Cancer Causes & Control (2020) 31:641–650
https://doi.org/10.1007/s10552-020-01305-0

ORIGINAL PAPER

Self-reported health and survival in older patients diagnosed with multiple myeloma

Nadia A. Nabulsi[1] · Ali Alobaidi[1] · Brian Talon[1] · Alemseged A. Asfaw[1] · Jifang Zhou[1] · Lisa K. Sharp[1] · Karen Sweiss[2] · Pritesh R. Patel[3] · Naomi Y. Ko[4] · Brian C.-H. Chiu[5] · Gregory S. Calip[1,6]

Received: 1 September 2019 / Accepted: 24 April 2020 / Published online: 30 April 2020

Abstract

Purpose Patient-reported outcomes such as self-reported health (SRH) are important in understanding quality cancer care, yet little is known about links between SRH and outcomes in older patients with multiple myeloma (MM). We evaluated associations between SRH and mortality among older patients with MM.

Methods We analyzed a retrospective cohort of patients ages ≥ 65 years diagnosed with first primary MM using the Surveillance, Epidemiology, and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) data resource. Pre-diagnosis SRH was grouped as high (excellent/very good/good) or low (fair/poor). We used Cox proportional hazards models to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between SRH and all-cause and MM-specific mortality.

Results Of 521 MM patients with mean (SD) age at diagnosis of 76.8 (6.1) years, 32% reported low SRH. In multivariable analyses, low SRH was suggestive of modest increased risks of all-cause mortality (HR 1.32, 95% CI 1.02–1.71) and MM-specific mortality (HR 1.22, 95% CI 0.87–1.70) compared to high SRH.

Conclusion Findings suggest that low pre-diagnosis SRH is highly prevalent among older patients with MM and is associated with modestly increased all-cause mortality. Additional research is needed to address quality of life and modifiable factors that may accompany poor SRH in older patients with MM.

Keywords Multiple myeloma · Self-reported health · Survival · Cancer-specific mortality

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy, comprising over 10% of all blood cancers [1]. MM primarily affects older adults, with the median age of diagnosis about 66–70 years [2]. Survival rates are improving due to new effective therapies, with estimated 5-year survival rates of 52% between 2009 and 2015 [3].

Contemporary treatment of MM utilizes various combinations of high-dose chemotherapy, stem cell transplantation, and novel therapies including proteasome inhibitors and immunomodulatory drugs [4, 5]. Measures of quality of life, such as self-reported health (SRH), could be predictors of clinical decision-making, treatment preferences and health outcomes among patients with cancer [6–8]. For example, in a randomized trial that assessed prognostic significance of scores from the quality of life questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) in MM, multiple domains of quality of life measured before and during treatment were significant predictors of survival [9]. Additionally, a study of patient-reported outcomes in bortezomib clinical trials demonstrated the value of patient-reported measures in providing prognostic information [10]. Among patients with myelodysplastic syndromes, self-reported fatigue severity was also a significant independent predictor of survival [11]. This evidence suggests these measures are critical in the understanding of quality cancer care. However, the association between general SRH and outcomes in older patients with MM is not well documented [12, 13]. SRH is a simple,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10552-020-01305-0) contains supplementary material, which is available to authorized users.

✉ Gregory S. Calip
gcalip@uic.edu

Extended author information available on the last page of the article

one-item self-assessment of health that may support clinical decision-making in MM treatment.

Patients' perceptions of their general health may suggest a need for closer surveillance and inform healthcare interventions [14]. Generally, less than optimal SRH is a non-specific measure of disease burden and can be a significant predictor of mortality risk for older adults [14–22]. Theoretical frameworks, such as the Subjective Health Evaluation Model described by Knäuper and Turner, have been proposed to describe the psychological processes pertaining to individuals' self-assessment of their health and its role as a predictor of mortality [23, 24]. Other evidence indicates a moderately strong association between SRH and deaths due to cancer [15]; however, this association has not been explored in patients with MM.

Our objective was to describe SRH prior to MM diagnosis and evaluate the association between SRH and survival in a retrospective cohort study of adults from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) data resource.

Methods

Study design and data source

The SEER-MHOS data resource, sponsored by the National Cancer Institute and the Centers for Medicare and Medicaid Services (CMS), combines population-based data sources comprised of detailed information about adults ≥ 65 years of age with cancer [25]. Registries in the SEER program capture clinical, demographic, and cause of death data for patients with cancer. The MHOS provides data from survey responses regarding health-related quality of life (HRQOL) of Medicare Advantage Organization beneficiaries including self-reported socioeconomic measures and comorbidity data. Medicare Advantage plans are health plans offered by private companies that contract with Medicare, such as health maintenance organizations (HMOs) and preferred provider organizations (PPOs) [26, 27]. The current data include information from fourteen SEER cancer registries [28]. The data resource represents over 400 Medicare Advantage managed care plans that participate in data collection every year from 1998 through 2014 and over 140,000 survey respondents who are patients with cancer and survivors.

Study population

Our sample included patients aged ≥ 65 years diagnosed with a first primary cancer of MM between 1998 and 2013 that also responded to an MHOS survey within five years prior to their diagnosis. Patients were excluded from our analytic cohort if they did not have a first primary cancer of MM, were non-responsive with respect to SRH, were missing data regarding survival time, completed the survey within one month of MM diagnosis, or died within one month of MM diagnosis. Figure 1 depicts the inclusion and exclusion criteria applied to our sample.

Exposures

Pre-diagnosis SRH was assessed using a single MHOS question asking: "In general, would you say your health is: excellent, very good, good, fair, or poor?" in which patients selected one response option. SRH was dichotomized as high (excellent/very good/good) or low (fair/poor); high was used as the reference category in regression analyses. Included patient surveys must have occurred within 5 years prior to MM diagnosis. If multiple surveys were performed within this time frame, most recent responses prior to MM diagnosis were used.

Summary measures of responses to questions in the 36-Item Short Form Health Survey (SF-36) and the Veterans RAND 12-Item Health Survey (VR-12) were also collected to describe HRQOL among patients in the sample. Details of the SF-36 and VR-12 have been described elsewhere [29,

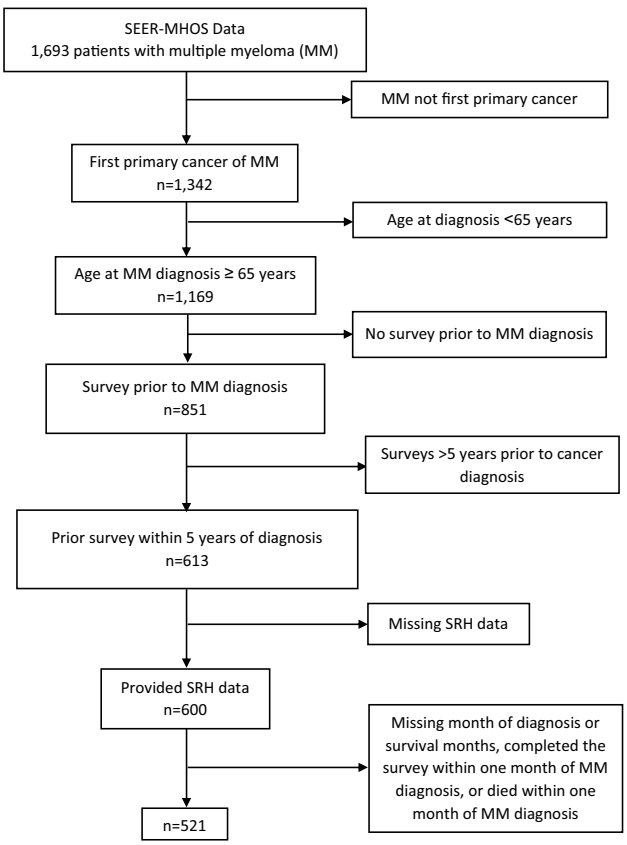

Fig. 1 Consort diagram illustrating study inclusion and exclusion criteria

30]. Algorithms developed by Boston University School of Public Health for the conversion of SF-36 to VR-12 scores were used in the SEER-MHOS data resource to account for changes in the survey instrument over time [31]. The VR-12 is a brief, generic health survey comprised of twelve items that correspond to eight principal physical and mental health domains including physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), general mental health (MH), role limitations due to emotional problems (RE), social functioning (SF), and vitality (VT) [32]. The items can be summarized into two scores, a mental component summary (MCS) score and physical component summary (PCS) score. The PCS and MCS scores utilize all eight scales in their calculation and are computed from weights derived from the 1999 Veterans Health Study [31–33].

Confounders

We collected information from SEER and MHOS data with respect to important clinical factors and characteristics considered to be a priori confounders associated with both SRH and risk of death. These variables included age at MM diagnosis (continuous), year of diagnosis (1998–2005, 2006–2010, 2011–2013 [categorized based on a timeline of changes in conventional MM therapies]), race/ethnicity (White, Black or African American, other), sex (male, female), marital status (married, not married), education level (less than high school, high school graduate/GED, college or above), smoking status (yes [every day or some days], not at all, unknown), and number of comorbid conditions (0–2, 3 or more, missing). Number of comorbid conditions was totaled from presence/absence of: angina pectoris/coronary artery disease, congestive heart failure, myocardial infarction, other heart conditions, stroke, emphysema/asthma/chronic obstructive pulmonary disease (COPD), Crohn's disease/ulcerative colitis/inflammatory bowel disease, arthritis of the hip/knee, arthritis of the hand/wrist, sciatica, diabetes/high blood sugar/sugar in urine, and hypertension. Patients with missing data on one or more comorbidities were classified as missing information on overall number of comorbid conditions. Survey characteristics included months between the MHOS survey and MM diagnosis (continuous) and who completed the survey (patient, proxy respondent).

Outcomes

The primary outcomes of interest were all-cause and MM-specific mortality, as documented from the SEER registries. Survival time was calculated as the number of months from the month and year of the first primary cancer diagnosis of MM until the month and year of death. For the analysis of all-cause mortality, patients were followed up until death for any reason, or censored at the end date of the follow-up period, November 30, 2016. For the analysis of MM-specific mortality, patients were followed up until death due to their first primary cancer, MM. In this cause-specific analysis, censorship occurred at death due to a non-MM-related cause or at the end date of the follow-up period.

Statistical analyses

We described the analytic sample of patients ($n = 521$) with first primary MM including demographics, clinical characteristics, survey responses, and comorbidities. Comparisons between patients with high and low SRH were assessed using independent sample *t*-tests for continuous variables and Chi-square tests of independence for categorical variables. HRQOL characteristics derived from the SF-36 and the VR-12 were described by SRH status. Median values for the HRQOL measures and corresponding interquartile ranges (IQR) were reported, and comparisons were made using Mann–Whitney *U* tests.

Hazard ratios (HR) and accompanying 95% confidence intervals (CIs) of mortality were estimated using Cox proportional hazards (PH) regression models to estimate the association between SRH and risk of all-cause mortality [34, 35]. To determine the association between SRH and risk of MM-specific mortality, Fine and Gray subdistribution hazard ratios were estimated to account for competing risks [36]. Minimally-adjusted and multivariable models were fit separately for all-cause and MM-specific mortality. The minimally-adjusted models accounted for the demographic variables of age, sex, and race; and fully-adjusted models also accounted for education level, marital status, smoking status, year of MM diagnosis, who completed the survey, and number of comorbidities [37]. Among the sample of 521 patients, 46 did not provide data on marital status, proxy response, and/or education. For Cox proportional hazards regression models, the proportionality assumption was evaluated graphically using the log of negative log survival distribution function versus log of survival time.

Sensitivity analyses were performed by restricting models to only those patients who completed their own survey to assess whether exclusion of proxy-reported outcomes regarding physical and mental health resulted in significantly different estimates from our main analysis combining patient- and proxy-reported outcomes [38, 39]. We also performed analyses in which the variable for proxy response was excluded from the fully-adjusted model. Lastly, a bootstrap sensitivity analysis was run using 10,000 resamples to assess the robustness of our findings.

Results

Demographic information, clinical characteristics, and survey responses for the analytic sample of 521 patients with MM are shown in Table 1. Patients included in the study had a mean (SD) age of 76.8 (6.1) years at diagnosis. Approximately half of the patients were male (50.7%) and the majority were non-Hispanic White (59.9%). Approximately one-third of the sample (32%) reported low SRH prior to MM diagnosis. Compared to patients who reported high SRH, patients who reported low SRH were older at diagnosis (mean 77.8 vs. 76.4, $p = 0.01$), had less than high school education (46.4% vs. 23.7%, $p < 0.01$), more comorbidities (3 or more: 58.4% vs. 33.0%, $p < 0.01$), and were more likely to have a proxy respondent (21.1% vs. 9.9%, $p < 0.01$). Our sample yielded a total follow-up time of 1,275 person years with 360 all-cause deaths of which 245 were attributed to MM.

HRQOL characteristics are shown in Table 2. Patients with low SRH had significantly lower HRQOL characteristics, reporting lower MCS (median [IQR] 43.9 [35.2–54.5] vs. 56.3 [48.5–60.2], $p < 0.01$) and PCS (median [IQR] 26.7 [20.5–36.0] vs. 43.6 [36.0–51.5], $p < 0.01$) scores, as well as lower scores for each of the eight principal health domains derived from the SF-36 and VR-12.

Results from multivariable models for the relation between SRH and all-cause and MM-specific mortality are summarized in Table 3. The fully-adjusted multivariable models accounting for age, sex, race, marital status, education level, smoking status, year of MM diagnosis, proxy response, and number of comorbidities, indicated a significantly increased risk of all-cause mortality (HR 1.32, 95% CI 1.02–1.71) for patients with low SRH as compared to patients with high SRH. Estimates were suggestive of greater risk of MM-specific mortality (HR 1.22, 95% CI 0.87–1.70) among patients reporting low SRH but confidence intervals included 1.0. There was no evidence to suggest violation of the proportional hazards assumption.

Sensitivity analyses restricting to only self-reporting respondents (i.e., proxy respondents were excluded) reduced our sample size, generating wider confidence intervals and non-statistically significant all-cause mortality HRs (see Supplemental Table 1). However, the direction and magnitude of the point estimates did not substantively change. Excluding the proxy response covariate from our models also did not impact the interpretation of our results (see Supplemental Table 2). The bootstrap sensitivity analysis demonstrated that our findings were robust across 10,000 resamples (see Supplemental Table 3). Thus, we report here on our main analyses.

Discussion

We analyzed pre-diagnosis SRH in older patients with MM and its association with all-cause and MM-specific mortality. Our results indicate a high prevalence of low SRH among older patients prior to diagnosis with MM. Additionally, patients with low SRH had a higher risk of all-cause mortality in comparison to patients with high SRH. Estimates were suggestive of excess risk of myeloma-specific mortality among patients reporting low SRH compared to those reporting high SRH, but confidence intervals included 1.0.

Examination of HRQOL using SEER-MHOS SF-36 and VR-12 data has revealed particularly poor health outcomes among survivors of MM relative to other cancers, with PCS and MCS scores less than those of non-cancer individuals by three or more points [26]. However, pre-diagnosis SRH in particular and its effect on survival in older patients with MM has not been thoroughly investigated. In a population-based longitudinal study of patients in the Israel Cancer Registry, cancer patients with poor pre-diagnosis SRH had a higher risk of all-cause mortality (HR 1.39, 95% CI 1.10–1.74); however, only 6.2% of the patients in the sample ($n = 676$) were diagnosed with MM [40].

Our results are consistent with other findings supporting an association between lower SRH and risk of all-cause mortality in older adults [14–22]. Among a general population sample of 498,103 UK Biobank participants, SRH was the strongest predictor of 5-year all-cause mortality in men (C-index including age = 0.74, 95% CI 0.73–0.75) [21]. Similarly, in examining the relation between SRH and mortality within different ethnic groups using data from over 700,000 National Health Interview Survey participants in the USA, SRH of fair or poor was significantly associated with at least a twofold increased risk of mortality in both men and women and all included ethnicities [22]. In a retrospective study examining self-rated health and physician-rated health as predictors of mortality utilizing the Zutphen Elderly Study cohort of older (aged 64–84 years) community-living Dutch men followed until death for fifteen years, individuals who self-rated their health more poorly had a significant 72% (HR 1.72, 95% CI 1.26–2.33) increased risk of all-cause mortality compared to those with higher SRH [16]. Another report on patients from multiple prospective cohort studies in Europe and the USA found a 1.5-fold and greater than twofold increased risk of all-cause mortality associated with an SRH of "fair" and "poor", respectively, relative to "at-least-good" [41]. Our findings showed a more modest association between SRH and all-cause mortality in multivariable models accounting for comorbid conditions.

Table 1 Demographic, clinical, and survey characteristics among patients with multiple myeloma reporting high and low pre-diagnosis self-reported health

Characteristics	Total $n=521$	High SRH $n=355$	Low SRH $n=166$	p
Demographics				
Age at diagnosis [mean (SD)]	76.8 (6.1)	76.4 (5.8)	77.8 (6.4)	0.01
Age at diagnosis [*n* (%)]				
65–74	216 (41.5)	156 (43.9)	60 (36.1)	0.01
75–84	243 (46.6)	167 (47.0)	76 (45.8)	
85 +	62 (11.9)	32 (9.0)	30 (18.1)	
Race/ethnicity [*n* (%)]				
White	312 (59.9)	219 (61.7)	93 (56.0)	0.38
Black or African American	95 (18.2)	64 (18)	31 (18.7)	
Other	114 (21.9)	72 (20.3)	42 (25.3)	
Sex [*n* (%)]				
Male	264 (50.7)	190 (53.5)	74 (44.6)	0.06
Female	257 (49.3)	165 (46.5)	92 (55.4)	
Marital status [*n* (%)]				
Married	290 (55.7)	206 (58.0)	84 (50.6)	0.07
Not married	222 (42.6)	141 (39.7)	81 (48.8)	
Education [*n* (%)]				
Less than high school	161 (30.9)	84 (23.7)	77 (46.4)	< 0.01
High school graduate or GED	157 (30.1)	104 (29.3)	53 (31.9)	
College or above	191 (36.7)	156 (43.9)	35 (21.1)	
Smoking status [*n* (%)]				
Yes (every day or some days)	49 (9.4)	33 (9.3)	16 (9.6)	0.69
Not at all	400 (76.8)	276 (77.7)	124 (74.7)	
Unknown	72 (13.8)	46 (13.0)	26 (15.7)	
Clinical characteristics				
Number of comorbid conditions [mean (SD)][a]	2.7 (2.0)	2.3 (2.4)	3.8 (2.1)	< 0.01
Number of comorbid conditions [*n* (%)][a]				
0–2	247 (47.4)	203 (57.2)	44 (26.5)	< 0.01
3 or more	214 (41.1)	117 (33.0)	97 (58.4)	
Heart conditions [*n* (%)][b]				
None	134 (25.7)	116 (32.7)	18 (10.8)	< 0.01
At least 1	386 (74.1)	239 (67.3)	147 (88.6)	
Stroke [*n* (%)]				
Yes	48 (9.2)	27 (7.6)	21 (12.7)	0.06
No	463 (88.9)	323 (91.0)	140 (84.3)	
Cardiovascular conditions [*n* (%)][c]				
None	130 (25.0)	113 (31.8)	17 (10.2)	< 0.01
At least 1	389 (74.7)	241 (67.9)	148 (89.2)	
Diabetes [*n* (%)]				
Yes	121 (23.2)	74 (20.8)	47 (28.3)	0.06
No	393 (75.4)	276 (77.7)	117 (70.5)	
Arthritis [*n* (%)]				
Yes	285 (54.7)	173 (48.7)	112 (67.5)	< 0.01
No	233 (44.7)	181 (51.0)	52 (31.3)	
Asthma/COPD/emphysema [*n* (%)]				
Yes	74 (14.2)	36 (10.1)	38 (22.9)	< 0.01
No	439 (84.3)	315 (88.7)	124 (74.7)	
Sciatica [*n* (%)]				
Yes	113 (21.7)	56 (15.8)	57 (34.3)	< 0.01
No	399 (76.6)	293 (82.5)	106 (63.9)	

Table 1 (continued)

Characteristics	Total $n=521$	High SRH $n=355$	Low SRH $n=166$	p
Year of MM diagnosis [n (%)]				
1998–2005	205 (39.3)	136 (38.3)	69 (41.6)	0.69
2006–2010	153 (29.4)	108 (30.4)	45 (27.1)	
2011–2013	163 (31.3)	111 (31.3)	52 (31.3)	
Survey characteristics				
Months from survey to MM diagnosis [mean (SD)]	23.0 (18.3)	23.5 (18.2)	21.8 (18.4)	0.34
MHOS survey administration mode [n (%)]				
Mail	450 (86.4)	310 (87.3)	140 (84.3)	0.35
Telephone	71 (13.6)	45 (12.7)	26 (15.7)	
Who completed survey [n (%)]				
Patient	415 (79.7)	301 (84.8)	114 (68.7)	< 0.01
Person other than patient	70 (13.4)	35 (9.9)	35 (21.1)	

MM multiple myeloma, *SRH* self-reported health

Column percentages do not sum to 100% for some variables due to missing data

[a]Number of comorbid conditions was totaled from presence/absence of: angina pectoris/coronary artery disease, congestive heart failure, myocardial infarction, other heart conditions, stroke, emphysema/asthma/COPD, Crohn's disease/ulcerative colitis/inflammatory bowel disease, arthritis of the hip/knee, arthritis of the hand/wrist, sciatica, diabetes/high blood sugar/sugar in urine, and hypertension. If patient is missing data on at least one comorbidity, then number of comorbid conditions is considered missing

[b]Possible patient-reported heart conditions include hypertension, angina or coronary artery disease, congestive heart failure, acute myocardial infarction, other heart conditions

[c]Includes heart conditions and stroke

Table 2 Health-related quality of life (HRQOL) characteristics derived from the Veterans RAND 12-Item Health Survey (VR-12) among patients with multiple myeloma reporting high and low pre-diagnosis self-reported health

Characteristics (median (IQR))	Total $n=521$	High SRH $n=355$	Low SRH $n=166$	p[a]
PCS	38.9 (29.6–48.8)	43.6 (36.0–51.5)	26.7 (20.5–36.0)	< 0.01
MCS	54.2 (43.5–59.3)	56.3 (48.5–60.2)	43.9 (35.2–54.5)	< 0.01
PF	58.3 (36.6–90.0)	76.1 (58.3–93.5)	35.0 (9.9–58.3)	< 0.01
RP	50.0 (0.49–100.0)	79.4 (25.0–100.0)	0.5 (0.0–25.0)	< 0.01
BP	56.3 (39.0–84.0)	56.3 (43.9–95.2)	31.5 (31.0–47.5)	< 0.01
GH	61.5 (40.0–77.0)	62.0 (61.5–83.7)	37.5 (30.0–40.0)	< 0.01
MH	83.7 (60.7–92.0)	84.0 (69.5–92.7)	65.5 (51.3–83.7)	< 0.01
RE	100.0 (33.3–104.1)	100.0 (66.7–104.1)	33.3 (0.0–100.0)	< 0.01
SF	87.5 (50.0–99.3)	99.3 (66.9–100.0)	50.0 (37.5–75.0)	< 0.01
VT	54.6 (40.9–79.3)	60.0 (50.0–79.3)	40.0 (30.0–45.9)	< 0.01

IQR interquartile range, *SRH* self-reported health, *PCS* physical component summary score, *MCS* mental component summary score, *PF* physical functioning, *RP* role limitations due to physical problems, *BP* bodily pain, *GH* general health perceptions, *MH* general mental health, *RE* role limitations due to emotional problems, *SF* social functioning, *VT* vitality

[a]Mann–Whitney *U* test

A related study aimed to develop an MHOS frailty index for older patients with newly diagnosed MM and explored the association between all-cause mortality and frailty, rather than SRH [42]. The analysis revealed that over half of patients with newly diagnosed MM were considered frail. Furthermore, the median overall survival of patients with MM classified as frail was 26.8 months, relative to 43.7 months ($p=0.02$) for those who were not.

Conflicting evidence exists on whether SRH is related to poorer cancer outcomes. An association between SRH and cancer-specific mortality has been observed in some epidemiological studies [17, 19], but not others [15, 16, 18, 41]. Hoffman et al. found that among men with localized prostate cancer, those with fair or poor SRH had significantly higher risk of non-cancer-related mortality but not cancer-specific mortality. This was owed in part to a low number of prostate

Table 3 Hazard ratios of all-cause and MM-specific mortality among patients with multiple myeloma with low versus high pre-diagnosis self-reported health

	Person years	Events	Crude		Minimally-adjusted[a]		Fully-adjusted[b]			
			$n=521$				$n=475$			
			HR (95% CI)	p	HR (95% CI)	p	Person years	Events	HR (95% CI)	p
All-cause mortality										
High SRH (reference)	887	230	1	–	1	–	828	210	1	–
Low SRH	388	130	1.28 (1.03–1.59)	0.02	1.27 (1.02–1.58)	0.03	338	113	1.32 (1.02–1.71)	0.04
MM-specific mortality[a]										
High SRH (reference)	887	165	1	–	1	–	828	150	1	–
Low SRH (vs. High SRH)	388	80	1.10 (0.84–1.44)	0.50	1.09 (0.83–1.44)	0.54	338	69	1.22 (0.87–1.70)	0.24

CI confidence interval, *HR* hazard ratio, *MM* multiple myeloma, *SRH* self-reported health

[a]Modeled using the fine and gray subdistribution hazards function

[b]Adjusted for age, sex, race

[c]Adjusted for age, sex, race, education level, marital status, smoking status, year of MM diagnosis, proxy response, and number of comorbidities (categorical variable as missing, 0–2, or 3+). Number of comorbid conditions was totaled from presence/absence of: angina pectoris/coronary artery disease, congestive heart failure, myocardial infarction, other heart conditions, stroke, emphysema/asthma/COPD, Crohn's disease/ulcerative colitis/inflammatory bowel disease, arthritis of the hip/knee, arthritis of the hand/wrist, sciatica, diabetes/high blood sugar/sugar in urine, and hypertension. If patient is missing data on at least one comorbidity, then number of comorbid conditions is considered missing

cancer deaths observed with localized disease [17]. Other studies also suggest a positive association between SRH and cancer-specific mortality after controlling for socioeconomic status, objective measures of health, and presence of comorbidities [41, 43–45]. Lower SRH (feeling moderately or not healthy) among the cohort of older Dutch men described previously was associated with a statistically significant 2.4-fold increase risk (HR 2.41, 95% CI 1.39–4.15) of cancer-specific death (including lung, colon, stomach, and prostate cancer) relative to higher SRH (feeling healthy) [16]. Also in support of a positive association between lower SRH and cancer-specific mortality, Stenholm et al. reported that patients who previously reported low SRH were 1.57 times more likely (95% CI 1.30–1.89) to die from non-smoking-related cancers; and these associations were observed in periods up to fifteen years prior to death [18].

SRH captures a variety of factors related to mortality, such as severity, symptoms, bodily sensations, dysregulation, and expected prognosis, that we may not be able to otherwise conceptualize, verbalize, or detect through other health indicators [23]. Evidence suggests that poor SRH may be indicative of pathological changes before a cancer diagnosis and may capture more informative aspects of health beyond the specific disease [18]. Knäuper and Turner proposed that patients may use information relevant to mortality (such as comorbidities, age, nutrition, and available medical treatments) and ignore irrelevant information (such as current mood or temporary health state) when evaluating their health [24]. People then compare information about their personal health to their idea of a comparative standard against which they can evaluate their health. This standard may depend on a person's experiences, future expectations, and/or what they believe their current health status should be. By assessing mortality-relevant information, which influences self-perceived general health, subjects who reported poor general health may be less likely to seek healthcare that ultimately impacts survival. If our findings of a modest association in older patients with MM are confirmed, it would be important to determine whether the relationship between SRH and death is causal or rather indicative of differences in individuals' health states.

Our study had limitations. Our estimates of MM-specific mortality were dependent on the documented cause of death in death certificates, which may not always be accurate. However, German et al. examined the agreement between death certificates and cancer diagnoses recorded in population-based cancer registries and reported concordance rates of over 95% for MM [46]. Additionally, SEER-MHOS has information on specific pre-existing chronic conditions reported in the health outcomes survey, but lacks other comorbidities and more detailed information on the severity of these conditions. Therefore, information on other common conditions among older patients such as osteoporosis,

benign prostatic hypertrophy, hepatitis C virus, or dementia was not available [27, 47]. Data regarding obesity are collected in MHOS, but were largely missing in our sample. Although SEER-MHOS provides detailed information on cancer site, stage, sociodemographic factors, and HRQOL, it lacks information on clinical and prognostic variables specific to MM, such as renal function, baseline fractures, International Staging System scores, lactate dehydrogenase (LDH) values, cytogenetics, specific treatments received, disease risk at diagnosis, and presence of other key laboratory parameters (e.g., β-2 microglobulin). Further, treatment of older patients with MM evolved over the study period with the introduction of immunomodulatory drugs, proteasome inhibitors and autologous stem cell transplantation which have improved survival, which is our primary outcome. This is a possible source of unmeasured confounding for which we were not able to adjust or account for in our analysis. Also, the Medicare Advantage enrollees included in the SEER-MHOS dataset may not be entirely representative of Medicare fee-for-service beneficiaries who account for the majority of Medicare beneficiaries and generally report more risk factors and poorer HRQOL, which may contribute to healthy participant bias [27, 48]. Similarly, our sample is limited to MHOS survey respondents who provide sufficient data. Survey respondents may be healthier and generally have different health behaviors compared to patients who do not respond to surveys or fail to provide complete information, introducing selection bias [49]. This common limitation to studies using longitudinal survey data may limit the generalizability of our findings. Another common limitation of observational research is the inability to draw causal inferences. Residual confounding remains possible in epidemiologic studies such as ours. Further detail regarding limitations of SEER-MHOS data have been described elsewhere [26, 27].

An additional important limitation of our study is that surveys were completed within five years prior to the MM diagnosis date which may differ from patients' experience at the time of diagnosis or treatment. Furthermore, many patients experience a diagnostic interval greater than 3 months until MM diagnosis is confirmed [50]. This may limit direct clinical applications of our findings, but was relevant to our research question specifically focused on pre-diagnosis self-reported health among older patients. In support of our approach, other studies of older adults with cancer have also assessed associations between self-reported exposures and survival in which the self-report data were collected several years before the date of cancer diagnosis [40, 51, 52]. Two studies used stratified analyses to show that associations between MHOS data and survival remained consistent between patients who completed the survey more and less than two years before their cancer diagnosis, indicating that self-awareness of general health status may be an important predictor of survival well before cancer is diagnosed [51, 52]. Furthermore, if SRH decreases as patients approach the date of cancer diagnosis, then the association between SRH and increased mortality observed in this study may be a conservative estimate of its impact on survival.

Given that SRH is a simple tool for assessing health, it may provide additional information to support clinical decision-making for treating MM. Additionally, some factors associated with a patient's perception of their own health are modifiable, such as bodily pain, health and risk behaviors, symptom management, and self-efficacy [24]. These factors present an opportunity to support older patients with MM with respect to HRQOL.

Conclusion

Our findings suggest that lower SRH is prevalent among older patients with MM prior to diagnosis and is modestly associated with increased all-cause mortality. The mechanism by which SRH affects all-cause mortality in older patients with MM should be further assessed. We did not observe a significant association between SRH and MM-specific mortality. While the value of SRH measures in the regular care of older adults with cancer is yet to be determined, low patient-reported measures of general health could signal to providers unmet needs that deserve clinical attention and evaluation.

Acknowledgments This study used data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) linked data resource. The authors acknowledge the efforts of the National Cancer Institute; the Centers for Medicare and Medicaid Services; MHOS; Information Management Services, Inc.; and the SEER Program tumor registries in the creation of the SEER-MHOS database. The National Cancer Institute provided suggested edits and approval of the manuscript before final journal submission.

Author contributions Study concepts: NAN, AA, BT, AAA, JZ, LKS, GSC; study design: NAN, AA, BT, AAA, JZ, LKS, GSC; data acquisition: AAA, JZ, GSC; quality control of data and algorithms: NAN, AA, BT, AAA, JZ, LKS, GSC; data analysis and interpretation: NAN, AA, GSC; statistical analysis: NAN, AA, GSC; manuscript preparation: NAN, AA, BT, AAA, JZ, LKS, KS, PRP, NYK, BCHC, GSC; Manuscript editing: NAN, AA, BT, AAA, JZ, LKS, KS, PRP, NYK, BCHC, GSC; manuscript review: NAN, AA, BT, AAA, JZ, LKS, KS, PRP, NYK, BCHC, GSC.

Funding The project described was supported by the National Institutes of Health, National Center for Advancing Translational Sciences through Grant Number KL2TR002002 (Calip), National Heart, Lung and Blood Institute through Grant Number R21HL140531 (Calip) and National Cancer Institute through Grant Number R01CA223662 (Chiu). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with ethical standards

Conflict of interest Alobaidi—funded by the UIC/AbbVie Health Economics and Outcomes Research Fellowship (2018–2020); Patel—consultancy (Celgene, Janssen) and honoraria (Celgene, Janssen, Amgen); no other authors have relevant conflicts of interest to disclose.

References

1. Kyle RA, Rajkumar SV (2008) Multiple myeloma. Blood 111(6):2962–2972
2. Kazandjian D (2016) Multiple myeloma epidemiology and survival: a unique malignancy. Semin Oncol 43(6):676–681
3. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) (2019) SEER Cancer Statistics Review, 1975–2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019
4. Colson K (2015) Treatment-related symptom management in patients with multiple myeloma: a review. Support Care Cancer 23(5):1431–1445
5. Gay F, Palumbo A (2010) Multiple myeloma: management of adverse events. Med Oncol 27(3):646–653
6. Molenaar S, Oort F, Sprangers M et al (2004) Predictors of patients' choices for breast-conserving therapy or mastectomy: a prospective study. Br J Cancer 90(11):2123–2130
7. Engelhardt EG, Revesz D, Tamminga HJ et al (2018) Clinical usefulness of tools to support decision-making for palliative treatment of metastatic colorectal cancer: a systematic review. Clin Colorectal Cancer 17(1):e1–e12
8. Latini DM, Hart SL, Knight SJ et al (2007) The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. J Urology 178(3):826–831
9. Wisloff F, Hjorth M (1997) Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma. Nordic Myeloma Study Group. Br J Haematol 97(1):29–37
10. Dubois D, Dhawan R, van de Velde H et al (2006) Descriptive and prognostic value of patient-reported outcomes: the bortezomib experience in relapsed and refractory multiple myeloma. J Clin Oncol 24(6):976–982
11. Efficace F, Gaidano G, Breccia M et al (2015) Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study. Lancet Oncol 16(15):1506–1514
12. Stover AM, Basch EM (2016) Using patient-reported outcome measures as quality indicators in routine cancer care. Cancer 122(3):355–357
13. Murthy HS, Wood WA (2015) The value of patient reported outcomes and other patient-generated health data in clinical hematology. Curr Hematol Malig Rep 10(3):213–224
14. Ul-Haq Z, Mackay DF, Pell JP (2014) Association between self-reported general and mental health and adverse outcomes: a retrospective cohort study of 19,625 Scottish adults. PLoS ONE 9(4):e93857
15. Benjamins MR, Hummer RA, Eberstein IW, Nam CB (2004) Self-reported health and adult mortality risk: an analysis of cause-specific mortality. Soc Sci Med 59(6):1297–1306
16. Giltay EJ, Vollaard AM, Kromhout D (2012) Self-rated health and physician-rated health as independent predictors of mortality in elderly men. Age Ageing 41(2):165–171
17. Hoffman RM, Koyama T, Albertsen PC et al (2015) Self-reported health status predicts other-cause mortality in men with localized prostate cancer: results from the prostate cancer outcomes study. J Gen Intern Med 30(7):924–934
18. Stenholm S, Kivimaki M, Jylha M et al (2016) Trajectories of self-rated health in the last 15 years of life by cause of death. Eur J Epidemiol 31(2):177–185
19. Shadbolt B, Barresi J, Craft P (2002) Self-rated health as a predictor of survival among patients with advanced cancer. J Clin Oncol 20(10):2514–2519
20. Mohan R, Beydoun HA, Beydoun MA et al (2011) Self-rated health as a tool for estimating health-adjusted life expectancy among patients newly diagnosed with localized prostate cancer: a preliminary study. Qual Life Res 20(5):713–721
21. Ganna A, Ingelsson E (2015) 5 year mortality predictors in 498,103 UK Biobank participants: a prospective population-based study. Lancet 386(9993):533–540
22. McGee DL, Liao Y, Cao G, Cooper RS (1999) Self-reported health status and mortality in a multiethnic US cohort. Am J Epidemiol 149(1):41–46
23. Jylha M (2009) What is self-rated health and why does it predict mortality? Towards a unified conceptual model. Soc Sci Med 69(3):307–316
24. Knauper B, Turner PA (2003) Measuring health: improving the validity of health assessments. Qual Life Res 12(Suppl 1):81–89
25. Institute NC (2020) Brief description of the SEER-MHOS data resource. https://healthcaredelivery.cancer.gov/seer-mhos/overview/. Published 2018. Accessed 19 Mar 2020
26. Kent EE, Ambs A, Mitchell SA, Clauser SB, Smith AW, Hays RD (2015) Health-related quality of life in older adult survivors of selected cancers: data from the SEER-MHOS linkage. Cancer 121(5):758–765
27. Ambs A, Warren JL, Bellizzi KM, Topor M, Haffer SC, Clauser SB (2008) Overview of the SEER—medicare health outcomes survey linked dataset. Health Care Financ Rev 29(4):5–21
28. Institute NC (2020) What is a cancer registry? https://seer.cancer.gov/registries/cancer_registry/index.html. Published 2019. Accessed 19 Mar 2020
29. Iqbal S, Rogers W, Selim A, et al. The Veterans rand 12 item health survey (VR-12): what it is and how it is used. https://www.bu.edu/sph/files/2015/01/veterans_rand_12_item_health_survey_vr-12_2007.pdf. Accessed 19 Mar 2020
30. Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6):473–483
31. Selim A, Rogers W, Qian S, Rothendler JA, Kent EE, Kazis LE (2018) A new algorithm to build bridges between two patient-reported health outcome instruments: the MOS SF-36(R) and the VR-12 Health Survey. Qual Life Res 27(8):2195–2206
32. Usman Iqbal S, Rogers W, Selim A, et al (2007) The Veterans Rand 12 Item Health Survey (Vr-12): what it is and how it is used. Technical Report
33. Farivar SS, Cunningham WE, Hays RD (2007) Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey V.I. Health Qual Life Outcomes 5:54
34. Gooley TA, Leisenring W, Crowley J, Storer BE (1999) Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 18(6):695–706
35. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C (2010) Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. Med Care 48(6 Suppl):S96–105
36. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94(446):496–509

37. Foundation IM (2020) Multiple myeloma drug guide. https://www.myeloma.org/multiple-myeloma-drugs. Published 2017. Accessed 19 Mar 2020
38. Roydhouse JK, Gutman R, Keating NL, Mor V, Wilson IB (2018) Proxy and patient reports of health-related quality of life in a national cancer survey. Health Qual Life Outcomes 16(1):6
39. Wolinsky FD, Jones MP, Wehby GL (2012) Gathering data from older adults via proxy respondents: research challenges. J Comp Eff Res 1(6):467–470
40. Rottenberg Y, Litwin H, Manor O, Paltiel A, Barchana M, Paltiel O (2014) Prediagnostic self-assessed health and extent of social networks predict survival in older individuals with cancer: a population based cohort study. J Geriatr Oncol 5(4):400–407
41. Bamia C, Orfanos P, Juerges H et al (2017) Self-rated health and all-cause and cause-specific mortality of older adults: Individual data meta-analysis of prospective cohort studies in the CHANCES Consortium. Maturitas 103:37–44
42. Mian HS, Wildes TM, Fiala MA (2018) Development of a medicare health outcomes survey deficit-accumulation frailty index and its application to older patients with newly diagnosed multiple myeloma. JCO Clin Cancer Inf. https://doi.org/10.1200/CCI.18.00043
43. Idler EL, Benyamini Y (1997) Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav 38(1):21–37
44. Kaplan G, Barell V, Lusky A (1988) Subjective state of health and survival in elderly adults. J Gerontol 43(4):S114–120
45. Mossey JM, Shapiro E (1982) Self-rated health: a predictor of mortality among the elderly. Am J Public Health 72(8):800–808
46. German RR, Fink AK, Heron M et al (2011) The accuracy of cancer mortality statistics based on death certificates in the United States. Cancer Epidemiol 35(2):126–131
47. Smith AW, Reeve BB, Bellizzi KM et al (2008) Cancer, comorbidities, and health-related quality of life of older adults. Health Care Financ Rev 29(4):41–56
48. Riley G (2000) Two-year changes in health and functional status among elderly Medicare beneficiaries in HMOs and fee-for-service. Health Serv Res 35(5 Pt 3):44–59
49. Keyes KM, Rutherford C, Popham F, Martins SS, Gray L (2018) How Healthy are survey respondents compared with the general population? Using survey-linked death records to compare mortality outcomes. Epidemiology 29(2):299–307
50. Koshiaris C, Oke J, Abel L, Nicholson BD, Ramasamy K, Van den Bruel A (2018) Quantifying intervals to diagnosis in myeloma: a systematic review and meta-analysis. BMJ Open 8(6):e019758
51. Pinheiro LC, Zagar TM, Reeve BB (2017) The prognostic value of pre-diagnosis health-related quality of life on survival: a prospective cohort study of older Americans with lung cancer. Qual Life Res 26(7):1703–1712
52. Doll KM, Pinheiro LC, Reeve BB (2017) Pre-diagnosis health-related quality of life, surgery, and survival in women with advanced epithelial ovarian cancer: A SEER-MHOS study. Gynecol Oncol 144(2):348–353

Affiliations

Nadia A. Nabulsi[1] · Ali Alobaidi[1] · Brian Talon[1] · Alemseged A. Asfaw[1] · Jifang Zhou[1] · Lisa K. Sharp[1] · Karen Sweiss[2] · Pritesh R. Patel[3] · Naomi Y. Ko[4] · Brian C.-H. Chiu[5] · Gregory S. Calip[1,6]

Nadia A. Nabulsi
nnabul2@uic.edu

Ali Alobaidi
aaloba3@uic.edu

Brian Talon
btalon2@uic.edu

Alemseged A. Asfaw
aasfaw2@uic.edu

Jifang Zhou
jzhou86@uic.edu

Lisa K. Sharp
sharpl@uic.edu

Karen Sweiss
ksweis2@uic.edu

Pritesh R. Patel
prpatel8@uic.edu

Naomi Y. Ko
naomi.ko@bmc.org

Brian C.-H. Chiu
bchiu@uchicago.edu

[1] Department of Pharmacy Systems, Outcomes and Policy, Center for Pharmacoepidemiology and Pharmacoeconomic Research, University of Illinois at Chicago, 833 S. Wood St. MC 871, Chicago, IL 60612, USA

[2] Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA

[3] Division of Hematology and Oncology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA

[4] Section of Hematology Oncology, Boston University School of Medicine, Boston, MA, USA

[5] Department of Public Health Sciences, The University of Chicago, Chicago, IL, USA

[6] Division of Public Health Sciences, Epidemiology Program, Fred Hutchinson Cancer Research Center, Seattle, WA, USA