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Original article

Association between preoperative potential sarcopenia and survival of cancer patients undergoing major surgical procedures

Associação entre provável sarcopenia pré-operatória e sobrevida de pacientes oncológicos submetidos a operações de grande porte

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ABSTRACT

Objective: to evaluate the impact of probable sarcopenia (PS) on the survival of oncological patients submitted to major surgeries. **Method:** prospective cohort bicentrical study enrolling adult oncological patients submitted to major surgeries at Cancer Hospital and Santa Casa de Misericordia in Cuiabá-MT. The main endpoint was the verification of postoperative death. Demographic and clinical data was collected. PS was defined as the presence of 1) sarcopenia risk assessed by SARC-F questionnaire and 2) low muscle strength measured by dynamometry. The cumulative mortality rate was calculated for patients with either PS or non PS using Kaplan Meier curve. The univariate and multivariate Cox regression model was used to evaluate the association of mortality with various investigated confounding variables. **Results:** a total of 220 patients with a mean (SD) age of 58.7±14.0 years old, 60.5% males participated of the study. Patients with PS had higher risk to postoperative death (RR=5.35 95%CI 1.95-14.66; p=0,001) and for infectious complications (RR=2.45 95%CI 1.12-5.33; p=0.036). The 60 days mean survival was shorter for patients with PS: 44 (IQR=32-37) vs 58 (IQR=56-59) days (log rank <0,001). The Cox multivariate regression showed that PS was an independent risk factor (HR=5.8 95%CI 1.49-22.58; p=0.011) for mortality. **Conclusion:** patients bearing PS submitted to major oncological surgery have less probability of short term survival and preoperative PS is an independent risk for postoperative mortality.

Keywords: Surgical Oncology. Sarcopenia. Mortality. Postoperative Complications.

INTRODUCTION

In the last decades, there has been a significant increase in the incidence of cancer accompanied by a high mortality rate[1]. In this scenario, the operation is one of the mainstays of the treatment available for patients with cancer[2]. It is estimated for 2030 that of the 21.6 million cancer patients, 17.3 million will require surgery[2].

However, despite the advances in surgical procedures and in the perioperative management techniques, some factors are predictive of complications and can increase postoperative mortality. In this sense, malnutrition and, more recently, the presence of sarcopenia, in cancer patients may increase the risk of postoperative complications and death. Thus, the success of surgery and of postoperative evolution also depends on this important risk factor [3-5].

The body composition plays an important role in the evolution of oncological diseases, as well as in response to treatment and quality of life of patients. In the last decade, the sarcopenia syndrome, characterized by the generalized and progressive loss of skeletal muscle

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and its function, has been associated with increased likelihood of adverse outcomes, including falls, fractures, disability and mortality, raising great concern among elderly and cancer patients[6-9]. This is because the presence of this syndrome is also associated with the increase of hospital admissions, longer hospitalization, increase of postoperative complications and readmissions[10-13].

The etiology of sarcopenia is multifactorial. It is classified as primary or age-related when no other specific cause is evidenced, and secondary, when causal factors other than aging are evident, such as the presence of systemic disease, physical inactivity and inadequate energy or protein intake[7]. Many studies have shown that sarcopenia as a negative prognostic factor in several clinical aspects of the cancer patient, such as treatment tolerance and overall survival[14-16].

However, in surgical oncology, sarcopenia received less attention, and evaluation of the muscle mass and / or function is not part of the routine preoperative approach in many care centers for patients with cancer[4]. Thus, the assessment of probable sarcopenia (PS) or preoperative sarcopenia in patients with cancer is necessary to evaluate the outcomes along the postoperative period.

Therefore, considering its clinical relevance, the European Working Group on Older People in Sarcopenia (EWGSOP2)[7], published in 2019, recommends using the SARC F questionnaire (Strength, Assistance with walking, Rise from the chair, Climbing stairs, and Falls) to screen for sarcopenia. This questionnaire is useful, simple, inexpensive, and easily applicable for screening and further contribution to the diagnosis of sarcopenia[17,18]. An ally of the SARC-F, and indicated by it, is the measuring of muscle strength for the diagnosis of SP[7]. The muscle strength changes rapidly and precedes the anthropometric changes, which allows more sensitive and rapid detection of sarcopenia[17-20].

Thus, considering that few national studies have evaluated the impact of sarcopenia in cancer patients who are candidates for surgical procedures, this research aimed to evaluate the impact of preoperative PS in the survival of cancer patients undergoing major operations.

Methods

This was a bicentric, prospective, cohort study conducted from July 2018 to April 2019, with adult cancer patients (age ≥ 18 years) admitted to the Cuiabá Cancer Hospital and to the Santa Casa de Misericordia. The study was approved by the Ethics in Research Committee of the Federal University of Mato Grosso (UFMT), under number 2,666,168 (CAAE 89216318.8.0000.8124). Patients who agreed to participate in the study signed an informed consent form (ICF).

Inclusion and exclusion criteria

We included adults with cancer and candidates for major oncological operations, which we defined as the ones with high probability of loss of fluids and blood, according to opinion 006/2015 of the Federal Council of Medicine[21]. We excluded patients diagnosed with non-melanoma skin cancer, advanced disease, and those who refused to sign the ICF or declined to participate in the study at any stage. We also excluded previously included patients whose data were lost or who have had operations suspended for any reason, or, even who were transferred to another hospital in the postoperative period.

Investigated variables and data collection

We classified patients as having PS or not preoperatively as defined below. The main outcome variable was death. As covariates, we recorded the presence of PS in the preoperative period, demographic data, body weight (kg), body mass index (kg/m2), nutritional status, American Society of Anesthesiologists (ASA) score, type of major surgery according to the location of the tumor, operative time (minutes) and hospital stay (in days, until discharge or death), and postoperative infectious complications. We collected the data in the preoperative period, about one to two hours before surgery and in the postoperative period, until hospital discharge or death. We recorded the survival time up to 60 days after admission.

Nutritional status

We determined the nutritional status of the studied patients according to the subjective global assessment (SGA). Nourished patients were classified as

SGA-A, potentially or moderately malnourished, as SGA-B, and severe malnourished, as SGA-C[22].

Diagnosis of probable sarcopenia

We defined probable sarcopenia (PS) when the patient who presents, in the immediate preoperative period, risk of sarcopenia by the SARC-F questionnaire and low muscle strength (Kgf). The SARC-F questionnaire consists of five questions that evaluate strength, walking, getting up from a chair, climbing stairs and a history of falls. The ratings vary from 0 to 10 points, with 0-2 points for each item. We considered patients who achieved a SARC F $\geq$ 4 as in risk of sarcopenia[17,18]. We assessed muscle strength by the handgrip strength (HGS; Kgf), measured in the dominant hand with the aid of a hydraulic dynamometer (Saehan Corporation, Masan, Corea®)[19]. We classified patients as having low muscle strength according to the cutoffs of < 27 Kgf and < 16 Kgf, for men and women, respectively[7].

Postoperative infectious complications

We considered infectious complications the presence of pneumonia, infection at the surgical site, dehiscence of anastomosis or abdominal wall, urinary tract infection, and sepsis. All definitions of infectious complications were cited in other articles published by the same group[23,24]. We also classified complications by the Clavien-Dindo criteria[25].

Statistical analysis

We used the Kolmogorov-Smirnov test to determine the normality of continuous data. We presented the normally distributed data in means and standard deviations, and those distributed in a non-normal way, in median and interquartile range (IQR). We used the Chi-square test (relative risk and 95% confidence interval) to determine the association of PS with death and infectious complications. We computed the Odds Ratio and its 95% confidence interval (OR, 95% CI) to determine the association of PS with the demographic variables.

We used the Kaplan-Meier non-parametric test to estimate the probability of survival (days) of patients with and without PS, compared by the Log-Rank test. We defined the survival time (median, interquartile rage) as the time in days from surgery until death or censoring (discharged cases).

Then, we used the univariate and multivariate Cox Proportional Hazards Regression, having the hazard ratio (HR) as an effect measure, with respective 95% confidence intervals to evaluate the association of mortality with categorical and continuous variables (clinical and demographic data). To avoid data collinearity in relation to nutritional status, in the univariate Cox regression we used only the severely malnourished classification (SGA-C).

In the multivariate Cox Proportional Hazards Regression, we included variables related to the occurrence of the event "survival" in the univariate analysis, with p value < 0.20. The variables selected for fitting the multivariate model were probable sarcopenia (PS), infectious complications, and digestive tract surgery.

We set the statistical significance threshold at 5% ($p < 0.05$). We used the Statistical Package for the Social Sciences 20.0 (SPSS Statistics; IBM, Armonk, NY, USA) for statistical analysis.

RESULTS

Sample and patients characterization

From 338 eligible patients, we excluded 12 due to non melanoma skin cancer, 14 due to advanced disease, 13 due to data loss, and 79 due to suspension of the procedure. Hence, 220 patients undergoing major operations participated in the study. They had average age of 58.7 ± 14.0 years, 111 (50.5%) being elderly. Table 1 brings the other clinical and demographic data.

Diagnosis of probable sarcopenia

Preoperatively, 39 (17.7%) patients were at risk for sarcopenia according to the SARC-F. The mean HGS was 31.2 ± 11.5 Kgf, with 27 (12.3%) patients having low HGS. Fourteen patients (6.4%) had PS. Among the elderly, PS was present in 6.3% (7/111).

Table 1. *Clinical and demographic characteristics of the studied patients.*

Variables	Values
Age (years) (A ± SD)	58.0 ± 14.0
Elderly (n;%)	111 (50.5)
Gender (n;%)	
Female	109 (49.5)
Male	111 (50.5)
Body weight (Kg) (A ± SD)	71.6 ± 15.8
BMI (kg/m2) (M; IQR)	26, 1 (23.0-30.1)
Nutritional status (n;%)	
SGA-A	120 (54.5)
SGA-B	71 (32.3)
SGA-C	29 (13.2)
ASA score I and II (n;%)	202 (91.8)
Type of operation according to tumor location	
Urological	86 (39.1)
Digestive tract	69 (31.4)
Breast	29 (13.2)
Head and neck	17 (7.7)
Others	19 (8.6
Surgery time (minutes) (M; IQR)	125 (90-205)
Length of hospital stay (days) (M; IQR)	3 (2-7)
Infectious complications (n;%)	35 (15.9)
Death (n;%)	15 (6.8)

BMI: body mass index; SGA: subjective global assessment; ASA: American Society of Anesthesiologists.
According to data distribution, values are expressed as average and standard deviation (A ± SD), number and percentage (n;%), and median and interquartile range (M; IQR).

In the preoperative period, patients undergoing digestive tract operations were those who were more likely to have PS (OR = 3.16, 95% CI 1.05 9.5, p = 0.032). The data also showed that patients diagnosed with preoperative severe malnutrition were about three times more likely to have PS (OR = 3.06, 95% CI 1.38 6.80; p = 0.010). There was no association between PS and the other variables studied (ASA 1 and 2, elderly, sex and urological surgery).

Postoperative complications

In the postoperative period, 37.7% (n = 83) of patients experienced at least one complication, of which 15.9% (n = 35) were infection. In addition, in most of the cases that had any complications, they were mild, 61 (27.7%) being classified as Clavien-Dindo I or II.

Survival

The occurrence of death was significantly higher among patients with PS [28.6% (4/14) vs 5.3% (11/206); p = 0.001]. The total survival time in 58 days was 57 (55-58) days. The Kaplan-Meier curve showed that the survival average during the study period of 60 days was shorter for patients with PS, 44 (IQR = 32 37) vs. 58 (IQR = 56 59) days (Log Rank < 0.001), as shown in Figure 1.

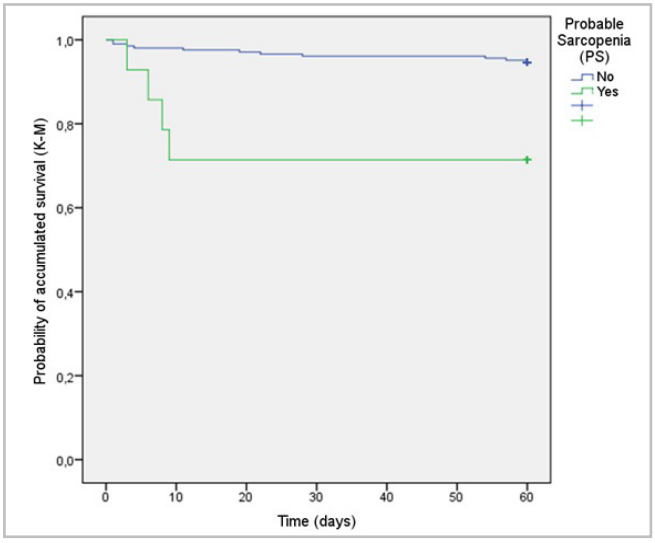

Figure 1. *Probability of accumulated survival over the 60-day period in patients with and without probable sarcopenia (PS).*

Univariate Cox Regression for mortality associated with clinical and demographic characteristics.

The univariate Cox regression analysis showed that PS (HR = 9.96, p = 0.001), infectious complications (HR = 4.8, p = 0.031), and patients undergoing digestive tract operations (HR = 5.55, p = 0.028) presented an increased risk for the occurrence of death (Table 2).

Table 2. *Univariate Cox Regression Analysis for the association of mortality with clinical and demographic characteristics of the studied patients.*

Event	*Hazard Ratio*	95% CI	p
Probable sarcopenia	9.96	2.66-37.37	0.001
Infectious complications	4.80	1.16-19.9	0.031
Digestive tract surgery	5.55	1.20-25.7	0.028
ASA I and II	0.90	0.11-7.14	0.922
Surgery time (min)	1.00	0.99-1.00	0.914
Age (years)	1.01	0.96-1.06	0.678
Elderly	0.82	0.28-2.40	0.722
Sex	0.92	0.26-3.22	0.896
Body Weight (Kg)	0.97	0.93-1.01	0.204
BMI (kg/m2)	0.94	0.84-1.06	0.347
SGA-C	1.97	0.66-5.98	0.232

95%CI: 95% confidence interval; ASA: American Society of Anesthesiologists, BMI: body mass index, SGA: Subjective global assessment.

Multivariate Cox Regression for mortality associated with clinical features

As shown in Table 3, in the multivariate Cox regression adjusted for PS, surgery of the digestive tract, and presence of infectious complications, only the effect of PS remained as risk of death, ie, PS was an independent risk factor (HR = 5.8, 95% CI 1.49 22.58, p = 0.011) for the mortality of cancer patients undergoing major operations.

Table 3. *Multivariate Cox Regression Analysis for the association of death with the characteristics of the studied patients.*

Condition	*Hazard Ratio*	95% CI	p
Probable sarcopenia	5.80	1.49-22.58	0.011
Digestive tract surgery	3.73	0.77-18.07	0.102
Infectious complications	2.57	0.62-10.74	0 194

IC 95%: confidence interval of 95%.

DISCUSSION

The results showed that cancer patients with PS undergoing major operation presented a lower probability of survival in 60 days. In addition, the diagnosis of PS was an independent risk factor for mortality. The data revealed that the risk of sarcopenia and low muscle strength are associated with a worse postoperative outcome, corroborating the results of other authors[26-29].

A study with 6,447 patients submitted to abdominal cancer surgery showed an association of sarcopenia with a higher occurrence of readmissions and postoperative complications[27]. In addition, sarcopenia was a risk factor for reduction of survival, in agreement with our results. Previously, another study from our group had found that patients undergoing major digestive tract operations and decreased HGS had 50% more risk of complications and five times more risk of death when compared with normal HGS individuals[26].

Other studies have shown that the reduction in functional capacity, as determined by strength, is a strong predictor of mortality in patients with different clinical conditions[30-33]. Moreover, muscle strength, according to the latest European Consensus[7] and other studies[34,35], gained more importance to the diagnosis of probable sarcopenia and sarcopenia compared with the determination of muscle mass[36,37]. Our data showed that 12.3% of the patients had low HGS in the preoperative period.

Furthermore, according to our results, patients with PS presented twice more risk for postoperative infectious complications. Recent studies found similar results[9,11,32,38,39], thus reinforcing the importance of early diagnosis of sarcopenia or PS. Supporting these data, a meta-analysis published by Wang et al. in 2020[30] showed that the presence of sarcopenia in cancer patients undergoing esophagectomy increased the chance of pneumonia and anastomosis dehiscence in the postoperative period.

We also found that patients submitted to digestive tract operations, different from the urological ones, were those who presented more than three times the chance of being with PS before undergoing the surgical intervention. This reaffirms the association that exists between the presence of cancer of the digestive

tract, especially in the upper part and in the head and neck, with alterations related to the intake of nutrients and nutritional condition[3,4,26,40].

Patients classified as having severe malnutrition by the SGA were three times more likely to have PS in the preoperative period. This does not surprise us, since malnourished patients usually have quite low muscle mass. This functional change was recently established by to the Global Leadership Initiative on Malnutrition (GLIM) as a criterion for classification of malnutrition[7,41]. Malnourished patients often also display changes in body composition[7,42,43].

Our data showed, with significant relevance, that patients with PS were less likely to survive in 60 days than those without PS. Many cancers, particularly of the digestive tract, which were the second leading cause of operations of our sample, occur with lower lifespan[1,28,32]. For instance, gastric cancer, whose treatment is predominantly surgical, is the fifth most common cancer and the third leading cause of death by cancer worldwide[1]. Huang et al. (2020)[29] showed that the overall and disease-free survival were lower among the sarcopenic patients receiving neoadjuvant treatment for esophageal cancer. Moreover, sarcopenic patients sustained more adverse events, such as mucositis, neutropenic fever, and lower muscle mass index than the non-sarcopenic individuals did.

Li et al.[44], in a recent meta-analysis comprising 2,264 patients diagnosed with urological cancer, showed that the ones who were sarcopenic in the preoperative period had shorter survival. The authors also stated that sarcopenia could serve as a promising prognostic marker for patients with urological cancer.

Therefore, the identification of PS is of great importance for the initiation of treatment strategies before the operation[5,45]. This may reduce the occurrence of complications and death. For though there is great advancement in nutritional therapy, in surgical techniques and in fast track type, multimodal programs of postoperative recovery acceleration[46-48], the cancer patients, the malnourished, and the sarcopenic ones still present with increased risk of morbidity and mortality[12,13,29,32,49].

We must also add that despite the PS's scientific and clinical relevance, this muscle syndrome is rarely diagnosed and treated in clinical practice[50]. In contrast, the latest European Consensus states that in face of the risk of sarcopenia assessed by SARC-F, one must start preventive nutritional intervention. This indication of the Consensus values the power of preoperative screening. It is important to note that both the SARC F and the HGS assessments, in addition to being simple, rapid and low cost, can be performed at bedside with the patient lying down or sitting, which optimizes time.

Thus, a research group recently created in Brazil a protocol called SARCPRO (Protocol Proposal for Sarcopenia in Hospitalized Patients)[51]. The protocol suggests nutritional intervention with protein supplementation associated with motor rehabilitation, highlighting the importance of a multi-professional team in this context.

In this sense, a study of patients submitted to radical cystectomy after consuming oral nutritional supplement twice a day for eight weeks in the perioperative period showed that these patients had a lower prevalence of sarcopenia, complications and hospital readmissions[52].

The results of our study, however, must be carefully evaluated because the sample is small and we evaluated patients undergoing different major operations. The study has limitations, such as the use of a hydraulic dynamometer of a brand different from the Jamar®, the one validated to obtain the cutoff point mentioned in the method and indicated by the European Consensus[7]. Another point that can be considered as a limitation was not excluding patients who already had cachexia. Nevertheless, we can consider that only patients who were candidates for operations participated in the study, with therapeutic, not just palliative, possibilities.

On the other hand, we prospectively evaluated all patients, and they underwent major cancer operations. Thus, the data from this study allow us to conclude that patients with PS undergoing major oncological procedures have lower probability of short-term survival. Moreover, preoperative PS is an independent risk factor for postoperative mortality.

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RESUMO

Objetivo: *avaliar o impacto de provável sarcopenia (PS) pré-operatória na sobrevida de pacientes oncológicos submetidos a operações de grande porte.* **Métodos:** *estudo bicêntrico de coorte prospectivo, realizado com pacientes oncológicos adultos, submetidos a operação de grande porte no Hospital de Câncer e na Santa Casa de Misericórdia em Cuiabá-MT. A variável principal foi a ocorrência de óbito pós-operatório. Coletou-se dados demográficos, clínicos e o diagnóstico de PS, definido pela presença de: 1) risco de sarcopenia pelo questionário SARC-F e 2) baixa força muscular (Kgf) mensurada pela dinamometria. Calculou-se a taxa de sobrevida acumulada para os pacientes com e sem PS pela curva de Kaplan-Meier. Aplicou-se o modelo de regressão de Cox uni e multivariado para avaliar a associação da mortalidade com covariáveis de confundimento investigadas.* **Resultados:** *participaram do estudo 220 pacientes com idade média (DP) de 58,7±14,0 anos, sendo 60,5% do sexo masculino. Quatorze (6,4%) pacientes foram considerados com PS. Os pacientes com PS apresentaram risco aumentado para a ocorrência de óbito (RR=5,35 IC95% 1,95-14,66; p=0,001) e para complicações infecciosas (RR=2,45 IC95% 1,12-5,33; p=0,036). A sobrevida média em 60 dias, foi menor para os pacientes com PS: 44 (IIQ=32-37) vs 58 (IIQ=56-59) dias (log rank <0,001). A regressão Multivariada de Cox, mostrou que a PS foi fator de risco independente (HR=5,8 IC95% 1,49-22,58; p=0,011) para a mortalidade.* **Conclusão:** *os pacientes com PS submetidos a operações oncológicas de grande porte apresentam menor probabilidade de sobrevida a curto prazo e a PS pré-operatória, é fator de risco independente para mortalidade pós-operatória.*

Palavras chave: *Oncologia Cirúrgica. Sarcopenia. Mortalidade. Complicações Pós-Operatórias.*

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