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Original Article

R–CSS: A clinically applicable score to classify cachexia stages in patients with cancer undergoing intensity-modulated radiation therapy

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ABSTRACT

Objective: Accurate cachexia staging is the key to its management. However, there is currently a lack of tools to distinguish the staging of cachexia in patients with cancer undergoing radiotherapy. The Radiotherapy Cachexia Staging Scale (R–CSS) was developed for the stratification of cachexia in patients undergoing cancer radiotherapy.
Methods: Patients with cancer undergoing radiotherapy were divided into four stages – noncachexia, precachexia, cachexia, and refractory cachexia – by the R–CSS scale, and the clinical outcomes of the four groups were compared.
Results: A total of 270 patients with cancer undergoing radiation therapy were included in the study. All participants were classified into four stages of cachexia: stage 0, I, II, and III. Patients with a higher cachexia stage had a higher prevalence of sarcopenia ($P = 0.015$). Scores on the 16-item M. D. Anderson Symptom Inventory were higher in patients with higher cachexia stages ($P < 0.05$), but levels of forgetfulness, numbness, and shortness of breath were not higher in these patients ($P > 0.05$). Patients with higher cachexia stages exhibited better scores on the QLQ-C30 scale ($P < 0.05$), except for in the domains of cognitive functioning, diarrhea, and dyspnea ($P > 0.05$). The incidence of treatment-related events (any grade III or higher grade of [non-]hematologic adverse events, the need for hospitalization, emergency room admission) was higher in patients with higher cachexia stages.
Conclusions: The R–CSS scale is a screening tool that can simultaneously distinguish different stages of cachexia.

Introduction

Cancer cachexia is a syndrome associated with reduced food intake and impaired metabolism and is characterized by catabolism and inflammatory changes.[1] Clinical outcomes of cachexia include weight loss (WL), altered body composition, reduced food intake, poor functional status, limited quality of life (QoL), and reduced overall survival.[2,3] Considering that cachexia affects 60%–80% of all patients with cancer,[4,5] different cachexia stages differentially impact the prognosis of those undergoing radiotherapy (RT), and cachexia should be diagnosed and classified promptly.

In the international consensus,[6] cancer cachexia is divided into three stages: precachexia, cachexia, and refractory cachexia. However, due to its complex physiopathology, the diagnosis and classification of cancer cachexia in clinical practice remains challenging. Cachexia stages play an important role in individual management. Therefore, a new tool for staging cachexia cancer patients was designed by Anotonio et al,[7] but it could not effectively classify the precachexia and cachexia stages. Geisiane et al[8] used the Glasgow prognostic score to classify cachexia in patients undergoing palliative treatment for advanced cancer, with good results; however, this study only involved predicting the 90-day mortality of patients and did not assess the disease burden and QoL of patients, which deviated from the definition of cachexia proposed by the international consensus to some extent. Zhou et al[9] successfully performed cachexia staging among patients with cancer; however, the relationship between cachexia stage and treatment-related events could not be analyzed.

Therefore, we aimed to develop a tool for classifying cancer cachexia and validating it to distinguish clinical outcomes, such as the incidence of sarcopenia, symptom burden, QoL, and treatment-related events, in RT patients.

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Methods

Patient selection

This study presents results from a prospective study conducted at Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University. We calculated the study sample size required to validate the clinical prediction rule based on the requirement of 100 patients with the outcome of interest, that is, the development of cachexia. This approach is supported by previously described statistical estimates for external validation of the clinical prediction rule. Based on previous studies,[10] we estimated the incidence of cachexia in the enrolled sample to be 40%, and thus, the total required sample size was calculated as 250 patients.

Patients who were at least 18 years old with a diagnosis of cancer (inpatients or outpatients received intensity-modulated radiation therapy at doses of 50–66 Gy) were included in this study between May 2021 and October 2021. The following patients were excluded from the study: mental illness, intellectual disability, unwillingness, or inability to complete the questionnaires. The reporting of the study adheres to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines,[11] The TRIPOD checklist is included in Additional file 1: Table S1. The study was approved by the Sun Yat-Sen Memorial Hospital Ethics Committee (SYSEC-KY-KS-20021-245).

Tumor staging was performed according to the American Joint Committee on Cancer tumor node metastasis staging system (AJCC 7th ed., 2010).[12]

Characteristics of patients with cancer

Demographics (age, gender, and body mass index [BMI]), clinical characteristics (diagnosis, stage, and treatment type of tumor), and routine blood test data (white blood cell count, hemoglobin, and albumin levels) were collected from the computerized hospital records. The clinician assessed the patient's Eastern Cooperative Oncology Group (ECOG) score.

R–CSS scale

To simplify the criteria of cachexia stages, Zhou et al[9] developed a cachexia staging score (CSS) for clinical use in patients with advanced cancer. Based on some RT studies and international consensus,[3,6,13] we added three items, including items that assess age, BMI, and decreased food intake, to form the Radiotherapy Cachexia Stage Scale (R–CSS) for patients with cancer undergoing radiation therapy.

After classifying patients into different stages, we compared the results of the eight components of the R–CSS scale between stages. In addition, we validated the effectiveness of R–CSS in discriminating cachexia by comparing differences in sarcopenia, symptom burden, QoL, and treatment-related toxicities among the four groups.

Participants were also asked to complete the SARC-F questionnaire to assess muscle function. The SARC-F questionnaire is a simple tool that is designed to quickly assess a patient's muscle function and screen for sarcopenia.[14] The SARC-F questionnaire assesses five dimensions: strength, assistance in walking, rising from a chair, climbing stairs, and falls. Each item is scored on a scale of 0–2, and higher total scores indicate worse muscle function.[15–17]

MDASI scale

The Chinese version of the M. D. Anderson Symptom Inventory (MDASI-C)[18] is a simple, patient-reported outcome measure used to assess the impact and severity of 19 cancer-related symptoms common across all cancer types. We used the MDASI to evaluate the symptom burdens (pain, fatigue, nausea, uneasy sleep, distress, shortness of breath, forgetfulness, poor appetite, drowsiness, dry mouth, sense of sadness, vomiting, numbness, general activity, mood, work, relationships with others, walking, life fun) of our patients. The score for each symptom ranged from 0 to 10, and higher scores indicated worse symptoms.

QoL scale

QoL was measured using QLQ-C30 version 3.0 (Chinese version 3.0).[19] The QLQ-C30 consists of 30 items, including one global health status scale, five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea, pain, and vomiting), and single-item symptom scales (dyspnea, appetite loss, insomnia, diarrhea, constipation, and financial difficulties). Twenty-five items were extracted from the QLQ-C30 questionnaire; questions about physical performance or food intake were withdrawn.

Outcome definition

Treatment-related events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0).[20] Treatment-related events were defined as any grade III or higher hematologic adverse events (such as Hgb < 8.0 g/dL, < 4.9 mmol/L, < 80 g/L, leukocytosis $> 100{,}000/mm^3$, transfusion indicated, life-threatening consequences, urgent intervention indicated, death), any grade III or higher nonhematologic adverse events (such as gastrointestinal disorders, general disorder, hepatobiliary disorders, immune system disorders, infections and infestations severe discomfort, or limiting self-care ADL), the need for hospitalization or emergency room visits, and incomplete RT. All adverse events and complications were recorded from RT initiation until 1 month after the completion of RT.

Body composition analysis was performed in patients with abdominal computed tomography images within 1 month. The outer circumference of the sternocleidomastoid muscle and paravertebral muscle was separated manually. Skeletal muscle was defined as -29 to $+150$ Hounsfield units,[21] and the total cross-sectional area was automatically calculated within the perimeter of the contour. Skeletal muscle cross-sectional area conversion at C3 was performed using the equation described by Swartz et al[22] to estimate skeletal muscle at L3. The SMI was then calculated based on the following equation: SMI (cm^2/m^2) = SMA (cm^2)/height^2 (m^2).[23] The lumbar skeletal muscle index (SMI) (cm^2/m^2) value was obtained to define sarcopenia. Sarcopenia was defined as an SMI < 39 cm^2/m^2 in female patients or < 55 cm^2/m^2 in male patients.[24]

According to some RT studies and international consensus,[3,6,13] the cutoff point for determining advanced age was > 70 years old; the cutoff point for BMI was ≥ 20 kg/m^2, 18.5-20 kg/m^2, < 18.5 kg/m^2; the point for WL in 6 months was stable or weight gain, $\leq 5\%$, 5%-10%, 10%-20%, $\geq 20\%$; and the decomposition point for food intake was reduced.

Data collection

Several nurses were trained to ensure that questionnaires were administered correctly and accurately. The first author trained the nurses on the purpose of the study and matters needing attention during the questionnaire distribution. To help patients better understand the questionnaire items, uniform language was used throughout the questionnaire delivery process. The primary outcomes (treatment-related affairs, body composition analysis, QoL scale, MDASI scale) were recorded by investigators who were unaware of the predictor variables.

Follow-up

All participants were followed through the follow-up system at the center where the study was conducted until October 2021, and the final event was either the end of RT or loss to follow-up. The main outcome of the study was treatment-related events. For patients with dyslexia or difficulty writing, the study nurse asked the questions and completed the questionnaires instead.

Data analysis

Categorical variables are represented as percentages, and variables with homogeneity of variance are presented as the mean ± standard deviation; for variables without homogeneity of variance, Kruskal–Wallis tests were used. Variables that were significant in univariate analysis were obtained to a logistic regression model after confirming there was no multicollinearity. Firth's method was implemented where complete or quasi separation was present. Factors in the univariate logistic regression analysis with $P < 0.100$ were subsequently entered into the multivariate model to determine independent risk factors for cachexia. Exploratory analyses were performed to determine appropriate weights for the added variables to more accurately evaluate the correlations of age, BMI, and food intake with the R–CSS questionnaire. For this purpose, the following variables were treated as categorical variables using the previously mentioned cut-offs: age > 70 years; BMI ≥ 20 kg/m^2, 18.5-20 kg/m^2, and < 18.5 kg/m^2; and weight stability or gain within 6 months, ≤ 5%, 5%-10%, 10%-20%, ≥ 20%. The reduction in food intake was used as a cutoff. Then, the values of these three variables were assigned differently (ranging from 0 to 12), and each variable was tested individually to find the best match (as assessed by the area under the curve [AUC]). The best choices were combined into a composite score, which already included 12 possible scores from the CSS questionnaire.[9] The cutoff point for the R–CSS was calculated by determining the area under the receiver operating characteristics curve. The receiver operating characteristic was used to assess the discriminatory power of the model.

All statistical analyses were completed using R software, MedCalc software (MedCalc 19.2.1; MedCalc, Mariakerke, Belgium), and SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was used to compare categorical variables, but when more than one-fifth of the expected frequencies were < 1, Fisher's exact tests were performed. Pairwise comparisons using nonparametric tests were performed. *P* values < 0.05 (two-sided) were considered statistically significant.

Results

A total of 305 patients were included in this study. Among them, 18 patients did not complete the MDASI or QLQ-C30, 8 patients did not complete the SARC-F scale, and 9 patients did not have treatment-related event data. Therefore, these patients were excluded from the study. Finally, data from 270 patients were collected for analysis (Additional file 1: Fig. S1). This study enrolled 270 patients who underwent RT. The ratio of male is 0.42 ($n = 114$), the ratio of female is 0.58 ($n = 156$), and the mean age of our patients was 50.0 ± 12.48 years. The mean BMI (kg/m^2) was calculated using weight (kg) and height (m) and was 21.1 ± 3.34 in our study. Most of the patients had the following tumor types: head and neck cancer (48.1%), breast cancer (23.7%), and gynecology cancer (8.1%). Other characteristics are summarized in Table 1.

Development of R–CSS

In univariate analysis, 11 factors were significantly associated with cachexia, as shown in (Additional file 1: Table S2) These potential factors were entered into the multivariate analysis. Subsequently, age ($P = 0.004$), BMI ($P = 0.060$), WL at 6 months ($P = 0.002$), SARC-F ($P = 0.028$), ECOG-PS ($P = 0.053$), appetite loss ($P = 0.002$), reduced food intake ($P = 0.012$), and abnormal biochemistry ($P = 0.008$) were identified as independent risk factors for cachexia.

The variance inflation factor between variables ranged from 1.041 to 2.336. No variance inflation factor was more than 10. Tolerance ranged from 0.04 to 0.960, indicating that multicollinearity was not a problem (Additional file 1: Table S3).

The R–CSS comprised eight components (Table 2): age (score range: 0–1); BMI (score range: 0–2); WL at 6 months (score range: 0–4); the strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire (score range: 0–3); ECOG performance status (score range: 0–2); appetite loss (score range: 0–1); reduced food intake (score range: 0–1); and abnormal biochemistry (score range: 0–2).

Using the previously mentioned method, the maximum screening power of R–CSS was obtained by adopting different weights. Thus, final scores ranged from 0 to 17, and the optimal cutoff point for cachexia screening was found to be 6 (Youden index: 0.77) (Additional file 1: Fig. S2). The calculated total score classified the noncachexia stage (0–3), precachexia stage (4–6), cachexia stage (7–12), and refractory cachexia

Table 1
Clinical characteristics of patients ($n = 270$).

Variables	Total ($n = 270$)
Age (years)[a]	50.0 (±12.48)
BMI (kg/m^2)[a]	21.1 (±3.34)
Gender	
Male	114 (42.22)
Tumor type	
HN[b]	130 (48.1%)
GI[c]	11 (4.1%)
Breast	64 (23.7%)
Lung	8 (3.0%)
Gynecology	22 (8.1%)
Others[d]	35 (13.0%)
Tumor stages	
I	28 (10.4%)
II	47 (17.4%)
III	79 (29.2%)
IV	116 (43.0%)
Treatment	4 (1.5%)
RT alone	88 (32.6%)
CRT postoperative (adjuvant) RT	178 (65.9%)

N, number of observations; %, frequency; BMI, body mass index; HN, head and neck; Gynecology, cervix uterus endometrium; CRT, concurrent chemoradiotherapy.
[a] Mean/standard deviation.
[b] Palate, tongue, oral and nasal cavity, tonsil, pharynx, larynx, buccal, zygomatic, salivary glands, gingival.
[c] GI, gastrointestinal, esophageal.
[d] Skin, central nervous system, liposarcoma, extranodal NK/T cell lymphoma, lymphoepitheliomatoid. rhabdomyosarcoma, cholangiocarcinoma, liver cancer.

Table 2
Criteria and scores for the clinical application of the cachexia stages.

Criteria	Values	Score
Age (years)	< 70	0
	≥ 70	1
BMI (kg/m^2)	≥ 20	0
	18.5-20	1
	< 18.5	2
Weight loss at 6 months	Weight stable or weight gain	0
	≤ 5%	1
	> 5% and ≤ 10%	2
	>10% and < 20%	3
	≥ 20%	4
SARC-F	0	0
	1–3	1
	4–6	2
	7–10	3
ECOG PS	0	0
	1–2	1
	3–4	2
Reduced food intake	No reduction or more	0
	Reduce	1
Appetite loss	0–3	0
	4–6	1
	7–10	2
Abnormal biochemistry		
Alb < 35 g/L	All normal	0
WBC > 10×10^9/L	One of the three abnormal	1
Hb < 120/110 g/L (male/female)	More than one abnormal	2

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; Alb, albumin; WBC, white blood cell; Hb, haemoglobin.

stage (13–17). It is therefore clear that the higher the score, the more severe the symptoms (Fig. 1).

Cancer cachexia staging

Based on the scale scoring criteria, a total of 270 patients were classified into four stages of cachexia (NCa, PCa, Ca, and RCa). Most patients (48.9%) were classified into the Ca stage, with 32.6% in the NCa stage and 16.3% in the PCa stage. Only 2.2% of patients were classified into the RCa stage (Table 3).

A significant difference was observed in all analyzed covariables (BMI, WL, SARC-F, ECOG score, appetite loss, reduced food intake, and abnormal biochemical indicators) among different stages of cachexia, but no difference was identified for age. The BMI, WL, SARC-F, ECOG score, appetite loss, reduced food intake, and abnormal biochemical indicators of the NCa group were significantly better than those of the other groups ($P < 0.001$). **(**The results of the comparison between groups are shown in Additional file 1**:** Table S4**)**

Analysis of sarcopenia in different cachexia stages

We also compared the prevalence of sarcopenia between different stages of cachexia (Fig. 2). The incidence of sarcopenia in the refractory cachexia groups (male, 50%; female, 60%) was significantly higher than that in the noncachexia (male, 5.6%, $P = 0.016$; female, 4%, $P = 0.009$) and precachexia groups (male, 7.7%, $P = 0.057$; female, 5.9%, $P = 0.024$) but not in the cachexia group (male, 27.1%, $P = 0.056$; female, 34%, $P = 0.342$).

Symptom burden and QoL in patients with different cachexia stages

Symptom burden

All patients completed the MDASI questionnaires. The symptoms (pain, fatigue, uneasy sleep, distress, shortness of breath, forgetfulness, poor appetite, drowsiness, dry mouth, sense of sadness, vomiting, numbness, general activity, mood, work, relationships with others, walking, and life fun) of patients in various stages of cachexia were more serious than those in the noncachexia group ($P < 0.05$), except numbness ($P = 0.094$) and shortness of breath ($P = 0.068$). Among the symptoms that were significantly different among different stages of cachexia ($P < 0.05$) (Additional file 1: Table S5), the most common symptoms in patients receiving RT were pain (73.3%), fatigue (87%), and dry mouth (85%) (noncachexia group [pain, 3.02 ± 2.2; fatigue, 3.94 ± 2.3; dry mouth, 3.68 ± 2.38], precachexia group [pain, 4.21 ± 2.5; fatigue, 4.46 ± 2.16; dry mouth, 5.13 ± 2.36], cachexia group [pain, 4.72 ± 2.8; fatigue, 5.34 ± 2.28; dry mouth, 5.75 ± 2.75], and refractory cachexia group [pain, 4.75 ± 2.9; fatigue, 6.25 ± 3.09; dry mouth, 5.82 ± 2.65]) (Fig. 3).

QoL

All patients ($n = 270$) completed the QLQ-C30 scale. Scores on the QLQ-C30 were evaluated in groups according to stages of cachexia (Fig. 4). Except for cognitive functioning (noncachexia, 77.58 ± 21.98; precachexia, 72.08 ± 21.14; cachexia, 74.73 ± 22.15; refractory cachexia, 63.33 ± 47.72; $P = 0.195$), diarrhea (noncachexia, 16.47 ± 22.66; precachexia, 20.83 ± 24.67; cachexia, 18.93 ± 22.25; refractory cachexia, 20.00 ± 29.81; $P = 0.680$), and dyspnea (noncachexia, 22.98 ± 23.46; precachexia, 26.66 ± 21.61; cachexia, 27.27 ± 23.95; refractory cachexia, 26.66 ± 36.51; $P = 0.591$), patients in the noncachexia group scored higher on functional items and significantly lower on symptom-related items on the QLQ-C30 scale ($P < 0.05$) (Fig. 4). Among the significant items, fatigue showed the largest difference among the different cachexia stages.

Treatment-related events among patients in different cachexia stages

Fig. 5 shows the ability of the R–CSS scale to predict treatment-related events among patients in the four stages of cachexia.

The R–CSS performed well in predicting treatment-related events. Compared to the noncachexia group (grade III or higher grade of hematologic adverse events [G–III–HGHAE], 4%, $P = 0.000$; grade III or higher grade of nonhematologic adverse events [G–III–NHGHAE], 3.4%, $P = 0.000$, need for hospitalization, 4%, $P = 0.000$; emergency room admission, 0%), the precachexia group (G–III–HGHAE, 5%, $P = 0.000$; G–III–NHGHAE, 8.1%, $P = 0.000$, need for hospitalization, 5%, $P = 0.000$; emergency room admission, 0%), and the cachexia group (G–III–HGHAE, 25%, $P = 0.002$; G–III–NHGHAE, 26.5%, $P = 0.003$, need for hospitalization, 27%, $P = 0.003$; emergency room admission, 3.1%), the refractory cachexia group (G–III–HGHAE, 85.7%; G–III–NHGHAE, 85.7%, need for hospitalization, 85.7%; emergency room admission, 28.5%) had the highest incidence of G–III–HGHAE.

Table 3
Associations to characteristics studied according to cachexia stages ($n = 270$).

Variables	NCa ($n = 88$)	PCa ($n = 44$)	Ca ($n = 132$)	RCa ($n = 6$)	*P*-value
Age (years) (mean) (SD)	47.64 (11.24)	49.60 (12.89)	50.90 (13.02)[a]	49.84 (12.53)[a]	0.012
BMI (kg/m^2) (mean) (SD)	22.62 (3.46)	22.23 (3.38)	20.88 (10.28)[a,b]	21.07 (2.93)	< 0.001
WL 6 month (%) (mean) (SD)	0.72 (1.30)	4.97 (6.22)[a]	11.49 (5.58)[a,b]	17.25 (6.69)[a,b]	< 0.001
SARC-F					< 0.001
0	41 (46.6%)	17 (38.6%)	31 (23.5%)	1 (16.7%)	
1–3	44 (50.0%)	20 (45.4%)	61 (46.2%)	1 (16.7%)	
4–6	2 (2.3%)	6 (13.7%)[a]	31 (23.5%)[b]	1 (16.7%)[a]	
7–10	1 (1.1%)	1 (2.3%)[a]	9 (6.8%)[a]	3 (50.0%)[a,b]	
ECOG PS					< 0.001
0	39 (44.3%)	8 (18.2%)	10 (7.6%)[b]	1 (16.7%)	
1–2	46 (52.3%)	32 (72.7%)	91 (68.9%)[b]	4 (66.7%)[a,c]	
3–4	3 (3.4%)	4 (9.1%)[a]	31 (23.5%)[b]	1 (16.7%)[a,c]	
Appetite loss (mean) (SD)	3.03 (1.99)	5.55 (2.52)[a]	6.06 (2.51)[a]	6.50 (2.42)[a]	< 0.001
Reduced food intake (mean) (SD)	0.72 (1.13)	2.05 (0.85)[a]	2.20 (1.05)[a]	2.67 (0.51)[a]	< 0.001
Abnormal biochemistry					< 0.001
All normal	57 (64.8%)	12 (27.3%)	21 (15.9%)	1 (16.7%)	
One abnormal	26 (29.5%)	19 (43.2%)[a]	48 (36.4%)[b]	0 (0.0%)[a,c]	
More than one abnormal	5 (5.7%)	13 (29.5%)[a]	63 (47.7%)[b]	5 (83.3%)[a,c]	

ECOG PS, Eastern Cooperative Oncology Group performance status; NCa, noncachexia; PCa, precachexia; Ca, cachexia; RCa, refractory cachexia; SD, standard deviation; BMI, body mass index; WL, weight loss.

[a] Statistically different from NCa.

[b] Statistically different from PCa.

[c] Statistically different from Ca.

R-CSS (0-17) = AG (0-1) + BMI (0-2) + WL (0-4) + SARC-F (0-3) + ECOG PS (0-2) + RFT (0-1) + AL (0-2) + AB (0-2) + AB (0-2)

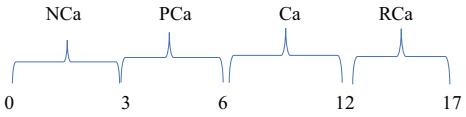

Fig. 1. Radiotherapy cachexia staging score. AG, age; BMI, body mass index; WL, weight loss; ECOG PS, Eastern Cooperative Oncology Group performance status; RFT, reduced food intake; AL, appetite loss; AB, abnormal biochemistry.

Discussion

This study provides a staging system for cachexia that can be used to identify, diagnose, and monitor cachexia at an early stage and stratify patient management so that a more standardized treatment and care plan can be designed for patients diagnosed with cachexia. First, based on the classification system proposed by Fearson[6] et al, the R–CSS scale was developed combining the characteristics of RT patients. Second, we used this scale to distinguish patients at different cachexia stages.

The literature shows that different cancer types have different prevalences of cachexia, among which the highest incidence of cancer cachexia is gastric cancer and pancreatic cancer (up to 80%), and the lowest incidence is leukemia and breast cancer (up to 40%).[10] In the present study, we found a high cachexia rate in patients with head and neck cancer (67.7%), and the lowest incidence was in breast tumors (26.5%). This could be because certain tumors, such as lung cancer, present different cachexia-inducing gene expression profiles.[25] In addition to increasing the morbidity and mortality of patients, aggravating the side effects of chemotherapy, and reducing the QoL of patients, cachexia is associated with the incidence of treatment-related events. In our study, different stages of cachexia were significantly associated with treatment-related events.[26] The exact mechanism by which higher cachexia stages lead to an increase in the occurrence of treatment-related events is unknown, but certain factors may be involved. For example, radiation-induced fatigue is known to be associated with elevated levels of proinflammatory cytokines, including TNF-α and IL-6, both of which are elevated in cachexia patients.[27] These factors have also been associated with oral mucositis in animal models.[28] TGF-β is another factor that is elevated in cachexia patients[29] and has been shown to mediate radiation-induced damage. Thus, the potentially proinflammatory state of cachexia patients may be worsened by RT. Alternatively, cachexia may be a marker of a clinically evident "frailty syndrome" characterized by decreased physiological reserves leading to an inability to cope with acute stressors.[30] These patients may be less suitable candidates for tolerating treatment-related events. Therefore, cachexia evaluation in patients with cancer undergoing RT is necessary.

Low BMI and WL are important criteria for the assessment of cachexia, and age-adjusted BMI is related to treatment-related events.[31–33] According to our results, NCa patients showed significantly higher BMI and lower WL than RCa patients ($P < 0.001$). In addition, previous studies showed inflammation as the major cause of WL in patients with cancer[34] and presented the concentration of albumin and C-reactive protein (CRP) as the best predictors of WL. Because white blood cell count (WBC) is more widely used in clinical practice than C-reactive protein (CRP), it has been used as an indicator of cachexia stage in previous studies.[7,35,36] Moreover, previous studies included haemoglobin as a biomarker.[7,9]

Reduced food intake and appetite loss are also necessary to diagnose cachexia in patients with cancer.[13] Many nutritional screening scales are widely used to assess patients' dietary intake reduction and appetite loss, such as the Scored Patient-Generated Subjective Global Assessment (PG-SGA),[37] nutritional risk screening 2002[38] (NRS2002) and the mini nutrition assessment.[39] Due to the complexity of these scales, patients' self-reported digital analogue score (NRS: 0–10 points) was used in this study to assess the degree of appetite loss. Dietary intake was divided into two grades: no reduction, increased (0 point), and decreased (1 point).

Decreased functions are prevalent in cancer patients and are related to cachexia.[24,39] Function was assessed by using the ECOG scale and SARC-F questionnaire. The SARC-F questionnaire[14] is a short, easy-to-use tool that has been validated in patients with cancer, and scores on this questionnaire have been shown to be associated with the main adverse outcomes of malnutrition and cachexia. The cutoff (score > 4) is associated with sarcopenia. Decreased function appears to be the critical transition point between stages of cachexia, and in our study, each stage was statistically significant ($P < 0.001$).

After designing the R–CSS rating scale, we evaluated the staging efficiency of the scale. In the sarcopenia assessment, the later the stage of cachexia in both male and female patients was, the higher the incidence of sarcopenia, and the difference between groups was statistically significant ($P < 0.05$). There were significant differences in sarcopenia across all cachexia stages except for Ca compared to RCa patients (all $P < 0.05$), which was similar to the study by Zhou[9] et al. However, the Cachexia Staging Scale (CSS) designed by Vigano et al[7] did not clearly distinguish between patients in the precachexia stage and patients in the cachexia stage during body composition verification. This finding could have different explanations. For example, the small number of patients in the RCa group (five patients) may have made the results less accurate.

Symptom burden and QoL were also important measures of cachexia.

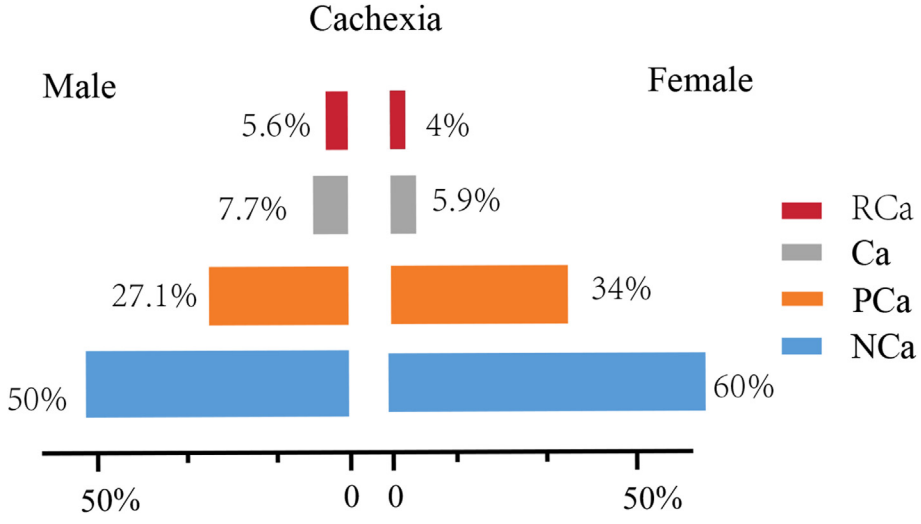

Fig. 2. Prevalence of sarcopenia in men and women at different stages of cachexia. NCa, noncachexia; PCa, precachexia; Ca, cachexia; RCa, refractory cachexia.

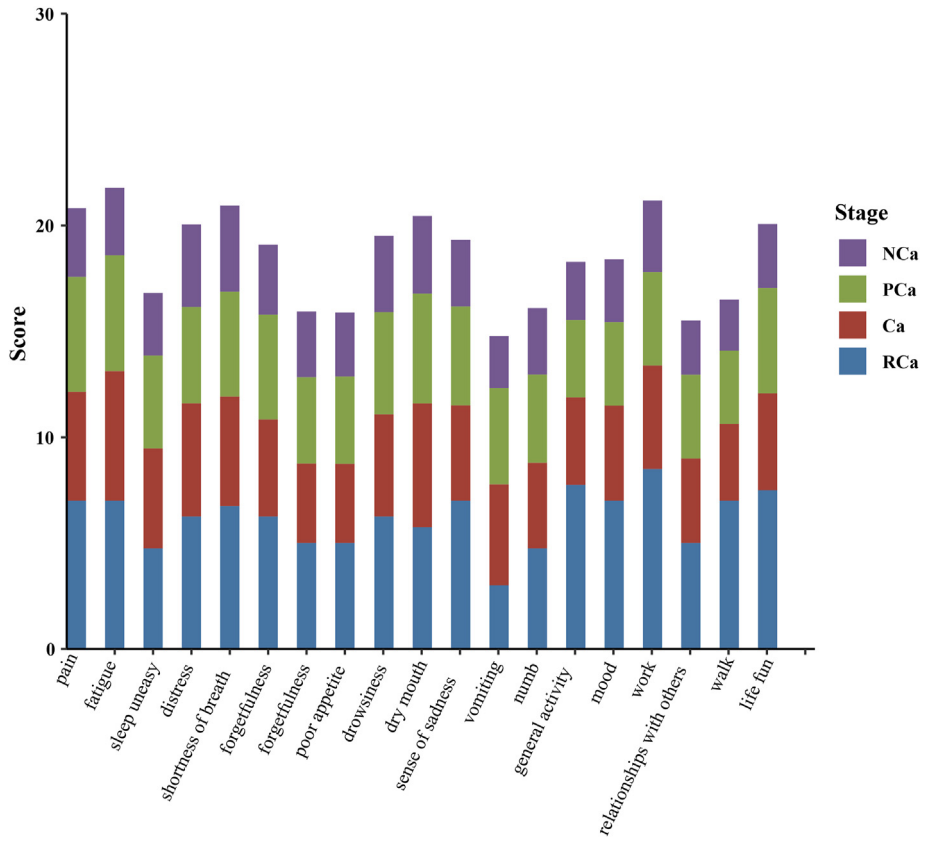

Fig. 3. Symptom burden scores of patients at different stages of cachexia. NCa, noncachexia; PCa, precachexia; Ca, cachexia; RCa, refractory cachexia.

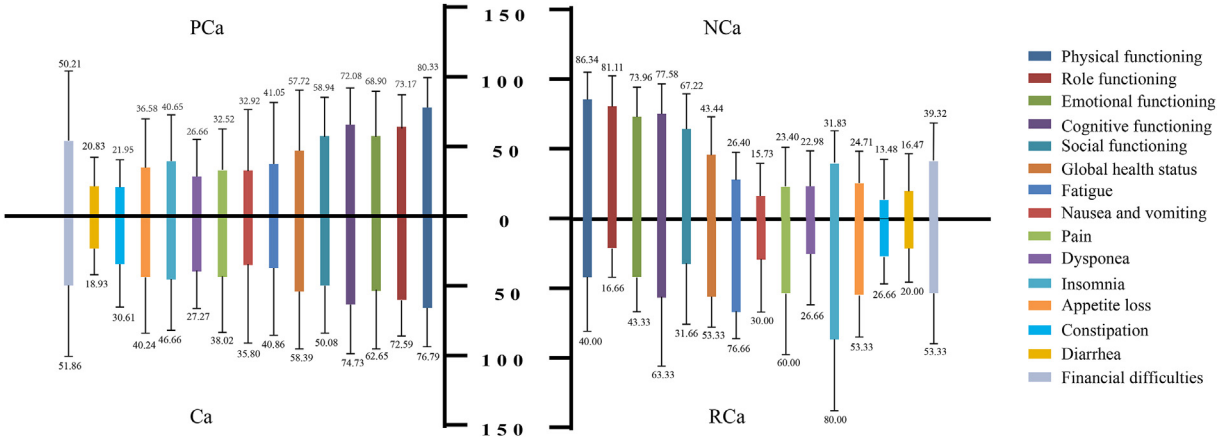

Fig. 4. Quality of life scores of patients at different stages of cachexia. NCa, noncachexia; PCa, precachexia; Ca, cachexia; RCa, refractory cachexia.

Overall, the severity of cachexia was effectively reflected by the subgroups according to the scale score, and the grade was negatively correlated with the QoL and disease burden of patients, which was consistent with previous research results.[41] The higher the degree of cachexia, the heavier the disease burden and the worse the QoL of patients. This finding supports the feasibility of using our score to assess the severity of cachexia in patients.

Cachexia is frequently associated with higher treatment-related toxicities in patients undergoing RT.[38,42,43] Our data showed significant differences among all groups. Compared to patients in the cachexia stage, patients in the noncachexia stage had the lowest incidence of emergency visits, hospitalization, grade III or higher hematological adverse events, and grade III or higher nonhaematological adverse events. This is similar to previous studies.[38,] While these treatment-related toxicities are not fatal, they inevitably worsen the physical and mental functioning of patients. This observation confirms that the importance of nutritional screening for patients with cachexia is universal, and the R–CSS scale designed in this study can effectively determine the prognosis of patients.

Zhang et al.[9] recently developed and validated a clinically applicable scoring system; however, the CSS is a clinically applicable tool with excellent discrimination for classifying cachexia stages. This scoring system is for patients with advanced cancer. Cong et al. found that the PG-SGA scoring system could rapidly screen patients with tumor cachexia; however, the PG-SGA could not be effectively used to define the degree of cachexia. R–CSS is a simple and easy-to-use tool. Our results

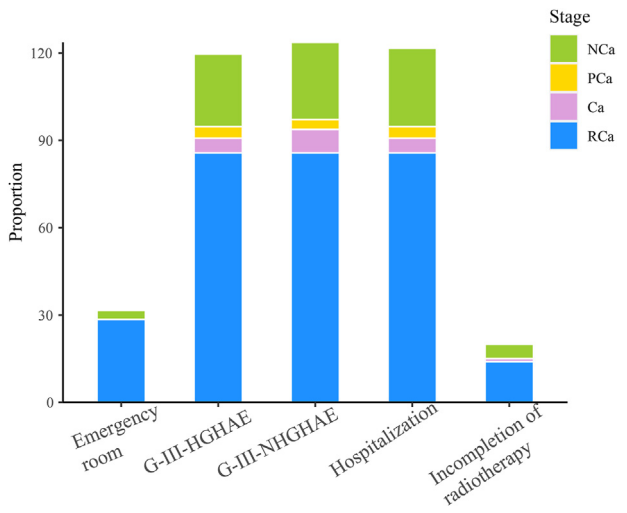

Fig. 5. Quality of life scores of patients at different stages of cachexia. NCa, noncachexia; PCa, precachexia; Ca, cachexia; RCa, refractory cachexia.

show that the sensitivity, specificity and stratification effect of R–CSS are good, and the higher the cachexia stage, the more likely it is that treatment-related adverse events. Therefore, R–CSS is suitable as a cachexia stratification tool for patients undergoing RT.

Limitations

There are some limitations to our study. First, our study was conducted in patients with many different cancers. Since the incidence of cancer cachexia varies by cancer type, it may not be practical to use the R–CSS in some cancer types. Second, oncologic treatments were disparate with regard to type, administration, and time interval from examination/interview of the patients, and we cannot exclude the possibility that some particularly aggressive therapies may adversely affect nutritional risk. Third, the R–CSS model only predicts patients 1 month after the completion of RT and lacks long-term prediction. Therefore, if more accurate long-term prediction is needed, new data and further update of the model are needed. Fourth, our study was a small-sample-size study that was conducted at a single center. Moreover, the number of patients in the RCa stage was small; therefore, multicentre studies with larger sample sizes are needed to further validate the R–CSS. Although this study was prospective, cachexia status changes were not followed up during follow-up; therefore, longitudinal data were not obtained.

To allow for the quick screening and grading of patients, muscle function assessments, such as grip strength and walking speed, and dual-energy X-ray or computed tomography/MRI measurements of the muscle areas of patients were not included in this evaluation scale, which could have led to reduced accuracy. However, the simple SARC-F questionnaire was used to for screen for sarcopenia and evaluate the muscle function of patients.

A simple digital analogue scoring method was used to evaluate patients' appetite loss and food intake, while conventional nutritional screening tools, such as PG-SGA and NRS2002, were not used, which may have led to imprecise results. In addition, there were few patients in the refractory cachexia stage, so the results still need to be further verified.

Conclusions

Our study developed a new type of cachexia staging scale that is simple and feasible for clinical use. This scale can be used to evaluate the stages of cachexia at the same time and has good distinguishing ability. Multicenter studies with larger sample sizes are needed to further validate the R–CSS.

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Author contributions

YHX first presented the idea and designed the outline of this article. LQY, YHX and LXL were responsible for all data extraction and analysis with the assistance of WY and CCL. The final version was revised by MXQ and YHX. LQY, WY and YHX were all responsible for the final submission.

Declaration of competing interest

None declared.

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Ethics statement

The study was approved by the Sun Yat-Sen Memorial Hospital Ethics Committee (SYSEC-KY-KS-20021-245).

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2022.100164.

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