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Usefulness of the Modified Frailty Index for Predicting Pneumonia Occurrence After Esophagectomy

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ABSTRACT

Background Esophagectomy is an invasive and complication-prone surgical procedure. Therefore, a tool that can predict the occurrence of postoperative complications may be useful for perioperative management. In this study, we investigated whether the modified frailty index (mFI) could be a useful tool for predicting the postoperative complications of esophagectomy.

Methods In this study, 162 patients who underwent curative esophagectomy for esophageal squamous cell carcinoma from 2004 to 2019 at our institution were included. The patients were divided into the high mFI (≥ 0.27) and low mFI (< 0.27) groups, and the short-term postoperative outcomes of each group were examined retrospectively.

Results Regarding background factors, age and the American Society of Anesthesiologists physical status classification were significantly higher in the high mFI group (P = 0.049 and P = 0.002, respectively); however, the other items were not significantly different between the two groups. Regarding surgical outcomes, no significant differences in operative time, blood loss, and hospital stay were observed between the two groups. Regarding postoperative complications, pneumonia was significantly more common in the high mFI group (P = 0.035). In multivariate analysis, high mFI (P = 0.034) was an independent predictor of pneumonia, along with operative time ≥ 613 min (P = 0.03) and preoperative BMI < 20.48 (P = 0.006).

Conclusion The mFI is useful for predicting pneumonia after esophagectomy.

Key words esophagectomy; frailty; modified frailty index

Annually, there are more than 480,000 new cases of esophageal cancer and 400,000 esophageal cancer-related deaths worldwide.[1] Surgery for esophageal cancer is highly invasive, and the 5-year survival rate after esophagectomy was reported to be 55.6%.[2]

There are reports of high perioperative mortality rates for esophagectomy in patients aged > 70 years,[3] and according to the Japanese guidelines,[4] chemotherapy and radiotherapy are the treatment of choice if surgery is contraindicated. However, drawing a clear line on the tolerability of surgery is difficult, and the condition is judged comprehensively using various factors, including underlying disease, age, and experience of the attending physician.

Recently, the concept of "frailty," originally known in geriatrics, has gained attention as a possible determinant of surgical indications, including perioperative complications and mortality. Because frailty can be assessed using various methods,[5–9] simply using frailty as a determinant of indication for surgery is complicated. The modified frailty index (mFI) was developed by Velanovich et al. and contains 11 assessment items to identify frailty.[10] These items consist mainly of medical history, making it easy to assess and collect information. Recently, there have been scattered reports examining the correlation between the mFI and surgical outcomes.[11–14] Therefore, in this study, we investigated whether the mFI can be used to determine the postoperative complications of esophagectomy.

SUBJECTS AND METHODS

Patients

In this study, 162 patients who underwent curative esophagectomy for squamous cell carcinoma (SCC) from 2004 to 2019 at our institution were included. We evaluated preoperative frailty using the mFI and set the cutoff to 0.27 based on previous literature.[15, 16] The patients were divided into two groups: the high mFI (≥ 0.27) and low mFI (< 0.27) groups. Then, we retrospectively

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Abbreviations: ASA-PS, American Society of Anesthesiologists physical status classification; BMI, body mass index; CT, computed tomography; HALS, hand-assisted laparoscopic surgery; ICU, intensive care unit; mFI, modified frailty index; NAC, neoadjuvant chemotherapy; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index; ROC, receiver operating characteristic; SCC, squamous cell carcinoma; SSI, surgical site infection; VATS, video-assisted thoracic surgery examined their short-term postoperative outcomes. Patients with multiple primary cancers were excluded from this study. The clinicopathological findings were determined according to the seventh edition of the Union for International Cancer Control TNM staging system.[17]

Patients with T1 who did not have lymph node metastasis underwent surgery without preoperative treatment. Patients with ≥ T2, non-T4, or node-positive tumors (stage ≥ 2) received neoadjuvant chemotherapy (NAC), followed by esophagectomy. Meanwhile, patients with T4 tumors that were suspected to have invaded other organs (T4b) received chemoradiotherapy. In principle, those who were treated with NAC underwent surgery 5–7 weeks after the completion of NAC to avoid the influence of NAC. As standard neoadjuvant chemotherapy, 5-fluorouracil (5-FU) and cisplatin were used for all eligible patients except those who had impaired renal function, who were treated with 5-FU and nedaplatin. The standard surgical procedure was subtotal esophagectomy and reconstruction using a gastric tube. In terms of thoracic and abdominal operations, the open method was used mostly before 2009, and thoracoscopic and laparoscopic methods have increased since then.

The diagnoses of postoperative complications are listed below. Recurrent nerve paralysis was diagnosed in patients who complained of hoarseness and dysphagia, and when the movement of the vocal cords, observed using a laryngo-fiberscope, was insufficient, recurrent nerve paralysis was diagnosed. Anastomotic leakage was diagnosed by esophagography and computed tomography (CT) in patients with cloudy drainage, fever, and inflammatory response. Pneumonia was diagnosed by the presence of new or progressive infiltrates on chest radiographs and bacterial sputum cultures, with two or more of the following: antibiotic treatment, temperature > 38°C, leukocytosis (leukocyte count > 12 × 10^3/μL) or leukopenia (leukocyte count < 4 × 10^3/μL), and purulent secretions.[14] Pneumonia found incidentally during CT for other reasons was also included. All of the aforementioned complications were considered within 30 days of surgery or hospitalization, whichever was longer.

The prognostic nutritional index (PNI) was calculated as follows: 10 × albumin concentration + 0.005 × total lymphocyte count.[18] The neutrophil–lymphocyte ratio (NLR) was obtained by dividing the peripheral neutrophil count by the peripheral lymphocyte count.

mFI

The mFI is obtained by assigning one point to each of the following items and dividing the total score by 11: (1) functional status (not independent); (2) diabetes; (3) chronic obstructive pulmonary disease or pneumonia; (4) congestive heart failure; (5) history of myocardial infarction; (6) prior percutaneous coronary intervention, previous coronary surgery, or history of angina; (7) hypertension requiring medication; (8) impaired sensorium; (9) peripheral vascular disease or rest pain; (10) history of either transient ischemic attack or cerebrovascular accident; (11) history of cerebrovascular accident with neurological deficit.

Higher scores mean higher frailty, and no cutoff value was originally defined. As noted earlier, this study considered 0.27 as the cutoff value.

Statistical analysis

Values are presented as medians with ranges or numbers with percentages. Differences in the clinicopathological features between the high mFI and low mFI groups were evaluated using the chi-square test or Mann–Whitney *U*-test.

Cox regression was used for univariate and multivariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using the Cox proportional hazards model. We performed univariate and multivariate analyses to identify risk factors for complications that were significantly more common in the high mFI group. The cutoff values for the factors used in the univariate and multivariate analyses were calculated by performing receiver operating characteristic (ROC) curve analysis for the presence of pneumonia.

All calculations were performed using Statistical Package for the Social Sciences, version 25.0 (IBM Corporation, Armonk, NY), and *P*-values of less than 0.05 were used to indicate statistical significance.

Ethical considerations

The Institutional Review Board of our institution approved this study (20A234). The need for informed consent requirement was waived because of the retrospective nature of this study. All procedures were performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

Of the 162 patients, 11 were classified into the high mFI group and 151 were classified into the low mFI group, using 0.27 as the cutoff value (Table 1). Pathological factors did not differ between the two groups; however, age

Table 1. Patient characteristics

	high mFI (n = 11)	low mFI (n = 151)	P value
Age	70 (57–79)	66 (41–81)	0.049*
Sex (Male/Female)	11 (100%)/ 0 (0%)	130 (86.1%)/ 21(13.9%)	0.362
BMI†	22.04 (15.34–26.27)	20.77 (12.91–31.19)	0.734
PNI†	48.62 (34.4–51.56)	50.33 (35.5–68.54)	0.083
NLR†	1.94 (0.69–3.2)	1.66 (0.56–6.83)	0.954
pT (0/1/2/3/4)	0 (0%)/6 (54.5%)/2 (18.2%)/3 (27.3%)/0 (0%)	3 (2%)/70 (46.4%)/28 (18.5%)/49 (32.4%)/1 (0.7%)	0.966
pN (0/1/2/3/4)	4 (36.4%)/3 (27.3%)/2 (18.2%)/1 (9.1%)/1(9.1%)	79 (52.3%)/25 (16.6%)/29 (19.2%)/12 (7.9%)/6 (4%)	0.475
pStage (0/1/2/3/4)	1(9%)/3 (27.3%)/4 (36.4%)/3 (27.3%)/0 (0%)	15 (9.9%)/38 (25.2%)/51 (33.8%)/44 (29.1%)/3 (2%)	0.840
Tumor locaton (upper/middle/ lower)	3 (27.3%)/5 (45.4%)/3 (27.3%)	19 (12.6%)/74 (49%)/58 (38.4%)	0.254
N A C (present/absent)	6 (54.5%)/5 (45.5%)	72 (47.7%)/79 (52.3%)	0.886
Smoking history within 1 year (present/ absent)	4 (36.4%)/7 (63.6%)	81 (53.6%)/70 (46.4%)	0.353
ASA-PS (1/2/3)	0 (0%)/7 (63.6%)/4 (36.4%)	21 (13.9%)/121 (80.1%)/9 (6%)	0.002**

BMI, PNI, and NLR are all preoperative values. Upper, Ce and Ut; Middle, Mt; Lower, Lt and Ae. †Values are presented as medians with ranges or numbers with percentages. P = 0.05 denotes a statistically significant difference. *P < 0.05, **P < 0.01, ***P < 0.001. ASA-PS, American Society of Anesthesiologists physical status classification; BMI, body mass index; mFI, modified frailty index; NAC, neoadjuvant chemotherapy; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index.

and the American Society of Anesthesiologists physical status classification (ASA-PS) were significantly higher in the high mFI group (P = 0.049 and P = 0.002, respectively). For PNI and NLR, there were no significant differences between the two groups, although PNI tended to be lower in the high mFI group.

No significant differences in the surgical factors, such as surgical technique, the method of reconstruction, operative time, and blood loss, were observed between the two groups (Table 2).

Moreover, no differences in anastomotic leakage, recurrent nerve paralysis, surgical site infection (SSI), or in-hospital mortality were found between the two groups; however, postoperative pneumonia was significantly more common in the high mFI group (P = 0.035).

A univariate analysis was performed for postoperative pneumonia. The cutoff value for age was 70 years.[3] The cutoff values for preoperative body mass index (BMI), operative time, and blood loss were calculated using ROC analysis. In the univariate analysis, gender (P = 0.043), preoperative BMI < 20.48 kg/m^2 (P = 0.024), high mFI (P = 0.034), operative time ≥ 613.5 min (P = 0.013), and blood loss ≥ 205 mL (P = 0.027) were identified as prognostic factors (Table 3).

Then, the parameters found to be significant (P < 0.05) in the univariate analysis were included in the multivariate analysis. Operating time ≥ 613 min (P = 0.03), preoperative BMI < 20.48 kg/m^2 (P = 0.006), and high mFI (P = 0.034) were independent factors for postoperative pneumonia.

DISCUSSION

Frailty was originally a concept known in the field of geriatrics, and in the 1980s, it was considered to refer to elderly patients who had difficulty continuing home care.[19–22] Over time, frailty came to be viewed as a condition reversible by medical intervention, that is, as a preliminary stage of activities of daily living impairment, as distinguished from a condition in which impairment is already present.[23] Although these concepts are useful in strategies to prevent an increase in the number of elderly requiring care, various assessment methods have been proposed.[5–9] Some reports have examined the correlation between the mFI and surgical outcomes; however, there was no report in esophageal cancer. Although the number of patients with high mFI was small in this study, the use of the mFI allowed an objective tool for determining frailty, which was found to be associated with the occurrence of postoperative pneumonia. This could be a useful piece of information when considering indications for esophagectomy. To the best of our knowledge, this was the first study that clarified that the mFI is an independent predictor of pneumonia following esophageal cancer.

Pneumonia is an serious complication after esophageal cancer surgery, which can lead to death if it becomes severe and affects the postoperative prognosis.[24] Interestingly, postoperative pneumonia was significantly more common in the high mFI group, despite no difference in recurrent nerve paralysis between the two groups. Postoperative recurrent nerve palsy after esophagectomy is primarily a complication caused by

Table 2. Surgical outcomes

	high mFI (*n* = 11)	low mFI (*n* = 151)	*P* value
Operation time (min)†	661(517–842)	609 (327–1127)	0.565
Blood loss (mL)†	170 (25–740)	180 (10–2250)	0.948
Route of reconstruction (ante-thoracic/retro-sternal/ posterior mediastinal)	2 (18.2%)/6 (54.5%)/3 (27.3%)	13 (8.6%)/91 (60.2%)/47 (31.1%)	0.520
Organ for substitution (stomach/other)	10 (90.9%)/1 (9.1%)	137 (90.7%)/14(9.3%)	1.000
Chest operation method (thoracotomy/VATS)	3 (27.3%)/8 (72.7%)	42 (27.8%)/109 (72.2%)	1.000
Abdominal operation method (laparotomy/ HALS/ laparoscopy)	8 (72.7%)/0 (0%)/3 (27.3%)	87 (58%)/32 (21.3%)/31 (20.7%)	0.576
Number of lymphnode dissection field (2/3)	3 (27.3%)/8 (72.7%)	50 (33.1%)/101 (66.9%)	0.640
Length of ICU stay (day)†	3 (3–29)	3 (0–70)	0.243
Length of hospital stay (day)†	36 (19–122)	31 (10–266)	0.238
Anastomotic leakage	6 (54.5%)	48 (31.8%)	0.182
Recurrent nerve paralysis	0 (0%)	29 (19.2%)	0.210
Surgical site infection	0 (0%)	2 (1.3%)	1.000
Postoperative pneumonia	6 (54.5%)	36 (23.8%)	0.035*
Death in hospital	1 (9.1%)	2 (1.3%)	0.191

†Values are presented as medians with ranges or numbers with percentages. $P = 0.05$ denotes a statistically significant difference. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. HALS, hand-assisted laparoscopic surgery; ICU, intensive care unit; mFI, modified frailty index; VATS, video-assisted thoracic surgery.

Table 3. Univariate and multivariate analyses of clinicopathological factors influencing postoperative pneumonia

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥ 70 vs. < 70 years)	1.928	0.936–3.969	0.075			
Sex (male vs. female)	8.2	1.065–63.125	0.043*	7.378	0.900–60.500	0.063
BMI (≥ 20.475 vs. < 20.475)	0.438	0.214–0.897	0.024*	0.307	0.133–0.709	0.006**
mFI (high vs. low)	3.833	1.104–13.306	0.034*	4.427	1.122–17.474	0.034*
FEV1% (< 70% vs. ≥ 70%)	1.265	0.602–2.660	0.535			
Tumor location (upper vs. lower/middle)	0.409	0.115–1.460	0.168			
NAC (present vs. absent)	1.005	0.497–2.031	0.989			
pStage (2/3/4 vs. 0/1)	0.843	0.407–1.747	0.647			
Operation time (≥ 613.5 min vs. < 613.5 min)	2.528	1.211–5.277	0.013*	2.574	1.095–6.051	0.030*
Blood loss (≥ 205mL vs. < 205mL)	2.335	1.099–4.960	0.027*	2.027	0.892–4.607	0.092
Chest operation method (VATS vs. thoracotomy)	0.697	0.326–1.491	0.352			
Abdominal operation method (HALS/ laparoscopy vs. laparotomy)	0.849	0.413–1.747	0.657			
Number of lymphnode dissection field (3 vs. 2)	1.517	0.693–3.322	0.297			
Anastomotic leakage (present vs. absent)	0.635	0.291–1.390	0.256			
Recurrent nerve paralysis (present vs. absent)	1.322	0.547–3.197	0.536			

$P = 0.05$ denotes a statistically significant difference. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. BMI, body mass index; CI, confidence interval; HALS, hand-assisted laparoscopic surgery; HR, hazard ratio; FEV1.0%, forced expiratory volume 1.0% in 1 s; mFI, modified frailty index; NAC, neoadjuvant chemotherapy; VATS, video-assisted thoracic surgery.

injury during surgery, and its association with frailty is uncertain. A study reported that pneumonia was more common in frail patients after gastrectomy.[14] They retrospectively reviewed 346 elderly patients with gastric cancer undergoing gastrectomy and found that the mFI independently predicted the occurrence of pulmonary infection after surgery. Aceto et al. also reported that the mFI was a good predictive tool in elderly patients undergoing major open abdominal surgery.[25] These results suggest that the mFI is useful for predicting postoperative pneumonia. Furthermore, one of the items used to calculate mFI is "chronic obstructive pulmonary disease or pneumonia". Since this item is a respiratory endpoint and considered to be related to the prediction of postoperative pneumonia after esophageal cancer surgery, we performed a χ-square test on this item and postoperative pneumonia and found $P = 0.328$. Thus, the results suggest that "mFI" evaluation is a more important predictor of postoperative pneumonia from esophageal cancer surgery than items related to respiratory disease alone. In contrast, a study reported that physiotherapy improves mortality in patients with aspiration pneumonia[26] and that patients with pneumonia with improved nutritional status were discharged earlier than those with impaired nutritional status.[27] Interventions involving rehabilitation and nutritional intake may improve the prognosis of pneumonia after esophageal cancer surgery in patients with high mFI.

This study has some limitations. First, this was a single-center retrospective study with a small sample size. Second, the study period was long, and there were several surgeons, so the surgical methods differed, such as thoracotomy or video-assisted thoracic surgery. Third, the patients selected in this study were those deemed suitable for surgery, and those who were clearly intolerant to surgery were excluded, which may have resulted in a smaller sample size of patients with high mFI.

In conclusion, the mFI is useful for predicting the occurrence of pneumonia after esophagectomy. Preoperative interventions, such as respiratory rehabilitation and nutritional support, must be considered in patients with high preoperative mFI.

The authors declare no conflicts of interest.

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