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Article

The Relationship of Furin with Inflammation in the Progression of Cervical Intraepithelial Neoplasia to Cancer: A Cross-Sectional Study

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Simple Summary: We demystified the relationship of furin with inflammation while cervical intraepithelial neoplasia progresses to cancer for the first time. Although the mechanism of entry of HPV into the cell has not been conclusively determined, the cleavage of the minor capsid protein L2 by furin is a *sine qua non* for HPV infection. The expression of furin increased stepwise along with the progression of cervical dysplasia to cervical cancer. It could be considered a new pathologic biomarker that signifies developing cervical cancer and denotes the severity of cervical intraepithelial neoplasia.

Abstract: *Objective:* The current study aimed to delineate the relationship of furin with inflammation while cervical intraepithelial neoplasia progresses to cancer. *Study Design:* This cross-sectional study included 81 women who required colposcopic examinations. The study groups were formed based on pathological results: Group I included women with cervical intraepithelial neoplasia (CIN) I (n=30); Group II included women with CIN II-III (n=28); and Group III included women with cervical cancer (CC) (n=23). Furin, ki-67, and p16 levels were evaluated based on immunostaining intensity. The inflammatory indices were calculated parallel with the literature from routine blood samples retrieved within one week before the procedure. *Results:* Furin expression gradually increased from CIN I to CIN II-III and from CIN II-III to CC, respectively ($p < .001$, $p = .005$). The NLR, MLR, PLR, and SII were significantly higher in the CC group ($p < .001$). ROC curve analysis unveiled that NLR, MLR, PLR and SII predicted the presence of CC with a cutoff value of 2.39 for NLR (sensitivity: 91.3%, specificity: 63.8%, AUROC: 0.79, $p < .001$); a cutoff value of 0.27 for MLR (sensitivity: 78.3%, specificity: 72.4%, AUROC: 0.77, $p = .009$); a cutoff value of 123 for PLR (sensitivity: 100%, specificity: 41.4%, AUROC: 0.70, $p = .04$); and a cutoff value of 747 for SII (sensitivity: 69.6%, specificity: 90.7%, AUROC: 0.71, $p = .014$). *Conclusion:* Furin expression increased gradually in parallel to the severity of cervical intraepithelial neoplasia. The inflammatory indices were higher in the presence of CC and denoted good discrimination ability for predicting cervical cancer.

Keywords: furin; cervical intraepithelial neoplasia; cervical cancer; neutrophil to lymphocyte ratio; monocyte to lymphocyte ratio; platelet to lymphocyte ratio; systemic immune-inflammatory index

Introduction



Cervical cancer (CC) is the fourth most common cancer among women worldwide. According to Global Cancer Observatory (GLOBOCAN) 2020 data, approximately 600,000 new CC cases and 350,000 deaths per year are predicted (1). Although the mechanism of entry of HPV into the cell has not been conclusively determined, the first step involves the attachment of the major L1 capsid protein of HPV to heparan sulfate proteoglycans (HSPGs) found within the plasma membrane of keratinocytes (2). In subsequent processes, the cleavage of the minor capsid protein L2 by furin is a *sine qua non* for HPV infection. The cleavage of viral particles by furin provide endosomal escape and a bypass mechanism for the first step of entry (3,4).

Furin participates in critical steps of the immune response by regulating T-cell and macrophage functions via TGF β 1 synthesis and modulating immune checkpoint signaling via programmed death-1 (PD-1) synthesis. Intriguingly, furin regulates the cancer microenvironment in favor of cancer cells by providing immune escape for cancer cells via accelerating the depletion of cytotoxic T cells. Although the mechanisms underlying its diverse functions have not been elucidated in depth yet, furin plays a crucial role in tumor immune microenvironment via regulating functions of myeloid and lymphoid cells and their regulatory molecules (5-9).

Currently, the tumor microenvironment (TME) has been subjected to comprehensive studies, and it has been proven that inflammatory cells such as neutrophils, lymphocytes, macrophages, and platelets, are critical components of the immune response to cancer (5-10). The number of circulating inflammatory cells and platelets and their indices are the most prominent indicators of immune response to cancer (9). Even if the role of neutrophils in cancer is ambiguous, a high neutrophil-to-lymphocyte ratio (NLR) is related to the poorer prognosis of various cancers, such as breast cancer, colorectal cancer, malignant melanoma, and gynecological cancer (11,12). Likewise, a high monocyte-to-lymphocyte ratio (MLR) and a high platelet-to-lymphocyte ratio (PLR) are also considered valuable prognostic markers in multiple cancers, such as head and neck, gastric, colorectal, and brain metastasis (13-16). Recently, the systemic immune inflammation index (SII), which takes into account the equation of platelet count, has been regarded as a superior prognostic factor for solid tumors, such as, esophageal, gynecological, and triple-negative breast cancer, and predicts the response to immunotherapy (17-19).

Circulating inflammatory cells and platelets are the most salient indicators of immune response to cancer and indirectly reflect the tumor immune microenvironment status. On the other hand, furin impresses the cancer microenvironment in favor of cancer cells by providing immune escape. Therefore, we hypothesized that both of these could interact with each other in the progression of cervical intraepithelial neoplasia to cancer. We aimed to elucidate the relationship of furin with inflammation in the progression of cervical intraepithelial neoplasia to cervical cancer.

Materials and Methods

Study Design

This cross-sectional study recruited 81 women admitted to the Gynecology Department of the Balikesir University School of Medicine between January 2018 and 2023. Women aged 30-65 who needed colposcopic examination based on abnormal PAP smear (Thin-prep) screening results or HR-HPV DNA (Rotor-Gene Q, Qiagen) positivity participated in the study. The participants were managed according to the current American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines (20). Participants either followed-up or underwent surgery consistent with the colposcopic biopsy results.

The study groups were formed based on the pathological results as follows. Women with cervical intraepithelial neoplasia (CIN) 1 biopsy results (Group I, n=30) were regularly followed; however, those with CIN 2 and 3 (Group II, n=28) underwent a conization operation. Women with squamous CC (Group III, n=23) underwent either simple or radical hysterectomy in conformity with their stage (Table 1). Routine blood samples were retrieved within one week before biopsy, conization, or surgery.

Women with acute infection and chronic inflammatory diseases, diabetes, a history of cancer, radiotherapy, or chemotherapy, receiving anti-inflammatory or immunosuppressive agents, vaginitis, cervicitis, and other sexually transmitted infections were excluded from the study. STROBE (The Reporting of Observational Studies in Epidemiology) guidelines were followed (21).

Immunohistochemistry & Evaluation

Standardized tissue preparation protocols were followed during the histopathological examination of cervical tissues as previously described (22). Subsequently, 1:100 diluted anti-furin antibodies (Santa Cruz Biotechnology Inc., Dallas, TX), 1:100 diluted anti-ki-67 antibodies (Santa Cruz Biotechnology Inc., Dallas, TX), and 1:50 diluted anti-p16 (Santa Cruz Biotechnology Inc., Dallas, TX) antibodies were applied. All slides were examined and scored concurrently by two experienced pathologists who were blinded to the clinical diagnoses. Using an image capture system, the furin expression in the study groups was randomly compared based on immunohistochemistry (IHC) staining density.

The IHC staining intensity of furin, ki-67, and p-16 was evaluated using a scoring system based on the staining ratio of the cervical cells. The furin scores were as follows: 10-40 staining 1(+); 41-70% staining 2(+); and >71% staining 3(+) (Figure 1A, 1B, and 1C, respectively). For ki-67, the intensity score was graded as follows: 10-30% staining 1(+); 31-50% staining 2(+); 51-70%, 3(+); and $\geq 71\%$, 4(+). For p16, block-positive staining was scored 1(+); on the other hand, equivocal or negative staining was scored 0.

Indices

NLR, PLR, and MLR were calculated as follows: the absolute number of neutrophils, platelets, and monocytes was divided by the absolute number of lymphocytes. SII was calculated using the following formula: $SII = \text{platelet count} \times \text{neutrophil count} / \text{lymphocyte count}$.

Statistics

Statistical and power analyses were performed using open-source Jamovi statistical software (version 2.3.21) and G* Power software (version 3.1.9.7). According to the literature, the minimum sample size was calculated as twenty-two per group based on an α error of 0.01, and power of 0.80. The distribution and homogeneity of the groups were evaluated by skewness, kurtosis, Levene's test, and Kolmogorov-Smirnov test.

The Kruskal-Wallis test was applied to nonparametric group variables, and pairwise comparisons were made using the Dwass-Steel-Critchlow-Fligner test. One-way ANOVA and Tukey's post-hoc tests were applied to the parametric group variables. Partial correlation analyses were performed using either Pearson or Spearman coefficients, according to variables with normal and abnormal distributions. A receiver operating characteristic (ROC) curve was plotted to denote the performance of inflammatory indices in discriminating the CC from cervical intraepithelial neoplasia. Statistical significance was set at $p < 0.05$.

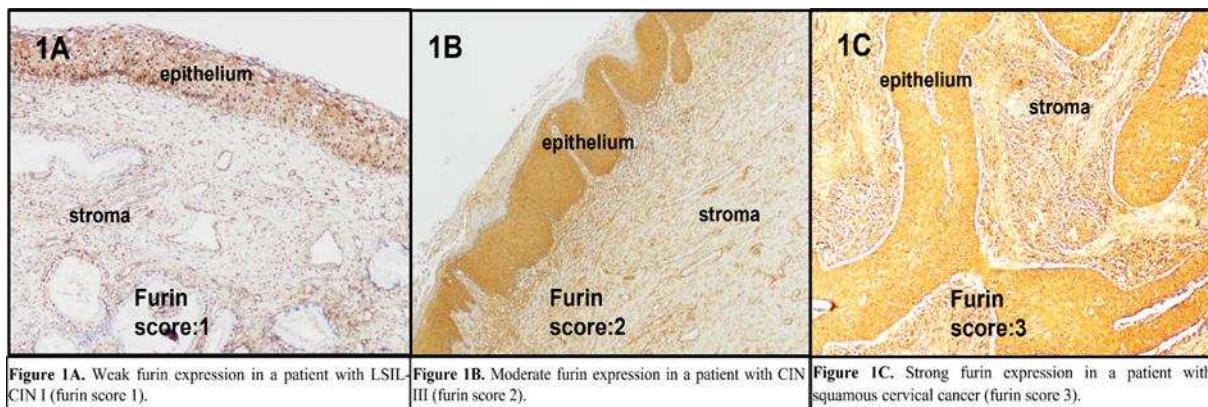


Figure 1. The expression levels of furin in the cervical epithelium (x200). A. Weak furin expression in a woman with LSIL-CIN I (furin score 1). B. Moderate furin expression in a woman with CIN III (furin score 2). C. Strong furin expression in a woman with squamous cervical cancer (furin score 3).

Results

This cross-sectional study reviewed the cervical pathology and laboratory results of 81 women. The mean age of the groups was 44.5 ± 13.7 years. There was a statistically significant difference

between CIN II-III and CC groups in the context of age (39.5 ± 12.9 years vs. 50.2 ± 13.7 years, respectively, $p < .05$); otherwise, the mean ages were similar between groups (Table 1).

Furin expression gradually increased from CIN I to CIN II-III and from CIN II-III to CC, respectively ($p < .001$, $p = .005$). ki-67 and p16 expression differed significantly between the study groups ($p < .001$), except for CIN II-III and CC ($p = .817$ and $p = .771$, respectively) (Table 1). The pathological results of the participants are summarized in Table 1.

Table 1. The pathological results of participants in the study groups.

	Participants	CIN I	CIN II-III	CC	p
	(n=81)	(n=30)	(n=28)	(n=23)	
Age (year)	44.5 ± 13.8	44.7 ± 13.2	39.5 ± 12.9	50.2 ± 13.7	.020
Furin					<.001
0	17%	16%	1%	0%	
1	44%	21%	17%	6%	
2	30%	0%	16%	14%	
3	9%	0%	0%	9%	
ki-67					<.001
1	23%	21%	2%	0%	
2	19%	11%	4%	4%	
3	22%	1%	11%	10%	
4	36%	4%	17%	15%	
p16					<.001
0	37%	26%	5%	6%	
1	63%	11%	30%	22%	

Note. * $p < .05$, ** $p < .01$, *** $p < .001$. SD: Standard deviation. Age is expressed as the mean \pm SD.

There was a slightly higher WBC count in CC group than in the CIN I group ($p = .012$) (Table 2). The NLR, MLR, PLR, and SII were significantly higher in the CC group ($p < .001$). However, these were similar between CIN I and CIN II-III groups (Table 2). The laboratory results of the participants are summarized in Table 2.

Table 2. The laboratory results and inflammatory indices of women in the study groups.

	Participants	Group I	Group II	Group III	
	(n=81)	(n=30)	(n=28)	(n=23)	p
WBC (10³/µL)	7.8 ± 2.1	6.2 ± 1.5	7.6 ± 2.0	8.8 ± 2.7*	.012
PLT (10³/µL)	295 ± 66	312 ± 76	283 ± 60	281 ± 64	.265
NLR	3.08 ± 4.96	2.26 ± 0.74	2.33 ± 0.77	5.05 ± 9.07***	<.001
MLR	0.29 ± 0.25	0.26 ± 0.07	0.22 ± 0.06	0.42 ± 0.43***	<.001
PLR	146 ± 100	146 ± 48	125 ± 30	163 ± 153***	<.001
SII	900 ± 1412	693 ± 231	665 ± 300	1353 ± 2268***	<.001

Note. * p <.05, ** p <.01, *** p <.001. WBC, white blood cell count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index.

The expression of furin was moderately correlated with the NLR, MLR, PLR, and SII (rho: 0.57 p <.001; rho: 0.43 p <.001; rho: 0.38 p <.001; rho: 0.68 p <.001; respectively), and the SII was strongly correlated with the NLR and PLR (rho: 0.92 p <.001; rho: 0.70 p <.001; respectively) (Table 3). Table 3 summarizes the correlation analysis of furin and SII with the inflammatory indices.

Table 3. Correlation analysis of furin and SII with other biochemical parameters.

	Furin		SII	
	CC	p	CC	p
NLR	0.57	<.001	0,92	<.001
MLR	0.43	<.001	0,49	<.001
PLR	0.38	<.001	0,70	<.001
SII	0.68	<.001	N/A	

Note. * p <.05, ** p <.01, *** p <.001. CC, correlation coefficient; N/A, not applicable; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index.

ROC curve analysis unveiled that NLR, MLR, PLR and SII predicted the presence of CC with a cutoff value of 2.39 for NLR (sensitivity: 91.3%, specificity: 63.8%, AUROC: 0.79, Youden index: 0.55, p <.001); a cutoff value of 0.27 for MLR (sensitivity: 78.3%, specificity: 72.4%, AUROC: 0.77, Youden index: 0.51, p = .009); a cutoff value of 123 for PLR (sensitivity: 100%, specificity: 41.4%, AUROC: 0.70, Youden index: 0.41, p = .04); and a cutoff value of 747 for SII (sensitivity: 69.6%, specificity: 90.7%, AUROC: 0.71, Youden index: 0.40, p = .014) (Figure 2).

Discussion

This cross-sectional study evaluated the pathological and inflammatory markers of women with cervical epithelial neoplasia and cancer to elucidate the relationship of furin with inflammation while the cervical intraepithelial neoplasia progresses to cancer. The expression of furin increased stepwise along with the advancement of cervical dysplasia to cervical cancer, similar to p16 and ki-67. On the other hand, inflammatory indices were elevated only in women with cervical cancer but not in cervical dysplasia. Also, the inflammatory indices displayed good performance for discriminating the CC from cervical intraepithelial neoplasia.

This study unveiled that the expression of furin was elevated in cervical cancer. Similarly, amplified furin expression has been revealed in gynecologic malignancies, especially in cervical and breast cancer, based on the Cancer Genome Atlas (TCGA) studies. It is considered either a poor prognostic marker or a proto-oncogene (23-25).

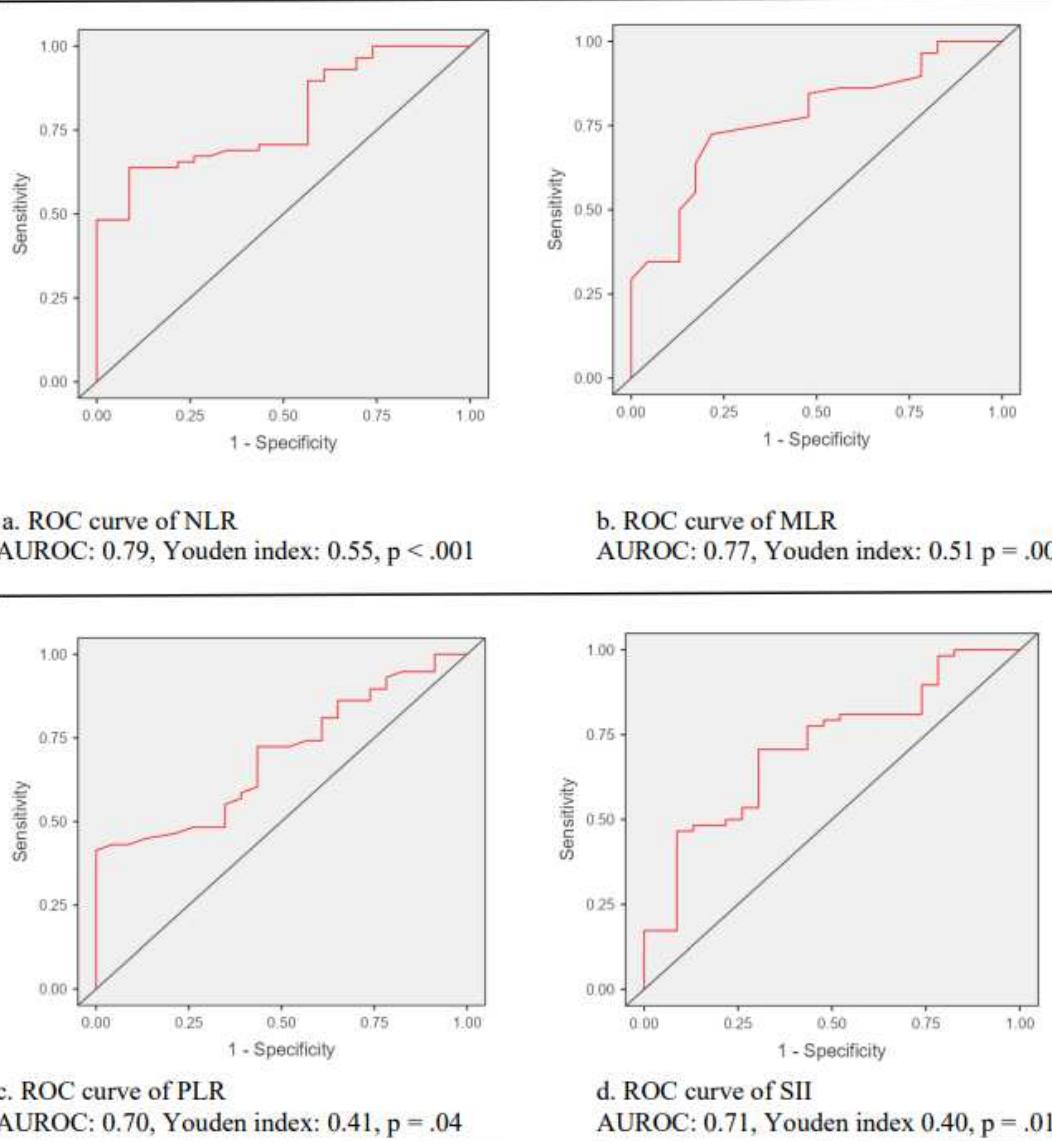


Figure 2. The predictive performance of inflammatory indices on cervical cancer. Note. ROC, receiver operating characteristic curve; AUROC, the area under the curve of receiver operating characteristic curve; NLR: neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index.

Nonetheless, we could not find any paper in the literature that has argued for the importance of furin in preinvasive conditions; this study elucidated that a gradual increase in furin correlated with the progression of cervical intraepithelial neoplasia to cervical cancer. It could be considered a new pathologic biomarker that signifies developing cervical cancer and denotes the severity of cervical

intraepithelial neoplasia; however, it needs to be supported by the following studies (26). Additionally, the current study confirmed the role of p16/ki-67 staining in the neoplastic progression of cervical intraepithelial neoplasia, similar to that reported in the literature (27).

This study uncovered that even if inflammatory indices (NLR, MLR, PLR, and SII) were raised in women with cervical cancer, those stayed in the normal range in women with cervical intraepithelial neoplasia. Also, the inflammatory indices in this study displayed good discrimination performance for discriminating the CC from cervical intraepithelial neoplasia. The literature indicated that those could be independently used to distinguish the preinvasive lesions of larynx, cervix, and endometrium from invasive counterparts (28-30). Additionally, NLR, MLR, PLR, and SII could be used to predict certain cancer prognoses (11-19).

Although this study parallels the literature in differentiating preinvasive and malignant conditions, it opposes Xu and colleagues' study because they claimed that inflammatory indices could predict the severity of cervical intraepithelial neoplasia (28-31). The laudable study of Li and colleagues disclosed the mystery of cervical TME in which HSIL tissue displayed amplified infiltration by lymphocytes and M1-like macrophages (32). Due to this reason, it could be speculated that the inflammatory indices are expected to be low in cervical intraepithelial neoplasia. In addition, it was denoted that furin orchestrates myriad pathways in cancer and inflammatory cells that can ultimately hamper immune cell infiltration into the TME (33).

Conclusion

The current study revealed that furin expression increases gradually in parallel to the severity of cervical intraepithelial neoplasia. The inflammatory indices (NLR, MLR, PLR, and SII) were higher in women with cervical cancer but similar in dysplasia groups. Inflammatory indices denoted good discrimination ability for the prediction of cervical cancer.

The limitations of the study

In addition to its retrospective nature, inflammatory indices are influenced by age, diet, activity level, and menstrual status. The limitations of this study include the absence of TILs, PD-L1, and furin mRNA expression in inflammatory and cervical cells in the study groups, which would make it easier to conclude the relationship between inflammation and cancer. As previously mentioned, little research has been conducted on the relationship between furin and preinvasive cervical disease; as a result, it could be assumed that the backlash of this study to conclude.

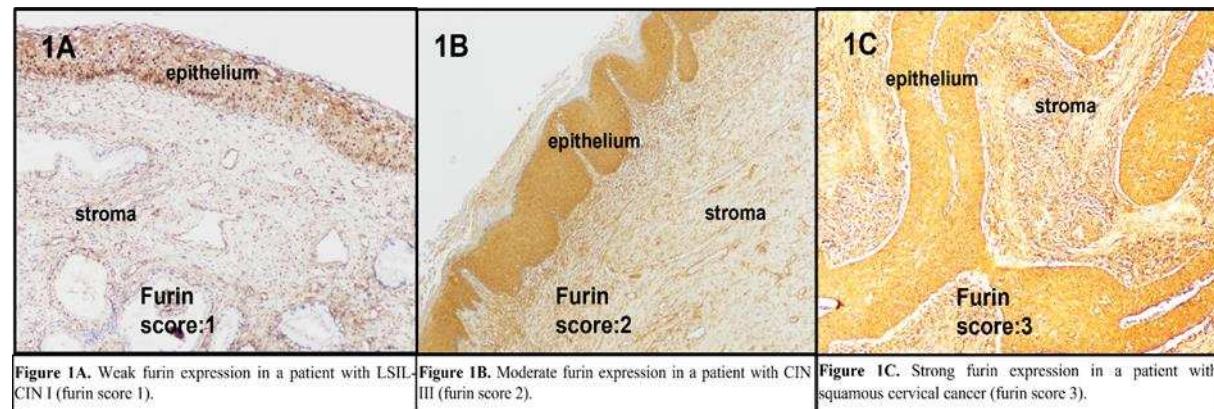


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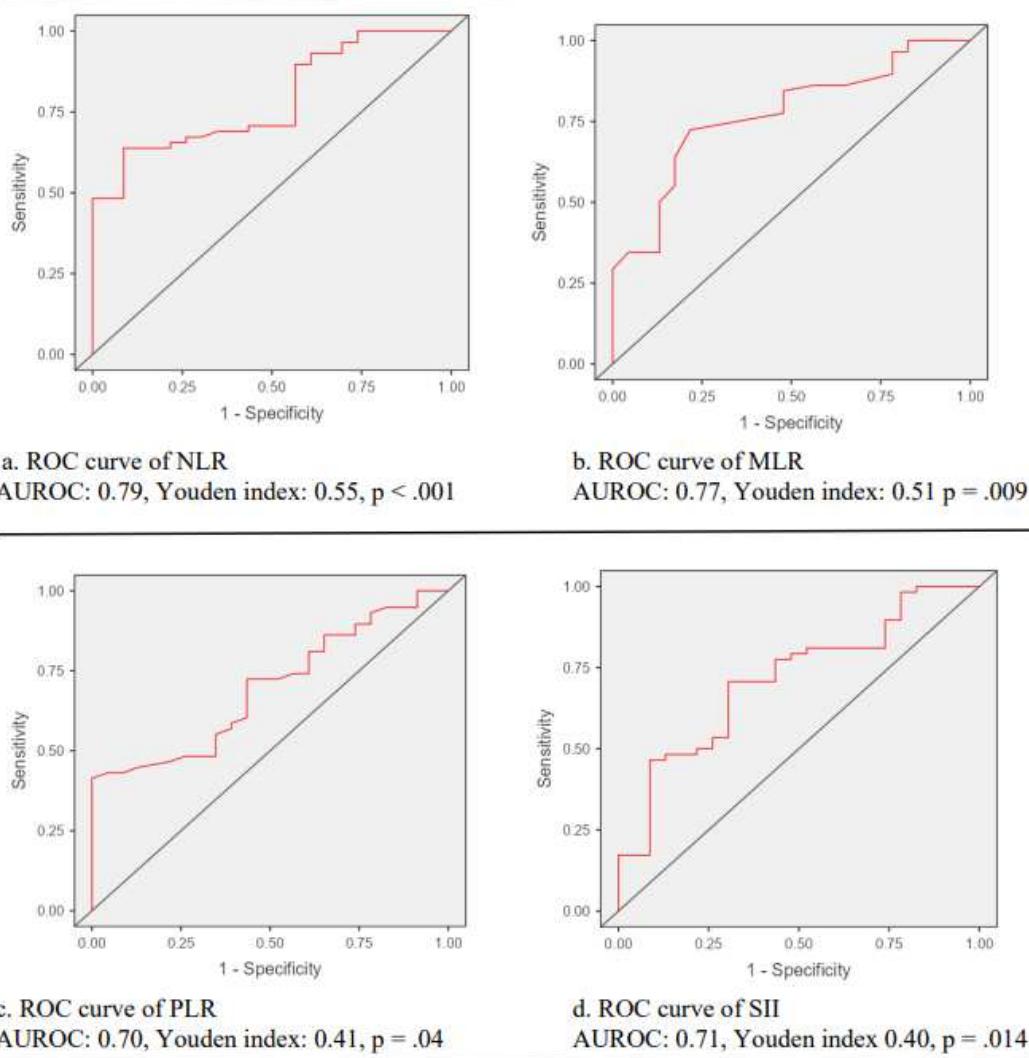


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ki-67					<.001
1	23%	21%	2%	0%	
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Author Contributions (in CRediT format) :**Author 1:** conceptualization, methodology, investigation, validation, visualization, writing-original draft, writing-review and editing, supervision **Author 2:** methodology, investigation, supervision **Author 3:** conceptualization, methodology, investigation, writing-review, and editing **Author 4:** visualization, validation, writing-review, and editing **Author 5:** validation, visualization, writing-review, and editing **Author 6:** conceptualization, visualization, writing-original draft, writing-review and editing, supervision.

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Ethics: This cross-sectional study was conducted in conformity with the principles of the Declaration of Helsinki after ethical approval by the local ethical committee (94025189-050.03-40925).

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study. Written informed consent has been obtained from the patients to publish this paper.

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Data Availability: Data are available upon reasonable request from the corresponding author.

Conflict of Interest: The authors declare no conflict of interest.

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