Original Article

Neoadjuvant programmed cell death protein 1 inhibitors combined with chemotherapy in resectable non-small cell lung cancer: an open-label, multicenter, single-arm study

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Background: Neoadjuvant therapy has significantly improved the 5-year overall survival (OS)of patients with resectable non-small cell lung cancer (NSCLC). The CheckMate 159 trial showed that neoadjuvant therapy with a single-drug programmed cell death protein 1 (PD-1) inhibitor (nivolumab) achieved major pathological response (MPR) and pathological complete response (pCR) in 45% and 15%of participants, respectively. We conducted an open-label single-arm study to evaluate the safety and efficacy of neoadjuvant PD-1 inhibitors in combination with chemotherapy in the treatment of resectable NSCLC.

Methods: This study was conducted in a total of 2 hospitals in the Chinese cities of Xi'an and Chongqing, and included eligible patients over 18 years of age with clinically staged IIA–IIIB NSCLC. All patients were scheduled to receive surgery within 4–6 weeks after neoadjuvant treatment (3–4 cycles) consisting of PD-1 inhibitors combined with a conventional chemotherapy regimen on day 1 of each 21-day cycle.

Results: Twenty-three patients, 22 males, and 1 female with just one of them with no smoking habits) were diagnosed with NSCL C in a stage IIA (3 cases), IIB (3 cases), IIIA (8 cases), and IIIB (9cases) and no druggable driver mutations/translocations were addressed to receive neoadjuvant treatment between June 2018 and June 2020. The treatment was well tolerated with just 3 typical immune-related adverse events (hyperthyroidism, hyperglycemia, and rash) recorded. There was a partial response (PR) and stable disease (SD) in 17 (73.9%) and 6 (26.1%) patients, with an overall response rate (ORR) of 73.9% according to the Response Evaluation Criteria in Solid Tumors (RECIST v.1.1). Six of these patients resulted in pCR (30%) while ten of them showed a MPR (50%). Twenty patients underwent surgical resection after treatment, while further 3 refused surgery. Surgical procedure included video-assisted thoracoscopic resection (10 cases), Vinci Robot surgery (4 cases), and thoracotomy in 4 cases while there were secondary compliance-related thoracotomy in two cases. The pathology analysis revealed a R0 in 19 cases (19/20, 95%).

Conclusions: Our results suggest that the neoadjuvant approach with chemotherapy and PD-1 blocking mAbs is safe and active in patients with resectable NSCLC where is associated with a promising high ORR, MPR and pCR.

Keywords: Neoadjuvant; programmed cell death protein 1 inhibitor combined with chemotherapy (PD-1 inhibitor combined with chemotherapy); pathological complete response (pCR); major pathological response (MPR); safety and efficacy

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Introduction

Neoadjuvant therapy is a promising treatment strategy for patients with resectable non-small cell lung cancer (NSCLC). This kind of treatment for many years has included chemotherapy, tyrosine kinase inhibitors (TKIs), radiotherapy, alone or in multiple combinations (1). A meta-analysis of data from NSCLC patients treated with neoadjuvant chemotherapy showed an absolute improvement in 5-year overall survival (OS) of 5 % (40–45%) (2). The mortality risk was significantly reduced in patients who achieved a major pathological response (MPR) after neoadjuvant therapy. Similarly, the results of various clinical trials in patients with bladder, breast, and gastroesophageal cancer showed an improved OS in those who achieved a pathological complete response (pCR) after neoadjuvant therapies (3). In this context further exploration concerning innovative neoadjuvant strategies in resectable NSCLC patients is strongly required.

In more recent years, immunocheckpoint blockade with mAbs to PD-1/PD-L1 alone or in combination with platinum doublets has been shown to significant efficacy in lung cancer patients. The KEYNOTE189 trial in particular, reported the efficacy of an anti-PD-1 mA, pembrolizumab, in combination with chemotherapy in patients with advanced Lung adenocarcinoma. In particular, this trial showed a 12-month OS of 69.2% in the experimental group compared with a 49.4% reported in the group of patients who received the chemotherapy alone (4). Furthermore, in the KEYNOTE407 trial, the OS reached 15.9 months for patients with advanced squamous cell carcinoma in the chemo-immunotherapy arm, compared with 11.3 months recorded in the group addressed to chemotherapy alone (5). The above-mentioned trials have established the role of PD-1 blockade and chemotherapy in the treatment of NSCLC. In line with these results a recent meta-analysis showed that NSCLC patients over-expressing with the programmed death ligand 1 (PD-L1) (PD-L1 score >50%) receiving pembrolizumab-chemotherapy combination showed a much greater ORR, and progression-free survival (PFS) compared with the groups of patients receiving chemotherapy- or pembrolizumab-alone (6). Finally, the CheckMate159 trial reported an MPR rate of 45% in NSCLC patients receiving neoadjuvant therapy with nivolumab, which was much higher than that achieved by any previously tested chemotherapy regimens in neoadjuvant setting (7). The trial therefore suggested that PD-1 blockade is effective and may have definite advantages in patients with resectable NSCLC. Therefore, the present study was conducted to evaluate the anti-tumor activity and safety of neoadjuvant PD-1 blocking mAbs used in combination with standard chemotherapy for potentially resectable (clinical stage IIA–IIIB) NSCLC patients for only Asian performed setting in two different oncology centers in China (Xi'an and Chongqing). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-21-130).

Methods

This study is a multinstitutional single-arm observational study, including 23 patients who received the neoadjuvant treatment in two different Chinese center study. Clinical stages IIA–IIIB NSCLC patients over the age of 18 years with were eligible for inclusion. All of the enrolled patients were scheduled to receive surgery within 4–6 weeks after neoadjuvant therapy that consisted in 3–4 cycles of a conventional chemotherapy regimen with PD-1 inhibitors on day 1 of each cycle according to the international consensus. The specific chemoimmunotherapy regimens are detailed in the *Table 1*. Additional inclusion criteria included eligibility for surgery, as indicated by auxiliary examination including lung function and blood gas analysis; no distant metastasis; and no contraindications for PD-1 inhibitor therapy. The patients' clinical staging was reviewed by 3 senior physicians and was confirmed if at least 2 of them agreed. Positron emission tomography/computed tomography (PET/CT) and immunohistochemicalPD-L1 detection were not necessary for inclusion. Patients with adenocarcinoma who had epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) rearrangement were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tangdu Hospital of the Fourth Military Medical University (202012-12-KY-02-XW-01) and informed consent was

Table 1 Specific chemoimmunotherapy regimens received by each patient

Patient no.	Chemoimmunotherapy	Cycles	Pathological type	Response as per RECIST v.1.1	pCR/MPR	PD-L1 (TPS)
P1	Pemetrexed disodium (500 mg/m^2, D1) + cisplatin (75 mg/m^2, D1) + nivolumab (360 mg, D1)	3	Adenocarcinoma	PR	pCR	N
P2	Nab-paclitaxel (260 mg/m^2, D1) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	3	Squamous carcinoma	PR		5%
P3	Gemcitabine (1000 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	2	Squamous carcinoma	PR		70%
P4	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + nivolumab (200 mg, D1)	3	Squamous carcinoma	PR	MPR	N
P5	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + nivolumab (200 mg, D1)	3	Squamous carcinoma	PR	MPR	N
P6	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	3	Squamous carcinoma	SD		<1%
P7	Gemcitabine (1,000 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	1	Squamous carcinoma	SD	MPR	N
P8	Gemcitabine (1,000 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	2	Squamous carcinoma	PR	MPR	N
P9	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	4	Squamous carcinoma	PR	pCR	N
P10	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	3	Squamous carcinoma	PR		5%
P11	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	3	Squamous carcinoma	PR		5%
P12	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	3	Squamous carcinoma	PR	pCR	N
P13	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	2	Squamous carcinoma	PR		10%
P14	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	2	Adenocarcinoma	SD	pCR	70%
P15	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	4	Squamous carcinoma	PR		1%
P16	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	3	Squamous carcinoma	SD		15%
P17	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	2	Squamous carcinoma	SD		<1%
P18	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + nivolumab (200 mg, D1)	4	Adenocarcinoma	PR	pCR	15.4%
P19	Pemetrexed disodium (500 mg/m^2, D1) + cisplatin (75 mg/m2, D1) + sintilimab (200 mg, D1)	3	Adenocarcinoma	SD		<1%
P20	Nab-paclitaxel (130 mg/m^2, D1, 8) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	3	Squamous carcinoma	PR	pCR	N

Table 1 (*continued*)

Table 1 (*continued*)

Patient no.	Chemoimmunotherapy	Cycles	Pathological type	Response as per RECIST v.1.1	pCR/MPR	PD-L1 (TPS)
P21	Nab-paclitaxel (130 mg/m², D1, 8) + nedaplatin (80 m/m^2, D1) + pembrolizumab (200 mg, D1)	3	Squamous carcinoma	PR		N
P22	Paclitaxel (175 mg/m², D1) + carboplatin (AUC=5, D1) + nivolumab (360 mg, D1)	2	Squamous carcinoma	PR		N
P23	Nab-paclitaxel (130 mg/m², D1, 8) + nedaplatin (80 m/m^2, D1) + sintilimab (200 mg, D1)	3	Squamous carcinoma	PR		N

pCR, pathological complete response; MPR, major pathological response; PR, partial response; SD, stable disease; N, none detected; AUC, area under the curve.

taken from all individual participants.

Study endpoints

The primary endpoints of the study were the safety and efficacy of neoadjuvant chemotherapy combined with PD-1 inhibitors. The safety-related endpoints included adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE, v.4.0). The efficacy-related endpoints included ORR according to the Response Evaluation Criteria in Solid Tumors (RECIST v.1.1), and postoperative pathological down-staging according to the eighth edition of the National Comprehensive Cancer Network (NCCN) guidelines for tumor-node-metastasis (TNM) staging of NSCLC.

The secondary study endpoints were pCR, which was defined as the complete absence of tumor cells, and MPR, which was defined as <10% residual viable tumor (RVT).

Statistical analysis

Adverse events and feasibility were continuously monitored. Continuous variables are presented as means with standard deviation, while categorical variables are presented as frequencies.

Results

Patient characteristics

Twenty-three eligible candidates were recruited for this study. There were 22 men and one woman with just one of them with no smoking habits. A squamous histology and an adenocarcinoma were respectively, recorded in 19 and 4 of these patients with no driver mutations/translocation (EGFR or ALK etc.). Three cases were in IIA stage, 3 cases in IIB, 8 cases in IIIA, and 9 cases of IIIB stage (*Table 2*). Twenty patients underwent surgical resection Fourteen of them completed 3–4 cycles of chemo-immunotherapy as described elsewhere (method section) prior surgery; five further patients experienced grade 1 or 2 irAEs and where addressed to surgery after two treatment cycles while one last patient presented a lung abscess and underwent surgery after just one neo-adjuvant treatment cycle. All data on specific chemo-immunotherapy regimens are shown in *Table 1*. Three patients did not receive; in fact, two of them who completed the neoadjuvant program refused the risk of the surgery (Patients #21 and #23, *Table 2*) while another one (#22) refused to complete the neoadjuvant program after he developed a severe (grade 3) hyperglycemia during the second chemotherapy cycle.

Surgical treatment

Among the 20 patients who underwent surgery, 11 patients underwent lobectomy, 5 patients underwent sleeve resection/bronchoplasty, 2 patients received bilobectomy, and 2 patients underwent pneumonectomy. The results for surgical treatment, morbidity, and mortality are reported in the *Table 3* shows. Surgical methods included Da Vinci's/video-assisted thoracoscopic surgery (VATS) (n=14), conversion to thoracotomy (n=2), and thoracotomy (n=4). Complete resection (R0) was achieved in 95% of patients (19/20) who received surgery that in one case was considered as R1 resection due to the patient being lymph-node positive at the highest station. The median amount of blood lost was 212.5 mL (50–600 mL), and the mean operative time was 250 minutes (65–390 minutes).

Table 2 Baseline characteristics of the intention-to-treat population (N=23)

Characteristics	Value	Surgery	Rejected surgery
Age, years			
Median (range)	61.83		
≥60 years	20	17	3
<60 years	3	3	0
Sex			
Male	22	19	3
Female	1	1	0
BMI, kg/m^2 (mean)	24.38		
History of smoking			
Current/ex-smoker	22	19	3
Never-smoker	1	1	0
KPS			
90	21	19	2
100	2	1	1
Pathological type			
Squamous carcinoma	19	16	3
Adenocarcinoma	4	4	0
Clinical T stage			
T1	2	2	0
T2	4	4	0
T3	11	8	3
T4	6	6	0
Clinical N stage			
N0	4	4	0
N1	9	8	1
N2	10	8	2
Clinical stage			
IIA	3	2	1
IIB	3	3	0
IIIA	8	8	0
IIIB	9	7	2

Table 3 Surgical procedures

Characteristics	Results
Extent of surgery	
Lobectomy	11
Bilobectomy	2
Sleeve resection/bronchoplasty	5
Pneumonectomy	2
Surgical method	
VATS/da Vinci	14
Conversion to thoracotomy	2
Thoracotomy	4
Operation time (min)	250 (65–390)
Bleeding (mL)	212.5 (50–600)
Hospital stay (days)	11.125 (6–22)
Chest tube duration (days)	4.18 (0–7)
Resection margins	
R0	19
R1	1
R2	0

Safety

The post-operative complications were considered to be unrelated to neoadjuvant therapy and are summarized in the *Table 4*. There was no 30- or 90-day mortality, or any postoperative arrhythmia episode. The occurrence of AEs is shown in detail in the *Table 5*. The most common grade 1 or 2 neoadjuvant treatment-related AEs were fatigue (39.1%), alopecia (39.1%), vomiting (34.7%), leucopenia (30.4%), neutropenia (30.4%), and anorexia (30.4%). The treatment-related grade 3 AEs included anorexia, vomiting, fatigue, alopecia, arthralgia, bone pain, and hyperglycemia. Three patients experienced typical immune-related AEs including grade 1–2 hyperthyroidism, grade 3 hyperglycemia, and grade 1–2 rash.

Antitumor activity

The activity of the neoadjuvant combination was evaluated according to the RECIST v.1.1 criteria after three/four treatment cycles. In particular, 17 out of the 23 showed a PR, while 6 further patients presented a SD (*Figure 1A*). The postoperative pathology results showed a MPR (50%) in 10 patients and a pCR (30%) in 6 patients (*Figure 1A*). A total of 15 patients (75%) resulted pathologically downstaged after surgery. On the overall, our analysis showed a median progression-free-survival (PFS) of 11.3 months

Table 4 Postoperative complications

Characteristics	N (%)
Intraoperative blood transfusion	2 (10%)
Death within 30 and 90 days	0
Heart failure	1 (5%)
Postoperative arrhythmia	0
Postoperative hoarseness	1 (5%)
Urinary tract infection or urinary retention	1 (5 %)

Table 5 Adverse events

Characteristics	Any grade	Grade 1–2	Grade 3	Grade 4
Anemia	3	3		
Leukopenia	7	7		
Neutropenia	7	7		
Anorexia	8	7	1	
Vomiting	9	8	1	
Diarrhea	2	2		
Constipation	1	1		
Fatigue	10	9	1	
Alopecia	10	9	1	
Hyperthyroidism	1	1		
Lung abscess	1	1		
Rash	1	1		
Arthralgia and bone pain	2	1	1	
Hyperglycemia	1		1	

(range, 3.1–18.7 months) (*Figure 1B*).

Discussion

This is a clinical trial testing that a neoadjuvant PD-1 blockade and chemotherapy combination for potentially resectable (clinical stage IIA–IIIB) NSCLC patients. Our study yielded promising results resulting in a MPR and a pCR of 50% and 30%, respectively. This finding is of critical interest considering that previous studies in neoadjuvant setting, clearly show that both pCR and MPR are associated with survival benefits (8). For instance, Melek *et al*. examined a recorded a large database of 1,076 NSCLC patients who received surgery reporting a prolonged survival in those patients who achieved a pCR after neoadjuvant or induction therapy showing an outcome which was roughly the same as that recorded in patients diagnosed in a stage IB (1). These findings indicated a clinically significant association of pCR with 5-year OS (9). However, neither neoadjuvant chemotherapy, radiotherapy, nor TKI monotherapy has shown optimal pCR. The L'Intergroupe Francophone de Cancérologie Thoracique (IFCT) clinical trial reported that while only 41 (8.3%) of the 492 study patients achieved pCR, the 5-year OS of these patients reached 80.0%, compared to 55.8% for patients without pCR (10). These clinical results clearly suggest that the OS outcomes of neoadjuvant patients are independently associated with pCR.

With the growing expansion of PD-1 immune checkpoint inhibitors in clinical practice, the CheckMate159 trial was conducted to investigate the effects of neoadjuvant therapy with the PD-1 inhibitor, nivolumab yielding an MPR rate of 45% and a pCR rate of 15% (n=3) (7). This trial also reported that the rates of pCR and MPR in patients treated with neoadjuvant nivolumab were much higher than those recorded in patients who received traditional neoadjuvant regimens with chemotherapy, TKI- or chemoradiation (11-13). Notably, in study concerning locally resectable NSCLC patients treated with neoadjuvant atezolizumab and chemotherapy, 10 (33%) of 30 patients achieved a pCR which is in line with the results of our study (14).

Our data on AEs and complications indicate that the regimens used in this study were well tolerated, with no grade 4–5 AEs observed. AEs and complications occurred in this study at a similar frequency to those reported in the published data on neoadjuvant chemotherapy (15). In this study, we found that immune-related AEs could be well monitored and managed (16), which is similar to the observations made in the NADIM study (17). Only in 1 case did neoadjuvant therapy need to be halted after 1 cycle of treatment, with this patient's complication being lung abscess caused by obstructive pneumonia, which was unrelated to PD-1 inhibitor treatment. After stopping the neoadjuvant treatment, the patient underwent surgery. Interestingly, he achieved MPR, despite only receiving 1 cycle of chemoimmunotherapy. Therefore, this study fully demonstrated that combination neoadjuvant chemoimmunotherapy has good safety and efficacy for the treatment of stage IIA–IIIB NSCLC.

In the present study, the rates of conversion to thoracotomy, completed thoracotomy, and completed

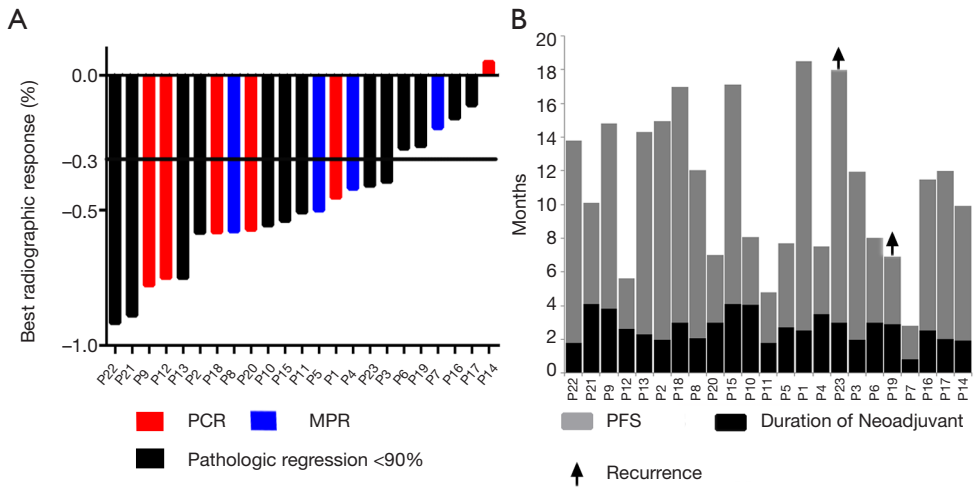

Figure 1 Waterfall plot. The horizontal dashed line represents partial response according to the RECIST v.1.1 criteria, and the different colors represent pathologic regression (A). Follow-up: duration of neoadjuvant therapy and PFS (B). pCR, pathological complete response; MPR, major pathological response; PFS, progression-free-survival.

pneumonectomy were 10%, 20%, and 10% respectively, which are similar to rates reported in a neoadjuvant chemotherapy study (conversion to thoracotomy, 26.5%; pneumonectomy, 17.6%) (18). This finding suggests that neoadjuvant chemoimmunotherapy does not increase the complexity of the surgical procedure compared with neoadjuvant chemotherapy.

There are several limitations to this research. First, this study mainly focused on the safety and efficacy of neoadjuvant therapy due to the small number of patients. In the future, we hope to observe the 5-year OS after neoadjuvant chemoimmunotherapy in a larger patient cohort. Secondly, PD-L1 was detected in some but not all of the patients, while the tumor mutational burden was not recorded for any patient in this study. Furthermore, we did not attempt to reach a conclusion on the relationship between potential biomarkers of PD-L1 and neoadjuvant therapy, and this will be explored in future study. Thirdly, 7 of the 23 patients included refused to continue the neoadjuvant treatment after 1–2 cycles, which might have caused bias regarding the safety and efficacy data. However, the safety and efficacy data of patients who accepted surgery treatment were analyzed according to the different centers, drug treatments, and cycles (Appendix 1). There was no statistical difference for pCR of patients according to the different drugs and cycles.

Conclusions

The existing data suggest that, in the neoadjuvant setting, PD-1 inhibitors combined with chemotherapy can significantly improve the rates of pCR and MPR among patients with resectable NSCLC. The safety profile and surgical complications of these combination regimens are the same as those previously observed among patients who have received chemotherapy alone as a neoadjuvant therapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tlcr-21-130

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-21-130). XY serves as an unpaid editorial board member of TLCR from Jun 2019 to Jun 2021. The other 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 study was approved by the Ethics Committee of Tangdu Hospital of the Fourth Military Medical University (202012-12-KY-02-XW-01) and informed consent was taken from all individual participants.

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