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Systemic Inflammation and Nutritional Status in Patients on Palliative Cancer Care: A Systematic Review of Observational Studies

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Abstract

Objective: This systematic literature review explores the results of studies that have analyzed the association between inflammation and nutritional status in patients with cancer in palliative care. **Methods:** The bibliographic research was performed in May 2019, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Group guidelines. The inclusion criteria were papers that (1) had an online abstract available, (2) were original, (3) used a cohort or cross-sectional design, (4) involved patients with advanced cancer in palliative care, and (5) assessed the association between inflammation and nutritional status. The quality assessment was performed using the Newcastle-Ottawa Scale. **Results:** Nine studies were selected. Weight loss (WL; n = 7) was the most common nutritional marker employed and C-reactive protein (CRP; n = 6) was the most common inflammatory marker. There was considerable variability (39.0%-92.2%) in the proportion of patients who had WL in a 6-month period, while CRP >5 mg/dL was common in 45.3% to 73.9% of patients. Systemic inflammation was related to nutritional status, highlighting the relationship between CRP and WL and lean mass (LM). Patients with CRP >10 mg/L have been found to have a lower LM ($P < .001$) and a faster rate of loss of LM at a faster rate during the disease trajectory ($P = .030$). **Conclusion:** Nutritional status is associated with systemic inflammatory response. Inflammatory markers should be considered an additional parameter for the nutritional diagnosis of patients with cancer in palliative care.

Keywords

nutritional status, cachexia, systemic inflammation, advanced cancer, survival

Introduction

Cancer is one of the leading causes of morbidity and mortality in the world.[1] A considerable proportion of cases are identified at an advanced stage,[2] increasing the demand for palliative care. More than 100 million people need palliative care worldwide each year.[3] However, it is common for patients with such needs to be treated inadequately, often with the undue use of invasive methods, which focus on attempting to cure them while failing to treat the most prevalent symptoms, and ultimately prolonging their suffering and pain.[4]

As cancer progresses, it is accompanied by an increased prevalence of malnutrition[5] related to systemic inflammation.[6] The inflammatory process is a key driver of energy imbalance and muscle wasting[7] and is related to altered concentrations of adipokines, other biochemical disorders, and several symptoms, including weight loss (WL), anorexia, reduced energy intake, and functionality.[8-9] However, more information is still needed regarding the nature of the relationship between malnutrition and inflammation in patients with advanced cancer in palliative care; the different phases in the cancer trajectory have been little explored in the scientific literature.

In addition, there are conflicting questions about the nutritional status classification criteria for patients with advanced cancer in palliative care, where the use of inflammatory markers could have great potential.[10] The main challenge is to build solid evidence and put it into practice so that the needs

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of patients are prioritized, knowing that for this field, actions of varying degrees of complexity are required. Thus, this systematic literature review explores the results of studies that analyzed the association between inflammation and nutritional status in patients with advanced cancer receiving palliative care.

Methods

Search Strategy

This systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Group (PRISMA) guidelines.[11] In May 2019, a single researcher carried out the literature search in PubMed, Scopus, LILACS, and Cochrane. The keywords used were advanced cancer, metastatic cancer, palliative care, systemic inflammation, inflammation, inflammatory markers, C-reactive protein, albumin, Glasgow prognostic score, modified Glasgow prognostic score, skeletal muscle depletion, skeletal muscle wasting, muscle mass, lean body mass, body composition, skeletal muscle loss, sarcopenia, cachexia, and malnutrition.

Based on the titles and abstracts, the publications of interest were retrieved in full for evaluation by 2 independent reviewers. The opinion of a third reviewer was called on when necessary. The inclusion criteria were papers that (1) had an online abstract available, (2) reported on original research, (3) used a cohort or cross-sectional design, (4) involved patients aged $\geq$18 years old with advanced cancer (ie, tumors at stage III or IV, metastatic disease, or incurable advanced cancer) who were in palliative care (ie, not receiving active treatment, such as chemotherapy, radiotherapy, or surgery), and (5) assessed the association of inflammatory condition and nutritional status.

Extraction of Data

The data extracted from the articles were age of participants, sample size, types of cancer, study design, objectives, statistics, nutritional assessment, systemic inflammation markers, and results. Two authors extracted these data. Discrepancies were resolved by consensus or, when necessary, by consulting a third researcher.

Evaluation of Methodological Quality

The methodological quality of the studies was assessed independently by 2 authors using the Newcastle-Ottawa Scale (NOS).[12] The studies were classified as being of high (7-9 points), moderate (4-6 points), or low (<3 points) quality. Discrepancies were resolved by consensus or, when necessary, by consulting a third researcher. The initial agreement between the authors was substantial ($k = 0.89$).[13]

Results

Nine articles were selected[7,8,14-20] (Figure 1), with publication dates ranging from 1999 to 2017, totaling data from 2970 patients aged 40 to 60 years. Most of these studies were considered to be of high methodological quality (Table 1).

Weight loss (7 articles) was the most common nutritional marker employed and C-reactive protein (CRP; 6 articles) was the most common inflammatory marker. Considerable variability (39%[20] to 92.2%[14]) was reported in the proportion of patients who had some WL in a 6-month period, and the prevalence of nutritional risk was found to be 38% (Patient-Generated Subjective Global Assessment >9 points).[18] C-reactive protein >5 mg/dL was found in 45.3%[8] to 73.9%[7] of patients, and most patients had a modified Glasgow prognostic score of 0 or 1[7,14,19] (Table 2).

The odds ratio (OR) of the occurrence of symptoms, including WL, was found to be significantly higher in patients with moderate (OR: 1.6), high (OR: 2.5), and very high (OR: 3.5) CRP.[8] Weight loss has been correlated with CRP >5 mg/dL ($P = .022$)[7] and also with reduced body weight ($P < .050$), in conjunction with increased CRP.[19] Patients with CRP >10 mg/L have been found to have a lower lean mass ($P < .001$) and a faster rate of loss of lean mass during the disease trajectory ($P = .030$).[16] For Fouladiun et al,[19] CRP was the primary explanation for variation in lean tissue and a secondary explanation for loss in body fat (Table 2).

Discussion

This is the first systematic literature review to evaluate the association between inflammation and nutritional status in patients with advanced cancer in palliative care, confirming their association. Although some systematic reviews have addressed other nutritional assessment tools and other inflammatory markers, the associated use of WL and CRP seems quite promising. Because of the negative impact of malnutrition on clinical outcomes in advanced cancer, knowledge of nutritional assessment criteria should be expanded.[6]

Patients with advanced cancer in palliative care usually have a limited prognosis. It is therefore essential to identify patients whose nutritional status is closer to the ideal for the severity of the disease.[21] The assessment of nutritional status must be prognostically relevant, being used to direct different care options and supporting personalized counseling and specialized treatment, thereby preventing clinical conduct that is disproportionate to the progression of the disease.

Weight loss was most common nutritional marker and CRP was the most common inflammatory marker employed in the selected studies. Unintentional WL is easy to occur. It is the phenotype most commonly related to cancer cachexia and is often one of the first symptoms that patients notice.[6] Despite current definitions, clinically significant WL is still not a homogeneous concept.[22] Nonetheless, it has been shown in studies to be a factor that consistently influences death rates.[23] In addition, increased CRP is the most widely accepted

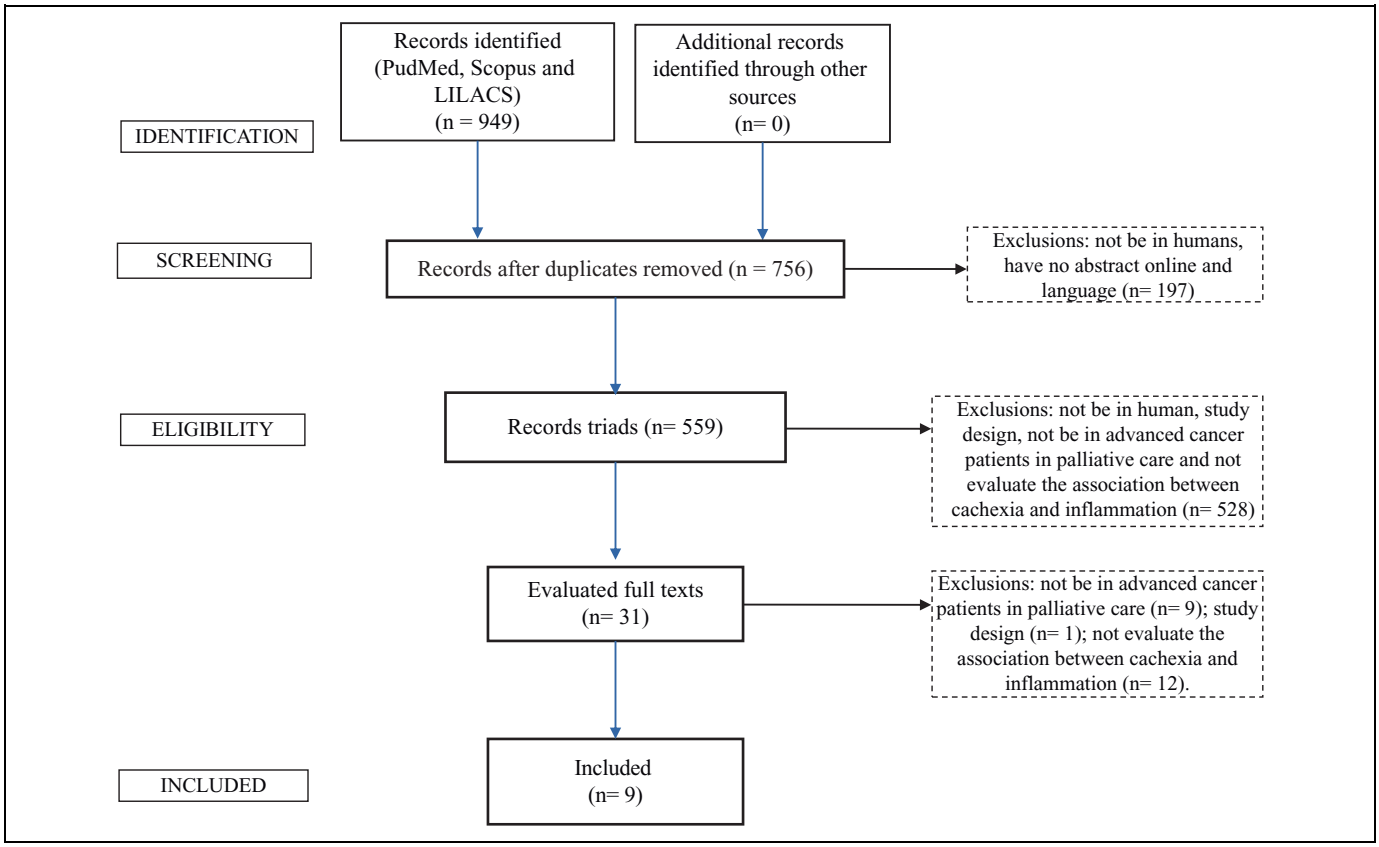

Figure 1. Flowchart of selection of studies. n = number of observation. Designed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses Group.[11]

indicator of systemic inflammation,[6] not least because of its sensitivity, although its use alone is debatable because it can be influenced by other factors, such as infections. Even occurring in conjunction with other factors, CRP is considered an independent prognostic factor[8,15] and high concentrations are usually detected in individuals with cachexia.[6]

The association between nutritional status and systemic inflammation[7,8,14-20] points to the possibility for these 2 domains to be considered concurrently, adding an important new dimension and making for a more sensitive nutritional assessment and probably better care provision for patients with advanced cancer in palliative care. The OR of patients with WL has been found to significantly increase with increasing CRP levels.[8] Patients with CRP concentrations >10 mg/L are found to have a lower lean mass and a faster rate of loss of lean mass during the disease.[16]

This association can be explained by the fact that in patients with cancer, the presence of the tumor generates changes in metabolic, immunological, and neuroendocrine pathways, which are characterized by a negative calorie–protein balance.[6] Regarding immunological pathways, it is known that tumor cells produce a chronic systemic inflammatory state, with increased activity of pro-inflammatory cytokines, interleukin 1, interleukin 6, interferon γ, and tumor necrosis factor α, which promote increased hepatic production of positive acute-phase proteins, with emphasis on CRP, with a consequent reduction of negative acute-phase proteins, producing reflexes in the metabolism. The main metabolic changes are characterized by marked glycolysis and gluconeogenesis, resulting in intense proteolysis with skeletal muscle depletion, lipolysis, and decreased lipogenesis, with depletion of body fat reserves, in an overall context of WL.[24-26]

The conventional nutritional diagnosis determined exclusively through unintentional WL may represent an oversimplification of the nutritional changes affecting individuals with cancer, since important changes in body composition may occur before being reflected in body weight.[6,27] Meanwhile, increases in systemic inflammation have been identified even in apparently adequately nourished individuals (as measured by WL),[14] while systemic inflammation may be related to variations in body composition that are not yet reflected in WL.[16,19] Thus, CRP can contribute to determining the nutritional diagnosis, filling gaps that WL assessments alone cannot address. Meanwhile, WL assessments can help reduce the bias that a CRP assessment alone could generate.

A simultaneous evaluation of WL with CRP could still better explain other relevant aspects in the field of palliative care. The growing importance of providing patient-centered outcomes, such as improved quality of life, functionality, and symptoms, imputes the need to manage multidimensional

Table 1. Description of Studies Regarding Authors, Year of Publication, Origin, Age of Participants, Sample Size, Cancer Type, Study Design, Objectives, and Methodological Quality.

ID	Author/Year	Origin	Age, Mean (±SD) or Median (IQR), years	N	Cancer Type	Design	Objectives	Quality[a]
1	Amano et al, 2017[8]	Japan	68.4 (±12.7)	1702	Lung; GI tract; liver/biliary system/pancreas advanced[b]	Cross-sectional	Investigate association between serum concentrations of CRP, symptoms, and activities of daily living	High
2	Quyen et al, 2017[14]	Vietnam	54.9 (±6.5)	64	Esophagus stage III/IV	Cross-sectional	Determine the NS of the individuals and to investigate its relation with functionality and prognosis	High
3	Bye et al, 2016[15]	Norway	67.5 (35.0-79.0)	20	Pancreas stage III/IV	Cohort	Examine the inflammatory changes in the course of the disease and its relationship to cachexia	High
4	Lindenmann et al, 2014[7]	Austria	67.0 (±11.8)	218	Esophagus inoperable	Cohort	Evaluate influence of serum concentrations of CRP and albumin on carcinoma	High
5	Wallengren et al, 2014[16]	Sweden	69.0 (±11.0)	471	GI tract advanced/metastatic[b]	Cohort	Evaluate impact of age, sex, tumor type, and inflammation on the loss of LM	High
6	Scheede-Bergdahl et al, 2012[17]	Canada	61.8 (±12.9)	83	GI tract; lung stage III/IV	Cohort	Evaluate relevance of serum concentrations of IL-6, IL-1β, IL-8, and TNF-α and its association with cachexia	High
7	Read et al, 2006[18]	Australia	UN	51	CR advanced/metastatic	Cohort	Evaluate novel inflammatory and nutritional prognostic factors	High
8	Fouladiun et al, 2005[19]	Sweden	68.0 (±3.0)	311	GI tract stage III/IV	Cohort	Evaluate changes in BC in relation to other changes in cachexia	High
9	O'Gorman et al, 1999[20]	United Kingdom	UN	50	GI tract advanced/metastatic	Cohort	Examine relationship between WL, appetite, functionality, and inflammation	Moderate

Abbreviations: BC, body composition; CR, colorectal; CRP, C-reactive protein; ID, number of identification; GI, gastrointestinal; IQR, interquartile range; IL, interleukin; LM, lean mass; N, sample size; NS, nutritional status; SD, standard deviation; UN, uninformed; TNF-α, tumor necrosis factor α; WL, weight loss.
[a]Newcastle-Ottawa Scale, 2013.
[b]More frequently.

aspects in care planning.[28] In this respect, it is important to mention that inflammatory markers have been associated with symptoms such as fatigue,[8,17] poor functionality,[17-20] and a poor quality of life.[17] In addition, it was found that some authors analyzed overall survival and identified inflammation as a prognostic marker,[7,17,18] once again reinforcing the need for this evaluation.

In this context, we highlight the need for prevention or early management of reversible nutritional conditions in patients with cancer. Patients with advanced cancer may have a potential for muscle anabolism under specific conditions (>90 days of survival).[29] In addition to their usefulness in identifying patients with poor nutritional conditions, CRP and WL, both modifiable parameters, could be considered for planning and monitoring nutritional interventions to improve outcomes in patients with advanced cancer. However, these implications need to be further studied.

Given the lack of well-defined criteria in the literature to adequately diagnose the nutritional status of patients with advanced cancer in palliative care, more studies are needed on the usefulness of WL assessment in conjunction with CRP in these individuals. Further investigations are required to improve a consistent basis for establishing the simultaneous use of these simple and inexpensive parameters to establish a model, with clearly defined cutoff points, that can be reproduced in various clinical situations and incorporated into the routine of cancer care and that can furthermore help to predict those individuals who will have worse outcomes.

Regarding the study's strengths, the methodology used in this systematic literature review was consistent with PRISMA[11] and the methodological quality evaluation by NOS.[12] The literature search was comprehensive, and there was no restriction on the period of publication in the different databases and reference lists of articles. The inclusion of different types of cancer in the studies could be considered a limitation; however, this research was the first systematic review of its kind to include only patients with advanced cancer in palliative care.

Table 2. Description of Studies Regarding Statistical Tests, Methods of Assessment of Nutritional Status, and Inflammation and Results.

ID	Statistic	Nutritional Assessment (Marker and Sample Distribution)	Systemic Inflammation (Marker and Sample Distribution)	Results
1	χ^2; logistic regression	WL in 1 month (y/n): 66.5%	CRP: 4.3 (1.3-9.6) mg/dL[a]; CRP classification: low <1 mg/dL = 21.5%; moderate 1 to <5 mg/dL = 33.2%; high ≥5 to <10 mg/dL = 22.1%; very high ≥10 mg/dL = 23.2%	Positive rates of symptoms and ADL disabilities increased with increasing CRP level. With CRP >10 mg/dL, the rates of anorexia, fatigue, and WL were 89.8%, 81.0%, and 79.2%, respectively ($P < .001$). Adjusted ORs of individuals exhibiting symptoms increased with the elevation of CRP, in the moderate CRP, high-CRP, and very high CRP groups, 1.6 (95% CI: 1.2-2.0); 2.5 (95% CI: 1.9-3.2); 3.5 (95% CI: 2.7-4.6), respectively
2	Pearson correlation; Spearman	BMI (LW): 43.8%; WL in 2 weeks (y/n): 68.8%; WL in 1 month (y/n): 84.4%; WL in 6 months (y/n): 92.2%; SGA (malnutrition): 50.0%; PG-SGA: 9.9 (±4.4)[b] points; AC (risk of malnutrition): 29.7%	mGPS: 0: 52.5%; 1: 42.6%; 2: 4.9%	PG-SGA and SGA were strongly correlated with the performance status but were poorly correlated with mGPS ($r = 0.332$ and 0.278, $P < .01$ and .05). BMI, AC, and WL did not correlate with mGPS
3	Wilcoxon test; Mann-Whitney; McNemar	Consensus 2011: PCa: 5.0%; Ca: 55.0%; mGPS: PCa: 25.0%; RCa: 10.0%.	IL-10: 0.7 (0-3.4) pg/mL[a]; INFγ: 0.1 (0-13.6) pg/mL[a]; TNF-α: 7.5 (4.1-22.7) pg/mL[a]; IL-6: 4.4 (2.2-34.6) pg/mL[a]	No differences in inflammation or OS were found between the Ca and NCa individuals, according to the consensus. When using mGPS for classification, Ca individuals had higher serum concentrations of IL-6 and lower OS (52 vs 25 weeks, $P = .08$). The mGPS should be considered as an additional framework for identification of Ca
4	χ^2; *t* test; Kaplan-Meier curves; log-rank test	WL (y/n): 81.9%	CRP >5 mg/dL: 73.9%; albumin <3.5 mg/L: 18.2%; mGPS: 0: 41.1%; 1: 44.4%; 2: 14.5%	WL was correlated with elevated plasma CRP ($P = .022$), to diarrhea ($P = .021$), and to dysphagia ($P = .008$). Patients with hypoalbuminemia (3.5 vs 10.4 months, $P = .001$), high CRP (6.8 vs 13.5 months, $P = .001$), and high mGPS (0: 3.0 vs 1: 6.8 vs 2: 12.8 months, $P = .001$) presented lower OS
5	LME; χ^2; Log-rank test; Fisher; Mann-Whitney	LM[c]: 24.6 (±4.0) kg[b]	CRP: 3.9 (±5.1) mg/dL[b]	Age was related to LM, −1.1 (±0.3)[b] kg, $P < .001$, LM depletion was higher in men ($P < .001$), and in pancreatic cancer, LM was lower ($P < .02$). Patients with serum concentrations of CRP >10 mg/L had lower LM ($P < .001$) and loss of LM at a faster rate during the disease trajectory, 0.7 (±0.3)[b] kg/year, $P = .03$.
6	Linear; logistics; and Cox regressions	LM index[c]: 16.1 (±2.7) kg/m^{2}[,b]; WL >5% in 6 months: 53.0%	IL-6: ≥296.4 vs ≤189.0 pg/mL; IL-1β: ≥90.6 vs ≤57.5 pg/mL; IL-8: ≥448.6 vs ≤322.8 pg/mL; TNF-α: ≥451.5 vs ≤261.4 pg/mL	Serum concentrations of IL-1β were associated with WL; IL-1β, IL-6, and IL-8 were associated with weakness and lack of appetite; TNF-α was associated with lack of appetite; IL-6 and IL-8 were associated with QL; IL-1β and TNF-α were associated with sarcopenia. All cytokines were associated with OS. In patients with advanced cancer, IL-1β is better associated with clinical features of the Ca
7	Spearman correlation; Kaplan-Meier curves; log-rank test; Cox regression	WL; BMI (LW): 56.0%; PG-SGA (≥9 points): 38.0%	CRP >10 mg/dL: 69.0%; CRP: 21.1 mg/dL[a]; albumin; mGPS 2: 15.0%	The OS was 9.9 (0.8-21.8)[a] months. The PG-SGA score and the serum CRP levels correlated ($r = 0.430$, $P = .003$). CRP was not related to BMI or WL. The type of treatment (HR = 1.48, 95% CI: 1.11-1.79), PS (HR = 2.37, 95% CI: 1.11-5.09), and mGPS (HR = 2.27; 95% CI: 1.09-4.73) were predictors of OS

(continued)

Table 2. (continued)

ID	Statistic	Nutritional Assessment (Marker and Sample Distribution)	Systemic Inflammation (Marker and Sample Distribution)	Results
8	Kaplan-Meier curves; log-rank test; ANOVA; Cox regression	BMI: 23.6 (±0.2) kg/m^{2,b}; WL: 10.0 (±9.0)%^{b}; LM^{c}: 46.5 (±9.4) kg^{b}	CRP: 45.0 (±5.4) mmol/L^{b}; albumin: 33.0 (±6.0) g/L^{b}	The WL was explained by the loss of BF of the trunk, leg, and arm. LM was lost from the arm. The trunk and leg compartments increased, concomitant with declining serum albumin concentrations and increased CRP. Systemic inflammation primarily explained variation in lean tissue and secondarily explained loss in BF. Albumin ($P < .001$), BF ($P < .02$), and caloric intake ($P < .001$) were predictors of OS
9	χ^2; Fisher test	WL >3%: 39.0%; TSF	CRP	At the baseline, the WL group had lower albumin concentrations and higher CRP ($P < .05$). At follow-up, there was an increase in CRP and reduction in WL, TSF, and KPS in the same group ($P < .05$). KPS improved in the group that gained weight ($P < .05$)

Abbreviations: AC, arm circumference; ADL, activities of daily living; ANOVA, analysis of variance; BF, body fat; BMI, body mass index; Ca, cachectic; CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IL, interleukin; INFγ, interferon γ; KPS, Karnofsky Performance Status; LM, lean mass; LME, linear mixed effects; LW, low weight; mGPS, modified Glasgow Prognostic Score; Nca, noncachectic; OR, odds ratio; OS, overall survival; PCa, precachectic; PG-SGA, patient-generated subjective global assessment; PS, performance status; QL, quality of life; r, correlation coefficient; RCa, refractory cachectic; SGA, subjective global assessment; TNF-α, tumor necrosis factor α; TSF, triceps skin fold; WL, weight loss; y/n, yes or no.
[a]Median (interquartile range).
[b]Mean (±standard deviation).
[c]Evaluated by densitometry by dual emission of X-rays.

Conclusion

Systemic inflammation has been related to nutritional status in advanced stages of cancer, and inflammatory markers should be considered as an additional parameter for nutritional assessments. Ours findings highlight the potential for using CRP in conjunction with WL to better determine nutritional status in patients with advanced cancer in palliative care.

Declaration of Conflicting Interests

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