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ORIGINAL RESEARCH

Efficacy and Safety of Contezolid as Salvage Treatment for Gram-Positive Bacterial Infections: A Retrospective Multicenter Study

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Objective: The primary objective of this study was to evaluate the efficacy and safety of contezolid from vancomycin or linezolid in cases of Gram-positive bacterial infections with insufficient clinical efficacy or adverse reactions.

Methods: This was a retrospective, multicenter study. Patients were eligible for inclusion if they were treated with vancomycin or linezolid for a diagnosis of Gram-positive bacterial infection and were switched to least 3 doses of contezolid due to poor efficacy or adverse effects. Relevant clinical details were collected by medical record review.

Results: A total of 191 patients from 34 hospitals in China were included. Based on clinical efficacy and microbiological clearance rate, the overall response rate of contezolid is 96.86%. Among patients switched to contezolid due to adverse reactions with linezolid or vancomycin, clinical improvement was observed in 121/131 (92.37%). Eight new adverse events occurred, six of which were related to contezolid (3.14%).

Conclusion: In this observational study, switching from vancomycin or linezolid to contezolid in cases of inadequate clinical efficacy or adverse reactions was associated with favorable clinical outcomes and demonstrated promising effectiveness in a real-world setting. Causality cannot be inferred from these data. Contezolid may represent a therapeutic option for patients intolerant to or failing initial therapy, though prospective controlled studies are needed to confirm these findings.

Keywords: contezolid, linezolid, vancomycin, gram-positive bacterial infections

Background

For infections caused by drug-resistant Gram-positive bacteria such as Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Methicillin-Resistant Coagulase-Negative *Staphylococci* (MRCoNS), the available antibiotics are limited, primarily including glycopeptides, oxazolidinones, and lipopeptides. Vancomycin, the most widely used glycopeptide antibiotic in clinical practice, is associated with ototoxicity and nephrotoxicity. Prolonged administration of linezolid may lead to serious adverse effects that necessitate careful monitoring, such as myelosuppression, peripheral neuropathy, and gastrointestinal reactions. For certain specialized infections, such as complicated *Staphylococcus aureus* bloodstream infections, osteomyelitis, and diabetic foot infections, treatment is challenging and prolonged. Due to factors like poor clinical outcomes, intravenous drug intolerance, and adverse drug reactions, it is often necessary to adjust the anti-infection regimen.

Contezolid, a new oxazolidinone antibacterial agent independently developed in China, was officially approved by the National Medical Products Administration of China on 1 June 2021, and it has not yet been marketed in other countries. As a new-generation oxazolidinone, contezolid adopts a distinctive non-coplanar conformation created by three fluorine atoms installed on the amine-bearing B-ring. Contezolid's modified structure demonstrates markedly lower risks of bone marrow suppression and monoamine oxidase (MAO)-related complications than prototype compounds.[1] In vitro studies have demonstrated that the antibacterial activity of contezolid is similar to that of linezolid.[2,3] Clinical trials demonstrated that contezolid is non-inferior to linezolid, with better safety in terms of haematological abnormalities.[4] Therefore,

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contezolid is a new option for the treatment of drug-resistant Gram-positive bacterial infections. The primary indication of contezolid is skin and soft tissue infection, with a typical treatment duration not exceeding 2 weeks. However, some patients may require longer durations of treatment with contezolid. The purpose of the current study was to evaluate the efficacy and safety of contezolid in patients with Gram-positive bacterial infections who were intolerant of or clinically failing treatment with vancomycin or linezolid. This study aimed to provide further evidence for the sequential oral treatment of Gram-positive bacterial infections.

Methods

Study Design

This was a multicenter, retrospective study involving patients diagnosed with Gram-positive bacterial infections who were initially treated with vancomycin or linezolid and switched by their treating clinicians to contezolid due to poor efficacy or adverse reactions. Patients who received at least three doses (≥36 hours of therapy) of contezolid were included; patients receiving concomitant antibiotics with activity against Gram-positive pathogens during contezolid therapy were excluded. During the routine treatment process, the included patients underwent at least one clinical follow-up and had laboratory tests performed.

Efficacy

The study considered two forms of efficacy: clinical and microbiological. For clinical efficacy, clinicians categorized the treatment outcomes into clinical cure, improvement, failure, or indeterminate outcomes. The primary microbiological outcome was the bacterial eradication rate. Microbiological outcomes were categorized as eradication, presumed eradication, replacement, or relapse. "Microbiological success" was defined as either eradication or presumed eradication. Presumed eradication was defined as clinical resolution of infection signs and symptoms without microbiological documentation of pathogen clearance. Clinical cure or improvement and microbiological success are ultimately defined as overall response.

Safety

All patients who had received three or more doses of contezolid were included in the safety assessment. The study identified adverse clinical events through medical history inquiries, physical examinations, liver and kidney function tests, and blood routine tests. The adverse reactions of the original drug, the outcomes following the switch to contezolid, and the occurrence of new adverse events were analyzed. Main evaluation items included rash, gastrointestinal symptoms such as nausea and vomiting, headache, dizziness, peripheral neuropathy, hematological effects, liver and kidney function impairment, among others.

Results

Patient Characteristics

A total of 206 cases from 34 sites in 10 provinces and cities (Beijing, Chongqing, Anhui, Hebei, Henan, Hubei, Jiangsu, Jiangxi, Shandong, Zhejiang) were collected. Of these, 15 were excluded due to inconsistence with the protocol, leaving 191 patients incorporated into data statistics. These patients were admitted from various clinical departments, predominantly including Hematology, Infectious Diseases, and Respiratory Medicine units. The majority of patients were male, totaling 118 cases, which accounted for 61.78%. Patients ranged in age from 15 to 94 years with a mean age of 54.83 years. Of these, 57 patients, or 29.84%, were aged 65y or above.

Infection Characteristics

The primary clinical diagnosis was skin and soft tissue infections (67 patients, 35.08%), followed by pneumonia (62 patients, 32.46%), bloodstream infections (20 patients, 10.47%) including 12 cases of complicated bloodstream infections (4 patients of infectious endocarditis), bone and joint infections (19 patients, 9.95%), and 10 patients (5.24%) with infections involving two or more sites. Other diagnoses included abdominal infections (5 patients, 2.62%), and 8 cases of

other infections such as implant-related infections, post-aortic dissection surgery infections, upper respiratory tract infections, or infections with a not specified site. Among the 191 patients, 159 had specimens sent for etiological culture, yielding 114 positive cultures with 118 bacteria strains. Of these, 90 strains were *Staphylococci*, including 73 strains of *Staphylococcus aureus* (*S. aureus*); 55 of these were identified as MRSA. Methicillin resistance was not determined in 1 strain of *S. aureus*.

Additionally, there were 17 strains of other coagulase-negative *staphylococci*, with 4 identified as MRCoNS and 9 as MSCoNS; methicillin resistance was not assessed in 4 strains. Furthermore, 18 strains of *Enterococcus* and 10 strains of other Gram-positive bacteria, such as *Streptococcus*, were identified.

Treatment duration with contezolid ranged from 3 to 129 days, with a median of 15 days. A total of 74 patients were treated for 15 to 28 days; 23 patients were treated for more than 4 weeks. Within this group, 13 patients were treated for more than 6 weeks, and 4 patients were treated for more than 12 weeks, including 2 patients of bone and joint infection (87 days and 104 days), 1 patient of muscle abscess (classified as skin and soft tissue infection, 117 days) and 1 patient of infective endocarditis (IE) (129 days).

Among the 191 patients, the initial antibiotic treatment prior to contezolid included 97 (50.79%) who were treated with only linezolid, 62 (32.46%) with only vancomycin, and 32 (16.75%) with both linezolid and vancomycin. A total of 55 patients (28.80%) switched medications due to poor clinical efficacy, 76 (39.79%) due to adverse drug reactions, and 55 (28.80%) for both reasons. Additionally, 5 patients switched to contezolid due to the lack of an oral vancomycin formulation with effective systemic therapy, concerns about renal impairment, and the presence of skin and soft tissue infections.

A total of 131 patients switched to contezolid due to adverse drug reactions; 82 experienced a single adverse reaction and 49 experienced at least two adverse reactions. The most common adverse reaction was myelosuppression, manifesting as leukopenia, thrombocytopenia, or anemia in 101 patients (77.10% of all cases with adverse reactions). The reasons for switching from initial vancomycin or linezolid treatment and the distribution of specific adverse reactions are detailed in Table 1.

Clinical Efficacy Evaluation

Of the 191 patients, 105 patients achieved clinical cure and 86 showed improvement in clinical symptoms. In the bacteriological efficacy results analysis, pathogen eradication or presumed eradication was achieved in 185 patients. The composite response rate is 96.86%. Six patients experienced composite response failure: the pathogen was not eradicated in 3 patients, there was a replacement of the pathogen in 2 patients, and relapse was judged in one patient. Among the 3 patients whose pathogens were not eradicated, one had MRSA pneumonia and was treated with contezolid for 9 days, one had a soft tissue infection in the ala nasi and was treated for 5 days, and the third patient with lymphoma and an underlying gastrointestinal infection was treated for 13 days. There was no etiological evidence for the latter two cases. One patient with a thoracic vertebrae *S. aureus* infection experienced pathogen relapse after 41 days of contezolid treatment.

Table 1 Distribution of Reasons for Switching to Contezolid in 191 Patients, Adverse Reactions from Initial Medications, and Details of Adverse Reactions

Reasons for Drug Switching and Adverse Reactions of Different Drugs		**All Patients N=191**	**Vancomycin n=62**	**Linezolid n=97**	**Vancomycin/ Linezolid n=32**
Reasons for drug switching	Poor clinical efficacy	55 (28.80%)	25 (40.32%)	20 (20.62%)	10 (31.25%)
	Adverse reactions	76 (39.79%)	13 (20.97%)	56 (57.73%)	7 (21.88%)
	Poor clinical efficacy + adverse reactions	55 (28.80%)	19 (30.65%)	21 (21.65%)	15 (46.88%)
	Others	5 (2.62%)	5 (8.06%)	0	0

(*Continued*)

Table 1 (Continued).

Reasons for Drug Switching and Adverse Reactions of Different Drugs		All Patients N=191	Vancomycin n=62	Linezolid n=97	Vancomycin/ Linezolid n=32
Adverse reactions	Rash	2	1	0	1
	Gastrointestinal symptoms: nausea and vomiting, etc.	17	1	13	3
	Headache and dizziness	7	0	5	2
	Leukopenia	9	2	6	1
	Anemia	33	2	21	10
	Thrombocytopenia	96	13	63	20
	Renal impairment	23	12	2	9
	Liver function abnormality	11	3	3	5
	Lactic acid increase	1	0	0	1
	Peripheral neuropathy symptoms including tingling in the fingertips	5	0	2	3
	Hearing loss	1	1	0	0

Safety Evaluation

After switching from vancomycin or linezolid to contezolid, clinical improvements in the adverse reactions were seen in 121/131 (92.37%). Reactions such as rash, headache, dizziness, renal impairment, liver function abnormality, lactic acid increase, peripheral neuropathy symptoms- including tingling in the fingertips-and hearing loss either returned to normal or improved, with an improvement rate of 100%. The improvement rate for the original adverse reactions of myelosuppression was over 85%, as detailed in Table 2. Of the initial 97 patients treated with linezolid who experienced adverse

Table 2 Adverse Reaction Outcomes After Switching to Contezolid from Original Drugs

Adverse Reactions	Number of Patients	Outcome of Adverse Reactions After Medication Change			
		Returned to Normal	Improved	No Improvement	Deterioration
Rash	2	2 (100.00%)	0	0	0
Gastrointestinal symptoms: nausea and vomiting, etc.	17	11 (64.71%)	6 (35.29%)	0	0
Headache and dizziness	7	5 (71.43%)	2 (28.57%)	0	0
Leukopenia	9	4 (44.44%)	4 (44.44%)	1 (11.11%)	0
Anemia	33	19 (57.58)	10 (30.30%)	3 (9.09%)	1 (3.30%)
Thrombocytopenia	96	40 (41.67%)	50 (52.08%)	4 (4.17%)	2 (2.08%)
Renal impairment	23	13 (56.52%)	10 (43.48%)	0	0
Liver function abnormality	11	6 (54.55%)	5 (45.45%)	0	0
Lactic acid increase	1	1 (100.00%)	0	0	0

(*Continued*)

Table 2 (Continued).

Adverse Reactions	Number of Patients	Outcome of Adverse Reactions After Medication Change			
		Returned to Normal	Improved	No Improvement	Deterioration
Peripheral neuropathy symptoms including tingling in the fingertips	5	3 (60.00%)	2 (40.00%)	0	0
Hearing loss	1	1 (100.00%)	0	0	0

reactions, primarily myelosuppression, over 80% either returned to normal or improved after switching to contezolid, as detailed in Table 3. Among the 62 patients initially treated with vancomycin, 12 experienced renal impairment, and one had hearing loss; after switching to contezolid, renal function returned to normal in 5 patients and improved in 7 patients, while the patient with hearing loss recovered. Among the 32 patients initially treated with both vancomycin and linezolid, 20 experienced thrombocytopenia; after switching to contezolid, the platelet count returned to normal in 8 patients and improved in 10, with no improvement in 2. Renal impairment was observed in 9 patients; after switching to contezolid, 7 patients returned to normal and 2 patients experienced improved.

After treatment with contezolid, 95.81% of patients did not experience any new adverse events. However, 4.19% of patients (8 patients) developed new adverse events, primarily including a decrease in blood cell counts in 5 patients, an increase in lactic acid in one case, and liver function abnormality in 2 patients. Of these, 3.14% (6 patients) were determined to be related to contezolid. One case of liver function abnormality was considered related to other medications, and one case of a decrease in platelet count was considered associated with the primary disease. See Table 4 for details.

This study collected data of 20 patients with bloodstream infections, comprising 8 patients of uncomplicated bloodstream infections and 12 patients of complicated bloodstream infections, among which 4 had IE The pathogens of bloodstream infection included *S. aureus* in 8 patients (7 were MRSA and 1 was MSSA), other *staphylococci* in 6

Table 3 Myelosuppression Outcomes After Switching from Linezolid to Contezolid

Adverse Reactions	Number of Patients	Outcome of Adverse Reactions			
		Returned to Normal	Improved	No Improvement	Deterioration
Leukopenia	6	3 (50.00%)	3 (50.00%)	0	0
Anemia	21	11 (52.38%)	6 (28.57%)	3 (14.29%)	1 (4.76%)
Thrombocytopenia	63	32 (50.79%)	28 (44.44%)	2 (3.17%)	1 (1.59%)

Table 4 New Adverse Events Following Salvage Treatment with Contezolid

New Adverse Events	Number of Patients	Percentage	Duration	Relationship with Contezolid
Liver function abnormality	2	1.04%	6 days and 4 days	1
Anemia	1	0.52%	7 days	Related
Lactic acid increase	1	0.52%	10 days	Related
Leukopenia	1	0.52%	9 days	Related
Thrombocytopenia	2	1.04%	3 days and 5 days	1
Thrombocytopenia + leukopenia	1	0.52%	11 days	Related
Total	8	4.19%	/	

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patients, and *Enterococcus* in 5 patients, with one patient's pathogen not specified. Linezolid was used as monotherapy in 8 patients, vancomycin in 6 patients, and a combination of both in another 6 patients for the treatment of these infections. After switching to contezolid, treatment duration varied from 3 days to 129 days, with a median of 15.5 days. The primary indications for therapeutic modification comprised insufficient clinical response (n=3), adverse drug reactions (n=11), and concurrent therapeutic failure with toxicity (n=6). Post-adjustment evaluations demonstrated complete clinical resolution in 9 patients and sustained improvement in 11 cases, while microbiological assessments revealed successful pathogen eradication/presumptive eradication in 19 patients alongside one incident of secondary pathogen emergence. The composite efficacy endpoint was achieved in 95% of cases. Of the 17 patients who initially had adverse reactions, 15 either returned to normal or experienced improvement after switching to contezolid. One patient's anemia worsened, and another's thrombocytopenia deteriorated. Additionally, one patient developed new-onset thrombocytopenia 3 days post-switch, which was attributed to contezolid.

Discussion

Multidrug-resistant Gram-positive bacterial infections present a significant challenge in clinical treatment and a huge threat to public health. Commonly used antibiotics in clinical practice, such as vancomycin, linezolid and daptomycin, often present various degrees of safety problems and clinical efficacy concerns. Contezolid was approved in China in 2021 for treating drug-resistant Gram-positive bacterial infections. Since its commercialization, skin and soft tissue infections have been the primary indications for contezolid, with limited clinical data available for its use in other types of infections. We collected real-world data of patients with Gram-positive bacterial infections who switched to contezolid from initial treatment of linezolid or vancomycin due to poor efficacy, adverse reactions, or intolerance. We then retrospectively analyzed the clinical efficacy and safety of contezolid in these patients.

The clinical data we collected showed that the Gram-positive bacterial infection cases came from multiple departments in the hospital, with a wide age distribution and approximately one third involving elderly patients. The infections varied, including skin and soft tissue infections, pneumonia, bloodstream infections, and bone and joint infections, with many cases of multi-site infections. This is consistent with the common types of Gram-positive bacterial infections in clinical practice, indicating that contezolid is used widely for various types of infections, including those in geriatric patients. Among the documented pathogens, *S. aureus*, particularly MRSA, accounted for the vast majority. Myelosuppression was the most significant adverse event, primarily presenting as thrombocytopenia, consistent with previously published reports.[5,6] In this study, myelosuppression was the most common adverse reaction and was also observed in patients initially treated with vancomycin. The underlying diseases might be part of the reason for this, as indicated by the patients' sources.

Among the 191 patients, 89 were from the department of hematology, providing more evidence for the use of contezolid in patients with hematological diseases. The overall response rate was 96.86% in 191 patients after switching to contezolid. In several in vitro drug susceptibility studies, contezolid demonstrated potent antimicrobial activity against clinically significant aerobic Gram-positive bacteria, including *Staphylococcus aureus, Streptococcus*, and *Enterococcus*. It showed slightly higher or comparable antimicrobial activity against *Staphylococcus* compared to linezolid.[2,3] A Phase III multicenter, randomized, double-blind trial to evaluate the efficacy and safety of oral contezolid versus linezolid in adults with complicated skin and soft tissue infections has been completed in China. The clinical cure rates for both contezolid and linezolid in the Full Analysis Set (FAS) population were over 90%, with no significant difference noted between the two groups. The pathogen eradication rate was 83.6% in the contezolid group and 87.0% in the linezolid group. In the microbiologically evaluable population, the bacterial eradication rate was 90% in the contezolid group and 88.5% in the linezolid group, with MRSA clearance rates of 92.9% and 92.3%, respectively ($P>0.05$).[4] The literature reports that in a case of community-acquired pneumonia caused by methicillin-sensitive S. aureus, switching to contezolid after adverse reactions to linezolid resulted in clinical cure and improved thrombocytopenia.[7] Additionally, there is a report of successful treatment with contezolid replacing vancomycin in a patient with refractory IE caused by MRSA, who had chronic renal failure and failed treatment with vancomycin combined with daptomycin and cefoperazone-sulbactam.[8]

In this study, a high incidence of adverse reactions was observed after treatment with vancomycin or linezolid, with a total of 131 cases of adverse drug reactions reported. Consistent with previous clinical experiences, the main adverse reaction associated with linezolid was myelosuppression, while renal impairment was predominantly associated with

vancomycin. After switching to contezolid, most adverse reactions from the original drugs improved or resolved, with a low incidence of new adverse reactions, mainly hematological effects. Historically, safety concerns with oxazolidinones have been the primary obstacle to their broader clinical application.

The innovative structure of contezolid has resulted in reduced myelosuppression as well as drug-drug interactions.[9,10] In a phase III clinical trial in China, among patients treated with contezolid tablets (800 mg every 12 hours N = 354), the incidence of reticulocytopenia, leucopenia and neutropenia was 0.3% (1/354) with no thrombocytopenia observed (0/354). In contrast, the incidences in linezolid-treated patients (600 mg q12h, N = 351) were 1.4% (5/351) for reticulocytopenia, 3.4% (12/351) for leucopenia, 1.7% (6/351) for neutropenia, and 2.3% (8/351) for thrombocytopenia, indicating a higher incidence of hematological abnormalities (greater than 1%) compared to contezolid.[4] In case reports of patients with special infections requiring long-term antibacterial therapy, switching to contezolid from linezolid due to adverse reactions led to various degrees of improvement. For instance, a 101-year-old patient treated with linezolid for vancomycin-resistant *Enterococcus* pneumonia developed thrombocytopenia, switching to contezolid for 4 months achieved excellent clinical efficacy and stable platelet levels.[11] A patient with tuberculous meningitis intolerant to linezolid due to peripheral neuropathy and myelosuppression saw improvements in these adverse reactions after switching to contezolid for about 8 months.[12]

Clinicians are also focused on the neurotoxicity caused by the long-term use of traditional oxazolidinones. In this study, a total of 5 patients with a history of linezolid use experienced symptoms of peripheral neuritis, such as tingling in the fingertips. After switching to contezolid, 3 patients recovered fully, and 2 showed improvement, attributed to the unique structural changes in contezolid. Other authors have also reported cases where peripheral neuropathy developed after linezolid use and improved upon switching to contezolid.[12] Contezolid is primarily metabolized in the liver. A single-center, open-label, parallel-group study of the pharmacokinetic parameters of contezolid and its metabolites showed that no dose adjustment was needed for patients with moderate hepatic impairment.[13] In completed clinical trials, the incidence of alanine aminotransferase increase was 9.6% in the contezolid group and 10.5% in the linezolid group, with no significant difference between the two.[4] In our study, 2 new cases of liver function abnormalities occurred after contezolid use, with one of judged to be related to contezolid. The proportion is lower than that observed in previous studies.

This study collected data from 20 patients with bloodstream infections. Although this sample size is limited, after switching from vancomycin or linezolid to contezolid, we observed favorable outcomes and significant amelioration of adverse reactions in this exploratory subgroup analysis. Traditionally, managing Gram-positive bacterial bloodstream infections, especially *Staphylococcus aureus*, required long-term intravenous antibacterial therapy. However, recent clinical studies have indicated that for complex bloodstream infections, including IE switching to oral antibacterial agents when clinically stable can achieve comparable efficacy with fewer adverse reactions.[14–16] A recent study on *S. aureus* bloodstream infections demonstrated that oral treatment after 5–7 days of intravenous therapy was not inferior to continuous intravenous antibacterial treatment for highly selected patients with low-risk *S. aureus* bacteremia. Importantly, 93% of patients screened for study enrollment were ineligible, limiting generalizability.[17] In this study, patients intolerate to linezolid were treated with contezolid, leading to improved clinical outcomes and reduction in adverse reactions.

Study Limitations and Interpretation

Several important limitations must be acknowledged when interpreting our findings. First, this was a retrospective observational study without a control group, and patients were switched mid-treatment due to clinical failure or adverse events. The duration of prior vancomycin or linezolid therapy was not standardized and varied among patients. These factors create potential for immortal time bias and confounding by indication; therefore, causality cannot be inferred from these data. The observed favorable outcomes may reflect patient selection or temporal trends rather than direct treatment effects.

Second, some patients received prolonged contezolid therapy exceeding 12 weeks (up to 129 days), which far exceeds the approved indication for skin and soft tissue infections (typically ≤14 days). These were exceptional salvage cases where treatment decisions were individualized based on clinical circumstances, and safety interpretations for such extended durations should be cautious.

Third, only 20 patients had bloodstream infections (including 4 with infective endocarditis), and findings in this subgroup should be considered exploratory. We have avoided broad generalizations regarding bloodstream infections and do not advocate promotion of contezolid for this indication based on limited data. Rather, these observations provide hypothesis-generating evidence warranting further investigation in prospective studies.

Conclusions

Clinical data of patients diagnosed with Gram-positive bacterial infections, initially treated with linezolid or vancomycin and then switched to contezolid due to poor clinical response or adverse reactions, were collected from multiple research centers in China. In this observational study, switching to contezolid was associated with favorable clinical outcomes and demonstrated promising effectiveness in a real-world setting. For patients requiring long-term treatment for specific infections including complicated bloodstream infections or bone and joint infections, the sequential long-term oral use of contezolid showed acceptable safety profiles in these salvage cases. This study provides real-world evidence supporting further investigation of contezolid in complex Gram-positive infections, particularly in patients intolerant to or failing initial therapy with vancomycin or linezolid. However, causality cannot be inferred, and our findings should be confirmed in prospective, randomized controlled trials.

Ethics

This study was approved by the local ethics committee of Sir Run Run Shaw Hospital with a waiver of informed consent (Acceptance Number: 2023-547-02, Approval No. 20230335). As patient consent to review their medical records was waived by the Sir Run Run Shaw Hospital Ethics Committee (Acceptance Number: 2023-547-02, Approval No. 20230335), the study was conducted in accordance with the Declaration of Helsinki. All patient data were de-identified before analysis, and confidentiality was strictly maintained throughout the study.

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Disclosure

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