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Inflammatory prognostic markers in endometrial carcinoma: systemic immune-inflammation index and prognostic nutritional index

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Abstract

Objective: Systemic inflammatory response markers have prognostic significance in many cancer types. Although the prognostic values of neutrophil/lymphocyte (NLR), and platelet/lymphocyte ratios (PLR) have been shown in patients with Endometrial Cancer (EC) there is no information in the literature about systemic immune-inflammation index (SII) and prognostic nutritional index (PNI). In our study, we aimed to reveal the prognostic role of SII and PNI in EC.

Material and Methods: Medical data for 101 patients with EC were reviewed retrospectively. NLR, PLR, SII and PNI values were dichotomized based on receiver operating characteristic (ROC) curve analysis (cut-off values: 3.3; 177; 1035.9, and 38, respectively). At the time of diagnosis concentrations of these four serum inflammatory markers were analyzed to determine their potential association with clinicopathologic characteristics and to assess their prognostic values via the Kaplan-Meier method and multivariate Cox regression analysis.

Results: Patients with higher NLR, PLR, SII, and lower PNI values had shorter progression-free survival (PFS) and overall survival (OS) times. Higher NLR, SII, and lower PNI, were associated with FIGO stages, lymph node involvement, lymphovascular invasion, and cervical stromal invasion while additionally NLR and PNI were associated with worse ECOG performance scores (2-3) and myometrial invasion. In univariate analyses, all these four variables were prognostic for both OS and PFS, whereas in multivariate analyzes only NLR, SII and PNI were found to be independent factors for OS and PFS.

Conclusion: For the first time in the literature SII and PNI were determined to be independent prognostic factors for both OS and PFS in EC.

Key words: Endometrial Neoplasms, Inflammation, Biomarkers, prognostic nutritional index.

Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed countries and according to 2018 data, it is the 6th most frequently seen cancer in women after breast, colorectal, lung, cervical and thyroid cancers worldwide (1). Although curative surgical treatments can be applied in the early stages of EC (stage 1-2), due to manifestations of irregular or postmenopausal bleeding, the mortality rate of EC has increased by 100% within the last 20 years (2). This circumstance is thought to be related to the increase in the incidence of high-risk histological subtypes (serous, mucinous, mixed and carcinosarcoma), prolongation of life span, increased incidence of obesity, and diagnosis of patients at advanced ages and stages (3). Five-year survival rates in advanced stages (stages 3-4) and in recurrent EC are between 15-17% due to the inability to apply curative treatment options (4). Although the patients have been tried to be classified according to the classical prognostic significance of factors including age, high-risk histopathologic subtype, stage, grade, cervical stromal invasion (CSI), lymphovascular invasion (LVSI), myometrial invasion (MM), and lymph node involvement (LNI), the prognosis of the EC cannot be accurately predicted (5). Therefore it is very important to identify new predictive biomarkers to detect high-risk patients at the time of diagnosis.

The systemic immune response (SIR) to cancer has a key role in the stages of initiation, invasion, progression, and metastasis of carcinogenesis (6). For this reason, inflammatory parameters have an importance in cancer prognosis. Not only albumin, C-reactive protein (CRP), neutrophil, lymphocytes, platelets but also neutrophil/lymphocyte (NLR), and platelet/lymphocyte ratios (PLR) derived from these peripheral blood units are practical, inexpensive, measurable indicators of SIR and their prognostic significance in many solid cancer types including gynecological cancers have been determined (7-8).

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However, in recent years the prognostic significance of the systemic immune-inflammation index (SII) has been increasingly emphasized in cancer patients which are calculated based on the combination of neutrophil, lymphocyte and platelet counts (9-10). Prognostic nutritional index (PNI) which reflects both nutritional and inflammatory status is another inflammatory parameter estimated based on lymphocyte counts and albumin values. PNI was initially used to predict morbidity before gastroenterological surgery, but its prognostic significance has recently been demonstrated in hepatocellular carcinoma (HCC), esophageal, gastric, colon, and lung cancers (11). The increasing amount of evidence is available on the importance of inflammatory markers used for a long time such as NLR and PLR in EC, while any study on the status of SII and PNI has not been performed yet. In this study, we aimed to determine the prognostic significance of these inflammatory markers in EC whose importance has been revealed in different types of cancer.

Material and Methods

This retrospective study was performed on 101 patients (101/ 140) with complete medical records, and without hematologic, autoimmune disease, and secondary malignancies who had been diagnosed as EC and followed up for at least 3 months between April 2001 and 2019 at Erzurum Ataturk University Medical Oncology Department. Following retrieval of clinicopathological data including age, sex, performance status, pathological features, treatment agents used and laboratory data were taken from patient archives and the hospital information operating system. The patients were re-staged according to the 2018 EC staging system criteria of the International Federation of Gynecology and Obstetrics (FIGO). Leucocyte, neutrophil, lymphocyte, hemoglobin, platelet, and albumin values at the diagnosis were recorded. The ratios between neutrophil (N) and lymphocyte (L) (NLR), also between platelet (P) and lymphocyte (L) (PLR) counts were calculated. SII and PNI were calculated based on the following formulas: SII: P x N/L and PNI: 10 x Albumin (g/L) + (0.005 x L)

Ethics committee approval was obtained from the ethics committee of Erzurum Ataturk University. All the procedures were performed according to the 1964 Helsinki declaration.

Statistical Analyzes

Overall survival (OS) was calculated from diagnosis to death and progression-free survival (PFS) was calculated from diagnosis to recurrence or death. Associations between clinicopathologic characteristics with survival times were analyzed by Kaplan-Meier curves and compared by the log-rank test. NLR, PLR, SII, and PNI were determined on the basis of receiver operating characteristic (ROC) analysis for OS. Cut off points for NLR, PLR, SII, and PNI were 3,3, 177, 1035,9, and 38, respectively. Area under the curve (AUC) was over 0.80 for all parameters. The association between NLR, PLR, SII, PNI and clinicopathological parameters was analyzed by chi-square test. Univariate and multivariate Cox-regression analyses were performed to determine effects of probable prognostic factors for OS and PFS, including ECOG performance status, FIGO stage, histological grade, cervical stromal invasion (CSI), lymphovascular invasion (LVSI), myometrial invasion (MM), and lymph node involvement (LNI) status. The number of events of all variables involved in multivariate analysis was more than 10. NLR, PLR and SII were not added to multivariate analyzes at the same time due to high correlation between them by Pearson correlation test.

Two separate multivariate analysis models were used to eliminate this multicollinearity problem: aThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, perineural invasion, SII, and PNI) were tested in a multivariate analysis. bThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, NLR and PLR) were tested in a multivariate analysis. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95 % confidence intervals (CIs). All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0). $P < 0.05$ was considered as statistically significant

Results

The clinicopathological data of 101 study patients including 14 (13.9%) premenopausal and 87 (86.1%) postmenopausal women with a median age of 62 (36-80) years are presented in Table 1. The patients had ECOG performance status scores of 0 (n=8), 1 (n=58), and 2-3 (n=35). According to histologic subtypes, the patients had endometrial adenocarcinoma (n=75), carcinosarcoma (n=12), serous carcinoma (n=7), mucinous carcinoma (n=3), mixed carcinoma (n=1), and According to FIGO staging system, the patients were in disease stages of 1A (n=14), 1B (n=23), 2 (n=8), 3A (n=7), 3D (n=1), 3C (n=24), 4A (n=5), and 4B (n=19). MM (n=86: 85.1%), CSI (n=39: 38.6%), LVSI (n=55: 54.5%), perineural invasion (n=17: 16.8%), and LNI (47:% 46.5) were also detected in respective number of patients. As treatment modalities the patients received brachytherapy (n=5), external radiotherapy (n=37 (36.6%), and chemotherapy (n=73: 72.3%) [as adjuvant (n=54), and palliative (n=19) therapy]. At the end of the median follow-up period of 20 months (3-141 months), disease had progressed in 59 (58.4%) patients while 53 (52.5%) patients died. Median, and average OS and PFS times were 33 vs 55.9 and 26 vs 49.5 months, respectively.

At the time of diagnosis, mean, and median (range) NLR, PLR, SII, PNI values were 3.82 ± 1.86 vs 3.55 (1.02-9.31), 214.2 ± 117.5 vs 184 (55.1-655.8), 1269.6 ± 828.4 vs 1069.6 (176.5-4617.6), and 1269.6 ± 828.4 vs 37.1 (19-38), respectively. Regarding OS, NLR cut-off value of 3.3 had AUC of 0.921 with 90.6% sensitivity and 87.5% specificity (95% CI: 0.867–0.975, p<0.000). While PLR cut-off value of 177 with AUC of 0.801 had 79.2% sensitivity, and 72.9% specificity (95% CI: 0.713–0.889, p<0.000), the SII cut-off value was 1035.9 (AUC=0.856, sensitivity; 81.1%, specificity; 75%, 95% CI: 0.782–0.930, p<0.000), the PNI cut-off value was 38 (AUC=0.854, sensitivity; 81.1%, specificity; 79.2%, 95% CI: 0.070–0.222, p<0.000) (Figure 1). Table 2 shows the relationship between the clinicopathological parameters and the NLR, PLR, SII, and

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PNI. Higher NLR (>3.3) and lower PNI (<38), were associated with worse ECOG performance scores (2-3) (p: 0.027, p: 0.026), FIGO stage (p: 0.005, p: 0,000), MM (p: 0.024, p: 0.045), CSI (p: 0.035, p: 0.003), LVSI (p: 0.002, p: 0.001), and LNI (p: 0.006, p: 0.001), while higher PLR (>177) values were correlated with FIGO stage (p: 0,000), MM (p: 0,005), LVSI (p: 0,043) and LNI (p: 0,001). Higher SII (>1035.9) values were associated with FIGO stages (p: 0,000), CSI (p: 0.006) LVSI (p: 0.043) and LNI (p: 0.000).

Patients with higher NLR, PLR, SII, and lower PNI had both shorter PFS (p: 0.000, p: 0.000, p: 0.000, p: 0.000, respectively) and OS (p: 0.000, p: 0.000, p: 0.000, p: 0.000, respectively) than those with lower NLR, PLR, SII and higher PNI values as demonstrated by Kaplan-Meier curves (Figure 2). The average PFS and OS times of patients with high NLR values were 18.6, and 25.1 months and those with lower NLR were 107.8 and 120 months, respectively.

The median OS times of the patients with higher, and lower PLR values were 18, and 105 months, respectively. Median PFS times for patients with higher, and lower PLR values were 11, and 67 months, respectively. Similarly, median PFS and OS times in patients with higher, and lower SII values were 11 vs 18, and 67 vs 105 months, respectively. In contrast to other inflammatory markers, those with higher PNI values have longer PFS and OS times. (PNI ⩾ 38: PFS: 95, and OS: 95 months, and PNI <38: PFS: 9 and, OS: 18 months).

The prognostic significance of clinicopathological data for OS and PFS by univariate and multivariate analysis is shown in Table 3; According to univariate analysis, ECOG performance status, FIGO stage, grade, MM, CSI, LVSI, LNI, NLR, PLR, SII, and PNI have prognostic significance for both OS and PFS. It was found that NLR, PLR, SII, and PNI were highly correlated with OS and PFS. However, in multivariate analysis of two separate models, NLR, SII, and PNI were independent prognostic factors for both OS and PFS.

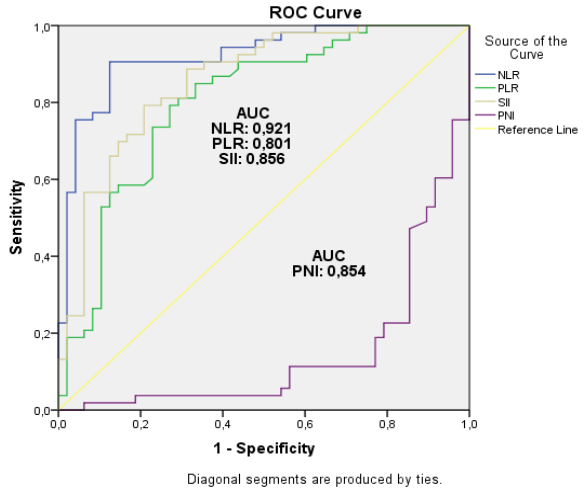

Figure 1: ROC analysis and AUC for sensitivity and specificity of inflammatory parameters: NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index

Table 1: Patient Demographics and Clinical Characteristics (n: 101)

	N (%)
Age	
<50	13 (12,9)
≥50	88 (87,1)
Menopausal status	
Premenopause	14 (13,9)
Postmenopause	87 (86,1)
ECOG performance status	
0	8 (7,9)
1	58 (57,4)
2-3	35 (34,7)
Histologic Subtype	
Endometrial adenocarcinoma	75 (74,3)
Mucinous carcinoma	3 (3)
Serous carcinoma	7 (6,9)
Mix carcinoma	4 (4)
Carcinocarcinoma	12 (11,9)
FIGO stage	
1A	14 (13,9)
1B	23 (22,8)
2	8 (7,9)
3A	7 (6,9)
3B	1 (1)
3C	24 (23,8)
4A	5 (5)
4B	19 (18,8)
Grade	
I	8 (7,9)
II	55 (54,5)
III	38 (37,6)
Myometrial invasion	
Yes	86 (85,1)
No	15 (14,9)
Cervical stromal invasion	
Yes	39 (38,6)
No	62 (61,4)
Lymphovascular space invasion	
Yes	55 (54,5)
No	46 (45,5)
Perineural invasion	
Yes	17 (16,8)
No	84 (83,2)
Lymph node involvement	
Yes	47 (46,5)
No	54 (53,5)
Brachytherapy	
Yes	5 (5)
No	96 (95)
External radiotherapy	
Yes	37 (36,6)
No	64 (63,4)
Chemotherapy	
Yes	73 (72,3)
No	28 (27,7)
Progression	
Yes	59 (58,4)
No	42 (41,6)
Status	
Alive	48 (47,5)
Death	53 (52,5)
Age (Mean±SD)	61,53±9,83
NLR (Mean±SD)	3,82±1,86
PLR (Mean±SD)	214,2±117,5
SII (Mean±SD)	1269,6±828,4
PNI (Mean±SD)	36,2±6,8

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Table 2: The association between pretreatment NLR, PLR, SII, PNI and clinicopathological parameters (n:101)

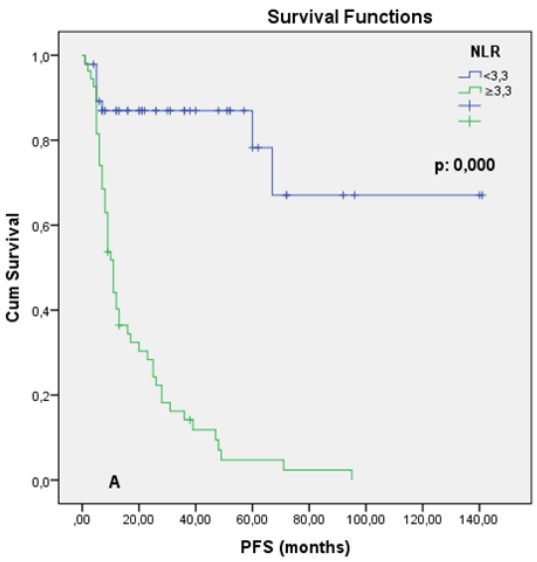
		NLR			PLR			SII			PNI		
	n	<3.3	≥ 3.3	*p*	<177	≥177	*p*	< 1036	≥ 1036	*P*	<38	≥ *38*	*P*
Age				0,134			0,583			0,962			0,353
<50	13	9	4		5	8		6	7		5	8	
≥50	88	38	50		41	47		40	48		46	42	
Menopausal status				0,151			0,426			0,828			0,538
Premenopause	14	9	5		5	9		6	8		6	8	
Postmenopause	87	38	39		41	46		40	47		45	42	
ECOG status				**0,027**			0,098			0,415			**0,026**
0-1	66	36	30		34	32		32	34		28	38	
2-3	35	11	24		12	23		14	21		23	12	
Histologic Subtype				0,616			0,942			0,701			0,078
Endometrial adenocarcinoma	75	36	39		34	41		35	40		34	41	
Others	26	11	15		12	14		11	15		17	9	
FIGO stage				**0,005**			**0,000**			**0,000**			**0,000**
1	37	24	13		26	11		27	10		8	29	
2	8	5	3		5	3		5	3		4	4	
3	32	13	19		9	23		10	22		20	12	
4	24	5	19		6	18		4	20		19	5	
Grade				0,151			0,089			0,115			0,056
1	8	4	4		4	4		2	6		3	5	
2	55	30	25		30	25		30	25		23	32	
3	38	13	25		12	26		14	24		25	13	
Myometrial invasion				**0.024**			**0,005**			0,075			**0,045**
Yes	86	36	50		34	52		36	50		47	39	
No	15	11	4		12	3		10	5		4	11	
Servical stromal invasion				**0,035**			0,051			**0,006**			**0,003**
Yes	39	13	26		13	26		11	28		27	12	
No	62	34	28		33	29		35	27		24	38	
Lymphovascular space invasion				**0,002**			**0,043**			**0,043**			**0,001**
Yes	55	18	37		20	35		20	35		36	19	
No	46	29	17		26	20		26	20		15	31	
Perineural invasion				0,308			0,143			0,143			**0,007**
Yes	17	6	11		5	12		5	12		14	3	
No	84	41	43		41	43		41	43		37	47	
Lymph node involvement				**0,006**			**0,001**			**0,000**			**0,001**
Yes	47	15	32		13	34		11	36		32	15	
No	54	32	22		33	21		35	19		19	35	
Progression				**0,000**			**0,000**			**0,000**			**0,000**
Yes	59	8	51		14	45		13	46		46	13	
No	42	39	3		32	10		33	9		5	37	
Status				**0,000**			**0,000**			**0,000**			**0,000**
Alive	48	42	6		35	13		36	12		10	38	
Death	53	5	48		11	42		10	43		41	12	

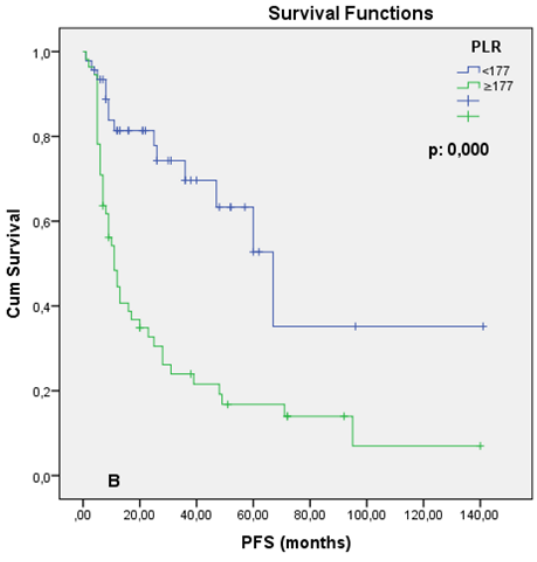
NLR: neutrophil-lymhocyte ratio, PLR: platelet-lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index. Statistically signifcant p-values (<0.05). Results were determined by Pearson x2. Fisher's Exact test was used if expected cell count is less than 5.

Table 3. Univariate and Multivariate Analysis of Potential Prognostic Factors for OS and PFS

OS	Univariate HR (%95 CI)	P	Multivariate HR (%95 CI)	P
Age (<50 vs ≥50)	1,934 (0,697-5,368)	0,205	-	-
Menopausal status (premanapuse vs postmenopause)	1,613 (0,641-4,057)	0,310	-	-
ECOG status (0-1 vs 2-3)	3,437 (1,923-6,143)	**0,000**	2,135 (1,078-4,227)	**0,030**[a]
Histologic Subtype (adenocarcinoma vs other)	0,549 (0,295-1,022)	0,059	-	-
FIGO stage (1-2 vs 3 and 4)	1,741 (1,252-2,423)	**0,001**	-	0,383[a]
			0,630 (0,261-1,523)	0,305[a]
			0,497 (0,183-1,348)	0,170[a]
Grade (1-2 vs 3)	2,246 (1,388-3,633)	**0,001**	1,760 (0,872-3,551)	0,115[a]
Lymphovascular space invasion (negative vs positive)	2,675 (1,459-4,903)	**0,001**	1,409 (0,656-3,024)	0,379[a]
Perineural invasion (negative vs positive)	1,962 (1,037-3,713)	**0,038**	0,880 (0,387-2,003)	0,761[a]
NLR (<3.3 vs ≥3.3)	15,472 (5,523-43,34)	**0,000**	11,300 (3,633-35,14)	**<0,000**[b]
PLR (<177 vs ≥177)	3,987 (2,046-7,773)	**0,000**	1,445 (0,675-3,092)	0,343[b]
SII (<1036 vs ≥1036)	4,993 (2,498-9,981)	**0,000**	4,561 (1,914-10,870)	**0,001**[a]
PNI (38 vs ≥38)	5,189 (2,670-10,085)	**0,000**	3,320 (1,518-7,262)	**0,003**[a]
PFS	Univariate		Multivariate	
	HR (%95 CI)	P	HR (%95 CI)	P
Age (<50 vs ≥50)	2,193 (0,793-6,063)	0,130	-	-
Menopausal status (premanapuse vs postmenopause)	1,859 (0,743-4,654)	0,185	-	-
ECOG status (0-1 vs 2-3)	2,830 (1,633-4,906)	**0,000**	1,493 (0,772-2,888)	0,234[a]
Histologic Subtype (adenocarcinoma vs other)	0,576 (0,323-1,026)	0,061	-	-
FIGO stage (1-2 vs 3 and 4)	1,650 (1,304-2,087)	**0,000**		0,241[a]
			0,674 (0,291-1,560)	0,357[a]
			1,260 (0,507-3,129)	0,619[a]
Grade (1-2 vs 3)	2,167 (1,385-3,390)	**0,001**	1,762 (0,913-3,401)	0,091[a]
Lymphovascular space invasion (negative vs positive)	2,364 (1,363-4,098)	**0,002**	1,339 (0,673-2,665)	0,406[a]
Perineural invasion (negative vs positive)	1,826 (1,002-3,400)	**0,049**	0,483 (0,213-1,092)	0,080[a]
NLR (<3.3 vs ≥3.3)	9,441 (4,421-20,362)	**0,000**	7,419 (3,123-17,621)	**<0,000**[b]
PLR (<177 vs ≥177)	3,449 (1,887-6,303)	**0,000**	1,150 (0,584-2,264)	0,686[b]
SII (<1036 vs ≥1036)	4,252 (2,287-7,905)	**0,000**	2,651 (1,206-5,824)	**0,015**[a]
PNI (38 vs ≥38)	6,661 (3,408-13,018)	**0,000**	5,118 (2,349-11,151)	**<0,000**[a]

Statistically signifcant p-values (<0.05). NLR: neutrophil lymhocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic immune-inflammation index, PNI: Prognostic nutritional index. aThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, perineural invasion, SII and PNI) were tested in a multivariate analysis. bThe variables (ECOG status, FIGO Stage, grade, lymphovascular space invasion, NLR and PLR) were tested in a multivariate analysis





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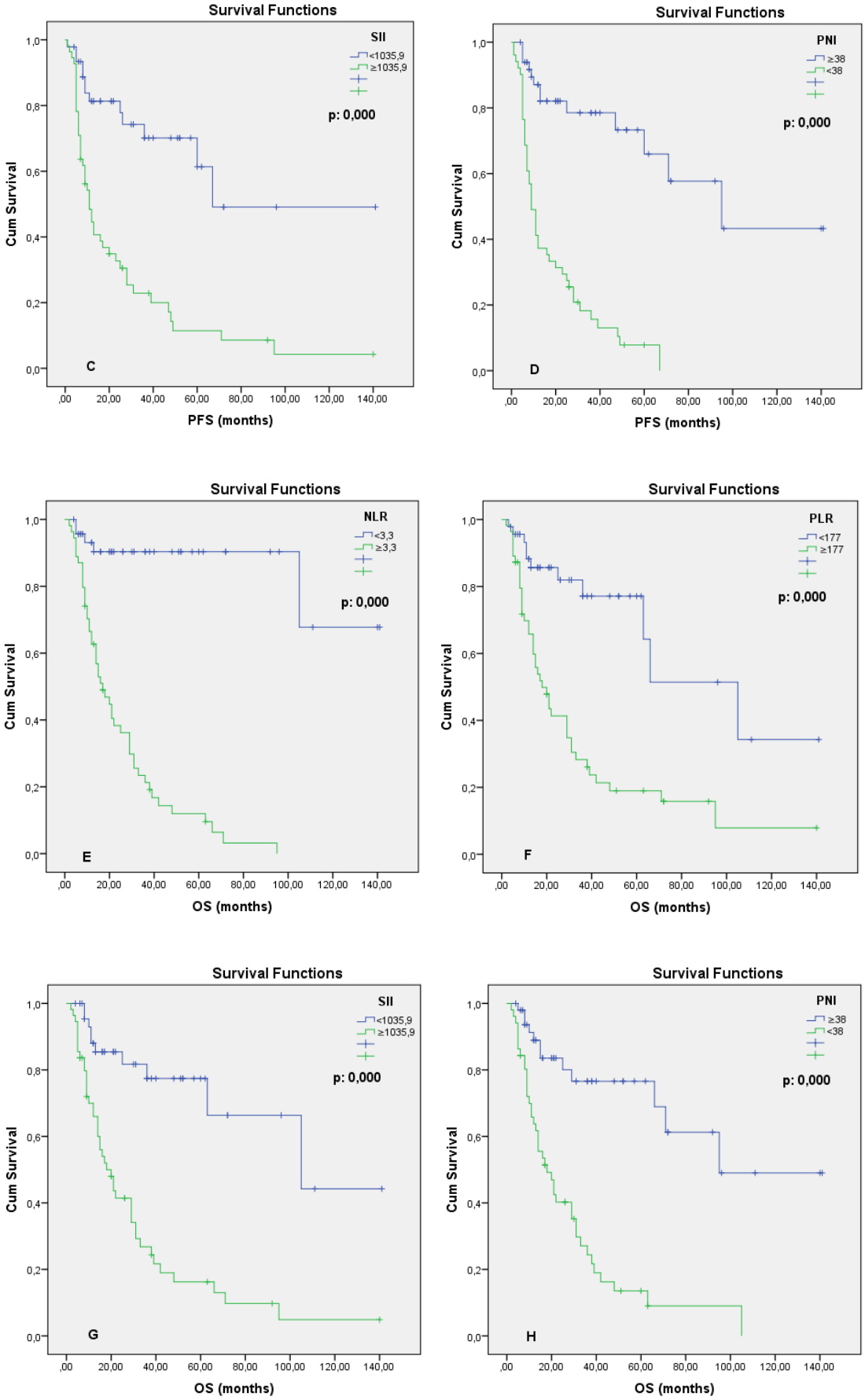

Figure 2: PFS and OS times according to inflammatory markers. NLR (A-E), PLR (B-F), SII (C-G), PNI (D-H). NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic immune-inflammation index, PNI: prognostic nutritional index

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Discussion

EC is the most frequently seen gynecological malignancy in developed countries and the risk of recurrence and death cannot be clearly defined despite the use of classical prognostic factors. Therefore, new predictive markers are needed. In this study, we aimed to demonstrate the prognostic significance of inflammatory markers such as NLR, PLR, SII, and PNI. For the first time in the literature, we found that higher SII and lower PNI values are related to shorter PFS and OS times in EC. Also, we found that SII and PNI are both independent prognostic factors for OS and PFS.

There are many clinical and pathological factors predicting survival in EC. The most important clinical factors are age and race. However, it is thought that the prognosis is mostly determined by the pathological factors such as FIGO stage and histology (subtype and grade) and it has been identified as an independent factor in many studies.

Especially those with endometrioid type and early FIGO stage lived longer (12). In our study, while age and histologic subtype were not prognostic, FIGO stage groups, histologic grade groups MM, CSI, LVSI, and LNI were prognostic factors for both PFS and OS according to univariate analyses. However, in multivariate analyses, no one is an independent factor for both PFS and OS. In particular, the fact that FIGO stage and subtypes could not be identified as independent factors does not seem to be fully compatible with the literature. When we look at the factors that cause this situation, the first findings that we notice are that the patients are not homogeneously distributed according to these two parameters and the number of patients is low. For example, as shown in Table 1, there are fewer than 10 patients in stage 2, 3A, 3B and 4A groups, while in the other stage groups there are 14 or more patients. However, although some of the classical factors in our study did not reveal prognostic significance independently, we think that age, FIGO stage, histologic subtype, and grade are the most important prognostic factors in EC.

In recent years the prognostic significance of inflammatory markers such as NLR, PLR in many cancer types has been identified due to the increasing number of studies, those aiming to understand the interactive mechanism between cancer types and inflammation. However, although the exact cause of this mechanism is still not clear, it is thought that depending on SIR increased neutrophil, platelet and decreasing lymphocyte counts may contribute to this situation (13). In particular release of inflammatory cytokines (interferon y), interleukins (IL-1a, IL-6, IL-7, IL-8, IL-9, IL-12) and phagocytic mediators (monocyte chemotactic protein 1, macrophage inflammatory protein 1β) increased by neutrophils which leads to induction of DNA damage, and angiogenesis and suppression of apoptosis has been presumed to be the foremost etiological factors. Another possible pathophysiologic mechanism of this condition is that by interacting directly with tumoral cells, the platelets secrete mediators that facilitate the growth and invasion of the cancer cells. Also, platelets inhibit the destruction of tumoral cells by natural killer cells. As opposed to the effects of all these cells, lymphocytes show antitumoral effects through their cell-dependent killing abilities (14). Although there are various hypotheses about the relationship between endometrial cancer and inflammation, the most important mechanism is thought to be increased inflammation-dependent cytokine and growth factors due to unmet estrogen. As a result, NF-κB activity increase and up-regulatıon of COX-2, PGE-2 occur in the endometrial cells. Due to these changes, free oxygen radicals initiate neoplastic tumoral transformation through DNA damage. Therefore, inflammatory markers provided to be prognostic in EC, like other cancers (15).

In two meta-analyses investigating 40,559 and 12,754 patients with many cancer types such as breast, esophagus, stomach, colon, ovary cancers (excl. endometrial cancer) higher NLR and PLR values have been associated with shorter OS (16-17). Either et al. reviewed 26 studies encompassing 10530 patients with only gynecologic malignancies, and detected correlations between higher NLR (>2.95) values with poor event-free survival rates (EFS) ($p < 0.001$) and OS ($p < 0.001$). In one of five EC studies have included in this meta-analysis, higher NLR (>2.4) and PLR (>240), while in another study only NLR was found to be an independent prognostic factor for OS. However in a univariate analysis, Li et al. found that NLR and PLR were related to OS and EFS, but they were not evaluated as prognostic independent factors (18-20). Güleç et al. examined the relationship between inflammatory markers and clinicopathological data in 763 endometrial cancer patients, in this study, they suggested that NLR and PLR are associated with advanced FIGO, MM, CSI, LVSI, and LNI. In addition to that NLR is also associated with histological type and metastasis. In univariate analyses, NLR was identified as a prognostic factor for OS, whereas in multivariate analyses it was suggested that NLR is not an independent prognostic factor (21). Similarly, in our study, patients with high NLR and PLR values had shorter OS and PFS. Besides in univariate analyses, NLR and PLR were prognostic markers for OS/PFS, but multivariate analyses revealed that NLR was also an independent factor for OS and PFS. We detected that NLR and PLR correlated also with advanced FIGO stage MM, LVSI, LNI, while NLR was also associated with ECOG performance status and CSI. Although different cut-off values have been used for the inflammatory markers in the aforementioned studies, as a common finding in all studies, including ours, higher NLR and PLR values have been associated with many adverse clinicopathological features, and in particular, NLR had a prognostic significance in EC. This situation supports the role of inflammation in carcinogenesis of EC.

SII is a brand new developed inflammatory marker which is a combination that allows the simultaneous evaluation of NLR and PLR. Therefore, it is thought that SII better reflects the balance between the inflammatory state and SIR (22). A study showing that SII correlates with the number of circulating tumor cells, which supports this assumption (23). In a meta-analysis, encompassing 7657 patients, but excluding cases with gynecologic malignancies, Yang et al associated high SII values with shorter OS in some cancer types such as urinary system (p

<0.001), HCC (p <0.001), acral melanoma (p <0.001), gastric (p = 0.005), esophageal squamous cell (p = 0.013), small and non-small cell lung cancer (p <0.001, p <0.001) (24). A recent study demonstrated the prognostic role of SII in cervical cancer patients and compared to NLR, PLR, and MLR, only SII was found to be an independent prognostic factor for OS, without any correlation with clinicopathological features (25). Nie et al. associated higher SII (>612) with shorter PFS and OS in 553 epithelial ovarian carcinoma cases and in multivariate analysis they were found to be independent prognostic factors also for both OS and PFS. Besides, they demonstrated that higher SII correlated with lymph node metastasis, advanced FIGO stage, and tumor recurrence (26). However, there is no study showing the relationship of SII with clinicopathological features and its prognostic role in patients with EC. For the first time in literature in our study, the association of SII with clinicopathologic characteristics in patients with EC, and its prognostic role have been demonstrated. Similar to the results of the studies on other types of cancer, higher SII has been associated with shorter OS and PFS and found to be an independent prognostic factor in multivariate analysis. Besides higher SII is associated with advanced FIGO stage, CSI, LVSI, and LNI. However, it was concluded that SII is more predictive for OS and PFS in esophageal, pulmonary cancers, and HCC when compared with other inflammatory markers (27). Contrarily in our study, NLR with the highest AUC value was the most predictive marker for OS followed by SII. We think that this finding may be related to the limited number of patients or the biologic differences between the tumors. To validate the prognostic significance of SII in patients with EC, independent cohort studies should be performed.

According to recent studies, not only the characteristic features of the tumor but also the nutritional and immunological status affects the progression of cancer (28). Although PNI was initially introduced to predict preoperative mortality and morbidity, its prognostic significance has been found in many types of cancer in recent years. It is the most widely used marker for detecting nutritional and immunological status since it is estimated by using lymphocyte counts and albumin values (29). Due to excessive and improper SIR, cytokines such as TNF alpha and IL-6 cause proteolysis in muscle cells leading to cancer cachexia. This pathophysiological process results in decreased albumin levels, and weight loss (30). For the same reason, lymphocytes, which are the main cells of cellular immunity, decrease in number and host cell's ability to kill tumor cells weakens. In light of all this information, a decrease in lymphocyte and/or albumin levels suggests the development of excessive inflammatory reaction and poor prognosis of the cancer patient. This situation explains the relationship between lower PNI values with shorter survival times and poor prognosis. In a meta-analysis of 3414 patients with mostly gastrointestinal cancers, Sun et al. showed that PNI was a prognostic factor in 6 cancer types for OS (pooled OR 2.29, 95% CI 1.42-,3.71) including HCC (pooled OR 1.55, 95% CI: 1.06 -2.26), and gastric (pooled OR 2.26, 95% CI: 1.63 -3.13), esophageal (pooled OR 1.80, 95% CI:1.16 -2.80), pancreatic (pooled OR 1.57, 95% CI:1.20- 2.05), colorectal (pooled OR 1.78, 95% CI:1.45-2.19) (31). Therefore, our study is the first study investigating the role of PNI in EC. According to the results of the only study that investigated the role of albumin in EC, an association between albumin deficiency and advanced FIGO stage, histological grade, and age was identified, and albumin was found to be an independent prognostic factor for PFS in multivariate analyses (32). Our study also confirmed the results of these studies. As an independent prognostic factor for both OS and PFS, PNI is strongly correlated with many worse clinicopathologic characteristics including poor ECOG performance score, advanced FIGO stage, MM, CSI, LVSI, and LNI. We also found that the inflammatory marker most associated with clinicopathologic characteristics is PNI. These results show that the combination of nutritional and inflammatory conditions has a prognostic significance in EC and indicate the necessity of confirmation of these results.

Although our study revealed new data, it has some limitations, including its retrospective design, relatively low number of patients and shorter median follow-up period. Because of these further large, prospective, and randomized controlled multicenter studies will be important to validate our findings.

Conclusion

SIR is also a predictive factor for survival in EC as in other types of cancer. In our study, it is shown that as newly developed inflammatory markers SII and PNI, which are thought to be novel indicators of SIR had prognostic significance as well as well-known markers (NLR, PLR). SII and PNI are independent prognostic factors for both OS and PFS and associated with many clinicopathological features.

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