PROGNOSTIC VALUE OF INFLAMMATORY AND IMMUNE INDICES IN NEOADJUVANT CONCURRENT CHEMORADIOTHERAPY FOR ESOPHAGEAL CANCER AT K HOSPITAL

Pham Khanh Toan*, Vo Van Xuan, Tran Trung Bach

ABSTRACT

Objectives: To evaluate the prognostic value of inflammatory–immune indices in patients with esophageal cancer treated with concurrent neoadjuvant chemoradiotherapy at K Hospital.

Subjects and Methods: This retrospective longitudinal study included 57 patients with middle-to-lower thoracic esophageal cancer, histologically confirmed squamous cell carcinoma, stage II–III according to the 8th edition of the AJCC staging system, who were treated with concurrent neoadjuvant chemoradiotherapy at K Hospital from January 2018 to December 2024. Clinical characteristics, paraclinical findings, treatment-related variables, and the NLR(Neutrophil/Lymphocyte), PLR(Platelet/Lymphocyte), and SII indices were collected. Optimal cut-off values were determined using time-dependent ROC curves based on mortality endpoints and the Youden index. Overall survival was analyzed using the Kaplan–Meier method, log-rank test, ROC analysis, and Cox regression.

Results: The median overall survival was 57 months; 3-year and 5-year overall survival rates were 73.3% and 41.9%, respectively. The optimal cut-off values for NLR, PLR, and SII were 5.3, 174.3, and 979.3. Patients with low SII had longer median survival than those with high SII (60 vs. 36 months; p=0.001). SII predicted 3-year overall survival with an AUC of 0.669 (p=0.035). In multivariable analysis, age >=60 years and nodal positivity were independent adverse prognostic factors, whereas low SII was an independent favorable prognostic factor (HR=0.131; 95% CI: 0.024-0.701; p=0.018).

Conclusions: Post-nCRT preoperative SII is a simple and clinically applicable index with prognostic value for overall survival in patients with locally advanced esophageal squamous cell carcinoma treated with neoadjuvant concurrent chemoradiotherapy.

Keywords: Esophageal cancer, concurrent neoadjuvant chemoradiotherapy, SII (Systemic Immune-Inflammation), NLR(Neutrophil/Lymphocyte), PLR(Platelet/Lymphocyte), overall survival.

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1. INTRODUCTION

Esophageal cancer (EC) is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide. [1] Esophageal cancer is primarily classified into esophageal squamous cell carcinoma (ESCC) and adenocarcinoma, of which ESCC accounts for approximately 85% [2]. Studies have shown that neoadjuvant chemoradiotherapy (nCRT), neoadjuvant chemotherapy combined with immunotherapy, and neoadjuvant chemotherapy (nCT) alone are the main treatment modalities that improve survival outcomes in patients with resectable locally advanced ESCC. However, the prognosis of esophageal cancer remains limited. [3] Therefore, further studies are needed to identify independent factors that can predict the efficacy of nCRT in patients with locally advanced EC, thereby enabling personalized treatment strategies and more intensive surveillance.

Over the years, accumulating evidence has demonstrated that neutrophils, lymphocytes, platelets, and other inflammatory indices are closely associated with the prognosis of several solid tumors. [4]. Inflammatory–immune indices derived from peripheral blood parameters, such as PLR (platelet-to-lymphocyte ratio), SII (systemic immune–inflammation index), and NLR (neutrophil-to-lymphocyte ratio), which depend on neutrophil, platelet, and lymphocyte counts, have emerged as independent prognostic factors in various cancers in recent years. Currently, the mechanisms by which SII influences the prognosis of esophageal cancer remain unclear. Some studies suggest that neutrophils can activate endothelial and stromal cells, enhance adhesion of circulating tumor cells, and promote distant metastasis. Lymphocytes play a crucial role in anti-tumor immunity, whereas platelets, activated by tumor cells, may disrupt endothelial barriers, facilitating tumor metastasis and dissemination. [4], [5] Retrospective studies have shown that NLR, PLR, and SII have certain predictive value for the efficacy of neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer [6].

Regarding SII in patients with locally advanced ESCC undergoing nCRT, Zhang H et al. (2024) reported that improved overall survival (OS) was associated with lower SII (≤916.6 × 10^9 / L) in the neoadjuvant chemoradiotherapy group ($p = 0.034$). Patients with lower SII receiving nCRT had significantly better OS ($p < 0.001$). Furthermore, higher SII was associated with a lower resection rate ($p = 0.035$) [7].

In Vietnam, there has been little evidence on studies conducted to clarify the role of systemic inflammatory–immune indices in predicting survival outcomes in patients with locally advanced esophageal cancer treated with neoadjuvant concurrent chemoradiotherapy. Therefore, this study was carried out with the objective: "Assessment of the prognostic value of inflammatory–immune indices in neoadjuvant concurrent chemoradiotherapy for esophageal cancer at K Hospital".

2. SUBJECTS AND METHODS

2.1. Research subjects

This study included 57 patients with esophageal cancer who underwent neoadjuvant concurrent chemoradiotherapy at K Hospital from January 2018 to December 2024, meeting the inclusion and exclusion criteria.

Inclusion criteria:

- Patients with middle-to-lower third esophageal cancer with histologically confirmed squamous cell carcinoma (SCC).

- Locally advanced stage: cT1b–cT2, N (+); cT3–cT4a, any N (stage II–III according to the AJCC 8th edition).

- Indicated for neoadjuvant concurrent chemoradiotherapy.

- Complete medical records, including inflammatory–immune indices.

Exclusion criteria:

- Not meeting inclusion criteria.

- Distant metastatic disease (M1) according to the AJCC 8th edition.

- Presence of a second primary malignancy.

- Incomplete neoadjuvant chemoradiotherapy regimen, defined as failure to complete the planned concurrent chemotherapy cycles and/or radiotherapy course because of toxicity, disease progression, withdrawal, or other medical reasons.

- Not eligible for surgery or refusal of surgery.

- Patients who declined participation in the study.

2.2. Methods

Study design: Retrospective descriptive study with longitudinal follow-up.

Sampling method: Convenience sampling.

Research procedure:

- Select patients meeting inclusion and exclusion criteria.

- Collect clinical and paraclinical characteristics: age, sex, tumor features on endoscopy, and computed tomography imaging (location, size, morphology, characteristics).

- Collect treatment-related variables: chemotherapy regimen, radiotherapy technique, prescribed radiation dose and fractionation, treatment compliance, and the interval between completion of concurrent chemoradiotherapy and surgery. Radiotherapy was delivered using 3D-CRT or IMRT/VMAT according to institutional practice, with a preoperative dose/fractionation schedule recorded from the medical record. The inflammatory and immune indices used in this analysis were measured after completion of neoadjuvant chemoradiotherapy and within 1-2 weeks before surgery, using the most recent complete blood count before surgery. NLR was calculated as absolute neutrophil count/ absolute lymphocyte count; PLR as platelet count/ absolute lymphocyte count; and SII as platelet count x absolute neutrophil count/absolute lymphocyte count. Optimal cut-off values were determined using ROC curves based on 3-year mortality endpoints and the Youden index.

Periodically follow up and record overall survival. Follow-up was completed in September 2025.

Statistical analysis:

- Data were analyzed using SPSS version 26.0.

- Descriptive statistics included mean, standard deviation, minimum, and maximum values.

Associations between variables were assessed us- ing the chi-square (χ^2) test or Fisher's exact test.

- Spearman correlation analysis was used to evaluate the relationships between NLR, SII, and PLR.

- Overall survival (OS) was estimated using the Kaplan–Meier method.

- Differences between groups were analyzed using the log-rank test.

- Hazard ratios (HRs) were estimated using Cox proportional hazards regression. To reduce the risk of overfitting in this small cohort, multivariable models were limited to clinically relevant variables and variables with $p<0.10$ in univariate analysis; results were interpreted as exploratory.

- Predictive performance was assessed using the area under the curve (AUC) of time-dependent ROC analysis to evaluate the prognostic value of SII for 1-year and 3-year overall survival.

A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Clinical and paraclinical characteristics and treatment regimens

Table 1. Clinical and paraclinical characteristics and treatment regimens

Characteristics		n	Percentage (%)
Age	≥60	32	56.1
	<60	25	43.9
	Total	57	100
	Mean	60.5±6.6 (48-75)	
Gender	Male	56	98.2
	Female	1	1.8
Tumor location	Middle third	23	40.4
	Lower third	34	59.6
Tumor length	≤ 7 cm	33	57.9
	>7 cm	24	42.1
T stage	T1	1	1.8
	T2	25	43.9
	T3	25	43.9
	T4	6	10.4
N stage	N0	16	28.1
	N1-2	41	71.9
Chemotherapy regimen	CF	7	12.3
	TC	50	87.7
Radiotherapy technique	3D-CRT	15	26.3
	IMRT/VMAT	42	73.7

Comment: The mean age of the study population was 60.5 ± 6.6 years. Patients aged ≥60 years accounted for the majority (56.1%). The oldest patient was 75 years and the youngest was 48 years. Most patients were male (98.2%). Tumors located in the lower third of the esophagus were predominant (59.6%), followed by the middle third (40.4%). Tumor length ≤7 cm was more common than >7 cm, accounting for 57.9% and 42.1%, respectively. T1–2 stage accounted for 45.7%, while 54.3% were in T3–4 stage. The majority of patients had nodal metastasis (N1–2),

accounting for 71.9%. Most patients (87.7%) received the TC concurrent chemotherapy regimen. A total of 73.7% of patients were treated with IMRT/VMAT radiotherapy techniques.

3.2. Inflammatory-immune indices

Table 2. Inflammatory-immune indices

Index	n	%
NLR		
≤5.3	51	89.5
>5.3	6	10.5
PLR		
≤174.3	38	66.7
>174.3	19	33.3
SII		
≤979.3	42	73.7
>979.3	15	26.3

Comment: Using ROC curve analysis based on mortality at the specified time point and the Youden index, the optimal cut-off values for inflammatory-immune indices were determined as follows: SII 979.3, NLR 5.3, and PLR 174.3. The majority of patients were in the low SII group (73.7%) and had NLR ≤5.3 (89.5%); approximately one-third had PLR >174.3 (33.3%).

3.3. Association between SII, NLR levels and related factors

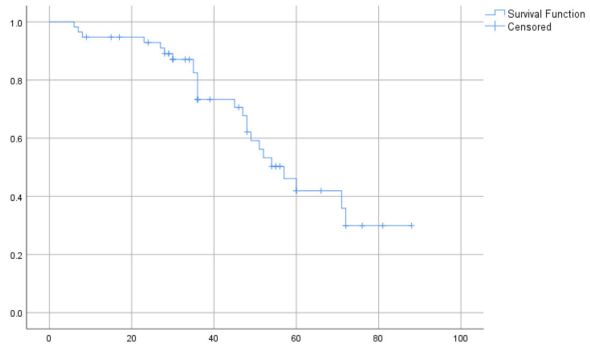
Table 3. Association between SII, NLR levels and related factors

Characteritics		SII		p	NLR		p
		High (n)	Low (n)		High (n)	Low (n)	
Age group	≥60	8	17	0.546	1	31	0.077
	<60	7	25		5	20	
Gender	Male	14	41	0.461	6	49	1.000
	Female	1	1		0	2	
T stage	T1-2	8	18	0.554	2	24	0.678
	T3-4	7	24		4	27	
N stage	N0	6	10	0.317	1	15	0.665
	N(+)	9	32		5	36	
Tumor location	Middle third	8	26	0.760	5	29	0.385
	Lower third	7	16		1	11	

Characteritics		SII		p	NLR		p
		High (n)	Low (n)		High (n)	Low (n)	
Tumor length	≤ 7cm	9	24	0.847	1	32	0.073
	>7cm	6	18		5	19	
Chemotherapy regimen	CF	4	3	0.070	2	5	0.153
	TC	11	39		4	46	
Radiotherapy technique	3D	6	9	0.949	5	10	0.197
	IMRT/VMAT	13	29		3	39	

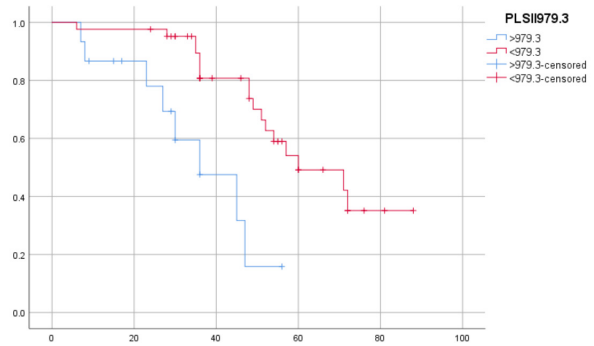
Comment: No statistically significant associations were observed between SII or NLR and age, sex, T/N stage, tumor length, chemotherapy regimen, or radiotherapy technique ($p > 0.05$). Borderline trends toward significance were noted for NLR with age ($p = 0.077$) and tumor length ($p = 0.073$), and for SII with chemotherapy regimen ($p = 0.070$).

3.4. Overall survival (OS)



Trung vị	ĐLC	95% CI
57.00	5.300	46.613-67.387

Figure 1. Overall survival of the study population



SII	Trung vị	ĐLC	95% CI	Log Rank (Mantel-Cox): 11.991 (p=0,001)
>979.3	36.000	8.492	19.355-52.645	
<979.3	60.000	9.909	40.578-79.422	

Figure 2. Overall survival according to SII groups

Comment: Among the 57 patients, the 3-year overall survival rate was 73.3% and the 5-year overall survival rate was 41.9%, with a median overall survival of 57 ± 5.3 months (95% CI: 46.4-67.4 months). The median overall survival was 36 months (95% CI: 19–52) in the high SII group and 60 months (95% CI: 46–67) in the low SII group. The corresponding 3-year overall survival rates were 47.5% and 80.8%, respectively (log-rank = 11.991; $p = 0.001$).

3.5. ROC curve of SII for predicting overall survival

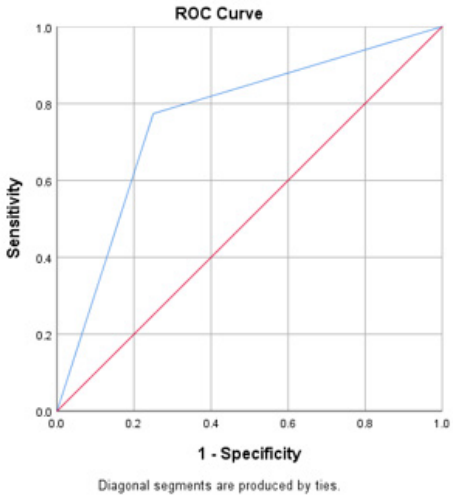


Figure 3. ROC curve of SII for predicting 1-year overall survival

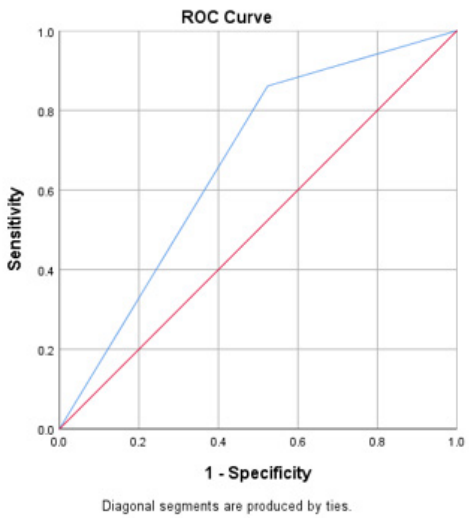


Figure 4. ROC curve of SII for predicting 3-year overall survival

Comment: Preoperative SII following neoadjuvant chemoradiotherapy showed a trend toward predicting 1-year overall survival (AUC = 0.762; 95% CI: 0.506-1.000), although this did not reach statistical significance (p = 0.083). For 3-year overall survival, SII demonstrated an AUC of 0.669 (95% CI: 0.516-0.882; p = 0.035), indicating a moderate but statistically significant ability to stratify long-term mortality risk.

3.6. Univariate and multivariable Cox proportional hazards regression analysis for overall survival

Table 4. Univariate and multivariable Cox proportional hazards regression model for overall survival

Characteristics	Univariate analysis			Multivariable analysis		
	HR	95% CI	p	HR	95% CI	p
Age group (≥60/<60)	1.879	0.879-4.285	0.136	6.602	1.821-20.195	0.003
T stage (T3-4/T1-2)	2.139	0.923-4.953	0.076	2.433	0.772-7.665	0.129
N stage (N+/N0)	2.210	0.757-6.451	0.147	5.228	1.328-20.579	0.018
Tumor location (Middle/Lower third)	1.054	0.471-2.359	0.898			
Tumor length (>7cm/≤7cm)	2.830	1.249-6.414	0.013	1.062	0.319-3.542	0.922
Chemotherapy (TC/CF)	1.414	0.480-4.162	0.529			
SII (≤979.3/>979.3)	0.225	0.089-0.567	0.002	0.131	0.024-0.701	0.018
PLR (≤174.3/>174.3)	0.131	0.044-0.389	<0.001	0.656	0.213-2.016	0.462
NLR (≤5.3/>5.3)	0.566	0.255-1.256	0.162	0.326	0.048-2.238	0.254

Comment: In univariate analysis, tumor length >7 cm was associated with poorer overall survival (HR = 2.830; p = 0.013); both SII and PLR were statistically significant (SII: HR = 0.225; p = 0.002; PLR: HR = 0.131; p < 0.001). Multivariable analysis demonstrated that age ≥60 years and positive nodal status (N+) were independent adverse prognostic factors for overall survival (HR = 6.602; 95% CI: 1.821-20.195; p = 0.003) and (HR = 5.228; 95% CI: 1.328-20.579; p = 0.018), respectively. PLR and NLR were no longer significant after adjustment. Notably, low SII was identified as an independent favorable prognostic factor for overall survival (HR = 0.131; 95% CI: 0.024-0.701; p = 0.018).

4. DISCUSSION

In this cohort of 57 patients, the mean age was 60.5 +/- 6.6 years, and most patients were male (98.2%), which is consistent with the epidemiological pattern of esophageal squamous cell carcinoma. Tumors were most frequently located in the lower third of the esophagus (59.6%), and most patients had locally advanced disease with nodal positivity (71.9%). These baseline findings are broadly comparable with previous cohorts of locally advanced ESCC treated with neoadjuvant chemoradiotherapy, including the study by Zhang H et al [7].

Most patients received the TC regimen (paclitaxel-carboplatin) and IMRT/VMAT was used in 73.7% of cases. These treatment characteristics reflect current institutional practice for patients eligible for neoadjuvant concurrent chemoradiotherapy followed by surgery. Because radiation dose, chemotherapy regimen, surgical approach, and patient condition may influence survival, they should be considered when interpreting associations between inflammatory indices and overall survival.

The biological mechanisms underlying inflammatory–immune indices are closely related to the role of inflammation in cancer progression. Neutrophils can activate endothelial and stromal cells, enhance the adhesion of circulating tumor cells, and promote metastasis. Lymphocytes play a key role in anti-tumor immune responses, whereas platelets, activated by tumor cells, facilitate tumor dissemination and metastasis. Therefore, these indices reflect the balance between tumor-promoting inflammation and anti-tumor immunity. In our study, the optimal cut-off values were SII = 979.3, NLR = 5.3, and PLR = 174.3. Based on these thresholds, 73.7% of patients had SII ≤979.3, 89.5% had NLR ≤5.3, and 66.7% had PLR ≤174.3. Zhang H et al. (2024) reported a similar SII cut-off of ≤916.6 × 10^9/L. [7] Zheng Z et al. (2021) reported a lower NLR cut-off (2.20), which may be explained by differences in study populations, cut-off determination methods (ROC curve vs. Cut-off Finder), and disease stages [9].

We did not observe statistically significant associations between SII and clinical factors such as age, sex, T/N stage, radiotherapy technique, or chemotherapy regimen (p > 0.05), consistent with Zhang's findings. [7] However, borderline trends were observed between SII and chemotherapy regimen (p = 0.070), and between NLR with age and tumor length (p = 0.077 and p = 0.073), suggesting a potential relationship between inflammatory response and treatment or tumor burden that warrants further investigation.

The median overall survival (OS) in our study was 57 ± 5.3 months, with 3-year and 5-year OS rates of 73.3% and 41.9%, respectively. These outcomes are better than those reported by Zhang et al. (median OS: 40 months; 3-year OS: 52.6%). [7] This may reflect differences in treatment strategies, radiotherapy techniques, and surgical management.

Our findings confirm the important prognostic role of SII. Zhang H et al. (2024) also demonstrated that patients with lower SII (≤916.6×10^9/L) had significantly better OS when treated with neoadjuvant chemoradiotherapy (p < 0.001). [7]

A meta-analysis by Gao GH reported that elevated SII was significantly associated with shorter OS in patients with surgically resected ESCC (HR: 1.34; 95% CI: 1.15–1.53; $p < 0.001$), supporting the role of SII as a prognostic biomarker. [5] The underlying mechanisms may include: (1) elevated neutrophils reflecting systemic inflammation that promotes tumor progression; (2) decreased lymphocytes indicating impaired anti-tumor immunity; and (3) increased platelets facilitating tumor embolism formation and immune evasion.

ROC curve analysis is a key method for evaluating predictive performance. The area under the curve (AUC) reflects discriminatory ability, with AUC >0.7 indicating good predictive value. In our study, SII showed an AUC of 0.762 for 1-year OS ($p = 0.083$) and 0.669 for 3-year OS ($p = 0.035$), indicating moderate predictive performance. Compared with Zhang et al. (AUC: 0.725 for 1-year and 0.634 for 3-year OS), our results suggest slightly improved predictive accuracy. [7] Thus, SII is a non-invasive, simple, and clinically applicable biomarker.

Univariate Cox analysis identified several prognostic factors, including tumor stage, tumor size, tumor length, treatment response, and inflammatory indices. Zhou XL et al. (2017) reported that elevated baseline NLR was independently associated with poorer progression-free survival (PFS) and OS (HR = 1.529 for PFS; HR = 1.856 for OS; $p < 0.001$). [8] Zheng Z et al. also confirmed the prognostic value of NLR and PLR in univariate analysis. [9]

Multivariable analysis is essential to identify independent prognostic factors. Zhang H et al. (2024) demonstrated that low SII (≤916.6 × 10^9/L) was an independent predictor of improved OS ($p = 0.040$), along with neoadjuvant chemoradiotherapy ($p = 0.034$). [7] Furthermore, higher SII was associated with a lower resection rate ($p = 0.035$), suggesting its role in predicting treatment response and surgical eligibility.

In our study, multivariable analysis identified three independent prognostic factors: age ≥60 (HR = 6.602; $p = 0.003$), 1/3 (HR = 5.528; $p = 0.018$), and low SII as a protective factor (HR = 0.131; $p = 0.018$). These findings are consistent with Zhang et al., in which SII was the strongest independent prognostic factor. [7] Therefore, SII is not only an inflammatory marker but also a valuable tool for clinical risk stratification in esophageal cancer.

Other studies have also confirmed the prognostic value of inflammatory-immune indices. Zheng Z identified NLR as an independent prognostic factor in resectable ESCC. [9] Man Q et al. (2024) reported that NLR, PLR, and TNM stage were independent predictors of both PFS and OS. [10] Additionally, studies evaluating PLR and SII in patients undergoing neoadjuvant chemoradiotherapy have demonstrated that both indices serve as independent prognostic factors.

Study limitations

This study has several limitations. First, the retrospective single-center design and small sample size may limit statistical power and external validity. Second, selection bias is possible because only patients who completed neoadjuvant chemoradiotherapy and proceeded to surgery were included; therefore, the findings may not apply to patients who were medically inoperable, refused surgery, or progressed before surgery. Third, inflammatory and immune indices were measured after nCRT and before surgery rather than at baseline; these indices may be affected by radiation-related inflammation, infection, leukopenia, nutritional status, or treatment toxicity. Fourth, the ROC-derived cut-off values were not externally validated and should be confirmed in larger independent cohorts. Fifth, the limited number of events increased the risk of overfitting in Cox regression, despite restricting the multivariable model. Finally, some important variables such as ECOG performance status,

pathological complete response, surgical margin status, disease-free survival, and recurrence patterns were not available for comprehensive analysis.

5. CONCLUSION

The systemic immune–inflammation index (SII) has prognostic value for overall survival in patients with locally advanced esophageal squamous cell carcinoma treated with neoadjuvant concurrent chemoradiotherapy. Low SII is an independent favorable prognostic factor, whereas age ≥60 years and positive nodal status are independent adverse prognostic factors. SII is a simple, readily applicable biomarker with potential utility for clinical risk stratification.

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