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Systemic inflammation and nutritional insufficiency in palliative cancer patients

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Abstract

Aim. To study the relationship between the symptoms of nutritional insufficiency and systemic inflammation in cancer palliative patients.

Methods. 106 palliative cancer patients were examined at Chelyabinsk Regional Clinical Center of Oncology and Nuclear Medicine: 54 (50.9%) men and 52 (49.1%) women aged 61 [54; 67] years. All patients underwent laboratory and instrumental examination within the approved standards of specialized medical care. Systemic inflammation was assessed by the levels of acute phase proteins (C-reactive protein, fibrinogen). The study of integrated clinical and laboratory, somatometric parameters was carried out. The nutritional risk index was assessed.

Results. Palliative cancer patients showed a statistically significant decrease in the concentration of hemoglobin, lymphocytes, and albumin. The activation of systemic inflammation that manifested by hyperfibrinogenemia and an increase in the level of C-reactive protein was revealed. The study of somatometric parameters revealed a statistically significant decrease in body mass index, shoulder circumference, subscapular skinfold thickness, and a tendency to reduce lean body mass. The nutritional risk index assessment showed mild nutritional insufficiency in 22 (20.8%) of the examined patients and severe nutritional insufficiency in 28 (26.4%) patients. The maximum diagnostic significance of the level of C-reactive protein for prediction the nutritional insufficiency was achieved at 80.4% sensitivity and 52.7% specificity (AUC=0.671, 95% confidence interval [0.573; 0.759], p=0.001), which corresponded to a C-reactive protein threshold of 31 mg/l.

Conclusion. 50 (47.2%) of the examined patients showed signs of nutritional insufficiency, a statistically significant decrease in hemoglobin and albumin concentration, as well as lymphocyte count, activation of systemic inflammation, manifested by hyperfibrinogenemia, and an increase in the level of C-reactive protein; it was revealed a statistically significant relationship between C-reactive protein level and malnutrition.

Keywords: nutritional insufficiency, systemic inflammation, palliative care.

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Background. Nutritional deficiency is a characteristic manifestation of malignancies of any localization, achieving maximum severity in patients with palliative oncological profile [1-4]. Several authors have identified many patients hospitalized for cancer had nutritional deficiency [5, 6].

Inflammation was identified as a sign of cancer and, possibly, the required state for tumor growth [7]. Most oncological symptoms are associated with inflammation. In response to the oncological development, inflammation mediators are released in the blood, which leads to metabolic dysfunction. Moreover, the level of inflammatory mediators correlates with the prevalence of the tumor process.

The activations of the sympathetic vegetative nerve and hypothalamic–pituitary–adrenal and hypothalamic and adrenal systems result to the hyperproduction of adrenal hormones, release of inflammation mediators, and an inflammatory response [7–9]. Mediators of the inflammatory response increase the synthesis of proteins of the acute phase; stimulate muscle proteolysis, gluconeogenesis, and glucose consumption; activate lipolysis; and reduce liponeogenesis. In addition, proinflammatory cytokines promote the synthesis of anorexigenic hormones, which is accompanied by decreased food intake and impaired metabolic processes [10].

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The lipid- and protein-mobilizing factors secreted by tumor-mobilizing factors contribute to the loss of fat and muscle tissues, increasing energy needs [11, 12]. Several studies have confirmed the relationship between systemic inflammation and general oncological manifestations, one of which is nutritional deficiency [13, 14].

This study aimed to examine the relationship between signs of nutritional insufficiency and systemic inflammation in patients with palliative oncological profile.

Materials and methods. This study followed an observational and simultaneous (transverse) design. The study protocol was approved by the Ethical Committee of the South Ural State Medical University (Protocol No. 8 of September 25, 2020).

The eligibility criteria for research were as follows:

– Presence of malignant neoplasms

– Patient age >18 years

– Availability of informed consent for study participation

The exclusion criteria were as follows:

– Presence of concomitant pathology, such as acute infectious diseases, systemic autoimmune diseases, mental illness, and aggravation of chronic noninfectious diseases

– Had surgical interventions over the last 2 months

– Failure of the patient to present during examination.

The study included 106 patients with cancer of palliative profile based on GBUZ "Chelyabinsk Regional Clinical Center of Oncology and Nuclear Medicine." Of these patients, 54 (50.9%) were men and 52 (49.1%) were women aged 61 [54–67] years. All patients underwent laboratory and instrumental examinations following the approved standards for the provision of specialized medical care. The control group was composed of 20 individuals (10 men and 10 women) of comparable age (59 [50–64] years) without malignant neoplasms, exacerbation and decompensation of chronic noncommunicable diseases, and acute and chronic infectious diseases assessed following the framework of preventive medical examination and dispensarization.

The CHARLSON comorbidity index [15] and Karnofsky index (ECOG) of the patients were calculated [16]. Chronic pain syndrome was evaluated on a 3-point verbal scale of pain severity and visual analog scale, on the basis of changes following administration of painkillers (change in the multiplicity of administration or transition to another stage of analgesic drugs) [17].

Systemic inflammation was evaluated by the level of sharp-phase proteins, namely, C-reactive protein (CRP) and fibrinogen. The level of highly sensitive CRP was determined using the solid-phase immunoferment method using an analyzer (Roche Diagnostics International Ltd., Switzerland). The fibrinogen level was determined using firm reagents (Technology-Standard, Russia) on the 4-channel semi-automatic coagulometer (DIAMED-CD-4, Switzerland).

Levels of laboratory markers of nutritional insufficiency, namely, peripheral blood lymphocytes (cell/ml^3), albumin (g/l), and total protein (g/l), were determined.

The body mass index (BMI, kg/m^2); shoulder circumference; skin fold thickness of the shoulder, abdomen, and thigh; shrunk body weight [SBW (kg) = 0.029 × actual creatinine excretion + + 7.39], ideal body weight [in men = (growth in cm − 100) − ((growth in cm − 152) × 0.2); in women = (growth in cm − 100) − ((growth in cm − 152) × 0.4)] were measured.

The nutritive risk index (NRI) was evaluated using the formula:

NRI = 1.519 × albumin (g/l) + 41.7 × real body weight (kg) / perfect body weight (kg). Consequently, the patients were divided into groups: a group without nutritional disorder (NRI > 97.5), group with mild nutritional insufficiency (NRI = 97.5–83.5), and group with severe nutritional deficiency (NRI < 83.5) [18].

Statistical analyses were performed using the IBM SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables that followed a normal distribution were presented as median and international scope (IU; 25%–75%). High-quality signs are described using absolute and relative frequencies with an estimate of intergroup differences using Pearson's $\chi 2$ criterion, and those with expected frequencies less than 5 were analyzed using the two-sided Fisher's exact test.

Quantitative indicators that followed a normal distribution were analyzed using the Kolmogorov–Smirnov. In numerical indicators that deviated from the normal distribution, the accuracy of the differences between two independent samples was analyzed using the Mann–Whitney U test, and differences in multiple groups were analyzed by Kruskal–Wallis H-test. To assess the correlation of processes, correlation coefficients were calculated (R).

To determine which of the independent predictors have the greatest effect on the dependent variables, a logistic regression analysis was performed, and receiver operating characteristics analysis was performed with the construction of characteristic curves of sensitivity and specificity ratios (ROC curves). Differences were considered significant at $p \leq 0.05$.

Table 1. Clinical and laboratory characteristics of patients with oncological palliative status

Specifications	Palliative oncological group (n = 106)	Control group (n = 20)	p
Age, years	61 [54.0; 67.0]	57 [50.0; 64.0]	0.659
Hemoglobin, g/l	95.0 [81.5; 108.3]	132 [123.0; 135.0]	0.002
Lymphocytes, × 10^9/l	1.77 [1.05; 1.97]	2.1 [1.3; 2.5]	0.041
Lymphocytes, %	18.0 [14.5; 26.2]	29.8 [23.3; 38.2]	0.012
Total protein, g/l	65.0 [60.0; 69.5]	67.0 [64.0; 72.5]	0.341
Albumin, g/l	33.4 [28.9; 40.0]	45.2 [43.5; 45.3]	0.001
C-reactive protein, mg/l	33.0 [9.0; 77.0]	5.0 [3.0; 13.0]	0.001
Fibrinogen, g/l	3.8 [3.25; 4.8]	3.4 [2.7; 3.5]	0.038

Table 2. Evaluation of the component composition of the body in the palliative oncological group

Specifications	Palliative oncological group (n = 106)	Control group (n = 20)	p
Shunk body weight, kg	9.54 [8.0; 10.2]	10.1 [9.7; 10.6]	0.051
Body weight, kg	67.0 [53.0; 76.0]	82.0 [75.0; 90.5]	0.001
Body mass index, kg/m^2	24.7 [20.5; 30.4]	29.1 [26.4; 32.2]	0.021
Shoulder circumference, mm	31 [24.0; 35.25]	35.0 [30.0; 42.0]	0.042
Shoulder skinfold thickness, mm	15.0 [10.0; 25.0]	26.0 [19.5; 33.0]	0.014
Abdominal skinfold thickness, mm	30.0 [14.3; 30.0]	29.0 [23.0; 36.0]	0.241
Femoral skinfold thickness, mm	28.0 [14.3; 30.0]	27.0 [22.5; 32.5]	0.325

Results. The comorbidity index was 3 [2–5], the intensity of chronic pain syndrome was 2 [2–3], and the Karnofsky index was 2 [2–3]. For the last 6 months, 86 (81.1%) patients had weight changes, from 2 to 30 kg. Moreover, 56 (52.8%) patients experienced nausea and 32 (30.2%) experienced vomiting.

As shown in Table 1, a significant reduction in hemoglobin, lymphocytes, and albumin was found in patients with oncological palliative status. Systemic inflammation was manifested by hyperfibrinogenemia and increased CRP level.

Assessment of somatometric indicators revealed a significant reduction in BMI, shoulder circumference, skinfold thickness of the shoulder pad, and tendency to a decrease in SBW in the oncological palliative group. Significant differences in the skinfold thickness of the abdomen and hips were not found (Table 2).

Regarding the NRI, 56 (52.8%) patients in the oncological palliative group did not show signs of nutritional insufficiency, 22 (20.8%) had mild nutritional insufficiency, and 28 (26.4%) had severe nutritional insufficiency.

In the correlation analysis, the relationship between the CRP level and nutritional insufficiency (R = 0.33; p = 0.002) and SBW (R = 0.3; p = 0.017). An association was noted between the levels of fibrinogen and CRP (R = 0.56; p = 0.0003) and SBW (R = 0.30; p = 0.050).

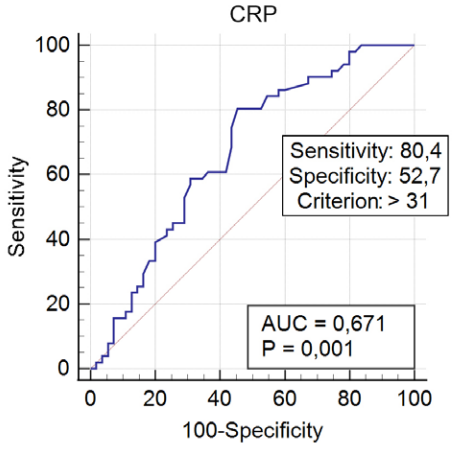

Fig. 1. Diagnostic efficiency of C-reactive protein to predict the presence of nutritional insufficiency in patients with palliative oncological profile

Results of the logistic regression analysis revealed a relationship between the CRP level in patients with a palliative profile and presence of nutritional insufficiency (β = 0.28, p = 0.011).

The maximum diagnostic significance of CRP to predict the presence of nutritional insufficiency was based on a sensitivity level of 80.4% and specificity of 52.7% (area under the curve = 0.671, 95% confidence interval 0.573–0.759, p = 0.001), which corresponded to the threshold value of CRP, i.e., 31 mg/L (Fig. 1).

Discussion. In this study, 50 (47.2%) patients with palliative oncological profile were identified to have signs of nutritional insufficiency. The results obtained are consistent with the data that nutritional insufficiency is the actual problem of modern oncology [19–21].

In the analyzed patients with palliative oncological profile, the intensity of the chronic pain syndrome was 2 [2; 3], weight loss was noted in 86 (81.1%) patients, nausea in 56 (52.8%), and vomiting in 32 (30.2%). Our data are consistent with the findings of several studies, i.e., intoxication syndrome, dysphagia (decrease in appetite, perverted food appetite), dyspeptic disorders, and chronic pain syndrome [22–24] play a key role in the development of cachexia.

The trend toward a decrease in SBW in the study cohort may indicate the development of hypermetabolism syndrome (protein–energy deficiency), in which, according to literature data, the proteolysis of skeletal muscles in hypermetabolism is accompanied by a decrease in amino acid level by 40% as well as loss of total muscle mass by 15%. Protein exchange in patients with cancer is accelerated, and protein degradation exceeds over protein synthesis, which leads to the loss of nitrogen-containing components of the body [25].

In this study, patients with cancer continued to receive specialized therapy; however, specific antitumor treatment worsened the existing nutritional disorders and contributes to the development of significant trophic deficiency in previously non-cachectic patients [26, 27].

Significant differences in the skinfold thickness of the thigh and abdomen in oncological palliative group and control groups were not found. Obviously, the combination of signs of nutritional deficiency with preserved skinfold thickness indicates the development of a sarcopenic type of obesity associated with aging, hypodynamics, concomitant comorbid pathology [28–30], as well as a proinflammatory state in the analyzed patients. In the oncological palliative group, systemic inflammation was manifested by hyperfibrinogenemia and increased CRP level. The relationships between the indicators of systemic inflammation and signs of nutritional insufficiency confirmed that systemic inflammation contributed to the occurrence of nutritional insufficiency [7, 14, 29].

Thus, patients with oncological palliative profile developed systemic inflammation, and one of its manifestations is nutritional insufficiency.

CONCLUSIONS

1. In 50 (47.2%) patients, signs of nutritional insufficiency were noted, and there was a significant reduction in the level of hemoglobin ($p = 0.002$), lymphocyte ($p = 0.012$), and albumin ($p = 0.001$), systemic inflammation manifested by hyperfibrinogenemia ($p = 0.038$), and increased CRP level ($p = 0.001$).

2. A significant relationship between CRP level and presence nutritional insufficiency ($\beta = 0.28$, $p = 0.011$) is revealed.

3. The presence of both malignant neoplasms and therapeutic comorbidity aggravates nutritional insufficiency, which affects the quality of life of the patient.

4. Our study shows the need for nutritional support at all stages of examination and treatment of patients with malignant neoplasms.

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