# Lithium-Associated Kidney Failure: Predictors and Outcomes

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**Introduction:** Despite the widespread use of lithium for bipolar disorders and depression, little is known about the characteristics of patients with lithium-associated kidney failure receiving kidney replacement therapy (KRT).

**Methods:** We conducted a retrospective study using the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) to investigate the predictors and outcomes of patients with lithium-associated kidney failure receiving KRT.

**Results:** A total of 437 patients with lithium-associated kidney failure were compared to 1280 ANZDATA allocated controls of patients with kidney failure not associated with lithium. Patients with lithium-associated kidney failure commenced KRT at significantly older age ($62 \pm 10$ vs. $58 \pm 15$ years; $P < 0.001$) and were more likely to be European (93% vs. 68%, $P < 0.001$), to be female (63% vs. 40%, $P < 0.001$), and to live in a postcode with a higher socioeconomic status (SES) ($P < 0.001$). In patients with lithium-associated kidney failure, there were lower rates of coronary artery disease (17% vs. 37%, $P < 0.001$), peripheral vascular disease (7% vs. 25%, $P < 0.001$), cerebrovascular disease (8% vs. 14%, $P = 0.004$) and diabetes mellitus (16% vs. 47%, $P < 0.001$). There were no differences between first KRT modality, although kidney transplantation and retransplantation rates were lower (21% vs. 27%, $P = 0.008$; 0.2% vs 3%, $P = 0.001$) with shorter wait-times to first transplantation (20 months vs. 29 months, $P = 0.02$) in the patients with lithium-associated kidney failure. Rates of at least 1 rejection episode was comparable (21% vs. 22%, $P = 0.85$) between the 2 groups. In addition, there were no survival differences regardless of KRT modality between the 2 groups.

**Conclusion:** Lithium-associated kidney failure represents a unique cohort which is predominantly older, female, European, with a higher SES and less comorbidities. Despite this, there are no differences in survival. Given the lower rate of transplantation, barriers to transplantation need further exploration.

L ithium therapy is a cornerstone in the management of bipolar disorders and refractory depression.[1] However, lithium has a narrow therapeutic index with a propensity to cause nephrogenic diabetes insipidus, occurring in approximately 40% of individuals.[2] A lesser studied outcome is its association with chronic kidney disease (CKD), affecting approximately 20% of patients and characterized by chronic tubulointerstitial nephropathy with interstitial fibrosis, thickening of the tubular basement membranes and renal tubular cysts with a latent period of approximately 20 years.[3-5] Correlations between lithium use and CKD were first described in the 1970s,[6] however its clinical significance has been debated. In a meta-analysis performed by McKnight *et al.*,[7] 385 abstracts regarding lithium toxicity were reviewed and found an insignificant reduction in glomerular filtration rate of up to 5 ml/min, however the major limitation in this study was an insufficient follow-up duration of only 1 year. Further retrospective analyses have found that gradual renal impairment with mild and sometimes nephrotic-range proteinuria may occur, with 21% to

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55% of patients subsequently developing stage 3 CKD and 1.5% of patients developing kidney failure after at least 15 years on therapy.[2,3,8] Although the absolute incidence is low, rates of patients with lithium-associated kidney failure receiving KRT have increased from 0.14 cases/million population/year in 1992 to 1996 to 0.78 cases/million population/year in Australia[9] and 0.74 cases/million population/year in New Zealand[10] between 2007 and 2011.

Risk factors for the development of lithium-associated kidney failure include cumulative lithium dose, duration of lithium therapy, female gender, older age, lower initial estimated glomerular filtration rate (eGFR), use of other nephrotoxins, repeated episodes of nephrogenic diabetes insipidus, and the presence of concomitant CKD risk factors.[3] In a qualitative study examining perspectives on lithium-associated kidney impairment, it was found that patients felt a lack of understanding and shared decision making when renal function deteriorated and that monitoring was not standardized, which may reflect the paucity of knowledge in this area.[4]

Lithium-associated kidney failure is a rare complication of chronic lithium use, which has been poorly studied given its overall low incidence and prolonged latency. Due to this, our understanding of its predictors and outcomes of patients requiring KRT is limited; and further elucidation of these would be beneficial in improving awareness and designing interventions to address modifiable risk factors.

The aims of our study were to determine the prevalence of lithium-associated kidney failure requiring KRT in Australia and New Zealand; and evaluate differences in characteristics of lithium-associated kidney failure in patients requiring KRT, including patient demographics and comorbidities, compared to those in patients with kidney failure not associated with lithium. In addition, we sought to evaluate the outcomes of lithium-associated kidney failure, including access to kidney transplantation, patient survival on KRT, and causes of mortality.

## METHODS

A retrospective cohort study was performed which included patients with kidney failure in the ANZDATA registry who had commenced KRT from January 1977 until December 2020. Data collected included cause of primary kidney disease, demographic information, body mass index (BMI, calculated as kg/m$^2$), smoking status, comorbidities (chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus, and cancer), KRT modality, date of commencement, late referral data, and

patient outcomes including mortality. Patients who were reported to have lithium-associated kidney failure by their nephrologist were compared to a population randomly selected at a ratio of 1:3 by ANZDATA statisticians with no specific matching criteria. Ethical approval for use of registry data was obtained from the Western Sydney Local Health District's Human Research Ethics Committee (approval number 2021/PID00594).

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 28 software (SPSS Inc., Cary, NC). Variables were differentiated according to categorical and continuous data, chi-square testing being the primary method used for categorical data; and unpaired t-tests, if normally distributed, or Mann-Whitney-U testing if non-normally distributed was used for continuous data. Where applicable, data were expressed as mean values with SD. Predictors were included in multivariate logistic regression analysis to adjust for known confounding factors. Survival analysis using Kaplan-Meier was used to determine survival outcomes of those with lithium-associated kidney failure compared to those with kidney failure without lithium exposure.

## RESULTS

Between January 1977 and December 31, 2020, 437 patients were identified to have lithium-associated kidney failure, and these were compared to 1280 in the comparative group. The earliest identified commencement of KRT due to lithium-associated kidney failure was in 1991. Eighty-three patients (19%) underwent a kidney biopsy to confirm the diagnosis of lithium-associated kidney failure. The point prevalence for lithium-associated kidney failure requiring KRT was 0.6% (201/32887) of the total number of patients with kidney failure in Australia and New Zealand as of 2020. There were 32 new cases of lithium-associated kidney failure in 2020 equating to an incidence rate of 8 cases per 1000 person-years of new patients with kidney failure.[11] As shown in Figure 1, the incidence of lithium-associated kidney failure has been steadily rising since 1991.

Patients with lithium toxicity were more likely of European heritage (93% vs. 68%, $P < 0.001$), female (63% vs. 40%, $P < 0.001$), overweight or obese (68% vs. 63%, $P = 0.02$), and living in postcodes with a higher SES ($P < 0.001$) (Table 1). In Australia, there was a significantly higher proportion of patients with lithium-associated kidney failure commencing KRT from the state of Victoria (26% vs. 20%, $P = 0.006$), and less in Western Australia (4% vs. 7%, $P = 0.026$) compared to the nonlithium-associated KRT population. There were
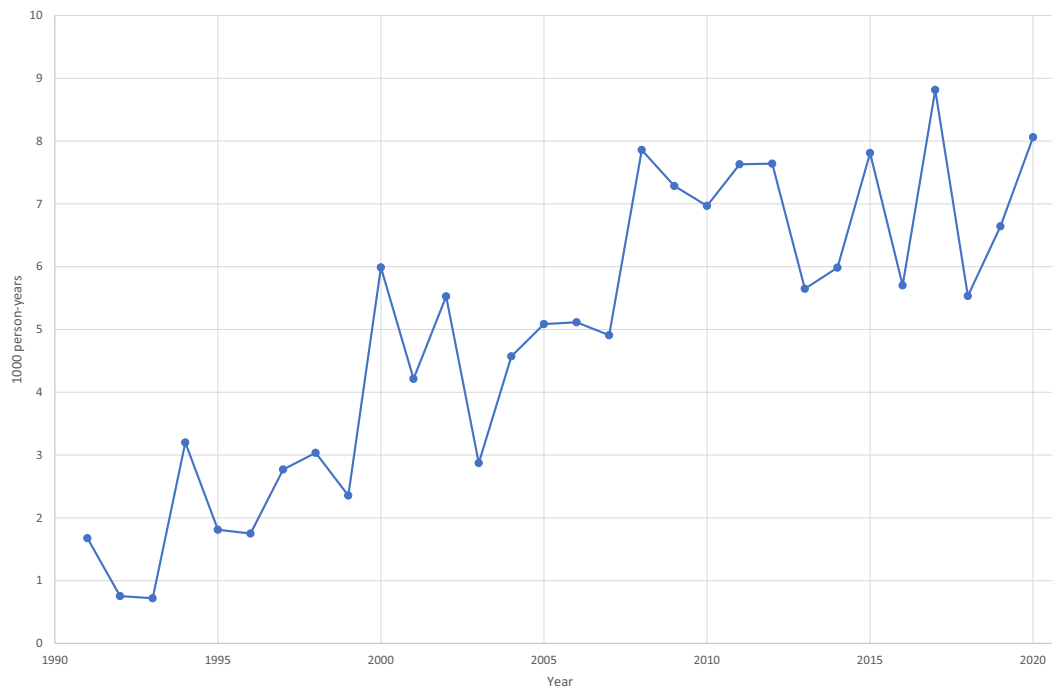
**Figure 1.** Incidence of lithium-associated kidney failure commencing kidney replacement therapy in Australia and New Zealand.

significantly fewer Aboriginal and Torres Strait Islanders (1% vs. 7%, $P < 0.001$), Maori and Polynesian Islanders (1% vs. 12%, $P < 0.001$) and Asian patients (3% vs. 8%, $P < 0.001$). At commencement of KRT, there were significantly lower rates of coronary artery disease (17% vs. 37%, $P < 0.001$), peripheral vascular disease (7% vs. 25%, $P < 0.001$), cerebrovascular disease (8% vs. 14%, $P = 0.004$) and diabetes (16% vs. 47%, $P < 0.001$); however, there were no significant differences in smoking status, chronic lung disease, or a diagnosis of cancer.

## Predictors of Lithium-Associated Kidney Failure
Binary logistic regression (Table 2) evaluating patient characteristics at commencement of KRT demonstrated that female gender, age 50 to 79 years, overweight and obese BMI classes, and a European heritage were positive predictors of lithium-associated kidney failure. Negative predictors included Maori and Pacific Islander ethnicity, as well as presence of coronary artery disease, peripheral vascular disease, and diabetes mellitus at KRT commencement.

## KRT Modalities
Patients with lithium-associated kidney failure commenced KRT at an older mean age of 62 ($\pm$10) years compared to 58 ($\pm$15) years in the control group ($P < 0.001$); and were less likely to be late presenters, that is, referred within 3 months of commencement of KRT (9% vs. 17%, $P < 0.001$) (Table 3). There were no significant differences in the initial KRT modality between the groups.

## Kidney Transplant Outcomes
Overall, kidney transplantation and retransplantation rates were lower within the lithium group (21% vs. 27%, $P = 0.008$; 0.2% vs. 3%, $P = 0.001$, respectively). Waitlist data for transplantation was made available from 2006, and there was no difference between lithium and nonlithium-associated kidney failure group in those waitlisted (13% and 13% respectively, $P = 0.93$). The waitlist time to first transplantation was significantly lower in the cohort with lithium-associated kidney failure as compared to the control group (20 months vs. 29 months, $P = 0.02$). Seven lithium patients (12%) versus 31 control patients (20%) died without receiving a transplant despite being waitlisted, although this did not reach statistical significance ($P = 0.5$). There were no significant differences in the proportion of patients experiencing at least 1 episode of rejection after kidney transplantation between lithium and control cohorts (21% vs 22% respectively, $P = 0.85$).

## Survival Outcomes
Regardless of the KRT modality used to treat kidney failure, there were no overall differences in survival on Kaplan-Meier analyses between both groups (Figure 2). Of note, the lithium group had a higher survival rate compared to the control group until 10 years post KRT; however, after excluding withdrawal as a cause of death, survival rates were significantly higher in the lithium group until 15 years post KRT ($P = 0.005$); of note, interpretation is limited by crossing survival curves. The median survival was 7 years in patients with

**Table 1.** Individual characteristics of patients with lithium-associated kidney failure compared to the control population

| Characteristics | Lithium-associated kidney failure (n = 437) | Nonlithium-associated kidney failure (n = 1280) | P value |
|---|---|---|---|
| Age | 62 ± 10 | 58 ± 15 | <0.001[a] |
| Age category (yr) | | | <0.001[a] |
| 18–49 | 45 (10%) | 335 (26%) | |
| 50–79 | 386 (88%) | 866 (68%) | |
| ≥80 | 6 (1%) | 79 (6%) | |
| Male gender | 161 (37%) | 770 (60%) | <0.001 |
| Ethnicity | | | |
| European | 408 (93%) | 873 (68%) | <0.001[a] |
| ATSI | 3 (1%) | 92 (7%) | <0.001[a] |
| MPI | 4 (1%) | 159 (12%) | <0.001[a] |
| Asian | 11 (3%) | 106 (8%) | <0.001[a] |
| Other | 11 (2%) | 39 (3%) | |
| Missing | 3 (1%) | 11 (1%) | |
| Location | | | |
| NT | 0 | 28 (2%) | NA |
| NSW | 123 (28%) | 312 (24%) | 0.12 |
| VIC | 115 (26%) | 256 (20%) | 0.006[a] |
| QLD | 61 (14%) | 198 (15%) | 0.45 |
| SA | 38 (9%) | 103 (8%) | 0.67 |
| WA | 19 (4%) | 95 (7%) | 0.03 |
| TAS | 8 (2%) | 22 (2%) | 0.88 |
| ACT | 6 (1%) | 25 (2%) | 0.43 |
| NZ | 67 (15%) | 241 (19%) | 0.1 |
| Socioeconomic disadvantage (SEIFA decile) average | 6.27 ± 2.9 | 5.24 ± 2.92 | 0.02[a] |
| Smoking | | | 0.998 |
| Ever smoked | 226 (52%) | 601 (47%) | |
| Never | 206 (47%) | 548 (43%) | |
| Unknown | 5 (1%) | 131 (10%) | |
| BMI (km/m$^2$) | | | 0.02[a] |
| Normal/underweight | 127 (29%) | 416 (33%) | |
| Overweight | 142 (32%) | 322 (35%) | |
| Obese | 156 (36%) | 373 (29%) | |
| Missing | 12 (3%) | 169 (13%) | |
| Chronic lung disease | | | 0.94 |
| Yes or suspected | 105 (24%) | 267 (21%) | |
| No | 332 (76%) | 911 (71%) | |
| Missing | 0 | 102 (8%) | |
| Coronary artery disease | | | <0.001 |
| Yes or suspected | 133 (30%) | 651 (51%) | |
| No | 304 (70%) | 535 (42%) | |
| Missing | 0 | 94 (7%) | |
| Cerebrovascular disease | | | 0.004[a] |
| Yes or suspected | 77 (18%) | 288 (22%) | |
| No | 360 (82%) | 892 (70%) | |
| Missing | 0 | 100 (8%) | |
| Peripheral vascular disease | | | <0.001[a] |
| Yes or suspected | 79 (18%) | 467 (36%) | |
| No | 358 (82%) | 713 (56%) | |
| Missing | 0 | 100 (8%) | |
| Diabetes | | | <0.001[a] |
| Type 1 diabetes | 2 (0.5%) | 56 (4%) | |
| Type 2 diabetes (insulin requiring) | 27 (6%) | 257 (20%) | |
| Type 2 diabetes (noninsulin requiring) | 72 (16%) | 308 (24%) | |
| No | 336 (77%) | 576 (45%) | |

*(Continued on following page)*

**Table 1.** (Continued) Individual characteristics of patients with lithium-associated kidney failure compared to the control population

| Characteristics | Lithium-associated kidney failure (n = 437) | Nonlithium-associated kidney failure (n = 1280) | P value |
|---|---|---|---|
| Missing | 0 | 83 (6%) | |
| Cancer | | | 0.96 |
| Yes | 129 (30%) | 365 (29%) | |
| No | 308 (70%) | 913 (71%) | |
| Missing | 0 | 2 (0.2%) | |

ACT, Australian Capital Territory; ATSI, Aboriginal and Torres Strait Islander; BMI, body mass index; MPI, Māori and Polynesian Islanders; NSW, New South Wales; NT, Northern Territory; NZ, New Zealand; QLD, Queensland; SA, South Australia; SEIFA, socioeconomic indexes for areas; TAS, Tasmania; VIC, Victoria; WA, Western Australia.
[a]Indicates significant differences.

lithium-associated kidney failure as compared to 6 years for the control group ($P = 0.53$), and there was no significance difference when death from withdrawal was excluded. There were significantly less infection-related deaths (3.4% vs. 7.7%, $P = 0.002$), cardiovascular deaths (11.4% vs. 22.8%, $P < 0.001$) and cancer-related deaths (2.5% vs. 4.7%, $P = 0.049$) in the lithium group (Figure 3). There were significantly more deaths as a result of withdrawal from KRT (24.7% vs. 13.8%, $P < 0.001$) in the lithium-associated kidney failure group, with psychosocial reasons making up 60% ($n = 65$) in the lithium group compared to 5% ($n = 62$) in the comparative group. Death due to suicide was documented in 7 cases, of which 4 were in the lithium group. Those receiving kidney transplants had significantly greater survival (further 13–18 years, $P < 0.001$) than patients who did not receive kidney transplant, and this was comparable to the control group.

**Table 2.** Multiple regression predictors of lithium-associated kidney failure

| Characteristics | Odds ratio |
|---|---|
| Male gender | 0.41 (0.31–0.53) |
| Age, yr | |
| 18–49 | Reference |
| 50–79 | 3.32 (2.38–4.63) |
| ≥80 | 0.57 (0.23–1.37) NS[a] |
| BMI | |
| Normal/underweight | Reference |
| Overweight | 1.78 (1.29–2.44) |
| Obese | 2.29 (1.64–3.19) |
| Ethnicity | |
| European | 2.74 (1.31–5.73) |
| ATSI | 0.26 (0.07–1.02) NS[a] |
| MPI | 0.18 (0.05–0.64) |
| Asian | 0.57 (0.22–1.49) NS[a] |
| Coronary artery disease | 0.55 (0.4–0.75) |
| Cerebrovascular disease | 0.9 (0.58–1.39) NS[a] |
| Peripheral vascular disease | 0.45 (0.29–0.7) |
| Diabetes mellitus | 1.4 (0.3–0.55) |

ATSI, Aboriginal and Torres Strait Islander; BMI, body mass index; MPI, Māori and Polynesian Islanders.
[a]NS, not significant.

**Table 3.** Individual characteristics of KRT modality data

| Characteristics | Lithium-associated kidney failure (n = 437) | Nonlithium-associated kidney failure (n = 1280) | P-value |
|---|---|---|---|
| Late referral | 39 (9%) | 212 (17%) | <0.001[a] |
| Initial KRT modality | | | |
|   Hemodialysis | 301 (69%) | 872 (68%) | 0.77 |
|   Peritoneal dialysis | 122 (28%) | 375 (29%) | 0.58 |
|   Renal transplant | 14 (3%) | 33 (3%) | 0.49 |
| Ever transplanted | 82 (19%) | 349 (27%) | <0.001[a] |
| Retransplantation | 1 (0.2%) | 38 (3%) | <0.001[a] |

KRT, kidney replacement therapy.
[a]Indicates significant differences.

## DISCUSSION

This observational study demonstrates that lithium-associated kidney failure remains rare and has a significantly greater occurrence among females, those aged from 50 to 79 years, those of European heritage, those living in postcodes with high SES, and those with a high BMI. Significant differences are summarized in Table 4. There were no significant differences in initial KRT modality compared to the wider KRT population, although the waitlist time for first transplantation was typically shorter for patients with lithium-associated kidney failure. Despite a lower burden of comorbidities at commencement of KRT in patients with lithium-associated kidney failure, there were no differences in survival after commencement of KRT, although after excluding withdrawal as a cause from death, there was significantly better survival among patients with lithium-associated kidney failure until 15 years post-KRT commencement. Patients with lithium-associated kidney failure had lower infection, cardiovascular and cancer-related deaths, but were more likely to die from withdrawal of KRT.

Our study found a 0.6% prevalence of lithium-associated KRT across Australia and New Zealand,

which is reflective of the previously reported ranges between 0.2% and 0.7%.[12] This was similarly observed in a French retrospective cohort study evaluating 130 dialysis centers reporting a prevalence of 0.22%, although transplant patients were excluded[13]. Notably, our reported prevalence was significantly lower than a Swedish registry study conducted by Bendz *et al.*[14] which found an 8.1% prevalence among patients receiving KRT. This marked difference may be influenced by the clinical criteria retrospectively applied in the Swedish registry study to identify patients with lithium-associated kidney failure rather than relying on the treating nephrologist's diagnosis such as in our study.[14]

The initial steep rise in incidence rate at the turn of the 21st century was likely contributed by increasing recognition, given the relative paucity of early longitudinal studies evaluating the chronic effects of lithium use. Unfortunately, there are similarly limited data on lithium prescribing patterns across this time-period, although daily dose statistics have shown that approximately 1150 people per million population are prescribed lithium across Australia.[15] A recent analysis demonstrated that lithium prescription patterns vary widely between countries, with an overall decrease in lithium use in recent years across Germany, United States, Scotland, Sweden, and Denmark. The main concern regarding long-term use among psychiatrists in this Spanish study was lithium's adverse effect profile[16].

We found that lithium-associated kidney failure requiring KRT is more likely to occur in females, those aged from 50 to 79 years, those of European heritage, those living in postcodes with high SES, and those with a high BMI. Roxanas *et al.*[9] performed a retrospective study, which similarly reported significantly higher rates of lithium-associated kidney failure in women and those with a higher BMI, in addition to those of Caucasian background and smokers. Hayes *et al.*[17]
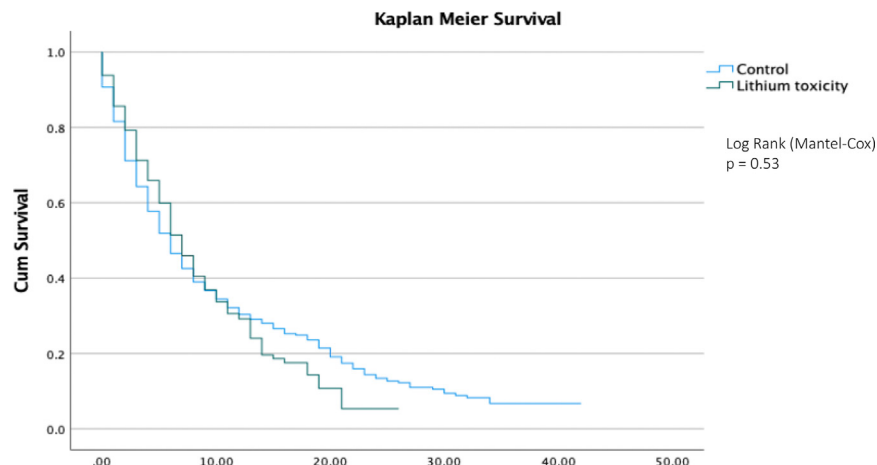


**Figure 2.** Kaplan Meier survival curve for lithium-associated kidney failure versus control group in patients with end-stage kidney disease with kidney replacement therapy in Australia and New Zealand.
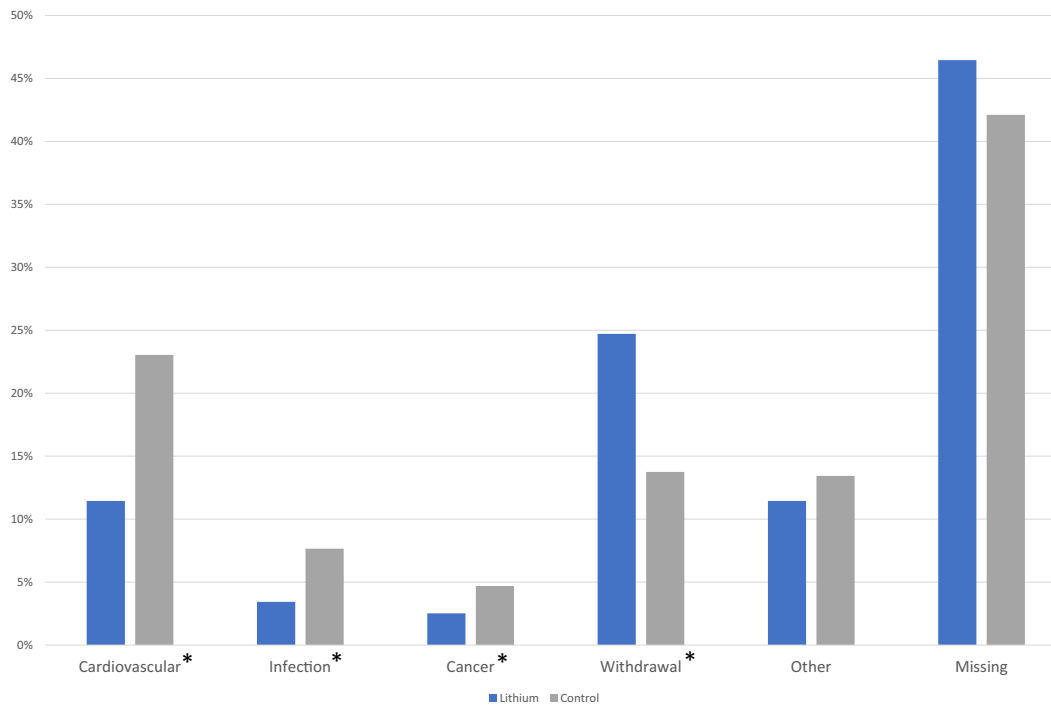
**Figure 3.** Causes of mortality between lithium-associated kidney failure and the control group.
There was significantly greater mortality due to withdrawal of renal replacement therapy and significantly less mortality for cardiovascular, infection and cancer-related deaths in the lithium group.
*Indicates significant differences.

evaluated a cohort of chronic lithium users and developed an externally validated model to predict the risk of eGFR decline, which also found that the females and obese individuals were more likely to be in the high-risk group. The higher preponderance of females in this cohort may be due to an increased frequency of bipolar disorder, and particularly higher rates of rapid cycling and suicidal attempts requiring more intensive treatment[18]. With regard to SES, an observational study performed by Eid *et al.*[19] found that a higher SES was significantly associated with lithium-responsive bipolar disorder, suggesting that those with a higher SES may be more likely to use lithium, and for a prolonged period of time. Interestingly, there were significantly more cases of lithium-associated kidney failure in Victoria and significant less cases in Western Australia, despite Western Australia holding over 99% of Australia's Economic Demonstrated Resources of lithium[20]. This

indicates that chronic lithium-associated kidney failure is most likely due to prescribed medication rather than environmental exposure.

Lithium-associated kidney failure was mostly clinically diagnosed in our cohort, with kidney biopsies performed in only 19% of patients. Clinical indicators of lithium-associated kidney failure described include a long duration of lithium use, a high cumulative dose, and episodes of acute toxicity[3]. Although no established risk prediction tools exist in clinical practice, Hayes *et al.*[17] evaluated the use of a prediction model to predict CKD risk in those receiving chronic lithium therapy and was able to stratify high risk patients likely to develop CKD stage 3A to 5 correctly in 87.96% of cases, using only age, sex, and baseline eGFR, which if widely validated would be a useful clinical tool in practice. We were unable to validate this tool within our cohort because we only included patients with CKD Stage 5 commencing KRT. Kidney Disease Improving Global Outcomes guidelines[21] acknowledge the potential for renal tubular dysfunction to occur even at therapeutic levels and advise against lithium use with an eGFR <60 ml/min per 1.73 m². Following commencement, eGFR, electrolytes, and lithium levels should be monitored at least every 6 months, or more frequently if a dose change or an acute illness arises.[21] National Institute for Health and Care Excellence guidelines[22] similarly suggest monitoring every 6 months; however, there are more stringent

**Table 4.** Review of significant variables relative to the lithium-associated kidney failure cohort

| Patient characteristics | Comorbidities | KRT characteristics |
|---|---|---|
| European/ATSI/MPI/Asian | Less coronary artery disease | Older age at KRT commencement |
| Less socioeconomic disadvantage | Less cerebrovascular disease | Less late referrals |
| Overweight or obese | Less peripheral vascular disease | Less transplanted |
| | Less diabetes | Less re-transplanted |

ATSI, Aboriginal and Torres Strait Islander; KRT, kidney replacement therapy; MPI, Māori and Polynesian Islanders.

caveats to the need for more frequent monitoring every 3 months that include older age, anticipated drug interactions, impaired renal or thyroid function, poor adherence, and high lithium levels. Following the detection of kidney function decline, specialist input is recommended in the National Institute for Health and Care Excellence guidelines to accurately diagnose lithium-associated kidney impairment before alteration of lithium therapy due to its important role in suicide prevention and mood stabilization.

There is limited evidence regarding KRT and its outcomes in chronic lithium-associated kidney failure. Our study found that KRT commencement occurred at an older age (64 ± 10 years) and that though initial modality on commencement did not differ, those in the lithium group were less likely to undergo kidney transplantation. This is despite the lower burden of comorbidities (including cardiovascular disease, peripheral vascular disease, cerebrovascular disease, and diabetes) in patients with lithium-associated kidney failure which suggests that there may be other factors that preclude kidney transplantation in this group. Poor medication adherence is an absolute contraindication to transplantation[23], and may well be a factor at play given that almost 1 in 2 patients prescribed lithium are reported to have partial or nonadherence to medications[24]. In addition, the ongoing use of lithium may deter from transplantation because of the increased unpredictable lithium clearance rates and the added potential for graft dysfunction[25]. Further, there may be concerns that patients with underlying bipolar disorder are at increased risk of central nervous system toxicities related to steroids and calcineurin inhibitors or may make fluid and electrolyte management more challenging posttransplant in patients continuing to need lithium to treat their mental disorder. Conversely, lithium discontinuation may also pose serious harm post transplantation in regard to suicide, manic relapse, or self-harm should other medications remain ineffective[26]. Given that only few case studies regarding lithium use in renal transplantation exist, this remains an area of uncertainty for many clinicians.

Interestingly, there were no differences in overall survival among patients with lithium-associated kidney failure, although a significant difference was found when withdrawal as a cause of death was excluded. We interpret this with some caution because log rank testing may be erroneous in the setting of crossing survival curves and subsequent reduction in sample size. When evaluating cause of death, there were significantly less infection, cardiovascular, and cancer-related deaths in the lithium group. This was despite being a less comorbid population with lower rates of coronary artery disease, peripheral vascular disease, cerebrovascular disease, and diabetes

mellitus. This may be in part explained by the older age of the lithium group at commencement of KRT, but also the morbidity and mortality of concurrent mental health illness, given that psychosocial reasons comprised 28% of all withdrawals from KRT in the lithium group compared to 5% in the control group.

Despite being a large observational study from a well-recognized prospectively collected binational database evaluating the prevalence, clinical characteristics, and outcomes of patients with lithium-associated kidney failure commencing KRT, our study has several limitations. Given that the control population was unmatched, individuals with lithium-associated kidney failure were significantly older with a higher female predominance which may both act as strong confounders for rates of comorbidities at KRT commencement and outcomes independent of lithium-use. In addition, the control population involved patients who started KRT from 1977, however the first recorded case of lithium-associated KRT was in 1991. Given the varying demographics, KRT referral patterns, and available modalities from 1977 to 1991, further confounders within the control population may have been introduced. The diagnosis of lithium-associated kidney failure was a clinical diagnosis, with only 19% undergoing a kidney biopsy. This may have led to either overdiagnosis in the absence of other clear causes of kidney disease or underdiagnosis particularly in the earlier years due to reduced awareness of lithium-associated kidney failure. In regard to mortality outcomes, almost half of the patients in the lithium-associated kidney failure and control groups had missing data. Unfortunately, ANZDATA does not encapsulate medication records, nor the overall duration of lithium therapy, cumulative dose, or episodes of acute toxicity, which have been widely reported in literature as major risk factors for chronic lithium-associated kidney impairment and have a large impact on decision to proceed to transplantation.

## Conclusion

Chronic lithium use is a rare cause of kidney failure, accounting for 0.6% of patients requiring KRT in Australia and New Zealand in 2020. Individuals are more likely female, of a European heritage, live in postcodes with a higher SES, and have less comorbidities. Future prediction models addressing these characteristics would be a useful tool to assist clinicians in quantifying the risk development of lithium-associated kidney failure. KRT commencement occurs at an older age and there is no difference in initial KRT modality. Despite being a less comorbid population, patients with lithium-associated kidney failure are less likely to receive a kidney transplant but have similar survival after commencement of KRT as those without lithium-

associated kidney failure. Barriers to transplantation should be further explored in order to improve survival, particularly in regard to medication adherence and continuation of lithium post transplantation, where there is a paucity of evidence.

## DISCLOSURE

## ACKNOWLEDGMENTS

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