High Systemic Immune-Inflammation Index is an Adverse Prognostic Factor for Patients With Gastroesophageal Adenocarcinoma

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Objective: The aim of this study was to determine the clinical role of the systemic immune-inflammation index in patients with resectable adenocarcinoma of the gastroesophageal junction treated with or without neoadjuvant therapy.

Background: Adenocarcinoma of the gastroesophageal junction is an aggressive disease, with less than 20% of overall patients surviving more than 5 years after diagnosis, while currently available clinical staging for esophageal cancer is lacking necessary accuracy. The systemic immune-inflammation index (SII) based on peripheral neutrophil, lymphocyte, and platelet counts has shown a prognostic impact in various malignancies.

Methods: Data of consecutive patients undergoing esophagectomy (n = 320, 1992 to 2016) were abstracted. The cut point for high and low SII before neoadjuvant treatment and before surgery was calculated for illustration of the Kaplan-Meier curves. SII was used for the correlation with patients' clinicopathological characteristics as a continuous variable. Survival was analyzed with Cox proportional hazards models using clinical or pathological staging, adjusting for other known survival predictors.

Results: In both neoadjuvantly treated and primarily resected patients, high SII was significantly associated with diminished overall [hazard ratio (HR) 1.3, 95% confidence interval (95% CI) 1.2–1.4; HR 1.2, 95% CI 1.2–1.3, respectively] and disease-free survival (HR 1.3, 95% CI 1.2–1.3; HR 1.2, 95% CI 1.2–1.3, respectively). In multivariable survival analysis, SII remained an independent prognostic factor for overall survival (HR 1.3, 95% CI 1.2–1.4; HR 1.2, 95% CI 1.2–1.3, respectively) and disease-free survival (HR 1.3, 95% CI 1.2–1.3; HR 1.2, 95% CI 1.2–1.3, respectively) in primarily resected and neoadjuvantly treated patients.

Conclusion: Elevated SII is an independent adverse prognostic factor in patients with resectable gastroesophageal adenocarcinomas with and without neoadjuvant treatment.

Keywords: esophageal cancer, gastroesophageal adenocarcinoma, neoadjuvant treatment, systemic immune inflammation index (SII)

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Inflammatory pathways in the initiation and progression of cancer have been investigated and inflammation has emerged as a key mediator of malignant diseases.[1–3] Tumorigenesis is not determined solely by the individual characteristics of the tumor but also by the host systemic immune-inflammatory response.[4] Current approaches aimed to identify and characterize new factors, which are easily available and cost-effective, to evaluate the patient's risk for disease progression and death after surgery. In a number of solid tumors, including esophageal cancer (EC), biomarkers, representing the grade of systemic-inflammation response, such as the Glasgow prognostic score (GPS), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), have been proven to be of significant prognostic value.[5–8] Further, the systemic immune-inflammation index (SII) was shown to be a useful prognostic indicator in patients with small cell lung cancer, hepatocellular carcinoma, and esophageal squamous cell carcinoma.[9–12] Until now, no data exist describing the prognostic role of the SII in adenocarcinomas of the gastroesophageal junction applying solely clinical parameters available before neoadjuvant treatment and surgical resection.

In the present study, we investigated the prognostic value of SII in patients with adenocarcinoma of the gastroesophageal junction who underwent primary resection or were treated with neoadjuvant therapy before surgery. In addition, we compared the prognostic value of SII in models using clinical staging (*cBase* model) available before and pathological staging (*pBase* model) available after treatment. Furthermore, we evaluated whether the SII was superior in predicting survival of patients with adenocarcinoma of the gastroesophageal junction when compared with NLR or PLR.

METHODS

Patients and Therapy

Consecutive patients who underwent curative resection of locally advanced adenocarcinomas of the gastroesophageal junction between January 1992 and April 2016 at the Department of Surgery at the Medical University Vienna were identified from a prospectively maintained database. Patients with distant metastasis at the time of surgery, positive resection margin, missing preoperative levels of platelet, neutrophil and lymphocyte counts, or other malignancies than AEG were excluded. At the time the complete blood count was drawn (before the start of neoadjuvant treatment or surgery

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in patients treated with primary surgery), none of the patients showed signs of pyrexia (axillary $\geq$37.2°C/99.0°F) or any form of active infection or chronic inflammatory disease. This study was approved by the ethics committee of the Medical University Vienna, Austria, according to the declaration of Helsinki (1652/2016). Patients' demographic, histopathologic, and laboratory variables were retrospectively reviewed and collected from the local database and patients' records. The clinical tumor stage was determined according to the pathological tumor-node-metastasis (TNM) classification of the Union for International Cancer Control (UICC), 7th edition. Preoperatively, every patient was discussed in the interdisciplinary tumor board meeting.

Patients receiving neoadjuvant therapy were treated according to the standards of the Comprehensive Cancer Center of the Medical University of Vienna at the time of presentation, either with oxaliplatin/capecitabine-based or cisplatine/5-fluoruracil based regimens, and radiation doses ranging from 42 to 46 Gray. Tumor regression grade (TRG) to neoadjuvant treatment was classified as defined by Mandard et al.[13]

The location of tumors at the gastroesophageal junction was classified according to Siewert and Stein.[14] The surgical procedure was chosen depending on primary tumor location (abdominothoracic enbloc esophagectomy or transhiatal extended gastrectomy, respectively). All patients were regularly followed up with physical examination, tumor marker, and computed tomography at our outpatient clinic every 3 months for the first 2 years and then every 6 months until 5 years after surgery.

Serum concentrations of platelets, neutrophils, and lymphocytes were measured within 3 days before the start of neoadjuvant treatment or surgery in patients treated with primary surgery. The SII, NLR, and PLR were calculated as follows: SII = platelet∗neutrophil/lymphocyte, NLR = neutrophil/lymphocyte, PLR = platelet/lymphocyte.

Statistical Analysis

Overall survival (OS) was defined as the time between primary surgery and the patient's death. Disease-free survival (DFS) was defined from the day of primary surgery until the first evidence of disease progression. Death from cause other than gastroesophageal cancer or survival until the end of the observation period (date of last alive contact) was considered as censored observations of OS and DFS. Differences of baseline characteristics between neoadjuvantly treated and primarily resected patients were assessed by 2-sample *t* tests for continuous variables and by Fisher exact tests for categorical variables, respectively. All continuous variables, including SII, NLR, and PLR, are presented by median and first and third quartile, respectively, and as absolute and relative frequency for categorical data. Median follow-up was estimated by the reverse Kaplan-Meier method. In order to visualize survival in relation to SII, NLR, and PLR by Kaplan-Meier curves, parameters were grouped into high and low by optimal cut points using function *cutp* (R package *survMisc*[15]).

Univariable Cox proportional hazards models were carried out to estimate the effect of each predictor on OS and DFS separately. Multivariable Cox proportional hazards models with standard parameters (called base model) and additional parameters such as SII, PLR, and NLR were estimated. Further multivariable models with interaction terms between SII and clinical parameters were included, whereas interactions were tested in models that contained only two variables of interest. Proportional hazard assumptions were assessed visually and tested using diagnostics based on weighted residuals. For both OS and DFS, the SII, NLR, and PLR were evaluated as continuous variables. In order to improve the readability of hazard ratios (HRs), SII, and PLR were divided by 100. Therefore, HRs for SII and PLR represent effects for a 100-point increase in SII and PLR on OS and DFS.

Cox & Snell R^2 values were derived for all models. Cox and Snell R^2 consists of the difference between the log-likelihood of the fitted model and the log-likelihood of the null model multiplied by a function of the number of observations. The log-likelihood of the null model, the number of observations, and the number of fitted parameters are all identical for all 3 models that are considered. The 3 models for SII, NLR, and PLR are identical for all other variables included in the model and no patient was lost from one model to the other due to missing data. Therefore, R^2-values can be used to compare the fit of the 3 models that contain SII, NLR, and PLR, respectively, meaning the higher the R^2-value, the better the prognostic value of the variable.

All tests were 2-sided and *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed with the statistical software R version 3.44 (Vienna, Austria).[15]

RESULTS

Clinicopathological Characteristics

A total of 320 patients with resectable gastroesophageal cancer were investigated for this study (Fig. 1). Of these patients, 158 (49.4%) were neoadjuvantly treated and 162 (50.6%) underwent primary resection. Significant differences between the groups of neoadjuvantly treated and primarily resected patients were found for the factors age ($P = 0.003$), tumor differentiation ($P < 0.001$), clinical and pathological tumor staging and lymph node staging ($P < 0.001$, respectively), and the ASA (American Society of Anesthesiologists) physical status classification system ($P = 0.04$).

Optimal cut points for SII, NLR, and PLR were 644, 2.07, and 146.8, respectively. SII $\geq$644 was significantly associated with tumor differentiation ($P = 0.005$) and clinical and pathological tumor staging and lymph node staging ($P < 0.001$ and $P = 0.005$, respectively). Clinicopathological characteristics are summarized in Table 1. When investigating the interactions between variables, preliminary analysis using Kaplan-Meier curves showed significant correlation for SII with the factors Mandard regression grade, tumor staging, and lymph node staging (Suppl. Figure 1–4, http://links.lww.com/SLA/B652). Results of testing the interactions between SII and cN, pN and G (2-variable models) are given in Suppl. Table 1, http://links.lww.com/SLA/B653.

Primarily Resected Patients—Overall Survival

Median time to OS follow-up of primarily resected patients was 128 months (range 80.0 to 168.4 months), whereas 120 patients died during the time of observation. The median OS was 38.0 months (range 11.9 to 127.1 months). The rate of 3- and 5-year OS was 51.0% and 41.9%, respectively. Kaplan-Meier curves show the relation of OS for SII, NLR, and PLR in the cohort of primarily resected patients (Fig. 2). The following factors were associated with poor OS in univariable Cox proportional hazard regression: poor tumor differentiation, advanced clinical and pathological tumor stage, positive lymph nodes, SII, NLR, and PLR (Suppl. Table 2, http://links.lww.com/SLA/B654). The multivariable Cox proportional hazard regression base model without SII (*cBase*, Table 2) using clinical staging revealed that well-differentiated tumor grade [$P = 0.004$, HR 0.54, 95% confidence interval (95% CI) 0.35–0.82] and N0/N1 lymph node status ($P < 0.001$, HR 0.42, 95% CI 0.26–0.66) were significantly associated with improved OS ($R^2 = 0.30$). The multivariable base model without SII (*pBase*, Suppl. Table 3, http://links.lww.com/SLA/B655) using pathological staging showed that N3 lymph node status (p = 0.006, HR 2.99, 95% CI 1.38–6.47) was significantly associated with worse OS ($R^2 = 0.36$). The

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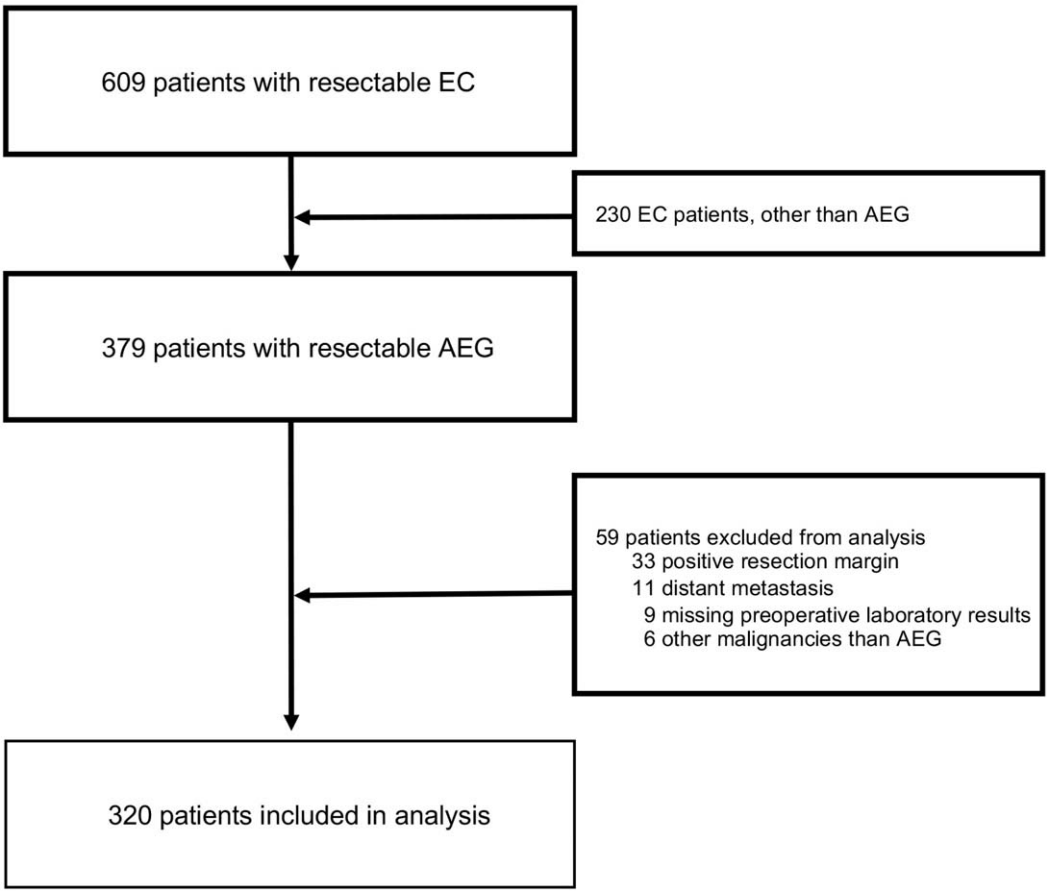

FIGURE 1. Study profile. AEG indicates adenocarcinoma of the gastroesophageal junction; EC, esophageal cancer.

multivariable Cox proportional hazard regression base model including SII (*cBase*+SII, Table 2) using clinical staging revealed that well-differentiated tumor grade ($P < 0.001$, HR 0.30, 95% CI 0.18–0.50), and N0/N1 lymph node status ($P = 0.005$, HR 0.53, 95% CI 0.35–0.83) were significantly associated with improved OS, while high SII ($P < 0.001$, HR 1.27, 95% CI 1.21–1.34) was significantly associated with worse survival ($R^2 = 0.59$). The multivariable base model including SII (*pBase*+SII, Suppl. Table 3, http://links.lww.com/SLA/B655) using pathological staging showed that N0/N1 lymph node status compared with N2/N3 was significantly associated with improved OS, while high SII ($P < 0.001$, HR 1.30, 95% CI 1.24–1.37) was significantly associated with impaired OS ($R^2 = 0.36$).

A significant interaction between SII and lymph node staging was found in both models *cBase* and *pBase* (Table 2 and Suppl. Table 3, http://links.lww.com/SLA/B655).

Primarily Resected Patients: Disease-free Survival

Median time to DFS follow-up was 128 months (range 83.9 to 167.7 months), whereas 123 patients sustained recurrence during the time of observation. Median DFS was 25.5 months (range 7.0 to 111.0 months). Three- and 5-year DFS for primarily resected patients was 41.9% and 37.9%, respectively. Kaplan-Meier curves illustrate the relation of DFS and SII, NLR, and PLR in the cohort of primarily resected patients (Fig. 2). Univariable Cox proportional hazard regression model revealed that poor tumor differentiation, advanced clinical and pathological tumor stage, positive lymph nodes, SII, NLR, and PLR were associated with impaired DSF (Suppl. Table 2, http://links.lww.com/SLA/B654). The multivariable Cox proportional hazard regression base model without SII (*cBase*, Suppl. Table 4, http://links.lww.com/SLA/B656) using clinical staging revealed that well-differentiated tumor grade ($P = 0.002$, HR 0.53, 95% CI 0.35–0.79) and N0/N1 lymph node status ($P < 0.001$, HR 0.46, 95% CI 0.30–0.71) were significantly associated with improved DFS ($R^2 = 0.31$). The multivariable base model without SII (*pBase*, Suppl. Table 5, http://links.lww.com/SLA/B657) using pathological staging showed that advanced tumor staging, positive lymph nodes, and patients' age were significantly associated with diminished DFS ($R^2 = 0.36$). In multivariable analysis including SII (*cBase*+SII, Suppl. Table 4, http://links.lww.com/SLA/B656) using clinical staging, well-differentiated tumor grade ($P = 0.009$, HR 0.57, 95% CI 0.37–0.87) and N0/N1 lymph node status ($P < 0.001$, HR 0.37, 95% CI 0.24–0.59) were significantly associated with improved DFS, while sex ($P = 0.04$, HR 1.62, 95% CI 1.03–2.55) and SII ($P < 0.001$, HR 1.23, 95% CI 1.17–1.28) were significantly associated with worse DFS ($R^2 = 0.54$). The multivariable base model including SII (*pBase*+SII, Suppl. Table 5, http://links.lww.com/SLA/B657) using pathological staging showed that advanced tumor staging, positive lymph nodes, and high SII were significantly associated with impaired DFS ($R^2 = 0.58$). SII and lymph node staging were found to be significantly interacting only in the *cBase* model (Suppl. Table 4, http://links.lww.com/SLA/B656).

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TABLE 1. Baseline Clinicopathologic Characteristics

	All Patients	Neoadjuvant Treatment	Primary Resection		SII	SII	
	n = 320 (%)	n = 158 (49.4%)	n = 162 (50.6%)	*P*	≤644	>644	*P*
Age, median, y		63.5	67.2	0.003	63.78	66.41	0.332
Age Q1		55.5	57.4		56.78	56.39	
Age Q3		70.1	73.8		70.55	72.90	
Sex							
Male	260 (81.3)	133 (84.2)	127 (78.4)	0.200	103	157	0.149
Female	60 (18.7)	25 (15.8)	35 (21.6)		30	30	
Tumor differentiation							
Gx	12 (3.8)	12 (7.6)	0 (0%)	<0.001	4	8	0.005
G1	6 (1.9)	1 (0.6)	5 (3.1)		3	3	
G2	133 (41.6)	58 (36.7)	75 (46.3)		70	63	
G3	169 (52.7)	87 (55.1)	82 (50.6)		56	113	
Clinical tumor stage		Before NT	Before OP				
cT 1	44 (13.8)	0 (0%)	44 (27.2)	<0.001	31	13	<0.001
cT 2	120 (37.5)	48 (30.4)	72 (44.4)		55	65	
cT 3	152 (47.5)	106 (67.1)	46 (28.4)		47	105	
cT 4	4 (1.2)	4 (2.5)	0 (0%)		0	4	
Clinical lymph node stage		Before NT	Before OP				
cN 0	82 (25.6)	25 (15.8)	57 (35.2)	<0.001	47	35	0.005
cN 1	193 (60.4)	102 (64.6)	91 (56.2)		70	123	
cN 2	43 (13.4)	31 (19.6)	12 (7.4)		15	28	
cN 3	2 (0.6)	0 (0%)	2 (1.2)		1	1	
Pathological tumor stage							
pT0	14 (4.4)	14 (8.9)	0 (0%)	<0.001	5	9	<0.001
pT1	69 (21.5)	18 (11.4)	51 (31.5)		46	23	
pT2	84 (26.3)	29 (18.4)	55 (33.9)		40	44	
pT3	139 (43.4)	89 (56.3)	50 (30.9)		39	100	
pT4	14 (4.4)	8 (5.0)	6 (3.7)		3	11	
Pathological lymph node stage							
pN0	138 (43.1)	61 (38.6)	77 (47.5)	<0.001	77	61	0.005
pN1	113 (35.3)	57 (36.1)	56 (34.6)		44	69	
pN2	37 (11.6)	18 (11.4)	19 (11.7)		9	28	
pN3	32 (10.0)	22 (13.9)	10 (6.2)		3	29	
ASA							
1	61 (19.1)	38 (24.1)	23 (14.2)	0.040	26	35	0.608
2	216 (67.5)	95 (60.1)	121 (74.7)		93	123	
3	38 (11.9)	22 (13.9)	16 (9.9)		12	26	
4	5 (1.5)	3 (1.9)	2 (1.2)		2	3	
Mandard regression grade*							
1		13 (8.2)	/		4	9	n.a.
2		15 (9.5)	/		7	8	
3		29 (18.4)	/		15	14	
4		51 (32.3)	/		18	33	
5		50 (31.6)	/		13	37	
NT start before OP, d							
<90		45 (28.5)	/		11	34	n.a.
91–120		70 (44.3)	/		33	37	
>120		43 (27.2)	/		13	30	
SII (median)		740	693	0.426	409	905	<0.001
SII Q1		535	404		329	774	
SII Q3		905	1041		483	1119	
NLR (median)		2.29	2.24	0.402	2	3	<0.001
NLR Q1		1.82	1.63		1.39	2.31	
NLR Q3		2.95	3.15		1.95	3.51	
PLR (median)		154.58	146.14	0.378	112.11	188.24	<0.001
PLR Q1		121.03	108.24		97.08	150.45	
PLR Q3		198.17	203.75		131.05	229.44	

*1 = Complete regression; 2 = Presence of rare residual cancer cells; 3 = increase of number of residual cancer cells, but fibrosis still predominant; 4 = residual cancer outgrowing fibrosis; 5 = absence of regressive changes.

ASA indicates American Society of Anesthesiologists; n.a., not available; NLR, neutrophil lymphocyte ratio; OP, operation; PLR, platelet lymphocyte ratio; SII, systemic immune-inflammation index.

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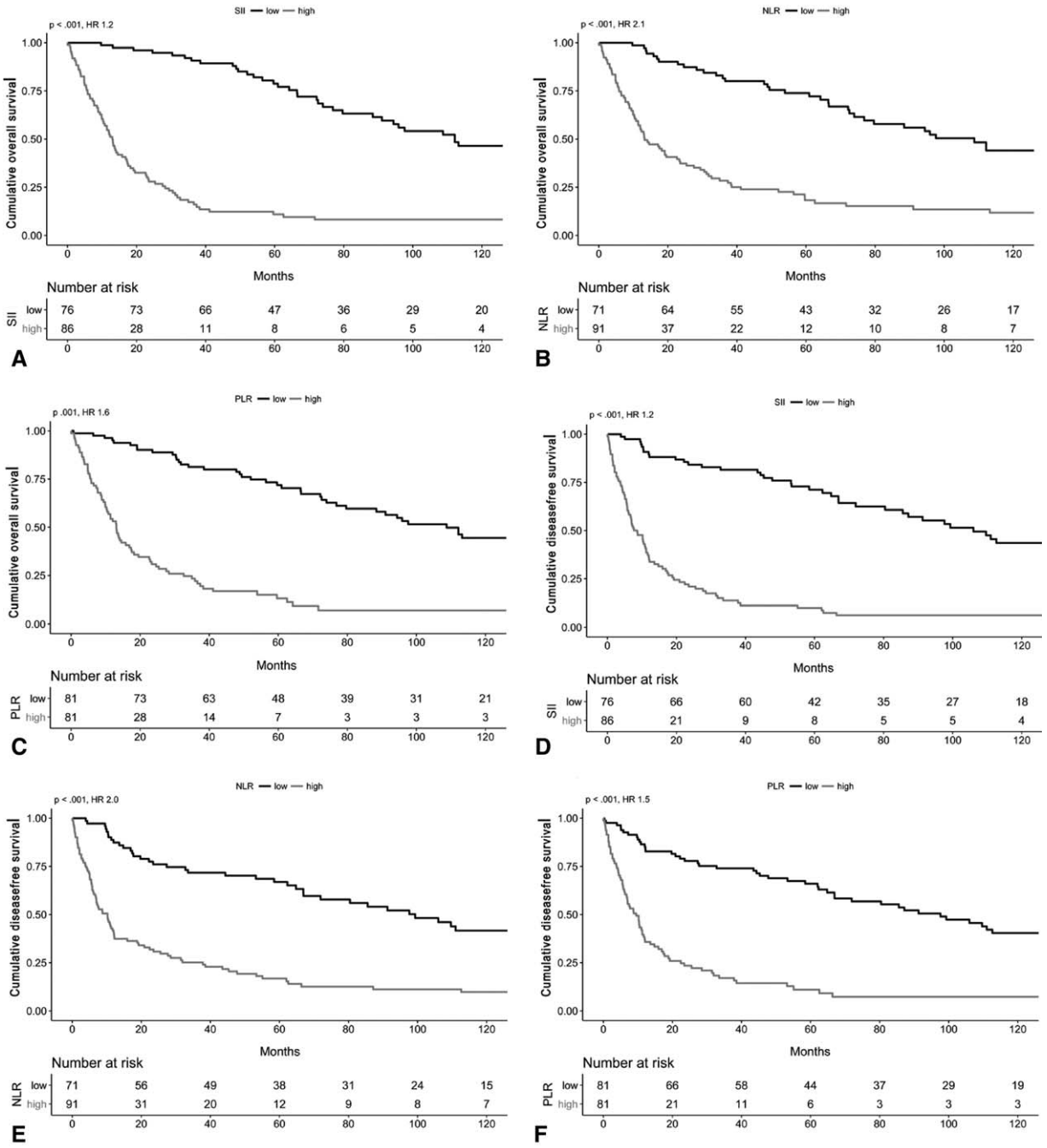

FIGURE 2. Kaplan-Meier survival curves for overall survival (A–C) and disease-free survival (D–F) for patients with primarily resected adenocarcinoma of the gastroesophageal junction with high (>644, >2.07, and >146.8) versus low (≤644, ≤2.07, and ≤146.8) SII, NLR, and PLR, respectively.

Neoadjuvantly Treated Patients: Overall Survival

Median time to OS follow-up of neoadjuvantly treated patients was 60.9 months (range 32.4 to 88.3 months), whereas 95 patients died during the time of observation. The median OS was 33.6 months (range 12.7 to 33.6 months). The rate of 3- and 5-year OS was 46.8% and 38.2%, respectively. Kaplan-Meier curves show the relation of OS and SII, NLR and PLR in the cohort of neoadjuvantly treated patients (Fig. 3). The following factors were associated with poor OS in univariable Cox proportional hazard regression: pathological lymph node staging, TRG, SII, NLR, and PLR (Suppl. Table 6, http://links.lww.com/SLA/B658). The multivariable Cox proportional hazard regression base models without SII (*cBase* and *pBase*,

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TABLE 2. Multivariable Cox Regression Analysis Estimating the Influence of the SII and Clinical Parameters (cT, cN) on Overall Survival in Patients With Primarily Resected Adenocarcinoma of the Esophagogastric Junction

Primary Resection						
Overall Survival						
	cBase	**cBase+PLR**	**cBase+NLR**	**cBase+SII**	**cBase+SII x cN**	**cBase+ SII x G**
Clinical tumor stage (ref.: cT2)						
cT1	0.82 (0.48, 1.4)	0.92 (0.53, 1.57)	0.73 (0.44, 1.24)	0.79 (0.47, 1.35)	0.91 (0.53, 1.55)	0.75 (0.43, 1.3)
cT3	1.67* (1.09, 2.57)	1.97† (1.26, 3.08)	1.59* (1.01, 2.5)	1.44 (0.91, 2.29)	1.62* (1.02, 2.58)	1.42 (0.89, 2.25)
Clinical lymph node stage (ref.: cN1)						
cN0	0.42‡ (0.26, 0.66)	0.44‡ (0.28, 0.7)	0.44‡ (0.28, 0.69)	0.3‡ (0.18, 0.5)	0.31‡ (0.19, 0.51)	0.31‡ (0.19, 0.51)
cN2	1.65 (0.9, 3.02)	1.78 (0.96, 3.3)	1.48 (0.8, 2.72)	1.28 (0.67, 2.44)	1.64 (0.85, 3.16)	1.32 (0.69, 2.54)
Age (in y)	1.02* (1, 1.04)	1.01 (0.99, 1.03)	1.02* (1, 1.04)	1.01 (0.99, 1.03)	1 (0.98, 1.02)	1.01 (0.99, 1.03)
Sex (ref.: male)						
female	1.35 (0.86, 2.13)	1.49 (0.94, 2.35)	1.35 (0.86, 2.12)	1.49 (0.94, 2.36)	1.35 (0.84, 2.16)	1.51 (0.95, 2.41)
Tumor differentiation (ref.: G3)						
G1 and 2	0.54† (0.35, 0.82)	0.63* (0.41, 0.97)	0.49† (0.32, 0.75)	0.53† (0.35, 0.83)	0.65 (0.41, 1.02)	0.54† (0.35, 0.84)
ASA (ref.: 2)						
1	1.13 (0.62, 2.08)	1.03 (0.55, 1.9)	1.37 (0.75, 2.52)	1.08 (0.59, 1.96)	1.04 (0.57, 1.89)	1.01 (0.54, 1.87)
3 and 4	0.89 (0.5, 1.59)	0.88 (0.49, 1.59)	0.62 (0.34, 1.14)	0.76 (0.41, 1.41)	0.9 (0.47, 1.71)	0.74 (0.39, 1.38)
PLR (per 100 units)		1.57‡ (1.36, 1.82)				
NLR			2.24‡ (1.82, 2.75)			
SII (per 100 units)				1.27‡ (1.21, 1.34)	1.51‡ (1.38, 1.65)	1.29‡ (1.22, 1.37)
SII x cN (ref.: SII for cN1)						
SII for cN0					0.8‡ (0.71, 0.89)	
SII for cN2					0.81† (0.7, 0.93)	
SII x Tumor differentiation (ref.: SII for G3)						
SII for G1 and 2						0.96 (0.87, 1.06)
R2	0.301	0.408	0.498	0.588	0.636	0.590

HR and 95% CI.
HRs for SII in Model SII x cN and SII x G are estimates for ref. (cN1 and G3).
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.
ASA indicates American society of anesthesiologists; CI, confidence interval; HR, hazard ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, systemic immune-inflammation index.

Table 3 and Suppl. Table 7, http://links.lww.com/SLA/B659) revealed that only well-differentiated tumor grade ($P = 0.014$, HR 0.58, 95% CI 0.37–0.90; $P = 0.03$, HR 0.58, 95% CI 0.35–0.96, respectively) was significantly associated with improved OS ($R^2 =$ 0.09 and 0.14, respectively). The multivariable Cox proportional hazard regression base models including SII (*cBase*+SII and *pBase*+SII, Table 3 and Suppl. Table 7, http://links.lww.com/SLA/B659) revealed that well-differentiated tumor grade ($P = 0.013$, HR 0.57, 95% CI 0.37–0.589; $P = 0.04$, HR 0.58, 95% CI 0.35–0.97, respectively) was associated with improved OS, while high SII ($P < 0.001$, HR 1.28, 95% CI 1.19–1.37; $P < 0.001$, HR 1.32, 95% CI 1.22–1.43, respectively) was significantly associated with worse OS ($R^2 = 0.31$ and 0.36, respectively). SII and lymph node staging were found to be the only significantly interacting factors in the *pBase* model (Suppl. Table 7, http://links.lww.com/SLA/B659).

Neoadjuvantly Treated Patients: Disease-free Survival

Median time to DFS follow-up was 63 months (range 35.6 to 88.3 months), whereas 104 patients sustained recurrence during the time of observation. The median DFS was 17.5 months (range 7.2 – 94.2 months). The rate of 3- and 5-year DFS was 34.9% and 32.2%, respectively. Kaplan-Meier curves show the relation of DFS and SII, NLR, and PLR in the cohort of neoadjuvantly treated patients (Fig. 3). The following factors were associated with poor DFS in univariable Cox proportional hazard regression: poor tumor differentiation, advanced pathological tumor stage, positive lymph nodes, sex, TRG, SII, NLR, and PLR (Suppl. Table 6, http://links.lww.com/SLA/B658). In the multivariable Cox proportional hazard regression base model without SII (*cBase*, Suppl. Table 8, http://links.lww.com/SLA/B660 using clinical staging), well-differentiated tumor grade ($P = 0.04$, HR 0.65, 95% CI 0.43–0.98) was significantly associated with improved DFS, while in the model without SII (*pBase*, Suppl. Table 9, http://links.lww.com/SLA/B661) using pathological staging, advanced lymph node stage N3 ($P < 0.001$, HR 3.41, 95% CI 1.70–6.86) was associated with worse DFS, respectively ($R^2 = 0.11$ and 0.18, respectively).

The multivariable Cox proportional hazard regression base model including SII (*cBase* + SII, Suppl. Table 8, http://links.lww.com/SLA/B660) using clinical staging revealed that well-differentiated tumor grade ($P = 0.04$, HR 0.66, 95% CI 0.43–0.99) was significantly associated with improved DFS, while high SII ($P < 0.001$, HR 1.24, 95% CI 1.16–1.33) was significantly associated with worse DFS ($R^2 = 0.23$). The multivariable base model including SII (*pBase* + SII, Suppl. Table 9, http://links.lww.com/SLA/B661) using pathological staging showed that positive lymph nodes ($P = 0.02$, HR 2.27, 95% CI 1.12–4.62), sex ($P =$ 0.04, HR 2.08, 95% CI 1.03–4.19), and high SII ($P < 0.001$, HR 1.26, 95% CI 1.17–1.36) were significantly associated with impaired DFS ($R^2 = 0.35$). Significant interaction between SII and lymph node

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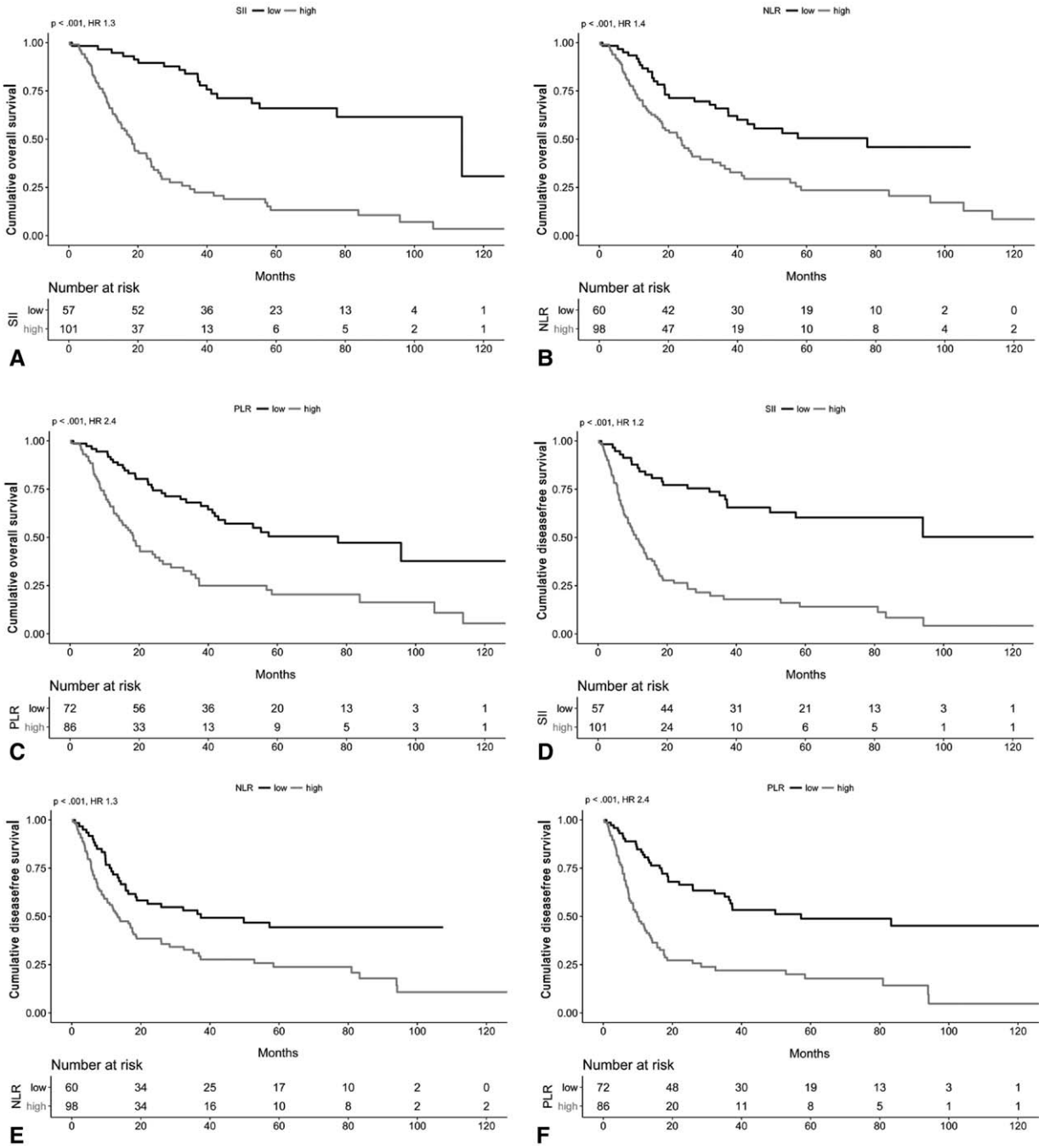

FIGURE 3. Kaplan-Meier survival curves for overall survival (A–C) and disease-free survival (D–F) for patients with neoadjuvantly treated adenocarcinoma of the gastroesophageal junction with high (>644, >2.07, and >146.8) versus low (≤644, ≤2.07, and ≤146.8) SII, NLR, and PLR, respectively.

staging was found in the model with pathological staging (Suppl. Table 9, http://links.lww.com/SLA/B661).

The models for *cBase* and *pBase* replacing SII by NLR or PLR for OS and DFS in neoadjuvantly treated and primarily resected patients can be found in Tables 2, 3, and Suppl. Tables 3 to 5 and 7 to 9, respectively. General assessment of R2 values showed marginally higher results for the *pBase* model in nearly all subgroups. Investigating the prognostic value of SII, a strong increase in R^2 values could be noticed adding the variable SII to the *cBase* and *pBase* model in the primarily resected and neoadjuvantly treated patients. The R^2 values at a glance are given in Suppl. Table 10, http://links.lww.com/SLA/B662.

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TABLE 3. Multivariable Cox Regression Analysis Estimating the Influence of the SII and Clinical Parameters (cT, cN) on Overall Survival in Patients With Neoadjuvantly Treated Adenocarcinoma of the Esophagogastric Junction

Neoadjuvant Treatment						
Overall Survival						
	cBase	**cBase+PLR**	**cBase+NLR**	**cBase+SII**	**cBase+SII x cN**	**cBase+ SII x G**
Clinical tumor stage (ref.: cT3 and cT4)						
cT2	0.92 (0.57, 1.51)	1 (0.61, 1.64)	0.89 (0.54, 1.45)	1.09 (0.66, 1.78)	1.09 (0.66, 1.79)	1.09 (0.66, 1.81)
Clinical lymph node stage (ref.: cN1)						
cN0	0.75 (0.4, 1.41)	1.02 (0.54, 1.96)	0.78 (0.41, 1.49)	0.94 (0.5, 1.76)	0.87 (0.45, 1.68)	0.95 (0.5, 1.81)
cN2	0.69 (0.37, 1.3)	0.72 (0.38, 1.35)	0.79 (0.42, 1.49)	0.93 (0.49, 1.77)	0.92 (0.48, 1.75)	0.93 (0.49, 1.78)
Age (in y)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)	0.99 (0.97, 1.02)	1.00 (0.98, 1.02)	0.99 (0.97, 1.02)
Sex (ref.: male)						
female	0.62 (0.32, 1.22)	0.75 (0.38, 1.49)	0.69 (0.35, 1.37)	0.70 (0.35, 1.4)	0.67 (0.33, 1.37)	0.70 (0.35, 1.41)
Tumor differentiation (ref.: G3)						
G0, 1, and 2	0.58* (0.37, 0.9)	0.54† (0.35, 0.84)	0.56* (0.36, 0.87)	0.57* (0.37, 0.89)	0.60* (0.39, 0.94)	0.57* (0.36, 0.89)
ASA (ref.: 2)						
1	1.13 (0.68, 1.87)	1.31 (0.8, 2.15)	1.09 (0.66, 1.79)	1.31 (0.8, 2.13)	1.31 (0.79, 2.16)	1.31 (0.8, 2.14)
3 and 4	1.14 (0.63, 2.06)	1.51 (0.82, 2.8)	1.19 (0.66, 2.15)	1.38 (0.75, 2.53)	1.34 (0.72, 2.49)	1.38 (0.75, 2.53)
PLR (per 100 units)		2.50‡ (1.77, 3.55)				
NLR			1.35‡ (1.14, 1.59)			
SII (per 100 units)				1.28‡ (1.19, 1.37)	1.25‡ (1.16, 1.36)	1.27‡ (1.16, 1.40)
SII x cN (ref.: SII for cN1)						
SII for cN0					1.10 (0.91, 1.33)	
SII for cN2					1.06 (0.86, 1.31)	
SII x Tumor differentiation (ref.: SII for G3)						
SII for G0, 1, and 2						1.01 (0.89, 1.15)
R2	0.090	0.221	0.149	0.311	0.316	0.312

HR and 95% CI.

HRs for SII in Model SII x cN and SII x G are estimates for ref. (cN1 and G3).

*$P < 0.05$.

†$P < 0.01$.

‡$P < 0.001$.

ASA indicates American society of anesthesiologists; CI, confidence interval; HR, hazard ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, systemic immune-inflammation index.

DISCUSSION

In the present study, we revealed that SII was an independent significant predictive factor for patients with resectable AEG. We assessed the value of biomarker reflecting inflammation and a number of established clinicopathologic factors, predicting OS and DFS in patients with neoadjuvantly treated and primarily resected AEG. In addition, we compared the predictive value of SII in models using either clinical or pathological staging and investigated whether SII is of better predictive value than NLR and PLR. Univariable and multivariable Cox proportional hazard regressions showed that elevated SII significantly correlates with poor survival rates of primarily resected and neoadjuvantly treated patients in both models, using clinical and pathological staging, respectively. Furthermore, we found SII to be a superior prognostic index compared with NLR and PLR. Whereas significant association of SII and lymph node status for OS and DFS was found, no significant association of SII with other parameters could be found.

There are increasing data showing that inflammation is closely connected with tumorigenesis, tumor progression, and metastasis.[1,2,16] The prognostic significance of inflammation-based biomarkers and scores has recently been shown in a number of solid tumors, including EC, whereas none of the studies used clinical factors available solely before treatment.[6,17–22] In the study by Peng et al,[23] PLR was significantly associated with tumor staging, depth of invasion, lymph node invasion, and poor outcome in patients with metastatic colorectal cancer. Feng et al[24] found that both NLR and PLR were significant prognostic predictors of survival in esophageal squamous cell carcinoma patients and that PLR was superior to NLR. These findings go in good accordance with our data, showing the predictive value of NLR and PLR in univariable and multivariable analysis for OS and DFS. However, it has to be stated that the prognostic value of PLR and NLR remains controversial, which underlines our findings that SII is a superior prognostic index compared with NLR and PLR.[9,25–28]

Whereas the prognostic role of SII could have been shown in a number of malignancies treated without neoadjuvant chemo-(radio) therapy, there are no data investigating the prognostic significance of SII in neoadjuvantly treated patients using factors available solely before neoadjuvant treatment or resection.[29-31]

On the basis of previously published data from the CROSS study group and FLOT4-AIO trial, surgical resection in combination with pre-(peri)operative chemo-(radio) therapy has become the current standard regimen for locally advanced AEG.[32–34] In addition, the use of immune checkpoint inhibitors was approved to be used in a number of cancers, including EC. Recently published data demonstrate an association between inflammatory biomarkers, such as NLR, and the grade of response to immunotherapy.[35–37] This highlights the development of prognostic immune-specific biomarkers and might, therefore, make SII suitable in selecting patients for immunotherapy.[38–40] Analyzing our 2 cohorts of neoadjuvantly treated and primarily resected patients, we found SII likewise to be an independent prognostic factor in both groups. However, Feng et al[24] investigated the prognostic role of SII in esophageal squamous

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cell carcinoma patients without neoadjuvant treatment, hypothesizing neoadjuvant treatment might influence inflammation. This goes in good accordance with our findings of lower R^2 values in neoadjuvantly treated patients when compared with those who underwent primary resection.

To assess the prognostic value of SII, we compared R^2 values throughout all subgroups to find increased values by adding SII to the multivariable base models *cBase* and *pBase*. Whereas we noticed substantial differences of R^2 values between primarily resected and neoadjuvantly treated patients, comparable R^2 values for multivariable models using *cBase* or *pBase* were found. However, one has to interpret our R^2 values carefully due to a broad variation from very low to statistically acceptable R^2 values.

One can state that identifying molecular markers can predict the prognosis of patients with adenocarcinoma of the gastroesophageal junction. Nevertheless, further investigations are needed to allow the determination of individual therapeutic strategies.

Response rates after neoadjuvant treatment vary throughout the literature (5% to 29%).[33,41] However, we did not find as high a complete response rate as had been reported in previously published studies.

In contrast to other prognostic factors, the inexpensive and often routinely performed laboratory results make the SII an easily accessible and a potentially prime candidate as a prognostic biomarker in AEG.

Even though the results of our study demonstrate that the SII is an independent prognostic factor in AEG, our study has certain limitations. Besides its retrospective nature, there might be some selection bias that was inevitably associated with only partial accessibility of patients' preoperative laboratory results. This limitation is based on the not routinely performed differential blood count in all patients undergoing surgical resection due to AEG in our observation period. Another limiting factor is that this is a single-center research study, even though our database is prospectively maintained.

CONCLUSION

This is the first study to show that the SII is a novel independent preoperative predictor for OS and DFS in patients undergoing radical esophagectomy for AEG with or without neoadjuvant treatment. Analysis of the predictive value of SII throughout subgroups revealed comparable results using clinical or pathological covariables, but showed differences between neoadjuvantly and primarily resected patients, emphasizing that further investigation upon the prognostic role of SII is needed.

However, the prognostic value of the SII is superior to PLR and NLR and shows, furthermore, the potential in improving the prognostication of patients with AEG. Our data underline the importance of inflammation-based biomarkers and provide indirect evidence for the high importance of the immune system in patients with AEG. Nevertheless, the SII, based on simple and inexpensive standard laboratory measurements, needs further examination in accurately designed studies to confirm its prognostic role in AEG.

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REFERENCES

1. Gukovsky I, Li N, Todoric J, et al. Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. *Gastroenterology.* 2013;144:1199–1209. e4.
2. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. *Nature*. 2008;454:436–444.
3. Yang L, Karin M. Roles of tumor suppressors in regulating tumor-associated inflammation. *Cell Death Differ.* 2014;21:1677–1686.
4. McMillan DC. Cancer and systemic inflammation: stage the tumour and stage the host. *Br J Cancer.* 2013;109:529.
5. Forrest LM, McMillan DC, McArdle CS, et al. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer.* 2003;89:1028–1030.
6. Jomrich G, Paireder M, Gleiss A, et al. Comparison of inflammation-based prognostic scores in a cohort of patients with resectable esophageal cancer. *Gastroenterol Res Pract.* 2017;2017:1678584.
7. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer.* 2013;109:416–421.
8. Szkandera J, Absenger G, Liegl-Atzwanger B, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. *Br J Cancer.* 2013;108:1677–1683.
9. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. *Medicine (Baltimore).* 2017;96:e5886.
10. Geng Y, Shao Y, Zhu D, et al. Systemic immune-inflammation index predicts prognosis of patients with esophageal squamous cell carcinoma: a propensity score-matched analysis. *Sci Rep.* 2016;6:39482.
11. Hong X, Cui B, Wang M, et al. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. *Tohoku J Exp Med.* 2015;236:297–304.
12. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res.* 2014;20:6212–6222.
13. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer.* 1994;73:2680–2686.
14. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg.* 1998;85:1457–1459.
15. R Development Core Team. *R: A Language and Environment for Statistical Computing.* Vienna: Austria: R Foundation for Statistical Computing; 2018.
16. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144:646–674.
17. Guthrie GJ, Roxburgh CS, Farhan-Alanie OM, et al. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. *Br J Cancer.* 2013;109:24–28.
18. Pinato DJ, Shiner RJ, Seckl MJ, et al. Prognostic performance of inflammation-based prognostic indices in primary operable non-small cell lung cancer. *Br J Cancer.* 2014;110:1930–1935.
19. Kinoshita A, Onoda H, Imai N, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. *Ann Surg Oncol.* 2015;22:803–810.
20. Lindenmann J, Fink-Neuboeck N, Avian A, et al. Preoperative Glasgow Prognostic Score as additional independent prognostic parameter for patients with esophageal cancer after curative esophagectomy. *Eur J Surg Oncol.* 2017;43:445–453.
21. Melling N, Gruning A, Tachezy M, et al. Glasgow Prognostic Score may be a prognostic index for overall and perioperative survival in gastric cancer without perioperative treatment. *Surgery.* 2016;159:1548–1556.
22. Jomrich G, Hollenstein M, John M, et al. The modified glasgow prognostic score is an independent prognostic indicator in neoadjuvantly treated adenocarcinoma of the esophagogastric junction. *Oncotarget.* 2018;9:6968–6976.
23. Peng HX, Lin K, He BS, et al. Platelet-to-lymphocyte ratio could be a promising prognostic biomarker for survival of colorectal cancer: a systematic review and meta-analysis. *FEBS Open Bio.* 2016;6:742–750.
24. Feng JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. *World J Surg Oncol.* 2014;12:58.
25. Jiang N, Deng JY, Liu Y, et al. The role of preoperative neutrophil-lymphocyte and platelet-lymphocyte ratio in patients after radical resection for gastric cancer. *Biomarkers.* 2014;19:444–451.
26. Nakamura T, Matsumine A, Matsubara T, et al. The combined use of the neutrophil-lymphocyte ratio and C-reactive protein level as prognostic predictors in adult patients with soft tissue sarcoma. *J Surg Oncol.* 2013;108:481–485.
27. Sato H, Tsubosa Y, Kawano T. Correlation between the pretherapeutic neutrophil to lymphocyte ratio and the pathologic response to neoadjuvant chemotherapy in patients with advanced esophageal cancer. *World J Surg.* 2012;36:617–622.

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28. Sharaiha RZ, Halazun KJ, Mirza F, et al. Elevated preoperative neutrophil:-lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. *Ann Surg Oncol*. 2011;18:3362–3369.
29. Lolli C, Basso U, Derosa L, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. *Oncotarget*. 2016;7:54564–54571.
30. Lolli C, Caffo O, Scarpi E, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with mCRPC treated with abiraterone. *Front Pharmacol*. 2016;7:376.
31. Tong YS, Tan J, Zhou XL, et al. Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer. *J Transl Med*. 2017;15:221.
32. Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16:1090–1098.
33. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074–2084.
34. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol*. 2016;17:1697–1708.
35. Dammeijer F, Lau SP, van Eijck CHJ, et al. Rationally combining immunotherapies to improve efficacy of immune checkpoint blockade in solid tumors. *Cytokine Growth Factor Rev*. 2017;36:5–15.
36. Kuzman JA, Stenehjem DD, Merriman J, et al. Neutrophil-lymphocyte ratio as a predictive biomarker for response to high dose interleukin-2 in patients with renal cell carcinoma. *BMC Urol*. 2017;17:1.
37. Sideras K, Braat H, Kwekkeboom J, et al. Role of the immune system in pancreatic cancer progression and immune modulating treatment strategies. *Cancer Treat Rev*. 2014;40:513–522.
38. Kollmann D, Ignatova D, Jedamzik J, et al. Expression of programmed cell death protein 1 by tumor-infiltrating lymphocytes and tumor cells is associated with advanced tumor stage in patients with esophageal adenocarcinoma. *Ann Surg Oncol*. 2017;24:2698–2706.
39. Joshi SS, Maron SB, Catenacci DV. Pembrolizumab for treatment of advanced gastric and gastroesophageal junction adenocarcinoma. *Future Oncol*. 2018;14:417–430.
40. Ilson DH, van Hillegersberg R. Management of patients with adenocarcinoma or squamous cancer of the esophagus. *Gastroenterology*. 2018;154:437–451.
41. Wright CD, Mathisen DJ, Wain JC, et al. Evolution of treatment strategies for adenocarcinoma of the esophagus and gastroesophageal junction. *Ann Thorac Surg*. 1994;58:1574–1578. discussion 8-9.

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