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The Relationship Between Systemic Immune-Inflammation Index and TNM Stage in Patients Underwent Pancreatic Cancer Surgery

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Abstract; The purpose of this study is to investigate the prognostic value of the systemic immune inflammation index (SII) by comparing it with postoperative TNM stages and other clinical-pathological data in patients undergoing curative surgery for pancreatic cancer. Pathological and clinical data of 44 patients who were operated for pancreatic cancer between January 2012 and January 2020 were retrospectively analyzed. Neutrophil, platelet and lymphocyte counts taken from preoperative complete blood samples were recorded and SII was calculated. The formula used in the calculation of the index is SII = Platelet x Neutrophil / Lymphocyte count. A comparison of the pathological stage and other clinical pathological findings was made for the two groups, which were formed with a cut-off value of 600 for SII. Twenty (45.4%) of the patients were female and 24 (54.5%) were male. Mean patient age was 65.4 ± 5.3 (21-86). In general, as the pathological stages of the patients increased, SII was also observed to increase creating a statistically significant difference ($p < 0.001$). The cut-off value for SII was taken as 600, forming two different groups. The difference in pathological stage distribution of these two groups was found to be statistically significant ($p < 0.001$). The difference between the groups according to differentiation degree, CA 19-9 level, presence of pancreatitis, pT, tumor diameter was statistically significant (respectively $p = 0.026$, $p = 0.009$, $p = 0.046$, $p = 0.047$, $p = 0.017$). It shows that preoperative SII significantly correlates with well-established prognostic factors in pancreatic cancer patients undergoing pancreatic surgery (resection). SII measurement is both low cost and easily applicable. SII can be used in conjunction with and supporting well-established prognostic factors.

INTRODUCTION

Regarding cancer-related mortality, pancreatic cancer (PC) is in the fourth place, whereas it is fifth among the most common cancers in the world [1]. Pancreatic Cancer has gained attention among gastrointestinal cancers with its increasing frequency in recent years and it is followed by gastric and colon cancer in our country in deaths related to gastrointestinal cancer [2]. PC is one of the 2 most deadly cancer types among all cancer types [3]. The 5-year survival rate of pancreatic cancer, which is among the most lethal cancer types due to its few symptoms, early detection an d lack of effective treatment options, is less than 5% and 50% of patients die within the first 6 months [4]. At the diagnosis, the vast majority of patients have already lost the chance of curative resection [5]. Only 20% of them have surgical resection chance [6]. It has been reported that many factors related to the patient affect survival in PC. The size, location, stage, and lymph node relationship of the tumor have been associated with clinical results [7]. The preferred staging system for all pancreatic cancers (exocrine and neuroendocrine) is the American Cancer Combination Committee (AJCC) / Union for International Cancer Control (UICC) tumor, lymph node, metastasis (TNM) system. The current staging system (eighth edition, 2017) is summarized in Table 1 [8].

Table 1. Pancreatic cancer TNM staging

Prognostic Staging Groups			
T	N	M	Stage
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IIB
T1	N2	M0	III
T2	N0	M0	IB
T2	N1	M0	IIB
T2	N2	M0	III
T3	N0	M0	IIA
T3	N1	M0	IIB
T3	N2	M0	III
T4	Any N	M0	III
Any T	Any N	M1	IV

In patients with pancreatic cancer resected according to prognostic stage groupings in the eighth edition, survival curves were obtained from a Surveillance, Epidemiology and End Results database analysis, and the analysis were based on the data of 8960 patients. According to this analysis, the median survival times for Stage IA, IB, IIA, IIB and III patients

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were 38, 24, 18, 17 and 14 months, respectively [9].

One of the factors that play a crucial role in the progression of cancer and survival of patients is the interaction between systemic inflammation and local immune response [10]. Regarding tumor-associated inflammation, systemic inflammatory response (SIR) has been shown to diminish the outcome and to be of major prognostic importance in various cancers [11,12]. Platelet-lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) are inflammation-based scores and their utility is based on the markers that are available before surgery. Hu et al. have first described SII [13]. Elevated SII was found to be associated with clinicopathological parameters; it was proven to be an independent prognostic factor in a number of malignancies, including PK [14,15,16]. In the study of Mohammad et al., SII was reported to be an independent predictor of both cancer-specific survival and recurrence in pancreatic cancer that can be resected [17]. There are many studies in the literature investigating potentially prognostic and promising histologic and immunologic biomarkers in PK [18,19]. But their evaluation is usually time-consuming and expensive. Metastatic lymph node ratio, tumor differentiation and resection margin can be named as the histological prognostic factors that are the predictors of survival in PK patients who can be resected [20,21]. The problem is that these well-established histological predictors are available for assessment only after the surgery.

Thus, it is crucial to investigate tumor-driving inflammation-based components, in addition focusing on the path of inflammatory response may be a cornerstone of cancer treatment [22]. Defining easily accessible markers can help identify individual treatment approaches. This study attempted to investigate the prognostic value of SII by comparing it with postoperative pathological TNM stages and other clinical-pathological data in patients undergoing curative surgery due to pancreatic cancer.

MATERIAL and METHOD

Ethical approval

No need for ethical approval

Patients and study design

Clinical and pathological data of 44 pancreatic cancer patients who underwent curative surgery between January 2012 and January 2020 were analyzed retrospectively. Clinicopathological data of the patients, such as, age, gender, tumor site, histopathological tumor grading, preoperative lymphocyte, neutrophil, and platelet counts, and staging (TNM) were collected from the medical records. Acute infection, diabetes, congestive heart failure, any autoimmune, hematological diseases and obese patients were excluded from our study. Preoperative data were collected before the surgery. Neutrophil, lymphocyte and platelet counts were recorded from the whole blood count samples and SSI was calculated. SII is based on the counts of neutrophil (N), platelet (P), and lymphocyte (L) and computed using the formula: SII = P*N/L [23]. Average SIIs were calculated according to pathological stages. Pathological stage comparison was made for the two groups formed by taking the cut-off value 600 for SII.

RESULTS

Twenty of the patients (45.4%) are women and twenty-four (54.5%) were male. Patients' average age was 65.4 ± 5.3 (21-86). Pathology results of the patients were 36 ductal adenocarcinoma, 5 neuroendocrine tumors, and 3 intra-ductal papillary mucinous neoplasia. Pancreaticoduodenectomy was performed in 27 patients (61.3%) and distal pancreatectomy in 17 patients (38.6%). In 12 (27.2%) of the cases, the tumor was found to be good, 25 (56.8%) of them were moderate, and 7 (15.9%) of them were badly differentiated. The mean tumor diameter of the patients was 4.9 ± 2.3 cm. While 26 of the patients had a history of pancreatitis, 18 of them had no history of pancreatitis. While CA19-9 was normal in 19 of the patients, it was observed that there was a high detection rate in 25 of them. The distribution of clinical-pathological characteristics belonging to two different groups created by taking the SII cut-off value of 600 is given in Table 2. The two groups were found to be differentiate significantly in terms of CA 19-9 level, the presence of pancreatitis, and pT (p= 0.026, p= 0.009, p= 0.046, p= 0.047, respectively)

Mean SII in Stage 1A was calculated as 280.5 ± 30.4, mean SII 423.4 ± 44.3 in Stage 1b, mean SII 584 ±82.3 in Stage 2A, mean SII 791.9 ± 119.6 in Stage 2B, mean SII 1010 ± 162.6 in Stage 3. In general, as the pathological stages of the patients increased, an increase was observed in SII, which was found to be statistically significant at p <0.001 (Table 3). The comparison of the groups among themselves showed that the difference between stage 1A and 1B (p = 0.271), and between stage 2B and 3 (p = 0.104) were not statistically significant (Figure 1).

Two different groups were formed by taking the cut-off value for SII as 600. There were a total of 19 patients in the group below SII 600, including 2 (10.5%) in Stage IA, 10 (52.6%) in Stage IB, 4 (21.1%) in Stage IIA, and 3 (15.8%) in Stage IIB. There was a total of 25 patients in the group with SII above 600, including 2 (8%) in Stage 2A, 16 (64%) in Stage

2B, and 7 (28%) in Stage 3. A statistically significant difference was observed in the pathological stage distribution of these two groups (p <0.001) (Table 4) (Figure 2).

Two different groups, which were formed with a cut-off value of 600 for SII, were compared according to pathological tumor size. The mean tumor diameter was found to be 3.16 cm in the group below SII 600, and 6.0 cm in the group above SII 600 (Table 5). A statistically significant difference was observed in tumor diameter of these two groups (p = 0.017).

Table 2. Distribution of clinical-pathological features of the cases according to SII.

Factors	All	SII <600	SII >600	p
N	44	19	25	
Sex				
Male	24	8	16	0,149
Woman	20	11	9	
pT				
1	6	5	1	0,047
2	14	9	5	
3	20	6	14	
4	4	1	3	
pN				
0	16	10	6	0,132
1	20	7	13	
2	8	2	6	
Grade				
1	12	9	3	0,026
2	25	10	15	
3	7	1	6	
CA19-9 U/ml				
<37	19	12	7	0,009
>37	25	6	19	
Pancreatitis				
yes	26	8	18	0,046
no	18	11	7	
Surgical procedure				
Whipple	27	12	15	0,583
Distal pancreatectomy	17	9	8	

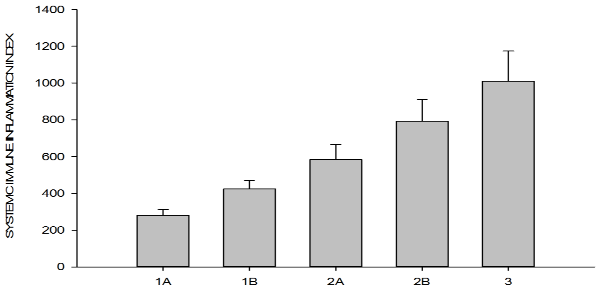

Figure 1. Average SII values according to the pathological stage

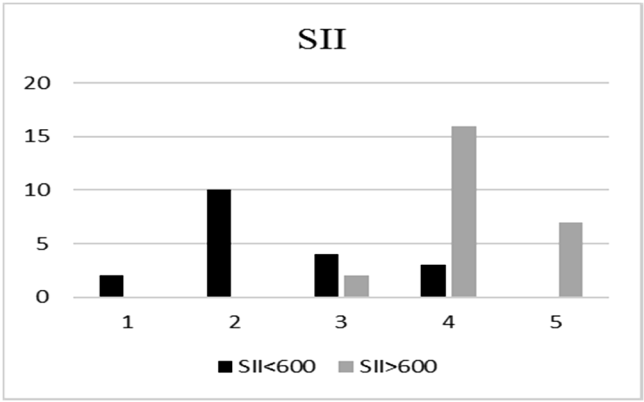

Figure 2. Distribution of pathological stages between groups.

Table 3. Average SII values according to the pathological stage

		SYSTEMIC IMMUNE INFLAMMATION INDEX								
		Minimum	Maximum	Mean	Standard Deviation	Percentile 25	Percentile 75	Median	IQR	p
Stage	1A	259,00	302,00	280,50	30,41	259,00	302,00	280,50	43,00	< 0,001
	1B	339,00	466,00	423,40	44,31	396,00	447,00	442,50	51,00	
	2A	476,00	729,00	584,00	82,34	554,00	591,00	577,00	37,00	
	2B	520,00	934,00	791,95	119,63	767,00	876,00	829,00	109,00	
	3	798,00	1256,00	1010,00	162,64	818,00	1112,00	1002,00	294,00	

Table 4. Pathological stage distribution between groups

		Stage					Total	Total
		1A	1B	2A	2B	3		
SII	SII <600	n	2	10	4	3	0	19	<0,001
		%	10,5	52,6	21,1	15,8	0,0	100,0
	SII >600	n	0	0	2	16	7	25
		%	0,0	0,0	8,0	64,0	28,0	100,0

Table 5. Tumor diameters by groups

	TUMOR DIAMETER								
	Minimum	Maximum	Mean	Standard Deviation	Percentile 25	Percentile 75	Median	IQR	P
SII <600	1,00	7,00	3,16	1,89	2,00	4,00	3,00	2,00	0,017
SII >600	2,00	13,00	6,00	4,00	3,00	9,00	4,00	6,00	

DISCUSSION

The relationship between cancer and chronic inflammation started with Rudolf Virchow's definition of leukocytes in tumor tissue about a hundred years ago [24,25]. Since then, many studies have been conducted to show that chronic inflammation, which occurs as a host response in tumor tissue, is effective in tumor development, metastasis, prognosis, and response to treatment. In recent studies, the relationship between the degree of systemic inflammation and cancer has been demonstrated by evaluating parameters such as systemic inflammation markers NLR, PLO, and SII [26,27]. Tumor microenvironment is regulated by inflammatory cells. Neutrophils and platelets, tumor cells block apoptosis, angiogenesis, DNA damage, proliferation and metastasis of tumor cells to prevent metastasis and proliferation of lymphocytes directly contributing to the secretion of protective and inflammatory factors [28]. Lymphocytopenia in the tumor tissue also causes the interruption of the immune response that the host should give. Systemically, NLR, PLR and SII will be higher due to the increase in neutrophil-platelet count and decrease in lymphocyte count. Based on these results, various inflammation-based scores were used in cancer patients as prognostic indicators. In this study, the relationship of SII, one of the inflammatory biomarkers, with the well-established prognostic clinical-pathological markers in patients resected for pancreatic cancer was revealed.

Inflammation-based biomarkers and scores have recently been shown to play a significant prognostic role in a number of malignant diseases [29,30]. SII, which is based on neutrophils, platelets, and lymphocytes count, is one of these new prognostic scores. SII, which reflects patient's inflammatory status, has been confirmed as a prognostic factor first in hepatocellular carcinoma, and then in small cell lung cancer [14,31]. Elevated preoperative SII has a key role in prognosis estimation in several malignancies, including PC [15,16,32,33,34].

In our study, we observed this as the pathological stage progressed, SII increased and there were only stage 2 and 3 patients in the group with SII over 600. This relationship may be due to different reasons. Thrombocythemia, lymphopenia, and neutrophilia causes high SII, which may be due to the combination of impairment of the adaptive immune system and nonspecific inflammation [35,36]. Pancreatic cancer is particularly associated with nonspecific inflammation, which is often ineffective against the cancer itself [37]. The recent data showed that the relation between cancer-associated thrombocytosis and the diminishing of the host immunity is due to the suppression of T-cell responses against tumors [38]. The survival of the patients having high SII may be worse due to the micrometastases. For instance, the adhesion of tumor cells to microvascular endothelium is supported by the platelets in pancreatic cancer [39]. Platelets in the circulation may built a defensive barrier around tumor cells, which allows tumorous cells to escape from the host's immune system surveillance [40]. High SII values, corresponding to high platelet and neutrophil counts, and low number of lymphocytes, indicate an inflammation activity caused by metastases and enhanced tumor invasion, which can be associated to poor survival. Regarding the studies on the prognostic capacity of SII, PLR, and NLR, our findings are consistent with the results of Chawla et al., who showed that in patients with resectable PC, preoperative SII is an independent prognostic factor for OS, rather than NLR and PLR. Haldar and Ben-Eliyahu have recently addressed the effect of COX2 inhibition and perioperative β-adrenergic blockade on cancer outcomes [41]. Accordingly, patients, who have a resectable PDAC and with high preoperative SII, might benefit from anti-inflammatory and/or anti-immunotherapy before and after surgery.

There is no consensus on the cutoff value of inflammation indices. The cutoff level is usually specified individually according to their relevance and significance in a patient cohort and in a way that they allow the survival rate of the group to be predicted significantly. Hence, the cut-off values for these indices vary in a wide range. We specified the cut-off value as 600 in accordance with the general belief.

CA19-9, which is a sialylated Lewis A blood group antigen, is commonly expressed and shed in many malignancies, including pancreatic and hepatobiliary disease. The increase of CA 19-9 is also observed in benign conditions such as bile cholangitis, duct obstruction, acute or chronic pancreatitis, inflammatory bowel disease, thyroid diseases, cystic fibrosis, and liver cirrhosis [42]. The body does not produce CA 19-9 in 5% of the population [43]. Healthy individuals may have high levels as well [43]. In our study, SII was found to be higher in patients with high CA19-9. This suggests that SII can be an alternative in benign and physiological conditions where CA 19-9, an important prognostic marker in pancreatic cancer, is elevated.

Chronic pancreatitis, which is known as a risk factor for PC, makes contribution to PC development through the formation of pancreatic intraepithelial lesions [44,45]. In our study, 26 patients had a history of pancreatitis, and SII of 18 of these patients were over 600. Eighteen patients did not have a history of pancreatitis and 11 of these patients had SII below 600. In our study, we evaluated that SII increased with the presence of

pancreatitis. Our study has limitations such as being retrospective, single centered, relatively low number of patients, and absence of a control group including healthy individuals.

CONCLUSION

In short, this study shows that in PDAC patients who underwent pancreatic resection, preoperative SII is an independent predictor of OS. Measurement of SII is both low cost and easily applicable. Anti-inflammatory and/or anti-immunotherapy may be beneficial for the patients who have high preoperative SII.

Conflict of interest

The authors declare that they have no conflict of interest.

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