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Impact of canagliflozin combined with metformin therapy on reducing cardiovascular risk in type 2 diabetes patients

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Abstract

Purpose To investigate the impact and safety of canagliflozin combined with metformin on reducing cardiovascular risk in patients with type 2 diabetes mellitus (T2DM).

Methods A total of 258 patients with T2DM admitted to our hospital from March 2021 to March 2022 were selected and divided into a control group and an observation group using a random number table. The control group received metformin combined with a placebo, while the observation group received canagliflozin combined with metformin therapy. All patients received drug treatment for 52 weeks. The primary endpoint of the study was major adverse cardiovascular events (MACE), including myocardial infarction, ischemic stroke, and cardiovascular death. Other study parameters included safety after medication, severe adverse reactions, levels of glycated hemoglobin (HbA1c), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and estimated glomerular filtration rate (eGFR).

Results After treatment, HbA1c, FPG, BMI, SBP, and DBP in both groups were lower than before treatment, and those indicators in the observation group were lower than those in the control group ($P < 0.05$). The eGFR, HDL-C, and LDL-C levels in both groups were higher than before treatment, with the eGFR in the observation group being higher than that in the control group ($P < 0.05$). The incidence of MACE (myocardial infarction, ischemic stroke, cardiovascular death) in the observation group (5.17%) was significantly lower than that in the control group (12.93%) (HR: 2.16, 95%CI:2.04–2.59, $P < 0.05$). There were no significant differences in the rates of hospitalization for heart failure (3.45% vs. 1.72%), renal adverse events (4.31% vs. 3.45%), non-cardiovascular death (1.72% vs. 0.86%), all-cause mortality (2.59% vs. 0.86%), and severe adverse reactions (12.07% vs. 9.48%) between the two groups ($P > 0.05$).

Conclusion In patients with T2DM who received the canagliflozin combined with metformin, the mortality rate of cardiovascular causes was significantly reduced. Compared with metformin monotherapy, there is no significant difference in the incidence of serious adverse reactions, and the safety of medication is better, while the blood sugar, blood pressure, and weight of T2DM patients are more actively improved. For T2DM patients with high risk of

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cardiovascular disease, the combination of canagliflozin and metformin could have a higher benefit in cardiovascular outcomes.

Keywords Type 2 diabetes mellitus, Canagliflozin, Metformin, Cardiovascular, Safety

Introduction

Patients with type 2 diabetes mellitus (T2DM) have a disorder of glucose and lipid metabolism and symptoms such as hyperglycemia, and hyperlipidemia, increasing the risk of atherosclerotic cardiovascular disease. Canagliflozin is a novel antidiabetic medication belonging to the class of sodium-glucose co-transporter 2 (SGLT2) inhibitors. Its mechanism involves inhibiting the reabsorption of glucose and sodium in the proximal tubules of the kidneys, which has been well-established in effectively lowering high blood glucose levels in T2DM patients [1]. Additionally, observations have shown that canagliflozin exerts positive effects on non-glycemic variables such as weight and blood pressure reduction, which can provide additional health benefits in lowering cardiovascular risk [2].

The 2020 American Diabetes Association (ADA) guidelines [3] and the 2019 European Diabetes Research Association (EDRA) guidelines [4] both recommend the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors with cardiovascular benefits for patients with type 2 diabetes mellitus (T2DM) who have concomitant atherosclerotic cardiovascular disease, multiple atherosclerotic cardiovascular disease risk factors, or diabetic kidney disease to reduce the risk of cardiovascular events and hospitalization for heart failure. Additionally, the insulin-independent nature of SGLT2 inhibitors supports their use throughout the natural progression of T2DM in patients [5]. A meta-analysis study on SGLT2 inhibitors has pointed out that after summarizing the results of recent large-scale randomized clinical trials, it was found that SGLT2 inhibitors not only had positive cardioprotective effects, but also benefited people beyond T2DM patients [6].

Current research has primarily focused on the effects of metformin and canagliflozin monotherapy on glycemic control and cardiovascular risk in patients [7]. However, as the duration of the disease progresses, metformin monotherapy may not provide sufficient glycemic control, necessitating other antihyperglycemic agents to maintain blood glucose levels. Therefore, it is often used in combination with other antihyperglycemic agents. Among the potential candidate drugs to supplement the efficacy of metformin, many antihyperglycemic agents may lead to hypoglycemia or weight gain, which could exacerbate insulin resistance[8]. Additionally, some safety issues associated with the use of canagliflozin in combination with metformin in patients with type 2 diabetes mellitus (T2DM), such as urinary tract infections and osmotic diuresis, have not been elucidated. Therefore, this study investigates the impact and safety of canagliflozin combined with metformin on reducing cardiovascular risk in T2DM patients, aiming to provide clinical reference for medication.

Materials and methods

Study design and patients selection

The number of samples was estimated by Gpower software in advance. Effect size $w=0.3$ (median value recommended by the system), $\alpha=0.05$, power$(1-\beta)=0.8$, P as the two-sided test and control group/observation group$=1$ were set, and the total number of samples≥ 88 was calculated (Supplementary Fig. 1).

A total of 258 patients diagnosed with T2DM and admitted to our hospital from March 2021 to March 2022 were selected for this study. The control group received metformin combined with a placebo treatment, while the observation group received canagliflozin combined with metformin treatment. This study employed a double-blind, randomized control, parallel-group design, including a 52-week double-blind treatment period. During the treatment period, patients were followed up every 3 months. The study was approved by The Ningbo University Affiliated People's Hospital of Ningbo University [2021-(ky)-015], and all patients signed informed consent forms before participating in the study.

Finally, the number of samples included was 232 cases. The statistical efficacy of major adverse cardiovascular events (MACE) difference between the control group and observation group was analyzed by Gpower software, and the calculated effect size $w=0.2312$, the setting parameter $\alpha=0.05$, and the total number of samples was 232 cases, and the calculated statistical efficacy was 0.9410, which was greater than 0.8, with statistical significance (Supplementary Figs. 2–3).

Inclusion and exclusion criteria

Inclusion criteria: (1) Confirmed diagnosis of T2DM based on the relevant diagnostic criteria of the World Health Organization (WHO) [9]; (2) Age$\geq$40 years old [10], according to the ACC/AHA guidelines for primary prevention of cardiovascular diseases, such patients have a higher risk of cardiovascular diseases and should be accepted routine cardiovascular disease assessment; (3) Estimated glomerular filtration rate (eGFR)$\geq$60 ml/min/1.73 m^2 [11], exclude the influence of renal dysfunction on the study; (4) Presence of at least one of the following cardiovascular high-risk factors: ①

Atherosclerotic cardiovascular disease, such as coronary artery disease, peripheral arterial disease, heart failure, or cerebrovascular disease; ② Risk factors for atherosclerotic cardiovascular disease, such as age≥55 years for males and ≥60 years for females, with accompanying hypertension, dyslipidemia, smoking, etc.; (5) Willing to cooperate with the study and having complete follow-up data.

Exclusion criteria: (1) Patients with type 1 diabetes mellitus, primary renal glucosuria, or secondary diabetes mellitus; (2) Occurrence of acute cardiovascular events (acute coronary syndrome, decompensated heart failure, transient ischemic attack) within 8 weeks prior to enrollment; (3) Presence of high-risk factors for mortality, such as malignant arrhythmias, cardiogenic shock, etc.; (4) Presence of other chronic diseases (such as chronic obstructive pulmonary disease, liver cirrhosis, malignant tumors, etc.); (5) History of dialysis or kidney transplantation; (6) Patients with mental illness.

Study methods

Before randomization, all patients received diet and exercise counseling, and then all patients included in the study received metformin (1500 mg/d) [12]. Canagliflozin (100 mg/d) or placebo were distributed and accepted by a computer-generated random number Tables [13, 14]. After the drugs were randomly distributed, the researchers were unaware of the HbA1c and FPG values to maintain the treatment blindness.

During the treatment period, all patients underwent outpatient or inpatient follow-up every 3 months. The follow-up included assessment of safety events (such as cardiovascular death, myocardial infarction, ischemic stroke, heart failure, hypoglycemia, diabetic ketoacidosis, urinary tract infection, liver adverse events, etc.) and assessment of compliance with the experimental treatment regimen (whether patients used medications according to the treatment regimen, whether there were any changes in treatment medications, etc.). During the interval of outpatient or ward follow-up, telephone follow-up should be conducted with the patient once a month to ask whether the patient has any symptoms of cardiovascular discomfort, including whether the patient feels chest tightness or chest pain, shortness of breath, palpitation, etc., and whether there is pain in the shoulder, neck and back and leg edema. If the patient has the above symptoms, detailed examination should be arranged in time.

In the control group, a total of 13 patients did not complete the follow-up, including 6 who withdrew from the study and 7 who were lost to follow-up. In the observation group, a total of 13 patients did not complete the follow-up, including 4 who withdrew from the study and 9 who were lost to follow-up. In the final study, 116 patients in the control group and 116 patients in the observation group.

Assessment criteria

Safety indicators after medication included: MACE, including cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. Hospitalization for heart failure, renal adverse events (eGFR continuously decreased by ≥40% and decreased to below 60 ml/min/1.73m^2, incident end-stage renal disease or renal-related death), non-cardiovascular death, and all-cause mortality.

Severe adverse reactions included hypoglycemia, diabetic ketoacidosis, urinary tract infection, liver adverse events, gastrointestinal reactions, etc. [15]. Hypoglycemia included biochemical episodes (fingerstick or blood glucose≤3.9 mmol/L), with or without symptoms, as well as severe episodes (requiring assistance from another person or leading to seizures, loss of consciousness, or cognitive dysfunction). Adverse reactions associated with osmotic diuresis included dry mouth, polyuria, polydipsia, and cystitis. Gastrointestinal adverse reactions included diarrhea, nausea, and vomiting. Liver adverse events included acute liver failure or the need for liver transplantation.

Other baseline indicators included glycated hemoglobin (HbA1c), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and eGFR levels on the day before treatment initiation and at the 52nd week of treatment. BMI=body weight (kg) / [height (m)]^2; eGFR=175 × serum creatinine-1.234 × age-0.179 × sex (male=1, female=0.79).

Statistical methods

Data analysis was conducted using SPSS 26.0 software. The data of patients who failed to complete the follow-up were deleted. Categorical data were presented as frequencies, and between-group comparisons were performed using the χ^2 test. Measurement data that did not conform to a normal distribution were represented by the M(QR). The Kruskal-Wallis test was employed to compare among groups. Continuous data following a normal distribution were presented as ($\bar{x} \pm s$), and between-group comparisons were analyzed using the t-test. Hierarchical Cox proportional hazard regression model was used to analyze the main outcome MACE. A significance level of $P<0.05$ was considered statistically significant.

Table 1 Comparison of general data between two groups of patients ($\bar{x} \pm s$, %)

Characteristic	Control group($n=116$)	Observation group($n=116$)	χ^2/t	*P*
Age(year)	58.28 ± 5.52	57.71 ± 5.69	0.773	0.440
Sex(number, %)			0.433	0.511
Male	64(55.17)	59(50.86)		
Female	52(44.83)	57(49.14)		
BMI(kg/m^2)	26.67 ± 3.07	26.63 ± 3.07	0.094	0.925
Smoking history(number, %)			0.069	0.793
Yes	56(48.28)	54(46.55)		
No	60(51.72)	62(53.45)		
Atherosclerotic cardiovascular disease(%)			0.548	0.908
Coronary artery disease	40(34.48)	41(35.34)		
Peripheral arterial disease	12(10.34)	14(12.07)		
Cardiac failure	10(8.62)	8(6.90)		
Cerebrovascular disease	13(11.21)	11(9.48)		
T2DM duration(year)	8.63 ± 2.14	8.93 ± 2.20	1.060	0.290
HbA1c(%)	7.94 ± 0.85	8.04 ± 0.85	0.854	0.394
FPG(mmol/L)	9.16 ± 1.45	9.07 ± 1.47	0.395	0.693
eGFR(ml/min/1.73 m^2)	95.85 ± 15.29	94.49 ± 15.46	0.673	0.502

Results

Comparison of baseline characteristics between the two groups

There were no statistically significant differences ($P>0.05$) in general demographic data such as gender, age, BMI, and smoking history between the two groups. Refer to Table 1.

Comparison of blood glucose, lipids, blood pressure, BMI, and eGFR before and after treatment in patients

Before treatment, there were no significant differences between the two groups in any of the indicators ($P>0.05$). After treatment, the levels of HbA1c, FPG, BMI, SBP, and DBP were all lower in both groups compared to before treatment, with the observation group showing lower levels than the control group ($P<0.05$). The eGFR, HDL-C, and LDL-C levels were higher in both groups after treatment compared to before treatment, with the eGFR being higher in the observation group than in the control group ($P<0.05$). However, there were no significant differences between the two groups in terms of HDL-C and LDL-C levels ($P>0.05$). Refer to Table 2.

Comparison of the incidence of MACE after treatment in patients

The incidence of MACE (including myocardial infarction, ischemic stroke, and cardiovascular death) in the

Table 2 Comparison of blood sugar, blood lipid, blood pressure, BMI and eGFR between the two groups before and after treatment

Characteristic	Time	Control group($n=116$)	Observation group($n=116$)	t	*P*
HbA1c(%)	before treatment	7.94 ± 0.85	8.04 ± 0.85	0.854	0.394
	after treatment	7.42 ± 0.75	6.85 ± 0.75	5.788	< 0.001
	change	-0.53 ± 0.10	-1.19 ± 0.10		
FPG(mmol/L)	before treatment	9.16 ± 1.45	9.07 ± 1.47	0.395	0.693
	after treatment	8.44 ± 1.20	7.25 ± 1.18	7.639	< 0.001
	change	-0.71 ± 0.18	-1.83 ± 0.18		
HDL-C(mmol/L)	before treatment	1.40 ± 0.28	1.33 ± 0.26	1.712	0.088
	after treatment	1.55 ± 0.33	1.49 ± 0.32	1.426	0.155
	change	0.15 ± 0.04	0.16 ± 0.04		
LDL-C(mmol/L)	before treatment	2.55 ± 0.77	2.51 ± 0.78	0.381	0.703
	after treatment	2.84 ± 0.66	2.90 ± 0.64	0.754	0.452
	change	0.29 ± 0.09	0.39 ± 0.09		
SBP(mmHg)	before treatment	137.09 ± 11.23	136.10 ± 10.51	0.688	0.492
	after treatment	134.16 ± 10.60	129.96 ± 9.24	3.216	0.002
	change	-2.93 ± 1.43	-6.15 ± 1.30		
DBP(mmHg)	before treatment	82.48 ± 8.58	82.83 ± 8.26	0.312	0.755
	after treatment	80.16 ± 6.70	77.99 ± 6.41	2.514	0.013
	change	-2.33 ± 1.01	-4.84 ± 0.97		
BMI(kg/m^2)	before treatment	26.67 ± 3.07	26.63 ± 3.07	0.094	0.925
	after treatment	25.70 ± 2.57	24.66 ± 2.59	3.077	0.002
	change	-1.71 ± 0.24	-1.98 ± 0.37		
eGFR(ml/min/1.73 m^2)	before treatment	95.85 ± 15.29	94.49 ± 15.46	0.673	0.502
	after treatment	99.51 ± 11.53	102.82 ± 10.42	2.289	0.023
	change	3.66 ± 1.78	8.32 ± 1.73		

Table 3 Comparison of the incidence of cardiovascular adverse events between the two groups after treatment

Characteristic (number, %)	Control group($n=116$)	Observation group($n=116$)	Hazard ratio (95% CI)	*P*
MACE	15(12.93)	6(5.17)	2.16(2.04–2.59)	0.040
cardiovascular death	1(0.86)	0(0.00)		
nonfatal myocardial infarction	6(5.17)	3(2.59)		
nonfatal stroke	8(6.90)	3(2.59)		

Table 4 Comparison of safety indexes between the two groups after medication

Characteristic (number, %)	Control group($n=116$)	Observation group($n=116$)	χ^2	*P*
heart failure	4(3.45)	2(1.72)	0.681	0.408
renal adverse events	5(4.31)	4(3.45)	0.124	0.734
non-cardiovascular death	2(1.72)	1(0.86)	0.338	0.561
all-cause death	3(2.59)	1(0.86)	1.018	0.313

Table 5 Comparison of the incidence of serious adverse reactions between the two groups

Characteristic (number, %)	Control group($n=116$)	Observation group($n=116$)	χ^2	*P*
Serious adverse reactions	14(12.07)	11(9.48)	0.404	0.525
Hypoglycemia	3(2.59)	4(3.45)	0.147	0.701
Diabetic ketoacidosis	2(1.72)	1(0.86)	0.338	0.561
Adverse reactions related to osmotic diuresis	1(0.86)	0(0.00)	1.004	0.316
Urinary tract infection	4(3.45)	5(4.31)	0.116	0.734
male	1(0.86)	2(1.72)		
female	3(2.59)	3(2.59)		
Gastrointestinal related adverse reactions	3(2.59)	1(0.86)	1.018	0.313
Adverse liver events	1(0.86)	0(0.00)	1.004	0.316

Note: Hypoglycemia includes biochemical episodes (fingerstick or blood glucose≤3.9 mmol/L), with or without symptoms, as well as severe episodes (requiring assistance from another person or leading to seizures, loss of consciousness, or cognitive dysfunction). Adverse reactions associated with osmotic diuresis include dry mouth, polyuria, polydipsia, and cystitis. Gastrointestinal adverse reactions include diarrhea, nausea, and vomiting. Liver adverse events include acute liver failure or the need for liver transplantation

observation group (5.17%) was significantly lower than that in the control group (12.93%), and the differences were statistically significant (HR: 2.16, 95%CI:2.04–2.59, $P<0.05$). Refer to Table 3.

Comparison of safety indicators after medication in patients

There were no significant differences between the two groups in terms of the incidence rates of hospitalization for heart failure, renal adverse events, non-cardiovascular death, or all-cause mortality ($P>0.05$). Refer to Table 4.

Comparison of the incidence of severe adverse reactions in patients

There were no significant differences in the overall incidence rates of severe adverse reactions such as hypoglycemia and diabetic ketoacidosis between the two groups ($P>0.05$). The severity of urinary tract infections in both groups was typically mild to moderate, and resolved after receiving local and/or oral antimicrobial treatment, without leading to study termination. The incidence of adverse reactions associated with osmotic diuresis was low. The percentage of documented hypoglycemic events was similar between the two groups, and no reports of severe hypoglycemia were observed. Refer to Table 5.

Discussion

T2DM is a progressive disease that requires antidiabetic medications to provide long-term glycemic control and additional benefits, such as weight reduction and favorable effects on blood pressure and lipid profiles [16, 17]. This study demonstrated that both groups of patients showed significant improvements in blood glucose, blood pressure, and lipid profiles after antidiabetic treatment. However, patients receiving combination therapy with canagliflozin and metformin had advantages in terms of glucose control, blood pressure reduction, and weight loss. Canagliflozin induces urinary glucose excretion by inhibiting renal glucose reabsorption, providing an insulin-independent mechanism for lowering blood glucose and improving glycemic control. The increased urinary glucose excretion also leads to additional calorie loss, further aiding in weight reduction [18, 19]. Many traditional therapies do not improve the weight of patients with T2DM obviously, but canagliflozin is useful for losing weight in clinic. A 26-week study by Stenlöf et al. [20] has evaluated the efficacy of canagliflozin monotherapy compared to placebo in poorly controlled T2DM subjects with diet and exercise control, showing better efficacy and good patient tolerance. The mechanism by which canagliflozin leads to an increase in LDL-C is unclear but may be related to metabolic changes associated with urinary glucose excretion. Improvement in HDL-C may be related to improved blood glucose control and weight loss associated with canagliflozin.

Research indicates that high blood glucose causes definite damage to the heart and blood vessels, primarily due to the generation of advanced glycation end products (AGEs) [21]. Accumulation of AGEs can trigger severe

oxidative stress and inflammatory reactions, which synergistically damage the vascular endothelium and induce apoptosis of myocardial cells. Damaged blood vessels and myocardial cells further stimulate inflammatory reactions and oxidative stress, forming a vicious cycle [22, 23]. The CREDENCE trial found that canagliflozin can reduce the risk of major adverse cardiovascular events (HR=0.80) in patients with T2DM, and its effects on comprehensive prognosis covering cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction are consistent in T2DM patients (HR=0.68) without cardiovascular disease and those with a history of cardiovascular events (HR=0.85) [24]. In this study, the incidence of major adverse cardiovascular events (myocardial infarction, ischemic stroke, and cardiovascular death) in the observation group was significantly lower than that in the control group. While metformin monotherapy can control blood glucose, it cannot reduce the risk of cardiovascular endpoint events. Combining canagliflozin with metformin treatment still provides beneficial effects in reducing the incidence of cardiovascular events.

The results of this study are consistent with those of Wiviott et al. [25], showing no significant difference in the rates of heart failure hospitalization, all-cause mortality, non-cardiovascular mortality, and renal adverse events between the two groups of patients. Canagliflozin combined with metformin treatment in patients with type 2 diabetes mellitus (T2DM) reduces cardiovascular deaths without increasing all-cause mortality rates, indicating that in T2DM patients at high risk of cardiovascular disease, canagliflozin combined with metformin treatment can prevent serious cardiovascular events. In the patients who received the treatment of canagliflozin combined with metformin, a variety of risk factors related to cardiovascular diseases have been positively changed, which is in line with the requirements of the current guidelines for diagnosis and treatment of T2DM, such as taking patients as the center, fully considering related complications and other factors, and formulating a safe and appropriate hypoglycemic plan [20].

The induction of glycosuria by SGLT-2 inhibition has raised concerns about the potential for hypoglycemia, urinary tract infections, and genital infections [26–28]. Close attention should be paid to adverse events related to the genitourinary system when using canagliflozin in patients with concomitant genitourinary tract infections [29]. However, in this study, there was no significant difference in the overall incidence of severe adverse reactions such as hypoglycemia and diabetic ketoacidosis between the two groups of patients, and no new medication safety events were observed. The incidence of hypoglycemia was similar between the two groups, with no reports of severe hypoglycemic events. While the incidence of urinary tract infections was slightly higher in the observation group compared to the control group, the difference between the groups was not statistically significant, and no clear relationship with combination therapy was observed. Additionally, the urinary tract infection cases in patients were not severe, improved after antimicrobial treatment, and did not lead to discontinuation of medication.

The limitations of this study are the small sample size and the low incidence of major end events. Therefore, a large-scale multicenter prospective randomized controlled trial is needed to verify the effect of canagliflozin combined with metformin on reducing the risk of cardiovascular diseases in patients with T2DM and increase the strength of evidence. Although the follow-up time of the study is longer than the usual clinical trials, which is helpful to evaluate the potential benefits of patients, the observation time of long-term cardiovascular protection is still short. Given that longer follow-up time is very important to determine whether this effect is temporary or continuous with time, it needs further verification and discussion in the follow-up study.

In summary, in patients with T2DM who received the canagliflozin combined with metformin, the mortality rate of cardiovascular causes was significantly reduced. Compared with metformin monotherapy, there is no significant difference in the incidence of serious adverse reactions, and the safety of medication is better, while the blood sugar, blood pressure, and weight of T2DM patients are more actively improved. For T2DM patients with high risk of cardiovascular disease, the combination of canagliflozin and metformin could have a higher benefit in cardiovascular outcomes.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Author contributions

This manuscript was written by Xiaoyu Chen， Yimin Shu and Xuebo Liu. Xiaoyu Chen worked independently on the research design and data analysis. Yimin Shu took the lead in writing the manuscript, Xuebo Liu proofread all drafts. Xiaoyu Chen and Yimin Shu gave first instructions for the paper, and Xuebo Liu objectively proofread the manuscript.

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Data availability

The datasets are available from the corresponding author on reasonable request.

Declarations

Ethical approval
The study was approved by The Ningbo University Affiliated People's Hospital of Ningbo University, and all patients signed informed consent forms before participating in the study.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare no conflict of interest.

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