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Report on post-transplantation cancer in southeast Asia from the Thai kidney transplantation cohort

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Post-transplantation cancer is a significant cause of mortality among kidney transplant recipients (KTR). The incidence of post-transplantation cancer varies based on geographic region and ethnicity. However, data on KTR from South East Asia, where characteristics differ from other parts of Asia, is lacking. We conducted a retrospective cohort study at a transplant center in Thailand to investigate the incidence of post-transplantation cancer and mortality rates. Factors associated with post-transplantation cancer and patient outcomes were analyzed using competing-risks regression. The study included 1156 KTR with a post-transplant follow-up duration of 5.1 (2.7–9.4) years. The age- and sex-adjusted incidence rate of post-transplant cancer was highest for urothelial cancer (6.9 per 1000 person-years), which also resulted in the highest standardized incidence ratio (SIR) of 42.5 when compared to the general population. Kidney cancer had the second-highest SIR of 24.4. Increasing age was the factor associated with an increased risk of post-transplant cancer (SHR 1.03; 95% CI 1.01–1.05). Human leukocyte antigen (HLA) DR mismatch was associated with a decreased risk of post-transplant cancer (SHR 0.72; 95% CI 0.52–0.98). Post-transplantation cancer was significantly associated with patient mortality (HR 3.16; 95% CI 2.21–4.52). Cancer significantly contributes to KTR mortality, and the risk profile for cancer development in Thai KTRs differs from that of Western and most Asian counterparts. Further research is essential to explore appropriate screening protocols for countries with high rates of urothelial and kidney cancer, including Thailand.

Keywords Cancer, Incidence, Kidney transplantation, Malignancy, Mortality, Thailand

Kidney transplantation offers substantial advantages for patients with end-stage renal disease (ESRD) in terms of both patient survival and quality of life when compared to those who remain on dialysis[1,2]. Thanks to advancements in the development of immunosuppressive medications, tissue typing, and organ allocation systems, the short-term survival of kidney transplant recipients (KTR) has significantly improved on a global scale, typically exceeding 95% at 1-year[3–5]. The rate of acute rejection in the first year post-transplant has been reduced to less than 10–15%[4,6]. Despite these remarkable achievements, the long-term survival of both patients and kidney allografts has not seen significant improvements over the past decade. Cardiovascular disease, infections, and cancer remain significant causes of death among KTR[7–10].

The risk of post-transplant cancer is higher for transplant recipients than in the general population. Several factors contribute to this increased risk among solid-organ transplant recipients[11–14]. While immunosuppressive medications are necessary for suppressing the allorecognition process, they also compromise viral immunity, leading to a higher incidence of viral-associated malignancies, such as Kaposi sarcoma, post-transplant proliferative disease (PTLD), anogenital cancers, and hepatocellular cancer[12,15,16]. Tumor surveillance and containment are also hampered by the use of immunosuppressive medications, both in the induction and maintenance regimens[17]. Commonly used immunosuppressants, like calcineurin inhibitors (CNIs), promote

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angiogenesis and tumor growth through increased expression of transforming growth factor β1 (TGFβ1) and vascular endothelial growth factor (VEGF)[11]. Furthermore, kidney transplant recipients have specific risks for developing kidney and urothelial cancers, such as prolonged dialysis resulting in acquired cystic kidney disease, or a history of aristolochic acid nephropathy as a cause of ESRD[12,14].

While skin cancer, lip cancer, and lymphoma are commonly recognized as post-transplantation cancers with the highest standardized incidence ratios (SIR) in cohorts from the US and European countries, data from East Asian countries, including Hong Kong, Taiwan, and South Korea, demonstrate that the post-transplant cancer incidences were different from those in Western countries[11,18–25]. Geographic region and ethnicity evidently influence the incidence of these post-transplantation cancers. To date, data regarding cancer after kidney transplantation in the Southeast Asian region, where the population differs from other parts of Asia, are lacking. Our study aims to elucidate the incidence, risk factors, and outcomes of post-kidney transplantation cancers in Thailand.

Methods

Study design and study population

We conducted a retrospective cohort study comprising KTR who underwent kidney transplantation at Praram 9 Hospital, Bangkok, Thailand, during the period from January 1, 1992, to December 31, 2022. Praram 9 Hospital is a specialized kidney transplantation center performing approximately 80 cases annually. KTR with a minimum of 30-day follow-up data were included in the cohort, while recipients with primary non-functioning kidney allografts were excluded from the analysis. Patient and kidney allograft statuses were recorded until the last follow-up date. The date of cancer diagnosis was documented upon presentation. Second primary cancers were identified if they occurred in organs distinct from the primary cancer with unrelated tissue histology or if they were of the same type as the primary cancer but with an interval exceeding 5 years. Demographic information at the time of transplantation was documented, encompassing the age and gender of recipients and donors, recipient's body mass index (BMI), medical comorbidities, dialysis duration, human leukocyte antigen (HLA) mismatch, panel reactive antibody (PRA) status, type of kidney transplantation (living donor vs. deceased donor), total ischemic time, induction regimen, and initial maintenance regimen at the time of hospital discharge.

Outcomes measurement

The primary outcome of this study was the incidence of post-kidney transplantation cancer. We conducted an analysis of the median time elapsed from kidney transplantation to the diagnosis of cancer, in addition to examining the mortality rates among KTR who developed specific types of cancer. The risk factors associated with post-transplantation cancer were evaluated. Allograft survival and patient survival were determined, with post-transplantation cancer included as one of the independent factors.

Statistical analysis

Continuous variables were presented as either mean ± standard variation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Categorical data were expressed as the count and percentage. The incidence of post-transplantation cancer was calculated per 1000 person-years (PY) and accompanied by a presentation of the corresponding 95% confidence interval (95% CI). Age and sex were utilized to compute adjusted incidence rates per 1000 PY for each specific cancer. Poisson regression was used to analyze the SIR by comparing with the cancer incidence in the general Thai population as reported by the National Cancer Institute[26]. Mortality rates for post-transplantation cancer were computed among KTR who developed cancer and compared to KTR without cancer to ascertain the mortality rate ratio. However, due to the unavailability of records on cancer mortality in the general population of Thailand, we refrained from conducting a standardized mortality ratio (SMR) compared with the non-transplant population. In the context of factors associated with cancer development, univariable and multivariable competing-risks regression analyses were conducted, using death as a competing event, and reported the results as subhazard ratios (SHR). Additionally, competing-risks regression was utilized to visualize the cumulative incidence function of deaths attributed to cancer, considering non-cancer deaths as competing events. The median time from kidney transplantation to cancer death were compared with non-cancer deaths by the Wilcoxon rannk-sum test. Competing-risks regression was also conducted to identify factors associated with graft loss, considering death as a competing event. Univariable and multivariable Cox proportional hazard regression analyses were performed to assess factors associated with mortality. In order to mitigate the potential for immortal time bias before the cancer diagnosis, we conducted separate analyses for the time period before and after the cancer diagnosis. This approach involved treating these time segments as time-updated variables for each KTR, thus ensuring a precise allocation of time at risk subsequent to a cancer diagnosis. In all the models, variables with a p-value of less than 0.1 in the univariable models were incorporated into the multivariable models. A significance level of $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using Stata 17.0 (StataCorp LLC, College Station, TX).

Results

Patient characteristics

A total of 1156 KTR with complete data were included in the cohort (Table 1). The mean age at transplantation was 52.2 ± 12.6 years. Living donor kidney transplantation accounted for 36.8% of cases, and 9.0% received preemptive transplantation. The majority of KTR received basiliximab as an induction therapy (76.2%), while antithymocyte globulin was utilized in 9.2% of cases. The median follow-up time after transplantation was 5.1 (2.7–9.4) years.

Characteristics at transplantation	Values
Total kidney transplant recipients	1156
Age at transplantation, years (mean ± SD)	52.2 ± 12.6
Male sex, n (%)	733 (64.4%)
Body mass index, kg/m^2 (mean ± SD)	23.9 ± 4.8
Previous kidney transplantation, n (%)	96 (8.3%)
Diabetes mellitus, n (%)	378 (32.7%)
Coronary artery disease, n (%)	118 (10.2%)
Cerebrovascular disease, n (%)	36 (3.1%)
Cause of ESRD, n (%)	
Hypertensive nephropathy	421 (36.4%)
Diabetic nephropathy	363 (31.4%)
Glomerulonephritis (including presumed non-biopsy glomerulonephritis)	292 (25.3%)
Biopsy-proven	
Lupus nephritis	27 (2.3%)
IgA nephropathy	52 (4.5%)
Focal segmental glomerulosclerosis	11 (1.0%)
Membranous nephropathy	4 (0.3%)
Others	80 (6.9%)
History of cancer before transplantation, n (%)	25 (2.2%)
Living donor transplantation, n (%)	425 (36.8%)
Preemptive kidney transplantation, n (%)	104 (9.0%)
Dialysis vintage, years (median and IQR)	1.0 (0.2–2.6)
Donor male sex, n (%)	832 (72.0%)
Donor age, years (mean ± SD)	38.4 ± 13.3
HLA A mismatch, n (%)	
0	251 (21.7%)
1	668 (57.8%)
2	237 (20.5%)
HLA B mismatch, n (%)	
0	139 (12.0%)
1	596 (51.6%)
2	421 (36.4%)
HLA DR mismatch, n (%)	
0	262 (22.7%)
1	663 (57.4%)
2	231 (20.0%)
Panel reactive antibody, % (median and IQR)	0 (0–0) (range 0–84)
Total ischemic time, hours (mean ± SD)	12.5 ± 9.9
Antithymocyte globulin induction, n (%)	106 (9.2%)
Tacrolimus, n (%)	785 (67.9%)
MPA, n (%)	1013 (87.6%)
Delayed graft function, n (%)	392 (33.9%)
Follow up time, years (median and IQR)	5.1 (2.7–9.4)

Table 1. Characteristic of kidney transplant recipients in the cohort. *ESRD* end-stage renal disease, *HLA* human leukocyte antigen, *IQR* interquartile range, *MPA* mycophenolic acid.

Post-transplantation cancer incidence and mortality

Table 2 presents the overall numbers and percentages of post-kidney transplantation cancer. Urothelial cancer was the most common primary cancer (31.9%), followed by hepatocellular cancer (14.3%). Urothelial cancer also ranked as the leading second primary cancer (25%). The incidence rate, age- and sex-adjusted incidence rate, and standardized incidence ratio (SIR) for each cancer are displayed in Table 3. Urothelial cancer exhibited the highest adjusted incidence rate (6.9 per 1000 person-years), followed by hepatocellular cancer (2.4 per 1000 person-years). Urothelial cancer and kidney cancer had the highest SIRs, with values of 42.5 and 24.4, respectively. Figure 1 illustrates the cumulative incidence of each post-transplant cancer and the median time from kidney transplantation to cancer diagnosis.

Using competing-risks regression, factors associated with the development of post-transplant cancer were identified as shown in Table 4. Increasing age at transplantation was linked to an increased risk of post-transplant

Cancer type	Primary cancer, n (%)	Second primary cancer, n (%)
Total	91 (100%)	8 (100%)
Urothelial cancer*	29 (31.9%)	2 (25.0%)
Hepatocellular cancer	13 (14.3%)	–
Skin cancer	9 (9.9%)	1 (12.5%)
Kidney cancer**	8 (8.8%)	1 (12.5%)
Colorectal cancer	6 (6.6%)	–
Prostate cancer	5 (5.5%)	1 (12.5%)
Other gastrointestinal tract cancers	5 (5.5%)	–
Post-transplant lymphoproliferative disease	4 (4.4%)	1 (12.5%)
Breast cancer	4 (4.4%)	–
Lung cancer	3 (3.3%)	1 (12.5%)
Thyroid cancer	3 (3.3%)	–
Parotid gland cancer	1 (1.1%)	1 (12.5%)
Uterine cancer	1 (1.1%)	–

Table 2. Post-kidney transplant cancer in the cohort. *All urothelial cancers occurred in the native urinary tract. **One case of kidney cancer was localized in the kidney allograft only, while another case of kidney allograft cancer occurred as a second primary cancer following native kidney cancer.

Type of cancer	Incidence rate (per 1000 person-year) with 95% CI	95% CI	Adjusted-incidence rate (per 1000 person-year)	95% CI	SIR	95% CI	p-value
Total	12.1	9.9–14.8	18.9	16.5–21.4	2.7	2.4–3.1	< 0.001
Urothelial cancer	3.8	2.7–5.4	6.9	5.4–8.4	42.5	32.9–54.9	< 0.001
Hepatocellular cancer	1.6	0.9–2.7	2.4	1.5–3.3	2.1	1.4–3.0	< 0.001
Skin cancer	1.1	0.6–2.1	1.8	1.1–2.6	7.7	5.0–11.9	< 0.001
Kidney cancer	1.1	0.6–2.1	1.4	0.7–2.0	24.4	14.3–41.5	< 0.001
Colorectal cancer	0.7	0.3–1.6	0.8	0.2–1.3	1.0	0.5–1.8	0.876
Other gastrointestinal tract cancers	0.6	0.2–1.4	2.2	1.4–3.0	6.7	4.5–9.9	< 0.001
Prostate cancer	0.6	0.2–1.4	0.9	0.3–1.4	3.3	1.8–6.1	< 0.001
Post-transplant lymphoproliferative disease	0.6	0.2–1.4	0.3	0.01–0.6	1.2	0.5–3.3	0.659
Lung cancer	0.5	0.2–1.3	0.6	0.2–1.0	0.6	0.3–1.3	0.218
Breast cancer	0.5	0.2–1.3	0.3	0.01–0.7	0.5	0.2–1.3	0.176
Thyroid cancer	0.4	0.1–1.1	0.6	0.1–1.0	3.8	1.7–8.1	0.001
Parotid gland cancer	0.2	0.1–1.0	0.1	0.01–0.3	3.2	0.5–21.9	0.244
Uterine cancer	0.1	0.01–0.9	0.2	0.01–0.5	7.7	0.9–59.7	0.051

Table 3. Incidence rate, age- and sex-adjusted incidence rate (per 1000 person-year), and SIR of post-kidney transplant cancer. *SIR* standardized incidence ratio.

cancer (SHR 1.03; 95% CI 1.01–1.05; p-value < 0.001) in the multivariable model. Interestingly, an increasing number of HLA DR mismatches was associated with a decreased SHR of post-transplant cancer (SHR 0.72; 95% CI 0.52–0.98; p-value = 0.038).

Secondary analyses were conducted, focusing on KTR who developed hepatocellular carcinoma. Using a multivariable model for competing-risks regression, it was found that age (SHR 1.05; 95% CI 1.01–1.09; p-value = 0.031), hepatitis B virus surface antigen (HBsAg) positivity (SHR 6.43; 95% CI 1.45–28.04; p-value = 0.013), and anti-hepatitis C virus (anti-HCV) positivity (SHR 20.69; 95% CI 4.11–104.26; p-value < 0.001) among KTR were strongly associated with the development of post-transplant hepatocellular carcinoma.

Table 5 presents the mortality rates of KTR with post-transplant cancer. Hepatocellular cancer displayed the highest mortality rate (145.1 per 1000 person-years), followed by lung cancer (97.8 per 1000 person-years) and gastrointestinal tract cancer (83.7 per 1000 person-years). Figure 2 illustrates the cumulative incidence of cancer-related deaths compared to infection and cardiovascular-related deaths. The median duration from kidney transplantation to cancer-related death was 7.9 (3.9–11.1) years, which was significantly longer than the time to infection-related deaths (4.4 (0.5–9.3) years; p-value = 0.004). However, it was comparable to the time to cardiovascular-related deaths (8.2 (3.9–13.9) years; p-value = 0.256).

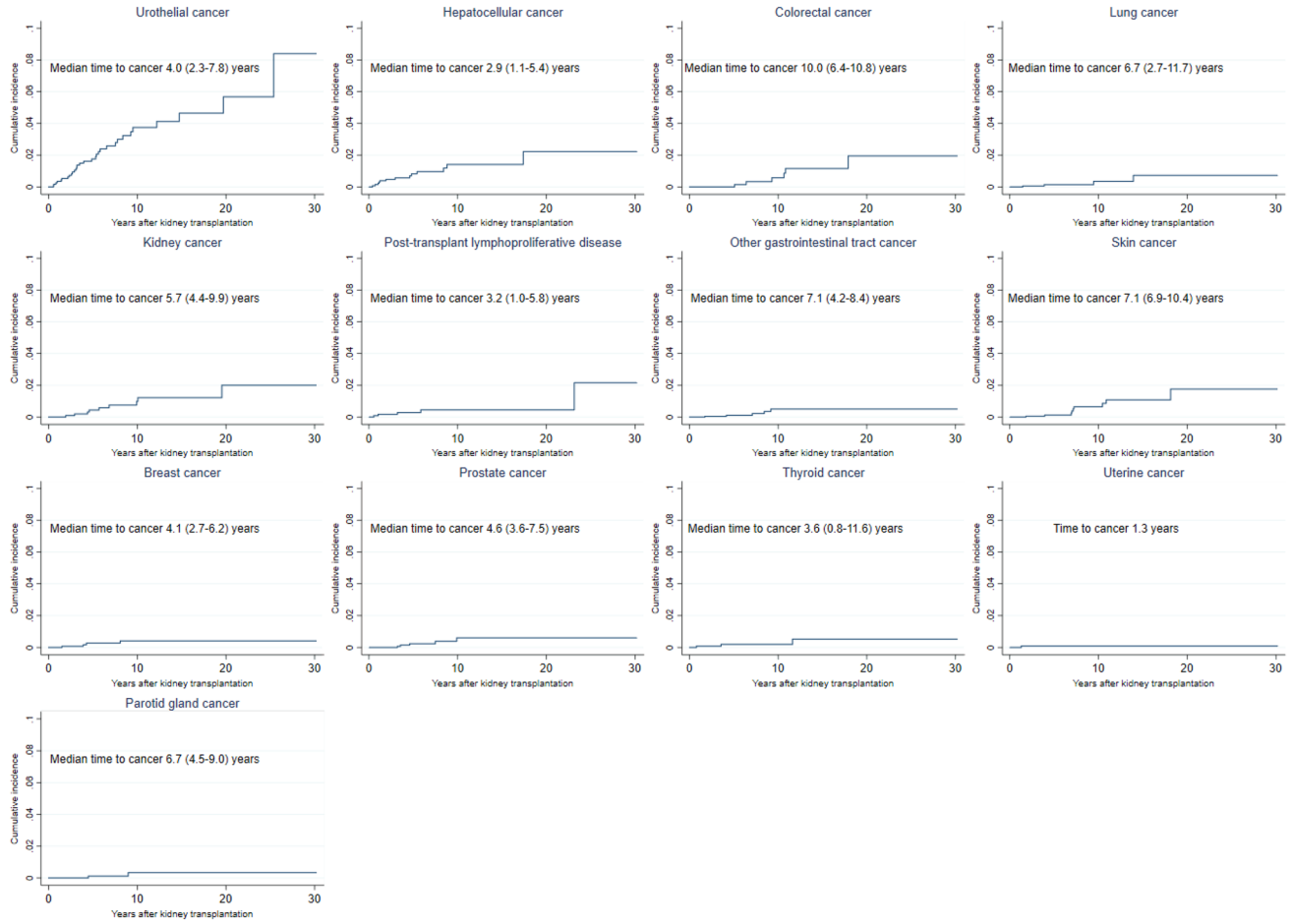

Fig. 1. Cumulative incidences of post-transplantation cancers and the median time from kidney transplantation to cancer diagnosis.

Factors associated with KTR death and allograft loss

Table 6 presents the results of univariable and multivariable Cox proportional hazard regression for death. The multivariable model demonstrated that post-transplantation cancer was significantly associated with death (HR 3.16; 95% CI 2.21–4.52; p-value < 0.001). Other factors contributing to death included recipient age (HR 1.04; 95% CI 1.02–1.05; p-value < 0.001), preemptive transplantation (HR 0.39; 95% CI 0.21–0.70; p-value = 0.002), donor male sex (HR 1.66; 95% CI 1.16–2.39; p-value = 0.006), and donor age (HR 1.02; 95% CI 1.01–1.03; p-value = 0.002). Figure 3 illustrates the survivor function of KTR with and without post-transplantation cancer, adjusted for recipient age and sex, comorbidities, preemptive transplantation, dialysis vintage, type of transplantation, donor age and sex, total ischemic time, and delayed graft function.

Factors affecting graft failure are detailed in Table 7. From the multivariable analysis, recipient age (SHR 0.98; 95% CI 0.97–0.99; p-value = 0.005), donor age (SHR 1.02; 95% CI 1.01–1.03; p-value < 0.001), delayed graft function (SHR 2.20; 95% CI 1.45–3.33; p-value < 0.001), and tacrolimus use (SHR 0.45; 95% CI 0.30–0.67; p-value < 0.001) were associated with graft failure. Post-transplantation cancer was not found to be associated with graft loss.

Discussion

This study represents the largest cohort of post-kidney transplantation cancer cases within the South East Asia region. Our findings demonstrate that urothelial cancer has the highest incidence rate among post-transplantation cancers. The incidence rates of urothelial cancer and kidney cancer were 42.5 and 24.4 times higher, respectively, compared to the general non-transplant population. While post-transplantation cancer was significantly associated with patient mortality, its incidence was lower than that of deaths resulting from infection and cardiovascular causes. The occurrence of post-transplantation cancer did not affect graft failure. Notably, recipient age was identified as a factor increasing the risk of post-transplantation cancer, whereas an increased number of HLA-DR mismatches was associated with a decreased risk. Notably, it was unsurprising that the presence of HBsAg and anti-HCV positivity among KTR was associated with the occurrence of post-transplant hepatocellular carcinoma.

Numerous studies have reported varying incidence rates of post-transplantation cancer across different geographic regions and ethnicities. Studies conducted in the United States, European countries, and the

Variable	Univariable analysis			Multivariable analysis		
	SHR	95% CI	p-value	SHR	95% CI	p-value
Male sex	1.00	0.65–1.53	0.999	–	–	–
Age (per 1 year increased)	1.03	1.02–1.05	< 0.001	1.03	1.01–1.05	< 0.001
BMI (per 1 kg/m^2 increased)	0.98	0.92–1.04	0.506	–	–	–
Previous KT	0.78	0.36–1.70	0.531	–	–	–
DM pre-KT	1.10	0.69–1.74	0.694	–	–	–
CAD pre-KT	2.50	1.34–4.52	0.004	1.75	0.97–3.14	0.062
CVA pre-KT	0.95	0.23–3.90	0.943	–	–	–
Glomerulonephritis as the cause of ESRD	0.93	0.56–1.55	0.773	–	–	–
Previous cancer pre-KT	2.65	0.89–7.90	0.079	1.50	0.55–4.09	0.432
Preemptive transplantation	1.52	0.88–2.63	0.130	–	–	–
Dialysis vintage (per 1 year increased)	0.97	0.88–1.05	0.422	–	–	–
Living donor KT	0.91	0.59–1.40	0.660	–	–	–
Donor male sex	0.78	0.50–1.19	0.248	–	–	–
Donor age (per 1 year increased)	1.01	0.99–1.02	0.500	–	–	–
Total HLA mismatches (per 1 mismatch increased)	0.93	0.82–1.05	0.232	–	–	–
HLA A mismatches (per 1 mismatch increased)	0.94	0.69–1.27	0.689	–	–	–
HLA B mismatches (per 1 mismatch increased)	1.00	0.74–1.35	0.987	–	–	–
HLA DR mismatches (per 1 mismatch increased)	0.70	0.52–0.96	0.025	0.72	0.52–0.98	0.038
PRA (per 1% increased)	1.01	0.99–1.02	0.260	–	–	–
ATG induction	0.53	0.22–1.30	0.167	–	–	–
Total ischemic time (per 1 h increased)	1.01	0.99–1.03	0.409	–	–	–
Delayed graft function	0.66	0.40–1.11	0.119	–	–	–
Tacrolimus	0.83	0.53–1.30	0.416	–	–	–
MPA	0.83	0.50–1.41	0.497	–	–	–

Table 4. Univariable and multivariable competing-risks regression for post-kidney transplantation cancer. *ATG* antithymocyte globulin, *BMI* body mass index, *CAD* coronary artery disease, *CVA* cerebrovascular disease, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *HLA* human leukocyte antigen, *KT* kidney transplantation, *MPA* mycophenolic acid, *PRA* panel reactive antibody, *SHR* subhazard ratio.

Type of cancer	Mortality rate among recipients with cancer (per 1000 person-year)	95% CI	Mortality risk ratio compared to recipients without cancer	95% CI	p-value
Total	61.4	47.1–79.9	3.3	2.4–4.5	< 0.001
Hepatocellular cancer	145.1	82.4–255.5	6.9	3.5–12.4	< 0.001
Lung cancer	97.8	31.6–303.4	4.7	1.0–13.9	0.032
Other gastrointestinal tract cancers	83.7	31.4–223.1	5.8	1.5–15.0	0.007
Post-transplant lymphoproliferative disease	75.6	28.4–201.4	5.2	1.4–13.5	0.001
Skin cancer	68.6	28.5–164.7	3.3	1.0–7.8	0.026
Colorectal cancer	62.1	25.8–149.2	4.4	1.4–10.4	0.008
Breast cancer	59.4	14.8–237.4	2.8	0.3–10.4	0.195
Parotid gland cancer	59.3	8.4–421.0	5.5	0.1–30.9	0.183
Urothelial cancer	57.0	34.9–93.0	2.8	1.6–4.7	< 0.001
Thyroid cancer	35.7	5.0–253.4	1.7	0.04–9.6	0.564
Prostate cancer	26.5	3.7–187.8	1.3	0.03–7.1	0.737
Kidney cancer	9.4	1.3–66.9	0.6	0.01–3.2	0.638
Uterine cancer	0	–	0	0–7.0	0.585
Patient without cancer	21.0	17.9–24.5	–	–	–

Table 5. Mortality rate of post-kidney transplant cancer (per 100 person-year) among recipients diagnosed with cancer.

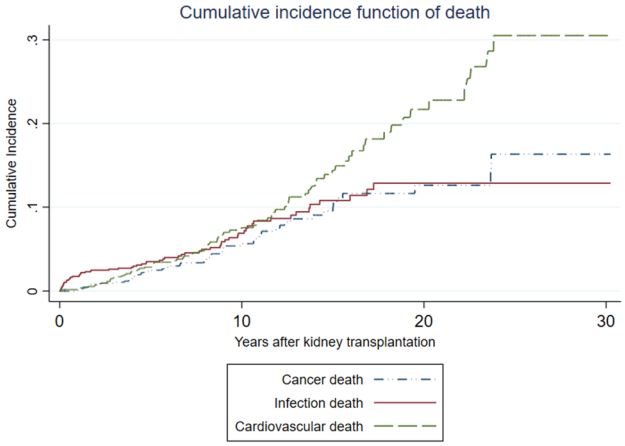

Fig. 2. Cumulative incidence function of cancer death compared with infection and cardiovascular death.

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Male sex	1.27	0.96–1.70	0.097	1.06	0.76–1.48	0.719
Age (per 1 year increased)	1.053	1.4–1.07	< 0.001	1.04	1.02–1.05	< 0.001
BMI (per 1 kg/m^2 increased)	1.01	0.97–1.05	0.722	–	–	–
Previous KT	1.12	0.72–1.74	0.622	–	–	–
DM pre-KT	2.28	1.70–3.06	< 0.001	1.34	0.95–1.90	0.100
CAD pre-KT	3.22	2.08–4.97	< 0.001	1.57	0.95–2.60	0.078
CVA pre-KT	2.40	1.18–4.89	0.016	1.38	0.64–3.00	0.416
Glomerulonephritis as the cause of ESRD	0.63	0.44–0.91	0.014	0.86	0.57–1.30	0.473
Previous cancer pre-KT	1.41	0.52–3.81	0.494	–	–	–
Preemptive transplantation	0.50	0.30–0.83	0.007	0.39	0.21–0.70	0.002
Dialysis vintage (per 1 year increased)	1.07	1.01–1.13	0.024	1.01	0.94–1.10	0.737
Living donor KT	0.58	0.44–0.78	< 0.001	1.41	0.59–3.40	0.441
Donor male sex	1.36	1.00–1.86	0.050	1.66	1.16–2.39	0.006
Donor age (per 1 year increased)	1.02	1.01–1.03	< 0.001	1.02	1.01–1.03	0.002
Total HLA mismatches (per 1 mismatch increased)	1.00	0.91–1.07	0.726	–	–	–
HLA A mismatches (per 1 mismatch increased)	1.07	0.87–1.32	0.520	–	–	–
HLA B mismatches (per 1 mismatch increased)	0.96	0.78–1.18	0.690	–	–	–
HLA DR mismatches (per 1 mismatch increased)	0.90	0.73–1.10	0.291	–	–	–
PRA (per 1% increased)	0.99	0.98–1.01	0.500	–	–	–
ATG induction	1.34	0.87–2.07	0.188	–	–	–
Total ischemic time (per 1 h increased)	1.02	1.01–1.04	0.002	1.00	0.96–1.04	0.984
Delayed graft function	1.69	1.25–2.29	0.001	1.26	0.82–1.93	0.297
Post KT cancer	3.10	2.27–4,23	< 0.001	3.16	2.21–4.52	< 0.001
Tacrolimus	1.14	0.82–1.58	0.423	–	–	–
MPA	1.05	0.75–1.46	0.786	–	–	–

Table 6. Univariable and multivariable Cox proportional hazard regression for death. *ATG* antithymocyte globulin, *BMI* body mass index, *CAD* coronary artery disease, *CVA* cerebrovascular disease, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *HLA* human leukocyte antigen, *HR* hazard ratio, *KT* kidney transplantation, *MPA* mycophenolic acid, *PRA* panel reactive antibody.

Australia-New Zealand registry indicated that the most commonly occurring post-transplantation cancers, as determined by SIRs, were lip cancer, Kaposi sarcoma, and non-melanoma skin cancer[21,24,25,27–29]. In contrast, among Asian populations, the incidence of post-transplantation cancers differs by country. Research conducted in Hong Kong revealed that non-Hodgkin lymphoma and kidney cancer were the predominant post-transplantation cancers[19]. A Korean cohort reported comparable SIRs for Hodgkin and non-Hodgkin lymphoma, non-melanoma skin cancer, and Kaposi sarcoma[22]. Intriguingly, the risk of bladder and kidney cancer in a Taiwanese cohort was exceptionally high[20], consistent with the SIRs observed in our study.

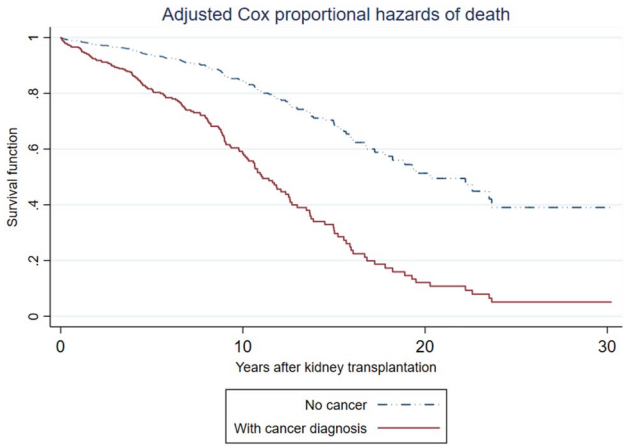

Fig. 3. Survivor function of kidney transplant recipients with and without post-transplantation cancer, adjusted for recipient age and sex, comorbidities, preemptive transplantation, dialysis vintage, type of transplantation, donor age and sex, total ischemic time, and delayed graft function. The hazard ratio of post-transplantation cancer for death was 3.16 (95% CI 2.21–4.52; p-value < 0.001).

	Univariable analysis			Multivariable analysis		
Variable	**SHR**	**95% CI**	**p-value**	**SHR**	**95% CI**	**p-value**
Male sex	0.93	0.69–1.24	0.603	–	–	–
Age (per 1 year increased)	0.98	0.97–0.99	0.001	0.98	0.97–0.99	0.005
BMI (per 1 kg/m^2 increased)	0.97	0.92–1.02	0.267	–	–	–
Previous KT	0.90	0.54–1.48	0.666	–	–	–
DM pre-KT	1.11	0.79–1.56	0.551	–	–	–
CAD pre-KT	1.08	0.57–2.07	0.809	–	–	–
CVA pre-KT	0.88	0.28–2.76	0.823	–	–	–
Glomerulonephritis as the cause of ESRD	1.55	1.11–2.18	0.011	1.30	0.91–1.88	0.151
Previous cancer pre-KT	0.35	0.05–2.51	0.298	–	–	–
Preemptive transplantation	0.58	0.35–0.95	0.032	0.73	0.43–1.22	0.226
Dialysis vintage (per 1 year increased)	1.02	0.96–1.09	0.523	–	–	–
Living donor KT	0.77	0.57–1.04	0.094	0.83	0.55–1.27	0.399
Donor male sex	1.04	0.77–1.42	0.781	–	–	–
Donor age (per 1 year increased)	1.02	1.01–1.03	0.001	1.02	1.01–1.03	< 0.001
Total HLA mismatches (per 1 mismatch increased)	0.97	0.89–1.06	0.512	–	–	–
HLA A mismatches (per 1 mismatch increased)	0.91	0.73–1.13	0.397	–	–	–
HLA B mismatches (per 1 mismatch increased)	0.92	0.74–1.14	0.439	–	–	–
HLA DR mismatches (per 1 mismatch increased)	1.00	0.81–1.23	0.990	–	–	–
PRA (per 1% increased)	1.00	0.98–1.01	0.806	–	–	–
ATG induction	1.26	0.79–2.01	0.324	–	–	–
Total ischemic time (per 1 h increased)	1.01	0.99–1.02	0.311	–	–	–
Delayed graft function	1.81	1.32–2.47	< 0.001	2.20	1.45–3.33	< 0.001
Post KT cancer	0.72	0.42–1.22	0.217	–	–	–
Tacrolimus	0.60	0.43–0.85	0.003	0.45	0.30–0.67	< 0.001
MPA	0.69	0.50–0.97	0.031	0.74	0.51–1.07	0.105

Table 7. Univariable and multivariable competing-risks regression for graft failure. *ATG* antithymocyte globulin, *BMI* body mass index, *CAD* coronary artery disease, *CVA* cerebrovascular disease, *DM* diabetes mellitus, *ESRD* end-stage renal disease, *HLA* human leukocyte antigen, *KT* kidney transplantation, *MPA* mycophenolic acid, *PRA* panel reactive antibody, *SHR* subhazard ratio.

Several explanations have been proposed to account for the significantly increased risk of urothelial and kidney cancer in KTR. While the mechanisms underlying the elevated risk of post-transplantation cancer typically involve the effects of immunosuppression, which reduce tumor surveillance and increase oncogenic viral replication, specific biological changes in ESRD patients predispose them to urothelial and kidney cancer[30–34]. For instance, peroxiredoxin, an antioxidant enzyme, is upregulated and highly expressed in dialysis kidneys with acquired cystic kidney disease and renal cell carcinoma, in contrast to renal cell carcinoma in non-dialyzed kidneys[35]. This finding suggests that one of the pathogenetic mechanisms of renal cell carcinoma in dialysis patients may involve increased oxidative stress, as indicated by the heightened antioxidant signal observed, potentially resulting in cumulative DNA damage[35]. Factors like hepatocyte growth factor (HGF), hypoxia-inducible factor protein 2 (HIP-2), hypoxia-inducible factor 1-alpha (HIF-1-alpha), and phosphorylated nuclear factor-kappa B (NF-kB) have been found to be upregulated in acquired cysts in chronic kidney disease (CKD) patients associated with renal cell carcinoma[36,37]. Additionally, uremic toxins, such as p-cresyl sulfate, have been linked to epithelial-mesenchymal transition (EMT), stress fiber redistribution, and the migration of malignant urothelial cells, leading to multifocal urothelial carcinomas in ESRD patients[38].

Notably, the heightened risk of urothelial and kidney cancer observed in our Thai cohort, as well as in the Taiwan cohort, may be influenced by additional factors unique to these regions. First, aristolochic acid, a known mutagenic carcinogen, is found in traditional medicine compounds in Taiwan and China[39]. Kidney and urothelial cancer have a higher prevalence in patients with aristolochic acid nephropathy as a cause of ESRD[39]. In Thailand, over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) and herbs play a significant but under-recognized role in CKD[40]. The use of the dried root of *Aristolochia tagala*, a plant containing aristolochic acid, has been reported in Thai traditional medicine[41]. It is plausible that KTR who developed urothelial and kidney cancer in our study might have a history of using herbs and traditional medicine. However, the retrospective nature of the study limits this information, as not every KTR underwent a native kidney biopsy to confirm the diagnosis before transplantation. This is especially pertinent among the group defined as having hypertensive nephropathy, as there may be other causes of ESRD within this population. Second, the risk of bladder cancer is associated with the cumulative dose of cyclophosphamide, which is one of the first-line treatments for lupus nephritis in systemic lupus erythematosus (SLE) patients[42,43]. Studies have shown that Asian SLE patients have a higher prevalence of renal involvement and disease severity compared to Caucasians[44,45]. It is plausible that the heightened risk of urothelial cancer is potentially linked to the increased utilization of cyclophosphamide and its higher cumulative dosage in Asian populations, which may contribute to the elevated incidence of urothelial cancer. Lastly, BK polyomavirus (BKV) has been established as a causative factor for urothelial cancer in KTR[46,47]. The prevalence of BKV reactivation after kidney transplantation varies and tends to be higher in Asian populations[48–51]. Additionally, recent research has shown that the risk of BKV-associated nephropathy is higher in Asians than in Caucasians[52]. These findings could contribute to the higher incidence of urothelial cancer in KTR of Asian ethnicity compared to those in Western countries. Furthermore, differences in BKV subtypes among geographic regions may also be linked to the varying incidence of post-transplantation urothelial carcinoma[53,54].

The significantly increased risk for urothelial and kidney cancer in KTR has prompted questions regarding screening protocols. Candidates for kidney transplantation typically undergo pre-transplant evaluation, which often includes screening for urinary tract cancer[55]. However, recommendations for post-transplant screening have been limited. Wong et al. demonstrated that routine post-transplant kidney cancer screening (annually or biennially) may not be cost-effective[56]. However, their study was based on data from countries with average post-transplant kidney cancer incidence. Further research is needed, especially in the context of the higher incidence of post-transplantation kidney cancer observed in Thailand and Taiwan. The proposed screening protocol currently involves biennial ultrasonography for high-risk KTR (those over 60 years of age with a dialysis history of over 5 years or those with native Bosniak stage 1 or 2 kidney cysts)[57]. More frequent screening is suggested for KTR with congenital cystic kidney disease or cysts classified as Bosniak stage 2F or higher[14,57]. For urothelial and bladder cancer, there are no routine screening guidelines[58]. However, urine cytology and cystoscopy may be recommended for high risk KTR, such as those with a history of high-dose cyclophosphamide exposure, regular use of compound analgesics, or a smoking history of more than 30 pack-years[14].

Surprisingly, an increased number of HLA DR mismatches were associated with a lower risk of post-transplantation cancer in this study. The underlying mechanism behind this finding remains unclear. Gao et al. demonstrated a similar protective effect of HLA mismatch in heart and lung transplant recipients against post-transplant skin cancer[59]. In this US national population-based cohort, HLA DR mismatch exhibited the strongest protective effect against skin cancer development. These results align with the findings from our study regarding the protective effect of HLA DR mismatch. It is postulated that a higher number of HLA mismatches enhance the immune response against tumor and oncogenic viral antigens by activating antigen-presenting cells. Additionally, allogenic T lymphocyte activation may cross-react with tumor antigens, leading to improved tumor surveillance and control[59,60].

This study addresses a significant gap in the literature by presenting a large cohort study of post-kidney transplant malignancies in the South East Asian region, where comprehensive data on this topic has been lacking. We conducted thorough analyses to examine the risks and outcomes associated with post-kidney transplantation malignancies compared to other causes of death among KTR. This includes the presentation of mortality rates and mortality risk ratios, which have not been extensively reported in previous studies. Furthermore, we provided detailed insights into the median times to cancer occurrence. Notably, our findings shed light on the impact of HLA DR mismatch, highlighting a promising area for future research.

However, it is important to acknowledge the study's limitations. First, our cohort lacked details on allograft rejection episodes and immunosuppressive medication concentrations and doses. The overall level of immunosuppression or the use of mammalian target of rapamycin inhibitors (mTORi) could potentially affect the incidence of post-transplantation cancer[61,62]. The study did include data on immunosuppression at the time of

first hospital discharge after transplantation, and the majority of patients had unchanged regimens throughout the post-transplantation course. However, since more than 95% of KTR were discharged from the hospital with CNI and mycophenolic acid (MPA), the information regarding the use of mTORi was limited in our cohort. Further studies with adequate power are required to evaluate the effect of mTORi on post-transplant malignancy. Additionally, anti-CD20 antibody is not routinely prescribed as an induction therapy in Thailand, resulting in limited data on this medication in our cohort. Second, the record of post-transplant cancer surveillance was not available. This includes information such as the development of new native kidney cysts after transplantation or de novo hepatitis virus infections, which may be associated with post-transplantation cancer[63]. Third, BKV reactivation surveillance was not consistently conducted in every case, particularly in the earlier era. This limitation prevented the inclusion of BKV as an independent factor for post-transplantation urothelial cancer. Finally, the calculation of SMR compared to the general population was not performed, as mentioned in the methods section. However, the study did analyze the mortality rate ratio compared to KTR without cancer to determine the impact of each post-transplant cancer.

In conclusion, this study reveals that the risk of developing cancer after kidney transplantation among Thai KTR is significantly increased, particularly for urothelial and kidney cancer. These findings diverge from those in Western countries and most of Asia. Increasing age was associated with an increased risk of post-transplantation cancer, while HLA DR mismatch was associated with a decreased risk. Future research exploring options for incidence-based post-transplantation cancer surveillance and conducting cost-effectiveness analyses are urgently needed to mitigate the burden of post-transplant cancer in Thailand.

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Author contributions

S.L. involved with study design, data collection, and writing the first draft of manuscript. N.N., K.B., U.P., N.A., P.L., W.L., R.K., and N.T. involved with data collection and manuscript review. V.M. involved with study design and manuscript review. S.U. involved with study design, statistical analysis, data presentation, writing the first draft of manuscript, manuscript review and edit.

Competing interests
The authors declare no competing interests.

Ethical approval
This study received approval from the Ethical Review Board of the Praram 9 Hospital, Bangkok, Thailand (RMD.R 002/2566) and the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No. 0856/66). It was conducted in compliance with the international guidelines for human research protection as described in the Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP). The patient data were de-identified to ensure complete anonymity and untraceability of individual patients. Informed consent for retrospective studies using anonymized existing data is exempted by the ethical committees.

Additional information
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