Cohort Study

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Prognostic value of systemic inflammation score in patients with esophageal cancer

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Introduction: The systemic inflammatory score (SIS), a new inflammatory marker based on a combination of the lymphocyte-to-monocyte ratio (LMR) and serum albumin concentration, has been reported to be a useful prognostic marker for several malignancies. The authors conducted this retrospective study on data from a cohort of esophageal cancer patients undergoing potentially curative resection to clarify the value of SIS as a prognostic marker for clinical outcome in this population.

Methods: This retrospective cohort study included 32 patients who underwent thoracoscopic esophagectomy after neoadjuvant chemotherapy for esophageal cancer between January 2016 and December 2019. Blood samples were collected within one week prior to the initiation of preoperative chemotherapy. Three inflammatory and nutritional markers; SIS, the neutrophil-to-lymphocyte ratio (NLR), and prognostic nutrition index (PNI) were examined in this study. Disease-free survival was assessed using the Kaplan–Meier method, and univariable and multivariable Cox models were applied to evaluate the predictive value of SIS, NLR and PNI.

Results: NLR and PNI were not associated with recurrence, while SIS scores of 1 and 2 were significantly associated with recurrence. In multivariate analysis, SIS scores of 1 or 2 were found to be independently associated with recurrence, each with a hazard ratio of 1.98. In addition, when examining immunologic and nutritional factors and survival rates, there was no significant difference in the survival rate for NLR and PNI; for SIS, however, the survival rate was significantly worse in patients with SIS scores of 1 or 2.

Conclusions: The authors demonstrated that a novel and easily obtained prognostic score, termed SIS, based on pre-treatment serum albumin and LMR, can serve as an independent prognostic factor in postoperative esophageal cancer patients. It could be incorporated into conventional clinical and pathological algorithms to enhance the prognostic accuracy in this population.

Keywords: esophageal cancer, the systemic inflammatory score

Introduction

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer-related mortality[1]. Despite recent advances in multidisciplinary treatment strategies, the outcomes of esophageal cancer treatment remain unsatisfactory.

Inflammation contributes to cancer development and growth of cancer[2,3]. Previous studies have reported that a systemic inflammatory response is associated with cancer progression[3]. Inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and the lymphocyte-to-monocyte ratio (LMR) have been reported to be associated with clinical outcomes in patients with various types of cancer[4,5]. Recently, the systemic inflammatory score (SIS), a new inflammatory marker based on the combination of LMR and serum albumin concentration, has been reported to be a useful prognostic marker for patients with clear cell renal cell carcinoma and colorectal cancer[6,7]. However, SIS is still a relatively new concept, and its prognostic value in patients with esophageal cancer has not been reported.

We conducted this retrospective study in a cohort of esophageal cancer patients undergoing potentially curative resection and clarified that SIS may improve the prognostic accuracy for clinical outcomes in esophageal cancer patients.

HIGHLIGHTS

- We demonstrated that a novel and easily obtained prognostic score, termed systemic inflammatory score (SIS).
- It can serve as an independent prognostic factor in esophageal cancer patients.
- Enhancing immune and nutritional status may be an effective target.

Patients and methods

Patients

This retrospective cohort study included 32 patients who underwent thoracoscopic esophagectomy after neoadjuvant

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Table 1

Clinical and pathologic characteristics

	All cases ($n = 32$)
Age (mean years)	65.5
Sex, *n* (%)	
Male	28 (87.5)
Female	4 (12.5)
Stage, *n* (%)	
II	11 (34.4)
III	21 (65.6)
NAC, *n* (%)	
FP	29 (90.6)
DCF	3 (65.6)
SIS, *n* (%)	
0	10 (31.4)
1,2	22 (68.6)
NLR, *n* (%)	
< 2.5	16 (50.0)
≥ 2.5	16 (50.0)
PNI, *n* (%)	
≥ 50	20 (62.6)
< 50	12 (37.5)

DCF, docetaxel with fluoropyrimidine plus platinum; FP, fluoropyrimidine plus platinum; NAC, neoadjuvant chemotherapy; NLR, the neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index; SIS, systemic inflammation score.

chemotherapy for esophageal cancer between January 2016 and December 2019. Patients in this study included esophageal cancer patients with histologic types of squamous cell carcinoma and adenocarcinoma, and excluded patients with esophagogastric junction tumors, patients with incomplete follow-up and patients with recurrent disease. All patients provided written informed consent. The institutional review board at our center approved the study protocol.

Methods

In this study, neoadjuvant therapy were conducted in cStage II and cStage III for esophageal cancer patients. One or two cycles of chemotherapy were conducted. Computed tomography (CT) scan and endoscopy were used to assess the response to neoadjuvant therapy. No patient was given as adjuvant therapy after esophagectomy. Blood samples were collected within one week prior to the initiation of preoperative chemotherapy. Three inflammatory and nutritional markers—SIS, NLR, and prognostic nutrition index (PNI)—were examined in this study. LMR was calculated by dividing the absolute number of circulating lymphocytes by the absolute number of circulating monocytes. The SIS was defined according to the methods of a previous report[6], using a combination of the LMR and serum albumin concentration: patients with LMR greater than 4.44 and serum albumin level greater than 4.0 g/dl were given a score of 0; patients with LMR less than or equal to 4.44 or serum albumin level less than or equal to 4.0 g/dl were given a score of 1; and patients with LMR less than or equal to 4.44 and 4 with a serum albumin level less than or equal to 4.0 g/dl were assigned a score of 2.

NLR is the neutrophil-to-lymphocyte ratio in peripheral blood and has been found to have a cut-off value of 2.5[8]. PNI was calculated using the following formula: (10 × albumin) + (0.005 × lymphocyte count). Based on previous reports, a cut-off value of 50 was used[9]. Disease-free survival was assessed using the Kaplan–Meier method, and univariate and multivariate Cox models were used to evaluate the predictive value of SIS, NLR,

Table 2

The association with recurrence

	Recurrence –	Recurrence +	Univariate *p* value	Multivariate *p* value	Multivariate HR (95% CI)
SIS					
0	8	2	0.02	0.01	1.98 (0.02–1.31)
1,2	7	15			
NLR					
< 2.5	9	7	0.792		
≥ 2.5	6	10			
PNI					
≥ 50	9	11	0.58		
< 50	6	6			
Stage					
II	6	5	0.71		
III	9	12			
Histological type					
SCC	15	15	0.49		
Adenocarcinoma	0	2			
Neoadjuvant chemothrapy					
FP	13	16	0.59		
DCF	2	1			
Resection margin status					
R0	15	17	1		
R1	0	0			

The statistical tests: multiple logistic regression analysis.

DCF, docetaxel with fluoropyrimidine plus platinum; FP, fluoropyrimidine plus platinum; HR, hazard ratio; NLR, the neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index; SCC, squamous cell carcinoma; SIS, systemic inflammation score.

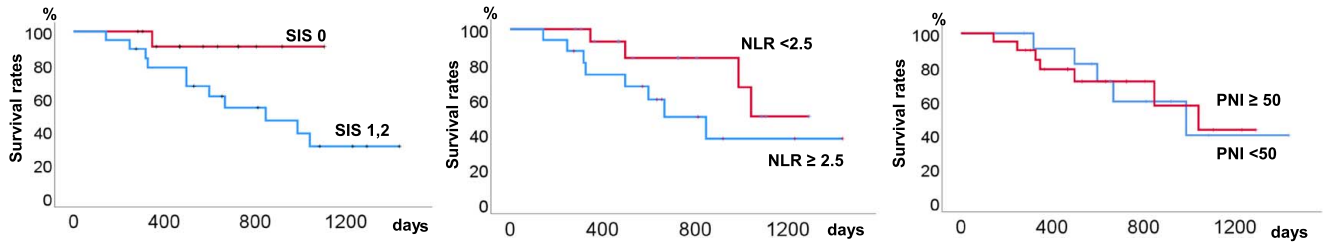

Figure 1. There was no significant difference in survival rate for NLR and PNI, but the survival rate was significantly worse in elevated-SIS patients. NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index; SIS, systemic inflammatory score.

and PNI. This study is reported according to STROCSS criteria[10]. The clinicopathological findings and cancer staging were made according to the criteria of the 12th edition of the Guidelines of the Japanese Society for Esophageal diseases. The average interval between neoadjuvant therapy and surgery was 1 month.

Results

Patient characteristics

The clinical and pathological characteristics of all the patients are summarized in Table 1. Of the 32 patients, 28 (87.5%) were males and four (12.5%) were females. The median age of the entire cohort was 65.5 years (range, 60–81 years). The median follow-up period was 26 months (range, 4.8-85 months). The pre-treatment clinical stage was stage 2 in 11 patients and stage 3 in 21 patients. Preoperative chemotherapy was Fluoropyrimidine plus platinum (FP) in 29 patients and Docetaxel with Fluoropyrimidine plus platinum (DCF) in three patients. The proportions of patients with pre-chemotherapy SIS, NLR, and PNI values are shown in Table 1.

The association with recurrence

NLR and PNI showed no association with recurrence, while SIS 1 and 2 were significantly associated with recurrence. Multivariate analysis showed that SIS 1 and 2 were independently associated with recurrence, with hazard ratio of 1.98 (Table 2). In addition, when examining the impact of each immunological and nutritional factor on survival rate, there was no significant difference in NLR and PNI, whereas the survival rate was significantly worse in patients with SIS 1 and 2 (Fig. 1).

Discussion

We investigated the clinicopathological characteristics and prognosis of 32 esophageal cancer patients using hematological and laboratory markers of nutritional condition and systemic inflammatory responses. We demonstrated that a new prognostic score termed the SIS, based on a combination of serum albumin and LMR after dichotomization, was associated with recurrence free survival in patients with esophageal cancer in multivariate analysis.

Recent evidence suggests that systemic inflammatory responses play an important role in cancer progression[11]. Markers based on systemic inflammation, such as NLR and PLR, have been reported to be useful in predicting the outcomes of cancer patients[12–17]. In the present study, a novel SIS based on preoperative serum albumin and LMR was explored in patients with esophageal cancer. The data indicated that the SIS could predict recurrence in patients with esophageal cancer after esophagectomy.

Recent evidence indicates that monocytes can be recruited to tumor tissues and can differentiate into tumor-associated macrophages (TAMs) that exert pro-tumoral action[18]. Lymphocytes can enhance cancer immune surveillance by inhibiting tumor cell proliferation, invasion and metastasis[19]. A decrease or deficiency in circulating lymphocytes may be due to an inadequate immune response to tumors, whereas an increase in circulating monocytes may reflect increased production of TAMs and a higher tumor burden.

Albumin is synthesized in the liver. In a state of systemic inflammation, the ability to synthesize albumin is reduced, resulting in hypoalbuminemia[20]. Therefore, low serum albumin level is associated with ongoing systemic inflammation. As persistent systemic inflammation promotes cancer progression[2,11], hypoalbuminemia is associated with poor survival[21]. Although the impact of SIS on esophageal cancer prognosis in patients with preoperative complications was not clear in this study, SIS could be integrative tool that can predict a patient's preoperative status, including preoperative complications. There were several limitations in present study. First, it was a retrospective study that caused some biases. Second, subjects were recruited in a single center and small sample size. Large-scale multicenter studies are required to enhance the reliability. Third, the follow-up period is short.

Conclusion

In conclusion, we have demonstrated that a novel and easily obtained prognostic score termed SIS, based on pre-treatment serum albumin and LMR, can serve as an independent prognostic factor in postoperative esophageal cancer patients. It can easily be incorporated into conventional clinical and pathological algorithms to enhance the prognostic accuracy in this population.

Although there are limitations due to the retrospective nature of the analysis, our study found a significant association between elevated SIS and esophageal cancer recurrence. This marker appears to reflect the association between the host immune and nutritional status and cancer recurrence. Likewise, Enhancing immune and nutritional status may be an effective target in esophageal cancer patients. We hope that further basic research studies will be performed to identify the detailed mechanisms by which inflammatory cells and mediators are involved in the pathogenesis and progression of esophageal cancer.

Ethical approval

Ethical approval for this study was provided by the Ethical Committee of the Institutional Review Board of Nagasaki Medical Center in accordance with the Declaration of Helsinki (Number 230130 Date: 20/11/2023).

Consent

Written informed consent was obtained from all the patients for publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

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Author contribution

A.Y.: principal investigator and writing the draft. R.O., S.R., K.Y., S.F., T.K., A.K., N.S., H.T., and S.M. participated in article drafting and supervision. T.K.: reviewing and editing.

Conflicts of interest disclosure

The authors declares no conflicts of interest.

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Not applicable.

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