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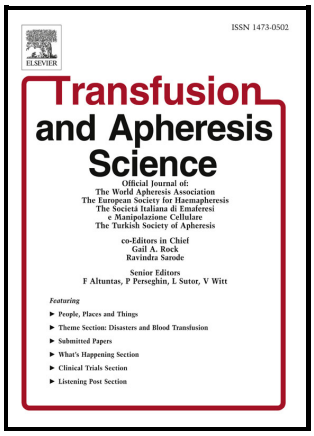

The safety of plasma apheresis from donors recovering from COVID-19 infection in Japan

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Title: The safety of plasma apheresis from donors recovering from COVID-19 infection in Japan.

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Abstract: Purpose: Since 2020, the novel coronavirus infection (COVID-19) has spread globally. A few studies have investigated the safety of COVID-19 convalescent plasma (CCP) apheresis from COVID-19. This study was the first retrospective observational study of CCP in Japan. Methods: We recruit donors

from April 2020 to November 2021 and plasmapheresis in our center (NCGM: national center for global health and medicine). We set the primary endpoint as the Donors Adverse Event (DAE) occurrence at the time of the CCP collection. Variable selection was used to explore the determinants of DAE. Results: Mean and SD age was 50.5 (10.6) years old. Seventy-three (42.2%) were female, and 87 (33.3%) were multiple-times donors. Twelve (6.97% by donors and 4.6% in total collections) adverse events occurred. The DAEs were VVR (Vaso Vagal Reaction), paresthesia, hypotension, agitation, dizziness, malaise, and hearing impairment/paresthesia. Half of them were VVR during apheresis. DAE occurred only in first-time donors and more in severe illnesses such as using ventilation and ECMO. From the donor characteristics and variable selection, the risk factors are as follows: younger age, female, the severity of disease at the time of the disease, and lower SBP before initiation. Our DAE incidence did not differ from previous studies. DAEs were more likely to occur in CCP apheresis than in healthy donors. Conclusion: We confirm the safety of CCP apheresis in this study, although DAEs were more than healthy donors. More caution should be exercised in the plasma collection for future outbreaks of emerging infectious diseases.

Keywords: COVID-19 infection, convalescent plasma, apheresis, donors' adverse event

1. Introduction

The novel coronavirus, SARS-CoV-2, that began spreading in Wuhan, Hubei Province, China by the end of December 2019, has spread worldwide and further outbreaks were observed globally, including in Japan. Although vaccination against coronavirus disease 19 (COVID-19) was introduced in late 2020, COVID-19 remains a global threat. Whilst a variety of therapeutic agents against COVID-19 exist, only a few are effective [1].

Convalescent plasma therapy uses plasma from individuals who have recovered from certain diseases and have neutralizing antibodies against the infection. Convalescent plasma therapy is thought to be effective against COVID-19 when the plasma is obtained from individuals who had infections during the primary outbreak since it takes two to three years to produce high-titer

immunoglobulin levels for emerging infectious diseases. An Italian group reported insufficient efficacy of COVID-19 convalescent plasma (CCP) for immunocompetent patients with hematological malignancies [2]. However, convalescent plasma therapy is a well-known therapeutic option that has been used for several infectious diseases, such as the Spanish flu and, in recent years, Severe Acute Respiratory Syndrome (SARS) [3] and Middle East Respiratory Syndrome [4].

Adverse events during apheresis are estimated to be 7.96% in first-time healthy donors [5]. Worldwide, a few studies have investigated the safety of apheresis using donors who have recovered from COVID-19. The total incidence of Donors Adverse Events (DAEs) was 2.58% (n=504) in an Italian study [6], 13.7% (n=14272) in a recent study by the American Red Cross [7], and 3.77% (n=37174) in a U.S. multicenter study [8]. Some studies also reported cardiovascular complications, such as arrhythmia [9].

In Japan, the collection of convalescent plasma is the first step of collecting plasma from donors recovering from infectious diseases. However, no Japanese data is available concerning DAEs, including cardiovascular events, of COVID-19 convalescent plasma (CCP) apheresis from donors recovering from COVID-19. Hence, this retrospective, observational study, aimed to evaluate the safety of CCP collection from donors who had recovered from COVID-19 and were identified as eligible for the "Collection and antibody measurement of convalescent

plasma foreseeing the use for COVID-19 treatment" conducted at the National Center for Global Health and Medicine (NCGM). We report the safety of CCP collection at the NCGM.

2. Methods

We recruited participants, including the patients hospitalized at NCGM, through the "Collection and antibody measurement of convalescent plasma foreseeing the use for COVID-19 treatment" conducted at the NCGM. Donors selection was described in Terada M et al. [10]. The first protocol was previously published [10], and the revised protocol (March 31, 2021) is shown in supplemental data 1. Qualified participants were divided into two groups: those who had their CCP collected at our center and those at the Japanese Red Cross Society. A total of 1,300 participants were enrolled from April 2020 to November 2021; 456 of them were eligible. Of these, 283 were referred to the Japanese Red Cross Society, 173 had their plasma collected at the NCGM, and 261 participants underwent more than one CCP collection. One participant who underwent two CCP collections was excluded as they were receiving contraindicated medications (Figure 1). The primary endpoint was the occurrence of DAEs at the time of CCP collection. Secondary endpoints were the characteristics of each DAE.

This study was conducted in accordance with the ethical principles described in the Declaration of Helsinki. The Ethics Committee at the NCGM approved the study protocol.

Informed consent was obtained from the donors.

2.1. CCP collection

CCP collection was performed under the observation of a physician, a nurse, and a clinical engineer. We used the plasma component separator (Spectra Optia® by Terumo BCT or COM.TEC® by Fresenius Kabi) based on the donors' vessel condition. The physician rechecked the criteria and obtained informed consent before CCP collection. The qualified participants were then administered 400 mg of calcium gluconate to prevent hypocalcemia and were also recommended to take fluids. The volume of plasma collected was 300–600 ml [10] (supplemental data 1), which was approximately 25% of the extracorporeal circulating blood volume. We checked the aggravating symptoms and the vital signs (blood pressure, heart rate, and SpO_2) and monitored the electrocardiogram (ECG) every 10 minutes during the apheresis. We took the utmost care to make the apheresis as relaxing as possible. After completing the apheresis, the donors were monitored for 30 minutes and returned home after confirmation that there was no change in their physical condition. Any participant with a change in their physical condition was called in and recorded as a DAE.

2.2. Data Sources

We used the electronic CCP donor information from the "Collection and antibody measurement of convalescent plasma foreseeing the use for COVID-19 treatment". Donor weights were recorded before collection and vital signs during the procedure. DAEs were classified according to the criteria specified by the Surveillance of Complications Related to Blood Donation (SSCRBD) [11]. In addition, the details of DAEs were classified by Hemovigilance [12], and Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [13] at the discretion of the physician. Hypertension was identified from the medical treatment. The participants' smoking history was classified based on the Japanese Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Heart Disease 2017 [14]. The body mass index (BMI) was classified according to the Obesity Treatment Guidelines 2016 by the Japan Society for the Study of Obesity [15].

2.3. Statistical Analyses

Continuous variables were expressed as means with standard deviation (SD) and categorical variables as frequencies and percentages. The Wilcoxon rank-sum tests were used to compare the continuous variables, and Fisher's exact test was used to compare the categorical variables. Sensitivity analysis was performed for all cases including the repeat donors. Univariable and multivariable analyses of the primary and secondary endpoints were performed using logistic

regression analysis, in which goodness of fit was evaluated by the Hosmer-Lemeshow test and the area under the Receiver Operating Characteristic (ROC) curve. The items with missing values of 10 or more were removed from the multivariable analysis, and the variables with a *P*-value of 0.2 or more in the univariable analysis were removed from the stepwise variable selection procedure. A variable selection was performed to achieve the minimum AIC (Akaike's Information Criterion) with backward elimination. Once BMI was included for variable selection, height and weight were excluded from the procedure. A two-sided *P*-value<0.05 was considered to be statistically significant. All the statistical analyses were conducted using R Version 4.1.2 (R Foundation for Statistical Computing, Vienna, http://www.R-project.org/).

3. Results

3.1. Donor characteristics

The clinical characteristics and DAEs summarized in Table 1 and Table S1. Table 1 shows the data of CCP donors (173 donors), and Table S1 shows that of total CCP donations (260 cases). The characteristics of CCP donors were as follows. The mean age (SD) was 50.5 years (10.6), and 42.2% of donors were female. The median height and body weight were 166.4 (9.0) cm and 70.5 (15.1) kg. The median BMI was 25.3 (4.2). The number of donors with respiration/extracorporeal membrane oxygenation (ECMO) was 13 (7.5%), 50 (28.9%) with

oxygen, and 110 (63.6%) without oxygen during the COVID-19 infection. Among those that we could confirm, 57 (93.4%) donors had previously donated blood and 4 were first-time donors. Most previous donations were whole blood donations, not apheresis. Fifty-two (20.1%) donors had a history of hypertension. The number of nonsmokers, current smokers, and past smokers was 99 (63.1%), 12 (7.6%), and 46 (29.3%), respectively. The number of donors with respiratory distress was 25 (15.6%). The mean interval between donation and symptom resolution was 108.3 (78.3) days.

The donor characteristics based on 260 CCP donations were as follows. Eighty-seven donors (50.3%) had multiple CCP collections with a median of 1.8 (1.5). Of the female participants, 21.8% were multiple-time donors. Nineteen participants (11.0%) donated three times or more, and the maximum number of donations by an individual was ten.

3.2. Apheresis

The first-time CCP apheresis parameters and DAEs are shown in Table 2. The mean required time for apheresis, collected volume, throughput volume, and volume of Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A) used, were 41.8 (12.6) minutes, 463.6 (82.6) mL, 2010 (710) mL, and 184.5 (70.8) mL, respectively. DAEs following CCP collection only occurred in donors who had not previously donated blood. DAEs were significantly related to the longer

time required for apheresis, collected volume, and throughput volume. However, there were no statistically significant differences between grade 1 and 2 DAEs.

We used two types of apheresis machines: 48 donors used the Spectra Optia (17.7%) and 125 donors used the COM.TEC (72.3%). The frequency of DAEs was higher in the Spectra Optia group, though insignificant. The number of grade 2 DAEs was significantly higher in the Spectra Optia group than in the COM.TEC group.

Details of the apheresis and adverse events in 260 cases are shown in Table S2. DAEs did not occur in the second or later rounds of apheresis.

3.3. Apheresis-related vital signs

Apheresis-related vital signs in first-time CCP donors are shown in Table 3. The mean systolic blood pressure (sBP) at the start of apheresis (baseline) was 149.0 (21.8) mmHg. The median baseline heart rate (HR) was 72.8 (10.8) bpm and SpO_2 was 97.6 (1.2) %. There were no variations in sBP, HR, and SpO_2 after needle puncture and during apheresis. The absolute value of the sBP variation was significantly lower in the DAEs group from baseline, but not significant when compared with grade 2 cases. Apheresis-related events are shown in Table S3.

3.4. DAEs

The details of the DAEs as a primary endpoint are shown in Table 4. There were 12 adverse reactions, four occurred during and eight after apheresis. Half of the DAEs were vasovagal reactions (VVR) with or without a decrease in blood pressure during apheresis. VVR was also seen in three cases after apheresis. Although three of six donors with VVR needed an infusion of saline, all participants rapidly recovered. The other cases of DAEs were grade 1 SSCRBD [11] and CTCAE 5.0 [13] criteria, except for three replenishment cases. Mild DAEs were paresthesia during apheresis, two incidences of malaise, and one each of agitation, dizziness, and hearing impairment/paresthesia after apheresis. All the DAEs improved within hours from onset.

3.5. Intentional difference

Sensitivity analyses were performed for all 178 donors and 260 cases, including the repeated donors. Some factors were significantly associated with DAEs (Table 5.1). However, there were no significant changes in all cases (Table 5.2). The factors associated with worse DAEs were female sex, the time interval between donation and symptom resolution, apheresis parameters, and baseline blood pressure. DAEs were seen more frequently in female donors (12.3%) than in males (3.0%, P=0.030). The mean time from donation to symptom improvement was 141.3 days in the DAEs group compared with 105.9 days in the non-DAEs group (P=0.044). The same

trend was seen for grade 2 DAEs.

The significantly worse apheresis parameters were more required time (P=0.010), a higher collected volume (P=0.027), and a higher volume of ACD-A used (P=0.015). Interestingly, significant differences were found between the grade 2 DAEs and non-grade 2 DAEs groups for the equipment used (P=0.020).

In addition, there was a significant difference in baseline sBP between the DAEs and non-DAEs groups (P=0.048) and a significant difference between the grade 2 DAEs and non-grade 2 groups regarding the change in sBP (P=0.005).

3.6. Variable selection for multivariable analysis

The univariable and the multivariable analysis of the DAEs are listed in Table 6. The factors of the variable selection were females, age, time to donation, equipment, baseline SpO_2, and degree of disease severity. In the same order, respiration use with or without ECMO, oxygen, and no oxygen during illness was related to DAEs, respectively. As shown in Figure 2, the ROC curve analysis showed that the area under the curve for the selected model was 0.868 (0.756–0.912), and the Hosmer-Lemeshow goodness of fit test showed P=0.552. These findings revealed the good fit of the selected model. We tried variable selection with possible patterns of DAE classification, such as grade 2 and VVR, but variables were only selected with and without

DAEs.

4. Discussion

We assessed the safety profiles during apheresis using CCP donors in this study. We never performed apheresis on non-healthy donors, although this is widely practiced worldwide. The collection of CCP was discussed on the practice and challenges at the International forum [16]. Therefore, we summarized the data and experience for future emerging infections and recommend starting CCP therapy quickly.

The incidence of DAEs was 6.94% among donors, and almost all donors underwent CCP plasmapheresis for the first time. The DAEs were reported to be 7.96% in first-time healthy donors compared with 1.01% in repeat donors for plasmapheresis in the U.S. [7]. Another study reported that the incidence of DAEs in first-time CCP donors was 5.00–5.59%, 1.79–2.50-fold higher than in repeat CCP donors [7, 8]. We also analyzed the CCP collection incidence compared to previous reports in other countries (Table 7 and Table 8) [6, 7]. Total DAEs were not significantly different from previous reports. We confirmed the same tendencies in the CCP collection incidence against another country. Moreover, we compared CPP collection by donor attributions. The incidence of DAEs during CCP apheresis was significantly higher in donors who had severe disease than in healthy donors in Japan and the U.S., according to Donor

HART™: 2014-2017 data, which reports the data of the healthy donors for plasma collection in the U.S. [8] (Table 9). No other details were available from the respective literature, but no significant differences were found concerning the main items. We confirmed that the results were generally the same as those of other countries. In addition, as in previous U.S. studies, the incidence of DAEs was significantly higher in donors with severe disease than in healthy donors. This suggests that more caution should be exercised when collecting CCP.

Variable selection showed that donors who were on oxygen or ventilator/ECMO were more likely to develop a DAE than donors who did not require oxygen at the time of illness. The total incidence of DAEs was 7.70% in the respiration or ECMO group, 8.00% in the oxygen group, and 6.36% in the no-oxygen group. However, the incidence of grade 2 DAEs was 7.70%, 2.00%, and 0.91%, respectively. To the best of our knowledge, these aspects have not previously been reported in the literature on CCP apheresis. Therefore, our study is the first to report these findings. Since we confirmed that the baseline SpO_2 was ≥96% before the start of the study, we established recovered pneumonia during COVID-19 infection at the apheresis. Despite recovering from pneumonia, these data suggest that patients requiring respiratory support due to the severity of the illness might be related to the presence of the DAEs following CCP apheresis.

In this study, females were significantly more likely to have a DAE compared with males, which was consistent with a previous study on healthy donors [17]. In addition, variable selection showed that younger age could be a factor concerning DAEs, as reported in a previous study [17]. Unexpectedly, DAEs occurred significantly more often in the longer time required for the apheresis group (141.3 vs. 105.9 days, P=0.044) from donation to symptom improvement. One of the reasons for this might be the period of this study. This study was conducted in the early phase of the COVID-19 outbreak, from April 2020 to November 2021. At the time, there was no standard therapy for COVID-19, therefore, this option was explored by physicians. Moreover, since it was mandatory to stay in a hospital or a hotel, the donors might be physically weak.

Baseline sBP was significantly different between DAE and non-DAE groups. A similar trend was observed for the grade 2 and non-grade 2 groups, although insignificant, which might be due to the small sample size. DAEs are less likely to occur in the higher blood pressure group. However, the criteria for sBP at the beginning of apheresis were the same as for healthy donor donation, and we do not foresee any problems. During the apheresis, there was a significant decrease in the sBP in those in the grade 2 group, which suggested the need for supplemental fluids for donors in the grade 2 group. The change in blood pressure was not validated in other

studies. Although blood pressure reduction was observed, the current results showed no difference in HR or SpO_2. We also analyzed atherosclerosis factors, such as hypertension or smoking history. There were no significant complications in this study. A possible explanation is that cardiac function was assessed adequately using an ECG and echocardiography during the screening phase, which suggests the importance of prior evaluation of cardiac function.

We used two types of collection machines (Spectra Optia and COM.TEC) in this study. Grade 2 DAEs occurred significantly more often when Spectra Optia was used. The sampling volume, sampling rate, and throughput were not significantly different in both settings. The same was true for variable selection. A possible explanation for this is yet to be determined. The device selection is similar to the univariate analysis, and we did not see any influencing factors.

There are some limitations in this study. First, our sample size was small; therefore, the DAE incidence is difficult to generalize among other studies [6, 7, 8] investigating CCP donors. Second, the participants were not all volunteers in this study. Some of them were asked to participate, unlike the regular blood donors. In addition, our medical staff always checked ECG monitors and vital signs during apheresis for each donor. Finally, apheresis is different from the usual blood donation environment, which may have contributed to some stress among the

donors.

5. Conclusions

This study is the first to report convalescent plasma collection in Japan. We evaluated the safety of plasma collection from donors who had recovered from COVID-19. The incidence of DAEs was 6.94% which was significantly higher in donors with severe disease than in healthy donors. However, we confirm the safety and characteristics of DAEs during CCP apheresis. It is necessary to prepare for future outbreaks of emerging infectious diseases.

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Compliance with Ethics Guidelines

This study was approved by the ethics committee of the National Center for Global Health and Medicine (NCGM) (approval no: NCGM-G-003536-08) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the participants.

Declaration of interest

None

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Table 1 Demographic and clinical characteristics and adverse events of CCP donors

	All CCP donors (N=173)	DAE (N=12)	Non-DAE (N=161)	p-value	DAE Grade 2 (N=3)	Non-Grade 2 (N=170)	p-value

Age	50.5 (10.6)	46.8 (12.6)	50.7 (10.4)	0.260	51.3 (8.5)	50.4 (10.6)	0.977
Generation, n (%)							
20s	6 (3.5)	1 (8.3)	5 (3.1)		0 (0.0)	6 (3.5)	
30s	22 (12.7)	2 (16.7)	20 (12.4)		0 (0.0)	22 (12.9)	
40s	48 (27.7)	5 (41.7)	43 (26.7)	0.151	2 (66.7)	46 (27.1)	0.480
50s	61 (35.3)	1 (8.3)	60 (37.3)		0 (0.0)	61 (35.9)	
60s	36 (20.8)	3 (25.0)	33 (20.5)		1 (33.3)	35 (20.6)	
Sex Female, n (%)	73 (42.2)	9 (75.0)	64 (39.8)	0.030	2 (75.0)	71 (41.8)	0.574
Body height (cm)	166.4 (9.0)	162.0 (6.3)	166.7 (9.1)	0.055	166.5 (9.0)	165.8 (5.7)	0.114
Body weight (kg)	70.5 (15.1)	65.5 (8.2)	70.8 (15.5)	0.270	68.4 (9.4)	70.5 (15.2)	0.921
Blood type, n (%)							
A	74 (42.8)	4 (33.3)	70 (43.5)		1 (33.3)	73 (42.9)	
B	38 (21.9)	4 (33.3)	34 (21.1)		0 (0.0)	38 (22.4)	
AB	21 (12.1)	1 (8.3)	20 (12.4)	0.755	1 (33.3)	20 (11.8)	0.543
O	40 (23.1)	3 (25.0)	37 (23.0)		1 (33.3)	39 (22.9)	
BMI	25.3 (4.2)	25.0 (3.3)	25.3 (4.3)	0.933	27.2 (2.6)	25.3 (4.3)	0.229
Low body weight, n (%)	4 (2.3)	0 (0.0)	4 (2.5)		0 (0.0)	4 (2.4)	
Normal weight, n (%)	93 (53.8)	6 (50.0)	87 (54.0)		1 (33.3)	92 (54.1)	
obesity1, n (%)	53 (30.6)	5 (41.7)	48 (29.8)	0.903	2 (66.7)	51 (30.0)	0.580
obesity2, n (%)	19 (11.0)	1 (8.3)	18 (11.2)		0 (0.0)	19 (11.2)	
obesity3, n (%)	3 (1.7)	0 (0.0)	3 (1.9)		0 (0.0)	3 (1.8)	
obesity4, n (%)	1 (0.6)	0 (0.0)	1 (0.6)		0 (0.0)	1 (0.6)	
Degree of severity of disease, n (%)							
Non-oxygen	110 (63.6)	7 (58.3)	103 (64.0)	0.897	1	109 (64.1)	0.141

					(33.3)		
Oxygen	50 (28.9)	4 (33.3)	46 (28.6)		1 (33.3)	49 (28.8)	
Respiration/ECMO	13 (7.5)	1 (8.3)	12 (7.5)		1 (33.3)	12 (7.1)	
Time interval between symptom resolution and donation(days)							
	108.3 (78.3)	141.3 (72.2)	105.9 (78.4)	0.044	150.3 (74.4)	107.6 (578.4)	0.172
Previous blood donation experience n (%)							
First-time donation donor	4 (6.6)	1 (11.1)	3 (5.8)		0 (0.0)	4 (6.8)	
Experienced donation donor	57 (93.4)	8 (88.9)	49 (94.2)	0.481	2 (100.0)	55 (93.2)	1.000
Diagnose of Hight blood pressure, n (%)							
Yes	35 (20.2)	0 (0.0)	35 (21.7)	0.128	0 (0.0)	35 (20.6)	1.000
Smoking experience, n (%)							
Never	99 (63.1)	7 (63.6)	92 (63.0)		1 (33.3)	98 (63.6)	
current smoker	12 (7.6)	0 (0.0)	12 (8.2)	0.788	0 (0.0)	12 (7.8)	0.399
past smoker	46 (29.3)	4 (36.4)	42 (28.8)		2 (66.7)	44 (28.6)	
Respiratory distress remaining, n (%)							
Yes	25 (15.6)	2 (16.7)	23 (15.5)	1.00	1 (33.3)	24 (15.3)	0.401

The classification is as follows: underweight with BMI < 18.5, normal range with 18.5 18.5 ≤ BMI < 25, obesity 1 with 25 ≤ B.M. <30, obesity 2 with 30 ≤ B.M. <35, obesity 3 with 35 ≤ BMI<40, and obesity 4 with 40 ≤ BMI.

Table 2 First time CCP donors Apheresis details and DAE

	Number of donors (N=173)	DAE (N=12)	Non-DAE (N=161)	p-value	DAE Grade2 (N=3)	Non-Grade2 (N=170)	p-value
Required time	38.0 (33.0,	50.0 (39.0, 56.3)	38.0 (33.0, 46.0)	0.010	56.0 (47.5, 64.0)	38.0	0.086

(min)	48.0)					(33.0, 47.8)	
Collected amount (ml)	463.6 (463.6, 519.2)	514.1 (486.1, 609.0)	463.6 (463.6,509.9)	0.101	509.0 (429.5, 559.0)	463.6 (463.6, 519.2)	0.882
Throughput (ml)	1834 (1515, 2343)	2486 (1791.8, 2629.8)	1827 (1474.0, 2309.0)	0.027	2593 (2134.0, 3171.5)	1833 (1503.8, 2342.0)	0.168
Used ACD-A liquid volume (ml)							
	164.0 (133.0, 221.0)	229.0 (172.3, 260.5)	160.0 (130.0, 216.0)	0.015	262.0 (219.0, 317.0)	163.0 (132.2, 219.0)	0.068
Used equipment, n (%)							
Spectra Optia	48 (17.7)	6 (50.0)	42 (26.1)	0.095	3 (100.0)	45 (26.5)	0.020
COM.TEC	125 (72.3)	6 (50.0)	119 (74.0)		0 (0.0)	125 (73.5)	

Table 3 First time CCP donors apheresis related event and DAE

	Number of donors (N=173)	DAE (N=12)	Non-DAE (N=161)	p-value	DAE Grade2 (N=3)	Non-Grade2 (N=170)	p-value
Baseline sBP(mmHg)	150.0 (133.0, 163.0)	132.5 (124.2, 149.5)	150.0 (134.0, 164.0)	0.048	130 (127.5, 135.5)	150.0 (133.3, 163.8)	0.114
Baseline HR(bpm)	71.0 (65.0, 80.0)	72.5 (68.5, 78.5)	72.0 (65.0, 80.0)	0.637	69.0 (64.0, 78.0)	72.0 (65.3, 79.8)	0.736
Baseline SpO_2(%)	98.0 (97.0, 98.0)	97.5 (97.0, 98.0)	98.0 (97.0 ,98.3)	0.736	97.0 (96.5, 97.0)	98.0 (97.0, 98.0)	0.136
After puncture variation from baseline							
sBP (mmHg)	0.0 (-7.0, 5.0)	-1.0 (-8.3, 1.0)	0.0 (-7.0, 6.0)	0.432	-1.0 (-7.0, -1.0)	0.0 (-7.0, 5.8)	0.334
HR (BPM)	-2.0 (-6.0, 1.0)	0.0 (-6.5, 1.3)	-3.0 (-6.0, 0.0)	0.881	0.0 (-7.0, 1.0)	-2.5 (-6.0, 1.0)	0.991

SpO_2 (%)	0.0 (0.0, 1.0)	0.0 (0.0, 0.3)	0.0 (0.0, 1.0)	0.577	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.400
Change from baseline to end of Apheresi							
sBP (mmHg)	-14.0 (-22.0, -6.0)	-20.0 (-30.3, -13.8)	-14.0 (-20.0, -5.0)	0.059	-55.0 (-57.5, -47.5)	-14.0 (-20.8, -6.0)	0.005
HR (BPM)	-6.0 (-9.0, -1.0)	-6.0 (-6.5, -4.0)	-5.0 (-9.0, -1.0)	0.756	-6.0 (-10.0, -3.5)	-5.0 (-9.0, -1.0)	0.696
SpO_2 (%)	-1.0 (-1.0, 0.0)	-1.0 (-2.0, -1.0)	-1.0 (-1.0, 0.0)	0.132	-1.0 (-1.5, -0.5)	-1.0 (-1.0, -0.0)	0.754

sBP: systolic blood pressure, PR: pulse rate

Table 2 DAE details

Expression period	Details of Adverse Events	fall in blood pressure	replenishment	return to origin	evaluation		
					SSCRBD Grade	JRCS	CTCAE5.0 Grade
During apheresis	Paresthesia	−	−	improvement	1	−	1
During apheresis	VVR hypotension	+	+	improvement	2	minor	3
During apheresis	VVR hypotension	+	−	improvement	1	minor	1
During apheresis	VVR hypotension	+	+	improvement	2	minor	3
Post-apheresis	Agitation	−	−	improvement	1	−	1
Post-apheresis	Dizziness	−	−	improvement	1	minor	1
Post-apheresis	Malaise	−	−	improvement	1	minor	1
Post-apheresis	Malaise	−	−	improvement	1	minor	1
Post-	Hearing	−	−	improvement	1	minor	1

apheresis	impaired/Paresthesia						
Post-apheresis	Vasovagal reaction	−	−	improvement	1	minor	1
Post-apheresis	Vasovagal reaction	−	−	improvement	1	minor	1
Post-apheresis	VVR hypotension	+	+	improvement	2	minor	3

Table 5-1 Demographic Characteristics of CCP Donors and Sensitivity Analysis of All 260 Cases (DAE and non-DAE group)

	All CCP donors (N=173)	DAE (N=12)	Non-DAE (N=161)	p-value	All 260 cases (N=260)	DAE (N=12)	Non-DAE (N=248)	p-value
Age	52.0 (44.0, 59.0)	47.5 (39.8, 55.8)	52.0 (45.0, 59.0)	0.260	52.5 (45.0, 59.3)	47.5 (39.8, 55.8)	53 (46.0, 59.3)	0.127
Generation, n (%)								
20s	6 (3.5)	1 (8.3)	5 (3.1)		7 (2.7)	1 (8.3)	6 (2.4)	
30s	22 (12.7)	2 (16.7)	20 (12.4)		27 (10.4)	2 (16.7)	25 (10.1)	
40s	48 (27.7)	5 (41.7)	43 (26.7)	0.151	67 (25.7)	5 (41.7)	62 (25.0)	0.088
50s	61 (35.3)	1 (8.3)	60 (37.3)		94 (36.2)	1 (8.3)	93 (37.5)	
60s	36 (20.8)	3 (25.0)	33 (20.5)		65 (25.0)	3 (25.0)	62 (25.0)	
Sex Female, n (%)	73 (42.2)	9 (75.0)	64 (39.8)	0.030	100 (38.5)	9 (75.0)	103 (36.7)	0.012
Body height (cm)	165.5 (159.9,173.1)	161.0 (157.8, 164.8)	166.7 (160.0, 174.0)	0.055	165.8 (159.5, 173.9)	161.0 (157.8, 164.8)	166.9 (159.8, 173.9)	0.051
Body weight (kg)	68.7 (60.3, 77.8)	63.3 (61.8, 67.5)	69.3 (59.9, 78.2)	0.270	68.0 (61.7,	63.3 (61.8,	68.2 (61.7, 77.4)	0.153

					77.3)	67.5)	
Blood type, n (%)							
A	74 (42.8)	4 (33.3)	70 (43.5)		116 (44.7)	4 (33.3)	112 (45.2)
B	38 (21.9)	4 (33.3)	34 (21.1)		56 (21.5)	4 (33.3)	52 (21.0)
AB	21 (12.1)	1 (8.3)	20 (12.4)	0.755	39 (15.0)	1 (8.3)	38 (15.3)	0.609
O	40 (23.1)	3 (25.0)	37 (23.0)		49 (18.8)	3 (25.0)	46 (18.5)
BMI	24.6 (22.6, 27.2)	25.0 (22.4, 27.2)	24.6 (22.7, 27.0)	0.933	24.9 (22.8, 27.0)	25.0 (22.4, 27.2)	24.9 (22.8, 27.0)	0.833
Low body weight, n (%)	4 (2.3)	0 (0.0)	4 (2.5)		5 (1.9)	0 (0.0)	5 (2.0)	
Normal weight, n (%)	93 (53.8)	6 (50.0)	87 (54.0)		131 (50.4)	6 (50.0)	125 (50.4)	
obesity1, n (%)	53 (30.6)	5 (41.7)	48 (29.8)	0.903	90 (34.6)	5 (41.7)	85 (34.3)	0.948
obesity2, n (%)	19 (11.0)	1 (8.3)	18 (11.2)		28 (10.7)	1 (8.3)	27 (10.9)	
obesity3, n (%)	3 (1.7)	0 (0.0)	3 (1.9)		5 (1.9)	0 (0.0)	5 (2.0)	
obesity4, n (%)	1 (0.6)	0 (0.0)	1 (0.6)		1 (0.38)	0 (0.0)	1 (0.4)	
Degree of severity of disease, n (%)							
Non-oxygen	110 (63.6)	7 (58.3)	103 (64.0)		153 (58.8)	7 (58.3)	146 (58.9)	
Oxygen	50 (28.9)	4 (33.3)	46 (28.6)	0.897	75 (28.8)	4 (33.3)	71 (28.6)	0.913
Respiration/ECMO	13 (7.5)	1 (8.3)	12 (7.5)		32 (12.3)	1 (8.3)	31 (12.5)	
Time interval between symptom resolution and donation(days)	81.0 (55.0, 130.0)	118.5 (99.5, 187.3)	77.0 (53.0, 129.0)	0.044			
Prior donation history n (%)							
First-time donation donor	4 (6.6)	1 (11.1)	3 (5.8)	0.481	7 (5.9)	1 (11.1)	3 (5.8)	0.432
Experienced donation donor	57 (93.4)	8 (88.9)	49 (94.2)		112	8	104 (94.5)	

					(94.1)	(88.9)		
Diagnose of Hight blood pressure, n (%)								
Yes	35 (20.2)	0 (0.0)	35 (21.7)	0.128	52 (20.1)	0 (0.0)	52 (21.0)	0.662
Smoking experience, n (%)								
Never	99 (63.1)	7 (63.6)	92 (63.0)		149 (62.5)	7 (63.6)	142 (62.6%)	
current smoker	12 (7.6)	0 (0.0)	12 (8.2)	0.788	14 (5.0)	0 (0.0)	14 (6.2%)	1.000
past smoker	46 (29.3)	4 (36.4)	42 (28.8)		75 (31.5)	4 (36.4)	71 (31.3%)	
Respiratory distress remaining, n (%)								
Yes	25 (15.6)	2 (16.7)	23 (15.5)	1.00	32 (13.2)	2 (16.7)	30 (13.0)	0.662
Apheresis details								
Required time (min)	38.0 (33.0, 48.0)	50.0 (39.0, 56.3)	38.0 (33.0, 46.0)	0.010	39.0 (34.0, 51.0)	50.0 (39.0, 56.3)	39.0 (33.0, 51.0)	0.027
Collected amount (ml)	463.6 (463.6, 519.2)	514.1 (486.1, 609.0)	463.6 (463.6,509.9)	0.101	463.6 (463.6, 519.2)	514.1 (486.1, 609.0)	463.6 (463.6, 519.2)	0.196
Throughput (ml)	1834 (1515, 2343)	2486 (1791.8, 2629.8)	1827 (1474.0, 2309.0)	0.027	1890 (1553, 2533)	2486 (1791.8, 2629.3)	1883 (1534.8, 2494.3)	0.079
Used ACD-A liquid volume (ml)	164.0 (133.0, 221.0)	229.0 (172.3, 260.5)	160.0 (130.0, 216.0)	0.015	170.0 (138.5, 214.0)	229.0 (172.2, 260.5)	168.0 (136.5, 235.5)	0.048
Used equipment, n (%)								
Spectra Optia	48 (17.7)	6 (50.0)	42 (26.1)		80 (30.8)	6 (50.0)	80 (32.3)	
				0.095				0.219
COM.TEC	125 (72.3)	6 (50.0)	119 (74.0)		168 (64.6)	6 (50.0)	168 (67.7)	
Apheresis related event and DAE								
Baseline sBP(mmHg)	150.0 (133.0, 163.0)	132.5 (124.2, 149.5)	150.0 (134.0, 164.0)	0.048	149.0 (133.0,	132.5 (124.3,	150.0 (134.0,	0.050

					164.0)	149.5)	164.0)	
Baseline HR(bpm)	71.0 (65.0, 80.0)	72.5 (68.5, 78.5)	72.0 (65.0, 80.0)	0.637	71.0 (65.0, 78.0)	72.5 (68.5, 78.5)	71.0 (65.0, 78.0)	0.383
Baseline SpO_2(%)	98.0 (97.0, 98.0)	97.5 (97.0, 98.0)	98.0 (97.0 ,98.3)	0.736	98.0 (97.0, 98.0)	97.5 (97.0, 98.0)	98.0 (97.0 ,98.0)	0.830
After puncture variation from baseline								
sBP (mmHg)	0.0 (-7.0, 5.0)	-1.0 (-8.3, 1.0)	0.0 (-7.0, 6.0)	0.432	0.0 (-8.0, 5.0)	-1.0 (-8.3, 1.0)	0.0 (-8.0, 5.0)	0.700
HR (BPM)	-2.0 (-6.0, 1.0)	0.0 (-6.5, 1.3)	-3.0 (-6.0, 0.0)	0.881	-2.0 (-6.0, 0.0)	0.0 (-6.5, 1.3)	-2.0 (-6.0, 0.0)	0.786
SpO_2 (%)	0.0 (0.0, 1.0)	0.0 (0.0, 0.3)	0.0 (0.0, 1.0)	0.577	0.0 (0.0, 1.0)	0.0 (0.0, 0.3)	0.0 (0.0, 1.0)	0.570
During apheresis minmax variation from baseline								
sBP (mmHg)	-14.0 (-22.0, -6.0)	-20.0 (-30.3, -13.8)	-14.0 (-20.0, -5.0)	0.059	-15.0 (-23.3, -7.0)	-20.0 (-30.3, -13.8)	-15.0 (-23.0, -6.8)	0.093
HR (BPM)	-6.0 (-9.0, -1.0)	-6.0 (-6.5, -4.0)	-5.0 (-9.0, -1.0)	0.756	-5.00 (-9.0, -1.0)	-6.0 (-6.5, -4.0)	-5.0 (-9.0, -1.0)	0.602
SpO_2 (%)	-1.0 (-1.0, 0.0)	-1.0 (-2.0, -1.0)	-1.0 (-1.0, 0.0)	0.132	-1.00 (-1.0, 0.0)	-1.0 (-2.0, -1.0)	-1.0 (-1.0, 0.0)	0.173

Table 5-2 Demographic Characteristics of CCP Donors and Sensitivity Analysis of All 260 Cases (DAE Grade2 and Non-Grade2 group)

	DAE Grade2 (N=3)	Non-Grade2 (N=170)	DAE Gra	DAE Grade 2	Non-Grade 2 (N=257)	p-value

			de2 (N=3)			
Age	48.0 (46.5, 54.5)	52.0 (44.0, 58.8)	0.977	48.0 (46.5, 54.5)	53.0 (45.0, 59.0)	0.760
Generation, n (%)						
20s	0 (0.0)	6 (3.5)		0 (0.0)	7 (2.7)	
30s	0 (0.0)	22 (12.9)		0 (0.0)	27 (10.5)	
40s	2 (66.7)	46 (27.1)	0.480	2 (66.7)	65 (25.3)	0.404
50s	0 (0.0)	61 (35.9)		0 (0.0)	94 (36.6)	
60s	1 (33.3)	35 (20.6)		1 (33.3)	64 (24.9)	
Sex Female, n (%)	2 (75.0)	71 (41.8)	0.574	2 (75.0)	98 (38.1)	0.561
Body height (cm)	160.0 (156.0, 161.5)	165.8 (159.9, 173.5)	0.114	160.0 (156.0, 161.5)	166.7 (159.5, 173.9)	0.115
Body weight (kg)	63.0 (63.0, 71.2)	68.8 (60.8, 77.7)	0.921	63.0 (63.0, 71.2)	68 (61.7, 77.2)	0.835
Blood type, n (%)						
A	1 (33.3)	73 (42.9)		1 (33.3)	115 (44.7%)	
B	0 (0.0)	38 (22.4)		0 (0.0)	56 (21.8%)	
AB	1 (33.3)	20 (11.8)	0.543	1 (33.3)	38 (14.8%)	0.383
O	1 (33.3)	39 (22.9)		1 (33.3)	48 (18.7%)	
BMI	27.3 (26.0, 28.6)	24.6 (22.5, 27.0)	0.229	27.3 (26.0, 28.6)	24.8 (22.8, 27.0)	0.250
Low body weight, n (%)	0 (0.0)	4 (2.4)	0.580	0 (0.0)	5 (1.9)	0.735
Normal weight, n (%)	1 (33.3)	92 (54.1)		1	130 (50.6)	

				(33.3)	
obesity1, n (%)	2 (66.7)	51 (30.0)		2 (66.7)	88 (34.2)
obesity2, n (%)	0 (0.0)	19 (11.2)		0 (0.0)	28 (10.9)
obesity3, n (%)	0 (0.0)	3 (1.8)		0 (0.0)	5 (1.9)
obesity4, n (%)	0 (0.0)	1 (0.6)		0 (0.0)	1 (0.4)
Degree of severity of disease, n (%)					
Non-oxygen	1 (33.3)	109 (64.1)		1 (33.3)	152 (59.1)
Oxygen	1 (33.3)	49 (28.8)	0.141	1 (33.3)	74 (28.8)	0.222
Respiration/ECMO	1 (33.3)	12 (7.1)		1 (33.3)	31 (12.1)
Time interval between symptom resolution and donation(days)					
	118.5 (99.5, 187.3)	77.0 (53.0, 129.0)	0.044	113.0 (107.7, 174.5)	79.0 (54.3, 130.0)	0.172
Prior donation history n (%)					
First-time donation donor	1 (11.1)	3 (5.8)		0 (0.0)	7 (6.0)	
Experienced donation donor	8 (88.9)	49 (94.2)	0.481	2 (100.0)	110 (94)	1.00
Diagnose of Hight blood pressure, n (%)					
Yes	0 (0.0)	35 (21.7)	0.128	0 (0.0)	52 (20.2%)	1.000
Smoking experience, n (%)					
Never	7 (63.6)	92 (63.0)		1 (33.3)	148 (63)	
current smoker	0 (0.0)	12 (8.2)	0.788	0 (0.0)	73 (31.1)	0.384
past smoker	4 (36.4)	42 (28.8)		2 (66.7)	14 (6)
Respiratory distress remaining, n					

(%)						
Yes	2 (16.7)	23 (15.5)	1.00	1 (33.3)	31 (12.9)	0.347
Apheresis details						
Required time (min)	56.0 (47.5, 64.0)	38.0 (33.0, 47.8)	0.086	56.0 (47.5, 64.0)	39.0 (34.0, 51.0)	0.115
Collected amount (ml)	509.0 (429.5, 559.0)	463.6 (463.6, 519.2)	0.882	509.0 (429.5, 559.0)	463.6 (463.6, 519.2)	0.997
Throughput (ml)	2593 (2134.0, 3171.5)	1833 (1503.8, 2342.0)	0.168	2593 (2134.0, 3171.5)	1890 (1549.0, 2506.0)	0.220
Used ACD-A liquid volume (ml)	262.0 (219.0, 317.0)	163.0 (132.2, 219.0)	0.068	262.0 (219.0, 317.0)	169.0 (138.0, 240.0)	0.096
Used equipment, n (%)						
Spectra Optia	3 (100.0)	45 (26.5)	0.020	3 (100.0)	83 (32.3)	0.035
COM.TEC	0 (0.0)	125 (73.5)		0 (0.0)	174 (67.7)	
Apheresis related event and DAE						
Baseline sBP(mmHg)	130 (127.5, 135.5)	150.0 (133.3, 163.8)	0.114	130 (127.5, 135.5)	150.0 (133.0, 164.0)	0.128
Baseline HR(bpm)	69.0 (64.0, 78.0)	72.0 (65.3, 79.8)	0.736	69.0 (64.0, 78.0)	71.0 (65.0, 78.0)	0.905
Baseline SpO_2(%)	97.0 (96.5, 97.0)	98.0 (97.0, 98.0)	0.136	97.0 (96.5,	98.0 (97.0, 98.0)	0.151

				97.0)		
After puncture variation from baseline						
sBP (mmHg)	-1.0 (-7.0, -1.0)	0.0 (-7.0, 5.8)	0.334	-1.0 (-7.0, -1.0)	0.0 (-8.0, 5.0)	0.426
HR (BPM)	0.0 (-7.0, 1.0)	-2.5 (-6.0, 1.0)	0.991	0.0 (-7.0, 1.0)	-2.0 (-6.0, 0.0)	0.920
SpO_2 (%)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.400	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.401
During apheresis minmax variation from baseline						
sBP (mmHg)	-55.0 (-57.5, -47.5)	-14.0 (-20.8, -6.0)	0.005	-55.0 (-57.5, -47.5)	-15.0 (-23.0, -7.0)	0.005
HR (BPM)	-6.0 (-10.0, -3.5)	-5.0 (-9.0, -1.0)	0.696	-6.0 (-10.0, -3.5)	-5.0 (-9.0, -1.0)	0.662
SpO_2 (%)	-1.0 (-1.5, -0.5)	-1.0 (-1.0, -0.0)	0.754	-1.0 (-1.5, -0.5)	-1.0 (-1.0, -0.0)	0.809

Table 6 The univariable and the multivariable analysis of the DAE

	Univariable		Multivariable		Variable Selection	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age	0.97 (0.92, 1.02)	0.211	0.91 (0.80, 1.00)	0.069	0.90 (0.82, 0.97)	0.012
Sex, Feamale	0.10 (0.02, 0.33)	0.027	0.02 (0.00, 0.14)	0.995	0.03 (0.00, 0.16)	0.006
Blood type B	2.06 (0.46, 9.19)	0.327	4.26 (0.66, 32.03)	0.132		
Blood type AB	0.88 (0.04, 6.34)	0.907	1.04 (0.03, 21.48)	0.979		
Blood type O	3.61 (0.46, 30.51)	0.212	3.61 (0.46, 30.51)	0.212		

BMI	0.98 (0.84, 1.12)	0.800	1.15 (0.91, 1.47)	0.232		
Degree of severity of disease,						
Oxygen	1.28 (0.32, 4.45)	0.705	4.30 (0.42, 58.43)	0.228	4.87 (0.72, 36.64)	0.103
Respiration/ECMO	1.23 (0.06, 7.78)	0.854	17.89 (0.34, 1349.33)	0.145	22.42 (0.74, 547.78)	0.044
Time interval between symptom resolution and donation						
	1.00 (1.00, 1.01)	0.140	1.00 (0.99, 1.01)	0.371	1.01 (1.00, 1.02)	0.094
Respiratory distress remaining	1.09 (0.16, 4.47)	0.918	1.27 (0.06, 18.40)	0.867		
Base line SBP	0.97 (0.94, 1.00)	0.051	0.97(0.93,1.01)	0.130	0.96 (0.92,0.99)	0.022
Base line HR	1.01 (0.96, 1.07)	0.635	0.98 (0.93, 1.04)	0.538		
Base line SpO_2	0.94 (0.58, 1.52)	0.800	0.74 (0.31, 1.63)	0.284	0.57 (0.28, 1.05)	0.085
Equipment, Spectra Optia	2.83 (0.84, 9.53)	0.085	2.60 (0.48, 16.93)	0.284	3.44 (0.83, 15.90)	0.094

OR : odds ratio 95%CI : 95%Confidence interval

Authorship contribution

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