Cancer-specific mortality in multiple myeloma: a population-based retrospective cohort study

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Received: March 7, 2023.
Accepted: July 4, 2023.
Early view: July 13, 2023.

https://doi.org/10.3324/haematol.2023.282905

Abstract

Survival has improved in patients diagnosed with multiple myeloma (MM) over the last two decades; however, there remains a paucity of data on the causes of death in MM patients and whether causes of death change during the disease trajectory. We conducted a retrospective population-based study to evaluate the rates of MM-specific *versus* non-MM cause of death and to identify factors associated with cause-specific death in MM patients, stratified into autologous stem cell transplant (ASCT) and non-ASCT cohorts. A total of 6,677 patients were included, 2,576 in the ASCT group and 4,010 in the non-ASCT group. Eight hundred and seventy-three (34%) ASCT patients and 2,787 (68%) non-ASCT patients died during the follow-up period. MM was the most frequent causes of death, causing 74% of deaths in the ASCT group and 67% in the non-ASCT group. Other cancers were the second leading causes of death, followed by cardiac and infectious diseases. Multivariable analysis demonstrated that a more recent year of diagnosis and novel agent use within 1 year of diagnosis were associated with a decreased risk of MM-specific death, whereas a history of previous non-MM cancer, older age, and the presence of CRAB criteria at diagnosis increased the risk of non-MM death. Our data suggests that despite improvement in MM outcomes in recent years, MM remains the greatest threat to overall survival for patients. Further advances in the development of effective MM therapeutic agents in both ASCT and non-ASCT populations and patient access to them is needed to improve outcomes.

Introduction

Multiple myeloma (MM) is common hematologic malignancy, representing 2% of all cancers[1] and affecting 27,000 patients per year in North America, with an age standardized incidence rate of 5.2/100,000.[2] It is predominantly an illness of older adults, with a median age of 69 years at diagnosis.[1] The treatment of patients with MM has changed dramatically over the last two decades, as therapy has evolved beyond the traditional backbone of corticosteroids and alkylating agents to combinations of 'novel' drugs including proteosome inhibitors (PI), immunomodulatory drugs (IMiD) and monoclonal antibodies.[3, 4] As a result, the overall survival of MM patients has improved steadily, with recent updates reporting median survival times exceeding 10 years in select patient groups.[5,6] Despite these improvements, MM remains incurable, with the vast majority of patients experiencing disease relapse and remaining at risk for MM-specific death.

There is a paucity of data on the proportion of MM-specific *versus* non-MM (COD) among MM patients in the novel agent era, and it is unclear whether this changes during the course of the illness. Previous population-based studies have shown MM to be the most common cause of death in MM patients, with approximately 75% of patients experiencing MM-specific death.[7-11] Two large US-based SEER analyses evaluating MM-specific survival between 1973-2008[10] and 1987-2013[8] showed improvements in MM-specific death rates in more recent years, however more modern patient cohorts with increasing novel agent use have not yet been evaluated. This information is becoming more important in the age of prolonged survival for MM patients, whereby patients may be at risk for non-MM complications and comorbidities, and therapeutic decisions may become even more complex.

Understanding the relative rates of MM-specific *versus* non-MM cause of deaths is critical in guiding decisions regarding treatment options, monitoring strategies, supportive care, and patient counseling to enable shared decision-making. Thus, we conducted a population-based study with following objectives: i) to evaluate rates of MM-specific *versus* non-MM cause of death and ii) to identify prognostic factors associated with cause-specific death among patients with MM.

Methods

We conducted a retrospective population-based study using data from ICES (formerly known as the Institute for Clinical Evaluative Sciences), a prospective administrative database that captures all health records in the publicly funded health care system in Ontario, Canada. Ontario has a universal, single payer, publicly funded system which provides access to health care expenditures including chemotherapy agents. Administrative records are maintained by the province's health care system, which captures virtually all health care encounters, with a loss of follow-up of less than 0.5% per year.[12] Linked administrative datasets used for this study included the Ontario Health Insurance Plan (OHIP), Registered Persons Database (RPDB), Ontario Cancer Registry (OCR) and the Ontario Registrar General Death database (ORGD), which receives information from death certificates completed by physicians (Form 16) and codes causes of death by ICD code.[13] These datasets were linked using unique encoded identifiers from the provincial health insurance number and analyzed at ICES. This study was approved by the Hamilton Integrated Research Ethics Board, REB number 5887.

Adult patients treated for newly diagnosed MM between 2007-2018 were identified using ICD-O-3 code 9732/3 (MM). Patients who did not receive MM treatment within 1 year following diagnosis were excluded to ensure that those with smoldering MM were not included in our analysis, consistent with prior population-based studies.[14] The cohort was then stratified into autologous stem cell transplant (ASCT) and non-ASCT groups, with the ASCT group being those who had ASCT within 1 year of diagnosis. Treatment sequencing in Ontario is largely uniform given the funding guidelines.[15] Briefly, all eligible patients (i.e., fit and age <70 years) undergo induction therapy with CYBORD (cyclophosphamide-bortezomib-dexamethasone) followed by ASCT in first line and lenalidomide maintenance (funded 2014) until disease progression. Due to the funding pathways in Ontario, for all eligible patients ASCT is largely done in first line (early-ASCT) as previously shown with nearly 70% of patients <65 years receiving an ASCT within 1 year of diagnosis.[16] Non-ASCT patients undergo treatment with PI- and/or IMID-based therapies with VMP (velcade-melphalan-prednisone) previously and Rd (lenalidomide-dexamethasone +/- bortezomib) in more recent years. At the time of relapse, patients have access to anti-CD38 (funded 2019), carfilzomib (funded 2018) and pomalidomide (funded 2015) based regimens.

Baseline patient and disease characteristics at the time of MM diagnosis were collected. Comorbidities were recorded based on health service use in the 24 months preceding MM diagnosis using the Johns Hopkins Adjusted Clinical Group system score (calculated using The Johns Hopkins ACG® System Version 10), whereby sum of the 32 ACG® System Aggregated Diagnosis Groups (ADG) was categorized as high (≥10) or low (<10) comorbidity burden.[17] Patient geographic and socioeconomic status (SES) was defined by neighborhood income quintile (rural, and among urban areas level 1 having the lowest SES and level 5 the highest SES status). MM CRAB features (hypercalcemia, renal failure, anemia, bone lesions) within 6 months before or after MM diagnosed were defined by respective ICD codes as published previously.[18] Prior cancer diagnosis within 15 years of the index MM diagnosis was recorded. As treatment algorithms for MM are largely consistent across the province due to funding criteria, all funded cancer drugs (alkylating agents, PI, IMiD, and monoclonal antibodies) available to patients during the study period were extracted.[19]

Among patients that died during the study follow-up period, the cause of death was identified using the antecedent cause of death as reported in the ORGD by ICD code. We estimated the cumulative incidence of MM-specific and non-MM cause of death. In order to identify the association of prognostic factors on the probability of MM-specific and non-MM deaths, we performed competing risks regression and estimated the multivariate Fine-Gray subdistribution hazard ratios adjusted for covariates. Results were reported as hazard ratio (HR) with 95% confidence interval (CI) and statistical significance defined as $P<0.05$. Analyses were conducted using Statistical analysis system (SAS version 9.4).

Results

A total of 6,677 patients were identified in the newly diagnosed MM cohort, 2,576 in the ASCT group and 4,101 in the non-ASCT group. Baseline patient characteristics are shown in Table 1. The median age at diagnosis for the overall cohort was 68 years (58 and 74 years in the ASCT group and non-ASCT group, respectively). Forty-three percent of the overall cohort was female. There was a low burden of comorbidities as indicated by a low ADG score (<10) in 74% of all patients, a high comorbidity burden (ADG ≥10) was more common in the non-ASCT group than the ASCT group (31% *vs*. 19%; $P<0.001$). In total, 824 pa-

tients (12%) of the overall cohort had a diagnosis of another cancer within 15 years prior to the MM diagnosis, which was present in a higher proportion of patients in the non-ASCT group (15%) compared to the ASCT patients (8%). Common cancers present prior to MM diagnosis were prostate (4% non-ASCT; 2% ASCT) breast (1% for both non-ASCT and ASCT groups) and colorectal cancers (2% non-ASCT cohort; <1% ASCT cohort). The majority of patients (87%) of the cohort were from urban centers, and SES by neighborhood income quintile was balanced across quintiles 1-5 with no significant difference between the ASCT and non-ASCT groups.

Patients diagnosed in 2007-2013 comprised 56% of the overall cohort with 44% being diagnosed between 2014-2017. The majority of patients received treatment with a novel agent within 1 year of diagnosis, 75% in the ASCT group and 81% in the non-ASCT group.

Eight hundred and seventy-three (34%) in the ASCT group and 2,787 (68%) in the non-ASCT group died during the study follow-up period, with median follow up time of 45 months (range, 25-73) and 27 months (range, 14-49) respectively. The median overall survival for the ASCT cohort was 8.4 years (95% confidence interval [CI]: 7.9-9.2) and for the non-ASCT cohort was 3.0 years (95% CI: 2.8-3.1). The cumulative incidence of MM-specific death was higher than non-MM death for both the ASCT (24.9%: MM-specific and 7.9 %: non-MM at 5 years) and non-ASCT cohort (47.6 %: MM-specific and 22.5%: non-MM at 5 years) throughout the disease trajectory (Figure 1).

Cause of death stratified by time from MM diagnosis (<3 years, 3-5 years and >5 years) for both cohorts is shown in Figure 2. MM-specific death was higher overall in the ASCT cohort (74% *vs*. 67% in the non-ASCT cohort) and at each respective time point. Other non-MM cancers accounted for 7% of deaths in the ASCT group and 6% in the non-ASCT group. These cancers included cancer of the lung (11% non-ASCT and ASCT), acute myeloid leukemia (7% non-ASCT and 10% ASCT) and colorectal cancers (4% non-ASCT cohort and 3% ASCT cohort). Additionally, in our cohort 2.5% and 5.8% of patients died from heart disease and 6.2% and 4.3% of infectious diseases in each ASCT and non-ASCT group respectively. Detailed causes of death are presented in the *Online Supplementary Table S1*.

Multivariable analysis showing factors associated with MM and non-MM cause of death is shown in Table 2. MM-specific mortality was decreased in the more recent 2014-2017 cohort in both ASCT hazard ratio [HR] =0.72; 95% CI: 0.65-0.80) groups, with similar effects observed for non-MM specific mortality. The use of novel agents was also associated with decreased MM-specific mortality for both groups, after adjusting for non-MM death as a competing risk: ASCT (HR=0.84; 95% CI: 0.70-1.00) and non-ASCT (HR=0.84; 95% CI: 0.75-0.94). CRAB features at diagnosis were associated with an increased risk of both MM-specific and non-MM causes of death across all groups, whereas a history of previous non-MM cancer was associated with an increased risk of non-MM cause of death among both the ASCT (HR=1.91; 95% CI: 1.29-2.82) and non-ASCT (HR=1.26; 95% CI: 1.05-1.50) groups.

Table 1. Baseline characteristics.

Variable	Value	Non-ASCT Cohort N=4,101	ASCT Cohort N=2,576	Total N=6,677
Age in years at diagnosis	Median (IQR)	75 (70-80)	59 (53-64)	69 (60-77)
Male sex, N (%)		2,319 (56.6)	1,478 (57.4)	3,797 (56.9)
Total ADG score* (%)	Low comorbidities (ADG <10) High comorbidities (ADG ≥10)	2,816 (68.7) 1,285 (31.3)	2,091 (81.2) 485 (18.9)	4,907 (73.5) 1,770 (26.5)
Rural status and neighbourhood income quintile◇, N (%)	Rural Urban - quintile 1 (low income) Urban - quintile 2-4 Urban - quintile 5 (high income)	564 (13.8) 686 (16.7) 2120 (51.7) 719 (17.5)	301 (11.7) 328 (12.7) 1410 (54.7) 534 (20.7)	865 (13.0) 1,014 (15.2) 3,530 (52.9) 1,253 (18.8)
Year of diagnosis	2007-2013 2014-2017	2,339 (57.0) 1,762 (43.0)	1,371 (53.2) 1,205 (46.8)	3,710 (55.6) 2,967 (44.4)
CRAB at diagnosis^, N (%)	1,923 (46.9)	991 (38.5)	2,914 (43.6)	2,914 (43.6)
Previous cancer within 15 years of MM diagnosis, N (%)	608 (14.8)	216 (8.4)	824 (12.3)	824 (12.3)
Novel drugs within 1 year of diagnosis#, N (%)	3,307 (80.6)	1,937 (75.2)	5,244 (78.5)	5,244 (78.5)

^Hypercalcemia, renal failure, anemia, bone lesions; *co-morbidities defined by John Hopkin aggregated diagnosis group (ADG) with high co-morbidities defined as ≥ 10; #lenalidomide, thalidomide or bortezomib within 1 year of diagnosis; ◇does not add to 100% due to missing values. ASCT: autologous stem cell trasnplant; IQR: interquartile range; MM: multiple myeloma.

Discussion

This study represents one of the largest real-world cohort studies to examine MM-specific *versus* non-MM cause of death among MM patients. Our data suggests that even though MM-specific mortality has decreased in more recent years and with novel agents, MM remains the greatest threat to survival for MM patients, including among the older non-ASCT cohort.

Our results show similar trends to those seen in a large cohort study evaluating MM-specific death using the US Surveillance, Epidemiology, and End Results Program (SEER) and Puerto Rico Central Cancer Registry (PRCCR) database between 1987-2013[8], showing 72% of patients having MM-specific death as compared to 69% in our cohort, with similar median ages at diagnosis of 69 and 68 years respectively. They also report a decrease in MM-specific death in more recent years, suggesting patients with access to novel therapeutics and resultant prolonged overall MM survival may have an increased risk of developing non-MM comorbidities with age and time. A second SEER analysis evaluating MM-survival by historical time cohorts and novel agent access further supported this observation, with markedly reduced MM-specific mortality following the advent of new treatments.[10] It is important to note that while MM-specific mortality has decreased over time, overall survival for older adults with MM remains poor with a median overall survival noted to be around 3 years consistent with previously published series.[20]

The SEER/PRCCR study also reported MM as the most

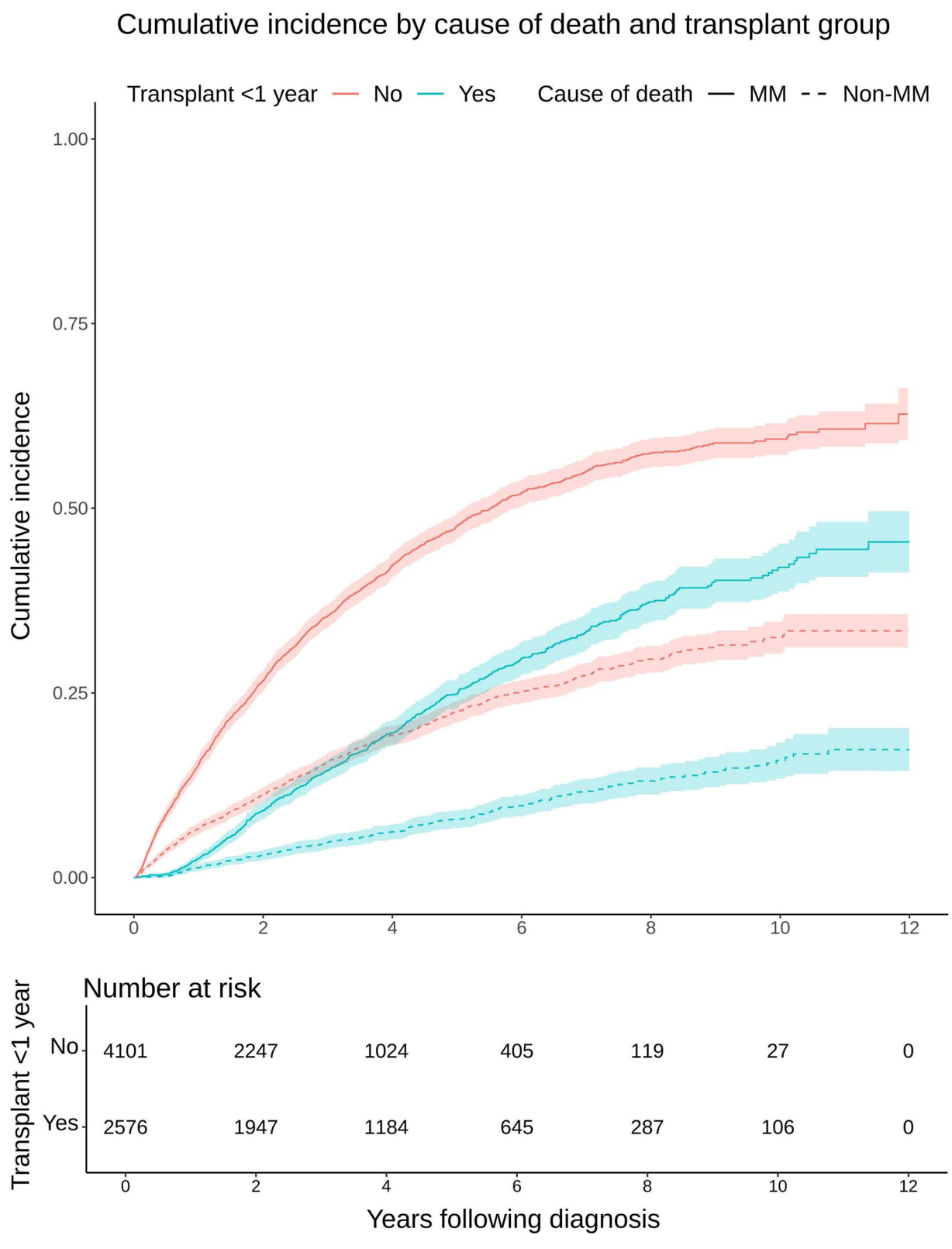

Figure 1. Cumulative incidence by cause of death and transplant group. MM: multiple myeloma.

common cause of death across time all time periods, with a slightly decreased risk of MM-specific death for patients alive at 2 (SEER) or 3 (PRCCR) years post MM diagnosis.[8] We saw similar outcomes, with fewer patients having MM as the primary cause of death amongst patients alive 5 years post-diagnosis. There are several factors that could contribute to this finding, including an increased risk of non-MM illnesses with age, chemotherapy adverse effects, and/or favorable MM disease biology.

Non-myeloma cancer was the second most common cause of death in our study, leading to 6% of deaths in the non-ASCT group and 7% in the ASCT group, followed closely by cardiac disease in 5.8% and 2.5% of patients respectively. Interestingly, in the aforementioned SEER/PRCCR study, patients in the PRCCR had an 11.2% mortality rate from other cancers followed by 5.3% from heart disease, whereas the SEER cohort had cardiac disease as the highest non-MM cause of death (11.5%) followed by closely by other cancers (5.2%).[8]

Little is known about the impact of a prior cancer diagnosis on survival in MM patients, and more work in this area is needed. While our study demonstrated that 12.8% of our cohort were diagnosed with a separate cancer within 15 years prior to the index MM diagnosis, we were not able to distinguish the relative contribution of these diagnoses *versus* secondary primary malignancies (SPM) acquired after the MM diagnosis to the overall non-MM cancer deaths in our cohort.

SPM are a known risk in patients with MM,[21] in particular associations with ASCT and lenalidomide have been reported.[22-24] A SEER analysis examining SPM in patient with MM over time and treatment eras showing a small increase in SPM over time, independent of improved MM-specific survival, from 4.7% of patients in a 1995-99 cohort to 6.3% in a 2005-09 cohort, potentially driven partly by an increased risk of developing lymphoma and other hematologic malignancies.[22]

In the DETERMINATION study that compared lenalidomide, bortezomib and dexamethasone (RVD) for eight cycles *versus* RVD + ASCT/RVD consolidation, both followed by lenali-

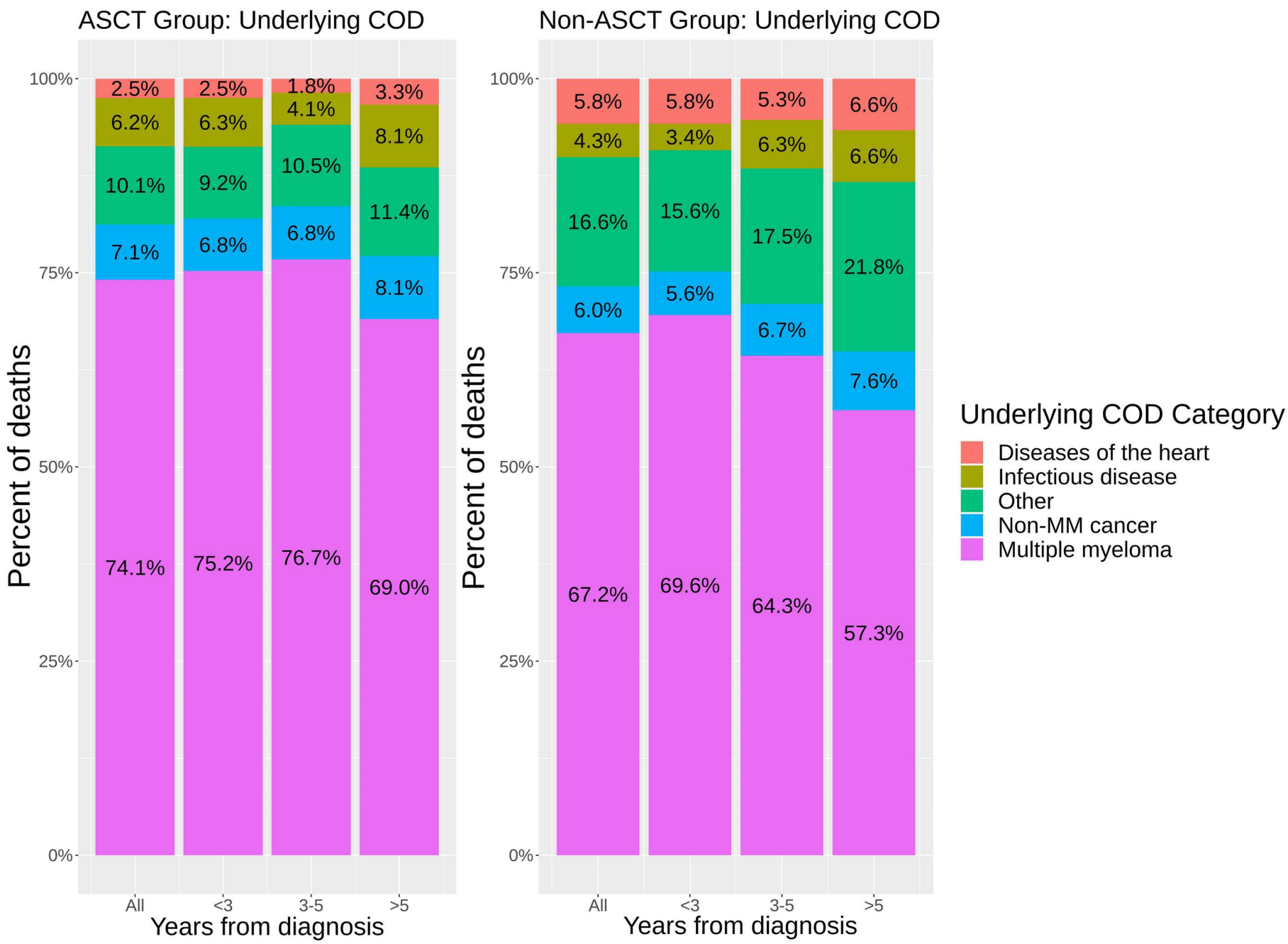

Figure 2. Causes of death by autologous stem cell transplant group and time from multiple myeloma diagnosis. COD: cause of death; MM: multiple myeloma; ASCT: autologous stem cell transplant.

Table 2. Multivariable Fine-Gray model showing factors associated with multiple myeloma specific *versus* non-multiple myeloma cause of death (sub-hazard ratio presented with 95% confidence interval).^

Variable	Value	ASCT <1 year following diagnosis		No ASCT <1 year following diagnosis	
		MM COD (95% CI)	Non-MM COD (95% CI)	MM COD (95% CI)	Non-MM COD (95% CI)
Age in years at diagnosis date	<50 (ref = 50-69) 70-79 (ref = 50-69) 80+ (ref = 50-69)	0.98 (0.79-1.20) 1.33 (0.81-2.18) 2.03 (0.64-6.39)	0.67 (0.44-1.02) 0.31 (0.08-1.23) 6.44 (2.19-18.99)	0.85 (0.52-1.39) 0.91 (0.81-1.02) 1.08 (0.94-1.23)	0.88 (0.43-1.78) 1.15 (0.96-1.37) 1.46 (1.20-1.76)
Sex	Male (ref = female)	1.20 (1.02-1.41)	1.31 (1.00-1.73)	0.99 (0.91-1.09)	1.12 (0.98-1.28)
Rural status and neighbourhood income quintile	Rural (ref = urban: 1) Urban: 2-4 (ref = urban: 1) Urban: 5 (ref = urban: 1)	1.00 (0.72-1.38) 1.09 (0.85-1.39) 0.85 (0.64-1.14)	1.12 (0.68-1.85) 0.84 (0.55-1.26) 1.14 (0.72-1.80)	1.13 (0.95-1.33) 1.12 (0.98-1.28) 1.00 (0.85-1.18)	0.88 (0.70-1.10) 0.77 (0.65-0.92) 0.73 (0.59-0.91)
Total ADG score*	High (ADG >=10) (ref = low [ADG <10])	1.06 (0.86-1.30)	1.12 (0.80-1.57)	1.06 (0.95-1.17)	1.11 (0.96-1.27)
Year of diagnosis	2014-2017 (ref = 2007-2013)	0.69 (0.55-0.86)	0.82 (0.57-1.18)	0.72 (0.65-0.80)	0.86 (0.74-1.00)
CRAB^	Yes (ref = No)	1.72 (1.48-2.01)	1.55 (1.19-2.02)	1.52 (1.38-1.66)	1.32 (1.16-1.51)
Cancer diagnosis in the previous 15 years	Yes (ref = No)	0.84 (0.61-1.15)	1.91 (1.29-2.82)	0.92 (0.80-1.06)	1.26 (1.05-1.50)
Novel drugs within 1 year of diagnosis#	Yes (ref = No)	0.84 (0.70-1.00)	0.92 (0.68-1.24)	0.84 (0.75-0.94)	0.85 (0.73-0.99)

*Comorbidities defined by John Hopkin aggregated diagnosis group (ADG) with high comorbidities defined as >/= 10; #lenalidomide, thalidomide or bortezomib within 1 year of diagnosis; ^hypercalcemia, renal failure, anemia, bone lesions. COD: cause of death; MM: multiple myeloma; ASCT: autologous stem cell transplant; ref: reference.

domide maintenance until progression, 10.4% of patients in the RVD group and 10.7% of patients in the RVD + ASCT group developed SPM.[23] While secondary hematologic malignancies developed in 2.5% of the RVD group and 3.6% of the RVD + ASCT group, no RVD patients developed acute myeloid leukemia (AML) or a myelodysplastic syndrome as opposed to 2.7% RVD + ASCT patients (*P*=0.002).[23] In the IFM 2009 trial, comparing RVD for eight cycles *versus* RVD + ASCT/RVD consolidation, both followed by maintenance lenalidomide for 1 year or until progression, SPM occurred in 6.0% of the RVD group and 7.1% of the RVD + ASCT group, with hematologic malignancies developing in one (0.3%) of RVD patients (MDS) and four (1.1%) RVD + ASCT patients (3 AML, 1 MDS).[24] Interestingly, in our study AML was the second most common non-MM cancer cause of death in both cohorts, accounting for 7% of non-MM cancer deaths in the non-ASCT group and 10% in the ASCT group. Patients in both cohorts had exposure to alkylating agents, with the use of cyclophosphamide for induction and high dose melphalan for conditioning in the ASCT group, as well as standard dose melphalan used for induction in many of the non-ASCT patients. Patients in our study were also older, with median age of 69 years at diagnosis, as compared to 57-59 years in the RVD groups and 55-60 years in the RVD + ASCT groups for DETERMINATION[23] and IFM2009[24] respectively.

The association of cardiovascular disease in MM patients has been previously reported, is higher than a control cohort without cancer,[25] and may occur due to both MM-related (treatment, anemia, renal failure) and MM-unrelated (age, obesity, diabetes)[26] factors, supporting it as a common cause of death in MM patients.[27] Two studies using the SEER database[27,28] and a large French administrative cohort[29] showed a decreased risk of cardiovascular mortality over the last several decades in MM patients, which we did not see over the time horizon in the present study. Our study has several strengths including the large study population, comprehensive database, and standardized provincial treatment algorithms that may minimize heterogeneity in treatment that could impact MM-specific death. However, there are also several limitations. We used the antecedent (underlying) cause of death by ICD-10 as captured in the ORGD, which is populated from death certificates filled out by physicians. Misclassification of some patients is possible, though a high level of agreement on cause of death between the ORGD and a large prospective cohort of cancer patients with rigorous clinical follow up has been previously reported.[30] Additionally, determining solely one underlying cause of death may not always be possible particularly among causes such as infections were untreated MM, treatment for MM as well as other underlying comorbidities may all contribute to infections. We were unable to capture some specific patient and disease characteristics that could impact patient outcomes, such as high-risk cytogenetics. Our population also represent a more homogenous group of patients

treated within a publicly funded health care system with relatively uniform treatment approaches and, therefore, our results may not be generalizable to all treatment settings. Finally, we are unable to evaluate outcomes in patients receiving the most modern therapies (i.e., monoclonal antibodies) as these therapies were not funded in the upfront treatment setting during the study period.

Our study demonstrated that MM remains the most likely cause of death in patients diagnosed with MM, despite impressive improvements in overall survival in recent years with a growing armamentarium of novel therapeutics. This data can be helpful for patients and clinicians in guiding shared treatment decision-making and estimating risk benefit of therapies. It strongly supports the notion that optimization of MM-directed care is paramount for patients, whose survival ultimately remains at greatest risk from MM. However, we must remain mindful of the risks associated with MM-directed treatment such as secondary malignancies with our past and currently available treatments, and significant infections with the advent of T-cell redirecting therapies.[31-33] Further advances in the delivery of safe and effective MM therapeutic agents in both ASCT and non-ASCT cohort is needed to further improve outcomes in this disease.

Disclosures

AM discloses consultancy/honoraria fees from BMS, Takeda, Janssen, Amgen, Sanofi, Forus, GSK and Pfizer; has received research funding from BMS. GP discloses to currently hold individual stocks of Roche Canada; discloses consultancy fees from Astra-Zeneca, Merck and Profound Medical; discloses membership on advisory committee for Takeda. RC discloses consultancy/advisory board fees from Janssen, Sanofi, and Adaptive Biotech. AV discloses honoraria/advisory fees from Janssen, Sanofi, Apotex and Pfizer. RK discloses honoraria/advisory fees fom Janssen, BMS, FORUS, Amgen, Sanofi and Pfizer. AD has received institutional research funding from Sanofi, Takeda, TeneoBio, Caelum and Prothena; discloses consultancy/advisory board fees fom Janssen, Prothena, Imbrium, Pfizer and BMS. TW has received consultancy fees from Janssen, Carevive, Seattle Genetics and Sanofi. RF discloses consultancy/honoraria fees AbbVie, Amgen, Bayer, BMS, GSK, H3 Therapeutics, Janssen, Juno, Karyopharm, Kite, Merck, Novartis, Oncopeptides, OncoTracker, Pfizer, Pharmacyclics, Regeneron, Sanofi and Takeda; is part of the scientific advisory board of Adaptive Biotechnologies, Caris Life Sciences, OncoMyx and OncoTracker. HM discloses consultancy/honoraria fees from BMS, Takeda, Janssen, Amgen, Sanofi, Forus, GSK and Pfizer; has receieved research funding Janssen. All other authors have no conflicts of interest to disclose.

Contributions

HM, AM, GP, HS and AG developed the concept and designed the study. AG and HM collected data. HM, AM, GP, HS and AG analyzed and interpreted data. All authors wrote the manuscript and approved the final version of the article.

Acknowledgments

This document used data adapted from the Statistics Canada Postal CodeOM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from ©Canada Post Corporation and Statistics Canada. Parts of this material are based on data and/or information compiled and provided by CIHI, the Ontario Ministry of Health, and Ontario Health (OH). The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this report are based on Ontario Registrar General (ORG) information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the authors and do not necessarily reflect those of ORG or the Ministry of Public and Business Service Delivery. We thank IQVIA Solutions Canada Inc. for use of their Drug Information File.

Funding

HM is currently funded by the Hamilton Health Sciences Early Career Award. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long-Term Care.

Data-sharing statement

The data that support the findings of this study are available at ICES but restrictions apply to the availability of these data.

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