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Mortality by Frailty Status as Defined by a Claims-Based Disability Status in Elderly Patients with Newly Diagnosed Multiple Myeloma in the United States

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INTRODUCTION

- Over the last decade, several novel therapies have been approved for multiple myeloma (MM), leading to significant improvement in the survival of MM patients[1]
- Frail patients in particular are at increased risk for poor outcomes[2,3]
- A frailty score developed among newly diagnosed elderly MM patients from 3 prospective trials predicted mortality and risk of toxicity in elderly MM patients[4]
- However, little is known about the treatment outcome of frail MM patients in the real-world setting
- In this study, we
  - applied a claims-based prediction model for poor disability status (DS)[5,6] as a proxy measure for frailty status, and
  - examined the association between poor DS and mortality in a population-based cohort of elderly adults with MM in the United States

METHODS

- Data source: the Centers for Medicare & Medicaid Services 100% Hematologic Cancer File (2007–2012)

Inclusion criteria

- Diagnosed with MM between January 1, 2008 and December 31, 2011, based on a validated algorithm using a combination of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 203.0X and diagnostic tests or treatment.[7] The diagnosis date was defined as the disease index date.
- Initiated a first-line therapy following the disease index date. The date of treatment initiation was identified as the first-line index date.
- Continuously enrolled in Medicare Part A, Part B, and Part D during the time period from 12 months before the disease index date to the first-line index date
- Aged 66 years or older at the disease index date

Exclusion criteria

- Received any of the following treatments in the 12 months before the disease index date:
  - Chemotherapy or radiotherapy
  - Drug treatments specific for MM
  - Stem cell transplant
- Missing census region

Line of therapy

- Patients who advanced to second, third, and fourth line were identified if a 90-day gap in all treatments was observed or a drug was added to a regimen >90 days after the line index date
- To further identify patients who initiated multiple lines of therapy, we require that they be continuously enrolled in Medicare Parts A, B, and D from first-line initiation to the current line initiation

Drug regimens

- Identified using National Drug Code from Medicare Part D prescription drug event claims and Healthcare Common Procedure Coding System codes from Part B line items and Part A outpatient claims
- Classified as monotherapy, doublets, and triplets based on the National Comprehensive Cancer Network MM treatment guidelines.[8] Regimens not identified as 1 of these 3 types were classified as "other."

Claims-based definition of frailty status

- A claims-based poor DS prediction model developed and validated by Davidoff et al[5,6] was used to estimate the probability of poor DS (PPDS) as a proxy measure for frailty status at line of therapy initiation for each patient via the following steps:
  - Step 1: Define the health care service predictors from Medicare claims during the baseline period for each line of therapy cohort
  - Step 2: Apply the estimated regression coefficients from the prediction model to the set of constructed measures for each patient to generate a predicted PPDS with high values representing a high PPDS
  - Step 3: Based on the predicted PPDS, we classified patients as frail (PPDS ≥0.11) or fit (PPDS <0.11)
    - The 0.11 cut-off for poor DS was developed in a cohort of Medicare beneficiaries[5]
    - We performed statistical analyses and did not find evidence to reject the use of this cut-off to identify patients with poor DS used as proxy for frailty for a cohort of elderly MM patients

Study period

- Baseline period was the 12 months before the treatment index date for each line of therapy, during which frailty status, comorbid conditions, Deyo-adapted Charlson Comorbidity Index (CCI)[9], length of hospital stay (LOS), and part D low-income subsidy (LIS) were defined
- Follow-up started on the treatment index date for each line of therapy and ended on the date of death, the last day of the current line of therapy, disenrollment from any of Medicare Part A, B, or D, or December 31, 2012, whichever occurred first

Statistical analyses

- Baseline characteristics were described by frailty status and lines of therapy. Overall survival (OS) was estimated using the Kaplan–Meier method with log-rank test to assess the differences in OS between fit and frail patients by lines of therapy. Cox proportional hazards models were used to evaluate the association between frailty status and risk of mortality with adjustment for baseline characteristics by lines of therapy.

RESULTS

- We identified 12,547 elderly MM patients who met the study inclusion criteria and initiated first-line therapy; of these, 5,841 (46.6%), 2,372 (18.9%), and 819 (6.5%) initiated second-, third-, and fourth-line therapy, respectively
- By line of therapy, percent of frail patients was 16.7% at first line, 21.8% at second line, 18.4% at third line, and 18.2% at fourth line
- Table 1 shows baseline characteristics for patients in each line by frailty status
  - Compared with fit patients at first line, frail patients were: older (mean age 78.9 vs 76.5 years); more often female (66% vs 52%) or African American (23% vs 12%); more often recipients of Part D LIS (57% vs 25%); of higher comorbidity level (CCI ≥5: 43% vs 16%); and, more often: hospitalized for ≥11 days during the baseline period (56% vs 16%), received monotherapy (32% vs 19%); less often received doublet (53% vs 61%) or triplet (10% vs 16%) therapy
  - Patterns were similar for patients who advanced to second-, third-, and fourth-line therapy

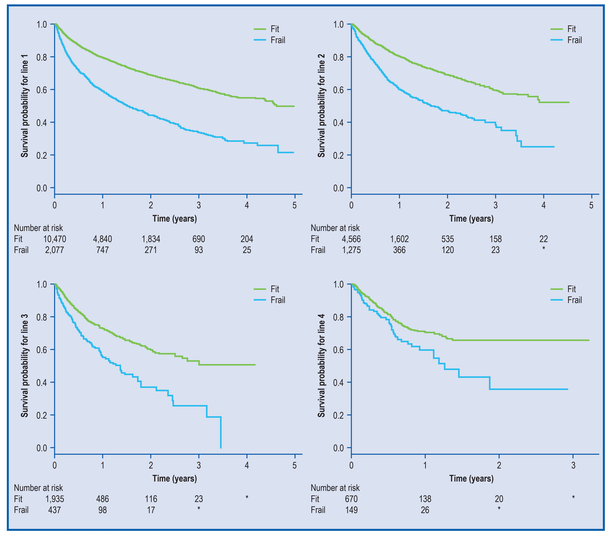
Table 1. Demographic and Clinical Characteristics of Study Population By Line of Therapy

	First line		Second line		Third line		Fourth line	
	Fit	Frail	Fit	Frail	Fit	Frail	Fit	Frail
N	10,470	2,077	4,566	1,275	1,935	437	670	149
Age[a] mean (SD), years	76.5 (6.5)	78.9 (7.2)	76.3 (6.1)	78.3 (6.6)	76.2 (5.9)	78.1 (6.2)	76.4 (5.8)	78.0 (5.9)
Age,[a] %								
66–69 years	18.9	12.6	17.1	11.8	16.3	9.2	13.3	7.4
70–74 years	26.5	20.2	29.6	23.1	31.6	24.7	32.4	28.2
75–79 years	24.1	22.4	24.6	25.1	25.5	28.6	28.2	28.2
≥80 years	30.5	44.8	28.7	40.0	26.6	37.5	26.1	36.2
Female, %	51.5	65.7	49.5	60.9	49.4	62.5	50.0	59.1
Race, %								
White	82.2	69.1	84.6	71.6	87.2	70.0	86.1	75.2
African American	12.3	22.8	10.0	20.6	8.3	20.6	8.7	18.1
Other	5.5	8.1	5.3	7.8	4.5	9.4	5.2	*
Line index year, %								
2008	20.4	18.7	5.4	4.2	0.6	*	*	*
2009	24.0	23.8	17.9	18.2	9.3	11.9	2.1	*
2010	24.9	24.9	24.9	25.4	22.2	24.0	17.3	18.1
2011	26.0	26.4	27.3	26.6	31.5	30.4	35.8	36.2
2012	4.8	6.1	24.4	25.7	36.5	33.4	44.8	41.6
Part D LIS, %	25.1	56.6	20.2	51.9	17.7	49.7	17.8	45.6
Hospitalizations LOS, %								
0 days	52.7	13.0	49.6	15.7	53.1	21.7	55.7	23.5
1–10 days	30.9	30.7	28.7	25.7	26.3	24.9	25.4	26.2
≥11 days	16.5	56.3	21.8	58.6	20.6	53.3	19.0	50.3
CCI, %								
0	17.0	3.6	0.6	*	0.7	*	*	*
1–2	39.4	21.5	38.3	16.1	38.1	16.3	39.1	16.1
3–4	27.3	32.5	29.4	27.9	31.2	27.0	31.0	33.6
≥5	16.3	42.5	31.8	55.8	30.0	56.5	29.4	50.3
Comorbidity not included in CCI, %								
Anemia	60.6	81.0	68.4	85.8	67.3	86.0	66.9	83.2
Dysrhythmia	22.9	37.0	25.6	37.4	23.5	38.0	27.3	34.9
Other cardiac dis.	18.0	30.6	20.8	33.3	20.0	31.6	18.4	28.9
Osteoporosis	13.8	24.4	12.5	23.0	11.5	18.8	12.2	14.8
Neutropenia	2.0	2.3	10.5	8.2	14.7	13.5	15.8	14.8
Thrombocytopenia	6.6	12.9	13.9	19.5	15.3	26.3	17.3	25.5
PN	7.5	16.2	16.1	26.1	21.1	30.9	23.7	32.9
VTE	3.9	10.0	10.1	18.5	10.6	20.8	9.9	20.1
SRE	32.0	53.8	35.6	57.9	30.0	52.0	26.9	44.3
Regimen, %								
Monotherapy	19.1	31.9	24.8	30.7	26.8	32.5	27.2	28.9
Doublets	60.7	53.4	49.2	49.3	43.2	45.3	41.9	43.6
Triplets	16.4	10.3	20.8	16.9	22.8	17.2	22.8	20.1
Other	3.9	4.3	5.2	3.2	7.2	5.0	8.1	7.4

[a]Age defined at line of therapy index date.
*Values for cells with 10 or fewer patients are suppressed.
CCI, Charlson Comorbidity Index; LIS, low-income subsidy; LOS, length of stay; PN, peripheral neuropathy; SREs, skeletal-related events; VTE, venous thromboembolism.

- Figure 1 depicts OS by frailty status for each line of therapy
  - OS was worse for frail than for fit patients consistently across first- to fourth-line therapy (P<0.001 for first- to third-line therapy; P=0.004 for fourth-line therapy)
  - Three-year OS for frail vs fit patients: 34% vs 61% at first line; 40% vs 59% at second line; 25% vs 53% at third line
  - One-year OS at fourth line for frail vs fit patients: 59% vs 71%, respectively

Figure 1. Kaplan–Meier Overall Survival By Frailty Status for Each Line of Therapy



*Values for cells with 10 or fewer patients are suppressed.

- Table 2 summarizes the crude and adjusted association between frailty and mortality by lines of therapy
  - Mean (SD) follow-up time for mortality was shorter for frail than for fit patients at each line of therapy and decreased consistently from first-line to fourth-line therapy for fit and frail patients, respectively (0.98 [0.92] vs 1.19 [0.98] at first line; 0.63 [0.50] vs 0.66 [0.55] at fourth line)
  - During first-line therapy, frail patients were more than twice as likely to die compared with fit patients (% died: 47% vs 24%; mortality rate: 48 vs 20 per 100 patient-years). Patterns were similar for advanced lines
  - Adjustment for baseline characteristics resulted in a hazard ratio (95% confidence interval [CI]) of 1.28 (1.18–1.40) at first-line, 1.55 (1.36–1.77) at second-line, 1.35 (1.10–1.65) at third-line, and 1.22 (0.84–1.76) at fourth-line therapy for frail compared with fit patients

Table 2. Association Between Frailty Status and All-Cause Mortality By Line of Therapy

					Unadjusted		Adjusted[a]	
Line of therapy	Total, *n*	Mean (SD) Follow-up, yrs	Death, *n* (%)	Mortality rate (per 100 pt-yrs)	HR (95% CI)	*P*	HR (95% CI)	*P*
First line								
Fit	10,470	1.19 (0.98)	2,542 (24.3)	20.4	Reference		Reference	
Frail	2,077	0.98 (0.92)	967 (46.6)	47.6	2.26 (2.10–2.43)	<0.001	1.28 (1.18–1.40)	<0.001
Second line								
Fit	4,566	0.97 (0.81)	911 (20.0)	20.6	Reference		Reference	
Frail	1,275	0.83 (0.74)	484 (38.0)	45.6	2.17 (1.94–2.42)	<0.001	1.55 (1.36–1.77)	<0.001
Third line								
Fit	1,935	0.76 (0.66)	447 (23.1)	30.4	Reference		Reference	
Frail	437	0.69 (0.60)	173 (40.3)	58.3	1.88 (1.58–2.25)	<0.001	1.35 (1.10–1.65)	0.004
Fourth line								
Fit	670	0.66 (0.55)	144 (21.5)	32.8	Reference		Reference	
Frail	149	0.63 (0.50)	51 (34.2)	54.1	1.60 (1.16–2.20)	0.004	1.22 (0.84–1.76)	0.29

[a]Covariates in the model included age, sex, race, index year, region, Deyo-adapted Charlson Comorbidity Index, dysrhythmia, other cardiac disease, anemia, osteoporosis, neutropenia, thrombocytopenia, peripheral neuropathy, venous thromboembolism, skeletal-related events, length of hospital stay, Medicare Part D low income subsidy status, and regimen.
CI, confidence interval; HR, Hazard ratio; pt-yrs, patient-years; SD, standard deviation; yrs, years.

- Table 3 presents the Cox model results by line of therapy
  - Older age, male sex, higher comorbidity level, presence of comorbid conditions (dysrhythmia, anemia, thrombocytopenia, skeletal-related events), and longer LOS were risk factors for mortality consistently at first- to fourth-line therapy, although some factors were not statistically significant at later lines due to small sample size
  - Patients who received doublets and triplets at first line had 30% and 37% reduced risk of mortality, respectively, compared with patients treated with monotherapy at first line (hazard ratio [95% CI]: 0.70 [0.65–0.76] doublets vs monotherapy; 0.63 [0.56–0.71] triplets vs monotherapy).

Table 3. Cox Proportional Hazards Model for Frailty-Associated Risk of All-Cause Mortality[a]

	First line		Second line		Third line		Fourth line	
Characteristics	HR (95% CI)[a]	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Frail vs fit	1.28 (1.18–1.40)	<0.001	1.55 (1.36–1.77)	<0.001	1.35 (1.10–1.65)	0.004	1.22 (0.84–1.76)	0.29
Age at line index								
70–74 years	1.07 (0.94–1.20)	0.31	1.38 (1.13–1.68)	0.002	1.49 (1.11–2.00)	0.009	1.20 (0.73–1.98)	0.46
75–79 years	1.31 (1.16–1.48)	<0.001	1.61 (1.31–1.97)	<0.001	1.75 (1.29–2.37)	<0.001	1.13 (0.67–1.91)	0.66
≥80 years	1.89 (1.69–2.11)	<0.001	2.61 (2.16–3.15)	<0.001	2.52 (1.87–3.40)	<0.001	1.34 (0.78–2.29)	0.29
Sex								
Female	0.84 (0.78–0.90)	<0.001	0.87 (0.78–0.97)	0.015	0.85 (0.72–1.00)	0.052	0.91 (0.67–1.23)	0.53
Race								
African American	0.85 (0.76–0.94)	0.002	0.88 (0.74–1.05)	0.16	1.08 (0.82–1.42)	0.58	0.74 (0.44–1.26)	0.27
Other race	0.95 (0.82–1.10)	0.47	1.15 (0.92–1.43)	0.22	0.85 (0.59–1.24)	0.40	0.97 (0.50–1.90)	0.93
CCI								
3–4	1.35 (1.24–1.48)	<0.001	1.20 (1.03–1.39)	0.021	1.27 (1.02–1.59)	0.031	1.09 (0.73–1.61)	0.67
≥5	1.71 (1.56–1.88)	<0.001	1.52 (1.31–1.75)	<0.001	1.27 (1.02–1.58)	0.033	1.30 (0.89–1.91)	0.18
Comorbidity not in CCI								
Dysrhythmia	1.12 (1.03–1.21)	0.005	1.22 (1.08–1.37)	0.001	1.02 (0.85–1.24)	0.80	1.04 (0.75–1.44)	0.81
Anemia	1.08 (1.00–1.18)	0.058	1.12 (0.97–1.30)	0.11	1.38 (1.11–1.73)	0.0043	1.88 (1.24–2.85)	0.003
Thrombocytopenia	1.21 (1.09–1.36)	<0.001	1.09 (0.95–1.26)	0.23	1.41 (1.16–1.72)	<0.001	0.96 (0.67–1.39)	0.83
SREs	1.07 (1.00–1.16)	0.053	1.14 (1.02–1.28)	0.021	1.29 (1.08–1.53)	0.004	1.72 (1.26–2.35)	<0.001
Hospitalization LOS								
1–10 days	1.54 (1.41–1.69)	<0.001	1.35 (1.16–1.57)	<0.001	1.31 (1.06–1.62)	0.014	1.74 (1.18–2.57)	0.005
≥11 days	2.16 (1.95–2.40)	<0.001	1.52 (1.29–1.79)	<0.001	1.33 (1.04–1.72)	0.025	1.91 (1.25–2.92)	0.003
Regimen								
Doublet	0.70 (0.65–0.76)	<0.001	0.98 (0.86–1.12)	0.73	1.04 (0.84–1.28)	0.72	1.20 (0.82–1.76)	0.34
Triplet	0.63 (0.56–0.71)	<0.001	1.12 (0.95–1.31)	0.17	1.41 (1.12–1.78)	0.004	1.18 (0.78–1.81)	0.43
Other	0.71 (0.60–0.85)	<0.001	1.46 (1.15–1.84)	0.002	1.57 (1.14–2.17)	0.006	1.56 (0.90–2.71)	0.12

[a]All factors listed in Table 1 were included in the Cox model. Reference groups: fit, ages 66–69 years, men, white race, line index year 2011, West region, Charlson Comorbidity Index (CCI) 0–2, no comorbid conditions, no hospital stay, no Part D low-income subsidy, monotherapy. This table only presents the factors that showed statistically significant effect on mortality at 0.05 level during at least one line of therapy.
CI, confidence interval; HR, hazard ratio; SREs, skeletal-related events.

CONCLUSIONS

- **This study demonstrates that the claims-based poor DS prediction model performed as expected when applied for defining frailty in elderly Medicare patients with MM**
- **Frail patients were older, had higher comorbidity levels, were more likely to be treated with monotherapy and less likely to be treated with triplets, and had worse OS than fit patients**
- **Claims-based poor DS (frailty) was associated with a significantly increased risk of mortality during each line of therapy among the first 4 lines after adjustment for baseline characteristics, indicating frailty is an independent risk factor for mortality**
- **Of 12,547 elderly MM patients who initiated first-line therapy, 47%, 19%, and 7% initiated second-, third-, and fourth-line therapy; however, the percent of frail patients remained similar over the lines of therapy, ranging from 17% at first-line to 22% at second-line. These findings suggest that most elderly patients do not transition through multiple lines of therapy regardless of their frailty status and the most effective therapies should be used earlier in the disease course**
- **Given the limitations of claims databases, further studies assessing whether frailty is an independent predictor for choice of treatment, and whether the association between frailty and mortality is consistent by age groups and regimens are warranted**

CONFLICT OF INTEREST DISCLOSURES

SL, TN, JL: Nothing to disclose; ***KM, WW, SV, AY:*** Amgen, Inc. employee/stock owner; ***VM:*** Consulting for Merck, GSK-zoster advisory committee, Takeda and Celgene; Honoraria: Celgene, Genentech, Pharmacyclics and Gilead; ***JS:*** Research Funding: Millennium

REFERENCES

1. Kumar SK,*et al. Blood.* 2008;111(5):2516–20.
2. Facon T, *et al. Blood* 2015; 125(23):4239.
3. Vesteli SGR, van Norden Y, Sonneveld P. *Clin Lymphoma Myeloma Leuk.* 2015;15(3):e69–e70.
4. Palumbo A, *et al. Blood.* 2015;125(13):2068–74.
5. Davidoff AJ, *et al. J Geriatr Oncol.* 2013;4(2):157–65.
6. Davidoff AJ, *et al. Med Care.* 2014;52(6):500–10.
7. Princic, N, et al. *Blood.* 2015;126:4521.
8. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma Version 2.2014.
9. Quan H, et al. *Med Care.* 2005;43:1130–9.