Authors' details

1. Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, No.197 Ruijin 2nd Road, Shanghai 201801, China
2. Tuberculosis and Respiratory Department, Wuhan Jinyin-tan Hospital, No.1 Yintan Road, Wuhan 430023, China
3. Department of Critical Care Medicine, Wuhan No.9 Hospital, 20 Jiling Street, Wuhan 430080, China
4. Department of Critical Care Medicine, Zhejiang Hospital, No.12 Lingyin Road□Hangzhou 310015, China
5. Intensive care unit, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi 43500,
6. Intensive care unit, Huazhong University of Science and Technology Union Jiangbei Hospital,111 Success Avenue, Caidian District, Wuhan 430100, China
7. Department of Health Statistics, Second Military Medical University, No.800 Xiangyin Road, Shanghai 200433, China
8. Intensive care unit, Tianyou hospital affiliated to wuhan university of science &technology, No.9 Tujialing Road, Wuhan 430064, China
9. Service de Médecine-Intensive Réanimation, Hôpital Bicêtre, AP-HP. Université Paris-Saclay, Inserm UMR 999, Université Paris-Saclay, Le Kremlin-Bicêtre 94270, France

Abbreviations

IVIG: Intravenous immunoglobulin; COVID-19: coronavirus disease; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IgG: immunoglobulin G; H1N1: influenza A; MERS: Middle East respiratory syndrome; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit; COPD: Chronic obstructive pulmonary disease; APTT: Activated partial thromboplastin time; CRP: C-reactive protein

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Figures

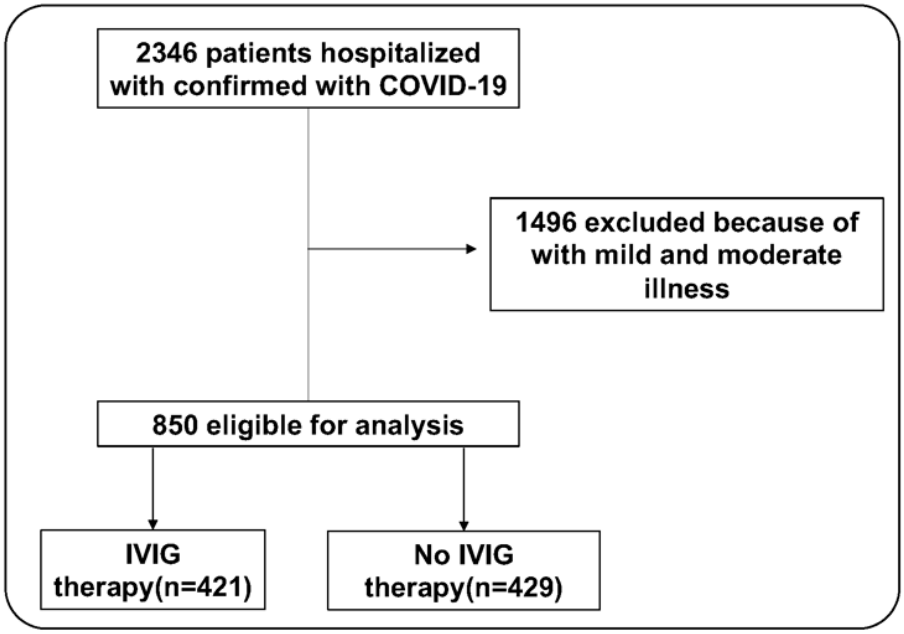

Figure 1

Flow chart of the present study

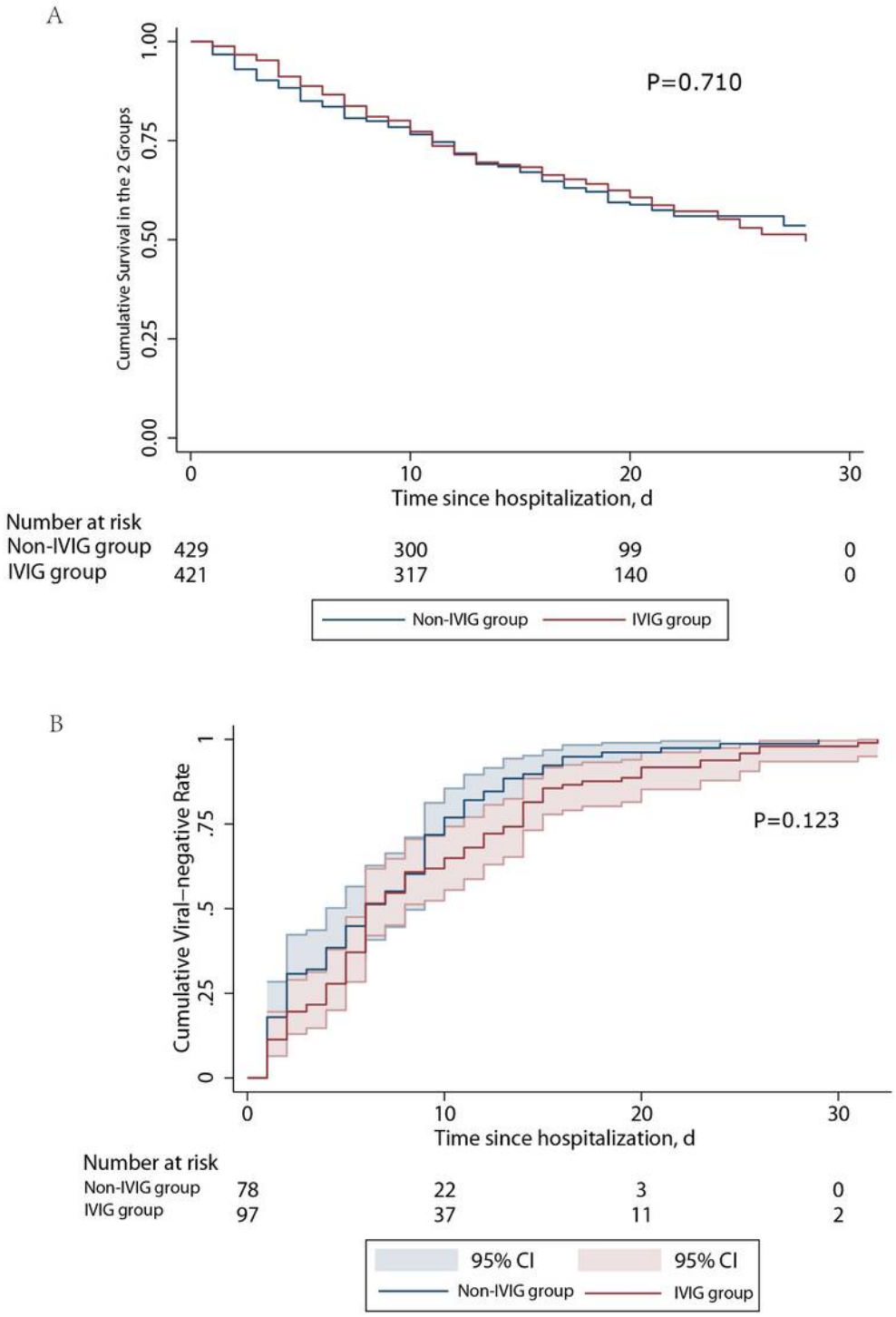

Figure 2

The effect of IVIG treatment on cumulative survival rate and SARS-CoV-2 RNA clearance time. A. Cox regression survival curve during hospitalization according to IVIG therapy after propensity scores matching. B. Cumulative incidence of SARS-CoV-2 RNA clearance according to IVIG therapy.

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