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Impact of Various Types of Comorbidities on the Outcomes of Laparoscopic Total Gastrectomy in Patients with Gastric Carcinoma

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ABSTRACT

Purpose: With increasing life expectancy, the presence of comorbidities has become a major concern in elderly patients who require surgery. However, little is known about the impact of different comorbidities on the outcomes of laparoscopic total gastrectomy (LTG). In this study, we investigated the impact of comorbidities on postoperative complications in patients undergoing LTG for gastric carcinoma.

Materials and Methods: We retrospectively reviewed the cases of 303 consecutive patients who underwent LTG for gastric carcinoma between 2005 and 2016. The associations between each comorbidity and postoperative complications were assessed using univariate and multivariate analyses.

Results: A total of 189 patients (62.4%) had one or more comorbidities. Hypertension was the most common comorbidity (37.0%), followed by diabetes mellitus (17.8%), chronic viral hepatitis (2.6%), liver cirrhosis (2.6%), and pulmonary (27.1%), ischemic heart (3.3%), and cerebrovascular diseases (2.3%). The overall postoperative morbidity and mortality rates were 20.1% and 1.0%, respectively. Patients with pulmonary disease significantly showed higher complication rates than those without comorbidities (32.9% vs. 14.9%, respectively, P=0.003); patient with other comorbidities showed no significant difference in the incidence of LTG-related complications. During univariate and multivariate analyses, pulmonary disease was found to be an independent predictive factor for postoperative complications (odds ratio, 2.14; 95% confidence interval, 1.03–4.64), along with old age and intraoperative bleeding.

Conclusions: Among the various comorbidities investigated, patients with pulmonary disease had a significantly higher risk of postoperative complications after LTG. Proper perioperative care for optimizing pulmonary function may be required for patients with pulmonary disease.

Keywords: Stomach neoplasms; Comorbidity; Postoperative complications; Laparoscopy; Gastrectomy

INTRODUCTION

Laparoscopic gastrectomy for gastric carcinoma yields better early postoperative outcomes including lesser pain, fewer wound complications, shorter hospital stays, and improved short-term quality of life than open surgery [1,2]. In Korea and Japan, early gastric carcinoma

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now accounts for nearly 50% of all gastric cancer cases, and laparoscopic gastrectomy is widely performed as a minimally invasive treatment [3,4]. The surgical techniques of laparoscopic distal gastrectomy, including gastric resection and lymph node dissection, are relatively well-standardized among gastric surgeons. Additionally, the technical and oncological feasibility of laparoscopic distal gastrectomy have been well-demonstrated in several previous studies including randomized controlled trials [4]. However, laparoscopic total gastrectomy (LTG) is still regarded as a challenging surgical procedure by many gastric surgeons, which is mostly attributed to the technical difficulties associated with extended lymphadenectomy and esophagojejunal anastomosis.

With the rise in the aging population, the proportion of elderly patients who undergo gastric resection is continuously increasing. According to a Korean nationwide survey, the proportion of patients aged ≥70 years undergoing gastric cancer surgery has markedly increased from 9.1% to 25.3% in 1995 and 2014, respectively [3]. With increasing age, patients demonstrate a greater number of comorbidities such as hypertension, diabetes mellitus, and cardiovascular and pulmonary diseases. Comorbidities adversely affect the normal physiologic healing process postoperatively and thus, can lead to the increased incidence of postoperative complications. Many previous studies on laparoscopic gastrectomy have shown that the presence of comorbidities is one of the major risk factors for increased complication and mortality rates [5-7]. However, little is known on the impact of various comorbidities on postoperative complications after laparoscopic gastrectomy.

LTG carries a higher risk of postoperative complications, especially those that are anastomosis-related, than laparoscopic distal gastrectomy [8,9]. Although several studies have investigated the risk factors for postoperative complications after LTG [10,11], the effects of comorbidities on LTG outcomes have not been fully elucidated. As an increasing number of elderly patients with comorbidities undergo LTG, a better understanding of the impact of these comorbidities on surgical outcomes is necessary to enable proper surgical decision-making and minimize postoperative complications. Therefore, we investigated the impact of each comorbidity on the postoperative complications of patients undergoing LTG for gastric carcinoma.

MATERIALS AND METHODS

Patients and data

We retrospectively reviewed the cases of 303 patients who underwent LTG for middle- or upper-third gastric carcinoma between 2005 and 2016 at Chonnam National University in South Korea. Patients who had previously undergone major abdominal operations (hepatobiliary or colorectal surgery) or had undergone combined major organ resection (spleen, kidney, or adrenal gland) were excluded from the study to rule out the effects of these procedures on the postoperative outcomes. All patients underwent upfront surgery without preoperative chemotherapy. The surgeries were conducted by 4 surgeons who performed about 150 to 700 operations by the time the study was initiated. The decision to perform LTG was made based on preoperative staging. LTG was originally indicated for patients with cT1N0 gastric carcinoma; however, as surgeons gain experience with laparoscopic surgery, they also performed LTG on patients with more advanced gastric cancers, such as cT2-3N0-2, during the latter stages of the study period. This study was approval by the Institutional Review Board at Chonnam National University Hwasun Hospital in South Korea (CNUHH-2017-153) was

performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type study, formal consent is not required.

The patients' demographic data, clinicopathological characteristics, and information on their surgical outcomes were retrospectively collected from our institution's database collection. Tumor characteristics and pathological stages were based on the guidelines of the Japanese classification of gastric carcinoma [12] and the 7th edition of the Union for International Cancer Control tumor, node, metastasis (TNM) classification [13], respectively. Postoperative complications were defined as those that occurred within 30 days after the surgery and were classified as local or systemic based on whether or not they occurred within the operating field. The severity of postoperative complications was graded based on the Clavien-Dindo classification [14].

Patients with a history of medical treatment for any disease were considered to have a comorbidity. Information regarding such comorbidities was obtained from medical history records or during the preoperative workup; the latter included complete blood count, coagulation, biochemical, and pulmonary function tests, electrocardiography, and chest radiography. If abnormal findings were observed in the preliminary workup, further appropriate tests were performed to diagnose any underlying diseases. We investigated the most common comorbidities including hypertension, diabetes mellitus, chronic viral hepatitis, liver cirrhosis, and pulmonary, ischemic heart, and cerebrovascular diseases; other less common types of comorbidities were recorded, as appropriate. Patients with abnormal preoperative pulmonary function tests that suggested the presence of chronic obstructive pulmonary disease (COPD), i.e., a forced expiratory volume in 1 second/forced vital capacity ratio <0.7, or those with a history of pulmonary disease (COPD, asthma, or pulmonary tuberculosis) were considered to have pulmonary disease.

Operative procedures and postoperative care

About 5–6 abdominal ports were used for LTG. The surgeon stood on the right side of the patient. After a pneumoperitoneum of 12 to 14 mmHg was achieved, gastric dissection was initiated by dividing the greater omentum and moving towards the left gastroepiploic area. All gastric and lymph node dissections were performed with the use of laparoscopic energy devices such as the Harmonic Scalpel™ (Ethicon Endo-Surgery, Cincinnati, OH, USA) or Ligasure™ (Valleylab, Boulder, CO, USA). The extent of lymph node dissection followed the Japanese treatment guidelines for gastric carcinoma; D2 lymph node dissection was indicated for patients with clinical stage ≥cT2 or cN+ disease [15]. The lymph nodes in the splenic hilum are usually dissected to preserve the spleen (i.e., the spleen-preserving technique).

Esophagojejunal anastomosis was performed via either the extracorporeal or intracorporeal method. For the extracorporeal method, esophagojejunal reconstruction was performed using a 25-mm circular stapler through a 6–7 cm mini-laparotomy on the epigastrium, which is similar to the conventional open technique. On the other hand, for the intracorporeal method, side-to-side esophagojejunostomy (overlap method) was performed using a 45-mm linear stapler after resecting the abdominal esophagus with a linear stapler. A common hole at the esophagojejunostomy site was closed using the hand-sewn method or a linear stapler.

A standardized care protocol was utilized in the management of patients. Early postoperative oral nutrition has been implemented since 2009, wherein an oral diet was initiated on postoperative day 1 or 2. Intravenous fluid restriction (20–25 mL/kg/day for 3 to 4

postoperative days) was performed in patients receiving early oral nutrition. Preoperative mechanical bowel preparation or nasogastric tube insertion was not routinely performed. Additionally, abdominal drainage was inserted in selected cases based on the surgeons' decision. Patients were discharged from the hospital on postoperative day 6 or 7 based on the predefined discharge criteria.

Statistical analysis

Data are expressed as a mean±standard deviation or number (%). Continuous variables were compared using a t-test while categorical variables were compared using the Fisher's exact or χ^2 test as appropriate. The binary logistic regression model was used for univariate and multivariate analyses of the risk factors for postoperative complications. In the logistic regression model, continuous data were analyzed after being categorized based on their median values. Variables that were statistically significant in the univariate model were subjected to multivariate analysis. All statistical analyses were performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). For all analyses, 2-sided P-values <0.05 were considered statistically significant.

RESULTS

Patient characteristics and comorbidities

This study included 212 men and 91 women with a mean age of 62.1±11.0 years and mean body mass index of 23.6±3.2 kg/m^2 (**Table 1**). Among them, 260 (85.8%) and 43 (14.2%) patients underwent extracorporeal and intracorporeal anastomoses, respectively. The mean length of hospital stay was 9.9±8.4 days. Based on the final pathological examination, 254 (83.8%), 36 (11.9%), and 13 (4.3%) patients had stages I, II, and III disease, respectively.

A total of 189 patients (62.4%) had comorbidities (**Table 1**); 89 patients (29.4%) had ≥2 comorbidities. The most common comorbidity was hypertension (37.0%) followed by diabetes mellitus (17.8%), chronic viral hepatitis (3.0%), liver cirrhosis (2.6%), and pulmonary (27.1%), ischemic heart (3.3%), and cerebrovascular diseases (2.3%). Among the 82 patients with pulmonary disease, 65 of them showed abnormal preoperative pulmonary function tests indicative of COPD while 16 patients had a history of pulmonary tuberculosis. Active treatment for COPD or asthma was conducted in 21 patients.

Postoperative complications

Table 2 shows the details of the postoperative complications. The overall morbidity and mortality rates were 20.1% and 1.0%, respectively. The ≥grade 3 complications occurred in 20 patients (6.6%). Three patients died including 1 each with anastomosis leakage, abdominal infection, and luminal bleeding. Luminal bleeding (n=16) was the most common local complication, followed by anastomosis leakage (n=11), paralytic ileus (n=9), and abdominal infection (n=8). Pulmonary complication was the most common systemic complication.

Impact of comorbidities on postoperative complications

A significant difference was noted in the incidence of the local (P=0.021), overall (P=0.006), and ≥grade 3 complications (P=0.025) and the number of comorbidities increased (**Fig. 1**). However, no significant difference was noted in the incidence of systemic complications. The postoperative complication rates in patients with 7 major types of comorbidities are shown in **Fig. 2**. Patients with pulmonary disease showed significantly higher complication rates than

Table 1. Clinicopathological characteristics

Characteristics	Patients (n=303)
Age (yr)	62.1±11.0
Gender	
Male	212 (71.0)
Female	91 (30.0)
Body mass index (kg/m²)	23.6±3.2
Preoperative hemoglobin (mg/dL)	13.7±1.8
Preoperative albumin (mg/dL)	4.5±0.4
ASA physical status	
1	89 (29.4)
2	203 (67.0)
3	11 (3.6)
No. of comorbidities	
None	114 (37.6)
1	100 (33.0)
2	69 (22.8)
3	15 (5.0)
4	5 (1.7)
Types of comorbidity	
Hypertension	112 (37.0)
Pulmonary disease	82 (27.1)
Diabetes mellitus	54 (17.8)
Ischemic heart disease	10 (3.3)
Chronic viral hepatitis	9 (3.0)
Liver cirrhosis	8 (2.6)
Cerebrovascular disease	7 (2.3)
Cardiac arrhythmia	3 (1.0)
Gout	3 (1.0)
Cardiomyopathy	2 (0.7)
Hypothyroidism	2 (0.7)
Others	7 (2.3)
Reconstruction method	
Extracorporeal	260 (85.8)
Intracorporeal	43 (14.2)
Extent of lymph node dissection	
D1+	260 (85.8)
D2	43 (14.2)
Combined cholecystectomy	15 (5.0)
Operating time (min)	281±90
Operative blood loss (mL)	150±152
Hospital stay	9.9±8.4
Tumor stage*	
Stage I	254 (83.8)
Stage II	36 (11.9)
Stage III	13 (4.3)

Data are expressed as mean±standard deviation or number (%).
ASA = American Society of Anesthesiologists physical status classification; TNM = tumor, node, metastasis.
*The 7th edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM classification.

those without comorbidities (32.9% vs. 14.9%, respectively, P=0.003). On the other hand, no significant differences were observed between patients with other comorbidities and the incidence of postoperative complications.

To further investigate the impact of each comorbidity on postoperative complications, we performed univariate and multivariate analyses of the risk factors for postoperative complications (**Table 3**). Results of the univariate analysis showed that old age, male sex, the number of comorbidities, presence of pulmonary disease, and intraoperative blood

Table 2. Postoperative complications

Characteristics	Patients (n=303)
Overall morbidity	61 (20.1)
Grade I	18 (5.9)
Grade II	23 (7.6)
Grade III	15 (5.0)
Grade IV	2 (0.7)
Grade V	3 (1.0)
Local complications	56 (18.5)
Luminal bleeding	16
Anastomosis leakage	11
Paralytic ileus	9
Abdominal infection	8
Abdominal bleeding	4
Duodenum stump leakage	3
Ascites	2
Others	3
Systemic complications	14 (4.6)
Pulmonary	10
Renal	3
Neurologic	1

Numbers in the parentheses indicate the percentage (%).

loss volume were significantly associated with postoperative complications. Multivariate analysis of these factors revealed that pulmonary disease was an independent risk factor for postoperative complications (odds ratio, 2.14; 95% confidence interval, 1.03–4.64) along with old age and intraoperative bleeding.

To identify the type of complications which increased because of pulmonary disease, we compared the incidence of each complication in patients with pulmonary disease to that in patients without comorbidities (**Table 4**). Luminal bleeding was found to be significantly more common in patients with pulmonary disease than in those without any comorbidities (12.2% vs. 3.5%, P=0.020). Most luminal bleeding events in patients with pulmonary disease occurred during esophagojejunal anastomosis (n=9), and all patients were successfully treated with conservative treatment or endoscopic intervention. There were no significant differences in the rates of other complications between the 2 groups.
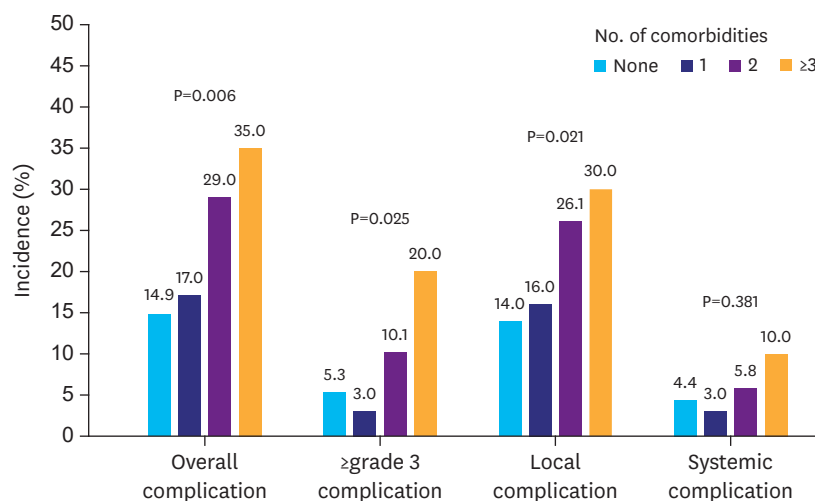

Fig. 1. Incidence of postoperative complications, according to the number of comorbidities.
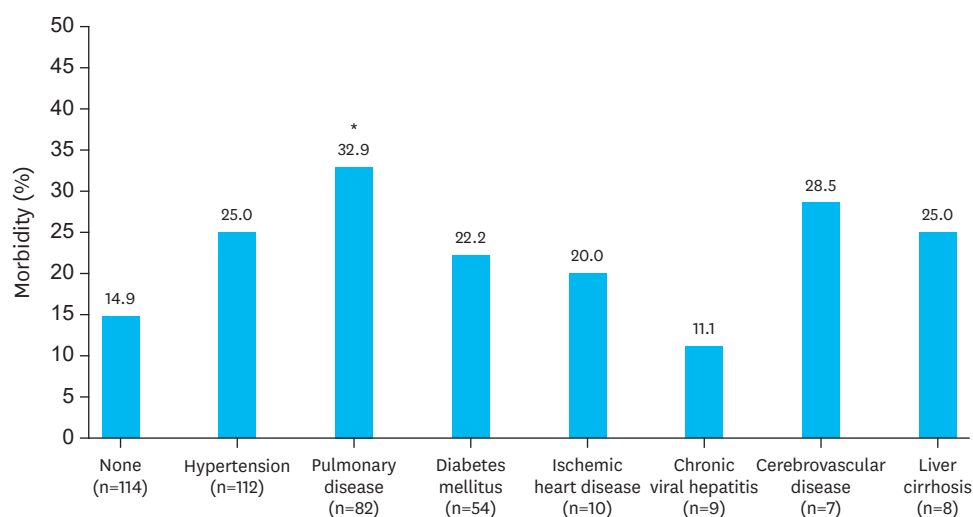
Fig. 2. Postoperative complication rate in various types of comorbidities.
*Statistically significant difference compared to patients without comorbidities.

DISCUSSION

Gastric carcinoma normally affects the elderly, with its incidence rate peaking among individuals in their sixth to seventh decade of life [16]. With the increasing number of elderly patients with gastric carcinoma, the incidences of various types of comorbidities are also increasing. This raises a concern on the influences of such comorbidities on the surgical outcomes following gastric cancer surgery. Several studies have shown that comorbidities are one of the most important predictors of postoperative complications after gastrectomy [5-7]. However, only a few studies have investigated the different aspects of each comorbidity

Table 3. Univariate and multivariate analyses of the risk factors for postoperative complication

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age (≥62 years)	2.36 (1.32–4.25)	0.004	2.03 (1.07–3.87)	0.031
Body mass index (≥24 kg/m²)	0.98 (0.90–1.07)	0.713		
Sex (male)	2.57 (1.24–5.32)	0.011	1.93 (0.88–4.24)	0.100
Preoperative Hgb (g/dL)	1.01 (0.86–1.18)	0.935		
Preoperative albumin (g/dL)	0.78 (0.37–1.64)	0.516		
No. of comorbidity (vs. none)		0.039		0.564
1	1.17 (0.56–2.43)	0.677	0.64 (0.28–1.49)	0.301
2	2.33 (1.12–4.84)	0.024	1.07 (0.43–2.65)	0.889
≥3	3.07 (1.07–8.81)	0.037	1.00 (0.28–3.68)	0.998
Hypertension	1.60 (0.90–2.82)	0.107		
Pulmonary disease	2.70 (1.50–4.86)	0.001	2.14 (1.03–4.64)	0.049
Diabetes mellitus	1.17 (0.57–2.38)	0.673		
Ischemic heart disease	1.74 (0.44–6.92)	0.434		
Chronic viral hepatitis	0.48 (0.06–3.89)	0.490		
Cerebrovascular disease	3.08 (0.67–14.13)	0.148		
Liver cirrhosis	1.33 (0.23–6.78)	0.729		
Operating time (≥280 min)	1.56 (0.89–2.75)	0.122		
Operative bleeding (≥100 mL)	2.35 (0.32–4.16)	0.003	2.65 (1.45–4.85)	0.002
Reconstruction (intracorporeal)	0.89 (0.39–2.04)	0.788		
Lymph node dissection (D2)	1.91 (0.93–3.94)	0.078		
Omentectomy	0.59 (0.32–1.09)	0.093		
Cholecystectomy	2.82 (0.97–8.27)	0.068		

OR = odds ratio; CI = confidence interval.

Table 4. Complications between patients without comorbidity and pulmonary disease

Characteristics	Patients without comorbidities (n=114)	Patients with pulmonary disease (n=82)	P
Local complications			
Luminal bleeding	4 (3.5)	10 (12.2)	0.020
Anastomosis leakage	3 (2.6)	5 (6.1)	0.283
Paralytic ileus	3 (2.6)	4 (4.9)	0.455
Abdominal infection	3 (2.6)	3 (3.7)	0.696
Abdominal bleeding	0	2 (2.4)	0.174
Duodenum stump leakage	1 (0.9)	0	1.000
Ascites	1 (0.9)	0	1.000
Systemic complications			
Pulmonary	4 (3.5)	3 (3.7)	0.882
Renal	1 (0.9)	0	1.000
Neurologic	0	1 (1.2)	0.605

Numbers in the parentheses indicate the percentage (%).

on their influence on the surgical outcomes. In this study, we investigated the impact of different comorbidities on postoperative complications in patients undergoing LTG and found that the incidence of pulmonary disease significantly increased the rate of postoperative complications. Thus, our data indicate that accurate screening and proper perioperative management of pulmonary disease ought to be performed to reduce complications after LTG.

Tissue hypoxia, poor nutritional status, and systemic inflammatory reactions associated with pulmonary disease may inhibit wound healing processes postoperatively [17]. Many previous studies found an increased risk of comorbidities after abdominal surgeries in patients who also have pulmonary disease [18-21]. A study conducted using the National Surgical Quality Improvement Program database in the United States found that the 30-day morbidity, mortality, and length of hospital stay after abdominal surgeries were all significantly higher in patients with pulmonary disease than in those without the disease [18]. Among the various comorbidities examined in a large Korean multicenter study conducted in patients who underwent laparoscopic distal gastrectomy, pulmonary comorbidity was related to most types of postoperative complications [19]. In another Korean multicenter study, the incidence of respiratory complications significantly increased after laparoscopic distal gastrectomy in elderly patients with a pulmonary disease [20]. Furthermore, a Chinese study that analyzed 1,657 patients who underwent LTG found that anemia and pulmonary and renal diseases significantly increased the incidence of local or systemic complications after LTG [21].

A careful assessment of the patient's history and physical examination are the initial and most important steps for identifying pulmonary diseases. These diseases are relatively common in elderly individuals caused by the physiologic changes associated with aging, including the loss of lung and chest wall compliance and decreased oxygen diffusion capacity. However, pulmonary disease is often overlooked in many patients unless they manifest overt respiratory symptoms. This is reflected in the relatively lower incidence rate of pulmonary diseases (ranging from 1.1% to 10.1%) that were previously reported [19,21-23]. In our study, we discovered that approximately 27% of the patients undergoing LTG had pulmonary diseases after performing preoperative pulmonary function tests. Consistent with our findings, Inokuchi et al. [24], who also subjected their patients to preoperative pulmonary function tests, reported that the incidence of pulmonary disease was 23.4%. Although the usefulness of a preoperative pulmonary function test remains controversial for abdominal surgery [25], its potential value for predicting postoperative complications has previously been demonstrated [26,27]. A pulmonary function test is a non-invasive method for preoperative screening that can improve the diagnosis of pulmonary diseases.

The impact of other types of comorbidities on the surgical outcomes of laparoscopic gastrectomy, such as diabetes and hypertension, is inconsistent with previous studies. Wang et al. [21] showed that diabetes significantly increased the incidence of local and systemic complications in patients undergoing LTG. Moreover, Hwang et al. [22] found that hypertension significantly increased the incidence of postoperative complications following laparoscopic gastrectomy (especially in elderly patients). However, our study showed that neither diabetes nor hypertension significantly influenced the postoperative outcomes after LTG, which may be attributable to our established management protocol for patients with such conditions. For example, preoperative blood sugar was maintained at a normal level 3–4 days before the surgery in patients with diabetes. During the fasting period, postoperative blood sugar was strictly controlled with a management algorithm using regular insulin [28]. For patients with hypertension, the normal blood pressure was maintained 3–4 days before the surgery, and administration of an anti-hypertensive drug was performed on the day and immediately after the surgery [29]. Therefore, a proper management plan for each comorbidity may help reduce the risk of complications.

For complication risk reduction in patients with pulmonary diseases, a comprehensive program for pulmonary rehabilitation involving physiotherapy, exercise, nutrition, and education is required [30]. Incentive spirometry, which is easy to learn and inexpensive, has been widely recommended as a useful tool for preoperative lung physiotherapy as it provides objective goals for the patients and monitors their lung performance. Although there is no convincing evidence supporting the routine use of incentive spirometry for abdominal surgery, it appears that preoperative physiotherapy is beneficial for patients with underlying lung diseases such as COPD [31]. Administration of perioperative inhaled bronchodilators such as beta-2 agonists, anticholinergics, and the systemic use of theophylline can help improve lung function, especially airway obstruction, in selected patients [32].

Among the complications observed, the incidence of luminal bleeding significantly increased with pulmonary disease. Additionally, previous studies have shown that COPD is associated with an increased risk of recurrent peptic ulcer bleeding [33,34]. This may be attributed to several factors, including cytotoxic mucosal injury via chronic hypoxia-induced oxidative stress and the COPD patient's exposure to both tobacco and steroids [35,36]. Therefore, it can be postulated that these factors might also be responsible for the increased risk of luminal bleeding in patients with pulmonary disease.

There were some limitations in this study. First, we only investigated patients who underwent LTG, which may limit the generalizability of our results. However, the impact of comorbidities on the surgical outcomes needs to be investigated for different operative procedures considering the differing natures of operative risk and complications. Second, because of the small sample size, the influences of relatively uncommon comorbidities could not be evaluated in this study. Lastly, we did not consider the duration and severity of the comorbidities when evaluating their impact on surgical outcomes.

In conclusion, among the various comorbidities investigated, patients with pulmonary disease had a significantly higher risk of postoperative complications after LTG. This suggests that patients undergoing LTG for gastric carcinoma will require both careful monitoring during postoperative care and adequate planning to optimize their pulmonary functions and improve their surgical outcomes.

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