Outcomes of elderly patients following thoracoscopic esophagectomy for esophageal cancer

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Research Article

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Abstract

Purpose: Thoracoscopic esophagectomy (TE) is widely used for esophageal cancer treatment. However, the short- and long-term outcomes of TE in older patients remain unknown. Thus, we investigated those outcomes as well as the effectivity of TE in this patient cohort.

Methods: A total of 228 consecutive patients who underwent TE for esophageal cancer from 2002 to 2015 were included in the study and divided into the elderly (≥75 years) and non-elderly (<75 years) groups. The background was adjusted by propensity score matching. The short- and long-term outcomes were then compared between the two groups.

Results: There was no difference in the short-term outcomes between the two groups. The elderly group had significantly lower overall survival (OS) and relapse-free survival (RFS) than the non-elderly group. When pulmonary complications occurred, the OS and RFS were significantly decreased in the elderly group but not in the non-elderly group. Without pulmonary complications, the OS and RFS in the elderly group did not differ from those in the non-elderly group. The multivariate analysis showed that pulmonary complications were independent poor prognostic factors for OS and RFS in the elderly group but not in the non-elderly group.

Conclusion: Minimally invasive esophagectomy is safe and feasible for older patients. However, the OS and RFS of the elderly group were significantly worse than those of the non-elderly group, especially when pulmonary complications occurred. Therefore, perioperative management to prevent pulmonary complications is essential to improve the long-term outcomes of older patients receiving TE.

Introduction

Esophageal cancer is the seventh most common cancer and sixth leading cause of death worldwide [1]. Due to the increasing life expectancy, the number of older patients with esophageal cancer has also been increasing. In Japan, the proportion of patients aged 75 years or older who underwent esophagectomy for esophageal cancer increased from 18% in 2011 to 25.4% in 2019 [2]. Esophagectomy with radical lymphadenectomy is an important modality in esophageal cancer treatment; however, it is the most invasive procedure in gastrointestinal surgery and has a high incidence of postoperative complications. The physiological function of organs declines with age, which increases the frequency of perioperative complications. In particular, esophagectomy with radical lymphadenectomy in older patients leads to higher complication and mortality rates than it does in younger patients because of the invasive nature of the procedure [3, 4].

Thoracoscopic esophagectomy (TE) is a less invasive procedure that has been widely performed. Many studies have reported the benefits of TE, such as shorter hospitalization stays, lower incidence of pneumonia, and faster recovery. Meanwhile, the long-term outcomes of TE were reported to be comparable to those of open esophagectomy (OE) [5]. However, these studies on TE focused on non-

elderly patients, and there are few studies on the safety and feasibility of TE for elderly patients. Thus, this study evaluated the short- and long-term outcomes of TE to confirm its validity in older patients.

Material And Methods

Patients

A total of 250 consecutive patients who underwent radical-intent TE for esophageal cancer at the Niigata City General Hospital between 2002 and 2015 were enrolled in this study. Patients who underwent noncurative and salvage esophagectomies and those requiring conversion to OE were excluded. The remaining 228 patients were classified into an elderly (age ≥ 75 years, n = 48) or non-elderly (age < 75 years, n = 180) group. Propensity score matching was used to balance the essential variables for the comparative analyses of both groups. The resulting score-matched pairs (46 patients in each group) were used in subsequent analyses.

Patient management

All patients underwent blood examinations, upper digestive tract endoscopy, and enhanced computed tomography for cancer staging; electrocardiography and spirometry examinations were performed to assess cardiopulmonary function. Patients with clinical stage II or higher cancer received cisplatin-based neoadjuvant chemotherapy (NAC). Esophagectomy with lymphadenectomy was performed under thoracoscopic maneuvers with bilateral lymphadenectomy along the recurrent laryngeal nerve. The abdominal procedure was performed via laparoscopy. In cases of abdominal lymph node metastasis, adhesions, or reconstruction of organs other than the stomach, open laparotomy was performed. In cases of mid or upper thoracic esophageal cancer, bilateral cervical lymph node dissection was performed (i.e., three-field lymphadenectomy) based on the surgeon’s choice. Either a gastric tube was created or the ileocolon was used in cases of post-gastrectomy or coexistence of gastric cancer for the esophageal substitute, which was pulled up to the neck via the posterior mediastinum or retrosternal (in cases of a narrow mediastinum) route and anastomosed to the cervical esophagus (McKeown procedure). Postoperative follow-up was performed, which included physical and blood examinations, tumor marker determination, and enhanced computed tomography, every three months until two years after the surgery and every six months from two to five years thereafter. When the patients had symptoms of cancer recurrence, examinations were performed immediately.

Evaluated outcomes

Data on preoperative clinicopathological characteristics, intraoperative data, and postoperative outcome data were retrospectively extracted from medical charts. Short-term outcomes included the total (thoracic and abdominal phases) operation time, blood loss, operative complications according to the Clavien–Dindo classification [6], anastomotic leakage, recurrent laryngeal nerve palsy, pulmonary complications, in-hospital death, duration of postoperative hospital stay, and rate of transfer to a rehabilitation hospital. Anastomotic leakage was defined as salivary discharge from the neck drain or detection of fluid

collection around the anastomotic point on computed tomography. Laryngoscopic findings of recurrent laryngeal palsy were evaluated by an otorhinolaryngologist on the seventh postoperative day. Pulmonary complications included respiratory failure, pneumonia, atelectasis, pneumothorax, and adult respiratory distress syndrome. Long-term survival was evaluated in terms of the overall survival (OS) and relapse-free survival (RFS) rates. The OS and RFS were calculated from the date of esophagectomy to death from any cause and day of recurrence of esophageal cancer, respectively.

Statistical analysis

Categorical data were compared using Fisher's exact test. Continuous variables are presented as median values. Non-parametric data were compared using the Mann–Whitney *U* test. Survival analysis was performed using the Kaplan–Meier method, and the difference in the survival curves was examined by the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model. Propensity score matching was performed using the logistic regression analysis and the following covariates: sex, p-stage [7], reconstructed organ, extent of lymphadenectomy, and NAC. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The characteristics of the 228 patients are shown in Table 1. Before propensity matching, 180 and 48 patients were classified into the non-elderly and elderly groups, respectively. In this whole cohort, there were significantly fewer men in the elderly group, and the rate of patients with an American Society of Anesthesiologists (ASA) score of II or more and the rate of those with any preoperative comorbidity were significantly higher in the elderly group than those in the non-elderly group. Additionally, the serum albumin level and estimated glomerular filtration rate (eGFR) were significantly lower in the elderly group when compared with those in the non-elderly group. After propensity score matching, 46 patients were included in each group. Even after the matching, the rate of patients with an ASA score of II or higher and rate of any preoperative comorbidity were still higher in the elderly group than in the non-elderly group. The albumin level and eGFR were significantly lower in the elderly group than in the non-elderly group. The rate of cerebrovascular disease or dementia and history of diabetes tended to be higher in the elderly group than in the non-elderly group, although the difference was not significant ($p = 0.05$). There was no difference between the two groups before and after the matching in terms of the body mass index, rate of pulmonary dysfunction, and electrocardiographic abnormalities.

Operative and clinicopathological characteristics

Table 2 shows the operative and clinicopathological characteristics of the non-elderly and elderly groups before and after propensity score matching. Before the matching, the elderly group had a significantly

lower frequency of three-field lymphadenectomy, a shorter operation time, and a lower number of dissected lymph nodes than the non-elderly group. Before and after the matching, there was no difference between the two groups regarding the rate of NAC, patients' position during the thoracic procedure, reconstructed organ, type of abdominal procedure, blood loss, tumor location, histological type, tumor size, lymph-vascular infiltration, or p-stage.

Short-term outcomes

Table 3 shows the postoperative outcomes of the non-elderly and elderly groups before and after propensity score matching. Before the matching, the occurrence of anastomotic leakage was significantly higher in the non-elderly group than in the elderly group, but this difference was diminished in the matched cohort. Before and after the matching, there was no difference between the two groups regarding the rate of complications according to the Clavien–Dindo classification, pulmonary complications, and recurrent laryngeal nerve palsy. There was no difference between the two groups in the duration of postoperative hospital stay at 20 and 19 days, respectively. The operation-related mortality was 0% in the non-elderly group and 4% in the elderly group, and no difference was detected between the groups. The rate of transfer to a rehabilitation hospital after surgery was significantly higher in the elderly group than in the non-elderly group (0% vs. 15%, $p < 0.01$).

Long-term outcomes

The 5-year OS rates were 42.2% and 66.9% in the elderly and non-elderly groups, respectively, and the difference was statistically significant ($p = 0.01$) (Fig. 1a). The elderly group had a significantly higher rate of death caused by diseases other than esophageal cancer than the non-elderly group before and after the matching (35.1% vs. 59.2%, $p = 0.04$; and 30% vs. 59.2%, $p = 0.03$) (Table 4). There were significant differences in the RFS between the two groups: 40% in the elderly group and 67.1% in the non-elderly group ($p = 0.01$) (Fig. 1b). In the elderly patients, the OS and RFS decreased significantly when pulmonary complications occurred (Fig. 2a, b), whereas in the non-elderly patients, the OS and RFS did not decrease when pulmonary complications occurred (Fig. 2c, d). Additionally, the OS and RFS did not differ between the elderly patients without pulmonary complications and the non-elderly patients (Fig. 3). Furthermore, univariate and multivariate analyses revealed that pulmonary complications were independent risk factors for OS and RFS in the elderly group (Table 5) but not in the non-elderly group.

Discussion

In this study, we compared the short-and long-term outcomes of elderly and non-elderly patients who underwent TE after adjusting the backgrounds of both groups by propensity score matching. In the elderly group, the proportion of patients with an ASA score II or higher, comorbidities, malnutrition, and renal dysfunction was significantly higher. Nevertheless, the rate of postoperative complications did not differ between the two groups. Regarding the long-term outcomes, the OS and RFS were significantly lower in the elderly than in the non-elderly group. Additionally, the OS and RFS significantly decreased when pulmonary complications occurred in the elderly group, but not in the non-elderly group. However,

the OS and RFS of the elderly group without pulmonary complications did not differ from those of the non-elderly group. Furthermore, the multivariate analysis revealed that postoperative pulmonary complications were independent factors for poorer OS and RFS in the elderly group.

Short-term outcomes

Surgical resection plays an important role in esophageal cancer treatment. Despite significant improvements in surgical techniques and perioperative care, esophagectomy remains one of the most challenging surgical procedures and is significantly associated with morbidity and mortality. Age-related changes cause a decline in physiological functions, and older patients have a higher risk of complications after invasive surgeries, such as esophagectomy. Previous studies reported that older patients had higher rates of postoperative morbidity and mortality than did younger patients [3, 4], whereas other studies have reported no difference in postoperative morbidity and mortality between the two groups [8, 9].

In recent years, the use of TE has become widespread, and clinical trials have reported that TE is less invasive than OE but with comparable outcomes [10, 11]. However, in these trials, the inclusion criteria were age ≤ 75 years. Additionally, studies on esophagectomy for esophageal cancer in older patients have targeted patients who have undergone OE or a mixture of OE or TE [12, 13]. Hence, the validity of TE in elderly patients has been unclear. In our study, only patients who underwent McKeown TE were examined and divided into the elderly and non-elderly groups, and the short-term outcomes were compared between the two groups. Postoperative complications and operative mortality did not differ between the groups, although the elderly patients had more comorbidities and poor nutritional and renal statuses. The results demonstrate that TE is a less invasive surgery and reduces operative complications in patients with an age-related poor physical status. Sugita et al. [14] categorized patients who underwent TE into elderly (age ≥ 75 years) and non-elderly (age < 75 years) groups, compared the two groups after propensity score matching, and demonstrated that there were no significant differences in short-term outcomes between both groups. This result is consistent with those of our study. Baranov et al. [15] also divided TE patients into elderly (age ≥ 75 years) and young (age < 75 years) groups, compared the perioperative results without propensity score matching, and demonstrated that there was no difference in the rate of complications between the two groups, except in the rates of cardiac complications and delirium and length of hospital stay. However, their study focused on the Ivor Lewis TE. Contrarily, our study focused on the McKeown TE. Li et al. [16] compared patients aged ≥ 70 years who underwent esophagectomy, divided them into OE and TE groups, and concluded that TE was preferred in older patients due to the lower morbidity and pulmonary complication rates. Similarly, Baranov et al. [17] conducted a meta-analysis of esophagectomy and revealed that the rates of 90-day mortality and in-hospital mortality did not differ between the elderly and non-elderly groups in the analysis of patients who underwent TE. They also mentioned that TE reduces surgical complications in older patients. In our analysis, the duration of postoperative hospital stay and rate of postoperative complications did not differ between the two groups, but the elderly group had a higher rate of transfer to the rehabilitation hospital than did the non-elderly group. This suggests that the elderly patients could not be discharged to

their homes due to decreased physical status and sarcopenia progression caused by surgery. Pre- and postoperative rehabilitation is essential for maintaining the physical status of older patients with esophageal cancer.

Long-term outcomes

The reported long-term outcomes of esophagectomy for esophageal cancer in older patients are controversial. Aoyama et al. [13] showed that the long-term outcomes of elderly patients were worse than those of non-elderly patients, but Kanda et al. [12] reported there was no difference between the two groups. Furthermore, many of these reports focused on OE or a mixture of OE and TE. In our study, we focused on TE only and revealed that the OS rate of elderly patients was significantly lower than that of non-elderly patients (5-year OS rate: 55.9% vs. 66.9%, $p = 0.01$). Sugita et al. [14] compared elderly and non-elderly patients who underwent TE after propensity score matching. They reported that the OS rate of elderly patients tended to be lower than that of non-elderly patients (5-year OS rate: 40.1% vs. 58.9%), albeit without significance. They speculated that this is because older patients often die from other causes. Similarly, in our study, the elderly group had a significantly higher rate of non-esophageal cancer death (59.2% vs. 30%, $p = 0.03$); hence, one of the reasons for the lower OS rate in the elderly group was the death of patients from causes other than esophageal cancer. On the other hand, Baranov et al. [15] and Zho et al. [18] reported that there was no difference in OS rates between the elderly and non-elderly groups. This difference might be caused by the type of surgical procedure, definition of the elderly, and eligibility criteria. Baranov et al. [15] focused on the analysis of Ivor Lewis TE, not McKeown TE. Zhao et al. [18] defined the elderly as those aged > 70 years, and the eligibility criteria were patients with no lymph node metastasis. In our analysis, the RFS of the elderly group was lower than that of the non-elderly group (5-year RFS rate: 40.0% vs. 67.1%, $p = 0.01$). This might be due to the insufficient pre- and postoperative chemotherapy regimens in terms of doses and cycles due to age, although the rate of NAC was not different between the two groups.

Relationship between complications and long-term outcomes

In our study, the OS and RFS were significantly decreased when pulmonary complications occurred in the elderly group. However, the OS and RFS did not decrease in the non-elderly group even when pulmonary complications occurred. Furthermore, there was no difference in OS and RFS between the elderly group without pulmonary complications and the non-elderly group. Additionally, in the elderly group, pulmonary complications were independent poor prognostic factors for OS (hazards ratio [HR]: 3.51, 95% confidence interval [CI]: 1.45–8.50, $p < 0.01$) and RFS (HR: 3.08, 95% CI: 1.29–7.34, $p = 0.01$). There have been several reports concerning the relationship between postoperative morbidity and prognosis in various cancers. Shimada et al. [19] reported that postoperative morbidity has a negative impact on esophageal, gastric, and colorectal cancers. Additionally, Rutegard et al. [20] also mentioned that the occurrence of postoperative morbidity decreases the survival rate of patients with esophageal cancer. Kinugasa et al. [21] reported that the occurrence of postoperative pneumonia decreased the OS and RFS rates of patients who received OE. Additionally, Booka et al. [22] revealed that pulmonary complications and anastomotic

leakage decreased the OS and RFS. On the other hand, some reports have shown no relationship between postoperative complications and survival in patients with esophageal cancer [23, 24]. Previous reports concerning the relationship between postoperative complications and survival have targeted patients who underwent a mixture of OE and TE; however, there are only two reports concerning the relationship between postoperative complications and survival in patients who underwent TE alone [25, 26]. Li et al. [25] reported no relationship between postoperative complications and survival in TE; however, Fransen et al. [26] reported that the occurrence of anastomotic leakage and its severity after TE had a negative impact on OS. Additionally, the ages of the patients in the reports by Li et al. and Fransen et al. were 60 [25] and 63 years [26], respectively, which were a mixture of elderly and non-elderly patients. In our study, we analyzed the relationship between postoperative complications and long-term outcomes between elderly and non-elderly patients who underwent TE. We revealed that postoperative pulmonary complications had a negative impact on OS and RFS in elderly patients but not in non-elderly patients. The three major complications after esophagectomy for esophageal cancer are anastomotic leakage, recurrent laryngeal nerve palsy, and pulmonary complications; the first two are local disorders, while the last is a systemic disorder. Inflammatory systemic disorders, such as pneumonia, have been reported to induce cancer cell proliferation, promote survival of residual cancer cells, and promote cancer cells to escape the host immune response [27, 28]. Furthermore, pulmonary complications could lead to delayed ambulation and prolonged hospital stay, which may worsen sarcopenia. In recent years, sarcopenia has been reported to worsen the prognosis of patients following esophagectomy. Nakajima et al. [29] examined the relationship between sarcopenia and survival in patients who underwent esophagectomy and reported that sarcopenia has a negative impact on the OS of elderly (age ≥ 65 years) patients, but it does not affect the OS of non-elderly patients. They concluded that sarcopenia was an independent negative factor for OS in a multivariate analysis. Older patients may have pre-existing pre-sarcopenic conditions and pulmonary complications, which are systemic complications that prolong the duration of bed rest and result in a greater loss of skeletal muscle, deterioration of nutrition, and progression of sarcopenia, leading to decreased OS. Contrarily, non-elderly patients often have a stronger physical status; even if pulmonary complications occur, their body may overcome them and there is no impact on the OS. A recent randomized control study reported that the rate of inflammatory pulmonary complications in TE was lower than that in OE [5, 30]. Furthermore, Biere et al. [5] reported that the OS and RFS after TE tended to be better than those after OE, albeit without significance. Additionally, Li et al. [16] mentioned that the pulmonary complication rate was lower in TE than in OE, even in older patients. In this study, the rate of pulmonary complications was not different between the elderly and non-elderly groups, but once pulmonary complications occurred, the OS and RFS decreased in the elderly group but not in the non-elderly group. More attention should be paid to pulmonary complications to improve the OS and RFS in elderly patients who received TE.

Limitations

The present study has limitations, such as including a small number of patients, being a single-institution study, and having potential selection bias due to the retrospective analysis even after propensity score matching. The present study also did not include patients with poor physical conditions or severe

comorbidities who were considered as unable to undergo TE. Additionally, patients who underwent noncurative TE were not included in this study.

Conclusion

Minimally invasive esophagectomy can be safely performed in elderly patients, and its short-term outcomes were not different from those in non-elderly patients. However, OS and RFS were significantly lower in elderly patients than in non-elderly patients. Additionally, the OS and RFS significantly decreased in older patients with pulmonary complications, but the OS and RFS of elderly patients without pulmonary complications and non-elderly patients did not differ. Furthermore, pulmonary complications were poor independent factors for OS and RFS in elderly patients based on the multivariate analysis. Therefore, strict perioperative management to prevent pulmonary complications is essential to improve outcomes in older patients undergoing TE.

Declarations

Authors' contributions:

Study conception and design: Shirou Kuwabara.

Acquisition of data: Shirou Kuwabara, Kazuaki Kobayashi and Natsuru Sudo.

Analysis and interpretation of data: Shirou Kuwabara, Kazuaki Kobayashi and Natsuru Sudo.

Drafting of manuscript: Shirou Kuwabara.

Critical revision of manuscript: Kazuaki Kobayashi and Natsuru Sudo.

Ethics approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Niigata City General Hospital (#21-064).

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Conflicts of interest:

The authors declare that they have no conflict of interest.

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Tables

Tables 1 to 5 are available in the Supplementary Files section

Figures

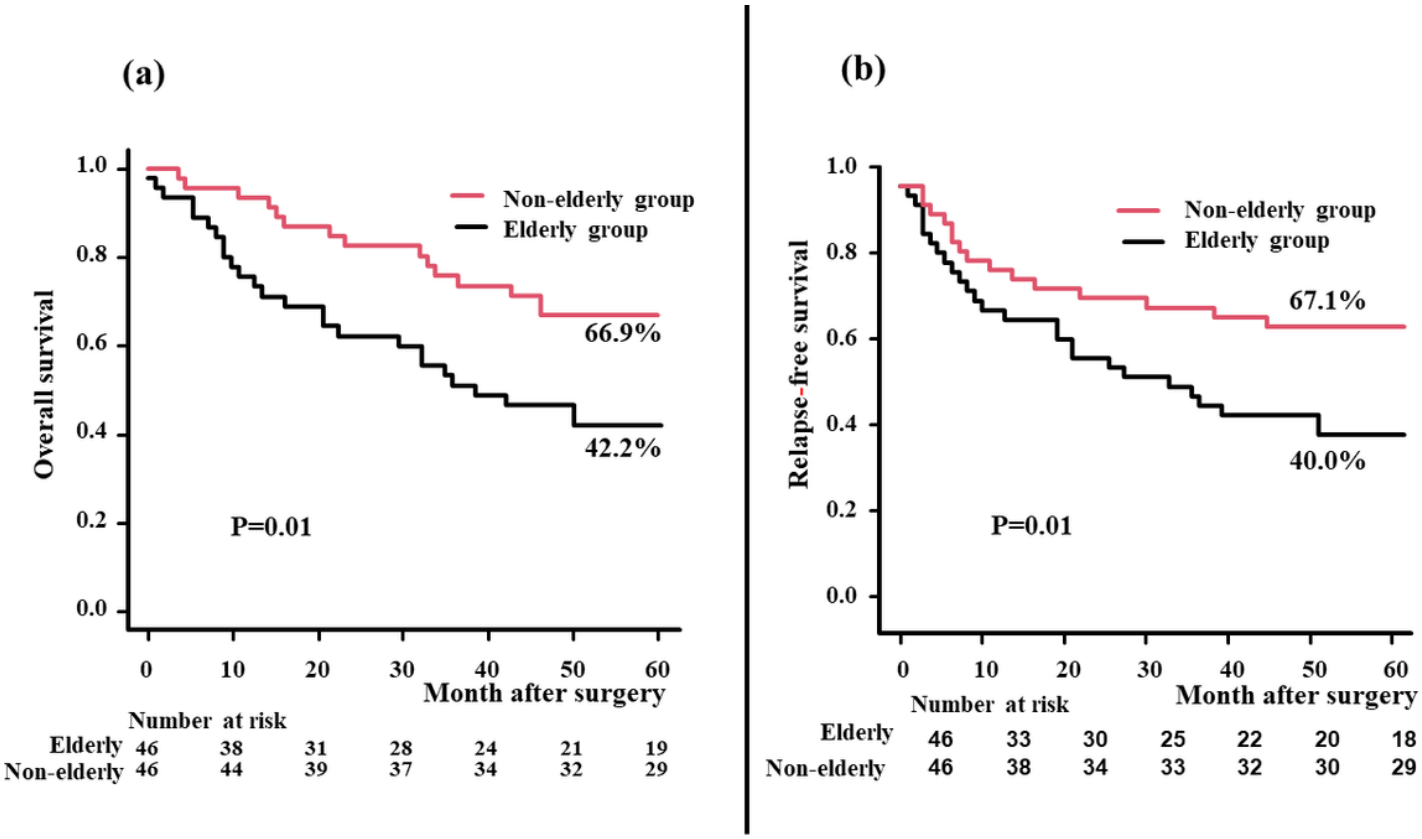

Figure 1

Kaplan–Meier curves for the overall survival (OS) (a) and relapse-free survival (RFS) (b) of elderly and non-elderly patients. The elderly patients have significantly lower OS and RFS rates than the non-elderly patients

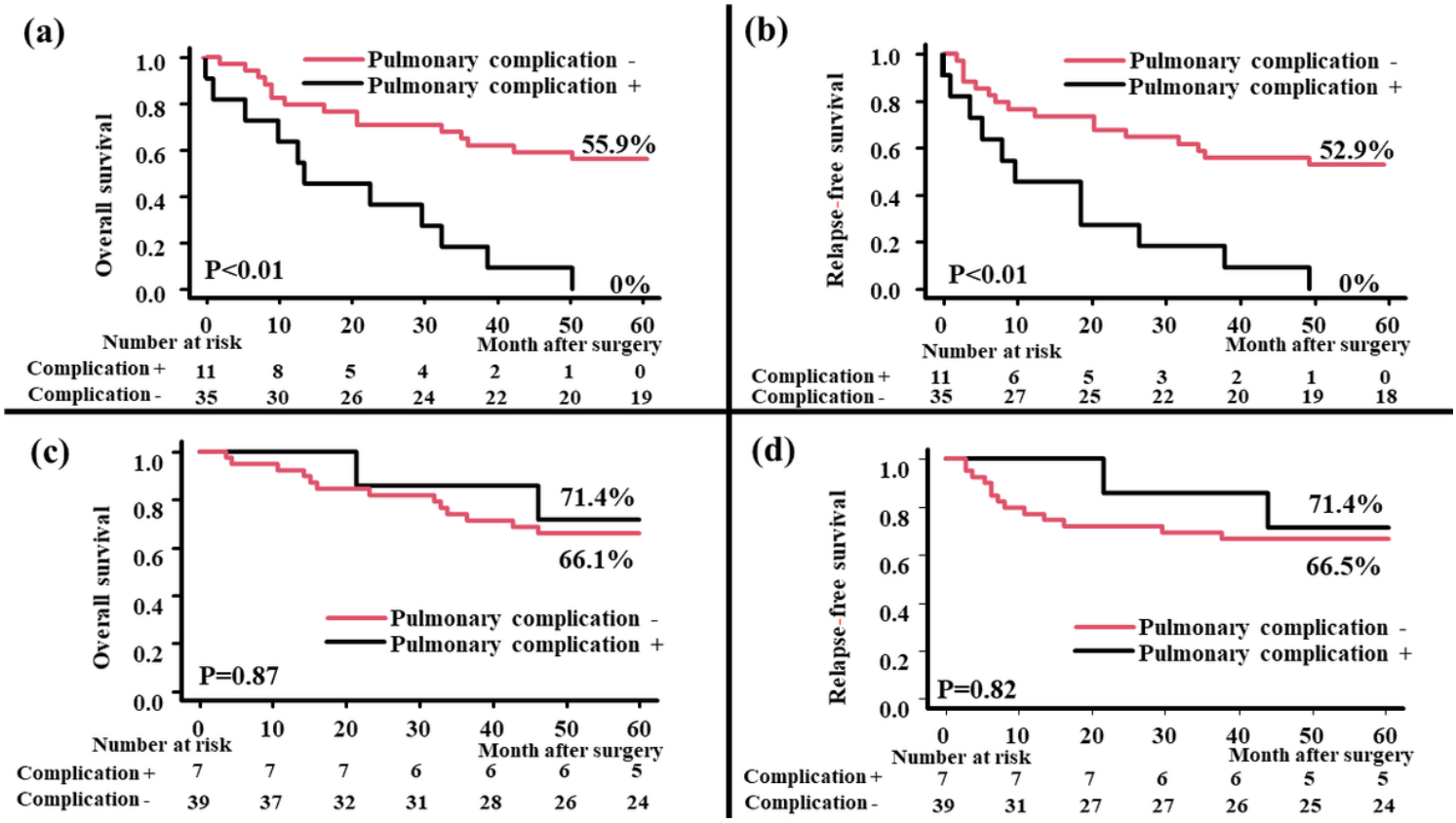

Figure 2

Relationship between pulmonary complications and survival. (a) Overall survival (OS) in elderly patients. (b) Relapse-free survival (RFS) in elderly patients. (c) OS in non-elderly patients. (d) RFS in non-elderly patients. The OS and RFS rates were significantly lower in elderly patients with pulmonary complications than in those without complications

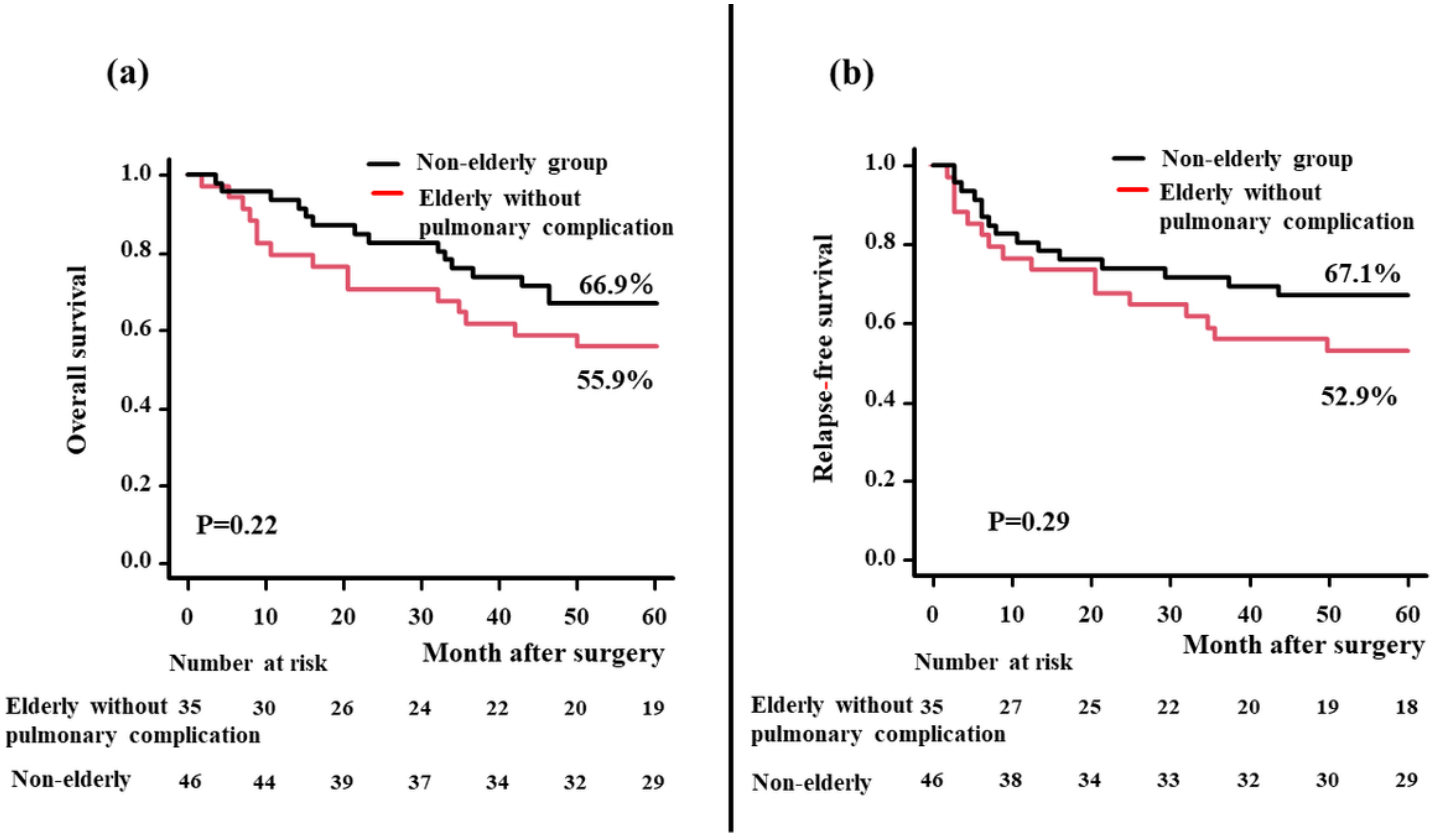

Figure 3

Kaplan–Meier curves for the overall survival (OS) (a) and relapse-free survival (RFS) (b) of elderly patients without pulmonary complications and non-elderly patients. The OS and RFS were not different between the two groups

Supplementary Files

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- Table1.docx
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