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blood advances

Drivers of temporal improvement in CAR T-cell therapy for large B-cell lymphoma: a Japanese nationwide registry analysis

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Key Points

- Real-world PFS after CAR T-cell therapy for R/R LBCL in Japan has improved in the recent era despite expanded treatment indications.
- High-risk gains were notable; overall PFS gains were linked to second-line CAR T, better pre-infusion control, and axi-cel/liso-cel shift.

Real-world CD19 chimeric antigen receptor (CAR) T-cell therapy for large B-cell lymphoma (LBCL) is characterized by expanded eligibility and evolving management practices. However, the prognostic impact of these changes remains inconsistent, and the specific drivers of outcomes remain unclear. This study analyzed 913 patients with relapsed/refractory (R/R) LBCL from a Japanese registry and compared the outcomes between 2 calendar periods (2019-2021 vs 2022-2024). The 2022-2024 cohort was older, had more adverse baseline features, and was less pretreated. Treatment patterns have shifted toward higher utilization of second-line therapy, a growing preference for axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel), and improved disease control before infusion. Accordingly, the 2022-2024 cohort achieved a longer progression-free survival (PFS; 6-month PFS, 63.2% vs 55.2%; $P = .005$), which persisted after adjusting for baseline characteristics using propensity score matching. Multivariable analysis identified second-line therapy, improved preinfusion disease control, and a shift in product selection from tisagenlecleucel to axi-cel or liso-cel as the primary drivers of this improvement. This benefit was pronounced in high-risk populations, including patients with stable or progressive disease at infusion (6-month PFS, 54.6% vs 43.8%; $P = .012$) and those who were refractory to first-line therapy (6-month PFS, 51.7% vs 40.3%; $P = .013$). Despite broader use in higher-risk populations and greater axi-cel exposure, 6-month nonrelapse mortality remained low (2.1% vs 1.5%). Real-world outcomes of CD19 CAR T-cell therapy for R/R LBCL have improved, predominantly driven by second-line therapy, enhanced preinfusion disease control, and increased use of more potent CAR T products.

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The data for this study are not publicly available because of ethical restrictions that exceed the scope of the recipient's or donor's consent for research use in the registry.

The full-text version of this article contains a data supplement.

Introduction

Chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment landscape for relapsed or refractory (R/R) large B-cell lymphoma (LBCL). Despite its efficacy, durable remission is achieved in ~40% of patients.[1-4] Outcomes are particularly poor among individuals with refractory disease or those with a high tumor burden at infusion, populations consistently associated with inferior survival in prior studies.[5-9]

Since its introduction, the clinical practice has evolved substantially beyond the rigid protocols of pivotal trials. Broader eligibility criteria, shifts in CAR T-cell product utilization, improvements in disease control before infusion, and refinements in toxicity management have reshaped real-world treatment strategies.[10-14] However, registry studies have yielded inconsistent findings regarding temporal survival improvement.[15,16] In addition, it remains uncertain whether any observed survival gain extends to high-risk populations.

In Japan, CAR T-cell products were introduced sequentially, with subsequent expansion of indications for second-line therapy. Tisagenlecleucel (tisa-cel) was approved for use in March 2019, followed by axicabtagene ciloleucel (axi-cel) in January 2021 and lisocabtagene maraleucel (liso-cel) in March 2021. In December 2022, indications for axi-cel and liso-cel were expanded to include second-line therapy.[17,18] This staggered introduction of products and evolving indications provides an opportunity to evaluate trends in temporal outcomes. Therefore, this study aimed to determine whether survival has improved over time in Japan and to quantify the relative contributions of product shift, second-line adoption, and improved preinfusion disease control to these temporal changes. We explored whether these temporal trends were associated with differences in nonrelapse mortality (NRM) and key treatment-related toxicities, including cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). We further examined whether temporal improvements differed according to the baseline risk status.

Methods

Data collection

This retrospective study analyzed patient data from the Japanese Society for Transplantation and Cellular Therapy (JSTCT)/Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT) and the Japanese adaptation of FormsNet3, which was developed in collaboration with the Center for International Blood and Marrow Transplant Research and the European Society for Blood and Marrow Transplantation.[19] Written informed consent was obtained from all participants. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ethics committees of the JSTCT and Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital.

Patients

We identified all consecutive patients with LBCL who received approved CAR T-cell products in Japan (tisa-cel, axi-cel, or liso-cel) between 2019 and 2024 from the nationwide JSTCT/JDCHCT registry, which systematically collects transplantation and cellular therapy data from centers across Japan. Patients without post-infusion survival follow-up data were excluded from the analysis. LBCL was pathologically diagnosed according to the World Health Organization classification.[20,21] Pathological diagnoses were established at each participating institution according to the institutional standards.

Definition

Patients were stratified according to the calendar period of infusion into early (2019-2021) and recent cohorts (2022-2024). Patient characteristics at the time of CAR T-cell infusion and the efficacy and toxicity of the therapy were analyzed. Disease status before CAR T-cell infusion and response to therapy were assessed by the treating physician at each hospital based on positron emission tomography–computed tomography or computed tomography findings using the Lugano classification.[22,23] Progression and relapse were defined based on biopsy, imaging, and/or clinical assessment findings. Consensus criteria were used to grade the severity of CRS and ICANS, according to the American Society for Transplantation and Cellular Therapy grading criteria.[24] The Karnofsky index of performance status (PS) was converted to Eastern Cooperative Oncology Group (ECOG) PS (0-4) whenever ECOG was unavailable or missing. Bridging therapy was defined as any treatment for lymphoma administered between leukapheresis and the initiation of lymphodepleting chemotherapy. Bridging therapy was classified as none (no bridging), systemic (steroids, chemotherapy, and/or targeted therapy), radiotherapy (administered as a single regimen), or combined (systemic therapy + radiotherapy). Systemic therapy was further categorized into polatuzumab vedotin–based, platinum-based, and other systemic therapies. If the patients had received lines of bridging therapy for $\geq$2 times, the last regimen was used for analysis. In this study, second-line CAR T-cell therapy was defined as treatment with axi-cel or liso-cel that had received (1) only 1 prior line of therapy before infusion or (2) 2 prior lines of therapy when the latter was administered as bridging therapy (which may also function as holding therapy) to maintain disease stability before infusion.

Statistical analysis

Survival times were calculated based on the date of CAR T-cell infusion. Progression-free survival (PFS) was defined as lymphoma progression, relapse, or death from any cause. Overall survival (OS) was defined as death from any cause. OS and PFS were estimated using the Kaplan-Meier method and compared with univariate analysis using the log-rank test. Follow-up time was estimated using the reverse Kaplan-Meier method. NRM was defined as death without relapse or disease progression. Cumulative incidence was calculated using a competing risk model, with relapse treated as a competing event and compared using Gray test. The χ^2 test was used to assess any association between categorical variables, and the Mann-Whitney test was used to compare continuous variables.

Propensity score matching (PSM) was performed to account for potential confounding factors arising from baseline differences between the 2019 to 2021 and 2022 to 2024 cohorts. PSM was performed using nearest-neighbor matching without replacement at a 1:2 ratio. Each patient in the 2019 to 2021 cohort was matched with 2 patients in the 2022 to 2024 cohort (MatchIt package in R). Covariate balance in the propensity-matched

groups was assessed using standardized mean differences, with absolute values >0.1 considered unacceptably imbalanced. Matching was based on baseline covariates, including age, sex, disease type, hematopoietic cell transplantation (HCT)–specific comorbidity index score, ECOG PS, response to first-line chemotherapy, previous autologous HCT, and the number of prior treatment lines.

To assess whether the calendar period remained independently associated with PFS after adjustment and to quantify the extent to which temporal changes in treatment-related variables accounted for the improvement in PFS, multivariable Cox proportional hazards models were constructed in both the unmatched and PSM cohorts. In the overall cohort, the model included calendar period, treatment-related variables, and baseline covariates that were significantly associated with PFS in univariate analyses. A similar multivariable Cox model was fitted to the PSM cohort using the same covariates. Statistical significance was set at P value $< .05$. All statistical analyses were performed using R version 4.3.3.

Results

Baseline patient characteristics

Of the 916 consecutive patients identified, 3 without available survival follow-up data were excluded, and 913 were included in the final analysis. In the entire cohort, the median age was 62 years (interquartile range [IQR], 54-69), and the median time for follow-up was 12.0 months (95% confidence interval [CI], 11.5-12.0). During the follow-up period, 338 patients developed progressive lymphoma, and 269 died. Compared to patients in the 2019 to 2021 cohort, those in the 2022 to 2024 cohort were older (median age, 64 vs 60 years; $P < .001$) and more frequently aged ≥70 years (25% vs 12%; $P < .001$; Table 1). Additionally, they had a higher proportion of LBCL subtypes other than diffuse LBCL, not otherwise specified (27% vs 23%; $P = .016$), HCT-CI ≥1 (24% vs 12%; $P = .001$), and ECOG PS ≥2 (9% vs 4%; $P = .016$). Previous lines of therapy ≥3 were less common in the 2022 to 2024 cohort (77% vs 89%; $P < .001$), as was a history of autologous stem cell transplantation (20% vs 34%; $P < .001$).

Treatment characteristics and preinfusion status

In the entire cohort, the product distribution differed substantially between the 2 periods, with 2022 to 2024 showing greater use of liso-cel (35% vs 4%) and axi-cel (16% vs 1%) and less use of tisa-cel (49% vs 96%; Table 2). None of the patients received second-line CAR T-cell therapy between 2019 and 2021. In contrast, 61 patients (10%) received second-line CAR T-cell therapy between 2022 and 2024 ($P < .001$). The interval from apheresis to infusion did not differ significantly between the 2 periods (2019-2021 [median, 60 days; IQR, 52-71] vs 2022-2024 [median, 60 days; IQR, 49-77]). The completeness of bridging therapy documentation improved over time (missing data, 51% vs 23%). Several shifts in clinical practice have been observed in patients for whom data are available. Among patients with available data, the bridging regimens differed significantly between the 2 periods ($P = .002$). Polatuzumab vedotin–based chemotherapy was more frequently used in 2022 to 2024 (21% vs 11%), whereas platinum-containing chemotherapy was less common (21% vs 35%). Notably, when comparing bridging chemotherapy, the polatuzumab vedotin–based group achieved a significantly higher

Table 1. Patient characteristics by treatment period

	2019-2021		2022-2024		
	n = 269	%	n = 644	%	*P* value
Age, y					**<.001**
Median	60		64		
IQR	53-65		56-69		
≥70	32	12	159	25	**<.001**
Missing/unknown	1		2		
Sex					.94
Male	153	57	363	56	
Female	116	43	281	44	
Histology					**.016**
DLBCL, NOS	208	77	467	73	
HGBL	7	3	26	4	
PMBCL	1	1	27	4	
t-FL	51	19	113	17	
t-Other	2	1	11	2	
Cell of origin*					.27
GCB type	86	32	177	29	
Non-GCB type	92	34	217	35	
Missing/unknown	90	34	223	36	
Double-hit (FISH)†					>.99
Yes	3	33	8	33	
No	6	67	16	67	
Unknown	260		620		
ECOG PS					**.016**
0-1	255	96	582	91	
≥2	11	4	58	9	
Missing/unknown	3		4		
HCT-CI score					**.001**
0	234	88	495	77	
1-2	23	9	100	16	
≥3	10	4	49	8	
Missing/unknown	2		0		
First-line chemotherapy					.21
CR	112	61	259	55	
Non-CR	73	39	214	45	
Missing/unknown	84		171		
Previous auto-HCT					**<.001**
Yes	84	34	125	20	
No	163	66	495	80	
Missing/unknown	22		24	0	
Previous lines					**<.001**
1-2	29	11	147	23	
≥3	240	89	496	77	
Missing/unknown	0		1		

Values are presented as n (%) unless otherwise noted. *P* values in bold indicate statistical significance ($P < .05$).

auto-HCT, autologous HCT; DLBCL, diffuse LBCL; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell like; HCT-CI, HCT comorbidity index; HGBL, high-grade B-cell lymphoma; NOS, not otherwise specified; PMBCL, primary mediastinal large B-cell lymphoma; t-FL, transformed follicular lymphoma.

*Excluding 28 patients with PMBCL.

†MYC and BCL2 and/or BCL6 rearrangements.

Table 2. Treatment details and toxicities by treatment period

	2019-2021		2022-2024		
	n = 269	%	n = 644	%	*P* value
CAR T-cell product					**<.001**
Axi-cel	1	0	105	16	
Liso-cel	11	4	223	35	
Tisa-cel	257	96	316	49	
Second line CAR T-cell therapy	0	0	61	10	**<.001**
Bridging therapy					**<.001**
No bridging	34	26	141	28	
Radiotherapy	6	5	10	2	
Polatuzumab vedotin–based chemotherapy	15	11	124	25	
Platinum-based chemotherapy	46	35	105	21	
Other systemic therapy	24	18	70	14	
Chemotherapy + radiotherapy	7	5	48	10	
Missing/unknown	137		146		
LDH					
Normal	97	46	271	42	.24
>ULN	88	42	308	48	
>2 ULN	25	12	60	9	
Missing/unknown	59		5		
Lymphocyte count					
<500/μL	93	39	232	37	.77
≥500/μL	148	61	391	63	
Missing unknown	28		21		
Disease status at infusion					**.004**
CR/PR	82	38	294	50	
SD/PD	134	62	299	50	
Missing/unknown	53		51		
Vein-to-vein intervals, d					.82
Median	60		60		
IQR	52–71		49–77		
CRS					
Any grade	197	74	492	76	.40
Grade ≥3	38	14	88	14	.90
Missing/unknown	1		0		
Days from onset to recovery	6		5		**<.001**
IQR	4–9		4–7		
ICANS					
Any grade	12	5	73	11	**.001**
Grade ≥3	4	2	33	5	**.011**
Missing/unknown	1		0		
Toxicity therapy					
Tocilizumab	136	51	422	66	**<.001**
Steroids	18	7	163	25	**<.001**
Neutropenia					
<500/μL	187	72	513	82	**<.001**
Missing/unknown	9		22		
Thrombocytopenia					
<20 × 10^9/L	116	46	258	41	.20
Missing/unknown	19		21		

Values are presented as n (%) unless otherwise noted. *P* values in bold indicate statistical significance ($P < .05$).

LDH, lactate dehydrogenase; PD, progressive disease; SD, stable disease; ULN, upper limit of normal.

complete response (CR)/partial response (PR) rate before infusion than the platinum-based group (56.5% vs 40.5%; $P = .011$). The use of radiotherapy as a bridging therapy remained relatively infrequent, although the use of combined chemoradiotherapy regimens increased in the later period (48/498 [9.6%] vs 7/132 [5.3%]). Further details are provided in supplemental Table 1. Overall, the proportion of patients with CR/PR at the time of infusion was significantly higher in the 2022 to 2024 period than in the 2019 to 2021 period (50% vs 38%; $P = .004$).

Response and survival after CAR T-cell infusion

The best overall response rate (ORR) after CAR T-cell infusion was higher in 2022 to 2024 (79% vs 72%; $P = .028$), with CR rates of 66% and 61%, respectively. Among patients who did not show CR at the time of infusion (2022-2024, n = 434; 2019-2021, n = 168), the ORR tended to be higher in the 2022 to 2024 cohort than in the 2019 to 2021 cohort (75% vs 64%; $P = .009$), with corresponding CR rates of 58% and 49%, respectively. In this subgroup, the ORR (67.9%, 76.7 %, and 82.1% for tisa-cel, liso-cel, and axi-cel, respectively; $P = .020$) and CR rates (52.8%, 60.0%, and 59.7% for tisa-cel, liso-cel, and axi-cel, respectively) were higher for liso-cel and axi-cel. Patients in the 2022 to 2024 cohort experienced longer PFS, which was 63.2% vs 55.2% at 6 months (hazard ratio [HR], 0.75; 95% CI, 0.61-0.92; $P = .005$; Figure 1A). OS did not differ between the groups, which was 80.7% vs 80.7% at 6 months (HR, 0.89; 95% CI, 0.69-1.15; $P = .39$; Figure 1B). PFS did not differ significantly across calendar years within each period: 2019 to 2021 (6-month PFS, 54.1% [2019-20202] vs 56.0% [2021]; $P = .48$) and 2022 to 2024 (6-month PFS, 63.8% [2022] vs 61.6% [2023] vs 70.8% [2024]; $P = .54$; supplemental Figure 1). In an exploratory comparison, PFS did not differ significantly between patients receiving polatuzumab vedotin– and platinum-based bridging chemotherapy, although a numerical trend toward improved outcomes was observed in the polatuzumab vedotin–based group across the different products (tisa-cel [HR, 0.82; $P = .34$]; liso-cel [HR, 0.72; $P = .34$]; supplemental Figure 2).

Subgroup analysis of high-risk populations

To assess whether temporal improvement differed across clinically relevant subgroups, we performed stratified analyses according to preinfusion disease status and response to first-line chemotherapy. Among patients with stable disease or progressive disease at the time of infusion, PFS was significantly longer in the

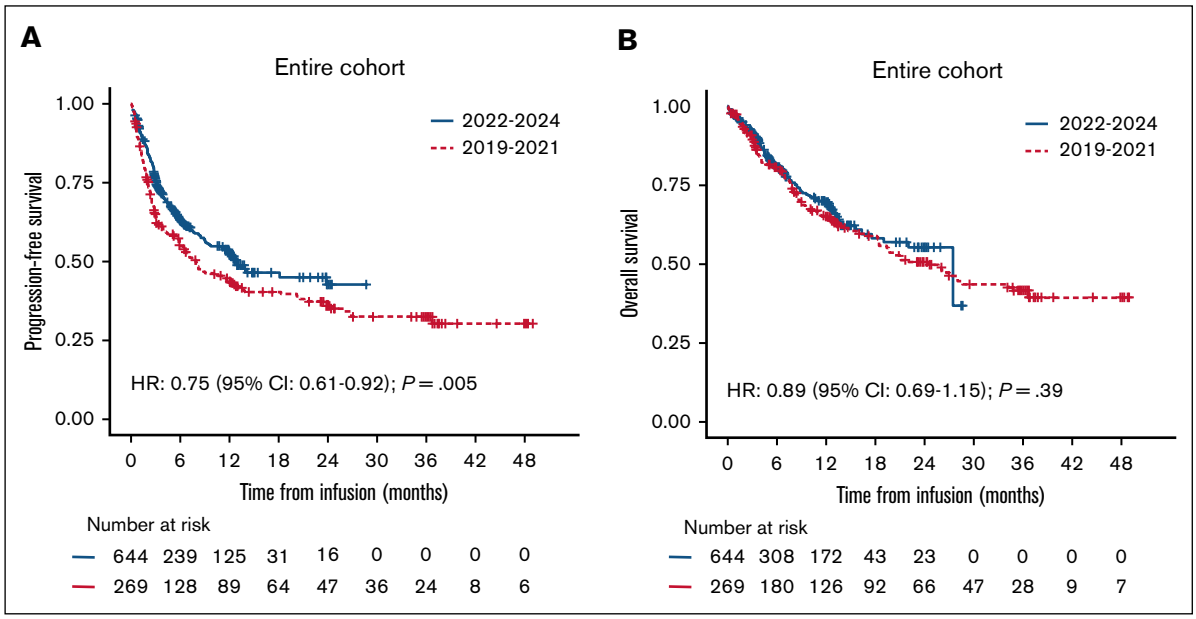

Figure 1. Kaplan-Meier estimates of survival by treatment period. (A-B) PFS (A) and OS (B) in the 2019 to 2021 cohort (n = 269) and the 2022 to 2024 cohort (n = 644).

2022 to 2024 period (PFS at 6 months, 54.6% vs 43.8% [HR, 0.69; 95% CI, 0.51-0.92; P = .012]; Figure 2A). Within this subgroup, product-specific differences were observed. Both axi-cel and liso-cel were associated with significantly longer PFS than tisa-cel (axi-cel vs tisa-cel [HR, 0.47; 95% CI, 0.29-0.77; P = .002]; liso-cel vs tisa-cel [HR, 0.58; 95% CI, 0.42-0.79; P < .001]; Figure 2B).

A similar pattern was observed when patients were stratified by response to first-line chemotherapy. Among those who did not achieve CR after first-line therapy, PFS was significantly longer in the 2022 to 2024 cohort (PFS at 6 months, 51.7% vs 40.3% [HR, 0.66; 95% CI, 0.47-0.91; P = .013]; Figure 2C). Within this subgroup, second-line CAR T-cell therapy was associated with significantly longer PFS than third- or later-line treatment with axi-cel or liso-cel (HR, 0.33; 95% CI, 0.13-0.84; P = .020). Among patients treated in third or later lines, use of liso-cel or axi-cel was associated with longer PFS than tisa-cel (HR, 0.69; 95% CI, 0.48-0.99; P = .046; Figure 2D). Baseline characteristics of these subgroups are summarized in supplemental Table 2.

In contrast, no significant temporal difference in PFS was observed among patients with CR/PR at infusion (PFS at 6 months, 71.9% vs 67.1% [HR, 0.76; 95% CI, 0.51-1.13; P = .17]; supplemental Figure 3A) or among those who achieved CR after first-line therapy (PFS at 6 months, 69.6% vs 62.7% [HR, 0.86; 95% CI, 0.61-1.20; P = .37]; supplemental Figure 2C). In these subgroups, differences in PFS according to the CAR T-cell product or treatment line were less consistent and generally smaller in magnitude (supplemental Figure 3B,D).

Toxicities

The incidence of ICANS was significantly higher in the 2022 to 2024 cohort than the 2019 to 2021 cohort (any grade, 11% vs 5% [P = .001]; grade ≥3, 5% vs 2% [P = .011]; Table 2). In contrast, CRS rate of any grade remained unchanged across the periods (any grade, 76% vs 74% [P = .40]; grade ≥3, 14% vs 14% [P = .90]), although the duration of CRS was significantly shorter in the later era (5 days vs 6 days; P < .001). Tocilizumab and systemic corticosteroid administration was significantly more common in the 2022 to 2024 cohort (tocilizumab, 66% vs 51% [P < .001]; corticosteroids, 25% vs 7% [P < .001]).

The incidence of CAR T-cell therapy–related toxicities varied according to the product. CRS occurred more frequently with axi-cel than with liso-cel or tisa-cel (axi-cel, 90%; liso-cel, 71%; tisa-cel, 75%). ICANS also occurred more often with axi-cel (31%) than with liso-cel (8%) or tisa-cel (6%). Severe events (grade ≥3) followed a similar pattern. CRS grade ≥3 was 23% with axi-cel vs 7% with liso-cel and 15% with tisa-cel administration. ICANS grade ≥3 was 14% with axi-cel vs 4% with liso-cel and 2% with tisa-cel administration.

The cumulative NRM incidence also did not differ significantly between groups. At 6 months, NRM was 2.1% in the 2022 to 2024 cohort and 1.5% in the 2019 to 2021 cohort (P = .52; supplemental Table 3; supplemental Figure 4A).

PSM

After excluding patients with missing baseline data, 616 patients were included: 167 in the 2019 to 2021 cohort and 449 in the 2022 to 2024 cohort. Of these, 443 (72%) were successfully matched using PSM, including 165 patients from the 2019 to 2021 cohort and 278 patients from the 2022 to 2024 cohort. After matching, the baseline characteristics were well balanced between the 2 groups according to the prespecified criteria outlined above (supplemental Table 4; supplemental Figure 5).

The treatment characteristics and preinfusion disease status showed similar trends after PSM. During 2022 to 2024, the use of second-line CAR T-cell therapy increased compared to that during

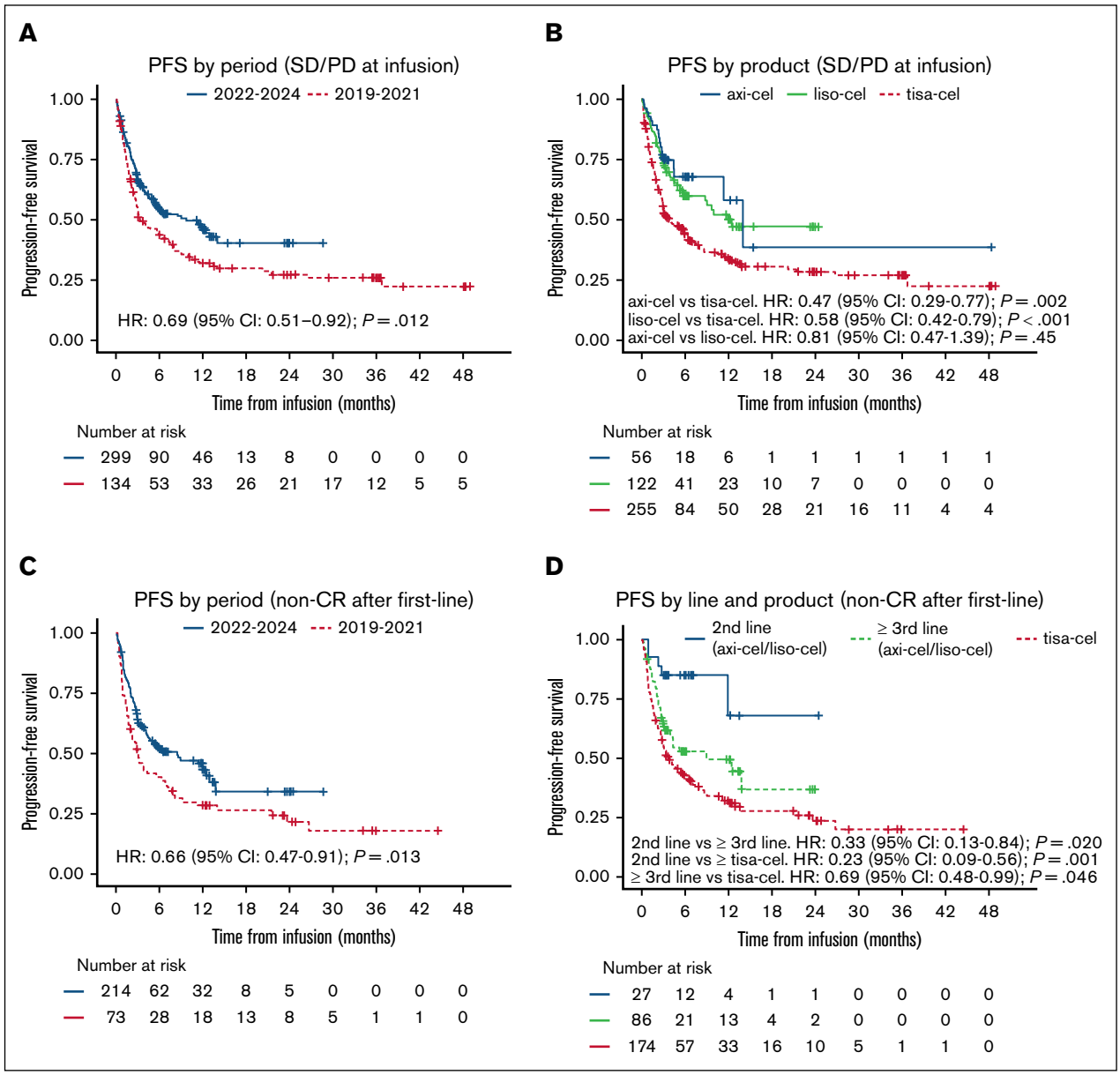

Figure 2. Survival improvement and clinical drivers in high-risk subgroups. PFS in patients with high-risk features. (A) Outcomes of patients with stable disease (SD) or progressive disease (PD) at infusion were compared between the 2019 to 2021 and 2022 to 2024 cohorts. (B) Comparison of PFS with CAR T-cell products (tisa-cel, liso-cel, or axi-cel) in patients with SD or PD upon infusion. (C) Outcomes of patients with primary disease refractory to first-line therapy compared between the 2019 to 2021 and 2022 to 2024 cohorts. (D) Comparison of PFS according to the timing of CAR T-cell therapy (second-line vs third-line or later) and the CAR T-cell product (liso-cel or axi-cel vs tisa-cel) in patients with primary refractory disease.

2019 to 2021 (6% vs 0%; $P = .004$). The 2022 to 2024 period showed greater use of liso-cel (27% vs 2%) and axi-cel (16% vs 1%). This period also showed less use of tisa-cel (57% vs 98%). During 2022 to 2024, polatuzumab vedotin–based regimens were used more often than during 2019 to 2021 (29% and 12%, respectively). Platinum-based regimens were used less often in the 2022 to 2024 period (23% vs 36%). Chemotherapy plus radiotherapy was used more often in the 2022 to 2024 period (12% vs 7%). The 2022 to 2024 period showed a higher CR/PR rate before infusion than the 2019 to 2021 period (53% vs 38%; $P = .004$; Table 3).

PSM analysis showed improved response and PFS in the 2022 to 2024 cohort. The 2022 to 2024 cohort showed a higher ORR than the 2019 to 2021 cohort, although the difference was not statistically significant (78% vs 70%; $P = .089$). PFS was significantly longer in the 2022 to 2024 cohort (PFS at 6 months, 62.4% vs 52.9% [HR, 0.67; 95% CI, 0.51-0.89; $P = .005$]; Figure 3A). OS did not differ significantly between the periods (OS at 6 months, 83.5% vs 79.1% [HR, 0.75; 95% CI, 0.53-1.07]; $P = .11$; Figure 3B). The toxicity profile remained similar after PSM, which was consistent with the findings before matching (Table 3; supplemental Figure 4B).

Table 3. Treatment details and toxicities in propensity score–matched patients

	2019-2021		2022-2024		
	n = 165	%	n = 278	%	*P* value
CAR T-cell product					**<.001**
Axi-cel	1	1	45	16	
Liso-cel	3	2	75	27	
Tisa-cel	161	98	158	57	
Second line	0	0	16	6	**.004**
Bridging therapy					**.001**
No bridging	26	27	58	26	
Radiotherapy	5	5	2	1	
Polatuzumab vedotin–based chemotherapy	11	12	64	29	
Platinum-based chemotherapy	34	36	51	23	
Other systemic therapy	12	13	21	9	
Chemotherapy + radiotherapy	7	7	27	12	
Missing/unknown	70		55		
LDH					
Normal	53	44	117	42	.35
>ULN	52	43	135	48	
>2 ULN	16	13	25	9	
Missing/unknown	44		1		
Lymphocyte count					
<500/μL	55	39	104	39	.96
≥500/μL	88	61	161	61	
Missing unknown	22		13		
Disease status at infusion					**.004**
CR/PR	55	38	140	53	
SD/PD	90	62	123	47	
Missing/unknown	20		15		
Vein-to-vein intervals					
Median	61		62		.42
IQR	53–71		52–78		
CRS					
Any grade	119	73	216	78	.27
Grade ≥3	25	15	62	22	.28
Missing/unknown	1		0		
Days from onset to recovery	6		5		**.019**
IQR	4–9		4–7		
ICANS					
Any grade	5	3	28	10	**.012**
Grade ≥3	1	1	14	5	**.026**
Missing/unknown	1		0		
Toxicity therapy					
Tocilizumab	87	53	186	67	**.004**
Steroids	13	8	75	27	**<.001**
Neutropenia					
<500/μL	111	70	221	83	**.002**
Missing/unknown	6		13		
Thrombocytopenia					
<20 × 10^9/L	61	39	108	40	>.99
Missing/unknown	10		6		

Values are presented as n (%) unless otherwise noted. *P* values in bold indicate statistical significance ($P < .05$).

Abbreviations are explained in Table 2 footnotes.

Sensitivity analysis

To evaluate whether the observed temporal improvement could be explained solely by the increased use of second-line CAR T-cell therapy in the later era, we repeated the PSM analysis after excluding patients treated in the second-line setting. Of the 566 patients, 441 (78%) were successfully matched (166 in the 2019-2021 cohort and 275 in the 2022-2024 cohort). The baseline characteristics were well balanced after matching (supplemental Figure 6A-C). In this restricted matched cohort, patients treated in the 2022 to 2024 period continued to demonstrate significantly longer PFS than those treated in the 2019 to 2021 period (HR, 0.70; 95% CI, 0.54-0.93; $P = .012$; Figure 3C). OS did not differ significantly between the periods (HR, 0.77; 95% CI, 0.54-1.10; $P = .15$; Figure 3D).

In a product-specific analysis restricted to tisa-cel recipients, 573 patients were identified. After excluding the patients with missing covariate data required for PSM, 389 patients were included in the matching procedure, of whom 356 (92%) were successfully matched between the 2 periods. The baseline characteristics were generally well balanced after matching (supplemental Figure 6D-F). No significant temporal differences in PFS were observed in either the unmatched or matched cohorts (unmatched cohort [HR, 0.90; 95% CI, 0.72-1.14; $P = .40$]; matched cohort [HR, 0.88; 95% CI, 0.66-1.17; $P = .39$]; supplemental Figure 7A-B).

Drivers of survival improvement (exploratory analysis)

In the unmatched cohort, after adjusting for potential confounders, including CAR T-cell product type, preinfusion disease status, laboratory markers, and baseline characteristics, the prognostic impact of the calendar period was attenuated and was no longer statistically significant (HR, 0.80; 95% CI, 0.59-1.10; $P = .17$; Figure 4). All multivariable results are summarized in supplemental Figure 8. Consistent results were observed in the multivariable analysis of the PSM cohort (HR, 0.73; 95% CI, 0.51-1.04; $P = .080$). However, second-line CAR T-cell therapy (HR, 0.38; 95% CI, 0.15-0.96; $P = .042$), a shift in CAR T-cell product use, increased liso-cel use (HR, 0.48; 95% CI, 0.33-0.70; $P < .001$), and achievement of CR/PR at infusion (HR, 059; 95% CI, 0.43-0.79; $P < .001$) increased significantly in the 2022 to 2024 period and were associated with improved PFS.

Discussion

This retrospective registry-based study using JSTCT/JDCHCT data found that PFS in patients with R/R LBCL receiving CAR

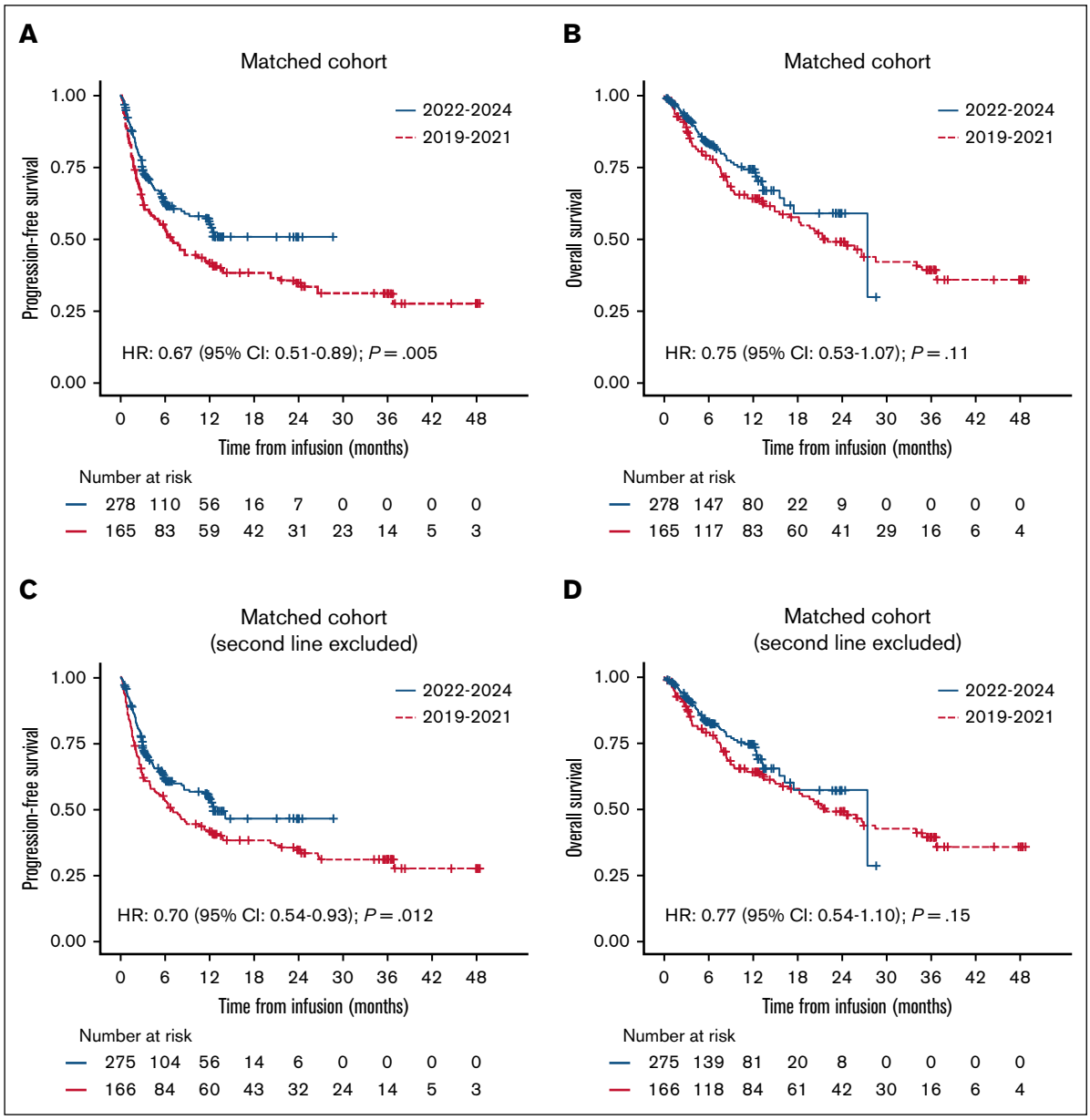

Figure 3. Kaplan-Meier estimates of survival in the propensity score–matched cohorts. (A-B) PFS (A) and OS (B) in the propensity score–matched cohort comparing the 2019 to 2021 cohort (n = 165) and the 2022 to 2024 cohort (n = 278). (C-D) PFS (C) and OS (D) in the propensity score–matched cohort after excluding patients who received second-line CAR T-cell therapy (2019-2021 cohort, n = 166; 2022-2024 cohort, n = 275).

T-cell therapy improved in recent years (2022-2024). This outcome remained robust after PSM and excluding patients who received second-line CAR T-cell therapy. In the multivariable analyses, the prognostic impact of the calendar period was attenuated after adjustment for treatment-related factors. The increased use of second-line CAR T-cell therapy, product shift, and higher rates of CR/PR at infusion were independently associated with improved PFS and were more frequent in recent years.

Our findings support the growing real-world evidence on the comparative efficacy of CAR T-cell products. Previous reports have shown that axi-cel and liso-cel achieve better survival than tisa-cel.[25-27] Consistent with these reports, both products were associated with favorable outcomes in the entire cohort. However, the statistical significance of axi-cel did not persist in the multivariable analysis. This likely reflects the limited statistical power due to the small number of axi-cel cases, which resulted from delayed adoption of axi-cel in Japan rather than a lack of clinical benefit. Notably, temporal improvement persisted even after excluding patients treated in the second-line setting. Together with the absence of temporal improvement among tisa-cel recipients, these findings suggest that differences in product efficacy may have contributed to the observed survival gain.

The survival benefit in the 2022 to 2024 cohort was not uniform across subgroups, appearing limited in patients with more

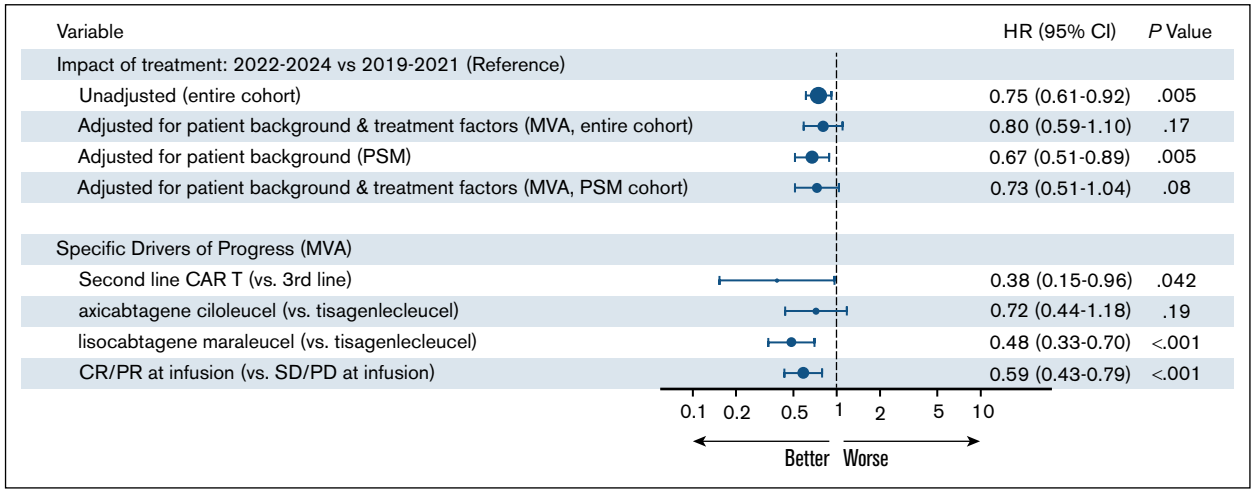

Figure 4. Analysis of clinical factors explaining the PFS improvement over time. The figure includes 2 complementary analyses. First, sequential adjustment was performed to evaluate the effect of treatment period on PFS: model 1, unadjusted; model 2, multivariable-adjusted (MVA) for all baseline and treatment-related covariates; model 3, PSM, adjusted for baseline patient characteristics; model 4, MVA for all covariates within the PSM cohort. Multivariable Cox proportional hazards models were fitted in the unmatched cohort (n = 913) and the PSM cohort (n = 443). Patients with missing values were excluded from the multivariable analyses (complete-case analysis). Second, a forest plot from the MVA model (model 2) was used to evaluate clinical and treatment-related factors associated with PFS. In the overall cohort, the model included calendar period, treatment-related variables, and baseline covariates that were significantly associated with PFS in univariable analyses. Together, these analyses show the effect of treatment period on PFS and the clinical and treatment-related factors potentially contributing to the observed survival difference between the 2 periods.

favorable disease status but more pronounced in those with suboptimal disease control. This included patients infused with stable disease or progressive disease and those who did not achieve CR with first-line treatment. Specifically, the shift in CAR T-cell product use likely played a decisive role. Axi-cel has been reported to outperform tisa-cel in patients with bulky disease[25] and to depend less on bridging therapy.[6]

The observed benefit of second-line CAR T-cell therapy, particularly among patients who did not achieve CR with first-line treatment, may partly reflect differences in immune competence before lymphodepleting chemotherapy. In exploratory analyses, patients treated in the second-line setting had higher absolute lymphocyte counts before lymphodepleting chemotherapy than those treated in later lines, suggesting better-preserved lymphocyte fitness (supplemental Figure 9). In multivariable analysis, lymphocytopenia (<500/μL) was a significant adverse prognostic factor for PFS (supplemental Figure 8). These findings are consistent with previous reports indicating improved outcomes with earlier-line CAR T-cell therapy, potentially reflecting preserved host immunity and CAR T-cell fitness.[28,29] Whether the prognostic impact of lymphocytopenia differs between axi-cel and liso-cel in the second-line CAR T-cell setting warrants further investigation.

Previous studies have suggested that a shorter time from apheresis to infusion is associated with improved outcomes after CAR T-cell therapy.[30,31] In our cohorts, the interval between apheresis and infusion did not decrease over time. Therefore, improvements in outcomes observed in the later period are unlikely to be explained by changes in manufacturing time alone. Instead, the increased proportion of patients achieving CR/PR before infusion in the 2022 to 2024 period suggests that enhanced bridging strategies played an important role.

In particular, the increased use of polatuzumab vedotin–based regimens may have contributed to improved disease control during the waiting period. Consistent with this interpretation, our subgroup analysis showed that polatuzumab vedotin–based bridging was associated with improved preinfusion response rates and numerically favorable PFS. These findings are in line with prior reports demonstrating the efficacy of polatuzumab vedotin–based regimens as bridging therapies before CAR T-cell infusion, including our previous nationwide registry analysis.[6,32,33] Radiotherapy has been reported as an effective and safe bridging modality in several international cohorts, particularly for localized or symptomatic disease.[34-36] In our study, radiotherapy was used in a limited proportion of patients, and its independent effect on response was not clearly demonstrated. Nevertheless, the increased use of combined chemoradiotherapy in the later period may reflect an increased adoption of multimodal bridging strategies.

In line with previous findings,[25,26,37] the safety profile in the 2022 to 2024 cohort was affected by the increased use of axi-cel, which was associated with higher rates of CRS and ICANS. Although the overall incidence of CRS, including grade ≥3 events, was comparable between the periods, the duration of CRS was shorter in the 2022 to 2024 cohort, likely reflecting optimized management with tocilizumab and corticosteroids. The incidence of ICANS increased over time, possibly due to greater exposure to axi-cel. Importantly, despite increased patient complexity and shifts in product use, NRM remained stable, indicating that overall safety was maintained.

This study has several limitations inherent to its retrospective design and the constraints of a multicenter registry. First, data on metabolic tumor volume, detailed inflammatory markers, and the interval from frontline therapy to relapse were not consistently available, preventing adjustment for these biological prognostic factors. Second, comprehensive information on treatment history before apheresis, including exposure to agents such as polatuzumab vedotin in the first-line setting, was not been consistently collected. Finally, this study focused on patients who underwent

CAR T-cell infusion; thus, an intent-to-treat analysis, including patients who underwent leukapheresis but did not proceed with infusion, could not be performed.

In summary, this large-scale registry analysis demonstrated a significant improvement in real-world outcomes of CAR T-cell therapy for R/R LBCL in Japan. This progress reflected the strategic evolution of clinical practice. Emerging evidence suggests that clinicians have achieved better preinfusion disease control with optimized bridging therapies, earlier application of CAR T-cell therapy in second-line settings, and broader adoption of CAR T-cell products. These advancements have extended the survival benefit to historically difficult-to-treat groups, including patients with active disease or chemotherapy-refractory status, without compromising safety.

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Authorship

Contribution: Y.Y. and Y.K. designed the study, performed analyses, and wrote the manuscript; T.T., M.K., T.J., T.S., and K. Kato assisted with data interpretation and manuscript preparation; H.K., K. Kataoka, H.G., K. Kato, and Y.A. assisted with statistical analyses; T.K., R.H., N.D., S.Y., N.F., N.I., G.Y., M.S., T.M., E.S., Y.N., A.Y., and Y.U. collected data; and all authors reviewed the final version of the manuscript.

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