Symptoms and Health-Related Quality of Life in Patients with Newly Diagnosed Multiple Myeloma: A Multicenter Prospective Cohort Study

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Abstract

Purpose

Cross-sectional observational studies indicate that patients with multiple myeloma (MM) experience negative physical and psychological symptoms and low health-related quality of life (HRQOL). The study aim was to determine symptom prevalence, symptom trajectories, HRQOL, and symptoms associated with HRQOL in patients with MM.

Methods

This multicenter longitudinal cohort study was conducted in four hospitals in Japan. Patients with newly diagnosed MM were asked to report their symptom intensity and HRQOL using validated questionnaires at three points: at diagnosis (T1), 1 month (T2), and 12 months after diagnosis (T3). Symptoms associated with HRQOL were explored using a mixed-effect model.

Results

A total of 106 patients completed the assessment at T1. The most frequently reported symptoms were pain and disturbed sleep at T1; pain and dry mouth at T2; and fatigue, numbness or tingling, and pain at T3. Three symptom trajectory patterns were identified: a peak at T1 and reduction over time (pain, disturbed sleep, distress, lack of appetite, sadness, depression), a peak at T2 (fatigue, drowsiness, dry mouth, nausea, vomiting), and a V-shaped pattern (shortness of breath, numbness or tingling, difficulty remembering). Pain, depression, and gastrointestinal symptoms were significantly associated with HRQOL.

Conclusion

The finding that more than 30% of MM patients experienced pain and various symptoms indicates that patients had substantial palliative care needs within a year after starting initial chemotherapy. Different symptom trajectories were identified. Pain, depression, and gastrointestinal symptoms should be the main targets of palliative care interventions to improve HRQOL in this population.

Introduction

Multiple myeloma (MM) is a common hematological malignancy; the 2015 incidence of MM in Japan was 5.61 per 100,000 individuals per year. There were 8600 new cases of MM in 2015, and the incidence of MM is expected to increase as society ages [1]. The treatment of MM has improved in recent decades, and the 5-year survival rate has increased to 53% [2]. However, MM remains an incurable disease.

Patients with MM frequently experience symptom burden from pain, fatigue, constipation, numbness, depression, and other symptoms shortly after diagnosis [3, 4] and throughout the disease trajectory [5]. In addition, some studies have shown that pain [5, 6, 7], depression [5, 6, 7], anxiety [5, 7], and fatigue [5, 6] reduce HRQOL in MM patients. However, these studies used cross-sectional designs [5, 6], or included patients with different illness trajectories [7, 8]. To our knowledge, there are few longitudinal investigations of symptom prevalence, symptom trajectories, and HRQOL.

MM patients experience more symptom burden and lower HRQOL than patients with other hematologic malignancies [8, 9], but receive less optimal palliative care services [10]. To establish and implement early palliative and supportive care for MM patients, it is necessary to understand patterns of symptoms and depression and their effect on HRQOL during initial chemotherapy.

The aim of this prospective longitudinal study was to clarify symptom prevalence, symptom trajectories, HRQOL, and factors relating to HRQOL in MM patients during the early treatment period.

Method

Study design and logistics

This was a multicenter longitudinal prospective study conducted in one tertiary care university hospital and three community hospitals in Japan. When eligible patients were admitted to the hospital, the attending physician explained the nature of the study to them before they started chemotherapy. After obtaining informed consent, patients were asked to complete the questionnaires described below at three time points: at diagnosis (T1), 1 month after diagnosis (T2), and 12 months after diagnosis (T3).

The study contained two cohorts that experienced the same study design (described below) but differed in terms of subjects and study period. Cohort 1 comprised patients with lymphoma and MM; Cohort 2 contained only patients with MM. Cohort 1 participated in the study at Nagoya City University Hospital from September 2010 to March 2016. Several papers have been published using Cohort 1 data [11, 12, 13, 14, 15, 16]. Cohort 2 participated in the study from April 2019 to May 2021 at Nagoya City University Hospital and another three hospitals, to increase the number of participants with MM. The data for 73 patients diagnosed with MM extracted from Cohort 1 and 33 patients from Cohort 2 were combined and analyzed in this study.

This study was conducted with the approval of the institutional review board and ethics committee of each participating site, and was conducted in accordance with the principles laid down in the Helsinki Declaration. Written consent was obtained from each eligible patient after a thorough explanation of the purpose and method of the study. Participants received a gift card of 1,000 yen (approximately 10 USD) as a reward.

Participants and setting

The eligibility criteria for study inclusion were 1) patients newly diagnosed with MM, 2) adult patients (≥ 20 years old), 3) ability to read and write Japanese, 4) patients admitted to Nagoya City University Hospital, Kainan Hospital, Nagoya Memorial Hospital, or Nagoya City West Medical Center (the latter three hospitals only participated in Cohort 2) to undergo chemotherapy (in Japan, most MM patients undergo their first chemotherapy in inpatient settings, to monitor side effects and increase safety). The exclusion criteria were 1) having any type of severe mental or cognitive disorder, 2) too ill to complete the survey questionnaire, and 3) patients whose attending physician considered participation was inappropriate for any reason.

Symptom assessment

The MD Anderson Symptom Inventory (MDASI) is a self-administered questionnaire that assesses patient-perceived symptom severity and symptom interference in daily life [17]. In this study, only the symptom severity part of the MDASI was used. The patient rates their experience of 13 symptoms in the previous 24 hours from 0 (not present) to 10 (as bad as you can imagine). We categorized scores of 0–3 as indicating no or mild symptoms and scores of 4–10 as indicating moderate or severe symptoms, according to previous studies on fatigue [18, 19]. The validity and reliability of the Japanese version of the MDASI have been established [20].

The Patient Health Questionnaire-9 (PHQ-9) consists of nine items that assess the symptoms of major depressive disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [21]. Response options for each PHQ-9 item are 0 (not at all), 1 (several days), 2 (more than half the days), or 3 (nearly every day). Items are rated according to the frequency of depression symptoms over the previous 2 weeks. The total possible score ranges from 0 to 27. The presence of depression was assumed if scores on at least two symptoms were ≥ 2, with at least one of the symptoms being depressed mood or anhedonia. The validity and reliability of the Japanese version of the scale have been established [22].

Quality of life assessment

The EuroQoL-5 (EQ-5D) was administered to evaluate patients' HRQOL [23]. This scale contains five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; each dimension has three response categories (severe, moderate, none). Each profile can be transformed into a corresponding single EQ-5D score (the "utility score") using a conversion table. Each country has a unique conversion table, because ratings of health status vary across countries. The EQ-5D also includes a single visual analog scale (VAS) on which the respondent evaluates their overall health status from 0 to 100 (0 = worst imaginable; 100 = best imaginable). The validity and reliability of the Japanese version of this scale have been established [24].

Demographic and medical information

Information on patient sociodemographic status (e.g., marital status, level of education, and employment status) was obtained from the questionnaire. Performance status as defined by the Eastern Cooperative

Oncology Group was evaluated by the attending physicians. All other medical information (e.g., clinical stage and anticancer treatment) was confirmed from patients' medical records.

Statistical analysis

The EQ-5D utility index was calculated using Japanese tariffs. We analyzed utility scores using a t-test to compare MM patients with age- and sex-matched population norms obtained from a survey of the Japanese population [25].

A mixed-effects model was used to analyze the longitudinal association between EQ-5D VAS score and severity of symptoms, including depression. The factors lack of appetite, nausea, and vomiting were integrated into a gastrointestinal symptom category based on the cluster analysis results for MDASI scores from a previous study [17]. Moreover, factors in the mood and mood-related symptom cluster (distress, sadness, fatigue, drowsiness, and disturbed sleep) overlapped with PHQ-9 symptoms, so these were not included in the mixed-effects model. Finally, we used a linear mixed-effects model with pain, fatigue, dry mouth, numbness, shortness of breath, difficulty remembering, gastrointestinal symptoms, and PHQ-9 scores as fixed effects; subject as a random effect; and age, sex, marital status, educational level, job, type of myeloma, international staging system (ISS) score at baseline, and time as covariates. Standardized partial regression coefficients were also estimated to compare the effect of adjusting for variation in fixed effects on the EQ-5D VAS score.

All p-values were two-sided, with those < 0.05 considered to indicate statistical significance. All analyses were performed using R version 4.0.4 for Windows [R Development Core Team, 2020]. For linear mixed-effects modeling, the 'lme4' and 'lmerTest' packages were used.

Results

Patient characteristics and medical characteristics

A patient flow diagram is shown in Fig. 1. A total of 130 potentially eligible participants were identified, and 106 patients completed questionnaires at baseline (73 patients were recruited in 2010–2016 and 33 patients were recruited in 2019–2020). Of the 106 patients, 88 (83.0%), 8 (7.5%), 7 (6.6%), and 3 (2.8%) were recruited at Nagoya City University Hospital, Kainan Hospital, Nagoya City West Medical Center, and Nagoya Memorial Hospital, respectively. Thirteen patients were considered ineligible; 5 patients were excluded for logistic reasons and 6 declined to provide consent for participation in the study. The sociodemographic and clinical characteristics of the 106 patients are shown in Table 1. Patients who did not participate in this study were significantly older and had worse performance status and ISS scores than those who participated (data not shown).

Table 1
Demographic and clinical characteristics of patients (N = 106)

Characteristics		N	(%)
Age (year), mean ± SD	67.7 ± 10.7 (range: 36–87; median: 69)		
Sex	Male	54	50.1
Education	≥High school	79	74.5
Marital status	Married	74	69.8
Job	Employed (full-time/part-time)	39	36.8
Type of myeloma	IgG	59	55.6
	IgA	23	21.7
	Light chain disease	23	21.7
	Others	1	0.9
International Staging System score	I	17	16.0
	II	50	47.2
	III	39	36.8
Performance status	0	31	29.2
(ECOG)	1	43	40.6
	2	11	10.4
	3	14	13.2
	4	6	5.7
Intensity of received treatments at T3[a]	Chemotherapy only	54	61.4
	Chemotherapy and ASCT	34	38.6
Chemotherapy at T3[b]	Chemotherapy free	49	59.8
	Relapsed or undergoing chemotherapy	33	40.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; ASCT, autologous stem cell transplantation; Ig, immunoglobin.

[a]88 patients completed the T3 survey.

[b]Treatment status data for 6 patients at T3 were missing.

A total of 93 participants completed at T2 and 88 at T3. The follow-up rate was 88.7% and 83.0%. Of the 88 patients participating at T3, 34 (38.6%) received autologous stem cell transplantation. Treatment status data for 6 patients at T3 were missing, 33 patients (40.2%) were undergoing chemotherapy.

Symptoms

Table 2 shows the proportion of patients with scores of ≥ 4 (moderate to severe) on each MDASI symptom. Symptoms reported by more than 30% of patients were pain, disturbed sleep, distress, dry mouth, sadness, and depression at T1; pain, dry mouth, disturbed sleep, fatigue, distress, and drowsiness at T2; and fatigue, numbness or tingling, and pain at T3. Mean score trajectories for each symptom are shown in Fig. 2. Various symptom trajectory patterns were found, such as a peak at T1 and reduction over time (pain, disturbed sleep, distress, lack of appetite, sadness, depression), a peak at T2 (fatigue, drowsiness, dry mouth, nausea, vomiting), and a V-shaped pattern (shortness of breath, numbness or tingling, difficulty remembering).

Table 2
Prevalence of symptoms

T1	% (N = 106)	T2	% (N = 93	T3	% (N = 88)
Pain	46	Pain	36	Fatigue	33
Disturbed sleep	41	Dry mouth	36	Numbness or tingling	32
Distress	38	Disturbed sleep	33	Pain	31
Dry mouth	35	Fatigue	33	Distress	24
Sadness	32	Distress	32	Drowsiness	24
Depression	30	Drowsiness	31	Dry mouth	23
Lack of appetite	28	Sadness	26	Disturbed sleep	18
Drowsiness	26	Depression	21	Lack of appetite	18
Fatigue	25	Lack of appetite	20	Sadness	17
Shortness of breath	22	Shortness of breath	16	Shortness of breath	16
Numbness or tingling	19	Numbness or tingling	15	Difficulty remembering	14
Difficulty remembering	12	Nausea	11	Depression	10
Nausea	7	Difficulty remembering	9	Nausea	6
Vomiting	3	Vomiting	5	Vomiting	3
Abbreviations: MDASI, MD Anderson Symptom Inventory; PHQ-9, Patient Health Questionnaire-9.					
Depression was assessed using the Patient Health Questionnaire-9. Other symptoms were assessed using the MDASI.					
Data show the proportion of patients reporting scores of ≥ 4 on each MDASI symptom. Definition of depression was described in the text.					

HRQOL

The mean EQ-5D utility index score was 0.64 (standard deviation (SD) = 0.27), 0.66 (SD = 0.24), and 0.78 (SD = 0.17) at T1, T2, and T3, respectively. The utility index score at T3 was significantly lower than the age- and sex-matched population norms (mean = 0.87, SD = 0.16). The mean EQ-5D VAS score was 59.0 (SD = 23.5), 64.9 (SD = 10.7), and 72.2 (SD = 18.5) at T1, T2, and T3, respectively.

Effect of symptoms on HRQOL

The mixed-effects model showed that pain, depression, and gastrointestinal symptoms were significantly associated with VAS HRQOL scores after adjustment for time, age, sex, marital status, education level, job, type of myeloma, ISS scores, and four other symptom scores (Table 3).

Table 3
Factors associated with quality of life (VAS scores): results of mixed-effects model

	Coefficient	95% CI	Standardized coefficient	95% CI	p-value
Pain	−1.80	−2.68, − 0.91	−0.26	−0.38, − 0.13	< 0.001
Fatigue	−0.15	−1.25, 0.94	−0.02	−0.16, 0.12	0.782
Dry mouth	−0.89	−1.80, 0.03	−0.11	−0.23, 0.00	0.059
Numbness or tingling	0.09	−0.85, 1.02	0.01	−0.11, 0.13	0.855
Gastrointestinal symptoms	0.66	0.06, 1.25	0.14	0.01, 0.26	0.030
Shortness of breath and difficulty remembering	−0.31	−1.08, 0.45	−0.05	−0.18, 0.07	0.418
Depression	−1.46	−2.01, − 0.90	−0.33	−0.45, − 0.20	< 0.001
Abbreviations: CI, confidence interval; VAS, visual analog scale.					
Depression was assessed using the Patient Health Questionnaire-9. Other symptoms were assessed using the MD Anderson Symptom Inventory.					
Results were adjusted for time, age, sex, marital status, educational level, job, type of myeloma, and International Staging System score.					

Discussion

To our knowledge, this is the first study to use a longitudinal observational design to explore symptom prevalence, symptom trajectories, HRQOL, and factors associated with HRQOL in patients with newly diagnosed MM. Our results showed that patients frequently experience a range of symptoms. Pain, depression, and gastrointestinal symptoms were significantly associated with HRQOL.

Patients experienced a wide range of symptoms that showed different trajectories. Medical staff should recognize these symptom patterns/trajectories to provide optimal palliative care for patients with MM. The symptom burden was highest at diagnosis and remained high 1 month later. This may partly reflect

acute illness exacerbation, which is the typical illness trajectory in hematologic malignancy. The prevalence of psychological symptoms such as depression, distress, and sadness at diagnosis could be attributed to the psychological effects of a cancer diagnosis. A previous study reported that early palliative care for patients with MM a median of 355 days after diagnosis is both feasible and beneficial [10]. We recommend that palliative care, including psychological support, should be initiated at the start of anticancer treatment in routine hematological oncology practice.

Our results also indicated that patients experienced various symptoms 1 year after starting chemotherapy. Medical staff should pay particular attention to symptoms of numbness or tingling, because although these symptoms were not initially severe, they gradually increased and were prominent 1 year after diagnosis. This symptom is attributed to chemotherapy-induced peripheral neuropathy (CIPN) [26]. For example, thalidomide and bortezomib are used to treat MM, and these agents often lead to painful CIPN. There is a lack of established management strategies for CIPN, so early recognition is importance to prevent irreversible neurological damage [27].

Pain, depression, and gastrointestinal symptoms were significantly associated with HRQOL, assessed using the VAS. As already mentioned, several cross-sectional studies have investigated the association between quality of life and symptoms [5, 6]; one longitudinal observational study included patients with different illness trajectories [7]. The novel findings of the present study include clarification of the relative effect of each symptom on HRQOL, determined using longitudinal data after adjusting for covariates. The findings suggest that it is very important to manage these symptoms shortly after diagnosis to ensure better patient quality of life.

Several study design issues may limit our confidence in these findings. First, patients who did not participate in this study were significantly older and had worse performance status and clinical staging scores than participants. This suggests that we may have underestimated the severity or prevalence of symptoms or overestimated quality of life levels. Participant attrition in both cohorts may also have caused underestimation, although we considered the attrition rate to be minimal. Second, the time gap between assessments of the two cohorts may have meant that there were differences in chemotherapy regimens because of developments in anticancer treatment. Third, assessments were only made at three time points.

Despite these limitations, this study had several strengths. This was a multicenter study of patients from both university and municipal hospitals, so selection bias was minimal. Patients were consecutively recruited, and the rejection rate was low. Patient-reported outcomes were assessed with widely used international measures validated for Japanese samples.

Conclusion

This longitudinal observational study of patients newly diagnosed with MM showed that patients experienced a wide range of symptoms during their illness trajectories and identified factors associated with HRQOL. The findings suggest that appropriate early management strategies for these symptoms

could improve HRQOL. In future studies, we plan to develop randomized controlled trials of interventions for MM patients from the time of diagnosis.

Declarations

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Conflicts of interest/Competing interests (include appropriate disclosures)

The authors have no directly conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material (data transparency)

The datasets obtained in the current study are available from the corresponding author on reasonable request.

Code availability (software application or custom code)

Not applicable

Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory)

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Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals

Not applicable

Ethics approval (include appropriate approvals or waivers)

This study was conducted with the approval of the institutional review board and ethics committee of Nagoya City University Graduate School of Medical Sciences, Japan, and was conducted in accordance with the principles laid down in the Helsinki Declaration. Written consent was obtained from each eligible patient after a thorough explanation of the purpose and method of the study.

Consent to participate (include appropriate statements)

Written informed consent was obtained from all individual participants included in the study.

Consent for publication (include appropriate statements)

The authors affirm that human research participants provided informed consent for publication.

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Figures

Fig. 1

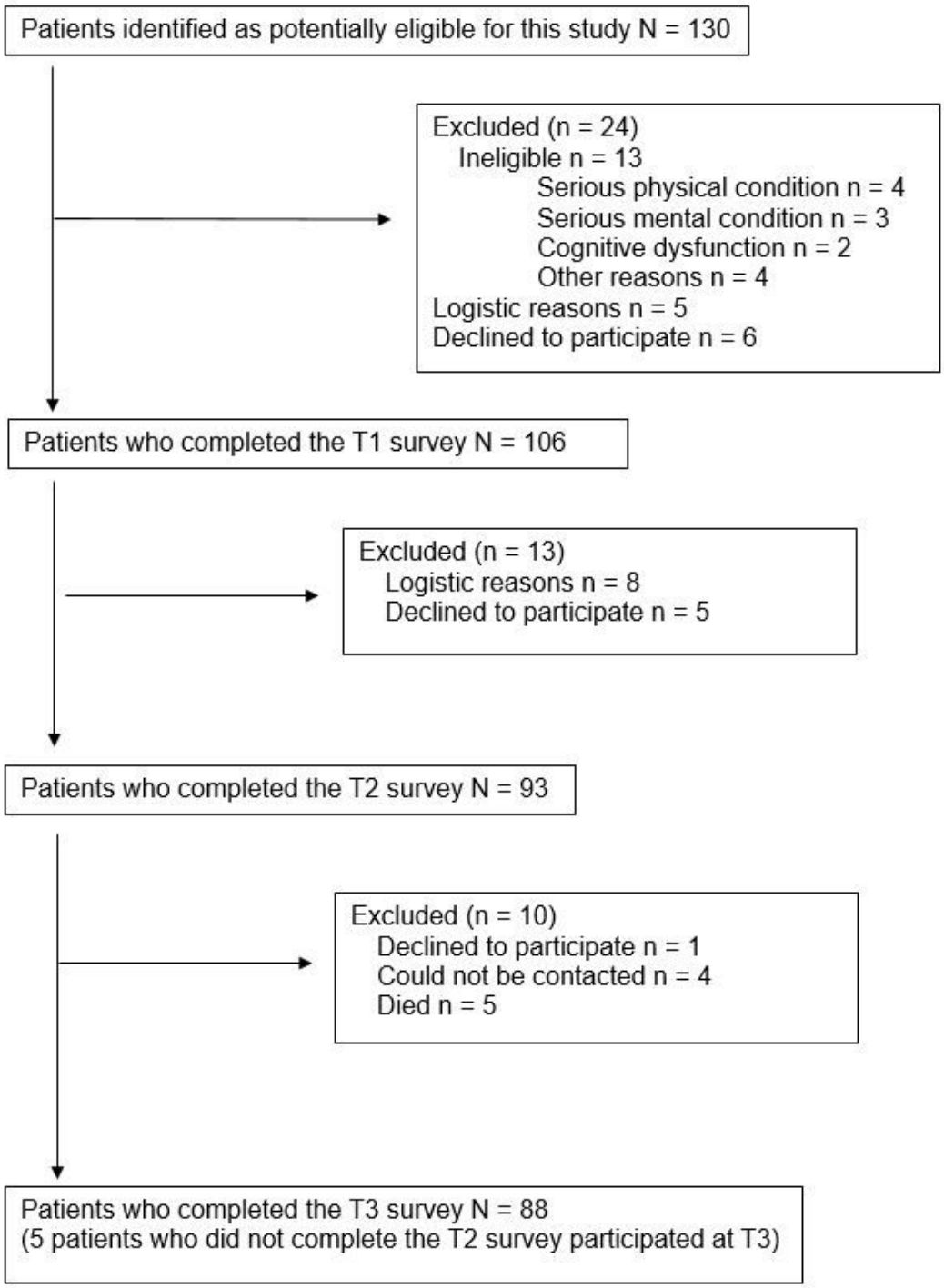

Figure 1

Flowchart showing the number of patients at each time point

Fig. 2

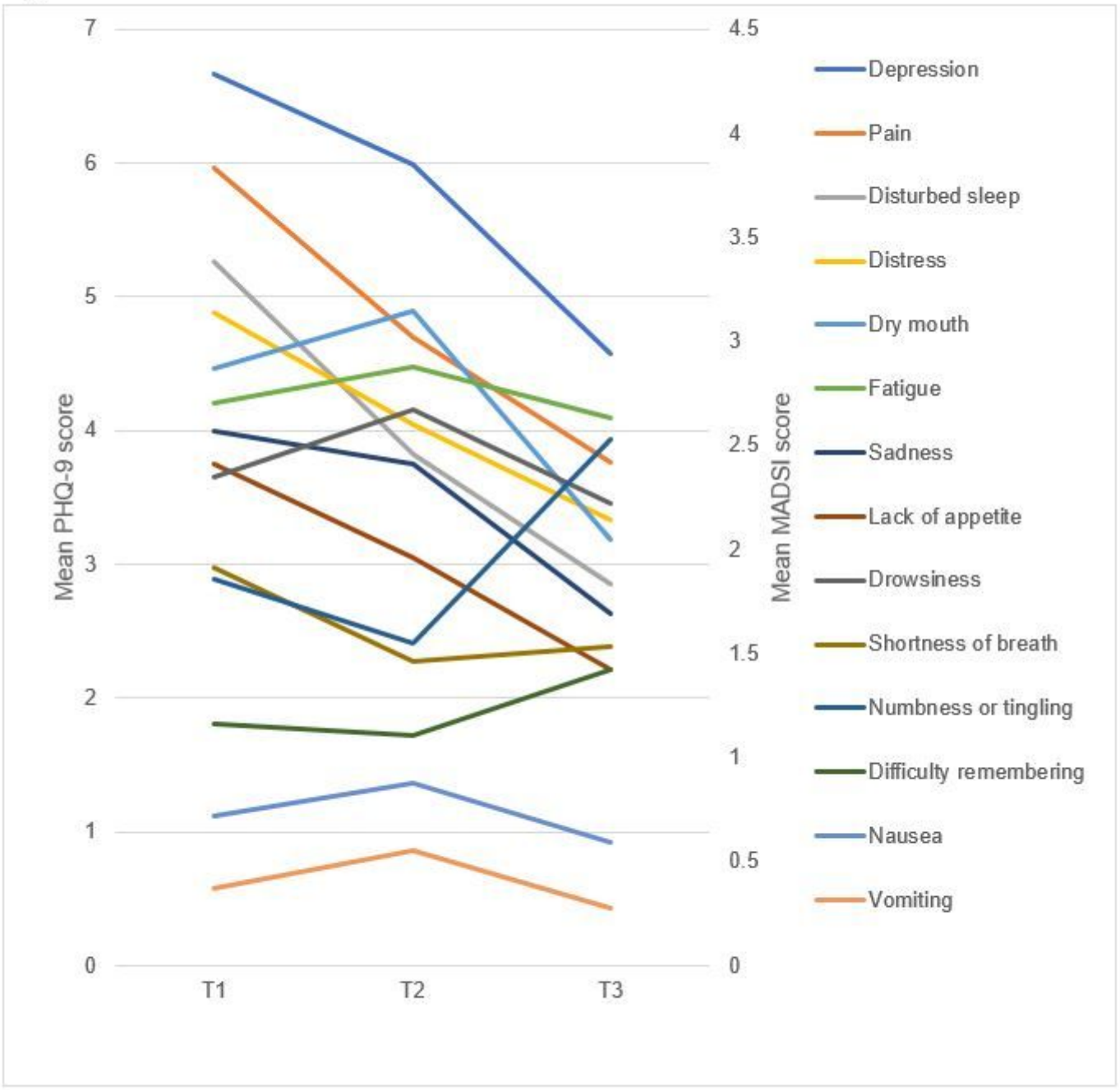

Figure 2

Longitudinal changes in symptom severity within a year after diagnosis. The y-axis indicates scores of MDASI or PHQ-9. MDASI MD Anderson Symptom Inventory, PHQ-9 Patient Health Questionnaire-9