



Applied nutritional investigation

Different methods for diagnosis of sarcopenia and its association with nutritional status and survival in patients with advanced cancer in palliative care



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ABSTRACT

Objectives: The aim of the present study was to evaluate the association between sarcopenia, diagnosed by different muscle mass measurement techniques, with nutritional status and overall survival in patients with advanced cancer under palliative care.

Aim: To investigate the association of sarcopenia, according to distinct muscle mass measurement methods, with nutritional status and overall survival (OS).

Methods: This observational and prospective study, including 334 patients, defined sarcopenia as reduced muscle mass and strength. Muscle mass was evaluated adopting 3 different methods, mid-upper arm muscle area (MUAMA), calf circumference (CC) and appendicular skeletal muscle mass (ASMI) described by Baumgartner (1998) and adjusted for height. Strength was defined using a handgrip dynamometer and OS was established based on a 90 days follow-up after inclusion date. Kaplan-Meier curves were conducted for survival analyzes and the association between sarcopenia and OS was evaluated by Cox regression model

Results: Prevalence of sarcopenia varied from 27–65% according to the method used to evaluate muscle mass. Malnutrition assessed by different parameters was significantly higher in patients with sarcopenia. Patients considered sarcopenic by MUAMA (43 versus 67 days, $p < 0.001$), CC (44 versus 77 days, $p < 0.001$) and ASMI (48 versus 75 days, $p < 0.001$) had significantly lower OS compared to non-sarcopenic patients. Sarcopenia evaluated by MUAMA (HR, 1.57; 95% CI, 1.12–2.18) and CC (HR, 2.00; 95% CI, 1.45–2.76) showed a higher risk of mortality.

Conclusion: Sarcopenia diagnosed by MUAMA and CC could predict mortality and CC proved to be the best prognostic method for estimating OS in patients with advanced cancer in palliative care.

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Introduction

The term *sarcopenia* is derived from the Greek words *sarx* (flesh) and *penia* (poverty) [1]. The international Consensus on Sarcopenia defines it as a syndrome characterized by concomitant and generalized loss of skeletal muscle mass and strength [1–4]. Although sarcopenia is primarily a condition of the elderly, it also may be associated with chronic diseases, including cancer [1].

Evidence of muscle loss and strength reduction exists for most cancer types and stages. However, these conditions are more evident in advanced phases of the disease and become significant in terms of functional disability, loss of autonomy, and decreased

quality of life [1,5–7]. Studies have shown that the presence of sarcopenia has been associated with adverse outcomes including decreased overall survival (OS) [8–10].

Current guidelines discuss the use of multiple measurement techniques and cut-points to diagnose sarcopenia. There are several methods available to assess depletion of skeletal muscle mass, such as computed tomography (CT), magnetic resonance imaging (MRI), dual energy x-ray absorptiometry (DXA), anthropometric measures, and bioelectrical impedance [5–7,11]. All of these techniques have various advantages and limitations. Although CT, magnetic resonance imaging, and DXA are considered gold standard methods, they are expensive, require skilled labor, and expose patients to radiation, rendering some of these methods as not feasible. On the other hand, anthropometric measures are classified as low cost, noninvasive, and easy to apply during routine clinical practice [12].

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Despite the associations between sarcopenia and various significant health outcomes, there has been very limited research comparing the associations between nutritional status, survival, and sarcopenia defined by anthropometric measurements. Therefore, the aim of the present study was to evaluate the association between sarcopenia, diagnosed by different muscle mass measurement techniques, with nutritional status and OS in patients with advanced cancer under palliative care.

Methods

Patients

This study presents the preliminary results from an observational consecutive cohort study conducted in the Palliative Care Unit at the National Cancer Institute José Alencar Gomes da Silva (INCA), Rio de Janeiro, Brazil. In all, 334 advanced cancer patients were recruited from March 2016 to July 2017. Muscle mass, strength, and nutritional status were measured and evaluated by trained dietitians at the first visit for outpatients and within the first 48 h of the first hospitalization for inpatients. Cancer type, disease stage, previous oncologic treatment, comorbidities, and the date of death were obtained from medical records.

Patients were included according to the following eligible criteria: ≥ 20 y of age, ability to answer the necessary information and/or accompanied by someone capable of it, and Karnofsky performance status (KPS) $\geq 30\%$. This study received ethical approval from the Research Ethics Committees of INCA and all patients signed an informed consent before joining the study.

Measurement instruments

Anthropometry

Measurements of weight and height were made with patients wearing light clothing and without shoes. Weight was obtained using a calibrated portable Wiso Digital scale (150 kg capacity). For those patients who were unable to stand, an in-bed scale system was used (Stryker, model Go Bed II). Weight loss (WL) history from the previous 6 mo was collected. WL $\geq 5\%$ was considered clinically significant.

Height was measured using a tape stadiometer on the wall, however, when not possible, height was estimated using the knee height, which was measured with the knee and ankle joints flexed at 90 degrees, using a measuring tape or an anthropometer. The estimated height was calculated through the Chumlea et al. [13] formulas. Body mass index (BMI) was calculated as body weight (kg) divided by the height squared (m^2).

Muscle mass

Three measures were used to assess muscle mass:

1. Appendicular skeletal muscle mass (ASM; kg) was determined using the prediction equation described by Baumgartner et al. [14], which uses body weight, height, hip circumference, and handgrip strength (HGS). The ASM index (ASMI) was measured using the following formula: $ASM/height^2$ [2].
2. Mid-upper arm muscle area (MUAMA; cm^2) was obtained through the equation proposed by Heymsfield et al. [15], which depends on sex and uses arm circumference and triceps skinfold thickness.
3. Calf circumference (CC; cm) was assessed with the patient seated, knees and ankles flexed at 90 degrees, and the largest circumference was measured using inextensible tape. Values were defined as the nearest 0.1 cm [16].

Muscle strength

Muscle strength was assessed by HGS using Jamar hydraulic hand dynamometer (Baseline, Fabrication Enterprises, Inc, Elmsford, NY, USA). Each participant was instructed to comfortably arrange the instrument in his or her hand and in sequence apply as much effort as possible with the dominant hand, while sitting with the elbow flexed at 90 degrees. Three trials were performed with a 1-min rest interval period. The first trial was discarded, functioning as a warm up and the higher HGS value of the other two trials was recorded for the study.

Sarcopenia criteria

Sarcopenia was defined as a reduction of muscle mass and strength, concomitantly. Low muscle mass was characterized when

- ASMI < 7.26 kg/m^2 for men and < 5.45 kg/m^2 for women [2].
- MUAMA < 32 cm^2 for men and < 18 cm^2 for women [11].
- CC ≤ 34 cm for men and ≤ 33 cm for women [17].

Low muscle strength was defined by HGS < 30 kg for men and < 20 kg for women [2].

Patient-Generated Subjective Global Assessment Short Form

Nutritional status was evaluated according to the Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF), available by Ottery in Pt.Goblal.org, after use permission. This tool consists of the first part of the PG-SGA SF, detecting issues on weight change (maximum score of 5), food intake (maximum score of 4), symptoms (maximum score of 24), and functional capacity (maximum score of 3). Patients were categorized as being at nutritional risk if PG-SGA SF score ≥ 9 points.

Laboratory assessments

On the study enrollment day, a single intravenous blood sample was drawn for the analysis of serum levels of albumin and C-reactive protein (CRP). Low serum albumin was diagnosed as a plasma concentration < 3.5 g/dL and high CRP with values ≥ 10 mg/dL.

Survival

Patient OS was defined by the time interval, in days, between the baseline date of the study and the date of death (of any cause). Patients who remained alive after 90 d were censored.

Statistical analysis

We processed statistical analysis using the software SPSSs version 21.0 (SPSS, Chicago, IL, USA). Kolmogorov–Smirnov test was performed to assess distribution symmetry. Descriptive statistics [count/frequency (%), means \pm standard deviation (SD), or median and interquartile ranges (IQR), as appropriate] were used to describe patient characteristics and prevalence of sarcopenia.

Differences in nutritional status between patients with and without sarcopenia based on different muscle measurements were evaluated using χ^2 test for categorical variables and independent *t* test for continuous variables.

Kaplan–Meier method was used to illustrate survival curves and the log-rank test to compare OS according to the presence of sarcopenia (by ASMI, MUAMA,

Table 1

Characteristics of advanced cancer patients treated at a palliative care unit in the city of Rio de Janeiro, Brazil (N = 334)

Variables	
Age (y)*	63 (55–72)
Age $\geq 60^{\dagger}$ (%)	208 (62.3)
Female [†] (%)	183 (54.8)
Types of tumor [†] (%)	
GI tract	104 (31.1)
Gynecologic	58 (17.4)
Head and neck	43 (12.9)
Lung	37 (11.1)
Breast	29 (8.7)
Others	63 (18.9)
Distant metastasis [†]	222 (66.5)
Comorbidities [†] (%)	
SAH	87 (26)
DM	32 (9.6)
KPS (30–40) [†]	115 (34.4)
PG-SGA SF (global score)*	14 (8–19)
PG-SGA SF (≥ 9 points) [†]	255 (74.6)
BMI (kg/m^2) [‡]	22.1 (± 5.2)
BMI (< 20 kg/m^2) [†]	129 (38.6)
Albumin (g/dL)*	3.4 (2.9–3.9)
Reduced muscle mass [†] (%)	
ASMI (kg/m^2)	287 (89.9)
MUAMA (cm^2)	108 (32.3)
CC (cm)	228 (68.3)
Reduced HGS [†] (%)	235 (70.4)

ASMI, appendicular skeletal muscle mass index; BMI, body mass index; CC, calf circumference; DM, diabetes mellitus; GI, gastrointestinal; HGS, handgrip strength; KPS, Karnofsky Performance Status; MUAMA, midupper arm muscle area; PG-SGA SF, Patient-Generated Subjective Global Assessment Short Form; SAH, systemic arterial hypertension

*Median/interquartile ranges (p25–p75).

[†]Number of observation (frequency)

[‡]Mean (\pm SD)

Table 2
Differences in nutritional characteristics between sarcopenia groups defined by different muscle measurements in advanced cancer patients treated at a palliative care unit in the city of Rio de Janeiro, Brazil (N = 334)

Variables	ASMI		P-value	MUAMA		P-value	CC		P-value
	Sarcopenia (n = 219)	No sarcopenia (n = 115)		Sarcopenia (n = 90)	No sarcopenia (n = 244)		Sarcopenia (n = 177)	No sarcopenia (n = 157)	
PG-SGA SF ≥ 9 points*	182 (54.5)	66 (19.8%)	<0.001	78 (23.4)	170 (50.9)	0.001	147 (44)	101 (30.2)	<0.001
WL $\geq 5\%$ in 6 Month*	142 (60.9)	63 (27)	0.016	67 (28.8)	138 (59.2)	0.034	119 (51.1)	86 (36.9)	0.009
BMI (kg/m ²) [†]	20.8 (\pm 4.4)	24.6 (\pm 5.8)	0.004	18.0 (\pm 3)	23.6 (\pm 5)	<0.001	19.7 (\pm 3.6)	24.8 (\pm 5.4)	<0.001
Albumin <3.5 g/dL*	140 (41.9)	37 (11.1%)	<0.001	66 (19.8)	111 (33.2)	<0.001	117 (35)	60 (18.0%)	<0.001

ASMI, appendicular skeletal muscle mass index; BMI, body mass index; CC, calf circumference; MUAMA, midupper arm muscle area; PG-SGA SF, Patient-Generated Subjective Global Assessment Short Form; WL, weight loss

Bold shows the statistical significance of differences.

*Number of observation (frequency %); χ^2

[†]Mean (\pm SD); independent t test.

and CC, respectively). In addition, the Cox proportional hazard model was used to assess hazard ratios (HRs) and confidence interval (CI) of prognostic factors. Adjustments were made in multiple Cox regression analysis for age ≥ 60 , female sex, gastrointestinal tract tumor, KPS 30% to 40%, CRP >10 mg/L, and PG-SGA SF score ≥ 9 . Statistical significance was set at $P < 0.05$.

Results

In all, 334 patients were included in this study. The majority were women (54.8%) with an average age of 63 y (IQR, 55–72). Table 1 describes the overall characteristics of patients, including nutritional status and laboratory markers. According to ASMI, MUAMA, and CC, low muscle mass was present in 89.9%, 32.3%, and 68.3% of patients, respectively. Low muscle strength was prevalent in 70.4% of the sample. The prevalence of sarcopenia varied from 27% to 65%, according to the diagnostic method.

At the end of the follow-up period, 127 (38%) patients were alive. The OS median was 60 (IQR, 30–131) days for the entire group.

Sarcopenia was significantly associated with worse nutritional status assessed by different parameters (WL $\geq 5\%$ in 6 mo, serum albumin <3.5 g/dL, and PG-SGA SF score ≥ 9), except for MUAMA, in which the presence of poor nutritional status by PG-SGA SF, weight loss, and serum albumin was higher among non-sarcopenic individuals. Furthermore, BMI average was significantly lower for sarcopenic patients than for non-sarcopenic patients for all muscle mass parameters (Table 2).

The survival curves are in Figure 1. Patients considered sarcopenic by MUAMA (43 versus 67 Days, $P < 0.001$), CC (44 versus 77 Days, $P < 0.001$), and ASMI (48 versus 75 Days, $P < 0.001$) had significantly lower OS compared with the non-sarcopenic group. In addition, in patients classified with nutritional risk according to the PG-SGA SF score, sarcopenia by MUAMA (38 versus 62 Days, $P < 0.001$), CC (43 versus 75 d, $P < 0.001$), and ASMI (44 versus 74 d, $P < 0.001$) were significantly associated with reduced survival rates (data not shown).

In the Cox proportional hazard models (Table 3), the univariate analysis showed a higher HR for mortality in the groups with sarcopenia, for the three different measurements, but in multivariate adjusted analysis, only sarcopenia by MUAMA (hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.12–2.18) and CC (HR, 2.00; 95% CI, 1.45–2.76) remained significant.

Discussion

The present study investigated the association of low muscle mass and strength combined (true sarcopenia), defined by different methods of muscle mass assessment, with nutritional status and OS. Three different muscle mass measurement techniques were

used, namely, CC, MUAMA, and ASMI. These methods were selected because they are reproducible and easily incorporated in the clinical routine. We showed that regardless of the method, patients considered sarcopenic had significantly lower OS.

Sarcopenia, a concept reflecting the degenerative low lean body mass (mostly muscle), is an objective indicator of cancer cachexia [6]. It is important to note that most published studies evaluating the association of sarcopenia with the OS classified sarcopenia simply by low skeletal muscle mass, which would be better designated as muscle atrophy [11]. Although it is a nutritionally related condition, it is a different disorder from diseases related to malnutrition, which have been defined as conditions that result from the activation of systemic inflammation by an underlying disease such as cancer [6].

The results of the present study demonstrated that patients with sarcopenia classified by the three different methods to assess muscle mass had lower survival curves than their respective groups. Some studies in patients with advanced cancer corroborate our findings. A study with patients receiving neoadjuvant treatment for locally advanced esophageal cancer showed the median OS rates for patients with sarcopenia was significantly reduced compared with patients without sarcopenia [8], similar to the works of Fukushima et al. [9] and Bronger et al. [18].

Concerning nutritional status, patients with sarcopenia, more frequently presented the highest PG-SGA SF score, greater weight loss, and lower BMI and serum albumin levels, than respective groups, confirming that sarcopenia served as a reflection of poor nutritional status. Corroborating these findings, Zhou et al. [19] conducted a prospective study with patients with gastric cancer and also found that sarcopenia was associated with lower BMI, serum albumin levels, and hemoglobin levels, and higher nutritional risk screening 2002 scores. Similarly, Kim et al. [20] evaluated patients with small cell lung cancer and demonstrated that sarcopenia determined by routine chest CT was found to be significantly associated with lower BMI, serum albumin levels, and weight.

The present results indicated that higher mortality ratios in the 90-d follow-up period were observed for low CC and low MUAMA, but not for low ASMI. The results suggest that two of the three methods considered in this study can predict mortality in patients with advanced cancer. Our primary hypothesis is that low ASMI does not correlate with survival because the proportion of patients classified as sarcopenic was overestimated when defined by this muscle mass measurement, as Baumgartner's prediction equation takes into account HGS and the fact that 70.4% of the sample was classified as dynapenic. Thus, non-sarcopenic individuals were possibly misclassified as sarcopenic according to this method. In addition, although Baumgartner's prediction equation has been extensively used to estimate muscle mass in adults and has been

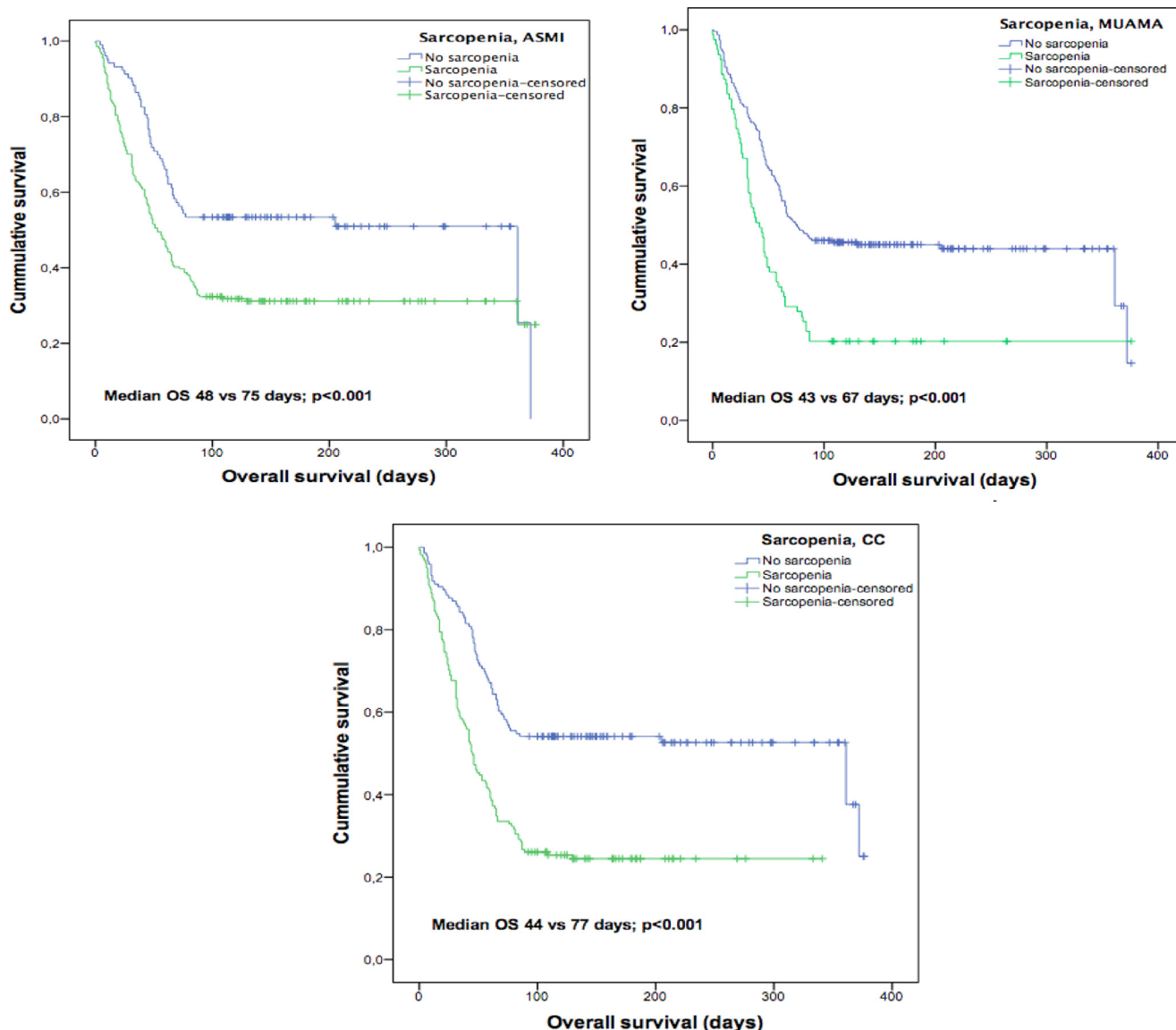


Fig. 1. Comparison of survival curves among patients with and without sarcopenia by ASMI, MUAMA, and CC (N = 334). ASMI, appendicular skeletal muscle mass index; CC, calf circumference; MUAMA, mid-upper arm muscle area; OS, overall survival. P-value refers to log-rank test.

Table 3

Multiple Cox regression analysis of the association between sarcopenia with different muscle measurements and survival in advanced patients treated at a palliative care unit in the city of Rio de Janeiro-Brazil (N = 334)

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)*	P-value
Sarcopenia, ASMI	1.97 (1.44–2.69)	<0.001	1.34 (0.94–1.92)	0.060
Sarcopenia, MUAMA	1.93 (1.45–2.58)	<0.001	1.57 (1.12–2.18)	0.007
Sarcopenia, CC	2.18 (1.64–.91)	<0.001	2.00 (1.45–2.76)	<0.001

ASMI, appendicular skeletal muscle mass index; CC, calf circumference; MUAMA, midupper arm muscle area

*Adjusted for age ≥60 y, female sex, gastrointestinal tract tumor, Karnofsky-Performance Status 30% to 40%, C-reactive protein >10 mg/L, and Patient-Generated Subjective Global Assessment Short Form score ≥9.

validated for this application in older individuals, additional studies are needed to validate the use of this method in patients with advanced cancer.

Related studies that evaluated the association between survival and sarcopenia defined it as the concurrent loss of muscle mass and strength, occurring in patients with cancer but not in the advanced stage of the disease. For example, Huang et al. [21], in a

prospective study of elderly patients who underwent curative gastrectomy for gastric cancer, showed that sarcopenia, with muscle mass evaluated by CT, was an independent risk factor for 1-y mortality. Likewise, sarcopenia with muscle mass, determined by ASM and assessed using multifrequency bioelectrical impedance, was a significant predictor of OS in patients with esophageal cancer who underwent esophagectomy [10].

Regarding anthropometric measurements, we did not find studies assessing the relationship between survival and sarcopenia using these methods with cancer patients.

Nevertheless, Tartari et al. [22] evaluated MUAMA as a potential prognostic factor in patients with stage IV non-small cell lung cancer and found significantly lower OS for those categorized as having depleted muscle mass, and Wallengren et al. [23] demonstrated that low muscle mass by MUAMA was associated with adverse quality of life, function, symptoms, and prognostic of survival in palliative care patients. In addition, Bourdel-Marchasson et al. [24] identified that calf circumference <31 cm was found to be associated with 1-y mortality in a prospective cohort of 606 patients with cancer (>70 y of age).

Accurate methods, such as CT and DXA, were not used to estimate muscle mass, disallowing a more precise and comprehensive evaluation of sarcopenia, which may be a limitation of the present study. The strength of the present study, on other hand, is the low-cost and user-friendly muscle mass measuring techniques applied as diagnostic criteria for sarcopenia. These methods are required for screening, particularly in developing countries, because the use of gold standard methods are not financially feasible on a large scale.

Conclusion

The results of the present study demonstrated that sarcopenia is a relevant indicator for poorer prognosis. The low muscle mass diagnosed by MUAMA and CC were the best prognostic method to estimate OS in patients with advanced cancer.

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