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ANALYSIS OF INFLAMMATORY, METABOLIC AND NUTRITIONAL PARAMETERS AS PROGNOSTIC FACTORS IN LOCALLY ADVANCED CERVICAL CANCER

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ABSTRACT

Multiple predictors have been studied and included in predictive models for locally advanced cervical cancer (LACC) treated with chemoradiation (CRT). Among published predictive models there is often heterogeneity for clinical setting, analyzed outcomes and included predictors, which makes it sometimes difficult to apply the model in the real daily practice. Therefore, there is growing interest in investigating emerging prognostic factors that can provide additional valuable information.

To improve the accuracy of outcome predictions and enable treatment customization based on prognostic profiles, we analyzed a large population of patients treated with CRT for LACC in our institution exploring the impact of several parameters on clinical oncological outcomes. We retrospectively analyzed pre-treatment systemic inflammatory indices, nutritional parameters (focusing on sarcopenic obesity), and metabolic parameters such as maximum standardized uptake value (SUVmax).

This analysis reported conflicting outcomes that currently do not support the routine use of the valuated parameters. However, sarcopenic obesity emerged as a novel and significant predictor of adverse outcomes and we confirmed the importance of pre-treatment hemoglobin assessment and anemia correction.

Advanced statistical methodologies and collaborative efforts are needed to enhance the accuracy of prognostic models. Constructing large databases through cooperative initiatives may provide a robust foundation for the development of reliable predictive models in the future.

SUMMARY

INTRODUCTION

Cervical cancer is one of the most common cancers worldwide [1]. Concurrent chemoradiation (CRT) is the standard treatment option for patients with locally advanced cervical cancer (LACC). Although CRT achieves high rates of local tumor control [2], about one third of patients show treatment failure after the treatment [3,4]. In the literature, several prognostic models, also for cervical cancer patients, have been published in last years. They could help clinicians in predict clinical outcomes allowing a more and more personalized treatment, based on stage, risk of recurrence, and demographic characteristics. Multiple predictors have been studied and included in predictive models and, in the LACC setting, tumor size, histological type, lymph node metastases, and International Federation of Gynecology and Obstetrics (FIGO) stage are prognostic factors significantly related to overall survival (OS) [5,6]. Furthermore, anemia has been known for decades to be a negative prognostic factor in LACC patients [7,8,9,10].

However, among published predictive models there is often heterogeneity for clinical setting, analyzed outcomes and included predictors, which makes it sometimes difficult to apply the model in the real daily practice.

As our understanding of cervical cancer biology and treatment response continues to evolve, there is growing interest in investigating emerging prognostic factors that can provide additional valuable information. In particular, factors such as inflammatory indices, functional imaging-related metabolic parameters, nutritional parameters, and radiomics have shown promise in enhancing our prognostic capabilities [11-14].

Literature evidence about these analyzed parameters is growing but it is largely heterogeneous, and it is leading to discordant results.

To improve the accuracy of outcome predictions and enable treatment customization based on prognostic profiles, we decided to analyze a large population of patients treated with CRT for LACC in our institution exploring the impact of several parameters on clinical oncological outcomes, including local control (LC), distant metastasis-free survival (DMFS), disease free survival (DFS), and OS.

The parameters we retrospectively analyzed were pre-treatment systemic inflammatory indices, nutritional parameters (focusing on sarcopenic obesity), and metabolic parameters such as maximum standardized uptake value (SUVmax). Moreover, we also included in the analysis parameters related to patients, tumor and treatment.

STUDY POPULATION

We conducted a single-center retrospective analysis of LACC patients treated at our institution between July 2007 and July 2021. These patients were part of an approved observational study (ESTHER study, code CE 973/2020/Oss/AOUBo) overseen by our local Ethical Committee. All patients provided informed consent to participate, and no exclusions were made to maintain the study's real-world applicability. However, patients were excluded from this analysis in case of treatment performed with palliative intent and if essential data from clinical records were unavailable.

LACCs were retrospectively classified according to the 2018 FIGO staging system [15]. Before treatment, each patient underwent a 18-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET/CT) scan for initial staging. The ^{18}FDG-PET/CT imaging procedure followed established protocols. Specifically, an intravenous injection of 3 MBq/kg of 18F-FDG was administered after a mandatory 6-hour fasting period. A uniform uptake time of 60 minutes was adhered to across all patients. Imaging data were acquired using a 3-D tomograph (Discovery STE; GE) for a duration of 2 minutes per bed position. To facilitate attenuation correction and provide anatomical context, a low-dose CT scan (120 kV, 80 mA) was conducted. FDG-PET images underwent reconstruction through an iterative 3-D ordered subsets expectation maximization method, encompassing two iterations and twenty subsets, followed by smoothing with a 3-D Gaussian kernel (6-mm), incorporating CT-based attenuation, scatter, and random coincidence event correction.

All 173 patients (**Table 1**) underwent definitive CRT using a combination of external beam radiotherapy (EBRT) to the pelvis (45–50 Gy, 1.8–2 Gy per fraction) and intracavitary interventional radiotherapy (brachytherapy-BRT, either with pulsed or high dose rate) to reach a total equivalent dose of 85–90 Gy on the macroscopic primary tumor. The clinical target volume (CTV) was defined as the gross tumor volume, the uterus, the upper third of the vagina, the parametria, and the pelvic nodes (internal, external, and common iliac, obturator, and presacral nodes) with a 7 mm expansion. Para-aortic lymph nodes were irradiated only in case of nodal metastases in this nodal region. The planning target volume was defined as the CTV plus 10 mm isotropic expansion. Suspicious or metastatic pelvic nodes received a sequential or simultaneously integrated boost up to a total equivalent dose of 55–65 Gy. A daily check of the patient set-up was performed by electronic portal imaging device until 2015 and subsequently by on-board cone-beam CT [16]. Concurrent chemotherapy consisted of intravenous Cisplatin (40 mg/m^2 weekly). Patients were followed up with physical examination every three months for two years and then every six months for the next three years. A thoracic-abdominal-pelvic computed tomography (CT) was performed if clinically indicated or every six months in the first two years and every year in the following three years.

Table 1: Patients and treatment characteristics

Patients *n*° (%)	**173 (100%)**
Median age (range), years	56 (27–85)
Histological type, number of patients (%)	
Squamous cell carcinoma	173 (85.0)
Adenocarcinoma	26 (15.0)
Federation of Gynecology and Obstetrics stage, number of patients (%)	
IB	1 (0.6)
IIA	3 (1.7)
IIB	73 (42.2)
IIIA	9 (5.2)

Patients *n*° (%)	**173 (100%)**
IIIB	3 (1.7)
IIIC1	39 (22.5)
IIIC2	22 (12.7)
IVA	23 (13.3)
Radiotherapy technique, number of patients (%)	
3-D conformal radiotherapy	87 (50.3)
Intensity modulated radiotherapy	66 (38.1)
Volumetric modulated arc therapy	20 (11.6)
Median radiotherapy dose (range), Gy	
Prophylactic pelvic nodes irradiation	46.0 (26.0–50.4)
Metastatic nodes	57.5 (52.5–61.0)
Brachytherapy boost	28.0 (4.0–42.0)

All three analyses encompassed patient-related details such as age and hemoglobin (Hb) level, beyond tumor-related information, including histological type, FIGO stage, clinical tumor stage, clinical nodal stage, and maximum tumor diameter. Moreover, treatment-related data comprised RT technique, EBRT dose and fractionation applied to the pelvic region, BRT boost dose, total tumor dose, and overall treatment time (including both EBRT and BRT, measured in days).

STATISTICAL ANALYSIS

We used basic statistics to describe patient and tumor characteristics, along with treatment details. Categorical data are shown as numbers and percentages, while continuous data are presented as median values and their ranges. We calculated several time-related outcomes: (I) LC: the time from the start of concurrent CRT until local-regional recurrence was detected or the last follow-up for patients without pelvic recurrence. (II) DMFS: the period from the initiation of CRT until distant failure was identified or the last follow-up for patients without distant recurrence. (III) DFS: the time from CRT initiation until any treatment failure occurred or until the last follow-up for patients without LACC recurrence. (IV) OS: the interval between CRT initiation and either the time of death or the most recent follow-up date. We analyzed these outcomes using survival curves generated by the Kaplan–Meier method and performed a simple comparison (log-rank analysis) that included all the mentioned variables. Additionally, we conducted multivariate Cox's regression analysis, including variables with a *p*-value of less than 0.1 from the univariate analysis. We considered a significance level of 5% ($p < 0.05$). Our analysis was carried out using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA).

CHAPTER 1: Systemic Inflammatory Indices

Background and Aim

Recent investigations evaluated the predictive role of several systemic inflammation indices (IIs) which were found to be significantly correlated with the therapeutic outcome in several cancers [17]. In particular, increased neutrophil-lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) were found to be related to worse DFS and OS [18-33] as well as worse cancer response after CRT [31] in LACC patients.
However, many of these studies have primarily focused on a single index [17,19,22,24,26,32,33] or a limited array of indices [18,20,21,25,29,31], often without a thorough assessment of potential confounding variables [19,22,23,28,29,31,32].

Therefore, first we analyzed the predictive role of a broad range of pre-treatment nutritional and systemic inflammatory markers, in a large population of patients with LACC treated with standard CRT, including clinical prognostic factors such as clinical, nutritional, tumor-related, and treatment-related data. Then, we tried to externally validate the predictive significance of the IIs' pre-treatment values, as well as the associated thresholds proposed in the existing literature, within the context of LACC [18-33]. Additionally, we pursued another goal of conducting an exploratory assessment regarding the predictive influence of IIs' values observed at the end of CRT, considering the relatively limited information available on the impact of post-treatment IIs' values [21]. Lastly, we assessed whether the differences between pre- and post-treatment values (Delta-indexes) showed significant correlations with the outcomes under examination: this evaluation was conducted due to the limited data existing in the literature on this aspect [21,29].

Evaluated parameters

The following patients related data were included in this analysis: age, body mass index (BMI), hemoglobin level (Hg, in g/100 mL), and prognostic nutritional index (PNI, calculated as serum albumin multiplied by 10 (g/dL) + 0.005 × total lymphocyte count (per mm3)). All these data refer to before CRT started.
Moreover, we included some tumor related data as histological type (squamous cell carcinoma, adenocarcinoma), FIGO stage, based on the 2018 version, clinical tumor stage, clinical nodal stage, and maximum tumor diameter, and treatment ones (radiotherapy technique, EBRT dose and fractionation on the pelvis, brachytherapy boost dose, total tumor dose, and overall treatment time).

As for IIs, the following were analyzed: NLR, PLR, monocyte-to-lymphocyte ratio (MLR), systemic immune inflammation index (SII, calculated as platelet × neutrophil/lymphocyte), leukocyte-to-lymphocyte ratio (LLR), combination of platelet (PLT) count and NLR (COP-NLR, scored as follows: 0: NLR < 3 and PLT < 300 × 109/L; 1: NLR > 3 or PLT > 300 × 109/L; 2: NLR > 3 and PLT > 300 × 109/L), aspartate aminotransferase/platelet count ratio index (APRI, calculated as [aspartate aminotransferase {IU/L}/upper limit normal/PLT {×109/L}] × 100), aspartate aminotransferase-to-lymphocyte ratio index (ALRI, calculated as aspartate aminotransferase value [U/L]/lymphocyte count [× 109/L]), systemic inflammatory response index (SIRI, calculated as neutrophil × monocyte/lymphocyte), aspartate transaminase to neutrophil ratio index

(ANRI, calculated as aspartate aminotransferase/neutrophils). As for collected patients′ data, all indices referred to routine blood exams performed before CRT.

Considering the external validation of a range of IIs, along with the varying threshold values outlined in the existing literature, we undertook the process of dichotomizing the index-related data. Specifically, we utilized the published cut-off points, particularly focusing on those associated with significant clinical outcomes. Additionally, we conducted an exploratory analysis on the prognostic significance of the IIs values assessed at the conclusion of concurrent CRT and of pre-post-treatment variations of the indices (Delta-indices). In this scenario, we dichotomized the parameters using the median value, owing to the relatively limited availability of published data in this context.

Results

Patients, tumor and treatment related data

Older patient age was significantly correlated with lower DMFS rates at both univariate and multivariate analyses. Similarly, older patients had lower OS rates at both univariate and multivariate analysis. Furthermore, higher BMI values were significantly correlated with worse DFS and worse OS, both in univariate and multivariate analysis. Moreover, Hb values >12 g/dL resulted (compared to patients with Hb < 10 g/dL) in better LC, better DFS, and higher OS rates. Finally, patients with Hb > 12 g/dL showed better DFS at multivariate analysis even compared to patients with Hb levels between 10 and 12 g/dL (**Table 2**).

As regards the clinical outcomes, compared to patients with FIGO stage I-II LACC, patients with FIGO stage III showed, at univariate analysis, worse results in terms of LC, DMFS, DFS, and OS. At multivariate analysis only negative correlations with DMFS, DFS and OS were confirmed. Furthermore, patients with FIGO stage IV, compared with stage I-II, showed worse LC and DFS (both: $p < 0.01$) at univariate analysis but these correlations were not confirmed at multivariate analysis. Finally, larger tumor diameter correlated with worse LC, DFS, and OS. Instead, multivariate analysis confirmed only the negative correlation with LC (**Table 2**).

Moreover, none of the treatment-related parameters was significantly correlated with any of the analyzed outcomes.

Table 2: Univariate and multivariable Cox′s analysis.

	LC				**DMFS**				**DFS**			
	Univariate		**Multivariable**		**Univariate**		**Multivariable**		**Univariate**		**Multivariable**	
	HR/95%CI	***p*:**	**HR/95%CI**	***p*:**	**HR/95%CI**	***p*:**	**HR/95%CI**	***p*:**	**HR/95%CI**	***p*:**	**HR/95%CI**	***p*:**
Age	0.98/0.95–1.02	0.23			1.03/1.01–1.09	0.03	1.03/1.00–1.06	0.02	1.02/0.98–1.04	0.76		
BMI	1.01/0.98–1.11	0.22			1.04/1.00–1.10	0.05			1.10/1.02–1.14	<0.01	1.05/1.01–1.10	0.03
PNI	1.00/0.97–1.02	0.81			0.99/0.97–1.05	0.68			1.03/0.98–1.06	0.98		
FIGO (I-II)	Rif.				Rif.				Rif.			
FIGO (III)	2.55/1.04–6.27	0.04			2.51/1.25–5.06	<0.01	2.86/1.41–5.82	<0.01	2.14/1.19–3.85	0.01	1.96/1.07–3.57	0.03

	LC				DMFS				DFS			
	Univariate		Multivariable		Univariate		Multivariable		Univariate		Multivariable	
	HR/95%CI	*p*:	HR/95%CI	*p*:	HR/95%CI	*p*:	HR/95%CI	*p*:	HR/95%CI	*p*:	HR/95%CI	*p*:
FIGO (IV)	4.91/1.77–13.58	<0.01			2.47/0.96–6.31	0.06			3.24/1.56–6.74	<0.01		
T diameter (maximum)	1.02/1.01–1.04	<0.001	1.02/1.01–1.03	<0.01	1.02/0.99–1.04	0.22			1.03/1.01–1.05	<0.001		
RBC	0.46/0.27–0.78	<0.01			1.11/0.64–2.12	0.68			0.78/0.51–1.27	0.28		
Hb (<10)	Rif.				Rif.				Rif.			
Hb (10–12)	0.41/0.17–1.01	0.05			0.41/0.13–1.25	0.11			0.44/0.19–1.01	0.05	0.41/0.17–0.98	0.04
Hb (>12)	0.11/0.04–0.28	<0.001	0.14/0.05–0.36	<0.001	0.52/0.21–1.35	0.18			0.32/0.15–0.67	<0.01	0.37/0.17–0.79	0.01
NLR	1.02/0.98–1.12	0.26			1.01/0.97–1.12	0.37			1.06/0.99–1.12	0.18		
PLR	1.01/0.99–1.03	0.28			1.03/1.01–1.05	0.02			1.02/1.01–1.03	0.02		
MLR	1.30/0.49–3.51	0.60			1.42/0.52–3.51	0.53			1.22/0.53–2.78	0.67		
SII	0.99/0.99–1.03	0.15			1.01/1.01–1.02	<0.01	1.02/1.01–1.03	<0.01	1.03/1.01–1.04	<0.01		
LLR	1.00/0.98–1.10	0.19			1.00/0.98–1.07	0.21			1.04/0.99–1.10	0.09		
COP-NLR (0)	Rif.				Rif.				Rif.			
COP-NLR (1)	1.11/0.44–2.77	0.81			0.79/0.40–1.58	0.51			0.69/0.38–1.23	0.21		
COP-NLR (2)	2.72/1.09–6.79	0.03			0.97/0.43–2.21	0.95			1.07/0.55–2.07	0.83		
APRI	0.23/0.01–7.70	0.42			0.75/0.19–3.11	0.69			0.81/0.39–1.71	0.59		
ALRI	0.99/0.96–1.01	0.77			1.01/0.99–1.03	0.46			1.03/0.98–1.06	0.67		
SIRI	0.99/0.96–1.02	0.37			0.99/0.98–1.02	0.52			0.99/0.98–1.03	0.36		
ANRI	0.79/0.64–0.98	0.02			1.01/0.92–1.09	0.73			0.99/0.90–1.11	0.81		

Legend: ALRI: aspartate aminotransferase to lymphocyte ratio index; ANRI: aspartate transaminase to neutrophil ratio index; APRI: aspartate aminotransferase/platelet count ratio index; BMI: body mass index; COP-NLR: combination of platelet count and neutrophil to lymphocyte ratio; DFS: disease free survival; DMFS: distant metastasis free survival; FIGO: International Federation of Gynecology and Obstetrics; Hb: hemoglobin; HR: hazard-ratio; LC: local control; LLR: leukocyte-to-lymphocyte ratio; MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; OS: overall survival; PLR: platelet to lymphocyte ratio; PNI: prognostic nutritional index; RBC: red blood cells; SII: systemic immune inflammation index; SIRI: systemic inflammatory response index; T: tumor.

Inflammatory Indices

Analysis of predictive role of IIs on clinical outcomes

In the first analysis considering IIs as continuous variables, higher COP-NLR scores and higher ANRI values were significantly correlated with lower LC rates at univariate analysis, but these correlations were not confirmed at multivariate analysis. Higher SII values were significantly correlated with lower DMFS rates at both univariate and multivariate analysis, as well as lower DFS rates, only at univariate analysis. None of the analyzed indices showed significant correlations with OS. (**Table 2**)

External validation of the IIs': univariate analysis

After that we have dichotomized data for external validation using threshold values outlined in literature.

As for pre-treatment IIs, in the univariate analysis, no significant correlations between the IIs and DMFS, DFS, and OS were observed. In relation to LC, significant improvements were associated with NLR values ≤ 1.6 (*p*-value = 0.022), ≤3.0 (*p*-value = 0.034), and ≤3.59 (*p*-value = 0.014). Similarly, higher LC rates were significantly linked to PLR values ≤210.00 (*p*-value = 0.017), but also with APRI values > 0.18 (*p*-value = 0.012), ANRI values > 3.47 (*p*-value = 0.044), and COP-NLR values ≤ 1 (*p*-value = 0.010). Conversely, only a trend was observed between superior LC rates and patients with SII ≤ 1000 (*p*-value = 0.077), MLR ≤ 0.26 (*p*-value = 0.100), LLR ≤ 4.17 (*p*-value = 0.088), or ALRI ≤ 9.62 (*p*-value = 0.117) (**Table 3**).

On the other hand, for post-treatment IIs, the sole statistically significant correlations were the most favorable LC in patients with NLR < 5.66 (p-value = 0.037) and the most favorable DMFS rate in patients with a systemic inflammatory response index (SIRI) < 3.50 (p-value = 0.018). Moreover, the dynamic assessment of the delta indices did not exhibit any significant correlation with the considered outcomes.

Table3: Univariate analysis of inflammatory indices (pretreatment values); survival outcomes are expressed in percentages. Only statistically significant values (and values with trend for significance) are shown.

Variable	Value #	Patients No	2-y LC	5-y LC	*p*-Value	2-y DMFS	5-y DMFS	*p*-Value	2-y DFS	5-y DFS	*p*-Value	2-y OS	5-y OS	*p*-Value
NLR	≤1.60	24	100.0	100.0	**0.022**	90.9	83.3	0.243	78.9	78.9	0.075	91.3	72.9	0.572
	>1.60	149	84.3	79.4		79.0	73.2		66.4	61.7		84.8	68.6	
NLR	≤3.00	99	88.8	87.0	**0.034**	81.2	73.7	0.804	69.9	62.1	0.958	89.9	67.4	0.389
	>3.00	74	75.4	75.4		79.9	75.9		68.2	66.2		80.3	70.9	
NLR	≤3.59	122	87.6	86.2	**0.014**	81.6	74.6	0.698	71.6	65.5	0.255	90.3	69.5	0.164
	>3.59	51	72.3	72.3		78.5	75.1		63.4	60.4		74.8	68.2	
PLR	≤210.00	127	88.3	85.9	**0.017**	83.1	77.3	0.147	72.7	66.7	0.185	88.8	73.6	0.080
	>210.00	46	71.4	71.4		73.6	67.5		59.2	56.4		77.4	63.3	
SII	≤1000.00	106	87.8	86.1	0.077	80.3	74.3	0.864	70.8	63.3	0.759	87.6	67.9	0.734
	>1000.00	67	75.6	75.6		81.2	75.0		66.4	64.2		82.8	70.7	
LLR	≤4.17	93	88.1	86.2	0.088	79.2	75.4	0.601	69.0	60.9	0.714	81.9	39.2	0.328
	>4.17	80	77.2	77.2		82.1	73.8		69.2	67.3		89.7	69.4	
APRI	≤0.18	96	76.4	76.4	**0.012**	80.1	77.4	0.769	64.7	64.7	0.325	84.4	70.7	0.327
	>0.18	77	91.5	89.1		79.6	71.3		74.7	62.6		91.0	70.2	
ANRI	≤3.47	87	77.6	77.6	**0.044**	81.5	78.2	0.822	66.8	65.3	0.462	84.0	69.9	0.186
	>3.47	86	88.6	88.6		78.3	71.6		71.5	62.8		90.6	71.2	
COP-NLR *	≤1	137	86.7	85.5	**0.010**	80.2	74.5	0.733	70.6	63.9	0.390	90.3	70.0	0.250
	>1	36	69.0	69.0		79.0	75.2		63.0	63.0		75.6	71.6	

Legend: ALRI: aspartate aminotransferase-to-lymphocyte ratio index; ANRI: aspartate transaminase-to-neutrophil ratio index; APRI: aspartate aminotransferase/platelet count ratio index; COP-NLR: combination of platelet count and neutrophil-to-lymphocyte ratio; DMFS: distant metastasis-free survival; DFS: disease-free survival; LC: local control; LLR: leukocyte-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PFS: progression-free survival; PLR: platelet-to-lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammatory response index; * COP-NLR scored as follows: 0: NLR < 3 and PLT < 300; 1: NLR > 3 or PLT > 300; 2: NLR > 3 and PLT > 300. #: different cut off from published studies.

External validation of the IIs': multivariate analysis

An initial multivariate analysis was then performed, including all IIs with significant correlations with LC while selecting cut-off values associated with lower p-values from the preceding univariate analysis. We also decided to include in the multivariate Cox's regression analysis those IIs that showed a trend for significance (a p-value < 0.1). This assessment confirmed a higher LC rate in patients with APRI > 0.18 (HR: 0.412; 95% CI: 0.174–0.976; p-value = 0.044). It is noteworthy that no substantial correlations were observed with DMFS, DFS, and OS. Only NLR > 3.59 revealed a trend for lower LC rates (HR: 1.990; 95% CI: 0.957–4.140; p-value = 0.065) (**Table 4**).

Table 4: Multivariate Cox's analysis of inflammatory indices (pre-treatment values); survival outcomes are expresses in percentages. Only statistically significant values (and values with trend for significance) are shown.

Parameter	Values	Patients N (%)	LC			DMFS			DFS			OS		
			HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
NLR	≤3.59	122	1	rif.					1	rif.				
	>3.59	51	1.990	0.957–4.140	0.065				1.360	0.795–2.328	0.262			
PLR	≤210.00	127				1	rif.					1	rif.	
	>210.00	46				1.360	0.706–2.620	0.357				1.646	0.885–3.059	0.115
APRI	≤0.18	96	1	rif.										
	>0.18	77	0.412	0.174–0.976	**0.044**									

Legend: APRI: aspartate aminotransferase/platelet count ratio index; DFS: disease free survival; DMFS: distant metastasis free survival; FIGO: International Federation of Gynecology and Obstetrics; LC: local control; NLR: neutrophil to lymphocyte ratio; OS: overall survival; PLR: platelet to lymphocyte ratio.

Subsequently, a secondary multivariate analysis was conducted, incorporating the clinical parameters with statistically significant correlations with at least one of the endpoints. In this analysis, no significant impact of IIs on any of the endpoints was recorded.

Discussion

Considering IIs as continuous variables, the multivariate analysis indicated a notable correlation between higher SII values and poorer DMFS. Instead, focusing on external validation of IIs, the multivariate analysis reveals a significant association between APRI and LC.

Moreover, the univariate and multivariate analyses confirmed that established clinical factors, such as age, FIGO stage, Hb levels, and RT dose, influence clinical outcomes [34]. The univariate analysis also showed a potential impact, primarily on LC, of IIs, like NLR, PLR, APRI, ANRI, and COP-NLR. However, our examination of post-treatment IIs showed a correlation only between SIRI with DMFS and between NLR and LC. This discrepancy suggests that the prognostic relevance of different IIs might vary based on their evaluation either before or after treatment, as previously reported [21].

Furthermore, the lack of correlations between Delta-IIs and outcomes suggests the limited utility of the dynamical assessment of IIs over time. Moreover, the primary clinical interest resides in pretreatment IIs values due to their potential to guide personalized treatment adjustments. Conversely, after CRT and BRT, there is no evidence to support additional treatments, particularly CHT, to improve clinical outcomes [35,36].

The outcomes of our analysis stand in contrast to those reported in other studies, demonstrating a significant impact of IIs on tumor response [31], DFS [19,21,23,24,25,28,32,33], and OS [21-26,28,30,32,33]. This prompts several considerations. First, it is worth noting that other investigations have also yielded results where IIs did not significantly influence clinical outcomes [17,18,20,29]. Furthermore, we cannot exclude the possibility of publication bias or other bias (selection bias, information bias, or confounding factors) due to the retrospective nature of all these studies.

Moreover, our analysis distinguishes itself by comprehensively addressing a broader spectrum of potential confounding factors compared to prior studies. In fact, certain analyses omitted the consideration of important factors, such as the FIGO stage [23,32] or nodal stage [19,22,28,29,31]. Additionally, treatment-related variables were frequently omitted in many studies [18,20,21,23,25,26,28-32]. Notably, only our study, and the paper of Koulis et al. [10], integrated Hb levels into the analysis. Interestingly, even in their analysis, no significant correlation was observed between the chosen II (NLR) and the outcome of interest, and only anemia emerged as a factor significantly associated with lower OS rates in the multivariable analysis.

On the basis of these considerations, we hypothesize that, compared to other analyses, our study has a lower risk of confounding bias. In fact, when confounding factors are not adequately controlled for in the study design or analysis, they can distort the observed relationship between the independent and dependent variables. This bias can either exaggerate or mask a real effect.

CHAPTER 2: Nutritional parameters

Background and Aim

Recent studies have explored the use of various body composition-related parameters in cancer patients. In particular, there is a growing awareness of the impact of parameters such as BMI, sarcopenia (SP), and sarcopenic obesity (SO) in cancer patients undergoing RT [37,38].

Also, in LACC, several studies have explored the impact of SP in patients treated with CRT. Kiyotoki et al. found that SP, defined as a ≥15.0% loss of iliopsoas muscle from baseline, was a significant independent prognostic factor for DFS and OS in CRT patients [39]. Similarly, Abe et al. emphasized the importance of maintaining muscle mass and quality during treatment, as extreme leanness, lower skeletal muscle quality, and muscle loss during therapy predicted poor prognosis [40]. Moreover, Lee et al. identified skeletal muscle loss as an imaging biomarker associated with outcomes after definitive CRT for LACC without specifically addressing SP [41].

Moving on to the relationship between BMI and LACC outcomes, Gnade et al. observed that obese and morbidly obese women had a disproportionately inappropriate screening before cervical cancer diagnosis, and morbidly obese women exhibited worse OS [42]. Moreover, Clark et al. found that both extremes of BMI (underweight and overweight/obesity) were associated with worse OS in LACC [43]. Additionally, Münstedt et al. did not find a negative impact of obesity on the prognosis of patients with LACC but observed that a higher BMI was associated with improved OS for endometrial and cervical carcinomas [44].

Finally, studies have explored the significance of the prognostic nutritional index (PNI = (10 × serum albumin [g/dL]) + (0.005 × lymphocytes/μL)) in LACC patients. Haraga et al. found that low PNI predicted poor prognosis in LACC patients undergoing CRT and RT [18]. In another study, Wang et al. supported the importance of PNI and systemic inflammatory indexes as predictors of prognosis in patients with stage IIB-III LACC receiving RT [45]. Furthermore, Guo et al. demonstrated that a low PNI was associated with lower quality of life, reduced tolerance to RT and CHT, lower objective response rates, and worse OS for LACC [46].

However, many of these studies have mainly focused on just one anthropometric parameter [42-44] or a limited set of such indices [18,39,45,46]. Furthermore, the impact of SO in LACC has not been previously evaluated and several studies did not thoroughly examine potential confounding variables [18,44].

Therefore, we investigated the predictive capabilities of a range of body composition-related parameters in a large group of LACC patients, considering relevant clinical prognostic factors, including clinical information, tumor-related characteristics, and treatment-related data. This analysis was conducted by a multidisciplinary team comprising radiation oncologists, radiologists specializing in body composition, medical physicists, RT technicians, and gynecological oncologists.

Evaluated parameters

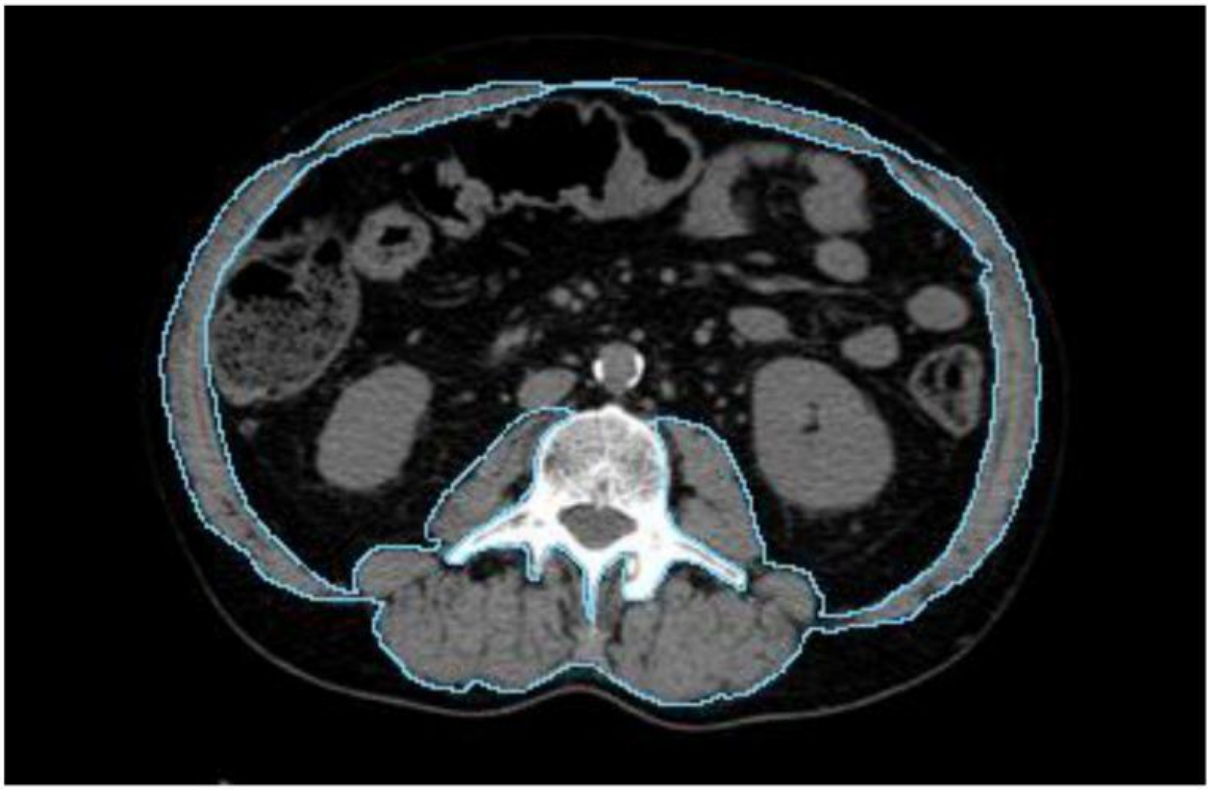
The analysis encompassed the evaluation of various body composition-related parameters, including BMI, SP, and SO. BMI was calculated as the ratio of an individual weight in kilograms to the square of their height in meters (BMI = weight in kg/(height in m^2) and it was stratified into four categories (underweight—

BMI <18.5 kg/m2; normal weight—18.5 to 24.9 kg/m2; overweight—25 < BMI < 29.9 kg/m2; and obesity—BMI ≥ 30 kg/m2) according to the cut-off points proposed by Weir et al. [47].

SP was calculated as follows. We collected all pre-treatment CT scans to perform an instrumental evaluation of the skeletal muscle area (SMA). At the level of the third lumbar vertebra (L3), we identified and contoured all relevant muscle structures, including the rectus abdominis, external oblique, internal oblique, transversus abdominis, quadratus lumborum, spinalis, longissimus thoracis, iliocostalis lumborum, and psoas muscles. This comprehensive assessment is based on the established correlation between muscle mass at this level and overall body muscle volume, as commonly performed in the field' [48], demonstrating the method reliability for evaluating SP [49] (**Figure 1**). The defined region of interest (SMA) was then divided by body surface area, obtaining the skeletal muscle index (SMI) [50]. SP patients were defined by using a cut-off established by calculating the median skeletal muscle index (SMI) value minus 2 standard deviations. Moreover, we derived the cut-off from Prado and Martin to establish if the sarcopenic condition was present or not [50,51].

Finally, SO was defined by assessing the prevalence of SP alongside the co-presence of a BMI ≥ 30 kg/m2, aligning with the criteria set forth by Prado et al. [50] in their landmark study on the prevalence and clinical implications of sarcopenic obesity in patients with solid tumors.

Figure 1: Delineation of the skeletal muscle area on a CT scan at the level of the third lumbar vertebra.

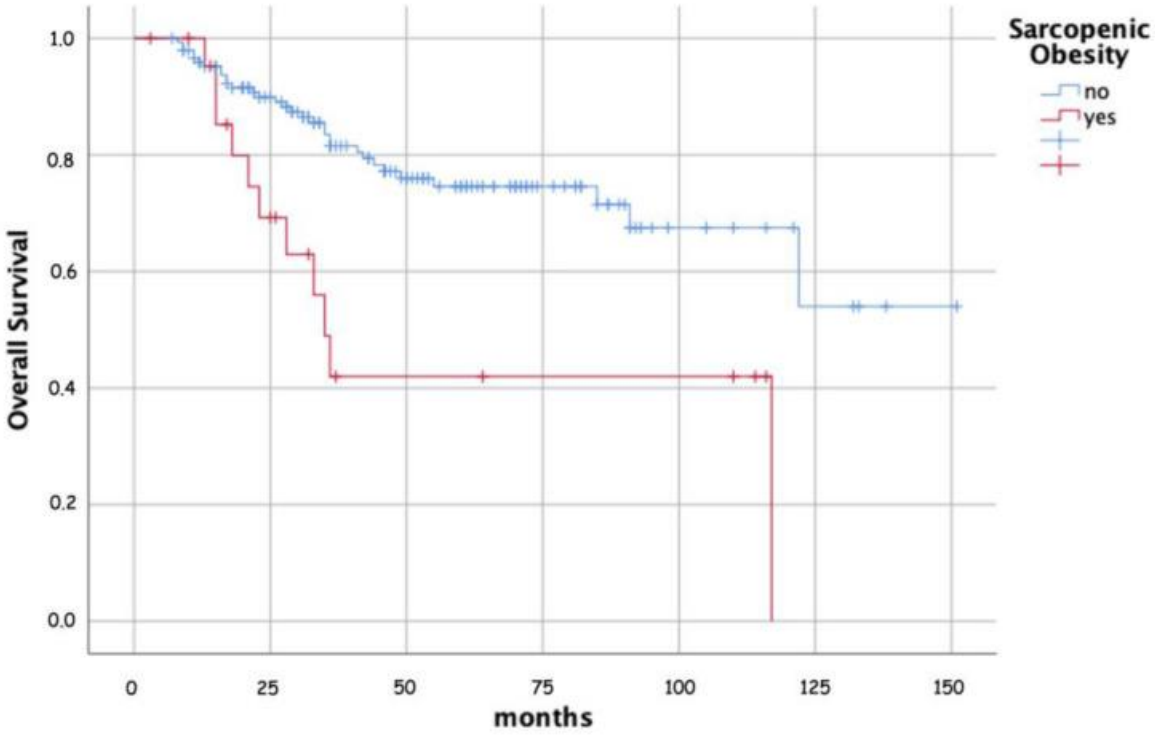


Results

At univariate analysis, the stratification of patients based on SP did not reveal any statistically significant correlations with the considered outcomes. Moreover, BMI was significantly correlated with DMFS ($p = 0.033$), DFS ($p = 0.018$), and OS ($p = 0.023$), with the highest rates recorded in normal-weight patients. Finally, patients with SO had a significantly worse DFS ($p = 0.005$) and OS ($p < 0.001$) in comparison with patients without this condition.

After, at multivariate analysis, both BMI and SP did not show statistically significant correlations with any of the endpoints analyzed. However, the condition of SO was found to be related to substantially worse DFS (p = 0.020) and OS (p = 0.009) (**Figure 2**).

Figure 2: Actuarial survival in patients with and without sarcopenic obesity.



Discussion

In this analysis, we investigated body composition-related parameters such as BMI, SP, and SO as prognostic factors in LACC treated with CRT. These parameters have gained attention in recent years as potential prognostic factors in cancer treatment, including cervical cancer [37,38]. Previous studies have explored the impact of SP on outcomes in LACC patients undergoing CRT. The findings from our study differ from some existing evidence, as we observed that SP did not show a statistically significant correlation with survival outcomes. In fact, the studies by Kiyotoki et al. [39] and Abe et al. [40] identified SP as a significant predictor of DFS and OS, respectively. However, it is important to note that these studies had different definitions and cut-offs for SP, highlighting the need for standardized criteria in future research.

In terms of BMI, our univariate analysis indicated a significant association with DMFS, DFS, and OS, with normal-weight patients showing the highest survival rates. These findings align with studies by Gnade et al. [42] and Clark et al. [43], which also reported worse OS in both underweight and overweight/obese individuals with LACC. However, it is important to note that we observed these associations only in the univariate analysis level. On the contrary, in multivariable analysis, the impact of BMI did not reach statistical significance, indicating that other factors may confound this relationship. The influence of obesity on prognosis in LACC remains a complex and debated topic, as evidenced by the contrasting results reported by Münstedt et al. [44] and Legge et al. [52]. Future studies should continue to explore the relationship between BMI and LACC outcomes, considering potential confounding factors and examining specific subgroups.

Notably, our analysis is among the first to investigate the significance of SO in LACC patients. We found that patients with SO had significantly worse outcomes in terms of DFS and OS compared to those without this condition. This underscores the importance of evaluating both muscle mass and body fat in cancer prognostication, as SO represents a distinct phenotype with unique clinical implications [37].

The differences observed in the impact of SP, BMI, and SO on LACC outcomes may be attributed to the complex interplay of these parameters with the tumor microenvironment, treatment response, and patient characteristics. While SP and BMI provide valuable information about body composition, SO takes into account the combined effect of muscle loss and excess body fat, potentially reflecting a more comprehensive assessment of a patient's status and health. In particular, the potential mechanisms underlying the adverse effects of SO on survival may include altered drug pharmacokinetics [50,53], increased systemic inflammation [54-56], and impaired immune responses [57,58]. However, further research is needed to elucidate these mechanisms and better understand the clinical implications of SO in cervical cancer.

Considering the conflicting results of studies on the relationship between BMI and LACC outcomes, further analyses on this topic, considering potential confounding factors and examining specific subgroups, are warranted. Moreover, future research in this area could also investigate the possibility of treating SO in LACC patients, recognizing the challenges posed by the short time frame for planning and delivering CRT. Evaluating whether an improvement in this parameter could translate into improved treatment outcomes is also of particular interest. Furthermore, understanding the dynamics of SO and its response to interventions within the context of LACC treatment could inform the development of predictive models. These models could incorporate SO along with other potential prognostic factors, such as indices of systemic inflammation, results from functional imaging, radiomic indices, and results of liquid biopsies. By comprehensively assessing how these factors interact and influence treatment outcomes, we may move closer to achieving more accurate prognostication and personalized treatment strategies for LACC patients.

Finally, recognizing the intricate interplay between sarcopenic obesity and treatment outcomes, further studies are warranted to assess changes in SO over the course of treatment. Such research would illuminate potential bidirectional relationships between body composition and treatment efficacy, side-effects, and overall prognosis, contributing significantly to personalized patient care in LACC.

CHAPTER 3: Functional imaging-related metabolic parameters

Background and Aim

The present analysis explores the prognostic significance of a simple and readily available functional imaging-related metabolic parameter, the SUV-max from ^{18}FDG-PET scans. The SUV of FDG-PET quantifies metabolic activity, with SUV-max being the highest voxel value within the region of interest. Prior investigations into the prognostic significance of SUV-max in LACC have yielded contradictory outcomes [59-72]. Therefore, by incorporating SUV-max into our comprehensive prognostic analysis, we aim to determine its independent impact on prognosis in LACC patients.

Evaluated parameters

SUVmax values from FDG-PET/CT were recorded and analyzed. For univariate analysis, SUVmax values were categorized into quartiles, while for multivariate analysis they were treated as continuous variables.

Results

Stratification of patients based on median SUV-max or into quartiles during univariate analysis did not reveal any statistically significant correlations with the considered outcomes. This absence of significant correlation was confirmed in multivariable analysis, employing SUV-max as a continuous variable. (**Table 5**).

Table 5: Univariate analysis; survival outcomes are presented in percentage format.

Variable	**Value**	**Patients No**	**2-y LC**	**5-y LC**	**P**	**2-y DMFS**	**5-y DMFS**	**P**	**2-y DFS**	**5-y DFS**	**p**	**2-y OS**	**5-y OS**	**p**
SUV max T pre-treatment*	< 19.0	119	86.7	86.7	0.101	81.0	77.1	0.499	72.6	67.5	0.242	89.0	76.4	0.179
	≥ 19.0	40	76.3	72.9		78.2	71.1		63.5	57.1		83.2	57.7	

Legend: DFS: disease free survival; DMFS: distant metastasis free survival; LC: local control; OS: overall survival; SUV max: maximum standardized uptake value; y year; *: highest quartile versus others.

Discussion

In this part of analysis, we focused on pre-treatment SUV-max and did not assess metabolic response or post-treatment SUV-max. This choice was guided by the recognition that predictive models in LACC are more valuable before the initiation of CRT, given the limited success of post-CRT interventions like adjuvant systemic therapies [73,74]. However, some studies have shown significant prognostic value for post-treatment SUV-max or metabolic response [75,76]. These findings could guide future trials evaluating the efficacy of post-CRT adjuvant therapies in high-risk patients.

Our analysis did not include other FDG-PET parameters, such as total lesion glycolysis and metabolic tumor volume, focusing instead on the commonly available SUV-max parameter. This pragmatic approach aimed to assess the prognostic impact of a standard FDG-PET report parameter.

Our findings diverge from previous analyses showing a clear impact of pre-treatment SUV-max in LACC patients undergoing CRT. A systematic review by Han et al. presented a significant correlation between pre-treatment SUV-max and event-free survival (EFS), with a hazard ratio (HR) of 1.94 and a 95% confidence interval (CI) of 1.20 to 3.05 [12]. However, within the studies analyzed by Han et al., only a few showed statistically significant impacts on EFS [59,62,63,68], while most did not establish a clear correlation [60,61,64–67,70,71].

Moreover, our case series appears to have a less favorable prognostic profile compared to those in Han et al.'s review, with 55.5% of our patients diagnosed with FIGO stage III-IV LACC, versus 18.2% to 44.2% (median 27.5%) in the review. Furthermore, Han et al.'s review identified a substantial risk of publication bias through Egger's test ($p=0.015$), suggesting that observed associations between pre-treatment SUV-max and outcomes might be influenced by this bias.

In summary, our findings, combined with divergent literature results, do not strongly support the use of SUV-max for reliable prognosis prediction in LACC. The feasibility of modifying therapeutic strategies based on SUV-max readings is inconclusive. However, there are indications that functional-metabolic imaging techniques might warrant further investigation for prognostication in LACC.

FINAL CONSIDERATIONS, CONCLUSIONS AND FUTURE PERSPECTIVES

In summary, our analysis, along with the discussed studies, presents conflicting outcomes that currently do not support the routine use of hematologic (IIs), metabolic (^{18}F-FDG PET-SUVmax), or nutritional parameters (BMI, PNI, SP, or SO) as independent prognostic tools in patients with LACC.

However, SO, in particular, emerged as a novel and significant predictor of adverse outcomes in LACC patients. These findings underscore the importance of considering both muscle mass and body fat in cancer prognostication and treatment planning.

Moreover, despite the inconclusive results of the explored parameters, we confirmed the importance of pre-treatment Hb assessment and anemia correction. They also emphasize the need to deliver sufficient total RT doses (over 75 Gy) to achieve effective disease control and overall survival.

We also highlighted the need for comprehensive evaluations encompassing multiple IIs, metabolic, and nutritional parameters all together to prove more effective in prognostication than the analysis of parameters individually considered. Furthermore, to enhance the clarity and reliability of future investigations, a comprehensive inclusion of all potential confounding variables is needed.

Advanced statistical methodologies and collaborative efforts could enhance the accuracy of prognostic models. Constructing large databases through cooperative initiatives may provide a robust foundation for the development of reliable predictive models in the future.

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