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Original

Association between an inflammatory-nutritional index and nutritional status in cancer patients

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Abstract

Introduction: **Cachexia is a multifatorial syndrome characterized by loss of body weight, fat and muscle, increasing morbidity and mortality. The use of an index accounting for both serum albumin and C Reactive Protein levels could make early identification of cachexia easier.**

Objective: **To evaluate the variation of an inflammatory nutritional index related to nutritional status in cancer patients.**

Methods: **Cross sectional study including patients with gastrointestinal and lung cancer of a public chemotherapy service in Brazil. Serum albumin and C Reactive Protein were measured and the nutritional status was defined by Subjective Global Assessment. Statistical analyses were performed using Stata 9.2™.**

Results: **A total of 74 patients were evaluated, 58.1% of them were male, mean age 63.4 ± 11.9 years old. Gastrointestinal cancer was the most prevalent type (71.6%). Only 13.7% of the patients were well nourished and 21.9% were severely malnourished. C Reactive Protein significantly increased according to nutritional status decline (p=0.03). When the albumin from patients with systemic inflammation was evaluated, there was no significant variation in relation to nutritional status (p=0.06). The Inflammatory Nutritional Index significantly varied in relation to nutritional status independent of the systemic inflammation (p=0.02).**

Conclusions: **Inflammatory Nutritional Index can be an adjuvant way for biochemical nutritional assessment and follow up in cancer patients with systemic inflammation.**

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Key words: *Cancer. Cachexia. C reactive protein. Albumin. Inflammatory Nutritional Index.*

ASOCIACIÓN ENTRE EL ÍNDICE INFLAMATORIO-NUTRICIONAL Y ESTADO NUTRICIONAL EN PACIENTES CON CÁNCER

Resumen

Introducción: **La caquexia es un síndrome multifactorial caracterizada por la pérdida de peso corporal, grasa y músculo, el aumento de la morbilidad y la mortalidad. El uso de un índice de la contabilidad para los dos niveles de albúmina sérica y la proteína C reactiva podría hacer que la identificación temprana de la caquexia más fácil.**

Objetivo: **Evaluar la variación de una índice inflamatorio-nutricional en relación con el estado nutricional en pacientes con cáncer.**

Métodos: **Estudio descriptivo incluyendo pacientes con cáncer gastrointestinal y los pulmones de un servicio de la quimioterapia pública en Brasil. La albumina y la proteína C reactiva fueron medidos y el estado nutricional se definió por la Evaluación Global Subjetiva. Los análisis estadísticos se realizaron utilizando Stata 9.2 ™.**

Resultados: **Un total de 74 pacientes fueron evaluados, el 58,1% de ellos fueron hombres y el promedio de 63,4 ± 11,9 años de edad. Cáncer gastrointestinal era el tipo más frecuente (71,6%). Sólo el 13,7% de los pacientes estaban bien nutridos y el 21,9% estaban gravemente desnutridos. Proteína C reactiva aumentaron significativamente de acuerdo a la declinación del estado nutricional (p=0,03). Cuando la albúmina de los pacientes con inflamación sistémica se evaluó, no hubo variación significativa en relación al estado nutricional (p=0,06). El índice inflamatorio-nutricional varió significativamente en relación al estado nutricional independiente de la inflamación sistémica (p=0,02).**

Conclusiones: **El índice inflamatorio-nutricional puede ser una manera adyuvante para la evaluación nutricional bioquímica y seguimiento en los pacientes con cáncer y la inflamación sistémica.**

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Palabras clave: *Cáncer. Caquexia. Proteína C reactiva. Albúmina. Índice inflamatorio-nutricional.*

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Abbreviations

CRP: C reactive protein.
SGA: Subjective Global Assessment.
BMI: Body Mass Index.
us-CRP: ultra-sensitive CRP.
GPS: Glasgow Prognostic Score.
INI: Inflammatory-Nutritional Index.
PINI: Prognostic Inflammatory and Nutritional Index.

Introduction

Progressive, involuntary weight loss, especially lean tissue loss, is common in advanced cancer patients. Cachexia is a multifatorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to an underlying disease[1,2]. Cachexia deteriorates patient performance and quality of life, increases morbidity and mortality, and is associated with worst responses to chemotherapy and poorer surgical outcomes in advanced cancer patients[3,4]. Up to 85% of gastrointestinal and lung cancer patients suffer from cachexia at the time of diagnosis[3].

Early identification of malnutrition is key for establishing successful cancer treatment regiments. But the identification of cachexia in cancer patients, especially in early stages, has proven difficult[4].

Most of the traditional nutritional assessment methods are not useful in advanced cancer patients due to their inaccuracy, excessive costs for routine use, and their insufficient ability to assess debilitated patients[5].

Among the biochemical parameters used for assessing nutritional status, serum albumin, synthesized in the liver, is the most prevalent blood protein[6]. Albumin concentration in the blood is associated with nutritional status, and its synthesis is decreased in individuals with systemic inflammation as the liver prioritizes acute phase protein synthesis[6].

There is evidence that chronic systemic inflammation has an important role in the development of cancer cachexia, inducing progressive weight loss and muscle loss[7].

Given the role of systemic inflammation in the genesis of progressive weight loss and muscle loss, cachexia can be identified by the presence of certain systemic inflammation indicators[8,9]. Systemic inflammation is marked by an imbalance between proinflammatory and antiinflammatory cytokines, leading to high C reactive protein (CRP) blood levels[3,10].

Therefore, the biochemical evaluation of nutritional status using serum albumin levels in patients with systemic inflammation becomes dubious and difficult. The use of an index accounting for both serum albumin and CRP levels could make early identification of cachexia easier. The ability to detect cachexia early is of significant clinical relevance, since this condition in its advanced state (last-stage cachexia) is practically untreatable with currently available therapies[1].

Thus, the aim of this study was to evaluate the variation of an albumin/CRP indicator relative to nutritional status, defined by the Subjective Global Assessment (SGA), in cancer patients.

Methodology

A cross sectional study enrolling cancer patients, from July-2008 to April-2010, was conducted in the Chemotherapy Service of the Federal University of Pelotas Teaching Hospital, Brazil, whose service is done exclusively through the health public system.

Patients 18 years of age or older diagnosed with gastrointestinal (including liver, gallbladder and pancreas) or lung cancer, before their first chemotherapy sessions were considered eligible.

Patients had a consult with a nutritionist, after signing a consent form. Standardized questionnaires were used to collect demographic and social data. Anthropometric data (weight and height) were collected through standardized techniques. Cancer diagnosis and treatment information was gathered from patient medical records. Nutritional assessment was performed through Subjective Global Assessment (SGA)[11,12] and calculating Body Mass Index (BMI = weight (Kg) / height (m)^2).

After the appointment with the nutritionist, patients were taken to the laboratory where a blood sample was taken to test ultra-sensitive CRP (us-CRP) and serum albumin levels. The us-CRP was obtained using immunoturbidimetry (Kit CRP Turbiquest, Labtest™) and serum albumin using bromocresol green methodology (kit Albumina, Labtest™).

The Inflammatory-Nutritional Index was calculated using the formula: INI = Albumin/CRP. It was also estimated the Glasgow Prognostic Score[13] (GPS): albumin <35 g/l = 1 and CRP >10 mg/l = 1 combined to form a prognostic score of 0 (normal) and 1 or 2 (abnormal).

This study was approved by the Research Ethics Committee from the Hospital in which it was conducted.

Data were processed with double typing and consistence checking using EpiInfo 6.04d™ software. Analyses were performed by Stata 9.2™ program.

Results

Seventy-four patients with gastrointestinal or lung cancer were enrolled. Most of them were male (58.1%). The mean age was 63.4 ± 11.9 years, ranging from 35.6 to 90.7 years. Most of the patients had gastrointestinal cancer (71.6%). Colon and rectum were the most prevalent types of cancer, followed by lung cancer.

According to SGA, only 13.7% of the sample was in good nutritional status (SGA «A») and almost 22% of the patients were severely malnourished (SGA «C»).

Table I
Demographic, disease related and nutritional characteristics of the cancer patients

Variable	*Frequency*	*%*
Gender		
Male	43	58.1
Female	31	41.9
Tumor's site		
Esophagus/Stomach	16	21.6
Colon/Rectum	33	44.6
Pancreas/Gallbladder	4	5.4
Lung	21	28.4
Chemotherapy		
Non-defined	9	12.2
Curative	1	1.3
Neo adjuvant	19	26.7
Adjuvant	9	12.2
Palliative	36	48.6
SGA[a♦]		
A	10	13.7
B	47	64.4
C	16	21.9
BMI[b] (Kg/m²)		
Underweight	6	8.1
Normal	43	58.1
Overweight	22	29.7
Obesity	3	4.1
Mean (SD)	23.51	(±3.84)
Total	**74**	**100%**

[a]Subjective Global Assessment. ♦One (1) patient is missing for this variable. [b]Body Mass Index

The full description of the sample is in table I, where it is possible to observe that almost half of the patients received palliative chemotherapy, indicating advanced cancer stage.

The serum albumin mean value was 3.74 g/dl (SD±0.39 g/dl) ranging from 2.66 g/dl to 4.41g/dl.

The CRP median value in this sample was 13.9 mg/l (IQI 3.3-59.3 mg/l), ranging from 0.10 mg/l to 169.9 mg/l. These values (with a non-parametric distribution) were considered high, since CRP above 10 mg/l indicates systemic inflammation.

The laboratorial parameters evaluated were altered (albumin < 3.5g/dL and CRP > 10mg/dL) in 68.9% and 55.4% of the sample, as shown on table II, in which it is possible to see a comparison of the sample population characteristics, according to normal or abnormal serum levels. Data show that high levels of CRP is more frequently found in gastrointestinal than in lung cancer (p=0.04).

When nutritional status was evaluated by SGA, there was an increase of CRP levels as nutritional status declined (p=0.003 Kruskal-Wallis test). Well-nourished patients had lower CRP median values (3.40 mg/l), and they increased linearly as nutritional status worsened (41.25 in SGA «C» patients). This association was not present when nutritional status was defined by BMI (table III).

Serum albumin levels were evaluated according to inflammation status (CRP levels). In patients without systemic inflammation (CRP≤10 mg/l), albumin varied significantly according to nutritional status (p = 0.02 ANOVA test). However, in those patients with CRP levels >10mg/l there was no relationship between serum albumin levels and SGA (p = 0.06 ANOVA test).

Thus, the Inflammatory-Nutritional Index (INI = albumin/CRP) was developed with the intent to investigate its relationship with nutritional status, according to SGA. The analysis showed that INI varied significantly according to SGA defined nutritional status, independent of the systemic inflammation presence (p=0.02 Kruskal-Wallis test). Well-nourished patients had INI 1.25, linearly decreasing in worst nutritional conditions (0.10 in SGA «C» patients) (table IV).

Glasgow Prognostic Scores[13] (GPS) were also compared with the INI ratios. Five individuals (6.8%) had normal GPS (score 0), while all of the remaining participants (93.2%) had an abnormal GPS (score 1: 46 individuals, 62.2% or score 2: 23 individuals, 31%). The INI decreased significantly as GPS increased (Kruskal-Wallis test, p=0.008), as shown in figure 1.

Discussion

The present study has as several limitations. The primary limitation is that serum albumin is not an established, reliable marker for nutritional status and should be used with caution for being an acute phase protein, situation that alter its specificity for diagnosis of visceral protein malnutrition[14]. Serum CRP is the most widely accepted proxy for systemic inflammation, but it is affected by several medical conditions, not having specificity for cancer-induced inflammation. Cachexia can also exist without overt systemic inflammation[2].

Cancer has been associated with systemic inflammation, often leading to malnutrition and cachexia, with muscle mass loss, which increases morbidity[14]. Therefore, tools are necessary to identify nutritional status and inflammation as early and precisely as possible in cancer patients[1,4].

The anorexia-cachexia syndrome affects up to 80% of the cancer patients and is the major cause of death in advanced cancer cases[10]. Lung and gastrointestinal cancer patients tend to lose considerable amounts weight[4].

In this study, up to 85% of the patients were at nutritional risk or malnourished, according to SGA. In a review article, Deans and Wigmore reported that cachexia remains an important cause of morbidity and mortality, affecting up to 85% of gastrointestinal cancer patients at diagnosis[3]. In a cross-sectional study of colorectal cancer patients, Read *et al* found that 56% were at nutritional risk, according to Patient-Generated SGA[15]. In a study conducted in Rio de Janeiro, Brazil,

Table II
Characteristics of cancer patients according risk values of serum albumin and C-reactive protein

	Albumin			*C-Reactive Protein*		
Variable	*≥ 3.5 g/dL n (%)*	*< 3.5 g/dL n (%)*	*p**	*≤ 10 mg/dL n (%)*	*>10 mg/dL n (%)*	*p**
Gender			0,85			0.30
Male	13 (56.5)	30 (58.8)		17 (51.5)	26 (63.4)	
Female	10 (43.5)	21 (41.2)		16 (48.5)	15 (36.6)	
Tumor's site			0.17			0.04**
GIa	14 (60.9)	39 (76.5)		28 (84.8)	25 (61.0)	
Lung	9 (39.1)	12 (23.5)		5 (15.2)	16 (39.0)	
Tumor Stage			0.49**			0.22**
I	0 (0.0)	1 (2.0)		1 (3.0)	0 (0.0)	
II	4 (17.4)	16 (31.4)		11 (33.4)	9 (21.9)	
III	12 (52.2)	17 (33.3)		14 (42.4)	15 (36.6)	
IV	7 (30.4)	15 (29.4)		6 (18.2)	16 (39.0)	
Unknown	0 (0.0)	2 (3.9)		1 (3.0)	1 (2.5)	
Chemother.			0.02**			0.02**
Undefined	6 (26.1)	3 (5.9)		2 (6.1)	7 (17.1)	
Curative	1 (4.4)	0 (0.0)		0 (0.0)	1 (2.4)	
Neo adjuvant	3 (13.0)	16 (31.4)		12 (36.4)	7 (17.1)	
Adjuvant	1 (4.3)	8 (15.7)		7 (21.2)	2 (4.9)	
Palliative	12 (52.2)	24 (47.0)		12 (36.3)	24 (58.5)	
SGA[b]♦			0.03**			0.16**
A	1 (4.5)	9 (17.7)		7 (21.2)	3 (7.5)	
B	12(54.6)	35(68.6)		21 (63.6)	26 (65.0)	
C	9 (40.9)	7 (13.7)		5 (15.2)	11 (27.5)	
BMI[c] (Kg/m²)			0.74**			0.86**
Underweight	3 (13.0)	3 (5.9)		3 (9.1)	3 (7.3)	
Normal	13 (56.5)	30 (58.8)		18 (54.5)	25 (61.0)	
Overweight	6 (26.1)	16 (31.4)		10 (30.3)	12 (29.3)	
Obesity	1 (4.4)	2 (3.9)		2 (6.1)	1 (2.4)	
Mean (SD)	23.06(±3.73)	23.71(±3.91)	0.50#	23.23(±4.4)	23.74(±3.31)	0.57#
Total	**23**	**51**	**74**	**33**	**41**	**74**
(%)	**(31.1)**	**(68.9)**	**(100)**	**(44.6)**	**(55.4)**	**(100)**

* Chi-squared Test. ** Fischer Exact Test. # T Test
[a]Gastrointestinal. [b]Subjective Global Assessment. [c]Body Mass Index
♦One (1) patient is missing for this variable

Table III
CRP (mg/l) variation according to nutritional status

Nutritional status	*CRP Median (IQI)*	*p**
SGA[a]		0.003
A	3.40 (1.90, 17.10)	
B	12.45 (4.20, 59.65)	
C	41.25 (7.55, 124.9)	
BMIb (Kg/m²)		0.982
Underweight	10.3 (7.1, 32.8)	
Normal	19.5 (2.2, 79.7)	
Overweight	14.9 (4.6, 59.3)	
Obesity	6.3 (2.2, 130.1)	

* Kruskal-Wallis test. [a]Subjective Global Assessment. [b]Body Mass Index.

Table IV
Inflammatory-Nutritional Index (INI) variation according to nutritional status

Nutritional status	*INI Median*	*IQI*
SGA A	1.25	0.23, 1.93
SGA B	0.31	0.06, 1.19
SGA C	0.10	0.03, 0.48

p = 0.02 – Kruskal-Wallis test.

Pereira Borges et al found 77,1% of malnutrition in cancer patients, according to SGA[16].

In this sample, most of the patients had advanced cancer and were receiving palliative chemotherapy

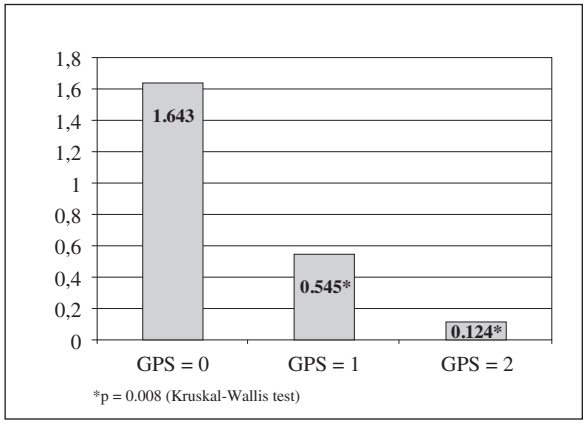

Fig. 1.—Inflamatory Nutritional Index variation according to Glasgow Prognostic Score (GPS).

indication. Cachexia is more prevalent in advanced disease patients and it worsens their prognosis, decreasing length and quality of life[3,5]. This could explain the high prevalence of nutritional risk/malnutrition in this study population.

Thirty percent of the patients had hypoalbuminemia, with the minimum value of 2.66g/dl and mean value of 3.74 g/dl. In their article, Nelson *et al*, while studying patients of a palliative medicine program, with none receiving chemotherapy, found a mean albumin of 2.4 g/dl in their sample population[5]. In the present study, only 50% of the patients were receiving palliative treatment. This could explain the lower albumin values in the Nelson study. In other study, conducted in Brazil [16], 45,6% of the patient had low serum albumin (<3.5 g/dl) *versus* 68.9% in the present study, being malnutrition (according SGA) more prevalent in this study (86.3% in the present study *versus* 77.1%).

Serum albumin is a safe indicator of morbidity and mortality, but not of nutritional status. Serum albumin concentration is influenced by many non-nutritional factors, resulting in low sensitivity and specificity to changes in nutritional status[10,14]. In chronic malnutrition, the albumin measurement becomes useless as a nutritional status marker[5].

Systemic inflammation was present in up to 50% of this sample, showing CRP values notably above 10 mg/l, reaching levels as high as 169.9 mg/l, with a mean value of 38.05 mg/l. In studies with advanced cancer patients, Nelson[5] and Walsh[10] found mean CRP of 106±87 mg/l, showing exacerbated systemic inflammation in patients with cancer.

In this study, CRP values significantly varied according to nutritional status (table III). Serum albumin was associated with nutritional status only in CRP<10 mg/l patients, as there was no relation in patients with systemic inflammation.

Cancer patients have an acute phase response stereotype, observed by a CRP increase and an albumin decrease. This relationship was similar between different cancer types, according to studies conduct by McMillan[4,17].

The albumin/CRP ratio was associated with SGA nutritional status, independent of systemic inflammation status. As the ratio decreased, patient nutritional state worsened. So, these parameters (CRP and albumin), appraised routinely in cancer patients, could be used to build a nutritional indicator. According to Elahi *et al* [18], scores based on hypoalbuminemia and elevated CRP have the advantage of being based on routinely available, well-standardized measurements that are simple to use.

Several studies use scores based on serum proteins and inflammatory markers to assess nutritional status and/or prognostic, such as *Prognostic Inflammatory and Nutritional Index* (PINI)[5,10] and *Glasgow Prognostic Score*[13,18], among others[19]. PINI, however, needs more complex testes, such as pre-albumin and alpha-1-acid glycoprotein serum levels. Thus, the Inflammatory-Nutritional Index (INI) could be a simpler complement to nutritional evaluation, if more studies confirm its usefulness.

In this study, the GPS, an inflammation-based prognostic score calculated using standard thresholds of C reactive protein (CRP) and albumin that has prognostic value in patients with advanced cancer, was also used. Despite the similarities between this study population and that of Brown et al.[13] (gastrointestinal and lung cancer patients), 93% of this sample had an abnormal GPS, compared 78% in their study. The INI was significantly associated with GPS. New studies, particularly longitudinal studies, are necessary to evaluate prognostic capacity of the INI.

The SGA[11,12], used as a nutritional status indicator in the present study, which relies on clinical history and physical examinations, appears to be a safe way to assess nutritional state in advanced cancer[10,20].

SGA is a subjective method, depending on the observer's ability and training level, which can lead to inter-observer agreement. The albumin/CRP ratio, named as INI, could be used as an auxiliary method to identify patients who are at nutritional risk, and to establish therapeutic targets based on nutritional decline.

More studies, with larger sample size, are necessary to evaluate the usefulness and reliability of this method as an indicator of nutritional status, and to determine logical end-points for nutritional risk categories. Also longitudinal studies are necessary to verify if INI has prognostic capabilities for cancer patients.

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Statement of Authorship

CAP participated in the design of the study, in collection and interpretation of data and drafted the manuscript. SPO coordinated the study, and critically reviewed the manuscript. MCG conceived the study, participated in its design and coordination, and performed the statistical analyses.

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