

# Impact of Immune, Inflammatory and Nutritional Indices on Outcome in Patients with Cervical Cancer Treated with Definitive (Chemo)radiotherapy

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## INTRODUCTION

Systemic immune, inflammatory, and nutritional indices have been shown to be prognostic for outcome across a range of tumor sites. However, a comprehensive analysis of these markers in patients with cervical cancer treated with definitive (chemo)radiotherapy [(C)RT] has not been performed.

## AIM

To measure systemic immune, inflammatory and nutritional indices, and determine their association with progression free survival (PFS) and overall survival (OS) in patients undergoing definitive (C)RT for cervical cancer.

## METHODS

Patients with cervical cancer treated with definitive (C)RT from 1999 - 2015 were identified from a single cancer institution's retrospective clinicopathological database. Pre-treatment immune, inflammatory, and nutritional parameters were documented, and indices derived.

Indices	Equation
<b>SII</b> - Systemic Immune-Inflammation Index	neutrophil count x platelet count / lymphocyte count(10 <sup>9</sup> /L)
<b>PLR</b> - Platelet Lymphocyte Ratio	platelet count / lymphocyte count (10 <sup>9</sup> /L)
<b>NLR</b> - Neutrophil Lymphocyte Ratio	neutrophil count / lymphocyte count(10 <sup>9</sup> /L)
<b>MLR</b> - Monocyte Lymphocyte Ratio	monocyte count / lymphocyte count (10 <sup>9</sup> /L)
<b>AAPR</b> - Albumin to Alkaline Phosphatase Ratio	serum albumin level (g/L)/ alkaline phosphatase level (U/L)
<b>PNI</b> - Prognostic Nutritional Index	serum albumin (g/L) + 5 x lymphocyte count (10 <sup>9</sup> /L)

- Univariate analysis was first performed on each parameter as continuous variables for PFS and OS.
- For variables with statistically significant associations, ROC curves were analyzed to determine if an optimal cut-point could be established for each outcome. Common cut points were then defined for each variable.
- PFS and OS were analyzed by the Kaplan-Meier method and the Log-Rank test.
- Multivariate analysis was performed using Cox regression with covariates of tumor stage, histology, and age.
- P-values of <0.05 were considered statistically significant.

## RESULTS

**Table 1: Patient Characteristics**

N=196; median follow up 7 years (IQR 2-11)

	Median or No.	IQR or %
<b>Age [years]</b>	52	42-60
<b>Stage [FIGO 2009]</b>		
I-II	131	67%
III-IV	65	33%
<b>Histology</b>		
Squamous	164	84%
Adenocarcinoma	28	14%
Other	4	2%
<b>Treatment</b>		
Chemoradiotherapy	187	95%
Radiotherapy alone	9	5%
<b>Immune, Inflammatory, and Nutritional Indices:</b>		
SII	1046	636-1798
PLR	199	140-278
NLR	3.5	2.2-5.0
MLR	0.32	0.25-0.47
AAPR	0.45	0.35-0.55
PNI	46	42-49

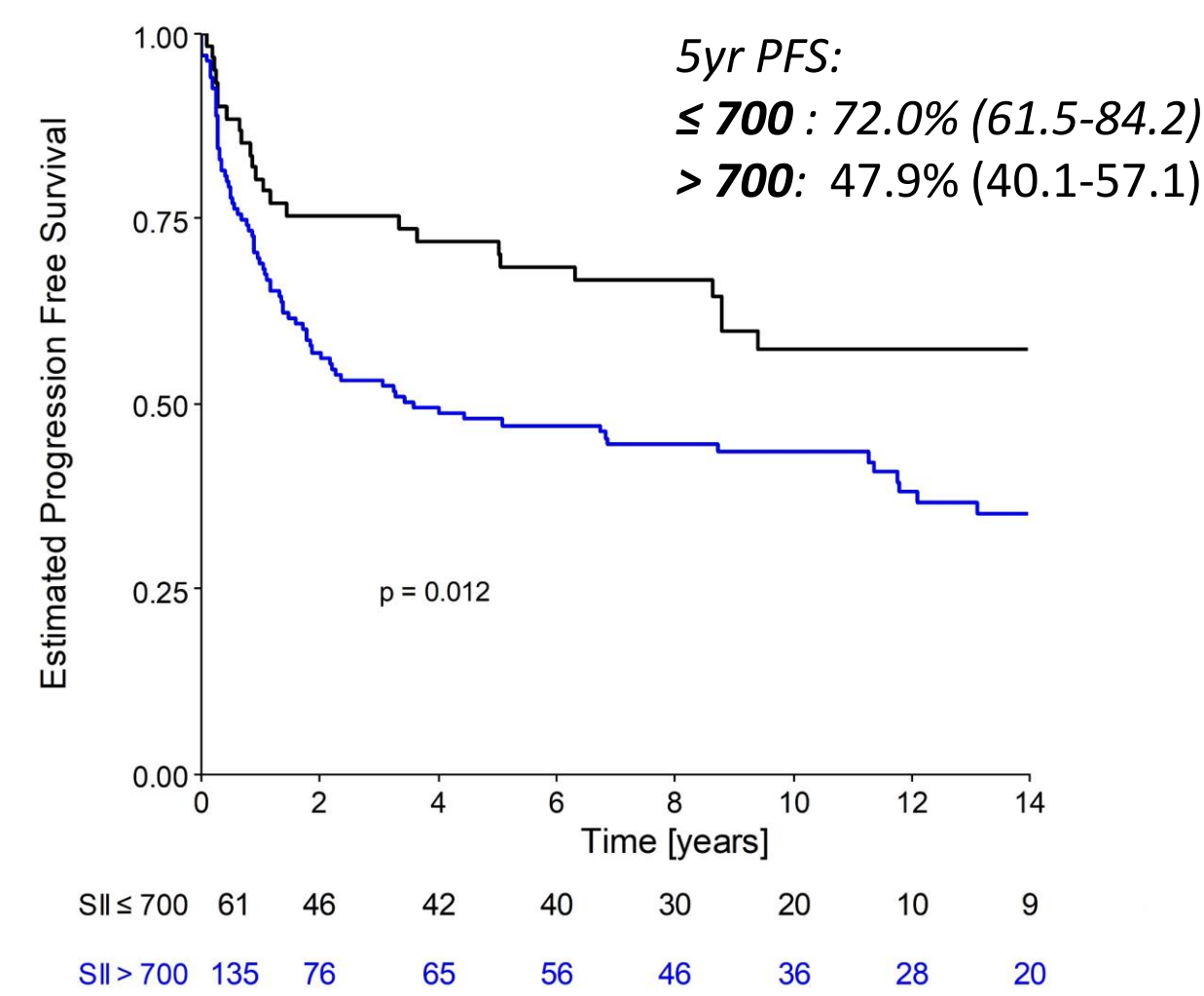
**Table 2: Univariate Analysis (continuous variable)**

Variable	Progression Free Survival			Overall Survival		
	HR	95% CI	p	HR	95% CI	P
<b>SII</b>	1.0001	1.0001 – 1.0002	<b>0.002</b>	1.0001	1.0000 – 1.0002	<b>0.013</b>
<b>PLR</b>	1.0018	1.0008 – 1.0027	<b>&lt;0.001</b>	1.0012	1.0003 – 1.0021	0.07
<b>NLR</b>	1.09	1.05 – 1.13	<b>&lt;0.001</b>	1.052	1.018 – 1.088	<b>0.003</b>
<b>MLR</b>	1.75	0.948 – 3.23	0.074	1.30	0.699 – 2.42	0.407
<b>AAPR</b>	0.604	0.173-2.11	0.429	0.399	0.102 - 1.568	0.188
<b>PNI</b>	0.969	0.937 – 1.00	0.062	0.972	0.935 – 1.01	0.117

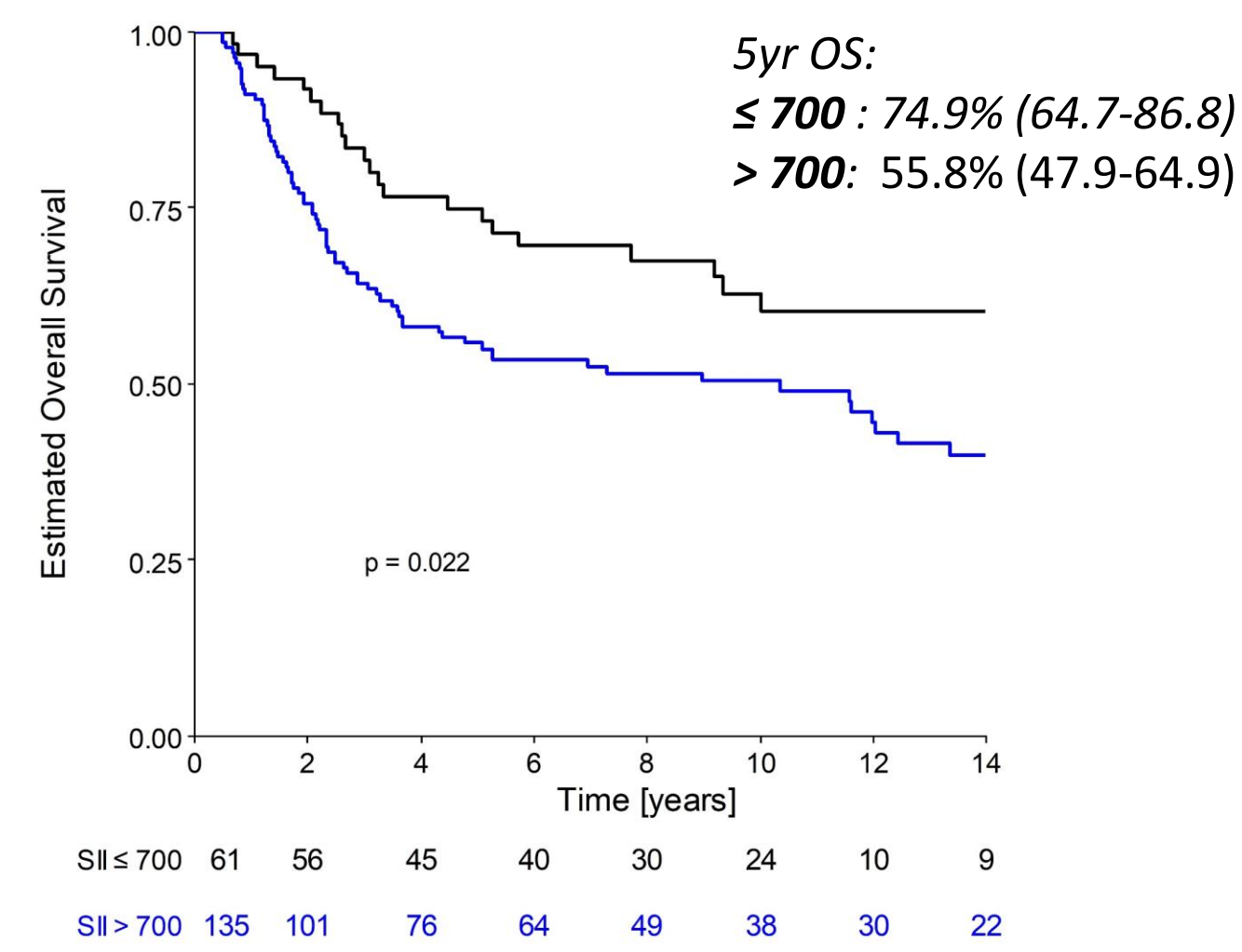
## CONCLUSIONS

- SII and PLR were independently associated with PFS and OS in patients with cervical cancer treated with definitive (C)RT. NLR, MLR, AAPR or PNI were not.
- Further evaluation of these systemic immune and inflammatory indices in a validation set will be required to better define their clinical utility.

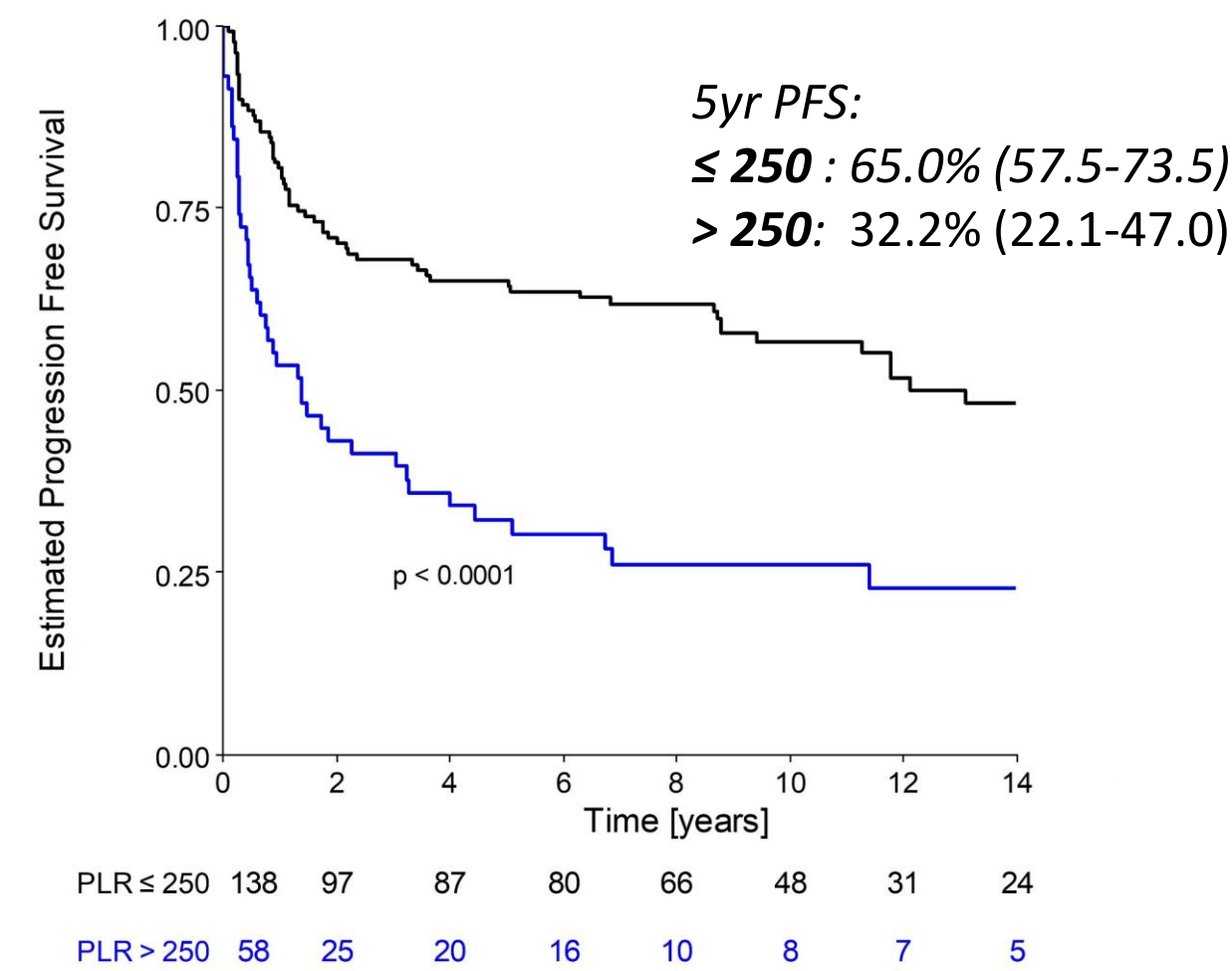
**Figure 1: Progression free survival by SII**



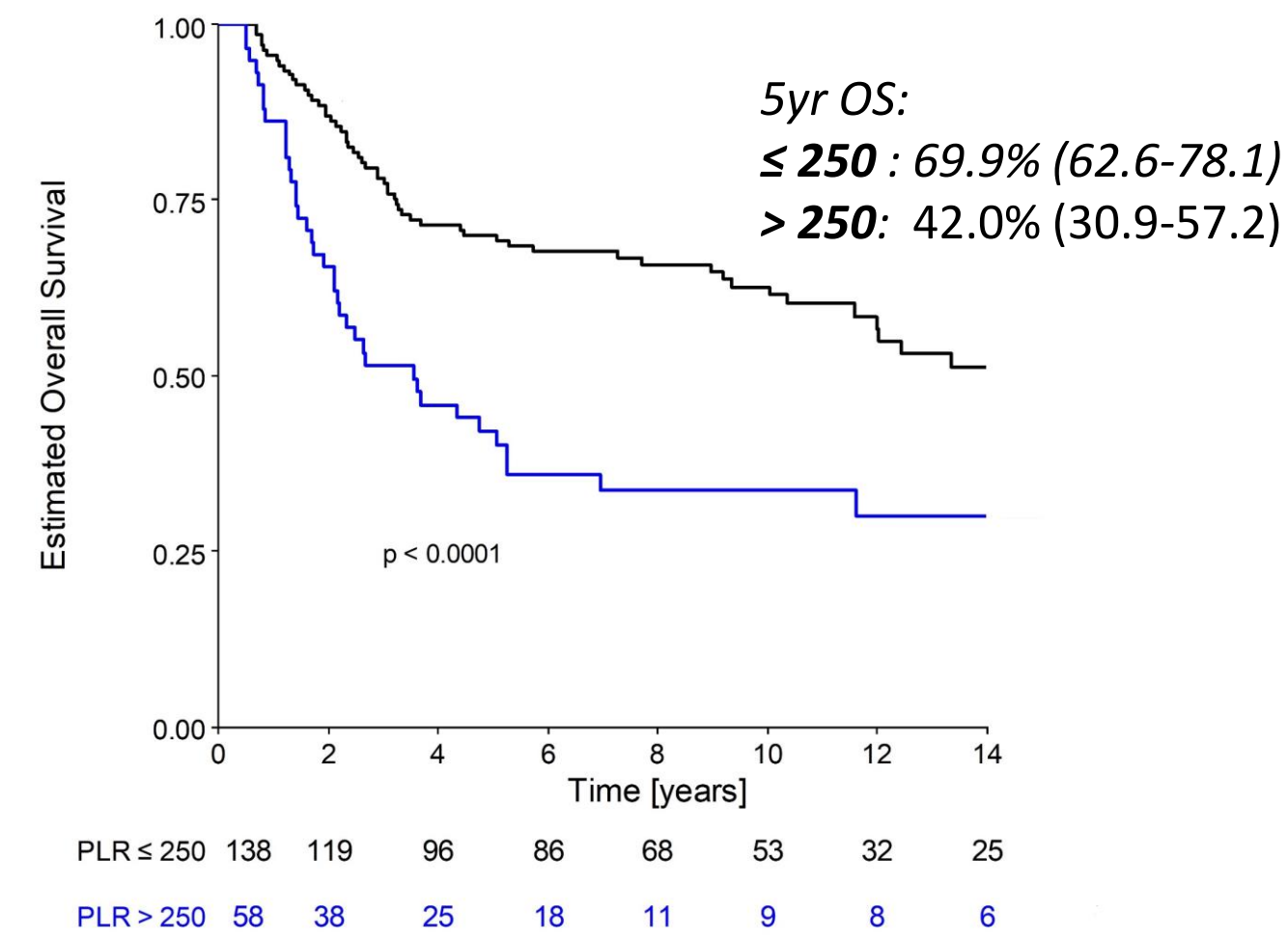
**Figure 2: Overall Survival by SII**



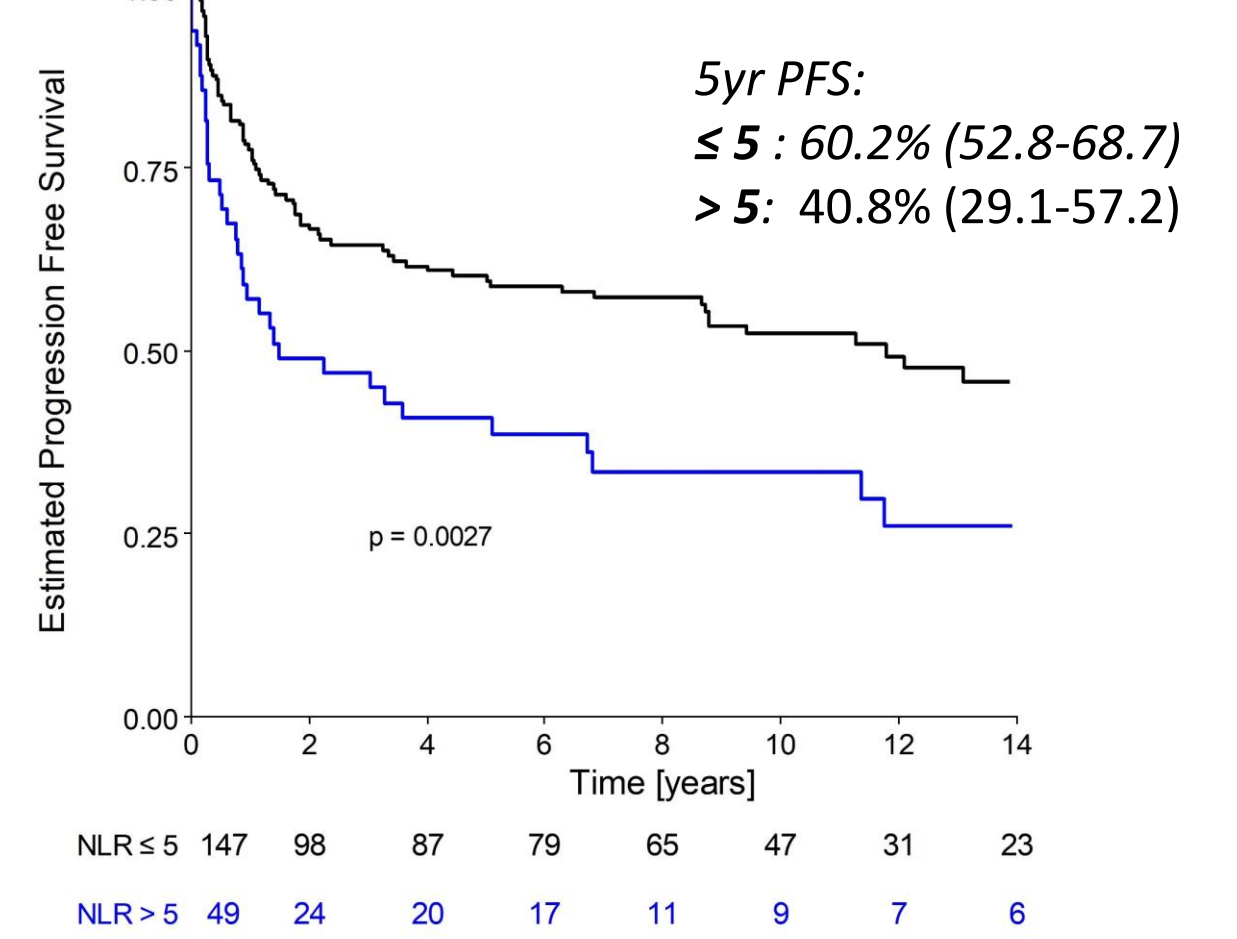
**Figure 3: Progression free survival by PLR**



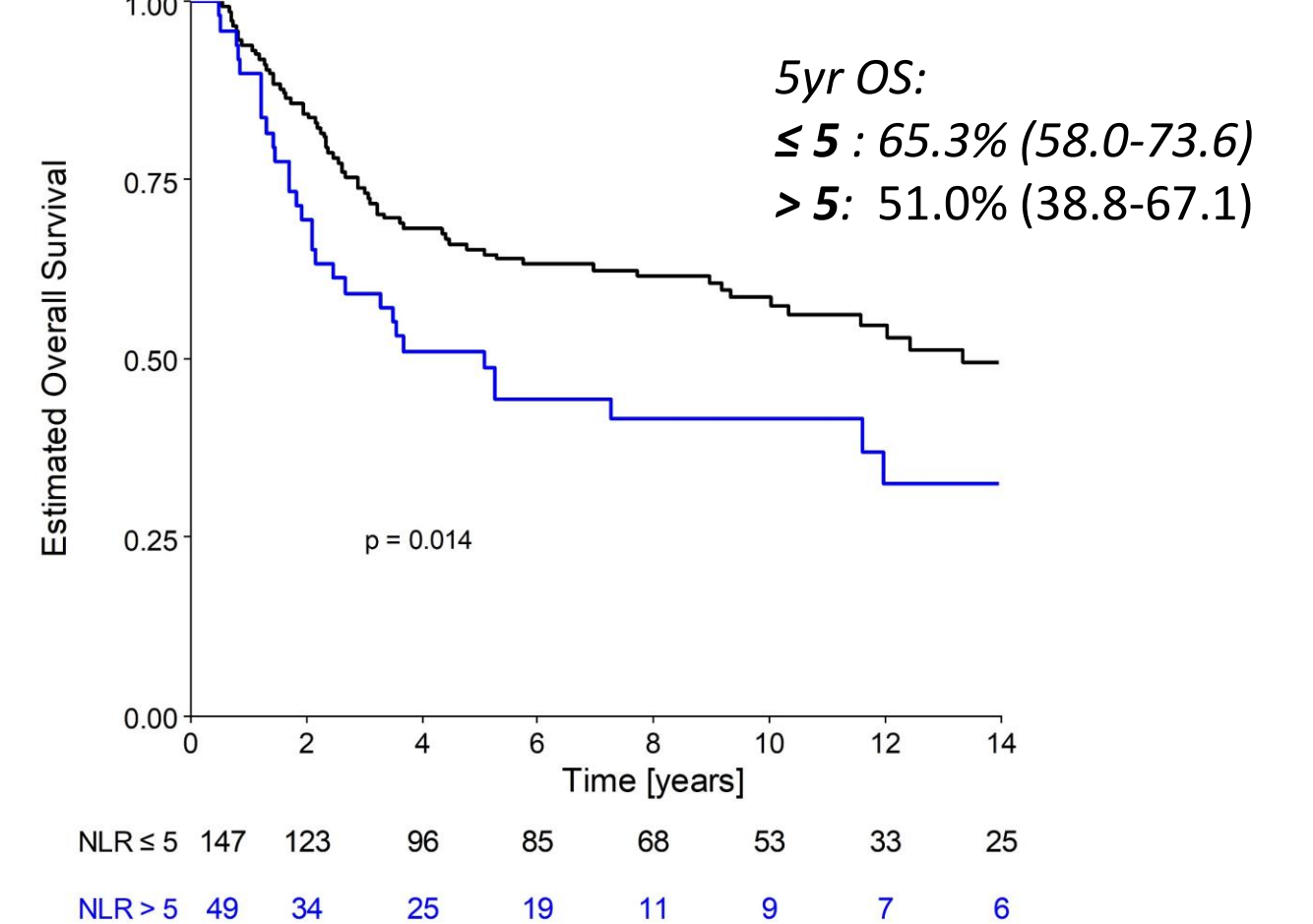
**Figure 4: Overall Survival by PLR**



**Figure 5: Progression free survival by NLR**



**Figure 6: Overall Survival by NLR**



**Table 3: Multivariate Analysis including SII**  
SII optimal cut-off 700

Variable	Progression Free Survival			Overall Survival		
	HR	95% CI	p	HR	95% CI	P
<b>SII</b> [≤ 700 vs >700]	1.6	1.0-2.6	<b>0.038</b>	1.6	1.0-2.7	<b>0.046</b>
<b>Age</b> [years]	1.02	1.00-1.03	<b>0.023</b>	1.02	1.01-1.04	<b>0.003</b>
<b>Stage</b> [III-IV vs I-II]	2.1	1.4-3.2	<b>&lt;0.001</b>	2.4	1.5-3.6	<b>&lt;0.001</b>
<b>Histology</b> [Other vs adeno vs squam]	1.3	0.8-2.0	0.238	1.3	0.79- 2.0	0.33

**Table 4: Multivariate Analysis including PLR**  
PLR optimal cut-off 250

Variable	Progression Free Survival			Overall Survival		
	HR	95% CI	p	HR	95% CI	P
<b>PLR</b> [≤ 250 vs >250]	2.3	1.5-3.5	<b>&lt;0.001</b>	2.2	1.4-3.4	<b>&lt;0.001</b>
<b>Age</b> [years]	1.02	1.01-1.03	<b>0.007</b>	1.03	1.01-1.04	<b>&lt;0.001</b>
<b>Stage</b> [III-IV vs I-II]	1.9	1.2-2.8	<b>0.003</b>	2.1	1.4-3.3	<b>&lt;0.001</b>
<b>Histology</b> [Other vs adeno vs squam]	1.38	0.90-2.1	0.14	1.3	0.84-2.1	0.227

**Table 5: Multivariate Analysis including NLR**  
NLR optimal cut-off 5

Variable	Progression Free Survival			Overall Survival		
	HR	95% CI	p	HR	95% CI	P
<b>NLR</b> [≤ 5 vs >5]	1.5	0.98-2.3	0.065	1.4	0.91-2.2	0.119
<b>Age</b> [years]	1.01	1.00-1.03	<b>0.04</b>	1.02	1.01-1.04	<b>0.005</b>
<b>Stage</b> [III-IV vs I-II]	2.1	1.4-3.2	<b>&lt;0.001</b>	2.4	1.6-3.7	<b>&lt;0.001</b>
<b>Histology</b> [Other vs adeno vs squam]	1.3	0.83-2.0	0.26	1.2	0.79-2.0	0.34

## REFERENCES

- Koulis TA, Kornaga EN, Banerjee R, Phan T, Ghatage P, Magliocco AM, Lees-Miller SP, and CM Doll. Anemia, leukocytosis and thrombocytosis as prognostic factors in patients with cervical cancer treated with radical chemoradiotherapy: A retrospective cohort study. Clin Transl Radiat Oncol 2017;4:51-56.
- Han X, Liu S, Yang G, Hoeseniffard H, Imami S, Yang L, Maghroudou M, Fu S, Wen Q, and Q Liu. Prognostic value of systemic hemato-immunological indices in uterine cervical cancer: A systematic review, meta-analysis, and meta-regression of observational studies. Gynecol Oncol 2021;160(1):351-360.
- Guo J, Lv W, Wang Z, Shang Y, Yang F, Zhang X, Xiao K, Zhang S, Pan X, Han Y, Zong L, and W Hu. Prognostic value of inflammatory and nutritional markers for patients with early-stage poorly to moderately-differentiated cervical squamous cell carcinoma. Cancer Control 2023 Jan-Dec;30:10732748221148913.
- Liu P, Jiang Y, Zheng X, Pan B, Xiang H, and M Zheng. Pretreatment systemic immune-inflammation index can predict response to neoadjuvant chemotherapy in cervical cancer at stages IB2-1IB. Pathol OncolRes. 2022 Apr 27; 28:1610294. Analysis. Med Sci Monit 2022 Mar 9;28:e934588.
- Onal C, Gültekin M, Yavas G, Oymak E, Yuce Sari S, Güler OC, Yigit E, and F Yildiz. The impact of serum albumin-to-alkaline phosphatase ratio in cervical cancer patients treated with definitive chemoradiotherapy. J Obstet Gynaecol 2022 Aug;42(6):2426-2432.
- Gangopadhyay A. Prognostic nutritional index and clinical response in locally advanced cervical cancer. Nutr Cancer 2020;72(8):1438-1442.
- Haraga, J, Nakamura, K, Omichi, C, Nishida, T, Haruma, T, Kusumoto, T, Seki, N, Masuyama, H, Katayama, N, Kanazawa, S, and Y Hiramatsu. Pretreatment prognostic nutritional index is a significant predictor of prognosis in patients with cervical cancer treated with concurrent chemoradiotherapy. Mol Clin Oncol 2016 Nov;5(5):567-574.

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## CONTACT INFORMATION

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