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Systemic Inflammation Score as a Predictor of Pneumonia after Radical Resection of Gastric Cancer: Analysis of a Multi-Institutional Dataset

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Keywords
Gastric cancer · Pneumonia · Systemic inflammation score · Predictor

Abstract
Background: Curative treatment for gastric cancer (GC) comprising gastrectomy with systematic lymph node dissection can result in postoperative complications. Postoperative pneumonia is sometimes fatal, like surgery-related complications such as anastomotic leakage. In this retrospective study, we analyzed a multi-institutional collaborative dataset with the aim of identifying predictors of postgastrectomy pneumonia. ***Methods:*** From a retrospective database of 3,484 patients who had undergone gastrectomy for GC at nine Japanese institutions between 2010 and 2014, 1,415 patients who met all eligibility criteria were identified as eligible for analysis. Predictive values of 31 candidate variables for postoperative pneumonia were assessed. ***Results:*** Forty-two patients (3.0%) had grade II or higher postoperative pneumonia. Preoperative systemic inflammation score (SIS) had the greatest area under the curve (0.655) for predicting postoperative pneumonia (optimal cutoff value = 2). The odds ratio (OR) of high SISs associated with postoperative pneumonia was 3.10 (95% confidence interval [CI], 1.54–6.07; $p < 0.001$). Multivariate binomial logistic analysis identified high SIS as an independent risk factor for postoperative pneumonia (OR, 2.31; 95% CI, 1.19–4.48; $p = 0.013$). A forest plot revealed that ORs of high SISs were highest in female patients. ***Conclusions:*** Our findings indicate that the preoperative SIS may serve as a simple predictor of postgastrectomy pneumonia, assisting physicians' efforts to take preventive measures against this complication.

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Introduction

Gastrectomy with systemic lymphadenectomy is one of the most important modalities of treatment for resectable gastric cancer (GC) [1, 2]. Despite advances in surgical techniques and perioperative management, some patients who undergo gastrectomy develop clinically relevant postoperative complications that delay recovery and administration of adjuvant chemotherapy and impair quality of life and double to triple hospital admission costs [3, 4]. Therefore, prevention and appropriate management of postoperative complications are important when treating patients with GC [5, 6].

Pneumonia is one of the most common complications after gastrectomy, occurring in 1.1–12.3% of patients [7]. With the aging of many societies, the number of older persons undergoing gastrectomy for GC has been increasing [8]. The incidence and mortality rate of postoperative pneumonia tend to be higher in older than younger patients because of age-related poor residual function and comorbidities; thus, management of pneumonia is becoming increasingly important in the field of gastric surgery. Moreover, several studies have reported that postgastrectomy pneumonia is associated with a worse prognosis [7, 9, 10]. Candidate factors that may be associated with postgastrectomy pneumonia include advanced age, diabetes mellitus, abnormal lung function, intraoperative bleeding, postoperative analgesia, and high postoperative C-reactive protein (CRP) concentrations with various drawbacks, such as not being objective or correctable and not being available preoperatively [7, 11–13]. Development of predictors that consist exclusively of preoperatively determined variables would be helpful in identifying individuals at high risk of postgastrectomy pneumonia. Such a predictor would enable physicians to provide their patients with an accurate assessment of the potential risks and outcomes of postoperative pneumonia, thereby improving shared decision-making, which in turn would result in more patients granting informed consent, more effective perioperative management, and minimization of medical costs [11, 14–16].

In this context, we therefore retrospectively analyzed a multi-institutional dataset with the aim of identifying a predictor of postgastrectomy pneumonia that is a component of routinely obtained laboratory data.

Methods

Patients and Perioperative Treatment

Relevant clinical data of 3,484 patients who had undergone gastrectomy for GC at nine institutions in Japan between January 2010 and December 2014 were retrospectively reviewed. The patients had provided written informed consent for surgery and for use of their clinical data, as required by the Institutional Review Board of each participating institution. Of the 3,484 patients, 1,415 were selected on the basis of the following inclusion criteria: no preoperative chemotherapy, R0 resection with systematic lymphadenectomy performed in accordance with the Japanese gastric cancer treatment guidelines [17], pathological stage I–III GC classified in accordance with the tumor-node-metastasis system of the *Union for International Cancer Control Classification of Malignant Tumors*, 8th edition [18], and availability of sufficient clinical data for accurate analysis (Fig. 1a). Patients who had undergone gastric stump cancer, extended (e.g., pancreaticoduodenectomy and Appleby's procedure) or limited, surgery without systematic lymphadenectomy were excluded. Routine preoperative screening included endoscopy, biopsy, and CT scan from the neck to the pelvis. Grade II or higher complications according to the Clavien-Dindo classification were regarded as clinically relevant complications [19].

Definition of Postoperative Pneumonia

The criteria for diagnosis of postoperative pneumonia were new inflammatory changes in the lung on computed tomography scans or X-ray films and high CRP concentrations within 30 days after surgery or during postoperative hospitalization. A positive sputum culture was not necessary. Atelectasis without infectious inflammatory reactions in lung parenchyma was not considered to denote postoperative pneumonia.

Candidate Indicators

Blood tests were routinely performed within 5 days before surgery. Data were collected retrospectively from the medical records focusing on four categories: tumor markers, blood count, coagulation, and biochemistry. The parameters investigated as candidate predictive factors for postoperative pneumonia, which can be rapidly measured in every hospital, included the following: carcinoembryonic antigen, carbohydrate antigen 19-9 (CA 19-9), white blood cell count, neutrophil count, total lymphocyte count (TLC), monocyte count, hemoglobin concentration, platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, total protein, albumin, cholinesterase, total cholesterol, urea nitrogen, Cr, total bilirubin, and CRP. Additionally, the following simple indices were assessed: estimated glomerular filtration rate, Cr clearance, neutrophil-lymphocyte ratio (neutrophil count/TLC), platelet-neutrophil ratio (neutrophil count/platelet count × 100), platelet-lymphocyte ratio (TLC/platelet count × 100), lymphocyte-monocyte ratio (LMR = TLC/monocyte count), systemic inflammation score (SIS), prognostic nutritional index, albumin-bilirubin grade, controlling nutritional status score, Glasgow prognostic score (GPS), and modified GPS [4, 15, 20].

Determination of SIS

SIS was based on the serum albumin concentration (ALB) and LMR as follows: ALB ≥ 4.0 g/dL and LMR ≥ 4.44 scored 0; either ALB < 4.0 g/dL or LMR < 4.44 scored 1; and both ALB < 4.0 g/dL and LMR < 4.44 scored 2 [16].

Subgroup Analyses

Subgroup analyses were performed to evaluate correlations between the selected predictive factors and the incidence of clinically relevant postoperative pneumonia.

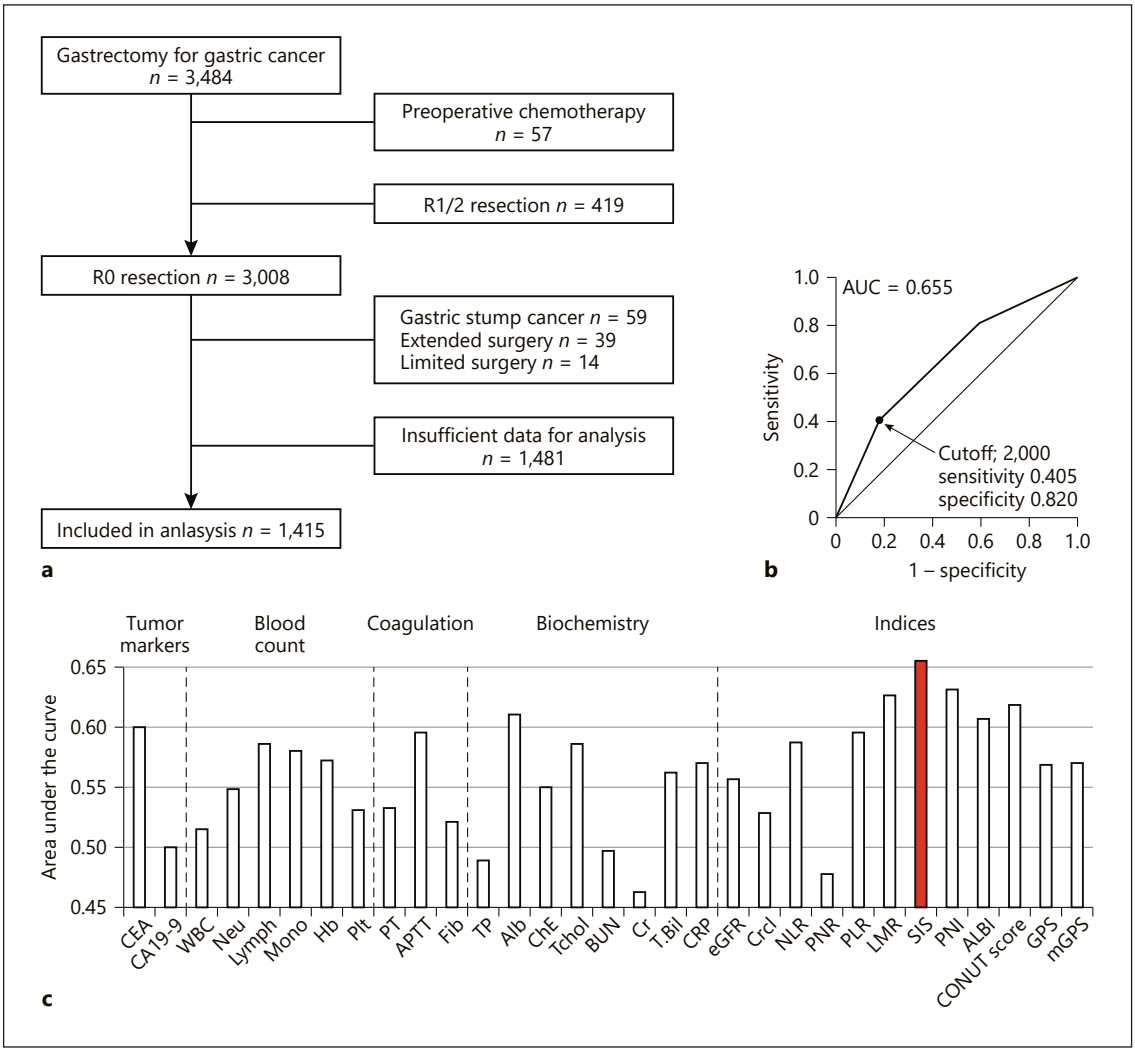

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Fig. 1. a Study design. **b** Predictive ability of preoperative SIS for postoperative pneumonia was evaluated using ROC curve analysis. **c** Comparison of AUC values of potential predictors of postoperative pneumonia. ROC, receiver operating characteristic; AUC, area under the curve.

Statistical Analyses

Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) and the optimal cutoff for predicting postoperative pneumonia. The quantitative Mann-Whitney test was used to compare the patient groups. One-way ANOVA or the Kruskal-Wallis test was used to compare continuous variables between three independent groups. Qualitative parameters were compared using Fisher's exact test or the χ^2 test. Multivariable binomial logistic analysis was performed to identify independent risk factors for pneumonia after gastrectomy, variables with $p < 0.05$ being included in the final model. EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used for all statistical analyses [21]. $p < 0.05$ indicated a significant difference.

Results

Patients' Characteristics

The patients' (n = 1,415) clinical characteristics are presented in Supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000506591). The median age was 68 years (range 26–91) and male-to-female ratio 1,009:406. The median preoperative BMI was 22.35 (range 11.19–36.33). Median ALB and LMR were 4.2 (range 1.95–5.20) g/dL and 4.45 (0.10–59.00), respectively. Total gastrectomy was performed on 345 (24.4%) patients. GC was pathologically diagnosed as tumor-node-metastasis stage IA (n = 701), IB (n = 168), IIA (n =

Table 1. Clinicopathological variables classified by preoperative SIS

Variable	SIS 0 (n = 565)	SIS 1 (n = 586)	SIS 2 (n = 264)	p value
Age (median, range), years	65 (26–87)	69 (30–90)	73 (39–91)	<0.001
Sex				<0.001
Male	368 (65.1)	432 (73.7)	209 (79.2)	
Female	197 (34.9)	154 (26.3)	55 (20.8)	
Preoperative BMI (median, range)	22.86 (15.44–36.33)	22.41 (14.01–36.29)	20.98 (11.19–32.58)	<0.001
Preoperative symptom				0.581
Absent	371 (65.7)	387 (66.0)	165 (62.5)	
Present	194 (34.3)	199 (34.0)	99 (37.5)	
Preoperative PS				<0.001
0	508 (89.9)	508 (86.7)	188 (71.2)	
1	54 (9.6)	62 (10.6)	60 (22.7)	
2/3	3 (0.5)	16 (2.7)	16 (6)	
Diabetes mellitus				0.931
Absent	483 (85.5)	503 (85.8)	224 (84.8)	
Present	82 (14.5)	83 (14.2)	40 (15.2)	
Cardiac comorbidities				<0.001
Absent	539 (95.4)	558 (95.2)	232 (87.9)	
Present	26 (4.6)	28 (4.8)	32 (12.1)	
Pulmonary comorbidities				0.381
Absent	543 (96.1)	558 (95.2)	248 (93.9)	
Present	22 (3.9)	28 (4.8)	16 (6.1)	
Tumor location				0.001
Entire	1 (0.2)	8 (1.4)	9 (3.4)	
Upper third	102 (18.1)	128 (21.8)	56 (21.2)	
Middle third	278 (49.2)	253 (43.2)	102 (38.6)	
Lower third	184 (32.6)	197 (33.6)	97 (36.7)	
Tumor size, mm				<0.001
<50	465 (82.6)	424 (72.5)	133 (50.8)	
≥50	98 (17.4)	161 (27.5)	129 (49.2)	
Type of gastrectomy				0.047
Total gastrectomy	121 (21.4)	147 (25.1)	77 (29.2)	
Partial gastrectomy	444 (78.6)	439 (74.9)	187 (70.8)	
Surgical approach				<0.001
Open	332 (58.8)	375 (64.0)	219 (83.0)	
Laparoscopic	233 (41.2)	211 (36.0)	45 (17.0)	
Lymphadenectomy				<0.001
D2	257 (45.5)	254 (43.3)	153 (58.0)	
Non-D2	308 (54.5)	332 (56.7)	111 (42.0)	
Splenectomy				0.203
Not performed	523 (92.6)	530 (90.4)	235 (89.0)	
Performed	42 (7.4)	56 (9.6)	29 (11.0)	
Intraoperative blood loss (median, range), mL	129.50 (0.00–6,362.00)	155.50 (0.00–1,578.00)	211.00 (0.00–2,465.00)	<0.001
Operative time (median, range), min	260.00 (56.00–745.00)	259.00 (67.00–817.00)	256.50 (118.00–652.00)	0.554
UICC pT factor				<0.001
pT0	4 (0.7)	1 (0.2)	1 (0.4)	
pT1	345 (61.1)	346 (59.0)	94 (35.6)	
pT2	77 (13.6)	67 (11.4)	30 (11.4)	
pT3	75 (13.3)	90 (15.4)	59 (22.3)	
pT4	64 (11.3)	82 (14.0)	80 (30.3)	
UICC pN factor				<0.001
pN0	402 (71.2)	384 (65.5)	124 (47.0)	
pN1	79 (14.0)	76 (13.0)	55 (20.8)	
pN2	43 (7.6)	72 (12.3)	35 (13.3)	
pN3	41 (7.3)	54 (9.2)	50 (18.9)	

Table 1 (continued)

Variable	SIS 0 (n = 565)	SIS 1 (n = 586)	SIS 2 (n = 264)	p value
TNM pStage				<0.001
IA	310 (54.9)	311 (53.1)	80 (30.3)	
IB	81 (14.3)	56 (9.6)	31 (11.7)	
IIA	48 (8.5)	60 (10.2)	25 (9.5)	
IIB	48 (8.1)	35 (6.0)	30 (11.4)	
IIIA	45 (8.0)	73 (12.5)	45 (17.0)	
IIIB	26 (4.6)	36 (6.1)	40 (15.2)	
IIIC	9 (1.6)	15 (2.6)	13 (4.9)	

Values presented as n (%). PS, performance status; SIS, systemic inflammation score; UICC, Union for International Cancer Control; TNM, tumor-node-metastasis.

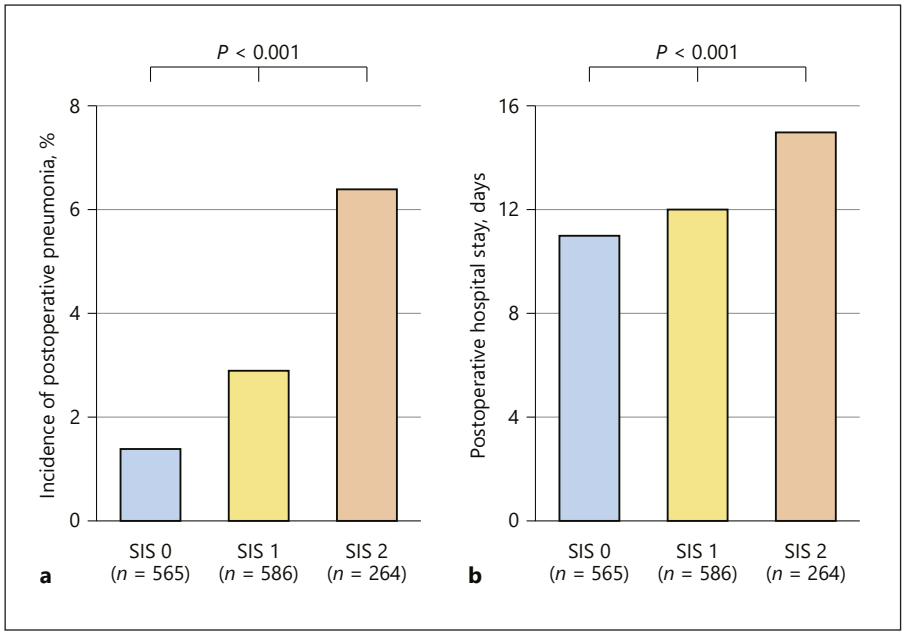

Fig. 2. a Categorization of patients by SIS. The incidence of pneumonia increased significantly in parallel with increasing SIS. **b** Length of postoperative hospital stay according to preoperative SIS. SIS, systemic inflammation score.

133), IIB (n = 111), IIIA (n = 163), IIIB (n = 102), and IIIC (n = 37).

Comparison of Predictive Values for Pneumonia among the Candidate Variables

Grade II or higher postoperative complications and pneumonia occurred in 319 (22.5%) and 42 (3.0%) patients, respectively. In 1,481 cases excluded from analysis due to insufficient data, grade II or higher postoperative pneumonia occurred in 47 (3.2%) patients.

The preoperative SIS had the highest AUC value (0.655) of the 31 candidate variables (Fig. 1b). The optimal cutoff value for predicting postoperative pneumonia using the SIS was defined as 2 (sensitivity = 40.5%, specificity = 82.0%; Fig. 1b).

Clinical Characteristics according to Preoperative SIS

Patients were categorized into the following three groups: SIS 0 (n = 565), SIS 1 (n = 586), and SIS 2 (n = 264) (Table 1). A high SIS was significantly associated with older age, male sex, low preoperative BMI, poor preoperative performance status (PS), cardiac comorbidities, large tumor size, more extensive primary tumor, and more advanced pathological disease stage (Table 1). In contrast, there were no significant differences in the prevalence of diabetes mellitus or pulmonary disease between

Table 2. Risk factors for grade II or higher postoperative pneumonia according to the Clavien-Dindo system

		Univariate			Multivariable		
		OR	95% CI	*p* value	OR	95% CI	*p* value
Age	≥65 years	1.95	0.93–4.49	0.090	1.43	0.68–3.04	0.346
Sex	Male	2.47	1.02–7.22	0.055	1.80	0.74–4.41	0.198
Preoperative BMI	≥22	1.02	0.53–2.00	1			
Preoperative PS	≥1	2.08	0.93–4.34	0.062	1.30	0.61–2.75	0.493
Diabetes mellitus	Present	1.40	0.55–3.15	0.529			
Cardiac comorbidities	Present	1.20	0.23–3.89	0.739			
Pulmonary comorbidities	Present	3.64	1.21–9.19	0.009	2.77	1.07–7.15	0.035
Preoperative SIS	≥2	3.10	1.54–6.07	<0.001	2.31	1.19–4.48	0.013
Type of gastrectomy	Total gastrectomy	3.23	1.66–6.31	<0.001	2.38	1.24–4.59	0.009
Splenectomy	Performed	1.72	0.58–4.24	0.343			
Lymphadenectomy	D2	1.14	0.58–2.21	0.804			
Operative time	≥240 min	1.31	0.66–2.72	0.509			
Estimated blood loss	≥200 mL	2.82	1.42–5.84	0.002	1.82	0.91–3.65	0.091

Analyses were performed using binomial logistic analysis. OR, odds ratio; CI, confidence interval; PS, performance status; SIS, systemic inflammation score.

the three groups (Table 1). The prevalence of postoperative pneumonia was increased gradually in parallel with SIS (Fig. 2a), as did the overall complication rate of SIS (20.4, 20.8, and 31.1% for SIS 0, SIS 1, and SIS 2 groups, respectively; $p = 0.001$). Moreover, postoperative hospital stay was longer with the increasing SIS (Fig. 2b).

Multivariable Analysis

Using the cutoff value (SIS = 2) derived from ROC curve analysis, the predictive value of the preoperative SIS was further evaluated. According to univariate analysis of possible risk factors for postoperative pneumonia, the odds ratio of high preoperative SIS was 3.10 (95% confidence interval 1.54–6.07; $p < 0.001$) (Table 2). Multivariable analysis using factors determined preoperatively revealed that high preoperative SIS is an independent risk factor for postgastrectomy pneumonia (odds ratio, 2.31; 95% confidence interval, 1.19–4.48; $p = 0.013$), along with pulmonary comorbidities and total gastrectomy (Table 2).

Subgroup Analyses

Subgroup analyses were performed to investigate the predictive value of preoperative SIS in more detail. It was found that most subgroups of the high-SIS group were at greater risk of postoperative pneumonia (Fig. 3). Notably, high SIS was associated with an increased risk of pneumonia, regardless of age, type of gastrectomy, surgical approach, and clinical disease stage, indicating that the incidence of postoperative pneumonia can be predicted by preoperative SIS in various clinical settings. For example, the incidence of pneumonia increased gradually in parallel with preoperative SIS in the subgroups of age (Fig. 4a) and type of gastrectomy (Fig. 4b).

Discussion

In this study, we identified a significant association between preoperative SIS and postoperative pneumonia after gastrectomy for GC by analyzing a large amount of data from multiple institutions. Preoperative SIS had the strongest association (highest AUC value) with the incidence of postoperative pneumonia among 31 candidate variables based on preoperative blood tests. High SIS was correlated with adverse biological (advanced age, male, lower preoperative BMI, and poor preoperative PS) and oncological (large tumor size, more extensive primary tumor, and more advanced pathological disease stage) characteristics. Multivariable analysis revealed that high SIS was an independent risk factor for postoperative pneumonia as well as pulmonary comorbidities, such as chronic obstructive pulmonary disease and bronchial asthma, and total gastrectomy. Pulmonary comorbidities are associated with chronic airway inflammation and increased sputum. Total gastrectomy reportedly increases a risk of reflux and aspiration [5–8]. Moreover, high SIS was associated with an increased incidence of postopera-

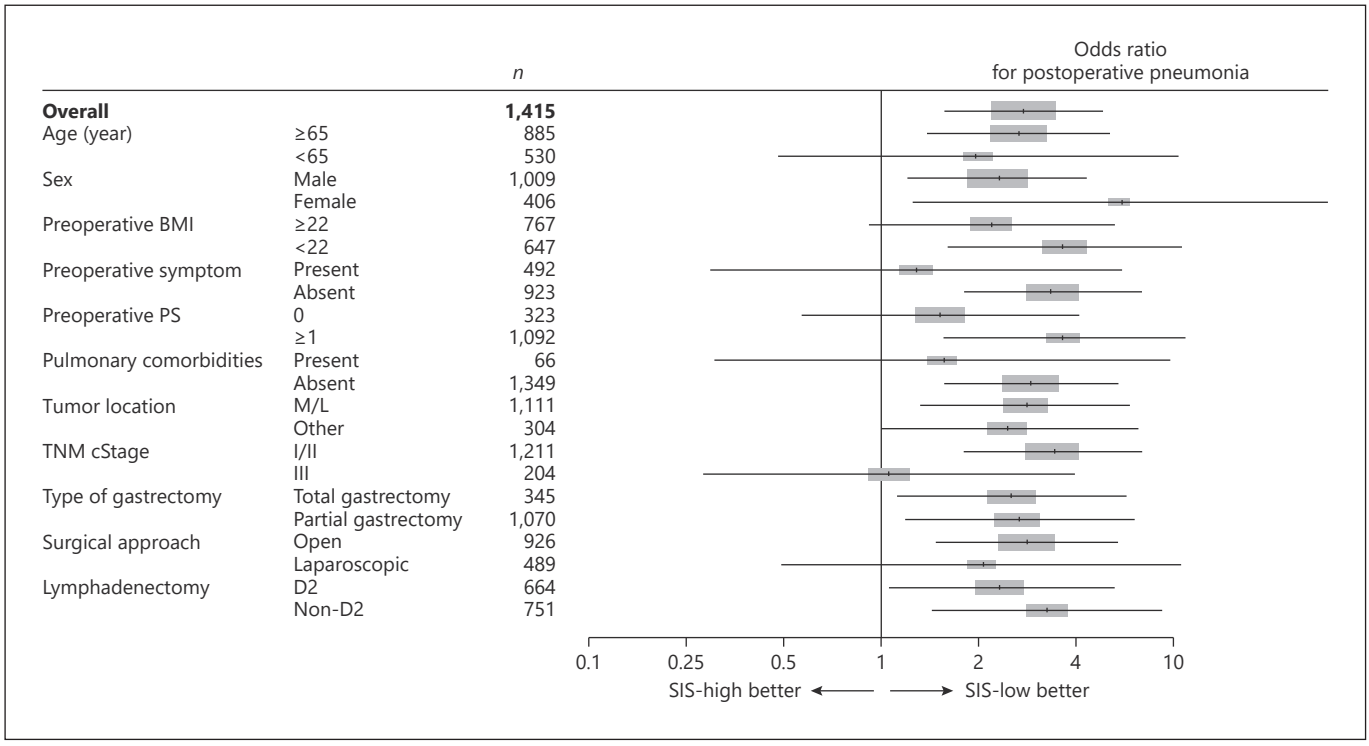

Fig. 3. Subgroup analyses. Comparison of the incidence of postoperative pneumonia between the high- and low-SIS groups. SIS, systemic inflammation score.

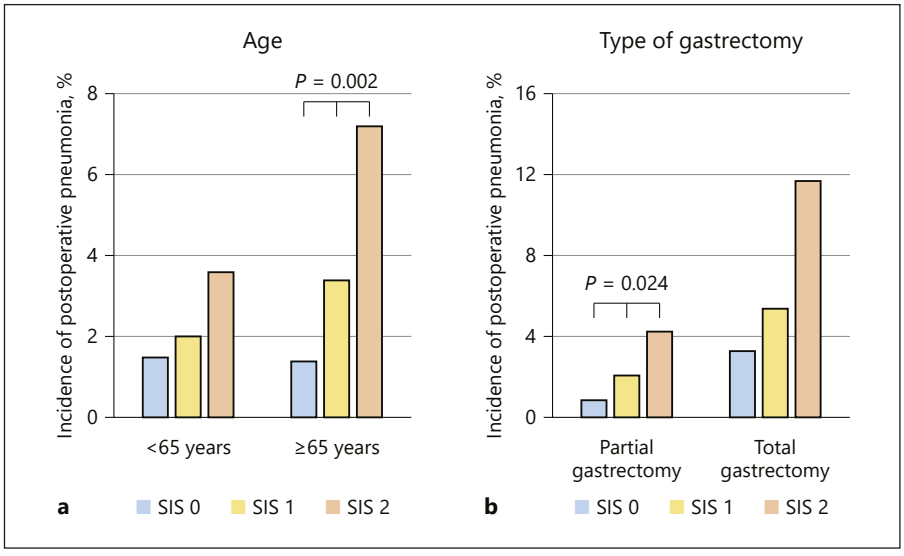

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Fig. 4. Incidence of postoperative pneumonia by preoperative SIS in patient subgroups of age (**a**) and type of gastrectomy (**b**). SIS, systemic inflammation score.

tive pneumonia in subgroups of age, sex, BMI, PS, comorbidity, and type of gastrectomy.

SIS is simply classified into three categories of 0–2 by ALB and LMR. Decreased ALBs are associated with both malnutrition and a sustained systemic inflammatory response [22]. Poor nutritional status leads to increased susceptibility to infection, protracted wound healing, impaired blood clotting, and vessel wall fragility and directly increases the incidence of postoperative pneumonia [23]. Various studies have shown that inadequate energy

and protein intake are independent risk factors for sarcopenia, which has been shown to be independently associated with postoperative pneumonia [24, 25]. Low LMR values indicate low total lymphocyte and high monocyte counts. Depletion of lymphocytes leads to attenuation of the antibacterial cell-mediated immune responses that involve them, leading to increased bacterial invasion and proliferation [15]. Furthermore, low circulating lymphocyte counts attenuate the immune surveillance that inhibits tumor cell proliferation, invasion, and metastasis, whereas high circulating monocyte counts promote recruitment into tumor tissues where they differentiate into tumor-associated macrophages, which exert a protumoral action [26, 27]. Thus, there have been many reports of a correlation between preoperative LMR and long-term outcomes in various cancers [27, 28]. The associated postoperative infectious complications reportedly shorten the long-term prognosis of GC, esophageal cancer, and colorectal cancer [29–31]. Compromised immunonutritional status is an important factor that is associated with increased postoperative complications and spread of tumor. These findings support our contention that the preoperative SIS is relevant in diverse clinical settings. To the best of our knowledge, no studies reported that the preoperative SIS is a predictor of postoperative pneumonia after radical gastrectomy for GC [16, 22, 28, 32, 33].

The relationship between malnutrition and inflammatory status and their association with postoperative infectious complications are complex and difficult to understand. In the present study, the SIS showed higher AUC values than the prognostic nutritional index and the modified GPS in ROC curve analysis of postoperative pneumonia. This may be because the SIS incorporates both ALB and LMR and because the objective predictor of LMR more accurately reflects the interactions between inflammatory conditions and immune responses than other indicators such as TLC and CRP. In this study, high SIS was significantly correlated with adverse biological and oncological characteristics. In addition, the incidence of pneumonia increased significantly in parallel with increasing SIS. These findings in part reflect the complex correlation between systemic inflammatory response and tumor progression. Furthermore, the incidence of pneumonia was associated with SIS in most subgroups, including age, sex, respiratory complications, and surgical procedure. Our findings suggested that SIS is a sensitive and universal predictor of postoperative pneumonia after gastrectomy for GC. In addition, analysis of sarcopenia (muscle mass) may enhance the risk stratification of pneumonia and be a useful tool for assessment of efficacy of perioperative rehabilitation [14, 24, 34].

Postoperative risk assessment scales such as the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity and Surgical Risk Preoperative Assessment System are widely used but do not accurately identify patients at high risk for postoperative pneumonia [35, 36]. It may be possible to incorporate SIS into these existing scales as an additional component. This could result in physicians more accurately identifying patients at high risk of postoperative pneumonia and implementing tailor-made perioperative management according to the Enhanced Recovery After Surgery protocol measures aimed at preventing this complication [37, 38]. Postoperative pneumonia increases mortality by contributing to deterioration in general condition and makes additional treatment for the cancer difficult. Therefore, prevention of postoperative pneumonia is important in improving short-term and long-term outcomes of GC. Although comprehensive interventions including perioperative pulmonary physiotherapy, respiratory exercises, and nutritional support are known to reduce the incidence of postoperative pneumonia, to the best of our knowledge, no clinical trials of these interventions have been conducted [39–41]. Therefore, clinical trials in which SIS is used as a predictor of postoperative pneumonia may result in improvement of management of patients after gastrectomy.

Our study has several limitations. Because it was retrospective, there may have been selection bias. Moreover, we have not elucidated the mechanism underlying our findings. The correlation between nutritional and immune status and the dynamics of cytokines and related proteins need to be further evaluated. Last, we did not evaluate the impact of sarcopenia; this requires further evaluation.

In conclusion, the preoperative SIS is a significant predictor of postoperative pneumonia in patients who have undergone gastrectomy with systemic lymphadenectomy for GC. In the future, development of an integrated risk stratification system incorporating SIS may allow physicians to identify patients at high risk of postoperative pneumonia, implement appropriate preventive measures, and provide patients with adequate information when seeking informed consent for gastrectomy.

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Statement of Ethics

All procedures performed in studies involving human participants 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.

Disclosure Statement

The authors declare that they have no conflict of interest.

Author Contributions

All authors met all of the following criteria: substantial contributions to the conception, design of the work, the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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