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

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Introduction

Early mortality in newly diagnosed multiple myeloma (NDMM) patients is infrequent in clinical trials. However higher rates of early mortality have been reported in population-level data. Identification of risk factors for early mortality may inform strategies to improve outcomes.

We aimed to describe early mortality in a real-world cohort of NDMM and explore factors predictive of early mortality.

Methods

We included all NDMM patients in the Myeloma and Related Diseases Registry from Jan 2013-May 2017. Patient and disease characteristics at diagnosis were obtained from the registry.

Mortality data, including primary cause of death, was obtained from the registry as well as through linkage with national death registries in Australia and New Zealand.

Early mortality was defined as death from any cause within the first 12 months of diagnosis.

Associations between early mortality and patient characteristics (age, gender, co-morbidities), year of diagnosis, disease characteristics (international staging system [ISS], cytogenetics, lactate dehydrogenase [LDH], beta-2 microglobulin [B2MG], albumin), baseline renal function, blood count and EQ5D were assessed.

Due to high rates of missing values, multiple imputation was performed using multivariate normal regression based on patterns in existing data.

Multivariable logistic regression models were developed using 1) the complete case ascertainment (CCA) data set and 2) the multiple imputation (MI) datasets. Of the two models, CCA relies on more restrictive assumptions regarding missing data compared to MI.

Variables with a significant association with one year mortality ($p<0.05$), and where the variance associated with the multiple imputation was less than 10% of the total variance in the MI dataset, were considered for inclusion in the model.

We also considered variables from a previously published predictive model[1] for 6-month mortality.

Results

1039 NDMM patients were included in the analysis. Overall survival for the included cohort is shown in Figure 1.

Early mortality was reported in 91 (8.8%) patients.

Patient characteristics according to early mortality are shown in Table 1.

Primary cause of death was disease-related in 53 (58%), infection 4 (5%), non-disease related 13 (14%) and unknown in 21 (23%) of cases

Figure 1: Overall survival

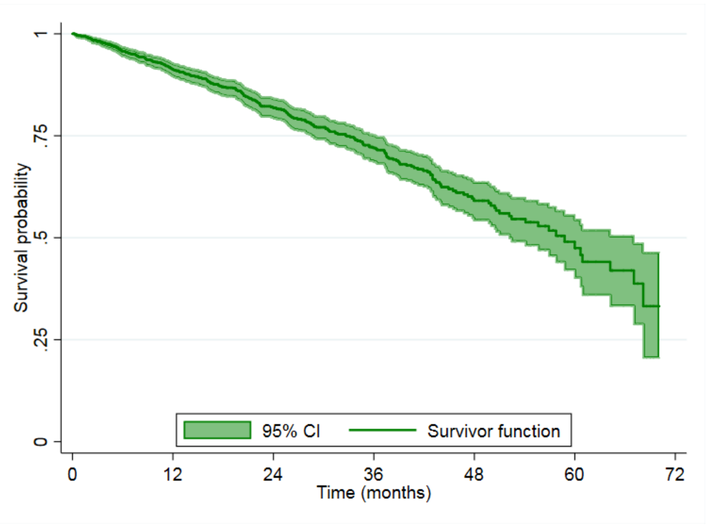

Table 1: Associations with early mortality

	Alive at 12 months	Deceased at 12 months	p
Number	948/1039 (91.2%)	91/1039 (8.8%)	
Age at diagnosis, median (IQR)	65.5 (57.6-73.0)	76.1 (67.3-82.7)	<0.001
ISS	2 (1-3)	3 (2-3)	<0.001
ECOG performance status	1 (0-1)	2 (1-2)	<0.001
eGFR	71.0 (51.0-89.0)	49.5 (28.0-73.0)	<0.001
Platelet count (>150 x 10^9/L)	750/877 (85.5%)	61/87 (70.1%)	<0.001
Serum Creatinine (> 176.8 µmol/L)	92/865 (10.6%)	25/89 (28.1%)	<0.001
Lactate Dehydrogenase (U/L)	189 (155-240)	223 (183-310)	<0.001
Albumin (g/L)	35 (30-39)	30 (26-36)	<0.001
Serum Beta 2 Microglobulin (mg/L)	3.6 (2.5-6.0)	7.0 (4.3-12.1)	<0.001
History of heart disease	80/948 (8.4%)	19/91 (20.9%)	<0.001
History of pulmonary disease	39/948 (4.1%)	11/91 (12.1%)	<0.001
EQ5D Mobility	2 (1-2)	2 (2-3)	0.011
EQ5D Usual Activities	2 (1-3)	3 (2-4)	0.013
EQ5D VAS	74 (66-85)	60 (48-75)	0.013

We show either median with interquartile range or, for binary variables, fractions with associated percentages, Only includes patients who died less than twelve months after diagnosis or with at least six months follow up

Predictive models for early mortality

Variables considered for inclusion in the multivariable model were those found to have significant association on univariate analysis as well as those found to be significant in the model by Terebelo et al[1]. Models were developed first for the CCA dataset and then repeated using the MI datasets.

Final variables included in the model using the CCA dataset are shown in Table 2:

Table 2: Model results using CCA data

Variable	Odds ratio (95%CI)	p
Age >75y	2.75 (1.31, 5.71)	<0.001
Albumin	0.93 (0.89, 0.99)	0.025
ISS	1.97 (1.08, 3.58)	0.026
LDH >300	3.13 (1.36, 7.19)	<0.001
Cardiac disease	2.86 (1.25, 6.51)	0.012
Pulmonary disease	3.22 (1.19, 8.74)	0.022

Receiver operating characteristic area under the curve 0.82 (95% CI 0.76, 089)

Final variables included in the model using MI datasets is shown in Table 3:

Table 3: Model results using MI data

Variable	Odds ratio (95%CI)	p
Age > 75y	3.14 (1.92-5.13)	<0.001
ECOG performance status	1.44 (1.08-1.93)	0.013
ISS	1.71 (1.18-2.49)	0.005
Platelet count (>150 vs ≤150 x 10^9/L)	0.54 (0.31-0.94)	0.029
Cardiac disease	1.99 (1.08-3.65)	0.027
Pulmonary disease	2.18 (0.99-4.82)	0.054
LDH >300	2.11 (1.04-4.29)	0.039

Receiver operating characteristic area under the curve 0.79 (95% CI 0.74, 084)

Conclusions

In a large cohort of NDMM patients, early mortality occurred in 8.8% with disease accounting for more than half of all deaths. This rate of early mortality is lower than reported in other studies[1].

Factors independently associated with early mortality were age at diagnosis, ECOG performance status, ISS stage, platelet count <150 x 10^9/L, cardiac disease and serum LDH levels. These are similar to those previously reported in other cohorts.

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