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Prediction of severe reflux after oesophageal cancer surgery

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ABSTRACT

Introduction: A common and burdensome consequence of oesophagectomy for cancer is reflux. This study aimed to develop a risk prediction model for postoperative reflux using variables available at the time of surgery enabling tailored preventive symptom management.

Methods: Data were obtained from a nationwide, population-based cohort of 921 adults who underwent oesophagectomy for cancer between 2013 and 2019. Among 569 eligible patients, 383 (67%) participated in the study. Patient and clinical characteristics were retrieved from national health registries and medical records. Postoperative reflux was self-reported 1 year after surgery in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire module for gastroesophageal symptoms. Multivariable regression models provided odds ratios (OR) with 95% confidence intervals (CI). The performance of the model was evaluated using the area under the receiver-operating characteristic curve.

Results: Female sex (OR 2.24, 95% CI: 1.00–5.00), preoperative reflux (OR 2.99, 95% CI: 1.61–5.52), and preoperative body mass index ≥30 (OR 2.45, 95% CI: 1.32–4.54) increased the risk of postoperative reflux. A model based on age, sex, preoperative reflux, body mass index, chronic obstructive pulmonary disease, and ventricle substitute predicted 72% of the severe cases.

Conclusion: Female sex, preoperative reflux, and preoperative body mass index increased the risk of postoperative reflux. A combination of readily available patient and preoperative clinical variables showed fairly good accuracy in predicting postoperative reflux after oesophagectomy. The clinical risk prediction model may be helpful for early symptom management but needs to be externally validated before wider use.

1. Introduction

Worldwide, more than 470,000 individuals develop oesophageal cancer each year [1]. The disease has a poor overall 5-year survival (<20%) [2] and causes more than 9.78 million disability-adjusted-life-years [1]. Curatively intended treatment for oesophageal cancer commonly involves resection of the oesophagus where the removed part is substituted by the upper part of the stomach [2]. Treatment for oesophageal cancer comprises a considerable risk of long-lasting symptoms and reductions in health-related quality of life (HRQL) [3,4]. One of the most common as well as most burdensome problems is severe postoperative reflux [5,6]. Reflux is often considered to be a consequence of the surgical procedure where the normal antireflux barrier is disrupted, and the intraabdominal pressure promotes reflux across the anastomosis [7]. Reflux is commonly characterised by heartburn and acid regurgitation of stomach content. Postoperative reflux, especially when in supine position, introduces a risk of aspiration pneumonia and can cause oesophagitis and Barrett's oesophagus in the oesophageal remnant [6,8]. Debilitating reflux has been reported up to 10 years after surgery [9] and is associated with impaired sleep quality and reductions in HRQL [10]. Since a patient's wellbeing is closely related to physical symptoms, it is

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important to refine care and treatments to avoid or reduce undesirable symptoms. Vocal cord palsy, retrosternal route of reconstruction, postoperative weight loss [11], shorter gastric conduit, and no perioperative chemoradiation have been shown to be independently associated with postoperative reflux [12]. However, it is unclear whether it is possible to identify patients at risk for reflux at an early postoperative state. Therefore, by using data from a comprehensive nationwide cohort study, we aimed to develop a prediction model, beneficial for preventive treatment planning, by identifying patients at risk of developing reflux one year after oesophagectomy.

2. Methods

This study was based on data from a population-based cohort study entitled: Oesophageal Surgery on Cancer patients – Adaptation and Recovery (OSCAR), which has been described in detail elsewhere [13]. In brief, patients were identified through collaboration with all eight pathology departments in the hospitals where these operations were conducted in Sweden. The entire cohort currently consists of 569 patients who underwent oesophageal cancer surgery between 2013 and 2020 and were alive one year after surgery and had a formal home address. All included patients were followed up by a research nurse who visited the patients in their homes one year after surgery and guided them through the self-reported computer-based questionnaire. Clinical data were collected from medical records and included tumour histology, site and stage, cancer treatment, and postoperative complications. Each medical record was reviewed by two researchers according to a predefined study protocol to ensure consistency and uniformity of the data collection. Cross-validation of randomly selected protocols was performed by an independent person. Data on patient characteristics were collected by linking the unique person identification number assigned to each Swedish resident to national health data registries. Socio-demographic information is obtained via linkage to the Longitudinal Integration Database for Health Insurance and Labor Market, which holds registration since 1990 and is updated yearly [14]. For information on comorbidities, the patients were linked to the Swedish Patient Registry and the Swedish Cancer Registry [15]. Comorbidities were classified according to the well-validated Charlson Comorbidity Index score [15,16]. The Swedish Register of the Total Population was used to retrieve survival data. All these registries hold nearly 100% complete nationwide information [17,18]. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (diary number: 2013/844-31/1) and all participants gave written informed consent.

2.1. Outcomes

The outcome was reflux measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) module for gastroesophageal symptoms (OG25) [19]. The QLQ-OG25 comprises of six symptom scales (dysphagia, eating restrictions, reflux, odynophagia, pain and discomfort, and anxiety) and ten single items (eating in front of others, dry mouth, trouble with taste, body image, trouble swallowing saliva, choking when swallowing, trouble with coughing, trouble talking, weight loss, and hair loss). There are four response alternatives: “not at all”, “a little”, “quite a bit” and “very much”. Reflux cases were identified in the questions “Have you had acid indigestion or heartburn?” and “Has acid or bile coming into your mouth been a problem?”. Patients who replied “quite a bit” or “very much” in either of the questions were considered to have severe reflux.

2.1.1. Candidate predictors

The selection of candidate predictors was based on literature and clinicians’ input regarding potential associations with postoperative reflux. These variables were age at surgery (continuous), sex (men/women), preoperative reflux (yes/no), preoperative body mass index (<30/≥30), tobacco smoking (ever/never), alcohol consumption (ever/never), diabetes mellitus (yes/no), chronic obstructive pulmonary disease surgery (yes/no), surgery type (open/laparoscopic), type of substitute (ventricle tube/colon or ileocolic segment), location of anastomosis (cervical/intrathoracic), and histology type (adenocarcinoma or dysplasia/squamous cell carcinoma).

2.2. Statistical analysis

The prediction model was built in a two-step approach. Firstly, the initial model was selected by assessing the association between the primary outcome and candidate predictors with univariable logistic regression modelling by including one covariable at a time. Predictors with a p value < 0.1 in the univariable analysis were included in the initial multivariable prediction model.

A receiver operating characteristic curve (ROC) shows diagnostic ability of a prediction model as its discrimination cut-off is varied. The ROC curve is created by plotting true positive rates against false positive rates. Area under the ROC curve (AUC) is a measure (between 0 and 1) of the overall accuracy of the prediction model: higher the AUC better the model. In the second step, all candidate predictors from the initial model were removed one at a time, and the corresponding model AUC was recalculated each time and predictors whose removal decreased the AUC by >1% were selected in the final model. To further evaluate the predictive accuracy of the model the mean AUC of 1000 bootstrap samples were calculated. Results from final model were presented as odds ratios (ORs) with 95% confidence intervals (CI) and AUCs. Hosmer and Lemeshow Goodness-of-Fit test was calculated for the final prediction model. A senior biostatistician (AJ) conducted all statistical analysis and data management using the statistical software SAS Statistical Package (version 9.4, SAS Institute Inc., Gary, NC).

3. Results

3.1. Patients

In total, 921 patients underwent oesophageal cancer surgery of which 700 (76%) survived until the 1-year follow-up. Among these, 569 (81%) were eligible for inclusion and 383 (67%) participated in the study. Twenty-five were excluded because of incomplete or missing data. In total, 348 (61%) patients participated in the study (Fig. 1). Characteristics of these patients are presented in Table 1. In brief, the mean age at surgery was 67 years (standard deviation 8 years) and 89% of the participants were men. The majority have undergone minimal invasive or hybrid surgery (69%) with replacement by a ventricle tube (95%). In the cohort, 86 (25%) suffered from severe reflux 1 year after oesophagectomy.

3.2. Development of the prediction model

After univariable models, 5 of the original 11 candidate predictors (age, sex, preoperative reflux, preoperative body mass index, and substitute), were selected for the AUC analysis. Thereafter, the previously removed predictors were re-entered in the model. Alcohol consumption and chronic obstructive pulmonary disease improved the AUC of the test model and were therefore kept for the final analysis. In the final analysis, all the previously selected predictors were kept in the model and one predictor at a time was

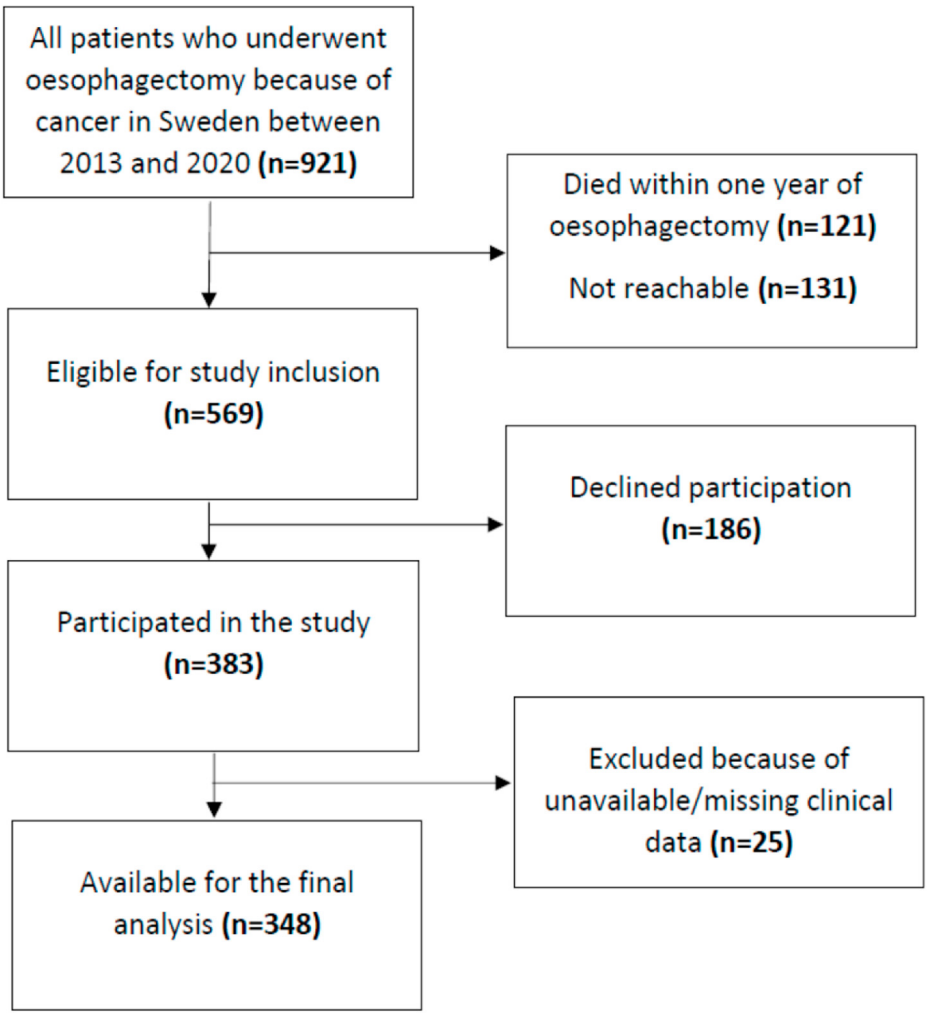

Fig. 1. Flow chart of study inclusion.

removed to determine their contribution to the overall AUC. The results showed that alcohol consumption was not contributing to the AUC and hence was removed. The final prediction model for postoperative reflux after oesophagectomy included the following 6 predictors: age (the risk decreases with older age), female sex, preoperative reflux, preoperative body mass index ≥30, chronic obstructive pulmonary disease, and ventricle substitute. The OR and 95% CIs of postoperative reflux for the predictors included in the model are presented in Table 2.

3.3. Model performance

The AUC statistics for the entire cohort was 0.72 (95% CI 0.65–0.78) and 0.68 (95% CI 0.61–0.74) after leaving one out cross-validation (Figs. 2 and 3). The p-value for the Hosmer and Lemeshow test was 0.696, confirming the null hypothesis of a good fit of the final model.

4. Discussion

This study indicates that the variables age, sex, preoperative reflux, preoperative body mass index, chronic obstructive pulmonary disease, and substitute can be combined for a fairly good prediction of postoperative reflux, while tobacco smoking, alcohol intake, diabetes, surgical approach, anastomosis location, or tumour histology do not predict postoperative reflux.

The nationwide and population-based cohort design with a relatively high participation rate (67%) provided an unselected cohort of oesophageal cancer patients, reducing the risk of selection bias. The information on predictors and reflux were retrieved from comprehensive assessments of medical records and from well-validated questionnaires. Missing data on the predictors were few, except for body mass index (n = 16). Yet, the missing data were not associated with gender and might therefore be considered as missing completely at random. Some potential predictors associated with reflux, such as vocal cord palsy and perioperative chemoradiation, could possibly have improved the model. Unfortunately, we did not have access to this information and future studies are warranted to reveal a possible influence. Reflux was self-reported which might introduce a bias risk. Currently, self-assessment of reflux is considered to be the Gold Standard [20], and the recall period of reflux was only 1 week. Also, a larger sample would likely have improved the precision of the estimates. The model was cross validated with an internal validation cohort. However, the risk of overfitting remains to some extent until external validation is performed by the use of an independent population.

Prediction models could be useful in identifying individuals with an increased risk of postoperative reflux. The finding that the risk of severe reflux increases with obesity and chronic obstructive pulmonary disease is supported by previous studies [21,22]. In contrast to our findings, results from a multicenter study indicated

Table 1
Characteristics of patients with and without reflux 1 year after oesophageal cancer surgery.

Variables	All patients No. (%)	No reflux No. (%)	Reflux No. (%)	p-values
Total number	348 (100)	262 (75)	86 (25)	
Age (Mean ± SD) in years	67 ± 8	68 ± 8	65 ± 9	0.017
Sex				
Men	314 (90)	242 (92)	72 (84)	0.019
Women	34 (10)	20 (8)	14 (16)	
Preoperative reflux				
No	285 (82)	229 (87)	56 (65)	NS
Yes	63 (18)	33 (13)	30 (35)	
Pre-operative body mass index (missing = 16)				
<30	264 (80)	208 (83)	56 (68)	0.004
≥30	68 (20)	42 (17)	26 (32)	
Tobacco smoking				
Never	56 (16)	43 (16)	13 (15)	NS
Ever	292 (84)	219 (84)	73 (85)	
Alcohol (missing = 3)				
Never	58 (17)	43 (17)	15 (17)	NS
Ever	287 (83)	216 (83)	71 (83)	
Comorbidity				
Diabetes				
No	297 (85)	224 (85)	73 (85)	NS
Yes	51 (15)	38 (15)	13 (15)	
Chronic obstructive pulmonary disease				
No	324 (93)	247 (94)	77 (90)	<0.001
Yes	24 (7)	15 (6)	9 (10)	
Surgical approach				
Minimal invasive or hybrid	241 (69)	181 (69)	60 (70)	NS
Open oesophagectomy	107 (31)	81 (31)	26 (30)	
Anastomosis location (missing = 2)				
Cervical	47 (14)	35 (13)	12 (14)	NS
Thoracic	299 (86)	225 (87)	74 (86)	
Substitute (missing = 2)				
Colon or ileocolic segment	17 (5)	15 (6)	2 (2)	NS
Ventricle tube	329 (95)	245 (94)	84 (98)	
Histology				
Adenocarcinoma or dysplasia	296 (85)	223 (85)	73 (85)	NS
Squamous cell carcinoma	52 (15)	39 (15)	13 (15)	

NS=No statistically significant differences (p > 0.05); SD=Standard deviation.

Table 2
Odds ratios (OR) and 95% confidence intervals (CI) of predictors for post-operative reflux 1 year after oesophageal cancer surgery.

Predictors	Severe reflux
	OR (95% CI)
Age (continuous)	0.98 (0.95–1.01)
Sex	
Men	Reference
Women	2.24 (1.00–5.00)
Pre-operative gastro-oesophageal reflux disease	
No	Reference
Yes	2.99 (1.61–5.52)
Pre-operative body mass index	
<30	Reference
≥30	2.45 (1.32–4.54)
Chronic obstructive pulmonary disease	
No	Reference
Yes	2.44 (0.68–44.20)
Substitute	
Colon or ileocolic segment	Reference
Ventricle tube	5.48 (0.56–36.9)

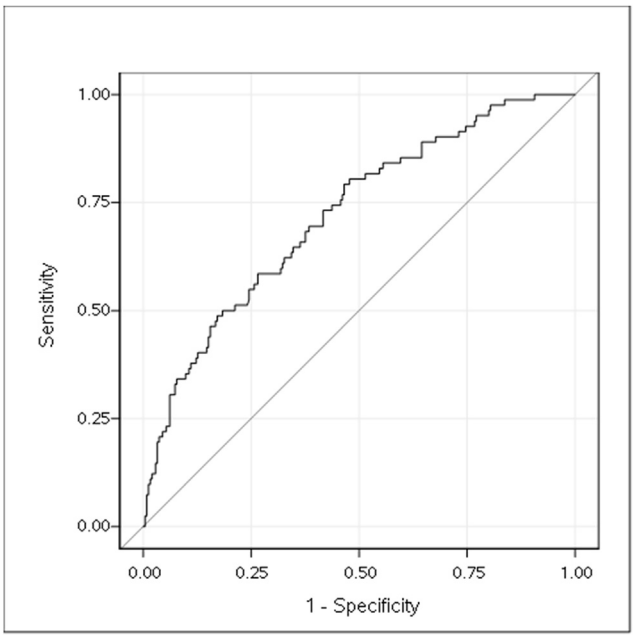

Fig. 2. Performance of the developed prediction model including age, sex, preoperative reflux, body mass index, chronic obstructive pulmonary disease, and ventricle substitute presented as the area under the receiver operating characteristic curve: 0.72 (95% CI 0.65–0.78).

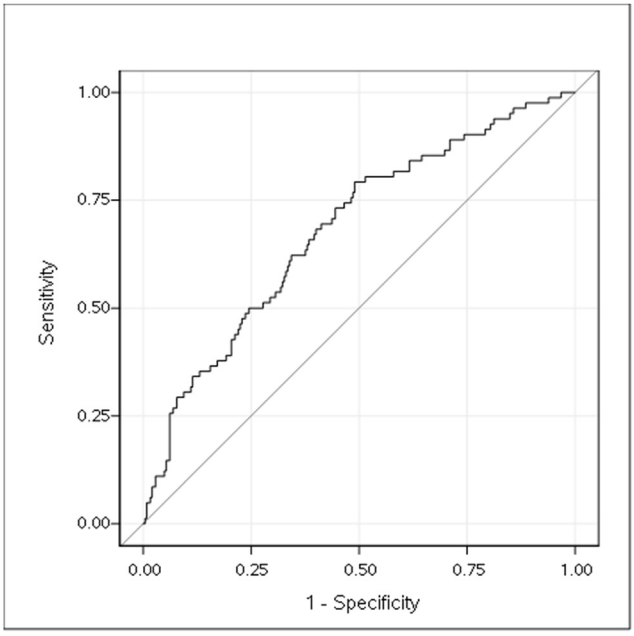

Fig. 3. Performance of the developed prediction model after cross-validation: 0.68 (95% CI 0.61–0.74).

that women were less likely to suffer from reflux approximately 4 years after oesophagectomy [23]. However, previous research on individuals with gastro-oesophageal reflux disease indicate that female sex hormones may play a role in symptom nociception since more women than men report symptoms of heartburn and regurgitation [24]. Postmenopausal oestrogen therapy has also been associated with an increased risk of gastro-oesophageal reflux disease [25]. As for oesophageal replacement, most surgeons prefer a stomach conduit, when available, because of its sufficient length and vascular supply [26]. Resection of the lower oesophageal sphincter together with excision of the vagus nerve are usually considered to be the main factors that inhibit gastric motor function [27].

Tobacco smoking is an established risk factor for reflux in individuals with gastro-oesophageal reflux disease [28,29], but did not predict postoperative reflux in this study. The aetiology for reflux after oesophageal resection may be somewhat different compared with gastro-oesophageal reflux disease as the anatomical and physiological anti-reflux barrier is disrupted with surgery. A meta-analysis including 29 studies, showed a potential association between alcohol consumption and gastro-oesophageal reflux disease, whereas a higher alcohol intake increased the likelihood of reflux symptoms [30]. In the present study, we found no role for alcohol intake in accelerating the symptom presentation.

Few prediction models have aimed to identify factors associated with long-term morbidity after oesophageal cancer surgery. Even though the long-term prognosis is poor, earlier detection, better quality of diagnostics, improved treatment options, and centralisation of surgery to high-volume surgeons have contributed to the improving survival rates [31–33]. Survivors of oesophageal cancer are likely to encounter a difficult recovery period with several long-lasting symptoms which may have an impact on their quality of life [3–5]. In addition to the survivorship burden that postoperative symptoms imply, HRQL scores are shown to have a prognostic value [34,35]. Therefore, it is of utmost importance that the remaining problems are identified and adequately treated. In order to prevent long-term HRQL reductions, clinicians who meet patients at follow-up consultations post-surgery should identify these seemingly benign symptoms. Today, this depends on the clinicians' knowledge and hospital site, and the content of suggested interventions may differ. This simple prediction model can, with fairly high accuracy, discriminate between high and low risk individuals as well as provide individualised estimates of the risk for postoperative reflux where most information can be obtained before the surgery. Additional predictors remain to be identified and evaluated for further improved accuracy. Most predictors in this model cannot be modified and therefore, the goal must be to help patients to plan for their personal future including preventive measures and for clinicians to tailor postoperative symptom management and follow-up. This, in turn, will indicate the need for early preventive interventions. Future steps should include the development of tailored interventions that may improve the long-term burden of survivorship. Symptom management beyond the end of treatment is important, especially since reflux seems to be a lifelong problem after oesophagectomy for many survivors [9].

Because of heterogeneities in patients' characteristics, healthcare systems, and treatment regimens across populations, the present model needs to be externally validated before being applied to other populations. However, if further validated, this clinical prediction model may contribute to more individually tailored symptom management after oesophageal cancer resection.

In conclusion, this nationwide population-based cohort study provides a model for the prediction of postoperative reflux in oesophageal cancer patients by combining information on several readily available clinical variables. The model has acceptable performance but needs to be externally validated before wider use. The model may be applicable to patients in estimating the risk of postoperative symptoms, but also in clinical practice for the planning of preventive postoperative treatment.

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CRediT authorship contribution statement

Pernilla Lagergren: Conceptualization, Conception and design, Collection and assembly of data. **Asif Johar:** Formal analysis, Data analysis. Interpretation of results: All authors; Final approval of manuscript: All authors. **Eivind Ness-Jensen:** Conceptualization, Conception and design. **Anna Schandl:** Conceptualization. Conception, design and manuscript writing.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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