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Association Between Nutrition Status and Survival in Elderly Patients With Colorectal Cancer

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Abstract

Background: Aging patients with cancer have a higher risk of mortality and treatment-associated morbidity than younger patients. Nutrition status may play an important role in cancer mortality. We aimed to evaluate the survival time of elderly patients with colorectal cancer and its association with body mass index (BMI), the patient-generated subjective global assessment (PG-SGA), and phase angle (PA). *Materials and Methods:* BMI, PG-SGA, and PA were determined for all patients (n = 250) at first assessment. *Results:* Seventy-one (28.4%) patients were in active oncologic treatment (group 1) and 179 (71.6%) were in remission (group 2). At the time of the analysis, 73 (29.2%) patients had died and 177 (70.8%) were censored. The mean (standard deviation) age was 70.9 (7.49) years; 17.2% were undernourished, 56% normal weight, and 26.8% were overweight. According to the PG-SGA, 35.2% of patients needed some nutrition intervention and 4.4% needed it urgently. The mean PA was 4.94 ± 1°. PG-SGA, tumor stage, and PA differed significantly ($P < .001$) between the groups; BMI did not ($P = .459$). Severe malnutrition (PG-SGA C), compared with PG-SGA A, was associated with a relative hazard of death of 12.04 (95% confidence interval [CI], 3.43–42.19, $P < .001$). PA >5° was associated with better prognosis: a relative hazard of 0.456 (95% CI, 0.263–0.792; $P < .005$). *Conclusion:* Among elderly patients with colorectal cancer, PA and PG-SGA were prognosis factors. PA >5° was associated with best survival and PG-SGA C with worst survival. (*Nutr Clin Pract*. XXXX;xx:xx-xx)

Keywords

colorectal cancer; nutrition assessment; PG-SGA; phase angle; survival; nutritional status; bioelectrical impedance

Background

In 2012, the Globocan project/International Agency for Research on Cancer (IARC) estimated that >60% of the 14 million cases of cancer arising globally each year occur in developing countries. Moreover, in terms of mortality, 70% of the 8 million expected deaths occur in those countries. Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer mortality worldwide, accounting for about 1.4 million new cases and almost 700,000 deaths in 2012.[1] By 2030, these figures are projected to increase by 60%, to >2.2 million new cases and 1.1 million deaths.[2] The risk of developing CRC increases with age and is greater in men than in women. Among men currently aged 60 years, 1.22% will get CRC over the next 10 years.[3] Moreover, the elderly have an increased risk of cancer mortality and are at higher risk of treatment-associated morbidity compared with younger patients.[4] The degree of weight loss varies according to the type of cancer; gastrointestinal (GI) cancers are associated with high degrees of weight loss because they impair the intake and absorption of food and nutrients, causing malnutrition.[5] The result is a complex syndrome of malnutrition, with a major impact on prognosis and on the desired beneficial effects of treatment.[6]

The use of a single parameter to assess nutrition status has been questioned because of low predictive value and lack of sensitivity and specificity, since many nonnutrition factors affect outcomes.[7] Thus, nutrition assessment should be routinely included in the preliminary evaluation of elderly people with cancer.[6] The decline in nutrition status in the geriatric oncology patient is the result of the effects of lower dietary intake (starvation), the effects of aging (sarcopenia), and the effects of the tumor (cachexia).[5] The resulting condition can lead to a complex malnutrition syndrome with a major impact on prognosis and the beneficial effects of the intended treatment.[6]

Body mass index (BMI) should be interpreted with caution in the elderly, although low values are associated with malnutrition because body composition is modified in the aging process by stature[6] and loss of muscle mass (sarcopenia).[8]

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The subjective global assessment (SGA) is a clinical technique that combines data from subjective and objective aspects of the medical history and physical examination. The patient-generated SGA (PG-SGA), adapted from the SGA, was developed specifically for patients with cancer.[9] Unlike the SGA, which provides a categorical result, the PG-SGA measures nutrition status on a continuous scale, allowing detection of subtle changes in nutrition status over a short period of time. The total PG-SGA score is the sum of questions about weight loss; food intake; symptoms that affect nutrition, activities, and function; disease; metabolic demand; and physical examination findings, where higher scores demonstrate greater risk of malnutrition.[10]

Bioelectrical impedance analysis (BIA) is a measurement of body composition and nutrition status that is widely used.[11] It is noninvasive and practical, can be measured at the bedside, and is used in healthy and sick people.[11–17] The analysis is based on measurement of total body resistance to the passage of an electric current of low amplitude (800 mA) and high frequency (50 kHz), measuring, by means of these, properties such as impedance, resistance (R), reactance (Xc), and the phase angle (PA). The BIA-derived PA, obtained by the relation between various measurements of R and Xc (AF = arctangent Xc/R), consists of a direct measure of cellular stability and reflects the distribution of water in the intracellular and extracellular spaces. It is interpreted as the membrane integrity indicator and predictor of body cell mass (BCM).[11,13] The lower values observed in elderly patients may indicate skeletal muscle reduction, with a consequent rise in intracellular water, which may be compounded by increased edema associated with aging.[14] Increase in body fat may, indeed, mimic the loss of muscle mass.[18] Depletion of lean body mass and the presence of edema may mask the true nutrition status. The use of PA, unlike other variables measured by BIA to estimate body composition, is described as valid, even in situations with variations in hydration status.[12,13] The PA has been studied as a prognostic tool, able to assess cell membrane function in various clinical situations. PA average values range between 4° and 10°, depending on sex and age. Low values of PA indicate reduction of cellular integrity and lean body mass and are associated with increased morbidity and mortality.[11–14,16]

The aim of this study was to evaluate the survival time of patients with CRC aged ≥60 years, from the date of first nutrition assessment to death, and its association with BMI, PG-SGA, and BIA-derived PA.

Patients and Methods

Patients

This cohort study involved 250 outpatients aged ≥60 years, treated by oncologists. It was conducted between July 2008 and September 2015. The study was approved by the local ethics committee (Protocol 1.621.550).

Objective Methods for the Assessment of Nutrition Status

The cutoff points to define the elderly population were based on the criteria of the Expert Group on Epidemiology and Aging of the World Health Organization (WHO), namely, age ≥60 years in developing countries and >65 years in developed countries.[19] Data were collected on a wide range of variables, including demographic characteristics: age, sex, pathology, and stage (TNM system[20]) and nutrition state (BMI, PG-SGA, and PA). To calculate BMI, weight (kg) and height (cm) were measured; patients were classified as undernourished, normal weight, or overweight depending on their BMI measurement.[21]

The PG-SGA is a questionnaire divided into 2 parts, the first part filled out by the patient himself or herself, with questions about weight loss, change in intake, symptoms, and altered functional capacity. The second part of the questionnaire was filled out, in this study, by an oncology dietitian, with questions involving metabolic demand and physical examination related to depletion. At the end of the questionnaire, the values added indicate the conduct, where 0–1 = no intervention required at this time; 2–3 = patient and family education by a dietitian, nurse, or other clinician; 4–8 = intervention by dietitian, in conjunction with a nurse or physician; and ≥9 = a critical need for improved symptom management and/or nutrient intervention options.[9] The categorical part of PG-SGA classified the patients into 3 categories: (A) well nourished, (B) moderately undernourished or suspected of being undernourished, and (C) severely undernourished.[22]

BIA measurements were performed with a QuadScan 4000 instrument (Bodystat Ltd, Douglas, Isle of Man), which applies a 200-µA current at frequencies of 5, 50, 100, and 200 kHz. Patients were positioned supine with their arms and legs abducted to ensure that no parts of the body were in contact with each other. The first set of electrodes was attached to the dorsal surface of the right wrist between the radial and ulnar processes and directly proximal to the knuckles on the dorsum of the hand. The second set of electrodes was positioned on the anterior surface of the ankle, midway between the medial and lateral malleoli, and just proximal to the toes on the dorsum of the foot. The results displayed on the analyzer were printed and stored for later analysis. The PA for the whole body at 50 kHz was calculated from the impedance values using software supplied by Bodystat Ltd. All procedures and controls for other variables affecting the validity, reproducibility, and precision of the measurements were performed according to the National Institutes of Health guidelines.[23]

Data Analysis and Statistical Methods

Continuous variables were compared using the Student *t* test. Survival was defined as the time from the date of undergoing the first nutrition evaluation to the date of death from any cause or the date of last contact/last known to be alive. The Kaplan-Meier method was used to calculate survival. The log-rank test statistic was used to evaluate the equality of survival distributions across different strata. Survival was also evaluated using univariate and multivariate Cox proportional hazards regression analysis. Variables evaluated included PG-SGA, PA, BMI, Eastern Cooperative Oncology Group Performance (ECOG) status, and TNM.[20] For the purpose of this analysis, the stage at diagnosis variable was dichotomized into early stage (stages I and II) and late stage (stages III and IV), and PA was categorized according to the median value of the sample. Differences were considered statistically significant if the *P* value was <.05. All data were analyzed using SPSS version 23 for Mac (SPSS, Inc, an IBM Company, Chicago, IL).

Results

A total of 250 outpatients were treated by the Oncology Group from July 2008 to September 2015. The mean (standard deviation [SD]) age of the patients was 70.9 (7.49) years, and 51.6% were men. Of these 250 patients, 71 (28.4%) were in active oncologic treatment (neoadjuvant or palliative), while 179 (71.6%) were in remission (followed up or receiving adjuvant chemotherapy). At the end of the study period, 73 (29.2%) patients had died and 177 (70.8%) were censored. In terms of tumor stage, 48% of patients were late stage (stages III and IV). The PG-SGA scores ranged from 1–24, with a mean (SD) value of 5.66 (4.67). The prevalence of malnutrition in this population, as determined by PG-SGA, was as follows: 60.4% were PG-SGA A (not requiring current intervention), 35.2% were PG-SGA B (requiring nutrition support), and 4.4% were PG-SGA C (requiring urgent nutrition-related symptom management and/or nutrition support) (Table 1). Overall, 46.8% of the patients were smokers and 13.6% reported consuming alcoholic beverages daily without specifying the amount and type of beverage used. The median BMI was 24.9 kg/m^2 (interquartile range [IQR], 16–43 kg/m^2), with 56% considered having a normal BMI measurement. In relation to ECOG status, only 6.4% of the group were ECOG status 2 or 3. The mean (SD) PA was 4.94° (1.00°) overall: 5.1° (1.08°) for men and 4.7° (0.92°) for women ($P < .01$). The descriptive and functional characteristics of the study participants are displayed in Table 1.

The Kaplan-Meier method was used to evaluate the ability of each variable to predict mortality. PG-SGA (Figure 1), stage, and PA (Figure 2) were significantly associated with long-term mortality risk ($P < .001$), while BMI was not ($P = .459$) (Table 2).

Univariate Cox proportional hazard regression was undertaken to verify the predictive value of the proposed scores; the results are reported in Table 3. The statistics were significant for all variables analyzed (tumor stage, ECOG, PG-SGA, and PA). In the same table, we can see the results of the multivariate Cox regression analysis, which found that stage IV was associated with a relative hazard of death of 2.7 (95% confidence interval [CI], 1.40–5.41; $P = .003$) compared with stages I and II. PG-SGA C (severe malnutrition) was associated with a relative hazard of death of 12.04 (95% CI, 3.43–42.19; $P < .001$), compared with PG-SGA A (well nourished). A PA >5° (compared with a PA ≤5°) was associated with a relative hazard of death of 0.456 (95% CI, 0.263–0.792; $P < .005$).

Table 1. Patient Characteristics.

Characteristic	Number	%	Mean ± SD
Vital status			
Died	73	29.2	
Censored[a]	177	70.8	
Time of follow-up, mo			10.83 ± 16.5
Age, y			70.9 ± 7.4
Female	121	48.4	
Male	129	51.6	
Smoking	117	46.8	
Alcoholism	34	13.6	
Tumor stage			
Stage I	39	15.6	
Stage II	91	36.4	
Stage III	64	25.6	
Stage IV	56	22.4	
Body mass index			25.5 ± 4.46
Undernourished	43	17.2	
Normal weight	140	56	
Overweight	67	26.8	
ECOG			
0	188	75.2	
1	46	18.4	
2/3	16	6.4	
PG-SGA			
A. Well nourished	151	60.4	
B. Moderately malnourished	88	35.2	
C. Severely malnourished	11	4.4	
PG-SGA score			5.6 ± 4.6
≥4	134	53.6	
≥9	47	18.8	
PA, deg[b]			4.94 ± 1
Female			4.7 ± 0.92
Male			5.1 ± 1.08

deg, degree; ECOG, Eastern Cooperative Oncology Group Performance; PA, phase angle; PG-SG, patient-generated subjective global assessment.
[a]Patients who reached the end of the study without experiencing death.
[b]Comparison between male and female ($P < .01$).

Discussion

The present study allowed us to examine the relationship between cancer, nutrition status, and survival, specifically in the elderly, and the importance of using various methods for assessing their nutrition status. Nutrition screening tools are a means to identify and/or classify nutrition status and have been widely used in clinical practice. However, the usefulness of these tools as prognostic markers in patients with cancer remains unclear. Some studies show that the presence of malnutrition in patients with cancer is influenced by the method used for evaluation of nutrition,[24] decreased food intake,[25] the location of the tumor,[24–26] and the

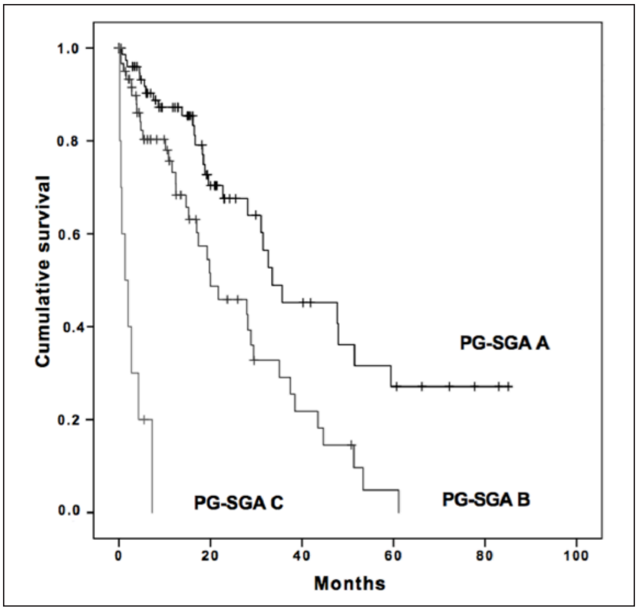

Figure 1. Kaplan-Meier survival analysis patient-generated subjective global assessment (PG-SGA). A, well nourished; B, moderately malnourished; C, severely malnourished.

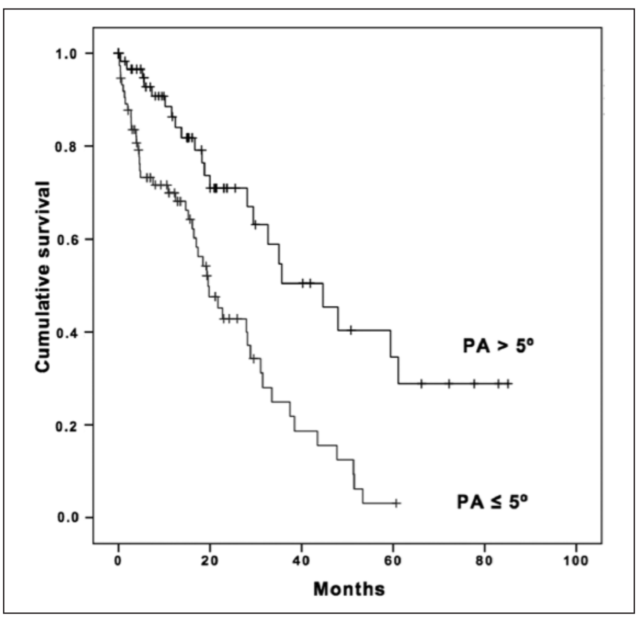

Figure 2. Kaplan-Meier survival analysis phase angle (PA).

Table 2. Univariate Kaplan-Meier Survival Analysis.

Variable	Survival, Median (Range), mo	Log-Rank Score	*P* Value
PG-SGA			
A. Well nourished	43.7 (34.3–53.2)		
B. Moderately malnourished	25.1 (19.5–30.6)		**<.001**
C. Severely malnourished	2.6 (0.9–4.3)		
Body mass index			
Undernourished	31.9 (21.1–42.6)		
Normal weight	31.0 (23.3–37.7)	1.555	.459
Overweight	36.36 (25.9–46.7)		
Tumor stage			
I	63.5 (38.5–88.5)		
II	43.95 (33–54.8)	29.69	**<.001**
III	32.1 (22.6–41.5)		
IV	17.7 (27.1–38.5)		
Phase angle, deg			
≤5	23.2 (18.5–27.9)	14.56	**<.001**
>5	46.2 (35.9–56.5)		

Bold *P* values represent statistical significance. deg, degree; PG-SGA, patient-generated subjective global assessment.

stage of disease.[24] Vandewoude[25] emphasized that malnutrition, very common in the elderly, is related more to preexisting diseases than aging itself. The present study allowed us to examine the relationship between cancer, nutrition status, and survival, specifically in the elderly.

It is known that the simple assessment by BMI is insufficient to detect changes in body composition associated with malignancy[26] and that the risk of malnutrition is not excluded in patients classified as normal weight or overweight on BMI measurement.[18,26,27] Moreover, less than half of our patients who needed nutrition intervention, according the PG-SGA, were classified as undernourished by BMI. A study by the American Cancer Nutrition showed that only 2% of patients with GI cancer do not need nutrition intervention, while most need not only nutrition intervention but also immediate management of symptoms.[28] In the present study, only a small proportion of patients needed immediate intervention, unlike the study by Santos et al,[29] in which half the sample required prompt intervention. This difference can be explained by the large number of patients with metastatic disease in the latter study, which aggravates the patients' clinical condition and therefore increases the need for immediate nutrition management.

In the present study, survival time was calculated from the date of undergoing the first nutrition assessment—using PG-SGA, PA, and BMI measures—to the date of outcome. The influence of stage on survival and nutrition status was also evaluated. Patients in stage I survived twice as long as those in stage III and about 4 times longer than those in stage IV. In terms of nutrition status, more than half of the patients who required immediate nutrition intervention (PG-SGA ≥9) had stage IV disease. Patients in PG-SGA C (severe malnutrition) had median survival times approximately 10 and 17 times lower than those in PG-SGA B (moderate risk of malnutrition) and PG-SGA A (not at risk of malnutrition), respectively. Although the advanced stage was the cause of worse survival, severe malnutrition and higher PA were independent prognostic factors, as demonstrated by the multivariate analysis. In relation to BMI, the differences in survival were detected but not confirmed in later statistical analysis. These findings reinforce the need to

Table 3. Univariate and Multivariate Cox Proportional Hazard Model.

	Univariate		Multivariate	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Tumor stage[a]				
IV	4.176 (2.378–7.334)	**<.001**	2.757 (1.405–5.410)	**.003**
ECOG[b]				
ECOG 1	2.494 (1.466–4.245)	**<.001**	2.021 (1.086–3.76 2)	.26
ECOG 2/3	6.026 (2.800–12.967)	**<.001**	1.510 (0.472–4.828)	.487
PG-SGA[c]				
B. Moderately malnourished	2.210 (1.342–3.641)	**.002**	0.949 (0.497–1.814)	.874
C. Severely malnourished	23.780 (9.846–57.434)	**<.001**	12.041 (3.436–42.195)	**<.001**
Phase angle, deg				
Cutoff 5[d]	0.375 (0.222–0.632)	**<.001**	0.456 (0.263–0.792)	**.005**

Bold *P* values represent statistical significance. deg, degree; ECOG, Eastern Cooperative Oncologic Group; HR, hazard ratio; PG-SGA, patient-generated subjective global assessment.
[a]Tumor stage I/II as referent.
[b]ECOG 0 as referent.
[c]PG-SGA A (well nourished) as referent.
[d]Phase angle ≤5 as referent.

use more comprehensive nutrition assessment tools (ie, ones that can evaluate more than just the ratio between weight and height). The ideal tool for assessment of nutrition status should have both high sensitivity and specificity. The scored PG-SGA could identify malnourished patients with 98% sensitivity, unlike the SGA, which only categorizes patients.[22]

Both parts of the PG-SGA take about 15 minutes to fill out. Sometimes, according to level of education or literacy, a health professional asks the questions instead of the patients filling them out by themselves. Because of this, the professional who is applying the questionnaire should be trained to ask the questions without interfering with the answers. A well-applied questionnaire by a trained person is a powerful tool for treatment as it provides early symptom management, resulting in a better prognosis with lower costs. The questionnaire score allows for the identification of high-risk patients through the observed symptoms. In addition, in this study, using the PG-SGA score, we could identify 4 times more patients with nutrition risk than when just classifying per se without the score (SGA).

PA is one of the best cell health indicators, where high values reflect the integrity of the cell membrane and good improved cellular function.[11–14,16] In 2010, Paiva et al[15] examined populations with breast and head and neck cancer, among others, and observed that a PA of 5.12° was a predictive factor for patients undergoing chemotherapy, regardless of mortality. In another study of patients with lung cancer, the average PA was 4.5°. The researchers observed that patients with PA values ≤4.5° had shorter survival times than those with higher values.[30]

Gupta et al[12] investigated the prognostic role of PA and concluded that patients with a PA >5.57° had a median survival 4.7 times longer compared with those with values below this angle. It is important to mention that this study was conducted with only 52 stage IV patients. In the present study, we had a total of 250 patients, almost half in advanced stages, where values >5° were associated with a lower risk of death. Moreover, the statistical analysis confirmed the increased risk of death among patients in stage IV, PG-SGA C, and PA <5°, although we had used the same cutoff level for men and women and also for newly diagnosed or progressive disease. Gupta et al considered it more appropriate to use specific cutoff levels of PA for sex as well as disease stages, although this conclusion was based on a retrospective study with a small sample.[17]

Nutrition assessment should not only focus on the identification of malnourished or patients at nutrition risk but also understand the causes that have impaired their nutrition status. This information enables adequate nutrition intervention and management of symptoms during treatment. Several factors may influence the survival of elderly patients with CRC, and in this sense, we cannot conclude that, in this study, the shortest survival was related only to the nutrition status. However, the tools used, besides the facility, demonstrated the ability to identify outpatients in oncological treatment with lower survival.

Conclusion

In conclusion, among elderly patients with CRC, PA and PG-SGA were prognosis factors. A PA >5° was associated with best survival and PG-SGA C with worst survival.

Statement of Authorship

K. Barao, M. Abe Vicente Cavagnari, and N. Manoukian Forones equally contributed to the conception and design of the research, and drafted the manuscript; P. Silva Fucuta contributed to the design of the research; and K. Barao, M. Abe Vicente Cavagnari, and P. Silva Fucuta contributed to the acquisition, analysis, and the interpretation of the data. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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