Impact of co-morbidity on reoperation or death within 90 days of surgery for oesophageal cancer

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Abstract

Background: The impact of preoperative co-morbidity on postoperative outcomes in patients with oesophageal cancer is uncertain. A population-based and nationwide cohort study was conducted to assess the influence of preoperative co-morbidity on the risk of reoperation or mortality within 90 days of surgery for oesophageal cancer.

Methods: This study enrolled 98 per cent of patients who had oesophageal cancer surgery between 1987 and 2015 in Sweden. Modified Poisson regression models provided risk ratios (RRs) with 95 per cent confidence intervals (c.i.) to estimate associations between co-morbidity and risk of reoperation or death within 90 days of oesophagectomy. The RRs were adjusted for age, sex, educational level, pathological tumour stage, neoadjuvant therapy, annual hospital volume, tumour histology and calendar period of surgery.

Results: Among 2576 patients, 446 (17.3 per cent) underwent reoperation or died within 90 days of oesophagectomy. Patients with a Charlson Co-morbidity Index (CCI) score of 2 or more had an increased risk of reoperation or death compared with those with a CCI score of 0 (RR 1.78, 95 per cent c.i. 1.44 to 2.20), and the risk increased on average by 27 per cent for each point increase of the CCI (RR 1.27, 1.18 to 1.37). The RR was increased in patients with pulmonary disease (RR 1.66, 1.36 to 2.04), cardiac disease (RR 1.37, 1.08 to 1.73), diabetes (RR 1.50, 1.14 to 1.99) and cerebral disease (RR 1.40, 1.06 to 1.85).

Conclusion: Co-morbidity in general, and pulmonary disease, cardiac disease, diabetes and cerebral disease in particular, increased the risk of reoperation or death within 90 days of oesophageal cancer surgery. This highlights the value of tailored patient selection, preoperative preparation and postoperative care.

Introduction

Oesophagectomy and neoadjuvant therapy is standard treatment for locally advanced oesophageal cancer without distant metastases1. Co-morbidity is present in around 40–60 per cent of patients who have an oesophagectomy2,3, and 40–50 per cent experience postoperative complications4,5.

Better knowledge about how co-morbidity influences outcome after oesophagectomy could help tailor clinical decision-making and modify preoperative preparation and postoperative care. Unlike variations in definition and different degrees of severity that exist for many of the complications that follow oesophagectomy, reoperation and short-term mortality are objective and accurately defined outcomes. When assessing short-term outcomes of oesophagectomy, most studies historically focused on in hospital or 30-day outcomes, although 90 days is nowadays often considered a better cut-off as a result of improvements in postoperative care6,7. Although co-morbidities are reported to increase the risk of 30-day complications in general, their influence on outcome at 90 days is less clear, and even less information has been reported on the influence of specific conditions, including diabetes, pulmonary disease, cerebral disease and cardiac disease3,8–11.

This study aimed to clarify how co-morbidity influences the risk of reoperation or mortality within 90 days of surgery for oesophageal cancer.

Methods

This was a nationwide population-based cohort study of patients with oesophageal cancer who had an oesophagectomy in Sweden between 1 January 1987 and 31 December 2015. The
study was approved by the Ethical Review Board in Stockholm, Sweden.

**Data source and data collection**

Patients with oesophageal adenocarcinoma or squamous cell carcinoma were identified from the Swedish Cancer Registry, which includes at least 98 per cent of all patients with oesophageal cancer in Sweden. To select the patients who had undergone oesophagectomy, the database was linked with the national Swedish Patient Registry, which has a 99.6 per cent positive predictive value for oesophagectomy records. Data on co-morbidity were also collected from the Swedish Patient Registry. Information on mortality was retrieved from the Swedish Cause of Death Register with 100 per cent completeness.

Information regarding calendar period, hospital volume, neoadjuvant treatment, and tumour characteristics (pathological tumour stage and tumour histology) was collected by review of all histopathology reports and operation charts according to a predefined protocol. Information about educational level was retrieved from the longitudinal integrated database for health insurance and labour market studies (LISA). Linkages of participants between registries and the national Swedish Register with 100 per cent completeness were also collected from the Swedish Patient Registry. Information on mortality was retrieved from the Swedish Cause of Death Register with 100 per cent completeness.

The cohort included 2576 patients who had undergone oesophagectomy. Of these, 1553 patients (60.3 per cent) had at least one co-morbidity included in the CCI. The most common co-morbidity group was other malignancy (561 patients, 21.8 per cent), followed by pulmonary disease (386, 15.0 per cent), cardiac disease (308, 12.0 per cent), diabetes (238, 9.2 per cent), and cerebral disease (192, 7.5 per cent). The most common co-morbidity group was other malignancy (561 patients, 21.8 per cent), followed by pulmonary disease (386, 15.0 per cent), cardiac disease (308, 12.0 per cent), diabetes (238, 9.2 per cent), and cerebral disease (192, 7.5 per cent). Most co-variables were distributed evenly between patients with and those without co-morbidity.

The Charlson Co-morbidity Index (CCI) includes chronic, coexisting, and mainly non-communicable diseases, which are recorded using the diagnosis code according to the ICD classification. The following 14 co-morbidities were included: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, liver disease, diabetes, hemiplegia/paraplegia, renal disease, malignancy, metastatic tumours, and acquired immune deficiency syndrome (AIDS). Oesophageal cancer diagnosis was excluded when calculating the CCI score.

The outcome was reoperation or all-cause death within 90 days of the oesophagectomy. This composite outcome was used to avoid competing risk of death when assessing reoperations, as any death within 90 days of surgery made it impossible to have a reoperation.

The following eight co-variables were considered as potential confounders because they could influence both the exposure (co-morbidity) and the outcome (reoperation or death): age, sex (male or female), educational level (less than 9, 9–12 or more than 12 years of formal education), pathological tumour stage (0–1, II, III or IV in the 7th version of cancer staging manual by the American Joint Committee on Cancer), neoadjuvant therapy (no or yes), annual hospital volume (fewer than 10 or 10 or more operations per year), tumour histology (adenocarcinoma or squamous cell carcinoma), and calendar period of oesophagectomy.

**Statistical analysis**

Co-morbidity was analysed in three ways: CCI score analysed as three separate categories (0, 1, or 2 or above); CCI score analysed as a discrete variable to explore linear trends; and five co-morbidity groups included in the CCI analysed separately (no or yes). The separate co-morbidity groups were: pulmonary disease (chronic bronchitis, emphysema, chronic obstructive pulmonary disorder, asthma, bronchiectasis, pneumoconiosis and chronic lung manifestations caused by chemicals, gases, smoke or radiation); cardiac disease (myocardial infarction and congestive heart failure); diabetes; cerebral disease (cerebrovascular disease, dementia, hemiplegia/paraplegia); and other malignancy (malignant lymphoma, leukaemia and solid malignant tumours, excluding oesophageal cancer and non-melanoma skin cancer). The reference category was patients without the specific co-morbidity.

A modified Poisson regression with robust error variance was used to calculate risk ratios (RRs) with 95 per cent confidence intervals (c.i.) adjusted for the co-variables listed and categorized as described above. Analyses stratified by median age (66 years or less and more than 66 years), annual hospital volume (fewer than 10 and 10 or more operations per year), tumour histology (adenocarcinoma and squamous cell carcinoma), and calendar period of surgery (1987–1999 and 2000–2015) were also conducted. In the stratified analyses, the RRs were adjusted for all eight co-variables, except for the stratification factor. When analysing the specific group of co-morbidities, further adjustment was made for other co-morbidities (no or yes), defined by the existence of other co-morbidities except for the analysed group. Interactions between pulmonary and cardiac disease were also explored in separate models. Because rates of missing data were low, complete case analyses were carried out. Two-sided tests at the 5 per cent level of significance were used for statistical testing. An experienced biostatistician was responsible for the statistical analyses, and SAS® software was used for all analyses.

**Results**

The cohort included 2576 patients who had undergone oesophageal cancer surgery. Of these, 1553 patients (60.3 per cent) had at least one co-morbidity included in the CCI. The most common co-morbidity group was other malignancy (561 patients, 21.8 per cent), followed by pulmonary disease (386, 15.0 per cent), cardiac disease (308, 12.0 per cent), diabetes (238, 9.2 per cent), and cerebral disease (192, 7.5 per cent). Most co-variables were distributed evenly between patients with and those without co-morbidity.

The risk increased by an average of 27 per cent for each additional CCI point (RR 1.27, 1.18 to 1.37). Analyses further adjusting for other co-morbidities showed similar estimates as those in Tables 2–4, and no statistically significant interactions.
Discussion

This study has indicated that preoperative co-morbidity, measured as higher CCI scores, was associated with an increased risk of reoperation or death within 90 days of oesophageal cancer surgery. Of the specific co-morbidity groups, pulmonary disease, cardiac disease, diabetes and cerebral disease, but not other malignancy, were associated with worse 90-day outcomes.

Among the strengths of this study are the nationwide and population-based cohort design with complete inclusion and follow-up, along with detailed and high-quality data on exposures, co-variables and outcome. The outcome was assessed objectively, using a combination of reoperation and death to represent severe postoperative adverse outcomes, as well as to handle the competing risk of death on the incidence of reoperation. Among weaknesses is possible unmeasured or residual confounding in this observational study, although the main risk factors for poor short-term outcomes were controlled for in the analyses. Life-threatening complications requiring intensive care were not included in the outcome due to incomplete data records, but this could only dilute the effects and would not change the conclusions. Missing data were limited and evenly distributed, alleviating concerns about this influencing results.

Although the CCI is widely accepted, it was not possible to assess the severity of co-morbidities in detail, or to examine co-morbidities not included in this index. Despite the large sample size, few patients selected for oesophagectomy had a high CCI score, which reduced the range of exposure and the statistical power in some subgroup analyses.

Most studies assessing co-morbidity in relation to short-term complications after oesophageal cancer surgery have focused on 30-day outcomes, and studies describing 90-day outcomes are

### Table 1 Characteristics of 2576 study patients who underwent esophagectomy for oesophageal cancer in Sweden in 1987-2015

| Charlson Co-morbidity Index score | 0 (n=1023) | 1 (n=922) | ≥2 (n=631) |
|----------------------------------|------------|------------|------------|
| Age (years)*                     | 63.8(9.9)  | 65.7(9.1)  | 67.1(8.9)  |
| Sex                              |            |            |            |
| M                                | 791 (77.3) | 691 (74.9) | 494 (78.3) |
| F                                | 232 (22.7) | 231 (25.1) | 137 (21.7) |
| Educational level (years)        |            |            |            |
| <9                               | 433 (42.3) | 413 (44.8) | 289 (45.8) |
| 9–12                             | 398 (38.9) | 335 (36.3) | 247 (39.1) |
| >12                              | 156 (15.2) | 145 (15.7) | 83 (13.2)  |
| Missing                          | 36 (3.5)   | 29 (3.3)   | 12 (1.9)   |
| Pathological tumour stage        |            |            |            |
| 0–I                             | 234 (22.9) | 185 (20.1) | 143 (22.7) |
| II                              | 316 (30.9) | 303 (32.9) | 216 (34.2) |
| III                             | 339 (33.1) | 316 (34.3) | 200 (31.7) |
| IV                              | 63 (6.2)   | 59 (6.4)   | 42 (6.7)   |
| Missing                          | 71 (6.9)   | 59 (6.4)   | 30 (4.8)   |
| Neoadjuvant therapy              |            |            |            |
| No                               | 585 (57.2) | 496 (53.8) | 392 (62.1) |
| Yes                              | 438 (42.8) | 426 (46.2) | 237 (37.6) |
| Missing                          | 0 (0.0)    | 0 (0.0)    | 2 (0.3)    |
| Annual hospital volume           |            |            |            |
| <10                              | 446 (43.6) | 393 (42.6) | 269 (42.6) |
| ≥10                              | 577 (56.4) | 529 (57.4) | 362 (57.4) |
| Tumour histology                 |            |            |            |
| Adenocarcinoma                   | 575 (56.2) | 462 (50.1) | 356 (56.4) |
| Squamous cell carcinoma          | 444 (43.4) | 458 (49.7) | 272 (43.1) |
| Missing                          | 4 (0.4)    | 2 (0.2)    | 3 (0.5)    |
| Calendar period                  |            |            |            |
| 1987–1996                        | 231 (22.6) | 329 (35.7) | 193 (30.6) |
| 1997–2006                        | 341 (33.3) | 231 (25.1) | 165 (26.1) |
| 2007–2015                        | 451 (44.1) | 362 (39.3) | 273 (43.3) |

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.).

### Table 2 Co-morbidity and risk ratios for reoperation or death within 90 days of oesophageal cancer surgery

| Co-morbidity and risk ratios for reoperation or death within 90 days of oesophageal cancer surgery |
|--------------------------------------------------------------------------------------------------|
| Reoperation or death                                      | Crude RR* | Adjusted RR† |
|----------------------------------------------------------|-----------|--------------|
|                                                                 | No (n=2130) | Yes (n=446) |
| CCI score                                                |            |              |
| 0                                                        | 1.00 (reference) | 1.00 (reference) |
| 1                                                        | 1.19 (0.96, 1.47) | 1.04 (0.83, 1.30) |
| ≥2                                                       | 1.88 (1.53, 2.31) | 1.78 (1.44, 2.20) |
| CCI‡                                                     | 1.28 (1.20, 1.38) | 1.27 (1.18, 1.37) |
| Co-morbidity group                                       |            |              |
| Pulmonary disease                                        |            |              |
| No                                                       | 1.00 (reference) | 1.00 (reference) |
| Yes                                                      | 1.58 (1.29, 1.92) | 1.66 (1.36, 2.04) |
| Cardiac disease                                          |            |              |
| No                                                       | 1.00 (reference) | 1.00 (reference) |
| Yes                                                      | 1.21 (0.93, 1.58) | 1.50 (1.14, 1.99) |
| Diabetes                                                 |            |              |
| No                                                       | 1.00 (reference) | 1.00 (reference) |
| Yes                                                      | 1.43 (1.09, 1.87) | 1.40 (1.06, 1.85) |
| Cerebral disease                                         |            |              |
| No                                                       | 1.00 (reference) | 1.00 (reference) |
| Yes                                                      | 1.09 (0.90, 1.33) | 1.19 (0.97, 1.47) |
| Other malignancy                                         |            |              |
| No                                                       | 1.00 (reference) | 1.00 (reference) |
| Yes                                                      | 1.09 (0.90, 1.33) | 1.19 (0.97, 1.47) |

Values in parentheses are percentages (reported across the row in each group) unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. †Adjusted for age, sex, educational level, pathological tumour stage, neoadjuvant therapy, annual hospital volume, tumour histology and calendar period. ‡Analysed as a discrete variable to evaluate the linear trend. RR, risk ratio.
Two Swedish studies and one from the USA found a preoperative CCI score of 2 or above to be associated with increased mortality or severe complications within 30 days of surgery, in line with the present 90-day results. Regarding specific types of co-morbidity, a French cohort study of 3009 patients reported an increased risk of 30-day postoperative mortality among those with cardiovascular, but not pulmonary disease, and a recent European multicentre study of 1590 patients found that cardiorespiratory co-morbidity was associated with an increased risk of 30-day postoperative complications. In the present study, the finding that patients with cardiac or pulmonary disease had a higher rate of reoperation or death within 90 days of surgery may be due to the fact that patients with these co-morbidities have a relatively low performance status and are more susceptible to postoperative cardiorespiratory complications, such as arrhythmia and pneumonia, that account for about half of the in-hospital mortality after oesophagectomy.

Studies have provided contradictory results regarding the impact of diabetes. A single-centre cohort study of 1282 patients from the Netherlands found no association between diabetes and 90-day mortality after oesophagectomy, which might be explained by well controlled perioperative glucose levels in a high-volume hospital. A cohort study from the USA, again involving over 1000 patients, however, found diabetes to be an independent predictor of complications and death within 30 days of oesophagectomy. The present study supports the findings of the latter study. Higher prevalence of microvascular disease of the kidneys and heart, and poor wound healing may all be important contributors to the development of postoperative complications in diabetic patients. The Dutch cohort study reported that a history of stroke increased the risk of 90-day mortality after oesophagectomy. This finding is also supported by the present results regarding cerebral disease, although this association must be interpreted cautiously owing to limited statistical power.

Table 3 Charlson Co-morbidity Index and risk ratios for reoperation or death within 90 days of oesophageal cancer surgery in stratified analyses

| No. of patients (n=2576)* | CCI score | | |
|---|---|---|---|
|  | 0 | RR†‡ | 1 | RR†‡ | ≥ 2 | RR†‡ |
| Age (years) | | | | | | |
| ≤66 | 1189 (46.2) | 1.00 | 1.02 (0.74, 1.40) | 1.80 (1.34, 2.44) | 1.27 (1.14, 1.41) |
| >66 | 1152 (44.7) | 1.00 | 1.09 (0.79, 1.50) | 1.81 (1.34, 2.43) | 1.28 (1.16, 1.41) |
| Annual hospital volume | | | | | | |
| <10 | 1043 (40.5) | 1.00 | 1.11 (0.82, 1.49) | 1.69 (1.27, 2.25) | 1.26 (1.14, 1.40) |
| ≥10 | 1298 (50.4) | 1.00 | 0.98 (0.69, 1.38) | 1.94 (1.41, 2.67) | 1.30 (1.16, 1.45) |
| Tumour histology | | | | | | |
| Adenocarcinoma | 1271 (49.3) | 1.00 | 0.81 (0.56, 1.17) | 1.83 (1.34, 2.50) | 1.31 (1.18, 1.46) |
| Squamous cell carcinoma | 1070 (41.5) | 1.00 | 1.22 (0.91, 1.62) | 1.66 (1.24, 2.22) | 1.21 (1.09, 1.34) |
| Calendar period | | | | | | |
| 1987–1999 | 924 (35.9) | 1.00 | 1.08 (0.81, 1.44) | 1.66 (1.25, 2.21) | 1.23 (1.12, 1.36) |
| 2000–2015 | 1417 (55.0) | 1.00 | 1.05 (0.74, 1.48) | 1.97 (1.43, 2.70) | 1.32 (1.18, 1.46) |

Values in parentheses are *percentages (reported across the column in each stratified group; may not add to 100 per cent because of missing data) and †95 per cent confidence intervals. ‡Adjusted for age, sex, educational level, pathological tumour stage, neoadjuvant therapy, annual hospital volume, tumour histology and calendar period, except the stratification variable in each model. §Analysed as a discrete variable to evaluate the linear trend. RR, risks ratio.

Table 4 Co-morbidity groups and risk ratios for reoperation or death within 90 days of oesophageal cancer surgery in stratified analyses

| Risk ratio* | Pulmonary disease | Cardiac disease | Diabetes | Cerebral disease | Other malignancy |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| ≤66 | 1.57 (1.15, 2.15) | 1.30 (0.87, 1.95) | 1.67 (1.12, 2.48) | 1.49 (0.93, 2.38) | 1.30 (0.96, 1.74) |
| >66 | 1.79 (1.38, 2.32) | 1.46 (1.10, 1.95) | 1.44 (0.97, 2.12) | 1.34 (0.95, 1.89) | 1.09 (0.81, 1.46) |
| Annual hospital volume | | | | | |
| <10 | 1.72 (1.33, 2.23) | 1.32 (0.96, 1.82) | 1.54 (1.04, 2.26) | 1.45 (1.01, 2.07) | 1.07 (0.79, 1.45) |
| ≥10 | 1.63 (1.18, 2.25) | 1.46 (1.04, 2.06) | 1.54 (1.03, 2.31) | 1.35 (0.86, 2.11) | 1.31 (0.97, 1.77) |
| Tumour histology | | | | | |
| Adenocarcinoma | 1.67 (1.23, 2.26) | 1.42 (1.02, 1.99) | 1.37 (0.95, 1.98) | 1.53 (1.04, 2.26) | 1.49 (1.12, 2.00) |
| Squamous cell carcinoma | 1.61 (1.23, 2.12) | 1.26 (0.90, 1.76) | 1.85 (1.24, 2.75) | 1.27 (0.85, 1.89) | 0.92 (0.68, 1.24) |
| Calendar period | | | | | |
| 1987–1999 | 1.83 (1.40, 2.39) | 1.36 (0.98, 1.90) | 1.56 (1.02, 2.40) | 1.25 (0.83, 1.87) | 0.96 (0.69, 1.34) |
| 2000–2015 | 1.46 (1.07, 1.99) | 1.39 (0.99, 1.94) | 1.53 (1.06, 2.19) | 1.62 (1.11, 2.38) | 1.39 (1.05, 1.84) |

Numbers of patients are as shown in Table 3. Values in parentheses are 95 per cent confidence intervals. *Adjusted for age, sex, educational level, pathological tumour stage, neoadjuvant therapy, annual hospital volume, tumour histology and calendar period, except the stratification variable in each model.
The lack of association between other malignancy and poor postoperative outcome within 30 days of surgery has been found previously\textsuperscript{10}, as well as in the present study of 90-day postoperative outcome. This could reflect conservative selection for surgery in patients with a history of another malignancy. Despite these limitations, it remains clear that careful assessment to look for co-morbidities, pretreatment optimization and tailored postoperative care are elements that still require investigation in order to improve outcomes for patients needing oesophagectomy.

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**References**

1. Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet 2017;\textbf{390}:2383–2396  
2. Ichikawa H, Kosugi S, Kanda T, Yajima K, Ishikawa T, Hanyu T et al. Surgical and long-term outcomes following oesophagectomy in oesophageal cancer patients with comorbidity. Int J Surg 2016;\textbf{36}:212–218  
3. Backemar L, Lagergren P, Djärv T, Johar A, Wikman A, Lagergren J. Comorbidities and risk of complications after surgery for esophageal cancer: a nationwide cohort study in Sweden. World J Surg 2015;\textbf{39}:2282–2288  
4. Kauppila JH, Johar A, Lagergren P. Postoperative complications and health-related quality of life 10 years after esophageal cancer surgery. Ann Surg 2020;\textbf{271}:311–316  
5. Oh T, Kim K, Jheon S, Do S, Hwang J, Jeon Y et al. Long-term oncologic outcomes, opioid use, and complications after esophageal cancer surgery. J Clin Med 2018;\textbf{7}:33  
6. Varagunam M, Hardwick K, Riley S, Chadwick G, Cromwell DA, Groene O. Changes in volume, clinical practice and outcome after reorganisation of oesophago-gastric cancer care in England: a longitudinal observational study. Eur J Surg Oncol 2018;\textbf{44}:524–531  
7. Rutegard M, Lagergren P, Johar A, Lagergren J. Time shift in early postoperative mortality after oesophagectomy for cancer. Ann Surg Oncol 2015;\textbf{22}:3144–3149  
8. Ra J, Paulson EC, Kucharzuk J, Armstrong K, Wirtalla C, Rapaport-Kelz R et al. Postoperative mortality after esophagectomy for cancer: development of a preoperative risk prediction model. Ann Surg Oncol 2008;\textbf{15}:1577–1584  
9. Dhungel B, Diggs BS, Hunter JG, Sheppard BC, Vetto JT, Dolan JP. Patient and peri-operative predictors of morbidity and mortality after esophagectomy. American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), 2005-2008. J Gastrointest Surg 2010;\textbf{14}:1492–501  
10. Messager M, Pasquier A, Duhamel A, Caranhac G, Fiessen G, Mariette C. Laparoscopic gastric mobilization reduces postoperative mortality after esophageal cancer surgery: a French Nationwide Study. Ann Surg 2015;\textbf{262}:817–823  
11. Talma AK, Lingsma HF, Steyerberg EW, Wijnhoven BP, Van Lanschot JJ. The 30-day versus in-hospital and 90-day mortality after esophagectomy as indicators for quality of care. Ann Surg 2014;\textbf{260}:267–273  
12. Lindblad M, Ye W, Lindgren A, Lagergren J. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg 2006;\textbf{243}:479–485  
13. Lagergren K, Derogar M. Validation of oesophageal cancer surgery data in the Swedish Patient Registry. Acta Oncol 2012;\textbf{51}:65–68  
14. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H et al. The Swedish case of death register. Eur J Epidemiol 2017;\textbf{32}:765–773  
15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekborn A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;\textbf{24}:659–667  
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;\textbf{40}:373–383  
17. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in registry-based research. Methods Inf Med 2017;\textbf{56}:401–406  
18. van der Schaaf M, Derogar M, Johar A, Rutegard M, Gossage J, Mason R et al. Reoperation after oesophageal cancer surgery in relation to long-term survival: a population-based cohort study. BMJ Open 2014;\textbf{4}:e004648  
19. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;\textbf{159}:702–706  
20. Backemar L, Lagergren P, Johar A, Lagergren J. Impact of comorbidity on mortality after oesophageal cancer surgery. Br J Surg 2015;\textbf{102}:1097–1105  
21. Klevebro F, Elliott JA, Slaman A, Vermeulen BD, Kamiya S, Rosman C et al. Cardiorespiratory comorbidity and postoperative complications following esophagectomy: a European Multicenter Cohort Study. Ann Surg Oncol 2019;\textbf{26}:2864–2873  
22. Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J. Analysis of reduced death and complication rates after esophageal resection. Ann Surg Oncol 2001;\textbf{23}:338–344  
23. Morita M, Nakanoko T, Fujinaka Y, Kubo N, Yamashita N, Yoshinaga K et al. In-hospital mortality after a surgical resection for esophageal cancer: analyses of the associated factors and historical changes. Ann Surg Oncol 2011;\textbf{18}:1757–1765