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Trends of participants in convalescent plasma donation for COVID-19 in Japan as the pandemic evolved

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ABSTRACT

Background: We aimed to investigate chronological changes in the characteristics of participants in a coronavirus disease 2019 convalescent plasma donation study that may benefit optimal collection methods in the future.

Methods: Data from a convalescent plasma donation study from April 30, 2020 to November 5, 2021 were collected and analyzed. After August 23, 2021, an interim analysis of factors linked to higher antibody titers led us to restrict our participant recruitment criteria to participants who were within 4 months of disease onset and to patients who were otherwise most likely to have sufficiently high antibody titers. Overall, 1299 samples from 1179 patients were analyzed.

Results: Over the duration of the study, 35.9% of the samples were deemed eligible for convalescent plasma collection. The overall eligibility rate initially declined, dipping to <20% after one year. During this period, the proportion of enrolled samples from patients who had severe illness also declined, and the proportion of samples from participants who were >120 days post disease onset increased. After the addition of days from onset and vaccination status to our participant recruitment criteria, the eligibility rate improved significantly.

Conclusions: As outbreaks of emerging infectious disease occur, it is desirable to construct and implement a scheme for convalescent plasma donation promptly and to monitor the eligibility

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rate over time. If it declines, promptly analyze and resolve the associated factors. Additionally, vaccine development and infection prevalence are likely to influence the effective recruitment of participants with high antibody titers.

1. Introduction

Convalescent plasma has been widely studied for the treatment of emerging infectious diseases, including Spanish influenza [1], Ebola virus disease [2], severe acute respiratory syndrome [3], and Middle East respiratory syndrome [4]. Convalescent serum or plasma obtained from the survivors has been used to obtain protective and therapeutic benefits against infectious diseases in the past [5]. With the development of effective treatments and preventive interventions, such as antibiotics, antiviral agents, and vaccines, the importance of convalescent plasma in the clinical settings has relatively declined. However, convalescent plasma can be an important treatment candidate during the pandemic of emerging infectious diseases, especially when effective antimicrobials and vaccines have not been made available yet. Studies involving the use of convalescent plasma have been conducted worldwide since the early stages of the COVID-19 pandemic but have ultimately failed to demonstrate any efficacy [6]. Nevertheless, convalescent plasma has various applications, including not only treatment by direct administration but also the development of antibody and immunoglobulin preparations [7]. Even if the efficacy of direct treatment against COVID-19 has not been demonstrated, convalescent plasma should be collected during pandemics of emerging infectious diseases to pursue the possibility of its treatment efficacy and the development of derivative products. Establishing, organizing, and maintaining a scheme to collect, store, and study convalescent plasma is important for preparedness against emerging and re-emerging infectious diseases [8].

To our knowledge, prior to the COVID-19 pandemic, there was no scheme in Japan for collecting convalescent plasma for emerging infectious diseases. Our group established a study to collect and store convalescent plasma in response to COVID-19, the details of which have been reported previously [9]. However, there are no reports on the trends of participants eligible for plasma donation, including how their backgrounds may have changed over time, during subsequent pandemics. During a pandemic, there is a great burden on medical institutions that respond to the acute phase of the emerging disease. Thus, it is essential to efficiently recruit eligible participants. By showing how participants respond in emerging infectious disease clinical trials over time, future research on emerging infectious diseases will be conducted more efficiently and appropriately. In this study, we aimed to investigate changes in the characteristics of participants in COVID-19 convalescent plasma donation at our institution over time and to highlight any findings that are deemed beneficial to the collection of convalescent plasma in future emerging infectious diseases.

2. Methods

2.1. Study design, setting, and participants

We performed a retrospective cross-sectional study analyzing the characteristics of patients who participated in a convalescent plasma donation study from April 30, 2020 to November 5, 2021. Our study was approved by the ethics committee of National Center for Global Health and Medicine (NCGM) (approval number: NCGM-G-003536-07). The details of the scheme for our convalescent plasma donation for this study has been already reported [9]. All participants provided written informed consent. The study initially included patients admitted to our hospital, and subsequently, expanded to also include external participants recruited through social network services and websites. The samples were obtained only from the NCGM. The inclusion criteria at initiation of this study are as follows [9]:

Candidates must satisfy all the following items to undergo pre-donation screening.

i) Written consent obtained from the candidate.
ii) Cleared from isolation or hospitalization under latest policy.
iii) At least 3 weeks from onset
iv) Weighs $\geq$45 kg for male or $\geq$40 kg for female
v) Previous COVID-19 diagnosis confirmed by official documentation
vi) At least 3 weeks from onset

We had previously analyzed and reported the data from the first 581 participants and found that age, systemic steroid use, fever, blood type AB, and earlier collection of plasma after disease onset were associated with higher antibody titers [10]. Therefore, after August 23, 2021, to focus on collection in participants who have these factors, we restricted recruitment to participants who were within 4 months of disease onset or to individuals who were expected to have sufficiently high antibody titers, such as those who were recently vaccinated. The inclusion criteria after August 23, 2021 was as follows:

Candidates must satisfy all the following items to undergo pre-donation screening.

i) Written consent obtained from the candidate. If re-screening is conducted after 3 months from the previous participation, re-consent should be obtained. Re-screening is possible if the patient is expected to have high antibody titer.
ii) Male or female aged 20–69 years. Those aged 65–69 years should have experienced blood donation at ages 60–64 years.

iii) Previous COVID-19 diagnosis confirmed by official documentation
iv) At least 3 weeks from onset and cleared from isolation or hospitalization under latest policy
v) Within 4 months of disease onset or individuals who were expected to have sufficiently high antibody titers (such as those who were recently vaccinated).
vi) Performance Status (ECOG criteria) is 0 or 1

2.2. Data sources/measurement

Participant characteristics, including the date of COVID-19 onset and diagnosis, symptoms, hospitalization, and treatment, were collected at enrollment. Any uncertainties were clarified by a physician and research assistant during the medical interview. Referral letters and medical records of the hospital were also used to confirm data, if available. As a screening test before convalescent plasma donation, serum anti-SARS-CoV-2 spike protein immunoglobulin G antibodies were examined at enrollment. As described previously [9], the antibody titer was measured by enzyme-linked immunosorbent assay with a full-length Spike protein in the research laboratory of our hospital until November 2020 (S-full ELISA). Thereafter, the antibodies were measured using a fully automated high-sensitivity chemiluminescence enzyme immunoassay (Sysmex Corporation, Kobe, Japan) (S-ELISA) and quantified using World Health Organization (WHO) standardized values. To enable the comparison of antibody titers between measurement methods, antibody titers of samples collected before November 2020 were re-measured and calculated using WHO standardized values. Eligibility for convalescent plasma donation was determined by the principal investigator based on the antibody titers measured at that time. The cut-off antibody titer for convalescent plasma donation was originally set as 1.0 optical density (450 nm) of the S-full ELISA (Supplemental Fig. 2) [9]. After conducting the S-ELISA, we re-evaluated the 224 pre-donation samples and set 93.9 SU/mL as the cut-off antibody titer (Supplemental Fig. 2). This cut-off value was re-evaluated after introducing WHO-standardized values and finally set

Table 1
Characteristics of enrolled samples, total and every 4 months (N = 1299).

	Missing	Total	Apr–Jul 2020	Aug–Nov 2020	Dec 2020–Mar 2021	Apr–Jul 2021	Aug–Nov 2021
Number of samples		1299	103	204	269	304	419
Male Sex, n (%)	0	595 (45.8)	59 (57.3)	108 (52.9)	128 (47.6)	127 (41.8)	173 (41.3)
Age (years old), median [IQR]	0	45 [38, 53]	46 [36.5, 55.5]	45 [35, 52]	47 [39, 54]	45 [35, 52]	45 [38, 52]
Comorbidities, n (%)	6						
Hypertension		166 (12.8)	17 (17.2)	32 (15.8)	39 (14.5)	40 (13.2)	38 (9.1)
Diabetes		60 (4.6)	13 (13.1)	12 (5.9)	17 (6.3)	14 (4.6)	4 (1)
Dyslipidemia		145 (11.2)	15 (15.2)	29 (14.3)	35 (13)	37 (12.2)	29 (6.9)
Current Smoking, n (%)	68	121 (9.8)	8 (18.6)	19 (9.7)	21 (7.8)	27 (8.9)	46 (11)
BMI (kg/m^2), median [IQR]	293	23.2 [20.8, 26.3]	24.1 [21.6, 26.9]	24.7 [22.7, 27.6]	23.8 [21.2, 26.1]	23 [20.8, 26.4]	22.8 [20.3, 25.7]
Blood type, n (%)	4						
A		552 (42.6)	44 (42.7)	90 (44.8)	115 (42.8)	124 (40.8)	179 (42.8)
B		293 (22.6)	23 (22.3)	38 (18.9)	69 (25.7)	73 (24)	90 (21.5)
O		305 (23.6)	27 (26.2)	48 (23.9)	56 (20.8)	66 (21.7)	108 (25.8)
AB		145 (11.2)	9 (8.7)	25 (12.4)	29 (10.8)	41 (13.5)	41 (9.8)
Vaccination history, n (%)	581						
None		373 (51.9)	Not obtained	Not obtained	Not obtained	255 (85.3)	118 (28.2)
One time		87 (12.1)	Not obtained	Not obtained	Not obtained	20 (6.7)	67 (16)
Two times		258 (35.9)	Not obtained	Not obtained	Not obtained	24 (8)	234 (55.8)
Days from symptom onset to sampling, median [IQR]	12	87 [53, 157]	67 [37.8, 96]	51.5 [35, 99.8]	70 [45, 113.8]	128 [78.8, 194]	96 [65, 227.5]
Symptoms at the time of onset, n (%)	5						
Fever		1125 (86.9)	88 (89.8)	174 (85.3)	227 (84.4)	253 (83.2)	383 (91.4)
Headache		591 (45.7)	15 (15.3)	78 (38.2)	115 (42.8)	160 (52.6)	223 (53.2)
Cough		670 (51.8)	41 (41.8)	89 (43.6)	131 (48.7)	157 (51.6)	252 (60.1)
Throat pain		378 (29.2)	13 (13.3)	39 (19.1)	70 (26)	108 (35.5)	148 (35.3)
Runny nose		289 (22.3)	15 (15.3)	15 (7.4)	60 (22.3)	91 (29.9)	108 (25.8)
Dysgeusia		447 (34.5)	28 (28.6)	59 (28.9)	94 (34.9)	119 (39.1)	147 (35.1)
Dysosmia		564 (43.6)	21 (21.4)	69 (33.8)	117 (43.5)	152 (50)	205 (48.9)
Diarrhea		286 (22.1)	21 (21.4)	27 (13.2)	61 (22.7)	68 (22.4)	109 (26)
Severity, n (%)							
Oxygen administered	17	175 (13.7)	19 (22.1)	39 (19.1)	35 (13)	32 (10.5)	50 (11.9)
Mechanical ventilation	18	23 (1.8)	6 (7.1)	9 (4.4)	3 (1.1)	4 (1.3)	1 (0.2)
ECMO	17	8 (0.6)	2 (2.3)	3 (1.5)	2 (0.7)	1 (0.3)	0 (0)
Immunomodulator during COVID-19, n (%)							
Steroid	36	145 (11.5)	8 (10.3)	19 (9.6)	32 (12.1)	27 (8.9)	59 (14.1)
Tocilizumab	29	8 (0.6)	1 (1.2)	3 (1.5)	1 (0.4)	1 (0.3)	2 (0.5)
Antibody titer (BAU/mL), median [IQR]	3	344 [103.7, 1761.2]	285.1 [139.8, 685.1]	223.3 [82.5, 543.8]	230.2 [100.4, 452.9]	129.1 [53.4, 503.1]	3567 [741.7, 7323.8]

644.20 BAU/mL. These cut-off antibody titers could select samples with neutralizing antibody ≤20 μg/mL [9]. Participants deemed eligible then donated their convalescent plasma in a subsequent hospital visit.

2.3. Statistical methods

Continuous variables were expressed as median and interquartile range, and categorical variables were expressed as number and percentage of cases. An interrupted time-series analysis (ITSA) was performed to estimate the effect of the change of recruiting criteria. The intervention was defined as the introduction of new criteria implemented on August 23, 2021. The ITSA includes the variable of week and two dummy variables, the change of the recruiting criteria, taking a value of 0 before intervention or 1 after intervention, and the interaction term of week and intervention, taking a value of 0 before intervention. The weekly change, intervention effect and interaction between week and intervention, were estimated based on a segmented linear regression model and p-value was calculated for each variable. The *lm* function in stats package was used for ITSA and parameter evaluation using least-squares method. All analyses were performed using the statistical software R (Ver. 4.0.3).

3. Results

A total of 1300 samplings were conducted from 1180 participants between April 30, 2020 and November 5, 2021. One participant withdrew consent after sampling, leaving 1299 samples from 1179 participants included in the analysis. Ninety participants who were not initially considered for convalescent plasma donation for various reasons (such as history of residence in a particular country or region, positive test results for certain infectious diseases, or positive results for irregular antibodies) were included in this analysis based on their anti-SARS-CoV-2 spike protein immunoglobulin G antibody titer results. Background information related to the 1299 samples is shown in Table 1. Supplemental Table 1 displays the data distributed by month instead of by 4-month periods.

The number of samplings per week, number of eligible samples, and eligibility rates are shown in Fig. 1A and B. Over the entire study period, 35.9% of the samples were eligible for convalescent plasma donation. The first half of the study period showed a large variation in eligibility rates, but it gradually declined over time, falling below 20% around April 2021. The results of ITSA is shown on Fig. 1B and Table 2. At the criteria modification, the eligibility rate were sharply increased and likely to chagne its trend from downward to upward. The eligibility rate improved to approximately 60% by the end of the study period (Fig. 1B). For reference, the trend of new infected patients in Tokyo during the same period as this study, the culumative number of reported cases in Tokyo, and cumulative number of vaccination in Japan are shown in Supplemental Figs. 1A, 1B, and 1C, respectively.

The percentage of eligible samples within 120 days of disease onset (Fig. 2A) and the percentage of samples from critically ill patients who required oxygen administration (Fig. 2B) are shown by week. The results of ITSA are shown in Tables 3 and 4. Beginning around April 2021 when the eligibility rate declined, the percentage of samples within 120 days of illness onset also declined, resulting in only a few eligible samples. The percentage of samples from critically ill patients requiring oxygenation was 22.1% in the April–July 2020 period but then showed a gradual downward trend, dropping to 10.5% in the April–July 2021 period (Table 1, Fig. 2B).

After April 2021, samples with onset of illness or vaccination within 120 days were highest (Fig. 3). The results of ITSA are shown in Table 5. Compared to Fig. 2A, it is clear that the majority of those eligible samples were within 120 days of vaccination. Fig. 4 shows the antibody titers with criteria modification. After criteria modification, several samples showed higher antibody titers than our cut-off even without vaccination. These results indicate that the vaccination and criteria modification both contributed to the recovery of

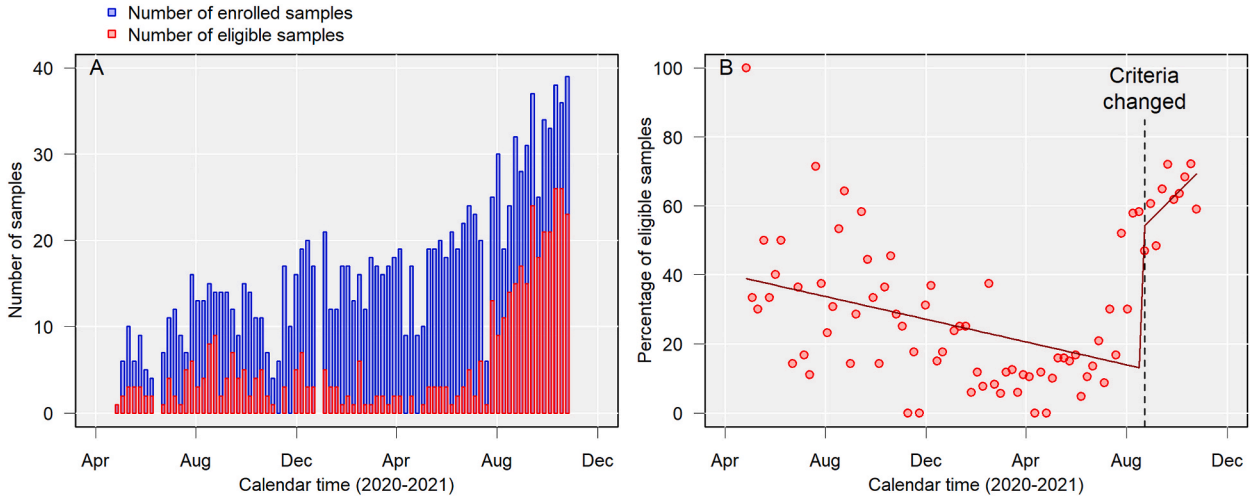

Fig. 1. Enrolled and eligible samples per week. A: Numbers, B: Percentage.
The fitting line in Fig. 1B is a segmented linear regression line estimated by the least-squares method using the eligible samples before and after the criteria changed.

Table 2
Results of interrupted time-series analysis to estimate the effect of change of recruiting criteria in Fig. 1B.

Variable	Estimate	95% CI	p value
(intercept)	39.3	[30.7, 47.9]	<0.001
Week	−0.4	[-0.6, −0.2]	<0.001
Change of criteria	39.5	[14.5, 64.4]	0.0023
Interaction of week and change of criteria	2.0	[-1.8, 5.8]	0.29

Abbreviation: CI; confidential interval.

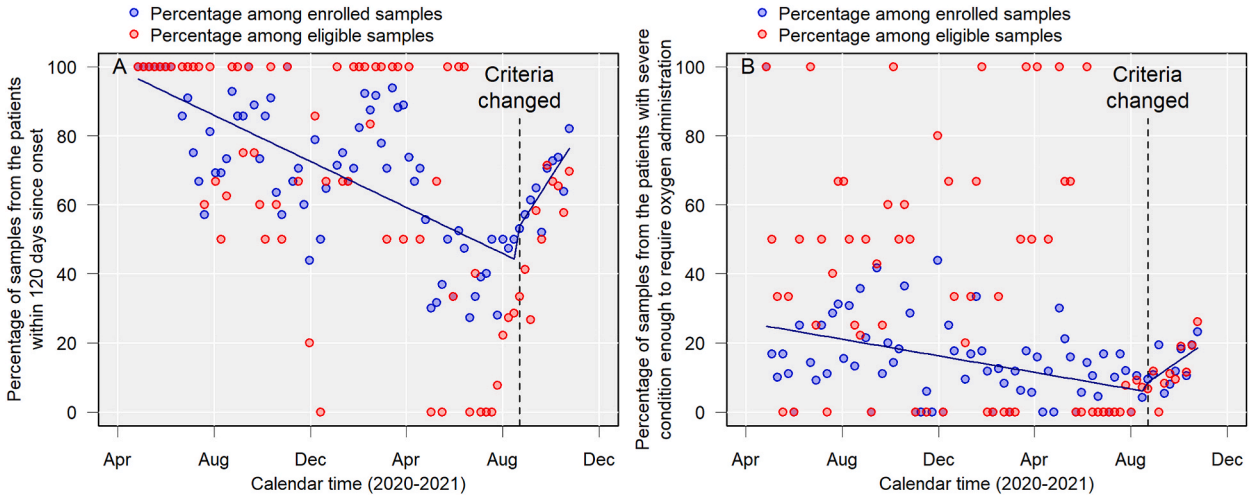

Fig. 2. Percentage of samples per week. A: Within 120 days since onset, B: With severe condition during disease.
The fitting line in Fig. 2A and B are segmented linear regression lines estimated by the least-squares method using the enrolled samples before and after the criteria changed.

Table 3
Results of interrupted time-series analysis to estimate the effect of change of recruiting criteria in Fig. 2A.

Variable	Estimate	95% CI	p value
(intercept)	97.3	[90, 104.5]	<0.001
Week	−0.8	[-0.9, −0.6]	<0.001
Change of criteria	7.1	[-14, 28.2]	0.51
Interaction of week and change of criteria	3.3	[0.1, 6.5]	0.046

Abbreviation: CI; confidential interval.

Table 4
Results of interrupted time-series analysis to estimate the effect of change of recruiting criteria in Fig. 2B.

Variable	Estimate	95% CI	p value
(intercept)	25.1	[18.3, 31.8]	<0.001
Week	−0.3	[-0.4, −0.1]	0.0015
Change of criteria	1.4	[-18.2, 21.1]	0.89
Interaction of week and change of criteria	1.4	[-1.6, 4.4]	0.36

Abbreviation: CI; confidential interval.

eligibility rate.

To discuss how the eligibility rate would have changed if we had applied the modified eligibility criteria throughout the study period, we analyzed the eligibility rate after excluding samples obtained after 120 days of disease onset or vaccination (Fig. 5A and B). As shown in Fig. 5B, if the modified eligibility criteria had been applied from the beginning of this study, the eligibility rate would have increased slightly after one year of the study.

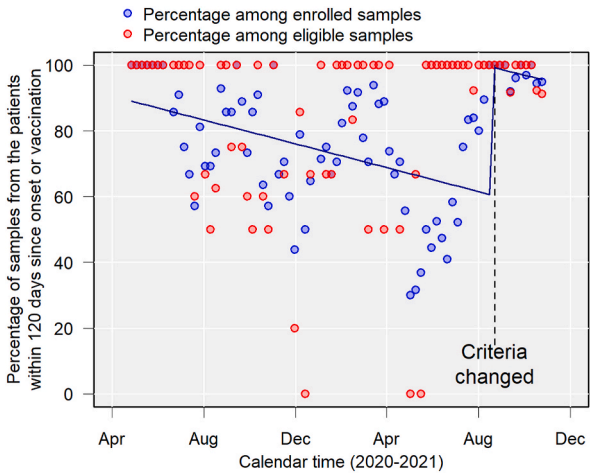

Fig. 3. Percentage of samples within 120 days since disease onset or vaccination per week
The fitting line in Fig. 3 is a segmented linear regression line estimated by the least-squares method using the enrolled samples before and after the criteria changed.

Table 5
Results of interrupted time-series analysis to estimate the effect of change of recruiting criteria in Fig. 3.

Variable	Estimate	95% CI	p value
(intercept)	89.5	[81.5, 97.4]	<0.001
Week	−0.4	[-0.6. −0.2]	<0.001
Change of criteria	38.9	[15.8, 62.1]	0.0013
Interaction of week and change of criteria	0	[-3.5, 3.5]	0.99

Abbreviation: CI; confidential interval.

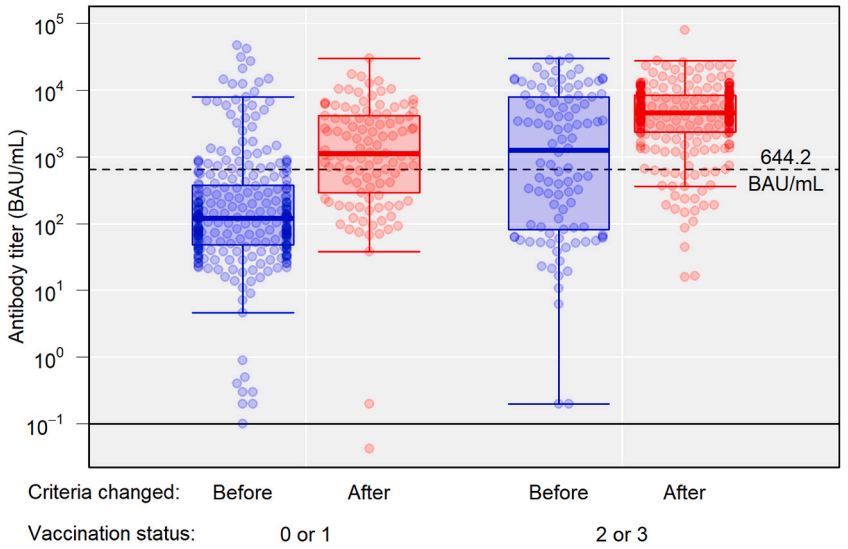

Fig. 4. Antibody titer with criteria modification.

4. Discussion

We analyzed the number of participants and their backgrounds over time in a COVID-19 convalescent plasma donation study to further advance the convalescent plasma project during future outbreaks of emerging and re-emerging infectious diseases. The eligibility rate decreased over time after the first year following the COVID-19 outbreak. Subsequently, modification of the recruitment criteria and widespread vaccination of the general public were thought to have significantly improved the eligibility rate.

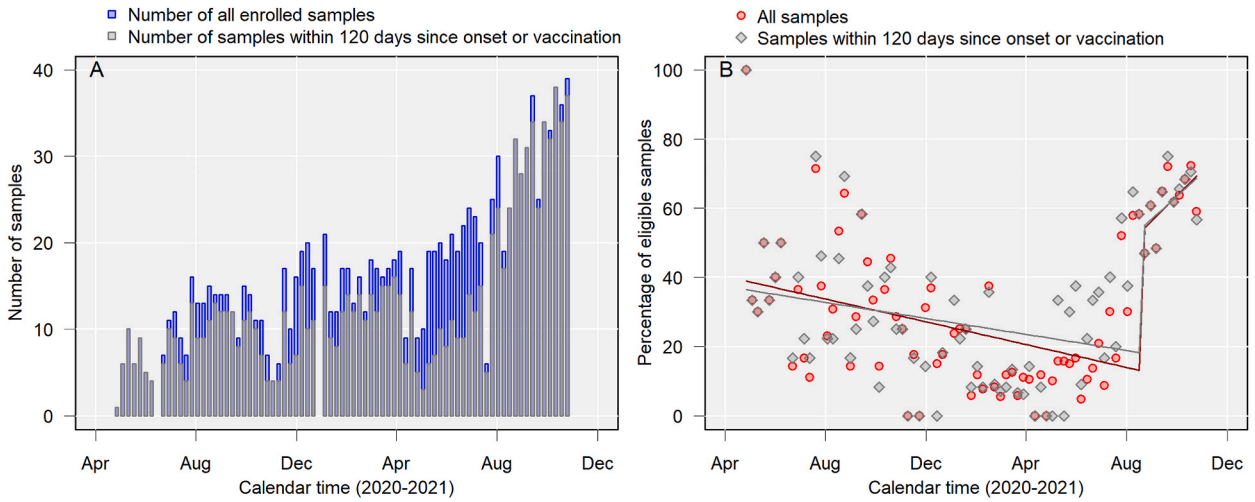

Fig. 5. Samples within 120 days since onset or vaccination. A: Numbers, B: Percentage.
The fitting lines in Fig. 5B are segmented linear regression lines estimated by the least-squares method using the enrolled samples before and after the criteria changed. Red line: using all samples. Gray lines: using samples within 120 days since onset or vaccination. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

We believe that the primary reason for the large drop in eligibility one year after study enrollment was the increase in the number of participants with low titers due to the longer duration from disease onset. As emerging infectious diseases, including COVID-19, spread through the community over time, the cumulative number of cases increases. As a result, the number of candidates for studies of this kind increases over time. This may be at least partially offset by a similar increase in the number of candidates with a lower antibody titer, as antibody titers decrease over time after infection [11]. Thus, a smaller proportion of candidates may be eligible for convalescent plasma donation over time. Prompt construction and implementation of a scheme that favors suitable donor eligibility is necessary for responding to future emerging and re-emerging infectious disease pandemics.

The proportion of critically ill patients in our study gradually declined over time. Because high antibody titers are associated with severe clinical illness [12], the eligibility rate may decrease because the proportion of patients with milder illness may increase. As community-acquired infection spreads, testing strategies strengthen, and public awareness increases, patients with mild or asymptomatic infections may become more likely to be tested or diagnosed, whereas they may have been less likely to be tested at the beginning of the outbreak. These factors may also contribute to a decline in the eligibility rate.

The large variation in eligibility rates in the first half of the study period could be attributed to the small number of enrolled participants. At the beginning of this study, this study was not well-known among patients and healthcare workers. Moreover, because this was a single-center study, shortage of staff made the acceptance of large amount of participants challenging. These factors could have influenced the variation in the eligibility rate.

The widespread use of vaccines over time was likely a major contributing factor to the significant improvement in the eligibility rate toward the end of the study period. Our study showed that even if the duration of days passed since the onset of the disease grew longer, patients were likely to be eligible if they had a recent vaccination. Therefore, once a vaccine becomes widely available to the general public in future emerging and re-emerging infectious disease pandemics, the inclusion of vaccination as a recruitment requirement to participate in convalescent plasma donation should be actively considered. However, there is no guarantee that vaccines will be rapidly developed in future emerging and re-emerging infectious disease pandemics. Moreover, vaccines might not be widely available in resourse-limited countries. Additionally, antibody titers decline over time after vaccination [13]. Thus, the modification of criteria other than the vaccine itself are important.

The eligibility rate increased sharply after the modification of recruitment criteria. Simultaneously, the number of patients with COVID-19 in Tokyo extensively increased. Thus, we could enroll the participants who were infected with COVID-19 recently, which contributed to the increase in the eligibility rate. To facilitate the collection of convalescent plasma without relying on vaccines, it is prudent to examine the factors that contribute to a decline in the eligibility rate and to reconsider recruitment criteria. For these reasons, it is critical to establish a system that best enables high participation among the candidates most likely to be eligible.

4.1. Limitations

This analysis was based on history taking at enrollment; therefore, the potential for recall bias is inherent. However, we believe that the combination of answers has an appropriate degree of reliability because specific items, such as oxygen supplementation and vaccination history, are likely to be accurate. The number of days since onset of illness, vaccination status, and severity of illness were primary factors of interest. It is possible that participant characteristics not included in the study may have influenced the results, including the particular COVID-19 variant associated with the participant's illness, as well as other confounding factors not listed. In

Japan, delta variants were dominant in August 2021; thus, it could have influenced our results. We were able to accept only a limited number of candidates on a single day during recruitment. Therefore, when the number of candidates exceeded the daily limit, participation was reduced. Selection bias may have occurred; however, we are not aware that it did. Eligibility was determined by the principal investigator. The antibody titer at that time was used as a reference; however, the lack of an objective indicator for eligibility is another limitation. The neutralization titer could be another factor for determining eligible participants for plasma donation. Because data on antibody titers and treatment efficacy after infection are scarce in the early phase of an emerging infectious disease pandemic, our data represent a realistic response. This study is a single-center study, which limits its external validity. Finally, the ability to accurately generalize the results of this study to countries with vastly different characteristics and backgrounds is limited.

5. Conclusion

When conducting clinical research on convalescent plasma donation during future outbreaks of emerging and re-emerging infectious diseases, promptly constructing and implementing a collection scheme is necessary to enhance the likelihood of a favorable outcome. The eligibility rate for convalescent plasma donation should be monitored over time. If it declines, potential contributing factors should be analyzed promptly. The results and our interpretation of findings should be used to amend the recruitment criteria for convalescent plasma donation so that participants with high antibody titers are more effectively recruited. This includes adding vaccination history after vaccines are developed and become widely available. All methods to efficiently recruit participants with high antibody titers should be considered to facilitate an effective response to future pandemics of emerging and re-emerging infectious diseases.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Tetsuya Suzuki: Data curation, Writing – original draft. **Yusuke Asai:** Writing – original draft. **Kozue Takahashi:** Data curation. **Mio Sanada:** Data curation. **Yumiko Shimanishi:** Data curation. **Mari Terada:** Data curation. **Lubna Sato:** Data curation. **Makoto Inada:** Data curation. **Gen Yamada:** Data curation. **Yutaro Akiyama:** Data curation. **Yusuke Oshiro:** Investigation. **Katsuyuki Shiratori:** Investigation. **Tomiteru Togano:** Investigation. **Yuki Takamatsu:** Formal analysis. **Maeda Kenji:** Formal analysis. **Akihiro Matsunaga:** Formal analysis. **Yukihito Ishizaka:** Formal analysis. **Hidetoshi Nomoto:** Data curation. **Noriko Iwamoto:** Formal analysis. **Sho Saito:** Formal analysis, Writing – review & editing. **Satoshi Kutsuna:** Conceptualization, Investigation. **Shinichiro Morioka:** Writing – review & editing, Formal analysis, Conceptualization, Funding acquisition, Methodology, Project administration, Supervision. **Norio Ohmagari:** Conceptualization, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20568.

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