CHAPTER 10

CANCER REPORT

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Survival of people with myeloma and end stage kidney disease treated with dialysis

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Background

Multiple myeloma is a plasma cell malignancy characterised by monoclonal protein production and lytic bone lesions. Each year approximately 1,200 people are diagnosed with myeloma in Australia, representing 1.2% of all new cancer cases. The age standardised incidence is 5.6 cases per 100,000 population, with more males affected than females (ratio 1:6) Renal disease is common in multiple myeloma, but has a heterogeneous pathology arising via different mechanisms, and can affect the glomeruli, tubules, interstitium in isolation or in combination. The presence and severity of renal disease correlates with patient survival, and overall prognosis is related to response of the renal disease to therapy. For people with myeloma and irreversible kidney failure, prognosis is regarded as particularly poor.

Myeloma usually affects the kidney as a consequence of monoclonal immunoglobulin light chains, although more rarely heavy chains or entire immunoglobulins may be involved, and non monoclonal protein injury may also occur. Glomerular injury arises as a result of immunoglobulin deposition (principally light chain disease), or via amyloidosis, cryoglobulinemia or proliferative glomerulonephritis due to monoclonal protein deposition. Tubular injury arises via cast nephropathy caused by light chains (classical “myeloma kidney”, which is the commonest renal disease in myeloma), but proximal and distal tubular dysfunction are not uncommon, and acquired Fanconi's syndrome is recognised. Interstitial disease can arise directly through plasma cell infiltration or through a generalised interstitial nephritis.

Renal disease is commonly the presenting manifestation of multiple myeloma, and myeloma cast nephropathy is the most common diagnosis in patients presenting with significant renal dysfunction. Patients may also present with nephrotic syndrome related to amyloidosis or light chain deposition disease, volume depletion secondary to hypercalcaemia, or a hyperviscosity syndrome. Hyperuricaemia, or treatment with nephrotoxic drugs (such as non steroidal anti-inflammatory drugs or antibiotics) may also exacerbate renal dysfunction.

Treatment of kidney disease in myeloma involves correction of any factors contributing to acute kidney injury, and plasmapheresis for those with cast nephropathy. With directed and supportive therapies, the majority of patients will have improved renal function in the short to medium term. However, those with dense cast nephropathy and significant tubular damage on biopsy are less likely to recover, and more likely to progress to end stage kidney disease. Survival with myeloma and established end stage kidney disease in case series was previously acknowledged to be universally poor, but more recent studies suggest the prognostic impact of ESKD may be lessening and overall survival improving.

We aimed to describe the characteristics and survival of Australian and New Zealander patients with myeloma and established end stage kidney disease who were treated with dialysis. We also aimed to examine changes in survival over time, and to identify any prognostic factors for improved survival.

Methods

We performed a cohort study using ANZDATA records from 1963-2009, and included all people treated with dialysis during this time. We categorised people into two groups; “myeloma”, and “non-myeloma”. The myeloma group comprised all incident dialysis patients whose primary renal disease was attributed to myeloma. As our previous work has shown the timeline of confirmation of myeloma diagnosis and dialysis initiation is often not clear cut and may occur in reversed sequence, we also included all people who had myeloma diagnosed within 1 year of starting dialysis, regardless of their listed primary renal disease. All other people were classified into the non-myeloma group. We classified people who went on to develop myeloma more than one year after starting dialysis into the “non-myeloma” group, as our aim was to report survival on dialysis for those with ESKD as a consequence of myeloma. When describing primary renal disease for both groups, we also considered “potentially myeloma related causes”, which were people who had a primary renal disease recorded as plasma cell leukaemia, amyloidosis, light chain nephropathy, and Waldenstrom’s macroglobulinaemia (because prior to the WHO reclassification in 1997, Waldenstrom’s was regarded as a myeloma related condition). If these people went on to develop myeloma within one year of commencing dialysis they appear in the myeloma group, and if not, they appear in the non-myeloma group.

To investigate survival on dialysis we performed two analyses using survival analysis techniques including Kaplan Meier curves and Cox proportional hazards, testing for difference using Wald tests. The first analysis included all dialysis patients, and looked at survival differences for myeloma and non-myeloma groups overall, and then after adjusting for age at ESKD (categorised as <55, 55-64, 65-74, 75+) and era of treatment (categorised as before 1990, 1990-94, 1995-99, 2000-04, 2005 onwards). The second analysis was a Cox model, and considered only the myeloma group, and examined potential prognostic factors for improved survival on dialysis. We considered age at ESKD, sex, race, dialysis modality (peritoneal or haemodialysis), era of dialysis initiation (before 1990, 1990-1994, 1995-1999, 2000-2004, and 2005 onwards), timing of myeloma diagnosis relative to start of dialysis, diagnosis of any other cancer prior to dialysis, the presence of diabetes comorbidity and smoking history (never, former or current) at ESKD. We tested the assumptions of proportional hazards using plots of the Schoenfeld residuals.

Results

A total of 54,178 people were treated with dialysis between 1963-2009, representing 332,003 person-years of observation. The characteristics of the cohort are described in **table 1**. A total of 807 people (1%) had myeloma diagnosed either before or within one year of starting dialysis, and 636 of these people had myeloma as their primary renal disease. A further 655 people had a potentially myeloma related cause of ESKD, but only 47 of these went on to develop myeloma within 12 months of commencing dialysis.

Table 1: Characteristics of people with and without myeloma treated by dialysis between 1963-2009

Characteristic	Myeloma		Non-Myeloma	
	n	%	n	%
Total (%)	807	1	53,371	99
Country of residence				
Australia	690	86	44,256	83
New Zealand	117	15	9,115	17
Primary renal disease				
Myeloma	636	79	0	0
Potentially Myeloma related	47	6	608	1
Glomerulonephritis/IgA nephropathy	35	4	15,906	30
Diabetes	24	3	12,728	24
Other	65	8	24,129	45
Age at ESKD				
<55	124	15	24,784	46
55-64	225	28	11,862	22
65-74	298	37	10,993	21
75+	160	20	5,732	11
Sex				
Female	300	37	22,482	42
Male	507	63	30,889	58
Era of ESKD				
<1990	80	10	12,956	24
1990-1994	70	9	6,491	12
1995-1999	97	12	9,051	17
2000-2004	256	32	11,211	21
2005-2009	304	26	13,662	26
First Dialysis modality				
Haemodialysis	668	83	36,539	68
Peritoneal dialysis	139	17	16,832	32
Racial background				
Non-white	47	6	11,792	22
White	760	94	41,579	78
Other malignancy prior to ESKD				
None	743	92	49,682	93
Pre-dialysis malignancy	64	8	3,689	7
Other malignancy subsequent to ESKD				
None	786	97	48,766	91
Post-dialysis malignancy	21	3	4,605	9
Smoking history at ESKD				
Never or unknown	344	43	31,667	59
Current or former	463	57	21,704	41
Diabetes Mellitus				
No	589	73	36,828	69
Yes	131	16	8,188	15
Unknown *	87	11	8,355	16
Status during follow-up				
Alive	117	15	21,149	40
Died	690	86	32,222	60

* Comorbidity with known diabetes at time of ESKD was only routinely recorded in ANZDATA from April 1991, hence before that date, the majority of people are classified as unknown.

Figure 1 shows the timing of myeloma diagnosis relative to ESKD and dialysis start for the cohort. Of the 807 people with myeloma, 84 (10.4%) were diagnosed with myeloma more than 5 years before ESKD, 197 (24.4%) were diagnosed between one and four years before starting dialysis, 167 (20.7%) were diagnosed with myeloma between two and 11 months before starting dialysis, 302 (37.4%) were diagnosed within 2 months before or 2 months after starting dialysis, and 57 (7.1%) were diagnosed between 2 months and 1 year after starting dialysis.

Figure 1: Plot of myeloma diagnosis relative to timing of ESKD and dialysis commencement

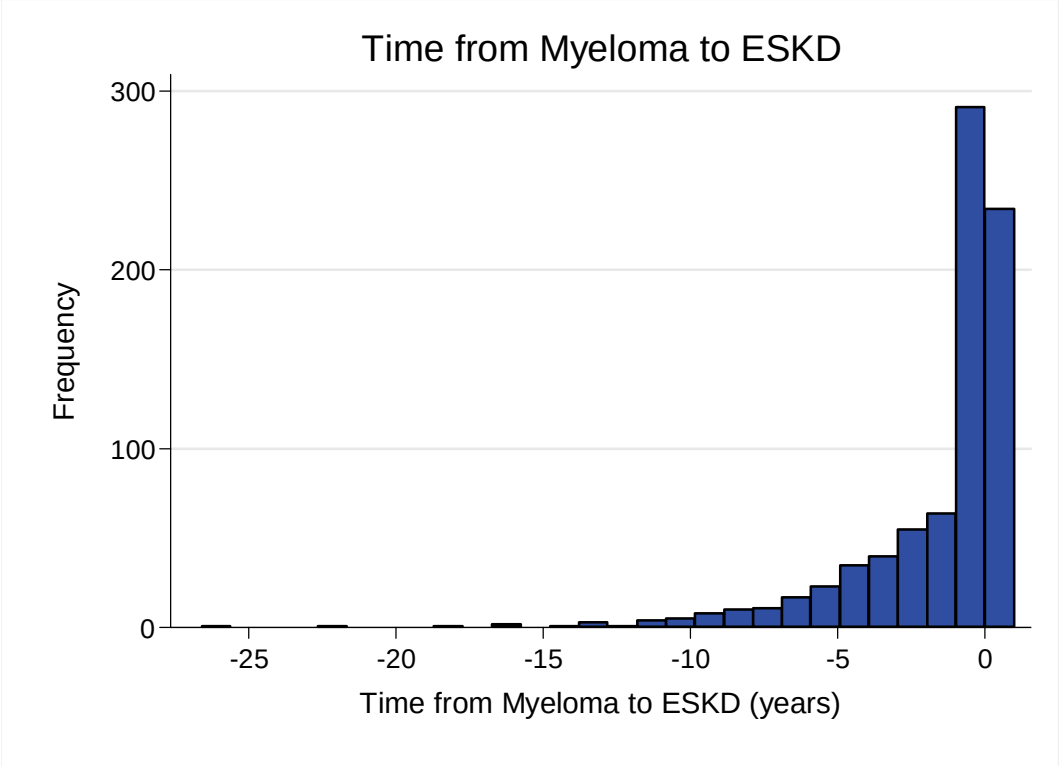


Figure 2a shows the overall survival of myeloma patients on dialysis relative to the non-myeloma population. Overall, survival for myeloma patients was 52.5% and 9.4% at 1 and 5 years, compared with 88.4% and 54.6% for the rest of the dialysis population (difference between myeloma and non myeloma groups P< 0.0001).

Figure 2a: Unadjusted survival on dialysis for myeloma versus non myeloma patients

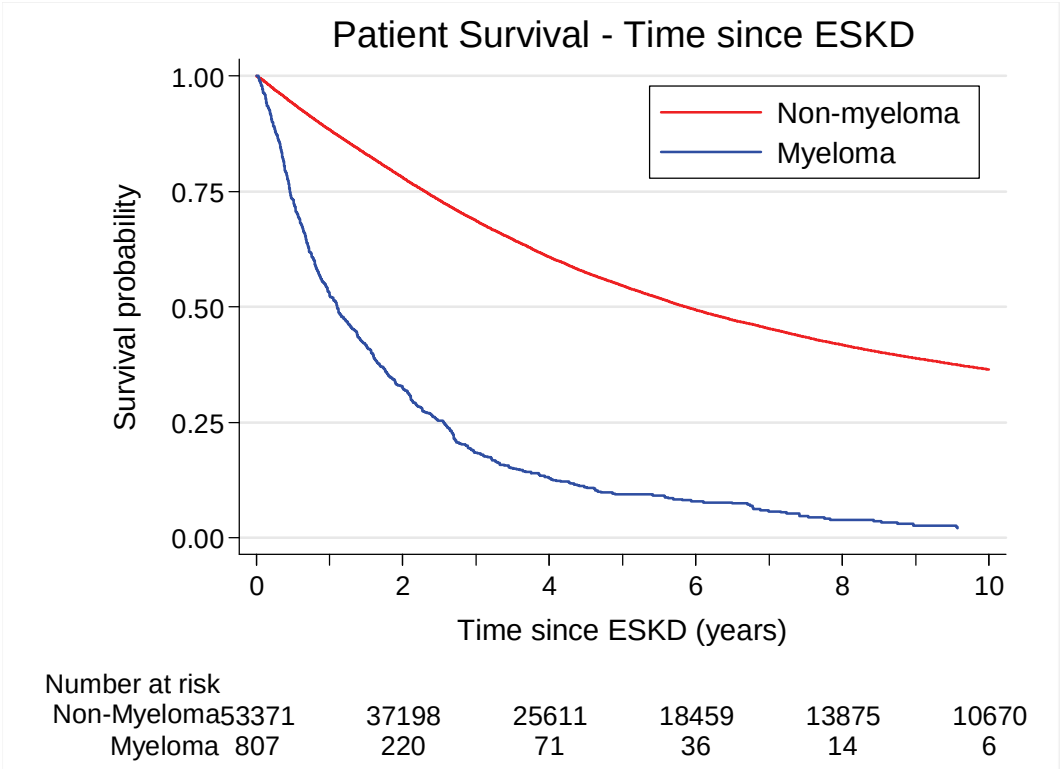


Figure 2b shows the overall survival of the dialysis population according to their primary renal disease. Unadjusted one and five year survival for those with myeloma as primary renal disease was 49.2% and 6.8% respectively, compared with potentially myeloma related 77.3% and 31.9%, glomerulonephritis or IgA nephropathy 92.1% and 68.3%, diabetes 86.2% and 38.5% and other causes 87.2% and 53.2%.

Figure 2b Unadjusted survival on dialysis, stratified by primary renal disease

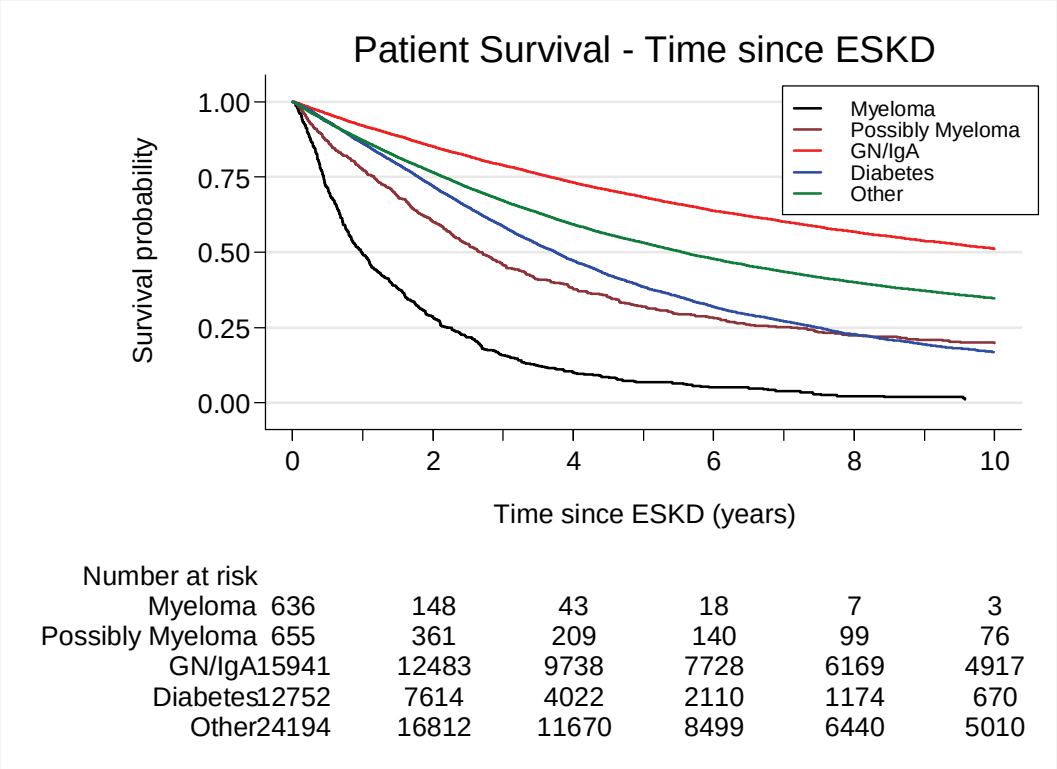


Table 2 shows the average age of people starting dialysis through time. On average, people with myeloma are older than the non-myeloma group, and although their age has increased over time, from 61.5 years before 1990 to 68.9 years between 2005-2009, the average age of the non myeloma group has increased more steeply, from 47.0 years before 1990, to 62.5years between 2005 and 2009.

Table 2: Average age of people starting dialysis through time

Era of dialysis	Myeloma		Non-myeloma	
	N	Median (IQR)	N	Median age (IQR)
<1990	80	61.5 (55.2 - 66.1)	12,956	47.0 (33.7 - 57)
1990-1994	70	64.6 (56.7 - 70.1)	6,491	55.4 (41.4 - 65.2)
1995-1999	97	65.8 (57.9 - 72.2)	9,051	58.6 (45.2 - 68.7)
2000-2004	256	68.4 (59.4 - 74.9)	11,211	61.4 (48.6 - 71.7)
2005-2009	304	68.9 (61.7 - 74.6)	13,662	62.5 (50.4 - 72.9)

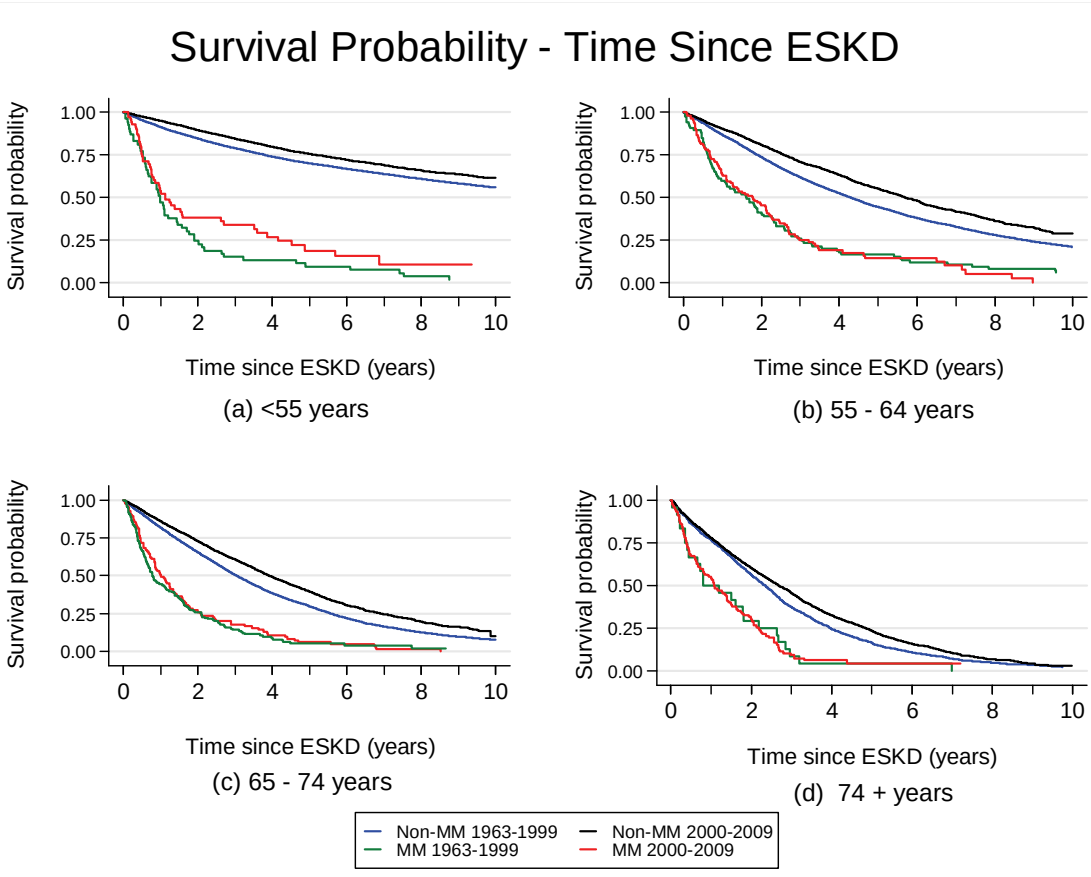
Figure 3 shows how overall survival has changed for the dialysis population through time, after allowing for these differences in age when starting dialysis. When comparing people on dialysis between 1963-1999 versus those starting dialysis between 2000-2009, there is a significantly improved survival at all ages for the non myeloma group (P<0.0001 for all ages). Five year survival in the non myeloma group starting dialysis after 2000 was 75.7% for those under 55 years, 55.1% for those 55-64 years, 39.5% for those 65-74 years, and 23.3% for those aged 75 years or older. However, these improvements over time have not been seen in the myeloma group, where there was no significant improvement in survival over time (comparing those starting dialysis 1963-1999 versus those starting between 2000-2009, aged <55 P=0.12, 55-64 years P=0.86, 65-74 years P=0.49 and 75 years and older P=0.96). One and five year survival for those with myeloma starting dialysis after 2000 was respectively 53.9% and 18.8% for those under 55 years, 63.5% and 14.3% for those aged 55-64 years, 44.3% and 5.2% for those aged 65-74 years, and 54.1% and 0% for those 75years and older. Cause of death for those with and without myeloma is shown in **table 3**.

Table 3: Cause of death for people on dialysis with and without myeloma in Australia and New Zealand 1963-2009 *

Cause of death	Myeloma Total deaths 609	Non myeloma Total deaths 32, 223
	N (%)	N (%)
Cardiovascular	102 (14.8)	12, 842 (39.9)
Vascular	23 (3.3)	3, 478 (10.8)
Infection	70 (10.1)	4, 785 (14.9)
Cancer	383 (55.5)	2, 739 (8.5)
Social	99 (14.4)	5, 934 (18.4)
Other	13 (1.9)	2, 445 (7.6)

see Anzdata main form for details of these categories,
see www.anzdata.org.au/forms/ANZDATA/ANZDATA2007.pdf

Figure 3: Unadjusted survival on dialysis for people with (MM) and without myeloma (non-MM), by age at starting dialysis and stratified by era of treatment *



***** Comparing survival for those starting dialysis during 1963-1999 versus 2000-2009, by age at commencing dialysis;
panel a <55years : with myeloma P=0.12, non myeloma P<0.0001panel b 55-64 years: with myeloma P= 0.86, non myeloma P<0.0001 panel c 65-74 years: with myeloma P= 0.49, non myeloma P<0.0001panel d 75 years and older: with myeloma P= 0.96, non myeloma P<0.0001

Within the myeloma group, **Table 4** shows the results of the analysis of potential prognostic factors associated with survival. In the univariate analysis, there were no differences in survival according to sex (P=0.73), era of dialysis (P=0.51), timing of myeloma diagnosis relative to starting dialysis (P=0.15), racial background (P=0.59), having another malignancy prior to ESKD (P=0.52) or smoking history (P=0.94). However, older age at ESKD, primary renal disease, haemodialysis as first dialysis modality and a history of diabetes all conferred poorer survival (P<0.05 for all, see table 4), and so these were included in the multivariate model. After allowing for the effects of age, dialysis modality and diabetes, having a primary renal disease attributed to causes other than myeloma was associated with between 30-40% better survival (P=0.0004). Having peritoneal dialysis rather than haemodialysis as first treatment modality also conferred a survival advantage (HR 0.7, CI 0.6-0.9, P= 0.0006). Conversely, age older than 65 at ESKD was strongly associated with poorer survival, with those aged 65-74 having a 60% and those over 75 years a 70% increased risk of death, compared to those <55 years (respectively HR 1.6, CI 1.3-2.1 and HR 1.7, CI 1.3-2.3, P<0.0001). Having a history of diabetes at ESKD also increased risk of death by 50% (HR 1.5, CI 1.2-1.8, P <0.001).

Table 4: Risk of death for people with myeloma treated with dialysis in Australia and New Zealand 1963-2009

	Univariate		Multivariate	
Characteristic	**Hazard ratio (95% CI)**	**P for difference**	**Hazard ratio (95% CI)**	**P for difference**
Primary renal disease				
Myeloma (referent)	1.0	0.0002	1.0	0.0004
Potentially Myeloma related	0.7 (0.5-0.9)		0.6 (0.5-0.9)	
Glomerulonephritis/IgA nephropathy	0.7 (0.5-1.0)		0.7 (0.5-1.1)	
Diabetes	0.7 (0.5-1.1)		0.7 (0.5-0.8)	
Other	0.6 (0.5-0.8)		0.6 (0.4-0.8)	
Age				
<55(referent)	1.0	<0.0001	1.0	<0.0001
55-64	0.8 (0.7-1.1)		0.9 (0.7-1.2)	
65-74	1.4 (1.1-1.7)		1.6 (1.3-2.1)	
75+	1.3 (1.0-1.7)		1.7 (1.3-2.3)	
Sex				
Female (referent)	1.0	0.73		
Male	1.0 (0.9-1.2)			
Era of dialysis				
<1990 (referent)	1.0	0.51		
1990-1994	1.1 (0.8-1.5)			
1995-1999	0.8 (0.6-1.1)			
2000-2004	1.0 (0.8-1.3)			
2005-2009	1.0 (0.7-1.2)			
Timing of myeloma diagnosis relative to ESKD				
> 5 years before ESKD (referent)	1.0	0.15		
1-5 years before ESKD	1.1 (0.8-1.4)			
1-11 months before ESKD	1.3 (1.0-1.7)			
Peri ESKD (within 1 month before or after ESKD)	1.3 (1.0-1.7)			
1-12 months after ESKD	1.1 (0.8-1.6)			
First Dialysis modality				
Haemodialysis (referent)	1.0	0.06	1.0	0.006
Peritoneal dialysis	0.8 (0.7-1.0)		0.7 (0.6-0.9)	
Racial background				
Non-white (referent)	1.0	0.59		
White	0.9 (0.7-1.3)			
Other malignancy prior to ESKD				
None (referent)	1.0	0.52		
Pre-dialysis malignancy	0.9 (0.7-1.2)			
Smoking history at ESKD				
Never (referent)	1.0	0.94		
Current or former	0.9 (0.9-1.2)			
Diabetes at ESKD				
No diabetes (referent)	1.0	0.002	1.0	<0.001
Diabetes	1.4 (1.1-1.7)		1.5 (1.2-1.8)	

Note: All P values are calculated using the Wald test.

Discussion

People with myeloma and established ESKD have poor survival, with approximately half dying within a year of commencing dialysis, with death attributed to their cancer in the majority of cases. People younger than 65 years, without diabetes co-morbidity, and who undertake peritoneal dialysis have better prognosis than other groups. There is no evidence that survival is improving, as over time, those with myeloma have not experienced the improved dialysis outcomes that those with ESKD from other causes can now expect.

There is little contemporary registry data on survival for people with established ESKD and myeloma. A recent study drawing from 13 European registries, showed a similar proportion of dialysis patients had myeloma as their primary renal disease, but showed that incidence had increased threefold between 1986 and 2005, and that these patients were increasingly older than those starting dialysis for other reasons. Whereas absolute numbers of people with myeloma starting dialysis has also increased in Australia and New Zealand, this is not so marked, and although those with myeloma are older, the average age of myeloma patients has not increased as steeply as those with ESKD from other causes. This paradox suggests differences in dialysis acceptance criteria across nations. Our finding that those on peritoneal dialysis had improved survival over those on haemodialysis is similar to data from the United States and Europe. Our interpretation of this finding is that it is likely to be an issue of selection bias and residual confounding: those fitter and more able patients are more likely to choose a home based therapy than those less able and with less supportive home environment.

Our choice of including those diagnosed with myeloma up to one year after starting dialysis was informed by our previous work, which found the chronology of cancer symptoms, confirmed cancer diagnosis and the commencement of renal replacement therapy may not always occur in that sequence. We reasoned that for people developing myeloma after 1 year on dialysis, this was more likely to be an incidental complication rather than causally implicated in their renal failure. However, this assumption is untested, and may not be entirely correct. We also opted to investigate those with potentially myeloma related causes of ESKD as a separate group, as diagnostic tools and criteria have changed over time since the inception of the ANZDATA registry in 1963, and we cannot be certain that, despite best intentions, incident cases would be classified similarly over time.

A limitation of the design of our study means that we are unable to investigate or comment on newer treatment options such as high flux haemodialysis for myeloma patients presenting with reversible acute kidney injury as our investigation was limited to those with established ESKD. The ability to investigate reversible kidney disease is not possible using ANZDATA, as the registry only holds records for those people where renal failure is irreversible and renal replacement therapy is intended to be indefinite, and thus does not capture data for people who are treated with dialysis but subsequently recover kidney function. As a result we were not able to compare survival of people with myeloma without ESKD. We also did not consider people treated with more recent and controversial interventions such as bone marrow transplant with kidney transplantation, as the number of such treatments in Australia and New Zealand is very small, and recent, so little useful information can be gained beyond case descriptions.

This study provides useful clinical estimates for clinicians and patients alike who are faced with difficult treatment decisions, and for whom an estimate of likely survival time on dialysis, appropriate for age and co-morbidity, may be helpful.

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