# Risk adjustment models for short-term outcomes after surgical resection for oesophago-gastric cancer

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**ABSTRACT**

**Background**

Outcomes for oesophago-gastric cancer surgery are compared with the aim to benchmark quality of care. Adjusting for patient characteristics is crucial to avoid biased comparisons between providers. The study objective was to develop a case-mix adjustment model for comparing 30-, 90-day mortality and anastomotic leakage rates after oesophago-gastric (O-G) cancer resections.

**Methods**

The study reviewed existing models, considered expert opinion and examined audit data in order to select predictors that were consequently used to develop a case-mix adjustment model for the National Oesophago-Gastric Cancer Audit, covering England and Wales. Models were developed on patients undergoing surgical resection between April 2011 and March 2013 using logistic regression. Model calibration and discrimination was quantified using a bootstrap procedure.

**Results**

Most existing risk models for O-G resections were methodologically weak, out-dated or based on detailed laboratory data not generally available. In 4882 O-G cancer patients used for model development, 30-day mortality was 2.3%, 90-day mortality was 4.4% and 6.2% of patients developed an anastomotic leakage. The internally validated models, based on predictors selected from the literature, showed moderate discrimination (AUC 0.65 for 30-day mortality, 0.66 for 90-day mortality and 0.59 for anastomotic leakage) and good calibration.

**Conclusion**

Based on available data, three case mix adjustment models for postoperative outcomes in patients undergoing curative surgery for O-G cancer were developed. These models should be used for risk adjustment when assessing hospital performance in the NHS, and should be tested in other large health systems.

***Keywords:*** *oesophago-gastric cancer resection, case mix adjustment, 30-day mortality, 90-day mortality, anastomotic leakage*

**Introduction**

As public interest in quality of hospital care is growing, outcome measures are increasingly used to benchmark hospital performance. When comparing outcomes between hospitals, risk adjustment for patient characteristics is crucial because when patient populations differ between hospitals, differences in outcome may represent differences in baseline risk rather than quality of care. Insufficient case-mix adjustment then leads to unfair comparisons. This is of particular relevance where surgery bears substantial risks, as in the case of O-G cancer resections.

The National Oesophago-Gastric Audit (NOGCA) was set up to monitor the quality of care provided to patients with O-G cancer in England and Wales, to evaluate care processes and patient outcomes [[1](#_ENREF_1)]. A recent systematic review concluded, however, that current models for prediction of outcomes after oesophagectomy had numerous limitations in regarding methodology and clinical credibility [[2](#_ENREF_2)]. Centralization of surgery, decision-making in multi-disciplinary teams and improved care pathways have already been shown to contribute to a decrease in short-term mortality [[3](#_ENREF_3), [4](#_ENREF_4)], so that earlier prediction models might no longer be valid. The aim of the present study was to develop a case-mix adjustment model for comparisons of 30- and 90-day mortality, and anastomotic leak rates after resections for O-G cancer between NHS trusts, based on a review of existing prediction models, expert opinion and audit data.

**METHODS**

**Data collection**

The study used data submitted to the National Oesophago-Gastric (O-G) Cancer Auditfrom all 154 English NHS trusts that provide O-G cancer care and from all 13 Welsh NHS organisations contributing to the Welsh Cancer Information System (CANISC). The Audit included adults diagnosed with invasive, epithelial cancer of the oesophagus or stomach between 1 April 2011 and 31 March 2013, and captured information using a prospectively developed database on the patient (age at diagnosis, gender, comorbidities, Eastern Co-operative Oncology Group (ECOG) functional performance), cancer details (cancer site oesophagus including Siewert types I-III junctional tumours, or stomach), histology, TNM stage (Tumour, Node Metastasis) version 7 [[5](#_ENREF_5)], , American Society of Anesthesiologists (ASA) score, comorbidities and procedure (performance of neoadjuvant treatment, operation mode), as described previously[[1](#_ENREF_1)]. All patients undergoing curative resection were included in the present study; those undergoing curative oncological treatment for squamous cell carcinoma and all palliative patients were excluded, (Appendix Figure A1).

**Review of existing models**

Potential prognostic factors for 30-day, 90-day mortality and anastomotic leak were selected on the basis of a review of the existing literature and clinical expert advice. Literature was searched for multivariable risk models of short-term mortality (30-, 90-days, or in-hospital mortality) or complications including anastomotic leaks following O-G cancer surgery. From studies meeting these inclusion criteria, risk factors included in the models that were available in routine clinical databases and not modifiable by the provider were selected (Appendix Table A1).

**Outcome Measures**

The short-term outcomes were 30-day and 90-day all-cause postoperative mortality and anastomotic leak rates[[6](#_ENREF_6)]. Date of death was obtained from the Office for National Statistics death certificate register. Anastomotic leak was defined as a severe disruption to the anastomosis (whether detected clinically or radiologically, and irrespective of whether it is managed conservatively or by re-operation) [[7](#_ENREF_7)]. All leaks, including those from conduit staple lines away from the oesophago-gastric anastomosis, were included in the study based on self-reported data from the surgeon/surgical team.

**Model development and statistical analysis**

Potential predictors were tested initially in univariable logistic regression models. Variable categories containing small number were regrouped in advance (ASA score, co-morbidity count, predominant histology by cancer location, performance status, histology type). The linearity of the continuous independent variable age at diagnosis with 30-, 90-day mortality and anastomotic leakage was tested by adding quadratic terms. As this did not significantly improve the models, no quadratic terms were included in the model. To prevent exclusion of predictors with borderline significance, a p-value of 0.10 was used rather than 0.05 for inclusion of variables in the model. Decisions to include and exclude predictors took into account primarily the evidence gathered in the literature review, anot only statistical information, but also drew on the evidence of predictors identified by the literature review, and expert clinical opinion. Odds ratios (OR) with t95% confidence intervals were used to express the strength of the predictive effects.

The model performance was assessed with respect to discrimination and calibration [[8](#_ENREF_8)]. Discriminative ability represents how well the model was able to discriminate between patients with and without the outcome of interest, expressed as the area under the receiver operating curve (AUC, c-statistic) ranging from 0.5 – 1.0, where 0.5 indicates no discriminative power and 1.0 perfect discrimination. Calibration of the model was assessed by using scatter plots of observed versus predicted outcomes in deciles of predicted risk on the imputed data set.

The internal validity of the models was evaluated using a bootstrapping procedure [[9](#_ENREF_9)]. With bootstrapping, multiple patient samples were drawn, considered as cases included under the same conditions as in the original data set. 800 bootstrap samples were used to re-estimate the multivariable logistic regression coefficients and consequently applied to the original dataset, resulting in 800 AUC statistics. The mean of these AUCs represented the optimism-corrected or internally validated AUC.

All analyses were performed in Stata and R. Missing data was assumed to be Missing at Random and was handled with the MICE (multiple imputation by chained equations) approach by White and Royston using Stata software (version 12 (StataCorp LP, College Station, Texas, USA)) [[10](#_ENREF_10)]. Chained equations with 10 imputation sets were used. The outcome measures and the independent variables deprivation, age at diagnosis, ECOG performance status, ASA score, gender, tumour location, number of comorbidities, size and/or extent of the primary tumour (T stage from the TNM classification) and regional lymph nodes (N stage of the TNM classification**)** were included in the imputation model. A sensitivity analysis comparing complete-case analysis with the one derived from the imputation model demonstrated no significant differences (Appendix Table A2, Table A3). The bootstrap procedure was performed with the *validate* function in the *rms* package in R statistical software, and the imputation with the MICE (multiple imputation by chained equations) approach by White and Royston using Stata software (version 12 (StataCorp LP, College Station, Texas, USA)) [[10](#_ENREF_10)].

**RESULTS**

**Published prognostic models**

The literature search resulted in the identification of 41 prediction models for short-term outcomes after O-G cancer surgery. Some of the studies that we identified had a dual aim, i.e. providing insight in predictor effects and providing predictions based on the combination of predictors in a multivariable model. 33 models addressed postoperative mortality (12 studies used 30-day mortality, three used 90-day mortality, 17 used in-hospital mortality, one postoperative mortality not further defined) and eight were predicting anastomotic leakages (AL) [[11-18](#_ENREF_11)] (Table 1). The majority of the studies considered outcomes after oesophagectomy [[13](#_ENREF_13), [14](#_ENREF_14), [16](#_ENREF_16), [18-34](#_ENREF_18)] and were designed as clinical prediction models as opposed to risk-adjustment models for provider comparisons. Numerous models were based on the POSSUM, O-POSSUM, P-POSSUM scores, a prediction score requiring detailed laboratory test values. These POSSUM scores are based on data not commonly available in audit data, such as white blood cell count or urea level [[12](#_ENREF_12), [17](#_ENREF_17), [21](#_ENREF_21), [26](#_ENREF_26), [27](#_ENREF_27), [31](#_ENREF_31), [35-37](#_ENREF_35)]. In addition, the majority of the studies were based on single centre data that either pooled data over long periods of time [[11](#_ENREF_11), [13-17](#_ENREF_13), [19-21](#_ENREF_19), [23](#_ENREF_23), [26](#_ENREF_26), [31](#_ENREF_31), [33](#_ENREF_33), [34](#_ENREF_34), [36](#_ENREF_36), [37](#_ENREF_37)] or had a small sample size (e.g. N = 70, 121, 143, 204, 232) [[11](#_ENREF_11), [16](#_ENREF_16), [20](#_ENREF_20), [21](#_ENREF_21), [37](#_ENREF_37)] and were performed in other countries than the UK [[11](#_ENREF_11), [14](#_ENREF_14), [16](#_ENREF_16), [18](#_ENREF_18), [20](#_ENREF_20), [22](#_ENREF_22), [23](#_ENREF_23), [27-29](#_ENREF_27), [33](#_ENREF_33), [34](#_ENREF_34)]. Event rates were typically far higher than those currently observed in the NOGCA, especially in the models developed in earlier years [[19-22](#_ENREF_19)]. The predictive ability of most models was limited, at maximum, moderate [[21](#_ENREF_21), [22](#_ENREF_22), [24](#_ENREF_24), [30](#_ENREF_30)].

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**Insert table 1 about here**

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A detailed description of the predictors identified in the literature search and reasons for in-or exclusion is available in the appendix (Appendix Table A1).

**Patient characteristics**

Of 22 766 patients identified the study included 4882 patients who had undergone O-G cancer resection in the period between April 2011 and March 2013 (Table 2). The patients had a mean age of 66 years (interquartile range=14 years) and the majority were male (74%). In 2747 (56%) patients, at least one comorbidity was present. Most patients had an adenocarcinoma histology (89%), while the most common location was the lower third of the oesophagus and Siewert type 1 tumour (39%). 30-day mortality was 2.3% (N=112) and 90-day mortality was 4.4% (N=216). 6.2% (N=305) of the patients developed an AL. Further descriptive information is shown in Table 2.

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**Model performance and validation**

The models AUC was of our primary interest as they present the models predictive ability. The discriminative ability was moderate for the mortality models (AUC 0.70 for the 30-day mortality and AUC 0.69 for the 90-day mortality outcome) and somewhat lower for the AL model (AUC=0.63). Internally validated AUCs were 0.65 for the 30-day mortality model, 0.66 for the 90-day mortality model and 0.59 for the anastomotic leakage model, indicating some over fitting.

**Model calibration**

The scatter plots of predicted and observed probabilities showed that patients had an overall low risk for developing one of the three tested outcomes. For example, patients in the highest risk decile for developing an AL had a risk below 0.2 on average in the overall cohort. The difference between observed and predicted risk for developing an AL was smaller than 0.1.

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**Insert figure 1a, 1b, 1c about here**

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**Univariable analyses**

In the following paragraphs odds ratio are presented to give an impression of the strength of the different predictors. However, our main aim is to give valid prediction and not valid estimates of the individual predictor effects.

The risk factor with the strongest association with all outcomes was the ASA grade (ASA grade 3 vs 1: 30-day mortality: OR=4.7 (95%CI=2.2-10); 90-day mortality: OR=5.0 (95%CI=2.8-8.8); AL: OR=1.4 (95%CI=1.0-2.0)). A greater number of comorbidities also increased the risk for all three outcomes (3 or more comorbidities vs.no comorbidities: 30-day mortality: OR 2.9 (95%CI: 1.5-5.6); 90-day mortality: OR 3.0 (95%CI: 1.8-4.8); AL: OR 1.7 (95%CI; 1.0-2.7)). Further, patients with an ECOG performance status of 3 or higher had a threefold risk of dying within 30- or 90-days compared to patients with an ECOG performance status of 0. In contrast, female gender and cancer located in the stomach compared to the oesophagus was associated with decreased risk of developing an AL (Table 3).

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**Multivariable analyses**

Predictors with a p-value of <0.1 in the univariable data analysis for 30-day mortality were patient age at diagnosis, the number of comorbidities, ECOG performance status and ASA score. Furthermore, for 90-day mortality, outcome gender and regional lymph nodes (N) were identified as important predictors. For the anastomotic leakage model, the following predictors were chosen on basis of the univariable data analysis: gender, number of comorbidities, ASA score, histologic tumour type and tumour location.In consistency with previous studies and clinical expert opinion, the predictors gender, age, TNM stage, and ECOG performance status and predominant histology by cancer locationand deprivation were entered into the multivariable models.

Table 4 presents the results for the multivariable case-mix adjustment models. For 30-day mortality, comorbidity count and ASA grade were the strongest predictors. A patient with an ASA grade of 4 or higher had an increase odds of 4.7 (95%CI 1.3-16.5) to die within 30-days compared to a patient with ASA grade 1. ASA grade was also the strongest predictor for the 90-day mortality outcome (ASA grade 4 or higher vs ASA grade 1 OR 5.1; 95% CI 2.0-13.3). Other predictors significantly associated with the mortality outcomes were: age at diagnosis, and the number of comorbidities.

The multivariable analysis for anastomotic leakage revealed that the number of comorbidities was strongly associated with the development of anastomotic leaks (3 or more comorbidities vs. no comorbidities OR=1.7; 95% CI 1.0-2.8). Further, patients with a tumour located in the stomach had a decreased of developing an AL (OR 0.4; 95% CI: 0.1-0.6).

The model equations are presented in table 5.

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**DISCUSSION**

This study developed models for case-mix adjustment of postoperative outcomes in oesophago-gastric (O-G) cancer patients undergoing curative resection. Our models are based on the largest contemporary patient cohort and exclusively based on data routinely available from the National Oesophago-Gastric Cancer Audit (NOCGA). Registries in other countries collect similar data items and may adopt the new risk models when pursuing obligatory outcome reporting and comparison between providers, as it is the case in the NHS.

ASA grade and the number of comorbidities were found to be the strongest predictors for both short-term mortality and anastomotic leakage (AL). This is in line with previous literature that identified severely ill patients being more likely to have an increased morbidity risk [[22](#_ENREF_22), [23](#_ENREF_23), [29](#_ENREF_29), [38](#_ENREF_38)]. Our three case-mix adjustment models, based on routinely available data in the NHS, had similar predictive ability to the ones found in the literature. While model performance might be improved by adding further clinical/laboratory based data items, we recommend against this for national comparisons. First, our review showed that the performance of models including complex clinical/laboratory data (such as the POSSUM score) differed substantially, and second, these clinical data elements are not routinely available in Cancer Registries or through the NOGCA database.

Other predictors identified in the literature include provider related variables such as choice of treatment and volume. But, as we aimed to develop a case-mix adjustment model to monitor outcomes between providers, factors that can be influenced by the provider, are not corrected for. For this reason, only those pre-operative factors were considered, which are found readily available in hospital databases and are not possible to be modified by the provider. The choice of variables might differ in a prognostic model which aims to predict risk in ‘new’ patients as opposed to a case-mix adjustment models which is usually used in retrospect on the data available. Taking into account patient characteristics that influence the postoperative outcome when comparing performance across providers is necessary to ensure that true differences in performance rather than differences in patient characteristics are being assessed [[39](#_ENREF_39)]. Nevertheless, outcome differences must be interpreted with caution even after sufficient case-mix adjustment there might be remaining unmeasured confounders which influence the outcome.

Further, the question remains which indicator best reflects quality of surgical care. 30-days mortality rates are decreasing over time. While studies using data from the UK from 1990 and 2002 report an average postoperative 30-day mortality rate of 11.4% [[21](#_ENREF_21), [36](#_ENREF_36)], a study using data from the period 2005-2009 report a 4% 30-day mortality rate [[37](#_ENREF_37)]. In our study, using data from April 2011 to March 2013, the 30-day mortality rate was 2.3%. While his is a positive development for clinical practice, 30-day mortality rates become less useful as quality indicators because the estimated mortality rates per hospital are based on smaller numbers of cases and hence more uncertain [[39](#_ENREF_39)]. Rates of 90-day mortality are higher and research showed that the causes of death at 90-days after surgery are still strongly associated with surgical performance [[40-42](#_ENREF_40)]. Deciding between measuring 30- or 90-day mortality can be regarded as a trade-off: with shorter follow-up, the included deaths will be mostly related to the surgery, but later deaths will be missed. While with a longer follow up period later deaths are included, potentially at the expense of including deaths unrelated to the surgery. Anastomotic leakages occur more frequently as well, which makes them attractive as quality indicator from a statistical point of view. The models for anastomotic leakage performed relatively poor. This is consistent with prior research which showed that postoperative complications are more difficult to predict on basis of patient characteristics than postoperative mortality [[43](#_ENREF_43)]. This raises the hypothesis that their occurrence is determined by the quality of surgical care and to a lesser extent by patient characteristics. Thus, for several reasons anastomotic leakage rates seem a valuable quality indicator. However, judging hospital quality based on one indicator is a simplistic approach that should not be advocated. Monitoring several outcome and process indicators together will probably provide the most global picture on hospital performance. Nevertheless, comparing outcomes across hospitals based on single indicators has become a common approach in the UK and many other countries. In this undertaking, case-mix adjustment is of crucial importance to make valid comparisons and avoid risk adverse behavior. We therefore aimed to develop the best possible risk adjustment model, although we recognize that some residual confounding will always remain and that also adjusted mortality rates should still be interpreted with caution.

A major strength of this study is its large, national representative, population-based cohort. The use of audit data enabled the analysis of reliable, clinical case mix adjustment information and robust outcome ascertainment by linking to the Office of National Statistics mortality data. Future studies should address additionally routinely available information possibly influencing patient outcomes. A potential limitation of this study is that missing data were observed for some key variables and that the coding of complications is subject to coding differences, and potentially under-reporting, between NHS trusts.

In conclusion, we developed well performing case mix adjustment models based on routinely available data for predicting postoperative short-term mortality following O-G cancer surgery. These can be used for the risk adjustment in the assessment of hospital performance in the NHS or other large health systems.

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**TABLES AND FIGURES**

**Table 1:** Descriptive information of currently available prediction models of O-G cancer short-term outcomes

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| AUTHOR(YEAR) | COUNTRY | PERIOD OF DATA COLLECTION | OPERATION TYPE | NUMBER OFCENTRES | PATIENTNUMBER | REPORTED RATE OF OUTCOME | EVENT RATE | DISCRIMINATION |
| Law (1994) [[34](#_ENREF_34)] | HKG | 1982-92 | Oesophageal | 1 | 1105 | In-hospital mortality | 15.5% | / |
| Bartels (1998)[[19](#_ENREF_19)] | GER | 1982-5(1996) | Oesophageal | 1 | 432 | 30-day mortality | 10% (1%) | / |
| Liu (2000)[[20](#_ENREF_20)] | AUT | 1994-7 | Oesophageal | 1 | 70 | In-hospital mortality& complication | 13% | / |
| Karl (2000)[[11](#_ENREF_11)] | USA | 1989-99 | Ivor Lewis Gastro-Oesophageal | 1 | 143 | 30-day mortalityAL | 2.1%3.5% | / |
| Zafirellis (2002)[[21](#_ENREF_21)] | UK | 1990-9 | Oesophageal | 1 | 204 | 30-day mortality | 12.7% | AUC=0.62 POSSUM |
| Bailey (2003)[[22](#_ENREF_22)] | USA | 1991-2000 | Oesophageal | 109 | 1777 | 30-day mortality | 9.8% | c-index 0.69 |
| McCulloch (2003)[[12](#_ENREF_12)] | UK | 1999-2002 | Gastro-oesophageal | 26 | 955 | In-hospital mortalitySurgical complications | 12%19% | AUC=0.68 POSSUM AUC=0.71POSSUM |
| Mariette (2004)[[13](#_ENREF_13)] | FR | 1982-93(1994-2002) | Oesophageal | 1 | 742 | In-hospital mortalityAL | 5.4%(2.9%) 9.8%(2.2%) | / |
| Law (2004)[[14](#_ENREF_14)] | HKG | 1990-5 | Oesophageal | 1 | 421 | In hospital mortality | 1.1% | / |
| Atkins (2004)[[23](#_ENREF_23)] | USA | 1996-2002 | Oesophageal | 1 | 379 | Operative mortality | 5.8% | / |
| Tekkis (2004)[[35](#_ENREF_35)] | UK | 1994-2000 | Gastro-oesophageal | 36 | 1042 | In-hospital mortality | 12% | AUC=79.7 O-POSSUMAUC=74.6 P-POSSUM |
| Junemann-Ramirez (2004)[[15](#_ENREF_15)] | UK | 1992-9 | Ivor Lewis gastro-oesophageal | 1 | 276 | AL | 5.1% | / |
| Steyerberg (2006)[[24](#_ENREF_24)] | USA/NL | 1991-1996 | Oesophageal | Population database/ clinical centre | 3592 | 30-day mortality (in 4cohorts) | 11% (10%,7%,4%) | AUC=0.66 |
| Viklund (2006)[[25](#_ENREF_25)] | SWE | 2001-3 | Oesophageal | Nationwide study | 275 | 30-day mortality & AL  | 3%8% | / |
| Nagabhushan (2007) [[36](#_ENREF_36)] | UK | 1990-2002 | Gastro-oesophageal | 1 | 313 | 30-day mortality | 10.2% | AUC=0.61 O-POSSUMAUC=0.68 P-POSSUM |
| Lagarde (2007)[[26](#_ENREF_26)] | NL | 1993-2005 | Oesophageal | 1 | 663 | In-hospital mortality | 3.6% | AUC=0.60 O-POSSUM |
| Lai (2007)[[27](#_ENREF_27)] | HKG | 2001-5 | Oesophageal | 14 | 545 | In-hospital mortality | 5.5% | AUC=0.776 POSSUMAUC=0.776 P-POSSUMAUC=0.676 O-POSSUM |
| Ra (2008)[[28](#_ENREF_28)] | USA | 1997-2003 | Oesophageal | Population database | 1172 | In-hospital mortality | 14%  |  / |
| Wright (2009)[[29](#_ENREF_29)] | USA | 2002-7 | Oesophageal | 73 STS General Thoracic Database | 2315 | Major morbidityc (incl. death and AL) |  | / |
| Park (2009)[[30](#_ENREF_30)] | UK | 1995-2007 | Oesophageal | ICNARC Case Mix Programme Database 181 | 7227 | In-hospital mortality | 11% | AUC=0.60 APACHE II dAUC=0.63 SAPSS IIeAUC=0.65 ICNARC f |
| Dutta (2011)[[37](#_ENREF_37)] | UK | 2005-9 | Gastro-oesophageal | 1 | 121 | 30-day mortality | 4% | AUC=0.759 POSSUMAUC=0.715 O-POSSUM |
| Bosch (2011)[[44](#_ENREF_44)] | NL | 1991-2007 | Oesophageal | 1 | 278 |  90-day mortality | 5.4% | AUC=0.766 P-POSSUM AUC=0.756 O-POSSUM |
| Morita (2011)[[33](#_ENREF_33)] | JPN | 1964-79 | Oesophageal | 1 | 1106 | In-hospital mortality | 16.1% | / |
| Sunpaweravong (2012) [[16](#_ENREF_16)] | THA | 1998-2007 | Oesophageal | 1  | 232 | 30-day mortalityAL | 3.8% 15.9%  | / |
| Noble (2012)[[17](#_ENREF_17)] | UK | 2005-102011 | Oesophageal | 1 | 258 | ALAL major complication/ death | 10%  | AUC=0.801 Nun scoregAUC=0.879 Nun scoreAUC=0.856 Nun score |
| Koppert (2012)[[45](#_ENREF_45)] | NL | 2005-9 | Gastro-oesophageal | Eindhoven Cancer Registry | 6223 | 30-day mortality | 7.7% | / |
| Rutegard (2012)[[32](#_ENREF_32)] | SW | 2001-5 | Oesophageal | Nationwide | 559 | 90-day mortality | 7.1% | / |
| Kassis (2013)[[18](#_ENREF_18)] | USA | 2001-11 | Oesophageal | STS General Thoracic Database | 7595 | AL | 10.6%  | / |

b Anastomotic leakage; c Including reoperation for bleeding, AL, pneumonia, re-intubation, ventilation beyond 48 hours, or death; d Acute Physiology and Chronic Health Evaluation; e Simplified Acute Physiology Score; fICNARC physiology score; g Nun score calculated using the log-likelihood ratio of blood-borne variables of the systematic inflammatory response (albumin, WCC and CRP from POD4)

**Table 2:** Descriptive information on study population

|  |  |  |
| --- | --- | --- |
| **Patient and prognostic information** | **No. of patients** | **%** |
| **Year of operation, 2013** |  |  |
| 2012 | 2417 | 49.5 |
| 2013 | 2465 | 50.5 |
| **Age, years**  | 4873 | 66.3\* |
| Missing values | 9 | 0.2 |
| **Comorbidity count** |  |  |
| No comorbidities | 2747 | 56.3 |
| One comorbidity | 1311 | 26.8 |
| Two comorbidities | 566 | 11.6 |
| Three or more comorbidities | 258 | 5.3 |
| **Gender** |  |  |
| Male | 3618 | 74.1 |
| **ECOG (WHO) performance status** |  |  |
| Carries out all normal activity | 2519 | 51.6 |
| Restricted but walks/does light work | 1557 | 31.9 |
| Walks, full self-care but no work | 527 | 10.8 |
| Limited self-care – fully disabled | 120 | 2.5 |
| Missing values | 159 | 3.3 |
| **Size and/or extent of the primary tumour (T)** |  |  |
| No evidence of primary tumour (T0) | 202 | 4.2 |
| Tumour invades lamina propria or submucosa (T1) | 929 | 19.0 |
| Tumour invades muscularis propria (T2) | 792 | 16.2 |
| Tumour invades adventitia (T3) | 2323 | 47.6 |
| Tumour invades adjacent structures (T4) | 490 | 10.0 |
| Missing values | 146 | 3.0 |
| **Regional lymph nodes (N)** |  |  |
| No regional lymph node metastasis (N0) | 2143 | 43.9 |
| Metastasis in 1 to 2 regional lymph nodes (N1) | 1498 | 30.7 |
| Metastasis in 3 to 6 (N2) | 615 | 12.6 |
| Metastasis in 7 or more (N3) | 508 | 10.4 |
| Missing values | 118 | 2.4 |
| **ASA Scale** |  |  |
| Normal healthy patient | 816 | 16.7 |
| Mild systemic disease | 2502 | 51.2 |
| Severe systemic disease | 1248 | 25.6 |
| Life-threatening disease/ Moribund patient | 60 | 1.2 |
| Missing values | 256 | 5.2 |
| **HISTOLOGY** |  |  |
| Adenocarcinoma | 4336 | 88.8 |
| Squamous cell carcinoma | 420 | 8.6 |
| Other carcinoma types | 126 | 2.6 |
| **Predominant histology by cancer location** |  |  |
| Squamous cell carcinomas of the oesophagus  | 492 | 10.1 |
| Adenocarcinomas of the upper and middle oesophagus | 184 | 3.8 |
| Adenocarcinomas of the lower third of the oesophagus and Siewert type 1 tumours  | 1906 | 39.0 |
| Siewert type II and type III tumours  | 844 | 17.3 |
| Tumours of the stomach  | 1456 | 29.8 |
| **Level of socio-economic deprivation (IMD quintile)** |  |  |
| 1 Least deprived | 840 | 17.2 |
| 2 | 860 | 17.6 |
| 3 | 846 | 17.3 |
| 4 | 800 | 16.4 |
| 5 Most deprived | 746 | 15.3 |
| Missing values | 790 | 16.2 |
| **Patient outcomes** |  |  |
| Anastomotic leak | 305 | 6.2 |
| 30-day postoperative mortality | 112 | 2.3 |
| 90-day postoperative mortality | 216 | 4.4 |

\*Mean

**Table 3** Univariable logistic regression analyses for 30-day and 90-day mortality and anastomotic leakage

|  |  |  |  |
| --- | --- | --- | --- |
| Predictor | 30-day Mortalityn=4882 | 90-day Mortalityn=4882 | Anastomotic leakagen=4882 |
|  | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** |
| Age per decade, years | **1.3\*** | **1.1-1.6** | **1.3** | **1.1-1.5** | 1.0 | 0.9-1.1 |
| Gender MaleFemale | 10.8 | 0.5-1.2 | 10.7 | 0.5-1.0 | 1**0.7** | **0.5-0.9** |
| Comorbidity countNo comorbiditiesOne comorbidityTwo comorbiditiesThree or more comorbidities | 1**1.5****2.4****2.9** | **1.0-2.4****1.4-4.1****1.5-5.6** | 1**1.5****2.5****3.0** | **1.1-2.1****1.7-3.7****1.8-4.8** | 1**1.5****1.7****1.7** | **1.2-2.0****1.2-2.5****1.0-2.7** |
| ECOG (WHO) performance statusCarries out all normal activityRestricted but walks/does light workWalks, full self-care but no workLimited self-care – fully disabled | 11.2**1.7****3.4** | 0.7-1.8**1.0-3.0****1.6-7.4** | 1**1.3****2.1****3.8** | **1.0-1.9****1.4-3.1****2.1-6.7** | 10.90.81.1 | 0.7-1.20.5-1.20.5-2.2 |
| ASA ScaleNormal healthy patientMild systemic diseaseSevere systemic diseaseLife-threatening disease/ Moribund patient | 11.8**4.7****7.1** | 0.9-3.9**2.2-10.0****2.1-24.4** | 1**2.3****5.0****8.7** | **1.3-4.0****2.8-8.8****3.5-21.6** | 11.0**1.4**0.8 | 0.7-1.4**1.0-2.0**0.2-2.7 |
| Predominant histology by cancer locationSquamous cell carcinomas of the oesophagus Adenocarcinomas of the upper and middle oesophagus Adenocarcinomas of the lower third of the oesophagus and Siewert type 1 tumours Siewert type II and type III tumours Tumours of the stomach  | 10.90.90.60.7 | 0.3-2.70.5-1.60.3-1.30.4-1.4 | 10.71.01.00.9 | 0.3-1.70.6-1.60.6-1.60.5-1.4 | 10.5**0.7**0.7**0.4** | 0.3-1.1**0.5-0.9**0.5-1.1**0.3-0.6** |
| HistologyAdenocarcinomaSquamous cell carcinomaOther type | 11.31.1 | 0.7-2.40.3-3.4 | 10.91.3 | 0.5-1.50.6-2.7 | 1**1.5**1.1 | 1**1.0-2.2**0.5-2.2 |
| Size and extent of primary tumour (T)No evidence of primary tumour (T0)Tumour invades lamina propria or submucosa (T1)Tumour invades muscularis propria (T2)Tumour invades adventitia (T3)Tumour invades adjacent structures (T4) | 10.60.80.60.7 | 0.2-1.40.3-1.90.3-1.40.3-1.7 | 10.71.20.91.5 | 0.3-1.50.6-2.60.5-1.90.7-3.2 | 11.00.90.90.7 | 0.5-1.80.5-1.70.5-1.60.4-1.4 |
| Regional lymph nodes (N)No regional lymph node metastasis (N0)Metastasis in 1 to 2 regional lymph nodes (N1)Metastasis in 3 to 6 (N2)Metastasis in 7 or more (N3) | 11.20.81.0 | 0.8-1.80.4-1.50.5-2.0 | 1**1.3**1.4**1.8** | **1.0-1.9**0.9-2.2**1.1-2.7** | 11.00.80.9 | 0.8-1.30.6-1.20.6-1.3 |
| Level of socio-economic deprivation (IMD quintile)  1 least deprived 2 3 4 5 most deprived | 10.80.60.80.8 | 0.5-1.40.3-1.10.4-1.40.5-1.5 | 10.70.80.81.0 | 0.4-1.10.5-1.20.5-1.30.7-1.5 | 10.90.8**0.6**0.9 | 0.6-1.30.6-1.2**0.4-0.9**0.7-1.3 |

\* Numbers in bold indicate significance

**Table 4** Multivariable logistic regression for 30-day and 90-day mortality and anastomotic leakage

|  |  |  |  |
| --- | --- | --- | --- |
| Predictor | 30-day Mortalityn=4882ROC 0.698 | 90-day Mortalityn=4882ROC 0.694 | Anastomotic leakagen=4882ROC 0.631 |
| Optimism corrected\*ROC 0.646 | Optimism corrected ROC 0.664 | Optimism corrected ROC 0.587 |
|  | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** |
| Age per decade, years  | 1.2 | 1.0-1.5 | 1.2 | 1.0-1.4 | 0.9 | 0.8-1.1 |
| Gender MaleFemale |  |  | 10.7 | 0.5-1.1 | 1**0.7** | **0.5-0.9** |
| Comorbidity count No comorbiditiesOne comorbidityTwo comorbiditiesThree or more comorbidities | 11.3 **1.8\*\*****2.1** | 0.8-2.1**1.1-3.2****1.0-4.1** | 11.3**1.9****2.0** | 0.9-1.9**1.3-2.8****1.2-3.3** | 1**1.5****1.7****1.7** | **1.1-2.0****1.2-2.4****1.0-2.8** |
| ASA GradeI Normal healthy patientII Mild systemic diseaseIII Severe systemic diseaseIV Life-threatening disease/Moribund patient | 11.6**3.5****4.7** | 0.7-3.5**1.6-7.8****1.3-16.5** | 1**1.9****3.5****5.1** | **1.1-3.4****1.9-6.3****2.0-13.3** | 11.0**1.4**0.8 | 0.7-1.4**1.0-2.1**0.2-2.8 |
| ECOG (WHO) performance statusCarries out all normal activityRestricted but walks/does light workWalks, full self-care but no workLimited self-care – fully disabled | 10.91.31.8 | 0.6-1.40.7-2.20.8-4.1 | 11.1**1.6****2.3** | 0.8-1.5**1.1-2.5****1.3-4.3** | 10.90.81.0 | 0.7-1.20.5-1.20.5-2.0 |
| Size and/or extent of the primary tumour (T)No evidence of primary tumour (T0)Tumour invades lamina propria or submucosa (T1)Tumour invades muscularis propria (T2)Tumour invades adventitia (T3)Tumour invades adjacent structures (T4) | 10.50.70.50.6 | 0.2-1.30.3-1.80.2-1.20.2-1.9 | 10.71.10.71.1 | 0.3-1.40.5-2.30.3-1.40.5-2.6 | 11.11.01.01.0 | 0.6-2.00.6-2.00.5-1.80.5-2.1 |
| Predominant histology by cancer locationSquamous cell carcinomas of the oesophagus Adenocarcinomas of the upper and middle oesophagus Adenocarcinomas of the lower third of the oesophagus and Siewert type 1 tumoursSiewert type II and type III tumours Tumours of the stomach  | 11.00.80.50.5 | 0.3-2.80.4-1.50.2-1.10.3-1.0 | 10.60.80.7**0.5** | 0.2-1.60.5-1.30.4-1.2**0.3-0.8** | 10.5**0.6****0.6****0.4** | 0.2-1.0**0.4-0.8****0.4-0.9****0.1-0.6** |
| Regional lymph nodes (N)No regional lymph node metastasis N(0)Metastasis in 1 to 2 regional lymph nodes N(1)Metastasis in 3 to 6 N(3)Metastasis in 7 or more N(4) | 11.30.81.2 | 0.8-2.10.4-1.70.6-2.5 | 1**1.4**1.4**1.8** | **1.0-2.0**0.9-2.2**1.1-2.9** | 11.00.91.0 | 0.8-1.30.6-1.30.6-1.5 |
| Deprivation1 Least deprived2345 Most deprived |  |  |  |  | 10.90.8**0.6**0.9 | 0.6-1.30.6-1.1**0.4-0.9**0.6-1.3 |

\* ROC derived from bootstrapped sample (internal validation)

\*\* Numbers in bold indicate significance

**Table 5:** Model equations for 30-day mortality, 90-day mortality and anastomotic leakage

|  |  |
| --- | --- |
| Model | Equation |
| 30-day mortality | Log(odds)= - 5.3205 + 0.0200 x (age) + 0.2984 x (one comorbidity) + 0.6168 x (two comorbidities) + 0.7318 x (three or more comorbidities) + 0.4760 x (ASA grade, mild systemic disease) + 1.2677 x (ASA grade, severe systemic disease) + 1.5399 x (ASA grade, life threatening disease/moribund patient) – 0.0971 x (ECOG performance status, restricted but walks/does light work) + 0.2315 x (ECOG performance status, walks, full self-care but no work) + 0.6159 x (ECOG performance status, limited self-care/fully disabled) - 0.6664 x (t, tumour invades lamina propria or submucosa) - 0.3077 x (t, tumour invades muscularis propria) - 0.6496 x (t, tumour invades adventitia) – 0.4202 x (t, tumour invades adjacent structures) + 0.2779 x (n, metastasis in 1 to 2 regional lymph nodes) – 0.1897 x (n, metastasis in 3 to 6) + 0.1920 x (n, metastasis in 7 or more) - 0.0238 x (tumour location, adenocarcinomas of the upper and middle oesophagus) - 0.1957 x (tumour location, adenocarcinomas of the lower third of the oesophagus and Siewert type I tumours) - 0.6097 x (tumour location, Siewert type II and type III tumours) - 0.6246 x (tumour location, tumours of the stomach) |
| 90-day mortality | Log(odds)= - 4.8534 - 0.0152 x (age) - 0.2884 x (female gender) + 0.0963x (one comorbidity) + 0.6472 x (two comorbidities) + 0.7033 x (three or more comorbidities) + 0.6452 x (ASA grade, mild systemic disease) + 1.2431 x (ASA grade, severe systemic disease) + 1.6439 x (ASA grade, life-threatening disease/moribund patient) + 0.0963 x (ECOG performance status, restricted but walks/does light work) + 0.5003 x (ECOG performance status, walks, full self-care but no work) + 0.8491 x (ECOG performance status, limited self-care/fully disabled) – 0.4057 x (t, tumour invades lamina propria or submucosa) + 0.0802 x (t, tumour invades muscularis propria) – 0.3967 x (t, tumour invades adventitia) + 0.1470 x (t, tumour invades adjacent structures) + 0.3290 x (n, metastasis in 1 to 2 regional lymph nodes) + 0.3344 x (n, metastasis in 3 to 6) + 0.5829 x (n, metastasis in 7 or more) - 0.4601 x (tumour location, adenocarcinomas of the upper and middle oesophagus) – 0.1990 x (tumour location, adenocarcinomas of the lower third of the oesophagus and Siewert type 1 tumours) – 0.3851 x (tumour location, Siewert type II and type III tumours) - 0.6925 x (tumour location, tumours of the stomach)  |
| Anastomotic leakage (AL) | Log(odds)= - 1.8702 – 0.0041 x (age) – 0.3540 x (female gender) + 0.4164 x (one comorbidity) + 0.5220 x (two comorbidities) + 0.5169 x (three or more comorbidities) - 0.0297 x (ASA grade, mild systemic disease) + 0.3451 x (ASA grade, severe systemic disease) – 0.1911 x (ASA grade, life-threatening disease/moribund patient) – 0.1031 x (ECOG performance status, restricted but walks/does light work) – 0.2274 x (ECOG performance status, walks, full self-care but no work) + 0.0049 x (ECOG performance status, limited self-care/fully disabled) + 0.0941 x (t, tumour invades lamina propria or submucosa) + 0.0571 x (t, tumour invades muscularis propria) - 0.0119 x (t, tumour invades adventitia) + 0.0411 x (t, tumour invades adjacent structures) + 0.0132 x (n, metastasis in 1 to 2 regional lymph nodes) – 0.1418 x (n, metastasis in 3 to 6) - 0.0188 x (n, metastasis in 7 or more) - 0.7059 x (tumour location, adenocarcinomas of the upper and middle oesophagus) – 0.5504 x (tumour location, adenocarcinomas of the lower third of the oesophagus and Siewert type 1 tumours) - 0.4800 x (tumour location, Siewert type II and type III tumours) - 0.9781 x (tumour location, tumours of the stomach) - 0.1101 x (deprivation 2) -0.2117 x (deprivation 3) – 0.5143 x (deprivation 4) -0.0692 x (deprivation 5 most deprived)  |

**Figure 1a,1b,1c:** 30-day, 90-day mortality and anastomotic leakage model calibration by deciles of risk

|  |  |
| --- | --- |
|  |  |





**APPENDIX**

**Figure A1** Flow chart patient inclusion process

Patients with primary diagnosis of OG cancer between 1.4.2011 and 31.3.2013

n=22 766

Excluded patients without surgical treatment plan (either oncology or endoscopic treatment only or best supportive care)

n= 17 403

Patients undergoing oesophagectomy or gastrectomy

n= 5567

Excluded patients with palliative surgical intent (n=377) and non-curative procedure (open-and-shut or bypass procedure, n=217)

n= 594

Patients with curative oesphago-gastric resection

n=4973

Excluded records with missing or incorrect consultant GMC codes

n=91

Patients with curative oesphago-gastric resection included in the analysis

n=4882

**Table A1a** Summary of in-/excluded predictors for postoperative mortality (30-day, 45-day, 90-day and in-hospital mortality) identified by literature review

|  |  |
| --- | --- |
|  | **Risk predictors for 30 and 90 day mortality** |
| ***Considered*** ***for inclusion*** ***in model?*** | **Patient****characteristics** | **Comorbidities** | **Tumour characteristics** | **Treatment process** | **Serum levels** | **Other** |
| ***Yes*** | Age;Patient performance score;ASA rating; | Comorbidity count Congestive heart failure/peripheral vascular disease /cardiac disease;Pulmonary comorbidity;(Insulin dependent)Diabetes; Renal comorbidity; | TNM stage;  |  |  |  |
| ***No: Can be influenced by provider*** |  |  | Urgency of operation; | Neoadjuvant therapy;Amount of blood loss;Incomplete resection;Type of operation;Postoperative pulmonary complications;PneumoniaNeed for transfusion |  | ALaSurgeon’s assessment on patients fit for surgery ; Worse swallowing score;  |
| ***No: Not routinely available in*** ***clinical datasets*** | Alcohol consumption; (History of previous) Smoking;Race;Steroid use;Mid-arm circumference;Number of stairs climbed; | Charlson score;Peripheral vascular disease;Coronary heart disease~Coronary artery disease;Hypertension;Hepatic disease;Ascites; |  |  | Forced expiratory volume in 1 second <60%;Alkaline phosphatase level more than 125 U/L; FEV1/FVC;Physiological measurements on admission to critical care: Partial pressure of arterial oxygen (PaO2): fraction of inspired oxygen (FiO2) ratio; Lowest arterial pH;Creatinine; Serum albumin;Urea; Mechanical ventilation; Incentive spirometry;Poor cardiac, respiratory, hepatic function; | POSSUM;bP-POSSUM; cO-POSSUM;d |
| ***No:*** ***Not applicable*** ***for this study*** |  |  |  |  |  | Hospital volume;Palliative resection;Year of operation; |

**a** Anastomotic leakage

b POSSUM (Physiological and Operative Severity Score for the enumeration of mortality and morbidity) includes the following variables: age(y), cardiac history, respiratory history, blood pressure, pulse rate, Glasgow coma score, haemoglobin (g/%), white cell count (X1012/L), urea, plasma sodium (mmol/l), plasma potassium (mmol/l), electrocardiogram, operative severity, multiple procedures, total blood loss (ml), peritoneal soiling, presence of malignancy, mode of surgery [[46](#_ENREF_46)]

c P-POSSUM (Portsmouth-modified Physiological and Operative Severity Score for the enumeration of Mortality and morbidity) includes the following variables: age (y), Glasgow Coma Score, cardiac signs, respiratory signs, electrocardiography, systolic pressure (mm Hg), pulse rate(beats/min), haemoglobin level (g/dL), white blood cell count (X1012/L), urea level (mmol/L), sodium level(mmol/L), potassium level(mmol/L), surgical severity, multiple procedures, total blood loss, peritoneal soiling, presence of malignancy, mode of surgery [[46](#_ENREF_46)]

d O-POSSUM (Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity Oesophagogastric surgery) includes the following variables: age (y), Glasgow Coma Score, cardiac signs, respiratory signs, electrocardiography, systolic pressure (mm Hg), pulse rate(beats/min), haemoglobin level (g/dL), white blood cell count (X1012/L), urea level (mmol/L), sodium level(mmol/L), potassium level(mmol/L), surgical severity, multiple procedures, mode of surgery [[46](#_ENREF_46)]

**Table A1b** Summary of in-/excluded predictors for postoperative complication/ anastomotic leakage identified by literature review

|  |  |
| --- | --- |
|  | Risk predictors for anastomotic leakage |
| *Considered* *for inclusion* *in model?* | ***Patient*** ***characteristics*** | ***Comorbidities*** | ***Tumour character-istics*** | ***Treatment process*** | ***Serum levels*** | ***Other*** |
| *Yes* | Age; ASA rating;Decreased functional status; Gender; | (Congestive) Heart failure; diabetes; Copd; a(Insulin dependent) Diabetes;Coronary (artery) disease; | **Tumour stage;** |  |  |  |
| *No: Can be influenced by provider* |  |  |  | Surgical procedure type;Additional organ resection; Procedure duration;Blood transfusion;Operation time; |  |  |
| *No: Not routinely available in clinical datasets* | Race;Smoking status;Steroid use;Low BMI; bObesity; | Hypertension;(Peripheral) Vascular disease;Dyspnoea; Coronary disease; Renal insufficiency; |  |  | Forced expiratory volume in 1second <60% of predicted;Alkaline phosphatase level of more than 125 U/L; Lower serum albumin concentration;WCC (white cell count); albumin; Post-operative CRP(C reactive protein);FEV1/FVC; | POSSUMcIncreased complexity score? |
| *No: Not applicable of this study* |  |  |  |  |  | Year of operation; |

aChronic obstructive pulmonary disease

bBody mass index

 c POSSUM (Physiological and Operative Severity Score for the enumeration of mortality and morbidity) includes the following variables: age(y), cardiac history, respiratory history, blood pressure, pulse rate, Glasgow coma score, haemoglobin (g/%), white cell count (X1012/L), urea, plasma sodium (mmol/l), plasma potassium (mmol/l), electrocardiogram, operative severity, multiple procedures, total blood loss (ml), peritoneal soiling, presence of malignancy, mode of surgery [[46](#_ENREF_46)]

**Table A2** Descriptive statistics in the complete case analysis and in the imputed dataset

|  |  |  |
| --- | --- | --- |
|  | Complete dataset | Imputed dataset |
| Year of operation |  |  |  |  |
| 2012 | 2417 | 49.5 | 2417 | 49.5 |
| 2013 | 2465 | 50.5 | 2465 | 50.5 |
| Age, years  | 4873 | 66.3\* | 4882 | 66.3\* |
| Missing values | 9 | 0.2 |  |  |
| Comorbidity count |  |  |  |  |
| No comorbidities | 2747 | 56.3 | 2747 | 56.3 |
| One comorbidity | 1311 | 26.8 | 1311 | 26.8 |
| Two comorbidities | 566 | 11.6 | 566 | 11.6 |
| Three or more comorbidities | 258 | 5.3 | 258 | 5.3 |
| Gender |  |  |  |  |
| Male | 3 618 | 74.1 | 3 618 | 74.1 |
| ECOG (WHO) performance status |  |  |  |  |
| Carries out all normal activity | 2519 | 51.6 | 2601 | 53.3 |
| Restricted but walks/does light work | 1557 | 31.9 | 1611 | 33.0 |
| Walks, full self-care but no work | 527 | 10.8 | 543 | 11.1 |
| Limited self-care – fully disabled | 120 | 2.5 | 127 | 2.6 |
| Missing values | 159 | 3.3 |  |  |
| Size and /or extent of the primary tumour (T) |  |  |  |  |
| No evidence of primary tumour T(0) | 202 | 4.2 | 205 | 4.2 |
| Tumour invades lamina propria or submucosa T(1) | 929 | 19.0 | 957 | 19.6 |
| Tumour invades muscularis propria T(2) | 792 | 16.2 | 820 | 16.8 |
| Tumour invades adventitia T(3) | 2323 | 47.6 | 2389 | 48.9 |
| Tumour invades adjacent structures T(4) | 490 | 10.0 | 511 | 10.5 |
| Missing values | 146 | 3.0 |  |  |
| Regional lymph nodes (N) |  |  |  |  |
| No regional lymph node metastasis N(0) | 2143 | 43.9 | 2182 | 44.7 |
| Metastasis in 1 to 2 regional lymph nodes N(1) | 1498 | 30.7 | 1544 | 31.6 |
| Metastasis in 3 to 6 N(2) | 615 | 12.6 | 634 | 13.0 |
| Metastasis in 7 or more N(3) | 508 | 10.4 | 522 | 10.7 |
| Missing values | 118 | 2.4 |  |  |
| ASA Scale |  |  |  |  |
| Normal healthy patient | 816 | 16.7 | 866 | 17.7 |
| Mild systemic disease | 2502 | 51.2 | 2651 | 54.3 |
| Severe systemic disease | 1248 | 25.6 | 1301 | 26.6 |
| Life-threatening disease/Moribund patient | 60 | 1.2 | 64 | 1.3 |
| Missing values | 256 | 5.2 |  |  |
| Histology |  |  |  |  |
| Adenocarcinoma | 4336 | 88.8 | 4336 | 88.8 |
| Squamous cell carcinoma | 420 | 8.6 | 420 | 8.6 |
| Other carcinoma types | 126 | 2.6 | 126 | 2.6 |
| Predominant histology by cancer location |  |  |  |  |
| Squamous cell carcinomas of the oesophagus  | 492 | 10.1 | 492 | 10.1 |
| Adenocarcinomas of the upper and middle oesophagus  | 184 | 3.8 | 184 | 3.8 |
| Adenocarcinomas of the lower third of the oesophagus and Siewert type 1 tumours  | 1906 | 39.0 | 1906 | 39.0 |
| Siewert type II and type III tumours  | 844 | 17.3 | 844 | 17.3 |
| Tumours of the stomach  | 1456 | 29.8 | 1456 | 29.8 |
| Deprivation |  |  |  |  |
| 1 Least deprived | 840 | 17.2 | 999 | 20.5 |
| 2 | 860 | 17.6 | 1047 | 21.4 |
| 3 | 846 | 17.3 | 999 | 20.5 |
| 4 | 800 | 16.4 | 942 | 19.3 |
| 5 Most deprived | 746 | 15.3 | 895 | 18.3 |
| Missing values | 790 | 16.2 |  |  |
| Patient outcomes |  |  |  |  |
| Anastomotic leak | 305 | 6.2 | 305 | 6.2 |
| 30-day postoperative mortality | 112 | 2.3 | 112 | 2.3 |
| 90-day postoperative mortality | 216 | 4.4 | 216 | 4.4 |

\*Mean

**Table A3** Univariable analysis in the complete case analysis and in the imputed dataset

|  |  |  |
| --- | --- | --- |
| Predictor | Original dataset | Imputed dataset |
|  | **30-day mortality** | **90-day mortality** | **Anastomotic leakage** | **30-day mortality** | **90-day mortality** | **Anastomotic leakage** |
|  | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** |
| Age per decade, years | **1.3\*** | **1.1-1.6** | **1.3** | **1.1-1.5** | 1.0 | 0.9-1.1 | **1.3\*\*** | **1.1-1.6** | **1.3** | **1.1-1.5** | 1.0 | 0.9-1.1 |
| Gender  |  |  |  |  |  |  |  |  |  |  |  |  |
| Female | 0.8 | 0.5-1.2 | 0.7 | 0.5-1.0 | **0.7** | **0.5-0.9** | 0.8 | 0.5-1.2 | 0.7 | 0.5-1.0 | **0.7** | **0.5-0.9** |
| Comorbidity count |  |  |  |  |  |  |  |  |  |  |  |  |
| No comorbidities | 1 |  | 1 |  | 1 |  | **1** |  | **1** |  | **1** |  |
| One comorbidity | **1.5** | **1.0-2.4** | **1.5** | **1.1-2.1** | **1.5** | **1.2-2.0** | **1.5** | **1.0-2.4** | **1.5** | **1.1-2.1** | **1.2** | **1.2-2.0** |
| Two comorbidities | **2.4** | **1.4-4.1** | **2.5** | **1.7-3.7** | **1.7** | **1.2-2.5** | **2.4** | **1.4-4.1** | **2.5** | **1.7-3.7** | **1.2** | **1.2-2.5** |
| Three or more comorbidities | **2.9** | **1.5-5.6** | **3.0** | **1.8-4.8** | **1.7** | **1.0-2.7** | **2.9** | **1.5-5.6** | **3.0** | **1.8-4.8** | **1.0** | **1.0-2.7** |
| ECOG (WHO) performance status |  |  |  |  |  |  |  |  |  |  |  |  |
| Carries out all normal activity | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
| Restricted but walks/does light work | 1.2 | 0.7-1.8 | 1.3 | 0.9-1.8 | 0.9 | 0.7-1.2 | 1.2 | 0.7-1.8 | **1.3** | **1.0-1.9** | 0.9 | 0.7-1.2 |
| Walks, full self-care but no work | 1.6 | 0.9-2.9 | **2.1** | **1.4-3.1** | 0.8 | 0.5-1.1 | **1.7** | **1.0-3.0** | **2.1** | **1.4-3.1** | 0.8 | 0.5-1.2 |
| Limited self-care – fully disabled | **3.7** | **1.7-8.1** | **3.7** | **2.0-6.8** | 1.1 | 0.6-2.3 | **3.4** | **1.6-7.4** | **3.8** | **2.1-6.7** | 1.1 | 0.5-2.2 |
| ASA Scale |  |  |  |  |  |  |  |  |  |  |  |  |
| Normal healthy patient | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
| Mild systemic disease | 1.9 | 0.8-4.2 | **2.2** | **1.2-4.0** | 1.0 | 0.7-1.4 | 1.8 | 0.9-3.9 | **2.3** | **1.3-4.0** | 1.0 | 0.7-1.4 |
| Severe systemic disease | **5.0** | **2.3-11.1** | **5.0** | **2.8-9.0** | **1.4** | **1.0-2.0** | **4.7** | **2.2-10.0** | **5.0** | **2.8-8.8** | **1.4** | **1.0-2.0** |
| Life-threatening disease/Moribund patient | **8.2** | **2.3-29.0** | **9.5** | **3.8-23.9** | 0.8 | 0.2-2.8 | **7.1** | **2.1-24.4** | **8.7** | **3.5-21.6** | 0.8 | 0.2-2.7 |
| Predominant histology by cancer location |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinomas of the oesophagus  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
| Adenocarcinomas of the upper and middle oesophagus | 0.9 | 0.3-2.7 | 0.7 | 0.3-1.7 | 0.5 | 0.3-1.1 | 0.9 | 0.3-2.7 | 0.7 | 0.3-1.7 | 0.5 | 0.3-1.1 |
| Adenocarcinomas of the lower third of the oesophagus and Siewert type 1 tumours | 0.9 | 0.5-1.6 | 1.0 | 0.6-1.6 | **0.7** | **0.5-0.9** | 0.9 | 0.5-1.6 | 1.0 | 0.6-1.6 | **0.7** | **0.5-0.9** |
| Siewert type II and type III tumours  | 0.6 | 0.3-1.3 | 1.0 | 0.6-1.6 | 0.7 | 0.5-1.1 | 0.6 | 0.3-1.3 | 1.0 | 0.6-1.6 | 0.7 | 0.5-1.1 |
| Tumours of the stomach  | 0.7 | 0.4-1.4 | 0.9 | 0.5-1.4 | **0.4** | **0.3-0.6** | 0.7 | 0.4-1.4 | 0.9 | 0.5-1.4 | **0.4** | **0.3-0.6** |
| Histology |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenocarcinoma | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
| Squamous cell | 1.3 | 0.7-2.4 | 0.9 | 0.5-1.5 | **1.5** | **1.0-2.2** | 1.3 | 0.7-2.4 | 0.9 | 0.5-1.5 | **1.5** | **1.0-2.2** |
| Other carcinoma type | 1.1 | 0.3-3.4 | 1.3 | 0.6-2.7 | 1.1 | 0.5-2.2 | 1.1 | 0.3-3.4 | 1.3 | 0.6-2.7 | 1.1 | 0.5-2.2 |
| Size and/or extent of the primary tumour (T) |  |  |  |  |  |  |  |  |  |  |  |  |
| No evidence of primary tumour T(0) | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
| Tumour invades lamina propria or submucosa T(1) | 0.6 | 0.2-1.4 | 0.7 | 0.3-1.7 | 1.0 | 0.5-1.8 | 0.6 | 0.2-1.4 | 0.7 | 0.3-1.5 | 1.0 | 0.5-1.8 |
| Tumour invades muscularis propria T(2) | 0.8 | 0.3-1.9 | 1.2 | 0.6-1.6 | 0.9 | 0.5-1.6 | 0.8 | 0.3-1.9 | 1.2 | 0.6-2.6 | 0.9 | 0.5-1.7 |
| Tumour invades adventitia T(3) | 0.6 | 0.3-1.4 | 0.9 | 0.6-1.6 | 0.9 | 0.5-1.6 | 0.6 | 0.3-1.4 | 0.9 | 0.5-1.9 | 0.9 | 0.5-1.6 |
| Tumour invades adjacent structures T(4) | 0.7 | 0.3-1.8 | 1.5 | 0.5-1.4 | 0.7 | 0.4-1.5 | 0.7 | 0.3-1.7 | 1.5 | 0.7-3.2 | 0.7 | 0.4-1.4 |
| Regional lymph nodes (N) |  |  |  |  |  |  |  |  |  |  |  |  |
| No regional lymph node metastasis N(0) | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
| Metastasis in 1 to 2 regional lymph nodes N(1) | 1.2 | 0.8-1.9 | **1.3** | **1.0-1.9** | 1.0 | 0.8-1.3 | 1.2 | 0.8-1.8 | **1.3** | **1.0-1.9** | 1.0 | 0.8-1.3 |
| Metastasis in 3 to 6 N(2) | 0.7 | 0.4-1.4 | 1.4 | 0.9-2.1 | 0.8 | 0.6-1.2 | 0.8 | 0.4-1.5 | 1.4 | 0.9-2.2 | 0.8 | 0.6-1.2 |
| Metastasis in 7 or more N(3) | 1.0 | 0.5-1.9 | **1.7** | **1.1-2.7** | 0.8 | 0.6-1.3 | 1.0 | 0.5-2.0 | **1.8** | **1.1-2.7** | 0.9 | 0.6-1.3 |
| Deprivation |  |  |  |  |  |  |  |  |  |  |  |  |
| 1 Least deprived | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  | 1 |  |
|  2 | 1.1 | 0.6-1.9 | 0.8 | 0.5-1.2 | 0.9 | 0.6-1.4 | 0.8 | 0.5-1.4 | 0.7 | 0.4-1.1 | 0.9 | 0.6-1.3 |
|  3 | 0.6 | 0.3-1.3 | 0.8 | 0.5-1.2 | 0.8 | 0.5-1.2 | 0.6 | 0.3-1.1 | 0.8 | 0.5-1.2 | 0.8 | 0.6-1.2 |
| 4 | 0.8 | 0.4-1.5 | 0.7 | 0.4-1.2 | 0.7 | 0.4-1.0 | 0.8 | 0.4-1.4 | 0.8 | 0.5-1.3 | **0.6** | **0.4-0.9** |
| 5 Most deprived | 1.1 | 0.6-2.0 | 1.2 | 0.8-1.8 | 0.9 | 0.6-1.4 | 0.8 | 0.5-1.5 | 1.0 | 0.7-1.5 | 0.9 | 0.7-1.3 |

\* Numbers in bold indicate significance