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Incidence trends and five-year survival of multiple myeloma and other plasma cell neoplasms in Girona, Spain: a population-based study, 1994–2020

Kleber Garrochamba · Alicia Villavicencio · Alberto Ameijide · Jan Trallero · Aina Romaguera · Arantza Sanvisens · Marc Saez · Rafael Marcos-Gragera

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Abstract

Multiple myeloma is the most common malignant tumor originating in plasma cells. Its incidence varies across populations according to demographic and environmental factors, although its exact etiology remains unclear; reports on survival and advances in treatment are lacking in some geographic areas. The aim of the study was to evaluate the incidence, trends, and survival of multiple myeloma and other plasma cell neoplasms (MM and other PCNs) using data from the Girona Cancer Registry between 1994 and 2020. Incidence trends, observed survival (OS), and net survival (NS) were evaluated using Joinpoint regression, Kaplan–Meier, Cox regression, and the Pohar-Perme method. A total of 1137 cases were identified, with a median age of 72 years [IQR 63.0–79.0]. Incidence trends remained stable in both men and women, with annual percent changes (APCs) of 0.2% [95% CI −1.1; 1.4] and −0.7% [95% CI: −1.9; 0.5], respectively. Median net survival significantly increased from 2.58 to 4.17 years between 1994–2001 and 2010–2016, respectively. Five-year net survival increased from 31.9% [95% CI 24.6–41.3] to 46.5% [95% CI 40.6–53.3] between 1994–2001 and 2010–2016, respectively. Incidence trends remained stable during the study period, whereas myeloma survival improved significantly. The impact of new immunotherapies on future myeloma survival remains promising.

Keywords Multiple myeloma · Plasma cells · Incidence · Trends · Survival

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm (PCN) that corresponds to the progression of smoldering multiple myeloma (SMM) and monoclonal gammopathy of undetermined significance (MGUS)[1]. MGUS is defined as the presence of serum M-protein (<3 g/dL) and<10% plasma cells (PCs), SMM as serum M-protein (≥3 g/dL) or≥10% PC, and MM as the presence of the classic criteria, hypercalcemia, renal impairment, anemia, and lytic lesions (CRAB), together with a monoclonal component (M-spike)[2].

MM is a malignant proliferation of plasma cells (PCs), characterized by progressive immune system dysfunction[3]. Among the clinical variants of plasma cell myeloma (PCM) or MM, plasma cell leukemia (PCL) is

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recognized. Primary PCL accounts for 2–4% of MM cases, while secondary PCL is a leukemic transformation that occurs in approximately 1% of MM cases. Among the types of plasma cell neoplasms (PCNs), plasmacytoma is identified, from which two types are distinguished: solitary plasmacytoma of bone (SPB) and solitary extraosseous plasmacytoma (extramedullary plasmacytoma/EMP), which account for 3–5% of all PCNs, respectively[4].

According to GLOBOCAN incidence data, the number of new MM cases worldwide in 2022 was 187,774. A total of 103,767 cases were reported in males, with an age-standardized rate (ASR_W) of 2.1 based on the standard World population, and 84,007 cases were reported in females, with an ASR_W of 1.5[5].

According to cancer incidence estimates for Spain in 2026 presented by the Spanish Network of Cancer Registries (REDECAN), MM is projected to have a total of 1874 cases in males, a crude rate (CR) of 7.6, and an age-standardized rate for the European population (ASR_E) of 7.5. In females, a total of 1,652 cases is projected, with a CR of 6.5, and an ASR_E of 5.3[6].

Overall survival, response rates, and disease-free survival for multiple myeloma have increased significantly in recent decades. According to the 2026 blood cancer statistics for Spain, the 5-year observed survival rate for MM was 42.9%, 41.2%, and 44.8% for men, women, and both sexes, respectively; however, when observed and net survival were evaluated in age groups over 60 years, survival rates decreased significantly[7].

The introduction of melphalan in 1960 was considered the only treatment for MM[8]. Subsequently, starting in 1990, high-dose chemotherapy combined with autologous stem cell transplantation (HDM-ASCT) improved survival rates[9]. Since 2000, there has been a significant change in the treatment of MM, with an increase in survival due to the introduction of thalidomide accompanied by treatment with immunomodulatory imide drugs (IMiDs)[10]. Proteasome inhibitors (PIs) emerged in 2003, followed by carfilzomib in 2012; monoclonal antibodies (mAbs) appeared in 2015 and 2016; and the most recent treatments emerged in 2020, including bispecific antibodies, antibody–drug conjugates (ADCs), and checkpoint inhibitors[10]. In particular, T-cell therapies, including chimeric antigen receptor (CAR-T) therapy and bispecific T-cell-engaging antibodies, have significantly advanced myeloma treatment and survival[11].

Over the past two decades, substantial progress has been made in the treatment of MM, with advances such as immunotherapy significantly improving and prolonging survival[10]. Despite these advances, most patients eventually relapse and die from complications related to the disease.

Multiple myeloma is the second most common hematological malignancy and remains incurable, although it is increasingly treatable. The study of the incidence, trends, and survival of multiple myeloma in the population is crucial for the healthcare system to improve detection, treatment, and prognosis.

In our study, we evaluated the incidence, incidence trends, and five-year survival of MM and other PCNs in the province of Girona during the period 1994–2020.

Results

Descriptive statistics

A total of 1,137 cases of MM and other PCNs were identified in the province of Girona between 1994 and 2020, of which 619 cases (54.4%) and 518 cases (45.6%) were diagnosed in men and women, respectively. The median age for MM and other PCNs was 72 years [IQR: 63–79], and was 71 years [IQR: 61.5–79.0] in men and 73 years [IQR: 64–80] in women. A total of 1069 cases (94%) of PCM or MM were identified among all cases of MM and other PCNs. Of the total cases of MM or PCM, 579 cases (54.2%) and 490 cases (45.8%) corresponded to men and women, respectively. The median age in MM or PCM was 72 years [IQR: 63–80], and was 72 years [IQR: 62–79] and 73 years [IQR: 64–80] in men and women, respectively **(**Table 1**)**. Of the total number of cases of MM and other PCNs, a total of 12 cases (1.1%) corresponded to PCL, 17 cases (1.5%) to EMP, and a total of 39 cases (3.4%) corresponded to SPB. For the SPB subtype, a higher number of cases were recorded, with 26 cases (66.7%) and 13 cases (33.3%) observed in men and women, respectively.

Table 1 Descriptive results for MM and other PCNs diagnosed in Girona, Spain, during the period 1994–2020.

Variable	Multiple myeloma and other plasma cell neoplasms (MM and other PCNs)		
	Total (Both)	Men	Women
	N = 1137 (100) (45.6)	N = 619 (54.4)	N = 518
MM and other PCNs, n (%)			
Age median [IQR]	72[63;79]	71[61.5;79]	73[64;80]
Age, CI [95% CI]	0.7[69.9–71.3]	0.9[68.8–70.6]	1.0[70.7–72.7]
Age groups (years), n (%)			
30–39	7(0.6)	2(0.3)	5(1.00)
40–49	57(5.0)	36(5.8)	21(4.1)
50–59	134(11.8)	80(12.9)	54(10.4)
60–69	273(24.0)	157(25.4)	116(22.4)
70–79	384(33.8)	203(32.8)	181(34.9)
80;>85	282(24.8)	141(22.8)	141(27.2)
Disease stage n, (%)			
I	66(5.8)	33(5.3)	33(6.4)
II	78(6.9)	40(6.5)	38(7.3)
III	171(15.0)	97(15.7)	74(14.3)
Unknown	822(72.3)	449(72.5)	373(72.0)
Period of diagnosis, n (%)			
1994–1999	192(16.9)	93(15.0)	99(19.1)
2000–2004	173(15.2)	95(15.3)	78(15.1)
2005–2009	252(22.2)	136(22)	116(22.4)
2010–2014	239(21.0)	126(20.4)	113(21.8)
2015–2020	281(24.7)	169(27.3)	112(21.6)
MM or PCM, n (%)*	N = 1069 (100)	N = 579 (54.2)	N = 490 (45.8)
Out of the total, n (%)**	1069 (94)	579 (50.9)	490 (43.1)
Age median [IQR]	72[63;80]	72[62;79]	73[64;80]
Age, CI [95% CI]	0.7[70.0–71.4]	0.9[68.8–70.7]	1.0[70.8–72.9]

MM and other PCNs, multiple myeloma and other plasma cell neoplasms; *MM or PCM*, multiple myeloma or plasma cell myeloma; *n*, number of cases; *IQR*, interquartile range; * Total number of *MM or PCM* cases, ** Out of the total of 1137 cases (*MM and other PCNs*).

Of the total cases of MM and other PCNs, 282 cases (24.8%) were observed in the age group ≥ 80 years, 384 cases (33.8%) in those aged 70–79 years, 273 cases (24.0%) in those aged 60–69 years, and 198 cases (17.4%) in those aged 30–59 years. The highest number of cases was observed in the 70–79-year age group in both men and women, accounting for 203 cases (32.8%) and 181 cases (34.9%), respectively (Table 1).

Regarding the number of cases of MM and other PCNs by period of diagnosis, a total of 192 cases (16.9%) were reported in 1994–1999, 173 cases (15.2%) in 2000–2004, 252 cases (22.2%) in 2005–2009, 239 cases (21.0%) in 2010–2014 and 281 cases (24.7%) in 2015–2020. A higher number of cases, 116 cases (22.4%) and 169 cases (27.3%), were observed in women and men during the periods 2005–2009 and 2015–2020, respectively (Table 1).

Incidence

The age-specific incidence rate of MM and other PCNs was higher in men than in women and in both sexes (49.6, 28.1, and 36.7 per 100,000, respectively), with a marked increase starting in the 60–64-year age group (Fig. 1). For the PCN subtypes (PCL, EMP, and SPB), age-specific rates were markedly lower and remained stable compared with those for MM and other PCNs and MM or PCM. The corresponding results are presented in Supplementary Fig. S1. The CR for MM and other PCNs was 6.36 [95% CI 5.99; 6.73] per 100,000 person-years. The CR was 5.98 per 100,000 person-years for MM or PCM and 0.44 per 100,000 person-years for PCN subtypes (PCL, EMP, and SPB). Incidence rates were higher in men than in women (Table 2). The ASR_E for MM and other PCNs was 7.32 [95% CI 6.90; 7.74] cases per 100,000 person-years. The ASR_E was higher in men than

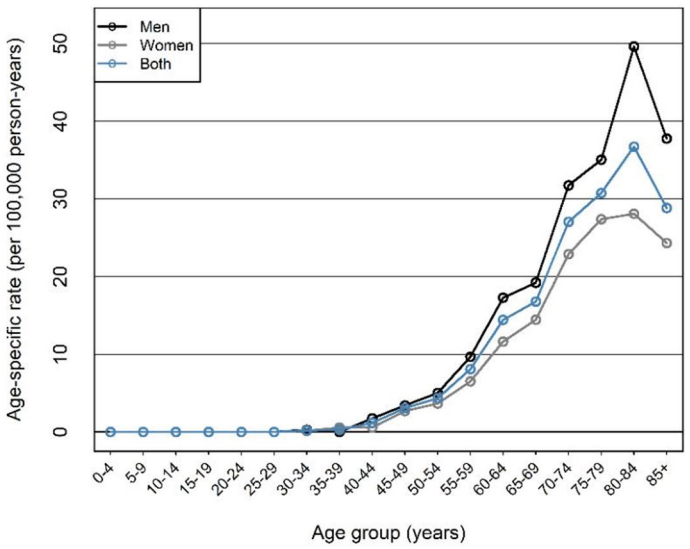

Fig. 1 Age-specific incidence rates of MM and other PCNs. *MM and other PCNs*, multiple myeloma and other plasma cell neoplasms. Girona, Spain, 1994–2020.

Table 2 Age-specific incidence rate, crude rate and age-standardized rates of MM and other PCNs, Girona, Spain, 1994–2020.

ICDO-3	n	Age-specific incidence rate* (30–34) (60–64) (80–84)			CR (95%CI)*	ASR_E (95%CI)*	ASR_W (95%CI)*	Ratio ASR_E Men/ Women
MM and other PCNs								
Both	1137	0.21	14.50	36.7	6.36 (5.99;6.73)	7.32 (6.90;7.74)	3.12 (2.92;3.32)	
Men	619	0.28	17.30	49.6	6.91 (6.38;7.47)	8.63 (7.95; 9.32)	3.66 (3.35;3.97)	1.44
Women	518	0.15	11.70	28.1	5.80 (5.31;6.32)	6.00 (5.48; 6.53)	2.58 (2.33;2.83)	
MM or PCM								
Both	1069	0.21	13.70	35.4	5.98 (5.62;6.34)	6.87 (6.46;7.28)	2.94 (2.74;3.13)	
Men	579	0.28	16.20	47.98	6.47 (5.95;7.0)	8.07 (7.41;8.73)	3.42 (3.12;3.72)	1.42
Women	490	0.15	11.23	26.90	5.49 (5.0;5.99)	5.68 (5.17;6.18)	2.43 (2.18;2.67)	
Other PCNs (PCL, EMP, SPB)								
Both	68	0.0	0.25	0.44	0.13 (0.10;0.16)	0.15 (0.11;0.18)	0.07 (0.05;0.09)	
Men	28	0.0	0.36	0.55	0.15 (0.11;0.20)	0.19 (0.13;0.25)	0.08 (0.05;0.11)	1.90
Women	40	0.0	0.14	0.37	0.10 (0.07;0.15)	0.10 (0.06;0.25)	0.06 (0.04;0.08)	

ICD-O-3, International Classification of Diseases for Oncology, third edition; *CR*, crude rate; ASR_E, age-standardized rate, European population (2013); ASR_W, age-standardized rate, World standard population (Segi-Doll, 1960); *MM and other PCNs*, multiple myeloma and other plasma cell neoplasms; *MM or PCM*, multiple myeloma or plasma cell myeloma; *PCL*, plasma cell leukemia; *EMP*, extramedullary (extraosseous) plasmacytoma; *SPB*, solitary plasmacytoma of bone; n, number of cases.* Expressed as cases per 100,000 person-years.

in women, at 8.63 and 6.0 cases per 100,000 person-years, respectively. The ASR_W for MM and other PCNs was 3.12 [95% CI 2.92; 3.32] cases per 100,000 person-years. The ASR_W was higher in men than in women, at 3.66 and 2.58 cases per 100,000 person-years, respectively. The ASR_E ratio (men: women) for MM and PCNs, MM or PCM, and PCN subtypes (PCL, EMP, and SPB) indicated higher incidence rates in men than in women (Table 2).

Incidence trends

The incidence trend based on the ASR_E for MM and other PCNs remained stable ($p > 0.05$) during the study period (1994–2020) with an APC of −0.2% (95% CI −1.2; 0.8). A similar trend was observed in men and women, with APCs of 0.2% [95% CI −1.1; 1.4] and -0.7% [95% CI −1.9; 0.5], respectively (Table 3) (Fig. 2A). The incidence trend based on ASR_W for MM and other PCNs also remained stable ($p > 0.05$) in men and women during

Table 3 Joinpoint analysis and incidence trends (ASR_E, 2013) for MM and other PCNs, Girona, Spain, 1994–2020.

ICDO-3	Year	Both			Men			Women		
		APC/ AAPC	95% CI	*p* value	APC/ AAPC	95% CI	*p* value	APC/ AAPC	95% CI	*p* value
MM and other PCNs	1994–2020	−0.2	[−1,2; 0,8]	0.68*	0,2*	[−1,1; 1,4]	0.79*	−0.7	[−1,9; 0,5]	0.25*
MM or PCM	1994–2020	−0.3	[−1,3; 0,8]	0.61*	0,1*	[−1,2; 1,3]	0.90*	−0.7	[−2.0; 0,60]	0.26*

MM and other PCNs, multiple myeloma and other plasma cell neoplasms; *MM or PCM*, multiple myeloma or plasma cell myeloma; *ICD-O-3,* International Classification of Diseases for Oncology, third edition; *APC*, annual percent change; *AAPC,* average annual percent change. **APC* is not significantly different from zero at the alpha = 0.05 level (two-sided).

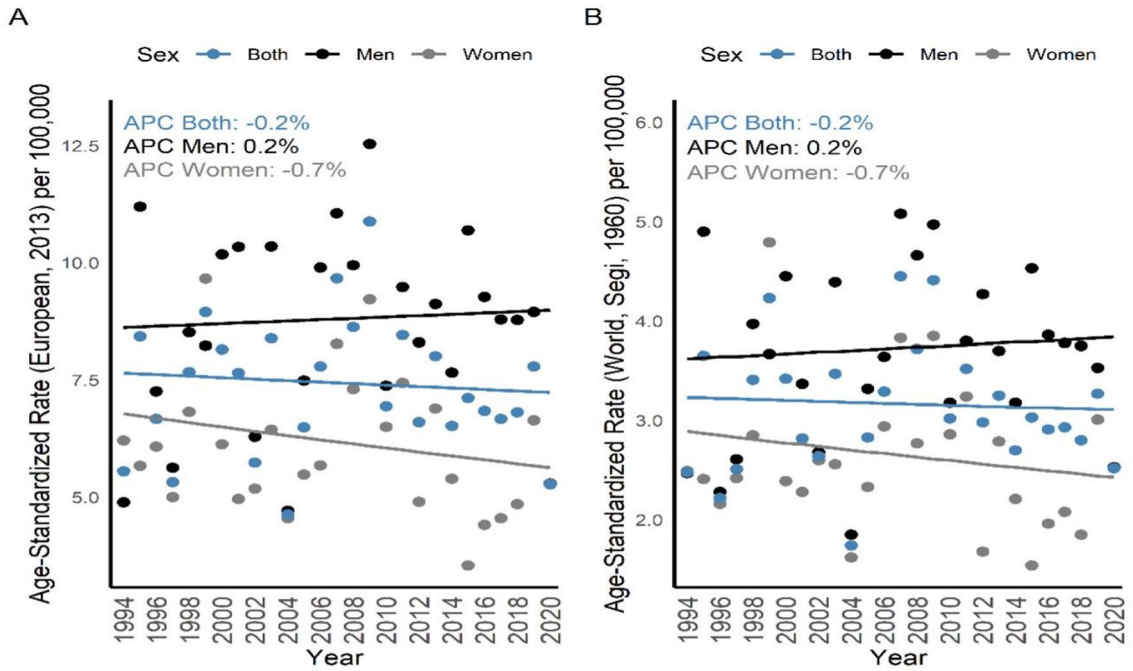

Fig. 2 Trends in age-standardized rates (*ASRs*) of multiple myeloma and other plasma cell neoplasms *(*MM and other PCNs). (**A**) European standard population (ASR_E, 2013) and (**B**) World standard population (ASR_W, Segi-Doll, 1960). *APC*, annual percent change.

the study period (1994–2020) (Table 3) (Fig. 2B). For MM or PCM, the incidence trend also remained stable in both sexes ($p > 0.05$) during the study period (1994–2020), with an APC of −0.3% [95% CI −1.3; 0.8]. A similar trend for MM or PCM was observed in men and women, with APCs of 0.1% [95% CI −1.2; 1.3] and −0.7% [95% CI −2.0; 0.6], respectively (Table 3).

Survival

For the survival analysis, patients were stratified into three diagnostic periods: 1994–2001, 2002–2009, and 2010–2016. Follow-up was available through December 2021, allowing for up to five years of follow-up for patients diagnosed in 2016. Of the 1,137 identified cases, 189 were diagnosed after 2016 and were therefore excluded. Among the remaining 948 cases, 130 had missing data, 29 were classified as death certificate only (DCO), and 6 had a 0-day follow-up interval. Thus, 783 patients were included in the survival analysis, including 425 (54.3%) men and 358 (45.7%) women. The patient selection process is shown in Fig. 3. Five-year OS showed a significant increase between the study periods 1994–2001 and 2010–2016, from 27.9% [95% CI 21.5–36.0] to 41.5% [95% CI 36.4–47.3], respectively, with a significant increase in median survival from 1.86 years [95% CI

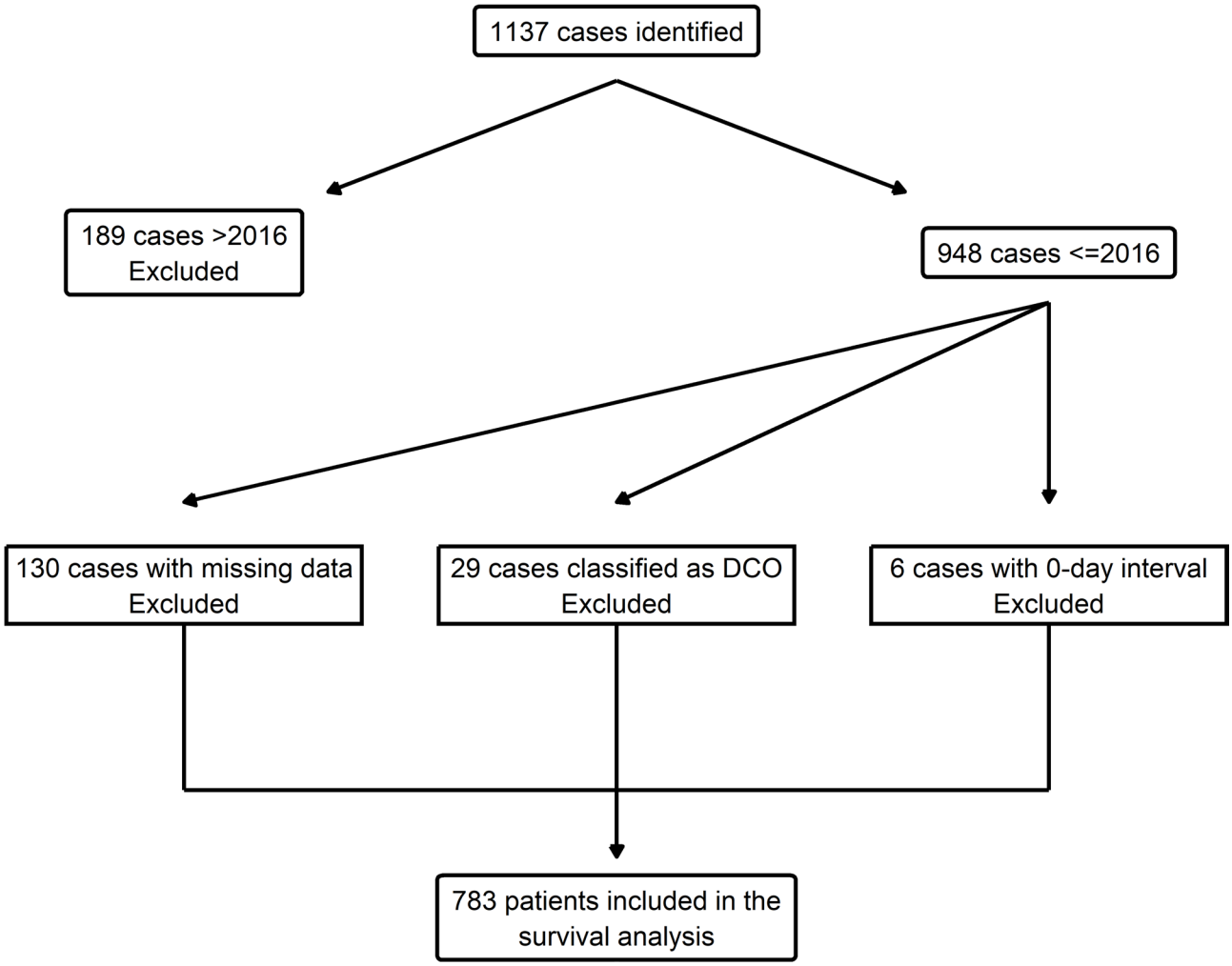

Fig. 3 Patient selection for the survival analysis. The flow diagram shows the selection of patients from the 1,137 identified cases to the 783 patients included in the survival analysis. *DCO, death certificate only.*

1.43–3.26] to 3.65 years [95% CI 2.94–4.58] ($p=0.02$) (Fig. 4A). Five-year NS increased from 31.9% [95% CI 24.6–41.3] to 46.5% [95% CI 40.6–53.3] between the study periods 1994–2001 and 2010–2016, respectively, with a significant increase in median survival from 2.58 years [95% CI 1.51–3.9] to 4.17 years [95% CI 3.34–NR; NR = not reached] ($p=0.03$) (Fig. 4B). In the multivariable Cox analysis, age, histological type (PCL), and study period (2002–2009 and 2010–2016) were predictors of the risk of death in patients with MM and other PCNs (Table 4). The global Schoenfeld test did not indicate evidence of a violation of the proportional hazards assumption ($\chi^2=9.84$, df = 7, $p=0.20$). Covariate-specific tests showed no evidence of non-proportionality for sex ($p=0.55$), histological type ($p=0.60$), or study period ($p=0.41$). Age showed evidence of non-proportionality ($p=0.01$); however, visual inspection of the Schoenfeld residuals indicated a gradual rather than marked departure from proportionality, and age was retained in the model as a continuous variable.

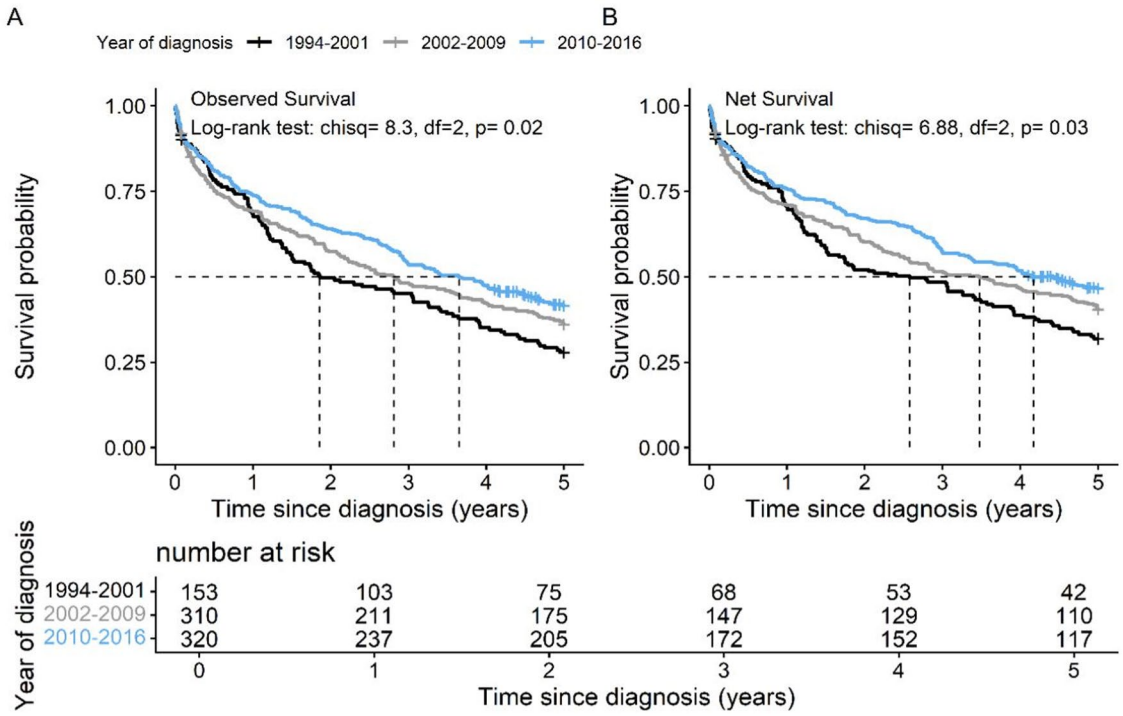

Fig. 4 Survival of multiple myeloma and other plasma cell neoplasms (MM and other PCNs). (**A**) Observed survival (OS) estimated using Kaplan–Meier method and (**B**) net survival (NS) estimated using the Pohar–Perme method, by period of diagnosis (1994–2001, 2002–2009, and 2010–2016). Girona, Spain. Patient follow-up until December 31, 2021.

Discussion

This population-based study of the incidence of MM and other PCNs in Girona, Spain, between 1994 and 2020 showed higher incidence in men than in women. The number of cases was also higher in men, and the median age was 72 years. CR and ASR_E were higher in men than in women, while incidence trends remained stable throughout the study period. Observed and net survival analyses of MM and other PCNs showed a significant increase in median survival between the 1994–2001 and 2010–2016 diagnosis periods, with patient follow-up through 2021.

Although the absolute number of cases increased over time, age-standardized incidence rates of MM and other PCNs remained stable, suggesting that population ageing may largely explain the growing disease burden, consistent with patterns reported in other countries[12–14]. A recent study by our group described 820 cases of MM and other PCNs between 1996 and 2015[15]. A study conducted in Girona between 1994 and 2001 described myeloma as the most common entity (17.8%) among lymphoid neoplasms, with CR and ASR_W comparable to those observed in our study[16]. The increase in the number of MM cases reported in different countries has been associated with various risk factors, including age, sex, ethnicity, family history, genetic factors, obesity, lifestyle, and environmental factors. However, the etiology of MM remains incompletely understood, and the evidence regarding the contribution of these factors is still limited[17,18]. Although it has been suggested that hyperphosphorylation of paraprotein target-7 or paratarg-7 (pP-7) may partially explain the higher incidence of MM in the African American population, evidence remains limited[17].

The incidence rate of myeloma in our study was similar to that reported in other European countries[19–22], although the incidence in our study was lower than that reported in North America, Northern Europe, Australia, and New Zealand[12,13,21]. In turn, the incidence in our study was higher than that reported in West Africa, Asia, and Melanesia[23–25].

Table 4 Cox regression model: univariate, and multivariable analysis of factors associated with survival in multiple myeloma and other plasma cell neoplasms (MM and other PCNs), Girona, Spain, 1994–2016.

Variable	Univariate analysis						Multivariable analysis					
	Estimator (β)	Standard error	HR	0.95 LCL	0.95UCL	*p* value	Estimator (β)	Standard error	HR	0.95 LCL	0.95 UCL	*p* value
Age	0.05	0.00	1.05	1.04	1.06	<0.001	0.06	0.00	1.05	1.04	1.08	<0.001
Sex												
Female	−0.00	0.09	0.99	0.83	1.19	0.9	−0.10	0.10	0.91	0.76	1.09	0.31
Male			1						1			
Histology group												
PCL	1.08	0.50	2.94	1.10	7.84	0.03	1.31	0.50	3.71	1.39	9.93	<0.01
MM or PCM	0.07	0.36	1.07	0.53	2.16	0.85	0.17	0.36	1.20	0.59	2.40	0.62
SPB	−0.35	0.44	0.70	0.30	1.66	0.42	−0.05	0.44	0.96	0.40	2.26	0.92
EMP			1						1			
Period of diagnosis												
2002–2009	−0.18	0.12	0.84	0.66	1.06	0.14	−0.27	0.12	0.77	0.60	0.96	0.03
2010–2016	−0.34	0.12	0.71	0.56	0.90	<0.01	−0.40	0.12	0.67	0.53	0.85	<0.001
1994–2001			1						1			

Patients were followed up through December 31, 2021. *PCL*, plasma cell leukemia; *MM or PCM*, multiple myeloma or plasma cell myeloma; *SPB,* solitary plasmacytoma of bone; *EMP*, extramedullary (extraosseous) plasmacytoma; *HR*, hazard ratio; *LCL*, lower confidence limit; *UCL,* upper confidence limit.

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In a recent study, MM was described as the most common lymphoid neoplasm (19.2%) according to projections of hematologic neoplasms for Spain in 2021[26]. In Spain, MM was considered the most common lymphoid pathology according to REDECAN data obtained for the period 2009–2018, with an ASR_E of 6.8 [95% CI 6.7; 7.0][7].

The higher number of cases observed in males in most age groups in our study was similar to that observed in other studies[20,21]. The reason for the higher incidence of MM in males is not entirely clear, although the possibility of a disease-modifying gene on the sex chromosomes has been proposed[27]. When evaluating the incidence of MM in women, attempts have been made to identify protective factors. However, a study conducted by the International MM Consortium found no association between reproductive history, hormone therapy use, and the etiology of myeloma in women[28]. A high ASR_E ratio (men: women) may reflect greater exposure of males to risk factors associated with MM in the population.

The number of cases of MM and other PCNs increased over time, which may be associated with population aging. As an important demographic factor, the population of Spain increased from 38,850,000 in 1990 to 47,679,488 in 2020, accompanied by a regressive population pyramid due to progressive aging[29].

Age as a risk factor and its possible association with the incidence of MM and PCNs are consistent with the changes observed in Spain's population pyramid over the years, with a lower proportion of younger people in the 1990s and a higher proportion of adults and older people in 2025[30]. Although age is a general risk factor for cancer, there is no evidence that aging as a biological process is considered a cause associated with the development of MM.

According to data from the province of Girona, the total aging index increased from 96.5 in 1994 to 113.2 in 2024. When considering the age structure for both sexes, in 1994, the population aged 0–15, 16–64, and > 65 years accounted for 18.4%, 65.5%, and 16.2%, respectively. In contrast, in 2020, for the same age groups, these proportions were 17.04%, 64.9%, and 18.04%, respectively[31]. As a result, the absolute number of cases of MM and other PCNs may continue to increase in the coming years as the population ages.

The high number of cases of MM and other PCNs may be related to the increase in the incidence of endocrine, nutritional, and metabolic diseases, which include obesity as a risk factor. Although no recent data are available on the incidence of obesity in Girona, the hospital morbidity rate for endocrine, nutritional, and metabolic diseases was 139 per 100,000 person-years in 2020[29], making it important for further studies to evaluate the association between obesity and MM in the population.

In our study, median observed survival for MM and other PCNs increased from 1.86 years among patients diagnosed between 1994 and 2001 to 3.65 years among those diagnosed between 2010 and 2016. These results are consistent with the improved survival observed by our group during the period 1996–2015[32] and are also comparable to those observed by Chang et al. in a study conducted in the provinces of Granada and Girona (1994–2016), which reported an increase in survival from 27.4 to 47.4%[33].

Our study found a significant increase in survival; these results are comparable to the MM survival projections for 2026 presented by REDECAN[7]. The improvement in survival likely reflects advances in MM management and the progressive introduction of novel therapeutic agents, including HDM-ASCT prior to 2000, the introduction of thalidomide and IMiDs starting in 2000, proteasome inhibitors in 2003, and monoclonal antibodies in 2015 and 2016[10,11,34]. However, the impact of recent treatments on MM survival, including bispecific antibodies, antibody–drug conjugates, checkpoint inhibitors, CAR-T cell therapy, and bispecific T-cell engaging antibodies, will become apparent in the coming years.

Our results are also comparable to those of a study conducted at the Hospital Clínic of Barcelona (1970–2015), which showed an increase in median survival from 3.0 to 5.1 years in the 1985–1999 and 2000–2015 periods, respectively[35]. Another study conducted at the University Hospital of Salamanca (1980–2020) also showed an increase in survival, with a median survival of 3.12 years and 8.63 years in the 1991–2000 and 2011–2020 periods, respectively[36].

The increase in survival associated with advances in myeloma treatment has also been reported in other European countries[20], with a similar pattern of increased survival observed in New Zealand[21] and South Korea[24]. In

addition to reporting an increase in survival rates, other studies analyzed factors associated with access to treatment and reimbursement by the National Health System[37]. According to EUROCARE-6 data, there is evidence of improved survival in myeloma. However, the study also highlights inequality in survival for lymphoid neoplasms across Europe in terms of quality of care and access to treatment[38].

This study has some limitations. The incidence study does not account for variables that could be associated with myeloma incidence, such as environmental factors, among others. Regarding the survival study, variables associated with prognosis such as comorbidities, laboratory tests, and treatment, were not considered; therefore, observed survival rates may differ in other regions depending on risk factors. Another limitation is the high number of unknown cases within the disease stage variable, which could lead to an overestimation of survival. In addition, the estimate for plasma cell leukemia (PCL) should be interpreted cautiously because only 8 of the 12 PCL cases identified in the overall cohort were included in the survival analysis, and all 8 died during follow-up, resulting in limited precision and a wide 95% CI. However, one of the study's strengths is that the data came from a population-based cancer registry, which allowed for a long-term assessment of incidence trends and survival, while also reducing certain biases that might arise in clinical trials, where the participants who benefit most are younger individuals. In contrast, older participants, for whom treatments typically offer less benefit in terms of treatment response, prognosis, and survival, are less represented.

In conclusion, this study found no significant changes in the incidence trends of MM and other PCNs in the province of Girona during the period 1994–2020. The incidence analysis showed no significant trends, with stable incidence in men, women, and both sexes. There was a significant increase in the survival of MM and other PCNs, which likely reflects advances in MM management and the progressive introduction of novel therapeutic agents. The impact of immunotherapy treatments, CAR-T cell therapy (allogeneic and autologous), BiTE antibodies, and CAR-NK in patients with relapsed/refractory MM may become evident in population-based survival studies in the coming years. The study of incidence, trends, and survival, as well as associated factors, is key to understanding the etiology of myeloma and guiding better clinical management, treatment, and prognosis in the population.

Methods

Study population

Cases of MM and other PCNs were ascertained from the Girona Cancer Registry (GCR), Spain, covering the period 1994–2020. The GCR covers the population of the province of Girona, located in northeastern Spain, with 781,788 inhabitants in 2020, according to the Instituto Nacional de Estadística (INE)[29]. Cases of MM and other PCNs were morphologically coded according to the International Classification of Diseases for Oncology, third edition (ICD-O-3)[39]. Specifically, multiple myeloma or plasma cell myeloma (MM or PCM) (M–9732/3 with topographic code C42.1), plasma cell leukemia (PCL) (M–9733/3 with topographic code C42.1), extraosseous plasmacytoma (EMP) (M–9734/3 with topographic code C40), and solitary plasmacytoma of bone (SPB) (M–9731/3 with topographic code C41) were included[39]. Disease stage was classified according to the Durie-Salmon Staging System and the International Staging System[40,41]. Demographic information (gender and age at diagnosis) and tumor information (year of diagnosis, topography, histology, behavior, and stage) were recorded for each type of neoplasm. For the survival study, patients were stratified into three periods according to the year of diagnosis: 1994–2001, 2002–2009, and 2010–2016, with follow-up through December 2021. These periods correspond to the introduction of advances in MM treatment according to GCR data. In this study, we used the term "multiple myeloma and other plasma cell neoplasms" (MM and other PCNs) to refer to cases of myeloma with a defining event (MM or PCM), as well as the clinical variant of myeloma, PCL, and other types of plasma cell neoplasms, such as SPB and EMP. MM and other PCNs were analyzed as a single entity. We also analyzed MM or PCM separately, since most reported cases corresponded to MM. Data collection and recording were

carried out in accordance with the International Agency for Research on Cancer (IARC) and the European Network of Cancer Registries (ENCR). The GCR is a member of the International Association of Cancer Registries (IACR), the ENCR, and the Spanish Network of Cancer Registries (REDECAN).

Statistical analyses

Quantitative variables were expressed as median and interquartile range (IQR), while qualitative variables were presented as percentages. Age-specific incidence rates, crude rates (CR), and age-standardized incidence rates based on the European standard population (ASR_E, 2013) and World standard population (ASR_W, Segi-Doll, 1960) were calculated using the direct method and expressed per 100,000 person-years. Age-specific and age-standardized rates were calculated using the csu_ageSpecific() and csu_asr() functions, respectively, from the Rcan R package[42]. Age-standardized rates were adjusted for age; analyses were stratified by sex. The 95% confidence intervals (95% CI) for ASR_E and ASR_W and the 95% CI for CR were determined using Poisson approximation and the inverse chi-square distribution, respectively[43,44]. The population at risk was obtained from the INE[29]. Temporal trends in age-standardized incidence rates were analyzed using a joinpoint regression model, estimating trend change points, annual percent changes (APCs), average annual percent changes (AAPCs), and their corresponding 95% confidence intervals, with the number of joinpoints set at a minimum of 0 and a maximum of 3, using calendar year as the regression variable[45]. The Monte Carlo permutation method was used to determine whether changes in trends were statistically significant[46]. In the description of trends, we define an increase or decrease when the APC or AAPC was statistically significant; otherwise, the trend was defined as stable. Joinpoint regression analyzes trends over consecutive time segments and evaluates the statistical significance of increases or decreases after performing the best model fit. For the observed survival (OS) and net survival (NS) analyses, cases of MM and other PCNs diagnosed between 1994 and 2016 were included, with follow-up available through December 2021. Cases of MM and other PCNs diagnosed by death certificate only (DCO), cases with missing data, and cases with a follow-up time of 0 days were excluded from the survival analysis. The nonparametric Kaplan–Meier estimator was used for the OS analysis. The log-rank test statistic was used to determine statistical differences in OS between study periods. For the proportional hazards analysis, univariate and multivariable Cox regression models were used, with age included as a continuous variable and study period as a categorical variable. The proportional hazards assumption was evaluated using Schoenfeld residuals, and both global and covariate-specific tests were considered. For the NS analysis, we used the nonparametric Pohar-Perme method implemented in the relsurv R package, using the rs.surv() function[47]. Differences in NS between study periods were assessed using the log-rank-type test[48], implemented in the rs.diff() function[47]. Population life tables for the province of Girona were obtained from the Institut d'Estadística de Catalunya (Idescat)[31], prepared in R and matched to patients by age, sex, and calendar year using the rmap argument[47]. Differences were considered statistically significant at $p<0.05$. The analyses were performed using R software version 4.4.0 and Joinpoint software version 5.4.0.

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Author contributions RMG, AS, and MS contributed to the study conception and design. Data collection was performed by JT and AR. Formal data analysis was performed by KG, AA and AV. The original draft of the manuscript was written by KG. Reviewing and editing was performed by KG, AV, AS, JT, AR, AA, MS and RMG. All authors contributed to the article and approved the submitted version.

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Data availability The datasets generated or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Competing interests The author(s) declare no competing interests.

Ethical approval This study was carried out using anonymized data from the Girona Cancer Registry (GCR), which complies with the legal regulations in the Law for Data Protection and Management of clinical data in force in Spain. Informed consent was not required according to Laws 14/1986 and 33/2011, General and Spanish Public Health, as well as Law 8/2001 of June 14, of the Pla Estadístic de Catalunya 2001–2004, which recognizes the GCR as a statistical file. No intervention has been performed on human or animal subjects. All procedures have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. This study was approved by the Institutional Review Board of the Hospital Universitari de Girona Dr. Josep Trueta (approval number 2022.063).

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Authors and Affiliations

Kleber Garrochamba[1,3] · Alicia Villavicencio[2,3] · Alberto Ameijide[4] · Jan Trallero[3,5,7] · Aina Romaguera[3,5,6,7] · Arantza Sanvisens[3,5] · Marc Saez[7,8] · Rafael Marcos-Gragera[3,5,7,8,9]

✉ Kleber Garrochamba
kggarrochamba@utpl.edu.ec

1 Departamento de Ciencias de La Salud, Universidad Técnica Particular de Loja, Loja, Ecuador

2 Facultad de La Salud Humana, Universidad Nacional de Loja, Loja, Ecuador

3 Epidemiology Unit and Girona Cancer Registry, Catalan Institute of Oncology, Girona Biomedical Research Institute Dr. Josep Trueta (IDIBGI-CERCA), Girona, Spain

4 Southern Catalonia Biomedical Research Institute - IRBCatSud, Sant Joan de Reus University Hospital, Reus, Spain

5 Josep Carreras Leukaemia Research Institute, Badalona, Spain

6 Department of Computer Science, Applied Mathematics and Statistics, University of Girona, Girona, Spain

7 Research Group on Statistics, Econometrics and Health (GRECS), University of Girona, Girona, Spain

8 CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain

9 Department of Medical Sciences, University of Girona, Girona, Spain