

Assessing the Effect of Adherence on Patient-reported Outcomes and Out of Pocket Costs Among Patients With Multiple Myeloma

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Abstract

It is unclear how medication adherence affects the burden of multiple myeloma (MM). Overall, 162 adults with MM completed an online survey. Better medication adherence related to less impairment to work productivity and functioning, lower out of pocket costs, and fewer office visits. With increased survival, considering the quality of life for patients with MM will be essential.

Background: The present study characterized the effect of multiple myeloma (MM) on work productivity, health care resource usage, and out of pocket costs (OOPCs) and examined the association of adherence with quality of life (QoL) and productivity loss. **Materials and Methods:** The present cross-sectional study included 162 patients categorized by their 4-item Morisky Medication Adherence Scale (MMAS-4) score (4 vs. ≤ 3). Online surveys included the Work Productivity and Activity Impairment questionnaire, Functional Assessment of Cancer Therapy–Multiple Myeloma (FACT-MM), and MM-specific questions. **Results:** On average, patients reported FACT-MM scores of 98.5 ± 29.3 , absenteeism of $18.3\% \pm 17.8\%$, presenteeism of $51.8\% \pm 30.2\%$, overall work productivity impairment of $57.3\% \pm 31.7\%$, and activity impairment of $49.9\% \pm 29.5\%$ in the previous 7 days. During the previous 3 months, the mean OOPCs were $\$709 \pm \1307 ; prescription medications accounted for 55% of these costs. Patients attended 4.1 ± 4.6 visits to oncologists or hematologists during that time, which accounted for 45% of the OOPCs. Patients spent an average of 6.8 ± 8.3 hours at MM-related monthly appointments, and 35.2% reported frustration while at the doctor's office. Patients with an MMAS-4 score of 4 reported higher FACT-MM scores (106.9 vs. 89.2; $P < .001$). Patients with an MMAS-4 score of ≤ 3 reported greater activity impairment (56.5% vs. 39.8%; $P = .015$) and feeling overwhelmed or frustrated with rescheduling MM appointments (64.0% vs. 26.0%; $P = .002$). **Conclusion:** MM was associated with significant workplace and functional impairment, high OOPCs, and frequent office visits. High medication adherence was associated with better outcomes across these domains. As survival for patients with MM improves, patient QoL should be considered to enhance these outcomes.

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Introduction

Multiple myeloma (MM) is a systemic malignancy of plasma cells that is highly treatable but rarely curable.¹ In the United States, MM is the second most prevalent hematologic cancer,² with nearly

100,000 Americans currently living with the disease.³ The mean 5-year survival rate for MM patients has been found to range from 15% to 20%.⁴ This represents a dramatic improvement during the past 20 years owing to rapid therapeutic advances.⁵⁻⁷

The current treatment options for MM include radiation therapy, surgery, targeted therapy, chemotherapy, steroids, and/or stem cell transplantation.⁸ The treatment choice is determined largely by the age and general health of the patient, their eligibility for stem cell transplantation, and previous therapy received.⁹ Adjunctive therapies can help to alleviate the symptoms of end organ damage and side effects of MM treatment. For example, bisphosphonates are commonly used to prevent pathologic fractures, and anticoagulants might be prescribed to decrease the risk of developing blood

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clots.⁸ Physicians have reported that treatment choice should closely adhere to the preferences of the patients and families.⁹

Little research has examined treatment adherence among MM patients. The results from a previous study from the United Kingdom suggested that > 90.0% of patients were adherent to oral chemotherapy.¹⁰ However, follow-up interviews with patients suggested some misunderstanding among certain age and ethnic groups that could have led to poor adherence. Using pharmacy claims data, another study found that the prescription costs incurred by patients did not influence their adherence to oral MM treatments.¹¹ Collectively, the limited available data have typically focused on adherence as an endpoint; however, the effect of adherence on subsequent humanistic and economic outcomes for patients with MM remains unexplored.

The diagnosis and treatment of MM have been consistently associated with impairments in quality of life (QoL).^{12,13} Pain, fatigue, and poor physical functioning are commonly reported by patients with MM, even among those with stable disease.¹⁴ When compared with gender- and age-matched controls, patients with MM had significantly lower QoL.¹⁵ However, a critical review of the published data found few studies that had used QoL as an endpoint in clinical trials involving patients with MM, despite the recognized effect of treatment on QoL and recommendations for QoL data to help guide clinical decision making.¹⁶

Previous research has indicated that fewer than half as many patients with MM were employed after treatment compared with before the diagnosis (66.0% vs. 33.0%), a significant decrease in employment.¹⁷ Additionally, the out of pocket costs (OOPCs) associated with care were found to be substantial, with respondents reporting that their initial treatment costs were equivalent to one third of their annual income. According to a recent study, most MM patients surveyed (71.0%) reported at least a modest financial burden associated with their disease.¹⁸ These results reinforce the considerable effect MM can have on both labor force participation and economic burden.

To date, the previous data have not quantified several dimensions of patient burden in MM or evaluated whether adherence might influence the nature and/or extent of this burden. In addition, few studies have examined health care resource usage (HRU), OOPCs, QoL, or work productivity and activity impairment among patients with MM. Because QoL and economic considerations can play a major role in treatment decisions for those with MM, it is imperative to understand the effect of MM on patient-reported outcomes in a real world setting. The present study characterized the burden of MM from the perspective of patients undergoing treatment in the modern era of therapy. We also assessed patient-reported adherence and its association with QoL, HRU, OOPCs, temporal burden, and impairment of work productivity and daily activities among patients with MM who were adherent to treatment.

Materials and Methods

Data Source

We performed a cross-sectional survey of 162 US adults (aged ≥ 18 years) with MM. A mixed recruitment strategy was used, such that patients were recruited from the Lightspeed Global Market Insite panel and its partners, through advocacy groups, and from social media platforms (ie, Rare Patient Voice [available at:

www.rarepatientvoice.com], Endeavour Clinical Solutions [available at: <http://endeavour-clinical.com>]) and included patients with MM who were currently receiving a treatment regimen of either oral therapy only or injectable therapy, with or without oral medication. The respondents were prescreened for eligibility using an online questionnaire, which consisted of an informed consent acknowledgment and the inclusion and exclusion criteria. Qualified respondents then proceeded to the main study questions. The respondents who completed the main survey received incentives, typically reward points or currency offered by their panels, which were of fair market value for their time.

To be eligible for enrollment in the study, the patients must have reported a diagnosis of MM, been aged ≥ 18 years, and agreed to participate. Patients who were taking their first medication for induction or maintenance treatment of MM had to have been taking this medication for ≥ 8 weeks (first-line therapy cohort). Patients who were not taking their first medication for MM treatment because the first medication had not worked or had stopped working must have been receiving their current treatment for a minimum of 6 weeks (second-line therapy or higher cohort). Patients who did not meet the inclusion criteria and/or who had reported a diagnosis of lymphoma, leukemia, or myelodysplastic syndrome were not eligible to participate in the present study. The Sterling Institutional Review Board (Atlanta, GA) approved the study protocol.

Disease History and Patient Characteristics

Demographic Data. The demographic variables included gender (male or female), age (continuous), race/ethnicity (white, black, Asian, Hispanic/Latino, unknown/other), marital status (single, married/in committed relationship, separated/divorced/widowed), employment status (currently employed, unemployed), household income ($< \$49,999$, $\geq \$50,000$, declined to answer), education (some high school, high school graduate or equivalent, some college, associate's degree, college graduate, some graduate school, completed graduate school), and health insurance (yes, no).

Health History. The body mass index (BMI; continuous), alcohol use (never vs. currently or used to drink), and comorbidity burden (Charlson comorbidity index [CCI])¹⁹ were measured. The CCI assesses the comorbidity burden by summing and then weighting the self-reported presence of several different medical conditions (eg, chronic pulmonary disease, myocardial infarction); higher scores represent a greater patient burden from comorbidities.

Disease and Treatment Characteristics. The disease and treatment characteristics assessed in the present study included the number of years since the diagnosis of MM (continuous), functional ability (categorical; able to perform housework or office work normally, able to perform housework or office work normally but restricted in ability to perform physical activities, or able to walk around at least one half the time awake but restricted in performing work activities), current treatments received (yes or no; radiation, stem cell transplantation), number of weeks receiving current treatment (continuous), number of times the treatment regimen was changed (categorical; 0 changes [first treatment], 1 change [second treatment], or ≥ 2 changes [third or later treatment]), number of days

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since the last dose of the current treatment was taken (continuous), and the total number of current treatments (continuous).

Health Status and QoL

Patient health status and QoL were measured using the Functional Assessment of Cancer Therapy—Multiple Myeloma (FACT-MM).²⁰ The FACT-MM is a validated self-assessment of 5 domains of health status and QoL. These include physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and MM-related well-being (14 items). All items use a 5-point rating scale (0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much) to score patient health status and QoL in these areas. The responses are summed to yield individual subscale scores, and the subscale scores are then summed to compute the FACT-MM total score, which range from 0 to 164. The FACT-MM Trial Outcome Index, which has a possible range of 0 to 112 points, is computed by summing the scores from the following 3 subscales: physical well-being, functional well-being, and MM-related well-being. Four of the 5 FACT-MM subscales constitute the FACT—General (FACT-G): physical well-being, social/family well-being, emotional well-being, and functional well-being.²¹ The scores for these 4 subscales are summed to calculate the FACT-G total score, which has a possible range of 0 to 108 points. Higher subscale and total scores on these measures indicate better health status and QoL.

Treatment Adherence

Treatment adherence was assessed using the 4-item Morisky Medication Adherence Scale (MMAS-4; use of the MMAS-4 is protected by US copyright laws; permission for use is required).²² The MMAS-4 is a 4-item self-report measure of patient adherence to medication. The total score range is 0 to 4, with higher scores representing greater adherence. For regression analysis, consistent with the approach used in previous research,²³ the patients were stratified by their MMAS-4 score (4 vs. ≤ 3).

Productivity Loss and Daily Activity Impairment

Impairment to work productivity and daily activities because of health was measured using the Work Productivity and Activity Impairment—General Health (WPAI) questionnaire.²⁴ The WPAI questionnaire is a 6-item validated instrument consisting of 4 metrics: absenteeism (percentage of work time missed because of health in the past 7 days), presenteeism (percentage of impairment experienced while at work in the past 7 days because of health), overall work productivity loss (overall impairment estimate that combines absenteeism and presenteeism), and activity impairment (percentage of impairment in daily activities because of health in the past 7 days). Only respondents who reported being employed provided data for absenteeism, presenteeism, and overall work impairment. All respondents provided data for activity impairment. Higher scores for these metrics represent greater impairment.

Temporal and Financial Burden

The temporal and financial burden was assessed through a series of questions on how MM affected the respondents in terms of time and financial expense. This burden was measured as follows: (1) the number of oncologist, hematologist, and oncology nurse visits because of MM in previous 3 months (continuous); (2) average

OOPCs for each doctor visit in the previous 3 months (continuous); (3) average total OOPCs for prescriptions, over the counter medications, transportation, and/or other MM-related expenses in the previous 3 months (continuous); (4) how often in the past month the patient felt overwhelmed by OOPCs for MM-related expenses (5-point Likert scale; truncated as moderate/high/extremely high burden vs. no burden/some burden for regression analysis); (5) time spent (in hours) at MM-related treatment appointments in the past month (continuous); (6) how often in the past month the patient felt overwhelmed or frustrated by having to schedule, reschedule, or keep MM-related doctor appointments (5-point Likert scale; truncated as somewhat often/often/very often vs. not at all/rarely for regression analysis); and (7) how often in the past month the patient felt upset or frustrated during an MM-related doctor visit (5-point Likert scale; truncated as somewhat often/often/very often vs. not at all/rarely for regression analysis).

Statistical Analysis

For the total sample ($n = 162$), descriptive statistics were calculated for all study variables. Frequencies and percentages are reported for categorical measures and the mean \pm standard deviation for continuous measures. Bivariate analyses were performed to examine differences between adherence groups (MMAS-4 score, 4 vs. ≤ 3) in the demographic characteristics. For categorical variables, χ^2 tests were used to determine significant bivariate differences, and independent samples t tests were used with the continuous variables for this purpose. To analyze whether the adherence groups differed in QoL (FACT-MM), OOPCs, and work productivity and activity impairment (WPAI), a series of generalized linear models (GLMs) were performed with the adherence grouping variable as the predictor. These analyses were performed for the subset of 118 respondents who used oral therapy (oral only or oral and injectable) for MM. The GLMs were used to test whether the outcomes differed across the adherence groups, after adjustment for covariates. The covariates included age, BMI, and total number of MM treatments the patient reported currently using. The adjusted mean and P values are reported for the outcomes of interest. P values $< .05$, 2 tailed, were considered to indicate statistical significance.

Results

For the total sample of 162 respondents, approximately one half (49.4%) were women, with an average age of 55.9 ± 13.5 years (Table 1). Among the 118 oral medication users, most (55.9%) were women, with a mean age of 55.9 ± 13.2 years. Most patients (total sample, 82.1%; oral medication users, 78.8%) self-identified themselves as white, nearly all (total sample, 97.5%; oral medication users, 96.6%) had health insurance, and approximately one half (total sample, 46.9%; oral medication users, 50.8%) were employed full-time or part-time or were self-employed. Most participants (total sample, 74.1%; oral medication users, 67.8%) were married or in a committed relationship, and just more than one half (total sample, 53.1%; oral medication users, 58.5%) reported an annual household income of $\geq \$50,000$. Almost two thirds of the respondents (total sample, 66.0%; oral medication users, 64.4%) had earned a college degree or higher. The mean BMI for the participants was 28.0 ± 5.6 kg/m² and 28.2 ± 5.7 kg/m² for the total sample and the oral medication users, respectively. More than three

Table 1 Patient Demographic Characteristics

Variable	Total Sample (n = 162)	Oral MM Rx Users (n = 118)
Age	55.9 ± 13.5	55.9 ± 13.2
BMI, ^a kg/m ²	28.0 ± 5.6	28.2 ± 5.7
Gender		
Male	82 (50.6)	52 (44.1)
Female	80 (49.4)	66 (55.9)
Race/ethnicity		
White	133 (82.1)	93 (78.8)
Black	8 (4.9)	7 (5.9)
Asian	2 (1.2)	1 (0.8)
Hispanic or Latino	16 (9.9)	14 (11.9)
Unknown/other	3 (1.9)	3 (2.5)
Marital status		
Single, never married	13 (8.0)	11 (9.3)
Married/committed relationship	120 (74.1)	80 (67.8)
Separated/divorced/widowed	29 (17.9)	27 (22.9)
Employment status		
Currently employed	76 (46.9)	60 (50.8)
Not employed	86 (53.1)	58 (49.2)
Income		
<\$49,999	68 (42.0)	46 (39.0)
≥\$50,000	86 (53.1)	69 (58.5)
Declined to answer	8 (4.9)	3 (2.5)
Education		
Less than high school	1 (0.6)	1 (0.8)
High school graduate or equivalent	9 (5.6)	7 (5.9)
Some college but no degree	19 (11.7)	15 (12.7)
Associate's degree	26 (16.0)	19 (16.1)
College graduate	61 (37.7)	39 (33.1)
Some graduate school but no degree	10 (6.2)	7 (5.9)
Completed graduate school	36 (22.2)	30 (25.4)
Health insurance		
Yes	158 (97.5)	114 (96.6)
No	4 (2.5)	4 (3.4)
Drink alcoholic beverages		
Never	30 (18.5)	17 (14.4)
Used to drink/currently drink	132 (81.5)	101 (85.6)

Data presented as mean ± standard deviation or n (%).
 Abbreviations: BMI = body mass index; MM Rx = multiple myeloma prescription medication.
^aTotal sample, n = 161; oral MM Rx user group, n = 117.

quarters (total sample, 81.5%; oral medication users, 85.6%) reported that they used to drink or currently drank alcohol.

Overall, the patients in the total sample reported a mean time since the MM diagnosis of 4.6 ± 4.3 years and a mean CCI score of 0.3 ± 0.9 (Table 2). The oral medication users reported a mean time since the MM diagnosis of 4.7 ± 3.6 years, with a CCI score of 0.4 ± 0.9. Most respondents (total sample, 51.2%; oral medication users, 52.5%) were receiving their first treatment regimen, and most (total sample, 62.3%; oral medication users, 55.9%) reported being

Table 2 Patient Health Characteristics

Variable	Total Sample (n = 162)	Oral MM Rx Users (n = 118)
Charlson comorbidity index score	0.3 ± 0.9	0.4 ± 0.9
Duration of MM, y	4.6 ± 4.3	4.7 ± 3.6
Interval since last took current MM prescription, d	3.2 ± 3.9	2.8 ± 3.4
Duration of current MM prescriptions, wk	96.0 ± 97.2	117.6 ± 102.3
Total current MM prescriptions, n	1.6 ± 0.9	1.7 ± 1.0
Functional ability		
Able to perform housework and/or office work normally	48 (29.6)	43 (36.4)
Housework/office work normal but restricted in ability to perform physical activity	101 (62.3)	66 (55.9)
Able to walk around at least half the time awake but no work activities	13 (8.0)	9 (7.6)
Treatment received		
Radiation therapy	11 (6.8)	9 (7.6)
Stem cell transplantation	24 (14.8)	21 (17.8)
How many times have you changed medication		
Currently my first treatment regimen	83 (51.2)	62 (52.5)
Currently my second treatment regimen (1 change)	45 (27.8)	33 (28.0)
Currently my third or later treatment regimen (≥2 changes)	34 (21.0)	23 (19.5)

Data presented as mean ± standard deviation or n (%).
 Abbreviations: MM = multiple myeloma; MM Rx = multiple myeloma prescription medication.

able to perform housework/office work but were restricted in their ability to perform physical activities. A number of patients (total sample, 14.8%; oral medication users, 17.8%) had undergone stem cell transplantation. On average, for the total sample, the interval since the current treatment was last taken was 3.2 ± 3.9 days, the mean interval of current MM treatment was 96.0 ± 97.2 weeks, and the mean number of current MM prescriptions was 1.6 ± 0.9. Among the oral medication users, the interval since the current treatment was last taken was 2.8 ± 3.4. These participants had been taking their current medication for an average of 117.6 weeks and were currently taking an average of 1.7 ± 1.0 MM medications.

The mean MMAS-4 score was 3.2 ± 1.1 for oral medication users (Table 3). Regarding QoL, the average FACT-MM and FACT-G total scores were 98.5 ± 29.3 and 67.5 ± 18.5, respectively, for the total sample. Similarly, FACT-MM and FACT-G total scores of 100.0 ± 30.3 and 68.3 ± 19.3, respectively, were reported by the oral medication users. For the individual FACT-MM domains, the mean scores were as follows, from highest to lowest, for the total sample: MM well-being, 31.0 ± 12.2; social/family well-being, 18.7 ± 5.7; physical well-being, 17.2 ± 6.7; functional well-being, 16.3 ± 5.9; and emotional well-being, 15.3 ± 5.5. The same order of FACT-MM domain scores, from highest to lowest, was found for oral medication users: MM well-being,

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Table 3 Patient Adherence, QoL, Work and Activity Impairment, Costs, and Temporal Burden

Variable	Total Sample (n = 162)	Oral MM Rx Users (n = 118)
MMAS-4 ^{a,b}		3.2 ± 1.1
FACT-MM		
Physical well-being	17.2 ± 6.7	17.5 ± 6.6
Social/family well-being	18.7 ± 5.7	18.8 ± 6.1
Emotional well-being	15.3 ± 5.5	15.5 ± 5.4
Functional well-being	16.3 ± 5.9	16.6 ± 6.2
Multiple myeloma well-being	31.0 ± 12.2	31.7 ± 12.5
FACT-MM trial outcome index	66.9 ± 20.7	68.0 ± 21.3
FACT-G total score	67.5 ± 18.5	68.3 ± 19.3
FACT-MM total score	98.5 ± 29.3	100.0 ± 30.3
WPAI		
Absenteeism, ^c %	18.3 ± 17.8	17.2 ± 19.2
Presenteeism, ^c %	51.8 ± 30.2	47.1 ± 31.5
Overall work impairment, ^c %	57.3 ± 31.7	52.3 ± 33.4
Activity impairment, %	49.9 ± 29.5	49.0 ± 30.1
HRU and OOPCs (3-mo period)		
Visits to oncologist/hematologist/ oncology nurse, n	4.1 ± 4.6	3.9 ± 5.0
Costs for oncologist/hematologist/ oncology nurse visit, \$	318.9 ± 637.2	282.7 ± 516.8
Amount paid out of pocket for medications prescribed by doctor, \$	388.0 ± 1063.4	324.0 ± 718.6
Amount paid out of pocket for over the counter medications, \$	191.4 ± 363.8	166.0 ± 347.2
Amount paid out of pocket for transportation, \$	67.3 ± 114.8	64.6 ± 117.4
Total out of pocket costs, \$	709.0 ± 1307.3	637.1 ± 1017.8
Temporal burden (1-mo period)		
Time spent at appointments, h	6.8 ± 8.3	6.2 ± 7.3
Time spent traveling to and from appointments, h	3.5 ± 4.3	3.2 ± 3.1
Financial burden related to MM out of pocket expenses		
None	40 (24.7)	31 (26.3)
Some	27 (16.7)	15 (12.7)
Moderate	50 (30.9)	38 (32.2)
High	28 (17.3)	20 (16.9)
Extremely high	17 (10.5)	14 (11.9)
Overwhelmed or frustrated by having to schedule, reschedule, or keep MM appointments		
Not at all	48 (29.6)	35 (29.7)
Rarely	46 (28.4)	36 (30.5)
Somewhat often	39 (24.1)	26 (22.0)
Often	22 (13.6)	15 (12.7)
Very often	7 (4.3)	6 (5.1)
Upset or frustrated while at doctor's office		
Not at all	42 (25.9)	32 (27.1)
Rarely	63 (38.9)	49 (41.5)

Table 3 Continued

Variable	Total Sample (n = 162)	Oral MM Rx Users (n = 118)
Somewhat often	34 (21.0)	20 (16.9)
Often	20 (12.3)	14 (11.9)
Very often	3 (1.9)	3 (2.5)

Data presented as mean ± standard deviation or n (%).

Abbreviations: FACT-G = Functional Assessment of Cancer Therapy—General; FACT-MM = Functional Assessment of Cancer Therapy—Multiple Myeloma; HRU = health care resource usage; MM Rx = multiple myeloma prescription medication; OOPCs = out of pocket costs; WPAI = Work Productivity and Activity Impairment—General Health questionnaire.

^aUse of the 4-item Morisky Medication Adherence Scale (MMAS-4) is protected by US copyright laws; permission for use is required.

^bOnly included respondents with an oral MM prescription medication.

^cOnly included employed respondents.

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31.7 ± 12.5; social/family well-being, 18.8 ± 6.1; physical well-being, 17.5 ± 6.6; functional well-being, 16.6 ± 6.2; and emotional well-being, 15.5 ± 5.4. In the previous 3 months, patients in the total sample reported a mean of 4.1 ± 4.6 visits to oncologists, hematologists, and oncology nurses. In contrast, the oral medication users reported a mean of 3.9 ± 5.0 visits in the previous 3 months. In the past month, patients in the total sample spent a mean of 6.8 ± 8.3 hours at MM-related appointments and 3.5 ± 4.3 hours traveling to these appointments. In contrast, oral medication users spent 6.2 ± 7.3 hours at MM-related appointments and 3.2 ± 3.1 hours traveling to their MM appointments.

On average, among the employed respondents in the total sample, the overall work productivity impairment was 57.3% ± 31.7%, which appeared to reflect presenteeism (51.8% ± 30.2%) much more so than absenteeism (18.3% ± 17.8%; Table 3). This was also the case among the oral medication users, although their average impairment was slightly lower, relative to the total sample. Specifically, the oral medication users reported 52.3% ± 33.4% overall work productivity impairment, with 47.1% ± 31.5% presenteeism and 17.2% ± 19.2% absenteeism. The mean overall activity impairment was 49.9% ± 29.5% and 49.0% ± 30.1% for the total sample and oral medication users, respectively, indicating a decreased ability to complete general daily activities, regardless of employment status. The mean total MM-related OOPCs for 3 months were \$709.00 ± \$1307.30 for the total sample, with somewhat lower total MM-related OOPCs found for the oral medication users (\$637.10 ± \$1017.80). For both the total sample and the oral medication users, the greatest OOPCs were found for MM-related prescription medications (\$388.00 ± 1063.40 and \$324.00 ± \$718.60, respectively), with the lowest OOPCs for transportation (\$67.30 ± \$114.80 and \$64.60 ± \$117.40, respectively). During 3-month period, the mean OOPCs incurred for visits to oncologists, hematologists, and/or oncology nurses was \$318.9 ± \$637.20 for the total sample and \$282.70 ± \$516.80 for the oral medication users.

When comparing the adherence groups, 118 respondents reported having an oral medication in their treatment regimen and were included in the analyses, of which 72 reported an MMAS-4

Table 4 Differences Between MM Adherence Groups in Quality of Life, Productivity Impairment, Health Care Resource Usage, Out of Pocket Costs, and Temporal Burden, Adjusted for Covariates (n = 118)

Dependent Variable	Adherence Score	Adjusted Mean ± SE	95% CI
Physical well-being	≤3	15.4 ± 0.8 ^b	13.9-17.0
	4	18.8 ± 0.6	17.6-20.0
Social/family well-being	≤3	16.8 ± 0.9 ^b	14.9-18.6
	4	20.1 ± 0.7	18.6-21.5
Emotional well-being	≤3	13.8 ± 0.6 ^b	12.6-15.1
	4	16.5 ± 0.5	15.5-17.5
Functional well-being	≤3	14.9 ± 0.9 ^c	13.1-16.7
	4	17.7 ± 0.7	16.3-19.1
MM well-being	≤3	28.3 ± 1.7 ^c	25.1-31.6
	4	33.9 ± 1.3	31.3-36.4
FACT-MM trial outcome index	≤3	60.5 ± 2.7 ^b	55.3-65.7
	4	72.7 ± 2.1	68.7-76.8
FACT-G total score	≤3	60.9 ± 2.5 ^b	56.1-65.7
	4	73.1 ± 1.9	69.3-76.8
FACT-MM total score	≤3	89.2 ± 3.8 ^b	81.7-96.6
	4	106.9 ± 3.0	101.1-112.7
Absenteeism, ^d %	≤3	21.8 ± 6.4	12.2-38.9
	4	10.3 ± 2.8	6.1-17.4
Presenteeism, ^d %	≤3	48.8 ± 8.4	34.9-68.3
	4	37.8 ± 5.8	28.0-51.0
Overall work impairment, ^d %	≤3	58.2 ± 9.5	42.3-80.1
	4	40.8 ± 5.9	30.7-54.3
Activity impairment, %	≤3	56.5 ± 6.0 ^c	45.9-69.5
	4	39.8 ± 3.3	33.9-46.8
Visits to oncologist, hematologist, oncology nurse	≤3	3.0 ± 0.6	2.1-4.3
	4	4.3 ± 0.6	3.3-5.6
Cost for oncologist, hematologist, oncology nurse visits, \$	≤3	147.7 ± 45.7	80.6-270.6
	4	210.3 ± 49.9	132.1-334.7
Amount paid out of pocket for medications prescribed by a doctor, \$	≤3	387.9 ± 168.4	165.7-908.1
	4	220.2 ± 68.4	119.8-404.8

Table 4 Continued

Dependent Variable	Adherence Score	Adjusted Mean ± SE	95% CI
Amount paid out of pocket for over the counter medications, \$	≤3	130.6 ± 34.0 ^c	78.3-217.6
	4	46.8 ± 9.1	32.0-68.4
Amount paid out of pocket for transportation, \$	≤3	83.0 ± 18.6 ^d	53.5-128.8
	4	43.3 ± 7.6	30.6-61.2
Total out of pocket costs, \$	≤3	828.3 ± 248.7	459.9-1491.8
	4	395.7 ± 87.2	256.8-609.5
Financial burden related to MM out of pocket expenses, %	≤3	0.7 ± 0.1	0.6-0.9
	4	0.6 ± 0.1	0.5-0.8
Time spent at appointments, h	≤3	5.0 ± 0.8	3.6-6.8
	4	6.2 ± 0.8	4.9-7.9
Time spent traveling to and from appointments, h	≤3	3.1 ± 0.5	2.3-4.2
	4	3.2 ± 0.4	2.5-4.0
Overwhelmed or frustrated by scheduling, rescheduling, or keeping MM appointments, %	≤3	0.6 ± 0.1 ^b	0.4-0.8
	4	0.3 ± 0.1	0.2-0.4
Upset or frustrated while at doctor's office, %	≤3	0.4 ± 0.1	0.2-0.6
	4	0.2 ± 0.1	0.1-0.3

All models controlled for age, body mass index, and total number of MM treatments patients reported currently using.

Abbreviations: CI = confidence interval; FACT-G = Functional Assessment of Cancer Therapy—General; FACT-MM = Functional Assessment of Cancer Therapy—Multiple Myeloma; MM = multiple myeloma; SE = standard error.

^aUse of the 4-item Morisky Medication Adherence Scale (MMAS-4) is protected by US copyright laws; permission for use is required.

^bP < .01.

^cP < .05.

^dOnly included employed respondents.

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score of 4 and 46 reported an MMAS-4 score of ≤ 3. Bivariate analyses of the demographic data showed that patients with an MMAS-4 score of 4 were older (mean, 59.2 years vs. 50.7 years; P < .001) and were taking fewer current MM treatments (mean, 1.4 vs. 2.1; P < .001) than those with an MMAS-4 score of ≤ 3. No differences in the mean BMI (score 4 vs. score ≤ 3, 28.8 kg/m² vs. 27.2 kg/m²; P = .15), CCI (score 4 vs. score ≤ 3, 0.4 vs. 0.2; P = .16), or other demographic characteristics were found between the 2 adherence groups.

In the GLMs, after adjusting for covariates, patients with an MMAS-4 score of 4 reported significantly higher FACT-MM total scores (mean, 106.9 vs. 89.2; P < .001) than patients with an

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MMAS-4 score of ≤ 3 , a trend illustrated in all FACT-MM subscales (Table 4). Patients with an MMAS-4 score of ≤ 3 had higher levels of absenteeism, presenteeism, and overall work impairment. However, only the differences in activity impairment were statistically significant (mean, 56.5% vs. 39.8%; $P = .02$). Patients with an MMAS-4 score of ≤ 3 also tended to report greater OOPCs and HRU. However, these differences did not reach statistical significance after adjustments for covariates, with the exception of OOPCs for over the counter medications (mean, \$130.55 vs. \$46.78; $P = .006$) and transportation (mean, \$83.02 vs. \$43.27; $P = .03$). After adjustment for covariates, patients with an MMAS-4 score of ≤ 3 were also more likely to report being overwhelmed or frustrated by having to reschedule MM appointments (mean, 64.0% vs. 26.0%; $P = .002$).

Discussion

The results showed that most patients were not currently employed, despite the relatively high educational attainment in the sample. This finding was generally in line with previous research indicating that employment among patients with MM decreased by one half after treatment.¹⁷ Furthermore, overall work productivity impairment in the present study was high and mostly due to elevated presenteeism, suggesting that MM patients continued to work but believed their ability to function at work remained impaired. Overall activity impairment was likewise high among MM patients. The degree of overall work productivity impairment observed in the present study was greater than that previously reported for patients with late-stage renal cell carcinoma (50.1%) and metastatic breast cancer (40.0%)^{25,26} and approximately double the 29.3% reported by patients with myeloproliferative neoplasms.²⁷ Hence, the negative effects of MM on employment outcomes is likely considerable, even compared with other incurable malignancies.

Previous studies have demonstrated that most MM patients report experiencing some financial burden associated with their disease.¹⁸ In some cases, the costs incurred by patients amounted to one third of their annual income.¹⁷ In the present study, during a 3-month period, the mean OOPCs were $> \$700$, translating to an average yearly expense of $> \$2800$. In the multivariable analyses, those with an MMAS-4 score of 4 had mean OOPCs during a 3-month period that were less than one half those incurred by patients with an MMAS-4 score of ≤ 3 . This result suggests a marginal trend for those with better adherence to incur fewer OOPCs than less-adherent respondents. The greatest contributor to the total OOPCs incurred by patients during a 3-month period was MM-related prescription medications, which accounted for 55%. After adjusting for covariates, a marginal trend was seen in which the total OOPCs of patients with an adherence score of ≤ 3 were, on average, more than twice those of patients with an adherence score of 4. Taken together, the present findings suggest that the substantial economic burden attributed to MM might be more heavily borne by those who do not adhere to their current treatment regimen.

For the FACT-MM, the mean total score observed in the present study was slightly lower than those (range, 114.8-119.7) reported by a previous study of patients with a diagnosis of MM in the previous 60 days who had recently undergone autologous stem cell transplantation.²⁸ This suggests that the respondents in our sample,

who had lived with MM for nearly 5 years, on average, had lower QoL than did patients with newly diagnosed MM and raises the possibility that the lower FACT-MM total scores found in the present study might, to some extent, reflect a deterioration of QoL as MM progresses.

The FACT-G scores (67.5) among the MM patients in the present study were lower than those reported in previous studies of patients with advanced cancer. The mean FACT-G score was 79.0, 73.1, and 78.0 for patients with stage 4 lung cancer and brain metastases,²⁹ myelodysplastic syndromes,³⁰ and stage III or IV cancer in ≥ 1 of 11 different sites,³¹ respectively. Based on a previous meta-analysis, these differences in FACT-G scores would be considered to be of medium magnitude.³² However, the FACT-G score of 61.2 for patients with advanced renal cell carcinoma²⁵ was similar to that of the patients in the present study and corresponded with differences of small magnitude (6-point mean difference).³² Overall, this suggests that, with some exceptions, the general QoL of patients with MM is moderately worse than the QoL associated with several different types of late-stage cancer.

Collectively, research has consistently linked the diagnosis and treatment of MM to decrements in QoL.^{12,13,15} This is likewise the case even for patients with stable disease.¹⁴ The results from the present study were consistent with these data but went further than previous studies by providing evidence for the differences in various dimensions of QoL by the level of adherence. Specifically, the results of the present study indicate that significant discrepancies exist between adherence levels regarding most QoL domains, such that those who self-reported greater adherence on the MMAS-4 (score, 4) also reported better QoL than did patients who self-reported poorer adherence (score ≤ 3), after adjustment for confounders.

Ultimately, high adherence to MM medications was associated with better QoL, a lower level of activity impairment, and less frustration in managing MM-related appointments. Therefore, better treatment adherence might also play a role in improving patient outcomes in the long term, although a future longitudinal study is needed to verify this possibility.

Study Limitations

MM diagnosis, treatment adherence, and other study variables could not be verified from a review of the patients' medical records or other objective means owing to the self-reported nature of the data. Thus, the validity of the study could be reduced, because self-reported data are potentially subject to recall bias, in which patients inaccurately remember previous details of treatment. Furthermore, the data were cross-sectional in nature and did not allow for causal explanations. Although the present study found that poor adherence was associated with worse patient-reported outcomes, we could not exclude the possibility that poor adherence was instead an outcome of lower QoL and functional performance and greater OOPCs and temporal burden. A prospective study is needed to verify any causal relationships and to confirm the direction of these associations, among the variables under consideration.

It is possible that patients might differ in health and economic outcomes depending on the treatment modality and not just by the level of adherence. However, such comparisons were beyond the scope of the present study, which focused on comparisons by adherence level within the population of patients using oral MM

medications. Future research is needed to determine whether the relationships observed in the present study generalized to patients with MM who only use injectable medications.

Although a number of respondent characteristics were adjusted for using robust statistical methods, additional variables could have been present that were not accounted for, which could have biased the results. Additionally, the study sample might not be representative of the general population of patients with MM because our study used an internet-based survey to collect the data. Specifically, those with insufficient facility with, or access to, the appropriate technology, lower socioeconomic status, and MM patients in poorer health might have been underrepresented. The present study had patients with different racial/ethnicities than previous studies in the National Cancer Database,³³ Centers for International Blood and Marrow Transplant Research,³⁴ Surveillance, Epidemiology, and End Results Program Medicare,³⁵ and California Cancer Registry.³⁶ Therefore, some selection biases might be present. Hence, these results must be interpreted with caution.

Conclusion

The aims of the present study were to more comprehensively describe the burden of MM and to determine whether differences exist in work productivity and activity impairment, QoL, HRU, temporal burden, and OOPCs for patients who use oral MM therapy when stratified by the level of treatment adherence. Data from the present study revealed that MM adversely affects multiple areas of QoL, especially emotional well-being. Furthermore, MM therapy is costly in terms of both time and OOPCs. Patients with higher adherence scores also reported a lower burden across multiple domains relative to their counterparts with lower levels of adherence.

Overall, the results suggest that high adherence is associated with better patient-reported outcomes, especially QoL. These findings help to enhance our understanding of the humanistic and economic burden associated with MM and underscore the importance of treatment adherence in potentially reducing this burden. During the past 20 years, advances in the treatment of MM have resulted in longer survival times. Future research efforts are needed to ensure that the burden of MM and its treatment similarly improve during the coming 20 years. Consideration of patient QoL will be integral to this endeavor.

Clinical Practice Points

- MM is the most prevalent hematologic cancer and has been associated with low 5-year survival rates.
- However, with the therapeutic advances in the past 2 decades, the survival rates for patients with MM have improved.
- Because patients are now living longer, it is important to more broadly assess the effect of MM on QoL and other pertinent patient reported outcomes; however, to date, few studies have assessed the burden of MM or the association of treatment adherence with patient-reported outcomes.
- Clarifying these issues will be integral to informing clinical decision making and policies that can reduce the burden of MM.
- Our findings indicated that MM has a negative effect on multiple areas of QoL, especially emotional well-being, and MM therapy is costly in terms of time and OOPCs.
- Patients with higher self-reported adherence also reported less burden across multiple domains relative to their counterparts with lower levels of adherence.
- The present study has therefore contributed to the data by providing a better understanding of the multifaceted burden of MM and the effects of treatment adherence on work productivity and activity impairment, QoL, HRU, temporal burden, and OOPCs among US adults with MM.
- Overall, in the present study, MM was characterized by a substantial humanistic and economic burden for patients, with high (vs. low) adherence associated with better patient-reported outcomes and less burden.
- These data can help clinicians to further educate patients with MM on the tangible benefits of adhering to their prescribed therapy regimens.

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Supplemental Data

The supplemental data accompanying this article can be found in the online version at <https://doi.org/10.1016/j.cml.2018.01.006>.

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