Original Article

Efficacy analysis of Arbidol treatment in patients with 2019 novel coronavirus pneumonia: a retrospective cohort study

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Background: The aim of this study was to determine whether Arbidol has a good antiviral effect on coronavirus disease 2019 (COVID-19).

Methods: A retrospective cohort study was performed in one of the treatment centers for COVID-19 patients in China from January 2020 to March 2020. The antiviral drug Arbidol (ARB) was administrated to some of the patients at 0.2 g tid po for 7 to 10 days. According to whether patients were given ARB, they were divided into 2 groups: the ARB group and the Non-ARB group. The primary outcome was the 14-day COVID-19 negativity rate.

Results: Of 146 patients, 140 were included. A total of 79 (56.4%) patients received ARB during hospitalization. In the overall cohort, the time of COVID-19 negativity in the ARB group compared with the Non-ARB group was 12.9 days versus 12.7 days (P=0.175; >0.05). The rates of 14-day COVID-19 negativity were 60.8% and 65.6% in the ARB and non-ARB groups, respectively (P=0.559; >0.05). Using an adjusted model, there were no obvious differences in the time of COVID-19 negativity and the rates of 14-day COVID-19 negativity (P>0.05). According to Kaplan-Meier analysis, the probabilities of 14-day COVID-19 negativity were similar in the 2 groups (log-rank P=0.130; >0.05). In a multivariate Cox analysis, the variables of age [hazard ratio (HR) 0.91, 95% confidence interval (CI): 0.83 to 0.99; P=0.039] and glucose (HR 0.90, 95% CI: 0.82 to 0.98; P=0.021) were independently associated with 14-day COVID-19 negativity.

Conclusions: Our results suggest that there was no apparent favorable clinical response with ARB both in clinical symptoms and the 14-day COVID-19 negativity rate.

Keywords: Coronavirus disease 2019 (COVID-19); COVID-19-related pneumonia; Arbidol; antiviral treatment; negativity rate

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel beta-coronavirus recently named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1-3). The 2019 novel coronavirus-infected pneumonia (NCIP) has become a worldwide pandemic that is overwhelming health care systems globally (4,5). The most severe symptom of COVID-19 is similar to severe acute respiratory syndrome (SARS) (1). The person-to-person transmission route of COVID-19 is similar to that of SARS (6). Supportive care and antiviral therapy remain the mainstay for treating patients with COVID-19; however, there is currently no proven effective specific antiviral drug available (7). Therefore, the antiviral activity drugs against SARS-CoV-2 are urgently needed to treat COVID-19 patients.

Arbidol (ARB) (also known as umifenovir) is a nonnucleoside antiviral agent approved in China for the prevention and treatment of influenza and other respiratory viruses. It is a broad-spectrum antiviral drug that has proven antiviral effects against influenza, Lassa, and Ebola, among others (8,9). The antiviral effect of ARB not only affects hemagglutinin but also can inhibit the endocytosis and fusion of the virus on the surface of the host cell. By blocking the virus outside of the host cell, ARB prevents the virus from host cell entry. It has been found that ARB has a good inhibitory effect against SARS-CoV-2 *in vitro* (10). Some academics have recommended to use of ARB in patients with COVID-19 (7,11-13); however, the antiviral effect of ARB on COVID-19-related pneumonia is still controversial (10,14). We retrospectively collected clinical data, including ARB treatment records and the time of COVID-19 negativity. This study might provide information on the clinical application of ARB in the treatment of SARS-CoV-2 infection. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2397).

Methods

Study design and patients

This study was a retrospective, observational, single-center study. Ethics approval was granted by the Enze Hospital Ethics Committee of Taizhou Enze Medical Center (Group) (Also called Taizhou Hospital of Zhejiang Province) (K20200204). All patients from Enze Hospital, Taizhou Enze Medical Center (Group), from 31 January 2020, to 11 May 2020 were included in the analysis. The participants were divided into 2 groups according to whether they received ARB: the ARB group, in which ARB was administered, and the Non-ARB group, in which ARB was not administered. The dosage and period of administration of ARB for COVID-19 treatment were 0.2 g tid po for 7–10 days. The primary clinical outcome was the time after the initiation of antiviral therapy at which the nucleic acid test for SARS-CoV-2 became negative. The secondary outcomes were the duration of fever and symptoms. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was provided by all participants before inclusion.

PCR-confirmed cases of COVID-19-infected pneumonia were consecutively included. The diagnostic criteria were as follows: (I) reverse transcription-polymerase chain reaction (RT-PCR)-confirmed infection with COVID-19; and (II) lung involvement confirmed with chest imaging. The diagnostic criteria for severe patients were as follows: any of the following: respiratory rate (RR) >30 breaths/min at rest, mean oxygen saturation ≤93%; arterial oxygen pressure/oxygen concentration (PaO_2/FiO_2) ≤300 mmHg (15). The exclusion criteria were as follows: pregnancy; age <18 years; and incomplete data.

Data collection

All participant data were extracted from electronic medical records, which included epidemiological characteristics, clinical signs and symptoms, and laboratory findings [including interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF), interferon (IFN)-γ, and COVID-19 RNA]. Chest computed tomography (CT) was employed as the imaging study. All participants included in the analysis were patients from Enze Hospital, Taizhou Enze Medical Center (Group).

Statistical analysis

Data were expressed as the means ± standard deviation (SD), medians with ranges, or percentages with numbers of patients. Normally distributed data was evaluated by using the Shapiro-Wilk test (P>0.05). Continuous variables that were normally distributed were carried out using Student's *t*-test or the corrected *t*-test. Non-parametric distribution variables were performed using the Mann-Whitney U test. Comparisons of categorical variables were performed using the χ^2 test or Fisher's test. Kaplan-Meier survival curves and the log-rank test were performed to estimate the

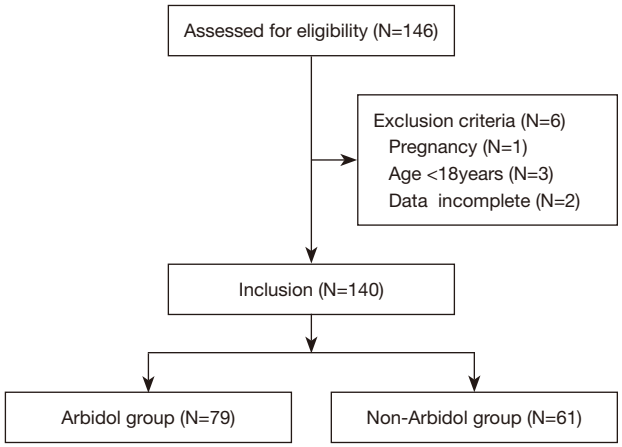

Figure 1 Flow chart of the enrollment of this study.

14-day COVID-19 negativity rate. The prognostic value of the variables was assessed using a univariate Cox proportional hazards regression adjusted model. Statistical significance was considered when P<0.05. All statistical analyses were performed with SPSS 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA).

Results

Participant and baseline characteristics

Of 146 patients, 140 patients with COVID-19 were included based on the inclusion and exclusion criteria (*Figure 1*). Among the 140 participants, 79 (56.4%) were treated with ARB during hospitalization. The mean age was 48 years, 53.6% were males, and 72.9% had a fever. In addition, 25% [35] of participants were identified as having severe NICP and none of the severe patients progressed to critical illness or died (*Table 1*). The participants in the two groups had normal white blood cell counts, and most participants had obvious lymphopenia. The participants in the ARB group had no prominent laboratory abnormalities (i.e., routine blood test, biochemical blood tests, hemagglutination series, blood gas analysis) compared with the non-ARB participants. The median time from symptom onset to hospitalization was 2 days (range, 0 to 14 days). The median time from symptom onset to the initiation of antiviral therapy was 4.0 days (range, 0 to 20 days) (Table S1). The baseline oxygen support of the participants between the 2 groups was not significantly different (Table S1). No significant differences were found between the 2 groups in the levels of inflammatory factors, such as IL-2, IL-4, IL-6, IL-10, TNF-α, and TFN-γ (Figure S1).

Primary and secondary outcomes

The mean time after the initiation of antiviral therapy at which the nucleic acid tests for SARS-CoV-2 became negative was 12.8±7.1 days and the 14-day COVID-19 negativity rate was 62.9% in the overall cohort (*Table 2*). The probabilities of negativity for COVID-19 at 14 days were 60.8% and 65.6% in the ARB group and non-ARB group, respectively, and there was no significant difference between the 2 groups (P=0.559) (*Table 2*). The duration of fever was 5.8±2.1 and 5.5±2.2 days, respectively, and there was no significant difference between the 2 groups (P=0.337). The duration of symptoms was 10.2±5.0 and 10.6±5.1 days, respectively, and there was no significant difference between the 2 groups (P=0.670) (*Table 2*). There were no obvious differences in the time of COVID-19 negativity, rates of 14-day COVID-19 negativity, duration of fever, and the duration of symptoms using the adjusted model (P>0.05).

Kaplan-Meier survival analysis

Kaplan-Meier survival analysis was used to compare the rate of 14-day COVID-19 negativity between the 2 groups. The probability of COVID-19 negativity at 14 days was similar in the ARB group and non-ARB group (log-rank P=0.130; >0.05) (*Figure 2A*). In a subgroup analysis of participants according to severity, in the non-severe population, the probability of COVID-19 negativity at 14 days was not significantly different between the ARB group and the non-ARB group (P=0.06; >0.05) (*Figure 2B*). In the severe population, the probability of COVID-19 negativity at 14 days was also not significantly different between the ARB group and the non-ARB group (P=0.655; >0.05) (*Figure 2C*).

Cox regression analysis

The univariate Cox regression analysis showed that age, use of gamma globulin, use of glucocorticoid, absolute lymphocyte value, creatine kinase, and PaO_2/FiO_2 were significantly (P<0.05) associated with 14-day COVID-19 negativity. In the multivariate analysis, the variables of age [hazard ratio (HR) 0.91, 95% confidence interval (CI): 0.83 to 0.99; P=0.039] and glucose (HR 0.90, 95% CI: 0.82 to 0.98; P=0.021) were independently associated with 14-day

Table 1 Baseline characteristics of 140 patients with COVID-19

Characteristic	All patients (N=140)	Non-ARB group (N=61)	ARB group (N=79)	P[a]
Age, mean ± SD, years	48±13	47±13	50±14	0.278
Gender (male), n (%)	75 (53.6)	39 (63.9)	36 (45.6)	0.031
Severe patients, n (%)	35 (25.0)	13 (21.3)	22 (27.8	0.376
Smoking history, n (%)	13 (9.2)	7 (11.3)	6 (7.6)	0.433
Exposure history, n (%)				
Recently been to Wuhan	67 (47.9)	25 (41.0)	42 (53.2)	0.113
Contact with people from Wuhan	72 (51.4)	35 (57.4)	37 (46.8)	0.190
Comorbidities, n (%)				
Hypertension	23 (16.4)	6 (9.8)	17 (21.5)	0.064
Diabetes	13 (9.3)	4 (6.6)	9 (11.4)	0.328
Chronic obstructive pulmonary disease	3 (2.1)	2 (3.3)	1 (1.3)	0.580
Chronic liver disease	4 (2.9)	3 (4.9)	1 (1.3)	0.318
Symptoms				
Fever, n (%)	102 (72.9)	42 (68.9)	60 (75.9)	0.349
Highest temperature, ℃	38.3±0.6	38.3±0.7	38.2±0.5	0.745
Cough, n (%)	90 (64.3)	41 (67.2)	49 (62.0)	0.525
Sore throat, n (%)	15 (10.7)	4 (6.6)	11 (13.9)	0.162
Headache, n (%)	12 (8.6)	3 (4.9)	9 (11.4)	0.175
Diarrhea, n (%)	13 (9.3)	4 (6.6)	9 (11.4)	0.328
Chest tightness, n (%)	29 (20.7)	14 (23.0)	15 (19.0)	0.566
Fatigue, n (%)	35 (25.0)	17 (27.9)	18 (22.8)	0.491

[a], Student's *t*-test, Mann-Whitney U test, χ^2 test and Fisher test. COVID-19, coronavirus disease 2019; ARB, Arbidol; SD, standard deviation.

Table 2 Clinical outcomes

Outcomes	All patients (N=140)	Non-ARB group (N=61)	ARB Group (N=79)	P[a]	P[b]
Primary outcomes					
Days until virus negativity, mean ± SD, days	12.8±7.1	12.9±9.2	12.7±5.1	0.175	0.055
14-day virus negativity rate, n (%)	88 (62.9)	40 (65.6)	48 (60.8)	0.559	0.322
Secondary outcomes					
Duration of fever, mean ± SD, days	5.6± 2.2	5.8± 2.1	5.5± 2.2	0.337	0.387
Duration of symptoms, mean ± SD, days	10.4±5.0	10.2± 5.0	10.6± 5.1	0.670	0.792

[a], non-adjusted model adjusted for: none; [b], adjusted for: gender. ARB, Arbidol; SD, standard deviation.

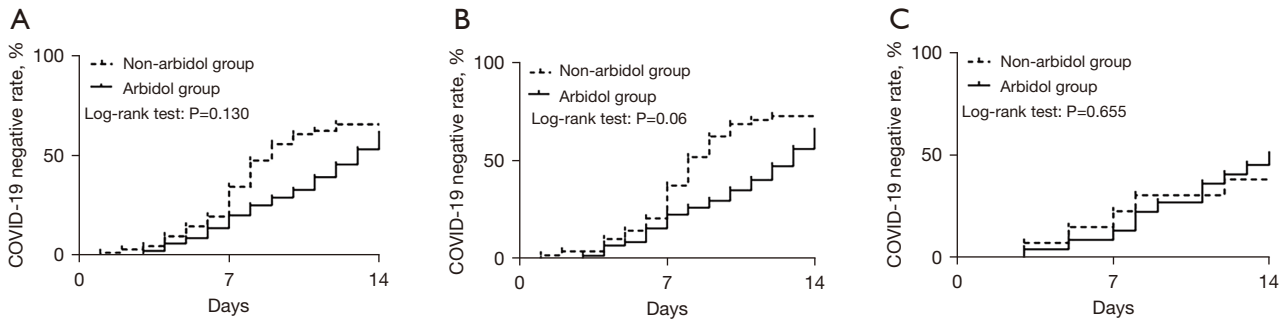

Figure 2 Kaplan-Meier curves stratified based on the time to SARS-CoV-2 negativity. (A) In the overall cohort, the probabilities of 14-day COVID-19 negativity were similar in the 2 groups (P=0.130; >0.05). (B) In a subgroup analysis of non-severe patients, no significant differences were found between the ARB group and Non-ARB group in the 14-day COVID-19 negativity rate (P=0.06; >0.05). (C) In a subgroup analysis of severe patients, no significant differences were found between the ARB group and Non-ARB group in the 14-day COVID-19 negativity rate (P=0.655; >0.05). P values were for differences in the time to SARS-CoV-2 negativity as assessed by the log-rank test. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; COVID-19, coronavirus disease 2019; ARB, Arbidol.

Table 3 Univariate and multivariate analyses for 14-day COVID-19 negativity

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	0.98 (0.96–0.99)	0.004	0.91 (0.83–0.99)	0.039
Severe patients (no *vs.* yes)	1.70 (0.99–2.93)	0.054		
Gamma globulin use (no *vs.* yes)	2.00 (1.09–3.69)	0.026		
ARB use (no *vs.* yes)	1.50 (0.98–2.29)	0.060		
Glucocorticoid use (no *vs.* yes)	1.86 (1.08–3.20)	0.025		
Absolute lymphocyte value, $\times 10^9$/L	1.50 (1.05–2.14)	0.027		
Glucose, mmol/L	0.89 (0.81–0.97)	0.011	0.90 (0.82–0.98)	0.021
Creatine kinase, U/L	1.00 (0.99–1.00)	0.027		
PaO_2/FiO_2, mmHg	1.00 (1.00–1.01)	0.019		

Adjusted for: gender. COVID-19, coronavirus disease 2019; ARB, Arbidol; HR, hazard ratio; CI, confidence interval; PaO_2/FiO_2, arterial oxygen pressure/oxygen concentration.

COVID-19 negativity (*Table 3*).

Discussion

The highly infectious SARS-CoV-2 is a single-stranded RNA beta-coronavirus (2). Due to the evidence of human-to-human transmission, early isolation and early antiviral treatment are very important for patients with COVID-19 (16,17). Currently, several antiviral agents have been suggested as treatment options for COVID-19, including remdesivir, chloroquine, and lopinavir-ritonavir, but no agent has yet been shown to have clinical benefits in patients with COVID-19 (18-20). The surface structural spike glycoprotein in coronaviruses is one of the most important therapeutic targets for antiviral agents because of its important role in virus-cell receptor interactions (21,22). Fortunately, some scientists have found that ARB has a certain inhibitory effect on SARS-CoV-2 *in vitro*, and ARB is currently the only known inhibitor of hemagglutinin (the spike-like glycoprotein on the envelope of the virus) (8,10,23). In a clinical setting, a study reported that among 4 patients who were given antiviral treatments, including lopinavir/ritonavir (Kaletra®) and ARB; 2 patients were confirmed to be SARS-CoV-2-negative and were discharged (11). In a retrospective cohort

study on 16 patients who received oral ARB combined with lopinavir/ritonavir, there was an apparent favorable clinical response (24). However, another study suggested that ARB might not improve the prognosis or accelerate SARS-CoV-2-negativity in non-intensive care unit (ICU) patients (14). In this study, we found that the time to negativity for the virus in patients with COVID-19 who were given SRB was not shorter than that in Non-ARB-treated patients. The rates of 14-day COVID-19 negativity were 60.8% and 65.6% in the ARB and non-ARB groups, respectively (P=0.559; >0.05) (*Table 2*). The improvement in clinical symptoms was not significantly different between the 2 groups. As we know, there are large differences in the antiviral effects of *in vitro* and *in vivo* drugs. A study of the concentrations of agents *in vivo* is also necessary. In this study, we found that ARB does not have an antiviral effect in patients with COVID-19. However, a large-sample randomized controlled trial (RCT) is needed to assess the efficacy of ARB.

The factors affecting the time of COVID-19 negativity are unknown, but they are vital for the treatment time. One study reported that serum lactate dehydrogenase or creatine kinase decline may predict a favorable response to treatment of COVID-19 infection (25). In this study, we found that age, the use of gamma globulin and glucocorticoid, glucose, creatine kinase, and PaO2/FiO2 were associated with 14-day COVID-19 negativity in the univariate analysis. In the multivariate analysis, the variables of age (HR 0.91, 95% CI: 0.83 to 0.99; P=0.039) and glucose (HR 0.90, 95% CI: 0.82 to 0.98; P=0.021) were independently associated with 14-day COVID-19 negativity (*Table 3*). This study was limited by the small size of the retrospective cohort. Furthermore, our study did not collect viral load data to confirm the antiviral effects of ARB or if there was any association between the baseline viral load and viral suppression, and clinical response.

Conclusions

In summary, our study suggests that Arbidol might not improve the prognosis or accelerate SARS-CoV-2 clearance. Further RCTs may be needed to evaluate the antiviral effect of ARB against SARS-CoV-2. It is necessary to find new potential targets for antiviral drugs to control the COVID-19 pandemic.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2397

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-2397

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2397). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethics approval was granted by Hospital Ethics Committee of Enze Hospital of Taizhou Enze Medical Center (Group) (Also called Taizhou Hospital of Zhejiang Province) (K20200204). Written informed consent was provided by all participants before inclusion.

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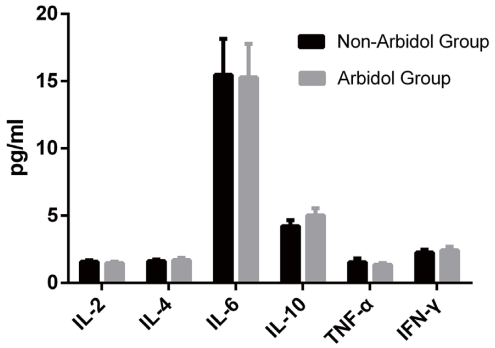

Figure S1 The levels of inflammatory factors, including IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ, at the time of hospital admission. There were no differences between the Arbidol group and the non-Arbidol group. ARB, Arbidol; IL-2, interleukin-2; TNF-α; tumor necrosis factor-α; IFN-γ; interferon-γ.

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Table S1 Blood biochemistry and treatments

Laboratory items	All patients (N=140)	Non-ARB group (N=61)	ARB group (N=79)	P[a]
Routine blood tests				
White blood cell count, $\times10^9$/L	5.9±3.0	6.2±3.6	5.6±2.4	0.204
Hemoglobin, g/L	138.4±16.3	139.6±16.7	137.3±16.0	0.412
Hematocrit, ratio	0.41±0.05	0.40±0.06	0.41±0.04	0.976
Platelet count, $\times10^9$/L	211.4±68.9	212.8±69.2	210.3±69.1	0.835
Absolute lymphocyte value, $\times10^9$/L	1.3±0.5	1.3±0.53	1.2±0.55	0.473
Absolute neutrophil value, $\times10^9$/L	4.1±3.0	4.5±3.6	3.8±2.4	0.166
Blood biochemistry tests				
Aspartate aminotransferase, U/L	26.8±14.0	27.1±16.3	26.5±11.8	0.801
Alanine aminotransferase, U/L	26.0±20.2	27.0±22.9	25.0±17.8	0.261
Serum creatinine, μmol/L	81.1±35.9	79.2±14.5	82.6±46.5	0.168
Creatine kinase, U/L	90.7±84.6	94.1±86.7	87.7±83.3	0.481
Sodium, mmol/L	138.0±2.7	137.8±2.8	138.1±2.6	0.565
Potassium, mmol/L	3.8±0.4	3.7±0.4	3.8±0.3	0.115
Calcium, mmol/L	2.2±0.2	2.2±0.2	2.2±0.1	0.367
Hemagglutination series				
International normalized ratio	1.0±0.1	1.0±0.1	1.1±0.1	0.180
Prothrombin time, s	11.9±0.8	12.0±0.7	11.8±1.0	0.437
Activated partial thromboplastin time, s	30.3±3.9	30.2±2.8	30.0±2.8	0.759
D-dimer, mg/L	0.40±0.50	0.40±0.40	0.43±0.60	0.185
Blood gas analysis				
pH	7.4±0.0	7.4±0.0	7.4±0.0	0.621
$PaCO_2$, mmHg	41.2±4.4	41.4±4.3	41.1±4.6	0.632
Lactate, mmol/L	1.8±0.7	1.8±0.6	1.8±0.8	0.824
PaO_2/FiO_2, mmHg	367.3±98.3	363.1±88.6	370.8±106.0	0.655
Treatments				
Onset to hospitalization, median (range), days	2 (0–14)	3 (0–14)	2 (0–12)	0.054
Onset to antiviral therapy, median (range), days	4 (0–20)	5 (0–19)	3 (1–20)	0.311
Glucocorticoid, no./total no. (%)	36/140 (25.7%)	14/61 (23.0%)	22/79 (27.8%)	0.511
Gamma globulin, no./total no. (%)	29/140 (20.7%)	11/61 (18.0%)	18/79 (22.8%)	0.491
Baseline oxygen support				
Ambient air	66/140 (47.1%)	27/61 (44.3%)	39/79 (49.4%)	0.549
Low-flow oxygen	58/140 (41.4%)	28/61 (45.9%)	30/79 (38.0%)	0.345
Nasal high-flow oxygen	16/140 (11.4%)	6/61 (9.8%)	10/79 (12.7%)	0.603

[a], Student's *t*-test, Mann-Whitney U test, χ^2 test and Fisher test.

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