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Original Article

Comparative Evaluation of Fibrosis-4 Index and FibroScan for Liver Fibrosis Estimation among Psoriatic Arthritis Patients on Methotrexate

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ABSTRACT

Background:
Psoriatic arthritis (PsA) often requires long-term methotrexate (MTX) therapy, which is associated with the risk of liver fibrosis. Non-invasive tests like elastography and the Fibrosis-4 (FIB-4) index have been studied to assess liver stiffness. This study aimed to compare the FIB-4 index with liver fibrosis severity measured by FibroScan in PsA patients on MTX.

Materials and Methods:
A cross-sectional study included patients with PsA on MTX at the Rheumatology Clinic of Hazrat Rasoul Akram Hospital. Data were collected on demographics, clinical characteristics, FIB-4 index, and liver stiffness measured by FibroScan. Statistical analyses evaluated correlations between FIB-4 and FibroScan results.

Results:
Among 70 participants, 21 (30%) were men. The mean (+ standard deviation [SD]) age of all study subjects was 55.11 (±15.15) years. The average (+SD) disease duration was 7.34 (±5.18) years. The mean (+SD) FIB-4 index was 1.19 (±0.64). A total of 53 (75.71%), 15 (21.43%), and 2 (2.86%) study subjects according to FIB-4 index, and 56 (80%), 8 (11.43%), and 6 (8.57%) according to Fibroscan grades were categorized as having 'normal to mild', 'mild to moderate', and 'moderate to severe' liver fibrosis, respectively. There was a weak positive but non-significant correlation between FIB-4 and FibroScan scores (r=0.01; P=0.936). A normal to mild FIB-4 index correctly excluded moderate to severe fibrosis in 51% of cases, which was not statistically significant (P=0.504).

Conclusion:
The FIB-4 index showed a limited correlation with liver fibrosis severity measured by FibroScan in patients with PsA on MTX therapy. While FIB-4 may be a potential screening tool, it is not sufficiently accurate to replace elastography. Further studies with larger samples are required.

Keywords: Psoriatic arthritis, Methotrexate, Liver fibrosis, FIB-4 index, FibroScan, Elastography

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disorder associated with pain, swelling, stiffness, and joint damage (1). It typically occurs alongside psoriasis, a chronic autoimmune condition characterized by inflamed, scaly skin patches, affecting both men and women equally across a wide age range (2). The systemic nature of PsA can involve various organs and is often accompanied by conditions such as uveitis, inflammatory bowel disease, and cardiovascular complications, significantly increasing morbidity (3,4).

Moreover, PsA is associated with a sedentary lifestyle, which increases the risk of developing comorbidities like metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) (5). The link between NAFLD and PsA has been established in various studies, suggesting that the systemic inflammation seen in PsA may predispose patients to hepatic involvement (6).

Methotrexate (MTX) remains a mainstay in treating PsA and is widely used due to its effectiveness and relatively good tolerability (7). However, long-term MTX use has been associated with hepatotoxicity, potentially leading to liver fibrosis or even cirrhosis in some cases (8). Current guidelines suggest monitoring liver function and considering liver biopsies for patients with risk factors for hepatotoxicity (9). Despite being the gold standard for diagnosing liver fibrosis, liver biopsy is invasive and associated with risks and patient discomfort (10).

In recent years, non-invasive alternatives such as serum biomarkers and imaging modalities have been developed to assess liver fibrosis. The Fibrosis-4 (FIB-4) index is a simple and readily available tool that uses age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count to estimate liver fibrosis (11). It has been validated in multiple hepatic conditions, including hepatitis C, hepatitis B, and NAFLD (12). Despite its utility, the accuracy of the FIB-4 index in assessing liver fibrosis in patients with PsA, particularly those undergoing MTX treatment, has not been fully established (13).

Another method for assessing liver fibrosis is transient elastography (FibroScan), a non-invasive imaging technique that measures liver stiffness (14). Studies have demonstrated that FibroScan is a reliable and reproducible tool for assessing liver fibrosis, providing a viable alternative to liver biopsy (15,16). The correlation between FIB-4 and FibroScan has been explored in some hepatic conditions; however, their applicability and accuracy in patients with PsA on MTX therapy remain under-researched (17).

Therefore, this study aimed to compare the FIB-4 index with the severity of liver fibrosis as determined by FibroScan in patients with PsA treated with MTX. By evaluating the correlation between these two measures, the study seeks to determine the efficacy of the FIB-4 index as a non-invasive tool for liver fibrosis assessment in this specific patient population.

MATERIALS AND METHODS

This cross-sectional analytical study was conducted from June 2022 to June 2023, targeting patients attending the Rheumatology Clinic at Hazrat Rasoul Akram Hospital in Tehran. Ethical approval for the study was obtained from the Ethics Committee of Iran University of Medical Sciences (approval code: 27325). Inclusion criteria were patients aged 18 and older, hospitalized, and treated with cumulative doses of MTX over a 12-month period (minimum 1 night for evaluation or treatment), with PsA diagnosis confirmed clinically and radiologically. Exclusion criteria encompassed a history of regular alcohol consumption or abuse; history of viral hepatitis or any acute, subacute, or chronic hepatitis; congenital metabolic diseases; hematological malignancies; clinical conditions affecting liver stiffness; and contraindications for FibroScan (e.g., pregnancy).

Data were collected using a standardized checklist that included patient details (name, diagnosis, hospitalization, contact information), demographic data (age, sex, body mass index [BMI]), comorbidity history (e.g., hypertension, diabetes), duration of MTX treatment, time since PsA diagnosis, and the date of elastography assessment. The FIB-4 index was calculated using the following formula (17):

$$\text{FIB-4}=\frac{\text{Age (years)} \times \text{AST(U/L)}}{\text{Platelet count } (10^9\text{L}) \times \sqrt{\text{ALT(U/L)}}}$$

The FIB-4 index was classified into three categories: values less than 1.45 indicated no or mild fibrosis, values between 1.45 and 3.25 represented moderate fibrosis, and values greater than 3.25 suggested severe fibrosis (17). Liver stiffness was further assessed using FibroScan, where mild fibrosis (F1) was defined as liver stiffness measurement (LSM) values between 7.0–8.1 kPa, moderate fibrosis (F2) as 8.2–9.6 kPa, advanced fibrosis (F3) as 9.7–13.5 kPa, and cirrhosis (F4) as values ≥13.6 kPa, according to a previous landmark study (18).

The sampling was conducted randomly until the target sample size was achieved. The sample size was determined based on a comparison of two means: the FIB-4 index and liver fibrosis score obtained via elastography. The calculated sample size was 70 participants, using the following formula:

$$n=\left(\frac{z_{1-\alpha/2}+z_{1-\beta}}{d}\right)^2\times 2\sigma^2$$

The sample size was calculated to achieve a power of 80% (β = 0.2) and a significance level of 5% (α = 0.05). The effect size was assumed to be 0.3, and the standard deviation (σ) was 0.63.

Statistical Analysis

The data were analyzed using SPSS software version 25. Continuous variables were presented as mean±standard deviation (SD) or median and interquartile range (IQR) for non-normally distributed data. Categorical variables were reported as frequencies and percentages. The normality of distributions was assessed using the Kolmogorov-Smirnov test. Parametric tests (t-test, ANOVA) were used for normal data, and non-parametric tests (Mann-Whitney U, Kruskal-Wallis) for skewed data. Pearson's correlation coefficient analyzed associations between continuous variables or Spearman's correlation if normality assumptions were violated. A logistic regression model assessed potential confounders, and odds ratios (OR) were reported.

RESULTS

In total, 70 patients with PsA were included in the study. The average age of the patients was 59.59±11.75 years, ranging from 35 to 82 years. Of these patients, 30% were men and 70% were women. The mean age was higher in women (60.85±11.3 years) compared with men (57±12.47 years); however, the difference was not statistically significant (P=0.20).

Demographic and Clinical Characteristics

The mean BMI was 26.58±3.91 kg/m², with a range of 19.5 to 37.33 kg/m². The BMI was slightly higher in women (26.7±3.98 kg/m²) than in men (26.35±3.85 kg/m²), though this difference was not statistically significant (P=0.588).

The mean duration of PsA was 7.34±5.18 years, ranging from 0.5 to 21 years. When examined by sex, the mean duration was 7.21±4.97 years in women and 7.61±5.69 years in men, without a statistically significant difference (P=0.766). A summary of the demographic and clinical characteristics of the study population is presented in Table 1.

Table 1. Demographic and clinical characteristics of patients with PsA

Parameter	Female Mean±SD	Male Mean±SD	Total Mean±SD	P value
Age (years)	60.85±11.3	57±12.47	59.59±11.75	0.20
BMI (kg/m²)	26.7±3.98	26.35±3.85	26.58±3.91	0.588
Disease duration (years)	7.21±4.97	7.61±5.69	7.34±5.18	0.766

The relationship between age and disease duration showed a moderate, positive correlation (r=0.31, P=0.01).

Methotrexate Dosage and Its Associations with Patient Characteristics

MTX Dosage Distribution

The distribution of MTX dosages among patients with PsA is detailed in Table 2. The most commonly administered dose was 10 mg, given to 44.29% of patients, followed by 15 mg (15.71%), and 7.5 mg (14.29%). Other doses were less frequently prescribed.

Associations Between MTX Dosage and Patients' Characteristics

The analysis revealed no significant associations between MTX dose and patient sex (P=0.233), age (P=0.799), or disease duration (P=0.653). However, there was a statistically significant positive association between MTX dose and BMI (P=0.018). A summary of the associations between MTX dosage and sex, age, BMI, and disease duration is presented in Table 3.

Table 2. Frequency and percentage of methotrexate doses among patients with PsA

Methotrexate dose (mg)	Frequency (%)
10	31 (44.29%)
15	11 (15.71%)
7.5	10 (14.29%)
5	7 (10%)
12.5	5 (7.14%)
20	5 (7.14%)
17.5	1 (1.43%)
Total	70 (100%)

Table 3. Relationship between methotrexate dose and patients' characteristics (sex, age, BMI, and disease duration).

Variable	B	Standard Error	Beta	t	p
Sex	-1.18	0.98	-0.14	-1.2	0.233
Age	-0.01	0.04	-0.03	-0.26	0.799
BMI	0.29	0.12	0.29	2.43	0.018
Disease Duration	0.04	0.09	0.06	0.45	0.653

B represents the unstandardized coefficient, t is the t-statistic for testing the coefficient's significance, and p is the associated P value, with significance set at < 0.05.

A Pareto chart (Figure 1) was generated to visually depict the standardized effects of various factors on MTX dosage. It clearly highlights that BMI has the most substantial impact on MTX dose, followed by sex, disease duration, and age.

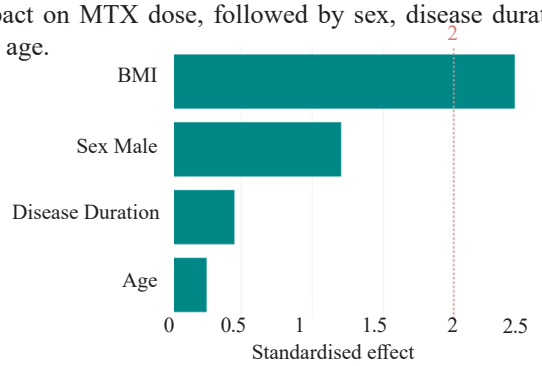

Figure 1. Standardized effect of patient characteristics on methotrexate dose

FIB-4 Index and Liver Fibrosis in Patients with PsA

The mean FIB-4 index among patients with (PsA was 1.19±0.64, ranging from 0.45 to 4.19 (Table 4). A raincloud plot (Figure 2) provides a visual representation of the distribution of FIB-4 values across the study population.

Table 4. Summary statistics of FIB-4 index in patients with PsA

Statistic	FIB-4 value
Mean	1.19
Std. Deviation	0.64
Minimum	0.45
Maximum	4.19

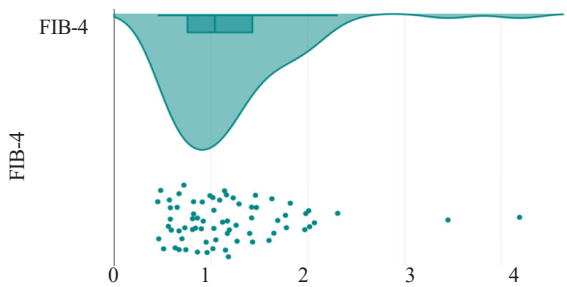

Figure 2. A raincloud plot illustrating the distribution of FIB-4 index values among patients with PsA

Stages of Liver Fibrosis Based on FIB-4

The distribution of liver fibrosis stages based on the FIB-4 index is presented in Table 5. The majority of patients had normal to mild fibrosis.

Table 5. Frequency and percentage of liver fibrosis stages based on FIB-4 index in patients with PsA

FIB-4 Stage	Frequency (%)
Normal to Mild	53 (75.71%)
Mild to Moderate	15 (21.43%)
Moderate to Severe	2 (2.86%)
Total	70 (100%)

Associations Between FIB-4 Index and Patients' Characteristics

The FIB-4 index did not show a significant association with sex (P=0.271), BMI (P=0.563), disease duration (P=0.42), or MTX dose (P=0.358). However, a significant positive correlation was observed between the FIB-4 index and age (P<0.001). The associations between the FIB-4 index and patients' characteristics are summarized in Table 6 and visually represented in the Pareto chart (Figure 3), highlighting the impact of age on FIB-4.

Table 6. Association between FIB-4 index and patient characteristics (gender, age, body mass index [BMI], and disease duration)*

Table 6. Association between FIB-4 index and patient characteristics (gender, age, body mass index [BMI], and disease duration)*

Variable	B	Standard Error	Beta	t	p
Sex	0.16	0.14	0.12	1.11	0.271
Age	0.03	0.01	0.58	5.23	<0.001
BMI	0.01	0.02	0.06	0.58	0.563
Disease duration	-0.01	0.01	-0.09	-0.81	0.42

* B represents the unstandardized coefficient; t is the t-statistic for testing the coefficient's significance; and P is the associated p-value, with significance set at < 0.05.

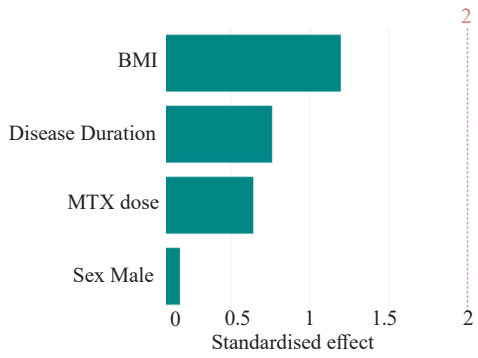

Figure 3. Pareto chart illustrating the standardized effect of patients' characteristics on the FIB-4 index

Distribution of Elastography Results

The distribution of elastography scores and fibrosis stages among patients with PsA is summarized in Table 7. Overall, 80% of patients were categorized as having normal to mild fibrosis, 11.43% had mild to moderate fibrosis, and 8.57% had moderate to severe fibrosis. Within the normal to mild stage, elastography scores were further detailed as 0-1 (55.71%), 0 (12.86%), and 1 (11.43%).

Table 7. Combined distribution of liver fibrosis stages and specific elastography scores in PsA patients.

Elastography stage	Elastography scores	Frequency (%)	Frequency by score (%)
Normal to Mild	0-1	56 (80%)	39 (55.71%)
	0		9 (12.86%)
	1		8 (11.43%)
Mild to Moderate	2	8 (11.43%)	7 (10%)
Moderate to Severe	3	6 (8.57%)	6 (8.57%)
	2-3		1 (1.43%)
Total		70 (100%)	70 (100%)

The elastography stage showed no significant associations with sex (P = 0.469), age (P = 0.279), BMI (P = 0.669), disease duration (P = 0.978), or MTX dose (P = 0.663), as summarized in Table 8.

Table 8. Association between elastography stage and patients' characteristics (sex, age, BMI, disease duration, and MTX dose).

Variable	B	Standard error	z	P	Odds ratio	95% CI
Sex	0.46	0.64	0.72	0.469	1.59	0.45 - 5.56
Age	0.03	0.03	1.08	0.279	1.03	0.98 - 1.09
BMI	0.04	0.09	0.43	0.669	1.04	0.87 - 1.23
Disease duration	0	0.06	0.03	0.978	1	0.89 - 1.13
MTX dose	-0.04	0.08	0.44	0.663	0.96	0.82 - 1.14

B represents the unstandardized coefficient indicating the effect size of each variable on the elastography stage. z is the z-statistic used to test the significance of the coefficient, and p is the associated p-value, with significance set at < 0.05.

The distribution of FIB-4 stages across different elastography categories is presented in Table 9. Most patients with a normal to mild FIB-4 stage also had a normal to mild elastography score (60%). Mild to moderate FIB-4 stages were primarily associated with a normal to mild elastography score (18.57%).

Table 9. Distribution of FIB-4 stages across different elastography categories in patients with PsA

Elastography stage	Normal to mild n (%)	Mild to moderate n (%)	Moderate to severe n (%)	Total n (%)
FIB-4 stage				
Normal to mild	42 (60%)	8 (11.43%)	3 (4.29%)	53 (75.71%)
Mild to moderate	13 (18.57%)	0 (0%)	2 (2.86%)	15 (21.43%)
Moderate to severe	1 (1.43%)	0 (0%)	1 (1.43%)	2 (2.86%)
Total	56 (80%)	8 (11.43%)	6 (8.57%)	70 (100%)

Agreement and Correlation Between FIB-4 Index and FibroScan

The agreement between the FIB-4 index and FibroScan stages was assessed using Weighted Cohen's Kappa, which showed a very weak agreement (κ=0.12, SE=0.18, 95%

CI: -0.24 to 0.48) that was not statistically significant (P=0.462). A Bland-Altman plot (Figure 5) was generated to visually depict the level of agreement between the FIB-4 index and the FibroScan stages. The mean difference was close to zero, with wide limits of agreement, indicating poor agreement between the two measurements.

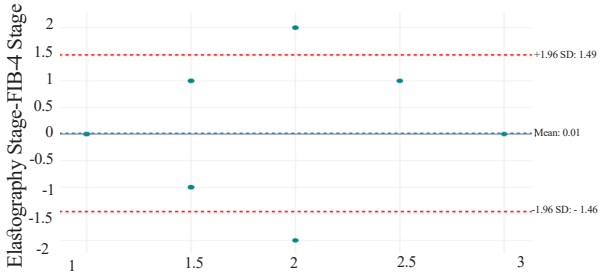

Figure 5. Bland-Altman plot showing the agreement between FIB-4 index and FibroScan stages. The mean difference is close to zero, with wide limits of agreement indicating poor agreement.

The Spearman correlation between the FIB-4 index and FibroScan stages indicated a very weak positive correlation (r=0.01), which was also not statistically significant (P=0.936). A scatter plot (Figure 6) was created to visualize the relationship between the FIB-4 index and FibroScan stages. The plot showed a weak positive association, which was consistent with the results of the Spearman correlation.

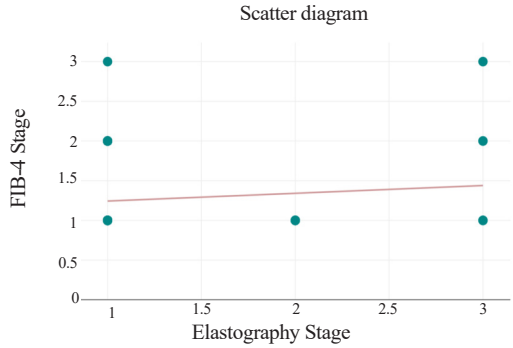

Figure 6. Scatter plot showing the relationship between FIB-4 index and FibroScan stages. A weak positive association is observed, consistent with the Spearman correlation findings.

Diagnostic Performance of FIB-4 Index

The FIB-4 index showed limited performance in identifying moderate to severe fibrosis based on FibroScan. In the best-case scenario, a normal to mild FIB-4 index correctly excluded moderate to severe fibrosis in 51% of cases; however, this finding was not statistically significant (P>0.05). A Chi-square test demonstrated no significant association (χ^2 =1.37, df=2, P=0.504).

A logistic regression model was performed to evaluate the predictive capacity of the FIB-4 stages for elastography outcomes. The model had poor explanatory power, as indicated by the -2 Log-Likelihood (68.69) and low R^2 values (Cox & Snell R^2=0.02, Nagelkerke R^2=0.03, McFadden's R^2=0.02). The odds of having moderate to severe fibrosis were higher among patients with a normal to mild or mild to moderate FIB-4 stage compared with those with more advanced stages, although these results were not statistically significant. Details of the logistic regression analysis are presented in Table 10.

DISCUSSION

The present study aimed to compare the FIB-4 index and FibroScan results to assess liver fibrosis in patients with PsA. The findings revealed that while the FIB-4 index was directly associated with age, it did not correlate with other factors such as sex, BMI, disease duration, or methotrexate dose. Furthermore, FibroScan grades were not significantly related to any of the mentioned risk factors, and there was a very weak and statistically non-significant correlation between the FIB-4 index and FibroScan results.

Table 10. Logistic regression analysis of FIB-4 stages for predicting elastography categories in patients with PsA

FIB-4 stage	B	Standard error	z	P value	Odds ratio	95% CI
Constant	0	1.41	0	1	1	0.06 - 15.99
Normal to Mild	1.34	1.45	0.92	0.357	3.82	0.22 - 66.02
Mild to Moderate	1.87	1.61	1.17	0.244	6.5	0.28 - 151.13

Keen and colleagues (19) investigated markers of liver fibrosis in patients with rheumatoid arthritis treated with MTX, finding that Hepascore moderately correlated with the AST to platelet ratio and FIB-4 but showed no correlation with elastography in this population. Their findings indicated that 36% of participants had Hepascore values suggestive of liver fibrosis, although this marker lacked sensitivity and specificity in detecting fibrosis in these patients. They concluded that Hepascore might not reliably indicate liver fibrosis in patients with rheumatoid arthritis treated with MTX, possibly due to false elevations. This is consistent with the present study's results, suggesting

that FIB-4 may also have limited utility in patients with PsA.

Similarly, Albaladejo and colleagues (20) demonstrated that the FIB-4 index did not significantly change during a 5-year follow-up of patients with PsA treated with MTX, further supporting the findings of the present study. This consistency across studies emphasizes that while the FIB-4 index may be a useful marker in other contexts, its application in patients with PsA under methotrexate therapy might be limited.

However, Ruiz-Ponce and co-workers (21) reported a significant increase in FIB-4 index values in patients with PsA exposed to hepatotoxicity, correlating with the cumulative MTX dose. This discrepancy could be due to methodological differences or variations in sample size and treatment regimens between the studies. The conflicting results indicate the need for larger, multicenter studies to further investigate the utility of FIB-4 in this specific population.

The possibility of falsely elevated FIB-4 index values in patients with rheumatoid arthritis has been reported, potentially due to platelets acting as acute-phase reactants that increase in inflammatory states (15). Given that the present study found neither sensitivity nor specificity for the FIB-4 index in patients with PsA, this index may not be a suitable screening tool for liver fibrosis in those undergoing MTX treatment. Moreover, the current study found no association between FibroScan results and age, sex, BMI, disease duration, or methotrexate dose, and no significant correlation between the FIB-4 index and FibroScan findings. However, several studies have demonstrated the utility of elastography in screening liver fibrosis in patients with rheumatoid arthritis on MTX therapy (22, 23).

Several factors could influence liver stiffness measurements by elastography. Although some were controlled for in our exclusion criteria, such as acute hepatitis, other factors like food intake up to 180 minutes before the procedure could also affect readings (24,25). As participants in this study generally did not fast before their scans, this may have impacted the results. Additionally, as a single-center study, the results may not be generalizable to all patients with PsA.

CONCLUSION

In conclusion, the FIB-4 index does not accurately predict FibroScan results in patients with PsA. Conversely, FibroScan findings may support and include those of the FIB-4 index. However, the sample size of this study was insufficient to confirm or reject a definitive relationship between the two. Given the present sample size, the FIB-4 index did not correspond well to FibroScan results and is not a reliable replacement for it in patients with PsA. Consequently, it is not possible to use the FIB-4 index alone to predict FibroScan outcomes in this population. Further research is needed, with larger cohorts and combined assessment tools, to establish more robust and accurate methods for liver fibrosis screening in patients with PsA on MTX therapy.

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

CONSENT FOR PUBLICATION

All participants provided informed consent for the publication of their anonymized data.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for this study was obtained from the Ethics Committee of Iran University of Medical Sciences (approval code: 27325).

COMPETING INTERESTS

The authors declare that they have no competing interests (financial or non-financial) directly or indirectly related to the work submitted for publication.

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