

Impacts of Complications After Esophageal Cancer Surgery on Health-Related Quality of Life and Nutritional Status

Kotaro Sugawara

The University of Tokyo Graduate School of Medicine Faculty of Medicine: Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu

Koichi Yagi (✉ yagik-tyk@umin.ac.jp)

The University of Tokyo Graduate School of Medicine Faculty of Medicine: Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu <https://orcid.org/0000-0001-8319-8005>

Shuntaro Yoshimura

The University of Tokyo Graduate School of Medicine Faculty of Medicine: Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu

Susumu Aikou

The University of Tokyo Graduate School of Medicine Faculty of Medicine: Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu

Hiroharu Yamashita

The University of Tokyo Graduate School of Medicine Faculty of Medicine: Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu

Yasuyuki Seto

The University of Tokyo Graduate School of Medicine Faculty of Medicine: Tokyo Daigaku Daigakuin Igakukei Kenkyuka Igakubu

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Abstract

Purpose:

The long-term impacts of postoperative complications, especially pulmonary complications and anastomotic leakage, on health-related quality of life (HRQoL), nutritional status and body composition remain to be fully addressed in patients undergoing esophageal cancer surgery.

Methods:

Patients who underwent esophagectomy between 2015 and 2019 and survived without recurrence were eligible. HRQoL (European Organization for Research and Treatment of Cancer QLQ-C30 and the QLQ-OES18 questionnaires), nutritional and body composition data were prospectively evaluated before and at 3, 6, 12 and 24 months after surgery. Collected Data was compared between patients with postoperative complications and those without.

Results:

In total, 88 patients were included. Overall complications, anastomotic leakage and pulmonary complications developed in 48 (54.5%), 20 (20.7%) and 18 (20.5%) patients, respectively. Patients with pulmonary complications had more reflux-related symptoms (dry mouth; $P = 0.03$, coughing; $P = 0.047$, reflux; $P = 0.1$), and more problems with eating (nausea/vomiting; $P = 0.051$, eating difficulties; $P = 0.06$) at 24 months after surgery, as compared to those without such complications. Anastomotic leakage increased pain, speaking problems and dysphagia up to 6 months after surgery. Patients with pulmonary complications had significantly lower prealbumin levels and lower prognostic nutritional index values over time after surgery than those without these complications. In contrast, anastomotic leakage was not associated with poor nutritional status postoperatively. Body composition was not affected by the occurrence of complications.

Conclusion:

Postoperative complications, especially pulmonary complications, exert long-lasting negative effects on HRQoL, leading to poor nutritional status after esophagectomy.

Introduction

Esophageal carcinoma (EC) remains a major cause of cancer-related mortality worldwide [1]. Curative treatment for EC usually involves esophagectomy with pre- or post-operative chemotherapy and/or radiotherapy [2]. Many patients undergoing esophagectomy experience considerable deterioration in health-related quality of life (HRQoL) even after surviving refractory disease [3]. As such, patient-reported outcome measures have become increasingly important in cancer treatment efficacy assessment [4].

Previous studies have identified several factors related to postoperative HRQoL; surgical approaches [5–7], tumor stage [8], preoperative comorbidities [9] and postoperative complications [10–12]. Less invasive surgical approaches, such as transmediastinal esophagectomy (TME) [5], minimally invasive esophagectomy (MIE) [6] and robot-assisted minimally invasive esophagectomy (RAMIE) [7], reportedly reduce pain-related problems, resulting in better long-term HRQoL outcomes, as compared with conventional transthoracic esophagectomy (TTE). In contrast, problems including reflux, coughing and eating difficulties have proven resistant to innovations in surgical approaches [5, 6].

Esophagectomy is still associated with considerable morbidity [13]. The negative survival impacts of postoperative complications have been elucidated in patients undergoing surgery for EC [14–16]. Furthermore, prior studies have revealed postoperative complications to result in deterioration of HRQoL after esophagectomy [11, 12, 17]; however, the time-course effects of specific complications on HRQoL, nutritional status and body composition, have yet to be addressed taking the tumor entity into consideration.

We conducted a longitudinal study, using well-validated HRQoL instruments, to elucidate the impacts of two major postoperative complications after esophagectomy, pulmonary complications and anastomotic leakage [16], on long-term changes in HRQoL scores, nutritional status and body composition of patients undergoing esophagectomy.

Materials And Methods

Patients

Between April 2015 and March 2019, a total of 229 patients with pathologically-confirmed EC underwent potentially curative esophagectomy at the University of Tokyo Hospital. Patients undergoing salvage surgery (n = 28), those receiving two-stage operations (n = 14), those having synchronous multiple malignancies (n = 16), the very elderly (age > 85) (n = 5), those undergoing transhiatal esophagectomy (n = 15) and patients who did not consent to participate in the survey (n = 28) were excluded. The remaining 123 patients were prospectively surveyed, and among them 88 long-term survivors without recurrence within 2 years after surgery were analyzed. The Charlson comorbidity index (CCI) [18] was used to assess patient frailty at the time of surgery. This prospective study was approved by the local ethics committee of the faculty of medicine at the University of Tokyo (UMIN ID: 000017565).

Surgical treatment and postoperative management

Robot-assisted transmediastinal esophagectomy, or TME, with three-field lymphadenectomy was performed using a robotic surgical system, da Vinci S or Xi (Intuitive Surgical, Sunnyvale, CA, USA) [19]. Our standard TTE procedures consisted of subtotal esophagectomy with mediastinal lymphadenectomy via right thoracotomy, upper abdominal lymphadenectomy and reconstruction with intrathoracic anastomosis using a gastric tube. During the study period, TME was generally employed for cT1-2N0-1

cases according to the 7th edition of the TNM classification [19, 20]. The 7th Edition of the TNM classification [20] was applied to stage the tumors.

Definition of complications

Postoperative complications were defined as adverse events occurring within 30 days of surgery or during the in-hospital period, and severities were assessed using the Clavien–Dindo (C–D) classification [21]. Patients with Grade II or higher severity were regarded as having complications. Each complication was categorized according to the international consensus [22].

Pulmonary complications were defined as the presence of one or more of the following postoperative conditions [14, 15]: initial ventilatory support for more than 48 hours, intubation for respiratory failure, acute respiratory distress syndrome, pneumonia, pleural effusion and atelectasis requiring bronchoscopy or antibiotics. Anastomotic leakage was defined as clinical signs of leaking, such as erythema, skin edema, emission of fluid or pus from a surgical wound or cervical drain or a radiographically detected leak confirmed by esophagography and/or computed tomography [23, 24].

Data collection

Written HRQoL questionnaire responses were collected at the time of admission for surgery and at 3, 6, 12 and 24 months after surgery. HRQoL was measured using well-established questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [25] and EORTC QLQ-OES18 [26]. Higher scores correspond to better HRQoL in the function scales and the global QOL scale, whereas higher scores for symptom scales and single items represent more problems [27]. The nutritional status (albumin and prealbumin) and body composition data were obtained on the same schedule. Body composition was measured by bioelectrical impedance analysis using an Inbody 770 machine (Biospace, Tokyo, Japan) [28].

Statistical Analysis

Categorical variables were expressed in numerical figures and percentages and compared using Fisher's exact test or the χ^2 test, as appropriate. Continuous variables were expressed as the median values (range) and compared using Wilcoxon's rank-sum test. Statistical analyses were carried out using JMP 13.0.0 (SAS Institute, Cary, NC).

Results

Patient characteristics

Among the 123 patients, 22 (17.9%) developed recurrence within 2 years of esophagectomy. One patient (0.8%) died due to pneumonia at 18 months after surgery and 12 (9.8%) did not return the questionnaires. The remaining 88 (71.5%) patients, who survived for at least 2 years after surgery without recurrence, were eligible for inclusion in the analysis. The clinicopathological features of these 88 patients are presented in Table 1. Eight (9.1%) patients had comorbidities (CCI \geq 2). Neoadjuvant chemotherapy was

performed in 32 patients (36.4%). Fifty-eight (65.9%) patients underwent TME. There were 37 (42.0%), 25 (28.4%), 23 (26.2%) and 3 (3.4%) patients with pStage 0-I, II, III and IV disease, respectively. High lymph node yield was achieved in our series.

Table 1
Characteristics of 88 patients included in the analysis

Variables	No. of patients (%)
Age, y Median (range)	67 (43–82)
Sex	
male	63 (71.6)
female	25 (28.4)
Comorbidity (CCI \geq 2)	8 (9.1)
Tumor location	
Lt	29 (33.0)
Mt	51 (57.9)
Ut	8 (9.1)
Neoadjuvant chemotherapy	32 (36.4)
Surgery	
TTE	30 (34.1)
TME	58 (65.9)
Tissue Type	
SCC	83 (94.3)
AC	5 (5.7)
pStaging	
pStage 0-I	37 (42.0)
pStage II	25 (28.4)
pStage III	23 (26.2)
pStage IV	3 (3.4)
Lymphadenectomy	
2 fields	13 (14.8)
3 fields	75 (85.2)
No. of retrieved lymph nodes, Median (range)	64 (9-158)
Curability, R1-2	3 (3.4)

Variables	No. of patients (%)
Abbreviations: CCI, Charlson comorbidity index; TTE, transthoracic esophagectomy; TME, transmediastinal esophagectomy; SCC, squamous cell carcinoma; AC, adenocarcinoma	

Postoperative complications

The details of the postoperative complications are shown in Table 2. Overall complications (\geq Grade II according to C-D classification) developed in 48 (54.5%) patients. The most common postoperative complications were anastomotic leakage, which occurred in 20 of the 88 patients (20.7%), pulmonary complications in 18 (20.5%) and recurrent nerve palsy in 8 (9.1%). Patient characteristics according to the presence of each complication are described in Supplementary Table 1. There were no significant differences in terms of demographic data, comorbidity, surgical procedures, pathological tumor staging and lymph node yield, between patients with and those without complications, the exceptions being that patients with overall complications had a significantly lower rate of neoadjuvant chemotherapy ($P= 0.02$) while those with anastomotic leakage underwent a significantly higher rate of 3-field lymphadenectomy ($P= 0.007$), as compared to those without such complications.

Table 2
Postoperative complications occurring within 30 days of esophageal cancer surgery in our cohort

Variables	No. of patients (%)
Overall complications (\geq Grade II [†])	
No	40 (45.5)
Yes	48 (54.5)
Medical complications	
Pulmonary complications	18 (20.5)
Pneumonia	11 (12.5)
Acute respiratory disease syndrome	4 (4.5)
Pleural effusion	1 (1.1)
Reintubation	1 (1.1)
Initial ventilatory support for more than 48 hours	1 (1.1)
Cardiovascular	
Atrial fibrillation	3 (3.4)
Deep vein thrombosis	1 (1.1)
Acute heart failure	1 (1.1)
Others	
Delirium	1 (1.1)
Urinary tract infection	2 (2.3)
Surgical complications	
Anastomotic leakage	20 (22.7)
Recurrent nerve palsy	8 (9.1)
Surgical site infection	3 (3.4)
Chylothorax	2 (2.3)
* Some patients had more than one type of complication.	
[†] Clavien-Dindo classification	

Longitudinal changes in global QOL and functional scales

The longitudinal changes in global QOL and functional scales determined by the QLQ-C30 questionnaire are presented in Supplementary Table 2. None of the baseline scores for global QOL and functional scales differed according to the presence of complications, except that patients developing pulmonary complications had significantly poorer scores for global QOL and physical functions preoperatively. After surgery, most of the HRQoL outcomes did not differ significantly between patients with and without complications. Patients with pulmonary complications showed significantly lower emotional function scores than those without these complications at 24 months postoperatively. Anastomotic leakage was associated with a significant decrease in emotional and social function scores at 3 months postoperatively. Overall, postoperative complications had a modest impact on global QOL and functional scales within 2 years after surgery.

Time-course changes in general and esophageal-related symptoms

Time-course changes in problems related to reflux and coughing (reflux, dry mouth, difficulty with coughing and taste abnormalities), symptoms related to eating (nausea/vomiting, appetite loss, eating difficulties and dysphagia) and pain-related symptoms (pain, fatigue, dyspnea and insomnia) are shown in Figs. 1, Supplementary Fig. 1 and Supplementary Fig. 2, respectively. Many of the symptoms and single items assessed by the QLQ-C30 and QLQ-OES18 questionnaires worsened markedly at three months after surgery, but improved during the first year of follow-up. Overall complications had no significant impacts on either symptoms or single items (Supplementary Table 3).

Notably, patients with pulmonary complications had more problems related to reflux and coughing than those without pulmonary complications (Fig. 1, Table 3); reflux ($P=0.1$ at 24 months), dry mouth ($P=0.02$ at 12 months and $P=0.03$ at 24 months) and coughing ($P=0.047$ at 24 months). Pulmonary complications also exacerbated some of the symptoms related to eating (nausea/vomiting and eating difficulties) at 24 months after surgery, although the differences did not reach statistical significance ($P=0.051$ and 0.06 , respectively, Supplementary Fig. 1, Table 3). Pain-related symptoms did not differ between the two groups, except for insomnia at 24 months after surgery (Supplementary Fig. 2, Table 3). Anastomotic leakage was associated with significantly poorer scores for pain, trouble speaking and dysphagia at 12 months after surgery, although the differences had disappeared by 24 months after surgery (Table 3).

Table 3

General and esophageal-related symptoms: comparison between patients with and those without pulmonary complications or anastomotic leakage

	Time Point of HRQoL measurement				
	Pre	3 months	6 months	1 year	2 years
Pulmonary complication; yes (n = 18) vs. no (n = 70)					
EORTC QLQ-C30					
Fatigue	0.09	0.59	0.35	0.54	0.09
Nausea and vomiting	0.92	0.83	0.91	0.059	0.051
Pain	0.052	0.77	0.48	0.26	0.59
Dyspnea	0.55	0.31	0.19	0.08	0.28
Insomnia	0.87	0.77	0.89	0.18	0.04
Appetite loss	0.2	0.41	0.39	0.63	0.11
Constipation	0.13	0.66	0.41	0.02	0.29
Diarrhea	0.99	0.07	0.78	0.66	0.29
Financial difficulties	0.42	0.88	0.55	0.84	0.45
EORTC QLQ-OES18					
Eating difficulties	0.62	0.51	0.94	0.83	0.06
Reflux	0.5	0.57	0.35	0.09	0.1
Esophageal Pain	0.29	0.48	0.88	0.77	0.61
Swallowing saliva	0.88	0.75	0.59	0.3	0.27
Choking when swallowing	0.049	0.9	0.78	0.12	0.71
Dry mouth	0.15	0.69	0.54	0.02	0.03
Taste abnormality	0.74	0.08	0.21	0.97	0.35
Trouble with coughing	0.39	0.74	0.94	0.16	0.047
Difficulty speaking	0.11	0.36	0.87	0.5	0.65
Dysphagia	0.65	0.98	0.44	0.72	0.37
Anastomotic leakage; yes (n = 20) vs. no (n = 68)					

	Time Point of HRQoL measurement				
	Pre	3 months	6 months	1 year	2 years
EORTC QLQ-C30					
Fatigue	0.22	0.59	0.37	0.69	0.07
Nausea and vomiting	0.83	0.13	0.44	0.63	0.09
Pain	0.69	0.61	0.047	0.92	0.59
Dyspnea	0.39	0.75	0.17	0.87	0.3
Insomnia	0.42	0.33	0.46	0.12	0.12
Appetite loss	0.42	0.22	0.57	0.33	0.02
Constipation	0.45	0.11	0.17	0.36	0.63
Diarrhea	0.61	0.81	0.83	0.87	0.57
Financial difficulties	0.79	0.87	0.94	0.46	0.98
EORTC QLQ-OES18					
Eating difficulties	0.49	0.51	0.93	0.79	0.87
Reflux	0.61	0.32	0.75	0.78	0.81
Esophageal Pain	0.34	0.58	0.28	0.78	0.27
Swallowing saliva	0.8	0.28	0.47	0.19	0.76
Choking when swallowing	0.47	0.82	0.86	0.81	0.62
Dry mouth	0.99	0.54	0.88	0.53	0.47
Taste abnormality	0.23	0.52	0.89	0.14	0.81
Trouble with coughing	0.69	0.74	0.96	0.77	0.15
Difficulty speaking	0.52	0.27	0.009	0.17	0.37
Dysphagia	0.49	0.36	0.024	0.78	0.69
* Data are presented with <i>P</i> values for the significance of differences between the groups.					
** HRQoL outcomes that are significantly poorer in patients with than in those without complications are in bold type.					
Abbreviations: HRQoL, health-related quality of life					

Longitudinal changes in body composition data and nutritional status

Patients with pulmonary complications had significantly lower prealbumin at 3, 6, 12 and 24 months after surgery than those without these complications ($P=0.049, 0.01, 0.02$ and 0.008 , respectively, Supplementary Table 4). The presence of pulmonary complications also decreased PNI at 12 and 24 months after surgery, although the differences did not reach statistical significance ($P=0.058$ and 0.09 , respectively, Supplementary Table 4). In contrast, the presence of overall complications and anastomotic leakage did not significantly change nutritional status. Figure 2 shows time-course changes in nutritional parameters. All parameters (albumin, prealbumin and PNI) declined markedly after surgery, then gradually improved and returned to near baseline levels in most of the patients (Fig. 2); however, patients with pulmonary complications exhibited poorer nutritional status than those without pulmonary complications over time. There was no influence of complications on the body composition data (Supplementary Table 4).

Discussion

Our current study revealed complications after esophageal cancer surgery, especially pulmonary complications, to exert long-term negative impacts on HRQoL outcomes and nutritional status. Pulmonary complications were associated with increases in problems related to reflux/coughing and eating, while not worsening pain-related symptoms. Notably, patients with pulmonary complications had long-lasting poor nutritional status.

Esophagectomy is still associated with considerable morbidity; the overall incidence of complications is reportedly approximately 60% [13]. These complications must be managed very carefully to prevent early postoperative mortality [16, 24]. Importantly, with an increasing number of long-term survivors after curative resection for EC, the long-term impacts of postoperative complications have recently been highlighted [29]. The influences of postoperative complications on survival outcomes [14, 15, 24] and HRQoL outcomes [10–12] have, in fact, been investigated.

Generally, the HRQoL of patients undergoing esophagectomy markedly deteriorates immediately after surgery, but then gradually recovers to a nearly preoperative level within 3 to 5 years after surgery [30]; however, some patients do not experience restored HRQoL after surgery [3], experiencing multiple concurrent long-persisting symptoms, such as reflux and eating problems [31]. Recently, minimally invasive surgical approaches have reportedly yielded good postoperative HRQoL outcomes [5, 32], due mainly to reducing pain-related symptoms [6, 33]. Our recent findings suggested robot-assisted transmediastinal esophagectomy to reduce reflux problems [5], but an abundance of evidence has shown that symptoms associated with eating, reflux and coughing are refractory and difficult to ameliorate with surgical modifications [6]. Rather, postoperative complications reportedly exert long-lasting negative effects on HRQoL outcomes including eating problems [10–12].

In our study, overall complications had modest impacts on HRQoL outcomes. Therefore, in order to further dissect the effects of each individual complication, we focused on two major complications and

investigated their individual impacts. Notably, the impacts of pulmonary complications on HRQoL and nutritional status differed from those of anastomotic leakage. Patients with anastomotic leakage had more pain, speaking and dysphagia problems at 6 months after surgery, although these negative effects had diminished at 2 years postoperatively, a finding in agreement with those of previous studies [12, 17].

Most importantly, pulmonary complications exerted negative impacts on several aspects of HRQoL over time. Most notably, pulmonary complications were associated with more dry mouth, coughing and reflux, all of which correlate highly with each other [34], at a later time after esophagectomy. These symptoms reportedly cause insomnia [29], which might explain the observation that patients with pulmonary complications had significantly worse insomnia at 2 years after surgery than those without such complications. Furthermore, patients with pulmonary complications had more symptoms of nausea/vomiting and eating difficulties than those without these complications at 2 years after surgery, although the differences were not statistically significant ($P = 0.051$ and 0.06 , respectively).

The presence of pulmonary complications was significantly associated with poor nutritional status. These observations raise the possibility that pulmonary complications led to an increase in reflux, coughing and eating difficulties, resulting in malnutrition [35]. On the other hand, previous studies have suggested that eating problems contributed to postoperative malnutrition, whereas dysphagia and reflux did not [36]. Although nutritional status appears to be a good indicator when estimating HRQoL, the relationship between each HRQoL measure and nutritional status has yet to be fully addressed [37]. We also evaluated body composition data, but detected no significant differences according to whether or not postoperative complications developed.

Poor HRQoL at 6 months after esophageal cancer surgery is reportedly associated with increased mortality risk [38]. Patients with postoperative complications, especially pulmonary complications, reportedly had poor survival outcomes [14, 15]. Notably, the negative survival impact of pulmonary complications is not due to an increase in cancer-related death, but rather mainly to more non-cancer deaths [14, 24]. Our observations, together with those of a recent study [15], indicate that pulmonary complications potentially worsen a patient's general medical conditions, resulting in increased all-cause mortality.

The proven impacts of postoperative complications allow clinicians to optimize perioperative strategies in order to minimize complications. Surgical complications can reportedly be reduced by improving surgeon volume and experience [39]. Pulmonary complications can be prevented by smoking cessation before surgery, perioperative pulmonary rehabilitation and minimally invasive surgery [40, 41]. The benefit of extended nutritional support in patients undergoing esophagectomy remains controversial [42], but intensive nutritional interventions might benefit patients with postoperative complications given that such aggressive interventions are known to be beneficial, especially for severely malnourished patients [43].

Our study has limitations. First, it was a single-institution study. It seems likely that a multi-center collaborative study with a large cohort could achieve more convincing results. On the other hand, all of our patients underwent the standardized surgical procedure with high lymph node yield at an experienced

center with a high volume of patients [44]; our findings are thus reliable. Second, the small patient number has limited statistical power. Additionally, the sample size of long-term survivors was further limited due to the poor long-term outcomes of EC patients. Third, we did not evaluate the association between the severity of the complications and HRQoL outcomes, which merits further detailed examination in future studies. Lastly, we evaluated the impacts of pulmonary complications and anastomotic leakage separately, but some patients had both of these complications since medical complications often lead to surgical complications and vice versa. This potential mixed cause-effect pattern must be taken into consideration when interpreting the results.

In conclusion, our findings suggest postoperative complications, especially pulmonary complications, to have a negative effect on HRQoL outcomes, leading to poor nutritional status over the long term after esophagectomy. Our results are anticipated to help clinicians take measures to prevent complications and optimize postoperative long-term strategies, thereby improving the HRQoL of patients.

Abbreviations

HRQoL, Health-related quality of life; EC, esophageal carcinoma; TME, transmediastinal esophagectomy; MIE, minimally invasive surgery; RAMIE, robot-assisted minimally invasive esophagectomy; TTE, transthoracic esophagectomy; CCI, Charlson comorbidity index; C–D, Clavien–Dindo; EORTC, European Organization for Research and Treatment of Cancer

Declarations

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Code availability: Not applicable

Authors' contributions: Kotaro Sugawara, Koichi Yagi, Shuntaro Yoshimura and Yasuyuki Seto are the authors mainly responsible for the study's conception and design, acquisition of data, and analysis and interpretation of data. Yasuhiro Okumura, Susumu Aikou and Hiroharu Yamashita contributed mainly to the drafting of the article and to revising it critically for important intellectual content. Drs Kotaro

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Consent to participate: Opt-out

Consent for publication: Not applicable

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Figures

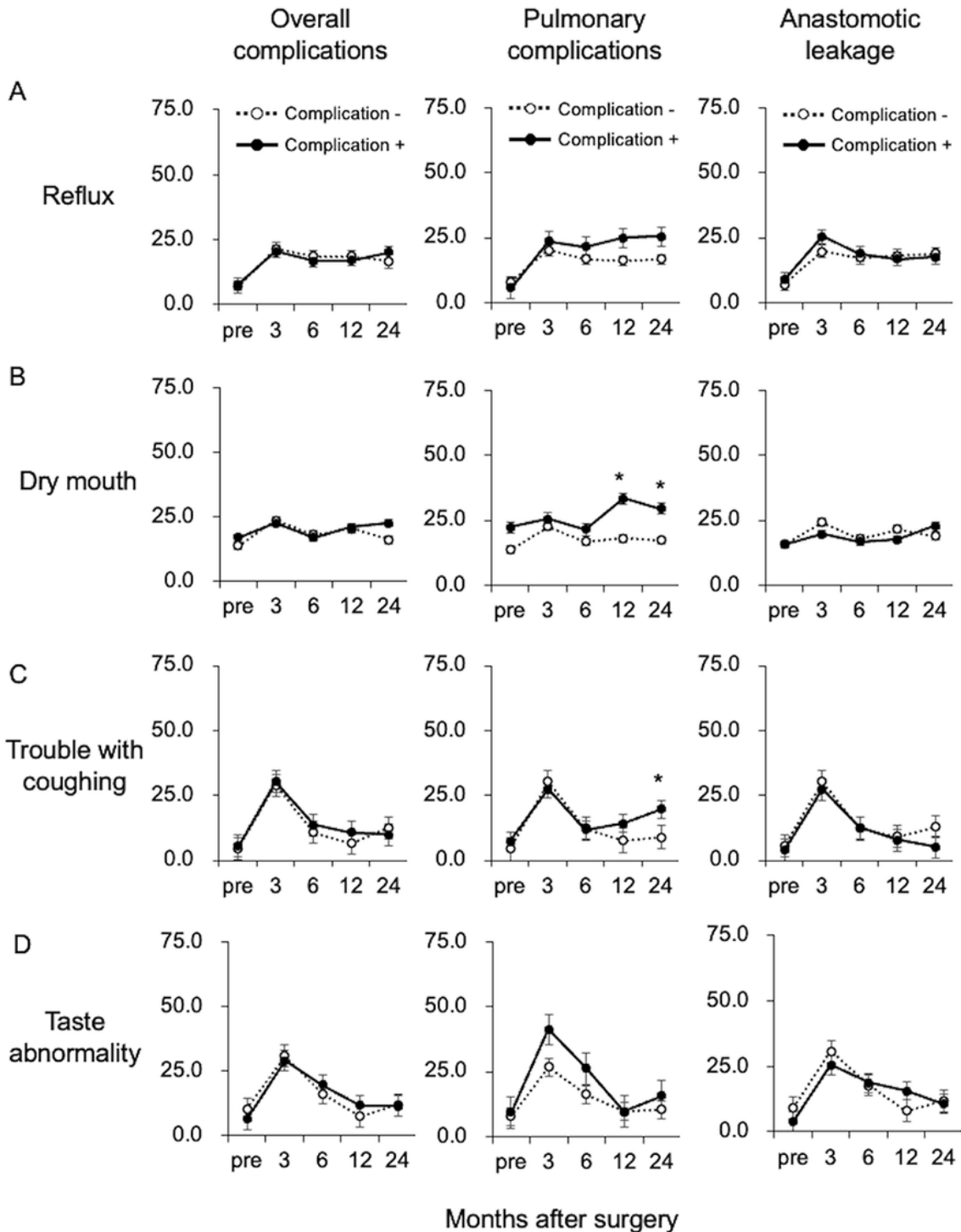


Figure 1

Time-course changes in symptoms related to reflux and coughing Mean scores for (A) reflux, (B) dry mouth, (C) excessive coughing, and (D) altered taste in patients with (●) and without (○) complications were calculated based on QLQ-OES18 questionnaire responses. Higher scores indicate more symptoms. Scores were compared between patients with overall complications (left), pulmonary complications (middle), and anastomotic leakage (right) and those without these complications. Patients with pulmonary complications had more problems related to reflux and coughing than those without pulmonary complications; reflux ($P = 0.1$ at 24 months), dry mouth ($P = 0.02$ at 12 months and $P = 0.03$ at 24 months) and excessive coughing ($P = 0.047$ at 24 months). Error bars represent standard errors. Student's t test was used to determine the statistical significance of differences ($*P < 0.05$).

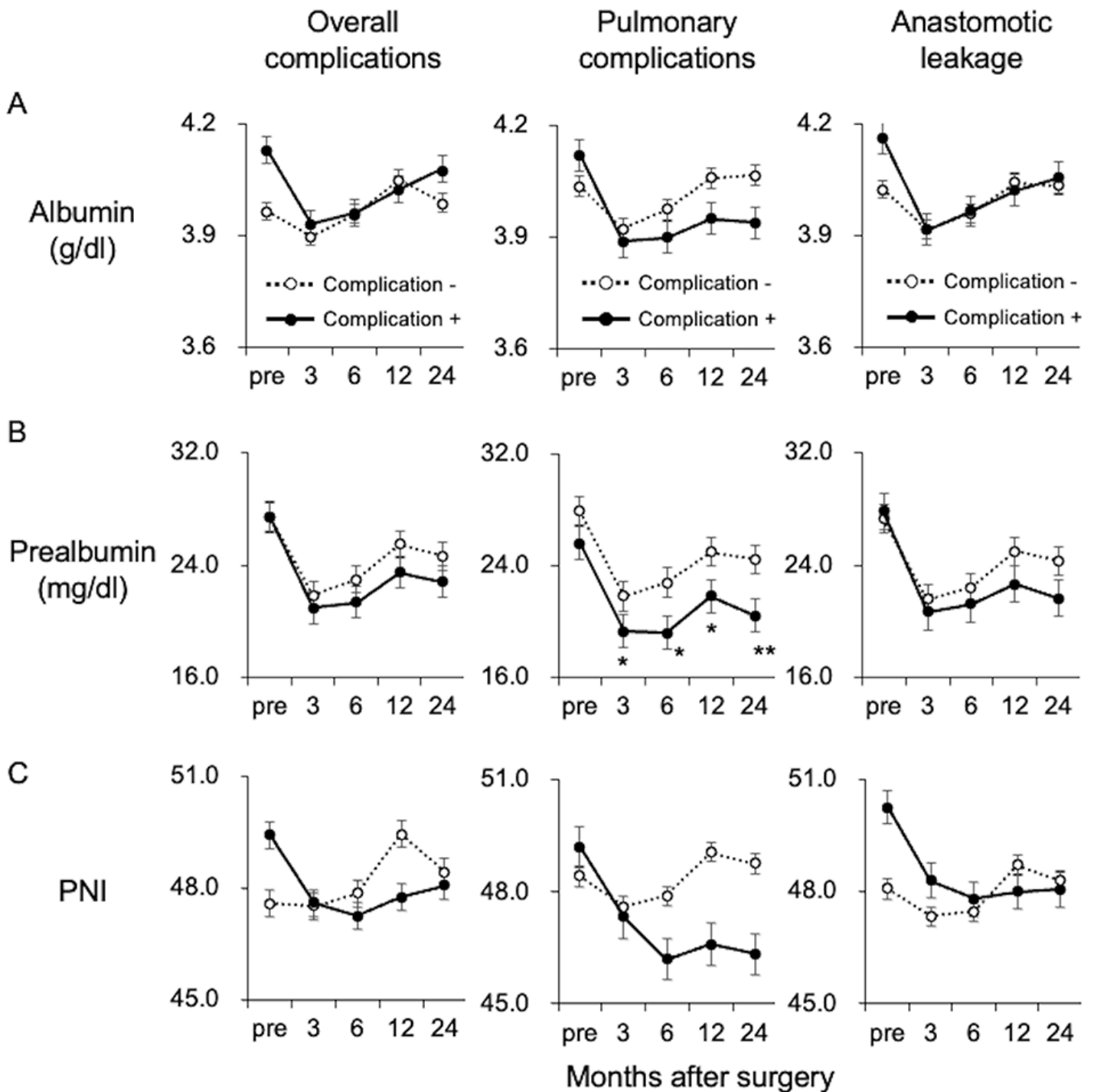


Figure 2

Longitudinal changes in nutritional status Nutritional markers (A; albumin, B; prealbumin, C; PNI) were measured before and after surgery up to 2 years, and were compared between patients with and without overall complications (left), pulmonary complications (middle), and anastomotic leakage (right). Patients with pulmonary complications had significantly lower prealbumin levels at 3, 6, 12 and 24 months after surgery ($P = 0.049, 0.01, 0.02$ and 0.008 , respectively), and also had lower PNI at 12 and 24 months after

surgery ($P = 0.058$ and 0.09 , respectively), as compared to those without pulmonary complications. Error bars represent standard errors. Student's t test was used to determine the statistical significance of differences ($*P < 0.05$, $**P < 0.01$).

Supplementary Files

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