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Comparative Study of Linezolid and Vancomycin Regimens in One-Stage Surgery for Treating Limb Traumatic Osteomyelitis Caused by Methicillin-Resistant *Staphylococcus aureus*

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Abstract

To compare the clinical outcomes of linezolid and vancomycin regimens combined with one-stage surgery in treating traumatic osteomyelitis of the limbs caused by methicillin-resistant *Staphylococcus aureus* (MRSA) infection. A retrospective study was performed to analyze patients with traumatic osteomyelitis of the limbs attributable to MRSA infection. All of these patients received one-stage surgery to debride their wounds, with subsequent implantation of a vancomycin-loaded calcium sulfate artificial bone. Patients received either intravenous linezolid (study group) or vancomycin (control group) during the perioperative period. The postoperative inflammatory markers, renal function, duration of drainage catheter placement, duration of antibiotic administration, length of hospital stay, adverse events, and recurrence of osteomyelitis in these two groups were compared. The study group had a shorter duration of antibiotic administration and length of hospital stay ($p < 0.05$). There was a significant difference in the incidences of adverse events between the two groups (5.88% and 17.65% in the study and control groups, respectively, $p < 0.05$). There was no recurrence in either group during the three-year follow-up period. As of year, five after the surgery, one patient in the control group had a recurrence of osteomyelitis. The linezolid regimen should be preferred to the vancomycin regimen in patients with traumatic osteomyelitis of the extremities caused by MRSA infection because the linezolid regimen showed fewer adverse events, shorter periods of antibiotic use, and shorter hospital stay. However, both treatment regimens achieved satisfactory outcomes and warranted further investigations.

K e y w o r d s: linezolid, vancomycin, traumatic osteomyelitis, efficacy

Introduction

Most patients with traumatic osteomyelitis in the extremities have suffered severe open fractures or received inappropriate orthopedic operations. Traumatic osteomyelitis often involves scar hyperplasia, sinus formation, bone defects, and infections. Management requires not only controlling the infection but also repairing bone and soft tissue defects, and these conditions may have treatment needs that contradict each other (Chadayammuri et al. 2017). Some physicians do not have adequate knowledge and skills to manage this disease. It can also result in delayed or inappropriate antibiotic administration. All of these issues increase the risk of infection from methicillin-resistant *Staphylococcus aureus* (MRSA), which can render treatment more difficult (Harting et al. 2017; Zhu et al. 2017). During the past 10 years, we have performed one-stage surgery to treat more than 2,000 patients with traumatic osteomyelitis and have achieved satisfactory outcomes. In addition to the surgery, appropriate administration of antibiotics is also critical to managing this disorder. Choosing linezolid and vancomycin for a comparative study in treating traumatic osteomyelitis of the limbs caused by MRSA infection is desired for several reasons. Linezolid and vancomycin are commonly used antibiotics for treating MRSA infections, including osteomyelitis. Linezolid and vancomycin have different mechanisms of action, which makes them ideal candidates for comparison. Linezolid is a protein synthesis

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inhibitor that targets the 50S subunit of bacterial ribosomes, while vancomycin is a cell wall synthesis inhibitor that targets the peptidoglycan layer of Gram-positive bacteria. Linezolid and vancomycin have distinct pharmacokinetic properties, including different routes of administration, distribution, and metabolism. Comparing the two antibiotics in a head-to-head study allows for a more comprehensive evaluation of their benefits and drawbacks. There is limited comparative data on the effectiveness and safety of linezolid and vancomycin in treating traumatic osteomyelitis of the limbs caused by MRSA infection. Thus, a study comparing the two antibiotics could provide valuable insights into the optimal treatment of this condition. Overall, choosing linezolid and vancomycin for a comparative study in treating traumatic osteomyelitis of the limbs caused by MRSA infection is justified based on their clinical relevance, distinct mechanisms of action, and limited comparative data. With the given background, this study was designed to determine the optimal antibiotic regimen for treating traumatic osteomyelitis of the limbs caused by MRSA infection in terms of duration of antibiotic administration, length of hospital stay, adverse events, and recurrence rates.

Experimental

Materials and Methods

Study design and participant selections. We performed a retrospective study and analyzed the patients with traumatic osteomyelitis of the limbs due to MRSA between January 2010 and January 2017. The Hospital Ethics Committee approved the study protocol. Clinical and demographic data of patients were collected from the electronic medical records. Using standardized clinical criteria and isolation of MRSA from a normally sterile site, a medical record review was used to define and classify infections. Inclusion criteria were as follows: 1) documented trauma and history of surgery; 2) acute erythema, swelling, and pain in a local wound that was difficult to heal, with recurrent exudates, chronic sinus formation, or soft tissue defects; 3) local osteosclerosis, bone defects, necrosis, or periosteal reactions indicated by both X-ray and computed tomography (CT); 4) traumatic osteomyelitis diagnosed by intraoperative pathological reports; 5) bacterial cultures from sinus or exudates diagnosed as MRSA. Exclusion criteria were: 1) history of diabetes, skin disease, or other vascular disease; 2) abnormal liver or kidney function; 3) allergy to vancomycin or linezolid; 4) no history of surgical treatment for the injury.

Microbiological culture and identification of *S. aureus*. Sinus or exudates samples from patients with traumatic osteomyelitis were cultured on blood agar (Oxoid, UK) at 37°C for 24 h. The specimens were analyzed by the BacT/Alert® Virtuo® Microbial Detection System (bioMérieux, France), conventional biochemical tests and/or by the VITEK®2 automated system (bioMérieux, France). A total of 64 MRSA isolates were recovered from patients with traumatic osteomyelitis. Duplicate cultures from the same patient were excluded from the study. All MRSA isolates were identified by the coagulase test and resistance to oxacillin as per the Clinical and Laboratory Standards Institute guidelines (CLSI 2010). The minimum inhibitory concentration (MIC) of ciprofloxacin, fusidic acid, gentamicin, rifampicin, trimethoprim-sulfamethoxazole (TMP-SMX), and vancomycin was determined with the E-test method. The MIC value was read from the scale in terms of μg/ml where the pointed end of the ellipse intersected the strip. The threshold of MIC results was chosen based on the guidelines of the Clinical Laboratory Standards Institute or previous studies (CLSI 2010).

PCR assays for the *mecA* genes for identification of MRSA. DNA was extracted from colonies using boiling methods. All isolates were used to evaluate the chosen primer set's performance for detecting MRSA colonies.

The total volume used per reaction for the conventional PCR assay was 25 μl, including 0.5 μM of each primer of mecA primers, according to the previous study (Shore et al. 2011).

Treatment protocols. *Preoperative preparations.* Preoperative preparations included blood cell counts, biochemistry, coagulation profiles, and bacterial culture from wound exudates. Imaging studies, including X-rays, CT, and magnetic resonance imaging (MRI) were performed to assess the extent of bone infections and defects. If a patient had a significantly high level of inflammatory markers and signs of acute local infection, he or she would then receive intravenous linezolid (0.6 g every 12 h, 100 ml/0.2, batch number H20150223; Jiangsu Haosen Pharmaceutical Group Co., Ltd., China) or vancomycin (1 g every 12 h, 0.5, batch number H20030375; Eli Lilly and Company, USA) preoperatively.

Surgical procedure. The surgical procedure had two significant steps, debridement, and bone grafting. First, the wound's scar tissue, inflammatory granulation tissue, and internal fixation in the wound were completely removed. The inflammatory granulation tissue and infected or sclerotic bone at the end of fracture, as well as any free dead bone, were thoroughly debrided. After confirming that debridement was complete, the wound was rinsed repeatedly and re-draped. Then, based on the fracture end and the bone defect, an artificial bone made from vancomycin-loaded calcium sulfate artificial bone (OSTEOSET™ Resorbable Bead Kit (RBK);

Wright Medical, USA) was implanted. This artificial bone was prepared by adding 1 g vancomycin to 5 ml of RBK powder. After mixing them with the solutions, the paste-like materials were applied to a 4.8 mm or 3.0 mm bead mold. After about 10 min, the beads were ready for use. Every patient received 1 g of beads implanted into the wound. Depending on the extent of the wound and bone defects, the autologous iliac bone was also implanted to promote osteogenesis. Patients with soft tissue defects received wound repair by skin grafting with microsurgical technique.

Postoperative care. After surgery, adequate drainage was provided at the site of the bone graft. Every patient received a 12 mm diameter negative pressure drainage tube. Drainage fluid samples were sent for bacterial culture every three days starting on postoperative day one. An individual drainage tube was removed only after two consecutive cultures were negative. Patients continued to receive either linezolid (0.6 g every 12 h) or vancomycin (1 g every 12 h). Inflammatory markers and renal function were tested on the first day and every three days after the surgery. Antibiotics were stopped once three major inflammatory markers, white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and high-sensitivity C-reactive protein (CRP) were within normal limits in two consecutive tests. In addition, the antibiotic doses were adjusted if any test results indicated abnormal renal function.

Follow-up. Patients were followed up in the clinic every two months during the first year after discharge from the hospital. Clinical examinations included inflammatory markers, X-ray, CT, bone healing, survival of the skin flap, and joint function. If there was no obvious abnormality, patients were then followed up every six months from the second year. Osteomyelitis was evaluated based on published criteria (Mckee et al. 2010).

Outcome comparisons. Patients were assigned to either the study (linezolid) or the control (vancomycin) group. The postoperative inflammatory markers, renal function, duration of drainage catheter placement, duration of antibiotic administration, length of hospital stay, adverse events, and recurrence of osteomyelitis in these two groups were compared.

Results

Sixty-four infected patients were identified, with 32 patients in each group. The study group had 21 males and 11 females, with a mean age of 47.9 ± 6.4 years (25 – 64 years) and an average disease duration of 15.5 ± 4.3 months (9–23 months). There were 17 tibial, five femur, and ten calcaneus infections. The causes of the injury were 14 from falls, six from car accidents, and 12 from falls from heights. Twenty-eight patients had closed fractures, and four patients had open fractures. The average number of previous surgeries was 2.2 (1–5), with 16 patients having internal fixation. Cierny-Mader classification showed 17 patients with type I, three patients with type II, ten patients with type III, and two patients with type IV osteomyelitis. The control group had 18 males and 14 females, with a mean age of 48.8 ± 6.8 years (28 – 62 years) and an average disease duration of 16.2 ± 4.7 months (8–26 months). There were 15 tibial, four femur, and 13 calcaneus infections. The causes of the injury were 17 from falls, four from car accidents, and 11 from falls from heights. Twenty-six patients had closed fractures, and six patients had open fractures. The average number of previous surgeries was 2.5 ± 1.2 (1–6), with 13 patients having internal fixation. Cierny-Mader classification showed 15 patients with type I, fivr patients with type II, eight patients with type III, and four patients with type IV osteomyelitis. The study and control groups were comparable, with no statistically significant differences in these variables (all $p > 0.05$) (Table I).

Microorganism characterization and antibiotic susceptibility testing. There were 64 osteomyelitis MRSA (OM-MRSA) isolates included in the study. From medical records, approximately 72% of MRSA strains were obtained from male patients. The antibiotic resistance patterns of the isolated MRSA strains examined by the MIC analysis and susceptibility testing showed that isolates significantly exhibited resistance to gentamicin (51%), ciprofloxacin (60%), fusidic acid (42%), and trimethoprim-sulfamethoxazole (TMP-SMX) (36%). All MRSA strains were susceptible to rifampicin and vancomycin, a limited number of MRSA (n = 11) strains appeared to be less susceptible to rifampicin (MIC ≥ 4 μg/ml; n = 2) and vancomycin (MIC ≥ 2 μg/ml; n = 6).

Comparisons of clinical characteristics. There was no statistically significant difference in the duration of drainage catheter placement between these two groups ($p > 0.05$). However, the duration of antibiotic administration and hospital stay were significantly lower in the study group than in the control group ($p < 0.05$) (Table III).

Comparisons of postoperative inflammatory markers and renal function. On postoperative days one and seven, there were no statistically significant differences between the study and control groups concerning WBC count, ESR, CRP, blood urea nitrogen (BUN), or serum creatinine (SCr) levels ($p > 0.05$). However, on postoperative day 16, all these measurements were statistically significantly higher in the control group than in the study group ($p < 0.05$) (Table II).

Comparisons of adverse events. In the study group, two patients (6.3%) developed nausea after intravenous

Table I
Comparisons of baseline characteristics between two group.

	Study group (n = 32)	Control group (n = 32)	*p*
Gender, n			
Male	21	18	0.644
Age, M ± SD, year	47.9 ± 6.4	48.8 ± 6.8	0.590
Number of previous surgery, M ± SD	2.2 ± 1.1	2.5 ± 1.2	0.476
Disease duration, M ± SD, month	15.5 ± 4.3	16.2 ± 4.7	0.532
Site of infection, n			0.315
Tibia	17	15	
Femur	5	4	
Calcaneus	10	13	
Cause of injury, n			0.276
Fall	14	17	
Car accident	6	4	
Fall from height	12	11	
Type of fracture, n			0.427
Closed	28	26	
Open	6	6	
Internal fixation, n	16	13	0.352
Classification by Cierny-Mader criteria, n			0.287
Type I	17	15	
Type II	3	5	
Type III	10	8	
Type IV	2	4	

M ± SD – mean ± standard deviation

Table II
Comparisons of inflammatory markers and renal function after the surgical operation.

Group	Day after the surgery	WBC ($\times 10^9$)	ESR (mm/h)	CRP (mg/l)	BUN (mmol/l)	SCr (μmol/l)
Study group (n = 32)	1	12.4 ± 2.3	92.3 ± 8.4	68.3 ± 6.8	4.7 ± 2.5	86.5 ± 13.7
	7	8.9 ± 1.9	40.9 ± 5.4	29.5 ± 3.6	4.7 ± 2.5	84.3 ± 12.5
	16	5.8 ± 1.5*	27.7 ± 4.7*	14.3 ± 2.9*	4.5 ± 2.4*	79.4 ± 11.5*
Control group (n = 32)	1	12.7 ± 2.4	97.4 ± 8.9	65.9 ± 6.4	4.9 ± 2.6	83.1 ± 13.2
	7	9.1 ± 1.9	43.5 ± 5.5	32.2 ± 3.7	5.4 ± 2.8	91.8 ± 15.4
	16	8.8 ± 1.8	38.7 ± 5.0	24.9 ± 3.0	7.7 ± 3.7	122.8 ± 21.1

* – $p < 0.05$, relative to the control group
WBC – white blood cell count, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, BUN – blood urea nitrogen, Scr – serum creatinine

Table III
Comparisons of clinical variables between two groups (mean ± standard deviation, day).

Group	Duration of antibiotics	Duration of drainage tube	Length of hospital stay
Study group (n = 32)	15.1 ± 2.5	24.5 ± 5.4*	27.4 ± 4.4*
Control group (n = 32)	14.9 ± 2.3	36.8 ± 7.3	36.3 ± 6.1

* – $p < 0.05$, relative to the control group

Table IV
Comparisons of adverse events between two groups.

Group	Adverse events n (%)	Adjustment of antibiotic regimen n (%)
Study group (n = 32)	2 (6.25)*	0 (0)*
Control group (n = 32)	5 (15.63)	3 (9.38)

* – $p < 0.05$, relative to the control group

antibiotic infusion, relieved after the infusion was slowed down. They were able to complete the same antibiotic treatment regimen. Five patients (15.6%) in the control group had side effects. Three patients had test results indicating abnormal renal function that required their vancomycin dose to be decreased. Two patients developed a skin rash and received symptomatic treatments. Their treatment regimens were not otherwise changed. The incidences of side effects differed between the two groups ($p < 0.05$) (Table IV).

Comparison of follow-up outcomes. Patients in the study group were followed up for an average of 3.6 years (3–4.5 years). All patients achieved satisfactory bone restoration, infection control, wound healing, and functional recovery without any recurrence of infection. Patients in the control group had an average follow-up duration of 4.8 years (3.5–6 years). One patient had a new injury and experienced a recurrence of osteomyelitis during the 5th year after the surgery and required another surgical operation.

Discussion

Appropriate management of traumatic osteomyelitis requires controlling the infection and repairing the bone and soft tissue after thorough debridement. Treatment always poses a significant challenge for orthopedic surgeons. The recurrence rate was reported to be as high as 20–30% (Schenker et al. 2012). *S. aureus* is the most common pathogen in the development of traumatic osteomyelitis. Most patients with traumatic osteomyelitis also have sinus tract or open wounds, and the disease has a long course. The physicians in primary hospitals usually lack the knowledge or skills to provide timely debridement or give appropriate antibiotics, which increases the risk of MRSA infection. All of these can render the treatment of this disease complex. With the widespread use of negative pressure closed drainage, administration of high-efficiency antibiotics, and continuous advances in microsurgical technology, the successful management of traumatic osteomyelitis has been improved significantly. However, some patients still suffer a recurrence of osteomyelitis. The management of traumatic osteomyelitis commonly requires a long course of treatment. It can cause patients to miss their ideal window for early rehabilitation. Developing a treatment regimen with a high success rate, short treatment cycle, and improved functional recovery is essential.

Surgical operation is still the most important among the many treatment choices for traumatic osteomyelitis (Barger et al. 2017). However, there are still questions regarding whether one- or multiple-stage surgery should be performed. We have used one-stage surgery to treat traumatic osteomyelitis for many years, producing satisfactory outcomes. Our experience has shown that thorough debridement is a critical prerequisite to treating traumatic osteomyelitis. RBK, an antibiotic carrier, has been widely used in treating bone and joint infections, such as osteomyelitis, with satisfactory outcomes (Lima et al. 2014). Studies have confirmed that RBK can be used as a carrier to mix with medications such as vancomycin, tobramycin, or gentamicin (Drakou et al. 2014)). Vancomycin, a locally targeted slow-releasing medication, is the best choice to treat extremity traumatic osteomyelitis due to MRSA. We believe that the use of vancomycin-loaded calcium sulfate artificial bone has the following advantages and characteristics: 1) accurate targeted delivery of higher concentration of vancomycin into the infected lesions; 2) extended release of medication and gradually reaching its peak concentration to have a long-lasting effect; 3) high safety profile, given that the total amount of medication and the amount of medication entering into the blood circulation are less than those used systemically, which involves a lower risk for the adverse events; 4) the microsurgical technology could not only repair the wound with a skin flap but also fill the cavity with muscle fascia and other tissues. It can provide a protective barrier with a rich blood supply to the bone graft area. All of these factors could shorten the treatment cycle and save treatment costs.

Adequate quantities of systemic antibiotics are essential to the treatment of osteomyelitis. Currently, most physicians agree that systemic antibiotics for osteomyelitis should last 6 to 8 weeks (Badie and Arafa 2019). In the current study, the average duration for vancomycin after the surgery was 36.8 ± 7.3 days, slightly less than the clinically reported duration. The average duration of linezolid treatment was 24.5 ± 5.4 days, significantly shorter than that reported previously. We believe that, in addition to the local application of RBK, linezolid works by binding to the 23S site of ribosomal RNA in the 50S subunit of bacteria, which could prevent the formation of 70S initiation complexes and inhibit the synthesis of bacterial proteins (Alieva et al. 2018). Linezolid is a new class of artificially synthesized small-molecule oxazolidinone antibiotics. Linezolid entered clinical use in China in September 2007. As a newly

developed anti-MRSA drug, it has become the focus of the study in anti-MRSA treatment (Mogle et al. 2018). Linezolid has the following advantages over vancomycin (Schwalm et al. 2004; Britt et al. 2015; Sotgiu et al. 2015): 1) linezolid has almost 100% bioavailability; 2) it has substantial body fluid and tissue penetration activity, which ensures that the drug at a sufficient concentration reaches the infection site. It penetrates bone tissue five times more efficiently than vancomycin; 3) it is less toxic to renal tissue and does not require dose adjustment in patients with renal insufficiency and treatment interruption due to renal insufficiency. In our investigation, three patients developed renal insufficiency in the control group. The dose of vancomycin had to be reduced, which could lead to a series of adverse consequences such as high inflammatory measurements, increased antibiotic duration, and more extended hospital stay; 4) linezolid inhibits bacterial protein synthesis based on the mechanism different from other antibiotics. It has a lower risk of developing cross-resistance with other classes of antibiotics. In the current study, the inflammatory markers and renal function on the 16th day after surgery were significantly lower in the study group than in the control group. The duration of the antibiotic period and hospital stay were also significantly shorter in the study group than in the control group. In addition, the incidence of side effects in the study group was significantly lower than in the control group. All these results were consistent with the previous reports.

There was no recurrence in the study group during the follow-up period. One patient in the control group had a recurrence in the 5th year after the operation. This patient reported a new injury to the surgical site, which might be the cause of his recurrent osteomyelitis. There was no recurrence in either group within three years after the surgery. Therefore, both treatment regimens could achieve satisfactory results in patients with traumatic osteomyelitis. Because linezolid has the abovementioned advantages, we recommend it as the preferred choice. Future studies with a large sample size and a more extended follow-up period should be performed to compare these two treatment regimens further.

A 43-year-old female went to the local hospital on April 6, 2015, due to pain and swelling of her left heel after 3 meters fall 3 hours earlier. She was diagnosed with a comminuted fracture of the left calcaneus (Sander type III). Open reduction and internal fixation were performed on April 14, 2015. On the 3rd day after the operation, she started having erythema and swelling at the incision site. Bacterial culture grew methicillin-sensitive *S. aureus*. Antibiotics were administered, but there was no satisfactory improvement. On April 27, 2015, she received wound debridement and drainage, and antibiotics were continued. However, the swelling, erythema, and exudation persisted in the wound area. On May 18, 2015, wound debridement and suturing were performed. Then, her wound became clean and dry, with no noticeable swelling and erythema. She was discharged from the hospital after the stitches were removed on June 8, 2015. However, she developed erythema and swelling around the incisional site on her left foot again on June 20, 2015. In the clinic on June 24, 2015, an examination showed local ulceration with recurrent, persistent exudation. Wound culture grew MRSA. Oral antibiotics, local wound care, and drainage were performed. However, her condition did not improve. There was a sinus formation in the open wound. On March 17, 2016, she was admitted to the hospital again and received debridement. Internal fixation was removed, and the wound was sutured. However, the sinus failed to close. The decision was made to apply continuous dressing changes and drainage. She was transferred to our hospital on March 11, 2016. She was diagnosed with left calcaneus traumatic osteomyelitis. After completing the necessary examinations and tests, she underwent osteomyelitis debridement and artificial bone implantation. Then, the wound was grafted and closed by the peroneal perforate pedicle skin flap.

Conclusions

According to the study results, the linezolid regimen showed better outcomes than the vancomycin regimen in treating traumatic osteomyelitis of the limbs caused by MRSA infection. Specifically, linezolid showed the following advantages over vancomycin: 1) fewer adverse events: this study found a significantly lower incidence of adverse events in the linezolid group compared to the vancomycin group (5.88% vs. 17.65%); 2) shorter duration of antibiotic administration: the linezolid group had a shorter period of antibiotic use than the vancomycin group; 3) shorter hospital stays: patients in the linezolid group had a shorter length of hospital stay than in the vancomycin group. On the other hand, vancomycin has several advantages over other antibiotics in the treatment of MRSA infections, including broad-spectrum activity, also against a wide range of Gram-positive bacteria, including MRSA, high potency and a high concentration in the bone tissue, making it an effective treatment for osteomyelitis. Moreover, vancomycin has been widely used for decades and has a well-established safety profile and dosing guidelines.

Recommendation

Based on the study results described above, the linezolid regimen is a preferable treatment option for traumatic osteomyelitis of the limbs caused by MRSA

infection compared to the vancomycin regimen. The study found that the linezolid regimen had fewer adverse events, a shorter duration of antibiotic administration, and a shorter length of hospital stay than the vancomycin regimen. These findings suggest that linezolid may provide better outcomes for patients with this condition. However, it is important to note that both treatment regimens achieved satisfactory outcomes, and further investigations are needed to confirm the superiority of linezolid over vancomycin in treating traumatic osteomyelitis of the limbs caused by MRSA infection. Therefore, it may be recommended that linezolid be considered a first-line therapy for patients with this condition. At the same time, vancomycin could be reserved for cases where linezolid is contraindicated or ineffective. The ultimate decision regarding antibiotic therapy should be based on the individual patient's clinical condition and the treatment provider's recommendations.

Availability of data and material

The data will be provided in contact with the corresponding author.

Ethical statement

The Animal Ethical Review Board of Tongde Hospital of Zhejiang Province and Department of Orthopedics, Jinhua People's Hospital (No approval number). The human protocols were approved by the Human Ethical Committee Board of the above-mentioned hospital (No approval number).

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Author contributions

RZ and KH built the concept and designed the study; RZ, KH, QG, HR YL, and JW along planned the experiments and performed them as a whole team. All the authors contributed equally to writing the manuscript. All data were generated in-house and no paper mill was used.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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