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Risk of infections in multiple myeloma. A population-based study on 8672 multiple myeloma patients diagnosed 2008-2021 from the Swedish Myeloma Registry

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Authors' contribution

CB designed the trial, sought the ethical approval, wrote the project plan and participated in analyzing data and wrote the manuscript. IS and GL analyzed the data, made the figures and the table. CD, MV, IT, GJ, SE, KC and MK participated in designing the trial and participated in analyzing data. All authors have critically reviewed, edited and approved the manuscript.

Disclosures

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ABSTRACT

In multiple myeloma (MM), advancements in treatments and toxicity management have enhanced survival rates. This, coupled with shifting age demographics in MM, necessitates an updated understanding of infection risks in MM patients compared to the general population. Using Swedish population-based registries, we investigated the incidence of infections in 8,672 Swedish symptomatic MM patients diagnosed 2008-2021 and 34,561 matched controls. Overall, MM patients had a 5-fold risk (hazard ratio (HR) = 5.30; 95%, Confidence Interval = CI 5.14-5.47) of developing any clinically significant infection compared to matched controls. Bacterial infections represented a 5-fold (HR 4.88; CI 4.70-5.07) increased risk, viral and fungal infections 7-fold compared to controls. The 1st year after MM diagnosis the risk of infections compared to controls was 7 –fold (HR 6.95; CI 6.61-7.30) and remained elevated up to 5 years after the myeloma diagnosis. The risk of infection compared to controls remained 5-fold in MM patients with follow-up till 2022. Preceding MM diagnosis, the risk compared to matched controls was significantly increased up to four years before MM diagnosis (HR1.16; CI 1.05-1.28). Among MM patients, 8% had died within 2 months of diagnosis and infection contributed to 32% of all deaths. After 1 year, 20% MM patients had died, and infection-related mortality was 27%.

Our data constitute the largest population-based study to date on the risk of infections compared to the normal population in the era of modern MM therapies and confirms that infections still represent a major threat to patients and underscores importance of preventive strategies.

INTRODUCTION

In multiple myeloma (MM), new treatments and improved management of toxicities have contributed to improved survival and transformed MM into a chronic disease [1, 2]. Managing the complications of the disease and its treatment, such as infections, thrombosis and neuropathy, has therefore become an important clinical issue.

Infections are a significant cause of morbidity and a leading cause of death in patients with MM [3]. In studies mainly from the chemotherapy era, infections contribute to an early death in 14-45% of patients [4, 5]. In a nationwide study of over 9,000 Swedish MM patients from the Swedish Cancer Register diagnosed from 1988 to 2004, in patients mostly treated with chemotherapy, cortisone and thalidomide, the risk of infection was seven-fold in MM patients compared to an age-matched healthy population, and the infection-related mortality was 22% the first year after diagnosis[6].

In the last 20 years, the treatment of MM has changed substantially towards immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies (MoAbs) as backbones in MM therapy and this has created a need for an update on basic facts to both evaluate and inform on the current risk of infections in MM.

We therefore performed a large population-based study on the incidence of infections overall and of specific infections among Swedish symptomatic MM patients diagnosed from 2008 to 2021 compared to matched controls. We also studied the risk of infection over time and the infection-related mortality.

METHODS

Patients and controls

All symptomatic MM patients from the Swedish Myeloma Registry (SMR), diagnosed from 2008 to 2021 were included in the study. The SMR contains patient characteristics at diagnosis and 1st line treatment with a coverage of > 95%, compared to the Swedish Cancer

Register[7]. The treatment strategies in Sweden in the current study period have been reported elsewhere[8]. In short, PIs and (IMiDs) were introduced after 2005 and monoclonal antibodies (MoABs) in 2020. Immunotherapies, such as bispecific antibodies and CAR T-cell therapy, were not reimbursed in the study period, so the number of patients treated with immunotherapy is considered negligible. For each MM patient, four population-based controls matched by sex, year of birth, and county of residence were chosen randomly from the Swedish Total Population Register (TPR). The control subjects had to be alive and without preceding hematologic malignancy at the date of diagnosis of the corresponding MM patient. From the Swedish Patient Register, which captures information on discharge diagnosis from inpatient and outpatient care with high coverage and accuracy[9], we obtained information on infections using the International Classification of Diseases (ICD-10), from five years before the MM diagnosis to the end of follow up which was 31st of December 2022 or time of death/emigration. Events were defined as the diagnosis of any specific infectious disorder leading to a hospital visit. Each infectious episode had to have occurred at different time points and at least one month apart. For COVID-19 this interval was set to three months, as prolonged viral replication is common in immunosuppressed patients. Furthermore, the cause of death registry was used to identify causes of death among patients and controls. As a sensitivity analysis, the prescription of antibiotics from the Swedish Prescribed Drug Register [10] was used as proxy for the incidence of infections in patients and controls. Data on comorbidities at time of diagnosis were retrieved from the Swedish Patient Register and the Swedish Cancer Register. To construct Charlson Comorbidity Index from register based data, the categories and weights proposed by the Royal College of Surgeons were used [11], including diagnoses registered within five years preceding myeloma diagnosis. Using the nationwide Cause of Death Register [12], we obtained information on date and cause of death for all

subjects who had died up to 31st of December 2022. Approval was obtained from the Swedish Ethical Review Board for this study (2020-01729 and 2021-06236-02).

Statistical analysis

Characteristics of patients and controls are presented as total number (n) and proportion (%). Patients were stratified into three calendar periods: 2008-2012, 2013-2017 and 2018- 2021, reflecting time periods with different treatment strategies, and both patients and controls were stratified by age. The absolute risk of infections was calculated and a multi-state Cox proportional hazard model with infection as a time dependent co-variate was used to estimate the overall, 1-and 5-year risk of infections, and the risk of infection before the MM diagnosis compared to controls. In addition, the effect of sex, age and calendar period of diagnosis, autologous stem cell transplantation (ASCT) and comorbidity, represented by the Charlson comorbidity score, were evaluated. All models were adjusted for sex, age and year of diagnosis. Hazard-ratios (HR) with 95% confidence intervals were calculated. Cumulative incidence was estimated with the Kaplan Meier method. Using the Cause of Death Register, we estimated the proportion of patients and controls that died from infection. Furthermore, the proportion of individuals in the study that died within 90 days of a confirmed infection was calculated and defined as all-cause mortality. To evaluate the risk of infection-related death, competing risk was calculated. In these analyses the censoring events were emigration or the end of follow-up. The competing events were defined as death from infection and death from other causes**.** In a sensitivity analysis, the accuracy of the Patient Register was evaluated using the Prescription Drug Register, and every antibiotic/antiviral/antifungal prescription before the diagnosis of MM was counted as a separate infection. The same method was applied for infections after MM diagnosis, but excluding antibiotics/antivirals/antifungals commonly used as prophylaxis.

RESULTS

In total, 8,672 multiple myeloma patients with symptomatic disease, diagnosed between 2008 and 2021 were identified from the Swedish Myeloma registry and 34,561 population-based controls were included in the analyses. Characteristics of patients and controls are shown in Table 1. The majority of patients (60 %) were 70 years or older at diagnosis, 57% were male, and 26% treated with up-front autologous stem cell transplantation (ASCT). In 12% of the MM patients a previous diagnosis of MGUS (monoclonal gammopathy of undetermined significance) was reported. A progression to MM from smoldering multiple myeloma (SMM) or plasmacytoma was reported in 8.4% and 2.3%, respectively. In the different calendar periods of 2008-2012, 2013-2017 and 2018-2021, the proportion of patients receiving an IMiD, PI or MoAb as a part of 1st line treatment was 68%, 90%, and 97%, respectively. The median time of follow-up for patients was 3.1 years, and for controls 5.7 (range 0-15).

Incidence and risk of infections

The absolute risk of a clinically significant infection in our study was 70% in patients compared to 32% for controls in the studied period. The absolute risk of pneumonia and sepsis stand out as the most frequent events, seen in 18% and 20% of MM patients respectively, in the course of their disease, as compared to age-matched controls where it was seen in 4 %, for both pneumonia and sepsis (Table S1 in Supplements). Analyzing the risk of infections preceding MM diagnosis, the increased risk compared to matched controls was significant from 3 months before (HR 1.21; CI 1.16-1.26), to four years before MM diagnosis (HR 1.16; CI 1.05-1.28) (Figure 2, panel A). Analyzing the risk of infection in only MM patients with previous MGUS (n=1,048) or SMM (n=729), we saw a highly elevated risk compared to controls in the 12 months preceding MM diagnosis (Figure 2, panels B and C).

Overall, patients with symptomatic MM had a 5-fold risk (HR 5.30; CI 5.14-5.47) of

developing a clinically significant infection compared to matched controls. Bacterial infections represented a 5-fold (HR 4.88; 4.70-5.07) increased risk, viral (HR 6.84; 6.46-7.26) and fungal infections a 7-fold risk (HR 6.77; 6.13-7.47) compared to controls. More specifically, MM patients had an increased risk of the following bacterial infections compared to controls: meningitis, septicemia, pneumonia, endocarditis, cellulitis, osteomyelitis, pyelonephritis, endocarditis, and for the viral infections: influenza, herpes zoster, CMV, EBV, Covid 19, and herpes simplex and RS virus infection (Table 2).

The overall risk of infections compared to controls was 7 –fold the 1st year after diagnosis, and remained elevated up to 5 years after the MM diagnosis (Table 2 and Figure 3). The risk of viral and fungal infections the 1st year after MM diagnosis was especially high, eleven-fold and eight-fold compared to controls, respectively (Table 2). The risk of infection compared to controls remained 5-fold in MM patients diagnosed in the three calendar periods as shown in Table 2.

Females had overall a significantly lower risk of infections compared to males (HR 0.88; 0.86-0.91). The analyses above were adjusted for Charlson Comorbidity Index in a separate model yielding the same results (data not shown). The risk of a first infection increases significant by age, compared to <65, the age groups 65-80 and ≥80 years had a HR of 1,21 and 1,75 respectively ($p<0.001$).

Patients >80 years at diagnosis had an increased risk of bacterial infections compared to younger patients (HR 1.11; 1.04-1.19). However, in viral and fungal infections, all patients >65 years had less reported infections compared to younger (Table S2 in Supplements). Comparing the risk of all infections in MM patients in the first calendar period 2008-2012 to the two following periods, the risk was slightly increased in the period 2013-2017 (HR 1.06; 1.0-1.11) but decreased in the latest calendar period 2018-2021 (HR 0.87; 0.82-0.93) (Table S3 in Supplements).

Mortality in infections

A total of 678 (8%) of MM patients had died within 3 months of diagnosis compared to 315 (1%) of controls. Infection contributed to 219 (32%) deaths among MM patients and 61 (19%) among controls. After 1 year, 1,609 (20%) MM patients had died, and infection-related mortality was 27% (Table 3). Six months and one year after MM diagnosis the observed 90-day all-cause mortality rate was 75% and 56 % in MM patients following a significant infection, compared to 56% and 42% in matched controls. Notably, the disparity in infection-related all-cause mortality was more pronounced nearer to MM diagnosis (Table 3). This trend was consistent for infection-related deaths recorded in the Cause of Death Register as either the primary or contributing cause of death (Table 3). In a competing risk analysis, we found a 3-fold risk (HR 3.14; 2.92-3.37) of dying of an infection among MM patients compared to controls (Figure 4).

DISCUSSION

This study constitutes the largest population-based study to date on the risk of infections compared to the normal population in the era of modern MM treatment. We found a 5-fold and 7-fold risk of infections overall and one year after diagnosis, respectively, and the risk of infections remained high during the course of the disease. There was a 30% infection-related death in multiple myeloma patients, and a 3-fold risk of dying from an infection compared to controls.

In the era of PIs, IMiDs and MoAbs, one could hypothesize that the risk of infections would be lower than in the chemotherapy era, as mucositis and neutropenia is less frequently seen. However, proteasome inhibitors and MoAbs are known to increase the risk of varicella zoster reactivation in seropositive patients [13, 14]. Furthermore, monoclonal antibodies increase the

risk of pneumonia and opportunistic infections [15, 16]. Modern immunomodulators like lenalidomide and pomalidomide can cause neutropenia, especially in advanced MM patients with low bone marrow reserve [17, 18]. Glucocorticoids are still the backbone of most treatment combinations, and the cumulative dose of steroids is known to increase the risk of infection [19].

In our population-based study the risk is still 5-fold compared to controls, and we could show that the risk of infection compared to controls remained 5-fold in MM patients diagnosed in the three calendar periods from 2008-2021. As shown in Table 2, including all infections over the years, the excess risk expressed in HR compared to controls remains high the first and five years after diagnosis, suggesting that the infection risk never decreases compared to controls. That is in coherence with several studies in patients treated with modern MM therapies. Dumontet et al. reported from the FIRST trial that 21.1% experienced Grade ≥ 3 infections in the first 18 months, and the risk of early infection was similar regardless of treatment [20]. Brioli found at least one infectious episode in 65% in a retrospective study of 348 patients treated with novel agents, the majority bacterial [21].

An increasing proportion of MM patients are elderly, and in the Swedish Myeloma Registry, twenty-four per cent are 80 years or older at diagnosis [22]. Comparing the different age groups in MM patients, we could see an increasing risk of a first infection with age and looking at the risk of different infections, bacterial infections were significantly higher in patients ≥ 80 years, but viral and fungal were not (Supplementary Table S2). We suspect this is partly due to a more ambitious treatment strategies including HD Melphalan and ASCT and more lines of different treatments in younger patients.

The finding of an increased risk of infections up to 4 years preceding an MM diagnosis is particularly interesting and supports the earlier studies of increased risk of infections in MGUS patients [23, 24]. In our cohort of 8,672 symptomatic MM patients, eleven per cent were

earlier reported as SMM or plasmacytoma before the MM diagnosis, and only twelve percent of MM patients had a known MGUS at diagnosis, leaving 77 percent with symptomatic MM as the first reported manifestation of the plasma cell disease. This proves to show that many patients can have infections as sign of an undetected clinically significant plasma cell disorder preceding symptomatic MM diagnosis. When we analyzed infection risk in MM patients with previous MGUS or SMM, we found an increased incidence, especially the 12 months leading up to MM diagnosis. Similarly, in a European survey conducted by Ludwig et. al. in 2020 on the rate of infectious complications and prophylaxis in 355 patients, 51% of patients had experienced at least one infectious episode in the twelve months preceding MM diagnosis and 42% of patients in the following six months [25]. These observations may help us draw attention to patients that perhaps need earlier detection and treatment.

In a study from Teh and coworkers, studying the clinical course on 199 patients and 771 infectious episodes, a bimodal peak in incidence of bacterial (4-6 and 70-72 months) and viral infections (7-9 and 52-54 months) following disease diagnosis was found [26]. The elevated risk of infections in MM compared to controls in our study remained high during both 1 -and 5-year follow-up, suggesting that infections represent a constant concern in MM patients throughout the course of their disease.

We found a high risk of pneumonia and septicemia, which was 8-fold compared to matched controls. This is in coherence with a Danish study, where Sörrig and coworkers utilized ICD codes in hospital registries and found sepsis and pneumonia to be the most important infections (46%) the first six months after MM diagnosis and the risk factors were high tumor burden and renal failure [27].

Most significant infections seen in our study were bacterial, but viral and fungal significant infections seem to gain importance. We see an even greater difference in the risk of viral infection such as RS virus infection compared to controls in the first year after diagnosis, and

it seems to be confirmed by other studies. Lim et al. (2021) found in a recent chart review study of 345 infectious episodes in 148 patients that 50% were due to viruses, where bortezomib and many lines of treatment were risk factors[28]. This study may have found less significant infections than in our study as they had several modes of detection, but points out that new infectious agents may play a more important role as the treatment panorama changes. In two comprehensive consensus recommendations on infection prophylaxis in MM from 2023 to 2024 the importance of anti-viral and antifungal prophylaxis is underscored, especially in patients with neutropenia[3, 29]. We saw a 3-fold risk of COVID-19 infections compared to controls but believe that the number in underestimated due to lack of testing in the beginning of the pandemic, and the total number of registered infections (n=278) was too small to draw any strong conclusions.

In our study, MM patients had a slight decrease in the risk of all, bacterial, fungal and viral infections in the last calendar period. There may be a number of reasons for this, but it may have to do with better guidelines and preventive measures. More effective treatments will also decrease the disease-related immunosuppression and therein the risk of infections.

In Sweden, we have also adjusted our treatment according to the result of studies by Rajkumar et al.[30] showing that low-dose dexamethasone added to lenalidomide was equal effective but with less infections than high dose dexamethasone in the elderly population. This is reflected in the Swedish National Multiple Myeloma Guidelines [31] which since 2016 have recommended lower doses of dexamethasone than in many original studies and refrained from high-dose dexamethasone over the ages 75. This may also have contributed to the relatively lower risk of viral and fungal infections in the elderly, as could the repeated and more intensive treatment more common in younger patients.

We found an infection- related mortality of approximately 30 % three months and one year after MM diagnosis. This was based on infections that were registered as a cause of death. In

participants surviving only 90 days after diagnosis or inclusion to the study, 49% of MM patients died within 30 days of infection compared to 37% of controls. This reflects the burden of infections in early mortality among MM patients. Similarly, in two retrospective registry studies from Denmark in patients diagnosed 2005-2012 and 2005-2013, in non-ASCT- eligible patients, infections were a cause of death in 51% of the 22% patients dying the first three months [32], and in patients eligible for ASCT 9.6% of patients suffered an early death (<2 years). Causes of early death were progressive disease and infections, and infections were seen in 44% of deceased patients[33]. Caravita et al. reported on 127 patients treated with lenalidomide combinations and found that OS was significantly shorter in patients developing an infection than not (median OS 26 vs 33 months, p= 0.001) [34]. In a single centre study by Hsu et al., a 60-day mortality was seen in 12.6 % of patients diagnosed 2002-2015, and pneumonia and other infections were the largest contributors to early mortality (65%)[35].

This study has several strengths, a large sample size, the population-based nature of the Swedish registries, and a matched control population. The study included a stable population of symptomatic MM patients from the Swedish Myeloma Registry with characteristics at diagnosis available, including the 1st line of treatment. Moreover, the whole population had access to public and free health care, with equal availability to new MM drugs. Close to every patient (92%) had received at least 1 line of treatment and 26% ASCT. Through the nationwide register-based design and age-matched controls we could avoid recall bias and ensure the generalization of our findings.

Our registry-based study has some limitations. In 4.9% of patients, we have no record on ASCT treatment. In patients diagnosed up to 2021 with follow-up through 2022, some may not yet have an annotation of 1st line treatment in the Swedish Myeloma Registry at data cut-

off, hence some transplanted patients would be part of the "ASCT Missing" cohort shown in Table 1. To support this statement, we have reported on a steady increase of ASCT-patients > 65 years, and in later years ASCT is performed in approx. 40% of patients 66-70 years at diagnosis in the Nordic countries [36]. Other patients younger than 70 years diagnosed 2020 and 2021 may however have received less intensive treatment due to Covid-19.

The discharge diagnosis in hospital registries as a single source of infection diagnosis may lead to underreporting of infections, as the hospital visit often is labelled only by the MM diagnosis. We therefore did a sensitivity analysis based on prescribed antibiotics, with each different prescription of antibiotics acting as a proxy for infection, excluding prophylactic antivirals and antibiotics commonly used. The results were the same, with a 5-fold increase in infections for MM patients compared to controls. On the other hand, the surveillance of infections in MM patients may be more vigilant than in the general population. Underreporting may happen even to a higher degree in the in the Cause of Death Register, where MM more often is annotated as the only cause of death. Another limitation is the lack of data on the severity of the infection. However, most infections that were shown to have increased risks in MM patients were severe, and would have been captured in the control group as they would need treatment in the hospital. To avoid the risk of overreporting infections, we only reported a registered infection of the same code if they were reported 1 month apart, and 3 months in the case of COVID-19. We also chose to exclude chronic infections that would lead to repeated annotation as e.g., Hepatitis, HIV, etc.

In summary, in this large population-based study from Sweden we can confirm that infections still represent a major threat to the lives of MM patients. The risk of infections compared to controls are five times higher than in age-matched controls, and even higher the first year after diagnosis. Infections propose a significant risk of early mortality despite more tolerable treatments and better survival. The continuous and repeated nature of current MM therapies

make it even more important to consider prophylactic measures to prevent morbidity and mortality in infections. Before the advent of immunotherapy in MM with CAR-T cell and T-cell engagers with their specific risks of infections, this study can constitute a baseline of the risk of infections in the pre-immunotherapy era.

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Tables

		Myeloma	Controls
Total, N		8,672	34,561
Sex, N (%)			
	Male	4,982 (57.4)	19,852 (57.4)
	Female	3,690 (42.6)	14.709 (42.6)
Age, median (range)		72 (20–101)	72 (20–101)
Age group N (%)			
	<40	50 (0.6)	200 (0.6)
	40-49	267 (3.1)	1,068 (3.1)
	50-59	928 (10.7)	3,710 (10.7)
	60-69	2,183 (25.2)	8,716 (25.2)
	70-79	3,060 (35.3)	12,205 (35.3)
	≥80	2,184 (25.1)	8,662 (25.1)
Year of diagnosis N (%)			
	2008-2012	2,833 (32.7)	11,306 (32.7)
	2013-2017	3,198 (36.9)	1,2741 (36.9)
	2018-2021	2,641 (30.4)	10,514 (30.4)
Earlier SMM	N (%)	729 (8.4)	
Earlier MGUS	N (%)	1,048 (12)	
Earlier Plasmacytoma	N (%)	200 (2.3)	
Charlson Comorbidity Index N (%)			
	0	5,380 (62)	2.3629 (68)
	1	2,029 (23)	6,740 (20)
	≥2	1,263 (15)	4,192 (12)
ISS Grade	N (%)		
Low risk		1,241 (20)	
Intermediate		2,716 (44)	
High risk		2,226 (36)	
Missing		2489	
Treatment	N (%)		
	Auto-SCT	2,216 (25.5)	
	Non-auto SCT	6,035 (69.6)	
	Missing	424 (4.9)	

Table 1. Characteristics of patients with symptomatic multiple myeloma, and their matched controls.
Abbreviations: SMM: smoldering multiple myeloma, MGUS: monoclonal gammopathy of undetermined significance, ISS: Int. Staging System, Auto-SCT: High dose Melphalan with stem cell support, Non-auto SCT: Not treated with high dose Melphalan and stem cell support

Disease	Myeloma (N=8,672)	Controls (N=34,561)	HR (95%CI)	
Patients with ≥ 1 infection	**N=5,985**	**N=10,978**		
All infections N	11,004	17,322	5.30 (5.14-5.47)	p<0.001
Bacterial infections N	6,510	10,545	4.88 (4.70-5.07)	p<0.001
Pneumonia	1,911	1,677	8.40 (7.84-8.99)	p<0.001
Osteomyelitis	136	339	2.63 (2.15-3.22)	p<0.001
Septicemia	2,063	1.,70	8.85 (8.27-9.47)	p<0.001
Pyelonephritis	382	1,540	2.54 (2.25-2.87)	p<0.001
Cellulitis	170	297	3.52 (2.90-4.27)	p<0.001
Meningitis	42	11	21.4 (11.0-41.6)	p<0.001
Endocarditis	93	116	5.32 (4.03-7.03)	p<0.001
Viral infections N	2,463	2,616	6.84 (6.46-7.26)	p<0.001
CMV	88	14	36.1 (20.1-65.0)	p<0.001
EBV	10	11	6.41 (2.88-14.3)	p<0.001
Influenza	486	333	10.2 (8.90-11.7)	p<0.001
Herpes Zoster	574	376	10.2 (9.00-11.7)	p<0.001
Covid-19	271	651	2.78 (2.40-3.23)	p<0.001
Herpes Simplex	189	208	5.72 (4.71-6.94)	p<0.001
RSV	199	71	16.1 (12.9-22.1)	p<0.001
Fungal infections N	813	770	6.77 (6.13-7.47)	p<0.001
All infections 1st year N	4,504	3,035	6.95 (6.61-7.30)	p<0.001
All bacterial infections	2,753	1,785	6.47 (6.08-6.89)	p<0.001
All viral infections	782	412	7.77 (6.87-8.78)	p<0.001
All fungal infections	356	136	10.9 (8.96-13.4)	p<0.001
All infections 5 years N	9,047	10,939	5.61 (5.43-5.80)	p<0.001
All bacterial infections	5,400	6,492	5.08 (4.88-5.28)	P<0.001
All viral infections	1,920	1,559	6.81 (6.36-7.29)	p<0.001
All fungal infections	674	502	7.00 (6.24-7.85)	p<0.001
Stratified by calendar period				
2008-2012			5.26 (5.01-5.54)	p<0.001
2013-2017			5.34 (5.08-5.60)	p<0.001
2018-2021			5.42 (5.08-5.85)	p<0.001

Table 2. Risk of selected infections compared to matched controls overall, at 1-and five years, and in different calendar periods. Abbreviations: CMV: Cytomegaly virus infection, EBV: Epstein Barr virus infection, RSV: Respiratory syncytial virus infection.

	Alive	Dead	90-days all-cause mortality after registered infection	Infection-related death (Cause of Death Register)
	N	N (%)	N (%)	N (%)
Overall				
Myeloma patients N=8,672	3,231	5,441 (63)	1,360 (24)	1,260 (23)
Controls N=34,561	25,005	9,556 (28)	1,938 (20)	1,855 (19)
At 90 days*				
Myeloma patients	7,994	678 (8)	332 (49)	219 (32)
Controls	34,246	315 (1)	115 (37)	61 (19)
At 180 days				
Myeloma patients	7,631	1,041(12)	778 (75)	305 (29)
Controls	33,939	622 (2)	350 (56)	122 (19)
At 1 year				
Myeloma patients	7,063	1,609 (19)	907 (56)	436 (27)
Controls	33,296	1,265 (4)	531(42)	249 (20)
At 3 years				
Myeloma patients	5,370	3,302 (38)	1,168 (35)	809 (25)
Controls	30,928	3,633 (11)	1,163 (32)	732 (20)
At 5 years				
Myeloma patients	4,377	4,385 (50)	1,314 (35)	1,033 (23)
Controls	28,976	5,585 (16)	1,532 (32)	1,117 (20)

Table 3. All-cause mortality after an infection diagnosis and infection-related mortality with infection as main or contributing cause of death in the Cause of Death Register at different time points after MM diagnosis in the study period.
*For the first 3 months of follow up, the all-cause mortality was shortened to 30 days

Figure Legends

Figure 1 Consort diagram of the MMBaSe study (Multiple MyelomaBaSe); a linked database from population-based registers in Sweden.

Figure 2. Incidence of infections before multiple myeloma (MM) diagnosis and over time in patients and controls. 2A) In MM patients, 2B) MM patients with previously known MGUS (monoclonal gammopathy with undetermined significance), and 2C) MM patients with previously known SMM (smoldering multiple myeloma).

Figure 3. Cumulative incidence of infection in multiple myeloma patients compared to controls.

Figure 4. Risk of death from infection or other causes in multiple myeloma patients and controls in a competing risk analysis.

Swedish Myeloma Registry
n=10222

Non-Swedish residents
n=18

Other diagnoses than symptomatic myeloma
n=1521

Swedish symptomatic myeloma patients
n=8683

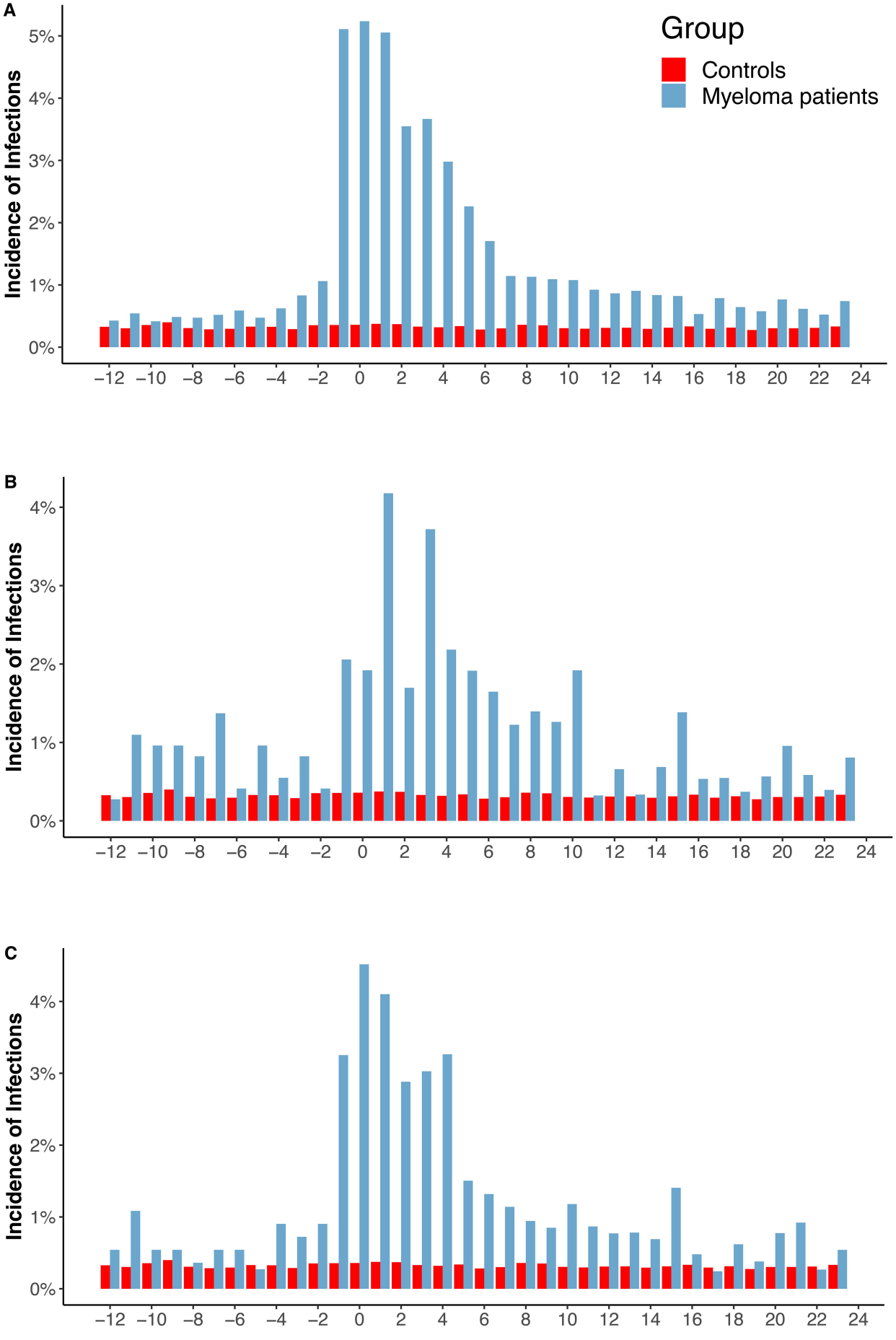
Deceased at time of diagnosis
n=11

Patients included in analyses
n=8672

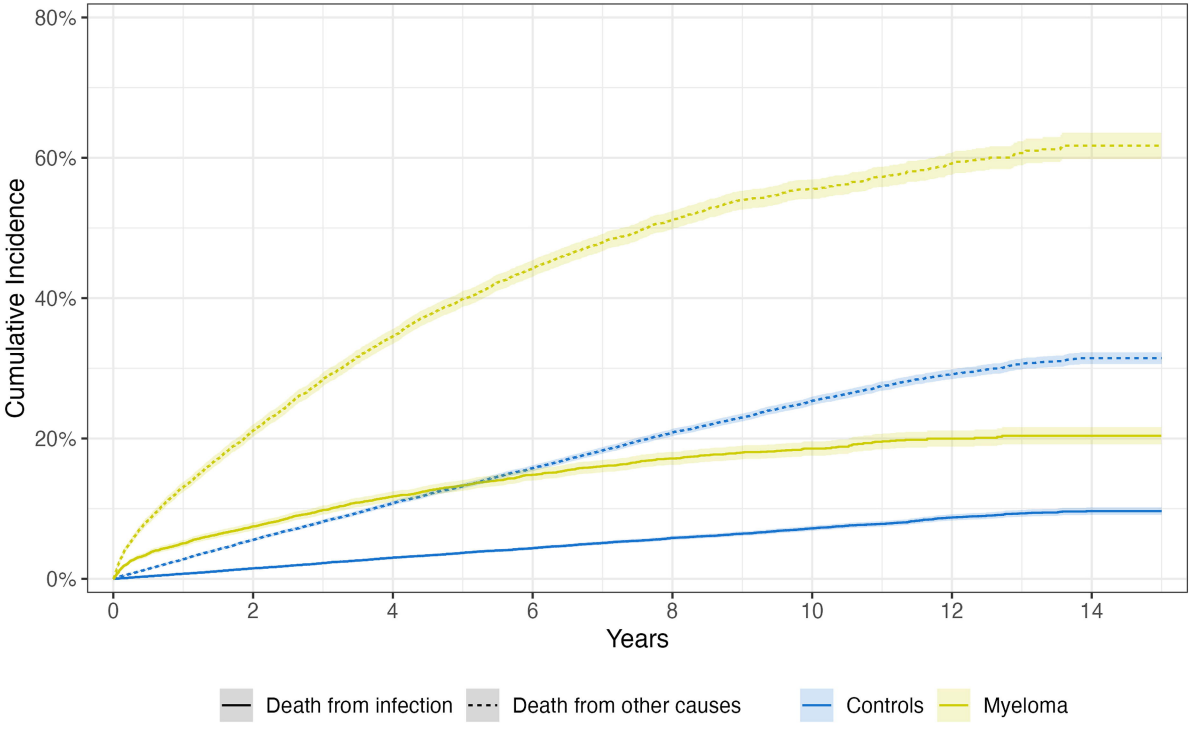
Individually matched controls
n=34732

Deceased at time of diagnosis
n=171

Controls included in analyses
n=34561


A
Incidence of Infections
5%
4%
3%
2%
1%
0%
Group
Controls
Myeloma patients
−12 −10 −8 −6 −4 −2 0 2 4 6 8 10 12 14 16 18 20 22 24
B
Incidence of Infections
4%
3%
2%
1%
0%
−12 −10 −8 −6 −4 −2 0 2 4 6 8 10 12 14 16 18 20 22 24
C
Incidence of Infections
4%
3%
2%
1%
0%
−12 −10 −8 −6 −4 −2 0 2 4 6 8 10 12 14 16 18 20 22 24


All Infections
Cumulative Incidence
100%
75%
50%
25%
0%
0
2
4
6
8
10
12
14
Time (years)
Controls
Myeloma


80%
60%
40%
20%
0%
Cumulative Incidence
0
2
4
6
8
10
12
14
Years
Death from infection
Death from other causes
Controls
Myeloma

Supplementary Material

Absolute risk	Myeloma	Controls
Number of patients	8,672	34,561
All infections	0.70	0.32
Bacterial infections	0.52	0.22
Pneumonia	0.18	0.04
Osteomyelitis	0.009	0.005
Septicemia	0.2	0.04
Pyelonephritis	0.04	0.03
Cellulitis	0.016	0.007
Meningitis	0.003	0.0003
Endocarditis	0.007	0.002
Viral infections	0.22	0.06
CMV	0.007	0.0003
EBV	0.001	0.0002
Influenza	0.05	0.009
Herpes Zoster	0.05	0.009
Covid 19	0.03	0.02
Herpes Simplex	0.02	0.003
Fungal infections	0.08	0.02

Table S1: The absolute risk of specific infections, compared to age-matched controls

Myeloma patients	Age (years)	HR	95% CI	p-value
All infections	<65	1.00 (ref)		
	65-80	0.91	0.85-0.98	0.009
	>=80	0.91	0.86-0.96	<0.001
All bacterial infections	<65	1.00 (ref)		
	65-80	1.04	0.96-1.13	0.4
	>=80	1.11	1.04-1.19	<0.001
All viral infections	<65	1.00 (ref)		
	65-80	0.72	0.64-0.80	<0.001
	>80	0.54	0.49-0.59	<0.001
All fungal infections	<65	1.00 (ref)		
	65-80	0.73	0.60-0.88	<0.001
	>=80	0.61	0.52-0.71	<0.001

Table S2: The risk of different types of infections in different age groups.

Only myeloma patients:	Calendar period	HR	95% CI	p-value
All infections	2008-2012	1.00 (ref)		
	2013-2017	1.06	1.00-1.11	0.037
	2018-2021	0.87	0.82-0.93	<0.001
All bacterial infections	2008-2012	1.00 (ref)		
	2013-2017	0.99	0.93-1.05	0.7
	2018-2021	0.78	0.73-0.84	<0.001
All viral infections	2008-2012	1.00 (ref)		
	2013-2017	1.01	0.92-1.11	0.8
	2018-2021	0.85	0.76-0.96	0.014
All fungal infections	2008-2012	1.00 (ref)		
	2013-2017	0.68	0.58-0.79	<0.001
	2018-2021	0.59	0.48-0.72	<0.001

Table S3: The risk of different types of infections in different calendar periods.