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Efficacy and safety of bivalirudin application during primary percutaneous coronary intervention in older patients with acute ST-segment elevation myocardial infarction

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Abstract

Objective: ST-segment elevation myocardial infarction (STEMI) is the most serious type of acute coronary syndrome. This study aimed to investigate the efficacy and safety of bivalirudin application during primary percutaneous coronary intervention (PPCI) in older patients with acute STEMI.

Methods: A total of 672 older patients with STEMI (>75 years) who underwent PPCI were studied. The primary endpoints were 30-day net adverse clinical events (NACEs) post-emergency percutaneous coronary intervention, including major adverse cardiac and cerebrovascular events (MACCEs) and Bleeding Academic Research Consortium grades 2 to 5 (BARC 2–5) bleeding events.

Results: The incidence of NACEs and BARC 2–5 bleeding events in the bivalirudin group was significantly lower than that in the unfractionated heparin group. Multivariate Cox regression analysis showed that bivalirudin significantly reduced 30-day NACEs (odds ratio: 0.700, 95% confidence interval: 0.492–0.995) and BARC 2–5 bleeding events (odds ratio: 0.561, 95%

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confidence interval: 0.343–0.918). At 1-year follow-up, these results were similar.
Conclusions: Bivalirudin can be safely and effectively used during PPCI in older patients with STEMI. Bivalirudin reduces the risks of NACEs and bleeding within 30 days after PPCI, without increasing the risks of MACCEs and stent thrombosis compared with heparin.

Keywords
Bivalirudin, unfractionated heparin, ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, older patient, major adverse cardiac and cerebrovascular events

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Introduction

Coronary artery disease refers to plaques or stenosis of the coronary artery, limited or diffuse spasm of the coronary artery, small-vessel disease, and microvascular dysfunction, and it is the main cause of death worldwide.[1,2] ST-segment elevation myocardial infarction (STEMI) occurs on the basis of coronary artery disease with a sharp reduction or interruption of coronary blood supply, resulting in myocardial infarction caused by severe and persistent myocardial ischemia. With an aging society in China, the incidence of STEMI is rising in the older population.

Primary percutaneous coronary intervention (PPCI) is still the preferred reperfusion method in older patients with STEMI.[3] PPCI therapy can rescue blocked blood vessels in time, restore myocardial blood perfusion, and significantly reduce the mortality and recurrence rates of infarction.[4] Current guidelines recommend routine anticoagulation during PPCI in patients with STEMI.[5] In addition to the treatment strategy and standard operation, the efficacy and safety of anticoagulant drugs in PPCI are important for a successful operation. In particular, older patients with STEMI have more risk factors of cardiovascular events than younger patients. Therefore, the risks of ischemia and bleeding during percutaneous coronary intervention (PCI) are higher in older patients.[6,7] Consequently, the benefits and risks of intra-PCI anticoagulation must be weighed in older patients.

Unfractionated heparin (UFH) has been used for decades in patients with STEMI undergoing PPCI.[8] In addition to UFH, the use of aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors (GPIs) has been shown to reduce early and late adverse cardiac events in patients with STEMI, with an unnecessary increase in bleeding events.[9,10] Bivalirudin is a novel direct thrombin inhibitor. Several large multicenter trials (EuroMAX,[11] HORISON AMI[12]) showed that during PPCI in patients with STEMI, bivalirudin was superior to UFH alone or in combination with a GPI in reducing bleeding events. However, the efficacy and safety of bivalirudin has not been established in older patients. Therefore, this study was designed to investigate the perioperative efficacy and safety of bivalirudin during emergency PPCI in older patients (>75 years old) with STEMI.

Patients and methods

Patients

Patients with STEMI who underwent PPCI in our hospital between February 2011 and December 2019 were included in this study. Inclusion criteria were as follows: (1) age $\geq$75 years (men and women); (2) a primary PPCI strategy was followed for patients with symptoms lasting longer than 12 hours in the presence of (i) evidence of a

persistent ischemic electrocardiogram (ECG); (ii) persistent or recurrent pain and dynamic ECG changes; and (iii) persistent or recurrent pain, symptoms, and signs of heart failure, shock, or malignant arrhythmias; (3) no revascularization for other non-culprit target vessels within 30 days after PPCI; and (4) use of antiplatelet agents (aspirin and clopidogrel or ticagrelor, and a loading or maintenance dose) before PCI according to relevant guidelines. Exclusion criteria were as follows: (1) intravenous thrombolytic therapy; (2) use of anticoagulants (heparin/low molecular weight heparin, sodium fondaparinux, warfarin, or new oral anticoagulants) or tirofiban within 48 hours before PCI; (3) intraoperative or postoperative intravenous infusion of a GPI; and (4) mechanical complications, such as ventricular septal rupture, papillary muscle rupture, and acute mitral regurgitation. This study was approved by the ethics committee of Anhui Provincial Hospital and all patients signed written informed consent.

Clinical data collection

For eligible participants, the baseline characteristics (sex, age, coronary risk factors, and laboratory tests), clinical medications, and detailed PPCI data were collected by designated staff involved in the study. The preoperative estimated glomerular filtration rate (eGFR) was calculated using the modified diet in renal disease study equation applicable for the Chinese population of adult men:[11] eGFR (mL/minute/1.73 m^2) = $175 \times (\text{serum creatinine})^{-1.234} \times (\text{age})^{-0.179}$ (women: $\times 0.79$). Patients were followed up by phone or clinical follow-up for 30 days after the emergency PCI. The primary clinical endpoint was net adverse clinical events (NACEs) 30 days after emergency PCI, including major adverse cardiac and cerebral events (MACCEs) and Bleeding Academic Research Consortium grades 2 to 5 (BARC 2–5) bleeding events.[12] MACCEs included all-cause death, recurrent myocardial infarction, ischemia-driven target vessel revascularization, and stroke. Secondary endpoints were MACCEs 30 days after emergency PCI, BARC 2–5 bleeding events 30 days after surgery, and stent thrombosis. Stent thrombosis was defined according to the Academic Research Consortium (ARC) (defined as certain or probable stent thrombosis).[13]

Medical treatment and main considerations of PCI

According to the anticoagulants provided during PPCI, patients with STEMI were divided into the bivalirudin group and the UFH group (n = 260). Patients in both groups took a single dose of aspirin (100–300 mg) and clopidogrel (300–600 mg) or ticagrelor (180 mg) before PPCI. In the bivalirudin group, bivalirudin (250 mg/vial; Salubris Pharmaceutical Co., Ltd., Shenzhen, China) was administered at a dose of 0.75 mg/kg (intravenously) during PPCI, followed by a maintenance dose of 1.75 mg/kg/hour intravenously. The activated clotting time (ACT) was monitored 5 minutes after initial administration. If the ACT was <225 s (Hemotec methods), additional bivalirudin (0.30 mg/kg, injection) was provided. At 30 minutes after the end of PCI, the interventional cardiologist decided whether to administer bivalirudin (1.75 mg/kg, intravenously) as required for no longer than 4 hours (starting from this dose). Patients in the UFH group were provided a loading dose (100 U/kg) of UFH. The ACT was monitored for 5 minutes after initial administration. If the ACT exceeded 225 s, an UFH (20 U/kg) bolus was administered.

Coronary angiography was performed via radial, femoral, or brachial access. Single-vessel or multi-vessel lesions were considered on the basis of the number of

coronary lesions with ≥50% stenosis. PPCI was performed after recording the type of lesion and the extent of calcification. For patients with left ventricular dysfunction or cardiogenic shock, an intra-aortic balloon pump was placed before PPCI. For patients with severe bradycardia, a temporary pacemaker was implanted before PPCI. After PPCI, the patients were instructed to take aspirin (100 mg, once daily) and clopidogrel (75 mg, once daily) or ticagrelor (90 mg, twice a day). After PPCI, the physician made a decision regarding the use of low molecular weight heparin on the basis of the patient's condition.

Definitions

Anemia was defined as hemoglobin levels <120 g/L for adult men or hemoglobin levels <110 g/L for adult women. All-cause death was defined as death associated with any cause. Cardiac death was defined as any death associated with cardiac factors (e.g., myocardial infarction, low-output heart failure, and fatal arrhythmia), undocumented death, unexplained death, and all procedure-related deaths, including concurrent treatment-related deaths. Myocardial infarction was defined according to the third edition of the updated global definition of myocardial infarction, which was released at the European Society of Cardiology conference in 2012 as typical chest pain for ≥30 minutes, with evolving ECG changes and creatine kinase and creatine kinase isoenzyme MB levels >3 × the upper limit of normal or troponin T levels >1 × the upper limit of normal. Ischemia-driven target vessel revascularization was defined as second PCI or coronary artery bypass grafting (CABG) due to re-stenosis of the target lesion or any part of the same major vessel (proximal part, distal part, branches, and the left main trunk) or to other reasons. Stroke was defined as an acute non-hemorrhagic cerebrovascular event that caused local or global neurological dysfunction, with symptoms lasting longer than 24 hours, and confirmation by clinical symptoms and imaging studies.

Statistical analysis

Categorical variables are expressed as percentage and were analyzed with the chi-square test or Fisher's exact test. Continuous variables are expressed as mean ± standard deviation and were analyzed with the t-test or analysis of variance. Multivariate logistic regression was used to examine the effect of patients' characteristics on the selection of a "one-time" procedure or staged approach. We adjusted all available variables listed in Table 1. The Kaplan–Meier method was used to analyze adverse events that occurred during follow-up. The Cox proportional hazard regression model was used to analyze the association between bivalirudin and the study endpoints during follow-up. Variables associated with primary endpoints ($P < 0.1$) as per univariate analysis and clinically relevant variables, including age, sex, anemia, diabetes, hypertension, stroke history, eGFR ≤60 mL/minute/1.73 m^2, and intervention access, were incorporated into the regression model. SPSS v24.0 (IBM Corp. Armonk, NY, USA) was used for statistical analysis. All tests were two-sided and $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics

A total of 672 patients with STEMI were included, and there were 412 patients in the bivalirudin group and 260 in the UFH group. The basic clinical characteristics of patients with STEMI are shown in Table 1. Patients in the bivalirudin group were significantly older than those in the UFH group ($P < 0.001$) and the incidence of

Table 1. Basic clinical characteristics.

Variable	Bivalirudin group (n = 412)	UFH group (n = 260)	P value
Age (years)	80.34 ± 4.54	78.73 ± 3.92	<0.001
Men, n (%)	257 (62.4)	157 (60.4)	0.605
Heart rate, beats/minute	77.40 ± 19.48	78.28 ± 19.74	0.566
LVEF, %	52.09 ± 11.88	52.11 ± 12.14	0.984
History of hypertension, n (%)	239 (58.0)	152 (58.5)	0.908
History of stroke, n (%)	86 (20.9)	41 (15.8)	0.100
History of MI, n (%)	32 (7.8)	27 (10.4)	0.243
History of diabetes, n (%)	115 (27.9)	77 (29.6)	0.634
eGFR ≤60 mL/minute/1.73 m^2, n (%)	122 (29.6)	75 (28.8)	0.832
Anemia, n (%)	124 (30.1)	56 (21.5)	0.015
Killip grade, n (%)			0.912
I	278 (67.5)	173 (66.5)	
II	67 (16.3)	46 (17.7)	
III	34 (8.3)	23 (8.8)	
IV	33 (8.0)	18 (6.9)	

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as n (%). UFH, unfractionated heparin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; eGFR, estimated glomerular filtration rate.

anemia (P = 0.015) was significantly higher than that in the UFH group. Additionally, the femoral artery was more frequent for arterial access in the bivalirudin group than in the UFH group (P = 0.043). The hospital stay in the bivalirudin group was significantly shorter than that in the UFH group (P = 0.005) (Table 2).

NACEs 30 days after PPCI

During the 30-day follow-up after PPCI, the rate of NACEs tended to be lower in the bivalirudin group than in the UFH group (P = 0.053) (Table 3). Multivariate Cox regression analysis showed that the incidence of NACEs was significantly lower in the bivalirudin group than in the UFH group (P = 0.047) (Table 3). The multivariate logistic regression model showed that patients with arterial access (femoral artery) (P = 0.033) and older age (P < 0.001) were more likely to use bivalirudin (Table 4).

MACCEs 30 days after PPCI

During the 30-day follow-up after PPCI, there was no significant difference in the incidence of MACCEs between the two groups (Table 3). Multivariate Cox regression analysis also showed that there was no significant difference in the incidence of MACCEs between the two groups. Moreover, for MACCEs, no significant difference was observed in all-cause mortality, cardiac death, recurrent myocardial infarction, stroke, or target vessel revascularization between the two groups (Table 3).

BARC 2–5 bleeding events 30 days after PPCI

During the 30-day follow-up after PPCI, the rate of BARC 2–5 bleeding events was significantly lower in the bivalirudin group than in the UFH group (P = 0.035). Moreover, multivariate Cox regression analysis showed that the incidence of BARC 2–5 bleeding events was significantly lower in the bivalirudin group than in the UFH group

Table 2. Treatment and procedural characteristics.

Variable	Bivalirudin group (n = 412)	UFH group (n = 260)	P value
IRA, n (%)			0.992
Left main artery	10 (2.4)	7 (2.7)	
Left anterior descending artery	203 (49.3)	130 (50.0)	
Left circumflex artery	53 (12.9)	33 (12.7)	
Right artery	146 (35.4)	90 (34.6)	
Lesion number, n (%)			0.500
1	111 (26.9)	81 (31.2)	
2	139 (33.7)	83 (31.9)	
3	162 (39.3)	96 (36.9)	
Left main trunk, n (%)	44 (10.7)	28 (10.8)	0.917
IABP, n (%)	70 (17.0)	41 (15.8)	0.678
Arterial access, n (%)			0.043
Radial artery	347 (84.2)	234 (90.0)	
Brachial artery	37 (9.0)	19 (7.3)	
Femoral artery	28 (6.8)	7 (2.7)	
Stent number	1.40 ± 0.73	1.38 ± 0.71	0.828
Total stent length, mm	35.99 ± 20.89	36.34 ± 26.18	0.878
Hospital stay, days	7 (6–10)	8 (6–12)	0.005

Normally distributed continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as n (%). UFH, unfractionated heparin; IRA, infarction-related artery; IABP, intra-aortic balloon pump.

Table 3. Thirty-day adverse events after emergency percutaneous coronary intervention in older patients with ST-segment elevation myocardial infarction.

Clinical event, n (%)	Bivalirudin group (n = 412)	UFH group (n = 260)	Crude		Adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value
NACEs	68 (16.5)	59 (22.7)	0.731 (0.518–1.030)	0.053	0.700(0.492–0.995)	0.047
MACCEs	45 (10.9)	34 (13.1)	0.832 (0.533–1.299)	0.416	0.778 (0.456–1.329)	0.358
All-cause death	40 (9.7)	28 (10.8)	0.901 (0.556–1.461)	0.673	0.812 (0.487–1.353)	0.424
Cardiac death	36 (8.8)	27 (10.4)	0.841 (0.511–1. 386)	0.496	0.861 (0.526–1.410)	0.551
MI	3 (0.8)	2 (0.8)	0.950 (0.159–5.686)	0.955	1.014 (0.162–6.357)	0.988
Stroke	1 (0.3)	1 (0.4)	0.628 (0.039–10.033)	0.742	0.781 (0.203–3.005)	0.719
TVR	4 (1.0)	5 (2.1)	0.506 (0.136–1.883)	0.309	0.848 (0.047–15.187)	0.911
BARC 2–5	33 (8.3)	34 (13.4)	0.602 (0.373–0.972)	0.035	0.561 (0.343–0.918)	0.021
BARC 2	20 (5.0)	19 (7.5)	0.661 (0.353–1.238)	0.191	0.660 (0.346–1.259)	0.207
BARC 3–5	13 (3.3)	15 (6.0)	0.542 (0.258–1.139)	0.100	0.479 (0.223–1.029)	0.059
Stent thrombosis	3 (0.8)	2 (0.8)	0.950 (0.159–5.686)	0.955	1.014 (0.162–6.357)	0.988
Certain	1 (0.3)	1 (0.4)	0.631 (0.039–10.091)	0.745	1.357 (0.069–26.726)	0.841
Probable	2 (0.5)	1 (0.4)	1.270 (0.115–14.003)	0.845	1.252 (0.104–15.010)	0.859

UFH, unfractionated heparin; OR, odds ratio; CI, confidence interval; NACEs, net adverse clinical events; MACCEs, major adverse cardiac and cerebrovascular events; BARC, Bleeding Academic Research Consortium.

Table 4. Multivariate logistic regression model of arterial access (femoral artery) or older age for use of bivalirudin.

Variables	HR (95% CI)	P value
Arterial access (femoral artery vs radial artery)	2.584 (1.078–6.192)	0.033
Age	1.096 (1.051–1.143)	<0.001

HR, hazard ratio; CI, confidence interval.

Table 5. One-year adverse events after emergency percutaneous coronary intervention in older patients with ST-segment elevation myocardial infarction.

Clinical event, n (%)	Bivalirudin group (n = 412)	UFH group (n = 260)	Crude		Adjusted	
			OR (95% CI)	P	OR (95% CI)	P
NACEs	108(26.3)	71(27.6)	0.926 (0.687–1.250)	0.644	0.878 (0.647–1.192)	0.404
MACCEs	80 (19.6)	48 (18.9)	1.025 (0.717–1.466)	0.892	0.951 (0.660–1.371)	0.789
All-cause death	73 (17.8)	40 (15.4)	1.138 (0.774–1.673)	0.510	1.025 (0.692–1.518)	0.902
Cardiac death	67 (16.4)	38 (14.8)	1.099 (0.738–1.637)	0.640	1.005 (0.669–1.508)	0.982
MI	10 (2.7)	6 (2.7)	1.036 (0.377–2.850)	0.945	1.072 (0.379–3.030)	0.896
Stroke	2 (0.8)	2 (0.5)	0.613 (0.086–4.356)	0.622	0.711 (0.084–5.994)	0.754
TVR	5 (1.3)	6 (2.5)	0.528 (0.161–1.729)	0.283	0.819 (0.245–2.736)	0.745
BARC 2–5	40 (9.8)	31 (12.1)	0.799 (0.500–1.278)	0.346	0.792 (0.489–1.281)	0.342
BARC 2	29 (7.5)	20 (8.0)	0.904 (0.511–1.597)	0.727	0.912 (0.508–1.640)	0.759
BARC 3–5	18 (4.7)	18 (7.2)	0.632 (0.329–1.214)	0.164	0.552 (0.282–1.083)	0.084
Stent thrombosis	3 (0.8)	3 (1.3)	0.628 (0.127–3.114)	0.566	0.668 (0.129–3.477)	0.632
Certain	1 (0.3)	2 (0.9)	0.311 (0.028–3.433)	0.314	0.327 (0.026–4.075)	0.385
Probable	2 (0.5)	1 (0.4)	1.268 (0.115–13.987)	0.846	1.246 (0.104–14.935)	0.862

UFH, unfractionated heparin; OR, odds ratio; CI, confidence interval; NACEs, net adverse clinical events; MACCEs, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; TVR, target vessel revascularization; BARC, Bleeding Academic Research Consortium.

(P = 0.021). BARC 2 and BARC 3–5 bleeding events were not significantly different between the two groups (Table 3).

Stent thrombosis and adverse events 30 days after PPCI

During the 30-day follow-up after PPCI the rate of stent thrombosis was not significantly different between the two groups (Table 3). The 1-year composite rate of NACEs was not significantly different between the two groups (Table 5). The 1-year incidence of MACCEs was also not significantly different between the two groups. Additionally, there were no significant differences in the 1-year rates of BARC 2–5 bleeding events, cardiac death, myocardial infarction, definite/probable stent thrombosis, and target vessel revascularization between the two groups.

Discussion

In recent years, the recommended class for the use of bivalirudin in patients with STEMI during PPCI has been evolving. According to the HORIZONS-AMI,[12] EUROMAX,[14] HEAT-PPCI,[15] and BRIGHT studies,[16] the 2014 European Society of Cardiology Revascularization Guidelines[17] and the 2017 European

Society of Cardiology STEMI Guidelines[5] recommended bivalirudin as a class IIa perioperative anticoagulant for patients with STEMI. However, according to additional evidence from the MATRIX[18] and SWEDEHEART studies,[19] the 2018 European Society of Cardiology Revascularization Guidelines[20] recommended bivalirudin as a class IIb anticoagulant. Therefore, the use of bivalirudin during emergency PPCI requires more evidence, and no such studies have been conducted, specifically in older patients with STEMI. The current study showed that in older patients with STEMI, bivalirudin significantly reduced the incidence of NACEs in 30 days after emergency PPCI compared with UFH. This was achieved mainly owing to fewer bleeding events, without increasing the incidence of MACCEs, all-cause death, cardiac death, stroke, recurrent myocardial infarction, target vessel revascularization, and stent thrombosis.

Studies have shown that age is an independent risk factor for bleeding, and the risk of bleeding increases by 2% for each additional year of age.[21] Bleeding events are independent predictors of death after PPCI, and therefore, reducing bleeding events can improve short-term and long-term outcomes.[22–24] Therefore, for older patients with STEMI at a high risk for bleeding, choosing an anticoagulant during PPCI to reduce the risk of bleeding is important. Compared with traditional UFH, bivalirudin has a shorter half-life, higher bioavailability, and more stable anticoagulant effect. Large studies, such as HORIZONS-AMI[12] and EUROMAX,[14] showed that bivalirudin significantly reduced the incidence of bleeding complications in patients with STEMI who underwent PPCI compared with UFH. The BRIGHT study[16] showed that the effect of bivalirudin lasted 2 to 4 hours after PPCI compared with UFH, which significantly reduced the risk of bleeding without increasing the risk of stent thrombosis. The MATRIX study[18] showed that bivalirudin reduced all-cause death and cardiac death, while reducing the risk of bleeding, compared with UFH alone. The above-mentioned evidence suggests that bivalirudin has more pronounced clinical benefits than UFH for older patients at a high risk of bleeding.

The REPLACE 2 study[25] showed that for older patients aged 75 years and older, bivalirudin reduced 1-year mortality compared with UFH plus a GPI. In the ACUITY study, subgroup analysis showed that bivalirudin reduced major and minor bleeding events in all age groups, especially in patients aged 75 years and older.[26] Additionally, the overall analysis and subgroup analysis per age group showed that bivalirudin did not increase the incidence of ischemic events and death.[26,27] Lemesle[28] et al. were one of the first research groups to evaluate the perioperative efficacy and safety of bivalirudin in patients aged 80 years and older undergoing PCI. These authors found showed that bivalirudin reduced the incidence of in-patient bleeding events and post-PCI 6-month mortality compared with UFH.[28] In an age-based subgroup analysis of the combined HORIZONS-AMI and EUROMAX datasets, bivalirudin was associated with a lower 30-day incidence of non-coronary artery bypass grafting major bleeding and NACEs, with a similar 30-day incidence of acute stent thrombosis and mortality in patients aged 65 years and older with acute STEMI.[8] The studies described above enrolled any patient with coronary heart disease who underwent selective PPCI or PPCI. However, our study enrolled older patients with STEMI who underwent PPCI, and we found that bivalirudin consistently showed clinical benefits across the older population. In a previous study, the adjusted risks for 1-year mortality, and 30-day and 1-year

stent thrombosis and re-infarction were not significantly different between patients with STEMI and UFH + GPI and those with bivalirudin + GPI.[29] In this study, we analyzed the efficacy and safety of bivalirudin alone and UFH alone.

This study has some limitations. First, this was a single-center retrospective study, with certain selection bias and confounding factors. Randomized, controlled trials are required to validate the results. Second, during follow-up, ECG, myocardial markers, and imaging studies were not performed or tested in the case of angina, which may have contributed to underestimation of the incidence of myocardial infarction.

Bivalirudin can be safely and effectively used during emergency PPCI in older patients with STEMI. Bivalirudin significantly reduces 30-day NACEs and bleeding events without increasing the risk of MACCEs or stent thrombosis compared with UFH.

Author contributions

Hongwu Chen is responsible for the experimental design, data and statistical analysis, and preparing the manuscript; Xiaofan Yu is responsible for the concept of the study, literature research, and acquisition of data; Xiangyong Kong, Longwei Li, and Jiawei Wu are responsible for the concept of the study and acquisition of data; and Likun Ma is the guarantor of integrity of the entire study, and provided the concept of the study, designed the study, performed clinical treatment, and performed acquisition of data. All authors approved the final version.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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