ARTICLE

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Nutrition in acute and chronic diseases

Nutritional status assessed by Patient-Generated Subjective Global Assessment is associated with toxicity to chemoradiotherapy in women with cervical cancer: a prospective study

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BACKGROUND: Patient-generated subjective global assessment (PG-SGA), a validated tool for nutritional assessment, has been associated with worse clinical outcomes in patients with cancer. However, studies assessing its relationship in chemoradiotherapy outcomes are scarce. The study aimed to determine the prevalence of malnutrition according to PG-SGA and its association with the incidence of toxicity to chemoradiotherapy treatment in women with cervical cancer.

METHODS: In a single-centre prospective observational study, we enrolled 391 women with locally advanced cervical cancer. Patients were assessed on the day of their first chemotherapy infusion, when nutritional status was evaluated by the PG-SGA form and anthropometric measurements. Sociodemographic and clinical data were also collected. Toxicity to chemoradiotherapy was assessed weekly and toxicity-induced modification of treatment (TIMT) was defined as any serious adverse event that resulted in treatment delay, interruption, or dose reduction. Multivariate mixed-effects Poisson and Logistic regression models were performed to identify the factors contributing to the outcome number of adverse events ≥ grade 3 and TIMT, respectively.

RESULTS: Malnutrition was found in 47.6% of the population. Roughly 1/3 had TIMT and 54.2% experienced at least one symptom ≥grade 3. In the adjusted models, PG-SGA B and C, as well as the score ≥9 were independent predictors of the number of toxicity events ≥grade 3 and higher incidence of TIMT.

CONCLUSIONS: PG-SGA may represent an important assessment tool to predict toxicity outcomes in women with cervical cancer, besides being considered a simple, fast, and low-cost tool, which allows early nutritional care.

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INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide. In developing countries, more than 60% of these cases are diagnosed in advanced stages [1], for which the standard protocol is the combination of pelvic radiotherapy with chemotherapy [2]. A high incidence of side effects is observed during the treatment, which in turn favors reduced food intake and weight loss [3, 4].

Malnutrition before the diagnosis is common among patients with gynecologic cancer and may occur in both under- or overweight patients [5, 6]. Therefore, the early identification of changes in nutritional status is crucial to providing timely nutritional support. The Patient-Generated Subjective Global Assessment (PG-SGA) is a subjective low-cost and easy-to-use tool validated for diagnosing and grading the severity of malnutrition in patients with cancer [7, 8]. It has high sensitivity and specificity when compared to other subjective instrument [9].

PG-SGA has been widely used to assess nutritional status among patients with gynecological cancer [6, 10, 11], and it has also been associated with unfavorable cancer outcomes [10–12]. However, there are few studies that investigate PG-SGA as a predictor of chemoradiotherapy toxicities [13–15]. Previous studies have several methodological limitations, such as the retrospective design, absence of sample size estimation and adjusted analysis. Also, other studies do not consider the presence of comorbidities nor the concomitant use of drugs for symptoms management as potential confounding factors [16, 17].

From the above, the present study aimed to determine the prevalence of malnutrition and its association with the incidence of toxicity to chemoradiotherapy treatment in women with cervical cancer.

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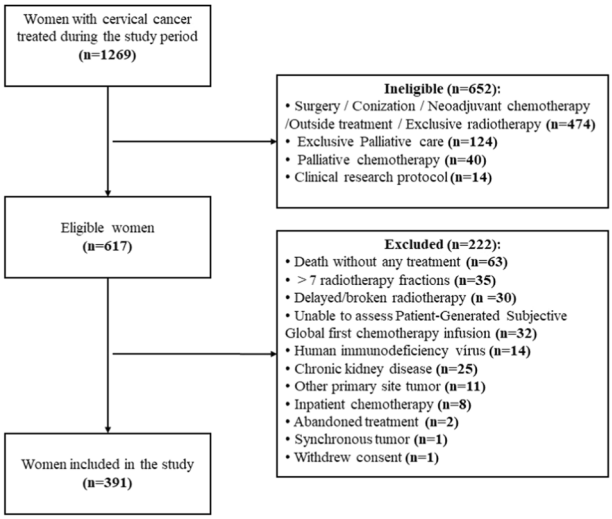

Fig. 1 Flowchart of selection of study patients.

MATERIALS AND METHODS

Study setting and participants

This is a single-centre prospective observational study that enrolled newly diagnosed women with locally advanced cervical cancer undergoing combined treatment with cisplatin and radiotherapy in a reference institute for the treatment of gynecological cancer in Brazil – Instituto Nacional de Câncer José Alencar Gomes da Silva. The study was conducted according to the ethical standards described in the 2013 Helsinki Declaration, and was approved by the institution´s Research Ethics Committee (CAAE No. 466.070/2013). A written informed consent was obtained from all patients.

Eligible participants included adult women (≥18 years) diagnosed with locally advanced cervical cancer confirmed by histopathology and treated consecutively between April 2018 and March 2021. Exclusion criteria were: patients with synchronous tumors, liver disease, chronic renal dysfunction, human immunodeficiency virus-infected patients, and those who underwent more than seven fractions of radiotherapy before starting the first infusion of chemotherapy (Fig. 1).

Sample size

The sample size was estimated based on the incidence rate of toxicity-induced modification of treatment (30%) observed in our institution for women with cervical cancer treated with cisplatin and radiotherapy, and the prevalence of malnutrition according to PG-SGA (47.2%) previously reported in this population [18] Assuming the frequency of such event in the exposed and unexposed (24% and 45%, respectively), the minimum number of patients to be enrolled, considering an alpha error of 5% and beta error of 20%, was 339.

Treatment plan

The treatment protocol of the institution consists of weekly cisplatin-based chemotherapy, with a dose of 40 mg/m^2 (maximum 70 mg), for 5 or 6 consecutive weeks, concomitant with pelvic radiotherapy, five days/week, up to 25 sessions or total dose of 45 Gy.

Data collection

Patients were invited to participate on the day of their first chemotherapy infusion. The weekly interviews were face-to-face and occurred along with the 5 to 6 weeks of treatment, except when interrupted. In the first interview, the trained researchers collected data regarding sociodemographic and clinicopathological characteristics. The presence of symptoms as well as drugs used for symptoms management or comorbidities control before first treatment were also assessed. Finally, nutritional status was assessed with anthropometric (weight and height) and PG-SGA tool. The subsequent interviews consisted of the assessment of treatment toxicity and use of drugs for symptoms management or comorbidities control (Fig. 2).

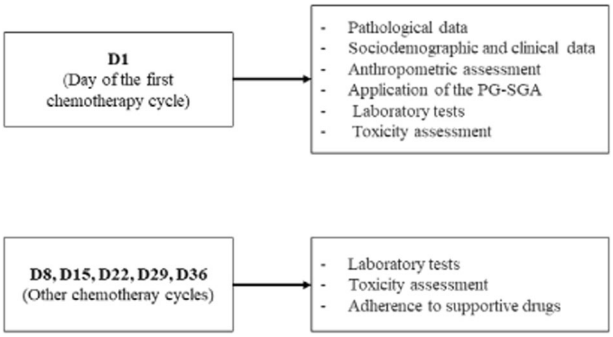

Fig. 2 Flowchart of data collection.

Sociodemographic, clinicopathological, and cancer treatment data

Data related to clinical and cancer treatment history were collected from the electronic medical records: pre-existing comorbidities, histopathological tumor report, as well as reasons for delay or treatment interruptions.

PG-SGA assessment

The Brazilian-validated version of PG-SGA [19] was evaluated using the standard boxes 1 to 4 and the worksheets, which include recent weight history, changes in food intake, symptoms with nutritional impact, activities and function capacity, as well as presence of disease and relation to nutritional requirements, metabolic stress and physical examination to detect loss/deficit of subcutaneous fat, muscle, and the presence of ascites or edema.

Patients were then classified as well-nourished (A), moderately malnourished or suspected malnutrition (B), and severely malnourished (C). We also considered the score ≥9 as a cutoff, since it indicates severe malnutrition symptoms control and urgent need for nutrition intervention according to the nutritional screening recommendations provided by the tool [13].

All patients received nutritional counseling before treatment onset according to the institution's protocol. Furthermore, patients identified as at nutritional risk were referred to a registered dietitian for appropriate nutritional intervention. Due to the observational design of the study, follow-up data on anthropometric changes after nutritional intervention were not considered in the analysess.

Pharmacotherapy and evaluation of drug interaction

A previous analysis of the medications dispensed at the outpatient pharmacy during the treatment period was performed and classified according to the Anatomical Therapeutic Chemical system [20]. Then drug-drug interaction was assessed by analyzing the drugs used for comorbidities treatment (i.e. antihypertensives and antiglycemics) or symptoms management (i.e. antiemetics, analgesics, and laxatives) before each chemotherapy cycle. The database IBM Watson Micromedex and Cerner Multum™ was used to identify if any medication interacted pharmacologically with cisplatin and no relevant severe drug-drug interactions were found [21].

Toxicity-related events, medications for symptoms management, and follow-up

Toxicity to chemoradiotherapy treatment was assessed weekly and graded according to the United States National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE/NCI), version 4.0 [22]. Toxicity-induced modification of treatment (TIMT) has been used to refer to any toxicity that resulted in delayed treatment, dose reduction, discontinuation of any given chemotherapy, and/or permanent discontinuation due to toxicity when related to the effects of chemotherapy toxicity [23].

The list of medications prescribed during the treatment was obtained through the patient´s recipes before each chemotherapy infusion. In the weekly interviews, patients were requested to inform whether they used or not the medications prescribed for symptoms and comorbidities control.

The standard protocol for nausea and vomiting prevention in the institutional routine is ondansetron and dexamethasone for three consecutive days after chemotherapy infusions. We considered adherence to

Table 1. Sociodemographic, clinical characteristics, and nutritional status of the population ($n = 391$).

Variables	Total (%)
Age (years)	
<65	354 (90.5)
≥65	37 (9.5)
Self-declared skin color	
Caucasian	136 (34.8)
Not Caucasian	255 (65.2)
Years of study	
0 to 8	161 (41.2)
9 to 12	195 (49.9)
>12	35 (8.9)
Income class[a]	
A/B	0 (0.0)
C	23 (5.9)
D	75 (19.2)
E	293 (74.9)
Presence of comorbidity	
No	253 (64.7)
Yes	138 (35.7)
Types of comorbidities	
SAH	114 (29.2)
DM	33 (8.4)
Heart disease	6 (1.5)
Others[b]	17 (4.3)
Histological Type	
Adenocarcinoma	52 (13.3)
Squamous cell carcinoma	338 (86.7)
FIGO staging[c]	
I	44 (11.3)
II	63 (41.8)
III	171 (43.8)
IV	7 (1.8)
N/I	5 (1.3)
BMI (kg/m²)	
Underweight	21 (5.4)
Normal weight	127 (32.5)
Overweight	126 (32.2)
Obesity	117 (29.9)
PG-SGA	
Well-nourished (A)	205 (52.4)
Suspected/Moderate malnutrition (B)	167 (42.7)
Severely malnutrition (C)	19 (4.9)
PG-SGA score (points)[d]	
<9	249 (63.7)
≥9	142 (36.3)

[a]Average monthly household income: Class A: >15 x minimum wage, Class B: 5–15 x minimum wage, Class C: 3–5 x minimum wage, Class D: 1–3 x minimum wage, Class E: <1 x minimum wage (IBGE, 2016); *SAH* Systemic arterial hypertension, *DM* Diabetes Mellitus; [b]Other comorbidities: hypothyroidism ($n = 5$), dyslipidemia ($n = 5$), hyperthyroidism ($n = 3$), depression ($n = 2$), hepatic steatosis ($n = 1$) and venous insufficiency ($n = 1$); [c]*FIGO* Staging according to the International Federation of Gynecology and Obstetrics; [d]PG-SGA Scores ≥9 indicate urgent need for nutrition intervention; N/I, Not informed, BMI, Body Mass |Index; PG-SGA, Patient-Generated Subjective Global Assessment.

the protocol when patients reported the use of the two medications prescribed for three consecutive days. Adherence or non-adherence were classified per cycle.

The use of pain and diarrhea medications were also recorded per cycle since they interfere with the occurrence and severity of symptoms. Regarding pain medications, the use of two or more analgesics from the opioid class and/or non-steroidal anti-inflammatory drugs were considered relevant for confounding adjustment. We excluded from the analysis the use of dipyrone, which is prescribed for fever cases. Other medications for symptom management, such as constipation and neuropathy were used by a small number of patients and were not associated with the study outcomes.

Statistical analysis

The collected data were analyzed with the aid of the statistical program Statistical Package for Social Sciences, version 25.0, SPSS (Chicago, USA). The Kolmogorov-Smirnov test was applied to evaluate the symmetry of the distribution curve of the variables. Normal distribution was found for all numerical variables in the study, except for the number of toxicity events greater than or equal to grade 3, which followed a Poisson distribution. Measures of central tendency and dispersion were calculated for continuous variables and proportions for categorical variables. Associations between categorical variables were calculated by the chi-square (χ^2) test or Fisher's exact test.

Independent variables tested in univariate analysis were: age ≥65 y (vs < 65 y), body mass index (BMI) classification as underweight and overweight/obese (vs normal weight), staging III/IV (vs I/II), DM (yes vs no), HAS (yes vs no), PG-SGA score ≥9 points (vs < 9 points), PG-SGA B and C (vs A), use of 2 or more pain protocol medications (yes vs no, per cycle), use of diarrhea protocol medications (yes vs no, per cycle), and adherence to nausea and vomiting protocol (vs nonadherence, per cycle).

Multivariate Mixed-effects Poisson Regression models were performed to identify possible factors contributing to the outcome number of adverse events ≥grade 3. The clinical variables that made up the models were selected according to their significance in the univariate analysis, when $p < 0.20$: age ≥65 y (vs < 65 y), BMI classification as underweight and overweight/obese (vs normal weight), PG-SGA score ≥9 points (vs < 9 points), PG-SGA B and C (vs A), use of 2 or more pain protocol medications (yes vs no, per cycle), use of diarrhea protocol medications (yes vs no, per cycle), and adherence to nausea and vomiting protocol (vs nonadherence, per cycle).

Multivariate Mixed-effects Logistic Regression models were performed to identify possible factors contributing to the outcome toxicity-induced modification of treatment. The independent variables that presented $p < 0.2$ in the univariate analysis were: age ≥65 y (vs < 65 y), staging III/IV (vs I/II), Systemic Arterial Hypertension diagnosis (vs no), BMI classification as underweight and overweight/obese (vs normal weight), PG-SGA B and C (vs A), PG-SGA score ≥9 points (vs < 9 points), use of 2 or more pain protocol medications (yes vs no, per cycle), use of diarrhea protocol medications (yes vs no, per cycle), and adherence to nausea and vomiting protocol (vs nonadherence, per cycle). The results of the univariate and multivariate analyses are presented as relative risk (RR) and 95% confidence interval (CI). Mixed-effects models were analyzed using R, version 04.2 (package lme4), with chemotherapy cycles as the clustering variables.

For all analyses, a p-value <0.05 was considered statistically significant.

RESULTS

The study included 391 women with cervical cancer, with a mean age of 47.0 (±12.6) years, mostly with low income and advanced cancer stage (III/IV). Regarding nutritional status, although most patients were overweight or obese before treatment onset, we identified by PG-SGA that 47.6% had some degree of malnutrition (Table 1). Besides, the PG-SGA identified that 22% had severe weight loss (≥10% in 6 months), almost half of the patients had decreased usual intake, and had moderate or severe impairment in functional capacity. Regarding the symptoms that interfered with the patients' food intake, the most prevalent were inappetence, nausea, vomiting, constipation, dysgeusia, and early satiety (Supplementary Table 1).

Treatment characteristics and their associations with PG-SGA are described in Table 2. Most patients had at least one toxicity

Table 2. Association between the Patient-Generated Subjective Global Assessment classification and its score with the characteristics of chemotherapy treatment.

Variables	PG-SGA classification				PG-SGA score		
	N (%) Total = 391	A (*n* = 205)	B/C (*n* = 186)	*p**	<9 points (*n* = 249)	≥9 points (*n* = 142)	*p**
Number of cycles performed							
<5 cycles	84 (21.5)	31 (15.1)	53 (28.5)	0.001	34 (13.7)	50 (35.2)	<0.001
≥5 cycles	307 (78.5)	174(84.9)	133 (71.5)		215 (86.3)	92 (64.8)	
	Treatment delay[a]						
No	341 (87.2)	179 (87.3)	162 (87.1)	0.948	217 (87.1)	124 (87.3)	0.960
Yes	50 (12.8)	26 (12.7)	24 (12.9)		32 (12.9)	18 (12.7)	
	Treatment suspension[b]						
No	310 (79.3)	174 (84.9)	136 (73.1)	0.004	215 (86.3)	95 (66.9)	<0.001
Yes	81 (20.7)	31 (15.1)	50 (26.9)		34 (13.7)	47 (33.1)	
Dose	**adjustment**[c]						
No	386 (98.7)	204 (99.5)	182 (97.8)	0.144	247 (99.2)	139 (97.9)	0.268
Yes	5 (1.3)	1 (0.5)	4 (2.2)		2 (0.8)	3 (2.1)	
	Toxicity ≥ grade 3[d]						
No	179 (45.8)	119 (58.0)	60 (32.3)	<0.001	139 (55.8)	40 (28.2)	<0.001
Yes	212 (54.2)	86 (42.0)	126 (67.7)		110 (44.2)	102 (71.8)	
TIMT[e]							
No	267 (68.3)	152 (74.1)	115 (61.8)	0.009	188 (75.5)	79 (55.6)	<0.001
Yes	124 (31.7)	53 (25.9)	72 (38.2)		61 (24.5)	63 (44.4)	

[a]Delay in treatment with a delay of at least 7 days, associated with medical report with the reason for the delay (toxicity); [b]Permanent discontinuation due to toxicity; [c]Need for ≥10% reduction of cisplatin from the initial dose; [d]Presence of any symptoms with toxicity ≥grade 3 according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE/NCI); TIMT, Toxicity-induced modification of treatment; [e]Any toxicity that resulted in delay, dose adjustment, or discontinuation of treatment. PG-SGA, Patient-Generated Subjective Global Assessment. *p** – Chi-square test.

event ≥grade 3, with the highest incidence being fatigue, pain, nausea, hyporexia, dysgeusia, asthenia and diarrhea (Supplementary Table 2). Moreover, about one-third had TIMT, represented by the need for dose adjustment, delay, or suspension of treatment. The main causes related to TIMT were worsening performance status (87.7%), hematologic toxicity (71.6%), ototoxicity (55.6%), and altered renal function (19.8%).

Both PG-SGA classification B and C, as well as the score ≥9, were significantly associated with fewer cycles of chemotherapy performed, treatment discontinuation, toxicity events ≥ grade 3, and TIMT (Table 2). All of the domain's boxes, except body weight change, were associated with toxicity ≥ grade 3. Body weight change, functional capacity impairment, and altered physical exam were associated with treatment discontinuation. In addition, body weight change and functional capacity impairment were associated with TIMT (Table 3).

In the adjusted multivariate Mixed-effects Poisson Regression models (Table 4), both score ≥9 points and the classification of suspected/moderate malnutrition and severe malnutrition (PG-SGA B and C) were associated with the number of toxicity events ≥grade 3. Being underweight (BMI < 18.5 kg/m2) and using medications for pain control were also predictors. Furthermore, using medications for diarrhea, and adhering to the nausea and vomiting protocol were protective factors for this outcome.

In the adjusted Mixed-effects Logistic Regression models (Table 4), the score ≥9 points as well as the suspected/moderate malnutrition and severe malnutrition as classified by PG-SGA were predictors of higher incidence of TIMT. Advanced stage, Systemic Arterial Hypertension, and being underweight were also associated with increased risk for this outcome. In contrast, adherence to nausea and vomiting prevention protocol, using medications for diarrhea, as well using medications for pain control were protective factors for this outcome.

DISCUSSION

To the best of our knowledge, this is the first prospective cohort that evaluated the association between nutritional status by PG-SGA and chemoradiotherapy toxicity in cervical cancer patients. In addition to the prospective design, this study took into account confounding factors that may influence the outcomes, such as pre-existing comorbidities and the use of supportive medications for symptoms management. Cervical cancer is highly incident in Brazil [24], and because cisplatin is a widely used drug in the treatment of other cancers, future research in this area may benefit from our results [25].

Despite several studies have been reported the association between changes in body composition and worse chemotherapy outcomes in different types of cancer [26–28], such studies are based on computed tomography assessment, which requires specialized professionals, is costly, and is restricted to research [29]. Thus, reporting the association between nutritional status assessed by PG-SGA and chemotherapy outcomes are fundamental to assist health care professionals in their clinical practice.

Regardless of the high prevalence of overweight and obesity, PG-SGA identified almost 48% of the population as having any grade of malnutrition, corroborating with other studies evaluating patients with gynecological cancer [30, 31]. Also, a high prevalence of symptoms with nutritional impact was detected, such as decreased habitual intake, and impaired functional capacity, which, in turn, may contribute to unfavorable clinical outcomes. Some domains that make up the PG-SGA, such as dietary intake, functional

Table 3. Association between Patient-Generated Subjective Global Assessment domains and characteristics of chemotherapy treatment.

Variables	Weight loss**				Food intake***			Activities and function****				Physical examination			
	Not changed/ Increased	Mild weight loss	Decreased	*p**	Unchanged/ more than usual	Less than usual	*p**	Normal with no limitation	normal self/ Not feeling up to most things	Able to do little activity/ Pretty much bed ridden	*p**	No deficit	Mild deficit	Moderate/ severe deficit	*p**
Number of cycles performed															
<5 cycles	58 (19.8)	6 (17.1)	20 (31.7)	0.090	57 (18.6)	27 (32.5)	0.006	13 (12.4)	35 (20.3)	36 (31.6)	0.002	52 (18.2)	23 (28.0)	9 (37.5)	0.023
≥5 cycles	235 (80.2)	29(82.9)	43 (68.3)		250 (81.4)	56 (67.5)		92 (87.6)	137 (79.7)	78 (68.4)		233 (81.8)	59 (72.0)	15 (62.5)	
Treatment delay[a]															
No	257 (87.7)	30 (85.7)	54 (85.7)	0.877	266 (86.6)	74 (89.2)	0.544	96 (91.4)	146 (84.9)	99 (86.8)	0.283	247 (86.7)	71 (86.6)	23 (95.8)	0.426
Yes	36 (12.3)	5 (14.3)	9 (14.3)		41 (13.4)	9 (10.8)		9 (8.6)	26 (15.1)	15 (13.2)		38 (13.3)	11 (13.4)	1 (4.2)	
Treatment suspension[b]															
No	239 (81.6)	29 (82.9)	42 (66.7)	0.026	249 (81.1)	60 (72.3)	0.079	89 (84.8)	140 (81.4)	81 (71.1)	0.029	233 (81.6)	63 (76.8)	14 (58.3)	0.021
Yes	54 (18.4)	6 (17.1)	21 (33.3)		58 (18.9)	23 (27.7)		16 (15.2)	32 (18.6)	33 (28.9)		52 (18.2)	19 (23.2)	10 (41.7)	
Dose adjustment[c]															
No	291 (99.3)	35 (100)	60 (95.2)	0.026	305 (99.3)	80 (96.4)	0.033	105 (100)	168 (97.7)	113 (99.1)	0.223	282 (98.9)	81 (98.8)	23 (95.8)	0.427
Yes	2 (0.7)	0	3 (4.8)		2 (0.7)	3 (3.6)		0	4 (2.3)	1 (0.9)		3 (1.1)	1 (1.2)	1 (4.2)	
Toxicity ≥ grade 3[d]															
No	144 (49.1)	12 (34.3)	23 (36.5)	0.068	157 (51.1)	21 (25.3)	0.000	64 (61.0)	82 (47.7)	33 (28.9)	0.000	143 (50.2)	33 (40.2)	3 (12.5)	0.001
Yes	149 (50.9)	23 (65.7)	40 (63.5)		150 (48.9)	62 (74.7)		41 (39.0)	90 (52.3)	81 (71.1)		142 (49.8)	49 (59.8)	21 (87.5)	
TIMT[e]															
No	208 (71.0)	74.3 (26)	33 (52.4)	0.012	214 (69.7)	52 (62.7)	0.221	83 (79.0)	116 (67.4)	68 (59.6)	0.008	200 (70.2)	53 (64.6)	14 (58.3)	0.355
Yes	85 (29.0)	25.7 (9)	30 (47.6)		93 (30.3)	31 (37.3)		22 (21.0)	56 (32.6)	46 (40.4)		85 (29.8)	29 (35.4)	10 (41.7)	

[a]Treatment delay of at least 7 days, associated with medical report with the reason for the delay (toxicity); [b]Permanent discontinuation due to toxicity; [c]Need for ≥15% reduction in cisplatin from the initial dose; [d]Presence of any symptoms with toxicity ≥grade 3 per the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE/NCI); *TIMT* Toxicity-induced modification of treatment; [e]Any toxicity that resulted in delay, dose adjustment, or discontinuation of treatment. *PG-SGA* Patient-Generated Subjective Global Assessment. *p** –Chi-square test. **Not change/Increased weight variation: No weight loss or weight gain or 1.9% weight loss within 6 months; Mild weight loss: 2% to 4.9% loss in 1 month or 2% to 9.9% in 6 months; Decreased weight loss: Weight loss >5% within 1 month or >10% within 6 months; ***No change/Less quantity: The same thing/more than usual or the same food in lesser amount than usual; ****Significant decrease: the same food in little or very little of anything, just liquids or nutritional supplements.

Table 4. Multivariate Mixed-effects regression model for the outcomes number of adverse events ≥grade 3 and for Toxicity-induced modification of treatment in women with cervical cancer.

Models	Number of adverse events ≥ grade 3[a]		Toxicity-induced modification of treatment[b]	
	RR	CI	RR	CI
Model 1 – PG-SGA score				
PG-SGA score ≥ 9 points (vs < 9)	1.13	1.08–1.18	1.80	1.44–2.25
BMI (Classification)[c]				
Underweight (vs normal weight)	1.09	1.01–1.19	1.61	1.09–2.62
Overweight/Obesity (vs normal weight)	1.02	0.98–1.07	0.92	0.73–1.14
Systemic arterial hypertension (vs no)	0.98	0.93–1.02	1.51	1.20–1.89
Adherence to nausea and vomiting protocol (vs nonadherence, per cycle)	0.88	0.83–0.94	0.26	0.20–0.34
Diarrhea protocol (yes vs no, per cycle)	0.91	0.85–0.99	0.59	0.38–0.91
Pain protocol (yes vs no, per cycle)	1.13	1.08–1.18	0.55	0.45–0.69
Stage III/IV (vs stage I/II)	—	—	1.35	1.10–1.66
Model 2 – PG-SGA classification[d]				
PG-SGA B (vs PG-SGA A)	1.17	1.12–1.22	1.46	1.18–1.79
PG-SGA C (vs PG-SGA A)	1.23	1.11–1.36	3.21	1.81–5.69
BMI (Classification)[c]				
Underweight (vs normal weight)	0.99	0.94–1.05	1.60	1.01–2.60
Overweight/Obesity (vs normal weight)	1.02	0.96–1.07	0.94	0.76–1.18
Systemic arterial hypertension (vs no)	0.97	0.93–1.02	1.50	1.19–1.89
Adherence to nausea and vomiting protocol (yes vs no, per cycle)	0.87	0.82–0.93	0.25	0.19–0.32
Diarrhea protocol (yes vs no, per cycle)	0.90	0.82–0.98	0.57	0.37–0.87
Pain protocol (yes vs no, per cycle)	1.12	1.07–1.17	0.57	0.46–0.71
Stage III/IV (vs stage I/II)	—	—	1.37	1.11–1.67

BMI body mass index; PG-SGA, *CI* Confidence Interval; Patient-Generated Subjective Global Assessment; *RR* Relative Risk; Nausea and vomiting protocol: optimal adherence to the protocol medications with dexamethasone + ondansetron during treatment; Diarrhea protocol: use of diarrhea protocol medications to control symptoms; Pain protocol: use of 2 or more pain protocol medications. [a]Multivariate Mixed effects Poisson Regression Model; [b]Multivariate Mixed effects Logistic Regression Model; [c]According to World Health Organization (1995): normal weight 18.5–24.9 Kg/m^2, underweight <18.5 Kg/m^2, overweight/obesity ≥25.0 Kg/m2; [d]well-nourished (PG-SGA A), moderately malnourished or suspected malnutrition (PG-SGA B) and severely malnourished (PG-SGA C); All models were additionally adjusted for age (years).

capacity, and physical exam were shown to be relevant when evaluated separately, as they were associated with the occurrence of toxicity ≥grade 3 and TIMT.

In addition, PG-SGA classification and its score (≥9 points) were also associated with worse treatment outcomes, such as fewer cycles of chemotherapy performed, presence of symptoms with toxicity ≥grade 3, and TIMT. This data suggests that professionals should be aware of both the overall result conferred by PG-SGA but also acknowledge isolated domain´s changes, even if minor. Detecting these alterations before the beginning of treatment would assure early nutritional and other prehabilitation intervention plans.

Regarding multivariate Mixed-effects Poisson and Logistic Regression models, both PG-SGA score and classification were independent predictors of the increased number of toxicity events ≥grade 3 and TIMT. There is scarce evidence on the relationship between PG-SGA and chemotherapy outcomes, especially among gynecological cancers. Only one study has been conducted in patients with ovarian cancer, in which the outcome assessed was febrile neutropenia [32].

Hill and colleagues (2011), assessing PG-SGA in patients with gastrointestinal cancer, observed a greater severity of chemotherapy toxicity as the nutritional status worsened [14]. However, the authors did not adjust for confounding factors. Esfahani and colleagues (2014), evaluating patients with leukemia, found no association with the occurrence of toxicity or length of hospitalization [15]. In another study with patients with metastatic colorectal cancer, PG-SGA B and C were associated with toxicity ≥grade 2 [13]. Although comparing our results with such studies might not be the most appropriate, there are no studies similar to ours that enable a better comparison.

Besides, the totality of the literature reports is based on retrospective study design, preventing proper statistical adjustment for potential confounding factors, such as pre-existing comorbidities and the use of supportive medications during treatment. Also, in retrospective data collection, chemotherapy toxicity events are commonly obtained from medical records and are usually underreported.

Patients with cancer are more susceptible to drug-drug interactions due to the high use of medications, either for support or comorbidities control. These drug interactions can interfere with treatment response, decreasing its effectiveness or increasing chemotherapy toxicity [33, 34]. In the present study, we did not identify patients taking medications that could interfere with cisplatin. However, we did observe an association between the use of medications for pain and the highest number of toxicity events ≥grade 3. This result was expected, due to the possibility of reverse causality, since more symptomatic patients are likely to use more supportive medications.

On the other hand, the use of medications for pain and diarrhea management, as well as the adherence to nausea and vomiting prevention protocol decreased the risk for TIMT, suggesting that

the use of these medications could attenuate the adverse events caused by chemotherapy treatment and consequently reduce the incidence of treatment delay or permanent discontinuation. These associations are of paramount importance since not adjusting for these factors can generate biased results.

This study has limitations: there were cases of treatment interruption for non-clinical reasons, such as non-attendance at the hospital due to financial or social problems, as well as broken radiotherapy equipment. In these cases, we excluded the patients from the analyses, which represented a small loss in our sample (<10%).

Also, sample size was estimated considering the prevalence of any grade of malnutrition (PG-SGA B and C), since the low prevalence of severe malnutrition (PG-SGA C) found in the study were already expected. Hence, to enable a more robust result for severe malnutrition, a larger number of patients would be required. Nevertheless, we chose to show the relative risks for PG-SGA B and C separately in all multivariate regression models. Finally, PG-SGA was only assessed prior to chemoradiotherapy treatment, which prevented us from evaluating whether changes in nutritional status could impact toxicity outcomes. However, we emphasize that the treatment lasts 5 to 6 weeks, during which patients who receive dietary counseling and oral nutritional supplements, if applicable, are not expected to experience substantial changes in nutritional status. Longitudinal studies assessing PG-SGA repeatedly throughout treatment should be conducted in the future, as well as randomized controlled trials evaluating the role of nutritional intervention in reducing the negative outcomes of chemoradiotherapy.

In conclusion, the PG-SGA may be useful to predict chemoradiotherapy toxicity outcomes in women with cervical cancer, besides being considered a simple, fast, and low-cost tool. PG-SGA B and C, as well as the score ≥9 points, were associated with the reduction in the number of chemotherapy cycles performed, treatment suspension, toxicity ≥grade 3, and TIMT. In the adjusted models, PG-SGA B and C as well as the score ≥9 were independently associated with the number of toxicity events ≥grade 3 and TIMT. Considering that malnutrition was determinant for several adverse events related to chemoradiotherapy, health care professionals should focus on the early identification of vulnerable patients, allowing multimodal prevention and treatment of pre-existing symptoms that may compromise treatment efficacy.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

All authors developed the idea for this study and approved the final version of the manuscript. APM and MAA participated with the data acquisition, analysis and interpretation; wrote the article and critically reviewed it. JOM participated with the data acquisition and interpretation; wrote the article and critically reviewed it. GVC participated with substantial contributions to conception and design; participated with the data analysis and interpretation; wrote the article and critically reviewed it with important intellectual contribution.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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