Thoracic Cancer

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Comparative Study on Associations Between Lung Cancer Prognosis and Diagnostic Criteria Set by the European Palliative Care Research Collaboration and the Asian Working Group for Cachexia

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Received: 9 June 2024 | **Revised:** 15 October 2024 | **Accepted:** 18 November 2024

Funding: This work was supported by Utae Katsushima, Grant in Aid for Scientific Research (C) (General) (23K10572).

Keywords: cancer cachexia | lung cancer | new cachexia diagnostic criteria for Asians | prognosis

ABSTRACT

Background: Cachexia is a poor prognostic factor in many advanced cancers. Cachexia diagnostic criteria of the European Palliative Care Research Collaboration (EPCRC) may underestimate cachexia in Asians; therefore, new criteria have been proposed by the Asian Working Group for Cachexia (AWGC). We compared both criteria to determine differences in diagnostic rates and their association with lung cancer prognosis.

Patients and Methods: This single-center, retrospective cohort study considered lung cancer outpatients receiving chemotherapy. Survival was analyzed using Kaplan–Meier curves and log-rank tests. The association between cachexia diagnosis and prognosis was examined for each set of criteria using a Cox proportional hazards model. C-statistic analysis was performed to compare the discriminative power for prognosis.

Results: Among the 106 participants analyzed (median age, 75 [71–79] years; 75 males [70.8%]; 91 [85.9%] with performance status [PS] 0–1), 58 (54.7%) and 77 (72.6%) cachexia cases were diagnosed using the EPCRC and AWGC criteria, respectively. The latter encompassed all but one patient diagnosed using the EPCRC criteria. Patients with cachexia had a significantly poorer prognosis according to both criteria (EPCRC, $p = 0.002$; AWGC, $p = 0.001$). Both criteria had almost equal discriminative power for prognosis (EPCRC, C-statistic = 0.658; AWGC, C-statistic = 0.658). CRP in the AWGC criteria was most strongly related to prognosis.

Conclusions: Cachexia was an independent poor prognostic factor in lung cancer patients receiving chemotherapy under the AWGC and EPCRC criteria, both of which had similar prognostic discriminatory power. Among CRP, anorexia, and grip strength, elevated CRP may be the most prognostically relevant parameter in the AWGC criteria.

1 | Introduction

Cancer cachexia is a condition with a poor prognosis that is associated with 80% of advanced cancers and is estimated to be responsible for 20% of deaths due to cancer. It is defined as "a persistent loss of skeletal muscle that cannot be completely reversed by normal nutritional support and leads to progressive functional impairment." [1–4]. Although there is no standard treatment for cancer cachexia, a multimodal intervention by a multidisciplinary team consisting mainly of exercise and nutritional and pharmacological therapies is important [5, 6]. Several diagnostic criteria for cachexia have been proposed; however, currently, the most widely used are the criteria of the European Palliative Care Research Collaboration (EPCRC). According to the guidelines, patients with body weight loss > 5% in the last 6 months, those with a body mass index (BMI) < 20 kg/m^2 and continuous weight loss > 2%, or individuals with sarcopenia and ongoing weight loss > 2% are diagnosed with cachexia [5–7].

Asian populations typically have a smaller stature than Western populations and exhibit diverse dietary habits, lifestyles, and metabolic profiles. Moreover, Konishi et al. concluded that existing international criteria, primarily emphasizing body composition and muscle mass decline, might underestimate the prevalence of cachexia among Asians [8]. Asians have a lower BMI than Caucasians [9], and cutoff values for muscle mass and physical function in Asians have been proposed by the Asian Working Group for Sarcopenia [10]. In response, the Asian Working Group for Cachexia (AWGC) proposed diagnostic criteria for diagnosing cachexia in Asians in 2023 [11]. According to this, a diagnosis of cachexia is made with chronic wasting disease and BMI < 21 kg/m^2 or weight loss > 2% in the previous 3–6 months (mandatory) in addition to anorexia, decreased grip strength (< 28 kg in men and < 18 kg in women), or C-reactive protein (CRP) > 0.5 mg/dL. The outcomes of cachexia include death, functional disability, and a reduced quality of life (QOL). Arai et al. stated that if the proposed new diagnostic criteria for cachexia in Asians could advance the diagnosis of cachexia in clinical practice and popularize early intervention, it could improve the prognosis and QOL of patients with cachexia [11].

Lung cancer, the leading cause of cancer-related death in Japan, has a poor prognosis and is associated with a high incidence of cachexia [12, 13]. Lung cancer is frequently diagnosed at advanced stages, and chemotherapy is the mainstay treatment for advanced lung cancer [14]. Appropriate diagnosis and intervention for cachexia in patients undergoing chemotherapy are important because cachexia decreases the efficacy of chemotherapy, increases toxicity, and worsens prognosis [15, 16]. Sakaguchi et al. validated the AWGC criteria in hospitalized patients with advanced cancer receiving palliative care and found that cachexia, as defined by the AWGC, had a significant prognostic value in advanced cancer. Sakaguchi et al. included 364 patients with cancer aged ≥ 18 years who received palliative care during hospitalization, 42% of whom had the best supportive care and a variety of cancer types, including lung, colon, stomach, and breast cancer [17]. Although the AWGC criteria have been studied in mixed cancer types, there are no reports comparing the differences in cachexia diagnosis rates and prognostic relevance between the new cachexia diagnostic criteria for Asians and the conventional criteria with a focus on patients with lung cancer undergoing chemotherapy. Arai et al. stated that these criteria have advanced cachexia research in Asia and that it is important to establish further evidence and review and improve this consensus [11]. In order to apply the newly proposed 2023 AWGC criteria to clinical practice, it is important to compare the difference in diagnostic and prognostic rates of cachexia between the conventional EPCRC and the newly proposed AWGC criteria. Therefore, we aimed to validate the new cachexia diagnostic criteria in patients with lung cancer undergoing chemotherapy rather than in patients with various types of cancers. We used the AWGC and EPCRC criteria to diagnose cachexia and determine differences in the diagnostic rate of cachexia and its association with prognosis in outpatients with lung cancer undergoing chemotherapy.

2 | Methods

2.1 | Patients

This single-center, retrospective cohort study was conducted at Kansai Medical University. The eligibility criteria were patients with lung cancer receiving outpatient cancer chemotherapy between November 2020 and December 2022, patients referred to the outpatient rehabilitation clinic, patients aged ≥ 20 years, and patients deemed eligible for physical function assessment. Exclusion criteria were patients who had difficulty communicating, whose general condition was too poor to be evaluated, who had orthopedic, cerebrovascular, or cardiovascular diseases that made evaluation of physical function difficult, and whose evaluation was judged to be difficult.

2.2 | Definition of Cachexia

Cachexia was diagnosed during the first visit to the rehabilitation outpatient clinic using both the cachexia diagnostic criteria proposed by Fearon et al. and the cachexia diagnostic criteria for Asians proposed by the AWGC. Weight loss within 6 months was considered [7]; however, skeletal muscle mass assessment was not included. Patients who lost < 5% of their body weight within 6 months were diagnosed with precachexia, but precachexia was included in the analysis. The AWGC criteria for the diagnosis of cachexia were a diagnosis of cancer, weight loss of 2% or more in 3–6 months, or BMI < 21 kg/m^2, as well as subjective symptoms such as anorexia and decreased grip strength. Decreased grip strength is an objective measure, and elevated CRP is a biomarker [11]. The cutoff values for grip strength were 28 and 18 kg for men and women, respectively; for CRP, the cutoff value was 5 mg/L (0.5 mg/dL), based on the conventional diagnostic criteria for cachexia [10, 18].

2.3 | Grip Strength

Grip strength was measured using a dynamometer. On the first visit to the rehabilitation outpatient clinic, the physician or

physical therapist measured the grip strength once on each side, and the stronger grip strength was adopted.

2.4 | Nutritional Status and Appetite

The Mini Nutritional Assessment Short-Form (MNA-SF), an established questionnaire for assessing nutritional status in older adults, was used to evaluate the nutritional status at the first rehabilitation outpatient visit [19]. Furthermore, no specific tool has been specified for the assessment of anorexia according to the AWGC criteria [11]; therefore, in this study, the MNA-SF was used to evaluate anorexia in older individuals. Anorexia was defined as a significant or moderate decrease in food intake in the anorexic section of the MNA-SF.

2.5 | Data Collection

Demographic information (age and sex), anthropometric information (height and weight), and disease characteristics (histological type, stage, treatment, and blood sampling data, including CRP levels) were collected from electronic medical records.

2.6 | Statistical Analysis

Kaplan–Meier curves and log-rank tests were used to examine the association between cachexia and the number of survival days from the first rehabilitation outpatient visit (SPSS Version 27). Cox proportional hazard models were used to examine the association between prognosis and cachexia for each criterion, with age, histological type, stage, treatment line, and disease status as adjustment factors.

Overall survival was defined as the period from the date of the first rehabilitation outpatient visit to the date of death, loss to follow-up, or end of follow-up. Those diagnosed with precachexia (with $<5\%$ weight loss) were included in the analysis. The significance level was set at 5%.

In addition, C-statistic analysis was performed to compare the discriminative power of the AWGC and EPCRC criteria for prognosis. For the AWGC criteria, we compared the prognostic discriminative power of the AWGC and EPCRC criteria when one of the parameters from elevated C-reactive protein, anorexia, or decreased grip strength was excluded. The same analysis was also performed for advanced recurrent non-small cell lung cancer. Statistical analysis was performed using R version 4.3.3.

2.7 | Ethics Statement

This study was approved by the Ethics Committee of Kansai Medical University in accordance with the Declaration of Helsinki. All examinations and evaluations were performed in the daily clinical practice of the Department of Rehabilitation Medicine, and the use of the data was obtained with blanket consent approved by the Ethics Committee of Kansai Medical University (approval number: 2023264).

3 | Results

3.1 | Patient Characteristics

Figure 1 shows the patient flowchart; five cases were excluded from the analysis due to missing data. Detailed patient characteristics are shown in Table 1. Among a total of 106 patients with a median age of 75 years (71–79), including 75 males (70.8%), 91 patients (85.8%) had a performance status (PS) of 0–1. A total of 101 patients (95.3%) had stage IIIB/IV disease and postoperative recurrence, while small cell carcinoma was observed in 27 (25.6%) patients. Twenty-three (21.7%) patients had genetic mutations. The most common treatment was initial chemotherapy in 73 patients (68.9%), and 63 patients (59.4%) received chemotherapy including immune checkpoint inhibitors.

Patient characteristics according to the use of the AWGC and EPCRC criteria are shown in Table 2. There was no significant bias in the background characteristics of patients assessed by each criterion.

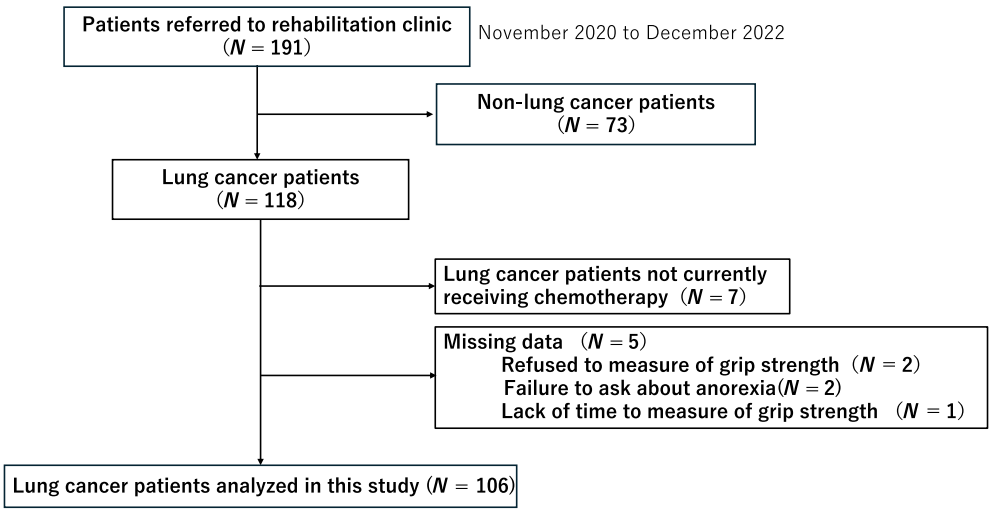


FIGURE 1 | Patient flowchart.

TABLE 1 | Patients' characteristics.

Characteristics	
Age, median (IQR), years	75 [71–79]
Sex, *N* (%)	
Male	75 (70.8)
Female	31 (29.2)
PS, *N* (%)	
0	1 (0.9)
1	90 (85.0)
2	14 (13.2)
3	1 (0.9)
Stage, *N* (%)	
I	0 (0.0)
II	0 (0.0)
IIIA	5 (4.7)
IIIB	7 (6.6)
IV	76 (71.7)
Recurrence	18 (17.0)
Pathology, *N* (%)	
Sm	27 (25.6)
Ad	12 (11.3)
Sq	8 (7.5)
Non-small cell lung cancer	58 (54.7)
Other	1 (0.9)
Treatment line, *N* (%)	
First line	73 (68.8)
Second line	20 (18.9)
Third line or over	13 (12.3)
Genetic mutation, *N* (%)	
None	78 (73.7)
EGFR	15 (14.2)
ALK	1 (0.9)
KRAS	5 (4.7)
ROS1	1 (0.9)
SMARCA4 deficiency	1 (0.9)
Unknown	5 (4.7)
PD-L1 Tumor Proportion Score, *N* (%)	
< 1%	29 (27.3)
1%–49%	20 (18.9)
≥ 50%	15 (14.2)
Unknown	42 (39.6)
Treatment, *N* (%)	
Chemotherapy + ICI	43 (40.6)
Chemotherapy	31 (29.2)
ICI	19 (17.9)
Molecular targeted	7 (6.6)
Chemotherapy + Molecular targeted	6 (5.7)
BMI, median (IQR), kg/m^2	21.5 [19.6–24.4]
Handgrip strength	
Male: < 28 kg, female: < 18 kg, no. (%)	67 (63.2)
Mini-nutritional assessment, median (IQR)	11 [9–11]
Appetite loss, yes, *N* (%)	52 (49.1)
CRP, median (IQR), mg/dL	0.55 [0.14–1.41]

Abbreviations: Ad, adenocarcinoma; BMI, body mass index; CRP, C-reactive protein; ICI, immune checkpoint inhibitors; IQR, interquartile range; *N*, number; PS, performance status; Sm, small cell carcinoma; Sq, squamous cell carcinoma.

3.2 | Prevalence of Cachexia

Of the 106 patients with lung cancer, 58 (54.7%) had cachexia, as determined by the EPCRC criteria, while 48 (45.3%) did not. A total of 77 (72.6%) cachexia and 29 (27.4%) noncachexia patients were assessed using the AWGC criteria; the 77 patients diagnosed with cachexia using the AWGC criteria had a BMI < 21 kg/m^2 but no weight loss within 6 months, a maintained activity level, a good appetite, and elevated C-reactive protein levels and grip strength. The 77 patients included those diagnosed with cachexia using the EPCRC criteria, except for one patient who had a BMI < 21 kg/m^2 but no weight loss within 6 months, a maintained activity level, a good appetite, no elevated CRP, and no grip strength loss (Figure 2). Furthermore, of the 77 patients, 27 (35.1%) had only weight loss, 12 (15.6%) were only underweight, and 38 (49.4%) lost weight and were underweight. Forty-four (57.1%) patients had anorexia, 46 (59.7%) had elevated CRP levels, 57 (74.0%) had decreased grip strength, and 21 (27.3%) met all criteria (Figure 3).

3.3 | Survival

The median OS was 282.0 days in the cachexia group but not reached in the noncachexia group according to the EPCRC criteria ($p = 0.002$), whereas it was 311.0 days in the cachexia group but not reached in the noncachexia group according to the AWGC criteria ($p = 0.001$). The 1-year survival rates according to the EPCRC criteria were 42.1% and 64.6% in the cachexia group and the noncachexia group, respectively, whereas according to the AWGC criteria, they were 43.9% and 74.7% in the cachexia group and the noncachexia group, respectively (Figure 4).

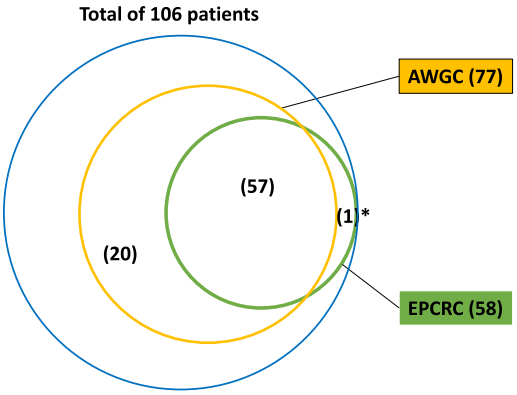
TABLE 2 | Characteristics of patients assessed by the EPCRC and AWGC criteria.

	EPCRC		AWGC	
	CC (*N* = 58)	**Non-CC (*N* = 48)**	**CC (*N* = 77)**	**Non-CC (*N* = 29)**
Age, median [IQR], years	75 [71–79]	75 [70–79]	75 [71–79]	75 [70–79]
Sex, *n* (%)				
Male	45 (77.5)	30 (62.5)	56 (72.7)	19 (65.6)
Female	13 (22.5)	18 (37.5)	21 (27.3)	10 (34.4)
PS, *n* (%)				
0	0 (0.0)	1 (2.1)	0 (0.0)	1 (3.4)
1	47 (81.0)	43 (89.6)	65 (84.4)	25 (86.3)
2	10 (17.3)	4 (8.3)	11 (14.3)	3 (10.3)
3	1 (1.7)	0 (0.0)	1 (1.3)	0 (0.0)
Stage, *n* (%)				
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IIIA	1 (1.7)	4 (8.3)	4 (5.2)	1 (3.4)
IIIB	2 (3.4)	5 (10.4)	5 (6.5)	2 (6.9)
IV	47 (81.0)	29 (60.5)	57 (74.0)	19 (65.5)
Recurrence	8 (13.9)	10 (20.8)	11 (14.3)	7 (24.2)
Pathology, *n* (%)				
Sm	14 (24.2)	13 (27.1)	19 (24.7)	8 (27.6)
Ad	6 (10.3)	6 (12.5)	7 (9.1)	5 (17.2)
Sq	5 (8.6)	3 (6.3)	7 (9.1)	1 (3.4)
NSCLC	33 (56.9)	25 (52.0)	44 (57.1)	14 (48.4)
Other	0 (0.0)	1 (2.1)	0 (0.0)	1 (3.4)
Treatment line, *n* (%)				
First line	40 (68.8)	33 (68.7)	54 (70.1)	19 (65.5)
Second line	8 (13.9)	12 (25.0)	12 (15.6)	8 (27.6)
Third line or more	10 (17.3)	3 (6.3)	11 (14.3)	2 (6.9)
Genetic mutation, *n* (%)				
None	42 (72.4)	36 (75.0)	55 (71.4)	23 (79.5)
EGFR	11 (19.0)	4 (8.3)	14 (18.2)	1 (3.4)
ALK	0 (0.0)	1 (2.1)	0 (0.0)	1 (3.4)
KRAS	1 (1.7)	4 (8.3)	2 (2.6)	3 (10.3)
ROS1	1 (1.7)	0 (0.0)	1 (1.3)	0 (0.0)
SMARCA4 deficiency	0 (0.0)	1 (2.1)	1 (1.3)	0 (0.0)
Unknown	3 (5.2)	2 (4.2)	4 (5.2)	1 (3.4)

(Continues)

TABLE 2 | (Continued)

	EPCRC		AWGC	
	CC ($N=58$)	Non-CC ($N=48$)	CC ($N=77$)	Non-CC ($N=29$)
PD-L1 TPS, *n* (%)				
< 1%	1 (29.3)	12 (25.0)	23 (29.9)	6 (20.7)
1%–49%	13 (22.4)	7 (14.6)	14 (18.2)	6 (20.7)
≥ 50%	7 (12.1)	8 (16.7)	9 (11.7)	6 (20.7)
Unknown	2 (36.2)	2 (43.7)	31 (40.2)	11 (37.9)
Treatment, *n* (%)				
Chemo + ICI	27 (46.6)	16 (33.3)	31 (40.2)	12 (41.4)
Chemo	16 (27.6)	15 (31.3)	23 (29.9)	8 (27.6)
ICI	9 (15.5)	10 (20.8)	12 (15.6)	7 (24.1)



	Cachexia/Non-cachexia	Prevalence of cachexia
AWGC	77/29	72.6%
EPCRC	58/48	54.7%

FIGURE 2 | Prevalence of cachexia. *BMI < 21 kg/m^2 but no weight loss within 6 months, good appetite, no elevated CRP, and no loss of grip strength. AWGC, Asian Working Group for Cachexia; BMI, body mass index; CRP, C-reactive protein; EPCRC, European Palliative Care Research Collaboration.

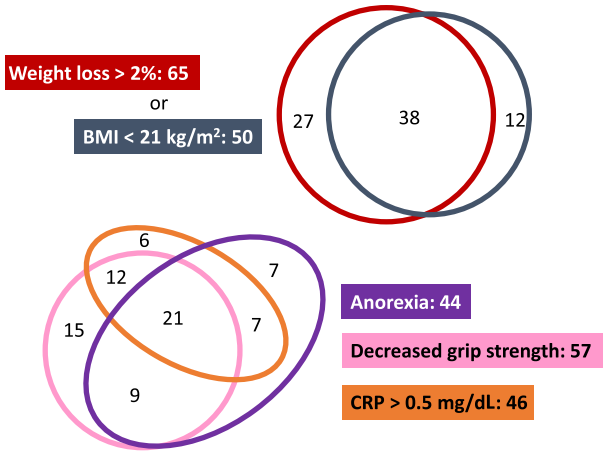


FIGURE 3 | Breakdown of 77 cases diagnosed with cachexia by AWGC criteria. AWGC, Asian Working Group for Cachexia; BMI, body mass index; CRP, C-reactive protein; EPCRC, European Palliative Care Research Collaboration.

3.4 | Survival in Relation to Each Criterion

In both the AWGC and EPCRC criteria, cachexia was shown to be an independent prognostic factor, even with age, sex, PS, pathology type, and line of treatment as adjustment factors. The C-statistics for the EPCRC and AWGC criteria were 0.658 (95% confidence interval [CI] 1.440 to 5.159) and 0.658 (95% CI 1.717 to 9.782), respectively; the discriminative power for prognosis was almost equal for the two criteria (Table 3). C-analysis to determine the parameter (grip strength, CRP, and anorexia) with the strongest correlation in the AWGC criteria revealed that CRP was the most strongly related indicator (Table 4). Furthermore, we performed a multivariate analysis and C-analysis for 74 patients with Stage IIIB, Stage 4, and postoperative recurrent non-small cell lung cancer. The results suggested that in this population, patients with cachexia had a poor prognosis by either criterion and that the AWGC criteria had a better discriminative power for prognosis (Table S1).

4 | Discussion

In our study, we identified differences in the diagnostic rate of cachexia as defined by the EPCRC and AWGC criteria in patients with lung cancer undergoing outpatient drug therapy and the association with prognosis. The results showed that:

1. Diagnosis of cachexia by AWGC criteria in patients with lung cancer undergoing chemotherapy screened a wider range of patients with cachexia than the EPCRC criteria.
2. Patients with cachexia had a poor prognosis based on either criteria type.
3. Both criteria are equally discriminative with respect to prognosis.

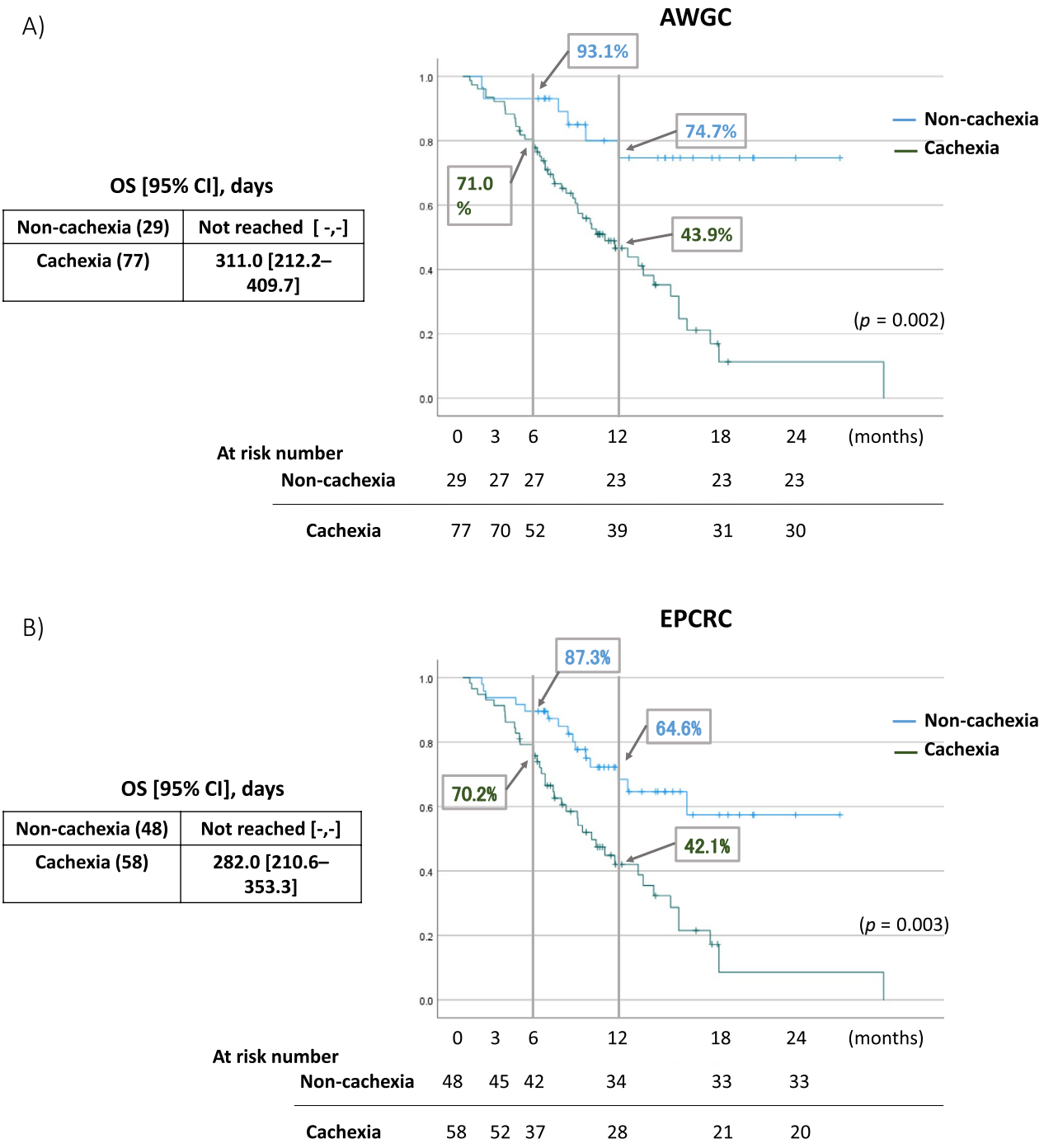


FIGURE 4 | Overall survival. (A) AWGC. (B) EPCRC. AWGC, Asian Working Group for Cachexia; CI, confidence interval; EPCRC, European Palliative Care Research Collaboration; OS, overall survival.

4. It was suggested that CRP may be the parameter most strongly related to prognosis in the AWGC criteria.

Cancer cachexia has been reported to reduce the efficacy of chemotherapy, increase toxicity, and worsen prognosis, emphasizing the importance of intervention at an early stage [7], and the ability to control cachexia during cancer treatment is key to the success of cancer treatment itself. The early detection of and intervention for cachexia in patients with lung cancer undergoing chemotherapy with appropriate diagnostic criteria are important because lung cancer is growing in incidence and mortality rates. It is frequently complicated by cachexia and is often detected in advanced stages of cancer, making chemotherapy the mainstay of treatment [14]. The new cachexia diagnostic criteria for Asians, which were proposed in 2023, were compared with conventional criteria, and the association with prognosis was verified.

4.1 | Prevalence of Cachexia

Compared to that in previous studies, the prevalence of cachexia in our study was higher [20–23]. The reasons for this may be that the lung cancer patients included in the study were those who came to the rehabilitation outpatient clinic because they were

TABLE 3 | Relationship with prognosis in each criterion.

Variable (reference)	Model I				Model II			
	HR	95% CI	*p*-value	C-statistic	HR	95% CI	*p*-value	C-statistic
AWGC	4.098	1.717 to 9.782	0.001	0.658				
EPCRC					2.726	1.440 to 5.159	0.002	0.658
Age	1.017	0.981 to 1.055	0.344		1.013	0.980 to 1.048	0.416	
Sex	1.369	0.693 to 2.706	0.364		1.232	0.621 to 2.444	0.550	
PS, 2–3 (0–1)	1.444	0.677 to 3.082	0.347		1.586	0.758 to 3.318	0.220	
Stage IIIB-IV, Rec (II-IIIA)	0.939	0.319 to 2.764	0.907		0.564	0.185 to 1.721	0.315	
Pathology, sm (non-sm)	1.032	0.544 to 1.959	0.922		1.026	0.539 to 1.955	0.936	
Treatment line, Third–(First, Second)	1.416	0.640 to 3.132	0.397		1.305	0.580 to 2.937	0.518	

Abbreviations: AWGC, Asian Working Group for Cachexia; CI, confidence interval; EPCRC, European Palliative Care Research Collaboration; HR, hazard ratio; PS, performance status; Sm, small cell carcinoma.

TABLE 4 | Impact of each parameter on prognosis.

Variable (reference)	HR	95% CI	*p*-value	C-statistic
AWGC	4.098	1.717 to 9.782	0.001	0.658
-Decreased grip strength	2.076	1.008 to 4.273	0.047	0.646
-Anorexia	1.852	0.846 to 4.056	0.123	0.643
-Elevated CRP	2.210	0.888 to 5.500	0.088	0.632

Abbreviations: AWGC, Asian Working Group for Cachexia; CRP, C-reactive protein.

concerned about muscle weakness and weight loss, were elderly, and many had advanced lung cancer. This may be further because patients referred to the rehabilitation outpatient clinic are those with or at risk for muscle weakness, grip weakness, and weight loss and may include more patients who already have cachexia or are at risk for cachexia compared to general lung cancer chemotherapy patients, which may have resulted in a higher cachexia prevalence. The prevalence of cachexia was 72.6% and 54.7% according to the AWGC and EPCRC criteria, respectively, with the AWGC criteria having a higher prevalence than that of the EPCRC criteria. The AWGC screens a wide range of patients with cachexia. The differences between the AWGC and EPCRC criteria were the addition of anorexia, grip strength (a measure of muscle strength), and CRP level, which reflects the degree of inflammation in addition to the change in weight and percentage of weight loss. This is a major advancement of the AWGC criteria. The cutoffs for anorexia, grip strength, and CRP included in the AWGC criteria are per the AWGC criteria paper, and we have included the rationale for these cutoffs in our methodology. The AWGC criteria do not specify a specific index for the degree of anorexia, and we used the MNA-SF to evaluate anorexia in this study. Cancer cachexia is a complex systemic metabolic disorder involving inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and IL-1, which results in muscle wasting, anorexia, malnutrition, energy expenditure at rest, and decreased physical activity [7, 24, 25]. Previous studies have indicated that in the AWGC diagnostic criteria endpoints, the three newly added items—anorexia, grip strength, and elevated CRP—are all indices that specifically capture the clinical picture characteristic of cachexia, a systemic inflammatory metabolic disorder. Previous studies have shown that low nutritional status, poor grip strength, and an elevated inflammatory response are poor prognostic factors in patients with lung cancer [26–28]. The AWGC criteria were loosely based on the degree of weight loss and BMI criteria for Asians, with the addition of parameters that appropriately captured the pathophysiology of cachexia, which may have screened a wider range of cachexia patients.

4.2 | Prognosis of Cachexia According to the AWGC and EPCRC Criteria

The prognosis of patients with lung cancer who had cachexia receiving chemotherapy was poor, regardless of whether cachexia was detected using the AWGC or EPCRC criteria. Previous studies have shown that cachexia decreases the efficacy of chemotherapy, increases toxicity, and worsens life expectancy [15, 16]. The present results support those of previous studies and suggest that the success or failure of cachexia control in patients

undergoing chemotherapy for lung cancer is a key factor in successful cancer treatment.

We used Kaplan–Meier curves and log-rank tests to examine the association between cachexia and survival days since the first rehabilitation outpatient visit, confirming that patients with cachexia have a poor prognosis regardless of which criteria they are diagnosed with. In addition, using the Cox proportional hazards model, we examined the association between prognosis and cachexia for each of the AWGC and EPCRC criteria, forcing age, sex, PS, histology, stage, line of treatment, and disease status as adjustment factors. We further performed C-statistic analysis to determine which criterion had a better prognostic discriminatory power. The results suggest that both criteria are equally discriminative for prognosis. Furthermore, as a response to the heterogeneity of the population, the same analysis was performed on 74 patients with advanced or recurrent non-small cell lung cancer. Although the analysis was conducted in a smaller sample size population, patients with cachexia had a significantly poorer prognosis, regardless of which criterion was used to judge them. Moreover, the C-statistics for prognosis showed that the AWGC criteria had a higher discriminative power for prognosis than the EPCRC criteria.

The diagnosis of cachexia requires evaluation of weight loss over a period of time. The EPCRC criteria diagnose cachexia by weight loss or BMI and sarcopenia in the past 6 months. Many reports exclude the evaluation of sarcopenia because it requires the skeletal muscle mass evaluation using a special machine called a body composition analyzer. In our study, we also did not evaluate sarcopenia. However, the diagnosis of cachexia using the EPCRC criteria can be made using noninvasive and easy-to-use indices, such as body weight and BMI, without the need for special equipment, except for the assessment of sarcopenia. Hence, the EPCRC criteria can be applied in a variety of healthcare settings. Contrarily, the AWGC standards are designed for Asians taking into account differences in physique, diet, and lifestyle between Europeans and Asians. Compared to the EPCRC criteria, the AWGC criteria are set with more relaxed standards for the rate of weight loss and BMI. Moreover, they are characterized by the addition of parameters for grip strength, CRP, and anorexia. The AWGC criteria are more lenient than the EPCRC criteria in setting weight loss rate and BMI; hence, weight and BMI loss can be noted at an earlier stage than with the EPCRC criteria, and any of the three parameters may be used to diagnose cachexia. Assessment of weight loss requires capturing changes over time, and prior studies have indicated that it is an unstable metric. Contrarily, because CRP, grip strength, and anorexia can be evaluated at a single point in the evaluation and as a result of the more relaxed rate of weight loss and BMI compared to the EPCRC criteria, many cachexia patients can be recruited at an earlier stage and diagnosed using the single-point parameters of CRP, grip strength, and anorexia in the AWGC criteria. This may be an advantage of the AWGC since cachexia is known to require intervention at an earlier stage. However, the AWGC criteria are more complicated than the EPCRC criteria because they require the evaluation of many more parameters. Grip strength measurement requires measuring equipment and is time-consuming. Measurement of CRP adds to the cost of medical care and invasiveness to the patient. There is no standardized tool to assess anorexia, and it is susceptible to chemotherapy-induced nausea as well as cachexia. The results of this study are based on a single institution in Japan with such tests and facilities, and therefore cannot necessarily be applied to other medical settings with different healthcare delivery systems or other Asian countries as there are limitations regarding the generalizability of the AWGC criteria. Furthermore, it is currently unclear whether the AWGC criteria can be applied to non-Asian countries, and further research is needed. Our additional analysis suggested that of the three parameters, elevated CRP is the most prognostically relevant indicator. Blood tests are required for CRP evaluation, which is a relatively common test at all medical institutions, and in patients undergoing chemotherapy, regular blood tests are an essential medical practice. Hence, CRP evaluation is unlikely to be an additional medical procedure required only for the diagnosis of cachexia. However, when there is a complication of infection during chemotherapy, the CRP results should be interpreted with caution. If it is difficult to evaluate all parameters of the AWGC criteria, evaluation of CRP may be a priority.

The EPCRC criteria are simple because they do not require invasive, costly, and time-consuming evaluation, except for the evaluation of sarcopenia, and similar to the AWGC criteria, it has been shown to be associated with prognosis in a variety of medical settings and non-Asian patients with cachexia. Therefore, the EPCRC criteria will also be a useful indicator for the diagnosis of cachexia in various healthcare settings and non-Asian patients.

4.3 | Limitations

Our study is a single-center, retrospective study involving a small sample size analysis with no power calculations. Moreover, since it is a single-center, retrospective study, it is not based on a sample size design with a priori power. Hence, the lack of reproducibility is a limitation of this study. We calculated patients by accumulating the maximum number of cases seen in rehabilitation outpatient clinics during the study period, which is a limitation of our study. We plan to conduct a study in the future at another institution with a prospective study design with a larger sample size and a power calculation. Additionally, the heterogeneity of the population in terms of treatment and treatment status is another potential limitation. To address this limitation, we made an effort to remove the confounding of heterogeneity by introducing age, sex, PS, stage, pathology, and line of treatment as adjustment factors. In addition, we performed multivariate and C-analysis on 74 patients with Stage IIIB, Stage 4, and postoperative recurrent non-small cell lung cancer in order to unify the stage and histologic types as much as possible. Due to missing data, five cases were excluded from the analysis. The possible effect of this was to include cases with poor prognosis rather than cachexia, which would have reduced the diagnostic accuracy of each criterion.

Since this is a retrospective study, the patients included were only those referred to our rehabilitation outpatient clinic; hence,

we were unable to evaluate all lung cancer patients who visited our clinic, and the possibility of selection bias cannot be ruled out. Future prospective studies would reduce patient selection bias and provide more reliable results.

4.4 | Conclusion

Cachexia was an independent poor prognostic factor in lung cancer patients receiving chemotherapy under both AWGC and EPCRC criteria both of which had similar prognostic discriminatory power. Among CRP, anorexia, and grip strength, elevated CRP may be the most prognostically relevant parameter in the AWGC criteria. Since this study was conducted in a heterogeneous population with a small sample size at a single institution, we plan to conduct a prospective study with a larger sample size to investigate the generalizability of the AWGC criteria and its association with prognosis.

Author Contributions

Takuya Fukushima: Substantial contributions to the conception or design of the work and to acquisition, analysis, or interpretation of data for the work; Jiro Nakano: Drafting of the work and revising it critically for important intellectual content; Naoya Ogushi: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Kazuki Fujii: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Yutaro Nagata: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Keisuke Kamisako: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Yukiko Okuno: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Yuta Okazaki: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Kentaro Nakanishi: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Kiyori Yoshida: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Tatsuki Ikoma: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Yuki Takeyasu: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Yuta Yamanaka: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Hiroshige Yoshioka: Substantial contributions to the acquisition, analysis, or interpretation of data for the work; Kimitaka Hase: Drafting of the work and revising it critically for important intellectual content; Takayasu Kurata: Final approval of the version to be published; Utae Katsushima: Substantial contributions to the conception or design of the work and acquisition, analysis, or interpretation of data for the work; provision of agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.