ORIGINAL ARTICLE – THORACIC ONCOLOGY

Risk Prediction of Postoperative Pneumonia After Subtotal Esophagectomy Based on Preoperative Serum Cholinesterase Concentrations

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ABSTRACT

Background. Patients undergoing subtotal esophagectomy for esophageal cancer frequently experience postoperative pneumonia. Development of preoperatively determined predictors for postoperative pneumonia will facilitate identifying high-risk patients and will assist with informing patients about their risk of postoperative pneumonia, enabling physicians to estimate with greater accuracy, will result in tailoring perioperative management.

Methods. Postoperative pneumonia was defined according to the revised Uniform Pneumonia Score. We analyzed the data for 355 patients to compare 32 potential predictive variables associated with postoperative pneumonia after subtotal esophagectomy.

Results. Forty-one patients (11.5%) had postoperative pneumonia. Preoperative cholinesterase (ChE) concentrations demonstrated the greatest area under the curve value (0.662) to predict postoperative pneumonia (optimal cutoff value = 217 IU/l). Univariate analysis identified a continuous value of preoperative ChE concentration as a significant risk factor for postoperative pneumonia ($P = 0.0014$). Multivariable analysis using factors potentially relevant to pneumonia revealed that preoperative ChE concentration was one of independent risk factors for pneumonia after esophagectomy ($P = 0.008$). Patients with low ChE concentrations were at increased risk of postoperative pneumonia in most patient subgroups. Moreover, the odds ratios of low ChE concentrations were highest in patients undergoing neoadjuvant treatment. A combination of preoperative serum ChE concentrations and Brinkman index stratified patients into low, intermediate, and high risk of postoperative pneumonia.

Conclusions. Our findings indicate that preoperative ChE concentrations, particularly in combination with Brinkman index, may serve simply as a determined predictor of pneumonia after subtotal esophagectomy and may facilitate physicians' efforts to reduce the incidence of postoperative pneumonia.

Although chemoradiotherapy is effective treatment of esophageal cancer, surgical resection has been considered the mainstay potentially curative treatment.[1] Subtotal esophagectomy with 2- or 3-field lymphadenectomy is highly invasive and is associated with high morbidity rates regardless of improvements in surgical technique and postoperative management.[2,3] Risk management of patients with esophageal cancer therefore is an increasingly important component of treatment.

Pulmonary complications reportedly occur in 20–40% of patients and represent the most frequent adverse events after subtotal esophagectomy.[4,5] Evidence indicates that the development of postoperative respiratory complications diminishes favorable surgical outcomes and impairs quality

of life for patients.[6,7] For example, pneumonia is the most common postoperative pulmonary complication experienced by patients who undergo esophagectomy, leading to an increased risk of death.[8–10] In contrast, pleural effusion is generally manageable.[1,11] Factors that may lead to pneumonia after esophagectomy include advanced age, diabetes mellitus, abnormal lung function, intraoperative bleeding, postoperative analgesia, and elevation of postoperative C-reactive protein (CRP) levels.[10,12–14] Development of prediction tools exclusively consisted of preoperatively determined parameters, which will be helpful for identifying individuals at highest risk of postoperative pneumonia after they undergo subtotal esophagectomy. Such a tool will enable physicians to provide their patients with an accurate assessment of their potential risks and outcomes, which may lead to informing patients about their risk of postoperative pneumonia and which may now be estimated with greater accuracy, will result in more patients granting informed consent, more effective perioperative management, and minimization of medical costs.[13,15] However, only limited comparative information focusing exclusively on preoperatively determined factors is available for patients undergoing subtotal esophagectomy.[4,12,16]

We therefore aimed to determine whether readily available routine laboratory data serve to predict postoperative pneumonia. We showed that preoperative cholinesterase (ChE) concentrations had the highest predictive value.

MATERIALS AND METHODS

Patients and Perioperative Treatment

Figure 1 presents the patient selection procedure. Consecutive patients ($n = 553$) with esophageal cancer underwent esophagectomy at Nagoya University Hospital (Department of Gastroenterological Surgery) between February 2005 and March 2017. We retrieved data for 355 patients in accordance with the criteria as follows: subtotal esophagectomy with systematic 2- or 3-field lymphadenectomy and sufficient data for analysis. Patients who underwent planned two-stage surgery were excluded. Written, informed consent according to the Institutional Review Board was granted from all patients for surgery and the use of clinical data. The medical team preoperatively managed the general condition and comorbidities of the patients. Routine preoperative screening included endoscopy, biopsy, and computed tomography (CT) scan from the neck to the pelvis. Neoadjuvant treatment was administered to patients with clinical Stage II or III
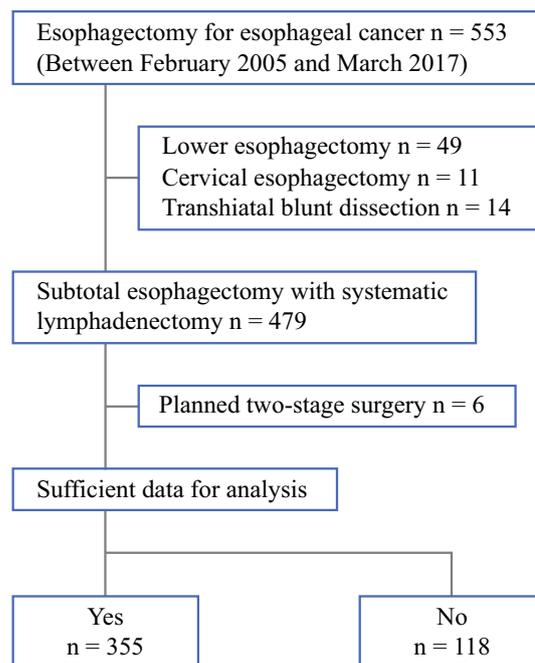

FIG. 1 Study design

histologically proven squamous cell carcinoma basically using 5-fluorouracil and cisplatin.[17]

Subtotal esophageal resection through a right thoracotomy or thoracoscopic approaches was performed with removal of nodes at the cervical, mediastinum, and intraabdominal areas.[18] The reconstruction method and route were determined depending on the patient's condition and the surgeon's discretion. Before closing the chest, a blake drain tube (15 Fr) was placed in the thoracic cavity. A second-generation cephem antibiotic was administered before surgery and every 3 h during surgery, followed by twice daily administration until postoperative day 2. Complications graded II or greater in the Clavien–Dindo classification were regarded as clinically relevant complications.[19] Oral intake is routinely started on postoperative day 7 for patients who underwent reconstruction using a gastric tube and on postoperative day 14 for patients who underwent reconstruction using a jejunum flap if postoperative course is uneventful.

Definition of Postoperative Pneumonia

In the present study, postoperative pneumonia was defined according to the revised Uniform Pneumonia Score proposed by Weijs et al. based on the following three diagnostic determinants retrospectively collected from the medical records: body temperature, leukocyte count, and pulmonary radiography findings (chest x-ray and/or CT scan) within 30 days after surgery or during postoperative hospitalization (Supplementary Table 1).[20] A sum score of

2 points or higher, of which at least 1 point is assigned due to infiltrative findings on pulmonary radiography, indicates postoperative pneumonia. A positive bacterial culture of sputum was not necessary.[20,21] Atelectasis without inflammatory reactions were not considered postoperative pneumonia.

Candidate Indicators

Data were retrospectively collected from blood tests within 5 days before surgery. Candidate parameters included age, Brinkman index, body mass index, preoperative lung functions, blood cell counts, coagulation tests, and biochemical blood test. Additionally, we employed some simple indices as follows: platelet-neutrophil ratio (PNR = neutrophil count/platelet count $\times$ 100), platelet–lymphocyte ratio (PLR = TLC/platelet count $\times$ 100), neutrophil–lymphocyte ratio (NLR = neutrophil count/total lymphocyte count (TLC)), lymphocyte–monocyte ratio (LMR = TLC/monocyte count), prognostic nutritional index, Controlling Nutritional Status (CONUT) score, Glasgow prognostic score (GPS), estimated glomerular filtration rate (eGFR), and the modified GPS.[22–24]

Statistical Analysis

Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the curve (AUC) and the optimal cutoff for predicting postoperative pneumonia. Quantitative Mann–Whitney and qualitative χ^2 tests were employed to compare the two groups. To identify independent risk factors for pneumonia after esophagectomy, a multivariable logistic analysis was performed and variables relevant to pneumonia were included in the final model. The performance of a combination of the two parameters were estimated by the logistic regression analysis. JMP 13 software (SAS Institute Inc., Cary, NC) was used for all statistical analyses. $P < 0.05$ indicates a significant difference.

RESULTS

Patients' Characteristics

The patients' ($n = 355$) demographic and preoperative characteristics are presented in Supplementary Table 2. The mean ($\pm$ standard deviation, SD) age was 65.1 $\pm$ 8.2 years, the male-to-female ratio was 296:59, and 99 (27.9%) had comorbidities. There were 102 (28.7%) patients who had decreased forced expiratory volume in 1 s as percent of forced vital capacity. The most frequent tumor location was the middle thoracic esophagus.

Preoperative clinical staging classified 112, 67, 148, and 28 patients with TNM stages 0/I, II, III, and IV, respectively. Most patients (92.4%) were histologically diagnosed as squamous cell carcinoma. Neoadjuvant treatment was administered to 183 (51.5%) patients.

Patients' Characteristics With and Without Postoperative Pneumonia

Grade II or higher postoperative complications were experienced by 140 patients (39.4%), and 41 (11.5%) patients had postoperative pneumonia based on the revised Uniform Pneumonia Score. Compared with patients without postoperative pneumonia, patients with pneumonia had significantly higher prevalence of diabetes mellitus, greater Brinkman index, decreased preoperative serum cholinesterase and cholesterol concentrations, advanced clinical stage, more neoadjuvant treatments and jejunal flap usage, and longer postoperative stay (Supplementary Table 3). In contrast, there were no significant correlations between the occurrence of pneumonia and age, body mass index, preoperative pulmonary function, surgical approach, number of field dissected, operative time, and initiation of oral intake.

Comparison of the Values of Candidate Parameters for Predicting Postoperative Pneumonia

Among the potential predictors for postoperative pneumonia, the preoperative ChE concentration had the highest AUC value (0.662) (Fig. 2a). The optimal cutoff value for predicting postoperative pneumonia using ChE was defined as 217 IU/l (sensitivity = 51%, specificity = 80%), which is identical to the lower limit of the normal range (213 IU/l) used in our institute (Fig. 2b).

Patients' Characteristics According to Preoperative ChE Concentrations

The median ChE concentration was 266 (range 96–496) IU/l. Using the cutoff value derived from ROC curve analysis, we further evaluated the clinical value of preoperative ChE concentrations. For this purpose, patients were categorized into ChE-low ($n = 84$) and ChE-high ($n = 271$) groups, using a ChE-concentration cutoff of 217 IU/l. Compared with the ChE-high group, the ChE-low group was significantly associated with advanced age, lower preoperative body mass index, more advanced clinical disease stage, and fewer neoadjuvant treatments (Supplementary Table 4). Levels of preoperative indicators of nutritional status (albumin and cholesterol) were significantly lower in the ChE-low group. However, no
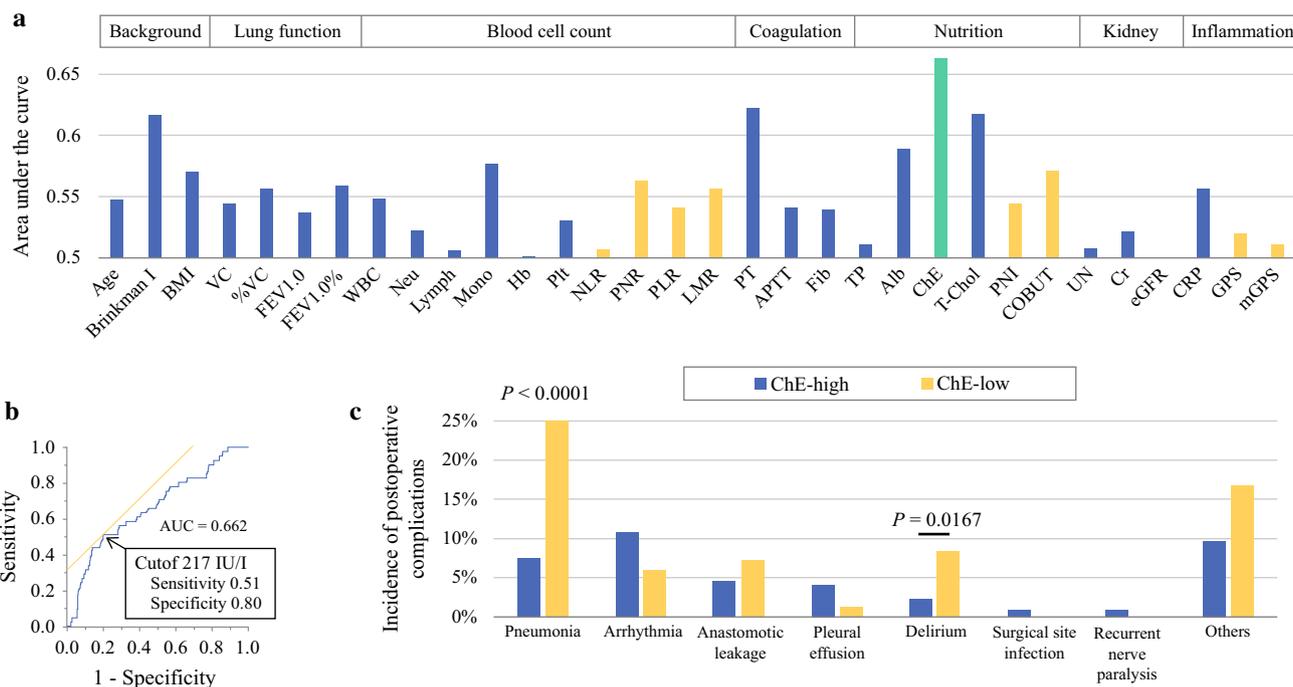
FIG. 2 Comparison of the predictive value of potential indicators of postoperative pneumonia. **a** Area under the curve values of potential predictors. **b** Predictive values of preoperative ChE concentrations for postoperative pneumonia was evaluated using receiver operating characteristic curve analysis. **c** Comparison of the prevalence of each complication between the ChE-high and -low groups

significant differences were observed between groups associated with the prevalence of comorbidities, history of cancer, smoking, total bilirubin levels, preoperative pulmonary function, and tumor location (Supplementary Table 4). Patients in the ChE-low group had a higher proportion of jejunal flap for reconstruction and subcutaneous reconstruction route, greater intraoperative blood loss, and larger number of dissected lymph nodes (Table 1).

Value of the Preoperative ChE Concentration as a Predictor of Postoperative Pneumonia

Compared with patients in the ChE-high group, those in the ChE-low group experienced significantly more frequent overall postoperative complications (Table 1). No significant differences were found in reoperation rates and length of postoperative hospitalization between the two groups. Three (3.6%) and two (0.7%) patients died 90 days after surgery in the ChE-low and -high groups, respectively ($P = 0.0807$). The ChE-low group experienced increased prevalence of pneumonia (20.2%) and delirium (8.3%) compared with those of the ChE-high group (Fig. 2c). In contrast, the incidences of arrhythmia, anastomotic leakage, pleural effusion, and surgical site infection were not significantly different between groups. The frequency of

postoperative pneumonia was significantly greater in patients with postoperative delirium (46.2%) compared with those without delirium (10.2%, $P = 0.0013$), indicating that postoperative pneumonia and delirium mutually affect each other.

Univariate analysis identified a continuous value of preoperative ChE concentrations as a significant risk factor for postoperative pneumonia ($P = 0.0014$; Table 2). Multivariable analysis using factors potentially relevant to pneumonia revealed that preoperative ChE concentration was one of independent risk factors for pneumonia after esophagectomy ($P = 0.008$), along with neoadjuvant treatment (Table 2).

Subgroup Analyses

Subgroup analyses was performed to further investigate the predictive value of preoperative ChE concentrations we found that most subgroups of the ChE-low group were at greater risk of postoperative pneumonia (Fig. 3a). Moreover, the odds ratio [OR] of low preoperative ChE concentrations was the highest (7.56; 95% confidence interval [CI], 2.25–25.4, $P < 0.0001$) in the subgroup undergoing neoadjuvant treatment.

TABLE 1 Intraoperative and postoperative findings

Characteristics	ChE-low group (n = 84)	ChE-high group (n = 271)	P
Surgical approach			0.6276
Open	81 (96.4%)	258 (95.2%)	
Thoracoscopic	3 (3.6%)	13 (4.8%)	
Number of fields dissected			0.1983
Two-field dissection	48 (57.1%)	176 (64.9%)	
Three-field dissection	36 (42.9%)	95 (35.1%)	
Reconstruction organ			0.0015
Gastric tube	61 (72.6%)	238 (87.8%)	
Jejunal flap	23 (27.4%)	33 (12.2%)	
Reconstruction route			0.0012
Subcutaneous	29 (34.5%)	45 (16.6%)	
Retrosternal	19 (22.6%)	57 (21.0%)	
Posterior mediastinal	36 (42.9%)	169 (62.4%)	
Operative time (minutes), mean ± SD	505 ± 125	479 ± 107	0.1093
Intraoperative blood loss (ml), median (range)	511 (67–2682)	428 (31–2353)	0.0234
Intraoperative transfusion (%)	16 (19.1%)	25 (9.2%)	0.0191
Number of dissected lymph nodes, mean ± SD	48.5 ± 21.4	46.6 ± 17.7	0.0004
Postoperative complications (%)			
Overall[a]	45 (56.3%)	100 (36.9%)	0.0070
Pneumonia	21 (25.0%)	20 (7.4%)	< 0.0001
Reoperation (%)	2 (2.4%)	13 (4.8%)	0.3069
Operative death[b] (%)	3 (3.6%)	2 (0.7%)	0.0807
Length of postoperative stay (days), median (range)	33.0 ± 28.2	29.9 ± 21.6	0.2612

ChE cholinesterase, *SD* standard deviation

[a]Pneumonia and other complications graded 2 or greater in the Clavien–Dindo classification

[b]Death within 90 days after surgery

Combination of ChE Concentrations and Brinkman Index

Despite significant correlations between preoperative serum ChE concentrations and postoperative pneumonia, the limited AUC value (0.662) and sensitivity (0.51) of preoperative serum ChE concentrations motivated us to seek a partner for ChE that can compensate the weakness of ChE concentrations. Based on the comparison of the sensitivity to detect postoperative pneumonia (Supplementary Fig. 1), Brinkman index was identified as a candidate partner for ChE concentrations. A combination of preoperative serum ChE concentrations and Brinkman index achieved a greater AUC value (0.702) (Fig. 3b). When patients were classified as score 0 (ChE-high and Brinkman index < 500), 1 (either ChE-low or Brinkman index ≥ 500), or 2 (ChE-low and Brinkman index ≥ 500), the incidence of postoperative pneumonia was gradually increased in parallel with the score (Fig. 3c), indicating that the combination of preoperative serum ChE concentrations and Brinkman index clearly stratified patients into low, intermediate, and high risk of pneumonia after subtotal esophagectomy.

DISCUSSION

We show a significant association between preoperative ChE concentrations and postoperative pneumonia after patients with esophageal cancer underwent subtotal esophagectomy. The preoperative ChE concentration had the highest AUC value associated with the incidence of postoperative pneumonia among the values of other preoperative blood tests. Multivariable analysis revealed that ChE-low was an independent risk factor for postoperative pneumonia. Moreover, a subgroup analysis was performed to answer the research question whether association between ChE concentrations and postoperative pneumonia varies among subgroups of patients defined by baseline characteristics.[25] ChE-low was consistently identified as a significant risk factor in most subgroups. These findings

TABLE 2 Predictors of postoperative pneumonia focused on preoperatively determined factors

Variables	Category	Univariate P	Multivariable P
Age	Continuous	0.2292	0.7760
Gender	Dichotomized	0.4211	
Preoperative symptoms	Dichotomized	0.6005	
Cardiovascular disease	Dichotomized	0.8324	
Respiratory disease	Dichotomized	0.7961	0.6528
Cerebrovascular disease	Dichotomized	0.3932	
Diabetes mellitus	Dichotomized	0.0324	0.1091
History of cancer	Dichotomized	0.0653	
Brinkman index	Continuous	0.0219	0.0618
Excessive alcohol consumption	Dichotomized	0.7051	
Body mass index	Continuous	0.2683	0.6672
%VC	Continuous	0.4279	
FEV1.0%	Continuous	0.2001	
Serum cholinesterase	Continuous	0.0014	0.0008
Tumor location (Lt or Ae)	Dichotomized	0.4478	
Clinical TNM stage (III or IV)	Dichotomized	0.0800	0.1753
Neoadjuvant treatment	Dichotomized	0.0200	0.0207

VC vital capacity, *FEV* forced expiratory volume, *Lt* lower thoracic, *Ae* abdominal esophagus
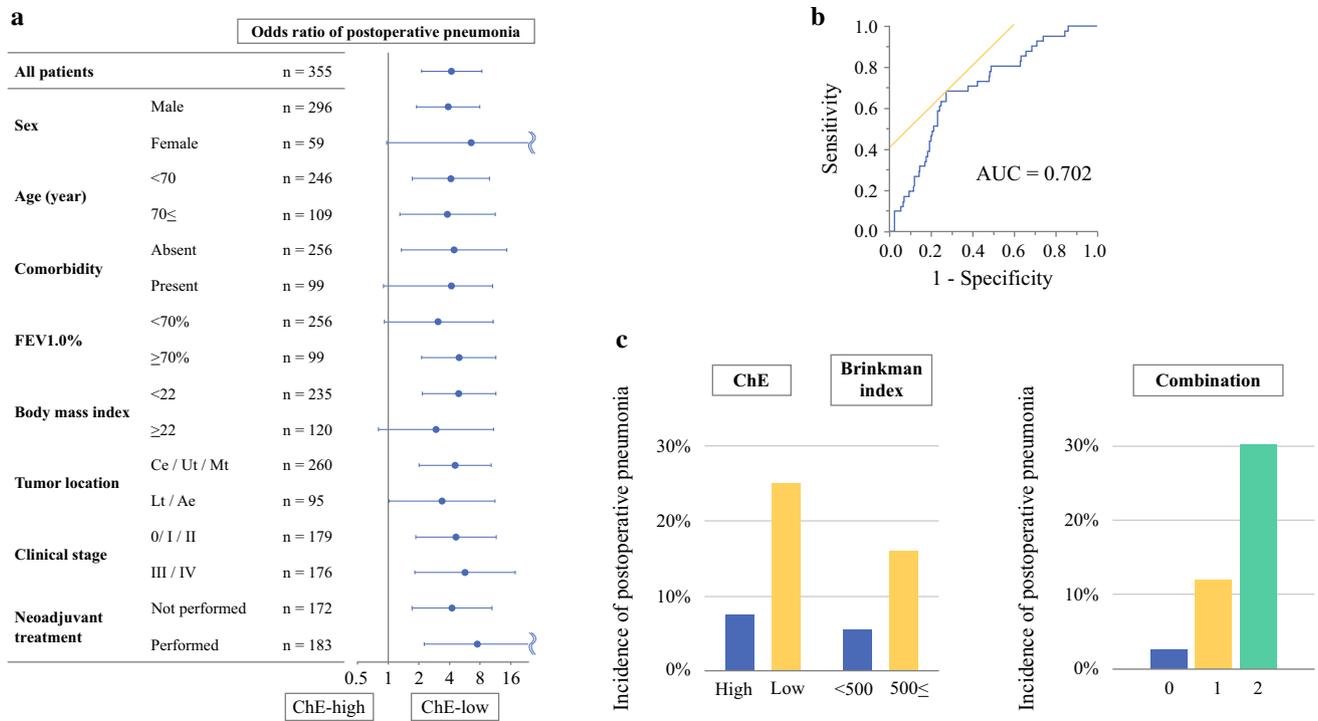

FIG. 3 a Forest plot to evaluate value of the association of preoperative ChE concentrations with postoperative pneumonia. **b** Predictive value of a combination of preoperative ChE concentrations and Brinkman index for postoperative pneumonia. **c** Incidence of postoperative pneumonia. Patients were categorized by preoperative ChE concentrations, Brinkman index, and the combination score. Incidence of pneumonia increased along with the score

support our conclusion that preoperative ChE concentrations are applicable to diverse clinical settings. A combination of preoperative serum ChE concentrations and Brinkman index provided a more precise risk stratification for pneumonia compared to preoperative ChE concentration alone.

Pneumonia after subtotal esophagectomy is associated with an increased risk of operative death (5–10%).[8,14] Unfortunately, improvements in perioperative patient care have failed to reduce the incidence of pneumonia after esophageal resection.[4,16,26] Furthermore, postoperative pneumonia adversely influences long-term outcomes after esophagectomy.[7,27] For example, inflammatory cytokines, which are produced at significantly higher concentrations by patients with pneumonia, impair immunity to cancer cells.[6,27] Moreover, pneumonia worsens a patient's general condition after esophagectomy, potentially leading to death from other diseases and to poor tolerance for additional therapy. Perioperative care to prevent pneumonia is therefore important to improve the short- and long-term outcomes of patients with esophageal cancer.

The mechanistic link between ChE concentrations and development of postoperative pneumonia is likely complex and remains to be identified. Serum ChE, also known as pseudo- or butyryl-ChE, is synthesized by hepatocytes, and its half-life in serum is 11 days.[28] Serum ChE concentrations decrease in people suffering from malnutrition, infections, and chronic liver damage.[29] For example, malnutrition is a possible cause of weak respiratory muscles and can increase the risk of aspiration because of impaired swallowing. Acetylcholine exerts immunosuppressive effects on macrophages and other cells of the immune system.[28,30] These cells express the α7-nicotinic acetylcholine receptor that mediates the inhibition of the production of inflammatory cytokines.[30,31] Therefore, low serum butyrylcholinesterase and acetylcholinesterase concentrations can facilitate unhydrolyzed acetylcholine-mediated immunosuppression, and subsequently activate cholinergic anti-inflammatory pathways.[29] Thus, a decreased ChE concentration maybe associated with an ineffective cellular immune response against bacteria and thereby contributes to increasing the invasiveness of bacteria, enabling them to proliferate in the lung.[28,30] Furthermore, impaired liver function attenuates drug metabolism and the production by hepatocytes of anti-inflammatory factors.[31,32] Eventually, the crosstalk of these complex factors likely increases the incidence of postoperative pneumonia, leading to a high predictive value of serum ChE concentrations.

Our findings raised two questions. First, why are serum ChE concentrations more sensitive than the other candidate parameters? We hypothesize that serum ChE concentrations is indicative of three elements, including immune disorders, malnutrition, and a decline in liver function, and therefore it was more closely associated with postoperative pneumonia than other parameters. Another question is whether preoperative modification of serum ChE concentrations by nutritional support reduces the adverse effects on the postoperative clinical course. To clarify whether corrections of preoperative serum ChE concentrations by nutritional support, such as oral or enteral immunonutrition, can reduce the incidence of postoperative pneumonia, prospective, clinical trials and serial measurement of immunological factors will be warranted.

The serum ChE concentration can be rapidly determined in every hospital and therefore is of interest as a marker of nutrition and liver function. For example, an analysis of 240 patients who underwent resection for the first manifestation of liver metastases from colorectal cancer found that a decreased postoperative serum ChE concentration was the only independent predictor of complications after minor liver resection.[33] Furthermore, decreased ChE concentrations independently predict the risk of morbidity after patients with hepatocellular carcinoma undergo hepatectomy.[34] The reasons that preoperative ChE concentrations influence the postoperative outcomes of patients who undergo a subtotal esophagectomy are unclear. However, our findings suggest that physicians can obtain accurate information for identification of high-risk patients who may be candidates for tailored perioperative care. Moreover, determination of preoperative ChE concentrations may enhance physicians' efforts to prevent postoperative pneumonia. To date, some systems that are widely used for calculating preoperative risk, such as the Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) model and the Surgical Risk Preoperative Assessment System (SURPAS), are available.[35,36] Our data suggest that preoperative ChE concentrations may serve as a component of such integrated scoring systems. We believe therefore that it is highly advisable for surgeons to include perioperative chest physiotherapy, breathing exercises, and nutritional support to reduce the incidence or exacerbation of postoperative pneumonia, particularly in patients with low ChE concentrations.[10,37] However, the effectiveness of such interventions to prevent pneumonia has not been fully demonstrated by clinical trials. A future clinical trial using preoperative ChE concentrations for an indicator of treatment effect or the eligibility criterion is expected to improve a clinical practice administered to patients undergoing subtotal esophagectomy.

The AUC value of preoperative serum ChE concentrations to predict postoperative pneumonia was adequate (0.662), and the sensitivity was as low as 0.51.[38] With the goal to enhance the predictive value, a combination of preoperative serum ChE concentrations and Brinkman index was successfully developed and clearly stratified patients as low, intermediate, or high risk of postoperative pneumonia. Because it is unlikely that a single parameter can faithfully represent the various patient conditions, the

concept of combining multiple parameters is considered the best alternative for overcoming the limitations of single parameters and will maximize their clinical usefulness.[39]

Our study includes several limitations. A retrospective nature might introduce selection bias. In addition, we were unable to identify the mechanisms responsible for our findings. For further evaluation of association of serum ChE concentrations with the host's nutritional status and immunity, dynamics of cytokines and relevant proteins are required. We did not evaluate the potential role of sarcopenia.[15] Last, this study included only Japanese patients, so that careful interpretation is needed to apply our data globally.

In conclusion, we show that readily determined preoperative ChE concentrations serve as a significant predictor of postoperative pneumonia of patients who undergo subtotal esophagectomy for esophageal cancer. Preoperative ChE concentrations, particularly in combination with Brinkman index, may facilitate a physician's ability to make decisions to reduce the incidence of pneumonia and to better educate patients on their risks before they undergo subtotal esophagectomy.

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