



Pharmacoeconomic evaluation of original and generic temozolomide capsules in the treatment of glioma



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ABSTRACT

Aim: Original patented drugs and generic drugs using the same pharmaceutical ingredients may have different clinical efficacies and prices. This study was designed to compare the clinical efficacy and cost-effectiveness of original imported temozolomide capsules and those generic capsules manufactured domestically, with a pharmacoeconomic evaluation being performed.

Methods: In this retrospective study, 103 glioma patients from 2008 to 2018 were divided into the generic temozolomide group (72 cases) and the imported temozolomide group (31 cases). The 2-year overall survival (OS) and disease progression free survival (PFS) of the two groups were analyzed using Kaplan Meier survival curves, and the 2-year disease control rate and 2-year survival rate were calculated. The incidence of adverse reactions was also compared between the two groups. A pharmacoeconomic evaluation was performed on the two groups according to the total cost of treatment per capita.

Results: The 2-year disease control rate of the domestic drug group was 52.8% and the imported drug group was 67.7%. The 2-year survival rate of the domestic drug group was 68.10%, with the imported drug group being 74.20%. The total cost of treatment per patient/2-year PFS time in the domestic drug group was 7000.55 yuan/month; while the imported drug group was 7705.41 yuan/month. The total cost of treatment per patient/2-year OS time in domestic drug group was 5821.20 yuan/month, while the imported drug group was 7035.53 yuan/month.

Conclusion: There was no significant difference between the domestic drug group and the imported drug group in treatment efficacy and the total cost/2-year PFS time of the two groups were not significantly different. However, the total cost/2-year OS time of the domestic group was significant lower than the imported group, revealing a certain cost-effective advantage.

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1. Introduction

Glioma accounts for 50%–60% of all primary intracranial tumors. A gradual trend of increased incidence has been observed in recent years.¹ Temozolomide is a second-generation imidazotetrazine prodrug, an alkylating agent with strong and wide antineoplastic activity.^{2–4} Some studies confirmed that the concurrent combination of Temozolomide with chemotherapy can prolong the survival time of patients with high-grade malignant glioma.^{5,6} However, original patented drugs and generic drugs with the same pharmaceutical ingredients may have different clinical efficacies and prices,⁷ and it is still unclear whether the more expensive original patented Temozolomide capsules exhibit better efficacy than the correspondent generic drug. Messali A et al reported that the generic product may be significantly more cost-effective compared with the brand option in the United States.⁸ A Pharmacoeconomic evaluation of original and generic Temozolomide capsules in China is necessary.

Therefore, this study was conducted to compare the efficacy and cost of the original patented and a generic Temozolomide Capsules used in the Tumor Center of Wuhan Union Hospital in treating malignant glioma by performing a pharmacoeconomic evaluation with a cost-effectiveness analysis. Our hope is to provide a reference for the rational use of drugs in clinical treatment and the selection of drugs covered by basic medical insurance.

2. Methods

2.1. Patients information

A retrospective study was conducted on glioma patients treated at the Tumor Center of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology, China, from January 2008 to December 2018. On the basis of the established inclusion and exclusion criteria, 103 glioma patients were selected from a total of 240 and divided into two groups (Fig. 1): the generic Temozolomide Capsules group that included 72 patients (manufacturer: Jiangsu Tianshili Diyi Pharmaceutical Co., Ltd.; Drug Approval Number: NMPA Approval Number H20040637, called the DiQing group) and the original patented Temozolomide Capsules group that included 31 patients (manufacturer: Merck Sharp & Dohme Corp.; Drug Approval Number: NMPA Approval Number J20180033; Import Drug License Number: H20171091, called the Temodal group).

Inclusion criteria: 1) age between 18 and 80 years; 2) patients with glioma pathologically diagnosed; 3) patients who were subjected to tumor resection and subsequent combination therapy of Temozolomide

and radiochemotherapy (Subtotal resection was defined as $\geq 90\%$ resection of tumor volume, partial resection was defined as 60%–90% resection of tumor volume); 4) Karnofsky performance score (KPS) score ≥ 70 before treatment; 5) normal blood cell count and classification, liver function, and kidney function (neutrophil count $> 1500/\text{ml}$; platelet count $> 100,000/\text{ml}$; creatinine level < 1.5 times of the normal upper limit; total bilirubin < 1.5 times of the normal upper limit; liver function < 3 times of the normal upper limit); 6) no change of the treatment protocol either before progression of the disease or during the study.

Exclusion criteria: 1) suffering from other malignant tumors or having a related medical history; 2) patients with severe heart, liver, or kidney disease; 3) having no progression of the disease but the treatment protocol was replaced during the study; 4) had a combined use of the original patented and generic Temozolomide capsules; 5) patients with poor compliance; 6) patients lost to follow-up for survival outcomes.

2.2. Study design

This study performed a cost-effectiveness evaluation based on the cost-effectiveness ratio and incremental cost-effectiveness ratio, and a pharmacoeconomic evaluation was carried out.

Treatment protocol: Total dose = 60 Gy, administered at a daily single fractional dose of 2 Gy for 30 times (five consecutive days a week, for six weeks in total). The chemotherapy with Temozolomide was administered concurrently with the radiotherapy and as adjuvant chemotherapy. In the concurrent radiochemotherapy, the Temozolomide Capsules were administered from the first day of radiotherapy at the dose of 75 mg/m² for 42 consecutive days. The adjuvant chemotherapy started after a four-week rest period. In each cycle (28 d), Temozolomide Capsules were administered for 5 days, and suspended for 23 days. In the first cycle, the dose was set as 150 mg/m²/day; in the second and subsequent cycles, it increased to 200 mg/m²/d until the end of this trial.

Efficacy evaluation criteria: 1) glioma recurrence: imaging that displayed a volume increase by $\geq 25\%$, or the occurrence of new lesions or clinical progression; 2) two-year disease control rate: percentage of patients without glioma recurrence after two years within the total number of patients enrolled in the study, calculated from the beginning of the Temozolomide treatment; 3) two-year survival rate: percentage of surviving patients after two years within the total number of patients enrolled in the study, calculated from the beginning of the Temozolomide treatment.

Criteria to evaluate adverse reactions: The adverse reactions in patients were evaluated and recorded at the end of the follow-up according to the *Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0)*.

2.3. Data collection

The age, gender, pathological type, WHO grade, KPS score, surgical resection range and times of adjuvant chemotherapy administration, as well as the first-line treatment protocol, radiotherapy dose and time, chemotherapy dose and time were collected from the inpatient and outpatient medical record system. The time of disease progression and the date of death were also recorded according to the inpatient and outpatient medical record system and telephone follow-up. The information that was collected on the costs involved the total cost of medical care (called “the total cost”), consisting of the costs of hospitalization, examinations, treatments, nursing care, and drugs. Among them, the cost of drugs was represented by the single-drug cost of the Temozolomide Capsules and the cost of drugs used to treat the adverse reactions. The cost of drugs was calculated according to the follow-up results.

2.4. Statistical analysis

Statistical analysis was performed using the SPSS software version 25.0. Gender, pathological type, KPS score, treatment protocol, disease

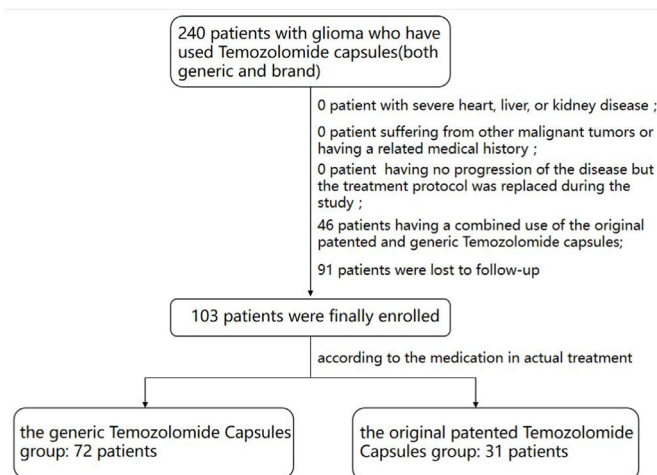


Fig. 1. Flowchart of patients inclusion and exclusion.

control rate, survival rate, and other numerical data were expressed in the form of constituent ratio or rate, and the intergroup comparison was performed using the Chi-square test. Data on the cost was expressed in the form of mean ± standard deviation, and intergroup comparisons were evaluated using the Mann–Whitney U test. The intergroup comparisons of PFS and OS were performed using the Kaplan–Meier survival curve, followed by the Log-rank test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline data comparison

The Diqing group and the Temodal group were compared in terms of age, gender, KPS score, pathological type, WHO grade, adjuvant chemotherapy times and surgical resection range as shown in Table 1. The results indicated that there were no significant differences between the Diqing group and Temodal group on age, gender, KPS score, pathological type, WHO grade, adjuvant chemotherapy times and surgical resection range, respectively. The results indicated that there is comparability between the two groups.

3.2. Multifactorial analysis

Multivariate cox regression analysis of possible independent risk factors were performed, including age, pathological type, WHO grade, KPS score, and times of adjuvant chemotherapy administration. As shown in Table 2, results indicated that WHO grade and times of adjuvant chemotherapy administration were two independent risk factors for the prognosis of patients with glioma. The risk of death of high-grade glioma in WHO grade III to IV was higher than that in WHO grade II, as HR was 11.944 (95%CI; 1.394, 103.20). Patients did not receive temozolomide adjuvant chemotherapy had a higher risk of death than those who received temozolomide adjuvant chemotherapy for 6 or more cycles (HR 0.312) (95%CI; 0.098, 0.992).

3.3. Clinical efficacy analysis

On the basis of the follow-up, information was recorded regarding the progression of the disease and survival conditions of the patients, the disease control rate and survival rate was calculated, and the PFS and OS was analyzed. The two-year disease control rate and two-year survival

Table 1
Clinical characteristics in the baseline datas [n(%)].

Clinical Data	Classification	Diqing Group (n = 72)	Temodal Group(n = 31)	P Value
Gender	Male	43(59.7)	21(67.7)	0.441
	Female	29(40.3)	10(32.3)	
Age	45.47 ± 12.01	45.47 ± 12.01	48.45 ± 11.86	0.247
KPS Score	≥80	59(81.9)	25(80.6)	0.549
	<80	5(6.9)	4(12.9)	
	ND ^a	8(11.1)	2(6.5)	
Pathological Types	Glioblastomas	31(43.1)	9(29.0)	0.187
	Anaplastic astrocytoma	11(15.3)	3(9.7)	
	Other Gliomas	30(41.7)	19(61.3)	
WHO Grade	Low-grade	20(27.8)	12(38.7)	0.271
	High-grade	52(72.2)	19(61.3)	
	None	20(27.8)	11(35.5)	
Adjuvant Chemotherapy	1~5times	29(40.3)	8(25.8)	0.371
	≥6times	23(31.9)	12(38.7)	
Surgical Resection Range	Subtotal excision	60(83.3)	28(90.3)	0.808
	Partial resection	8(11.1)	2(6.5)	
	ND	4(5.6)	1(3.2)	

a:ND = not defined.

Table 2
Multifactorial analysis of possible independent risk factors.

Clinical date	Multivariate cox regression analysis	
	HR(95%CI)	P Value
Age	1.017 (0.978, 1.057)	0.395
KPS score		
<80/≥80	1.944 (0.713, 5.299)	0.194
ND/≥80	0.952 (0.179, 5.052)	0.954
WHO Grade		
High-grade/Low-grade	11.944 (1.394, 103.20)	0.024*
Pathological Types		
Anaplastic astrocytoma/Glioblastoma	0.950 (0.319, 2.124)	0.926
Other Gliomas/Glioblastoma	0.560 (0.204, 1.539)	0.261
Adjuvant Chemotherapy		
1 ~ 5 times/0 time	0.706(0.268,1.860)	0.481
≥6 times/0 time	0.312(0.098,0.992)	0.048*

a:ND = not defined.

*p < 0.05, statistically significant difference.

rate of the Temodal group were both slightly higher than those of the Diqing group (67.7% vs. 52.8%, 68.1% vs. 74.2%), but none of the differences was statistically significant ($P > 0.05$) (Table 3).

PFS and OS in the Diqing group and the Temodal group were also compared using the Kaplan–Meier survival curve, followed by the Log-rank test (Fig. 2 The comparison of PFS between Diqing group and Temodal group and Fig. 3 The comparison of OS between Diqing group and Temodal group) which showed that the mean PFS of the Diqing group was 17.72 months (95% CI: 15.88–19.55 months), and that of the Temodal group was 20.27 months (95% CI: 17.97–22.56 months), however the difference was not statistically significant ($P = 0.149$). The mean OS of the Diqing group was 21.31 months (95% CI: 20.07–22.55 months), and that of the Temodal group was 22.20 months (95% CI: 20.51–23.89 months). Again, the difference was not statistically significant ($P = 0.494$).

3.4. Adverse reactions

The types and severity of any adverse reactions were also analyzed in the 103 patients. The adverse reactions related to the hematological system mainly included leukopenia, thrombocytopenia, neutropenia, and anemia; those related to the digestive system were mainly manifested as nausea and vomiting. Abnormalities of liver function were mainly manifested as the rise of ALT, AST, and bilirubin. Other adverse reactions were also observed, including dizziness, headache, and alopecia. Overall, no significant difference was observed between the Diqing group and the Temodal group in the occurrence of adverse reactions (Table 4).

3.5. Cost analysis

The above analysis observed no significant difference between the Diqing group and the Temodal group in two-year disease control rate, two-year survival rate, PFS, or OS. Direct cost analysis was then performed to evaluate any economic differences between the two groups. K–S normality test indicating that the cost related data was non-normal distribution, mann-Whitney U test was performed. The total medical cost per patient (the total cost C1) in the Diqing group was slightly lower than that in the Temodal group with no significant difference ($P = 0.067$). The cost of the Temozolomide Capsules in the Diqing group was

Table 3
Two-year disease control rate and survival rate [% (n)].

	Diqing Group (n = 72)	Temodal Group(n = 31)	P Value
Two-year disease control rate	52.8(38)	67.7(21)	0.159
Two-year survival rate	68.1(49)	74.2(23)	0.533

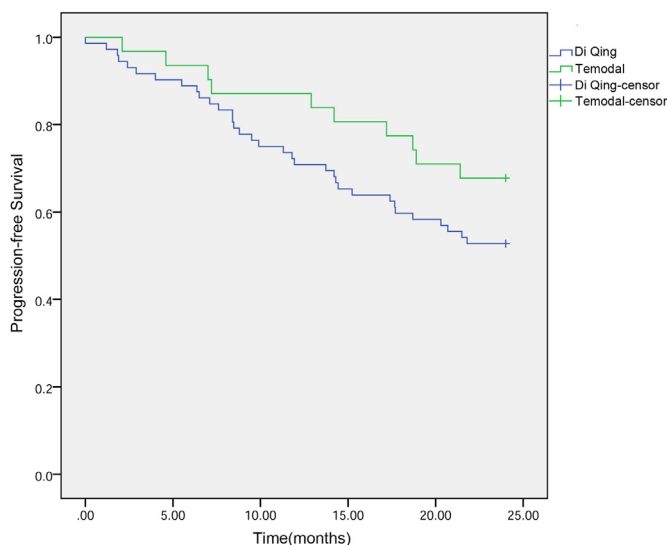


Fig. 2. The comparison of PFS between Diqing group and Temodal group.

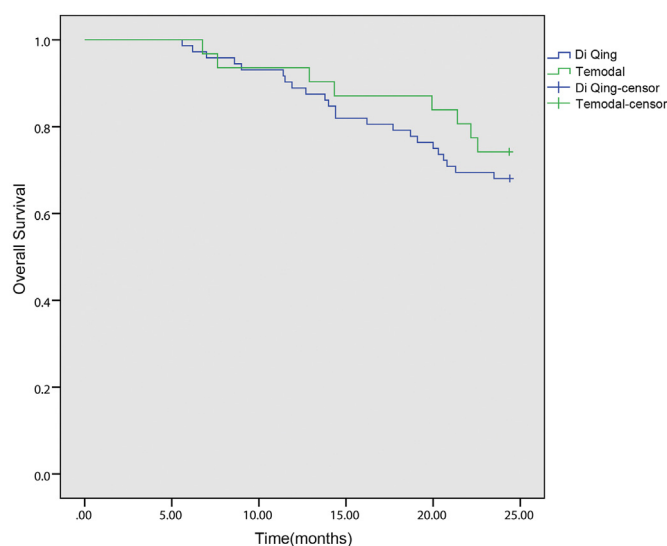


Fig. 3. The comparison of OS between Diqing group and Temodal group.

Table 4
The characteristics of adverse reactions [n(%)].

	Diqing Group (n = 72)	Temodal Group(n = 31)	P Value
Hematological toxicity	35(48.6)	16(51.6)	0.780
Gastro-intestinal damage	10(13.9)	1(3.2)	0.166
Hepatic injury	25(34.7)	11(35.5)	0.941
Other adverse reactions	8(11.1)	2(6.5)	0.719
Sever adverse reactions	6(8.3)	3(9.7)	1.000

significant lower than that in the Temodal group ($P = 0.006$). However, there was no significant difference observed between the two groups in adverse reaction-related cost ($P = 0.923$) (Table 5).

3.6. Cost-effectiveness analysis

Because the efficacy analysis revealed no significant differences between the Diqing group and the Temodal group, any potential difference in the cost-effectiveness would largely come down to the costs. The two-

Table 5
Direct cost comparison (Yuan).

	Diqing Group (n = 72)	Temodal Group(n = 31)	P Value
Total cost C1	124049.81	156188.7	0.067
Cost of Temozolomide capsules C2	53639.40	78194.64	0.006*
The cost of adverse reactions C3	3057.64	3342.88	0.923

* $p < 0.05$, statistically significant difference.

year disease control rate and two-year survival rate in the Temodal group had the trend of being slightly higher than those in the Diqing group, so the cost-effectiveness ratio and incremental cost-effectiveness ratio were then analyzed. The results of the cost-effectiveness ratios (total cost/2-year PFS time, or C1/E1) suggested that each time the two-year PFS time increased by 1 month, the Diqing group would consume a total of 7000.55 yuan, while the Temodal group would consume 7705.41 yuan, but the difference was not statistically significant($p = 0.275$). The results also showed that the cost-effectiveness ratio (total cost/2-year OS time, or C1/E2) of the Diqing group was 5821.20 yuan/month which was significant lower than the Temodal group 7035.53 yuan/month ($p = 0.032$) (Table 6).

Table 6 also shows the results of the incremental cost-effectiveness ratio analysis, which suggests that as the 2-year disease PFS time increased by 1 month, the Temodal group would generate an additional total cost of 12,603.50 yuan compared to the Diqing group; and that the 2-year OS time increased by 1 month, the Temodal group would generate an additional total cost of 36,111.15 yuan compared to the Diqing group.

3.7. Sensitivity analysis

Considering the uncertainty and potential bias in pharmacoeconomic evaluations, it was necessary to explore the stability of the cost-effectiveness ratio using a sensitivity analysis. This study assumed that the Temozolomide cost of both groups was raised or lowered by 10%, while other costs remained unchanged. Table 6 shows the sensitivity analysis results after raising or lowering the prices of Temozolomide Capsules by 10%, with the C1/E1 and C1/E2 values remaining unchanged, indicating stability of the analysis. The results also revealed that the C1/E2 of the Diqing group was significant lower than that in the Temodal group, which indicated the OS time increased by 1 month, the total cost of Diqing group was lower than Temodal group.

4. Discussion

A study by Chu, Yan et al showed that Diqing and Temodal were bioequivalent in Beagle dogs.⁹ However, few reports are currently available on any differences between them in clinical efficacy. In this study, the efficacy analysis on the Diqing group and the Temodal group showed no statistically significant differences between them in the two-year disease control rate, two-year survival rate, PFS, or OS. The total medical cost and Temozolomide single-drug cost in the Diqing group were lower than in the Temodal group when directly comparing costs, while no significant differences between the two groups was observed in the adverse reaction-related cost. Cost-effectiveness ratio analysis suggested that the Temodal group may be superior to the Diqing group in terms of C1/E1 (total cost/2-year PFS time), although without a significant difference being observed; the Diqing group was shown to be superior to the Temodal group in terms of C1/E2 (total cost/2-year OS time). The sensitivity analysis clarified that raising or lowering the Temozolomide cost by 10% would not affect this conclusion.

Adverse reactions related to the hematological system, the gastrointestinal system, and liver function are common adverse reactions due to Temozolomide Capsules.¹⁰ In this study, the adverse reactions related to the hematological system, the gastrointestinal system, and liver function

Table 6

Cost-Effectiveness, incremental cost effectiveness ratio and sensitivity (Yuan/1%) analysis.

	Diqing Group(n = 72)	Temodal Group(n = 31)	P Value
Total cost C1(Yuan)	124049.81	156188.73	
PFS E1(month)	17.72	20.27	
OS E2(month)	21.31	22.20	
C1/E1(Yuan/month)	7000.55	7705.41	0.275
C1/E2(Yuan/month)	5821.20	7035.53	0.032*
△C1/△E1(Yuan/month)	0	12603.50	
△C1/△E2(Yuan/month)	0	36111.15	
C1/E1 was increased by 10%	7303.26	8091.18	0.246
C1/E2 was increased by 10%	6072.91	7387.76	0.027*
△C1/△E1 was increased by 10%	0	13566.45	
△C1/△E2 was increased by 10%	0	38870.16	
C1/E1 was reduced by 10%	6697.85	7319.65	0.312
C1/E2 was reduced by 10%	5569.49	6683.30	0.039*
△C1/△E1 was reduced by 10%	0	11640.55	
△C1/△E2 was reduced by 10%	0	33352.13	

*p < 0.05, statistically significant difference.

had no statistically significant differences between the Diqing group and the Temodal group. Among them, the adverse reactions related to the hematological system had the highest occurrence rate in both the Diqing group and the Temodal group (48.6% and 51.6%, respectively), followed by the adverse reactions related to liver function (34.7% and 35.5%, respectively). Severe drug-related adverse reactions can be fatal or life-threatening, and may cause significant or permanent human disabilities or organ damages, or hospitalization/prolonged hospitalization. As a consequence of that, the occurrence rate of severe adverse reactions (grade III or above) in the Diqing group and Temodal group were analyzed, and the results revealed that they were respectively 8.3% and 9.7%, without a significant difference between them.

While a cost comparison revealed that the direct total cost and the Temozolomide drug cost in the Diqing group were both lower than those in the Temodal group, lower costs do not always mean a higher pharmacoeconomic effectiveness.¹¹ In this regard, cost-effectiveness analysis was performed to also evaluate efficacy in relation to treatment cost. Since the PFS time of the Diqing group and Temodal group had no significant difference, a C/E comparison between them was further carried out, which revealing no significant difference between them in C1/E1(total cost/2-year PFS time). This result suggested that the Temodal group may have some pharmacoeconomic advantages over the Diqing group, although without a statistically significant improvement. The Diqing group was superior to the Temodal group in terms of C1/E2(total cost/2-year OS time). The adverse reaction-related cost resulted in no significant difference between the two groups, as well as the occurrence rate of adverse reactions.

5. Conclusion

Our study demonstrated that the total cost and Temozolomide single-drug cost of the Diqing group were lower than those of the Temodal group, when a direct cost comparison was performed, with no significant difference between the two groups in adverse reaction-related cost being observed. The cost-effectiveness ratio analysis suggested that the Diqing group and the Temodal group were basically at the same level in terms of C1/E1 (total cost/2-year PFS time), and that the Diqing group was superior to the Temodal group in terms of C1/E2 (total cost/2-year OS time). The sensitivity analysis clarified that raising or lowering the

Temozolomide cost by 10% would not affect this conclusion.

Author contributions

Data curation: Ming Gu, Bin Deng, Yu Zhang, Chen Shi. Funding acquisition: Yu Zhang, Mitchell A Sullivan, Bin Deng. Project administration: Ming Gu, Chen Shi. Software: Changdong Diao, Haixia Zhu. Writing – original draft: Ming Gu, Bin Deng, Qi Yuan, Jinmei Liu. Writing – review & editing: Shijun Li, Chen Shi, Mitchell A Sullivan.

Data availability statement

After publication, we can provide the data to others with the permission of the corresponding author. A proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided.

Ethical statement

This study was conducted in compliance with the Helsinki Declaration and Good Clinical Practice and was approved by the Ethics Committee of Wuhan Union Hospital. The requirement for informed consent was waived by the ethics committee due to the nature of the study.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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