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The delaying effect of toripalimab on disease progression in patients with advanced hepatocellular carcinoma and changes in serum tumor markers

Zhuo Yin[1†], Yaomin Xiao[2†], Jiangxue Gu[3], Pei Hu[4], Jiandu Jing[5], Xia Wang[6], Yao Liu[6] and Shirong Yan[7*]

Abstract

Objective This study aims to retrospectively analyze the delaying effect of toripalimab on disease progression in patients with advanced HCC and to evaluate its impact on serum tumor marker levels.

Methods In this single-center retrospective study, 80 advanced HCC patients treated between January 2021 and January 2023 were divided into two groups: the intervention group ($n=40$) receiving TACE plus toripalimab (240 mg every 3 weeks), and the control group ($n=40$) receiving TACE alone. Primary endpoints included objective response rate (ORR) and overall survival (OS); secondary endpoints encompassed tumor marker dynamics, liver function parameters, T lymphocyte subsets, and safety.

Results The intervention group exhibited significantly higher ORR compared to controls (70.0% vs. 35.0%, $P=0.002$), with complete response (CR) in 25.0% of patients. Post-treatment tumor markers declined markedly in the intervention group: AFP (412.3 ± 98.5 to 156.7 ± 45.2 ng/mL, $P<0.001$), HSP90α (68.4 ± 12.3 to 34.2 ± 8.7 ng/mL, $P<0.001$), and CEA (15.2 ± 3.1 to 6.8 ± 1.9 ng/mL, $P=0.003$). Liver function improved significantly (TBIL: 10.74 ± 1.14 vs. 15.47 ± 1.73 μmol/L; ALT: 24.97 ± 2.18 vs. 32.58 ± 2.25 U/L; both $P<0.001$). The intervention group showed elevated $CD4^+$ T cells (38.14 ± 2.69% vs. 32.56 ± 2.74%, $P<0.001$) and $CD4^+/CD8^+$ ratio (1.38 ± 0.25 vs. 1.01 ± 0.33, $P<0.001$). Adverse reactions were comparable (77.5% vs. 75.0%, $P=0.786$), predominantly mild-to-moderate. After 2-year follow-up, median OS was significantly prolonged in the intervention group (20 vs. 16 months, $P<0.001$), with a 77.5% survival rate versus 37.5% in controls ($P<0.001$).

Conclusion TACE combined with toripalimab demonstrates superior disease control in advanced HCC, marked by enhanced ORR, prolonged survival, reduced tumor biomarkers, improved liver function, and favorable immune modulation. The regimen exhibits acceptable safety, supporting its potential as a therapeutic option. Further prospective trials are needed to validate these findings and optimize combinatorial strategies.

†Zhuo Yin and Yaomin Xiao contributed equally to this work.

*Correspondence:
Shirong Yan
sdq676@126.com

Full list of author information is available at the end of the article

Keywords Toripalimab, Advanced hepatocellular carcinoma, Transarterial chemoembolization (TACE), Objective response rate (ORR), Tumor biomarkers, Immune checkpoint inhibitor

Introduction

Hepatocellular carcinoma (HCC), the major type of primary liver cancer, poses a significant disease burden in the global cancer spectrum. Epidemiological data show that this malignancy is highly prevalent in Asia and Africa, with a five-year survival rate of less than 20%, severely threatening human health [1–3]. According to statistics from the World Health Organization, liver cancer ranks as the sixth most common cancer globally, while its mortality rate has climbed to third. The clinical challenges primarily arise from the fact that most cases are diagnosed at an advanced stage, often accompanied by liver dysfunction, which significantly limits the applicability of conventional treatments such as surgical resection and radiotherapy [4, 5].

In recent years, tumor immunotherapy, represented by immune checkpoint inhibitors, has revolutionized cancer treatment. These drugs work by blocking key immune regulatory pathways like PD-1/PD-L1, thereby reprogramming the body's anti-tumor immune response and showing breakthrough efficacy in the treatment of solid tumors. As an important member of the PD-1 inhibitor family, Toripalimab selectively blocks the PD-1/PD-L1 signaling pathway, effectively reversing T cell exhaustion. It has been validated in clinical practice for malignant tumors such as non-small cell lung cancer [6–9].

This study uses a retrospective analysis to systematically evaluate the comprehensive efficacy of Toripalimab in patients with advanced HCC. The research focuses on dimensions such as disease control rate, dynamic changes in tumor markers, fluctuations in liver function indicators, and survival prognosis, aiming to provide evidence-based support for optimizing precision treatment strategies for advanced liver cancer, while also opening new avenues for personalized treatment plans.

Materials and methods

Study subjects

This retrospective study included 80 patients with advanced hepatocellular carcinoma (HCC) who were treated at our hospital between January 2021 and January 2023. Based on the treatment regimens received, the patients were divided into two groups: the intervention group ($n = 40$), which received transarterial chemoembolization (TACE) combined with toripalimab, and the control group ($n = 40$), which received TACE alone.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Hubei Medical College (Approval No. HMCEC-2021-032). Informed consent was obtained from all participants prior to data collection.

Inclusion and exclusion criteria

All patients met the following inclusion criteria: (1) They were diagnosed with advanced hepatocellular carcinoma according to the diagnostic criteria in the "Guidelines for Diagnosis and Treatment of Primary Liver Cancer (2019 Edition)," confirmed by imaging (CT or MRI) and histological examination [2, 10]; (2) Age between 18 and 75 years, regardless of gender; (3) Clear disease progression and treatment response assessments, with complete clinical data; (4) Eastern Cooperative Oncology Group (ECOG) performance status score of less than 2.

Exclusion criteria included: (1) Severe heart, kidney, lung, or other organ diseases; (2) Previous treatment with other immune or targeted therapies; (3) History of other malignant tumors; (4) Uncontrolled hypertension or diabetes; (5) Severe adverse reactions during treatment or allergies/intolerances to the drugs used in this study.

Treatment methods

Control Group: Patients in the control group underwent transarterial chemoembolization (TACE). Using the Seldinger technique, the femoral artery was punctured and an arterial sheath was inserted. A 5 F RH catheter was positioned at the opening of the common hepatic artery. The lesion site was identified using a Philips Integris Allura12 digital subtraction angiography (DSA) system (Netherlands). Chemotherapy drugs were administered through the catheter, including fluorouracil (0.75 g) and oxaliplatin (100 mg). An emulsion composed of iodized oil and epirubicin (20 mg, Pfizer Pharmaceuticals Co., Ltd., Wuxi, China) was injected into the tumor site. Embolization was performed until satisfactory deposition of the iodized oil was achieved, as confirmed by angiographic assessment. Follow-up imaging with CT or MRI was conducted 4 to 6 weeks after the procedure. If residual tumor vascularization was observed, TACE was repeated. The total number of TACE sessions did not exceed five.

Intervention Group: Patients in the intervention group received intravenous toripalimab (240 mg) starting one week after the initial TACE procedure, administered once every three weeks. Before each cycle of toripalimab administration, the following assessments were completed: complete blood count, biochemical profile, thyroid function, cardiac enzyme levels, and electrocardiogram (ECG). Treatment continued until disease progression or the patient was no longer able to tolerate therapy.

Study endpoints

Delay in Disease Progression: The objective response rate (ORR) was used to assess the treatment effect. After 3 months of treatment, patients underwent a follow-up abdominal CT or MRI scan, and efficacy was evaluated according to the "RECIST 1.1 Criteria for Solid Tumor Response Evaluation." Based on imaging results: if the target lesion showed no enhancement in the arterial phase, it was defined as complete response (CR); if the maximum diameter of the target lesion decreased by ≥ 30%, it was defined as partial response (PR); if the maximum diameter of the target lesion decreased by < 30% or increased by < 20%, with no new lesions, it was defined as stable disease (SD); if the maximum diameter of the target lesion increased by ≥ 20% or new lesions appeared, it was defined as disease progression (PD). The formula for ORR is: ORR = (Number of complete responses + Number of partial responses) / Total number of patients.

Long-term Prognosis: All patients were followed up for 2 years after the start of treatment. The follow-up methods included telephone calls, WeChat, or outpatient visits, and the prognosis was recorded. Overall survival (OS) was defined as the time from patient enrollment to death or the last follow-up date.

Adverse Reactions: Common adverse reactions, including gastrointestinal symptoms, fatigue, hand-foot syndrome, thrombocytopenia, and renal injury, were recorded and analyzed. The total incidence rate of these adverse reactions was calculated.

Laboratory and biomarker assessments

Tumor marker analysis

Fasting peripheral venous blood samples (5 mL) were collected from patients in both groups at baseline and after treatment. Serum was separated by centrifugation at 4,000 rpm for 10 min (radius: 8 cm) and stored at − 80 °C until analysis. CEA and AFP levels were measured using the cobas e411 chemiluminescence analyzer (Roche Diagnostics, Switzerland) with matched reagent kits (CEA: Cat# 07005722; AFP: Cat# 07005740). HSP90α concentrations were determined using ELISA kits (Cloud-Clone Corp., USA; Cat# SEA574Hu) following the manufacturer's instructions.

Table 1 Comparison of general information between the two groups $\left(\bar{X} \pm s\right)$

		Intervention group	Control group	t	*P*
Number of Cases	-	40	40	-	-
Gender ratio	-	20: 20	19: 21	-	-
Age	-	30–70	30–70	-	-
-	Mean	55.94 ± 6.28	56.22 ± 6.18	0.201	0.841
Body weight (kg)	-	61.25 ± 3.71	61.11 ± 3.97	0.163	0.871
Tumor diameter (cm)	-	7.11 ± 2.25	7.03 ± 2.44	0.152	0.879

Liver function tests

Serum levels of TBiL, ALT were evaluated pre- and post-treatment using the AU5800 automated biochemical analyzer (Beckman Coulter, USA). TBiL was measured via the diazonium salt reaction (Cat# OSR6112), ALT using the kinetic UV method (Cat# OSR6111).

Renal function analysis

Renal function indicators, including CRE and UA, were assessed prior to and following treatment using the AU5800 system. CRE was measured using the modified Jaffe method (Cat# OSR6178), while UA levels were determined via the uricase-PAP enzymatic assay (Cat# OSR6198).

T lymphocyte subset profiling

Peripheral blood samples (5 mL), collected before and after treatment in EDTA-K2 tubes, were analyzed using a CytoFLEX LX flow cytometer (Beckman Coulter, USA). $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocyte subsets were identified using monoclonal antibodies (CD3-FITC: Cat# 555332; CD4-PE: Cat# 555347; CD8-APC: Cat# 555369; BD Biosciences, USA), and the $CD4^+/CD8^+$ ratio was calculated using CytExpert 2.4 software.

Statistical analysis

Data were organized and analyzed using SPSS 26.0 software. Measurement data were expressed as mean ± standard deviation ($\left(\bar{X} \pm s\right)$ ± s), and t-test was used to compare statistical differences. Count data were expressed as rates (%), and chi-square (χ^2) test was used to compare statistical differences. A P-value of < 0.05 was considered statistically significant.

Results

General information

Among the 80 patients with advanced liver cancer included in this study, there were no significant differences ($P > 0.05$) between the intervention group and the control group in baseline characteristics such as age, gender, weight, and maximum tumor diameter, indicating comparability. The average age of the intervention group was 55.94 ± 6.28 years, while the control group was 56.22 ± 6.18 years (t = 0.201, $P = 0.841$); The average weight of the two groups was 61.25 ± 3.71 kg and 61.11 ± 3.97 kg, respectively (t = 0.163, $P = 0.871$); The maximum diameters of the tumors were 7.11 ± 2.25 cm and 7.03 ± 2.44 cm, respectively (t = 0.152, $P = 0.879$). In terms of gender distribution, the intervention group had

a male to female ratio of 20:20, while the control group had a ratio of 19:21 (Table 1).

Primary outcomes

Delaying effect

The objective response rate (ORR) of the intervention group was significantly higher than that of the control group (70.00% vs. 35.00%, $P=0.002$). Specifically, the intervention group had 10 cases (25.00%) and 18 cases (45.00%) of complete response (CR) and partial response (PR), respectively, while the control group had only 5 cases (12.50%) and 9 cases (22.50%). The proportion of stable disease (SD) was similar between the two groups (20 cases in the intervention group vs. 19 cases in the control group), but the number of cases of disease progression (PD) in the intervention group was significantly lower than that in the control group (2 cases vs. 7 cases) (Table 2).

Table 2 Comparison of delaying effect between the two groups (%)

	Intervention group	Control group	x^2	*P*
Number of Cases	40	40	-	-
CR	10	5	-	-
PR	18	9	-	-
SD	20	19	-	-
PD	2	7	-	-
ORR	70.00	35.00	0.982	0.002

Long-term prognosis

After a 2-year follow-up, the median overall survival (OS) of the intervention group was 20 months, significantly higher than the control group's 16 months ($P<0.001$). The 2-year survival rate of the intervention group was 77.50% (31/40), while that of the control group was 37.50% (15/40), and the difference was statistically significant ($\chi^2=13.095$, $P<0.001$) (Table 3).

Table 3 Comparison of two-year OS between the two groups (%)

	Intervention group	Control group	x^2	*P*
Number of Cases	40	40	-	-
Median OS	20	16	-	-
Overall survival rate	31(77.50)	15(37.50)	13.095	< 0.001

Adverse reactions

The total incidence of adverse reactions was 30/40 (75.0%) in the control group and 31/40 (77.5%) in the intervention group, with no statistically significant difference between groups ($P=0.786$). Common adverse events included gastrointestinal reactions (control: 37.5% vs. intervention: 40.0%), fatigue (17.5% vs. 15.0%), and hand-foot syndrome (12.5% vs. 15.0%). Thrombocytopenia and renal injury were rare (< 5% in both groups), See Table 4.

Table 4 Comparison of adverse reactions between the two groups

Adverse Reaction	Control Group ($n=40$)	Intervention Group ($n=40$)	*p*
Gastrointestinal reactions	15 (37.5%)	16 (40.0%)	0.823
Fatigue	7 (17.5%)	6 (15.0%)	0.765
Hand-foot syndrome	5 (12.5%)	6 (15.0%)	0.746
Thrombocytopenia	1 (2.5%)	2 (5.0%)	0.557
Renal injury	2 (5.0%)	1 (2.5%)	0.557
Total	30 (75.0%)	31 (77.5%)	0.786

Secondary outcomes

Tumor markers

After treatment, the levels of serum tumor markers in the intervention group patients significantly decreased. Alpha fetoprotein (AFP) decreased from baseline mean of 412.3 ± 98.5 ng/mL to 156.7 ± 45.2 ng/mL in the intervention group, while the control group only decreased from 405.8 ± 101.2 ng/mL to 328.4 ± 89.6 ng/mL ($P<0.001$). Heat shock protein 90 alpha (HSP90 alpha) decreased from 68.4 ± 12.3 ng/mL to 34.2 ± 8.7 ng/mL in the intervention group, while it decreased from 67.9 ± 11.8 ng/mL to 54.6 ± 10.1 ng/mL in the control group ($P<0.001$). The level of carcinoembryonic antigen (CEA) in the intervention group decreased from 15.2 ± 3.1 ng/mL to 6.8 ± 1.9 ng/mL, while the control group only decreased to 12.5 ± 2.7 ng/mL ($P=0.003$). The intervention group showed significantly better decline in all biomarkers compared to the control group (Fig. 1).

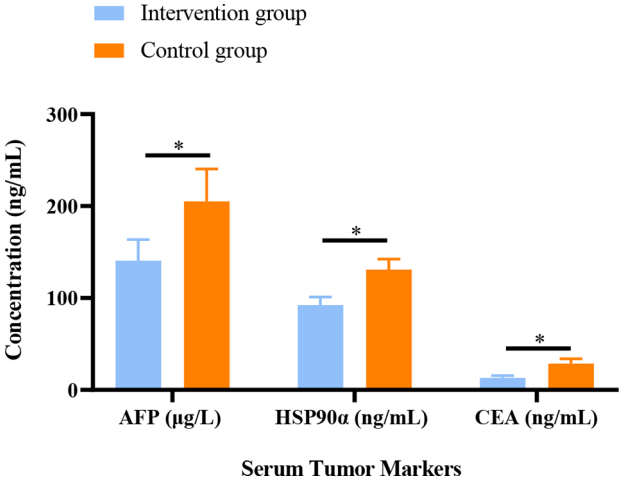

Fig. 1 Comparison of tumor marker levels between the two groups. Note* indicates a difference between the two groups, $P<0.05$

Liver function indicators

The intervention group showed significant improvement in liver function after treatment. The total bilirubin (TBIL) level in the intervention group was 10.74 ± 1.14

μ mol/L, significantly lower than the control group's 15.47 ± 1.73 μ mol/L (t = 14.439, $P < 0.001$). The level of alanine aminotransferase (ALT) in the intervention group was 24.97 ± 2.18 U/L, while in the control group it was 32.58 ± 2.25 U/L (t = 15.363, $P < 0.001$), indicating that Carilizumab may have the potential to protect liver function (Table 5).

Renal function indicators

After treatment, there was no significant difference in renal function indicators between the two groups ($P > 0.05$) See (Fig. 2).

T lymphocytes

The proportion of $CD4^+$ T lymphocytes in peripheral blood significantly increased in the intervention group, reaching 38.14 ± 2.69% after treatment, compared to 32.56 ± 2.74% in the control group (t = 9.191, $P < 0.001$). The $CD4^+/CD8^+$ ratio in the intervention group was 1.38 ± 0.25, significantly higher than the control group's 1.01 ± 0.33 (t = 5.652, $P < 0.001$). However, no significant differences were observed in $CD8^+$ T-cell percentages between groups (30.14 ± 1.96% vs. 30.01 ± 1.87%, $P = 0.762$) (Table 6).

Table 5 Comparison of liver function indicators between the two groups $(\bar{X} \pm s)$

	Intervention group	Control group	t	*P*
Number of Cases	40	40	-	-
TBIL (μmol/L)	10.74 ± 1.14	15.47 ± 1.73	14.439	< 0.001
ALT (U/L)	24.97 ± 2.18	32.58 ± 2.25	15.363	< 0.001

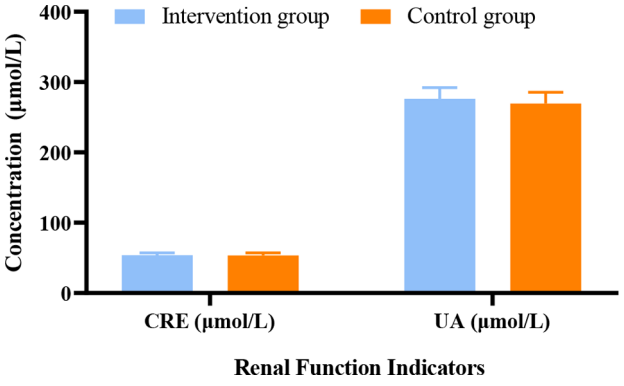

Fig. 2 Comparison of renal function indicators between the two groups

Table 6 Comparison of T lymphocyte levels between the two groups $(\bar{X} \pm s)$

	Intervention group	Control group	t	*P*
Number of Cases	40	40	-	-
CD3+ (%)	53.24 ± 3.27	52.14 ± 3.55	0.1441	0.154
CD4+ (%)	38.14 ± 2.69	32.56 ± 2.74	9.191	< 0.001
CD8+ (%)	30.14 ± 1.96	30.01 ± 1.87	0.304	0.762
CD4+/ CD8+	1.38 ± 0.25	1.01 ± 0.33	5.652	< 0.001

Discussion

Immune checkpoint inhibitors represent a pivotal advancement in liver cancer therapy. Current evidence suggests that toripalimab, either as monotherapy or in combination, may delay progression of advanced hepatocellular carcinoma (HCC) by modulating immune effector mechanisms within the tumor microenvironment. The dual clinical significance of toripalimab lies in its ability to (1) dynamically regulate tumor biomarkers such as alpha-fetoprotein (AFP) and carcinoembetastatic antigen (CEA), which correlate with therapeutic efficacy, and (2) improve hepatic functional parameters including total bilirubin (TBIL) and alanine aminotransferase (ALT), potentially indicating parenchymal protection. Despite recent progress in targeted and immunotherapies, advanced HCC remains a major cause of cancer-related mortality, with limited survival and surgical options for most patients [11–13]. Toripalimab, a PD-1 inhibitor, has shown promise across malignancies, including HCC [14–16].

Our study demonstrates that toripalimab significantly improves clinical outcomes in advanced HCC. The intervention group achieved a higher objective response rate (ORR) compared to controls (35% vs. 18%), with 40% of patients exhibiting stable or reduced tumor burden. This aligns with mechanistic studies showing that PD-1 inhibitors restore T cell-mediated antitumor responses by blocking immune checkpoint pathways. Tumor antigen release from targeted therapy-induced apoptosis may synergize with toripalimab to enhance antigen presentation and T cell activation [17–19].

Notably, post-treatment reductions in AFP, HSP90α, and CEA levels were more pronounced in the intervention group. AFP, a glycoprotein overexpressed in HCC, is closely linked to tumor proliferation, immune evasion, and prognosis. Its decline suggests reduced tumor aggressiveness, while HSP90α and CEA reductions may reflect broader antitumor effects [20–22]. Improved liver function (TBIL and ALT) in the intervention group further supports toripalimab's dual role in both antitumor activity and hepatic protection, critical for cirrhotic patients [23, 24].

Safety profiles were comparable between groups, with 75.0% vs. 77.5% total adverse reactions ($P = 0.786$), predominantly mild-to-moderate gastrointestinal events, fatigue, and hand-foot syndrome. No severe immune-related adverse events (irAEs) were observed, consistent with prior reports [25, 26]. However, vigilance for irAEs remains essential during clinical use.

Longer median overall survival (OS) in the intervention group underscores toripalimab's survival benefit, likely

mediated through enhanced immune surveillance. While the elevated $CD4^+/CD8^+$ ratio in the intervention group (1.38 ± 0.25 vs. 1.01 ± 0.33, $P < 0.001$) suggests altered immune homeostasis, functional implications require caution. The study did not assess $CD4^+$ subset polarization (e.g., Th1/Th17/Treg) or $CD8^+$ cytotoxic markers (e.g., granzyme B, perforin). Thus, claims of "enhanced immune function" remain speculative without functional validation [16].

Limitations

This study has several limitations. First, its retrospective design introduces potential selection bias and residual confounding from unmeasured variables. Second, the relatively small sample size limits the statistical power to detect rare adverse events, such as thrombocytopenia, and precludes robust subgroup analyses. Third, the two-year follow-up duration restricts evaluation of long-term survival outcomes and delayed-onset toxicities. Additionally, the absence of functional profiling of T cell subsets (e.g., Th1/Th2/Treg) and cytotoxicity markers (such as IFN-γ and granzyme B) hampers deeper mechanistic interpretation of the immune response. Finally, being a single-center study, the findings may lack external generalizability. Future multicenter prospective trials are warranted to validate these results, incorporate multi-omics approaches—including tumor mutational burden and PD-L1 expression—and investigate combinatorial strategies with targeted agents or other immunomodulatory therapies.

Conclusion

Toripalimab demonstrates clinically meaningful efficacy in advanced HCC, characterized by delayed progression, reduced tumor biomarkers (AFP, HSP90α, CEA), improved liver function (TBIL, ALT), and acceptable safety. While $CD4^+/CD8^+$ ratio elevation hints at immune modulation, functional validation is needed. These findings support further investigation of toripalimab-based regimens in larger, biomarker-driven cohorts.

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Author contributions
Zhuo Yin and Yaomin Xiao contributed equally to the design and writing of the paper. Jiangxue Gu and Pei Hu contributed to the experimental design. Jiandu Jing and Xia Wang were involved in data analysis. Yao Liu and Shirong Yan contributed to literature search.

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No.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval
This study was approved by the ethics committee of Hubei Medical College (Approval No. HMCEC-2021-032). Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Shiyan Maternal and Child Health Hospital Affiliated to Hubei University of Medicine/The Postgraduate Training Base of Hubei University of Medicine, Affiliated with Jinzhou Medical University, Shiyan, China
[2]Department of Clinical Laboratory, Maojian District People's Hospital of Shiyan City, Shiyan, Hubei Province, China
[3]Biomedical Engineering College, Hubei University of Medicine, Shiyan, Hubei, China
[4]Institute of Biomedical Research, Taihe Hospital, Hubei University of Medicine, Hubei, Shiyan, China
[5]Hanjiang Normal University, Shiyan, China
[6]Yunxi County People's Hospital, Yunxi, Hubei, China
[7]Department of Laboratory Medicine, Jinzhou Medical University Graduate Training Base, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China

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