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## **Outcome data from >10,000 multiple myeloma patients in the Danish and Swedish national registries**

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Short title: **Outcome data from >10,000 multiple myeloma patients**

**The data that support the findings of this study are available from [third party]. Restrictions apply to the availability of these data, which were used under license for this study. Data are available [from the authors / at URL] with the permission of [third party].**

#### Statement of Significance

1. We have used national registries with a very high accuracy and completeness to demonstrate implementation of new treatments and survival in a large unselected myeloma population.
2. We have shown how new treatments have been introduced following national guidelines and have resulted in improvement of outcome in all age groups, also in the great majority of patients that are not included in RCTs.
3. Our registry data provide a basis for planning of care for myeloma patients, can help to validate prognostic scores based on RCTs and identify patients with inferior prognosis that need special attention and for whom new clinical trials should be designed.

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#### Abstract

We describe real-world evidence (RWE) from the nationwide Swedish and Danish registries that provide important information on incidence and outcome in multiple myeloma (MM).

We find that both the incidence of MM and the median age at diagnosis is higher in national registries compared to results from referral centres, indicating a more complete coverage. This highlights the need of validation of prognostic scoring systems and indices in e.g., SMM and high-risk MM in a real- world-population.

First line treatment data on more than 10.000 MM patients from Denmark and Sweden between 2005-2018 are presented, showing how national guidelines, generated on results from randomized clinical trials (RCTs) are rapidly implemented and improve overall survival (OS).

Key results from research conducted within the Swedish and Danish myeloma registries are summarized, describing subgroups of patients with comorbidity, myeloma complications, and early relapse. We show that these subgroups are unlikely to be captured in RCTs with narrow inclusion and exclusion criteria, that they have worse survival, and are in need of new treatment approaches.

## Conclusion

National registries that include all MM patients are an important source of knowledge on epidemiology, treatment and outcome with implications for the planning of MM care. Despite the introduction of new and better treatments, rapidly implemented in our countries, our registries uncover subgroups of patients that still have inferior outcome. Our RWE can help to identify important research questions to be studied in further clinical trials also in patients currently not included in RCTs.

## Introduction

Multiple myeloma (MM) is an incurable disease caused by malignant transformation of the plasma cells. New treatment modalities, including immunotherapy with antibodies, immune modulating drugs (IMiDS) and proteasome inhibitors (PI) have improved survival for patients both in randomized clinical trials (RCTs) and population-based studies(1-4).

In RCTs, randomization is used to achieve equal distribution between arms of known and unknown non-treatment-related factors that may influence outcome. In addition, strict inclusion and exclusion criteria are applied to further minimize the influence of other factors than treatment. This limits the generalizability of the results. Therefore, real world observational data is important as a complement to better evaluate new treatments in the whole myeloma population.

Many studies have now shown, that the majority of MM patients are not eligible for RCTs and these patients have a worse outcome(5, 6). Real-world evidence (RWE) is therefore becoming increasingly important to evaluate treatment and outcome in this group. In Sweden and Denmark, we can provide high quality data on RWE from nationwide registers. Due to longer life expectancy in the general population and improved survival achieved with the introduction of better treatments, both the crude incidence, and prevalence of multiple myeloma are expected to rise in the next future, which will emphasize the importance of RWE, as it affects outcome and will have a profound impact on the planning of health care(7) (1).

Denmark and Sweden have a long tradition of universal health care available for a population of approximately 5.8 and 10.1 million people, respectively. Continued validation of the health care efforts are based on information from national population-based registers with almost complete coverage and high accuracy, such as the national cancer registries, and national patient registries (Table 1). Important information on incidence, prevalence, outcome and complications has been provided by these registries (Table 2, Supplementary table S1).

However, the information available in these registries is limited and there was a need for development of disease-specific registers that prospectively include clinical characteristics, laboratory data, treatment, response, complications and survival. Myeloma-specific clinical registers

with this information have been established in e.g., the CONNECT registry in the US(8), Australia and New Zealand(9), the Czech Republic(10). As of now, only the Danish National Multiple Myeloma Registry (DMMR) and the Swedish Myeloma Registry (SMR), include myeloma patients nationwide with close to 100% coverage.

The DMMR and SMR, established in 2005 and 2008, respectively, include patients with multiple myeloma (MM), smoldering multiple myeloma (SMM), plasma cell leukemia (PCL), and solitary bone-and extramedullary plasmacytomas (SBP and EMP) and web-reported clinical and laboratory data, including treatment on all patients(11, 12). From 2014, the DMMR also includes patients with monoclonal gammopathy of undetermined significance (MGUS), POEMS and paraprotein associated polyneuropathies (PPAP).

The completeness of the SMR and DMMR is close to 100%. A validation study of 10% of the patients registered in the DMMR confirmed that each parameter was correct in > 95% of cases(11, 13). Both registers provide publicly available annual reports online. Annually updated clinical guidelines for treatment were introduced in Sweden in 2007 ([www.sfhem.se](http://www.sfhem.se))(14) and in Denmark in 2009 ([www.myeloma.dk](http://www.myeloma.dk))(15) with the aim to standardize treatment strategies based on RCTs.

In this overview, we present the most important research conducted within the nationwide Swedish and Danish myeloma registries and other population-based registries and how they can be utilized to generate real-world evidence on epidemiology, comorbidity and outcome of plasma cell disorders. Next, we show that new treatment strategies are rapidly implemented in coherence with new treatment guidelines. Finally, we discuss the results in comparison with knowledge achieved from RCTs and referral centres.

## Methods

Treatment data on patients with MM 2008-2018 was collected from the Swedish Myeloma Registry (SMR), and in patients diagnosed 2005-2018 from the Danish Multiple Myeloma Registry (DMMR). Data cut-off for data collection was 1<sup>st</sup> of April 2020 for the DMMR and 13<sup>th</sup> of October 2020 for the SMR. The changes in treatments over time in the 2 countries are presented in Figure 1 A-D and Supplementary Table S2. The new data included in the study on implementation of treatment strategies was approved by the Ethics committees and Data Protection Authorities in Denmark and Sweden. Approval from authorities in DK: DaMyDa-2019-02-06. Ethical approval in Sweden: Dnr 2020-01729 and from Data Protection authorities: Datauttagsansökan SV-2079.

Further, the most important studies generated from the DMMR and SMR were reviewed and the most interesting findings presented in the text and in Table 1.

## Results

### Rapid national implementation of new treatment guidelines

National registries can give fast information on the implementation and effect of new treatment strategies. The changes in treatment of MM in Denmark (DK) and Sweden (SWE) based on data from 10,062 MM patients treated from 2005-2018, n=4177 (DK) and 2008-2018, n=5885 (SWE) are shown in Figure 1 for patients treated with high-dose melphalan and autologous stem cell transplant (HDM/ASCT) (Figure 1A and 1B) and non-HDM/ASCT patients (Figure 1C and 1D).

Treatment strategies were similar in Denmark and Sweden, with a clear shift in the study period following the implementation of national guidelines. In both countries, 30% of newly diagnosed patients received HDM/ASCT upfront. Before 2010, induction treatment consisted of two-drug combinations of either cyclophosphamide/dexamethasone (Cydex) or bortezomib/dexamethasone (Vd) in both countries. Later, the 3-drug combination

bortezomib/cyclophosphamide/dexamethasone (VCD) was introduced and soon became a commonly used induction treatment. From 2015 an increasing proportion of patients received 3-drug combinations containing an immunomodulatory drug (IMiD), a proteasome inhibitor (PI) and dexamethasone (Figure 1B). In 2017-2018, the proportion of patients treated with the induction treatment VCD, thalidomide combinations and VRD was 79.8 %, 4.7% and 9.8 % in Denmark and VCD, VTd and VRD 32%, 32%, and 22% in Sweden respectively. (Supplementary Table S2).

In elderly patients, the use of 2-drug alkylator-based regimens melphalan/prednisone (MP) in Sweden and MP or CyDex in Denmark gradually shifted towards 2- or 3-drug combinations with an IMiD or a PI (Figure 1C). In Sweden the use of MP decreased from 50 % in 2008 to 5 % in 2017-2018 and was replaced first by the combination of melphalan/thalidomide/prednisone (MPT) and later by melphalan/bortezomib/prednisone (MPV). In Denmark, a similar decrease in the use of MP was observed with a shift from MP to MPT followed by MPV (Figure 1D). After 2015 an increasing proportion in both countries were treated with the combinations Vd and VCD while the use of lenalidomide-based combinations differed, with more patients treated with VRd in Denmark. In 2017-2018 the proportion of elderly patients treated with VD, VCD, Rd or VRD in 1<sup>st</sup> line were 13.1%, 20.7%, 8.7%, 15.0% in Denmark and 21%, 11%, 10%, and 7% in Sweden, respectively (Supplementary Table S1).

#### Incidence and outcome in MM

Incidence of MM varies, even between countries with universal health care. Using data from the SMR, we have reported incidence, outcome and survival in 4904 MM patients, diagnosed during the 9-year period 2008-2015 in which newer drugs were implemented into standard practice. The age-adjusted incidence was 6.8 myeloma cases per 100,000 inhabitants/year including asymptomatic and localized forms, the median age was 71 years, and 72 % were  $\geq 65$  years, and 24 % 80 years and older (12). This is higher than in most previous studies, indicating a more complete coverage of older patients. The median age at diagnosis in a Mayo Clinic myeloma population reported 2014 was 66 years, and the proportion of patients 75 years or older was 14 % (4).

In all myeloma patients in the SMR (SMM and MM) diagnosed 2008-2015, the 1, -3, and -5-year observed survival (OS) was 81%, 59%, 42%, and the corresponding relative survival (RS, age-adjusted) was 84%, 65%, and 49%, respectively. There was a significant survival difference according to age at diagnosis, with median RS ranging from 7.8 years in patients 60 years and younger to 1.5 years in octogenarians. Median relative survival in the whole cohort increased from 4.6 years in patients diagnosed before 2011 to 5.8 years in those diagnosed after 2011. Improvement was seen in all patients but was more pronounced in the age group 66-80 years(12). In an updated SMR-report from 2020, a further increase in OS was observed in all patients diagnosed 2008-2019. The 5-year OS is now 70% in patients  $\leq 65$  and 35%, in patients  $> 65$  years, respectively. The DMMR reported a median OS of 6 years for MM patients  $< 60$  years registered in the database in the calendar period 2005 until July 2015(11, 13). Recently published data from the DMMR show an increase in 5-year OS in patients  $\leq 65$  year from 59.8% in the calendar period 2008-2013 to 73.4% in the calendar period 2014-2019. In the same calendar periods an increase in 5-years OS was also noted for patients  $> 65$  years from 27.5% (2008-2013) to 39.8% (2014-2019)(16).

Myeloma survival in In Denmark and Sweden is comparable to other large registry studies(8, 17). We observed, that responses and survival improved during the study period parallel to the changes in treatment with the introduction of new drugs.

#### High-risk smoldering multiple myeloma

In recent years, studies have reported that patients with high-risk SMM may benefit from early intervention(18). However, the definition and incidence of high-risk SMM in the general population is debated. Several risk scores have been reported, widely used initially were the PETHEMA(19) and Mayo Clinic models, both based on single center cohort studies(20, 21).

We analyzed the incidence and outcome of SMM and high-risk SMM in a population-based material in 2013 using the SMR(22). Between 2008-2012, a total of 2494 patients received a diagnosis of myeloma and 14.4 % (n=360) were classified as SMM using IMWG criteria(23). Applying the Mayo Clinic risk model for SMM (BMPC  $> 10\%$  and M-spike  $> 3$  g/dL)(21), we classified 8.8% (n=104) as

high-risk. The age-standardized incidence of SMM was 0.44 cases /100,000 persons, and the incidence of high-risk SMM was 0.14 cases/100,000 persons. After 2 years, 56.6% of the patients with high-risk SMM in our study had progressed to symptomatic disease, and after a median follow-up time of 29.8 months, 70.4% had progressed to MM. The discriminatory power of this simple risk score compares favorably to the recently published IMWG 20-20-20 risk score based on a relatively limited number of patients(24).

#### Rare plasma cell disorders

Solitary plasmacytoma of bone (SBP), extramedullary plasmacytoma (EMP), plasma cell leukemia (PCL) and oligo- or non-secretory myeloma are rare forms of plasma cell malignancy and information on the incidence and natural history mostly comes from small single institution series (25), while populations-based data are scarce. In a study of 4518 patients reported to the SMR we identified 124, 67 and 43 cases of SBP, EMP and PCL respectively corresponding to an incidence (age adjusted to European standard population) of 0.191, 0.078, and 0.051 cases per 100 000 person-years for men and 0.090, 0.063 and 0.044 for females (26). Both SBP and EMP had significantly longer survival than MM. The risk of transformation into MM at two years was higher in SBP (35%) than in EMP (7%) but this did not translate in superior survival in EMP (relative survival at 8 years 68.1 and 62.0 % respectively) (Table 2)(26). In PCL, the outcome was dismal, with a 2-year RS of 27 %. In summary, we could use real world data from the SMR to estimate incidence and outcome in these rare plasma cell disorders. The poor prognosis in PCL underlines the need to design clinical trials to improve the outcome of these patients.

Patients with oligo-secretory myeloma, defined by serum M-protein concentration less than 10 g/l and urine M-protein < 200 mg/24 hours, and non-secretory MM defined by absence of detectable serum or urine M-protein have been suggested to constitute approximately 10 % of all MM patients. There are few data on the incidence in a real-world population. In 2019 , a study of 4325 patients with MM from the SMR found that 253 patients (6 %) had oligo-secretory and 136 (3%) had non-

secretory MM(27). The median survival for secretory MM was 42.7 months, oligo-secretory MM 38.6 months and non-secretory MM 44.6 months (ns). The finding of 3 % non-secretory MM is consistent with earlier reports from smaller non population-based cohorts of 3% and 1.8%(28, 29). A clear-cut useful classification is needed in order to study oligo-and non-secretory disease and criteria to evaluate response remain a practical challenge, but in our real-world population survival was comparable to that of secretory MM.

### **High-risk MM patients in need of adapted strategies**

Although overall survival of myeloma patients has improved in the era of IMiDs and PI, early death is still a problem. Two studies from the DMMR showed that progressive disease and infections are the major causes of early death in both younger and elderly MM patients(30, 31). In 613 HDT/ASCT treated patients diagnosed 2005-2013, 9.6% died within two years from diagnosis. Eighty-three percent had progressive disease, 44.1% had an infection and 11.9% had renal failure at the time of death(31). In 1497 transplant-ineligible patients diagnosed 2005-2012, 22% died within 180 days from diagnosis(30).The major cause of death was infection in 50.9% and renal failure in 9.9%. Our findings are similar to those published earlier (32, 33).

Early relapse after HDM/ASCT is one of the most important markers for poor prognosis in transplant-eligible patients. Although the fraction of patients suffering from an early relapse have decreased with the introduction of PI and IMiDs outcome is still poor. In a nationwide multicentre study including all patients treated with HDM-ASCT in the calendar period 1994-2004, before PI and IMiDs were used as induction treatment, 43% relapsed within 18 months and median OS was 28,7 months (34). Our findings are comparable with those from a single center study before introduction of Pi from the Mayo Clinic in 2008 where 24 % of patients relapsed within 12 months after HDM-ASCT with a median OS of 20.1 months(35). In a subsequent study from the DMMR from the calendar period 2009-2014, after the introduction of bortezomib in the standard induction regimens, the proportion of patients progression within 18 months was lower (29%) with a median OS of 35.2 months(36). Thus, median OS did only improve 6.5 months compared to the earlier calendar period 1994-2004. Our findings should be compared with those of a single

center study where all patients received induction treatment with IMiDs or PI and post- transplant maintenance was given to 18 % of patients. The proportion of patients progressing within 1 year was low (5.8%) but the median OS was short (23.1 months)(37).

Interestingly, in our cohort of patients from 2009-2014 only 25% with an early relapse had high-risk cytogenetic abnormalities t(4,14); t(14,16) or del17p. This result was supported by findings from *Corre et al (38)* who showed that 25.4% of patients with t(4;14) and del(17p) suffered from an ER.

Cast nephropathy is a high-risk factor for early death. In a recent study from the DMMR of 2252 patients diagnosed 2013-2017, we described the prognosis of 204 (9%) patients presenting with clinically-suspected cast nephropathy, defined as serum creatinine concentration >177  $\mu$ mol/L and serum free light chain concentration >1000 mg/L. Despite prompt initiation of bortezomib-based therapy, 33% of patients died in the first year. One-year mortality was high among transplant-ineligible patients (43%). Achievement of very good partial response or better in the first line of therapy and deep reduction of involved serum free light chains at three months after initiation of therapy were associated with superior OS in multivariate analysis(39).

Another important challenge in treatment of MM is comorbidity, as reflected in the frailty score proposed by the International Myeloma Working Group (40, 41). Patients with comorbidity are often excluded from clinical trials and we therefore have limited data on the impact of comorbidity on outcome in unselected myeloma patients(5, 7)(6, 7). In a study based on DMMR comorbidity data prior to diagnosis of MM were compared between 2,190 patients and 21,900 population controls, matched by age and sex(42). Comorbidity was assessed by the Charlson comorbidity index based on ICD-10 codes. The overall comorbidity rate was higher in MM patients as compared to population controls (40.9% versus 34.9%), and mortality was higher in MM patients with co-morbidity independent of age, ISS, LDH, creatinine, CRP and performance status. The importance of comorbidity is further highlighted in a recent study where we showed that only 36 % of non

HDM/ASCT patients, and 45 % of HDM/ASCT patients registered in the DMMR fulfilled the criteria for inclusion in pivotal randomized clinical trials due to severe comorbidity, kidney failure, cancer within 5 years and performance status(7). OS was inferior in both groups of patients that would have been ineligible for RCTs.

Myeloma patients that do not meet the criteria for RCTs are at risk of poor outcome(7). Established scoring systems and prognostic factors, are generally based on RCTs and not validated in an unselected MM population. We validated the myeloma risk profile (MRP) for NDMM ineligible for HDM/ASCT generated by The UK Myeloma Research Alliance(43) in 1803 NDMM elderly patients above 65 years ineligible for HDM/ASCT in the DMMR.

The MRP used data from two RCTs and included the easily accessible parameters PS, ISS, age, and C-reactive protein (CRP) as prognostic variables. The score identified 3 risk groups; low, medium and high-risk for poor outcome(43). We confirmed the validity of this score on 1803 NDMM elderly patients above 65 years ineligible for HDM/ASCT(44). Interestingly, in the DMMR the percentage of high-risk patients was 46.3% (n=835, median OS 13.9 months) as compared to 43.9% in the UK MRP test set (n=520 patients, median OS 20 months) and 33.3% in the UK MRP validation set (n=1852 patients, median OS 25 months), which indicate that more patients in the real-world setting are high-risk by the MRP score.

## Discussion

National registers are an important source of information on epidemiology, treatment and outcome with implications for the planning of MM care. The Danish and Swedish myeloma registries cover the entire MM population of each country and here we present real-world data on more than 10.000 patients. Our data confirm, that both the absolute incidence and prevalence of multiple myeloma have increased and are expected to further increase in the near future due to longer life expectancy of the general population and improved survival achieved with the introduction of novel treatments. An increasing proportion of MM patients will be elderly(1). Many referral centers report

lower median age at MM diagnosis than the Danish Myeloma Registry and the Swedish Myeloma registry, suggesting that the populations captured in the different studies and countries worldwide are very different, which affect the reported outcome. As we have reported in our validation study of prognostic markers a higher proportion of patients in our unselected population had high risk myeloma(44).

One of the most important challenges is to understand the differences in outcome presented in RCTs compared to results from RWE(45). The real-world population of MM patients in national registers differs in clinical characteristics and outcome compared to patients recruited to RCTs.

The cost of new MM treatment represents a heavy burden on the medical system. An emerging number of pivotal RCTs leading to approval of new drugs use surrogate markers of survival as primary endpoint, and it is unknown whether these results are valid in patients that are not included in RCTs. A study from the Danish Myeloma Registry and RWE from other regions have shown that a large proportion of MM patients would not have fulfilled inclusion criteria for clinical trials and that patient's ineligible for RCTs have worse outcome(46) (5-7). Our data on RWE provide supplementary information on patients not eligible for RCTs and we have shown that patients with kidney impairment, severe comorbidity, and poor performance status have worse survival(39) (42) (47). How to treat these patients represents a knowledge gap to be addressed in further studies.

The Danish and Swedish registries give rapid information on the implementation and outcome of new treatment strategies. In HDT/ASCT patients, the treatment is similar in Sweden and Denmark and in elderly, we have seen a harmonization in treatment strategies in the last 5 years. The implementation of new treatment strategies in both countries have resulted in increased OS for myeloma patients.

One limitation of the DMMR and SMR is the lack of information on all lines of therapy. Ongoing studies in both registries examine if other national registries, such as the national patient registry and the prescription registry can be utilized to obtain information on comorbidity and data on later treatments. The Swedish Myeloma registry has since 2020 introduced the registration of all lines of

treatment including personal online access to registered data to patients and caregivers (INCA Patientöversikt)(48).

The retrospective nature of real-world data makes it difficult to compare the effect of different regimes. Nevertheless, register-based RWE give important and necessary insight in choice of therapy, response and adherence to treatment guidelines. Furthermore, we can study outcome in patients with high burden of comorbidity, concurrent infections or aggressive disease with early relapse that require immediate treatment, not allowing inclusion in RCTs(26, 39, 49, 50) (Table2). This enables us to establish clinically relevant hypotheses, to be addressed in clinical trials.

The national myeloma registries (DMMR and SMR) now include more than 12.000 myeloma, plasmacytoma and PCL cases and can be used to confirm outcome of treatment in real life for different age -and subgroups. Despite the introduction of new and better treatments, patients with functional high-risk; such as MM with early relapse, comorbidity, plasma cell leukemia, have inferior outcome and these patients deserve special attention in treatment protocols.

## Conclusions

National registries that include all MM patients are an important source of knowledge on epidemiology, treatment and outcome with implications for the planning of MM care. With the introduction of new treatment strategies, evolved from results from RCTs, OS has improved in the real-life MM population, but not to the same extent as described in RCTs. A future challenge will be to design studies that include elderly as well as patients with more severe comorbidities and those with high risk of early relapse to better understand how to use novel treatments in these groups. We encourage international collaboration to improve our understanding of differences between RCTs and RWE.

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Figure Legends:

Table 1. Important population-based registries in Denmark and Sweden

Table 2. Population based studies on myeloma using data from Swedish Myeloma Registry (SMR) and the Danish Multiple Myeloma Registry (DMMR).

Figure 1 A-D. Induction treatment in HDT-patients 2008-2018 in Sweden (A), and 2005-2018 in Denmark (B). Induction treatment in non-HDT-patients 2008-2018 in Sweden (C) and 2005-2018 in Denmark (D) **The national MM guidelines in Sweden 1 st line: In HDT-patients CTD and VCD induction was introduced from 2010 and VTD added in 2016. In 2018 VRD and VTD was standard induction. In non-HDT patients, in 2005 MPT was incorporated as a treatment option to MP. In 2010, MPV was added as treatment option. Rdex was introduced in the Swedish national guidelines 2016 and VRD 2018.**

**The national Danish guidelines 1<sup>st</sup> line: in HDT-patients VCD, CTD was introduced in 2009 and VTD was an option since 2014. In 2017 VCD or VRD was recommended as standard induction. In-non-HDT patients MPT was introduced in 2005 followed by MPV in 2010. In 2015 Rdex or MPV was standard up-front treatment and in 2017 VRd was recommended as first line therapy.**

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**Table 1. Important population-based registries in Denmark and Sweden**

Register	Established	Information collected
Civil Registration system(48) (49)	1947 (SE) 1968 (DK)	All individuals alive and living in are identified by a unique 10-digit personal identification number. Register of name, address, birth, citizenship, church membership, parentage, marital status.
National Cancer Registry (SCR) (50) (51)	1958 (SE) 1942 (DK)	Diagnosis, sex, date of birth, date of diagnosis, and hospital where the diagnosis was made for all incident cancers. Survival of all cancer diseases is published yearly.
National Patient Registry (52, 53)	1964 (SE) 1977 (LPR) (DK)	Individual patient-based discharge diagnosis from inpatients since the start and from 2000 and 1995 also visits to the emergency departments and outpatient clinics. Since 1994, diagnostic information has been coded by physicians according to the international Classification of Diseases, Tenth Edition system
Swedish Multigeneration Registry(54)		Parent-offspring relations (all first-degree relatives, parents and siblings) for all Swedish citizens who were born 1932 and later
National Myeloma Registries(11, 12)	2008 (SMR) (SE) 2005 (DMMR) (DK)	Web-reported clinical and laboratory data including treatment and response to treatment on all patients diagnosed with MM, SMM, PCL, SBP and EMP at time of diagnosis. In DK, POEMS, amyloid light-chain amyloidosis, MGUS and polyneuropathy is registered since 2014
Registry of Causes of Death(55, 56)	1952 (SE) 1875 (DK)	Causes of death broken down by age and sex. Computerized in 1970 in DK.
Drug prescription register(57, 58)	2005 (SE) 1994 (DK)	All prescribed drugs delivered by a pharmacy for each individual inhabitant. In DK annotation of prescribed medicine since 1997 and non-prescribed medicine from

		stores since 2001
Occupational Register(59, 60)	2005 (SV) 1980 (DK)	Occupations reported according to the Swedish Standard Classification of Occupations (SSYK 2012). Denmark use the ICSE classification system. Information on demographics, education and workplace (dst.dk/en/statistik)
Pathology Diagnosis Registry (LRP)(61)	1997 (DK)	Includes data from 1970, but only nationwide data since 1997. Up-dated daily. Histological and cytological specimens are routinely stored in pathology department archived. Diagnostic information coded according to the international Classification of Diseases, Tenth Edition system
Microbiology registry (62)	2010 (MiBa) (DK)	All microbiology findings nationwide
National biobank(63) National myeloma biobank	2009(DCB)(DK)  2005 (SE)	All hematological cancer became part of the biobank in 2012.  Vital frozen bone marrow mononuclear cells , plasma or serum and bone marrow smears from diagnosis (MGUS, MM).
The Laboratory Databases (64)	2014 (DK)	Laboratory results since 2014
The Hospital Medicine Registry(65)	2018 (DK)	Medicine used at hospitals including treatment for cancer
Transfusion database(66)	1997 (DTDB) (DK)	Nationwide information of number of blood units, patient data, diagnosis, operations, treatment
Hospital acquired infections (67)	2010 HAIBA(DK)	Information collected from the MiBa, LPR and regional medicine modules on hospital acquired infections.
Vaccination	2015 (DK)	Registration of all vaccinations given.

registry (68)		
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Abbreviations: MM active myeloma, SMM smoldering myeloma, PCL plasma cell leukemia, SBP solitary plasmacytoma of bone, EMP extramedullary plasmacytoma SMR Swedish myeloma registry. DMMR Danish multiple myeloma registry, SBP solitary plasmacytoma of bone, EMP solitary extramedullary plasmacytoma. PCK plasma cell leukemia., OSSM oligoscretory myeloma. NSMM non secretory myeloma. SMM smoldering myeloma

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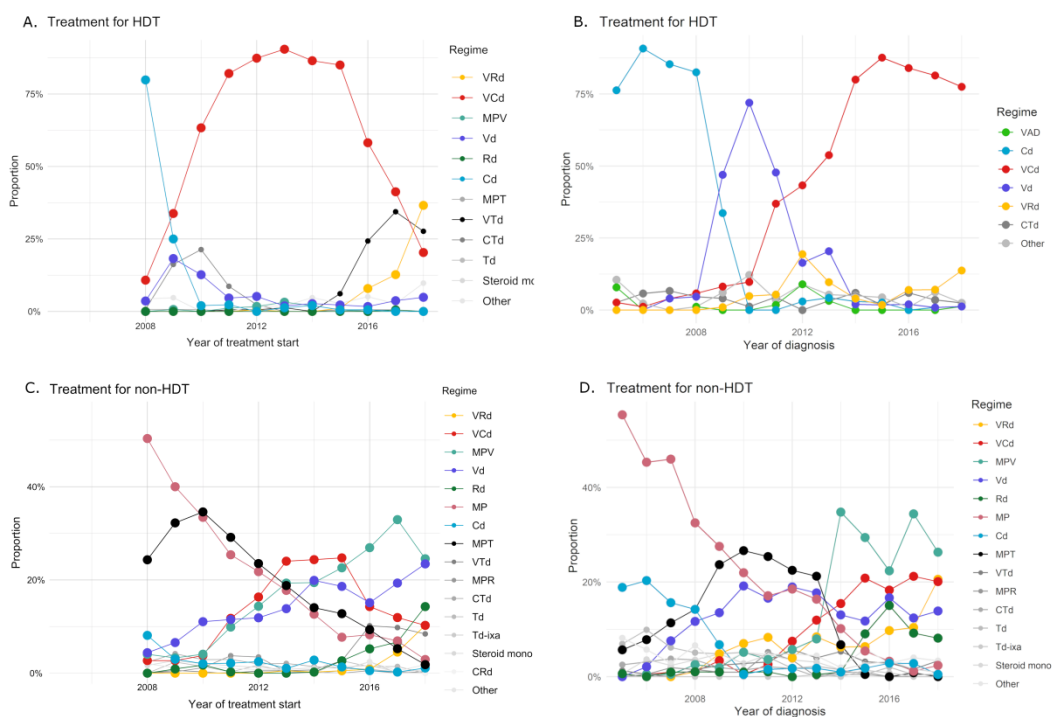
**Table 2. Population based studies on myeloma using data from Swedish Myeloma Registry (SMR) and the Danish Multiple Myeloma Registry (DMMR).**

Reference	Calendar period	Register	Number of patients	Main finding
Hveding Blimark C 2018 N=4904(12)	2008-2015	SMR	MM, N=4904	Increasing crude incidence but unchanged age-adjusted incidence over time. Improvement of response and survival in parallel with introduction of new treatments. Not significant OS -difference in patients with PR or better on 1 <sup>st</sup> line treatment in patients <65
Nahi H et al 2017(26)	2008-2014	SMR	N=4518 of these: SBP N=124 EMP N=67 PCL N=43	Solitary plasmacytoma and plasma cell leukaemia rare diseases with an incidence of 0.191(SBP), 0.078 (EMP) and 0.051 (PCL) for men and 0.090, 0.063 and 0.044 for women per 100 000 person-years <sup>1</sup> . Survival is dismal in PCL with a 2-year RS of 27 %
Wålinder G et al 2017(27)	2008-2016	SMR	OSMM N= 253 NSMM N= 136	Non-secretory myeloma (NSMM) and oligosecretory myeloma (OSMM) are rare diseases constituting 3 and 6 % of all myeloma patients with no significant difference in OS (42.7 months) compared to secretory myeloma.
Kristinsson SY et al 2013(22)	2008-2012	SMR	SMM N=360 High risk SMM N=104	Applying Mayo Clinic criteria and risk classification SMM constituted 14 % of all myeloma patients and 29 % of these had high risk disease. Fifty-seven % of high risk SMM progressed to MM within 2 years.

Holmstrøm et al. 2014 (31)	2005-2012	DMMR CVR	MM, N=1497	Twenty-two % of patients not eligible for HDT-ASCT died within 180 days from diagnosis. Causes of early death among was infections (50.9%), renal failure (9.9%), cardiovascular failure (10.8%), respiratory failure (6.6%) and stroke (3.8%)
Gimsing et al. 2016(11)	2005-2015	DMMR CVR	MM, N=2907	Presentation of the DMMR. OS for MM decreases with increasing age and is < 24 months for patients >80 years
Sørrig et al. 2016(69)	2008-2012	DMMR CVR	SMM N=360	The age-standardized incidence of SMM was 0.44 cases /100.000. 56.6% of high-risk MM, according to the Mayo Clinic risk model, progressed to MM within 2 years.
continued				
Gregersen et al. 2017.(39)	2005-2013	DMMR CVR DNPR	MM, N=2190 Control N= 21.900	Increased comorbidity among MM patients compared to controls (OR: 1.4). Comorbidity increased markedly within the year preceding diagnosis. Patients with comorbidity had increased mortality.
Thidemann Andersen et al. 2017(32)	2005-2013	DMMR CVR	MM, N=613	9.6% of patients treated with HDT-ASCT suffered from early deaths (<2 years). Causes of early death were progressive disease and infections.
Sørrig et al. 2017(47)	2005-2013	DMMR CVR	MM, N=2500	Immunoparesis had no effect on OS but was associated with shorter PFS
Sørrig et al. 2018(46)	2010-2013	DMMR CVR DMD DNPR	MM, N=1154	Within 60 preceding the diagnosis MM, the risk of blood stream infection increases (BSI). Patients with aggressive disease presentation have the highest risk of BSI.

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Helm-Petersen et al. 2018.(70)	2005-2014	DMMR CVR	MM, N=575	Poor outcome for patients with an early relapse (<18 months) after HDT-ASCT. Only 25% of these patients had high risk cytogenetic with t(4;14); t(14;16) and del17p
Klausen et al. 2019.(7)	2005-2013	DMMR CVR DNPR	MM, N=2189	Less than half of all patients with MM are eligible for RCT and OS is worse for patients not fulfilling the inclusion criteria in RCT.
Redder et al. 2020(41)	2005-2014	DMMR CVR	MM= 1377	Validation of the UK Myeloma Research Alliance Myeloma Risk Profile (MPR) in patients not eligible for HDT-ASCT.
Szabo et al. 2020(36)	2013-2017	DMMR	2252	The importance of kidney impairment and high free light-chain levels for outcome of MM
Szabo et al. 2021 (71)	2005-2019	DMMR	MM, N=5116	5.5% of patients in the DMMR have MGUS-like MM

1 European standard population Abbreviations: SMR Swedish myeloma registry. DMMR Danish multiple myeloma registry, SBP solitary plasmacytoma of bone, EMP solitary extramedullary plasmacytoma. PCK plasma cell leukemia., OSSM oligosclerotic myeloma. NSMM non secretory myeloma. SMM smoldering myeloma, CVR: civil registration system, DMMR: Danish Multiple Myeloma registry; DNPR: Danish National Patient Registry; OD odds ratio; HDT-ASCT: high dose melphalan with haematopoietic stem cell transplantation; PFS: progression free survival. SMM: smoldering myeloma; DMD: Danish Microbiology Database, PERSIMUNE: The PERSIMUNE Data Warehouse (PDWH; www.persimune.dk)



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