Classification of Cancer Cachexia

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Katherine Petersen, MS, RD, CSO, CNSC
Chair, Oncology Nutrition Clinical Subcommittee
VHA Nutrition Field Advisory Board

Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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Disclosures

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Main Report

Evidence Synthesis Program

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ABBREVIATIONS TABLE

Abbreviation	Definition
AUC	Area under the curve
BMI	Body mass index
CAS	Cachexia assessment scale
CASCO	Cachexia score
CRP	C-reactive protein
CT	Computed tomography
CI	Confidence interval
CXI	Cachexia Index
CCSG	Cancer cachexia study group
CSS	Cachexia staging score
CCSI	Cancer Cachexia Staging Index
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ESAS	Edmonton Symptom Assessment System
ESP	Evidence Synthesis Program
GLIM	Global Leadership Initiative on Malnutrition
GNRI	Geriatric nutritional risk index
GPS	Glasgow Prognostic Score
HR	Hazard ratio
KQ	Key questions
L3-SMI	L3 skeletal muscle index
MeSH	Medical subject headings
MUST	Malnutrition universal screening tool
MST	Malnutrition screening tool
NRCS	Nonrandomized comparative studies
NLR	Neutrophil to lymphocyte ratio
NRS	Nutritional risk screening
NS	Nutrition screening
OR	Odds ratio
PG-SGA	Patient-generated subject global assessment
PM-SMI	PM skeletal muscle index
QLQ-C30	Quality of life questionnaire C30
REML	Restricted maximum-likelihood estimation
R-CSS	Radiotherapy cachexia staging score
RCT	Randomized controlled trial
SARC-F	Strength, assistance walking, rising from a chair, climbing stairs, and falls
SNAQ	Short nutritional assessment questionnaire

Abbreviation	Definition
SMI	Skeletal muscle index
SRDR+	Systematic Review Data Repository
WBC	White blood cell
VA	Veterans Affairs
VAS	Visual analogue scale
VHA	Veterans Health Administration
US	United States
TEP	Technical expert panel

BACKGROUND

Cachexia is a progressive wasting syndrome characterized by loss of weight and muscle mass,[1] as well as accompanying changes in inflammatory and metabolic processes.[2-4] A recent systematic review estimated that more than half of cancer patients in the United States (US) develop cachexia.[5] Cancer cachexia is associated with poor outcomes including mortality, reduced quality of life, and decreased physical and psychological functioning.[6-8] Cancer cachexia is also associated with increased hospital length of stay and health care costs.[8, 9] Generally, the prevalence of cachexia is higher in more advanced stages of cancer.[10, 11] More advanced cancer cachexia stages may be associated with worse clinical, person-centered, and health care utilization outcomes.[12,13] There may, therefore, be a benefit to understanding the different cachexia staging tools available in order to identify people who may be at risk for worse outcomes. Cachexia management generally focuses on appetite improvement through nutritional interventions; however, this does not address all aspects of the disorder. Other interventions may include medications for anorexia or physical activity, but there are currently no proven management strategies for cachexia.[2]

There are multiple proposed tools or algorithms to diagnose and stage cancer cachexia.[14] These algorithms use a variety of criteria or measures, some of which may not be easily obtained in routine clinical settings.[15] For example, a computed tomography (CT) scan for sarcopenia might require an additional scan beyond what is ordered for the underlying cancer, or these images may be obtained for other clinical purposes but not evaluated for sarcopenia. In addition, some strategies use only a limited number of components or stages to define cachexia, which may oversimplify staging of these patients by assuming equal risk of poor outcomes within these groups.[15] Malnutrition screening tools are sometimes used to stage cachexia, despite malnutrition and cachexia being separate diagnoses.[16] While weight loss, malnutrition, and sarcopenia are all intertwined with cachexia, they do not individually encompass the diagnosis of cancer cachexia. For example, patients may experience muscle loss without loss of adipose tissue or may experience fluid accumulation (and thus weight gain) related to cancer or its treatments.[1, 4] In these situations, weight change alone may not detect cachexia. More recent literature has highlighted the potential for biomarkers to help identify cachexia before clinical signs appear;[17] although, to date, no biomarker has been validated for cachexia diagnosis.

Although multiple cancer cachexia diagnostic and staging algorithms are available, it remains unclear whether classifying patients based on any of the algorithms is associated with clinical and patient-important outcomes. There is also little guidance available for diagnosing the severity of cancer cachexia. As an integrated health system for 9 million Veterans, the Department of Veterans Affairs (VA) diagnoses over 50,000 Veterans with cancer annually[18] and is committed to the whole health of Veterans.[19, 20] Because cachexia may impact cancer outcomes, VA is interested in systematic ways to diagnose, treat, and mitigate cancer cachexia. The Veterans Health Administration (VHA) Nutrition Field Advisory Board requested the present review of evidence on classification systems for staging cancer cachexia among adults and the short- and long-term outcomes associated with cachexia stages using the classification systems. We first describe the classification algorithms that have been published and the performance of these algorithms, then synthesize available evidence on the association between cachexia and clinical and patient-important outcomes. The Nutrition Field Advisory Board intends to use the findings of this review to inform guidance on strategies to identify and stage patients with cancer cachexia across the VA.

METHODS

TOPIC DEVELOPMENT

We worked with representatives from the VHA Nutrition Field Advisory Board and our technical expert panel (TEP), which included individuals from the VHA Nutrition & Food Services and Geriatrics & Extended Care, to refine the key questions (KQ). We focus on studies that report classification or staging algorithms for cancer cachexia, their performance metrics, and the clinical and patient-important health outcomes based on these classification algorithms. We define classification or staging algorithms as those that use more than 1 criterion or variable to classify cancer cachexia and that use measures beyond weight. We excluded cancer cachexia algorithms that used only single predictors or variables, including single laboratory measures or imaging techniques.

KEY QUESTIONS AND PROTOCOL

The following key questions were the focus of this review:

Key Question 1	What cancer cachexia classification algorithms have been described and what criteria have been used to develop these?
Key Question 2	What are their performance characteristics?
Key Question 3	What are the short- and long-term outcomes for patients following cachexia classification with the tools identified in KQ1?

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (CRD42023458540).

SEARCHING AND STUDY SELECTION

We conducted a preliminary search in Medline (via PubMed) that was focused on Medical Subject Headings (MeSH) terms specific to cachexia, cancer, classification, and measures, with confirmation that several known relevant publications were captured. We also explored and adopted aspects of search strategies from several existing systematic reviews relating to the terms specified as appropriate.[5, 21-36]

For our final searches, we searched Medline, Embase, the Cochrane library, and ClinicalTrials.gov from dates of inception to August 1, 2023 (see Appendix for complete search strategies). For the final searches, we used MeSH and free text terms for *cachexia*, *emaciation*, and *wasting syndrome*; terms specific to cancer, including *neoplasm*, *carcinoma*, and *tumor*; and terms relating to classification systems, including *severity assessment*, *prognostic factor*, or *staging*. Additional citations were identified from hand-searching reference lists of relevant systematic reviews and consultation with experts.

Citations were entered into EndNote where duplicates were removed. Remaining citations were screened in Systematic Review Data Repository (SRDR+) (https://srdrplus.ahrq.gov/). To ensure common understanding of the eligibility criteria, we ran 3 pilot rounds of 100 citations each, where all team members screened the same citations, until we achieved acceptable agreement. After the pilot rounds, we screened citations in duplicate. Conflicts that arose between screeners were adjudicated by discussion with the research team or by the lead researcher. Abstracts were excluded if they used the term cachexia (to describe presence or absence) but did not name the cachexia tool used or describe the

components used to define cachexia. We also excluded abstracts that did not mention any outcomes of interest. Accepted abstracts underwent full-text review by 2 independent reviewers; an additional team member was consulted to resolve conflicts as necessary. A list of studies extracted at full-text review, along with the reason for their exclusion, can be found in Appendix.

Study eligibility criteria are listed in Table 1. For all KQs, eligible studies included people ≥18 years of age with any type of cancer. Studies had to evaluate cancer cachexia diagnostic or classification algorithms that included multiple predictors or variables to define or stage cachexia. Evaluations of single measures (*eg,* weight loss, laboratory values, imaging findings) were excluded.

For KQs 1 and 2, our focus was on reporting the components (*eg,* weight and albumin) and performance characteristics (*eg,* sensitivity and specificity) of cancer cachexia classification algorithms. We included any study design, including validation studies, randomized controlled trials (RCTs), nonrandomized comparative studies (NRCSs), and single group studies.

For KQ3, eligible studies reported the association between cachexia stage using a classification algorithm described for KQ1 that compared either cachexia stages or cachexia diagnosis (*ie,* versus no cachexia). For KQ 3, the study could be of any design, but the study had to report on analyses that compared cachexia stages or cachexia to no cachexia (as defined by the evaluated algorithm). We excluded studies that describe cachexia algorithms that included outcomes of interest as part of their classification algorithm (*eg,* if a quality of life measure was included in the cachexia algorithm and then also assessed the same quality of life measure in the outcomes). Finally, studies had to use an analytic method to account for confounding between cancer cachexia and the prioritized outcomes (*eg,* inclusion of potential confounders in multivariable regression).

Table 1. Eligibility Criteria

	Inclusion Criteria	Exclusion Criteria
Population	KQ1, 2, & 3: Adults (≥18 years) with any type of cancer at risk for cachexia or with cachexia.	• Non-cancer populations • Non-humans • Studies in children
Exposure (Algorithm)	KQ1 & 2: • Cancer cachexia diagnostic strategies, screening, and classification/severity scoring algorithms (including modified algorithms) • Studies that identify patients as having cachexia using a multicriteria classification algorithm but only use weight to determine stage are included if they meet all other inclusion/exclusion criteria. • Studies that use multiple laboratory measurements or biomarkers but do not include any other clinical information for classification are included if they meet all other inclusion/exclusion criteria. KQ 3: • Cachexia stage or diagnosis as determined by a described algorithms eligible for KQ1	• Studies evaluating only individual predictors/variables, individual laboratory tests, strategies that solely rely on weight measures (*eg,* weight change, BMI, serum albumin) • Studies evaluating sarcopenia or malnutrition classification algorithms without mention of cachexia (in title or abstract at screening level) • Classification algorithms using single imaging or single lab techniques without any other accompanying classification criteria • Studies that analyze cachexia as present/absent but do not provide criteria for this definition in the abstract and did not report outcomes interest in the abstract • Undefined cachexia classification system (*eg*, ICD code, use of the term “cachexia” without naming a tool/algorithm or description of components) • Tools that use outcomes as part of their staging/classification definitions

	Inclusion Criteria	Exclusion Criteria
Comparator	KQ1 & 2: None, reference standard, alternate classification algorithms. KQ3: Lower cachexia stage or classification of no cachexia.	
Outcomes	KQ1 & 2 • Components for classification • Performance measures KQ3 • Survival (overall, cancer specific, *etc*) • Cachexia symptom burden/severity (anorexia, nausea, vomiting) • Functional levels (quality of life, Eastern Cooperative Oncology Group Score, Karnofsky Performance Scale Index, Activities of Daily Living, measures of mobility, exercise tolerance, fatigue, *etc*) • Hospitalizations • Feeding tube placement (including location and type) • Cachexia progression	
Timing	KQ1, 2, & 3: Any	
Setting	KQ1, 2, & 3: Any	
Study Design	KQ1, 2, & 3 • Validation • RCT • NRCS • Single group studies KQ1 & 2 • N ≥ 10 KQ3 • Studies that evaluate the association between cachexia tools and eligible outcomes in multivariable regression models, and that explicitly report the association between the tool and the outcome • N ≥ 10 per cachexia group	KQ1 & 2 • Protocols • Conference abstracts or other non-peer-reviewed sources KQ3 • Unadjusted associations between tools and outcomes

Abbreviations. KQ=key question; NRCS=non-randomized comparative study; RCT=randomized controlled trial.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

For all KQs, we extracted details about the study design, total sample size, and the cachexia assessment algorithm used. For KQs 1 and 2, we extracted details on the components of the cancer cachexia classification algorithm, coding or scoring scheme, and cutoffs used. Performance characteristics were collected for studies that compared algorithms against a reference standard of either clinical exam or another cachexia algorithm, including sensitivity, specificity, positive and negative predictive values, and interrater reliability and correlation measures. For KQ3, we extracted details on study design, baseline population characteristics, and prioritized outcomes (survival, function, hospitalization, cachexia progression and symptom burden, and feeding tube placement). For all KQs, all data extraction was first completed by 1 reviewer and then confirmed by a second reviewer, with consultation from other team members as needed to resolve conflicts.

For KQ3, study risk of bias was independently assessed by 1 reviewer using questions derived from the Risk of Bias In Non-randomized Studies – of Interventions tool (see Appendix). We additionally evaluated whether the article was free of discrepancies and adequately reported patient eligibility criteria, protocols, setting, and outcome assessments. Studies had low risk of bias if they used propensity score adjustment and had ≤1 other concern. Studies had moderate risk if they used a multivariable regression to adjust for confounding and had ≤1 other concern or if they used propensity score adjustment and had 2 concerns for bias in other domains. Studies were high risk of bias if there were concerns about the adjustment used, used a propensity score but had ≥2 other concerns, or used multivariable regression and had ≥2 concerns for bias in other domains.

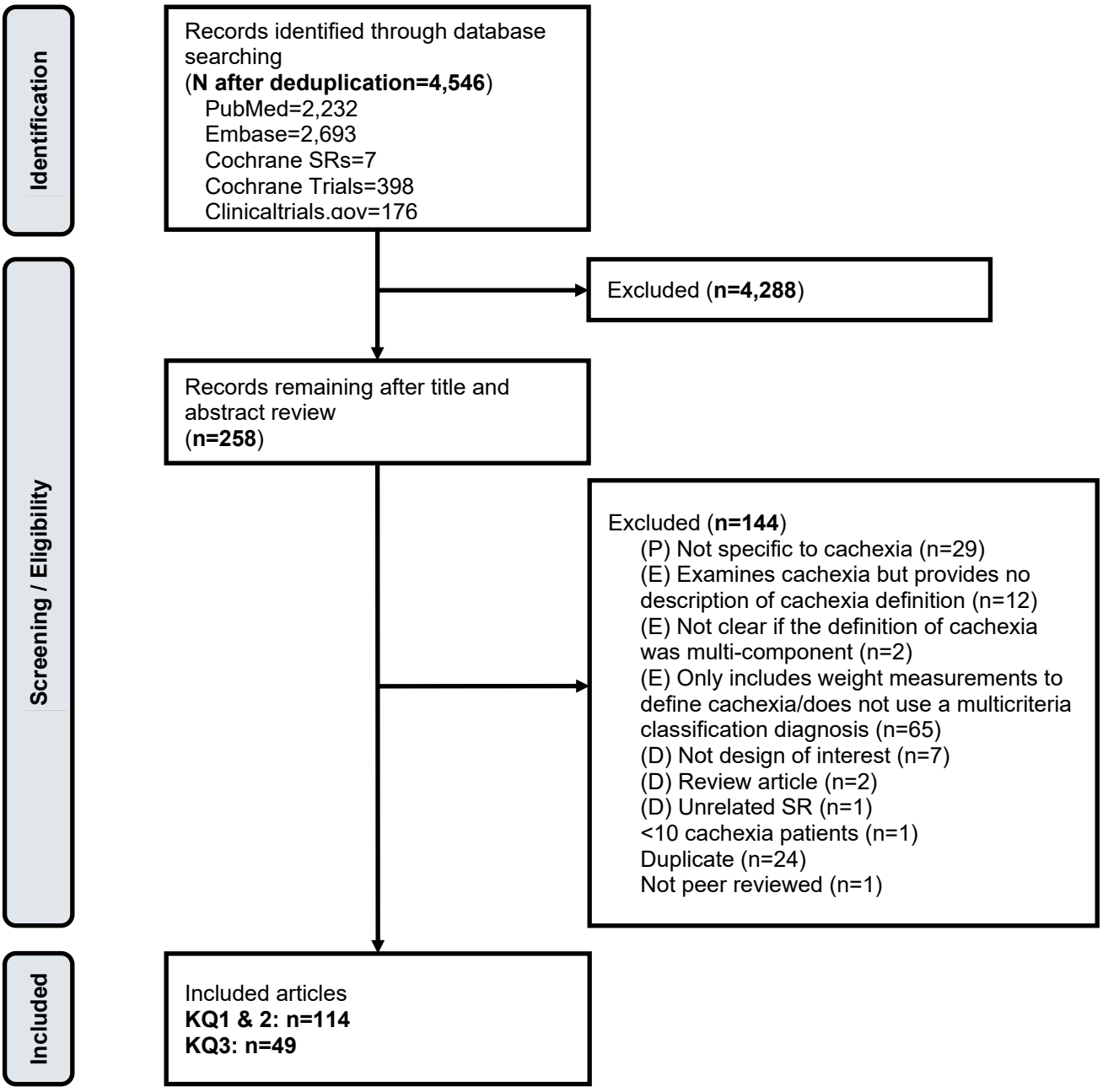
SYNTHESIS

For KQ1 and 2, we described the features of the classification algorithm including their scoring and performance characteristics. For KQ3, we extracted results data from reported multivariable regression models including odds ratios (OR), risk ratios (RR), hazard ratios (HR), or beta coefficients. Where there were at least 3 studies reporting results from sufficiently similar analyses (based on population, interventions, comparators, and outcomes), we conducted random-effects meta-analyses using the *meta* package for R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).[37] Statistical heterogeneity was estimated using restricted maximum-likelihood estimation (REML) and is reported using the I^2 statistic, which is the proportion of all variability in effects (within and between studies) that is attributable to between-study variation (*ie*, heterogeneity). We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to determine certainty of evidence for cachexia algorithms that had 3 or more comparative studies.

RESULTS

LITERATURE FLOW AND OVERVIEW

Of 4,546 records screened, 258 were accepted for full-text review. After reviewing these, 114 were eligible for KQ1 and 2, and 49 (a subset of the 114) were eligible for KQ3. The most common reasons for exclusion included not reporting a multicriteria classification algorithm ($N = 65$) and not being specific to cancer cachexia ($N = 29$).



CLASSIFICATION ALGORITHMS TO DIAGNOSE AND STAGE CACHEXIA

For KQ1, 114 studies described 137 (32 unique) cancer cachexia algorithms. These studies were conducted mostly in Europe (*N* = 36), China (*N* = 23), and Japan (*N* = 21); 11 studies were conducted in the US. The included studies were published between 2006 and 2023. Two studies were conducted within the VA. Most studies (*N* = 99) described algorithms that had a dichotomous definition of cachexia (*ie,* present or absent), 19 studies described a 3-category definition (*eg,* no cachexia, mild cachexia, severe cachexia), and 15 studies described a 4-category definition (*eg,* no cachexia, precachexia, cachexia, refractory cachexia). Four described a continuous risk score. Table 2 shows the 32 different cancer cachexia classification algorithms and their components (see Appendices for full definitions of cachexia algorithms and their components). The Fearon 2011 algorithm, or a modification of it, was the most frequently reported algorithm (*N* = 68), followed by the Cachexia Index (CXI) (*N* = 16), the Evans 2008 algorithm (*N* = 8), and the Glasgow Prognostic Score (GPS) or a modification of it (*N* = 6). All other classification algorithms were reported in fewer than 5 studies. Eleven studies described an unnamed investigator-developed algorithm. Eight studies, including the 6 that used GPS, described algorithms originally designed to measure other aspects of health, such as malnutrition or inflammation.

Studies described cancer cachexia classification algorithms with a diverse range of components. The individual components included: anorexia, appetite loss, or nutrition measures (*N* = 18); sarcopenia or skeletal muscle index (SMI) (*N* = 15); weight loss (*N* = 15); body mass index (BMI) (*N* = 15); albumin (*N* = 14); performance, function, or muscle strength (*N* = 13); C-reactive protein (CRP) (*N* = 12); hemoglobin (Hb) (*N* = 11); white blood cell (WBC) count (*N* = 4); fatigue (*N* = 4); neutrophil to lymphocyte ratio (NLR) (*N* = 3); quality of life (*N* = 2); dysphagia (*N* = 1); stomatitis (*N* = 1); edema (*N* = 1); ascites (*N* = 1); serum creatinine (*N* = 1); or some other component (*N* = 19), which included: impaired glucose tolerance, diarrhea, nausea, vomiting, abdominal pain, other gastrointestinal symptoms (unspecified), plasma IL-6, plasma pre-albumin, plasma lactate, plasma triglycerides, plasma urea, ROS plasma levels, tumor volume, test/HOMA index altered, absolute lymphocyte number, PG-SGA, GNRI, MUST, MST, SNAQ, NRS-2002, age, cancer site and stage, advanced lung cancer inflammation index, time from symptom onset to hospitalization, platelets, direct bilirubin, dinking (yes/no), total protein, <3 months expected survival, combined or other inflammatory markers (not specified), and underlying chronic disease (not specified). See component details in Appendix for a detailed description of the heterogeneous measures used to evaluate these components. For example, 14 algorithms included physical function measured by the Patient Generated Subjective Global Assessment (PG-SGA), hand grip strength, Karnofsky performance score, Eastern Cooperative Oncology Group (ECOG) scale, or other undefined functional or physical status scores. There were no temporal relationships identified in parameters included in the algorithms; however, several of the more recent algorithms identified developed nomograms as part of their assessment for cachexia. The component details table (see Appendix) also provides a detailed description of the different cutoffs for each measure. For example, weight loss was a component in 15 studies with cutoffs ranging from <2% to >20%.

In summary, 114 studies described 32 unique cancer cachexia algorithms. The most frequently evaluated algorithms included the Fearon 2011 algorithm, the Cachexia Index, and the Evans 2008 algorithm.

Table 2. Components Included in Identified Algorithms

Algorithm	Number of Cachexia Classifications/Stages	Weight Loss	Body Mass Index	Sarcopenia or Skeletal Muscle Index	C-Reactive Protein	Albumin	Neutrophil to Lymphocyte Ratio (NLR)	Anorexia or Appetite Loss or Nutrition	Performance/Function/ Muscle Strength[c]	White Blood Cell Count	Hemoglobin (Hb)	Dysphagia	Stomatitis	Edema	Ascites	Creatinine	Quality of Life	Fatigue	Other	Number of Studies
Fearon 2011 (without modification)[a,b]	2	X	X	X																53
Fearon 2011 (with modification or staging)[a,b]	2-4	X	X	X	X			X	X										X	15
Cachexia Index (CXI)[a,b]	Continuous, 2			X		X	X													16
Cachexia Staging Score (CSS)[a]	3	X		X		X		X	X	X	X									2
Radiotherapy Cachexia Staging Score (R-CSS)	3	X	X	X		X		X	X	X	X								X	1
Cachexia Assessment Scale (CAS)[b]	4	X	X			X		X	X		X	X	X	X	X	X			X	1
Evans 2008[a,b]	2	X	X	X	X	X		X	X		X							X	X	8
Cancer Cachexia Score (CCS)[a]	3		X	X				X											X	1
Cancer Cachexia Staging Index (CCSI)[a,b]	3	X	X	X		X		X	X										X	1
Cancer Cachexia Study Group (CCSG)/Fearon 2006[a,b]	2	X			X			X												4
Cachexia SCOre (CASCO) and miniCASCO[b]	3-4	X			X	X		X	X		X						X	X	X	3

Algorithm	Number of Cachexia Classifications/Stages	Weight Loss	Body Mass Index	Sarcopenia or Skeletal Muscle Index	C-Reactive Protein	Albumin	Neutrophil to Lymphocyte Ratio (NLR)	Anorexia or Appetite Loss or Nutrition	Performance/Function/ Muscle Strength[c]	White Blood Cell Count	Hemoglobin (Hb)	Dysphagia	Stomatitis	Edema	Ascites	Creatinine	Quality of Life	Fatigue	Other	Number of Studies
Glasgow Prognostic Score or modified Glasglow Prognostic Score[a,b]	3 or 4				X	X														6
Patient-Generated Subjective Global Assessment (PG-SGA)[b]	2 or 3																		X	3
Fearon 2011 and Evans 2008 combined[a]	2 - 4	X	X	X	X	X		X	X	X	X									4
Hand Grip Strength Cachexia Index (H-CXI)[a,b]	2					X	X		X											1
Wallengren 2013[a,b]	2	X			X													X		2
Nutritional Status Algorithm[a]	4	X	X	X	X	X		X	X		X							X	X	1
Orell-Kotikangas 2017[a]	2			X					X											1
Solheim 2011	3		X		X			X	X											1
Go 2020[a]	2			X															X	1
Namikawa 2022[a]	2	X	X		X	X		X			X									1
Huo 2022[b]	Continuous							X									X		X	1
Liu 2022[b]	Continuous					X					X								X	1
Tan 2023[a,b]	Continuous		X	X			X	X											X	1
Yin 2022[b]	Continuous		X		X			X			X								X	1
Vigano 2017[a,b]	4	X			X	X		X	X	X	X									1

Algorithm	Number of Cachexia Classifications/Stages	Weight Loss	Body Mass Index	Sarcopenia or Skeletal Muscle Index	C-Reactive Protein	Albumin	Neutrophil to Lymphocyte Ratio (NLR)	Anorexia or Appetite Loss or Nutrition	Performance/Function/ Muscle Strength[c]	White Blood Cell Count	Hemoglobin (Hb)	Dysphagia	Stomatitis	Edema	Ascites	Creatinine	Quality of Life	Fatigue	Other	Number of Studies
Wiegert 2021[a]	3		X	X																1
Global Leadership Initiative on Malnutrition (GLIM)[b]	2	X	X	X				X											X	1
Malnutrition Universal Screening Tool (MUST)[b]	2																		X	1
Nutritional Risk Screening (NRS)-2002[b]	2																		X	1
Malnutrition Screening Tool (MST)[b]	2																		X	1
Short Nutritional Assessment Questionnaire (SNAQ)[b]	2																		X	1
Number of Algorithms Using Each Component		**15**	**15**	**15**	**12**	**14**	**3**	**18**	**13**	**4**	**11**	**1**	**1**	**1**	**1**	**1**	**2**	**4**	**19**	**137**

Notes. [a] Included in KQ 3; [b] Compared against clinical exam or compared to another cachexia algorithm; [c] Measures of muscle strength were included with physical function or performance.

Fearon 2011 and Its Modifications

Sixty-eight studies described the Fearon 2011 algorithm ($N = 53$)[7, 16, 38-88] or some modification of this ($N = 15$).[8, 89-102] Both of the studies conducted within the VA used the Fearon 2011 algorithm. The main definition of Fearon 2011 consisted of either weight loss, a combination of weight loss and low BMI, or a combination of weight loss and sarcopenia. Generally, cutoffs for weight loss were ≥5% for weight loss alone and ≥2% when combined with BMI or sarcopenia; although these thresholds and the timing of measurement varied by study (see Appendix). BMI cutoffs included <20 kg/m^2 and <18.5 kg/m^2 depending on the study population. Measurements for sarcopenia varied widely and included CT; dual x-ray absorptiometry (DEXA) scan; mid-upper arm mass area (MUAMA); bioelectrical impedance (BIA); strength, assistance walking, rising from a chair, climbing stairs, and falls screening tool (SARC-F); European working group on sarcopenia in older people (EWGSOP) criteria; and other methods. Fifteen studies included modifications ($N = 5$) or additional staging ($N = 10$) to the Fearon 2011 algorithm. Additional components used in these studies included CRP measurements ($N = 3$), appetite, anorexia, or nutritional assessments ($N = 4$), function, performance, or muscle strength measures ($N = 3$), impaired glucose tolerance measures ($N = 1$), unresponsiveness to treatment ($N = 1$), and expected survival estimates ($N = 1$). Three studies described modifications with 4 stages, 6 studies with 3 stages, and 1 with 2 stages. Stages included no cachexia or normal status, precachexia, cachexia, and refractory cachexia. Weight loss thresholds for modified and staged versions for the Fearon 2011 algorithm ranged from no weight loss for precachexia to ≥15% weight loss for refractory stage cachexia. BMI thresholds for modified or staged Fearon 2011 algorithm ranged from <20 to ≥22 kg/m^2. Again, definitions of sarcopenia varied across studies (see Appendix).

Cachexia Index and Its Modifications

Sixteen studies describe the CXI,[49, 80, 103-116] which was used in most studies to classify patients as either low CXI or stage II (*ie*, cachectic) or high CXI or stage I (*ie*, noncachectic). One study classified patients into 3 stages based on SMI using both the L3 vertebral muscles and the pectoralis muscles (PM) at the T4 vertebral level. High CXI had both high L3-CXI and high PM-CXI, intermediate had high L3-CXI and low PM-CXI, and low-CXI groups had low L3-CXI and low PM-CXI, with CXI cutoffs based on the Youden index.[107] Components for the CXI include measurements of SMI, albumin, and NLR. The CXI was calculated as (SMI × albumin)/NLR, with cutoffs for cachexia varying by sex, measurement of SMI used, and unit of measurement for albumin. Generally, cutoffs were determined by the Youden index or median CXI value for the study sample. One study described a modified version of the CXI that incorporated hand grip strength (H-CXI) as an additional component.[84] Similar to the original CXI, the H-CXI was calculated as [hand grip strength (kg)/height (m)^2 × serum albumin (g/L)]/NLR, and cutoffs for cachexia were 175 for males and 113 for females.

Evans 2008

Eight studies[60, 78, 79, 88, 102, 117-119] described the Evans 2008 algorithm, which defined cachexia as weight loss or low BMI, plus any 3 of the following: fatigue, anorexia, decreased muscle strength, low fat-free mass index, abnormal serum biochemistry (including increased inflammatory markers, anemia, and low serum albumin).[14] All 8 studies reported weight loss cutoffs ≥5% over 6-12 months and BMI cutoffs from 18.5-22 kg/m^2. When specified, sarcopenia was measured using fat-free mass index (measuring low muscle), low muscle mass assessed by appendicular skeletal muscle index or mid-arm muscle circumference, or lean muscle depletion measured by bioelectrical impedance analysis. Decreased muscle strength was measured by hand grip strength, and anorexia was assessed by visual analog scale (VAS), energy intake, or European Organization for Research and Treatment of Cancer

(EORTC) questionnaire appetite loss score. Fatigue was measured by the EORTC or VAS. Cutoffs for albumin were <32 g/L or <35 g/L for serum albumin, >5 mg/L for CRP, and Hb cutoffs were <120 g/L or <117 g/L. Other components included unspecified inflammatory markers, IL-6 >4pg/ml, and underlying chronic disease.

Combined Evans and Fearon

Four studies described a combined Evans 2008 and Fearon 2011 algorithm, which was attributed to Vigano et al.[120-123] One study included a 2-stage definition of cachexia (*eg,* yes/no) that was based on weight loss or weight loss and BMI, in conjunction with abnormal laboratory values (CRP, albumin, or Hb)[120]. Two studies included a four-stage definition of cachexia defined as no cachexia, precachexia, cachexia, and refractory cachexia groups, with both subdividing the stage of cachexia as either "cachexia" or "cachexia caused by low BMI or sarcopenia." The classifications were based on a combination of abnormal laboratory values (CRP, albumin, WBC, or Hb), anorexia or decreased food intake based on the Edmonton Symptom Assessment System (ESAS) or PG-SGA, physical function or muscle strength based on PG-SGA or hand grip strength, and a combination of BMI, weight loss, or sarcopenia measures. A fourth study classified patients into precachexia, cachexia, and refractory cachexia groups, with the refractory cachexia category incorporating the physical function measures.[123]

Cancer Cachexia Study Group (CCSG)/Fearon 2006

Four studies described the Cancer Cachexia Study Group (CCSG) criteria, which is sometimes called the Fearon 2006 algorithm.[76, 79, 81, 124] The CCSG classifies patients as cachectic if they meet 2 of the following criteria: CRP ≥10 mg/L, weight loss ≥10%, or caloric intake of ≤1500 kcal/d. One study applied 2 different approaches to classify patients: 1) patients who met 2 criteria and 2) patients who met all 3 criteria.[79]

Cachexia Score (CASCO) and Mini Cachexia Score (miniCASCO)

Three studies describe the cachexia score (CASCO) and miniCASCO.[61, 125, 126] The CASCO uses body weight loss and lean body mass; inflammation, metabolic disturbances, fatigue, anemia, immunosuppression; physical performance; anorexia; and quality of life to generate a composite score for cachexia. For the CASCO, 40% of the summary score is based on weight loss or body composition, 20% on inflammatory or metabolic disturbances or immunosuppression, 15% on performance assessed through 5 questions about physical activity, 15% on anorexia assessed by the SNAQ, and 10% on quality of life assessed by the QLQ-C30.[127] The miniCASCO is an abbreviated version of this tool that uses investigator-developed questions to assess performance, anorexia, and quality of life rather than formal tools, like the SNAQ, and also includes fewer blood components. In the included studies, both the CASCO and miniCASCO used a numeric scale from 0-100 to classify patients into 4 groups: no cachexia (≤14), mild (15–28), moderate (29–46), and severe (>46) cachexia. However, 1 identified study used the CASCO to classify patients into 3 cachexia groups: no cachexia, precachexia, and cachexia without specifying any scoring system.

Cachexia Staging Score and Radiotherapy Cachexia Staging Score

Three studies used either the Cachexia Staging Score (CSS) or the Radiotherapy Cachexia Staging Score (R-CSS), a modification of the CSS.[13, 128, 129] The CSS assigns points to measurements of weight loss, strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire score, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, appetite loss, and abnormal biochemistry, defined as WBC count >10 × 10^9/L, albumin <35 g/L, and

Hb of <120 g/L for males and 110 g/L for females. Total CSS score ranges from 0-12, which is used to classify patients as noncachectic (0-2), precachexia (3-4), cachexia (5-8), or refractory cachexia (9-12). The R-CSS added 3 additional components for age, BMI, and food intake. The total score for the R-CSS ranges 0-17 with scores of 0-3 indicating no cachexia, 4-6 indicating precachexia, 7-12 indicating cachexia, and 13-17 indicating refractory cachexia.

Cancer Cachexia Staging Index

One study described the Cancer Cachexia Staging Index (CCSI).[130] The CCSI assigns point values to subjective and objective measures. Subjective measures include BMI adjusted weight loss grade with cutoffs of 0, 1, 2, 3, and 4, weight loss rates with cutoffs of 0.38 and 1.7 kg/month, inflammation defined by a combination of NLR (cutoff of 3.5) and CRP levels (cutoffs of 2.9 or 2.3mg/L), prealbumin with a cutoff of 180 mg/L, and skeletal muscle index with cutoffs of 44.4 and 35.7 cm^2/m^2 in males and 37.5 and 30.9 cm^2/m^2 in females. Objective measures include appetite and physical status, both assessed as good, fair, or poor. Total scores range from 0-27 with scores <9 defined as no cachexia, score of 9-18 indicating mild or moderate cachexia, and those ≥19 indicating severe cachexia.

Wallengren 2013 Algorithm

Two studies described the Wallengren 2013 algorithm.[79, 123] This algorithm used weight loss, fatigue, and CRP to categorize patients as cachectic or noncachectic based on cutoff values of >2% for weight loss, >3 for fatigue score on a visual analog scale of 1–10 or the ESAS, and CRP >10 mg/L for CRP.

Nomograms to Identify Cachexia

Four studies described nomograms to classify patients as cachectic.[53, 58, 75, 85] The Liu 2022 nomogram was specific to lung cancer patients and included components for cancer stage, albumin, anemia, advanced lung cancer inflammation index, and surgery. The nomogram developed by Huo 2022 included age, nutritional risk screening (NRS 2002), PG-SGA, quality of life (EORTC QLQ–C30), and cancer category (based on site of primary cancer). The nomogram developed by Tan 2023 included cancer site, cancer stage, time from symptom onset to hospitalization, appetite loss (not defined), BMI, SMI [skeletal muscle area (cm^2)/height (m^2)], and NLR. The nomogram by Yin 2022 included BMI, cancer type, anorexia, platelet count, early satiety, abdominal pain, diarrhea, vomiting, CRP, other gastrointestinal symptoms, Hb, direct bilirubin, drinking status, tumor stage, and total protein. Each nomogram utilized the indicated algorithm to calculate a composite score that was associated with cachexia risk.

Cachexia Assessment Scale

One study described the Cachexia Assessment Scale (CAS).[131] The CAS assigns points to investigator-developed assessment questions about functional status, weight loss, BMI, stomatitis, edema, ascites, albumin, Hb, serum creatinine, dysphagia, loss of appetite, diarrhea, nausea, and vomiting. For each component, a score of 0-4 is assigned, with lower scores indicating better outcomes. If 0-1 components receive a score of 1-2 and no components receive a score of 3-4, patients are classified as not cachectic. A combination of 2 or more components receiving a score of 1-2 and 0 receiving a score of 3-4 corresponds with mild cachexia, a combination of 2 or more components receiving a score of 1-2 and 1-2 receiving a score of 3-4 corresponds with moderate cachexia, and any components receiving a score of 1-2 with 3 or more receiving a score of 3-4 corresponds with severe cachexia.

Nutritional Instruments Adapted to Classify Cachexia

Eleven studies described the application of instruments originally developed to identify other symptoms/disease (*eg,* malnutrition and nutritional status) to identify cachexia. It is important to consider that these instruments were originally developed with the intended purpose of identifying conditions related to cachexia and may therefore present challenges in distinguishing between cachexia and the original condition of interest.

Six studies described the Glasgow Prognostic Score (GPS), which was also referred to as the modified Glasgow Prognostic Score (mGPS).[91, 132-136] GPS uses a combination of albumin and CRP to determine a summary score (0 to 2). The CRP cutoffs were 5 and 10 mg/dL, and all 6 studies used the same cutoff for albumin (35 g/L). Four studies used a 4-stage definition which consisted of no cachexia/normal (CRP<10 mg/L, ≤10 mg/L, or ≤0.5 mg/L and albumin ≥35 g/L; score = 0), undernourished (CRP≤10 mg/L, <10 mg/L, or ≤5mg/L and albumin <35 g/L; score = 0), precachexia (CRP>10 mg/L, ≥10mg/L, or >5 mg/L and albumin ≥35 g/L; score = 1), and cachexia or refractory cachexia (CRP>10 mg/L or ≥10 mg/L and albumin <35 g/L; score = 2. One study classified patients as either cachectic or not (score of 2 equated to cachexia[135]), and another study used a 3-stage definition of cachexia including no cachexia (0 component met), precachexia (1 component met), and cachexia (2 components met).

One study described a nutrition status (NS) algorithm.[137] The NS uses a combination of handgrip strength (cutoff of 30 kg), fat-free mass index (cutoff of 14.6 kg/m^2), fatigue, appetite loss, weight loss (cutoff of 5% over 12 months), BMI (cutoff of 20 kg/m^2), CRP (5 mg/L cutoff), Hb (120 g/L cutoff), albumin (32g/L cutoff), and the PG-SGA (cutoff score of 4). Based on these measures, patients were classified as having cachexia, sarcopenia, nutritional risk without sarcopenia or cachexia, or well nourished. Those with handgrip strength or fat-free mass index below the cutoff and at least 2 of the following were classified as cachectic: fatigue, appetite loss, weight loss or BMI, and abnormal blood chemistry. Those who did not meet handgrip or free-fat mas index criteria but had 3 of these components were also classified as cachectic.

Three studies reported on the PG-SGA to identify cachexia.[69, 92, 118] The PG-SGA was originally developed to assess nutritional status using patient-reported weight, symptoms, food intake, activities and function. Each component is scored. Total scores ranged from 0-52. Scores ≥ 9 indicated need for nutritional intervention.[138, 139]

One study used the Global Leadership Initiative on Malnutrition (GLIM) as a tool to identify cachexia, with and without nutritional risk screening using the nutritional risk screening 2002 (NRS-2002).[69] The GLIM was originally developed to assess malnutrition, using measures of weight loss, low BMI, reduced muscle mass, and disease burden. The GLIM was used with and without nutrition risk screening to assess cachexia.

One study used 4 different malnutrition tools to identify cachexia: the malnutrition universal screening tool (MUST), NRS-2002, malnutrition screening tool (MST), and the short nutritional assessment questionnaire (SNAQ)[16]. Cutoffs tested for cachexia identification were ≥1 for the MUST, ≥3 for the NRS-2002, ≥2 for the MST, and ≥2 for the SNAQ.

Other Investigator-Developed Cachexia Assessments

Seven studies reported other investigator-identified algorithms for assessing cachexia. One study described a 4-stage definition, 3 studies described a 3-stage definition, and 3 studies described a 2-stage definition.

Vigano 2017 used a combination of abnormal biochemistry (CRP >10mg/L, WBC >11,000/L, albumin <32 g/L, or Hb <120 g/L in men and <110 g/L in women), decreased food intake (aPG-SGA), moderate or significant weight loss (5% cutoff), and decreased activities and functioning (aPG-SGA) to classify patients into 4 stages (noncachexia, precachexia, cachexia, and refractory cachexia) depending on the combination of criteria met.

Solheim 2011 used BMI (20 kg/m^{-2} cutoff), Karnofsky score (<80), CRP (≥10 $mg1^{-1}$), and appetite loss (EORTC QLQ-C30) to classify patients into 3 stages: no cachexia (less than 2 components), mild cachexia (2-3 components), or severe cachexia (all 4 components). One study described the Cancer Cachexia Score (CCS). The CCS assigns point values of 0 or 1 to sarcopenia (yes/no), BMI (cutoff $20kg/m^2$), prognostic nutritional index (cutoff of 40), and tumor volume (size by T-stage, with a cutoff of 57.5). Three cachexia stages are defined as mild (score of 0-1), moderate (2), and severe (3-4).[115] Wiegert 2021 used a combination of BMI (cutoffs of 21.0 to 26.4), mid-upper-arm muscle area (cutoffs of 38.0 cm^2 for men and 35.5 cm^2 for women), and weight loss (15.0% cutoff) to classify patients into 3 stages (precachexia, cachexia, or refractory cachexia) depending on the combination of criteria met.

Orell-Kotikangas 2017 used the combined definition of low muscle mass (mid-arm muscle area <10^{th} percentile) and low muscle function (hand grip strength <85% normal median value) to categorize patients into 2 stages (cachectic and noncachectic). Of note, this definition included components more closely related to assessing sarcopenia. Go 2020 used a combination of sarcopenia (measured by L3-SMI or PM-SMI) and the geriatric nutritional risk index (GNRI) into 2 stages (high cachexia risk and low cachexia risk). Patients considered to be at high risk for cachexia were those with major GRNI risk, sarcopenia using both L3-SMI and PM-SMI, or moderate GNRI risk plus sarcopenia using 1 measure; otherwise, patients were flagged as low risk of cachexia. Namikawa 2022 classified patients into 2 stages (cachectic and noncachectic) based on either a) weight loss (5%) or weight loss (2%) and BMI (<20 kg/m^2); b) anorexia (not defined); or c) 2 or more of the following: albumin <32 g/L, CRP >5.0 mg/L, and Hb <12 g/dL.

PERFORMANCE CHARACTERISTICS OF ALGORITHMS

Twenty-two of the 32 identified algorithms were compared to either clinical exam or to another cachexia algorithm. In terms of performance characteristics, the Fearon 2011 algorithm was frequently used as a comparator for other cachexia assessments (see Appendix). No study evaluated the performance characteristics of Cachexia Staging Score or Radiotherapy Cachexia Staging Score, Cancer Cachexia Score, nutritional status algorithm, the algorithms developed by Orell-Kotikangas 2017, Solheim 2011, Go 2020, Namikawa 2022, Wiegert 2021, or the combined use of the Fearon 2011 and Evans 2008 algorithms. Among algorithms that were compared to either clinical exam or to another cachexia algorithm performance, there is no obvious best choice.

Fearon 2011 and Its Modifications

One study found only slight agreement, defined by the study as a Kappa of 0.00–0.20, between the Fearon 2011 algorithm and a clinical assessment of cachexia based on oncologists' opinion (Kappa 0.049, 95% CI [–0.079, 0.176], $p = 0.457$).[77]

Cachexia Index and Its Modifications

Three NRCS compared the CXI or H-CXI to the Fearon 2011 algorithm.[49, 84, 130] One study found that significantly more patients were classified as cachectic (according to Fearon 2011) in the low-CXI compared to the high-CXI group (35% vs 22%, $p = 0.01$).[80] The other NRCS found no significant difference in the proportion of patients classified as cachectic (according to Fearon 2011) in the low-CXI versus high-CXI groups (50.9% vs 41.6%, $p = 0.09$).[49] Finally, 1 study found a greater proportion of patients in the low H-CXI group were classified as cachectic using the Fearon 2011algorithm compared to the high-H-CXI group (31.0% vs 17.6%; *p* NR). The same study found a low H-CXI was independently associated with risk of developing cancer cachexia as defined by the Fearon 2011 algorithm in the multivariable analysis. [84]

Evans 2008

Three NRCS compared the Evans 2008 to the Fearon 2011 algorithm.[78, 88, 102] Two studies found more patients were classified as cachectic using the Evans compared to the Fearon (27.5% vs 17.5%, *p* NR). In this study, 31.0% of patients classified as noncachectic by the Evans 2008 algorithm were classified as precachexia by the Fearon algorithm.[102] Another study found that 45.5% of patients with cancer were classified as cachectic using the Evans 2008 algorithm compared to 39.4% using the Fearon 2011 algorithm (*p* NR).[88] One other NRCS reported fewer patients were classified as cachectic according to the Evans 2008 algorithm compared to Fearon 2011 (40% vs 70%, *p* NR).[78]

Modified Glasgow Prognostic Score

Two studies compared the mGPS to the Fearon 2011 algorithm. One study found that fewer patients were classified as cachectic using the mGPS compared to Fearon 2011 criteria (60% no cachexia, 5% undernourished, 25% precachectic, and 10% refractory cachexia vs 40% noncachectic, 5% precachectic, and 55% cachectic), but these differences were not significant (McNemar's test $p = 0.43$).[91] Another study found that patients identified as cachectic using the Fearon 2011 criteria had greater odds of being classified as having refractory cachexia (OR = 2.83, [1.73, 4.60]) or undernourished (OR = 1.84, [1.23, 2.75]) in the mGPS.[136]

PG-SGA

Three studies compared the PG-SGA to Evans 2008. One NRCS compared the PG-SGA with a cutoff of 6.5 to the Evans 2008 algorithm (sensitivity = 79.8%, specificity = 72.3%, and AUC of 0.846).[118] Another NRCS compared the PG-SGA to the Fearon 2011 algorithm (sensitivity = 86.2%, specificity = 58.3%, and AUC = 0.778).[69] A third NRCS reported a positive correlation between PG-SGA score and the categories of cachexia proposed by Fearon ($r = 0.54$; $p < 0.0001$).[92]

Wallengren 2013

Two studies compared the Wallengren 2013 algorithm to a reference algorithm. One NRCS found that more patients were classified as cachectic according to the Wallengren algorithm (37%) compared to the Fearon 2006 algorithm (12% based on all 3 components of the Fearon 2006 algorithm and 45%

based on 2 of 3 of these components) and the Evans 2008 algorithm (33%). The same study found that fewer patients were classified as cachectic according to the Wallengren algorithm compared to the Fearon 2011 algorithm (37% vs 85%, *p* NR).[79] Another NRCS found fewer patients were classified as cachectic according to Wallengren algorithm (13.8%) compared to the Vigano 2017 algorithm (8.2% not cachectic, 20.8% were precachectic, 17.3% cachectic, and 53.3% refractory cachexia).[123]

Nomograms

All 4 identified nomograms were compared against the Fearon 2011 algorithm. Liu 2022 reported AUCs of 0.702 for the training set and 0.688 for the validation set.[58] Huo 2022 reported a sensitivity of 0.826, specificity of 0.862, and AUC of 0.925 in the development cohort and 0.854, 0.829, and 0.923 (*p* NR) in the validation cohort.[53] Tan 2023 reported an AUC of 0.751 (95% CI [0.725, 0.777], $p < 0.001$) in the application cohort, indicating that this tool can identify those with and without cachexia.[75] Yin 2022 reported an accuracy of 0.714, kappa of 0.396, sensitivity of 0.580, specificity of 0.808, positive predictive value of 0.679, and negative predictive value of 0.733 for on the final model used to create the nomogram.[85]

Other Algorithms

One NRCS compared the CCSG/Fearon 2006 algorithm to the Fearon 2011, and found both algorithms classified a similar proportion of patients as cachectic (64% vs 60%, McNamar's test $p = 0.75$).[81]

One NRCS reported a moderate correlation between CASCO and subjective cachexia diagnoses from specialized oncologists ($\rho = 0.412$, $p < 0.001$). The same study reported a strong correlation between the CASCO and miniCASCO ($r = 0.964$, $p < 0.001$.)[125]

Using the Fearon 2011 algorithm as the reference determination of cachexia, the CCSI had an area under the receiver operating characteristics curve (AUC) to evaluate test accuracy of 0.911.[130]

One NRCS compared the GLIM to the Fearon 2011 algorithm. The GLIM had a sensitivity of 100%, specificity of 60.7%, accuracy of 67.4%, and AUC of 0.835. When nutritional risk screening (NRS-2002) was added, the GLIM had a sensitivity of 88.8%, specificity of 91.8%, accuracy of 91.3%, and AUC of 0.910.[69]

One study compared the MUST, NRS-2002, MST, and SNAQ to the Fearon 2011 definition of cachexia.[16] For 3 instruments, sensitivity was between 76.6% and 87.3% and in 1 instrument (SNAQ) sensitivity was 54.3%. For all 4 instruments, specificity was between 77.7% and 98.6%, accuracy was between 80.9% and 93.5%, and AUC was between 0.751 and 0.914.

One NRCS found a significant correlation between the CAS and PG-SGA ($r = 0.58$, $p = 0.04$). However, it was not clear if the PG-SGA was used by the authors to define cachexia or malnutrition.[131]

OUTCOMES FOR PATIENTS FOLLOWING CACHEXIA CLASSIFICATION

Forty-nine studies reported the adjusted association between cachexia as determined with a described algorithm and a prioritized outcome. The majority of studies were from Japan ($N = 13$), China ($N = 9$), and Korea ($N = 5$), with 3 conducted in the US. The studies were conducted between 1991 and 2002 and with a wide range of follow-up durations (10 days to 12 years). A total of 31,317 patients were included. The mean age of patients in 24 studies ranged from 57.8 to 75.6 years; the median age in 22 studies was between 57 and 83 years. In 2 studies, the majority of patients were ≤65 years old, and 1

study reported that the majority of patients were ≥60 years old. Males made up 40.5% to 100% of patients. Only 3 studies reported information on patient race/ethnicity, with White patients making up less than half of all participants in these studies (34.4-48%), Black patients making up 52% and 16.5% of samples in 2 of these studies, and 1 study reporting 40.5% of patients of "other" race. The studies included patients with a variety of cancers, including cancers of the head and neck; gastrointestinal tract; lung; breast; prostate; pancreas; skin, bones, and soft tissue; gynecological; genitourinary; and others, with patients with more advanced stages making up the majority of patients included. See the Appendix for further details on cancer treatments and patient comorbidities in each study. Overall survival was the most commonly reported outcome (reported on 50 times in 44 studies) followed by progression-free survival ($N = 11$), disease-free survival ($N = 8$), and relapse-free survival ($N = 2$). Other outcomes included function ($N = 2$), hospitalization ($N = 2$), or cachexia relevant burden or severity ($N = 2$). No study evaluated cachexia progression or feeding tube placement.

Two studies used propensity score matching to adjust for confounding and had no other concerns (therefore both low risk of bias). The remaining 47 studies used multivariable regression to adjust for confounding. Forty studies had moderate risk of bias due to concerns over attrition bias due to large loss to follow-up, lack of clear reporting or clear eligibility criteria, or because of analysis used for adjustment. Seven studies had high risk of bias. Six of these either adjusted for multiple cachexia algorithms in the same model, or adjusted for variables that were also included components of the cachexia algorithm. The seventh study had concerns surrounding high loss to follow-up, unclear reporting or eligibility criteria, and adjustment method used.

Overall, regardless of classification algorithm, overall survival, cancer progression-free survival, and disease-free survival were worse for patients with cancer cachexia. Those with cancer cachexia also had worse relapse-free survival, worse symptom burden, and longer hospital length of stay. Results in functional outcomes were inconsistent. No study reported feeding tube placement or cachexia progression outcomes.

Fearon 2011 Algorithm

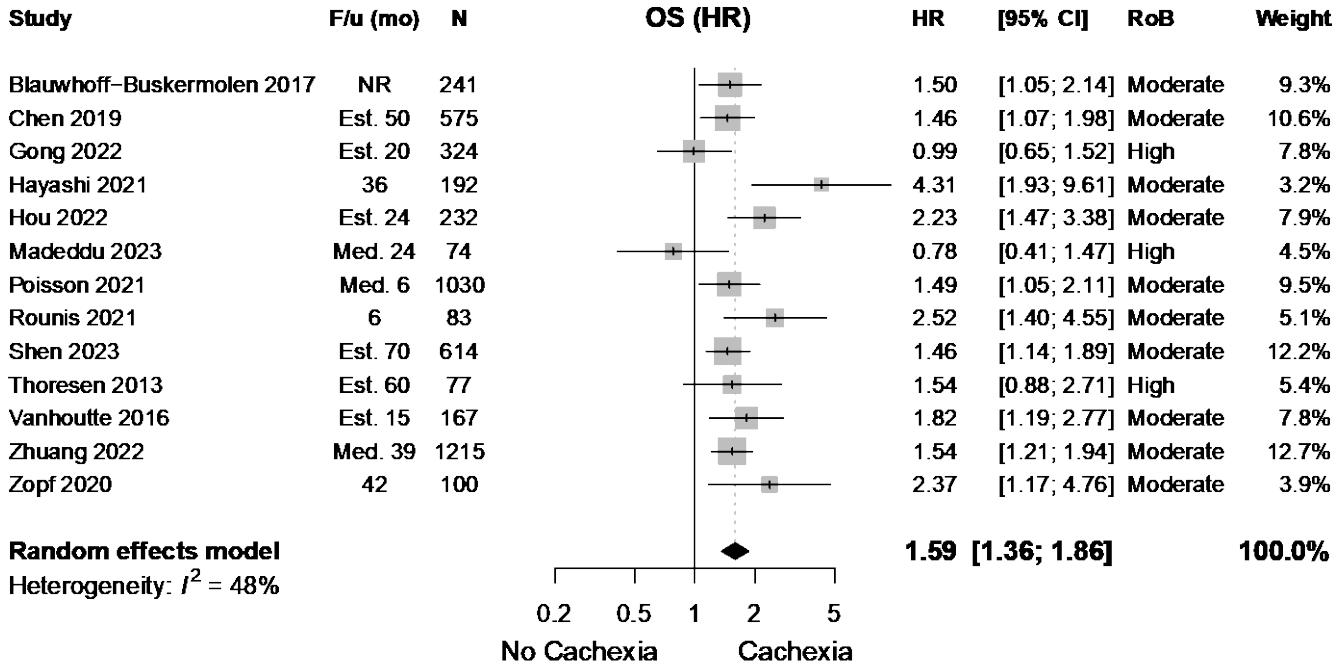
In summary (Table 3), patients identified as cachectic using the Fearon 2011 algorithm had worse overall mortality (moderate confidence), progression-free survival (moderate confidence), and disease-free survival (low confidence) when compared to noncachectic patients. Cachectic patients also had greater hospital and ICU length of stay (low confidence) and greater perception of dysphagia (low confidence). No studies used the Fearon 2011 algorithm to assess function outcomes, cachexia progression, or feeding tube placement.

Overall Survival

Fifteen studies reported overall survival for patients with and without cachexia based on the Fearon 2011 algorithm or some modification of this algorithm. Two studies were excluded from meta-analysis. One NRCS classified patients by the number of Fearon 2011 algorithm criteria met (see Appendix).[65] The NRCS found worse mortality for patients who met all 3 Fearon 2011 criteria compared to those who only met 1 or 2 of the criteria (HR = 1.40, 95% CI [1.078, 1.819]). Another NRCS used a modified version of the Fearon 2011, and thus was excluded from the meta-analysis, but found a similar association (HR = 2.93, 95 % CI [1.03, 8.34]). They also found an imprecise estimate of survival difference between precachectic and noncachectic patients (HR = 0.78, 95 % CI [0.30, 2.03]).[102]

Thirteen NRCSs found a significantly worse mortality among people with cachexia (pooled HR= 1.59, 95% CI [1.36, 1.86]; Figure 1). Only 1 study found a lower hazard of dying among those with cachexia, but the estimate was non-significant with a wide confidence interval.[61] Notably, this study controlled for multiple definitions of cachexia within the same models, raising concerns of collinearity.[49]

Figure 1. Overall Survival for Fearon 2011

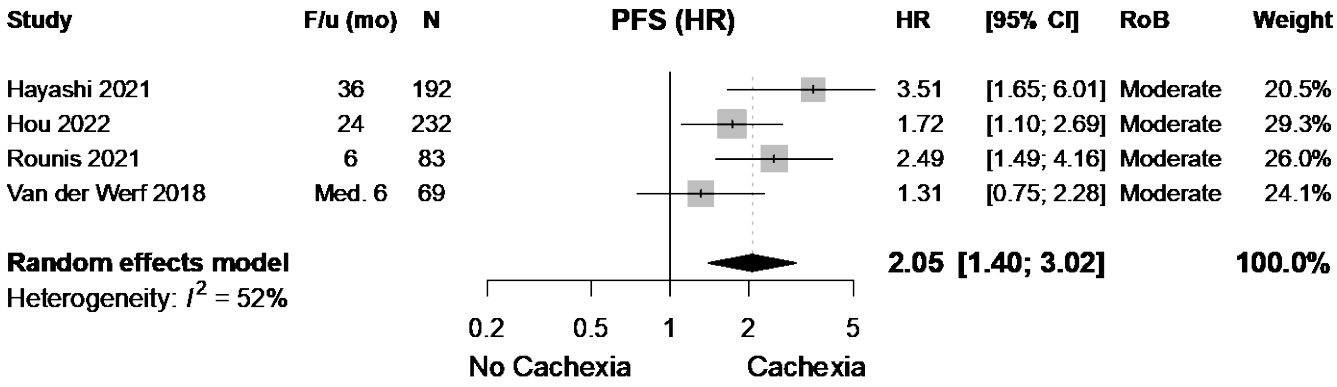


Abbreviations. Est=estimated based on KM curve; F/u=follow-up; HR=hazard ratio; Med=Median; mo=month; N=sample size; NR=not reported; OS=overall survival; RoB=risk of bias.

Cancer Progression-Free Survival

Four NRCSs reported cancer progression-free survival for people classified with and without cachexia following the Fearon 2011 algorithm. Pooled data from 4 studies found significantly worse cancer progression-free survival for people with versus without cachexia (pooled HR = 2.05, 95% CI [1.40, 3.02]; Figure 2).

Figure 2. Progression-Free Survival for Fearon 2011



Abbreviations. F/u=follow-up; HR=hazard ratio; Med=median; mo=month; N=sample size; PFS=progression-free survival; RoB=risk of bias.

Disease-Free Survival

One NRCS found worse disease-free survival among people classified as cachectic using the Fearon 2011 algorithm (HR= 1.53, 95% CI [1.21, 1.94]).[87]

Hospital Length-of-Stay-Related Outcomes

Two NRCSs reported hospital length of stay for people with and without cachexia using the Fearon 2011 algorithm. One NRCS found a significantly longer postoperative length of stay for patients with cachexia compared to their noncachectic counterparts (β = 2.41 days, 95% CI [0.28, 4.55]).[48] Another NRCS found a significantly longer median hospital stay for patients classified as cachectic than their noncachectic counterparts matched on propensity score (10.0 vs 7.0 days, $p < 0.001$).[54] The same study also reported cachectic patients had significantly longer intensive care unit (ICU) stays (median [IQR] 2.0 [2–3] vs 2.0 [2–2], $p < 0.001$), and cachectic patients had a greater risk for having an ICU stay >48 hours compared to patients without cachexia (RR [95% CI] = 2.06 [1.40, 3.04]). A prospective study found a greater risk of a score of 3 or more on the EAT-10 among those with cachexia (HR = 9.00, 95% CI [2.48, 32.62]), which indicated a greater perception of oropharyngeal dysphagia.[83]

Table 3. Summary of Findings for Fearon 2011[a]

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary[a]	Overall Confidence
Overall Survival	15 (4,924); NRCS, Validation[43, 44, 51, 52, 61, 63-65, 68, 76, 78, 87, 88, 102, 118]	Moderate[b]	Direct	Precise	Consistent	None	Fearon: sumHR 1.59 (1.36, 1.86) Mod Fearon: HR 2.93 (1.03, 8.34)[c] 3 vs 1-2 criteria: HR 1.40 (1.08, 1.82)[c]	Moderate
Progression-Free Survival	4 (576); NRCS[51, 52, 64, 77]	Moderate[d]	Direct	Precise	Consistent	None	SumHR 2.05 (1.40, 3.02)	Moderate
Disease-Free survival	1 (1215); NRCS[87]	Moderate[d]	Direct	Precise	Consistent	Single Study	HR 1.53 (1.21, 1.94)	Low
Hospitalizations	2 (350); NRCS[48, 54]	Moderate[e]	Direct	Imprecise[f]	Consistent	N/A	Overall LOS and ICU day significantly longer in those with cachexia compared to no cachexia. Greater risk of prolonged IUC stay (RR = 2.06 [1.40, 3.04])	Low
Cachexia Symptom Burden	1 (66); NRCS[83, 140]	Moderate[d]	Direct	Precise	Consistent	Single Study	EAT-10 ≥3 HR = 9.00 (2.48, 32.62)	Low
Cachexia Progression	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Function	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Feeding Tube Placement	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence

Notes. [a] HR estimates >1 indicate worse outcome (*eg,* higher likelihood of death); [b] Three studies were rated as high risk of bias and 12 were rated as moderate risk of bias; [c] One study; [d] All included studies were rated as having moderate risk of bias; [e] One study was rated as low risk of bias and 1 was rated as moderate risk of bias; [f] Imprecise estimate for postoperative length of stay.

Abbreviations. EAT-10=eating assessment tool; HR=hazard ratio; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; N/A=not applicable; NRCS=nonrandomized comparative study; RR=relative risk; sumHR=summary (or pooled) hazard ratio.

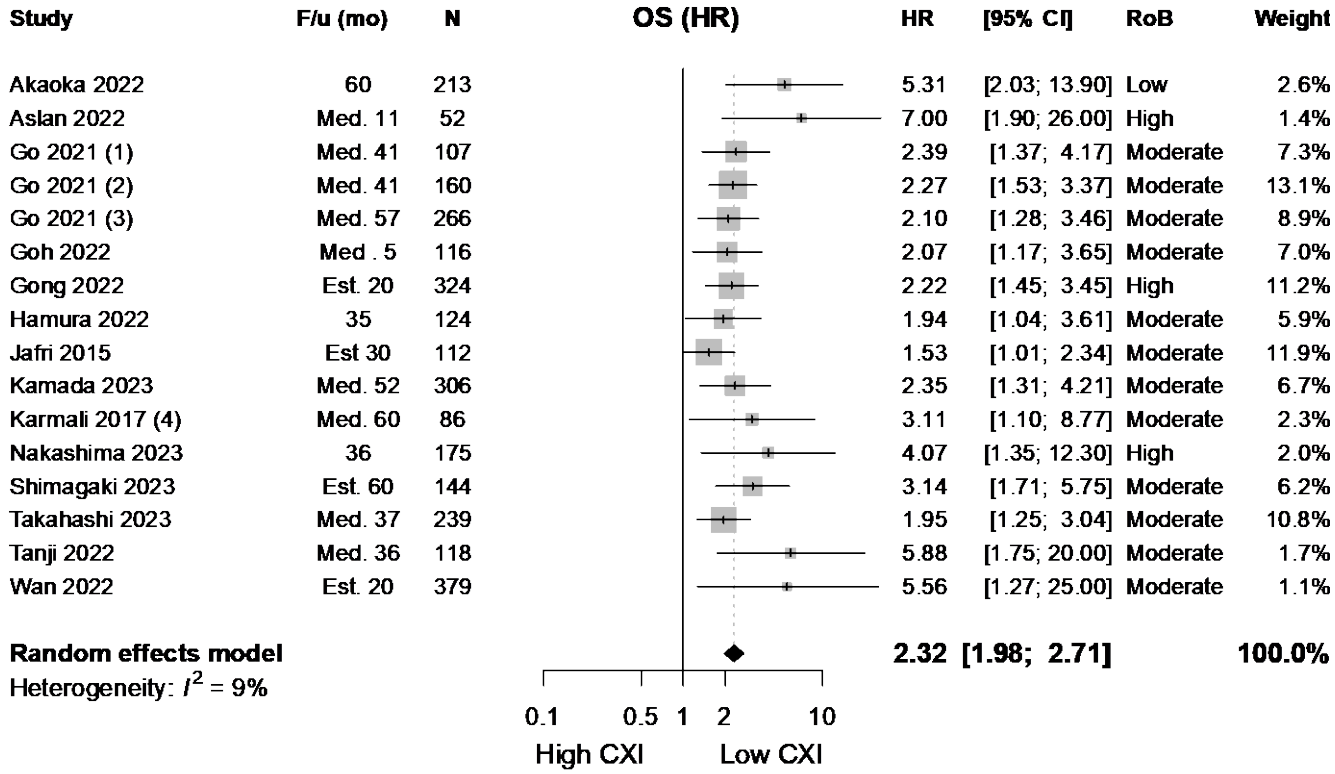
Cachexia Index

In summary (Table 4), using the CXI, people identified as cachectic, having low CXI, or stage II cachexia had worse overall mortality (low confidence), progression-free survival (moderate confidence), disease-free survival (moderate confidence), or relapse-free survival (low confidence) compared to those who were not. No studies used the CXI to assess cachexia symptom burden, functional levels, hospitalization outcomes, cachexia progression, or feeding tube placement.

Overall Survival

Sixteen studies evaluated overall survival based on the Cachexia Index (CXI) or a modification of this algorithm. Studies applied unique cutoffs (*eg,* based on population specific Youden's index values or based on median values) to classify patients as low CXI or high CXI. One study used median CXI values to classify patients as stage I cachexia and stage II cachexia, with those in stage II having a lower CXI.[110] The majority of these studies used the CXI as a biomarker for cachexia and its prognosis, but only 2 studies explicitly labeled the low-CXI group as "cachectic" and the high-CXI group as "noncachectic." One study used a modified version of the CXI that included hand grip strength and, thus, was excluded from the pooled analysis. This study reported greater mortality in patients with low H-CXI group versus high H-CXI (HR = 1.61, 95% CI[1.45, 1.79]).[84] The pooled data from 15 studies found a significantly worse overall mortality for patients with low CXI compared to high CXI (pooled HR = 2.32, 95% CI [1.98, 2.71]; Figure 3).

Figure 3. Overall Survival



Notes. CXI indicates cachexia or cachexia risk. (1) Estimate from Go 2021 (PMID 34001060) for patients with limited-stage disease; (2) Estimate from Go 2021 (PMID 34001060) for patients with extensive-stage disease; (3) Estimate from PMID 34676685; (4) 95% CI calculated from reported *p*-value.

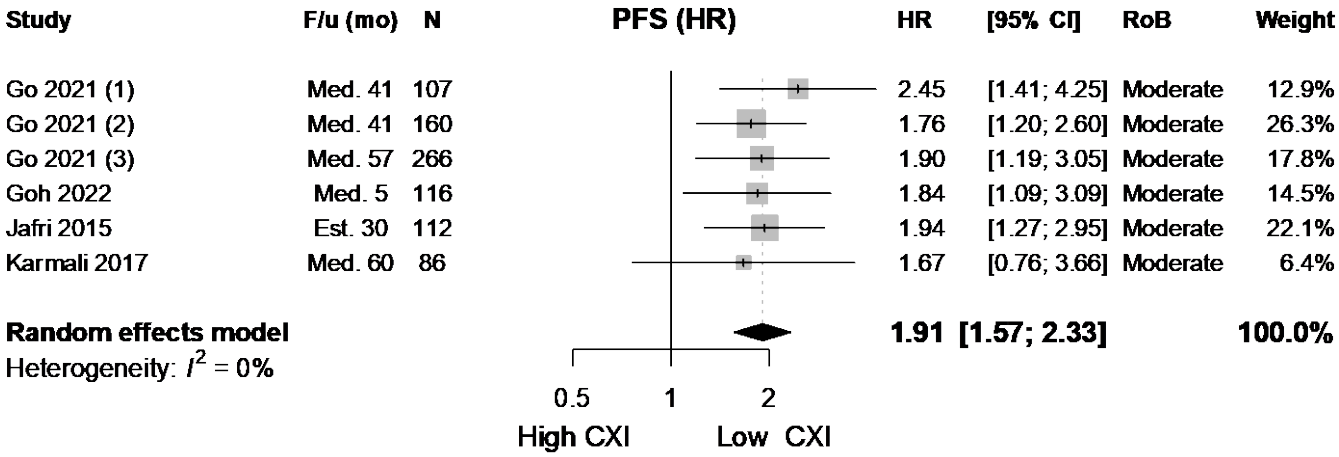
Abbreviations. Est=estimated based on KM curve; F/u=follow-up; H=high CXI; HR=hazard ratio; L=low CXI; Med=median; mo=month; N=sample size; OS=overall survival; RoB=risk of bias.

One NRCS found no significant difference in overall survival between patients classified as intermediate-CXI compared to high CXI (HR =1.72, 95% CI [0.99, 2.97]).[107] This was the only study to use the intermediate-CXI classification. While the results of the intermediate versus high-CXI groups were excluded from the meta-analysis, this study also compared low-CXI versus high-CXI groups, the results of which were included in the meta-analysis. Importantly, 1 NRCS conducted a propensity score match analysis and multivariable regression. The propensity score match analysis but not multivariable regression analysis found a significantly worse mortality for those in the low-CXI group ($p = 0.041$ and $p = 0.940$, respectively).[103]

Cancer Progression-Free Survival

Five NRCSs found a significantly worse progression-free survival for patients classified as low CXI (pooled HR = 1.91, 95% CI [1.57, 2.33]; Figure 4).

Figure 4. Progression-Free Survival



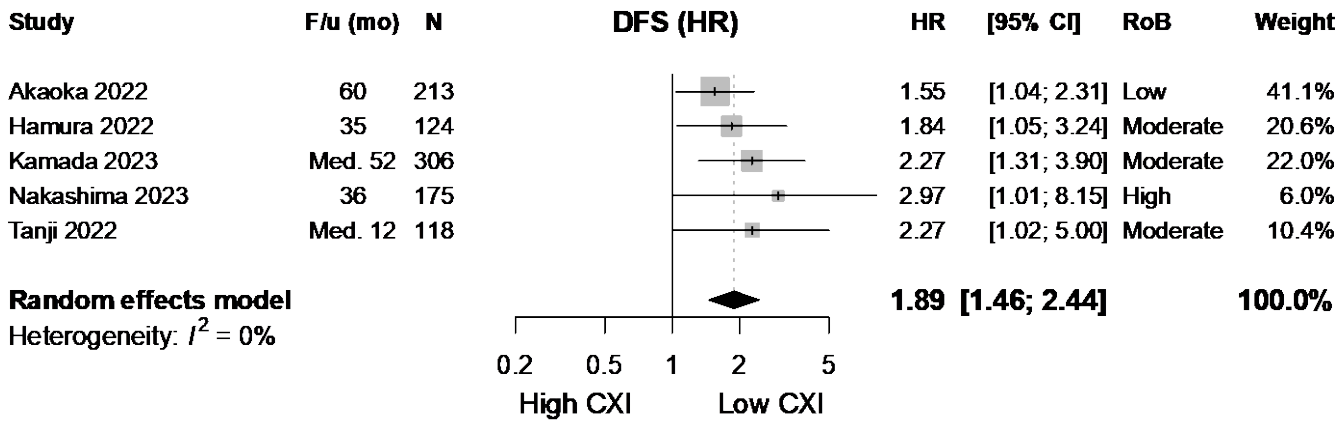
Notes. Go 2021 (1) = Patients with limited-stage small cell lung cancer from PMID 34001060; Go 2021 (2) = Patients with extensive-stage small cell lung cancer from PMID 34001060; Go 2021 (3) = patients with diffuse large B-cell lymphoma from PMID 34676685.

Abbreviations. Est=estimated based on KM curve; F/u=follow-up; HR=hazard ratio; Med=median; mo=month; N=sample size; PFS=progression-free survival; RoB=risk of bias.

Disease-Free Survival

Pooled data from 5 studies showed significantly worse disease-free survival for patients classified low CXI (pooled HR = 1.89, 95% CI [1.46, 2.44]; Figure 5).

Figure 5. Disease-Free Survival



Abbreviations. CXI=cancer cachexia index; DFS=disease-free survival; F/u=follow-up; HR=hazard ratio; Med=median; mo=month; N=sample size; RoB=risk of bias.

Relapse-Free Survival

One study reported significantly worse relapse-free survival for those classified as low CXI compared to high CXI (HR = 1.58, 95% CI [1.06, 2.34]).[141]

Table 4. Summary of Findings for Cachexia Index[a]

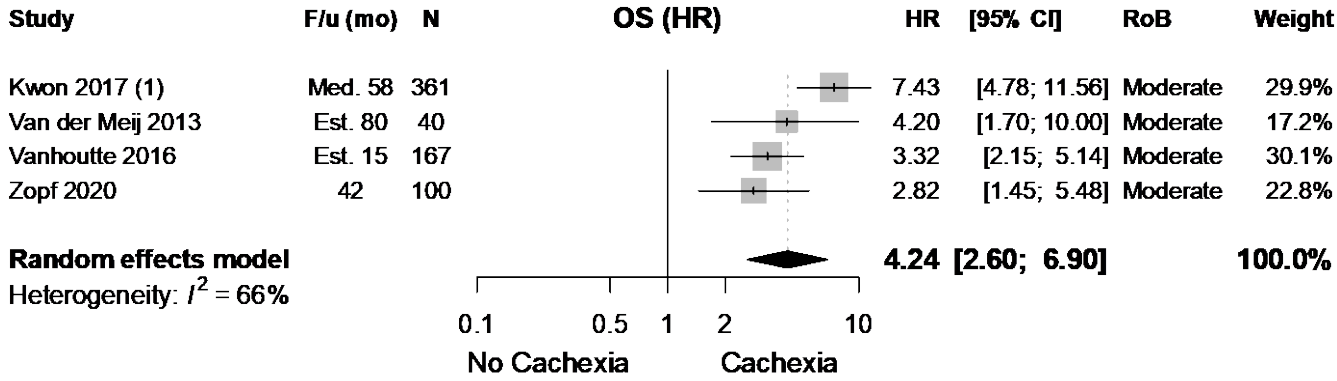
Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	Summary	Overall Confidence
Overall Survival	16 (8,191); NRCS; Validation[49, 80, 84, 103, 104, 106-114, 116, 141]	Moderate[b]	Indirect[c]	Precise	Consistent		Pooled HR = 2.32 (1.98, 2.71) Modified CXI[a] HR = 1.61 (1.45, 1.79)	Low
Progression-Free Survival	5 (847); NRCS[106-108, 110, 112]	Moderate[d]	Direct	Precise	Consistent		Pooled HR = 1.91 (1.57, 2.33)	Moderate
Disease-Free Survival	5 (936); NRCS [103, 109, 111, 113, 116]	Moderate[e]	Direct	Precise	Consistent		Pooled HR = 1.89 (1.46, 2.44)	Moderate
Relapse-Free Survival	1 (239); NRCS[141]	Moderate[f]	Direct	Precise	Consistent	Single study	HR = 1.58 (1.06, 2.34)	Low
Function	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Hospitalizations	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Cachexia Progression	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Cachexia Symptom Burden	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Feeding Tube Placement	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence

Notes. [a] One study used a modified version of the CXI; [b] Three studies were rated as high risk of bias, 1 was rated as low risk, and 12 were rated as moderate risk;[c] Studies used different cutoff values to distinguish low versus high groups; [d] All studies were rated as moderate; [e] One study was rated as high risk of bias, 1 study was rated as low, and 3 were rated as moderate risk of bias; [f] Study was rated as moderate risk due to use of multivariable regression for adjustment.

Evans 2008 Algorithm

In summary (Table 5), 4 studies compared overall survival by cachexia based on the Evans 2008 algorithm. Pooled data showed significantly worse overall survival among those classified as cachectic (pooled HR = 4.24, 95% CI [2.60, 6.90]; Figure 6). No studies used the Evans 2008 algorithm to assess cachexia symptom burden, functional levels, hospitalization outcomes, cachexia progression, and feeding tube placement.

Figure 6. Overall Survival for Evans 2008



Notes. (1) = Comparison in this study was between patients with sustained cachexia both before and after treatment versus patients without cachexia at all time periods.

Abbreviations. Est=Estimated based on KM curve; F/u=follow-up; HR=hazard ratio; Med=median; mo=month; N=sample size; OS=overall survival; RoB=risk of bias.

Table 5. Summary of Findings for Evans 2008

Outcome	Studies (Patients); Design	Methodological Limitations	Indirectness	Imprecision	Inconsistency	Other Issues	HR (95% CI)	Quality
Overall Survival	4 (668); NRCS[78, 88, 102, 119]	Moderate[a]	Direct	Precise	Consistent		Pooled HR = 4.24 (2.60, 6.90)	Moderate
Function	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Hospitalizations	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Cachexia Progression	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Cachexia Symptom Burden	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence
Feeding Tube Placement	0	N/A	N/A	N/A	N/A	N/A	N/A	No evidence

Notes. [a] All studies rated as moderate risk of bias.

Fearon 2006

Two studies used the Fearon 2006 algorithm (see Appendix), which included weight loss, CRP, and energy intake components and found worse mortality for people classified with cachexia. One study reported significantly worse overall survival among those classified as cachectic compared to their counterparts without cachexia (HR = 2.26, 95% CI [1.18, 4.32]).[76] Another study found significantly worse 6 month mortality rates among patients who met 2 of 3 of the Fearon 2006 criteria or all 3 criteria compared to people who did not meet any criteria (HR = 2.23, $p < 0.001$ and HR = 2.96, $p < 0.001$). The same study found worse mortality rates among patients with stage II or III cancer who met 2 of 3 and all 3 Fearon 2006 compared to people not meeting any criteria (HR = 2.40, $p < 0.001$ and 4.94, $p < 0.001$). However, there were no significant differences in mortality in patients with stage IV cancer who met 2 of 3 or all 3 Fearon 2006 compared to people not meeting any criteria (HR = not reported).[124] No studies used the Fearon 2006 algorithm to assess cachexia symptom burden, functional levels, hospitalization outcomes, cachexia progression, or feeding tube placement.

Glasgow Prognostic Score

Two studies used the GPS to classify patients as cachectic (see Appendix). One study found significantly worse overall survival among patients classified as precachectic or with refractory cachexia compared to no cachexia (HR = 2.00, 95% CI [1.34, 2.98] and HR = 2.45, 95% CI [1.34, 2.98]).[136] The same study also reported no significant difference in hyporexia between those with precachexia and no cachexia, but people with refractory cachexia had greater odds of hyporexia (OR = 3.20, 95% CI [2.25, 4.55]), nausea (OR = 2.13, 95% CI [1.52, 2.99]), intestinal constipation (OR = 1.75, 95% CI [1.26, 2.44]), xerostomia (OR = 2.00, 95% CI [1.43, 2.80]), dysgeusia (OR = 1.89, 95% CI [(1.36, 2.63]), and fatigue (OR = 1.06, 95% CI [0.53, 1.59]). Another study found those classified as noncachectic (GPS) had greater odds of stable or improved Karnofsky performance status outcomes compared to those classified as having refractory cachexia (OR = 1.95 [1.01, 3.47]). In the same study, quality of life measured by improved or stable (vs not) Karnofsky performance status appeared to differ between patients classified as cachectic and those with refractory cachexia (OR = 0.45, 95% CI [0.29, 1.03]), but this difference was not significant.[132] No studies used the GPS to assess hospitalization outcomes, cachexia progression, or feeding tube placement.

Other Assessments

Eleven other studies applying 12 different algorithms to classify patients as cachectic reported on overall ($N = 11$),[75, 115, 120, 123, 128, 130, 137, 142-145] progression-free ($N = 2$),[120, 142] disease-free ($N = 2$),[115, 144] relapse-free survival ($N = 1$),[75] or function ($N = 1$)[137](see Appendix).

Nine of 11 studies found significantly worse overall survival (range in HR = 1.34 to 11.0) for people classified as cachectic compared to those without cachexia, or to those with more severe cachexia. One study reported worse overall survival for people classified to the severe cachexia group compared to those with moderate or mild cachexia by the Cancer Cachexia Score (HR = 2.94, 95% CI [1.81, 4.75]).[115] In a sample of people with cancer who were receiving support from a palliative care team, 1 study used the Cachexia Staging Score and reported worse overall survival in patients with precachexia (HR = 2.78, 95% CI [0.62, 12.46]), cachexia (HR = 4.77, 95% CI [1.09, 20.80]), and refractory cachexia (HR = 11.00, 95% CI [2.37, 51.07]) compared to those without cachexia.[128] Another study used the Cachexia Staging System in palliative care patients and reported worse overall survival among those with cachexia (HR = 1.35, 95% CI [1.12, 1.99]) and refractory cachexia (HR = 1.84, 95% CI [1.21, 2.79]) compared to those with precachexia.[145] A study of patients with cancers of various

sites used the Cancer Cachexia Staging Index to identify patients with mild, moderate, or severe cachexia. The study reported worse overall survival for people with mild or moderate cachexia (HR = 2.17, 95% CI [1.64, 2.88]) or severe cachexia (HR = 3.99 (2.45, 6.49) compared to people without cachexia.[130] One study of palliative care patients with cancer reported worse overall survival in people identified as cachectic using the algorithm developed by Wallengren (HR = 2.21, 95% CI [1.86, 2.62]) compared to those who did not.[123] The same study also used an algorithm developed by Vigano and found worse survival in patients with precachexia (HR = 1.87, 95% CI [1.28, 2.73]), cachexia (HR = 2.39, 95% CI [1.64, 3.49]), and refractory cachexia (HR = 2.87, 95% CI [2.01, 4.10]) compared to people without cachexia.[123]

An NRCS found worse overall survival among those in the high compared to low cachexia risk group using an algorithm that combined the GNRI and sarcopenia (HR = 3.35, 95% CI [2.17, 5.17]).[142] One study reported worse overall survival for patients with cachexia (a combination of mid-arm muscle area and hand grip strength to identify cachexia) compared to those without (HR = 2.8, 95% CI [1.30, 6.13]).[144] One study used an investigator-developed algorithm based on a combination of several published definitions of cachexia and found worse overall survival for patients with advance gastric cancer who developed cachexia within 6 months of chemotherapy compared to those who did not (HR = 1.34, 95% CI [1.16, 2.09]).[143] Another study reported worse overall survival (HR = 7.80, 95% CI [1.43, 42.48]) in the high cancer cachexia risk group (investigator-developed nomogram) compared to the low cachexia risk group.[75] An NRCS found no significant difference in overall survival between people with non-small lung cancer classified as cachectic (combined Evans 2008 and Fearon 2011 algorithms) and those who were noncachectic (HR = 1.27, CI % [0.71, 2.27]).[120] Another NRCS found no significant difference in overall survival (*p* NR) between patients with metastatic castrate-resistant prostate cancer classified with cachexia (nutritional status algorithm) compared to those classified as well nourished.[137]

Two studies reported significantly worse progression-free survival among people with cachexia. One NRCS found worse progression-free survival among those in the high compared to low cachexia risk group using a combination of the GNRI and sarcopenia (HR = 2.77, 95% CI [1.83, 4.12]) [142] An NRCS of people with non-small lung cancer found significantly worse progression-free survival in cachectic patients (combined Evans 2008 and Fearon 2011 algorithms) compared to noncachectic patients (HR = 1.64, 95% CI [1.06, 2.55]).[120]

Two studies reported worse disease-free survival among people with cachexia. One study reported worse disease-free survival for people classified to the severe cachexia group compared to those with moderate or mild cachexia by the Cancer Cachexia Score (HR = 2.33, 95% CI [1.55, 3.51]).[115] A study of patients with cancers of the head and neck reported worse disease-free survival (2.8, 95% CI [1.38, 5.82]) for patients with cachexia (a combination of mid-arm muscle area and hand grip strength to identify cachexia) compared to those without.[144]

One study reported worse relapse-free survival (HR = 4.79, 95% CI [1.80, 12.78]) in the high cancer cachexia risk group (investigator-developed nomogram) compared to the low cachexia risk group. [75] One study reported worse health-related quality of life between patients with metastatic castrate-resistant prostate cancer classified with cachexia (nutritional status algorithm) compared to those classified as well nourished (OR = 1.75, 95% CI [0.37, 8.33]).[137]

COMPARISONS BETWEEN ALGORITHMS

Three studies found worse overall mortality for patients identified as cachectic using the Evans 2008 criteria compared to the Fearon 2011 algorithm or a modified form of this (HR = 3.32, 95% CI [2.15, 5.14] vs 1.82 [1.19, 2.77]; 2.82 [1.45, 5.48] vs 2.37 [1.174, 4.764]; and 4.2 [1.7, 10.0] vs 2.93 [1.03, 8.34], *p* NR for all).[78, 88, 102] One study found greater mortality in patients identified as cachectic using the CXI algorithm compared to Fearon 2011 (HR = 2.22, 95% CI [1.45, 3.45] vs 0.99 [0.65, 1.52], *p* NR).[46] One study found worse mortality in patients identified as cachectic using the Fearon 2006 algorithm compared to Fearon 2011 (HR = 2.26, 95% CI [1.18, 4.32] vs 1.54 [0.88, 2.71], *p* NR).[49, 76] Another study reported similar overall mortality for patients identified as cachectic using the Vigano and Wallengren algorithms (HR = 2.39, 95% CI [1.64, 3.49] vs 2.21, 95% CI [1.86, 2.62], *p* NR).[123] No study compared algorithms for outcomes related to function, hospitalization, symptom burden, cachexia progression, or feeding tube placement.

DISCUSSION

We identified 114 studies that described 32 unique algorithms to diagnose or stage cachexia. Of the 32 algorithms, 22 were compared to a clinical exam or against the Fearon 2011 algorithm, 5 compared results to another cachexia algorithm, and 1 compared the developed algorithm to several existing algorithms (including Fearon 2011). Forty-nine studies evaluated the adjusted association between cachexia and a prioritized outcome in analyses. Across the 32 algorithms, anorexia, appetite, or nutrition; sarcopenia; and weight loss, BMI, and albumin were the most commonly used components, but there were more than 20 different components used across all algorithms. The most frequently evaluated outcomes were related to survival. Few studies reported on function, hospitalization, or cachexia symptom burden. Key findings include the following:

Key Findings

- The most frequently evaluated algorithms included the Fearon 2011, the Cachexia Index, and Evans 2008 algorithms.
- Twenty-two algorithms were compared against a clinical exam or another cachexia algorithm in 23 studies. Fearon 2011 was used as a comparison algorithm in 17 of these studies.
- Fearon 2011, Cachexia Index, and Evans 2008 algorithms found worse survival outcomes for people with cachexia compared to those without cachexia. Among other algorithms, the majority found worse survival in cachectic compared to noncachectic patients.
- The cachexia algorithms that categorized patients by severity, including the Glasgow Prognostic Score, Cancer Cachexia Score, Cancer Cachexia Staging Index, Vigano 2017 algorithm, Cachexia Staging System, and Cachexia Staging Score, found worse survival outcomes in those with more severe cachexia compared to less severe cachexia.
- Patients with cachexia based on the Fearon 2011 criteria had longer hospital and ICU stays.
- There may not be a difference in survival outcomes between precachectic and noncachectic populations.
- There was sparse reporting of outcomes relating to function, hospitalization, and cachexia symptom burden. No studies reported outcomes of cachexia progression or feeding tube placement.
- Worse overall mortality is predicted by the Evans 2008 algorithm, Fearon 2006 algorithm, or CXI compared to the Fearon 2011 algorithm.

A recent systematic review estimated that as many as half of cancer patients in the US develop cachexia,[5] but in practice diagnosing cachexia is difficult. There is great clinical interest in being able to prospectively identify people at high risk of developing cachexia or in the early stages of the disorder. Complicating practice are the wide variety of cachexia definitions and algorithms described in medical literature. To improve measurement of cachexia requires consensus definitions with algorithms that are easy to implement in routine practice. Recent guidelines from the European Society for Medical Oncology state that a comprehensive cachexia assessment should include information about nutritional, metabolic, and functional status; nutritional barriers; gastrointestinal dysfunction;

distress and quality of life; and cancer-related factors.[140] However, we found the algorithms of cachexia described in the literature included only some of these criteria. For example, Fearon 2011, which was the most commonly reported algorithm, includes only information on weight loss, BMI, and sarcopenia, leaving out many of these assessment criteria. Further, while there have been recent efforts to distinguish cachexia from malnutrition or sarcopenia alone,[146, 147] the nuanced relationship between these syndromes was not always clear in the identified algorithms. Some algorithms assessing cachexia used only components to identify malnutrition or sarcopenia, while other algorithms included components to help distinguish cachexia from these conditions.

Five studies reported worse overall mortality when using the Evans 2008 algorithm, CXI, or Fearon 2006 compared to the Fearon 2011 algorithm. The Evans 2008, CXI, and Fearon 2006 algorithms each include components beyond weight to assess cachexia, such as markers of inflammation. The differences in the strength of these associations and the algorithms used underscore the need for careful consideration, not only of availability of components but also of the outcomes being targeted when selecting an algorithm to use to identify cachexia. Although survival is important, patients may value other outcomes (*eg*, quality of life). Studies did not systematically evaluate the association between other patient-centered outcomes and the algorithms. Understanding the ability of different algorithms to assess these patient-centered outcomes is important when selecting which may be best to use.

While 69% of the algorithms were empirically compared to a clinical exam or another cachexia algorithm, validating cachexia algorithms is challenging given the lack of a well-established gold standard or reference case. Cachexia prevalence varied widely based on algorithms used. For instance, 1 study found that 52% of patients were identified as cachectic using the Fearon algorithm, but only 9% of those same patients were cachectic when identified by clinical assessment.[77] Another study comparing Fearon 2006, Fearon 2011, and Evans 2008 algorithms reported prevalence rates of 12% to 85% depending on the algorithm.[79] Variation in measures or tools to assess individual components also made it challenging to evaluate algorithms. For example, across studies that used the Fearon 2011 algorithm, sarcopenia was measured by CT, BIA, MUAMA, DEXA, SARC-F, and other tools. Further, cutoffs for what was considered "sarcopenia" varied widely by study. For instance, a study comparing 3 different methods of measuring sarcopenia reported that in 241 patients, 13% of patients were identified as sarcopenic by MUAMA, but 59% of these same patients were identified as sarcopenic using CT, and 93% using BIA.[43] While cost, burden, and availability of tools for measuring components are important considerations,[148] the lack of consistency adds further complication to the identification of cachexia. Additionally, few of the included studies (that were not conducted in East Asia) provided detailed information about the racial makeup of study samples, but racial differences in body composition should also be considered when establishing component cutoffs, such as BMI.[149]

An important limitation of the evidence base is the sparse reporting of outcomes of interest to the operational partners. Most studies reported survival-related outcomes. No study reported feeding tube placement or cachexia progression outcomes, and few studies reported on function, hospitalizations, or cachexia symptom burden. Additionally, a large number of studies were excluded because they did not report adjusted associations between cachexia and outcomes (see Appendix). Some included studies adjusted for individual components of the cachexia algorithm which raised concerns of collinearity, and some studies adjusted for multiple definitions of cachexia in the same model.

Strengths and Limitations of the Systematic Review Process

A strength of our review was the detailed coding of algorithm components, scoring functions, and definitions. Our approach to evaluating algorithms provides a foundation to understand nuanced scoring criteria beyond face level labels of the individual algorithm components (*eg,* BMI or weight loss). For example, sarcopenia was commonly included in the algorithms and our coding conveys how this measure was collected and incorporated within and across algorithms.

One limitation of this review relates to the terminology surrounding cachexia. In the literature, the term cachexia was sometimes used interchangeably with related syndromes, such as malnutrition or anorexia. We included only studies that explicitly used the term "cachexia" to avoid incorrectly including studies that were not specific to cachexia. Because of this approach, it is possible that we excluded studies that may have assessed cachexia but used a different term. Conversely, this approach may also have led to the inclusion of studies that did not explicitly distinguish between cachexia and other related conditions such as malnutrition or sarcopenia, since these terms may be used interchangeably in the literature. This review was intended to focus on classification algorithms that used >1 component, such as weight, to identify cachexia. However, for the Fearon 2011 algorithm, cachexia could be defined by either weight measures alone, or weight loss in combination with sarcopenia. It is possible that patients included in these studies were identified as cachectic based solely on weight measures. As mentioned, the assessment of many components, such as sarcopenia or SMI, was not uniform across studies, even across studies using the same algorithm. The variation in the measurement of these criteria made comparing outcomes across studies challenging. Further, for some assessment tools, such as the CXI, we had to use study-specific cutoffs for cachexia classifications, which may make these definitions less applicable to other external samples. Additionally, while necessary in order to reduce any potential confounding between groups, our choice to only include studies that adjusted for confounding limited the number of studies and type of outcomes included in our analyses of the association between algorithms and outcomes, but by doing so, we excluded studies with clear confounder bias.

IMPLICATIONS FOR VA POLICY AND PRACTICE

VA diagnoses over 50,000 Veterans with cancer annually[18] and has made significant investments to deliver the most effective treatments to Veterans regardless of their location through cancer genomics, tele-oncology, and clinical trials. More broadly, the advent of immunotherapies and other targeted therapies has led to rapid advances in treating cancers that, until relatively recently, were considered untreatable. For people with cachexia, the accompanying weight loss, functional decline, and malnutrition hamper their ability to tolerate treatments and associated adverse effects.[150, 151] As VA continues to invest in oncology programs, collecting patient-reported outcomes (and cachexia factors) such as anorexia, fatigue, and quality of life could inform both oncologic and cachexia end points. Among the studies we identified, only 2 were conducted within the VA and both reported on the Fearon 2011 algorithm. The components of other well-performing cachexia algorithms (*eg*, weight loss, sarcopenia, anorexia) can by readily measured among VA patients with cancer. However, it is important to note that nearly 40% of available studies were conducted in China or Japan, which may limit the generalizability of evidence on the contribution of each component to algorithm performance.

Systematic collection of cachexia-related data is a necessary but complex task in a busy clinical environment, with implications for both front-line health care staff and VA's data infrastructure. For example, weight loss can be obtained from the VA medical record. In contrast, anorexia and functional decline are neither systematically measured in Veterans nor stored in a common location in the VA

electronic medical record. Thus, implementation of a standardized cachexia measure would require VA leadership support, development of the collection infrastructure, education of the oncology field, and the monitoring/re-enforcement of the importance of collection. Alongside these steps, it will likely be valuable to implement predictive analytics to identify those Veterans most at risk for cachexia and focus assessments on them.

Effective management of cachexia requires timely identification. The importance of identifying cachexia early and by severity is also highlighted by the role of emerging therapeutics. Few studies reported on patient quality of life or function, which are measures that may be sensitive to health system features. Again, this represents an opportunity for VA, which has the capability of collecting patient-reported outcomes and other measures.[152] Being able to uniformly collect these data points could help improve understanding and identification of cachexia.

FUTURE RESEARCH

While a variety of cachexia algorithms have been reported, few studies directly compared cachexia algorithms. Direct comparisons are needed to understand which algorithm may be best for early identification of cachexia patient outcomes. Future studies should be explicitly designed to compare algorithms and evaluate outcomes using propensity score or regression adjustment methods that control for known and potential sources of confounding. There is also a need to validate algorithms against, at minimum, an agreed upon reference standard (*eg,* Fearon 2011), and to validate these within specific populations, such as Veterans. This includes validation of biomarkers and other surrogate end points. Most cachexia classification algorithms included only 2 stages (presence or absence of cachexia), and there is a need to expand research on algorithms that more finely characterize cachexia severity and outcomes associated with cachexia severity. Few studies reported prioritized outcomes of interest. While survival outcomes based on cachexia status are of interest, other more modifiable outcomes such as patient quality of life or functional status should be included in future studies to clarify the impact of cachexia and cachexia interventions on these outcomes. Further, clinically meaningful outcomes should be considered when developing future algorithms. Finally, if new algorithms are developed, these should take a comprehensive approach to assessing potential components of cachexia beyond those of weight and sarcopenia.

CONCLUSIONS

Standardizing the identification of cancer cachexia can improve practice and support targeted interventions. Health systems aiming to implement an algorithm in routine practice should focus on feasibility and ease of use. The Fearon 2011, Cachexia Index, and Evans 2008 algorithms were the most frequently described. While many of the identified algorithms incorporate components for anorexia, appetite, or nutrition; albumin; sarcopenia; and/or weight loss to assess cachexia, the overall literature base included more than 20 different components in a variety of combinations. Patients classified as cachectic had worse survival outcomes. Studies are needed to identify optimal cachexia algorithms and to better understand the relationship between cachexia severity and outcomes such as cachexia progression, function, or quality of life.

REFERENCES

1. Bruggeman AR, Kamal AH, LeBlanc TW, Ma JD, Baracos VE, Roeland EJ. Cancer Cachexia: Beyond Weight Loss. *J Oncol Pract*. Nov 2016;12(11):1163-1171. doi:10.1200/jop.2016.016832
2. Baker Rogers J, Syed K, Minteer JF. Cachexia. *StatPearls*. StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.; 2024.
3. Nutrition in Cancer Care (PDQ®)–Health Professional Version. Updated November 2023. https://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-hp-pdq#_23_toc
4. Dev R. Measuring cachexia-diagnostic criteria. *Ann Palliat Med*. Jan 2019;8(1):24-32. doi:10.21037/apm.2018.08.07
5. Anker MS, Holcomb R, Muscaritoli M, et al. Orphan disease status of cancer cachexia in the USA and in the European Union: a systematic review. *J Cachexia Sarcopenia Muscle*. Feb 2019;10(1):22-34. doi:10.1002/jcsm.12402
6. Vaughan VC, Martin P, Lewandowski PA. Cancer cachexia: impact, mechanisms and emerging treatments. *J Cachexia Sarcopenia Muscle*. Jun 2013;4(2):95-109. doi:10.1007/s13539-012-0087-1
7. Song M, Zhang Q, Tang M, et al. Associations of low hand grip strength with 1 year mortality of cancer cachexia: a multicentre observational study. *J Cachexia Sarcopenia Muscle*. Dec 2021;12(6):1489-1500. doi:10.1002/jcsm.12778
8. Naito T, Okayama T, Aoyama T, et al. Unfavorable impact of cancer cachexia on activity of daily living and need for inpatient care in elderly patients with advanced non-small-cell lung cancer in Japan: a prospective longitudinal observational study. *BMC Cancer*. Nov 28 2017;17(1):800. doi:10.1186/s12885-017-3795-2
9. Arthur ST, Van Doren BA, Roy D, Noone JM, Zacherle E, Blanchette CM. Cachexia among US cancer patients. *J Med Econ*. Sep 2016;19(9):874-80. doi:10.1080/13696998.2016.1181640
10. Li X, Hu C, Zhang Q, et al. Cancer cachexia statistics in China. *Precision Nutrition*. 2022;1(1)
11. Gannavarapu BS, Lau SKM, Carter K, et al. Prevalence and Survival Impact of Pretreatment Cancer-Associated Weight Loss: A Tool for Guiding Early Palliative Care. *J Oncol Pract*. Apr 2018;14(4):e238-e250. doi:10.1200/jop.2017.025221
12. Ozorio GA, Barão K, Forones NM. Cachexia Stage, Patient-Generated Subjective Global Assessment, Phase Angle, and Handgrip Strength in Patients with Gastrointestinal Cancer. *Nutr Cancer*. Jul 2017;69(5):772-779. doi:10.1080/01635581.2017.1321130
13. Zhou T, Wang B, Liu H, et al. Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients. *J Cachexia Sarcopenia Muscle*. Apr 2018;9(2):306-314. doi:10.1002/jcsm.12275
10.1002/jcsm.12275. Epub 2018 Jan 25.
14. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clin Nutr*. Dec 2008;27(6):793-9. doi:10.1016/j.clnu.2008.06.013
15. Martin L. Diagnostic criteria for cancer cachexia: data versus dogma. *Curr Opin Clin Nutr Metab Care*. May 2016;19(3):188-98. doi:10.1097/mco.0000000000000272
16. Chen XY, Zhang XZ, Ma BW, et al. A comparison of four common malnutrition risk screening tools for detecting cachexia in patients with curable gastric cancer. *Nutrition*. Feb 2020;70:110498. doi:10.1016/j.nut.2019.04.009
10.1016/j.nut.2019.04.009. Epub 2019 Apr 26.
17. Cao Z, Zhao K, Jose I, Hoogenraad NJ, Osellame LD. Biomarkers for Cancer Cachexia: A Mini Review. *Int J Mol Sci*. Apr 26 2021;22(9)doi:10.3390/ijms22094501

18. Zullig LL, Sims KJ, McNeil R, et al. Cancer Incidence Among Patients of the U.S. Veterans Affairs Health Care System: 2010 Update. *Mil Med*. Jul 2017;182(7):e1883-e1891. doi:10.7205/milmed-d-16-00371
19. Affairs UDoV. Veterans Health Administration. https://www.va.gov/health/aboutvha.asp
20. Affairs UDoV. National Oncology Program. https://www.cancer.va.gov/index.html
21. Roeland EJ, Bohlke K, Baracos VE, et al. Management of Cancer Cachexia: ASCO Guideline. *J Clin Oncol*. Jul 20 2020;38(21):2438-2453. doi:10.1200/jco.20.00611
22. Cosci F, Fava GA. Staging of mental disorders: systematic review. *Psychother Psychosom*. 2013;82(1):20-34. doi:10.1159/000342243
23. Grande AJ, Silva V, Sawaris Neto L, Teixeira Basmage JP, Peccin MS, Maddocks M. Exercise for cancer cachexia in adults. *Cochrane Database Syst Rev*. Mar 18 2021;3(3):Cd010804. doi:10.1002/14651858.CD010804.pub3
24. Hammond S, Erridge S, Mangal N, Pacchetti B, Sodergren MH. The Effect of Cannabis-Based Medicine in the Treatment of Cachexia: A Systematic Review and Meta-Analysis. *Cannabis Cannabinoid Res*. Dec 2021;6(6):474-487. doi:10.1089/can.2021.0048
25. Jin X, Xu XT, Tian MX, Dai Z. Omega-3 polyunsaterated fatty acids improve quality of life and survival, but not body weight in cancer cachexia: A systematic review and meta-analysis of controlled trials. *Nutr Res*. Nov 2022;107:165-178. doi:10.1016/j.nutres.2022.09.009
26. Mbeutcha A, Rouprêt M, Kamat AM, et al. Prognostic factors and predictive tools for upper tract urothelial carcinoma: a systematic review. *World J Urol*. Mar 2017;35(3):337-353. doi:10.1007/s00345-016-1826-2
27. Millar SC, Arnold JB, Thewlis D, Fraysse F, Solomon LB. A systematic literature review of tibial plateau fractures: What classifications are used and how reliable and useful are they? *Injury*. Mar 2018;49(3):473-490. doi:10.1016/j.injury.2018.01.025
28. Moore ZE, Patton D. Risk assessment tools for the prevention of pressure ulcers. *Cochrane Database Syst Rev*. Jan 31 2019;1(1):Cd006471. doi:10.1002/14651858.CD006471.pub4
29. Niels T, Tomanek A, Freitag N, Schumann M. Can Exercise Counteract Cancer Cachexia? A Systematic Literature Review and Meta-Analysis. *Integr Cancer Ther*. Jan-Dec 2020;19:1534735420940414. doi:10.1177/1534735420940414
30. Potter R, Probyn K, Bernstein C, Pincus T, Underwood M, Matharu M. Diagnostic and classification tools for chronic headache disorders: A systematic review. *Cephalalgia*. May 2019;39(6):761-784. doi:10.1177/0333102418806864
31. Rahman A, O'Connor DB, Gather F, et al. Clinical Classification and Severity Scoring Systems in Chronic Pancreatitis: A Systematic Review. *Dig Surg*. 2020;37(3):181-191. doi:10.1159/000501429
32. Schiavo G, Forgerini M, Lucchetta RC, Mastroianni PC. A comprehensive look at explicit screening tools for potentially inappropriate medication: A systematic scoping review. *Australas J Ageing*. Sep 2022;41(3):357-382. doi:10.1111/ajag.13046
33. Simon L, Baldwin C, Kalea AZ, Slee A. Cannabinoid interventions for improving cachexia outcomes in cancer: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. Feb 2022;13(1):23-41. doi:10.1002/jcsm.12861
34. Stevenson JM, Williams JL, Burnham TG, et al. Predicting adverse drug reactions in older adults; a systematic review of the risk prediction models. *Clin Interv Aging*. 2014;9:1581-93. doi:10.2147/cia.S65475
35. Stynes S, Konstantinou K, Dunn KM. Classification of patients with low back-related leg pain: a systematic review. *BMC Musculoskelet Disord*. May 23 2016;17:226. doi:10.1186/s12891-016-1074-z

36. Wang J, Wang Y, Tong M, Pan H, Li D. Medical Cannabinoids for Cancer Cachexia: A Systematic Review and Meta-Analysis. *Biomed Res Int*. 2019;2019:2864384. doi:10.1155/2019/2864384
37. Balduzzi S RG, Schwarzer G "How to perform a meta-analysis with R: a practical tutorial. *Evidence-Based Mental Health*. 2019:153–160.
38. Anderson LJ, Chong N, Migula D, et al. Muscle mass, not radiodensity, predicts physical function in cancer patients with or without cachexia. *Oncotarget*. 2020;11(20):1911-1921. doi:https://dx.doi.org/10.18632/oncotarget.27594
39. Du C, Wang C, Guan X, et al. Asprosin is associated with anorexia and body fat mass in cancer patients. *Support Care Cancer*. Mar 2021;29(3):1369-1375. doi:10.1007/s00520-020-05621-8 10.1007/s00520-020-05621-8. Epub 2020 Jul 13.
40. Álvaro Sanz E, Abilés J, Garrido Siles M, Pérez Ruíz E, Alcaide García J, Rueda Domínguez A. Impact of weight loss on cancer patients' quality of life at the beginning of the chemotherapy. *Support Care Cancer*. Feb 2021;29(2):627-634. doi:10.1007/s00520-020-05496-9 10.1007/s00520-020-05496-9. Epub 2020 May 18.
41. Anderson LJ, Lee J, Mallen MC, et al. Evaluation of physical function and its association with body composition, quality of life and biomarkers in cancer cachexia patients. *Clin Nutr*. Mar 2021;40(3):978-986. doi:10.1016/j.clnu.2020.07.001 10.1016/j.clnu.2020.07.001. Epub 2020 Jul 15.
42. Blauwhoff-Buskermolen S, Langius JA, Heijboer AC, Becker A, de van der Schueren MA, Verheul HM. Plasma Ghrelin Levels Are Associated with Anorexia but Not Cachexia in Patients with NSCLC. *Front Physiol*. 2017;8:119. doi:10.3389/fphys.2017.00119 10.3389/fphys.2017.00119. eCollection 2017.
43. Blauwhoff-Buskermolen S, Langius JAE, Becker A, Verheul HMW, de van der Schueren MAE. The influence of different muscle mass measurements on the diagnosis of cancer cachexia. *J Cachexia Sarcopenia Muscle*. Aug 2017;8(4):615-622. doi:10.1002/jcsm.12200 10.1002/jcsm.12200. Epub 2017 Apr 26.
44. Chen X, Zeng Y, Huang Y, et al. Preoperative Cachexia predicts poor outcomes in young rather than elderly gastric cancer patients: a prospective study. *Cancer Manag Res*. 2019;11:8101-8110. doi:10.2147/cmar.S213237 10.2147/CMAR.S213237. eCollection 2019.
45. da Rocha IMG, Marcadenti A, de Medeiros GOC, et al. Is cachexia associated with chemotherapy toxicities in gastrointestinal cancer patients? A prospective study. *J Cachexia Sarcopenia Muscle*. Apr 2019;10(2):445-454. doi:10.1002/jcsm.12391 10.1002/jcsm.12391. Epub 2019 Mar 28.
46. De Waele E, Demol J, Caccialanza R, et al. Unidentified cachexia patients in the oncologic setting: Cachexia UFOs do exist. *Nutrition*. Jul-Aug 2019;63-64:200-204. doi:10.1016/j.nut.2019.02.015 10.1016/j.nut.2019.02.015. Epub 2019 Feb 27.
47. Deng M, Aberle MR, van Bijnen AAJHM, et al. Lipocalin-2 and neutrophil activation in pancreatic cancer cachexia. *Frontiers in Immunology*. 2023;14:1159411. doi:https://dx.doi.org/10.3389/fimmu.2023.1159411
48. Fukuta A, Saito T, Murata S, et al. Impact of preoperative cachexia on postoperative length of stay in elderly patients with gastrointestinal cancer. *Nutrition*. Feb 2019;58:65-68. doi:10.1016/j.nut.2018.06.022 10.1016/j.nut.2018.06.022. Epub 2018 Oct 11.

49. Gong C, Wan Q, Zhao R, Zuo X, Chen Y, Li T. Cachexia Index as a Prognostic Indicator in Patients with Gastric Cancer: A Retrospective Study. *Cancers (Basel)*. Sep 10 2022;14(18)doi:10.3390/cancers14184400 10.3390/cancers14184400.
50. Hadzibegovic S, Porthun J, Lena A, et al. Hand grip strength in patients with advanced cancer: A prospective study. *J Cachexia Sarcopenia Muscle*. Jun 15 2023;doi:10.1002/jcsm.13248 10.1002/jcsm.13248.
51. Hayashi N, Sato Y, Fujiwara Y, et al. Clinical Impact of Cachexia in Head and Neck Cancer Patients Who Received Chemoradiotherapy. *Cancer Manag Res*. 2021;13:8377-8385. doi:10.2147/cmar.S329581 10.2147/CMAR.S329581. eCollection 2021.
52. Hou YC, Chen CY, Huang CJ, et al. The Differential Clinical Impacts of Cachexia and Sarcopenia on the Prognosis of Advanced Pancreatic Cancer. *Cancers (Basel)*. Jun 26 2022;14(13)doi:10.3390/cancers14133137 10.3390/cancers14133137.
53. Huo Z, Chong F, Yin L, et al. Development and validation of an online dynamic nomogram system for predicting cancer cachexia among inpatients: a real-world cohort study in China. *Support Care Cancer*. Dec 22 2022;31(1):72. doi:10.1007/s00520-022-07540-2 10.1007/s00520-022-07540-2.
54. Jones AJ, Davis KP, Novinger LJ, et al. Postoperative consequences of cancer cachexia after head and neck free flap reconstruction. *Head Neck*. Jul 2022;44(7):1665-1677. doi:10.1002/hed.27072 10.1002/hed.27072. Epub 2022 Apr 29.
55. LeBlanc TW, Nickolich M, Rushing CN, Samsa GP, Locke SC, Abernethy AP. What bothers lung cancer patients the most? A prospective, longitudinal electronic patient-reported outcomes study in advanced non-small cell lung cancer. *Support Care Cancer*. Dec 2015;23(12):3455-63. doi:10.1007/s00520-015-2699-4 10.1007/s00520-015-2699-4. Epub 2015 Mar 21.
56. LeBlanc TW, Nipp RD, Rushing CN, et al. Correlation between the international consensus definition of the Cancer Anorexia-Cachexia Syndrome (CACS) and patient-centered outcomes in advanced non-small cell lung cancer. *J Pain Symptom Manage*. Apr 2015;49(4):680-9. doi:10.1016/j.jpainsymman.2014.09.008 10.1016/j.jpainsymman.2014.09.008. Epub 2014 Nov 4.
57. Liao WC, Chen PR, Huang CC, et al. Relationship between pancreatic cancer-associated diabetes and cachexia. *J Cachexia Sarcopenia Muscle*. Aug 2020;11(4):899-908. doi:10.1002/jcsm.12553 10.1002/jcsm.12553. Epub 2020 Feb 25.
58. Liu CA, Zhang Q, Ruan GT, et al. Novel Diagnostic and Prognostic Tools for Lung Cancer Cachexia: Based on Nutritional and Inflammatory Status. *Front Oncol*. 2022;12:890745. doi:10.3389/fonc.2022.890745 10.3389/fonc.2022.890745. eCollection 2022.
59. Loumaye A, De Barsy M, Nachit M, et al. Role of activin A and myostatin in human cancer cachexia. *Journal of Clinical Endocrinology and Metabolism*. 2015;100(5):2030-2038. doi:https://dx.doi.org/10.1210/jc.2014-4318
60. Luvián-Morales J, Castillo-Aguilar J, Delgadillo-González M, et al. Validation of the QLQ-CAX24 instrument in cervical cancer and its association with cachexia classifications. *Jpn J Clin Oncol*. Mar 30 2023;53(4):304-312. doi:10.1093/jjco/hyac199 10.1093/jjco/hyac199.

61. Madeddu C, Busquets S, Donisi C, et al. Effect of Cancer-Related Cachexia and Associated Changes in Nutritional Status, Inflammatory Status, and Muscle Mass on Immunotherapy Efficacy and Survival in Patients with Advanced Non-Small Cell Lung Cancer. *Cancers*. 2023;15(4):1076. doi:https://dx.doi.org/10.3390/cancers15041076
62. Ohmae N, Yasui-Yamada S, Furumoto T, et al. Muscle mass, quality, and strength; physical function and activity; and metabolic status in cachectic patients with head and neck cancer. *Clin Nutr ESPEN*. Feb 2023;53:113-119. doi:10.1016/j.clnesp.2022.12.006
10.1016/j.clnesp.2022.12.006. Epub 2022 Dec 9.
63. Poisson J, Martinez-Tapia C, Heitz D, et al. Prevalence and prognostic impact of cachexia among older patients with cancer: a nationwide cross-sectional survey (NutriAgeCancer). *J Cachexia Sarcopenia Muscle*. Dec 2021;12(6):1477-1488. doi:10.1002/jcsm.12776
10.1002/jcsm.12776. Epub 2021 Sep 14.
64. Rounis K, Makrakis D, Tsigkas AP, et al. Cancer cachexia syndrome and clinical outcome in patients with metastatic non-small cell lung cancer treated with PD-1/PD-L1 inhibitors: results from a prospective, observational study. *Transl Lung Cancer Res*. Aug 2021;10(8):3538-3549. doi:10.21037/tlcr-21-460
10.21037/tlcr-21-460.
65. Ruan GT, Yang M, Zhang XW, et al. Association of Systemic Inflammation and Overall Survival in Elderly Patients with Cancer Cachexia - Results from a Multicenter Study. *J Inflamm Res*. 2021;14:5527-5540. doi:10.2147/jir.S332408
10.2147/JIR.S332408. eCollection 2021.
66. Ruan GT, Zhang Q, Zhang X, et al. Geriatric Nutrition Risk Index: Prognostic factor related to inflammation in elderly patients with cancer cachexia. *J Cachexia Sarcopenia Muscle*. Dec 2021;12(6):1969-1982. doi:10.1002/jcsm.12800
10.1002/jcsm.12800. Epub 2021 Sep 29.
67. Schwarz S, Prokopchuk O, Esefeld K, et al. The clinical picture of cachexia: a mosaic of different parameters (experience of 503 patients). *BMC Cancer*. Feb 14 2017;17(1):130. doi:10.1186/s12885-017-3116-9
10.1186/s12885-017-3116-9.
68. Shen XD, Wang X, Zheng ZJ, et al. The differential effects of sarcopenia and cachexia on overall survival for pancreatic ductal adenocarcinoma patients following pancreatectomy: A retrospective study based on a large population. *Cancer Med*. May 2023;12(9):10438-10448. doi:10.1002/cam4.5779
10.1002/cam4.5779. Epub 2023 Mar 20.
69. Song M, Zhang Q, Liu T, et al. Efficacy of Global Leadership Initiative on Malnutrition as potential cachexia screening tool for patients with solid cancer. *Nutr J*. Dec 7 2022;21(1):73. doi:10.1186/s12937-022-00829-2
10.1186/s12937-022-00829-2.
70. Srdic D, Plestina S, Sverko-Peternac A, Nikolac N, Simundic AM, Samarzija M. Cancer cachexia, sarcopenia and biochemical markers in patients with advanced non-small cell lung cancer-chemotherapy toxicity and prognostic value. *Support Care Cancer*. Nov 2016;24(11):4495-502. doi:10.1007/s00520-016-3287-y
10.1007/s00520-016-3287-y. Epub 2016 May 28.
71. Stene GB, Balstad TR, Leer ASM, et al. Deterioration in Muscle Mass and Physical Function Differs According to Weight Loss History in Cancer Cachexia. *Cancers (Basel)*. Dec 3 2019;11(12)doi:10.3390/cancers11121925
10.3390/cancers11121925.

72. Sullivan ES, Daly LE, Scannell C, et al. A large, multi-centre prospective study demonstrating high prevalence of malnutrition associated with reduced survival in ambulatory systemic anti-cancer therapy patients. *Clin Nutr ESPEN*. Dec 2022;52:208-217. doi:10.1016/j.clnesp.2022.10.009 10.1016/j.clnesp.2022.10.009. Epub 2022 Oct 25.
73. Sun L, Quan XQ, Yu S. An Epidemiological Survey of Cachexia in Advanced Cancer Patients and Analysis on Its Diagnostic and Treatment Status. *Nutr Cancer*. 2015;67(7):1056-62. doi:10.1080/01635581.2015.1073753 10.1080/01635581.2015.1073753. Epub 2015 Aug 28.
74. Suno M, Endo Y, Nishie H, Kajizono M, Sendo T, Matsuoka J. Refractory cachexia is associated with increased plasma concentrations of fentanyl in cancer patients. *Ther Clin Risk Manag*. 2015;11:751-7. doi:10.2147/tcrm.S79374 10.2147/TCRM.S79374. eCollection 2015.
75. Tan S, Xu J, Wang J, et al. Development and validation of a cancer cachexia risk score for digestive tract cancer patients before abdominal surgery. *J Cachexia Sarcopenia Muscle*. Apr 2023;14(2):891-902. doi:10.1002/jcsm.13207 10.1002/jcsm.13207. Epub 2023 Mar 7.
76. Thoresen L, Frykholm G, Lydersen S, et al. Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. *Clin Nutr*. Feb 2013;32(1):65-72. doi:10.1016/j.clnu.2012.05.009 10.1016/j.clnu.2012.05.009. Epub 2012 Jun 12.
77. van der Werf A, van Bokhorst QNE, de van der Schueren MAE, Verheul HMW, Langius JAE. Cancer Cachexia: Identification by Clinical Assessment versus International Consensus Criteria in Patients with Metastatic Colorectal Cancer. *Nutr Cancer*. Nov-Dec 2018;70(8):1322-1329. doi:10.1080/01635581.2018.1504092 10.1080/01635581.2018.1504092. Epub 2018 Sep 20.
78. Vanhoutte G, van de Wiel M, Wouters K, et al. Cachexia in cancer: what is in the definition? *BMJ Open Gastroenterol*. 2016;3(1):e000097. doi:10.1136/bmjgast-2016-000097 10.1136/bmjgast-2016-000097. eCollection 2016.
79. Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. *Support Care Cancer*. Jun 2013;21(6):1569-77. doi:10.1007/s00520-012-1697-z 10.1007/s00520-012-1697-z. Epub 2013 Jan 13.
80. Wan Q, Yuan Q, Zhao R, et al. Prognostic value of cachexia index in patients with colorectal cancer: A retrospective study. *Front Oncol*. 2022;12:984459. doi:10.3389/fonc.2022.984459
81. Wesseltoft-Rao N, Hjermstad MJ, Ikdahl T, et al. Comparing two classifications of cancer cachexia and their association with survival in patients with unresected pancreatic cancer. *Nutr Cancer*. 2015;67(3):472-80. doi:10.1080/01635581.2015.1004728
82. Willemsen ACH, De Moor N, Van Dessel J, et al. The predictive and prognostic value of weight loss and body composition prior to and during immune checkpoint inhibition in recurrent or metastatic head and neck cancer patients. *Cancer Med*. Apr 2023;12(7):7699-7712. doi:10.1002/cam4.5522 10.1002/cam4.5522. Epub 2022 Dec 9.
83. Willemsen ACH, Pilz W, Hoeben A, Hoebers FJP, Schols A, Baijens LWJ. Oropharyngeal dysphagia and cachexia: Intertwined in head and neck cancer. *Head Neck*. Apr 2023;45(4):783-797. doi:10.1002/hed.27288 10.1002/hed.27288. Epub 2022 Dec 30.

84. Xie H, Ruan G, Wei L, et al. Hand grip strength-based cachexia index as a predictor of cancer cachexia and prognosis in patients with cancer. *J Cachexia Sarcopenia Muscle*. Feb 2023;14(1):382-390. doi:10.1002/jcsm.13139
10.1002/jcsm.13139. Epub 2022 Nov 29.
85. Yin L, Cui J, Lin X, et al. Identifying cancer cachexia in patients without weight loss information: machine learning approaches to address a real-world challenge. *Am J Clin Nutr*. Nov 2022;116(5):1229-1239. doi:10.1093/ajcn/nqac251
10.1093/ajcn/nqac251. Epub 2023 Feb 10.
86. Zhou D, Zhang Y, Mamtawla G, et al. Iron overload is related to muscle wasting in patients with cachexia of gastric cancer: using quantitative proteome analysis. *Medical Oncology*. 2020;37(12):113. doi:https://dx.doi.org/10.1007/s12032-020-01439-w
87. Zhuang CL, Dong QT, Shi HP, et al. Cachexia Versus Sarcopenia in Clinical Characteristics and Prognostic Value After Radical Gastrectomy for Gastric Cancer: A Large-Scale Prospective Study. *Ann Surg Oncol*. Apr 2022;29(4):2348-2358. doi:10.1245/s10434-021-11084-w
10.1245/s10434-021-11084-w. Epub 2021 Nov 19.
88. Zopf Y, Schink K, Reljic D, et al. Assessing cachexia in older patients: Different definitions - But which one is the most practical for clinical routine? *Archives of Gerontology and Geriatrics*. 2020;86:103943. doi:https://dx.doi.org/10.1016/j.archger.2019.103943
89. Aktas A, Lorton CM, Griffin O, et al. Application of the 2011 international consensus cancer cachexia classification in routine oncology dietetic practice: An observational study. *Nutr Clin Pract*. Aug 2023;38(4):790-797. doi:10.1002/ncp.10915
10.1002/ncp.10915. Epub 2022 Nov 9.
90. Antoun S, Morel H, Souquet PJ, et al. Staging of nutrition disorders in non-small-cell lung cancer patients: utility of skeletal muscle mass assessment. *J Cachexia Sarcopenia Muscle*. Aug 2019;10(4):782-793. doi:10.1002/jcsm.12418
10.1002/jcsm.12418. Epub 2019 Apr 1.
91. Bye A, Wesseltoft-Rao N, Iversen PO, et al. Alterations in inflammatory biomarkers and energy intake in cancer cachexia: a prospective study in patients with inoperable pancreatic cancer. *Med Oncol*. Jun 2016;33(6):54. doi:10.1007/s12032-016-0768-2
10.1007/s12032-016-0768-2. Epub 2016 Apr 27.
92. Cavalcante Martins FF, de Pinho NB, de Carvalho Padilha P, et al. Patient-generated subjective global assessment predicts cachexia and death in patients with head, neck and abdominal cancer: A retrospective longitudinal study. *Clin Nutr ESPEN*. Jun 2019;31:17-22. doi:10.1016/j.clnesp.2019.03.013
10.1016/j.clnesp.2019.03.013. Epub 2019 Apr 5.
93. ÉB NB, Daly LE, Power DG, Cushen SJ, MacEneaney P, Ryan AM. Computed tomography diagnosed cachexia and sarcopenia in 725 oncology patients: is nutritional screening capturing hidden malnutrition? *J Cachexia Sarcopenia Muscle*. Apr 2018;9(2):295-305. doi:10.1002/jcsm.12258
10.1002/jcsm.12258. Epub 2017 Dec 21.
94. Gumpper-Fedus K, Hart PA, Belury MA, et al. Altered Plasma Fatty Acid Abundance Is Associated with Cachexia in Treatment-Naive Pancreatic Cancer. *Cells*. 2022;11(5):910. doi:https://dx.doi.org/10.3390/cells11050910
95. Jager-Wittenaar H, Dijkstra PU, Dijkstra G, et al. High prevalence of cachexia in newly diagnosed head and neck cancer patients: An exploratory study. *Nutrition*. Mar 2017;35:114-118. doi:10.1016/j.nut.2016.11.008
10.1016/j.nut.2016.11.008. Epub 2016 Dec 14.

96. Johns N, Hatakeyama S, Stephens NA, et al. Clinical classification of cancer cachexia: phenotypic correlates in human skeletal muscle. *PLoS One*. 2014;9(1):e83618. doi:10.1371/journal.pone.0083618
10.1371/journal.pone.0083618. eCollection 2014.
97. Johns N, Stretch C, Tan BH, et al. New genetic signatures associated with cancer cachexia as defined by low skeletal muscle index and weight loss. *J Cachexia Sarcopenia Muscle*. Feb 2017;8(1):122-130. doi:10.1002/jcsm.12138
10.1002/jcsm.12138. Epub 2016 Aug 5.
98. Morikawa A, Naito T, Sugiyama M, et al. Impact of Cancer Cachexia on Hospitalization-associated Physical Inactivity in Elderly Patients with Advanced Non-small-cell Lung Cancer. *Asia Pac J Oncol Nurs*. Oct-Dec 2018;5(4):377-382. doi:10.4103/apjon.apjon_20_18
10.4103/apjon.apjon_20_18.
99. Op den Kamp CM, Langen RC, Snepvangers FJ, et al. Nuclear transcription factor κ B activation and protein turnover adaptations in skeletal muscle of patients with progressive stages of lung cancer cachexia. *Am J Clin Nutr*. Sep 2013;98(3):738-48. doi:10.3945/ajcn.113.058388
10.3945/ajcn.113.058388. Epub 2013 Jul 31.
100. Penafuerte CA, Gagnon B, Sirois J, Murphy J, MacDonald N, Tremblay ML. Identification of neutrophil-derived proteases and angiotensin II as biomarkers of cancer cachexia. *Br J Cancer*. Mar 15 2016;114(6):680-7. doi:10.1038/bjc.2016.3
10.1038/bjc.2016.3. Epub 2016 Mar 8.
101. Solís-Martínez O, Álvarez-Altamirano K, Cardenas D, Trujillo-Cabrera Y, Fuchs-Tarlovsky V. Cancer Cachexia Affects Patients with Head and Neck Cancer in All Stages of Disease: A Prospective Cross-Sectional Study. *Nutr Cancer*. 2022;74(1):82-89. doi:10.1080/01635581.2020.1869792
10.1080/01635581.2020.1869792. Epub 2021 Jan 16.
102. van der Meij BS, Schoonbeek CP, Smit EF, Muscaritoli M, van Leeuwen PA, Langius JA. Pre-cachexia and cachexia at diagnosis of stage III non-small-cell lung carcinoma: an exploratory study comparing two consensus-based frameworks. *Br J Nutr*. Jun 28 2013;109(12):2231-9. doi:10.1017/s0007114512004527
10.1017/S0007114512004527. Epub 2012 Nov 16.
103. Akaoka M, Haruki K, Taniai T, et al. Clinical significance of cachexia index in patients with hepatocellular carcinoma after hepatic resection. *Surg Oncol*. Dec 2022;45:101881. doi:10.1016/j.suronc.2022.101881
10.1016/j.suronc.2022.101881. Epub 2022 Nov 3.
104. Aslan V, Kılıç ACK, Sütcüoğlu O, et al. Cachexia index in predicting outcomes among patients receiving immune checkpoint inhibitor treatment for metastatic renal cell carcinoma. *Urol Oncol*. Nov 2022;40(11):494.e1-494.e10. doi:10.1016/j.urolonc.2022.07.018
10.1016/j.urolonc.2022.07.018. Epub 2022 Sep 20.
105. Demirelli B, Babacan NA, Ercelep Ö, et al. Modified Glasgow Prognostic Score, Prognostic Nutritional Index and ECOG Performance Score Predicts Survival Better than Sarcopenia, Cachexia and Some Inflammatory Indices in Metastatic Gastric Cancer. *Nutr Cancer*. 2021;73(2):230-238. doi:10.1080/01635581.2020.1749290
10.1080/01635581.2020.1749290. Epub 2020 Apr 9.
106. Go SI, Park MJ, Lee GW. Clinical significance of the cachexia index in patients with small cell lung cancer. *BMC Cancer*. May 17 2021;21(1):563. doi:10.1186/s12885-021-08300-x
10.1186/s12885-021-08300-x.
107. Go SI, Park MJ, Park S, et al. Cachexia index as a potential biomarker for cancer cachexia and a prognostic indicator in diffuse large B-cell lymphoma. *J Cachexia Sarcopenia Muscle*. Dec 2021;12(6):2211-2219. doi:10.1002/jcsm.12837

10.1002/jcsm.12837. Epub 2021 Oct 21.
108. Goh MJ, Kang W, Jeong WK, et al. Prognostic significance of cachexia index in patients with advanced hepatocellular carcinoma treated with systemic chemotherapy. *Sci Rep*. May 10 2022;12(1):7647. doi:10.1038/s41598-022-11736-1
10.1038/s41598-022-11736-1.
109. Hamura R, Haruki K, Shirai Y, et al. Preoperative cachexia index can predict the prognosis of extrahepatic biliary tract cancer after resection. *Surg Oncol*. Sep 2022;44:101825. doi:10.1016/j.suronc.2022.101825
10.1016/j.suronc.2022.101825. Epub 2022 Jul 31.
110. Jafri SH, Previgliano C, Khandelwal K, Shi R. Cachexia Index in Advanced Non-Small-Cell Lung Cancer Patients. *Clin Med Insights Oncol*. 2015;9:87-93. doi:10.4137/cmo.S30891
111. Kamada T, Haruki K, Nakashima K, et al. Prognostic significance of the cachexia index in patients with stage I-III colorectal cancer who underwent laparoscopic surgery. *Surg Today*. Feb 1 2023;doi:10.1007/s00595-023-02646-4
10.1007/s00595-023-02646-4.
112. Karmali R, Alrifai T, Fughhi IAM, et al. Impact of cachexia on outcomes in aggressive lymphomas. *Ann Hematol*. Jun 2017;96(6):951-956. doi:10.1007/s00277-017-2958-1
10.1007/s00277-017-2958-1. Epub 2017 Apr 17.
113. Nakashima K, Haruki K, Kamada T, et al. Usefulness of the cachexia index as a prognostic indicator for patients with gastric cancer. *Annals of Gastroenterological Surgery*. 2023;doi:https://dx.doi.org/10.1002/ags3.12669
114. Shimagaki T, Sugimachi K, Mano Y, et al. Cachexia index as a prognostic predictor after resection of pancreatic ductal adenocarcinoma. *Annals of Gastroenterological Surgery*. 2023;doi:https://dx.doi.org/10.1002/ags3.12686
115. Takano Y, Kodera K, Tsukihara S, et al. Association of a newly developed Cancer Cachexia Score with survival in Stage I-III colorectal cancer. *Langenbecks Arch Surg*. Apr 12 2023;408(1):145. doi:10.1007/s00423-023-02883-8
10.1007/s00423-023-02883-8.
116. Tanji Y, Furukawa K, Haruki K, et al. Significant impact of cachexia index on the outcomes after hepatic resection for colorectal liver metastases. *Annals of Gastroenterological Surgery*. 2022;6(6):804-812. doi:https://dx.doi.org/10.1002/ags3.12578
117. Chen HW, Chen YC, Yang LH, et al. Impact of cachexia on oncologic outcomes of sarcopenic patients with upper tract urothelial carcinoma after radical nephroureterectomy. *PLoS One*. 2021;16(4):e0250033. doi:10.1371/journal.pone.0250033
10.1371/journal.pone.0250033. eCollection 2021.
118. Cong M, Song C, Xu H, et al. The patient-generated subjective global assessment is a promising screening tool for cancer cachexia. *BMJ Support Palliat Care*. May 2022;12(e1):e39-e46. doi:10.1136/bmjspcare-2020-002296
10.1136/bmjspcare-2020-002296. Epub 2020 Aug 21.
119. Kwon M, Kim RB, Roh JL, et al. Prevalence and clinical significance of cancer cachexia based on time from treatment in advanced-stage head and neck squamous cell carcinoma. *Head Neck*. Apr 2017;39(4):716-723. doi:10.1002/hed.24672
10.1002/hed.24672. Epub 2016 Dec 21.
120. Morimoto K, Uchino J, Yokoi T, et al. Impact of cancer cachexia on the therapeutic outcome of combined chemoimmunotherapy in patients with non-small cell lung cancer: a retrospective study. *Oncoimmunology*. 2021;10(1):1950411. doi:10.1080/2162402x.2021.1950411
10.1080/2162402X.2021.1950411. eCollection 2021.

121. Vigano AAL, Del Fabbro E, Bruera E, Borod M. The cachexia clinic: From staging to managing nutritional and functional problems in advanced cancer patients. *Critical Reviews in Oncogenesis*. 2012;17(3):293-304. doi:https://dx.doi.org/10.1615/CritRevOncog.v17.i3.70
122. White R, Weekes CE, Grant R, Baldwin C, Ahmed H. Determining the prevalence and severity of cancer cachexia in advanced non-small cell lung cancer and its relationship with chemotherapy outcomes. *Support Care Cancer*. Sep 2020;28(9):4373-4380. doi:10.1007/s00520-019-05259-1 10.1007/s00520-019-05259-1. Epub 2020 Jan 8.
123. Wiegert EVM, de Oliveira LC, Calixto-Lima L, Mota ESLMSD, Peres WAF. Cancer cachexia: Comparing diagnostic criteria in patients with incurable cancer. *Nutrition*. Nov-Dec 2020;79-80:110945. doi:10.1016/j.nut.2020.110945
124. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. *Am J Clin Nutr*. Jun 2006;83(6):1345-50. doi:10.1093/ajcn/83.6.1345 10.1093/ajcn/83.6.1345.
125. Argilés JM, Betancourt A, Guàrdia-Olmos J, et al. Validation of the CAchexia SCOre (CASCO). Staging Cancer Patients: The Use of miniCASCO as a Simplified Tool. *Front Physiol*. 2017;8:92. doi:10.3389/fphys.2017.00092
126. Ballyuzek MF, Mashkova MV, Arutjunyan AV, Duke VA. [Melatonin as a marker of the grade of cardiac disorders during cachexia development in oncological patients of different ages]. *Adv Gerontol*. 2017;30(1):70-77.
127. Argilés JM, López-Soriano FJ, Toledo M, Betancourt A, Serpe R, Busquets S. The cachexia score (CASCO): a new tool for staging cachectic cancer patients. *J Cachexia Sarcopenia Muscle*. Jun 2011;2(2):87-93. doi:10.1007/s13539-011-0027-5
128. Ueshima J, Maeda K, Shimizu A, et al. Cachexia staging score predicts survival in patients with cancer who receive palliative care. *Nutrition*. Feb 2023;106:111880. doi:10.1016/j.nut.2022.111880
129. Yi H, Wang Y, Liang Q, Li X, Chen C, Mao X. R-CSS: A clinically applicable score to classify cachexia stages in patients with cancer undergoing intensity-modulated radiation therapy. *Asia Pac J Oncol Nurs*. Jan 2023;10(1):100164. doi:10.1016/j.apjon.2022.100164 10.1016/j.apjon.2022.100164. eCollection 2023 Jan.
130. Wang J, Tan S, Xu J, et al. Development and application of the Cancer Cachexia Staging Index for the diagnosis and staging of cancer cachexia. *Nutrition*. Jun 4 2023;114:112114. doi:10.1016/j.nut.2023.112114 10.1016/j.nut.2023.112114.
131. Gabison R, Gibbs M, Uziely B, Ganz FD. The cachexia assessment scale: Development and psychometric properties. *Oncology Nursing Forum*. 2010;37(5):635-640. doi:https://dx.doi.org/10.1188/10.ONF.635-640
132. de Oliveira LC, Rosa K, Gaspar T, Paiva BSR, Paiva CE, Peres WAF. Clinical usefulness of the Patient-Generated Subjective Global Assessment and modified Glasgow Prognostic Score in decision making concerning the indication of enteral nutritional therapy in patients with incurable cancer receiving palliative care. *Nutrition*. Aug 2023;112:112057. doi:10.1016/j.nut.2023.112057 10.1016/j.nut.2023.112057. Epub 2023 Apr 24.
133. Fukushima T, Nakano J, Ishii S, et al. Characteristics of muscle function and the effect of cachexia in patients with haematological malignancy. *Eur J Cancer Care (Engl)*. Mar 2019;28(2):e12956. doi:10.1111/ecc.12956 10.1111/ecc.12956. Epub 2018 Oct 25.

134. Matsuzuka T, Suzuki M, Saijoh S, et al. [Assessment of Cachexia in Head and Neck Cancer Patients Based on a Modified Glasgow Prognostic Score]. *Nihon Jibiinkoka Gakkai Kaiho*. Feb 2016;119(2):125-8. doi:10.3950/jibiinkoka.119.125
10.3950/jibiinkoka.119.125.
135. Naito T, Tashiro M, Ishida T, Ohnishi K, Kawakami J. Cancer cachexia raises the plasma concentration of oxymorphone through the reduction of CYP3A but not CYP2D6 in oxycodone-treated patients. *J Clin Pharmacol*. Aug 2013;53(8):812-8. doi:10.1002/jcph.112
10.1002/jcph.112. Epub 2013 Jun 3.
136. Silva GAD, Wiegert EVM, Calixto-Lima L, Oliveira LC. Clinical utility of the modified Glasgow Prognostic Score to classify cachexia in patients with advanced cancer in palliative care. *Clin Nutr*. May 2020;39(5):1587-1592. doi:10.1016/j.clnu.2019.07.002
10.1016/j.clnu.2019.07.002. Epub 2019 Jul 20.
137. Cavka L, Pohar Perme M, Rotovnik Kozjek N, Seruga B. Prognostic Impact of Nutritional Status on Overall Survival and Health-Related Quality of Life in Men with Advanced Prostate Cancer. *Nutrients*. Feb 20 2023;15(4)doi:10.3390/nu15041044
10.3390/nu15041044.
138. V IJ-H, Heerschop S, Wanten G, van den Berg M. Evaluation of the Validity and Feasibility of the GLIM Criteria Compared with PG-SGA to Diagnose Malnutrition in Relation to One-Year Mortality in Hospitalized Patients. *J Acad Nutr Diet*. Mar 2022;122(3):595-601. doi:10.1016/j.jand.2021.07.011
139. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. *Curr Opin Clin Nutr Metab Care*. Sep 2017;20(5):322-329. doi:10.1097/mco.0000000000000389
140. Arends J, Strasser F, Gonella S, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines(☆). *ESMO Open*. Jun 2021;6(3):100092. doi:10.1016/j.esmoop.2021.100092
141. Takahashi K, Masuda T, Ishikawa Y, et al. A Novel Frailty Grade Combined with Cachexia Index and Osteopenia in Esophagectomy. *World J Surg*. Jun 2023;47(6):1503-1511. doi:10.1007/s00268-023-06942-5
10.1007/s00268-023-06942-5. Epub 2023 Feb 21.
142. Go SI, Kim HG, Kang MH, Park S, Lee GW. Prognostic model based on the geriatric nutritional risk index and sarcopenia in patients with diffuse large B-cell lymphoma. *BMC Cancer*. May 18 2020;20(1):439. doi:10.1186/s12885-020-06921-2
10.1186/s12885-020-06921-2.
143. Namikawa T, Marui A, Yokota K, et al. Frequency and prognostic impact of cachexia during drug treatment for unresectable advanced gastric cancer patients. *Surg Today*. Nov 2022;52(11):1560-1567. doi:10.1007/s00595-022-02493-9
10.1007/s00595-022-02493-9. Epub 2022 Mar 24.
144. Orell-Kotikangas H, Österlund P, Mäkitie O, et al. Cachexia at diagnosis is associated with poor survival in head and neck cancer patients. *Acta Otolaryngol*. Jul 2017;137(7):778-785. doi:10.1080/00016489.2016.1277263
10.1080/00016489.2016.1277263. Epub 2017 Jan 26.
145. Wiegert EVM, de Oliveira LC, Calixto-Lima L, Chaves GV, Silva Lopes MS, Peres WAF. New cancer cachexia staging system for use in clinical practice. *Nutrition*. Oct 2021;90:111271. doi:10.1016/j.nut.2021.111271
146. Muscaritoli M, Imbimbo G, Jager-Wittenaar H, et al. Disease-related malnutrition with inflammation and cachexia. *Clin Nutr*. Aug 2023;42(8):1475-1479. doi:10.1016/j.clnu.2023.05.013

147. Meza-Valderrama D, Marco E, Dávalos-Yerovi V, et al. Sarcopenia, Malnutrition, and Cachexia: Adapting Definitions and Terminology of Nutritional Disorders in Older People with Cancer. *Nutrients*. Feb 26 2021;13(3)doi:10.3390/nu13030761
148. Dunne RF, Loh KP, Williams GR, Jatoi A, Mustian KM, Mohile SG. Cachexia and Sarcopenia in Older Adults with Cancer: A Comprehensive Review. *Cancers (Basel)*. Nov 25 2019;11(12)doi:10.3390/cancers11121861
149. Ueshima J, Inoue T, Saino Y, et al. Diagnosis and prevalence of cachexia in Asians: A scoping review. *Nutrition*. Mar 2024;119:112301. doi:10.1016/j.nut.2023.112301
150. Chowdhry SM, Chowdhry VK. Cancer cachexia and treatment toxicity. *Curr Opin Support Palliat Care*. Dec 2019;13(4):292-297. doi:10.1097/spc.0000000000000450
151. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer*. Mar 1998;34(4):503-9. doi:10.1016/s0959-8049(97)10090-9
152. Coles TM, Wilson SM, Kim B, Beckham JC, Kinghorn WA. From obligation to opportunity: future of patient-reported outcome measures at the Veterans Health Administration. *Transl Behav Med*. Nov 25 2019;9(6):1157-1162. doi:10.1093/tbm/ibz121