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Racial/Ethnic Disparities in Inflammatory Gene SNPs as Predictors of High Risk for Symptom Burden in Patients with Multiple Myeloma 1 Year Post-Diagnosis

Qiuling Shi, PhD[a], **Xin Shelley Wang, MD, MPH**[a], **Guojun Li, MD, PhD**[b], **Nina D. Shah, MD**[c], **Robert Z. Orlowski, MD, PhD**[d], **Loretta A. Williams, PhD, RN**[a], **Tito R. Mendoza, PhD**[a], and **Charles S. Cleeland, PhD**[a]

[a]Department of Symptom Research, Unit 1450, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA

[b]Department of Head & Neck Surgery, Unit 1445, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA

[c]Department of Stem Cell Transplantation, Unit 423, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA

[d]Department of Lymphoma/Myeloma, Unit 429, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA

Abstract

Background—We conducted a study to determine whether any regulatory single-nucleotide polymorphism (SNP) in an inflammatory gene was associated with high symptom burden in patients 1 year after diagnosis with multiple myeloma (MM).

Methods—MM patients rated symptoms using the MD Anderson Symptom Inventory (MDASI)-MM module and provided buccal-swab DNA samples. SNPs for 4 cytokine genes (*IL6* –174G>C, *IL1β* –511C>T, *TNFα* –308G>A, *IL10* –1082G>A) were tested. Logistic regression models were used to identify SNPs that might predict moderate/severe symptoms (rated ≥4 on the MDASI-MM's 0–10 scale). To evaluate the relationship between SNPs and overall symptom burden, we used 2-step cluster analysis to divide patients into subgroups with high or low symptom levels.

Results—Of the 344 patients enrolled, 41% had high overall symptom burden. The most prevalent moderate/severe symptoms were fatigue (47%), pain (42%), numbness (38%), and bone aches (32%). For non-Hispanic whites, the *IL1β* –511 CC genotype was associated with high overall symptom burden (OR, 2.35; 95% CI, 1.25–4.72; $P = .004$), while *IL6* –174 GG genotype predicted less moderate/severe fatigue (OR, 0.53; 95% CI, 0.29–0.88; $P = .013$). For other patients, *IL6* –174 GG genotype predicted moderate/severe pain (OR, 3.36; 95% CI 1.23–13.64; $P = .010$).

Corresponding Author: Xin Shelley Wang, MD, MPH, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1450, Houston, TX 77030, Phone: 713/745-3504; FAX: 713/745-3475; xswang@mdanderson.org.

Conflicts of Interest: None.

Conclusions—Our results support growing evidence that inflammation is associated with cancer-related symptoms and suggest that racial/ethnic factors contribute to this association.

Keywords

symptom; MDASI; inflammatory gene; SNP; multiple myeloma; racial/ethnic variation

Introduction

Multiple myeloma (MM) is the second-most-prevalent hematological malignancy.[1] Significant progress has been achieved in the treatment of MM in recent decades.[2–4] High-dose chemotherapy with stem cell transplantation (SCT) has improved disease-free survival and overall survival, compared with conventional melphalan–prednisone chemotherapy.[5] However, this increased longevity and longer disease course often result in a distinct symptom burden that substantially reduces health-related quality of life (HRQoL).[6] Therefore, identifying individual MM patients at risk for high symptom burden that could influence treatment planning would be of potential benefit both to patients undergoing active therapy and to disease-free survivors.

Recent research findings suggest that genetic disposition may influence a patient's experience of cancer-related and treatment-related symptoms and HRQoL.[7,8] Inflammation is a candidate mechanism underlying the expression of cancer-related symptoms.[9,10] We have demonstrated a significant association between symptom outcomes and circulating cytokines (interleukin (IL)-6, tumor necrosis factor (TNF)-α, and soluble TNR receptor 1 (sTNF-R1)) during aggressive cancer treatments such as allogeneic or autologous hematopoietic SCT[11,12] and chemoradiotherapy.[13,14]

Polymorphisms in proinflammatory and anti-inflammatory cytokine genes, particularly in regulatory regions, have been linked to intraindividual variations in cytokine production: the C allele of the –174G>C single-nucleotide polymorphism (SNP) in the *IL6* promoter region was related to significantly lower levels of plasma IL-6 in healthy subjects[15]; the –511C>T polymorphism of *IL1β* has biological relevance in the regulation of IL-1 production[16]; and the –308G>A polymorphism in the promoter region of the *TNFα* gene increases expression of TNF-α.[17] These SNPs have also been correlated with risk for MM,[18,19] suggesting the necessity of addressing how disease development is involved in the gene–symptom association.

Evidence of gene–symptom associations are limited but emerging. Cytokine gene polymorphisms have been associated with cancer-related symptoms and toxicities in patients with cancer[20,21] but to our knowledge have not been studied in MM. Furthermore, higher incidence and mortality rates of MM among blacks[22] indicates the need to consider racial differences in studying symptom burden related to MM development and/or treatment.

The objectives of this study were to identify a subset of MM patients with higher risk of persistent symptom burden and to determine whether any regulatory SNP in a cytokine gene was associated with such high symptom burden. We focused on SNPs in genes encoding cytokines that have been linked at the protein level to symptoms reported in cancer patients,

including *IL6* –174G>C (rs1800795), *IL1β* –511C>T (rs16944), and *TNFα* –308G>A (rs1800629). Another SNP, *IL10* –1082G>A (rs1800896), is associated with varied expression of IL-10[23], whose SNPs have been linked to pain in lung cancer survivors.[21] We hypothesized that alleles related to increased proinflammatory cytokine expression (G of *IL6* –174, C of *IL1β* –511, G of *TNFα* –308) and the allele related to decreased anti-inflammatory cytokine expression (G of *IL10* –1082) would be risk alleles for high symptom burden in MM patients.

Materials and methods

For this prospective, cross-sectional study, MM patients were consecutively recruited from November 2011 to March 2013 in the outpatient clinics of the Departments of Lymphoma/Myeloma and Stem Cell Transplantation at The University of Texas MD Anderson Cancer Center in Houston, Texas. Eligible patients had a confirmed pathological diagnosis of MM for at least 12 months prior to enrollment, were at least 18 years old, and were under clinical follow-up or therapy. The study was approved by the MD Anderson Institutional Review Board. All participants gave written informed consent.

Patient characteristics and clinical parameters (age, sex, cancer stage, Eastern Cooperative Oncology Group performance status (ECOG PS), body mass index, comorbid conditions, years since MM diagnosis, previous SCT, previous radiotherapy, current maintenance therapy, and anemia status) were recorded by research staff.

Multisymptom Assessment

Patients provided self-reported ratings of symptom severity upon enrollment. The psychometrically validated MM module of the MD Anderson Symptom Inventory (MDASI-MM) assesses the severity of 13 common cancer-related symptoms from the core MDASI[24] and 7 additional MM-specific symptoms (bone aches, muscle weakness, sore mouth/throat, rash, difficulty concentrating, constipation, diarrhea).[25] Patients rate symptom severity over the previous 24 hours on a 0–10 scale ranging from “not present” to “as bad as you can imagine.” Six items related to symptom interference with function are rated over the previous 24 hours on a 0–10 scale ranging from “did not interfere” to “interfered completely.”

SNP Assay

Patients provided buccal swab samples upon enrollment. Isohelix SK-2S DNA buccal swabs (Cell Projects Ltd, Harrietsham, Kent, UK) were used to collect DNA samples[26] at least 1 hour after eating, drinking, or cleaning teeth. Gentra Puregene Blood Kit (QIAGEN, Venlo, The Netherlands) was used for purification of archive-quality DNA from buccal cells.[27] Purified DNA was stored at –80°C for later genotyping.

Polymerase chain reaction (PCR) was performed as previously described.[28,29] For *IL6* –174G>C, 219 base pair (bp) PCR products were digested with NlaIII (New England Biolabs, Ipswich, MA, USA) at 37°C overnight; the G allele was uncut, and the C allele was cut into 126-bp and 93-bp bands. For *IL1β* –511C>T, 348-bp PCR products were digested with Bso BI (New England Biolabs, Ipswich, MA, USA) at 37°C overnight; the T allele was uncut,

and the C allele was cut into 184-bp and 164-bp bands. For *IL10* G>A and *TNFα* –308 G>A, restriction fragment length polymorphism genotyping was performed as previously described.[28,29] Positive and negative controls were used in each genotyping assay, and 10% of samples were randomly selected and assayed in duplicate. Concordance between duplicates was 100%.

Statistical Analysis

We dichotomized single symptoms into none/mild (rated 0–3 on the MDASI-MM's 0–10 scale) and moderate/severe (rated 4–10).[30] To evaluate overall symptom burden, we applied SPSS 2-step cluster analysis[31]: Using patients' ratings on 20 MDASI-MM symptoms, in Step 1 we created pre-clusters of patients by constructing a cluster feature tree algorithm. In Step 2, pre-clusters were merged using agglomerative hierarchical clustering. The optimal number of clusters was determined using Schwarz's Bayesian information criterion. We expected 2 groups of patients with either high or low symptom levels. To confirm that 2-step clustering effectively differentiated patients according to symptom burden, we used Student's *t*-test and Cohen's *d* effect size to compare the severity of individual symptoms between the high-symptom and low-symptom groups. We expected the 2-step clustering to generate subgroups of patients with distinct levels of symptoms with at least a medium effect size (Cohen's *d*: 0.2=small, 0.5=medium, 0.8=large).[32]

Considering the possibility of differences related to race/ethnicity,[33,34] we first examined the genotype distribution of the 4 SNPs among race/ethnicity groups and found significant differences by group. We therefore stratified patients by race/ethnicity (non-Hispanic white vs. others) in the remaining analyses. We conducted logistic regression analyses to identify the genetic factors for single symptoms (moderate/severe vs none/mild) and overall symptom burden (high vs low), controlling for demographic and clinical confounders (age, sex, cancer stage, ECOG PS, body mass index, co-morbid conditions, years since MM diagnosis, previous SCT, previous radiotherapy, current maintenance therapy, and anemia status). To clarify the association among SNPs, disease development and symptom burden, we controlled disease status (tumor response) in all models. Stepwise selection was used to identify the optimal models, and odds ratios (OR) were estimated for the effect size of associations between SNPs and symptoms. The Hosmer–Lemeshow test of goodness-of-fit[35] was performed to see if the model fits the data. A bootstrap resampling technique[36,37] with 1,000 bootstrap samples was applied for internal model validation, providing a bias-corrected estimate of the 95% confidence interval (CI) of the ORs. Bonferroni correction was used for multiple comparisons of the 4 SNPs, with $\alpha = .013$ (.05/4).

Results

Patient and Treatment Characteristics

Of the 363 eligible patients approached, 3 declined to participate, 16 had incomplete symptom assessments (>50% of MDASI-MM items missed), and the remaining 344 were included in the analysis. Table 1 presents patient demographic and clinical characteristics. All enrolled patients contributed buccal samples and symptom data. Most had received autologous SCT (81%) and 58% were still undergoing MM maintenance therapy. Non-

Hispanic white was the most prevalent race/ethnicity (65%), followed by black (22%) and Hispanic (9%). Approximately half (44%) of patients reported ≥1 comorbidities, and one-fourth of patients (23%) had stage III disease.

Symptom Patterns and Severities

The 5 most-severe symptoms were fatigue (mean 3.4±2.8), pain (3.2±3.1), numbness (2.8±2.9), bone aches (2.3±2.9), and drowsiness (2.1±2.6). No significant differences in total symptom score were found between non-Hispanic whites (1.4±1.1) and other racial groups (1.6±1.4) (P = .073). The percentages of patients reporting moderate/severe (≥4) symptom levels were: fatigue (47%), pain (42%), numbness (38%), bone aches (32%), drowsiness (27%), dry mouth (27%), disturbed sleep (27%), and muscle weakness (26%).

Two-step clustering generated 2 groups: a low-symptom group (n=203, 59%) and a high-symptom group with significantly higher mean symptom severity (n=141, 41%). Table 2 presents scores by symptom-severity group for average score of all MDASI-MM symptom items and the 5 most-severe individual symptoms. As expected, all symptom scores differed significantly between the high and low severity groups (P < .001, t test). Effect sizes (Cohen's d) of differences between the high-symptom and low-symptom groups for all symptom and interference items exceeded 0.8, indicating a large magnitude of effect.

SNP Profiles and Associations with Symptoms

Except for the *TNFα* –308 SNP, all other examined SNPs showed different genotype frequencies by race/ethnicity. Patients who were non-Hispanic white showed higher frequencies of *IL6* –174 CC genotype, *IL1β* –511 CC genotype, and *IL10* –1082 GG genotype than did all other races (Table 3). Thus, we dichotomized the study population by race/ethnicity (non-Hispanic white vs. others) for all analyses with SNP data.

After controlling for all demographic and clinical factors and other cytokine SNPs, logistic regression modeling indicated that, compared with patients having an *IL1β* –511 CT or TT genotype, those with the CC genotype in the non-Hispanic white population demonstrated double the risk for experiencing high overall symptom burden and moderate/severe pain (OR, 2.35; 95% CI, 1.25–4.72; P = .004). This result was not replicated in other races. The *IL6* –174 GG genotype showed diverse associations with moderate/severe symptoms by ethnic group. Non-Hispanic whites with GG genotype were less likely to report moderate/severe fatigue (OR, 0.53; 95% CI, 0.29–0.88; P = .013), whereas in patients other than non-Hispanic whites, the GG genotype predicted moderate/severe pain (OR, 3.36; 95% CI 1.23–13.64; P = .010) (Table 4). Other than SNPs, comorbidities and ECOG PS ≥1 were both predictors for high overall symptom burden and moderate/severe levels of the top 5 symptoms. Supplemental Table 1 shows the associations between SNPs and individual symptoms. The goodness-of-fit test results were insignificant, suggesting that the models fit the data well (Supplemental Table 2).

Discussion

One year post-diagnosis and after initial treatment for MM, ~40% of patients in this study experienced moderate/severe symptoms, with fatigue, pain, numbness, drowsiness, and bone

aches being the most severe. We identified host genetic factors linked to inflammation as potential risk factors for higher symptom burden. A high-cytokine-expression genotype (*IL1β* –511 CC) was predictive of moderate/severe symptoms and high overall symptom burden for non-Hispanic white patients, but not for other patients. The other high-cytokine-expression genotype (*IL6* –174 GG) was predictive of moderate/severe fatigue, pain, and numbness in patients other than non-Hispanic whites.

The prevalence and etiology of MM-related symptoms are poorly understood, and risk factors for high symptom burden have not been determined. This finding builds on our studies and those of others reporting circulating proinflammatory cytokines with symptom burden in patients with cancer.[11,13,14] Although research has found a positive association between critical circulating cytokines and multiple symptoms related to cancer therapy, few studies have examined this association at a host genetic background level, and results from these few studies are controversial. For example, the *IL6* –174 and *TNFα* –308 polymorphisms were independently associated with fatigue in breast cancer survivors.[20] The *IL1β* –511 CC genotype was associated with fatigue severity in 171 breast cancer survivors,[20] but this association was not observed in a larger sample (N=302) of breast cancer survivors with chronic and persistent fatigue[38] or in prostate cancer patients.[39] In lung cancer survivors, 2 other polymorphisms of *IL1β* were associated with fatigue.[21] Our results, in a mixed sample of MM patients, are the first to show that expression of the regulatory SNP *IL1β* –511C>T is associated with multiple symptoms and overall symptom burden. IL-1β participates in activating T cells and induces IL-6 in fibroblasts, endothelial cells, keratinocytes, and peripheral blood monocytes.[40] The association between the expression of a regulatory SNP,[16] *IL1β* –511C>T, and symptom burden not only supports inflammation as a major pathway underlying cancer-related symptoms, but also provides a candidate marker for individualized symptom management. However, the complex mechanisms underlying symptom development as a result of acute and chronic illness and cancer therapy-induced toxicities suggest the need for a broader search of genetic markers in all potential pathways and for evaluation of the interactive effects of those markers, using carefully selected phenotypes.

Unlike similar studies that treated race/ethnicity as a covariate[20,41] or that included participants of a single race,[21] we dichotomized our study population by race/ethnicity into “non-Hispanic white” and “other” groups, due to differences in allelic frequency among races. We found different associations between SNPs and multiple symptoms by racial/ethnic group, suggesting that those polymorphisms have race-specific effects in modulating symptoms. Racial/ethnic associations with host genetic variations have been found in the development of cancers[42] but have never been addressed in gene–symptom association studies. Studies using data from the Surveillance, Epidemiology, and End Results project indicate that MM incidence and mortality rates demonstrate significant racial differences. For example, compared with non-Hispanic whites, blacks had a much higher concentration of patients aged <65 years and a much lower concentration of patients aged >75 years.[43] The significant effects of the *IL6* –174 polymorphism in predicting major symptoms (fatigue, pain, numbness) in other patients, primarily black, suggest that race/ethnicity-specific

biomarkers should be considered when developing personalized symptom management strategies, especially for younger black MM patients who have better overall survival.[43]

This study had several limitations. First, although a significant association between one SNP and symptom burden was found for non-Hispanic whites, the small sample sizes of the other racial/ethnic groups, especially blacks, hindered our attempt to identify genetic risk factors in those groups. Our finding of racial/ethnic disparity should be interpreted in consideration of this limitation and should be verified in a larger population. In addition, validation of genetic associations in a subgroup of patients was not feasible with such a small sample. Although we used bootstrapping to estimate the confidence intervals of effect sizes of SNP markers, the scientific credibility of the results still needs to be validated in a larger sample, with randomly generated subsample sets for initial screening of the SNPs and for confirmatory tests on those SNPs. Second, besides the 4 selected SNPs, there are other genetic variations that may modify multiple pathways underlying symptom development, which should be considered in future research. Moreover, individualized symptom management will require genome-wide association studies to identify previously unknown genetic markers that may indicate novel biological pathways underlying gene–symptom associations. Third, the overall symptom burden based on all 20 symptoms may cause underestimation of SNP–symptom associations, because of insignificant relationships between SNPs and some symptoms; moreover, such clustering cannot identify genetic markers in different pathways. However, results from our studies of circulating inflammatory marker levels and the current genetic study both support the hypothesis that inflammation is a common underlying mechanism of cancer-related symptom development. Finally, the patient's experience of symptoms will usually change during and after the course of cancer treatment,[44] and longitudinal associations between symptoms and circulating cytokines have been confirmed.[11] Future studies with longitudinal symptom assessments will clarify how cytokine gene markers modulate symptom change during treatment and into survivorship.

Conclusions

More than one-third of MM patients experienced significant symptom burden after the initial year of standard anticancer treatment in this study. Non-Hispanic whites with the high-expression variant of *IL1β* and other patients with the high-expression variant of *IL6* may be at particular risk for high symptom burden. These genetic markers and consideration of the patient's racial/ethnic background could help to identify high-risk patients early in the treatment trajectory and could inform individualized symptom-management strategies during and after aggressive cancer treatment. Our results confirm previous findings on the potential contribution of the inflammatory pathway to cancer symptom development, which could guide the design of targeted interventions to combat multiple symptoms experienced by patients with MM, whether induced by cancer itself or by its treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Clinical Characteristics (N=344)

	Mean (SD)	**Median (range)**
Age	63.3 (9.7)	63.7 (27.0–96.1)
Body mass index	30.5 (7.5)	29.3 (14.5–81.5)
Years since cancer diagnosis	4.5 (3.3)	3.5 (1.0–24.6)
	n	**(%)**
Sex		
Male	185	53.8
Female	159	46.2
Race/ethnicity		
Non-Hispanic white	222	64.5
Black	75	21.8
Hispanic	32	9.3
Other	15	4.4
ECOG PS		
0	90	26.2
1+	254	73.8
MM stage		
I/II	264	76.7
III	80	23.3
Co-morbid conditions		
0	192	55.8
1+	152	44.2
Tumor response		
Response	134	38.9
Stable disease	137	39.8
Progression/relapse	73	21.2
Previous SCT	277	80.5
Previous radiotherapy	94	27.3
Current maintenance therapy	198	57.5
Anemia (Hgb <11)	106	30.8
Current opioid use	134	38.9

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MM, multiple myeloma; SCT, stem cell transplant; SD, standard deviation.

Table 2

Overall Symptom Burden, the 5 Most Severe Symptoms, and Symptom Interference in High vs Low Symptom Subgroups (0–10 scale)

MDASI-MM items	Low-symptom group (n=203)		High-symptom group (n=141)		Effect size (Cohen's *d*)
	Mean	**SD**	**Mean**	**SD**	
Symptom severity[a]					
Mean score of all MDASI-MM symptoms	0.69	0.47	2.70	1.04	2.49
Fatigue	2.00	2.19	5.55	2.29	1.58
Pain	1.78	2.35	5.28	2.77	1.36
Numbness	1.74	2.08	4.35	3.15	0.98
Bone aches	1.15	2.01	4.04	3.13	1.10
Drowsiness	0.77	1.36	3.90	2.95	1.36

Abbreviations: MDASI-MM, MD Anderson Symptom Inventory multiple myeloma module; SD, standard deviation.

[a]Differences between high-symptom and low-symptom groups for all symptom items were significant ($P < .0001$).

Table 3

Cytokine Genotype Distribution by Race/Ethnicity

Genotype	Non-Hispanic white (n=222)	Black (n=75)	Hispanic (n=32)	Other (n=15)	*p*[a]
IL6 –174					
CC	26 (11.7%)	1 (1.3%)	1 (3.1%)	0	<.001
GC	119 (53.6%)	14 (18.7%)	10 (31.3%)	2 (13.3%)	
GG	77 (34.7%)	60 (80.0%)	21 (65.6%)	13 (86.7%)	
IL1β –511					
CC	90 (40.5%)	13 (17.3%)	9 (28.1%)	2 (13.3%)	<.001
CT	110 (49.6%)	39 (52.0%)	15 (46.9%)	7 (46.7%)	
TT	22 (9.9%)	23 (30.7%)	8 (25.0%)	6 (40.0%)	
TNFα –308					
GG	71 (32.0%)	24 (32.0%)	9 (28.1%)	4 (26.7%)	.617
GA	113 (50.9%)	41 (54.7%)	19 (59.4%)	8 (53.3%)	
AA	38 (17.1%)	10 (13.3%)	4 (12.5%)	3 (20.0%)	
IL10 –1082					
AA	20 (9.0%)	8 (10.7%)	7 (21.9%)	2 (13.3%)	.007
AG	37 (16.7%)	21 (28.0%)	6 (18.8%)	8 (53.3%)	
GG	165 (74.3%)	46 (61.3%)	19 (59.4%)	5 (33.3%)	

[a]Chi-square test.

Table 4

Risk Factors for High Overall Symptom Burden and Top 5 Moderate/Severe Symptoms

	Non-Hispanic white		Other	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Overall symptom burden				
ECOG PS, ≥1 vs 0	4.07 (1.95–11.67)	.002	5.14 (1.79–31.91)	.003
Comorbid conditions, ≥1 vs 0	1.88 (1.00–3.91)	.034		
IL1β –511 CC vs CT/TT	2.35 (1.25–4.72)	.004		
Fatigue				
ECOG PS, ≥1 vs 0	3.49 (1.69–7.98)	.0002	3.79 (1.51–13.01)	.011
Comorbid conditions, ≥1 vs 0	1.84 (1.02–3.63)	.045		
IL6 –174 GG vs GC/CC	0.53 (0.29–0.88)	.013	2.76 (1.04–7.25)	.034
Pain				
ECOG PS, ≥1 vs 0			5.59 (1.87–28.93)	.0001
MM stage, III vs I/II			2.73 (1.00–9.54)	.030
Previous radiotherapy	1.99 (1.07–3.87)	.023		
IL1β –511 CC vs CT/TT	1.77 (1.11–3.52)	.014		
IL6 –174 GG vs GC/CC			3.36 (1.23–13.64)	.010
Bone aches				
Comorbid conditions, ≥1 vs 0	1.88 (1.07–3.36)	.033		
IL1β –511 CC vs CT/TT	1.94 (1.07–3.72)	.026		
Numbness				
ECOG PS, ≥1 vs 0	2.24 (1.18–4.52)	.015	3.74 (1.23–21.18)	.017
Year of MM			1.19 (1.02–1.42)	.012
Drowsiness				
ECOG PS, ≥1 vs 0			26.86 (2.86–251.91)	.004
Body mass index			1.06 (1.00–1.12)	.034
Previous radiotherapy	2.40 (1.27–4.56)	.007		

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; MM, multiple myeloma; OR, odds ratio.