



Prognostic Value of Systemic Immune Index in Patients with Metastatic Gastric Cancer

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Abstract

Objective: Immune indexes are used to predict prognosis and survival in patients with cancer. Systemic immune-inflammation index (SII) is an index that is calculated using neutrophils (N), lymphocytes (L), and platelet (P) counts ($SII=N \times P/L$). SII is shown to be associated with prognosis in many tumors. The objective of this study is to evaluate the relationship between SII and prognosis in patients with metastatic gastric cancer.

Methods: In this study, the data of 187 patients who were followed up with the diagnosis of metastatic gastric cancer in the medical oncology outpatient clinic of the tertiary training and research hospital were retrospectively reviewed. SII was calculated using the formula $N \times P/L$ and the optimal cut-off was determined as 600, which was the median value. Values below 600 were grouped as low SII and values above 600 were grouped as high SII. The effect of SII on survival was evaluated by the log-rank test and the Kaplan-Meier curve.

Results: For the study, medical files of 253 patients who were diagnosed with metastatic gastric cancer were scanned. Patients who had no follow-up and whose pre-treatment hemogram data were not available at that time were excluded. Finally, this study included 187 patients. In total, there were 63 (33.7%) female and 124 (66.3%) male patients, with a median age of 63 (27-88) years. Although survival was shorter in patients with SII above 600, no statistical significance was detected (9 months vs. 12 months; $p=0.13$). In primary surgically resected patients, survival was significantly better (13 months vs. 4 months $p<0.001$), but there was no difference in SII between the operated and non-operated groups.

Conclusion: Our study suggests that a high SII may be a poor prognostic factor in patients with metastatic gastric cancer, despite no statistical significance. Well-designed prospective studies with a larger number of patients are needed to evaluate the prognostic significance of SII and determine the optimal cut-off value before its inclusion into the clinical routine in this group of patients.

Keywords: Gastriccancer, prognosis, systemicimmune-inflammation index (SII)

INTRODUCTION

Gastric cancer is the fifth most common cancer in the world and ranks third among all cancer-related deaths. Globally, more than one million patients were diagnosed with gastric cancer in 2018, resulting in over 780,000 deaths. Despite the decreasing incidence and mortality of gastric cancer in recent years, it is

still a major public health challenge (1,2). The highest cancer incidence in the world is found in East Asia, Eastern Europe, and South America, followed by Japan and Korea, where the incidence is also quite high (3).

Gastric cancer is still a high mortality disease with a poor prognosis despite the new developments in treatment such



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as new surgical techniques, chemotherapy, radiotherapy, and immunotherapy (4). Because gastric tumors exhibit late clinical manifestations, they are usually diagnosed at an advanced stage, with only around 10% of patients diagnosed at an early stage with the five-year survival rate of 10-30% (5,6).

Surgery combined with adjuvant chemotherapy and radiotherapy when diagnosed at an early stage increases survival chances, whereas systemic chemotherapy and radiotherapy aim to improve the survival and palliation of symptoms in patients diagnosed at the metastatic stage (5,7).

Systemic inflammation is known to play an important role in the development of many cancers, including gastric cancer. Chronic inflammation and chronic atrophic gastritis, especially due to *Helicobacter pylori* infection, increase the developmental risk of gastritis cancer (8,9). Cancer-related inflammation is a vital component of the tumor microenvironment, and inflammatory cells play an essential role in tumor development and progression. Researchers have shown that systemic inflammatory responses include DNA damage, angiogenesis, and tumor invasion and migration (10). Furthermore, another group of researchers have assessed the use of some histological and immunological markers in evaluating the prognosis of gastric cancer; however, many of these markers require tissue, cost, and time (6,11). Inflammatory cells such as white blood cells, neutrophils (N), lymphocytes (L), monocytes, platelets (P) and parameters such as N/L ratio, monocyte/L ratio, P/L ratio, are used routinely and believed to be indicators of systemic inflammatory and recommended as a prognostic factor in many types of cancers (6,10,12-14).

Recently, systemic immune-inflammation index (SII) based on N, P counts, and L counts in the peripheral blood has been used for a better reflection of the balance between host immune response and inflammation. Prognostic value of the results obtained from this calculation has been confirmed in many solid tumors such as colon, esophagus, hepatocellular and lung cancers (15-18).

SII has been reported to be associated with prognosis in patients operated for gastric cancer, as well as in patients with locally advanced gastric cancer who receive neoadjuvant chemotherapy. However, its prognostic use in patients with metastatic gastric cancer is not clear (6,19). The objective of this study is to evaluate whether the systemic immune index has a prognostic significance in patients with metastatic gastric cancer.

METHODS

Our study included 187 patients who were diagnosed with pathologically confirmed metastatic gastric cancer between 2006

and 2017 at the Medical Oncology Clinic of Kayseri Training and Research Hospital. In addition, their pre-treatment hemogram values and follow-up data were also recorded. Patients with steroid use that may affect hemogram parameters or patients with autoimmune disease, systemic inflammatory disease, and active infection at the time of diagnosis were not included in the study. Consent was obtained from the patients that the file information would be used before the study. Participating patients' gender, age, pathological tumor type, metastasis regions, type of surgery, hemogram, and tumor marker levels were then determined and evaluated. SII was calculated with the hematological parameters of the patients with the formula $P \times (N/L)$, and the median SII value of 600 was accepted as the cut-off value. Those with the SII cut-off value ≥ 600 were considered as high and those with < 600 as low.

Statistical Analysis

All analyses were performed using Statistical Package for Social Sciences version 22.0 software (SPSS Inc, Chicago, IL).

Categorical variables in the clinicopathological database were presented as frequency and percentage (%) and compared using the chi-square test or Fisher exact test. The basic characteristics of the patients were expressed as median for qualitative variables. Independent t-test was used in the analysis of numeric parameters that do not comply with normal distribution and cases who did not have a normal distribution were evaluated using Mann-Whitney U test.

The Kaplan-Meier curve was used for determining the effect of SII on overall survival (OS), whereas the log-rank test was used for the comparison of survival rates.

Ethical Approval

Ethical approval, dated 23/07/2020/07 decision number 126, was obtained from the Ethics Committee of Kayseri Training and Research Hospital.

RESULTS

For the study, the medical files of 253 patients who were diagnosed with metastatic gastric cancer were scanned. Patients who had no follow-up and whose pre-treatment hemogram data were not available were excluded. Finally, this study included 187 patients. In total, there were 63 (33.7%) female and 124 (66.3%) male patients, with a median age of 63 (27-88) years. Surgery was performed for primary gastric cancer in 150 patients (69.5%) before staging the patients and the most common surgery was total gastrectomy (37%). As for the pathological subtypes, adenocarcinoma was the

most frequently observed at a rate of 73.8%, among which 28.3% were poorly differentiated, 24.1% were moderately differentiated, 3.7% were well-differentiated tumors according to the differentiation status.

Evaluation of the metastasis sites revealed that the most common metastasis sites were liver (25%) and peritoneum (24%), whereas 20.3% of the patients had multiple metastases at the time of diagnosis. Tumor marker elevation was observed in 114 (61%) patients at the time of diagnosis (Table 1).

The median white blood cells, hemoglobin, N, P, and L counts in blood parameters were $7 \times 10^3 \mu\text{dL}$, 11.9 g/dL, $4.44 \times 10^3 \text{ u/dL}$, and $1.615 \times 10^3 \text{ u/dL}$, respectively. A significant relationship was observed between hemogram parameters and SII when the

optimum SII cut-off value was determined as the median SII value (Table 2).

Patients were divided into two groups according to SII levels: Those with SII <600 were accepted as the low group, and those with SII >600 as the high group. There were 60 patients in the low SII group and 127 patients in the high SII group. Although the median OS was 10 (8.2-11.7) months in the whole study group, there was no significant relationship among age ($p=0.61$), gender ($p=0.97$), pathological subtype ($p=0.28$), serum tumor elevation ($p=0.06$), and survival. However, survival was statistically significantly better in patients undergoing primary surgery ($p<0.001$) (Table 3, Figure 1).

Evaluation of the relationship between SII and survival showed that the median OS was 12 (9.5-14.4) months in the low SII

Table 1. Clinical characteristics of the study group

Age	(Mean ± SD) 61.6±12.26	Median (min-max) 63 (37-75)				
Gender	Male	Female				
n (%)	124 (66.3)	63 (33.7)	-	-	-	-
Histologic subtype	Signet ring cell	Adenocarcinoma	Mucinous	Mixed		
n (%)	46 (24.6)	138 (75.4)	1 (0.5)	1 (0.5)		
Surgery	Yes	No	NA	-	-	-
n (%)	130 (70)	27 (14.4)	30 (15.6)	-	-	-
Metastasis site	Lung	Liver	Lymph node	Bone	Peritoneum	Multiple
n (%)	10 (5.3)	47 (25.1)	28 (15)	6 (3.2)	45 (24.1)	38 (20.3)
BMI	Mean ± SD 22.5±4.14	Median (min-max) 22.0 (17-32)	-	-	-	-

SD: Standard deviation, min: Minimum, max: Maximum, BMI: Body mass index

Table 2. Clinico-pathologic characteristics of the patients according to SII groups.

Category	SII <600	SII >600	p value
n (%)	60 (32.1%)	127 (67.9%)	
Age (mean ± SD)	61.5±12.23	63±12.27	$p=0.94^1$
Gender (male/female) (%)	54/28 (38.3/61.7)	114/57 (31.5/68.5)	$p=0.89^{\chi^2}$
Surgery (total/subtotal) (n/%)	26 (43.3)/20 (33.7)	44 (34.6)/29 (22.8)	$p=0.51^{\chi^2}$
BMI (mean ± SD)	22.8±3.67	22.3±4.37	$p=0.88^1$
Pathology adenocarcinoma/signet ring cell (n/%)	47 (78.3)/13 (21.7)	91 (71.7)/33 (26.0)	$p=0.39^{\chi^2}$
Operated/non-operated (n/%)	66 (78.3)/10 (16.7)	118 (65.4)/19 (13.4)	$p=0.88^{\chi^2}$
Differentiation (good/moderate/poor) (n/%)	4/21/20	8/49/58	$p=0.26^{\chi^2}$
Hemoglobin (g/dL) (IQR 25-75)	12 (11-13)	11.8 (10-13)	$p=0.27^z$
Lymphocyte (u/dL) (IQR 25-75)	1790 (410-4370)	1595 (470-4500)	$p=0.13^z$
Neutrophil (u/dL) (IQR 25-75)	2795 (1975-3457)	5750 (4105-7587)	$p<0.001^z$
Monocyte (u/dL) (IQR 25-75)	430 (330-579)	600 (440-837)	$p<0.001^z$
Platelet (u/dL) (IQR 25-75)	224000 (181500-281000)	354500 (277750-450250)	$p<0.001^z$

SD: Standard deviation, ¹: Independent t-test, ²: Mann-Whitney U test, ^{χ²}: Chi-square test, SII: Systemic immun infalammation index, BMI: Body mass index, IQR: Interquartile range

group and 9 (6.9-11.0) months in the high SII group. Although no statistically significant difference was observed in survival, it was 3 months longer in the low SII group (Figure 2).

No significant difference was found in age, gender, body mass index, histological subtype, previous gastric surgery, and pre-treatment elevation in markers between the patients in the low and high SII groups (Table 2).

DISCUSSION

In our study, we found that a low SII value was associated with a better survival in patients with metastatic gastric cancer, even though it was not statistically significant.

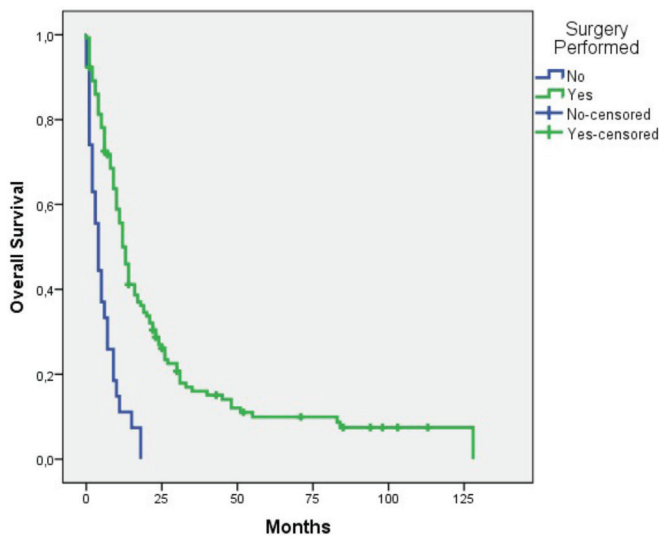


Figure 1. Kaplan-Meier survival curve according to the surgical procedure

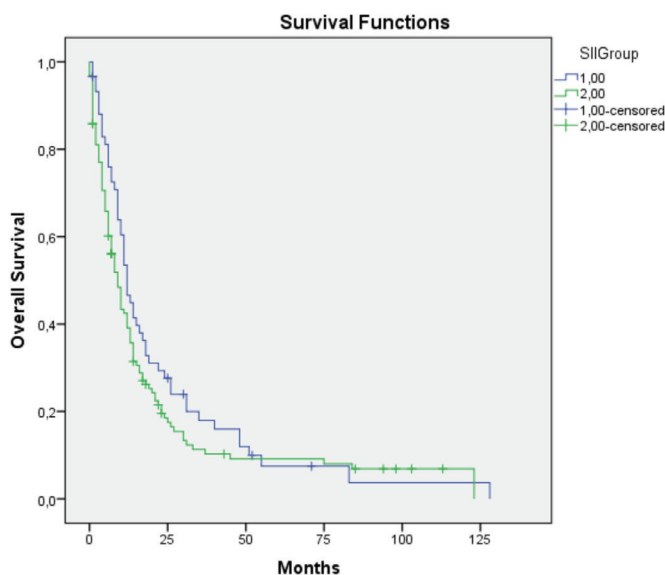


Figure 2. The effect of SII on OS in metastatic gastric cancer
SII: Systemic immune-inflammation index, OS: Overall survival

Recent studies have shown that systemic immune response stimulates malignant tumor development, is associated with a more aggressive clinical course and shorter survival, and predicts prognosis in patients with malignant tumors. SII is used in practice and has been reported to show immune and inflammatory status in various tumors in the preoperative period and can predict prognosis (20-22). SII is calculated with the formula - P x (N/L). It is known that N help tumor cells escape immune surveillance and, thus, the development of invasion, proliferation, and metastasis while inhibiting the proliferation and migration of tumor cells in L. With this mechanism, a high SII value shows a stronger inflammatory response but a weaker immunity and can be used as an applicable inflammation index in clinical practice that can predict cancer prognosis.

Previous studies showed that SII is associated with prognosis during the preoperative and neoadjuvant treatment period in patients with gastric cancer, but as far as we know, there is no study evaluating SII focused on a patient group with metastatic gastric cancer.

Table 3. Clinical characteristics and survival of the study group			
	n	Median OS (95% confidence interval)	p value
Gender			
Female	63	10 (8.32-11.6)	p=0.97*
Male	124	10 (7.52-12.4)	
Age (years)			
<65 years	115	12(8.6-15.3)	p=0.61*
>65 years	72	9 (6.5-11.4)	
Pathology			
Adenocarcinoma	138	11 (8.7-13.2)	p=0.28*
Signet ring cell	46	9 (5.43-12.5)	
Mucinous	1	26 (8.23-11.7)	
Differentiation			
Good	7	21 (0.36-41.6)	p=0.26*
Moderate	45	10 (5.7-14.2)	
Poor	53	12 (9.06-14.9)	
SII			
<600	60	12 (15.3-30.6)	p=0.13*
>600	127	9 (13.9-25.8)	
Marker elevation			
Yes	140	12 (11.3-22.6)	p=0.06*
No	107	17 (9.3-14.6)	
Surgery			
Yes	130	13 (11.1-14.8)	p<0.001*
No	27	4 (2.3-5.6)	

*Kaplan-Meier survival analysis, OS: Overall survival

The study conducted by Wang et al. (20) in patients with gastric cancer found that a high SII value was associated with poor prognosis in stage 1-3 patients with cancer. It also showed that high SII values were associated with advanced age, advanced stage, poor histological subtype, increased local lymph node involvement, and distant metastasis. Again, this study revealed no significant relationship between SII and survival in stage 4 patients. Similarly, in our study, no statistically significant relationship was found between survival and SII in patients with metastatic gastric cancer. However, survival was shorter in the high SII group (20).

Chen et al. (6) evaluated the prognostic significance of SII in the pre-neoadjuvant period in patients with advanced gastric cancer, where patients with metastatic cancer were not included. Moreover, they found that patients with low SII levels had a higher survival rate and were better in terms of 1-3 and 5-year disease-free survival compared to the group with high SII. They also showed that SII is an independent prognostic factor (6).

A meta-analysis conducted by Sun et al. (23) on patients with metastatic gastric cancer who underwent palliative gastric surgery concluded that gastrectomy significantly and positively affected survival. In our study, in line with the results of this meta-analysis, the median survival was statistically significantly better in patients who underwent primary surgery than those who did not (13 months vs. 4 months; $p < 0.001$).

Serum tumor markers are tests used in the evaluation of response to the treatment and during the follow-up in patients with gastric cancer. Various studies have reported that high carcinoembryonic antigen (CEA) levels at the time of diagnosis are an independent prognostic factor and associated with a shorter survival (24,25). In our study, patients with high serum CEA levels exhibited shorter survival as compared to the group with low levels, but they did not reach the limit of significance, which was attributed to the low number of cases.

Study Limitations

There were several limitations to our study. First, it was designed as a retrospective, single-center study and had a limited number of patients. Second, although SII is an independent predictor in many tumors, its sensitivity and specificity are not high. In future, prospective, randomized, and well-designed studies are needed to optimize the appropriate cut-off value.

CONCLUSION

SII is an effective, easily applicable, reproducible, and inexpensive marker, and can be used in patients at an early and

advanced stage cancer to show prognosis. In our study, we found that a high SII value was associated with poor survival, although not statistically significant. It was also found that patients with metastatic gastric cancer who underwent primary surgery exhibit higher survival. However, larger prospective studies are needed to clarify the prognostic value of SII in patients with metastatic gastric cancer.

Ethics

Ethics Committee Approval: Ethical approval, date: 23/07/2020/07, decision number: 126, was obtained from the Ethics Committee of Kayseri Training and Research Hospital.

Informed Consent: Consent was obtained from the patients that the file information would be used before the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.D., Design: H.D., M.İ., Data Collection or Processing: H.D., İ.B., Y.K., Analysis or Interpretation: H.D., İ.B., Literature Search: H.D., S.K.E., M.İ., Writing: H.D.

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