Efficacy of diammonium glycyrrhizinate combined with vitamin C for treating hospitalized COVID-19 patients: a retrospective, observational study

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Abstract:

Background: The current global coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown limited responses to medical treatments.

Aims: To observe the effect of combination treatment of giammonium glycyrrhizinate and vitamin C （DV）on the prognoses of patients with COVID-19.

Methods: This retrospective observational study recruited 207 COVID-19 patients from Tongji Hospital， patients were assigned to DV and non-DV groups on the basis of the DV treatment. To make the results more credible, a propensity-score matching (PSM) approach was adopted at a 1:3 ratio to determine the participants. Logistic analysis was used to assess the effect of DV therapy in the progress of COVID-19.

Results: In the DV group, the new onset incidence rate of acute respiratory distress syndrome (ARDS) after admission was clearly lower than that in the non-DV group (DV vs non-DV groups, 15.2% vs 35.7%; P=0.002). Compared with the non-DV group, the DV group showed fewer new onset of complications (such as ARDS, acute liver injury and acute myocardial injury) (DV vs non-DV groups,19.6% vs 46.1%; P=0.000). Moreover, DG+VC may help to recover the count of NK cells and decrease the level of sIL-2R.

Conclusions: DG+VC might be a promising candidate for preventing the deterioration of COVID-19 patients, which is worthy to be studied in large and perspective cohort.

Keywords: COVID-19, Giammonium glycyrrhizinate, vitamin C, complication, prevent

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. Given the outbreak reaching epidemic proportions and the limited effective therapy, alternative medicine is urgently needed [1-2]. A recent bioinformatics analysis predicted that glycyrrhizic acid (GA) and vitamin C (VC) combinatorial treatment for COVID-19 is associated with elevated immunity and suppressed inflammatory stress, including the activation of the T cell receptor signaling pathway and the regulation of Fc gamma R-mediated phagocytosis [3]. GA is a major bioactive ingredient extracted from Rhizoma Glycyrrhizae, has potent pharmacological efficacy against viral infections and regulates the immune response [4-5]. During the SARS outbreak in 2003, it was reported that GA could effectively inhibit the replication, adsorption and penetration of two clinical isolates of SARS-associated coronavirus (FFM-1 and FFM- 2) in Vero cells. Diammonium glycyrrhizinate (DG) is a derivative of glycyrrhizic acid (GA). With a chemical structure similar to those of corticosteroids, DG functions as a glucocorticoid-like agent that might have an effect on cytokine storms or inflammation with few reported side effects [6].

Vitamin C supplements possess antiviral and immune-supportive properties, making this compound useful for preventing various conditions [7]. During the SARS epidemic, VC was recommended as a preventive medication and adjuvant therapy that significantly lowered the incidence of pneumonia [8]. A randomized controlled trial of 56 critical COVID-19 patients who received intravenous vitamin C at a dose of 12 g/50 ml every 12 hours for 7 days reported a diminishing trend in 28-day mortality [9]. However, high-dose VC may have side effects, including oxalate nephropathy, hypernatremia and nephrolithiasis [10]. Therefore, a regular dose of VC oral administration was preferred in this study and we supposed that DG+VC may enhance their effectiveness while minimizing the side effects.

Method

Patient involvement

This retrospective, single-centre, observational study enrolled 207 COVID-19 patients from Tongji Hospital at Huazhong University of Science & Technology (Wuhan, China) during February 11 and March 31st, 2020. The diagnosis and severity of COVID-19 were based on the New Coronavirus Pneumonia Prevention and Control Program (Trial Version 5) published by the

National Health Commission of China. Patients who met any of the following criteria were excluded: 1) younger than 18 years old; 2) short hospital duration of less than 7 days; and 3) testing negative for SARS-CoV-2 viral infection. The study complied with the edicts of the 1975 Declaration of Helsinki and was approved by the principal investigator center, Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (No.:(2020) Linlun-34th). Written informed consent was obtained from patients or their immediate relatives.

According to the COVID-19 guidelines, COVID-19 severity is classified as follows:

1. Mild cases

The clinical symptoms were mild, and there was no sign of pneumonia upon imaging.

2. Moderate cases

Showing fever and respiratory symptoms with radiological findings of pneumonia.

3. Severe cases

Adult cases meeting any of the following criteria;

1) Respiratory distress (≧30 breaths/ min);

2) Oxygen saturation≤93% at rest;

3) Arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤300 mmHg (l mmHg=0.133 kPa).

4. Critical cases

Cases meeting any of the following criteria:

1) Respiratory failure requiring mechanical ventilation;

2) Shock;

3)Other organ failure requiring ICU care.

The severity of each case was defined based on the clinical information collected upon admission.

Data Collection

The patients' data were collected between February 11 and March 31st, 2020. We recorded participants' demographic information, symptoms, physical examination, comorbidities, routine laboratory examinations, treatment and outcomes. All of the information was extracted from electronic medical records or through direct communication with the patients and their health care providers. Two physicians independently reviewed the data, and a third researcher decided whether

there was any difference in data collection between the two primary reviewers.

DG plus VC treatment and group assignment

In this study, the eligible patients under study were categorized into the DV group and the non-DV group. Patients in the DV group received DG (150mg Tid po) + VC (500 mg Tid po) treatment continuously for at least 7 days within 48 hours after hospital admission. The remaining patients, who were not treated with DG+VC were defined as the non-DV group. Diammonium glycyrrhizinate has been used for more than 40 years as treatment for liver diseases with few reported side effects. Thus, diammonium glycyrrhizinate at clinical dose of 150mg Tid po was added to the standard therapy of COVID-19 patients in this study. Given that majority of patients on admission were mild cases, and the uncertain side effects of high-dose intravenous vitamin C in COVID-19 patients, a regular dose of VC oral administration (500 mg Tid po) was adopted in this study.

Co-interventions

The treatment given to inpatients with COVID-19 followed the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 5). All of the patients received antiviral therapy, and arbidol was the most frequently used antiviral drug among our participants. Glucocorticoids were given to patients with a progressive deterioration of oxygenation indicators, rapid progress in imaging or excessive activation of the patient's inflammatory response. Invasive mechanical ventilation was considered when conditions did not improve or even worsened within a short time (1-2 hours) after receiving standard oxygen therapy, high-flow nasal cannula oxygen therapy or non-invasive ventilation. When the outcome of prone position ventilation is poor, extracorporeal membrane oxygenation (ECMO) was adopted. The indications for CRRT include: 1) hyperkalaemia; 2) acidosis; 3) pulmonary oedema or water overload; and 4) fluid management in multiple organ dysfunction. Critical cases can be given an intravenous infusion of γ-globulin.

Definitions

ARDS was defined according to the Berlin definition [11]. Liver injury was defined according to the ACG Clinical Guideline [12]. Acute myocardial injury was diagnosed if the serum levels of cardiac biomarkers (e.g., troponin I) were above the 99th percentile upper reference limit or new abnormalities were shown by electrocardiography and echocardiography [13]. Shock was defined according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

[14]. Acute kidney injury was identified and classified on the basis of the highest serum creatinine level or urine output criteria according to kidney disease, improving the global outcome classification [15].

Outcomes

The primary outcome was the composite end point. The composite end point was either death or requiring invasive mechanical ventilation. The secondary outcomes were complications, including ARDS, liver injury, acute myocardial injury, acute kidney injury and septic shock.

Statistical analysis

Propensity score matching was performed in the current study. We calculated a propensity score using patients' sex and age in a logit model and used the nearest-neighbour matching method without replacement at a ratio of 1:3 within a caliper of 0.01. Absolute standardized differences were used to assess the performance of the matching, in which ≤ 10% was considered to be negligible imbalances between the DV and non-DV groups. Then, the clinical characteristics were compared before and after the propensity score matching (Table S1).

Firstly, we defined risk factors for COVID-19 according to previous studies, as follows: age≥60 years, male sex, comorbidities (diabetes, hypertension, and chronic cardiovascular disease), elevated IL-6, elevated LDH, elevated D-dimer and decreased lymphocytes [16-18]. Glucocorticoid therapy and infusion of γ-globulin therapy are closely related to the progression of COVID-19, thus, we also defined them as covariates [19-20]. Secondly, a univariate logistic analysis was used to screen out the significant variables of these covariates ($P<0.5$) for further multivariate analysis. Thirdly, to determine the performance of the DG+VC treatment, significant variables were included in the multivariate logistic regression model, which was performed using a backward stepwise approach after propensity score matching. Akaike information criterion (AIC) values were used to assess the performance of parametric models. Thus, there were two logistic regression models for composite endpoints and complications respectively in this research. It was noteworthy that glucocorticoid therapy and the infusion of γ-globulin therapy were irrelevant to new onset complications of COVID-19 because the majority of patients received these therapies after new onset complications. Therefore, glucocorticoid therapy and γ-globulin infusion were not included in the logistic model for complications.

A generalized estimation equation approach was adopted to perform a comparison of the

dynamic changes in laboratory tests among patients who received treatment or those who did not.

Continuous variables are presented as the median and interquartile range (IQR). Categorical variables are described as numbers and percentages. SPSS (version 26.0) and R (Version 3.5.3) were used for all the statistical analyses. A two-sided α value of < 0.05 was considered statistically significant.

Results

Characteristics of participants

A total of 302 patients were admitted to Tongji Hospital at Huazhong University of Science & Technology (Wuhan, China) during February 11 through March 31st, 2020. Among them, 29 patients were not diagnosed with COVID-19. A further 53 records were excluded due to missing treatment history or laboratory examination, and 13 cases were excluded for short hospital duration of less than 7 days. Finally，the remaining 207 records were included in the study(Figure1).

Propensity score matching yielded 46 subjects in the DV group, who matched with 105 subjects in the non-DV group. Of the 161 inpatients with COVID-19 after propensity score matching, the median age was 61 (54–69) years, and 47.2% were male. Patients defined as moderate, severe and critical illness were 73.3%, 24.2%, 2.5%, respectively. In this PSM based nested case-control study, there were no significant differences between the DV group and non-DV group in terms of demographics, clinical characteristics, incidence of comorbidities, severity of illness or laboratory tests upon admission (all P>0.05, Table 1). Compared with the DV group, there were more severely ill patients who needed glucocorticoid therapy in the non-DV group (DV vs non-DV group, 8.7% vs 27.8%; P=0.008, Table 1).

Outcomes

The incidence of primary endpoint was 9.3% among all patients and 2.2% among patients received DG+VC therapy. Complication rate of all patients was 38.5% and 19.6% among patients received DG+VC treatment (Table1). By using logistic regression, we found that DV therapy was univariably associated with less complications (DV vs non-DV groups 19.6% vs 46.1%; P=0.000; odds ratio, 0.29; 95% confidence interval, 0.13-0.64, Supplementary table1).

Factors associated with primary endpoint and complications were included in the multivariate regression model and listed in Supplementary table2 and Supplementary table3.The multivariate regression analysis that adjusted for major risk factors suggested that the DG+VC treatment had no

influence in relation to the death rate or the use of invasive mechanical ventilation (DV vs non-DV groups, 2.2% vs 12.2%; P=0.74, Table 2). However, in the DV group, the new onset incidence rate of acute respiratory distress syndrome (ARDS) after admission was clearly lower than that in the non-DV group (DV vs non-DV groups 15.2% vs 35.7%; P=0.002; odds ratio, 0.19; 95% confidence interval, 0.06-0.5, Table 2). Compared with the non-DV group, the DV group showed fewer new onset of complications (such as ARDS, acute liver injury and acute myocardial injury) (DV vs non-DV groups, 19.6% vs 46.1%; P=0.000; odds ratio, 0.15; 95% confidence interval, 0.05-0.39, Table 2).

Immunologic features

We assessed the immune state including proinflammatory factors (IL-1β, IL-6, IL-8, TNF-α), anti-inflammatory cytokine (IL-10), sIL-2R and the number of immune cells (T cells， B cells， NK cells). All the values were collected from electronic medical records three times or four times with an interval of approximately one week during patients' hospitalization.

The dynamic changes of proinflammatory factors and IL-10 had no difference between DV and non-DV groups. Compared with non-DV patients, the count of NK cells showed better recovery in DV group (DV vs non-DV groups, mean value changed from 275.9/ul to 372.6/ul vs 215.8/ul to 145.3/ul, P=0.03, Table 3) and the sIL-2R level was decreased to reach lower in the DV group after admission (DV vs non-DV groups, mean value fell from 597.7 pg/mL to 349.9 pg/mL vs from 797.6 pg/mL to 572.2 pg/mL, P=0.02, Table 3).

Disscusion

In this single-centre observational study, administration of VC (orally 500 mg 3 times daily) combined with DG (orally 150 mg 3 times daily) treatment was associated with lower incidence of new onset complications including ARDS, acute liver injury and acute myocardial injury in COVID-19 inpatients. Besides, this combined treatment could accommodate immunologic function，including help restore NK cells and decrease the plasma level of sIL-2R. We haven't observed the effect of the combined treatment on either death or requirement for invasive mechanical ventilation.

SARS-CoV-2 was associated with organ dysfunction such as ARDS, acute heart injury, acute kidney injury, shock and acute liver injury， significant cases progressed rapidly to severe forms [21]. It was showed that the patients with SARS-CoV2-associated ARDS had extremely low level of vitamin C. The latest research comprised 18 adult ICU patients COVID-19 who met ARDS

criteria according to the Berlin definition. Vitamin C levels of seventeen patients (94.4%) were undetectable and 1 patient had low levels (2.4 mg/L) [22]. Two therapeutic trials of Vitamin C against COVID-19 were identified. One was an RCT with critically ill COVID-19 patients, finding a dose of intravenous vitamin C of 24 g/day for 7 days could improve the ratio of PaO2/FiO2 over time, decrease the level IL-6 level, prevent worsening disease and reduce mortality. Another one is case series of high-risk COVID-19 patients who were requiring at least 30% of FiO_2 or more. A total of 17 patients were received intravenous vitamin C which was administered at a dose of 1 g every 8 h for 3 days intravenously. It noted a significant decrease in inflammatory markers, including ferritin and D-dimer, and a trend to decreasing FiO2 requirements after vitamin C administration [23].

A recent case report, reporting a case of severe COVID-19 who was failed to relieve under the regular COVID-19 treatment in the hospital but improved overtime after taking VC (orally 200 mg 3 times daily) combined with DG (orally 150 mg 3 times daily) treatment regimen for eight consecutive days [24]. However, the mechanism for the combination treatment remains unclear. A recent bioinformatics analysis predicted that GA and vitamin C (VC) combinatorial treatment for COVID-19 is associated with elevated immunity and suppressed inflammatory stress, including the activation of the T cell receptor signaling pathway, the regulation of Fc gamma R-mediated phagocytosis, the ErbB signaling pathway and the vascular endothelial growth factor signaling pathway [3]. Consistent with this research, another system biology analysis found that combination of Vitamin C, Curcumin and Glycyrrhizic Acid could regulate immune response by acting on NOD-like and Toll-like signaling pathways to promote interferons production, activate and balance T-cells to combat CoV infections and inhibit excessive inflammatory responses by inhibiting PI3K/AKT, NF-κB and MAPK signaling pathways to prevent the onset of cytokine storm[25].Our results implied that DG+VC may influence the level of sIL-2R and help to regulate the inflammatory response. DV+VC also may recover the number of NK cells and enhance immune defenses against COVID-19.

There were several limitations to this work. First, our study was a unicentric retrospective observational study with limited sample size, which reduces the precision of the efficacy estimates. Secondly, data on the monitoring of serum vitamin C and diammonium glycyrrhizinate as well as related metabolites' concentration were unavailable during hospitalization.

In conclusion, we shared preliminary evidence that DG+VC could reduce the incidence of new-onset complications in COVID-19 patients, and might influence the immune response in these patients. Our results suggested that combined treatment of DG +VC might be a low-cost, less side effect promising candidate for preventing the deterioration of COVID-19 patients, awaiting large and perspective cohort to confirm.

Abbreviations

COVID-19: Coronavirus disease 2019 infection； SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; GA: glycyrrhizic acid; VC: vitamin C; DG: Diammonium glycyrrhizinate; CVD: Chronic cardiovascular disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; ALT: glutamic pyruvic transaminase; AST: glutamic oxaloacetic transaminase; LDH: lactate dehydrogenase; T-pro-BNP: T-pro brain natriuretic peptide. *PMS:* Propensity score matching; DV: giammonium glycyrrhizinate and vitamin C

Ethical approval

The study complied with the edicts of the 1975 Declaration of Helsinki and was approved by the principal investigator center, Institutional Review Board of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (No.(2020) Linlun-34th). Informed consent was obtained from all subjects or if subjects are under 16, from a parent and/or legal guardian.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used in this study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no competing interests.

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Authors' contributions

LJL and HPQ contributed to study concept and design. RMT and XGX contributed to the literature

search and writing of the manuscript. RMT, XGX and WGH contributed to the data collection. RMT, XGX, HPQ and LJL contributed to the data analysis and data interpretation. RMT and XGX contributed equally and share first authorship. All authors provided critical revision of the manuscript and approved the final draft for publication.

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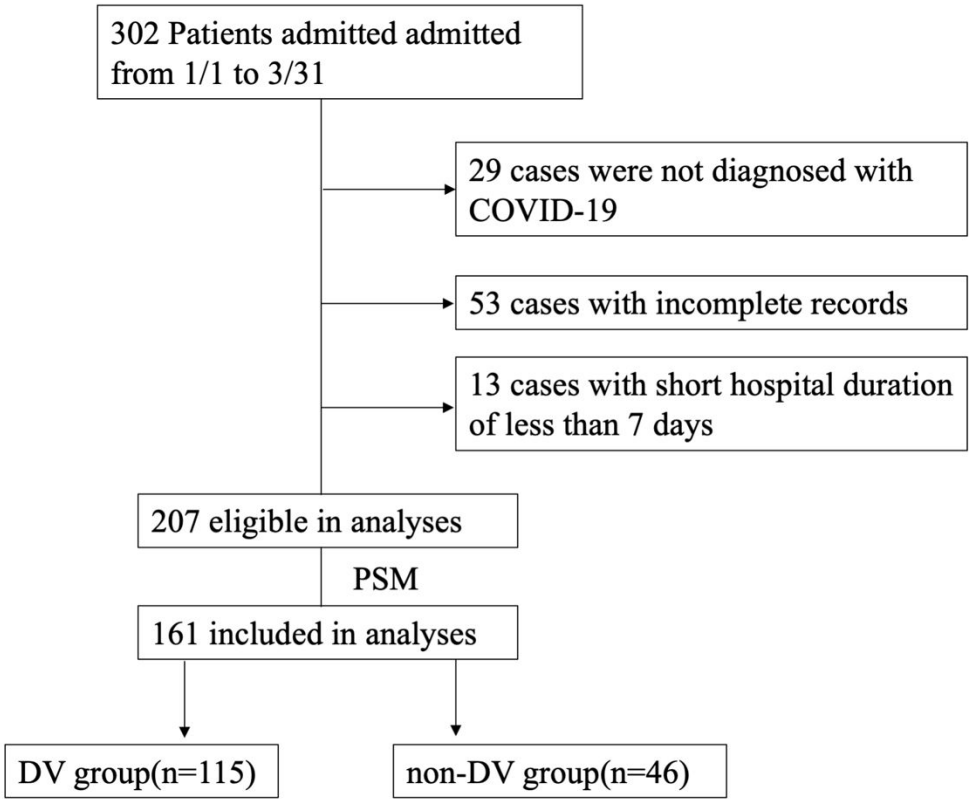

381 Figure1. Flow chart of the study.

382 *COVID-19*: Coronavirus disease 2019 infection; *PMS*: Propensity score matching; *DV*:
383 giammonium glycyrrhizinate and vitamin

384

Table 1. Clinical characteristics between COVID-19 inpatients received DG+VC treatment or not

	Unmatched cohort			**Matched cohort**		
	Clinical characteristics			**Clinical characteristics**		
	non-DV (n=157)	**DV (n=50)**	**P value**	**non-DV (n=115)**	**DV (n=46)**	**P value**
Age, median (IQR),y	63(55-73)	62(48-68)	0.16	62(54-69)	64(54-69)	0.92
Gender-No,%						
Male	78(49.7)	27(54)	0.6	53(46.1)	23(50)	0.65
Female	79(50.3)	23(46)		62(53.9)	23(50)	
Comorbidities- No, %	86(54.8)	33(66.0)	0.16	61(53)	29(63)	0.25
Severity- No, %			0.43			0.31
Moderate	116(73.9)	34(68)		87(75.7)	31(67.4）	
Severe	38(24.2)	15(30)		25(21.7)	14(30.4)	
Critical	3(1.9)	1(2)		3(2.6）	1(2.2)	
Therapy- No, %						
Antiviral therapy	157(100)	50(100)	1	115(100)	46(100)	1
Glucocorticoid therapy	39(24.8)	6(12)	0.06	32(27.8)	4(8.7)	0.008

Infusion of γ-globulin therapy	26(16.6)	6(12)	0.44	19(16.5)	4(8.7)	0.2
Oxygen inhalation	156(99.4)	50(100)	1	114(99.1)	46(100)	1
Mechanical ventilation	14(8.9)	2(4)	0.26	9(7.8)	1(2.2)	0.18
ECMO	2(1.3)	1(2)	0.57	1(0.9)	0(0)	1
CRRT	4(2.5)	0(0)	0.25	3(2.6)	0(0)	0.56
Laboratory tests at admission (IQR)						
Lymphocyte count, 10^9/L	1.14(0.83-1.6)	1.26(0.97-1.7)	0.19	1.2(0.88-1.7)	1.3(0.99-1.7)	0.51
ALT, U/L	31(20-59)	34(19-62)	0.94	32(21.5-63)	30(18-58)	0.39
Creatinine, μmol/L	66(55.5-78)	70.5(56.8-92.5)	0.20	66(55-77.8)	69(55.3-81)	0.59
cTnI, pg/ml	4.4(1.9-13.1)	3.9(2.13-8.8)	0.65	4(1.9-12.8)	4.1(2.1-8.8)	0.98
IL-6, pg/ml	6.6(2.6-31.7)	5.37(3-15)	0.57	6.2(2.4-25.8)	5.9(3.1-17.4)	0.71
LDH, U/L	239(193-317)	251.5(208.3-348)	0.38	239(195-313)	253(206.5-340)	0.4
D-dimer , μg/mL	0.9(0.4-2.2)	1.32(0.47-2.9)	0.42	0.81(0.4-2.5)	1.3(0.52-3)	0.39
Duration of hospital stay , (IQR)	26(15-36)	23(15-36)	0.46	25(14-34)	24(16-36)	0.99
Primary endpoint	20(12.7)	2(4)	0.08	14(12.2)	1(2.2)	0.05
Complications						
ARDS	53(33.8)	8(16)	0.02	41(35.7)	7(15.2)	0.01

Septic shock	11(7)	3(6)	0.81	8(7)	2(4.3)	0.54
Acute liver injury	34(21.7)	7(14)	0.24	28(24.3)	6(13)	0.11
Acute kidney injury	22(14)	8(16)	0.73	17(14.8)	6(13)	0.78
Acute myocardial injury	32(20.4)	6(12)	0.18	21(18.3)	5(10.9)	0.25
Any complications	73(46.5)	10(20)	0.001	53(46.1)	9(19.6)	0.002

Data are presented as the No./total No. (%) and median (IQR). The P values were calculated by Mann-Whitney U test, t test, $\chi 2$ test, or Fisher's exact test. Propensity score matching was performed in the current study.

Table 2. Outcomes among COVID-19 inpatients before and after propensity score matching

	Unmatched cohort				**matched cohort**			
	non-DV (n=157)	**DV (n=50)**	**P value**	**Odds ratio (95% CI)**	**non-DV (n=115)**	**DV (n=46)**	**P value**	**Odds ratio (95% CI)**
Primary endpoint								
death or requiring invasive mechanical ventilation	20(12.7)	2(4)	0.24	0.37(0.05-1.66)	14(12.2)	1(2.2)	0.74	0.73(0.09-4.1)
Secondary endpoint								
Complications								
ARDS	53(33.8)	8(16)	0.01	0.32(0.12-0.76)	41(35.7)	7(15.2)	0.002	0.19(0.06-0.5)

Septic shock	11(7)	3(6)	0.74	0.73(0.09-4.1)	8(7)	2(4.3)	0.96	1.04(0.2-4.4)
Acute liver injury	34(21.7)	7(14)	0.25	0.58(0.21-1.4)	28(24.3)	6(13)	0.17	0.5(0.17-1.28)
Acute kidney injury	22(14)	8(16)	0.68	1.26(0.41-3.63)	17(14.8)	6(13)	0.95	1.04(0.3-3.31)
Acute myocardial injury	32(20.4)	6(12)	0.53	0.71(0.22-1.99)	21(18.3)	5(10.9)	0.3	0.53(0.15-1.7)
Any complications	73(46.5)	10(20)	0	0.17(0.06-0.42)	53(46.1)	9(19.6)	0	0.15(0.05-0.39)

Data are presented as the No./total No. (%) and median (IQR). The P values were calculated by multivariate regression analysis. Propensity score matching was performed in the current study.

Table 3. Dynamic changes in the laboratory tests of COVID-19 inpatients who received DG+VC treatment or not after propensity score matching

Laboratory tests	Group	1st	2nd	3rd	4th	P value
T cells,/ul	non-DV	1542.6±2131.8	983.1±559.3	615.3±390.4	-	0.4
	DV	1143.1±382.7	1186.2±358	1362±395.6	-	
B cells,/ul	non-DV	222.8±126.4	198.5±133	141±95.2	-	0.15
	DV	173.4±89.3	188.9±114.7	180.5±88.2	-	
NK,/ul	non-DV	215.8±155.2	211.8±169.4	145.3±154.1	-	0.03
	DV	275.9±187.1	305.5±212.3	372.6±196.6	-	
IL-1β, pg/mL	non-DV	6±5.2	6.6±5.8	5.9±2.9	5.2±0.9	0.49
	DV	6.6±4.5	7±6.9	6.7±5.5	7.3±8.9	
TNF-α, pg/mL	non-DV	8.9±4	13.1±26.6	8.6±5.6	9.4±3	0.93
	DV	10.8±9.1	8.7±4.1	9.6±5.8	12.7±13.3	
IL-6, pg/mL	non-DV	20±29.2	93.7±599.4	39.3±190.5	9.1±17.3	0.21
	DV	21.2±69.8	14.9±43.6	6.9±11.5	5.3±5.1	
IL-10, pg/mL	non-DV	7.1±9	26.2±116.3	8.3±13.2	6.9±6.1	0.06
	DV	5.2±0.8	5.1±0.5	5.1±0.5	5±0	
sIL-2R, pg/mL	non-DV	797.6±1149.7	715.3±710.5	648±982.8	572.2±283	0.02
	DV	597.7±383.9	477.4±309.8	447.4±292.4	349.9±208.3	

Data are presented as the mean ± SD. A generalized estimation equation approach was adopted to perform a comparison of the dynamic changes in laboratory tests

among patients who received treatment or those who did not. All the values were collected from electronic medical records three times or four times with an interval of approximately one week. Propensity score matching was performed in the current study.

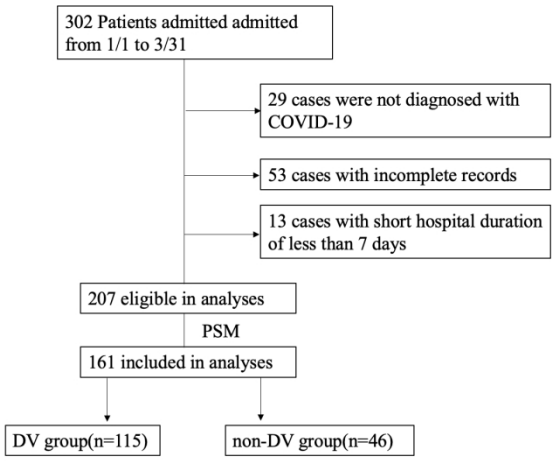

Figure1. Flow chart of the study.
COVID-19: Coronavirus disease 2019 infection; PMS: Propensity score matching; DV: giammonium glycyrrhizinate and vitamin C

338x190mm (150 x 150 DPI)

Table 1. Clinical characteristics between COVID-19 inpatients received DG+VC treatment or not

	Unmatched cohort			**Matched cohort**		
	Clinical characteristics			**Clinical characteristics**		
	non-DV (n=157)	**DV (n=50)**	**P value**	**non-DV (n=115)**	**DV (n=46)**	**P value**
Age, median (IQR),y	63(55-73)	62(48-68)	0.16	62(54-69)	64(54-69)	0.92
Gender-No,%						
Male	78(49.7)	27(54)	0.6	53(46.1)	23(50)	0.65
Female	79(50.3)	23(46)		62(53.9)	23(50)	
Comorbidities- No, %	86(54.8)	33(66.0)	0.16	61(53)	29(63)	0.25
Severity- No, %			0.43			0.31
Moderate	116(73.9)	34(68)		87(75.7)	31(67.4)	
Severe	38(24.2)	15(30)		25(21.7)	14(30.4)	
Critical	3(1.9)	1(2)		3(2.6)	1(2.2)	
Therapy- No, %						
Antiviral therapy	157(100)	50(100)	1	115(100)	46(100)	1
Glucocorticoid therapy	39(24.8)	6(12)	0.06	32(27.8)	4(8.7)	0.008

Infusion of γ-globulin therapy	26(16.6)	6(12)	0.44	19(16.5)	4(8.7)	0.2
Oxygen inhalation	156(99.4)	50(100)	1	114(99.1)	46(100)	1
Mechanical ventilation	14(8.9)	2(4)	0.26	9(7.8)	1(2.2)	0.18
ECMO	2(1.3)	1(2)	0.57	1(0.9)	0(0)	1
CRRT	4(2.5)	0(0)	0.25	3(2.6)	0(0)	0.56
Laboratory tests at admission (IQR)						
Lymphocyte count, 10^9/L	1.14(0.83-1.6)	1.26(0.97-1.7)	0.19	1.2(0.88-1.7)	1.3(0.99-1.7)	0.51
ALT, U/L	31(20-59)	34(19-62)	0.94	32(21.5-63)	30(18-58)	0.39
Creatinine, μmol/L	66(55.5-78)	70.5(56.8-92.5)	0.20	66(55-77.8)	69(55.3-81)	0.59
cTnI, pg/ml	4.4(1.9-13.1)	3.9(2.13-8.8)	0.65	4(1.9-12.8)	4.1(2.1-8.8)	0.98
IL-6, pg/ml	6.6(2.6-31.7)	5.37(3-15)	0.57	6.2(2.4-25.8)	5.9(3.1-17.4)	0.71
LDH, U/L	239(193-317)	251.5(208.3-348)	0.38	239(195-313)	253(206.5-340)	0.4
D-dimer , μg/mL	0.9(0.4-2.2)	1.32(0.47-2.9)	0.42	0.81(0.4-2.5)	1.3(0.52-3)	0.39
Duration of hospital stay , (IQR)	26(15-36)	23(15-36)	0.46	25(14-34)	24(16-36)	0.99
Primary endpoint	20(12.7)	2(4)	0.08	14(12.2)	1(2.2)	0.05
Complications						
ARDS	53(33.8)	8(16)	0.02	41(35.7)	7(15.2)	0.01

Septic shock	11(7)	3(6)	0.81	8(7)	2(4.3)	0.54
Acute liver injury	34(21.7)	7(14)	0.24	28(24.3)	6(13)	0.11
Acute kidney injury	22(14)	8(16)	0.73	17(14.8)	6(13)	0.78
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