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A comparison of inflammatory markers' potential to predict weight loss in advanced cancer: a prospective observational study

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ABSTRACT

Background: Systemic inflammation is crucial in cancer cachexia, but the optimal measurement method remains unclear. This study compares markers of systemic inflammation (MoSI) in predicting weight loss in patients with metastatic cancer.

Methods: This prospective, observational multi-center study involved patients undergoing radiotherapy for bone metastases. Baseline assessments included demographics, clinical characteristics, previous weight loss, and appetite loss. MoSI included: C-reactive protein (CRP), albumin, white blood cells, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, interleukin-6 (IL-6), modified Glasgow Prognostic Score (mGPS), and Prognostic Nutritional Index. Body weight was recorded at baseline, 3, and 8 weeks post-radiotherapy. Multiple linear regression assessed MoSI's predictive ability for weight loss, adjusting for previous weight loss, appetite loss, and primary tumour type. Goodness-of-fit was assessed using adjusted R^2.

Results: Out of 574 recruited patients, 540 and 470 were analyzed at 3 and 8 weeks, respectively. The median age (IQR) was 67 (15), 330 (61%) were male, and 397 (74%) had a Karnofsky performance status ≥70. In a base model without MoSI, significant predictors of weight loss at 3 weeks were appetite loss and urological, lung, and gastrointestinal cancer (adjusted R^2 of 0.064), while at 8 weeks, urological and lung cancer were significant (adjusted R^2 of 0.035). At 3 weeks, all MoSI significantly improved the base model, with adjusted R^2 between 0.078 and 0.091. At 8 weeks: CRP, mGPS, albumin and IL-6 improved the model; however only CRP and mGPS retained an adjusted R^2 of ~0.09.

Conclusions: All MoSI predicted weight loss, but CRP and mGPS were the most optimal.

Keywords: Cancer, Cachexia, Biomarkers, Inflammation

Introduction

Cachexia is particularly prevalent in patients with advanced cancer, but also occurs in earlier stages of the disease (1). The condition results from altered metabolism and is characterized by loss of muscle, with or without loss of fat mass. Appetite loss, systemic inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia, and unlike undernutrition, cachexia cannot be reversed by nutritional support alone (2).

While cachexia is a major cause of weight loss in patients with cancer, there are also other etiologies of cancer-associated weight loss, such as bowel obstruction, treatment-related nausea or other side effects, and psychosocial factors. Differentiating between etiologies of weight loss or assessing their relative impact remains challenging. This is particularly challenging in clinical studies, where a lack of reliable biomarkers for cancer cachexia can result in

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heterogenous study samples. To address this, study selection criteria often include a range of cachexia-associated parameters, such as weight loss, appetite loss, fatigue, various laboratory tests, and primary tumor types highly associated with cachexia (3-5).

Systemic inflammation is integral to the pathophysiology of cachexia (6,7), and this is recognized in the 2011 international consensus paper on the definition of cachexia, but not implemented in the proposed diagnostic criteria, which are based on weight loss and body composition (2). To differentiate between changes in weight and body composition due to either cachexia or undernutrition, the Global Leadership Initiative on Malnutrition (GLIM) has suggested that the presence of systemic inflammation is necessary to diagnose cachexia (8). However, the optimal method to measure systemic inflammation in cancer cachexia is not established.

For a marker of systemic inflammation to be of value in clinical assessment of cachexia, it needs to be easily accessible, reliable, discriminate against other conditions, and have the potential to predict cachexia development. While several inflammatory biomarkers have been associated with cachexia and proposed as potential diagnostic markers (9), their predictive strength has not been directly compared, leaving the choice of biomarker unclear.

Although optimal treatment strategies remain to be established, identifying biomarkers of cachexia is important to identify patients at risk and in need of special follow-up, nutritional advice, and treatment. Additionally, patients with cachexia have a poor prognosis and may have reduced tolerance to anti-cancer treatment (10,11) and identifying the condition can therefore affect cancer treatment decisions. Knowledge of biomarkers may also lead to improved patient selection in cachexia clinical trials and to greater insight into the pathophysiology of cancer cachexia (2,6,7). Moreover, markers of systemic inflammation are increasingly being used as targets for new treatment (12,13).

Our group has previously proposed a model that predicts cachexia development in patients with incurable cancer, identifying primary tumor type, appetite loss, and early weight loss (<5%) as significant predictors (14). A weakness of this model is that it lacks a marker of systemic inflammation.

In order to enable early detection and consequently facilitate prompt management of cachexia, the objective of this study is to evaluate and compare the ability of different markers of systemic inflammation (MoSI) to predict weight loss in a cohort of patients with metastatic cancer.

Material and methods

Patients

This study was a preplanned part of the Palliative Radiotherapy and Inflammation study (PRAIS) (15). Patients were recruited from seven European oncological centers (Norway, Italy, Spain and UK) between December 2013 and December 2017. Key eligibility criteria were age > 18, a verified cancer diagnosis, and about to undergo palliative radiotherapy for painful bone metastases. Other details are published previously (15). The reporting is guided by the STROBE checklist for cohort studies (16).

Assessments

Patients were assessed at baseline and at study visits 3 and 8 weeks after the end of radiotherapy. Age, sex, primary tumor type, and Charlson Comorbidity Index were recorded at baseline. The Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) was used to assess weight loss in the 6 months prior to baseline (17) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C15 PAL was used to assess appetite loss (18). Appetite loss is scored on a single-item 4-point Likert scale and linearly transformed to a score between 0 and 100, where a higher score indicates worse appetite. Height was recorded at baseline and weight was measured with light clothing at each study visit. In case of missing weight measurements, the patient reported weight was accepted. Weight loss was chosen as the endpoint in this study in favor of cachexia to maximize the use of data. Choosing cachexia as the endpoint in this longitudinal study would necessitate discarding all observations related to patients already suffering from cachexia at baseline. The current definition of cachexia is based on weight loss and body composition, and a change in body composition over time would almost certainly be reflected by weight loss (2).

C-reactive protein (CRP) (mg/L), albumin (g/L), white blood cell count (WBC) (10^9/L), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), Interleukin-6 (IL-6) (pg/mL), modified Glasgow Prognostic Score (mGPS) and Prognostic Nutritional Index (PNI) were used to assess systemic inflammation at baseline. Clinical chemistry analyses were performed at local laboratory facilities at each study site. IL-6 was included in the analysis because it is a central mediator of cancer cachexia (6) and because we wanted to evaluate the predictive effect of a cytokine alongside more easily accessible MoSI. IL-6 analyses were performed with Bio-Plex Pro™ Human Cytokine Plex-27 Assay (Bio-Rad Laboratories, Hercules, CA, USA) at Nordland Hospital Trust (Bodø, Norway). The mGPS is based on CRP and albumin levels, and patients are scored 0 (CRP ≤ 10 mg/L, any albumin), 1 (CRP > 10 mg/L, albumin ≥ 35 g/L) or 2 (CRP > 10 mg/L, albumin < 35 g/L). PNI is calculated as albumin (g/L) + 5 × lymphocytes (10^9/L). The mGPS and PNI were included in the analyses in addition to CRP, albumin, NLR and MLR because they are well validated, accessible and frequently used scores to assess systemic inflammation and cancer prognosis (19,20). Further details on the analytical methods are published previously (15).

Ethical considerations

This study was approved by The Regional Committee for Medical and Health Research Ethics in Central Norway (2013/1126) as well as medical research ethics committees in each participating country. The study was conducted in keeping with the 1964 Declaration of Helsinki and its later amendments. All patients gave written informed consent prior to the inclusion in the study.

Statistical analysis

Sample size was estimated based on the primary outcome of the PRAIS-study, and not on the outcome used in

this secondary analysis. A detailed justification for the sample size is provided in the protocol paper (21). Descriptive statistics were used to analyze baseline characteristics. To evaluate ability to predict weight loss after 3 and 8 weeks, linear regression was used with percentage weight loss from baseline to 3 and 8 weeks after end of radiotherapy, respectively, as dependent variables. Two base models, one for 3 weeks' weight loss and one for 8 weeks' weight loss, were created with primary tumor type and appetite loss as independent variables, based on a previously published model (14). Both models were adjusted for reported weight loss prior to baseline. The different MoSI were added to the two base models one by one, and adjusted R^2 were used to compare goodness-of-fit between models. CRP, NLR, MLR and IL6 were logarithmically transformed after a sensitivity analysis conducted to determine which inflammatory markers would benefit from such transformation. To aid clinical decision-making, an analysis was performed to find the optimal cutoffs of the best-performing inflammatory marker(s). To accomplish this, regression analyses were performed multiple times with the inflammatory marker dichotomized with consecutive cutoffs, and the optimal cutoff was determined based on which regression model resulted in the highest explained variance in terms of adjusted R^2.

To maximize use of collected data and address bias due to missing data, multiple imputations with chained equations were applied, using all variables included in the regression analyses, as well as Charlson comorbidity index and survival time as auxiliary variables. Ninety imputations were performed. Estimates and variances were combined using Rubin's rules (22). Stata MP ver. 18.0 (College Station, TX, USA) was used for the statistical analysis.

Results

Figure 1 shows the selection of patients for the final analysis. A total of 574 patients were recruited. Two patients were excluded for not meeting inclusion/exclusion criteria, two withdrew before completing the baseline case report form (CRF), and for one patient, the baseline CRF was lost. Additionally, 29 patients died before the first follow-up and 99 patients died before the second follow-up. Consequently, the analysis 3 and 8 weeks after end of radiotherapy included 540 and 470 patients, respectively. Regarding missing data, 210 (38%) at 3 weeks and 189 (40%) at 8 weeks had at least one missing variable. The variable most frequently missing at both 3 and 8 weeks was weight loss with 106 (20%) and 90 (19%) missing observations, respectively. Table 1 shows the baseline characteristics. For the full sample of 540 patients, the median age (IQR) was 67 (15), 210 (39%) were female and 397 (74%) had a Karnofsky performance status of 70 or higher. The mean (SD) patient-reported weight loss prior to baseline was 3.1% (7.8) (2.7 kg [6.1]). The subsample of 470 patients had a slightly longer time since diagnosis, but had otherwise similar baseline characteristics, which are shown in Table 1.

The mean (SD) weight loss from baseline to 3 weeks was 1.5% (4.2) (1.1 kg [3.2]) and the mean (SD) weight loss after 8 weeks was 1.9% (5.6) (1.5 kg [4.1]). Tables 2a and 2b shows the results of the regression analysis. Lung cancer and urological cancer were predictive of weight loss in both 3 and 8 weeks. GI-cancer and appetite loss were predictive of weight loss in 3 weeks, but not in 8 weeks. Adjusted R^2 for the base model was 0.064 in 3 weeks and 0.035 in 8 weeks. All MoSI significantly improved prediction of weight loss in 3 weeks. CRP, Albumin, mGPS, and IL6 improved prediction of weight loss in 8 weeks, of which CRP and mGPS yielded the highest explained variance. Adjusted R^2 for all models using MoSI to predict weight loss in 3 weeks ranged from 0.076 to 0.091. Only the two models using CRP and mGPS maintained this level of goodness-of-fit after 8 weeks, with adjusted R^2 of 0.096 and 0.093, respectively.

As CRP, which proved to be one of the more robust and predictive markers, is a continuous variable, an exploratory analysis was performed to establish the optimal cutoff for predicting weight loss. Figure 2 shows the explained variance of weight loss after 3 and 8 weeks using consecutive cutoffs of CRP from 5 to 100 in increments of 5. A cutoff of 25 yielded

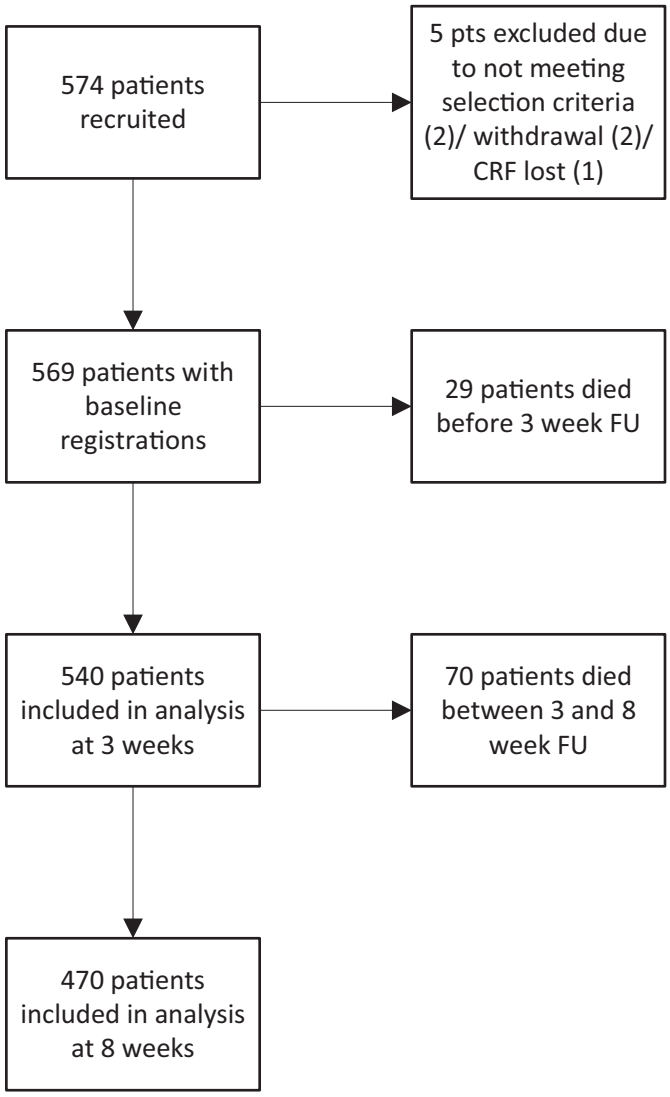

FIGURE 1 - Patient selection.

TABLE 1 - Baseline characteristics

	3 wk. cohort		8 wk. cohort	
N	540		470	
Age (years) median (IQR)	67	(15)	67	(14)
Sex f (%)				
Male	330	(61)	283	(60)
Female	210	(39)	187	(40)
Primary tumor type f (%)				
Breast cancer	110	(20)	104	(22)
Prostate cancer	140	(26)	131	(28)
Lung cancer	95	(18)	82	(17)
Gastrointestinal cancer	87	(16)	67	(14)
Urological cancer	59	(11)	47	(10)
Other	49	(9)	39	(8)
Location of metastases outside bone f (%)				
Lung	156	(29)	129	(27)
Liver	139	(26)	111	(24)
CNS	34	(6)	26	(6)
Other	219	(41)	184	(39)
None	207	(38)	194	(41)
Time since diagnosis (wks.) median (IQR)	82	(230)	96	(246)
KPS f (%)				
0-60	143	(26)	103	(22)
70-100	397	(74)	367	(78)
WL (%) at baseline mean (SD)	3.1	(7.8)	2,6	(7.5)
BMI (kg/m^2) mean (SD)	25.9	(4.6)	26	(4.6)
Lack of appetite at baseline f (%)				
Not at all	228	(43)	207	(44)
A little	158	(29)	139	(30)
Quite a bit	89	(17)	76	(16)
Very much	61	(11)	44	(9)
Skeletal region of radiation f (%)				
Vertebral column	277	(51)	231	(49)
Pelvis	206	(38)	183	(39)
Extremities	60	(11)	53	(11)
Thorax (excl. vertebral column)	58	(11)	53	(11)
Other	12	(2)	12	(2)
Radiation dose[a)] f (%)				
8 Gy x 1	189	(35)	167	(36)
4 Gy x 5	155	(29)	132	(28)
3 Gy x 10	144	(27)	125	(27)
Other	52	(10)	46	(10)
Concurrent systemic anti-cancer treatment (within 6 wks.) f (%)				
Yes	353	(72)	319	(74)
No	139	(28)	111	(26)

Abbreviations: Wk, week; IQR, Interquartile Range; f, frequency; KPS, Karnofsky performance status; WL, weight loss; SD, standard deviation; BMI, body mass index.
a) for the 119 patients that received two parallel treatments, the highest total dose is reported.

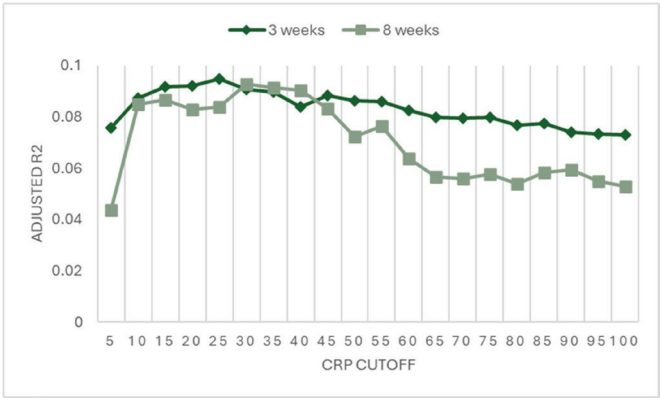

FIGURE 2 - Explained variance in weight loss after 3 and 8 weeks according to CRP cutoff. Cutoffs of CRP between 10 and 60 or 10-45 yields an explained variance of weight loss (adjusted R2) > 0.08 after 3 and 8 weeks, respectively.

the highest explained variance at 3 weeks, with adjusted R^2 of 0.095, while a cutoff of 30 yielded the highest explained variance at 8 weeks, with adjusted R^2 of 0.093. However, cutoffs between 10 and 60 or 10 and 45, all yielded comparable explained variance for the 3- and 8-week cohorts, respectively.

Discussion

In this study, we demonstrate that MoSI improve prediction of weight loss compared to other clinical markers. Specifically, CRP and the partly CRP-derived mGPS predict weight loss with higher accuracy and reliability than other MoSI included in this analysis.

In a previous longitudinal observation study, we identified early weight loss (<5%), primary tumor type and appetite loss as predictors for future development of cachexia (14). Building on this model, our aim was to evaluate whether MoSI would improve the ability to predict future weight loss in a similar patient population. In the current study we confirm that both primary tumor type and appetite loss predict weight loss in the short term. Although gastrointestinal cancer was not statistically significant in predicting weight loss after 8 weeks, urological and lung cancer remained highly significant in this time frame. The association between cachexia and certain primary tumor types has been shown in several cross-sectional studies (1,10,23). In the present study, we show that effect of tumor type remains significant even when contrasted by MoSI. This suggests that the association between weight loss and specific tumor types cannot be solely attributed to the tumor's ability to trigger systemic inflammation.

Contrary to the effect of systemic inflammation, effect of appetite loss seemed to dissipate over time as appetite loss was not significant in predicting weight loss after 8 weeks. This may indicate that weight loss associated with non-inflammatory appetite loss may have a greater potential for recovery. This is supported by a finding in a small retrospective study evaluating predictors of the appetite stimulant anamorelin, where MoSI negatively predicted the effect of

TABLE 2a - Clinical factors and MoSI predicting weight loss in 3 weeks post-radiotherapy

	Base model			Base model + WBC			Base model + NLR (log)			Base model + MLR (log)			Base model + CRP (log)			Base model + Albumin			Base model + mGPS			Base model + IL-6 (log)			Base model + PNI		
	β	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**	**β**	**SE**	**p**
Appetite loss (0-100)	.62	.22	.006	.66	.22	.003	.60	.22	.006	.60	.22		.44	.22	.05	.55	.22	.01	.46	.23	.04	.56	.22	.01	.54	.22	.01
Primary tumour type																											
Breast cancer	0			0			0			0			0			0			0			0			0		
Prostate cancer	.71	.54	.19	.67	.54	.21	.66	.54	.22	.65	.54	.23	.48	.54	.38	.55	.54	.31	.38	.54	.48	.59	.54	.28	.62	.54	.25
Lung cancer	1.8	.61	.003	1.5	.61	.01	1.6	.61	.009	1.6	.61	.009	1.4	.61	.03	1.7	.60	.005	1.3	.62	.04	1.6	.61	.009	1.7	.60	.004
GI cancer	2.0	.64	.002	1.9	.63	.003	1.7	.63	.006	1.6	.64	.01	1.7	.63	.01	1.9	.63	.002	1.7	.64	.009	1.9	.63	.003	1.9	.63	.003
Urological cancer	2.6	.74	<.001	2.5	.73	<.001	2.4	.73	<.001	2.4	.73	.001	2.0	.74	.008	2.5	.73	<.001	2.0	.74	.006	2.4	.74	.002	2.4	.73	<.001
Other	1.1	.76	.16	.84	.76	.27	.88	.76	.25	.82	.76	.28	.90	.76	.23	.86	.76	.26	.86	.76	.25	1.1	.76	.15	.89	.76	.24
WL (%) at baseline	.013	.030	.66	.008	.029	.79	.006	.029	.84	.011	.030	.71	.007	.030	.78	.005	.030	.87	.002	.030	.93	.003	.030	.91	.006	.030	.85
WBC				.15	.049	.002																					
NLR (log)							.76	.27	.005																		
MLR (log)										.85	.31	.007															
CRP (log)													.54	.16	<.001												
Albumin																-.11	.045	.02									
mGPS																											
0																			0								
1																			1.1	.44	.02						
2																			2.3	.76	.003						
IL-6 (log)																						.34	.14	.02			
PNI																									-.084	.033	.01
Goodness-of-fit (adjusted R^2)	.064			.083			.085			.084			.090			.078			.091			.076			.080		

TABLE 2b - Clinical factors and MoSI predicting weight loss in 8 weeks post-radiotherapy

	Base model			Base model + WBC			Base model + NLR (log)			Base model + MLR (log)			Base model + CRP (log)			Base model + Albumin			Base model + mGPS			Base model + IL-6 (log)			Base model + PNI		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Appetite loss (0-100)	.26	.31	.40	.29	.31	.34	.27	.31	.38	.24	.31	.45	-.083	.31	.79	.14	.31	.66	-.066	.31	.83	.20	.31	.52	.18	.31	.57
Primary tumour type																											
Breast cancer	0			0			0			0			0			0			0			0			0		
Prostate cancer	1.3	.77	.10	1.3	.77	.10	1.3	.77	.10	1.2	.77	.12	.82	.75	.27	1.1	.77	.17	.64	.75	.40	1.1	.76	.14	1.2	.77	.12
Lung cancer	3.2	.87	<.001	3.0	.88	<.001	3.1	.88	<.001	3.0	.88	<.001	2.2	.87	.01	3.0	.87	<.001	2.0	.88	.02	2.9	.87	.001	3.1	.87	<.001
GI cancer	1.7	.93	.07	1.6	.92	.08	1.6	.93	.09	1.4	.93	.12	1.1	.90	.22	1.6	.92	.08	.96	.91	.29	1.6	.92	.09	1.6	.92	.09
Urological cancer	3.3	1.0	.002	3.3	1.0	.002	3.3	1.1	.002	3.2	1.1	.002	2.1	1.0	.05	3.2	1.0	.002	2.3	1.0	.03	3.0	1.0	.004	3.2	1.0	.002
Other	1.8	1.1	.11	1.7	1.1	.13	1.7	1.1	.12	1.6	1.1	.14	1.6	1.1	.14	1.5	1.1	.18	1.6	1.1	.15	1.8	1.1	.10	1.6	1.1	.14
WL (%) at baseline	-.018	.044	.69	-.020	.044	.65	-.020	.044	.66	-.017	.044	.70	-.026	.043	.55	-.028	.045	.54	-.031	.043	.48	-.031	.044	.49	-.022	.044	.62
WBC				.12	.075	.12																					
NLR (log)							.27	.38	.48																		
MLR (log)										.56	.42	.18															
CRP (log)													1.1	.25	<.001												
Albumin																-.16	.069	.018									
mGPS																											
0																			0								
1																			2.6	.67	<.001						
2																			3.9	1.0	<.001						
IL-6 (log)																						.45	.19	.02			
PNI																									-.076	.047	.11
Goodness-of-fit (adjusted R^2)	.035			.039			.035			.038			.096			.053			.093			.047			.041		

Abbreviations: WBC, white blood cell count; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; CRP, C-reactive protein; mGPS, modified Glasgow prognostic score; IL-6, interleukin-6; PNI, Prognostic Nutritional Index; WL, weight loss.

the treatment (24). Thus, weight loss associated with systemic inflammation seems more refractory, aligning with the treatment resilience seen in cancer cachexia.

Patient-reported weight loss at baseline did not have any effect on future weight loss. This might seem surprising as one would believe that patients with a history of weight loss would be at risk of further weight loss. Lack of effect could possibly be attributed to the uncertainty of patient reporting; however, it also should be noted that the time frame for assessment of baseline weight loss is six months prior to baseline. Thus, the lack of observed effect of prior weight loss could mean that many have experienced weight loss some time ago, but that body weight is now stabilized (but not regained) due to anti-cancer treatment or other interventions. If weight loss closer to baseline had been assessed, the results might have been different.

Systemic inflammation occurs when pro-inflammatory cytokines are released from immune cells and chronically activates the innate immune system. Systemic inflammation can lead to development or progression of several diseases such as cardiovascular disease, diabetes mellitus, chronic kidney disease or cancer (25). MoSI have known prognostic value in cancer (19,26,27), and have been shown to be associated with weight loss and cachexia in cross-sectional studies (28,29). Recently, also a longitudinal analysis was published, showing that activation of several pro-inflammatory pathways and circulating growth differentiation factor 15 (GDF15) was predictive of cachexia in lung cancer (30). In the present longitudinal study, we now show that readily available MoSI predict weight loss independent of tumor type, appetite loss and previous weight loss, and may therefore serve as markers of cachexia development or progression.

Although all evaluated MoSI significantly improved prediction of weight loss at three weeks, CRP and mGPS demonstrated the highest levels of explained variance. Notably, these two markers were the only ones retaining the same level of explained variance at 8 weeks. This suggests that CRP and mGPS are the most robust predictors of weight loss, indicating a stronger and more sustained relationship with weight loss than the other MoSI in this study. mGPS scores systemic inflammation from 0-2 based on serum elevation of CRP and/or albumin (19). CRP and albumin are acute phase proteins synthesized in the liver. While CRP is upregulated in response to pro-inflammatory cytokines, albumin is downregulated, thus they are termed positive and negative acute phase proteins, respectively. Neither CRP nor albumin has a known direct role in the pathophysiology of cachexia (31). However, the regulation of both CRP and albumin depends on pro-inflammatory cytokines such as Interleukin-1 (IL-1), Tumor Necrosis Factor alpha (TNFα), Transforming Growth Factor beta (TGFβ), and IL6 (32), which are all implicated in cachexia pathophysiology (6). CRP and albumin, which are more readily available in clinical practice, may therefore serve as surrogate markers of cytokine activation and cachexia. Notably, both CRP and albumin more accurately predicted weight loss than IL-6 in this study.

According to our model, predicted weight loss increased with increasing CRP. In order to find the cutoff most accurately predicting weight loss, we explored several consecutive cutoffs of CRP and found that an optimal compromise for both short- and long-term prediction is a CRP cutoff in the lower end of the scale (between 10 and 45). The mGPS uses a CRP cutoff of 10 and with the addition of low albumin (mGPS 2), the predicted weight loss increased considerably compared to patients with elevated CRP only (mGPS 1). However, the explained variance was similar between CRP and mGPS. This means that although addition of low albumin increases the amount of predicted weight loss, it did not explain more of the variation in future weight loss. Thus, combining low albumin and elevated CRP as a required criterion for cachexia probably means that many patients with relevant weight loss will not be detected. Consequently, a slightly elevated CRP seems like the most optimal inflammatory marker to diagnose cachexia. However, mGPS is useful to grade severity of cachexia.

In this study, weight loss in patients with metastatic cancer was chosen as the outcome. The rationale behind this decision is that the cachexia diagnostic criteria are mainly based on weight loss. A 5% weight loss in the last 6 months in patients with normal or obese body composition, or 2% in patients with lean body composition is diagnostic of cachexia, and while the definition additionally states that the weight loss is caused by metabolic alterations and cannot be reversed by nutritional intervention alone, this is not integrated in the diagnostic criteria (2). Weight loss in cancer may have several different causes, many of which may not be related to cachexia, according to the definition. Typical examples are weight loss related to dysphagia or other types of malignant bowel obstruction, in which weight loss often can be significantly improved by nutritional intervention. Using weight loss as the only diagnostic criterion is thus not sufficiently specific. An obvious pitfall is that patients with weight loss not related to cachexia might be recruited to cachexia intervention studies, potentially obscuring the actual effect of the intervention on the outcome. Consequently, many intervention studies in the later years have used additional ad hoc criteria to diagnose cachexia, such as appetite loss, fatigue, or laboratory markers, including various MoSI (4,33,34). In the GLIM criteria for malnutrition, it is advocated that systemic inflammation is a necessary criterion for cachexia; however, no specific marker for systemic inflammation was named (8). Our results show that MoSI are indeed predictive of weight loss in cancer and may serve as biomarkers of cachexia development. Furthermore, we identify CRP and mGPS as the most robust and predictive markers among several other MoSI, and they should be considered implemented in the diagnostic criteria of cachexia and used in future clinical trials as selection criteria to identify patients with cachexia.

Limitations

This is a preplanned secondary analysis of a study, whose primary objective was to identify predictors of response to palliative radiotherapy for painful bone metastases (21). The strengths of this study include the availability of MoSI in a longitudinal dataset of patients with metastases from various primary tumor types and with a considerable spread in weight loss. A limitation is that all patients have bone metastases, thus the sample is not representative of the total population of patients with metastatic cancer. However, bone

metastases are common in advanced cancer and found in 85% of patients dying from prostate, breast, and lung cancer (35). Furthermore, animal models of cancer-induced bone pain have been shown to be a useful platform to study cancer cachexia (35). Additionally, all patients in this study received palliative radiotherapy after baseline observations, and although this treatment is generally very well tolerated, this may have affected development of symptoms such as appetite loss. It is difficult to deduce the significance of these two limitations, and the results should be interpreted with caution. Adjusted R^2 of the investigated models can be perceived as low with a value around 0.09 for the best models (CRP and mGPS), meaning that 9% of the variance in weight loss is explained by the predictors in the model. This may be owed to the multifactorial nature of weight loss, meaning that other factors not included in the models are important to the prediction of weight loss. The aim of this study was not to identify all relevant predictors, but to compare predictive ability of several MoSI. With respect to that, we chose to rely on a previously published model when selecting prior weight loss, primary tumor type, and appetite loss as covariates for the base model (14). The observed increase in R^2 following the addition of MoSI indicates that these markers significantly enhance the predictive accuracy for weight loss. The measurements of IL6 were not standardized to a specific time of day. As IL6 is known to have some diurnal variation (36), this may have introduced variance in the measurements, weakening a possible association with weight loss. As is common in studies with patients with advanced cancer, the attrition was high. To compensate for the bias that might arise from this, we have performed multiple imputations of missing values at baseline, and for patients still alive, but with missing data at follow-up. The results of this study are not validated in another patient cohort and should be considered exploratory. The results must therefore be seen in conjunction with previous publications, and future multi-center studies on the subject are necessary.

Conclusion

Systemic inflammation is an important biomarker for cachexia/cancer associated weight loss, and several specific MoSI are applicable. However, CRP and mGPS seem the most accurate and robust in predicting weight loss both short- and long-term. Smaller elevations in CRP serum levels seem to optimally stratify risk of future weight loss, while mGPS is useful for grading severity of future weight loss.

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Disclosures

Conflict of interest: The authors have no conflicts of interests to declare.

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Availability of data and materials: The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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