Seminars in Oncology 51 (2024) 149–153

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

Deep Myometrial Infiltration leads to a measurable Inflammatory Response in Endometrial Cancer. A Prospective Observational Study ☆

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ARTICLE INFO

Article history:
Received 25 July 2024
Revised 29 September 2024
Accepted 2 October 2024

Keywords:
Endometrial Cancer
Myometrial infiltration
Inflammation Index
Cancer Pathogenesis
Tumor microenvironment
NLR

ABSTRACT

Backgrounds: This study aims to evaluate the correlation between inflammation indices, such as neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR) and deep myometrial infiltration (≥50%) prospectively in patients with endometrial carcinoma, providing insights into the interaction between these parameters

Material and Methods: A prospective observational cohort study was conducted at AOU Vanvitelli in Naples, Italy, from August 2023 to March 2024. Data from 161 patients undergoing surgery for endometrial cancer, including preoperative blood counts and histopathological information, were collected. Statistical analyses were performed using R software.

Results: After logistic regression, NLR and MLR showed a statistically significant association with deep myometrial infiltration (NLR log(OR) 0.15, $P = .040$; MLR log(OR) 0.30, $P = .008$). However, after multivariate logistic regression which included other risk factors such as grading, histotype, and MSI only NLR retained statistical significance, (Log(Or) 0.18, $P = .031$).

Conclusion: Our results demonstrate noticeable changes in inflammation indices associated with deep myometrial infiltration in endometrial carcinoma. Moreover, a correlation between NLR and deep myometrial infiltration exists regardless of microsatellite instability, histotype, and grading.

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Background

Myometrial infiltration represents one of the major prognostic factors in endometrial carcinoma. It manifests natural tumor progression, deepening locally before facilitating the development of distant metastases [Table 1] [1]. Its importance has long been known, and it is an independent prognostic factor, so much so that it is a parameter included in tumor staging and risk class stratification [2,3]. It is easy to see how the macroscopically detectable factor of myometrial infiltration is sustained by microscopic mechanisms of tissue invasion [4]. Such events could produce an immune response, altering indices of inflammation, such as the neutrophil-lymphocyte ratio (NLR), monocytes-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) [5,6]. In addition, NLR, MLR, and PLR can be predictive of a neoplasm's invasiveness in gynecological malignancies [7,8]. In particular, existing evidence demonstrates that NLR and PLR subtend stromal involvement in ovarian cancer and endometrioid endometrial cancer [7,8]. Moreover, levels of CA-125 accompany the ratios of inflammatory indices in predicting stromal invasiveness in ovarian cancer [7]. Their relationship can be interpreted in a bivalent manner: the progression of the microscopic tumor can influence the subject's inflammatory response, and the inflammatory state can promote its progression [9]. What is unclear today is whether this response can be of such a magnitude that it becomes clinically detectable. Therefore, the design of our study involves a prospective observational cohort study that enrolled patients undergoing surgery for endometrial carcinoma, to identify a correlation between parameters of inflammation

Abbreviations: LVSI, lymphovascular space invasion; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; BMI, Body Mass Index; MS (I/S), Microsatellite (in-) stability.

☆ Take Home Message: the attainment of deep myometrial infiltration by endometrial carcinoma results in a measurable inflammatory response, which may predict patients in need of further diagnostic investigation.

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https://doi.org/10.1053/j.seminoncol.2024.10.002
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Table 1
Existing evidence inflammatory indices predict invasiveness in endometrial cancer.

Author, year of publication	Country	Period of enrollment	Study design	Neoplasm	No. of participants	Preoperative inflammatory indices	Invasiveness
Polat 2016 [7]	Turkey	2013-2015	Prospective Monocenter Cohort	Ovary	275	NLR, PLR, CA-125	Stromal
Acikgoz 2017 [8]	Turkey	2000-2013	Prospective Monocenter Cohort	Endometrioid endometrial	118	NLR, PLR	Cervical stroma

measured by blood count and the condition of deep myometrial infiltration, defined as ≥50% of the entire wall thickness [1]. Understanding the interrelation between these parameters could provide a comprehensive view of the inflammatory response and its impact on disease progression and patient outcomes since deep myometrial infiltration is an independent risk factor for endometrial cancer [2,10]. In addition, while deep myometrial infiltration can be estimated preoperatively by pelvic ultrasound it requires a second-level diagnosis by MRI, increasing costs and prolonging diagnostic pathways [11-15]. In this context, a possible correlation between indices of inflammation and deep infiltration would help to select patients worthy of further investigation better. Our study prospectively evaluated the correlation between indices of inflammation and myometrial infiltration ≥50% in our population to identify the interaction between these parameters.

Materials and Methods

The research methods were established a priori and authorized through evaluation by the Ethics Committee of the individual centers (Ethical Committee "Campania 2″ IRB 30661/2022 of 31/03/2022). The study was then registered on the clinicaltrials.gov platform under NCT05657483.

Between August 2023 and March 2024, all women referred to AOU Vanvitelli in Naples, Italy, with endometrial cancer who met all the inclusion criteria and none of the exclusion criteria were prospectively enrolled in the study with no randomization. All patients freely participated in the study and signed an informed consent.

The inclusion criteria were age ≥18 years, histological diagnosis of endometrial cancer, and patients undergoing surgical staging of pathology, with complete anatomopathological information obtainable. The exclusion criteria were patients with chronic inflammatory diseases (IBD; rheumatological conditions and similarities), patients with an additional synchronous oncological diagnosis or within the previous 3 years, and patients on steroid therapy within the last 30 days before recruitment.

Data Collection

All patients enrolled in the study underwent blood sampling the day before surgery.

The data collected preoperatively were blood counts of neutrophils, leukocytes, monocytes, platelets, eosinophils, and basophils. The hematochemical parameters were then expressed as Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Platelet-to-Lymphocyte Ratio (PLR). The ratio was defined as absolute cell count divided by absolute lymphocyte count. All patients then underwent surgery according to international standards of care [2-16].

We also collected histopathological data on myometrial infiltration, grading, histotype, and lymph node positivity (micrometastases and macrometastases) [17-19], microsatellite stability and LVSI was expressed as a semiquantitative evaluation [20-22]. Negative or focal involvement was considered negative. The primary outcome of interest, myometrial infiltration, was expressed as a dichotomous variable <50% and ≥50%, defined as deep. All the parameters collected were kept in unique Clinical Registration Forms (CRF) and digitized in an electronic database on Excel software anonymously, under the responsibility of the Principal Investigator. They will be destroyed after the results are published.

Statistical Analysis

The sample was analyzed according to the outcome of myometrial infiltration, expressed as < or ≥50% of its millimetric thickness. The nominal variables were expressed as absolute frequency and percentages and compared using Fisher's exact [23] and Chi-square tests [24]. Continuous variables were expressed as median and interquartile range and compared using the Wilcoxon test [25].

The null hypothesis of our study was that there was no difference in the mean values of NLR, MLR, PLR, between patients with <50% or ≥50% myometrial infiltration. (H0: $\mu 1 = \mu 2$; H1: $\mu 1\text{-}\mu 2 \neq 0$ two-sides).

The weights of the individual values on the dichotomous dependent variable myometrial infiltration were calculated as a logarithmic regression [26]. The significance of the model used was assessed using the maximum likelihood method [27]. The distribution of the continuous variables for the individual parameters of the reference outcome was graphed in boxplots. The statistical significance level was set at 0.05. All statistical investigations were performed using R software and R Studio version 2023.12.1 + 402.

Results

Our prospective observational cohort study, conducted at our institution between August 2023 and March 2024, examined the inflammatory index and ultrasound endometrial thickness of 161 patients undergoing surgery for endometrial cancer. The sample was stratified according to myometrial infiltration: 99 samples, <50% versus 62 samples, ≥50%.

Population Characteristics

Population in the exam was analyzed depending on the distribution of the most important clinical and pathological pathways. Analyses revealed significant differences in characteristics related to microsatellite instability (MSI, 12% *v* 27%, in <50% *v* ≥50% myometrial infiltration, $P = .014$), LVSI (positive 12% *v* 64%, in <50% *v* ≥50% myometrial infiltration, $P < .001$), grading (3, 21% *v* 52%, in <50% *v* ≥50% myometrial infiltration, $P < .001$), histology (nonendometrioid, 5% *v* 17.8%, in <50% *v* ≥50% myometrial infiltration, $P = .025$), and risk class (other than low risk, 18% *v* 97%, in <50% *v* ≥50% myometrial infiltration, $P < .001$) between the 2 groups. The demographic characteristics of the sample are shown in Table 2.

Outcomes

The study's primary outcome was to compare the mean of the inflammation indices expressed as NLR, MLR, and PLR in the 2

Table 2
Population characteristics.

Myometrial Infiltration			
Characteristic	<50%, N=99[1]	≥50%, N=62[1]	*P*-value[2]
Age	60 (13)	63 (13)	.2
BMI	29 (7)	30 (6)	.8
MSI			**.014**
MSI	12 (12%)	17 (27%)	
MSS	87 (88%)	45 (73%)	
LVSI			**<.001**
Negative	87 (88%)	22, (36%)	
Positive	12 (12%)	39 (64%)	
Missing	0	1	
Grading			**<.001**
1	56 (57%)	5 (8.1%)	
2	22 (22%)	25 (40%)	
3	21 (21%)	32 (52%)	
Histology			**.025**
Endometrioid	94 (95%)	51 (82%)	
Other	1 (1.0%)	5 (8.1%)	
Serous	4 (4.0%)	6 (9.7%)	
Lymph nodes			.12
Negative	93 (95%)	49 (88%)	
Positive	5 (5.1%)	7 (13%)	
Missing	1	6	
Risk Class			**<.001**
Low	18 (82%)	1 (3.0%)	
Intermediate	0 (0%)	6 (18%)	
High-Intermediate	1 (4.5%)	15 (45%)	
High	3 (14%)	8 (24%)	
Metastatic	0 (0%)	3 (9.1%)	
Missing	77	29	
Neutrophils	4.66 (2.31)	5.34 (2.95)	.4
Lymphocytosis	2.14 (0.97)	1.97 (1.01)	.057
Monocytosis	0.46 (0.22)	0.46 (0.24)	.6
Eosinophils	0.12 (0.14)	0.10 (0.09)	.3

[1] Median, (IQR); n, (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 3
Outcomes.

Myometrial Infiltration			
Characteristic	<50%, N=99[1]	≥50%, N=62[1]	*P*-value[2]
NLR	2.15 (1.18)	2.51 (2.67)	.062
MLR	0.20 (0.08)	0.23 (0.21)	.10
PLR	125 (67)	126 (77)	.2

[1] Median, (IQR)
[2] Wilcoxon rank sum test

groups of patients. No statistically significant difference was detected, but all the parameters showed a trend: NLR (2.15 *v* 2.51, $P=0.062$), MLR (0.20 *v* 0.23, $P=0.10$), PLR (125 *v* 126, $P=0.20$) were observed between the groups with <50% or ≥50% myometrial infiltration, respectively. The results are summarized in Table 3.

The distribution of the 4 analyzed parameters was graphed as boxplots, stratifying the observed values based on LVSI positivity or negativity, as shown in Fig. 1.

Logarithmic Regression

We first conducted a univariate logarithmic regression for each parameter to assess their association with myometrial infiltration ≥50%. NLR, MLR, showed a statistically significant association with deep myometrial infiltration. The association values of the univariate regression are summarized in Table 4.

Finally, we conducted a multivariate analysis by combining separately the 2 statistically significant parameters (NLR and MRL) with other known risk factors for deep myometrial infiltration, such as grading, histotype and MSI. Following this procedure, only NLR retained statistical significance ($P=.031$), showing an increased risk of 18% for each additional unit value, to have ≥50% myometrial infiltration (CI 95%, 2%-35%). On the contrary, MLR, with a correction factor of 10, slightly failed to reach statistical significance ($P=.056$), but gave an additional 24% (CI 95%, 1%-51%) risk for each unit augmentation. The data from the multivariate logistic regression are summarized in Tables 5 and 6.

Table 4
Univariate logarithmic regression.

Characteristic	log(OR)[1]	95% CI[1]	*P*-value
NLR	0.15	0.01, 0.29	**.040**
MLR*10	0.30	0.09, 0.53	**.008**
PLR/100	0.40	0.00, 0.84	.40

[1] OR = Odds Ratio, CI = Confidence Interval

Table 5
Multivariate logarithmic regression for NLR.

Characteristic	log(OR)[1]	95% CI[1]	*P*-value
NLR	0.18	0.02, 0.35	**.031**
Grading			
1	—	—	—
2	2.6	1.5, 3.8	**<.001**
3	2.7	1.6, 3.9	**<.001**
Histotype			
Endometrioid	—	—	—
Other	1.4	−0.59, 4.4	.2
Serous	0.44	−0.98, 2.0	.6
MSI			
MSI	—	—	—
MSS	−0.70	−1.7, 0.22	.14

[1] OR = Odds Ratio, CI = Confidence Interval

Table 6
Multivariate logarithmic regression for MLR.

Characteristic	log(OR)[1]	95% CI[1]	*P*-value
MLR*10	0.24	0.01, 0.51	.056
Grading			
1	—	—	
2	2.3	1.3, 3.5	**<.001**
3	2.6	1.5, 3.8	**<.001**
Histotype			
Endometrioid	—	—	
Other	1.5	−0.51, 4.5	.2
Serous	0.30	−1.2, 1.9	.7
MSI			
MSI	—	—	
MSS	−0.69	−1.6, 0.23	.15

[1] OR = Odds Ratio, CI = Confidence Interval

Discussion

By its natural evolution, endometrial carcinoma tends towards local infiltration [28-29]. As suggested by our data, this progression causes a change in the patient's immune system, leading to imbalances measurable by the parameters we examined (NLR, MLR, PRL). In particular, logarithmic regression showed how these parameters correlated with the probability of ≥50% myometrial infiltration, resulting in a proportion between the NLR and MLR increase of 15% and 30% for each unit increase. In this regard, we would like to point out that given the decimal nature of the observed variations in MLR, its OR was calculated with a correction factor of 10 to facilitate clinical applicability. It should be noted, however, that since deep myometrial infiltration is an expression of a more aggressive disease, it is easily associated with other risk factors such as grading, histotype, lymph node positivity, and LVSI [2,28,30,31]. Therefore, it is not surprising that in the 2 groups under investigation, these parameters are unbalanced in favor of the ≥50% group, possibly leading to a worse prognosis. But, in our opinion, it did not affect the genuineness of the observation of our

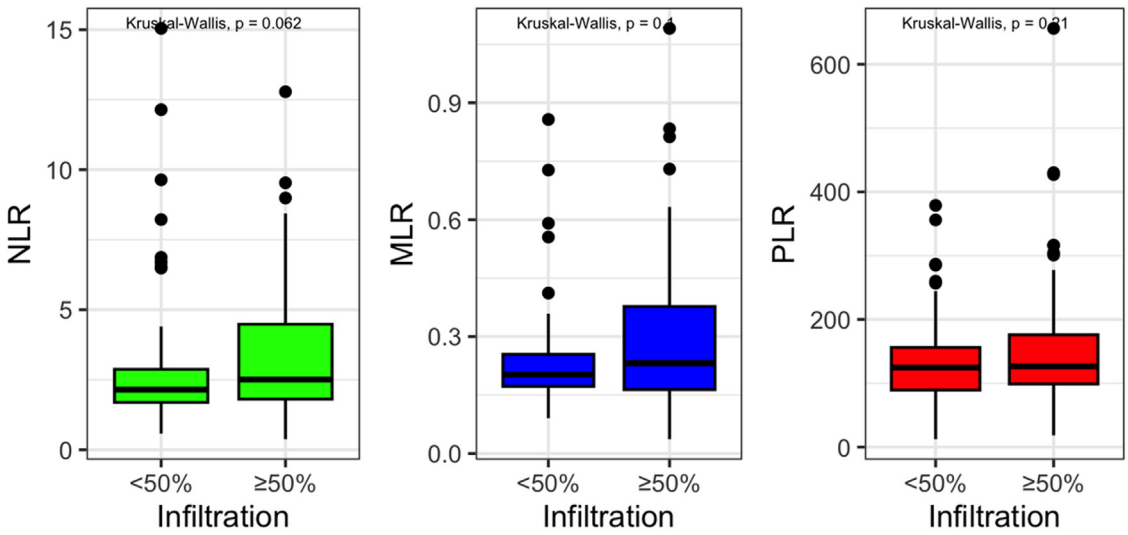

Fig. 1. Withe Blood Cells distribution according to myometrial infiltration.

data as we focused only on the association between the parameters under investigation and myometrial infiltration and not their prognostic significance. Therefore, in light of the hypothetical role played by other intrinsic factors of aggressiveness such as histotype, grading and microsatellite instability, we conducted a multivariate logarithmic regression in light of these parameters. Corroborating our intuition, NLR maintained a statistically significant relationship with the probability of deep myometrial infiltration, an 18% per unit increase. Unfortunately, on the other hand, MLR, corrected by a factor of 10 showed an even greater weighting (24%) but lost statistical significance by a very small margin ($P = .056$). This finding is to be understood as a trend, which could be clarified as exposures increase. From a clinical point of view, our results may help to deepen the diagnostic data available to us. In fact, on the one hand, myometrial infiltration represents a well-known risk factor, so much to be a parameter on which to direct adjuvant therapeutic choices or in fertility-sparing treatment pathways and follow-up [2,32-38]; on the other hand, it finds its specific measurement only in the postsurgical anatomopathological evaluation. The instruments capable of predicting this parameter with good approximation are transvaginal pelvic ultrasound and MRI [9-16]. While ultrasound is easily accessible in Western countries nowadays, it still shows less diagnostic power than the MRI, which, on the other hand, is associated with higher costs and is less routinely applicable [15,16]. In light of what has been demonstrated, alterations in the proportions of inflammatory cells can act as a red flag and help to identify the patients most deserving of further investigation and more aggressive surgery. The limitations of our study are related to the number of patients and the lack of prognostic information, which will only be obtainable after extended follow-up of our cohort. The strengths are represented by the prospective nature that, with strict inclusive criteria, limited the risk of committing bias and, first of all, the risk of observing a population with an altered inflammatory response linked to other systemic conditions [39-40]. In our opinion, our study may represent a further building block to discern more deeply the pathogenic mechanisms of endometrial carcinoma progression.

Conclusion

Our results showed that deep myometrial infiltration results in an appreciable alteration in measurable indices of inflammation such as NLR, MLR and PRL. Furthermore, there is a correlation between NLR and deep myometrial infiltration irrespective of MSI, histotype and grading. These data may help clinical conduct, especially in diagnosis and decision-making. However, future studies are needed to measure the prognostic impact of these relationships.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Carlo Ronsini: Conceptualization, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **Irene Iavarone:** Data curation. **Eleonora Braca:** Data curation, Writing – review & editing. **Maria Giovanna Vastarella:** Data curation, Writing – review & editing. **Luigi Della Corte:** Data curation, Investigation, Project administration, Software, Supervision. **Clorinda Vitale:** Data curation, Investigation. **Giada Andreoli:** Data curation, Formal analysis. **Elvira La Mantia:** Investigation, Methodology. **Luigi Cobellis:** Supervision, Validation, Visualization. **Pasquale de Franciscis:** Supervision, Validation, Visualization.

Ethics Declaration

The study was conducted in 2 university clinics where all patients treated must sign a dedicated consent for anonymous data processing. The research was conducted following the Declaration of Helsinki. The research methods were established a priori and authorized through evaluation by the Ethics Committee of the individual centers (Ethical Committee “Campania 2” IRB 30661/2022 of 31/03/2022). The study was then registered on the clinicaltrials.gov platform under NCT05657483.

Funding Declaration

The research was conducted without receiving any funding.

Declaration of Generative AI in Scientific Writing

The authors declare that no AI was used to write the original draft. Grammar correction tools (Grammarly, Inc) were used to improve the quality of English and readability. The technology has been used under human oversight and control.

Submission Declaration

The present article has not been submitted to any other Journal.

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