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Advanced Stage of Disease and Systemic Inflammation as Factors Associated With Referral of Patients With Colorectal Cancer to a Palliative Care Unit

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Abstract

Objective: To identify factors associated with referral to an exclusive palliative care unit (PCU) in patients with colorectal cancer (CRC). **Methods:** Retrospective cohort study with patients having CRC of both sexes treated at a hospital unit, aged ≥20 years. Data were extracted from the medical records of pretreatment patients between January 2008 and August 2014. The outcome was referral to the PCU within 5 years. Logistic regression analyses were performed to assess whether sociodemographic, clinical, nutritional, and biochemistry data were associated to referral, generating odds ratios (OR), and 95% confidence intervals (CI). **Results:** Four hundred fifteen patients were evaluated. The Patient-Generated Subjective Global Assessment demonstrated a prevalence of malnutrition of 57.3%. One hundred one (24.3%) patients were referred to the PCU after 16.3 months (interquartile range: 7.2-33.5). These patients were more likely to be at an advanced stage of the disease and have malnutrition and exacerbated systemic inflammation. Tumor stage III and IV (OR: 2.05; 95% CI: 1.12-3.76) and neutrophil-to-lymphocyte ratio (NLR) ≥3 (OR: 1.89; 95% CI: 1.12-3.17) were predictors of an increased chance of referral to the PCU. **Conclusion:** Advanced disease stage and NLR were associated with referral of patients with CCR to a PCU.

Keywords

nutritional status, inflammation, colorectal neoplasms, palliative care, advanced cancer

Introduction

Colorectal cancer (CRC) is the fourth leading cause of cancer-related mortality.[1] Although survival in patients with cancer has increased markedly in the past few decades, a considerable proportion of patients are diagnosed with distant metastasis, and more than a third of patients with cancer still die within 5 years of the diagnosis.[2,3] In addition, many patients have psycological distress, anxiety, and impaired quality of life.[4,5] In dealing with oncology disease, the conception of comprehensive treatment must include palliative care.[6]

According to the World Health Organization, palliative care is an approach that aims to improve the quality of life of patients and their families in the face of a disease that threatens the continuity of life through prevention and relief of suffering, early identification, assessment, and treatment of pain and other physical, psychosocial, and spiritual symptoms and should be initiated upon the onset of any manifestations of a life-threatening disease, together with therapies capable of modifying its course.[7] However, access to palliative care is currently inequitable, owing to variable detection of such patients and differential thresholds for referral.[8]

However, routine oncological care generally does not involve concurrent palliative care. In addition, there is a lack of consensus in the literature about which patients with cancer should be referred and when referral should occur for exclusive palliative care.[6,9] Previous studies have shown that the time and referral process for this care varies widely, which underscores the need to define standardized criteria that may contribute to more appropriate clinical judgments.[9,10] Therefore, it is important to identify predictive triggers for referral to exclusive palliative care unit (PCU).

In this context, prognostic markers can play a pivotal role in directing the care plan in oncology treatment.[11] Serum inflammatory markers such as C-reactive protein (CRP), inflammatory

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cells, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been shown to have important prognostic value in several stages and types of neoplasms.[12-14] Furthermore, studies have linked nutritional status with prognosis in neoplastic diseases. Nutritional disturbances related to cancer promote changes in nutrient metabolism and body composition as well as impaired quality of life[15,16] and survival.[17]

Considering the difficulty of the clinical decision about when to transition from curative treatment to exclusively palliative care and the fact that prognostic indicators could help in this decision-making process, the aim of this study was to identify factors associated with referral of patients with CRC to an exclusive PCU.

Methods

The study was done using a retrospective cohort of patients undergoing pretreatment between January 2008 and August 2014 at the José Alencar Gomes da Silva National Cancer Institute (INCA), in Rio de Janeiro, Brazil. Data were obtained and recorded from the medical records kept at the institution. Trained researchers extracted data of interest retrospectively and recorded them on a specific form. The INCA Ethics Committee (Protocol 00994818.4.0000.5274 of 2018) approved the study.

Eligibility criteria were age $\geq$20 years and diagnosis confirmed by histopathological analysis. Exclusion criteria were diagnosis of other types of cancer; active hematological, inflammatory, or autoimmune infectious disease; receiving hormone therapy; with decompensated respiratory disease; occurrence of heart failure or acute myocardial infarction within the last 6 months; use of immunomodulatory drugs (eg, corticosteroids and cyclosporine); and transfusion within the past 3 months.

The following data were collected: age (years), sex (male vs female), side of colon tumor (colon vs rectum and anus), stage of tumor (I and II vs III and IV), Patient-Generated Subjective Global Assessment (PG-SGA; A vs B and C; global score), body mass index (BMI, kg/m^2), weight loss (WL, %), lymphocytes (/μL), neutrophils (/μL), platelets (/μL), albumin (mg/L), CRP (g/dL), and dates of treatment and referral to the exclusive PCU. Lymphocyte, platelet, and neutrophil counts; nutritional status data; and clinical and demographic characteristics were obtained prior to initiation of treatment and medical follow-up at the INCA.

The PG-SGA, developed and validated for use in oncology settings, was used to classify nutritional status. It consists of a questionnaire divided into 2 sections. The first section consists of 4 boxes: Box 1 focuses on weight changes, with a maximum score of 5; box 2 on food intake, with a maximum score of 4; box 3 on symptom profiling, with a maximum score of 24; and box 4 on functional status, with a maximum score of 3. The second section focuses on patient history, such as diagnosis, age, metabolic demand, use of corticosteroids, and physical examination, including loss of subcutaneous fat, muscle wasting, and edema or ascites. Each patient was classified as (a) well nourished, (b) moderately malnourished, or (c) severely malnourished. The total PG-SGA score was determined by summing the scores for all the boxes; the higher the PG-SGA score, the greater the risk of malnutrition.[18]

Patient-reported weight history was collected over the following time frames: previous 1, 2, 3, and/or 6 months and/or usual body weight. Patient reporting is part of the standard medical approach in completing the weight history for box 1 of PG-SGA. Percentage of WL was calculated as follows: [(current weight in kg − previous weight in kg) / previous weight in kg] × 100. BMI was reported as current weight (kg) / height (m^2). WL was assessed and graded (grades 0-4) by combining WL and BMI.[19]

Serum lymphocyte, neutrophil, platelet, albumin, and CRP concentrations were categorized into distribution tertiles. Serum lymphocyte, neutrophil, and platelet concentrations were used to calculate NLR and PLR. These variables were dichotomized, with the cutoff based on the medians and the literature on NLR[20] and PLR.[21]

Referral to a PCU was defined as the time in years from the date of histopathological diagnosis of the disease. The segment for the study was accomplished during 5 years from the diagnosis date.

Statistical Analysis

The statistical analyses were done using Stata 13.0 (Stata Corp., College Station, Texas). The Kolmogorov-Smirnov test was performed to assess the distribution of variables. Descriptive statistics are presented as numbers of observations (n) and percentages (%), and chi-square for the categorical variables and as means and standard deviations (SD), Student *t* test or median, interquartile range (IQR; 25th and 75th percentiles), and Mann-Whitney *U* test for the continuous variables.

Logistic regression was performed to assess risk factors for the referral of patients with CRC to the PCU, generating odds ratios (OR) and 95% confidence intervals (CI). In determining potential confounders in our regression model, we examined variables associated with CRC-specific exclusive palliative care outcomes in previous epidemiologic studies and those suggested in preliminary analyses. All factors with a P value $\leq$.200 in the bivariate analysis were included in the multivariate analysis. The final model was obtained using backward stepwise regression and included all variables with $P < .050$.

Results

Four hundred and fourteen patients were evaluated. Their mean age was 62.5 ($\pm$12.2) years, and there were slightly more males (50.8%), more colon tumors (76.8%), and the majority with stage III and IV CRC (92.6%). According to the PG-SGA, most of the patients (57.3%) had malnutrition even before starting cancer treatment (Table 1).

One hundred one patients (24.3%) were referred to the PCU within 16.3 (IQR: 7.2-33.5) months of the start of curative treatment. These patients were generally distinct from others in relation to most of the domains studied, with a higher proportion with stage III and IV tumors ($P = .006$), moderate or

Table 1. Clinical, Nutritional, and Biochemistry Characteristics of Patients With Colorectal Cancer According to Referral to the PCU.[a]

Variables	N	Total	Referral to the PCU		*P* Value
			No, n = 314 (75.7%)	Yes, n = 101 (24.3%)	
Age, years[b]	414	62.5 (11.2)	62.7 (12.0)	61.7 (12.7)	.468
Sex[c]	414				
Female		204 (49.2%)	161 (78.9%)	43 (21.1%)	.128
Male		211 (50.8%)	153 (72.5%)	58 (27.5%)	
Tumor location[c]	414				
Rectum and anus		96 (23.2%)	61 (63.5%)	35 (36.4%)	**.002**
Colon		318 (76.8%)	252 (79.2%)	66 (20.8%)	
Tumoral stage[c]	365				
I-II		27 (7.4%)	27 (100%)	0	**.006**
III-IV		338 (92.6%)	262 (77.5%)	76 (22.5%)	
PG-SGA[c]	227				
A		97 (42.7%)	86 (88.7%)	11 (11.3%)	**.032**
B-C		130 (57.3%)	101 (77.7%)	29 (22.3%)	
PG-SGA (global score)[c]	227	7.9 (6.6)	7.6 (6.5)	9.7 (6.8)	.073
BMI, kg/m^2[b]	407	25.2 (5.5)	25.6 (5.6)	24.0 (5.0)	**.015**
WL (%)[c]	197	5.3 (6.7)	4.7 (6.3)	7.1 (7.4)	**.028**
Grade of BMI and WL[c]	210				
0-2		123 (58.6%)	103 (83.7%)	20 (16.3%)	**.002**
3-4		87 (41.4%)	55 (63.2%)	32 (36.8%)	
Neutrophil, μL[c]	406				
First to second tertile (≤6853)		271 (66.7%)	216 (79.7%)	55 (20.3%)	**.004**
Third tertile (>6853)		135 (33.3%)	90 (66.7%)	45 (33.3%)	
Platelets, μL[c]	406				
First to second tertile (≤351)		271 (66.7%)	215 (79.3%)	56 (20.7%)	**.005**
Third tertile (>351)		135 (33.3%)	90 (66.7%)	45 (33.3%)	
Lymphocyte, μL[c]	405				
First to second tertile (≤2102)		270 (66.7%)	196 (72.6%)	74 (27.4%)	.073
Third tertile (>2102)		135 (33.3%)	109 (80.7%)	26 (19.3%)	
Albumin, g/dL[c]	210				
First tertile (≤3.7)		68 (32.4%)	49 (72.1%)	19 (27.9%)	.460
Second to third tertile (>3.7)		142 (67.6%)	109 (76.8%)	33 (23.2%)	
CRP, mg/L[c]	128				
First to second tertile (≤4.6)		85 (66.4%)	71 (83.5%)	14 (16.5%)	.353
Third tertile (>4.6)		43 (33.6%)	33 (76.7%)	10 (23.3%)	
NLR[c]	405				
<3		215 (53.1%)	177 (82.3%)	38 (17.7%)	**<.001**
≥3		190 (46.9%)	128 (67.4%)	62 (32.6%)	
PLR[c]	405				
<150		176 (43.5%)	147 (83.5%)	29 (16.5%)	**.001**
≥150		229 (56.5%)	156 (68.7%)	71 (31.3%)	

Abbreviations: BMI, body mass index; CRP, C-reactive protein; NLR, neutrophil–lymphocyte ratio; PCU, palliative care unit; PG-SGA, Patient-Generated Subjective Global Assessment; PLR, platelets–lymphocyte ratio; WL, weight loss.

[a]Bold values signifies p-value <0.05.

[b]Mean/standard deviation/*t* test.

[c]Number of observation/frequency/χ^2.

severe malnutrition ($P = .032$), WL grade of 3 to 4 ($P = .002$), and more inflammation (serum neutrophil and platelet concentrations in the third tertile, $P = .004$ and $P = .005$, respectively; NLR ≥3, $P < .001$; and PLR ≥150, $P = .001$; Table 1).

According to Figures 1 to 3, the time to referral to the PCU was lower in the patients who were moderately or severely malnourished ($P = .048$), with higher concentrations of neutrophils ($P = .018$) and CRP ($P = .017$), higher NLR ($P = .001$) and PLR ($P < .001$) values, and lower concentrations of lymphocytes ($P = .007$) and albumin ($P = .002$).

Table 2 shows the most significant variables (identified by logistic regression analysis) associated with referral to the PCU. In the bivariate analysis, significant factors associated with referral to the PCU were stage III and IV tumors, PG-SGA classified as B or C, WL grade of 3 to 4, NLR ≥3, and PLR ≥150. In the multiple model, stage III and IV tumors (OR: 2.05; 95% CI: 1.12-3.76) and NLR ≥3 (OR: 1.89; 95% CI: 1.12-3.17) were independent factors associated with the increased chance of referral to palliative care.

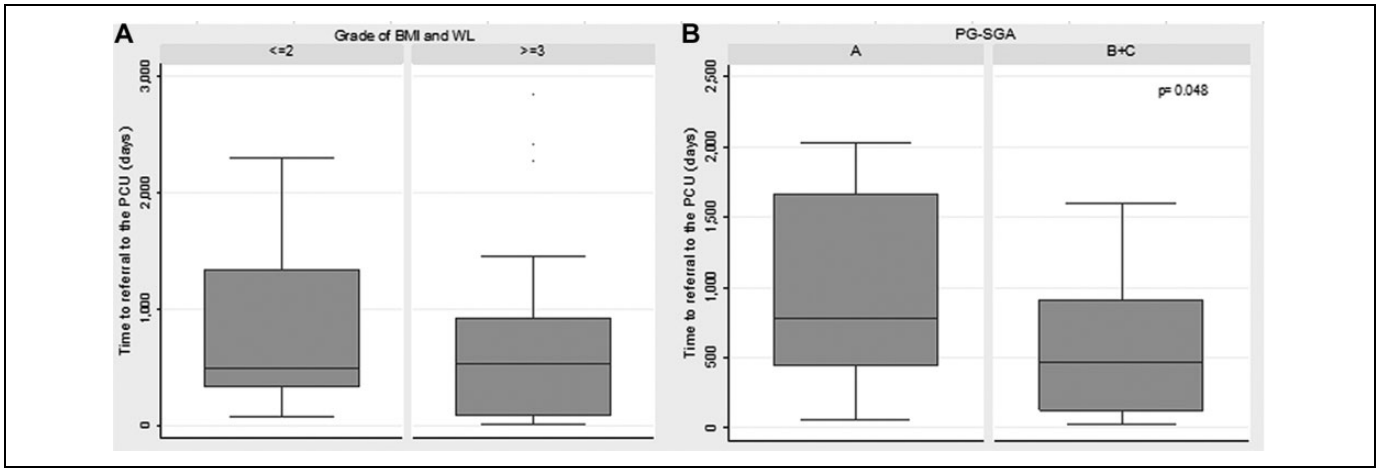

Figure 1. Time to referral to the PCU according to the nutritional characteristics of patients with colorectal cancer. Median time to referral to the PUC: (A) Grade ≤2: 490.50 (333.50-1341.00) days; ≥3: 526.00 (88.00-920.00) days; *P* value* = .380. B, PG-SGA A: 756.00 (267.50-2231.00) days; B + C: 425.00 (98.00-1600.00) days; *P* value* = .048. * *P* value refers to Mann-Whitney *U* test. BMI indicates body mass index; PCU, palliative care unit; PG-SGA, Patient-Generated Subjective Global Assessment; WL, weight loss.

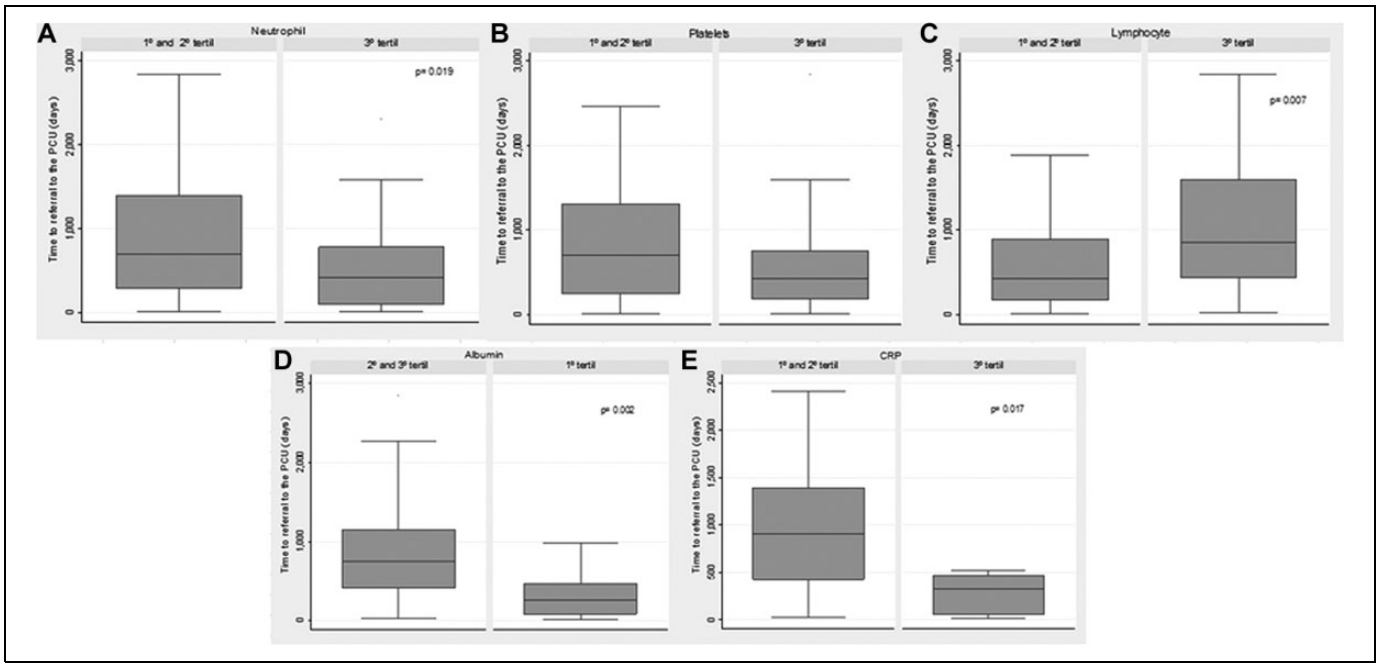

Figure 2. Time to referral to the PCU according to biochemistry characteristics of colorectal cancer patients. Median time to referral to the PUC: (A) Neutrophils first to second tertile: 693.00 (295.00-1392.00) days; third tertile: 412 (97.00-783.00) days; *P* value* = .019. B, Platelets first to second tertile: 704.00 (143.50-1311.50) days; third tertile: 425.50 (181.00-758.00) days; *P* value*= .060. C, Lymphocytes first to second tertile: 426.00 (174.00-888.00) days; third tertile: 855.50 (433.00-1599.00) days; *P* value*= .007. D, Albumin second to third tertile: 748.00 (412.50-1154.00) days; first tertile: 266.00 (84.00-471.00) days; *P* value*= .002. E, CRP first to second tertile: 900.00 (426.00-1392.00) days; third tertile: 321.00 (60.00-471.00) days; *P* value*= .017. **P* value refers to Mann-Whitney *U* test. BMI indicates body mass index; CRP, C-reactive protein; PCU, palliative care unit.

Discussion

This study is composed of unpublished data on predictors of referral to a PCU in a sample of patients with CRC at a national referral center. Our main results showed that advanced-stage cancer and exacerbated systemic inflammation were factors associated with the referral of patients to the PCU, which occurred late in the disease trajectory.

Most patients were diagnosed with stage III or IV cancer (92.6%) and had moderate or severe malnutrition (57.3%). Corroborating our findings, previous publications have shown

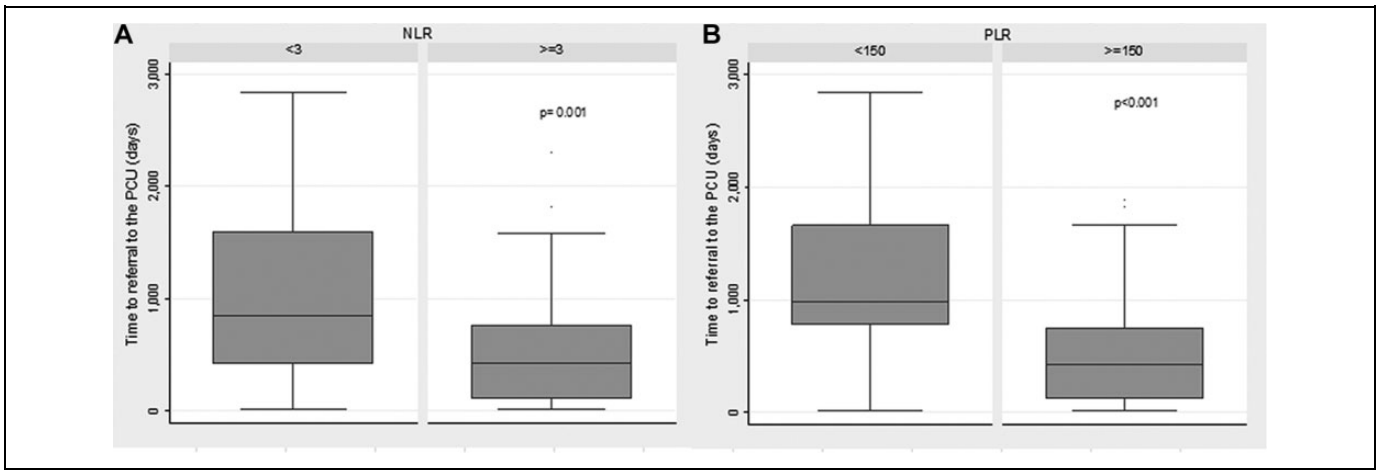

Figure 3. Time to referral to the PCU according to neutrophil–lymphocyte and platelet–lymphocyte ratio in patients with colorectal cancer. Median time to referral to the PUC: (A) NLR <3: 855.50 (425.00-1599.00) days; ≥3: 425.00 (111.00-767.00) days; *P* value*= .001. B, PLR <150: 777.00 (979.00-1660.00) days; ≥150: 418.50 (124.00-748.00) days; *P* value*<.001. * *P* value refers to Mann-Whitney *U* test. NLR indicates neutrophil–lymphocyte ratio; PCU, palliative care unit; PLR, platelet–lymphocyte ratio.

Table 2. Clinical, Nutritional, and Biochemistry Factors Related to Referral of Patients With Colorectal Cancer to the PCU.

	Patients Referred to the PCU	
Variables	Crude OR (95% CI)	Adjusted OR (95% CI)
Age ≥60 years	0.99 (0.63-1.58)	–
Gender male	1.42 (0.90-2.23)	–
Side colon	0.96 (0.57-1.63)	–
Tumoral stage III-IV	2.11 (1.15-3.85)[a]	2.05 (1.12-3.76)[a]
PG-SGA B-C	2.24 (1.06-4.76)[a]	–
Grade of BMI and WL 3-4	3.00 (1.57-5.72)[a]	–
Albumin first tertile (>3.7 g/dL)	0.58 (0.27-1.25)	–
CRP third tertile (>4.6 mg/L)	1.54 (0.62-3.82)	–
NLR ≥3	2.26 (1.42-3.59)[a]	1.89 (1.12-3.17)[a]
PLR ≥150	2.31 (1.42-3.75)[a]	–

Abbreviations: CI, confidence interval; CRP, C-reactive protein; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PCU, palliative care unit; PG-SGA, Patient-Generated Subjective Global Assessment; PLR, platelets–lymphocyte ratio.
[a] *P* value <.05.

a high proportion of cases with cancer diagnosed at a late stage, when the prognosis tends to be worse.[22,23] In addition, the occurrence of malnutrition in patients with cancer can be high, showing a high proportion of impaired nutritional status.[24] In cancer, nutritional depletion results from metabolic changes caused by tumor–host interactions, that result in changes in body composition, translated into musculoskeletal depletion, expansion of fluid space, and depletion of adipose tissue reserves.[25]

In a hospital setting, patients with advanced cancer who have no prospect of success with disease-modifying treatments often still receive inadequate care.[26] A study has revealed that even in well-integrated oncology–palliative care programmers, only approximately 50% of patients receive palliative care before death.[27] Alongside the limited offer of palliative care services in many places, one of the main difficulties for health professionals is identifying the right time to stop curative treatment and turn to exclusive palliative care.[6] About a quarter of our sample were referred to the PCU within 16.3 (IQR: 7.2-33.5) months of beginning curative treatment. This time was shorter in the malnourished patients and the patients with exacerbated systemic inflammation. For Hui et al,[8] the ideal time and criteria for referral to exclusive palliative care remain unclear. In France, in a study of data from 40 941 patients with cancer, the median time between diagnosis and first access to PCU was 144.0 (32.0-344.0) days.[28]

The decision to refer a patient to palliative care often occurs late in the disease process; opportunities for earlier referral, which could bring greater potential benefits for patients, tend to be missed.[27] In the complexity of the situations involving the provision of support for patients at an advanced stage of the disease, health services, and interdisciplinary teams are constantly challenged to provide increasingly specialized and individualized care management. Late referral can result in suboptimal pain control, increased suffering, failure to adhere to palliative care, and unplanned hospital deaths.[29] Regarding time to referral and quality of life, in a randomized controlled trial, patients with metastatic lung cancer assigned palliative care within 8 weeks of diagnosis of the disease had a better quality of life.[30]

We found that patients referred to the PCU were at a more advanced stage of the disease and had malnutrition and exacerbated systemic inflammation. In systematic review, Hui et al[8] found that one of the most common characteristics of patients with cancer referred to palliative care is the advanced disease trajectory. Besides that, we know that the presence of a tumor generates a state of chronic systemic inflammation, which evolves with its progression[31] in parallel with deteriorated nutritional status.[32] Systemic inflammatory response may be considered a key factor in energy imbalance and muscle mass loss in cancer, contributing to worse clinical outcomes in

palliative care patients.[33,34] Caro et al[35] found that 64.0% of patients with cancer were malnourished, a proportion that rose to 81.0% of patients in palliative care. Using the PG-SGA short form, Cunha et al[34] found that most patients in exclusive palliative care (70.7%) were at nutritional risk.

Accurately predicting the expectation of referral to palliative care would enable clinicians to provide more appropriate care. For this, it is necessary to identify easy-to-use and objective prognostic tools. Using logistic regression analyses, we verified that tumor stages III and IV (OR: 2.05; 95% CI: 1.12-3.76) and NLR $\geq$3 (OR: 1.89; 95% CI: 1.12-3.17) were predictors of an increased chance of referral to the PCU. The other variables, including malnutrition, did not contribute significantly (95% CI) to explaining referral to the PCU in the presence of independent markers.

Studies have shown advanced cancer is independently associated with referral to palliative care,[36] which could provide improved symptom relief and quality of life for these patients.[37] Although we also identified cancer stage as a predictor of referral to PCU, it is already a consolidated prognostic factor in the scientific literature and known by the professionals involved in the clinical management of patients with cancer.

To our knowledge, this is the first study to explore the relationship between pretreatment NLR and referral of patients with CRC to palliative care. Our results suggest NLR as a possible "trigger" that could be used as early referral to PCU.

Immune system plays an important role in CRC cells. The factors that drive the systemic inflammatory response in patients with CRC are complex, and therefore the mechanisms are unclear. A high neutrophil count may promote tumor growth, angiogenesis, and metastasis through remodeling of the extracellular matrix, release of reactive oxygen species, and suppression of lymphocyte activity and natural killer cells. Increased NLR indicates a relative reduction in lymphocytes and lymphocyte-mediated immune response, which plays a crucial role in cytotoxic cell death.[38] A low lymphocyte count might result in an inadequate immune response in the control of tumor.[39] Thus, NLR may represent a balance between the tumor promotion reaction and antitumor immune function.

Neutrophil-to-lymphocyte ratio is an easily measured, reproducible, inexpensive, and objective marker of systemic inflammation in clinical practice. Mounting evidence has demonstrated the association between high NLR and negative survival in patients with CRC[22] and terminal cancer.[40] However, its potential, clinical, and practical value in referring patients with CRC to palliative care and the medical decision-making process involved in this remain unclear.

There are strengths and limitations of this study that should be considered when interpreting the findings. First, the analyses are based on data obtained from a single institution. Second, this was a retrospective study, making the potential for selection bias unavoidable. While the sample size is comparable and even larger than other studies investigating NLR, it is still a relatively small number of patients to make any nationwide extrapolations. Nevertheless, this is a new focus for the use of NLR, and larger prospective studies will be needed to confirm these preliminary results. One strength of this study is its use of a homogenous sample with a single tumor type. Its results have the potential to be of clinical relevance and significance.

Conclusion

Advanced stage CRC and systemic inflammation were factors associated with the referral of patients with CRC to the PCU. Although already established as a predictor of worse clinical outcomes, the progress of the disease alone is not sufficient grounds for making an early decision to refer to exclusive palliative care. However, given the ease of determining NLR from routine blood tests at no additional cost, this indicator could yield clinical advances in the identification of patients with CRC and could be used by cancer clinicians to assist in identifying patients who need exclusive palliative care. However, the relationship between NLR and this outcome requires future exploration.

Authors' Note

The authors have full control of all primary data and agree to allow the journal to review our data if requested.

Declaration of Conflicting Interests

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