Symptom Clusters and Quality of Life in Ambulatory Patients With Multiple Myeloma

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Abstract

Purpose: The aim of this study was to investigate the symptom clusters and associated clinical factors in ambulatory multiple myeloma patients undergoing medication therapy. We also aim to determine the correlations between symptom clusters and the patients' quality of life.

Methods: A total of 174 multiple myeloma patients hospitalized in the hematology day unit were included in this study. A cross-sectional survey aimed to examine the symptoms and quality of life was conducted. The symptoms were assessed by the Chinese version of Condensed Memorial Symptom Assessment Scale. The quality of life was measured with the Functional Assessment of Cancer Therapy-General. Principal component analysis was used to identify symptom clusters. Independent-Samples *t* test and Chi-square test were used for comparisons between groups. Spearman's Rank Correlation Analysis was used to identify correlations.

Results: We identified three symptom clusters in multiple myeloma patients: psychological, pain-dry mouth-difficulty sleep, and fatigue symptom cluster. For each symptom cluster, the patients could be categorized in severe-symptom group or mild-symptom group based on the distress of the symptoms. The patients in each group exhibited differential demographic and clinical features. The distress of each symptom cluster was adversely correlated with patients' quality of life.

Conclusions: The ambulatory multiple myeloma patients undergoing medication therapy experience multiple symptoms, which can be categorized into three symptom clusters. The distress of each symptom cluster was associated with patients' demographic and clinical characteristics. The presence and distress of these symptom clusters have adverse impact on patient's quality of life.

Introduction

Multiple myeloma (MM) is a common seen hematological malignancy without cure[1]. Since 1990, the incidence of MM has increased uniformly in different countries[1]. In 2020, there are over 32,000 estimated new MM cases in the United States and approximate 13,000 MM-related patients lost[2]. Although remains incurable, MM patients' survival time have been significantly prolonged in the past decades because of application of new drugs and advances of the disease management[3]. Kumar et al. reported that the median survival of MM treated with modern therapy was nearly 6 years[4]. After the disease diagnosis, the aim of MM nursery care includes symptom control and quality of life (QOL) maintenance.

Previous studies have shown that cancer patients often experienced multiple symptoms, and some symptoms could cluster together as symptom clusters (SCs)[5–7]. The symptoms in a SC may share the similar physiological or pathological mechanisms, thus provide ideas for more efficient interventions targeted to SCs[8]. MM patients may experience various symptoms that depend on the patient's stage of disease and treatment regimen. Jordan et al. reported that fatigue, bone pain, sleepiness, hypoesthesia or paresthesia, and muscle cramps were most common seen symptoms in MM patients[9]. Ramsenthaler et

al. found that MM patients experienced different level of fatigue, pain, drowsiness, tingling in hands/feet, sleeping problems from baseline to 8 months[10]. Ramsenthaler et al. also showed that the four most prevalent symptoms in MM (prevalence $\geq 50\%$) were fatigue, constipation, pain and tingling in the hands/feet[11]. However, the SCs in MM had yet been demonstrated. Hereby, we initiated this study to investigate MM SCs, determine the influencing factors of SCs, and analyze the correlations between SCs and QOL in MM patients.

Methods

Design and participants

We conducted a cross-sectional survey to assess the symptoms, and QOL of MM patients who had been admitted in the hematology day unit of West China hospital, Sichuan University, from June 27, 2019 to January 31, 2020. Patients inclusion criteria were: (1) diagnosed with MM, without any other co-existing cancers; (2) age ≥ 18 years old; (3) receiving medication therapy during the survey; (4) not receiving hematopoietic stem cell transplantation or bone marrow transplantation during the survey; (5) estimated length of stay ≤ 24 h; (6) with normal cognitive ability and capable of listening, speaking, reading, and writing; (7) willing to participate in the study. The patients who admitted to the day unit more than one time only participated in this study once. The eligible patients were identified by the registered nurses who worked in the hematology day unit at the hospital. The study's objectives and patients' rights were explained to the eligible patients. A written informed consent was obtained from the participants by a research assistant. A total of 248 MM patients was invited to join the study, while 186 patients agreed to participate. Among 186 participants, 12 (6.45%) MM patients were excluded because of missing data $> 20\%$. A total of 174 MM patients was finally enrolled. This study was pre-approved by the Biomedical Research Ethical Committee of West China Hospital (No. 2019504), and was conducted in accordance with the principles of the Declaration of Helsinki.

Measurement of demographic and clinical variables

Demographic characteristics including age, gender, marital status, and educational level were recorded in 24 hours after admission. Clinical characteristics including time since MM diagnosis, Revised International Staging System (R-ISS) stage of MM[12], current treatment regimen, cycle number of treatment, treatment response, relapsed/refractory or not, comorbidities (such as diabetes, anemia), and biomarkers of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), serum albumin, serum globulin, lactate dehydrogenase, and beta-2 microglobulin in 24 hours after admission or in the last 7 days before admission was retrieved from the hospital information system.

Symptom measurement

Symptoms were assessed using the Chinese version of the Condensed Memorial Symptom Assessment Scale (CMSAS), a validated questionnaire to assess cancer patients' symptoms in the past 7 days[13, 14].

The CMSAS consists of 14 symptom items: lack of energy, lack of appetite, pain, dry mouth, weight loss, feeling drowsy, shortness of breath, constipation, difficulty sleeping, difficulty concentrating, nausea, worrying, feeling sad and feeling nervous. The first 11 items were physical symptoms, recording the prevalence and distress of each symptom. The distress of each symptoms were assessed as scores: score of 0 for “not present”, 0.8 for “not at all”, 1.6 for “a little bit”, 2.4 for “some what”, 3.2 for “quite a bit” and 4.0 for “very much”. The last 3 items were psychological symptoms, recording the prevalence of each symptom as scores: score of 0 for “not present”, 1 for “rarely”, 2 for “occasionally”, 3 for “frequently”, 4 for “almost constantly”. The average score of the 14 symptoms represented the total symptom distress[14]. The higher scores indicate more symptom distress. In this study, the CMSAS showed good internal consistency: the Cronbach’s α of the scale was 0.834.

Quality of life measurement

The QOL was measured with the Functional Assessment of Cancer Therapy-General (FACT-G), which consists of 27 items in 4 subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being[15]. Each item was scored from 0 (not at all) to 4 (very much). The score range is 0–28, 0–28, 0–24, 0–28 for physical well-being, social/family well-being, emotional well-being, functional well-being subscale, respectively. The total score of QOL is the sum of all subscales (range 0 to 108). The higher scores indicate better QOL. The Chinese version of the FACT-G has been previously validated[16]. In this study, the Cronbach’s α of the scale was 0.893.

Data collection

Two research assistants approached the patients for survey and data collection. The demographic and symptom data were collected through print-out survey forms, and participants were asked to fill out the forms at their bedside. The patients could read the questions by themselves or by the assistants according to patient’s preference. Participants’ clinical characteristics were retrieved from the medical records through the hospital information system.

Statistical analysis

All data were analyzed by SPSS (Version 21.0). Frequency, percentage, mean and standard deviation were calculated to demonstrate the patients’ demographic information, clinical features, symptom prevalence and distress. The differences between two groups were analyzed by Independent-Samples *t* test for quantitative data, or Chi-square test for qualitative data. The correlation between the SC and QOL was analyzed by Spearman’s Rank Correlation Analysis. A $p < 0.05$ was considered statistical significant.

Symptom cluster and subgroup identification

To identify SCs, we conducted a principal component analysis (PCA), which is commonly used for SC identification[17]. First, to increase clinical significance, only symptoms with a prevalence rate $\geq 30\%$ were included for the analysis. Second, the distress scores of selected symptoms (prevalence rate $\geq 30\%$) were analyzed using the PCA with varimax rotation. The symptoms were identified as a SC when 1) Eigen values > 1 ; 2) factor loadings ≥ 0.5 (if one symptom’s factor loadings were ≥ 0.5 in multiple components,

the symptom was allocated to the component with maximum factor loadings); 3) at least two symptoms was categorized in a component, with a Cronbach's $\alpha \geq 0.60$.

To identify the subgroups of MM patients, we conducted a K-means cluster analysis separately for each SCs. K-means cluster analysis was a grouping method that could classify the samples into several groups based on the similarity measurement calculated by the squared Euclidean distance. K-means cluster analysis had been used for SC subgroups identification[18]. For each SCs, the patients were clarified into two subgroups, severe symptom group or mild symptom group.

Results

Patient characteristics, symptom prevalence and distress

A total of 174 patients were included in this study (Table 1). Most MM patients reported multiple symptoms simultaneously (151/174, 84.8%). On average, each patient reported 5.7 (range 0–14, median 5.0) symptoms simultaneously, and the total symptom distress of each patient was 0.7 (range 0–2.5, median 0.6). The most prevalent symptoms were difficulty sleeping (60.9%), pain (59.8%), and lack of energy (54.6%) (Table 2).

Table 1
Demographic characteristics and clinical information of MM
patients (N = 174)

Variable	Mean or n	SD or %
Age(yrs)	62.82	9.88
Gender		
Male	98	56.3
Female	76	43.7
Educational level		
≤Junior high shcool	96	55.2
Senior high school	38	21.8
≥College degree	40	23.0
Marital status		
Unmarried/Divorced/Widowed	11	6.3
Married	163	93.7
Time since MM diagnosis (months)		
<24	114	65.5
≥24	60	34.5
R-ISS stage of MM		
I	63	36.2
II	90	51.7
III	21	12.1
Current treatment		
PI-based therapy	112	64.4
IMiD-based therapy	38	21.8
PI + IMiD	16	9.2
Others	8	4.6
Cycle number of chemotherapy		
<5	62	35.6
5-10	33	19.0

Variable	Mean or n	SD or %
≥10	79	45.4
Treatment response		
≥PR	92	52.9
<PR	70	40.2
Not assessed	12	6.9
Relapsed or refractory		
Yes	31	17.8
No	143	82.2
Diabetes		
Yes	19	10.9
No	155	89.1
Anemia		
Yes	61	35.1
No	113	64.9

Table 2
Prevalence and distress of the experienced symptoms in MM [N = 241, n(%)]

Symptoms	Prevalence	Distress or Frequency				
		Not at all	A little bit or rarely	Some what or occasionally	Quite a bit or frequently	Very much or almost constantly
Difficulty sleeping	106(60.9)	8(4.6)	56(32.2)	25(14.4)	12(6.9)	5(2.9)
Pain	104(59.8)	8(4.6)	52(29.9)	26(14.9)	13(7.5)	5(2.9)
Lack of energy	95(54.6)	14(8)	57(32.8)	29(16.7)	14(8.0)	1(0.6)
Dry mouth	81(46.6)	19(10.9)	33(19)	18(10.3)	8(4.6)	3(1.7)
Worrying	80(46.0)	94(54.0)	38(21.8)	28(16.1)	11(6.3)	3(1.7)
Feeling sad	73(42.0)	101(58)	41(23.6)	25(14.4)	7(4.0)	0(0.0)
Difficulty concentrating	64(36.8)	8(4.6)	37(21.3)	15(8.6)	3(1.7)	1(0.6)
Feeling nervous	63(36.2)	111(63.8)	32(18.4)	22(12.6)	7(4.0)	2(1.1)
Feeling drowsy	59(33.9)	3(1.7)	39(22.4)	13(7.5)	4(2.3)	0(0.0)
Constipation	57(32.8)	10(5.7)	30(17.2)	10(5.7)	5(2.9)	2(1.1)
Weight loss	51(29.3)	19(10.9)	18(10.3)	7(4.0)	7(4.0)	0(0.0)
Lack of appetite	50(28.7)	16(9.2)	18(10.3)	10(5.7)	5(2.9)	1(0.6)
Nausea	48(27.6)	15(8.6)	17(9.8)	11(6.3)	5(2.9)	0(0.0)
Shortness of breath	32(18.4)	9(5.2)	15(8.6)	6(3.4)	2(1.1)	0(0.0)

Symptom clusters in myeloma patients

Three SCs were identified: psychological SC (including symptoms of feeling nervous, worrying and feeling sad), pain-dry mouth-difficulty sleep SC (including symptoms of pain, dry mouth, and difficulty sleep), and fatigue SC (including symptoms of feeling drowsy, difficulty concentrating, and lack of energy). These SCs accounted for 60.32% of the total variance. Cronbach's α coefficients of the psychological SC, pain-dry mouth-difficulty sleep SC, and fatigue SC were 0.857, 0.608, and 0.612, respectively (Table 3).

Table 3
Symptom clusters identified by the principal component analysis (N = 174)

Symptoms	Cluster1	Cluster 2	Cluster 3
	Psychological SC	Pain-Dry mouth-Difficulty sleep SC	Fatigue SC
Feeling nervous	0.861	0.131	0.185
Worrying	0.851	0.183	0.167
Feeling sad	0.774	0.381	0.101
Pain	0.194	0.775	-0.041
Dry mouth	0.184	0.749	0.196
Difficulty sleeping	0.098	0.508	0.427
Feeling drowsy	-0.019	0.034	0.673
Difficulty concentrating	0.245	0.380	0.639
Lack of energy	0.270	0.308	0.620
Constipation	0.335	-0.172	0.464
Cronbach's α	0.857	0.608	0.612
Eigenvalues	3.882	1.135	1.014
Variance explained (%)	23.91	18.86	17.56
Total variance explained (%)	23.91	42.76	60.32

Myeloma patients subgroup analyses based on symptom clusters

We identified two patient subgroups by K-means cluster analysis for each SC. The severe-symptom group represented the group with the high distress score, while the mild-symptom group represented the group with the low distress score. For each SC, the demographic and clinical characteristics in these two subgroups were presented in **Table 4**. In psychological SC, the average patients' age in the severe-symptom group was younger than those in the mild-symptom group ($p = 0.033$). In addition, there were higher ratios of female patients, patients with treatment response < PR, anemia, or lactate dehydrogenase > 220 IU/L in the severe-symptom group than the ratios in the mild-symptom group ($p = 0.027, 0.034, 0.024, 0.000$, respectively). In pain-dry mouth-difficulty sleep SC, there were higher ratios of female patients, patients with treatment response < PR, relapsed or refractory, with diabetes, serum globulin > 40 g/L, or beta-2 microglobulin ≥ 3.5 mg/L in the severe-symptom group than those in the mild-symptom group ($p = 0.044, 0.002, 0.022, 0.019, 0.040, 0.007$, respectively). In fatigue SC, there were higher ratios of patients with time since MM diagnosis ≥ 24 months, treatment response < PR, relapsed or refractory, or

MLR $\geq P_{50}$ (0.39) in the severe-symptom group than those in the mild-symptom group ($p = 0.038, 0.000, 0.008, 0.025$, respectively).

Correlations between Symptom Clusters and patient's quality of life

The patients' total score of QOL was 79.54 ± 14.46 . The subscale score of physical well-being, social/family well-being, emotional well-being, and functional well-being was 23.21 ± 4.20 , 21.38 ± 5.38 , 19.92 ± 3.76 , and 15.02 ± 5.80 , respectively. The total score and each subscale score of QOL were all negatively correlated with the psychological SC, pain-dry mouth-difficulty sleep SC and fatigue SC (all $p < 0.05$; Table 5).

Table 5
Correlations between Symptom Clusters and Quality of Life (N = 174)

Variables	Psychological SC		Pain-dry mouth-sleep SC		Fatigue SC	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Physical well-being	-0.536	.000	-0.519	.000	-0.540	.000
Social/family well-being	-0.416	.000	-0.192	.011	-0.239	.001
Emotional well-being	-0.657	.000	-0.326	.000	-0.328	.000
Functional well-being	-0.521	.000	-0.302	.000	-0.281	.000
Total score of QOL	-0.671	.000	-0.414	.000	-0.448	.000

Discussion

To our knowledge, this was the first report of SC investigation in MM. In this study, we identified three SCs in 174 MM patients who had been treated in the hematology day unit in our institute. The first SC was psychological SC which included symptoms of feeling nervous, worrying and feeling sad. Although the specific symptom items might be different in the cluster, psychological SC has been demonstrated as a common SC in patients with cancer, either solid tumor or hematological malignancy[5–7]. Specific psychological symptom in MM had been reported in previous studies[19]. Ramsenthaler et al. found that almost one third of MM patients claimed anxiety[10]. Our data showed that in psychological SC, the patients with severe symptom distress were younger than those with mild symptom distress. Van der Poel et al. also reported that elderly MM patients (> 65 years) had better emotional functioning than young patients(≤ 65 years)[20]. The reason for such difference was still unknown. It might be because elderly patients had better coping strategies due to more life experience than that of young patients. Furthermore, in agree with previous studies, our data suggested that more female patients reported severe symptom distress of psychological SC than the male[7, 21]. At last, the distress of psychological SC was influenced by the patients' treatment outcome. Patients with treatment response < PR, anemia, or serum lactate dehydrogenase > 220 IU/L were likely to report severe symptom distress of psychological SC than

the counterpart patients. The pain-dry mouth-difficulty sleep SC was also identified in our MM patients. Studies have shown that pain and sleep disturbance are always co-existing in a SC in cancer patients[22–24]. Krause et al. showed that sleep deprivation enhanced pain responses within the primary sensing regions in the brain, and weakened the activity in other regions that modulated pain processing[25]. Such findings provided physiology evidences of co-existence of pain and sleep disturbance in cancer patients. The symptoms of pain and sleep disturbance were reported in MM patients[26, 27]. In our study, the female patients were more likely to be bothered by pain-dry mouth-difficulty sleep SC. It's consistent with the findings that the female had lower pain acceptance than male[28] and being female was significantly associated with poor sleep[29]. We also found that the patients with diabetes reported severe distress of pain-dry mouth-difficulty sleep SC. Dry-mouth symptom was commonly seen in diabetes. If the MM patients had diabetes, the dry-mouth symptom might be even worse. At last, the severity of the MM disease and the treatment outcome highly affected the distress of pain-dry mouth-difficulty sleep SC. In this study, the symptoms of feeling drowsy, difficulty concentrating, and lack of energy were categorized into the fatigue SC, which include physical and cognitive fatigue. Fatigue is the most frequent symptom reported in MM patients, with a high prevalence of 55%–98.8%[11, 26, 27]. We found that the patients with a long time since diagnosis (≥ 24 months), bad treatment response ($< PR$), relapsed or refractory disease, and $MLR \geq P_{50}$ (0.39) tended to report severe symptom distress of fatigue SC than the counterpart patients. Mols et al. found that patients with MM complained a significant increase of fatigue from baseline to one year follow-up[30]. Previous study also observed that the fatigue were significantly higher in relapsed or refractory MM patients than the control group[31]. Furthermore, Shi et al. reported that elevated MLR (cut-offs of 0.3) predicted poor clinical outcome in MM patients[32]. In this study, we found the increased MLR was associated with severe symptom distress of fatigue SC. Therefore, the MLR may serve as a cost-effective and available predictive biomarker for fatigue SC in MM.

QOL improvement is one of the most important goals for MM management. Based on our findings, the MM patients with severe symptom distress in psychological SC, pain-dry mouth-difficulty sleep SC and fatigue SC had inferior QOL in all domains and overall scores. These results are consistent with the previous studies in other cancer[33–35]. Although no studies had assessed the correlation between SCs and QOL in MM patients, the correlations between specific symptoms and QOL had been addressed in MM. For example, symptoms of pain, fatigue, anxiety, and depression correlated with QOL in MM[9, 11]. With the determinant role of symptom distress in cancer patients' QOL, one unique feature of MM, compared with other cancers, was that the overall survival of MM was significantly prolonged in the past decades, yet the disease was still incurable. Thus, living with cancer and experiencing multiple rounds of treatment might be more common in MM patients than patients diagnosed with other human cancers. At least for some patients, MM might be considered as a chronic disease, and QOL for those patients was as important as the outcome of cancer therapy. Targeting to the SCs rather than single symptoms allows for more thorough symptom assessment, simplified interventions and more efficient symptom management[8]. Additionally, because individual symptoms of MM are associated with decreases in QOL[9, 10], it's logical that clusters of symptoms may have greater impact on QOL than single symptoms.

Therefore, our data provided first-hand evidence to show that the inter-correlations of the MM disease status, SC and QOL. Our data also encouraged health care givers' attention to specific patient groups, such as young female MM patients.

Limitations

There were some limitations in this study. First, the study was carried out in the day hematology unit of one hospital. Thus, the results could not fully represent all MM patients who underwent treatment. Furthermore, MM patients receiving some treatment regimen, such as transplantation, were excluded in this study. Second, like many other similar studies, we assessed each symptom by only one item with a general symptom scale for cancer. Third, the cross-sectional survey could neither clarify the causal relationships between associated factors and SCs, nor the patterns of SCs over time. A longitudinal study was needed to address those issues.

Implications for clinical practice

Symptom management and QOL improvement are in particularly important for MM patients because many patients had more than 5-year overall survival with the cancer. We have identified three SCs in MM patients, psychological SC, pain-dry mouth-difficulty sleep SC, and fatigue SC. The correlations of patients' characteristics, CS and QOL have been investigated. In general, the patients with more severe disease conditions and less encouraging treatment responses have increased distress of SCs. Some patient subgroups, such as female MM patients and young MM patients, may experience severe distress of SCs. Clinical practitioner should develop individualized SC interventions based on the patients' demographic and clinical characteristics. For example, the female MM patients may experience more distress from the psychological SC and pain-dry mouth-difficulty sleep SC, thus assessing psychological status, pain symptom and sleep quality, and providing appropriate interventions are essential for these patients. The patients with treatment response < PR might suffer from all the three SCs of psychological, pain-dry mouth-difficulty sleep, and fatigue, so a series of comprehensive interventions might be needed. Additionally, a cost-effective and available indicator of MLR calculated by monocyte and lymphocyte from peripheral blood test might predict patients' fatigue, so that early interventions could be provided beforehand. Further studies are necessary to address this point. In addition, some influencing factors of SCs and the pattern of SCs change over time are still unclear; further researches are needed to provide evidence for the precise symptom management.

Conclusions

We assessed the symptoms in ambulatory MM patients ongoing medication therapy in day unit of our hospital, and identified three SCs: psychological SC, pain-dry mouth-difficulty sleep SC, and fatigue SC. The distress level of SCs was associated with patients' demographic and clinical characteristics. In MM patients, the distress level of each SC was negatively correlated with QOL. Since the symptoms within a SC are interconnected, targeting the cluster might benefit patients' QOL and thus improve healthcare quality.

Declarations

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Code availability: N/A

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Ethics approval: Approval was obtained from the Biomedical Research Ethical Committee of West China Hospital (No. 2019504). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate: Written informed consent was obtained from all individual participants included in the study.

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