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ORIGINAL ARTICLE

Convalescent plasma transfusion in severe COVID-19 patients: Clinical and laboratory outcomes

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Abstract

Introduction: The objective of this study was to investigate the effect of convalescent plasma (CP) transfusion on clinical and serial laboratory parameters in severe COVID-19 patients. The Coronavirus Disease 2019 (COVID-19) pandemic presents a challenge to the healthcare system worldwide due to the limited treatment options available. The body of evidence reported that CP containing anti-COVID-19 antibodies could be effective against the infection. *Materials and Methods:* This was a cross-sectional study that involved retrospective data collection of severe COVID-19 adult patients who received CP transfusion along with the best-of-care (CP group, n: 53) and best-of-care only (control group, n: 53). An age, gender, and comorbidity were manually matched approximately at a 1:1 ratio. *Results:* The prevalence of adverse transfusion reactions was 5.7%. A shorter duration of oxygen support (median: 12 days vs 14 days, P=0.030) and a shorter duration of mechanical ventilation (median: 6 days vs 10 days, P=0.048) were found in the CP group. The laboratory parameters were also improved. However, there was no significant difference in the mechanical ventilation rate, length of hospital stay, length of intensive care unit (ICU) stay, and mortality rate across both groups (P = 0.492, 0.614, 0.793, 0.374). *Conclusion:* CP transfusion is safe and effective in the treatment of severe COVID-19 patients. However, a revision of our approaches such as early CP transfusion and use of a high-titre anti-COVID-19 neutralising antibody (nAb) unit is necessary to unlock the full potential benefits of CP transfusion among COVID-19 patients.

Keywords: COVID-19, convalescent plasma, oxygen support, mechanical ventilation

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic presents a unique challenge to the healthcare system worldwide including in Malaysia due to limited treatment options available. Our healthcare system has devised strategies to manage patients including repurposed drugs and rejuvenate older therapeutic measures such as convalescent plasma (CP) transfusion. CP is defined as plasma from an individual who has recovered from the COVID-19 infection and contains neutralising antibodies against the COVID-19 virus.[1]

Passive immunity is an option for patients who have yet to develop an antibody response against an infection. When there is no proven therapeutic measure available for the disease in question, plasma from patients in the convalescent phase has been collected as empirical treatment. Previously, CP has been used as immunotherapy in the treatment of measles, Spanish influenza A (H1N1) pneumonia, poliomyelitis, mumps, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and

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ebola virus disease.[2-9] The postulated protective mechanisms of CP are pathogen neutralisation via the delivery of neutralising antibodies, antibody-dependent cellular cytotoxicity (ADCC), complement activity, and phagocytosis. In addition, CP might have anti-inflammatory properties that are capable to reduce the severity of acute respiratory distress syndrome (ARDS) in COVID-19 pneumonia.[10]

During the current pandemic, CP was first commenced in five patients with severe COVID-19 in Wuhan, China. Inflammatory markers and pulmonary computed tomography (CT) scan findings were improved in four patients.[11] In another study, CP transfusion to COVID-19 infected patients resulted in significant improvements in their clinical outcomes such as reduced length of hospital stay, mortality rate, and mechanical ventilation rate.[12] Among severe and critically ill COVID-19 infected patients, CP transfusion was associated with a shorter duration of intensive care unit (ICU) stay, reduce rate of mechanical ventilation, and vasopressor support.[13] Therefore, the objective of this study was to investigate the effect of CP transfusion on clinical and serial laboratory parameters in severe COVID-19 patients.

MATERIALS AND METHODS

Research location and ethic

This was a cross-sectional study that involved retrospective data collection of 106 adult patients who were admitted to public hospitals across Malaysia (Hospital Sungai Buloh, Hospital Sultanah Bahiyah, Hospital Pulau Pinang, Hospital Tuanku Ja'afar, and Hospital Nukleus Labuan) that were designated to treat COVID-19 patients in Malaysia from 1st August 2020 to 28th February 2021. Commencement of CP in the respective hospitals was coordinated by National Blood Centre (NBC). NBC is a centre of referral for transfusion medicine services in Malaysia. Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (research number NMRR-21-58-58089 (IIR)).

Convalescent plasma donor

The CP donor was defined as an individual who has recovered clinically from COVID-19 infection and laboratory-confirmed negative for COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR). Clinical recovery for the symptomatic individual was defined as resolution of fever without medication for a minimum of 24 hours and improvement in respiratory symptoms such as shortness of breath or cough for at least 10 days. Clinical recovery for an asymptomatic individual was defined as 10 days after the first positive nasopharyngeal or oropharyngeal swab.[14-15] Each donor was subjected to eligibility criteria according to the national guidelines.[14,16] Among the eligibility criteria were age between 17 to 60 years old, weight ≥ 40 kg, haemoglobin 11.0 g/dl to 18.0 g/dl, blood pressure 100/70 mmHg to 150/100 mmHg, good venous access, and fit for blood donation. A variation to standard eligibility criteria was considered for age, weight, and haemoglobin to widen the potential donor pool. The pre-donation assessment was performed by the transfusion medicine physician and infectious disease physician. Informed consent for CP donation in the treatment of COVID-19 infection was taken from the donor.

The presence of anti-COVID-19 antibody was determined before CP donation using Diagnostic Kit for Antibody IgM/IgG of Novel Coronavirus COVID-19, Shanghai Liangrun BioMedicine Technology Co., Ltd, China. However, an anti-COVID-19 neutralising antibody (nAb) titre test was not performed routinely. CP was collected via apheresis technique using either Fenwal Autopheresis-C Plasma apheresis System, Baxter Healthcare Corporation, USA, or PCS2 system, Haemonetics Corporation, USA. The total volume of CP collected per session was based on the donor's body weight which was either 250 ml (weight 40-50kg) or 500ml (weight > 50kg). Transfusion transmitted illness (TTI) screening of all CP units was negative. Nucleic acid test (NAT) for human immunodeficiency virus 1 and 2 (HIV-1/2), hepatitis B (HBV), and hepatitis C virus (HCV) using Procleix Panther System, Grifols, Spain.Serology test for HIV, HBV, and HCV using ARCHITECT Analyzers, Abbott, USA. Rapid plasma reagin (RPR) test for syphilis using Syphilis Kits, Lorne Laboratories Limited, UK. All CP units were stored using Dometic Plasma Storage Freezer, B Medical Systems, Luxembourg at temperature ≤-25.0°C. The pathogen inactivation process was not performed.

Convalescent plasma group and control group

A total of 53 patients who received CP transfusion during the study period were included in the CP group. The patients that were eligible for CP transfusion were identified by the infectious

disease physician incharge. The indication of CP transfusion was based on the Guideline for Collection, Processing and Use of Convalescent Plasma (CP) for Experimental Treatment of COVID-19, Ministry of Health Malaysia (adapted from WHO clinical management of COVID-19 and a previous study protocol on plasma therapy in patients with the Middle East respiratory syndrome coronavirus (MERS) infection).[14,17-18] The indications were laboratory-confirmed COVID-19 infection and severe illness as defined by the presence of dyspnea or respiratory rate >30 breath/minute or oxygen saturation <93% on room air or arterial partial pressure of oxygen (PaO2) fraction of inspired oxygen (FiO2) (PaO2/FiO2 ratio) <300 mmHg, or lung infiltrates >50% of lung fields within 24-48 hours (if chest X-ray available). Other criteria such as admission to an ICU or on oxygen support (invasive or non-invasive ventilation) or on intravenous vasoactive medications to maintain mean arterial pressure (MAP) >65 mmHg.

Another 53 patients who did not receive CP transfusion with severe COVID-19 infection were selected as control. An age, gender, and comorbidity were manually matched approximately at a 1:1 ratio. All patients in both groups received best-of-care treatment and oxygen support as per Guidelines COVID-19 Management in Malaysia.[15] For severe COVID-19 infection in Malaysia, the antiviral used was Favipiravir. The immunomodulators used were dexamethasone or methylprednisolone with consideration addition of IV Tocilizumab. Low molecular weight heparin (LMWH) enoxaparin was used as prophylaxis therapy against venous thromboembolism (VTE). Throughout the study period, the standard of care received by COVID-19 patients has evolved rapidly based on the emergence of new evidence. The exclusion criteria for CP transfusion were a history of severe or life-threatening allergic transfusion reaction and known IgA deficiency.[14]

Convalescent plasma transfusion

Informed consent for blood transfusion (CP transfusion) was taken from the patient or authorised next-of-kin. The patients were transfused according to ABO-specific plasma. The volume of CP transfused approximately 250ml as a single dose over 1 to 2 hours. Another unit of CP was transfused after 24 hours based on the clinical decision of the responsible physician. Monitoring of patients during and after the CP transfusion followed our national guidelines.

Variables and research tools

Data regarding demographics (age, race, blood group, comorbidity), clinical characteristics (symptom, interval between initiation of symptom until hospital admission, initiation of symptom to CP transfusion, interval between severe COVID-19 staging to CP transfusion, and the number of CP unit transfused), outcomes (duration of oxygen support, mechanical ventilation rate, duration of mechanical ventilation, vasopressor support rate, duration of vasopressor support, length of hospital stay, length of ICU stay, mortality rate, and adverse transfusion reaction), and laboratory parameters (absolute neutrophil count (ANC), absolute lymphocyte count (ALC), C-reactive protein (CRP), D-dimer, and procalcitonin) of the patients were collected. A significant proportion of data was retrieved manually using the patient's bed-head-ticket (BHT) or medical note. A Blood Bank Information System (BBIS) was used to trace the patient's blood group and transfusion history. Laboratory online system was used to collect laboratory parameters. The day of CP transfusion was defined as 'day 0' for CP recipients. The median interval between severe COVID-19 staging and CP transfusion was 2 days (IQR: 2 days). Therefore, 2nd day after a diagnosis of severe COVID-19 infection was used as 'day 0' for the control group. An adult was defined as a person at least the age of 18 years old.

Statistical analysis

All the data were tabulated and analysed using International Business Machines Corporation (IBM) Statistical Package for the Social Science (SPSS) Statistics Version 26 IBM, New York, USA. The distribution normality of numerical variables was assessed with the Shapiro-Wilk test. Numerical variables were analysed with the Mann-Whitney *U* test (except age which was analysed using an independent t-test). Numerical variables were expressed as median (interquartile range, IQR) except for age which was expressed as mean (standard deviation, SD). Categorical variables were analysed with the Pearson Chi-square or Fisher's Exact Test. Categorical variables were expressed as count (percentage, %). The level of significance was set at $P<0.05$.

RESULT

Demographics of patients

Most of the selected patients were male (60.4%),

Malay (83.0%), blood group O (29.2%), and at least has a comorbid (74.5%)(Table 1). The commonest comorbidities were hypertension (47.2%) and diabetes mellitus (44.3%). The distribution of the ABO blood group was unknown for 27 patients in the control group because it was not routinely tested for all patients, especially those that was not required blood transfusion. The failure to match for ABO blood group between the two population arms may affect the outcome findings due to group O maybe protective for infection risk and severity, as compared to A and B groups.[19,20]

Clinical characteristics and outcomes of the patients

A small proportion of patients (3.8%) were asymptomatic upon diagnosis of COVID-19 infection (Table 2). A shorter duration of oxygen support (median: 12 days vs 14 days, P=0.030) and mechanical ventilation (median: 6 days vs 10 days, P=0.048) were found in the CP group. In terms of transfusion safety, a patient developed mild bilateral eye redness during the CP transfusion, and two patients had generalized urticaria after the CP transfusion. Nevertheless, CP transfusion was completed. The patients received intravenous (IV) hydrocortisone 200mg and IV Chlorphenamine 10mg STAT and the symptoms resolved. An acute pulmonary embolism was reported in a patient with underlying hypertension on day 3 post-CP transfusion. The CT pulmonary angiogram revealed filling defects in the artery of the inferior lingular segment of the left upper lobe, and the lateral basal segment of the right lower lobe of the lung. He was started on IV enoxaparin sodium 80mg BD (which was later was stopped after INR level reached 2-3), and oral warfarin 4mg OD. He was stable and discharged from the hospital on day 17 post-CP transfusion. However, the event was concluded by the attending physician as an

TABLE 1: Demographics of the patients

Variable(s)	All patients (n=106)	CP group (n=53)	Control group (n=53)	P-value
Age (years)	55.93 (11.60)[a]	56.11 (11.47)[a]	55.70 (11.61)[a]	0.853[b]
Gender				
Male	64 (60.4%)	32 (60.4%)	32 (60.4%)	1.000[c]
Female	42 (39.6%)	21 (39.6%)	21 (39.6%)	
Race				
Malay	88 (83.0%)	47 (88.7%)	41 (77.4%)	0.353[d]
Chinese	6 (5.7%)	2 (3.8%)	4 (7.5%)	
Indian	12 (11.3%)	4 (7.5%)	8 (15.1%)	
Blood group				
O	31 (29.2%)	21 (39.6%)	10 (18.9%)	0.490[d]
A	25 (23.6%)	19 (35.8%	6 (11.3%)	
B	17 (16.0%)	10 (18.9%)	7 (13.2%)	
AB	6 (5.7%)	3 (5.7%)	3 (5.7%)	
Unknown	27 (25.5%)	0 (0.0%)	27 (50.9%)	
Comorbidity				
No	27 (25.5%)	14 (26.4%)	13 (24.5%)	0.824[c]
Yes	79 (74.5%)	39 (73.6%)	40 (75.5%)	
Type of comorbidity				
Hypertension	50 (47.2%)	26 (49.1%)	24 (45.3%)	0.697[c]
Diabetes mellitus	47 (44.3%)	21 (39.6%)	26 (49.1%)	0.328[c]
Dyslipidaemia	17 (16.0%)	10 (18.9%)	7 (13.2%)	0.427[c]
Cardiovascular disease	17 (16.0%)	8 (15.1%)	9 (17.0%)	0.791[c]
Respiratory disease	10 (9.4%)	6 (11.3%)	4 (7.5%)	0.506[c]
Renal disease	3 (2.8%)	1 (1.9%)	2 (3.8%)	0.558[c]

Abbreviations: CP, convalescent plasma. [a]mean (standard deviation, SD) [b]P-value is by independent t-test. [c]P-value is by Pearson Chi-square. [d]P-value is by Fisher's Exact Test.

TABLE 2: Clinical characteristics and outcomes of the patients

Variable(s)	All patients (n=106)	CP group (n=53)	Control group (n=53)	P-value
Symptomatic				
No	4 (3.8%)	3 (5.7%)	1 (1.9%)	0.308[b]
Yes	102 (96.2%)	50 (94.3%)	52 (98.1%)	
Type of symptom				
Fever	64 (60.4%)	30 (56.6%)	34 (64.2%)	0.427[b]
Shortness of breath	18 (17.0%)	8 (15.1%)	10 (18.9%)	0.605[b]
Cough	67 (63.2%)	31 (58.5%)	36 (67.9%)	0.314[b]
Running nose	15 (14.2%)	9 (17.0%)	6 (11.3%)	0.403[b]
Sore throat	16 (15.1%)	10 (18.9%)	6 (11.3%)	0.278[b]
Anosmia	9 (8.5%)	6 (11.3%)	3 (5.7%)	0.296[b]
Headache	7 (6.6%)	2 (3.8%)	5 (9.4%)	0.241[b]
Arthralgia/Myalgia	9 (8.5%)	4 (7.5%)	5 (9.4%)	0.727[b]
Diarrhoea	10 (9.4%)	2 (3.8%)	8 (15.1%)	0.046[b]
Lethargy	13 (12.3%)	3 (5.7%)	10 (18.9%)	0.038[b]
Initiation of symptom until admission (days)	4 (3)[a]	3 (3)[a]	4 (3)[a]	0.051[c]
Initiation of symptom to CP transfusion (days)	NA	7 (3)[a]	NA	NA
Interval between severe COVID-19 staging and CP transfusion (days)	NA	2 (2)[a]	NA	NA
Number of CP units transfused				
1 unit	NA	35 (66.0%)	NA	NA
2 unit		18 (34.0%)		
Duration of oxygen support (days)	13 (9)[a]	12 (9)[a]	14 (9)[a]	**0.030[c]**
Mechanical ventilation				
No	82 (77.4%)	40 (75.5%)	42 (79.2%)	0.492[b]
Yes	24 (22.6%)	13 (24.5%)	11 (20.8%)	
Duration of mechanical ventilation (days)	8 (7)[a]	6 (6)[a]	10 (13)[a]	**0.048[c]**
Vasopressor support				
No	93 (87.7%)	48 (90.6%)	45 (84.9%)	0.374[b]
Yes	13 (12.3%)	5 (9.4%)	8 (15.1%)	
Duration of vasopressor support (days)	9 (8)[a]	6 (6)[a]	12 (10)[a]	0.078[c]
Length of hospital stay (days)	19 (9)[a]	19 (9)[a]	19 (9)[a]	0.614[c]
Length of ICU stay (days)	7 (7)[a]	7 (7)[a]	6 (8)[a]	0.793[c]
Mortality				
No	93 (87.7%)	48 (90.6%)	45 (84.9%)	0.374[b]
Yes	13 (12.3%)	5 (9.4%)	8 (15.1%)	
Adverse transfusion reaction	NA	3 (5.7%)	NA	NA

Abbreviations: CP, convalescent plasma; ICU, intensive care unit; NA, not applicable.
[a]median (interquartile range, IQR).
[b] P-value is by Pearson Chi-square. $P \leq 0.05$ is considered significant.
[c]P-value is by Mann-Whitney U test. $P \leq 0.05$ is considered significant

acute pulmonary embolism due to COVID-19 infection.

Laboratory investigation of the patients

ANC in the CP group was significantly lower than the control group on day 3, day 5, day 7, and day 12 (P= 0.006, 0.023, 0.009, 0.017) (Table 3). Both groups developed borderline lymphopenia on day 5. However, recovery in ALC in the CP group was faster if compared

TABLE 3: Laboratory investigation of the patients

Variable(s)	CP group	Control group	P-value
ANC (x 10^3 /μL) (NR: 2.00-7.00 x 10^3 /μL)			
Day 0	3.52 (2.74)	4.42 (3.96)	0.122
Day 1	3.69 (3.31)	4.58 (5.22)	0.133
Day 3	4.40 (3.31)	7.05 (7.14)	**0.006**
Day 5	4.95 (3.80)	7.26 (5.93)	**0.023**
Day 7	5.12 (4.62)	7.47 (5.84)	**0.009**
Day 12	5.77 (5.75)	8.76 (7.33)	**0.017**
ALC (x 10^3 /μL) (NR: 1.00-3.00 x 10^3 /μL)			
Day 0	1.46 (0.73)	1.53 (0.95)	0.721
Day 1	1.44 (0.99)	1.26 (0.98)	0.172
Day 3	1.25 (1.15)	1.17 (0.51)	0.216
Day 5	1.01 (1.16)	0.99 (0.82)	0.641
Day 7	1.26 (1.58)	1.03 (1.18)	0.155
Day 12	2.11 (1.42)	1.44 (1.47)	**0.027**
CRP (mg/L) (NR: <5.00 mg/L)			
Day 0	19.76 (26.33)	47.39 (69.47)	**0.002**
Day 1	33.62 (58.33)	50.14 (58.38)	0.232
Day 3	34.38 (36.85)	35.11 (50.38)	0.681
Day 5	16.79 (34.42)	25.01 (45.33)	0.585
Day 7	10.97 (18.78)	12.94 (34.72)	0.221
Day 12	2.77 (13.06)	15.85 (22.65)	**0.002**
D-dimer (μg/ml) (NR: <0.5 μg/ml)			
Day 0	0.55 (0.54)	0.65 (0.95)	0.161
Day 1	0.66 (0.52)	0.72 (1.37)	**0.013**
Day 3	0.64 (0.56)	0.84 (0.88)	0.058
Day 5	0.60 (0.63)	0.92 (1.75)	**0.022**
Day 7	0.76 (0.60)	0.94 (1.04)	0.075
Day 12	0.75 (0.86)	1.39 (1.55)	0.082
Procalcitonin (ng/ml) (NR: <0.05ng/ml)			
Day 0	0.12 (0.13)	NA	NA
Day 1	0.07 (0.12)		
Day 3	0.12 (0.54)		
Day 5	0.06 (0.28)		
Day 7	0.09 (0.16)		
Day 12	0.04 (0.09)		

Note: Data are presented as median (interquartile range, IQR). P-value is by Mann-Whitney U test. P ≤0.05 is considered statistically significant.

Abbreviations: CP, convalescent plasma; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; CRP, C-reactive protein; NR, normal range; NA, not applicable

with the control group and it was statistically significant on day 12 (P=0.027). CRP level was significantly lower for the CP group on day 0 (P=0.002) and reached maximum level on day 3. The CRP level in the CP group decreased at a faster rate until it was significantly lower on day 12 (P=0.002). The level of D-dimer in the CP group was significantly lower than the control group on day 1 and day 5 (P=0.013, 0.022). The procalcitonin test was not routinely performed in the control group.

DISCUSSION

In our study, the prevalence of adverse transfusion reactions was 5.7%. It was slightly higher as compared to other previous studies which were ranged from 0.0% to 4.8%.[21-24] However, the severity of adverse transfusion reaction among our patients was mild and resolved without any serious complication. The risk of adverse transfusion reaction after CP transfusion (COVID-19 immune) was comparable to standard plasma transfusion (COVID-19 non-immune).[25] The prevalence of thromboembolic episodes after CP transfusion was reported as less than 1.0%.[26] There was no reported case of antibody-dependant enhancement (ADE), which was postulated to occur when the development of antibodies due to the previous infection may exacerbate the severity of infection with a different viral serotype.[27]

CP transfusion was associated with a shorter duration of oxygen support (P=0.030) and mechanical ventilation (P=0.048) as compared to the control group. The earlier studies published at the beginning of the pandemic reported an improvement of patients' oxygen status after CP transfusion.[11,28] A retrospective propensity-score matched study involving 195 patients (39 CP vs 156 controls) who were hospitalised with COVID-19 reported 17.9% of CP recipients developed worsening of oxygen requirement as compared to 28.2% non-CP recipients (adjusted odds ratio (OR), 0.86; 95% CI, 0.75–0.98; P=0.025).[29] In moderate COVID-19 infection, the oxygen saturation was improved by 5.4% (95% CI 3.3 – 7.4) on day 1 and 4.1% (95% CI 2.3– 5.9) on day 3 after CP transfusion. However, a similar association was not found in severe COVID-19 infection.[30]

The rate of ANC increment was lesser and the rate of ALC recovery was faster in the CP group. Neutrophilia and lymphopenia or higher neutrophil-lymphocyte ratio (NLR) is a feature of the patient with severe COVID-19 infection. Pro-inflammatory cells such as neutrophils are triggered by virus-induced cytokines such as TNF-a, IL-1, IL-6, and IL-8 during a hyperinflammatory state. On the other hand, COVID-19 infection was reported to cause pronounced lymphopenia with low counts of CD3+ cells and CD4+ cells. Besides that, COVID-19 infected T-cells may exert cytopathic effects.[31] Our finding on the effect of CP transfusion on lymphocytes was consistent with another study whereby a significant increase in ALC was reported on day 7 (moderate infection) and day 11 (severe infection) after admission in the CP group.[30] A systematic review reported that high ANC, low ALC, high CRP, high D-dimer, and high procalcitonin were bad prognostic markers for severity and mortality in COVID-19 patients.[32] Other studies reported improvement in the laboratory parameters after CP transfusion in COVID-19 patients.[28,30,33] The immunomodulatory and passive immunity effect of CP may contribute to the improvement of laboratory parameters by inhibiting inflammatory cytokine, complement, autoantibodies, and immune cell infiltration.[34,35] The effect will be reflected clinically as improvement in oxygen saturation and radiological findings of the lung.[36]

Even though our study found a shorter duration of oxygen support and improvement in laboratory markers after CP transfusion, however, it does not translate into reducing mechanical ventilation rate (P=0.492), vasopressor support rate (P=0.374), length of hospital stay (P=0.614), length of ICU stay (P=0.793), and mortality rate (P=0.374). In our study, the median interval between initiation of symptom and CP transfusion was 7 days. The American Association of Blood Bank (AABB) recommended CP should be commenced as close to symptom onset as possible due to less therapeutic value for patients at late-stage or on mechanical ventilation.[25] Administration of CP to mildly-ill older adults (>75 years old or between 65–74 years old with comorbidity) within 72 hours of symptom onset had a 48% reduced risk of progression to the severe stage.[21] An observational study conducted among 3,082 hospitalised COVID-19 patients reported lower 30-day mortality among patients who received CP within 72 hours after being diagnosed with COVID-19. A similar benefit was not seen in patients who had received mechanical ventilation before CP transfusion.[26] The benefit of reducing mortality was also reported by a matched propensity study among 351 COVID-19 patients that received CP transfusion within 44 hours of hospital admission.[37]

In our study, an anti-COVID-19 nAb titre in the CP unit was not measured before transfusion. A unit of CP with high-titre nAb against COVID-19 is recommended for patients infected with COVID-19. Alternatively, 2 units of CP with low-titre nAb against COVID-19 is acceptable.[25] The 30-day mortality risk was lower in non-mechanically ventilated COVID-19 patients that received CP with high-titre nAb (>18.45 S/CO) as compared to the low-titre group (<4.62 S/CO) (RR, 0.66; 95% CI, 0.48 to 0.91).[26] The Convalescent-plasma-for-COVID (ConCOVID) trial reported CP with nAb against COVID-19 (1:160) similar to the recipients was not beneficial.[38] The PLACID trial reported CP with low-titre nAb against COVID-19 (1:40) was not effective.[23] Therefore, a revision of strategies such as early CP transfusion and use of high-titre nAb CP unit is necessary to harness full potential therapeutic benefit in clinical and laboratory outcomes of severe COVID-19 patients.

Our study is limited by the retrospective nature of data collection. Other therapeutic agents such as antiviral and immunomodulation may contribute to the recovery of patients in our sample. The effect of other treatment modalities on patient outcomes was not analysed due to the variation of COVID-19 patient management among hospitals and the rapid emergence of new treatment evidence throughout the study period. Variation of CP volume transfused between patients and unmeasured anti-COVID-19 antibody may cause heterogeneity in the therapeutic effect of each CP unit. At our best, a consensus has been made to use 2nd day after a diagnosis of severe COVID-19 infection as the reference point for the control group and it might affect the laboratory results comparison between the two groups. In conclusion, CP transfusion is safe and effective in the treatment of severe COVID-19 infected adult patients. CP therapy reduces the duration of oxygen therapy, duration of mechanical ventilation, and improvement of the laboratory parameters. A revision of our approach based on current evidence is necessary to unlock the potential benefits of CP transfusion among COVID-19 patients.

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Authors' contribution: Mohd Redzuan Abdullah: Conceptualisation, Formal analysis, Data curation, Methodology, Investigation, Project administration, Roles/Writing – original draft. Afif Alam Faizli: Data curation, Methodology, Investigation, Writing – review & editing. Noor Sheereen Adzaludin: Data curation, Methodology, Investigation, Writing – review & editing. Noryati Abu Amin: Resources, Investigation, Supervision, Writing - review & editing. Nor Arisah Misnan: Investigation, Supervision, Writing - review & editing. Low Lee Lee: Investigation, Supervision, Writing - review & editing. All authors read and approved the final manuscript.

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