Improved survival in myeloma patients–a nationwide registry study of 4,647 patients ⩾75 years treated in Denmark and Sweden

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Received: January 10, 2022.
Accepted: August 16, 2022.
Prepublished: October 27, 2022.

https://doi.org/10.3324/haematol.2021.280424

Abstract

The prevalence of multiple myeloma (MM) is increasing in Nordic countries and the rest of the western world. Patients aged ≥75 years at diagnosis constitute an increasing proportion of all MM patients, but are underrepresented in randomized clinical trials. There is an urgent need for studies of the characteristics, treatment and outcome in this cohort. We present data from two nationwide population-based registries of all MM patients diagnosed in Denmark from January 1, 2005 until February 18, 2020, and in Sweden from January 1, 2008 until December 31, 2019, including treatment data for patients diagnosed until 2018 (Denmark) and 2019 (Sweden). In total 4,647 patients were ≥75 years at diagnosis, compared to 7,378 younger patients. Patients ≥75 years, accounting for approximately 40% of all MM patients, are a distinct cohort with more advanced disease at diagnosis, reflected by higher International Staging System (ISS) stage, and a higher proportion have renal failure and anemia. We found a more gradual introduction of modern medications in the older cohort than in the younger, despite simultaneous changes in guidelines. Compared to the cohorts in randomized controlled trials that guide the treatment of non-transplant eligible patients, we found a higher proportion of patients ≥75 years and presenting with ISS III in the real-world populations. Nevertheless, response rates and survival are increasing, indicating that modern treatment regimens are effective and well tolerated also in elderly MM patients in real-world populations.

Introduction

The incidence of multiple myeloma (MM) increases with advancing age.[1-3] In recent population-based studies with high case ascertainment in the western world, the median age at diagnosis was 71-72 years.[1,4] In the Surveillance, Epidemiology and End Results (SEER) database in the USA, approximately one third of patients are ≥75 years at diagnosis.[5] With an aging population in many countries and improved life expectancy for patients with MM,[1,3] the number of elderly patients living with MM is increasing rapidly.

Turesson *et al.* have previously described the increasing crude incidence and prevalence of MM in Europe and the USA, and the expected increase in Asia and Africa.[3] Data from the NORDCAN database of the Association of the Nordic Cancer Registries, show a striking increase in the prevalence of plasma cell neoplasms. This is particularly evident in the older cohort, in which the prevalence has doubled in Denmark for the population ≥75 years in 2005-2018, with

a similar increase in Sweden (Figure 1, *Online Supplementary Table S1*).[6]

Current treatment guidelines[7-10] are based on results from randomized clinical trials,[11-14] only some of which report results separately for patients aged ≥75 years. Patients in randomized clinical trials do not reflect the real-world population; in particular elderly and frail patients are underrepresented, and it has been shown that patients ineligible for inclusion in trials have a poorer outcome than patients who are eligible.[15-18] This highlights the need for knowledge on disease characteristics, optimal treatment and outcome in patients aged ≥75 years.

The aim of this study was to examine the differences in clinical characteristics between patients aged ≥75 years and <75 years, and how their characteristics and outcome compare to the patients in randomized clinical trials underpinning national and international treatment guidelines. In two nationwide real-world populations, we investigated how treatment patterns change over time and whether this translates into a better outcome in MM patients, particularly in the older cohort.

Methods

The Danish Multiple Myeloma Registry (DMMR) and the Swedish Myeloma Registry (SMR) are population-based nationwide registries, and have previously been described in

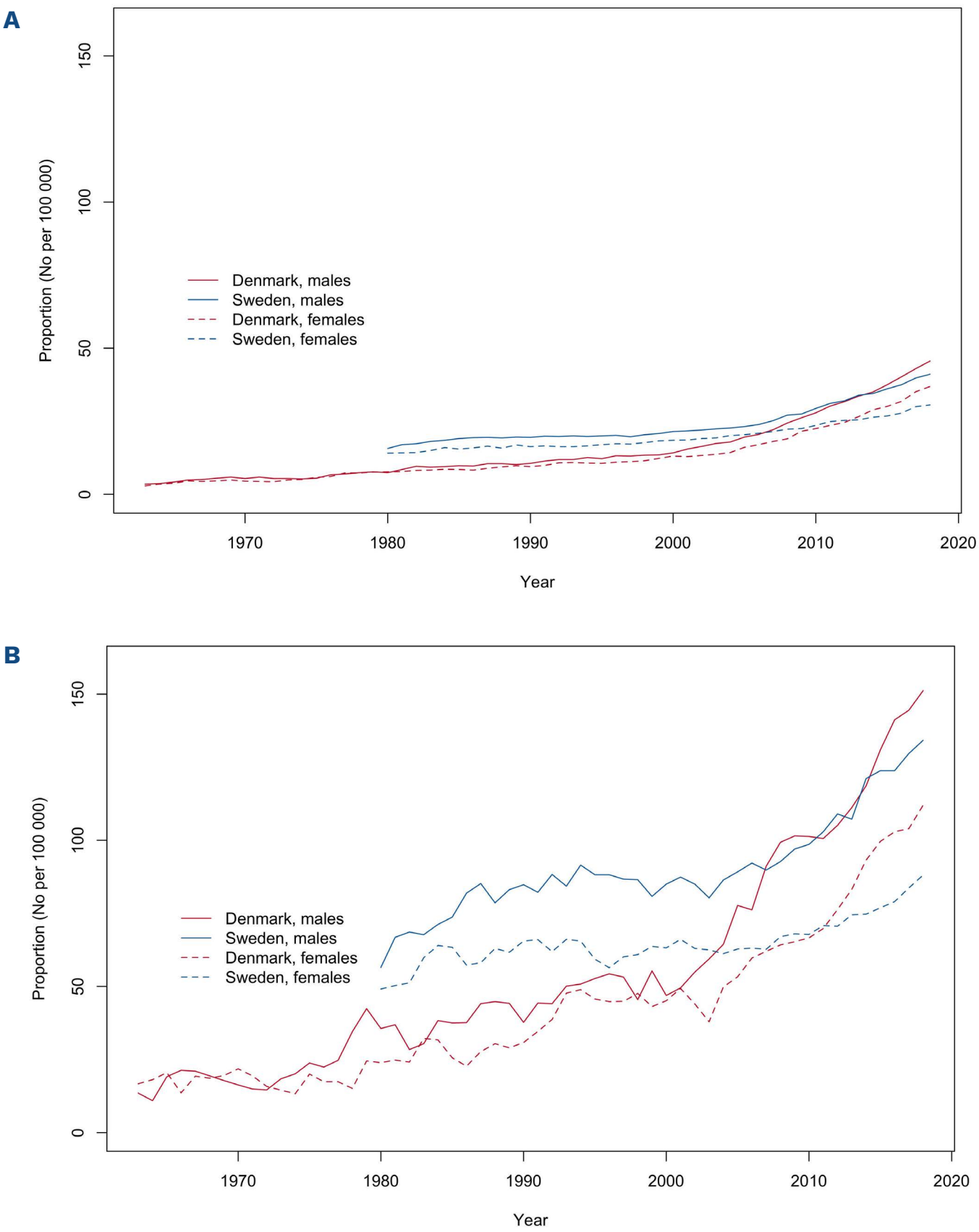


Figure 1. Prevalence (numbers per 100,000) of plasma cell neoplasms. (A) Patients <75 years at diagnosis in Denmark 1962-2018 and Sweden 1980-2018. (B) Patients ≥75 years at diagnosis in Denmark 1962-2018 and Sweden 1980-2018. Data from the NORDCAN database of the Association of the Nordic Cancer Registries May 3, 2021. The increasing prevalence is particularly evident in the older cohort. In Denmark the prevalence increased from 77.7 to 151.2 per 100,000 men aged ≥75 years, and from 53.33 to 112 per 100,000 women ≥75 years 2005-2018. In Sweden the prevalence increased from 92.7 to 134.2 per 100,000 in men aged ≥75 years, and from 99.3 to 151.2 per 100,000 women ≥75 years from 2008 to 2018.

detail.[19-21] They were established on January 1, 2005 and January 1, 2008, respectively. Both Denmark and Sweden have personal identification code systems which are unique for every citizen and enable close to 100% coverage and follow-up. In this study, we analyzed baseline characteristics and survival for patients diagnosed with MM reported to the registries from their establishment until February 18, 2020 (DMMR), and December 31, 2019 (SMR). Patients with smoldering MM reported to the registries were included only after progression to MM. Treatment and response data were reported with at least 1-year follow-up and included patients diagnosed until December 31, 2018 (DMMR) and December 31, 2019 (SMR) to allow adequate time for reporting. Patients were followed for survival until March 20, 2020 (DMMR) and April 30, 2021 (SMR).

We performed a retrospective analysis of baseline characteristics of two age cohorts, patients ≥75 years or <75 years at diagnosis in both nationwide registries, and compared treatment, response, and outcome among Danish and Swedish patients in the older cohort. Furthermore, we compared the characteristics of our older cohort with patients included in the randomized clinical trials that are the foundation of Danish, Swedish and international treatment guidelines: VISTA (bortezomib, melphalan and prednisolone [VMP] *vs*. melphalan and prednisolone [MP]), FIRST (lenalidomide and dexamethasone continuous [Rd] *vs*. lenalidomide and dexamethasone for 18 months [Rd18] *vs*. melphalan, prednisolone and thalidomide [MPT]), ALCYONE (daratumumab, bortezomib, melphalan and prednisolone [D-VMP] *vs*. bortezomib, melphalan and prednisolone [VMP]) and MAIA (daratumumab, lenalidomide and dexamethasone [D-Rd] *vs*. lenalidomide and dexamethasone [Rd])

Statistical methods

For categorical variables we used the χ^2 test to examine statistical significance. *P* values <0.05 were considered statistically significant. Survival time was calculated from diagnosis until death or censoring. Patients were censored at the end of the study (April 30, 2021 [SMR] and March 20, 2020 [DMMR]) and at loss to follow-up. Overall survival and relative survival ratios are presented as graphs of 6-, 12- and 36-month survival by year of diagnosis with 95% confidence intervals. When estimating relative survival we used the Ederer II method for expected survival, relative to the expected survival of each country's population.[22] We used a Cox proportional hazards model to compare the outcomes of the subgroups of patients 75-84 and ≥85 years compared to those <75 years, for the entire follow-up period, while adjusting for year of diagnosis. Early death was defined as death within 6 months of myeloma diagnosis. Patients who did not receive any treatment were excluded from analyses regarding treatment. We handled missing data by complete case analysis. R software was used for statistical analyses.[23]

Ethical approval

The study was approved by the Danish Data Protection Agency (18/22825) and the Danish Patient Safety Authority (3-3013-2047/2r). Ethical approval was also obtained in Sweden (Dnr 2020-01729) and from the Data Protection authorities (Datauttagsansökan SV-2079). The study was conducted in accordance with the Helsinki Declaration of 1975, revised in 2008.

Results

In total, we compared the characteristics of 4,647 Danish and Swedish MM patients aged ≥75 years or older at diagnosis with those of 7,378 Danish and Swedish MM patients <75 years. The proportion of all newly diagnosed MM patients ≥75 years was similar in both registries, 36% in DMMR and 40% in SMR (Table 1). Altogether, 3,904 patients ≥75 years were available for analysis of treatment data, and 3,490 patients were analyzed for response. There were no missing data for survival.

Baseline characteristics

Significant differences in International Staging System (ISS) stage and CRAB-criteria (hypercalcemia, renal failure, anemia, osteolytic skeletal lesions) were found between age groups. Patients ≥75 years had more advanced disease, as 46% of patients in this age group presented with ISS stage III in both registries, compared to 30% in the Swedish cohort <75 years, and 35% in the Danish cohort <75 years. This difference was consistent over time. The proportion of patients presenting with anemia was higher in the older group compared to the younger cohort, as was the proportion with renal failure (Table 1). There were more men than women diagnosed in both age groups, but the difference was less pronounced among patients aged ≥75 years due to the higher number of women in the population in higher age groups (Table 1). Overall, data describing patients aged ≥75 years from the two registries were consistent.

First-line treatment

The first-line treatment guidelines in patients not eligible for autologous stem cell transplantation were similar in Denmark and Sweden during the study period.[19] We found that MP was replaced by bortezomib-based regimes from around 2012, while lenalidomide-based treatment increased in recent years (Figure 2, *Online Supplementary Table S2*). The proportion of patients receiving an immunomodulatory drug or proteasome inhibitor as part of first-line treatment increased dramatically in patients ≥75 years (from 18.1% in 2005 to 89.1% in 2018 in Denmark, and from 29.9% in 2008 to 95.5% in 2018 in Sweden) (Figure 3, *Online Supplementary Table S3*).

Treatment response and survival

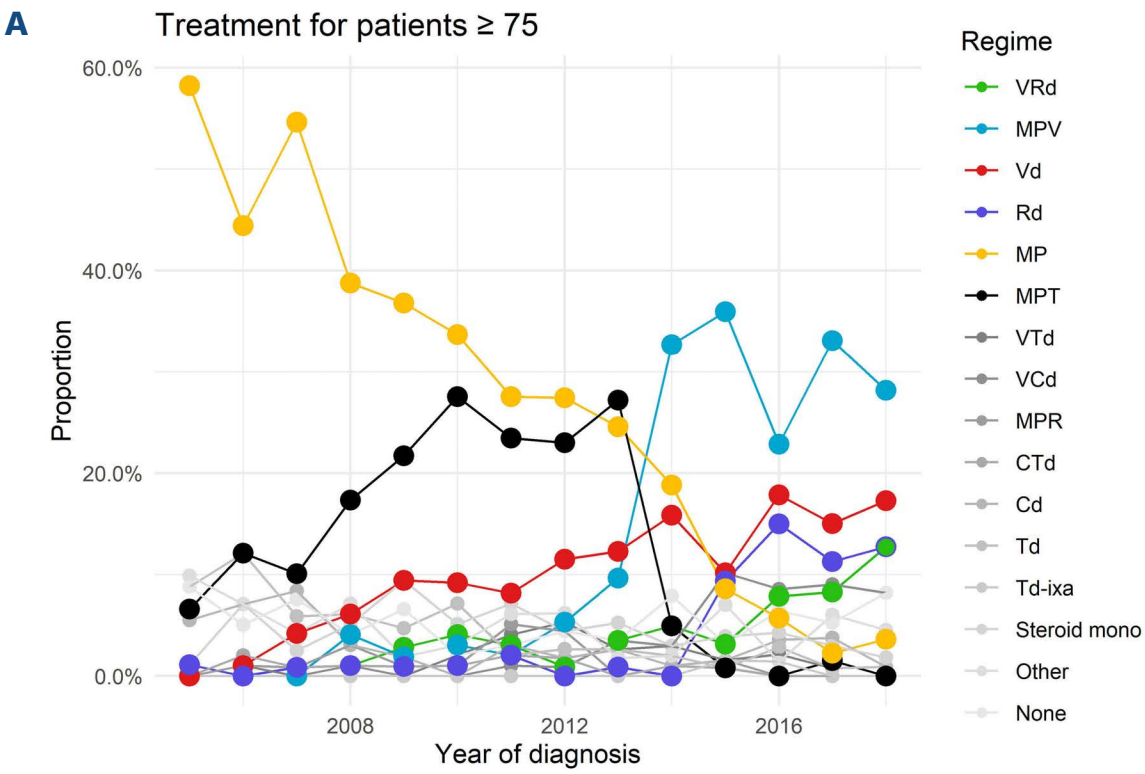
Parallel to the increased use of modern agents, the proportion of patients aged ≥75 years who achieved at least very good partial remission more than doubled in the studied time period to 40% in Denmark and 45% in Sweden (Figure 4, *Online Supplementary Table S4*).

Simultaneously, the median relative survival for the same patient group in Denmark increased from 25 months for patients diagnosed in 2005-2007 to 36 months for patients diagnosed in 2015-2016. In Sweden the median relative survival increased from 24 months for patients diagnosed in 2008-2009 to 42 months in patients diagnosed in 2016-

Table 1. Baseline characteristics of patients in the Danish Multiple Myeloma Registry and Swedish Myeloma Registry.

Population	Danish Multiple Myeloma Registry N=4,691		*P* value	Swedish Myeloma Registry N=7,334		*P* value
Age group	<75 years	≥75 years		<75 years	≥75 years	
Number (%)	3,003 (64.0)	1,688 (36.0)		4,375 (59.7)	2,959 (40.3)	
Age in years, median (range)	65 (30-74)	80 (75-98)		66 (19-74)	81 (75-100)	
Gender			0.0009			<0.0001
Male, N (%)	1,736 (57.8)	891 (52.8)		2,649 (60.5)	1,567 (53.0)	
Female, N (%)	1,267 (42.2)	797 (47.2)		1,726 (39.5)	1,392 (47.0)	
Multiple myeloma type						
IgG, N (%)	1,597 (57.6)	937 (61.2)		2,195 (50.6)	1,571 (53.8)	
IgA, N (%)	595 (21.5)	345 (22.5)		821 (18.9)	588 (20.1)	
IgD, IgE, IgM, N (%)	49 (1.8)	17 (1.1)		44 (1.0)	19 (0.7)	
Light chain disease, N (%)	444 (16.0)	202 (13.2)		1,078 (24.8)	647 (22.2)	
Non-secretory, N (%)	76 (2.7)	26 (1.7)		151 (3.5)	60 (2.1)	
Mixed, N (%)	11 (0.4)	4 (0.3)		50 (1.2)	35 (1.2)	
Missing, N	231 (NA)	157 (NA)		36 (NA)	39 (NA)	
ISS stage			< 0.0001			<0.0001
I, N (%)	724 (28.5)	201 (15.1)		860 (25.6)	191 (10.6)	
II, N (%)	936 (36.9)	511 (38.4)		1,482 (44.1)	774 (42.8)	
III, N (%)	877 (34.6)	617 (46.4)		1,019 (30.3)	845 (46.7)	
Missing, N	466 (NA)	359 (NA)		1,014 (NA)	1149 (NA)	
Hb <100 g/L			< 0.0001			<0.0001
No, N (%)	1,834 (61.9)	903 (54.0)		3,035 (69.5)	1,809 (61.3)	
Yes, N (%)	1,131 (38.1)	770 (46.0)		1,332 (30.5)	1,143 (38.7)	
Missing, N	38 (NA)	15 (NA)		8 (NA)	7 (NA)	
Calcium	Ionized calcium >1.35 (mmol/L)		0.4	Ionized calcium >1.35 (mmol/L) or total calcium >2.75 (mmol/L)		0.005
No, N (%)	2,119 (72.7)	1,205 (73.9)		3,790 (86.6)	2,630 (88.9)	
Yes, N (%)	797 (27.3)	426 (26.1)		585 (13.4)	329 (11.1)	
Missing, N	87 (NA)	57 (NA)		75 (NA)	52 (NA)	
Creatinine >177 μmol/L or CrCl <40 mL/min			0.04			0.01
No, N (%)	2,438 (82.4)	1,329 (80.0)		3,677 (84.3)	2,418 (82.0)	
Yes, N (%)	519 (17.6)	332 (20.0)		686 (15.7)	531 (18.0)	
Missing, N	46 (NA)	27 (NA)		12 (NA)	10 (NA)	
Skeletal disease			<0.0001			<0.0001
≥ 1 osteolytic lesions, N (%)	2,201 (77.4)	1,035 (66.7)		2,903 (68.0)	1,636 (59.2)	
Osteopenia and vertebral compression, N (%)	79 (2.8)	119 (7.7)		482 (11.3)	400 (14.5)	
None, N (%)	565 (19.9)	398 (25.6)		882 (20.7)	728 (26.3)	
Missing, N	158 (NA)	136 (NA)		107 (NA)	195 (NA)	

CrCl: creatinine clearance; DMMR: Danish Multiple Myeloma Registry; Hb: hemoglobin; ISS: International Staging System; NA: not applicable; SMR; Swedish Multiple Myeloma Registry.



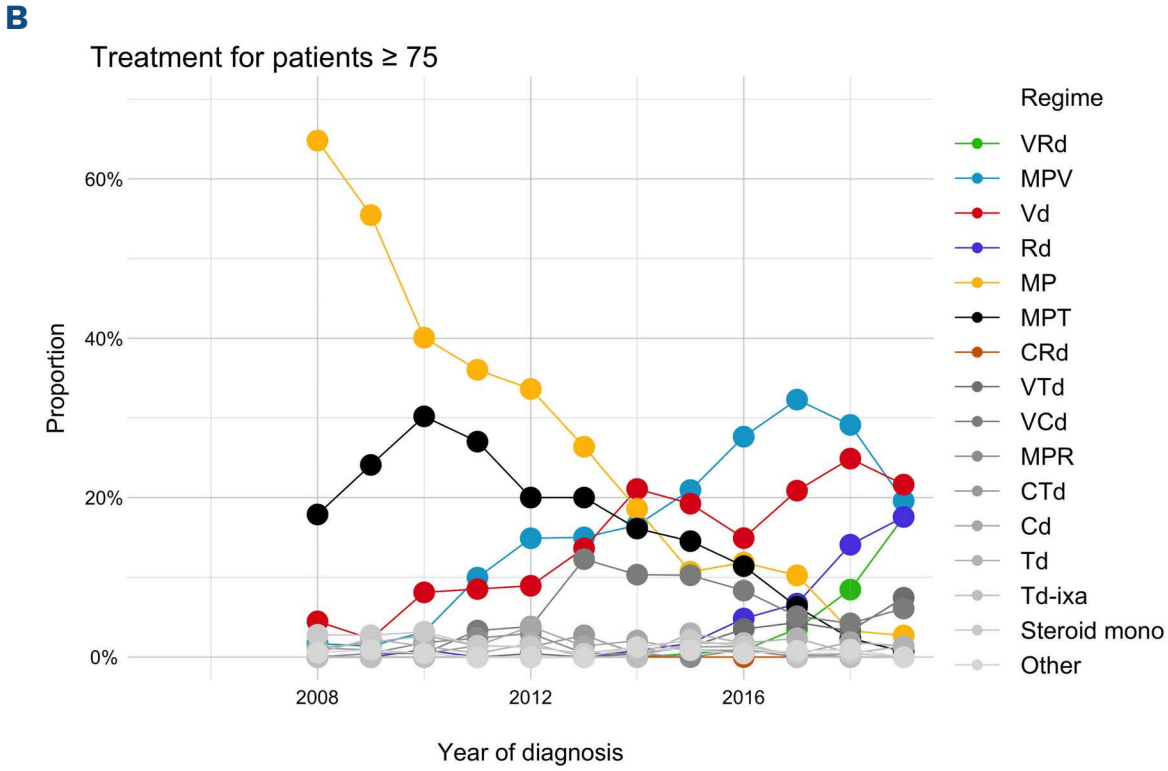


Figure 2. Changes in first-line treatment over time for patients ≥75 years in (A) Denmark and (B) Sweden. Cd: cyclophosphamide, dexamethasone; CRd: cyclophosphamide, lenalidomide, dexamethasone; CTd: cyclophosphamide, thalidomide, dexamethasone; Mono: monotherapy; MP: melphalan, prednisolone; MPR: melphalan, prednisolone, lenalidomide; MPT: melphalan, prednisolone, thalidomide; MPV: melphalan, prednisolone, bortezomib; Rd: lenalidomide, dexamethasone; Td: thalidomide, dexamethasone; Td-ixa: thalidomide, dexamethasone, ixazomib; VCd: bortezomib, cyclophosphamide, dexamethasone; Vd: bortezomib, dexamethasone; VRd: bortezomib, lenalidomide, dexamethasone; VTd: bortezomib, thalidomide, dexamethasone.

2017 (*Online Supplementary Table S5*). The 3-year overall survival in Sweden was 30.9% for patients diagnosed in 2008-2009 and 44.3% for those diagnosed in 2018-2019 among patients ≥75 years. In Denmark, the 3-year overall survival for patients ≥75 years was 32.3% in 2005-2007 compared to 44.1% from 2017 (Figure 5B, *Online Supplementary Table S6*).

To further study this improvement in survival, we performed a *post hoc* subgroup analysis, splitting the age cohort ≥75 year into two age groups: 75-84 and ≥85 years at diagnosis, and compared them with the <75-year-old cohort (*Online Supplementary Table S7*). Using a Cox proportional hazards model, we found a hazard ratio for death for Danish patients ≥85 years of 4.24 (95% confidence interval [95% CI]: 3.75-4.79) while it was 2.43 (95% CI: 2.24-2.63) for Danish patients 75-84 years. For Swedish patients ≥85 years the hazard ratio for death was 5.78 (95% CI: 4.60-7.26) while it was 2.72 (95% CI: 2.36-3.14) for those aged 75-84 years at diagnosis.

Finally, we analyzed possible interactions, and found that there was no association between the difference between the age groups and the year of diagnosis, and that the difference between the age groups appeared to be constant during the study period.

However, there was no improvement in relative survival at 6 months for either age group, which remained stable in the range of 78.2-83.9% (SMR) and 68.4-81.1% (DMMR) for patients ≥75 years (Figure 6, *Online Supplementary Table S6*).

Comparison with randomized clinical trials

In a comparison with important randomized clinical trials (VISTA, FIRST, ALCYONE and MAIA) supporting guidelines in MM patients not eligible for autologous stem cell trans-

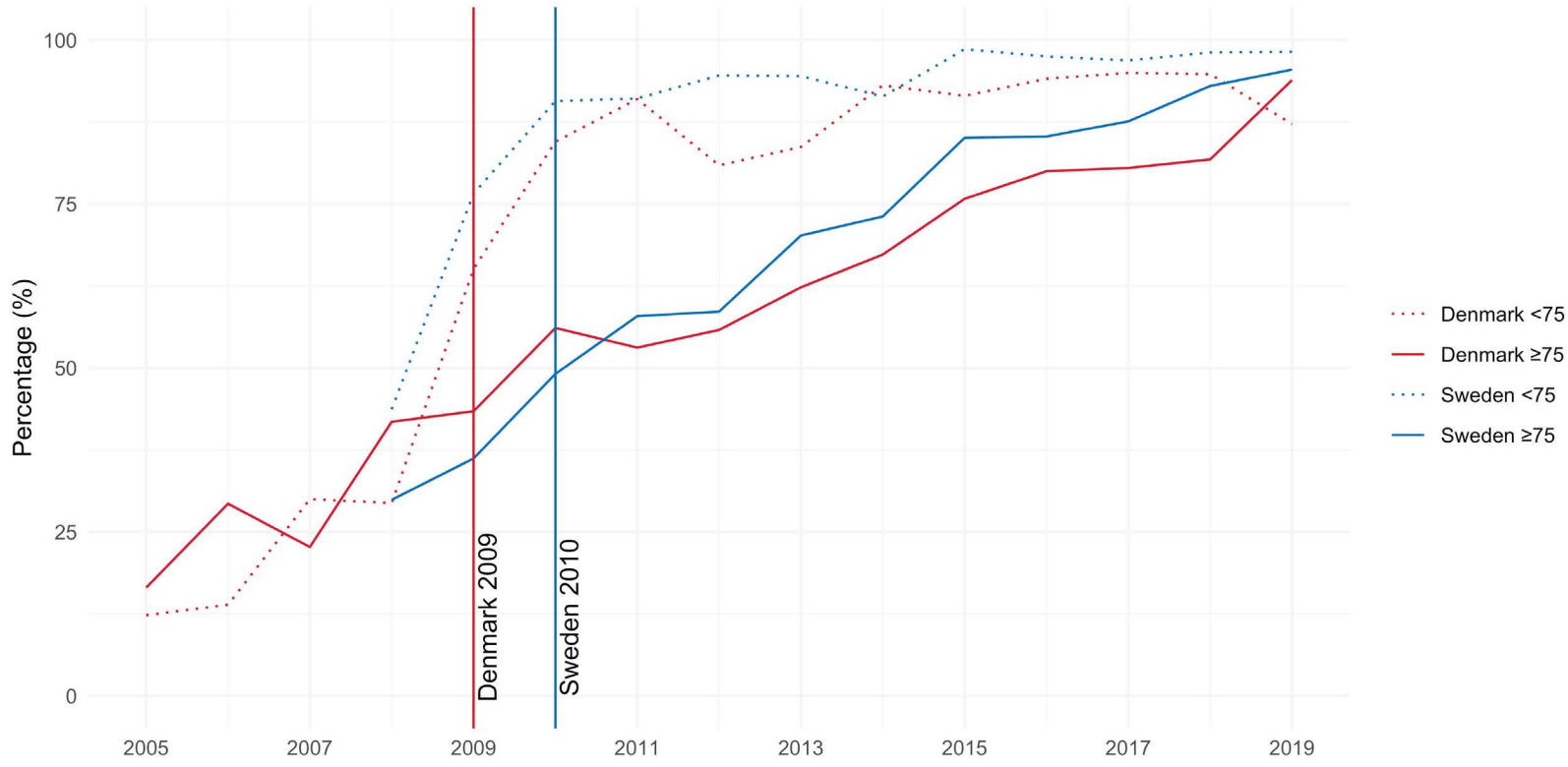


Figure 3. Use of immunomodulatory drugs and/or proteasome inhibitors in first-treatment line of multiple myeloma by country and age group. In 2009 the Danish treatment guidelines changed to recommending bortezomib and dexamethasone (VD) in first line for patients eligible for autologous stem cell transplant (ASCT) and melphalan, prednisolone and thalidomide (MPT) or melphalan, prednisolone and bortezomib (MPV) for those ineligible (marked by the red vertical line). In Sweden, the treatment guidelines changed in 2010 (blue vertical line). Bortezomib and thalidomide were recommended as part of standard induction treatment before ASCT. MPT was recommended as standard for patients not eligible for ASCT, while MPV and melphalan and prednisolone were treatment options.

plantation, we found a higher proportion of patients ≥75 years and more patients with advanced disease at diagnosis (Table 2).

The exception is the FIRST trial which reports the results of patients >75 years using International Myeloma Working Group criteria and overall survival. A similar proportion of patients in this age cohort on the trial presented with ISS stage III (48%), yet response rates were significantly higher than for patients receiving standard of care in Denmark and Sweden in the same time period (Table 2). In the FIRST trial 42-45% of patients treated with lenalidomide and 31% treated with MPT, achieved very good partial remission or better, compared to an average of 16.8% of Danish patients and 23.1% of Swedish patients achieving the same response rates during the trial period 2008-2011.[12] In contrast, 69% of patients aged ≥75 years in more recent trials with CD38-antibody combinations achieved very good partial remission or better.[13]

A similar difference was seen for survival with the median overall survival being 46-48 months for FIRST trial patients treated with lenalidomide, and 38 months for those receiving MPT, while contemporaneous Danish and Swedish patients had a median overall survival of approximately half of this (20.9 months and 20.3-21.5 months, respectively) (Table 2). This is as expected with selected populations in clinical trials. However, the overall survival for our real-world population is increasing in parallel to the increasing use of modern medications in more recent time periods.

Discussion

The prevalence of plasma cell neoplasms has increased in Nordic countries and the entire western world, particularly in the elderly. At least three important factors contribute to this; increasing crude incidence as the population ages, improved case ascertainment, and increased survival of patients diagnosed with MM. This makes the description of the characteristics, treatment and survival of the elderly MM population urgent.

In this study, we present data on 12,025 patients from two nationwide registries including all patients diagnosed with MM. We report real-world data on the characteristics, treatment and outcome of the largest, unselected population of patients aged ≥75 years to date. The results from the DMMR and SMR are consistent with those from other registry studies regarding the proportion of patients ≥75 years at diagnosis.[29-31] We clearly show that the older MM cohort differs from the younger in clinical characteristics, with more advanced disease stage and higher rates of myeloma complications, such as anemia and renal failure, at diagnosis.

Even so, our comparison shows that randomized clinical trials supporting guidelines in elderly MM patients include a lower proportion of patients ≥75 years at diagnosis, and fewer patients with ISS stage III than our population, with the exception of the FIRST trial.[26] An age-related decline in albumin and renal function, associated with increasing β_2-

microglobulin levels, may account for some of the difference in ISS staging between the age cohorts in our study. However, age alone does not explain the difference in proportion of patients with ISS stage III disease between real-world populations and populations in randomized clinical trials.

Our data show that more than 90% of patients diagnosed at ≥75 years received first-line treatment in Denmark and Sweden in 2008-2019. Other European registry and cross-sectional studies have shown similar results.[30,32] Data from the SEER database in the USA for the period 2007-2013 documented that only 51% of patients aged ≥80 years received treatment within the first 6 months of diagnosis, although this rate has increased in recent years.[33]

We found that the introduction of modern agents in the treatment of older patients has been much more gradual compared to that for younger patients in Denmark and Sweden, despite simultaneous changes in national guidelines (Figure 3, *Online Supplementary Table S3*). Mian *et al.* examined Canadian administrative health care data and found the same when comparing myeloma patients ≤65 years and >65 years from 2007 to 2017.[34]

Our data clearly show improved response rates and increased survival with modern treatment, also in MM patients ≥75 years. A subgroup analysis revealed that this improvement is also seen in the patients ≥85 years at MM diagnosis, although this age group has a significantly higher hazard ratio for death compared to patients 75-84 years and may constitute a possible new age-defined frail population. This is important information that requires data from an unselected real-world population and cannot be obtained from randomized clinical trials that commonly exclude a high proportion of elderly MM patients. Other possible contributions to increased survival are improved supportive measures and better treatment of comorbidities.[35] However, the improvement in relative survival over time supports that myeloma treatments and response are significant contributors to improved survival.

Despite more effective treatment, early mortality did not decrease for patients ≥75 years in our study. This matches findings in a study of Canadian patients diagnosed between 2007-2017.[34] There remains an unmet clinical need to tailor treatment and supportive measures for elderly patients, particularly in the critical, early months after diagnosis when the risk of complications of both their MM and toxicity of treatment is high.[36]

We propose that future trials differentiate between frailty caused by myeloma tumor cell burden which may improve during treatment,[37] and frailty related to age and comorbidity. It is hoped that ongoing and planned clinical studies, such as the Myeloma XIV study, which adjusts treatment regimens according to repeated assessments of patient frailty (clinicaltrials.gov NCT03720041), will contribute to finding tools to improve treatment strategies. Another possible strategy is to allow rescue treatment to correct myeloma-related complications such as renal failure before patients' inclusion into randomized clinical trials.

Our study is limited by lack of data on comorbidities, frailty status, quality of life, detailed information on medication dosing schedules, and later lines of treatment. However, providing the best possible first-line treatment is important, as two European studies have shown that between 20% and 30% of patients never receive any later myeloma treatment.[38,39] As in other population-based registries, the reporting of fluorescence *in situ* hybridization data is limited in patients ≥75 years, but increasing rapidly and has been reported for more than 50% since 2014.

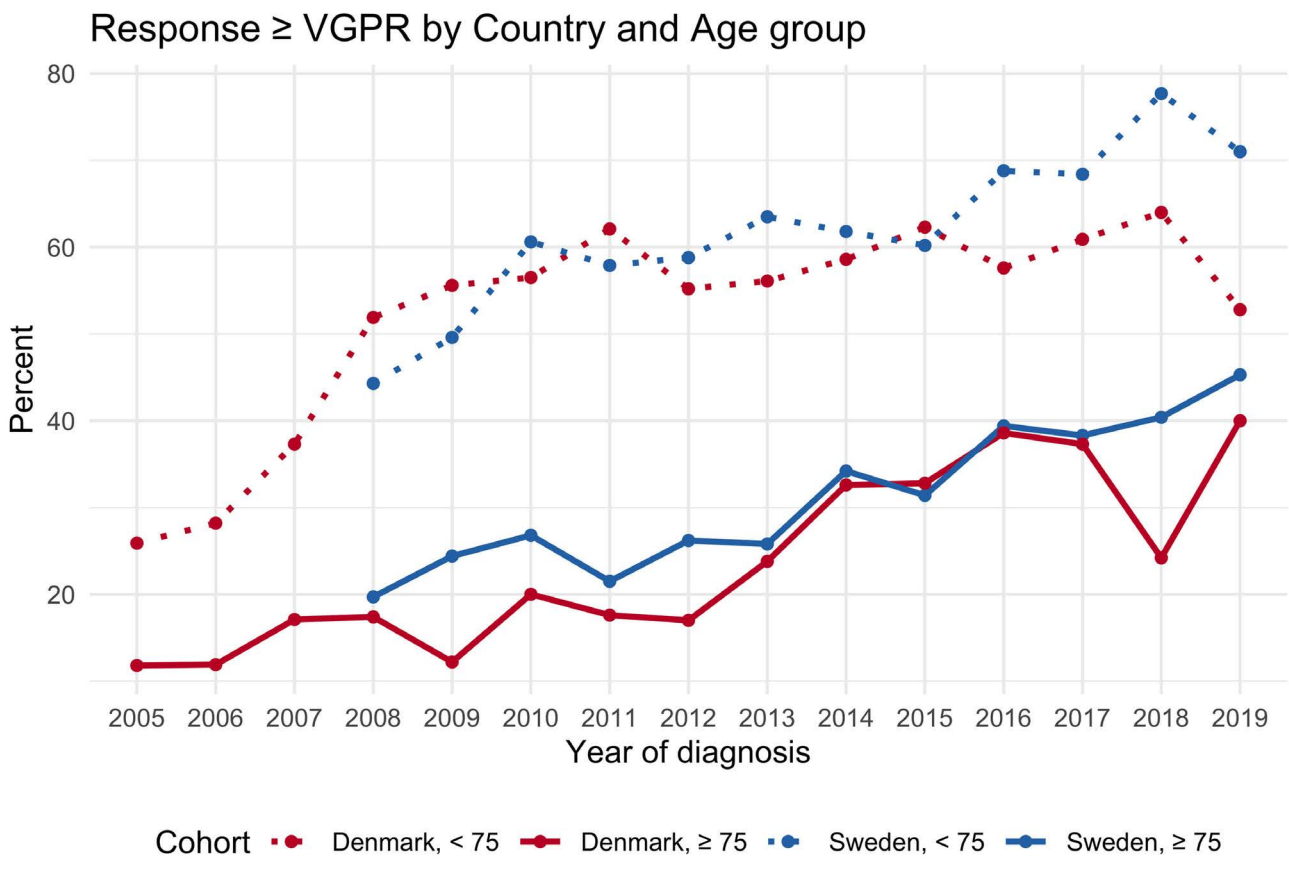


Figure 4. Response rate for very good partial remission or better by country and age group. From 2013, multiple myeloma patients ≥75 years are gradually approaching the high response rates on first-line treatment seen among younger patients. Simultaneously, the proportion of non-responders decreased significantly from 57.9% in 2005 to 32.2% in 2019 in Denmark, and from 38% to 16.8% from 2008 to 2019 in Sweden (*Online Supplementary Table S4*). VGPR: very good partial remission.

The greatest strength of our study is the large number of unselected patients from two nationwide registries, as well as close to 100% case ascertainment. Both Denmark and Sweden have national publicly funded health care systems and national treatment guidelines, and our study shows that the patient populations are very similar. Another strength of our study is the population-based design that allows the use of relative survival rather than overall survival to measure outcome. In an elderly population, comorbidities not related to MM contribute more to mortality than in younger patients and there is a risk that using overall survival could underestimate the beneficial effect of MM treatment in the elderly.

In conclusion, MM patients aged ≥75 years have more advanced disease at diagnosis. This is not reflected in the selected patient populations of the majority of randomized clinical trials guiding the treatment of elderly patients. Both healthcare policy makers and designers of

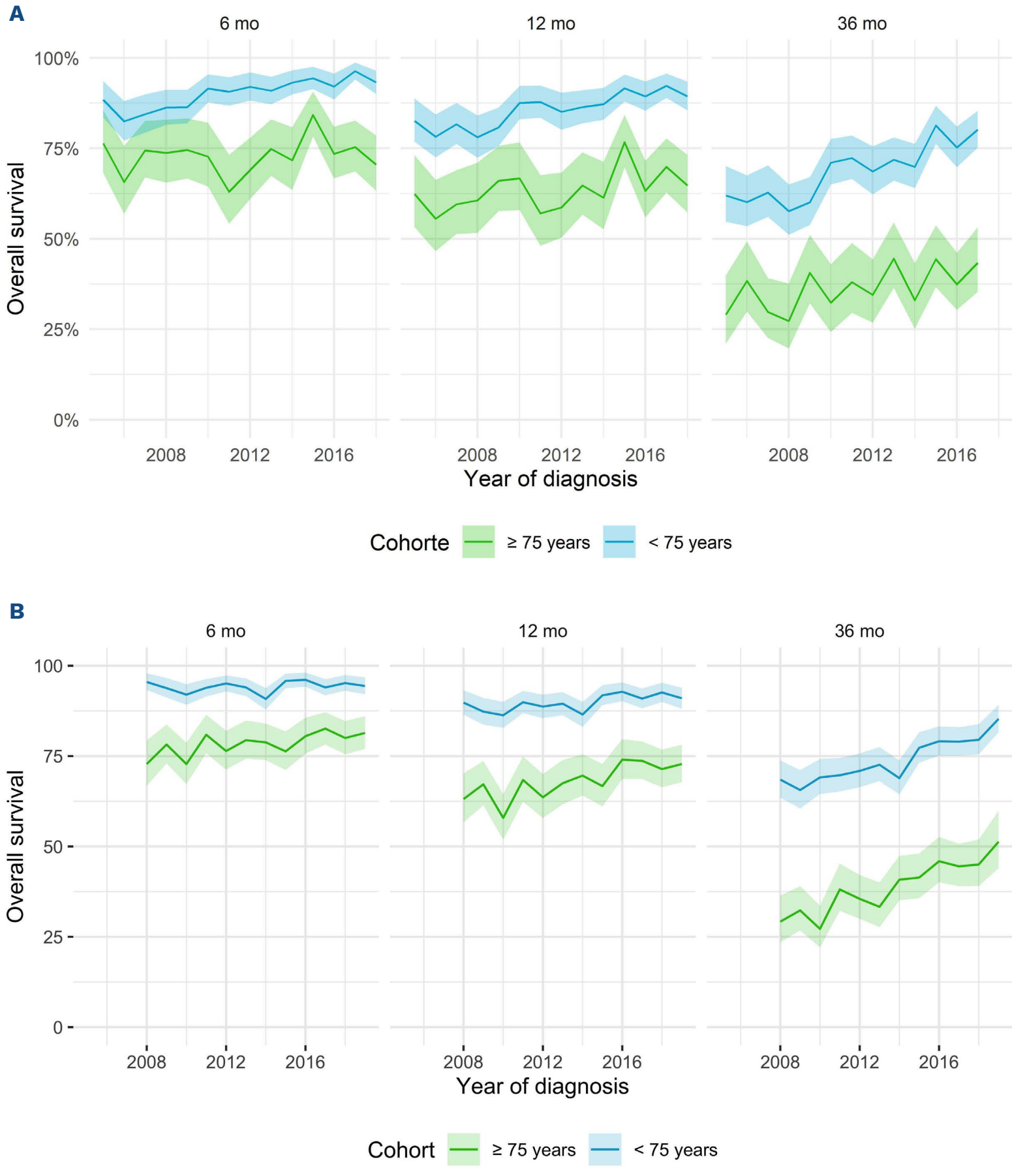


Figure 5. Overall survival by country and age group. (A, B) Overall survival of patients with multiple myeloma in Denmark 2005-2018 (A) and Sweden 2008-2019 (B). mo: months.

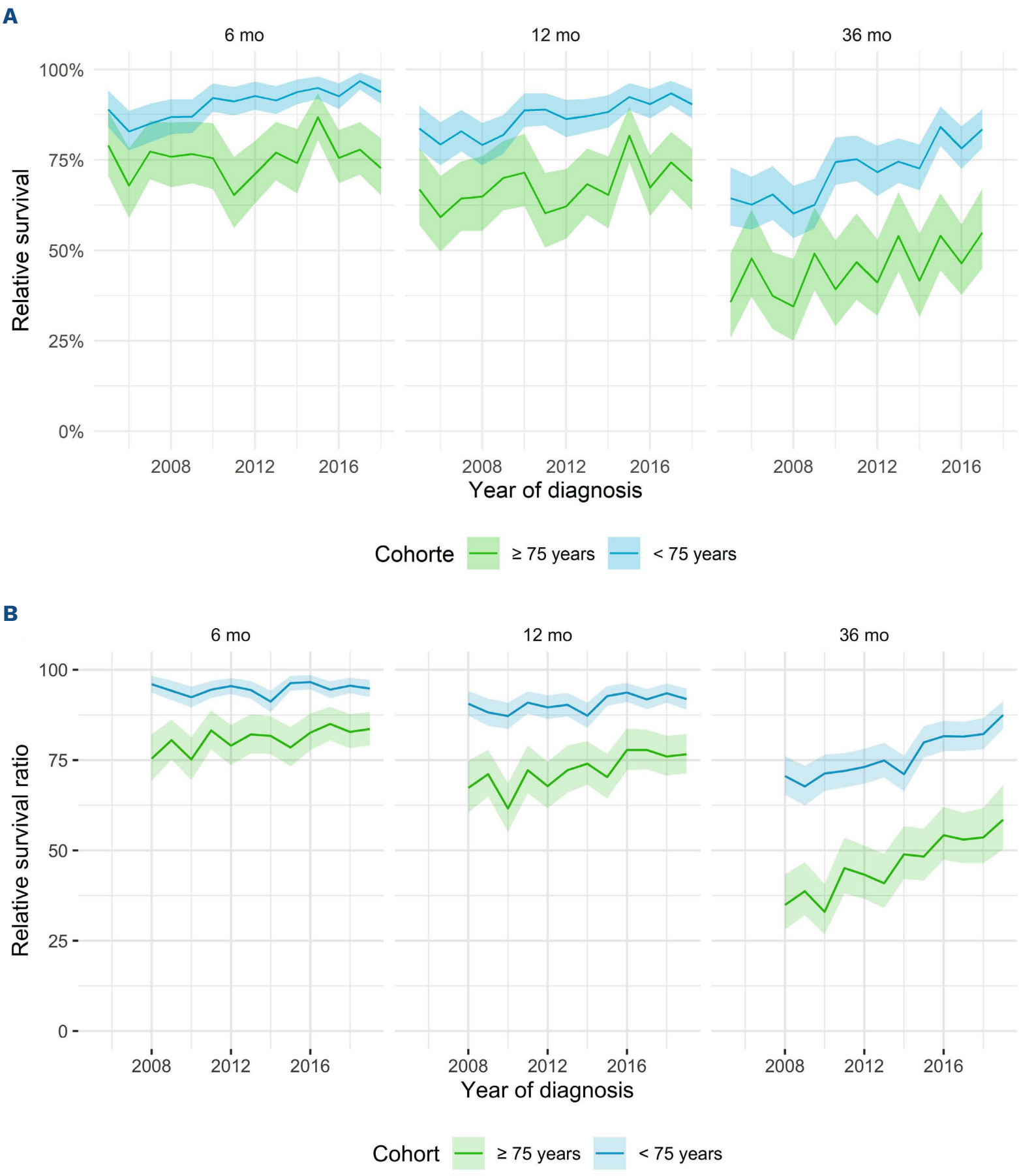


Figure 6. Relative survival by country and age group. (A, B) Relative survival of patients with multiple myeloma in Denmark 2005-2018 (A) and Sweden 2008-2019 (B). mo: months.

clinical trials must consider this for the benefit of future MM patients. The introduction of modern treatment is more gradual in patients ≥75 years, but coincides with improved response rates and survival.

Disclosures

IT has received honoraria from Bristol-Myers Squibb. LR has received research funding from Janssen-Cilag. JT has received speaking fees from Astra Zeneca. CHB has received honoraria from Amgen, BMS, Takeda and Janssen unrelated to this work.

Contributions

AJV, CHB, and IT conceived and designed the study. KLFM, CHB, AJV, and IT wrote the manuscript. TK and JT (Denmark) and AG (Sweden) performed the statistical analysis. AJV, CHB, IT, KLFM, LR, DKB, IS, AG, TK, and JT revised and commented on the manuscript.

Table 2. Baseline characteristics, response rates and survival of patient populations in the Danish Multiple Myeloma Registry, Swedish Myeloma Registry and key randomized controlled trials.

	DMMR ≥75 years	SMR ≥75 years	VISTA	FIRST	ALCYONE	MAIA
Time period	2005-2019	2008-2019	2004-2006	2008-2011	2015-2016	2015-2017
Patients ≥75 years, N (%)	1,688 (100)	2,959 (100)	208 (30)	567[$] (35)	211 (30)	321 (44)
Patients with ISS III	N=617 (46%)	N=845 (47%)	VMP: 35% MP: 34%	N=659 (41%) >75: N=273 (48%)	N=271 (38%)	N=227 (29%)
Patients with anemia	Hb <100 g/L: N=770 (46%)	Hb <100 g/L: N=1,143 (39%)	VMP: Median Hb: 104 g/L (range, 64-159)* MP: Median Hb: 106 g/L (range, 73-165)*	Not reported. No IC/EC	IC: Hb ≥75 g/L	IC: Hb ≥75 g/L
Patients with renal failure	CrCl <40 mL/min or creatinine >177 μmol/L (>2 mg/dL): N=332 (20%)	CrCl <40 mL/min or creatinine >177 μmol/L (>2 mg/dL): N=531 (18%)	CrCl <60 mL/min: VMP: 54% MP: 55% 30-60 mL/min: VMP: 48% MP: 50% <30 mL/min: VMP: 6% MP: 5%	EC: dialysis <60 mL/min: N=779 (48%) <30 mL/min: N=147 (9.1%) >75 years CrCl <30 mL/min: N=74 (13%) CrCl 30-49 mL/min: N=209 (37%)	IC: CrCl ≥40 mL/min CrCl <60 mL/min: N=295 (42%)	IC: CrCl ≥30 mL/min CrCl ≤60 mL/min: N=304 (41%)
≥VGPR, N(%)	2005: 9 (12) 2016: 49 (39) 2019: 12 (40) Overall: 334 (24)	2008: 27 (20) 2016: 74 (39) 2019: 62 (45) Overall: 654 (31)	EBMT criteria CR or PR: VMP: 238 (71) MP: 115 (35) CR: VMP: 102 (30) MP: 12 (4)	Rd cont: 258 (48) Rd18: 255 (47) MPT: 166 (30) >75 years: Rd cont: 84 (45) Rd 18: 81 (42) MPT: 58 (31)	D-VMP: 255 (73) VMP: 177 (50) ≥75 years: D-VMP: 72 (69) VMP: 52 (49)	D-Rd: 298 (81) Rd: 210 (57)
Overall survival	3-year OS ≥75 years 2005-07: 32% 2017-18: 44% Median OS ≥75 years: 2005-07: 20 mos 2017-18: 30 mos	3-year OS ≥75 years: 2008-09: 31% 2018-19: 44% Median OS ≥75 years: 2008-09: 20 mos 2018-19: 34 mos	3-year OS: VMP: 69% MP: 54%. Median OS: VMP: NR MP: 43 mos Median OS ≥75 years: VMP: 43 mos	3-year OS: Rd cont: 70% Rd18: 66% MPT: 62% Median OS: Rd cont: 59 mos Rd18: 62 mos Median OS >75 years: Rd cont: 48 mos Rd18: 46 mos MPT: 38 mos	3-year OS: D-VMP: 78% Median OS NR in either group at 60 mos	Estimated 60-month OS: D-Rd: 66.3% Rd: 53.1% Median OS NR in either group at 40.1 mos

[$]>75 years, not reported for ≥75 years. *Range. DMMR: Danish Multiple Myeloma Registry; SMR: Swedish Myeloma Registry; VISTA: bortezomib, melphalan and prednisolone (VMP) *vs*. melphalan and prednisolone (MP).[11,24] FIRST: lenalidomide and dexamethasone continuous (Rd) vs. lenalidomide and dexamethasone for 18 months (Rd18) *vs*. melphalan, prednisolone and thalidomide (MPT).[12,25,26] ALCYONE: daratumumab, bortezomib, melphalan and prednisolone (D-VMP) *vs*. VMP[13,27]. MAIA: daratumumab, lenalidomide and dexamethasone (D-Rd) *vs*. Rd.[28] CR: complete response; CrCl: creatinine clearance; EBMT: European Society for Blood and Marrow Transplantation; EC: exclusion criteria; Hb: hemoglobin; IC: inclusion criteria; ISS: International Staging System; mos: months; NR: not reached; OS: overall survival; PR: partial response; VGPR: very good partial response.

Acknowledgments

The authors would like to thank the steering groups of the DMMR and SMR for maintaining high quality registries and all the patients, as well as their doctors and nurses who have reported to the registries. We would also like to thank Tom Børge Johannesen at NORDCAN and the Association of the Nordic Cancer Registries.

Funding

This investigation was supported by the Nordic Cancer Union, project grant number R241-A15003 to the NMSG Real-World-Evidence group, the Swedish State under the Agreement between the Swedish Government and the City Councils, and the ALF-agreement ALFGBG- 523261 to CHB.

Data-sharing statement

The data that support the findings of this study are available from the Danish and Swedish myeloma registries. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at www.myeloma.dk and www.cancercentrum.se/myelom with the permission of the CPUA authorities in Sweden and The Danish Myeloma Study Group.

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