Changing survival of people with myeloma and end stage kidney disease; a cohort study using ANZDATA 1963-2013

Angela C Webster PhD [1] [2], Ashley B Irish MBBS [3], Patrick J Kelly PhD[1]

1. Sydney School of Public Health, University of Sydney, NSW, Australia

2. Centre for Transplant and Renal research, Westmead Hospital, Westmead, NSW, Australia

3. Fiona Stanley Hospital renal unit, Murdoch, WA, Australia

Corresponding author

Associate Professor Angela Webster

Sydney School of Public Health

The University of Sydney

Room 304a, Edward Ford Building A27, NSW 2006

t +61 2 9036 9125

f +61 2 9351 5049

angela.webster@sydney.edu.au

Running title: Survival with myeloma and ESKD over time

Word count: abstract 275, manuscript 2,987

Tables and figures: 4 tables, 4 figures.

Abstract

Background: It is unclear whether recent advances in myeloma therapy have improved survival for all those with myeloma and end stage kidney disease (ESKD).

Methods: population based registry cohort study using Australia and New Zealand Dialysis and Transplant Registry data 1963-2013. We measured survival of people with myeloma and other plasma cell dyscrasias and ESKD over time, and investigated prognostic factors for improved survival using survival analysis (results expressed as hazard ratios HR with 95% confidence intervals).

Results: We included 65,940 people (207,595 person-years); 1,067 people (1.6%) with myeloma, and 572 (0.9%) with other plasma cell dyscrasia. Myeloma ESKD rose from 0.8% before 1994 to 2.2% in 2004 and remained stable. People with myeloma were older, and age increased over time, from 62.5 before 1994 to 70.1 years from 2010, but the non-myeloma group age increased more steeply (52.0 before 1994; 62.2 from 2010). In myeloma patients, survival improved (p<0.001) with recent predicted 5 year survival of 27.5% aged <55, 32.2% aged 55-64, 16.3% for 65-74 and 12.7% aged ≥75 years. Survival did not improve for plasma cell dyscrasia patients (p = 0.70). Myeloma patients on peritoneal dialysis had improved survival compared with those on haemodialysis (HR0.7, CI 0.6-0.9), but those aged ≥65 had poorer survival (65-74 years HR1.5, CI1.2-1.9; ≥75 HR1.7, CI1.3-2.1), as did diabetics (HR1.3, CI1.1-1.6).

Conclusions: The proportion of people with myeloma and ESKD remains stable, but their survival has progressively improved in Australia and New Zealand. On starting ESKD treatment with myeloma, a 59 year old without diabetes on peritoneal dialysis can expect a 45% 5 year survival, where a 75 year old diabetic on haemodialysis has 9% 5 year survival.

5 Keywords: myeloma, dialysis, ESKD, survival, prognosis

Introduction

Myeloma is a plasma cell malignancy characterised by monoclonal protein production and lytic bone lesions and diagnoses represent approximately 1-2% of all new cancer cases. The annual age standardised incidence is 5-7 cases per 100,000 per year in Europe, the USA and Australasia. More males are affected than females (ratio 6:1), and myeloma is more common in African Americans[1]. Renal disease is common in myeloma, but has a heterogeneous pathology arising via different mechanisms, and can affect the glomeruli, tubules and interstitium in isolation or in combination. [2,3] Glomerular diseases occur as a result of light or heavy chain deposition, giving rise to diverse manifestations including but not limited to amyloidosis, cryoglobulinemia or proliferative glomerulonephritis. Tubular injury is caused by light chains with classical "myeloma kidney" due to cast nephropathy the commonest renal disease associated with ESKD. Interstitial nephritis without cast formation and proximal tubular dysfunction with acquired Fanconi's syndrome are also recognised. [4,5]

The diagnostic criteria for myeloma and other plasma cell dyscrasias have evolved over time, reflecting greater knowledge of their biology and natural history.[6] In the last decade there have also been major advances in myeloma therapy and management, specifically autologous stem cell transplant, and the use of novel therapeutic agents such as protease inhibitors and immunomodulatory drugs (eg bortezomib, lenalidomide and thalidomide) along with greater diagnostic precision and monitoring provided by the use of the free light chain assay. These changes facilitate rapid tumour killing and lowering of the light chain burden with real time monitoring to adjust therapy in response to disease progression. Subsequently, the prognosis and survival in patients with myeloma have improved over the last 20 years. Change is particularly notable in the last five to 10 years, with improvement in early mortality across all age groups[7,8].

Renal failure is noted at presentation in up to one half of newly diagnosed myeloma patients but is frequently responsive to correction of factors contributing to acute kidney injury such as hypercalcemia or volume depletion. Chemotherapy and in some cases, plasmapheresis or high cut-off membranes for haemodialysis might also improve renal function in the short to medium term by the rapid reduction of light chains, although definitive evidence is awaited. [4,9] However, those with chronic myeloma cast nephropathy and significant tubular damage on biopsy are less likely to recover, and more likely to progress to end stage kidney disease.[10] The presence and severity of renal disease correlates with patient survival, and overall prognosis is related to response of the renal disease to therapy. Survival with myeloma and established end stage kidney disease in case series was previously acknowledged to be universally poor, [11,12] but more recent studies suggest the prognostic impact of ESKD may be lessening and overall survival improving. [5,13-15] It is not clear whether recent advances in myeloma therapy have translated to improved survival for all those with ESKD, and/or whether the new diagnostic and treatment paradigms for myeloma alter the characteristics of those who develop ESKD from their myeloma. Survival for people with ESKD and other plasma cell dyscrasia is less well characterised.[16]

We aimed to describe the characteristics and survival of Australian and New Zealander patients with myeloma or other plasma cell dyscrasia and established ESKD who were treated with dialysis. We also aimed to examine changes in survival on dialysis over time, and to identify any prognostic factors for improved survival, to provide evidence for patient-clinician shared decision making.

Materials and methods

We used data from the Australian and New Zealand dialysis and transplant registry (ANZDATA), which has recorded detailed demographic, clinical and treatment data for all patients with ESKD since the inception of renal replacement therapy in Australia and New Zealand in 1963. ANZDATA records data for only those people regarded as having established ESKD and who are treated with the expectation of chronic renal replacement therapy. ANZDATA does not include records of people expected to have reversible ESKD. Data is collected in real time and by regular survey of all renal providers (which occurred every six months until 2004, yearly thereafter). ANZDATA records past cancer diagnoses and new incident cancer diagnoses, coded for site and type using adapted International Classification of Diseases for Oncology codes, where possible supported by pathology reports. The registry accords with the Australian Commonwealth Privacy Act and associated state legislation governing health data collection. For further information, see www.anzdata.org.au

To investigate survival of people with myeloma on dialysis we performed a cohort study using ANZDATA records from 1963-2013, and included all people treated with dialysis during this time. We categorised people into three groups; "myeloma", "other plasma cell dyscrasia" and "non-myeloma". The myeloma group comprised all incident dialysis patients whose primary renal disease was attributed to myeloma or malignant plasma cell neoplasms (ICD-10 code C90). 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. [17] We considered "other plasma cell dyscrasia" to be people who had a primary renal disease recorded as amyloidosis, light chain nephropathy, or Waldenstrom's macroglobulinaemia (because prior to the WHO reclassification in 1997, Waldenstrom's was regarded as a myeloma related condition), or were noted to have monoclonal gammopathy of uncertain significance (MGUS) [18] . 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 whose ESKD was a consequence of myeloma.

To investigate survival on dialysis we performed two analyses, using survival analysis techniques including Kaplan Meier and Cox proportional hazards, and testing for difference using Wald tests. In these analyses death was an event, and people were censored at last known follow-up, transplantation or 31st December 2013, which ever occurred first. The first analysis included all dialysis patients, and looked at survival differences for myeloma, other plasma cell dyscrasia 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 2000, 2000-04, 2005-2009, 2010 onwards). In this model we tested for interactions between age at starting dialysis and era for each of the three patient populations. The second analysis considered only the myeloma group, and examined potential prognostic factors for improved survival on dialysis. We considered age at ESKD, sex, race, initial dialysis modality (peritoneal or haemodialysis), era of dialysis initiation (before 2000, 2000-2004, 2005-2009 and 2010 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. The final model was reached through backwards elimination, using P<0.05 as the significance level for retention in the model. We retained sex in the model regardless. We tested the assumptions of proportional hazards using plots of the Schoenfeld residuals.

Results

A total of 65,940 people were treated with dialysis between 1963-2013 in Australia and New Zealand, representing 207,595 person-years of observation. The characteristics of the cohort are described in **table 1**. A total of 1,067 people (1.6%) had myeloma diagnosed either before or within one year of starting dialysis, and 832 of these people had myeloma as their primary renal disease. Of the 1,067 people with myeloma, 107 (10.2%) were diagnosed with myeloma more than 5 years before ESKD, 246 (23.5%) were diagnosed between one and four years before starting dialysis, 207 (19.8%) were diagnosed with myeloma between two and 11 months before starting dialysis, 428 (40.1%) were diagnosed within 2 months before or 2 months after starting dialysis, and 79 (7.4%) were diagnosed between 2 months and 1 year after starting dialysis (**figure 1**). A further 572 (0.9%) people had a plasma cell dyscrasia as the attributed cause of their ESKD, and the majority of these had amyloid as their primary renal disease (88.2%). In addition to the 572 people with plasma cell dyscrasia, a further 73 people initially thought to have plasma cell dyscrasia went on to develop myeloma within 12 months of commencing dialysis, and so were analysed in the myeloma group. Overall, from the entire cohort 353 (0.5%) were lost to follow-up, 32,103 (49%) died and 20,484 (31%) received a kidney transplant. Of those transplanted the majority were in the non-myeloma group 20,415 (99.7%), with 11 (0.05%) myeloma patients transplanted and 58 (0.25%) of other plasma cell dyscrasias transplanted. As a proportion of ESKD patients, myeloma comprised 0.8% of patients between 1963-94, 1.1% between 1995-99, and then stabilised at 2.2% from 2000-2013.

Figure 2 shows the overall survival of myeloma patients on dialysis relative to the other plasma cell dyscrasia and non-myeloma populations, without any adjustment for differences in age or treatment era. Overall, survival for myeloma patients was 55.6% and 11.5% at 1 and 5 years, compared with 88.9% and 47.0% for the rest of the dialysis population (difference between myeloma and non-

myeloma group P< 0.0001). People with other plasma cell dyscrasias had a 1 year survival of 74.6% and 5 year survival of 21.1%.

Table 2 shows the average age of people starting dialysis through time. On average, people with myeloma were older, and although their age increased over time, from 62.5 years in 1963-1994 to 70.1 years from 2010 onwards, the average age of the non-myeloma group increased more steeply, from 52.0 years in 1963-1994, to 62.2 from 2010. The age distribution of people with other plasma cell dyscrasias showed less change over time.

Figure 3 shows how overall survival has changed for the dialysis population through time, for each patient group, stratified by age at starting dialysis. Improvement in survival over time is markedly different among the three patient groups. Survival for myeloma patients has improved over time (p<0.001). The predicted one year survival for myeloma patients with ESKD prior to 2000 was 56.5% for people under 55 years, 60.5% for aged 55-64 years, 44.8% for 65-74 years and 40.1% aged 75 years and over. By 2010-2013, this compared to 70.1% people under 55 years, 73.9% for those aged 55-64 years, 61.7% for 65-74 years and 57.7% aged 75 years and over. The predicted five year survival for myeloma patients with ESKD prior to 2000 was 11.7% for people under 55 years, 15.2% for aged 55-64 years, 4.9% for 65-74 years and 3.2% aged 75 years and over. By 2010-2013 this compared to 27.5% for non-myeloma people under 55 years, 32.2% for those aged 55-64 years, 16.3% for 65-74 years and 12.7% aged 75 years and over. Although it appeared that improved survival was greatest in the younger age groups, there was insufficient evidence to conclude this with certainty (interaction p = 0.24).

In contrast, survival had not improved over time for other plasma cell dyscrasia patients (p = 0.70, **figure 3)**. The predicted one year survival for people with ESKD and other plasma cell dyscrasia prior to 2000 compared with 2010-13 was 81.7% versus 81.1% for <55 years, 74.3% versus 73.6% aged 55-64 years, 73.8% versus 73.0% aged 65-74 years and 58.7% versus 57.6% aged 75 and over. The

predicted five year survival for people with ESKD and other plasma cell dyscrasia prior to 2000 versus 2010 and later was 32.8% versus 31.5% for <55 years, 19.4% versus 18.4% aged 55-64 years, 18.6% versus 17.6% aged 65-74 years and 5.3% versus 4.8% aged 75 and over. Survival for non-myeloma dialysis patients improved over time, but has most markedly improved more for the older age group (interaction p <0.001). The predicted one year survival for non-myeloma patients with ESKD prior to 2000 compared with 2010-13 was 92.6% versus 95.3%, for <55 years, 86.8% versus 88.4% aged 55-64 years, 82.3% versus 88.4% aged 65-74 years and 74.6% versus 83.1% aged 75 and over. The predicted 5 year survival for non-myeloma patients with ESKD prior to 2000 compared with 2010-13 was 62.6% versus 72.9%, for <55 years, 39.7% versus 58.4% aged 55-64 years, 29.0% versus 46.1% aged 65-74 years and 17.3% versus 31.6% aged ≥ 75.

Cause of death for those with and without myeloma is shown in **table 3**. The majority of people with myeloma died from their myeloma (56.1%), whereas for people with other plasma cell dyscrasia and those with non-myeloma ESKD died predominantly from cardiovascular disease (36.8% and 40.4% respectively).

Within the myeloma group, **figure 4** shows the results of the analysis of potential prognostic factors associated with survival. (P=0.51). In univariate analysis, there were no differences in survival according to sex (P=0.67), timing of myeloma diagnosis relative to starting dialysis (P=0.41), racial background (P=0.73), initial dialysis modality (0.13), having another malignancy prior to ESKD (P=0.41) or smoking history (P=0.24). However, older age at ESKD, earlier era of dialysis and a history of diabetes all conferred poorer survival (P<0.05 for all, see **figure 4**). Once allowing for other effects in the adjusted model, peritoneal dialysis rather than haemodialysis as first treatment modality conferred a survival advantage (HR 0.7, CI 0.6-0.9, P= 0.002). Conversely, age older than 65 at ESKD was strongly associated with poorer survival, with those aged 65-74 having a 50% and those over 75 years a 70% increased risk of death, compared to those <55 years (respectively HR 1.5, CI 1.2-1.9

and HR 1.7, CI 1.3-2.1, P<0.0001). Having a history of diabetes at ESKD also increased risk of death by 30% (HR 1.3, CI 1.1-1.6, P=0.01). There was no survival advantage for females (P=0.79).

Discussion

People with myeloma and established ESKD have poor survival, with almost half dying within a year of commencing dialysis, with death attributed to their cancer in the majority of cases. However, there is strong evidence of improvement in survival at 1 and 5 years for all age groups in recent years. People younger than 65 years, without diabetes co-morbidity, and who are treated with peritoneal dialysis have better prognosis than other people with myeloma. People with other plasma cell dyscrasias (predominantly amyloidosis) also have poorer survival than other dialysis patients, but better survival than those with myeloma, but this has not improved over time. These data suggest that newer strategies for myeloma treatment may be conferring benefit to patients with established ESKD. The majority of new diagnoses myeloma causing ESKD continued to occur within a few months of presentation indicating that the effect of rapid diagnosis and early treatment will likely have the greatest impact on survival after diagnosis, and not in preventing ESKD. Patients who develop irreversible ESKD are much more likely to have Light-chain only or IgD disease, which are usually associated with poorer survival.[19]

There are some 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. [14] Whereas the absolute numbers of people with myeloma starting dialysis has also increased in Australia and New Zealand, the proportion of patients with ESKD attributed to myeloma remained stable since 2000, and although those with myeloma were older, the average age of myeloma patients has not increased as steeply as those with ESKD from

other causes. This paradox might be due to differences in dialysis acceptance criteria across nations, or differences in approach to conservative non-dialytic care pathways. A recent USRDS study also showed higher mortality rates for people with myeloma on dialysis, with some recent improvement. [15] Our finding that those on peritoneal dialysis had improved survival over those on haemodialysis is similar to data from the United States and Europe. [14,15,20] 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, or better supported patients are more likely to choose a home based therapy than those less able and with less supportive home environment.[21] There is little comparable published registry data on survival with ESKD and other plasma cell dyscrasia. [16]

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. [17] We reasoned that for people developing myeloma after 1 year on dialysis, this was more likely to be an incidental new 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 other plasma cell dyscrasias as a cause 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. [18] It may be that there is further potential misclassification within the plasma cell dyscrasia group eg of primary versus secondary amyloidosis, that we have been unable to address within the limitations of registry data. There has been little published robust prognostic information about this patient group previously.

A limitation of the design of our study means that we are unable to investigate or comment on newer treatment options such as high cut-off haemodialysis for myeloma patients presenting with

reversible acute kidney injury as our investigation was limited to those with established ESKD. [22,23] 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 do not have data to determine the myeloma classification by heavy or light chain type, which may impact management and outcomes. We did not consider people treated with more recent interventions such as bone marrow transplant with kidney transplantation, as the number of such treatments in Australia and New Zealand is very small, and follow-up time still limited, so little useful information can be gained beyond case descriptions. [24,25] ANZDATA does not routinely link to drug treatment data, and so the association of improved survival with more recent drug therapies cannot me tested more directly.

Applying results of this research in practice, absolute estimates of predicted survival for people with myeloma and ESKD, with and without diabetes, and for different renal replacement modalities can be seen in **table 4**. On average, a patient with myeloma starting peritoneal dialysis aged 59 years has a 45% chance of survival at 5 years, falling to 36% if comorbidity with diabetes is present. A 69 year old starting haemodialysis has a 15% 5 year survival, falling to 9% if they are diabetic.

This study provides both evidence for improvement in patient survival with myeloma and 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.

Authors acknowledge all those working in nephrology in Australia and New Zealand, now and in the past, who have contributed to ANZDATA.

References

1.   Röllig C, Knop S, Bornhäuser M. Multiple myeloma. *The Lancet.* 2015;385(9983):2197-2208.

2.   Eleutherakis-Papaiakovou V, Bamias A, Gika D, et al. Renal failure in multiple myeloma:
incidence, correlations, and prognostic significance. *Leukemia & Lymphoma.* 2007;48(2):337-
341.

3.   Dimopoulos MA, Terpos E, Chanan-Khan A, et al. Renal Impairment in Patients With Multiple
Myeloma: A Consensus Statement on Behalf of the International Myeloma Working Group.
Journal of Clinical Oncology. 2010;28(33):4976-4984.

4.   Johnson WJ, Kyle RA, Pineda AA, O'Brien PC, Holley KE. Treatment of renal failure associated
with multiple myeloma. Plasmapheresis, hemodialysis, and chemotherapy. *Archives of
Internal Medicine.* 1990;150(4):863-869.

5.   Pozzi C, D'Amico M, Fogazzi GB, et al. Light chain deposition disease with renal involvement:
clinical characteristics and prognostic factors. *American Journal of Kidney Diseases.*
2003;42(6):1154-1163.

6.   Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group
updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology.*
2014;15(12):e538-e548.

7.   Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple
myeloma: changes in early mortality and outcomes in older patients. *Leukemia.*
2014;28(5):1122-1128.

8.   Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in
multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to
2003. *Journal of clinical oncology : official journal of the American Society of Clinical
Oncology.* 2007;25(15):1993-1999.

9.   Zucchelli P, Pasquali S, Cagnoli L, Ferrari G. Controlled plasma exchange trial in acute renal failure due to multiple myeloma. *Kidney International.* 1988;33(6):1175-1180.

10.   Kaplan AA. Therapeutic apheresis for the renal complications of multiple myeloma and the dysglobulinemias. *Therapeutic Apheresis.* 2001;5(3):171-175.

11.   Torra R, Blade J, Cases A, et al. Patients with multiple myeloma requiring long-term dialysis: presenting features, response to therapy, and outcome in a series of 20 cases. *British Journal of Haematology.* 1995;91(4):854-859.

12.   Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *European Journal of Haematology.* 2000;65(3):175-181.

13.   Iggo N, Palmer AB, Severn A, et al. Chronic dialysis in patients with multiple myeloma and renal failure: a worthwhile treatment. *Quarterly Journal of Medicine.* 1989;73(270):903-910.

14.   Tsakiris DJ, Stel VS, Finne P, et al. Incidence and outcome of patients starting renal replacement therapy for end-stage renal disease due to multiple myeloma or light-chain deposit disease: an ERA-EDTA Registry study. *Nephrology Dialysis Transplantation.* 2010;25(4):1200-1206.

15.   Reule S, Sexton DJ, Solid CA, Chen S-C, Foley RN. ESRD due to Multiple Myeloma in the United States, 2001–2010. *Journal of the American Society of Nephrology.* 2015.

16.   Decourt A, Gondouin B, Delaroziere JC, et al. Trends in Survival and Renal Recovery in Patients with Multiple Myeloma or Light-Chain Amyloidosis on Chronic Dialysis. *Clinical journal of the American Society of Nephrology : CJASN.* 2016;11(3):431-441.

17.   Webster AC, Supramaniam R, O'Connell DL, Chapman JR, Craig JC. Validity of registry data: agreement between cancer records in an end-stage kidney disease registry (voluntary reporting) and a cancer register (statutory reporting). *Nephrology.* 2010;15(4):491-501.

18.   Harris N, Jaffe E, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. *Histopathology.* 2000;36(1):69-86.

19.   Drayson M, Begum G, Basu S, et al. Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. *Blood.* 2006;108(6):2013-2019.

20.   Abbott KC, Agodoa LY. Multiple myeloma and light chain-associated nephropathy at end-stage renal disease in the United States: patient characteristics and survival. *Clinical Nephrology.* 2001;56(3):207-210.

21.   Noordzij M, Jager KJ. Survival comparisons between haemodialysis and peritoneal dialysis. *Nephrology Dialysis Transplantation.* 2012;27(9):3385-3387.

22.   Grima DT, Airia P, Attard C, Hutchison CA. Modelled cost-effectiveness of high cut-off haemodialysis compared to standard haemodialysis in the management of myeloma kidney. *Current Medical Research & Opinion.* 2011;27(2):383-391.

23.   Gondouin B, Hutchison CA. High cut-off dialysis membranes: current uses and future potential. *Advances in Chronic Kidney Disease.* 2011;18(3):180-187.

24.   Bird JM, Owen RG, D'Sa S, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. *British Journal of Haematology.* 2011;154(1):32-75.

25.   Spitzer TR, Sykes M, Tolkoff-Rubin N, et al. Long-term follow-up of recipients of combined human leukocyte antigen-matched bone marrow and kidney transplantation for multiple myeloma with end-stage renal disease. *Transplantation.* 2011;91(6):672-676.

Table 1: Characteristics of people with and without myeloma treated by dialysis from 1963-2013

Characteristic	Myeloma N (%)	Other plasma cell dyscrasia N (%)	Non-Myeloma N (%)
Total 65,940 (%)	1,067 (1.6)	572 (0.9)	64,301 (97.5)
Status during follow-up			
Alive	181 (17)	129 (23)	33527 (52)
Died	886 (83)	443 (77)	30774 (48)
Sex			
Female	396 (37)	246 (43)	26681 (41)
Male	671 (63)	326 (57)	37620 (59)
Country of residence			
New Zealand	156 (15)	69 (12)	11021 (17)
Australia	911 (85)	503 (88)	53280 (83)
Primary renal disease			
Myeloma	832 (78)	0 (0)	0 (0)
Other plasma cell dyscrasia	73 (7)	572 (100)	0 (0)
Glomerulonephritis/IgA nephropathy	44 (4)	0 (0)	18465 (29)
Diabetes	33 (3)	0 (0)	17281 (27)
Other	85 (8)	0 (0)	28555 (44)
Age at ESKD			
<55	163 (15)	146 (26)	28467 (44)
55-64	273 (26)	156 (27)	14472 (23)
65-74	389 (36)	192 (34)	13517 (21)
75+	242 (23)	78 (14)	7845 (12)
Era of ESKD			
1963-1994	151 (14)	175 (31)	19266 (30)
1995-1999	97 (9)	79 (14)	8974 (14)
2000-2004	256 (24)	115 (20)	11097 (17)
2005-2009	312 (29)	113 (20)	13690 (21)
2010-2013	251 (24)	90 (16)	11274 (18)
First Dialysis modality			
Haemodialysis	901 (84)	402 (70)	44548 (69)
Peritoneal dialysis	166 (16)	170 (30)	19753 (31)
Racial background			
Non-white	74 (7)	65 (11)	15561 (24)
White	993 (93)	507 (89)	48740 (76)

Other malignancy prior to ESKD*			
None	978 (92)	521 (91)	59634 (93)
Pre-dialysis malignancy	89 (8)	51 (9)	4667 (7)
Other malignancy subsequent to ESKD*			
None	1036 (97)	542 (95)	58364 (91)
Post-dialysis malignancy	31 (3)	30 (5)	5937 (9)
Smoking history at ESKD			
Current or former	599 (56)	382 (67)	36447 (57)
Never or unknown	468 (44)	190 (33)	27854 (43)
Diabetes Mellitus			
No	819 (77)	415 (73)	34112 (53)
Type I	4 (0)	1 (0)	2681 (4)
Type II	156 (15)	53 (9)	19218 (30)
Unknown †	88 (8)	103 (18)	8290 (13)

* Any notifiable cancer excluding non-melanocytic skin cancers. † 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.

Table 2: Average age in years of people starting dialysis through time

Era of dialysis	Myeloma		Other plasma cell dyscrasia		Non-myeloma	
	N	Median (IQR)	N	Median age (IQR)	N	Median age (IQR)
1963-1994	151	62.5 (55.6-67.9)	175	58.9 (48.7-66.9)	19266	52.0 (38.5-63.1)
1995-1999	97	63.7 (56.3-70.1)	79	60.7 (50.7-67.3)	8974	58.5 (45.1-68.7)
2000-2004	256	68.4 (59.4-74.9)	115	67.5 (57.7-73.3)	11097	61.3 (48.4-71.7)
2005-2009	312	68.9 (61.7-74.9)	113	67.0 (60.4-73.8)	13690	62.4 (50.3-72.9)
2010-2013	251	70.1 (60.8-77.3)	90	64.9 (57.3-74.2)	11274	62.4 (50.5-72.5)

IQR: interquartile range

Table 3: Cause of death for people on dialysis with and without myeloma in Australia and New Zealand 1963-2013 *

Cause of death*	Myeloma (Total 886)	Other plasma cell dyscrasia (Total 443)	Non myeloma (Total 30,774)
Total 32,103	N (%)	N (%)	N (%)
Cardiovascular	126 (14.2)	163 (36.8)	12,440 (40.4)
Vascular	31 (3.5)	37 (8.4)	2,998 (9.7)
Infection	90 (10.2)	66 (14.9)	3,873 (12.6)
Cancer	497 (56.1)	18 (4.1)	2,099 (6.8)
Social†	122 (13.8)	106 (23.9)	7,293 (23.7)
Other	20 (2.3)	53 (12.0)	2,071 (6.7)

* Cause of death recorded in ANZDATA is that attributed by the treating Nephrologist, and may not be the same as that recorded on death certificates. Coding options for cause of death can be found on http://www.anzdata.org.au/forms/ANZDATA/anzdata_A3_2013.pdf

† "social" causes of death are those attributed to dialysis withdrawal, suicide and accidental deaths.

Table 4: Predicted survival of people with myeloma and ESKD starting dialysis in the current era, stratified by age, presence of diabetes, and initial dialysis modality.*

Age at ESKD (years)	Comorbidity	1 year survival %		5 year survival %	
		PD	HD	PD	HD
<55	No diabetes	79	72	41	29
	Diabetes	74	66	32	21
55-64	No diabetes	81	75	45	33
	Diabetes	77	69	36	24
65-74	No diabetes	70	61	26	15
	Diabetes	64	54	18	9
75 and over	No diabetes	68	58	23	13
	Diabetes	61	50	15	7

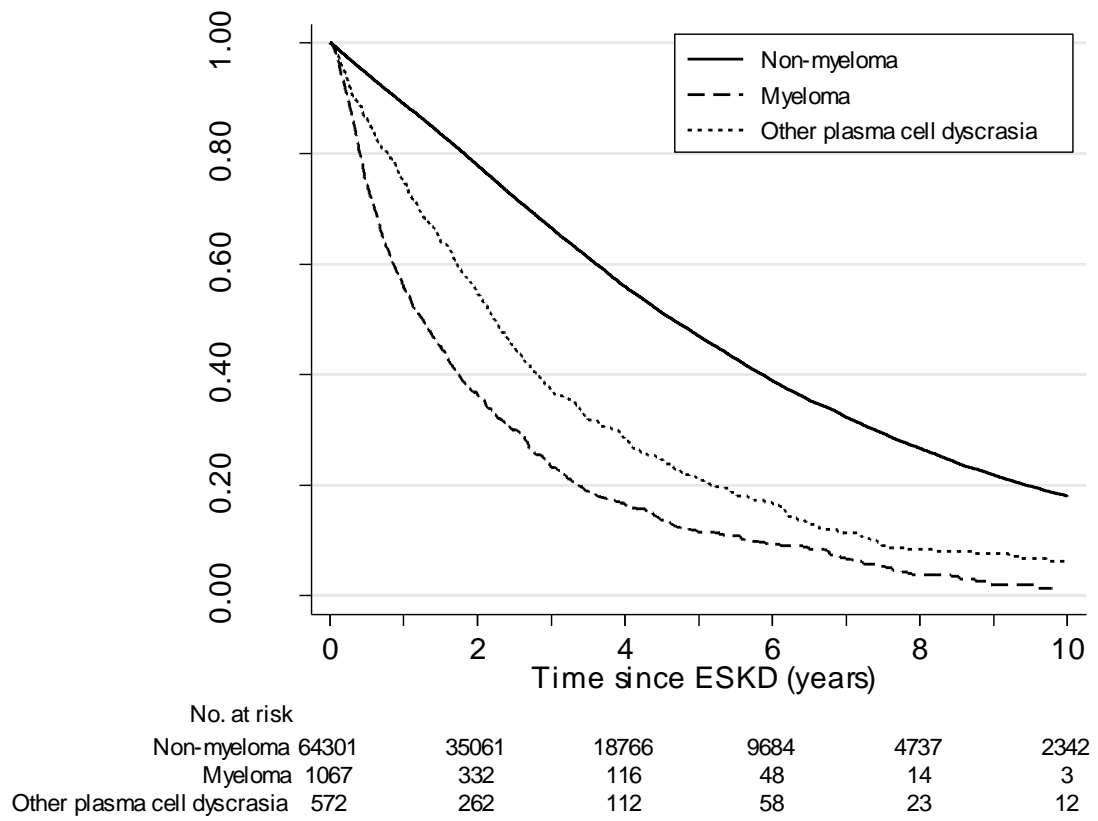initial treatment PD = peritoneal dialysis, HD = haemodialysis

* generated from the adjusted cox model for survival from people starting dialysis 2010-2013

Figure 1: Timing of myeloma diagnosis relative to start of chronic renal replacement therapy, in Australia and New Zealand, 1963-2013.
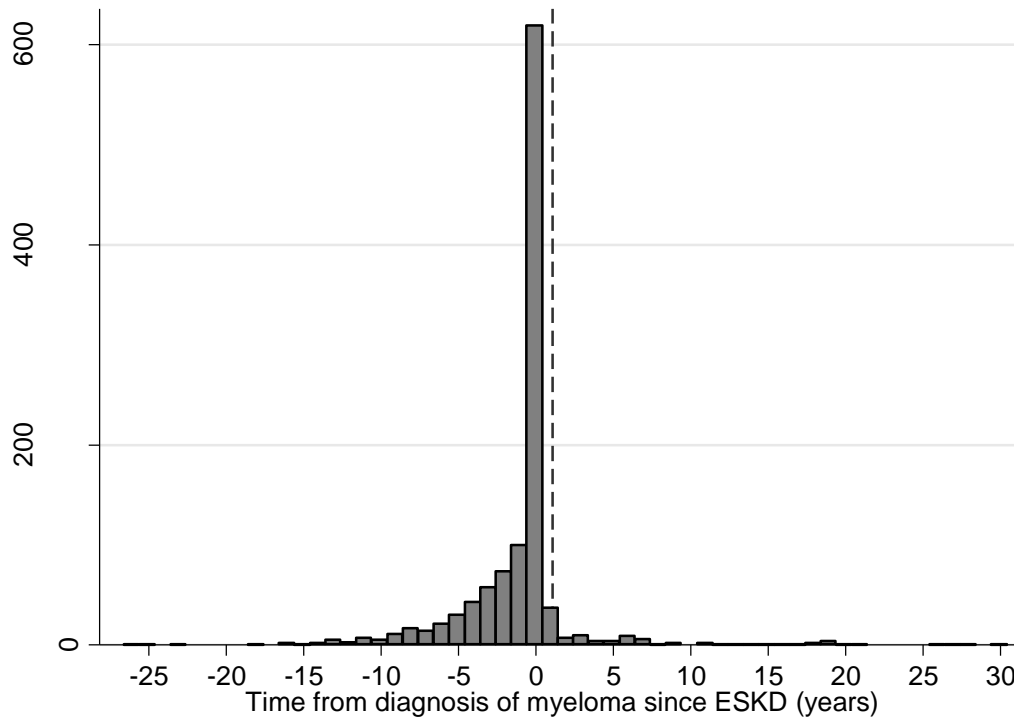

In our analysis, all those developing myeloma up to one year after starting renal replacement therapy, were classified as having myeloma causing ESKD. This is marked by the vertical dotted line. All those developing myeloma after 12 months of dialysis, were analysed in the non-myeloma group.

Figure 2: Unadjusted survival from time of starting dialysis for myeloma, plasma cell dyscrasia and non-myeloma patients 1963-2013


No. at risk						
Non-myeloma	64301	35061	18766	9684	4737	2342
Myeloma	1067	332	116	48	14	3
Other plasma cell dyscrasia	572	262	112	58	23	12

Figure 3: Survival on dialysis for people with and without myeloma by era of dialysis stratified by age at starting dialysis *
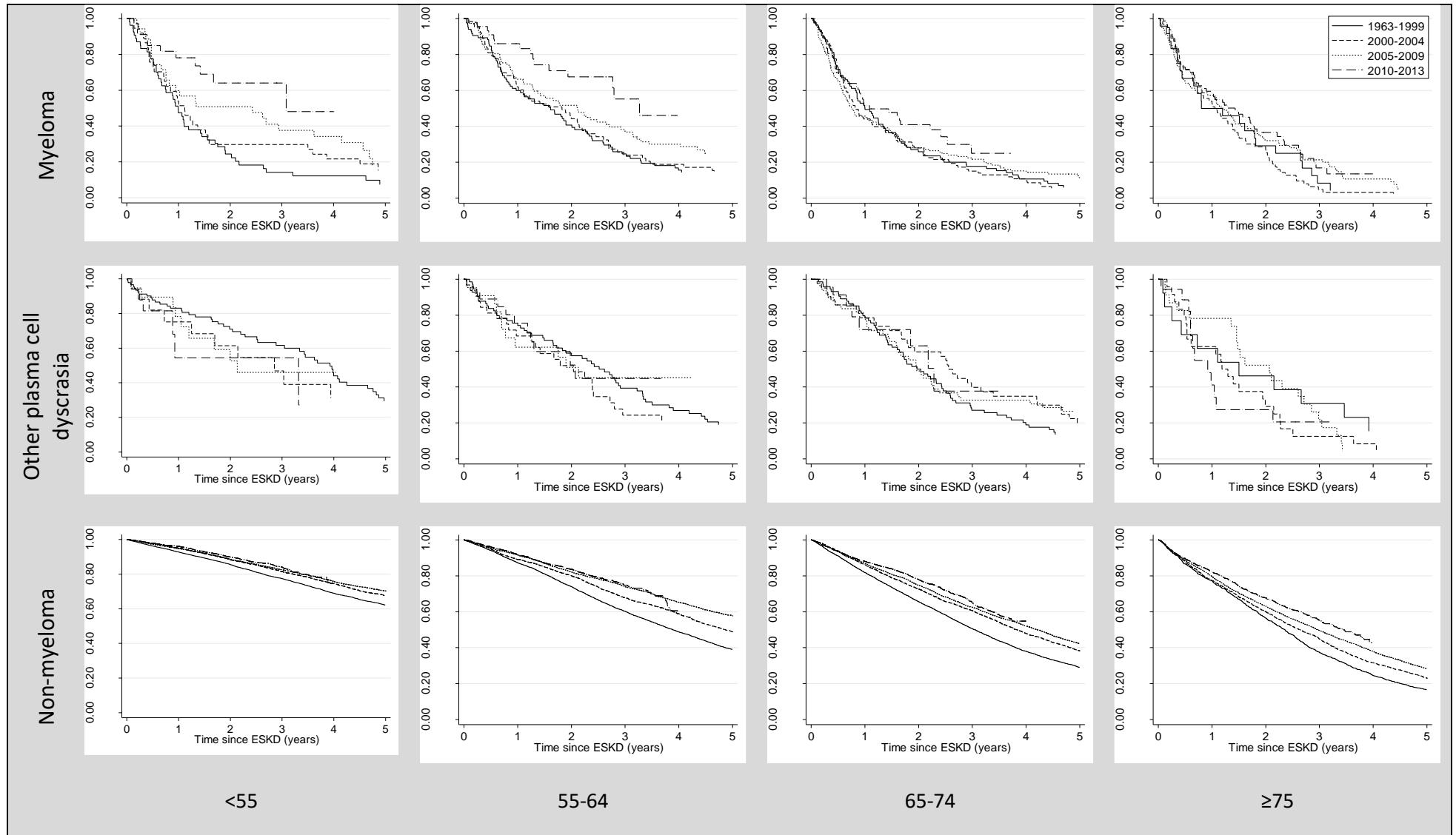
Figure 4: Risk of death for people with myeloma treated with dialysis in Australia and New Zealand 1963-2013. Panel A shows univariable associations; panel B shows adjusted multivariable analysis.
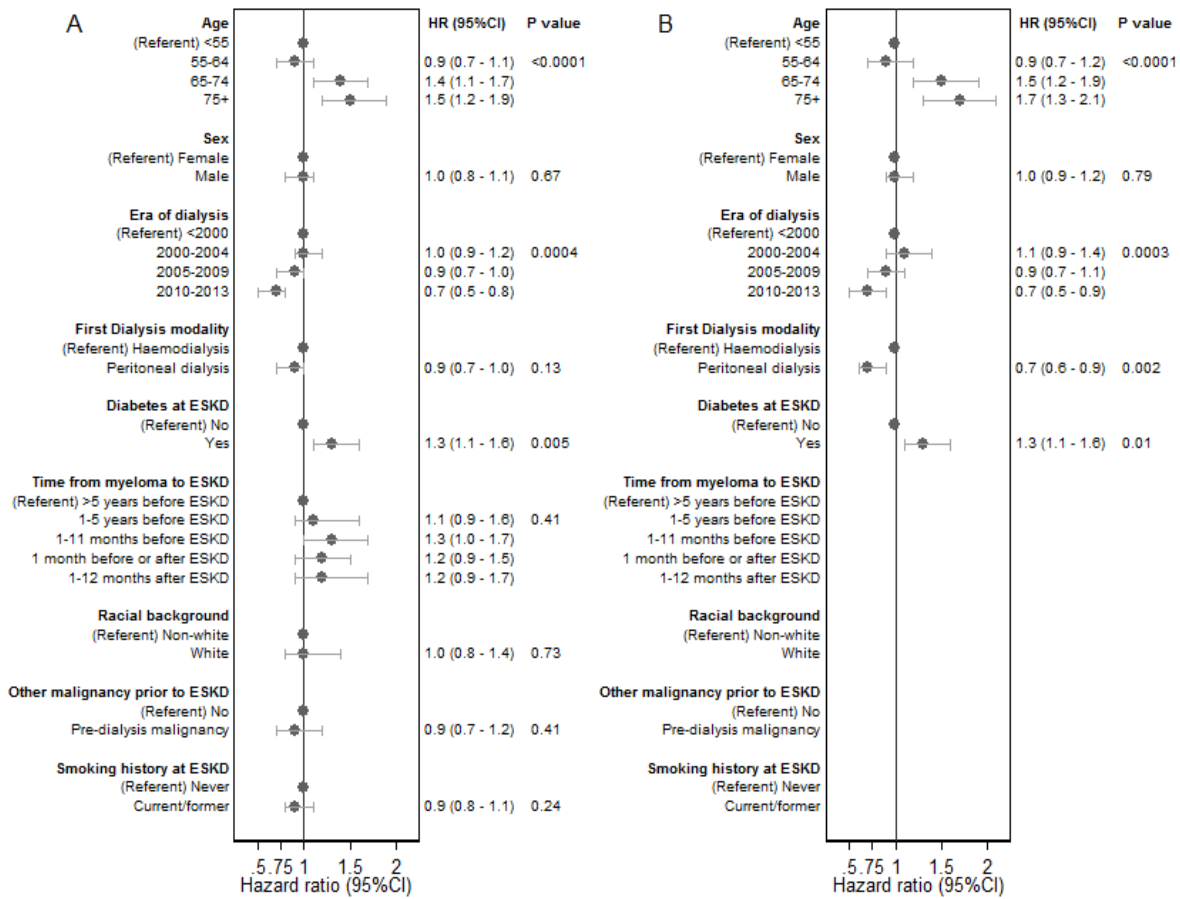
All P values are calculated using the Wald test