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Assessment of Different Prognostic Scores for Early Postoperative Outcomes after Esophagectomy

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Rezumat

Evaluarea scorurilor prognostice pentru morbiditatea postoperatorie în chirurgia esofagiană

Obiectiv: Chirurgia rămâne cea mai bună opțiune terapeutică pentru cancerul esofagian și se însoțește de rate crescute de mortalitate și morbiditate postoperatorie. Scopul acestui articol a fost analiza factorilor de risc și a câtorva scoruri prognostice pentru predicția acestor complicații.
Metode: A fost efectuat un studiu retrospectiv pe o bază de date colectată prospectiv. A fost analizată capacitatea de predicție a scorului POSSUM, P-POSUM, O-POSSUM, Charlson, Charlson corelat cu vârsta, ASA.
Rezultate: Din 137 pacienți diagnosticați cu cancer esofagian, rezecția a fost posibilă în 43 cazuri. Mortalitatea postoperatorie (11.62%) a fost cel mai bine prezisă de scorul POSSUM (10.48; 95% CI 9.37 -11.66). Morbiditatea observată de 58.13%, a fost mai mare decât cea prezisă de POSSUM (48.24%; 95%CI, 44.82-51.66) cu o rată O/E de 1,2. Aria de sub curba ROC pentru scorul fiziologic POSSUM și scorul Charlson a indicat o bună discriminare. Cel mai performant test a fost POSSUM cu cea mai mare arie de sub curbă (0.826; 95%CI, 0.67-0.92).
Concluzii: O atentă selecție a pacienților candidați la esofagectomie impune o cuantificare a comorbidităților și a stării clinice prezente. Scorurile prognostice pot încadra pacientul într-o clasă de risc.

Cuvinte cheie: cancer esofagian, esofagectomie, scoruri prognostice, morbiditate postoperatorie

Abstract

Objective: Surgery remains the best curative option for oesophageal cancer. This demanding intervention performed on a high risk patient is accompanied by high morbidity and mortality rates. The aim of this study was to analyse the pre-operative risk assessment using different comorbidity models in patients operated for esophageal cancer in a tertiary unit.
Methods: A retrospective study was conducted on a prospectively collected database. The performance of several prognostic scores (POSSUM, P-POSSUM, O-POSSUM, Charlson and age adjusted Charlson, ASA score) was assessed in terms of early postoperative outcomes.
Results: Out of 137 patients diagnosed with oesophageal cancer, esophagectomy was performed in 43 cases. Postoperative mortality (11.62%) was best predicted by POSSUM score (10.48; 95% CI 9.37 -11.66). The observed morbidity was 58.13%, higher than that expected by POSSUM (48.24%; 95%CI, 44.82-51.66) with a morbidity ratio O/E of 1.2. The area under the ROC curve for the physiological score of POSSUM and age adjusted Charlson index showed a good discriminatory power. The best performance was obtained for POSSUM equation, who showed to have the highest area under the ROC curve (0.826; 95%CI, 0.67-0.92).
Conclusions: A thoroughly assessment of comorbidities and the surgeon's clinical assessment remain the best tool for patient selection for surgery.

Key words: esophageal cancer, esophagectomy, prognostic scores, postoperative complications

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Introduction

Esophagectomy remains the best treatment option in order to give the best chance for cure in a patient with esophageal cancer, and it is more often performed in specialised centres. Despite this fact, many cases of oesophageal cancer are still treated in so-considered low volume centres focused on oncological surgery. Outcomes after esophagectomy seem to be influenced by the patient and tumour characteristics and the centralisation of cases (1). A thorough assessment of patient comorbidities represents the best tool to make the most accurate selection of patients suitable for surgery. Several prognostic scores based on the physiology of the patient or on the operative findings were developed in order to have a good prediction of early postoperative outcomes. Most of those prognostic scores were developed using large series of patients with different surgical conditions in elective and emergency surgery and were further validated for specific malignancies. This scores included Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) (2), which was evaluated for vascular (3), colorectal (4), pancreatic (5,6) and esophageal (7) surgery. Due to the overprediction of mortality, different modifications were developed: Portsmouth-POSSUM (8), and O-POSSUM (a modification of the previous one for gastric and esophageal surgery) (9). Other prognostic scores currently used are: American Society of Anaesthesiologists score (10), Charlson comorbidity index (CCI) (11), age-adjusted Charlson comorbidity index (ACCI) (12) and modified Glasgow Prognostic Score model (13). Only a few studies were performed to validate the predictive power of the CCI, ACCI, and ASA scores after esophagectomy (14,15), all of those studies have been performed on series of patients operated in highly experienced, high-volume centres. The mortality and morbidity rates after esophagectomy are believed to be higher than the results published by the high-volume centres.

The aim of this study was to analyse the preoperative risk assessment using different comorbidity models in patients operated for esophageal cancer in a tertiary unit which cannot be considered a specialised centre for esophageal surgery.

Materials and Methods

We performed a retrospective study on a prospectively conducted database containing all the patients diagnosed with oesophageal cancer in whom surgery was performed between January 2004 and March 2013. Patients with unresectable tumours on laparotomy or thoracotomy or those with palliative surgery were excluded. Preoperative evaluation consisted of physical examination, standard laboratory tests and functional assessment of mainly cardiac and pulmonary function. Staging was done by thoracoabdominal computed tomography. Since 2009, all patients diagnosed with locally advanced tumours were submitted to a neoadjuvant protocol which consisted in chemo-radiotherapy. Surgery was performed by 4 experienced surgeons and consisted in radical esophagectomy through thoracotomy with cervical or thoracic anastomosis, or transhiatal techniques. Postoperative morbidity and mortality were defined as any complication or death which occurred within 30 days after surgery. Postoperative complications were graded according to the Dindo-Clavien classification (16) based on therapeutic consequences of complications. Grade I complication was considered any deviation from the normal postoperative course without the need for pharmacological treatment, grade II as a complication which requires pharmacological treatment, grade III requiring surgical, endoscopical or radiological treatment, grade IV as life- threatening complications and grade V death of the patient. Grade I and II were considered minor complications and grade III-V as major complications.

Overall comorbidity was assessed using POSSUM and its variants: P-POSSUM and O-POSSUM scores, Charlson comorbidity index, age adjusted Charlson comorbidity index and ASA scores. The POSSUM prediction models are based on a 12 factor preoperative physiological score and a 6 factor surgical severity score obtained after surgery. The physiological and operative score for each patient were calculated based on the original description (2). The expected morbidity and mortality for POSSUM and P-POSSUM was calculated using the calculation sheet available at www.sfar.org and for O-POSSUM at www.riskprediction.org.uk.

Charlson comorbidity index reflects the number and the gravity of comorbid diseases and consists in a 19 condition scale of medical conditions which were found to influence postoperative course and were given a value from 1 to 6 for an individual patient (11). The age adjusted Charlson comorbidity index uses a correction factor which represents the impact of age and comorbidity on disease progression and survival after surgery (17). ASA physical status was assigned by the anaesthesiologist before the patient's surgical intervention.

Statistical analysis

The descriptions of the quantitative variables were done, giving mean and standard deviation (SD) after showing normality from the variant. The categorical variables were described by way of percentages and 95% confidence interval (CI). Categorical data were compared among the two groups using Fisher's exact test and continuous data using Mann-Whitney U test. A p-value less than 0.05 was considered significant. Statistical analysis was performed using MedCalc v9.2.0.1. The observed numbers of events (morbidity and mortality) were compared with expected/predicted numbers by all three scoring systems. The performance of each prognostic score was evaluated through discrimination and was measured by the area under the receiver operating curve (ROC). An area under the curve (AUC) below 0.70 indicates poor discrimination, values between 0.70 and 0.80 an average discrimination and values over 0.80 a good discrimination. A logistic regression model was estimated to identify independent predictors of severe morbidity.

Results

During the study period 137 patients diagnosed with oesophageal cancer were surgically evaluated; of those, esophagectomy was performed in 43 cases. In *Table 1* the clinical and pathological characteristics of the patients are shown. The average age of the patients was 59.3 years (95% CI: 56.6 - 62). The mean Charlson index was 3 (2-3, range 2-7) and the age adjusted Charlson index was 4 (3-5, range 2-8). All of the patients were considered of being ASA II (69.76%) or ASA III (30.23%). Based on tumour localisation, one patient presented a tumour located in the upper third of the oesophagus; the rest of them presented tumours located in the middle third in 22 (51.1%) cases or in the lower third of the oesophagus in 21(48.8%) cases. Based on preoperative assessment 17 patients presented a chronic pulmonary condition, 6 patients a cardiovascular medical condition, 5 were diabetics, two presented a chronic kidney disease and in two cases a cirrhotic liver was found on laparotomy. The mean physiologic score was 15 (14-16, range 12-21) and the operative score was 17 (17-18, range 15-19).

In *Table 2* the adverse events of the patients are described. The expected mortality according to POSSUM was 10.48 (95%CI, 9.37 - 11.66), P-POSSUM was 2.71 (95%CI, 2.31 - 3.12), O-POSSUM was 6.83 (95%CI, 6.21-7.25), whereas the observed mortality in our series was 11.62%, thus giving a mortality ratio observed/expected of 1.1 for POSSUM, 4.28 for P-POSSUM and 1.7 for O-POSSUM. The observed morbidity given was 58.13%, higher than that expected by the POSSUM (48.24%; 95%CI, 44.82 - 51.66) with a morbidity ratio O/E of 1.2. The frequencies of minor and major complications were relatively equal; there were cases in which one or more complications occurred in a single patient. For those cases, only the most important complication was assessed together with those which were not directly related to the major one. The most common postoperative adverse events were pulmonary complications (pneumonia, pleural effusion or ARDS) in 39.5% of cases. Surgery related complications such as anastomotic fistula, recurrential paralysis or postoperative haemorrhage occurred in 30.2% of cases. Postoperative causes of death were: major stroke, acute myocardial infarction, ARDS, hepatic failure in a cirrhotic patient and sepsis. As seen on *Table 3*, by performing a comparative analysis we found that age (p=0.006), age adjusted Charlson index (p=0.009) and physiological score of POSSUM (p=0.007) were significantly different in patients who developed a postoperative complication. No difference was found in terms of Charlson morbidity index, POSSUM operative score, preoperative haemoglobin levels, neoadjuvant treatment, the transthoracic approach or the histologic type of cancer.

The discriminative ability of different prognostic scores is shown in *Table 4*. The area under the ROC curve for POSSUM operative score and Charlson index showed a poor discriminatory power, for the physiological score of POSSUM and the age adjusted Charlson index and age as an independent factor showed a good discriminatory power. The best performance of tested prognostic scores was obtained for POSSUM equation, who showed to have the highest area under the ROC curve (0.826; 95%CI, 0.67-0.92).

Table 1. *Patients' characteristics*

N	43
Age	59.3 (56.6 - 62)
Male/female ratio	40/3
ASA II	30
ASA III	13
Charlson comorbidity index	3 (2-3)
Age adjusted Charlson index	4 (3-5)
Tumour localisation	
Upper thoracic	1
Middle third	22
Lower third	20
Histologic type	
Squamocellular	33
Adenocarcinoma	9
Carcinosarcoma	1
Neoadjuvant treatment	22
Stage I	5
Stage II	17
Stage III	21
Physiological score	15 (14-16)
Operative score	17 (17-18)
Mc Keown	23
Ivor Lewis	5
Transhiatal	15

Table 2. *Outcomes after surgery*

	N (%)
Overall mortality	5 (11.62)
Overall morbidity	25 (58.13)
Minor complications	13 (30.23)
Major complications	14 (32.55)
Cardiac	5 (11.62)
Pulmonary	17 (39.53)
Fistula	5 (11.62)
Reccurential paralysis	6 (13.95)
Postoperative bleeding	2 (4.65)
Acute pancreatitis	1 (2.32)
Myocardial infarction	1 (2.32)
Stroke	2 (4.65)

Discussion

Several prognostic scores or risk adjusted models for postoperative morbidity based on the physiology of the patient and on the severity of the surgical intervention have been developed in order to stratify the patients submitted to surgery. Especially in oncological surgery, with special regards to upper digestive tumours, a thorough preoperative assessment is required in

Table 3. *Comparison of different characteristics depending on postoperative outcome*

	Complications	No complications	P-value	OR
Charlson index	3 (2-4)	2.5 (2-3)	0.23	
Age adjusted Charlson index	5 (4-6)	3.5 (3-4)	0.009	1.4004 (0.6347 - 3.0901)
Physiological score	17 (14-19)	15 (14-15)	0.007	1.4415 (0.9726 - 2.1366)
Operative score	17 (17-19)	17 (17-18)	0.23	
ASA II/III	15/10	15/3	0.17	
Age	63 (57.3-68.5)	56 (51-58.3)	0.006	1.0128 (0.8803 -1.1653)
Hb	11.3 (10.6-13)	11.7 (10.7-14)	0.5	
Neoadjuvant therapy	13 (52%)	8 (44%)	0.75	
Thoracotomy	17 (68%)	11 (50%)	0.75	
Histology (Scc/Adk)	22/3	12/6	0.13	

order to have proper postoperative results. A patient with an oesophageal tumour is at high risk due to the nutritional impairment due to mechanical obstruction of the upper digestive tract, the cancer related anorexia and the effects of neoadjuvant treatment (18). Also, based on an observational study, a particular risk configuration in patients with oesophageal cancer was described. Patients with adenocarcinoma are more likely to have an impaired cardiovascular function. On the other hand, patients with squamous cell tumours predominantly suffer from an impaired pulmonary and hepatic dysfunction due to a markedly increased nicotine and alcohol consumption (19). Patients with a high preoperative risk score had a more complicated postoperative course compared to patients with low preoperative risk. The general status is often associated with the patient's age and it is not based on objective parameters, being strongly influenced by the surgeon's clinical judgment.

This study aimed to assess the ability of different prognostic scores in the prediction of adverse postoperative events after esophagectomy in a consecutive series of patients operated in a teaching hospital which cannot be considered a high volume centre focused on oesophageal surgery.

Based on the results of our study, oesophageal cancer in our series had a poor resectability rate of 29.25%, the two main reasons for this rate being the poor status of the patients and the locally advanced tumours which were considered not suitable for surgery. Cardiac and pulmonary comorbidities in patients with resectable tumours were the two main causes for inoperability. Our results are concordant with those of the literature, previous reports showing a resectability rate around 50% (20). Although all the patients submitted to surgery had clinical and functional evaluation, mainly of pulmonary and cardiac functions, no prognostic score was calculated prior to surgery to better quantify the severity of comorbidities; the only scale used was the ASA functional status, given prior to surgery by the anaesthesiologist. All the other scores were calculated based on the medical records of the patients.

Our study focused only on oesophageal tumours and excluded gastroesophageal junction tumours (Siewert type II) which are included in most of the previous published studies focused on oesophageal cancer management (7,15,19), due to the low incidence of this subtype and type III Siewert tumours which are considered and managed as gastric tumours. Most of the tumours were squamous type developed in heavy smokers with an impaired pulmonary function which was directly reflected by the incidence of postoperative complications. Surgical approach was based on surgeon's experience and on the severity of pulmonary impairment. In cases where open transthoracic esophagectomy was performed, the level of anastomosis was chosen based on tumour localisation: for the tumours located in the lower third of the oesophagus a mediastinal anastomosis above the azygos vein and for the medial third of the oesophagus a cervical anastomosis. For patients considered non suitable for a thoracotomy, a trans-hiatal approach with cervical anastomosis was preferred.

The percentage of mortality observed in our series was best predicted by the POSSUM score, being included in the 95% confidence interval with an O/E ratio of 1.1. External validation of POSSUM score and its derivates for prediction of postoperative mortality showed a lack of suitability, with O/E ratios between 0.37 to 0.66 (7, 21) for POSSUM and 0.29 to 0.71(21,22,23,24) for O-POSSUM. The P-POSSUM in our series showed an underestimation of mortality contrary to the available literature which showed a better prediction of mortality; the published O/E ratios for P-POSSUM are: 0.83 (9), 1.17 (21), 1.03 (23), 1.05 (15). One possible explication of the best predictability for mortality of the POSSUM score in our series is that originally it was created based on a large series

Table 4. *ROC curve analysis for prognostic scores*

	N (%)	
AUC	p-value	
POSSUM score	0.826 (0.67-0.92)	0.0001
Physiological score	0.74 (0.58-0.86)	0.0014
Operative score	0.607 (0.44-0.75)	0.21
Charlson comorbidity index	0.608 (0.44-0.75)	0.21
Age adjusted Charlson index	0.736 (0.58-0.85)	0.0018
Age	0.744 (0.58-0.86)	0.001
Hb	0.56 (0.40-0.71)	0.5

of patients operated on in all kinds of hospitals; the P-POSSUM and O-POSSUM attribute different degrees of importance to age as an independent factor and were developed for elective patients in specialised tertiary centres. Moreover, all the external validations on large series of the above mentioned scores were done on patients operated in centres with high experience in oesophageal cancers. Due to the centralisation of cases there is a continuous descendant trend of postoperative mortality, with rates below 5% (25) in specialised high-volume hospitals; in low volume centres the mortality exceeds 10%.

In terms of postoperative morbidity 58.13% patients developed a postoperative complication; a percentage above the upper limit of the 95% confidence interval of POSSUM predicted morbidity, giving an O/E ratio of 1.2. The published O/E ratio for morbidity on validation series for POSSUM were 0.86 (7) and 0.82 (24). Even with the exclusion of the 5 postoperative deaths (grade V postoperative complication) we have a postoperative morbidity of 52.63%, underestimated by the POSSUM equation. Although the percentage of postoperative complications is comparable to the published rates between 40% and 80%, depending on the applied criteria and the extent of resection (26,27) we consider that it is above the latest percentages from larger, multicentre studies around 40% (28). This is also a direct effect of the centralised management of patients with oesophageal cancer.

Regarding the discriminative ability of prognostic scores used for preoperative risk stratification, POSSUM equation had the highest area under the ROC curve with a good discriminatory power, thus a good ability to attribute the correct outcome to a specific patient. This is the reason why we consider that it is not accurate to compare the equation of POSSUM with other prognostic scores, but instead to compare the components of the POSSUM equation, the physiologic and operative components with the other scores. Based on the results of our study the physiologic score of POSSUM had the same discriminatory power in terms of severe complications as the age adjusted Charlson index. The age adjusted Charlson index is based on the quantification of comorbidities and showed a good ability to predict 1 year survival on cancer patients (29) and is directly related to post-operative mortality after esophagectomy. The physiological score of POSSUM includes a functional assessment of cardiac, pulmonary, neurologic and renal status and includes the results of routine blood count and biochemistry. We believe that the age adjusted Charlson score is more comprehensive than the physiological score, in term of a wide range of medical conditions and it is more easy to use, the physiologic score of POSSUM having the advantage of a more detailed assessment of previous mentioned conditions. The ASA classification, which is one of the most utilised scores, has been proved to be interobserver dependant (30) and might be influenced by differences in clinical assessment.

Our study has two major drawbacks; one of them is the relatively small number of cases included in the analysis, which can limit the accuracy of the results. This is due to the relatively low percentage of patients suitable for surgery. The other major drawback is the relatively heterogeneous cohort of patients; neoadjuvant treatment was not systematically applied to all patients with locally advanced tumours in the first period of the study, the perioperative management in terms of pain management, perioperative fluid restriction, respiratory rehabilitation was different, and thus can influence the incidence of postoperative complications.

Conclusions

Morbidity and mortality occur in significant numbers following oesophageal resection despite improvements in preoperative staging, patient selection, surgery technique and perioperative care. Accurate prediction of surgical mortality and morbidity is important for appropriate selection of candidates for esophagectomy, but also for the evaluation of quality of care between institutions. Up to present, there is no specific factor for accurate prediction of complications after esophagectomy. Based on the results of this study and the previous studies, a thorough assessment of comorbidities together with the visiting surgeon's clinical assessment remain the best tool for patient selection for surgery. A good evaluation of the functional status represents also a guideline for postoperative management of complications.

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