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Young Women With Endometrial Cancer: A Portuguese Perspective

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Abstract

Background/Aim: Endometrial cancer (EC) is rare in premenopausal women. The aim of this study was to describe the demographic, clinical and pathological characteristics and compare survival in the light of pathological aspects of EC in young women.

Patients and Methods: We performed a retrospective observational cohort study, analyzing data from 29 women up to 45 years of age diagnosed between 2003 and 2023 at our Institution.

Results: The most common risk factor for EC was excess weight (75% of patients), followed by nulliparity (62.1%), diabetes mellitus (20.7%) and hypertension (17.2%). Twenty-seven patients were submitted to total hysterectomy and salpingo-oophorectomy, and additional procedures were performed for half of the patients, in particular lymph node staging (46.4%), omentectomy (17.9%) and debulking (7.1%). The majority of tumors were low-grade endometrioid (79.3%). In six cases (21.4%), synchronous ovarian cancer occurred. EC was staged FIGO I-II in 22 patients (75.9%) and 13 (46.4%) received adjuvant therapy. Univariate survival analysis showed worse progressive-free and overall survival in patients with high-grade endometrioid tumor (median survival and standard deviation of 39.8±24.2 *vs.* 156.3±12.7 months, p=0.001; and 56.4±28.5 *vs.* 156.3±12.7 months, p=0.009, respectively); those with lymphovascular space invasion (68.6±21.9 *vs.* 161.3±12.5 months, p=0.011; and 79.2±22,5 *vs.* 161.3±12.5 months, p=0.035, respectively) and with FIGO stages III-IV (68.1±24.9 *vs.* 146.2±15.2 months, p=0.047; and 68.1±24.9 *vs.* 152.6±14.5 months, p=0.023, respectively).

Conclusion: Excess weight is a main risk factor for EC and the most prevalent risk factor in our study. In patients with EC, lymphovascular space invasion, poor tumor differentiation and FIGO stage III-IV are important factors associated with reduced progression-free and overall survival.

Keywords: Endometrial cancer, young women, premenopausal.

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Introduction

Despite being the most common gynecological malignancy in developed countries, endometrial cancer (EC) is rare in premenopausal women, with an age standardized incidence rate of 3.27/100000. The overall incidence has been on the rise, possibly due to the increasing prevalence of obesity (1).

Risk factors for EC have been subject to a large number of studies. Well-established risk factors for EC are excess weight (2, 3), diabetes (3, 4), nulliparity (3), polycystic ovary syndrome (5, 6) and hereditary causes such as Lynch Syndrome and DNA repair-associated (BRCA) mutation (7).

One study investigated the menstrual and reproductive characteristics of 833 women newly diagnosed with EC, aged 30-69 years, and found risk of EC increased with advanced age and number of years menstruating. Other risk factors were menarche before the age of 13 years, irregular cycles, more than 7 days of menstrual bleeding, nulligravidity and induced menopause (8).

A large cohort study was published in 2023, pooling data from 13 Asian prospective cohort studies, with a total of 1,005 women diagnosed with EC. They found a significantly higher risk for EC in women with early menarche, late menopause and a low number of deliveries (9).

However, there are women without any known risk factors that are diagnosed with EC and those have been subject to several studies. Some studies investigated the possible influence of dietary and environmental factors, such as elevated vitamin C or fat intake (10), as well as exposure to cadmium, an estrogen-mimicking metal present in some food and tobacco (11), or acrylamide (12). An association of several risk factors entails a higher risk of EC (13).

EC in premenopausal women can be missed or diagnosed late, as the main symptom, namely abnormal uterine bleeding, and the main finding, endometrial thickening on ultrasound, commonly occur due to benign causes in premenopausal women. Endometrial biopsy is often not the first initiated measure, especially in the absence of further risk factors such as advanced age and excess weight (14, 15).

If diagnosed and treated early, EC has a good prognosis. Treatment depends strongly on disease staging and desire to preserve fertility. The recommended treatment by the European Society of Gynaecological Oncology for women with early-stage disease and no further childbearing wish is minimally invasive total hysterectomy with bilateral adnexectomy and sentinel lymph node biopsy. Peritoneal staging is recommended in patients with non-endometrioid carcinomas (16).

Women who have not fulfilled their family planning should be intensely studied to eliminate hereditary forms of malignancy, concurrent ovarian malignancy, and myometrial invasion. They must be comprehensively informed about the standard surgical treatment and risks associated with fertility-sparing options, despite normally positive outcomes (17).

The aim of this study was to describe the demographic, clinical and pathological characteristics and compare survival in the light of pathological aspects in women diagnosed with EC, up to the age of 45 years, treated at a tertiary oncological institute, between 1st January 2003 and 31st December 2023.

Patients and Methods

This was a retrospective observational cohort study conducted at the Department of Gynecology of the Instituto Português de Oncologia de Lisboa, in Portugal. We analyzed data from 29 women. To identify these cases, we enquired the Portuguese National Oncologic Registry for a list of all patients with EC, diagnosed between 2003 and 2023, up to the age of 45 years, who were treated at our Institution. Retrieved data included in this study were date of birth, date of first appointment, date of recurrence, date of death, body mass index, age at menarche, type of menstrual cycle, parity, comorbidities, family history, pre-operative cancer antigen 125 (CA125) level, type of surgery, histological subtype, tumor differentiation, presence of myometrial invasion, cervical invasion, invasion of the serosa, lymphovascular space invasion (LVSI), presence of synchronous ovarian cancer, International Federation of Obstetrics and

Gynecology (FIGO) 2009 staging and type of adjuvant therapy. A database was elaborated using Microsoft Office Excel LTSC Professional Plus 2021 (Redmond, WA, USA) and SPSS version 26 (IBM, Armonk, NY, USA). Descriptive and survival analyses were performed. Categorical variables are presented as frequencies and percentages and continuous variables as means or median with standard deviations or range. Normality of data distribution was checked using Shapiro-Wilk test. Analysis of progression-free (PFS) and overall (OS) survival was performed using Kaplan-Meier curves. PFS and OS were defined as the mean time in months elapsed from the first appointment at our Institution and the date of either diagnosis of recurrence or of death. Reported *p*-values are two-tailed, with values of $p \leq 0.05$ considered as significant. Data supporting this study's findings are registered in our Institution's software or physical records and are available from the corresponding author.

Results

Between 2003 and 2023, 29 women under the age of 46 years were diagnosed with EC at our center. Demographic data and clinical characteristics are shown in Table I. All women were premenopausal. Six patients (20.7%) did not have any risk factors for EC, whereas 19 (65.5%) had multiple risk factors. The most common risk factor was excess weight (75% of all patients), followed by nulliparity (62.1%), diabetes mellitus (20.7%), hypertension (17.2%) and hereditary factors (10.3%). Two patients had polycystic ovary syndrome and only one patient had early menarche. Twenty-seven (96.4%) out of all patients that underwent surgery were submitted to total hysterectomy and salpingo-oophorectomy. One patient, 39 years old, was operated outside our center for abnormal uterine bleeding, was then diagnosed postoperatively with EC and maintained her ovaries. Disease in her case was staged FIGO IA. Additional procedures were performed in half of the patients, in particular lymph node staging (46.4%), omentectomy (17.9%) and debulking (7.1%). The majority of tumors were low-grade endometrioid (79.3%). In six cases (21.4%), synchronous ovarian cancer occurred, endometrioid ovarian cancer in four cases, plus one serous and one mixed (endometrioid and serous). Twenty-two patients (75.9%) had EC staged as FIGO I-II and 13 (46.4%) received adjuvant therapy.

After evaluating descriptive statistics, we performed survival analysis using Kaplan-Meier curves (Figure 1), in order to understand the influence of tumor characteristics on survival. The results are displayed in Table II and showed significantly shorter progression-free and overall survival in patients with high-grade endometrioid tumor (39.8±24.2 *vs.* 156.3±12.7 months, $p=0.001$; and 56.4±28.5 *vs.* 156.3±12.7 months, $p=0.009$, respectively), presence of LVSI (68.6±21.9 *vs.* 161.3±12.5 months, $p=0.011$; and 79.2±22.5 *vs.* 161.3±12.5 months, $p=0.035$, respectively) and FIGO stages III-IV (68.1±24.9 *vs.* 146.2±15.2 months, $p=0.047$; and 68.1±24.9 *vs.* 152.6±14.5 months, $p=0.023$, respectively). Variables such as elevated pre-surgical CA125 and cervical invasion, although showing a tendency to worse survival, were not statistically significant.

Discussion

Cancer is traditionally associated with advanced age. EC in particular is rarely suspected in premenopausal women and abnormal uterine bleeding may not prompt immediate evaluation, especially in the absence of additional risk factors. Six of our patients did not have any risk factors for EC. Excess weight was present in 75% of our patients, with a mean body mass index of 31.8±7.6 kg. A large study including almost 14,000 women with EC identified excess weight as the most important risk factor for EC, independent of age (13). Approximately one-fifth of our patients had irregular menstrual cycles and 62.1% were nulliparous. Excess weight, menstrual abnormalities and nulliparity are well-established risk factors for EC and well documented in literature (8, 9, 13, 15, 18-21). In normal-weight women, hormonal factors seem to play an important role for the development of EC, with one study demonstrating high rates of nulliparity, infertility and menstrual cycle irregularities in affected women (22).

Table I. *Clinical characteristics, type of surgery and pathology results for study patients with endometrial cancer (EC) (n=29).*

Clinical characteristics		Value
Age at first appointment, years	Median (range)	40 (28-45)
Follow-up, months	Mean±SD	57.6±47.9
BMI, kg/m^{2*}	Mean±SD	31.8±7.6
Age at menarche, years*	Median (range)	12 (6-19)
Menstrual cycle, n (%)*	Regular	15 (78.9)
	Irregular	3 (15.8)
	Amenorrhea	1 (5.3)
Nulliparity, n (%)	Yes	18 (62.1)
Comorbidities, n (%)	BMI >25 kg/m^{2*}	21 (75)
	Diabetes	6 (20.7)
	Hypertension	5 (17.2)
	PCOS	2 (6.9)
	Family history of EC	2 (6.9)
	Lynch Syndrome	1 (3.4)
	BRIP1 mutation	1 (3.4)
Presentation, n (%)*	Abnormal uterine bleeding	21 (77.8)
	Incidental ultrasound finding	6 (22.2)
Pre-operative CA125, n (%)*	<35 U/l	14 (60.9)
	≥35 U/l	9 (39.1)
Type of surgery, n (%)**	TAH+bilateral salpingo-oophorectomy	27 (96.4)
	TAH+bilateral salpingectomy	1 (3.6)
Additional procedures, n (%)	Lymph node staging	13 (46.4)
	Omentectomy	5 (17.9)
	Debulking	2 (7.1)
Pathological characteristics		
Histological subtype, n (%)	Low-grade endometrioid (grade 1-2)	23 (79.3)
	High-grade endometrioid (grade 3)	5 (17.2)
	Serous	1 (3.4)
Myometrial invasion, n (%)	None	3 (10.7)
	<50%	16 (57.1)
	≥50%	9 (32.1)
Cervical invasion, n (%)	Yes	6 (21.4)
LVSI, n (%)	Yes	9 (32.1)
Synchronous ovarian cancer, n (%)	Low-grade endometrioid (grade 1-2)	4 (66.7)
	Mixed, grade 1 endometrioid and serous	1 (16.7)
	Serous	1 (16.7)
FIGO 2009 staging, n (%)	I	20 (69.0)
	II	2 (6.9)
	III	6 (20.7)
	IV	1 (3.4)
Adjuvant therapy, n (%)	CTx only	6 (21.4)
	CTx+pelvic radiation+brachytherapy	2 (7.1)
	CTx+pelvic radiation	2 (7.1)
	Pelvic radiation+brachytherapy	1 (3.6)
	Pelvic radiation only	1 (3.6)
	Brachytherapy only	1 (3.6)

BMI: Body mass index; BRIP1: BRCA1-interacting protein 1; CA: cancer antigen; CTx: chemotherapy; LVSI: lymphovascular space invasion; PCOS: polycystic ovary syndrome; TAH: total abdominal hysterectomy. *Missing values due to incomplete data: BMI: 1; age at menarche: 6; menstrual cycles: 10; presentation: 2; pre-operative CA125: 6; tumor grading: 1; presence of synchronous ovarian cancer: 2. **One patient had only palliative treatment and one other only had total hysterectomy for abnormal uterine bleeding, during which EC was an incidental finding.

Six of our patients (21.4%) had synchronous ovarian cancer. This is consistent with a study published by Walsh *et al.* in 2005, which found synchronous ovarian malignancy in 22.5% of 102 young women with EC (23). In a study conducted in 2018 by Li *et al.*, six out of 144 premenopausal patients aged ≤45 years presented with

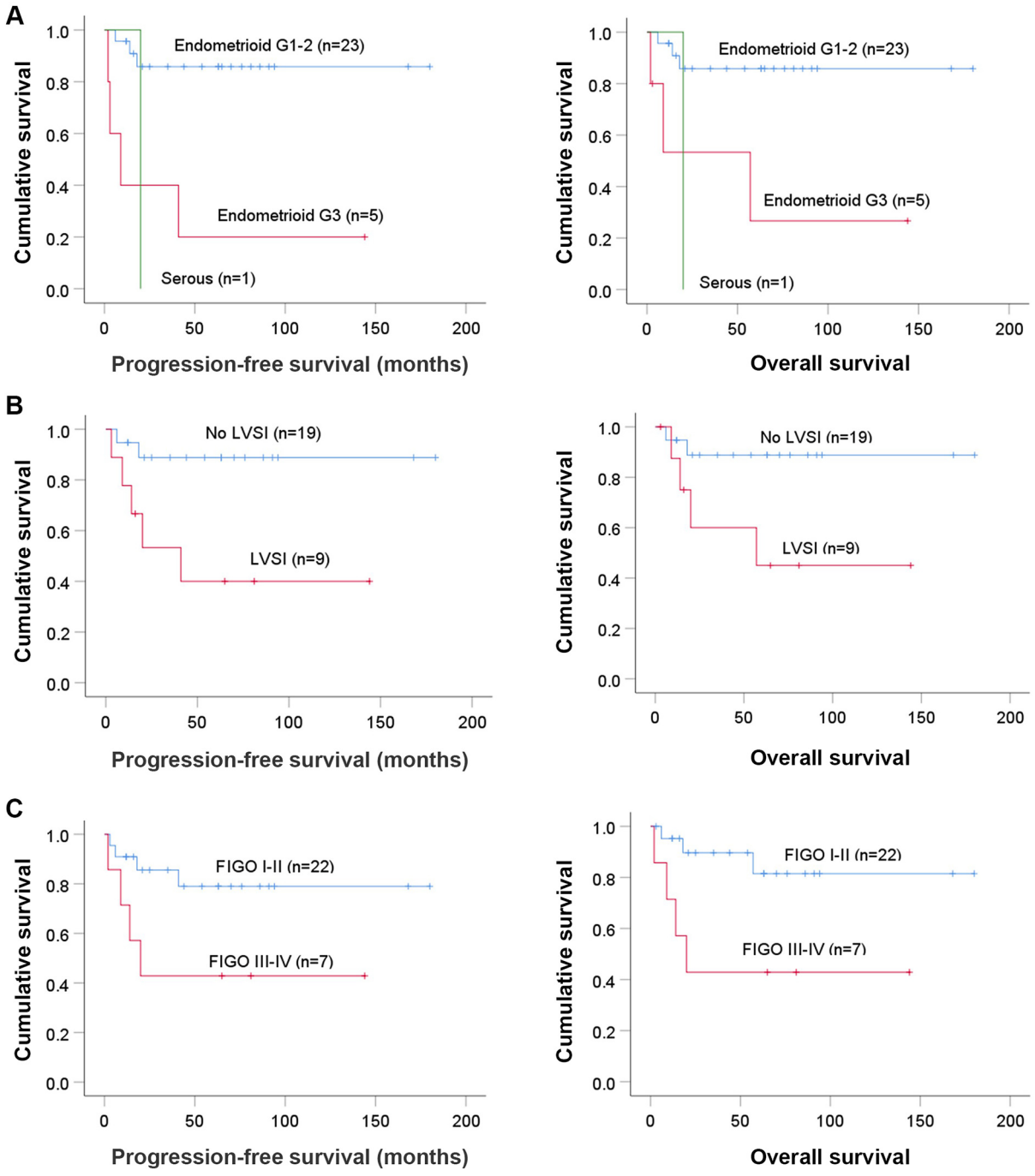

Figure 1. *Kaplan-Meier plots of progression-free (PFS) (left) and overall (OS) (right) survival according to (A) histological tumor subtype, (B) presence of lymphovascular space invasion (LVSI), and (C) International Federation of Obstetrics and Gynecology (FIGO) staging in study patients with endometrial cancer (EC). For grade (G) 1-2 endometrioid, grade 3 endometrioid and serous EC, respectively: mean PFS with confidence interval (CI) was 156.3 (131.4-181.2) vs. 39.8 (0-87.2) vs. 20.0 (20.0-20.0) months (p=0.001); and mean OS was 156.3 (131.4-181.2) vs. 56.4 (0.5-112.3) vs. 20.0 (20.0-20.0) months (p=0.009). For patients without and with LVSI, respectively: mean PFS was 161.3 (136.7-185.8) vs. 68.6 (25.7-111.5) months (p=0.011) and mean OS was 161.3 (136.7-185.8) vs. 79.2 (35.1-123.4) months (p=0.035). For FIGO stages I-II and III-IV respectively: mean PFS was 146.2 (116.5-176.0) vs. 68.1 (19.3-117.0) months (p=0.047) and mean OS was 152.6 (124.2-181.0) vs. 68.1 (19.3-117.0) months (p=0.023).*

Table II. *Univariate analysis of factors contributing to survival of patients with endometrial cancer. Data are the mean±standard deviation (95% confidence interval).*

Variable		Survival duration, months			
		Progression-free	*p*-Value	Overall	*p*-Value
Pre-operative CA125	<35 U/l	154.1±16.9 (121.0-187.2)	0.144	154.1±16.9 (121.0-187.2)	0.154
	≥35 U/l	57.9±13.3 (32.0-83.9)		60.0±13.0 (34.4-85.5)	
Histological subtype	Endometrioid grade 1-2	156.3±12.7 (131.4-181.2)	**0.001**	156.3±12.7 (131.4-181.2)	**0.009**
	Endometrioid grade 3	39.8±24.2 (0-87.2)		56.4±28.5 (0.5-112.3)	
	Serous	20.0±0 (20.0-20.0)		20.0±0 (20.0-20.0)	
Myometrial invasion	<50%	142.2±13.7 (115.3-169.0)	0.135	142.2±13.7 (115.4-169.0)	0.331
	≥50%	103.1± 28.1 (48.1-158.2)		118.0±27.9 (63.4-172.6)	
Cervical invasion	No	147.5±14.7 (118.8-176.3)	0.236	154.4±13.7 (127.6-181.2)	0.152
	Yes	84.5±24.5 (36.4-132.6)		87.2±23.8 (40.4-133.9)	
LVSI	No	161.3±12.5 (136.7-185.8)	**0.011**	161.3±12.5 (136.7-185.8)	**0.035**
	Yes	68.6±21.9 (25.7-111.5)		79.2±22.5 (35.1-123.4)	
Synchronous ovarian cancer	No	145.6±15.3 (115.6-175.6)	0.911	145.2±15.5 (114.9-175.5)	0.937
	Yes	141.0±24.6 (92.7-189.3)		141.0±24.6 (92.7-189.3)	
FIGO 2009 staging	FIGO I-II	146.2±15.2 (116.5-176.0)	**0.047**	152.6±14.5 (124.2-181.0)	**0.023**
	FIGO III-IV	68.1±24.9 (19.3-117.0)		68.1±24.9 (19.3-117.0)	

CA: Cancer antigen; CI: confidence interval; LVSI: lymphovascular space invasion; FIGO: International Federation of Gynecology and Obstetrics. Statistically significant *p*-values are shown in bold.

synchronous ovarian cancer, corresponding to 4.2% of the total cohort. In a multivariate analysis they identified deep myometrial infiltration as an independent risk factor for ovarian involvement (24). Other studies found a rate of synchronous ovarian cancer of 5.6% in premenopausal women (18) and 9% in women aged ≤40 years (25).

Our univariate analysis of survival showed a significantly reduced survival in patients with LVSI, poor tumor differentiation and advanced disease. LVSI occurred in 32.1% of our patients, lowering PFS and OS from 161.3±12.5 months to 68.6±21.9 months (p=0.011) and from 161.3±12.5 to 79.2±22.5 months (p=0.035), respectively. This result consolidated the findings of the PORTEC -1 and 2 trials, which included 926 patients with stage I endometrioid EC, showing reduced overall survival in patients with substantial LVSI (26). A Danish national cohort study found a higher 5-year recurrence rate and a lower PFS and OS in patients with LVSI (27). In a 2019 analysis of the United States National Cancer Database, Veade *et al.* reported LVSI and grade 3 differentiation as being significantly associated with lower OS (p<0.001) (28). An Italian retrospective cohort study conducted 2023 by Laliscia *et al.* found a higher rate of pelvic recurrence in patients with LVSI (29).

The poorly differentiated endometroid histological subtype was also associated with poorer survival in our study (PFS 39.8±24.2 *vs.* 156.3±12.7 months, p=0.001; and OS 56.4±28.5 *vs.* 156.3±12.7 months, p=0.009). These results were also consistent with findings of Son *et al.*, in whose study grade 3 histological differentiation was associated with a significantly lower PFS (p<0.001) (25).

One of the limitations of our study is the small sample size, further affected by some incomplete datasets. Many patients were still in follow-up, with their future outcome unknown. Our pathology reports also do not always include information about the type of LVSI (focal or substantial). Due to the retrospective nature of this study, it was not possible to evaluate for further possible risk factors or causes of EC in our six patients without any classical risk factor. Many of our cases occurred more than 10 years ago, time during which the approach to EC has developed, and many of the earlier records are incomplete, regarding, for example, the status of molecular markers in the pathology report.

Conclusion

Excess weight is a main risk factor for EC and was the most prevalent risk factor in our study. In patients with EC, LVSI, poor tumor differentiation and FIGO stages II-IV are important factors associated with reduced PFS and OS.

Conflicts of Interest

The Authors declare they have no conflicts of interest.

Authors' Contributions

Conceptualization: Cassandra Lemper and Vera Veiga. Data curation: Cassandra Lemper and Vera Veiga. Formal analysis: Cassandra Lemper, Mariana Ormonde and Vera Veiga. Funding acquisition – not applicable. Investigation: Cassandra Lemper, Mariana Ormonde and Vera Veiga. Methodology: Cassandra Lemper, Mariana Ormonde and Vera Veiga. Project administration: Vera Veiga. Resources: Cassandra Lemper, Mariana Ormonde and Vera Veiga. Software: Cassandra Lemper. Supervision: Vera Veiga. Validation: Cassandra Lemper, Mariana Ormonde and Vera Veiga. Visualization: Cassandra Lemper, Mariana Ormonde and Vera Veiga. Roles/Writing – original draft: Cassandra Lemper. Writing – review and editing: Mariana Ormonde and Vera Veiga. The manuscript was read and approved by all Authors.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine-learning software, were used in the preparation, analysis, or presentation of this manuscript.

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