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Assessment of Risk Factor for Development of Non-Alcoholic Fatty Liver Disease in Type 2 Diabetic Mellitus Patients of Raigarh Chhattisgarh

KEYWORDS: NAFLD, DM, BMI, SGOT, SGPT, HDLLDL

Dr. Harish Kumar Uraon
Assistant Professor Department of Biochemistry Late Shri Lakhiram Agrawal Memorial Medical College, Raigarh, Chhattisgarh, India

Dr. Onkar Kashyap
Assistant Professor Department of Biochemistry G. M. C. Rajnandgaon, India

Dr. Deba priya rath
Assistant Professor Department of Biochemistry, Pt. J. N. M. Medical College, Raipur

ABSTRACT

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common liver diseases. It is a histological spectrum of disease and includes the simple steatosis and NASH. NAFLD may progress to cirrhosis, liver failure, and hepatocellular carcinoma. NAFLD is strongly associated to the features of metabolic syndrome. The purpose of this study was to identify the risk factor for development of Non-Alcoholic Fatty Liver Disease in Type 2 diabetic mellitus patients.

Aims & Objective: To evaluate the various risk factor for development of NAFLD in Type2 diabetes mellitus patients.

Method: This study was done between May 2015 to June 2016 at the Department of Biochemistry, Late Shri Lakhiram Agrawal Memorial Medical College Associated KGH Raigarh CG. All patients attending the Medicine OPD & IPD for their blood pressure, Anthropometry, Biochemical parameters and Ultrasound abdomen was done. The data were analyzed using SPSS version 20. Descriptive statistics, correlation, regression and one way student's t-test were performed for data analysis.

Results: NAFLD was observed in 52% of patients who had greater BMI ($p < 0.001$), 94% of hypertension with frequency ($p<0.001$). Metabolic syndrome was more frequent in those with NAFLD ($p = 0.005$). The mean levels of Triglyceride, FBS, PPBS, HBA1C, SGOT, ALP, Urea, Creatinine, T. Bilirubin, D. Bilirubin, Triglyceride, HDL, LDL and VLDL were significantly higher in patients with NAFLD than those without NAFLD ($p<0.001$). The mean value of Creatinine and ALP had significant correlation with age ($p<0.01$). Urea, Creatinine, SGOT and HDL showed significant correlation with Hb ($p<0.01$).

Conclusion: There is higher prevalence of all the components of metabolic syndrome in cases of NAFLD. Its early detection will help in modifying the disease course, delaying complications and will also play a major role in preventive cardiology. Almost half of patients with DM2 were found to have NAFLD, and they have more elevated BMI, as well as higher levels of Triglyceride, FBS, PPBS, HBA1C, SGOT, ALP, Urea, Creatinine, T. Bilirubin, D. Bilirubin, Triglyceride, HDL, LDL and VLDL than subjects without NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered one of the most common liver diseases in the Western world affecting around one third of the general population and may be linked to conditions of insulin resistance (IR) such as type 2 *diabetes mellitus* (DM2), obesity, and dyslipidemia [1]. NAFLD is characterized by the accumulation of liver fat without the consumption of alcohol [2]. The definition of nonalcoholic fatty liver disease (NAFLD) requires that [3]. There is evidence of hepatic steatosis, either by imaging or by histology and there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders[4]. In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia. NAFLD is histologically further categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis [5]. Non-alcoholic fatty liver disease (NAFLD) is operationally defined as fatty liver (FL), i.e. an accumulation of lipids inside the hepatocytes exceeding 5% of the weight of the liver, without hepatitis B virus or hepatitis C virus infection and in the absence of 'excessive' ethanol intake [5,6]. The prevalence of NAFLD is rapidly increasing worldwide in parallel with the increase in obesity and type 2 diabetes. Obesity is a common and well documented risk factor for NAFLD. Both excessive BMI and visceral obesity are recognized risk factors for NAFLD. In patients with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90% and up to 5% of patients may have unsuspected cirrhosis [7,8]. NAFLD is considered to be a hepatic expression of metabolic syndrome (MS) and recent studies have pointed to DM2 as an aggravating factor for liver fibrosis irrespective of other MS factors [8,9]. Liver disease in patients with NAFLD and DM2 is more intense and carries a greater risk of developing into cirrhosis and a higher mortality rate [9,10].

Material and Method: - This observational and analytical study was conducted between May 2015 to June 2016 at the Department of Biochemistry, Late Shri Lakhiram Agrawal Memorial Medical College Associated KGH Raigarh CG. A patient attending the Medicine OPD & IPD for their blood pressure, Anthropometry, Biochemical parameters and Ultrasound abdomen was done. The study subjects were 100 patients with type 2 diabetes mellitus. 52 diabetic patients had fatty liver and 48 without fatty liver act as a control. Approval of Ethics committee of the hospital was taken prior to starting the study. Written informed consent was taken from all the participants. Inclusion criteria included to be selected for the present study individuals had to be diagnosed with Non-Alcoholic fatty liver disease (NAFLD) through non invasive technique abdominal ultrasonography, age more than 20 years and less than 80 years, without history of alcohol consumption & hepatotoxic substances intake (eg. steroids).

Exclusion criteria were patients consuming alcohol, patients with congestive heart failure and renal failure on hepatotoxic drug.

After careful history and clinical examination including anthropometry (waist hip ratio and BMI) was done. 5 ml venous blood samples were collected under aseptic conditions from all the subjects by phlebotomy, 2 ml whole blood transfer to EDTA coated tube for HbA1C estimation and 3 ml blood transfer to plain tube for biochemical parameters quantification. HbA1C estimation was done by HPLC BIO-RAD hemoglobin variant testing system. The biochemical parameters Serum fasting blood sugar, PPBS, SGOT, SGPT, ALP, T. Protein, Albumin, Urea, Creatinine, fasting lipid profile TG, Total cholesterol (TC) and HDL cholesterol (HDL-C) was measured by enzymatic methods using ERBA kits on Micro Lab 300

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semi auto analyzer. Serum LDL & VLDL cholesterol was calculated by Frederickson-Friedwald's formula. According to which LDL cholesterol = Total cholesterol - (HDL cholesterol+ VLDL cholesterol) & VLDL cholesterol (VLDL-C) was calculated as 1/5 of Triglycerides.

Those patients who had increased echogenicity of liver as compared to kidney by USG were considered to have fatty liver. Anthropometric and metabolic parameters in diabetic patients with fatty liver were compared with diabetic patients without fatty liver.

Statistical analysis

With the aim of characterizing the sample studied relative (%) and absolute (N) frequencies were employed for all classes of each qualitative variable. In order to verify the differences between the groups of different categories, the Pearson Chi-square test or the Fisher's Exact Test were employed. Descriptive statistics i.e. mean values, standard deviations, minimums and maximums were used to indicate the quantitative variables of the data. In order to compare the groups of diabetic patients with fatty liver and diabetic patients without fatty liver the Student t-test was applied to quantitative variables for both the groups. Statistical analysis was done by comparing diabetic patients with fatty liver and diabetic patients without fatty liver. Correlation and regression were also performed to measure the association.

Results considered statistically significant were those with descriptive values (p-values) less than 0.05; and a confidence interval of 95%.

For the technical analysis the following software were employed: MSOffice Excel 2010 to administer the database, and "Statistical Package for the Social sciences - SPSS version 20 for Windows 10.0" to execute the statistical data, and to create and edit the graphs.

Results

A total of 100 patients participated in the study. Data of 52 diabetic patients with fatty liver was compared with 48 diabetic patients without fatty liver. Of the 100 patients evaluated, 57 (57%) were female and 43 (43%) were male, the mean age was 56.43 years, with a variation of 26 to 78 years; 52 patients (52%) presented NAFLD. In relation to the qualitative variables such as sex, alcohol consumption, smoking, exercise and hypertension, only hypertension was more frequent ($p < 0.001$) amongst patients with NAFLD (Table 1).

Table1. Details illustrating clinical characteristics, demographics, habits and co-morbid conditions of 100 patients with type 2 diabetes mellitus, divided into two groups with and without non-alcoholic fatty liver disease (NAFLD)

Variables		N total =100	NAFLD		p-value
			Absent (n = 52)	Present (n = 48)	
Sex	Female&male	100	57 (57%)	31 (31%)	0.00
Alcohol	No	100	59 (57%)	38 (38%)	0.001
Smoking	No	100	67 (67%)	33 (33%)	0.00
Exercise	No	100	45 (45%)	55 (%)	0.00
Hypertension	Yes	100	68 (68%)	42 (42%)	0.005

Patients with NAFLD presented higher weight ($p < 0.001$); BMI ($p < 0.001$), waist measurement ($p < 0.001$) and hip measurement ($p < 0.001$) than those without NAFLD, however, there was no significant difference between the waist to hip ratio (Table 2). Analyzing the weight utilizing the normality limits, it was confirmed that the majority (97%) of the patients with NAFLD were either overweight or obese ($p = 0.006$).

Patients with NAFLD presented higher weight ($p < 0.001$); BMI ($p < 0.001$), waist measurement ($p < 0.001$) and hip measurement ($p < 0.001$) than those without NAFLD, however, there was no significant difference between the waist to hip ratio (Table 2).

Table 2. Demographic and anthropometric characteristics of 100 patients with type 2 diabetes mellitus divided into two groups with and without nonalcoholic fatty liver disease (NAFLD)

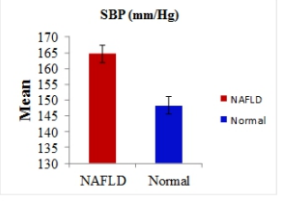
S. No.	Variables	Average (SD)	Total	Variation (min-max)	NAFLD		
					Present	Absent	p-value
1.	Age (years)	56.43 (10.41)	100	26-78	52	48	0.005
2.	Weight (kg)	97.72 (9.55)	100	50-98	52	48	0.002
3.	Height (m)	162.74 (7.87)	100	149-179	52	48	0.001
4.	BMI (kg/m2)	28.94 (3.63)	100	21-40	52	48	0.00
5.	W/H (cm)	0.89 (0.05)	100	0.76-0.98	52	48	0.00

BMI: body Mass Index; W/H-Waist/hip ratio.
T: student-T test.

Table 3. Laboratory data of 100 patients with type 2 diabetes mellitus divided into two groups with and without non-alcoholic fatty liver disease (NAFLD)

S. No.	Variables	Average (SD)	Total	Variation (min-max)	NAFLD		p-value
					Present	Absent	
1.	HbA1c %	8.04 (2.31)	100	06-15	52	48	0.00
2.	SGOT(IU/L)	46.61 (16.01)	100	22-85	52	48	0.00
3.	SGPT(IU/L)	75.92 (28.16)	100	29-138	52	48	0.005
4.	ALP(IU/L)	112.05 (25.68)	100	58-210	52	48	0.00
5.	UREA (mg/dl)	50.74 (27.83)	100	16-124	52	48	0.005
6.	CREATININE (mg/dl)	2.31 (1.84)	100	00-09	52	48	0.00
7.	T.BILIRUBIN (mg/dl)	1.28 (0.63)	100	01-04	52	48	0.00
8.	HDL(mg/dl)	29.53 (6.64)	100	20-48	52	48	0.005
9.	LDL (mg/dl)	194.93 (37.43)	100	89-289	52	48	0.005
10.	VLDL(mg/dl)	37.43 (13.09)	100	10-54	52	48	0.05
11.	SBP (mm Hg)	156.78 (21.40)	100	110-192	52	48	0.00
12.	FBS (mg/dl)	167.485 7.67	100	84 -354	52	48	0.00
13.	PPBS (mg/dl)	269.56 (96.42)	100	112-554	52	48	0.005

HbA1c: Glycated hemoglobin



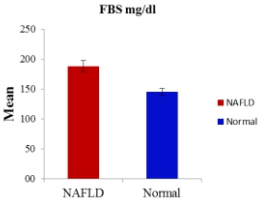


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Fig (a): Comparison of SBP between NAFLD and Normal Fig (b): Comparison of FBS between NAFLD and Normal

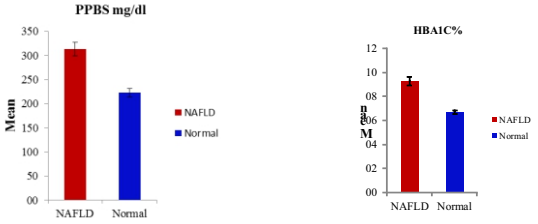

Fig (c): Comparison of PPBS between NAFLD and NormalFig (d): Comparison of HBA1C% between NAFLD and Normal

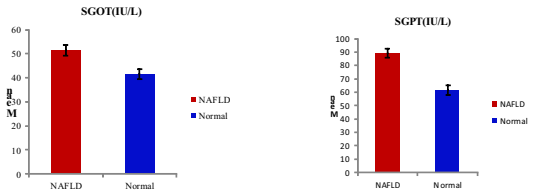

Fig (e): Comparison of SGOT between NAFLD and Normal

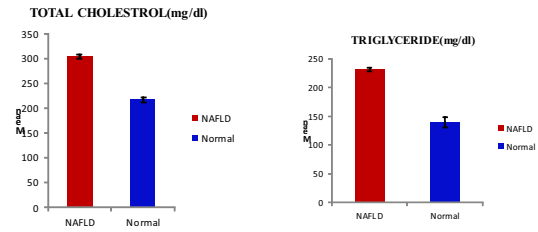

Fig (g): Comparison of total cholesterol between NAFLD and NormalFig (h): Comparison of triglyceride between NAFLD and Normal

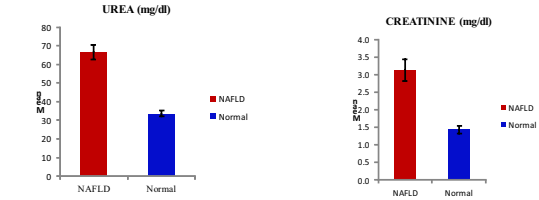

Fig (i): Comparison of Urea between NAFLD and NormalFig (j): Comparison of Creatinine between NAFLD and Normal

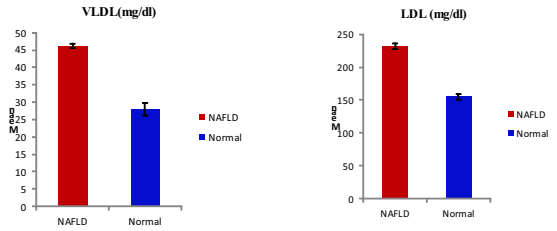

Fig (k): Comparison of VLDL (mg/dl) between NAFLD and NormalFig (l): Comparison of LDL (mg/dl) between NAFLD and Normal

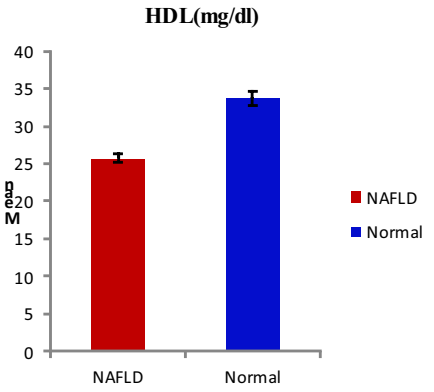

Fig (m): Comparison of HDL (mg/dl) between NAFLD and Normal

Correlations

		SBP	DBP	FBS	PPBS	HBA 1C%	SGOT	SGPT	ALP	T. PROTEIN	ALBUMIN	UREA	Creatinine	T.bilirubin	D.bilirubin	T. Cholesterol	TG	HDL	LDL	VLDL	
SBP	Pearson Correlation	1	.063	.657**	.515**	.471**	-.055	.128	-.068	.087	.166	.347*	.157	-.387**	-.370**	.212	.376**	-.034	.106	.376**	
	Sig. (2-tailed)		.672	.000	.000	.001	.713	.387	.647	.558	.261	.016	.286	.007	.010	.149	.008	.817	.473	.008	
	N		48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	
DBP	Pearson Correlation		1	.014	.048	.073	.109	.198	-.171	-.136	-.101	.398**	.209	.022	-.028	.224	.192	-.191	.222	.192	
	Sig. (2-tailed)			.922	.747	.624	.460	.177	.245	.355	.493	.005	.153	.882	.851	.127	.190	.194	.130	.190	
	N			48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	
FBS	Pearson Correlation			1	.607**	.514**	.210	.322*	.082	.126	.095	.250	.088	-.313*	-.249	.375**	.435**	-.206	.306*	.435**	
	Sig. (2-tailed)				.000	.000	.152	.026	.578	.395	.520	.087	.553	.030	.088	.009	.002	.159	.034	.002	
	N				48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	
	Sig. (2-tailed)					.000	.158	.040	.761	.580	.862	.192	.621	.064	.093	.006	.002	.018	.015	.002	
	N					48	48	48	48	48	48	48	48	48	48	48	48	48	48	48	
HBA 1C%	Pearson Correlation					1	.206	.523**	.262	-.051	.006	.694**	.161	-.421**	-.434**	.660**	.782**	-.659**	.591**	.782**	
	Sig. (2-tailed)						.159	.000	.073	.731	.969	.000	.274	.003	.002	.000	.000	.000	.000	.000	

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	N						48	48	48	48	48	48	48	48	48	48	48	48	48	48
SGOT	Pearson Correlation						1	.733**	.127	-.109	-.078	.085	.250	.027	.063	.164	.263	-.352*	.157	.263
	Sig. (2-tailed)							.000	.389	.460	.598	.564	.087	.855	.669	.264	.070	.014	.287	.070
	N							48	48	48	48	48	48	48	48	48	48	48	48	48
SGPT	Pearson Correlation							1	.278	-.102	-.031	.421**	.206	-.197	-.189	.302*	.495**	-.417**	.239	.495**
	Sig. (2-tailed)								.056	.490	.832	.003	.160	.180	.197	.037	.000	.003	.101	.000
	N								48	48	48	48	48	48	48	48	48	48	48	48
ALP	Pearson Correlation								1	-.173	-.177	.200	.168	-.178	-.144	.217	.187	-.278	.233	.187
	Sig. (2-tailed)									.241	.228	.173	.255	.227	.329	.139	.204	.056	.110	.204
	N									48	48	48	48	48	48	48	48	48	48	48
T. Protein	Pearson Correlation									1	.859**	-.211	-.194	-.152	-.133	-.113	-.120	.097	-.104	-.120
	Sig. (2-tailed)										.000	.150	.187	.303	.368	.444	.417	.510	.483	.417
	N										48	48	48	48	48	48	48	48	48	48
ALBUMIN	Pearson Correlation										1	-.137	-.120	-.165	-.155	-.165	-.073	.124	-.188	-.073
	Sig. (2-tailed)											.354	.415	.262	.293	.261	.624	.403	.201	.624
	N											48	48	48	48	48	48	48	48	48
UREA	Pearson Correlation											1	.423**	-.237	-.308*	.466**	.566**	-.493**	.417**	.566**
	Sig. (2-tailed)												.003	.105	.033	.001	.000	.000	.003	.000
	N												48	48	48	48	48	48	48	48
Creatinine	Pearson Correlation												1	-.010	-.021	.118	.079	-.045	.115	.079
	Sig. (2-tailed)													.946	.890	.424	.592	.763	.437	.592
	N													48	48	48	48	48	48	48
T. Bilirubin	Pearson Correlation													1	.974**	-.346*	-.404**	.192	-.282	-.404**
	Sig. (2-tailed)														.000	.016	.004	.192	.052	.004
	N														48	48	48	48	48	48
D. Bilirubin	Pearson Correlation														1	-.372**	-.422**	.213	-.309*	-.422**
	Sig. (2-tailed)															.009	.003	.146	.033	.003
	N															48	48	48	48	48
T. Cholesterol	Pearson Correlation															1	.786**	-.598**	.971**	.786**
	Sig. (2-tailed)																.000	.000	.000	.000
	N																48	48	48	48
TG	Pearson Correlation																1	-.635**	.647**	1.000**
	Sig. (2-tailed)																	.000	.000	0.000
	N																	48	48	48
HDL	Pearson Correlation																	1	-.641**	-.635**
	Sig. (2-tailed)																		.000	.000
	N																		48	48
LDL	Pearson Correlation																		1	.647**
	Sig. (2-tailed)																			.000
	N																			48
VLDL	Pearson Correlation																			1
	Sig. (2-tailed)																			
	N																			

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

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Discussion

In our study we found that anthropometric parameters like BMI and waist hip ratio had significant association with occurrence of NAFLD. In our study SGPT / SGOT ratio>1 was associated with increased incidence of fatty liver there by implying its role as a screening test in detection of fatty liver. Deranged lipid parameters particularly hypertriglyceridemia was seen in diabetic patients with fatty liver [11].

NASH was first described in 1980 in a series of patients of the Mayo Clinic [12]. In 1980, Ludwig et al. described an alcoholic hepatitis-like pattern of injury in the liver of non-alcoholic patients [13]. They introduced the term 'non-alcoholic steatohepatitis' (NASH) to describe this disease entity [14]. The histologic features characteristic of steatohepatitis in the absence of significant alcohol consumption can be seen in a wide variety of conditions like drugs and toxins exposure, jejuno-ileal bypass, extensive small bowel resection and Wilson's disease[15].

Obesity and in particular central obesity has been described as one of the strongest risk factors for NAFLD and fibrosis, with NASH being prevalent in 18.5% of the obese patients [16]. Goland et al have showed that patients with NAFLD had a significantly higher BMI [17]. Marchesani et al showed that 80% of patients with NAFLD were obese [18]. In our study BMI and waist hip ratio were high in diabetic patients with NAFLD thereby implying role of abdominal obesity and hence BMI in pathogenesis of fatty liver in diabetic patients and need of weight control in these patients. NAFLD is commonly characterized by elevated levels markers of liver injury like alanine aminotransferase (ALT), aspartate aminotransferase (AST) and Gamma glutamyl transferase (GGT). Of these liver enzymes, ALT is most closely related to liver fat accumulation, and is often used in epidemiological studies as a surrogate marker for NAFLD [19]. It is now clearly known that the whole spectrum of histological findings of fatty liver and NASH may exist without elevation of transaminases [20]. In our study 60% of diabetic patients with fatty liver had SGPT /SGOT ratio was >1. The ratio of AST/ALT is usually less than 1 in patients who have either no or minimal fibrosis, although this ratio may be greater than 1 with the development of cirrhosis [21]. Gamma-glutamyl transferase (GGT) in the serum is frequently elevated in patients with NAFLD, and it has been reported to be associated with increased mortality [22]. Although GGT is a marker of alcoholic liver disease. We found that there was no statistical correlation of HbA1c with NAFLD, reason for this observation could be due to the smaller sample size

Conclusion

NAFLD has become a common diagnosis in clinical practice reflecting its increased prevalence and incidence in the general population. We think that it is important to reach a 'positive' operational definition of NAFLD which can be shared by researchers worldwide. Simple NAFL is present in almost 40–50% of the general population and must be considered benign in light of the available evidence. The main task for the future is to become able to distinguish NAFL from NAFLD. Population cohort studies with long-term follow-up are essential to better define the incidence and natural history of NAFLD. Genetic studies are also needed to determine to what extent the genetic background predisposes to the development of serious liver disease and cardio metabolic disease.

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Conflict of interest: None declared

Ethical Approval: The study was approved by the Institutional Ethics Committee.

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