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## Geriatric assessment in older adults with multiple myeloma

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### Abstract

**Background/Objectives**—The incidence of myeloma in older adults is increasing, yet little is known about geriatric impairments in these patients. We aimed to examine the prevalence of geriatric impairments in older adults with myeloma and association between geriatric assessment and autologous stem cell transplant eligibility.

**Design**—Prospective cohort study

**Setting**—Two academic medical centers

**Participants**—40 adults aged 65 years with newly diagnosed myeloma were enrolled.

**Measurement**—Participants completed a primarily self-administered geriatric assessment, including measures of functional status, comorbidities, polypharmacy, psychosocial status, social support, quality-of-life, cognition and physical performance. Outcomes were autologous stem cell transplant eligibility and receipt.

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T.W. designed the study & performed research, analyzed & interpreted data and wrote the manuscript. S.T. contributed to acquisition of subjects, data interpretation & manuscript preparation. H.K. contributed to data analysis & interpretation and manuscript preparation. J.M. contributed to research design, data interpretation and manuscript preparation. K.T. performed data analysis & interpretation. K.S.G. contributed to acquisition of subjects, data interpretation and manuscript preparation. R.V. contributed to acquisition of subjects, data interpretation and manuscript preparation. G.C. contributed to study design, data interpretation and manuscript preparation.

**Results**—Forty patients enrolled; mean age was 71. Geriatric impairments were common: 62% reported dependence in 1 instrumental activities of daily living (IADL), 76.9% had polypharmacy ( 4 medications), and 47.5% had 1 comorbidities. Median time on the Timed Up and Go was  $13.3 \pm 4.9$  seconds. Those considered candidates for autologous stem cell transplant (N= 26) were younger, with fewer comorbidities, better performance status, and faster performance on the Timed Up and Go test. Factors independently associated with receiving autologous stem cell transplant (N=21) included age and IADL dependence.

**Conclusion**—Impairments in geriatric domains are common in this population, even among those considered to have a good performance status. Geriatric assessment domains are associated with both transplant eligibility and receipt.

### Keywords

geriatric assessment; multiple myeloma; elderly; aged; hematopoietic stem cell transplantation

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### Introduction

With the aging of the population, within fifteen years, nearly 3 of every 4 patients diagnosed with myeloma will be aged 65–84.<sup>1</sup> While advances in treatment over the past 2 decades have improved survival for patients with myeloma, these advances have disproportionately benefited younger patients.<sup>2</sup> Autologous stem cell transplant (ASCT) is an aggressive myeloma treatment which is feasible in selected older patients and lengthens survival.<sup>3</sup> Treatment algorithms for myeloma diverge based on the patient’s ASCT-eligibility, yet there is no established definition for ASCT-eligibility.

Geriatric assessment encompasses the complex and heterogeneous health of older adults, comprising measures of function, comorbidity, polypharmacy, depression and other geriatric syndromes.<sup>4</sup> In general older cancer populations, geriatric assessment is predictive of chemotherapy toxicity<sup>5,6</sup> and prognostic of survival.<sup>7</sup> In myeloma, comorbidities and functional dependence are prognostic of survival,<sup>8</sup> but to date, other geriatric domains, including cognition, psychosocial status, and geriatric syndromes, have not been examined.

In this study, we examined the prevalence of geriatric impairments and identified associations between geriatric assessment and ASCT-eligibility, as well as whether the patient ultimately underwent this intensive treatment.

### Methods

This pilot prospective cohort study was approved by the Human Subjects Committees at Washington University and Duke University. Patients aged 65 with newly diagnosed myeloma were enrolled within 3 months of diagnosis from two tertiary care institutions. Because of referral patterns to academic medical centers and the sometimes-urgent need to initiate therapy for myeloma, participants who had started antimyeloma therapy were eligible. Patients were excluded if they had a life expectancy <6 months, were not returning to the participating institutions for ongoing care or had concomitant amyloidosis.

Participants completed the Cancer and Aging Research Group Geriatric Assessment Tool,<sup>5</sup> including functional status, comorbidities, polypharmacy, psychosocial status, social support, cognition, and physical performance. Self-administered measures included the Lawton instrumental activities of daily living (IADLs)<sup>9</sup>, Medical Outcomes Survey – Physical health,<sup>10</sup> the Mental Health Inventory-17,<sup>10</sup> and items on falls, weight loss, medications, and sensory impairments. A research coordinator administered the Timed Up and Go<sup>11</sup> and Blessed Orientation-Memory-Concentration test.<sup>12</sup> Laboratory data, International Staging System stage,<sup>13</sup> cytogenetics, Charlson Comorbidity Index<sup>14</sup> and clinician-rated Karnofsky Performance Status (KPS)<sup>15</sup> were also documented.

Aside from Centers for Medicare & Medicaid Services guidance that individuals undergoing ASCT should have responsive myeloma and “adequate cardiac, renal, pulmonary & hepatic function,” there are no objective, universally applied criteria for transplant eligibility; ASCT-eligibility is at the discretion of the myeloma physician, incorporating their clinical gestalt of the risk of this intensive treatment approach. At enrollment, the treating hematologist/ oncologist, blinded to the results of the geriatric assessment, was asked whether, based on their clinical assessment, the patient was ASCT-eligible.

Data were summarized using descriptive statistics as appropriate. Frequencies in unordered categorical variables were compared using Fisher’s Exact test, ordinal scales with an ordinal test for trend (Jonckheere’s test) and fully continuous but non-Gaussian variables with a Kruskal-Wallis test.

Single and multivariate logistic regression was performed to examine factors associated with whether the patient underwent ASCT and estimate the odds of undergoing ASCT with 95% confidence intervals. Variable selection was based on partial non-collinearity, information measures (e.g., Akaike’s information criterion) and, for comparison of nested models, likelihood ratio tests. P-values <0.05 were considered significant. Analyses were performed with SAS 9.4/SAS/STAT 13.2.

## Results

Forty patients enrolled between 2012 and 2015. Twenty-three patients (57.5%) had started myeloma therapy at enrollment, and 17 (42.5%) had not. The median number of days between diagnosis of myeloma and assessment was 24.0 ± (standard deviation) 25.5. Among those who had not started treatment, the median time from diagnosis to enrollment was 10.0 ± 11.8 days. Among those who had started treatment, the median time from diagnosis to assessment and from initiation of treatment to assessment was 34.0 ± 25.2 days and 25.0 ± 23.7 days, respectively. Data on the exact number of cycles of treatment are not available, but 25 days would be about 1 cycle of therapy (a typical cycle length is 21 or 28 days).

Baseline characteristics are described in Table 1. Geriatric assessment revealed a high prevalence of functional limitations and other geriatric impairments (Table 2). Almost two-thirds of the participants (62.5%) required assistance in 1 IADLs. Over one-fourth (28.2%) reported one or more falls in the prior 6 months. Polypharmacy was present in almost all patients, with 92.5% taking 4 medications. No standard cut-points are published for the

MHI-17, but to provide context, 7.5% scored 2 standard deviations below the mean score for euthymic individuals.<sup>16</sup> The only geriatric domain that differed between patients who had versus had not started myeloma therapy was greater number of medications among patients who had started therapy (Supplementary Table 1).

Even among those with a clinician-rated Karnofsky performance status  $\geq 80$ , geriatric impairments were common. Prevalent limitations included limitation in vigorous activities (95.9%), in moderate activities (70.8%), in one or more IADLs (54.2%), in bathing or dressing (25%) and  $\geq 1$  falls (21.7%). Figure 1 demonstrates the frequency of limitations in additional domains, stratified by Karnofsky performance status.

Almost 2/3 of the cohort (26/40, 65%) were deemed ASCT-candidates by their myeloma physician, who was blinded to the results of the geriatric assessment. Aside from age, demographics and disease-characteristics were similar between those who were ASCT-eligible and ineligible. ASCT-eligible and ineligible patients differed in their clinician-rated Karnofsky Performance Status, number of comorbidities and the Timed Up and Go test (Table 2). Of the 26 ASCT-candidates, 21 did undergo ASCT. Reasons for not proceeding to up-front ASCT included progression (N=1), failed mobilization (N=1), patient preference (N=2) and unknown (N=1). Factors associated with receipt of ASCT are detailed in Supplementary Table 2.

## Discussion

In this pilot prospective study, we demonstrated that 1) impairments in geriatric domains are highly prevalent in older adults with myeloma (both ASCT-eligible and ineligible, and those with KPS  $\geq 80$ ), and 2) geriatric assessment domains were associated with ASCT-eligibility and with the participant undergoing ASCT.

We demonstrated a high prevalence of geriatric impairments. Almost 2/3 (62.5%) of patients required assistance with one or more of their IADLs, which is slightly higher than the 40–50% noted in other studies of older adults with hematologic malignancies.<sup>17</sup> IADL dependence is predictive of adverse outcomes in older adults with cancer, including chemotherapy toxicity, functional decline, and falls.<sup>6,18</sup> Over one-quarter (28%) of the patients in our cohort reported one or more falls in the prior 6 months. This was remarkably similar to the fall-rate in over 400 patients with newly diagnosed myeloma (26%), which was higher than matched controls, suggesting that people with newly diagnosed myeloma are at increased risk for falls.<sup>19</sup> Polypharmacy was also extremely prevalent in our cohort with the median number of medications being 9; polypharmacy in older adults with cancer is associated with increased risk for use of potentially inappropriate medications, falls, and drug interactions. Patients who completed the geriatric assessment after initiation of myeloma therapy tended to be taking more medications, likely reflecting new prescriptions for supportive care.

Even among those considered to have a “good” performance status (Karnofsky performance status  $\geq 80$ ), geriatric impairments were quite prevalent in our cohort. The ability of geriatric assessment to detect limitations in patients with good performance status has been shown in

patients with acute myeloid leukemia,<sup>20</sup> patients undergoing allogeneic stem cell transplantation,<sup>21</sup> and solid tumors.<sup>22,23</sup> The fact that many of these factors have prognostic significance or predict chemotherapy toxicity in other malignancies supports the premise that geriatric assessment adds information beyond traditional oncologic assessment and may aid in risk-stratification and shared decision-making in older adults with myeloma.<sup>5-8,24</sup>

Geriatric assessment components are associated with older adults with myeloma being considered eligible for and actually undergoing ASCT. ASCT utilization is increasing among older patients, with similar outcomes between younger and selected older adults.<sup>3</sup> Yet it is not clearly defined *which* older adults are ASCT-eligible. In our study, as would be expected, performance status and comorbidities are associated with the patient being considered ASCT-eligible. Interestingly, speed on the Timed Up and Go test is also associated with ASCT-eligibility, suggesting that clinicians may observe slower physical performance to some degree in their standard clinical assessment. Geriatric assessment may allow development of objective criteria to correspond to the currently subjective assessment of an older patient's ASCT-eligibility.

Another important finding is that, independent of age, dependence in IADLs was associated with lower odds of undergoing ASCT, while Karnofsky performance status was not. Two prior observational studies comparing survival in older adults who did versus did not undergo ASCT have shown a survival benefit with ASCT, with 40–50% lower hazard for mortality.<sup>25,26</sup> Both of these studies controlled for comorbidities, and one controlled for performance status. Yet, neither of these retrospective studies included data on IADL dependence. Thus, because IADL dependence is associated with mortality in the general geriatric population and in myeloma, residual confounding could be present.<sup>8</sup> Comparative-effectiveness studies comparing ASCT and non-ASCT strategies need to account for differences in patient population beyond just comorbidities and performance status to yield valid conclusions.

Strengths of our study include the assessment of a multiple geriatric domains, extending beyond the functional status and comorbidities incorporated into prior studies in older adults with myeloma.<sup>8,27</sup> We have demonstrated highly prevalent geriatric vulnerabilities, including falls, cognitive impairment, sensory impairments and polypharmacy, which have not been demonstrated previously. Importantly, in general oncology populations, falls and hearing impairment are independently associated with toxicity of chemotherapy.<sup>5</sup> Cognitive impairment and impaired physical performance are associated with survival in both acute myeloid leukemia and chronic lymphocytic leukemia.<sup>24,28</sup> The impact of these impairments in other hematologic malignancies underscores the need for assessment of domains beyond comorbidity and functional status.

Our study has several limitations. First, our population was derived from two tertiary care centers and may not be generalizable to the population of older adults who are patients not referred to a tertiary care center. Some patients had started on treatment at the time of enrollment, which may have impacted their geriatric assessment results, though we found no significant differences between those who had versus had not initiated treatment, aside from number of medications. While some have may have had decline in their function due to

toxicity of treatment,<sup>18</sup> those who were highly symptomatic of their myeloma may have had improvements with response to therapy. In addition, the limited number of myeloma providers at the enrolling sites may not reflect the heterogeneity in the clinical ascertainment of ASCT-eligibility across hematology providers.

Another limitation is our sample size. Our small study was powered to detect rather large differences in the two groups; it was originally powered to detect a 47% difference in the prevalence of dependence in IADLs between the groups, assuming that, overall, 38% of patients were dependent in one or more IADLs. The actual rate of dependence in the whole cohort was higher than expected at 62%, and the observed difference was 14%. Thus, the sample size may have limited our ability to detect smaller but clinically meaningful differences in the individual geriatric parameters. Our limited sample size also did not allow for inclusion of all potential predictors in the multivariate model to avoid overfitting the model; indeed, some would argue that including 3 variables in our multivariate model could result in overfitting, while others have argued that as few as 5 events per predictor is acceptable.<sup>29</sup> Our study was not powered to determine whether geriatric assessment components are associated with outcomes such as survival or toxicity in this population. Finally, we are unable to compare our findings with the International Myeloma Working Group (IMWG) frailty model<sup>8</sup> or the Revised Myeloma Comorbidity Index<sup>30</sup> which were published after our study was developed, as the geriatric assessment tool utilized in our study does not capture all of the variables necessary to calculate each.

In conclusion, we have demonstrated that impairments in geriatric domains are prevalent in this population. ASCT-eligible patients were younger, had fewer comorbidities, better performance status and faster time on the Timed Up and Go test than transplant-ineligible patients. Factors independently associated with whether the patient ultimately underwent transplant were age and IADL dependence. Future study is needed to define whether these prevalent geriatric impairments predict adverse outcomes and shorter survival in older adults with myeloma and how geriatric assessment may aid in decision-making and risk-stratification among older adults with myeloma.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts:

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**Impact statement**

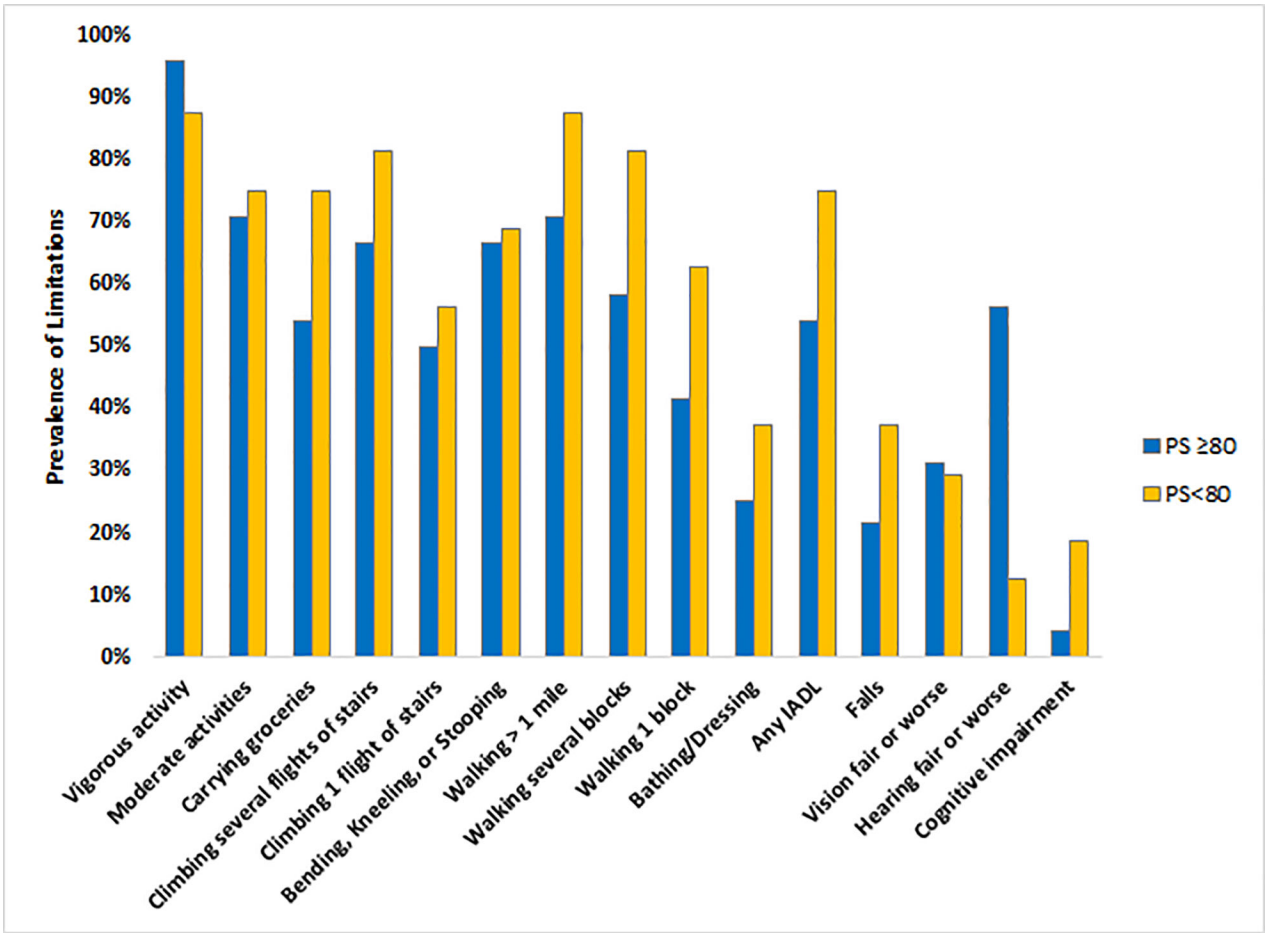
We certify that this work is **novel** clinical research. This research adds estimates of the prevalence of geriatric impairments in older adults with multiple myeloma and gives insight into which older adults with multiple myeloma are considered eligible for high dose therapy and autologous stem cell transplantation.

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**Figure 1.**  
Prevalence of functional limitations in older adults with myeloma  
IADLs, instrumental activities of daily living; PS, Karnofsky performance status

**Table 1.**

Baseline characteristics of cohort of older patients with myeloma within 3-months of diagnosis

Variable	Entire cohort (N=40)	Transplant ineligible (N=14)	Transplant eligible (N=26)
Age (Mean $\pm$ standard deviation)	71.1 $\pm$ 5.1	74.0 $\pm$ 6.0	69.6 $\pm$ 3.8
Male gender, No. (%)	25 (62.5%)	7/14 (50%)	18/26 (69.2%)
Race, No. (%)			
White	31 (77.5%)	11/14 (78.6%)	20/26 (77.5%)
Black	5 (12.5%)	2/14 (14.3%)	3/26 (11.5%)
Other	4 (10%)	1/14 (7.1%)	3/26 (11.5%)
Marital status: married, No. (%)	30 (75%)	12/14 (85.7%)	18/26 (69.2%)
International Staging System Stage, No. (%) <sup>*</sup>			
Stage I	11/35 (31.4%)	3/13 (23.1%)	8/22 (36.4%)
Stage II	13/35 (37.1%)	5/13 (38.5%)	8/22 (36.4%)
Stage III	11/35 (31.4%)	5/13 (38.5%)	6/22 (27.3%)
Chromosomal abnormalities, No. (%) <sup>*</sup>			
T4;14	2/30 (6.7%)	0/9 (0%)	2/21 (9.5%)
T11;14	6/29 (20.7%)	1/8 (12.5%)	5/21 (23.8%)
Deletion 13 by FISH	21/31 (67.7%)	6/9 (66.7%)	15/22 (68.2%)
Deletion 17p	8/31 (25.8%)	3/8 (37.5%)	5/23 (21.7%)

\* Denominator reflects staging/FISH not performed

**Table 2.**

Geriatric assessment measures in older adults with myeloma within 3-months of diagnosis (N=40)

Variable	Entire cohort	Transplant ineligible (N=14)	Transplant eligible (N=26)	P value
Functional status				
Any IADL dependence, No. (%)	25 (62.5%)	10/14 (71.4%)	15/26 (57.7%)	0.50
MOS: Patient limited a lot in vigorous activities, No. (%)	27 (67.5%)	11/14 (78.6%)	16/26 (61.5%)	0.44
Karnofsky Performance Status (clinician-rated) (mean $\pm$ standard deviation)	77.0 $\pm$ 13.2	70.7 $\pm$ 14.9	80.4 $\pm$ 11.1	0.026
Report of one or more falls in prior 6 months, No. (%)	11/39 (28.2%)	4/14 (28.6%)	7/25 (28.0%)	1.00
Timed Up and Go time (mean seconds $\pm$ standard deviation)	13.3 $\pm$ 4.9	15.8 sec $\pm$ 6.1	11.9 $\pm$ 3.4	0.013
Number of Medications (mean $\pm$ standard deviation)	9.8 $\pm$ 5.6	10.2 $\pm$ 6.3	9.6 $\pm$ 5.3	0.75
Charlson comorbidity index (mean $\pm$ standard deviation)	1.0 $\pm$ 1.6	1.9 $\pm$ 2.1	0.6 $\pm$ 1.0	0.0065
Cognition: Short Blessed Test score (mean $\pm$ standard deviation)	4.2 $\pm$ 5.2	5.0 $\pm$ 6.2	3.7 $\pm$ 4.6	0.47
Psychological status: Mental Health Inventory-17 score (mean $\pm$ standard deviation)	73.2 $\pm$ 15.6	67.4 $\pm$ 19.6	76.2 $\pm$ 12.4	0.10
Sensory impairments				
Self-reported vision: fair or poor, No. (%)	12/40 (30%)	5/14 (35.7%)	7/26 (26.9%)	0.41
Self-reported hearing: fair or poor, No. (%)	12/40 (30%)	5/14 (35.7%)	7/26 (26.9%)	0.41
Self-reported weight loss, No. (%)	22/40 (55.0%)	7/14 (50.0%)	15/26 (57.7%)	0.64

IADL, instrumental activity of daily living; MOS, Medical Outcomes Study