Dapagliflozin treatment alleviates fatty liver in patients with type 2 diabetes

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Abstract. Non-alcoholic fatty liver disease (NAFLD) is common in patients with type 2 diabetes mellitus (T2DM). The present study evaluated the effect of dapagliflozin on the liver fat content in patients with T2DM and NAFLD. The changes in biochemical data and metabolic parameters were analyzed. Clinical data of patients with T2DM and NAFLD treated by dapagliflozin were retrospectively collected between June 2022 and December 2022. A total of 35 patients, with a mean age of 45.8±2.2 years, consisting of 60.0% male patients, were included in the final analysis. After 20 weeks of dapagliflozin treatment, the parameters of diabetes improved. Plasma glucose and hemoglobin $A1_C$ levels significantly decreased (P<0.01), and insulin resistance improved. The change in liver fat content was evaluated by quantitative computed tomography, which revealed a decrease from 16.1±2.2 to 11.2±1.3% after treatment (P<0.01). Liver function (alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase levels) also improved. Visceral and subcutaneous fat areas showed a significant decrease after treatment, and there was a more significant reduction in visceral fat area. The factors associated with liver fat content were determined by Pearson's correlation and regression analyses. Pearson's correlation analysis indicated that the post-treatment decrease in liver fat content was positively correlated with the change in body weight (r=0.642, P=0.033), index of homeostasis model assessment-insulin resistance (r=0.670, P=0.048), triglycerides (r=0.627, P=0.039), high sensitivity C-reactive protein (r=0.608, P=0.047) and interleukin (IL)-6 (r=0.604, P=0.049). Linear regression analysis revealed that body weight (β=0.416, P=0.001), IL-6 (β=0.284, P=0.009), triglycerides (β=0.262, P=0.011) and total cholesterol (β=0.388, P=0.001) were independent factors related to liver fat content. In conclusion, dapagliflozin can reduce liver fat in patients with T2DM and NAFLD. The reduction in liver fat is associated with improvement of metabolic parameters and inflammatory cytokines.

Introduction

As a common metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) is commonly observed in patients with type 2 diabetes mellitus (T2DM). According to studies, NAFLD is present in >60% of patients with diabetes (1,2). NAFLD can progress to cirrhosis and hepatocellular carcinoma. Currently, effective treatments for NFALD remain elusive. For patients with T2DM and NAFLD, hypoglycemic medications that can go beyond decreasing blood glucose and alleviate hepatic steatosis would be a better option.

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are anti-diabetic drugs that suppress glucose reabsorption in the kidney and increase urinary glucose excretion to lower the blood sugar level. Studies have shown that some SGLT2i can reduce liver fat deposition (3-5), and different SGLT2i have varying effects on NAFLD (6). Dapagliflozin, an SGLT2i, can effectively decrease blood glucose in diabetic patients (7), and is also beneficial in improving body weight, lipid profiles, blood pressure and uric acid excretion (8-10). Dapagliflozin has been shown to reduce renal endpoint events and cardiovascular mortality (11,12). The effect of dapagliflozin on NAFLD in patients with T2DM is uncertain.

The present study evaluated the effect of dapagliflozin treatment on liver fat content using quantitative computed tomography (QCT) in patients with T2DM and NAFLD. The factors associated with change in liver fat content were analyzed by correlation analysis and linear regression. The present study aimed to provide a new therapeutic measure for NAFLD.

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Abbreviations: $HbA1_C$, glycated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FIB-4, fibrosis-4; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase

Key words: dapagliflozin, liver fat, type 2 diabetes mellitus, non-alcoholic fatty liver disease, inflammatory cytokines

Patients and methods

Study design. The present study was a single-site, retrospective study. Patients with T2DM and NFALD who were treated with dapagliflozin at Beijing Aerospace General Hospital (Beijing, China) between June 2022 and December 2022 were included in the study. The inclusion criteria were as follows: i) Age between 20 and 59 years; ii) T2DM with poor glucose control before dapagliflozin treatment; iii) patients with NAFLD and without the use of any liver-protecting drugs before treatment; and iv) patients receiving dapagliflozin treatment for ≥20 weeks. The exclusion criteria were as follows: i) Patients with alcoholic liver diseases, chronic viral hepatitis, autoimmune hepatitis or other liver diseases; ii) renal dysfunction, heart failure or other organ dysfunction; iii) diabetic ketoacidosis; and iv) patients with malignant tumors. The diagnosis of T2DM was made according to the American Diabetes Association standard (13). NAFLD was diagnosed by abdominal ultrasonography and/or CT (14).

Data collection. The following clinical data were collected at baseline and after 20 weeks of treatment: i) Characteristic parameters: Age, sex, weight, body mass index (BMI) and blood pressure; ii) laboratory parameters: Blood cell counts, glycated hemoglobin ($HbA1_C$), fasting plasma glucose, fasting insulin, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), creatinine and uric acid levels, estimated glomerular filtration rate (eGFR), homocysteine, blood calcium, blood phosphorus and 25-hydroxyvitamin D [25(OH)D] levels, urine microalbumin-to-creatinine ratio, and high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) levels. The index of homeostasis model assessment-insulin resistance (HOMA-IR) was used to evaluate insulin resistance, and was calculated as HOMA-IR=plasma glucose x fasting insulin/22.5. The homeostatic model assessment of β-cell function (HOMA-β) was used to evaluate β-cell function, and was calculated as HOMA-β=20 x fasting insulin/(plasma glucose-3.5). The fibrosis 4 index (FIB-4) was used to assess liver fibrosis, and was calculated as follows: FIB-4=[age (years) x AST (U/l)]/[platelet count (10^9/l)] x ALT (U/l)$^{1/2}$].

Evaluation of liver fat content and abdominal fat. The patients underwent non-contrast abdominal CT scanning (GE Healthcare) at baseline and after 20 weeks of treatment. Contiguous images with a 5-mm slice thickness were used for data analysis. Patients underwent abdominal QCT examination (GE Bright Speed 16-slice CT; GE Healthcare), which was performed by a skilled imaging technician at Beijing Aerospace General Hospital, in order to evaluate liver fat content. The scanned data were uploaded to the QCT analysis workstation (Mindways' Model4 QCT measurement system), and liver fat content was measured according to the conversion formula provided by Mindways software. The area of visceral adipose tissue and subcutaneous adipose tissue was also analyzed by Mindways software.

Table I. Clinical characteristics of patients in the present study.

Characteristics	Values
Age, years	45.8±2.2
Male sex	21 (60.0)
Body weight, kg	80.5±2.4
BMI, kg/m^2	29.0±0.8
Duration of diabetes, years	6.6±1.4
Hypertension	18 (51.4)
Dyslipidemia	27 (77.1)
Hyperuricemia	11 (31.4)

Data are expressed as the mean ± SD or number (%). BMI, body mass index.

Statistical analysis. Quantitative variables are presented as the mean ± standard deviation for normal distribution, or the median (lower quartile-upper quartile) for skewed distribution. Categorical variables are summarized as frequencies and percentages. The differences between pre-treatment and post-treatment parameters were analyzed by the paired t-test for quantitative variables with normal distribution and the Wilcoxon signed-rank test for non-normally distributed variables. The correlations between liver fat and clinical parameters were determined using Pearson's correlation and linear regression analyses. Statistical analyses were performed using SPSS 20.0 software (IBM Corp.) and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 35 patients were included in the final analysis. The mean age of the patients was 45.8±2.2 years (range, 35-55 years), with a mean BMI of 29.0±0.8 kg/m^2, and 21 patients (60.0%) were male. The mean duration of diabetes was 6.6±1.4 years. Among the patients, 18 (51.4%) had hypertension, 27 (77.1%) had dyslipidemia and 11 patients (31.4%) had hyperuricemia (Table I).

Changes in diabetes and metabolic parameters after treatment. After 20 weeks of dapagliflozin treatment, the diabetes parameters improved. There was a significant decrease in plasma glucose from 11.5±0.6 to 7.0±0.3 mmol/l ($P<0.001$), and $HbA1_C$ decreased from 8.8±0.3 to 7.2±0.2% ($P<0.001$). Insulin resistance was improved, and HOMA-IR decreased from 5.6±0.7 to 2.6±0.4 ($P<0.001$). β-cell function recovered, and HOMA-β increased from 32.8±4.6 to 61.1±11.4 ($P=0.007$). Metabolic parameters were also improved. After treatment, TG, TC, LDL-C and uric acid levels were also significantly decreased (all $P<0.001$) (Table II). Pro-inflammatory cytokine levels of hsCRP and IL-6 declined after treatment ($P=0.043$ and $P=0.027$, respectively).

Effect of dapagliflozin on liver fat content and body fat indices. QCT revealed a significant decrease in liver fat content after 20 weeks of dapagliflozin treatment. The liver

Table II. Change of diabetes parameters after dapagliflozin treatment.

Parameters	Baseline	Week 20	t/Z value	P-value
FPG, mmol/l	11.5±0.6	7.0±0.3	8.429	<0.001
$HbA1_C$, %	8.8±0.3	7.2±0.2	6.492	<0.001
HOMA-β	32.8±4.6	61.1±11.4	3.103	0.007
HOMA-IR	5.6±0.7	2.6±0.4	6.317	<0.001
TG, mmol/l	1.75 (1.17-3.05)	1.34 (0.94-1.79)	-4.361	<0.001
TC, mmol/l	4.5±0.2	3.9±0.1	4.583	<0.001
LDL-C, mmol/l	2.8±0.1	2.2±0.1	4.614	<0.001
HDL-C, mmol/l	1.2±0.1	1.2±0.1	0.509	0.614
Uric acid, μmol/l	370.4±21.1	301.5±14.6	4.137	<0.001
hsCRP, mg/l	9.6±3.4	3.5±0.9	2.180	0.043
IL-6, pg/ml	8.4±1.4	5.5±0.9	2.600	0.027

Data are presented as the mean ± SD, or median (lower quartile-upper quartile). FPG, fasting plasma glucose; $HbA1_C$, glycated hemoglobin; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.

Table III. Changes of liver fat content and liver function after dapagliflozin treatment.

Parameter	Baseline	Week 20	t value	P-value
Liver fat content, %	16.1±2.2	11.2±1.3	5.319	<0.001
ALT, U/l	30.3±3.5	20.2±1.7	4.116	<0.001
AST, U/l	24.0±2.1	19.0±0.9	2.911	0.007
GGT, mmol/l	36.8±8.2	23.1±2.4	2.176	0.038
FIB-4 index	1.22±0.14	1.15±0.13	1.402	0.174

Data are presented as the mean ± SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; FIB-4, fibrosis-4.

fat content in patients reduced from 16.1±2.2% at baseline to 11.2±1.3% post-treatment (P<0.001). In addition, liver function also improved after treatment, and the levels of ALT, AST and GGT were decreased (P<0.001, P=0.007 and P=0.038). Analysis showed that the FIB-4, an index associated with liver fibrosis, decreased from 1.22±0.14 to 1.15±0.13 after treatment, but the difference was not statistically significant (P=0.174) (Table III).

The changes in body fat indices were also evaluated. The patients exhibited a significant reduction in body weight (from 80.5±2.4 to 76.8±2.8 kg; P=0.002) and BMI (from 29.0±0.8 to 28.0±0.8 kg/m^2; P<0.001). Abdominal CT revealed that the abdominal fat area decreased from 416.8±26.6 to 363.6±21.7 cm^2 after treatment (P<0.001). The changes in the visceral and subcutaneous fat area were also assessed after treatment, and the analysis showed that the amount of visceral fat and subcutaneous fat significantly decreased. The visceral fat area declined from 240.6±18.7 to 208.3±17.4 cm^2 (P<0.001), and the subcutaneous fat area decreased from 176.2±20.5 to 155.3±15.4 cm^2 (P=0.015) (Table IV). Furthermore, there was a more significant reduction in the visceral fat area than the subcutaneous fat area (13.4 vs. 11.9%).

Factors associated with the change in liver fat content. Pearson's correlation analysis was performed. It was found that the reduction in liver fat content was positively correlated with the reduction in body weight (r=0.642, P=0.033), HOMA-IR (r=0.670, P=0.048), TG (r=0.627, P=0.039), hsCRP (r=0.608, P=0.047) and IL-6 (r=0.604, P=0.049) (Table V).

Linear regression analysis revealed that body weight (β=0.416, P=0.001), IL-6 (β=0.284, P=0.009), TG (β=0.262, P=0.011) and TC (β=0.388, P=0.001) were independent factors associated with liver fat content (Table VI).

Adverse events. None of the patients in this study experienced hypoglycemia. A single patient developed an asymptomatic urinary tract infection, but did not discontinue the medication and improved after treatment. No other adverse events were reported, and no patients withdrew from the trial. The blood calcium, blood phosphate and 25(OH)D levels, eGFR and bone

Table IV. Changes body fat indices after treatment.

Parameter	Baseline	Week 20	t value	P-value
Body weight, kg	80.5±2.4	76.8±2.8	3.630	0.002
BMI, kg/m^2	29.0±0.8	28.0±0.8	7.391	<0.001
Abdominal fat area, cm^2	416.8±26.6	363.6±21.7	5.900	<0.001
Viscera fat area, cm^2	240.6±18.7	208.3±17.4	8.568	<0.001
Subcutaneous fat area	176.2±20.5	155.3±15.4	2.943	0.015

Data are presented as the mean ± SD. BMI, body mass index.

Table V. Correlation between liver fat content change and clinical parameters changes according to Pearson's correlation analysis.

	Bivariate correlation	
Reduction of liver fat content	r	P-value
Reduction of body weight	0.642	0.033
Reduction of HOMA-IR	0.670	0.048
Reduction of TG	0.627	0.039
Reduction of hsCRP	0.608	0.047
Reduction of IL-6	0.604	0.049

HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglyceride; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.

mineral density showed no significant changes after treatment (P>0.05) (Table VII).

Discussion

T2DM and NAFLD are closely associated. T2DM can aggravate the progression of NAFLD and increase the risk of cirrhosis (15), and NAFLD can accelerate the progression of diabetes-related organ damage. However, there is insufficient attention paid to NAFLD treatment, especially in young patients. The correct treatment can prevent the progression of NAFLD to end-stage liver disease. For patients with T2DM and NAFLD, anti-diabetic medications that target both glycemic control and NAFLD are preferred. Previous studies have shown that dapagliflozin not only effectively controls blood glucose, but can also reduce weight and improve blood lipids (8,9). Dapagliflozin may be helpful in alleviating NAFLD. The Effect-II study found that dapagliflozin monotherapy could improve the indicators of liver injury, but that it did not reduce the liver fat content in patients with T2DM (16). Another study found that dapagliflozin treatment could reduce liver and visceral fat content (17).

The present results demonstrated that 20 weeks of dapagliflozin treatment reduced hepatic steatosis in patients with T2DM. Analysis showed that liver fat content decreased by 30% after treatment. Liver function also improved, and ALT, AST and GGT levels declined. In addition, visceral and subcutaneous fat areas also significantly decreased compared with those before treatment. The decrease in visceral fat area was more significant than the decrease in subcutaneous fat area.

A previous study investigated the effects of dapagliflozin and dipeptidyl peptidase-4 inhibitor (DPP4i) on liver enzymes in patients with T2DM and NAFLD who had elevated ALT levels. It was found that dapagliflozin treatment reduced the ALT level compared with DPP4i, and the difference remained statistically significant after adjusting for confounding factors such as weight loss (18). Another study found that SGLT2i treatment for 24 weeks decreased liver and visceral fat content in patients with T2DM and NAFLD, and the decrease in liver fat was positively correlated with changes in weight and HOMA-IR (19). A randomized study also found that 12 weeks of dapagliflozin treatment reduced liver and visceral fat content in patients with T2DM and NAFLD (20). Research by Kinoshita *et al* (21) showed that dapagliflozin had comparable effectiveness to pioglitazone in terms of improving NAFLD, and that it was superior to metformin. The present study found that 20 weeks of dapagliflozin treatment reduced liver and visceral fat content, which is consistent with previous studies, and QCT was used to determine the decrease in liver fat content after dapagliflozin treatment.

There are no head-to-head studies comparing the effects of various SGLT2i on NAFLD. RCT studies showed that SGLT2i treatment (particularly dapagliflozin or empagliflozin) was associated with lower liver fat content. It was found that empagliflozin reduced liver fat and improved ALT levels compared with the control group in two RCT studies (22,23). Another study showed that treatment with canagliflozin for 12 months in 20 patients with T2DM and NAFLD reduced the liver fat content and liver enzyme levels, but did not improve the FIB-4 score (24). In addition, Sumida *et al* (25) showed that luseogliflozin significantly reduced hepatic fat content in patients with T2DM and NAFLD (25). Ito *et al* (26) found that ipragliflozin was equivalent to pioglitazone in improving hepatic fat content in patients with T2DM (26). Overall, we speculate that use of SGLT2i may have a similar effect to improve NAFLD.

In the present study, the factors associated with the changes in liver fat after dapagliflozin treatment were further investigated. It was demonstrated that the decrease in liver fat content after dapagliflozin treatment was positively correlated with the changes in body weight, HOMA-IR, and TG, hsCRP and IL-6 levels. Multivariate regression analysis showed that

Table VI. Linear regression analysis on relationship between liver fat content and clinical parameters.

	Univariate analysis		Multiple linear regression	
Liver fat content, %	β	P-value	β	P-value
Body weight, kg	0.836	<0.001	0.416	0.001
BMI, kg/m^2	0.761	<0.001	NE	
HOMA-IR	0.698	0.001	NE	
TG, mmol/l	0.538	0.010	0.262	0.011
TC, mmol/l	0.727	<0.001	0.388	0.001
LDL-C, mmol/l	0.693	<0.001	NE	
hsCRP, mg/l	0.719	<0.001	NE	
IL-6, pg/ml	0.744	<0.001	0.284	0.009

β, regression coefficient; NE, does not enter the final model; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.

Table VII. Changes of indicators associated with side-effects after treatment.

Parameter	Baseline	Week 20	t/Z value	P-value
eGFR, ml/min/1.73 m^2	102.2±5.1	101.8±4.8	0.131	0.897
U-ACR, mg/gCr	19.20 (4.40-154.80)	12.20 (4.20-71.00)	-2.659	0.008
HCY, μmol/l	13.7±1.4	12.2±1.1	2.122	0.048
Calcium, mmol/l	2.30±0.02	2.27±0.03	0.953	0.349
Phosphate, mmol/l	1.26±0.03	1.20±0.03	1.925	0.064
25(OH)D, nmol/l	38.8±3.9	41.9±4.3	-0.880	0.391
Bone mineral density	133.3±11.4	135.1±10.3	-0.905	0.387

Data are presented as the mean ± SD, or median (lower quartile-upper quartile). eGFR, estimated glomerular filtration rate; U-ACR, urinary albumin/creatinine ratio; HCY, homocysteine; 25(OH)D, 25-hydroxyvitamin D.

body weight, and IL-6, TG and TC levels were independent factors for liver fat content.

The specific mechanism of NAFLD improvement after dapagliflozin treatment remains unclear. Improvement in body fat, dyslipidemia, insulin resistance and inflammation may contribute to the efficacy of dapagliflozin. In animal studies, dapagliflozin has ameliorated hepatic steatosis via a reduction in *de novo* lipogenesis (27), an increase in fatty acid oxidation and the induction of autophagy via the AMPK-mTOR pathway (28). Decreased liver inflammation (29,30) and increased insulin sensitivity have also been demonstrated as possible mechanisms in preclinical studies (27).

Inflammation-induced oxidative stress plays an essential role in the pathogenesis of NAFLD. Bellanti *et al* (31) found that SGLT2i treatment for 6 months in patients with T2DM and NAFLD reduced the levels of pro-inflammatory cytokines, such as IL-1β and IL-6, and oxidative stress. Another study showed that the 52 weeks of canagliflozin treatment increased the serum adiponectin level and reduced the serum IL-6 level (32). It has been well documented that obesity and inflammation-induced oxidative stress are closely related. Obesity induces the release of inflammatory cytokines and oxidative substances, such as reactive oxygen species or oxidized-LDL (33). Therefore, weight loss can improve the chronic inflammatory and oxidative stress state. Minciuna *et al* (34) found that diet-induced weight loss reduced inflammatory markers and oxidative stress. In the present study, the reduction in inflammatory cytokines by dapagliflozin may be due to its weight loss effect. The reduction in inflammatory cytokines indicated an improvement in the chronic inflammatory stage, which might be related to the improvement in NAFLD during dapagliflozin treatment. The present study found that the reduction of liver fat content was positively correlated with the reduction of hsCRP and IL-6. The levels of inflammatory marker hsCRP and inflammatory cytokine IL-6 were detected in the study; however, other inflammatory cytokines associated with NAFLD, such as TNF-α, IL-1β and reactive oxygen species, will be determined in future studies.

There is still controversy regarding the effect of SGLT2i on liver fibrosis. The study by Shimizu *et al* (35) showed that dapagliflozin treatment resulted in a reduction in visceral fat and hepatic steatosis in patients with T2DM and NAFLD, and could also lower liver stiffness and reduce liver fibrosis (35).

Akuta *et al* (36) also reported that 24 weeks of canagliflozin treatment could improve liver histology and reduce liver fibrosis in patients with T2DM and NAFLD (36). However, in a study of 20 patients with T2DM and NAFLD treated with canagliflozin for 12 months, it was shown that canagliflozin reduced liver fat content and liver enzyme levels, but did not improve the FIB-4 score (24). In the present study, liver fibrosis was evaluated using the FIB-4 index, which showed a downward trend after 20 weeks of dapagliflozin treatment, but without statistical significance. This may have been due to the small sample size and short study period.

In the present study, following 20 weeks of dapagliflozin treatment, the blood glucose level significantly decreased, and insulin resistance and β-cell function improved. In addition, there were significant improvements in TG, uric acid and urinary microalbumin levels after treatment. These findings indicated that dapagliflozin treatment may improve metabolic syndrome, diabetic nephropathy and macrovascular complications, which is consistent with previous reports (37,38). Furthermore, dapagliflozin treatment had no significant impact on the markers of bone metabolism, such as calcium, phosphate and 25(OH)D levels, and bone density, similar to the results of a previous study (39).

There are some limitations to the present study. Firstly, although regression and correlation analyses were performed to control for confounding factors, the retrospective nature of the analysis is still a weakness of the study. The present conclusions should be further evaluated by prospective studies. Secondly, the sample size of the study was not large, and increasing the sample size would make the results more robust. Thirdly, the evaluation of liver histology by invasive biopsy was not conducted.

In conclusion, dapagliflozin reduced liver fat content in patients with T2DM and NAFLD, in addition to improving plasma glucose level. Visceral and subcutaneous fat areas were also significantly decreased. The improvement in NAFLD may be related to the improvement in metabolic parameters and inflammatory cytokines.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LW designed the study and revised the article. XG collected and analyzed the data, and wrote the manuscript. CZ and WZ participated in the statistical analysis and drafting of the initial manuscript. XG and LW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments, and was approved by the Ethics Committee of Beijing Aerospace General Hospital (approval no. 2020-clinical-21). The requirement for informed consent was not applicable due to the retrospective design of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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