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ORIGINAL PAPER

Predictors of early mortality in multiple myeloma: Results from the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR)

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Summary

The frequency and causes of early mortality in patients with newly diagnosed multiple myeloma (NDMM) have not been well described in the era of novel agents. We investigated early mortality in a prospective cohort study of all patients with NDMM registered on the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR) at 36 institutions between July 2011 and March 2020. Early mortality was defined as death from any cause within the first 12 months after diagnosis. A total of 2377 patients with NDMM were included in the analysis, with a median (interquartile range) age of 67.4 (58.9–74.60 years, and 60% were male. Overall, 216 (9.1%) patients died within 12 months, with 119 (4.5%) having died within 6 months. Variables that were independent predictors of early mortality after adjustment in multivariable regression included age (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.05–1.08; $p < 0.001$), Eastern Cooperative Oncology Group performance status (OR 1.50, 95% CI 1.26–1.79; $p < 0.001$), serum albumin (OR 0.95, 95% CI 0.93–0.98; $p < 0.001$), cardiac disease (OR 1.96, 95% CI 1.35–2.86; $p < 0.001$) and International Staging System (OR 1.40, 95% CI 1.07–1.82; $p = 0.01$). For those with a primary cause of death available, it was reported as disease-related in 151 (78%), infection 13 (7%), other 29 (15%). Infection was listed as a contributing factor for death in 38% of patients.

KEYWORDS
infection, mortality, myeloma, registry

INTRODUCTION

Outcomes for patients with multiple myeloma (MM) have improved over the previous two decades with the widespread introduction of novel therapies (namely proteasome inhibitors [bortezomib] and immunomodulatory drugs [thalidomide, lenalidomide]) and use of autologous stem cell transplantation (ASCT) in eligible patients.[1–5] However, recent studies show that improvement in survival in older patients, particularly those aged >75 years, has been limited despite advances in therapy.[6]

Prior to the introduction of novel therapies, early mortality in newly diagnosed MM (NDMM) was reported to occur in 10%–25% of patients within the first 6 months.[7] A study of clinical trials conducted between 1980 and 2002, reported overall that 10% of patients died within the first 60 days of therapy.[8] More recent reports suggest that rates of early mortality have decreased in the era of novel therapies.[9–12] However, these studies are limited due to single-centre design,[9] selection bias (e.g., use of clinical trial data)[13] or small sample sizes. Furthermore, the most common cause of death previously was reported to be infection;[8] however, this may have changed over time with changes in myeloma therapies.

Previous reported risk factors for early mortality include comorbidities, age, disease characteristics and performance status. A recent analysis of 1493 patients with NDMM diagnosed between 2009 and 2011 in the USA developed a predictive model for early mortality (defined as death within 6 months).[14] Whether this model applies more generally in other treatment settings/regions is not known.

We therefore aimed to investigate the frequency and causes of early mortality with our current standards of care for NDMM, and to explore predictors of early mortality, using a clinical quality registry that includes all NDMM patients at 36 hospitals across Australia and New Zealand.

METHODS

Study design

This is a prospective cohort study of all patients with NDMM registered on the Australia and New Zealand Myeloma and Related Diseases Registry (MRDR) at 36 institutions between July 2011 and March 2020. The MRDR is a prospective clinical quality registry of patients at participating sites with newly diagnosed cases of MM, monoclonal gammopathy of undetermined significance (MGUS), smouldering myeloma, plasma cell leukaemia, solitary bone plasmacytoma, and solitary extramedullary plasmacytoma. The details of the MRDR study design have been published previously.[15]

Participants

All patients with NDMM aged ≥18 years included on the registry with a diagnosis date up to March 2020 were included. This allowed a minimum of 12-months survival follow-up for all patients in the analysis. Patients are identified at participating sites by the local investigator or staff under their direction. Patients consent to participate in the registry through an opt-off consent, with consent waived for early deaths (where there is insufficient time to obtain consent from the patient or family prior to death). This consent model is used to maximise capture of all patients with MM at participating sites and has been shown to reduce risk of selection bias in clinical registries.[16] MM was defined according to International Myeloma Working Group (IMWG) diagnostic criteria.[17]

Data collection

Data were sourced from the MRDR and from national death registries in Australia and New Zealand. The MRDR collects patient demographics, laboratory and radiology investigations, disease staging and comorbidities at diagnosis, as well as detailed data on initial treatment, ASCT (whether an ASCT is planned upfront, reasons for not performing an ASCT and, if undertaken, date and response), maintenance therapy and subsequent lines of therapy are collected. Patient outcomes (including disease progression, survival status and date and cause of death) are reviewed and recorded every 4 months. Quality of life as measured by the EuroQoL five Dimensions five Levels (EQ-5D-5L) questionnaire was also collected at diagnosis. Data are collected via a web-based case report form and stored securely within Monash University.

The MRDR data were linked with the Australian National Death Index (NDI) and the New Zealand Death Registry to provide supplementary information on date and cause of death for participants in the registry, including those lost to follow-up at time of analysis. The death registries provide contemporaneous date of death; however, as there is a delay of up to 18 months in the availability of cause of death, this was only available for a subset.

Definitions

Early mortality was defined as death from any cause within the first 12 months after diagnosis. Early mortality is variably defined in the literature, including at 60-days, 6- and 12-months. In this study we define early mortality as death within 12 months of diagnosis to be comparable to other recent publications.[9,11,12] Primary cause of death was classified as disease-related (if directly attributable to MM progression or complications), infection, other non-disease causes and unknown if not recorded within the MRDR or national death registries. Secondary causes of death are recorded with the national death registry (not the MRDR), and these were also reviewed.

Statistical analysis

Data were summarised as number (proportions), median (interquartile range [IQR]) and mean (standard deviation

[SD]) as appropriate. Hypothesis testing was performed using chi-square for categorical variables and Wilcoxon rank-sum or *t*-tests, as appropriate, for continuous variables.

Missing data were assessed and reported. As a significant number of variables had missing values, multiple imputation was performed using multivariable normal regression to impute missing values for independent parameters based on patterns in the existing data. The imputation was performed using the 'mi impute mvn' function in Stata 16 (StataCorp), and 'mi estimate' was used to perform the logistic regression. A total of 250 sets were calculated to ensure the variance associated with the imputation was <10% of the total estimate variance for each variable.

The association between baseline patient and disease characteristics with early mortality was modelled using logistic regression. This was performed on two datasets: (i) a complete case ascertainment (CCA) dataset, which excluded patients with missing data for one or more variables of interest and (ii) a multiple imputation (MI) dataset. Variables were selected a priori based on published literature, and included age, gender, disease stage (International Staging System [ISS]), karyotypic metaphase analysis and fluorescent in situ hybridisation results, European Cooperative Oncology Group (ECOG) performance status, estimated glomerular filtration rate (eGFR), creatinine, platelet count, lactate dehydrogenase (LDH), albumin, serum β_2-microglobulin, calcium and comorbidities at diagnosis (moderate-to-severe heart disease, moderate-to-severe pulmonary disease, diabetes requiring treatment, liver disease, peripheral neuropathy, hypertension). In both analyses, treatment hospital was included as a random effect.

All analyses were performed using Stata version 16.1 (StataCorp).

Ethics

The study has approval from the Human Research Ethics Committee at Monash University, Alfred Health and the Human Research Ethics Committee (HREC) at all MRDR participating sites.

RESULTS

Patients

There were 2377 patients with NDMM included in the analysis. The patients' flow chart is shown in Figure 1. Patient characteristics for the whole cohort are shown in Table 1. The median (IQR) age at diagnosis was 67.4 (58.9–74.6) years, and 60% were male, 31% had an ISS stage of 3 and 60% had one or more comorbidities at diagnosis.

Initial therapy

The initial therapy delivered was available for 94% of the cohort. Bortezomib-based regimens were the most common

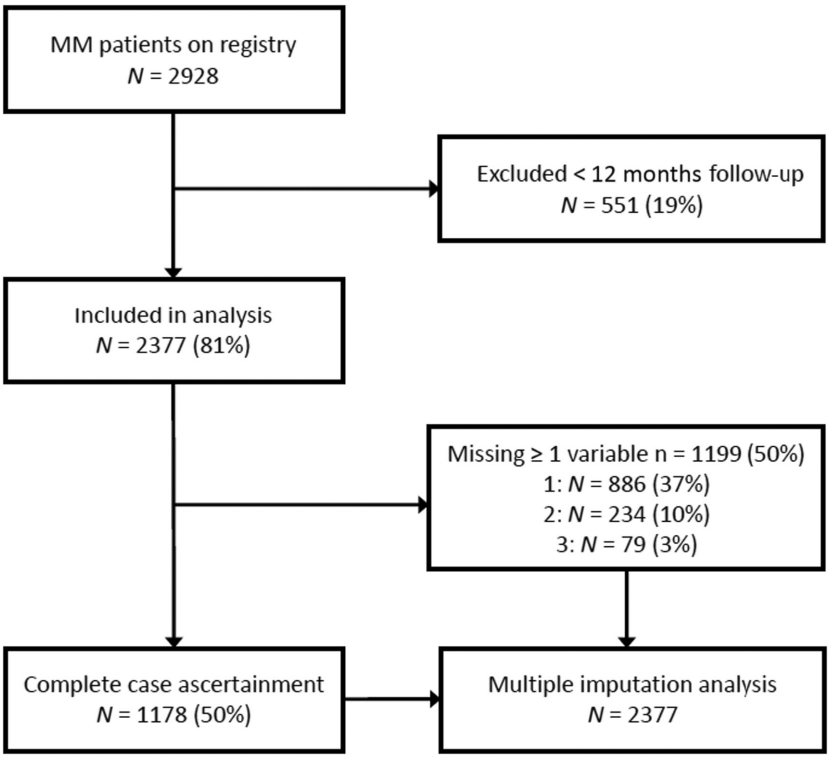

FIGURE 1 Patient flow chart. MM, multiple myeloma.

TABLE 1 Patient characteristics

Variable	All patients *N* = 2377	Early mortality (<12 months) *N* = 216	Survivor at 12 months *N* = 2161	*p*
Age, years, median (IQR)	67.4 (58.9–74.6)	77.3 (69.1–83.0)	66.5 (58.4–73.6)	<0.001
Male, *n/N* (%)	1435/2376 (60.4)	132/216 (61.1)	1303/2160 (60.3)	0.82
ISS = 3, *n/N* (%)	531/1730 (30.7)	72/131 (55.0)	459/1599 (28.7)	<0.001
Cytogenetic abnormality[a], *n/N* (%)	218/1202 (18.1)	24/89 (27.0)	194/1113 (17.4)	0.025
ECOG Performance status = 2–4, *n/N* (%)	117/1566 (7.5)	35/138 (25.4)	82/1428 (5.7)	<0.001
eGFR, ml/min/1.73 m^2, median (IQR)	70.0 (48.0–87.0) [*n* = 2135]	47.5 (28.5–69.5) [*n* = 196]	72.0 (51.0–88.0) [*n* = 1939]	<0.001
Cardiac disease, *n/N* (%)	252/2377 (10.6)	52/216 (24.1)	200/2161 (9.3)	<0.001
Pulmonary disease, *n/N* (%)	115/2377 (4.8)	25/216 (11.6)	90/2161 (4.2)	<0.001
Liver disease, *n/N* (%)	30/2377 (1.3)	5/216 (2.3)	25/2161 (1.2)	0.15
Platelet count, $\times 10^9$/l, median (IQR)	219.0 (173.0–274.0) [*n* = 2245]	199.5 (142.0–266.0) [*n* = 204]	221.0 (176.0–275.0) [*n* = 2041]	<0.001
Serum creatinine, μmol/l, median (IQR)	89.0 (72.0–120.0) [*n* = 2235]	113.5 (80.0–176.0) [*n* = 206]	87.0 (71.0–114.0) [*n* = 2029]	<0.001
LDH, u/l, median (IQR)	196.0 (158.0–251.0) [*n* = 1656]	248.0 (195.0 0335.0) [*n* = 139]	192.0 (157.0–244.0) [*n* = 1517]	<0.001
Albumin, g/l, median (IQR)	34.0 (29.0–38.0) [*n* = 2244]	30.0 (26.0–35.0) [*n* = 205]	34.0 (30.0–39.0) [*n* = 2039]	<0.001
β_2-microglobulin, mg/l, median (IQR)	3.7 (2.6–6.3) [*n* = 1734]	6.1 (4.3–11.3) [*n* = 131]	3.6 (2.6–5.9) [*n* = 1603]	<0.001
EQ-5D VAS[b] score, median (IQR)	70.0 (55.0–82.5) [*n* = 676]	60.0 (40.0–75.0) [*n* = 59]	75.0 (60.0–85.0) [*n* = 617]	<0.001

Abbreviations: ECOG, European Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; EQ-5D VAS, EuroQoL five Dimensions Visual Analogue Scale; ISS, international staging system; IQR, interquartile range; LDH, lactate dehydrogenase.

Notes: Values reported are either median (IQR) or *n/N* (%). P values are for survivor vs early mortality.

[a]One or more of the following cytogenetic abnormalities, as determined by fluorescence in situ hybridisation: Del(17p), t(4;14), t(14;16).

[b]EQ-5D VAS scored from 0–100 with higher values indicating better health.

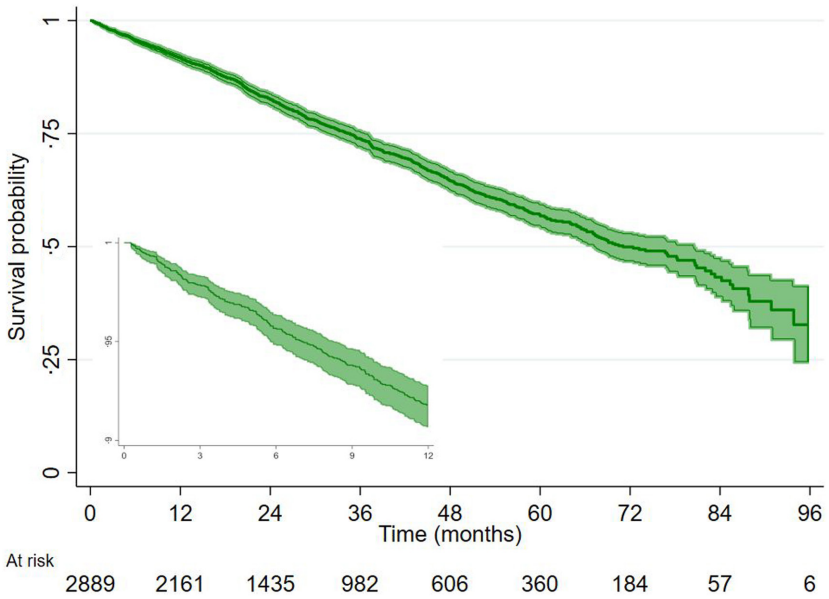

FIGURE 2 Survival curve for all patients with multiple myeloma in the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR). Insert is the 12-month survival curve. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Predictors of early mortality (within 12 months)

	Complete case ascertainment dataset *n* = 1178		Multiple imputation dataset *n* = 2377		
	OR (95% CI)	*p*	OR (95% CI)	*p*	Number of imputed observations (%)
Age (years)	1.04 (1.02–1.06)	<0.001	1.07 (1.05–1.08)	<0.001	0
Albumin (g/l)	0.93 (0.90–0.96)	<0.001	0.95 (0.93–0.98)	<0.001	133/2377 (6)
ECOG performance status	1.85 (1.47–2.34)	<0.001	1.50 (1.26–1.79)	<0.001	811/2377 (34)
Cardiac disease	3.00 (1.73–5.18)	<0.001	1.96 (1.35–2.86)	<0.001	0
ISS	1.56 (1.06–2.30)	0.03	1.40 (1.07–1.82)	0.01	647/2377 (27)

Abbreviations: CI, confidence interval; ECOG, European Cooperative Oncology Group; ISS, International Staging System; OR, odds ratio.

(84%), followed by lenalidomide-containing regimens. The most common regimen was bortezomib, cyclophosphamide and dexamethasone (VCD) in 71%, lenalidomide and dexamethasone (Rd) in 6%, bortezomib and dexamethasone (VD) in 3%. Among all patients, 1097 (51%) had an ASCT within the first 12 months of diagnosis. Of patients aged ≤70 years, 1029 (77%) had an ASCT within the first 12 months of diagnosis.

Early mortality

Overall, 216 (9.1%) patients died within 12 months, with 119 (4.5%) within 6 months. The Kaplan–Meier predictions for the 1-year and 6-month mortality rates (with 95% CIs) were 8.2% (7.2%–9.3%) and 4.3% (3.6%–5.2%) respectively. The survival curve is shown in Figure 2.

Cause of death was reported in 193 (89%) patients, and secondary causes of death from linkage with death registry were available for 69 (32%). For those with a primary cause of death available, it was reported as disease-related in 151 (78%), infection 13 (7%), other 29 (15%). Other reported causes included heart disease, renal failure, liver failure, other cancers, and trauma. For those who had secondary causes of death available, infection was a contributing cause of death (either primary or secondary) in 38% (26/69).

Table 1 compares patient characteristics in those who died within 12 months with those who were alive at 12 months after diagnosis. Patients who died within 12 months were older, more likely to have cardiac and pulmonary disease, had higher creatinine, lower platelet count, lower albumin, higher serum β_2-microglobulin, higher LDH, higher ISS and ECOG and lower EQ-5D-Visual Analogue Scale score.

Predictors of early mortality

Variables that remained independent predictors of early mortality after adjustment using the CCA dataset included age odds ratio (OR) 1.04 (95% CI 1.02–1.06, $p < 0.001$), ECOG performance status OR 1.85 (95% CI 1.47–2.34, $p < 0.001$), cardiac disease OR 3.00 (95% CI 1.73–5.18, $p < 0.001$), ISS OR 1.56 (95% CI 1.06–2.30, $p = 0.03$) and albumin OR 0.93 (95% CI 0.90–0.96, $p < 0.001$). Despite being a factor used in calculating ISS, the albumin level was found to be an independent predictor of mortality along with the ISS, reflecting the observation that, even when stratified by ISS stage, increasing albumin was associated with a decrease in mortality. The receiver operating characteristic (ROC) area under the curve (AUC) for this model was 0.83. Of the total cohort, 1178 (50%) cases had values for all of these variables and were included in the CCA analysis.

In an attempt to overcome the limitations imposed by missing data, we performed multiple imputation, the results of which were similar, with the same set of variables remaining significant in the two and the MI model had a ROC AUC of 0.80. Results of the CCA and MI multivariable logistic regression are shown in Table 2.

We then repeated the analysis for early mortality within 6 months rather than 12 months. The results were similar, with the exception that cardiac disease and ISS were not significantly associated with 6-month mortality (see Table S1).

DISCUSSION

In this large, binational, prospective cohort of NDMM treated with novel therapy, we found 12-month mortality of 9.1% (and 6-month mortality of 4.5%). The most common primary cause of death within 12 months of diagnosis was reported as directly attributable to MM, accounting for 78% of deaths for which the cause was known. Infection was the primary cause of death in 7%; however, it was also a contributing factor for death in 38% of patients in whom secondary causes of death were available. Older age, ECOG performance status, ISS, cardiac disease, and albumin were each independently associated with early mortality.

Comparison with the literature

There have been previous studies reporting rates of early mortality following the introduction of novel therapies.

Kumar et al.,[9] in a single-centre retrospective study of 1038 patients who started therapy for MM at the Mayo clinic between 2001 and 2010, reported 12-month mortality of 13% overall, with a lower rate in those treated with a novel agent (thalidomide, lenalidomide or bortezomib) in initial therapy (8% vs 19%, $p < 0.001$). Other studies from single or few centres have reported similar rates of early mortality. A study of 542 patients with NDMM from three hospitals in Korea reported 12-month mortality in 13.8%.[11] A single centre from Taipei reported early mortality at 6 months of 12.6%.[18] However, population-based studies have reported overall higher rates of early mortality. A study of 621 patients with NDMM over a longer time period (31 years) reported an overall 12-month mortality in those fit for therapy of 28.6%, with a lower rate in those diagnosed between 2010–2015 (although still >20%).[12] An analysis of patients with NDMM ineligible for high-dose therapy using a nationwide database from Denmark reported a 6-month mortality of 22%. In comparison, clinical trials report much lower rates of early mortality.[19] A recent pooled analysis of 1146 patients with NDMM enrolled in two large phase III clinical trials reported a low early mortality rate of 1.6% at 60 days and 11.4% at 24 months, consistent with a significant selection bias between those patients who were, or were not, eligible for front-line clinical trials.[10]

Our early mortality rate is more in keeping with the single- or three-centre studies, rather than the population-based or clinical trial-derived data. In comparison to single- and few-centre studies, our registry-based prospective cohort study includes NDMM treated at a large number of institutions, which include a range of services (regional and smaller centres as well as academic, specialist hospitals) and we employ an opt-off consent with a waived consent for early deaths, ensuring more critically unwell patients are included, therefore minimising selection bias.

With regards to cause of death, we found death due to progression of disease was the most commonly reported primary cause, accounting for more than half of all early deaths, and that although infection was a contributing factor in 38%, it was only listed as the primary cause in 7% of cases. In a previous study of trials conducted before the introduction of novel therapies, infection was reported to be primary cause in almost half of all early mortality deaths (within 60 days).[8] The study from the Danish MM registry of non-transplant eligible patients reported infection as the cause of death in approximately half of all early mortality cases.[19] In the study by Jung et al.[11] at three centres in Korea, infection accounted for 36% of all deaths at 12 months, and comorbidities another 24%. In the population-based study by Rios-Tamayo et al.,[12] infection was the most common cause of early mortality. In contrast, the study from Terebelo et al.[14] using registry data from the USA, disease progression was the most common cause of death within 6 months, accounting for 39%, and infection accounted for ~13%, which is similar to our findings.

Similar to our study, previous studies have reported age,[12,14] performance status (ECOG[14] or World Health Organisation[19]), ISS,[14] and albumin[9,19] as being associated with early mortality. Other reported factors that were not independent predictors in our study are creatinine,[12] liver disease,[12] hypertension,[14] low platelet count,[14] LDH,[19] and β_2-microglobulin,[9] although the latter is captured in the ISS. Unlike previous studies, we also found that a history at diagnosis of moderate-to-severe cardiac disease was predictive of early mortality.

With age and comorbidities as independent predictors of early mortality, and with disease progression the most common cause of early mortality, our data raises questions about whether improved treatment delivery to elderly and/or frail patients may improve outcomes. Frailty has been shown to impact adversely on the likelihood of receiving or completing the intended course of treatment in transplant-ineligible patients with NDMM.[13,20] Emerging trial data in relapsed MM and transplant-ineligible NDMM have demonstrated correlation between ability to deliver continuous therapy and both likelihood of achieving deep treatment responses and improved survival.[21–24] Furthermore, early disease control in MM correlates with improved long-term survival.[25,26] However, treatment-related adverse events in transplant-ineligible NDMM frequently mandate early treatment discontinuation and are associated with an increased risk of death.[13] A recent analysis of our registry data showed in transplant-ineligible NDMM, receiving four or fewer cycles of therapy predicts poor survival in patients who are treated with bortezomib-based induction.[27] Recognition of this has informed recent recommendations by the IMWG to empirically reduce treatment doses based on a frailty assessment[28] to improve tolerability and deliverability of therapy, and to the design of new studies stratifying treatment according to frailty assessments.[29,30]

STRENGTHS AND LIMITATIONS

Our study has a number of strengths, including its prospective design, large sample size, inclusion of 36 sites across two countries and use of opt-off/waived consent to increase capture of all NDMM at participating sites, which all contribute to the generalisability of our findings. Our registry data is linked with national death registries, ensuring the robustness of our outcome data. However, our study does have limitations. One such limitation, common to many registry-based studies, is the lack of universal data completeness for most fields in the registry. We attempted to address this with multiple imputation, using correlations in the observed data to impute missing values. This can have advantages over the approach of complete case ascertainment, which inherently assumes that there is no pattern to the missing data and is, therefore, likely to introduce bias if this is not the case.[31] There were also limitations in the coding of death, for which we used two data sources. We used the national death registry, which relies on cause of death information recorded on death certificates and classifies the primary cause of death as that which initiated the events that led directly to a person's death, as well as secondary causes of death. However, there

is often a delay in the availability of cause of death data, and so it was only available from the national registry in 32% of cases. We also used the MRDR that only collects the primary cause of death and that is classified based on a review of the medical record. The MRDR does not collect frailty assessments, so we could not assess administration of therapy according to frailty at diagnosis. As this is a 'real-world' study, treatments were determined by local availability and funding of novel agents in the two countries, which may limit the generalisability to some jurisdictions with different access to novel therapies for NDMM. Finally, the observational design limits conclusions that can be made regarding causality.

CONCLUSION

In a large, prospective, registry-based analysis of 2377 patients with NDMM, we found early mortality at 12 months to be 9.1%, with disease progression the most common cause of death. Independent predictors for early mortality were age, comorbidities (especially cardiac and pulmonary disease), performance status, and measures of disease severity. These findings support the need for future research into optimising treatment delivery to elderly and/or frail patients with NDMM and the ongoing unmet need for more effective and deliverable treatment modalities, particularly in the elderly NDMM population.

AUTHOR CONTRIBUTIONS

All authors contributed to study design. Zoe McQuilten and Cameron Wellard analysed the data. Zoe McQuilten drafted the manuscript. All authors revised and approved the final manuscript.

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CONFLICT OF INTEREST

The MRDR has received funding from: Abbvie, Amgen, Antengene, Bristol-Myers Squibb, Celgene, Gilead, GSK, Janssen, Novartis, Sanofi, and Takeda.

DATA AVAILABILITY STATEMENT

The data from the Myeloma and Related Diseases Registry that support the findings of this study are available on request and following approval from the corresponding author and the registry. The data are not publicly available due to privacy or ethical restrictions. The Data Access Policy is available at www.mrdr.net.au

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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