



The usefulness and prognostic value of Memorial Symptom Assessment-Short Form and Condensed Memorial Symptom Assessment Scale in assessment of lung cancer patients

Haci Ahmet Bircan¹ · Gonul Seven Yalcin¹ · Sumeyye Fidanci¹ · Adnan Karaibrahimoglu² · Hatice Celik Tuglu¹

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Abstract

Purpose Lung cancer is associated with high level of symptoms and patient-reported symptoms have been rarely used as a prognostic score to predict patients survival.

Methods Frequency and burden of symptoms in lung cancer patients were evaluated before the diagnosis with the Memorial Symptom Assessment-Short Form (MSAS-SF) and Condensed Memorial Symptom Assessment Scale (CMSAS) questionnaires. Performance status, stage of disease, serum albumin, and C-reactive protein (CRP) levels were recorded. Patients were staged according to 8th TNM classification. A survival analysis was applied.

Results The mean age of 116 patients (adenocarcinoma 51, squamous cell 43, non-small cell 5, small cell 17) was 65.2 ± 10.1 (28–87) years. The most common seen physical and psychological symptoms were cough (86.3%), lack of energy (74.3%), dyspnea (70.1%), and feeling sad (61.5%), feeling nervous (61.5%), and worrying (53.8%). Total and subscores of MSAS and CMSAS are significantly higher in M1 disease than M0 disease. All MSAS-SF and CMSAS scores, but not MSAS-PSYCH and CMSAS-PSYCH, positively correlated with age, high serum CRP, white blood cells/neutrophils counts, and TNM stage, and negatively correlated with albumin levels, performance status, and overall survival (OS). Median survival was 77, 195, 370, and 579 days for the four prognostic interquartile groups according to CMSAS-SUM score ($p < 0.0001$).

Conclusion MSAS-SF and CMSAS questionnaires can be useful tool for discriminating metastatic from non-metastatic disease in treatment-naïve patients with lung cancer. Since both questionnaires well correlated with OS and important prognostic factors, they can use to plan palliative care and to help for predicting survival of lung cancer patients.

Keywords Assessment · Lung cancer · Performance status · Prognosis · Questionnaire · Symptoms · TNM stage

Introduction

Lung cancer (LC) is the leading cause of cancer deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of LC [2]. Despite recent advances in treatment options, patient survival has not improved substantially due to lack of commonly expressed molecular targets and effective targeted therapeutics [3].

The histopathological subtypes of tumor and the tumor-node-metastasis (TNM) staging system have been the most important clinicopathological variables for prognosis and treatment [4, 5]. Nowadays, many prognostic models have been used in clinical studies in patients with LC [6–9], mostly generated in the fact that the chronic inflammation is important in tumorigenesis and in inflammatory micro-environment around tumor [10]. Chronic inflammation is also one of the main contributors involved in cancer cachexia which is associated with reduced survival [11–13]. Among the acute phase proteins, albumin is a good indicator of the extent of cachexia and it decreases in cancer patients as negative acute phase reactant, but C-reactive protein (CRP) increases as positive acute phase reactant [14]. The CRP/albumin ratio greater than 0.441 is an independent prognostic factor in patients with SCLC, and is a measurable biomarker in patients with SCLC [9].

✉ Haci Ahmet Bircan
ahbircan@yahoo.com; hacibircan@sdu.edu.tr

¹ Department of Pulmonary Medicine, Suleyman Demirel University Faculty of Medicine, Isparta, Turkey

² Department of Biostatistics and Medical Informatics, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey

LC is associated with high level of symptoms and unmet needs influencing health-related quality of life (HRQoL) of patients [15]. The most common unmet needs are in the domains of health system and information, psychological, and physical and daily living. These needs are influenced by sociodemographic factors such as age, sex, marital status, and income level; and clinical factors such as location of cancer, stage of disease, and tumor size [15]. Therefore, symptom assessment has a critical role in the palliative care of patients with LC. In this context, there are various multidimensional validated tools such as Edmonton Symptom Assessment Scale (ESAS) [16], the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, and the lung cancer-specific module (EORTC QLQ-C30 and QLQ-LC13) [17, 18] or Memorial Symptom Assessment Scale (MSAS) [19]. ESAS quantifies the burden and severity of nine common symptoms and well-being on. Patients are requested to score each of these symptoms on an 11-point visual analog scale. EORTC QLQ-C30 quantifies general aspects of health-related quality of life of patients and QLQ-LC13 comprises lung cancer-associated symptoms (i.e., coughing, haemoptysis, dyspnea, and pain) and side effects from conventional chemotherapy and radiotherapy (i.e., hair loss, neuropathy, sore mouth, and dysphagia). MSAS is also a cancer-related symptom assessment tool which evaluates 32 prevalent physical and psychological symptoms due to cancer and/or its treatment, and offers a complete description of these symptoms with higher scores indicating greater frequency, more severity, and higher distress [19]. To minimize patient burden, the short form of MSAS (MSAS-SF) is designed by Chang et al. [20]. Condensed Memorial Symptom Assessment Scale (CMSAS) includes 14 symptoms (11 physical and three psychological) which some of them also present in the MSAS-SF form and has validation in cancer patients [21]. The EORTC QLQ-C30 and its lung cancer-specific module QLQ-LC13 are the most frequently used instruments in LC patients [22], although there is no consensus on which of these instruments better predicts survival [23].

There is a growing interest for daily clinical use of patient-reported outcomes (PROs) which may improve clinical adverse event monitoring and reporting, and management of patient in combination with clinician scoring systems [22, 24, 25]. Besides that, PROs have an independent prognostic value for survival in LC but it has been rarely included to prognostication of LC patients [22, 25].

In this context, PROs have been rarely evaluated using MSAS and CMSAS questionnaires in Turkish cancer patients with some limitations such as small number of patients and lack of survival analysis [26–28]. In this study, we aimed to identify the usefulness of these instruments in assessing the symptom burden and palliative care needs of Turkish LC patients at the time of diagnosis, and also to assess their correlation with the 8th TNM stage and overall survival.

Materials and methods

We have included 116 patients with newly diagnosed LC to our study between January 2014 and January 2018 in Suleyman Demirel University Practice and Research Hospital, Department of Pulmonary Medicine.

The validity and reliability of MSAS-SF have been established in multiple studies worldwide including Turkey and demonstrated good convergent validity and high variability in the most frequent symptoms in various oncology patients [20, 26–28]. It takes approximately 5 min to be completed by a participant or with the help of a staff. Since educational deficit is still a problem in Turkey, the questionnaires were applied in an interview format at the time of initial presentation while the patients were not aware of either official diagnosis or the stage of the disease. Illiterate or patients with hearing problems were excluded from the study. Patients indicated whether or not they had experienced the symptom in the past week. For each experienced symptom, frequency, severity, and distress of the symptom were rated using a 5-point Likert scale. The symptom experience with higher scores reflects higher symptom burden. Global distress index (MSAS-GDI), physical (MSAS-PHYS), and psychological (MSAS-PSYCH) are 3 subscale scores of MSAS-SF. The global distress index (GDI) measures four psychological (feeling sad, worrying, feeling irritable, and feeling nervous) and six physical symptoms (lack of energy, pain, lack of appetite, feeling drowsy, constipation, and dry mouth). The physical symptom subscale (PHYS) distress score comprises 12 physical symptoms (lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness). The psychological symptom subscale (PSYCH) distress score includes six symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating).

Performance status of patients was determined by a pulmonologist according to the Eastern Cooperative Oncology Group (ECOG) [29]. The diagnostic and staging procedures such as computerized tomography, magnetic resonance imaging and 18-FDG positron emission tomography/computerized tomography, bronchoscopy, and endobronchial ultrasonography and/or surgery were done in our clinic but the therapy planning was done in the oncology department in our or in another center. For analysis, staging images and procedures were reevaluated according to the International Association for the Study of Lung Cancer Report (8th version of TNM staging) [4]. Since patients with oligometastasis (metastasis to only limited number of sites) have generally better prognosis than those with systemic metastatic disease, we defined an oligometastatic disease group which had up to five metastatic foci. Clinical trials have generally included up to 3–5 metastases, although limited number is not universally defined [30, 31].

For survival analyses, the overall survival (OS) was accepted as the length of time from the date of diagnosis to the date of death from any cause. Complete blood count, CRP, and serum chemistry including albumin were collected from routine laboratory tests. Informed consent was obtained from all individual participants included in the study. The study was approved by the local research ethics committee (216/2018).

Statistical analysis

Statistical analyses were performed by SPSS 22.0 for Windows (IBM Inc., Chicago, IL, USA). Descriptive statistics were expressed as frequency (percentage) for categorical and means $\pm$ SD for continuous variables. Correlation analysis was performed by using Spearman's Rho and Pearson correlation coefficients for non-parametric and parametric values, respectively. Pearson pairwise correlation coefficients were calculated among MSAS-SUM and CMSAS-SUM scores and subscores, ECOG scores, and TNM stage and survival. One-way ANOVA test was used to compare scores among patient groups with respect to TNM stages. Kruskal-Wallis test was used to compare scores among patient groups with respect to ECOG performance status. The Kaplan-Meier method was used to estimate the OS of the cases. Cox regression method was used to describe whether CMSAS-SUM and MSAS-SUM may predict the prognosis of patients. A two-sided *p* value less than 0.05 was considered statistically significant for all analyses.

Results

The demographic and clinicopathologic characteristics of the subjects are shown in Table 1. Eighty-six percent of the cohort was male, and the mean age was 65.2 ± 10.1 years (range, 28–87 years). As expected, the majority of patients were current or former smokers (83.6%), with a mean 57.2 ± 29.5 of smoking pack-years (range, 5–150). Patients' performance status ECOG 0–1 found in 74 (63.8%) patients and ECOG 2–4 found in 42 (36.2%) patients while the mean ECOG score was 1.38 ± 1.03 . Of the patients, only 16 (13.8%) had early stage disease (stage 1A–2B), 32 (27.6%) had locally advanced disease (stage 3A–C), and 68 (58.6%) had metastatic disease (stage 4A–B). Of the metastatic patients, 19/68 (27.9%) patients had oligometastatic disease. The detailed staging frequencies are shown in Table 1.

The symptom prevalence and symptom severity are shown in Table 2. The most commonly seen physical symptoms in our patients are cough (86.3%), lack of energy (74.3%), dyspnea (70.1%), weight loss (66.2%), sweats (63.2%), dry mouth (60.2%), and pain (58.5%). The most frequent psychological symptoms were feeling sad (61.5%), feeling nervous (61.5%), and worrying (53.8%). According to histologic

Table 1 Demographic and clinicopathologic characteristics of lung cancer patients

Patient characteristic	<i>n</i> (%)
Male/Female	100/16 (86.2/13.8)
Smoking history	
Never smoker	19 (16.4)
Current Smoker	71 (61.2)
Former smoking	26 (22.4)
Histology	
Adenocarcinoma	51 (44)
Squamous cell carcinoma (SCC)	43 (37.1)
Undifferentiated, non-small cell lung cancer (NSCLC)	5 (4.3)
Small cell lung cancer (SCLC)	17 (14.7)
Performance status, ECOG	
0	20 (17.2)
1	54 (46.6)
2	24 (20.7)
3	13 (11.2)
4	5 (4.3)
cT	
T1	7 (6.0)
T2	30 (25.9)
T3	25 (21.6)
T4	54 (46.5)
cN	
N0	21 (18.1)
N1	10 (8.6)
N2	38 (32.8)
N3	47 (40.5)
Metastatic sites	
Liver	8 (6.9)
Adrenal	16 (13.8)
Bone	34 (29.3)
Brain	13 (11.2)
Lung	21 (18.1)
Pleura	12 (10.3)
TNM stage	
1A/1B	4 (3.4)
2A/2B	12 (10.4)
3A	11 (9.5)
3B	12 (10.4)
3C	9 (7.8)
4A	20 (17.2)
4B	48 (41.4)

ECOG, Eastern Collaboration Oncology Group Performance Status; cT, clinic T status; cN, clinic N status; TNM stage, The International Association for the Study of Lung Cancer (8th version)

subtypes, the most frequent symptoms were cough (94.1%), lack of energy (76.5%), weight loss (76.5%), and dyspnea

Table 2 Symptom frequency and severity of patients evaluated with MSAS-SF and CMSAS questionnaires in order to frequency

MSAS-SF and CMSAS symptoms	Occurrence (%)	Severity among those with and without the symptom (mean $\pm$ SD)	Severity among those with the symptom (mean $\pm$ SD)
Cough	86.3	2.48 $\pm$ 1.41	2.51 $\pm$ 1.21
Lack of energy*	74.3	1.75 $\pm$ 1.45	2.44 $\pm$ 1.03
Dyspnea*	70.1	1.70 $\pm$ 1.49	2.50 $\pm$ 1.13
Weight loss*	66.2	1.59 $\pm$ 1.46	2.40 $\pm$ 1.13
Sweats	63.2	1.46 $\pm$ 1.44	2.32 $\pm$ 1.13
Feeling sad*	61.5	1.36 $\pm$ 1.30	2.22 $\pm$ 0.92
Feeling nervous*	61.5	1.37 $\pm$ 1.32	2.23 $\pm$ 0.96
Feeling irritable	61.5	1.37 $\pm$ 1.32	2.23 $\pm$ 0.96
Dry mouth*	60.2	1.30 $\pm$ 1.39	2.22 $\pm$ 1.11
Pain*	58.5	1.32 $\pm$ 1.42	2.40 $\pm$ 1.12
Worrying *	53.8	1.16 $\pm$ 1.27	2.17 $\pm$ 0.89
Lack of appetite*	50.8	1.23 $\pm$ 1.48	2.44 $\pm$ 1.18
Difficulty sleeping*	49.3	1.05 $\pm$ 1.35	2.42 $\pm$ 1.21
Feeling drowsy*	46.6	1.09 $\pm$ 1.40	2.33 $\pm$ 1.15
Numbness/tingling hands/feet	41.9	0.84 $\pm$ 1.22	2.00 $\pm$ 1.09
Dizziness	37.6	0.77 $\pm$ 1.20	2.09 $\pm$ 1.08
Difficulty in concentration*	37.1	0.72 $\pm$ 1.11	2.02 $\pm$ 0.99
Constipation*	31.6	0.68 $\pm$ 1.13	2.13 $\pm$ 0.99
Difficulty in swallowing	28.2	0.70 $\pm$ 1.27	2.48 $\pm$ 1.12
Difficulty in urination	27.4	0.62 $\pm$ 1.19	2.28 $\pm$ 1.19
Feeling bloated	25.6	0.53 $\pm$ 1.09	2.13 $\pm$ 1.15
Changes in food tastes	23.9	0.48 $\pm$ 1.01	2.07 $\pm$ 1.07
Nausea*	22.2	0.46 $\pm$ 0.87	1.88 $\pm$ 0.88
Itching	17.1	0.32 $\pm$ 0.82	2.00 $\pm$ 0.88
Vomiting	17.1	0.34 $\pm$ 0.86	2.00 $\pm$ 1.02
Hair loss	13.7	0.22 $\pm$ 0.68	1.62 $\pm$ 1.08
Mouth sores	13.7	0.25 $\pm$ 0.69	1.80 $\pm$ 0.83
Changes in skin	13.7	0.25 $\pm$ 0.72	1.88 $\pm$ 0.88
“I do not like myself”	13.7	0.33 $\pm$ 0.95	2.43 $\pm$ 1.20
Diarrhea	12	0.23 $\pm$ 0.75	1.92 $\pm$ 1.20
Swelling of arms or legs	11.3	0.23 $\pm$ 0.78	2.45 $\pm$ 1.03
Problems with sexual interest or activity	7.7	0.21 $\pm$ 0.8	2.77 $\pm$ 1.09

*The symptoms in Condensed MSAS and MSAS-SF

MSAS-SF; Memorial Assessment Scale Short Form Test; CMSAS, Condensed MSAS

(71.6%) in small cell LC (SCLC); cough (84.3%), lack of energy (78.4%), dyspnea (78.4%), and weight loss (72.5%) in adenocarcinoma (AC); and cough (86%), lack of energy (72.1%), dyspnea (62.8%), and weight loss (60.5%) in squamous cell carcinoma (SCC) cases. Mean MSAS-SUM and CMSAS-SUM values were 27.1 ± 13.9 and 16.05 ± 8.5 in SCLC, 31.6 ± 18.5 and 17.6 ± 11.0 in AC, and 27.3 ± 18.6 and 15.4 ± 11.4 in SCC patients, respectively.

Correlations among demographic and radiologic features, laboratory parameters, performance status, TNM stage, overall survival, and the scores of MSAS-SF and CMSAS are shown in Table 3. All MSAS-SF and CMSAS scores, but

not MSAS-PSYCH and CMSAS-PSYCH, were correlated with TNM stage and negatively correlated with ECOG performance status and survival. Physical domains of MSAS-SF and CMSAS were correlated with high serum CRP and low serum albumin levels and also with other important prognostic parameters such as age, serum white blood cell count (WBC), and neutrophil count, but not with smoking cigarettes, tumor diameter, SUVmax, or number of metastatic sites (Table 3).

The mean MSAS-SF scores (MSAS-GDI, global distress index; MSAS-PHYS, physical symptom distress; MSAS-PSYCH, psychological symptom distress; MSAS-SUM; sum MSAS-SF) and mean CMSAS scores (CMSAS-PHYS,

Table 3 Pearson correlation coefficients among performance status, TNM stage, overall survival, and laboratory parameters of the patients and the scores of MSAS-SF and CMSAS

	MSAS-GDI	MSAS-PHYS	MSAS-PSYCH	MSAS-SUM	CMSAS-PHYS	CMSAS-PSYCH	CMSAS-SUM
Age	0.261 $p=0.005$	0.188 $p=0.043$	0.140 $p=0.133$	0.226 $p=0.015$	0.236 $p=0.011$	0.174 $p=0.062$	0.249 $p=0.007$
Smoking	-0.011 $p=0.905$	-0.063 $p=0.511$	-0.031 $p=0.743$	-0.029 $p=0.764$	0.019 $p=0.843$	-0.004 $p=0.968$	0.014 $p=0.879$
Albumin	-0.298 $p=0.001$	-0.351 $p=0.000$	-0.119 $p=0.208$	-0.286 $p=0.002$	-0.340 $p=0.000$	-0.106 $p=0.262$	-0.213 $p=0.001$
WBC	0.201 $p=0.030$	0.227 $p=0.014$	0.013 $p=0.886$	0.184 $p=0.048$	0.264 $p=0.004$	0.053 $p=0.575$	0.234 $p=0.012$
CRP	0.211 $p=0.025$	0.231 $p=0.013$	0.098 $p=0.298$	0.191 $p=0.042$	0.246 $p=0.008$	0.028 $p=0.770$	0.211 $p=0.024$
Neutrophil	0.201 $p=0.031$	0.233 $p=0.012$	0.013 $p=0.893$	0.188 $p=0.043$	0.273 $p=0.003$	0.043 $p=0.647$	0.239 $p=0.010$
ECOG	0.392 $p=0.000$	0.480 $p=0.000$	0.188 $p=0.043$	0.428 $p=0.000$	0.456 $p=0.000$	0.146 $p=0.117$	0.421 $p=0.000$
Tumor diameter	0.068 $p=0.471$	0.045 $p=0.635$	0.080 $p=0.398$	0.064 $p=0.501$	0.068 $p=0.471$	0.020 $p=0.834$	0.063 $p=0.508$
SUVmax	-0.084 $p=0.377$	0.004 $p=0.963$	-0.028 $p=0.773$	0.020 $p=0.837$	0.022 $p=0.821$	-0.071 $p=0.459$	-0.003 $p=0.971$
Number of metastasis	0.080 $p=0.393$	0.183 $p=0.051$	0.034 $p=0.716$	0.121 $p=0.197$	0.136 $p=0.148$	0.015 $p=0.872$	0.117 $p=0.212$
Stage	0.375 $p=0.000$	0.360 $p=0.000$	0.278 $p=0.003$	0.331 $p=0.000$	0.294 $p=0.001$	0.259 $p=0.005$	0.322 $p=0.000$
OS	-0.338 $p=0.000$	-0.356 $p=0.000$	-0.156 $p=0.094$	-0.304 $p=0.001$	-0.371 $p=0.000$	-0.094 $p=0.315$	-0.335 $p=0.000$

CMSAS, Condensed MSAS; CMSAS-PHYS, physical symptom score; CMSAS-PSYCH, psychological symptom score; CMSAS-SUM, sum of CMSAS scores; CRP, C-reactive protein; ECOG, Eastern Collaboration Oncology Group Performance Status; MSAS, Memorial Assessment Scale Test; MSAS-GDI, global distress index; MSAS-SUM, sum MSAS; MSAS-PHYS, physical symptom distress; MSAS-PSYCH, psychological symptom distress; OS, overall survival; WBC, white blood cell

CMSAS-PSYCH and CMSAS-SUM) according to ECOG performance status and metastasis status are shown in Table 4 and Table 5, respectively. All the scores obtained from the domains of questionnaires were gradually increasing according to the ECOG groups, although psychologic domains

did not reach statistical significance (Table 4). Total scores and all the subscores of both MSAS and CMSAS questionnaires were significantly higher in M1 disease than M0 disease. But the scores we found in M1 disease were similar between in subgroups of oligometastatic and diffuse metastatic diseases

Table 4 The descriptive analyses of MSAS and CMSAS scores according to patients' performance status

	ECOG, 0 <i>n</i> , 20	ECOG, 1 <i>n</i> , 54	ECOG, 2 <i>n</i> , 24	ECOG, 3 <i>n</i> , 13	ECOG, 4 <i>n</i> , 5	<i>p</i>
MSAS-GDI	8.94 ± 7.21	11.35 ± 7.82	14.33 ± 7.79	18.61 ± 8.75	22.8 ± 5.49	0.002
MSAS-PHYS	7.36 ± 6.02	9.55 ± 7.78	14.79 ± 8.28	18.30 ± 9.96	26.80 ± 10.64	0.000
MSAS-PSYCH	6.15 ± 6.42	6.75 ± 5.08	7.12 ± 4.73	9.23 ± 6.79	10.40 ± 5.65	Ns
MSAS-SUM	20.31 ± 15.15	25.68 ± 15.06	32.16 ± 16.65	40.46 ± 19.09	54.2 ± 18.59	0.001
CMSAS-PHYS	8.42 ± 6.04	10.05 ± 7.32	14.75 ± 8.57	19.77 ± 10.41	23.8 ± 6.61	0.000
CMSAS-PSYCH	3.26 ± 3.66	3.87 ± 3.20	3.45 ± 3.00	5.07 ± 3.61	5.6 ± 3.84	Ns
CMSAS-SUM	11.68 ± 8.35	13.92 ± 9.30	18.20 ± 10.03	24.84 ± 12.74	29.4 ± 7.76	0.001

CMSAS, Condensed MSAS; CMSAS-PHYS, physical symptom score; CMSAS-PSYCH, psychological symptom score; CMSAS-SUM, sum of CMSAS scores; ECOG: Eastern Collaboration Oncology Group Performance Status; GDI, global distress index; MSAS, Memorial Assessment Scale Test; MSAS-SUM, sum MSAS; MSAS-PHYS, physical symptom distress; MSAS-PSYCH, psychological symptom distress; *p*, Kruskal Wallis test; *ns*, not significant

Table 5 The descriptive analyses of MSAS and CMSAS scores according to metastatic status of patients

	Non-metastatic <i>n</i> , 48	Oligometastatic <i>n</i> , 19	Metastatic <i>n</i> , 49	<i>p</i>
MSAS-GDI	0.94 ± 0.72	1.70 ± 0.87	1.48 ± 0.81	< 0.001
MSAS-PHYS	0.71 ± 0.61	1.26 ± 0.80	1.19 ± 0.80	0.002
MSAS-PSYCH	0.92 ± 0.94	1.65 ± 0.80	1.27 ± 0.84	0.008
MSAS-SUM	0.72 ± 0.54	1.11 ± 0.56	1.01 ± 0.50	0.007
CMSAS-PHYS	0.89 ± 0.75	1.37 ± 0.85	1.29 ± 0.76	0.017
CMSAS-PSYCH	0.99 ± 1.13	1.80 ± 1.07	1.40 ± 1.00	0.016
CMSAS-SUM	0.91 ± 0.72	1.46 ± 0.82	1.31 ± 0.70	0.006

CMSAS, Condensed MSAS; CMSAS-PHYS, physical symptom score; CMSAS-PSYCH, psychological symptom score; CMSAS-SUM, sum of CMSAS scores; MSAS, Memorial Assessment Scale Test; MSAS-GDI, global distress index; MSAS-SUM, sum MSAS; MSAS-PHYS, physical symptom distress; MSAS-PSYCH, psychological symptom distress

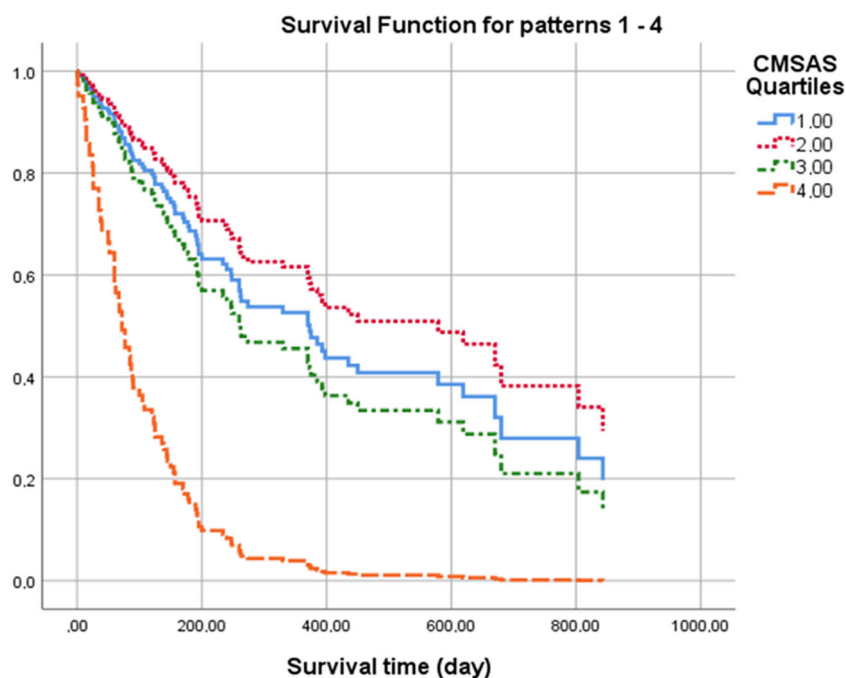
(Table 5). Although it is not significant, the OS time differed by histologic subtypes for LCs (SCC, 369.9 ± 339.6 days; AC, 272.1 ± 280.6 days; and SCLC, 189.1 ± 193.2 days). According to the TNM stage, OS was 211.7 ± 233.7 in M1 disease, 389.4 ± 339.8 in locally advanced disease, and 492.8 ± 321.7 in early stage disease ($p < 0.0001$).

To determine whether MSAS-SUM and CMSAS-SUM scores are associated with prognosis, we performed a multivariate Cox regression analysis where MSAS-SUM and CMSAS-SUM scores, serum WBC, neutrophil counts, serum CRP and albumin levels, ECOG performance status, TNM stage, SUVmax, and number of metastatic sites were included. Serum albumin level, ECOG performance status, and TNM stage were found as independent prognostic factors, but MSAS-SUM and CMSAS-SUM scores were not. Breaking MSAS-SUM and CMSAS-SUM by quartile of symptom

burden based on scoring showed us a significant negative correlation between survival and CMSAS-SUM. We found that estimated median survival time was graded as 77, 195, 370, and 579 days for the quartiles of symptom burden based on CMSAS-SUM scoring ($p < 0.0001$), indicating OS was much worse in patients with high symptom burden than low symptom burden (Fig. 1).

Discussion

LC is associated with high level of symptoms which may result from local effects of the tumor, from regional or distant spread, or from distant effects not related to metastases (paraneoplastic syndromes) [32, 33], but tumor specific treatments such as chemotherapy/radiotherapy, or some comorbidities of patients,

Fig. 1 Kaplan-Meier curves of overall survival (OS) for patients with lung cancer according to CMSAS prognostic groups

may also create certain symptoms [23, 34]. These symptoms occur from unmet needs influencing HRQoL of patients. Therefore, symptom assessment has a critical role in assessing the palliative care needs of patients with LC. Understanding of the baseline symptom burden is reasonably useful especially to separate disease-related symptoms from future potential treatment-related toxicities [34]. In this study, symptom assessment was performed prior to the initiation of any treatment and therefore, the symptoms that the patients experienced were related to cancer itself rather than the anticancer treatment.

There are a few studies which evaluate the baseline symptoms of LC in Turkish patients, but none of them include OS or other prognostic data [26–28, 35], excluding national multicenter project which includes 299 advanced LC patients [23].

In this study, the population studied was primarily elderly male. This result is concordant with previous two studies showing that LC among women in Turkey was reported as 9.6% and 11.3% [35, 36]. This may due to the rating of smoking cigarette among women is not as common as among men, almost half of men (43.8%) and 11.6% of women were current daily smokers [37].

Our study showed that high frequency of patients with LC is symptomatic at presentation. The symptoms experienced by our patients were quite similar to what were found in previous studies [20, 26, 28]. The most common physical symptoms were coughing, lack of energy, dyspnea, weight loss, and sweating while the psychological symptoms were feeling sad, feeling nervous, worrying, and difficulty sleeping. The study done by Bulbul et al. evaluated the symptoms of 1215 LC patients (88.7% males and 11.3% females) with ESAS from 26 different centers in Turkey and showed that the most commonly seen four symptoms were tiredness (82.1%), dyspnea (69.3%), appetite loss (65.7%), and pain (65.4%) [35].

Our study includes both SCLC and NSCLC histology in all stages of disease and according to histologic subtypes, symptom variety or symptom burden was found similar in NSCLC and SCLC patients. Dyspnea was the most frequently seen symptom in adenocarcinoma whereas cough was the most commonly seen in SCLC and SCC. According to Mendoza et al. the most severe pain and shortness of breath were reported by patients with SCLC whereas worse lack of appetite was reported by patients with SCC compared with the other cancer groups [34].

Symptom burden evaluated with MSAS and CMSAS questionnaires is associated with TNM stage and prognosis, consistent with previous studies [20, 26]. It is possible that a multitude of other factors may also contribute to prognosis such as comorbid conditions. Although we did not evaluate the effect of comorbid conditions on PROs or survival, there are contradictive reports about the presence of any comorbidity was a predictor of worse survival [23, 34, 38].

This study clearly demonstrated that MSAS-SF and CMSAS questionnaires are useful tool especially in

differentiating M1 disease among LC patients. The descriptive analyses of MSAS and CMSAS scores showed that patients with metastatic disease have higher levels of total symptom score and symptom subscores of MSAS and CMSAS, as similar with previous studies [20, 26, 28]. To the best of our knowledge, this is the first study to evaluate symptom burden difference between systemic metastatic and oligometastatic disease and showed no difference, possibly due to either having small number of patients in both groups or doing this evaluation before any treatment. It is known that patients with oligometastasis may have improved survival after completion of aggressive treatment to both primary tumor and to metastatic focuses [30, 33].

In general, PROs have been found to be significant predictors of clinical outcomes such as OS, but the effect of demographic and clinical factors on the prognostic ability of PROs is less understood [39]. Our study showed that LC patients not only have physical symptoms, but also have high psychological symptom burden related to the negative emotional state that develops in the patient if he/she was under evaluation for cancer. The total and subscores, excluding psychological subscores, of CMSAS and MSAS-SF questionnaires are well correlated with ECOG performance status and TNM stage. This may be related to the fact that physical symptoms are often more reflective of the underlying disease burden than psychological symptoms [16].

Malnutrition and cachexia in cancer patients are significant problems due to a variety of mechanisms involving the tumor, the host response to the tumor, and anticancer therapies [40]. Serum albumin is used as a marker for estimating visceral protein function; in the advanced stage of cancer, malnutrition and inflammation suppress albumin synthesis [41]. Low serum albumin has been associated with not only inflammation but also worse response to cisplatin-based chemotherapy in patients with advanced NSCLC [42, 43]. Consistent with the previous studies, in this study, low serum albumin and high serum CRP remained their roles as independent prognostic markers [6, 42, 44, 45]. Beside this, our study showed that physical domain and total scores of CMSAS and MSAS-SF questionnaires were weakly but significantly correlated with hypoalbuminemia and high levels of CRP, WBC, and neutrophil counts. Our findings supported the literature that suggests a positive relationship between inflammatory markers, HRQoL, and PROs in cancer patients [46, 47]. In a mesothelioma study, it has been found a positive relationship between the inflammatory markers, in particular neutrophil-lymphocyte ratio (NLR), CRP and vascular endothelial growth factor (VEGF), and patient's systemic symptoms of anorexia and fatigue and the summation items [47]. In another study, done with NSCLC patients, elevated pro-inflammatory cytokines such as serum soluble receptor 1 for tumor necrosis factor (sTNF-R1) were found to be associated with a significant worsening of symptoms [46].

In this study, both MSAS-SF and CMSAS scores were negatively correlated with OS in LC patients. Our study confirmed previous studies that patients with high symptom burden have much shorter OS than patients with low symptom burden according to CMSAS questionnaire. We showed a statistically difference in median survivals of these quartile prognostic groups 579, 370, 195, and 77 days, respectively. We suggest that CMSAS–SUM score may be used to predict OS in LC patients. Similar study done in advanced cancers (28% LC) using patient-reported MSAS-SF questionnaire showed a statistically significant difference in median survivals according to these prognostic groups [24].

We have certain limitations to the present study. First, although all histologic subtypes in all stage groups were included in our study, the sample size of groups was relatively small which may create a bias in the results. Patients with different tumor biology might have different symptoms. But the distribution of patients according to histologic subtypes was not strong enough to have any conclusion about the usage of these questionnaires to explore the difference in symptomatology of patients. Besides, symptom burden might be independently predictive of outcome if all patients were in the same stage. A greater number of patients in all histologic subtypes are required in future studies. Second, this study was performed in a single center. To provide more representative results and validation of our study, a multicenter study should be performed. Third, we have no data about our patients' oncological treatment and treatment responses. So, we could not define any change in the symptom burden or HRQoL with consecutive tests in the same patient (test-retest). But internal consistency and test-retest reliability of MSAS questionnaire were previously done and have been determined a valid and reliable instrument for the use of comprehensive symptom assessment in planning palliative care cancer patients [26, 27, 48]. Future prospective in large-scale studies is needed to evaluate the usefulness of MSAS and CMSAS questionnaires in the assessment of treatment response to different treatment modalities in patients with all types of LC.

As a conclusion, patients with LC have high amount of distress and symptom burden which constitutes supportive care needs. MSAS-SF and its condensed form CMSAS questionnaires have key roles as a prognostic tool for either discriminating metastatic disease from non-metastatic disease in diagnosis period or doing symptom management and optimal treatment plans for patients because higher symptom burden correlates with shortened survival, which may in fact be a result of their correlation with stage.

Authorship and contribution HAB: designed the study, collected patients, collected and analyzed the data, and wrote the manuscript; AK: performed statistical analyzing the data; GSY, HCT, and SF: collected the patients, performed the

questionnaires, and collected the data. All listed authors read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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