Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

The Impact of Genetic Polymorphisms on the Anti-Hyperglycemic Effect of Dapagliflozin

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Background: The influence of genetic variants on the glucose-lowering effects of dapagliflozin remains unclear. This study aims to investigate the impact of polymorphisms in solute carrier family 5 member 2 (*SLC5A2*), uridine diphosphate glucuronosyltransferase 1A9 (*UGT1A9*), solute carrier family 2 member 2 (*SLC2A2*) and member 4 (*SLC2A4*) on the anti-hyperglycemic effect of dapagliflozin in patients with type-2 diabetes mellitus (T2DM).

Methods: A total of 141 patients with T2DM were included in this prospective cohort study. Twenty-nine single nucleotide polymorphisms (SNPs) were selected and genotyped using the Sequenom MassArray platform or Sanger sequencing. Glycated hemoglobin (HbA1c) and fasting blood glucose (FBG) levels were compared before and after the treatment with dapagliflozin.

Results: Among the 29 SNPs selected, 27 were successfully analyzed. After three months of dapagliflozin treatment, FBG levels were significantly reduced (8.00 mmol/L (5.45–10.71) mmol/L vs 6.40 mmol/L (5.45–9.20) mmol/L, $p = 0.003$) in patients with T2DM. However, there was no significant change in HbA1c levels (8.10% (6.88–10.00)% vs 8.10% (6.83–10.00)%, $p = 0.452$). Analysis of covariance showed that patients with the minor allele homozygote or heterozygote of rs12471030 (CT/TT), rs12988520 (AC/CC) or rs2602381 (TC/CC) had higher FBG levels compared to those with the major allele homozygote ($p = 0.014$, $p = 0.024$, and $p = 0.044$, respectively). After adjusting for baseline FBG level, age, gender, body mass index, use of insulin and use of metformin, three SNPs—rs12471030, rs12988520 and rs2602381—were associated with the anti-hyperglycemic effect of dapagliflozin. However, using a stringent significance threshold ($p < 0.002$ with Bonferroni correction), none of these selected SNPs were significantly associated with FBG and HbA1c levels after dapagliflozin treatment.

Conclusion: After adjusting for confounding variables, polymorphisms in *SLC5A2, UGT1A9, SLC2A2* and *SLC2A4* genes were not associated with the anti-hyperglycemic effect of dapagliflozin in the Chinese population.

Clinical Trial Registration Number: ChiCTR2200059645.

Keywords: dapagliflozin, fasting blood glucose, glycated hemoglobin, polymorphisms, UGT1A9

Introduction

Dapagliflozin is a highly potent and selective sodium-glucose cotransporter 2 (SGLT2) inhibitor. Initially developed to treat type 2 diabetes mellitus (T2DM), dapagliflozin has also been shown to reduce the risk of worsening heart failure or death from cardiovascular-related deaths.[1–3] Current guidelines recommend dapagliflozin treatment for patients with T2DM, chronic kidney disease, and heart failure, covering the full range of left ventricular ejection fraction (LVEF).[4–6] Dapagliflozin increases glucose excretion through urine by inhibiting SGLT2, responsible for most glucose reabsorption in the kidney.[7] SGLT2 is encoded by the solute carrier family 5 member 2 (*SLC5A2*) gene on the human chromosome 16p11.2. Mutations in this gene can affect SGLT2 expression, membrane localization, or transport capacity and are associated with familial renal glucosuria.[8,9] Additionally, the uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9) enzyme, encoded by the *UGT1A9* gene cluster on the human chromosome 2q37, metabolizes dapagliflozin in the kidney and liver.[10,11] Polymorphisms in the *UGT1A9* gene can influence enzyme expression and activity,

Received: 18 February 2024
Accepted: 24 July 2024
Published: 31 July 2024

potentially affecting drug exposure.[12] Furthermore, glucose transporter 2 (GLUT2) and 4 (GLUT4), encoded by solute carrier family 2 member 2 (*SLC2A2*) and member 4 (*SLC2A4*) are crucial for glucose transport and homeostasis.[13,14] Genetic polymorphisms in *SLC2A2* and *SLC2A4* have been linked to the response to antidiabetic drugs like insulin and metformin, particularly regarding their anti-hyperglycemic effects.[15,16]

Therefore, variability of *SLC5A2, UGT1A9, SLC2A2* and *SLC2A4* may affect the response to dapagliflozin treatment. However, data on the role of genetic variants in these genes are still lacking. This study aims to identify the potential polymorphisms in *SLC5A2, UGT1A9, SLC2A2* and *SLC2A4* in the Chinese population and investigate their influence on the anti-hyperglycemic effect of dapagliflozin in patients with T2DM. The primary outcome was the impact of dapagliflozin-related genetic polymorphisms on fasting blood glucose levels. The secondary outcome was their influence on glycated hemoglobin levels in these patients.

Methods

Patients and Study Design

This prospective cohort study enrolled patients aged 18–80 with T2DM who had poor blood glucose control despite prior treatment with metformin or insulin therapy. Exclusion criteria included recent use (within seven days prior to enrollment) of SGLT2 inhibitors (dapagliflozin, empagliflozin, sotagliflozin, or ertugliflozin), as well as other anti-hyperglycemic medications such as insulin secretagogues, glucagon-like peptide-1 receptor agonists, thiazolidinediones, or α-glucosidase inhibitors. Upon enrollment, patients were initiated on dapagliflozin (10 mg once daily). Baseline characteristics, encompassing age, gender, body mass index (BMI), history of hypertension, and clinical parameters including hemoglobin level, red blood cell count, platelet count, estimated glomerular filtration rate, activated partial thromboplastin time, fasting blood glucose (FBG) level, glycated hemoglobin (HbA1c) level, and medication regimen, were meticulously documented. Changes in HbA1c and FBG levels were assessed before and after the three months of dapagliflozin treatment. Throughout the follow-up period, patients were regularly monitored via monthly telephone consultations or outpatient visits to ensure adherence. This study adhered to the Declaration of Helsinki principles and received approval from the ethics review committee of Zhongshan Hospital, Fudan University (B2022-333R). Written informed consent was obtained from all the participants.

Single Nucleotide Polymorphism Selection

We selected four genes—*SLC5A2, UGT1A9, SLC2A2*, and *SLC2A4*— for screening single nucleotide polymorphisms (SNPs). SNPs with minor allele frequencies (MAFs) > 0.1 were identified in the HapMap Chinese Han in Beijing (CHB) database (http://hapmap.ncbi.nlm.nih.gov). Tag SNPs were determined based on the linkage disequilibrium (LD) analysis using the HaploView 4.2 software (Broad Institute of MIT and Harvard, Cambridge, USA) with an r^2 threshold > 0.8. In total, 29 tag SNPs were selected, representing common genetic variations in the Chinese population.

Genotyping

Genome DNA samples were extracted from 2 mL of peripheral venous blood with ethylene diamine tetraacetic acid (EDTA) as an anticoagulant using a TIANamp blood DNA kit (Tiangen Biotech, Beijing, China) according to the manufacturer's instructions. Of the 29 tag SNPs, 27 were genotyped using the Sequenom MassArray system and MassArray Typer 4.0 software (Sequenom, San Diego, USA).[17] Multiplex polymerase chain reaction (PCR) and locus-specific extension primers were designed using the MassARRAY Assay Design 3.0 software (Sequenom, San Diego, USA). The DNA samples were amplified through multiplex PCR and locus-specific single-base extension reactions. The products were cleaned, transferred to a 384-element SpectroCHIP array, and analyzed using matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS). MassArray Typer 4.0 software (Sequenom, San Diego, USA) analyzed the resultant spectrograms and genotype data. The remaining two SNPs, rs9924771 and rs28898568 were genotyped by Sanger sequencing. DNA was amplified under the following conditions: pre-denaturation at 95°C for 5 min, followed by 10 cycles of denaturation at 94°C for 30 s, annealing at 63°C for 30 s, and extension at 72°C for 30 s. This was then followed by 30 cycles of denaturation at 95°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 30 s, with a final extension at 72°C for 10 min. The Sanger sequencing was performed using the ABI 3730XL Analyzer (Applied Biosystems Inc., CA, USA) according to the manufacturer's specification. Five percent of all the

samples were randomly selected for duplicate analyses as quality controls, showing a genotype concordance rate of 100%. Negative controls confirmed the absence of amplification inhibitors. DNA quality and quantity were assessed before genotyping. Primer information for the selected tag SNPs is presented in Table 1, with all the primers were synthesized by Sangon biotech (Shanghai, China).

Statistical Analysis

The sample size was estimated using the dominant model. Based on the mutation frequency of the studied genes in Asian populations from the 1000 Genomes Project, it was estimated that 80% of the genotypes were major allele homozygotes, while the minor allele homozygotes or heterozygotes accounted for 20%. The estimated difference in fasting blood glucose before and after dapagliflozin treatment was 2 mmol/L, with a 3 mmol/L standard deviation. With a power of 0.80 (1-β), and a significance level of 0.05 (α), 80 cases of major allele homozygotes and 20 cases of minor allele homozygotes or heterozygotes were required, totaling 100 cases. To account for a 10% potential loss to follow-up, a minimum of 110 cases was necessary. The normality of variables was tested using the Kolmogorov–Smirnov test. Continuous variables are presented as the mean ± standard deviation for normally distributed variables or as the median and interquartile range (IQR) for the non-normally distributed variables. Categorical variables are expressed as frequencies or percentages. All the SNPs were assessed for deviation from the Hardy-Weinberg equilibrium. Three different genetic models (dominant, recessive, and additive) were used to analyze SNP effects comprehensively. Missing data were handled using average imputation. The proportions of missing data were 1.41% (2/141) for body mass index (BMI), 0.71% (1/141) for estimated glomerular filtration rate, and 0.71% (1/141) for activated partial thromboplastin time. Differences in FBG and HbA1c levels between patients with different genotypes were analyzed using the analysis of covariance with the baseline levels as covariates. Confounding variables, including age, gender, BMI, insulin and metformin use, were adjusted using linear regression analysis. The multicollinearity of baseline variables was assessed by Spearman correlation ($r^2 > 0.7$ was regarded as a high correlation and removed from models) and variance inflation factor (VIF) using a cut-off value of 5. The R squared test assessed the goodness of fit and F-statistic was used to assess the model's significance. The Kruskal–Wallis test was used to assess changes in FBG and HbA1c levels among genotype groups from baseline to three months. The Wilcoxon Signed-Rank Test was employed to compare paired variables before and after treatment. Bonferroni correction was performed for multiple comparisons, with $p < 0.002$ (0.05/25) was considered statistically significant.[18] This p threshold was chosen because 27 SNPs were sequenced; one violated Hardy–Weinberg, and another was monomorphic. For the baseline characteristics analysis and the Hardy–Weinberg equilibrium test, $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS version 25.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics of Patients

A total of 158 patients with T2DM were enrolled in this study. After three months of follow-up, 17 patients were lost during follow-up, resulting in a final analysis of 141 patients (Figure 1). The mean age of these patients was 62.27 ± 11.79 years, and 102 patients (72.3%) were males. Baseline characteristics are presented in Table 2. The baseline FBG level was 8.00 mmol/L (5.45–10.71) mmol/L, and the baseline HbA1c level was 8.10% (6.88–10.00)%.

Sequencing Results of Genotypes

Among the 29 SNPs selected for genotyping, 27 were successfully analyzed, while 2 SNPs (rs10929285 and rs9924771) failed to be sequenced. The genotype distributions were in Hardy–Weinberg equilibrium except for rs2070959. The distribution of the genotypes matched those reported in the East Asian population in the SNP database (https://www.ncbi.nlm.nih.gov/snp/) (Supplementary Table 1). To analyze the genotypes related to the anti-hyperglycemic effect of dapagliflozin, patients were divided into three groups: major allele homozygotes, heterozygotes and minor allele homozygotes. FBG and HbA1c levels were compared among these groups using three genetic models (dominant, recessive, and additive) to comprehensively analyze the SNP effects. We also examined the association of variants with the change in FBG and HbA1c levels from baseline to 3 months. Due to the limited number of patients with specific genotypes, we could not further analyze rs202203863, as no patients had the minor allele G for this SNP.

Table 1 Primer Design

Rs Number	Gene	Forward Primers	Reverse Primers	Extension Primers
rs3813007	*SLC5A2*	ACGTTGGATGCTCAAAGTCCTCACTCAAGC	ACGTTGGATGCAAAGGCTTCCTCTCTTTCC	CCCCAGTCCTCACTCAAGCCCAGCA
rs9934336		ACGTTGGATGAGCCTTGTTTCTGGCTGAAG	ACGTTGGATGTGAGTGTCTGGGAGGAGTTG	CGAGCCAAGTTTCCCTGAT
rs9924771		CTCAGTACTTTGGGAGGCTGAG	AGACAGAGTCTTGCTCTTGTTGC	Sanger sequencing
rs3813008		ACGTTGGATGGGAAGATTTAGCAGCTCTTG	ACGTTGGATGGGGTTTTGCCAGAGATCTTG	TGAACACCTGGGAGA
rs12471030	*UGT1A9*	ACGTTGGATGCTTGGACAGAAACCAAGCAG	ACGTTGGATGTTGCGACTTTGACCAAAGCC	CCCTCTGAGACGGCCAC
rs2070959		ACGTTGGATGATCTGTGTACCTCTTCAGGG	ACGTTGGATGTTGTGTAGCACCTGGGAATG	CGTGTTCCCTGGAGCAT
rs202203863		ACGTTGGATGTCACTTCTCAGACAGGGCAG	ACGTTGGATGCGTCTTCACCCGGCCGCCATC	TCCCCACATCTCAGA
rs1104892		ACGTTGGATGTTCCACCTTTGGACAGAACC	ACGTTGGATGTTGCAGGCCTGCCTTCTCT	GGGAACCATGGGACAGGCAG
rs7595138		ACGTTGGATGCAAGCACCAGAATGTAAGGC	ACGTTGGATGCATTTTCTGCCTTCACGGAC	CCCCATCTTTTCCTTTCAAGGCT
rs4233633		ACGTTGGATGTTCCAAGATACATGGGCCTC	ACGTTGGATGCAACATCTCAGCCTCTGAAC	GACACCAATGTCATCTAATTTCTA
rs10929303		ACGTTGGATGGCACGTCCTCTGAAAAATGG	ACGTTGGATGAGACTCGCTAGTCAGTAAAG	GGGTTCATCCTGATCAAAGACACC
rs7349250		ACGTTGGATGCCCAGAGGAAATGGTCTTAG	ACGTTGGATGGAACTTGTCAAATCTGTCTG	TTTGCATTTTTCACTTGCCAAT
rs10929285		ACGTTGGATGCAGTTAAGAGAATAGGGCCG	ACGTTGGATGATGGCACGATCTTGGCTCTC	AGGGAATCCCAGCTACTCGG
rs12988520		ACGTTGGATGAGAGGTTACCATGAGAAAGG	ACGTTGGATGTTGAAAACCATAGCTTGGTG	GGAGCTTTCTTTCTGAATCATAGCA
rs4148328		ACGTTGGATGCCCCATTAGATTTAAAACTCC	ACGTTGGATGTCTGTGCAGGAAACTTATGG	CCCATTAGATTTAAAACTCCAATTTA
rs28898568		TATCATCTGCAAATTATTCCCTCC	CTTTCACCAAACATCTGCCAATA	Sanger sequencing
rs2361501		ACGTTGGATGACATTCGTGTCTACTTCCTC	ACGTTGGATGTCTCAGGTCTGTATTGGTGC	GAAGCAATTTTAAATAAATACATTTTTT
rs12469671		ACGTTGGATGAGATTCCTCTGGCTAGTGTC	ACGTTGGATGTCTCCTGTGAGCTTTGACTG	TGTCCAGTGCAGACA
rs45531144		ACGTTGGATGCCAAAGACCCTTACCTCTCT	ACGTTGGATGCTTTTCACAGTGGCTACTGC	CCCTTACCTCTCTTCTTTA
rs28898622		ACGTTGGATGGCCCTTCCAGTTTTTCTTTC	ACGTTGGATGGCAGGAAACCAACATGGCAC	GGACTTTAAGTTCTAGGGTACAT
rs2602381		ACGTTGGATGACCTAAGAATGGATAAGTGG	ACGTTGGATGTTGGTGGACAAGACTAAGGC	GGATAAGTGGGTGCTC
rs6717546		ACGTTGGATGGCATAAATGCATGAGAAAAG	ACGTTGGATGTTGCCACAATTGTAACTGGG	AGAAAAGAAAAATAACCAGTAATC
rs17862880		ACGTTGGATGGATTATGACAGAAAGTTTGG	ACGTTGGATGGGGTTATTTCTGGGCGATG	AGCTGGAAAATATAGAGGTTCACA
rs77410236		ACGTTGGATGTGACTAGGACTGCTCGAAAC	ACGTTGGATGTATGGCACATCCATCACAAC	AAGGAGAGTCTGAGAAACC
rs2011425		ACGTTGGATGAAGAACCCTTGAGTGTAGCC	ACGTTGGATGTGAGAGTGGAAAGGTGTTGG	GGGGACTCTGGCATGGAGCTCCCGCA
rs5398	*SLC2A2*	ACGTTGGATGTTTCCTCTTTGCTGGAGTGC	ACGTTGGATGGACTTTCCTTTGGTTTCTGG	GTCATGGCCTTTACCCTGTT
rs5418	*SLC2A4*	ACGTTGGATGATGGGACCCACAGCCACAAG	ACGTTGGATGTTCTCGCGTCTTTTCCCCCA	CAGCCACAAGCCAAGGA
rs5435		ACGTTGGATGTGCTGGTCAACAATGTCCTG	ACGTTGGATGCGTCCAAGGATGAGCATTTC	GAATCCTCATGGGCCTGGCCAA
rs16956647		ACGTTGGATGTATCATCAGCCACTGTCCTC	ACGTTGGATGCCTTTCTGGAACAGCACTTC	GGAAGGAGGCCCCCAACA

Abbreviations: *SLC5A2*, solute carrier family 5 member 2; *UGT1A9*, uridine diphosphate glucuronosyltransferase 1A9; *SLC2A2*, solute carrier family 2 member 2; *SLC2A4*, solute carrier family 2 member 4.

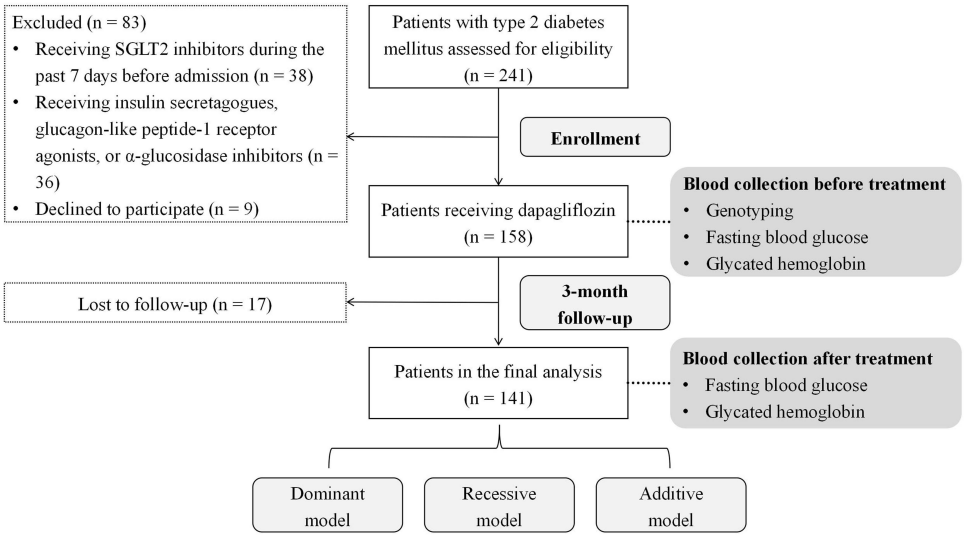

Figure 1 Flowchart of the study. SGLT2: Sodium-glucose cotransporter 2.

FBG and HbA1c Levels with Genotypes

After three months of dapagliflozin treatment, FBG levels significantly decreased in patients with T2DM (8.00 mmol/L (5.45–10.71) mmol/L vs 6.40 mmol/L (5.45–9.20) mmol/L, $p = 0.003$). However, there was no significant change in the HbA1c levels (8.10% (6.88–10.00) % vs 8.10% (6.83–10.00) %, $p = 0.452$) (Figures 2 and 3).

After adjustment for baseline FBG using analysis of covariance, three SNPs (rs12471030, rs12988520 and rs2602381) were found to affect the anti-hyperglycemic effect of dapagliflozin. The top five SNPs with the smallest

Table 2 Baseline Characteristics of Patients

Variables	
Age, yrs	62.27 ± 11.79
Male, n (%)	102 (72.3)
BMI, kg/m^2	25.59 ± 4.57
Hypertension, n (%)	91 (64.5)
Baseline Hb, g/L	134.48 ± 21.94
Baseline RBC counts, ×10^{12}/L	4.53 ± 0.59
Baseline PLT counts, ×10^9/L	200.97 ± 59.98
Baseline eGFR, mL/min/1.73 m^2	81.79 ± 23.65
Baseline APTT, s	26.10 ± 2.15
Baseline Fasting blood glucose, mmol/L	8.00 (5.45–10.71)
Baseline HbA1c, %	8.10 (6.88–10.00)
Use of insulin, n (%)	81 (57.4)
Use of metformin, n (%)	88 (62.4)
Use of β blockers	38 (27.0)
Use of ARB/ACEI, n (%)	49 (34.8)
Use of CCB, n (%)	54 (38.3)
Use of statins, n (%)	91 (64.5)
Use of antiplatelet agents, n (%)	45 (31.9)

Notes: Continuous variables are presented as the mean ± standard deviation or as the median and interquartile range. Categorical variables are presented as frequencies or percentages.

Abbreviations: BMI, body mass index; Hb, hemoglobin; RBC, red blood cell; PLT, platelet; eGFR, estimated glomerular filtration rate; APTT, activated partial thromboplastin time; HbA1c, glycated hemoglobin; ARB, angiotensin II receptor blockers; ACEI, angiotensin converting enzyme inhibition; CCB, calcium channel blockers.

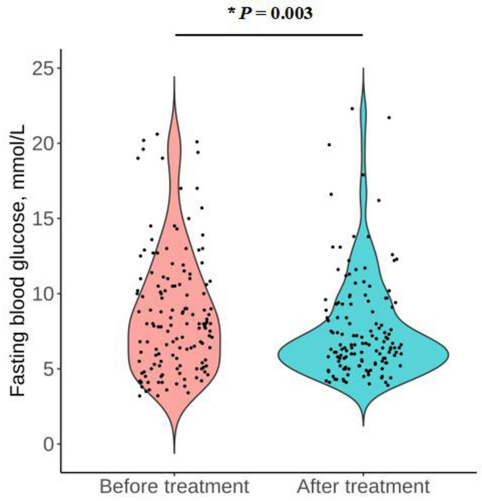

Figure 2 Change of fasting blood glucose after dapagliflozin treatment. Data are presented as the median and interquartile range and compared using Wilcoxon Signed-Rank Test. A *p* value < 0.05 was considered statistically significant. *Indicates a *p* value less than 0.05.

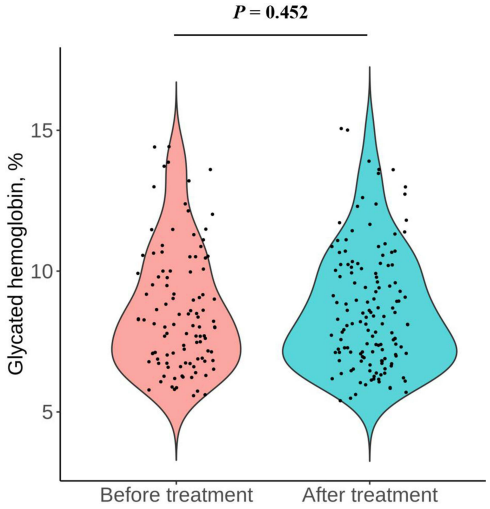

Figure 3 Change of glycated hemoglobin after dapagliflozin treatment. Data are presented as the median and interquartile range and compared using Wilcoxon Signed-Rank Test. A *p* value < 0.05 was considered statistically significant.

p in the dominant model are listed in Table 3, with information on the remaining SNPs in Supplementary Table 2. Patients with the CC genotype of rs12471030 in the dominant models exhibited lower FBG levels than those with the CT or TT variants after adjusting for the baseline levels ($p = 0.014$, $R^2 = 0.131$, $F = 6.184$). Similarly, the AA genotype of rs12988520 and TT genotype of rs2602381 were associated with lower FBG levels compared to the AC/CC and TC/CC genotypes, respectively, after adjustment ($p = 0.024$, $R^2 = 0.125$, $F = 5.175$; $p = 0.044$, $R^2 = 0.119$, $F = 4.132$). Regression analysis, which included the baseline FBG levels, age, gender, BMI, insulin use, and metformin use as confounding variables, revealed the differences in FBG levels post-treatment between the major allele homozygotes and heterozygotes in the additive models for rs12471030 ($p = 0.030$, $R^2 = 0.233$, $F = 4.803$), rs12988520 ($p = 0.040$, $R^2 = 0.225$, $F = 5.211$), and rs2602381 ($p = 0.021$, $R^2 = 0.235$, $F = 5.562$) (Table 3). The VIF values were all less than 2, indicating slight multicollinearity. Using a stringent significant threshold ($p < 0.002$ with Bonferroni correction), none of the selected SNPs were associated with FBG levels after dapagliflozin treatment.

After adjusting for the baseline HbA1c level, none of the SNPs impacted HbA1c following dapagliflozin treatment. These findings were consistent with regression analysis, which considered confounding variables such as baseline HbA1c

Table 3 Fasting Blood Glucose with Genotypes Before and After Dapagliflozin Treatment (Top Five SNPs with the Smallest p values)

	Model		Before Treatment (mmol/L)	After Treatment (mmol/L)	P*	P†	P§
rs1104892 (G>A)		GG (N = 71)	8.00 (6.00–10.82)	6.30 (5.20–9.30)			
		GA (N = 56)	7.83 (5.28–10.38)	6.70 (5.83–9.55)			
		AA (N = 14)	7.60 (4.65–11.03)	6.35 (5.75–7.18)			
		P^λ value	0.713				
	Dominant	GG vs GA + AA			0.141	0.151	0.176
	Recessive	GG + GA vs AA			0.454	0.621	0.724
	Additive	GA (vs GG)			0.067	0.089	0.118
		AA (vs GG)			0.818	0.988	0.934
rs12471030 (C>T)		CC (N = 97)	8.00 (6.05–10.91)	6.30 (5.40–8.40)			
		CT (N = 40)	7.15 (5.05–9.73)	7.20 (5.88–10.13)			
		TT (N = 4)	10.90 (5.98–12.98)	5.75 (4.50–10.60)			
		P^λ value	0.239				
	Dominant	CC vs CT + TT			0.014	0.020	0.056
	Recessive	CC + CT vs TT			0.537	0.639	0.463
	Additive	CT (vs CC)			0.007	0.011	0.030
		TT (vs CC)			0.730	0.831	0.681
rs12988520 (A>C)		AA (N = 82)	8.00 (5.48–10.94)	6.40 (5.28–8.40)			
		AC (N = 55)	8.00 (5.50–10.60)	7.10 (5.70–10.20)			
		CC (N = 4)	6.95 (4.63–10.78)	5.95 (5.65–6.55)			
		P^λ value	0.892				
	Dominant	AA vs AC + CC			0.024	0.022	0.060
	Recessive	AA + AC vs CC			0.436	0.561	0.569
	Additive	AC (vs AA)			0.014	0.014	0.040
		CC (vs AA)			0.655	0.815	0.799
rs2602381 (T>C)		TT (N = 86)	8.00 (6.10–11.08)	6.25 (5.20–9.30)			
		TC (N = 52)	7.15 (5.00–9.98)	7.10 (5.88–9.25)			
		TC (N = 3)	8.90 (5.00–11.40)	6.10 (5.80–6.70)			
		P^λ value	0.267				
	Dominant	TT vs TC + CC			0.044	0.037	0.031
	Recessive	TT + TC vs CC			0.468	0.582	0.494
	Additive	TC (vs TT)			0.029	0.027	0.021
		CC (vs TT)			0.632	0.784	0.686
rs5398 (G>A)		GG (N = 92)	7.83 (5.05–10.77)	6.35 (5.23–7.85)			
		GA (N = 45)	8.70 (5.90–11.15)	7.30 (5.70–10.05)			
		AA (N = 4)	7.95 (5.15–9.78)	7.75 (4.48–12.30)			
		P^λ value	0.575				
	Dominant	GG vs GA + AA			0.058	0.090	0.149
	Recessive	GG + GA vs AA			0.608	0.583	0.757
	Additive	GA (vs GG)			0.068	0.109	0.160
		AA (vs GG)			0.470	0.466	0.630

Notes: *Analysis of covariance with the baseline fasting blood glucose as a covariate. †Adjustment with baseline fasting glucose, age, gender and body mass index in the regression analysis. §Adjustment with baseline fasting glucose, age, gender, body mass index, use of insulin and use of metformin in the regression analysis. ^λ^Baseline fasting blood glucose levels among the different genotypes in one-way analysis of variance. Data are presented as the median and interquartile range. A p value < 0.002 (0.05/25) was considered statistically significant.

Abbreviation: SNP, single nucleotide polymorphism.

level, age, gender, BMI, insulin use, and metformin use. The top five SNPs with the smallest p are listed in Table 4, and information on the remaining SNPs is in Supplementary Table 3. Gender-specific subgroup analysis also yielded similar results; after Bonferroni correction, none of the studied SNPs significantly affected the anti-hyperglycemic effect of dapagliflozin (Supplementary Table 4).

Table 4 Glycated Hemoglobin with Genotypes Before and After Dapagliflozin Treatment (Top Five SNPs with the Smallest p values)

	Model		Before Treatment (%)	After Treatment (%)	P*	P†	P§
rs2602381 (T>C)		TT (N = 86)	7.90 (6.80–10.00)	8.35 (6.88–10.13)			
		TC (N = 52)	8.50 (6.90–10.10)	8.00 (6.80–10.18)			
		TC (N = 3)	8.50 (6.90–10.10)	8.00 (6.80–10.18)			
		P^λ value	0.832				
	Dominant	TT vs TC + CC			0.266	0.362	0.193
	Recessive	TT + TC vs CC			0.570	0.676	0.586
	Additive	TC (vs TT)			0.160	0.188	0.224
		CC (vs TT)			0.446	0.530	0.465
rs28898568 (C>T)		CC (N = 101)	8.20 (6.90–10.00)	7.90 (6.80–9.90)			
		CT (N = 32)	8.05 (6.73–10.58)	8.60 (6.93–10.70)			
		TT (N = 8)	7.90 (6.80–11.60)	9.20 (7.48–9.60)			
		P^λ value	0.951				
	Dominant	CC vs CT + TT			0.064	0.115	0.160
	Recessive	CC + CT vs TT			0.676	0.710	0.914
	Additive	CT (vs CC)			0.071	0.093	0.110
		TT (vs CC)			0.497	0.527	0.866
rs28898622 (G>A)		GG (N = 106)	8.15 (6.78–10.50)	8.10 (6.90–9.95)			
		GA (N = 34)	8.10 (7.28–9.65)	7.90 (6.78–10.23)			
		AA (N = 1)	Not Applicable (Only one patient)				
		P^λ value	0.950				
	Dominant	GG vs GA + AA			0.318	0.303	0.900
	Recessive	GG + GA vs AA			/	/	/
	Additive	GA (vs GG)			0.605	0.625	0.826
		AA (vs GG)			/	/	/
rs5398 (G>A)		GG (N = 92)	8.25 (6.70–10.03)	7.75 (6.50–9.60)			
		GA (N = 45)	8.00 (7.10–10.08)	9.00 (7.60–10.25)			
		AA (N = 4)	8.30 (8.10–10.90)	6.85 (5.70–10.40)			
		P^λ value	0.763				
	Dominant	GG vs GA + AA			0.101	0.111	0.245
	Recessive	GG + GA vs AA			0.479	0.510	0.431
	Additive	GA (vs GG)			0.085	0.081	0.169
		AA (vs GG)			0.617	0.663	0.552
rs5435 (T>C)		TT (N = 23)	8.90 (7.13–10.08)	7.80 (6.70–10.20)			
		TC (N = 60)	7.65 (6.68–10.03)	8.00 (6.80–9.60)			
		CC (N = 58)	8.10 (7.10–10.20)	8.45 (7.30–10.20)			
		P^λ value	0.405				
	Dominant	TT vs TC + CC			0.132	0.161	0.558
	Recessive	TT + TC vs CC			0.269	0.316	0.630
	Additive	TC (vs TT)			0.242	0.242	0.659
		CC (vs TT)			0.109	0.129	0.514

Notes: *Analysis of covariance with the baseline glycated hemoglobin as a covariate. †Adjustment with baseline glycated hemoglobin, age, gender and body mass index in the regression analysis. §Adjustment with baseline glycated hemoglobin, age, gender, body mass index, use of insulin and use of metformin in the regression analysis. λBaseline glycated hemoglobin levels among the different genotypes in one-way analysis of variance. Data are presented as the median and interquartile range. A p value < 0.002 (0.05/25) was considered statistically significant.

Abbreviation: SNP, single nucleotide polymorphism.

When comparing the changes in FBG level among different genotypes, variants in rs12471030 (p = 0.039), rs16956647 (p = 0.019), rs2011425 (p = 0.019), and rs2602381 (p = 0.022) affected FBG levels. However, these differences also did not reach statistical significance after the Bonferroni correction. The top five SNPs with the smallest p are listed in Table 5, with information on the remaining SNPs in Supplementary Table 5. Additionally, none of these SNPs were related to the changes in HbA1c after dapagliflozin treatment (Table 6 and Supplementary Table 6).

Table 5 Change of Fasting Blood Glucose Levels with Genotypes (Top Five SNPs with the Smallest p values)

		Change of Fasting Blood Glucose Levels (mmol/L)	P
rs12471030 (C>T)	CC (N = 97) CT (N = 40) TT (N = 4)	2.30 (0.25–5.41) 0.10 (–0.68–3.30) 3.80 (0.60–7.60)	0.039
rs16956647 (C>T)	CC (N = 86) CT (N = 44) TT (N = 11)	2.10 (–0.20–4.98) 1.00 (–0.30–3.18) 4.30 (2.90–6.50)	0.019
rs2011425 (T>G)	TT (N = 95) TG (N = 45) GG (N = 1)	2.60 (0.30–5.20) 0.20 (–0.70–3.45) /	0.019
rs2602381 (T>C)	TT (N = 86) TC (N = 52) CC (N = 3)	2.60 (0.48–5.20) 0.15 (–0.68–3.53) 3.20 (0.20–6.30)	0.022
rs3813008 (G>A)	GG (N = 102) GA (N = 38) AA (N = 1)	2.25 (0.00–4.98) 0.85 (–0.25–4.43) /	0.125

Notes: Data are presented as the median and interquartile range and compared by Kruskal–Wallis test. A *p* value < 0.002 (0.05/25) was considered statistically significant.
Abbreviation: SNP, single nucleotide polymorphism.

Table 6 Change of Glycated Hemoglobin Levels with Genotypes (Top Five SNPs with the Smallest p values)

		Change of Glycated Hemoglobin Levels (%)	P
rs12471030 (C>T)	CC (N = 97) CT (N = 40) TT (N = 4)	0.00 (–1.20–0.65) 0.00 (–1.40–0.50) 1.20 (0.65–1.90)	0.104
rs5398 (G>A)	GG (N = 92) GA (N = 45) AA (N = 4)	0.10 (–0.55–0.60) –0.45 (–1.95–0.78) 0.90 (–3.30–5.40)	0.175
rs5435 (T>C)	TT (N = 23) TC (N = 60) CC (N = 58)	0.40 (–0.43–1.85) 0.00 (–1.45–0.35) 0.00 (–1.15–0.73)	0.155
rs7595138 (T>C)	TT (N = 51) TC (N = 67) CC (N = 23)	–0.10 (–1.43–0.33) 0.10 (–0.95–0.90) 0.35 (–0.68–1.45)	0.078
rs77410236 (C>T)	CC (N = 111) CT (N = 28) TT (N = 2)	0.10 (–1.15–0.80) –0.15 (–1.30–0.33) /	0.225

Notes: Data are presented as the median and interquartile range and compared by Kruskal–Wallis test. A *p* value < 0.002 (0.05/25) was considered statistically significant.
Abbreviation: SNP, single nucleotide polymorphism.

Discussion

Dapagliflozin, a highly selective SGLT2 inhibitor, is widely used for treating type 2 diabetes mellitus (T2DM). Previous studies have identified various genetic variants influencing the activity of transporters and metabolic proteins like SGLT2,

UGT1A9, GLUT2, and GLUT4, which play crucial roles in dapagliflozin's metabolism and mechanism.[19–24] However, limited research has explored how these variants affect dapagliflozin's glucose-lowering effects. This study aims to fill this gap by comprehensively investigating the influence of gene polymorphisms on dapagliflozin's anti-hyperglycemic effects, emphasizing its metabolic pathways and mechanisms.

This study included the common genetic variants in *SLC5A2, UGT1A9, SLC2A2* and *SLC2A4* within the Chinese population to explored their clinical value. Figure 4 summarizes our SNP screening process and the results of our analysis. A recent study examined the effects of common *SLC5A2* variants in the response to empagliflozin in 2229 subjects at increased risk for T2DM. It found no significant associations between the tested SNPs and various metabolic and physiological parameters, except for a nominal association of rs3116150 with plasma glucose and blood pressure.[25] However, in our study, *SLC5A2* SNPs were not related to the anti-hyperglycemic effect of dapagliflozin. This difference may be due to the variation in mutation frequency across different populations. For example, this locus rs3116510 lacks SNPs in the East Asian population. In our analysis, we found that after adjusting for baseline FBG levels, three SNPs (rs12471030, rs12988520 and rs2602381) were associated with FBG levels post-treatment with dapagliflozin in the dominant model. Additionally, similar association were observed in the additive models after further adjusting for baseline FBG levels and other potential confounders. Specifically, there were different FBG levels after dapagliflozin treatment between patients with major allele homozygote and heterozygote for rs12471030, rs12988520, and rs2602381. These differences were not observed in the recessive models, likely due to the low number of patients with minor allele homozygote (eg only four patients had TT for rs12471030, four had CC for rs12988520, and three had CC for rs2602381). Although the dominant and additive models suggested these SNPs were associated with the anti-hyperglycemic effect of dapagliflozin, these associations did not remain significant after Bonferroni correction. Given the stringent Bonferroni correction threshold ($p = 0.002$) applied in our research, these SNPs (rs12471030, rs12988520 and rs 2602381) warrant further investigation. These three SNPs are located within the intronic regions of *UGT1A9*. However, there is limited research on these specific SNPs. Only two published studies have reported on rs12988520 and

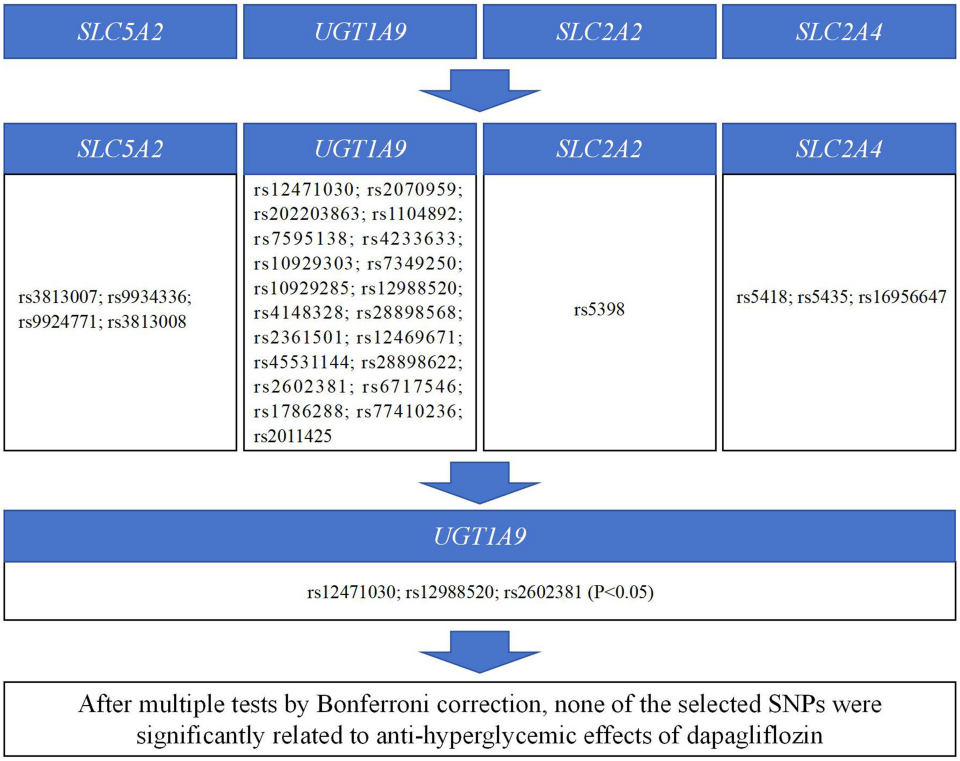

Figure 4 Graphical representation.
Abbreviations: *SLC5A2*, solute carrier family 5 member 2; *UGT1A9*, uridine diphosphate glucuronosyltransferase 1A9; *SLC2A2*, solute carrier family 2 member 2; *SLC2A4*, solute carrier family 2 member 4. SNP, single nucleotide polymorphism.

rs2602381. A recent study included 430 participants with metabolic syndrome and analyzed gene–diet interactions on total serum bilirubin and identified more than 55 SNPs associated with serum bilirubin at a genome-wide significance level ($p < 5\times10^{-8}$), demonstrating that rs12988520 was associated with bilirubin concentrations in subjects with metabolic syndrome.[26] Another study examined the association between SNPs and attention-deficit hyperactivity disorder but found that the rs2602381 ($p = 3.85\times10^{-6}$) did not reach genome-wide significance (5×10^{-8}).[27]

Previous studies reported polymorphic expression and variable levels of glucuronidation activities mediated by the UGT1A9 protein, suggesting that genetic factors may control the expression level, activity, or stability of the UGT1A9 protein and influence its functions.[28] This regulation can impact the metabolism and therapeutic effect of various drugs, including mycophenolic acid, tacrolimus, fluoroquinolone and propofol.[21,29–31] SGLT2 inhibitors, including dapagliflozin, are primarily eliminated through o-glucuronidation, a process facilitated by uridine diphosphate glucuronosyltransferases (UGTs). Given that genetic polymorphisms can impact the expression and activity of the UGT1A9 protein,[24] it is reasonable to speculate that the SNPs examined in this study might influence the glucuronidation process. Consequently, this could also affect the metabolism and therapeutic efficacy of dapagliflozin. However, there is still debate whether polymorphisms in genes encoding uridine 5'-diphosphoglucuronosyltransferase affect SGLT2 inhibitors pharmacokinetics.[32,33] Pharmacogenomic analysis of 134 participants from seven phase-1 studies revealed that genetic variations in *UGT1A9*3* (rs72551330) significantly increased plasma canagliflozin exposure, highlighting the involvement of *UGT1A9* in the metabolism of canagliflozin.[32] In contrast, a recent study examined the effect of *UGT1A9* polymorphisms (*UGT1A9**2, *UGT1A9**3, I.399C>T, rs2011404, rs1105880, rs6759892, rs7577677, and rs4148323) on the apparent oral clearance (CL/F) of dapagliflozin. The study's findings indicated that the geometric mean ratio of dapagliflozin CL/F for all of the *UGT1A9* polymorphisms studied was within the range of wild-type *UGT1A9* CL/F values, suggesting these polymorphisms did not have a clinically meaningful impact on the CL/F of dapagliflozin.[34] A meta-analysis investigated the impact of *UGT1A9* polymorphisms on another SGLT2 inhibitor, ertugliflozin, and revealed that the *UGT1A9* genotype did not influence ertugliflozin exposure in healthy subjects, indicating that no ertugliflozin dose adjustment would be required for patients with the *UGT1A9* variants assessed.[35] Notably, many previously reported SNPs were not included in our study (eg, *UGT1A9*3*, ie rs72551330) because their mutation frequency is very low in the Chinese population. This suggests differences in metabolic genes among different races. In the current study, the SNPs examined did not influence the anti-hyperglycemic effect of dapagliflozin. Although several SNPs may be potentially related to the response of dapagliflozin, these effects were not significant after Bonferroni correction.

In our study, dapagliflozin effectively reduced FBG levels in patients with T2DM. The median value of FBG levels decreased by 1.6 mmol/L after receiving dapagliflozin, which is consistent with the results of a previous randomized, double-blind placebo-controlled clinical trial that found FBG decreased by 1.3 mmol/L after 24-week treatment of dapagliflozin with metformin.[36] However, there was no significant change in the HbA1c levels before and after the dapagliflozin treatment. This contrasts with the findings of other studies that routinely observed a reduction in HbA1c with dapagliflozin.[30,37] None of the SNPs examined showed any association with the HbA1c levels in patients receiving dapagliflozin. One possible explanation for this discrepancy could be the shorter follow-up in the present study. Given that the normal red blood cell lifetime is 120 days, HbA1c usually fluctuates less than blood glucose, indicating an average of blood glucose levels over the past 120 days.[38,39] Consequently, changes in Hb1Ac levels may occur later than changes in blood glucose. To further investigate this, future studies with a larger sample size and longer follow-up periods are warranted.

As a widely used anti-hyperglycemic drug, increasing evidence has demonstrated the clinical benefits of dapagliflozin in cardiovascular and renal diseases. In the prespecified patient-level pooled analysis of Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER), the response to dapagliflozin was similar between men and women.[40] Similarly, several studies reported that the overall efficacy and safety of dapagliflozin are consistent regardless of age.[41–43] In addition, recent research suggests that dapagliflozin, and other SGLT2 inhibitors can reduce inflammatory burden and oxidative stress, improve metabolism, and enhance cardiac function in T2DM.[44–46] This evidence indicates that dapagliflozin can significantly improve the prognosis of patients with diabetes, especially those with heart failure. In

this study, dapagliflozin showed an obvious anti-hyperglycemic effect in the short term. We explored dozens of SNPs that might affect the efficacy of dapagliflozin and found that, after adjusting by baseline characteristics, including age, gender, and BMI, dapagliflozin's effectiveness was less influenced by these SNPs. With stable and reliable efficacy, dapagliflozin can bring clinical benefits and be used as a first-line treatment for diabetes, heart failure, and kidney disease.

There are several limitations in the study. First, the number of cases enrolled may be too small, which might affect the statistical power to detect associations. This study only provided preliminary findings and needs validation in a larger population. Second, the successful sequencing of two genetic polymorphisms (rs10929285 and rs9924771) was not achieved. The effect of these two polymorphisms remains uncertain and still needs to be investigated. Third, this study only examined a portion of the genes related to the metabolic enzymes and target transporters of dapagliflozin, potentially omitting other relevant genes. Fourth, the Bonferroni correction was performed to adjust for multiple comparisons, which might have been too stringent and could have influenced the significance of the results, leading to false negatives. Furthermore, this study only included patients from the Chinese population. Given that the frequency of genetic mutations varies widely among different populations, there might be variations in drug responses with different genotypes across various ethnic groups. For instance, SNPs that did not show a statistical difference in this study could be linked to drug response in other populations due to mutation frequency and environmental factors disparities. Therefore, clinicians should thoroughly consider the patient's ethnic background and genetic information to achieve personalized treatment and rational drug use, relying on additional research.

Conclusion

In conclusion, the patients carrying heterozygous and homozygous mutant genotypes of rs12471030 (CT/TT), rs12988520 (AC/CC), or rs2602381 (TC/CC) had higher fasting blood glucose levels compared to patients carrying wild-type genotypes after receiving dapagliflozin. However, after adjusting for confounding variables, none of the *SLC5A2, UGT1A9, SLC2A2* and *SLC2A4* gene polymorphisms were associated with the anti-hyperglycemic effect of dapagliflozin in the Chinese population. Additional studies are needed, including larger-scale studies with diverse populations, investigations into the specific biological mechanisms, and exploration of additional genetic variants related to dapagliflozin metabolism or action.

Data Sharing Statement

The data that support the findings of this study will be available from the Qianzhou Lv upon reasonable request.

Ethical Approval Statement

This study complies with the Declaration of Helsinki. The ethics review committee of Zhongshan Hospital, Fudan University, approved this study (B2022-333R). All participants signed the written informed consent.

Funding

The Youth Foundation of Zhongshan Hospital, Fudan University (2021ZSQN18); Shanghai Key Clinical Specialty Project (shslczdzk06504).

Disclosure

The authors report no conflicts of interest in this work.

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