Risk Factors for Dialysis Withdrawal: An Analysis of the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, 1999–2008

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Summary

Background and objectives Dialysis withdrawal (DW) in patients with ESRD is increasing in importance. This study assessed causes of death and risk factors for DW in Australia and New Zealand in the first year of dialysis.

Design, setting, participants, & measurements This retrospective observational cohort study included all adult Australians and New Zealanders beginning renal replacement therapy in 1999–2008.

Results A total of 24,884 patients with 10,073 deaths were included. Deaths from cardiac and social causes (predominantly DW) accounted for 38% and 28% of all deaths, respectively. Cumulative incidence of DW was 3.5% at 1 year (95% confidence interval [CI], 3.3%–3.8%), 9.0% at 3 years (95% CI, 8.6%–9.4%), and 13.4% at 5 years (95% CI, 12.8%–13.9%). In multivariate analysis, predictors for DW in the first year were older age (subhazard ratio [SHR], 1.70 per decade [95% CI, 1.59–1.83]; $P<0.001$), late referral (SHR, 1.83 [95% CI, 1.59–2.11]; $P<0.001$), comorbid conditions (SHR, 1.33 per each additional comorbid condition [95% CI, 1.25–1.41]; $P<0.001$), and diabetes (SHR, 1.16 [95% CI, 1.00–1.34]; $P=0.05$). Negative predictors for DW included male sex (SHR, 0.75 [95% CI, 0.66–0.87]; $P<0.001$), indigenous ethnicity (SHR, 0.74 [95% CI, 0.58–0.95]; $P=0.02$), other nonwhite race (SHR, 0.66 [95% CI, 0.48–0.91]; $P=0.01$), and peritoneal dialysis user (SHR, 0.59 [95% CI, 0.49–0.72]; $P<0.001$).

Conclusions DW is common among dialysis patients in Australia and New Zealand. Risk factors include older age, female sex, white race, diabetes, higher comorbidity burden, hemodialysis user, and late referral to nephrologist.

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Introduction

Dialysis withdrawal (DW) has become a major cause of death in ESRD patients. In the United States, one in four deaths results from DW (1). In 2009, deaths from social causes (37%) overtook cardiac deaths (34%) as the leading cause of death in Australian dialysis patients, followed by infectious (12%) and vascular (9%) causes (2). In this study we examined the causes of death and factors associated with DW in the first year after initiation of dialysis in Australia and New Zealand.

Materials and Methods

This retrospective observational cohort study used data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry. We included patients with ESRD who were 18 years of age or older and commenced renal replacement therapy (RRT) in Australia or New Zealand from January 1, 1999, to December 31, 2008. Patients were followed until December 31, 2008, death, or loss to follow-up. Demographic data included age at commencement of RRT, date of commencement of RRT, sex, ethnicity, baseline comorbid conditions, initial modality of RRT, time of nephrology referral, and place of residence. The ANZDATA registry included five comorbid conditions: diabetes mellitus, chronic lung disease, coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Outcome data included date and cause of death.

Late referral was defined as first nephrology referral occurring within 3 months of commencing RRT. Indigenous race was self-reported and included Australian Aboriginals and Torres Strait Islanders and New Zealand Māoris or Pacific Islanders. Remoteness of Australian patients was determined by matching postal codes at commencement of RRT with statistical local areas, then mapping these areas to remoteness classification according to the Australian Bureau of Statistics postal concordance data. Remoteness was classified as major cities, inner regional, outer regional, remote, or very remote. Remoteness could not be ascertained for New Zealand patients. Renal unit size was based on tertiles of the number of patients commencing RRT during the study period.

Classification of Cause of Death

The primary cause of death is reported to the ANZDATA Registry by the corresponding center using prespecified codes and can subsequently be classified into the broad categories of cardiac, vascular, infection, social, and other causes. "Social causes" include withdrawal from treatment, suicide, and accidental death. DW was considered to be any "social" cause of death other than accidental death in a patient who commenced dialysis during the study period. Before October 2003, deaths from treatment withdrawal were coded simply as "patient refused further treatment" or "treatment ceased for any other reason." In October 2003, the codes were expanded to include "withdrawal for psychosocial reasons," "withdrawal for cardiovascular comorbid conditions," "withdrawal for cerebrovascular comorbid conditions", "withdrawal for peripheral vascular comorbid conditions," "withdrawal related to malignancy," and "withdrawal related to dialysis access difficulties."

Statistical Analyses

We used SPSS software, version 17.0 (SPSS, Inc., Chicago, IL), for demographic statistics and graphs. We used a competing-risks survival analysis (3) to identify predictors of death due to withdrawal of treatment, with death from other causes considered a competing risk. Because of presumed qualitative differences between early withdrawal (*e.g.*, frail elderly patients withdrawing after a trial of dialysis), and late withdrawal (*e.g.*, patients withdrawing as a result of complications of vascular access or post-transplant malignancy), we restricted this analysis to the first year of RRT. Patients who received pre-emptive transplants were excluded from this analysis because they almost never withdrew and represent a different demographic. Age and number of comorbid conditions at commencement of dialysis (range, 0–4), representing coronary artery disease, cerebrovascular disease, peripheral vascular disease, and chronic lung disease, were modeled as continuous variables. Sex, race, dialysis modality, late referral, and remoteness were modeled as categorical variables. Factors potentially associated with DW on univariate analysis ($P<0.25$) were included in a multivariable model. Two-way interaction terms were tested and included if they were significant at the 1% level and clinically important. Backward selection was used to remove nonsignificant covariates, with $P<0.05$ considered to represent a statistically significant difference.

The final model included age, sex, race, dialysis modality, late referral, diabetic status, and number of comorbid conditions. The proportional subhazards assumption was tested using time-varying covariates and Schoenfeld-like residuals. The linearity assumption for age and number of comorbid conditions was assessed by plotting coefficients. Multivariable analyses were conducted using Stata software, version 11.1 (Stata Corp., College Station, TX).

Results

A total of 24,884 patients commenced RRT during the study period. The baseline demographic and clinical variables of the overall cohort and those of patients who died of DW or other causes are shown in Table 1. The mean age ± SD of the overall cohort at commencement of RRT was 59±15 years, and 59.6% of patients were male. Most patients were white (73.9%). Hemodialysis (71.6%) was the most common initial modality. In the DW group, the mean age ± SD at the start of RRT was 69±11 years, and 57.1% of patients were male. Again, the predominant racial origin was white (84.4%), and hemodialysis (74.5%) was the mainstay RRT.

The overall 1-, 3- and 5-year survival rates were 88% (95% confidence interval [CI], 88%–88%), 68% (95% CI, 67%–68%), and 52% (95% CI, 52%–53%), respectively. A total of 10,073 patients died during follow-up, with a mortality rate of 12.6 per 100 patient-years. Of these, cardiac disease was the leading cause of death, accounting for 3861 (38%) of all deaths. Social causes were the second most common cause of death, accounting for 2844 (28%) of all deaths (Figure 1). The trend of cause of death for this incident cohort over the 10 years is shown in Figure 2. The overall proportion of cardiac deaths decreased from 2000 to 2008, whereas that of social deaths gradually increased.

DW was common, with a cumulative DW incidence of 3.5% at 1 year (95% CI, 3.3%–3.8%), 9.0% at 3 years (95% CI, 8.6%–9.4%), and 13.4% at 5 years (95% CI, 12.8%–13.9%). Table 2 summarizes the reasons for DW in 2004–2008, the era for which detailed withdrawal data were collected.

We analyzed the predictors for withdrawal in the first year of dialysis (Table 3). After patients receiving pre-emptive transplants ($n=687$) were excluded from the analysis, the cumulative incidence of withdrawal in the first year of dialysis was 3.6% (95% CI, 3.4%–3.9%). Old age was a strong predictor of DW. For every decade increment of age at initiation of dialysis, there was a 70% increased risk for DW (subhazard ratio [SHR], 1.70 [95% CI, 1.59–1.83]; $P<0.001$). Late referral for dialysis was associated with an 83% increased risk for DW compared with patients referred to nephrologists earlier (SHR, 1.83 [95% CI, 1.59–2.11]; $P<0.001$). Each additional comorbid condition was associated with a 33% increased risk for DW (SHR, 1.33 [95% CI, 1.25–1.41]; $P<0.001$). Diabetes was associated with a 16% increased risk for DW compared with nondiabetic patients (SHR, 1.16 [95% CI, 1.00–1.34]; $P=0.05$). Male patients had a 15% lower risk for DW than female patients (SHR, 0.85 [95% CI, 0.66–0.87]; $P<0.001$). Compared with white patients, indigenous and other ethnicities (predominantly Asian) were associated with a 16% (SHR 0.84 [95% CI, 0.58–0.95]; $P=0.02$) and a 14% (SHR, 0.86 [95% CI, 0.48–0.91]; $P=0.01$) decreased risk for DW, respectively. Peritoneal dialysis users had a 41% decreased risk for DW compared with hemodialysis users (SHR, 0.59 [95% CI, 0.49–0.72]; $P<0.001$).

Discussion

The proportion of deaths from cardiac causes decreased as the proportion of deaths due to social causes increased over the study period. Aggressive control of cardiovascular risk factors and popularity of cardiovascular intervention (1) can explain the reduction in cardiovascular mortality over time. The reason for the increasing proportion of social deaths is unclear but may be related to more easily accessible dialysis facilities and increasing acceptance of withdrawal policies for patients in whom the treatment benefit is unclear (4).

Table 1. Baseline demographic characteristics of the overall cohort and comparison between patients who died of dialysis withdrawal and those who died of causes other than dialysis withdrawal

Characteristic	Overall Cohort	DW Deaths	Non-DW Deaths	*P* Value[a]
Total patients (*n*)	24,884	2844	7229	
Age at time of RRT (yr)	59±15	69±11	64±13	<0.001
Men, *n* (%)	14837 (59.6)	1625 (57.1)	4265 (59.0)	0.09
BMI at entry (kg/m^2)	27±6	26±6	27±6	<0.001
Racial origin, *n* (%)				<0.001
white	18,390 (73.9)	2399 (84.4)	5195 (71.9)	
Asian	1646 (6.6)	113 (4.0)	365 (5.0)	
Aboriginal/Torres Strait Islander	1921 (7.7)	136 (4.8)	643 (8.9)	
Māori	1514 (6.1)	122 (4.3)	657 (9.1)	
Pacific Islander	997 (4.0)	56 (2.0)	290 (4.0)	
other	416 (1.7)	18 (0.6)	79 (1.1)	
Primary renal disease, *n* (%)				<0.001
diabetes mellitus	7901 (31.8)	881 (31.0)	2753 (38.1)	
GN	6264 (25.2)	491 (17.3)	1214 (16.8)	
renal vascular disease/hypertension	3487 (14.0)	528 (20.5)	1244 (17.2)	
polycystic kidney disease	1597 (6.4)	68 (2.4)	225 (3.1)	
unknown	204 (0.8)	19 (0.7)	63 (0.9)	
other	5431 (21.8)	803 (28.2)	1730 (23.9)	
Comorbidity at entry, *n* (%)				
diabetes mellitus	10,258 (41.2)	1239 (43.6)	3591 (49.7)	<0.001
chronic lung disease	3926 (15.8)	606 (21.3)	1562 (21.6)	0.74
coronary artery disease	9867 (39.7)	1588 (55.8)	3912 (54.1)	0.12
peripheral vascular disease	6414 (25.8)	1087 (38.2)	2605 (36.0)	0.04
cerebrovascular disease	3738 (15.0)	740 (26.0)	1483 (20.5)	<0.001
Late referral, *n* (%)	6021 (24.2)	833 (29.3)	2050 (28.4)	0.35
Modality of RRT at entry, *n* (%)				0.18
hemodialysis	17,812 (71.8)	2120 (74.5)	5259 (72.7)	
peritoneal dialysis	6385 (25.7)	719 (25.3)	1954 (27.0)	
Pre-emptive transplantation, *n* (%)	687 (2.8)	5 (0.2)	16 (0.2)	
Place of residence at entry, *n* (%)[b]				<0.001
major cities	13,757 (67.3)	1675 (69.8)	3641 (63.9)	
inner regional	3661 (17.9)	474 (19.8)	1045 (18.3)	
outer regional	2027 (9.9)	190 (7.9)	684 (12.0)	
remote	662 (3.2)	47 (2.0)	217 (3.8)	
very remote	332 (1.6)	14 (0.6)	114 (2.0)	
Size of renal unit, *n* (%)				<0.001
large	16,941 (68.1)	1749 (61.5)	5022 (69.5)	
medium	6606 (26.5)	895 (31.5)	1877 (26.0)	
small	1337 (5.4)	200 (7.0)	330 (4.6)	

Values expressed with a plus/minus sign are the mean ±SD. *P* value is the comparison between patients who died of DW and those who died of causes other than DW. DW, dialysis withdrawal; BMI, body mass index; RRT, renal replacement therapy.
[a]Continuous variables were analyzed with the use of *t* tests, and all categorical data were analyzed with the use of chi-squared test and one-way ANOVA.
[b]Available only for Australian patients.

The reasons for higher prevalence of DW in Australia and New Zealand than in the United States are not known. We postulate that it could be related to the difference in cultural and health care systems between these countries. Furthermore, the method for coding DW as a cause of death between the ANZDATA registry and U.S. Renal Data System (USRDS) registry could contribute to the difference. As mentioned in the Materials and Methods section, a new coding system for DW in a variety of situations was introduced in the ANZDATA registry in October 2003 to avoid misclassification of DW in other categories. In addition, large number of patients withdrew from dialysis in Australia because of psychosocial reasons. Ashby *et al.* reported that the desire not to burden others and the personal experience of deteriorating quality of life were crucial elements in the decision to discontinue dialysis (5). Further qualitative studies in this area might help to explain why the rate of DW is higher in Australia and New Zealand than in the United States.

The incidence of RRT has remained relatively constant among younger age groups but has progressively increased in older age groups in Australia and New Zealand in recent years (6). According to the ANZDATA registry report, in 2004 there were 244 (390 per million population [pmp] per year) and 244 (445 pmp per year) incident patients commenced on dialysis for the 70- to 74-year-old and 75- to

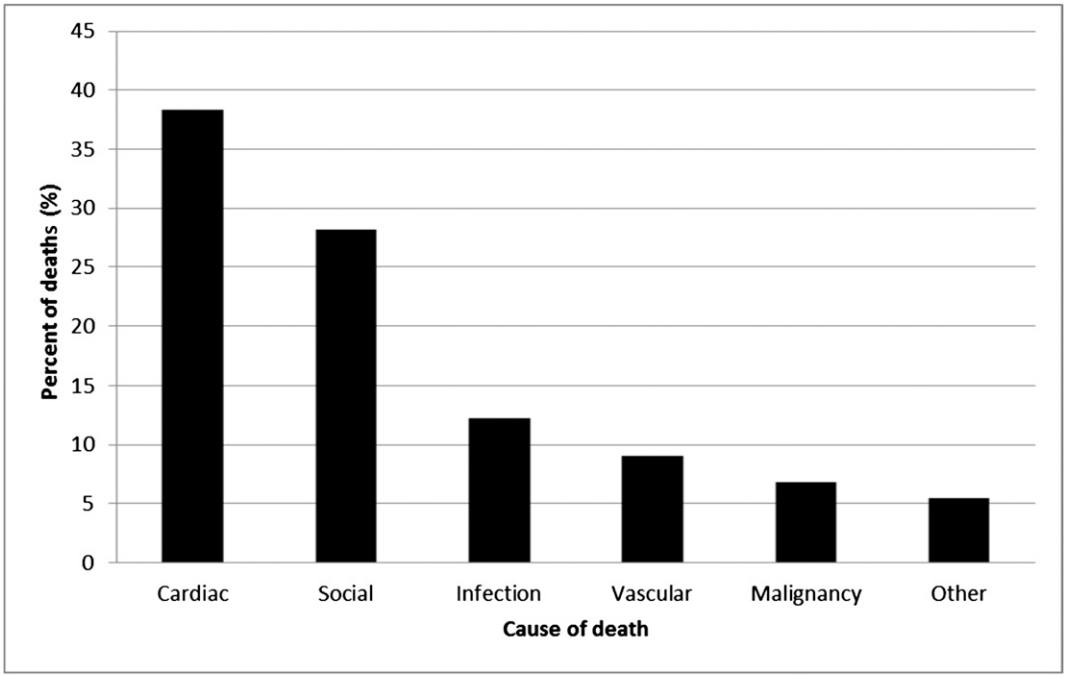

Figure 1. | **Cause of death for patients commencing renal replacement therapy from 1999 to 2008.**

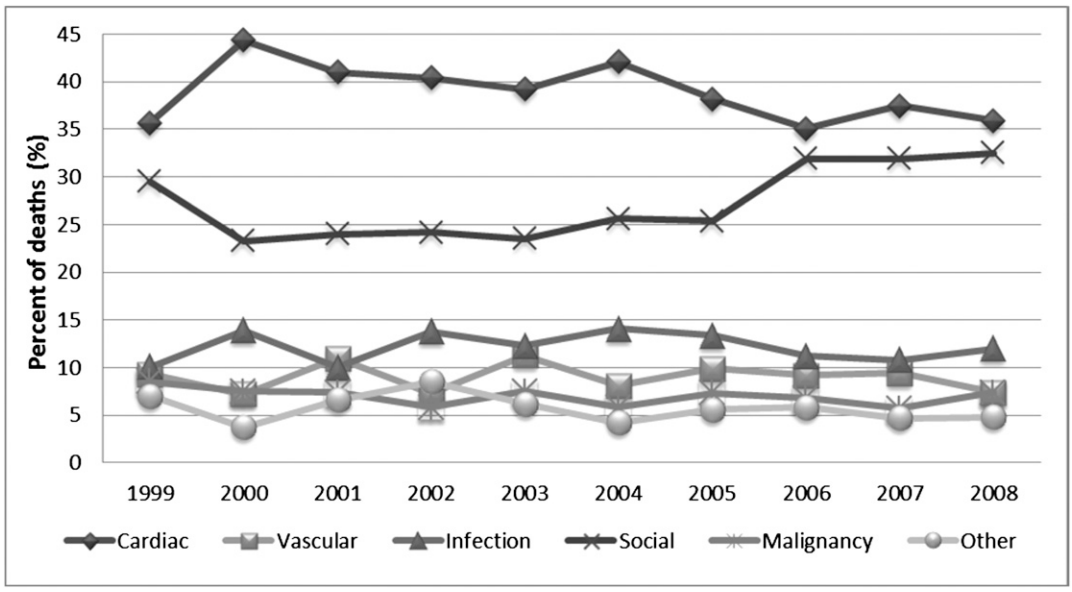

Figure 2. | **Cause of death for patients commencing renal replacement therapy from 1999 to 2008, by year.**

79-year-old age groups, respectively. These numbers increased to 311 (469 pmp per year) and 277 (504 pmp per year) incident patients in 2008 for the two age groups, respectively (7).

Numerous studies on DW have shown an increased risk in older age groups (4,8–14). In the ANZDATA registry report, among social causes of death, 74% of all deaths were in patients age 65–84 years (15). In the United Kingdom renal registry report, DW accounted for 19% of deaths in patients age 65 years or older but only 8% of deaths in patients younger than age 65 years (16). Our study revealed similar findings; as a result, it can be concluded that as the patients get older, they will tend to choose DW.

The association between sex and DW has been inconsistent. Some studies showed an increase in DW among women (4), whereas others showed no significant sex difference in the rate of DW (11,17). In our study, women

Table 2. Reasons for dialysis withdrawal, 2004–2008

Reason	Data
Total patients (*n*)	2154
Withdrawal for psychosocial reasons	832 (38.6)
Withdrawal for cardiovascular comorbid conditions	348 (16.2)
Withdrawal related to malignancy	345 (16.0)
Withdrawal for peripheral vascular comorbid conditions	265 (12.3)
Withdrawal for cerebrovascular comorbid conditions	212 (9.8)
Withdrawal related to difficulties with dialysis access	98 (4.5)
Therapy ceased for any other reason	38 (1.8)
Suicide	12 (0.6)
Patient declined further treatment	4 (0.2)

Unless otherwise noted, data are the number (percentage) of patients. As described in the Materials and Methods section, the Australia and New Zealand Dialysis and Transplant Registry changed its codes for causes of withdrawal in October 2003; consequently, in the 2004–2008 era the reasons for withdrawal are more clearly delineated.

were more likely to withdraw from dialysis than men. It has been suggested that there may be sex disparities in clinical decision-making. Societal value judgments placed on gender roles may put women at a disadvantage in the context of receiving certain treatments, such as dialysis and renal transplantation. It has been suggested that a general perception that men's social role obligations or contributions to society are greater than women's may fuel these disparities (18).

Our study also showed that DW was more common in whites than in indigenous persons (Aboriginal or Torres Strait Islander, Māori and Pacific Islander) or patients of other ethnicities (predominantly Asian). A similar finding was reported by Leggat *et al.*, who noted a higher rate of DW in white persons than African Americans and Asians (4). DW was also more prevalent in white than in black patients in the United States (10). Social and cultural origin probably contribute to the marked ethnic differences in the decision to withdraw dialysis. The more liberal acceptance of frail patients for a trial of dialysis, combined with the greater likelihood of DW among white persons, may contribute to the higher rate of DW in this group.

There is conflicting evidence concerning the relationship between diabetic status and DW. Some reports showed that diabetes mellitus is associated with higher rates of DW (4,9,10,13), whereas other studies showed no significant difference (14,17,19). Our study revealed that diabetic status was associated with an increased risk for DW. We postulate that patients with diabetes may be more likely to have cardiovascular events, peripheral vascular diseases, and dialysis access problems, which may predispose them to withdrawal from treatment.

Previous studies reported that comorbidity at start of dialysis was associated with a higher rate of DW (11,14). Our study shows similar findings. Kjellstrand postulated

Table 3. Predictors of withdrawal from renal replacement therapy in the first year

Variable	Patients (*n*)	Univariate Analysis		Multivariate Analysis	
		SHR (95% CI)	*P* Value	SHR (95% CI)	*P* Value
Age (per decade)	24,197	1.87 (1.75–1.99)	<0.001	1.70 (1.59–1.83)	<0.001
Male sex	24,197	0.86 (0.75–0.99)	0.04	0.75 (0.65–0.86)	<0.001
Race					
white	24,197	1 (reference)	<0.001[a]	1 (reference)	0.005[a]
indigenous		0.48 (0.38–0.60)		0.74 (0.58–0.95)	
other		0.49 (0.36–0.68)		0.66 (0.48–0.91)	
Late referral	24,197	1.96 (1.71–2.26)	<0.001	1.83 (1.59–2.11)	<0.001
Diabetes	24,197	1.14 (0.99–1.30)	0.07	1.16 (1.00–1.34)	0.05
Comorbid burden[b] (per 1 additional comorbid condition)	24,197	1.58 (1.50–1.66)	<0.001	1.33 (1.25–1.41)	<0.001
Peritoneal dialysis	24,197	0.53 (0.44–0.64)	<0.001	0.59 (0.49–0.72)	<0.001
Remoteness					
major cities	19,883[c]	1 (reference)	0.02[a]		
inner regional		1.11 (0.92–1.33)		—	—
outer regional		0.87 (0.67–1.14)		—	—
remote		0.55 (0.32–0.96)		—	—
very remote		0.34 (0.13–0.91)		—	—
				—	—

SHR, subhazard ratio; CI, confidence interval.
[a]*P* value for category as a whole.
[b]Number of comorbid conditions (from 0 to 4): coronary artery disease, cerebrovascular disease, peripheral vascular disease, and chronic lung disease.
[c]Available only for Australian patients.

that chronic comorbid conditions, such as ischemic heart disease or diabetes mellitus, often caused an acute complication that in turn led to other acute problems; this cascade of problem ultimately wore out the patient and caused him or her to stop all treatment (20). On the other hand, Evans *et al.* reported that perceived subjective quality of life by patients with ESRD had no correlations with comorbidity (21). In their study, patients undergoing dialysis had subjective scores on standardized tests for well-being and life satisfaction that were similar to scores of the healthy general population. Qualitative studies are warranted to explore the discrepancy in these observations.

Maillouex *et al.* have found that "dissatisfaction with life" was associated with DW (13). Cohen *et al.* reported that deterioration of chronic diseases (66%) and acute intercurrent disorders (22%) were the most common primary reasons for patients and their family to withdraw from dialysis (22).

In our cohort, DW was more common in hemodialysis users than in peritoneal dialysis users. This finding is in contrast to those of other studies, which found that dialysis modality had no effect on DW (17,23). The effect of modality was strong and persisted even after adjustment for confounders. It may reflect differences in illness perception between peritoneal dialysis and hemodialysis patients (24). Most patients undergoing peritoneal dialysis are responsible for performing the dialysis treatment themselves; they have a greater sense of control than do hemodialysis patents. The sense of personal control is important because it can reduce fear, promote active participation, and facilitate adherence to the suggested treatment. It is therefore not surprising that peritoneal dialysis patients were less prone to DW than were hemodialysis patients. However, selection bias and unmeasured confounders may also contribute to this finding because frail patients were probably more likely to commence hemodialysis than peritoneal dialysis. This could partially explain why hemodialysis patients were more likely to choose DW.

Late referral for dialysis is well known to be associated with higher mortality not only within the first year (25–27) but also more than 1 year after initiation of dialysis (28). Innes *et al.* showed a higher prevalence (25%) of deaths due to DW in the late-referred population (26). Our cohort showed a significantly increased risk for DW in the late-referred patients probably because late referral does not allow enough time for nephrologists to discuss with patients and their family members about different aspects of the disease and subsequent treatment (29). We also hypothesize that patients presenting late had more severe uremic symptoms and poor clinical conditions with prolonged hospitalization (30); they were not physically or psychologically prepared for long-term RRT (31). This may explain the higher rate of DW in this group of patients due to psychosocial burden or complications of medical illnesses.

Major strengths of this study include its size, completeness of data (there were no missing data for the variables included in the final multivariable model), and completeness of follow-up (only 28 of 24,884 patients were lost to follow-up). To our knowledge, this is the first study to use a competing-risks model to analyze predictors for DW, taking into account the competing risk for death from other causes.

The most important limitation of this study is the difficulty in classifying causes of death. For example, if a patient stopped dialysis because of terminal cancer, some units may have reported this as a death due to malignancy and some may have reported it as a withdrawal due to malignancy. However, this is a common problem in most studies using registries. Another limitation of our study is that the ANZDATA registry includes only 5 comorbid conditions compared with 11 in USRDS data (32). Because a comorbid condition is the single most important determinant of clinical outcome in patients with ESRD (33), a more robust analysis of comorbid conditions in the ANZDATA population may have led to an even stronger association between number of comorbid conditions and DW.

DW is common, accounting for more than one in four deaths among patients with ESRD in Australia and New Zealand. Risk factors for DW in the first year include older age, female sex, white race, diabetes mellitus, comorbid burden, use of hemodialysis, and late referral to a nephrologist. Further qualitative research examining decisions to withdraw from dialysis is warranted.

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Disclosures

None.

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