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Association of Systemic Immune-Inflammation Index with Long-Term All-Cause Mortality in Pancreatic Cancer Patients after Pancreaticoduodenectomy

Pankreas Kanseri Hastalarında Pankreatikoduodenektomi Sonrası Sistemik İmmün-İnflamasyon İndeksi ile Uzun Dönem Mortalite Arasındaki İlişki

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Abstract

Aim: Systemic immune-inflammation (SII) index may provide more promising prognostic information in patients with cancer surgery. However, to the best of our knowledge, the prognostic value of SII index in patients with pancreatic cancer who underwent pancreaticoduodenectomy has not been studied. Thus, this study aimed to evaluate and compare the prognostic value of SII index in patients with pancreatic cancer who underwent pancreaticoduodenectomy.

Material and Method: All patients over 18 years-old that underwent successful pancreaticoduodenectomy due to pancreatic cancer between February 20, 2019 and June 30, 2021 at Ankara City Hospital Department of General Surgery were included. The main predictor of interest was SII index which was measured by neutrophil*platelet / lymphocyte count. The main outcome of the study was long-term all-cause mortality.

Results: A total of 223 patients were included in the current study. Multivariable cox regression analysis revealed that history of congestive heart failure [HR (95%CI): 3.682 (1.140-11.892)], and SII index [HR (95%CI): 1.001 (1.001-1.001)] were independently associated with all cause long-term mortality. The accuracy of predicting mortality for SII index was assessed by the area under the ROC curve which was = 0.77. A higher value of 1305 of SII index was found with 76% sensitivity and 67% specificity for predicting all-cause long-term mortality.

Conclusions: The results of the study suggest that measurement of the SII index, an easily available and relatively cheap marker, is an independent predictor of long-term survival after pancreaticoduodenectomy in patients with pancreatic cancer.

Keywords: inflammation, mortality, pancreatic cancer, SII index

Öz

Amaç: Sistemik immün inflamasyon (Sİİ) indeksi, kanser cerrahisi geçiren hastalarda umut verici prognostik bilgiler sağlayabilir. Pankreatikoduodenektomi yapılan pankreas kanseri tanılı hastalarda Sİİ indeksinin prognostik değeri daha önce araştırılmamıştır. Bu nedenle, bu çalışmada pankreatikoduodenektomi yapılan pankreas kanserli hastalarda Sİİ indeksinin prognostik değerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: 20 Şubat 2019 - 30 Haziran 2021 tarihleri arasında Ankara Şehir Hastanesi Genel Cerrahi Kliniği'nde pankreas kanseri nedeniyle pankreatikoduodenektomi yapılan 18 yaş üstü tüm hastalar çalışmaya dahil edildi. İlgilenilen ana belirteç, nötrofil*trombosit/lenfosit sayısı ile ölçülen Sİİ indeksiydi. Çalışmanın ana sonlanım noktası, tüm nedenlere bağlı uzun dönem mortaliteydi.

Bulgular: Çalışmaya toplam 223 hasta dahil edildi. Çok değişkenli Cox regresyon analizi, konjestif kalp yetmezliği öyküsü [HR (%95 GA): 3.682 (1.140-11.892)] ve Sİİ indeksinin [HR (%95 GA): 1.001 (1.001-1.001)] uzun dönem mortalite ile bağımsız olarak ilişkili olduğunu gösterdi. Sİİ indeksinin mortalite öngörü doğruluğunu değerlendirmek için yapılan ROC analizinde eğri altında kalan alan 0.77 olarak belirlendi. Sİİ indeksinin 1305 ve üzerinde olmasının uzun dönem mortaliteyi öngörü duyarlılığı %76, özgüllüğü %67 olarak hesaplandı.

Sonuçlar: Çalışmanın sonuçları, kolay elde edilebilen ve nispeten ucuz bir belirteç olan Sİİ indeksinin, pankreas kanseri tanılı hastalarda pankreatikoduodenektomi sonrası uzun dönem sağkalımı bağımsız olarak öngördürebilecek bir parametre olduğunu göstermektedir.

Anahtar Kelimeler: inflamasyon, mortalite, pancreas kanseri, Sİİ indeksi

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INTRODUCTION

Pancreaticoduodenectomy also known as Whipple surgery is the only potentially curative intervention for pancreatic cancer.[1] However, the majority of patients with pancreatic cancer present with metastatic or locally advanced unresectable disease; thus only 15-20% of patients are candidates for the Whipple procedure.[2] It has been reported that the 5-year survival rate after surgical resection ranged from 40.9% to 67.9%.[3-6] However, up to 50% of patients develop recurrence after curative resection of such a disease and this clearly affects survival.[7] Therefore, evaluation of prognostic indicators in patients with pancreatic cancer who underwent pancreaticoduodenectomy is important.

There is increasing evidence shows that the interplay between local immune response and systemic inflammation may play a key role in the development of various cancers,[8,9] including pancreatic cancer.[10,11] Neutrophil, lymphocyte, and platelet levels through a complete blood count can shed light on the systemic inflammatory response. However, inflammatory parameters alone can be easily affected by other factors, so combined inflammatory index tools, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), are perhaps theoretically more reliable and have potential to assess inflammatory status. Systemic immune-inflammation index (SII) is a novel systemic inflammatory index, based on neutrophil, platelet and lymphocyte counts. It has been previously reported that SII may provide more promising prognostic information than NLR and PLR in patients with colorectal cancer surgery.[10] In addition, it is also showed that higher SII is independently associated with worse outcomes in patients with metastatic renal cell carcinoma.

However, to the best of our knowledge, the prognostic value of SII index in patients with pancreatic cancer who underwent pancreaticoduodenectomy has not been studied. Thus, this study aimed to evaluate and compare the prognostic value of SII index in patients with pancreatic cancer who underwent pancreaticoduodenectomy.

MATERIAL AND METHOD

In the current study, all patients over 18 years-old that underwent successful pancreaticoduodenectomy due to pancreatic cancer between February 20, 2019 and June 30, 2021 at Ankara City Hospital Department of General Surgery were included. Patients demographic characteristics including age and sex were recorded. Patients' comorbidities including history of congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatoid disease, peptic ulcer disease, liver disease, hemiplegia or paraplegia, and renal disease were recorded. In addition, laboratory markers including complete blood count parameters (hemoglobin, neutrophil, lymphocyte, platelet, mean platelet volume, monocyte and red cell distribution) and other laboratory markers (estimated glomerular filtration rate [eGFR], total bilirubin, lactate dehydrogenase, gamma glutamyl transferase, albumin, amylase, alkaline phosphatase, alanine aminotransferase, sodium, potassium and total protein) were recorded. Blood samples were collected after fasting for at least 6 hours before pancreaticoduodenectomy. Patients who had missing laboratory biomarkers were excluded from the study. An automated blood cell counter (Beckman Coulter analyzer, California, USA) was used for measuring complete blood count parameters. Blood biochemistry parameter levels that were measured using an automatized analyzer (Beckman Coulter analyzer) using nephelometric measurement before pancreaticoduodenectomy. The main predictor of interest was SII index which was measured by neutrophil*platelet / lymphocyte count. The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 18.05.2021, Decision No: E2-22-529).

Outcome

The main outcome of the study was long-term all-cause mortality. Patients were separated into two groups according to survival status. Time to death was calculated as the time period between the first date of surgery and the date of death. Patients were censored as of June 30, 2021, which marked the end of the follow-up period for all-cause mortality.

Statistical Analyses

Stata statistical package program (version 15.1 / IC; StataCorp) was used to perform all data analyses. Kolmogorov-Smirnov test was used to analyze the distribution pattern. Normally distributed numerical variables were presented as mean ± standard deviation. Categorical variables were presented as number and percent (%). To show significant predictors of mortality, univariable cox regression models were used for each variable, and then those which had <0.1 p-values were tested in the multivariable cox regression model. Multivariable cox regression model results [Hazard ratios (HRs) and their 95% confidence intervals (CIs)] were presented. Receiver operating characteristic (ROC) analysis was used to show the discrimination of the performance of the SII index. Youden's index, a common summary measure of the ROC curves, was used to identify the best threshold to discriminate mortality. Then, the corresponding sensitivity and specificity values were calculated. According to best threshold SII index value, Kaplan Meier survival curves was plotted. All p<0.05 was considered significant in all statistical analyzes.

RESULTS

A total of 223 patients were included in the current study. Baseline demographic and clinical comorbidities of patients according to survival status were presented in Table 1. In total, 97 (43.5%) patients were dead during the follow up time period (median 317 days (25^{th} and 75^{th} 161 and 530 days). As shown in **Table 1**, age [61.0 (11.3) vs 65.3 (11.3); p<0.001] and history of congestive heart failure [8 (6.3%) vs 14 (14.4%); p=0.045], and hemiplegia or paraplegia [0 (0%) vs 3 (3.1%);

p=0.047] were significantly higher in the non-survivor group. Baseline laboratory parameters of patients according to survival status were presented in **Table 2**. Neutrophil [6.1 (3.9) vs 7.8 (3.5); p<0.001], platelet [283.2 (89.3) vs 334.3 (88.7); p<0.001], alkaline phosphatase [226.1 (229.9) vs 361.9 (317.9); p<0.001] and SII index [1657.4 (2262.0) vs 4022.6 (3647.4); p<0.001] were significantly higher in the non-survivor group. On the other hand, hemoglobin [12.5 (1.6) vs 11.9 (1.9); p=0.021], lymphocyte [1.5 (0.7) vs 1.2 (0.6); p<0.001] and albumin [37.1 (6.3) vs 35.1 (6.6); p=0.031] were significantly lower in the non-survivor group.

Multivariable cox regression analysis revealed that history of congestive heart failure [HR (95%CI): 3.682 (1.140-11.892)], and SII index [HR (95%CI): 1.001 (1.001-1.001)] were independently associated with all cause long-term mortality (**Table 3**).

Table 3. Multivariable cox regression analysis results

	Hazard Ratio	95% Confidence Interval	p-value
Age	1.023	0.992 - 1.055	0.155
History of congestive heart failure	3.682	1.140 - 11.892	0.029
Hemoglobin	0.826	0.661 - 1.031	0.092
Mean platelet volume	1.207	0.865 - 1.686	0.269
Gama glutamyl transferase	1.000	0.999 - 1.001	0.993
Albumin	1.055	0.984 - 1.132	0.132
Alkaline phosphatase	1.002	0.999 - 1.004	0.057
Systemic immune-inflammation index	1.001	1.001 - 1.001	0.003

Table 1. Baseline demographic and clinical comorbidities of patients according to survival status

	Total n=223	Survivors n=126	Non-Survivors n=97	p-value
Age, y,	62.9 (11.4)	61.0 (11.3)	65.3 (11.3)	0.005
Sex, n (%)				
Male	154 (69.1%)	85 (67.5%)	69 (71.1%)	0.56
Female	69 (30.9%)	41 (32.5%)	28 (28.9%)	
Comorbidities				
History of congestive heart failure, n (%)	22 (9.9%)	8 (6.3%)	14 (14.4%)	0.045
Peripheral vascular disease, n (%)	4 (1.8%)	4 (3.2%)	0 (0.0%)	0.077
Cerebrovascular disease, n (%)	21 (9.4%)	11 (8.7%)	10 (10.3%)	0.69
Dementia, n (%)	3 (1.3%)	2 (1.6%)	1 (1.0%)	0.72
Chronic obstructive pulmonary disease, n (%)	4 (1.8%)	1 (0.8%)	3 (3.1%)	0.20
Rheumatoid disease, n (%)	5 (2.2%)	5 (4.0%)	0 (0.0%)	0.047
Peptic ulcer disease, n (%)	18 (8.1%)	11 (8.7%)	7 (7.2%)	0.68
Liver disease, n (%)	10 (4.5%)	8 (6.3%)	2 (2.1%)	0.13
Hemiplegia or paraplegia, n (%)	3 (1.3%)	0 (0.0%)	3 (3.1%)	0.047
Renal disease, n (%)	12 (5.4%)	7 (5.6%)	5 (5.2%)	0.90

Table 2. Baseline laboratory parameters of patients according to survival status

	Total n=223	Survivors n=126	Non-Survivors n=97	p-value
Complete Blood Count Parameters				
Hemoglobin, g/dL, mean (SD)	12.2 (1.8)	12.5 (1.6)	11.9 (1.9)	0.021
Neutrophil, 10^3 cells/µL, mean (SD)	6.9 (3.8)	6.1 (3.9)	7.8 (3.5)	0.001
Lymphocyte, 10^3 cells/µL, mean (SD)	1.4 (0.7)	1.5 (0.7)	1.2 (0.6)	<0.001
Platelet, mL, mean (SD)	306.2 (92.4)	283.2 (89.3)	334.3 (88.7)	<0.001
Mean platelet volume, fL, mean (SD)	8.6 (1.0)	8.5 (0.9)	8.8 (1.1)	0.051
Red cell distribution width, fL, mean (SD)	15.5 (2.1)	15.4 (2.4)	15.6 (1.6)	0.56
Monocyte, 10^3 cells/µL, mean (SD)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	0.99
Other Laboratory Parameters				
eGFR, mL/min, mean (SD)	92.1 (19.2)	92.7 (19.1)	91.3 (19.4)	0.62
Total bilirubin, mg/dL, mean (SD)	120.5 (1002.5)	77.1 (619.4)	173.1 (1328.7)	0.50
Lactate dehydrogenase, mg/dL, mean (SD)	241.3 (136.5)	228.6 (79.2)	256.0 (181.1)	0.17
Gama glutamyl transferase, units/L, mean (SD)	318.0 (410.5)	267.6 (386.0)	379.1 (432.7)	0.058
Albumin, g/dL, mean (SD)	36.2 (6.5)	37.1 (6.3)	35.1 (6.6)	0.031
Amylase, units/L, mean (SD)	137.1 (226.0)	153.7 (280.8)	116.7 (129.7)	0.25
Alkaline Phosphatase, units/L, mean (SD)	287.2 (280.6)	226.1 (229.9)	361.9 (317.9)	<0.001
Alanine aminotransferase, units/L, mean (SD)	121.2 (157.0)	120.9 (181.0)	121.5 (122.1)	0.98
Sodium, mmol/L, mean (SD)	139.3 (3.7)	139.3 (3.9)	139.3 (3.4)	0.99
Potassium, mmol/L, mean (SD)	4.2 (0.5)	4.1 (0.5)	4.2 (0.5)	0.90
Total Protein, g/dL, mean (SD)	59.0 (9.4)	59.5 (9.0)	58.4 (9.9)	0.41
Systemic Immune-inflammation Index, mean (SD)	2721.7 (4894.5)	1657.4 (2262.0)	4022.6 (3647.4)	<0.001

The accuracy of predicting mortality was assessed by the area under the ROC curve which was = 0.77 as shown in **Figure 1**. A higher of value of 1305 of SII index was found with 76% sensitivity and 67% specificity for predicting all-cause long-term mortality. As shown in **Figure 2**, the optimal cut-off value for SII index as derived from ROC curve was significantly related with all-cause long-term mortality (log-rank p-value <0.001).

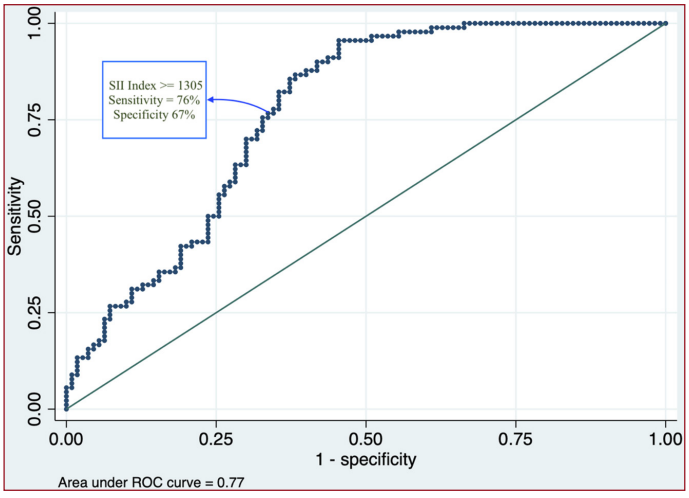

Figure 1. The area of under the curve for systemic immune-inflammation index of mortality

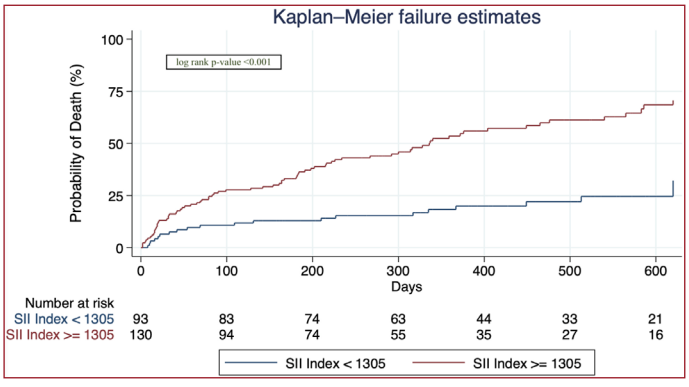

Figure 2. Kaplan Meier mortality curve according to systemic immune-inflammation index cut-off value (1305)

DISCUSSION

Based on our current knowledge and the results of our literature research, this study is the first to study the SII index in patients with pancreatic cancer who underwent pancreaticoduodenectomy. According to our data, we have shown that SII index, an easily applicable and inexpensive method, is significantly associated with long-term all-cause mortality in these patients.

It is a very common research method to try to have an idea about some diseases by looking at the ratio of laboratory values. There are studies showing that hematological parameters such as neutrophil and lymphocyte counts, and platelet size can provide information about disease severity and prognosis in oncological diseases including pancreatic cancer.[12-14] In particular, getting information about the prognosis and mortality rates of oncological diseases is one of the subjects that patients and their relatives are most curious about. Clinicians also want to predict the course and survival rates of their oncology patients, especially those who underwent surgery. Although the parameters such as cancer stages of the patients, the success of the surgery, and the age of the patient are indicative, it may still be necessary to look at some additional findings.[15]

According to the results we found, the presence of heart failure and higher SII index of patients who underwent pancreaticoduodenectomy independently associated with higher mortality rates in pancreatic cancer patients. All characteristics of the patient should be considered and evaluated as a whole. Some signs and symptoms are likely to come to the fore, some laboratory data are high or low, and their ratios to each other are likely to predict some outcomes. When we look at our patient population, it seems that many patients have been operated in a very short time. Our hospital is a reference center with a high volume of surgeries. In a center where such intensive patient treatment is provided, data collection, analysis, and interpretation are required.

There are some limitations of the current study. Even if one of the strengths of our study is that a large number of patients were operated during the COVID-19 pandemic period and that we have analyzed an important and large data, our retrospective evaluation of the data and the incompleteness of some data can be counted among the limitations of our study.

Every clinician and center, especially hospitals that accept many patients and can perform specialized surgical operations, should collect their own data, frequently analyze it, find data related to survival and death, and focus on these parameters and work on survival and mortality by trying to solve other related clinical problems of these parameters. Especially in patients who have undergone oncological surgery, re-surgery planning, chemotherapy planning, survival and prognosis should be tried to be predicted so that changes and new plans can be made regarding these issues.

CONCLUSIONS

The results of the study suggest that measurement of the SII index, an easily available and relatively cheap marker, is an independent predictor of long-term survival after pancreaticoduodenectomy in patients with pancreatic cancer. Further studies are needed to validate our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 18.05.2021, Decision No: E2-22-529).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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