Original article

Risk adjustment models for short-term outcomes after surgical resection for oesophagogastric cancer

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Background: **Outcomes for oesophagogastric cancer surgery are compared with the aim of benchmarking 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- and 90-day mortality and anastomotic leakage rates after oesophagogastric 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Results: **Most existing risk models for oesophagogastric resections were methodologically weak, outdated or based on detailed laboratory data that are not generally available. In 4882 patients with oesophagogastric cancer used for model development, 30- and 90-day mortality rates were 2·3 and 4·4 per cent respectively, and 6·2 per cent of patients developed an anastomotic leak. The internally validated models, based on predictors selected from the literature, showed moderate discrimination (area under the receiver operating characteristic (ROC) curve 0·646 for 30-day mortality, 0·664 for 90-day mortality and 0·587 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 oesophagogastric cancer were developed. These models should be used for risk adjustment when assessing hospital performance in the National Health Service, and tested in other large health systems.**

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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 oesophagogastric cancer resections.

The National Oesophago-Gastric Audit (NOGCA) was set up to monitor the quality of care provided to patients with oesophagogastric cancer in England and Wales, in order to evaluate care processes and patient outcomes[1]. A recent systematic review[2] concluded, however, that current models for prediction of outcomes after oesophagectomy had numerous limitations regarding methodology and clinical credibility. Centralization of surgery, decision-making in multidisciplinary teams and improved care pathways have already been shown to contribute to a decrease in short-term mortality[3,4], 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 oesophagogastric cancer between National Health Service (NHS) Trusts, based

on a review of existing prediction models, expert opinion and audit data.

Methods

The study used data submitted to the NOGCA from all 154 English NHS Trusts that provide oesophagogastric cancer care and from all 13 Welsh NHS organizations 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 that recorded[1]: age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) functional performance, American Society of Anesthesiologists (ASA) grade, cancer details, including cancer site (oesophagus including Siewert types I–III junctional tumours, or stomach), histology and TNM stage (version 7[5]), and procedure (neoadjuvant treatment, type of operation). All patients undergoing curative resection were included in the present study; those receiving curative oncological treatment for squamous cell carcinoma and all patients receiving palliative care were excluded.

Review of existing models

Potential prognostic factors for 30- and 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-day, 90-day or in-hospital mortality) or complications including anastomotic leaks following oesophagogastric cancer surgery. From studies meeting these inclusion criteria, risk factors included in models that were available in routine clinical databases and not modifiable by the provider were selected (*Tables S1* and *S2*, supporting information)[6].

Outcome measures

The short-term outcomes were 30- and 90-day all-cause postoperative mortality and anastomotic leak rates[7]. 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 was managed conservatively or by reoperation)[8]. All leaks, including those from conduit staple lines away from the oesophagogastric anastomosis, were included in the study based on self-reported data from the surgical team.

Model development and statistical analysis

Potential predictors were tested initially in univariable logistic regression models. Variable categories containing small numbers were regrouped in advance (ASA grade, co-morbidity count, predominant histology by cancer location, performance status, histological type). The linearity of the continuous independent variable age at diagnosis with 30- and 90-day mortality and anastomotic leakage was tested by adding quadratic terms. As this did not improve the models significantly, no quadratic terms were included in the model. To prevent exclusion of predictors with borderline significance, a P value of 0·100 rather than 0·050 was used for inclusion of variables in the model. Decisions to include and exclude predictors were based primarily, however, on the evidence gathered from the literature review and complemented with information generated from the statistical analyses and expert clinical opinion. Odds ratios (ORs) with 95 per cent c.i. were used to express the strength of the predictive effects.

Model performance was assessed with respect to discrimination and calibration[9]. Discriminative ability represented 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 characteristic (ROC) curve (AUC, c-statistic); this ranges from 0·5 to 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[10]. With bootstrapping, multiple patient samples were drawn, considered as cases included under the same conditions as in the original data set. Eight hundred bootstrap samples were used to re-estimate the multivariable logistic regression coefficients and consequently applied to the original data set, resulting in 800 AUC statistics. The mean of these AUCs represented the optimism-corrected or internally validated AUC.

Missing data were assumed to be missing at random and were handled with the multiple imputation by chained equations (MICE) approach[11]. Chained equations with ten imputation sets were used. The outcome measures and the independent variables deprivation, age at diagnosis, ECOG performance status, ASA grade, sex, tumour location, number of co-morbidities, size and/or extent of the primary tumour (T category of the TNM classification) and regional lymph nodes (N category of the TNM classification) were included in the imputation model. A

Table 1 Descriptive information for currently available prediction models for short-term outcomes of oesophagogastric cancer surgery

Reference	Country	Data collection period	Operation type	No. of centres	No. of patients	Reported outcomes	Event rate (%)	Discrimination
Law *et al.*[31]	Hong Kong	1982–1992	Oesophageal	1	1105	In-hospital mortality	15·5	–
Bartels *et al.*[12]	Germany	1982–1985	Oesophageal	1	432	30-day mortality	10	–
Liu *et al.*[34]	Austria	1994–1997	Oesophageal	1	70	In-hospital mortality	13	–
Karl *et al.*[13]	USA	1989–1999	Ivor Lewis gastro-oesophageal	1	143	30-day mortality Anastomotic leakage	2·1 3·5	–
Zafirellis *et al.*[14]	UK	1990–1999	Oesophageal	1	204	30-day mortality	12·7	AUC 0·62 (POSSUM)
Bailey *et al.*[15]	USA	1991–2000	Oesophageal	109	1777	30-day mortality	9·8	c-index 0·69
McCulloch *et al.*[33]	UK	1999–2002	Gastro-oesophageal	26	955	In-hospital mortality	12	AUC 0·68 (POSSUM)
						Surgical complications	19	AUC 0·71 (POSSUM)
Mariette *et al.*[32]	France	1982–1993	Oesophageal	1	742	In-hospital mortality	5·4	–
						Anastomotic leakage	9·8	–
Law *et al.*[30]	Hong Kong	1990–1995	Oesophageal	1	421	In-hospital mortality	1·1	–
Atkins *et al.*[37]	USA	1996–2002	Oesophageal	1	379	Operative mortality	5·8	–
Tekkis *et al.*[29]	UK	1994–2000	Gastro-oesophageal	36	1042	In-hospital mortality	12	AUC 79·7 (O-POSSUM) AUC 74·6 (P-POSSUM)
Junemann-Ramirez *et al.*[38]	UK	1992–1999	Ivor Lewis gastro-oesophageal	1	276	Anastomotic leakage	5·1	–
Steyerberg *et al.*[21]	USA/The Netherlands	1991–1996	Oesophageal	Population database/ clinical centre	1327	30-day mortality	11	AUC 0·66
Viklund *et al.*[16]	Sweden	2001–2003	Oesophageal	Nationwide study	275	30-day mortality	3	–
						Anastomotic leakage	8	–
Nagabhushan *et al.*[17]	UK	1990–2002	Gastro-oesophageal	1	313	30-day mortality	10·2	AUC 0·61 (O-POSSUM) AUC 0·68 (P-POSSUM)
Lagarde *et al.*[28]	The Netherlands	1993–2005	Oesophageal	1	663	In-hospital mortality	3·6	AUC 0·60 (O-POSSUM)
Lai *et al.*[27]	Hong Kong	2001–2005	Oesophageal	14	545	In-hospital mortality	5·5	AUC 0·776 (POSSUM) AUC 0·776 (P-POSSUM) AUC 0·676 (O-POSSUM)
Ra *et al.*[26]	USA	1997–2003	Oesophageal	Population database	1172	In-hospital mortality	14	–
Wright *et al.*[35]	USA	2002–2007	Oesophageal	73 STS General Thoracic Database	2315	Major morbidity (including death and anastomotic leakage)*		–
Park *et al.*[25]	UK	1995–2007	Oesophageal	ICNARC Case Mix Programme Database 181	7227	In-hospital mortality	11	AUC 0·60 (APACHE II) AUC 0·63 (SAPS II) AUC 0·65 (ICNARC physiology score)

Table 1 Continues on next page.

Table 1 Continued

Reference	Country	Data collection period	Operation type	No. of centres	No. of patients	Reported outcomes	Event rate (%)	Discrimination
Dutta *et al.*[18]	UK	2005–2009	Gastro-oesophageal	1	121	30-day mortality	4	AUC 0·759 (POSSUM)
								AUC 0·715 (O-POSSUM
Bosch *et al.*[23]	The Netherlands	1991–2007	Oesophageal	1	278	90-day mortality	5·4	AUC 0·766 (P-POSSUM)
								AUC 0·756 (O-POSSUM)
Morita *et al.*[24]	Japan	1964–1979	Oesophageal	1	1106	In-hospital mortality	16·1	–
Sunpaweravong *et al.*[19]	Thailand	1998–2007	Oesophageal	1	232	30-day mortality	3·8	–
						Anastomotic leakage	15·9	–
Noble *et al.*[36]	UK	2005–2010	Oesophageal	1	258	Anastomotic leakage	10	AUC 0·801 (Nun score)†
		2011				Anastomotic leakage	–	AUC 0·879 (Nun score)
		2011				Major complication/death	–	AUC 0·856 (Nun score)
Koppert *et al.*[20]	The Netherlands	2005–2009	Gastro-oesophageal	Eindhoven Cancer Registry	6223	30-day mortality	7·7	–
Rutegard *et al.*[22]	Sweden	2001–2005	Oesophageal	Nationwide	559	90-day mortality	7·1	–
Kassis *et al.*[39]	USA	2001–2011	Oesophageal	STS General Thoracic Database	7595	Anastomotic leakage	10·6	–

*Including reoperation for bleeding, anastomotic leakage, pneumonia, reintubation, ventilation beyond 48 h, or death. †Nun score calculated using the log-likelihood ratio of bloodborne variables of the systematic inflammatory response (albumin, white cell count and C-reactive protein from postoperative day 4). POSSUM, Physiological and Operative Severity Score for the enumeration of Mortality and morbidity; P-POSSUM, Portsmouth modification of POSSUM; O-POSSUM; POSSUM – oesophagogastric surgery; STS, Society of Thoracic Surgeons; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; ICNARC, Intensive Care National Audit and Research Centre.

sensitivity analysis comparing complete-case analysis with the one derived from the imputation model demonstrated no significant differences (*Tables S3* and *S4*, supporting information). All analyses were performed in Stata® (StataCorp LP, College Station, Texas, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). The bootstrap procedure was performed with the *validate* function in the *rms* package in R, and the imputation with the MICE approach in Stata® version 12.

Results

Published prognostic models

The literature search resulted in the identification of 41 prediction models for short-term outcomes after oesophagogastric cancer surgery. Some studies had a dual aim, such as providing insight into predictor effects and providing predictions based on the combination of predictors in a multivariable model. Thirty-four models addressed postoperative mortality (12 studies used 30-day mortality[12–21], 3 used 90-day mortality[22,23], 16 used in-hospital mortality[24–34], 2 used major morbidity including death[35,36], and 1 used postoperative mortality not further defined[37]) and seven were predicting anastomotic leaks[13,16,19,32,36,38,39] (*Table 1*). The majority of the studies considered outcomes after oesophagectomy[12,14–16,19,21–28,30–32,34–37,39] and designed clinical prediction models as opposed to risk-adjustment models for provider comparisons. Numerous models were based on the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM), Portsmouth modification of POSSUM (P-POSSUM) and POSSUM – oesophagogastric surgery (O-POSSUM) prediction scores, which required 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[14,17,18,23,27–29,33]. In addition, the majority of the studies were conducted in single centres that either pooled data over long periods of time[12–14,17–19,23,24,28,30–32,34,36–38] and/or had a small sample size (for example 70[34], 121[18], 143[13], 204[14], 232[19]), and were performed in countries other than the UK[12,13,15,16,19–24,26–28,30–32,34,35,37,39]. Event rates were typically far higher than those currently observed in the NOGCA, especially in the models developed in earlier

Table 2 Descriptive information on study population

	No. of patients* (*n* = 4882)
Year of operation	
2012	2417 (49·5)
2013	2465 (50·5)
Age	4873 (99·8)
Missing values	9 (0·2)
Mean (years)	66·3
Sex ratio (M : F)	3618 : 1264
Co-morbidity count	
0	2747 (56·3)
1	1311 (26·9)
2	566 (11·6)
≥ 3	258 (5·3)
ECOG (WHO) performance status	
Carries out all normal activity (ECOG 0)	2519 (51·6)
Restricted but walks/does light work (ECOG 1)	1557 (31·9)
Walks, full self-care but no work (ECOG 2)	527 (10·8)
Limited self-care – fully disabled (ECOG ≥ 3)	120 (2·5)
Missing values	159 (3·3)
ASA fitness grade	
Normal healthy patient (I)	816 (16·7)
Mild systemic disease (II)	2502 (51·2)
Severe systemic disease (III)	1248 (25·6)
Life-threatening disease/moribund (IV)	60 (1·2)
Missing values	256 (5·2)
Size and/or extent of primary tumour	
No evidence of primary tumour (T0)	202 (4·1)
Tumour invading lamina propria or submucosa (T1)	929 (19·0)
Tumour invading muscularis propria (T2)	792 (16·2)
Tumour invading adventitia (T3)	2323 (47·6)
Tumour invading adjacent structures (T4)	490 (10·0)
Missing values	146 (3·0)
No. of regional lymph nodes with metastasis	
0 (N0)	2143 (43·9)
1–2 (N1)	1498 (30·7)
3–6 (N2)	615 (12·6)
≥ 7 (N3)	508 (10·4)
Missing values	118 (2·4)
Histology	
Adenocarcinoma	4336 (88·8)
Squamous cell carcinoma	420 (8·6)
Other carcinoma type	126 (2·6)
Predominant histology by cancer location	
Squamous cell carcinoma of oesophagus	492 (10·1)
Adenocarcinoma of upper and middle oesophagus	184 (3·8)
Adenocarcinoma of lower third of oesophagus and Siewert type I tumour	1906 (39·0)
Siewert type II and type III tumours	844 (17·3)
Gastric tumour	1456 (29·8)
Social deprivation†	
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)

*With percentages in parentheses unless indicated otherwise. †Index of Multiple Deprivation. ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; ASA, American Society of Anesthesiologists.

years[12,14,15,34]. The predictive ability of most models was limited, at most rated as moderate[14,15,21,25].

A detailed description of the predictors identified in the literature search and reasons for inclusion or exclusion is available in *Tables S1* and *S2* (supporting information).

Patient characteristics

Of 22 766 patients identified, the study included 4882 patients who had undergone oesophagogastric cancer resection in April 2011 and March 2013 (*Fig. S1*, supporting information). The patients had a mean age of 66·3 (i.q.r. 60–74) years and the majority were men (74·1 per cent) (*Table 2*). At least one co-morbidity was present in 2135 patients (43·7 per cent). Most patients had an adenocarcinoma (88·8 per cent), and the most common location was the lower third of the oesophagus and Siewert type I tumours (39·0 per cent). The 30-day mortality rate was 2·3 per cent (112 patients) and the 90-day mortality rate was 4·4 per cent (216 patients). Some 6·2 per cent of the patients (305) developed an anastomotic leak. Further descriptive information is shown in *Table 2*.

Model performance and validation

The AUC of the model was the primary interest as it presents its predictive ability. The discriminative ability was moderate for the mortality models (AUC 0·698 for 30-day mortality and 0·694 for 90-day mortality) and somewhat lower for the anastomotic leakage model (AUC 0·631). Internally validated AUCs were 0·646 for the 30-day mortality model, 0·664 for the 90-day mortality model and

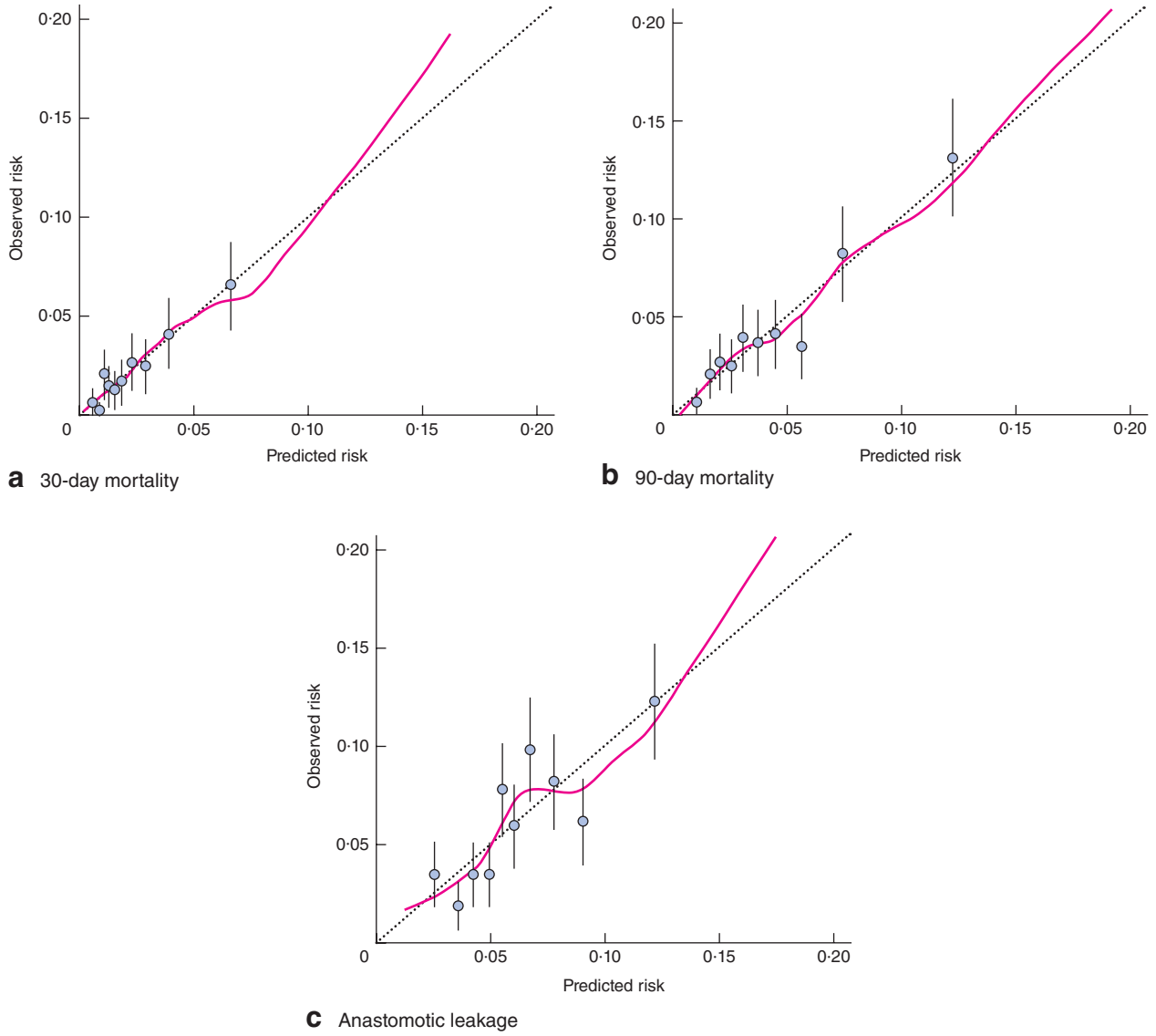

Fig. 1 **a** Thirty-day mortality, **b** 90-day mortality and **c** anastomotic leakage model calibration by deciles of risk. Observed outcomes are shown with 95 per cent c.i.

0·587 for the anastomotic leakage model, indicating some overfitting.

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 (*Fig. 1*). For example, patients in the highest-risk decile for developing an anastomotic leak had a risk below 0·2 on average in the overall cohort. The difference between observed and predicted risk for developing an anastomotic leak was less than 0·1.

Univariable analyses

In the following paragraphs ORs are presented to give an impression of the strength of the different predictors. The main aim, however, is to give valid prediction and not valid estimates of the individual predictor effects.

The risk factor that had the strongest association with all outcomes was ASA grade; for ASA grade III *versus* I, the OR was 4·73 (95 per cent c.i. 2·24 to 9·99) for 30-day mortality, 5·01 (2·84 to 8·83) for 90-day mortality and 1·42 (1·00 to 2·02) for anastomotic leakage. A greater number of co-morbidities also increased the risk for all

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

	Odds ratio		
	30-day mortality	90-day mortality	Anastomotic leakage
Age per decade (years)	1·32 (1·01, 1·62)	1·27 (1·10, 1·47)	0·96 (0·86, 1·08)
Sex			
M	1·00 (reference)	1·00 (reference)	1·00 (reference)
F	0·78 (0·49, 1·22)	0·74 (0·53, 1·04)	0·72 (0·54, 0·95)
Co-morbidity count			
0	1·00 (reference)	1·00 (reference)	1·00 (reference)
1	1·55 (0·98, 2·44)	1·54 (1·11, 2·15)	1·53 (1·17, 2·00)
2	2·43 (1·45, 4·08)	2·51 (1·72, 3·66)	1·75 (1·24, 2·46)
≥ 3	2·93 (1·53, 5·61)	2·99 (1·85, 4·83)	1·67 (1·04, 2·70)
Performance status			
ECOG 0	1·00 (reference)	1·00 (reference)	1·00 (reference)
ECOG 1	1·17 (0·76, 1·80)	1·36 (0·99, 1·86)	0·94 (0·73, 1·22)
ECOG 2	1·75 (1·01, 3·02)	2·12 (1·43, 3·14)	0·78 (0·52, 1·18)
ECOG ≥ 3	3·43 (1·59, 7·40)	3·78 (2·12, 6·74)	1·10 (0·55, 2·20)
ASA fitness grade			
I	1·00 (reference)	1·00 (reference)	1·00 (reference)
II	1·85 (0·87, 3·94)	2·26 (1·28, 3·98)	1·01 (0·72, 1·40)
III	4·73 (2·24, 9·99)	5·01 (2·84, 8·83)	1·42 (1·00, 2·02)
IV	7·15 (2·09, 24·42)	8·78 (3·50, 21·59)	0·82 (0·25, 2·71)
Size and/or extent of primary tumour			
T0	1·00 (reference)	1·00 (reference)	1·00 (reference)
T1	0·57 (0·24, 1·38)	0·73 (0·34, 1·55)	1·00 (0·54, 1·78)
T2	0·82 (0·34, 1·93)	1·23 (0·59, 2·57)	0·90 (0·49, 1·67)
T3	0·62 (0·28, 1·38)	0·94 (0·47, 1·89)	0·91 (0·52, 1·61)
T4	0·68 (0·26, 1·75)	1·50 (0·71, 3·20)	0·73 (0·37, 1·43)
Regional lymph node metastasis			
N0	1·00 (reference)	1·00 (reference)	1·00 (reference)
N1	1·21 (0·79, 1·85)	1·35 (0·98, 1·88)	0·99 (0·76, 1·29)
N2	0·78 (0·40, 1·52)	1·43 (0·94, 2·18)	0·84 (0·58, 1·24)
N3	1·05 (0·55, 1·98)	1·76 (1·15, 2·69)	0·88 (0·59, 1·32)
Histology			
Adenocarcinoma	1·00 (reference)	1·00 (reference)	1·00 (reference)
Squamous cell carcinoma	1·28 (0·70, 2·36)	0·91 (0·55, 1·51)	1·51 (1·06, 2·17)
Other carcinoma type	1·06 (0·33, 3·41)	1·27 (0·58, 2·76)	1·06 (0·52, 2·20)
Predominant histology by cancer location			
Squamous cell carcinoma of oesophagus	1·00 (reference)	1·00 (reference)	1·00 (reference)
Adenocarcinoma of upper and middle oesophagus	0·95 (0·34, 2·69)	0·69 (0·27, 1·71)	0·54 (0·27, 1·10)
Adenocarcinoma of lower third of oesophagus and Siewert type I tumour	0·86 (0·47, 1·58)	1·01 (0·63, 1·61)	0·67 (0·48, 0·96)
Siewert type II and type III tumours	0·62 (0·29, 1·29)	0·96 (0·56, 1·63)	0·72 (0·49, 1·08)
Gastric tumour	0·74 (0·39, 1·41)	0·86 (0·52, 1·41)	0·41 (0·28, 0·61)
Social deprivation*			
1 (least deprived)	1·00 (reference)	1·00 (reference)	1·00 (reference)
2	0·81 (0·47, 1·41)	0·70 (0·45, 1·07)	0·91 (0·64, 1·28)
3	0·62 (0·35, 1·16)	0·77 (0·51, 1·18)	0·82 (0·58, 1·17)
4	0·79 (0·44, 1·40)	0·84 (0·55, 1·29)	0·61 (0·42, 0·91)
5 (most deprived)	0·83 (0·47, 1·48)	1·01 (0·67, 1·52)	0·94 (0·66, 1·34)

Values in parentheses are 95 per cent c.i. *Index of Multiple Deprivation. ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists.

three outcomes; for three or more co-morbidities *versus* none, the OR was 2·93 (1·53 to 5·61) for 30-day mortality, 2·99 (1·85 to 4·83) for 90-day mortality and 1·67 (1·04 to 2·70) for anastomotic leakage. Furthermore, patients with an ECOG performance status of 3 or higher had a threefold greater risk of dying within 30 or 90 days than those with ECOG 0. In contrast, female sex and cancer located in the stomach compared with the oesophagus were associated with a decreased risk of developing anastomotic leakage (*Table 3*).

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

	Odds ratio		
	30-day mortality	90-day mortality	Anastomotic leakage
Age per decade (years)	1·22 (0·98, 1·52)	1·16 (0·99, 1·36)	0·96 (0·85, 1·09)
Sex			
M		1·00 (reference)	1·00 (reference)
F		0·75 (0·52, 1·07)	0·70 (0·52, 0·95)
Co-morbidity count			
0	1·00 (reference)	1·00 (reference)	1·00 (reference)
1	1·35 (0·85, 2·14)	1·34 (0·96, 1·88)	1·52 (1·15, 1·99)
2	1·85 (1·08, 3·17)	1·91 (1·29, 2·83)	1·68 (1·18, 2·41)
≥ 3	2·08 (1·05, 4·10)	2·00 (1·21, 3·31)	1·68 (1·02, 2·76)
Performance status			
ECOG 0	1·00 (reference)	1·00 (reference)	1·00 (reference)
ECOG 1	0·91 (0·58, 1·42)	1·10 (0·79, 1·53)	0·90 (0·69, 1·18)
ECOG 2	1·26 (0·71, 2·23)	1·65 (1·09, 2·49)	0·80 (0·52, 1·22)
ECOG ≥ 3	1·85 (0·83, 4·15)	2·34 (1·27, 4·31)	0·99 (0·48, 2·05)
ASA fitness grade			
I	1·00 (reference)	1·00 (reference)	1·00 (reference)
II	1·61 (0·75, 3·46)	1·91 (1·07, 3·39)	0·97 (0·69, 1·37)
III	3·55 (1·62, 7·78)	3·47 (1·91, 6·28)	1·41 (0·96, 2·07)
IV	4·66 (1·32, 16·51)	5·17 (2·01, 13·29)	0·83 (0·24, 2·78)
Size and/or extent of primary tumour			
T0	1·00 (reference)	1·00 (reference)	1·00 (reference)
T1	0·51 (0·21, 1·26)	0·67 (0·31, 1·44)	1·10 (0·60, 2·02)
T2	0·73 (0·30, 1·78)	1·08 (0·51, 2·31)	1·06 (0·57, 1·98)
T3	0·52 (0·22, 1·23)	0·67 (0·23, 1·41)	0·99 (0·54, 1·79)
T4	0·66 (0·23, 1·87)	1·16 (0·50, 2·65)	1·04 (0·50, 2·15)
Regional lymph node metastasis			
N0	1·00 (reference)	1·00 (reference)	1·00 (reference)
N1	1·32 (0·83, 2·08)	1·40 (0·98, 1·98)	1·01 (0·76, 1·35)
N2	0·83 (0·40, 1·69)	1·40 (0·87, 2·23)	0·86 (0·57, 1·31)
N3	1·21 (0·58, 2·51)	1·79 (1·09, 2·94)	0·98 (0·62, 1·55)
Predominant histology by cancer location			
Squamous cell carcinoma of oesophagus	1·00 (reference)	1·00 (reference)	1·00 (reference)
Adenocarcinoma of upper and middle oesophagus	0·98 (0·34, 2·79)	0·63 (0·25, 1·60)	0·49 (0·24, 1·01)
Adenocarcinoma of lower third of oesophagus and Siewert type I tumour	0·82 (0·44, 1·52)	0·82 (0·50, 1·35)	0·58 (0·40, 0·84)
Siewert type II and type III tumours	0·54 (0·25, 1·15)	0·68 (0·39, 1·19)	0·62 (0·41, 0·94)
Gastric tumour	0·53 (0·27, 1·06)	0·50 (0·29, 0·85)	0·38 (0·24, 0·57)
Social deprivation*			
1 (least deprived)			1·00 (reference)
2			0·89 (0·63, 1·26)
3			0·81 (0·56, 1·16)
4			0·60 (0·40, 0·89)
5 (most deprived)			0·93 (0·65, 1·34)
Area under ROC curve			
Uncorrected	0·698	0·694	0·631
Optimism-corrected†	0·646	0·664	0·587

Values in parentheses are 95 per cent c.i. *Index of Multiple Deprivation. †Receiver operating characteristic (ROC) curve derived from bootstrapped sample (internal validation). ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists.

Multivariable analyses

Predictors with $P < 0{\cdot}100$ in the univariable analysis for 30-day mortality were patient age at diagnosis, number of co-morbidities, ECOG performance status and ASA grade. For 90-day mortality, sex and regional lymph nodes (N category) were identified as important predictors. For the anastomotic leakage model, the following predictors were chosen on the basis of univariable analysis: sex, number of co-morbidities, ASA grade, histological tumour type and tumour location. Consistent with previous studies and clinical expert opinion, the predictors sex, age, TNM stage, ECOG performance status, predominant histology

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 × (age) + 0·2984 × (1 co-morbidity) + 0·6168 × (2 co-morbidities) + 0·7318 × (≥ 3 co-morbidities) + 0·4760 × (ASA II) + 1·2677 × (ASA III) + 1·5399 × (ASA IV) − 0·0971 × (ECOG 1) + 0·2315 × (ECOG 2) + 0·6159 × (ECOG ≥ 3) − 0·6664 × (T1) − 0·3077 × (T2) − 0·6496 × (T3) − 0·4202 × (T4) + 0·2779 × (N1) − 0·1897 × (N2) + 0·1920 × (N3) − 0·0238 × (adenocarcinomas of upper and middle oesophagus) − 0·1957 × (adenocarcinomas of lower third of oesophagus and Siewert type I tumours) − 0·6097 × (Siewert type II and type III tumours) − 0·6246 × (gastric tumours)
90-day mortality	Log(odds) = − 4·8534 − 0·0152 × (age) − 0·2884 × (female sex) + 0·0963 × (1 co-morbidity) + 0·6472 × (2 co-morbidities) + 0·7033 × (≥ 3 co-morbidities) + 0·6452 × (ASA II) + 1·2431 × (ASA III) + 1·6439 × (ASA IV) + 0·0963 × (ECOG 1) + 0·5003 × (ECOG 2) + 0·8491 × (ECOG ≥ 3) − 0·4057 × (T1) + 0·0802 × (T2) − 0·3967 × (T3) + 0·1470 × (T4) + 0·3290 × (N1) + 0·3344 × (N2) + 0·5829 × (N3) − 0·4601 × (adenocarcinomas of upper and middle oesophagus) − 0·1990 × (adenocarcinomas of lower third of oesophagus and Siewert type I tumours) − 0·3851 × (Siewert type II and type III tumours) − 0·6925 × (gastric tumours)
Anastomotic leakage	Log(odds) = − 1·8702 − 0·0041 × (age) − 0·3540 × (female sex) + 0·4164 × (1 co-morbidity) + 0·5220 × (2 co-morbidities) + 0·5169 × (≥ 3 co-morbidities) − 0·0297 × (ASA II) + 0·3451 × (ASA III) − 0·1911 × (ASA IV) − 0·1031 × (ECOG 1) − 0·2274 × (ECOG 2) + 0·0049 × (ECOG ≥ 3) + 0·0941 × (T1) + 0·0571 × (T2) − 0·0119 × (T3) + 0·0411 × (T4) + 0·0132 × (N1) − 0·1418 × (N1) − 0·0188 × (N3) − 0·7059 × (adenocarcinomas of upper and middle oesophagus) − 0·5504 × (adenocarcinomas of lower third of oesophagus and Siewert type I tumours) − 0·4800 × (Siewert type II and type III tumours) − 0·9781 × (gastric tumours) − 0·1101 × (deprivation category 2) −0·2117 × (deprivation category 3) − 0·5143 × (deprivation category 4) − 0·0692 × (deprivation category 5)

ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

by cancer location and deprivation were entered into the multivariable models.

For 30-day mortality, co-morbidity count and ASA grade were the strongest predictors (*Table 4*). The OR for death within 30 days was 4·66 (95 per cent c.i. 1·32 to 16·51) for ASA grade IV compared with grade I. ASA grade was also the strongest predictor of 90-day mortality: OR 5·17 (2·01 to 13·29) for ASA IV *versus* grade I. Other predictors significantly associated with the mortality outcomes were age at diagnosis and number of co-morbidities.

The multivariable analysis for anastomotic leakage revealed that the number of co-morbidities was strongly associated with the development of anastomotic leaks: OR 1·68 (1·02 to 2·76) for three or more *versus* no co-morbidities. Patients with a tumour located in the stomach had a decreased risk of developing an anastomotic leak: OR 0·38 (0·24 to 0·57) *versus* patients with squamous cell carcinomas of the oesophagus.

The model equations are presented in *Table 5*.

Discussion

In this study models were developed for case-mix adjustment of postoperative outcomes in patients with oesophagogastric cancer undergoing curative resection. These models are based on the largest contemporary patient cohort and based exclusively on data routinely available from the 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 is the case in the NHS.

ASA grade and number of co-morbidities were found to be the strongest predictors of both short-term mortality and anastomotic leakage. This is in line with previous studies[15,35,37,40] that identified severely ill patients as being more likely to have an increased morbidity risk. The present three case-mix adjustment models, based on routinely available data in the NHS, had similar predictive ability to those found in the literature. Although model performance might be improved by adding further clinical/laboratory-based data items, the authors recommend against this for national comparisons for two reasons. First, the present review showed that the performance of models including complex clinical/laboratory data (such as POSSUM score) differed substantially and, second, these clinical data elements are not available routinely cancer in registries or through the NOGCA database.

Other predictors identified in the literature include provider-related variables such as choice of treatment and volume. However, as the aim here was to develop a case-mix adjustment model to monitor outcomes between providers, factors that can be influenced by the provider were not corrected for. For this reason, only preoperative factors were considered, which are readily available in hospital databases and cannot be modified by the provider. The choice of variables might differ in a prognostic model that aimed to predict risk in 'new' patients, as opposed to case-mix adjustment models which are usually used retrospectively on the data available. When comparing performance across providers, it is necessary to take into account patient characteristics that influence postoperative outcome to ensure that true differences

in performance rather than differences in patient characteristics are being assessed[41] Nevertheless, outcome differences must be interpreted with caution; even after sufficient case-mix adjustment there might be remaining unmeasured confounders that influence the outcome.

The question remains: which indicator best reflects quality of surgical care? Thirty-day mortality rates are decreasing over time. Studies[14,17] using data from the UK from 1990 and 2002 reported a mean postoperative 30-day mortality rate of 11·4 per cent, whereas a study[18] using data from 2005–2009 reported a rate of 4 per cent. In the present study, using data from April 2011 to March 2013, the 30-day mortality rate was 2·3 per cent. Although this 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 patients and are therefore more uncertain[41]. Rates of 90-day mortality are higher, and research has shown that the causes of death at 90 days after surgery are still strongly associated with surgical performance[42–44]. Deciding between measuring 30- or 90-day mortality can be regarded as a trade-off; with shorter follow-up, the included deaths will be related mostly to the surgery, but later deaths will be missed. On the other hand, with longer follow-up later deaths are included, potentially at the expense of including deaths unrelated to the surgery.

Anastomotic leaks occur more frequently than deaths, which makes them attractive as a quality indicator from a statistical point of view. The performance of models for anastomotic leakage was relatively poor. This is consistent with previous research[45] showing that postoperative complications are more difficult to predict on the basis of patient characteristics than postoperative mortality. 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. Judging hospital quality based on a single indicator, however, is a simplistic approach that should not be advocated. Monitoring several outcome and process indicators together will probably provide the best overall picture of hospital performance. This is particularly true where the indicator is based on self-reported data (as in the case of anastomotic leak rates in this study, which should be interpreted in conjunction with return-to-theatre rates and intensive care use). Nevertheless, when comparing outcomes, case-mix adjustment is of crucial importance to make valid comparisons and avoid risk-averse behaviour. The authors therefore aimed to develop the best possible risk adjustment model, although they recognize that some residual confounding will always remain and also that adjusted mortality rates should still be interpreted with caution.

A major strength of this study is its large, nationally 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 for National Statistics mortality data. Future studies should address other 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.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Flow chart showing selection of patients for inclusion in the study (Word document)

Table S1 Summary of included and excluded predictors for postoperative mortality (30-day, 90-day and in-hospital mortality) identified by literature review (Word document)

Table S2 Summary of included and excluded predictors for postoperative complication/anastomotic leakage identified by literature review (Word document)

Table S3 Descriptive statistics in the complete-case analysis and imputed data sets (Word document)

Table S4 Univariable logistic regression analyses in the complete-case analysis and in the imputed data set (Word document)