The long-term impact of postoperative pulmonary complications after video-assisted thoracic surgery lobectomy for lung cancer

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Background: Pulmonary complications (PCs) may influence long-term survivor. We sought to determine the long-term impacts of major pulmonary complications (MPCs) and identify the independent risk factors in non-small cell lung cancer (NSCLC) patients.

Methods: A retrospective study was conducted to analyze the PCs of 828 NSCLC patients who underwent video-assisted thoracic surgery (VATS) lobectomy in Peking University Hospital, the complications were graded according to TMM classification. The effects of PCs on the long-term prognosis were analyzed by using the Kaplan-Meier method. Multivariate logistic regression analysis was used to determine the risk factors of MPCs.

Results: Of 828 patients, 139 had PCs, including 66 (8%) MPCs, those patients who developed a PC had longer drainage time, hospital stay and higher perioperative mortality rate. Excluding perioperative deaths, those who develop a MPC had a reduced 3-year disease-free survival (DFS) and 5-year DFS (68.2% vs. 78.7%, 44.7% vs. 70.3%; P=0.001), as well as the reduced 3-year overall survival (OS) and 5-year OS (81.8% vs. 88.6%, 66.6% vs. 80.9%; P=0.023). MPCs were independent prognostic factors of patients with lung cancer. Multivariate logistic regression analysis showed that the independent risk factors for MPCs were age [P=0.007; hazard ratio (HR): 1.05, 95% confidence interval (CI): 1.01–1.08], male (P=0.001; HR: 3.33, 95% CI: 1.87–5.94) and American Society of Anesthesiologist (ASA) grade.

Conclusions: MPC after VATS lobectomy is associated with a poorer long-time outcome. The independent risk factors for MPCs were age, male and ASA grade.

Keywords: Video-assisted thoracic surgery (VATS); lung cancer, major pulmonary complication (MPC); American Society of Anesthesiologist (ASA)

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Introduction

Lung cancer is still the leading cause of cancer death in China (1), for those patients with early stage non-small cell lung cancer (NSCLC), complete resection remains the standard treatment with unfavorable prognosis (2,3). However, the incidence rate of postoperative pulmonary complications (PCs) ranging from 15% to 37% for patients who undergo lobectomy (4-6), in which prolonged air leak and pneumonia are the most common (7-9). PCs prolong hospitalization, ICU care, increased medical cost (9,10), but limited researches focus on the potential impact of PCs on long-term survival for lung cancer patients (11).

To date, though video-assisted thoracic surgery (VATS) lobectomy has been proved to be more safe and reliable than thoracotomy because of its obvious minimally invasive advantages, quicker postoperative recovery, less postoperative complications, especially for the elderly patients with low pulmonary function or comorbidities (12-16), PCs are still inevitable, therefore, accurate prediction of PCs is of great clinical significance, which can improve the quality of life and long-term survival of lung cancer patients. However, most of the studies concerned about the presence of PCs, without the severity of the complications. It is vital to evaluate and determine the risk factors of major pulmonary complication (MPC) objectively.

In this study, we sought to determine the long-term effect of MPCs, develop and validate a nomogram predictive of them. Our study aims were: (I) to assess the long-term influence of MPCs in NSCLC patients who underwent VATS lobectomy; (II) to identify risk factors for MPCs.

Methods

Patients and study design

A retrospective study was conducted among the primary NSCLC patients who underwent VATS lobectomy at the Peking University People's Hospital (PUPH) between January 2007 and December 2015, a cohort of 828 patients were identified who satisfied the following inclusion criteria: (I) preoperative clinical stage must be I-II; (II) age >18 years old; (III) physical status ECOG score of 0-1. Exclusion criteria were as follows: (I) pathologically confirmed as adenocarcinoma in situ (AIS); (II) patients who accepted neoadjuvant chemotherapy or radiation; (III) patients who had received thoracic surgery before, except for previous diagnostic thoracoscopic surgery; (IV) history with malignant tumors in the last 5 years. We explore the impact of MPCs on the long-term prognosis and identify the independent risk factors for MPCs. The ethical review and informed consent of this study were approved by institutional ethics board of Peking University People's Hospital (No. 2014PHB033-01).

Data collective

We collected clinical variables of patients including: demographics [age, sex, comorbidities, smoking status, pulmonary function, American Society of Anesthetist (ASA) score]; surgical data (estimated blood loss, surgery time, numbers of dissected lymph nodes and dissected lymph nodes stations); pathological data (histology type, pathologically positive number of lymph nodes and number of stations, TNM stage); postoperative data [length of stay (LOS), drainage time, etc.].

Chest CT scan and abdominal ultrasound/CT are performed on follow-up visits every 6 months, after operation for 5 years. MRI and bone scan are performed every 1 year for 5 years or any time with symptoms. The overall survival (OS) was estimated from the date of surgical resection until death of any cause or the date of last followup. Disease-free survival (DFS) was defined as the time from the day of surgery until the first event (relapse, metastasis or death from any cause) or last follow-up.

Complications

Perioperative mortality was defined as death at the time of hospitalization or within 30 days after surgery. Postoperative complications were defined and graded according to the TM&M classification (17) and the common terminology criteria for adverse events (CTCAE 4.0), which grades complications on a severity scale from grades I to V based on the effort required to treat the events. Grades I and II include events that deviate from the normal postoperative course but require either no intervention or pharmacologic therapy, respectively, which were defined as minor complication. Grade III and IV complications were defined as major complication, a grade III event required medical intervention, without general anesthesia (IIIa), and with general anesthesia (IIIb). Grade IV events were lifethreatening and require intensive care unit management owing to single organ dysfunction (IVa) or multi organ dysfunction (IVb). Grade V events resulted in death of the patient.

VATS technique

Under single-lung anesthesia, a patient was placed in the lateral decubitus position with an air pillow underneath, and the upper extremities were extended forward. A 30-degree thoracoscope was placed in the 7th intercostal space (ICS) at the midaxillary line; the working port (often 4–5 cm) was placed in the 4th ICS at the anterior axillary line; the assistant's port was put in the 7th or 8th ICS between the posterior axillary and subscapular lines. The process and skills of VATS lobectomy followed the operational guidelines of Peking University People's Hospital described in 2010 (18). The main points include: (I) a specially made curved aspirator and electrocautery were used concurrently through working port and double-crossed in the same

direction, known as Wang's technique; (II) deal with the bronchial artery firstly in the hilum through coagulation or ligation; (III) pulmonary artery and pulmonary vein are freed in the subadventitial plane and transected by endo stapler after removing the surrounding lymph nodes to "vascular skeletalization" status; (IV) for smaller vessels, we can also use Hem-o-Lok automatic ligation clip, ligasure bipolar electric knife and suture. All lung cancer patients would undergo systematic mediastinal lymph node dissection.

Statistical analysis

Continuous variables were compared using Student's *t*-test or Mann-Whitney non-parametric test for variables with an abnormal distribution, frequency distributions were compared using the chi-square test or Fischer's exact test. Kaplan-Meier method and the log-rank test were used to assess the impact of PCs on survival. Univariable and multivariable survival analysis was performed using the Cox proportional hazards model, with results presented as hazard ratio (HR) with 95% confidence interval (CI). A P value of <0.05 was considered to represent a statistically significant difference. Statistical analysis was performed using SPSS v.22.0 (IBM, Chicago, IL, USA).

Results

Clinicopathologic characteristics of patients

There were 828 lung cancer patients who underwent VATS lobectomy during the period, 417 (50.4%) of who were male. The age of the group was 64.5±10.3 years. Mean body mass index (BMI) was 24.0±3.1 kg/m². No intraoperative deaths occurred. The median operation time was 170 min (range, 140–206 min), with the estimated blood loss of 50 mL (range, 50–100 mL). Most common histology type was adenocarcinoma (82.9%), followed by squamous cell carcinoma (13.2%) and other type (4%). There were 9 perioperative deaths (1.1%). Patient characteristics are shown in *Table 1*.

Postoperative PCs

A total of 139 patients (16.8%) had clinical evidence of a PC, in which 75 patients (9%) had MPCs. The most common PCs included prolonged air leak (7.5%), pneumonia (5%), pleural effusion (3.1%) and pulmonary atelectasis (1.4%). The details of PCs are listed in *Table 2*. As is shown in *Table 3*,

patients who suffer from postoperative PCs or MPCs had longer median hospital LOS and drainage time. In the PCs group, there was also higher perioperative mortality rate.

Impact of MPCs on long-term outcomes

Excluding 9 patients who died of a postoperative complication, of the remaining 819 patients, there were 128 (15.5%) deaths with a median follow-up of 41 months (rang, 22–59 months). Those who developed a postoperative pulmonary complication (PPC) presented a tendency of decrease in 3-year DFS and 5-year DFS (74.7% vs.78.4%, 64.3% vs. 69.4%; P=0.088) (Figure 1), as well as a tendency of decrease in 3-year OS and 5-year OS (86.8% vs. 88.2%, 78.3% vs. 80%; P=0.893) (Figure 2), there was no significant difference in long-term survival between the two groups. However, those who develop a MPC had a reduced 3-year DFS and 5-year DFS (68.2% vs. 78.7%, 44.7% vs. 70.3%; P=0.001) (Figure 3), as well as the reduced 3-year OS and 5-year OS (81.8% vs. 88.6%, 66.6% vs. 80.9%; P=0.023) (Figure 4). Using multivariate analysis, the significant risk factors associated with late deaths in lung cancer patients were MPCs (HR: 2.02, 95% CI: 1.24-3.28; P=0.005), age (HR: 1.05, 95% CI: 1.03-1.08; P=0.029), diffusing capacity of carbon monoxide (D_{LCO}) (HR: 0.98, 95% CI: 0.97-0.99; P=0.004), and N stage and tumor diameter (Table 4). Significant independent risk factors for recurrence in patients with NSCLC were MPCs (HR: 1.93, 95% CI: 1.3-2.87; P=0.001), N stage and tumor diameter (Table 5).

Risk factors for MPCs

Multivariate analysis demonstrated that age (P=0.007, HR: 1.05, 95% CI: 1.01–1.08), male (P=0.001, HR: 3.33, 95% CI: 1.87–5.94), ASA grade were independent risk factors for MPCs in primary cohort (*Table 6*).

Discussion

Although complete surgical resection is still the standard treatment for patients with lung cancer, the 5-year overall survival rate after lobectomy is currently ranging from 57% to 82% (4,5). Surgical and perioperative management improvements reduce postoperative mortality, But the incidence of PCs is still very high, ranging from 17% to 37% (11,19), which lead to prolonged hospitalization, ICU stay, increased rate of rehospitalizations, as well as significant increased perioperative mortality. Previous

Table 1 Patient characteristics

Variable	Values	Percentage (%)
Gender		
Male	417	50.4
Age (years)	64.5±10.3	-
BMI body mass index (kg/m ²)		
Smoking	24.0±3.1	-
Non-smoker	562	67.9
Ex-smoker	136	16.4
Current smoker	130	15.7
ASA score		
1	307	37.1
2	488	58.9
3	33	4.0
Comorbidities		
Hypertension	284	34.3
Coronary heart disease	97	11.7
Diabetes	93	11.2
Stroke	30	3.6
FEV ₁ ≥70%	657	79.3
FEV₁ (pred) ≥80%	639	77.2
D _{LCO} (pred) ≥60%	738	89.1
Tumor size (cm)	2.5±1.4	-
Location		
Upper lobe	481	58.1
Middle lobe	72	8.7
Lower lobe	275	33.2
Lateral (right)	520	62.8
Central	71	8.6
CCI		
0	309	37.3
1	306	37
≥2	213	25.7
Histology		
Adenocarcinoma	686	82.9
Squamous carcinoma	109	13.2
Others	33	4

Table 1 (continued)

Table 1 (continued)		
Variable	Values	Percentage (%)
TNM staging		
T	632	76.3
II	98	11.8
III	98	11.8
Lymph nodes		
Stations of sampled LNs	6 [5–7]	-
No. of harvested LNs	15 [11–21]	-
Operative time [min]	170 [140– 206]	-
Estimated blood loss [mL]	50 [50–100]	-
Drainage time [day]	5 [4–7]	-
Length of hospital stay [day]	7 [6–9]	-

pred, predicted; ASA, American Society of Anesthesiologists; FEV_1 , forced expiratory volume in 1 second; D_{LCO} , diffusing capacity of carbon monoxide; CCI, Charlson comorbidity index.

studies on the prognosis of lung cancer are often focused on tumor size, lymph node metastasis, distant metastasis, chemotherapy sensitivity and other clinical pathology features (20). In recent years, more and more research began to focus on the patient's own factors, such as: the patient's physical condition, immune status, depression (21). However, the impact of perioperative complications on the outcome of the lung cancer patients has been seldom studied (11), this study is the first to determine the association between MPCs and long-term outcomes among patients undergoing VATS lobectomy for NSCLC. Excluding perioperative deaths, MPC is an important independent risk factor for recurrence and long-term death of lung cancer, which provides an understanding new insight of the important clinical and pathological features associated with cancer.

The frequency of PCs (16.8%) in our study was consistent with previous studies (17–37%). They reported a significant difference in the incidence of PCs after lung surgery due to the absence of a standard definition of PCs. In this study, TMM classification and CTCAE4.0 were used to define and grade all PCs, which made the results more reliable and practical.

Our study showed that OS and RFs are reduced in patients who developed a MPC after VATS lobectomy for NSCLC. There are few studies on the effect of MPC on the long-term prognosis of lung cancer. A retrospective study conducted by

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Table 2 PCs of patients after VATS lobectomy

Complications grade	Number	Percentage (%)
Patients with complications	139	16.8
Total complications	193	
Minor	118	14.3
Grade I		
Pneumothorax (without intervention)	7	0.8
Grade II		
Pneumonia	27	3.3
Prolonged air leak (only need suction)	38	4.6
Effusion	20	2.4
Atelectasis	5	0.6
Chylothorax (conservative treatment)	12	1.4
Sub-cutaneous emphysema (modification of chest tube position)	8	1
Hemothorax	1	0.1
Major	69	8.3
Grade Illa		
Prolonged air leak (need endoscopic or pleural interventions)	22	2.7
Effusion (need thoracentesis or pleurodesis)	8	1.0
Sub-cutaneous emphysema (chest tube reinsertion)	6	0.7
Atelectasis (bronchoscopic suction of sputum)	7	0.8
Empyema	1	0.1
Grade IIIb		
Chylothorax (need ligation of thoracic duct)	4	0.4
Hemothorax (need operation)	2	0.2
Grade IVa		
Bronchial pleural fistula	3	0.4
Acute respiratory failure	2	0.2
Acute respiratory distress syndrome	2	0.2
Grade IVb		
Severe pneumonia	10	1.2
Respiratory failure combined with heart failure	2	0.2
Mortality	6	0.7
Grade V		
Respiratory failure	3	0.4
Bronchial pleural fistula	2	0.2
Idiopathic pulmonary interstitial fibrosis	1	0.1

PCs, pulmonary complications; VATS, video-assisted thoracic surgery.

Table 5 inipact of PCs on perioperative outcomes						
Variables —	PCs			MPCs		
	+	-	Р	+	-	Р
Drainage time [days]	9 [8–11]	5 [4–6]	<0.001	10 [7–12]	5 [4–7]	<0.001
Hospital LOS [days]	12 [10–14]	6 [5–8]	<0.001	12 [9–17]	7 [5–9]	<0.001
Mortality (%)	4.3	0.4	0.001	12	0	<0.001

LOS, length of stay; PCs, pulmonary complications; MPCs, major pulmonary complications



Figure 1 DFS of patients with and without pulmonary complications. Blue line: no PCs; grey line: PCs. DFS, disease-free survival; PC, pulmonary complication.



Figure 2 OS of patients with and without PCs. Blue line: no PCs; grey line: PCs. OS, overall survival; PC, pulmonary complication.



Figure 3 DFS of patients with and without MPCs. Blue line: no MPCs; grey line: MPCs. DFS, disease-free survival; MPC, major pulmonary complication.



Figure 4 OS of patients with and without MPCs. Blue line: no MPCs; grey line: MPCs. OS, overall survival; MPC, major pulmonary complication.

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Table 4 Univariable analysis and Cox proportional Hazards regression analysis for OS in patients						
Variables —	Univariable an	alysis	Multivariable ar	Multivariable analysis		
	HR (95% CI)	Р	HR (95% CI)	Р		
Gender						
Male	1.81 (1.27–2.6)	0.001	1.05 (0.62–1.80)	0.847		
Age	1.05 (1.03–1.07)	<0.001	1.05 (1.03–1.08)	0.029		
Smoking						
Non	ref	-	ref	-		
Ex	1.77 (1.14–2.77)	0.011	1.25 (0.72–2.17)	0.433		
Current	1.71 (1.09–2.7)	0.02	1.42 (0.79–2.57)	0.239		
ASA score						
1	ref	-	ref	-		
2	2.02 (1.32–3.13)	0.001	1.29 (0.78–2.14)	0.316		
3	3.40 (1.60–7.21)	0.001	1.54 (0.68–3.46)	0.3		
FEV ₁ (pred) <80%	1.86 (1.23–2.81)	0.003	1.32 (0.74–2.35)	0.352		
FEV ₁ /FVC <70%	1.82 (1.21–2.74)	0.004	0.80 (0.43–1.47)	0.465		
D _{LCO}	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	0.004		
Central	2.06 (1.24–3.4)	0.005	1.32 (0.74–2.35)	0.343		
N stage						
0	ref	-	ref	-		
1	3.95 (2.47–6.33)	<0.001	4.90 (3.01–7.99)	<0.001		
2	3.77 (2.47–5.76)	<0.001	2.71 (1.71–4.31)	<0.001		
Tumor size (cm)						
<3	ref	-	ref	-		
3–5	2.23 (1.31–3.78)	0.003	2.11 (1.2–3.71)	0.01		
5–7	3.90 (2.31–6.58)	<0.001	3.12 (1.77–5.51)	<0.001		
>7	2.64 (1.16–6.00)	0.02	1.41 (0.60–3.33)	0.428		
PCs	1.29 (0.84–1.97)	0.24	-	-		
MPCs	2.82 (1.81–4.36)	<0.001	2.02 (1.24–3.28)	0.005		

Table 4 Univariable analysis and Cox proportional Hazards regression analysis for OS in patients

pred, predicted; ref, reference; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; D_{LCO}, diffusing capacity of carbon monoxide; MPCs, major pulmonary complications; ASA, American Society of Anesthesiologists; OS, overall survival.

Rueth in 2011 which include patients who have underwent lobectomy for stage I NSCLC shows that, patients with postoperative complications were associated with poorer cancer-specific survival (70.9% *vs.* 78.9%; P<0.001) and reduced 5-year OS (52.7% *vs.* 65.9%, P<0.001), postoperative complication is an independent risk factors for mortality (HR: 1.46, 95% CI: 1.24–1.73) (22). In a prospective

observational study involved 670 lung resections in 2016, Sebastian found that COPD, smoking were independent risk factors for PCs, those who developed a PPC resulted in a significantly reduced overall survival (40 *vs.* 46; P=0.006) and higher rate of non-cancer-related deaths (11% *vs.* 5%; P=0.020). PPC is a significant independent risk factor for late deaths in NSCLC patients (HR: 2.0, 95% CI: 1.9–3.2;

	Univariable an	alysis	Multivariable analysis		
Variables	HR (95% CI)	Р	HR (95% CI)	Р	
Gender					
Male	1.52 (1.17–2.00)	0.003	1.22 (0.82–1.8)	0.322	
Age	1.03 (1.02–1.05)	<0.001	1.02 (1–1.03)	0.08	
Smoking					
Non	ref	-	ref	-	
Ex	1.64 (1.18–2.27)	0.003	1.07 (0.7–1.63)	0.753	
Current	1.27 (0.88–1.84)	0.196	0.86 (0.54–1.37)	0.523	
ASA score					
1	ref	-	ref	-	
2	1.91 (1.4–2.63)	<0.001	1.44 (1–2.09)	0.052	
3	2.88 (1.6–5.19)	<0.001	1.89 (0.95–3.75)	0.068	
FEV ₁ (pred) <80%	1.47 (1.05–2.04)	0.024	1.30 (0.82–2.06)	0.368	
FEV ₁ /FVC <70%	1.34 (0.96–1.87)	0.082	0.87 (0.53–1.42)	0.564	
D _{LCO}	0.99 (0.98–1.00)	0.004	0.99 (0.98–1.00)	0.138	
Central	1.52 (1–2.31)	0.048	1.19 (0.73–1.92)	0.485	
N stage					
0	ref	-	ref	-	
1	4.04 (2.82–5.78)	<0.001	4.23 (2.84–6.29)	<0.001	
2	4.24 (3.08–5.84)	<0.001	3.38 (2.36–4.86)	<0.001	
Tumor size (cm)					
<3	ref	-	ref	-	
3–5	1.62 (1.13–2.33)	0.008	1.53(1.04-2.25)	0.031	
5–7	2.57 (1.79–3.69)	<0.001	1.75(1.16-2.64)	0.008	
>7	2.11 (1.18–3.77)	0.011	1.78(0.64–2.17)	0.601	
PCs	1.52 (1.09–2.08)	0.012	1.05 (0.69–1.59)	0.836	
MPCs	2.51 (1.74–3.6)	<0.001	1.93 (1.3–2.87)	0.001	

pred, predicted; ref, reference; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; D_{LCO}, diffusing capacity of carbon monoxide; MPCs, major pulmonary complications; ASA, American Society of Anesthesiologists; DFS, disease-free survival.

Variables	В	SE	Р	HR	95% CI
Age	0.044	0.016	0.007	1.05	1.01-1.08
Male	1.203	0.295	0.001	3.33	1.87–5.94
ASA 2 (vs. 1)	1.457	0.421	0.001	4.29	1.88–9.79
ASA 3 (vs. 1)	1.923	0.623	0.002	6.84	2.01–23.2

B, partial regression coefficient; SE, standard error of mean; HR: hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; MPCs, major pulmonary complications.

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P=0.006) (11). In our study, we not only evaluated the presence of PC, but also the severity of them, we find that developing a MPC after VATS lobectomy is associated with poorer long-term prognosis. These data suggest that, in addition to general systemic inflammatory response itself, complications, particularly major complications, may further exacerbate inflammatory and immunosuppressive states, resulting in the negative impact on the long-term outcomes.

Male and elderly patients are more likely to developing MPCs after lung resection. Fernandez et al. [2016] indicated that being male and elderly patients have consistently been identified as negative predictors of major postoperative complications after lung cancer surgery (23). Perioperative mortality in male patients was also significantly increased. Tong et al. also found a significant increase in hospitalization stay after lung resection in male patients, possibly because that men were less tolerant of pain and were often associated with more comorbidities (24). Elderly patients are often accompanied by more comorbidities, hence the risk of postoperative complications increases. However, Dominguez-Ventura et al. indicated that elderly lung cancer patients could still benefit from radical lobectomy, the mortality was only 0-8.8%, but with higher rate of postoperative complications, but postoperative complications increased significantly with age, our study also shows this trend (25). Rueth et al. showed that complications in patients over 75 years old after lobectomy was 1.3 times more compared with patients less than 70 years old, the further stratification analysis showed that age was the independent risk factor for cardiac complications, but not a risk factor for PCs and other complications (22).

Nicholas firstly proposed that ASA score has a strong ability to predict surgical complications and perioperative mortality (21), and then Agostini showed that the risk of PCs increased by 3.9 times in patients with ASA score \geq 3 after lung resection (4), our study also shows that ASA score was associated with MPCs in NSCLC patients after VATS lobectomy.

There are several limitations to this study. First, because of its retrospective nature, there is inevitable bias in the data collection and assessment of postoperative complications. In addition, there is a relatively short follow-up time in the analysis of impact on long-term outcomes.

Conclusions

In summary, we found that MPCs after VATS lobectomy were associated with a poorer long-time outcome in lung

cancer patients. Age, male, ASA score were the independent risk factors of MPCs.

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Footnote

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

Ethical Statement: The study was approved by the Institutional Review Board of Peking University People's Hospital (No. 2014PHB033-01) and written informed consent was obtained from all patients.

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