Original Article

Clinical assessment of airway stent placement in patients with malignant airway lesions

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Background: Airway stent placement has been proven as a satisfactory treatment of advanced malignant airway lesions. However, stent-related complications could impact the therapeutic effect of this treatment. This study aimed to assess the application of airway stents, including the clinical effects, and to explore high-risk factors for stent-related complications.

Methods: A retrospective cohort study of lung cancer (LC) patients and esophageal cancer (EC) patients was conducted at our center. Patients who received stent placement for malignant airway lesions from January 2014 to July 2017 were included in the study. Patient clinical status and stent-related complications, including granulation tissue formation, restenosis, atelectasis, migration, mucous plugging and infection were comprehensively analyzed.

Results: Fifty-six symptomatic patients who underwent 66 stent procedures were included. There was an immediate relief of symptoms after stent placement, and the Karnofsky Performance Status (KPS) scores significantly improved (56.67±23.52 versus 79.05±20.71; P<0.001). Among all the patients, general anesthesia (P=0.038) and pre-stent non-surgical therapy (P=0.048) were risk factors for granulation. A Charlson comorbidity index (CCI) <3 (P=0.008) and a procedure duration time >110 min (P=0.005) were associated with an increased risk of restenosis. Stent placement only in the main trachea (P=0.049) increased the risk of stent migration. Stent placement in the carina or upper airways (P=0.041) increased the risk of mucous plugging. The stent length (>60 mm) had a direct correlation with both mucous plugging in LC patients (P=0.003) and granulation tissue formation in EC patients (P=0.019).

Conclusions: Airway stent placement immediately and significantly improved the clinical symptoms for patients with advanced malignant airway lesions. High-risk factors for different stent-related complications were identified, which provided evidence for further clinical improvement with airway stents.

Keywords: Bronchoscopy; malignant airway lesions; airway stent placement; stent-related complications; risk factors

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Introduction

Central airway obstruction (CAO) or tracheoesophageal fistulas are life-threatening conditions of progressive stage lung cancer (LC) patients or esophageal cancer (EC) patients after esophagectomy. CAO is defined as occlusion of >50% of the trachea, main bronchi, bronchus intermedius, or a lobar bronchus. Malignant CAO can cause clinical symptoms including dyspnea, stridor and obstructive pneumonia, which account for 20–30% of

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patients with primary LC (1-3).

Airway stenting is the optimal palliation therapy for advanced cancer patients with extrinsic compression, endoluminal tumors or tracheoesophageal fistulas. By maintaining airway patency in patients with malignant airway stenosis and establishing airway integrity in patients who suffer from tracheoesophageal fistulas, stent placement can improve symptoms rapidly. However, stents-related complications also occur, including mucous plugging, tumor restenosis, stent migration, granulation tissues formation, fistula enlargement, stent fracture, perforation and hemorrhage. These short- or long-term complications can occur with both silicone stents and self-expandable metallic stents (SEMSs) (4,5).

Therapeutic bronchoscopy includes stent placement; to be more specific, it also contains the technique for tumor debulking, which includes mechanical debulking, thermocoagulation, argon-plasma coagulation, laser therapy, cryotherapy, balloons dilation and microdebriders (4). It has been reported that the 30-day mortality after placement of stents was 14.8%, and one of the risk factors for increased 30-day mortality was stent deployment. Thus, the balance between intervention and expected complications is very important for the clinical application of the stent (6). Some bronchoscopists have reported their single or multi-center experiences with the effectivity of airway stenting and accompanied procedural complications; however, few studies have analyzed the risk factors for each stent-related complication or compared the incidence of complications between different cancers (7-15).

The present study aimed to assess the application of airway stents, including the clinical effects, and to explore the high-risk factors for specific complications. We described our monocentric experience to determine the safety and feasibility for the deployment of SEMSs or silicone stents in the management of patients with malignant airway obstruction or fistulas.

Methods

Patients

This study includes a retrospective cohort of LC patients and EC patients with malignant CAO or tracheoesophageal fistulas who presented for placement of an airway stent in parallel between January 2014 and July 2017 at our center. Ethics review approval from the First Affiliated Hospital, Zhejiang University School of medicine was obtained for this study (ethics approval number: 2017-668).

Symptomatic patients with malignant CAO or tracheoesophageal fistula of the trachea, carina, or lobar bronchia had a flexible bronchoscopy and computed tomography (CT) scan of the chest. A full medical history, physical examination, CT imaging, type of stents, type of bronchoscope, treatment modalities, operation-related complications and outcomes were assessed by electronic medical records. The Charlson comorbidity index (CCI) was calculated to evaluate the physical condition in each patient. The severity of stenosis or fistulas and the diameter and length of the trachea were measured by 3-dimensional (3D) airway reconstruction. In all the patients, dyspnea or dysphagia grading and Karnofsky Performance Status (KPS) were precisely assessed before and after the placement of stents. The first follow-up bronchoscopy was performed 24 hours after stent placement.

During the follow-up period, esophageal and respiratory symptoms as well as dyspnea or dysphagia grading were monitored. All the possible stent-related complications were confirmed with bronchoscopic and 3D airway reconstruction. Flexible bronchoscopy was used to reassess the patency and stent position. The follow-up data were obtained from the outpatient clinic chart reviews systems or by telephone calls to patients. The last follow-up occurred in August 2017.

Stent placement

The procedures for the placement of the SEMSs were as follows. First, bronchoscopists checked the position of stenosis or fistula by a bronchoscope. Next, the guide-wires were inserted into the diseased trachea or the right and left bronchi. Under bronchoscopic guidance, the delivery system was advanced over the guide-wires into the position of the carina. By retracting the introducer sheath rapidly, the stents were then released. After confirmation that the stents were deployed at the right level, bronchoscopists completely withdrew the introducer sheath and guide-wires.

General anesthesia was required for rigid bronchoscopy (Karl-Storz, Tuttlingen, Germany), while the procedure using the flexible bronchoscopy (BF 1T260, Olympus, Tokyo, Japan) was performed under local anesthesia by sprinkling 2–3 mL of 2% lidocaine via the catheter.

The self-expanding covered metallic stent had a tracheal limb measuring 10 to 22 mm in diameter and 20 to 100 mm in length. For the Y stent, the diameter of the left or right main bronchi varied from 10 to 18 mm, and the

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length varied from 10 to 40 mm. The size of the stents was customized to fit different patients' airways. A silicone stent was seldom used for therapeutic bronchoscopy in our center. During the placement, if needed, we would inflate an expansion balloon three or four times for 20 seconds, and argon plasma coagulation (40-Watt, blended mode-continuous flow) was used for cutting the neoplasm in the airway.

Statistical analysis

Binary logistic regression models were adopted to determine the association between stent-related complications and known covariates including gender, age, presence of malignant disease, pathology, history of smoking or drinking, CCI, pre-stent therapy, stent location, airway situation, deployment duration and stent length. Continuous variables were compared by Student's *t*-test and summarized by means and ranges. The categorical data were compared using a Fisher's exact text and summarized with frequencies. A two-sided significance level of 0.05 was used for all the statistical tests, unless specifically clarified. All the statistical analyses were performed using SPSS software 24.0 (IBM statistics, SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Between January 2014 and July 2017, a total of 56 patients with malignant airway stenosis or fistula underwent stent placement. Twenty-five patients (12 in LC group, 13 in EC group) received a total of 33 Y-shaped stents. Only 3 patients received Y-shaped silicone stents. For metallic tube stents, 31 patients (17 in LC group, 14 in EC group) received a total of 33 stents. The baseline characteristics of these patients and the univariate analysis of the risk factors for the overall complications are shown in *Table 1*.

Clinical outcome

The stents were all successfully deployed, and there were no acute complications with any stent placement. More than half of the patients (66%) had remarkably downgraded dyspnea levels after the intervention therapy. Sixteen (28%) patients whose dyspnea grade was equal or less than grade I maintained their former grades. Additionally, three patients underwent mechanical ventilation after placement so that

Table 1 Clinical characteristics and risk factors analysis for the overall complications

Variable	Total cohort			Lung cancer group			Esophageal cancer group		
	N [n]	OR (95% CI)	P value	N [n]	OR (95% CI)	P value	N [n]	OR (95% CI)	P value
Gender			0.316			0.707			0.312
Female	11 [6]	1.0 (reference)		4 [2]	1.0 (reference)		7 [4]	1.0 (reference)	
Male	45 [17]	0.51 (0.13–1.92)	0.316	25 [10]	0.67 (0.08–5.54)	0.707	20 [7]	0.4 (0.07–2.34)	0.312
Age			0.999			0.999			0.999
<50	3 [3]	1.0 (reference)		3 [3]	1.0 (reference)		0	1.0 (reference)	
≥50	53 [20]	–	0.999	26 [9]	–	0.999	27 [11]	–	0.999
Primary disease			0.961						
Esophageal cancer	27 [11]	1.0 (reference)		–	–	–	–	–	–
Lung cancer	29 [12]	1.03 (0.35–2.98)	0.961	–	–	–	–	–	–

Table 1 (*continued*)

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Table 1 (*continued*)

Variable	Total cohort			Lung cancer group			Esophageal cancer group		
	N [n]	OR (95% CI)	P value	N [n]	OR (95% CI)	P value	N [n]	OR (95% CI)	P value
Smoking history			0.104			0.059			0.779
No	23 [7]	1.0 (reference)		10 [2]	1.0 (reference)		13 [5]	1.0 (reference)	
Yes	24 [13]	2.7 (0.82–8.95)	0.104	15 [9]	6 (0.93–38.63)	0.059	9 [4]	1.28 (0.23–7.19)	0.779
Unknown	9 [3]	–	–	4 [1]	–	–	5 [2]	–	–
Drinking history			0.77			0.679			0.937
No	27 [11]	1.0 (reference)		17 [7]	1.0 (reference)		10 [4]	1.0 (reference)	
Yes	20 [9]	1.19 (0.37–3.83)	0.77	8 [4]	1.429 (0.26–7.74)	0.679	12 [5]	1.07 (0.19–5.91)	0.937
Unknown	9 [3]	–	–	4 [1]	–	–	5 [2]	–	–
CCI			0.101			0.427			0.123
>3	37 [13]	1.0 (reference)		20 [8]	1.0 (reference)		17 [5]	1.0 (reference)	
≤3	11 [7]	3.23 (0.8–13.12)	0.101	5 [3]	2.25 (0.3–16.63)	0.427	6 [4]	4.8 (0.66–35.2)	0.123
Unknown	8 [3]	–	–	4 [1]	–	–	4 [2]	–	–
Indication			0.509			0.372			0.818
Airway neoplasm	28 [13]	1.0 (reference)		20 [10]	1.0 (reference)		8 [3]	1.0 (reference)	
Extrinsic compression	11 [5]	0.96 (0.24–3.9)	0.956	3 [1]	0.5 (0.04–6.44)	0.595	8 [4]	1.67 (0.23–12.22)	0.615
Fistula	17 [5]	0.48 (0.13–1.73)	0.262	6 [1]	0.2 (0.02–2.03)	0.174	11 [4]	0.95 (0.14–6.28)	0.96
Pathology			0.667			0.478			0.97
Others & unknown	17 [6]	1.0 (reference)		12 [4]	1.0 (reference)		4 [2]	1.0 (reference)	
Squamous carcinoma	35 [17]	1.73 (0.52–5.72)	0.368	13 [8]	2.8 (0.53–14.74)	0.224	23 [9]	1.04 (0.14–7.53)	0.97
Adenocarcinoma	4 [0]	–	0.999	4 (0)	–	0.999	0 (0)	–	–
Dyspnea grade			0.948			0.56			0.75
0 (none)	13 [5]	1.0 (reference)		6 [1]	1.0 (reference)		7 [4]	1.0 (reference)	
I (slight)	17 [8]	1.42 (0.33–6.17)	0.638	9 [5]	6.25 (0.5–77.49)	0.154	8 [3]	0.45 (0.06–3.57)	0.45
II (severe)	13 [5]	–	>0.999	5 [2]	3.33 (0.2–54.53)	0.398	8 [3]	0.45 (0.06–3.57)	0.45
III (stridor)	13 [5]	–	>0.999	9 [4]	4 (0.32–49.6)	0.28	4 [1]	0.25 (0.02–3.77)	0.317
Pre-stent therapy			0.621			0.551			0.93
Non-surgery	27 [12]	1.0 (reference)		15 [7]	1.0 (reference)		12 [5]	1.0 (reference)	
Surgery	29 [11]	0.76 (0.26–2.22)	0.621	14 [5]	0.64 (0.14–2.82)	0.551	15 [6]	0.93 (0.2–4.37)	0.93

Table 1 (*continued*)

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Table 1 (*continued*)

Variable	Total cohort			Lung cancer group			Esophageal cancer group		
	N [n]	OR (95% CI)	P value	N [n]	OR (95% CI)	P value	N [n]	OR (95% CI)	P value
Type of stents			0.689			0.43			0.816
Tube	31 [12]	1.0 (reference)		17 [6]	1.0 (reference)		14 [6]	1.0 (reference)	
Y-shapes	25 [11]	1.24 (0.43–3.63)	0.689	12 [6]	1.83 (0.41–8.27)	0.43	13 [5]	0.83 (0.18–3.88)	0.816
Stent length			0.814			0.314			0.528
<60 mm	27 [9]	1.0 (reference)		15 [4]	1.0 (reference)		12 [5]	1.0 (reference)	
≥60 mm	15 [5]	0.84 (0.21–3.44)	0.814	6 [3]	2.75 (0.39–19.67)	0.314	9 [2]	0.53 (0.08–3.76)	0.528
Unknown	14 [9]	–	–	8 [5]	–	–	6 [4]	–	–
Procedure duration			0.401			0.819			>0.999
<110 min	44 [18]	1.0 (reference)		24 [10]	1.0 (reference)		20 [8]	1.0 (reference)	
≥110 min	3 [2]	2.89 (0.24–34.31)	0.401	2 [1]	1.4 (0.08–25.14)	0.819	1 [1]	–	>0.999
Unknown	9 [3]	–	–	3 [1]	–	–	6 [2]	–	–
Number of stents			0.939			0.632			0.496
1	46 [19]	1.0 (reference)		23 [9]	1.0 (reference)		23 [10]	1.0 (reference)	
2	10 [4]	0.95 (0.24–3.82)	0.939	6 [3]	1.56 (0.26–9.47)	0.632	4 [1]	0.43 (0.04–4.82)	0.496
General anesthesia			0.689			0.979			0.582
No	31 [12]	1.0 (reference)		17 [7]	1.0 (reference)		14 [5]	1.0 (reference)	
Yes	25 [11]	1.24 (0.43–3.63)	0.689	12 [5]	1.02 (0.23–4.57)	0.979	13 [6]	1.54 (0.33–7.23)	0.582
Stent in the left main bronchus			0.805			0.913			0.816
No	33 [14]	1.0 (reference)		19 [8]	1.0 (reference)		14 [6]	1.0 (reference)	
Yes	23 [9]	0.83 (0.3–2.58)	0.805	10 [4]	0.92 (0.19–4.36)	0.913	13 [5]	0.83 (0.18–3.88)	0.816
Stent in the right main bronchus			0.689			0.822			0.701
No	25 [11]	1.0 (reference)		9 [4]	1.0 (reference)		16 [7]	1.0 (reference)	
Yes	31 [12]	0.8 (0.28–2.35)	0.689	20 [8]	0.83 (0.17–4.09)	0.822	11 [4]	0.74 (0.15–3.55)	0.701
Stent in the carina			0.164			0.173			0.466
No	42 [15]	1.0 (reference)		25 [9]	1.0 (reference)		17 [6]	1.0 (reference)	
Yes	14 [8]	2.4 (0.7–8.23)	0.164	4 [3]	5.33 (0.48–59.14)	0.173	10 [5]	1.83 (0.37–8.98)	0.455
Stent in the main trachea			0.31			0.303			0.496
No	24 [8]	1.0 (reference)		20 [7]	1.0 (reference)		4 [1]	1.0 (reference)	
Yes	32 [15]	1.77 (0.59–5.28)	0.31	9 [5]	2.32 (0.47–11.55)	0.303	23 [10]	2.31 (0.21–25.66)	0.496

N, number of patients; n, number of patients developing complications; CI, confidence interval; CCI, Charlson comorbidity index; OR, odds ratio.

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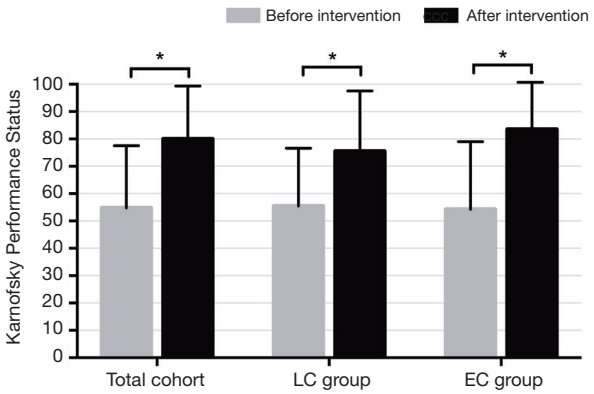

Figure 1 Change in Karnofsky Performance Status (KPS) after stent placement. *, statistically significant change. LC, lung cancer; EC, esophageal cancer.

dyspnea grade was not possible to assess. The 24-hour post-stent placement mean KPS significantly improved (79.05±20.71 *vs.* 56.67±23.52, P<0.001). By the subgroup analysis, the KPS improved in both the LC and EC groups (LC group: 55.45±21.15 *vs.* 75.45±22.07; P=0.001, and EC group: 54.29±24.72 *vs.* 83.57±16.92; P<0.001) (*Figure 1*). No patients died in the hospital. However, 10 patients (17.9%) died within 30 days.

Risk factors for specific complications

The multivariable analysis showed that patients with low CCI (<3) (P=0.048) were associated with an increased risk for overall complications (*Table 2*). The summary of specific stent-related complications is listed in *Table 3*. Fourteen percent of patients had more than two complications. All the complications occurred in the patients with metallic stents. The incidence of specific complications was similar in both groups. The median follow-up duration was 545 days.

We thoroughly analyzed all the potential risk factors in the total cohort, including the LC group and the EC group (*Table S1*), and identified the high-risk factors (*Table 4*). Among all the patients, pre-stent non-surgical therapy (P=0.048) and general anesthesia (P=0.038) were associated with an increased risk of granulation. Low CCI (<3) (P=0.008) and a long procedure duration (>110 min) (P=0.005) were associated with increased risk for restenosis. Stents only in the main trachea (P=0.049) led to stent migration. In addition, pre-stent surgical therapy (P=0.05) and extrinsic compression (P=0.058) had a marginal effect on migration. A tubular stent in the left/right bronchus (P=0.023) had a significant impact on atelectasis. Stenting the carina or the upper airways was associated with mucous plugging (P=0.041). Double placement was more common in EC patients (P=0.04), where pre-stent surgical therapy (P=0.012) and low CCI (<3) (P=0.028) became two high-risk factors for double placement. In the LC group, small cell lung cancer (P=0.035) and the stent length (>60 mm) (P=0.003) increased the risk of atelectasis and mucous plugging, respectively. In the EC group, a long procedure duration (>110 min) (P=0.037) and the stent length (>60 mm) (P=0.019) were associated with a higher incidence of lung infection and granulation, respectively.

Discussion

In this study, we revealed the efficacy and feasibility of placing airway stents for the management of malignant airway lesions, including airway neoplasm (*Figure 2*), tracheoesophageal fistula and extrinsic compression (*Figure 3*). The improvement of dyspnea grades and KPS suggested the immediate relief of symptoms. Almost all the patients received metallic stents because the advantages of metallic stents for treating malignant airway lesions were obvious, including higher long-time stent patency rates and lower migration rates (7,8). However, high complication rates have restricted the use of metallic stents. The Food and Drug Administration (FDA) advised the use of SEMSs only in cases in which surgery or placement of silicone stents were ineligible (9). In the current study, no significant factor was identified to increase the risk of overall complications. Nonetheless, the results might be affected by many factors, such as the different comorbidities, various baseline characteristics and patient heterogeneity. Then, we focused on each specific stent-related complication and made assessments systematically on this issue.

We found that pre-stent non-surgical therapy and general anesthesia were associated with higher granulation rates. Ingrowth of granulation tissue is a well-recognized complication for metallic stent placement with an occurrence rate of 20% (5,10-12). The higher incidence rates of granulation tissue were related to the underlying malignancies. Prior studies have shown that trauma and bacterial contamination can cause granulation (13). Additionally, general anesthesia was required for rigid bronchoscope, which may cause trauma, and the longer operation duration compared with conscious sedation increased the potential infection rates. A prior study suggested that conscious sedation was associated with

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Table 2 Multivariable logistic regression analysis for the overall complications

Variable	Total cohort			Lung cancer group			Esophageal cancer group		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Primary disease			0.810						
Esophageal cancer	1.0 (reference)	–	–	–	–	–	–	–	–
Lung cancer	1.25	0.20–7.63	0.810	–	–	–	–	–	–
Pre-stent therapy			0.479			0.468			0.795
Non-surgery	1.0 (reference)	–	–	1.0 (reference)	–	–	1.0 (reference)	–	–
Surgery	0.57	0.12–2.71	0.479	0.28	0.01–8.60	0.468	0.71	0.06–9.24	0.795
CCI[a]			0.048			0.461			0.158
>3	1.0 (reference)	–	–	1.0 (reference)	–	–	1.0 (reference)	–	–
≤3	8.27	1.02–66.94	0.048	4.26	0.09–200.46	0.461	8.40	0.44–161.40	0.158
Indication			0.826			0.981			0.996
Airway neoplasm	1.0 (reference)	–	–	1.0 (reference)	–	–	1.0 (reference)	–	–
Extrinsic compression	1.21	0.14–10.31	0.863	1.36	0.06–30.40	0.844	0.89	0.03–27.91	0.949
Fistula	0.59	0.07–4.95	0.629	–	–	0.999	1.05	0.05–20.55	0.977
Stent length[a]			0.674			0.169			0.465
<60 mm	1.0 (reference)	–	–	1.0 (reference)	–	–	1.0 (reference)	–	–
≥60 mm	1.52	0.21–10.88	0.674	10.19	0.37–279.28	0.169	0.27	0.01–8.94	0.465
General anesthesia			0.825			0.593			0.361
No	1.0 (reference)	–	–	1.0 (reference)	–	–	1.0 (reference)	–	–
Yes	1.26	0.16–9.63	0.825	0.42	0.02–9.95	0.593	5.82	0.13–254.64	0.361
Stent in the main trachea			0.945			0.917			0.888
No	1.0 (reference)	–	–	1.0 (reference)	–	–	1.0 (reference)	–	–
Yes	0.92	0.09–9.13	0.945	0.82	0.02–31.33	0.917	1.34	0.02–75.19	0.888

[a], unknown data was excluded from analysis. CI, confidence interval; CCI, Charlson comorbidity index; OR, odds ratio.

increased complication rates (6). We also observed that the length of stents (>60 mm) was a risk factor for granulation in the EC group. Longer stents mean a larger contact area on the inner surface of the trachea, with much more mucosal inflammation and granulation formation.

Several studies have reported the incidence of stent restenosis, ranging from 5% to 19.4% (13-16). The main causes of restenosis are the overgrowth of endoluminal tumors or granulation tissue, followed by fibrosis. Tumor or granulation tissue grows at the covered stent ends or through the uncovered stent wires. Our results suggest that a CCI <3 and a procedure duration >110 min are associated with an increased risk of restenosis. It is worth noting that a higher CCI was associated with a higher probability of deterioration after bronchoscopic therapy. The short life expectancy of patients with a high CCI may be inadequate for the development of long-term complications, such as stent restenosis. In our center, all the cases of restenosis were caused by fibrosis, and all of these patients suffered from airway neoplasm and received debulking therapies, including electrocautery, argon plasma coagulation or cryotherapy. All the debulking therapies were time-

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Table 3 Summary of the specific stent-related complications

Specific complications	Total cohort (N=56) (%)	Lung cancer group (N=29) (%)	Esophageal cancer group (N=27) (%)
Hemorrhage	1 (1.79)	1 (3.45)	0 (0)
Vocal cord paralysis	4 (7.14)	2 (6.9)	2 (7.41)
Lung infection	3 (5.36)	2 (6.9)	1 (3.7)
Restenosis	3 (5.36)	2 (6.9)	1 (3.7)
Fistula	2 (3.57)	0 (0)	2 (7.41)
Stent migration	5 (8.93)	1 (3.45)	4 (14.81)
Granulation	7 (12.5)	3 (10.34)	4 (14.81)
Mucous plugging	7 (12.5)	4 (13.79)	3 (11.11)
Bad expanding	1 (1.79)	0 (0)	1 (3.7)
Atelectasis	1 (1.79)	0 (0)	1 (3.7)
Pneumothorax	0 (0)	0 (0)	0 (0)
Double placement	10 (17.86)	2 (6.9)	8 (29.63)

Table 4 High-risk factors for each specific complication

Specific complications	High-risk factors	No. (%)	P value
All patients			
Granulation	Pre-stent non-surgical therapy	6 (10.71)	0.048
	General anesthesia	5 (8.93)	0.038
Restenosis	Low CCI (<3)	3 (5.36)	0.008
	Long procedure duration (>110 min)	2 (3.57)	0.005
Stent migration	Pre-stent surgical therapy	5 (8.93)	0.05
	Stents only in the main trachea	4 (7.14)	0.049
	Extrinsic compression	3 (5.36)	0.058
Atelectasis	Tubular stent in left/right bronchus	2 (3.57)	0.023
Mucous plugging	Stent in the carina or upper	6 (10.71)	0.041
Double placement	Pre-stent surgical therapy	9 (16.07)	0.012
	Esophageal cancer	8 (14.29)	0.04
	Low CCI (<3)	5 (8.93)	0.028
Lung cancer group			
Granulation	Low CCI (<3)	2 (6.9)	0.064
Atelectasis	Small cell lung cancer	1 (3.45)	0.035
Mucous plugging	Stent length (>60 mm)	4 (13.79)	0.003
Esophageal cancer group			
Lung infection	Long procedure duration (>110 min)	1 (3.7)	0.037
Granulation	Stent length (>60 mm)	4 (14.81)	0.019
Double placement	Tubular stents	7 (25.93)	0.034

CCI, Charlson comorbidity index.

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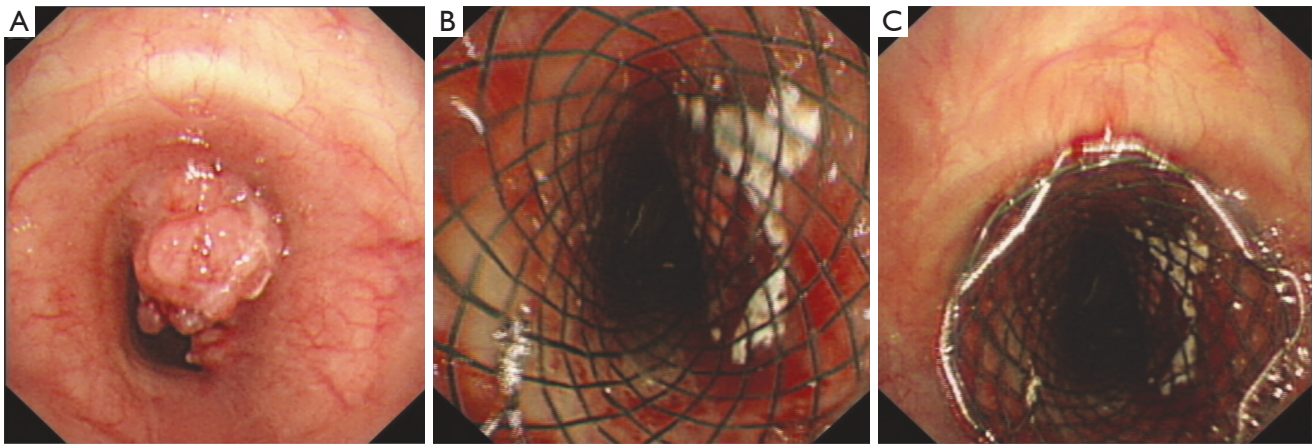

Figure 2 The treatment of a patient with airway neoplasm. (A) The bronchoscopy revealed an endobronchial airway neoplasm with a stenotic bronchus; (B,C) a self-expandable metallic stent was inserted after treatment with electrocautery.

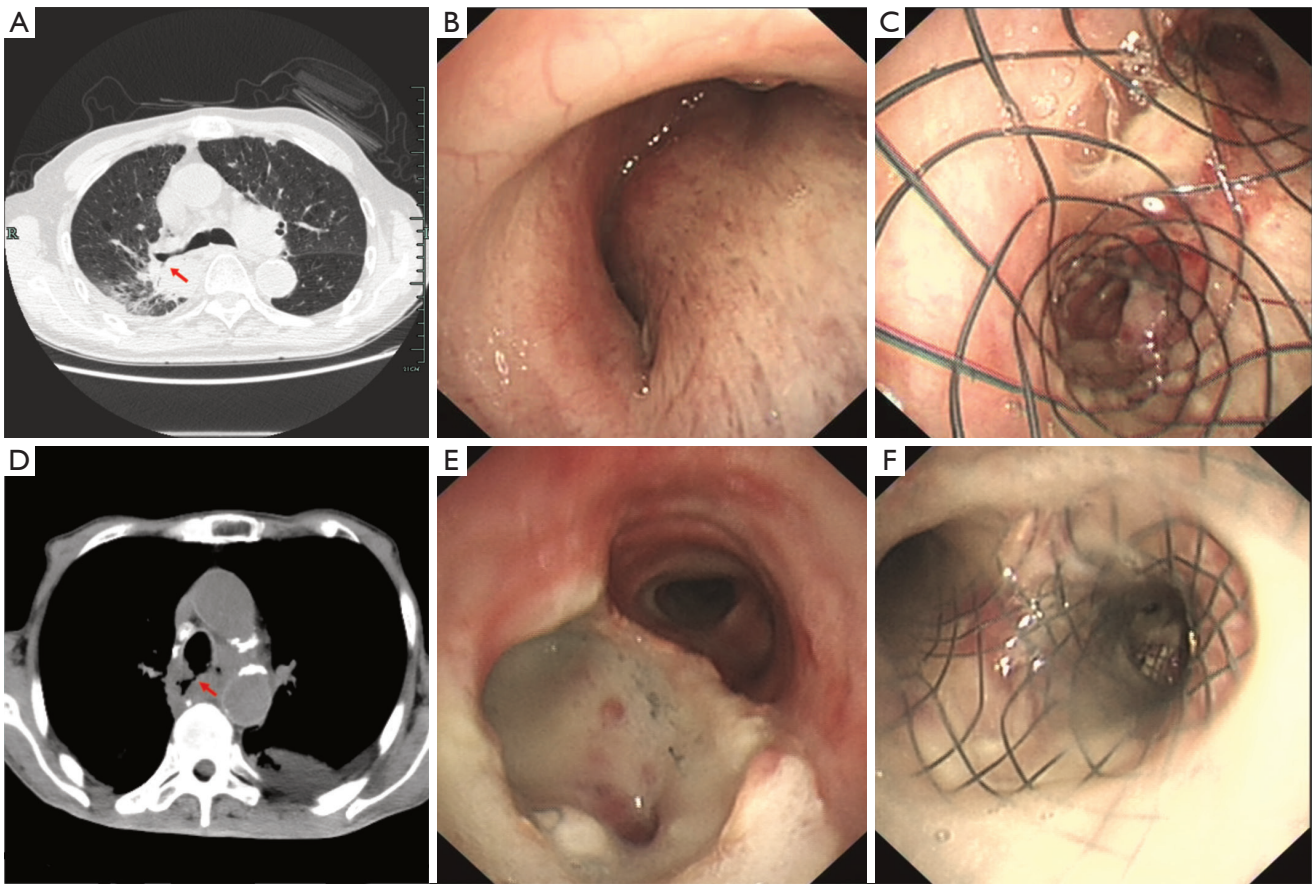

Figure 3 The treatment of extrinsic compression and thoracostomach-tracheal fistula. (A) Computed tomography (CT) scan showed the extrinsic compression of right lobar bronchi (arrow); (B) the bronchoscopy revealed the severe bronchial stenosis; (C) a Y-shaped stent was inserted at the lobar bronchi to maintain patency; (D) spiral CT reconstruction before intervention showed a thoracostomach-tracheal fistula at the carina (arrow); (E) the bronchoscopy revealed the secretion was flowing into the airway through the partial tracheal defect; (F) a covered Y-shaped stent was inserted at the carina.

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consuming and traumatic.

In comparison with silicone stents, SEMSs had a lower rate of migration due to their better resistance, pliability and lower contraction (13,17-20), especially for the Y-shaped stents (14,16,21,22). However, migration in the metallic stents still occurred because of stent under-sizing, extrinsic compression, severer cough, and bad expanding or shrinkage of the tumor following chemotherapy and/or radiotherapy (15). These results are consistent with our analysis that the patients with extrinsic compression and stents only in the main trachea had a higher incidence of migration.

Mucous plugging, as a common stent-related complication, has a high occurrence rate (5,11). In our study, 12.5% of patients developed mucous plugging, and stenting in the carina or the upper airways was a risk factor for this complication. Covered stents played an important role in the occurrence of mucous plugging. The main cause of mucous retention is dysfunction of the cilia when a covered metallic stent is placed. A longer length of a covered stent results in an increase in dysfunctional cilia, which could explain why long stents (>60 mm) were associated with a greater risk of mucous plugging in the LC group. The irritation from the stent or operation induced severe cough, which then increased mucous production. Therefore, nebulization should be routinely used for these patients, and phlegm suctioning should be performed using fiberoptic bronchoscopy when necessary.

Prior studies have suggested that infections are more common in patients undergoing airway interventions, and these infections were associated with an increased 30-day mortality rate (6,13,23). Additionally, infections were also a risk factor for granulation formation (13). Whereas the infection rates after stent placement are rarely reported in recent studies, the reported infection rates range widely from 5.7% to 40% (1,5,16). Only 3 (5.4%) cases of lung infection were detected in this study, and a long procedure duration (>110 min) was a risk factor for a lung infection in the EC group.

A large improvement of symptoms and an immediate palliation of CAO or airway fistulas have been observed in many studies (24-30). However, complications after stent placement are inevitable due to the limitations of materials and bronchoscopic technology. Nevertheless, the specific complications can be managed with many feasible treatments. The rapid treatment of complications will result in greater benefits for patients. Thus, bronchoscopists should pay particular attention to high-risk factors for stent-related complications and take prompt and proactive actions to manage complications to eliminate the suffering of patients.

Limitations of this study include the relatively small sample size and the monocentric design. This study was not a blinded, randomized, controlled or prospective study. We did not find any evidence that stent placement impacted the survival.

In conclusion, this is the first study of airway stents to systematically analyze and investigate the risk factors for each stent-related complication. Our results suggested that granulation rates were higher in patients who underwent general anesthesia and those who did not received surgery before stenting. Restenosis rates were higher in patients who had a low CCI or a long duration of the intervention. The stent location was strongly associated with stent migration and mucus impaction. Additionally, our findings also revealed that the length of the stent was directly associated with mucous plugging and granulation tissue formation. We believe that our findings will assist clinicians and bronchoscopists in quickly identifying complications and devising early interventions to manage stent-related complications in patients with malignant airway lesions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Ethics review approval from the First Affiliated Hospital, Zhejiang University School of medicine was obtained for this study (ethics approval number: 2017-668).

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Supplementary

Table S1 Analysis of all potential risk factors for each specific complication

	Hemorrhage		Vocal cord paralysis		Lung infection		Restenosis		Fistula		Stent migration		Granulation		Mucous plugging		Bad expanding		Atelectasis		Double placement	
	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value	n (%)	P value
All patients																						
Gender (male)	1 (1.8)	>0.999	3 (5.36)	0.78	3 (5.36)	0.999	2 (3.57)	0.548	2 (3.57)	0.999	4 (7.14)	0.983	4 (7.14)	0.116	4 (7.14)	0.116	0	0.997	2 (3.57)	0.999	10 (17.86)	0.999
Age (>50)	1 (1.8)	>0.999	4 (7.14)	>0.999	3 (5.36)	0.999	2 (3.57)	0.073	2 (3.57)	0.999	5 (8.93)	0.999	5 (8.93)	0.02	6 (10.71)	0.293	1 (1.8)	0.999	2 (3.57)	0.999	10 (17.86)	0.999
Primary disease (lung cancer)	1 (1.8)	>0.999	2 (3.57)	0.941	2 (3.57)	0.602	2 (3.57)	0.602	0	0.998	1 (1.8)	0.17	3 (5.36)	0.615	4 (7.14)	0.762	0	0.998	1 (1.8)	0.959	*2 (3.57)*	*0.04*
Squamous carcinoma	1 (1.8)	>0.999	4 (7.14)	0.998	2 (3.57)	0.981	1 (1.8)	0.232	2 (3.57)	0.998	4 (7.14)	0.532	6 (10.71)	0.287	6 (10.71)	0.287	0	0.998	1 (1.8)	0.602	6 (10.71)	0.585
Adenocarcinoma	0	–	0	–	0	0.999	0	0.999	0	–	0	0.999	0	0.999	0	0.999	0	0.999	0	0.999	0	0.999
History of drinking[a]	1 (1.8)	>0.999	1 (1.8)	0.74	2 (3.57)	0.401	1 (1.8)	0.828	1 (1.8)	0.998	2 (3.57)	0.903	2 (3.57)	0.424	6 (10.71)	0.05	0	–	2 (3.57)	0.998	5 (8.93)	0.221
History of smoking[a]	1 (1.8)	>0.999	2 (3.57)	0.583	2 (3.57)	0.583	0	–	0	0.998	3 (5.36)	0.674	4 (7.14)	0.728	4 (7.14)	0.728	0	–	1 (1.8)	0.975	5 (8.93)	0.481
Low CCI (<3)[a]	0	–	0	–	1 (1.8)	0.661	3 (5.36)	0.008	0	0.999	2 (3.57)	0.349	3 (5.36)	0.189	2 (3.57)	0.365	0	–	1 (1.8)	0.38	5 (8.93)	0.028
Indication (extrinsic compression)	0	–	1 (1.8)	0.838	1 (1.8)	0.838	3 (5.36)	0.999	1 (1.8)	0.497	3 (5.36)	0.058	1 (1.8)	0.665	0	0.999	0	0.999	0	0.999	0	0.732
Indication (fistula)	0	–	1 (1.8)	0.87	0	0.998	0	0.998	0	0.999	1 (1.8)	0.718	2 (3.57)	0.81	4 (7.14)	0.26	0	0.999	0	0.998	6 (10.71)	0.05
Dyspnea grade I	0	–	2 (3.57)	0.714	1 (1.8)	0.844		0.998	0	0.998	2 (3.57)	0.714	4 (7.14)	0.999	3 (5.36)	0.869	1 (1.8)	0.999	0	0.998	2 (3.57)	0.033
Dyspnea grade II	0	–	1 (1.8)	>0.999	0	0.999	1 (1.8)	>0.999	0	0.999	2 (3.57)	0.547	1 (1.8)	0.999	1 (1.8)	0.458	0	–	0	0.999	1 (1.8)	0.159
Dyspnea grade III	1 (1.8)	>0.999	0	0.999	1 (1.8)	>0.999	1 (1.8)	>0.999	0	0.999	0	0.999	2 (3.57)	0.999	1 (1.8)	0.458	0	–	1 (1.8)	>0.999	0	0.998
Pre-stent surgical therapy	0	–	1 (1.8)	0.292	2 (3.57)	0.602	2 (3.57)	0.602	1 (1.8)	0.959	5 (8.93)	0.05	*1 (1.79)*	*0.048*	4 (7.14)	0.762	0	0.998	1 (1.8)	0.959	9 (16.07)	0.012
General anesthesia	1 (1.8)	>0.999	2 (3.57)	0.823	1 (1.8)	0.688	0	0.998	0	0.998	3 (5.36)	0.476	5 (8.93)	0.038	2 (3.57)	0.146	1 (1.8)	0.998	0	0.998	2 (3.57)	0.259
Y-shaped	1 (1.8)	>0.999	2 (3.57)	0.823	1 (1.8)	0.688	0	0.998	0	0.998	2 (3.57)	0.827	5 (8.93)	0.146	3 (5.36)	0.919	1 (1.8)	0.998	0	0.998	2 (3.57)	0.568
Tubular stent	0	–	2 (3.57)	0.823	2 (3.57)	0.688	3 (5.36)	0.998	2 (3.57)	0.998	3 (5.36)	0.827	2 (3.57)	0.146	4 (7.14)	0.919	0	0.998	2 (3.57)	0.998	8 (14.29)	0.568
Long procedure duration (>110 min)[a]	0	–	0	>0.999	1 (1.8)	0.098	2 (3.57)	0.005	1 (1.8)	0.053	0	0.999	0	0.999	0	0.999	0	0.999	1 (1.8)	0.053	3 (5.36)	0.051
Stent Length (> 60mm)[a]	0	–	2 (3.57)	0.398	1 (1.8)	0.926	0	0.999	0	0.141	0	0.999	2 (3.57)	0.398	3 (5.36)	0.398	0	–	0	0.999	1 (1.8)	0.235
Stent in left main bronchus	0	–	2 (3.57)	0.708	2 (3.57)	0.375	1 (1.8)	0.78	1 (1.8)	0.795	2 (3.57)	0.959	4 (7.14)	0.363	3 (5.36)	0.918	0	0.998	1 (1.8)	0.795	3 (5.36)	0.436
Stent in right main bronchus	0	–	3 (5.36)	0.427	2 (3.57)	0.688	1 (1.8)	0.445	0	0.998	3 (5.36)	0.827	5 (8.93)	0.369	3 (5.36)	0.481	0	0.998	1 (1.8)	0.877	3 (5.36)	0.087
Stent in the carina	1 (1.8)	>0.999	2 (3.57)	0.253	1 (1.8)	0.734	0	0.999	0	0.999	2 (3.57)	0.426	3 (5.36)	0.255	3 (5.36)	0.255	0	0.999	0	0.999	2 (3.57)	0.688
Stent in the main trachea	1 (1.8)	>0.999	3 (5.36)	0.466	1 (1.8)	0.409	1 (1.8)	0.409	1 (1.8)	0.836	4 (7.14)	0.049	4 (7.14)	>0.999	6 (10.71)	0.135	1 (1.8)	0.998	0	0.998	6 (10.71)	0.84
Tubular stent in the left/right bronchus	0	–	1 (1.8)	>0.999	2 (3.57)	0.484	2 (3.57)	>0.999	1 (1.8)	>0.999	1 (1.8)	0.599	1 (1.8)	>0.999	1 (1.8)	0.333	0	–	2 (3.57)	0.0228	3 (5.36)	0.433
Stent in the carina and upper	1 (1.8)	>0.999	3 (5.36)	0.355	1 (1.8)	0.521	1 (1.8)	0.521	1 (1.8)	0.959	3 (5.36)	0.701	4 (7.14)	0.762	6 (10.71)	0.041	1 (1.8)	0.998	0	0.998	5 (8.93)	0.901
Lung cancer patients																						
Gender (male)	1 (3.45)	0.999	2 (6.9)	0.999	2 (6.9)	0.999	1 (3.45)	0.177	0	–	1 (3.45)	0.999	2 (6.9)	0.327	3 (10.3)	0.495	0	–	1 (3.45)	0.999	2 (6.9)	0.999
Age (>50)	1 (3.45)	0.999	2 (6.9)	0.999	2 (6.9)	0.999	1 (3.45)	0.113	0	–	1 (3.45)	0.999	1 (3.45)	0.014	3 (10.3)	0.327	0	–	0	0.999	0	0.999
Primary disease (lung cancer)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Squamous carcinoma	1 (3.45)	0.999	2 (6.9)	0.999	1 (3.45)	0.916	0	0.999	0	–	1 (3.45)	0.999	2 (6.9)	0.469	3 (10.3)	0.242	0	–	0	0.999	0	–
Adenocarcinoma	0	–	0	0.999	0	0.999	0	0.999	0	–	0	0.999	0	0.999	0	0.999	0	–	0	0.999	0	–
History of drinking[a]	1 (3.45)	0.998	1 (3.45)	0.578	1 (3.45)	0.578	0	–	0	–	0	0.999	1 (3.45)	0.958	0	0.999	0	–	1 (3.45)	0.998	0	–
History of smoking[a]	1 (3.45)	0.999	2 (6.9)	0.999	2 (6.9)	0.999	0	–	0	–	1 (3.45)	0.999	2 (6.9)	0.802	3 (10.3)	0.512	0	–	1 (3.45)	0.999	0	–
Low CCI (<3)[a]	0	0.999	0	0.999	0	0.999	1 (3.45)	0.998	0	–	0	0.999	2 (6.9)	0.064	1 (3.45)	0.219	0	–	0	0.999	0	–
Indication (extrinsic compression)	0	0.999	0	0.999	1 (3.45)	0.133	0	0.999	0	–	0	0.999	0	0.999	0	0.999	0	–	0	0.999	0	–
Indication (fistula)	0	0.999	0	0.999	0	0.999	0	0.999	0	–	0	0.999	0	0.999	1 (3.45)	0.921	0	–	0	0.999	1 (3.45)	0.323
Dyspnea grade I	0	–	1 (3.45)	0.999	1 (3.45)	0.999	0	–	0	–	1 (3.45)	0.999	2 (6.9)	0.999	2 (6.9)	0.793	0	–	0	–	0	0.999
Dyspnea grade II	0	–	1 (3.45)	0.999	0	–	1 (3.45)	0.999	0	–	0	–	0	–	0	0.999	0	–	0	–	1 (3.45)	0.887
Dyspnea grade III	1 (3.45)	0.999	0	–	1 (3.45)	0.999	1 (3.45)	0.999	0	–	0	–	1 (3.45)	0.999	1 (3.45)	0.758	0	–	1 (3.45)	0.999	0	0.999
Pre-stent surgical therapy	0	0.999	1 (3.45)	0.96	1 (3.45)	0.96	1 (3.45)	0.96	0	–	1 (3.45)	0.999	0	0.999	3 (10.3)	0.273	0	–	0	0.999	2 (6.9)	0.999
General anesthesia	1 (3.45)	0.998	1 (3.45)	0.798	1 (3.45)	0.798	0	0.999	0	–	0	0.999	2 (6.9)	0.367	1 (3.45)	0.483	0	–	0	0.999	0	0.999
Y-shaped	1 (3.45)	0.998	1 (3.45)	0.798	1 (3.45)	0.798	0	0.999	0	–	0	0.999	2 (6.9)	0.367	2 (6.9)	0.707	0	–	0	0.999	1 (3.45)	0.798
Tubular stent	0	0.998	1 (3.45)	0.798	1 (3.45)	0.798	2 (6.9)	0.999	0	–	1 (3.45)	0.999	1 (3.45)	0.367	2 (6.9)	0.707	0	–	1 (3.45)	0.999	1 (3.45)	0.798
Long procedure duration (>110 min)[a]	0	–	0	0.999	0	0.999	1 (3.45)	0.072	0	–	0	0.999	0	0.999	0	0.999	0	–	0	0.999	1 (3.45)	0.072
Stent length (>60 mm)[a]	0	–	1 (3.45)	0.495	1 (3.45)	0.495	1 (3.45)	0.495	0	–	0	–	0	0.999	4 (13.79)	0.003	0	–	0	0.999	0	0.999
Stent in left main bronchus	0	0.999	1 (3.45)	0.638	1 (3.45)	0.638	0	0.999	0	–	0		1 (3.45)	0.965	2 (6.9)	0.488	0	–	0	–	0	0.999
Stent in right main bronchus	0	0.998	2 (6.9)	0.999	2 (6.9)	0.999	1 (3.45)	0.558	0	–	1 (3.45)	0.999	2 (6.9)	0.928	2 (6.9)	0.388	0	–	1 (3.45)	0.999	2 (6.9)	0.999
Stent the in carina	1 (3.45)	0.998	1 (3.45)	0.177	1 (3.45)	0.177	0	0.999	0	–	0	–	0	0.999	1 (3.45)	0.495	0	–	0	0.999	0	–
Stent in the main trachea	1 (3.45)	0.998	1 (3.45)	0.588	1 (3.45)	0.559	1 (3.45)	0.558	0	–	0	–	0	0.999	3 (10.3)	0.071	0	–	0	0.999	0	–
Tubular stent in the left/right bronchus	0	–	0	–	0	–	1 (3.45)	0.228	0	–	0	–	0	0.999	1 (3.45)	0.2279	0	–	0	–	0	–
Stent in the carina and upper	1 (3.45)	0.998	1 (3.45)	0.478	1 (3.45)	0.478	1 (3.45)	0.478	0	–	0	–	0	0.999	2 (6.9)	0.297	0	–	0	0.999	0	–
Esophageal cancer patients																						
Gender (male)	0	–	1 (3.7)	0.998	1 (3.7)	0.999	1 (3.7)	0.999	2 (7.41)	0.999	3 (11.11)	0.963	2 (7.41)	0.253	1 (3.7)	0.126	0	0.998	1 (3.7)	0.999	8 (29.63)	0.999
Age (>50)	0	–	2 (7.41)	0.999	1 (3.7)	0.999	1 (3.7)	0.999	2 (7.41)	0.999	4 (14.81)	0.999	4 (14.81)	0.999	3 (11.11)	0.999	1 (3.7)	0.999	1 (3.7)	0.999	8 (29.63)	0.999
Primary disease (Lung cancer)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Squamous carcinoma	0	–	2 (7.41)	0.999	1 (3.7)	0.999	1 (3.7)	0.999	2 (7.41)	0.999	3 (11.11)	0.719	4 (14.81)	0.999	3 (11.11)	0.999	0	–	1 (3.7)	0.999	6 (22.22)	0.577
Adenocarcinoma	0	–	0	–	0	0.999	0	0.999	0	–	0	–	0	–	0	0.999	0	–	0	0.999	0	–
History of drinking[a]	0	–	0	0.999	1 (3.7)	0.999	1 (3.7)	0.999	1 (3.7)	0.999	2 (7.41)	0.84	1 (3.7)	0.215	1 (3.7)	0.44	0	–	1 (3.7)	0.999	5 (18.52)	0.286
History of smoking[a]	0	–	0	0.999	0	0.999	0	0.999	0	0.999	2 (7.41)	0.684	2 (7.41)	0.684	1 (3.7)	0.775	0	–	0	0.999	5 (18.52)	0.059
Low CCI (<3)[a]	0	–	0	0.999	0	0.998	1 (3.7)	0.998	1 (3.7)	0.998	2 (7.41)	0.249	1 (3.7)	0.957	1 (3.7)	0.76	0	–	1 (3.7)	0.998	4 (14.81)	0.038
Indication (Extrinsic compression)	0	–	1 (3.7)	>0.999	0	0.999	0	0.999	1 (3.7)	>0.999	3 (11.11)	0.999	1 (3.7)	>0.999	0	–	1 (3.7)	0.999	0	0.999	2 (7.41)	0.592
Indication (Fistula)	0	–	1 (3.7)	0.999	0	0.999	0	0.999	0	0.999	1 (3.7)	0.999	2 (7.41)	0.739	3 (11.11)	0.999	0	0.999	0	0.999	3 (11.11)	0.637
Dyspnea grade I	0	–	1 (3.7)	0.999	0	0.999	0	0.999	0	0.999	1 (3.7)	0.919	2 (7.41)	0.999	1 (3.7)	0.919	1 (3.7)	0.999	0	0.999	0	0.999
Dyspnea grade II	0	–	0	–	0	0.999	0	0.999	0	0.999	2 (7.41)	0.609	1 (3.7)	0.999	1 (3.7)	0.919	0	–	0	0.999	3 (11.11)	0.919
Dyspnea grade III	0	–	0	–	0	0.999	0	0.999	0	0.999	0	0.999	1 (3.7)	0.999	0	0.999	0	–	0	0.999	0	0.999
Pre-stent surgical therapy	0	–	0	0.999	1 (3.7)	0.999	1 (3.7)	0.999	1 (3.7)	0.87	4 (14.81)	0.999	1 (3.7)	0.211	1 (3.7)	0.426	0	0.999	1 (3.7)	0.999	7 (25.93)	0.052
General anesthesia	0	–	1 (3.7)	0.999	0	0.999	0	0.999	0	0.999	3 (11.11)	0.268	3 (11.11)	0.268	1 (3.7)	0.591	1 (3.7)	0.999	0	0.999	2 (7.41)	0.131
Y-shaped	0	–	1 (3.7)	0.999	0	0.999	0	0.999	0	0.999	2 (7.41)	0.936	3 (11.11)	0.268	1 (3.7)	0.591	1 (3.7)	0.999	0	0.999	*1 (3.7)*	*0.034*
Tubular stent	0	–	1 (3.7)	0.999	1 (3.7)	0.999	1 (3.7)	0.999	2 (7.41)	0.999	2 (7.41)	0.936	1 (3.7)	0.268	2 (7.41)	0.591	0	0.999	1 (3.7)	0.999	7 (25.93)	0.034
Long procedure duration (>110 min)[a]	0	–	0	–	1 (3.7)	0.037	1 (3.7)	0.998	1 (3.7)	0.09	1 (3.7)	0.098	1 (3.7)	0.279	0	0.999	0	–	1 (3.7)	0.998	2 (7.41)	0.495
Stent length (>60 mm)[a]	0	–	1 (3.7)	0.999	0	0.999	0	0.999	0	0.999	0	0.999	4 (14.81)	0.019	1 (3.7)	0.718	0	–	0	0.999	1 (3.7)	0.223
Stent in left main bronchus	0	–	1 (3.7)	0.999	1 (3.7)	0.999	1 (3.7)	0.999	1 (3.7)	0.957	2 (7.41)	0.936	3 (11.11)	0.268	1 (3.7)	0.591	0	0.999	1 (3.7)	0.999	3 (11.11)	0.475
Stent in right main bronchus	0	–	1 (3.7)	0.999	0	0.999	0	0.999	0	0.999	2 (7.41)	0.685	3 (11.11)	0.162	1 (3.7)	0.783	0	0.999	0	0.999	1 (3.7)	0.078
Stent in the carina	0	–	1 (3.7)	0.998	0	0.999	0	0.999	0	0.999	2 (7.41)	0.565	3 (11.11)	0.121	2 (7.41)	0.286	0	0.999	0	0.999	2 (7.41)	0.406
Stent in the main trachea	0	–	2 (7.41)	0.999	0	0.998	0	0.998	1 (3.7)	0.196	4 (14.81)	0.999	4 (14.81)	0.999	3 (11.11)	0.999	1 (3.7)	0.999	0	0.998	6 (22.22)	0.347
Tubular stent in the left/right bronchus	0	–	1 (3.7)	>0.999	0	–	0	–	1 (3.7)	>0.999	2 (7.41)	>0.999	1 (3.7)	>0.999	2 (7.41)	>0.999	0	–	0	–	5 (18.52)	0.433
Stent in the carina and upper	0	–	2 (7.41)	0.999	0	–	0	–	1 (3.7)	0.274	3 (11.11)	0.999	4 (14.81)	0.999	3 (11.11)	0.999	1 (3.7)	0.999	0	–	5 (18.52)	0.557

P values of protective factors were words in italic. [a], unknown data was excluded from analysis. CCI, Charlson comorbidity index.