

# Clinical outcomes of intravenous immunoglobulin therapy in COVID-19 related acute respiratory distress syndrome: a retrospective cohort study

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## Research Article

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# Abstract

**Background:** Immunomodulatory property of intravenous immunoglobulin (IVIG) has been used to counteract severe systemic inflammation in coronavirus disease 2019 (COVID-19). However, its use in acute respiratory distress syndrome (ARDS) due to COVID-19 pneumonia is not well established.

**Methods:** In this retrospective study, we analyzed electronic health records of COVID-19 patients admitted to intensive care units (ICUs) at Hazm Mebaireek General Hospital, Qatar, between March 7, 2020, and September 9, 2020. Patients receiving invasive mechanical ventilation for moderate-to-severe ARDS were divided into two groups based on whether they received IVIG therapy. The primary outcome was all-cause ICU mortality. Secondary outcomes studied were ventilator-free days and ICU-free days at day-28 and incidence of acute kidney injury (AKI). Propensity score matching was used to adjust for confounders, and the primary outcome was compared using competing-risks survival analysis.

**Results:** Among 590 patients included in the study, 400 received routine care, and 190 received IVIG therapy in addition to routine care. One hundred eighteen pairs were created after propensity score matching with no statistically significant differences between the groups. Overall ICU mortality in the study population was 27.1%, and in the matched cohort, it was 25.8%. Mortality was higher among IVIG-treated patients (36.4% vs. 15.3%; sHR 3.5; 95% CI 1.98- 6.19;  $P < 0.001$ ). Ventilator-free days and ICU-free days at day-28 were lower ( $P < 0.001$  for both), and the incidence of AKI was significantly higher (85.6% vs. 67.8%;  $P = 0.001$ ) in the IVIG group.

**Conclusion:** IVIG therapy in mechanically ventilated patients with COVID-19 related moderate-to-severe ARDS was associated with higher ICU mortality. A randomized controlled study is required to confirm this observation further.

## Background

Coronavirus disease 2019 (COVID-19) is a highly infectious acute respiratory disease caused by a novel coronavirus, subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The first human cases of COVID-19 were reported in Wuhan City, China, in December 2019. Since then, the disease has rapidly spread, with World Health Organization (WHO) formally declaring it a pandemic on March 11, 2020 [2].

Over three million deaths have been reported worldwide due to COVID-19 [3]. The leading cause of death is respiratory failure due to acute respiratory distress syndrome (ARDS). Almost half of the patients with COVID-19 receiving invasive mechanical ventilation died, based on the case fatality rates reported in a recent meta-analysis [4]. There is increasing evidence that a hyperinflammatory response to SARS-CoV-2 contributes to disease severity and death in COVID-19. Patients with severe disease have increased serum levels of proinflammatory cytokines such as interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor (TNF)- $\alpha$ , and interferon (IFN)- $\gamma$  [5, 6]. An effective therapy that modulates inflammation and improves mortality is urgently needed.

Intravenous immunoglobulin (IVIG) is a blood product prepared from the serum pooled from thousands of healthy donors. The main component of IVIG is the serum IgG fraction with traces of IgA and IgM. IVIG exerts an immunomodulatory action, involving both innate (phagocytic leukocytes, natural killer cells, and cytokines) and adaptive (B cells, T cells, and antibodies) immunity [7]. It has been successfully used to treat dermatomyositis, Guillain–Barre syndrome, immune cytopenia, post-bone marrow transplantation, vasculitis, and Kawasaki disease [8]. Due to its anti-inflammatory effect, IVIG may suppress the hyperactive immune response associated with severe COVID-19 pneumonia and improve mortality. Only a few studies with inconsistent results have investigated the use of IVIG in critically ill SARS-CoV-2 infected patients [9, 10]. Moreover, none of the available literature reports outcomes of IVIG therapy in COVID-19 related ARDS. Hence, we conducted a retrospective study to evaluate the clinical outcomes of IVIG in COVID-19 pneumonia patients requiring invasive mechanical ventilation for moderate-to-severe ARDS.

## Methods

### Study population, design, and setting:

We retrospectively analyzed electronic health record data of patients admitted to ICUs at Hazm Mebaireek General Hospital, Qatar, between March 07, 2020, and September 09, 2020. The Medical Research Center (MRC) at Hamad Medical Corporation, Qatar, approved this study and waived the requirement for informed consent (protocol ID MRC-01-20-853). All methods were carried out in accordance with relevant guidelines and regulations. Inclusion criteria were: COVID-19 positivity as determined by reverse-transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs, age above 18 years, respiratory failure requiring invasive mechanical ventilation, and moderate-to-severe ARDS ( $\text{PaO}_2/\text{FiO}_2$   $\leq 200$  mm Hg) as defined by the Berlin criteria [11]. Patients who received IVIG for indications other than COVID-19 related ARDS or had cardiac arrest before ICU admission were excluded. The study population was divided into two groups based on receiving either routine care or IVIG plus routine care during their ICU stay. All patients received steroid and anti-viral therapy based on the hospital's policy for COVID-19 management unless contraindicated. IVIG was given to patients if there was a persistent increase in oxygen requirement, hemodynamic instability, and worsening laboratory parameters (C-reactive protein and serum ferritin level), suggesting disease progression. The IVIG treatment group received a minimum of one dose of 0.4 gram/kg of IVIG. Further doses of IVIG were given on consecutive days, to a maximum of 5 doses, based on the treating physician's discretion. Patients were closely monitored for immediate adverse effects like skin rash, arrhythmias, hypotension, and anaphylaxis.

### Data collection:

Baseline data were collected at the time of ICU admission. Information collected were demographic characteristics, comorbid conditions, blood test results,  $\text{PaO}_2/\text{FiO}_2$  ratio, vasopressor use, sequential organ failure assessment (SOFA) score, immune-modulating, and anti-viral drugs received.

### Outcomes:

The primary outcome studied was all-cause ICU mortality. Secondary outcomes included ventilator-free days and ICU-free days at day-28, and incidence of acute kidney injury (AKI) defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine level by  $\geq 0.3$  mg/dl ( $\geq 26.5$  mmol/L) within 48 hours or increase in serum creatinine to  $\geq 1.5$  times baseline [12]. Subgroup analysis was done for patients based on PaO<sub>2</sub>/FiO<sub>2</sub> ratio, serum ferritin level, time from ICU admission to IVIG therapy, and doses of IVIG received.

### **Statistical Analysis:**

We used propensity score matching to account for the non-random treatment allocation and to adjust for confounders. Propensity scores were generated based on age, sex, body mass index (BMI), comorbidities, SOFA score, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, baseline laboratory results, and other drug therapies. The propensity score overlap was assessed graphically. One-to-one matching with a caliper width of 0.2 of the standard deviation of the logit of the propensity score and no replacement was used to select a matching control group [13]. The post-matching covariate balance was assessed using the standardized differences. The primary outcome was compared using survival analysis. To minimize the risk of immortal time bias, we included the treatment with IVIG as a discrete time-dependent covariate. Because the discharge from ICU does not fulfill the assumption of non-informative censoring, Fine-and-Gray's competing risk model was used for the primary outcome with ICU discharge as a competing event. The treatment effect on the primary outcome was described as a sub-distribution hazard ratio (sHR) with a 95% confidence interval. A robust variance estimator was used to account for correlations resulting from matching. Multiple imputation procedures were used to deal with missing data (BMI, seven values; D-dimer, nine values; ferritin, three values). P values of less than 0.05 were considered statistically significant. All statistical analyses were conducted using Stata /MP 16.0 for Windows.

## **Results**

### **Characteristics of patients:**

During the study period (between March 07, 2020, and September 09, 2020), 1417 patients were admitted to ICUs at Hazm Mebareek General Hospital with the diagnosis of COVID-19. Seven hundred eighty-seven patients received invasive mechanical ventilation, of which 595 (75.6%) had moderate-to-severe ARDS. We excluded three patients who received IVIG for other indications from the treated group and two patients admitted to the ICU post-cardiac arrest from the control group. Of the remaining 590 patients, 400 received routine care, and 190 received IVIG plus routine care (Fig. 1).

Comparison between unmatched and propensity score-matched groups is shown in Table 1. Before matching, the patients in the IVIG group were older, had a higher prevalence of hypertension, dyslipidemia, and hemodialysis, had lower PaO<sub>2</sub>/FiO<sub>2</sub> ratio, lesser vasopressor use, lower SOFA score, raised alanine transaminase (ALT), more use of dexamethasone and lesser use of methylprednisolone, hydrocortisone, tocilizumab, lopinavir-ritonavir, and oseltamivir. In the IVIG group, the median time from ICU admission to

initiation of IVIG therapy was 6.28 days (IQR 2.1–11.9 days). The median cumulative dose of IVIG received was 150.0 grams (IQR 105.0-235.0 grams), and the median number of doses received was 4.0 (IQR 3.0–5.0).

Table 1  
Patient characteristics

| Variable                        | Total<br>(n = 590) | Unmatched                    |                   |            | Matched                      |                   |            |
|---------------------------------|--------------------|------------------------------|-------------------|------------|------------------------------|-------------------|------------|
|                                 |                    | Routine<br>care (n =<br>400) | IVIG (n =<br>190) | P<br>Value | Routine<br>care (n =<br>118) | IVIG (n =<br>118) | P<br>Value |
| <b>Age</b> (years)              | 53 (42–62)         | 51 (41.5–61)                 | 56.5 (47–65)      | < 0.001    | 52 (42–60)                   | 53.5 (44–60)      | 0.36       |
| <b>Gender:</b>                  | 555 (94.1%)        | 377 (94.2%)                  | 178 (93.7%)       | 0.79       | 112 (94.9%)                  | 112 (94.9%)       | 1.00       |
| Male                            |                    |                              |                   |            |                              |                   |            |
| Female                          | 35 (5.9%)          | 23 (5.8%)                    | 12 (6.3)          |            | 6 (5.1%)                     | 6 (5.1%)          |            |
| <b>BMI</b> (kg/m <sup>2</sup> ) | 27.2 (24.2–30.4)   | 26.9 (24.2–30.7)             | 27.6 (24.7–30.1)  | 0.50       | 26.7 (23.9–30.1)             | 27.69 (24.7–29.4) | 0.54       |
| <b>Co-morbidities:</b>          | 288 (48.8%)        | 198 (49.5%)                  | 90 (47.4%)        | 0.63       | 51 (43.2%)                   | 55 (46.6%)        | 0.60       |
| Diabetes mellitus               |                    |                              |                   | 0.03       |                              |                   | 0.9        |
| Hypertension                    | 290 (49.2%)        | 184 (46.0%)                  | 106 (55.8%)       | 0.03       | 59 (50.0%)                   | 58 (49.2%)        | 0.65       |
| Dyslipidemia                    | 68 (11.5%)         | 38 (9.5%)                    | 30 (15.8%)        | 0.06       | 10 (8.5%)                    | 12 (10.2%)        | 0.68       |
| Coronary artery disease         | 77 (13.1%)         | 45 (11.3%)                   | 32 (16.8%)        | 0.17       | 12 (10.2%)                   | 14 (11.9%)        | 1.00       |
| Chronic kidney disease          | 58 (9.8%)          | 44 (11.0%)                   | 14 (7.4%)         | < 0.001    | 4 (3.4%)                     | 5 (4.2%)          | 1.00       |
| Hemodialysis                    |                    | 0 (0%)                       |                   | 0.07       | 0 (0%)                       | 0 (0%)            | 0.55       |
| Chronic respiratory illness     | 33 (5.6%)          | 22 (5.5%)                    | 33 (17.4%)        | 0.12       | 13 (11%)                     | 8 (6.8%)          |            |
| Chronic liver disease           | 40 (6.8%)          | 10 (2.5%)                    | 18 (9.5%)         | 0.35       | 1 (0.8%)                     | 1 (0.8%)          |            |
| Malignancy                      | 11 (1.9%)          | 11 (2.8%)                    | 1 (0.5%)          |            | 7 (5.9%)                     | 5 (4.2%)          |            |
|                                 | 19 (3.2%)          |                              | 8 (4.2%)          |            |                              |                   |            |

Data are presented as No. (%) or median (interquartile range) unless otherwise indicated.

BMI: body mass index, PaO<sub>2</sub>/FiO<sub>2</sub> ratio: ratio of partial pressure arterial oxygen and fraction of inspired oxygen, SOFA score: sequential organ failure assessment score, CRP: C-reactive protein, ALT: alanine transaminase, AST: aspartate aminotransferase.

Laboratory data and SOFA score were obtained at baseline on ICU admission.

| Variable  | Total<br>(n = 590)    | Unmatched              |                     |         | Matched                |                      |         |
|---|-----------------------|------------------------|---------------------|---------|------------------------|----------------------|---------|
|   |                       | Routine care (n = 400) | IVIG (n = 190)      | P Value | Routine care (n = 118) | IVIG (n = 118)       | P Value |
| <b>PaO<sub>2</sub>/FiO<sub>2</sub> ratio</b><br>(mm Hg) | 124<br>(92–141)       | 130<br>(97.5–150)      | 105.35<br>(80–134)  | < 0.001 | 123 (81–140)           | 110.7<br>(87.1–136)  | 0.38    |
| <b>Vasopressor:</b>                                     | 415<br>(70.3%)        | 303<br>(75.8%)         | 96<br>(50.5%)       | < 0.001 | 71<br>(60.2%)          | 67<br>(56.8%)        | 0.60    |
| <b>Sofa score</b>                                       | 2 (2–5)               | 3 (2–5)                | 2 (1–4)             | < 0.001 | 2 (2–4)                | 2 (1–4)              | 0.06    |
| <b>Laboratory data:</b>                                 | 163.3<br>(91.9–246.7) | 166.5<br>(99.6–245.3)  | 156.2<br>(69.5–255) | 0.29    | 175.4<br>(90.9–257)    | 152 (72–232.1)       | 0.16    |
| CRP (mg/L)  |                       |                        |                     | 0.14    |                        | 1118.5<br>(688–1924) | 0.27    |
| Ferritin (mcg/L)  | 1057<br>(637–1625)    | 1017.5<br>(638.5–1559) | 1118<br>(638–1942)  | 0.60    | 1168.5<br>(693–1565)   |                      | 0.99    |
| D-Dimer (mcg/mL)  |                       |                        |                     | 0.06    |                        | 1.13<br>(0.74–2.88)  | 0.51    |
| Platelets (10 <sup>9</sup> /L)                          | 1.25<br>(0.68–3.95)   | 1.35<br>(0.68–4.23)    | 1.17<br>(0.74–3.24) | 0.08    | 1.43<br>(0.61–4.6)     |                      | 0.07    |
| Creatinine (micromol/L)                                 |                       |                        |                     | 0.74    |                        | 236<br>(186–308)     | 0.95    |
| Bilirubin (micromol/L)                                  | 233.5<br>(184–306)    | 240<br>(188–312)       | 221<br>(176–293)    | 0.03    | 249.5<br>(195–317)     |                      | 0.053   |
| ALT (IU/L)  | 85 (70–111)           | 84 (69–110)            | 93 (71–113)         | 0.07    | 78 (64–98)             | 86 (68–108)          | 0.42    |
| AST (IU/L)  | 11 (8–15)             | 11 (8–15)              | 11 (7–16)           |         | 10 (8–14)              | 10.25 (7–14.5)       |         |
|   | 40 (25–64)            | 38 (24–59)             | 45 (26–70)          |         | 37 (23–64)             | 45 (28–70)           |         |
|   | 51 (35–80)            | 50 (35–77)             | 54 (35–91)          |         | 50.5<br>(36–86)        | 54.5<br>(36–91)      |         |

Data are presented as No. (%) or median (interquartile range) unless otherwise indicated.

BMI: body mass index, PaO<sub>2</sub>/FiO<sub>2</sub> ratio: ratio of partial pressure arterial oxygen and fraction of inspired oxygen, SOFA score: sequential organ failure assessment score, CRP: C-reactive protein, ALT: alanine transaminase, AST: aspartate aminotransferase.

Laboratory data and SOFA score were obtained at baseline on ICU admission.



| Variable                 | Total<br>(n = 590) | Unmatched              |                |            | Matched                |                |         |
|--------------------------|--------------------|------------------------|----------------|------------|------------------------|----------------|---------|
|                          |                    | Routine care (n = 400) | IVIG (n = 190) | P Value    | Routine care (n = 118) | IVIG (n = 118) | P Value |
| <b>Steroid:</b>          | 168<br>(28.5%)     | 96<br>(24.0%)          | 72<br>(37.9%)  | <<br>0.001 | 32<br>(27.1%)          | 41<br>(34.7%)  | 0.2     |
| Dexamethasone            |                    |                        |                |            |                        |                | 0.2     |
| Methylprednisolone       | 446<br>(75.6%)     | 331<br>(82.8%)         | 115<br>(60.5%) | <<br>0.001 | 88<br>(74.6%)          | 79<br>(66.9%)  | 0.84    |
| Hydrocortisone           | 142<br>(24.1%)     | 110<br>(27.5%)         | 32<br>(16.8%)  | 0.005      | 15<br>(12.7%)          | 14<br>(11.9%)  |         |
| <b>Tocilizumab</b>       | 329<br>(55.8%)     | 251<br>(62.7%)         | 78<br>(41.1%)  | <<br>0.001 | 56<br>(47.5%)          | 54<br>(45.8%)  | 0.79    |
| <b>Interferon</b>        | 65<br>(11.0%)      | 49<br>(12.3%)          | 15(7.9%)       | 0.12       | 11 (9.3%)              | 10<br>(8.5%)   | 0.82    |
| <b>Anti-viral drugs:</b> | 78<br>(13.2%)      | 47<br>(11.8%)          | 31<br>(16.3%)  | 0.13       | 17<br>(14.4%)          | 23<br>(19.5%)  | 0.30    |
| Favipiravir              |                    |                        |                | <          |                        |                | 0.36    |
| Lopinavir-Ritonavir      | 306<br>(51.9%)     | 229<br>(57.3%)         | 77<br>(40.5%)  | 0.001      | 58<br>(49.2%)          | 51<br>(43.2%)  | 0.51    |
| Oseltamivir              | 355<br>(60.2%)     | 267<br>(66.8%)         | 88<br>(46.3%)  | <<br>0.001 | 63<br>(53.4%)          | 58<br>(49.2%)  | 0.60    |
| Remdesivir               |                    |                        |                | 0.10       |                        |                |         |
| Ribavirin                | 2 (0.3%)           | 0 (0%)                 | 2 (1.1%)       | 0.01       | 0 (0%)                 | 0 (0%)         |         |
|                          | 61<br>(10.3%)      | 50<br>(12.5%)          | 11<br>(5.8%)   |            | 9 (7.6%)               | 7 (5.9%)       |         |

Data are presented as No. (%) or median (interquartile range) unless otherwise indicated.

BMI: body mass index, PaO<sub>2</sub>/FiO<sub>2</sub> ratio: ratio of partial pressure arterial oxygen and fraction of inspired oxygen, SOFA score: sequential organ failure assessment score, CRP: C-reactive protein, ALT: alanine transaminase, AST: aspartate aminotransferase.

Laboratory data and SOFA score were obtained at baseline on ICU admission.

Propensity score matching generated 118 matched sets. Post matching, the two groups did not have any statistically significant differences (Table 1). In the matched cohort, the median time from ICU admission to initiation of IVIG therapy was six days (IQR 2.2–11.1 days). The median cumulative dose of IVIG received was 152.0 grams (IQR 108.0-235.0 grams), and the median number of doses received was 5.0 (IQR 3.0–5.0).

### Outcomes:

The all-cause ICU mortality for COVID-19 pneumonia patients admitted with respiratory failure requiring invasive mechanical ventilation for moderate-severe ARDS was 27.1%, and for the matched cohort, it was 25.8%. ICU mortality was significantly higher in the IVIG group (36.4% vs. 15.3% for IVIG and routine care,

respectively; sHR 3.5; 95% CI 1.98- 6.19; P<0.001). There was an increased risk of death in the IVIG group in the propensity score-matched and propensity score-adjusted survival analysis compared to the routine care group (Table 2). Results were similar, with increased risk of death in the IVIG-treated patients for the subgroups based on PaO<sub>2</sub>/FiO<sub>2</sub> ratio and serum ferritin level. ICU mortality did not change based on the time to IVIG therapy, and the number of doses received (Table 3).

Compared to routine care group, ventilator-free days at day-28 were lower in the IVIG group [median (IQR); 0 (0-18) vs. 22 (7-24) days; P<0.001], and ICU-free days at day-28 were also lower in the IVIG group [median (IQR); 0 (0-8.8) vs. 16 (0-20) days; P<0.001]. Additionally, the incidence of AKI was significantly higher in the IVIG group (85.6% vs. 67.8% for IVIG and routine care, respectively; P=0.001).

## Discussion

Our single-center retrospective study revealed a significant association of IVIG therapy with higher ICU mortality in patients with COVID-19 pneumonia receiving invasive mechanical ventilation for moderate-to-severe ARDS. We confirmed these results after propensity score matching to account for the differences between the two groups.

Only a few randomized controlled studies have evaluated the efficacy of IVIG therapy in COVID-19 pneumonia. Gharebaghi et al. have reported that administration of IVIG to 30 patients with severe COVID-19 infection who did not respond to initial treatment significantly reduced the in-hospital mortality (20.0% in the treatment group vs. 48.3% in the control group; P = 0.025). However, the severity of ARDS and the percentage of patients receiving invasive mechanical ventilation were not reported by the authors [14]. Another pilot randomized controlled trial showed that IVIG 0.5g/kg daily for three days with concomitant methylprednisolone 40 mg significantly improved hypoxia and reduced progression to mechanical ventilation in COVID19 patients [15]. The clinical improvement found in this study cannot be generalized because of the small sample size and concomitant use of methylprednisolone therapy that may have confounded the results. Recently, Tabarsi et al. demonstrated that IVIG, combined with hydroxychloroquine and lopinavir/ritonavir for SARS-CoV-2 patients, did not reduce mortality, the need for mechanical ventilation and improve radiological findings. However, the potential benefit of IVIG monotherapy could not be evaluated in this study due to combination therapy with hydroxychloroquine and lopinavir/ritonavir [16].

The novelty of our work comes from exclusively studying critically ill COVID-19 pneumonia patients receiving invasive mechanical ventilation for moderate-severe ARDS. Based on a global literature survey, the mortality rate in COVID-19 associated ARDS was 45%, and the incidence of ARDS among non-survivors of COVID-19 was 90%. In the same study, the mortality rate of patients who received invasive mechanical ventilation was 59% [17]. The overall ICU mortality of our patients with moderate-to-severe ARDS receiving invasive mechanical ventilation was lower (27.1%), which could be attributed to the younger age of our population (median age 53 years, Table 1) and is consistent with previous reports of higher mortality with increasing age [18].

The higher mortality observed in our patients who received IVIG could be related to multiple factors. Firstly, IVIG was administered after ICU admission and receiving invasive mechanical ventilation for moderate-to-severe ARDS, which is late in the disease. The median time from ICU admission to IVIG therapy was 6.28 days in our study. Xie et al. has reported that IVIG therapy for COVID-19 pneumonia within 48 hours of ICU admission improved clinical outcomes [19]. Secondly, thromboembolic events are high in SARS-CoV-2 infected individuals with significantly increased odds of mortality [20]. Also, previous studies have suggested an association between IVIG and increased risk of thromboembolic events [21, 22]. Hence, the initiation of IVIG therapy in patients with predictive factors for thrombotic complication could have resulted in worse clinical outcomes in our cohort. Thirdly, we observed a higher incidence of AKI in the IVIG group, and based on a recent report, the occurrence of AKI had increased the risk of death by 60% in patients with COVID-19 [23]. Fourthly, various anti-viral agents and other immunomodulatory therapies like steroid, tocilizumab, and interferon were used in our patients. Hence, we cannot exclude the potential role of these drugs in the clinical outcomes we obtained. Lastly, though the control and treatment groups were matched based on their baseline characteristics (including PaO<sub>2</sub>/FiO<sub>2</sub> ratio and SOFA score) at ICU admission, IVIG was administered by physicians to deteriorating patients who had not responded to initial management.

In our study, IVIG's dose and duration were based on established practice in immune modulation therapy for other diseases [24] since there are no standardized guidelines for its use in COVID-19 patients. In a retrospective case series of 12 patients where IVIG appeared to improve the clinical course, the total dose administered ranged from 0.5 g/kg to 2.0 g/kg (median 1.25 g/kg) distributed over 1–4 daily doses [25]. Further studies are required to investigate the dose, duration, and appropriate time for initiation of IVIG therapy which might benefit COVID-19 patients without having adverse effects.

Our study has few limitations. We used propensity score matching to adjust for known confounders. However, due to the retrospective design, we could not entirely exclude the possibility of unmeasured confounding factors that might have led to worse outcomes in the IVIG group. The study was conducted in a single center in Qatar, limiting the generalizability of these results to other institutions. Although we were rigorous in our approach towards data collection and analysis, there were missing data for some variables that could have affected the outcomes. We did not define the phenotype of our patients as hypo- or hyper-inflammatory based on the severity of systemic inflammation [26]. Thus, we could not study the role of IVIG in modulating the immune response in hyper-inflammatory COVID-19 ARDS.

## Conclusions

The results of our single-center retrospective study revealed a higher ICU mortality rate, lesser ventilator-free days and ICU-free days at day-28, and higher incidence of AKI in mechanically ventilated patients who received IVIG therapy for COVID-19 related moderate-to-severe ARDS. Despite the limitations, this study highlights the possibility of unfavorable outcomes with IVIG therapy in SARS-CoV-2 infected patients. A multicenter, randomized clinical trial is warranted to investigate further the efficacy and safety of IVIG in critically ill COVID-19 patients.

# Declarations

## **Ethics approval and consent to participate:**

The Medical Research Center (MRC) at Hamad Medical Corporation, Qatar, approved this study and waived the requirement for informed consent (protocol ID MRC-01-20-853). All methods were carried out in accordance with relevant guidelines and regulations.

## **Consent for publication:**

Not applicable.

## **Availability of data and materials:**

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

## **Competing interests:**

The authors declare that they have no competing interests.

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## **Authors' contributions:**

HSA, the principal investigator, had complete access to data and contributed to the study design, result interpretation, and writing of the manuscript. MAW and AA conducted electronic health record review and data collection. MOS and HAM performed data analysis, literature review and contributed to writing the manuscript. MSE, NS, DCA, MAA, SG, and MYK contributed to the literature review, study design, drafting, and editing of the manuscript. AJN and ASM contributed to the conceptualization, data analysis, and editing of the manuscript.

## **Acknowledgments:**

Not applicable.

# Abbreviations

AKI = Acute kidney injury

ARDS = Acute respiratory distress syndrome

COVID19 = Coronavirus disease 2019

ICU = Intensive care unit

IVIG = Intravenous immunoglobulin

PaO<sub>2</sub>/FiO<sub>2</sub> = Ratio of partial pressure arterial oxygen and the fraction of inspired oxygen

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

SOFA = Sequential organ failure assessment

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## Tables 2-3

**Table 2. Association of IVIG treatment with mortality**

|                      | Total (n) | sHR (95% confidence interval) | P value |
|----------------------|-----------|-------------------------------|---------|
| PS matched analysis  | 236       | 3.50 (1.98 – 6.19)            | <0.001  |
| PS adjusted analysis | 556*      | 2.98 (1.92 – 4.60)            | <0.001  |

IVIG: intravenous immunoglobulin, PS: propensity score, sHR: sub-distribution hazard ratio.

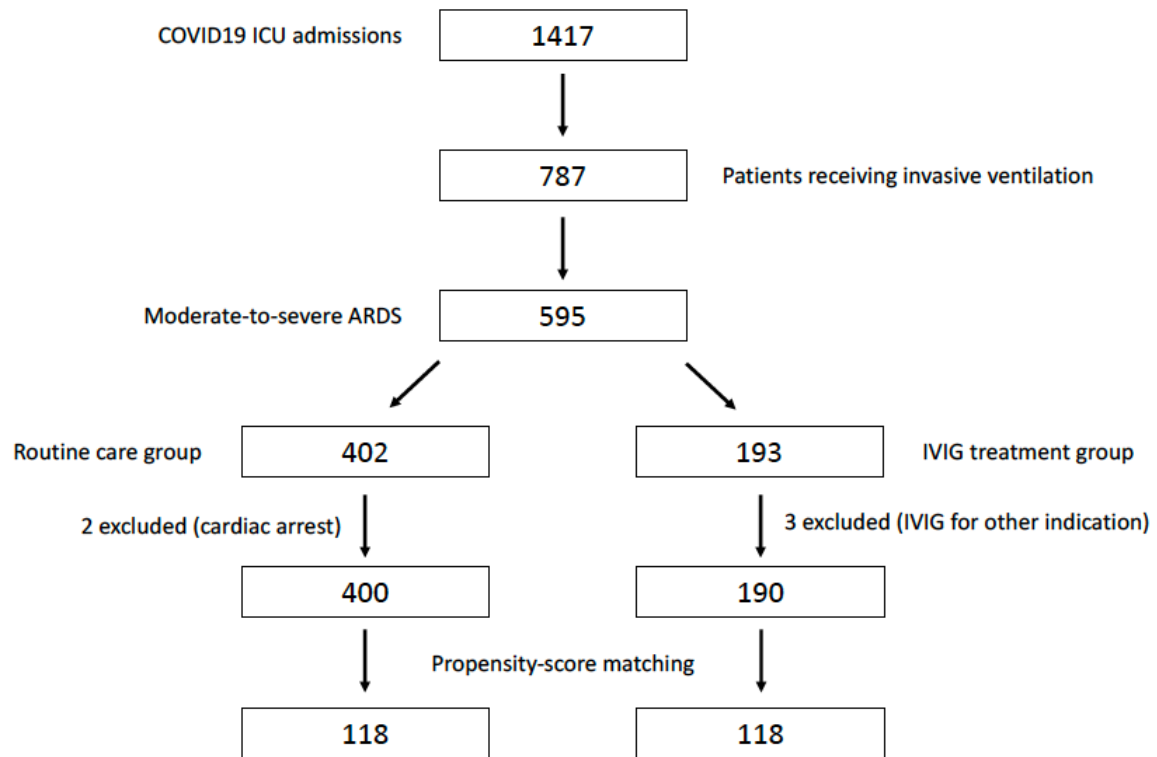
\* Propensity score could not be calculated for 34 patients due to complete separation by baseline characteristics.

**Table 3. Association of IVIG treatment with mortality among sub-groups**

| Sub-groups                               | sHR (95% confidence interval) | P value |
|--|-------------------------------|---------|
| PaO <sub>2</sub> /FiO <sub>2</sub> ratio |                               |         |
| > 100 mm Hg                              | 3.44 (2.04 – 5.78)            | < 0.001 |
| £ 100 mm Hg                              | 2.17 (1.07 – 4.41)            | 0.03    |
| Serum ferritin level                     |                               |         |
| < 1000 mcg/L                             | 3.45 (1.87 – 6.38)            | < 0.001 |
| ³ 1000 mcg/L                             | 2.79 (1.52 – 5.11)            | 0.001   |
| Time from ICU admission to IVIG therapy  |                               |         |
| < 5 days                                 |                               |         |
| ³ 5 days                                 | 2.65 (1.07 – 6.56)            | 0.035   |
|  | 3.89 (1.85 – 8.18)            | <0.001  |
| No. of IVIG doses received:              |                               |         |
| £ 3 doses                                | 3.72 (1.39 – 9.91)            | 0.009   |
| > 3 doses                                | 3.42 (1.69 – 6.93)            | 0.001   |

IVIG: intravenous immunoglobulin, sHR: sub-distribution hazard ratio, PaO<sub>2</sub>/FiO<sub>2</sub> ratio: ratio of partial pressure arterial oxygen and fraction of inspired oxygen, mcg/L: microgram per liter.

## Figures



COVID19: corona virus disease 2019; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; IVIG: intravenous immunoglobulin.

**Figure 1**

Flow chart showing selection of patients.