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CLINICAL RESEARCH

Calciphylaxis Episodes in the Australia and New Zealand Dialysis and Transplant Registry

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Introduction: Calciphylaxis is a rare disorder associated with significant morbidity and mortality. Data registries are an invaluable source of information for rare diseases. We reviewed cases of calciphylaxis recorded in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) and evaluated associations and outcomes of this condition.

Methods: Data was obtained on all cases of calciphylaxis reported between 2019 and 2022 in Australian and New Zealand patients on kidney replacement therapy (KRT). This cohort was compared to all patients in the registry who received KRT from 2019 to 2022 without an episode of calciphylaxis. Cox proportional hazards regression including a time-varying covariate for calciphylaxis episode was conducted for mortality with models restricted to patients on dialysis only.

Results: From 2019 to 2022, 333 patients had calciphylaxis episodes reported. Overall incidence rate for patients on dialysis was 4.5 (4.1–5.1) episodes per 1000 patient-years on dialysis. Median age was 63 (interquartile range [IQR]: 55–73) years, 54% were female, 66% had diabetes, 59% were obese (body mass index [BMI] $\geq$ 30 kg/m^2) and 77% were receiving hemodialysis (HD) treatment. Compared to patients without calciphylaxis (n = 46,526), patients with calciphylaxis were more likely to be older, female, and have diabetes, greater BMI, coronary artery, and peripheral vascular disease. The median time to calciphylaxis was 3.2 (IQR: 0.9–6.7) years after KRT commencement. Half of the patients with calciphylaxis died by 12 months from diagnosis. Adjusted hazard ratio (HR) of mortality for patients on dialysis with calciphylaxis <1 year and 1 to 4 years after an episode was 5.8 (4.9–6.9) and 1.5 (1.0–2.1), respectively compared to patients on dialysis without calciphylaxis.

Conclusion: Calciphylaxis is a rare but life-threatening condition in people on KRT with the greatest mortality burden within 12 months of diagnosis.

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Calciphylaxis is a rare disorder predominantly affecting individuals with chronic kidney disease, particularly those with kidney failure on dialysis. Calciphylaxis has also been described less commonly in people with normal kidney function and after kidney transplantation.[1] Calciphylaxis is characterized by

painful skin lesions that frequently advance to nonhealing necrotic ulcers. Due to the progressive and unrelenting nature of cutaneous calcification, calciphylaxis is associated with significant morbidity and mortality related to extreme pain, nonhealing wounds, and lengthy hospitalizations.[2,3] One-year mortality is reported to be as high as 45% to 80%, mainly due to complications of wound sepsis, adverse effects of treatment, and treatment withdrawal due to uncontrollable disease burden.[2,4]

Management of calciphylaxis is challenging and there are currently no completed, randomized controlled trials to guide diagnosis or treatment, with evidence largely based on case series or observational studies that are predominantly retrospective in nature.[4,5] There are also no uniform criteria for diagnosis of calciphylaxis, the condition largely being a clinical diagnosis based on the appearance of cutaneous lesions which range in appearance from a dusky skin discoloration to stellate, malodorous ulcers with black eschars.[6] Occasionally, imaging or skin biopsy is performed for confirmation, although clinicians are often fearful that a biopsy will worsen skin lesions.[7] Treatment often involves wound care, measures to optimize nutrition, symptom management, optimizing treatment of mineral and bone abnormalities, and extra dialysis; however, these are often inadequate because many patients eventually succumb to progressive disease.

Registries for calciphylaxis may provide important insights and information to increase knowledge about the epidemiology and clinical aspects of calciphylaxis and may help to optimize diagnosis and therapeutic management.[4,8] Calciphylaxis registries have been established in several countries to provide real-world information regarding risk factors, diagnosis, and management of this rare disease. The German Calciphylaxis Registry was the first online registry,[8] however, this registry was limited to collecting data at a single time point and did not collect data on longer-term outcomes, including mortality. The Australian Calciphylaxis Registry demonstrated common risk factors for calciphylaxis from data collected over 5 years from 7 participating institutions.[4] The primary limitation of this study was that although the Australian Calciphylaxis Registry was developed as a nationwide registry, only 7 nephrology centers were involved, and therefore the true incidence, risk factors and outcomes of calciphylaxis in Australian and Aotearoa, New Zealand patients remain unknown.

The ANZDATA Registry captures clinical information, including outcomes for all people receiving KRT in Australia and Aotearoa, New Zealand. In 2019, episodes of calciphylaxis were added to the formal data ANZDATA collects. Data collection was limited to the occurrence and date; the diagnostic criteria were simply "in the opinion of the treating physician." The aims of this study were to review all cases of calciphylaxis recorded in the ANZDATA Registry from 2019 to 2022, to determine the incidence of calciphylaxis, evaluate associations and outcomes of patients with kidney failure with this condition in a prospective cohort study using registry-based data, and to compare characteristics and outcomes to patients with kidney failure in the Registry with no calciphylaxis.

METHODS

Study Design

An observational cohort study was conducted involving Australian and Aotearoa, New Zealand patients with kidney failure on KRT and reported episodes of calciphylaxis. The ANZDATA Registry was utilized and full details of the structure and methods of ANZDATA have been published elsewhere.[9] In brief, ANZDATA collects demographic and clinical information about all patients who are resident in Australia or Aotearoa, New Zealand and are receiving long-term KRT for kidney failure with either dialysis or kidney transplantation. Patient data is provided by the patient's treating unit through an annual survey. Additional data is also provided in "real-time," for prespecified events, such as change in dialysis modality, or patient death. This analysis of the ANZDATA Registry was approved by the local ethics committee (Melbourne Health Human Research Ethics Committee reference number HREC/77298/MH-2021).

Study Population and Outcomes

Australian and Aotearoa, New Zealand patients with kidney failure receiving KRT during 2019 to 2022 (on HD, peritoneal dialysis [PD] or kidney transplant recipients) and recorded as having episodes of calciphylaxis in the ANZDATA registry between 2019 and 2022 inclusive were the particular focus of this study. This time period was chosen because specific data collection of calciphylaxis episodes using the ANZDATA Registry commenced in 2019. Although it was possible for patients to report their first calciphylaxis episode from earlier than 2019, for this study only patients with their first reported calciphylaxis episode in 2019 to 2022 were included. The main outcomes for this study were incidence of first calciphylaxis episode and overall mortality. Baseline characteristics for the incidence analysis were evaluated at the start of that observation period (accounting for changes in modality, KRT duration, and parent center), and for the mortality analysis at the start of follow-up time after a calciphylaxis episode. Characteristics included age,

sex, primary kidney disease, country, ethnicity, smoking status, BMI, diabetes mellitus, coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Details pertaining to KRT were also obtained, including modality, duration, and whether the patient was a late referral for KRT. Late referral was defined as referral to a nephrologist within 3 months of commencing KRT. For the outcome of mortality, the cohort was restricted to adult patients on dialysis during 2019 to 2022 only, who commenced dialysis from 2002 to 2022, excluding patients who had previously failed kidney transplants. The criteria to commence dialysis from 2002 was chosen because this was the earliest year in which a dialysis patient with a reported calciphylaxis episode started dialysis.

Statistical Analysis

Categorical variables were expressed as numbers and percentages and were compared using Chi-square tests. Continuous variables were expressed as median with IQR due to their skewed distribution and were compared using the Wilcoxon rank-sum test. A multivariate mixed effects Poisson regression model was used to investigate the effects of age, sex, ethnicity, late referral, BMI, cause of kidney failure, diabetes as a comorbidity only, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, smoking, state/country, KRT modality, era of commencement of KRT (1967–2002, 2003–2012, 2013–2022) and time since KRT start (<1 year, 1 – <3 years, 3 – <10 years, 10 years+) on the incidence of first calciphylaxis episode. Backward elimination of nonsignificant variables resulted in the final model. A random effect was included for parent center of treatment, with robust standard errors used. Any changes in time since KRT start, modality, and parent center resulted in a separate observation period. Age, BMI, and comorbidities were determined as at the start of the observation period, according to the latest information available.

Survival analysis for the outcome of mortality was conducted for patients on dialysis to provide a description of long-term survival and to estimate median survival time after calciphylaxis episode. To investigate the effect of age, sex, BMI, ethnicity, time on dialysis at baseline (KRT start, after KRT start and <1 year, 1 – <3 years, 3 – <10 years, 10 years+), biochemical parameters within target ranges at baseline (serum calcium and phosphate; and hemoglobin), late referral, cause of kidney failure, smoking, state/country, dialysis modality at baseline (HD or PD), era of dialysis commencement (2002–2012 or 2013–2022) and comorbidities (diabetes as a comorbidity only, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and chronic lung disease) at baseline on survival time, adjusted survival analysis (Cox proportional hazards regression) was performed. For this analysis, a time-varying covariate was used for calciphylaxis episode exposure, with the exposure commencing at first episode date and continuing thereafter. Survival time commenced on January 1, 2019, for patients on prevalent dialysis, or at dialysis start for patients on incident dialysis from 2019 to 2022. Follow-up continued until the outcome of mortality, with censoring for transplantation, loss to follow-up, kidney function recovery or on December 31, 2022. Testing for proportional hazards was done using Schoenfeld residuals. Complete case analyses were performed, excluding patients with missing values for any variables. Subgroup analyses were also performed in patients on KRT without peripheral vascular disease, given the potential for this condition to result in ulceration, which could be a differential diagnosis for calciphylaxis. All analyses were performed using Stata Version 17.0 (StataCorp LLC, College Station, TX).

RESULTS

Incidence of Calciphylaxis

Of 46,859 patients receiving KRT in Australia or Aotearoa, New Zealand in 2019 to 2022 (including prevalent patients at the start of 2019 and incident KRT patients from 2019–2022), there were 333 incident episodes of calciphylaxis. Of the 333 KRT patients with calciphylaxis, 23 patients were reported to have had 2 episodes of calciphylaxis (1 episode each during 2 separate years, because it was only possible to report 1 episode per year in the ANZDATA Registry). Therefore, there was a total of 356 episodes of calciphylaxis for the study cohort. The second episodes were not accounted for in the analyses. There were an additional 16 patients with chronic kidney disease who were reported in the Registry to have developed calciphylaxis just before commencing KRT, and 1 patient reported to have developed calciphylaxis after withdrawal from dialysis. These 17 patients were excluded from the analysis.

The overall incidence rate for patients on dialysis from 2019 to 2022 was 4.5 (95% confidence interval: 4.1–5.1) episodes per 1000 patient-years on dialysis (Table 1). The incidence rates by dialysis modality were 4.5 (4.0–5.1) episodes per 1000 patient-years for HD and 4.7 (3.7–6.1) episodes per 1000 patient-years for PD. The incidence rates for females and males receiving dialysis were 6.1 (5.2–7.1) and 3.5 (3.0–4.1) episodes per 1000 patient-years on dialysis respectively. The incidence rate for kidney transplant recipients was 0.2

Table 1. Incidence rates of calciphylaxis

Patient characteristics	Incidence rates (IQR) (episodes per 1000 patient-years)
Overall, for patients on dialysis	4.5 (4.1–5.1)
Dialysis modality	
HD	4.5 (4.0–5.1)
PD	4.7 (3.7–6.1)
Gender for patients on dialysis	
Female	6.1 (5.2–7.1)
Male	3.5 (3.0–4.1)
Time on KRT for patients on dialysis	
<1 year	6.3 (5.1–7.7)
1 to <3 years	3.4 (2.6–4.3)
3 to <10 years	4.6 (3.8–5.5)
≥10 years	4.2 (3.0–5.7)
Transplant recipients	0.2 (0.1–0.4)

HD, hemodialysis; IQR, interquartile range; KRT, kidney replacement therapy; PD, peritoneal dialysis.

(0.1–0.4) episodes per 1000 patient-years. Adjusted incidence rate ratios for the first episode of calciphylaxis in patients on KRT are shown in Figure 1. Factors significantly associated with an increased incidence of calciphylaxis in the adjusted model included female gender (incidence rate ratio 2.0 [95% confidence interval: 1.6–2.7]), overweight (1.6 [1.1–2.1]) and obese (2.5 [1.8–3.4]) BMI, diabetes (1.4 [1.1–1.8]), coronary artery disease (1.4 [1.1–1.7]), and peripheral vascular disease (1.5 [1.2–1.9]). Factors significantly associated with a lower incidence of calciphylaxis in the adjusted model included having a functioning kidney transplant (0.063 [0.037–0.11] vs. HD), receiving KRT for 1 to <3 years (0.53 [0.41–0.69]) or 3 to <10 years (0.73 [0.57–0.93]) compared to less than 1 year and all ethnicity categories other than Australia/New Zealand European and Māori.

Characteristics of Patients With Calciphylaxis

Median patient age for those with calciphylaxis was 63 (IQR: 55–73) years, with 53.5% female (Table 2). The majority of patients were Australia/New Zealand European (64.0%) and 58.8% had a BMI in the obese range (≥30 kg/m^2). Calciphylaxis cases predominantly involved patients on HD (76.6%), with 19.2% of patients on PD and 4.2% being kidney transplant recipients. Diabetic kidney disease was the most common cause of kidney failure (48.3%), although 65.8% of patients with calciphylaxis had diabetes. Patients with calciphylaxis also had higher rates of other significant comorbidities, including coronary artery disease (51.4%), cerebrovascular disease (17.7%), peripheral vascular disease (37.2%), and chronic lung disease (22.2%). Those on dialysis first developed calciphylaxis at a median of 3.2 (IQR: 0.9–6.3) years after KRT commencement. Kidney transplant recipients first developed calciphylaxis at a median of 6.6 (IQR: 3.5–21.9) years posttransplantation.

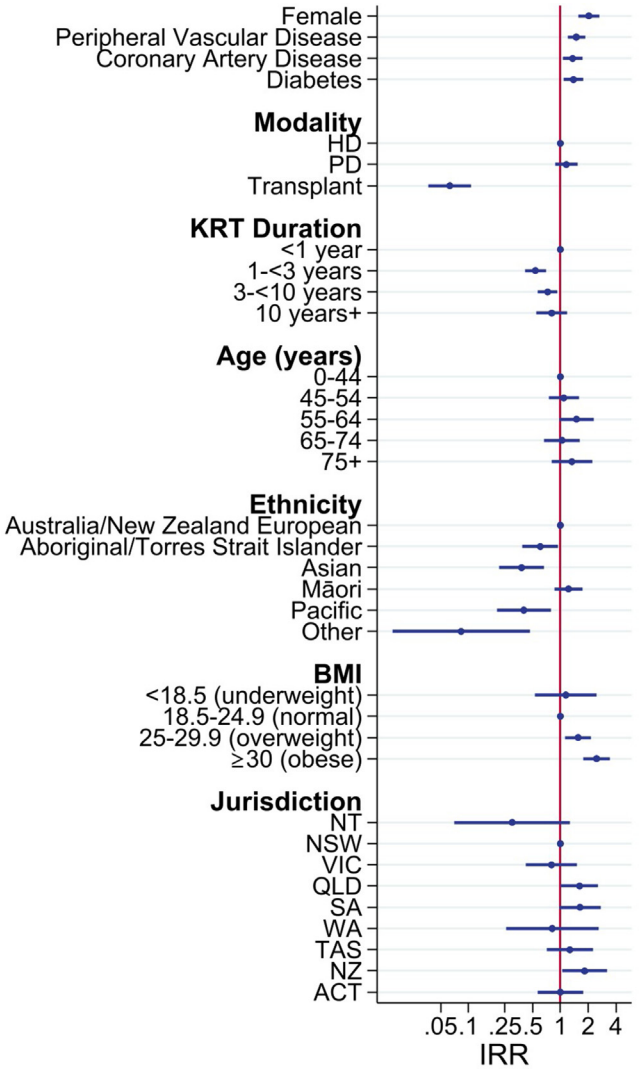

Figure 1. Incidence rate ratios using multivariate mixed effects Poisson model for incidence. BMI, body mass index; HD, hemodialysis; IRR, incidence rate ratio; KRT, kidney replacement therapy; PD, peritoneal dialysis; NZ, New Zealand; Australia States and Territories [ACT, Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia]. #43,916 patients included as missing data in some variables.

Comparison Between Patients With and Without Calciphylaxis

Compared to patients on KRT without calciphylaxis in Australia and Aotearoa, New Zealand, recorded as receiving KRT in the ANZDATA Registry between 2019 and 2022 ($n = 46{,}526$), patients with calciphylaxis were more likely to be older and female, have a higher BMI and a history of diabetes as well as peripheral vascular, cerebrovascular, and coronary artery disease (Table 2). There was a greater proportion of Māori patients with

Table 2. Characteristics of study cohort – comparison of patients with and without calciphylaxis

Characteristics	Calciphylaxis (n = 333)	No Calciphylaxis (n = 46,526)	P value
Age, median (IQR), yr	63 (55–73)	61 (49–71)	<0.001
Sex (female)	178 (53.5)	17,903 (38.5)	<0.001
Ethnicity (n = 45,262)			<0.001
Australia/New Zealand European	208 (64.0)	28,719 (63.9)	
Aboriginal/Torres Strait Islander	28 (8.6)	3732 (8.3)	
Asian	12 (3.7)	5561 (12.4)	
Māori	60 (18.5)	2278 (5.1)	
Pasifika	16 (4.9)	2785 (6.2)	
Other	1 (0.3)	1862 (4.1)	
Country			<0.001
Australia	240 (72.1)	38,973 (83.8)	
New Zealand	93 (27.9)	7553 (16.2)	
Primary kidney disease (n = 46,483)			<0.001
Diabetes	161 (48.3)	14,736 (31.9)	
Glomerular disease	56 (16.8)	12,287 (26.6)	
Hypertension/renal vascular	35 (10.5)	4664 (10.1)	
Familial/hereditary	22 (6.6)	4567 (9.9)	
Tubulointerstitial disease	25 (7.5)	5234 (11.3)	
Other systemic diseases affecting the kidney	3 (0.9)	902 (2.0)	
Miscellaneous kidney disorders	31 (9.3)	3760 (8.1)	
BMI category (n = 45,297)			<0.001
<18.5 kg/m^2	6 (1.8)	1524 (3.4)	
18.5–24.9 kg/m^2	46 (14.0)	13,440 (29.9)	
25–29.9 kg/m^2	83 (25.3)	14,273 (31.7)	
≥30 kg/m^2	193 (58.8)	15,657 (33.8)	
Diabetes (n = 46,653)	219 (65.8)	21,620 (46.7)	<0.001
Coronary artery disease (n = 46,656)	171 (51.4)	15,657 (33.8)	<0.001
Cerebrovascular disease (n = 46,657)	59 (17.7)	5423 (11.7)	<0.001
Peripheral vascular disease (n = 46,663)	124 (37.2)	9229 (19.9)	<0.001
Chronic lung disease (n = 46,662)	74 (22.2)	7156 (15.4)	<0.001
Smoker (current or former) (n = 45,602)	173 (52.4)	20,663 (45.6)	0.014
Modality of KRT			<0.001
HD	255 (76.6)	24,130 (51.9)	
PD	64 (19.2)	7635 (16.4)	
Transplant	14 (4.2)	14,761 (31.7)	
Patients referred late[a] (n = 45,285)	45 (13.7)	7341 (16.3)	0.2
Era of starting KRT			<0.001
1967–2002	16 (4.8)	5366 (11.5)	
2003–2012	54 (16.2)	9601 (20.6)	
2013–2022	263 (79.0)	31,559 (67.8)	
Time on KRT Category			<0.001
KRT start	54 (16.2)	15,984 (34.4)	
<1 year	35 (10.5)	3598 (7.7)	
1–<3 years	70 (21.0)	5889 (12.7)	
3–<10 years	124 (37.2)	11,158 (24.0)	
10 years+	50 (15.0)	9897 (21.3)	

BMI, body mass index; HD, hemodialysis; KRT, kidney replacement therapy; PD, peritoneal dialysis.
[a]Referral to a nephrologist within three months of commencing KRT.
Results presented in n (%) or median [interquartile range].

calciphylaxis as a proportion than of the general KRT cohort without calciphylaxis in the ANZDATA Registry (18.5% vs. 5.1%); however, a lower proportion of Asian patients reported with calciphylaxis than the proportion of Asian patients without calciphylaxis (3.7% vs. 12.4%). Although HD was the predominant modality of KRT for all patients, a greater proportion of patients with calciphylaxis were on HD than other forms of KRT when compared to the overall KRT population without calciphylaxis. There was a similar proportion of patients with calciphylaxis on PD compared to those without calciphylaxis. The difference in KRT modality mostly relates to kidney transplant recipients who were less likely to have calciphylaxis (31.7% of the overall KRT population without calciphylaxis compared to 4.2% of those with calciphylaxis).

Outcomes of Patients With Calciphylaxis, and Compared to Those Without

In Figure 2, we show a Kaplan-Meier survival curve for KRT patient outcomes from the first calciphylaxis episode and over the first 3 years from diagnosis. Half of the patients with calciphylaxis had died by 12 months from diagnosis of this condition.

In Supplementary Table S1, we outline characteristics of patients on dialysis used in the following outcome analyses. In an unadjusted Cox model for patient survival after an episode of calciphylaxis compared to those without calciphylaxis (time-varying), the proportional hazards assumption did not hold ($P < 0.0001$) reflecting that the increase in mortality associated with calciphylaxis was substantially greater in the first year after diagnosis. This was addressed by separating the follow-up time into <1 year and 1 to 4 years, after which the hazards were proportional ($P = 0.12$).

Interactions between late referral and time on dialysis, and dialysis modality and time on dialysis were tested and found to be highly significant ($P < 0.0001$). The effect of late referral and modality were clinically plausible to differ by time on KRT because they are related to preparation at the start of KRT. In the adjusted Cox model for patient survival, nonproportional hazards were identified for several variables (age 65–74 years, age ≥75 years, peripheral vascular disease, within target serum calcium, time on dialysis 3–10 years, PD at KRT start, PD 1–3 years after KRT start, PD 3–10 years after KRT start, primary kidney disease "other systemic diseases affecting the kidney" and primary kidney disease "miscellaneous kidney disorders"). This was addressed by separating the follow-up time into <1 year and 1 to 4 years for these variables, after which the proportional hazards assumption held.

The unadjusted HR of mortality for <1 year after a calciphylaxis episode was 5.8 (4.9–6.9) and for 1 to 4 years after an episode was 1.6 (1.1–2.2) compared to patients without calciphylaxis (Table 3). In the fully adjusted model, the HR of mortality for <1 year after a calciphylaxis episode was 5.8 (4.9–6.9) and for 1 to 4 years after an episode was 1.5 (1.0–2.1) compared to patients without calciphylaxis (Table 3).

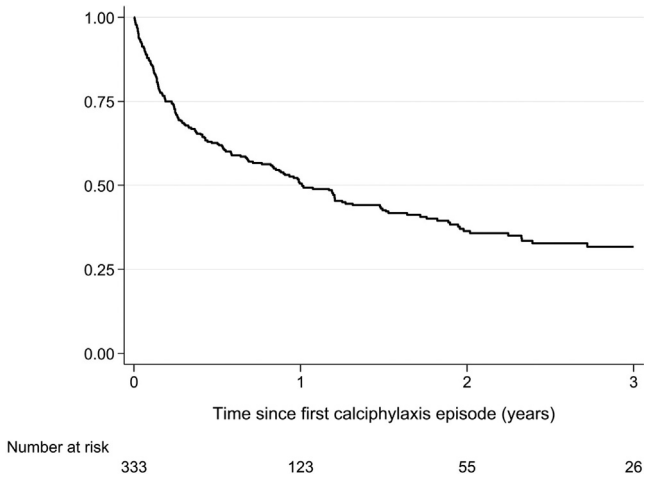

Figure 2. Unadjusted Kaplan-Meier curve for patient survival from the first calciphylaxis episode.

Table 3. Cox proportional hazards regression models for mortality between patients with and without calciphylaxis (including a time-varying covariate for calciphylaxis episode exposure, and all models censored for transplantation and restricted to patients on dialysis)

Model of analysis	Hazard ratio <1 yr after calciphylaxis diagnosis (95% CI)	Hazard ratio 1–4 yr after calciphylaxis diagnosis (95% CI)
Unadjusted ($n = 30,092$)	5.8 (4.9–6.9)	1.6 (1.1–2.2)
Adjusted[a] ($n = 27,034$)	5.7 (4.8–6.8)	1.4 (0.99–2.0)
Adjusted[b] ($n = 27,034$)	5.8 (4.9–6.9)	1.5 (1.01–2.1)

CI, confidence interval.
[a]Adjusted for age, sex, ethnicity, late referral, BMI, cause of kidney failure, diabetes as a comorbidity only, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, smoking, state/country, dialysis modality, era of commencement of dialysis, time on dialysis, biochemical parameters within target ranges (serum calcium and phosphate; and hemoglobin), plus interactions between late referral and time on dialysis, and dialysis modality and time on dialysis.
[b]Adjusted for same as[a], with shared frailty by parent center.

Incidence and Outcomes of Calciphylaxis in Patients Without Peripheral Vascular Disease

Among 37,368 patients without peripheral vascular disease, 209 had a calciphylaxis episode. In Supplementary Figure S1 and Supplementary Table S2, we show the adjusted incidence rate ratios and HR for mortality, respectively, for calciphylaxis in patients on KRT without documented peripheral vascular disease. The incidence rate ratios for patients without peripheral vascular disease were similar to the main analysis, except that diabetes and age were no longer significantly associated with the incidence of calciphylaxis, the effect of obese BMI was greater, and it was only Asian/Other ethnicities with significantly lower incidence than Australia/New Zealand European and Māori patients (Supplementary Figure S1). Among patients without peripheral vascular disease, the unadjusted HR of mortality for <1 year after a calciphylaxis episode was 6.5 (5.3–8.0) and for 1 to 4 years after an episode was 1.7 (1.1–2.6) compared to patients without calciphylaxis (Supplementary Table S2). In the fully adjusted model, the HR of mortality for <1 year after a calciphylaxis episode was 6.8 (5.4–8.4) and for 1 to 4 years after an episode was 1.8 (1.1–2.8) compared to patients without calciphylaxis.

DISCUSSION

We report 4-years' data collection of calciphylaxis episodes from the ANZDATA Registry to describe associations and outcomes in Australian and Aotearoa, New Zealander patients on KRT with this condition. In 333

patients with calciphylaxis, we highlight an association with age 55 to 64 years, female gender, diabetes, cardiovascular disease, and greater BMI; and report significant mortality with half of the patients not surviving the first 12 months after diagnosis of calciphylaxis. We report that the incidence of calciphylaxis in Australia and Aotearoa, New Zealand is 2.5 episodes per 1000 patient-years in patients on KRT (4.5 episodes per 1000 patient-years for patients on dialysis), which is consistent with what was previously reported in the Australian Calciphylaxis Registry.[4] This incidence is also similar to the estimated annual incidence of 0.35% in patients on HD in the United States, which has been increasing over time.[10]

Several case series have been reported describing associations and outcomes of patients with calciphylaxis; and there are similarities between our current data and those publications, including from the German and Australian calciphylaxis registries and the United Kingdom Calciphylaxis study.[4,8,10-21] The initial Australian Calciphylaxis Registry confirmed previously identified risk factors for calciphylaxis in Australia, including obesity, diabetes, and long dialysis vintage.[4] Other common associations with calciphylaxis previously reported in international case series have included warfarin use, known cardiovascular disease, abnormalities in bone and mineral metabolism, and markers of inflammation and malnutrition.[11-19]

Demographic details of patients in our current study using ANZDATA, including a median age of 63 years, were similar to those reported in the United Kingdom Calciphylaxis study and the German calciphylaxis registry, with median ages of 59 and 70 years, respectively, and a nearly an equal gender ratio.[8] Case reports and case series often highlight female gender as a risk factor[11,13,14,19] and although we report a relatively equal gender ratio, the proportion of female patients with calciphylaxis in our study is significantly greater than the overall proportion of female patients on KRT in Australia and Aotearoa, New Zealand (53.5% vs. 38.5%). European ethnicity has also traditionally been described as a risk factor for calciphylaxis and previous international cases series found that most patients were of European ethnicity.[8,13,19] The most common ethnicity in the ANZDATA Registry overall is Australia/New Zealand European (64%) and the majority of patients with calciphylaxis in our study were of this ethnicity (64.0%). However, there was a greater proportion of Māori patients with calciphylaxis in our study compared to Māori patients without calciphylaxis (18.5% vs. 5.1%). This is the first report where calciphylaxis rates are higher in a non-European population although none of the previous papers have included Māori patients. Māori New Zealander patients have significantly higher rates of KRT and significantly higher rates of diabetes than the overall ANZDATA population.[22] Once on dialysis, Māori patients have worse survival than Australia/New Zealand Europeans and shorter transplant graft survival than non-Māori patients.[23]

The median time to diagnosis of calciphylaxis from commencement of KRT was 3 years in our study, similar to previous reports, which range from 30 to 50 months in the US, China, and Germany; to 105 months in Japan.[8,10,11,15] HD was also the predominant KRT modality in our study, similar to most case series, with a similar proportion of patients on PD with calciphylaxis when compared to Australian and Aotearoa, New Zealanders without calciphylaxis. A very small proportion of kidney transplant recipients were reported to have calciphylaxis in the ANZDATA Registry (n = 14, 4.2%), with calciphylaxis diagnosed at a median of 7 years post-transplantation. The largest separate cases series that reported calciphylaxis primarily in patients with a kidney transplant was also relatively small (n = 14),[24] with most publications of kidney transplant recipients with calciphylaxis being individual case reports.

Mortality among patients with calciphylaxis remains high with a mortality rate of ~50% in the first 12 months after diagnosis of this condition reported to ANZDATA. This was similar to that initially reported in the Australian Calciphylaxis Registry, with a 50% mortality at a median of 1.6 (0.2–2.5) years after diagnosis; however, it is more promising when compared to historically published data on outcomes with calciphylaxis.[4,10,21] Calciphylaxis cases in the United Kingdom Calciphylaxis study were reported to be a strong independent risk factor for all-cause mortality (HR: 6.96), with an annual mortality of 67% compared to 10.2% in HD patients without calciphylaxis.[19] The United States Renal Data System, which identified 649 incident cases of calciphylaxis in a report from 2014, reported mortality rates that were 2.5 to 3 times higher than the average mortality rates for patients on HD in the United States.[20]

In our study, we reported that the adjusted HR of mortality for patients with a calciphylaxis episode who were less than 1 year after an episode was 5.8 compared to patients without calciphylaxis, and the adjusted HR for mortality was 1.5 for patients who were 1 to 4 years after an episode compared to patients without calciphylaxis. This again highlights the significant burden of disease and associated mortality for patients within their first year of diagnosis of calciphylaxis. Controlled clinical studies to investigate therapeutic strategies are desperately needed for this disease given the considerable mortality rates. There have not been any

randomized controlled trials reported to date evaluating therapies to address calciphylaxis, although some are underway.[25]

Although the previously reported Australian Calciphylaxis Registry was developed as a nationwide registry, only 7 Australian nephrology centers were involved, with the vast majority of centers not participating in data collection. Considering that this was a significant study limitation in determining the true disease incidence in Australia, our current study using ANZDATA provides a more comprehensive report of the incidence of calciphylaxis in Australia, as well as in Aotearoa, New Zealand, with the ANZDATA Registry being a comprehensive record of all patients requiring KRT across both countries. There is a possibility, however, that there were more cases of calciphylaxis not reported to ANZDATA between 2019 and 2022; and that there may have been false positive cases reported that were not actually calciphylaxis, due to the absence of systematic diagnostic standards for calciphylaxis and decentralized patient care within the Registry.

Strengths of our study include the relatively large cohort of cases; the robust statistical analyses, including time-varying analyses with comparison to the Australian and Aotearoa, New Zealand dialysis population without calciphylaxis; and the long-term follow-up of cases to identify clinical outcomes, specifically mortality. Limitations of our study include an absence of information on warfarin use, serum albumin, and parathyroid hormone levels as potential associations with calciphylaxis; and lack of information about investigations (including skin biopsies) and management strategies for episodes of calciphylaxis, because these data are not routinely collected in the ANZDATA Registry. In addition, despite prospective data collection, laboratory markers at the time of calciphylaxis diagnosis are cross-sectional, whereas trends may be more important as contributors to calciphylaxis development. Despite these limitations, the ANZDATA Registry is able to collect a significant amount of patient data associated with a rare condition.

In summary, calciphylaxis is a complex disorder manifested as painful cutaneous lesions resulting from microvascular calcification. We highlight risk factors for calciphylaxis, including a higher percentage of females and a greater proportion of patients with diabetes, obesity, and cardiovascular disease than in the background dialysis population without calciphylaxis. We also report an increased incidence in Māori patients, and we outline the natural history of patients with calciphylaxis in Australia and Aotearoa, New Zealand. Prognosis is generally poor with significant 1-year mortality, although this may not be as high as previously reported.

DISCLOSURE

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DATA AVAILABILITY STATEMENT

Data presented in this manuscript is available from ANZDATA at www.anzdata.org.au.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Incidence rate ratios using multivariate mixed effects Poisson model for incidence of first calciphylaxis episode in patients without peripheral vascular disease.

Table S1. Characteristics of study cohort – comparison of patients on dialysis with and without calciphylaxis (patients used for outcome analysis).

Table S2. Cox proportional hazards regression models for mortality in patients without peripheral vascular disease, between patients with and without calciphylaxis (including a time-varying covariate for calciphylaxis episode exposure, and all models censored for transplantation and restricted to patients on dialysis).

STROBE Statement.

REFERENCES

1. Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol*. 2008;3:1139–1143. https://doi.org/10.2215/CJN.00530108
2. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis*. 2015;66:133–146. https://doi.org/10.1053/j.ajkd.2015.01.034
3. Chang JJ. Calciphylaxis: diagnosis, pathogenesis, and treatment. *Adv Skin Wound Care*. 2019;32:205–215. https://doi.org/10.1097/01.ASW.0000554443.14002.13
4. Ruderman I, Toussaint ND, Hawley CM, et al. The Australian Calciphylaxis Registry: reporting clinical features and outcomes of patients with calciphylaxis. *Nephrol Dial Transplant*. 2021;36:649–656. https://doi.org/10.1093/ndt/gfz256
5. Nigwekar SU. Calciphylaxis. *Curr Opin Nephrol Hypertens*. 2017;26:276–281. https://doi.org/10.1097/MNH.0000000000000328
6. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med*. 2018;378:1704–1714. https://doi.org/10.1056/NEJMra1505292
7. Chiriac A, Grosu OM, Terinte C, Perţea M. Calcific uremic arteriolopathy (calciphylaxis) calls into question the validity of guidelines of diagnosis and treatment. *J Dermatol Treat*. 2020;31:545–548. https://doi.org/10.1080/09546634.2019.1618435
8. Brandenburg VM, Kramann R, Rothe H, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. *Nephrol Dial Transplant*. 2017;32:126–132. https://doi.org/10.1093/ndt/gfv438
9. McDonald SP, Russ GR. Australian registries -ANZDATA and ANZOD. *Transplant Rev (Orlando)*. 2013;27:46–49. https://doi.org/10.1016/j.trre.2013.01.003
10. Nigwekar SU, Zhao S, Wenger J, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Nephrol*. 2016;27:3421–3429. https://doi.org/10.1681/ASN.2015091065
11. Hayashi M, Takamatsu I, Kanno Y, et al. A case-control study of calciphylaxis in Japanese end-stage renal disease patients. *Nephrol Dial Transplant*. 2012;27:1580–1584. https://doi.org/10.1093/ndt/gfr658
12. Santos PW, He J, Tuffaha A, Wetmore JB. Clinical characteristics and risk factors associated with mortality in calcific uremic arteriolopathy. *Int Urol Nephrol*. 2017;49:2247–2256. https://doi.org/10.1007/s11255-017-1721-9
13. Harris C, Kiaii M, Lau W, Farah M. Multi-intervention management of calcific uremic arteriolopathy in 24 patients. *Clin Kidney J*. 2018;11:704–709. https://doi.org/10.1093/ckj/sfy007
14. Gaisne R, Péré M, Menoyo V, Hourmant M, Larmet-Burgeot D. Calciphylaxis epidemiology, risk factors, treatment and survival among French chronic kidney disease patients: a case-control study. *BMC Nephrol*. 2020;21:63. https://doi.org/10.1186/s12882-020-01722-y
15. Liu Y, Yang C, Yang X, et al. Prevalence and clinical characteristics of calciphylaxis in Chinese hemodialysis patients. *Front Med (Lausanne)*. 2022;9:902171. https://doi.org/10.3389/fmed.2022.902171
16. Jiao Y, Sun L, Xie X, et al. Clinical features and outcomes of calciphylaxis in Chinese patients with chronic kidney disease. *Nephrol (Carlton)*. 2023;28:305–314. https://doi.org/10.1111/nep.14156
17. Ababneh EI, Hassanein M, Saad AM, et al. Calciphylaxis in uraemic and nonuraemic settings: clinical risk factors and histopathological findings. *Clin Exp Dermatol*. 2022;47:700–708. https://doi.org/10.1111/ced.15009
18. Wen W, Krinsky S, Kroshinsky D, et al. Patient-reported and clinical outcomes among patients with calciphylaxis. *Mayo Clin Proc Innov Qual Outcomes*. 2023;7:81–92. https://doi.org/10.1016/j.mayocpiqo.2022.12.006
19. Chinnadurai R, Huckle A, Hegarty J, Kalra PA, Sinha S. Calciphylaxis in end-stage kidney disease: outcome data from the United Kingdom Calciphylaxis Study. *J Nephrol*. 2021;34:1537–1545. https://doi.org/10.1007/s40620-020-00908-9
20. Nigwekar SU, Solid CA, Ankers E, et al. Quantifying a rare disease in administrative data: the example of calciphylaxis. *J Gen Intern Med*. 2014;29(suppl 3):S724–S731. https://doi.org/10.1007/s11606-014-2910-1
21. Mazhar AR, Johnson RJ, Gillen D, et al. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. *Kidney Int*. 2001;60:324–332. https://doi.org/10.1046/j.1523-1755.2001.00803.x
22. ANZDATA registry 45th Report. Chapter 11 Kidney failure among Māori in Aotearoa New Zealand. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia. Published 2022. Accessed January 7, 2024. https://www.anzdata.org.au
23. ANZDATA registry [45th Report]. Chapter 9: Kidney Failure in Aotearoa New Zealand. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia. Published 2022. Accessed January 7, 2024. http://www.anzdata.org.au
24. Guillén-Olmos E, Torregrosa JV, Garcia-Herrera A, Ganau S, Diekmann F, Cucchiari D. Development of calciphylaxis in kidney transplant recipients with a functioning graft. *Clin Kidney J*. 2021;15:663–671. https://doi.org/10.1093/ckj/sfab205
25. Sinha S, Gould LJ, Nigwekar SU, et al. The CALCIPHYX study: a randomized, double-blind, placebo-controlled, Phase 3 clinical trial of SNF472 for the treatment of calciphylaxis. *Clin Kidney J*. 2021;15:136–144. https://doi.org/10.1093/ckj/sfab117