Impact of weight loss after treatment on survival outcomes of overweight and obese patients with early-stage endometrial cancer

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Abstract. Despite the fact that obesity is the main risk factor for endometrial cancer, there is limited evidence regarding the effects of body weight change on overweight and obese women treated for early-stage endometrial can its impact on cancer outcomes. A retrospective cohort study was performed including all overweight and obese patients with early-stage type-I endometrial cancer that were treated at the Insular University Hospital of Las Palmas (Las Palmas de Gran Canaria, Spain) between January 2007 and December 2019. Body weight change at 12 months of treatment was evaluated, as well as its impact on cancer outcomes. Weight loss ≥5% was independently evaluated regarding its impact on survival. A total of 526 women were studied, of which 152 (28.90%) were overweight (BMI ≥25 and <30) and 374 (71.10%) were obese (BMI ≥30). The median follow-up was 76.17 months, during which time 77 (14.64%) women died. In the survivor group, body weight at initial diagnosis was 86.4±17.9 kg compared with 84.6±16.4 kg 1 year after treatment, which corresponded to a significant mean weight loss of 1.47 kg (P<0.001). However, in the group of non-survivors, body weight at initial diagnosis was 84.7±15.7 kg compared with 84.7±14.6 kg 1 year after treatment, which demonstrated a non-significant mean weight loss of 0.63 kg (P=0.180). When comparing between the patients who maintained or gained ≥5% weight and those who lost ≥5% weight, there were no significant differences taking into account the whole cohort and follow-up time; however, when adjusting for the period between 32 and 98 months, survival was significantly higher in those patients that lost ≥5% of their initial body weight (P=0.025; log-rank test). Based on the final univariate and cer and multivariate analyses, body weight change at 12 months was not indicated to be a factor significantly affecting overall survival; adjusted hazard ratio was 1.01 (95% CI 0.97-1.05, P=0.723). In conclusion, even if greater weight loss is observed in patients with endometrial cancer that survive the disease, no significant impact on survival outcomes is observed based on multivariate analysis.

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Introduction

Endometrial cancer is the most common gynecological cancer in developed countries. An estimated 65,950 new cases of endometrial cancer have been diagnosed in 2022 in USA, with 12.550 estimated deaths (1). The majority of women are diagnosed in an early stage, resulting in a 5-year overall survival of 81.2% (2). Endometrial cancer has been grouped into two main clinicopathological and molecular types: Type I comprises endometrioid adenocarcinoma and is the more frequent (80-90%) and Type II includes non-endometrioid subtypes such as serous, clear cell, undifferentiated carcinomas, and carcinosarcoma (10-20%) (3).

Obesity is one of the main risk factors for the development of Type I endometrial cancer and its precursor, the atypical hyperplasia (4). In fact, 60% of these women are obese (5). Renehan *et al*, found that a 5 kg/m^2 increase in BMI is related to an increased risk of 59% of having endometrial cancer (6). Also, women with obesity at diagnosis have a higher risk of death than those without obesity (7-9). Overweight and obesity are related to diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, osteoarthritis, and obstructive sleep apnea (10). Cardiovascular co-morbidities are the main cause of death among endometrial cancer survivors secondary to obesity (11).

It has been shown that the incidence of endometrial cancer in obese women can be reduced by weight loss (12,13), while

it has been observed that medical history of bariatric surgery is associated with reduced risk for endometrial cancer (14,15). Also, there may be further benefits to weight loss in this context, such us improved metabolic and cardiovascular health in women known to be at high risk of cardiovascular events (16). The AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (17) states that a 5% weight loss produces clinically significant improvements in some cardiovascular risk factors such as diabetes, lipid profile and hypertension.

Survival benefits of weight loss following endometrial cancer treatment are sparse and they are not well established in the literature. There is evidence that many women do not lose weight after surgical treatment for endometrial cancer (18), and postoperative body weight loss may have a better survival compared with body weight gain (18). So, identifying percentage of weight loss and whether this weight loss may have scientific impact is an essential consideration in the management of women with endometrial cancer.

Main objective of the present study was to evaluate the percentage of overweight and obese women who lose weight after one year of treatment and to examine its potential impact on cancer outcomes.

Materials and methods

Study design. A single-center retrospective cohort study which included 526 overweight and obese women was performed in Insular University Hospital of Las Palmas. An electronic search was performed from our electronic database in order to retrieve endometrial cancer patients meeting inclusion criteria. Our Department consistently records prospectively all elements of cancer patients treated in our Department by a dedicated senior data administrator, while all elements are verified on a monthly basis. The study was approved by the Ethical Committee of University of Las Palmas de Gran Canaria (CEIm Las Palmas, approval no. 2022-414-1) in October 2022.

Inclusion criteria for the present analysis concerned early-stage, type-I (endometrioid) endometrial cancer patients that were overweight or obese who have BMI ≥25 kg/m^2 and ≥18 years old and treated between 2007 and 2019. Apparent early-stage (stage I-II) disease was assessed preoperatively by vaginal ultrasound or pelvic magnetic resonance imaging and/or intraoperatively by revision of the surgical specimen by the pathologist. Cases with final histology different from endometrioid (serous, clear cells, carcinosarcoma, undifferentiated, mixed carcinoma), FIGO (The International Federation of Gynecology and Obstetrics) stage III-IV and BMI <25 kg/m^2 were excluded. Women with incomplete medical reports, with synchronous cancers or treated by radiotherapy, chemotherapy or hormonal therapy at first intention were also not included in the present analysis.

All patients underwent total hysterectomy and unilateral or bilateral adnexectomy by minimally invasive surgery (laparoscopy, robot, or vaginal) or laparotomy. Assessment of lymph nodes was variable over the years and included sentinel pelvic lymph node, pelvic or/and para-aortic lymphadenectomy. Treatment of patients was based on current ESGO guidelines. Furthermore, in our institution, as a standard of our treatment policy, all obese and overweight women are advised to lose weight and a healthy life. Also, the cardiovascular and carcinogenic risks of obesity are explained to them.

Cohort selection and study variables. Epidemiological, histopathological and survival outcomes of patients were retrieved and analyzed from patient records. Specifically, we set in the center of our analysis the following data: age (years), height (cm), weight (kg) at diagnosis, clinical tumor stage (FIGO), type of surgery, tumor grade (Grade 1-3), depth of myometrial invasion (<=50%, >50%) lymphovascular invasion (present or absent), type of surgery (laparoscopy, robot or laparotomy), pelvic and para-aortic lymphadenectomy performance. Survival or not (death) as well as weight in kg at the end of 1st year of follow-up were recorded. Finally, data of adjuvant treatment (vaginal brachytherapy, external beam radiation, or combination of both) were also evaluated.

Study outcomes. Main objective of the present study was to determine weight loss for overweight and obese early-stage, type-I endometrial cancer patients at the end of 1st year of follow-up after treatment as well as to assess the impact of this body weight change on survival outcomes. Impact of ≥5% weight loss on endometrial cancer survival was also set in the scope of our analysis. A 5% of weight loss was chosen because he AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (15) states that a 5% weight loss produces clinically significant improvements in some cardiovascular risk factors, so we wanted to evaluate whether this cut-off point also impacts on survival.

Statistical analysis. Data were summarized by mean ± standard deviation for all continuous variables if they followed a normal distribution. Categorical variables were reported as absolute number and percentage. To compare continuous variables, Wilcoxon test was used, as they did not have a normal distribution. Survival was assessed using Kaplan-Meier curves, while log-rank tests were used to compare the curves. Logistic regression was used to assess potential association between weight loss and survival. Univariate and multivariate Cox regression analyses were performed to determine the association between various factors and survival outcomes. Factors included in the multivariate model were FIGO (The International Federation of Gynecology and Obstetrics) stage, age, grade, lymphovascular invasion and body weight change at 12 months. All statistical tests were two-tailed and $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was conducted using SPSS and JASP.

Results

Patient characteristics. All included patients underwent total hysterectomy with bilateral adnexectomy. Surgery was performed by laparoscopy or robot, laparotomy and vaginal approach in 441 cases (83.84%), 45 cases (8.56%) and 40 cases (7.60%), respectively. The most common FIGO stage was IA (412 patients, 78.33%), followed by stage IB (17.30%) and stage II (4.37%). Most of the tumors were classified as grade 1 (76.81%) and grade 2 (18.25%). Lymphovascular invasion was present in 80 women (15.21%). The majority of women

(74.71%), did not receive any adjuvant treatment. Pelvic and para-aortic lymphadenectomy was performed in 78 (14.83%) and 22 (4.18%) women, respectively. Main epidemiological and histopathological outcomes of patients are reported in Table I.

Body weight change. A total of 526 women were studied of which 152 (28.9%) were overweight (BMI ≥25 and <30) and 374 (71.10%) were obese (BMI ≥30). Initial body weight was 85.73±17.42 kg (median: 83 kg, min: 56 kg, max: 160.20 kg) which corresponds to an initial BMI of 34.35±6.62 (kg/m^2) [median: 33.22 (kg/m^2), min: 25, (kg/m^2) max: 63.56 (kg/m^2)]. One year after treatment, body weight was 84.52±16.16 kg (median: 81.00 kg, min: 53.00 kg, max: 151.00 kg). In total, one year after treatment 271 (52.1%) women lost weight, 207 (39.8%) women gained weight and 42 (8.1%) women presented a stable weight. Significant differences were found in body weight change (P≤0.001).

The median follow-up was 76.17 months during which time 77 (17.15%) women died. Regarding the survivor group, body weight at initial diagnosis was 86.4±17.9 kg (BMI 34.22±6.69 kg/m^2) vs. 84.6±16.4 kg one year after treatment, which corresponded to a significant mean weight loss of 1.47 kg (P<0.001). However, in the group of non-survivors, body weight at initial diagnosis was 84.7±15.7 kg (BMI 35.24±6.72 kg/m^2) vs. 84±14.6 kg one year after treatment, which demonstrated a non-significant mean weight loss of 0.63 kg (P=0.180) (Table II). Former results shown in Table II were calculated based on Wilcoxon test.

Five percent weight loss. One hundred and five (20.2%) women lost 5% or more of their total body weight by 12 months, while another 415 (79.8%) women maintained or gained more than 5% of their initial body weight. When comparing between those who maintain or gain ≥5% weight and those who lose ≥5% weight, there were no significant differences taking into account at the whole cohort and time (P=0.218; Log-Rank test). However, when adjusting for the period between 32 and 98 months, survival was significantly higher in favor of those losing more than 5% of their initial body weight (P=0.025; Log-Rank test). Fig. 1 presents the relative survival curves within two groups.

Univariate and multivariate analysis for overall survival and recurrence. Univariate and multivariate analysis included FIGO stage, age, grade, lymphovascular invasion, adjuvant treatment and body weight change at 12 months.

Body weight change at 12 months was not indicated to be a factor significantly affecting overall survival. Adjusted hazard ratio was 1.01 (95% CI 0.97-1.05, P=0.723).

Parameters indicated to significantly affect overall survival were age (HR 1.11, 95% CI 1.08-1.14, P<0.001), FIGO stage (stage IB: HR 1.96, 95% CI 1.16-3.32, P=0.013; stage II: HR 2.87 95% CI 1.35-6.10, P=0.006) and adjuvant treatment (Brachytherapy alone: HR 3.24, 95% CI 1.45-7.20, P=0.004, Radiotherapy + Brachytherapy: HR 1.73, 95% CI 1.04-2.89, P=0.036). However, in the multivariate analysis, only age was independently associated with overall survival (HR 1.12, 95% CI 1.09-1.15, P<0.001). FIGO stage II was marginally not significant predictor of overall survival (stage II: HR 3.07, 95% CI 0.95-9.95, P=0.006). Furthermore, brachytherapy alone or with radiotherapy were not indicated as significant covariates based on multivariate analysis. (Table III). Finally, kind of complementary therapy was not significantly associated with weight loss based on a univariate regression model (P=0.34).

Table I. Epidemiological and histopathological characteristics of patients.

Characteristic	Patients (n=526)
Mean age, years (SD)	63.12 (10.81)
BMI, n (%)	
Overweight	152 (28.9)
Obese	374 (71.10)
FIGO stage, n (%)	
IA	412 (78.33)
IB	91 (17.30)
II	23 (4.37)
Grade, n (%)	
1	404 (76.81)
2	96 (18.25)
3	26 (4.94)
Lymphovascular invasion, n (%)	
No	446 (84.79)
Yes	80 (15.21)
Pelvic lymphadenectomy, n (%)	
Yes	78 (14.83)
No	448 (85.17)
Para-aortic lymphadenectomy, n (%)	
Yes	22 (4.18)
No	504 (95.82)
Type of surgery, n (%)	
Laparoscopy	441 (83.84)
Vaginal	40 (7.60)
Laparotomy	45 (8.56)
Adjuvant treatment, n (%)	
No	393 (74.71)
Radiotherapy alone	1 (0.19)
Brachytherapy alone	25 (4.75)
Radiotherapy + Brachytherapy	107 (20.34)
Patterns of recurrence, n (%)	
Vaginal vault	13 (30.95)
Peritoneal carcinomatosis	9 (21.43)
Metastatic lymph nodes	5 (11.90)
Visceral metastases	14 (33.33)
Port site metastases	1 (2.38)
Death, n (%)	
No	449 (85.36)
Yes	77 (14.64)

SD, standard deviation; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Weight change in the survivor and death group.

Group	Initial weight, kg	Weight at 12 months, kg	Weight change at 12 months, kg	P-value
Survivor group (n=520)	86.1±17.9	84.6±16.4	-1.47±6.73	<0.001
Non-survivor group (n= 77)	84.7±15.7	84±14.6	-0.63±4.97	0.180

Data are presented as the mean ± SD.

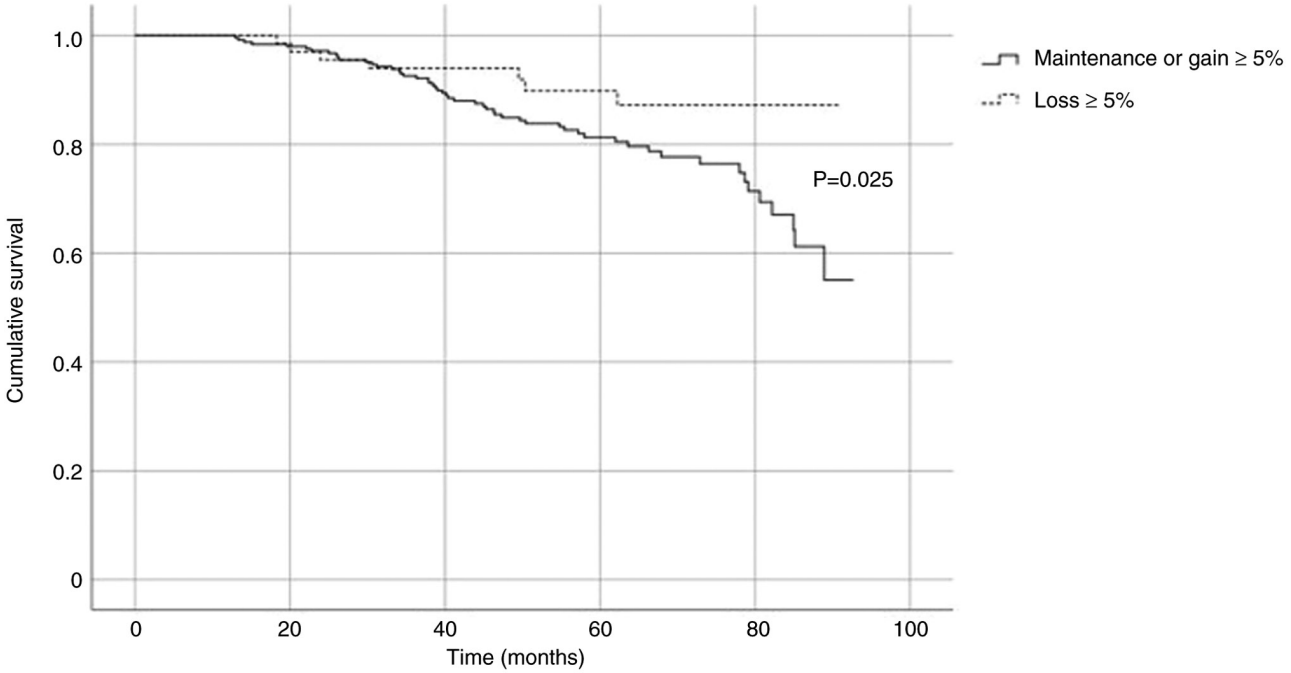

Figure 1. Cumulative survival curves for patients with and without loss of weight more than 5%.

Relative remarks were also made regarding risk for recurrence. Specifically, weight change has not been indicated as significant predictor for recurrence (HR 1.01, 95% CI 0.97-1.07, P=0.640). In contrary, age, grade, LVSI and FIGO stage were demonstrated as significant parameters affecting possibility of recurrence. Univariate and multivariate models for possibility of death and recurrence have been mentioned in Tables III and IV.

Discussion

Our study mainly indicated that, even if greater weight loss is observed in endometrial cancer patients finally surviving from disease, no significant impact on survival outcomes is observed based on multivariate analysis. Furthermore, weight loss ≥5% was also not indicated to affect significantly survival parameters, except from the interim interval of 32 and 98 months.

To our knowledge, there is only one study which analyses changes in body weight cancer patients who are finally surviving from disease concluded that these weight changes had repercussions on survival outcomes (18). Regarding breast cancer survivors, one study concluded that BMI gain between 0.5 and 2.0 kg/m^2 (RR 1.35; 95% CI, 0.93-1.95) or more than 2.0 kg/m^2 (RR, 1.64; 95% CI, 1.07-2.51) was related to higher rates of death (19). However, Goodwin *et al* (20), randomized 171 breast cancer women to a telephone-based weight loss lifestyle intervention vs. 167 to an education-only arm. They observed that lifestyle intervention arm had higher weight loss compared to education-only arm (-5.3% vs. -0.6% at 6 months, -5.5% vs. -0.6% at 12 months, and -3.7% vs. -0.4% at 24 months) (P<0.001). Also, they did not find significant differences regarding disease free survival between both groups (HR 0.71, 95% CI: 0.41-1.24, P=0.23). Moreover, increased BMI was not significantly associated with higher risk of colon cancer recurrence or death (P=0.54) in stage III colon cancer patients during and 6 months after adjuvant chemotherapy (21). It appears that data published in literature on different types of cancers reflect conflicting results in terms of oncological outcomes.

Literature had shown that endometrial cancer patients with obesity have reduced quality of life and increased risk of morbidity (22-25). There have been clinical trials which have analyzed the impact of weight loss programs vs. usual physician care on obese endometrial cancer women. Bell *et al* (26) found a remarkable BMI reduction at 6 months and 12 months in endometrial cancer women with obesity that followed a behavioral weight loss program. In the behavioral weight loss program group, 80.0% patients lost greater than 5% of initial

Table III. Univariate and multivariate Cox regression analysis for overall survival.

	Univariate		Multivariate	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.11 (1.08-1.14)	<0.001	1.12 (1.09-1.15)	<0.001
Grade	1.23 (0.68-2.22)	0.485		
Lymphovascular invasion	1.45 (0.81-2.59)	0.214		
FIGO stage	2.87 (1.35-6.10)	0.006	3.07 (0.95-9.95)	0.061
Weight change at 12 months	1.01 (0.97-1.05)	0.723		
Adjuvant treatment				
Radiotherapy alone	0.00 (0.00-inf)	0.996	0.00 (0.00-inf)	0.995
Brachytherapy alone	3.24 (1.45-7.20)	0.004	2.63 (0.86-8.03)	0.090
Radiotherapy + Brachytherapy	1.73 (1.04-2.89)	0.036	1.16 (0.41-3.24)	0.779

HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

Table IV. Univariate and multivariate Cox regression analysis for recurrence.

	Univariate		Multivariate	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.06 (1.03-1.09)	0.001	1.06 (1.02-1.09)	<0.001
Grade	4.03 (1.38-10.35)	0.006	3.6 (1.11-10.67)	0.022
Lymphovascular invasion	4.03 (2.09-7.60)	<0.001	2.2 (1.02-4.87)	0.0045
FIGO stage	8.26 (3.08-20.98)	<0.001	8.05 (2.57-24.19)	<0.001
Weight change at 12 months	1.01 (0.97-1.07)	0.640		
Adjuvant treatment				
Radiotherapy alone	0.00 (0.00-inf)	0.996	0.00 (0.00-inf)	0.995
Brachytherapy alone	4.35 (1.45-7.48)	0.013	2.68 (0.89-4.13)	0.090
Radiotherapy + Brachytherapy	2.23 (1.04-2.89)	0.036	1.24 (0.41-3.28)	0.779

HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

weight compared to 28.6% individuals in the control group. These findings differ from the results of Zamorano *et al* (27) which did not find differences in weight loss after personalized text-message-based intervention among endometrial cancer survivors with obesity. At 6 months, 9.2% of women randomized into the text-message-based intervention had lost at least 5% of their body weight vs. 11.2% of women randomized into enhanced usual care arm. On the other hand, McCarroll *et al* (28) randomized 75 early-stage endometrial cancer women to a lifestyle intervention group that was offered a nutrition, exercise, and behavioral modification counseling or a usual care group. These authors found that there was a significant BMI loss for the intervention group vs. the control group at the 6-and 12-time points (P<0.001 and P=0.008, respectively). Those randomized prospective studies had a short follow-up period of six and 12 months, however they did not analyze oncological outcomes. Moreover, evidence clearly highlights that dietary interventions are beneficial for patients with gynecological cancer as they may improve quality of life and also optimize treatment results on a level of multidisciplinary approach (29-32). Another important conclusion of our study is that no correlation between weight loss and the final outcome may be attributed to complementary treatment. Firstly, no chemotherapy was administered in our patients' group, as they were all early-stage disease, thereafter no detrimental effect of chemotherapy toxicity might have affected weight loss. Furthermore, no significant correlation was observed between weight loss and radiotherapy administration. Therefore, weight loss in endometrial cancer patients of our study has not been affected from complementary treatments.

Limitations of this study may be considered its retrospective nature, and its relatively not so large sample size, which did not allow us to find significant differences due to the low rate of recurrences in endometrial cancer. Potential variations on the surgical staging and adjuvant treatment over the years may have partially affected our results. Lack of basal nutritional data as well as exact dietary and lifestyle interventions could be also considered as limitations. Moreover, we have not included a normal-weight control group. However,

our objective was to examine whether body weight loss had an impact on survival on obese patients, while normal-weight endometrial cancer are not consistently advised to lose weight because of lack of benefit on such a strategy. Despite potential limitations, though, this is one amongst few studies including long-term survival data from a trustworthy electronic registry which powered the results of the study. Furthermore, all different types of minimally invasive approaches and laparotomy surgery were included, while only women with histology confirmation in the final surgical specimen were included to decrease the risk of selection bias. Thereafter, our findings may considerably contribute in the debate of impact of weight loss on endometrial cancer survival outcomes and potentially trigger further research in a field with high clinical impact.

In conclusion, our study indicated that weight loss did not significantly affect prognosis in early-stage, type-I, overweight and obese endometrial cancer patients. Further prospective cohorts should rather be performed in order to further study potential impact of weight loss on endometrial cancer prognosis and eventually the impact of such a policy.

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Availability of data and materials

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

Authors' contributions

BNS was involved in collecting and verifying raw data, conceptualization, methodology, formal analysis, investigation, writing the original draft and visualization. JVS was involved in formal analysis, verification of the repeated results, reviewing and editing. BNS and JVS confirm the authenticity of all the raw data. OA was involved in methodology, investigation and writing the original draft. SP and CMS were involved in statistical analysis, reviewing and editing. ML was responsible for statistical analysis, identification and collection of relative references, reviewing and editing. DG was involved in methodology, resources, reviewing and editing. AR was responsible for analysis and interpretation of data and writing the original draft. AMM significantly contributed to the conception and design of the study, and was responsible for reviewing and editing, validation of data analysis and supervision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of University of Las Palmas de Gran Canaria (CEIm Las Palmas, approval no. 2022-414-1) in October 2022. All patients provided written informed consent for participation.

Patient consent for publication

All patients provided written informed consent for data analysis and potential publication.

Competing interests

The authors declare that they have no competing interests.

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