Original Article

Efficacy and safety analysis of anlotinib combined with PD-1 inhibitors in advanced non-small cell lung cancer: a retrospective cohort study

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Background: Programmed cell death 1 (PD-1) inhibitors are beneficial for patients with advanced lung cancer. However, the population who will benefit from PD-1 inhibitors is limited, and their efficacy needs to be further improved. Antiangiogenic agents may regulate tumor microenvironment to improve immunotherapy efficacy. This real-world study sought to investigate the efficacy and safety of anlotinib combined with PD-1 inhibitors in the treatment of advanced non-small cell lung cancer (NSCLC).

Methods: In total, 42 advanced NSCLC patients were included in this retrospective study. All the patients received anlotinib combined with PD-1 inhibitors from May 2020 to November 2022. The progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs) of the patients were evaluated.

Results: The patients had an overall median PFS of 5.721 months [95% confidence interval (CI): 1.365–10.076]. The median PFS and ORRs of the male patients compared to the female patients were 10.553 *vs.* 4.340 months, and 36.4% *vs.* 0.0%, respectively (P=0.010 and 0.041). The DCRs for the first-, second-, and third-line therapies were 100%, 83.3%, and 64.3%, respectively (P=0.096). In relation to the pathological types, the ORRs of the sarcoma, squamous, and adenocarcinoma patients were 100.0%, 33.3%, and 18.5%, respectively (P=0.025). The DCRs of patients with the tumor protein 53 (TP53) mutation, other status, and epidermal growth factor receptor (EGFR) mutations were 100.0%, 81.5%, and 40.0%, respectively (P=0.020). All-grade AEs occurred in 52.38% of the patients. The grade 3 AEs were hypertension (7.14%), pneumonia (2.38%), and oral mucositis (2.38%). In total, 3 patients discontinued treatment due to anemia, oral mucositis, and pneumonia, respectively.

Conclusions: Anlotinib combined with PD-1 inhibitors has potentially good efficacy and a tolerated safety profile in the treatment of advanced NSCLC patients.

Keywords: Anlotinib; non-small cell lung cancer (NSCLC); advanced; PD-1 inhibitors

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Introduction

Due to the absence of effective screening programs and the late onset of symptoms, lung cancer is mostly diagnosed at an advanced stage, and has a 5-year survival rate of only 5% (1). As a treatment for non-small cell lung cancer (NSCLC), classic chemotherapy has only shown overall response rates of 6.7–10.8% (2) and 5-year survival rates of 7–14% (3).

Immune checkpoint inhibitors (ICIs) can restore active T-cell infiltration, stimulate cancer-specific immune responses, and improve the long-term survival and durable response (4). In addition to the traditional gold standards overall survival (OS) and objective response rate (ORR), the unique evaluation standards for ICIs such as treatment-free time survival (5) and durable responses (6), which are distinctively clinical benefits of ICIs. ICIs rechallenge might be an effective therapy for patients who discontinue treatment due to immune-related adverse events (AEs) (7). ICIs have been shown to prolong the survival time of advanced lung cancer patients (8). However, only about 20% of NSCLC patients benefit from immune monotherapy (9,10). Thus, it is necessary to explore combined therapy strategies to improve the efficacy of immunotherapy.

There is increasing evidence that antiangiogenic agents regulate T cells, which modulate the systemic effects of immune cell function (11) and improve tumor vascular perfusion and oxygenation (12). Combining immunotherapy and antiangiogenic agents may synergistically increase treatment efficacy. Anlotinib is a small-molecule multi-targeted antiangiogenic agent that has an inhibitory action not only on tumor cells but also on angiogenesis (13). Anlotinib could stimulate the infiltration of the innate immune cells (14). The therapy of anlotinib combined with programmed cell death 1 (PD-1) inhibitors is efficacy, durability, and safety (15). This combination of immunotherapy and anlotinib may provide an effective treatment for advanced lung cancer patients who cannot tolerate chemotherapy or have non-treatable gene mutations. However, evidence on the efficacy and safety of anlotinib combined with PD-1 inhibitors in the treatment of advanced NSCLC is limited. The diversity and flexibility of real-world research make it powerful evidence for responding to practical clinical difficulties. Thus, we retrospectively explored the efficacy and safety of the combination of anlotinib and PD-1 inhibitors in advanced NSCLC. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-289/rc).

Highlight box

Key findings

- This study indicated that anlotinib combined with programmed cell death 1 (PD-1) inhibitors provides an effective and safe treatment strategy for patients with advanced lung cancer.

What is known and what is new?

- The use of PD-1 inhibitors in the treatment of lung cancer has been widely reported.
- We examined the use of anlotinib combined with PD-1 inhibitors in the treatment of advanced non-small cell lung cancer, which has rarely been reported in previous studies.

What is the implication, and what should change now?

- We found that anlotinib combined with PD-1 inhibitor therapy is effective and safe in the treatment of non-small cell lung cancer. In the future, the further research needs to be conducted on the overall survival of the patients who receive this treatment.

Methods

Patients and treatment

This was a retrospective, longitudinal study. The medical records of advanced NSCLC patients who received anlotinib and PD-1 inhibitors from May 2020 to November 2022 at the Shanghai Chest Hospital, China were retrospectively reviewed. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have pathologically confirmed stage IIIB–IV NSCLC according to the 8th edition of the American Joint Committee on Cancer staging manual; and (II) have received anlotinib (10 mg/12 mg) and PD-1 inhibitors (including pembrolizumab, nivolumab, tislelizumab, sintilimab, and camrelizumab). Patients without complete medical records or follow-up information affected the evaluation of efficacy and safety were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013). The Institutional Review Board of the Shanghai Chest Hospital approved the study (No. IS22010), and written consent was obtained from all patients.

Data collection and follow-up

The clinical data, including the age, gender, pathological type, clinical stage, smoking history, treatment line, and metastatic site. Therapeutic and prognostic information were retrospectively collected. Clinical response was assessed according to the Response Evaluation Criteria in Solid Tumor (version 1.1) by computed tomography (CT) scans every 6 weeks (±7 d), and included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as achieving a CR or PR. The disease control rate (DCR) was defined as achieving a CR, PR, or SD. The disease status and survival status data were acquired from the follow-up records, and the progression-free survival (PFS) and overall survival (OS) of the patients were then calculated. PFS was defined as the time from which the oral administration of anlotinib was started to PD or to the last follow-up. The adverse events (AEs) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

The Chi-square test and Fisher's exact test were used to compare the differences between the subgroups in terms of the clinical characteristics and efficacy. PFS was analyzed by Kaplan-Meier method. Hazard ratio (HR) was estimated with the use of a Cox proportional-hazards model. SPSS 25.0 statistical software (IBM, USA) was used to perform the statistical analysis and generate the figures. A 2-sided P value <0.05 was considered statistically significant.

Results

Baseline characteristics

Among the 48 initially screened patients, 6 were excluded due to incomplete medical records or follow-up information. Thus, a total of 42 patients were included in the study. The patients had a median age of 63 years (range, 47–81 years). Of the 42 patients, 33 (78.6%) were male patients, 25 (59.5%) were ever smokers, and 27 (64.3%) patients were diagnosed with adenocarcinomas. Most of the patients (35, 83.3%) were confirmed to have stage IV NSCLC at the time of diagnosis. Among the patients, 10 (23.8%) had the epidermal growth factor receptor (EGFR) mutation, and 3 (7.1%) had brain metastases, and 6 (14.3%) had liver metastases. The number of patients with programmed cell death-ligand 1 (PD-L1) <1%, PD-L1 1–49%, PD-L1 ≥50%, or PD-L1 unknown was 10 (23.8%), 12 (28.6%), 2 (4.8%), and 18 (42.9%), respectively. The baseline characteristics among the patients with the 4 PD-L1 expression subtypes did not differ significantly. In this study,34 patients had treated chemotherapy, 10 patients had treated EGFR-TKI, and 11 patients had treated ICIs. At the data cut-off date, the median follow-up duration was 13.973 months (range, 1.282–25.085 months) (*Table 1*).

Efficacy evaluation

The overall median PFS (mPFS) (data cut-off date: 25 December 2022) was 5.721 months [95% confidence interval (CI): 1.365–10.076 months]. The between subgroup comparisons revealed significant differences in the PFS and ORRs based on sex. Specifically, the male patients had a longer mPFS (10.554 months; 95% CI: 2.741–18.366 months) than the female patients (4.340 months; 95% CI: 0.723–7.956 months, P=0.010). The ORRs and DCRs of male patients and female patients were 36.4% *vs.* 0.0% (P=0.041) and 78.8% *vs.* 55.6% (P=0.209). The mPFS of the patients who received anlotinib plus PD-1 inhibitors as a first-, second-, and third-line and above therapy were 17.753, 11.244, and 4.570 months, respectively (P=0.103). The ORRs of the patients who received anlotinib plus PD-1 inhibitors as a first-, second-, and third-line and above therapy were statistically significant by 87.5% *vs.* 16.7% *vs.* 14.3% (P<0.001). The DCRs of the patients who received anlotinib plus PD-1 inhibitors as a first-, second-, and third-line and above therapy were 100.0%, 83.3%, and 64.3% (P=0.096). Further sub-combined analysis of mPFS for first/second line therapy and third line and above therapy were 17.753 and 4.570 months (P=0.055, HR 0.416, 95% CI: 0.166–1.047, *Figure 1*). The mPFS of the stage III patients was not reached, the ORR was 28.6%, and the DCR was 100.0%. The mPFS of the stage IV patients was 5.392 months, the ORR was 28.6%, and the DCR was 68.6%. In terms of the different pathological types, the sarcoma patients had a significantly higher ORR (100.0% *vs.* 33.3% *vs.* 18.5%, P=0.025) and DCR (100.0% *vs.* 83.8% *vs.* 66.7%, P=0.692) than the squamous and adenocarcinoma patients, respectively.

Table 1 Comparison of the baseline characteristics of the patients with different PD-L1 expression levels

Characteristics	PD-L1 <1% (n=10), n (%)	PD-L1 1–49% (n=12), n (%)	PD-L1 ≥50% (n=2), n (%)	PD-L1 unknown (n=18), n (%)	P value
Age (years)					0.316
<65	6 (60.0)	9 (75.0)	0 (0.0)	11 (61.1)	
≥65	4 (40.0)	3 (25.0)	2 (100.0)	7 (38.9)	
Sex					0.519
Male	7 (70.0)	11 (91.7)	2 (100.0)	13 (72.2)	
Female	3 (30.0)	1 (8.3)	0 (0.0)	5 (27.8)	
Smoking history					0.282
No	4 (40.0)	3 (25.0)	0 (0.0)	10 (55.6)	
Ever	6 (60.0)	9 (75.0)	2 (100.0)	8 (44.4)	
Histology					0.069
Adenocarcinoma	5 (50.0)	7 (58.3)	0 (0.0)	15 (83.3)	
Squamous	4 (40.0)	4 (33.3)	2 (100.0)	2 (11.1)	
Sarcoma	1 (10.0)	1 (8.3)	0 (0.0)	0 (0.0)	
NSCLC	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	
Stage					0.185
IIIB/IIIC	3 (30.0)	0 (0.0)	0 (0.0)	4 (22.2)	
IV	7 (70.0)	12 (100.0)	2 (100.0)	14 (77.8)	
Gene status					
EGFR	2 (20.0)	1 (8.3)	0 (0.0)	7 (38.9)	0.569
TP53	1 (10.0)	2 (16.7)	0 (0.0)	2 (11.1)	
Other	7 (70.0)	9 (75.0)	2 (100.0)	9 (50.0)	
Brain metastasis					0.408
No	10 (100.0)	12 (100.0)	2 (100.0)	15 (83.3)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	3 (16.7)	
Liver metastasis					0.474
No	9 (90.0)	11 (91.7)	1 (50.0)	15 (83.3)	
Yes	1 (10.0)	1 (8.3)	1 (50.0)	3 (16.7)	
Anlotinib dose					0.732
10 mg	5 (50.0)	7 (58.3)	2 (100.0)	9 (50.0)	
12 mg	5 (50.0)	5 (41.7)	0 (0.0)	9 (50.0)	

PD-L1, programmed cell death-ligand 1; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor.

The patients with the tumor protein 53 (TP53) mutation had a significantly higher DCR (100.0% *vs.* 40.0% *vs.* 81.5%, P=0.020) than those with the EGFR and other mutations, respectively. Similarly, the patients with the TP53 mutation had a better PFS (10.685 *vs.* 2.038 *vs.* 7.989 months, P=0.144) and ORR (40.0% *vs.* 10.0% *vs.* 33.3%, P=0.406) than those with the EGFR and other mutations, respectively. There was no statistically significant difference

	Median PFS (95% CI), m	P	HR (95% CI)
First/second line	17.753 (8.126–27.381)	0.055	0.416 (0.166–1.047)
Third-line and above	4.570 (3.851–5.289)		

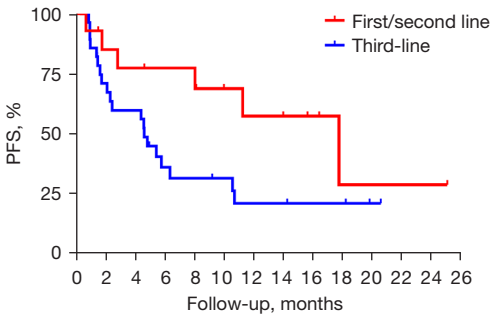

Figure 1 Comparison of survival curves among patients with first/second line and third-line and above in the overall population. PFS, progression-free survival; CI, confidence index; m, months; HR, hazard ratio.

in the treatment efficacy among the patients with different expressions of PD-L1 (PD-L1 negative, 1–49%, and ≥50%), and their mPFS were 7.989, 2.762, 1.414, and 5.392, months, respectively (P=0.849), their ORRs were 40.0%, 25.0%, 50.0%, and 22.2%, respectively (P=0.557), and their DCRs were 80.0%, 75.0%, 50.0%, and 72.2%, respectively (P=0.817, *Table 2*).

Safety

All-grade AEs occurred in 22 patients (52.38%) and mainly included fatigue (45.24%), anorexia (40.48%), hypertension (30.95%), pneumonia (7.14%), and hemoptysis (7.14%). The grades 3 AEs were hypertension (7.14%), pneumonia (2.38%), and mucositis oral (2.38%). A total of 3 patients discontinued treatment due to anemia, mucositis oral, and pneumonia respectively (*Table 3*).

Discussion

Anlotinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) that selectively inhibits the vascular endothelial growth factors 1–3, fibroblast growth factors 1–4, platelet-derived growth factor, C-proto-oncogenic receptor tyrosine kinase, and proto-oncogene rearrangement during transfection (RET). It has the dual effects of regulating tumor angiogenesis and repressing tumor cell growth. Advanced NSCLC patients who received anlotinib as a third-line or above therapy have been reported to have a mPFS of 5.4 months, a mOS of 9.6 months, an ORR of 9.2%, and a DCR of 81.0% (16). Anlotinib could improve PFS in NSCLC patients with liver metastases (17). Patients with brain metastases treated with anlotinib have been reported to have a mPFS of 4.17 months and a mOS of 8.57 months. Additionally, the following patients have been reported to have a significantly longer time to brain progression: those aged >60 years, those with EGFR mutations, non-smokers, those with an Eastern Cooperative Oncology Group performance status of 1, those with IV stage, and those who have previously received targeted TKI therapy, or surgery (18).

PD-L1 expression is not the only criterion to evaluate the efficacy of anti-PD-1 therapies, others such as tumor-infiltrating lymphocytes, mutational burden, immune gene signatures, and multiplex immunohistochemistry are effective predictive biomarker (19). Neoadjuvant nivolumab plus chemotherapy resulted in significantly longer disease-free survival than chemotherapy alone (20). The immunostimulatory properties of the treatment appear to be positively correlated with the dose of anlotinib, which differs from other antiangiogenic agents (21,22). Anlotinib could stimulate the infiltration of the innate immune cells (e.g., the natural-killer cells and antigen-presenting cells), and thus convert the tumor immune microenvironment from an immune-suppressive to immune-supportive phenotype. Anlotinib has been shown to upregulate interferon (IFN)-γ expression in $CD4^+$ T cells and to significantly reduce the percentages of M2-like tumor-associated macrophages (14).

Previous studies have confirmed the efficacy of anlotinib combined with PD-1 inhibitors in the treatment of advanced NSCLC patients. In one study, advanced NSCLC patients without EGFR/anaplastic lymphoma kinase (ALK)/tyrosine kinase receptor c-ros-oncogene 1 (ROS1) mutations received sintilimab and anlotinib as a first-line therapy and achieved a DCR of 100%, a mPFS of 15 months, and a 12-month PFS rate of 71.4% (15). Compared to mOS of 9.2–13.8 months in ICI monotherapy (23), the patients who received the combination treatment as a second-line and above treatment had a mPFS of 11.4 months, a mOS of 27.0 months, an ORR of 40.0%, and a DCR of 82.5% (24). The most common AEs were fatigue (45.5%), anorexia (40.9%), and hypertension (45.5%). The ≥3 grade AEs were hypertension (9.1%), mouth ulceration (9.1%), rash (9.1%), pneumonitis (4.6%), and diarrhea (4.6%) (25).

In this study, we found that the PFS of the patients treated with anlotinib combined with PD-1 inhibitors as a first-, second-, and third-line and above therapy were 17.753, 11.244, and 4.57 months, respectively, while the

Table 2 Efficacy of anlotinib combined with PD-1 inhibitors in the treatment of NSCLC

Characteristics	N	PFS		ORR		DCR	
		Median (95% CI) (m)	P value	n (%)	P value	n (%)	P value
Age (years)			0.468		1.000		0.720
<65	26	5.721 (3.212–8.230)		7 (26.9)		20 (76.9)	
≥65	16	NR		5 (31.3)		11 (68.8)	
Sex			0.010		0.041		0.209
Male	33	10.553 (2.741–18.366)		12 (36.4)		26 (78.8)	
Female	9	4.340 (0.723–7.956)		0 (0)		5 (55.6)	
Smoking history			0.266		0.300		0.733
No	17	4.570 (4.127–5.012)		3 (17.6)		12 (70.6)	
Ever	25	7.989 (0.243–15.735)		9 (36.0)		19 (76.0)	
Histology			0.173		0.025		0.692
Adenocarcinoma	27	4.570 (1.476–7.664)		5 (18.5)		18 (66.7)	
Squamous	12	7.989 (3.370–12.608)		4 (33.3)		10 (83.8)	
Sarcoma	2	NR		2 (100.0)		2 (100.0)	
NSCLC	1	NR		1 (100.0)		1 (100.0)	
Stage			0.066		1.000		0.161
IIIB/IIIC	7	NR		2 (28.6)		7 (100.0)	
IV	35	5.392 (3.437–7.347)		10 (28.6)		24 (68.6)	
Gene status			0.144		0.406		0.020
EGFR	10	2.038 (0.969–3.108)		1 (10.0)		4 (40.0)	
TP53	5	10.685 (NR–NR)		2 (40.0)		5 (100.0)	
Other	27	7.989 (0.756–15.222)		9 (33.3)		22 (81.5)	
PD-L1 expression			0.849		0.557		0.817
<1%	10	7.989 (0.000–20.092)		4 (40.0)		8 (80.0)	
1–49%	12	2.762 (0.000–8.398)		3 (25.0)		9 (75.0)	
≥50%	2	1.414 (NR–NR)		1 (50.0)		1 (50.0)	
Unknown	18	5.392 (2.703–8.080)		4 (22.2)		13 (72.2)	
Treatment line			0.103		<0.001		0.096
First-line	8	17.753 (3.668–31.839)		7 (87.5)		8 (100.0)	
Second-line	6	11.244 (NR–NR)		1 (16.7)		5 (83.3)	
Third-line and above	28	4.570 (3.851–5.289)		4 (14.3)		18 (64.3)	
Brain metastasis			0.074		0.545		0.163
No	39	7.989 (0.909–15.069)		12 (30.8)		30 (76.9)	
Yes	3	2.038 (1.302–2.775)		0 (0.0)		1 (33.3)	

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	N	PFS		ORR		DCR	
		Median (95% CI) (m)	P value	n (%)	P value	n (%)	P value
Liver metastasis			0.379		0.655		0.644
No	36	6.312 (0.000–12.902)		11 (30.6)		27 (75.0)	
Yes	6	4.340 (0.000–9.114)		1 (16.7)		4 (66.7)	
Anlotinib dose			0.821		0.495		1.000
10 mg	23	5.721 (3.085–8.356)		8 (34.8)		17 (73.9)	
12 mg	19	7.989 (0.00–16.570)		4 (21.1)		14 (73.7)	

PD-1, programmed cell death 1; NSCLC, non-small cell lung cancer; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate; CI, confidence interval; m, months; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death-ligand 1; NR, not reached.

Table 3 AEs in the overall population

AEs	Any, n (%)	Grade 3, n (%)
Total	22 (52.38)	5 (11.90)
Fatigue	19 (45.24)	0 (0)
Anorexia	17 (40.48)	0 (0)
Hypertension	13 (30.95)	3 (7.14)
Pneumonia	3 (7.14)	1 (2.38)
Hemoptysis	3 (7.14)	0 (0)
Creatinine increased	2 (4.76)	0 (0)
Mucositis oral	1 (2.38)	1 (2.38)
Palmar-plantar erythrodysesthesia syndrome	1 (2.38)	0 (0)
Proteinuria	1 (2.38)	0 (0)
Hypothyroidism	1 (2.38)	0 (0)
Anemia	1 (2.38)	0 (0)

AE, adverse event.

DCRs were 100%, 83.3%, and 64.3%, respectively. Further sub-combined analysis of mPFS for first/second line therapy and third line and above therapy were 17.753 and 4.570 months (P=0.055, HR 0.416, 95% CI: 0.166–1.047). Numerical values show a difference and P values are close to statistically significant. Thus, this treatment appears to have a better effect as an early line treatment and especially used before the third line. The sarcoma and TP53 mutation patients achieved a DCR of 100%. The male patients benefited more than the female patients. Anlotinib combined with PD-1 inhibitors is a useful treatment for patients after an EGFR-TKI treatment. There was no significant difference in clinical efficacy between patients with different PD-1 expression levels and different PD-1 inhibitors. The 10 mg and 12 mg doses of anlotinib had similar efficacy. All-grade AEs occurred in 52.38% of the patients.

The grade 3 AEs were hypertension (7.14%), pneumonia (2.38%), and mucositis oral (2.38%). Further, the AEs occurred in the patients who received 10 mg of anlotinib were less than those who received 12 mg of anlotinib. A total of 3 patients discontinued treatment due to anemia, mucositis oral, and pneumonia, respectively.

This study has a few limitations. First, the relatively small sample size may affect the results, descriptive data for efficacy and safety profile are needed to be confirmed in future large-scale studies. Second, this is an observational study without setting a matched control group for PD-1 monotherapy or PD-1 inhibitors combined with chemotherapy, our results in line with some of previous studies and can provide a degree of real-world understanding of anlotinib combined with PD-1 inhibitors in advanced NSCLC patients. Despite these limitations, our study enriches the clinical evidence for the efficacy and safety of anlotinib combined with PD-1 inhibitors in patients with advanced NSCLC. In the future, the efficacy and safety assessment of anlotinib combined with PD-1 inhibitors should be explored in prospective clinical trials with larger sample sizes.

Conclusions

This real-world observational study showed that anlotinib combined with PD-1 inhibitors has good efficacy and a

well-tolerated safety profile in advanced NSCLC patients. The combination therapy provides a new strategy for patients with advanced lung cancer.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-289/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-289/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-289/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of the Shanghai Chest Hospital approved the study (No. IS22010), and all the patients provided written informed consent.

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