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Malignancy risk and mortality after lung transplantation: A single-institution experience over 31 years

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BACKGROUND: Malignancy is a long-term complication of lung transplantation (LTx); however, contemporary Australian data and detailed evaluation of nonreportable cancers are lacking.
METHODS: Retrospective review of LTx recipients' medical records and registry data linkage were performed to identify histologically proven malignancies. Baseline clinico-demographic variables were collected, and cancer incidence was compared with reported data for the general Australian population.
RESULTS: There were 1,715 LTx in 1,631 patients between 1989 and 2021, with a follow-up of 9,696 person-years. Eight hundred and ninety-three (54.8%) patients were male, and the median age at first LTx was 54.7 years. There were 886 deaths with a median overall survival of 7.5 years (95% confidence intervals (CI) 6.8-8.3 years). One thousand seven hundred and seventy-four separate invasive cancer events occurred across 407 patients, of which, 1,588 (89.5%) were nonmelanoma skin cancers (NMSCs). This translated to a 9-fold increased incidence of NMSCs and a 4-fold increased incidence of other cancers compared with the general population. Cancer mortality reached parity with chronic lung allograft dysfunction 10 years postfirst transplant and was independently associated with age (hazard ratios (HR) per year increase in age 1.02 [95% CI 1.01-1.03], $p = 0.001$), Epstein-Barr virus primary mismatch (HR 3.24 [95% CI 1.68-6.25], vs nonmismatch, $p = 0.002$), and cancer count (HR per cancer event 1.19 [95% CI 1.13-1.24], $p < 0.0001$), but was not associated with a pretransplant malignancy history.
CONCLUSIONS: Our 31-year single-center experience demonstrates that malignancies are a significant mortality burden to long-term LTx survivors, dominated by NMSCs that are poorly reported in cancer

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datasets. A history of pretransplant malignancy was associated with a shorter time to post-transplant malignancy but was not associated with cancer death.
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Background

Lung transplantation (LTx) is a well-established therapeutic option for end-stage respiratory diseases, with survival rates continuously improving with progressive advances in transplantation care.[1] However, as the survivorship of transplant recipients lengthens, the morbidity and mortality burden of transplant-associated malignancies are expected to increase.

Among transplant recipients, the most common cancers to develop following transplantation are nonmelanoma skin cancers (NMSCs), post-transplant lymphoproliferative disorders (PTLD), and lung cancers.[2-8] Notably, cutaneous squamous cell carcinomas (cSCCs), which are typically indolent and easily curable malignancies in immunocompetent individuals, can have an aggressive phenotype in immunosuppressed individuals.[9,10]

Contemporary Australian data quantifying the malignancy burden in the LTx population are lacking, and prior studies have used data linkage analyses, which have not accurately quantified the incidence of NMSCs because, unlike other cancers, NMSCs are excluded from statutory reporting.[5,8] Therefore, we sought to evaluate the prevalence and outcomes of malignancy in the LTx cohort with extended follow-up, to compare this with the general Australian population, and to identify risk factors associated with cancer development and mortality.

Methods

This study was approved by the Alfred Health Human Research Ethics Committee (Alfred Ethics Committee Project No: 411/21) and all procedures were conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice.

Study population and data sources

All LTx recipients at The Alfred Hospital between March 1990 and December 2021 were included in this study. Demographic and transplant information were sourced from the LTx Service. The medical records of recipients were reviewed to identify all documented malignancies from histopathology reports after LTx until the data cutoff date of December 31, 2021. Data on the date of diagnosis, anatomic site, and histological subtype of cancer were collected. Data linkage was concurrently performed with the Victorian Cancer Registry (VCR), which collects mandatory-reporting data on all histologically proven malignancies in the state of Victoria, excluding NMSCs.

Clinical management and follow-up of transplant recipients

Selection of LTx candidates followed the International Society for Heart and Lung Transplantation (ISHLT) guidelines. LTx immunosuppression included (where tolerated) a calcineurin inhibitor, an antiproliferative, and prednisolone. All patients within 500 km were followed indefinitely with at least 3-monthly reviews by the Alfred LTx Service clinics. The majority of cancer screening and management occurred through referrals to Alfred Hospital specialized clinics.

Data handling

Cancer diagnosis events were considered duplicates if they referred to lesions with the same histological type and anatomic site, and diagnosed in procedures performed within 2 months of each other, accounting for standard clinical practice of histologic confirmation with biopsy before definitive excision or re-excision (e.g., for adequate margins) of most malignancies. Invasive cancers were defined as malignancies invading surrounding healthy tissue and are distinct from in situ neoplasms.

Disease indication for transplantation was defined as obstructive (including chronic obstructive pulmonary disease, bronchiolitis obliterans, and alpha-1-antitrypsin disease), restrictive (including idiopathic pulmonary fibrosis and other interstitial lung disease), septic (including cystic fibrosis and bronchiectasis), pulmonary hypertension, and other (all other causes). Epstein-Barr virus (EBV) primary mismatch was defined as donor seropositive and recipient seronegative (D+/R-).

Cause of death for the LTx cohort was manually determined by an experienced LTx clinician, who reviewed the medical records and data captured by the LTx database. Where the cause of death was multifactorial, the major contributor was listed. Disputed cases were resolved by consensus after review of medical records and discussion by multiple clinicians. Causes of death were grouped as malignancy, infection, chronic lung allograft dysfunction (CLAD), cardiovascular, hemorrhage, acute graft rejection, other organ failure, and other/unknown causes, which included secondary graft dysfunction. Patients for whom a cancer diagnosis was known, but date of diagnosis was unknown, were excluded from cancer-free survival analyses.

Geography of participants was classified using the Modified Monash (MM) Model definition of rurality and remoteness, used by the Australian Government to determine access to health services. We categorized this factor as metropolitan (MM category 1), regional/rural (MM category 2 and 3), and all others, which range from very remote to medium rural communities.

Statistical analyses

All statistical analyses were performed with StataBE Version 17.0 (Stata Corp., College Station, TX) and R (v4.2.1). Survival analyses were performed using the "survival Analysis" package (v0.3.0), and plots generated using "ggplot2" (v3.3.6) in R.[11,12] Associations between demographic variables and cancer outcomes were determined using chi-square or Fisher's exact test for categorical variables and Kruskal-Wallis tests for continuous variables. Cumulative time-at-risk was calculated as person-years from date of transplant to date of death, date of last follow-up, or the study censor date, whichever was first. Cancer incidence for the Australian population was obtained from the Australian Institute of Health and Welfare (AIHW), from 1990 to the most recent reporting period of 2018[13]; however, the incidence of NMSCs in Australia is not reported to the AIHW. We have compared the incidence of NMSCs with estimates from population-based surveys and Medicare-billing data, reported by the AIHW and Perera et al.[14,15] Standardized incidence ratios (SIR) and the corresponding 95% confidence intervals (95% CI) were determined.

Univariable and multivariable analyses for cancer death and incidence were performed using competing risk regression with results reported as hazard ratios (HR) and 95% CI. In the analyses of cancer-related death, all other causes of death were considered as a competing risk. The risk of cancer incidence was separated into 2 groups for analysis given the predominance of NMSCs. In the analysis for NMSCs, other cancers were considered as a competing risk and vice versa. The risk factors for cSCC and basal cell carcinoma (BCC) were determined using Cox proportional hazards regression. Variables with a $p < 0.05$ on univariable analysis or those deemed clinically relevant were considered for inclusion in the multivariable models to identify independent risk factors for cancer death and cancer diagnosis. All calculated p-values were 2-tailed and a $p < 0.05$ indicated statistical significance.

Results

Cohort characteristics

Between March 1990 and December 2021, there were 1,713 LTx performed in 1,631 patients at The Alfred Hospital. Two patients underwent first LTx procedure at external institutions, with their repeat LTx and ongoing care performed at our institution, one of whom underwent their first LTx in 1989. The cumulative follow-up for the cohort was 9,696 person-years. Demographic characteristics at time of first LTx are shown in Table 1. The median duration of follow-up was 4.3 years (interquartile range, IQR 1.9-8.3). Of the 1,631 recipients, 893 (54.8%) patients were male, 1,553 (95.2%) were Caucasian, and the median age at transplantation was 54.7 years (IQR 37.7-61.7). Obstructive disease was the predominant LTx indication (n = 691, 42.4%) and most patients underwent only 1 LTx procedure (n = 1,552, 95.2%). The most common first LTx procedure performed was double lung (n = 1,220, 74.8%), followed by single lung (n = 331, 20.3%), heart and lung (n = 72, 4.4%), double lung and kidney (n = 7, 0.4%), or double lung and liver (n = 1, 0.1%).

Growth and evolution in the transplant population over 3 decades

Significant growth was noted in the patient volume of the LTx program, with 312 recipients between 1989 and 1999 (era 1), 412 recipients between 2000 and 2009 (era 2), and 907 recipients between 2010 and 2021 (era 3). These changes are described in Supplementary Table S1. Notably, the proportion of transplant recipients aged >65 years increased across eras (era 1: 0.3%, era 2: 4.9%, and era 3: 22.3% ($p < 0.0001$)), along with the median age (45.5 (IQR 29.0-53.5), 50.8 (IQR 33.7-58.8) and 58.9 (IQR 45.6-64.5), respectively ($p = 0.0001$)). The rate of double LTx increased with time (42.6%, 72.1%, and 87.1%, respectively ($p < 0.0001$)), as did restrictive lung disease indications for LTx (10.3%, 16.0%, and 31.4%, respectively ($p < 0.0001$)), with a parallel reduction in septic lung disease indications.

Invasive cancer events and cancer incidence

A total of 1,774 separate invasive cancer events occurred in 407 (25.0%) patients. The most frequent cancer events were NMSCs (n = 1,588, 89.5%), which far exceeded other cancer types (Figure 1, Supplementary Table S2).

Cancer incidence in the LTx cohort was compared to the general population, summarized in Table 2 and Supplementary Figure S1. Overall, the incidence of NMSCs in our cohort was 16,378/100,000 person-years, with an SIR (observed/expected cases) of 9 (95% CI 8.5-9.7, $p < 0.001$) compared to the general population. Although the incidence rates of NMSCs increased with time in the LTx cohort, the SIR remained stable across the 3 eras (Table 2). The SIR of non-NMSC cancers was 4 (95% CI 3.4-4.7, $p < 0.001$) compared with the general population. Cancer incidence was higher in the LTx population compared to the general population for all cancer types, excluding leukemia, melanoma, breast, head and neck, and brain cancers. The characteristics and clinical outcomes of PTLD and select cancers are described in Supplementary Table S3.

Risk of cancer events

The risks for cancer events are summarized in Table 3. On multivariable analysis, non-NMSC cancer events were

Table 1 Clinical Characteristics of the Lung Transplant Cohort at Time of First Transplantation, With Comparison Between Patients Who Did and Did Not Develop Malignancy

Variables	Total population *n* (%)	Patients who did not develop cancer *n* (%)	Patients who developed cancer *n* (%)	*p*-value
Total number of patients	1,631	1,224	407	
Median age at transplantation (IQR)	54.7 (37.7-61.7)	52.7 (34.0-61.1)	57.7 (47.5-63.2)	< 0.0001
Age at transplantation by group				< 0.0001
≤18	58 (3.6)	56 (4.6)	2 (0.5)	
19-35	307 (18.8)	264 (21.6)	43 (10.6)	
36-50	290 (17.8)	218 (17.8)	72 (17.7)	
51-65	753 (46.2)	529 (43.2)	224 (55.0)	
> 65	223 (13.7)	157 (12.8)	66 (16.2)	
Sex				< 0.0001
Female	738 (45.2)	603 (49.3)	135 (33.2)	
Male	893 (54.8)	621 (50.7)	272 (66.8)	
Ethnicity				< 0.0001
Caucasian	1,553 (95.2)	1,147 (93.7)	406 (99.8)	
Non-Caucasian	78 (4.8)	77 (6.3)	1 (0.3)	
Number of lung transplants received per patient				0.155
1	1,552 (95.2)	1,171 (95.7)	381 (93.6)	
2	75 (4.6)	51 (4.2)	24 (5.9)	
3	3 (0.1)	2 (0.2)	1 (0.3)	
4	1 (0.1)	0	1 (0.3)	
First transplant type				0.170
Double lung	1,220 (74.8)	918 (75.0)	302 (74.2)	
Single lung	331 (20.3)	240 (19.6)	91 (22.4)	
Combined	80 (4.9)	66 (5.4)	14 (3.4)	
Disease indication for first transplantation				< 0.0001
Obstructive	691 (42.4)	489 (40.0)	202 (49.6)	
Restrictive	383 (23.5)	279 (22.8)	104 (25.6)	
Septic	405 (24.8)	328 (26.8)	77 (18.9)	
Pulmonary hypertension	151 (9.3)	128 (10.5)	23 (5.7)	
Other	1 (0.1)	0	1 (0.3)	
Postcode of usual residence at time of transplantation				0.194
Major city	1,044 (64.0)	791 (64.6)	253 (62.2)	
Regional/rural	321 (19.7)	245 (20.0)	76 (18.7)	
Other	266 (16.3)	188 (15.4)	78 (19.2)	
EBV status at transplantation				0.126
Primary mismatch (D+/R-)	92 (5.6)	61 (5.0)	31 (7.6)	
No primary mismatch	1,022 (62.7)	769 (62.8)	253 (62.2)	
Unevaluable	517 (31.7)	394 (32.2)	123 (30.2)	
ABO blood group				0.136
A	725 (44.5)	557 (45.5)	168 (41.3)	
AB	65 (4.0)	49 (4.0)	16 (3.9)	
B	182 (11.2)	143 (11.7)	39 (9.6)	
O	659 (40.4)	475 (38.8)	184 (45.2)	
Pretransplant malignancy				< 0.0001
Yes	78 (4.8%)	43 (3.5%)	35 (8.6%)	
No	1,553 (95.2%)	1,181 (96.5%)	372 (91.4%)	
Deaths	886 (54.3)	663 (54.2)	223 (54.8)	0.827

Abbreviations: EBV, Epstein-Barr virus; IQR, interquartile range; n, number.

independently associated with age (HR per year increase in age 1.02 [95% CI 1.00-1.03], $p = 0.007$) and EBV primary mismatch (HR 3.29 [95% CI 1.81-5.97] vs nonmismatch, $p = 0.0001$). On further analysis, EBV primary mismatch was not associated with malignancies other than PTLD (HR 1.07 (95%CI 0.69-1.66), $p = 0.767$).

NMSC events were found on multivariable analysis to be independently associated with age (HR 1.04 per year increase in age [95% CI 1.03-1.06], $p < 0.0001$), male sex (HR 2.48 [95% CI 1.89-3.25] vs female sex, $p < 0.0001$), and a history of any cancer diagnosis pretransplant (HR 1.96 [95% CI 1.26-3.05] vs no pretransplant malignancy, $p = 0.003$).

Given our cohort was predominantly Caucasian (95.2%), risk analysis of the association between ethnicity and cancer events was not statistically meaningful. Of the 407 patients

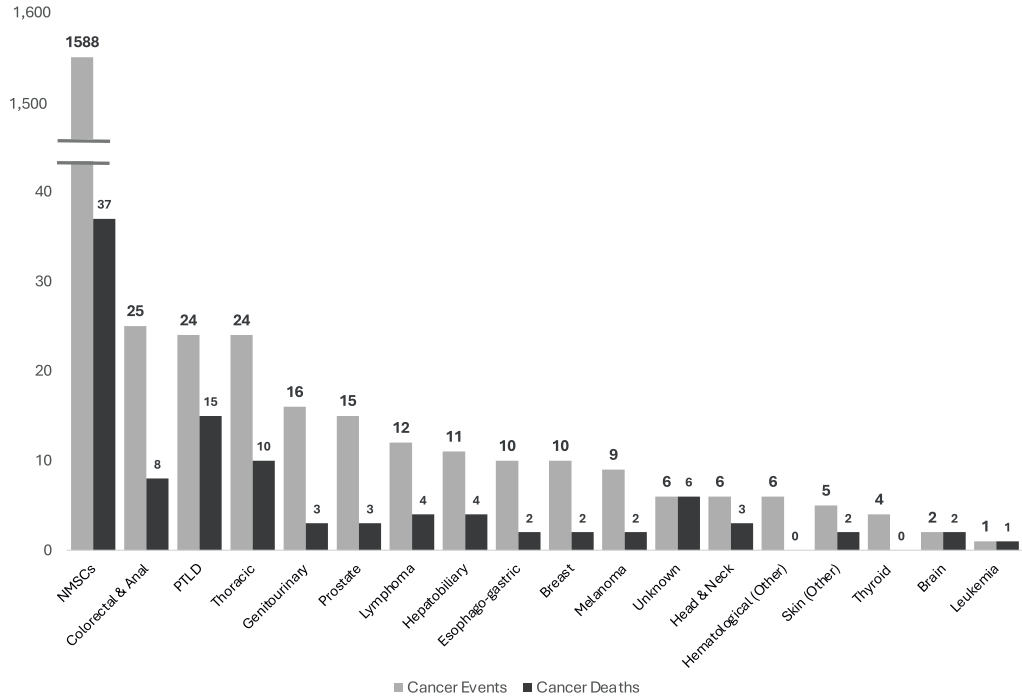

Figure 1 Number of cancer events and causes of cancer-related death in the lung transplant cohort. PTLD, post-transplant lymphoproliferative disorders; NMSCs, nonmelanoma skin cancers.

who developed cancer events, 406 (99.8%) were Caucasian, and all 295 patients who developed NMSCs were Caucasian.

Pretransplant malignancies

There were 89 events in 78 LTx recipients who had an invasive cancer before LTx, shown in Figure 2. Of these events, the most common diagnoses were NMSCs ($n = 18$, 20.2%) and prostate cancer ($n = 16$, 18.0%). The median time between the pretransplant malignancy and transplantation was 7.1 years (IQR 2.6-11.5). A total of 38 cancer events occurred within 5 years of first LTx. Any pretransplant malignancy diagnosis was associated with reduced time to cancer following first LTx (median 5.3 vs 14.4 years for those without pretransplant malignancy; HR 2.58 [95% CI 1.83-3.66], $p < 0.0001$) (Supplementary Figure S2A).

Nonmelanoma skin cancers

Of the 1,588 NMSC events, 65.9% ($n = 1,047$) were cSCCs and 34.1% ($n = 541$) BCCs, with a SCC:BCC ratio of 2:1. In the 295 patients who developed NMSCs, the mean (range) number of events was 5.38 (1-77) and 118 (40%) patients had both types of NMSCs. The clinical associations of cSCC and BCC are provided in Supplementary Table S4. The demographic characteristics and clinical outcomes were also analyzed between 3 subgroups of patients who had both BCC/cSCC, BCC only, and cSCC only. Patients who only had cSCC appeared to have a more aggressive clinical course with a shorter time from first NMSC to cancer death (HR 5.24 [95% CI 2.51-10.98], $p < 0.0001$), despite developing first NMSC further from transplant, and cancer was a more prominent cause of death in this cohort compared with other groups (Supplementary Figure S3, Supplementary Table S5).

Thoracic cancers

There were 24 thoracic cancer events occurring in 23 patients, of which 45.8% ($n = 11$) occurred in the native lung, 41.7% ($n = 10$) in the transplanted lung, and 12.5% ($n = 3$) were unknown. In comparison with bilateral LTx recipients, thoracic cancers were a more prominent cause of cancer in single LTx recipients (Supplementary Figure S4, Supplementary Table S6). Single LTx recipients had a significantly reduced time to thoracic cancers (HR 7.08 [95% CI 3.1-16.2], $p < 0.001$) and cancers excluding NMSCs and thoracic cancers (HR 1.55 [95% CI 1.06-2.26], $p = 0.024$), but not for NMSCs (Supplementary Figure S5, Supplementary Table S3).

Time to cancer

The cumulative incidence of cancer at 1, 5, 10, 15, and 20 years from transplantation was 5.3%, 22.6%, 38.9%, 51.6%, and 57.2%, respectively. First cancer diagnoses occurred markedly earlier in men than women (median 10.8 vs 23.1 years, respectively; HR 2.01 [95% CI 1.63-2.47], $p < 0.0001$), and in patients aged ≥65 at transplantation (median 8.4 vs 22.4 years for those aged < 50, respectively;

Table 2 Cancer Incidence in the Lung Transplant Cohort Compared With Cancer Incidence for the General Population Stratified by Era of Transplantation, per 100,000 Person-Years

Variables	All					1989-1999					2000-2009					2010-2021				
	LTx	AIHW	Obs	SIR	*p*-value	LTx	AIHW	Obs	SIR	*p*-value	LTx	AIHW	Obs	SIR	*p*-value	LTx	AIHW	Obs	SIR	*p*-value
All (excluding NMSCs)	1,918.4	480.6	186	4 (3.4-4.7)	< 0.001	1,361.3	457.5	34	3 (2.1-4.2)	< 0.001	2,151.0	489.2	68	4.4 (3.4-5.7)	< 0.001	2,080.9	441.2	84	4.7 (3.7-6)	< 0.001
Hepatobiliary	113.5	18.4	11	6.2 (2.9-13.1)	< 0.001	120.1	15.7	3	7.7 (2.2-26.3)	0.02	63.3	18.0	2	3.5 (0.8-15.2)	0.25	148.6	21.8	6	6.8 (2.8-16.8)	0.01
Brain	20.6	7.3	2	2.8 (0.6-13.5)	0.37			0	0 (0-0)		31.6	7.4	1	4.3 (0.5-34.5)	0.44	24.8	7.3	1	3.4 (0.4-27.4)	0.54
Breast	103.1	60.4	10	1.7 (0.9-3.3)	0.18	120.1	57.0	3	2.1 (0.7-6.7)	0.36	31.6	60.2	1	0.5 (0.1-3.8)	0.88	148.6	64.4	6	2.3 (1-5.3)	0.11
Colorectal and Anal	257.8	84.0	25	3.1 (2-4.8)	< 0.001	80.1	86.5	2	0.9 (0.2-3.8)	1.00	348.0	87.2	11	4 (2.1-7.5)	< 0.001	297.3	77.8	12	3.8 (2.1-7)	< 0.001
Genitourinary	165.0	72.2	16	2.3 (1.3-3.9)	0.01	200.2	70.8	5	2.8 (1.1-7)	0.08	158.2	67.2	5	2.4 (0.9-5.8)	0.14	148.6	79.3	6	1.9 (0.8-4.3)	0.23
Hematological (Other)	61.9	11.3	6	5.5 (2-14.7)	0.01			0	0 (0-0)		158.2	12.2	5	13 (4.6-36.7)	< 0.001	24.8	14.7	1	1.7 (0.2-12.8)	0.94
Head and neck	61.9	21.1	6	2.9 (1.2-7.3)	0.06			0	0 (0-0)		63.3	20.0	2	3.2 (0.7-13.5)	0.29	99.1	19.3	4	5.1 (1.7-15.1)	0.02
Leukemia	10.3	14.7	1	0.7 (0.1-5.3)	1.00			0	0 (0-0)		0.0	0.0	0	0 (0-0)		24.8	15.3	1	1.6 (0.2-12.2)	0.94
PTLD or lymphoma	371.3	17.7	36	21 (11.9-37.1)	< 0.001	240.2	16.4	6	14.7 (5.8-37.3)	< 0.001	379.6	17.9	12	21.2 (10.2-44.1)	< 0.001	445.9	19.1	18	23.4 (12.3-44.4)	< 0.001
Melanoma	92.8	47.4	9	2 (1-4)	0.11			0	0 (0-0)		63.3	48.7	2	1.3 (0.3-5.3)	0.93	173.4	51.3	7	3.4 (1.5-7.4)	0.01
NMSCs	1,6378.4	1,812.0	1,588	9 (8.5-9.7)	< 0.001	11,330.5	1,109.0	283	10.2 (9-11.6)	< 0.001	14,930.4	1,878.0	472	8 (7.2-8.8)	< 0.001	20,635.9	2,448.0	833	8.4 (7.8-9.1)	< 0.001
Esophago-gastric	103.1	15.5	10	6.7 (3-14.7)	< 0.001	120.1	17.3	3	6.9 (2-23.7)	0.02	126.5	15.2	4	8.3 (2.8-25)	0.01	74.3	13.9	3	5.3 (1.5-18.6)	0.05
Prostate	154.7	69.9	15	2.2 (1.3-3.9)	0.01	40.0	59.5	1	0.7 (0.1-4.9)	1.00	126.5	76.4	4	1.7 (0.6-4.5)	0.46	247.7	74.2	10	3.3 (1.7-6.5)	0.01
Skin (other)	51.6	2.3	5	22.4 (4.7-106.9)	< 0.001			0	0 (0-0)		94.9	2.8	3	33.9 (6.7-172.7)	< 0.001	49.5	3.4	2	14.6 (2.5-83.6)	0.03
Thoracic	247.5	44.5	24	5.6 (3.4-9.1)	< 0.001	280.3	45.7	7	6.1 (2.8-13.6)	< 0.001	379.6	44.3	12	8.6 (4.5-16.2)	< 0.001	123.9	43.5	5	2.8 (1.1-7.2)	0.08
Thyroid	41.3	7.7	4	5.4 (1.6-18)	0.03	40.0	4.5	1	8.9 (1-77.7)	0.28	31.6	7.5	1	4.2 (0.5-34)	0.49	49.5	11.4	2	4.3 (1-19.5)	0.18

Abbreviations: AIHW, Australian Institute of Health and Welfare; LTx, Lung transplant; NMSCs, nonmelanoma skin cancers; Obs, observations; PTLD, post-transplant lymphoproliferative disorders; SIR, standardized incidence ratio.

Table 3 Univariable and Multivariable Competing Risk Regression Analyses for Cancers Excluding NMSCs, and Analyses for NMSCs

Variables	Cancers excluding NMSCs				NMSCs			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at transplantation[a]	1.02 (1.01-1.03)	0.004	1.02 (1.00-1.03)	0.007	1.05 (1.04-1.06)	< 0.0001	1.04 (1.03-1.06)	< 0.0001
< 50 years	Reference				Reference			
50-65 years	1.29 (0.90-1.86)	0.164	-		3.01 (2.29-3.96)	< 0.0001	-	
> 65 years	1.51 (0.87-2.63)	0.145	-		4.72 (3.27-6.80)	< 0.0001	-	
Sex								
Female	Reference				Reference			
Male	0.95 (0.67-1.34)	0.762	0.82 (0.57-1.17)	0.272	2.69 (2.08-3.49)	< 0.0001	2.48 (1.89-3.25)	< 0.0001
EBV mismatch status								
No	Reference				Reference			
Yes (D+/R-)	2.84 (1.65-4.90)	0.0002	3.29 (1.81-5.97)	0.0001	1.25 (0.69-2.27)	0.467	1.21 (0.68-2.15)	0.521
Unevaluable	1.30 (0.90-1.88)	0.165	1.47 (0.96-2.24)	0.075	0.53 (0.41-0.69)	< 0.0001	0.79 (0.59-1.06)	0.121
Reason for transplantation								
Obstructive	Reference				Reference			
Restrictive	0.79 (0.50-1.26)	0.327	-		1.20 (0.91-1.58)	0.205	1.00 (0.75-1.35)	0.988
Other	0.68 (0.46-1.01)	0.053	-		0.42 (0.31-0.56)	< 0.0001	1.00 (0.67-1.50)	0.995
Geography								
Metropolitan	Reference				Reference			
Regional/rural	0.96 (0.62-1.48)	0.842	-		0.89 (0.65-1.22)	0.468	0.82 (0.59-1.14)	0.244
Other	0.83 (0.49-1.40)	0.479	-		1.57 (1.17-2.10)	0.003	1.35 (0.99-1.84)	0.058
ABO blood group								
A	Reference				Reference			
AB	1.13 (0.48-2.64)	0.777	-		1.05 (0.54-2.05)	0.875	0.86 (0.44-1.70)	0.674
B	0.81 (0.43-1.54)	0.526	-		1.22 (0.80-1.85)	0.358	1.17 (0.76-1.80)	0.487
O	0.90 (0.62-1.30)	0.575	-		1.33 (1.04-1.71)	0.025	1.28 (0.99-1.66)	0.065
Transplant type								
Double lung	Reference				Reference			
Single lung	1.78 (1.22-2.59)	0.003	1.45 (0.93-2.26)	0.104	1.07 (0.80-1.43)	0.660	-	
Combined	0.27 (0.07-1.06)	0.061	0.30 (0.07-1.18)	0.084	0.73 (0.44-1.22)	0.230	-	
Number of transplants								
1 transplant	Reference				Reference			
> 1 transplant	0.63 (0.28-1.44)	0.277	-		0.99 (0.65-1.49)	0.956	-	
History of cancer before transplant								
No	Reference				Reference			
Yes	1.13 (0.51-2.46)	0.767	1.05 (0.46-2.38)	0.908	3.13 (2.12-4.61)	< 0.0001	1.96 (1.26-3.05)	0.003

Abbreviations: CI, confidence interval; EBV, Epstein-Barr virus; HR, hazard ratio; NMSCs, nonmelanoma skin cancers.
[a]Analyzed as a continuous variable.

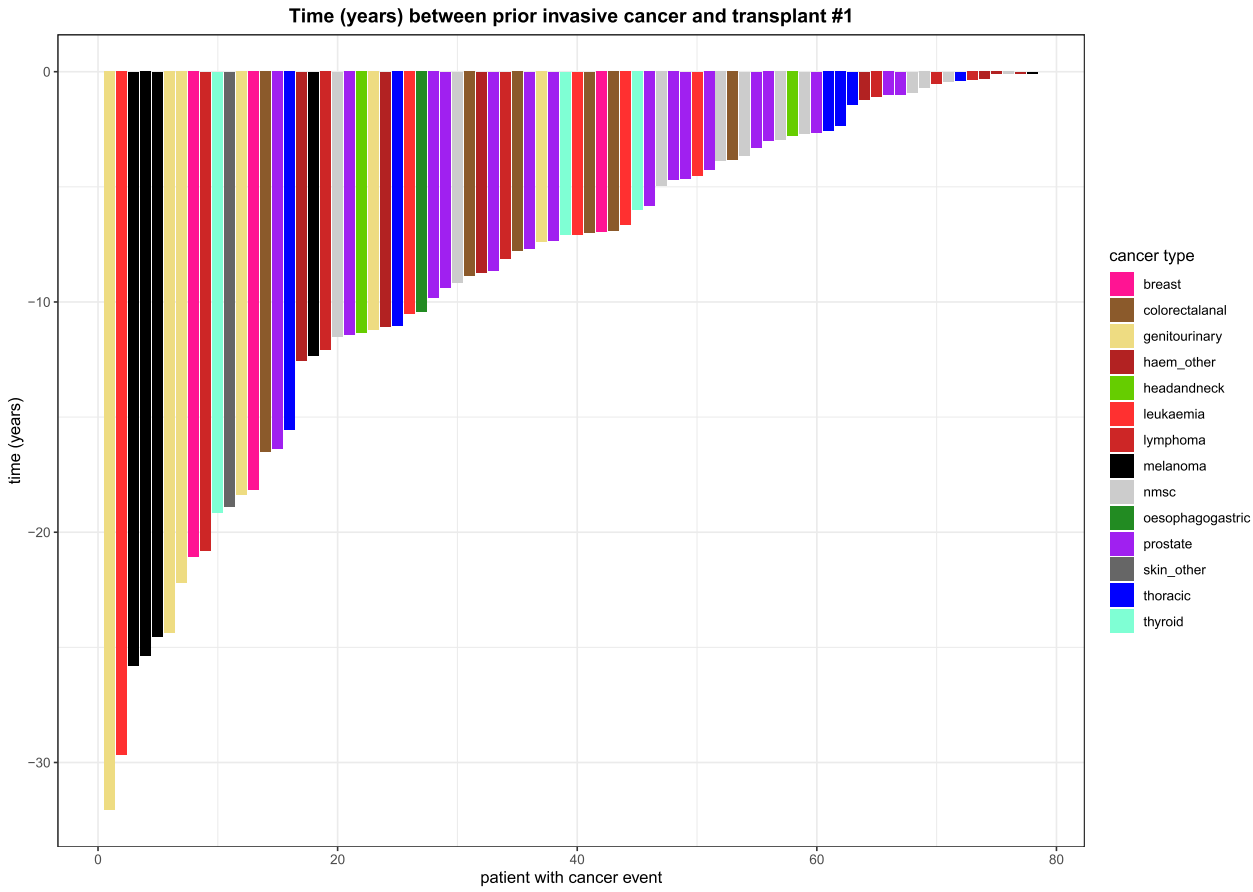

Figure 2 Cancer events occurring before first LTx procedure. NMSC, nonmelanoma skin cancer.

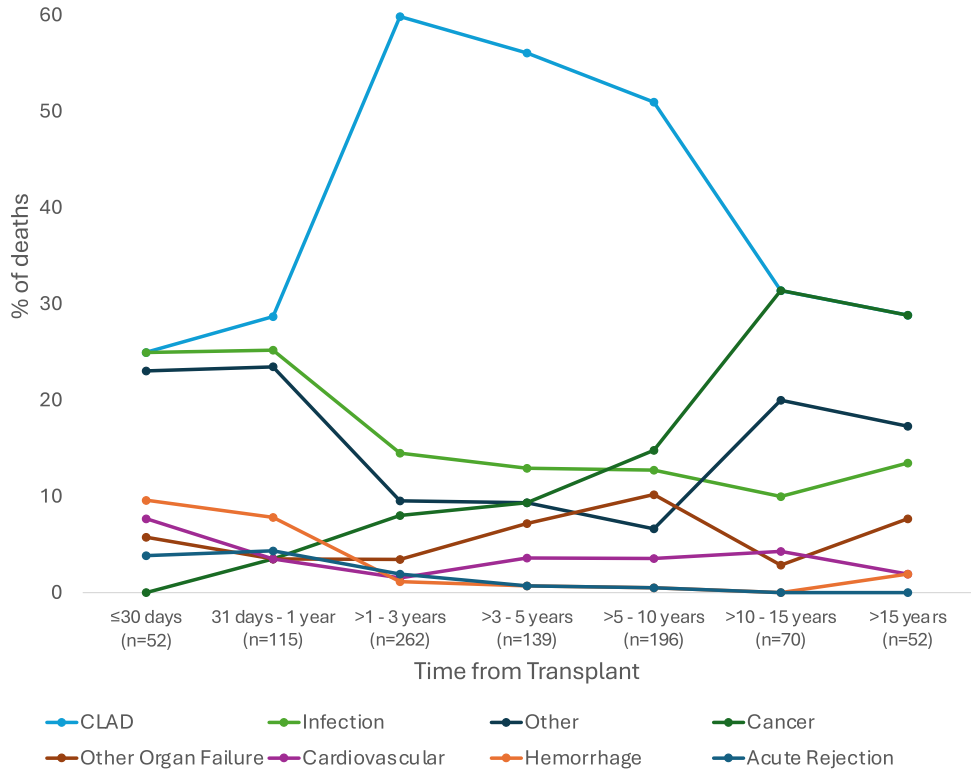

Figure 3 Cause of deaths from time of first transplantation. CLAD, chronic lung allograft dysfunction.

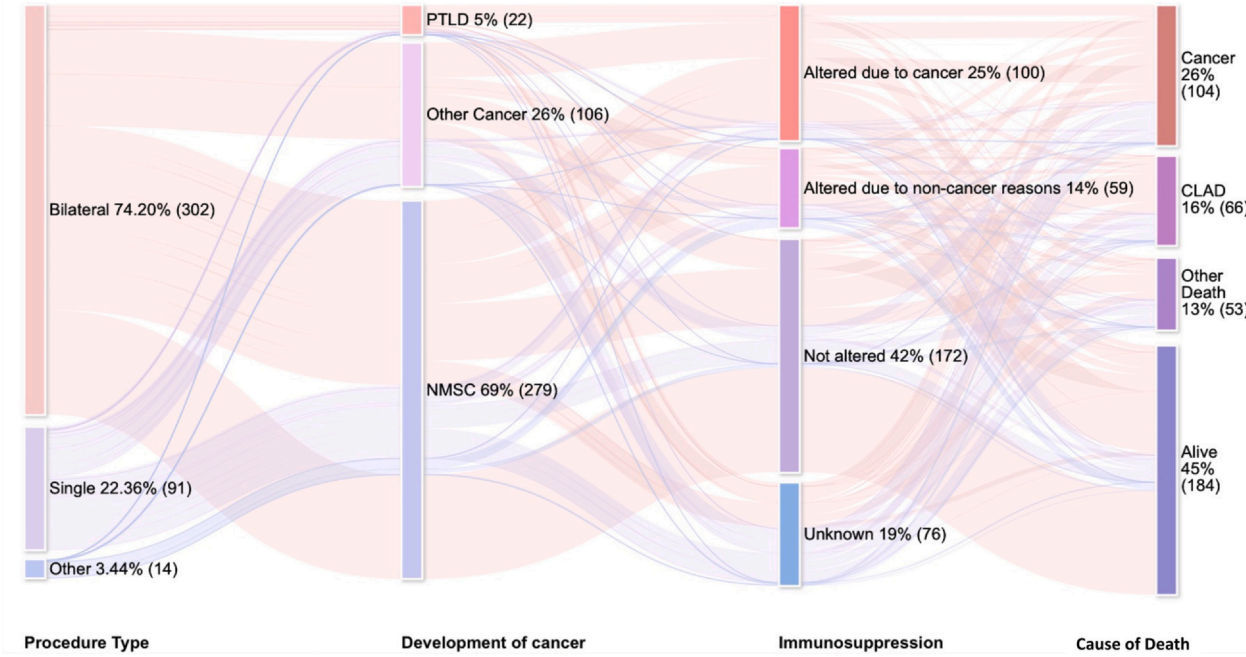

Figure 4 Sankey diagram demonstrating progression from transplant to death in patients who developed cancer ($n = 407$), and the proportion who had immunosuppression altered. CLAD, chronic lung allograft dysfunction; PTLD, post-transplant lymphoproliferative disorders; NMSCs, nonmelanoma skin cancers.

HR 4.46 [95% CI 3.26-6.12], $p < 0.0001$) (Supplementary Figure S2).

Survival and cause of death

Median overall survival from the date of first LTx for our cohort was 7.5 years (95% CI 6.8-8.3), with particularly marked improvement in the most recent era (median 5.5, 5.1, and 9.3 years for eras 1, 2, and 3 respectively) (Supplementary Figure S6). Over the entire cohort, landmark survivals at 1, 5, 10, 15, and 20 years from first transplant were 89.8%, 61.4%, 41.1%, 29.0%, and 19.9%, respectively. Recipients of single LTx had significantly shorter overall survival than recipients of double LTx (median 3.6 vs 7.2 years, respectively; HR 1.99 [95% CI 1.72-2.31], $p < 0.0001$).

Out of 886 deaths, the most common cause of death was CLAD ($n = 418$, 47.2%), consistent across all 3 eras (Supplementary Table S7). This was followed by infection ($n = 137$, 15.5%), other/unknown ($n = 113$, 12.8%), and cancer ($n = 104$, 11.7%).

Most deaths occurred within 5 years of LTx ($n = 568$, 64.1%); however, causes of death varied according to time post-LTx (Figure 3 and Supplementary Table S8). CLAD was the leading cause of death within 10 years of LTx ($n = 381$, 49.9% of 764 deaths). However, beyond 10 years, cancer reached parity with CLAD as the leading cause of death ($n = 37$, 30.3% of 122 deaths). Of the 104 cancer-related deaths, the most common causes were NMSCs ($n = 37$, 35.6%), followed by PTLD ($n = 15$, 14.4%) and thoracic malignancies ($n = 10$, 9.6%) (Figure 1, Supplementary Table S9).

Of the patients who developed cancer, 24.6% ($n = 100$) had immunosuppression altered because of their cancer diagnosis, 14.5% ($n = 59$) had immunosuppression altered due to noncancer reasons (e.g., toxicity and renal impairment), 42.3% ($n = 172$) were not altered and 18.7% ($n = 76$) unknown (Figure 4, Supplementary Table S10). Cancer mortality was higher in patients who had immunosuppression altered due to cancer (75.0%), compared to patients in whom immunosuppression was altered for noncancer-related reasons (42.9%) (Supplementary Table S11).

Cancer-related death

The clinical and demographic features associated with death from cancer are presented in Table 4. Multivariable analysis revealed that cancer-related deaths were independently associated with age (HR per year increase in age 1.02 [95% CI 1.01-1.03], $p = 0.001$), EBV primary mismatch (HR 3.24 [95% CI 1.68-6.25], vs nonmismatch, $p = 0.002$), and invasive cancer count (HR per increase in event 1.19 [95% CI 1.13-1.24], $p < 0.0001$). A history of pretransplant malignancy was not associated with cancer mortality.

Discussion

This study provides a contemporary and comprehensive analysis of cancer trends within a large Australian LTx cohort over a 31-year period. We have found that malignancy reaches parity with CLAD as the leading cause of death 10 years after LTx, with NMSCs being the leading cause of cancer-related deaths, uniquely demonstrating the magnitude and scale of malignancy as a late-term complication.

Table 4 Univariable and Multivariable Competing Risk Analyses for Cancer Death in the Lung Transplant Cohort, Accounting for the Competing Risk of Deaths Not Associated With Cancer

Variables	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at transplantation[a]	1.03 (1.01-1.04)	< 0.0001	1.02 (1.01-1.03)	0.001
< 50 years	Reference			
50-65 years	1.80 (1.19-2.71)	0.005	-	
> 65 years	1.85 (0.95-3.60)	0.072	-	
Sex				
Female	Reference			
Male	1.60 (1.08-2.39)	0.020	1.11 (0.72-1.71)	0.634
EBV mismatch status				
No	Reference			
Yes (D+/R-)	2.78 (1.44-5.35)	0.002	3.24 (1.68-6.25)	0.002
Unevaluable	0.91 (0.62-1.35)	0.655	1.23 (0.81-1.85)	0.336
Reason for transplantation				
Obstructive	Reference			
Restrictive	1.56 (0.97-2.49)	0.064	-	
Other	0.80 (0.51-1.25)	0.324	-	
Geography				
Metropolitan	Reference			
Regional/rural	1.04 (0.64-1.70)	0.864	-	
Other	1.23 (0.73-2.07)	0.435	-	
ABO blood group				
A	Reference			
AB	1.09 (0.44-2.71)	0.858	-	
B	0.89 (0.43-1.81)	0.742	-	
O	1.04 (0.69-1.57)	0.842	-	
Transplant type				
Double lung	Reference			
Single lung	1.29 (0.85-1.97)	0.237	-	
Combined	0.43 (0.14-1.32)	0.139	-	
Number of transplants				
1 transplant	Reference			
> 1 transplant	0.93 (0.41-2.07)	0.850	-	-
Cancer event count[b]	1.21 (1.16-1.26)	< 0.0001	1.19 (1.13-1.24)	< 0.0001
History of cancer before transplant				
No	Reference			
Yes	1.78 (0.81-3.93)	0.154	1.22 (0.52-2.83)	0.649

Abbreviations: CI, confidence interval; EBV, Epstein-Barr virus; HR, hazard ratio; NMSCs, nonmelanoma skin cancers.
[a]Analyzed as a continuous variable.
[b]Analyzed as a continuous variable, from zero to a maximum of 10 events, with recipients who had 10 or more cancer events analyzed together.

Although the cancer mortality data in the present study are consistent with ISHLT registry and other single-institution data approximately 5 to 10 years post-LTx, we have identified much higher rates of cancer mortality beyond 10 years. Prior Australian data similarly demonstrates cancer mortality to be a prominent secondary cause of death beyond 5 years, however, it provides limited insights into cancer mortality beyond 10 years.[1,16] This finding is of particular significance especially given the median survival time from transplant in recipients transplanted between 2010 and 2021 was 9.3 years. In our cohort, malignancy accounted for 30.3% of deaths beyond 10 years, however, in the ISHLT registry, cancers (including lymphoma) accounted for only 17.9% of deaths, with similar findings in other cohorts.[17,18] Additionally, we also report slightly higher rates of malignancy compared to ISHLT registry data; at 1, 5, and 10 years post-LTx, ISHLT reports rates of 5.3%, 19.6%, and 31.7% vs the present study: 5.3%, 22.6%, and 38.9%, respectively.[19] It is possible that this difference reflects our cohort's slightly longer survival, differing population risks, as well as our study's long follow-up, and our institution's centralized provision of multidisciplinary survivorship care for LTx recipients, enabling comprehensive detection of these events. Age, LTx indications, and the proportion of recipients with a pretransplant malignancy history were similar between our cohort and the ISHLT registry.[17,20]

We observed a high rate of non-NMSC cancers, being 4 times greater than that of the general Australian population. This is double the estimates provided by international LTx

cohorts,[3,6,18] but more consistent with prior Australian data.[8] Age and EBV primary mismatch were strong risk factors for both cancer deaths and non-NMSC cancer events, likely driven by PTLD. EBV primary mismatch is a known risk factor for PTLD, which demonstrated a disproportionately high mortality rate in this cohort (third most common cancer diagnosis, second highest cause of cancer death).[21-23]

Prior Australian and international studies have identified associated factors for NMSCs in cardiothoracic and other organ transplant recipients.[24-28] We have also found that NMSCs were strongly associated with male sex, previously hypothesized as linked to socially-driven differences in occupational and recreational sun exposure.[29-32] Additionally, we report a strong association between a pretransplant history of malignancy with the risk of developing post-transplant NMSCs, but not with cancer death. These results are consistent with ISHLT data, but discordant with data from other solid organ transplant types, likely reflecting organ transplant type-specific differences.[33,34] Our findings do not support the routine contraindication of transplantation due to a history of cancers, including NMSCs, which is consistent with ISHLT recommendations that suggest the contraindication of transplantation for patients with a history of malignancy only if there is a high risk of recurrence or death related to cancer.[35] However, risk stratification and prognostication for NMSC recurrence in the transplant population are required. Although there are consensus guidelines based on high-risk tumor factors providing recommendations on the appropriate disease-free interval before transplant eligibility, large-scale data predicting NMSC recurrence in LTx recipients are lacking.[36-39] For all pretransplant malignancies, we recommend consultation with an appropriate oncologist to prognosticate the disease-specific survival and evaluate the appropriateness of transplantation with consideration of the type of cancer and stage at diagnosis; the molecular subtype and other prognostic histopathological risk factors; what definitive treatment was received and if it was optimal; the likelihood that recurrent (or new unrelated) cancer would be treatable; and finally, whether the cancer is expected to be aggravated by the post-transplant course.[40]

The demographic evolution and improvements in survival observed in our population over the 3-decade study period are consistent with international and Australian data and reflect steady improvements in LTx medicine.[1,17,20] Age is a particularly potent risk factor for cancer, and with ever more—and older—transplant recipients surviving longer with prolonged exposure to immunosuppressive agents, we expect that cancer mortality will continue to rise as transplant survival outpaces parallel improvements in cancer prevention and treatment in this cohort. This clinical conundrum is further exacerbated by the unique complexities of treating cancers in transplant recipients now that immune-checkpoint inhibitors form the basis of systemic therapy for many advanced cancers, at the exclusion of transplant recipients, given the risk of catastrophic transplant rejection, as has been previously reported.[41]

Notably, cancer deaths in patients who had immunosuppression altered due to cancer were high, with corresponding lower rates of CLAD-related deaths, compared with the overall population. This likely reflects the clinical practice of altering immunosuppressive regimens in response to aggressive malignant disease, rather than the interpretation that they are causative of cancer deaths. It is not possible from our analysis to conclude whether altering immunosuppression affected CLAD outcomes. Following an NMSC diagnosis, immunosuppression was individually tailored but typically included minimizing the calcineurin inhibitor and ceasing the antiproliferative. Everolimus has been associated with reduced skin cancer risk in transplant recipients, and at our institution, is commonly used in response to aggressive or repeated skin cancers.[42] Previous work from our unit demonstrated that at the introduction of everolimus as a second-line agent, the minimization of calcineurin inhibitor had better survival outcomes compared to its elimination, with no difference in CLAD-related mortality.[43] Nevertheless, there is limited data to support the optimal immunosuppression regimen in the setting of aggressive malignancy and it likely impacts CLAD-related outcomes. In considering reducing immunosuppression in the presence of malignancy, the absolute immunological risk must be evaluated. This is best assessed by reviewing the extent of donor-recipient human leukocyte antigens/eplet mismatching and prior allo-rejection history.[40]

Our study describes a large single-institution experience of cancer incidence within an LTx cohort, approximately double the size of comparable analyses.[6,18,44-47] In using both VCR data linkage and manual review of patient records, we were able to comprehensively detect a much larger number of cancer events, especially NMSCs, than other studies. Of the 1,774 events detected in this study, only 62 (3.5%) were detected via VCR linkage, 29% ($n = 54$) of cancer events excluding NMSCs. Of the 89 pretransplant events, the VCR linkage detected 65.2% ($n = 58$) of events.

The inclusion of NMSCs is a key strength of this study, providing a comprehensive and complete description of the malignancy burden within LTx recipients. Previous Australian studies in LTx recipients have been data linkage analyses, which have not reported the incidence rates of NMSCs.[5,8] In addition, the usage of competing risk regression analysis provides more accurate estimation of cancer mortality and incidence by accounting for its competing risks. Limitations of this study include the potential under-reporting of gynecological cancers, which are generally managed by community services, and cancers in the 29.6% ($n = 483$) of patients who continued follow-up in their home states. Furthermore, there is also a possibility of ascertainment bias given the protocolized follow-up offered to LTx recipients, and the lack of accurate NMSC reporting in the general Australian population. However, it is also possible that despite the high numbers of NMSCs we have detected through manual review, many events have not been captured because the standard management of early invasive skin cancers often occurs in primary care settings,

often without biopsy. Additionally, this study involved a retrospective review of historical records. EBV serostatus was not readily available and therefore unevaluable for most recipients from era 1, and individual exposure to specific immunosuppressive and antifungal agents cannot be accurately captured, thus limiting the evaluation of these factors on cancer outcomes.

Our study provides a contemporary and comprehensive characterization of the morbidity and mortality burden related to malignancy within a large LTx center in Australia over 31 years. This data have led to the refinement of our cancer screening and management protocols, with increased multidisciplinary services and improved patient education, as well as the prospective recording of all cancers, given the limitations of registry recording, particularly for NMSCs. As the life expectancy of LTx recipients extends, and recipient demographics evolve, we expect malignancy to be an increasing problem. Further research is needed to mitigate risk factors for malignancy, improve active cancer prevention, and streamlined services to screen, detect and manage cancers in organ transplant recipients are crucial.

CRediT authorship contribution statement

The authors verify contribution to the manuscript as follows: study conception and design: M.C.A., H.L.Y., G.S., B.L., M.V., M.S.; data collection: H.S., H.L.Y., B.L., M.C.A.; analysis and interpretation of results: H.L.Y., M.C.A., E.P., G.S., B.L., H.S., M.S., M.V., A.H.; draft manuscript preparation: H.L.Y., M.C.A., G.S., and B.L. All authors reviewed the results and approved the final version of the manuscript.

Disclosure statement

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Miles C. Andrews reports a relationship with Merck Sharp & Dohme (Australia) Pty Limited that includes board membership, funding grants, and speaking and lecture fees. Miles C. Andrews reports a relationship with Pierre Fabre Australia that includes speaking and lecture fees. Miles C. Andrews reports a relationship with Bristol Myers Squibb Co that includes funding grants. Mark Voskoboynik reports a relationship with AstraZeneca Pharmaceuticals LP that includes consulting or advisory and speaking and lecture fees. Mark Voskoboynik reports a relationship with Merck Sharp & Dohme UK Ltd that includes consulting or advisory and speaking and lecture fees. All other authors declare that they have no financial conflicts of interest pertaining to the content of this manuscript.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100094.

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