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Original Research Article

Therapeutic outcome of saroglitazar, a peroxisome proliferator activated receptor α/γ agonist in diabetic and non-diabetic metabolic dysfunction associated steatotic liver disease

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ABSTRACT

Background: Metabolic dysfunction associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease (CLD)and its consequences throughout the world, more so in developed countries. It is more concerning in view of the lack of a definitive treatment. Aside from lifestyle changes and vitamin E, we are still looking for a drug that can improve outcome in this group of patients.
Methods: Authors evaluated the safety and effectiveness of saroglitazar in MASLD/MASH patients in this 48-week prospective observational study, with the primary goal of evaluating the therapeutic outcome of saroglitazar on the NAFLD fibrosis score (NFS) in both diabetics and non-diabetics. After receiving written informed consent from each patient, a total of 292 patients who met the inclusion criteria were enrolled. However, only 257 individuals completed the study. Eligible patients were put on saroglitazar 4 mg per day for 24 weeks and followed on an OPD basis for 48 weeks with special emphasis on NFS, BMI, HbA1c, lipid levels, and liver biochemistry. Authors observed a male dominance (61.9%), a significant improvement in lipid profile, liver biochemistry, HbA1c, NFS, and liver stiffness measurement (LSM), and also an improvement in BMI though not statistically significant. Authors did not observe any significant drug related adverse events during the treatment with saroglitazar.
Conclusion: In our study, saroglitazar at a dose of 4 mg per day for 24 weeks resulted in marked improvements in liver biochemistry, lipid profile, HbA1c, NFS, and LSM, in patients of MASLD/MASH in both diabetics and non-diabetics.

Keywords: Metabolic dysfunction, Associated steatotic liver disease, NFS score, Metabolic syndrome, Liver fibrosis

INTRODUCTION

Metabolic dysfunction associated steatotic liver disease and metabolic dysfunction associated steatohepatitis (MASLD/MASH) are considered as the most common cause of chronic liver disease in both developed as well as developing countries. The entity includes patients with simple steatosis and those with steatohepatitis (MASH). MASH is an advanced stage of MASLD and has a higher risk of progression to liver cirrhosis or hepatocellular carcinoma.[1] MASLD/MASH has been recognized as one of the leading causes of cirrhosis in adults in the United States and MASLD related cirrhosis being currently the second indication for liver transplant over there.[1-4]

Clinically, MASLD patients tend to be obese, with insulin resistance and/or type 2 diabetes, dyslipidemia, hypertriglyceridemia and hypertension, which are all risk factors for cardiovascular diseases (CVDs).[4,5] In fact, prevalence of MASLD in patients with components of the metabolic syndrome is quite high, and has been reported in over 76% of type 2 diabetics.[6-8] Furthermore, over 90% of severely obese patients undergoing bariatric surgery have MASLD.[9-11] Given the common risk factors between MASLD and CVDs, cardiac-related death is one of the leading causes of death in MASLD patients.[12,13] It is alarming that the prevalence of MASLD worldwide is on the rise and the same in the United States is reported to be between 10% and 30%, with similar rates reported from Europe and Asia.[4,14]

A key issue in the diagnosis and management of MASLD is the distinction between simple steatosis and MASH, as the former is considered an indolent condition while the latter is a progressive form with increased morbidity and mortality.[15] The diagnosis of MASLD requires evidence of hepatic steatosis on imaging or histology, when other causes of liver disease and steatosis have been excluded. MASLD is usually asymptomatic, so diagnosis usually follows the incidental findings of abnormal liver enzymes or steatosis on imaging.[15]

Several scoring systems have been described for adults. NAFLD fibrosis score (NFS) consisting of six variables (Age, BMI, AST/ALT ratio, hyperglycemia, platelet count, and albumin), can reliably predict advanced fibrosis. A low cut off point (score <-1.455) signifies the absence of advanced fibrosis, whereas a high cut off point (score >0.676) signifies advanced fibrosis. It has been concluded that the MASLD fibrosis sore can be utilized as a triaging tool for optimizing liver biopsy yield in terms of identifying or excluding advanced fibrosis.[16]

In recent years, PPAR agonists have gained interest mainly because of their affinity for binding to multiple isoforms. PPARs are nuclear transcription factors that have complex biological effects, resulting from the trans-activation or trans-repression of dozens of genes that play an important role in glucose and lipid homeostasis. A new dual agonist, saroglitazar has shown promising results in both experimental models and real-world evidence. Its dual PPAR activity causes a synergistic effect and ameliorates the unwanted side effects caused by the alpha and gamma isoforms individually. In this study, we evaluated the effectiveness of saroglitazar in both diabetic and non-diabetic MASLD patients.

Aims and objectives

The primary objective of this study was to evaluate the outcome of saroglitazar on the NAFLD fibrosis score (NFS) in patients with MASLD/MASH. The secondary objective of this study was to evaluate the effects of saroglitazar on lipid (TG, HDL-C, LDL-C, total cholesterol) levels, body mass index (BMI), glucose parameters (HbA1c) and liver biochemistry.

METHODS

This was an observational, prospective, single center, open label, hospital-based study conducted in department of Medicine and Gastroenterology, Government Medical College Srinagar, Jammu and Kashmir over a period of one year commencing from November 2021, to evaluate the safety and effectiveness of saroglitazar in patients with MASLD/ MASH. The study was approved by the Institutional Ethical Committee of Govt. Medical College, Srinagar (vide endorsement no. 207/ETH/GMC/ICM, dated 28-10-2021).

Study population

A total of 292 patients who met the inclusion criteria and showed willingness to comply with all protocol-required evaluations were enrolled after obtaining their informed consent.

Inclusion criteria

Patients aged 18 and above, including both non-diabetics and diabetics (the cut off for diabetes was HbA1c >6.5% or FBG>126 mg/dl), with an established diagnosis of MASLD or MASH by imaging (USG, CT, MRI), and triglycerides greater than 150 mg/dl, were included in the study.

Exclusion criteria

Consumption of >3 units of alcohol per day (>21 units per week) in case of males and >2 units of alcohol per day (>14 units per week) in case of females, documented liver disease such as chronic hepatitis C (HCV) infection, hepatitis B, hemochromatosis, pregnant or lactating females, patients receiving feno-fibrate therapy, history of unstable angina, acute myocardial infarction in the preceding 3 months, and heart failure classified as New York Heart Association class III-IV.

Study design

In this prospective study, all the patients with an established diagnosis of MASLD/MASH were assessed as per the inclusion and exclusion criteria mentioned above for their inclusion in the study. Patients underwent a thorough general physical examination and necessary laboratory and radiological investigations. Eligible patients who met the inclusion criteria received treatment with saroglitazar 4 mg once daily for continuous 24 weeks in addition to life style modification and proper dietary advice. The patients were followed on an OPD basis for a total duration of 48 weeks. NAFLD fibrosis score (NFS), body mass index (BMI) kg/m^2, HbA1c, lipid levels and liver biochemical tests were measured at the time of screening and after each follow-up as per the flow chart. Routine physical examination was carried out at every follow-up visit and at the end of the study. Adverse events observed or volunteered, if any, were recorded and

accessed. All the patients were prescribed saroglitazar 4 mg once daily in addition to their prescription medicine for hypertension, diabetes, and dyslipidemia (if any).

Statistical methods

The recorded data were compiled and entered in a spreadsheet (Microsoft Excel) and then exported to the data editor in SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. To evaluate the effects of saroglitazar on various parameters, repeated measures ANOVA was employed. A p value <0.05 was considered statistically significant.

RESULTS

In this study, a total of 292 patients were enrolled, out of which 257 completed treatment (Table 1) and follow-up, however, Fibro scan data were available for 60 patients only. Majority (92%) of our study population was between 40-69 years of age with 38% belonging to 50-59 years followed by 28% to 60-69 years and 26% to 40-49 years age group and the mean age observed was 53.9±9.73 years. Our study showed a male predominance, with 159 (61.9%) males and 98 (38.1%) females.

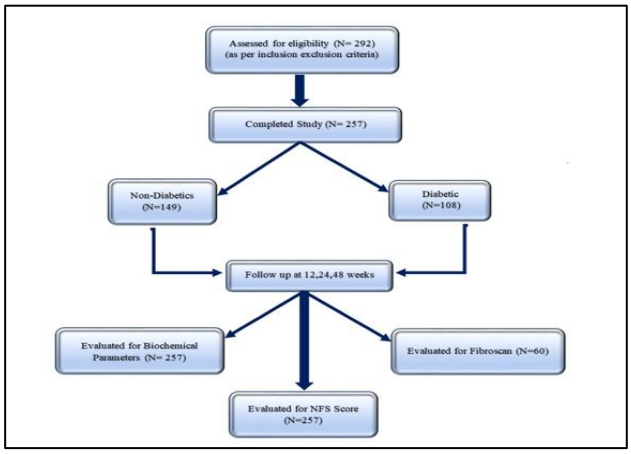

Figure 1: Study design.

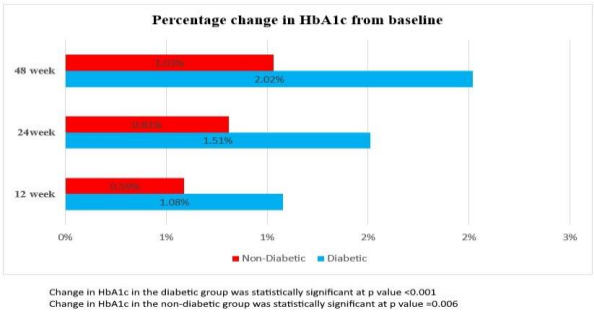

Figure 2: Percentage change in HbA1c from baseline in diabetic and non- diabetic MASLD patients.

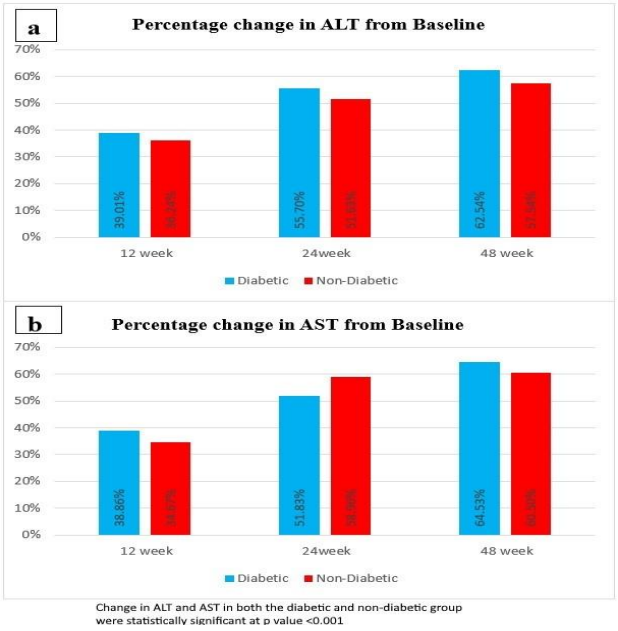

Figure 3 (a and b): Percentage change in AST/ALT from baseline in diabetic and non- diabetic MASLD patients.

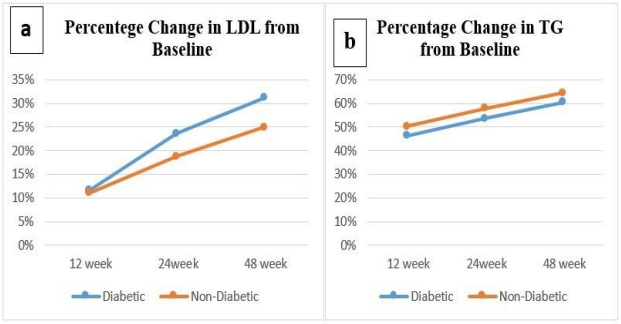

Figure 4: Percentage change in a) LDL b) TG from baseline in diabetic and non- diabetic MASLD patients.

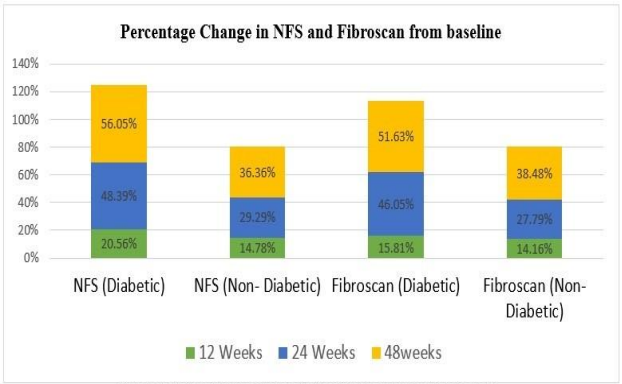

Figure 5: Percentage change in NFS and fibro scan following saroglitazar treatment in diabetic and non-diabetic patients.

Table 2 compares the patient baseline and follow up characteristics in both diabetic and non-diabetic patients. The parameters include NFS, LSM, AST, ALT, TG, TC, LDL, HDL, and HbA1c values, along with the percentage change. It depicts the change in different parameters from the baseline to six months of treatment with saroglitazar.

Table 1: Demographic characteristics of studied subjects.

Gender	Frequency	Percent	
Male	159	61.9	**Mean Age±SD (years) 53.9±9.73**
Female	98	38.1	
Diabetic status			**Mean baseline BMI±SD(Kg/m^2)**
Diabetic	108	42	29.14
Non-diabetic	149	58	25.47

Male: Female Ratio=1.6:1, Diabetic: Non diabetic Ratio=1:1.37

Table 2: Baseline and 6 months follow up for various parameters (n=257).

	Patient category	Baseline	6 months	Absolute % change at 6 months	P value
HbA1c	Diabetic	9.23	7.18	2.02	<0.001*
(%)	Non-diabetic	55.26	4.59	1.03	0.006*
HDL-C (mg/dl)	Diabetic	35.61	41.65	-16.96	<0.001*
	Non-diabetic	37.24	41.82	-12.3	<0.001*
LDL-C (mg/dl)	Diabetic	135.42	93.15	31.21	<0.001*
	Non-diabetic	112.61	84.57	24.9	<0.001*
TC (mg/dl)	Diabetic	202.63	151.72	25.12	<0.001*
	Non-diabetic	219.46	153.18	30.2	<0.001*
TG (mg/dl)	Diabetic	469.41	185.09	60.57	<0.001*
	Non-diabetic	490.71	175.03	64.33	<0.001*
AST (IU/dl)	Diabetic	86.05	30.52	64.53	<0.001*
	Non-diabetic	81.46	32.18	60.5	<0.001*
ALT (IU/dl)	Diabetic	80.54	30.17	62.54	<0.001*
	Non-diabetic	71.58	30.39	57.54	<0.001*
LSM (Kpa)	Diabetic	15.43	9.82	36.36	<0.001*
	Non-diabetic	14.97	9.21	38.48	<0.001*
NFS	Diabetic	2.48	1.09	56.05	<0.001*
	Non-diabetic	2.15	1.04	51.63	<0.001*

* p value <0.05 is significant

DISCUSSION

MASLD and MASH are multifaceted conditions, and the ideal drug for managing these conditions is expected to display beneficial effects on insulin resistance, steatosis, inflammation, oxidative stress, mitochondrial dysfunction, and fibrosis. Since, PPAR-α and PPAR-γ receptors are involved in regulation of all these attributes, it is not surprising that saroglitazar, a dual PPAR agonist showed an overall improvement in NFS score and fibro scan. The major biochemical event in MASLD is the accumulation of triglycerides in hepatocytes and PPARs are key regulators of lipid homoeostasis.[17,18] PPAR-α expression in the liver is primarily observed in hepatocytes, where its activation is expected to prevent steatosis and steatohepatitis by inhibiting intra-hepatic lipid and lipo-peroxide-accumulation.[19,20] On the other hand, PPAR-γ is predominantly observed in adipocytes, where its activation increases insulin sensitivity and thereby decreasing fatty acid (FA) flux to the liver.[21] PPAR-γ agonists (pioglitazone, rosiglitazone) showed some benefits with their anti-fibrotic properties but because of their side effects like weight gain, risk of bladder cancer and cardiac events went into disrepute. Obeticholic acid phase 3 data have shown promising results but requires more data on the safety aspects.[22] saroglitazar, a dual α/γ agonist with predominant PPAR-α activity, has shown improvement in biopsy proven MASH patients. The effects of saroglitazar appear better than pure PPAR-α agonists (fenofibrate) and PPAR-γ agonist (pioglitazone).

In our study, no significant weight loss or weight gain was observed in patients (diabetics and non-diabetics) after the completion of the study, although there was a small reduction in BMI in both diabetic and non-diabetic patients, but it was statistically insignificant. This finding is in contrast with the results of Bhosle et al, who conducted a study on 40 patients with derangement of sugars and lipids and found that saroglitazar reduced the weight of the study participants within twenty-four weeks of treatment.[23] The mean baseline weight (kg) in their study was 74.02±3.66, which decreased by twenty-four weeks of follow-up to 73.9±3.92.

As far as HbA1c is concerned, we did observe a significant change in this parameter in both diabetic and non-diabetic patients after 48 weeks (Table 2). Our findings are comparable to those of Shetty et al who had conducted an observational study on saroglitazar in 2804 patients of diabetes with dyslipidemia.[24] They had observed a significant decrease in HbA1c from baseline values of 8.3±1.3% to 7.40±0.9 in 12 weeks.

In a similar study, Bhosle et al had studied 40 patients with pre-diabetes and dyslipidemia, who they had given saroglitazar for 24 weeks and a significant reduction was seen in HbA1c (%) levels at a follow up of 24 weeks which is evident by comparing the baseline values of 6.3±0.16 with 5.5±0.30 at 24 weeks.[23] Addition of saroglitazar to anti-diabetic medications had led to a significant reduction (0.9% absolute reduction) in HbA1c and a significant improvement in fasting as well as postprandial plasma glucose levels.[23]

Though liver enzymes are usually misinterpreted in the diagnosis of MASLD, but there is a high probability of having normal transaminase levels in MASLD patients (up to 50% may have a normal transaminase level). But because of its availability, it is used in most of the clinical trials. In our study, saroglitazar significantly reduced ALT and AST in diabetic and non-diabetic patients, as shown in Table 2. In a randomized controlled phase 2 clinical trial where efficacy and safety of saroglitazar in patients with MASLD/MASH were evaluated, saroglitazar 4 mg had led to a significant improvement in liver function test, insulin resistance, and atherogenic lipids in participants with MASLD/MASH.[25] They had observed that saroglitazar 4 mg significantly reduced ALT (baseline: 64.1±6.2 IU/l) to week 24 (28.7±3.2 IU/l) in MASLD patients with diabetic dyslipidemia.[31] Also, Joshi et al, conducted a single center, single arm, prospective, open-label study involving 221 patients with diabetic dyslipidemia who were diagnosed with MASLD using transient elastography (Fibroscan™).[26] They had found that saroglitazar led to a significant reduction in ALT (baseline: 89.0IU/l) to week 24 (21.0 IU/l) in diabetic patients.

In our study, saroglitazar showed significant beneficial effects on the lipid profile. Triglycerides, LDL, HDL, and TC were significantly reduced after 48 weeks of treatment in both diabetic and non-diabetic groups (Table 2). Chatterjee et al had conducted a 58-weeks observational study using saroglitazar in 158 patients of diabetes with dyslipidemia and could find significant reduction in TG (baseline: 319.9±178.8 mg/dl) to week 58 (174.0±113.6 mg/dl).[27] Our results are also consistent with the study findings of Bhosle et al who had studied 40 patients of pre-diabetes with dyslipidemia and observed a significant reduction in TG, TC, and LDL levels after 24 weeks of treatment with saroglitazar.[23]

Shetty et al and others had conducted an observational study using saroglitazar in 2804 patients with deranged sugars and lipids and had observed a significant reduction in LDL-C (mg/dl) in 2694 patients from baseline (139.5±42.16) to (112.4±30.83) after 3 months of follow-up.[24] Kaul et al studied the effects of saroglitazar on HDL-C using 104 patients with diabetes and dyslipidemia and observed that there was a significant increase in HDL-C, as was evident from the levels (baseline: 37.3±18.4 mg/dl and at week 24: 43.4±15.6 mg/dl) in the study population.[28] Similar results were further reiterated in a post-marketing study wherein at 3 months follow-up, the use of saroglitazar 4 mg in patients with diabetic dyslipidemia led to significant reductions in triglycerides (35.8%), LDL-C (16.4%), total cholesterol (19%), and non-HDL-C (23.4%).[24]

Non-invasive scoring system can be helpful in excluding the presence of significant fibrosis. In MASLD patients, we used NFS scoring to evaluate the effectiveness of saroglitazar and there was a statistically significant reduction in diabetic and non-diabetic patients with a p value of <0.05. We couldn't come across any study on saroglitazar with the NFS scoring system as an end point.

A non-invasive technique (fibro scan) is widely used in clinical practice because of its accuracy and reproducibility. In our study, we did fibro scan of 60 patients at baseline, 12 weeks, 24 weeks, and 48 weeks. Saroglitazar is effective in improving liver stiffness in a significant number of patients (Table 2). Using fibro scan, Joshi et al conducted a single center, single arm, prospective, open label study on 221 patients of diabetes and dyslipidemia and found a significant improvement in 39% (86/221) of their population on Saroglitazar.[26]

Another non-invasive modality is magnetic resonance imaging derived proton density fat fraction (MRI-PDFF), which precisely quantifies hepatic steatosis. Saroglitazar, a dual peroxisome proliferator activated receptor α/γ agonist, approved for diabetic dyslipidemia (DD), is potential therapeutic option for metabolic dysfunction associated steatotic liver disease (MASLD). A prospective, observational, real-world study aimed to determine efficacy and safety of Saroglitazar in patients with MASLD and DD was conducted wherein patients with DD and MASLD received Saroglitazar 4 mg once daily for 24 weeks.[29] Blood investigations, liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) using fibro scan were compared at baseline and 24 weeks. Out of 163 patients screened, 107 were included, and 101 completed 24 weeks treatment. The mean age was 50.4±12.3 years with 78.5% being males having mean body mass index of 28.8±4.2. After 24 weeks, alanine transaminase (ALT) reduced significantly from 94 (47–122) to 39 (31–49) (p<0.0001) and aspartate aminotransferase (AST) (U/l) from 89 (43–114) to 37 (30–47) (p<0.0001) and LSM (kPa) from 8.4 (7.1–9.3) to 7.5 (6.4–8.4) (p=0.0261). CAP, glycated hemoglobin and lipid parameters also improved significantly. On linear regression, there was significant association between percent change in ALT and AST with TG reduction after treatment (p=0.024 and 0.037 respectively). From this

study, it was concluded that Saroglitazar results in a significant improvement in transaminases, LSM, and CAP in MASLD patients with DD. but before recommending and expanding its use to all patients with MASLD/MASH, further case-control studies and more randomized control trial (RCT) results are required to supplement and support these observations.

Limitations of the study was that it was an observational study with a smaller number of patients. Fibroscan was not done in most of the patients. Non diabetics out numbered the diabetics, should have been equal in number. Only cases were studied, no controls studied. Lifestyle and diet changes should have been studied simultaneously which has an impact on outcome of all parameters.

CONCLUSION

Out of 292 patients who were enrolled, only 257 completed the study. Males out numbered females with a ratio of 1.6:1. Both diabetics and non-diabetics were studied with a ratio of 1:1.37. Predominant age group involved was 40-59 years, meaning that fatty liver is a disease of middle-aged people. Saroglitazar has no impact on body mass index (BMI) in both diabetics as well as non-diabetics. Saroglitazar significantly improved HbA1c%, ALT, AST, TG, LDL-C, HDL-C and total cholesterol levels. Saroglitazar significantly improved NAFLD fibrosis score (NFS) over a period of 48 weeks with 24 weeks of treatment. Saroglitazar regresses fibrosis significantly in both diabetics and non-diabetics.

So, to conclude our observations, metabolic dysfunction associated liver diseases metabolic associated steato hepatitis (MASLD/MASH) are leading causes of liver diseases and associated with high hepatic and extra-hepatic morbidity and mortality. The ideal drug for fatty liver disease and metabolic syndrome is yet to be manufactured and marketed. Saroglitazar, a PPAR alpha/gamma receptor agonist has shown remarkable improvement in metabolic profile, including lipid profile, liver chemistry and liver stiffness of our studied patients. We suggest further studies involving more patients before recommending this molecule as first line treatment for MASLD/MASH.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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