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Sarcopenia and Anemia Are Predictors of Poor Prognostic in Cervical Cancer Patients

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Abstract

Objective: Evaluate pretreatment sarcopenia and anemia as prognostic factors in women undergoing treatment for cervical cancer (CC) with concurrent chemoradiotherapy (CCRT). **Methods:** 151 women with CC were analysed in this cohort study. Pretreatment computed tomography (CT) images were analysed to assess skeletal muscle index (SMI). Hazard ratios (HR) and multivariate Cox proportional HR were used to analyse association between low SMI, age, body mass index (BMI), haemoglobin levels, histological type, and International Federation of Gynaecology and Obstetrics (FIGO) stage with PFS and OS. **Results:** A total of 151 patients were included, 53 (35.1%) presented pretreatment sarcopenia; 51 (34%) stage I/II and 100 (66%) stage III/IV. Among those patients in advanced stage (III/IV) 37 (70%) (p = 0.28) were sarcopenic at the beginning of treatment. Sarcopenia was associated with worse progression-free survival (PFS) and overall survival (OS) in our cohort [HR 0.97 (p = 0.01)] [HR 0.73 (p = 0.001)], as well as anemia [HR 0.73 (p = 0.001)] [HR 0.78 (p = 0.001)]. Linear regression models indicated that despite showing no association with age, neutrophil or platelet counts, sarcopenia was associated with pretreatment anemia levels (p = 0.01). After a multivariate analysis, only haemoglobin (anemia) and complete CCRT remained associated with PFS and OS. Sarcopenia and anemia were associated with worse PFS and OS in FIGO stage I/II. **Conclusion:** Pretreatment sarcopenia was significantly associated with low haemoglobin levels. Anemia and incomplete CCRT were independently associated with poor prognosis in women with

CC. Pretreatment sarcopenia, as low SMI, was a predictor of poor prognostic in early stages of CC.

Keywords

Cervical Cancer, Sarcopenia, Anemia, Chemoradiotherapy

1. Introduction

Cervical cancer (CC) is the fourth most frequently diagnosed cancer among women and responsible for approximately 342,000 deaths in 2020. It is one of the leading causes of cancer-related deaths in women worldwide, mostly in low-income countries [1]. The main prognostic factor in women with CC is the stage of disease at diagnosis according to FIGO [2].

Locally advanced tumours (*i.e.*, FIGO stages IB3-IVA) are preferred treated with concurrent chemoradiotherapy (CCRT) [3]. Some systemic conditions, such as sarcopenia (reduced skeletal muscle index) and anemia (low haemoglobin levels) are also related to a worse prognosis [4] [5] [6] [7] [8].

Furthermore, a significant skeletal muscle decrease has emerged as another critical prognostic factor in CC patients. Current data suggests SMI is an independent predictor of clinical outcomes among cancer patients, such as worse PFS and OS [9]-[15]. Sarcopenia is characterized as a progressive and generalized syndrome of loss of skeletal muscle mass, which can result in worsening quality of life and even death. According to The European Working Group on Sarcopenia in Older People (EWGSOP), this condition may be related to low muscle mass and low muscle function [16].

The gold standard for assessing skeletal muscle index is a CT scan at the level of the third lumbar vertebra (L3) [16] [17]. Considering previous results investigating patients with CC and other types of cancer, we hypothesized that pre-treatment low SMI would be a predictor of patient outcomes.

2. Methods

2.1. Participants

Retrospective cohort with 151 women with locally advanced invasive cervical carcinoma treated with CCRT between 2015-2019, and followed up until 2022. Proposed standardized treatment was performed with external beam RT (50 Gy in 25 fractions over 5 weeks) concurrent weekly cisplatin chemotherapy (40 mg/m^2 per week). Exclusion criteria were patients previously diagnosed with other cancers who had undergone chemotherapy or radiotherapy, as well as pregnant women.

2.2. Diagnosis and Staging

Clinical and pathological data were obtained from the medical records. The staging was performed according to the classification established by FIGO [2], as-

sessed by clinical examination, chest radiograph, pelvic and abdominal ultrasounds, and planning pelvic CT scans before the start of treatment so that this does not represent a bias in the result of the muscle mass index after treatment.

2.3. Response to Treatment, Follow-Up, and Adverse Effects

The response to treatment was evaluated according to the WHO criteria—the Response Evaluation Criteria in Solid Tumors (RECIST) [18]. Clinical examination, total abdominal and chest CT, as well as MRI, were used during and after treatment to classify the response.

Haematological toxicity was evaluated before each course and graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [19].

2.4. CT Image Analysis

Pretreatment planning CT images were analysed to assess SMI within measurements of psoas and paraspinal muscles, bilaterally. For each muscle, two measurements were taken to determine the muscle mass index. Each assessment was carried out multiple times, at different times, by different researchers. Muscle tissue was delineated on an axial image at L3 level using Arya® software and a cutoff point of <38.9 cm^2/m^2 for identifying patients with sarcopenia due to low muscle indices [20] [21].

2.5. Statistical Analysis

Categorical data were presented in relative and absolute frequencies. The association between pretreatment low SMI and age, BMI, anemia, FIGO stage, adverse effects, treatment response, and site of progression was assessed using χ^2 tests and expressed in terms of odds ratios (OR) with 95% confidence intervals. A p-value < 0.05 was considered significant.

3. Results

Table 1 describes the patient's socio-demographics, tumour characteristics, and

Table 1. Describes the patient's socio-demographics, tumour characteristics, and association with pretreatment SMI.

Variable	Overall N = 151 (100%)	Normal SMI N = 98 (64.9%)	Low SMI N = 53 (35.1%)	*p*
	n (%)			
Menopausal Status				0.37
Post-menopausal	63 (41.7)	44 (44.9)	19 (35.8)	
Pre-menopausal	88 (58.3)	54 (55.1)	34 (64.2)	
Smoker				0.54
No	135 (89.4)	86 (87.8)	49 (92.5)	

Continued

Yes	16 (10.6)	12 (12.2)	4 (7.5)	
Previous Radical Hysterectomy				1.0
No	146 (96.8)	95 (96.9)	51 (96.2)	
Yes	5 (3.2)	3 (3.1)	2 (3.8)	
Histological Type				0.21
Squamous	126 (83.4)	85 (86.7)	41 (77.4)	
Adenocarcinoma/others	25 (16.6)	13 (13.3)	12 (22.6)	
FIGO stage				0.28
I	11 (7.3)	10 (10.2)	1 (1.9)	
II	40 (26.5)	25 (25.5)	15 (28.3)	
III	81 (53.7)	50 (51)	31 (58.5)	
IV	19 (12.5)	13 (13.3)	6 (11.3)	
Parametrial Infiltration				0.15
Infiltered	121(80.2)	75 (76.5)	46 (86.8)	
Not Infiltered	30 (19.8)	23 (23.5)	7 (13.2)	
Nodal Status				0.16
Negative	13 (22)	11 (28.9)	2 (9.5)	
Positive	46 (78)	27 (71.1)	19 (90.5)	
Largest Tumour Diameter (cm)				0.46
≤4	63 (49.2)	39 (47)	24 (53.3)	
<4≤6	34 (26.6)	25 (30.1)	9 (20.0)	
>6	31 (24.2)	19 (22.9)	12 (26.7)	
Pretreatment Creatinine > 1.09				0.17
No	126 (86.9)	84 (90.3)	42 (80.8)	
Yes	19 (13.1)	9 (9.7)	10 (19.2)	

SMI = skeletal muscle index.

association with sarcopenia.

Survival outcomes

In the univariate analysis, SMI, BMI, and FIGO stage were significantly associated with PFS. However, after adjustment in a multivariate Cox proportional model, only pretreatment haemoglobin and incomplete CCTR remained as significantly associated with PFS (Table 2).

Similarly, as evidenced by the results of the univariate analysis, SMI, BMI, pretreatment neutrophil count, haemoglobin levels, CCRT, and FIGO stage were significantly associated with OS (Table 3). However, after a multivariate analysis, only haemoglobin levels and CCRT remained associated with OS.

Table 2. Cox proportional hazard ratio of progression free survival analysis considering key clinical features.

Variable	Progression free survival					
	Univariate			Multivariate		
	HR	(95% CI)	p	HR	(95% CI)	$p_{adjusted}$
Skeletal mass index (cm^2/m^2)	0.97	(0.94 to 0.99)	0.01	0.99	(0.96 to 1.03)	0.93
Age (Years)	1.00	(0.98 to 1.02)	0.68	1.00	(0.98 to 1.02)	0.88
BMI (Kg/m^2)	0.96	(0.92 to 0.99)	<0.001	0.98	(0.94 to 1.02)	0.58
Pretreatment Neutrophil count (mm^3)	1.09	(1.03 to 1.14)	<0.001	1.01	(0.93 to 1.10)	0.64
Pretreatment Platelet count (mm^3)	1.00	(1.00 to 1.00)	0.7	1.00	(0.99 to 1.00)	0.40
Pretreatment Haemoglobin (g/dL)	0.73	(0.66 to 0.81)	<0.001	0.73	(0.64 to 0.84)	<0.001
Pretreatment creatinine (mg/dL)	1.80	(0.95 to 3.43)	0.07	0.85	(0.40 to 1.83)	0.69
Histological type	0.73	(0.36 to 1.46)	0.37	1.12	(0.53 to 2.35)	0.75
Incomplete CCTR	1.95	(1.23 to 3.11)	<0.001	2.84	(1.64 to 4.91)	<0.001
Advanced Stage	1.99	(1.16 to 3.43)	0.01	1.09	(0.57 to 2.07)	0.79

Cox proportional hazard ratio: HR (95% confidence interval). Adjusted by skeletal mass index (SMI), age, body mass index (BMI), neutrophil, platelet, haemoglobin, Pretreatment creatinine (normal vs > 1.09), histological type (squamous vs adenocarcinoma/others), Complete vs incomplete concurrent chemoradiotherapy (CCTR); Stage: I, II, III or IV.

Table 3. Cox proportional hazard ratio of overall survival analysis considering key clinical features.

Variable	Overall survival					
	Univariate			Multivariate		
	HR	(95% CI)	p	HR	(95% CI)	$p_{adjusted}$
Skeletal mass index (cm^2/m^2)	0.97	(0.94 to 0.99)	0.01	0.99	(0.95 to 1.02)	0.57
Age (Years)	1.01	(0.99 to 1.02)	0.36	1.01	(0.99 to 1.03)	0.20
BMI (Kg/m^2)	0.95	(0.91 to 0.98)	0.01	0.97	(0.93 to 1.01)	0.29
Pretreatment Neutrophil count (mm^3)	1.07	(1.01 to 1.13)	0.01	1.02	(0.94 to 1.12)	0.51
Pretreatment Platelet count (mm^3)	1.00	(1.00 to 1.00)	0.7	0.99	(0.99 to 1.00)	0.89
High pretreatment Haemoglobin (g/dL)	0.78	(0.69 to 0.86)	<0.001	0.79	(0.69 to 0.91)	<0.001
Normal pretreatment creatinine (mg/dL)	1.2	(0.59 to 2.41)	0.61	0.59	(0.25 to 1.39)	0.23
Histological type	0.57	(0.27 to 1.18)	0.13	1.20	(0.27 to 1.38)	0.24
Incomplete CCTR	2.07	(1.28 to 3.31)	<0.001	2.69	(1.55 to 4.67)	<0.001
Advanced Stage	1.71	(0.99 to 2.92)	0.05	1.20	(0.63 to 2.28)	0.57

Cox proportional hazard ratio: HR (95% confidence interval). Adjusted by skeletal muscle index (SMI), age, body mass index (BMI), neutrophil, platelet, haemoglobin, pretreatment creatinine (normal vs > 1.09), histological type (squamous vs adenocarcinoma/others), Complete or incomplete concurrent chemoradiotherapy (CCTR); Stage: I, II, III or IV.

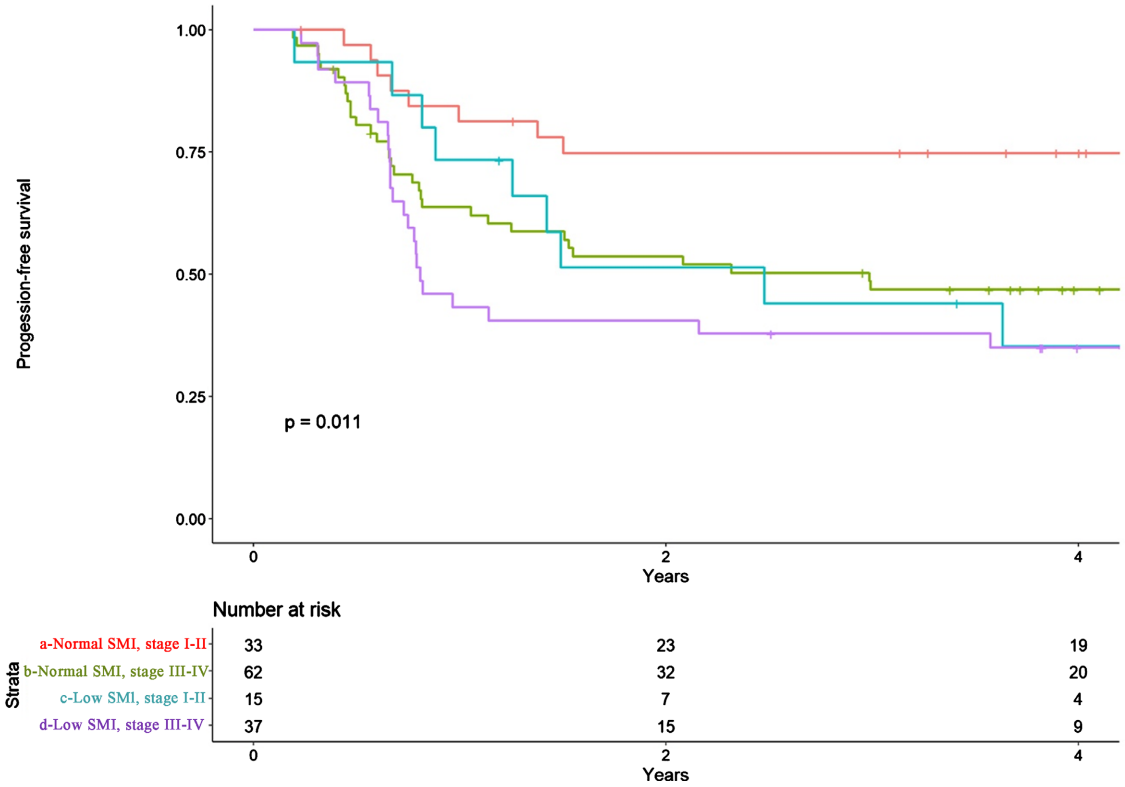

Figure 1. Depicted that low SMI is associated with PFS when analysed by FIGO stage. Patients with normal SMI at stages I and II presented higher PFS compared to patients with sarcopenia at the same stages (p = 0.04). No significant difference was found between patients with normal SMI at stages III and IV and patients with sarcopenia at these advanced stages (p = 0.24).

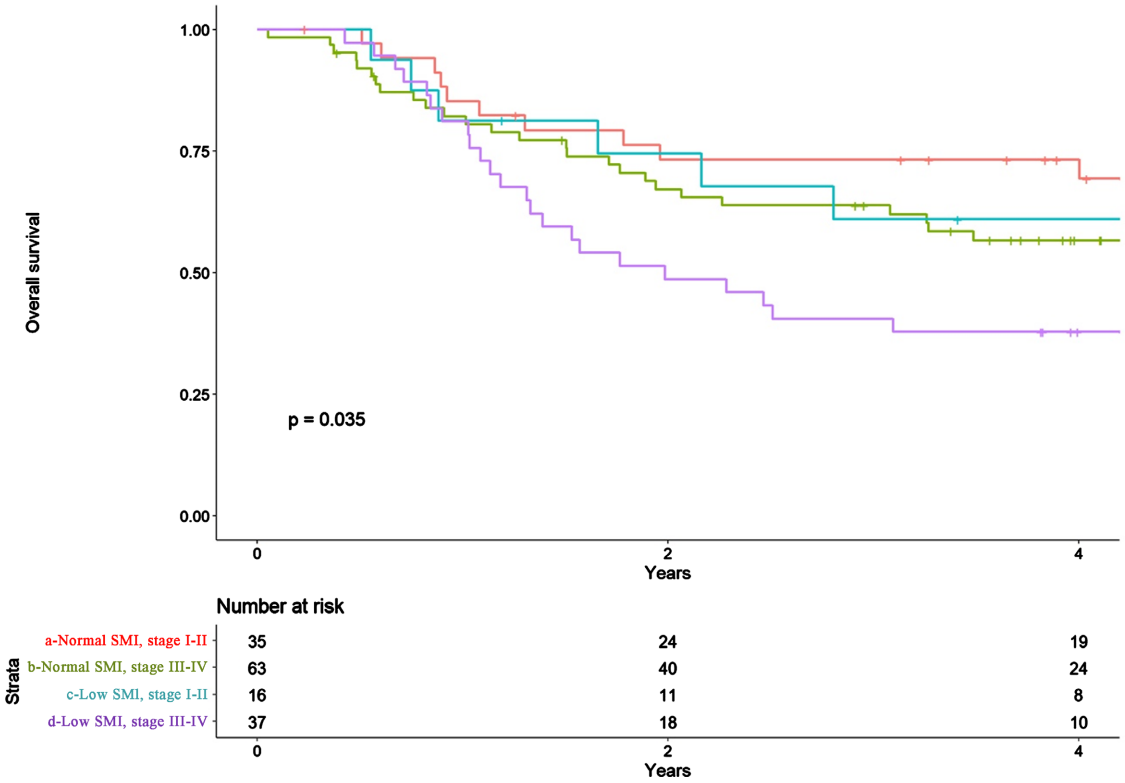

Figure 2. Shows that sarcopenia (low SMI) is significantly associated with overall survival (p < 0.001).

4. Discussion

4.1. Summary of Main Results

This study aimed to evaluate sarcopenia and anemia are prognostic factors in women diagnosed with CC who underwent CCRT. Accordingly, the main results of this investigation showed that pretreatment sarcopenia (low SMI) was associated with low haemoglobin levels. Although sarcopenia appears as a worse prognostic factor in the univariate analysis, only haemoglobin levels (anemia) and complete CCRT remained independently associated with progression-free survival and overall survival. Sarcopenia was significantly associated with worse PFS and OS in FIGO stage III/IV. Patients with normal SMI at stages I and II presented higher PFS and OS.

4.2. Results in the Context of Published Literature

According to Wassie *et al.* [22] (2021) anemia affects about 1 in 2 women with CC and is significantly associated with worse survival. In women with CC, pretreatment anemia is a result of diverse factors: the aggressiveness of advanced stage, bleeding, renal failure. And even in women without bleeding and renal failure, the chronic inflammatory status associated with advanced stage and proinflammatory cytokines by immune and cancer cells can lead to anemia. In these cases, biological and hematologic features resemble those described in anemia associated with chronic inflammatory disease. Anemia leads to worse performance status, quality of life, cognitive function, energy-activity capacity and increase of fatigue, lethargy, dyspnea, anorexia with a consequent difficulty to adhere to full treatment [9]. A low haemoglobin (Hb) is related to tumour hypoxia which interferes with the effectiveness of both chemotherapy and radiotherapy. In addition to reducing the sensitivity of the tumor to treatment, anemia promotes tissue acidosis, production of ROS, immunodepression, and alterations in tumor cells apoptosis [23]. We previously demonstrated that a low level of haemoglobin during treatment (< 10 mg/dL) was significantly associated with a poorer DFS and OS even in women who completed CCRT [24]. Since anemia is associated with shorter survival times for patients with CC [4], it is suggested to treat anemia before and during cancer treatment. Previous studies showed that anemia, among other factors, have been pointed out as an essential biomarker for low muscle mass in the general population. Tseng *et al.* [7] found that haemoglobin levels were independently associated with sarcopenia, and that older adults with anemia had a higher risk of muscle weakness. In the present study, patients with anemia presented a higher rate of pretreatment sarcopenia.

Few studies have assessed pretreatment sarcopenia as a prognostic factor in women with CC, and the results are controversial. Matsuoka *et al.* [25] investigated pretreatment SMI patients undergoing CCRT: their study included 236 patients (155 CCRT and 81 radiotherapy alone) and used two indexes to evaluate pre and post-treatment muscle indexes: psoas muscle and skeletal muscle index. Thus, results showed that both indexes were not prognostic factors of outcome

in CC. However, it must be emphasized that the results were not separated by treatment and that muscle mass was evaluated as a prognostic factor regardless of FIGO stage. Still, Yoshikawa *et al.* [26] showed that pretreatment low skeletal muscle mass, assessed through psoas muscle index, was a prognostic factor for patients with visceral metastases in CC, even with a lower number of participants (28 patients undergoing CCRT and 12 undergoing other treatments). Finally, Han *et al.* [27], in a group of women with early stage CC (IB1-IIA) found a significantly worse PFS and OS when low muscle mass was assessed volumetrically, although this difference was not observed when evaluated by area of skeletal muscle and adipose tissue at the third lumbar vertebral. Aichi *et al.* [28] concluded that a low pretreatment SMI is an independent prognostic factor for OS in patients diagnosed with stage III cervical cancer and treated with concurrent chemotherapy. In their study, the optimal cutoff value for predicting 5-year survival was 35.6 cm^2/m^2, defined based on data derived from 24 patients with a low SMI and 68 patients without a low SMI. A low SMI was significantly associated with shorter OS, with no significant difference in PFS. In their study, a low SMI remained as an independent OS-defining prognostic factor after multivariate analysis [28].

4.3. Strengths and Weaknesses

In our series, pretreatment normal SMI was not associated with more chances of survival without progression, after multiple analyses. Recently, a systematic review and meta-analysis pointed out adverse effects of pretreatment sarcopenia in OS and PFS in CC patients [15]. Contrary, Yoshikawa *et al.* [26] found that metastatic CC patients with a higher psoas muscle index (PMI) had a significantly better OS when treated by CCRT than those with a lower PMI, even after multivariate analysis. One explanation for this phenomenon is that when patients with sarcopenia are diagnosed in an advanced stage, they probably enter a vicious cycle cause their conditions already represent a progressive systemic chronic inflammation, worsening skeletal muscle loss from the beginning of treatment, and, consequently, the prognostic. Recently, a systematic review and meta-analysis pointed out adverse effects of pretreatment sarcopenia in OS and PFS in CC patients [15]. Even though we did not find a relationship between the SMI measured in the pretreatment with FIGO stages, we found that patients at the advanced stage and low SMI had lower PFS and OS.

Despite CCRT being the standard of care for patients with locoregional cervical cancer [29], it is already clear that not completing the planned CCRT is a factor associated with worse PFS and OS [30]. In our sample, women who received incomplete treatment were associated with lower PFS and OS. Disparities in the receipt of standard of care are due to many factors such as treatment toxicities, comorbidities, hospital facilities, socioeconomic disparities, age, race and ethnicity. For example, Uppal *et al.* [30] evaluated the disparities in guideline-based care in locally advanced CC using the National Cancer Database (women diagnosed between 2004 and 2012) and the final cohort consisted of 16,195 pa-

tients. The rate of complete guideline-based care varied between 58.4% for non-Hispanic white and 51.5% for Hispanic women.

Our sample had a limited number of women treated for cervical cancer, but it has a similar distribution to other articles and, in addition, our institution where the patients underwent treatment is a national reference for this type of cancer. As a result, the distribution of patients is heterogeneous, as it receives patients from all states in the country.

A strength of our work is the assessment of sarcopenia through direct and objective analysis of the SMI of the lumbar area from the CT scan used for treatment planning. Other studies analyze sarcopenia by measuring the SMI using software, which is not always available, and thus reduces the chance of reproducibility in other centers.

4.4. Implications for Practice and Future Research

Our study has limitations; we investigated 151 patients with different FIGO stages of CC under a single treatment type. Although this fact brings up robustness regarding the association between pretreatment sarcopenia and the prognosis of CC patients, the sample is still heterogeneous, which can induce divergent results. In the meta-analysis conducted by Sutton *et al.* [15], psoas-based sarcopenia measurements showed negative effects on survival outcomes. However, psoas atrophy at L3 only represents < 10% of the total SMA. Thus, while the assessment of psoas-based sarcopenia may have some prognostic suitability, further investigation is required. We suggest including a volumetric calculation of low muscle mass under the same treatment protocol in future studies to confirm our results. Also, skeletal muscle density could be analysed as a predictor of outcomes. Future studies are challenged to investigate strategies such as protein intake and exercise to prevent low muscle mass before and during treatment.

5. Conclusion

In summary, our data showed pretreatment low SMI was associated with low haemoglobin levels. Although low SMI appears as a worse prognostic factor in the univariate analysis, only haemoglobin level and complete CCRT remained independently associated with PFS and OS. Patients with normal SMI at FIGO stage I and II presented higher PFS and OS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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