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Original Article

ORIGINAL ARTICLE

The incidence of cancer recurrence and new cancer following commencement of dialysis

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ABSTRACT

Background. Patients with kidney failure have a higher cancer risk compared with the age-matched general population. However, the outcomes of incident dialysis patients with a prior cancer history are unknown.

Methods. Using Australia and New Zealand Dialysis and Transplant Registry data (2000–2019), the outcomes and survival probabilities of incident dialysis patients with prior cancers and having experienced a cancer recurrence or having developed a new cancer after dialysis commencement were described.

Results. Of 4912 patients with prior cancers before dialysis commencement, 323 (7%) and 343 (7%) patients experienced cancer recurrence or developed new cancers after dialysis initiation, respectively. The median time from dialysis commencement to cancer recurrence was 1.2 years [interquartile range (IQR) 0.5–2.8] and was 2.0 years (IQR 0.7–4.0) for new cancer occurrence. Of those with cancer recurrence, 80% presented with metastatic disease and one in two patients died from cancer, with a median time from cancer recurrence to death of 0.5 years (IQR 0.2–1.7). Of those who developed

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new cancer, urinary tract and respiratory cancers were the most frequent cancer types, with a median time from new cancer diagnosis to death of 1.3 years (IQR 0.4–3.1). The 3-year survival probabilities on dialysis following cancer recurrence and new cancer were 19% [95% confidence interval (CI) 15–24] and 41% (35–47), respectively.
Conclusion. Among incident dialysis patients with a prior cancer history, 14% experienced cancer recurrence or developed a new cancer. Patients who experienced cancer recurrence or developed new cancer have poor outcomes, with <50% surviving beyond 3 years. These findings suggest the need to have a greater understanding of the characteristics, cancer screening, treatment responses and reasons for commencing dialysis in patients with kidney failure and prior cancer history, which may help in the shared clinical decision-making process when considering dialysis for these patients.

Keywords: cancer mortality, cancer recurrence, dialysis, mortality, new cancer, prior cancer

INTRODUCTION

Cancer remains one of the dominant causes of death in patients with kidney failure, attributed in part to uraemia-induced impairment of tumour immune surveillance [1–5]. In Australia, cancer accounted for 2% and 26% of overall deaths in dialysis and kidney transplant patients, respectively, in 2019 [6]; with similar trends observed both in the UK and the USA [7–10].

The incidences of several cancers and cancer mortality are substantially increased in patients with chronic kidney disease and kidney failure compared with an age- and sex-matched general population [11–15]. In kidney transplant recipients, the incidences of a number of cancers are considerably increased, with the standardized incidence ratio (SIR) exceeding 3-fold, particularly for viral and immune-related cancers [16, 17]. In dialysis patients, the patterns of increased SIRs of several cancers are different from those of the transplant population and mostly confined to increased incidences of kidney and thyroid cancers [1, 16]. Even though the standardized mortality ratios (SMRs) in patients with kidney failure are almost 3-fold greater compared with an age- and sex-matched general population, the increased SMRs were predominantly driven by pre-existing cancers in patients on dialysis and *de novo* cancers in patients who have received kidney transplants [14].

In a population cohort study of 651 kidney transplant recipients with a prior history of cancer, the development of recurrent or second primary cancers was infrequent, with no significant impact on the cancer-specific and overall survival of these recipients [18]. However, the risk of developing recurrent or new cancers and cancer mortality following commencement of dialysis in patients with kidney failure and prior or *de novo* cancers remains poorly defined. The aims of this study were 2-fold: to estimate the incidences and patterns of cancer recurrence and new cancer development in patients with a prior cancer history before dialysis commencement and to determine the all-cause and cancer death rates of these patients with prior cancers.

MATERIALS AND METHODS

Study population

Using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, all incident patients with kidney failure and prior solid and haematological cancers initiated on peritoneal dialysis or haemodialysis in Australia and New Zealand between 2000 and 2019 were included. Patients who had received pre-emptive kidney transplants, patients who had died or recovered native kidney function (to allow for dialysis discontinuation) within 90 days of dialysis initiation and patients with prior failed kidney allografts were excluded. Patients without solid or haematological cancers prior to dialysis initiation or those with non-melanoma skin cancer (without another solid or haematological organ cancer) or carcinoma *in situ* (including cervical cancer) prior to dialysis commencement were also excluded. The follow-up period of this cohort was from the time of dialysis commencement until death, kidney transplantation or the end of the survey period on 31 December 2019, whichever came first. The conduct of this study was approved by the University of Western Australia Human Research Ethics Committee and is reported here according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [19].

Data collection

Baseline patient characteristics included age, sex, ethnicity (White, Indigenous, Aotearoa New Zealand Māori, Asian, other), body mass index (BMI) at dialysis initiation [calculated by weight (kg)/height (m^2)], type of initial dialysis treatment, primary cause of kidney failure, prevalent comorbid conditions at dialysis initiation (coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes and smoking history) and estimated glomerular filtration rate [eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation] [20] at dialysis initiation. The year of dialysis initiation and kidney transplant status were also extracted from the registry.

Exposure groups

Patients were categorized into three groups for analysis: patients with prior cancer(s) who did not develop cancer recurrence or a new different cancer type after dialysis commencement (patients who experienced cancer recurrence or a new cancer prior to dialysis commencement were included in this group), patients with prior cancer(s) who experienced cancer recurrence after dialysis commencement and patients who developed a new cancer (*de novo*) after dialysis commencement. Patients who experienced cancer recurrence as well as developed a new cancer(s) after dialysis commencement were included in the cancer recurrence group in the pre specified analyses. In a sensitivity analysis, each exposure group was further stratified into patients who had experienced cancer recurrence prior to the commencement of dialysis.

Ascertainment of cancers

All cancers (prior cancers, cancer recurrence or *de novo* cancers) pre- and post-initiation of dialysis were reported to the ANZDATA Registry. Although the ANZDATA Registry does not verify the accuracy of reporting or require confirmatory histology of reported cancers, cancer(s) reported to the ANZDATA Registry has been shown to be accurate with a high concordance rate compared with those reported to the New South Wales Cancer Registry, a mandatory requirement for cancer reporting in New South Wales, Australia [21]. All cancers are recorded by cancer sites and cell types according to the International Classification of Disease for Oncology, third edition, first revision (ICD-O-3.1) [22].

Cancer recurrence occurring before or after dialysis commencement was defined as the occurrence of cancer that was of the same type as the prior primary cancer(s) before dialysis initiation and could include local recurrence, lymph node involvement or metastatic disease of the same primary cancer type. *De novo* new cancer(s) was defined as the occurrence of cancer(s) of a different type or at a different location (i.e. may have been the same cancer type but not thought to be a cancer recurrence of the prior primary cancer) to that of the prior primary cancer after dialysis commencement. The ascertainment of cancer occurring after dialysis commencement as a recurrent or a new cancer was prespecified in the ANZADATA Registry Cancer Survey Form (https://www.anzdata.org.au/wp-content/uploads/2021/02/CancerSurveyForm_CA.pdf). Cancer recurrence and new cancers that occurred after kidney transplantation were not included.

Clinical outcomes

The primary outcomes of this study included the types, sites and stages (including the presence of local recurrence, lymph node involvement and metastatic disease) of recurrent and new cancers, comparing between the exposure groups. Secondary outcomes included all-cause and cancer-related mortality on dialysis. Cancer mortality was defined as deaths attributed to 'malignant disease' and 'withdrawal from malignancy,' with these reasons for the causes of death prespecified in the ANZDATA registry (Supplementary data).

Statistical analyses

Baseline characteristics were reported as number (percentage), mean [standard deviation (SD)] or median [interquartile range (IQR)]. Comparisons of baseline characteristics and prior cancer types between the exposure groups were undertaken using the chi-squared test for categorical data and analysis of variance or the Kruskal–Wallis test for continuous data. The median time periods from first cancer diagnosis before dialysis-to-dialysis commencement and from dialysis commencement to cancer recurrence or new cancer on dialysis and death (or transplant) were described for all three cancer exposure groups. For patients with prior cancer who experienced a cancer recurrence or a new cancer, the types, frequency and outcomes of these recurrent and new cancers were reported. The survival probabilities at 1, 3 and 5 years following the first reported occurrence of cancer recurrence (cancer recurrence group) or new cancer (new cancer group) after dialysis commencement were estimated using the Kaplan–Meier method.

Three sensitivity analyses were undertaken. First, we described the median time periods from first cancer diagnosis before dialysis commencement to dialysis commencement of each exposure group, stratified by cancer recurrence pre-dialysis. Second, we reported the outcomes of each exposure group, stratified by cancer recurrence pre-dialysis. Third, in patients with prior cancer but without recurrence or new cancer on dialysis, the overall and cancer-free survival probabilities at 1, 3 and 5 years from the time of dialysis commencement according to the occurrence of pre-dialysis cancer recurrence were estimated using the Kaplan–Meier method. Statistical analyses were performed using Stata statistical software (version 9.4; StataCorp, College Station, TX, USA). Two-tailed *P*-values <.05 were considered statistically significant.

RESULTS

Baseline characteristics

The study cohort comprised of 4912 incident dialysis patients with prior solid or haematological cancers (Fig. 1). Of these, 4246 (86%) patients did not experience cancer recurrence or develop new cancers, 323 (7%) patients experienced cancer recurrence and 343 (7%) developed new cancers dialysis initiation. There were 19 patients who experienced both cancer recurrence and new cancer and were included in the cancer recurrence group in Table 1. Fig. 2 shows the median time periods between the first cancer that occurred in the pre-dialysis period to dialysis commencement and from dialysis commencement to cancer recurrence/new cancer on dialysis or death/transplantation according to each cancer exposure group. The median follow-up time after dialysis commencement was the longest for patients with prior cancer and new cancer on dialysis, with the shortest follow-up time observed for those with recurrence on dialysis.

Table 1 shows the baseline characteristics of the study cohort, stratified by the three cancer status groups. The baseline demographics and comorbidities were similar across all three groups. The mean age was 68 years and >80% of patients were White. There was a temporal increase in the number of patients with prior cancers who had initiated dialysis ($n = 975$ in 2000–2004 versus $n = 1310$ in 2015–2019), but the proportions of total incident dialysis patients decreased from 11% with cancer recurrence and 7% with new cancer in the era between 2000 and 2005 to 2% with cancer recurrence and 5% with new cancer in the era between 2015 and 2019.

Frequency and incidence of prior cancer types

In patients with prior cancers, 501 (12%) had at least two prior cancer types [37 (0.9%) with three prior cancer types]. In patients with prior cancers and cancer recurrence, 43 (13.3%) patients had cancer recurrences for at least two prior cancer types [2 (0.6%) with recurrences in three prior cancer types], whereas for patients with prior cancers and subsequent new cancers, 39 (10.8%) had developed at least two new cancer types [1 (0.3%) developed three new cancer types]. Table 2 shows the frequency of the cancer types by exposure groups. For prior cancers, urinary tract (29%), prostate (18%) and colorectal cancers (14%) were the three most common prior cancer types, similar to those with prior cancer and cancer recurrence (36%, 20% and 14%, respectively). In contrast, urinary tract cancer was the most frequent new cancer type (25%), followed by respiratory cancer (14%) and melanoma (10%).

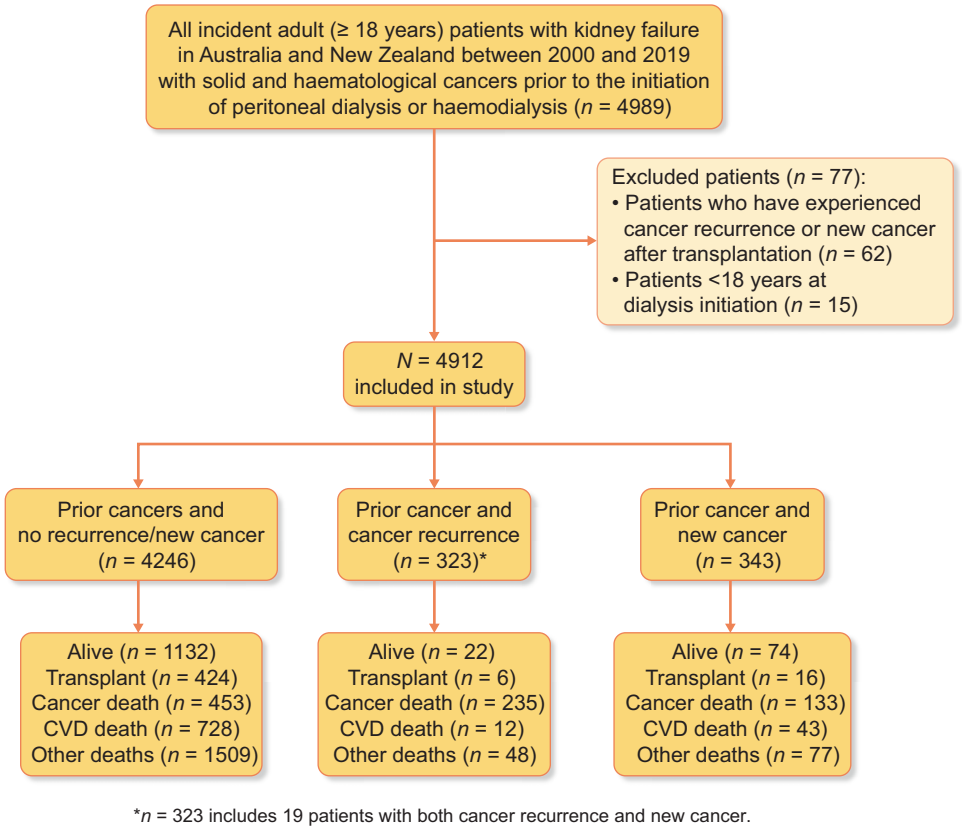

FIGURE 1: Flow diagram of the study cohort of incident patients with kidney failure and prior cancer.

Pattern of cancer recurrence in patients with prior cancer and cancer recurrence

The median time from dialysis commencement to cancer recurrence was 1.2 years (IQR 0.5–2.8). Of the 666 patients with colorectal cancer prior to dialysis initiation, 45 (7%) experienced a cancer recurrence. Similar recurrence rates were observed for urinary tract cancer [116/1421 patients (8%)], prostate cancer [64/863 patients (7%)], breast cancer [35/550 patients (6%)] and female genital cancers [17/351 patients (5%)] (Table 2).

Table 3 shows the patterns of cancer recurrence by prior cancer types. The majority of patients with colorectal, urinary tract, female genital, melanoma, respiratory, prostate and breast cancer recurrences experienced metastatic disease after dialysis initiation. The cause of death in 50% of these patients was attributed to cancer. For patients with colorectal cancer recurrence, 84% experienced metastatic disease and 76% of these deaths were directly attributed to cancer. For patients with urinary tract cancer recurrence, local recurrence and metastatic disease occurred in 19% and 70% of patients, respectively. For patients with prostate and breast cancer recurrences, 73% and 74% of patients experienced metastatic disease, respectively, with 59% and 77% of deaths attributed to these cancers.

Frequency and type of new cancer in patients with prior and new cancer

Table 4 shows the frequency and type of new cancers according to prior cancer types. The median time from dialysis commencement to new cancer occurrence was 2.0 years (IQR 0.7–4.0). Urinary tract and respiratory cancers were the most frequent new cancer types. For patients with prior colorectal cancers ($n = 61$), 14 (23%) and 10 (16%) developed respiratory and urinary tract cancers after dialysis initiation, respectively. For patients with prior prostate cancers, the most frequent new cancer type was urinary tract cancer (23%), followed by haematological (15%) and respiratory cancers (13%). For urinary tract, melanoma and breast cancers, 38%, 35% and 21%, respectively, were recorded to have developed a new cancer type within the same category as the prior cancer, but these new cancers occurred at a different site and region or may have been of a different cancer cell type to the prior cancer(s).

Incidences of all-cause and cancer mortality

Fig. 3 shows the outcomes of patients in the follow-up period. More than 60% of all patients died within the follow-up time, with cancer deaths being the predominant cause of death for patients with cancer recurrence and new cancer. In all, >5% of patients who experienced cancer recurrence or new cancer received kidney transplants. The other predominant causes of death in all three groups were deaths from cardiovascular disease and dialysis withdrawal. For patients with prior cancer who had died in the follow-up period, the median time from dialysis commencement to death was 2.9 years (IQR 1.5–5.1).

For patients with cancer recurrence post-dialysis who died in the follow-up period, the median time from cancer

Table 1. Baseline characteristics of the study cohort

Characteristics	Prior cancer only ($n = 4246$)	Prior cancer + recurrence ($n = 323$)	Prior cancer + new cancer ($n = 343$)	P-value
Demographics				
Age (years), mean (SD)	68.4 (11.4)	68.2 (10.1)	68.5 (10.2)	.39
Male, *n* %	2712 (63.9)	213 (65.9)	234 (68.2)	.22
Race, *n* %				.11
White	3520 (82.9)	279 (86.6)	300 (87.7)	
Indigenous	118 (2.8)	6 (1.9)	9 (2.6)	
Aotearoa New Zealand Māori	164 (3.8)	15 (4.7)	14 (4.1)	
Asian	185 (4.4)	18 (5.6)	8 (2.3)	
Others	172 (4.1)	4 (1.2)	11 (3.3)	
Missing	87 (2.0)	1 (<0.1)	1 (<0.1)	
BMI (kg/m^2), mean (SD)	28.0 (6.6)	27.7 (6.0)	28.2 (6.2)	.49
Missing, *n* %	39 (0.9)	4 (1.2)	3 (0.9)	
Cause of kidney failure, *n* (%)				.26
Glomerulonephritis	691 (16.3)	44 (13.6)	61 (17.8)	
Diabetic nephropathy	1065 (25.1)	68 (21.1)	82 (23.9)	
Cystic	172 (4.1)	16 (4.9)	14 (4.1)	
Hypertension/vascular	765 (18.0)	57 (17.6)	73 (21.3)	
Reflux nephropathy	70 (1.6)	6 (1.9)	8 (2.3)	
Others	1483 (34.9)	132 (40.9)	105 (30.6)	
Comorbid conditions, *n* (%)				
Cardiovascular disease	1533 (36.1)	99 (30.7)	120 (35.0)	.21
Missing data	6 (0.1)	0 (0.0)	0 (0.0)	
PVD	695 (16.4)	49 (15.2)	55 (16.0)	.21
Missing data	7 (0.1)	0 (0.0)	0 (0.0)	
Cerebrovascular disease	513 (12.1)	35 (10.8)	52 (15.2)	.21
Missing data	6 (0.1)	0 (0.0)	0 (0.0)	
Diabetes	1717 (40.4)	111 (34.4)	124 (36.1)	.03
Missing data	13 (0.3)	0 (0.0)	0 (0.0)	
Smoking status				.38
Non-smoker	1852 (43.6)	124 (38.5)	149 (43.6)	
Former	1985 (46.7)	162 (50.3)	163 (47.7)	
Current	382 (9.1)	36 (11.2)	30 (8.8)	
Missing	27 (0.6)	1 (<0.1)	1 (<0.1)	
Dialysis characteristics				
eGFR at initiation (mL/min/1.73 m^2), mean (SD)	7.8 (4.3)	7.3 (3.8)	7.6 (3.5)	.67
Missing, *n* %	25 (<0.1)	2 (<0.1)	4 (<0.1)	
Dialysis type at initiation, *n* %				.80
Peritoneal dialysis	961 (22.6)	69 (21.4)	73 (21.3)	
Home HD	26 (0.6)	1 (0.3)	1 (0.3)	
Satellite HD	3259 (76.8)	253 (78.3)	269 (78.4)	
Year of initiation, *n* %				<.01
2000–2004	797 (18.8)	105 (32.5)	73 (21.3)	
2005–2009	1088 (25.6)	110 (34.1)	107 (31.2)	
2010–2014	1142 (26.9)	80 (24.8)	100 (29.1)	
2015–2019	1219 (28.7)	28 (8.6)	63 (18.4)	

PVD, peripheral vascular disease; HD, haemodialysis.

recurrence to death was 0.5 years (IQR 0.2–1.7). The 1-, 3- and 5-year patient survival probabilities were 42% [95% confidence interval (CI) 36.6–47.4], 19% (95% CI 15.2–24.0) and 8% (95% CI 5.6–12.1), respectively. The 1-, 3- and 5-year cancer-free survival probabilities were 47% (95% CI 41.2–52.3), 27% (95% CI 22.3–32.9) and 18% (95% CI 13.4–24.1), respectively. Figs. 4A and B show the probabilities of all-cause and cancer mortality, respectively, with time to mortality from the onset of cancer recurrence.

For patients with new cancer post-dialysis who died in the follow-up period, the median time from new cancer diagnosis to death was 1.3 years (IQR 0.4–3.1). The 1-, 3- and 5-year patient survival probabilities were 65% (95% CI 60.1–70.4), 41% (95% CI 35.4–46.6) and 26% (95% CI 20.7–31.4), respectively. The 1-, 3- and 5-year cancer-free survival probabilities were 74% (95% CI 68.7–78.4), 61% (95% CI 54.9–66.6) and 53% (95% CI 45.7–59.4), respectively. Figs. 5A and B show the probabilities of all-cause and cancer mortality, respectively, with time to mortality from the onset of new cancer.

Sensitivity analysis: cancer recurrence pre-dialysis

Of the study cohort, 456 (9.3%) experienced cancer recurrence before dialysis commencement, with a greater proportion occurring in those who had experienced cancer recurrence after dialysis commencement (Supplementary data, Table S1). Fig. 2

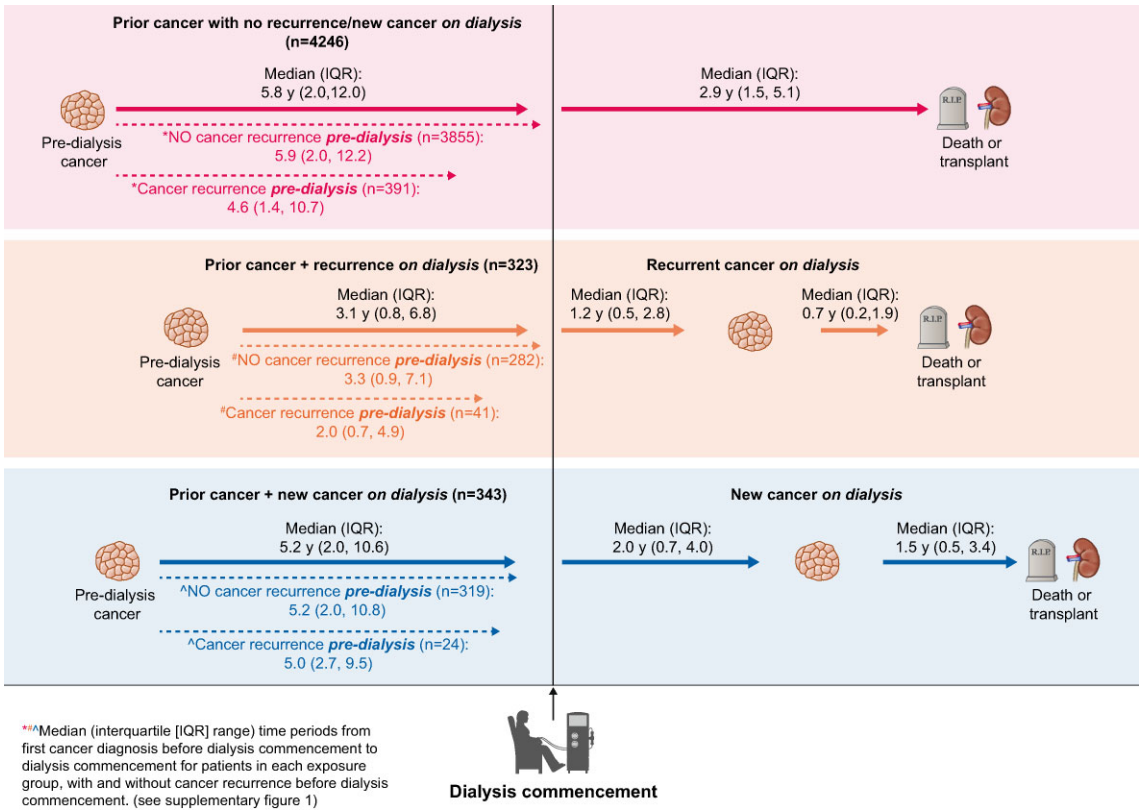

FIGURE 2: The median (IQR) time periods from cancer occurring pre-dialysis to dialysis commencement, cancer recurrence or new cancer on dialysis and death (or transplant) for all three cancer exposure groups.

Table 2. Frequencies of prior cancer types of the exposure groups

Prior cancer type	Prior cancer only ($n = 4246$)	Prior cancer + recurrence ($n = 323$)	Prior cancer + new cancer ($n = 362$)[a,b]
Colorectal	596 (14.0)	45 (13.9)	25 (6.8)
Urinary	1214 (28.6)	116 (35.9)	91 (25.1)
Female genital	318 (7.5)	17 (5.3)	16 (4.4)
Melanoma	296 (7.0)	17 (5.3)	36 (9.9)
Respiratory	127 (3.0)	23 (7.1)	50 (13.8)
Haematological	255 (5.9)	15 (4.7)	35 (9.7)
Myeloma	65 (1.5)	8 (2.5)	17 (4.7)
Lymphoma	142 (3.3)	7 (2.2)	8 (2.2)
Others	48 (1.1)	0 (0.0)	10 (2.8)
Prostate	773 (18.2)	64 (19.8)	26 (7.2)
Breast	492 (11.6)	35 (10.8)	23 (6.4)
Brain	20 (0.5)	0 (0.0)	3 (0.8)
Thyroid	83 (2.0)	1 (0.3)	9 (2.5)
Other gastrointestinal	160 (3.8)	3 (0.9)	33 (9.1)
Others	450 (10.6)	32 (9.9)	54 (14.9)

[a]Includes the additional 19 patients with both cancer recurrence and new cancers. [b]Only new cancer types are shown.

and Supplementary data, Figure S1 and Table S1 show the timeline and median time periods between first cancer that occurred in the pre-dialysis period to cancer recurrence before dialysis commencement (if present) and to dialysis commencement. For patients who did not develop cancer recurrence or new cancer after dialysis commencement, those who had experienced cancer recurrence before dialysis commencement were more likely to die from cancer compared with those who did not experience cancer recurrence before dialysis commencement. For patients who had developed cancer recurrence or new cancer after dialysis commencement, the proportion who died from cancer was similar to those with or without cancer recurrence before dialysis commencement.

For patients with prior cancer and no recurrence/new cancer on dialysis but who had experienced cancer recurrence prior to dialysis commencement, the respective 1-, 3- and 5-year

Table 3. Frequencies and outcomes of kidney failure patients with prior cancer(s) and cancer recurrence

	Cancer recurrence (sites)			
Prior cancer type	Local, *n* (%)	Lymph node, *n* (%)	Systemic (metastasis), *n* (%)	Cancer deaths, *n* (%)
Colorectal ($n = 45$)	5 (11.1)	1 (2.2)	38 (84.4)	34 (75.6)
Urinary ($n = 116$)	22 (19.0)	5 (4.3)	81 (69.8)	84 (72.4)
Female genital ($n = 17$)	1 (5.9)	1 (5.9)	13 (76.5)	11 (64.7)
Melanoma ($n = 17$)	2 (11.8)	2 (11.8)	11 (64.7)	11 (64.7)
Respiratory ($n = 23$)	3 (13.0)	0 (0.0)	16 (69.6)	18 (78.3)
Haematological	2 (13.3)	0 (0.0)	7 (46.7)	6 (40.0)
Myeloma ($n = 8$)	0 (0.0)	0 (0.0)	2 (25.0)	2 (25.0)
Lymphoma ($n = 7$)	2 (28.6)	0 (0.0)	5 (71.4)	4 (57.1)
Others ($n = 0$)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prostate ($n = 64$)	8 (12.5)	1 (1.6)	47 (73.4)	38 (59.4)
Breast ($n = 35$)	3 (8.6)	4 (11.4)	26 (74.3)	27 (77.1)
Brain ($n = 0$)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid ($n = 1$)	0 (0.0)	0 (0.0)	1 (100)	1 (100.0)
Other gastrointestinal ($n = 3$)	0 (0.0)	1 (33.3)	2 (66.7)	2 (66.7)
Others ($n = 32$)	5 (15.6)	4 (12.5)	16 (50.0)	22 (68.7)

Each cancer type is only coded as one type of recurrence (metastasis > lymph node > local).

patient survival probabilities from dialysis commencement were 76% (95% CI 71.7–80.2), 49% (95% CI 43.8–54.1) and 32% (95% CI 26.7–36.8), respectively, and the respective 1-, 3- and 5-year cancer-free survival probabilities were 85% (95% CI 80.8–88.1), 71% (95% CI 66.0–76.0) and 63% (95% CI 56.9–68.9). These compared less favourably than with patients who had not experienced cancer recurrence prior to dialysis commencement, with respective 1-, 3- and 5-year patient survival probabilities of 91% (95% CI 89.7–91.6), 65% (95% CI 63.1–66.3) and 44% (95% CI 42.2–45.8), and respective 1-, 3- and 5-year cancer-free survival probabilities of 97% (95% CI 96.4–97.5), 92% (95% CI 91.0–93.0) and 89% (95% CI 87.7–90.2). Figs. 6A and B show the probabilities of all-cause and cancer mortality for patients with prior cancer with and without cancer recurrence pre-dialysis, respectively, with regards to time to mortality from dialysis commencement.

DISCUSSION

In this contemporaneous study of incident dialysis patients with prior cancer spanning two decades, colorectal, prostate, respiratory and urinary tract cancers were the most frequent prior cancer types. Patients who had experienced cancer recurrence had the poorest survival, with >80% of deaths attributed to cancer. Of those who developed new cancer, respiratory and urinary tract cancers were the most frequent new cancer types. The 3-year patient survival probability following the detection of cancer recurrence after dialysis commencement was <20%, whereas in patients who experienced a new cancer after dialysis commencement, the 3-year patient survival probability after new cancer diagnosis was 41%. In patients with prior cancer who had no recurrence or new cancer on dialysis, those who experienced cancer recurrence before dialysis commencement were more likely to experience premature death on dialysis compared with patients without recurrence, predominantly from cancer death.

Epidemiological studies have shown that the SIRs of several cancers were substantially increased in patients with kidney failure, with the magnitude and pattern of increased risk more apparent in patients who had received kidney transplants [SIR 3.27 (95% CI 3.09–3.46)]. In contrast, the SIRs for cancer in patients with kidney failure prior to and after commencing dialysis were 1.16 (95% CI 1.08–1.25) and 1.35 (95% CI 1.27–1.45), respectively, with the risks of many common cancers such as colorectal, respiratory, breast and prostate cancers not consistently increased during these periods [16]. Uraemia-induced immune dysfunction and inflammation resulting in reduced antitumour surveillance were likely responsible for the increased risk of cancer in patients with kidney failure, with the added combined effect of chronic immunosuppression contributing to the greater cancer risk in those who have received kidney transplants [3, 4, 23, 24]. The SMRs of patients with kidney failure who commenced dialysis were almost three times higher compared with age- and sex-matched controls in the general population, with the excess mortality predominantly observed in cancers that were directly responsible for kidney failure, such as multiple myeloma [14]. For patients with multiple myeloma, the predicted 5-year survival ranged between 13% and 28%, with the poorest survival occurring in older patients [25]. However, the clinical outcome of patients with kidney failure and prior cancers other than multiple myeloma remains poorly defined, with our study reporting that the survival on dialysis following the development of cancer recurrence or new cancer was relatively poor. Colorectal and prostate cancers were the most frequent prior cancer types, which parallels the common cancers reported in the general population [26], although urinary tract cancers were also frequently observed, likely related to the consistent pattern of increased risk of kidney parenchymal cancers in patients receiving dialysis [27]. In patients who experienced cancer recurrence, the 5-year patient survival on dialysis following the diagnosis of cancer recurrence was <10%. In patients who developed new cancer after dialysis commencement, the 5-year patient survival on dialysis following the diagnosis of new cancer was 26%. These suggest that the survivals of patients who developed cancer recurrence or new cancer are relatively poor, with fewer than one in four surviving beyond 5 years on dialysis. Nevertheless, these estimates may have been relatively imprecise because of the presence of immortal time bias for patients who have developed new cancer, and there were likely differences in the consideration and management of patients with kidney failure and prior cancers, a proportion of which may have never commenced dialysis treatment. Comparisons of the recurrence and survival rates

Table 4. Frequencies and types of new cancers occurring in kidney failure patients with prior cancer(s) after dialysis initiation

	New cancer type											
Prior cancer type	Colorectal	Urinary	Female genital	Melanoma	Respiratory	Haematological	Prostate	Breast	Brain	Thyroid	Other GI	Others
Colorectal ($n = 61$)	2	10	2	5	14	7	5	2	0	0	8	10
Urinary ($n = 105$)	9	40	2	5	17	5	8	8	1	1	12	12
Female genital ($n = 20$)	0	8	4	1	1	0	0	4	0	0	1	5
Melanoma ($n = 31$)	2	3	0	11	0	5	4	0	0	0	1	10
Respiratory ($n = 6$)	2	0	1	1	1	0	1	0	0	1	0	0
Haematological ($n = 13$)	1	1	0	0	1	3	4	0	1	1	1	0
Prostate ($n = 60$)	5	14	1	6	8	9	0	0	0	1	8	12
Breast ($n = 34$)	2	5	5	3	4	4	0	7	1	5	0	1
Brain ($n = 0$)	0	0	0	0	0	0	0	0	0	0	0	0
Thyroid ($n = 6$)	0	3	0	0	1	0	0	1	0	0	0	1
Other GI ($n = 7$)	1	4	0	0	0	0	1	1	0	0	0	0
Others ($n = 19$)	1	3	0	4	3	2	2	0	0	0	2	4
Total	25	91	15	36	50	35	25	23	3	9	33	55

In those with the same type(s) of new cancer(s) as prior cancer(s), the new cancer(s) was recorded in the registry as a cancer that may have occurred at a different site and/or region or different cancer cell type than the prior cancer.

following cancer recurrence between patients on dialysis and the general population are challenging. For example, the recurrence rate for stages 1–3 colorectal cancer in the general population is between 15 and 23%, with the majority of cancer recurrence occurring within the first 2 years after surgery. The 5-year survival after colorectal cancer recurrence is between 25 and 79%, and those with early recurrence generally have a poorer prognosis [28, 29]. Although it would seem that survival after cancer recurrence in dialysis patients is much worse (<10% at 5 years), this relative comparison must be interpreted with caution. The presence of kidney failure and the severity of related competing comorbidities, clinicians' and patients' preferences with regards to the uptake of anti-cancer treatment(s) and the adequacy or efficacy of anti-cancer treatment (including the lack of trial data in patients with kidney failure and the potential hesitancy in prescribing novel anti-cancer treatment such as immunotherapies [30], excess adverse events requiring dose reduction, inadequate duration/truncated treatment regimen) may have contributed to the survival disadvantage. However, these factors are not available in the ANZDATA Registry and will need to be explored in greater detail.

In a study of 21 415 patients with kidney failure who received kidney transplants in Australia and New Zealand between 1965 and 2012, 651 (3%) patients had a prior cancer history. Only 13% developed cancer post-transplant, with <1% experiencing cancer recurrence. The risks of all-cause and cancer mortality were similar among recipients who had experienced cancer recurrence or had developed new cancer, which is likely to reflect the selection and listing practices of patients with prior cancers for transplantation [18]. Consistent with these findings, our study shows that up to 10% of patients who commenced dialysis with prior cancers received kidney transplants, and was even less in those with cancer recurrence (2%) or who had developed new cancers (5%) on dialysis.

The pattern and outcome of cancer recurrence and development of new cancer in patients with prior cancer who receive dialysis remain unknown. Even though <10% of patients with prior colorectal, urinary tract, prostate and breast cancers experienced recurrence, the outcomes of patients who had experienced recurrence were poor. In patients with cancer recurrence, >70% of those with prior colorectal, urinary tract, prostate and breast cancers experienced metastatic disease after dialysis initiation, with almost 80% of deaths directly attributed to cancer recurrence. For patients who developed a new cancer, urinary tract and respiratory cancers were the most frequent new cancer types. In patients with prior urinary tract cancer or melanoma, almost 40% reported a new cancer occurring in the same site(s) or of the same type, suggesting the possibility of misclassification bias. However, it is possible that these new cancers (of the same type or at the same site) may represent cancers occurring in a different site (melanoma occurring in the leg and back) or at a different site in the same region (e.g. prior cancer in the kidney with new cancer occurring in the bladder), suggesting that the classification of recurrent versus new primary cancers is often challenging. The ANZDATA Registry does not verify the accuracy of cancer reporting (recurrence or new cancers) or reliably collect data on the tumour cell type, stage, grade and treatments/responses of prior cancer(s), and information relating to the screening and follow-up practices of patients with prior cancers are unknown.

The decision to initiate dialysis in patients with prior cancer is often individualized, involving a shared decision-making process among patients, caregivers and the healthcare team (often including oncologists and nephrologists). In patients with

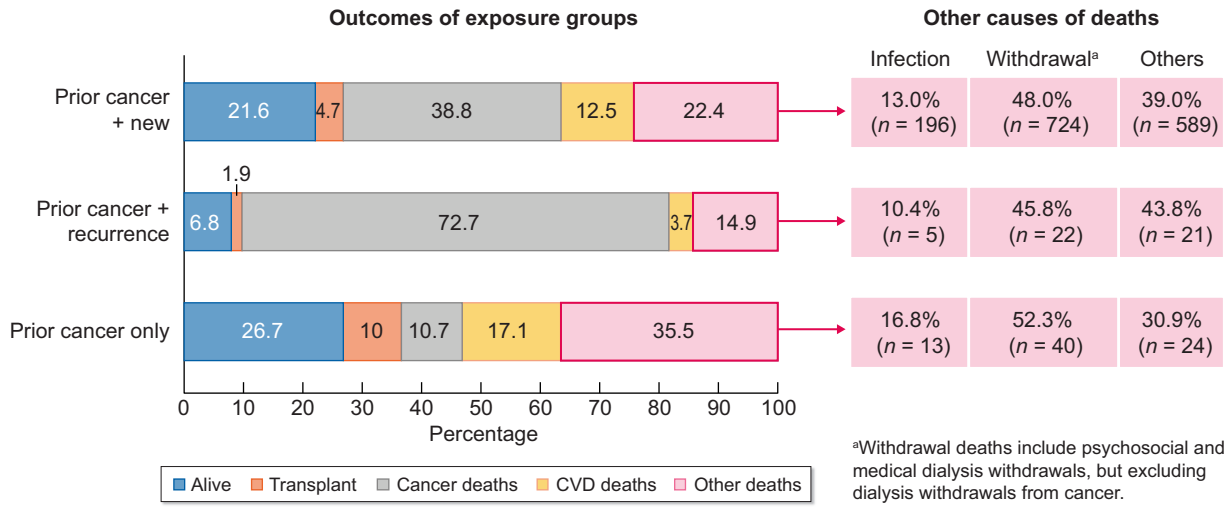

FIGURE 3: Bar graph showing the outcomes of patients with kidney failure and prior cancer only, prior cancer and cancer recurrence and prior and new cancer during the follow-up period. For the outcome of 'other deaths', the proportion of deaths from infection, withdrawal and other causes is shown for each exposure group.

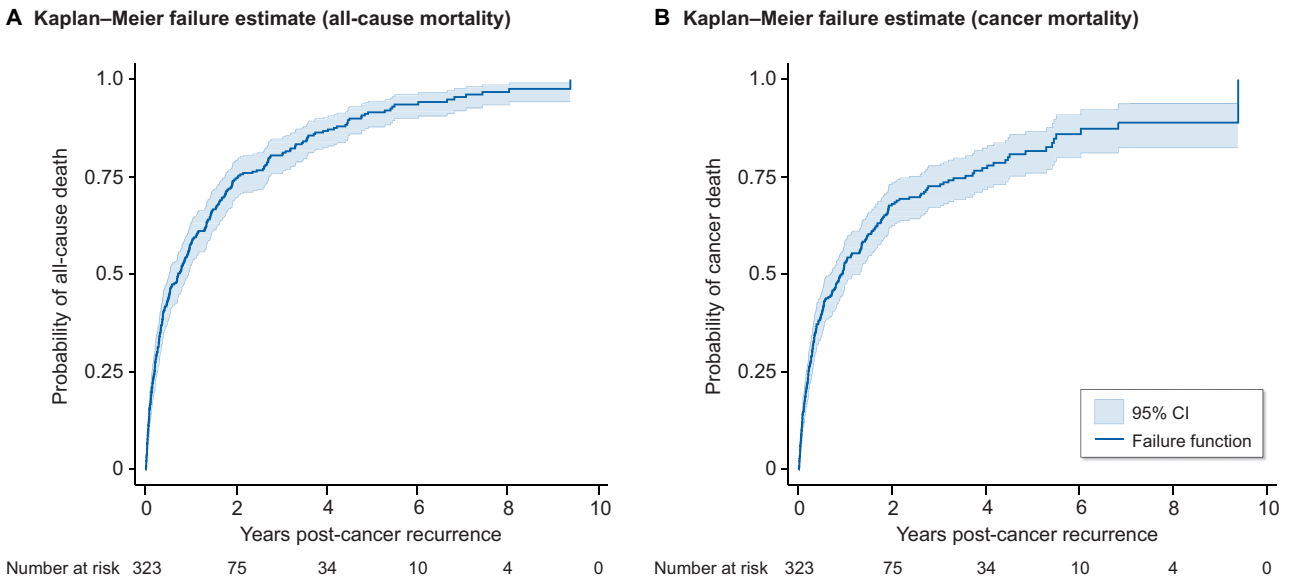

FIGURE 4: Kaplan–Meier failure curve (with 95% CI band and number at risk) for **(A)** all-cause and **(B)** cancer mortality for patients with kidney failure who experienced a cancer recurrence following commencement of dialysis. Time 0 represents the time of diagnosis of cancer recurrence.

prior cancer who had experienced cancer recurrence prior to starting dialysis, the decision to initiate dialysis is often complex, balancing between the expected anti-cancer treatment response and survival with the competing survival disadvantage of kidney failure and comorbidities. The higher incidence of overall (74% versus 62%) and cancer (29% versus 9%) deaths in patients with pre-dialysis cancer recurrence compared with those without recurrence pre-dialysis may reflect the biological aggressiveness of the recurrent cancer. However, there are likely to be systematic and biological differences in the cancer, treatment and clinicians'/patients' preferences with regards to dialysis and anti-cancer treatments (including the characteristics of patients with kidney failure and cancer who had declined dialysis) and the presence of survival bias (including immortal time bias in those who have experienced and survived the cancer recurrence before dialysis commencement) that will require further consideration but are likely to influence the accuracy of the survival estimates. Even though our study does not provide clear insights into the pathogenesis of cancer recurrence or the development of new cancer in patients with kidney failure, it does provide important survival estimates of kidney failure patients with prior cancers following dialysis initiation, which is often practical when determining whether dialysis treatment may be an appropriate option for these patients. In addition, the poor prognostic significance of cancer recurrence suggests the need to investigate potential clinical and genomic risk factors for recurrence, but the value and practicality of targeted (and adherence to) screening measures remain unclear in patients with kidney failure and prior history of cancer.

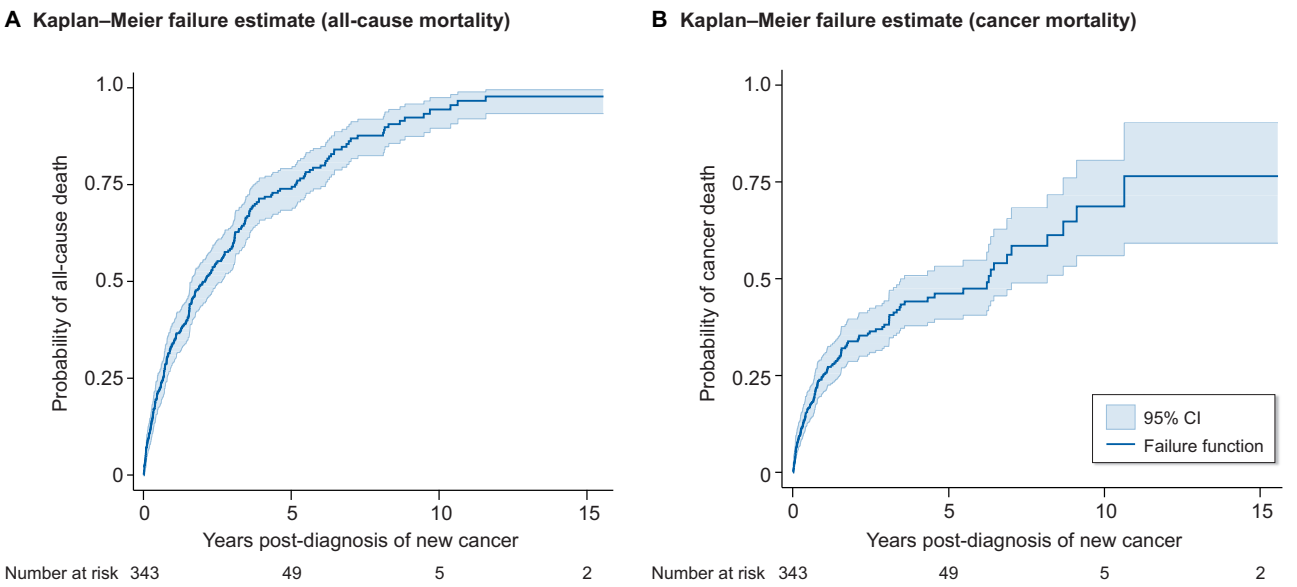

FIGURE 5: Kaplan–Meier failure curve (with 95% confidence interval band and number at risk) for **(A)** all-cause and **(B)** cancer mortality for patients with kidney failure who experienced a new cancer following commencement of dialysis. Time 0 represents the time of new cancer diagnosis.

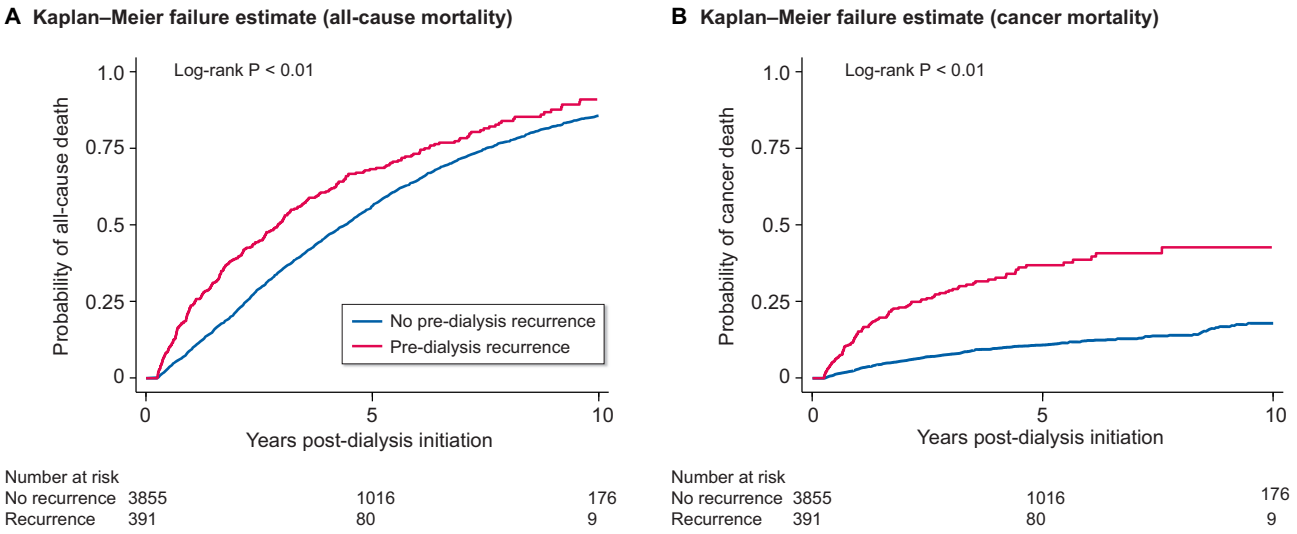

FIGURE 6: Kaplan–Meier failure curves (with number at risk) for **(A)** all-cause and **(B)** cancer mortality for patients with kidney failure and prior cancer with no recurrence/new cancer on dialysis, stratified by cancer recurrence status pre-dialysis.

Our study has several notable limitations. Selection bias remained likely because of possible systematic differences in the acceptance for dialysis and management of patients with kidney failure and prior cancers, which were likely to differ between clinicians and treatment sites. There were likely to be other unmeasured and residual patient and cancer treatment factors, such as cancer stage, adherence/response to cancer treatment(s), severity of comorbid conditions, accessibility to healthcare resources and differences in clinician and patient preferences for treatment, which were not collected by the ANZDATA Registry but were likely to have influenced our study findings and estimates.

CONCLUSION

Our study findings provide evidence of the prognostic significance of a history of prior cancer in patients with treated kidney failure, with a significant survival disadvantage being observed for patients who experienced cancer recurrence. The increased risks of cancer recurrence and mortality documented in relation to specific prior cancer subtypes suggest the need to carefully monitor these high-risk patients, although the clinical relevance of the adherence to appropriate cancer screening strategies and potential implementation of a targeted cancer screening approach in selected patients is unknown and cannot be recommended based on our study findings. The

identification of mechanistic pathways through which dialysis treatment may modulate cancer prognosis in patients with prior cancer remains unclear and a subject of immense scientific interest.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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CONFLICT OF INTEREST STATEMENT

No financial conflicts of interest are identified for all authors for this manuscript.

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