



# Effectiveness and safety of anlotinib plus anti-programmed cell death 1/ligand 1 (anti-PD-1/PD-L1) antibodies as maintenance therapy after first-line chemotherapy combined with anti-PD-1/PD-L1 antibodies in extensive-stage small cell lung cancer: a real-world study

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**Background:** Currently, chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy is the preferred first-line treatment option for extensive-stage small cell lung cancer (ES-SCLC), but with limited overall survival (OS) and progression-free survival (PFS) benefits. The combination of anti-angiogenic drugs with immunotherapy has shown encouraging anti-tumor activity and tolerability, with some degree of overcoming immune resistance. This study aimed to evaluate the effectiveness and safety of anlotinib plus anti-programmed cell death 1/ligand 1 (anti-PD-1/PD-L1) antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC.

**Methods:** Between June 2020 and December 2021, 12 patients with newly diagnosed ES-SCLC in the First Affiliated Hospital of Army Medical University were retrospectively analyzed. All patients without disease progression after 4–6 cycles of first-line platinum-containing chemotherapy plus anti-PD-1/PD-L1 antibodies received anlotinib (12 mg oral/day, days 1–14, followed by 1 week off, every 3 weeks per cycle) plus anti-PD-1/PD-L1 antibodies as maintenance therapy. Several patients underwent chest radiotherapy (intensity-modulated radiotherapy using a 6 MV X-ray) without disease progression before maintenance therapy. The effectiveness and safety of anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC were evaluated.

**Results:** The median follow-up time was 31.1 months. During first-line treatment (including maintenance therapy), one patient achieved a complete response, eight patients achieved a partial response (PR), and three patients had stable disease, with an objective response rate of 75.0% and a disease control rate of 100.0%. During maintenance therapy with anlotinib plus anti-PD-1/PD-L1 antibodies, 50.0% of patients achieved further lesion remission on the basis of the prior initial treatment, of which one patient achieved a PR. The median PFS was 13.6 [95% confidence interval (CI): 11.2–15.6] months, and the median OS was 19.5 (95% CI: 14.5–24.5) months. Treatment-related any grade and grade 3–4 adverse events (AEs) were reported in 100.0% and 58.3% of patients, respectively. No life-threatening AEs were observed. Grade 3–4 AEs included leukocytopenia (58.3%, 7/12), thrombocytopenia (33.3%, 4/12), nausea (33.3%, 4/12), anemia (16.7%, 2/12), and fatigue (8.3%, 1/12). All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis.

**Conclusions:** The combination of anlotinib with anti-PD-1/PD-L1 antibodies demonstrated encouraging effectiveness and safety in treating patients with ES-SCLC, suggesting that it may be a preferred option for

maintenance therapy after first-line chemotherapy combined with immunotherapy.

**Keywords:** Anlotinib; anti-programmed cell death 1/ligand 1 antibodies (anti-PD-1/PD-L1 antibodies); maintenance therapy; small cell lung cancer (SCLC)

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## Introduction

Small cell lung cancer (SCLC) originates from neuroendocrine cells in the lung epithelium and accounts for appropriately 15–20% of all lung cancer cases (1). Due to the high malignancy of SCLC and its rapid progression and early metastasis characteristics, most patients present with obvious signs of metastasis at the time of initial diagnosis, resulting in a poor prognosis (2). Data from 1983 to 2012 showed that the median overall survival (OS) of patients with SCLC was only 7 months, with a 5-year OS of only 1–2% (3). Based on the American Veterans Administration Lung Study Group (VALG) staging system, SCLC can be divided into limited-stage (LS-SCLC) and extensive-stage (ES-SCLC) SCLC. The previous standard first-line treatment for patients with ES-SCLC was platinum-containing chemotherapy (carboplatin or cisplatin) combined with etoposide, with an objective response rate (ORR) of 60–65% and a median OS of approximately

10 months (4,5). In recent years, although immune maintenance therapy after first-line immune checkpoint inhibitors (ICIs) combined with carboplatin and etoposide has shown superior OS compared with chemotherapy alone, the progression-free survival (PFS) benefit is limited (6,7). In the real world, a domestic multicenter retrospective study investigated the effectiveness and safety of programmed cell death 1/ligand 1 (PD-1/PD-L1) combined chemotherapy in treating advanced SCLC, followed by immune maintenance therapy alone. The study involved 154 patients with extended PFS and OS (8). Moreover, the treatment options after disease relapse are extremely limited with a poor prognosis.

Abnormalities in the tumor vascular system are characterized by disordered, immature, disorganized, poorly perfused, and permeable vessels (9) and may be one of the mechanisms of immune resistance. It plays direct immunosuppressive roles, including inhibition of dendritic cells differentiation and maturation (10), reduction of T cell migration and tumor infiltration (11,12), induction or maintenance of regulatory T cells and myeloid-derived suppressor cells (13,14), recruitment of tumor-associated macrophages leading to T cell inactivation (15), up-regulation of PD-1 expression on T cells to induce T cell exhaustion (16), and direct inhibition of T cell proliferation and cytotoxic activity (17,18).

Numerous studies indicate that anti-angiogenic therapies targeting vascular endothelial growth factor (VEGF) or VEGF receptor-2 (VEGFR-2) can modulate the tumor immunosuppressive microenvironment and may help to reverse immune resistance (19–21). The combined blockade of PD-1 and VEGFR in mouse tumor models induces strong synergistic antitumor responses, such as inhibition of VEGF-A expression and thus reducing T cell exhaustion in tumors (16,22). Anlotinib is a multitarget tyrosine kinase inhibitor (TKI) with anti-angiogenic, anti-tumor growth, proliferation, and migration properties by targeting VEGFR 1–3, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and

### Highlight box

#### Key findings

- The combination of anlotinib with anti-programmed cell death 1/ligand 1 (anti-PD-1/PD-L1) antibodies proved to be a favorable choice for maintenance therapy following first-line chemotherapy in conjunction with immunotherapy.

#### What is known and what is new?

- Chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy is the preferred first-line treatment option for extensive-stage-small cell lung cancer (ES-SCLC), but with restricted therapeutic advantages.
- This study demonstrated that anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC could significantly prolong progression-free survival and overall survival with an acceptable safety profile.

#### What is the implication, and what should change now?

- The main limitation of this study was the small sample size. We will increase our sample size and follow up with more patients.

stem cell growth factor receptor (c-Kit) (23). The ALTER 1202 trial assessed the anti-tumor activity of anlotinib as a third- or further-line treatment in patients with ES-SCLC. The results showed that anlotinib extended the median PFS by 3.4 months ( $P < 0.0001$ ) and reduced the risk of disease progression by 81% compared to placebo (24). Therefore, anlotinib has been approved as a third-line therapy for SCLC by National Medical Products Administration (NMPA). However, the safety and efficacy of first-line maintenance therapy with anlotinib and anti-PD-1/PD-L1 antibodies in ES-SCLC are still unknown. Thus, the retrospective study was conducted to evaluate the effectiveness and safety of anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with anti-PD-1/PD-L1 antibodies in ES-SCLC. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroupp.com/article/view/10.21037/jtd-24-394/rc>).

## Methods

### Participants

Between June 2020 and December 2021, patients with newly diagnosed ES-SCLC in the Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Army Medical University were retrospectively analyzed. The main inclusion criteria included: (I) patients with histopathologically confirmed ES-SCLC according to the VALG staging system; (II) patients who did not receive systemic therapy for ES-SCLC; (III) the assessment of tumor effectiveness adhered to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (IV) patients who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients who were complicated with other malignant tumors, serious infections, tuberculosis, or poor cardiopulmonary function were excluded from this study. This study was conducted following the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Army Medical University [No. (B)KY2023090]. Informed consent from patients was exempted from the ethical review due to the retrospective design.

### Procedures

Patients without disease progression after 4–6 cycles of

first-line platinum-containing chemotherapy plus anti-PD-1/PD-L1 antibodies received anlotinib (Chia-tai Tianqing Pharmaceutical Co., Ltd., Nanjing, China) plus anti-PD-1/PD-L1 antibodies as maintenance therapy. The anti-PD-1/PD-L1 antibodies included atezolizumab (F Hoffmann-La Roche Ltd., Kaiseraugs, Switzerland), durvalumab (AstraZeneca, London, England), tislelizumab (BeiGene Co., Ltd., Shanghai, China), and sintilimab (Innovent Biologics, Suzhou, China). The choice of anti-PD-1/PD-L1 antibodies was mainly based on the approved drug indications, enrollment in phase III clinical trials, patient willingness, and drug accessibility. Several patients underwent chest radiotherapy (intensity-modulated radiotherapy using a 6 MV X-ray) without disease progression before maintenance therapy. The use of chest radiotherapy was based on the 2020 Chinese Society of Clinical Oncology (CSCO) guidelines (25) for the diagnosis and treatment of SCLC and patient selection. Maintenance therapy was continued until the disease progression or unacceptable toxicity.

### Data collection and outcomes assessment

The medical records of each patient were retrospectively collected, including patients' demographic characteristics, disease history, treatment history, laboratory test results, tumor biomarker levels, treatment modalities, efficacy, and safety. The primary endpoint was PFS. Secondary endpoints included OS, ORR, disease control rate (DCR), and safety. The tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the RECIST version 1.1. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0).

### Statistical analysis

The categorical variables were expressed as percentages and numbers, while the continuous variables were presented as mean with standard deviation or median with range. The PFS and OS were estimated using the Kaplan-Meier method and expressed as a median with a 95% confidence interval (CI). The survival curve was generated using R Statistical Language (version 3.5.0). All statistical analyzes were performed using SPSS (version 27.0) software, and a  $P < 0.05$  was considered statistically significant.

**Table 1** Baseline characteristics of the study population

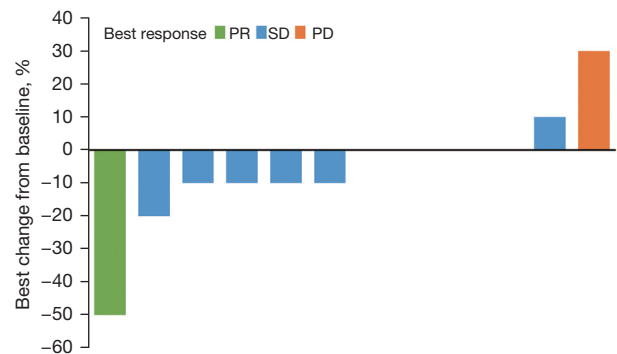
Characteristics	Patients (n=12)
Age (years), median (range)	57.0 (35.0–72.0)
Sex, n (%)	
Male	10 (83.3)
Female	2 (16.7)
ECOG performance status, n (%)	
0–1	7 (58.3)
2	5 (41.7)
Smoking status, n (%)	
≥20 pack-years	9 (75.0)
<20 pack-years	3 (25.0)
Stage, n (%)	
III	9 (75.0)
IV	3 (25.0)
Liver metastasis, n (%)	
Yes	2 (16.7)
No	10 (83.3)
Metastasis sites, n (%)	
≤3	7 (58.3)
>3	5 (41.7)
Radiotherapy, n (%)	
Yes	9 (75.0)
No	3 (25.0)
Anti-PD-1 or PD-L1 antibodies, n (%)	
Atezolizumab	2 (16.7)
Durvalumab	4 (33.3)
Tislelizumab	4 (33.3)
Sintilimab	2 (16.7)

ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

## Results

### Patient and treatment

Between June 2020 and December 2021, 12 patients with newly diagnosed ES-SCLC were included in this study. The baseline demographic and clinical characteristics of patients are shown in *Table 1*. The majority of patients were male, with a male-to-female ratio of 5:1. The median age of the



**Figure 1** Assessment of the best percentage change from baseline in target lesion size from the time of maintenance therapy (n=12). PD, progressive disease; PR, partial response; SD, stable disease.

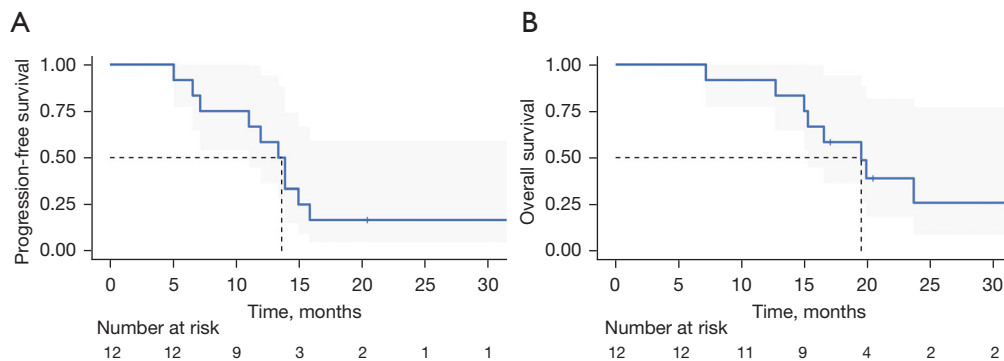
12 patients was 57.0 (range, 35.0–72.0) years. Five (41.7%) patients were aged >60 years and nine (75.0%) patients had a smoking history of ≥20 pack-years. Nearly half of the patients (5/12, 41.7%) had more than three metastatic sites. The proportions of patients treated with anti-PD-1 antibodies (tislelizumab and sintilimab) and anti-PD-L1 antibodies (atezolizumab and durvalumab) were 50.0% and 50.0%, respectively. Nine patients (75.0%) underwent chest radiotherapy after chemotherapy combined with immunotherapy (*Table 1*).

### Efficacy

Up to the study cutoff date of May 11, 2023, the median follow-up time was 31.1 (95% CI: 14.8–47.5) months. During first-line treatment (including maintenance therapy), one patient achieved a CR, 8 patients achieved a PR, and three patients had SD, with an ORR of 75.0% and a DCR of 100.0%. During maintenance therapy with anlotinib plus anti-PD-1/PD-L1 antibodies, 50.0% of patients achieved further lesion remission on the basis of the prior initial treatment, of which one patient achieved a PR (*Figure 1*). The median PFS was 13.6 (95% CI: 11.2–15.6) months and the median OS was 19.5 (95% CI: 14.5–24.5) months (*Figure 2A,2B*). At the time of the last follow-up, 8 (66.7%) patients had died, and 4 (33.3%) patients were still alive with the longest OS of 32.7 months.

### Safety

Treatment-related AEs of any grade were reported in 100.0% of patients, the majority of which were regarded



**Figure 2** Patient survival curve. (A) Kaplan-Meier curve for progression-free survival. (B) Kaplan-Meier curve for overall survival.

**Table 2** Treatment-related adverse events occurring in >10% of patients (n=12)

Adverse events	All grades, n (%)	Grades 1–2, n (%)	Grades 3–4, n (%)
Any	12 (100.0)	5 (41.7)	7 (58.3)
Fatigue	11 (91.7)	10 (83.3)	1 (8.3)
Radiation pneumonitis	9 (75.0)	9 (75.0)	0
Leukocytopenia	11 (91.7)	4 (33.3)	7 (58.3)
Thrombocytopenia	8 (66.7)	4 (33.3)	4 (33.3)
Anemia	11 (91.7)	9 (75.0)	2 (16.7)
Nausea	8 (66.7)	4 (33.3)	4 (33.3)
Hand-foot syndrome	2 (16.7)	2 (16.7)	0
Hypothyroidism	1 (8.3)	1 (8.3)	0
Diarrhoea	1 (8.3)	1 (8.3)	0

as grade 1–2 (Table 2). Seven (58.3%) patients experienced grade 3–4 treatment-related AEs. No life-threatening AEs were observed. Grade 3–4 AEs (Table 2) included leukocytopenia (58.3%, 7/12), thrombocytopenia (33.3%, 4/12), nausea (33.3%, 4/12), anemia (16.7%, 2/12), and fatigue (8.3%, 1/12). All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis.

## Discussion

Currently, there is no standard first-line maintenance treatment regimen for ES-SCLC. Although chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy is the preferred first-line treatment option for ES-SCLC, the OS and PFS benefits are limited. The present study evaluated the effectiveness and safety of

anlotinib plus immunotherapy as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC. The median PFS and OS of our patients were 13.6 (95% CI: 11.2–15.6) months and 19.5 (95% CI: 14.5–24.5) months, respectively, which were higher than those reported from chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy. All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis. Besides, no patients occurred treatment interruption due to AEs. These findings suggested that anlotinib plus immunotherapy might be a preferable first-line maintenance treatment option for ES-SCLC.

The IMPOWER-133, CASPIAN, ASTRUM-005, and CAPSTONE-1 trials demonstrated that adding anti-PD-1/PD-L1 antibodies to chemotherapy improved the OS of patients with ES-SCLC compared with

chemotherapy alone, providing novel prospects for first-line treatment of patients with this disease. However, the immunotherapy combined with chemotherapy in the IMPOWER-133 (atezolizumab), CASPIAN (durvalumab), and CAPSTONE-1 [adebreliumab (SHR-1316)] (26) trials only extended the median OS by 2.0–2.5 months compared to chemotherapy alone. Moreover, serplulimab plus chemotherapy improved median OS *vs.* chemotherapy alone by only 4.5 months in the ASTRUM-005 trial (27).

In the present study, the median PFS was 13.6 (95% CI: 11.2–15.6) months and the median OS was 19.5 (95% CI: 14.5–24.5) months, which were higher than those reported in the IMPOWER-133, CASPIAN, ASTRUM-005, and CAPSTONE-1 trials. It has been shown that ICI monotherapy is unsatisfactory as first-line maintenance therapy for ES-SCLC. Results from the CheckMate 451 trial indicated that maintenance therapy with nivolumab plus ipilimumab (median PFS, 1.7 months; median OS, 9.2 months) or nivolumab monotherapy (median PFS, 1.9 months; median OS, 10.4 months) following first-line chemotherapy did not prolong the PFS and OS (28). Gadgeel *et al.* conducted a single-arm phase II study to assess the efficacy of maintenance pembrolizumab in patients with ES-SCLC who had a response or SD after first-line platinum-etoposide chemotherapy, with an ORR of 11.1%, median PFS of 1.4 months, a 6-month PFS of 20.0%, a 12-month PFS of 13.0%, and a median OS of 9.6 months (29). The exploratory analysis in the subset of patients who reached the maintenance phase from the IMPOWER-133 trial demonstrated a median PFS of 2.6 months for maintenance treatment with atezolizumab monotherapy (30). These findings suggest the importance of maintenance therapy in the first-line setting of ES-SCLC and reflect that the survival benefits from first-line maintenance therapy with ICI monotherapy warrant to be further improvement.

Therefore, the excellent survival results in our study were considered to be attributable to the addition of anlotinib in the maintenance therapy. The unsatisfactory efficacy of ICI monotherapy maintenance therapy after first-line chemotherapy plus immunotherapy in ES-SCLC may be associated with the heterogeneity of SCLC as well as primary and secondary immune resistance (31). Since anti-angiogenic therapies can modulate the tumor immunosuppressive microenvironment and eliminate immunosuppression, the combination of anti-angiogenic agents with immunotherapy might overcome primary and secondary immune resistance (32,33). At present,

anti-tumor angiogenesis drugs are classified into four main categories: VEGF monoclonal antibodies (e.g., bevacizumab), recombinant human endostatin injection, anti-angiogenesis fusion proteins (e.g., aflibercept), and small-molecule TKIs (e.g., anlotinib, apatinib, sorafenib, etc.). Anlotinib is a multitarget TKI that facilitates tumor vessel normalization by improving the distribution of pericytes/endothelial cells (34) and increases the infiltration of immune cells by downregulating PD-L1 expression on the surface of endothelial cells (35). In addition, anlotinib regulates immune cells to alleviate the immunosuppressive state in the tumor microenvironment (34,36), and modulates cytokine levels to enhance the anti-tumor immune response (35,37,38). A single-arm phase II study revealed the encouraging efficacy of anlotinib plus toripalimab as maintenance treatment after first-line platinum-based chemotherapy in ES-SCLC, with an ORR of 6.7%, a DCR of 80.0%, and a median PFS of 12.5 months (39). The real-world data from this study showed that the addition of anlotinib in the maintenance therapy did not increase the toxicity of ICI monotherapy and had a manageable safety profile. In the present study, grade 3–4 AEs were reported in 58.3% of patients, which was lower than that reported in the IMPOWER-133, CASPIAN, and CAPSTONE-1 trials (66.0–86.0%). Moreover, no life-threatening AEs were observed. All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis. In conclusion, as a multi-target small-molecule anti-tumor angiogenesis drug, anlotinib not only regulates the tumor microenvironment and enhances immune synergism, but also demonstrates good efficacy, mild side effects, and convenient oral administration.

The main limitation of this study was the small sample size. Since there were few anti-PD-1/PD-L1 antibodies available for the first-line treatment of ES-SCLC between 2020 and 2021, and the high economic burden of the study drugs at that time, making only a small percentage of patients in the real-world setting received maintenance therapy with anlotinib and anti-PD-1/PD-L1 antibodies. However, with the approval of more immunologic drugs and the reduction in drug costs in recent years, the treatment regimen is accessible to more patients, allowing us to enlarge our sample size and follow-up more patients. Although the combination of anti-angiogenic agents with immunotherapy has been proven to be a promising therapeutic strategy in the treatment of a variety of solid tumors, there are still many issues that need to be resolved

in clinical practice, such as determining the optimal beneficial populations, optimal dosage, and duration of administration, with the expectation of making the combination regimen more effective and safer, which is also a priority in future research.

## Conclusions

The present study demonstrated that anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC could significantly prolong PFS and OS with an acceptable safety profile, which brings new hope for the long-term survival of patients with this disease.

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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-24-394/rc>

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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-24-394/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. This study was conducted following the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Army Medical University [No. (B)KY2023090]. Informed consent from patients was exempted from the ethical review due to the retrospective design.

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