Research Article

Predictive Values of Systemic Inflammation Index in Prognosis of Patients with Laryngeal Cancer

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Abstract

Objectives: Laryngeal cancer is the most common cancer in head and neck cancer group, of which it constitutes 75%. Squamous cell carcinoma (SCC) is the most common histological subtype. Systemic or local inflammation is a well known promotor for cancer development and progression. Systemic immune inflammation index (S II) has been reported as an independent prognostic parameter in various cancers. We aimed to evaluate the capability of SII in predicting the risk of recurrence in patients with operable laryngeal cancer.

Methods: We retrospectively collected the data of 100 laryngeal SCC patients who underwent surgery between 2016 and 2018. Neutrophil, lymphocyte, and platelet (Plt) counts were recorded. The SII was calculated as follows: SII= Neutrophile counts *platelet counts/lymphocyte counts.

Results: SI index was found to be an independent prognostic factor as affecting disease recurrence (p<0.05). We found that patients with SII >891 had a risk of disease recurrence of approximately three times more than patients with SII = <891.78 (HR: 3.06 (95% CI: 3.42-132.64).

Conclusion: This was the first study to demonstrate that preoperative SI index is a simple and powerful independent predictive index that predicts the risk of disease recurrence in patients with laryngeal cancer.

Keywords: Disease free survival, laryngeal cancer, prognosis, systemic inflammation index

Laryngeal cancer is the most common cancer in the head and neck cancer group, of which it constitutes seventy-five percent. Squamous cell carcinoma (SCC) is the most common histological subtype.[1] According to data gathered from 2017, approximately 13360 new patients were diagnosed with laryngeal cancer, in addition to an estimated 3660 deaths due to complications stemming from laryngeal cancer. Fifty-three percent of the patients are diagnosed at the local stage.[2] The most important risk factors are smoking, alcohol and HPV status (especially for su-

praglottic tumors).[3-5] Quality of life in early-stage disease is the main factor determining the treatment approach. Larynx preserving methods are recommended in the early stages. Therefore, radiation therapy (RT) or endoscopic microsurgery are prefered in stages I and II, but total laryngectomy recommended in locally advanced disease.[6-7]

Systemic or local inflammation is well known for promoting cancer development and progression. Several studies have shown the relationship between inflammation and cancer development or progression.[8-10] Recently, the sys-

temic immune inflammation index (S II) (platelet counts × neutrophil counts/lymphocyte count) shown to act as an independent prognostic parameter in various cancers including nasopharyngeal carcinoma, small cell lung cancer, hepatocellular cancer, and renal cell carcinoma.[11–13] However, the SII for larynx cancer has not been reported, and little is known about its prognostic value for patients with laryngeal cancer. For these reasons, in this study, we aimed to evaluate the capability of SII to predict the risk of recurrence in patients with operable laryngeal cancer.

Methods

We retrospectively collected the data of 100 laryngeal SCC patients who underwent surgery between 2009 and 2018 in Umraniye Research and Training Hospital and Acıbadem University Medical Oncology Outpatient clinic. We obtained all the parameters from their preoperative complete blood counts (CBC). CBC testing was performed using an automated hematology analyzer (CELL-DYN 3700. Abbott. USA) prior to surgery. Neutrophil, lymphocyte, and platelet (Plt) counts were recorded.

The SII was calculated as follows: SII= Neutrophile counts * platelet counts/lymphocyte counts.

Exclusion Criteria

Patients who had any evidence of a heart disease (such as myocardial infarction, valvular heart disease,congestive heart failure), autoimmune disease (such as Behcet's disease or Hashimoto Thyroiditis) or suffered from an acute infection (patients with elevated White blood cell (WBC) count (>12.000/mL) or neutrophilia (>70%)), hematological diseases, and the patients who had nonsquamous histology or distant metastasis were excluded. Also, patients who used any drugs such as corticosteroids or immunosuppressive that could affect blood results were not included in the study.

Ethical Considerations

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all participants included in the study.

Ethics/institutional review board approval of research Faculty of Medicine, Acibadem University, Istanbul, Turkey. Number: 2018-17/21 Date: 08.11.2018

Statistical Analysis

R-3.5.0 program (R Core Team. 2018)* was used for statistical analysis. The variables were evaluated for normal dis-

tribution using the Shapiro Wilks test. Student t-test was used to evaluate descriptive statistical methods (mean. standard deviation, frequency) and quantitative data between two groups. Qualitative data was evaluated using the Chi-Square test and Continuity (Yates) Correction. Survival curves were calculated by the Kaplan-Meier method. To evaluate the optimal cut-off value for SII in predicting the risk of recurrence receiver operating characteristic (ROC) analysis was performed. All p values were 2-sided in the tests and p values of 0.05 were considered statistically significant. Multivariate analysis was carried out using the Cox proportional hazards model to assess the effect of prognostic factors on survival.

* R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna. Austria. URL https://www.R-project.org/.

Results

Ninety-seven of one -hundred patients were male (97%) and the median age was 59 (range 39-79 years). Twenty-nine patients were poorly differentiated (29%), forty-two (42%) patients had intermediate differentiation and 29 (29%) patients were well differentiated. Forty-one of the patients were post-operative AJCC stage I, three were stage II, 28 were stage III, and 28 were stage IV. Perineural invasion and lymphovascular invasion were detected in fifty-six and twenty-one patients respectively. Sixty -eight patients received adjuvant chemoradiotherapy. Radiotherapy was performed a total of 60 grays in 30 fractions for six weeks. Concurrently, cisplatin was administration dosing as 100 mg/m^2/day every three weeks or 35 mg/m^2/day weekly. Thirty-two patients did not receive any adjuvant treatment. The data for demographic and clinicopathologic findings and preoperative complete blood count results were outlined in Tables 1 and 2, respectively.

Median follow up time was 50 months (min 1 months-max 108 months). During follow-up, the recurrent disease was detected in thirteen patients, and three patients died. The ideal cut-off value of SII that predicted the risk of recurrence was 891.78 in the ROC analysis [AUC: 0.82 (0.80-0.94)/p<0.01] with a sensitivity of 84% and specificity of 84 (Fig. 1). There were 76 (76%), and 24 (24%) patients in SII ≤891, and SII>891, respectively based on the SII cut off value. Recurrence was detected in 3 patients with SII ≤891, however, ten of 24 patients with SII >891.There was a statistically significant difference between the two groups (p<0.01, Fig. 2). Univariate and multivariate analysis results are summarized in Table 3. N stage, T stage, and SI index were found as the prognostic factors affecting disease recurrence (p<0.05). In multivariate analysis, only the SI index was found to be an in-

Table 1. Demographic and Clinicopathological findings

	SII		
	≤891 (n=76)	>891 (n=24)	p
Gender, %			
Male	73 (96.05)	24 (100)	-
Female	3 (3.95)	0 (0)	
Age (years)			
Mean±SS	59.01±9.68	59.83±9.63	10.72
T stage, %			
T1	10 (13.16)	2 (8.33)	20.23
T2	29 (38.16)	2 (8.33)	
T3	32 (42.11)	9 (37.51)	
T4	5 (6.57)	11 (45.5)	
N stage, %			
N0	47 (61.84)	3 (32.5)	3~1
N1	29 (38.16)	21 (67.5)	
AJCC stage* (n=97), %			
I	32 (43.24)	9 (39.13)	20.20
III	20 (27.03)	8 (34.78)	
IV	22 (29.73)	6 (26.09)	

[1]Student-t Test; [2]Chi-Square; [3]Chi-Square and Continuity (Yates) Correction; *Patients with AJCC stage 2 were the small number. Therefore excluded from statistical analysis.

Table 2. Preoperative Complete Blood Counts Results

Laboratory parameters	Median (Min-Max)
Hemoglobin (g/dL)	14.6 (11.7-17.5)
Neutrophile (ц/L)	4800 (2210-10400)
Lymphocte (ц/L)	2240 (610-4120)
Platelet (ц/L)	259500 (155000-450000)
Neutrophile/Lymphocte	2.24 (0.84-8.22)
Sytemic Inflamation Index	612.31 (198.61-3121.41)

Figure 1. The ideal cut-off value of SII that predicted the risk of recurrence was 891 in the ROC analysis with a sensitivity of 84% and specificity of 84.

Figure 2. Kaplan meier survival curves according to SII groups and the patients with SII >891 had a higher risk of disease recurrence than patients with SII ≤891.

dependent prognostic factor as affecting disease recurrence (p<0.05). We found that patients with SII >891 had a risk of disease recurrence of approximately three times more than patients with SII ≤891 (HR: 3.06 (95% CI: 3.42-132.64).

Discussion

Our study is a report describing prognostic models based on peripheral neutrophil, platelet, and lymphocyte counts. SI index is a simple, inexpensive and feasible prognostic model in clinical practice. In literature, SII has been reported to have significant prognostic significance in various solid malignant tumors.[11-13] In the present study, SII was shown to be an independent predictor of recurrence for patients with laryngeal cancer after surgery for the first time in literature.
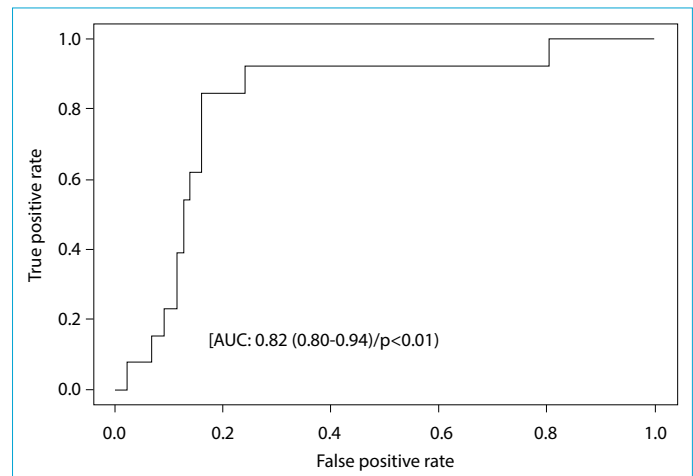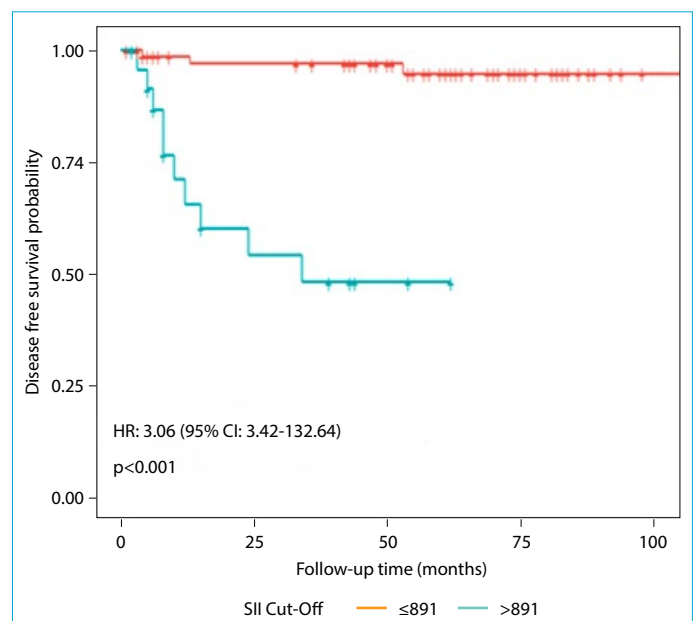
Several studies have reported on the importance of inflammation-based markers in patients with stage I-IV laryngeal cancer. Summer et al. showed that the prognostic value of the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) laryngeal cancer patients. In that trial, PLR and RWD have been reported to be poor prognostic values that increase the risk of local recurrence in laryngeal cancer.[14] In another trial, Yan et al. found that NLR was an independent prognostic factor in patients with laryngeal cancer undergoing total laryngectomy.[15] Hu et al. defined that systemic

Table 3. Univariate and Multivariate Cox regression analysis results

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95 %CI)	p	HR (95% CI)	p
Gender				
Female vs Male	3.24 (0.42-25.01)	0.26	7.40 (0.61-90.43)	0.59
Age (years)	1.01 (0.94-1.06)	0.88	1.02 (0.92-1.05)	0.12
N stage				
N1 vs N0	16.12 (2.09-124.60)	<0.01	7.01 (0.78-63.41)	0.08
T stage* (n=88)				
T2		Ref.	-	
T3	3.32 (0.37-29.72)	0.283	-	
T4	31.20 (3.80-256.32)	<0.01	-	
AJCC stage**				
I		Ref.	-	
III	8.25 (0.96-70.74)	0.054	-	
IV	7.31 (0.82-65.65)	0.07	-	
SII				
>891 vs ≤891	16.50 (4.44-61.33)	<0.01	3.06 (3.42-132.64)	<0.01

HR: Hazard ratio; CI: Confidence interval; *In the Cox analysis performed with the only univariate analysis, the T1 stage was excluded because the recurrence dispersion of T stages was not good. Therefore, 88 patients with Stage T2, T3, and T4 were analyzed; **Cox analysis could not be performed with multivariate analysis as the recurrence rate was not good dispersion in AJCC stages.

inflammation index related to prognosis in patients with hepatocellular carcinoma. Statistically, SII was found to be superior to NLR and PLR.[13] Inflammatory based indices evaluated in two studies including patients with esophageal squamous cell carcinoma. SII, PLR, and NLR have been shown to be predictor indexes for survival. In the study of Gang et al. the PLR was superior to NLR for predicting prognosis. In the other study, high SII was associated with poor progression-free survival and overall survival.[16,17] Chen JH et al. showed the prognostic value of NLR, PLR, and SII in patients with colorectal cancer. The overall survival (OS) and disease-free survival (DFS) were worse in patients with elevated NLR, PLR, and SII. But only SII was found to be an independent predictor of OS and DFS by multivariate analysis. In this study, researchers concluded that SII was a more powerful index for predicting survival outcome in patients with colorectal cancer.[18] In another trial, Yang et al. evaluated systemic inflammation index as a predictor for survival in patients with colorectal cancer who received neoadjuvant chemoradiotherapy. Conversely, Researchers did not find SII as an independent predictor index for survival but reported NLR.[19] In our trial, We found that SII as an independent predictive index that predicts the risk of disease recurrence in patients with laryngeal cancer. This risk was approximately 3-folds higher in patients with high SI index.

There were some limitations to this study. First, the relatively low number of patients may have caused selection bias. Therefore, a large-scale prospective validation study is required to validate the results of the present study. Second, only the patients who received radical surgery were enrolled and thus, the results of the present study are not applicable for incurable patients or those treated with definitive chemoradiotherapy. As a positive point, we included patients with laryngeal cancer who underwent curative surgery. Also, we excluded patients who had confounding factors such as heart disease (myocardial infarction, valvular heart disease, and congestive heart failure), autoimmune disease or suffered from an acute infection, and hematological disease. Therefore, in our study, we showed that the prognostic value of inflammatory-based indices in a more specific patient population.

Conclusion

In conclusion, this was the first study to demonstrate that preoperative SII is a simple and powerful independent predictive index that predicts the risk of disease recurrence in patients with laryngeal cancer. A larger prospective study is warranted for the validation of the preliminary results obtained in the present study.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.D.; Design – A.D., O.A.; Supervision – O.A.; Materials – A.D., M.S.; Data collection &/or processing – A.D., M.S.; Analysis and/or interpretation – O.A.; Literature search – A.D., O.A.; Writing – A.D.; Critical review – O.A.

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