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COMPLICATIONS RISK ASSESSMENT FOR ESOPHAGEAL STENT POSITIONING

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1. Introduction

Esophageal cancer is the eighth most common cancer worldwide (Ferlay *et al.*, 2013). Unfortunately, despite many advances in diagnosis and therapy, the larger amount of patients have inoperable disease at the diagnosis stage. For these persons, palliative treatment is required in order to mitigate symptoms (usually dysphagia) and to re-establish an acceptable quality of life.

Self-Expanding Metal Stent (SEMS) placement is the recommended method for palliation of dysphagia due to esophageal cancer. However, life-threatening complications may occur after SEMS placement such as perforation, massive bleeding, aspiration pneumonia (ASGE, 2013; Didden *et al.*, 2012).

The issue concerning the identification of predictors for complication due to self-expanding stents in patients with esophageal cancer has been largely debated without achieving a definite conclusion (Didden *et al.*, 2012; Lecleire *et al.*, 2006; Homs *et al.*, 2004; Iraha *et al.*, 2006; Ross *et al.*, 2007).

This work intends to study and discuss an approach to identify predictor variables for assessing the risk of developing SEMS-related complications. The results, based on a multivariate logistic regression model, allow clinicians to group patients according to the risk of developing complications in such a way to design the most suitable palliative treatments.

The paper is organized as follows: the next section introduces the data; Section 3 contains the estimation of the logistic regression model; Section 4 reports results and discussion; finally, Section 5 contains the concluding remarks.

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2. The data

The data set used in the present work has been conveniently extracted from SEMS database of Veneto Oncology Institute (IOV) in Padua (Italy), which serves as tertiary referral center for esophageal diseases. The patients who consecutively underwent SEMS placement for stricture due to esophageal cancer between 2002 and 2011 were identified. Only patients for whom SEMS placement was technically and clinically successful and where follow-up data was available were included. In the $2002 - 2011$ period a total of 356 patients with dysphagia due to esophageal cancer were treated with SEMS placement with 42 subjects having been excluded since they did not satisfy the inclusion criteria. The remaining 314 patients were included in the study.

The follow-up for each patient starts at the moment of SEMS positioning and the outcome of interest, Y, is the occurrence of a major complication ($Y = 1$) during the follow-up. A major complication is defined as a complication for which a repeated endoscopic intervention or hospitalization was required.

A summary of the clinical characteristics of our population study is presented in Table[2] 1.

3. The model

Logistic regression is well suited for studying the relation between a categorical or qualitative outcome variable and one or more predictors.

Consider a collection of p independent variables denoted by the vector $\mathbf{x}' = (x_1, x_2, ..., x_p)$ and let the conditional probability that the outcome is present be denoted by $\pi(\mathbf{x}) = Pr(Y = 1|\mathbf{x})$.

The multivariate logistic regression model has the general form

$$\pi(\mathbf{x}) = \frac{1}{1 + \exp\{-g(\mathbf{x})\}} \tag{1}$$

where $g(\mathbf{x}) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_p x_p$ is the logit of the model, β_0 is the intercept and β_j $(j = 1, 2, ..., p)$ are the slope parameters.

Since SEMS-related complications may be influenced by several factors we initially fit a multivariate logistic model including all clinically and intuitively relevant covariates.

With the aim of finding the best fitting and most parsimonious clinically interpretable model within the constraint of the available data we disclose that: Age and Lesion length, considered as continuous covariates, did not result statistically significant; Lesion site, Karnofsky score , Histology and Cancer stage all considered as polychotomous covariates and included in the model using design variables (three design variables for Lesion site, three design variables for Karnofsky score,

[2] In Table 1 Karnofsky score quantifies the functional status of a patient: 100-80 the patient is able to carry on normal activity and to work; 80-60 the patient is unable to work and requires occasional assistance; 60-40 the patient requires considerable assistance and frequent medical care; < 40 the patient is severely disabled and requires hospital care.

TABLE 1
Baseline patients characteristics

Patient characteristics	**Continuous Variables** (mean ± SD; min; max; median) **Categorical Variables** n (%)
Age (years)	$69.54 \pm 12.05; 32; 93; 70$
Length of the follow-up since SEMS placement (days)	$139.99 \pm 124.42; 1; 870; 109.50$
Lesion length (cm)	$6.09 \pm 2.92; 0; 17; 6$
Stent diameter (mm)	$17.67 \pm 1.80; 10; 28; 18$
Gender	
Male	254 (80.9%)
Female	60 (19.1%)
Prior anti-tumoural therapy	
Chemotherapy and/or radiotherapy	184 (58.6%)
None	130 (41.4%)
Lesion Site	
Upper esophagus	63 (20.1%)
Mid esophagus	111 (35.4%)
Lower esophagus	122 (38.9%)
Anastomosis	18 (5.7%)
Karnofsky score	
$100 - 80$	83 (26.4%)
$80 - 60$	103 (32.8%)
$60 - 40$	95 (30.3%)
< 40	33 (10.5%)
Histology	
Squamous cell carcinoma	198 (63.1%)
Adenocarcinoma	116 (36.9%)
Cancer stage	
Ib	2 (0.6%)
IIa	4 (1.3%)
IIb	24 (7.6%)
IIIa	71 (22.6%)
IIIb	1 (0.3%)
IIIc	42 (13.4%)
IV	152 (48.5%)
Recurrence	18 (5.7%)
Patients who had a complication during the follow-up	96 (30.6%)
Patients dead at the end of follow-up	305 (97.1%)

TABLE 2
Estimation results for the SEMS-related complications model

Predictors	Est. Coeff.	Std. Err.	z-value	p-value	Est.odds ratio (95%CI)
Intercept	-1.9230	0.2853	-6.739	< 0.001	
P_CRT	0.6176	0.2697	2.290	0.0220	1.8545 (1.0932 − 3.1461)
L_FUP	0.0049	0.0011	4.482	< 0.001	1.0049 (1.0027-1.0070)

one design variable for Histology and seven design variable for Cancer stage) did not result statistically significant; all interaction effects did not result statistically significant (Hosmer *et al.*, 2013).

The logistic regression analysis showed that only two covariates are significant in estimating the risk of SEMS-related complications:

1. Prior anti-tumoural treatments -Chemotherapy and/or Radiotherapy- (***P_CRT***: $YES = 1$; $NO = 0$)

2. Length of the follow-up since SEMS placement (***L_FUP***, in days).

The maximum likelihood estimates are shown in Table 2.

Therefore the estimated logit (or risk score) is

$$\widehat{g}(\mathbf{x}) = -1.9230 + 0.6176 \times P\_CRT + 0.0049 \times L\_FUP \tag{2}$$

3.1. Model performance assessment

For the evaluation of model performance we consider overall performance, calibration and discrimination.

The generalized likelihood ratio, which assesses the overall significance of the model, is $L.R. = 26.87$ (p-value< 0.001) and the goodness of fit test (le Cessie and van Houwelingen, 1991) is $z = 1.5382$ (p-value$= 0.1240$). Therefore we can conclude that there is no evidence of lack of fit (Harrell, 2001; Agresti, 2002).

The model calibration, i.e. the agreement between predicted probabilities and observed frequencies of the event of interest, can be assessed by means of Figures 1 and 2. Figure 1 shows the estimated probability curves for subjects who did not receive any prior anti-tumoural treatments and for those who received prior anti-tumoural therapy as a function of the duration of the follow-up. The Figure also shows the observed proportions of subjects who experienced a SEMS-related complication among those who received a prior anti-tumoural therapy (triangles) and who did not receive any therapy (circles) obtained by grouping the data into L_FUP intervals $(\leq 90], (90, 180], ..., (810, 900])$.

Figure 2 shows the validation graph for the estimated model: "Non-parametric" is a smoothed function of observed events plotted versus predicted probabilities

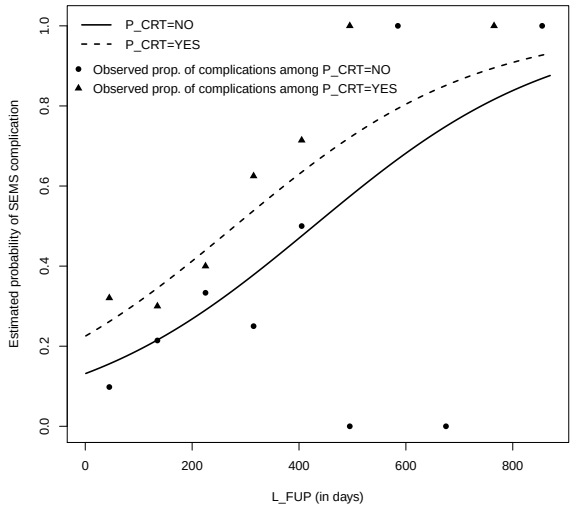

Figure 1 – Estimated risk curves and observed proportions stratified for P_CRT versus length of the follow-up.

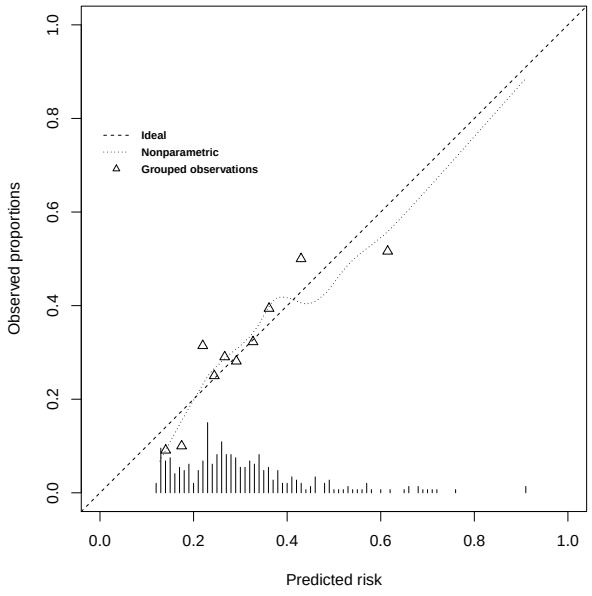

Figure 2 – Validation graph for the estimated model.

while "Ideal" is the ideal 45-degree line and the triangles indicate the outcomes for deciles of prediction.

Examining the results we note an appreciable agreement between predicted probabilities and observed frequencies of the event of interest in particular for values of risk ranging from 0.25 to 0.4.

The model's ability to discriminate between those subjects who experience the outcome of interest versus those who do not, can be assessed by means of several measures. The concordance statistic, or c-index, is the most commonly used performance measure to indicate the discriminative ability of generalized linear regression models (Royston and Altman, 2010). It is the proportion, among all pairs of patients with different outcomes, in which the event probabilities predicted by the model are in the same order as the actual outcomes. The c-index is thus the probability, across all patients, that a model will be correct in predicting that one patient has a higher probability of the outcome than another patient.

For a binary outcome, the c-index is identical to the AUC: the Area Under the Receiver Operating Characteristic (ROC) Curve.

Usually, the outcome prediction is $\widehat{Y} = 1$ when $\widehat{\pi}(\mathbf{x}) > \pi_0$ and $\widehat{Y} = 0$ when $\widehat{\pi}(\mathbf{x}) \leq \pi_0$, where π_0 is the cut-off probability. Let us denote with TP the number of true positives (i.e. $\widehat{Y} = 1$ when $Y = 1$), TN the true negatives (i.e. $\widehat{Y} = 0$ when $Y = 0$), FP the false positives ($\widehat{Y} = 1$ when $Y = 0$) and FN the false negatives ($\widehat{Y} = 0$ when $Y = 1$). *Sensitivity* and *specificity* are defined in terms of TP, TN, FN and FP:

$$sensitivity = \frac{TP}{TP + FN} \tag{3}$$

$$specificity = \frac{TN}{TN + FP} \tag{4}$$

The ROC curve plots the *sensitivity* against one minus *specificity* for a range of possible cut-off probabilities.

The ROC curve for the fitted model is shown in Figure 3. In our case AUC=0.670 (95%CI: $0.607 - 0.733$) which indicates that the estimated model has a moderate discrimination ability.

4. Results and discussion

The estimation results show that previous anti-tumoural therapy is significantly associated with SEMS-related complications: the estimated risk of developing a SEMS-related complication increases among those who underwent prior anti-tumoural therapy ($P\_CRT = YES$, Figure 1) and the odds of developing a complication for subjects who did receive prior anti-tumoural treatments is 1.8545 (95%CI: $1.0932 - 3.1461$) greater than the odds of a complication among subjects who did not receive treatments (Table 2).

As far as the covariate L_FUP is concerned, the estimated probability of developing a complication increases as the duration of the follow-up increases. The estimated odds ratio reported in Table 2 is referred to a one-unit (i.e. one day)

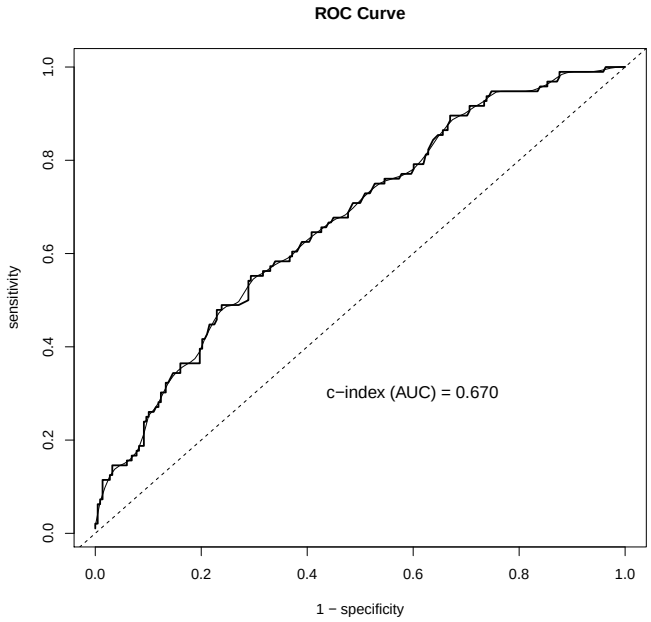

Figure 3 – ROC curve for the fitted logistic regression model.

increment in the predictor. Since a one-day increment is not likely to be clinically interesting we complete the picture by introducing Table 3 which contains the estimated odds ratios for one month (30 days) increments in the covariate.

As an example, for an increase of two months in the duration of the follow-up the odds of developing a complication are estimated to increase 1.34 times (34%).

These results, conveniently contextualized in a clinical context can be very helpful.

Let us consider, as an example, a patient who did not undergo prior anti-tumoural therapy: for $L\_FUP = 90$ the estimated probability of a SEMS complication is 0.1848 (95% CI: $0.1256 - 0.2633$). In other words, a patient not previously treated with chemo and/or radiotherapy with a supposed life expectancy of three months at the moment of SEMS placement, has an 18.48 percent risk of developing a SEMS related complication. Let us now consider a subject who underwent prior anti-tumoural therapy: for $L\_FUP = 90$ the estimated probability of a complication is 0.2959 (95%CI: $0.2317 - 0.3693$). In other words, a patient previously treated with chemo and/or radiotherapy with, a supposed life expectancy of three months at the moment of SEMS placement, has a 29.59 percent risk of developing a complication.

To facilitate the use and the interpretation of our results we provide a nomogram and a point scoring system (see the Appendix for details) which allow to compute the probability of developing a SEMS-related complication.

TABLE 3
Estimated odds ratios for SEMS complications for monthly increments in the predictor L_FUP

***L_FUP* increments**	**Estimated OR**	**95% CI**
1 month	1.157	1.086-1.234
2 months	1.340	1.179-1.522
3 months	1.550	1.280-1.878
4 months	1.795	1.390-2.318
5 months	2.077	1.509-2.860
6 months	2.404	1.638-3.528

4.1. Cut-off analysis

The discrimination ability of the estimated model is moderate (AUC=0.670). However, our result is similar to other scores used in clinical medicine (Greenland *et al.*, 2004; Steyerberg *et al.*, 2005, 2010). Therefore, even with several cautions, we shall explore the potentialities of a prognostic decision rule based on the estimated model.

The optimal probability cut-point π_0 for the purposes of classification is usually chosen according several criteria among which we mention:

- a) the criterion based on Youden's J-statistic (Royston and Altman, 2010) where the optimal cut-off point maximizes the sum of *sensitivity* and *specificity* minus 1

$$J = max(sensitivity + specificity - 1) \tag{5}$$

- b) the cut-off which minimizes the distance d between the curve and the upper left corner of the graph, where

$$d = \sqrt{(1 - sensitivity)^2 + (1 - specificity)^2} \tag{6}$$

- c) the cut-off which maximizes both *sensitivity* and *specificity*.

For the fitted model: the probability cut-off that satisfies criteria a) and b) is $\pi_0 = 0.3197885$ for which $J = 0.258505$ and $d = 0.535553$ ($sensitivity = 0.552083$, $specificity = 0.706422$); the cut-off which maximizes both sensitivity and specificity is $\pi_0 = 0.290114$, this "optimal" choice for the probability cut-point is approximately where the sensitivity and specificity curves cross ($sensitivity = 0.614583$ and $specificity = 0.614679$). These results are summarized in Figure 4 and 5 respectively.

Choosing as cut-off $\pi_0 = 0.290114$ (*sensitivity=specificity*) the corresponding value of the risk-score is $g_{\pi_0}(\mathbf{x}) = -0.8948$. The estimated risk-score (2) equals the value $g_{\pi_0}(\mathbf{x}) = -0.8948$ when $L\_FUP = 84.25$ for subjects who underwent a prior therapy and when $L\_FUP = 211$ for who did not undergo any therapy.

Thus contextualizing these findings in a prognostic framework, a patient with a life expectancy equal or less than 84 days who underwent prior anti-tumoral

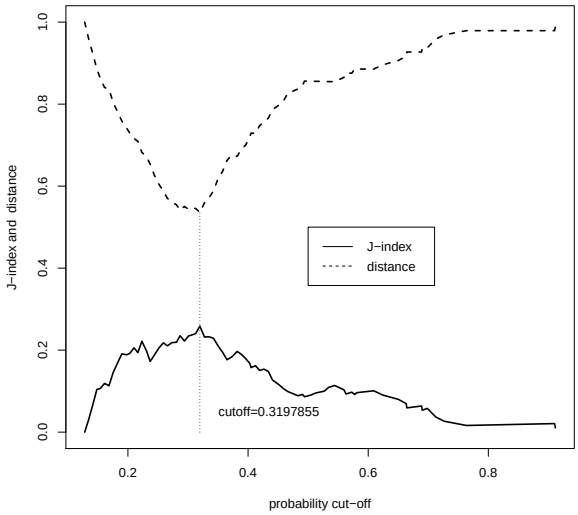

Figure 4 – Plot of Youden's J statistic and d (top-left corner distance) versus all possible probability cut-off points.

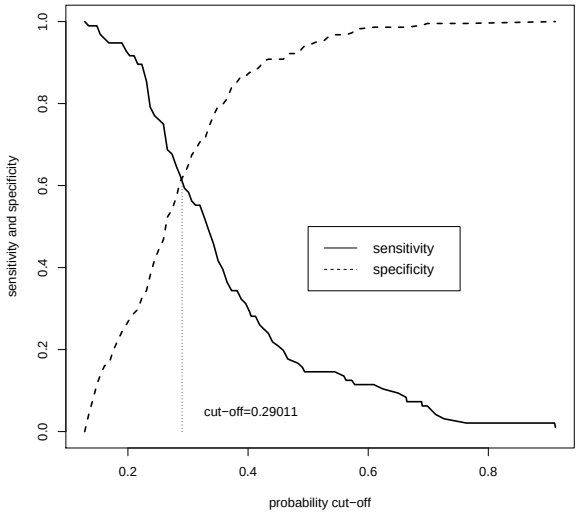

Figure 5 – Plot of *sensitivity* and *specificity* versus all possible probability cut-off points.

therapy is classified by the model as $\widehat{Y} = 0$: a subject that likely will not develop a SEMS complication. A patient who underwent prior anti-tumoral therapy with a life expectancy equal or greater than 85 days is classified by the model as $\widehat{Y} = 1$: a subject that likely will experience a SEMS-related complication.

Similarly, a person who did not receive any therapy with a life expectancy of less than 211 days is classified as $\widehat{Y} = 0$: a patient that likely will not have a complication. Finally, a patient who did not receive any therapy with a life expectancy equal or greater than 211 likely will develop a SEMS complication.

Summarizing: patients with a poor prognosis not previously treated with anti-tumoral therapy might benefit from SEMS-placement, since the risk of developing stent-related complications is very low; for patients with good prognosis it is possible to estimate the probability of having a complication and possibly alternative palliative procedures might be considered.

5. Concluding remarks

To sum up the estimated model might provide a useful clinical decision aid. We have identified the two main predictors for the probability of developing SEMS-related complications and discussed their contribution to the risk estimation.

This quantification of the risk could allow clinicians to group patients according to the probability of developing complications in order to design the most suitable and effective palliative treatments for improving the patients quality of life.

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Appendix

A nomogram (Figure 6) is a convenient graphical tool to compute the probability of an outcome of interest. Each predictor variable has a corresponding point value based on its position on the top point scale and contribution to the model. A total score is given to each subject by adding up the points. The probability of developing a SEMS-related complication for each subject can be calculated by the total score from the scale presented on the bottom line. The nomogman has been obtained by using the *R* "rms" package (Harrell, 2014; R Core Team, 2013).

For instance, let us consider a patient who did not receive any prior therapy ($P\_CRT = NO$) and with a supposed life expectancy of 120 days: this subject has 0 points due to prior therapy and about 14 points due to the length of follow-up (120 days); thus the total points are 14 and the corresponding estimated probability of having a complication is about 21%.

A point scoring system is also provided to readily calculate the risk score and the total point score (Table 4). For example, a patient who did receive prior anti-tumoural therapy (15 points) and with a length of the follow-up equal to 6

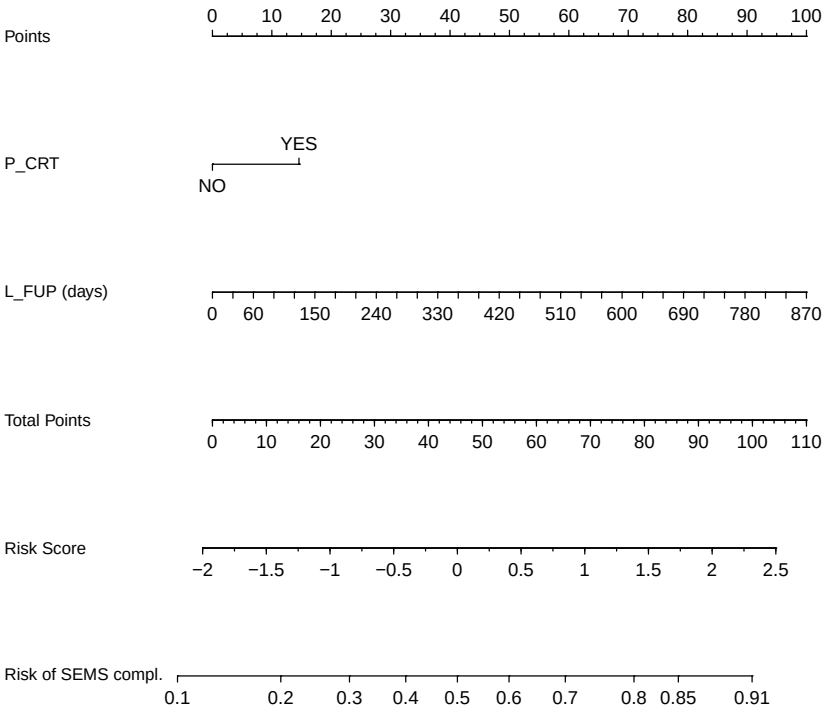

Figure 6 – Nomogram for computing the estimated risk of developing a complication.

TABLE 4
Point scoring system for the predictor variables and probability of complication at different total point scores

Predictor variables		**Points assigned**
P_CRT		
NO		0
YES		15
L_FUP		
1 month		3
2 months		7
3 months		10
4 months		14
5 months		17
6 months		21
7 months		24
8 months		28
9 months		31
10 months		34
11 months		38
12 months		41
Total points score	**Risk score**	**Risk of SEMS complication %**
-6	-2.1972	10
13	-1.3863	20
25	-0.8473	30
36	-0.4055	40
45	0.0000	50
55	0.4055	60
65	0.8473	70
78	1.3863	80
86	2.1972	85
100	2.3763	91.15

months, or 180 days, (21 points), is assigned a total score of 36, which translates into a 40% probability of developing a complication.

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Summary

Self-expanding metal stent positioning is the recommended method for palliation of dysphagia due to esophageal cancer, although it is not free from complications. In this work we identify predictor variables for quantifying the risk of stent-related complications. The results, based on a multivariate logistic regression, would allow clinicians to stratify patients according to the risk of developing complications in such a way to design the most suitable palliative treatments.

Keywords: Logistic regression; Risk assessment; Esophageal stent; Nomogram, Prognostic rule