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RESEARCH

Comorbidities and survival of multiple myeloma patients diagnosed in Finland between 2000 and 2021

Kai Kysenius[1] · Anna Anttalainen[1] · Iiro Toppila[1] · Tatu Miettinen[1,2] · Mariann Lassenius[1] · Juha Lievonen[3] · Anu Partanen[4] · Raija Silvennoinen[3] · Mervi Putkonen[5]

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Abstract
Advances in treatment have improved the survival of multiple myeloma (MM) patients, but the disease remains incurable. Here, in this nationwide retrospective real-world evidence (RWE) study, we report the patient characteristics, incidence, overall survival outcomes, comorbidities, and healthcare resource utilization (HCRU) of all adult MM patients diagnosed between 2000 and 2021 in Finland. A total of 7070 MM patients and their 21,210 age-, sex- and region-matched controls were included in the analysis. The average MM incidence doubled from 4.11 to 8.33 per 100,000 people during the follow-up. The average age-standardized incidence also showed a significant increase over time (2.51 in 2000 to 3.53 in 2021). An increase in incidence was particularly seen in older population, indicative of improved diagnosis praxis. The median overall survival (mOS) of the MM patients and their matched controls was 3.6 and 15.6 years, respectively. The mOS of all MM patients increased significantly from 2.8 years (2000–2004) to 4.4 years (2017–2021) during the follow-up period. Distinctively, in patients who received autologous stem cell transplantation (ASCT), the mOS was 9.2 years, while in patients who did not receive ASCT, the mOS was only 2.7 years. MM patients showed more comorbidities at index and increased HCRU than their matched controls. The longer median survival and decreased risk of death indicate improved treatment outcomes in MM patients in Finland.

Keywords Multiple myeloma · Real-world evidence (RWE) · Hematology · Oncology · Autologous stem cell transplant (ASCT) · Comorbidities

Introduction

Multiple myeloma (MM) is an incurable hematological cancer that develops from the plasma cells in the bone marrow. MM accounts for approximately 10% of all hematological malignancies and affects primarily the elderly [1]. Globally, the age-standardized incidence rate of MM has been estimated to be approximately 2 per 100 000 people, with the highest incidence in Western Europe, North America and Australasia [2]. In Finland, the current median age at diagnosis is 70 years, and the age-standardized incidence rate is 2.5-3 per 100,000 people [3, 4].

MM is a heterogenic disease both clinically and molecularly. This, together with the genomic instability associated with the disease progression, presents a great challenge for the treatment [5]. Advances in treatment strategies have improved the progression-free survival of MM patients tremendously over the past decade. In particular, the development of immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and targeted monoclonal antibody therapies together with the introduction of autologous stem cell transplantation (ASCT), have improved the overall survival (OS) of MM patients significantly [5–9]. For newly diagnosed MM patients who are fit, aged < 70 years and have no comorbidities, the current treatment recommendation according to the European Hematology Association (EHA)

✉ Kai Kysenius
kai.kysenius@medaffcon.fi

1 Medaffcon Oy, Espoo, Finland

2 Takeda Oy, Helsinki, Finland

3 Department of Hematology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

4 Department of Medicine, Kuopio University Hospital, Kuopio, Finland

5 Department of Hematology, Turku University Hospital, Turku, Finland

and European Society for Medical Oncology (ESMO), include a triplet novel agent-based induction with ASCT and lenalidomide maintenance [10]. In addition, cumulative data exist on quadruplet regimens including CD38Ab with remarkable progression-free survival (PFS) benefit in transplant-eligible patients with newly diagnosed MM [11, 12].

The overall survival (OS) estimates for MM patients range from 2 to 3 years to over a decade, depending on the patient's age, the risk profile of myeloma, overall health status and thereby the possible treatment options. Notably, as many as 50% of MM patients present with comorbidities at diagnosis [13]. Although safer treatment options have been developed for the older patients and the median age of patients receiving ASCT has increased over the recent years, the frailty and comorbidities of the elderly patients impact both treatment decisions and outcomes [14]. Although previous RWE studies have shown that the risk of death increases with comorbidity load in MM [13, 15], the impact of particular comorbidities on the prognosis remains to be explored in an RWE setting.

Here, we utilized several nationwide healthcare registries of Finland and identified all adult MM patients diagnosed between 2000 and 2021. Importantly, to investigate the patient characteristics, MM incidence, OS, comorbidities and healthcare resource utilization (HCRU) relative to the background population, an age-, sex- and region-matched control group in a ratio of 3:1 was included in the study. We also compared the characteristics and outcomes of patients that have received ASCT to the ones that did not receive a transplant (nASCT). Furthermore, we studied the overall survival of aged patients over 70 years old over time. This study provides an in-depth look into longitudinal patient characteristics and outcomes within the Finnish real-world MM population.

Methods

The study included MM patients diagnosed between 2000 and 2021 and their age-, sex and region matched controls at 1:3 ratio. The population was characterized at baseline by basic, clinical and socioeconomic variables.

The incidence of MM patients was studied annually and by age-group. Overall survival (OS) was assessed for several different strata, including the ASCT status, age-group (under/over 70 years at diagnosis) and diagnosis year, and the effects of the covariates were studied by Cox proportional hazards models. The baseline comorbidities were characterized and their effect on OS was studied by Cox proportional hazards model. The healthcare resource utilization (HCRU) of MM patients was compared to their matched controls by specialty area and diagnosis type. The analyses were performed separately for ASCT and nASCT cohorts. Please see Supplementary information for detailed methods and data sources.

Results

Patient population

A total of 7070 adult multiple myeloma (MM) patients diagnosed in Finland during 2000–2021, and 21 210 of their matched controls (in 3:1 ratio) were included in the study (Fig. 1).

The cohort was identified as patients with at least four records for MM during 2000–2021 with ICD-10 diagnosis code C90.0, or with a survival of ≤ 14 days and at least one MM record. Patients who had prohibited data disclosure, were non-Finnish at index, did not have a MM diagnosis (C90.0) between 1.1.2000-31.12.2021, and prevalent patients with initial MM diagnosis before 1.1.2000, were excluded from the study cohort. Age < 18 years old at index was used as an exclusion criterion, however, no patients under 18 years old were identified. In addition, patients surviving longer than a year post index without receiving treatment were excluded from the study cohort. Abbreviations: DVV = Digital and Population Data Services agency; HILMO = Care register for health care; MM = multiple myeloma.

The characteristics of MM patients at diagnosis and their matched controls are shown in Table 1 and Supplementary Table S1. The median age of both the MM and matched control cohort was 71.2 years with 51.7% male patients. The median follow-up times for MM and matched control cohorts were 2.6 and 6.5 years, respectively. Comorbidities were more common in MM patients at index: 39.1% of had a Charlson's comorbidity index (CCI) ≥ 1, compared to 19.1% of the matched controls. Altogether 89.2% of the MM patients received treatment for the MM during the follow-up period and 21.4% of all patients received autologous stem cell transplantation (ASCT). A total of 44% of patients under 70 years old received ASCT during the entire follow-up period, with a notable increase from 14% in 2000–2004 to 56% during 2017–2021 (data not shown). At the end of follow-up (EOF), 68.1% of MM patients had died compared to 31.1% of matched controls.

We further compared the characteristics of MM patients that had received ASCT to the ones that did not receive a transplant (nASCT) (Table 2, Supplementary Table S2). As expected, the median age of ASCT patients was significantly lower than in nASCT patients: (61.4 vs. 74.3 years; $p < 0.001$). The observed median follow-up times were 4.9 and 2.1 years, for ASCT and nASCT patients, respectively.

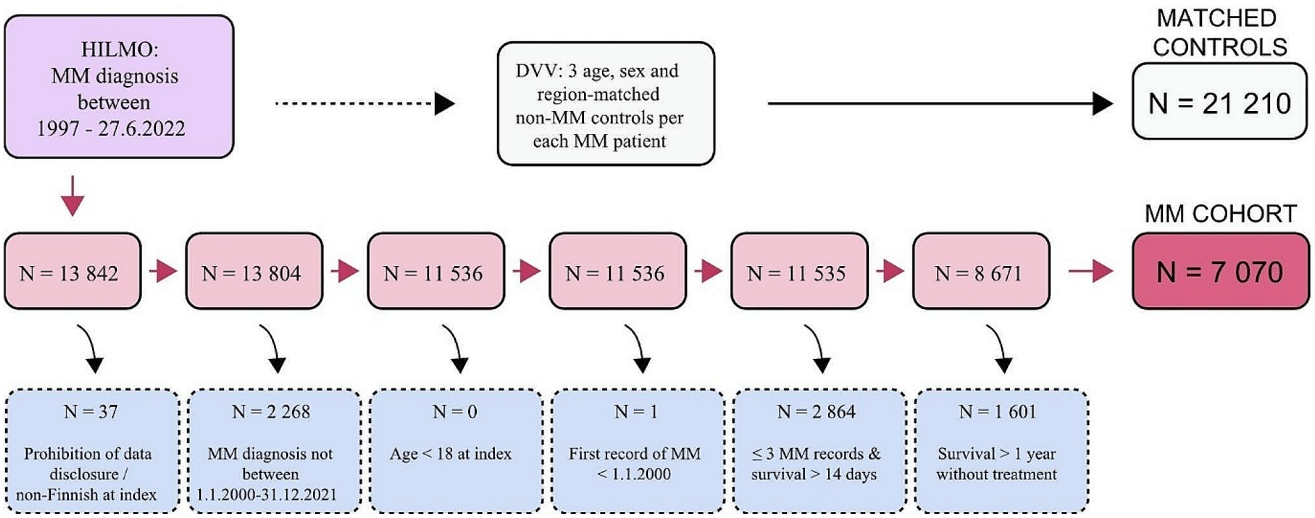

Fig. 1 MM cohort formation

Table 1 Clinical characteristics of the MM patients diagnosed in Finland during 2000–2021, and their matched controls

		MM ($N=7\,070$)	Control ($N=21\,210$)	p
Age (years; median [IQR])		71.17 [63.20, 78.25]	71.16 [63.20, 78.26]	*1*
Follow-up time (years; median [IQR])		2.57 [0.90, 5.32]	6.49 [2.79, 11.25]	*< 0.001*
Sex (N, %)	Female	3415 (48.3)	10,245 (48.3)	*1*
	Male	3655 (51.7)	10,965 (51.7)	
CCI (N, %)	0	4306 (60.9)	17,163 (80.9)	*< 0.001*
	1–2	2113 (29.9)	3269 (15.4)	
	3+	651 (9.2)	778 (3.7)	
Treatment status (N, %)	Treated	6308 (89.2)	0 (0.0)	*< 0.001*
	No treatment	762 (10.8)	21 210 (100.0)	
Transplant status (N, %)	ASCT	1514 (21.4)	0 (0.0)	*< 0.001*
	nASCT	5556 (78.6)	21 210 (100.0)	
Index year (N, %)	2000–2004	1156 (16.4)	3468 (16.4)	*1*
	2005–2010	1746 (24.7)	5238 (24.7)	
	2011–2016	2129 (30.1)	6387 (30.1)	
	2017–2021	2039 (28.8)	6117 (28.8)	
Mortality (N, %)	Alive at EOF	2254 (31.9)	14,621 (68.9)	*< 0.001*
	Dead at EOF	4816 (68.1)	6589 (31.1)	

Abbreviations: EOF: end of follow-up, CCI: Charlson's comorbidity index; Interquartile range is presented for median age and follow-up time; Statistical significances were calculated using Kruskal-Wallis Rank Sum Test for continuous variables (age, follow-up length) and Chi-squared test for categorical variables

46.2% of the ASCT patients were female (compared to 48.9% females in the nASCT cohort, $p=0.065$). Comorbidities were less common in ASCT patients: 26.2% of ASCT patients had a CCI ≥ 1, compared to 42.6% of nASCT patients ($p<0.001$). As expected, matched controls had longer follow-up times, lower mortality and fewer comorbidities. For the ASCT and nASCT age, sex and region-matched controls, CCI ≥ 1 were 10.6% and 21.4%, respectively. 62.2% of the ASCT patients were alive at EOF, compared to only 23.6% of the nASCT patients.

Incidence of multiple myeloma in Finland during 2000 to 2021

Next, we assessed changes in MM incidence over time. The average incidence of MM in Finland during 2000–2021 was 5.98 cases per 100,000 persons, with a statistically significant increase in incidence observed over time (from 4.11 in 2000 to 8.33 in 2021; $p<0.001$; Fig. 2a, Supplementary Table S3). The age-standardized incidence during the same time was 3.01 cases per 100,000 persons; with a statistically significant increase over time (from 2.51 in 2000 to 3.53 in 2021; $p<0.001$; Fig. 2b, Supplementary Table S3).

We stratified MM patients by age groups and found that the highest incidence of MM during 2000–2021 was in the age groups of 75–79 and 80–84 years old, with 28.1 and 29.1 cases per 100 000 persons, respectively (Fig. 2c). The incidence of MM decreased steadily in younger age groups with an incidence of 22.1, 11.6, 4.1 and 1.1 per 100 000 persons in age groups of 70–74, 60–64, 50–54 and 40–44 years old, respectively.

Table 2 Clinical characteristics of ASCT and nASCT MM patients and their matched controls during 2000–2021

		ASCT		*p*	nASCT		*p*	*p* (ASCT vs. nASCT)
		Case	Control		Case	control		
		N = 1 514	*N* = 4 542		*N* = 5 556	*N* = 16 668		
Age (years; median [IQR])		61.35 [55.05, 65.93]	61.33 [55.03, 65.93]	*0,998*	74.26 [67.45, 80.1]	74.25 [67.45, 80.10]	*0,999*	*< 0.001*
Follow-up time (years; median [IQR])		4. 85 [2.60, 7.76]	6.68 [3.53, 10.26]	*< 0.001*	2.06 [0.68, 4.5]	6.45 [2.56, 11.51]	*< 0.001*	*< 0.001*
Sex (N, %)	Female	699 (46.2)	2097 (46.2)	*1*	2716 (48.9)	8148 (48.9)	*1*	*0,065*
	Male	815 (53.8)	2445 (53.8)		2840 (51.1)	8520 (51.1)		
CCI (N, %)	0	1117 (73.8)	4061 (89.4)	*< 0.001*	3189 (57.4)	13,102 (78.6)	*< 0.001*	*< 0.001*
	1–2	341 (22.5)	425 (9.4)		1772 (31.9)	2844 (17.1)		
	3+	56 (3.7)	56 (1.2)		595 (10.7)	722 (4.3)		
Treatment status (N, %)	Treated	1513 (99.9)	4542 (100.0)	*< 0.001*	4795 (86.3)	0 (0.0		
	No treatment	< 5	0 (0.0)		761 (13.7)	16 668 (100.0)		*< 0.001*
Index year (N, %)	2000–2004	81 (5.4)	243 (5.4)	*1*	1075 (19.3)	3225 (19.3)	*1*	*< 0.001*
	2005–2010	292 (19.3)	876 (19.3)		1454 (26.2)	4362 (26.2)		
	2011–2016	628 (41.5)	1884 (41.5)		1501 (27.0)	4503 (27.0)		
	2017–2021	513 (33.9)	1539 (33.9)		1526 (27.5)	4578 (27.5)		
Mortality (N, %)	Alive at EOF	942 (62.2)	4178 (92.0)	*< 0.001*	1312 (23.6)	10,443 (62.7)	*< 0.001*	*< 0.001*
	Dead at EOF	572 (37.8)	364 (8.0)		4244 (76.4)	6225 (37.3)		

Abbreviations: EOF: end of follow-up, CCI: Charlson's comorbidity index; Interquartile range is presented for median age and follow-up time; Statistical significances were calculated using Kruskal-Wallis Rank Sum Test for continuous variables (age, follow-up length) and Chi-squared test for categorical variables

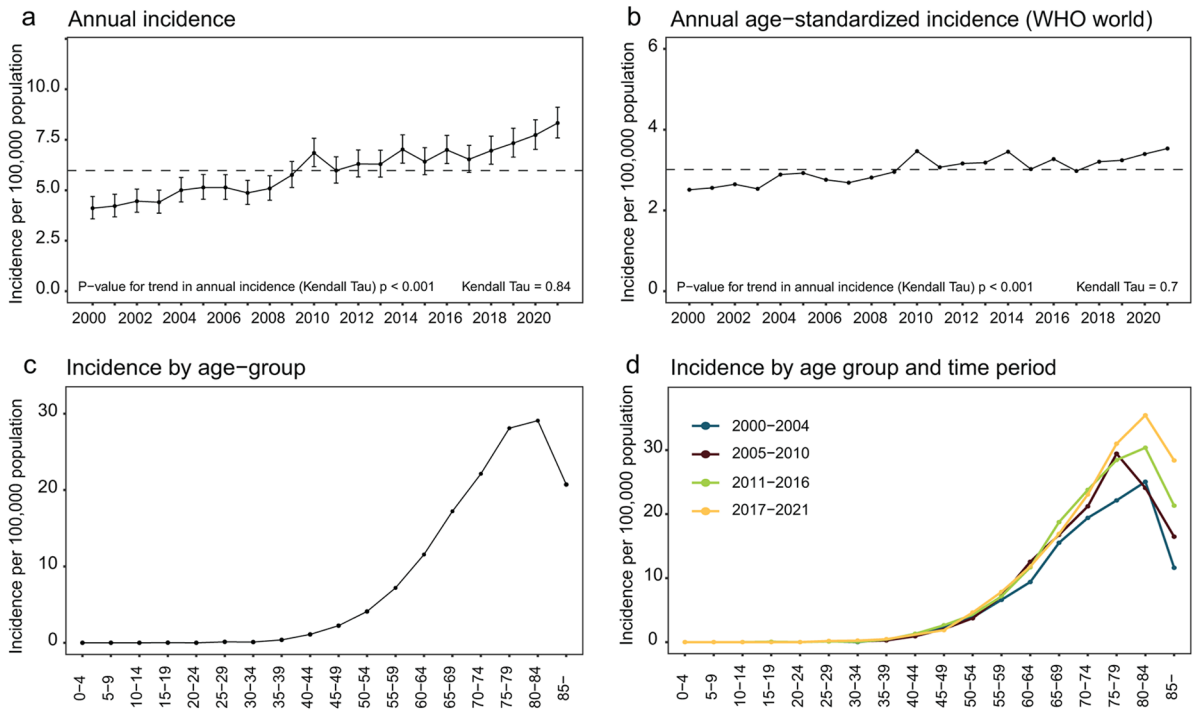

Fig. 2 MM incidence in Finland during 2000–2021. (**a**) Annual, (**b**) age-standardized and (**c**) age-group specific incidence. (**d**) MM incidence over time (2000–2004, 2005–2010, 2011–2016 and 2017–2021) in different age groups. The dotted line indicates the average incidence over time/age group

We further divided the population into 4 cohorts based on their diagnosis years: 2000–2004, 2005–2010, 2011–2016 and 2017–2021 (see Supplementary Table S4 for time stratified patient characteristics). MM incidence has increased over time (2000–2004 vs. 2017–2021) particularly in older population, with a 2.45, 1.41 and 1.40 -fold increase in age groups 85+, 80–84 and 75–79 years old, respectively, compared to a 1.09–1.26 -fold increase in age groups 50–74 years old (Fig. 2d and Supplementary Table S3).

Development in the overall survival of MM patients during 2000–2021

During 2000–2021 in Finland, the mOS of all MM patients and their matched controls was 3.6 and 15.6 years, respectively (Fig. 3a). To assess changes in survival over time, we studied the mOS in 4 different time windows based on the diagnosis year. The mOS of all Finnish MM patients improved significantly from 2.8 years in 2000–2004 to 4.4 years in 2017–2021 ($p < 0.001$; Fig. 3b), while the mOS of the matched controls increased only slightly over time ($p = 0.044$; Fig. 3c).

Next, we looked at the mOS of MM patients depending on their ASCT-status. During the entire study follow-up period of 2000–2021, the mOS of patients who received ASCT was 9.2 years compared to 2.7 years for patients that did not receive a transplant (nASCT) ($p < 0.001$; Fig. 3d). Although not statistically significant, the mOS of ASCT patients increased from 8.2 years in 2000–2004 to 9.4 years in 2011–2016 (mOS not reached for 2017–2021 group), and from 2.6 years in 2000–2004 to 2.9 years in 2017–2021 for nASCT patients (Supplementary Fig. S1a and S1b).

This change is reflective of the change in ASCT criteria, namely age, over time, as also the median age of ASCT patients increased from 52.5 to 63.4 years between 2000 and 2005 and 2017–2021, while the median age for the nASCT increased from 71.3 to 76.0 years in the same period (Supplementary Table S5). During 2000–2021, only 2.2% of patients ≥ 70 years old received ASCT compared to 43.9% of patients < 70 years old (Supplementary Table S6). Also, it is important to note that the mOS of ASCT patients includes some immortality survival bias, as the patients were alive at least until the transplantation. The median time from MM diagnosis to ASCT was 5.8 months.

Due to this significant shift in the ASCT group, we looked at the mOS of MM patients based on both their age and ASCT status. During 2000–2021, the mOS of MM patients ≥ 70 years old was 2.4 years compared to 9.4 of their matched controls ($p < 0.001$; Fig. 3e; patient characteristics provided in Supplementary Table S6). The mOS of MM patients ≥ 70 years old improved from 1.7 years in 2000–2004 to 2.5 years in 2011–2016 ($p < 0.001$) and to 3.1 years in 2017–2021 ($p < 0.001$; Supplementary Fig. S1c), while the mOS of MM patients < 70 years old improved from 4.6 years in 2000–2004 to 6.8 years in 2011–2016 ($p < 0.01$; Supplementary Fig. S1d; mOS not reached for 2017–2021 group). During 2000–2021, the mOS for ASCT patients over and under 70 years old were 6.7 and 9.3 years, respectively (Fig. 3e and f). For nASCT patients, the mOS for over and under 70 years old were 2.3 and 3.9 years, respectively (Fig. 3e and f).

When further analyzing the development of mOS in these groups, we found that the mOS of ≥ 70 years old ASCT patients improved from 2.4 years in 2005–2010 to 6.7 years in 2011–2016 ($p = 0.398$; Supplementary Fig. S2a), although the increase was not statistically significant due to small sample size. During the same time, the mOS of ≥ 70 years old nASCT patients improved significantly from 2.1 to 2.5 years ($p < 0.001$; Supplementary Fig. S2b). During the entire study time, the mOS of ≥ 70 years old nASCT patients improved significantly from 1.7 years in 2000–2004 to 2.9 years in 2017–2021 ($p < 0.001$; Supplementary Fig. S2b). For ASCT patients < 70 years old, the mOS improved from 8.2 years in 2000–2004 to 9.8 years in 2011–2016 ($p = 0.568$; Supplementary Fig. S2c; mOS not reached for 2017–2021 group). Interestingly, the mOS for nASCT patients < 70 years old decreased significantly over time from 4.0 years in 2000–2004 to 3.5 years in 2017–2021 ($p = 0.041$) Supplementary Fig. S2d).

Risk factors affecting the survival of MM patients

Next, we investigated the different factors affecting overall survival of MM patients. To this end, Cox proportional hazards risk estimates for overall survival were stratified by multiple covariates (Fig. 4). Model 1, including ASCT status (time varying covariate) and diagnosis year, indicated that if only time and ASCT were considered, the year of diagnosis improved the survival 1% per year ($p = 0.002$; Fig. 4a), and ASCT decreased the risk to 39% compared to nASCT. In Model 2, where age and sex were also included, the year of diagnosis indicated an improved survival of 3% annually (Fig. 4b). In Model 3, when accounting for CCI, the effect of index year was estimated at 3% annual improvement in the risk of death (Fig. 4c).

MM patients show an increase in the recorded comorbidities during the month preceding MM diagnosis

MM patients are known to present with more comorbidities at diagnosis [15], and we also wanted to get a comprehensive view on the comorbidity-load on MM patients in Finland. First, we looked at all the co-occurring diagnoses

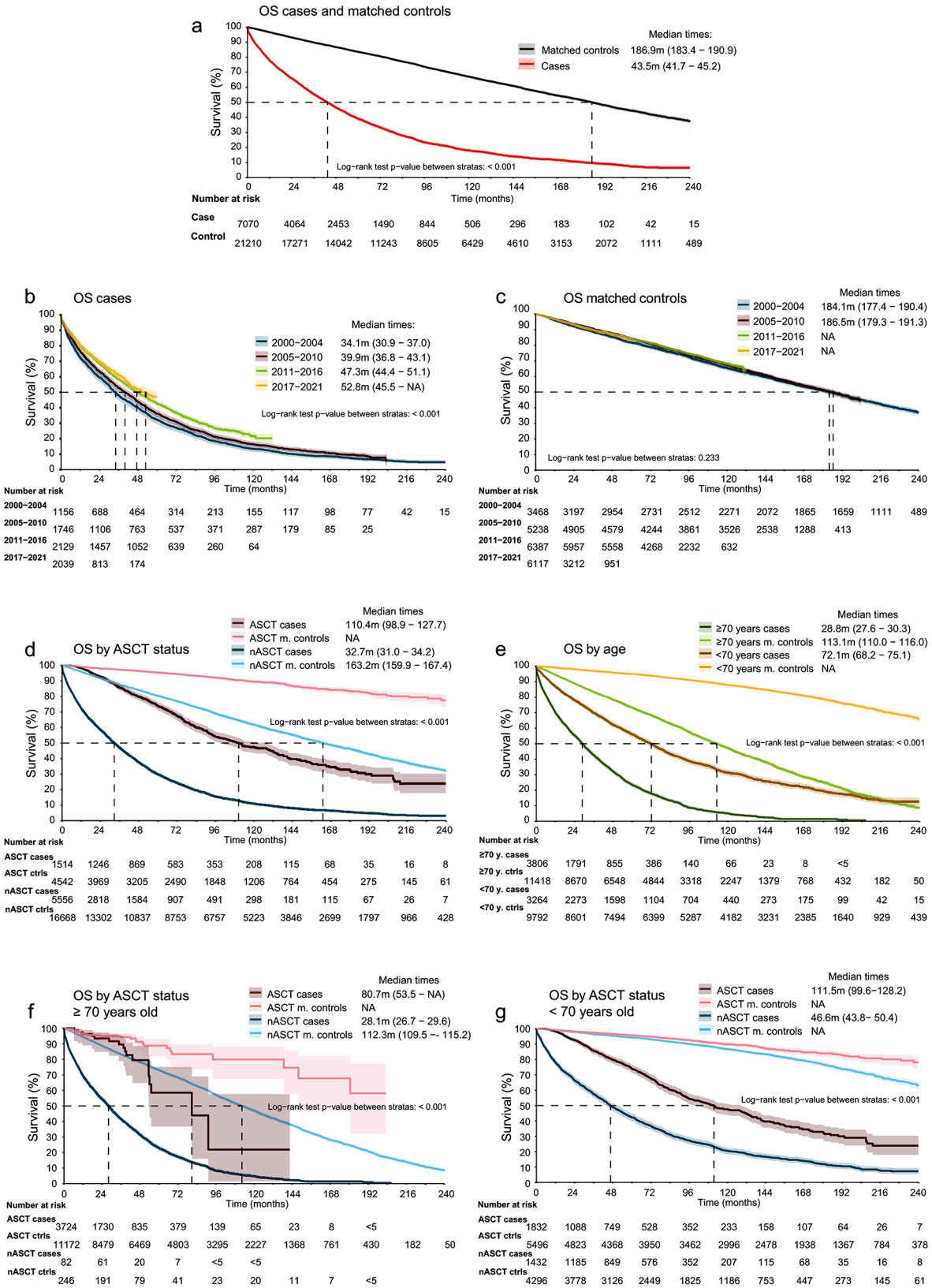

Fig. 3 The overall survival of MM patients in Finland during 2000–2021. (**a**) The mOS of all diagnosed MM patients and their matched controls in Finland during 2000–2021. (**b**) The mOS of MM patients and (**c**) their matched controls during 2000–2004, 2005–2010, 2011–2016 and 2017–2021. (**d**) The mOS of ASCT and nASCT patients and their matched controls during 2000–2021. (**e**) The mOS of MM patients ≥ and < 70 years old and their matched controls in Finland during 2000–2021. The mOS of ASCT and nASCT MM patients ≥ 70 (**f**) and < 70 years old (**g**) and their matched controls in Finland during 2000–2021

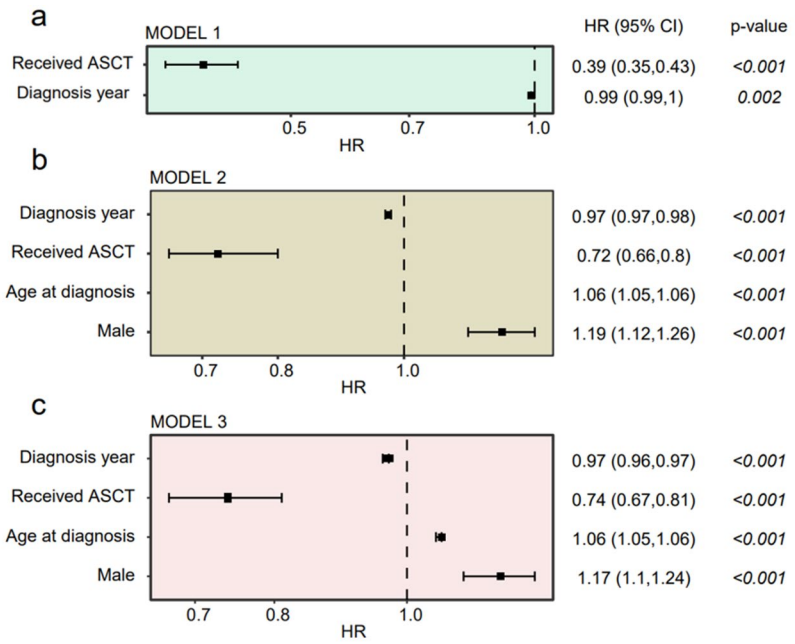

Fig. 4 Cox proportional hazards risk estimates for overall survival of the MM patients in Finland during 2000–2021. (**a**) Model 1 with diagnosis year and ASCT status (time-varying covariate) as covariates. (**b**) Model 2 with diagnosis year, ASCT status, age and sex. (**c**) Model 3 with diagnosis year, ASCT status, age and sex with CCI as stratifying factor, allowing different baseline hazards for each CCI group (0, 1–2 and 3+). The models show more recent diagnosis and receiving ASCT significantly decrease the HR, whereas age and male sex significantly increase it

Table 3 Comorbidities of MM patients and their matched controls in Finland during 2000–2021

ICD-10	Diagnosis	At index			With 1 month washout period			FOLD CHANGE
		Cases *N* (%)	Controls *N* (%)	*p*	Cases *N* (%)	Controls *N* (%)	*p*	case vs. ctrl index vs. 1mo
I10	Essential (primary) hypertension	1714 (24.2)	2515 (11.9)	*< 0.001*	1143 (16.2)	2448 (11.5)	*< 0.001*	1,5
I48	Atrial fibrillation and flutter	812 (11.5)	1563 (7.4)	*< 0.001*	639 (9)	1528 (7.2)	*< 0.001*	1,3
I25	Chronic ischaemic heart disease	655 (9.3)	1344 (6.3)	*< 0.001*	511 (7.2)	1314 (6.2)	*0.002*	1,3
E11	Non-insulin-dependent diabetes mellitus	650 (9.2)	1140 (5.4)	*< 0.001*	431 (6.1)	1120 (5.3)	*0.009*	1,5
I50	Heart failure	536 (7.6)	665 (3.1)	*< 0.001*	389 (5.5)	645 (3)	*< 0.001*	1,4
J18	Pneumonia, organism unspecified	536 (7.6)	645 (3)	*< 0.001*	399 (5.6)	625 (2.9)	*< 0.001*	1,4
H25	Senile cataract	525 (7.4)	1592 (7.5)	*0.82*	507 (7.2)	1550 (7.3)	*0.696*	1,0
N17	Acute renal failure	519 (7.3)	63 (0.3)	*< 0.001*	102 (1.4)	63 (0.3)	*< 0.001*	5,2
E78	Disorders of lipoprotein metabolism and other lipidaemias	459 (6.5)	767 (3.6)	*< 0.001*	310 (4.4)	742 (3.5)	*< 0.001*	1,5
N18	Chronic renal failure	388 (5.5)	180 (0.8)	*< 0.001*	205 (2.9)	174 (0.8)	*< 0.001*	1,9

The most common comorbidities (> 5% prevalence) in MM patients and their matched controls diagnosed during the 3 years prior to MM diagnosis, and during the month prior to index in MM patients. Comorbidities with prevalence of < 5% were also included in the 1-month washout analysis to enable comparison

(ICD-10 codes) of MM patients recorded during the three years prior to index. We found a marked difference when compared to their matched controls reflected both by different CCI distribution between MM patients and controls ($p < 0.001$, Table 1), and by individual co-diagnosis comparisons (Supplementary Table S7). After excluding the diagnoses that can be largely attributed to symptoms and pain states reportedly related to MM [16, 17], the most common comorbidities presented by MM patients at diagnosis were essential (primary) hypertension (I10), atrial fibrillation and flutter (I48), chronic ischemic heart disease (I25), non-insulin-dependent diabetes mellitus (E11), heart failure (I50) and both acute and chronic renal failure (N17 and N18) (Table 3).

Previous studies have shown that MM patients record a large number of diagnoses during the month leading up to MM diagnosis [15]. Consistently, the MM patients diagnosed in Finland during 2000–2021 show an increase in the recorded co-diagnoses during the month prior to index (Table 3 and Supplementary Table S7). The diagnosis that showed most increase (fold change) in the month leading up to the MM diagnosis was acute renal failure (5.2-fold increase in 3 years vs. 1 month washout).

We also looked at the morbidities in ASCT vs. nASCT patients at MM diagnosis and found that the cardiovascular

Table 4 Relative risk of death by each CCI comorbidity class in MM patients at index

	MM patients at index		
Comorbidity class	**N (events)**	**HR (CI)**	***p***
Myocardial infarction	273	2.05 (1.79–2.34)	*< 0.001*
Congestive heart disease	592	2.41 (2.19–2.65)	*< 0.001*
Peripheral vascular disease	164	1.87 (1.56–2.23)	*< 0.001*
Cerebrovascular disease	385	1.43 (1.28–1.62)	*< 0.001*
Dementia	163	3.02 (2.55–3.57)	*< 0.001*
Chronic pulmonary disease	455	1.34 (1.20–1.50)	*< 0.001*
Rheumatoid disease	207	1.17 (0.99–1.38)	*0.062*
Peptic ulcer disease	107	1.53 (1.23–1.89)	*< 0.001*
Mild liver disesae	49	1.48 (1.07–2.03)	*0.017*
Diabetes without chronic complications	505	1.45 (1.30–1.62)	*< 0.001*
Diabetes with chronic complications	161	1.68 (1.41–2.01)	*< 0.001*
Hemiplegia or paraplegia	66	1.15 (0.86–1.53)	*0.339*
Renal disease	579	1.33 (1.20–1.48)	*< 0.001*
Cancer (any malignancy)	1125	1.11 (1.02–1.19)	*0.010*
Moderate or severe liver disease	17	1.91 (1.72–4.92)	*< 0.001*
Metastatic solid tumor	116	1.61 (1.28–2.01)	*< 0.001*
AIDS/HIV	< 5	0.70 (0.10–4.99)	*0.725*

related conditions were especially more common in nASCT patients, including heart failure (I50), chronic ischemic heart disease (I25) and atrial fibrillation and flutter (I48), with 6.6-, 3.7- and 3.4 -fold higher levels when compared to ASCT patients, respectively (Supplementary Table S8).

Effects of comorbidities on MM patient prognosis

A previous study on MM patients in Denmark estimated the relative risk of death for different disease classes included in the Charlson's Comorbidity Index (CCI) [15, 18]. To compare our findings to the Danish study, we did a similar analysis for Finnish MM patients. In addition, we analysed the relative risk of death for each CCI class in ASCT and nASCT patients.

At diagnosis, the MM patients presented with a significantly higher number of comorbidities (Table 1), which was also reflected in the overall higher relative risk of death across the CCI classes (Table 4). Specifically, dementia (HR 3.02), congestive heart disease (HR 2.41) and myocardial infarction (HR 2.05) were associated with significantly increased relative risk of death among all MM patients.

We further compared the ASCT and nASCT patients, and as expected, nASCT patients presented with a significantly higher overall relative risk of death across the CCI classes (Table 5). Specifically, moderate or severe liver disease (HR 2.70), dementia (HR 2.37), congestive heart disease (HR 2.01), myocardial infarction (HR 1.71) and peripheral vascular disease (HR 1.60), were associated with significantly increased relative risk of death in nASCT patients ($p < 0.05$, Table 5). For ASCT patients, only congestive heart disease (HR 1.87) and diabetes without chronic complications (HR 1.65) increased the relative risk of death significantly ($p < 0.05$, Table 5).

Table 5 The relative risk of death by each CCI comorbidity class in ASCT and nASCT patients

	ASCT			nASCT		
Comorbidity class	**N (events)**	**HR (CI)**	***p***	**N (events)**	**HR (CI)**	***p***
Myocardial infarction	15	2.00 (1.00-4.03)	*0.051*	258	1.71 (1.49–1.96)	*< 0.0001*
Congestive heart disease	26	1.87 (1.08–3.25)	*0.026*	566	2.01 (1.83–2.21)	*< 0.0001*
Peripheral vascular disease	11	1.78 (0.80–3.98)	*0.161*	153	1.60 (1.33–1.91)	*< 0.0001*
Cerebrovascular disease	36	0.97 (0.53–1.76)	*0.918*	349	1.27 (1.12–1.44)	*0.0001*
Dementia	< 5	2.86 (0.40-20.34)	*0.295*	162	2.37 (2.00-2.80)	*< 0.0001*
Chronic pulmonary disease	49	0.96 (0.60–1.53)	*0.858*	406	1.23 (1.10–1.38)	*0.0004*
Rheumatoid disease	32	0.74 (0.38–1.43)	*0.366*	175	1.15 (0.97–1.36)	*0.11*
Peptic ulcer disease	8	0.92 (0.30–2.87)	*0.886*	99	1.34 (1.08–1.66)	*0.008*
Mild liver disesae	5	0.75 (0.19–3.02)	*0.688*	44	1.45 (1.04–2.01)	*0.026*
Diabetes without chronic complications	58	1.65 (1.09–2.48)	*0.017*	447	1.27 (1.14–1.42)	*< 0.0001*
Diabetes with chronic complications	15	1.14 (0.54–2.40)	*0.732*	146	1.57 (1.30–1.88)	*< 0.0001*
Hemiplegia or paraplegia	12	0.90 (0.37–2.16)	*0.807*	54	1.21 (0.89–1.63)	*0.22*
Renal disease	82	1.20 (0.84–1.73)	*0.317*	497	1.25 (1.12–1.38)	*< 0.0001*
Cancer (any malignancy)	196	0.88 (0.69–1.12)	*0.296*	929	1.10 (1.02–1.19)	*0.02*
Moderate or severe liver disease	< 5	2.57 (0.36–18.28)	*0.346*	16	2.70 (1.57–4.66)	*0.0004*
Metastatic solid tumor	24	1.52 (0.72–3.20)	*0.275*	92	1.67 (1.32–2.12)	*< 0.0001*
AIDS/HIV	0	-	-	2	0.54 (0.076-3.9)	*0.54*

Healthcare resource utilization (HCRU) of MM patients in Finland during 2000–2021

To assess the economic burden of multiple myeloma in Finland, we also assessed the HCRU of MM patients and their matched controls, including hospitalizations, outpatient visits and emergency room (ER) visits. When examining the total number of events per patient year (PPY) following diagnosis, MM patients had nearly 15-fold more events during the first year after diagnosis when compared matched controls (44 vs. 3; Fig. 5a and b). Although the events in MM patients dropped to a steady level of 21–25 events PPY in the following years, they remained prominently higher until the end of follow-up, when compared to their matched controls (Fig. 5a and b). Outpatient visits were the most common visit type, followed by hospitalizations and ER visits. Hospitalizations decreased by over 50% after the first year in MM patients.

HCRU between ASCT and nASCT patients was also different with ASCT patients having an average of 47 events PPY during the first year after diagnosis compared to 41 events in nASCT patients (Fig. 5c and d, Supplementary Fig. S3a and S3b). After the first year post diagnosis, the events dropped in both ASCT and nASCT patients to a level of 20–28 in subsequent years (Fig. 5c and d). The biggest difference was in the outpatient contact numbers, which were higher for ASCT patients while hospitalizations and ER visits were slightly more frequent in nASCT patients.

With the high number of cardiovascular comorbidities at diagnosis, and the information that infections are the leading cause of death in MM patients [19–21], we also looked the HCRU separately due to cardiovascular diseases (CVD), other malignancies and infections in MM patients and their matched controls (Fig. 5e and f). First year number of PPY events for MM patients due to CVD, other malignancies and infections were 2.3-, 2.7- and 10.5-fold greater than in matched controls, respectively. Interestingly, in subsequent years, the numbers of PPY events due to infections remained 5-7-fold higher than in matched controls, whereas PPY events due to CVD and other malignancies returned to similar levels with matched controls. Comparisons between ASCT and nASCT patients and their matched controls, revealed a higher number of PPY events due to CVD and other malignancies in nASCT patients when compared to ASCT patients (Supplementary Fig. S3c-S3f).

Discussion

This retrospective nationwide study investigated the real-world treatment outcomes, comorbidities and epidemiological characteristics of MM patients and their matched controls in Finland from 2000 to 2021. The study utilized multiple national registries, including Finnish Care Register for Health Care (primary care; avoHILMO and specialty care; HILMO), Statistics Finland, Digital and Population Data Services Agency (DVV) and Finnish Social Insurance Institution (SII), and has, to our knowledge, the longest follow-up time of any registry-based RWE studies conducted on MM in Finland. The long study time of 21 years, together with a large age-, sex- and region-matched control group, provides the most comprehensive overview on the current patient characteristics and treatment outcomes of MM in Finland to date. The importance of RWE studies on MM patients is highlighted by the reports that as many as 40% of MM patients do not meet the criteria of phase 3 clinical trials, the ”gold standard” for evaluating the effects of experimental therapies and obtaining regulatory approvals [22].

We found a significant increase from 4.11 in 2000 to 8.33 in 2021 in the MM incidence in Finland. This is in line with previous reports, including Toppila et al. 2021, where we reported a slight increase in MM incidence in Finland during 2005–2016 [3]. Also the average age-standardized incidence rate of 3.01 was similar to the previously reported 3.2 per 100 000 persons [3], but we also report here a significant increase in the age-standardized incidence over time. It is likely that demographical change, namely the aging population of Finland, drives most of the observed increase in the overall incidence. Furthermore, the change in diagnostics in 2016, particularly utilization of imaging in diagnosis could have contributed to the increased incidence.

The median overall survival of MM patients in Finland improved significantly, confirming the positive trend seen in our previous studies [3, 4]. Overall, as expected, the patients who received ASCT had a significantly higher mOS when compared to patients who did not receive a transplant, although it is important to note that the mOS of ASCT patients includes some immortality survival bias, as the patients were alive at least until the transplantation (median delay from MM diagnosis to ASCT was 5.8 months). The improvement in OS of ASCT patients was not statistically significant, but this is likely to be a consequence of inadequate recording practices of ASCT in the early years of the study resulting in too small sample size to reach statistical significance. Findings from the Cox proportional hazards model suggested that ASCT status or diagnosis year alone did not explain the improved survival. However, when age, sex, and comorbidity load were added to the model, the risk of death decreased by 3% annually. This suggest that the improved mOS of MM patients in Finland can be attributed to several factors, including ASCT-status, age, sex and comorbidity load.

We report a high comorbidity/co-diagnosis burden in the Finnish MM cohort at MM diagnosis and throughout the

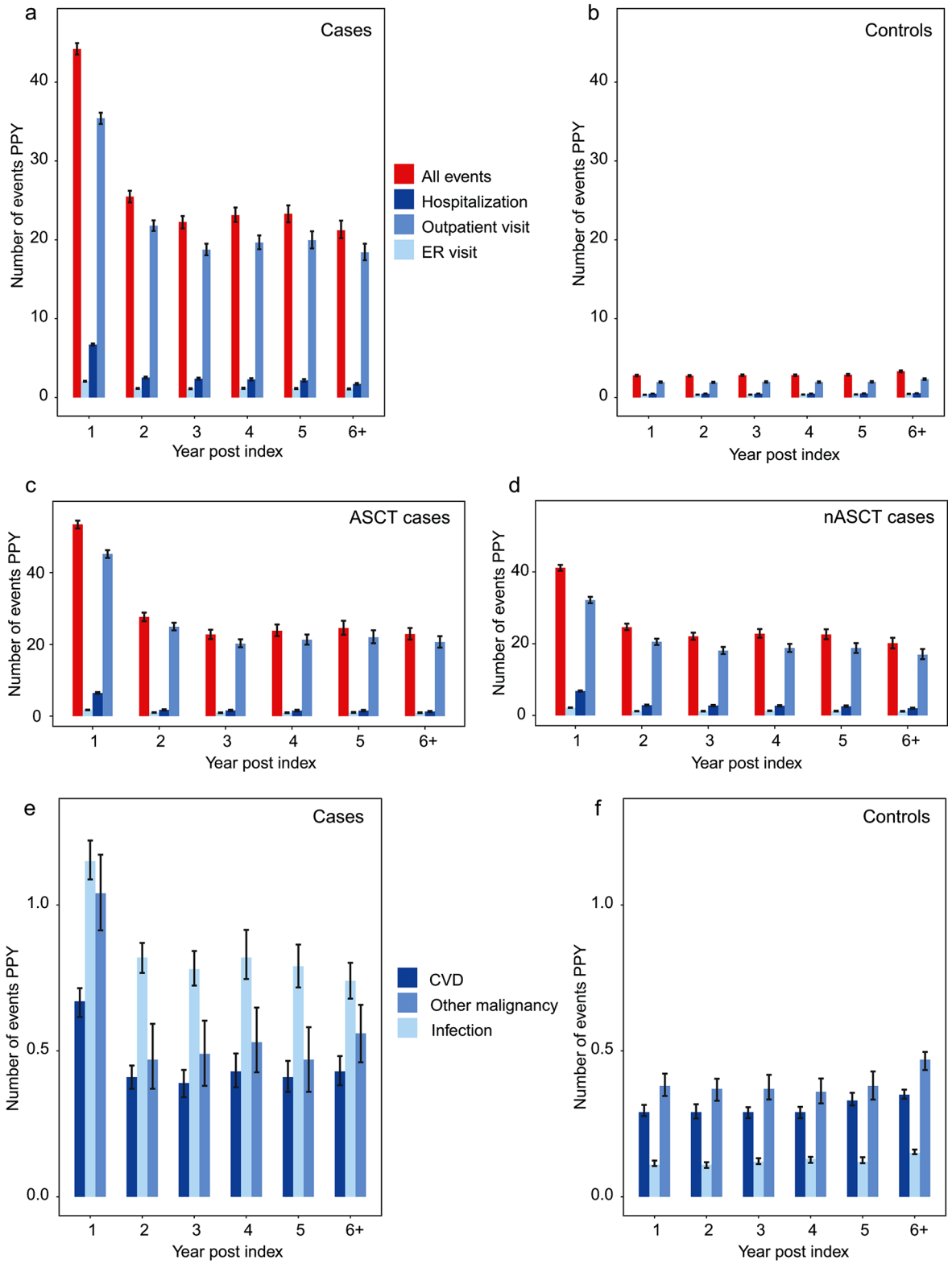

Fig. 5 HCRU of MM patients in Finland during 2000–2021. HCRU by total number of events per patient year (PPY) of (**a**) MM patients and (**b**) their matched controls. HCRU by total number of events PPY in (**c**) ASCT and (**d**) nASCT patients. HCRU of (**e**) MM patients and (**f**) their matched controls due to cardiovascular disease (CVD), other malignancies and infections

follow-up period when compared to their matched controls. Compared to a previous large RWE study on Danish MM patients by Gregersen et al., we found a similar comorbidity load in Finnish MM patients at index (30.9% vs. 40.9 in the Danish cohort from 2005 to 2012) [15]. Accordingly, dementia was found to be associated with the highest relative risk of death among the comorbidity classes analyzed, by both our study (HR 3.02; all MM patients) and Gregersen et al. (HR 2.8) [15]. Similarly to the Gregersen et al. study and our previous RWE studies, we found a significant increase in the co-diagnoses in the month leading to MM diagnosis.

MM develops from an asymptomatic premalignant state known as MGUS (monoclonal gammopathy of unknown significance) and/or asymptomatic MM (smoldering MM, SMM) to the malignant disease [23, 24]. Factors determining MGUS/SMM progression into MM are still largely unknown. Research on the time window of increasing comorbidities leading to MM diagnosis, including the possibility of early identification of the patients progressing from MGUS/SMM to MM, holds a great potential for future advancements in earlier diagnosis thereby improved treatment options. Furthermore, identification and development of efficient therapeutic strategies for high-risk MM patients remains a great challenge [25], and whether certain comorbidities affect the risk status are still largely unknown.

The development of new treatment regiments for elderly and nASCT patients is still in its infancy. A large Swedish study reported no improvement in the long-term relative survival in patients over 80 years old during 1973–2013 [26]. Elderly patients are likely to present a high number of comorbidities, and many MM patients are known to have especially cardiovascular comorbidities or risk factors. On the other hand, MM and/or some MM treatments may affect cardiovascular health [27]. Together, the underlying and during treatment presented comorbidities require careful risk assessment, monitoring and, when feasible, prophylactic therapy, particularly in elderly MM patients. Accurate evaluation of overall health status of myeloma patients is recognized as an increasingly valuable and important part in evaluating optimal treatment plan and thus ensure the best possible treatment outcome [14]. Importantly, the assessment of frailty is challenging, and has been subjected to criticism as many patient populations are still designated for treatment based on age, which alone does not reflect the overall health status, and thus for example eligibility for ASCT [14].

This study has limitations related to registry-based RWE studies. The data may be non-standardized, incomplete, and subject to missing data, differing coding practices and residual confounding factors between MM patients and matched controls that may have influenced the results. For example, the coding practice of ASCT has been incomplete during the beginning of this data extraction. The study used reimbursement start and open care medications to indicate treatment start as medication administered to patients in hospitals was unavailable. HCRU presented in this paper consists of primarily the specialty healthcare data with some data from primary care between 2011 and 2021 included. These descriptions are better describing the patient burden than the monetary HCRU costs, as medications make up a majority of actual costs [28]. Our data also did not include genotype or staging data, making observations between disease subtypes and/or risk status unavailable in the current study setting. Furthermore, the study indicated that patients with MM present comorbidities that may affect treatment and outcomes. A comparison between randomized controlled trials and real-world patients could shed further light on the differences in patient profiles and help improve real-life treatment outcomes.

Conclusions

Although the prognosis of Finnish MM patients has improved significantly, the comorbidity and HCRU burden are significant especially in elderly patients not eligible for ASCT treatment. Although treatment practices have improved and are reflected in improved overall survival, a holistic approach accounting for individual factors is required for optimizing treatment. With an aging population, the prevalence of MM is likely to increase even further [29]. Importantly, it will remain a challenge to find efficient and well-tolerated therapies for elderly MM patients who often present with comorbidities affecting the choice of treatment options.

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Author contributions IT, TM, MIL, JL, AP, RS, MP contributed to the study design and objectives, interpretation of results and revising the manuscript. AA and KK contributed to the interpretation of results, data analysis and wrote the first manuscript draft. IT was further responsible for data analysis and MIL was responsible for manuscript development. JL, AP, RS and MP critically reviewed the results and contributed to interpretation as well as revision of the manuscript. All authors have reviewed and approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval The study was approved by Findata, permission THL/3276/14.02.00/2021 and Statistics Finland, permission TK/1449/07.03.00/2022 in accordance with the act on the secondary use of health and welfare data in Finland.

Competing interests KK, IT, AA and MIL are employees of Medaffcon Oy. TM was an employee of Takeda Finland and Medaffcon Oy. JL has received consultation fees from Amgen, Celgene, Bristol-Myers Squibb, Sanofi, Takeda, Janssen, and travel grants from Janssen, Celgene, Amgen, Novartis, TEVA, Takeda, Roche, Abbvie and Pfizer. AP reports honoraria from Behring and Abbvie and has participated in Scientific Advisory Board meetings organized by Abbvie, Janssen-Cilag, Novartis, Pfizer and Takeda. RS has received research funding from Amgen, BMS, Celgene, Janssen-Cilag and Takeda and honoraria from the same companies (Advisory Board and presentations).MP has received honoraria from Amgen, Celgene, Janssen-Cilag and Takeda (Advisory Board and presentations). TM was an employee of Takeda Finland and Medaffcon Oy. JL has received consultation fees from Amgen, Celgene, Bristol-Myers Squibb, Sanofi, Takeda, Janssen, and travel grants from Janssen, Celgene, Amgen, Novartis, TEVA, Takeda, Roche, Abbvie and Pfizer. AP reports honoraria from Behring and Abbvie and has participated in Scientific Advisory Board meetings organized by Abbvie, Janssen-Cilag, Novartis, Pfizer and Takeda. RS has received research funding from Amgen, BMS, Celgene, Janssen-Cilag and Takeda and honoraria from the same companies (Advisory Board and presentations). MP has received honoraria from Amgen, Celgene, Janssen-Cilag and Takeda (Advisory Board and presentations).

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