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RESEARCH

A real-world study on the impact of infection load on mortality in multiple myeloma patients in Finland

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Abstract

Infections are a clinically significant cause of mortality in multiple myeloma (MM) patients. The high number of infections in MM patients is due to the immunosuppressive effects of the disease itself as well as treatment-related immunosuppression. In this real-world evidence (RWE) study, we used several nationwide healthcare registries of Finland to investigate the effect of infection load on mortality in MM patients during 1997–2021. The highest number of infections was recorded during the first year after MM diagnosis. In patients who received allogenic or autologous stem cell transplantation (ASCT), the number of infections during the first two years post diagnosis was significantly higher than in those treated without ASCT. When compared to their age-, sex-, and region-matched controls, MM patients accrued more infections during the year prior to diagnosis. Intriguingly, patients under 70 years old had significantly more infections already 3 years before diagnosis when compared to their matched controls. Prior to MM diagnosis, the relative proportion of streptococcal septicaemia and pneumonia due to *Streptococcus pneumoniae* increased the most. Of note, even one recorded infection prior to diagnosis was associated with significantly shorter median overall survival. Importantly, Cox proportional hazard models show that recorded infections both before and after diagnosis increase the independent risk of mortality in MM patients.

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

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm, with an annual, age standardized global incidence of 2 cases per 100 000 people [1]. MM typically affects the elderly: the average age at diagnosis is 70 years [2].

Infections are a clinically significant cause of morbidity and mortality in MM patients [3]. Infection and renal failure have been reported to be the main causes of early mortality [4–6]. Augustson et al. reported as high as 50% of the early deaths (< 6 months from diagnosis) to be caused by infection [4], and Blimark et al. found infection-related deaths in 27% of early deaths (< 1 year from diagnosis) [6]. The increased susceptibility to infection in MM patients is multifactorial, involving both the complex nature of the disease itself affecting the immune system, but also the range of different treatments including immunomodulatory drugs (IMiDs), immunostimulatory monoclonal antibodies (mAbs), proteasome inhibitors (PIs) and allogenic and autologous stem cell transplantation (ASCT), all known to increase the risk of severe infections [7–13]. Moreover, the high average age of MM patients is accompanied by high comorbidity load [14], which further increases risk to infections.

MM patients have increased susceptibility to both bacterial and viral infections and the risk is highest during the first year post diagnosis. In a Swedish Real-World Evidence

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(RWE) study on 8672 MM patients and their 34 561 population-based controls, the overall increased risk for bacterial and viral infection in MM patients was 5- and 7-fold, and during the first year post diagnosis, 6- and 8-fold, respectively [6].

Elderly patients who often present with comorbidities are rarely eligible for clinical trials and thus the information on infection load and related outcomes typically require RWE based studies. Here, we utilized the Finnish nationwide healthcare registries to investigate the infection load, distribution, and infection types in 7070 MM patients and their 21,210 age-, sex-, and region-matched controls during 1997–2021. Furthermore, we studied the infection load and types in different patient groups, including patients who had received ASCT (including also patients with an allogenic transplant) vs. those who had not (nASCT), and also in different age categories (≥ and < 70 years old). Finally, with Cox proportional hazard models, we studied the effect of infections on the mortality in MM patients over time. This study provides important knowledge on the cumulative effects of infection load during the MM disease progression.

Materials and methods

The study included MM patients diagnosed between 2000 and 2021 in Finland and their age-, sex-, and region-matched controls at 1:3 ratio. This study utilized data from two main sources: the specialty care register (HILMO), which encompasses special healthcare records, and the primary care register (AVOHILMO). Specialty care diagnosis records served as the primary data source due to its availability for the entire study period 1997–2021 (including three years of baseline data for each patient), whereas primary care data was available only from 2011 and was thus utilized for result validation purposes only. In addition, death dates were acquired from digital and population data service agency (DVV) and treatment reimbursement data from Finnish Social Insurance Institution (SII) was used for cohort formation. The number of infections per patient year (PPY) was calculated by scaling the count of independent infection events by lived patient years, accounting for mortality and end of follow-up. Diagnoses were categorized based on unified diagnostic codes, excluding long-term diagnoses and consolidating events occurring within 30 days. See Supplementary table S1 for all the ICD-10 codes used in this study. For grouped analyses, infections were categorized by systematic and functional groups (Supplementary tables S2 and S3).

Stratified analyses were conducted based on age at diagnosis and ASCT status. The impact of infection load on survival was assessed by categorizing patients based on the number of infections in the year preceding diagnosis.

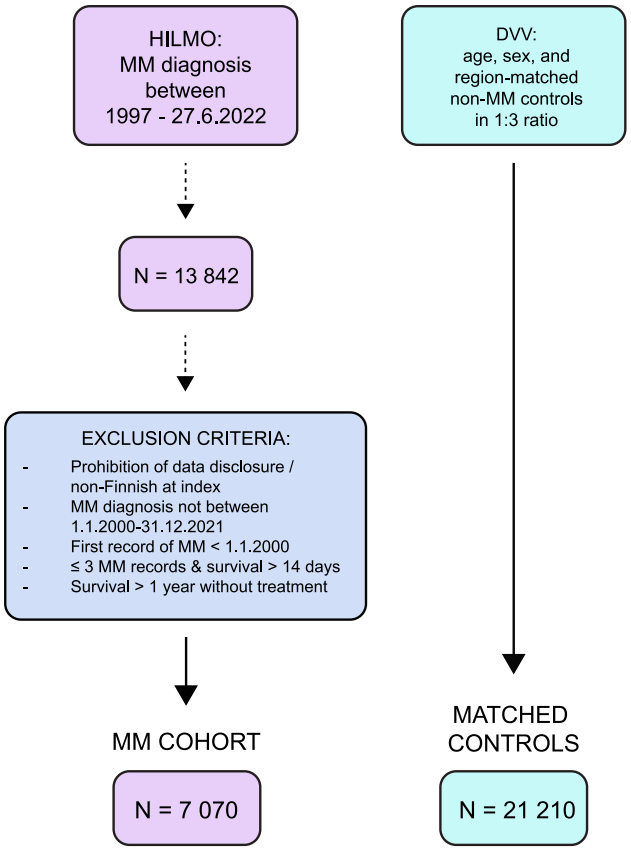

Fig. 1 Cohort formation: Multiple myeloma patients in Finland during 2000–2021. Abbreviations: DVV = Digital and Population Data Services agency; HILMO = specialty care register; MM = multiple myeloma

Cox proportional hazards models were employed to assess the impact of both the number of pre-diagnosis infections as well as cumulative number of infections during the follow-up on the overall survival (OS) among MM patients. The models were adjusted for relevant covariates and the cumulative number of infections was treated as a time-dependent variable to avoid survival bias. Controls were excluded from survival and proportional hazard analyses to focus solely on MM patient outcomes. Additionally, a Cox model was employed to assess the risk of infections among MM patients compared to controls, with relevant adjusting variables. Detailed methods are described in Supplementary information.

Results

Patient population

In total, 7070 MM patients diagnosed in Finland during 2000–2021 and their 21,210 age-, sex-, and region-matched

controls were included in the final cohort (Fig. 1). The cohort formation is described in detail in Supplementary information.

Infection load in MM patients in Finland during 1997–2021

First, we assessed the number of infections in MM patients in Finland. To this end, infection diagnoses recorded in the specialty care register were retrieved for 3 years prior to MM diagnosis and for the follow-up time of 2000–2021 (see Supplementary table S1 for the detailed ICD-10 code list used in the study). MM patients had a significantly higher number of infections per patient year (PPY) when compared to their age-, sex-, and region-matched controls (Figure 2a and Supplementary table S4). A notable increase in the number of infections PPY in MM patients was observed during the year before diagnosis, and in fact, the number of infections recorded in the 2–3 year period before diagnosis was significantly higher in MM patients when compared to the matched controls. The highest number of infections was recorded during the first year after diagnosis, after which, the infection load decreased to a steady, yet high level, for the rest of the follow-up. Based on a Cox model, the risk of having any infection during the follow-up was 6.9-fold for the MM patients when compared to the matched controls

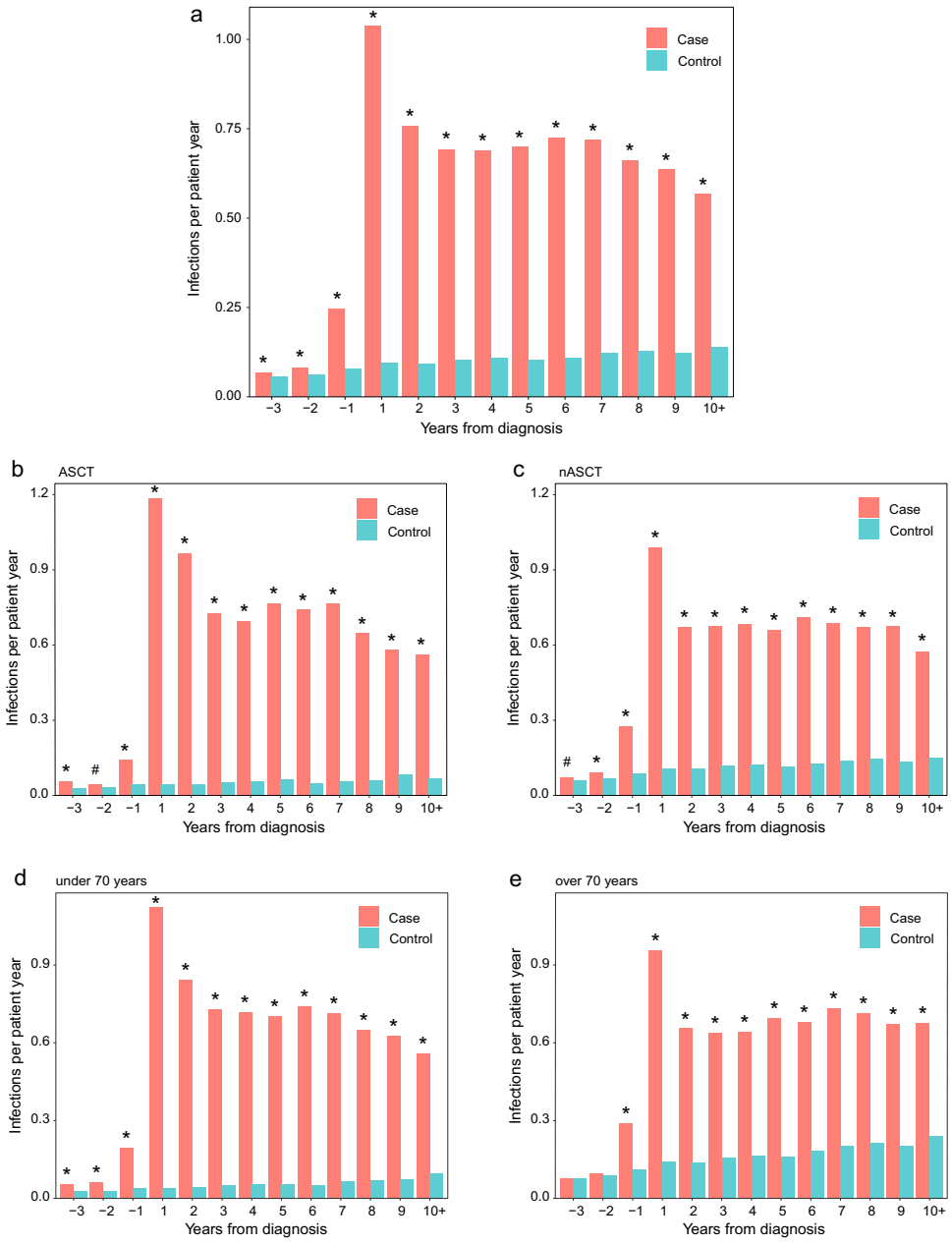

Fig. 2 Infection load in Finnish patients with multiple myeloma during 1997–2021. Infection load in **(a)** all MM patients, **(b)** ASCT, **(c)** nASCT, **(d)** under 70 years and **(b)** over 70 years old patients and their matched controls 3 years prior to diagnosis and throughout the follow-up period of 2000–2021. The presented data includes all specialty care diagnosis during 1997–2021 (see Supplementary table S1 for the ICD10-code used). An average of the follow-up years 10+ is presented. Statistical significance was calculated using Poisson regression. * $p < 0.001$, # $p < 0.05$

(hazard ratio (HR) 6.9, 95% CI: 6.6–7.1, $p < 0.001$). In age-stratified analysis, under 70-year-old patients had a 11.6-fold risk for any infection when compared to controls (HR 11.6, 95 % CI: 10.9–12.3, $p < 0.001$), whereas for over 70-year-old patients the risk was only 4.9-fold (HR 4.9, 95 % CI: 4.6–5.1, p<0.001). The proportional hazard assumptions were not fulfilled for all covariates and thus the HR is not constant over time, but the reported HR represents an average risk.

We next looked at the infection load in ASCT vs. nASCT patients. Prior to diagnosis, nASCT patients had a higher infection load compared to ASCT patients (Figures 2b and2c and Supplementary table S4). During the first two years after diagnosis, the number of infections PPY recorded in ASCT patients was higher than in nASCT patients. The number of infections recorded in both ASCT and nASCT patients during the years before diagnosis was significantly higher when compared to their matched controls.

We also looked at the infection load in different age groups. The infection load profiles of patients under and over 70 years old followed the same patterns as in ASCT and nASCT patients (Fig. 2d and e and Supplementary table S4), with post diagnosis patients under 70-year-old having more recorded infections PPY and on the other hand over 70-year-old patients having more infections prior to diagnosis. Importantly, while there was no significant difference in the infection load 2–3 years before diagnosis in patients over 70 years old when compared to their matched controls, patients under 70 years old had significantly more infections in all the 3 years before diagnosis (Fig. 2d and e and Supplementary table S4).

We also looked at the number and proportion of infections PPY recorded in MM patients and their matched controls in the primary versus specialty care. Similarly to specialty care, MM patients had significantly more infection diagnoses recorded in primary care during the 3 years prior to MM diagnosis (Supplementary Fig. S1a-b and Supplementary table S5). However, the amount and proportion of specialty care infection diagnoses increased substantially during the year leading to diagnosis (41.8% 2 years prior and 64.6 % during the year prior to MM diagnosis for cases and 46.0 % and 51.7 % for controls, respectively), whereas the proportion of primary care infection diagnoses decreased during the year after diagnosis (Supplementary Fig. S1a-b and Supplementary table S5). As the data from primary care was available only from 2011, and most infections are recorded in specialty care for MM patients, we focused mainly on the specialty care data for the remainder of the analyses.

Distribution of infections among MM patients

The majority (84.7 %) of patients had no specialty care recorded infections during the year before diagnosis (Table 1). However, the number of recorded infections was still significantly higher compared to the matched controls, of which 94.7 % had no recorded infections ($p < 0.001$ for 0 infections vs 1+ infections). Furthermore, the percentages of patients who had 1, 2 or 3 recorded infections were 9.5 %, 3.6 % and 1.5 %, respectively, while the corresponding percentages of the matched controls were 3.7 %, 0.9 % and 0.3 %. The infection load in MM patients during the first year after diagnosis was substantial: only 56.7 % patients had no recorded infections while 94 % of the matched controls had no infections (Table 1; $p< 0.001$ for 0 infections vs 1+ infections). During the first year after diagnosis the percentage of patients who had 1, 2 or 3 recorded infections was 21 %, 11 % and 5.6 %, respectively, while the corresponding percentages of the matched controls were 4.2 %, 1.1 % and 0.4 %. It is, however, important to note that there is a post diagnosis bias as some of the patients had died during the first year after diagnosis.

Patient characteristics in subgroups based on infection load

Next, we examined the patient characteristics in more detail based on the infection load. We formed subgroups of patients with 0, 1 and 2+ infections recorded the year before MM diagnosis, and the characteristics of these subgroups are presented in Table 2. Older age was found to be associated

Table 1 Number of infections in MM patients and controls one year before and one year after diagnosis

	1 year before diagnosis				1 year after diagnosis			
N infections	N case	N control	% case	% control	N case	N control	% case	% control
0	5986	20096	84.7	94.7	4010	19929	56.7	94.0
1	670	786	9.5	3.7	1487	899	21.0	4.2
2	258	201	3.6	0.9	775	228	11.0	1.1
3	105	73	1.5	0.3	396	95	5.6	0.4
4	26	34	0.4	0.2	212	38	3.0	0.2
5	13	10	0.2	0	95	14	1.3	0.1
6	10	6	0.1	0	47	<5	0.7	0
7+	<5	<5	0	0	48	<5	0.7	0

Table 2 Patient characteristics of 3 subgroups (0, 1, 2+ infections during 1 year prior to diagnosis)

		Overall (*N* = 7070)	0 (*N* = 5986)	1 (*N* = 670)	2+ (*N* = 414)	*p*
age (median [IQR]		71.17 [63.20, 78.25]	70.57 [62.91, 77.74]	73.53 [65.07, 80.15]	74.87 [65.92,81.47]	*<0.001*
follow up length (years, median [IQR])		2.57 [0.90, 5.32]	2.74 [1.00, 5.59]	1.74 [0.54, 4.06]	1.54 [0.46, 3.66]	*<0.001*
infections PPY during follow-up (median [IQR])		0.51 [0.00, 1.39]	0.48 [0.00, 1.33]	0.65 [0.00, 1.79]	0.90 [0.00, 2.31]	*<0.001*
sex (%)	Female	3415 (48.3)	2902 (48.5)	314 (46.9)	199 (48.1)	*0.727*
	Male	3655 (51.7)	3084 (51.5)	356 (53.1)	215 (51.9)	
mortality (%)	Alive at EOF	2254 (31.9)	1989 (33.2)	172 (25.7)	93 (22.5)	*<0.001*
	Dead at EOF	4816 (68.1)	3997 (66.8)	498 (74.3)	321 (77.5)	
CCI (%)	0	4306 (60.9)	3839 (64.1)	322 (48.1)	145 (35.0)	*<0.001*
	1–2	2113 (29.9)	1699 (28.4)	239 (35.7)	175 (42.3)	
	3+	651 (9.2)	448 (7.5)	109 (16.3)	94 (22.7)	
ASCT status (%)	ASCT	1514 (21.4)	1374 (23.0)	94 (14.0)	46 (11.1)	*<0.001*
	nASCT	5556 (78.6)	4612 (77.0)	576 (86.0)	368 (88.9)	
diagnosis year (%)	2000–2004	1156 (16.4)	1021 (17.1)	89 (13.3)	46 (11.1)	*0.001*
	2005–2010	1746 (24.7)	1499 (25.0)	152 (22.7)	95 (22.9)	
	2011–2016	2129 (30.1)	1773 (29.6)	220 (32.8)	136 (32.9)	
	2017–2021	2039 (28.8)	1693 (28.3)	209 (31.2)	137 (33.1)	

ASCT = allogenic or autologous stem cell transplantation; *CCI* = Charlson comorbidity index; *EOF* = end of follow-up; *IQR* = interquartile range; *PPY* = per patient year. The differences between groups were tested using Chi-squared for categorical variables and Kruskal-Wallis Rank-Sum test for continuous variables.

with a higher number of infections, shorter follow-up time and increased mortality. We looked at the median number of infections PPY (scaled to the time lived) during the follow-up period and found that higher infection load at baseline reflected higher number of infections also later during the follow-up. However, the distribution of cumulative infections was highly skewed, meaning that the infections accumulate on a small group of patients, while most have few or no infections at all. It is important to note that these subgroups differ demographically from each other significantly (including age and Charlson comorbidity index, CCI) and cannot thus be directly compared.

When looking at the number of infections recorded at different time periods, we found that during recent years (2017–2021) there has been a small increase in the number of patients with high number of infections recorded (137 out of 2039 patients (6.7 %) diagnosed in 2017–2021 vs. 46 out of 1156 patients (4.0%) diagnosed in 2000–2004 had 2+ baseline infections).

Infection types in MM patients

We found that among Finnish MM patients diagnosed during 2000–2021, most of the recorded infections were bacterial (68.3 % in MM patients and 75.8 % in matched controls, Figure 3a-b and Table 3). The proportion of bacterial vs. viral infections changed during the study period. Two years prior to diagnosis, MM patients had a similar proportion of bacterial and viral infections when compared to their matched controls (70.8 % and 25 % in patients and 70.5 % and 26 % in matched controls, respectively), however, during the year before diagnosis, the proportion of bacterial infections increased to 80.1 % in MM patients (Figure 3a and Table 3). During the following years, MM patients had proportionally more viral infections when compared to their matched controls (Table 3).

To get an insight of the spectrum of infections in MM patients, we next divided the infections into 10 subgroups (functional grouping): pneumonia, sepsis, upper-, and lower respiratory track, urinary track, gastrointestinal track, skin, cytomegalovirus infections (CMV), undefined bacterial infections, and other infections. Notably, the proportion of pneumonia, sepsis, and undefined bacterial infection diagnoses increased substantially in MM patients during the year before diagnosis (Fig. 4 and Table 4). After diagnosis, especially the proportion of undefined bacterial infections increased in MM patients. In later follow-up years, upper respiratory tract and undefined bacterial infections were relatively more common in MM patients when compared to years before diagnosis, and also to matched controls.

We also looked at the infection load recorded in the primary care both by systematic and functional grouping. Compared to secondary care infection recordings where bacterial infections formed the highest proportion of all infections recorded throughout the follow-up period, an almost equal proportion of bacterial and viral infections were recorded in

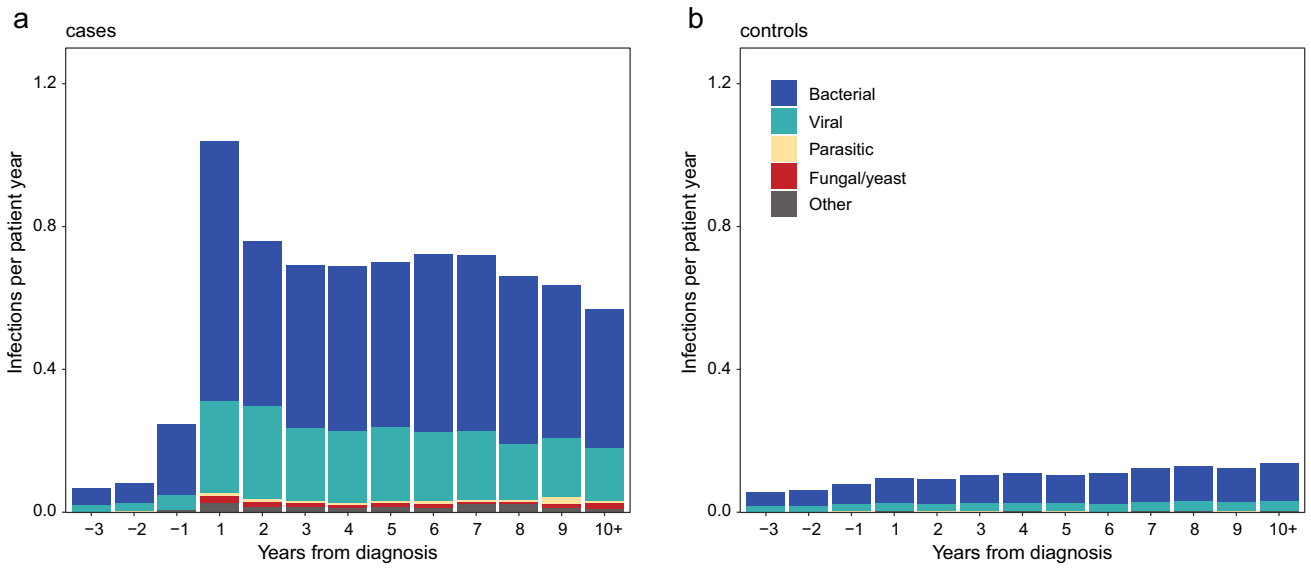

Fig. 3 Bacterial, viral and fungal/yeast and parasitic infection load in MM patients and their matched controlsin Finland during 1997–2021. Bacterial, viral, fungal/yeast and parasitic infection load in (**a**) MM patients and (**b**) their matched controls 3 years prior to diagnosis and throughout the follow-up period of 2000–2021. The presented data includes all specialty care diagnoses (see Supplementary tableS2 for systematic groupings of the ICD10-codes). An average of the follow-up years 10+ is presented.

Table 3 Yearly percentages of bacterial, viral and fungal/yeast and parasitic infections of all recorded infections in MM patients and their matched controls

Patient type	Infection type	total %*
case	Bacterial	68.3
case	Viral	27
case	Fungal/yeast	1.7
case	Parasitic	0.9
case	Other	2.1
control	Bacterial	75.8
control	Viral	20.8
control	Fungal/yeast	1.5
control	Parasitic	0.3
control	Other	1.5

Patient type	Infection type	Year from diagnosis*												
		-3	-2	-1	1	2	3	4	5	6	7	8	9	10+
case	Bacterial	71.3	70.8	80.1	70	61.1	66	66.9	66	69.1	68.6	71	67.3	68.6
case	Viral	25.8	25	16.8	24.8	34	29.4	29.2	29.2	26.7	26.6	23.6	25.8	26
case	Fungal/yeast	1.3	1.4	0.6	1.9	1.8	1.8	1.4	1.7	1.6	1	0.8	1.9	3.4
case	Parasitic	0.2	0.3	0.4	0.9	1.1	0.7	0.8	1	1.1	0.7	1.2	3.3	0.6
case	Other	1.5	2.4	2.1	2.5	2	2.1	1.7	2	1.6	3.1	3.4	1.7	1.4
control	Bacterial	68.7	70.5	72.4	74.9	76.7	76.4	75.9	77.1	79.1	76.4	76.8	77.7	77.9
control	Viral	26.3	26	23.9	21.1	19.7	20.4	20.6	19.3	18.5	20.2	20.2	19.7	19.2
control	Fungal/yeast	2.7	1.9	1.8	1.9	1.7	1.1	1.6	1.2	1.3	1.6	1.2	1.1	1.4
control	Parasitic	0.6	0.1	0.2	0.3	0.1	0.2	0.4	0.8	0.3	0.3	0.4	0.5	0.3
control	Other	1.7	1.5	1.7	1.8	1.8	1.9	1.6	1.7	0.8	1.5	1.4	1	1.2

*In total percentages, the color scale represents the total percentage scale, whereas in the yearly table, the color scales highlight row-wise changes in percentages

primary care both in MM patients and their matched controls (Supplementary Fig.S2a-b and Supplementary Table S6). A small increase in the proportion of urinary tract infection and pneumonia diagnoses was detected in MM patients during the year before diagnosis (Supplementary Fig. S2c-d and Supplementary table S7). Pneumonia diagnoses in primary

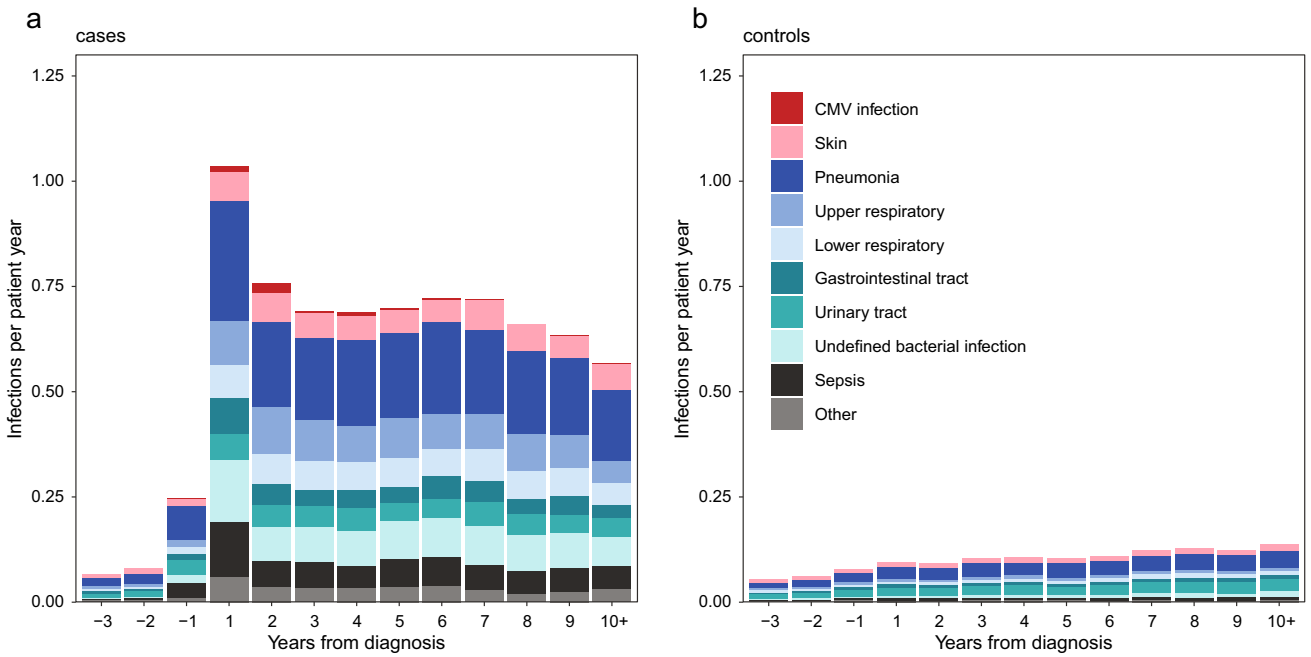

Fig. 4 Infection load by infection type (functional grouping) in MM patients and their matched controls in Finland during 1997–2021. Infection load by infection type (functional grouping) in **(a)** MM patients and **(b)** matched controls 3 years prior to diagnosis and throughout the follow-up period of 2000–2021. The presented data includes all specialty care diagnosis (see Supplementary table S3 for functional groupings of the ICD10-codes). An average of the follow-up years 10+ is presented.

Table 4 Yearly percentages of the infection types (functional grouping) in MM patients and their matched controls of all recorded infections

Patient type	Infection type	Year from diagnosis*												
		-3	-2	-1	1	2	3	4	5	6	7	8	9	10+
case	CMV infection	0	0.2	0.3	1.5	3.1	1	1.2	0.9	0.6	0.2	0	0.4	0.2
case	Gastrointestinal tract	9.5	6.5	6.7	8.4	7.1	5.8	6.3	5.6	7.8	7.1	5.5	7.1	5.7
case	Lower respiratory	7.6	8.8	6.9	7.4	9.3	9.7	10	10	8.8	10.8	10	10.9	9.1
case	Other	6.5	7.7	4.7	5.8	4.7	5	4.9	5.1	5.4	4.2	3.2	3.8	5.7
case	Pneumonia	29.4	28.8	33.7	27.5	26.9	28.2	29.9	28.8	30.6	28.2	30	28.8	29.9
case	Sepsis	6.3	5.3	14	12.7	8.3	8.9	7.8	9.7	9.6	8.2	8	9.2	9.4
case	Skin	13.9	16.8	6	6.6	8.8	8.4	8.1	7.6	7.2	9.6	9.5	8.1	10.9
case	Undefined bacterial infection	4.2	3.3	8.1	14.1	10.5	12	11.9	12.6	12.6	12.8	13.1	12.9	12.1
case	Upper respiratory	9.9	7.2	5.9	10	14.7	14	12.2	13.4	11.3	11.2	13.2	12.1	9.1
case	Urinary tract	12.8	15.4	13.8	5.9	6.6	6.9	7.7	6.1	6.1	7.6	7.4	6.7	7.8
control	CMV infection	0	0.1	0.1	0.1	0.1	0.1	0	0,1	0	0	0	0.1	0.1
control	Gastrointestinal tract	9.2	10.3	9.3	10.2	9.6	8.4	8	8.3	8.3	7.3	8.1	8.4	7.1
control	Lower respiratory	10.7	8.5	8.5	6.9	6.9	8	7.2	7	7.4	9	9.7	7.9	7.6
control	Other	7.6	6.5	6.8	5.1	4.8	4.9	5.2	4.4	3.5	4.3	3.4	3.4	3.7
control	Pneumonia	24.9	27.5	27.4	29.9	30.6	32.5	29.4	34.1	32.1	28.9	30.1	31.2	29.8
control	Sepsis	3.1	4.4	5.3	5.2	5.9	5.8	5.4	6	5.4	5.9	5.8	5.9	6.6
control	Skin	15.1	12.9	11.4	11.7	11.9	9.7	12	9.7	10.6	10.1	9.8	9.1	10.9
control	Undefined bacterial infection	5.1	4.8	6.1	6.4	7	6.5	6.1	7	6.1	9.1	9.5	7.4	9
control	Upper respiratory	6.7	6.6	6.6	5.6	5	4.6	6.8	6.6	5.3	5.6	4.9	4.7	5
control	Urinary tract	17.7	18.3	18.6	18.9	18.2	19.5	19.9	17	21.3	19.9	18.7	22	20.3

* The color scales highlight row-wise changes in percentages

care remained at a higher level in MM patients throughout the follow-up period when compared to their matched controls (Supplementary Fig. S2c-d and Supplementary table S7).

Streptococcus infections increase in MM patients during the year before MM diagnosis

Next, we looked at the specific infection diagnoses (ICD-10 codes) in MM patients. During the 3 years before diagnosis, the relative risk of streptococcal septicaemia and pneumonia due to *Streptococcus pneumoniae* increased the most when compared to the matched controls, and this increase was especially prominent during the year before diagnosis (Table 5. and Supplementary tableS8). During the year after diagnosis, the overall infection load increased, with cytomegaloviral disease, Herpes simplex, acute maxillary sinusitis, influenza, and streptococcal septicaemia showing most relative increase (Table 6.). During rest of the follow-up, cytomegaloviral disease, acute maxillary sinusitis, streptococcal septicaemia and herpes infections were the most increased infection diagnoses in MM patients when compared to their matched controls (Supplementary table S9).

ASCT patients have more viral infections during the year after diagnosis

We also looked at the infection types in ASCT (*N*=1514, median age 61.4 years, 53.8% male) vs. nASCT (*N*=5556, median age 74.3 years, 51.1% male) patients (Supplementary Table 10), and in different age groups (under 70 years old: *N*=3264, median age 62.5 years, 55.3 % male; over 70 years old: *N*=3806, median age 77.7 years, 48.6 % male) (Supplementary Table 11). During the first two years after diagnosis, ASCT patients had a notable increase in the relative amount of viral infections when compared to nASCT patients (Supplementary Fig. S3 and Supplementary table S12). A similar trend was observed in different age groups with patients under 70 years old patients having more viral infections after diagnosis when compared to patients over 70 years old (Supplementary Fig. S4 and Supplementary Table S13). After diagnosis, ASCT patients had

Table 5 Top 20 infection diagnoses (ICD-10 codes) in MM patients and matched controls during one year before MM diagnosis (baseline). The percentual difference between cases and controls is demonstrated by the difference between number of infections PPY scaled by their sum

ICD-10	Description	N case	N control	infections PPY case	infections PPY control	Diff. case vs. control
J189	Pneumonia, unspecified	406	341	0.05743	0.01608	0.56
A41	Other septicaemia	163	76	0.02306	0.00358	0.73
N10	Acute tubulo-interstitial nephritis	140	169	0.01980	0.00797	0.43
A49	Bacterial infection of unspecified site	138	100	0.01952	0.00471	0.61
J159	Bacterial pneumonia, unspecified	102	85	0.01443	0.00401	0.57
N30	Cystitis	100	138	0.01414	0.00651	0.37
A40	Streptococcal septicaemia	77	11	0.01089	0.00052	0.91
A09	Diarrhoea and gastroenteritis of presumed infectious origin	63	98	0.00891	0.00462	0.32
A46	Erysipelas	62	129	0.00877	0.00608	0.18
J209	Acute bronchitis, unspecified	49	64	0.00693	0.00302	0.39
J069	Acute upper respiratory infection, unspecified	45	71	0.00636	0.00335	0.31
A04	Other bacterial intestinal infections	39	38	0.00552	0.00179	0.51
J010	Acute maxillary sinusitis	26	21	0.00368	0.00099	0.58
J13	Pneumonia due to Streptococcus pneumoniae	26	<5	0.00368	0.00014	0.93
B02	Zoster [herpes zoster]	23	25	0.00325	0.00118	0.47
B99	Other and unspecified infectious diseases	22	9	0.00311	0.00042	0.76
J181	Lobar pneumonia, unspecified	18	6	0.00255	0.00028	0.80
J22	Unspecified acute lower respiratory infection	15	11	0.00212	0.00052	0.61
B00	Herpesviral [herpes simplex] infections	12	6	0.00170	0.00028	0.71
J09	Influenza due to identified zoonotic or pandemic influenza virus	11	21	0.00156	0.00099	0.22

*The color scales for the infections PPY illustrate the magnitudes of the infection loads, while the color scale for the difference (case vs. control) illustrates the size of difference (green=similar, red=different) between cases and controls.

Table 6 Top 20 infection diagnoses (ICD-10 codes) in MM patients and matched controls during the first year after diagnosis. The percentual difference between cases and controls is demonstrated by the difference between number of infections PPY scaled by their sum

ICD10	Description	N case	N control	infections PPY case	infections PPY control	Diff. case vs. control
J189	Pneumonia, unspecified	1200	451	0.20079	0.02228	0.80
A49	Bacterial infection of unspecified site	873	122	0.14607	0.00603	0.92
A41	Other septicaemia	663	87	0.11094	0.00430	0.93
J069	Acute upper respiratory infection, unspecified	337	60	0.05639	0.00296	0.90
J159	Bacterial pneumonia, unspecified	310	89	0.05187	0.00440	0.84
A09	Diarrhoea and gastroenteritis of presumed infectious origin	266	122	0.04451	0.00603	0.76
N10	Acute tubulo-interstitial nephritis	229	199	0.03832	0.00983	0.59
A04	Other bacterial intestinal infections	220	50	0.03681	0.00247	0.87
J010	Acute maxillary sinusitis	205	16	0.03430	0.00079	0.95
J209	Acute bronchitis, unspecified	182	76	0.03045	0.00375	0.78
B02	Zoster [herpes zoster]	159	21	0.02660	0.00104	0.92
A46	Erysipelas	141	165	0.02359	0.00815	0.49
N30	Cystitis	136	162	0.02276	0.00800	0.48
A40	Streptococcal septicaemia	114	12	0.01907	0.00059	0.94
B99	Other and unspecified infectious diseases	94	14	0.01573	0.00069	0.92
B25	Cytomegaloviral disease	90	<5	0.01506	0.00005	0.99
B37	Candidiasis	83	13	0.01389	0.00064	0.91
B00	Herpesviral [herpes simplex] infections	76	7	0.01272	0.00035	0.95
J09	Influenza due to identified zoonotic or pandemic influenza virus	67	7	0.01121	0.00035	0.94
B34	Viral infection of unspecified site	56	7	0.00937	0.00035	0.93

* The color scales for the infections PPY illustrate the magnitudes of the infection loads, while the color scale for the difference (case vs. control) illustrates the size of difference (green=similar, red=different) between cases and controls.

relatively more CMV infections when compared to nASCT patients, whereas nASCT patients had relatively more pneumonia when compared to ASCT patients (Supplementary Fig. S5 and Supplementary Table S14). A similar trend was observed in patients under and over 70 years of age (Supplementary Fig. S6 and Supplementary Table S15).

Risk factors of survival

To examine the effect of infection load on the survival of MM patients in Finland during 2000–2021, we first looked at the OS of MM patients in three different subgroups based on the infection load (0, 1, 2+ infections) during the year before to diagnosis. Intriguingly, having just one recorded infection during the year before diagnosis was associated with significantly shorter median OS (mOS) of 2.3 years (27.4 months) compared to 3.9 years (46.6. months) in patients with no recorded infections (Fig. 5).

Finally, we used a Cox proportional hazard model to study if any underlying factors between the subgroups, including age and comorbidities (CCI), would have a significant impact on the risk of survival. Interestingly, the model showed that recorded infections before MM diagnosis increase the independent risk of mortality. Having just one recorded infection during the year before diagnosis decreased OS significantly, even when adjusted for age, sex and the year of diagnosis (Fig. 6). In addition, the model showed that male patients have higher risk of mortality, and that the mortality decreases with later diagnosis year. The proportional hazard assumptions were not fulfilled for CCI and the number of infections on the previous year, as there was a slight increase in the HR over time for both covariates, but the reported HRs represent average risk over the follow-up time (Supplementary Fig. S7).

We also modeled the effect of cumulative infections on patient survival during the follow-up period (Fig. 7). Age, sex, CCI and diagnosis year were included in the model for

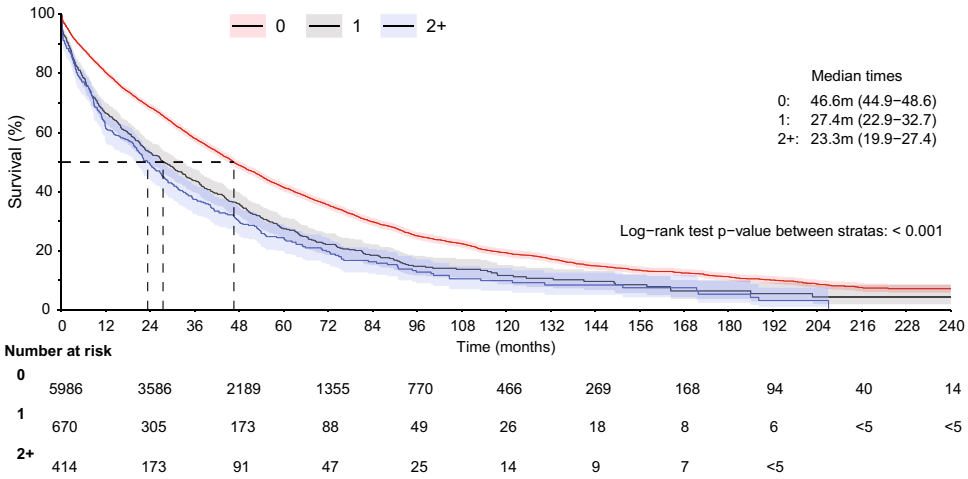

Fig. 5 The overall survival of MM patients with 0, 1 or 2+ recorded infections during the year before diagnosis

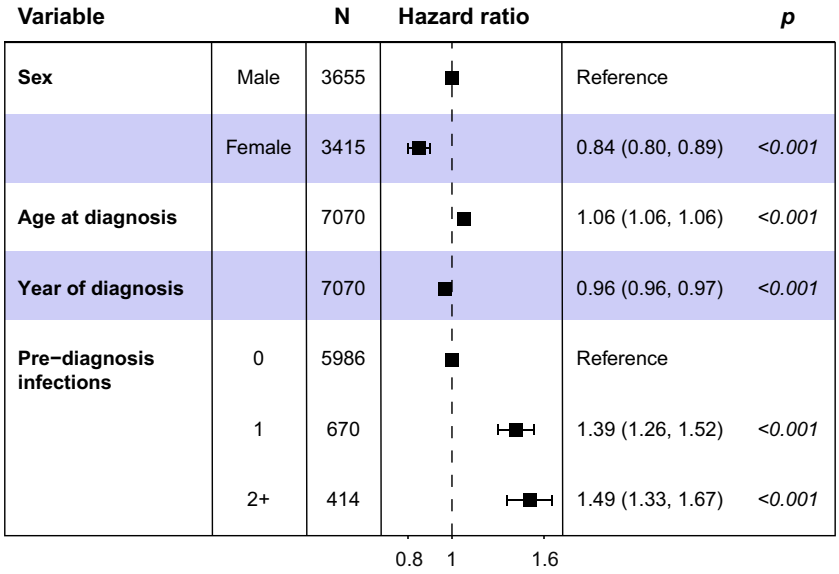

Fig. 6 Cox proportional hazards risk estimates for overall survival of the MM patients in Finland during 2000–2021

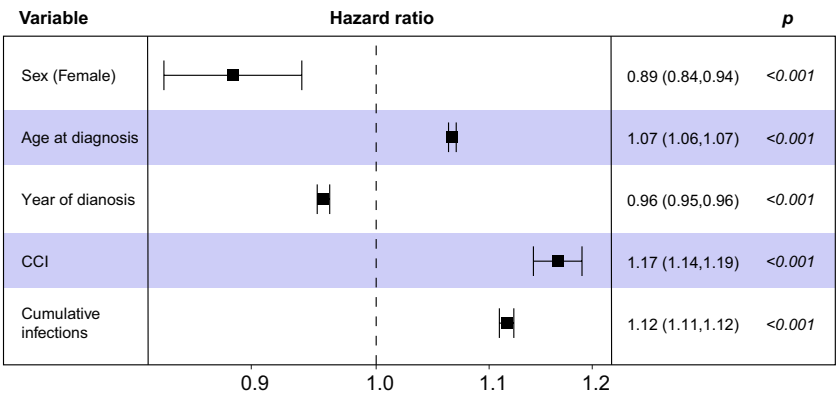

Fig. 7 Cox proportional hazards risk estimates for the cumulative effect of infections on overall survival of the MM patients in Finland during 2000–2021

adjustment and the cumulative number of infections was treated as a time-dependent variable. The HR for cumulative infections represents the independent risk of mortality that a single infection adds for the patient. The follow-up time was limited to 10 years, and events after that were censored, to better satisfy the proportional hazard assumptions. Interestingly, the risk of mortality increased 1.12-fold for each new infection ($p < 0.001$). The proportional hazard

assumptions were not fulfilled for age, CCI, and cumulative number of infections, but the reported HRs represent average risk over time.

Discussion

In this RWE study, we dissected the infection risk in different MM patient cohorts and show that having at least one recorded infection before MM diagnosis was associated with significantly shorter mOS, and that infections are associated with increased independent risk of mortality in MM patients. Moreover, patients under 70 years old had significantly more recorded infections already 3 years before MM diagnosis when compared to their matched controls, while for patients over 70 years old the difference was not statistically significant. In addition, and in line with a previous study [10], a change in the infection spectrum during the progression of the disease was observed. Of the most common infections, pneumonia, septic, and undefined bacterial infection diagnoses showed most relative increase before MM diagnosis, and cytomegaloviral disease, Herpes zoster, maxillary sinusitis and streptococcal septicemia the year after diagnosis.

MM patients have been reported to have an increased risk of both bacterial and viral infections [5, 6, 15]. Moreover, the spectrum of infections has been suggested to change during the MM disease progression [10] and patients with MM are known to be susceptible to certain infection types, including pneumonia, septicemia, meningitis, herpes zoster and influenza [5]. Here, we found that the relative risk of streptococcal septicaemia and pneumonia due to *Streptococcus pneumoniae* increased the most during the 3 years before diagnosis. We also found that the infection load was highest during the first year after MM diagnosis and ASCT patients have higher infection load than patients treated without ASCT. In concordance with previous Swedish RWE studies [5, 6], a 6.9-fold risk of developing any infection during the follow-up time was found in MM patients when compared to their matched controls.

In addition to factors related to individual's own risk, including the high average age of MM patients, the risk of infection depends on the disease stage and treatment. The early increase in the risk of infection is caused by the global suppression of uninvolved polyclonal immunoglobulins (immunoparesis) including dysfunction of B cells, disruption of the global T cell diversity and changes in the functionality of dendritic and natural killer cells [16]. During the later stages, the risk of infection depends also on the choice and course of the treatment. For example, especially new immunological treatments cause hypogammaglobulinemia and neutropenia, a decrease in CD4 cell count is known to be associated with increasing cycles of chemotherapy, proteasome inhibitor bortezomib depletes T cells and impairs viral antigen presentation and glucocorticoids can increase the risk of opportunistic infections [16, 17]. ASCT patients have higher risk of infection and complications both due to neutropenia and mucositis during transplant, and then due to the slow recovery of T cells after transplant [10, 18]. The advances in MM treatment have improved the treatment outcomes but at the same time resulted in cumulative immunosuppression and higher risk of infection [10].

Infections are known to cause significant morbidity and mortality in MM patients [4]. Here we show that having just one recorded infection before diagnosis was associated with decreased mOS and increased the independent risk of mortality in MM patients. Moreover, our model of the cumulative effect on patient survival showed that the risk of mortality increased 1.12-fold with every new infection. Thus, preventing infections is crucial for MM patients. There are international recommendations for infection prophylaxis in MM patients including vaccinations, prophylactic antimicrobial treatment, and immunoglobulin replacement in selected patients [16], which are also applied in Finland, but further studies are required to investigate novel vaccination strategies and the optimal use of antimicrobial prophylaxis.

Study limitations

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 was incomplete during the beginning of this data extraction and the recording practices on infection diagnoses might have changed during the study period. Due to changes in the diagnostic criteria for MM in 2014 [19], it is possible that some individual cases of smoldering multiple myeloma (SMM) patients diagnosed before 2014 are included in the MM cohort. Only specialty care (HILMO) data was used for outcome analyses because the primary care (AVOHILMO) data was available only from 2011 onwards and thus infections recorded only in primary care are not included. Due to the nature of record-based real-world data (RWD), some infection diagnoses may be counted multiple times, if the same disease has been recorded with multiple diagnosis codes or the diagnosis has changed over time. The improving recording practices during the study period may add to the observed increase in the infection rates over time. Although the COVID-19 -pandemic started during the study period, ICD10-codes for COVID-19 were not included in the infection code lists used in this study. Due to the lack of data on hospital-administrated medications, the therapy profiles of the study cohort and the possible effects of changes in treatment practices could not be analyzed within this study.

Conclusions

We report a significantly higher infection load in MM patients during the 3 years, and especially during the year before diagnosis. The relative risk of streptococcal septicaemia and pneumonia due to *Streptococcus pneumoniae* increased the most in MM patients before diagnosis when compared to their matched controls. Most importantly, having just one recorded infection during the year before diagnosis was associated with significantly reduced mOS and increased the independent risk of mortality in MM patients.

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Author contributions AA, EH, KK, IT, TM, MIL, RS, AP, and MP contributed to the study design and objectives, interpretation of results and revising the manuscript. AA and EH 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. RS, AP, 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 The original data were obtained from the national registries: Finnish Care Register for Health Care (primary care, AVOHILMO and specialty care, HILMO), Digital and Population Data Services Agency (DVV) and Finnish Social Insurance Institution (SII). Data can be acquired with data permission by following the guidance and application process by the registries. All authors had access to the pseudonymized aggregate data, whereas pseudonymized single-level registry data were available only to the authors who analyzed the data. Only the personnel of the registries had full access to the patient data. The single-level data cannot be shared. Only the registry holders can grant rights to third parties to use the data in accordance with the Act on Secondary Use of Health and Social Data.

Declarations

Competing interests AA, EH, KK, IT, and MIL are employees of Medaffcon Oy. TM was an employee of Takeda Finland and Medaffcon Oy. RS has received research funding, administered by Hospital Science Centers, from Amgen, BMS, Celgene, Janssen-Cilag and Takeda and honoraria from the same companies (Advisory Board and presentations).AP reports honoraria from Behring and Abbvie and has participated in Scientific Advisory Board meetings organized by Abbvie, Janssen-Cilag, Novartis, Pfizer and Takeda. MP has received honoraria from Amgen, Celgene, Janssen-Cilag and Takeda (Advisory Board and presentations).

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.

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