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Development and validation of a patient-reported outcome measure to assess symptom burden after CAR T-cell therapy

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Abstract

This cross sectional study aims to develop and validate patient-reported outcomes (PROs) assessment tool to assess symptom burden and daily functioning in patients after chimeric antigen receptor (CAR) T-cell therapy, the MD Anderson Symptom Inventory (MDASI-CAR). The items were generated based on literature review, content elicitation interviews with patients, and clinician's review. The patients completed the MDASI core and module, single item quality of life (QoL) measure and Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29). The psychometric validation analysis was based on the acceptability after item reduction process. The final 10 MDASI-CAR module items included tremors, fever/chills, headache, balance, dizziness, attention, difficulty speaking, coughing, sexual dysfunction, and diarrhea with high internal consistency (Cronbach's alpha: MDASI Core 0.865, MDASI Interference 0.915, CAR-T module 0.746). The MDASI–CAR has excellent known-group validity that was demonstrated by differentiate patients based on patient's performance status (Cohen's d for MDASI core=−1.008, interference=−0.771, module=−0.835). Criterion validity was demonstrated by the significant correlations between the MDASI-CAR composite score, the single QoL item and the relevant domains on PROMIS-29 (all P<.05). This study established the MDASI-CAR module as a reliable and valid PRO tool for monitoring symptom burden after CAR T-cell therapy in patients with hematologic malignancies. The findings need to be validated with a longitudinal design.

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INTRODUCTION

The successes achieved with the chimeric antigen receptor (CAR) T-cell therapy in more recent years have led to a paradigm shift in the standard of care (SOC) treatment for patients with relapsed or refractory B-cell lymphoid malignancies and multiple myeloma. (1–3) Attributed to both, the underlying hematologic neoplasm and its treatment adverse effects, cancer-related symptoms can cause not only poor quality of life (QoL) but may also have great impact on making the proper treatment interventions for these patients. Efforts to capture early symptom development and to prevent and/or reduce symptom burden are essential in order to improve quality of life and functioning outcomes among patients receiving CAR T-cell therapy. An instrument that accurately measures a selected set of symptoms that are clinically meaningful in these patients may provide unique information for improving the effectiveness of supportive care.

The M. D. Anderson Symptom Inventory (MDASI) is a well-established and is a reliable and validated tool for assessing cancer-related symptoms (4). The MDASI includes 13 core items assessing common symptoms with the severity at its worst in the last 24 hours and 6 items assessing symptom-related interference in the last 24 hours, all rated on a 0–10 numeric scale. MDASI modules, which include the addition of disease- and treatment-specific symptom items to the core MDASI, have been developed for different cancer subtypes, however, there is no MDASI module specific to the symptom burden of patients receiving CAR T-cell therapy. The use of universal PRO measures may not provide clinically meaningful information in special clinical settings where patients may experience a unique set of symptoms and toxicities following therapy as in the case of CAR T-cell therapy. Although the MDASI was one of four PRO assessment tools that the Center for Medicare and Medicaid Services (CMS) panel approved for use in assessing symptoms following CAR T-cell therapy, there remains no established PRO assessment tool that could be used in routine patient care for monitoring symptom burden after CAR-T therapy (5). Moreover, a concise and easy-to-use measure is needed for clinical practice and for research purposes to facilitate repeated measurements.

The MDASI is well-established, reliable and has been extensively validated for reporting symptoms and functioning status aspects of PROs among patients with hematological malignancies during chemotherapy and hematopoietic stem cell transplant, stimulating our interest to examine PRO’s in patients receiving CAR T-cell therapy (4, 6–8). A MDASI-CAR module could allow a comprehensive measurement of disease- and treatment-related symptom burden in these high-risk patients, which would eventually be used as a complimentary tool to capture early toxicity and provide proper timely interventions. We have previously reported, in both qualitative and quantitative studies, (9) (10) on the unique symptom burden among patients with hematological malignancies receiving CAR T-cell therapy. In addition to the MDASI-core items, we identified 18 additional PRO items reported by these high-risk patients. In this cross-sectional observational study, we aimed to develop and psychometrically validate a MDASI module for patients with hematological malignancies (MDASI–CAR). We developed the MDASI-CAR in accordance with the U.S. Food and Drug Administration (FDA) guidance (11) which recommends that PRO measures include both patient and clinician contributions towards item generation and also calls for

a psychometric validation of the developed scale. This study defines final items of this module of MDASI-CAR and examines the psychometric properties of it in patients with hematological malignancies receiving SOC commercial CAR T-cell therapy.

METHODS

Patients and Data Collection

This prospective, cross-sectional study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center (MDACC). Patients eligible for this study were required to be at least 18 years old, speak English, have received SOC CAR-T therapy at MDACC, and signed informed consent for enrollment. Patients were consecutively recruited between July 2019 and July 2021. A trained study coordinator conducted survey and collected information from patients' medical records. Patients were approached at any time within the first 12 months following CAR T-cell therapy, either in-person or via phone. Upon signing the electronic informed consent, patients completed PROs only once, either receiving the REDCap link online or in-person using an iPad, to rate their symptom severity, functioning, and health status.

Development of the MDASI-CAR

To develop the MDASI-CAR in accordance with FDA guidelines for creating and validating PRO tools (11), we followed a 3-step process that involved, first, generating CAR-specific candidate items with input from hematologists and qualitative interviews with patients (9) and adding these to the core MDASI for testing; second, dropping candidate module items using qualitative and quantitative approaches (clinical judgment, cluster analysis, evaluation of low prevalence); and finally, validating the psychometric properties (validity, reliability, sensitivity) of the resulting MDASI-CAR. The core MDASI (4) included 13 symptom items (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling), and 6 symptom interferences (general activity, mood, work, walking, relation with others and enjoyment of life), all rated on a recall of past 24 hours.

(1) ***Module item generation.*—**In a previous qualitative study (9), 20 patients receiving CAR-T therapy were asked about the symptoms they experienced, by a semi-structured qualitative interviews that been conducted by trained interviewers. The descriptive exploration identified relevant symptoms. Further, a peer review of potential MDASI-CAR symptom items from which a set of unique CAR T-cell therapy-related-symptom items were identified from the MDASI-item library by an expert panel of clinicians who manage CAR T-cell therapy patients. With this combined information, a total of 22 items were added to the validated MDASI core items and formed the "provisional" MDASI-CAR, including diarrhea, inability to eat, rash, malaise, lack of energy, weakness, tremors, muscle weakness, fever, headache, irritability, balance, mouth, dizziness, swallowing, attention, bone ache, heartbeat, swelling, speaking, coughing, and sexual dysfunction.

(2) Item reduction to form final MDASI-CAR module items.—In the planned item reduction strategy, candidate items were dropped based on symptom severity and prevalence,

clinical interpretability, and rate of reporting from a cross-sectional study involving 78 patients who had received CAR T-cell therapy.

(3) Psychometric Validation.—In addition to the provisional MDASI-CAR, all study participants completed the Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29) (12), the global health tool EQ5D (13), and the single-item quality of life (SIQOL) scale (14) to allow for evaluation of the correspondence of the MDASI-CAR with a widely-used QOL outcome instrument. Demographic information and current disease information (cancer diagnosis, disease status, prior treatment, treatment information, acute toxicity, and comorbidities) were recorded. Patient functional status was evaluated by clinicians using the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) (15). The American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria were used for diagnosis and grading of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity (ICANS) in patients receiving CAR T-cell therapy (16).

Statistical Analysis

Determining sufficient sample size to evaluate and validate the module items was based on the ability of the MDASI to distinguish between patients with poor and good performance status as a measure of known-group validity (15). Patients with good ECOG PS were expected to have lower symptom severity than patients with poor ECOG PS. In the case of ECOG PS group comparison for Core and CAR-T module, a total sample size of 78 patients or 39 patients per group could detect an effect size of 0.64 or greater with 80% power using a two-tailed significance level of 0.05. In the case of ECOG PS group comparison for interference, physical functioning [work, activity and walk (WAW)] and psychological functioning [relation with others, enjoyment of life and mood (REM)], a total sample size of 76 patients or 38 patients per group could detect an effect size of 0.65 or greater with 80% power using a two-tailed significance level of 0.05.

The MDASI-CAR items were examined for their reliability, validity, and clinical interpretability.

To establish internal consistency, Cronbach coefficient α values for symptom severity and symptom interference were calculated. They are usually considered to be acceptable when Cronbach's alpha ≥ 0.70 (Special Advisory Committee of the Medical Outcomes Trust) (17).

Known-group validity was measured by differentiating of symptom burden among patients according to their ECOG PS and phase of post CAR T-cell patientcare within and after 90 days from infusion. Means of differences, 95% confidence limits, medians, and significance tested by independent-sample *t* tests, and Cohen's d effect size (18) were reported. These calculations used a global symptom component score (mean of the 13 core MDASI symptom items and the candidate module items) and an interference component score (mean of the 6 interference items). With expected patients with good ECOG PS to have lower symptom severity than patients with poor ECOG PS, an effect size of 1 between good and poor ECOG performance status groups would has 90% power to detect this difference with 22 patients per group using a two-tailed test at 5%.

The convergent validity was tested by calculating Spearman rank correlation coefficients between composite scores of subscales in the MDASI–CAR and the SIQOL, EQ5D and 7 domains of PROMIS 29. The interference composite scores were derived from the categorization of interference items, on the basis of our previous research (19), into a composite score of work, activity, and walking, representing the physical-functioning domain, and a composite score of relations with other people, enjoyment of life, and mood, representing the mental health or social functioning domains. These combinations were specified a priori to limit the number of comparisons with these pairs to control type I error rates.

Descriptive statistics were used to describe the symptoms burden of 3 patient subgroups who were surveyed one time at distinct time points following CAR T-cell therapy infusion. One-way ANOVA tests were used to determine differences between groups. Kruskal-Wallis tests were used if the normal distribution assumption was not met. The 95% confidence intervals were calculated around effect sizes. The Spearman correlation coefficient was also used to assess the association between core PRO items on MDASI and domains of PROMIS-29.

All statistical procedures were performed using SAS Statistical Software Program for Windows (20). All *P* values reported are 2-tailed.

Results

Patient and treatment characteristics

Seventy-eight patients with a median age of 59.78 (range, 18.72 – 78.60) years were enrolled during the study period. Majority of patients had large B-cell lymphoma (n=63, 81.8%), and axicabtagene ciloleucel (Yescarta) was the most frequent SOC CAR T-cell used (n=68, 87.2%). Baseline patient, disease and treatment characteristics are summarized in Table 1.). The median time from CAR T-cell infusion to the survey was 41 (range, 1–365) days; 60% of the surveys were conducted within 3 months, 18% within 3–6 months, 22% within 6–12 months from the infusion. For all study patients, CRS and/or ICANS rates of any grade were observed in 88.3% of all patients, in the first two weeks following CAR T-cell therapy infusion. For the highest score of CRS until the date of survey, 28.3% of patients had grade 2 and 3.8% had grade 3–4 CRS.

Candidate module items for MDASI-CAR

The selection of 22 CAR T-cell-related items was based on data derived from the published qualitative study (10), physician expertise and on the review of published literature related to CAR T-cell therapy (21–29).

These provisional module items were added to the core MDASI symptom items to form the MDASI CAR T-cell therapy module. The added 22 items included lack of energy, feeling of malaise (not feeling well), bone aches, coughing, changes in sexual function, inability to eat, irritability, difficulty speaking, muscle soreness or cramping, problems with paying attention (concentrating), headache, balance or falling, fever or chills, dizziness, problems with racing heartbeat or palpitation, swelling of the hands, legs, feet, abdomen, or around

the eyes, tremors, difficulty swallowing, mouth/throat sores, diarrhea, and skin rash. Our qualitative work from a subset of study sample of patients undergoing CAR T-cell therapy (n=21/78) confirmed the content validity of these items (9).

In this study, we attempted to retain only the meaningful symptom items, and hence, we report the validation results for the 10 module items included in the final version of the MDASI-CAR in addition to the 13 MDASI core symptom items and the 6 MDASI core interference items. These 10 module items included diarrhea, tremors, fever/chili, headache, balance, dizziness, attention, speaking, coughing, and sexual dysfunction. As an example for the item elimination process, “skin rash” and “hot flashes” were dropped as only 5% and 4% of patients rated them as moderate to severe (≥ 5 on the 0–10 scale), whereas 87% and 83% of patients rated zero. Other eliminated items included “mouth sore, “difficulty swallowing”, “bone ache”, “heartbeat”, and “swelling on arm/legs”, as these were observed in low prevalence. Some items were dropped for lack of independence (closely related to other relevant symptoms that is captured by the MDASI-core); as an example, “lack of energy”, “malaise”, and “museal weakness” correlated with “fatigue”, “inability to eat” correlated with “poor appetite”, and “irritability” correlated with “distress”.

Psychometric Validation of the MDASI-CAR

For the quantitative psychometric evaluation, 78 patients responded to the provisional MDASI-CAR (13 core symptoms, 6 interference items and the 22 potential module items for CAR-T therapy). All participants completed the SIQOL, MDASI-CAR, and PROMIS-29 modules, while 96.7% of the patients completed the EQ5D-5L.

Internal consistency

A high degree of internal consistency within the symptom severity items and the interference items was observed (Table 2). The Cronbach α was 0.892 for the symptom severity scale (23 items) and 0.927 for the interference scale (6 items). Deleted each single symptom item and recalculated the Cronbach coefficient, it consistently remained similar and above the minimum threshold to the overall coefficient for that factor, indicating that each symptom contributed to the factor and should remain in the scale.

Known-group validity

The MDASI–CAR was sensitive enough to detect different levels of symptom severity. Patients with poorer performance status (ECOG PS 2–4 vs. 0–1) reported significantly higher severity for both core MDASI and CAR-specific symptoms (all $P < .001$; Table 3). Based on data collection time to the infusion date within the first year, there was observed significantly higher severity of multiple symptoms on MDASI-CAR during the first 90 days compared to those patients reporting after 90 days of therapy (All P<.05, Table 4).

Convergent validity of the interference items

The validity of the MDASI-CAR core and module symptom items, as well as symptom interferences items were evaluated against the SIQoL, EQ5D, and with the corresponding

domains from PROMIS 29 in this study. The Spearman correlation with single item MDASI-Fatigue item and PROMIS-Fatigue domain (r=.747, P<.001), MDASI-Sad item and PROMIS-depression domain (r=0.515, P<.001), MDASI-Sleep disturbance item and PROMIS-Sleep domain (r=0.801, P<.001), MDASI-Distress item and PROMIS-Anxiety domain (r=0.525, P<.001), MDASI-Pain item and PROMIS-Pain item (r=0.807, P<.001).

MDASI activity items (walking, activity, work) moderately correlated with the SIQOL, EQ5D and physical function domain of PROMIS 29 (r=−.540, −0.433, −0.470, all P<.001). Mood-related interference items (relations with others, enjoyment of life, mood) also moderately correlated with SIQOL and EQ5D (r=−.561, −0.430, all P<.001). Mood-related interference moderately correlated with the social role subscale from PROMIS 29 (r=−0.446, p<.001)

The MDASI-CAR total interference score was significantly associated with a single item assessing patient-rated quality of life on a 0–10 scale ($r = -.54$, $P < .001$), EQ5D (r=−0.449, P<.001), and pain interference of PROMIS (r=.594, P<.001).

Discussion

To our knowledge, this study is the first to report on developing a treatment-specific PRO assessment tool for patients undergoing CAR-T therapy. The MDASI-CAR is a concise and sensitive instrument for measuring the severity of multiple symptoms and determining their interference with function in patients who received CAR T-cell therapy. The development of this novel instrument included data derived from qualitative and quantitative studies and on data collected from an expert panel review survey. Ten items (tremors, fever/chills, headache, balance, dizziness, attention, difficulty speaking, coughing, sexual dysfunction, and diarrhea) were confirmed as the module items to be added to the core MDASI for the final instrument.

This study included assessments of two CMS recommended measures that could be considered for PRO data collection in patient care, namely MDASI-CAR and PROMIS 29. MDASI-CAR provided 10 additional CAR-T specific symptom items for using in patient care, although MDASI-CAR and PROMIS 29 assess pain, fatigue, sleep, distress, sadness and physical functioning and showed similar effect sizes. This is not surprising as other measures were not designed specifically for CAR-T therapy. Multiple symptoms were significantly more severe within 3 months of therapy compared to 3–6 and 6–12 months after therapy (Table 4), including pain, fatigue, poor appetite, drowsiness, dry mouth, balance and general activity. The excellent completion rate of the surveys by patients included in this study indicate that the MDASI-CAR imposes minimal burden on these high-symptomatic patients, and hence the feasibility of frequent survey administration, particularly during the early phase after treatment within 3 months where the symptom burden is highest.

The tool could be particularly useful in providing valuable information to health care providers that would facilitate timely treatment interventions in order to mitigate toxicity after CAR T-cell therapy and hence decrease patient symptom burden. This is expected

to enhance patient recovery after therapy. The comprehensive final symptom item dataset (Table 4) suggests that this tool can capture much of the symptoms of interest that could be experienced by patients and would make it ideal to use for close monitoring in routine patient care. It should be noted that fatigue, poor appetite and drowsiness were the most severe symptoms during the first 3 months of therapy and should prompt proactive management and interventions.

There are several intrinsic favorable attributes of this newly validated tool. For example, the MDASI's 24-hour recall period is uniquely favorable for daily assessment to satisfy the need to capture the rapid changes in symptom for a given patient. The 0–10 numeric scale is simple, familiar, and easy to use in conjunction with modern survey delivery technology, such as computerized tools in the clinic, computer-aided telephone systems or web-based patient portals from home (30). This feature gives both providers and patients the flexibility to communicate efficiently and effectively in describing symptom severity and symptom interference in real time between clinical encounters.

We acknowledge the limitations of our single institutional study. First, majority of patients received axicabtagene ciloleucel, which may raise concerns for its applicability in other CAR-T cell products. However, although they differ in their incidence, the spectrum of toxicities is similar among the different approved CAR T-cell products. Second, the sensitivity to changes in the tool will need to be reported through a longitudinal study with the same cohort of patients. Furthermore, to reduce the survey fatigue but capture the dynamic changes and test-retest stability, the frequency and timing of MDASI-CAR assessments should be carefully selected and tested in a prospective longitudinal study. Based on the high-prevalence of toxicities early after CAR T-cell therapy, for a purpose of patient care, we suggest more frequent assessments in the first 2 weeks after treatment (2–3 times a week), weekly for 1 month after treatment, and interval can be increased thereafter given the lower incidence of toxicities after 1 month. Third, the use of the tool might be limited during the acute phase in patients with grade 2 or higher ICANS. Fourth, we collected very limited cases for cognitive debriefing of this new instrument, and this should be best done in a separate study to support the clinical adoption in patients.

In conclusion, the MDASI-CAR is a valid, reliable, and concise tool for measuring symptom severity and functional interference in patients undergoing CAR T-cell therapy in patients with hematological malignancies. The instrument represents patient's symptom experience during the first year after therapy, with highest symptom burden is observed during the first 3 months. As a PRO tool for symptom assessment in this population, the MDASI-CAR can be potentially applied in routine patient care and could be an important tool for PRO measurement in clinical trials.

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Abbreviations

CAR	Chimeric Antigen Receptor
CRS	Cytokine Release Syndrome
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
HRQoL	Health-Related Quality of Life
MDACC	MD Anderson Cancer Center
MDASI	MD Anderson Symptom Inventory
PRO	Patient-Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System

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Table 1.

Demographic and clinical characteristics of study cohort (N=78)

Cohort description	**ALL (N=78)**	
	Mean (sd)	**Median (min, max)**
Age, years	58.82 (14.28)	59.78 (18.72 – 78.60)
Cohort description	**ALL (N=78)**	
	N	**%**
Sex		
Female	22	28.21
Male	56	71.79
Ethnicity		
Hispanic or Latino	17	21.79
Not Hispanic or Latino	61	78.21
Race		
White or Caucasian	63	80.77
Other	15	19.23
Select only the highest grade completed:		
High school and under	26	33.33
some college and higher	52	66.67
*CCI Total scored:		
0	15	19.23
1+	63	80.77
*Patient’s ECOG Performance Status (Grade 0–5)		
0–1 (Good)	57	73.08
2–4 (Poor)	21	26.92
Diagnosis		
Diffused Large B-Cell Lymphoma	68	87.18
Follicular Lymphoma	5	6.41
Acute Lymphoblastic Leukemia	3	3.85
Mantle Cell Lymphoma	2	2.56
CAR-T therapy product		
Axicabtagene ciloleucel (Yescarta)	68	87.18
Tisagenlecleucel (Kymriah)	8	10.26
Brexucabtagene autoleucel (Tecartus)	2	2.56
Acute toxicities in the first two weeks after the CAR-T infusion		
No	9	11.69
Yes	68	88.31

ECOG, Eastern Cooperative Oncology Group; CCI, Commodity Channel Index; CRS, Cytokine Release Syndrome; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome

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Table 2.

Reliability by Internal Consistency

Deleted Symptom Item	n	α
MDASI-Core + Module (13+10 items) Overall α = 0.892		
Pain	78	0.888
Fatigue	78	0.881
Nausea	78	0.887
Sleep Disturbance	78	0.887
Distress	78	0.884
Shortness of Breath	78	0.889
Remember	78	0.887
Appetite	78	0.882
Drowsy	78	0.879
Dry Mouth	78	0.884
Sad	78	0.885
Vomiting	78	0.889
Numbness	78	0.892
Tremors	78	0.887
Fever	78	0.887
Headache	78	0.889
Balance	78	0.890
Dizziness	78	0.889
Attention	78	0.884
Speaking	78	0.887
Coughing	78	0.890
Sexual	75	0.893
Diarrhea	78	0.891

Deleted Symptom Item	n	α
MDASI Interference Baseline Overall α = 0.915		
Activity	76	0.908

Deleted Symptom Item	n	α
MDASI Interference Baseline Overall α = 0.915		
Mood	76	0.888
Work	75	0.892
Relations	76	0.909
Walking	75	0.906
Enjoyment of life	76	0.892

Deleted Symptom Item	n	α
MDASI-Core Baseline Overall α = 0.865		
Pain	78	0.856
Fatigue	78	0.845
Nausea	78	0.859
Sleep Disturbance	78	0.854
Distress	78	0.851
Shortness of breath	78	0.864
Remember	78	0.861
Appetite	78	0.848
Drowsy	78	0.839
Dry Mouth	78	0.854
Sad	78	0.852
Vomiting	78	0.864
Numbness	78	0.870

Deleted Symptom Item	n	α
MDASI Module (Final 10 Items) Baseline Overall α = 0.746		
Tremors	78	0.710
Fever	78	0.711
Headache	78	0.723
Balance	78	0.746
Dizziness	78	0.708
Attention	78	0.704

Deleted Symptom Item	n	α
MDASI Module (Final 10 Items) Baseline Overall α = 0.746		
Speaking	78	0.724
Coughing	78	0.738
Sexual	75	0.727
Diarrhea	78	0.755

Table 3.

Known Group Validity by ECOG PS Status

Subscale	ECOG Group	N	Mean	Std Dev	Lower 95%	Upper 95%	P-Value	Cohen's D
Core	0 – 1	57	1.58	1.26	1.25	1.92	< 0.001	−1.008
	2 – 4	21	2.96	1.64	2.21	3.71		
Interference	0 – 1	56	1.86	2.02	1.32	2.4	0.009	−0.771
	2 – 4	20	3.56	2.67	2.31	4.80		
CAR-T Module	0 – 1	57	0.95	1.11	0.66	1.25	0.002	−0.835
	2 – 4	21	1.96	1.45	1.30	2.62		
WAW	0 – 1	56	1.89	2.14	1.32	2.47	0.016	−0.836
	2 – 4	20	3.93	3.15	2.45	5.40		
REM	0 – 1	56	1.59	1.95	1.07	2.11	0.065	−0.659
	2 – 4	20	3.08	2.98	1.69	4.48		

WAW = physical functioning-related interference items (work, general activity, and walking ability). REM = psychological functioning-related interference items (relations with people, enjoyment of life, and mood)

Table 4.

Symptom Severity Difference on MDASI-CAR by Time of Survey

	0–3 Months					3–6 Months					6–12 Months					P-Value (ANOVA)
	N	Mean	Std	Min	Max	N	Mean	Std	Min	Max	N	Mean	Std	Min	Max	
Core Items																
Fatigue	47	4.96	2.6	0	10	14	3.64	2.98	0	8	16	2.38	2	0	6	0.0027
Drowsy	47	3.91	2.9	0	10	14	2.43	2.71	0	8	16	2	2.53	0	8	0.034
Lack of Appetite	47	3.64	2.87	0	10	14	1.57	1.87	0	5	16	0.5	1.1	0	3	< 0.0001
Pain	47	2.83	3.05	0	10	14	1.21	1.63	0	5	16	1.13	1.96	0	7	0.0317
Disturbed Sleep	47	2.66	2.94	0	10	14	2.14	2.07	0	5	16	3.06	2.89	0	8	0.669
Dry Mouth	47	2.66	3.15	0	9	14	1.14	2.03	0	7	16	0.75	1.34	0	5	0.026
Distress	47	2.06	2.76	0	9	14	1.29	1.98	0	6	16	1.13	1.63	0	5	0.3187
Numbness	47	1.66	2.43	0	10	14	0.64	1.22	0	4	16	1.94	1.48	0	4	0.1974
Remember	47	1.55	2.09	0	8	14	1.57	1.95	0	5	16	1.5	1.55	0	5	0.9942
Sadness	47	1.49	2.55	0	8	14	1.36	1.78	0	5	16	0.63	1.78	0	7	0.4285
Nausea	47	1.45	2.23	0	8	14	0.86	1.88	0	6	16	0.13	0.34	0	1	0.0622
Shortness of Breath	47	0.94	1.83	0	8	14	1.86	2.48	0	9	16	1.69	2.15	0	7	0.2162
Vomiting	47	0.66	1.7	0	7	14	0.21	0.8	0	3	16	0.06	0.25	0	1	0.2611
Module Items																
Sexual Function	44	2.3	3.76	0	10	14	1.93	3.47	0	10	16	1.25	2.27	0	6	0.5823
Concentrating(paying attention)	47	1.87	2.58	0	9	14	1.07	1.54	0	5	16	1.38	1.2	0	3	0.434
Balance/Falling	47	1.74	2.51	0	10	14	0.5	1.09	0	3	16	0.44	0.73	0	2	0.0338
Headache	47	1.6	2.93	0	10	14	0.64	1.28	0	4	16	0.56	0.73	0	2	0.2115
Coughing	47	1.53	2.45	0	10	14	0.79	1.67	0	5	16	2.06	2.86	0	10	0.3579
Dizziness	47	1.34	2.38	0	8	14	1.43	2.34	0	7	16	0.31	0.6	0	2	0.222
Tremors	47	1.21	2.48	0	10	14	0.14	0.36	0	1	16	0.06	0.25	0	1	0.0583
Diarrhea	47	1.21	2.87	0	10	14	0.43	0.85	0	2	16	0.38	0.72	0	2	0.327
Fever/Chills	47	1.19	2.15	0	9	14	0.43	1.34	0	5	16	0.44	0.89	0	3	0.2156
Difficulty speaking	47	1.06	2.17	0	9	14	0.93	2.4	0	9	16	0.63	1.09	0	3	0.7599
Interference Items																

	0–3 Months					3–6 Months					6–12 Months					P-Value (ANOVA)
	N	Mean	Std	Min	Max	N	Mean	Std	Min	Max	N	Mean	Std	Min	Max	
General Activity	45	3.64	3.08	0	10	14	3.07	3.47	0	9	16	1.25	1.88	0	6	0.0251
Enjoyment of Life	45	2.82	3.24	0	10	14	3.07	2.7	0	8	16	1.19	1.52	0	4	0.1142
Walking	44	2.77	2.74	0	9	14	2.43	3.06	0	8	16	1.5	2.1	0	6	0.2736
Work	44	2.66	3.23	0	10	14	3.36	3.27	0	9	16	1.31	1.58	0	4	0.1526
Mood	45	2.4	2.76	0	8	14	2.71	2.89	0	8	16	0.81	1.28	0	4	0.0703
Relations with Others	45	1.49	2.44	0	9	14	2.07	2.76	0	8	16	0.5	1.1	0	4	0.162