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Outcome and survival of myeloma patients diagnosed 2008-2015. Real world data on 4904 patients from the Swedish Myeloma Registry (SMR).

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Running title: Experiences from the Swedish Myeloma Registry

ABSTRACT

Epidemiology and outcome of myeloma is mainly reported from large university centers and collaborative groups and do not represent real world patients.

The Swedish Myeloma Registry is a prospective population-based registry documenting characteristics, treatment and outcome in newly diagnosed myeloma, including asymptomatic and localized forms, with the purpose to improve the management and outcome. This report presents information on patients diagnosed between 2008 and 2015, including data on first line treatment in patients diagnosed up to 2014, with a follow-up until December 2016. We present age-adjusted incidence, patient characteristics at baseline, treatment, response, and survival.

Baseline data was available with a 97% coverage in 4,904 patients (median age 71 years, males 70 years, females 73 years, 72% were 65 years or older), and at one-year follow-up in 3,558 patients with symptomatic disease (92% of patients initially reported). The age-adjusted incidence was 6.8 myeloma cases per 100 000 inhabitants and year. Among initially symptomatic patients (n=3,988), 77% had osteolytic lesions or compression fractures, 49% had anemia, 18% impaired kidney function, and 13% hypercalcemia. High-dose therapy with autologous stem cell transplantation was given to 77% of patients up to 66 years, and to 22% of patients 66-70 years. In the study period, 68% received bortezomib, thalidomide, and/or lenalidomide as part of the first line treatment, rising from 31% in 2008 to 81% 2014. In MM, the median relative survival of patients 65 years or younger was 7.7 years, and 3.4 years in patients 66 years and older. Patients diagnosed with myeloma in more recent years were associated with significantly higher rates of complete or very good partial remission ($p<0.05$), and with a significant higher survival with a HR of 0.84 (95% CI 0.77-0.92; $p< 0.05$). There

was small, but significant survival benefit in patients treated in university hospitals (HR 0.93; 95% CI 0.87-0.99, $p<0.05$).

We here report on a near complete real world population of myeloma patients during an 8-year period, when newer drugs were implemented into standard practice. The overall incidence and median age were both higher than in most previous studies, indicating a more complete coverage of older patients. Myeloma survival in Sweden compare to other large registry studies and responses and survival improved during the study period.

INTRODUCTION

In the recent decades, new treatment options have emerged in myeloma, with great expectations of better survival. The introduction of high-dose melphalan with autologous stem cell support (HDM-ASCT) and newer drugs, such as the immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), proteasome inhibitors (bortezomib and carfilzomib), monoclonal antibodies, and other classes, has led to a rapid implementation of these drugs into international guidelines. [1 2 3-6 7] To date, most studies on myeloma are based on selected patients from large referral centers and collaborative groups, with defined inclusion and exclusion criteria, often omitting elderly patients, and thus do not reflect the true real-world population [8]. Also, there is limited information on the use of new therapies and their efficacy and tolerability in standard practice, supporting the need for representative population-based prospective studies on characteristics, diagnostics, treatment and outcome in myeloma patients.

Survival data from Cancer Registries are available, but often lack information on baseline characteristics and treatment. EUROCARE, covering nearly 50% of patients diagnosed with plasma cell neoplasms 2000-2007 in Europe, report age-standardised 5-year relative survival (RS) of 39.2%, increasing from 29.8% in 1997. Outcome was significantly better in the younger patients (68.6% versus 21.8% 5-year relative survival), and in women (40.4% versus 38.1%)[9]. These results have later been confirmed by other cancer registry data [10-12]. In a Swedish study from 2010, baseline characteristics and treatment on consecutive patients in Malmö, from retrospective data, found a similar trend on improved survival, which correlated to the introduction of new treatment modalities. [13, 14]

The Swedish Myeloma Registry was established in 2008, and the first Swedish guidelines on diagnostics and treatment of myeloma was published in 2010. This is the first report on our populations-based data on characteristics, treatment and survival on Swedish myeloma patients diagnosed from January 2008 through December 2015.

METHODS

The Swedish Cancer Registry The Swedish Cancer Registry is a nation-wide compulsory dual-report system developed in 1958, aided by the personal identification code system for all Swedish citizens, established in 1947. First, all pathology specimens indicating malignancy are reported by the pathologist to the Regional Tumor Registry; and second, data on date and type of cancer diagnosis on all patients with a newly diagnosed cancer are reported by clinicians, with missing data actively requested to secure high completeness. In a validation study, the completeness (95%) and diagnostic accuracy (98%) of the Cancer Registry was found to be very high for multiple myeloma patients.[15]

The Swedish Myeloma Registry The Swedish Myeloma Registry comprises web-reported clinical and laboratory data on all patients diagnosed with active myeloma, smoldering myeloma, plasma cell leukemia, and solitary bone and extramedullary plasmocytomas since 2008 in Sweden, at time of diagnosis, and after one year of follow-up. Coverage is analyzed through the compulsory Swedish Cancer Registry. Survival is achieved from the Swedish Population Registry. Patients diagnosed by autopsy are included in the Swedish Cancer Registry, but not in the Swedish Myeloma Registry. The registry is publicly financed, and the patients are reported by treating physicians and nurses. Courses for reporters in inclusion criteria, parameters, and the manual of the Swedish Myeloma Registry are held to assure coherent reporting in all regions and hospitals. Criteria for the diagnosis of active myeloma (MM), smouldering myeloma (SMM), plasmocytoma, and plasma cell leukemia are defined according to the International Myeloma Working Group (2003)[16]. Other gammopathies, such as monoclonal gammopathy of uncertain significance (MGUS) and AL-amyloidosis are not included in the registry. Age-specific incidence, age distribution at diagnosis, median time from diagnosis to registry report and distribution of the diagnoses in the registry are reported.

The adherence to treatment guidelines concerning diagnostics and ISS-staging (International Staging System) is asserted by studying the use of different diagnostic tools as bone-marrow sample, cytogenetics including fluorescence in-situ-hybridization (FISH), beta 2–microglobulin (β2m) and s-albumin. Baseline characteristics at diagnosis are collected, including M-protein isotype, percentage of plasma cells in the bone marrow, serum free-light chain (FLC), and laboratory parameters capturing CRAB criteria (CRAB; calcium, renal insufficiency, anemia or bone lesions). One year after diagnosis of symptomatic MM, data on first line therapy, occurrence and date of first relapse or complications are requested. The study was performed in agreement with the ethics committee of Stockholm and the Swedish Society of Hematology.

Treatment of MM in Sweden In Sweden, patients with myeloma are typically diagnosed and followed clinically by physicians at hospital-based hematology centers, and no patients are seen at private hospitals. In the study period, the treatment of MM was guided by the British/Nordic treatment program for multiple myeloma (2005)[17], the Swedish National Guidelines 2010, with an updated version 2013. In short; high-dose melphalan and autologous transplantation (HDM-ASCT) was recommended as up front treatment for all MM patients 65 years and younger, and in patients 66-70 years if in good performance status. In 2005, vincristine, adriamycin, and dexamethasone (VAD) or similar combinations were recommended as induction treatment before HDM-ASCT, and later, in the guidelines of 2010, bortezomib and thalidomide was part of standard induction, after a time of introduction after approval in 2004. Patients at smaller hospitals are as a rule only referred to University hospitals for the ASCT procedure and afterwards return to their hospital of origin. For patients 66 years and older, melphalan and prednisone (MP) or cyclophosphamide and dexamethasone (CyDex) was standard up front until 2004, when melphalan, prednisone and thalidomide (MPT) was incorporated as a treatment option. In 2010, MPT was the standard

for patients not eligible for ASCT, and MP and bortezomib (MPV) were treatment options. In the version from 2013, both MPT and MPV were standard up-front treatments in the patients not eligible for ASCT.

Statistical analysis

Incidence was extracted from the Swedish National Board of Health statistical database on cancer 1970-2015, which includes all patients with the diagnosis ICD 203*[18]. All other analyses were performed on patients reported to the Myeloma registry with a 97 % coverage compared to the Swedish Cancer Registry[19]. For the diagnoses MM and SMM we summarized descriptive statistics at diagnosis. We tabulated categorical variables such as sex, Ig-class and use of new drugs. Summary statistics, for example median and range, were calculated for continuous variables such as age and β2M. Significance test of difference in proportions was done using Chi squared test. Statistics on treatment was only done on MM patients with reported one year follow up, including patients who had developed to symptomatic disease after SMM or plasmacytoma. We estimated observed survival using the Kaplan Meier method. When estimating relative survival (RS), relative to the general Swedish population, we used the Ederer II method for expected survival. For observed survival (OS), we estimated hazard ratios using Cox's proportional hazards regression modelling. Also for RS, we estimated hazard ratios using proportional hazards regression, but in transformed time[20] Survival time was calculated from date of diagnosis to death or censoring. Patients were censored at the end of follow-up in the study or loss to follow-up. Age standardized relative survival was calculated in each age group separately and then weighted together using weights from a standard population – in this case international Cancer Survival Standard (ICSS) 1. We used a proportional hazard model of RS by year of diagnosis in all patients to estimate changes in survival over time. The survival analysis by year of diagnosis included both SMM and MM and the date of diagnosis refers to the date of the primary diagnosis,

whether it was SMM or MM. To evaluate the impact of treating hospital, we estimated a proportional hazard model of RS by hospital type; in the categories university hospital or not, and hospital reporting treatment on more or less than 10 patients per year. The survival analysis by treatment response and by hospital type was done on symptomatic MM patients only (including patients who had developed to symptomatic disease after SMM or plasmacytoma) with reported one-year follow-up, to enable comparison with statistics on treatment. When adjusting for ISS stage in regression analysis we treated patients with missing values in the stage variable as a category within the ISS stage variable in order to not exclude the cohort of patients with missing data on ISS stage. P-values <0.05 were considered statistically significant. All data preparation and analysis were done using R statistical software [21].

RESULTS

A total of 5,222 patients with plasma cell diseases diagnosed 2008–2015 had been reported to the SMR as of December 31st 2016, with 97% coverage when compared with the Swedish Cancer Registry.

Clinical data at diagnosis was available for 4,904 MM and SMM patients diagnosed 2008-2015 (Table 1), and at one-year follow-up for 3,558 of all MM cases diagnosed 2008-2014 being 92% of all MM initially reported 2008-2014. Data was reported from 74 different centers in Sweden, approximately 40% from University hospitals, and 60% from regional and smaller hospitals, all in public care. The median time of follow-up of all SMM and MM patients was 4.9 years

The total crude and age-adjusted (to the population in Sweden in year 2000) incidence was 7.0 and 6.8 cases per 100 000 inhabitants, respectively (for men 8.0 and 8.2, and for women 6.0 and 5.3 per 100 000 inhabitants). The corresponding incidences for European and World standard populations are 4.8 and 3.2 respectively. Due to the difference in age distribution in the population, the total number of women was higher in the cohort > 85 years (Figure 1), However, the age-specific incidence was higher amongst men in all ages, and the difference increased with advancing age (Figure S1 in Supplemental files). The median age of patients reported to the registry with a diagnosis of MM or SMM was 71 years (70 years for men and 73 years for women, 71 years for all MM and 72 years for all SMM). Twenty-four per cent of patients were 80 years or older at the time of diagnosis. Notably, the percentage below 65 years was 28.3%, where 61.4% were male and 38.6 women.

Baseline characteristics

Serum protein electrophoresis was performed in 99.5 % of all patients and in 97%, a skeletal survey was performed. A bone marrow sample was done in 97% of patients at diagnosis, with a median of 27% plasma cells in MM patients, and 15% in SMM. Among patients with MM at diagnosis (n=3988), 77% had reported osteolytic lesions and/or compression fractures at diagnosis, and this did not increase in the study period. Anemia was seen in 49%, renal insufficiency (S-creatinine >173 umol/L) in 18%, and creatinine levels >110 μmol/l was reported in 33% of MM patients. Hypercalcemia was noted in 13% of MM patients at the time of diagnosis (Table 2). The number of patients 80 years and younger who had FISH performed at diagnosis, increased over the study period, from 30% in the period 2008-2010, to 43% in 2011-2015. Staging according to the ISS was reported in 71% of patients with MM in the study period. In MM patients with reported ISS-stage, 23 % were in ISS stage I, 44% in stage II, and 33% in stage III. (Table 2)

Treatment

Of all patients with reported follow-up, 77 % of patients 65 years or younger at diagnosis and 5% of patients more than 66 years, received HDM-ASCT as first line treatment. In patients 66-70 years, HDM/ASCT was performed in 22%. Allogeneic transplantation as part of first line treatment was performed in only 1% of patients in the study period. A total of 5.2% of reported MM patients did not receive any anti-myeloma treatment the first year after diagnosis, and notably 11% in patients above 80 years. Bisphosphonates were given in 79% of patients 65 years and younger, and in 67% in patients over the age of 65 years. Treatment with one or more of the novel drugs (thalidomide, lenalidomide, and bortezomib) increased in the study period is depicted in table 3.

Response

The proportion of patients achieving very good partial remission (VGPR) or better after 1st line treatment increased from 36% in patients diagnosed in 2008 to 54% ($p<0.05$) in 2014. The increase was seen in all age groups, but was more pronounced in patients >80 years, where the proportion of patients reaching VGPR or better rose from 14% to 33% (Table 4).

Survival in all myeloma patients

The 1-, 3-, and 5-year OS in all patients (SMM+MM) was 81%, 59%, 42%, and the corresponding RS was 84%, 65%, and 49%, respectively. Survival in 10-year cohorts in all myeloma patients is displayed in Figure S2 and Table S1 in Supplements. Early death (<1 year after diagnosis) was observed in 19% of patients. The 3-year RS was 62% (95%CI: 59.7-64.6) years in women, and 67% (95%CI: 65.0-69.3) in men. After age standardization, the 3-year RS in women was 67% (95%CI: 65.1-69.6) and 70% in men (95% CI: 67.8-71.8). Survival per SMM and MM diagnosis are shown in Table S2 and S3 in Supplements.

Survival in MM

In patients with MM and reported follow-up (n=3,558), the median OS varied considerably depending on age at diagnosis, ranging from 7.8 years in patients $\leq$ 60 years, to 1.5 years for patients 80-89 years. (Table S4 in Supplements). After a median follow-up of 5.5 years, the median OS in the youngest cohort (<50 years) was not yet reached (Figure 2). The median relative survival of patients 65 years or younger was 7.7 years, and 3.4 years in 66 years and older. The 5-year OS and RS in MM patients was 38.3% and 44.9%, respectively. The median RS according to ISS stage was 3.2 years and 5.6 years for stages III and II, and 8.2 years for stage I. Patients with no reported stage had a similar median RS as stage III patients of 3 years.

Survival according to response

Overall, better response to first line treatment was significantly associated with superior survival, ($p<0.05$) (Table S5 in Supplemental files). In younger patients, there was not a significantly different 5-year RS in patients in PR, VGPR and CR, respectively (Figure 3)

Survival according to year of diagnosis

Patients diagnosed in the period 2011-2015 had a trend to better 1-, 3- and 5-year RS compared to patients diagnosed 2008-2010. In patients older than 65 years this trend was more evident than in the younger (Table S5 and Figure S3 in Supplements). In a proportional hazard model of RS by year of diagnosis in all patients, later calendar year of diagnosis was significantly associated with improved RS with a HR of 0.93 (95% CI 0.92-0.95; $p< 0.05$).

Survival according to treating hospital

The 1, -3 –and 5 -year survival was significantly higher in university hospitals (Table S7 in Supplements). In a proportional hazards model for the RS, the HR was 0.93 (95 % CI 0.87-0.99, $p <0.005$. Even when adjusting for age, sex, and ISS-stage, the HR was in the border of significance (HR=0.91; 95 % CI 0.83-1.0, p-value 0.04). Similar results were obtained when analyzing centers that treated 10 or more MM patients per year (data not shown).

DISCUSSION

In this study from the SMR, we report incidence, baseline characteristics and survival, in an unselected population comprising more than 97% of all myeloma patients diagnosed in Sweden 2008-2015. We found an age-adjusted incidence of 6.8 per 100 000 inhabitants, translated to 4.8 and 3.2 in European and World standard, respectively. This is higher than most populations-based studies have reported earlier [22, 23], but coherent with data from a previous large Swedish study [24]. The high age-adjusted incidence might be explained by better case ascertainment in the elderly. Overall, the proportion of elderly (65 years and older) myeloma patients at diagnosis was 72%, and this exceeds the number of reported elderly patients in most known registries today, but supported in population-based data from the Danish Myeloma registry [25] and a recent report on a large cohort European patients from K. Yong [26]. We observed a median age of 71 years at diagnosis, which is higher compared to other myeloma studies [8], and a steep increase in age-specific incidence extending to the oldest age cohorts. This indicates that our population, with a very high coverage, reflects the real-world situation in myeloma today.

Our study shows encouraging survival data on the MM population. In our population-based study, the 5-year OS was 38%, similar to the data from the EUROCARE study [27]. In a report from the Mayo clinic from 2014, based on 1,084 MM patients (median age 66 years), the median OS from diagnosis was 5.2 years and the 6-year OS estimate was 45%[8]. We showed, that with increasing use of novel agents, there was an improvement in response rates. We can show that the proportion of elderly receiving novel drugs increased in the study period. The difference in survival between age cohorts was less pronounced in RS compared to OS, which demonstrates the importance of including RS in survival analyses in MM.

In the European Registry data from 2008 (EUROCARE)[28], a 2% survival advantage was seen in women. We could however, after age standardization, in our more recent study from 2008 to 2015, not find a difference in survival in men and women.

We found, as expected and shown before [29, 30], that achievement of response was predictive of prolonged survival. Noting a significant difference in survival in patients above 65 years of age, we investigated the impact of response grade on survival in different age cohorts in patients with MM at diagnosis. The analysis revealed that responding patients in all age groups had a better outcome than non-responding patients, and that patients achieving CR had the longest survival. However, of interest, in patients ≤65 years, there was no significant difference in survival according to the degree of response (CR, VGPR or PR). This is contrary to result from many randomized studies [31, 32 33], and may indicate that achievement of a high quality response on first line treatment may not have the same importance for survival in a young, unselected myeloma population where the majority of patients will eventually receive many lines of treatment.

We found a survival benefit in patients reported from University hospitals and hospitals treating many MM patients. This may not be surprising, regarding the speed of progress in diagnostics and new treatment in the recent years, and has been reported in other studies[34, 35]. We could not detect a significant difference in referral patterns, but still, our results should be interpreted with caution, as residual confounding factors may influence the outcome. However, this underlines the importance of high volume centers with knowledge in MM treatment and the need of further studies to surveille the access to myeloma care.

The strength of the study is the large, and population-based cohort and excellent coverage to the Swedish Cancer Registry. Another strength is the public Swedish Heath Care system. In Sweden, all patients with a cancer diagnosis are treated in public hospitals enabling publicly financed and equal treatment for all MM patients, reducing the risk of information- and

selection-bias in this study. The SMR has given valuable information on how new treatments have been introduced and established as standard of care in clinical practice leading to improved response rates in all age groups. Importantly we were able to show that there is good adherence to guidelines in all regions of Sweden, both with regards to diagnostics and management, and the registry has helped to define areas where an improvement is needed. The proportion of patients with prognostic classification according to ISS and were FISH was performed as part of diagnostic work-up has increased, however FISH has still not been established as clinical practice in all hospitals. A limitation is the missing treatment data on 8% of patients, and some baseline characteristics, such as ISS-stage. We also do not have detailed data on cytogenetics and comorbidities. We did not have sufficient follow-up data to perform analyses on progression-free survival after first line treatment, which is a limitation of this study

Many large and important studies on characteristics and survival in MM patients are tampered with the bias of reporting from referral centers, being university hospital registries with a low median age at MM diagnosis or selected patients in clinical trials, not necessarily reflecting the real-world scenario in myeloma. A great effort is made to make the SMR complete, and to present population-based data on management and outcome in Sweden. We can now present a near complete real world population of myeloma patients, and show that the overall incidence and median age is higher than in most previous studies, indicating a more complete coverage of older patients. Myeloma survival in Sweden was similar to other large registry studies, and responses and survival improved in the study period.

Authorship and disclosures

Contribution: S.Y.K., and C.H.B and the SMR steering group designed the report and initiated this work; Data was obtained by hematologists from all hematology centers in Sweden. Monitoring and all statistical analyses were performed by the Swedish Regional Cancer Center of Western Sweden and statistician Anna Genell. C.H. B., IT and S.Y.K. wrote the report; all the authors were involved in the interpretation of the results; read, gave comments, and approved the final version of the manuscript; had full access to the data in the study; and take responsibility for the accuracy of the data analysis.

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TABLES AND LEGENDS

Characteristics	**Patients**
Total, n (%)	4904 (100 %)
Diagnosis, n (%)	
Multiple myeloma	3988 (81.3%)
Smoldering multiple myeloma	916 (18.6%)
Age in years at dx, median	
All	71
Male	71
Female	73
Immunoglobuline class n (%)	
IgG	2882 (58.8)
IgA	1033 (22.3)
Bence-Jones MM	688 (14.0)
Non-secretory MM	143 (2.9)
IgD	19 (0.4)
IgM	14 (0.3)
Not known	23 (0.5)
More than one Ig	41 (0.8)
IgE	1 (0.0)

Table 1. Characteristics of MM and SMM patients in the Swedish Myeloma Registry

	Patients N=3988
ROTI (%)	
Anemia*	49%
Renal impairment**,	18%
Hypercalcemia***	13%
Skeletal disease	77%
ISS stage (%)	
Stage I	23
Stage II	44
Stage III	33

in patients with report on:
* Anemia defined as hemoglobin < 10g/dl and reduction of 2g/dl from the normal value
** Renal failure defined as creatinine >173 µmol/l
*** Hypercalcemia defined as S-Calcium (uncorrected) > 2.75 mmol/l or
ionized calcium>1.45 mmol/l

Table 2. Prevalence of ROTI (Myeloma-Related-Organ and Tissue Impairment) and ISS stage at diagnosis in patients with MM at diagnosis in the Swedish Myeloma Registry

Patients with novel drugs 1st line	*All ages n=2400 (%)*	*≤65 years n= 913 (%)*	*66-80 years n= 1212 (%)*	*>80 years n=275 (%)*
2008-2014	**67.5**	**81.3**	**72.6**	**35.6**
2008	31.1	24.4	42.0	17.7
2009	56.1	76.8	55.7	24.8
2010	69.1	91.6	74.1	32.6
2011	75.2	93.8	76.0	34.5
2012	77.0	98.1	83.3	37.3
2013	81.0	95.6	88.1	49.2
2014*	81.1	92.2	86.2	54.3

Table 3. Proportion of patients who received novel drugs (thalidomide, bortezomib or lenalidomide) as 1st line treatment among MM patients with reported follow up, by year of diagnosis and by age group (-65, 66–80, >80) in the Swedish Myeloma Registry
*2014 has less follow-up on patients reported (at data cut-off 78.7% of initially reported)

Patients VGPR or better	*All ages n (%)*	*≤65 years n (%)*	*66-80 years n (%)*	*>80 years n (%)*
2008-2014	**1415 (45.8)**	**725 (68.3)**	**575 (38.9)**	**115 (20.8)**
2008	152 (36.1)	87 (55.1)	56 (28.0)	9 (14.3)
2009	173 (40.3)	97 (62.2)	58 (23.4)	18 (23.4)
2010	209 (47.5)	104 (67.5)	86 (43.9)	19 (21.1)
2011	223 (45.4)	123 (72.4)	91(35.1)	9 (14.5)
2012	223 (46.4)	114 (73.5)	91(39.6)	18 (18.8)
2013	230 (51.6)	117 (78.0)	94(46.8)	19 (20.0)
2014*	205 (53.5)	83 (70.3)	99(50.5)	23 (33.3)

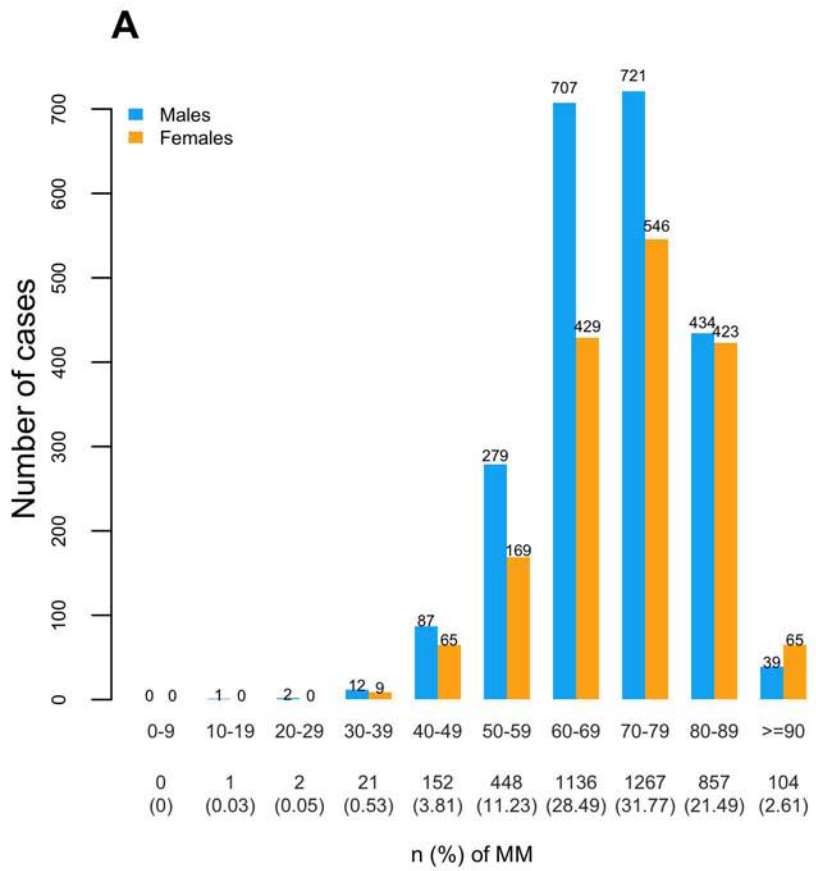
Table 4: Proportion with VGPR (Very Good Partial Remission) or better among MM patients with reported follow-up after first line treatment in patients diagnosed 2008-2014 in the Swedish Myeloma Registry, by year of diagnosis and by age group (-65, 66-80, >80).
*2014 has less follow-up on patients reported (at data cut-off 78.7% of initially reported)

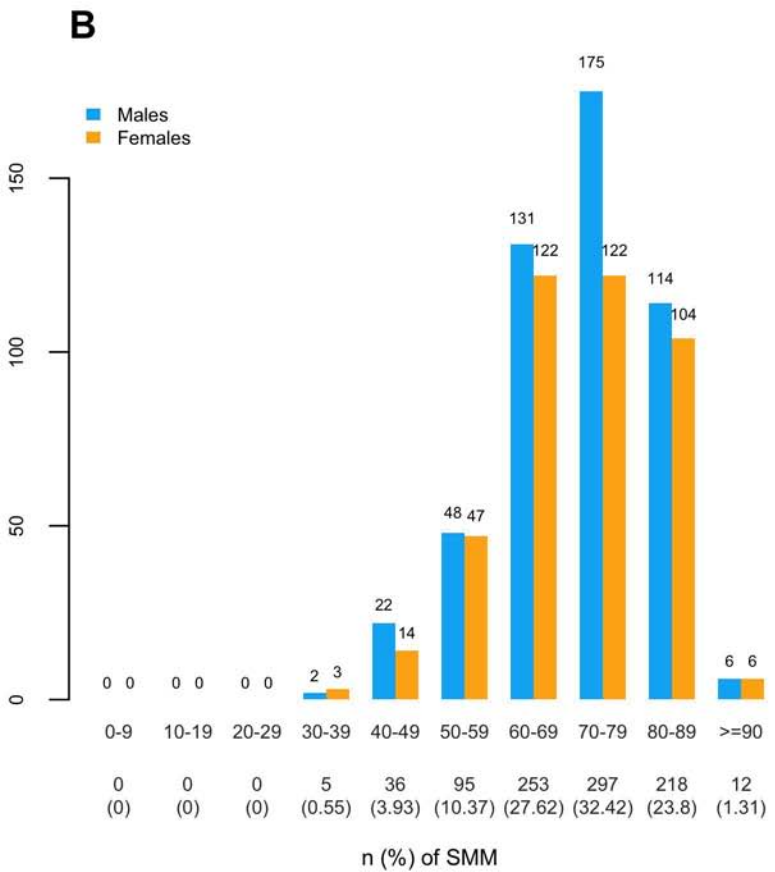
Legends to Figures

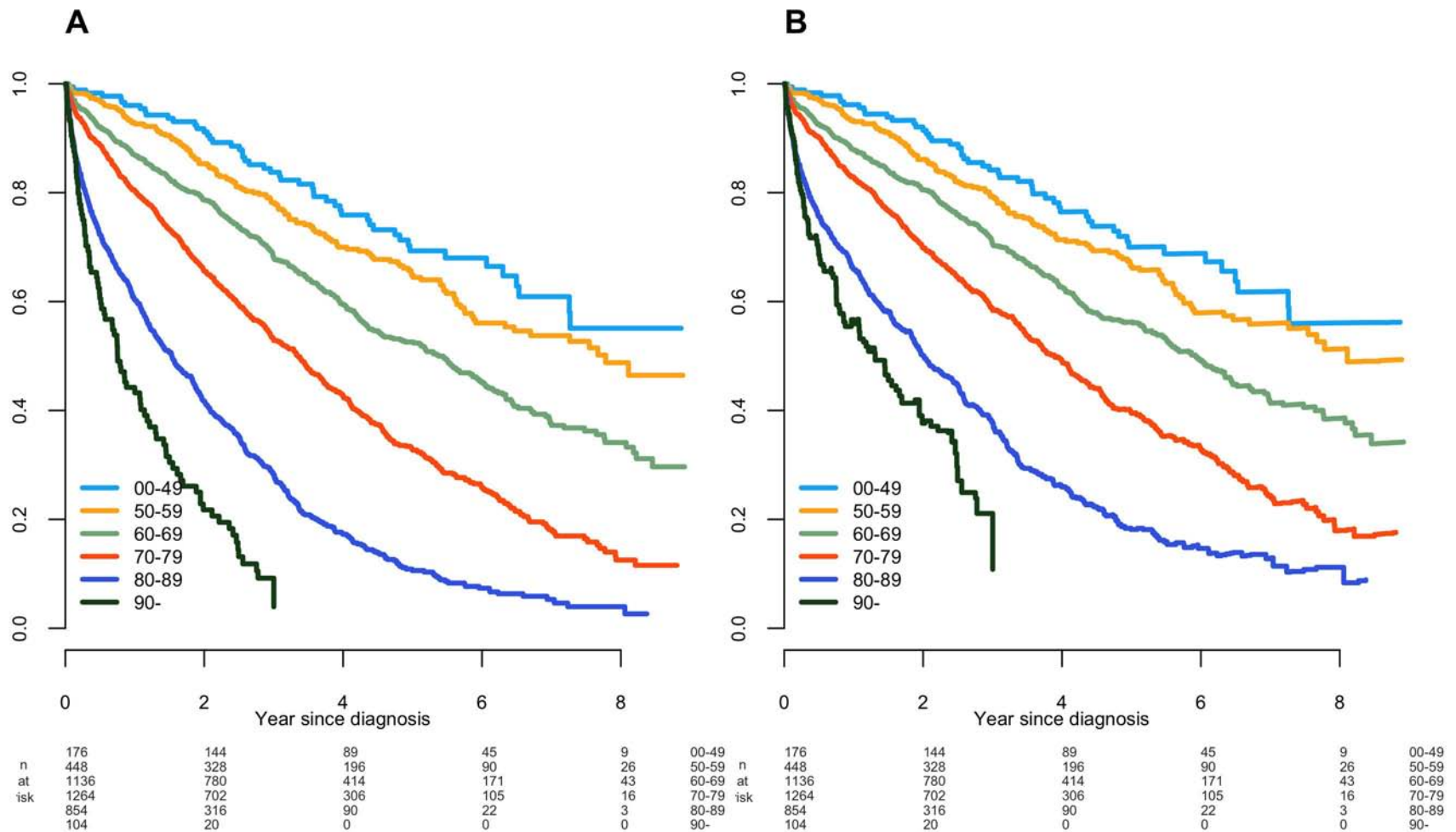
Figure 1: Age distribution in in the Swedish Myeloma Registry in men and women. In A) MM, and B) SMM.

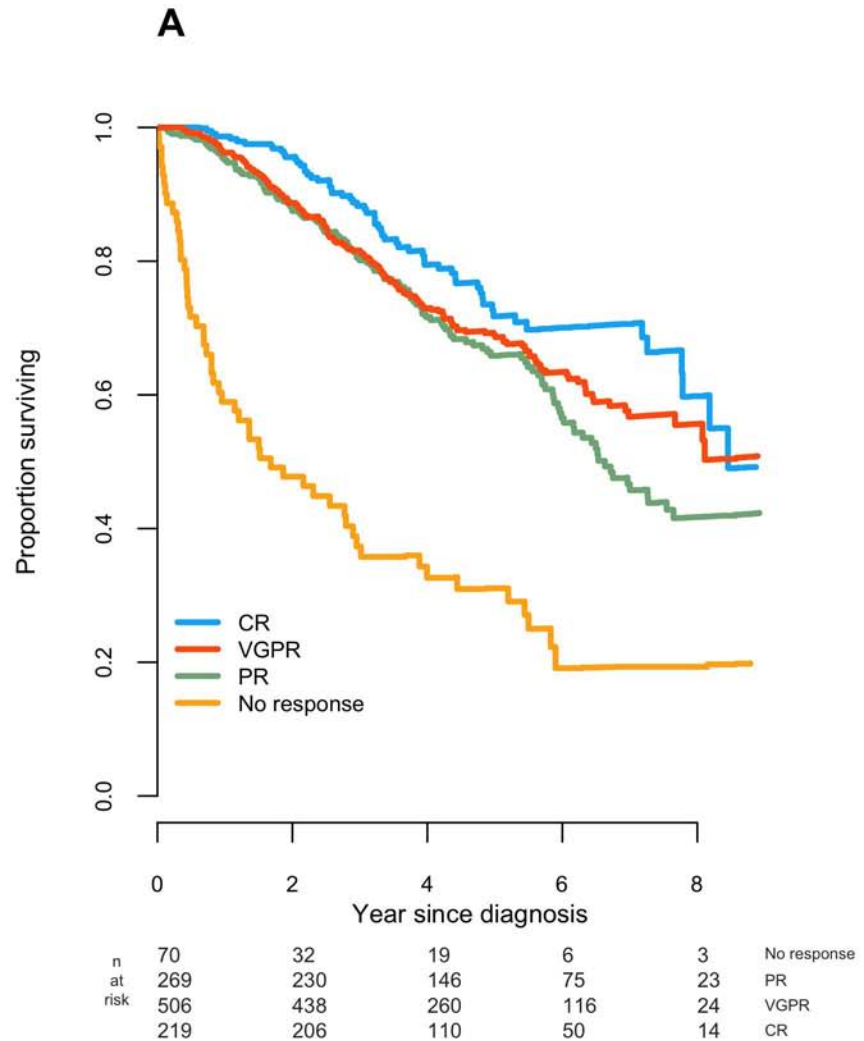
Figure 2: Survival in MM in the Swedish Myeloma Registry. Observed (A) and relative (B) survival, by 10 -year age cohorts.

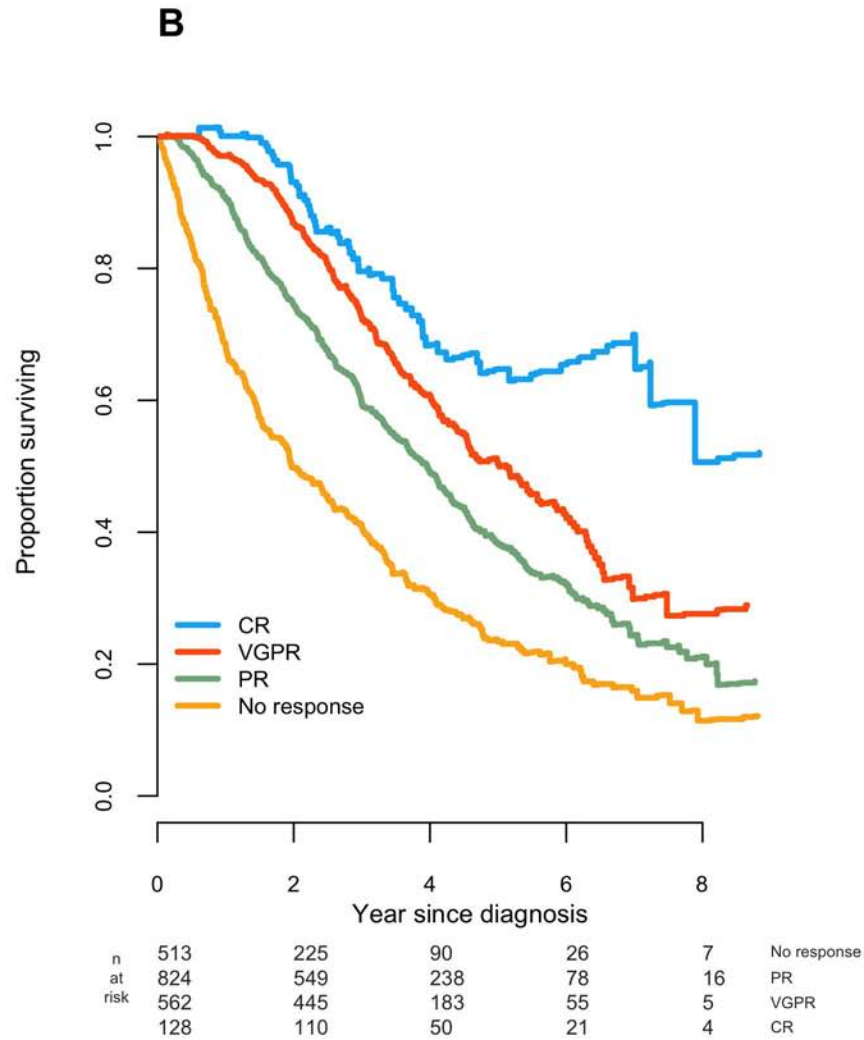
Figure 3: Relative survival in MM by treatment response in the Swedish Myeloma Registry. In age cohorts -65 (A), and 66+ years (B).


A
Males
Females
Number of cases
0
100
200
300
400
500
600
700
0 0
1 0
2 0
12 9
87 65
279 169
707 429
721 546
434 423
39 65
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
>=90
0 (0)
1 (0.03)
2 (0.05)
21 (0.53)
152 (3.81)
448 (11.23)
1136 (28.49)
1267 (31.77)
857 (21.49)
104 (2.61)
n (%) of MM


B
Males
Females
0
50
100
150
0 0
0 0
0 0
2 3
22 14
48 47
131 122
175 122
114 104
6 6
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
>=90
0 (0)
0 (0)
0 (0)
5 (0.55)
36 (3.93)
95 (10.37)
253 (27.62)
297 (32.42)
218 (23.8)
12 (1.31)
n (%) of SMM


A
B
1.0
0.8
0.6
0.4
0.2
0.0
00-49
50-59
60-69
70-79
80-89
90-
0
2
4
6
8
Year since diagnosis
n at risk
176 144 89 45 9 00-49
448 328 196 90 26 50-59
1136 780 414 171 43 60-69
1264 702 306 105 16 70-79
854 316 90 22 3 80-89
104 20 0 0 0 90-


A
Proportion surviving
1.0
0.8
0.6
0.4
0.2
0.0
CR
VGPR
PR
No response
0
2
4
6
8
Year since diagnosis
n at risk
70 269 506 219
32 230 438 206
19 146 260 110
6 75 116 50
3 23 24 14
No response
PR
VGPR
CR


B
Proportion surviving
1.0
0.8
0.6
0.4
0.2
0.0
CR
VGPR
PR
No response
0
2
4
6
8
Year since diagnosis
n at risk
513 824 562 128
225 549 445 110
90 238 183 50
26 78 55 21
7 16 5 4
No response
PR
VGPR
CR

age category	Time int. (Years)	n at risk	Obs. surv. (%)	CI	Rel. surv.(%)	CI
00-49	1	208	96.8	94.5 - 99.2	96.9	94.6 - 99.3
50-59	1	505	93.7	91.7 - 95.8	94.1	92.1 - 96.2
60-69	1	1215	88.5	86.8 - 90.2	89.5	87.8 - 91.2
70-79	1	1276	82.8	81.0 - 84.7	85.3	83.4 - 87.3
80-89	1	691	64.9	62.1 - 67.8	71.0	67.9 - 74.2
90-	1	53	45.7	37.4 - 55.7	59.1	48.5 - 72.0
00-49	3	147	85.7	81.0 - 90.8	86.2	81.4 - 91.3
50-59	3	332	80.9	77.5 - 84.5	82.0	78.6 - 85.6
60-69	3	722	71.0	68.5 - 73.6	73.7	71.1 - 76.3
70-79	3	622	57.4	54.8 - 60.1	63.4	60.5 - 66.4
80-89	3	267	32.8	30.0 - 36.0	44.0	40.2 - 48.2
90-	3	9	10.3	5.7 - 18.6	23.4	13.2 - 41.6
00-49	5	86	73.1	66.5 - 80.3	73.8	67.2 - 81.1
50-59	5	195	68.2	63.8 - 72.9	70.0	65.5 - 74.8
60-69	5	357	56.1	53.1 - 59.3	60.0	56.8 - 63.4
70-79	5	268	37.3	34.4 - 40.3	45.0	41.6 - 48.7
80-89	5	64	13.4	11.0 - 16.2	23.2	19.2 - 28.1
90-	5	0	4.6	1.8 - 11.7	12.3	5.8 - 26.2

Table S1: Observed and relative 1-year, 3-year and 5-year survival (percentages) with 95 % confidence interval, by age category, in the Swedish Myeloma Registry (MM+ SMM)

Diagnosis	Time int. (Years)	n at risk	Obs. surv. (%)	CI	Rel. surv.(%)	CI
MM	1	3112	79.0	77.8 - 80.3	81.8	80.5 - 83.1
SMM	1	836	92.0	90.3 - 93.8	95.4	93.6 - 97.3
MM	3	1611	55.0	53.4 - 56.7	60.7	59.0 - 62.6
SMM	3	488	74.5	71.5 - 77.6	83.4	80.1 - 86.9
MM	5	726	38.3	36.5 - 40.1	44.9	42.9 - 47.1
SMM	5	246	57.2	53.4 - 61.1	69.4	64.9 - 74.2

Table S2: Observed and relative 1-year, 3-year and 5-year survival (percentages) with 95 % confidence interval, by diagnosis

	Observed median survival (Years)	Relative median survival (Years)
MM	3.50	4.23
SMM	5.96	8.01

Table S3**:** Observed and relative median survival, by diagnosis all patient reportad at diagnosis

	Observed median survival (Years)	Relative median survival (Years)
00-49		
50-59	7.78	8.11
60-69	5.37	5.92
70-79	3.34	3.90
80-89	1.53	2.01
90-	0.75	1.31

Table S4: Observed and relative median survival in MM, by 10 year cohorts

Response	Time int. (Years)	n at risk	Obs. surv. (%)	CI	Rel. surv.(%)	CI
CR	1	339	97.7	96.1 - 99.3	99.2	97.6 - 100.8
VGPR	1	1012	94.8	93.4 - 96.1	96.7	95.4 - 98.1
PR	1	973	88.9	87.1 - 90.8	91.8	89.8 - 93.8
No response	1	379	64.8	61.1 - 68.8	67.2	63.2 - 71.4
CR	3	239	81.7	77.7 - 86.0	85.3	80.9 - 89.8
VGPR	3	660	72.1	69.4 - 74.9	76.9	74.0 - 79.9
PR	3	568	58.6	55.7 - 61.7	64.9	61.6 - 68.4
No response	3	185	35.5	31.8 - 39.7	40.2	35.9 - 45.1
CR	5	112	64.1	58.6 - 70.2	69.1	63.0 - 75.8
VGPR	5	315	54.1	50.8 - 57.5	60.2	56.5 - 64.1
PR	5	264	38.9	35.9 - 42.2	45.9	42.2 - 49.9
No response	5	76	19.7	16.5 - 23.5	24.7	20.6 - 29.8

Table S5: Survival by response grade in MM patients, all ages

Diag. period	Time int. (Years)	n at risk	Obs. surv. (%)	CI	Rel. surv.(%)	CI
1	1	1468	80.4	78.6 - 82.3	83.2	81.3 - 85.1
2	1	2480	82.1	80.8 - 83.5	85.1	83.7 - 86.5
1	3	1034	56.7	54.5 - 59.1	62.6	60.1 - 65.2
2	3	1065	60.0	58.1 - 61.9	66.6	64.5 - 68.8
1	5	732	40.1	38.0 - 42.5	47.3	44.7 - 50.0
2	5	240	43.3	40.9 - 45.9	51.3	48.4 - 54.3

Table S6 Observed and relative 1-year, 3-year and 5-year survival (percentages) with 95 % confidence interval, in MM, by period of diagnosis (Period 1 2008-2010, Period 2 2011-2015)

Hospital type	Time int. (Years)	n at risk	Obs. surv. (%)	CI	Rel. surv.(%)	CI
Not university hospital	1	1622	77.7	75.9 - 79.5	80.0	78.1 - 81.9
University hospital	1	1216	82.9	81.0 - 84.8	85.0	83.0 - 87.0
Not university hospital	3	964	52.5	50.4 - 54.7	57.3	54.9 - 59.8
University hospital	3	762	60.4	58.0 - 63.0	65.6	62.9 - 68.5
Not university hospital	5	424	35.2	33.1 - 37.6	41.5	38.9 - 44.3
University hospital	5	375	44.3	41.6 - 47.2	49.9	46.7 - 53.3

Table S7: Observed and relative 1-year, 3-year and 5-year survival (percentages) with 95 % confidence interval, by hospital type (uni./not uni. hosp.)

SUPPLEMENTAL FIGURES

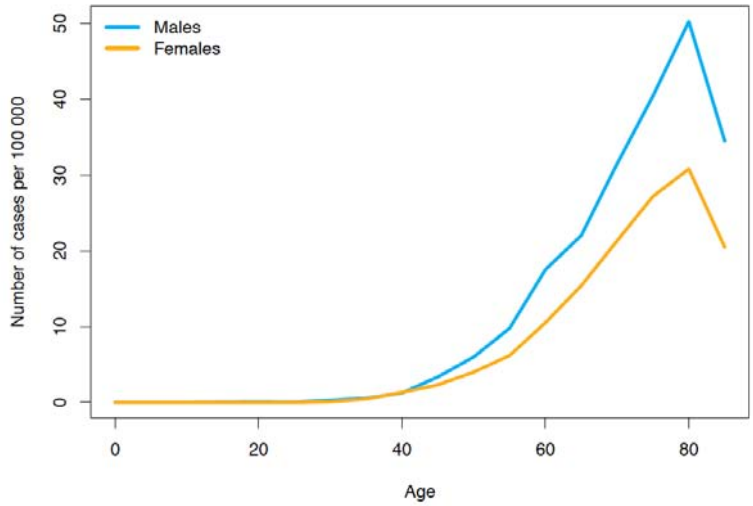


Figure S1 Age specific incidens (per 100 000 personyears) of myeloma (including plasmocytoma) in Sweden, Data from The Swedish National Health Board, mean over the years 2008–2015

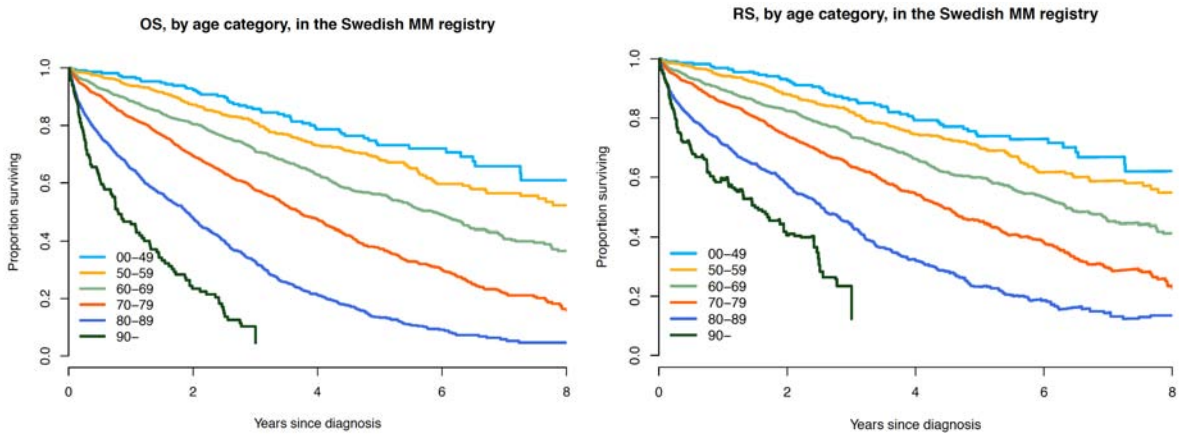


Figure S2: Observed and relative survival in myeloma (SMM+MM) patients by age cohorts
In the Swedish Myeloma Registry

SUPPLEMENTAL FIGURES

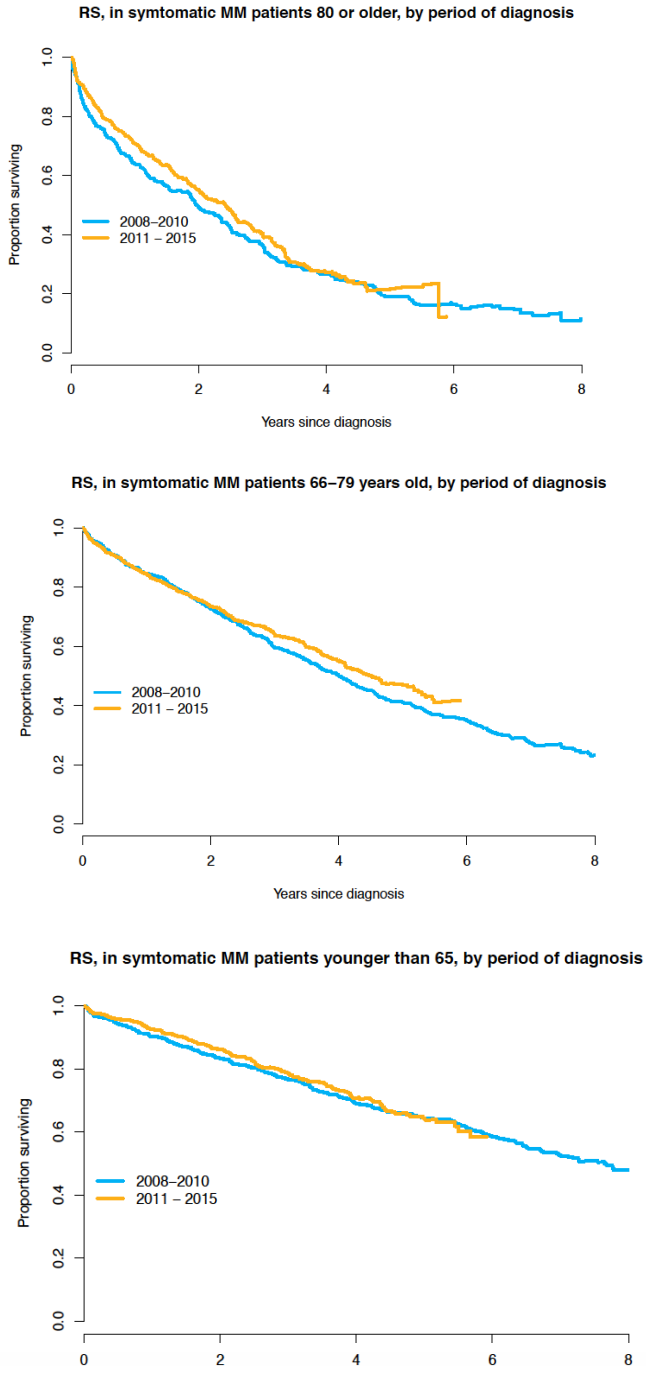


Figure S3: Relative survival by period of diagnosis, by age cohort (-65, 66–79, 80-)