Ann Surg Oncol (2019) 26:4773–4781
https://doi.org/10.1245/s10434-019-07914-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Modified Systemic Inflammation Score is Useful for Risk Stratification After Radical Resection of Squamous Cell Carcinoma of the Esophagus

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ABSTRACT

Background. Inflammation plays a critical role in the development and progression of cancers. We evaluated the clinical significance of the preoperative modified systemic inflammation score (mSIS) to predict long-term outcomes of patients with esophageal squamous cell carcinoma (ESCC).

Methods. We included 443 patients who underwent curative resection of ESCC. The mSIS was formulated according to the serum albumin level (ALB) and lymphocyte-to-monocyte ratio (LMR) as follows: mSIS 0 (ALB $\geq$ 4.0 g/dL and LMR $\geq$ 3.4), mSIS 1 (ALB $<$ 4.0 g/dL or LMR $<$ 3.4), and mSIS 2 (ALB $<$ 4.0 g/dL and LMR $<$ 3.4).

Results. Patients were categorized into preoperative mSIS 0 (n = 165), mSIS 1 (n = 183), and mSIS 2 (n = 95) groups. Preoperative mSIS was significantly associated with age, preoperative body mass index, and pathological disease stage. The disease-specific survival times of patients in preoperative mSIS 0, 1, and 2 sequentially shortened (P = 0.009), and mSIS 2 was identified as an independent prognostic factor (hazard ratio 2.63, 95% confidence interval 1.33–5.27, P = 0.0053). In most patient subgroups, the mSIS was associated with greater risk of disease-specific death. A stepwise increase in the prevalence of hematogenous recurrences was directly proportion to the mSIS. When patients were subdivided by mSIS before neoadjuvant treatment, there were no significant differences in disease-specific survival.

Conclusions. Our findings demonstrate that the preoperative mSIS may serve as a powerful prognosticator of ESCC that definitively stratifies clinical outcomes as well as a tool for selecting treatment strategies.

Esophageal cancer is the sixth most common cause of cancer death worldwide and is therefore a major global health challenge.[1]. Esophageal squamous cell carcinoma (ESCC) accounts for 70% of cases of esophageal cancer and is particularly common in Asian countries.[2,3] ESCC is a highly aggressive malignancy of digestive tissue, which is characterized by rapid tumor growth and early metastasis.[2,4] Despite progress in radical resection and perioperative treatment, the 5-year overall survival rates of patients with ESCC range from 20% to 40%, emphasizing an urgent need to identify effective prognosticators.[5] An ideal prognosticator will have high accuracy that can be determined preoperatively and would help to guide surgery or adjuvant treatment.

The hallmark of cancer-associated inflammation involves the infiltration of tumor tissues with inflammatory cells and the production of mediators of inflammatory, which contribute to angiogenesis, restructuring of the extracellular

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07914-7) contains supplementary material, which is available to authorized users.

First Received: 14 July 2019;
Published Online: 11 October 2019

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matrix, and the formation of premetastatic niches.[6] Moreover, cancer-related inflammation alters the tumor microenvironment to increase the propensity for tumor recurrence and metastasis.[6,7] However, there is no widely accepted optimal value for circulating blood cell biomarkers or an established scoring system that integrates the biomarkers to refine the prognostic prediction of cancer patients. Moreover, there are no widely accepted markers of inflammation or established scoring systems that integrate the biomarkers to increase the accuracy of the prognostic prediction of patients with cancer. Recently, the systemic inflammation score (SIS), based on the preoperative serum albumin (ALB) level and the lymphocyte-to-monocyte ratio (LMR), represents a novel a scoring system to predict prognosis of malignancies such as clear-cell renal cell carcinoma, colorectal cancer, and gastric cancer.[8–10] Lin et al., who proposed the modified SIS (mSIS) to enhance predictive value, demonstrated its superiority to the original SIS when applied to gastric cancer.[11] We evaluated the clinical significance of the preoperative mSIS for predicting long-term outcomes after curative resection of ESCC.

METHODS

Patients

We screened consecutive patients (n = 655) with esophageal cancer who underwent esophagectomy at Nagoya University Hospital (Department of Gastroenterological Surgery) between February 2005 and December 2018, and we retrospectively collected data for 443 patients who met the inclusion criteria as follows: squamous cell carcinoma, R0 resection with systematic lymphadenectomy, follow-up for $\geq$ 3 months, and sufficient data for analysis (Fig. 1). Patients who underwent planned two-stage surgery were excluded. Written, informed consent in accordance with the requirements of the Institutional Review Board was granted by all patients for surgery and the use of their clinical data. The medical team preoperatively managed the general condition and comorbidities of the patients.

Patient Management

Routine preoperative screening included endoscopy, biopsy, and computed tomography (CT) of the neck to the pelvis. Neoadjuvant treatment with 5-fluorouracil and cisplatin was administered to patients with histologically proven clinical Stage II or III squamous cell carcinoma.[12] A routine blood test was performed 5 days before esophagectomy. Patients underwent esophagectomy with systematic lymphadenectomy according to tumor location, and the reconstruction method was determined at the surgeon's discretion according to the accessibility of the

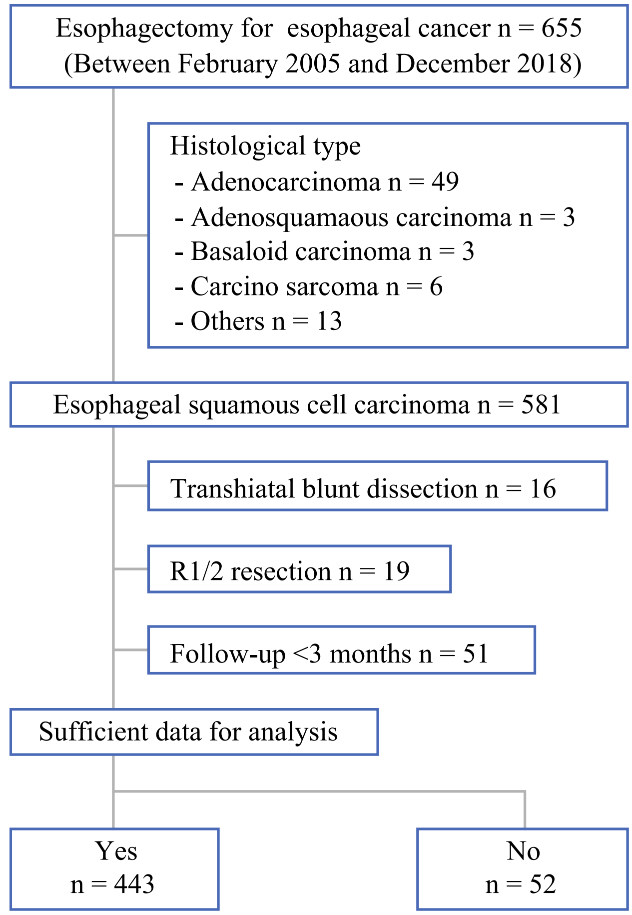


FIG. 1 Study design

stomach and general risk assessment.[13] Complications graded $\geq$ II of the Clavien-Dindo classification were regarded as clinically relevant.[14] Pathological staging was performed in accordance with the American Joint Committee on Cancer Staging Manual (8th edition).[15] Patients received postoperative follow-up that included physical examinations, laboratory tests, enhanced CT (chest and abdominal cavity) once every 6 months, and upper gastrointestinal endoscopy once annually for 10 years. Treatment after recurrence was determined according to the evidence available at the time of treatment, the patient's condition, and with the patient's consent.

Definition of mSIS

The mSIS was formulated according to the ALB and LMR scores as follows: (0) indicates patients with ALB $\geq$ 4.0 g/dL and LMR $\geq$ 3.4; (1) indicates those with ALB $<$ 4.0 g/dL or LMR $<$ 3.4; and (2) indicates those with ALB $<$ 4.0 g/dL and LMR $<$ 3.4.[11] We compared the performance of the modified Glasgow prognostic score (mGPS) with that of the mSIS.[16]

Statistical Analysis

The χ^2 and Mann–Whitney tests were used to compare patient groups. Survival curves were estimated using Kaplan–Meier analysis, and differences were evaluated using the log-rank test. The Cox proportional hazards model was employed to calculate the hazard ratio (HR) and 95% confidence interval (CI) as well as for multivariable analysis. Age, sex, and variables potentially associated with prognosis were included in the final model of multivariable analysis. Statistical analysis was performed using JMP 13 software (SAS Institute, Cary, NC), and $P < 0.05$ was considered statistically significant.

RESULTS

Patients' Characteristics

Demographic and preoperative characteristics of the selected 443 patients are presented in Supplementary Table 1. The mean (± standard deviation, SD) age was 66.1 ± 8.2 years, and the male-to-female ratio was 374:69. The middle thoracic esophagus was the most frequent tumor location (57.2%). Neoadjuvant treatment was administered to 266 (60.0%) patients, and 416 (93.9%) underwent subtotal esophagectomy. Pathological staging classified 148, 123, 122, and 50 patients with TNM stages 0/I, II, III, and IV, respectively. Median follow-up was 41.8 months.

Comparison of Clinicopathological Parameters of Each mSIS

The associations between the mSIS and clinicopathological parameters were evaluated. No significant differences were found for sex, history of other malignancies, macroscopic tumor size, and incidence of postoperative complications (Table 1). In contrast, the mSIS was significantly associated with age, preoperative body mass index, and pathological disease stage (Table 1).

Relevance of Preoperative mSIS for Long-Term Outcomes

The disease-specific, 5-year survival rates of patients assigned an mSIS of 0, 1, or 2 were 89.1%, 77.0%, and 69.2%, respectively; $P = 0.009$ (Fig. 2a). Patients with hypoalbuminemia had significantly shorter disease-specific survival than those without. LMR was not significantly associated with differences in survival (Fig. 2a), and mGPS was not significantly associated with disease-specific survival (Supplementary Fig. 1). Because mSIS has an advantage of being measurable before surgery, multivariate analysis was performed with preoperatively determined variables. Multivariable analysis identified mSIS 2 as an independent prognostic factor of disease-specific survival (HR 2.21, 95% CI 1.10–4.46, $P = 0.0266$) together with elevated serum SCC levels and clinical N factor (N1-3) (Table 2). Disease-free survival decreased according to mSIS (2-year survival rates of 84.0%, 71.6%, and 64.7%, respectively; $P = 0.0017$, Fig. 2b).

When we conducted subgroup analyses to further investigate the prognostic value of preoperative mSIS, we found that most subgroups of the mSIS 1 or mSIS 2 group were at greater risk of disease-specific death (Fig. 3a). Moreover, the HR associated with mSIS 1 or 2 was the highest (3.39; 95% CI, 1.68–7.55) in the subgroup aged < 70 years. In contrast, the mSIS had insufficient prognostic value for patient subgroups aged ≥ 70 years, body mass index ≥ 22, and tumor located at the lower or abdominal esophagus.

The overall recurrence rates of patients with mSIS 1 and mSIS2 were 30.1% and 30.5%, respectively, and were significantly higher compared with those with mSIS 0 (18.2%; $P = 0.0171$, Fig. 3b). The mSIS was significantly associated with the prevalences of hematogenous recurrences (mSIS 0, 1, and 2: 7.9%, 15.9%, and 21.1%, respectively; $P = 0.0069$; Fig. 3b).

Association Between Neoadjuvant Treatment and mSIS

Chemotherapy and radiation therapy influence on bone-marrow functions and nutrition status. Neoadjuvant treatment was administered to 266 (60.0%) patients, which raised the question of when is the best time to evaluate the mSIS before neoadjuvant treatment or surgery. The distribution of the mSIS before neoadjuvant treatment and surgery is shown in Fig. 3c. Migration rates were 51.7%, 45.1%, and 48.9% for mSIS 0, 1, and 2, respectively, before neoadjuvant treatment. When patients were subdivided according to the mSIS before neoadjuvant treatment, no significant differences were found in disease-specific survival times contrary to the preoperative mSIS (Fig. 3c), indicating that the preoperative mSIS may provide better performance as a prognosticator of patients with ESCC.

Next, we analyzed survival times and initial recurrence patterns exclusively in patients who underwent neoadjuvant treatment. The disease-specific survival became incrementally worse as the preoperative mSIS increased ($P = 0.0122$; Fig. 4a) and mSIS was significantly associated with the prevalences of hematogenous recurrences (mSIS 0, 1, and 2: 8.0%, 19.2%, and 21.1%, respectively; $P = 0.0425$; Fig. 4b) in common with analysis of the entire cohort.

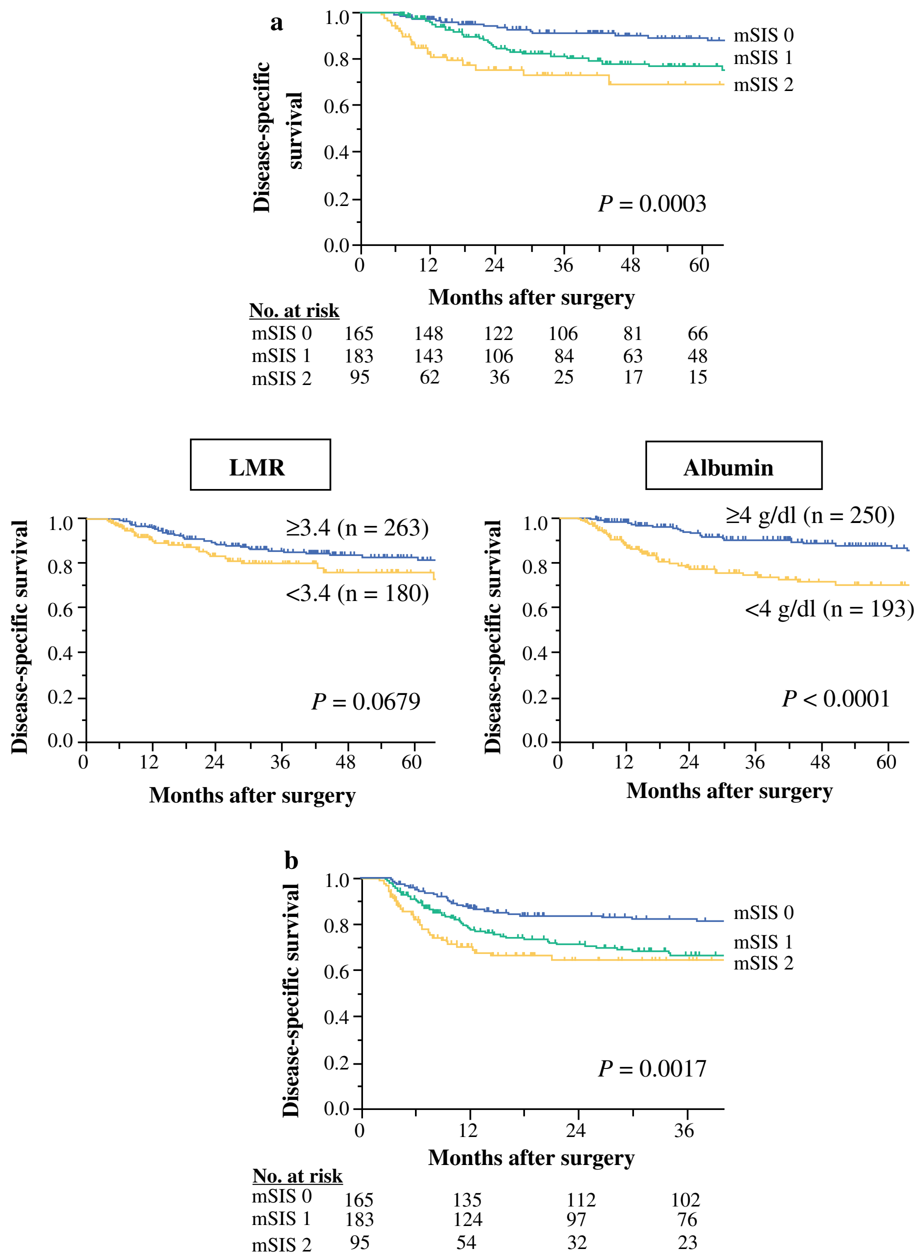
TABLE 1 Association between the modified systemic inflammation score (mSIS) and clinicopathological parameters

Characteristic		mSIS 0 (n = 165)	mSIS 1 (n = 183)	mSIS 2 (n = 95)	P
Age (year)	< 70 years	123	112	51	0.0014
	≥ 70 years	42	71	44	
Sex (male/female)	Male	138	155	81	0.9328
	Female	27	28	14	
History of other malignancies	Present	25	27	18	0.6444
	Absent	140	156	77	
Brinkman index	< 1000	117	137	69	0.7074
	≥ 1000	48	46	26	
Excessive alcohol consumption	Present	111	103	57	0.1046
	Absent	54	80	38	
Body mass index	< 22	100	120	74	0.0141
	≥ 22	65	63	21	
CEA (ng/ml)	< 5	154	165	79	0.0395
	≥ 5	11	18	16	
SCC (ng/ml)	< 1.5	138	117	42	< 0.0001
	≥ 1.5	27	66	53	
Tumor location	Cervical	7	9	6	0.1418
	Upper thoracic	22	21	10	
	Middle thoracic	103	98	44	
	Lower thoracic	29	48	33	
	Abdominal esophagus	4	7	2	
Tumor size (mm)	< 40	102	110	47	0.1294
	≥ 40	63	73	48	
Postoperative complication*	Present	53	77	33	0.1415
	Absent	112	106	62	
Tumor differentiation	Poorly differentiated	19	17	14	0.4023
	Others	146	166	81	
Lymphatic involvement	Present	85	95	57	0.3545
	Absent	80	88	38	
Vessel invasion	Present	32	48	22	0.3156
	Absent	133	135	73	
Pathological T factor	0/1	100	93	28	< 0.0001
	2	25	25	12	
	3	39	62	49	
	4	1	3	6	
Lymph node metastasis	Present	72	96	59	0.0145
	Absent	93	87	36	
Pathological stage	0/I	71	58	19	0.0002
	II	44	57	22	
	III	30	52	40	
	IV	20	16	14	

CEA carcinoembryonic antigen; *SCC* squamous cell carcinoma antigen

*Grade 2 or higher in the Clavien-Dindo classification

FIG. 2 **a** Comparison of survival according to the mSIS and its components: LMR and albumin. **b** Disease-free survival curves according to the preoperative mSIS. *LMR* lymphocyte-to-monocyte ratio; *mSIS* modified systemic inflammation score



DISCUSSION

We analyzed 443 patients with ESCC who underwent curative surgery and found that disease-specific and disease-free survival decreased incrementally in relation to the mSIS. The mSIS, which was associated with an increased risk of disease-specific death in the entire cohort and most of the subgroups, was identified by multivariable analysis as an independent prognostic factor. Moreover, a stepwise increase in the prevalence of hematogenous recurrences was significantly associated with the mSIS. This is the first study, to our knowledge, to describe the use of the mSIS according to ALB and LMR, which is rapidly measurable using preoperative routine blood tests as a prognosticator of patients with ESCC undergoing curative resection.

Several potential mechanisms may explain the prognostic values of SIS in ESCC. The LMR reflects the balance between the immunity of the host and the degree of tumor burden.[17] Lymphocytes play a key role in anticancer immunity, and a decreasing number of lymphocytes is associated with poor prognosis.[18] In contrast, monocytes contribute to cancer progression. Thus, circulating monocytes differentiate into macrophages in the cancer

TABLE 2 Preoperatively determined prognostic factors of disease-specific survival of 443 patients with esophageal cancer

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (≥ 70 year)	1.54	0.93–2.51	0.0938	1.56	0.94–2.59	0.0842
Male sex	1.44	0.78–2.48	0.2337	1.51	0.83–2.72	0.1754
History of other malignancies	1.39	0.73–2.47	0.2985			
Brinkman index (≥ 1000)	1.45	0.83–2.71	0.2044			
Excessive alcohol consumption	1.21	0.74–1.95	0.4467			
Preoperative body mass index (≥ 22)	0.66	0.37–1.12	0.1307			
Double cancer	0.96	0.49–1.73	0.8925			
Preoperative mSIS						
0	1.00	Referent		1.00	Referent	
1	2.01	1.11–3.78	0.0208	1.49	0.78–2.83	0.2273
2	3.63	1.89–7.09	0.0001	2.21	1.10–4.46	0.0266
CEA (> 5 ng/ml)	1.54	0.64–5.08	0.3689			
SCC (> 1.5 ng/ml)	2.50	1.54–4.05	0.0002	2.02	1.21–3.36	0.0067
Tumor location (Lt or Ae)	0.75	0.40–1.29	0.3016			
Tumor size (≥ 40 mm)	1.35	0.83–2.18	0.2290	0.93	0.55–1.56	0.7857
Clinical T factor (T3-4)	2.77	1.63–4.72	0.0002	1.28	0.67–2.44	0.4574
Clinical N factor (N1-3)	4.52	2.37–8.62	< 0.0001	4.13	1.84–9.29	0.0006
Neoadjuvant treatment	1.59	0.95–2.64	0.0752	1.46	0.80–2.65	0.2173

CI confidence interval; *mSIS* modified Systemic Inflammation Score; *CEA* carcinoembryonic antigen; *SCC* squamous cell carcinoma-related antigen

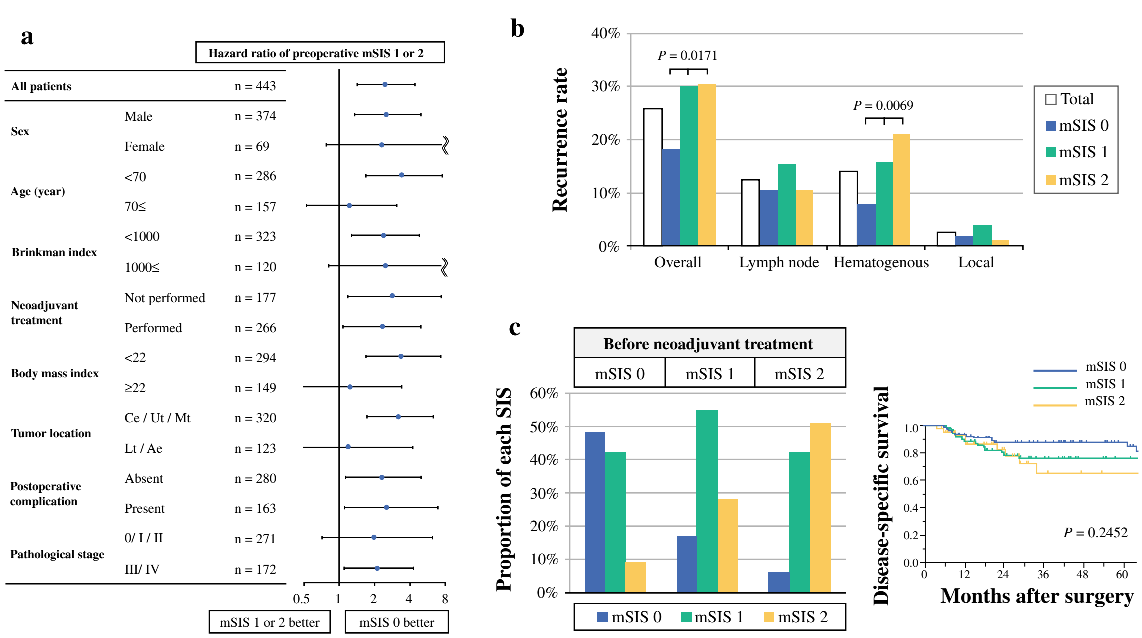


FIG. 3 **a** Forest plot to evaluate value of the association of the preoperative mSIS with disease-specific survival. **b** Frequencies of the sites of initial recurrence of each mSIS group. **c** Distribution of the mSIS before neoadjuvant treatment and surgery. Disease-specific survival curves of patients with mSIS 0, 1, and 2 before neoadjuvant treatment. *mSIS* modified systemic inflammation score

microenvironment.[6,18] Most macrophages in the cancer microenvironment have an M2-like phenotype and promote tumor growth, angiogenesis, and metastasis.[19,20] Thus, an increasing number of monocytes is associated with poor prognosis, which in turn accounts for the association of a low LMR with poor prognosis.

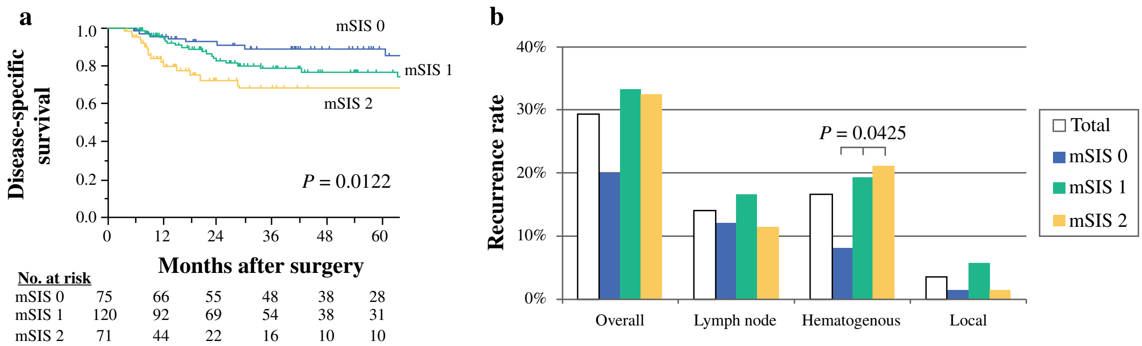


FIG. 4 **a** Disease-specific survival curves according to the preoperative mSIS in patients who underwent neoadjuvant treatment. **b** Frequencies of the sites of initial recurrence of each mSIS group in patients who underwent neoadjuvant treatment. *mSIS* modified systemic inflammation score

In the presence chronic of systemic inflammation, the ability of the liver to synthesize albumin decreases, causing hypoalbuminemia.[21,22] Therefore, a low serum albumin concentration is associated with ongoing systemic inflammation, which promotes cancer progression, culminating in poor survival.[8,23] Moreover, ALB is usually regarded as a good index for malnutrition and cachexia in patients with cancer. The mSIS, which is based on the LMR and the serum albumin level, may enable a better assessment of the effects of the tumor on ongoing systemic inflammation and malnutrition. The prognostic significance of markers of inflammation and hematological indices, including the GPS, mGPS, neutrophil–lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) have been evaluated in various malignancies.[24,25] The mSIS more precisely stratified patients compared with the mGPS in our present cohort, possibly representing a comprehensive reflection of systemic inflammation and malnutrition.

Chang et al., who conducted the first study of the prognostic impact of the SIS, modified the SIS to incorporate ALB and LMR.[8] They reported that a high preoperative SIS is significantly associated with aggressive tumor behavior and serves as an independent prognostic factor of clear-cell renal cell carcinomas.[8] Subsequently, the SIS as a clinically significant predictor of postoperative complications and prognosis was reported for malignancies such as colorectal cancer and gastric cancer.[10,21] For example, Suzuki et al. compared the SIS with the mGPS of patients with colorectal cancer and found that the predictive performance of the SIS was superior to that of the mGPS, consistent with our present findings.[26] Lin et al. used X-tile software to determine that the optimal cutoff value of LMR is 3.4 for predicting the survival of patients with gastric cancer.[11] They found that the performance of the preoperative mSIS was superior compared with that of the original SIS.[11] This indicates that determining the appropriate cutoff for each disease may further enhance the performance of the mSIS.

The accuracy of prognostic evaluation is critical for the care of patients with ESCC. We show here that the mSIS was superior in performing detailed stratification and identifying definitive cutoffs compared with its components: ALB and LMR. The fact that mSIS was significantly associated with advanced pathological disease stage raised a question if mSIS only projected TNM stages. To answer it, we performed the multivariate analysis and it revealed that preoperative mSIS was found to be an independent prognostic factor after adjustment with confounding factors, indicating that mSIS does not simply reflect advanced stage and it appears promising as a prognosticator of ESCC. A subgroup analysis was performed to answer the research question whether association between preoperative mSIS and prognosis among subgroups of patients defined by baseline characteristics, and it revealed that preoperative mSIS was identified as a significant prognostic factor in most subgroups emphasizes the usefulness of mSIS as a prognosticator in various clinical settings. However, mSIS had limited impact in patient subgroups of elderly, high BMI and tumor location Lt/Ae groups is an important finding of the subgroup analysis. When estimating risks of patients, it is recommendable to modify magnitude of mSIS in those populations.

mSIS can be determined before surgery, so that it has the potential to improve the decision-making process of perioperative treatment and preoperative informed consent with better estimation of postoperative outcomes. Moreover, a high preoperative mSIS was significantly associated with increased risk of hematogenous recurrence, but not nodal or local recurrence. Moreover, our results indicate that the mSIS can predict patients with circulating micrometastasis, which contributes to postoperative hematogenous tumor recurrences. In clinical practice, intensive postoperative surveillance for lung, bone, and liver metastases (e.g., detected using positron-emission tomography) may be advisable for patients with a high preoperative mSIS. The mSIS may therefore serve as a simple, preoperatively accessible, and promising prognosticator of patients with resectable ESCC that will facilitate selection of the appropriate perioperative management strategy.

mSIS, especially LMR, is strongly affected by neoadjuvant treatment. Therefore, there is an important question of whether the mSIS should be evaluated before administration of neoadjuvant treatment. Compared with the performance of risk stratification using mSIS before neoadjuvant treatment and before surgery, the preoperative mSIS performed better as a prognosticator than the mSIS before neoadjuvant treatment. A possible explanation is that inflammatory and nutritional conditions during surgical stress are closely related to subsequent clinical course rather than the baseline condition.[25,27] We focused on patients who underwent neoadjuvant treatment to further evaluated the clinical significance of preoperative mSIS. In the subgroup analysis, high preoperative mSIS was associated with adverse prognosis in both patient groups with and without neoadjuvant treatment. Moreover, the survival curves and initial recurrence patterns in patients who underwent neoadjuvant treatment were analyzed. The disease-specific survival curves of patients with preoperative mSIS 0, 1, or 2 were clearly distinguished, and preoperative mSIS was significantly associated with incidence of hematogenous recurrences in common with analysis of the entire cohort. These findings indicated that preoperative mSIS shows promise for a prognosticator of ESCC patients who underwent neoadjuvant treatment.

There are several limitations to the present study. For example, we conducted a retrospective analysis whose statistical power was limited by the relatively small sample size, particularly in subgroup analyses. We were unable to clarify whether preoperative modification of the mSIS by with anti-inflammatory agents and nutritional support reduced the adverse effect on the postoperative course. Prospective clinical trials are warranted that are designed to evaluate the efficacy of anti-inflammatory treatment and nutritional support administered according to the mSIS.

Together, our findings strongly support the conclusion that the preoperative mSIS serves as a powerful tool for risk stratification after curative resection of ESCC. Moreover, the mSIS represents a readily measured and inexpensive prognosticator that has potential as a routine clinical test.

ACKNOWLEDGMENT The authors thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

FUNDING None.

DISCLOSURE None.

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