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ORIGINAL ARTICLE

C-reactive protein to albumin ratio is a key indicator in a predictive model for anastomosis leakage after esophagectomy: Application of classification and regression tree analysis

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Anastomotic leak; C-reactive protein; decision tree; esophagectomy; logistic model.

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Abstract

Background: Anastomotic leakage (AL), a serious complication after esophagectomy, might impair patient quality of life, prolong hospital stay, and even lead to surgery-related death. The aim of this study was to show a novel decision model based on classification and regression tree (CART) analysis for the prediction of postoperative AL among patients who have undergone esophagectomy.
Methods: A total of 450 patients (training set: 356; test set: 94) with perioperative information were included. A decision tree model was established to identify the predictors of AL in the training set, which was validated in the test set. A receiver operating characteristic curve was also created to illustrate the diagnostic ability of the decision model.
Results: A total of 12.2% (55/450) of the 450 patients suffered AL, which was diagnosed at median postoperative day 7 (range: 6–16). The decision tree model, containing surgical duration, postoperative lymphocyte count, and postoperative C-reactive protein to albumin ratio, was established by CART analysis. Among the three variables, the postoperative C-reactive protein to albumin ratio was identified as the most important indicator in the CART model with normalized importance of 100%. According to the results validated in the test set, the sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the prediction model were 80%, 98.8%, 88.9%, 97.6%, and 96.8%, respectively. Moreover, the area under the receiver operating characteristic curve was 0.95.
Conclusion: The decision model based on CART analysis presented good performance for predicting AL, and might allow the early identification of patients at high risk.

Introduction

The morbidity and mortality resulting from anastomotic leakage (AL) after esophagectomy have steadily decreased during the last several decades with improvements in surgical techniques and management during the perioperative period[1] In spite of these advances, AL remains a significant cause of surgery-related death and an impairment to quality of life[2] AL prolongs hospital stay, increases expenses, and has been proven to be associated with postoperative tumor recurrence[3] Without timely or correct treatment, AL can lead to severe chest or mediastinal infections, which can be life-threatening[4] Therefore, it is particularly important to construct methods that could help to identify high-risk postoperative patients in order to administer timely treatment.

The process of AL development induces a strong systematic inflammatory response. Previous studies have shown that some circulating acute phase proteins (such as C-reactive protein [CRP] and albumin) are associated with surgery-related systematic inflammatory response[5] Postoperative CRP has been assessed as a good indicator for the early detection of AL after colorectal surgery and esophagectomy and in rectal cancer and esophageal cancer in both neoadjuvant and non-neoadjuvant patients[6–8] Albumin is a sensitive response indicator to surgical stress; postoperative albumin has been evaluated as a potential predictor of clinical complications[9] A novel indicator, the CRP to albumin ratio (CAR), is used to identify patients who have a high probability of postoperative complications; the diagnostic accuracy of the ratio is superior to CRP alone for the prediction of postoperative complications after colorectal surgery[10] However, few studies have reported an association between CAR and AL after esophagectomy. In this study, we hypothesized that postoperative CAR could be a potential predictor for AL after esophagectomy.

In addition, the mainstream methods for predicting AL after esophagectomy are based on traditional statistical techniques (e.g. logistic regression, Cox proportional hazards regression) and some serological and biochemical indicators[4,11–13] However, shortcomings in traditional regression analysis exist. Particularly, in this study, CAR as a composite indicator has a multicollinearity relationship with CRP and albumin, which may lead to the wrong identification of relevant predictors in regression analysis[14] Classification and regression tree (CART), as a data mining technique, is ideally suitable for the generation of clinical rules, which often enables the detection of complex interactions between predictors (including predictors with multicollinearity), which may be difficult or impossible to uncover using traditional statistical techniques[15] CART has been shown to perform as well or better than other traditional statistical techniques, such as logistic regression analysis, and is increasingly being applied to diagnose disease and predict outcomes or complications in patients, including diabetes, trauma, and cancer.[16–19] To the best of our knowledge, CART analysis has not previously been used to assess the predictors of AL in patients after esophagectomy.

In the present study, we used CART analysis to construct a decision model for predicting the presence of AL in patients after esophagectomy using perioperative data (including CAR) and then evaluated the predictive performance of the decision model.

Methods

General information

The data of 461 patients who underwent esophagectomy and reconstruction of the esophageal tract in Jinling Hospital of Nanjing Medical University from January 2017 to April 2018 were retrospectively evaluated and enrolled. Patients were diagnosed by pathological examination of tumor tissue obtained during surgery. Of the 461 patients, we excluded four cases without sufficient clinicopathological data, five who suffered from distant metastasis, and two who died of early cancer recurrence. Of the remaining 450 cases, 353 men and 97 women were included (mean age 64.26 $\pm$ 8.4 years).

The perioperative data of the 450 patients were collected and summarized and included: gender, age, body mass index, history of prior chemotherapy and/or radiotherapy, diabetes, smoking history, drinking history, chest operation history, and location of tumor recorded from the postoperative histology findings. The biochemical parameters included preoperative: leukocyte, lymphocyte, neutrophil, erythrocyte, hemoglobin, thrombocyte, CRP, and albumin counts.

The surgery-related data included were the duration of surgical produce (from skin incision to closure), American Society of Anesthesiologists (ASA) score, methods of anastomosis, and the type of surgery. The following surgical parameters were considered: tumor size, tumor histology, pathologic tumor stage, and tumor differentiation.

In all cases, white blood cells (WBCs), lymphocytes, neutrophils, red blood cells (RBCs), hemoglobin (Hb), thrombocyte, CRP, and albumin were measured on the third postoperative day (POD 3). None of the patients in our study were administered intravenous albumin supplementation. The postoperative CAR was calculated based on the results of laboratory tests. The calculation formula is as follows: CAR = (CRP on POD3)/(albumin on POD 3).

Definition of anastomotic leakage

AL was defined as follows: (i) the disruption of the anastomosis that leads to the outflow of the intraluminal content, which is sufficient to cause clinical symptoms[20] and/or (ii) leaks confirmed by chest computed tomography, endoscopy, or surgical exploration.

Decision tree modeling and validation

The 450 cases were split into two sets (training set with 356 patients; test set with 94 patients) according to the principle of simple random sampling. The training set was used to construct the decision tree model, which was then verified by the test set. All patients agreed to participate and signed informed consent. The Institutional Ethics Committee approved the study based on the principles of the Declaration of Helsinki.

Univariable analysis was performed to screen the candidate variables. CART was then performed on the training set to construct a decision tree model using these candidate variables. Beginning with a root node that contained all patients in the training set, all candidate variables were checked by recursive iterative algorithm to find the best variable to split the root node into two branches based on the Gini impurity index[21] The tree branches were then divided into different child nodes that included a subgroup of patients. The process of node splitting was repeated for each predictor in the model and continued recursively until the cases were divided into two homogeneous groups: with and without AL.[22] Pre pruning was carried out to avoid overfitting the CART model. The maximum tree depth was set to three layers; the minimum cases of parent and child node were both set to five. The optimal tree model was selected according to its predictive accuracy and clinical relevance.

The performance of the prediction model was validated by the test set. In order to evaluate the accuracy of the prediction model, we calculated the overall sensitivity, specificity, false positive and negative rates, positive and negative predictive values, and diagnostic accuracy of the model and established receiver operating characteristic (ROC) curves.

Statistical analysis

We used the χ^2 or Fisher's exact test, as appropriate, for categorical variables. A Shapiro–Wilk test was used to assess whether the continuous data was normally distributed. On the basis of the results of the Shapiro–Wilk test, continuous variables were compared using Student's *t* or Mann–Whitney non-parametric tests, as appropriate. Data were analyzed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). *P* values < 0.05 were defined as statistically significant.

Results

Patient characteristics

The prevalence of AL among 450 patients was 12.2% (55/450). Patients with AL in this study were diagnosed at median postoperative day 7 (range: 6–16). Characteristics of the training and validation datasets are presented in Table 1. There were no statistical differences between the two groups in any of the 35 variables studied ($P > 0.05$), indicating that clinical characteristics in the two data sets were well distributed. Considering that leakages at cervical anastomosis and intrathoracic anastomosis may cause different degrees of infection, we performed independent sample T analysis to identify whether there was a statistical

Table 1 Characteristics of patients used in the data set

No.	Variable	Training (*n* = 356)	Test (*n* = 94)	*P*
1	Gender			
	Male	281	72	0.90
	Female	75	22	
2	Age (years)	64.34 ± 8.41	64.12 ± 8.39	0.82
3	BMI (kg/m^2)	23.01 ± 3.22	23.19 ± 3.16	0.57
4	History of prior chemotherapy and/or radiotherapy			
	Yes	292	83	0.16
	No	64	11	
5	Diabetes			
	Yes	331	88	0.83
	No	25	6	
6	Smoking history			
	Yes	177	47	0.96
	No	179	47	
7	Drinking history			
	Yes	199	59	0.23
	No	157	35	
8	Chest operation history			
	Yes	350	93	0.80
	No	6	1	
9	Location of tumor			
	Upper	35	4	0.16
	Middle	215	56	
	Lower	106	34	
10	Preoperative WBC (10^9/L)	5.81 ± 1.97	5.68 ± 1.70	0.53
11	Preoperative lymphocyte (10^9/L)	1.66 ± 0.56	1.65 ± 0.59	0.85
12	Preoperative neutrophil (10^9/L)	3.61 ± 1.80	3.51 ± 1.49	0.62
13	Preoperative RBC (10^{12}/L)	4.31 ± 0.56	4.42 ± 0.46	0.10
14	Preoperative Hb (g/L)	131.6 ± 19.9	132.0 ± 15.5	0.25
15	Preoperative thrombocyte (10^9/L)	188.6 ± 60.8	204.3 ± 68.9	0.26
16	Preoperative CRP (mg/L)	6.3 ± 22.6	4.14 ± 6.0	0.35
17	Preoperative albumin (g/L)	41.17 ± 4.66	41.90 ± 4.19	0.16
18	ASA score			
	1	288	77	0.97
	2	57	14	
	3	11	3	
19	Method of anastomosis			
	Cervical anastomosis	267	69	0.75
	Intrathoracic anastomosis	89	25	
20	Type of surgery			
	Open operation	180	49	0.08
	VATS	135	27	
	RATS	41	18	
21	Tumor size (cm)			
	< 3	129	31	0.77
	3–5	156	45	
	> 5	71	18	
22	Tumor histology			
	SCC	326	89	0.62
	AC	5	1	
	ASC	2	1	

Table 1 Continued

No.	Variable	Training (n = 356)	Test (n = 94)	P
	Other	23	3	
23	Pathologic tumor stage			
	I	140	36	0.96
	II	75	21	
	III	130	35	
	IV	11	2	
24	Tumor differentiation			
	High	96	22	0.72
	Medium	214	61	
	Low	46	11	
25	Surgical duration (minutes)	246.4 ± 65.8	244.9 ± 68.5	0.54
26	Postoperative WBC (10^9/L)	11.12 ± 3.36	11.30 ± 3.37	0.64
27	Postoperative lymphocyte count (10^9/L)	0.74 ± 0.34	0.78 ± 0.36	0.15
28	Postoperative neutrophil count (10^9/L)	9.72 ± 3.16	9.83 ± 3.20	0.76
29	Postoperative RBC (10^{12}/L)	3.84 ± 0.58	3.88 ± 0.47	0.13
30	Postoperative Hb (g/L)	116.9 ± 19.3	118.9 ± 14.5	0.28
31	Postoperative thrombocyte (10^9/L)	173.8 ± 59.2	182.8 ± 57.8	0.19
32	Postoperative CRP (mg/L)	77.7 ± 70.5	73.1 ± 51.4	0.48
33	Postoperative albumin (g/L)	33.6 ± 3.93	33.9 ± 3.74	0.51
34	Postoperative CRP/albumin	2.41 ± 2.31	2.23 ± 1.79	0.50
35	AL			
	Yes	311	84	0.59
	No	45	10	

AC, adenocarcinoma; ASC, adenosquamous carcinoma; AL, anastomotic leakage; ASA, American Society of Anesthesiologists; BMI, body mass index; CRP, C-reactive protein; Hb hemoglobin; RATS, robot-assisted thoracic surgery; RBC, red blood cell; SCC, squamous cell carcinoma; VATS, video-assisted thoracic surgery; WBC, white blood cell.

difference between the two methods. A total of 55 patients suffered from AL; there was no statistical difference between the CARs of the two anastomotic methods: (cervical anastomosis n = 45, CAR value: 5.67 ± 2.54; intrathoracic anastomosis n = 10, CAR value: 5.64 ± 2.59; P = 0.97). The non-AL group consisted of 395 patients; the results of independent sample T analysis were: cervical anastomosis (n = 291) CAR value: 2.01 ± 1.84; intrathoracic anastomosis (n = 104) CAR value: 1.67 ± 1.34 (P = 0.09).

Classification and regression tree (CART) modeling in the training set

The results of univariate analysis in the training set revealed that ASA score, tumor size, pathologic tumor stage, surgical duration, postoperative lymphocyte count, postoperative CRP, preoperative RBC, postoperative albumin, and postoperative CAR were significantly different (P < 0.05). The results are summarized in Table 2.

CART analysis was performed using the above nine candidate variables screened by univariate analysis. Postoperative CAR was the most important factor, with normalized importance of 100%. (Fig 1).

In order to avoid overfitting the predictive model, prepruning was performed to ensure the optimal predictive accuracy of the decision tree.[23] We removed some variables that were relatively less important (normalized importance < 20%), such as preoperative RBC, tumor node metastasis, tumor size, and ASA score. As illustrated in Figure 2, the ultimate tree model consisted of three variables (postoperative CAR, surgical duration, postoperative lymphocyte count) with four terminal nodes.

By traversing every possible value of each variable, the best split point could be identified by CART algorithm basing on the Gini impurity index[24] the cutoff values of the three variables were chosen by the CART algorithm. The postoperative CAR was considered the initial splitting variable, with a cutoff value of 4.25. Among patients with a postoperative CAR ≤ 4.25, surgical duration was considered as the second splitting variable, with a cutoff value of 405 minutes. A low-risk group was composed of node 3 (postoperative CAR ≤ 4.25, surgical duration ≤ 405 minutes), with a possibility of AL of 3.5% (10/289). A high-risk group was composed of node 4 (postoperative CAR ≤ 4.25, surgical duration > 405 minutes), with a possibility of AL of 75% (3/4). Among patients with a postoperative CAR > 4.25, the cutoff values were 0.39 for postoperative lymphocytes. A relatively high-risk group consisted of node 6 (postoperative CAR > 4.25, postoperative lymphocyte > 0.39), with a possibility of AL of 41.5% (22/53). A high-risk group was made up of node 5 (postoperative CRP/albumin > 4.25, postoperative lymphocyte ≤ 0.39), with a possibility of AL of 100% (10/10).

Using all of the variables in the model, we constructed ROC curves to access the accuracy of the CART model. The area under the ROC curve was 0.92 (Fig 3).

Validation of CART analysis in the test set

To evaluate the predictive accuracy of the model, the established CART model was verified in the test set (n = 94). According to the results, the overall sensitivity, specificity, false positive and negative rates, positive and negative predictive values, and diagnostic accuracy of the tree model for AL were 80%, 98.8%, 1.2%, 20%, 88.9%, 97.6%, and 96.8%, respectively (Table 3). An ROC curve for the CART model in the test set was built, the area of which was 0.95 (Fig 4).

Table 2 Univariate analysis of factors affecting AL after esophagectomy

No.	Variable	Non-AL (n = 311)	AL (n = 45)	P
1	Gender			
	Male	241	40	0.08
	Female	70	5	
2	Age (years)	64.26 ± 8.42	64.87 ± 8.42	0.65
3	BMI (kg/m^2)	23.07 ± 3.31	22.62 ± 2.56	0.29
4	History of prior chemotherapy and/or radiotherapy			
	Yes	256	37	0.99
	No	55	8	
5	Diabetes			
	Yes	292	39	0.08
	No	19	6	
6	Smoking history			
	Yes	157	20	0.45
	No	154	25	
7	Drinking history			
	Yes	170	29	0.22
	No	141	16	
8	Chest operation history			
	Yes	305	45	0.39
	No	6	0	
9	Location of tumor			
	Upper	33	2	
	Middle	181	34	
	Lower	97	9	0.08
10	Preoperative WBC (10^9/L)	5.80 ± 1.86	5.93 ± 2.60	0.66
11	Preoperative lymphocyte (10^9/L)	1.66 ± 0.57	1.67 ± 0.50	0.94
12	Preoperative neutrophil (10^9/L)	3.60 ± 1.68	3.75 ± 2.54	0.59
13	Preoperative RBC (10^{12}/L)	4.28 ± 0.55	4.52 ± 0.63	0.006
14	Preoperative Hb (g/L)	130.8 ± 20.1	136.6 ± 18.4	0.07
15	Preoperative thrombocyte (10^9/L)	187.5 ± 59.1	196.3 ± 71.5	0.36
16	Preoperative CRP (mg/L)	5.78 ± 15.42	10.28 ± 49.25	0.55
17	Preoperative albumin (g/L)	41.1 ± 4.60	41.65 ± 5.02	0.47
18	ASA score			
	1	263	25	0.00
	2	41	16	
	3	7	4	
19	Method of anastomosis			
	Cervical anastomosis	245	38	0.38
	Intrathoracic anastomosis	66	7	
20	Type of surgery			
	Open operation	156	24	0.55
	Vats	117	18	
	Rats	38	3	
21	Tumor size (cm)			
	< 3	120	9	0.03
	3–5	132	24	
	> 5	59	12	
22	Tumor histology			
	SCC	286	40	0.81
	AC	4	1	
	ASC	0	2	
	Other	21	2	
23	Pathologic tumor stage			
	I	121	19	0.04
	II	72	3	
	III	110	20	

Table 2 Continued

No.	Variable	Non-AL (n = 311)	AL (n = 45)	P
	IV	8	3	
24	Tumor differentiation			
	High	84	11	0.57
	Medium	185	30	
	Low	42	4	
25	Surgical duration (minutes)	240.5 ± 63.89	286.4 ± 65.79	0.00
26	Postoperative WBC (10^9/L)	11.19 ± 3.35	10.64 ± 3.42	0.31
27	Postoperative lymphocyte count (10^9/L)	0.74 ± 0.34	0.64 ± 0.31	0.048
28	Postoperative neutrophil count (10^9/L)	9.78 ± 3.18	9.35 ± 3.06	0.40
29	Postoperative RBC (10^{12}/L)	3.84 ± 0.58	3.83 ± 0.64	0.85
30	Postoperative Hb (g/L)	117.3 ± 19.7	114.8 ± 17.1	0.41
31	Postoperative thrombocyte (10^9/L)	174.23 ± 58.73	170.73 ± 63.18	0.71
32	Postoperative CRP (mg/L)	64.24 ± 59.15	170.5 ± 72.99	0.00
33	Postoperative albumin (g/L)	33.81 ± 3.85	31.9 ± 4.14	0.00
34	Postoperative CRP/albumin	1.96 ± 1.87	5.52 ± 2.66	0.00

AC, adenocarcinoma; AL, anastomotic leakage; ASA score, American Society of Anesthesiologists (ASA) score; ASC, adenosquamous carcinoma; BMI, body mass index; CRP, C-reactive protein; Hb hemoglobin; RATS, robot-assisted thoracic surgery; RBC, red blood cell; SCC, squamous cell carcinoma; VATS, video-assisted thoracic surgery; WBC, white blood cell.

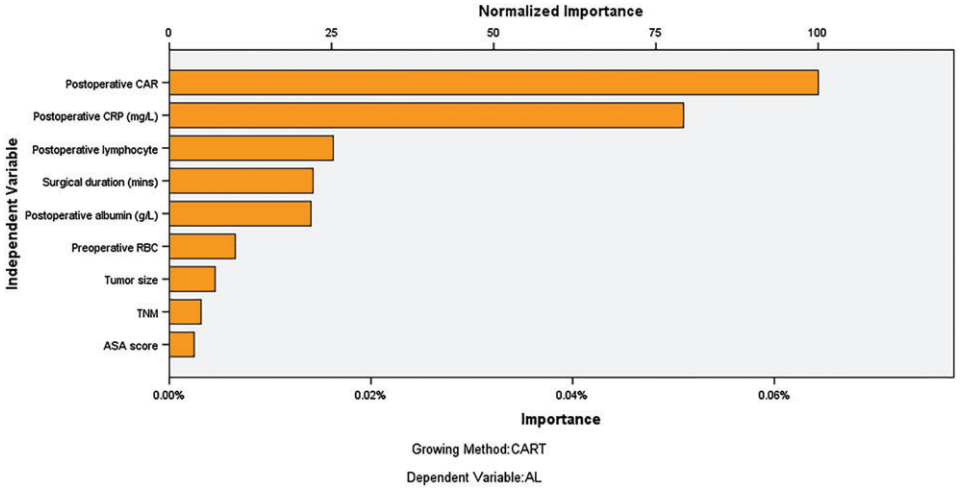

Figure 1 Normalized importance of variables in predicting anastomotic leakage (AL) after esophagectomy in decision model tree. ASA, American Society of Anesthesiologists; CAR, C-reactive protein to to albumin ratio; CRP, C-reactive protein; CART, classification and regression tree; RBC, red blood cell; TNM, tumor node metastasis.

Discussion

AL is defined as an esophagogastrostomy anastomotic dehiscence diagnosed during the postoperative period. If it cannot be diagnosed in time, it may result in disastrous consequences, such as septic shock, mediastinitis, acute respiratory distress syndrome, and death.[25] A diagnosis of AL is usually made on the seventh postoperative day, after the onset of clinical symptoms[1,26] Therefore, precise prediction of patients at high risk of AL prior to the incidence of symptoms may decrease morbidity and mortality. In this study, a decision model for predicting the presence of AL in patients after esophagectomy was constructed from a training dataset using the CART algorithm. The accuracy of the prediction model was then validated with a test dataset. According to results verified by the test set, the decision model had good performance and may help clinicians to diagnose and administer treatment in a timely manner.

Recently, decision tree algorithms have been found to accomplish the same goals but with fewer assumptions or greater accuracy than other traditional statistical techniques, such as logistic regression analysis[27] As a technique that is ideally suited to the generation of clinical decision rules, CART analysis has a number of advantages compared to other traditional statistical methods[28,29] There have been examples of CART tree algorithms being used to create clinical decision rules with proven effectiveness. For instance, one study used CART analysis to develop a decision model that may help clinicians to make an early diagnosis of severe acute pancreatitis[30] Another study established a decision tree model for the prediction of congestive heart failure; the sensitivity and specificity of the

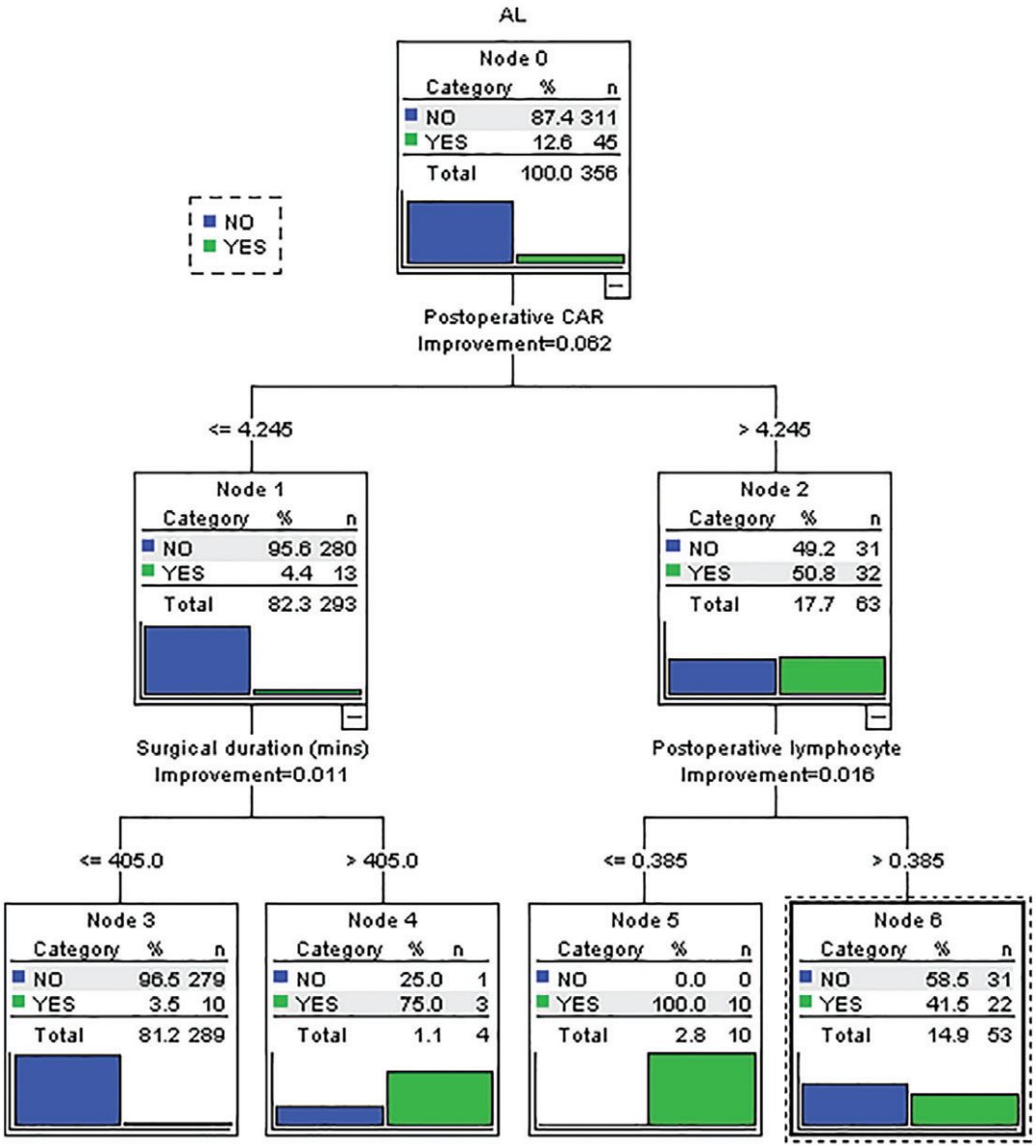

Figure 2 Decision tree model for the prediction of anastomotic leakage (AL) in the training set by classification and regression tree analysis. CAR, C-reactive protein to to albumin ratio.

prediction model were 97.2% and 97.7%, respectively[31] Yang Fei *et al.* designed CART and logistic regression models for the prediction of portosplenomesenteric vein thrombosis and found that the CART model demonstrated better overall properties than the logistic regression model[11] However, CART analysis has not been used to predict the occurrence of AL after esophagectomy.

In the present study, we presupposed that the novel indicator CAR might be a potential predictor for AL in patients after esophagectomy. CAR is a composite indicator composed of CRP and albumin, which means that if the three indicators (CAR, CRP, and albumin) were applied to multiple regression analysis, the collinearity between them will affect the accuracy of the regression equation and contribute to unreliable results[14] However, CART analysis is not hindered by multicollinearity; collinearity is often used to an advantage in tree algorithms[32] As illustrated in Figure 1, we successfully integrated the three indicators into the prediction model using CART analysis and obtained their normalized importance for AL, which were 100%, 79.2%, and 21.8%, respectively.

According to the results verified in the test set, the area under ROC curve revealed that the CART model had good predictive accuracy (sensitivity 80%, specificity 98.8%,

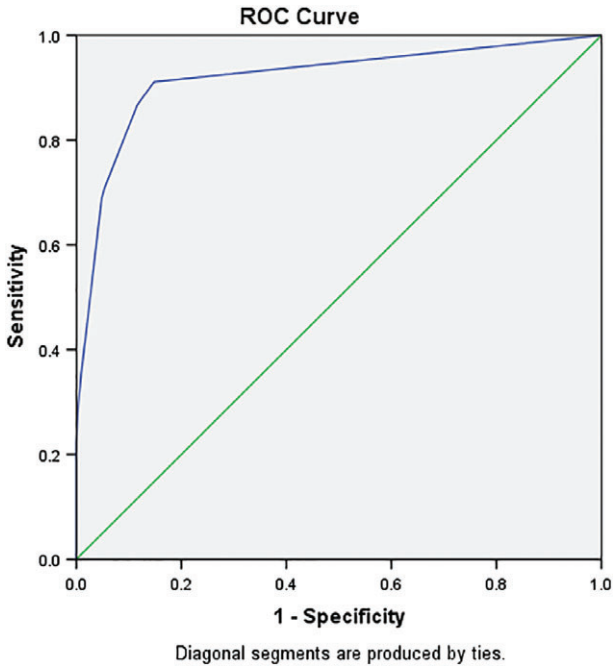

Figure 3 Receiver operating characteristic (ROC) curve for the classification and regression tree model in the training set.

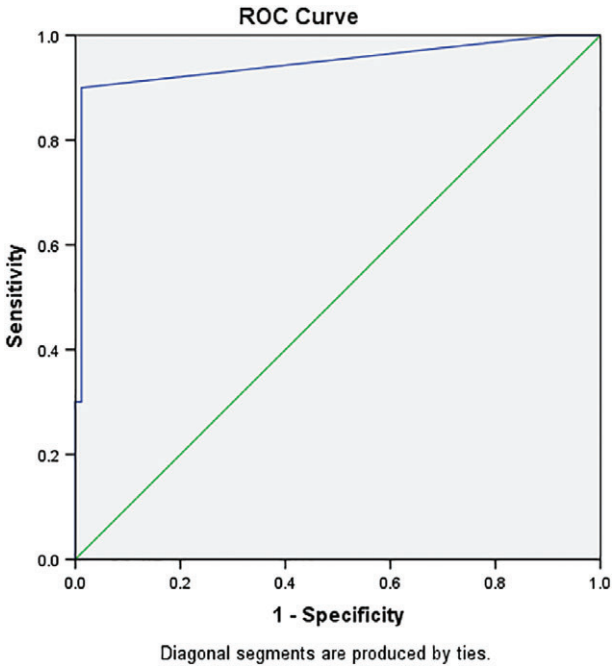

Figure 4 Receiver operating characteristic (ROC) curve for the classification and regression tree model in the test set.

Table 3 Performance of the predictive model for AL verified in the test set

	Observed		
Predicted	Yes	No	
Yes	8	1	PPV 88.9% (8/9)
No	2	83	NPV 97.6% (83/85)
	Sensitivity	Specificity	Diagnostic accuracy
	80% (8/10)	98.8% (83/84)	96.8%

AL, anastomotic leakage; NPV negative predictive value; PPV positive predictive value.

diagnostic accuracy 96.8%, area under ROC curve 0.95). CAR was identified as the most important indicator of AL in this trial. The novel index CAR, as a sensitive marker of systemic inflammatory response, is a potential predictive indicator for clinical outcomes. For example, one study showed that CAR at admission can be used as an independent predictor of 180-day mortality in patients with severe sepsis or septic shock and proved the predictive value of the indicator[33] Gibson *et al.* found that elevated CAR is an early predictor of steroid-refractory acute severe ulcerative colitis.[34] In our study, we clarified the association between CAR and AL; patients with elevated CAR on POD 3 had a higher tendency to develop AL, approximately four days prior to the median time to AL diagnosis. This indicates that clinicians could monitor these indicators to determine patients at high risk of AL, prior to the appearance of clinical symptoms. To exclude AL in high-risk patients we could conduct close clinical assessment and radiological examination in our center; however, we prefer to continue with the administration of enteral nutrition to low-risk patients. This measure may bring significant benefits to patients because postoperative enteral nutrition has been proven to reduce the incidence of life-threatening surgical complications and improve the completion rate of clinical pathways for thoracic esophagectomy[35]

In conclusion, the decision tree model (consisting of surgical duration, postoperative lymphocyte count, and postoperative CAR) showed good performance for predicting AL after esophagectomy using the CART algorithm; the CAR was proven the key indicator to the model. The CART model may help clinicians to identify patients at high risk of developing AL and to administer timely treatment.

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Disclosure

No authors report any conflict of interest.

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