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Role of systemic immune-inflammation index in predicting mortality in cancer patients in palliative care units

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ABSTRACT

Aim: In our study, we aimed to investigate whether the systemic immune-inflammation index (SII) can evaluate mortality in cancer patients treated in the palliative care unit (PCU).

Material and Method: Cancer patients who received palliative care treatments in the PCU were screened retrospectively, and 309 patients were included in the study. The patients were divided into two groups; hospitalizations ending with discharge as Group 1 (n=154) and hospitalizations ending with exitus as Group 2 (n=155). SII values of the two groups were compared. SII was calculated with the formula of neutrophil count x platelet count / lymphocyte count. To determine the best cut-off value for the mortality distinction ability of the SII, a Receiver Operating Curve (ROC) analysis was used.

Results: The mean age and distribution of genders of the two groups were similar (p=0.706, p=0.964). There was a statistically significant difference between the SII values of the two groups (p<0.001). SII was successful in predicting mortality in cancer patients hospitalized in PCU, and the probability of mortality in patients with an SII value of 1426.29 and above at the time of hospitalization was approximately 1.8 times higher than in patients with a value below 1426.29.

Conclusion: We found that high SII values could predict mortality in cancer patients receiving palliative care in PCU. We think that SII, which is inexpensive, easily accessible, and easily calculated with only peripheral blood cell count, will provide clinicians working in PCU with important benefits, such as achieving more accurate prognostic results for the selection of treatment modalities and mortality estimation when combined with their own clinical experience. We recommend that SII be calculated in all cancer patients hospitalized in PCUs and that patients with high SII values should be followed more closely.

Keywords: Palliative care, SII, cancer, mortality

INTRODUCTION

Palliative care is a multidisciplinary approach that aims to relieve symptoms of diseases with high morbidity and mortality and improve the quality of life of patients and their families (1,2). Cancers constitute a critical part of these severe diseases with high morbidity and mortality (3,4). It has been determined that systemic and local inflammation have a role in cancer initiation, development, and progression (5,6). This inflammation network is the target in the prevention and treatment of cancer (7). Prediction of cancer prognosis is vital in reducing preventable risks (8). SII, an inflammatory index, has been associated with mortality in many types of cancer. In more than one study, high SII was found to be associated with a significant increase in mortality and a decrease in survival time. Systemic immune-inflammatory index (SII) is calculated as neutrophil count x platelet count / lymphocyte count (9-11).

Clinicians aim to identify easily accessible and easily calculated reliable markers for predicting prognosis and mortality in cancer patients. In this study, we aimed to investigate whether SII can be used as an index to predict mortality in cancer patients under palliative follow-up.

MATERIAL AND METHOD

This study was planned as a retrospective study and carried out with the permission of Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.12.2022, Decision No: 2022-106). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All malignancy-related hospitalizations at the Palliative Care Unit (PCU) between January 2018, and June 2022, were screened retrospectively. Patients under 18, patients with a known hematological disease, patients who are using drugs that

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could affect hematologic parameters (such as steroids, chemotherapeutic agents, and antibiotics), patients with acquired immune deficiency syndrome (AIDS), pregnancy, or breastfeeding status, and those whose blood results on the first day of hospitalization could not be obtained were excluded. A total of 309 palliative care patients were included in the study. The gender, age, hospitalization duration, serum neutrophil, lymphocyte, platelet counts, hemoglobin, and albumin levels of 309 patients, and the mortality status of the patients were obtained from the archive system retrospectively. All patients were divided into two groups: Hospitalizations ending with discharge as Group 1 and hospitalizations ending with exitus as Group 2. These groups were compared in terms of demographic characteristics, hospitalization duration, peripheral blood cell count, albumin, and SII values. The SII value was calculated as SII = Neutrophil count (10^9/L) x Platelet count (10^9/L) / Lymphocyte count (10^9/L).

Statistical Analysis

For statistical analysis IBM SPSS Statistics for Windows software was used (Version 26; IBM Corp., Armonk, N.Y., USA). Descriptive statistics were reported using numbers and percentages for categorical variables. Numerical variables were reported as mean ± standard deviation and median value in parentheses. Data distribution was evaluated using the Shapiro-Wilks test. Using Pearson and Spearman correlation coefficients, relationships between variables were analyzed. Distribution-based analysis was used to compare the numerical measures of two separate study groups. Age, length of hospital stay, serum neutrophil, lymphocyte, platelet counts, albumin level, and SII value were evaluated with the Mann-Whitney U test, and serum hemoglobin level was assessed using student t-test. The Chi-Square test was used to evaluate the statistical significance of categorical variable differences across groups. By drawing the Receiver Operating Curve (ROC) and determining the area under it, the cut-off values with the best sensitivity and specificity that separate the groups based on mortality were calculated using the Youden index. Sensitivity, specificity, PPV, NPV, test precision, and odds ratio were calculated for cut-off values. For the statistical significance level, $p<0.05$ was accepted as meaningful.

RESULTS

In the whole group, 191 (61.81%) patients were male, and 118 (38.19%) were female. The median age of all hospitalizations was calculated as 72 years. The median duration of hospitalization was 11 days.

The median neutrophil count of all patients was 6.69 109/L, the median lymphocyte count was 0.96 109/L, and the median platelet count was 212 109/L. The median hemoglobin was 10 g/dL, and the median albumin value was 2.6 g/dL.

In the whole group, 155 (50.16%) patients died in the same admission to the hospital. All patients' median SII value was 1536.56 (**Table 1**).

When types of cancer were investigated in the whole group, the most frequent cancer types in palliative care were lung cancer (17.80%), gastric cancer (14.56%), colorectal cancer (13.27%), pancreatic cancer (10.36%), and breast cancer (7.44%). Most deaths were seen in patients with cholangiocellular carcinoma (87.50%), ovarian carcinoma (66.67%), and bladder carcinoma (66.67%). Every malignancy's mean SII score and the standard deviation are shown in **Table 2**.

Comparison between Discharged and Exitus Patient Groups

61.69% (n=95) of the discharged patients and 61.94% (n=96) of the deceased patients were male, and no statistically significant difference was found between the two groups (p=0.964). When examined in terms of age differences between the two groups, the median of Group 1 was 73 years, while the median of Group 2 was 72 years. The median age of the two groups did not show a statistically significant difference (p=0.706).

Table 1: Evaluation of all patients and comparison between patient groups

Variables	All Hospitalizations (n=309)	Alive (n=154)	Exitus (n=155)	Statistical significance
Gender				0.964
Male	191 (61.81%)	95 (61.69%)	96 (61.94%)	
Female	118 (38.19%)	59 (38.31%)	59 (38.06%)	
Age (years)	70.14±14.31 (72)	70.18±14.87 (73)	70.1±13.78 (72)	0.706
Hospitalization Duration (days)	15.71±15.03 (11)	12.79±13.93 (8)	18.61±15.55 (15)	<0.001
Neutrophil count (10^9/L)	7.95±5.74 (6.69)	6.81±4.41 (5.95)	9.09±6.64 (7.78)	0.001
Lymphocyte count (10^9/L)	1.1±0.81 (0.96)	1.25±1 (1.13)	0.95±0.53 (0,84)	<0.001
Platelet count (10^9/L)	231.41±139.52 (212)	235.36±135.62 (209.5)	227.48±143.61 (213)	0.785
Hemoglobin (g/dL)	10.09±2 (10)	10.21±2.11 (10.1)	9.97±1.88 (9.8)	0.302
Albumin (g/dL)	2.77±0.67 (2.6)	3.08±0.69 (3)	2.45±0.46 (2,4)	<0.001
SII	2338.21±3134.14 (1536.56)	2095±3671.24 (1085.41)	2579.84±2477.34 (1891.23)	<0.001
Mortality	155 (50.16%)			

SII: systemic immune-inflammation index

Table 2: Types of malignancies in hospitalized patients

Types of Malignancy	Patient Count (Column Percent) (n=309)	Alive (Row Percent) (n=154)	Exitus (Row Percent) (n=155)	SII (Mean±SD)
Lung	55 (17.80%)	30 (54.55%)	25 (45.45%)	2234.82±2457.879
Gastric	45 (14.56%)	17 (37.78%)	28 (62.22%)	2366.97±1953.002
Colorectal	41 (13.27%)	25 (60.98%)	16 (39.02%)	1920.86±1858.45
Pancreas	32 (10.36%)	16 (50.00%)	16 (50.00%)	1747.66±1523.459
Breast	23 (7.44%)	11 (47.83%)	12 (52.17%)	2046.60±1930.764
Prostate	23 (7.44%)	10 (43.48%)	13 (56.52%)	2775.35±2389.322
Hepatocellular	13 (4.21%)	5 (38.46%)	8 (61.54%)	2530.57±1717.702
Ovarian	12 (3.88%)	4 (33.33%)	8 (66.67%)	2108.73±1437.407
Skin	9 (2.91%)	5 (55.56%)	4 (44.44%)	5156.59±6292.337
Larynx	9 (2.91%)	6 (66.67%)	3 (33.33%)	8441.31±11720.56
Brain	8 (2.59%)	6 (75.00%)	2 (25.00%)	1454.96±939.9612
Cholangiocellular	8 (2.59%)	1 (12.50%)	7 (87.50%)	1452.52±1307.536
Renal	6 (1.94%)	4 (66.67%)	2 (33.33%)	1827.49±1661.831
Head and Neck Tumors	5 (1.62%)	3 (60.00%)	2 (40.00%)	2675.26±1208.922
Cervix	5 (1.62%)	4 (80.00%)	1 (20.00%)	3260.31±5438.002
Endometrium	5 (1.62%)	2 (40.00%)	3 (60.00%)	5153.71±6621.9
Oesophagus	5 (1.62%)	2 (40.00%)	3 (60.00%)	2376.42±1444.313
Bladder	3 (0.97%)	1 (33.33%)	2 (66.67%)	3664.44±2450.972
Soft Tissue	2 (0.65%)	2 (100.00%)	0 (0.00%)	1798.43±1672.861

SD: Standard Deviation, SII: systemic immune-inflammatory index

While the discharged patients were hospitalized for a median of 8 days, the median hospitalization period of the patients who died was 15 days, and the patients who were discharged were hospitalized for significantly longer (p<0.001).

The median neutrophil count of surviving patients was 5.95, the median neutrophil count of the deceased patients was 7.78, and the median neutrophil count was statistically significantly higher in patients who died (p=0.001). The median lymphocyte count of Group 1 was 1.13, and the median of Group 2 was 0.84; the lymphocyte count of the patients who died was statistically significantly lower (p<0.001). There was no statistically significant difference between platelet counts (p=0.785).

When the SII values were calculated, the median SII value of the patients who did not die was 1085.41, and the median SII value of the patients with mortality was calculated as 1891.23. There was a statistically significant difference between the SII values of the two groups. (p<0.001) (**Table 1**).

Prognostic Value of the SII in Terms of Mortality

To determine the best cut-off value for the mortality distinction ability of the SII, a ROC curve analysis was used [AUC 0.623 (0.032), %95 CI = 0.560-0.685, p<0.001]. The cut-off value for the SII was found to be 1426.29 with 65.8% sensitivity, 59.7% specificity, 62.2% positive predictive value, 63.4% negative predictive value, and 62.8% test accuracy (OR = 2.856, %95 CI = 1.798-4.535, p<0.001) (**Table 3** and **Figure 1**).

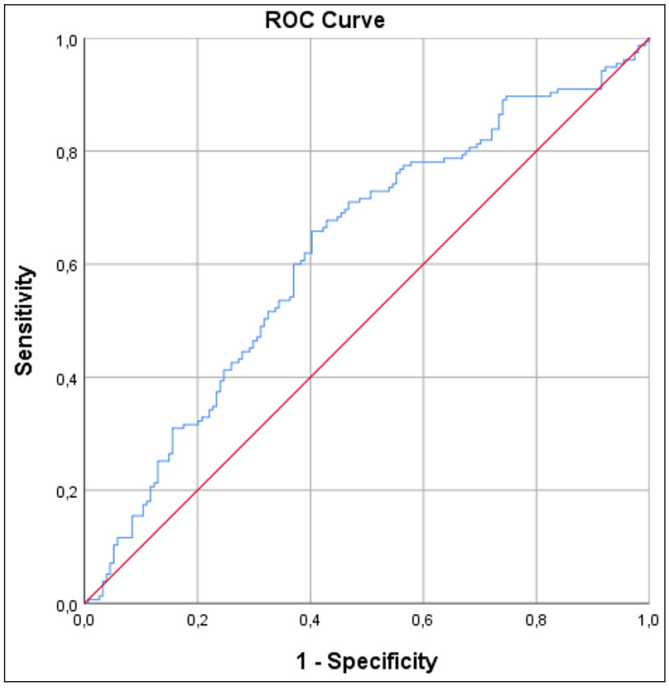

Figure 1: ROC analysis of SII and mortality

Table 3: SII cut-off values for mortality prediction in palliative care patients with malignancy

Variables	Cut-Off	Diagnostic Values					ROC Curve			Odds ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	Area (SE)	%95 CI	p	Odds ratio	%95 CI	p
SII	≥1426.29	65.8%	59.7%	62.2%	63.4%	62.8%	0.623 (0.032)	0.560-0.685	<0.001	2.856	1.798-4.535	<0.001

SII: systemic immune-inflammation index CI: Confidence interval, PPV: positive predictive value, NPV: negative predictive value, SE: standard error, ROC: Receiver Operating Curve

The SII values predicted mortality in cancer patients hospitalized in the palliative care service. A patient with an SII value of 1426.29 or above was about 1.8 times more likely to die during hospitalization than a patient below 1426.29.

DISCUSSION

In the PCU, advanced-stage cancer patients who have no chance of curative cancer treatment and receive supportive or maintenance treatments are usually hospitalized (12). Therefore, high mortality in this patient population is an expected result. Predicting this mortality may benefit the patient, their relatives, and clinicians. Providing early palliative support in patients with advanced cancer using mortality predictors is very important in positively affecting the patient's quality of life and increasing survival (13-16). In this study, we investigated whether SII can evaluate and predict mortality in patients with cancer receiving palliative care in PCU. We demonstrated that SII could accurately predict death in this patient group. We found that the probability of mortality was 1.8 times higher in patients with an SII value of 1426.29 and above.

Markers that can predict mortality for cancer patients in PCU may provide clinicians with significant benefits in intensifying supportive treatments to support patients' quality of life and reduce mortality rates (17). For these purposes, some prognostic indexes have been developed and are also used by clinicians (18). Feliu Prognostic Nomogram (FPN), Palliative Performance Scale (PPS), Palliative Prognostic Index (PPI), and Palliative Prognostic (PaP) Score are some of the prognostic indexes used in cancer patients (19,20). PaP score is a score calculated by the parameters of Clinical Prediction of Survival (CPS), Karnofsky Performance Status (KPS), total white blood count (WBC), lymphocyte percentage, anorexia, and dyspnea. PPI is calculated according to the criteria of PPS, nutritional status of the patient, edema, delirium, and dyspnea. FPN is calculated based on the time from the initial diagnosis to detection of terminal fatal disease, serum albumin, lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) performance status, and lymphocyte counts. PPS is a functional status measurement designed for use in palliative care. It has been shown that these indexes can successfully predict mortality in patients with cancer in palliative care (19). However, these indices are calculated based on clinician evaluations, laboratory parameters, clinical symptoms, signs, or combinations thereof. These calculations may present some difficulties and complexities for the clinician. The fact that SII can only be calculated with a simple peripheral blood cell count is an essential difference from other indices. From this perspective, we believe that SII will give a significant advantage to practitioners who cannot conduct further examinations and clinical assessments when estimating the mortality of cancer patients.

The SII, which can be easily calculated by the count of neutrophils, platelets, and leukocytes, is a biomarker showing systemic inflammatory activity (21). It is also useful in determining the balance between pro-tumor and anti-tumor immune status in cancer patients (10). Studies have found that SII is associated with mortality and prognosis in many cancer types, such as breast, stomach, esophagus, pancreas, and gastrointestinal stromal tumors (22-26). It has been found that it can be used as a prognostic marker in cancer patients, and its elevation is associated with poor outcomes (27,28). The results of our study are also in parallel with the results of these studies. In the literature, studies investigating the prognostic value of SII in cancer patients receiving palliative care regardless of cancer type are limited (29). In this study, we determined that SII could be a prognostic index independent of cancer subtype in cancer patients receiving palliative care.

The SII is a useful prognostic index for predicting mortality. However, the prognosis is not only related to the host's inflammatory response but also to the clinicopathological features of the tumor (30). The SII can evaluate the prognosis and mortality risk of cancer patients by reflecting the patient's immune-inflammatory status and may provide significant benefits to clinicians. In cancer patients, we think that more accurate prognostic predictions can be achieved by evaluating the patient's tumor characteristics, general condition, and additional comorbidities according to the clinician's experience and estimations, together with the SII.

The limitations of our study are that it was conducted retrospectively, was based on data from a single center, and involved a relatively small number of patients.

CONCLUSION

This study showed that high SII values could predict prognosis in cancer patients receiving palliative care in PCU. With this feature, SII can contribute to more reliable estimations when evaluated with clinicians' experience and other prognostic markers for estimating mortality in cancer patients receiving palliative care. The essential advantages of SII are that it can be easily calculated with only a peripheral blood cell count and that additional laboratory tests and clinical evaluations are unnecessary. We suggest calculating SII in all cancer patients hospitalized in PCUs, and monitoring patients with high values more closely. We believe that prospective studies with more patients should support our study results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.12.2022, Decision No: 2022-106).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have 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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