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ORIGINAL RESEARCH

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Clinical efficacy of Anlotinib combined with radiotherapy in treating brain metastases of lung cancer in male patients

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Abstract

Background: This study analyzed the clinical efficacy of the anti-angiogenic drug Anlotinib in combination with radiotherapy for the treatment of brain metastases in male lung cancer patients. **Methods**: From existing case records, a retrospective analysis was performed on data from 63 male lung cancer patients with brain metastases treated at our hospital between January 2019 and December 2023. Based on the different treatment methods recorded, of them, 33 patients underwent intensity-modulated radiotherapy (IMRT) alone (radiotherapy group), and 30 underwent Anlotinib combined with IMRT (combined treatment group). The clinical outcomes of both treatment approaches were compared. **Results**: The results showed that 1 month after treatment, the objective response rate (ORR) of intracranial tumors was relatively higher in the combined treatment group than in the radiotherapy group (70.00% *vs.* 48.48%), though the difference was not statistically significant ($p > 0.05$), while the incidence of progressive disease (PD) was significantly lower in the combined treatment group (6.67% *vs.* 33.33%; $p < 0.05$), indicating that the addition of Anlotinib significantly reduced disease progression ($p < 0.05$). Moreover, patients in the combined treatment group had a shorter duration of dehydrating medication use and faster headache relief compared to the radiotherapy group ($p < 0.05$), as well as significantly longer progression-free survival (PFS) and overall survival (OS) compared to the radiotherapy group ($p < 0.001$). **Conclusions**: In conclusion, these findings suggest that Anlotinib, when combined with radiotherapy, could enhance the therapeutic benefits of male lung cancer patients with brain metastases. Further large-scale randomized controlled trials are required to confirm these results.

Keywords

Anlotinib; Intensity-modulated radiotherapy; Brain metastases of lung cancer

1. Introduction

Lung cancer is one of the most prevalent and lethal malignancies worldwide. Its initial symptoms often include a paroxysmal, irritative dry cough with minimal or no sputum production [1]. However, since the early clinical manifestations of lung cancer are typically subtle, this frequently results in delayed diagnosis and disease progression, often resulting in the occurrence of metastasis by the time of diagnosis, with the brain being a common site for hematogenous spread from primary lung cancer [2]. Over 50% of lung cancer patients develop brain metastases and have dismal 5-year survival rate [3]. As such, early detection and timely treatment of brain metastases in lung cancer patients are essential for improving therapeutic outcomes and overall quality of life.

The current clinical management of brain metastases in lung cancer mainly controls tumor progression as an attempt to extend patient survival. In this regard, radiotherapy is considered a cornerstone in the treatment of brain metastases as it can extend patient survival by 7 to 12 months. However, disease recurrence occurs in approximately 55% of patients within 6 months of radiotherapy [4]. Angiogenesis has been shown to inhibit tumor growth and metastasis, making anti-angiogenic therapies a promising approach for treating cancer [5]. The advent of targeted therapies in recent years has significantly improved the survival rates of lung cancer patients. Anlotinib, a novel small-molecule tyrosine kinase inhibitor developed in China, targets multiple signaling pathways by exerting anti-tumor angiogenic effects, inhibiting tumor cell proliferation, and promoting apoptosis [6]. This oral drug is convenient to administer and has shown favorable efficacy and safety in lung cancer treatment [7]. However, despite these advancements, limited data are available regarding the efficacy of combining Anlotinib with radiotherapy in treating lung cancer brain metastases.

Male patients represent a substantial portion of lung cancer

cases [8], as they are often more prone to lifestyle risk factors such as smoking, which contributes to a higher incidence of lung cancer [9]. Additionally, in Asia, gene-driven lung cancer is more prevalent than in Western populations, especially among female non-smokers [10]. Third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), which can effectively penetrate the blood-brain barrier, are often preferred by asymptomatic patients with brain metastases for primary treatment [11]. However, male lung cancer patients tend to have a lower incidence of EGFR mutations, and their response to EGFR-targeted therapy is less favorable compared to female patients [12]. Therefore, radiotherapy plays an important role in managing brain metastases in male lung cancer patients.

Given the increasing prominence of vascular-targeted therapies and their demonstrated efficacy in lung cancer salvage treatments [13], this study aims to evaluate whether combining small -molecule anti-angiogenic drugs, such as Anlotinib, with radiotherapy can enhance therapeutic efficacy in male patients with brain metastases from lung cancer.

2. Materials and methods

2.1 General data

From existing case records, this retrospective study analyzed 63 male lung cancer patients with brain metastases treated at our hospital between January 2019 and December 2023. The cases were divided into two groups according to the different treatment methods recorded, such as intensity-modulated radiotherapy (IMRT) for brain metastases (the radiotherapy group; n = 33), or combination of Anlotinib and IMRT (the combined treatment group, n = 30) (Fig. 1). The study protocol was approved by the hospital's ethics committee.

The inclusion criteria for patient selection were as follows: (1) lung cancer confirmed by histopathological or cytological examination; (2) individuals with locally advanced or metastatic non-small cell lung cancer who had experienced progression or recurrence after receiving at least two prior systemic chemotherapy regimens; (3) no prior treatments related to metastatic tumors before the study examination; (4) no history of allergies related to the study drugs; (5) normal baseline function of vital organs; (6) age $\leq$70 years; and (7) signed informed consent.

The study exclusion criteria were: (1) presence of concurrent malignant tumors; (2) death within 60 days of study initiation; (3) incomplete clinical data; (4) poor compliance or withdrawal from the study; and (5) patients assessed to be at high risk of bleeding.

2.2 Methods

As a retrospective study, the treatment methods were already recorded in existing case records.

Patients in the radiotherapy group underwent IMRT using 6 MV X-rays for the treatment of brain metastases. The patients were positioned supine with a pillow placed under the head, arms resting at the sides, and immobilization was achieved with a 2.4 mm thick mesh head-neck-shoulder mold. Enhanced computerized tomography (CT) scans (slice thickness: 3 mm) were performed to delineate the treatment target areas, with some cases incorporating magnetic resonance (MR) imaging. The gross tumor volume (GTV) was defined as the visible intracranial metastatic lesions, while the clinical target volume (CTV) included the entire brain tissue. The planning target volume (PTV) consisted of the CTV plus a 0.3 cm margin in all directions. The treatment plan was developed using the Advanced Data Acquisition Corporation (ADAC) Pinnacle 3 planning system, which used five evenly distributed fields covering 360°. The prescribed dose for the PTV was 30 Gy, delivered in 10 fractions at 3 Gy per fraction, with one fraction administered per day, five days per week. The GTV received a prescription dose of 39 Gy, administered in 13 fractions of 3 Gy per fraction, also with one fraction per day, five days per week, and completed within two weeks. The treatment plan evaluation required that 95% of the PTV received at least 95% of the prescribed dose and 100% of the GTV received at least 100% of the prescribed dose.

In the combined treatment group, Anlotinib hydrochloride (Chia Tai Tianqing Pharmaceutical Group, Lianyungang, Jiangsu, China, H20180004) was administered concurrently with radiotherapy, following the same regimen as the radiotherapy group. Anlotinib was initiated on the first day of radiotherapy, with patients receiving an oral dose of 10 mg one hour after a meal, once daily for 14 consecutive days, followed by a 7-day drug cessation period. The treatment cycle was repeated for a total of four cycles, each lasting 21 days. Tumor assessments were conducted before treatment initiation, one month after completing radiotherapy, and after every four treatment cycles. Efficacy and safety were evaluated by comparing cranial magnetic resonance imaging (MRI) with enhanced CT scans of the chest and abdomen.

2.3 Observation indicators

As a retrospective study, the outcome indicators results were already recorded in existing case records. (1) Treatment efficacy: Tumor evaluations were performed before treatment, 1 month after completing radiotherapy, and after 4 cycles of medication. The primary observation indicators included objective response rate (ORR) and disease control rate (DCR). Efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 3.0 criteria, which categorizes responses as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Complete response (CR) was defined as the absence of detectable lesions for at least four weeks post-treatment, partial response (PR) was characterized by a significant reduction in the primary lesion, with at least a 30% decrease in the sum of the maximum diameters within four weeks post-treatment, stable disease (SD) referred to a reduction in lesion size between 0% and 29% over the same time period, while progressive disease (PD) indicated no reduction or an increase in lesion size, or the appearance of new lesions within four weeks. ORR was calculated as the sum of CR and PR, and the DCR was determined based on the sum of CR, PR and SD. (2) Clinical indicators: The duration of dehydrating medication use and the time to headache relief were recorded for both treatment groups. (3) Follow-up: Patients were followed for a period

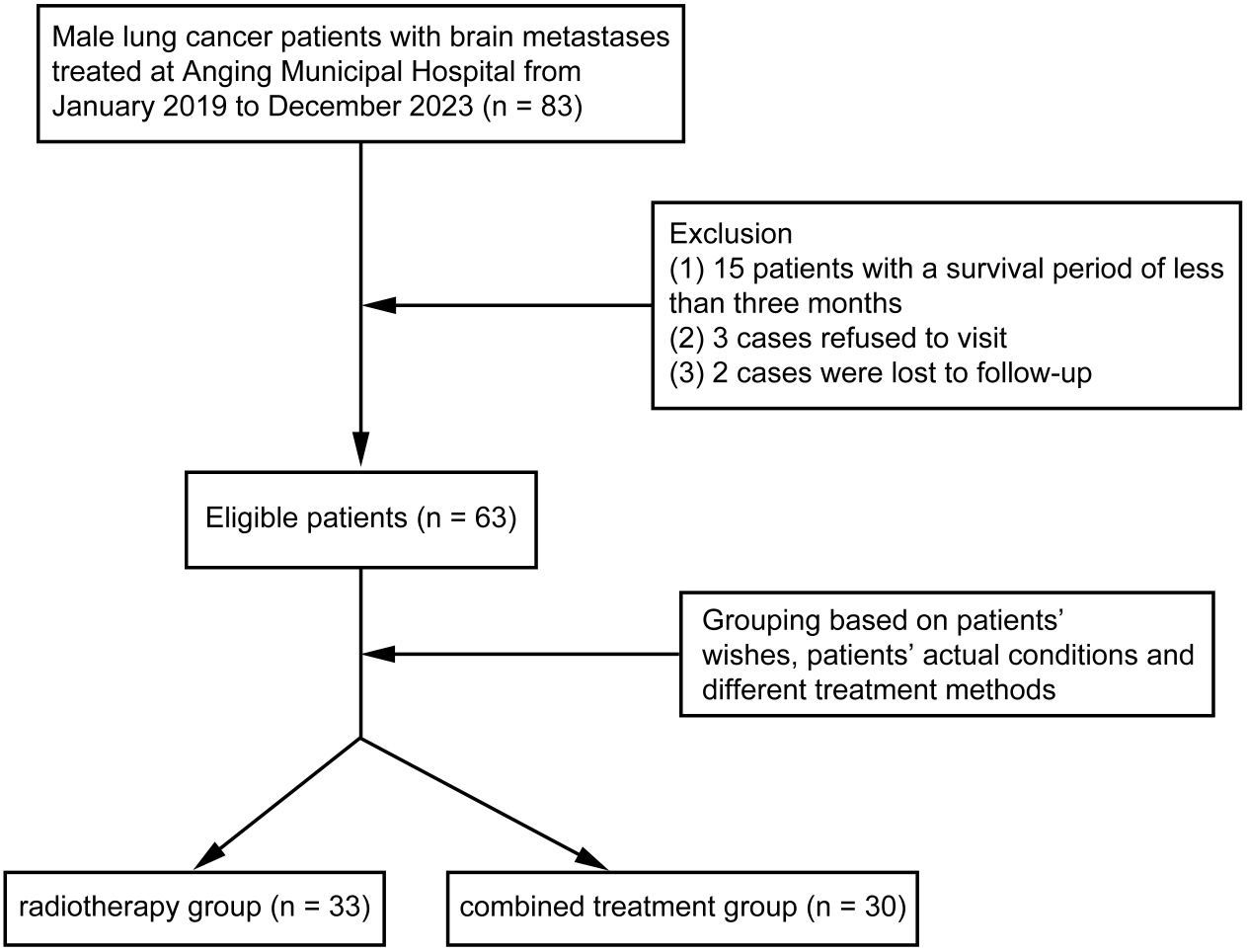

FIGURE 1. Flow chart of the study design and grouping.

ranging from 6 to 26 months after treatment. Progression-free survival (PFS) and median overall survival (OS) were recorded for both groups.

2.4 Statistical methods

Data were analyzed using the SPSS 22.0 statistical software (IBM, Armonk, NY, USA). Measurement data are presented as mean $\pm$ standard deviation (SD) ($\bar{x} \pm s$) and were compared between groups using the t-test. Categorical data are expressed as percentages and compared using the chi-squared (χ^2) test. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1 General data

The general characteristics of both the radiotherapy group and the combined treatment group are summarized in Table 1, and data analysis showed that the characteristics of the two groups were comparable ($p > 0.05$).

3.2 Comparison of treatment efficacy

One month after treatment, the ORR for intracranial tumors was higher in the combined treatment group than in the radiotherapy group; however, the difference was not statistically significant ($p > 0.05$). Conversely, the incidence of PD was significantly lower in the combined treatment group compared to the radiotherapy group, and combination therapy notably reduced the number of disease progressions ($p < 0.05$). The time to PD showed no significant difference between the two groups ($p > 0.05$), as detailed in Table 2.

3.3 Clinical indicators

The duration of dehydrating medication use and the time to headache relief were both significantly shorter in the combined treatment group than in the radiotherapy group ($p < 0.05$), as shown in Table 3.

TABLE 1. Comparison of general data between radiotherapy versus Anlotinib plus radiotherapy.

Variables	Radiotherapy group (n = 33)	Combined treatment group (n = 30)
Age (yr) (diagnosis period of lung cancer)	63.85 ± 5.20	64.01 ± 5.09*
Smoking history (previously smoked)		
Yes	23 (69.70)	21 (70.00)*
No	10 (30.30)	9 (30.00)*
Family or personal history of cancer	4 (12.12)	6 (20.00)*
Other comorbidities		
Diabetes mellitus	5 (15.15)	4 (13.33)*
Hypertension	13 (39.39)	10 (33.33)*
Hyperlipemia	10 (30.30)	7 (23.33)*
Interval between lung cancer diagnosis and brain metastasis diagnosis (mon)	2.50 ± 0.65	2.23 ± 0.71*
Location of brain metastases		
Parietal lobe	21 (63.64)	20 (66.67)*
Frontal lobe	7 (21.21)	5 (16.67)*
Occipital lobe	5 (15.15)	5 (16.67)*
Tumor volume of metastatic lesions (cm^3)	36.10 ± 5.64	35.26 ± 5.21*
Pathological type		
Squamous cell carcinoma	12 (36.36)	14 (46.67)*
Adenocarcinoma	14 (42.42)	10 (33.33)*
Adenosquamous carcinoma	7 (21.21)	6 (20.00)*
Stage of lung cancer during diagnosis		
IA–IIIA phase	18 (54.55)	16 (53.33)*
IB–IIB phase	15 (45.45)	14 (46.67)*
No. of malignant nodules in the lungs	3.50 ± 1.20	3.75 ± 1.25*
Location		
Left upper lobe	13 (39.39)	11 (36.67)*
Left lower lobe of lung	3 (9.09)	3 (10.00)*
Right upper lobe	11 (33.33)	9 (30.00)*
Right middle lobe	2 (6.06)	2 (6.67)*
Inferior lobe of right lung	4 (12.12)	5 (16.67)*
Size (cm)	3.50 ± 0.98	3.34 ± 1.02*
Received similar lung cancer treatment (chemotherapy or other treatments) before brain metastasis	33 (100.00)	30 (100.00)*
Number of brain metastases		
≤3	19 (57.58)	17 (56.67)*
>3	14 (42.42)	13 (43.33)*
Symptoms of brain metastasis	20 (66.67)	18 (60.00)*
EGFR genic mutation		
Positive	8 (24.24)	7 (23.33)*
Negative	15 (45.45)	14 (46.67)*
Unknown	10 (30.30)	9 (30.00)*

*(Compared to the radiotherapy group, *$p > 0.05$; *χ^2/t test was used). EGFR: epidermal growth factor receptor.*

TABLE 2. Comparison of the efficacy indicators between radiotherapy and Anlotinib plus radiotherapy.

Efficacy	Radiotherapy group (n = 33)	Combined treatment group (n = 30)	χ^2/t	p
CR	2 (6.06)	4 (13.33)	0.965	0.326
PR	14 (42.42)	17 (56.67)	1.275	0.259
SD	6 (18.18)	7 (23.33)	0.255	0.614
PD	11 (33.33)	2 (6.67)	6.823	0.009
ORR	16 (48.48)	21 (70.00)	3.001	0.083
DCR	22 (66.67)	28 (93.33)	6.823	0.009
PD time (d)	21.60 ± 3.54	20.65 ± 3.15	1.121	0.267

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

TABLE 3. Comparison of clinical indicators between radiotherapy and Anlotinib plus radiotherapy ($\bar{x} \pm s$).

Clinical indicators	Radiotherapy group (n = 33)	Combined treatment group (n = 30)	p	95% confidence interval for the difference	
				Lower limit	Upper limit
Time of dehydration drug use (d)	13.61 ± 7.20	8.50 ± 6.59	0.005	3.5663	10.6646
Headache relief time (d)	11.60 ± 4.55	6.68 ± 3.64	<0.001	2.8767	7.1227

TABLE 4. Comparison of progression-free survival and median overall survival between radiotherapy and Anlotinib plus radiotherapy ($\bar{x} \pm s$, month).

Group	n	PFS	OS
Radiotherapy group	33	7.46 ± 0.98	12.34 ± 1.73
Combined treatment group	30	10.89 ± 1.34	14.87 ± 1.50
t	-	11.704	6.188
p	-	<0.001	<0.001

PFS: progression-free survival; OS: overall survival.

3.4 Progression-free survival time and median survival time

Survival analysis showed that the PFS and OS were significantly longer in the combined treatment group compared to the radiotherapy group ($p < 0.05$, Table 4).

4. Discussion

The brain is a frequent site of metastasis for lung cancer, with cancer cells often spreading to it through the bloodstream, leading to severe clinical consequences. The incidence of brain metastases is influenced by the location and pathological type of the primary lung tumor [14]. Brain metastasis in lung cancer is primarily attributed to low rates of early diagnosis and limited intervention, which result in extrapulmonary spread by the time the cancer is diagnosed. In advanced stages, lung cancer commonly disseminates systemically through the bloodstream, crossing the blood-brain barrier and leading to intracranial metastasis [15]. Clinically, brain metastases may present with stroke-like symptoms, causing significant neurological impairment and rapid disease progression, which greatly reduces patients' quality of life and overall survival [16]. Current clinical treatment options for lung cancer brain metastases include surgery, radiotherapy, chemotherapy, and molecular-targeted therapies. However, surgery is generally not viable in advanced-stage lung cancer, making radiotherapy and chemotherapy the more commonly employed treatment modalities.

With ongoing and rapid advancements in medical technology, various therapeutic options are now available for cancer treatment, and multiple approaches have been shown to effectively control brain metastases from lung cancer, with each method exhibiting varying degrees of efficacy [17]. The choice of treatment is influenced by several factors, including patient age, tumor location, and volume. Current treatment modalities include surgery, radiotherapy, chemotherapy, and stereotactic radiosurgery [18]. IMRT has been shown to enhance the delivery of varying radiation intensities to distinct target areas, allowing for more accurate dose distributions that ensure adequate radiation to the target while minimizing exposure to surrounding tissues. However, despite these advancements,

the survival of these patients remains dismal [19].

Anlotinib is a novel small-molecule multi-target TKI that has been shown to exhibit both anti-angiogenic and tumor growth-inhibitory effects. The mechanisms underlying brain metastasis are complex and may involve angiogenesis, driven by several pro-angiogenic factors, with vascular endothelial growth factor (VEGF) playing a key role [20]. Studies have identified an inverse correlation between VEGF expression levels in tumors and patient prognosis [21]. In our present study, after 1 month of treatment, the ORR for intracranial tumors showed no significant difference between the radiotherapy group and the combined treatment group. However, the PD rate was significantly lower in the combined treatment group (33.33% *vs.* 6.67%), indicating that the combination therapy was more effective than radiotherapy alone for lung cancer brain metastases. This superiority could be attributed to IMRT's ability to target and deliver precise radiation doses, minimizing irradiation of normal brain tissue and surrounding structures while reducing the likelihood of missing lesions, ultimately delaying disease progression.

Anlotinib can enhance treatment efficacy through its dual mechanism of inhibiting angiogenesis, thereby depriving the tumor of its nutrient supply, and normalizing the disorganized tumor vasculature, akin to repairing damaged infrastructure, which improves the delivery and distribution of anti-tumor drugs within the tumor [22, 23]. Additionally, it can reprogram tumor cells to directly inhibit their growth, proliferation and migration, while promoting apoptosis and regulating the hypoxic conditions that facilitate tumor growth and metastasis [24, 25]. Anlotinib can also modulate the tumor immune microenvironment, strengthening anti-tumor immune cells and enhancing the immune response against the tumor [26, 27]. When combined with radiotherapy, these treatments exert a synergistic effect that can effectively kill tumor cells and further delay disease progression. In this study, the combined treatment group experienced shorter durations of dehydrating drug use and faster headache relief compared to the radiotherapy-only group, indicating that the combination therapy more effectively alleviates clinical symptoms. The primary efficacy of Anlotinib lies in controlling vasogenic edema. However, when used alone, it functions primarily as symptomatic relief [28], and when combined with radiotherapy, Anlotinib enhances the sensitivity of the tumor to radiation by reducing neovascularization, promoting normalization of vascular structures, and improving cellular hypoxia [29]. This combination exerts a synergistic effect, leading to more effective tumor cell destruction and symptom improvement while also delaying disease progression.

The PFS and OS in this study were significantly longer in the combined treatment group compared to the radiotherapy group, suggesting that Anlotinib, when combined with radiotherapy, can significantly extend patient survival, potentially due to its ability to downregulate both VEGF mRNA and protein expression, which enhances the radiotherapy sensitization effect [30, 31]. Tumor progression after radiotherapy often depends on neovascularization, and by inhibiting angiogenesis, Anlotinib reduces tumor oxygen content, thereby slowing tumor growth [32, 33]. Additionally, radiotherapy can disrupt the blood-brain barrier, increasing the permeability of the blood-cerebrospinal fluid barrier, which allows Anlotinib to more effectively enter cerebrospinal fluid circulation post-radiotherapy [34] and facilitates adequate therapeutic drug concentrations in the cerebrospinal fluid, thereby enhancing its anti-tumor effects [35]. As a multi-target drug, Anlotinib blocks the receptors VEGFR, PDGFR, FGFR and C-kit, thereby reducing tumor invasiveness, improving ORR, and increasing OS. However, due to the relatively small sample size of this study, the results may be subjected to a certain level of bias. Thus, future research could aim to increase the sample size and conduct multicenter studies to improve the accuracy and generalizability of the findings.

5. Conclusions

In summary, this study demonstrates the potential therapeutic effect of Anlotinib in combination with radiotherapy for the treatment of brain metastases in lung cancer patients. However, large-scale randomized controlled trials are required to confirm these findings. The relatively small sample size in this study highlights the need for further clinical observation and more comprehensive future research to validate these results and provide a clearer understanding of the clinical efficacy of this combined treatment approach.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

JGL and CHL—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. JGL, CHL, YG, LLX, TTL and TL—supervised the data collection. JGL, CHL, YG, LLX and TTL—analyzed the data. JGL, CHL, YG and LLX—interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Anqing Municipal Hospital (Approval no. 2021aqykj13). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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