

Comparative Analysis of Immune-based Combination Therapy as First-line Treatment for Advanced Renal Cell Carcinoma

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Abstract


Background/Aim: In advanced renal cell carcinoma (RCC), immune checkpoint inhibitor (ICI) combinations (ICI-ICI) and ICI plus tyrosine kinase inhibitor (TKI) combinations (ICI-TKI) are standard first-line therapies. However, real-world data directly comparing these approaches remain limited. This study aimed to compare treatment outcomes between ICI-ICI and ICI-TKI therapies.

Patients and Methods: We retrospectively analyzed 58 patients who received first-line ICI-ICI therapy (ipilimumab plus nivolumab) or ICI-TKI therapy (pembrolizumab plus axitinib, avelumab plus axitinib, nivolumab plus cabozantinib, or pembrolizumab plus lenvatinib) for advanced RCC at Nagasaki University Hospital (March 2018 to June 2024). Primary endpoints were progression-free survival (PFS), overall survival, and objective response rate (ORR). Safety profiles were also evaluated.

Results: We included 36 patients in the ICI-ICI group and 22 in the ICI-TKI group. The median follow-up was 17.5 months. The median age of patients in the ICI-TKI group was significantly older than that in the ICI-ICI group (74 vs. 66 years, $p < 0.001$). The median PFS was 30 months in the ICI-ICI group and 25 months in the ICI-TKI group. The median overall survival was 51 months in the ICI-ICI group and 49 months in the ICI-TKI group, with no significant difference observed for either endpoint. The ORR was also similar between the groups. Notably, two complete responses occurred in the ICI-ICI group. The treatment discontinuation rate due to grade ≥ 3 adverse events was not significantly different between the ICI-ICI and ICI-TKI groups (30.6% vs. 40.9%).

Conclusion: Across all International Metastatic RCC Database Consortium risk groups, PFS, OS, and ORR showed no significant differences between ICI-ICI and ICI-TKI therapies. Treatment selection should consider patient-specific factors. Validation through larger prospective studies is warranted.

Keywords: Renal cell carcinoma, immune checkpoint inhibitor, tyrosine kinase inhibitor, combination drug therapy, survival rate.

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Introduction

The introduction of immune checkpoint inhibitors (ICIs) to systemic therapy for advanced renal cell carcinoma (RCC) has substantially improved treatment outcomes. Currently, based on results from several phase III trials, the first-line treatment for advanced RCC is ICI combinations (ICI-ICI) or ICI plus tyrosine kinase inhibitor (TKI) combinations (ICI-TKI), both of which have demonstrated superiority over sunitinib (1-6). In Japan, the available therapeutic regimens for advanced RCC include ipilimumab plus nivolumab (Ipi + Nivo) for ICI-ICI therapy, and pembrolizumab plus axitinib, avelumab plus axitinib, nivolumab plus cabozantinib, and pembrolizumab plus lenvatinib for ICI-TKI therapy. According to the International Metastatic RCC Database Consortium (IMDC) risk classification, Ipi + Nivo is indicated for intermediate- and high-risk groups, while ICI-TKI therapies can be used across all risk groups.

The availability of multiple treatment regimens presents challenges in optimal treatment selection. To the best of our knowledge, there are no direct comparisons between ICI-ICI and ICI-TKI therapies, and validated biomarkers for treatment selection remain to be established. Ipi + Nivo therapy is characterized by complete response rates exceeding 10% and a prolonged duration of response in selected patients (7). In contrast, ICI-TKI therapy shows a lower rate of early progression and a higher overall response rate than Ipi + Nivo therapy. Several network meta-analyses have suggested that ICI-TKI therapies, particularly nivolumab plus cabozantinib and pembrolizumab plus lenvatinib, tend to provide superior overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), albeit with increased grade ≥ 3 adverse events (AEs) (8-10). In contrast, Ipi + Nivo shows a higher complete response rate, fewer grade ≥ 3 AEs, and superior quality-of-life maintenance compared with ICI-TKI therapy, although treatment discontinuation rates due to AEs are elevated (8-10).

Currently, there are no evident criteria for the selection of patient-specific regimens to treat advanced RCC. Furthermore, available data are primarily derived from

large-scale, randomized, controlled trials with highly selected patient populations. In real-world clinical practice, the selection of regimens often depends on the physician's preference, patients' characteristics, and comorbidities, frequently presenting therapeutic dilemmas. Therefore, accumulation and analysis of real-world data are important to provide guidance for treatment selection. This study aimed to compare treatment outcomes between ICI-ICI and ICI-TKI therapies across all IMDC risk groups at our institution.

Patients and Methods

Study design and patients. This study was approved by the Human Research Ethics Committee of the Nagasaki University Hospital (Nagasaki, Japan; approval number: 20111606-6) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. We retrospectively analyzed data from 58 patients who received first-line treatment with ICI-ICI (Ipi + Nivo) or ICI-TKI therapy (pembrolizumab plus axitinib, avelumab plus axitinib, nivolumab plus cabozantinib, and pembrolizumab plus lenvatinib) for advanced RCC at the Nagasaki University Hospital. ICI-ICI therapy was administered only to patients in IMDC intermediate- or high-risk groups, while ICI-TKI therapy was used in all risk groups. The inclusion criteria were as follows: (i) no prior systemic therapy, (ii) availability of complete clinical data, and (iii) treatment initiation between March 2018 and June 2024.

The treatment efficacy was evaluated using computed tomography scans performed at 4- to 12-week intervals on the basis of the patient's status. The tumor response was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (11). The ORR was defined as the proportion of patients who achieved a complete response (CR) or partial response (PR). PFS was defined as the time from treatment initiation to disease progression (according to Response Evaluation Criteria in Solid Tumors) or death from any cause. OS was defined as the time from treatment initiation to death from any cause.

To evaluate safety, the AE incidence rate and treatment discontinuation rate were calculated. The classification

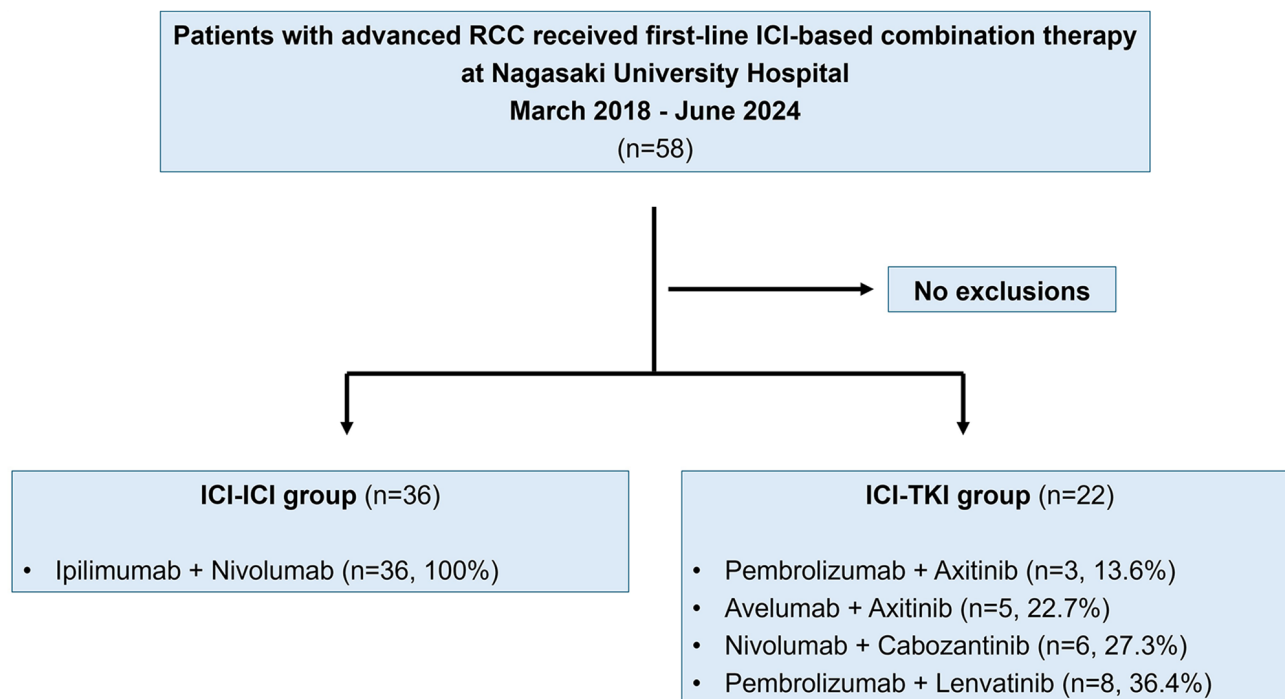


Figure 1. Strobe flowchart depicting the patient selection process.

and grading of AEs were determined using Common Terminology Criteria for Adverse Events version 5.0 (12).

Statistical analysis. Continuous variables are presented as the median with interquartile range (IQR), and categorical variables as numbers with percentages. Variables were compared using the Mann–Whitney *U* test for continuous data and Fisher’s exact test for categorical data. A Kaplan–Meier analysis was used to evaluate PFS and OS, with comparisons performed using the log-rank test. All reported *p* values are two-sided, with statistical significance set at $p < 0.05$. All analyses were performed using BellCurve for Excel version 4.07 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Patient characteristics. Of the 58 patients analyzed, 36 received ICI-ICI therapy and 22 received ICI-TKI therapy.

A STROBE flowchart and the proportions of the therapy received in the ICI-TKI group are shown in Figure 1.

The patient characteristics are shown in Table I. The median age at treatment initiation was 66 years (IQR=59.75–72) in the ICI-ICI group and 74 years (IQR=70.25–80.75) in the ICI-TKI group, which indicated that ICI-TKI was preferentially selected for older patients ($p < 0.001$). The IMDC risk distribution (favorable/intermediate/poor) was 0/20/16 in the ICI-ICI group and 9/8/5 in the ICI-TKI group. Clear cell carcinoma predominated in both groups. Sarcomatoid features appeared to be more frequent in the ICI-ICI group than in the ICI-TKI group (27.8% vs. 9.1%), but this difference was not significant ($p = 0.11$). Prior nephrectomy had been performed in more than half of patients in both groups.

Treatment outcomes. The median follow-up duration was 17.5 months overall (IQR=5–32), with 17.0 months in the ICI-ICI group (IQR=3–37.25) and 17.5 months in the ICI-

Table I. Baseline characteristics of patients in the ICI-ICI and ICI-TKI therapy groups.

	ICI-ICI (n=36) n (%)	ICI-TKI (n=22) n (%)	p-Value
Age, years (median and IQR)	66 (59.75-72)	74 (70.25-80.75)	<0.001
Male	26 (72.2)	14 (63.6)	0.49
IMDC risk			<0.001
Favorable	0 (0)	9 (40.9)	
Intermediate	20 (55.6)	8 (36.4)	
Poor	16 (44.4)	5 (22.7)	
Prior nephrectomy	21 (58.3)	14 (63.6)	0.79
Clear cell RCC	30 (83.3)	20 (90.9)	0.70
With sarcomatoid features	10 (27.8)	2 (9.1)	0.11
Metastasis			
Bone	12 (33.3)	4 (18.2)	0.24
Liver	5 (13.9)	4 (18.2)	0.72

ICI-ICI: Immune checkpoint inhibitor combinations; ICI-TKI: immune checkpoint inhibitor plus tyrosine kinase inhibitor combinations; IQR: interquartile range; IMDC: International Metastatic RCC Database Consortium; RCC: renal cell carcinoma.

TKI group (IQR=7–27.75). There was no significant difference in the median PFS (30 vs. 25 months; $p=0.88$) or OS (51 vs. 49 months; $p=0.75$) between the ICI-ICI and ICI-TKI groups for all types of risk (Figure 2). However, the 3-year survival rate was 25.0% in the ICI-ICI group versus 13.6% in the ICI-TKI group for all types of risk. When the analysis was limited to intermediate- and high-risk groups, the 3-year survival rate was 25.0% in the ICI-ICI group versus 0% in the ICI-TKI group. The ORR was not significantly different between the ICI-ICI and ICI-TKI groups (55.6% vs. 59.1%, $p=0.79$, Table II). When the analysis was restricted to IMDC intermediate/poor-risk patients, there was no significant difference in the median PFS (30 vs. not reached; $p=0.72$) or OS (51 vs. 24 months; $p=0.58$) between the ICI-ICI and ICI-TKI groups. Notably, two patients achieved a CR in the ICI-ICI group, and an additional patient achieved a CR following nephrectomy after an initial PR.

Grade ≥ 3 AEs are shown in Table III. The ICI-TKI group showed higher rates of TKI-related AEs, including hypertension, proteinuria, and diarrhea, than the ICI-ICI group. Treatment discontinuation due to AEs was

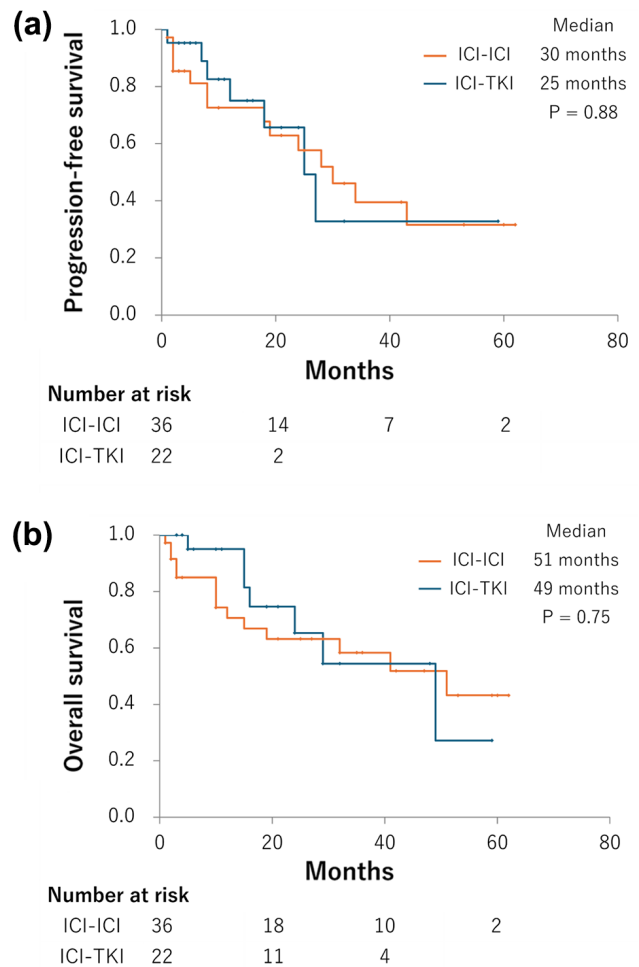


Figure 2. Kaplan–Meier curves comparing (a) progression-free survival and (b) overall survival between the ICI-ICI and ICI-TKI groups. The log-rank test was used for statistical comparison. ICI-ICI: Immune checkpoint inhibitor combinations, ICI-TKI: immune checkpoint inhibitor plus tyrosine kinase inhibitor combinations.

not significantly different between the two groups. One treatment-related death due to severe hypopituitarism occurred in the ICI-ICI group. The frequency of corticosteroid administration was not significantly different between the two groups.

Among patients in the ICI-ICI group, 16 (44.4%) received second-line TKI monotherapy. In the ICI-TKI group, six (27.3%) patients received second-line treatment, predominantly TKI monotherapy (n=5), and one patient received nivolumab monotherapy.

Table II. Best confirmed response in treated patients.

	ICI-ICI (n=36) n (%)	ICI-TKI (n=22) n (%)	
CR	2 (5.6)	0 (0.0)	
PR	18 (50.0)	13 (59.1)	
SD	11 (30.6)	8 (36.4)	
PD	5 (13.9)	1 (4.5)	
ORR	55.6%	59.1%	<i>p</i> =0.79

ICI-ICI: Immune checkpoint inhibitor combinations; ICI-TKI: immune checkpoint inhibitor plus tyrosine kinase inhibitor combinations; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate.

Discussion

This study showed no significant difference in PFS or OS between the two treatment groups. Although the ICI-ICI group achieved two CRs, there was a trend toward a higher progressive disease rate. ICI-TKI was preferentially selected for older patients and showed a non-significant trend toward a higher treatment discontinuation rate due to AEs. Corticosteroid use for managing AEs was similar between the two groups.

Regarding PFS, several real-world analyses have reported findings that are in contrast to those in our study, concluding that ICI-TKI therapy shows superior PFS efficacy to ICI-ICI therapy. A Japanese study by Ishihara *et al.*, which involved 175 patients with IMDC intermediate- and high-risk advanced RCC, reported a significantly longer PFS in the ICI-TKI group than in the ICI-ICI group (15.6 vs. 8.3 months, *p*=0.039) using inverse probability of treatment weighting analysis (13). Additionally, a large real-world study by Ostrowski *et al.* (n=1,438) examined first-line treatment selection in IMDC intermediate- and high-risk metastatic clear cell RCC (14). They found that ICI-TKI therapy had a significantly longer time to next treatment than Ipi + Nivo (13.1 vs. 7.8 months, *p*<0.001). Furthermore, a real-world analysis that compared 1,506 patients with metastatic RCC treated with Ipi + Nivo or pembrolizumab plus axitinib showed a superior median PFS with pembrolizumab plus axitinib (15). In our study, the preferential use of ICI-TKI in older patients and the relatively short observation

Table III. Grade ≥3 treatment-related adverse events in treated patients.

Event	ICI-ICI (n=36) n (%)	ICI-TKI (n=22) n (%)	
Adrenal insufficiency	5 (13.9)	4 (18.2)	
Rash	3 (8.3)	0 (0.0)	
Colitis	3 (8.3)	0 (0.0)	
Hypopituitarism	2 (5.6)	0 (0.0)	
Pneumonitis	1 (2.8)	2 (9.1)	
Acute kidney injury	1 (2.8)	1 (4.5)	
Arthritis	1 (2.8)	0 (0.0)	
Myositis	1 (2.8)	0 (0.0)	
Sepsis	1 (2.8)	1 (4.5)	
Cholangitis	1 (2.8)	0 (0.0)	
Platelet count decreased	1 (2.8)	0 (0.0)	
ALT/AST increased	0 (0.0)	5 (22.7)	
Hypertension	0 (0.0)	4 (18.2)	
Proteinuria	0 (0.0)	4 (18.2)	
Diarrhea	0 (0.0)	2 (9.1)	
Hypothyroidism	0 (0.0)	2 (9.1)	
Aortic dissection	0 (0.0)	1 (4.5)	
Treatment discontinuation	11 (30.6)	9 (40.9)	<i>p</i> =0.42

ICI-ICI: Immune checkpoint inhibitor combinations; ICI-TKI: immune checkpoint inhibitor plus tyrosine kinase inhibitor combinations; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

period may have accounted for the absence of significant differences in PFS between the groups.

Ishihara *et al.* (46.7 vs. 49.0 months, *p*=0.465) and Ostrowski *et al.* (28.8 vs. 25.0 months, *p*=0.91) reported no significant difference in OS between the ICI-ICI and ICI-TKI groups (13-14), consistent with our findings. However, Santoni *et al.* reported that, although there was no significant difference in OS between groups in the IMDC high-risk cohort, the ICI-TKI group showed superior OS in the intermediate-risk cohort (16). Several network meta-analyses that compared outcomes between Ipi + Nivo and ICI-TKI therapy, including patients with an IMDC favorable risk, also showed trends favoring OS and PFS in the ICI-TKI groups, particularly nivolumab plus cabozantinib and pembrolizumab plus lenvatinib (9-10). However, in recent years, the 3-year landmark OS rather than the median value has been considered more important as an endpoint (17). In our study, the 3-year survival rate of patients in the ICI-ICI group was higher than that of patients in the ICI-TKI group. When the analysis was limited to intermediate- and high-risk groups, the difference in the 3-year survival

rate between these two groups was more obvious. In our study, no significant difference in OS was observed by the log-rank test. The 3-year survival rate was higher with ICI-ICI than with ICI-TKI, suggesting that the evaluation of OS may change with an extended follow-up. While ICI-TKI may offer broad efficacy across a wide range of patients, our findings also suggest that ICI-ICI may be extremely effective in certain patient subsets.

This study showed no significant difference in the ORR between the two groups, although two CRs occurred in the ICI-ICI group. Other real-world analyses have similarly reported no significant difference in the ORR between the ICI-ICI and ICI-TKI groups (13, 18). Network meta-analyses have indicated that ICI-TKI is associated with a higher ORR than ICI-ICI, although the CR rate remained highest with ICI-ICI (8-10). In our study, there was a high initial progressive disease rate in the ICI-ICI group. The CheckMate-214 trial with an 8-year median follow-up also reported a high progressive disease rate (19.3%) as the best overall response in intermediate- or high-risk patients but showed a median response duration of 82.8 months (7).

Regarding safety, previous real-world analyses reported a higher incidence of AEs and treatment discontinuation rate in ICI-TKI groups and a higher corticosteroid administration rate in ICI-ICI groups (13). In particular, attention must be paid to immune-related adverse events such as uveitis that reduce quality of life (19). However, our study showed no significant difference in treatment discontinuation due to AEs or the corticosteroid administration rate between the groups. Network meta-analyses have shown that the incidence of grade ≥ 3 AEs is higher with ICI-TKI, particularly nivolumab plus cabozantinib and pembrolizumab plus lenvatinib, than with Ipi + Nivo, although treatment discontinuation is more frequent with Ipi + Nivo (8-10). Additionally, concomitant medications may influence the incidence and pattern of immune-related adverse events. A recent study has suggested that acid suppressants may have diverse effects on ICI-induced adverse events, with varying impacts on different organ systems. In this study, co-administration with acid suppressants, particularly proton pump inhibitors, was associated with an increased risk of

acute kidney injury, while the incidence of endocrine-related AEs tended to decrease with acid suppressants (20).

In metastatic RCC, validated biomarkers for selection of the optimal treatment regimen remain undeveloped. Currently, the choice between Ipi + Nivo and ICI-TKI requires shared decision-making and considering drug characteristics and patients' goals. The BIONIKK trial was the first prospective biomarker-driven treatment selection trial of metastatic RCC, and it classified patients into four molecular subtypes (ccrcc1-4) on the basis of transcriptional analysis and selecting treatments according to biological characteristics (21). In the angiogenesis-predominant ccrcc2 group, vascular endothelial growth factor (VEGF) receptor-TKI monotherapy and Ipi + Nivo achieved an approximately 50% response rate, and PFS was slightly longer with VEGF receptor-TKI (14.4 vs. 11.1 months). Future larger scale biomarker-based trial designs are anticipated (21). Additionally, Motzer *et al.* demonstrated that tumors from favorable risk patients were enriched in angiogenic clusters characterized by higher VEGF pathway gene expression. This finding provides biological rationale for considering VEGF receptor-TKI monotherapy as a treatment option in favorable risk patients (22). However, our previous study specifically comparing ICI-TKI combination therapy with TKI monotherapy in favorable risk patients found that, despite no significant differences in OS or PFS, ICI-TKI therapy demonstrated superior ORR (82% vs. 50%) and showed lower rates of grade ≥ 3 adverse events compared to TKI monotherapy (55% vs. 83%) (23).

Study limitations. First, because this was a single-center retrospective study with a limited sample size ($n=58$), statistical power may have been insufficient. Second, the relatively short median follow-up of 17.5 months limited long-term prognostic assessment. Third, significant differences in the patients' characteristics between the ICI-ICI and ICI-TKI groups (*e.g.*, age and IMDC risk classification) introduced potential selection bias that cannot be completely eliminated. Larger, multicenter, collaborative or prospective studies are required to validate our findings because of these limitations.

Conclusion

In this analysis encompassing all IMDC risk groups, no significant differences in PFS, OS, or ORR were observed between ICI-ICI and ICI-TKI therapies. Safety profiles, including the treatment discontinuation rate and incidence of serious AEs, were similar between the two types of therapy. The preferential selection of ICI-TKI therapy for older patients suggests that differences in patients' characteristics may affect treatment outcomes.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: Yuta Mukae and KO; Data curation: Tsuyoshi Matsuda; Formal analysis: Yuta Mukae; Investigation: HN and KK; Methodology: MO; Project administration: KO; Supervision: RI; Validation: KM, Tomohiro Matsuo and Yasushi Mochizuki; Visualization; Roles/Writing - original draft: Yuta Mukae and KO; Writing - review & editing: Yuta Mukae and KO.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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