Systemic Immune-Inflammation Index as a Prognostic Marker of Late Recurrence in Operable Gastric Cancer: A Dual Center Study

Emre Yekedüz (emreyekeduz@gmail.com)
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi https://orcid.org/0000-0001-6819-5930
İzzet Doğan
Istanbul University: Istanbul Universitesi
Dılşa Mızrak Kaya
Hatay Devlet Hastanesi
İlker Özgür
Istanbul University: Istanbul Universitesi
Güngör Utkan
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi
Sezai Vatansever
Istanbul University: Istanbul Universitesi
Salim Demirci
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi
Hakan Akbulut
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi
Yüksel Ürün
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi

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Abstract

Aim

To evaluate the prognostic role of the systemic immune-inflammation index (SII) in patients with operable gastric cancer.

Methods

We assessed 354 patients with operable gastric cancer from tertiary centers in Turkey. SII was calculated by following formula: [neutrophil (cellsx10^9/L) x platelet (cellsx10^9/L)] / lymphocyte (cellsx10^9/L). The best cut-off value for SII was determined by using “receiver operating characteristics (ROC)” analysis. We used log-rank and Cox-regression analysis for survival analyses.

Results

One hundred twenty patients were in the late recurrence group (recurrences have developed 36 months after the surgery). SII was not a prognostic factor in the early recurrence group. However, relapse-free survival (RFS) was longer in SII-low patients than SII-high patients in the late recurrence group. In multivariable analysis, SII was the only independent prognostic factor for RFS in the late recurrence group (Hazard Ratio (HR): 5.42, 95% CI:1.18-24.82, p=0.03).

Conclusion

SII was an independent prognostic factor for RFS in GC patients with late recurrence. Late recurrence risk was higher in SII-high patients than SII-low patients. Inflammation contributes to tumor progression, invasion, and metastasis. Prolonged exposure to chronic inflammation could explain the results of this study.

1. Introduction

Localized gastric cancer (GC) still has a higher recurrence rate despite improvements in surgical techniques and adjunctive treatment options.[1] Most recurrences are observed within the first 2-3 years after surgery.[2] Approximately 90% of recurrences occur in the first three years.

Immunity is the mainstay of fighting against cancer. With the start of the immunotherapy era, tumor immunity became more popular in cancer research. However, immunity plays a dual role in cancer development. Hosts’ immune response against tumors is crucial in cancer treatment. On the other hand, uncontrolled tumor-associated systemic inflammation increases tumor growth, angiogenesis, metastasis, and resistance to cancer treatment.[3–5]

Neutrophil and platelet counts are considered the main markers in response to inflammation. Both increases with the inflammation.[6, 7] Lymphocyte is the chef of orchestra in the immune response against the tumor. In this regard, declining in lymphocyte count may cause a poor prognosis.[8]

There are multiple options combining neutrophil, platelet, and lymphocyte as a prognostic factor in cancer patients. Neutrophil to lymphocyte ratio, neutrophil to platelet ratio, and systemic immune-inflammation index (SII) are the most known inflammatory markers used to predict survival in solid tumors.[9–11]

Besides the unknown mechanisms for early and late recurrences of GC, the extent of the performed surgery, pathological T and N stages, histological type, and the adequacy of the adjunctive treatment were the well-known factors to predict early and late recurrences of GC.[12] Also, different clinicopathological factors may play a prognostic role in the early and late recurrence groups.[13, 14] In this study, we aimed to assess the prognostic value of SII for RFS in the operable gastric cancer patients with early and late recurrence.

2. Methods

We conducted this retrospective study in two cancer research centers (i.e., Ankara University and Istanbul University) in Turkey. The local ethical committee approved this study.

2.1. Patient Cohort

Patients diagnosed with gastric cancer between 01.01.2004 and 31.12.2019 were determined using the “International Classification of Disease” codes. We included all operable gastric cancer patients older than 18-years in this study and excluded the patients with distant metastasis at diagnosis, gastric lymphomas, gastrointestinal stromal tumors, and other than a primary tumor of the stomach, and patients who underwent R2 resection. Of note, we included all patients who met the inclusion and exclusion criteria irrespective of lymphadenectomy type (D1 or D2). Because of the retrospective nature of this study, the type of lymphadenectomy was based on the surgeon preference.

2.2. Data Extraction and Analysis

Electronic patient records were searched. Patients’ clinical and pathological data were extracted to the database. Patients with recurrence within 36 months after surgery were grouped as early recurrence, and the remaining patients were grouped as late recurrence. To calculate SII, we used following formula: [neutrophil (cellsx10^9/L) x platelet (cellsx10^9/L)] / lymphocyte (cellsx10^9/L). All values were obtained from a complete blood count (CBC) performed in the last month before surgery. If there were more than one CBC results, the closest to the surgery time was used. The best cut-off value for SII was determined using “receiver operating characteristics (ROC)” analysis; thus, an SII value equal to 708 x 10^9/L was the best cut-off point with 52.3% sensitivity and 52.1% specificity for relapse-free survival (RFS).

2.3. Statistical Analysis

Descriptive analyses were presented using *mean ± standard deviation* or *median with interquartile range (IQR)* for continuous variables and *percentages* for categorical variables. *Independent samples t-test* or *Mann-Whitney U* test for continuous variables and *chi-square* or *Fisher's exact test* for categorical variables were performed to compare the variables. Univariable and multivariable survival analyses were performed with the *log-rank test* and *Cox proportional hazards regression model*. Kaplan-Meier survival estimates were also calculated. A p-value of less than 0.05 was considered to show a statistically significant result. ROC analysis was performed to determine the best cut-off value for SII. We used SPSS 27.0 for Mac (IBM Corp., Armonk, NY) for all statistical analyses.

3. Results

A total of 354 patients were included in this study. There were 234 (66.2%) and 120 (33.8%) patients in the early and late recurrence groups, respectively. The median follow-up was 25.5 months (IQR:15.9-50.7). The median RFS was 57 months (95% Confidence Interval (CI): not calculated), and the median overall survival (OS) was 136.4 months (95% CI: 98.6-174.3) for all patients. Five-year OS and RFS rates were 64% and 48%, respectively. The median RFS was 17.9 months (95% CI: 16.1-19.7) for the early recurrence group. However, the median RFS was not reached for the late recurrence group. Baseline characteristics of all patients are shown in Table 1.

Table 1
Baseline Characteristics of All Cohort

	Early Recurrence (≤36 months)		Late Recurrence (>36 months)	
	n=234	(%)	n=120	(%)
Age-years, median (IQR)	58 (50-65)		53 (47-59)	
Sex				
Male	158	*(68)*	77	*(64)*
Female	76	*(32)*	43	*(36)*
Tumor Location				
Proximal	59	*(25)*	32	*(27)*
Mid	37	*(16)*	20	*(17)*
Distal	93	*(40)*	55	*(46)*
Grade				
1	8	*(3)*	15	*(13)*
2	67	*(29)*	36	*(30)*
3	113	*(48)*	46	*(38)*
LVI				
Yes	182	*(78)*	70	*(58)*
No	14	*(6)*	12	*(10)*
Pathological T Stage				
1	11	*(5)*	8	*(6)*
2	15	*(6)*	15	*(13)*
3	86	*(37)*	67	*(56)*
4	120	*(51)*	28	*(23)*
Pathological N Stage				
0	35	*(15)*	30	*(25)*
1	44	*(19)*	31	*(26)*
2	47	*(20)*	30	*(25)*
3	106	*(45)*	28	*(23)*

	Early Recurrence (≤36 months)		Late Recurrence (>36 months)	
	n=234	(%)	n=120	(%)
Histological Type				
Signet-Ring	81	*(35)*	36	*(30)*
Mucinous	12	*(5)*	7	*(6)*
Not specified	140	*(60)*	77	*(64)*
Lymph Node Dissection				
D1	50	*(21)*	24	*(20)*
D2	182	*(77)*	96	*(80)*
Resection				
R0	212	*(90)*	118	*(98)*
R1	22	*(10)*	2	*(2)*
Gastrectomy Type				
Subtotal	138	*(59)*	67	*(56)*
Total	96	*(41)*	53	*(44)*
Adjuvant Treatment				
Chemotherapy	80	*(34)*	19	*(16)*
Chemoradiotherapy	138	*(59)*	89	*(74)*
Radiotherapy	1	*(1)*	1	*(1)*
None	15	*(6)*	11	*(9)*
SII				
Low (≤708x10^9 cells/L)	105	*(45)*	41	*(34)*
High (>708x10^9 cells/L)	103	*(44)*	42	*(35)*
Abbreviations: IQR=Interquartile Range, LVI=Lymphovascular Invasion, SII=Systemic Inflammatory Index				

SII was calculated for 83 patients in the late recurrence group. Baseline characteristics were similar in the SII-low and -high patients (Table 2). In the early recurrence group, the median RFS was 19.1 months (95% CI:16.2-21.9) and 17.9 months (95% CI:15.6-20.3) for SII-low and -high patients, respectively. There was no statistical significance between the groups (log-rank p=0.8) (Figure 1a). In the late recurrence group,

the median RFS was not reached for SII-low and -high patients. However, RFS was better in SII-low patients than SII-high patients (log-rank p=0.028) **(**Figure 1b**).** After adjusting for confounding factors (i.e., age, tumor grade, pathological N stage, adjuvant treatment), SII was the only factor associated with RFS in the late recurrence group. Late recurrence risk was higher in SII-high patients than SII-low patients (Hazard Ratio (HR): 5.42, 95% CI:1.18-24.82, p=0.03) **(**Table 3**).**

Table 2
Baseline Characteristics of Late Recurrence Cohort According to Systemic Inflammatory Index (SII)

	SII Low ($\leq 708x10^9$ cells/L)		SII High ($>708x10^9$ cells/L)		p value
	n=41	(%)	n=42	(%)	
Age-years, median (IQR)	53 (46-62)		58 (51-64)		0.08
Sex					0.6
Male	28	*(68)*	27	*(64)*	
Female	13	*(32)*	15	*(36)*	
Tumor Location					0.3
Proximal	14	*(36)*	14	*(37)*	
Mid	3	*(8)*	7	*(18)*	
Distal	22	*(56)*	17	*(45)*	
Grade					0.2
1	1	*(3)*	5	*(13)*	
2/3	32	*(97)*	32	*(87)*	
LVI					1
Yes	23	*(89)*	18	*(90)*	
No	3	*(11)*	2	*(10)*	
Pathological T Stage					1
1/2	7	*(17)*	7	*(17)*	
3/4	34	*(83)*	34	*(83)*	
Pathological N Stage					0.5
0	8	*(20)*	12	*(29)*	
1	9	*(23)*	11	*(26)*	
2	14	*(35)*	9	*(21)*	
3	9	*(22)*	10	*(24)*	
Histological Type					0.7

	SII Low ($\leq 708x10^9$ cells/L)		SII High ($>708x10^9$ cells/L)		p value
	n=41	(%)	n=42	(%)	
Not specified	28	*(68)*	30	*(71)*	
Signet-Ring/Mucinous	13	*(32)*	12	*(29)*	
Lymph Node Dissection					0.5
D1	6	*(15)*	8	*(19)*	
D2	35	*(85)*	34	*(81)*	
Gastrectomy Type					0.9
Subtotal	22	*(54)*	22	*(52)*	
Total	19	*(46)*	20	*(48)*	
Adjuvant Treatment					0.7
Chemotherapy	8	*(20)*	10	*(24)*	
Chemoradiotherapy	31	*(80)*	32	*(76)*	
Abbreviations: IQR=Interquartile Range, LVI=Lymphovascular Invasion					

Table 3
Univariate and Multivariate Analysis for Relapse-Free Survival

	Univariate (Log-Rank) p-value	Multivariate		p-value
		HR	95% CI	
Age	*	1.01	0.95-1.07	0.6
Sex	0.4	*		
Male				
Female				
Tumor Location	0.3	*		
Proximal				
Mid				
Distal				
Grade	0.2			0.3
1		1		
2		6.7	*0.35-127.84*	
3		2.3	*0.19-28.71*	
LVI	0.7	*		
No				
Yes				
Pathological T Stage	†	*		
1/2				
3/4				
Pathological N Stage	0.06	1	*0.16-23.53*	0.1
0		1.97	*1.03-99.17*	
1		10.12	*0.88-97.62*	
2		9.27		
3				
Histological Type	0.7	*		

	Univariate (Log-Rank) p-value	Multivariate		p-value
		HR	95% CI	
Not specified				
Signet-Ring/Mucinous				
Lymph Node Dissection	0.8	*		
D1				
D2				
Gastrectomy Type	0.6	*		
Subtotal				
Total				
Adjuvant Treatment	0.2			0.3
Chemotherapy		1		
Chemoradiotherapy		0.42	*0.06-4.76*	
SII	**0.02**			**0.03**
SII Low		1	*1.18-24.82*	
SII High		5.42		
Abbreviations: IQR=Interquartile Range, LVI=Lymphovascular Invasion, SII=Systemic Inflammatory Index				
*Not Included in Cox Regression Model, †All cases were censored.				

4. Discussion

This study was the first that assessed the prognostic effect of SII in GC patients with late recurrence to the best of our knowledge. We showed that SII was the only prognostic factor for RFS in the GC patients with late recurrence. Recurrence rates were higher for SII-high patients than SII-low patients in the late recurrence group. However, there was no prognostic effect of SII for RFS in the GC patients with early recurrence.

In a study evaluating prognostic effect of SII on operable GC patients, Wang et al. showed that SII was an independent prognostic factor for disease-free survival (DFS) and OS.[15] This study did not stratify the patients as early and late recurrence. In addition, 13% of all patients had R2 resection, and about 1 out of 4 patients had not received adjuvant chemotherapy.[15] However, no patient was performed R2 resection, and the rate of patients without adjuvant treatment was 7.3% in our study. Another study that included operable GC patients also showed that SII was an independent prognostic factor for DFS and OS. This

study also showed that SII-low patients had a better prognosis than SII-high patients in 1, 3, and 5 years after surgery.[16] However, similar to the study of Wang et al., patients who underwent R2 resection and metastatic patients were included in this study.[16]

In our study, we determined that SII could be a prognostic factor for late recurrences in operable gastric cancer, but not for early recurrences. It should be kept in mind that extent of resection and adjunctive treatment could affect the recurrence in patients with operable GC.[17, 18] Unlike the studies mentioned above, we did not include patients with R2 resection. Besides, the rate of adjuvant chemotherapy was higher in our study.

Tumor-associated inflammation is divided into three categories as preceding inflammation, tumor-elicited inflammation, and therapy-induced inflammation.[5] The calculation of SII before surgery may exclude the effect of therapy-induced inflammation. The prognostic impact of SII on the late tumor recurrence can be explained by the chronic effect of the inflammatory process. It is well-known that systemic inflammation contributes to tumor growth, metastasis, therapy resistance.[5] Besides, increased tumor invasion, and inhibition of adaptive immunity are considered a result of tumor-associated inflammation.[19] Neutrophil increases inflammation in the tumor microenvironment (TME) by secretion chemokines, cytokines, and reactive oxygen species (ROS), thus, causes tumor growth and therapy resistance.[20] On the other hand, platelets also have a significant effect on tumor-associated inflammation. It plays an essential role in tumor angiogenesis.[21] Furthermore, cytokines secreted by platelet contribute to tumor-associated inflammation in the TME; thus, causing drug resistance.[22]

Our study suggested that more prolonged chronic inflammation may be associated with recurrence. To date, there was no clear evidence for the relation between the duration of inflammation and cancer recurrence in the operable solid tumors. However, it is well-known that the duration of chronic inflammation is one of the critical factors for cancer pathogenesis.[23] The prognostic effect of SII on the late recurrences may be explained with prolonged exposure to chronic inflammation.

Recently, a study conducted by Hirahara et al. did not show the prognostic value of SII on OS in the overall population.[24] Similar to our study, there were no patients with R2 resection in this study. However, Hirahara et al. showed that SII was a prognostic factor in elderly patients.[24] In fact, it may be contributed to our hypothesis regarding the association between the late recurrence and more prolonged chronic inflammation exposure.

Our study has several limitations. First, it was a retrospective study; thus, we had missing data for some patients. It also resulted in a small patient cohort. Second, we conducted this study in multicenter. This resulted in using different laboratory devices for peripheral complete blood counting. Furthermore, surgical techniques and adjunctive treatment options might show differences between the centers. Third, we did not know the causes of death for all patients, and cancer-specific survival may differ from overall survival. All these shortcomings may have affected the outcomes.

In conclusion, SII might be an independent prognostic factor for late recurrence in patients with operable GC. If validated in well-designed prospective studies, SII could help predict long-term oncologic outcomes and help in making better treatment decisions in these patients.

Declarations

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Conflict of Interest: The authors declare that they have no conflict of interest.

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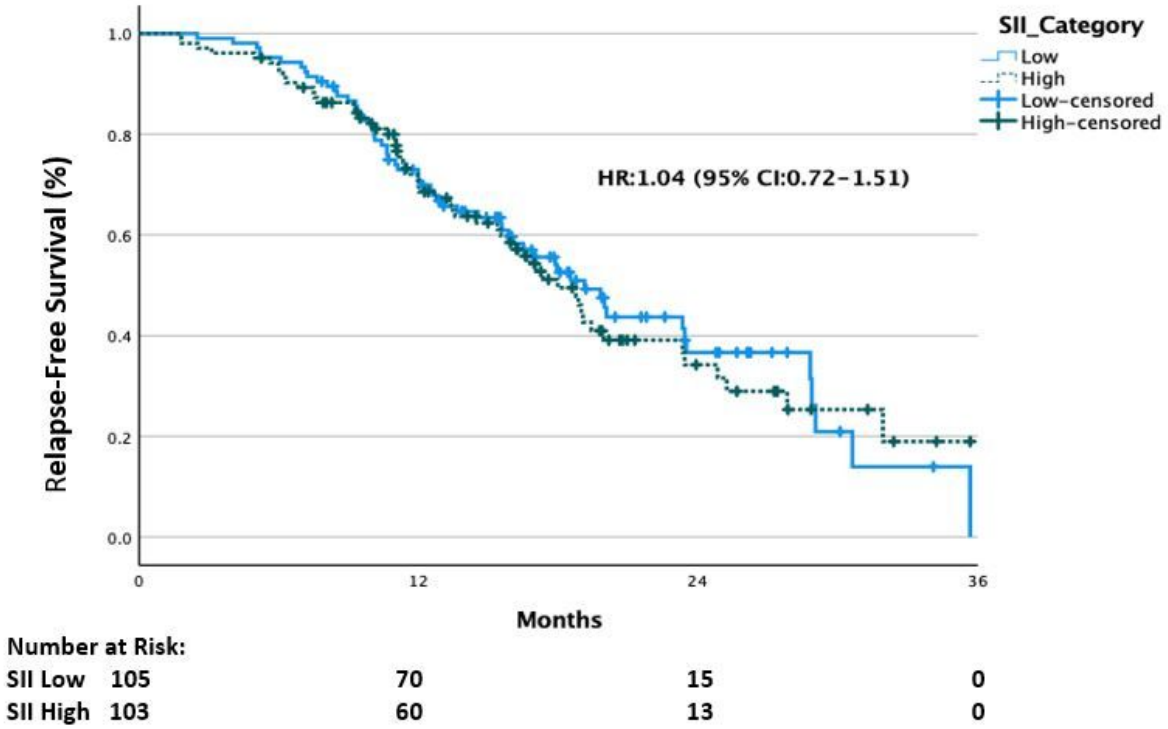
Figures



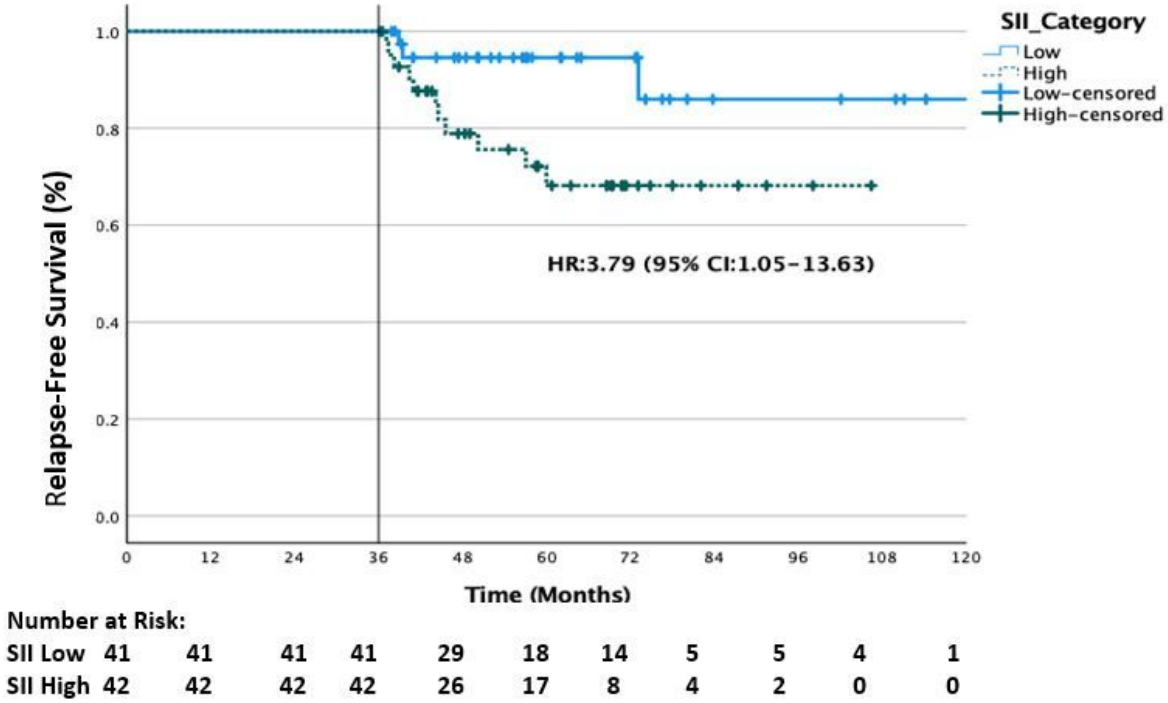


Figure 1

Survival Analysis a) The Kaplan-Meier estimates of relapse-free survival - according to SII category in the patients with recurrence in three years b) The Kaplan-Meier estimates of relapse-free survival - according to SII category in the patients with recurrence after three years