Journal for ImmunoTherapy of Cancer

Impact of immune-related adverse events on the therapeutic efficacy of pembrolizumab in urothelial carcinoma: a multicenter retrospective study using time-dependent analysis

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To cite: Kawai T, Taguchi S, Nakagawa T, *et al*. Impact of immune-related adverse events on the therapeutic efficacy of pembrolizumab in urothelial carcinoma: a multicenter retrospective study using time-dependent analysis. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e003965. doi:10.1136/jitc-2021-003965

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jitc-2021-003965).

Accepted 31 January 2022

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ABSTRACT

Background Several studies have reported the incidence of immune-related adverse events (irAEs) as a predictor of the efficacy of anti-programmed cell death protein 1 antibodies in patients with cancer. However, immortal time bias has not always been fully addressed in these studies. In this retrospective multicenter study, we assessed the association between the incidence of irAEs and the efficacy of pembrolizumab in urothelial carcinoma (UC) using time-dependent analysis, an established statistical method to minimize immortal time bias.

Methods The study included 176 patients with advanced UC who underwent pembrolizumab treatment at seven affiliated institutions between January 2018 and July 2020. Patients with irAEs were compared with those without irAEs in terms of overall survival (OS) and cancer-specific survival (CSS). Immortal time bias was eliminated by using time-dependent analysis.

Results Of the 176 patients, irAEs occurred in 77 patients (43.8%), with a median of 60 days. The irAEs (+) cohort showed significantly favorable OS and CSS compared with the irAEs (–) cohort (p=0.018 and p=0.005, respectively), especially in the cohort with grade 1–2 irAEs (OS and CSS; p=0.003 and p=0.002, respectively). Multivariate analyses identified any irAEs and grade 1–2 irAEs as independent favorable prognostic factors for OS and CSS.

Conclusion Even after minimizing immortal time bias by time-dependent analysis, the incidence of irAEs, especially grade 1–2 irAEs, could be a significant predictor of favorable prognoses in patients with UC who have undergone pembrolizumab treatment.

BACKGROUND

Immune checkpoint inhibitors (ICIs), including programmed cell death protein 1 (PD-1) antibodies, have led to remarkable advances in the treatment of various types of cancers. Pembrolizumab, a PD-1 antibody, has been shown to prolong overall survival (OS) in patients with advanced urothelial carcinoma (UC) following disease progression after platinum-containing chemotherapy.[1] Pembrolizumab has thus been established as a second-line treatment for advanced UC.[2 3] However, ICIs can produce immune-related adverse events (irAEs), such as rash, colitis, hepatitis, endocrinopathies, pneumonitis, myositis, and nephritis.[4 5]

Several previous studies have reported that the incidence of irAEs is associated with a good therapeutic response to ICIs in malignancies,[6 7] including melanoma,[8] non-small cell lung cancer,[9 10] gastric cancer,[11 12] and UC.[13–15] However, immortal time bias has not always been fully addressed in these studies. We previously reported the correlation between irAEs and favorable efficacy of pembrolizumab in patients with UC using single-center preliminary data[13]; however, immortal time bias was not eliminated.

Immortal time bias occurs when a group of patients does not survive long enough to receive an intervention.[16–18] Thus, irAE development and patient survival occur because the shorter the survival, the lower the chance of an irAE development. Time-dependent analysis (or called Mantel–Byar method) and landmark analysis are both established methods for avoiding immortal time bias, whereas the former is much superior to the latter in minimizing the immortal time bias.[16] To the best of our knowledge, no previous studies have conducted time-dependent analysis to assess the association between irAEs and response to ICIs. In the present study, we assessed the association between irAEs and

the efficacy of pembrolizumab in patients with UC using multicenter data. Immortal time bias was eliminated by conducting time-dependent analysis.

METHODS

Patients

This retrospective study included 176 patients with advanced (metastatic or locally advanced) UC who underwent pembrolizumab treatment. Of the 176 patients, 175 patients were treated with pembrolizumab as a second-line therapy following disease progression after first-line chemotherapy, and the remaining one patient was treated as a first-line therapy because he was on hemodialysis and ineligible for platinum-containing chemotherapy. The study cohort includes 150 patients who were analyzed in our previous article, which assessed the association of the albumin-to-globulin ratio with conventional oncological outcomes in the setting of advanced UC treated with pembrolizumab.[19] All patients received pembrolizumab at a dose of 200 mg/body intravenously every 3 weeks at seven affiliated institutions between January 2018 and July 2020.

Data collection

The patients' clinical data were retrospectively extracted as follows: sex, age, occurrence and grade of irAEs, use of glucocorticoids for irAEs, OS, and cancer-specific survival (CSS). The time for irAEs to occur following the start of pembrolizumab treatment was also noted. The grade of irAEs was evaluated according to the Common Terminology Criteria for Adverse Events V.5.0.[20] Furthermore, to guarantee the quality of data on irAE grades, an investigator at each institution retrospectively reviewed and interpreted clinical records to determine irAE grades, and another investigator at the same institution double-checked the results. Follow-up information was obtained in October 2020.

Statistical analysis

The maximum therapeutic effect and frequency of glucocorticoid use was analyzed using the χ^2 test or Fisher's exact test. Survival data of patients were analyzed using time-dependent analysis, whereby the survival time of each patient who experienced irAEs from time of starting pembrolizumab treatment to time of final observation was divided into time from the start of pembrolizumab to the onset of initial irAE and time after the onset of initial irAE. The former time period was assigned to the irAEs (−) cohort and the latter period to the irAEs (+) cohort. Meanwhile, regarding patients who did not experience irAEs, all of the survival time was assigned to the irAEs (−) cohort (figure 1). Survival curves were generated using the Kaplan-Meier method and compared using log-rank tests. Similar time-dependent analyses were performed for each group of irAE grades (grade 1–2 and grade 3–5), each type of irAEs, and each route of glucocorticoid administration. Time-dependent Cox model was used for multivariate analyses of OS and CSS. All statistical analyses, except time-dependent multivariate Cox analyses, were performed using the JMP Pro software (V.15.0.0, SAS Institute). Time-dependent multivariate Cox analyses were conducted by a biostatistician (YU) using SAS V.9.4. All p values were two-sided and considered significant at $p<0.05$.

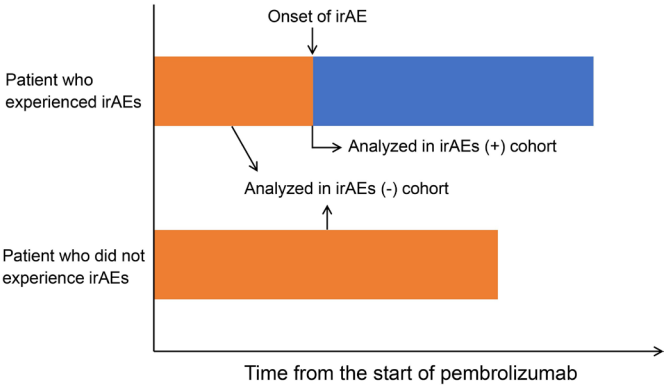

Figure 1 Time-dependent analysis in this study. The survival time of each patient with urothelial carcinoma who experienced immune-related adverse events (irAEs) was divided into time from the start of pembrolizumab treatment to the onset of initial irAE and time after the onset of initial irAE. The former was assigned to the irAEs (–) cohort (orange) and the latter to the irAEs (+) cohort (blue). Meanwhile, regarding patients who did not experience irAEs, all of the survival time which meant from the start of pembrolizumab treatment to last follow-up were assigned to the irAEs (–) cohort (orange).

RESULTS

Patients' characteristics

The clinical characteristics of patients at the start of pembrolizumab treatment are shown in table 1. A total of 176 patients comprised 132 men (67.2%) and 44 women (32.8%) with a median age of 71 years (IQR, 66–76 years). The median follow-up duration was 8.1 months (IQR, 4.0–15.2 months). No patients had any baseline immune dysfunction, immunosuppressive medication, or pre-existing autoimmune condition.

Incidence of irAEs

As shown in table 2, irAEs occurred in 77 patients (43.8%) with a median onset of 60 days (IQR, 25–126 days) from the initiation of pembrolizumab treatment. Grade 1–2 and grade 3–5 irAEs occurred in 35.8% and 11.9% of patients, respectively. The most common irAEs were skin disorders (eg, pruritus, rash, and dermatitis; 22.2%), followed (in decreasing order of prevalence) by endocrine disorders (eg, thyroid dysfunction, adrenal insufficiency, and type 1 diabetes; 13.6%), respiratory disorders (eg, interstitial pneumonia; 5.7%), intestinal disorders (eg, diarrhea and colitis; 5.1%), hepatitis, nephritis, stomatitis, myositis, and myocarditis. When glucocorticoid administration was required due to irAEs, treatments were administered externally, orally, or intravenously (33.8%, 28.6%, and

Table 1 Clinical characteristics of 176 patients at the start of pembrolizumab treatment

Factor	Value
Age, years, median (IQR)	71 (66–76)
Sex, no (%)	
Male	132 (75.0)
Female	44 (25.0)
ECOG PS, no (%)	
0	104 (59.1)
1	52 (29.5)
≥2	20 (11.4)
Primary site, no (%)	
Bladder	76 (43.2)
Upper tract	78 (44.3)
Both	22 (12.5)
No of lesions, no (%)	
1–4	101 (57.4)
5–9	39 (22.2)
≥10	36 (20.5)
Liver metastasis, no (%)	
Yes	29 (16.5)
No	147 (83.5)
No of prior regimens, no (%)	
1	131 (74.4)
2	31 (17.6)
≥3	12 (6.8)

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

14.3%, respectively). Patients with respiratory disorders required frequent oral or intravenous administration of glucocorticoids (60% and 40%, respectively).

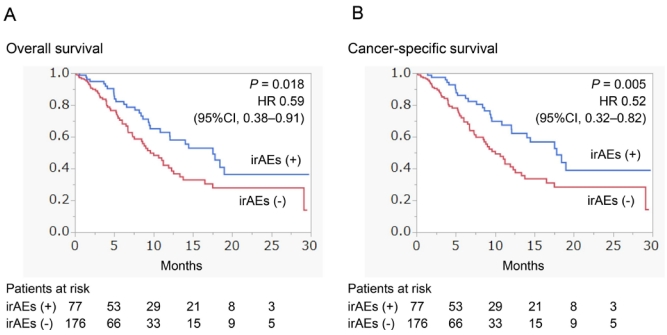

Figure 2 Overall survival (A) and cancer-specific survival (B) in the immune-related adverse events (irAEs (+)) cohort (blue) and the irAEs (–) cohort (orange).

Survival analyses

The Kaplan-Meier curves with survival analyses are shown in figures 2 and 3 (and in online supplemental figures 1 and 2). Time-dependent univariate analyses of patient survival among characteristics of irAEs are shown in table 3. The irAEs (+) cohort showed significantly favorable OS and CSS compared with the irAEs (–) cohort (HR=0.59, p=0.018 and HR=0.52, p=0.005, respectively; figure 2). The grade 1–2 irAEs (+) cohort showed significantly favorable OS and CSS compared with the cohort without grade 1–2 irAEs (HR=0.49, p=0.003 and HR=0.47, p=0.002, respectively; figure 3). Among the types of irAEs, the cohort with respiratory disorders showed significantly poor OS compared with the cohort without respiratory disorders (HR=2.66, p=0.011; online supplemental figure 1). Among the routes of glucocorticoid administration, the cohort with irAEs requiring intravenous administration showed significantly poor OS compared with cohort without the intravenous administration (HR=2.12, p=0.029; online supplemental figure 2). Multivariate analyses of patient survival using time-dependent Cox model are shown in table 4. The incidence of any irAEs

Table 2 Immune-related adverse events (irAEs) in 176 patients treated with pembrolizumab

	Incidence of irAEs			irAEs requiring glucocorticoid use		
	Any grade	Grade 3–5	Days to onset	External	Oral	Intravenous
irAE	No (%)	No (%)	Median (IQR)	No (%*)	No (%*)	No (%*)
Any irAEs	77 (43.8)	21 (11.9)	60 (25–126)	26 (33.8)	22 (28.6)	11 (14.3)
Skin disorders	39 (22.2)	3 (1.7)	60 (25–138)	25 (64.1)	9 (23.1)	4 (10.3)
Endocrine disorders	24 (13.6)	10 (5.7)	90 (51–158)	6 (25.0)	9 (37.5)	4 (16.7)
Respiratory disorders	10 (5.7)	4 (2.3)	144 (76–306)	6 (60.0)	6 (60.0)	4 (40.0)
Intestinal disorders	9 (5.1)	3 (1.7)	77 (29–140)	3 (33.3)	3 (33.3)	1 (11.1)
Hepatitis	5 (2.8)	1 (0.6)	46 (18–501)	1 (20.0)	3 (60.0)	1 (20.0)
Nephritis	3 (1.7)	1 (0.6)	136 (84–147)	1 (33.3)	2 (66.7)	1 (33.3)
Stomatitis	3 (1.7)	1 (0.6)	109 (27–180)	1 (33.3)	1 (33.3)	0 (0.0)
Myositis	3 (1.7)	1 (0.6)	43 (23–147)	0 (0.0)	0 (0.0)	1 (33.3)
Myocarditis	1 (0.6)	1 (0.6)	23	0 (0.0)	0 (0.0)	1 (33.3)

*Percentage of patients with each irAE.

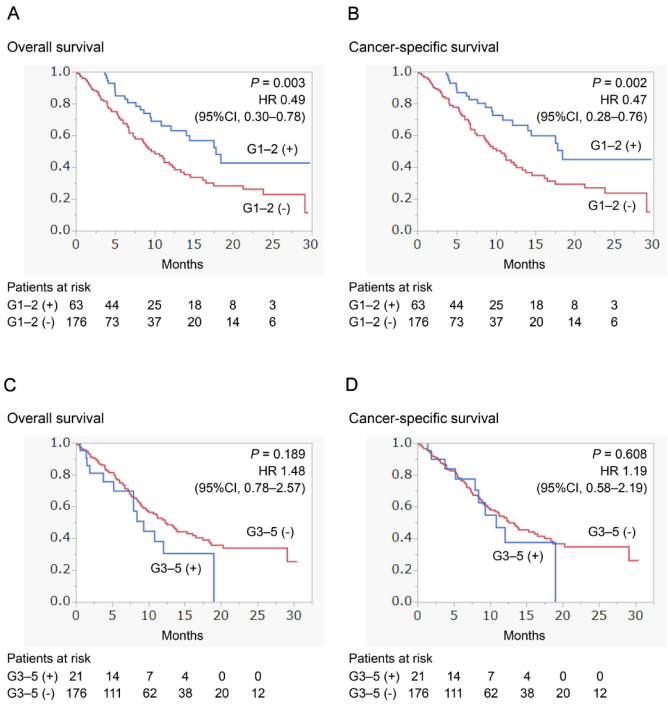

Figure 3 Overall survival (A, C) and cancer-specific survival (B, D) in the cohorts with (blue) or without (orange) grade 1–2 immune-related adverse events (irAEs) (A, B) and grade 3–5 irAEs (C, D).

and grade 1–2 irAEs was identified as independent favorable prognostic factor for OS and CSS along with Eastern Cooperative Oncology Group Performance Status of 0, primary site of the bladder, and number of lesions of 4 or less.

DISCUSSION

Immortal time bias is an often-overlooked phenomenon in time-dependent studies. Landmark analysis is a method that was proposed by Anderson *et al*[21] in the 1980s. A fixed time after the initiation of therapy is selected as the landmark, and patients who die before the landmark time are excluded from the analysis. Although this approach is effective in removing the immortal time bias, it is inferior in that the results differ depending on the choice of the landmark.[18] Time-dependent analysis (proposed by Mantel and Byar[22]) has proved to be superior to landmark analysis in minimizing immortal time bias in observational studies of survival outcomes.[16] Previous studies that assessed the incidence of irAEs and the efficacy of ICIs have either not considered immortal time bias at all[6 7 13–15] or they have avoided using landmark analysis.[8–12] The present study is the first study to assess the association between the incidence of irAEs and the efficacy of ICIs using time-dependent analysis. In the present study, the survival time of irAEs (+) cohort was calculated only after the onset of initial irAE according to time-dependent analysis. Given that the median time from the start of pembrolizumab to the onset of initial irAE was 60 days, the survival time of irAEs (+) cohort might be estimated to be approximately 2 months shorter than its actual duration. Time-dependent analysis could therefore be considered as a more 'conservative' approach than landmark analysis because it should underestimate the survival time of the irAE (+) group. In other words, showing the superiority of the irAE (+) group by time-dependent analysis could be regarded as more 'impressive' than by landmark analysis.

Table 3 Time-dependent univariate analyses of patient survival among characteristics of irAEs

		OS			CSS		
Characteristics of irAEs	**n**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Any irAEs	77	0.59	0.38 to 0.91	0.018*	0.52	0.32 to 0.82	0.005*
CTCAE grade							
Grade 1–2	63	0.49	0.30 to 0.78	0.003*	0.47	0.28 to 0.76	0.002*
Grade 3–5	21	1.48	0.78 to 2.57	0.189	1.19	0.58 to 2.19	0.608
Type of irAEs							
Skin disorders	39	0.62	0.34 to 1.05	0.091	0.62	0.33 to 1.06	0.097
Endocrine disorders	24	0.73	0.36 to 1.35	0.352	0.70	0.33 to 1.33	0.312
Respiratory disorders	10	2.66	1.10 to 5.44	0.011*	2.04	0.71 to 4.63	0.119
Intestinal disorders	9	1.32	0.47 to 2.95	0.541	1.44	0.50 to 3.21	0.429
irAEs requiring glucocorticoid use							
External use	26	0.77	0.40 to 1.35	0.386	0.75	0.37 to 1.35	0.363
Oral use	22	1.11	0.58 to 1.97	0.728	0.98	0.48 to 1.82	0.963
Intravenous use	11	2.12	1.06 to 4.24	0.029*	1.49	0.58 to 3.16	0.343

*Statistically significant.
CSS, cancer-specific survival; CTCAE, Common Terminology Criteria for Adverse Events; irAE, immune-related adverse event; OS, overall survival.

Table 4 Time-dependent multivariate Cox analyses of patient survival

	OS			CSS		
Factor	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Any irAEs						
Age (continuous)	0.99	0.97 to 1.02	0.586	0.99	0.96 to 1.02	0.496
Sex (male vs female)	0.70	0.41 to 1.18	0.184	0.80	0.47 to 1.37	0.421
ECOG PS (0 vs ≥1)	4.31	2.74 to 6.78	<0.001*	4.34	2.71 to 6.97	<0.001*
Primary site (upper tract vs bladder)	0.52	0.34 to 0.80	0.003*	0.55	0.35 to 0.86	0.009*
No of lesions (1–4 vs ≥5)	1.62	1.04 to 2.52	0.034*	1.71	1.08 to 2.72	0.022*
Liver metastasis (no vs yes)	1.90	1.09 to 3.31	0.023*	1.64	0.91 to 2.96	0.100
No of prior regimens (0–1 vs ≥2)	1.13	0.70 to 1.82	0.613	1.25	0.77 to 2.03	0.373
Any irAEs (no vs yes)	0.59	0.36 to 0.96	0.032*	0.50	0.30 to 0.83	0.007*
Grade 1–2 irAEs						
Age (continuous)	0.99	0.97 to 1.02	0.579	0.99	0.97 to 1.02	0.546
Sex (male vs female)	0.67	0.40 to 1.14	0.142	0.77	0.45 to 1.32	0.341
ECOG PS (0 vs ≥1)	4.48	2.83 to 7.11	<0.001*	4.50	2.79 to 7.27	<0.001*
Primary site (upper tract vs bladder)	0.55	0.36 to 0.85	0.007*	0.57	0.36 to 0.90	0.016*
No of lesions (1–4 vs ≥5)	1.57	1.01 to 2.45	0.047*	1.66	1.05 to 2.63	0.031*
Liver metastasis (no vs yes)	1.87	1.08 to 3.25	0.026*	1.66	0.93 to 2.97	0.088
No of prior regimens (0–1 vs ≥2)	1.11	0.69 to 1.79	0.676	1.23	0.76 to 2.01	0.401
Grade 1–2 irAEs (no vs yes)	0.47	0.28 to 0.80	0.005*	0.45	0.26 to 0.76	0.003*
Grade 3–5 irAEs						
Age (continuous)	1.00	0.97 to 1.03	0.898	1.00	0.97 to 1.03	0.853
Sex (male vs female)	0.68	0.41 to 1.15	0.148	0.80	0.47 to 1.35	0.401
ECOG PS (0 vs ≥1)	4.28	2.72 to 6.71	<0.001*	4.25	2.66 to 6.76	<0.001*
Primary site (upper tract vs bladder)	0.50	0.32 to 0.77	0.002*	0.51	0.33 to 0.80	0.003*
No of lesions (1–4 vs ≥5)	1.60	1.03 to 2.48	0.037*	1.71	1.08 to 2.70	0.021*
Liver metastasis (no vs yes)	2.19	1.28 to 3.76	0.005*	1.93	1.09 to 3.42	0.025*
No of prior regimens (0–1 vs ≥2)	1.23	0.77 to 1.99	0.387	1.36	0.84 to 2.20	0.219
Grade 3–5 irAEs (no vs yes)	1.44	0.78 to 2.65	0.242	1.10	0.56 to 2.18	0.784

*Statistically significant.
CSS, cancer-specific survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; irAE, immune-related adverse event; OS, overall survival.

ICIs generate irAEs by unbalancing the immune system in patients. From another point of view, irAEs may suggest the good responsiveness of the patient's immune system to ICIs. In this study, we found that the incidence of irAEs correlated with the favorable therapeutic effect of pembrolizumab in patients with advanced UC. The irAEs (+) cohort showed significantly favorable OS and CSS compared with the irAEs (−) cohort. Our result is significant in that the incidence of irAE correlates with favorable survival even if the immortal time bias has been eliminated by means of time-dependent analysis as detailed above.

We found that the cohort with grade 1–2 irAEs showed significantly favorable OS and CSS, whereas the cohort with grade 3–5 irAEs showed a tendency towards poor OS. The greater severity of irAEs in the latter cohort may account for the shortening of OS in the cohort. Moreover, the cohort with respiratory disorders and the cohort with intravenous administration of glucocorticoids both showed significantly poor OS. Poor OS in the latter cohort may be a coincidental reflection of the requirement to administer intravenous glucocorticoids when irAEs become life threatening. Faje *et al*[23] reported that high-dose glucocorticoids for irAEs were associated with reduced survival in patients who received ICIs. Our results are consistent with those of their study because intravenous administration of glucocorticoids is usually high dose. It is controversial whether high-dose glucocorticoids reduce the antitumor effects of ICIs.[23 24] In our study, the cohort with intravenous administration of glucocorticoids did not show significantly poor CSS. However, it is imperative that intravenous administration of glucocorticoids be performed urgently because delayed treatment can be fatal. Similarly, poor OS in the

cohort with respiratory disorders is because such disorders are frequently life-threatening and require intravenous glucocorticoid treatment. Although the proportion of grade 3–5 respiratory disorders was similar to that of endocrine disorders (40.0% vs 41.7%, respectively), respiratory disorders were the more life-threatening ones of the irAEs, resulting in requiring more frequent intravenous glucocorticoid use.

Interestingly, multivariate analyses of patient survival revealed that primary site of the upper tract had significantly poor OS and CSS compared with the bladder. Advanced upper tract urothelial carcinoma (UTUC) has different molecular and genetic features from the most common carcinoma of the bladder,[25] suggesting a possible different sensitivity to ICI. However, UTUC is underrepresented in clinical trials because of its minority.[26] The significant results obtained in this study may be due to the high UTUC ratio of 44%.

Our study had some limitations. First, it was retrospective and did not represent prospective clinical trials. Second, the sample size was small; although compared with previous studies that have reported on the correlation between irAEs and efficacy in UC, this study has been the largest. Further studies with larger populations are required to validate our results.

CONCLUSION

Even after minimizing immortal time bias by time-dependent analysis, the incidence of irAEs, especially irAEs of grade 1–2, could be a significant predictor of favorable prognoses in patients with UC who have undergone pembrolizumab treatment.

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Acknowledgements We would like to thank Editage (www.editage.com) for English language editing.

Contributors T Kawai and S Taguchi contributed to the conception, study design, analysis, and interpretation of data, and drafted the first manuscript. TN contributed to the conception and study design, supervised the study, and revised the manuscript critically for important intellectual content. JK, YN, DO, KY, T Kaneko, SK, MT, and YS contributed to acquisition of data. YU contributed to the analysis and interpretation of data. TF, HF, YE, HN, S Takahashi, and HK supervised the study, helped to draft the manuscript, and were involved in revising it critically for important intellectual content. All authors read and approved the final manuscript. T Kawai and S Taguchi accept full responsibility for the overall work as the guarantors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of The University of Tokyo (approval number: 10565). Because of the retrospective design of the study, written informed consent was waived. Each participant was given the opportunity to decline participation in the study through the opt-out form on our website.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The raw data underlying this study are available from the corresponding author upon reasonable request.

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