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Evaluation of changes in the global longitudinal strain for left ventricular function before and after eight weeks of taking high dose of atorvastatin in patients with coronary slow flow phenomenon

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Abstract

Background Coronary Slow Flow Phenomenon (CSFP) is a well-recognized clinical entity characterized by delayed opacification of coronary arteries in the presence of a normal coronary angiogram. The objective of this study was determined and compared left ventricle (LV)strain in patients with CSFP before and after receiving a high-dose atorvastatin.

Materials and methods This cross-sectional study was conducted on 51 patients with CSFP from the beginning of 2021 to the end of September 2022. Trans-thoracic Echocardiogram (TTE) was performed by an echocardiography specialist. Thereafter, the patient's basic information was entered into the researcher's checklist after treatment with atorvastatin 40 mg daily for eight consecutive weeks. After eight weeks, the patients were subjected again to TTE. The data were analyzed in SPSS statistical software.

Results The mean LV-GLS before taking atorvastatin was − 16.53%±3.63%. The mean LV-GLS after taking atorvastatin was 17.57%±3.53% (P.value = 0.01). The mean LV function before taking atorvastatin was 48.82%±9.19%. Meanwhile, the mean LV function after taking atorvastatin was 50.59%±7.91% ($P = 0.01$). There was no significantly change in left atrium volume (49.88 ± 0.68 vs. 49.9 + 0.67) after 8 weeks taking atorvastatin ($P = 0.884$).

Conclusion The plasma ET-1 levels are elevated in CSFP patients, and atorvastatin improves coronary flow and endothelial function. As evidenced by the results of this study, the daily intake of 40 mg of oral atorvastatin during eight consecutive weeks in patients with CSFP significantly improved LV strain and LV function, however atorvastatin does not have a significant effect on improving the right ventricular function and pulmonary artery systolic pressure.

Keywords Atorvastatin, Global longitudinal strain, Left ventricular function, Slow coronary flow

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Background

A well-known clinical condition known as Coronary Slow Flow Phenomenon (CSFP) is defined by delayed opacification of the coronary arteries even in the presence of a normal coronary angiography [1]. Numerous variables, including endothelial and microvascular dysfunction, have been linked to this condition [2, 3]. This phenomenon is related to the contractile function of the heart muscle, wherein the time taken for the angiographic material to reach the distal vessel is increased in patients who undergo angiography [4].

Global Longitudinal Strain (GLS) Speckle Tracking Echocardiography (STE) technique is a sensitive method to evaluate cardiac function. Strain indicates the percentage of deformation between two regions, which includes the shortening of the myocardial muscle in systole or its lengthening in diastole. Strain images, which are obtained based on the 2-Dimensional-STE technique, are very accurate and reliable and it used to evaluate longitudinal indices of left ventricular (LV) deformation [5].

GLS-STE technique has been validated utilizing sonomicrometry and speckle in myocardial tissue to determine the areas that contract and move passively. Strain can be evaluated longitudinally, circumferentially, and radially using appropriate images [6]. Numerous studies have shown its incremental diagnostic and prognostic value in multiple cardiovascular conditions, such as ischemic heart disease [7] and cardiomyopathies [8].

A number of studies have demonstrated that receiving atorvastatin can be used as a factor in improving left ventricular function [9], however there is a dearth of studies investigating LV function by strain method in people with CSFP, especially in patients receiving high-dose atorvastatin. Therefore, the present study aimed to compare GLS-STE for LV Function in patients with CSFP before and after receiving a high-dose atorvastatin.

Materials and methods

This observational, perspective, monocentric single group study was conducted on patients with CSFP referred to the Farshchian Cardiovascular Training Center affiliated to Hamedan University of Medical Sciences from the beginning of April 2021 to the end of September 2022. Patients with angiographically normal coronary arteries who underwent coronary angiography on suspicion of ischemic heart disease due to typical chest pain or ischemic findings on a treadmill exercise test or myocardial scintigraphy were diagnosed with CSFP and provided informed consent to participate were included in this study.

Inclusion and exclusion criteria

Exclusion criteria were as follows: a history of allergy to atorvastatin, an increasing trend in the blood concentration of creatine kinase, symptoms of myositis while taking atorvastatin, unavailability of files in the archives of Farshchian Hospital, having visited Farshchian Hospital and refusal to continue treatment in that hospital, having visited Farshchian Hospital and transferal to another hospital for further treatment, simultaneous commencement of other medications that may have caused LVEF to improve, ACS presentations with regional wall motion abnormalities or myocardial stunning at the time of the initial echo that may have caused a lower presenting LVEF, abnormal liver function test, and incomplete or illegibly completed medical files.

Determination of thrombolysis in myocardial infarction (TIMI) frame count

During the procedure, selective coronary angiography was performed using the standard Judkins technique at a rate of 15 frames per second, capturing multiple angulated views. The left anterior descending coronary artery (LAD) and circumflex coronary artery (CX) were observed in a right anterior oblique projection with caudal angulations, while the right coronary artery (RCA) was viewed in a left anterior oblique projection with cranial angulations. Iopromide (Ultravist®, BAYER, Germany) was used as the contrast agent for all patients, and no other agents such as nitrate, verapamil, or nicorandil were administered during the procedure.

"To calculate the TIMI frame count, we followed the method described by Gibson et al. [10]. The first frame was determined as the frame when the opaque material entered the coronary artery ostium, and the last frame was defined as the frame required for imaging the distal landmark by the opaque material. The difference between the first and last frames was considered the TIMI frame count. Normal TIMI frame count values for the LAD, CX, and RCA were reported as 36.2±2.6, 22.2±4.1, and 20.4±3.0 frames within 30 frames/s, respectively (at 30 frames/s) [10]. Since our images were acquired at 15 frames/s, all values were multiplied by 2."

Study protocol and data acquisition

In this study, 51 subjects were selected via convenience sampling from eligible patients. The data collection tool in this study was a researcher-made checklist to record the demographic characteristics of the patient, coronary angiography data of the patient, slow flow CAD, as well as echocardiography data, including LV strain, LV ejection fraction (LVEF), Right ventricular ejection fraction (RVEF), and systolic pulmonary artery pressure (sPAP). After the first echocardiography the patients were treated with atorvastatin 40 mg daily for eight consecutive weeks. After eight weeks, the patients were again subjected to echocardiography, and the mentioned data were again recorded in the checklist.

Echocardiographic evaluation

The Trans-Thoracic Echocardiogram (TTE) was conducted in the echocardiography department at Farshchian Hospital by a cardiologist specializing in echocardiographic imaging with at least 15 years of experience. The examination was performed in accordance with the guidelines of the American Society of Echocardiography and the European Society of Cardiovascular Imaging. Before the echocardiographic assessment, each patient was positioned in a supine position for 5 min in a quiet room. Each patient's echocardiography film was stored separately in the patient's electronic patient record for future evaluations.

The 2D-guided linear measurements were taken from a parasternal long axis for the LV septum diameter and end-diastole LV diameter, and from a short axis view for the right ventricular outflow tract diameter. From the apical four-chamber view, the LV end diastolic volume, LV end systolic volume, left atrium volume, and TAPSE (Tricuspid Annular Plane Systolic Excursion) were obtained.

The LVEF was obtained from the LV end-diastolic and end-systolic volumes using the biplane disk summation method. The RVEF was also evaluated by the fractional area change, using the end-diastolic and end-systolic area of the right ventricle.

A pulsed-wave Doppler was performed at the mitral inflow, followed by Tissue Doppler Imaging at the mitral annular septal and lateral levels in the four-chamber view. The E/A ratio was then calculated. A continuous wave Doppler was utilized to assess the tricuspid regurgitation jet velocity to estimate the SPAP. Color flow evaluation was utilized to semi-quantitatively define the presence of valvular disease.

The LV GLS-STE was calculated by a dedicated software from the apical four, two and three chamber view using an automated tracking algorithm to outline the myocardial borders throughout the cardiac cycle. If necessary, manual adjustments were performed to ensure the correct tracing of the endocardial border. A value around −20% was considered as a cut off for normality [11].

Two experienced echocardiographers assessed strain parameters in 10 random patients independently for inter-observer analysis. 3 months later, one of the investigators repeated assessment to determine the intra-observer variability.

Ethical considerations

This study was started after receiving the necessary introduction letters from the relevant authorities and obtaining the Code of Ethics (IR.UMSHA.REC.1401.646). Moreover, all patients were included in the study if they gave informed consent. The patients were assured that if they did not agree to participate in the research, there would be no disturbance in their treatment process and no compulsion to enter the study. All information was collected by maintaining the principle of confidentiality and without mentioning the name of the patient. Consent was obtained from all patients.

Study endpoints

The endpoint of the study was to assess cardiac functional changes by echocardiography and, in particular, by GLS-STE, comparing the baseline data with the 8-week follow-up. Since there was no previous data on the effects of atorvastatin on the endpoints analyzed, a sample size determination was not performed due to the exploratory nature of the study.

Statistical analysis

The obtained information was analyzed using SPSS software (version 20). Differences in the values of the explanatory variables were compared by a t-test for paired samples in cases of normally distributed data. The percentage was used to describe qualitative variables, and quantitative variables were presented as mean±standard deviation or median [Interquartile range]. The tests used in this study included paired t-test to compare quantitative variables with normal distribution, a Wilcoxon test to compare quantitative variables with non-normal distribution, and a McNemar test to compare qualitative variables. In this study, a statistically significant level of 5% was considered.

Result

A total of 51 patients who were referred for coronary angiography and were diagnosed with CSFP were examined in this study. The mean age of the patients was 60.42±10.29 years (the age range: 45–87 years). In terms of gender, 26 (51%) cases were male, and 25 (49%) subjects were female. In our population, 18 patients had slow flow in all three vessels, four patients had slow flow in the LAD and CX, eight patients had slow flow in the CX and RCA, five patients had slow flow in the LAD and RCA, five patients had slow flow in the LAD only, five patients had slow flow in the CX only, and six patients had slow flow in the RCA only (Table 1). No liver complication caused by atorvastatin occurred in any of the patients.

The average heart rate before statin therapy was 71±10 bpm, with systolic and diastolic blood pressures of 134±13 mmHg and 79±10 mmHg respectively. After 8 week the average heart rate was 72±8 bpm (P.value=0.45), with systolic and diastolic blood pressures of 132±10 mmHg and 78±8mmHg (P.value=0.054) respectively (Table 2).

The echocardiographic data are summarized in Table 1. Based on this, the mean LVEF before taking atorvastatin was 48.82±9.19%, while the mean LVEF after taking atorvastatin was 50.59±7.91%. During the study, 14

Table 1 Demographic and clinical characteristics of the patients

Age (Mean ± SD)	60.42 ± 10.29
Male gender (Number (%))	26 (51%)
LAD TIMI frame count (Mean ± SD)	40.56 ± 2.90
CX TIMI frame count (Mean ± SD)	27.07 ± 2.91
RCA TIMI frame count (Mean ± SD)	24.72 ± 2.47
Slow flow in LAD + CX + RCA (Number (%))	18(35.29%)
Slow flow in the LAD + CX (Number (%))	4(7.84%)
Slow flow in the RCA + CX (Number (%))	8(15.68%)
Slow flow in the RCA + LAD (Number (%))	5(9.81%)
Slow flow in the LAD (Number (%))	5(9.81%)
Slow flow in the CX (Number (%))	5(9.81%)
Slow flow in the RCA (Number (%))	6(11.76%)
Smoking (Number (%))	13(25.49%)

LAD: Left Anterior Descending coronary artery, CX: Circumflex coronary artery, RCA: Right Coronary Artery

patients showed an improvement in their LVEF. However, the LVEF of 37 patients remained unchanged after taking 40 mg of oral atorvastatin for eight consecutive weeks. Interestingly, none of the patients had a lower LVEF after the study compared to the beginning (P.value=0.01) (Table 2).

The sPAP of all patients under the study before and after taking atorvastatin was reported as 30±0.0 mm Hg (*P*-value=1.00), also there was no significant change in RVEF before and after taking atorvastatin in TTE (51.27±2.7 VS 51.64±1.59 (*P*-value=0.165)).

The mean score of LV-GLS before taking atorvastatin was −16.53%±3.63% (within the range of 7-22%). However, the mean score after taking atorvastatin was −17.57%±3.53% (within the range of 7 -23%). Based on this, the amount of LV-GLS after taking atorvastatin is significantly higher than the LV-GLS score before taking atorvastatin (*P*-value=0.001) (Table 2) (Fig. 1), with 0.935 correlation coefficient.

Reproducibility was excellent for all measured parameters. The intraclass correlation coefficients ranged from 0.944 to 0.982 for intra-observer agreement and ranged from 0.913 to 0.964 for inter-observer agreement (Table 3).

Discussion

To the best of our knowledge, this is the first clinical study that has sought to evaluate the effect of atorvastatin on cardiac function by employing echocardiography and, in particular, GLS-STE in a cohort of CSFP patients. The main results of the current analysis are that myocardial function, as assessed by GLS-STE, significantly improved after eight weeks of atorvastatin therapy. The plasma levels of ET-1 are elevated in CSF patients and atorvastatin improves coronary flow and endothelial function in patients with coronary slow flow [12].

GLS-STE has become increasingly popular in recent years for evaluating myocardial deformation in various clinical situations. Preclinical detection of cardiac dysfunction is possible through GLS-STE before the development of abnormalities in standard echocardiographic parameters [13].

The overall prevalence of CSFP among patients undergoing coronary angiography, particularly in patients

Table 2 Echocardiographic data at baseline and after 8weeks of atorvastatin treatment. (paired t-test & Wilcoxon test)

Variable	Baseline	After 8 weeks	*P*.value
Heart rate (bpm/min)	71 ± 10	72 + 8	0.45
Blood Pressure (mmHg)	134 ± 13	132 ± 10	0.054
LVEF (mean ± Standard deviation) (%)	48.82 ± 9.19	50.59 ± 7.91	0.01
sPAP (mean ± Standard deviation) (mmHg)	30 ± 0.0	30 ± 0.0	1.00
LV-GLS (mean ± Standard deviation) (%)	-16.53%±3.63	-17.57%±3.53	0.01
RVEF (mean ± Standard deviation) (%)	51.27 ± 2.7	51.64 ± 1.59	0.165
RVOT median [IQR] (mm)	25[2]	25[2]	0.825
RV basal, median [IQR]	3.2[0.3]	3.2[0.3]	1
TAPSE, median [IQR] (mm)	17.63[2.48]	17.63[2.48]	0.825
E wave, median [IQR] (cm/s)	0.98 [0.11]	0.98[0.11]	1
A wave, median [IQR] (cm/s)	1.118 [0.11]	1.118 [0.11]	1
DT, median [IQR] (msec)	216.22 [23]	216.22 [23]	0.854
E' lateral, median [IQR] (cm/s)	7.2[0.36]	7.2[0.36]	1
E' medial, median [IQR] (cm/s)	6.24[0.38]	6.24[0.38]	0.841
E' average, median [IQR] (cm/s)	9.78 [0.75]	9.78 [0.75]	1
S' lateral, median [IQR] (cm/s)	9.64 [2.39]	9.64 [2.39]	0.949
LV septum, median [IQR] (mm)	10.73 [1.24]	10.73 [1.24]	3.91
LV end diastole, median [IQR] (mm)	56 [7]	56 [7]	0.97
LA area, median [IQR] (cm^2)	19.85 [6]	19.85 [6]	1
LA Volume, (mean ± Standard deviation) (ml)	49.88 ± 0.68	49.9 + 0.67	0.884

LV: Left Ventricle; EF: Ejection Fraction; TAPSE: Tricuspid Annular Plane Systolic Excursion; LA: Left Atrium; RVOT: Right Ventricle Outflow Tract; RV: Right Ventricle; DT: Deceleration Time; SPAP: Systolic Pulmonary Artery Pressure; GLS: Global Longitudinal Strain

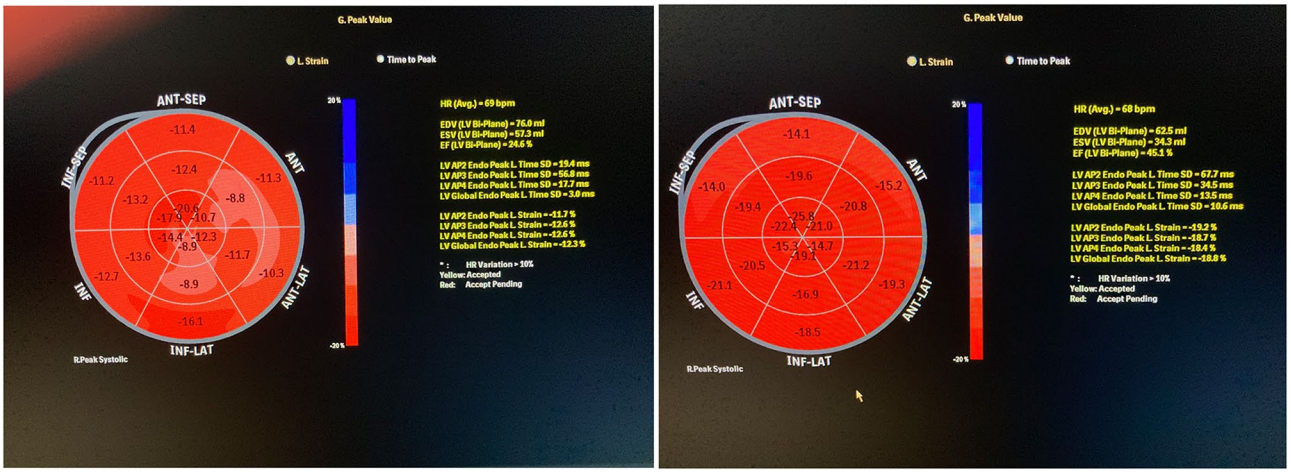

Fig. 1 GLS-STE figures before (GLS=-12.3%) (a)and after (GLS=-18.8%) (b)taking atorvastatin for eight weeks

Table 3 Inter- and intra-observer variability of echocardiography parameters

Variable	Intra-observer		Inter-observer	
	ICC	95% CI	ICC	95% CI
LVEF	0.982	0.921 to 0.993	0.964	0.921 to 0.984
sPAP	0.979	0.941 to 0.993	0.962	0.932 to 0.983
LV-GLS	0.944	0.916 to 0.976	0.913	0.879 to 0.973

presenting with acute coronary syndrome, has been reported to be 1% [14]. In another study, the prevalence of CSFP was approximately 4% among patients presenting with unstable angina and had no or insignificant CAD [14]. While Hawkins et al. reported an overall prevalence of 5.5% among patients undergoing coronary angiography [15]. According to the studies, metabolic syndrome, along with insulin resistance or impaired glucose tolerance, high cholesterol, high fasting glucose, and high body mass index are more prevalent in CSFP patient [16, 17]. In our study, there was no significant difference in the prevalence of CSFP among women and men.

The diagnosis of CSFP can be determined based on the TIMI flow grade or TIMI frame count. TIMI-2 flow grade (which requires ≥ 3 beats to opacify the vessel) or a corrected TIMI frame count > 27 frames are commonly used measurements. The latter is based on images captured at 30 frames/second and a correction factor of 1.7 for the LAD [18]. Gokhan Aksan et al. found a strong correlation between elevated neutrophil gelatinase-associated lipocalin levels in CSFP patients and coronary blood flow. Also, elevated neutrophil gelatinase-associated lipocalin levels might be a useful tool in predicting CSFP in patients who undergo coronary angiography [19].

Clinically, CSFP occurs most commonly in young men and smokers, and patient admitted with acute coronary syndrome. more than 80% of these patients experienced recurrent chest pain, and 20% required readmission for acute exacerbation [3, 20]Most importantly, CSFP has been described to be associated with life-threatening arrhythmias and sudden cardiac death, due to acute coronary syndrome and increased QTc dispersion in these patients [21].

Although CSFP has been known to interventional cardiologists for almost four decades, its pathogenic mechanisms are not fully understood. Small vessel disease, endothelial dysfunction (generalized process affecting both coronary and peripheral vasculature), inflammation, anatomic factors, and subclinical atherosclerosis have been proposed as possible pathogens of this disease [3]. Some studies have shown that endothelial dysfunction and coronary microvascular reactivity can be improved using atorvastatin [22, 23]. Elevation of hematocrit level and the number of eosinophils, basophils and urotensin-II may have direct or indirect effects on coronary blood flow velocity. These values are significantly higher in patients with CSFP [24, 25].

According to the Serkan Yuksel et al. study, abnormalities in nail fold capillaries suggesting the presence of inflammation and anatomical changes are significantly higher in patients with CSFP. As a result, this disease may reflect a generalized pathology affecting different microvascular systems accompanied by generalized inflammation [26].

According to the Gulel et al. study, CSFP results in significant changes to the left LV's myocardial deformation parameters, particularly circumferential parameters, which are followed by LV dysfunction based on GLS-STE [13]. In our study the mean score of LV-GLS before taking atorvastatin was −16.53%±3.63%, while the mean LV-GLS after taking atorvastatin was −17.57%±3.53%, which indicates the positive effect of the atorvastatin on LV function. Also, regarding the effectiveness of atorvastatin on improving LV-EF, the findings of the present study are consistent with the results of the research by Bakakos et

al. who assessed the effect of statins on LV function in a meta-analysis and systematic review [27].

In line with our study, in the study by Seyed Mohammad Zad et al. in 2021, the mean LV-GLS of patients with the CSFP was −15.86±0.91%. Meanwhile, the mean among the control group was −18.59±0.59%, and it was shown that the amount of LV-GLS in CSFP patients is significantly lower than that in the normal population (P=0.01) [28]. also our finding was compatible with a study by Wang et al. that reported LV diastolic and systolic functions were impaired in patients with CSFP than in the control group [29].

However, Narimani et al. found no significant relationship between the CSFP and the systolic and diastolic longitudinal traction, showing that CSFP could not impair the systolic and diastolic longitudinal function [30]. In other hands study by Nurkalem et al. also showed that the LV- GLS was different between the CSFP and control groups [31]. Therefore, the presence of LV dysfunction in CSFP is still controversial, so further studies are needed to elucidate this relationship. According to the literature, longitudinal traction impairment of the left ventricle occurs earlier than the marginal and radial traction impairments [32].

In the referred research, from a total of 51 patients studied, 49 (96.1%) cases had normal right ventricular function, and 2 (3.9%) subjects had mild dysfunction in their right ventricle before and after taking atorvastatin. In line with our study on the study by Zhu et al., there was no significant difference in the right ventricular function between slow-flow coronary syndrome patients and the control group [33]. However, in the study of Yu Meng Xing et al., the GLS of the LV (−19.03% vs. −21.42%, P<0.001) and RV (−19.72% vs. −22.96%, P=0.001) was significantly impaired in CSFP patients compared with that in controls [34].

Study limitations

This study has some limitations. First, the reduced sample size led to weak statistical power. The identification of a difference between the baseline and after eight weeks LV-GLS requires further studies with a larger sample size and a longer follow-up period to confirm these results. The second limitation is the absence of a control group and the lack of blinding, which may have led to bias in the evaluation of the echocardiographic parameters during the follow-up.

Suggestions

Due to the limited statistical population in our research center, it is recommended to conduct multi-center studies in cooperation with several cardiovascular centers.

Conclusion

In general, the results of this study pointed out that the daily intake of 40 mg of oral atorvastatin for eight consecutive weeks in patients with CSFP significantly improved the level of LV-GLS and LV function despite the fact that the use of atorvastatin does not have a significant effect on improving the RVEF and sPAP.

Abbreviations

CSFP	Coronary Slow Flow Phenomenon
GLS	Global Longitudinal Strain
STE	Speckle Tracking Echocardiography
TIMI	Thrombolysis in Myocardial Infarction
LAD	Left Anterior Descending coronary artery
CX	Circumflex coronary artery
RCA	Right Coronary Artery
TAPSE	Tricuspid Annular Plane Systolic Excursion
LV	Left Ventricular
TTE	Trans-Thoracic Echo
RVEF	Right ventricular ejection fraction
sPAP	systolic Pulmonary Artery Pressure

Author contributions

Conceptualization: Nakisa Khansari and Amir Mohammad Salehi.; methodology: Niloofar Mohammadiand Amir Hossein Yazdi.; software, Zahra sanaei.; investigation, Niloofar Mohammadi.; data curation, Nakisa Khansari and Niloofar Mohammadi.; writing-original draft preparation, Amir Mohammad Salehi; writing-review and editing: All authors. All authors read and approved the final manuscript.

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Data availability

Because the consent given by study participants did not include data sharing with third parties, anonymized data can be made available to investigators for analysis on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hamadan University of Medical Science (IR.UMSHA.REC.1401.646).

Human and animal rights

No animals were used in this research. All procedures performed in studies involving human participants were by the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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