Cachexia Index in Advanced Non-Small-Cell Lung Cancer Patients

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ABSTRACT

INTRODUCTION: Cancer cachexia affects many advanced non-small-cell lung cancer (NSCLC) patients. Cachexia index (CXI) was developed to assess the degree of cachexia in these patients.

METHODS: Patients with metastatic NSCLC diagnosed between January 1, 2000, and June 30, 2011, at our institution were retrospectively studied. Abdominal computed tomography scans done within 1 month of diagnosis were reviewed to estimate skeletal muscle area (SMA) and skeletal muscle index (SMI) at the L3 level. CXI was developed as follows: $CXI = \dfrac{SMI \times Alb}{NLR}$ where SMI is the skeletal muscle index, Alb is the serum albumin, and NLR is the neutrophil-to-lymphocyte ratio. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Survival among various factors was calculated using the log-rank test. Multivariate Cox regression was used to perform survival analysis in order to estimate the effects of various factors.

RESULTS: Patients were divided into two groups around the median into stage I cachexia (CXI $\geq$35, $n = 56$) and stage II cachexia (CXI $<$35, $n = 56$). Groups did not differ in age, gender, ethnicity, or histology of cancer. Patients with stage II cachexia had significantly worse PFS (2.45 vs 5.43 months, $P < 0.0001$) and OS (3.45 vs 8.8 months, $P = 0.0001$) than those with stage I cachexia. On multivariate analysis adjusting for gender, race, and histology, patients with stage II cachexia were found to have worse PFS (hazard ratio [HR] 1.94, 95% confidence interval [CI] 1.27–2.95) and OS (HR 1.53, 95% CI 1.0009–2.34).

CONCLUSION: The CXI is a novel index for estimating cachexia that also correlates with prognosis in both men and women with advanced NSCLC.

KEYWORDS: lung cancer, cancer cachexia, systemic inflammation, sarcopenia

Introduction

Cancer is the leading cause of death in people aged 40–79 years and is overall the second leading cause of death in the United States. Among all the cancer types, lung cancer is the main cause of cancer-related mortality. It is estimated that in the United States, 224,210 new cases of lung cancer were diagnosed and 159,260 deaths occurred in 2014 alone. Lung cancer causes more deaths than those from the next three most common types of cancers, such as colorectal, breast, and pancreatic cancers, combined together. More than half of all lung cancer patients at the time of diagnosis have stage IV disease that has a 5-year survival rate $<$5%.[1]

Cachexia is a wasting syndrome seen not only in cancer but also in chronic obstructive pulmonary disease,[2] chronic heart failure,[3] and acquired immune deficiency syndrome.[4] Cancer cachexia is defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition support and leads to progressive functional impairment.[5] The incidence of cachexia varies with tumor type, being lowest in sarcoma and breast cancers, whereas 80%–90% of patients with pancreatic and gastric cancers experience weight loss.[6] It is estimated that 60% of lung cancer patients have cancer cachexia.[7] The different incidence of cachexia among various cancer types may be explained by differing biology of the tumor.

The variability in the estimation of cachexia among cancer patients has also been due to lack of a consensus clinical definition for cancer cachexia.[8] Recently, various definitions of cachexia have been proposed including weight loss $>$5% of body weight or body mass index (BMI) $<$20 kg/m^2 (where weight loss is not available) along with the presence of fatigue, anorexia, decreased muscle strength, low fat-free mass index, and abnormal biochemistry.[9] In another definition and classification of cancer-specific cachexia, a proposal by the SCRINIO (screening of the nutrition risk of 1307 oncology patients) working group, cachexia was defined as $\geq$10% loss of body weight in the setting of underlying malignancy.[10]

More recently, an international consensus definition and classification of cancer cachexia were proposed. Cancer cachexia was defined as weight loss of $>$5% in the preceding

6 months or >2% in individuals showing depletion based on BMI (<20 kg/m^2) and sarcopenia.[5] Cancer cachexia is also described as a continuum, with three stages of clinical relevance: pre-cachexia, cachexia, and refractory cachexia depending on the degree of weight loss, sarcopenia, and shortened expected survival. However, although the consensus definition and criteria are important developments, it remains that arbitrary definition is not validated by prospective clinical studies. In a recent report, when this definition was applied to patients with stage III non-small-cell lung cancer (NSCLC), 18% of patients were diagnosed with cachexia and another 23% with pre-cachexia.[11]

Cancer cachexia has a complex multifactorial pathogenesis and is not simply due to reduced nutritional intake. The presence of metastatic tumor inside the body alters normal physiology and metabolism, resulting in a variety of host responses. These responses include tumor-induced systemic inflammation, sympathetic activation, hypogonadism, and insulin resistance, which coupled with poor food intake lead to a wasting syndrome characterized by muscle wasting, decline in performance status (PS), poor tolerability to cancer treatment, and eventual death of the patient.[12]

The key clinical features of cancer cachexia are poor nutritional status, systemic inflammation, and reduced muscle mass. Clinical measures of these features, that is, serum albumin, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and skeletal muscle index (SMI), are independently associated with poor outcome.[13–16] Since cachexia has a complex pathophysiology and affects various organ systems, we wanted to develop a composite index that gives a better estimate of ongoing cachexia as opposed to using a single measure, like weight loss or BMI alone. In the present study, we have incorporated clinical measures of key clinical features of cachexia into a combined index called the cachexia index (CXI) and correlated it with the outcome in patients with advanced NSCLC.

Materials and Methods

Patients. All patients diagnosed with stage IV NSCLC at Louisiana State University Health Science Center between January 1, 2000, and June 30, 2011, were reviewed for this study. Patients were excluded if they had prior history of NSCLC presenting with relapse, prior history of another cancer in the preceding 5 years, and those with incomplete medical information or follow-up. Following data points were recorded from patient charts: height, weight, absolute neutrophil count, absolute lymphocyte count, and serum albumin either from the date of diagnosis or from the date closest to the diagnosis (within 2 weeks of diagnosis).

Date of progression and radiological response were recorded from charts as judged by the treating physician at that time. We recorded date of death from medical records or obtained it from tumor registry. We defined progression-free survival (PFS) as the time period from the date of diagnosis to

radiological progression, deterioration in PS making patient ineligible for further treatment, or death of the patient. Overall survival (OS) was defined as the time period from date of diagnosis to the date of death (or date of last contact if exact date of death was not available).

Skeletal muscle index. Abdominal computed tomography scan done within 1 month of diagnosis was reviewed to determine the skeletal muscle area (SMA) using MIPAV version 7.0 (Medical Image Processing, Analysis, and Visualization; National Institutes of Health) software at the lumbar spine (L3) level using axial images as described in the literature.[15] Abdominal and paraspinal muscles were identified by using boundaries in Hounsfield units set to −29 to +150 and bordered.[16,17] SMA was determined by two investigators who were blinded to the patient outcome. Interobserver variation was not calculated. SMI was calculated as SMA/height (m^2).

Cachexia Index

CXI was calculated as follows:

$$CXI = \frac{SMI \times Alb}{NLR}$$

where SMI is the skeletal muscle index, Alb is the serum albumin in g/dL and NLR is the neutrophil-to-lymphocyte ratio (absolute neutrophil count/absolute lymphocyte count).

Statistical methods. In order to estimate the effect of CXI on OS and PFS, we dichotomized CXI at the median value of 35 into stage I and stage II cachexia groups in the analysis. Age was also dichotomized into age <60 years and age >60 years. Descriptive statistics such as means and proportion were presented for continuous and categorical variables, respectively. Student's t-test, the chi-square test, or Fisher's exact test, where it was appropriate, was used to compare the difference between groups. The Kaplan–Meier method and log-rank test were used to estimate and compare survival between factors. The Cox proportional hazard model was used to estimate the risk ratio in univariate and multivariate analysis. Statistical software SAS 9.4 (SAS Institute Inc.) was used for data management and statistical analyses. All two-sided P-values < 0.05 were considered statistically significant. The study was performed after obtaining approval from Louisiana State University Institutional Review Board (IRB). The research complied with the principles of declaration of Helsinki.

Results

After a review of nearly 400 charts, a total of 112 patients with complete medical information and follow-up were included in the final analysis. Most patients were excluded due to insufficient medical information. Table 1 summarizes the characteristics of patient population. The median age for the entire group was 57 years. Half of all the patients were African Americans, which is consistent with the demographics of the city. Two-thirds of the participants were men; 55% of all cancers

Table 1. Patient characteristics with advanced non-small-cell lung cancer.

AGE (MEDIAN, RANGE)	N = 112(%) 57 (34–88)
Race	
African American	58 (52)
White	54 (48)
Gender	
Male	78 (70)
Female	34 (30)
Histology	
Adenocarcinoma	62 (55)
Non-adenocarcinoma	50 (45)
Performance status	
0–1	85 (76)
2–4	27 (34)
Number of metastatic sites	
1–2	61 (54)
>2	51 (46)
Chemotherapy	
No chemotherapy	39 (35)
Any chemotherapy	73 (65)
Response to chemotherapy	
Any response	27 (24)
Stable disease	14 (13)
Progression of disease	25 (22)
Decline in performance status	46 (41)
Survival (Months)	
Median progression free survival	3.8
Median overall survival	5.4

Table 2. Patient characteristics and outcome between stage I and stage II cachexia based on cachexia index (CXI).

VARIABLE	STAGE I CACHEXIA (CXI ≥35) (N = 56) (%)	STAGE II CACHEXIA (CXI <35) (N = 56) (%)	*P* VALUE
Age <60	30 (53)	39 (70)	0.11
Male	40 (71)	38 (68)	0.83
White	23 (41)	31 (55)	0.18
PS 0–1	47 (84)	38 (67)	0.04*
Adenocarcinoma	36 (64)	35 (62)	1.00
No chemotherapy	11 (20)	28 (50)	0.001*
Mets >2	20 (36)	31 (55)	0.05*
Response to chemo	30 (67)	11 (39)	0.0297*
Median PFS (month)	5.42	2.45	<0.0001*
Median OS (months)	8.8	3.45	0.0001*

Note: *Statistically significant; Mets >2, more than two sites of metastatic disease.
Abbreviations: PS, performance status; PFS, progression-free survival; OS, overall survival.

were adenocarcinoma and the rest were different histologies (squamous, large cell, NSCLC [not otherwise specified]). Only one patient was positive for epidermal growth factor receptor (EGFR) mutation. Two-thirds of the patients had good PS (0–1), which is not expected as all of them were newly diagnosed. Half of the patients had only one to two sites of metastatic disease, and 35% did not receive any chemotherapy. Median PFS for all the patients was 3.8 months, and OS was 5.4 months (Table 1).

CXI values ranged from 1.08 to 248. CXI as a continuous variable is statistically significant in predicting PFS and OS when the change of CXI is one unit (data not shown). The hazard ratio (HR) changes are about 1% when the CXI changes in one unit for PFS and OS. Patients were divided into two groups around the median of 35 into stage I cachexia (CXI ≥35) and stage II cachexia (CXI <35). There was no statistical difference between the two groups in terms of age, gender, race, and tumor histology. Patients with stage I cachexia had better PS and fewer sites of metastatic disease. They were more likely to receive chemotherapy. They also

had a better response to chemotherapy. The median PFS and OS for stage I cachexia were 5.4 and 8.8 months as opposed to 2.45 and 3.45 months for stage II cachexia (P = 0.0001) (Table 2; Fig. 1).

The CXI was able to predict poor outcome in both men and women. Patients with stage II cachexia had a poor outcome irrespective of patient's gender. PFS in stage II cachexia for both men (2.45 months) and women (2.18 months) was worse than that of men (5.49 months) and women (4.75 months) with stage I cachexia (P < 0.001). Similarly patients with stage II cachexia had a worse OS for both men (3.27 months) and women (4.62 months) than men (8.88 months) and women (7.88 months) with stage I cachexia (P = 0.001) (Table 4; Fig. 2).

When patients with weight loss (>5%) were compared with those with <5% or no weight loss, there was no difference in OS (P = 0.72). Similarly, when patients with BMI ≤20 were compared with those with BMI >20, there was no difference in OS between the two groups (P = 0.45).

On univariate analysis, PS 0–1 was associated with better PFS (HR 0.46, 95% confidence interval [CI] 0.27–0.79 P = 0.0048) and OS (HR 0.41, 95% CI 0.21–0.79, P = 0.0081). There was no statistical difference in the outcome based on histology. Not receiving chemotherapy was linked with poor PFS (HR 2.81, 95% CI 1.46–5.4, P = 0.002) and OS (HR 3.1, 95% CI 1.75–5.56, P = 0.0001). SMI (>40) was not associated with better OS (HR 1.36, 95% CI 0.943–1.96, P = 0.10), but both NLR (≤5) and albumin <3 were significantly associated with better OS (HR 0.60, 95% CI 0.41–0.90, P = 0.0187 and HR 1.9, 95% CI 1.22–3.13, P = 0.0048, respectively). Patients with stage II cachexia also had poor PFS (HR 2.43, 95% CI 1.52–3.88, P = 0.0002) and OS (HR 2.08, 95% CI 1.38–3.12, P = 0.0005) (Table 3).

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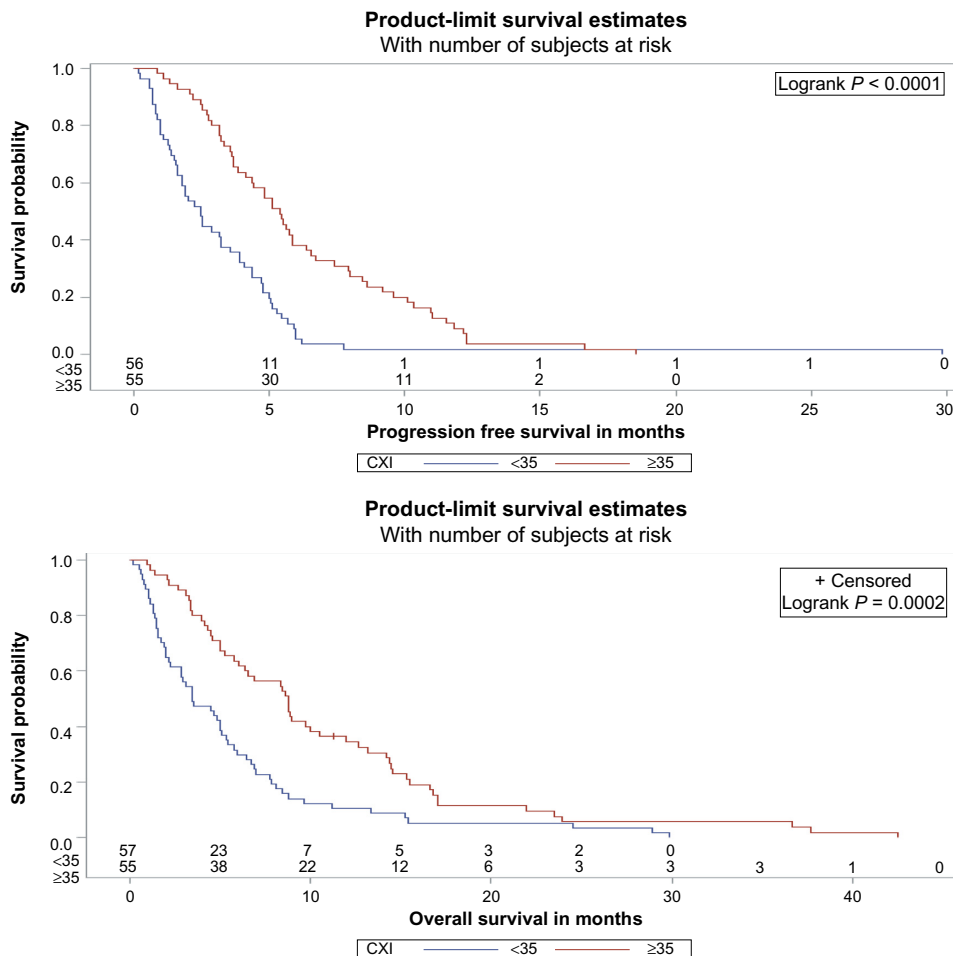With number of subjects at risk

Figure 1. Kaplan–Meier curve for progression-free survival (PFS) and overall survival (OS) in patients with stage I cachexia (CXI ≥35) and stage II cachexia (CXI <35).

On multivariate analysis, controlling for gender, race, and histology, stage II cachexia remained independently associated with worse PFS (HR 1.94, 95% CI 1.27–2.95, *P*-value 0.0022) and OS (HR 1.53, 95% CI 1.009–2.34, *P*-value 0.045). In other words, patients with stage II cachexia at diagnosis were 53% more likely to have early progression of disease and die sooner as compared to patients with stage I cachexia (Table 3).

Discussion

Cancer cachexia remains a challenging condition affecting many cancer patients, especially those with advanced disease. Identifying mechanism and treatment of cancer cachexia is one of the provocative questions recently put forward by the National Cancer Institute (NCI). Currently, there are no Food and Drug Administration-approved treatments for cancer cachexia (http://provocativequestions.nci.nih.gov/archived-rfas-and-pqs/rfa-archive-2012/mainquestions_listview?mqCategory = Group+D). One of the current challenges in managing cancer cachexia is to reliably identify it at the onset and estimate the degree of cachexia. The current consensus definition of cancer cachexia (weight loss >5%) is based on the degree of weight loss prior to diagnosis.[5] What is not known is whether this degree of weight loss also correlates with ability to receive cancer treatment or with overall outcome. Moreover, a definition of cancer cachexia based on weight loss alone may be a good way of screening patients for cancer cachexia, but it does not take into account muscle wasting (sarcopenia) or nutritional status of the patient.

In the current study, we reviewed patients newly diagnosed with advanced NSCLC at our institution over a 10-year period. Because sarcopenia is a hallmark of cancer cachexia, we estimated SMI at L3 level using the method described above. Because cancer cachexia is also characterized by systemic inflammation and poor nutritional status, we estimated the degree of systemic inflammation using the NLR (for which a high value is associated with higher systemic inflammation) and nutritional status with serum albumin. In order to estimate the degree of cancer cachexia, we developed a composite index that incorporates features of sarcopenia, systemic inflammation, and nutritional status into a combined index called the CXI.

Table 3. Univariate and multivariate analysis of clinical characteristics on PFS and OS in patients with metastatic non-small-cell lung cancer Univariate analysis.

VARIABLE	PFS HR	*P*	OS HR	*P*
F/M	1.24 (0.85–1.83)	0.2662	1.08 (0.72–1.62)	0.6939
AA/W	0.885 (0.607–1.290)	0.5251	0.95 (0.65–1.38)	0.8016
PS 0–1/2–4	0.464 (0.272–0.792)	0.0048*	0.41 (0.21–0.79)	0.0081*
Adeno/No	0.883 (0.613–1.274)	0.5067	0.94 (0.65–1.37)	0.7704
No Chemo	2.815 (1.462–5.419)	0.0020*	3.12 (1.75–5.56)	0.0001*
SMI (<40)	1.665 (1.042–2.660)	0.033*	1.36 (0.94–1.96)	0.1
NLR ≤5	0.47 (0.29–0.75)	0.001*	0.6 (0.41–0.90)	0.018*
Alb <3	2.03 (1.26–3.41)	0.004*	1.9 (1.22–3.13)	0.0048*
CXI <35	2.432 (1.522–3.885)	0.0002*	2.08 (1.38–3.12)	0.0005*
Age (<60 years)	0.92 (0.75–1.13)	0.4270	0.819 (0.67–0.998)	0.0475
PS 0–1	0.51 (0.32–0.83)	0.0053*	0.44 (0.27–0.71)	0.0008*
No chemo	2.83 (1.76–4.54)	<0.0001*	3.26 (2.02–5.26)	<0.0001*
Stage II cachexia (CXI <35)	1.94 (1.27–2.95)	0.0022*	1.53 (1.009–2.34)	0.0459*

Notes: *Statistically significant. Multivariate analysis adjusting for sex, race, and histology.
Abbreviations: F/M, female/male; AA/W, African American/White; PS, performance status; adeno, adenocarcinoma; SMI, skeletal muscle index; NLR, neutrophil-to-lymphocyte ratio; Alb, serum albumin; CXI, cachexia index; PFS, progression-free survival; OS, overall survival.

Table 4. PFS and OS of patients with stage I and stage II cachexia based on gender.

GENDER	STAGE I CACHEXIA (CXI ≥35)		STAGE II CACHEXIA (CXI <35)		*P* VALUE
N = 111	M (N = 40)	F (N = 16)	M (N = 37)	F (N = 18)	
PFS	5.49	4.75	2.45	2.18	<0.001*
OS	8.88	7.88	3.27	4.62	<0.001*

Notes: *Statistically significant, one observation with invalid time, strata, or censoring was deleted.
Abbreviations: PFS, progression-free survival; OS, overall survival; CXI, cachexia index.

Patients were divided around the median into stage I (CXI ≥35) and stage II (<35) cachexia. Patients with stage II cachexia are deemed to have advanced cachexia than those with stage I since low CXI is associated with lower SMI, lower albumin, and higher NLR.

Patients with stage II cachexia were more likely to have more than two sites of metastatic disease and PS of ≥2. They were also less likely to receive chemotherapy and have a poor response to it. The PFS and OS were significantly shorter for these patients than for those with stage I cachexia (Table 2).

Dichotomization of a continuous variable though often discouraged is a common practice in medical literature, for example, hypertension >140/90 or BMI >30. From a practical point of view, dichotomization around median would help clinicians use the index to categorize and explain the risk of progression or dying when the median value is compared.

Because men and women have different muscle mass, we also determined whether the CXI correlates with outcome in men and women separately. Patients with stage II cachexia had worse PFS and OS independent of the gender (Table 4) (*P* < 0.001).

On univariate analysis PS >2, not receiving chemotherapy, serum albumin, NLR, and CXI ≤35 correlated with poor PFS and OS. On multivariate analysis adjusting for race, gender, and histology, CXI was independently associated with worse PFS and OS. Thus, patients with CXI of ≤35 were 53% more likely to die earlier from NSCLC than patients with CXI >35.

In our study, weight loss >5% (current clinical consensus definition) and BMI <20 alone did not correlate with poor outcome. This may be due to less accurate estimate and reporting of weight loss in a retrospective review. Also in the era of endemic obesity, sometimes BMI may not be a good estimate of muscle wasting as seen in patients with cachexia.

We had previously shown using advanced lung cancer inflammation index (ALI) that when BMI is combined with serum albumin and NLR, patients with advanced NSCLC can be divided into good and poor prognosis.[18] CXI is an improvement on ALI as CXI incorporates SMI that is a hallmark of cancer cachexia. If SMI is not readily available, ALI can be used to identify patients with high inflammation and risk of early progression.

Cancer cachexia manifests as a spectrum divided into pre-cachexia, cachexia, and refractory cachexia, but the distinction between these stages can be difficult. Others have also attempted to quantify or stage cachexia by developing tools like inflammatory-nutritional index (based on CRP and serum albumin)[19] and cachexia score (needs validation in patient population).[20] However, it is not known if these correlate with patient outcome also. Another important score

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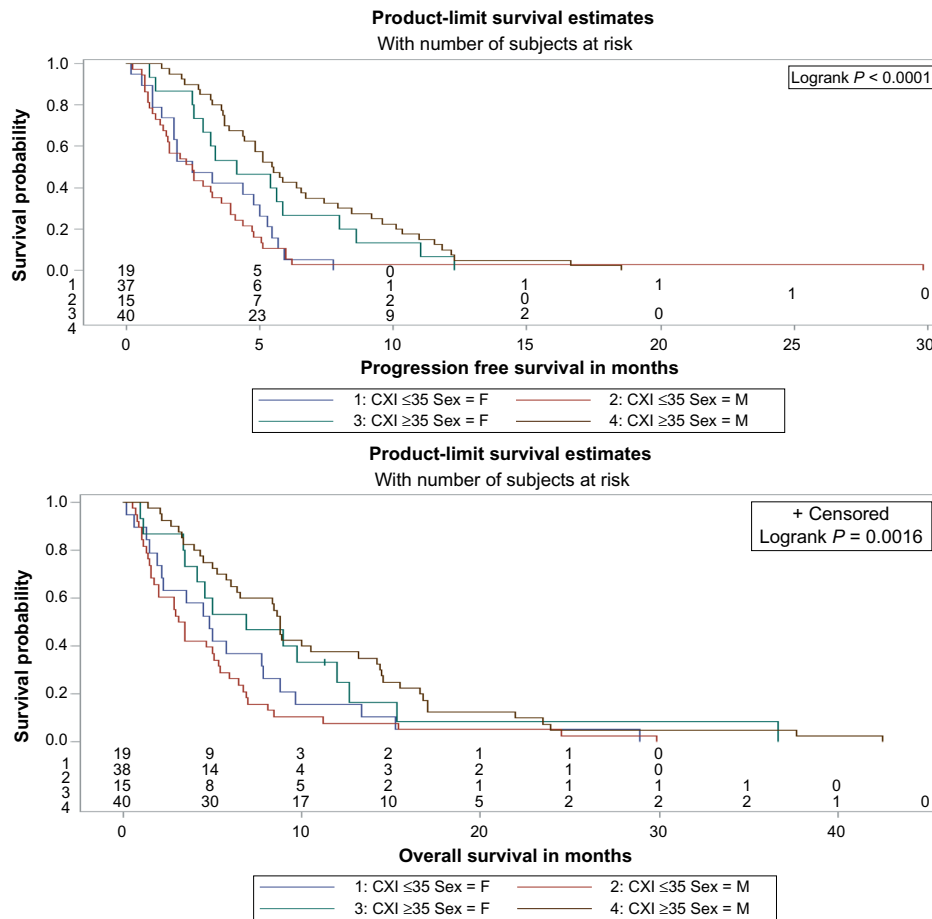With number of subjects at risk

Figure 2. Kaplan–Meier curve for progression-free survival and overall survival with stage I cachexia (CXI ≥35) and stage II cachexia (CXI <35) based on gender.
Abbreviations: M, male; F, female.

described in the literature is Glasgow prognostic score (based on CRP and serum albumin). This has been shown to be correlated with outcome in cancer patients but does not take into account muscle wasting that is a hallmark of cancer cachexia.[21] More recently, Kasymjanova et al has proposed an inflammatory score based on CRP and total white blood cell count as a prognostic marker in patients with advanced NSCLC. The score is able to predict response to chemotherapy as well as outcome. This score is based only on inflammatory parameters and does not take into account measures like BMI or muscle mass.[22] Gagnon et al has also proposed a five-point Montreal prognostic score as a way of estimating survival in patients with advanced NSCLC. This score also incorporates two cancer stages (stage III vs IV) in estimating the outcome, which in our opinion is a limitation of this score as stage III and IV lung cancers have a very different natural history, treatment, and outcome.[23]

CXI has been developed using a uniform patient population, that is, all patients were newly diagnosed with stage IV NSCLC. None of the patients had received any treatment to account for weight loss or poor nutritional status. CXI is a composite index that takes into account key features of cancer

cachexia, that is, sarcopenia, systemic inflammation, and serum albumin. It is applicable to both men and women independently. CXI is calculated using objective observations and is not limited by recall bias as would be possible if the degree of weight loss was used as the sole measure of cancer cachexia. Another limitation of using only weight loss as a definition of cancer cachexia is that weight loss can vary during a patient's clinical course; it can be affected by cancer treatment and factors that may mask true weight loss such as fluid retention.

Lung cancer is the leading cause of cancer-related mortality in the United States. Even stage-to-stage survival for lung cancer is worse than other common cancer types such as colorectal, prostate, and breast.[1] One of the possible reasons for such poor outcome can be development of cancer cachexia in patients with advanced lung cancer. Many patients with advanced NSCLC lose weight, have a poor PS, and are unable to receive cancer chemotherapy. Most of the focus of lung cancer research has been on targeting proliferating cancer cells either through cytotoxic chemotherapy, targeted agents, or, more recently, immunotherapy. Very little focus has been laid on developing therapies that target systemic inflammation or cancer cachexia in the context of

managing advanced lung cancer patients. Hopefully, this will change with inclusion of cachexia in the provocative question initiative by the NCI.

Another thing to consider will be to identify if the presence of certain mutations makes a patient more prone to develop cancer cachexia, and hence, poor outcome, for example, presence of K-ras as opposed to EGFR. Currently, there is paucity of literature in this regard.

This study has several limitations. It is a retrospective chart review, and many patients were excluded due to insufficient information. CXI as such does not tell us if the patient has cachexia or not, but it does categorize the patient into low risk and high risk based on clinical variables known to be associated with cancer cachexia. Because CXI is a continuous variable, there may be little difference in clinical course of someone with CXI of 37 and 34 though they fall into stage I and stage II cachexia, respectively. Additionally, although the CXI is easy to calculate, it may be difficult to measure in routine clinical practice, thus limiting its applicability to research settings only. It can, however, be very useful identifying high-risk patients who take part in cachexia intervention studies stratifying them into good risk and poor risk.

Despite these limitations, the CXI is an objective method of estimating the degree of cancer cachexia in patients with advanced NSCLC. It can thus be used to identify patients who are at high risk of early progression and less likely to receive cancer treatment. It can also be used to identify which patients should be treated with therapies directed against cancer cachexia. The CXI should be validated in larger prospective studies of both early- and advanced-stage NSCLC and other cancers.

Author Contributions

Conceived and designed the experiments: SHRJ. Analyzed the data: SHRJ, CP, KK, RS. Wrote the first draft of the manuscript: SHRJ. Contributed to the writing of the manuscript: SHRJ, CP, KK, RS. Agree with manuscript results and conclusions: SHRJ, CP, KK, RS. Jointly developed the structure and arguments for the paper: SHRJ, CP, RS. Made critical revisions and approved final version: SHRJ, RS, CP. All authors reviewed and approved of the final manuscript.

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