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Original Article

Efficacy of convalescent plasma therapy for COVID-19 in Japan: An open-label, randomized, controlled trial

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ABSTRACT

Background: Convalescent plasma is a potential therapeutic option for patients with coronavirus disease 2019 (COVID-19). Despite its use for treating several viral infections, we lack comprehensive data on its efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: We conducted a multicenter, open-label, randomized controlled trial of convalescent plasma therapy with high neutralizing activity against SARS-CoV-2 in high-risk patients within five days after the onset of COVID-19 symptoms. The primary endpoint was the time-weighted average change in the SARS-CoV-2 viral load in nasopharyngeal swabs from days 0–5.

Results: Between February 24, 2021, and November 30, 2021, 25 patients were randomly assigned to either convalescent plasma (n = 14) or standard of care (n = 11) groups. Four patients discontinued their allocated convalescent plasma, and 21 were included in the modified intention-to-treat analysis. The median interval

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between the symptom onset and plasma administration was 4.5 days (interquartile range, 3–5 days). The primary outcome of the time-weighted average change in the SARS-CoV-2 viral load in nasopharyngeal swabs did not significantly differ between days 0–5 (1.2 $\log_{10}$ copies/mL in the convalescent plasma vs. 1.2 $\log_{10}$ copies/mL in the standard of care (effect estimate, 0.0 [95% confidence interval, −0.8–0.7]; P = 0.94)). No deaths were observed in either group.

Conclusions: The early administration of convalescent plasma with high neutralizing activity did not contribute to a decrease in the viral load within five days compared with the standard of care alone.

Abbreviations

COVID-19	coronavirus disease 2019
NCGM	National Center for Global Health and Medicine
DSMB	data and safety monitoring board
NEWS	National Early Warning Score
SD	standard deviation
ITT	intention to treat
IQR	interquartile range
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Ct	cycle threshold
RCT	randomized controlled trial
CI	confidence interval

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic began in December 2019 and has resulted in over 753 million cases and 6.8 million deaths worldwide [1]. Antiviral drugs, such as remdesivir [2], anti-inflammatory and immunomodulatory drugs, such as dexamethasone [3] and baricitinib [4], and neutralizing antibodies, such as sotrovimab [5], are reportedly effective against COVID-19. Furthermore, several vaccines, such as BNT162b2, are being used to prevent the onset and severity of COVID-19 [6]. However, as of 2020, treatment options remain limited, and research is ongoing to identify a cure.

Convalescent plasma is administered for viral infections, such as Lassa [7] and Bolivian hemorrhagic fever [8]. A randomized controlled trial (RCT) conducted in the 1970s for Argentine hemorrhagic fever reported reduced mortality upon convalescent plasma administration [9]. Furthermore, it was highly effective against Spanish influenza-related pneumonia, particularly when administered early during the disease [10]. Recently, convalescent plasma has also been administered for H5N1 avian influenza [11] as well as diseases, such as Middle East respiratory syndrome, caused by coronaviruses; however, there is limited data on its efficacy [12,13].

We collated the results from basic research and animal experiments to assess the efficacy of convalescent plasma with high neutralizing activity against COVID-19 [14]. To administer convalescent plasma to patients with COVID-19 in Japan, antibody titer screening and plasma collection were performed in individuals with post-acute COVID-19 [15]; the plasma was administered to some patients with COVID-19 [16]. In this study, we aimed to compare the efficacy and safety of convalescent plasma therapy for patients with early-onset COVID-19 and that of the standard of care in an RCT.

2. Patients and methods

We conducted a multicenter, open-label RCT to compare the efficacy of the early administration of convalescent plasma with the standard of care in hospitalized patients with COVID-19. This study was a collaborative effort of multiple institutions, including the National Center for Global Health and Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japanese Red Cross Narita Hospital, Tokyo Bay Urayasu Ichikawa Medical Center, Tokyo Metropolitan Bokutoh Hospital, Tokyo Medical and Dental University, JCHO Tokyo Shinjuku Medical Center, Japanese Red Cross Central Blood Institute, and the National Institute of Infectious Diseases, in Japan. Patients were enrolled between February 24, 2021, and November 30, 2021, in these medical centers. The follow-up was completed on January 21, 2022.

All the patients provided written informed consent. This study was approved by the Certified Review Board of National Center for Global Health and Medicine (NCGM-C-004126-08). A Data and Safety Monitoring Board (DSMB), consisting of two independent infectious disease physicians, a hematologist, and a statistician, was established for the safety monitoring and interim analysis. The study protocol has been described previously [17]. For quality control of the sampling technique, we prepared a standard operating procedure for swab collection and explained it to the participating institutions.

2.1. Inclusion criteria

Inclusion criteria were the following: signed informed consent; aged ≥20 years; hospitalized patients with a firstconfirmed diagnosis of COVID-19 based on polymerase chain reaction (PCR), loop-mediated isothermal amplification assay, or antigen test; and patients meeting all of the following criteria on admission: (1) who can receive convalescent plasma within five days of the onset, (2) individuals with SpO_2 ≥95% on room air, and (3) aged ≥40 years or with the following diseases: renal impairment, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, malignancy, obesity, diabetes mellitus, hypertension, and immunosuppressive state.

2.2. Exclusion criteria

The exclusion criteria were as follows: (1) pregnant or lactating women; (2) those refusing blood transfusion owing to their religious beliefs; (3) participating in any other clinical trial for COVID-19; (4) vaccinated for SARS-CoV-2; (5) previously administered convalescent plasma; (6) allergic to blood products; (7) deficiency of plasma proteins, such as immunoglobulin A; (8) New York Heart Association class III or IV heart failure; or (9) other contraindications as determined by the physician of the patient.

2.3. Randomization

The patients were randomly assigned in a 1:1 ratio to receive standard of care with convalescent plasma therapy (convalescent plasma group) or standard of care alone (control group) using an electronic randomization system (Fig. 1). Randomization was stratified by age (≥60 or <60 years), time from the onset to convalescent plasma therapy (≤3 or ≥4 days), and study site. The patients and physicians were not blinded to the treatment allocation.

2.4. Convalescent plasma therapy

Convalescent plasma was collected as described previously [15]. We determined the neutralizing activity of the convalescent plasma as the total neutralizing units by the purified IgG neutralizing activity, the amount of total human IgG in the plasma, and the total volume of the

plasma. The activity of convalescent plasma was classified into three grades [17]. For grades A, B, and C, the patients received 200 mL, 400 mL, and 800 mL of convalescent plasma, respectively. For grade C, 400 mL of convalescent plasma was administered on two different days. Type A, B, and O plasma were administered to patients of the same type; type AB plasma could only be administered to patients of types A, B, and O if the plasma of the same type was unavailable at each site. Convalescent plasma was administered at 40 mL/h for the first 15 min and subsequently increased to approximately 100 mL/h under close patient monitoring [18].

2.5. Standard of care

The standard of care was performed as described in the "Guidance for the treatment of COVID-19" published by the Ministry of Health, Labor and Welfare of Japan, "The concept of drug treatment for COVID-19" published by the Japanese Association for Infectious Diseases, or as documented at each study site. Possible treatments included medications such as antivirals, steroids, and anticoagulants.

3. Outcomes

The primary endpoint was the time-weighted average change in the SARS-CoV-2 viral load in nasopharyngeal swabs from days 0–3 and day 5. Secondary endpoints included the following: (1) mortality (days 14 and 28), (2) the prevention of mechanical ventilation (days 14 and 28), (3) the percentage of patients using oxygen, (4) the time to clinical improvement, (5) the time to improvement in the National Early Warning Score (NEWS), (6) decrease in the viral load, (7) adverse events, and (8) variants. Clinical improvement was scored as 1, 2, or 3 on the eight-category ordinal scale [2]. Improvement in the NEWS was defined as a discharge or NEWS $\leq$2 (maintained for 24 h), whichever occurred first.

3.1. Statistical analysis

Information on convalescent plasma therapy at our site was limited to patients with mild COVID-19, and we used their cycle threshold (Ct) values to evaluate the sample size. The changes in values on days 3 and 7 were 4.2 (standard deviation [SD] 5.1) and 7.7 (SD 7.1), respectively. Conversely, the Ct value was 2.7 (SD 2.2) and 2.9 (SD 9.5) for days 5 and 7, respectively, for those who did not undergo convalescent plasma therapy. Assuming an expected group difference of 2.0 (SD 4.6) by day 5 in mildly ill patients, we estimated a required sample size of 192, an allocation ratio of 1:1 between the randomized groups, an alpha error of 5%, and a power of 90%.

The modified ITT analysis set included all patients who underwent randomization, except those who did not meet the inclusion criteria, those without efficacy data, and those who did not receive convalescent plasma therapy in the convalescent plasma group as defined earlier. All patients in the control group and those who underwent convalescent plasma therapy in the convalescent plasma group were included in the safety analysis set.

The time-weighted average from baseline through day 5 was calculated for each patient as the area under the concentration-time curve, with the linear trapezoidal rule for the change from baseline divided by the time interval of the observation period. The difference in this time-weighted average change among the groups was analyzed with the analysis-of-covariance model and the following covariates: treatment group, baseline viral load, age, and the time from onset to hospitalization. Similarly, we assessed the time-weighted average from the change from baseline through day 3. The time to clinical improvement and the time to improvement on NEWS were evaluated using the Cox regression model. Statistical analyses were performed using the SAS software, version 9.4 or higher (SAS Institute).

3.2. Early study termination

Vaccination against SARS-CoV-2, the exclusion criterion for this study, has progressed rapidly in Japan, with the two-dose vaccination rate exceeding 70% as of November 2021 [19]. In addition, the monoclonal antibody products, casirivimab/imdevimab and sotrovimab, have been approved in Japan, and their distribution has been stable. Under these circumstances, we terminated patient enrollment after a discussion in the DSMB.

4. Results

Twenty-five patients were enrolled in this RCT; all patients were included in the safety analysis population (Fig. 1). Four patients discontinued their allocated convalescent plasma, and 21 patients were included in the modified ITT analysis. They were randomized in a 1:1 ratio to either the convalescent plasma or the control group. Table 1 summarizes their baseline demographic and clinical characteristics. The median age was 56 years (interquartile range [IQR], 52–71 years) and 68 years (IQR, 47–74 years) in the convalescent plasma and control groups, respectively. Of all patients, there were 17 (81.0%) males; the convalescent plasma and control groups comprised 80.0% and 81.8%

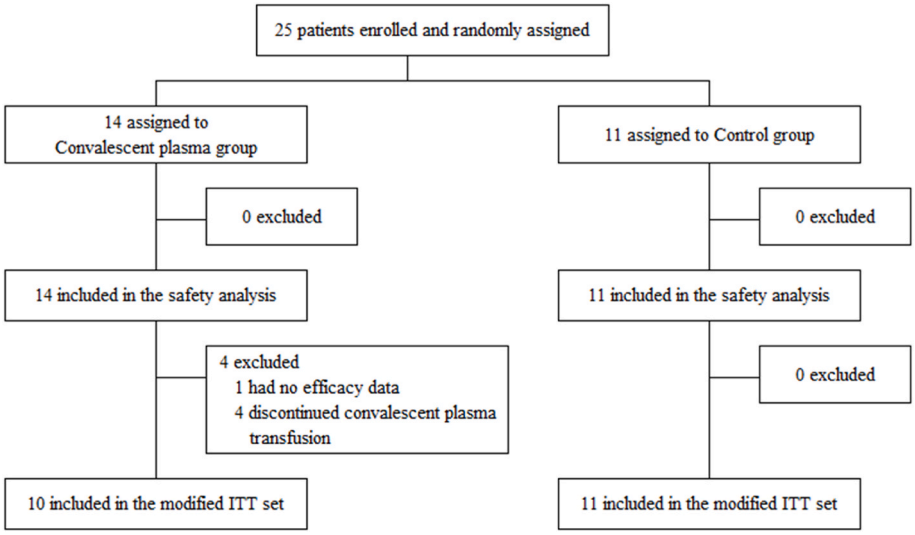

Fig. 1. Randomization and treatment allocation Abbreviations: ITT, intention to treat.

Table 1
Baseline demographics and clinical characteristics of patients.

	Convalescent plasma group (n = 10)	Control group (n = 11)
Demographic and clinical characteristics		
Age (years), median (IQR)	56.0 (52.0, 71.0)	68.0 (47.0, 74.0)
Male	8 (80.0)	9 (81.8)
Japanese ethnicity	10 (100.0)	11 (100.0)
Former or current smoker	7 (70.0)	6 (54.5)
BMI (kg/m^2), median (IQR)	24.7 (24.0, 30.5)	24.0 (21.8, 32.6)
Travel to countries within 14 days	0 (0)	0 (0)
Comorbidities		
Hypertension	7 (70.0)	7 (63.6)
Hyperlipidemia	3 (30.0)	4 (36.4)
Diabetes	3 (30.0)	2 (18.2)
Cerebrovascular disease	0 (0)	3 (27.3)
Hemiplegia	0 (0)	1 (9.1)
COPD	1 (10.0)	0 (0)
Hemodialysis before admission	1 (10.0)	0 (0)
Laboratory values		
BT (°C), median (IQR),	36.9 (36.6, 37.6)	36.7 (36.5, 38.0)
RR (breaths per minute), median (IQR),	16.0 (16.0, 18.0)	16.0 (16.0, 18.0)
HR (bpm), median (IQR),	88.0 (74.0, 95.0)	83.0 (80.0, 92.0)
Systolic BP (mmHg), median (IQR),	120.5 (109.0, 131.0)	128.0 (116.0, 140.0)
SpO_2 (%), median (IQR),	96.0 (95.0, 97.0)	97.0 (95.0, 98.0)
White blood cell count (cells/μL), median (IQR)	4270 (3900, 5090)	4750 (3200, 5820)
Lymphocyte (%), median (IQR)	22.4 (15.7, 27.5)	21.0 (14.5, 32.2)
Hemoglobin (g/dL), median (IQR)	15.2 (13.7, 15.4)	15.1 (14.1, 16.2)
Platelet count (× 10^4/μL), median (IQR)	16.0 (14.3, 20.6)	16.4 (13.7, 19.7)
D-dimer (μg/mL), median (IQR)	0.6 (0.5, 0.9)	0.5 (0.5, 0.6)
CRP (mg/dL), median (IQR)	2.8 (0.6, 3.4)	0.9 (0.1, 4.6)
ALT (U/L), median (IQR)	38.5 (24.0, 53.0)	37.0 (17.0, 68.0)
AST (U/L), median (IQR)	29.0 (25.0, 44.0)	40.0 (24.0, 86.0)
Serum creatinine (mg/dL), median (IQR)	0.9 (0.9, 1.1)	0.9 (0.8, 1.2)
LDH (U/L), median (IQR)	187.5 (177.0, 228.0)	211.0 (171.0, 232.0)
X-ray findings; positive	3 (30.0)	3 (27.3)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: IQR, interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; BT, body temperature; RR, respiratory rate; HR, heart rate; BP, blood pressure; SpO2, saturation of percutaneous oxygen; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; and LDH, lactate dehydrogenase.

males, respectively. Hypertension was the most common comorbidity in both groups (70.0%, 63.6%), with median body temperatures of 36.9 °C and 36.7 °C in the convalescent plasma and control groups, respectively (Table 1).

The median interval between symptom onset and admission was three days (IQR, 2–4 days) for patients in both groups. The median interval between the symptom onset and plasma administration was 4.5 days (IQR, 3–5 days) for patients in the convalescent plasma group. Patients in either group did not require oxygen support during randomization; the geometric mean nasal swab SARS-CoV-2 viral load was 5.352 and 5.182 $\log_{10}$ copies/mL in the convalescent plasma and control groups, respectively. Before plasma administration, therapeutic agents for COVID-19 for the convalescent plasma group included remdesivir, steroids, such as dexamethasone, and anticoagulants in seven (70%), six (60%), and six (60%) cases, respectively. For the control group, remdesivir, steroids, and anticoagulants were used in eight (72.7%), three (27.3%), and four (36.4%) cases, respectively. The alpha variant was the most common (40% in the convalescent plasma group and 45.5% in the control group), followed by the R.1 (20% and 45.5%) and delta (30% and 9.1%) variants (Table 2).

4.1. Primary outcome

In the modified ITT patients, there was no significant difference in the primary outcome of the time-weighted average change in the SARS-CoV-2 viral load in nasopharyngeal swabs from days 0–5 (1.2 $\log_{10}$ copies/mL in the convalescent plasma group vs. 1.2 $\log_{10}$ copies/mL in the control group (effect estimate, 0.0 [95% CI, −0.8 to 0.7]; P = 0.94)) and from days 0–3 (0.8 vs. 0.7 $\log_{10}$ copies/mL (effect estimate, 0.1 [95% CI, −0.7 to 0.9]; P = 0.73)) (Table 3).

4.2. Secondary outcomes

No deaths were observed in either group, and the secondary endpoint of the 28-day mortality did not significantly differ. Noninvasive mechanical ventilation was used for only one patient in the control group (P = 0.34). We observed no significant difference in oxygen therapy (60.0% in the convalescent plasma group vs. 45.5% in the control group (HR, 1.6 [95% CI, 0.5–5.1]; P = 0.45). The median time to clinical improvement was 9.5 days and 8.0 days in the convalescent plasma and control groups, respectively, without significant difference (HR, 1.3 [95% CI, 0.5–3.1]; P = 0.59). The time-weighted average change in the SARS-CoV-2 viral load in nasopharyngeal swabs from days 0–5 of the three patients in each group who did not receive the remdesivir, showed a decrease in viral load of 1.4 $\log_{10}$ copies/mL in the convalescent plasma group and 2.3 $\log_{10}$ copies/mL in the control group (effect estimate, −0.8 [95% CI, −2.3 to 0.7]; P = 0.20).

4.3. Adverse events

Convalescent plasma therapy was discontinued in four patients for the following reasons: Two patients were diagnosed with type I hypersensitivity owing to pruritus and generalized wheals. They were treated with d-chlorpheniramine maleate, and their conditions improved within

Table 2
Clinical status of patients at randomization.

	Convalescent plasma group (n = 10)	Control group (n = 11)
Days between symptom onset and admission, median (IQR)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Days between symptom onset and administration, median (IQR)[a]	4.5 (3.0, 5.0)	4.0 (4.0, 5.0)
Oxygen therapy	0 (0)	0 (0)
SARS-CoV-2 virus load ($\log_{10}$ copies/ml), geometric mean ± geometric SD[b]	5.352 ± 0.904	5.182 ± 0.996
Medication before convalescent plasma therapy		
Remdesivir	7 (70.0)	8 (72.7)
Baricitinib	0 (0)	1 (9.1)
Tocilizumab	0 (0)	1 (9.1)
Steroids	6 (60.0)	3 (27.3)
Anticoagulant	6 (60.0)	4 (36.4)
Variants		
B.1.1.7	4 (40.0)	5 (45.5)
B.1.617.2	3 (30.0)	1 (9.1)
R.1	2 (20.0)	5 (45.5)
Unknown	1 (10.0)	0 (0)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: IQR, interquartile range; SD, standard deviation.
[a] The expected administration date during randomization is described for the control group.
[b] In nasopharyngeal swabs.

Table 3
Primary and secondary outcomes.

	Convalescent plasma group (n = 10)	Control group (n = 11)	Effect estimate (95% CI)	*P* value
Time-weighted average change in the SARS-CoV-2 viral load in nasopharyngeal swabs				
From days 0–5 (log_{10} copies/ml), geometric mean (geometric SE)*	1.2 (0.3)	1.2 (0.3)	0.0 (−0.8, 0.7)	.94
From days 0–3 (log_{10} copies/ml), geometric mean (geometric SE) *	0.8 (0.3)	0.7 (0.3)	0.1 (−0.7, 0.9)	.73
28-day mortality	0 (0)	0 (0)	NA	NA
Mechanical ventilation[a]				
On day 14	0 (0)	1 (9.1)	NA	.34
On day 28	0 (0)	1 (9.1)	NA	.34
Oxygen therapy	6 (60.0)	5 (45.5)	HR, 1.6 (0.5–5.1)	.45
Time to clinical improvement (days), median (IQR)	9.5 (6.0, 13.0)	8.0 (6.0, 13.0)	HR, 1.3 (0.5–3.1)	.59
Time to improvement on the NEWS (days), median (IQR)	1.0 (1.0, 4.0)	2.0 (2.0, 2.0)	HR, 1.8 (0.7–4.6)	.10

Data are presented as n (%) unless otherwise indicated.
Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard errors; HR, hazard ratio; NA, not applicable; and NEWS, National Early Warning Score.
[a] Includes noninvasive mechanical ventilation.

48 h. One patient had chills, shivering, and elevated blood pressure; we administered nifedipine, and the patient improved the subsequent day. Other patients had fever, chills, and shivering while undergoing convalescent plasma therapy. Vancomycin and cefepime were administered, and their symptoms improved the subsequent day. Blood and convalescent plasma culture results were negative.

5. Discussion

In this RCT of patients with mild COVID-19, there was no significant difference in time-weighted average changes in the SARS-CoV-2 virus load in nasopharyngeal swabs from days 0–5 between patients who received convalescent plasma therapy combined with standard of care and those who received standard of care alone. Further, we observed no significant difference in the secondary outcomes of 28-day mortality, mechanical ventilation, and oxygen therapy.

In this study, the viral load in the nasopharyngeal swabs from the convalescent plasma group did not decrease compared with that in the control group. However, in 2022, Koen et al. reported that the administration of high-titer convalescent plasma suppressed viral growth in the lung of SARS-CoV-2-infected rhesus monkeys despite the lack of decrease in the nasopharyngeal viral load [20]. The nasopharyngeal viral load was used as the primary endpoint because of the feasibility of the number of cases in the study design phase; however, it may underestimate the effect of convalescent plasma therapy against SARS-CoV-2 because the nasal and lung viral loads may diverge in response to convalescent plasma administration.

We selected patients with high SARS-CoV-2 antibody titers and collected their convalescent plasma [15]. Further, we selected plasma with high neutralizing activity from the collected plasma and administered it to the patients [17]. Previously, some studies investigating the efficacy of convalescent plasma in patients with COVID-19 used high titers of recovered plasma [18,21], whereas others did not use a specific titer [22,23]. Furthermore, even in studies with specified antibody titers, the neutralizing activity was not measured for feasibility reasons. The antibody titer was determined as a cut-off based on the correlation between the titer and neutralizing activity [18,24]. Antibody titers influence the outcome of convalescent plasma therapy [25]. Furthermore, the approved neutralizing antibodies exhibit high neutralizing activity [26]. Nonetheless, no statistically significant results were obtained in this study; plasma with high titer and neutralizing activity should be used to accurately evaluate convalescent plasma.

We included patients who could receive convalescent plasma within five days of COVID-19 onset based on reports during the study design that convalescent plasma administration is more effective during this phase [27]. Joyner et al. conducted a retrospective analysis of over 3, 000 patients with COVID-19 in the United States who received convalescent plasma under an expanded access program; they reported that the administration of convalescent plasma within three days of diagnosis reduced the mortality [25]. Thus, the early administration of convalescent plasma for COVID-19 appeared crucial.

The convalescent plasma used in this study had high neutralizing activity against COVID-19. Further, we designed the study assuming that neutralizing antibodies would contribute to the prevention of severe COVID-19 infection. Therefore, we used vaccination history as an exclusion criterion; however, the number of eligible patients rapidly decreased because of the rapid vaccination progress in Japan immediately after the study commenced in 2021 [28]. In addition, casirivimab/imdevimab, a neutralizing antibody cocktail, was granted special approval in July 2021 [29], and the administration criteria overlapped substantially with the inclusion criteria for this study. Therefore, patient enrollment did not proceed as planned, and the study was terminated prematurely. Therefore, a rapid research system had to be established, and the study had to be conducted more promptly. Since the advent of the Omicron variant, monoclonal antibodies have not been used as a therapeutic option due to their reduced *in vitro* activity [30]. The role of convalescent plasma seemed to have been lost with the advent of monoclonal antibodies; however, with the introduction of diverse variants, such as the Omicron variant, convalescent plasma may assume a new role.

Our study had several limitations. First, the sample size was small, and the study was discontinued. The study may have been underpowered to detect the microbiological effects of convalescent plasma therapy. Second, we performed an open-label study. However, this bias is minimal because the primary outcome was the viral load, an objective measure. Third, the use of the standard of care was not protocolized in both groups, which could have influenced the results. Fourth, administering plasma to the control group as well would have been ideal; however, this could not be done for ethical reasons, including unknown infections. Fifth, although we measured the neutralizing activity against the wild strain in plasma, the predominant SARS-CoV-2 virus changed to its alpha and delta variants during this study. Since the neutralizing activity in plasma varies across variants, the efficacy of convalescent plasma may vary over time.

6. Conclusions

In patients with early-onset mild COVID-19 disease, the combination of convalescent plasma and standard therapies did not contribute to a decreased viral load within five days compared with that using standard therapy alone.

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Author contributions

Conceptualization, SS, SK, YT, KM, WS, NO, and HM; Methodology, SS, SK, JT, YU, YT, KS, MS, TT, AM, KO, IH, KM, NHT, MK, MK, KT, EI, YI, AH, AM, WS, NO, and HM; Formal Analysis, YS, and YU; Investigation, SS, SK, IA, RH, RO, NS, YM, and HS; Data Curation, AY; Writing, SS, YU, and YT; Supervision, WS, NO, and HM; Project Administration, SS, SK, JT, KF, MN, SA, MT, AK, and AM; Funding Acquisition, SS, SK, SM, NO, and KM.

Authorship statement

All authors meet the ICMJE authorship criteria.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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