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Anemia, nutritional status and inflammatory activity in patients with gastrointestinal tumors in the preoperative phase

Anemia, estado nutricional y actividad inflamatoria de pacientes con tumores gastrointestinales en el preoperatorio

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ABSTRACT

Introduction: Weight loss, especially the loss of lean mass, and anemia are common in patients with gastrointestinal tumors and systemic inflammation is considered an aggravating factor.

Objective: Investigate the nutritional status, occurrence of anemia and inflammatory activity in patients with gastrointestinal tumors in the preoperative phase.

Methods: A cross-sectional study was conducted in northeastern Brazil involving patients with gastrointestinal tumors with no previous treatment. Evaluations involved anthropometrics, biochemical blood analysis and a subjective nutritional assessment (patient's opinion).

Results and discussion: The prevalence of undernutrition was high based on the subjective nutritional assessment (97.9%), percentage weight loss (97.9%), triceps skin fold (83.3%), arm circumference (72.9%) and arm muscle circumference (64.6%). A significant reduction between the habitual and current body mass index was found in the entire sample of adults and elderly individuals ($p < 0.001$). Albumin and transferrin were below normal in 97.9% of the sample and C-reactive protein was high in all patients. A large portion of the sample exhibited normochromic normocytic anemia (45.8%) and the majority exhibited immune depletion based on total lymphocyte count (72.9%). The percentage weight loss was significantly associated with the time since the onset of symptoms ($r = 0.574$; $p < 0.001$).

Conclusion: High prevalence rates of anemia, undernutrition and systemic inflammation were found in patients with gastrointestinal tumors. The onset of symptoms occurred long before the diagnosis, which underscores the need for nutritional intervention as soon as gastrointestinal disorders arise in order to minimize complications in the postoperative period.

KEYWORDS

Gastrointestinal tumors. Nutritional assessment. Nutritional status. Cachexia.

RESUMEN

Introducción: La pérdida de peso, principalmente masa magra, y la anemia son frecuentes entre pacientes con neoplasias gastrointestinales, siendo la inflamación sistémica considerada un factor agravante.

Objetivos: Investigar el estado nutricional, la presencia de anemia y la actividad inflamatoria de pacientes con neoplasias gastrointestinales en el preoperatorio.

Métodos: Estudio transversal realizado en el Nordeste de Brasil, en pacientes con neoplasias gastrointestinales, en el período preoperatorio, sin tratamiento previo que fueron sometidos a la evaluación antropométrica, bioquímica y evaluación nutricional subjetiva producida por el propio paciente.

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Resultados y discusión: Se verificó una elevada prevalencia de desnutrición por la evaluación nutricional subjetiva producida por el paciente (97.9%), por el porcentaje de pérdida de peso (97.9%) pliegue cutáneo tricipital (83.3%), circunferencia del brazo (72.9%) y circunferencia muscular del brazo (72.9%), 64.6%), con una reducción significativa del índice de masa corporal habitual para el actual, tanto en los adultos (p <0.001) como en los ancianos (p <0.001). La albúmina y transferrina estuvieron por debajo de la normalidad en el 97.9% del grupo, a diferencia de la PCR que se mostró elevada en todos los pacientes. La mayoría reveló anemia normocrómica y normocítica (45.8%) y depleción inmunológica por el conteo total de linfocitos (72.9%). El porcentaje de pérdida de peso presentó una relación significativa con el período de inicio de los síntomas (r = 0.574; p <0.001).

Conclusiones: Se observaron altas tasas de anemia, desnutrición e inflamación sistémica en pacientes con neoplasias gastrointestinales en estos pacientes. Sin embargo, la presencia de síntomas ocurrió en un período muy superior al tiempo de diagnóstico, reforzando la necesidad de la intervención nutricional desde el surgimiento de los trastornos gastrointestinales para minimizar complicaciones en el postoperatorio.

PALABRAS CLAVE

Cáncer Gastrointestinal. Evaluación nutricional. Estado Nutricional. Caquexia.

ABBREVIATIONS

CRP: C-reactive protein

IMC: body mass index

WHO: World Health Organization

TSF: Triceps skin fold

AC: arm circumference

AMC: arm muscle circumference

NHANES I: National Health and Nutrition Examination Survey

%WL: percentage of weight loss

PG-SGA: Subjective Global Assessment

MCV: mean corpuscular volume

MCH: mean corpuscular hemoglobin

MCHC: mean corpuscular hemoglobin concentration

RDW: red cell distribution width

TCL: total lymphocyte count

SPSS: Statistical Package for the Social Sciences

INTRODUCTION

Studies report high prevalence rates of anemia, undernutrition and inflammation in patients with cancer, the intensity of which varies in accordance with the type and location of the tumor[1-4]. Diagnosis in an advanced phase of the disease and the aggressive nature of cancer treatments are associated with an accentuated reduction in food intake and are the main causes of protein-energy malnutrition and anemia in affected individuals[3,5].

There is no nutritional assessment indicator that is both sensitive and specific enough for the detection of undernutrition. Thus, various techniques are combined, such as anthropometrics, diagnostic imaging methods, clinical/biochemical evaluations, subjective assessments and food intake logs[1,6]. When used in an isolated manner for a nutritional assessment, laboratory indicators fail to identify individuals with a poor nutritional status, since many conditions affect the serum levels of these indicators. An example of this is an increased acute-phase protein response, identified by high levels of C-reactive protein, which is a significant factor in the depletion of adipose tissue as well as the catabolism of muscular and visceral protein and, when not controlled, constitutes a poor prognosis in cases of cancer[2].

The aim of the present study was to investigate nutritional status, anemia and inflammatory activity in patients with gastrointestinal tumors in the preoperative phase.

PATIENTS AND METHODS

A cross-sectional study was conducted with all patients at the digestive surgery clinic of the university hospital pertaining to *Universidade Federal de Pernambuco* between March and November 2010 who met the following inclusion criteria: age 20 years or older; histopathological diagnosis of gastrointestinal tumor; and no prior treatment for the disease. This study received approval from the Human Research Ethics Committee of the Center for Health Sciences of the university. The data were collected after the patients received clarifications regarding the objectives, were assured confidentiality and agreed to participate in the study by signing a statement of informed consent. Each patient was recruited to undergo an evaluation of his/her nutritional status based on anthropometrics, a subjective nutritional assessment (patient's opinion) and biochemical blood analysis prior to any therapeutic intervention.

The anthropometric evaluation involved the calculation of the body mass index (BMI), triceps skinfold (TSF), arm circumference (AC) and arm muscle circumference (AMC). Weight was determined using a scale (Filizola®) with a capacity of 150 Kg and precision of 0.1 Kg. Height was measured using a stadiometer coupled to the scale. TSF was determined using skinfold calipers (Lange®) with a precision of 1 mm. AC and AMC were determined using a non-flexible

metric tape with a precision of 1 mm. BMI was calculated as weight by height squared (kg/m^2) and nutritional status was classified using the recommendations of the World Health Organization (WHO)[7] for adults (< 60 years of age) and the criteria proposed by Lipschitz for elderly individuals[8].

For AC, the non-dominant arm was flexed toward the thorax, forming a 90º angle to locate the midpoint between the acromion and olecran. The arm was then extended along the body with the palm of the hand turned toward the thigh. A non-flexible metric tape was placed around the arm at the previously marked midpoint, avoiding both compression of the skin and slack. TSF was determined at the same midpoint, separating the skin from the muscle tissue. Measured AC and TSF were compared to reference values of the US National Health and Nutrition Examination Survey (NHANES I) demonstrated in a percentile table by Frisancho[10]. AMC was calculated as follows: AC (cm) – π x [TSF (mm) ÷ 10]. Adequacy of AC, TSF and AMC was determined using the following equation: Measured indicator (cm) ÷ 50th percentile of indicator x 100. The criteria proposed by Blackburn & Thornton were used for the classifications[9]. Weight loss percentage (%WL), which is related to unintentional weight loss in a given period of time, was calculated as follows: (habitual weight – current weight) x 100 ÷ habitual weight. %WL was classified with regard to nutritional status based on Blackburn & Bristian[11].

The Patient-Generated Subjective Global Assessment (PG-SGA) adapted for cancer patients was determined[12]. For such, each patient filled out a standardized questionnaire addressing weight loss, gastrointestinal disorders, changes in food intake, physical capacity and functional capacity. Following an analysis of the responses, the patients were classified into three groups: A (no undernutrition), B (nutritional risk or moderate undernutrition) or C (severe undernutrition).

Blood samples were collected from each patient upon recruitment and prior to any therapeutic intervention. In the laboratory, C-reactive protein (CRP), transferrin, ferritin and albumin were determined and a full blood count was performed. Systemic inflammation was evaluated based on the serum concentration of CRP determined using nephelometry (BN II Nephelometer, Dade Behring, USA). A concentration of 0 to 3 ng/mL was considered normal and a concentration > 10 ng/mL was considered indicative of systemic inflammation. Transferrin and ferritin also determined using nephelometry, with values ranging from 2 to 3 g/L and 20 to 280 ng/mL, respectively, considered normal. Albumin was measuring using the polychromatic end-point method (Dimension LXR, Dade Behring, USA), with values ranging from 3.4 to 5.0 g/dL considered normal. The full blood count was performed using electric impedance spectophotometry (Horiba ABX Diagnostics), considering the following values indicative of normality: hemoglobin: 12 to 16 g/dL for women and 14 to 18 g/dL for men; hematocrit: 37 to 47% for women and 42 to 52% for men; mean corpuscular volume (MCV) between 82 and 98 µ/dL; mean corpuscular hemoglobin (MCH) between 27 and 31 pg/dL; mean corpuscular hemoglobin concentration (MCHC) between 32 and 36 g/dL; and red cell distribution width (RDW) between 11 and 14.5%. Total lymphocyte count was also calculated (% lymphocytes x leukocytes ÷ 100) and classified as normal (> 2000/mm^3), mild depletion (2000 to 1200/mm^3), moderate depletion (1199 to 800/mm^3) or severe depletion (< 800/mm^3)[13].

Data analysis was performed using the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, U.S.A.). Spearman's correlation coefficients were calculated for the investigation of correlations between variables with non-normal distribution. The paired Student's t-test was used for comparisons of means of variables with normal distribution. Fisher's exact test was used to determine associations between categorical variables. Analysis of variance was used for comparisons with more than two groups. The Mann-Whitney U-test was used for the comparison of unpaired data. The level of significance was set to 5% for the rejection of the null hypothesis ($p < 0.05$).

RESULTS

Forty-eight individuals were evaluated. Mean age was 61.04 ± 14.0 years (range: 30 to 85 years). The male sex accounted for 64.6% of the sample. The prevalence of intestinal tumors and 35.5% and the prevalence of gastric tumors was 33.3%. The most reported symptoms were anorexia (60.4%) and early satiety (54.2%). Only 12.5% of the sample reported no changes in food intake. Based on the PG-SGA and %WL, 97.9% of the sample was diagnosed with moderate to severe undernutrition. The prevalence of undernutrition varied with the different indicators: 83.3% based on TSF, 72.9% based on AC and 64.6% based on AMC. Mean time elapsed since the diagnosis was 19.1 days, whereas median time elapsed since the onset of symptoms was five months (Table 1).

Based on the BMI, the elderly patients were classified as undernourished. However, although the adults were classified in the ideal range based on the BMI, this group also demonstrated severe weight loss, as demonstrated by the significant reduction in the habitual BMI to the current BMI ($p < 0.001$). A significant reduction was also found in the elderly group ($p < 0.001$) (Table 2).

The biochemical analysis revealed a high prevalence rate of normochromic normocytic anemia (45.8%), with no significant differences when the sample was stratified by sex ($p = 0.814$). Based on the total lymphocyte count, the majority of patients demonstrated immune depletion (72.9%) (Table 3). No abnormal serum concentrations of ferritin were found, but both albumin and transferrin were below normal concentrations in 97.9% of the sample and CRP was high in 100% of the sample, characterizing systemic inflammation (data not presented in tables).

Table 1. Demographic and nutritional variables of patients in preoperative period.

Variable	n	%	95% CI*
Sex			
Male	31	64.6	49.4-77.8
Female	17	35.4	22.1-50.5
Primary tumor site			
Esophagus	5	10.4	3.4-22.6
Stomach	16	33.3	20.3-48.4
Intestine	17	35.5	22.1-50.5
Pancreas	5	10.4	3.4-22.6
Liver and bile ducts	5	10.4	3.4-22.6
Symptoms			
No eating problems	3	6.3	1.3-17.1
Anorexia	29	60.4	45.2-74.2
Nausea	8	16.7	7.4-30.2
Constipation	4	8.3	2.3-19.9
Vomiting	9	18.8	8.9-32.6
Diarrhea	3	6.3	1.3-17.1
Early satiety	26	54.2	39.1-68.6
Sore throat	4	8.3	2.3-19.9
Change in food intake			
Unchanged	6	12.5	4.7-25.2
Few solid foods	7	14.6	6.0-27.7
Only fluids	16	33.3	20.3-48.4
Very little solid food and fluids	19	39.6	25.7-54.7
%WL			
Severe	44	91.6	80.0-97.6
Significant	3	6.3	1.3-17.1
Non-significant	1	2.1	0.1-11.0
AC			
Severe undernutrition	12	25.0	13.6-39.5
Moderate undernutrition	11	22.9	12.0-37.3
Mild undernutrition	12	25.0	13.6-39.5
Normal range	10	20.8	10.4-34.9
Excess weight	3	6.3	1.3-17.1

* 95% confidence interval.

Table 1 continuación. Demographic and nutritional variables of patients in preoperative period.

Variable	n	%	95% CI*
TSF			
Severe undernutrition	28	58.3	43.2-72.3
Moderate undernutrition	7	14.6	6.0-27.7
Mild undernutrition	5	10.4	3.4-22.6
Normal range	3	6.3	1.3-17.1
Excess weight	5	10.4	3.5-22.6
AMC			
Severe undernutrition	24	50.0	35.2-64.7
Moderate undernutrition	4	8.3	2.3-19.9
Mild undernutrition	3	6.3	1.3-17.1
Normal range	0	0.0	0.0-7.3
Excess weight	17	35.4	22.1-50.5
ASG			
A	1	2.1	0.0-11.0
B	14	29.2	16.9-44.0
C	33	68.7	53.7-81.3

* 95% confidence interval.

Table 2. Habitual BMI prior to onset of symptoms and current BMI stratified by age group.

Age group	BMI		
	Habitual Mean ± SD	Current Mean ± SD	p-value *
Adult (n = 21/43.7%)	25.9 ± 4.3	21.3 ± 4.2	< 0.001
Elderly (n = 27/56.3%)	26.1 ± 5.1	21.7 ± 5.0	< 0.001

* paired Student's t-test.

A significant correlation was found between %WL and time elapsed since the onset of gastrointestinal symptoms ($r = 0.574$; $p < 0.001$) (Figure 1). No significant difference between the adult group and elderly group was found with regard to the nutritional diagnosis based on the PG-SGA ($p = 0.157$) (Table 4). A significant association was found between the results of the nutritional assessment based on the %WL and PG-SGA ($p = 0.04$). A significant difference regarding serum levels of albumin was found among the three classification groups of the PG-SGA ($p = 0.010$). However, the same was not true with regard to transferrin ($p = 0.416$) (data not presented in tables).

Table 3. Biochemical analysis in preoperative period.

Variables	n	%	95% CI *
Anemia			
Absent	10	20.8	10.4-34.9
Normochromic normocytic	22	45.8	31.3-60.8
Iron deficiency	15	31.3	18.6-46.2
Megaloblastic	1	2.1	0.0-11.0
Total lymphocyte count			
Normal	13	27.1	15.2-41.8
Mild depletion	16	33.3	20.3-48.4
Moderate depletion	15	31.3	18.6-46.2
Severe depletion	4	8.3	2.3-19.9
Variable	**Mean**	**SD**	
Hemoglobin (men)	10.7	2.5	
Hemoglobin (women)	10.6	1.7	
Hematocrit (men)	32.2	7.6	
Hematocrit (women)	32.2	5.5	
MCV	84.5	8.9	
MCH	28.2	3.4	
MCHC	33.4	1.2	
Leukocytes	9383.0	3295.5	
Albumin	2.5	0.6	
Transferrin	1.9	0.6	
Ferritin	225.4	181.7	
	Median	**Q1, Q3**	
RDW	14.9	13.5, 15.9	
Lymphocytes	15.4	12.6, 19.0	
CRP	10.9	6.4, 15.2	

* 95% confidence interval; SD: standard deviation; Q1: 25th percentile; Q3: 75th percentile.

DISCUSSION

The high percentage of patients with some degree of undernutrition was the same when based on the PG-SGA and %WL (97.9%). The percentage of severe undernutrition based on the PG-SGA (68.7%) lies within the range described in the literature (31 to 87.1%)[12,14,15]. Weight loss, which is considered one of the risk factors for a prolonged hospital stay[16] and an increase in mortality[17], resulted in a significant reduction in the BMI among the patients. These methods are easy to employ in clinical practice for the assessment of nutritional status and important to the diagnosis of undernutrition as well as the early institution of nutritional intervention[18].

Table 4. Nutritional diagnosis of adults and elderly individuals according to patient-generated subjective global assessment in preoperative period.

PG-SGA	Age		p-value *
	< 60 years	≥ 60 years	
No nutritional risk	1 (4.8%)	0 (0.0%)	p = 0.157
Nutritional risk/moderate undernutrition	8 (38.1%)	6 (22.2%)	
Severe undernutrition	12 (57.1%)	21 (77.8%)	

* Fisher's exact test.

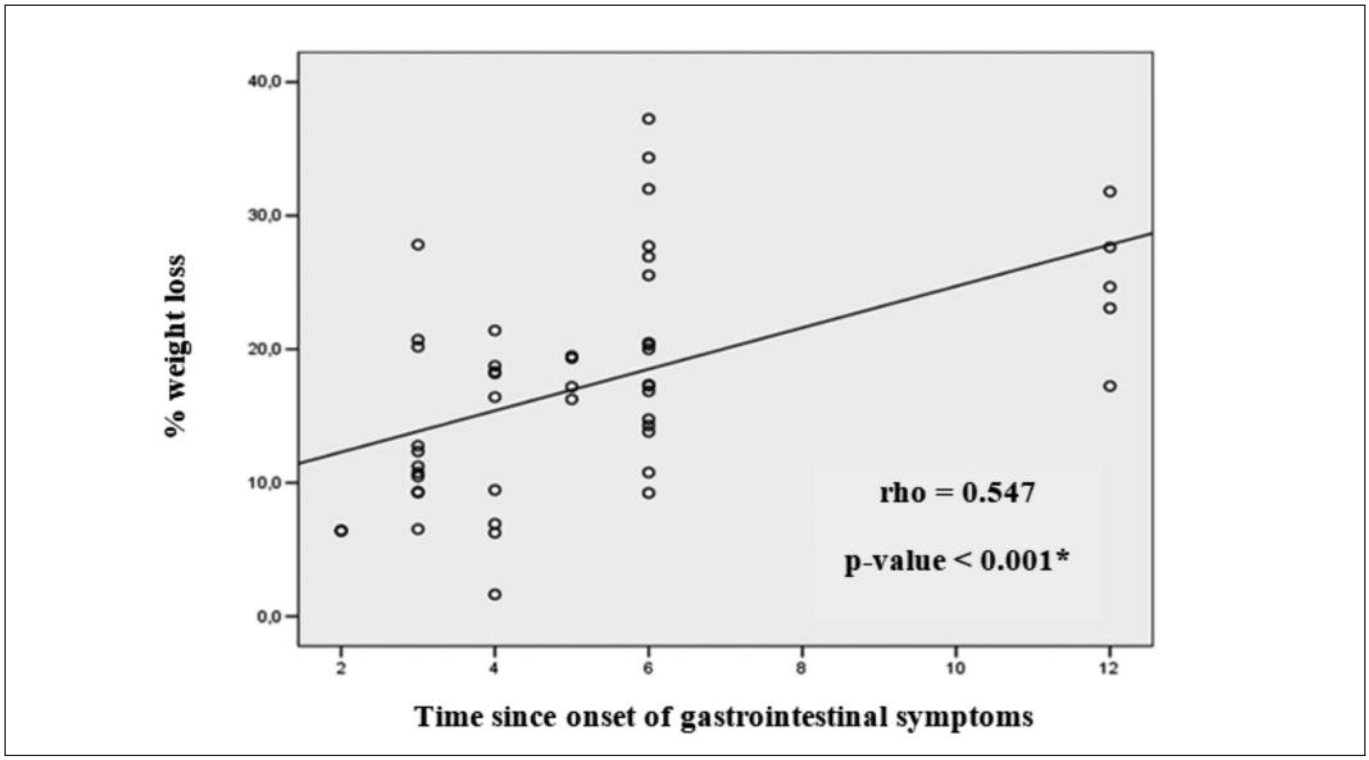
Other parameters for a more detailed anthropometric evaluation, such as AC, AMC and TSF, are important for the reevaluation and redefinition of nutritional conduct. These indicators demonstrated varied degrees of malnutrition in more than half of the patients, which is in agreement with findings described in previous studies[19], and reflects both the depletion of adipose tissue and visceral protein catabolism.

Although tumors in organs directly related to digestion and the absorption of nutrients are associated with undernutrition, weight loss, which is commonly associated with gastrointestinal tumors, is not caused only by the local effect of the tumor (obstruction, dysphagia, sore throat, early satiety, nausea and vomiting), but also by the effects of systemic inflammation, with an increase in the production and release of biological mediators, such as pro-inflammatory cytokines, which contribute to changes in the metabolism and result in anorexia/wasting syndrome[2,20].

As the patients in the present study had not undergone prior treatment, one may infer that the process of undernutrition was the result of anorexia, which was the most frequently reported symptom (60.4% of patients), followed by early satiety (54.2%). In contrast, only 12.5% of the patients reported no changes in food intake. It is necessary to perform a detailed nutritional assessment of individuals with gastrointestinal tumors in the preoperative phase, with the identification of changes in body composition and food intake, to establish an appropriate nutritional intervention and minimize complications in the postoperative period[21].

Undernutrition was also investigated using biochemical analysis. Albumin and transferrin were below the normal range in 97.9% of the sample, which is the same prevalence rate of undernutrition established when using the %WL and PG-SGA. Different factors affect the serum concentration of these proteins and lower than normal blood concentrations suggest the onset of undernutrition. However, abnormal readings can also

Figure 1. Correlation between weight loss and time since onset of gastrointestinal symptoms.



* Spearman's correlation.

be the result of other conditions, such as the acute-phase response (which can diminish the synthesis of these proteins, increase their catabolism and/or increase vascular permeability), over-hydration, liver disease (which leads to reduced synthesis), kidney disease and inflammatory bowel syndrome (which lead to urinary or gastrointestinal losses)[22].

The prevalence and incidence of anemia are high among cancer patients[3,23]. Scientific evidence suggests that anemia adversely affects the patient survival[3,24] due to the multiple factors involved in the occurrence of anemia in cases of cancer, such as depression of erythropoiesis and endogenous erythropoietin, which may occur as a result of the secretion of pro-inflammatory cytokines, inhibiting erythropoiesis[23]. In the present sample, anemia was not associated with cancer treatment, as the patients had not yet undergone treatment. Factors linked to systemic inflammation stemming from the malignant tumor (all patients had high CRP levels) may explain the normochromic normocytic anemia found in these patients.

An association between nutritional status and immunity has been reported[13,25]. In the present study, a high percentage of the patients demonstrated immunological impairment, as demonstrated by the total lymphocyte count. The depression of cellular and humoral immunity increases with the progression of undernutrition, as the reduction in food intake leads to a reduction in substrates for the production of immunoglobulins and defense cells[13,25].

The tumor production of inflammatory mediators and catabolic factors leads to an increased acute-phase protein response, identified by an increase in CRP levels, which is a significant factor in the depletion of adipose tissue as well as the catabolism of muscular and visceral protein and, when not controlled, constitutes a poor prognosis in cases of cancer[2,20]. High concentrations of acute-phases proteins, such as ferritin and CRP, have been associated with weight loss[2,4,20], whereas the opposite is reported for albumin and transferrin[22]. The present findings suggest systemic inflammation among patients in the preoperative phase with no prior treatment, demonstrated by the high CRP levels in 100% of the sample as well as hypoalbuminemia and low serum transferrin levels in 97.9%. Moreover, the significant correlation between %WL and time elapsed since the onset of symptoms suggests that metabolic and nutritional changes had already begun with the appearance of the symptoms.

The difficulty of obtaining a reliable measure of circulating cytokines is widely documented[26] and it was not within the scope of the present study to measure such substances. The production of cytokines by inflammatory or tumor cells is reported to be the best indicator of inflammatory activity in patients with cancer. However, high levels of acute-phase proteins, such as CRP, combined with the depletion of fat and muscle tissue resulting from muscular and visceral protein catabolism support the notion of systemic inflammation[26].

CONCLUSION

High prevalence rates of anemia, undernutrition and systemic inflammation were found in patients with gastrointestinal tumors in the preoperative phase with no prior treatment. A reduction in food intake and mechanical obstruction by the tumor are not the only factors involved in nutritional decline in these patients. The recognition of the interaction between systemic inflammation and undernutrition in cancer patients demonstrates the need to develop adequate therapeutic strategies to minimize the effects of severe weight loss and ensure greater tolerance to the treatment process. The occurrence of symptoms long before the diagnosis underscores the need for nutritional intervention as soon as gastrointestinal disorders arise in order to minimize complications in the postoperative period.

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