



Research Article

Neutrophil-to-lymphocyte Ratio and Nutritional Status in Patients with Cancer in Hospital Admission

¹Laís Pessanha Leal, ¹Marina Schmidt Mognhol, ¹Letícia Ribeiro Carvalho, ¹Ágata Depolo Echebarrie, ¹Naira Marcelli Fraga Silva, ²Glenda Blaser Petarli, ³Taísa Sabrina Silva Pereira and ⁴Valdete Regina Guandalini

¹Department of Integrated Education in Health, Health Sciences Centre, Federal University of Espírito Santo, Vitória, ES, Marechal Campos Avenue, 1468-Maruípe. Postal Code: 29040-090, Brazil

²Nutrition University Cassiano Antônio Moraes Hospital, Vitória, ES, Marechal Campos Avenue, 1355-Santa Cecília, P.O. Box 29043-260, Brazil

³Universidad de las Américas Puebla, Cholula, Puebla, México, ExHacienda Sta. Catarina Mártir S/N, San Andrés Cholula, Puebla, P.O. Box 72810, México

⁴Department of Integrated Education in Health, Health Sciences Centre, Federal University of Espírito Santo, Vitória, ES, Marechal Campos Avenue, 1468-Maruípe, Postal Code: 29040-090, Brazil

Abstract

Background and Objective: Evidence of the relationship between malnutrition and the systemic inflammatory process is growing, a condition in the cancer patient that may be even more exacerbated. This study aimed to evaluate the relationship between NLR and the presence of malnutrition in patients with cancer and verify the association of nutritional status evaluation with objective and subjective methods. **Materials and Methods:** Descriptive cross-sectional study conducted with adult and elderly individuals of both sexes with diagnosis of GI and adnexal gland cancer evaluated during the first 48 h of hospital admission. The nutritional status was evaluated through classical anthropometric and biochemical variables as well as subjective global assessment (SGA). The percentage of weight loss (% WL) at 6 months, the Nutritional Risk Index (NRI) and the NLR with cut-off points defined for this study >3 were calculated. Association and correlation tests were applied. The significance level adopted for the tests was 5%. **Results:** The 87 patients were included, mean age 57.3 ± 15.3 years. The SGA identified 73.6% of malnutrition patients of varying degrees and 46.0% presented with weight loss greater than 10.0% in 6 months. Regarding NLR, 55.2% of the patients presented values above the recommended cut-off point. There was an association of NLR with %WL ($p = 0.002$) and SGA ($p = 0.009$). Serum levels of albumin and total protein and the NRI were inversely correlated with NLR ($p < 0.005$), while a positive correlation was observed with PP % ($p = 0.008$). **Conclusion:** The NLR was associated with varying degrees of malnutrition indicated by SGA, high weight loss and nutritional risk according to the NRI, with the possibility of being a useful and complementary marker in nutritional evaluation.

Key words: Nutritional assessment, nutritional status, malnutrition, nutritional risk index, adnexal gland cancer, subjective global assessment

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Corresponding Author: Valdete Regina Guandalini, Department of Integrated Education in Health, Health Sciences Centre, Federal University of Espírito Santo, Vitória, ES, Marechal Campos Avenue, 1468-Maruípe, P.O. Box 29040-090 Brazil Tel: +55 (27) 997778404

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Nutritional status is a crucial factor for the cancer patient. In this scenario, malnutrition is associated with innumerable negative repercussions, such as an increase in hospitalization time, a decrease in tolerance to anti-neoplastic treatment, an increase in complications and a reduction in quality of life and survival¹⁻⁵. The prevalence of malnutrition may vary according to the tumor characteristics and the treatment used, with rates between^{1-3,6} 19 and 84%. According to Planas *et al.*² in patients with gastrointestinal tract (GIT) cancer, malnutrition rates in patients with cancer in the upper and lower portions and in the glands attached to the GIT are 47.9, 39.1 and 45.0%, respectively.

Although curing by multiple factors, the systemic inflammatory process has been highlighted in the genesis and progression of malnutrition. Often found in cancer patients, systemic inflammation affects important metabolic and neuroendocrine pathways and studies have shown associations with increased weight loss, elevated energy expenditure at rest, decreased lean mass and physical performance^{5,7-9}.

As aforementioned above, identifying nutritional changes early is strongly recommended. However, recent guidelines still do not point to a gold standard method for such an assessment^{9,10}. The European Society for Clinical Nutrition and Metabolism in the pre-operative nutritional care setting recommended systematically assessing dietary intake, weight variation and body mass index (BMI) of surgical patients if necessary¹⁰. In a guideline for cancer patients, the company recommended an objective and quantitative evaluation of food intake, symptoms of nutritional impact, muscle mass, physical performance and the degree of systemic inflammation for individuals at nutritional risk⁹.

Currently, no nutritional assessment tool covers all these domains. Some tools are often used and can be evaluated, such as the Patient-Generated Subjective Global Assessment (PG-SGA®), Subjective Global Assessment (SGA) and Mini Nutritional Assessment (MNA®); however, these do not assess the presence of systemic inflammation, which is known as one of the pillars of malnutrition.

Soeters *et al.*¹¹ reinforced the urgency of including an assessment of inflammatory activity in the diagnosis of malnutrition. An inflammatory marker that was distinguishing itself was the neutrophil-to-lymphocyte ratio (NLR)¹²⁻¹⁴. Studies showed that NLR is an independent prognostic factor in cancer^{12,15-17} and is associated with disease recurrence¹⁴ as

well as with nutritional status^{4,13}. It is routinely available and easily applicable. But so far, few studies have evaluated its relationship to nutritional status.

Thus, this study aimed to (1) Evaluate the relationship between NLR and the presence of malnutrition in patients with GIT and adnexal gland cancer attached to hospital admission and (2) Verify the association of the NLR with objective and subjective methods of nutritional status evaluation.

MATERIALS AND METHODS

Study design and population: This was a descriptive cross-sectional study of an open cohort performed at the General Surgery and Rehabilitation Unit of a public tertiary care hospital located in Vitoria, Espírito Santo, Brazil. Adult (<60 years) and elderly (≥60 years old), classification used in Brazil¹⁸ patients of both sexes, with a confirmed clinical diagnosis of GIT and anexal gland cancer were evaluated regarding their nutritional status in the first 48 h of hospital admission. Patients were excluded in precaution of contact and/or isolation, when in palliative care or when information, for any reason, could not be reliably collected.

Data collection: Data were collected from July, 2016 to May, 2017, through a specific protocol containing information on sex, age, diagnosis and tumor location. For the evaluation of nutritional status, conventional anthropometric and biochemical variables, the Nutritional Risk Index (NRI) and the SGA were used.

Anthropometric assessment: This study was performed by previously trained researchers and consisted of the measurement of body weight (kg), stature (m), arm circumference (AC) (cm), calf circumference (CC) (cm), triceps skinfold (TSF) (mm) and the thickness of the adductor pollicis muscle (TAPM) (mm). All measurements were performed as recommended by Lohman *et al.*¹⁹, except for the TAPM that was performed according to Lameu *et al.*²⁰. The arm muscle circumference (ACM) (cm), corrected arm muscle area (CAMA) in cm² and body mass index (BMI) were determined.

For the classification of TAPM, the proposal of Bragagnolo *et al.*²¹ specific for surgical patients, who considered values of eutrophy for the non-dominant hand with TAPM >13.1 mm and <13.1 mm for malnutrition. For the ACM (cm) and the CAMA (cm²) measurements, the percentile values proposed by Frisancho²² were used.

The BMI for adult was classified according to the World Health Organization (WHO) guidelines²³ as: Underweight ($<18.5 \text{ kg m}^{-2}$), eutrophy (≥ 18.5 to 24.9 kg m^{-2}) and overweight ($>24.9 \text{ kg m}^{-2}$). The elderly's BMI was classified according to Lipschitz²⁴ as low weight ($\leq 22 \text{ kg m}^{-2}$), eutrophic ($22-27 \text{ kg m}^{-2}$) and overweight ($\text{BMI} > 27 \text{ kg m}^{-2}$).

Biochemical evaluation: The following parameters were considered: serum albumin (mg dL^{-1}), transthyretin (mg dL^{-1}), C-reactive protein (CRP), total proteins, neutrophils and total lymphocytes. All the exams were performed in the clinical routine and were available in the medical records.

The determination of the neutrophil-to-lymphocyte ratio (NLR) was obtained by the equation:

$$\text{NLR} = \frac{\text{Neutrophils (cells mm}^3\text{)}}{\text{Lymphocytes (cells mm}^3\text{)}}$$

Patients were divided into two groups according to the NLR: High NLR ($\text{NLR} > 3.0$) and low NLR ($\text{NLR} \leq 3.0$)¹³.

Nutrition risk index (NRI): To determine the NRI, serum albumin values and the percentage of adequacy of the current weight were used in relation to the usual one by using the equation:

$$\text{NRI} = [1,519 \times \text{serum albumin (g L}^{-1}\text{)}] + 0.417 \times \left(\frac{\text{Current weight}}{\text{Habitual weight}} \times 100 \right)$$

From the score obtained in the equation, patients were classified as having no risk (>100), mild risk ($100-97.5$), moderate risk ($97.5-83.5$) or severe risk (<83.5)²⁵.

Subjective global assessment (SGA): The SGA is a subjective tool for assessing nutritional status based on different aspects of clinical history, such as weight changes, changes in food intake, presence of gastrointestinal symptoms and changes in functional capacity and physical examination (loss of subcutaneous fat, muscle and presence of edema or ascites) of the patient. The results are expressed in three categories: A (nourished), B (moderately malnourished or with suspected malnutrition) and C (severely malnourished)²⁶.

Statistical analysis: Means and standard deviations were used to describe the continuous and percentage variables for the categorical variables. The normality of the quantitative variables was tested using the Kolmogorov-Smirnov test. The difference between the proportions was evaluated by the chi-squared test and for comparing the means according to

the categories of the NLR, Student's and Mann-Whitney t-tests were applied. The presence of correlations between variables was analyzed by Pearson's correlation and Spearman's correlation. Correlation coefficients vary from -1 to +1 and are categorized as weak ($r < 0.3$), moderate ($r = 0.3-0.7$) or strong ($r > 0.7$)²⁷. For the NRI analyses the categories mild and moderate risk were grouped. The data were analyzed using SPSS 21.0 software. A significance level of 5.0% was adopted for all tests.

Ethics statement: This study was approved by the Ethics and Research Committee of the Federal University of Espirito Santo, under the number CAAE 27954014.0.0000.5060 and all participants gave written informed consent.

RESULTS

During the study period, 120 patients were included and evaluated. After a detailed analysis of the data and information collected, 33 patients were excluded due to the absence of one or more parameters, totaling a sample of 87 patients. The mean age was 57.3 ± 15.3 years, 52.9% were male, 48.3% were elderly, 50.6% were non-white and 75.9% had tumors located in the gastrointestinal tract. According to BMI, 39.1% of the patients were eutrophy. In relation to WL (%) in 6 months, 46.0% had weight loss greater than 10.0% and according to SGA the majority of the patients were under severe malnutrition (C) (46.0%). The NLR showed significant difference with WL (%) ($p = 0.002$), SGA ($p = 0.009$) and age (0.012) (Table 1).

Table 2 showed the prevalence of malnutrition by different diagnostic methods. The SGA was the method with the greatest capacity to identify nutritional risk (73.6%) when compared to the other methods.

The percentage of weight loss was significantly higher in patients with $\text{NLR} \geq 3$ (9.20% vs. 16.43%, $p = 0.003$), also observed for CRP (26.62 mg dL^{-1} vs. 52.55 mg dL^{-1} , $p = 0.018$). Serum albumin (3.80 vs. 3.39 mg dL^{-1} , $p = 0.001$), total proteins (6.30 vs. 5.82 mg dL^{-1} , $p = 0.010$) and NRI (99.47 vs. 89.50 , $p = <0.001$) were significantly lower in patients with NLR values ≥ 3 (Table 3).

The correlation between the NLR values with nutritional markers, including WL (%), albumin, total proteins and NRI and CRP were analyzed and presented in Fig. 1. Serum levels of albumin, total proteins and NRI were inversely correlated with NLR values ($p < 0.005$), while WL (%) was directly proportional to NLR values ($p = 0.008$), which shows the influence of inflammation in the nutritional status, in this study represented by NLR (Fig. 1).

Table 1: Characteristics of patients with cancer of the gastrointestinal tract and anexal gland according to the categories of neutrophil-to-lymphocyte ratio (NLR)

Variables	Total n (%)	Low NLR (<3) n (%)	High NLR (≥3) n (%)	p-value
Sex	87 (100.0)	39 (44.8)	48 (55.2)	
Male	46 (52.9)	23 (50.0)	23 (50.0)	0.389
Female	41 (47.1)	16 (39.0)	25 (61.0)	
Life stage				
<60 anos	45 (51.7)	18 (40.0)	27 (67.0)	0.393
≥60 anos	42 (48.3)	21 (50.0)	21 (50.0)	
Skin color				
White	43 (49.4)	19 (44.2)	24 (55.8)	1.000
Non-white	44 (50.6)	20 (45.5)	24 (54.5)	
Tumor location				
GI	66 (75.9)	29 (43.9)	37 (56.1)	0.805
Anexalgland	21 (24.1)	10 (47.6)	11 (52.4)	
Weight loss (%)				
Without weight loss	11 (12.6)	6 (54.5)	5 (45.5)	0.002*
≤10.0	36 (41.4)	23 (63.9)	13 (36.1)	
>10.0	40 (46.0)	10 (25.0)	30 (75.0)	
Body mass index				
Underweight	28 (32.2)	14 (50.0)	14 (50.0)	0.369
Eutrophy	34 (39.1)	12 (35.3)	22 (64.7)	
Overweight	25 (28.7)	13 (52.0)	12 (48.0)	
Nutrition risk index				
No risk	42 (48.3)	27 (64.3)	15 (35.7)	0.001
Mild and moderate risk	30 (34.5)	10 (33.3)	20 (66.7)	
Severe risk	15 (17.2)	2 (13.3)	13 (86.7)	
Subjective global assessment				
Well nourished (A)	23 (26.4)	15 (65.2)	8 (34.8)	0.009*
Moderately malnourished or suspected malnutrition (B)	24 (27.6)	13 (54.2)	11 (45.8)	
Severely malnourished (C)	40 (46.0)	11 (27.5)	29 (72.5)	
Age (mean±SD)	57.3±15.3	51.7±12.5	60.3±15.9	0.012

*Chi-squared test, GI: Gastrointestinal tract. **Test t-student

Table 2: Prevalence of malnutrition by different diagnostic methods in patients with cancer of the gastrointestinal tract and anexal gland

Methods	Malnutrition (%)
SGA	73.6
ACM (cm)	57.5
CAMA (cm ²)	55.2
TAPM (mm)	49.4
BMI (kg m ⁻²)	32.2

SGA: Subjective global assessment, ACM: Arm muscle circumference, CAMA: Corrected arm muscle area, TAPM: Thickness of the adductor pollicis muscle, BMI: Body mass index

Table 3: Comparison of age, anthropometric, biochemical and nutritional risk index with NLR in patients with cancer of the gastrointestinal tract and anexal gland

Variables	Neutrophil-to-lymphocyte ratio (NLR)		p-value
	Low (<3) (n = 39)	High (≥3) (n = 48)	
Age	57.72±15.80	57.00±15.10	0.820
Weight (kg)	62.75±12.91	61.00±14.07	0.565
WL (%)	9.20±7.26	16.43±12.12	0.003*
BMI (kg m ⁻²)	23.65±4.21	23.07±4.38	0.538
CC (cm)	33.70±3.19	32.77±3.93	0.239
ACM (cm)	22.60±3.20	22.21±3.58	0.597
CAMA (cm ²)	33.33±11.63	32.48±11.67	0.734
TAPM (mm)	13.65±3.64	13.73±4.82	0.928
Albumin (mg dL ⁻¹)	3.80±0.46	3.39±0.60	0.001*
Prealbumin (mg dL ⁻¹)	19.50±8.46	16.64±8.36	0.118
Total protein	6.30±0.71	5.82±0.94	0.010*
CRP	26.62±47.51	52.55±52.0	0.018
NRI	99.47±8.40	89.50±11.43	<0.001*

Student t-test; *Man-Whitney test; *p<0.005; WL (%): Weight loss, BMI: Body mass index, CC: Calf circumference, ACM: Arm muscle circumference, CAMA: Corrected arm muscle area, TAPM: Thickness of the adductor pollicis muscle, CRP: C-reactive protein, NRI: Nutritional risk index

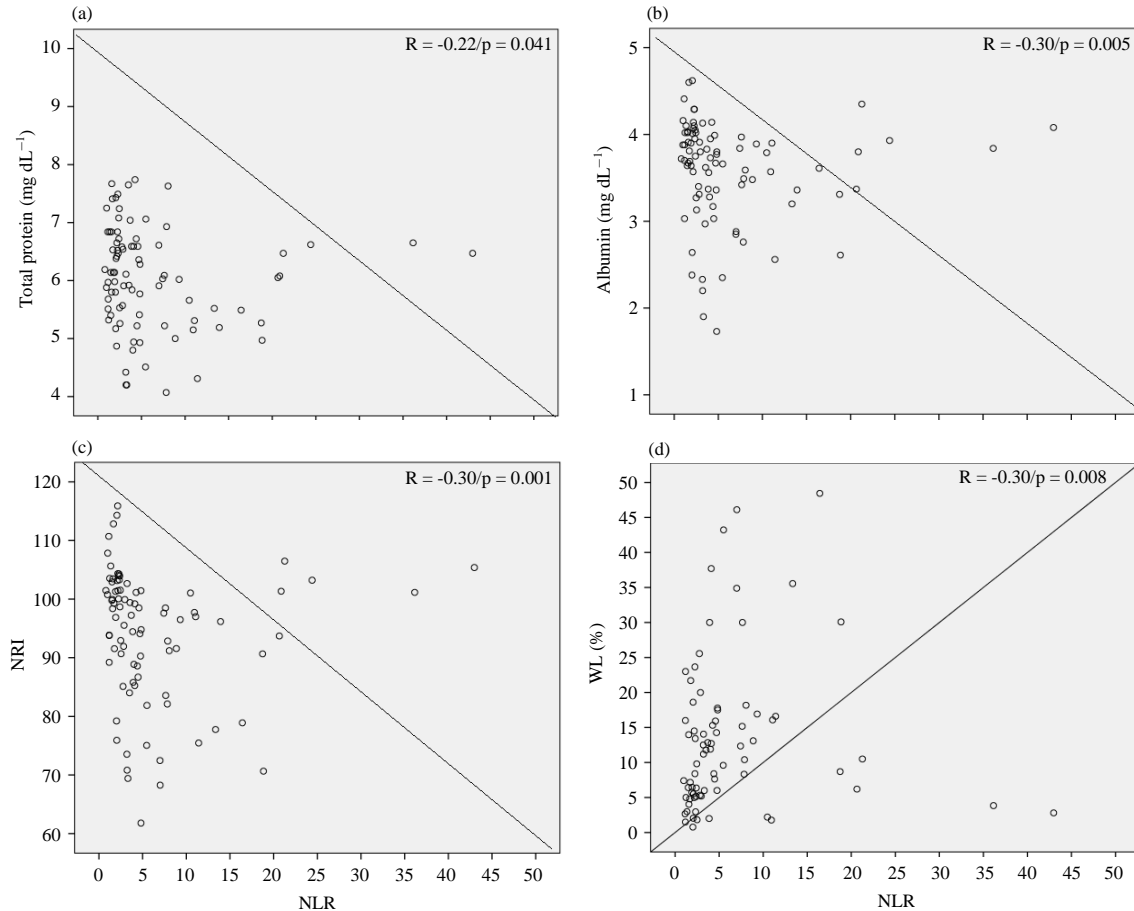


Fig. 1(a-d): Correlation neutrophil-to-lymphocyte ratio (NLR) between nutritional parameters and C-reactive protein (CRP) in patients with cancer of the GIT and anexalgland. NLR: Neutrophil-to-lymphocyte ratio; NRI: Nutritional risk index

DISCUSSION

The main findings of this study showed a predominance of nutritional risk, malnutrition high weight loss and NLR values above the recommended cut-off point as well as an association between nutritional status and NLR.

The SGA identified the highest percentages of malnutrition in the study population. This tool contemplates several aspects of the nutritional status and although not consensual is an often indicated method for the evaluation of cancer patients. Bauer *et al.*²⁸ found that 76.0% of patients presented some degree of malnutrition according to the SGA (B or C), whereas, Ryu and Kim²⁹ observed that 31.0% of patients were malnourished according to the SGA (B+C) the same obtained in evaluating nutritional risk by NRI. In this study, 73.6% of the patient evaluated were malnutrition (B+C), a condition that demonstrates the fragility of this population and how early diagnosis can be critical in recovery and care through an individualized intervention.

Severe weight loss is common in cancer patients and is common with gastric, pancreatic, colorectal, lung and head and neck tumors²⁹ and can may lead to a reduction in physical performance, worsening of quality of life, as well as poorer survival and response to treatment^{8,29,30}.

Due to the difficulty of using tools and indicators of nutritional status in isolation, studies have suggested a combination of assessment measures, such as anthropometric variables, laboratory tests and subjective tools, in order to increase the sensitivity and specificity of these methods, which would allow evaluate and define more specific nutritional interventions for these patients³¹.

Studies involving the inflammatory response and nutritional status are increasing, especially in cancer patients, given the pathophysiological characteristics of this disease^{4,5,7,8,13,32-35}. The involvement of the inflammatory response occurs through proinflammatory cytokines released by the tumor and host in response to the presence of neoplasia. Together, these changes result in metabolic and

neuroendocrine disturbances that culminate in anorexia and a reduction in lean mass and fat mass^{4,8}. In this scenario, albumin, a negative acute phase protein, is not a reliable nutritional marker. Studies have shown that hypoalbuminemia is often secondary to the systemic inflammatory process^{8,14,32}.

Elevated CRP levels are considered a sensitive marker of the systemic inflammatory process and are often observed in cancer patients. Scott *et al.*³⁶ demonstrated an association between systemic inflammation, exacerbated by CRP, with severe weight loss and decreased serum albumin values. In the present study, both CRP and hypoalbuminemia were related to the NLR, reflecting the inflammatory process present in these patients.

In this scenario, albumin, a negative acute phase protein, is not a reliable nutritional marker in the evaluation of nutritional status in the presence of inflammation, a condition present in the cancer patient, since its reduction is often secondary to the systemic inflammatory process^{8,12,30}.

The association between NLR with nutritional status has aroused interest in recent years, as this is a routine and easily available test. Tan *et al.*⁴ found a positive association between malnutrition in cancer patients, determined by the PG-SGA and the NLR. Sato *et al.*¹³ and Gonda *et al.*³³ observed that serum levels of pre-albumin and retinol-binding protein, used for the nutritional assessment were inversely correlated with the NLR, which led them to conclude that the NLR is a useful marker to evaluate malnutrition.

The present study found an association between nutritional status, determined by the SGA, WL % and NRI, with the NLR. The classic anthropometric variables were not related to the NLR, possibly because they are not sensitive enough to recent nutritional status changes when assessed in a discrete way. These results suggested that the NLR may be a promising biomarker in the assessment of nutritional status. Its role in complementing a nutritional diagnosis should be investigated.

Fruchtenicht *et al.*³⁷ found a correlation with WL % and NLR and other inflammatory markers in their study, showing that the more altered they were the greater the percentage of weight loss during the evaluated period. Therefore, considering that changes in inflammatory markers are potential indicators of nutritional risk, it allows adequate and early nutritional intervention to maintain and improve the response to treatment, nutritional status and quality of life, as well as to reduce treatment time and hospital costs³⁸.

As a contribution, this study presents the hypothesis of complementing the early detection of malnutrition with a simple, low-cost biomarker available routinely in the clinical

setting. It is also among the few studies investigating this relationship. Future investigations are required to determine a specific cutoff for nutritional status.

The limitations of this study include the absence of an association with tumor staging and the presence of infections, factors that define the inflammatory response and the nutritional status of these patients. Although the sample size was small, all the patients with cancer of the GIT and adjacent glands who were candidates for surgery during the study period were evaluated.

CONCLUSION

A high prevalence of malnutrition was confirmed by the different methods used, with an emphasis on the SGA. The NLR was associated with SGA, WL % and NRI, indicating that it may be a useful and complementary marker in nutritional assessments. However, new studies should be performed with the prospect of determining a cut-off point for this test and considering other factors involved in the inflammatory response of cancer patients.

SIGNIFICANCE STATEMENT

This study discovered that the NLR can be beneficial for malnutrition diagnosis in patients with cancer, due to its relation with inflammation and immune suppression, conditions that directly influence malnutrition. The findings of this study will help the researchers to uncover the critical areas of the NLR like prognostic markers of the nutritional status that many researchers were not able to explore. Thus a new theory on NLR and association with malnutrition in patients with cancer may be arrived.

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