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ORIGINAL ARTICLE

Quantitative computed tomography for predicting cardiopulmonary complications after lobectomy for lung cancer in patients with chronic obstructive pulmonary disease

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Abstract

Objectives In lung cancer resection, chronic obstructive pulmonary disease is a risk factor for post-operative complications. Few studies on post-operative complications of lung cancer resection have considered radiographic emphysematous change as an index. Here, we have examined the relationship between the regional ratio of the emphysematous area in pre-operative computed tomography images and cardiopulmonary complications in patients with chronic obstructive pulmonary disease who underwent lung cancer resection.

Methods We retrospectively evaluated 159 patients with chronic obstructive pulmonary disease who underwent lobectomy for lung cancer at Shizuoka Cancer Center Hospital, Shizuoka, Japan, between 2002 and 2011. Pre-operative factors, including the proportion of the emphysematous area measured by computed tomography as a percentage of the low attenuation area (LAA%), as well as intraoperative factors were analyzed. Cardiopulmonary complications, including pyothorax, pneumonia and atelectasis, acute pulmonary injury, indwelling chest tube, long duration of oxygen supply, and arrhythmia, were evaluated.

Results Cardiopulmonary complications were observed among 61 patients (38%). Univariate analysis revealed that patient age, percentage of forced expiratory volume in 1 s, LAA%, and volume of blood loss were significantly associated with cardiopulmonary complications. Multivariate analysis indicated patient age and LAA% as being significant independent predictors of cardiopulmonary complications.

Conclusions The regional ratio of the emphysematous area is useful for predicting cardiopulmonary complications in patients with chronic obstructive pulmonary disease who undergo lobectomy for lung cancer. In such patients who are also ≥ 70 years of age and exhibit LAA% ≥ 1.0%, careful intra- and post-operative management is warranted.

Keywords Chronic obstructive pulmonary disease · Complications · Low attenuation area · Quantitative computed tomography

Introduction

In lung cancer resection, chronic obstructive pulmonary disease (COPD) is a risk factor for post-operative complications [1]. The severity of COPD is analyzed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, which is based on the percentage of forced expiratory volume in 1 s (%FEV1.0). In addition, an association between percentage predicted post-operative FEV1.0 (%ppoFEV1.0) and post-operative complications has previously been reported [2]. However, few studies on post-operative complications have considered radiographic emphysematous change as an index. In this study,

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we retrospectively examined the relationship between the regional ratio of the emphysematous area in pre-operative computed tomography (CT) images and cardiopulmonary complications in patients with COPD who underwent lung cancer resection.

Subjects and methods

Patients

Among 1174 patients who underwent complete resection for primary lung cancer between October 2002 and September 2011 at Shizuoka Cancer Center Hospital, Shizuoka, Japan, 159 patients with COPD, who underwent lobectomy for lung cancer, were included in this study. COPD was defined, based on spirometry, as an FEV1.0% < 0.7 in a patient with symptoms of dyspnea and/or chronic cough/sputum production, with a history of exposure to cigarette smoke or other known toxins (i.e., biofuels, occupational dusts, etc.). FEV1.0% was calculated as FEV1.0/forced vital capacity (FVC).

Patient data were retrospectively evaluated to determine the association of cardiopulmonary complications with patient background, pulmonary function, proportion of the emphysematous area (LAA%) in pre-operative CT images, and surgical factors. Patients were excluded according to the following criteria: presence of interstitial and other diffuse changes in pre-operative CT images; history of bronchial asthma; complications due to pre-operative infection (e.g., pneumonia or abscess formation); and history of lobectomy for lung cancer. In addition, as very few cases underwent video-assisted thoracic surgery at our hospital, we removed these cases to ensure a more homogeneous subject group (thoracotomy only).

The following parameters were evaluated for association with post-operative complications: baseline demographic and clinical characteristics—age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG-PS), and body mass index; pulmonary function factors—partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), percentage of vital capacity (%VC), and FEV1.0%;and surgical factors—resected lobe of the lungs, lymph node dissection, operative time, and volume of blood loss. In our hospital, diffusing capacity of the lungs for carbon monoxide (DLCO) is evaluated only in subjects exhibiting interstitial changes in pre-operative CT images. Therefore, DLCO was excluded from the pulmonary function evaluation in the present study.

There were 25 cases in which an inhaled bronchodilator was administered before surgery and 107 cases in which rehabilitation by physiotherapist was performed in the peri-operative period. There were no cases in which non-invasive positive pressure ventilation was performed after surgery.

This study was approved by the institutional review board of Shizuoka Cancer Center (approval no. 27-J61-27-1-3), and all subjects gave informed consent.

Computed tomography and measurement of the emphysematous area

Computed tomography was performed with a multi-detector CT scanner (Aquilion16; Toshiba Medical Systems Corporation, Tochigi, Japan). Images were acquired in the helical mode, with a slice thickness of 5 mm, and without intravascular contrast material. With the patient in a supine position, images were acquired at full inspiration [3] from the apex area to the base of the lungs. Digital images were transferred to a teleradiology workstation, and volume-rendered three-dimensional (3D) models of the lungs were reconstructed using Synapse Vincent imaging software (FUJIFILM, Tokyo, Japan). The total number of voxels with specific attenuation values in the lung model was automatically calculated by the software. Threshold limits from -600 to -1024 Hounsfield units (HU) were applied to segment the whole lung, while excluding the soft tissues surrounding the lungs as well as the large vessels within the lungs. Based on previous reports that showed that LAA% is accurately depicted at a maximum attenuation threshold of -950 HU [4–9], the ratio of the number of voxels with attenuation values < −950 HU to the total number of voxels for the whole lung was considered to indicate the percentage of the low attenuation area (LAA%) in the present study. Additionally, pneumatization in the trachea, extrapulmonary bronchus, and the gastrointestinal tract were selectively eliminated (Fig. 1).

Cardiopulmonary complications

Cardiopulmonary complications, including pyothorax, bronchopleural fistula, pneumonia (body temperature > 38° for 48 h, purulent sputum production, and infiltrates on chest radiograph) and atelectasis, acute pulmonary injury, prolonged air leak (> 7 days), a long duration of O_2 supply (> 7 days), and arrhythmia were evaluated. Among patients with a long duration of O_2 supply, those who started home oxygen therapy after being discharged were included.

Arrhythmia was diagnosed by identification of pulse irregularity on electrocardiograms; this included atrial fibrillation. Atrial fibrillation was judged as representative of cardiac complications, because the pulmonary vascular bed is often reduced in cases with COPD. We did not use prophylactic agents for atrial fibrillation before surgery. Because there were no cases with heart failure (as indicated by acute emergence of symptoms and signs

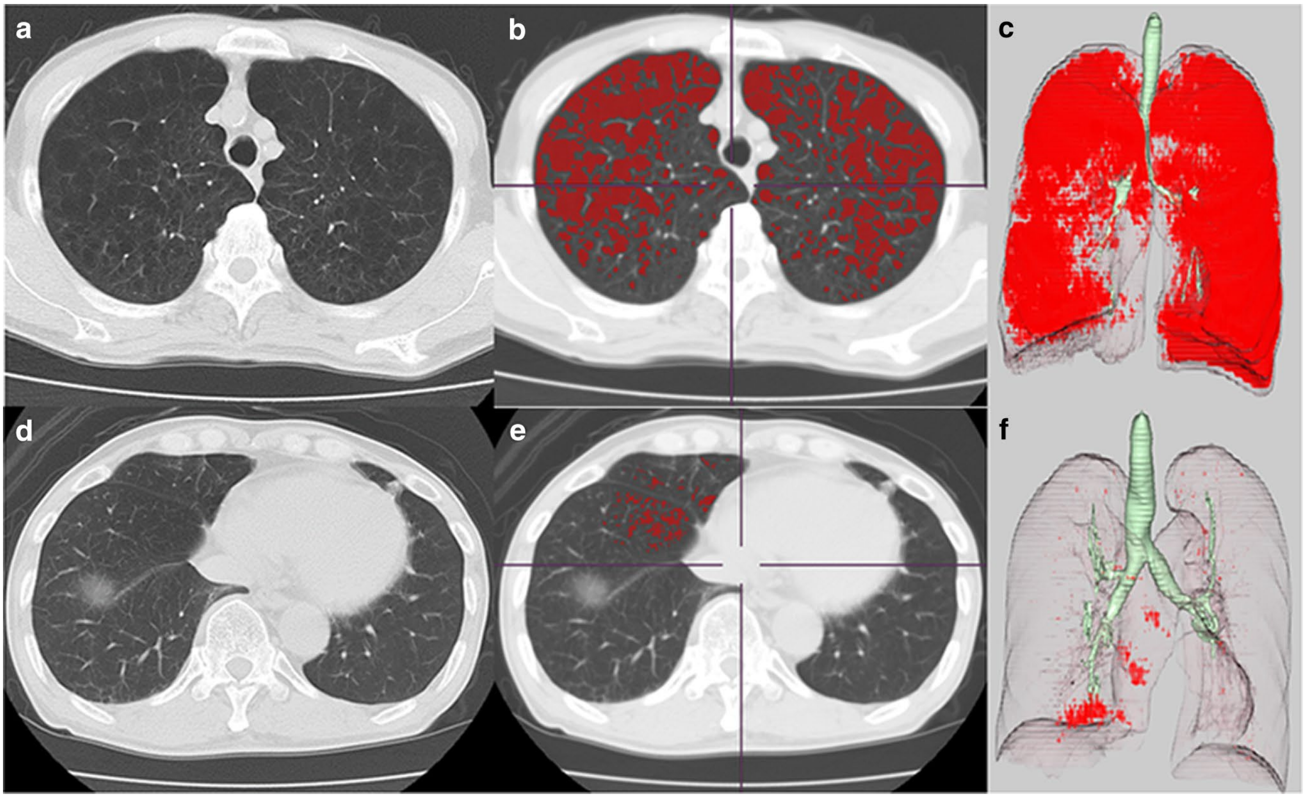

Fig. 1 CT findings of two cases with low attenuation area (LAA%) of 28.9% (**a–c**) and 0.50% (**d–f**). **a, d** Axial computed tomography image. **b, e** Emphysematous area in the same section (from −950 to 1024 Hounsfield units) displayed in red. **c, f** Representation of the emphysematous region in a three-dimensional model

indicating a breakdown of the compensatory action of the cardiac pump, increased ventricular end-diastolic pressure, and failure of perfusion of the main organs) or acute coronary syndrome (caused by rapid coronary stenosis), we excluded those items from this study.

Statistical analysis

Relationships between cardiopulmonary complications and patient background, pulmonary function, LAA%, and surgical factors were evaluated by univariate and multivariate analyses. The Mann–Whitney test and Fisher's exact test were used for univariate analysis.

p values less than 0.05 were considered to indicate statistically significant differences. Factors with $p < 0.05$ in univariate analysis were included in the multivariate analysis. Risk of cardiopulmonary complications was evaluated by logistic regression analysis. Statistical analyses were performed using the JMP software version 9.0 (SAS Institute, Cary, NC, USA).

Results

One-hundred-and-fifty-nine patients (male 141; female 18; mean age, 69 years; age range 48–89 years) with COPD who underwent lobectomy for lung cancer were included in our study. More men were heavy smokers. While 98 patients were current smokers, 61 were former smokers. The median LAA% was 1.0% (range 0.0–28.9%). Patient characteristics are summarized in Table 1.

A total of 84 instances of cardiopulmonary complications were observed in 61 patients (38%); complications included pyothorax ($n = 1$), bronchopleural fistula ($n = 2$), pneumonia and atelectasis ($n = 10$), acute respiratory distress syndrome ($n = 1$), prolonged air leak (> 7 days; $n = 17$), a long duration of O_2 supply (> 7 days; $n = 37$), and arrhythmia (paroxysmal atrial fibrillation; $n = 16$); some patients experienced more than one complication. Cardiopulmonary complications occurred in 35 of 98 current smokers and 26 of 61 former smokers. In this study, there were no deaths during the peri-operative period.

Table 1 Patient characteristics ($n = 159$)

Variables	
Age (years)	69 (48–89)
Sex (male/female)	141/18
Smoking history (current/former)	98/61
ECOG-PS (0/≥ 1)	127/32
BMI (kg/m^2)	21.9 (15.4–30.1)
PaO_2 (mmHg)	84.2 (57.9–123.0)
$PaCO_2$ (mmHg)	39.9 (26.7–48.7)
%VC	101.4 (60.4–164.8)
FEV1.0%	62.0 (31.7–69.9)
ppoFEV1.0 (l)	1.6 (0.7–2.7)
%ppoFEV1.0	68.7 (29.5–116.3)
GOLD classification (I/II/III)	105/46/8
LAA%	1.0 (0.0–28.9)
Lobectomy (upper/middle/lower)	112/8/39
LND (systematic/hilar)	104/55
Operative time (min)	270 (140–588)
Blood loss (ml)	150 (8–1400)

Data are presented as median (range) or number

BMI body mass index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *FEV1.0* forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *LAA%* percentage of low attenuation area, *LND* lymph node dissection, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, *ppo* predicted post-operative, *VC* vital capacity

Univariate analysis revealed age ($p < 0.001$), FEV1.0% ($p = 0.005$), LAA% ($p < 0.001$), and volume of blood loss ($p = 0.043$) as being significantly related to post-operative cardiopulmonary complications (Table 2).

The median age was approximately 70 years old, and therefore, the cut-off value was set at 70 years. Similarly, operative time and blood loss were sorted and analyzed according to the median, respectively. Based on receiver operating characteristic (ROC) curve analysis, 1.0% was selected as the optimal LAA% cut-off value for predicting cardiopulmonary complications with both high sensitivity and high specificity (sensitivity 75.4% and specificity 62.2%) (Fig. 2). The incidences of cardiopulmonary complications among patients with LAA% < 1.0% and ≥ 1.0% were 19.5% and 56.0%, respectively ($p < 0.001$; Table 3).

The results of multivariate analysis indicated that age ($p < 0.001$) and LAA% ($p < 0.001$) were significant independent predictors of post-operative cardiopulmonary complications (Table 4).

Discussion

At present, LAA% is known as the most accurate quantitative index of pulmonary emphysema [10–12]. It can be measured within a few minutes, not only by radiologists, but even by physicians without specialized training, and has excellent objectivity and reproducibility. Attenuation values

Table 2 Operative factors associated with cardiopulmonary complications (univariate analysis)

	Complications ($n = 61$)	No complications ($n = 98$)	p value
Age (≥ 70 years/< 70 years)	43/18	37/61	< 0.001*
Sex (male/female)	57/4	84/14	0.13
Smoking history (current/former)	35/26	63/35	0.38
ECOG-PS (0/≥ 1)	45/16	82/16	0.13
BMI	21.7 (16.7–30.1)	22.0 (15.4–29.8)	0.41
Lower lobectomy/others	16/45	23/75	0.69
Systematic/Hilar LND	39/22	65/33	0.75
Operative time (≥ 270 min/< 270 min)	25/36	36/62	0.59
Blood loss (≥ 150 ml/< 150 ml)	22/39	21/77	0.04*
PaO_2 (mmHg)	79.3 (58.7–123.0)	84.9 (57.9–111.0)	0.05
$PaCO_2$ (mmHg)	39.8 (26.7–46.3)	39.9 (29.7–48.7)	0.87
%VC	99.0 (72.0–159.5)	103.0 (60.4–164.8)	0.17
FEV1.0%	59.3 (31.7–69.9)	63.6 (34.6–69.9)	0.005*
ppoFEV1.0 (L)	1.46 (0.65–2.46)	1.65 (0.72–2.73)	0.52
%ppoFEV1.0	65.2 (29.5–116.3)	70.3 (35.0–102.2)	0.45
GOLD classification (1/≥ 2)	35/26	70/28	0.06
LAA%	2.1 (0.1–28.0)	0.6 (0.0–28.9)	< 0.001*

BMI body mass index, *ECOG-PS* Eastern Cooperative Oncology Group performance status, *FEV1.0* forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *LAA%* percentage of low attenuation area, *LND* lymph node dissection, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, *ppo* predicted post-operative, *VC* vital capacity

*Values of $p < 0.05$ were considered statistically significant

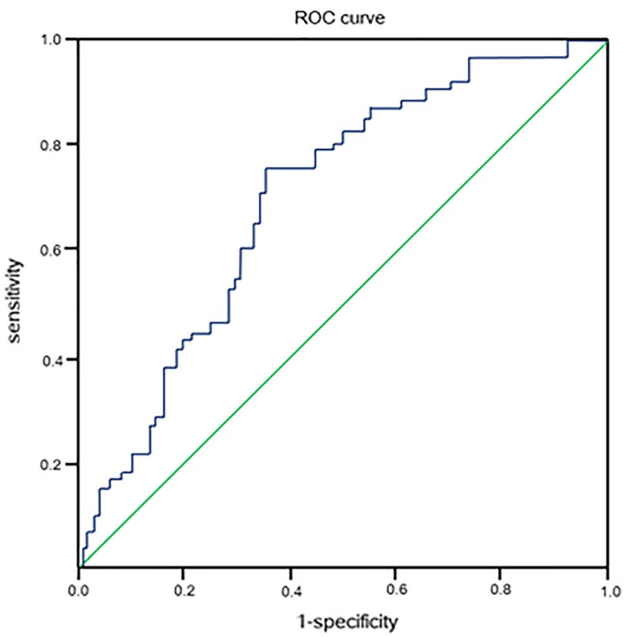

Fig. 2 Receiver operating characteristic curve of percentage of the low attenuation area (LAA%)

Table 3 Incidence of cardiopulmonary complications according to the LAA%

LAA%	*n*	Complications (*n* = 61)	No complications (*n* = 98)	*p* value
< 1.0%	77	15 (19.5%)	62 (80.5%)	< 0.001
≥ 1.0%	82	46 (56.0%)	36 (46.0%)	

LAA% percentage of low attenuation area

Table 4 Operative factors associated with cardiopulmonary complications (multivariate analysis)

Variables	Odds ratio	95% confidence interval	*p* value
Age (≥ 70 years)	4.61	2.02–10.48	< 0.001
FEV1.0%	1.04	0.97–1.11	0.24
GOLD	2.04	0.85–4.87	0.10
PaO2	0.97	0.94–1.00	0.12
LAA% (≥ 1.0%)	5.57	2.30–13.48	< 0.001
Blood loss (≥ 150 ml)	2.07	0.87–4.89	0.09

FEV1.0 forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *LAA%* percentage of low attenuation area, *PaO_2* partial pressure of arterial oxygen

can now be obtained without the need for data transfer to other computer systems. Three-dimensional lung models can be constructed automatically with volumetric data using imaging software. The ratio of the emphysematous area can be easily calculated at low attenuation thresholds. Additionally, the LAA% is known to be more effective than pulmonary function tests for detecting early emphysematous changes [13]. Conventionally, the Goddard classification system has been used for rating chest CT findings in COPD [14]. However, it is a subjective method of evaluation, and discrepancies in ratings among different observers are a drawback.

Previous studies have reported that LAA% is correlated with pulmonary function [15–17], exercise capacity in patients with COPD [18], and risk factors for lung cancer [19]. The possibility of clinical application of quantitative CT in surgery has been studied in lung volume reduction surgery [20–24]. Few studies have reported significant parameters for quantifying emphysema based on CT images for predicting post-operative cardiopulmonary complications.

In previous studies, LAA% was not a significant index of post-operative cardiopulmonary complications. Rather, predicted post-operative arterial oxygen saturation (ppoSaO2) and %ppoFEV1.0 were demonstrated to be significant predictors of such complications [25, 26]. These reports concluded that the use of LAA% in combination with spirometry could help to predict post-operative cardiopulmonary complications, because ppoSaO2 is calculated by a regression equation incorporating pre-operative arterial oxygen saturation (preSaO_2) and LAA%.

The present study included only patients with COPD. Neither FEV1.0% nor %ppoFEV1.0 exhibited significant correlation with cardiopulmonary complications, whereas LAA% was identified as a significant independent predictor of cardiopulmonary complications in multivariate analysis. A previous study had reported that patients without baseline airway obstruction in spirometry who developed it during follow-up had significantly more severe emphysematous changes at baseline than those who did not develop obstruction [27]. This suggests that airflow limitation cannot manifest unless the severity of emphysema exceeds a specific threshold, and that LAA% can detect subclinical COPD that can cause airway obstruction in the future. Furthermore, another report found that 10.4% of patients with radiographic emphysema and clinical COPD were found to exhibit normal spirometry findings [28]. From the above, we concluded that LAA% is able to detect alveolar disorders associated with smoking more sensitively than spirometry, which can be derived from its strong correlation with post-operative cardiopulmonary complications. In our study, there were 105 cases corresponding to GOLD I, which seemed to indicate mild airway obstruction. There were 49 cases with LAA% ≥ 1.0% and 56 with LAA% < 1.0% in this group. Cardiopulmonary complications were significantly different between the groups (25 versus 10 cases, respectively; $p < 0.001$), which was consistent with our speculations about LAA%.

Therefore, LAA% may be an objective and excellent predictor of complications in addition to spirometry findings, which were previously identified as being useful for predicting cardiopulmonary complications in patients with COPD undergoing lobectomy for lung cancer.

Cardiopulmonary complications occurred at a higher rate in former smokers than in current smokers in this study. The smoking index was compared in each group, but no marked difference was found between the median values in current smokers (1060; range 50–5000) and those in former smokers (1020; range 100–4500). This suggested that the destruction of alveolar structure and the decrease in the pulmonary vascular bed caused by smoking are irreversible changes and reduction of cardiopulmonary complications cannot be achieved by abstaining from smoking. Although the reason why cardiopulmonary complications occurred more frequently in former smokers than current smokers is not clear in this study, we would like to study this point again after accumulating more cases.

The use of LAA% as a predictor of cardiopulmonary complications presents a few challenges. Lesions of interstitial pneumonia cannot be evaluated by measuring LAA%. For example, in a honeycomb lung, which is a characteristic finding of usual interstitial pneumonia, the radiodensity (HU values) of fibrotic tissues is high, while that of the pneumatic center is low, which makes it challenging to evaluate honeycomb lungs based only on HU values. A CT-based quantitative index that can evaluate interstitial pneumonia and predict post-operative complications, such as acute exacerbation, should be developed.

Furthermore, the most important sites of airflow obstruction in COPD are airways smaller than 2 mm in diameter. Structurally, airflow obstruction involves airway narrowing and wall thickening, peribronchial fibrosis, and luminal inflammatory mucous exudate. In the present study, these small airways could not be assessed directly by LAA%, because air trapping can be considered as an indirect sign of small airway dysfunction on expiratory CT images. Therefore, we might not have accurately estimated the risk of post-operative cardiopulmonary complications in subjects with small-airway dominant COPD. Recently, the percentage of lung voxels below − 856 HU in expiratory CT images has been proposed to represent a measure of air trapping in COPD [29].

The present study had some limitations. First, this study was a retrospective review that included patients from a single institution. Further prospective studies are required to validate the present findings. Second, there were differences among the study population in terms of the resected lobe, and this might have influenced our results because the average LAA% of the upper lobes is known to be slightly higher than those of the lower lobes [4]. In the future, the ratio of the LAA% between the lobe of the lung targeted for resection and the whole lung should be calculated to assess the risk of post-operative complications corresponding to individual lobes of the lungs. Third, the LAA% cut-off value of 1.0% was calculated from an ROC curve in this study only. In the future, more cases should be accumulated to investigate whether this cut-off value is accurate.

In conclusion, LAA% is useful for predicting cardiopulmonary complications in patients with COPD undergoing lobectomy for lung cancer. In such patients who are also ≥ 70 years old and who exhibit an LAA% ≥ 1.0%, careful intra- and post-operative management is warranted.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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