Simplified Graded Baseline Symptom Assessment in Patients With Lung Cancer Undergoing First-Line Chemotherapy: Correlations and Prognostic Role in a Resource-Constrained Setting

abstract

Purpose There are limited data from developing countries on graded baseline symptom (BS) assessment in lung cancer. This prospective study aimed to assess the prognostic role of BS and correlation of BS with comorbidity, demographic, and investigation profiles in a cohort of 238 patients with lung cancer undergoing first-line chemotherapy over a 15-month period.

Methods The Medical Research Council (MRC) scale was used to assess dyspnea, whereas the visual analog scale (VAS; score of 1 to 10) was used to assess anorexia, fatigue, chest pain, and cough. Weight loss (WL) was noted as percentage of pre-illness baseline. All patients received histology-guided platinum doublet chemotherapy. Outcomes assessed were overall survival (OS) and radiologic responses by RECIST.

Results Significant correlations (Spearman ρ) were noted for fatigue and anorexia with all other BSs. Dyspnea differed significantly among groups on the basis of either the simplified comorbidity score or Charlson comorbidity index. Median OS was 287 days (95% CI, 232 to 342 days). OS was significantly higher for anorexia VAS score less than 4 (388 *v* 229 days for VAS score ≥ 4), fatigue VAS score less than 3 (388 *v* 213 days for VAS score ≥ 3), WL less than 5% (410 *v* 259 days for WL ≥ 5%), and MRC dyspnea grade less than 3 (377 *v* 187 days for MRC grade ≥ 3). On univariable Cox proportional hazards analysis, worse OS was noted for all BSs, stage, and performance status, but on multivariable analysis, only fatigue (hazard ratio [HR], 1.21), Eastern Cooperative Oncology Group performance status ≥ 2 (HR, 1.57), and stage IV disease (HR, 1.61) were significant. Nonresponders (stable disease and progressive disease [PD]) had a higher percentage of WL and higher mean VAS scores for cough, chest pain, anorexia, and fatigue. On multivariable logistic regression analysis, PD was associated with fatigue and percentage of WL.

Conclusion BSs are prognostic for patients with lung cancer on first-line chemotherapy. Fatigue is prognostic for worse OS and PD. Comorbidity and investigation profiles do not correlate with either OS or response rates.

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Authors' disclosures of potential conflicts of interest and contributions are found at the end of this article.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths globally. A majority of the patients present with advanced or metastatic disease (stages IIIB to IV) and are managed primarily nonsurgically, with histology-guided platinum doublet chemotherapy being the mainstay for those with good performance status (PS).[1,2] The search for predictive and prognostic biomarkers that can help improve the efficacy of chemotherapy while simultaneously minimizing toxicity continues even as the world moves into an era of precision medicine characterized by increasing development and use of molecularly targeted therapies.[3,4] We have recently published an article on the prognostic role of comorbidity as assessed by the Charlson comorbidity index (CCI) and simplified comorbidity score (SCS) on clinical outcomes (toxicity, objective response rates, and overall survival [OS]) in a prospective cohort of patients with newly diagnosed lung cancer undergoing chemotherapy at a tertiary care center in North India.[5] Herein, we describe the correlations

of graded baseline symptom (BS) assessment with baseline investigations and comorbidity as well as the prognostic role of BSs in this cohort.

METHODS

Our prospective cohort included 238 newly diagnosed patients with cytologically or histopathologically proven lung cancer who were initiated on chemotherapy at the authors' institute from January 2012 to March 2013. Demographic variable assessment, comorbidity assessment by CCI and SCS, chemotherapy protocols, outcome assessments, and statistical methods have been previously described in detail in the primary publication on this cohort,[5] as well as in other recent publications.[1,6-10] These details are briefly summarized here.

Symptom Assessment

The Medical Research Council (MRC) scale[11] was used to assess dyspnea, whereas the visual analog scale (VAS; score from 1 to 10) was used to assess anorexia, fatigue, chest pain, and cough. Patients were asked to mark the severity of each of these symptoms on a scale of 1 to 10 before initiation of chemotherapy. Weight loss (WL) was noted as a percentage of pre-illness baseline (%WL) and also in absolute terms.

Comorbidity Assessment

Comorbidity assessment was done using both CCI and SCS.[12,13] For SCS, patients were grouped as having an SCS score of 9 or lower or greater than 9 (173 and 65 patients, respectively). For the CCI, 88 patients had a score of 0, 97 had a score of 1, and 53 had a score of ≥ 2.

Fig 1 –
Bar diagrams showing distribution of the following baseline symptoms in the patient population as assessed by visual analog scale (VAS): (A) fatigue, (B) anorexia, (C) chest pain, and (D) cough. Horizontal axis represents the absolute value of VAS from 1 to 10 cm, whereas vertical axis represents the percentage of patients with each value.
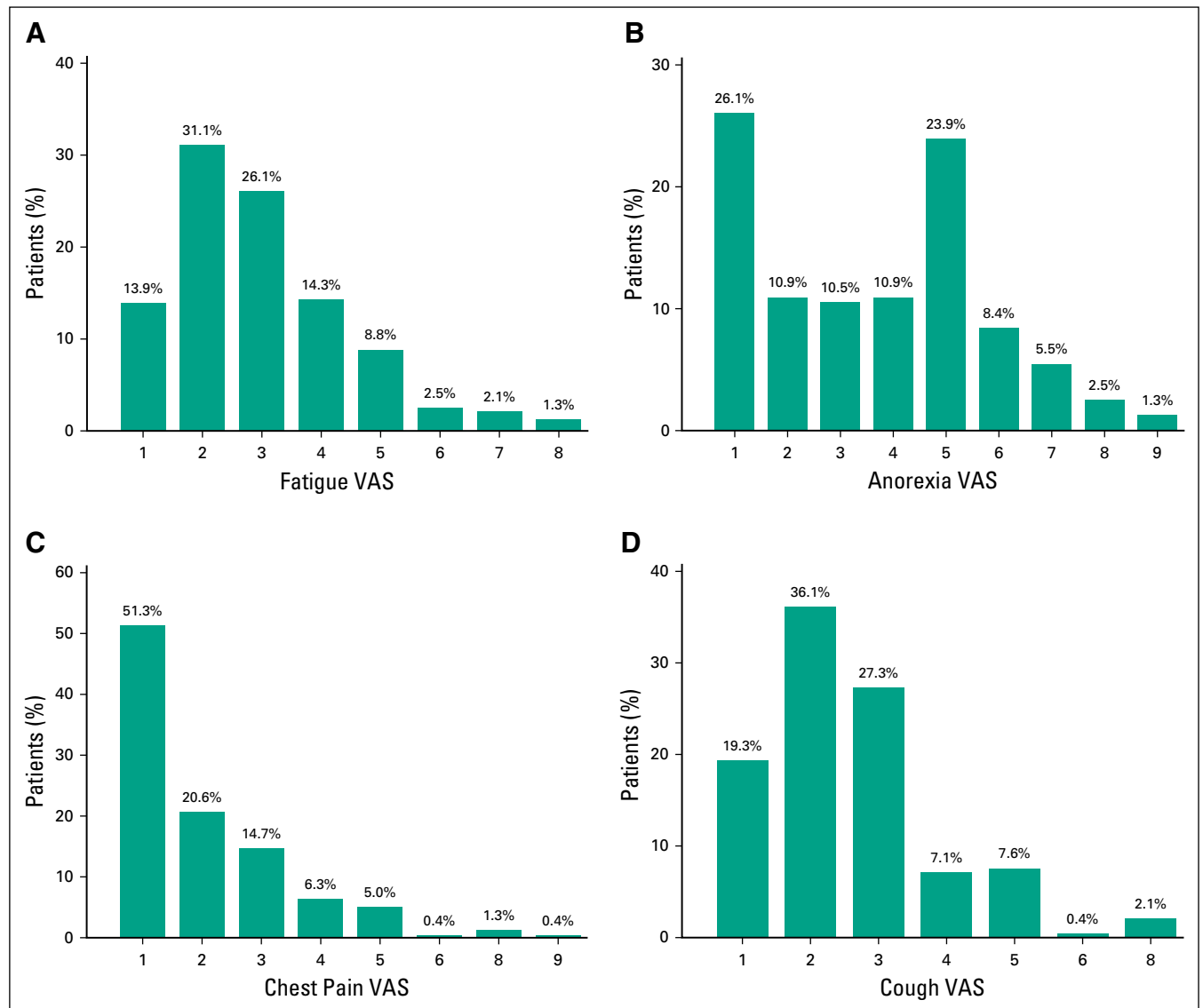
Histologic Classification, Staging, and Management Protocols

Tumors were histologically classified on the basis of morphology and, if needed, relevant immuno-chemistry using the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification of lung tumors.[14] Staging was done using the seventh edition of the TNM classification on the basis of tumor size and extension (T), lymph nodal involvement (N), and presence of distant metastasis (M).[15] Before treatment initiation, demographic and clinical characteristics (including age, sex, Karnofsky and Eastern Cooperative Oncology Group [ECOG] PS, and body mass index), histology, disease stage, and quantified smoking status were noted for all patients. All patients received standard histology-guided platinum doublets, with pemetrexed, docetaxel, and irinotecan being the preferred nonplatinum compounds for nonsquamous non–small-cell lung cancer, squamous cell lung carcinoma, and small-cell lung cancer, respectively.[2,16] Tumor response assessment was done using RECIST.[17] OS was calculated in days from date of initiation of chemotherapy to date of death or last follow-up, as applicable. Informed consent was acquired from all patients, and the study was cleared by the institutional ethics committee.

Statistical Analysis

Data were analyzed using SPSS statistical software (version 22.0; SPSS, Chicago, IL). Descriptive data are presented as means with standard deviations (SDs), medians with interquartile ranges (IQRs), or percentages. Comparison between the groups was done using the χ^2 or Fisher's exact test (for categorical variables), unpaired t test (for continuous

Table 1 – Correlation of Baseline Symptoms, Investigation Profile, and Comorbidity Assessed by SCS and CCI

| Symptom | Spearman Correlation Coefficient (P) | | | | | |
	% Weight Loss	Anorexia	Fatigue	SCS	CCI	Age
% Weight loss	—	0.495 (< .001)	0.310 (< .001)	0.114 (.080)	0.019 (.775)	−0.036 (.577)
Anorexia	0.495 (< .001)	—	0.603 (< .001)	0.148 (.022)	0.075 (.247)	−0.085 (.192)
Fatigue	0.310 (< .001)	0.603 (< .001)	—	0.107 (.098)	−0.017 (.795)	−0.142 (.029)
Dyspnea	0.102 (.116)	0.343 (< .001)	0.327 (< .001)	0.161 (.013)	0.225 (< .001)	0.013 (.837)
Cough	0.166 (.010)	0.256 (< .001)	0.363 (< .001)	0.094 (.148)	0.170 (.009)	−0.027 (.677)
Chest pain	0.211 (.001)	0.301 (< .001)	0.333 (< .001)	0.058 (.375)	−0.028 (.669)	−0.123 (.058)
Hemoglobin	−0.170 (.008)	−0.133 (.041)	−0.006 (.929)	−0.154 (.017)	−0.048 (.460)	−0.060 (.357)
Protein	−0.083 (.205)	−0.068 (.297)	0.018 (.787)	−0.088 (.177)	−0.015 (.817)	0.068 (.300)
Albumin	−0.093 (.154)	−0.081 (.217)	−0.146 (.026)	−0.058 (.380)	−0.035 (.594)	−0.006 (.925)
HbA1c	0.055 (.540)	0.030 (.738)	0.093 (.295)	0.455 (< .001)	0.456 (< .001)	−0.053 (.551)
FVC%	−0.191 (.017)	−0.275 (.001)	−0.324 (< .001)	−0.005 (.956)	−0.238 (.003)	0.154 (.057)
FEV$_1$%	−0.208 (.010)	−0.313 (< .001)	−0.262 (.001)	−0.152 (.059)	−0.387 (< .001)	0.033 (.682)
SCS	0.114 (.080)	0.148 (.022)	0.107 (.098)	—	0.474 (< .001)	0.293 (< .001)
CCI	0.019 (.775)	0.075 (.247)	−0.017 (.795)	0.474 (< .001)	—	0.205 (.001)
Age	−0.036 (.577)	−0.085 (.192)	−0.142 (.029)	0.293 (< .001)	0.205 (.001)	—
BMI	−0.463 (< .001)	−0.250 (< .001)	−0.139 (.032)	−0.056 (.390)	0.053 (.416)	0.038 (.560)
TNM stage	−0.009 (.894)	0.053 (.413)	0.023 (.727)	−0.103 (.112)	0.103 (.113)	−0.120 (.065)
T stage	0.135 (.039)	0.025 (.702)	0.136 (.038)	0.027 (.683)	0.067 (.308)	−0.127 (.052)
N stage	0.020 (.755)	0.135 (.038)	0.097 (.134)	0.039 (.552)	0.081 (.213)	−0.138 (.033)
M stage	−0.071 (.275)	0.016 (.809)	−0.008 (.904)	−0.092 (.157)	0.070 (.281)	−0.092 (.155)
Smoking index	0.015 (.839)	0.156 (.029)	0.096 (.183)	0.344 (< .001)	0.091 (.206)	0.214 (.003)
KPS	−0.264 (< .001)	−0.444 (< .001)	−0.391 (< .001)	−0.078 (.233)	−0.103 (.111)	−0.020 (.755)
ECOG PS	0.249 (< .001)	0.403 (< .001)	0.374 (< .001)	0.053 (.413)	0.078 (.229)	0.002 (.978)

NOTE. A visual analog scale of 1 to 10 was used for anorexia, fatigue, cough, and chest pain.
Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ECOG PS, Eastern Cooperative Oncology Group performance status; FEV$_1$%, forced expiratory volume in 1 second as percentage of predicted; FVC%, forced vital capacity as percentage of predicted; HbA1c, hemoglobin A1c; KPS, Karnofsky performance status; SCS, simplified comorbidity score.

variables in two groups), or one-way analysis of variance for continuous variables with three or more groups. Correlations were assessed using Spearman correlation coefficient (ρ). On the basis of the values of the correlation coefficient (ρ), the correlation was considered very weak (0.001 to 0.199), weak (0.200 to 0.399), moderate (0.400 to 0.599), strong (0.600 to 0.799), or very strong (0.800 to 1.00). Survival probability and median OS were calculated using the Kaplan-Meier method, and group differences were analyzed using the log-rank test. Factors affecting OS were assessed using Cox proportional hazards regression analysis and calculation of hazard ratio (HR) with 95% CI. Logistic regression analysis was performed for factors associated with radiologic responses and calculation of odds ratio (OR) with 95% CI. For all analyses, $P <$ .05 was considered significant.

Table 2 – Baseline Symptom and Investigation Profile Among Patients With Lung Cancer Grouped on the Basis of SCS and CCI

| Symptom or Measure | SCS | | | CCI | | | |
	SCS ≤ 9 (n = 173)	SCS > 9 (n = 65)	*P*	CCI = 0 (n = 88)	CCI = 1 (n = 97)	CCI ≥ 2 (n = 53)	*P*
Weight loss, kg	4.1 (3.4)	4.2 (3.2)	.565	4.0 (3.1)	4.3 (3.7)	4.1 (3.1)	.754
Weight loss, %	7.0 (5.8)	7.3 (4.8)	.261	7.0 (5.5)	7.1 (5.8)	7.2 (5.3)	.977
Hemoptysis, No. of patients (%)	77 (44.5)	27 (41.5)	.681	31 (35.2)	47 (48.5)	26 (49.1)	.130
MRC dyspnea grade, No. of patients (%)			.114				.025
1	37 (21.4)	12 (18.5)		27 (30.7)	16 (16.5)	6 (11.3)	
2	61 (35.3)	21 (32.3)		30 (34.1)	37 (38.1)	15 (28.3)	
3	48 (27.7)	13 (20.0)	.417*	20 (22.7)	25 (25.8)	16 (30.2)	.015*
4-5	27 (15.6)	19 (29.2)	.018†	11 (12.5)	19 (19.6)	16 (30.2)	.036†
Cough, VAS	2.5 (1.3)	2.7 (1.6)	.527	2.3 (1.3)	2.7 (1.4)	2.8 (1.4)	.073
Chest pain, VAS	2.0 (1.5)	2.1 (1.3)	.529	2.2 (1.5)	1.8 (1.3)	2.3 (1.6)	.101
Anorexia, VAS	3.5 (2.1)	4.1 (2.2)	.059	3.3 (2.2)	3.9 (2.1)	3.7 (2.2)	.244
Fatigue, VAS	2.9 (1.4)	3.2 (1.6)	.153	2.9 (1.3)	2.9 (1.6)	3.0 (1.6)	.936
Hemoglobin, g/dL	12.3 (1.7)	11.7 (1.5)	.004	12.1 (1.8)	12.1 (1.7)	12.0 (1.4)	.912
TLC, $10^3/\mu$L	9.9 (3.4)	10.2 (3.0)	.135	10.2 (4.0)	9.7 (2.6)	10.3 (3.2)	.521
ANC, $10^3/\mu$L	7.0 (3.0)	7.3 (2.8)	.224	7.2 (3.4)	6.8 (2.4)	7.3 (3.0)	.627
Platelet count, $10^5/\mu$L	3.1 (1.2)	2.8 (1.1)	.159	3.0 (1.3)	3.1 (1.1)	3.0 (1.0)	.833
Urea, mg/dL	24.8 (7.9)	35.1 (14.4)	< .001	26.5 (10.3)	26.4 (10.8)	31.7 (12.0)	.009
Creatinine, mg/dL	0.8 (0.2)	1.1 (0.5)	< .001	0.8 (0.2)	0.9 (0.3)	1.0 (0.6)	.002
Uric acid, mg/dL	4.6 (1.2)	5.0 (1.5)	.047	4.7 (1.3)	4.8 (1.2)	4.7 (1.5)	.722
Calcium, mg/dL	9.1 (1.0)	9.2 (1.2)	.674	9.1 (1.0)	9.2 (0.9)	9.1 (1.3)	.821
Phosphorus, mg/dL	3.6 (0.7)	3.8 (0.9)	.257	3.6 (0.8)	3.7 (0.8)	3.7 (0.8)	.736
Bilirubin, mg/dL	0.7 (0.4)	0.6 (0.2)	.312	0.7 (0.3)	0.7 (0.5)	0.6 (0.2)	.365
AST, IU/L	31.6 (20.8)	34.8 (24.1)	.294	30.8 (16.2)	32.7 (23.2)	34.8 (26.7)	.580
ALT, IU/L	35.8 (37.6)	33.5 (24.7)	.950	34.4 (21.8)	35.6 (40.8)	35.5 (39.4)	.970
ALP, IU/L	139.4 (97.0)	136.9 (86.9)	.400	131.4 (64.7)	139.3 (84.9)	149.5 (140.8)	.543
Protein, g/dL	7.3 (0.7)	7.3 (0.7)	.472	7.3 (0.7)	7.3 (0.7)	7.3 (0.7)	.908
Albumin, g/dL	3.8 (0.5)	3.8 (0.5)	.453	3.8 (0.6)	3.9 (0.5)	3.7 (0.5)	.127
Fasting BS, mg/dL	94.8 (13.0)	99.6 (22.0)	.367	94.8 (12.2)	94.4 (13.9)	100.3 (21.8)	.103
PPBS, mg/dL	135.7 (30.5)	164.8 (60.9)	.017	131.9 (30.2)	145.8 (37.9)	154.9 (58.0)	.107
HbA1C, %	6.0 (0.6)	7.0 (1.4)	< .001	5.9 (0.5)	6.3 (1.2)	6.9 (1.0)	< .001

NOTE. Values are expressed as mean (SD) unless otherwise indicated.
Abbreviations: ALP, alkaline phosphatase; ANC, absolute neutrophil count; BS, blood sugar; CCI, Charlson comorbidity index; HbA1c, hemoglobin A1c; MRC, Medical Research Council; PPBS, postprandial blood sugar; SCS, simplified comorbidity score; SD, standard deviation; TLC, total leukocyte count; VAS, visual analog scale (score of 1 to 10).
*For comparison of grades 3 to 5 versus grades 1 to 2.
†For comparison of grades 4 to 5 versus grades 1 to 3.

RESULTS

The distribution of VAS scores for anorexia, fatigue, cough, and chest pain at baseline is shown in Figure 1. For dyspnea, the distribution was as follows: MRC grade 1, n = 49 (20.6%); grade 2, n = 82 (34.5%); grade 3, n = 61 (25.6%); grade 4, n = 38 (16.0%); and grade 5, n = 8 (3.4%). At baseline, the mean weight was 58.8 kg (SD, 11.1 kg); mean and median WL were 4.2 kg (SD, 3.4 kg) and 3.8 kg (IQR, 2 to 5 kg), respectively, corresponding to mean and median %WL of 7.1% (SD, 5.5%) and 6% (IQR, 3.8% to 9.7%), respectively. Mean and median time for WL was 4.1 months (SD, 3.9 months) and 3 months (IQR, 2 to 5 months), respectively. Hemoptysis, another relevant pulmonary symptom, was present in 104 patients (43.7%).

Correlation of BSs, investigation profile, and comorbidity is shown in Table 1. Strong correlation was noted between fatigue and anorexia ($\rho = 0.603$; $P < .001$), whereas moderate correlations were observed between anorexia and %WL ($\rho = 0.495$; $P < .001$), between BMI and

%WL ($\rho = -0.463$; $P < .001$), and between CCI and SCS ($\rho = 0.474$; $P < .001$). Anorexia also correlated moderately with both PS systems (Karnofsky PS: $\rho = -0.444$; $P < .001$; ECOG PS: $\rho = 0.403$; $P < .001$). Spirometric parameters (forced vital capacity and forced expiratory volume in 1 second) had a moderate and inverse correlation with dyspnea (ρ for percent forced vital capacity $= -0.473$; $P < .001$; ρ for percent forced expiratory volume in 1 second $= -0.511$; $P < .001$). Glycated hemoglobin (hemoglobin A1c) showed moderate correlation with both measures of comorbidity (SCS: $\rho = 0.455$; $P < .001$; CCI: $\rho = 0.456$; $P < .001$). Interestingly, age did not show either moderate or strong correlation with any of the variables tested (including comorbidity), and the highest value observed among all its correlation coefficients was that with SCS ($\rho = 0.293$; $P < .001$). All of the other correlations listed in Table 1 were either nonsignificant or weak to very weak.

BS and investigation profile values among patients grouped on the basis of SCS and CCI are listed in Table 2. The group with an SCS of greater than 9,

Table 3 – Baseline Symptom and Investigation Profile Among Patients With Lung Cancer Grouped on the Basis of Radiologic Response

Symptom or Measure	CR+PR (n = 99)	SD+PD (n = 63)	P	CR+PR+SD (n = 143)	PD (n = 19)	P
Weight loss, kg	3.6 (3.2)	4.4 (3.0)	.031	3.6 (2.9)	5.9 (4.0)	.007
Weight Loss, %	6.1 (5.4)	7.4 (4.8)	.033	6.1 (5.0)	10.4 (5.6)	.001
Hemoptysis, No. of patients (%)	45 (45.5)	28 (44.4)	.900	61 (61.6)	12 (63.2)	.139
MRC dyspnea grade, No. of patients, %			.898			
1	22 (22.2)	17 (27.0)		33 (23.1)	06 (31.6)	
2	38 (38.4)	24 (38.1)		58 (40.6)	04 (21.1)	
3	24 (24.2)	14 (22.2)	.567*	34 (23.8)	04 (21.1)	.352*
4-5	15 (15.2)	08 (12.7)	.663†	18 (12.6)	05 (26.3)	
Cough, VAS	2.4 (1.1)	3.0 (1.8)	.041	2.5 (1.3)	3.4 (1.9)	.022
Chest pain, VAS	1.8 (1.2)	2.4 (1.6)	.018	1.9 (1.3)	2.8 (1.8)	.007
Anorexia, VAS	3.1 (1.9)	3.9 (2.3)	.026	3.3 (2.1)	4.0 (2.3)	.139
Fatigue, VAS	2.5 (1.3)	3.0 (1.4)	.044	2.6 (1.2)	3.7 (1.8)	.004
Hemoglobin, g/dL	12.4 (1.6)	11.8 (1.8)	.033	12.2 (1.6)	11.6 (2.1)	.072
Albumin, g/dL	3.8 (0.5)	3.8 (0.6)	.404	3.8 (0.5)	3.7 (0.6)	.243
Fasting BS, mg/dL	96.2 (15.6)	95.0 (13.4)	.838	96.3 (15.0)	91.2 (11.2)	.203
PPBS, mg/dL	143.9 (36.5)	141.8 (44.1)	.601	145.4 (40.5)	124.3 (25.9)	.081
HbA1c, %	6.2 (0.9)	6.5 (1.3)	.171	6.4 (1.1)	6.0 (0.4)	.309
FVC%	74.2 (20.1)	73.7 (23.3)	.937	75.0 (21.8)	67.3 (16.4)	.208
FEV$_1$%	65.1 (20.3)	65.2 (21.5)	.745	65.5 (21.1)	62.5 (17.9)	.699

NOTE. Values are expressed as mean (SD) unless otherwise indicated.

Abbreviations: BS, blood sugar; CR, complete response; FEV$_1$%, forced expiratory volume in 1 second as percentage of predicted; FVC%, forced vital capacity as percentage of predicted; HbA1c, hemoglobin A1c; MRC, Medical Research Council; PD, progressive disease; PPBS, postprandial blood sugar; PR, partial response; SD, stable disease; VAS, visual analog scale (score of 1 to 10).

*For comparison of grades 3 to 5 versus grades 1 to 2.

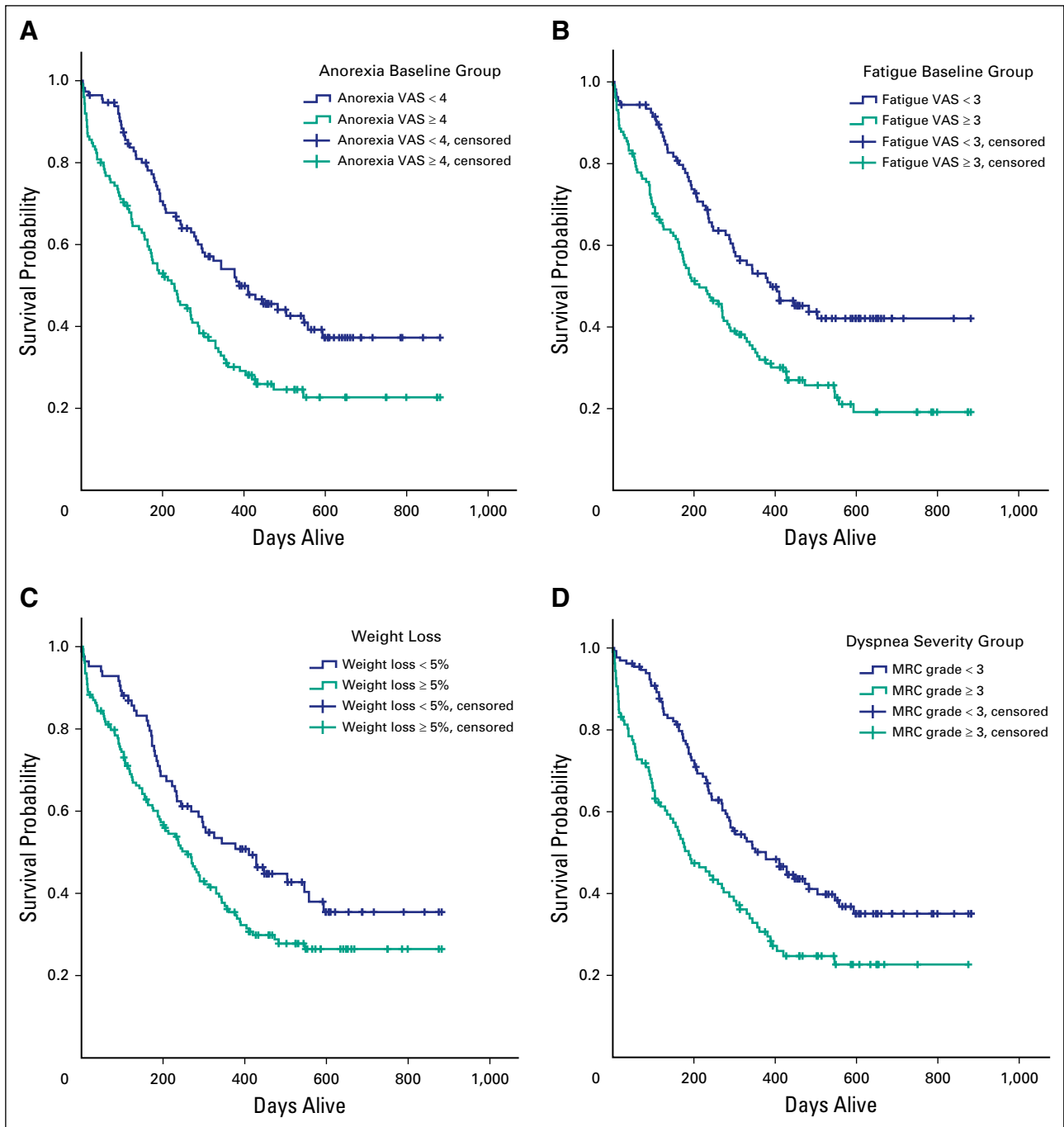†For comparison of grades 4 to 5 versus grades 1 to 3.

Fig 2 –
Probability of overall survival (OS) for patients grouped on the basis of baseline symptoms (anorexia visual analog scale [VAS], fatigue VAS, percent weight loss, and dyspnea Medical Research Council [MRC] grade; Kaplan-Meier analysis). Patients with lower symptom scores had significantly better

compared with an SCS of 9 or lower, had a higher prevalence of grade 4 or 5 dyspnea, lower hemoglobin values, and higher values of renal function tests and indicators of glycemic control. Dyspnea grades, renal function test values, and glycemic indicator abnormalities were also significantly different among the three CCI groups (highest in CCI $\geq$ 2 and lowest in CCI of 0).

Among patients grouped on the basis of radiologic responses (Table 3), those with an objective response (complete response or partial response),

compared with those without a response (stable disease or progressive disease [PD]), had lesser WL (absolute and percentage), cough, chest pain, anorexia, and fatigue, as well as higher hemoglobin. Except for anorexia, these differences were also apparent when patients with disease control (complete response, partial response, or stable disease) were compared with patients with PD. Median OS of the cohort was 287 days (95% CI, 232 to 342 days). Figure 2 shows that OS was significantly higher for patients with anorexia VAS

median OS than those with higher scores: (A) anorexia: 388 days (95% CI, 261 to 515 days) for VAS score less than 4 versus 229 days (95% CI, 162 to 296 days) for VAS score ≥ 4 (log-rank $P < .001$); (B) fatigue: 388 days (95% CI, 256 to 520 days) for VAS score less than 3 versus 213 days (95% CI, 136 to 290 days) for VAS score ≥ 3 (log-rank $P < .001$); (C) weight loss: 410 days (95% CI, 265 to 555 days) for weight loss less than 5% versus 259 days (95% CI, 198 to 320 days) for weight loss ≥ 5% (log-rank $P = .017$); and (D) dyspnea: 377 days (95% CI, 267 to 487 days) for MRC grade less than 3 versus 187 days (95% CI, 118 to 256 days) for MRC grade ≥ 3 (log-rank $P < .001$).

score less than 4 (388 days [95% CI, 261 to 515 days] v 229 days [95% CI, 162 to 296] for VAS ≥ 4; $P < .001$), for fatigue VAS score less than 3 (388 days [95% CI, 256 to 520 days] v 213 days [95% CI, 136 to 290 days] for VAS ≥ 3; $P < .001$), for %WL less than 5% (410 days [95% CI, 265 to 555 days] v 259 days [95% CI, 198 to 320 days] for %WL ≥ 5%; $P = .017$), and for dyspnea MRC grade less than 3 (377 days [95% CI, 267 to 487 days] v 187 days [95% CI, 118 to 256 days] for MRC grade ≥ 3; $P < .001$). On univariable Cox proportional hazards analysis for factors affecting OS (Table 4), worse OS was noted for all BSs (both as categorical and continuous variables), serum albumin, spirometric indices, stage, and PS. On multivariable analysis, only fatigue (HR, 1.21; 95% CI, 1.09 to 1.36), ECOG PS ≥ 2 (HR, 1.57; 95% CI, 1.05 to 2.33), and stage IV disease (HR, 1.61; 95% CI, 1.02 to 2.55) were significant. Logistic regression analysis (Data Supplement) carried out to look for associations between BSs and disease progression also showed that baseline fatigue (OR, 1.49; 95% CI, 1.03 to 2.16) and WL (OR, 1.11; 95% CI, 1.01 to 1.21) were the only variables that had an independent association.

DISCUSSION

To the best of our knowledge, this is the first prospective study from South Asia to assess the correlations and prognostic role of graded BS assessment in a general population of patients with lung cancer. There were several highlights of this study. First, this study showed that there was a strong correlation between two BSs—fatigue and anorexia. Anorexia and %WL both showed important and clinically relevant correlations with each other and with some of the other key prognostic baseline variables (PS and BMI), although these were, in statistical terms, moderate. Second, baseline fatigue also demonstrated an important prognostic role for two clinically relevant outcomes, namely OS and disease progression, and this was independent of other variables influencing these outcomes as evidenced by multivariable analyses. In fact, for OS, the independent determinants apart from fatigue were only PS (ECOG PS ≥ 2) and the TNM disease stage (stage IV). The difference in OS (as shown in Fig 1) was also evident for individuals with higher grades of anorexia and dyspnea, as well as those with WL greater than 5% of pre-illness (baseline) weight. Third, this study showed that BSs, apart from dyspnea, were similar among patients grouped on the basis of comorbidity, and the likely explanation for this is that the primary symptom for chronic airflow obstruction, a descriptor used for comorbidity

assessment, is dyspnea. Expectedly, the only other differences observed in comorbidity-based groups were those reflective of renal function and of glycemic control, and all of these are among the variables used for determining the comorbidity scores for both SCS and CCI. Fourth, all of the BSs, other than dyspnea, were significantly different among groups on the basis of radiologic responses (both responders v nonresponders and disease control v PD).

The important implications of this study are that, in resource-constrained settings, a simple method such as VAS can be used effectively for assessment of severity of BSs. Graded BS assessment also provides better prognostic information in combination with disease stage and PS than what is obtained by using formal comorbidity scoring systems (eg, CCI and SCS) or stratifying patients into different age groups because neither of the latter influenced survival in our cohort.[5] The symptoms assessed in the current study involving patients with lung cancer were of two types, symptoms reflecting the local disease process (cough, chest pain, and dyspnea) and symptoms reflecting the overall disease burden (WL, anorexia, and fatigue). In general, the latter group of symptoms had better prognostic value than the former, and this is consistent with previously published literature. The prognostic importance of fatigue in predicting survival has been shown in unresectable non–small-cell lung cancer[18] as well as in other tumor types (including esophageal, colorectal, and breast cancer).[19-21] Similarly, previous studies have shown WL to be predictive of not just shorter survival but also greater toxicity.[22] We believe that a simple assessment of these symptoms in routine practice can help alert clinicians in busy overburdened cancer centers to specific interventions directed at amelioration of these symptoms, in particular of those reflecting disease burden in view of their important prognostic role.[23]

A few limitations of the current study need mention. First, we did not compare the prognostic role of BSs assessed by VAS with that of BSs assessed using a more formal symptom assessment tool such as the Functional Assessment of Anorexia/Cachexia Therapy or the Mini Nutritional Assessment.[24,25] It is possible that the weak correlation observed between different baseline characteristics, symptoms, and investigations in the current study might have been of a higher degree had assessment been done using a formal symptom assessment tool. However, the use of more formal assessment tools in resource-constrained settings wherein both manpower and time are limiting factors remains a challenging task.

Table 4 – Cox Proportional Hazards Analyses for Factors Affecting Overall Survival

Variable	Univariable Analysis		Multivariable Analysis (Model 1)		Multivariable Analysis (Model 2)	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Dyspnea						
MRC grade < 3	1		1		1	
MRC grade ≥ 3	1.79 (1.30 to 2.47)	< .001	1.50 (1.06 to 2.12)	.023	1.19 (0.81 to 1.74)	.370
Cough*	1.11 (1.00 to 1.24)	.042	0.95 (0.84 to 1.07)	.415		
Chest pain*	1.18 (1.07 to 1.30)	.001	1.09 (0.98 to 1.21)	.131		
Anorexia						
VAS < 4	1					
VAS ≥ 4	1.77 (1.28 to 2.45)	.001				
Anorexia*	1.17 (1.09 to 1.25)	< .001	1.07 (0.98 to 1.17)	.138		
Fatigue						
VAS < 3	1					
VAS ≥ 3	1.86 (1.34 to 2.59)	< .001				
Fatigue*	1.31 (1.19 to 1.45)	< .001	1.19 (1.04 to 1.36)	.011	1.21 (1.09 to 1.36)	.001
Weight loss						
< 5%	1					
≥ 5%	1.51 (1.07 to 2.13)	.018				
% Weight loss*	1.03 (1.00 to 1.05)	.066	1.00 (0.96 to 1.03)	.794		
Hemoglobin, g/dL						
≥ 12	1					
< 12	1.23 (0.89 to 1.69)	.207				
Hemoglobin*	0.96 (0.87 to 1.06)	.385				
Serum albumin, g/dL						
> 3.7	1					
≤ 3.7	1.45 (1.04 to 2.01)	.027				
Serum albumin*	0.88 (0.66 to 1.18)	.393			1.04 (0.77 to 1.41)	.809
Fasting BS*	0.99 (0.98 to 1.01)	.330				
PPBS*	1.00 (0.99 to 1.01)	.973				
HbA1c*	0.98 (0.80 to 1.22)	.884				
FVC						
≥ 60% predicted						
< 60% predicted	1.59 (1.05 to 2.43)	.030				
FVC%*	0.99 (0.98 to 1.00)	.036				
FEV$_1$						
≥ 50% predicted						
< 50% predicted	1.94 (1.26 to 2.96)	.002				
FEV$_1$%*	0.99 (0.98 to 1.00)	.027				
Karnofsky PS						
90-100	1					
80	1.92 (1.21 to 3.05)	.005				
≤ 70	3.22 (2.04 to 5.08)	< .001				
ECOG PS						
< 2	1				1	
≥ 2	2.10 (1.52 to 2.90)	<.001			1.57 (1.05 to 2.33)	.028

(Continued on following page)

Table 4 – Cox Proportional Hazards Analyses for Factors Affecting Overall Survival (Continued)

	Univariable Analysis		Multivariable Analysis (Model 1)		Multivariable Analysis (Model 2)	
Variable	**Hazard Ratio (95% CI)**	**P**	**Hazard Ratio (95% CI)**	**P**	**Hazard Ratio (95% CI)**	**P**
TNM stage						
I-IIIA	1				1	
IIIB	1.61 (1.02 to 2.54)	.043			1.50 (0.93 to 2.39)	.094
IV	1.67 (1.07 to 2.59)	.023			1.61 (1.02 to 2.55)	.040

Abbreviations: BS, blood sugar; ECOG, Eastern Cooperative Oncology Group; $FEV_1\%$, forced expiratory volume in 1 second as percentage of predicted; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FVC%, forced vital capacity as percentage of predicted; HbA1c, hemoglobin A1c; MRC, Medical Research Council; PPBS, postprandial blood sugar; PS, performance status; VAS, visual analog scale (score of 1 to 10).

*Used as a continuous variable.

Second, we did not assess the prognostic role of symptom clusters (combination of two or more of the symptoms assessed). However, the observation of fatigue being the most important among the symptoms assessed in the current study is consistent with another recent study wherein a combination of fatigue, dyspnea, and cough was not better than fatigue alone in predicting survival.[26] Third, we did not use a cutoff time (specific time duration) in which patients had experienced WL related to the current illness, although we did note the time period over which it had occurred (see Results). However, a decade earlier, it was shown that among the different ways of assessing WL, the one representing the percentage of difference between weight at diagnosis and last weight recorded while in good health had the best predictive value.[27] In the current study, WL, both in absolute terms and as a percentage of pre-illness value, differed significantly between patient groups on the basis of radiologic responses. In addition, percentage of WL (both as continuous variable and dichotomized as < or ≥ 5%) predicted both OS and radiologic responses well.

In summary, this prospective study involving patients with newly diagnosed lung cancer on chemotherapy in India highlights the prognostic role of graded BS assessment (using simple VAS). Baseline fatigue, in particular, has an adverse influence on both radiologic responses and OS. Additional studies in resource-constrained settings should focus on using simple symptom assessment methods to detect individuals at high risk of poor outcomes in whom directed interventions can be initiated as soon as possible.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Potsangbam Sarat Singh
No relationship to disclose

Ashutosh Nath Aggarwal
No relationship to disclose

Digambar Behera
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No relationship to disclose

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No relationship to disclose

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