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Risk of malignant neoplasms of tacrolimus in kidney transplant patients: a retrospective cohort study conducted using the Japanese National Database of Health Insurance Claims

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Abstract

Background Although the long-term survival of kidney transplant recipients has significantly improved, malignant neoplasms remain one of the leading causes of death in this population. The recipients face a 1.8-fold increased risk of developing malignant neoplasms compared with the general population. This risk increases with time after transplantation. Tacrolimus (TAC) is preferred over cyclosporine A (CyA) in terms of efficacy against organ rejection, but evidence on the risk of malignant neoplasms is lacking. We aimed to describe the incidence and types of malignant neoplasms in kidney transplant recipients and evaluate the association between malignant neoplasms development and the type of prescribed CNI.

Methods This retrospective cohort study was conducted using the Japanese National Database of Health Insurance Claims, including data covering 99% of kidney transplant patients in Japan. Patients who underwent kidney transplantation and were prescribed TAC or CyA between April and June 2011 were included. The primary outcome included the incidence of malignant neoplasms, and secondary outcomes included overall survival and graft survival.

Results A total of 7,590 patients were included, with 11.0% developing malignant neoplasms during the follow-up period. The most common malignant neoplasms were in the digestive organs and urinary tract. No statistically significant difference in malignant neoplasms incidence was observed between TAC and CyA users (hazards ratio: 0.97, 95% CI: 0.84 to 1.12; estimated average treatment effect: −24.05, 95% CI: −184.90 to 136.80). The patient and graft survival rates were also comparable between the groups.

Conclusions This large study suggests that TAC is not associated with an increased risk of malignant neoplasms compared to CyA in the late post-transplant period.

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Clinical trial number Not applicable.

Keywords Calcineurin inhibitors, Cyclosporine A, Kidney transplant, Malignant neoplasms, Tacrolimus

Background

In Japan, the overall survival of patients with kidney transplants has improved significantly, with long-term survival rates showing that 95% of patients who receive a kidney from a living donor remain alive for up to 20 years [1]. Despite these improvements, cardiovascular diseases, infections, and malignant neoplasms remain the leading causes of death among kidney transplant recipients [2].

Kidney transplant recipients face a higher risk of developing malignant neoplasms, with a 1.8-fold increased risk compared with that faced by the general population [3]. The most common malignant neoplasms include skin cancer, lymphoma, and kidney cancer. The risk factors for these conditions include older age, male sex, long-term use of immunosuppressive drugs, and longer time since transplantation [4–6]. The longer a person lives after transplantation, the higher their risk of developing malignant neoplasms, with the incidence reaching 10% at 10 years post-transplant [7].

Calcineurin inhibitors (CNIs), such as tacrolimus (TAC) and cyclosporine A (CyA), have been reported to increase the incidence of malignant neoplasms in patients who receive solid organ transplants [8]. CNIs are crucial for kidney transplantation and serve as the main drugs for preventing the immune system from rejecting the transplanted organ. These drugs have greatly reduced the rate of acute rejection and are used in over 90% of kidney transplant recipients [9]. TAC has become the preferred treatment choice because of its effectiveness in reducing rejection rates. A large-scale randomized controlled trial (RCT) reported that TAC compared with CyA reduced rejection rates by 15% in kidney transplant recipients [10]. However, the available evidence does not clearly indicate the association of either TAC or CyA administration with an increased risk of malignant neoplasms in transplant patients. Two meta-analyses reported conflicting results regarding the incidence of tumors between patients treated with TAC and those treated with CyA [11, 12]. Another study found that cumulative exposure to TAC was an independent predictor of malignant neoplasms after liver transplants [13]. These conflicting results may be due to limitations in the study design, observation periods, and adjustment of confounding factors in observational studies.

Methods

Aim

The aims of this study were to (1) describe the incidence and type of malignant neoplasms in kidney transplant patients and (2) evaluate the association between the development of malignant neoplasms and the types of CNIs prescribed, using a comprehensive administrative claims database that covers most kidney transplant patients in Japan.

Study design and data source

In this retrospective cohort study, we used data from the Japanese National Database of Health Insurance Claims and Specific Health Checkups (NDB). The NDB is one of the largest national administrative claim databases. The NDB comprises medical, dental, and pharmacy claims data, each linked by a unique ID. The NDB includes data from over 126 million people and handles 1.9 billion electronic claims every year, gathering information from 99% of the medical facilities in Japan [14]. Since 2011, the Japanese Ministry of Health, Labour, and Welfare (MHLW) has allowed the use of the NDB for research purposes, and the NDB has been used in various fields of medical research [15]. From the NDB data, we used medical and pharmacy claims data. The use of the NDB data for this study was approved by the MHLW in September 2020. We obtained the dataset, which includes data from April 2011 to March 2020, in July 2021.

Participants

Patients with (1) kidney transplants and (2) TAC or CyA prescriptions between April and June 2011 (the index date) were included in the study. Patients who underwent kidney transplantation were identified based on Japanese standardized disease codes. The kidney transplant-related disease names, codes, and their corresponding ICD-10 codes were as follows: deceased donor kidney transplantation (8847618, ICD-10: Z94.0), brain-dead donor kidney transplantation (8847671, ICD-10: Z94.0), living-donor kidney transplantation (8847643, ICD-10: Z94.0), and kidney transplantation (9968003, ICD-10: Z94.0). TAC or CyA prescriptions on the index date were identified using the National Health Insurance (NHI) drug price listing code [16] (Supplementary 1). Two unique IDs were used to avoid duplicating the same patient due to changes in the health insurance number. Of these patients, we excluded those who had malignancy-related diseases (ICD-10 codes C00-C97 and D00-D09) before the index date. We also excluded patients with hepatitis B- or C-related disease names in the Japanese standardized disease codes. (Supplementary 2).

Exposure

Exposure was defined as TAC use, whereas control was defined as CyA use on the index date. For evaluation as

a time-dependent variable, changes in treatment were evaluated for up to 5 years.

Outcomes

The primary outcome measure was incidence of malignant neoplasms. The development of malignant neoplasms was identified based on the ICD-10 codes (C00-C97 and D00-D09) and assigned dates. The secondary outcome measures were patient and graft survival rates. To prevent underestimation, deaths were identified from five different codes in the medical claims data: (1) outcome of disease name codes; (2) additional cost codes for end-of-life care (Supplementary 3); (3) comment codes for deaths under special situations (Supplementary 4); (4) death within 24 h of admission in records of exclusions from the Diagnosis Procedure Combination (DPC) system, which is a Japanese healthcare payment system; and (5) outcome codes in DPC records. Graft loss was identified based on dialysis-related claim codes more than 3 months after the index date (Supplementary 5).

Other variables

Based on previous studies and clinical insights from transplant nephrologists, the following variables with demonstrated or plausible associations with malignant neoplasms development and the types of CNI prescribed were selected as confounding variables: age, sex, duration since transplantation, mycophenolate mofetil (MMF) use, azathioprine (AZA) use, and glucocorticoid use. Immunosuppressant prescriptions other than TAC or CyA and glucocorticoid prescriptions at the index date were identified using the NHI drug price listing code [16] (Supplementary 6 and Supplementary 7).

Statistical analysis

Patient characteristics are described as the mean (standard deviation [SD]). Survival curves were plotted using the Kaplan-Meier method to compare the event probability at different time points and between patients treated with TAC and those treated with CyA. A log-rank test was used to determine the statistical significance between two groups.

For the primary analysis, Cox proportional hazard models were used to estimate hazard ratios (HRs), with adjustment for confounders, for the association between malignant neoplasms incidence and types of CNI. For sensitivity analysis, the average treatment effect (ATE) on the incidence of malignant neoplasms was estimated using inverse probability weighting (IPW) methods. We applied the same analyses to assess the association between the CNI type, patient survival, and graft survival.

We used multiple imputations to handle the uncertainty caused by missing values of time since transplantation under the assumption of missing values at random. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the Statistical Package of Stata (version 18.0; StataCorp, College Station, TX, USA).

Results

Patient characteristics

A flowchart describing the patient selection process is shown in Fig. 1. Of 23,125 eligible patients, 7,590 were included in the analysis. The mean (SD) age of the patients was 46.5 (14.6) years, and 2,998 (39.5%) were female. The mean (SD) time since transplantation was 2,031 (1,758) days. Glucocorticoids, AZA, and MMF were used in 6, 894 (90.8%), 734 (9.7%), and MMF in 5,692 (75.0%) patients, respectively. Almost equal numbers of patients were treated with TAC and CyA: 3,746 (49.4%) with TAC and 3,844 (50.6%) with CyA. Among the 2,809 patients whose prescriptions were confirmed at the 5-year from the index date, only 18 of 1,229 (1.5%) switched from TAC to CyA, while only 17 of 1,580 (1.1%) switched from CyA to TAC.

Frequency and types of malignant neoplasms

Of the 7,251 patients, excluding those who may have had malignant neoplasms before the start of the observation period, 795 (11.0%) developed malignant neoplasms after the index date during the mean of 1,667 (SD 1,242) days. Among patients with a malignant neoplasms diagnosis prior to the index date, 712 cases were included in the analysis after resolving duplicates. Information on TAC or CyA use was missing in 12 cases. Of the remaining patients, 329 received TAC, including 88 with digestive malignant neoplasms, 75 with urinary tract malignant neoplasms, and 40 with hematologic malignant neoplasms. A total of 371 patients received CyA, including 87 with digestive malignant neoplasms, 69 with urinary tract malignant neoplasms, and 51 with hematologic malignant neoplasms. The patients who developed malignant neoplasms were older, had longer duration after transplantation, and used AZA more frequently than those who did not develop (Supplementary 8). The breakdown of organs by ICD classification was as follows: digestive organs (C15-C26), 204 (25.7%); urinary tract (C64-C68), 129 (16.2%); lymphoid, hematopoietic, and related tissue (C81-C96), 96 (12.1%); respiratory and intrathoracic organs (C30-C39), 66 (8.3%); skin (C43-C44), 65 (8.1%); male genital organs (C60-C63), 49 (6.2%); female genital organs(C51-C58), 43 (5.4%); breast (C50-C50), 38 (4.8%); thyroid and other endocrine glands (C73-C75), 34 (4.3%); ill-defined, other secondary and unspecified sites (C76-C80), 27(3.4%); others including in situ neoplasms (D00-D09), lip, oral cavity and pharynx(C00-C14), mesothelial and soft tissue (C45-C49), eye, brain and other parts of central nervous system (C69-C72), and bone and articular cartilage (C40-C41), 44 (5.5%) (Table 1). Among the

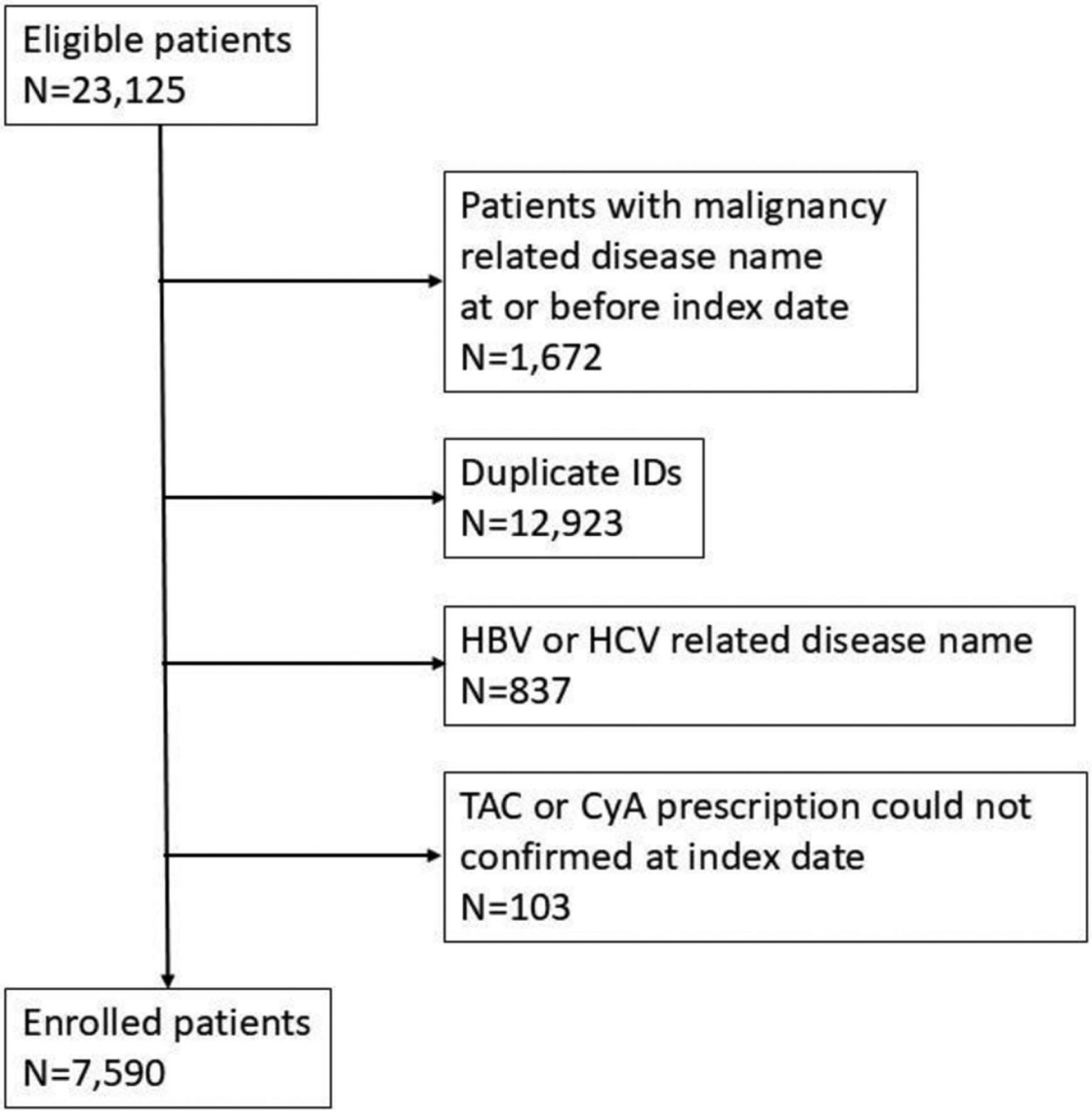

Fig. 1 Patient selection flow chart

204 malignant neoplasms of the digestive organs, the most common sites were the colorectum ($n = 88$), stomach ($n = 59$), and hepatobiliary and pancreas ($n = 39$), with 18 cases classified as other digestive sites. After the diagnosis of malignant neoplasms, 71 patients (8.9%) died during a mean (SD) observation period of 1,160 (903) days.

Risk of malignant neoplasms development between TAC and CyA users

Characteristics of TAC and CyA users are shown in Table 2. Patients using TAC were younger, had a higher proportion of females, had a shorter duration since transplantation, had lower usage of GC and AZA, and higher MMF usage than those using CyA.

Malignant neoplasms development was found in 381 of 3,544 patients treated with TAC and in 414 of 3615 patients with CyA. The cumulative incidence of malignant neoplasms in the TAC group was 2.0% at 1 year, 10.5% at 5 years, and 15.0% at 7 years, whereas in the CyA group, it was 2.5% at 1 year, 10.9% at 5 years, and 15.5% at 7 years. The breakdown of the organs according to the ICD classification for each group is shown in Table 1. The log-rank test showed no statistically significant differences in the incidence of malignant neoplasms between patients treated with TAC and those treated with CyA (Fig. 2; $p = 0.25$).

Subsequently, we estimated the HRs between TAC and CyA users after adjusting for potential confounders (age, sex, duration since transplantation, MMF use, AZA use,

Table 1 Frequency and types of malignant neoplasms

Type	ICD-10 code	All	With TAC	With CyA
		(*n* = 795)	(*n* = 381)	(*n* = 414)
Digestive organs, % (n)	C15-C26	25.7 (204)	23.9 (91)	27.3 (113)
Urinary tract, % (n)	C64-C68	16.2 (129)	17.3 (66)	15.2(63)
Lymphoid, hematopoietic, and related tissue, % (n)	C81-C96	12.1 (96)	11.8 (45)	12.3 (51)
Respiratory and intrathoracic organs, % (n)	C30-C39	8.3 (66)	6.8 (26)	9.7 (40)
Skin, % (n)	C43-C44	8.2 (65)	6.8 (26)	9.4 (39)
Male genital organs, % (n)	C60-C63	6.2 (49)	6.0 (23)	6.3 (26)
Female genital organs, % (n)	C51-C58	5.4 (43)	7.1 (27)	3.8 (16)
Breast, % (n)	C50-C50	4.8 (38)	7.3 (28)	2.4 (10)
Thyroid and other endocrine glands, % (n)	C73-C75	4.3 (34)	4.2 (16)	4.3 (18)
Ill-defined, other secondary and unspecified sites, % (n)	C76-C80	3.4 (27)	3.7 (14)	3.1 (13)
Others, including	D00-D09	5.5 (44)	5.0 (19)	6.0 (25)
In situ neoplasms	C00-C14			
Lip, oral cavity, and pharynx				
Mesothelial and soft tissue	C45-C49			
Eye, brain, and other parts of central nervous system	C69-C72			
Bone and articular cartilage, % (n)				
	C40-C41			

CyA, cyclosporine A; ICD, International Classification of Diseases; TAC, tacrolimus

Table 2 Characteristics of patients with TAC and CyA

	With TAC (*N* = 3,746)	With CyA (*N* = 3,844)	*p* - value
Age, mean SD, years	45.1 (14.9)	47.8 (14.2)	< 0.0001
Female patients, % (n)	41.9 (1,571)	37.1 (1,427)	< 0.0001
Duration after transplantation, mean SD, days	1,718 (1,414)	2,335 (1,911)	< 0.0001
Glucocorticoids use, % (n)	90.1 (3,375)	91.5 (3,519)	0.029
Mycophenolate mofetil use, % (n)	80.3 (3,007)	69.8 (2,685)	< 0.0001
Azathioprine use, % (n)	7.2 (269)	12.1 (465)	< 0.0001

CyA, cyclosporine A; SD, standard deviation; TAC, tacrolimus

and glucocorticoid use) in Cox proportional hazard models. The HR with the Cox proportional hazard models was 0.97 (95% CI = 0.84 to 1.12). ATE on the malignant neoplasms development, estimated using IPW methods, had no significant difference between the patients with TAC and those with CyA (ATE, − 24.05 [95% CI = − 184.90 to 136.80]) (Table 3).

Secondary outcome analysis

During the mean (SD) observation period of 1,805 (1,257) days, 224 patients (3.0%) died. Among the 7,444 patients

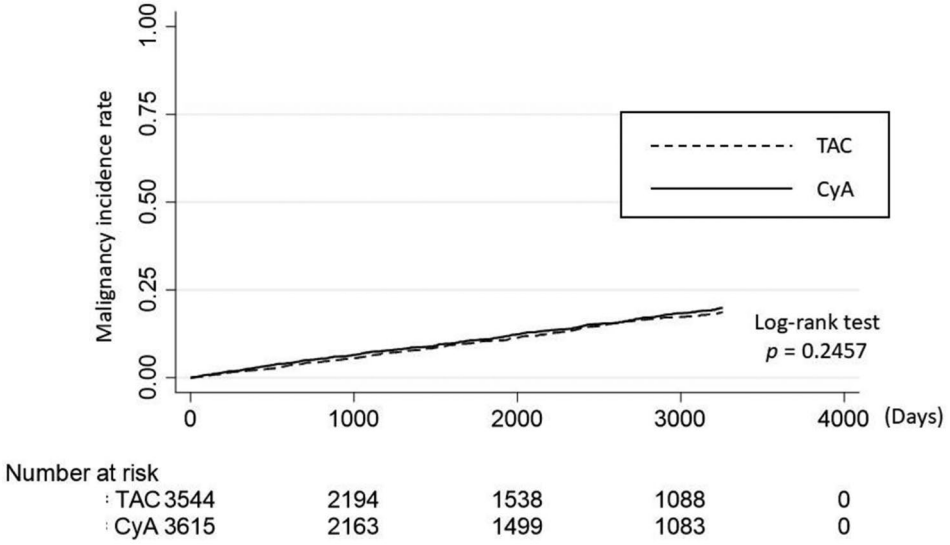

Fig. 2 Cumulative incidence curve of malignant neoplasms among patients with TAC and those with CyA calculated using the Kaplan–Meier method. CyA, cyclosporine A; TAC, tacrolimus

Table 3 Comparison of malignant neoplasms development, survival, and graft survival between patients with TAC and CyA

	HR (95%CI)	ATE (95%CI)
Malignant neoplasms development	0.97 (0.84 to 1.12)	−24.05 (−184.90 to 136.80)
Survival	1.09 (0.83 to 1.43)	213.4 (−24.1 to 450.8)
Graft survival	0.96 (0.83 to 1.11)	58.4 (−86.9 to 203.6)

ATE, average treatment effect; CI, confidence interval; CyA, cyclosporine A; HR, hazard ratio; TAC, tacrolimus

excluding those potentially on maintenance dialysis at the index date, 767 (10.3%) progressed to graft loss during the mean (SD) observation period of 1,680 (1,229) days, excluding those potentially on maintenance dialysis at the index date. The log-rank test showed statistically significant differences in patient survival but no significant differences in graft survival between patients treated with TAC and those treated with CyA (patient survival: Fig. 3, $p = 0.033$; graft survival: Fig. 4: $p = 0.82$).

After adjusting confounding factors, the HRs for survival and graft survival were 1.09 (95% CI = 0.83 to 1.43) and 0.96 (95% CI = 0.83 to 1.11). ATEs on survival and graft survival were 213.4 (−24.1 to 450.8, $p = 0.08$) and 58.4 (95% CI = −86.9 to 203.6, $p = 0.43$) (Table 3).

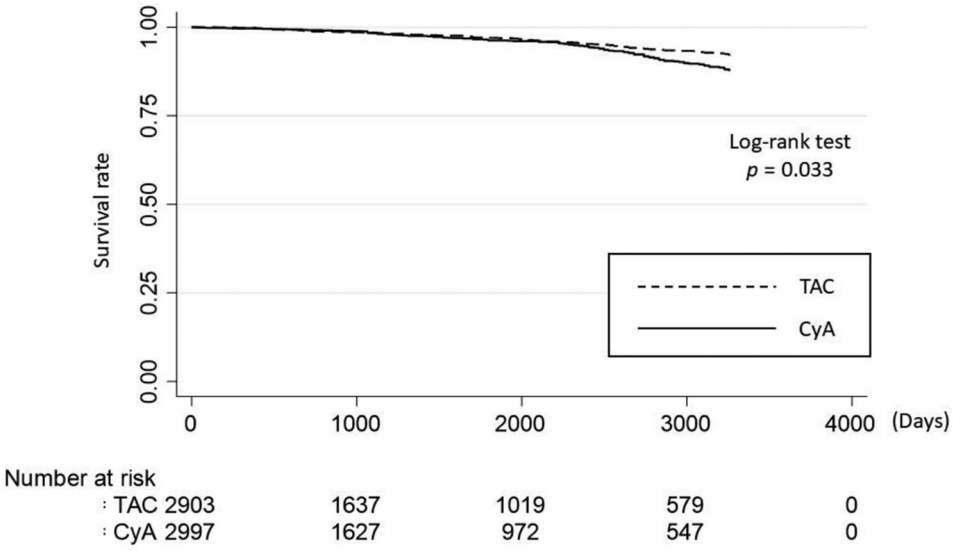

Fig. 3 Patient survival curve among patients with TAC and those with CyA calculated using the Kaplan–Meier method. CyA, cyclosporine A; TAC, tacrolimus

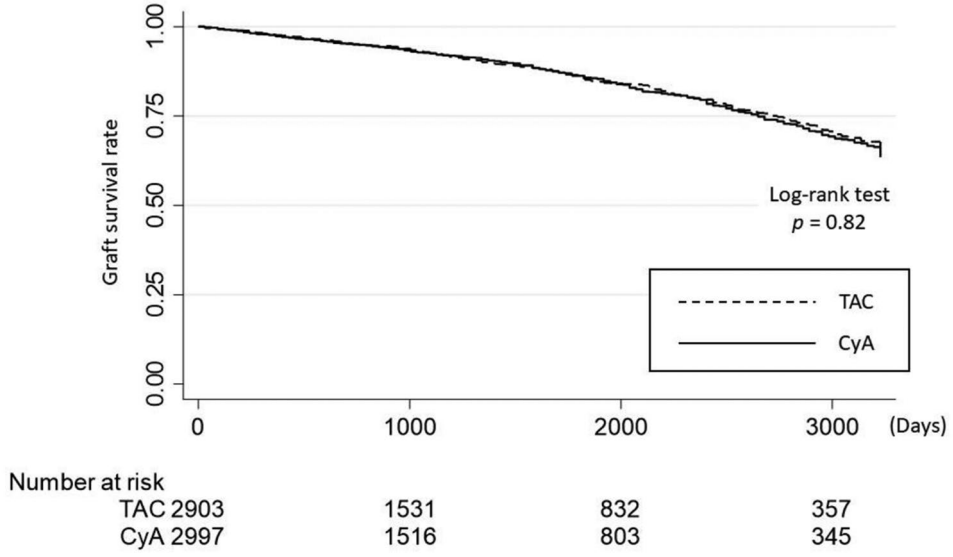

Fig. 4 Graft survival curve among patients with TAC and those with CyA calculated using the Kaplan–Meier method. CyA, cyclosporine A; TAC, tacrolimus

Discussion

The carcinogenic risk associated with calcineurin inhibitors (tacrolimus and cyclosporine) is not limited to the post-transplant setting but may arise from their immunosuppressive effects. However, clinical data on cancer risk in non-transplant populations, such as those with autoimmune or inflammatory diseases, are extremely limited. Therefore, this discussion focuses primarily on evidence derived from kidney transplant recipients. In the present study, we investigated the incidence and types of malignant neoplasms in kidney transplant recipients and evaluated their association with prescribed CNIs, specifically TAC and CyA. We used the NDB, an administrative claims database that encompasses the majority of kidney transplant patients in Japan. The 7,590 patients in the study were nearly evenly divided between the TAC and CyA groups. Among the enrolled patients, 11% developed malignant neoplasms after transplantation, with neoplasms of the digestive organs and urinary tract being the most prevalent. Notably, we found no statistically significant difference in the incidence of malignant neoplasms between TAC and CyA users. Secondary outcomes, including graft loss and overall mortality, were similar between groups.

Malignant neoplasms of the urinary tract, lymphatic system, blood, and skin are common in kidney transplant recipients treated with CNIs. Previous reports have shown that the standardized incidence ratios of all cancers in kidney transplant recipients is at least 1.8 to 1.9 times higher than that of the general population matched for age and sex. The highest risks were observed in patients with melanoma, urinary tract, and lymphoid/hematopoietic malignant neoplasms, with cancer-related mortality risks exceeding 5 to 10 times those of non-kidney transplant recipients [17]. Consistent with other studies in Asian countries, skin malignant neoplasms were relatively high at 8.2% (China 2.7%, South Korea 2.2%) [18, 19], though these were not the major types observed in Western populations (Sweden 40.2%, Spain 45%) [20, 21]. The cumulative incidence of solid organ cancer ranges between 10% and 15% at approximately 15 years post-transplantation [17] and a recent Korean study reported that 6.0% of patients developed malignant neoplasms during a median follow-up duration of 4.9 years [19]. The incidence of malignant neoplasms in our study was higher than that in a Korean report, which can be attributed to the longer post-transplantation period. As the duration of life post-transplantation increases, the risk of developing malignant neoplasms also increases, with the incidence reaching 10% at 10 years post-transplant [7]. Given that our enrolled patients had a mean duration of 5.6 years on the index date, the observed incidence of malignant neoplasms was consistent with previous findings.

Our results suggest that the selection of CNIs may not be significantly associated with the development of malignant neoplasms. CNIs are known to increase the incidence of malignant neoplasms in solid organ transplant recipients due to continuous immunosuppression [8]. Recent research has indicated that reduced exposure to CNIs may reduce the post-transplantation cancer burden post-transplantation [22]. Among the CNIs, TAC is often preferred over CyA because of its effectiveness in lowering rejection rates, as demonstrated by the results of an RCT [10]. However, the same study reported no significant difference in graft survival or overall survival between the two groups. Consistent with these findings, our study also found no significant differences between the TAC and CyA groups in either patient survival or graft survival. These results suggest that the choice of CNI may not have a substantial impact on short- to mid-term outcomes in kidney transplant recipients. Existing evidence does not definitively show whether TAC or CyA administration carries a higher risk of malignant neoplasms in transplant patients. One meta-analysis based on RCTs reported a significantly increased risk of overall malignant neoplasms associated with TAC exposure compared with non-TAC therapy, including sirolimus, but no difference was found between kidney transplant patients treated with TAC and those treated with CyA [11]. Conversely, another meta-analysis based on observational studies indicated that patients receiving CyA developed more new malignant neoplasms than those receiving TAC [12]. This meta-analysis included approximately 80,000 participants; however, the comparability of all studies was judged to be 'not high. ' Our large-scale, well-designed observational study supports the results of a previous meta-analysis based on RCTs, suggesting comparable risks of malignant neoplasms between TAC and CyA groups. There was no significant difference in either HR or the estimated ATE for the effect on the time to tumor development.

The patient survival rate, which was evaluated as a secondary endpoint, showed significantly higher results in the TAC group compared to the CyA group; however, no significant difference was observed in the adjusted analysis. This discrepancy may reflect the influence of confounding factors such as age and post-transplant duration. On the other hand, no significant difference was observed in graft survival rates between the two groups. These results suggest that the type of CNI may not have a decisive impact on short- to mid-term patient outcomes or graft outcomes.

The use of NDB data in this study has two significant strengths. First, we examined the effects of TAC and CyA on carcinogenesis on a large scale. As the NDB includes data from 99% of the medical facilities in Japan, the administrative claims data of approximately all kidney transplant patients were included. Although the exact number of graft survivors as of 2011 for post-kidney transplant patients has not been reported, considering that there were fewer than 1,500 kidney transplants per year in Japan until 2011 [23], the selection of 23,125 patients using CNIs suggests that the patient selection for this study was extremely

comprehensive. Second, the database offers exceptional traceability with data available from most medical institutions. If a facility providing kidney transplantation care does not coincide with one providing malignant neoplasms care, the occurrence of malignant neoplasms may not be captured in hospital-specific databases. Furthermore, there may be a significant loss to follow-up regarding survival after malignant neoplasms development in facilities providing kidney transplantation care. In the present database, the effect of loss to follow-up on survival after the development of malignant neoplasms was minimal.

This study has limitations specific to database research. First, a limited index date was set to align with the historical background of the practice and to ensure a consistent observation period. As a result, the enrolled population had a mean duration of 5.6 years post-transplantation which excluded malignant neoplasms that developed earlier after transplantation. In particular, early-onset malignancies such as Kaposi sarcoma and post-transplant lymphoproliferative disorder—often occurring within the first 2–3 years after transplantation—were likely underrepresented in this analysis [24]. However, this definition allowed us to evaluate its association with long-term immunosuppression. Second, database studies require validation of the accuracy of disease codes. High accuracy has been reported for certain malignant neoplasms disease codes [25]. The extraction of dialysis patients with dialysis-related codes may have led to an underestimation of the actual number of dialysis patients [26]. In the present study, dialysis codes were used to define graft loss, which were further limited by the implementation period and may have led to an underestimation of the actual graft loss. However, considering that the 5th and 10th -year graft survival rates were 83% and 71%, respectively, in patients who underwent kidney transplantation between 2001 and 2009 [23], the graft survival data did not appear to be significantly underestimated. Finally, CNIs may have been switched based on the index date. However, the small number of treatment changes after the index date suggests that the impact of treatment switches was minimal.

Conclusions

In this large, population-based study of kidney transplant recipients in the late post-transplant period, we found no evidence of an increased risk of malignant neoplasms associated with TAC compared to CyA. The two drugs also showed comparable outcomes in terms of graft loss and overall mortality. While these findings suggest that TAC does not confer a higher risk of malignant neoplasms in the late post-transplant period, further research is needed to evaluate its impact on early-onset malignancies.

Abbreviations

ATE	Average treatment effect
AZA	Azathioprine
CNI	Calcineurin inhibitor
CyA	Cyclosporine A
DPC	Diagnosis Procedure Combination
IPW	Inverse probability weighting
MHLW	Ministry of Health, Labour, and Welfare
MMF	Mycophenolate mofetil
NDB	National Database of Health Insurance Claims and Specific Health Checkups
RCT	Randomized controlled trial
SD	Standard deviation
TAC	Tacrolimus

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04405-8.

Supplementary Material 1

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Author contributions

KE. Sada had full access to all of the data in the study. He took responsibility for the data's integrity and the data analysis's accuracy. Study conception and design: R. Kubota and KE. Sada. Interpretation of data and manuscript writing support: M. Tokunaga, K. Yoshinaga, T. Yamanoi, T. Kawada, Y. Tominaga, T. Sadahira, S. Katayama, T. Iwata, S. Nishimura, K. Bekku, K. Edamura, T. Kobayashi, Y. Nakagawa, N. Ichimaru, K. Wada, and M. Araki. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to legal restrictions of the NDB, but are available from the corresponding author on reasonable request and with permission from the MHLW.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Epidemiologic Research in Japan. This study was approved by the Ethics Committee of Kochi Medical School, Kochi University (2021 – 160), which also approved the waiver of informed consent. The NDB data were fully anonymized by the MHLW prior to access.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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