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Type of menopause, age of menopause and cardiovascular disease: a cross-sectional study based on data from Rafsanjan cohort study

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Abstract

Background Cardiovascular disease is the leading cause of death among women, but sex-specific risk factors are incompletely understood. In this study, we aimed to assess the associations between the type of menopause, and age at natural menopause with the odds of cardiovascular disease (CVD), and coronary heart disease (CHD).

Methods This cross-sectional study is a part of data from the Rafsanjan Cohort Study (RCS) which is a branch of the Prospective Epidemiological Research Studies in Iran (PERSIAN). A sample of 1767 postmenopausal women were included. The diagnosis for CVD and CHD was based on self-report questionnaires. Menopause age was categorized as < 40, 40–44, 45–49, and ≥ 50. Also, the menopause types were classified as natural and induced menopause (surgery or chemotherapy). The association was evaluated by logistic regressions.

Results The menopause age < 40 years had higher odds of CVD compared to women with menopause age > 40 years (OR: 2.66; 95%CI 1.29–5.48). Women with induced menopause had higher odds of CVD compared to women with natural menopause (OR = 1.44, 95% CI 1.04–1.98). In terms of the odds of CHD, the results showed that the odds of CHD increased in menopause age < 40 years and induced menopause compared to reference groups (OR: 2.49, 95% CI 1.15–5.37, OR = 1.48; 95% CI 1.06–2.07, respectively).

Conclusion Premature menopause and induced menopause should be considered as important risk factors for CVD, and CHD. Health policymakers should pay more attention to the type of menopause and the age of menopause in postmenopausal women to predict the risk of CVD and preventive strategies.

Keywords Menopause, Early menopause, Premature menopause, Cardiovascular diseases, Coronary disease, Rafsanjan cohort study (RCS), Prospective epidemiological research studies in Iran (PERSIAN)

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Introduction

Among women, cardiovascular disease (CVD) is one of the leading causes of death, accounting for 50% of cases; from this 20% can be attributed to ischemic heart disease (IHD), and 13% to stroke [1]. In addition to obstructive coronary heart disease (CHD) in middle-aged women, other important causes of IHD include coronary artery spasm and coronary microvascular dysfunction [2]. Although IHD occurs 7–10 years later in women than in men, largely due to the protective effect of estrogen on the atherosclerotic process, the risk gradually increases after menopause [2]. It is mostly seen in women with early menopause (defined as starting menopause below 45 years old) or premature ovarian insufficiency (defined as starting menopause below 40 years old) [3, 4].

In Western countries, studies between the 1990s and 2000s reported the mean age of menopause was 51 to 52 years [5]. Up to 10% of women experienced menopause before the age of 45 and 1% before 40 years old [6]. Some previous studies reported that premature menopause, for both natural and surgical reasons, was associated with a significantly higher risk for cardiovascular diseases in women [7–9]. Inconsistently, a previous study found that premature natural menopause (not premature surgical menopause) was associated with a higher risk of adverse cardiovascular outcomes [10]. In a systematic review and meta-analysis by Muca et al., women with early menopause (<45 years) had a greater risk for coronary heart disease (50%) compared to women with menopause at 45 years or older, but there was a controversy in the correlation between age at menopause and stroke [11]. Furthermore, two previous prospective studies did not find a relationship between age at menopause and atrial fibrillation [12, 13].

However, CVD causes women's deaths worldwide [14], and the sex-specific factors are unknown or poorly understood [15]. Adverse changes in the CVD risk factors that take place around menopause indicate a need for early recognition of these risk factors and the initiation of appropriate preventive or curative modalities [11]. Women with menopause or early menopause are not only at risk of early onset of cardiovascular events from a younger age, but they also live with an increased risk of adverse outcomes [16]. It's of great importance to evaluate the association between CVD and both age and time of onset of menopause.

We hypothesized that immature menopause or early menopause and induced menopause would lead to higher odds of cardiovascular disease. So, in this study, the aim was to assess the associations between the type of menopause, and age at natural menopause with the odds of CVD and CHD. For this purpose, we evaluated the odds of CHD and CVD in women with natural vs. induced menopause and related them to the age at menopause. However, the relationship between the age of menopause and cardiovascular risk has been studied in previous studies. This study is a large-scale population-based study that was conducted to determine the relationship between type of menopause, age of menopause, and cardiovascular disease among Iranian women in the southeast of Iran.

Methods

Study design

This cross-sectional study is a part of data from the Rafsanjan Cohort Study (RCS), which is a branch of the Prospective Epidemiological Research Studies in Iran (PERSIAN) [17]. RCS is a population-based study launched in August 2015 in Rafsanjan, a city in the southeast of Iran. At the enrollment phase of the study, trained questioners measured anthropometric characteristics and collected data on socio-demographic factors, medical history, personal habits, and reproductive factors of participants using a laptop-based questionnaire. Written informed consent was obtained from all participants. The study protocol was approved by the ethics committee of Rafsanjan University of Medical Sciences (Ethical codes: ID: IR.RUMS.REC.1400.145). All the study was conducted according to the relevant guidelines and regulations of the institution. A more detailed description of the RCS, including the study recruitment and design, has been published previously [18]. In this study, 9991 subjects, including 5336 women aged 35–70 years participated. Among them, 2359 women had valid data on menopause age and were considered postmenopausal women. Women who had a history of cancer, hormone replacement therapy (HRT), and women who had experienced CVD events before menopause were excluded from the study. Also, women with hysterectomy but with ovaries conserved were omitted, as their menopausal age could not be determined for certain. Finally, 1767 postmenopausal women were included in the present study.

Socio-economic status was determined based on the wealth score index (WSI), which is estimated by multiple correspondence analysis (MCA) of the economic variables of subjects such as access to a laptop, owning a house, and having international trips in a lifetime. Marriage status was categorized as married and single. Single women were including never married, divorced, widowed, or other. Smoking status was categorized as smokers and non-smokers. Women who reported smoking at least 100 cigarettes during their lifetime were considered smokers. Women who reported using opium at least once per week for 6 months during their lifetime were defined as opium users. Metabolic equivalent task hours (MET-hours/day) were used to determine the level of physical activity. The diagnosis for myocardial infarction (MI), cardiac diseases (CHD: including ischemic

heart disease, heart failure), and stroke was based on self-report in the Cohort questionnaire. CVD included MI, CHD, or stroke. Dyslipidemia was defined based on the Third Report of the National Cholesterol Education Program (NCEP-Adult Treatment Panel III). LDL≥130 mg/dL, or TC≥200 mg/dL, or HDL≤40 mg/dL in men and 50 mg/ dl in women, or TG≥150 mg/dL and/or consuming medications for lowering lipids in the past two weeks [19].

Diabetes was defined as FBS≥126 mg/dL or taking the antidiabetic drugs [20]. Systolic blood pressure of 140 mmHg or more, diastolic blood pressure of 90 mmHg or more, or taking antihypertensive drugs was considered hypertension [21].

The age of women was categorized into three groups based on the 25th and 50th percentiles. Based on the response to the self-reported questionnaire, menopause age was categorized as <40 (premature menopause), 40–44 (early), 45–49 (relatively early), and ≥50 (reference category) [22]. Also, menopause age was divided into two groups (<40 and >40) [23]. Menopause type was classified as natural and induced menopause (induced menopause with surgery or chemotherapy). Natural menopause was defined as the absence of menstruation over 12 months for those who did not experience hysterectomy [17]. The frequency difference between the total number and some of the variables was related to missing data.

Statistics analysis

Since the frequency of MI and stroke were so low in the present study (MI: 42 and stroke: 31), the models were run for the association between menopause status and CHD and CVD. Quantitative variables were described as the mean (standard deviation) or median [IQR] as appropriate, and categorical variables as the frequency and percentage. The series of characteristics of individuals were compared across the groups (CVD, no CVD) using the chi-square test for categorical variables, and T-test for normally distributed quantitative variables, and the Mann–Whitney U test for nonnormally distributed quantitative variables. The assumption of normality of the distribution of continuous variables was tested using normal probability plots (skewness and kurtosis index). Additionally, we used logistics regression models to determine the odds ratios (ORs) and the corresponding 95% confidence intervals (CI) for the association between type of menopause, age of menopause, and cardiovascular disease. The models were run for the association between menopause status and CHD and CVD. Potential confounding variables were sequentially entered into the model according to their hypothesized strengths of association with the type of menopause, age of menopause and cardiovascular disease. Variables with a p-value<0.25 were considered as confounders.

The crude model is stratified on the status of menopause. The adjusted Model 1 was run for confounding variables age (continuous variable), education (continuous variable), WSI (continuous variable), cigarette smoking (never, current, former), opium consumption (yes/no), and physical activity level (continuous variable). The adjusted model 2 was adjusted for confounding variables in adjusted model 1 and BMI (continuous variable) diabetes (yes/ no), hypertension (yes/no), dyslipidemia (yes/no), and first-degree family history of CVD (yes/no).

All analyses were performed using Stata V.14. All p-values are two-sided, and p-values<0.05 and 95% confidence intervals were considered statistically significant.

Results

Table 1 gives descriptive statistics and the menopause status of study participants by CVD status. There were 221 women with a history of CVD (CHD: 197, MI: 42, and stroke: 31). As expected, female participants with CVD were significantly older (≥56 years old) than no CVD group ($P<0.001$). However, cigarette smoking was not differing between the two groups ($p=0.225$). Opium consumption was significantly higher in the CVD group (10.41% vs. 5.83%). In addition, the median of education, physical activity, and WSI were lower in the CVD group than the no CVD group.

Table 2 presents the medical history and menopause status of study participants by CVD status. The prevalence of hypertension (67.87), diabetes (52.51%), dyslipidemia (90.83%), and history of CVD in first-degree relatives (62.9) in the CVD group were significantly higher than no CVD group (hypertension: 45.99, diabetes: 40.13%, dyslipidemia: 85.36%, and history of CVD in first degree relatives: 52.2%)). There was a significant difference in CVD prevalence among women based on menopause age (<40 and >40, $P=0.022$).

Table 3 shows the results of the crude and multiple logistic regression analysis between CVD, CHD, and menopause indices. Based on menopause age<40 and >40, the results showed that women with menopause age<40 years had higher odds of CVD compared to women with menopause age>40 years after adjusting the confounders, (adjusted model 1: OR=2.48; 95% CI 1.29–4.75 and adjusted model 2: OR=2.38; 95% CI 1.17–4.84). Additionally, women with menopause age<40 years had higher odds of CVD compared to women with menopause age≥50 years in a fully adjusted model (OR: 2.66, 95% CI: 1.29–5.48). It was also observed that women with induced menopause had higher odds of CVD (adjusted model 1: OR=1.51; 95% CI 1.10–2.07 and adjusted model 2: OR=1.44; 95% CI 1.04–1.98) compared to natural menopause group. In terms of the odds of CHD, the same

Table 1 Demographic characteristics of study participants according to CVD history ($n=1767$)

characteristic	Total ($n=1767$)	CVD ($n=221$)	No-CVD ($n=1546$)	*P*-Value
Age- years. n (%)				< 0.001
≤ 45	14(0.79)	0(0)	14(0.91)	
46–55	496(28.07)	19(8.60)	477(30.85)	
>=56	1257(71.14)	202(91.40)	1055(68.24)	
Mean ± SD	58.63 ± 5.39	61.43 ± 4.54	58.23 ± 5.39	< 0.001
Education- years. n (%)				< 0.001
≤ 5	1180(66.78)	165(74.66)	1015(65.65)	
6–12	480(27.16)	45(20.36)	435(28.14)	
≥ 13	107(6.06)	11(4.98)	96(6.21)	
Median (IQR)	5(0–8)	5(0–8)	8(5–12)	< 0.001
Physical activity				< 0.001
Median (IQR)	37.33(35.27–39.48)	36.6(34.55–38.68)	37.85(35.87–39.7)	
WSI				0.005
Median (IQR)	-0.506(-1.078-0.480)	-0.438(-01.978-0.108)	-0.060(-0.625-0.480)	
Marital status. n (%)				0.003
Single	340(19.24)	59(26.70)	281(18.18)	
Married	1427(80.76)	162(73.30)	1265(81.82)	
Cigarette smoking. n (%)				0.225
Current	43(2.43)	9 (4.03)	34(2.20)	
Former	35(1.98)	5(2.26)	3.(1.94)	
Never	1688(95.58)	2.7(93.67)	1481(95.86)	
Opium consumption. n (%)				0.009
Yes	113(6.40)	23(10.41)	90(5.83)	
No	1653(93.60)	198(89.59)	1455(94.17)	
Alcohol consumption. n (%)				N/A
Yes	0	0	0	
No	1766(100)	221(100)	1545(100)	
BMI- kg/m^2. n (%)				0.613
< 25	291(16.47)	32(14.48)	259(16.75)	
25_29.99	678(38.37)	90(40.72)	588(38.03)	
>=30	798(45.16)	99(44.80)	699(45.21)	
Median (IQR)	29.40(26.17–32.50)	29.78(27.19–33.05)	28.92(25.90-32.15)	0.137

Abbreviations Wealth score index (WSI); Body mass index (BMI), Cardiovascular disease (CVD), Inter quartile range (IQR)

Table 2 Medical characteristics and menopause status of study participants according to CVD history ($n=1767$)

Characteristic	Total ($n=1767$)	CVD ($n=221$)	No-CVD ($n=1546$)	*P*-Value
Hypertension. n (%)				< 0.001
Yes	861(48.73)	150(67.87)	711(45.99)	
No	906(51.27)	71(32.13)	835(54.01)	
Diabetes. n (%)				0.001
Yes	735(41.67)	115(52.51)	620(40.13)	
No	1029(58.33)	104(47.49)	925(59.87)	
Dyslipidemia. n (%)				< 0.001
Yes	1516(86.04)	198(90.83)	1318(85.36)	
No	246(13.96)	20(9.17)	226(14.64)	
History of CVD in first-degree relatives. n (%)				0.003
Yes	946(53.54)	139(62.90)	807(52.2)	
No	821(46.46)	82(37.10)	739(47.8)	
History of CHD in first-degree relatives. n (%)				0.138
Yes	586(33.15)	83(37.56)	503(32.54)	
No	1181(66.84)	138(62.44)	1043(67.46)	
Menopause age. n (%)				0.029
< 40	66(3.74)	14(6.33)	52(3.36)	
≥ 40	1701(96.26)	207(93.67)	1494(96.64)	
Menopause age-years. n (%)				0.170
≥ 50	975(55.18)	118(53.30)	857(55.43)	
45–49	513(29.03)	65(29.41)	448(28.93)	
40–44	213(12.05)	24(10.86)	189(12.23)	
< 40	66(3.74)	14(6.33)	52(3.36)	
Median (IQR)	50(46–52)	49(45–52)	49(45–52)	0.188
Menopause type– n (%)				0.362
Natural	1619(77.99)	204(75.84)	1415(78.31)	
Induced	457(22.01)	65(24.16)	392(21.69)	

Abbreviations Cardiovascular disease (CVD). Inter quartile range (IQR)

results were observed. The results showed that the odds of CHD increased in women with menopause age < 40 years and induced menopause compared to the reference group in a fully adjusted model.

The association of CVD and CHD with age at menopause, as a continuous variable was also analyzed. The results showed that the odds of CVD and CHD were decreased with increasing menopause age in a fully adjusted model (OR: 0.96, 95% CI: 0.93–0.99), OR: 0.96, 95% CI: 0.93–0.99), respectively).

In this papulation, we excluded women who reported HRT usage ($n=89$) before analysis. We included them in the further analysis (supplementary data), and the results were not changed. Due to the small sample size of the HRT group ($n=89$), it was not possible to run an adjusted model for HRT users.

Discussion

In this study, which was a population-based study of 1767 postmenopausal women in Rafsanjan, the relationship between the type, and age of menopause and cardiovascular diseases was investigated. Recently many studies have paid attention to women's health, and one of the main topics was the distinction between the effect of women's age, with the effect of menopause, on women's health [24]. This study was done to answer one of the most important issues; can decreased age at menopause compromise long-term cardiovascular health seriously or

Table 3 The odds ratio of CVD and CHD by menopause status

	Crude Model	Adjusted Model 1	Adjusted Model 2
CVD			
Menopause age			
≥ 40	1	**1**	**1**
< 40	**1.94(1.06–3.57)**	**2.48(1.29–4.75)**	**2.38(1.17–4.84)**
Menopause age. years	0.98(0.95–1.01)	**0.96(0.93–0.99)**	**0.96(0.93–0.99)**
Menopause age			
≥ 50	1	1	1
45–49	1.05(0.76–1.46)	1.34(0.96–1.87)	1.33(0.95–1.88)
40–44	0.92(0.58–1.47)	1.09(0.67–1.76)	1.16(0.71–1.90)
< 40	**1.96(1.05–3.64)**	**2.75(1.41–5.35)**	**2.66(1.29–5.48)**
Menopause type			
Natural	1	1	1
Induced	1.15(0.85–1.55)	**1.51(1.10–2.07)**	**1.44(1.04–1.98)**
CHD			
Menopause age			
≥ 40	1	1	1
< 40	1.85(0.97–3.52)	**2.40(1.21–4.77)**	**2.25(1.06–4.80)**
Continues	0.98(0.95–1.01)	**0.96(0.93–0.99)**	**0.96(0.93–0.99)**
Menopause age			
≥ 50	1	1	1
45–49	1.01(0.71–1.42)	1.29(0.90–1.84)	1.29(0.90–1.85)
40–44	0.94(0.58–1.53)	1.12(0.68–1.85)	1.19(0.71–1.97)
< 40	1.84(0.95–3.55)	**2.63(1.30–5.31)**	**2.49(1.15–5.37)**
Menopause type			
Natural	1	1	1
Induced	1.17(0.85–1.59)	**1.54(1.11–2.14)**	**1.48(1.06–2.07)**

The crude model was stratified on the status of menopause

The adjusted Model 1 was adjusted for confounding variables age (continuous variable), education (continuous variable), WSI (continuous variable), cigarette smoking (never, current, former), opium consumption (yes/no), and physical activity level (continuous variable)

The adjusted model 2 was adjusted for confounding variables in adjusted model 1 and BMI (continuous variable) diabetes (yes/ no), hypertension (yes/ no), dyslipidemia (yes/no), and first-degree family history of CVD (yes/no)

Abbreviations Body mass index (BMI); Wealth score index (WSI); cardiovascular disease (CVD); coronary heart disease (CHD)

not? This cross-sectional study will answer this question based on RCS data in Rafsanjan, southeast of Iran.

The primary analysis of the relationship between demographic and selected medical characteristics of study participants showed that the prevalence of CVD significantly increased with the increase in age. However multi-factorial risks are involved in cardiovascular disease (CVD) such as diabetes, obesity, and etc [25]. , . The result showed a higher prevalence of CVD among women with lower levels of education, which has been approved previously [26, 27]. However, there was a controversial result, when the finding showed a higher frequency of CVD among women with higher levels of education [28]. Also, a higher frequency of CVD was reported in subjects with opium consumption, lower physical activity, and lower WSI. The prevalence of hypertension, diabetes, dyslipidemia, and history of CVD in first-degree relatives was significantly higher in the CVD group than in the non-CVD group.

In the present study, one of the main findings was that the odds of CVD and CHD increased about 2.5 times in premature menopause (˂40) compared to the reference group after adjusting for the confounders. This finding confirms the results of the previous studies which concluded that premature menopause acts as a risk factor for CVD [29]. A pooled analysis study from 15 observational studies on 301,438 women conducted between 1946 and 2013, showed that women who underwent premature menopause (age < 40 years; HR 1.55, 95% CI, 1.38–1.73), early menopause (age 40–44 years; HR: 1.30, 95% CI, 1.22–1.39), and relatively early menopause (age 45–49 years; HR: 1.12, 95% CI, 1.07–1.18), had an elevated risk of CVD compared to the women who experienced menopause at age 50–51 years. Similar associations were also found for incidents of coronary heart disease and stroke [28]. Also, Torbati showed that experiencing early menopause (< 45 years) or premature menopause (< 40 years) among 1.4 million post-menopausal women following 9 years of follow-up, increased the risk for adverse cardiovascular outcomes [10]. On the other hand, two previous prospective studies did not find a relationship between age at menopause and atrial fibrillation [12, 13]. Inconsistencies in these findings could be due to differences in sample size, diet, race, study design (cross-sectional or follow-up), study type (population-based or hospital-based), statistical analysis methods, CVD diagnostic criteria, menopause status, as well as differences in the adjusted confounding factors in different studies.

In the present study, the calculated odds remained significant when other confounders for cardiovascular disease were included in the statistical model. The results are inconsistent with the other studies which elevated risk (two times higher) of coronary heart disease for early menopause became insignificant after adjusting the model for some confounders [30]. Also, the primary estimated risk (2.2) in the other study became insignificant when the participants were classified based on menopausal hormone therapy [31].

Several mechanisms have been suggested to describe the observed association. Besides the other hormonal mechanisms that may be involved, endogenous estrogen deficiency plays a role in increasing the risk of CVD development [32]. A hypoestrogenic state has been

reported in both premature menopause and surgical oophorectomy [33].

Our study showed that not only premature menopause but also induced menopause was associated with significantly increased odds of CVD. This result was in line with the previous studies, which concluded that premature menopause, for both natural and surgical reasons, was associated with a significantly higher risk for cardiovascular diseases in women [7, 8]. The related literature believes that the decrease in endogenous estrogen, in menopause, is accompanied by the risk, and estrogen therapy plays a protective role in this setting [8, 32]. The proposed mechanism is that estrogen decreases low-density lipoprotein cholesterol (LDL), and increases high-density lipoprotein (HDL) and triglyceride (TG) levels in plasma [34].

Regarding CHD, the present study found that the odds were higher in the induced menopause group compared to natural menopause. Similarly, the results from another cohort and meta-analysis studies suggest that CHD has a higher risk among premature menopausal women, spontaneous or surgical oophorectomy, compared with intact women [11, 24]. Also, it was shown that premature menopause increased the chance of Clonal hematopoiesis of indeterminate potential (CHIP), a known risk factor for CHD [29]. However, there is a study that didn't find a significantly higher risk of HF in surgically premature menopause, they suspected this may be because of the shorter time duration for gathering data related to bilateral oophorectomy compared to natural menopause [23].

It was mentioned that menopause plays a role as a risk factor, through some complex biochemical and metabolic changes, such as an increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), triglycerides, and apolipoprotein B and a decrease in high-density lipoprotein cholesterol (HDL). They defined menopause as the stage of women's transition from low-risk to high-risk of CHD [35, 36]. Menopausal women become more susceptible to cardiometabolic risk factors such as hypertension, as their natural estrogen levels decrease [23]. Body fat distribution changes during menopause, and other conditions such as visceral adiposity and insulin resistance will develop metabolic syndrome. Consequently, as these events and lipid profiles shift towards proatherogenicity, the risk of CVD will increase [37].

Recently, it was shown that the prevalence of premature (3·7%) and early menopause has increased considerably [38]. It was estimated that 47 million women became menopausal each year [39]. Our findings overall showed that premature menopause should be considered as a main risk factor for cardiovascular disease and coronary heart disease in women. The higher estimated risk, in different studies worldwide, emphasizes some public health implications for the communities; considering early or premature menopause as a risk factor for CVD, having plans to decrease the probability of early menopause, having special plans such as active screening, and close monitoring for other risk factors, in the aim to reduce the overall risk for cardiovascular disease in postmenopausal women.

One of our study's strengths was a population-based study with a large sample size and an evaluation of the various potential confounders. However, there were some limitations, which are inevitable, such as the cross-sectional nature of the study which does not allow the presentation of causal relationships. More longitudinal studies are needed to verify these associations. Another limitation was self-reported age at natural menopause. The person reminder is a risk for non-differential misclassification. Nevertheless, a previous study showed that self-reported age at natural menopause by recall is reliable data [40].

Conclusions

Our findings showed that premature menopause and induced menopause should be considered as important risk factors for CVD, and CHD in women, and they also can be effective in increasing the awareness of health policy makers to have specific preventive and therapeutic programs such as active screening and careful monitoring for other risk factors, with the aim to reduce the overall risks for cardiovascular diseases in postmenopausal women.

Author contributions

Dr. Vatanparast: Conceptualization, Methodology Dr. Jamali: Data collection and Data analysis Dr. Ayoobi: Manuscript editing, final approval of the version to be submitted Dr. Esmaeili-Nadimi: Writing – original draft Dr. Khalili: Designed the model and software Dr. Vatankhah: Analysed the data Dr. Esmaeili ranjbar: Data collectionAll authors have seen and approved the final version of the manuscript being submitted.

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Data availability

Derived data supporting the findings of this study are available from the corresponding author on request.

Declarations

Ethical approval

The study protocol was approved by the ethics committee of Rafsanjan University of Medical Sciences (Ethical codes: ID: IR.RUMS.REC.1400.145).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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