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Evaluation of Fracture Risk by Fracture Risk Assessment (FRAX) Algorithm in Patients with Rheumatoid Arthritis

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Abstract

***Objective:** An increased incidence of osteoporosis has been reported in patients of Rheumatoid Arthritis (RA). However, studies evaluating fracture risk and its predictors in such patients are limited. This study aimed to assess the fracture risk, using the FRAX algorithm, and its predictors in patients of RA.*

***Material and Methods:** This cross-sectional observational study, conducted in a tertiary care hospital at New Delhi, enrolled 40 cases of RA. Demographic characteristics and anthropometric measurements were recorded along with Lab investigations including Rheumatoid factor (RF), Anti-citrullinated protein antibody (ACPA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Disease severity was calculated using DAS28-ESR score. Bone Mineral Density (BMD) was measured using Dual-energy X-ray Absorptiometry (DEXA) and FRAX score was calculated using India specific FRAX calculator. Regression analyses were done to find predictors of increased fracture risk in these patients.*

***Results:** The overall prevalence of osteoporosis in study population was 55%. The BMD at femur neck was found to be the lowest. The mean FRAX score for major osteoporotic fracture was 4.5 ± 5.18% and for hip fracture was 2.11 ± 2.95%. 9 patients (22.50%) were having FRAX score above the cut-off for initiating anti-osteoporotic treatment according to National Osteoporosis Foundation (NOF) guidelines. Age, disease duration, swollen joint count, ESR, CRP, DAS28-ESR, and FRAX scores for major osteoporotic fracture and hip fracture were significantly higher in patients with osteoporosis. The independent predictors for higher FRAX scores were age, history of previous fracture, current smoking, history of glucocorticoid intake and T-score at femur neck.*

***Conclusion:** There is a high prevalence of osteoporosis in patients with RA. An increased 10-year risk of major osteoporotic and hip fracture was observed in patients with RA as assessed by FRAX algorithm. We suggest that patients with RA should be assessed for fracture risk early in the course of the disease.*

***Key words:** Rheumatoid arthritis, FRAX, osteoporosis, bone mineral density, major osteoporotic fracture, hip fracture.*

Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease leading to symmetrical, progressive and erosive polyarthritis leading to joint deformities and functional disability[1].

RA patients have reduced bone density due to chronic inflammation; corticosteroids use and limited mobility further add to increased risk of osteoporosis[2,3,4]. Incidence of osteoporosis in RA patients has been reported twice as high as that seen in the general population[5]. As a result, patients with RA have a higher fracture risk, affecting their quality of life and causing increased morbidity and possibly mortality[6,7]. Considering the younger age group of RA patients, fracture risk assessment and intervention in the stage of early disease can reduce long-term morbidity.

Bone Mineral Density (BMD) is measured for diagnosing and assessing severity of osteoporosis. Currently, BMD measurement by dual energy X-ray absorptiometry (DEXA) is considered as the gold standard for assessing osteoporosis. However, it fails to incorporate osteoporotic risk factors when considering the probability of fractures in this subset of patients[8]. Also, there is limited availability of the DEXA scan in countries like India. Hence, there is a need for development of an inexpensive and an easily available tool to assess the fracture risk.

The FRAX tool is an online algorithm, that calculates the 10-year probability of hip fracture and major osteoporotic fracture (hip, vertebral column, humerus and forearm) based on readily identifiable risk factors. FRAX incorporates demographic data and risk factors such as age, gender, body mass index (BMI), history of fragility fracture or parental hip fracture, current smoking and consumption of alcohol, use of corticosteroids, conditions of secondary osteoporosis,

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rheumatoid arthritis, and BMD at femur neck, to calculate the probability of major osteoporotic and hip fracture over 10 years[9-12]. Femoral neck BMD is an optional parameter while calculating FRAX score.

FRAX score is a well accepted tool to assess the fracture risk in post-menopausal women. Recently, some studies have used FRAX tool to calculate the probability of osteoporotic fractures in patients with Ankylosing spondylitis and RA. However, there is paucity of studies in Indian population[13].

The present study was undertaken to assess the fracture risk in Indian patients with RA, using country (India) specific FRAX algorithm, and to determine the predictors of increased fracture risk in these patients.

Material and Methods

Study Population and Design

The study was approved by the ethics committee and institutional review board. A written informed consent was taken from all participants.

Patient Assessment

Detailed history including joints involved, duration of disease, early morning stiffness, any extra-articular symptoms, smoking, alcohol consumption, prior history of any fracture, treatment received for osteoporosis or glucocorticoid use was obtained. History of fracture in parents was enquired. Anthropometric measurements were taken and patients were examined clinically with particular attention to musculoskeletal system. Tender Joint Count (TJC), Swollen Joint Count (SJC) and disease activity by DAS28-ESR score were recorded. Patients were investigated for laboratory tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Rheumatoid factor (RF), Anti-citrullinated protein antibody (ACPA) and X-rays of joints.

Patients were evaluated for BMD by DEXA using densitometer- HOLOGIC, INC. 35 CROSBY DRIVES BEDFORD, MA01730, USA (Model ASY- 00409). It was measured at 3 sites: femur neck, lumbar spine (L1-L4) and non-dominant forearm; values were obtained as T-score which was standard deviation from reference value. India-specific FRAX tool was used to calculate10-year risk for hip fracture and major osteoporotic fracture. (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=51).

Statistical Analysis

Categorical variables were presented as numbers and percentage (%) and quantitative data were presented as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was applied to check the data normality. The associations of quantitative variables, not normally distributed were analysed using Kruskal-Wallis test and those which were normally distributed were analysed using Analysis of Variance (ANOVA). The associations of the qualitative variables were analysed using Fisher's exact test. Univariate and multivariate linear regression was used to find out factors affecting FRAX score for major osteoporotic fracture and hip fracture. p-value less than 0.05 was considered statistically significant. Data entry and analysis was done in Microsoft EXCEL using Statistical Package for Social Sciences (SPSS) software, Chicago, USA, ver. 21.0.

Results

A total of 40 patients of RA were recruited in the study. Mean age of the study population was 43.92 ± 8.8 years and majority patients were females. The mean disease duration was 9.4 ± 4.4 years with a maximum of 20 years and minimum of 3 years.

12 patients (30%) had history of glucocorticoid intake, amongst which 4 had osteopenia and 8 had osteoporosis according to T-score at femur neck. This underlines the fact that glucocorticoid use is a major cause for reduced BMD in RA patients.

Mean DAS-28 ESR score in our patients was 3.94 ± 1.17, maximum being 6.4 and minimum 1.6. Twenty-six patients out of 40 (70%) had moderate to high disease activity.

The mean BMD at femur neck was -2.3 ± 0.72 gm/cm^2. Eighteen patients (45%) each had osteopenia and osteoporosis, while 4 (10%) had normal BMD. The mean BMD of lumbar spine and forearm was -2.19 ± 0.82 gm/cm^2 and -1.81 ± 0.91 gm/cm^2, respectively. Out of these,16 patients (40%) had osteoporosis, 21 (52.5%) had osteopenia and 3 (7.5%) had normal BMD at lumbar spine while 11 patients (27.5%) had osteoporosis, 21 (52.5%) had osteopenia and 8 (20 %) had normal BMD at forearm.

Overall prevalence of osteoporosis was 55%. The prevalence of osteoporosis in pre-menopausal females was 34.61%.

Patients were divided, on the basis of the T-score at femur neck, into 3 groups and baseline characteristics were compared. It was found that age, duration of the disease, swollen joint count, ESR, CRP, DAS28-ESR and FRAX score for hip fracture and major osteoporotic fracture were significantly higher in patients with osteoporosis (Table I).

Table I: Baseline characteristics of patients according to T-score at Femur neck.

Patient Characteristics	Normal (n = 4) T-score > -1	Osteopenia (n = 18) T-score -1 to -2.5	Osteoporosis (n = 18) T-score < -2.5	Total	p value
Age (years)	34.75 ± 4.27	40.11 ± 3.66	49.78 ± 9.55	43.92 ± 8.84	**<0.001**
Gender (Female)	4 (100%)	17 (94.44%)	12 (66.67%)	33 (82.50%)	0.101
BMI (kg/m^2)	25.8 ± 3.43	26.11 ± 1.67	26.3 ± 2.21	26.17 ± 2.07	0.904
Weight (kg)	58 ± 9.52	58.94 ± 2.6	61.94 ± 5.71	60.2 ± 5.17	0.148
Height (cm)	149.75 ± 5.44	150.39 ± 4.94	153.61 ± 8.13	151.78 ± 6.68	0.293
Duration (years)	4 ± 0.82	7.5 ± 2.26	12.5 ± 4.45	9.4 ± 4.47	**<0.001**
Current Smoker	0 (0%)	1 (5.56%)	2 (11.11%)	3 (7.50%)	1
Alcohol Intake	0 (0%)	1 (5.56%)	1 (5.56%)	2 (5%)	1
Previous Fracture	0 (0%)	0 (0%)	3 (16.67%)	3 (7.50%)	0.311
Parent with Hip Fracture	1 (25%)	0 (0%)	0 (0%)	1 (2.50%)	0.1
Glucocorticoid use	0 (0%)	4 (22.22%)	8 (44.44%)	12 (30%)	0.166
Tender Joint Count	2.75 ± 1.5	3.22 ± 2.39	5.22 ± 3.52	4.08 ± 3.03	0.111
Swollen Joint Count	0 ± 0	0.67 ± 0.97	1.33 ± 1.33	0.9 ± 1.17	**0.043**
ESR (mm/hr)	14 ± 4.32	20.44 ± 8.58	31 ± 14.52	24.55 ± 12.8	**0.007**
CRP (mg/L)	2.62 ± 2.5	6.58 ± 4.11	9.47 ± 4.99	7.49 ± 4.83	**0.019**
Rheumatoid Factor (IU/mL)	24.12 ± 12.22	17.5 ± 6.03	23.53 ± 9.56	20.88 ± 8.76	0.085
Anti CCP Antibody (IU/mL)	58.75 ± 42.53	99.53 ± 110.97	147.94 ± 221.98	117.24 ± 167.08	0.384
DAS28-ESR	3.08 ± 0.51	3.58 ± 1.05	4.49 ± 1.16	3.94 ± 1.17	**0.015**
FRAX Score for Major Osteoporotic Fracture	1.27 ± 0.49	2.27 ± 1.47	7.45 ± 6.52	4.5 ± 5.18	**<0.001**
FRAX Score for Hip Fracture	0.05 ± 0.06	0.74 ± 0.93	3.93 ± 3.54	2.11 ± 2.95	**<0.001**

The mean FRAX score for major osteoporotic fracture was 4.5 ± 5.18% with minimum of 1% and maximum of 23% whereas for hip fracture 2.11 ± 2.95% with minimum of 0 and maximum of 12%. There were 9 patients having FRAX score >= 3% for hip fracture while 2 patients had FRAX score >= 20% for major osteoporotic fracture. Overall, 9 (22.50%) patients were having FRAX score above the cut-off for initiating anti-osteoporotic treatment according to NOF and FRAX guidelines.

Univariate linear regression analysis was done to find out correlation between FRAX scores and factors affecting it. It was found that age, disease duration, tender joint count, ESR, DAS28-ESR score, glucocorticoid intake and history of previous fracture had a significant positive correlation, while T-score at femur neck, lumbar spine and forearm had a significant negative correlation with FRAX scores. Current smoking showed positive correlation with FRAX score for hip fracture (Tables IIA and IIB).

On further analysis by multivariate regression, it was found that age, history of previous fracture, glucocorticoid intake and T-score at femoral neck were independent predictors of FRAX score for major osteoporotic fracture and similarly age, history of previous fracture, smoking and T-score at femoral neck were independent predictors of FRAX score for hip fracture (Table III).

Discussion

This study is amongst the few Indian studies which evaluated fracture risk in patients with RA using FRAX calculator.

The present study showed a prevalence of osteoporosis as 55% in patients with RA, which was significantly higher compared to that seen in general population in community studies[14,15]. In a cross-sectional study by Gandhi AB *et al*, evaluation of femur neck and lumbar spine BMD in healthy females above 40 years of age showed a prevalence of osteoporosis as 8 %[14]. Another cross-sectional study by Nidhi S Kadam *et al*, done in healthy adults aged 40 years and above, found 5.7% of males and 12.7% of females having osteoporosis at the hip[15]. In our study, in spite of

Table IIA: Univariate regression analysis for association of FRAX score (for hip fracture) with various factors.

FRAX Score for Hip Fracture	Beta Co-efficient	Standard Error	p value	Lower Bound (95%)	Upper Bound (95%)
Age (years)	0.278	0.030	**<0.0001**	0.217	0.338
Duration (years)	0.538	0.062	**<0.0001**	0.413	0.663
Tender Joint Count	0.379	0.145	**0.013**	0.085	0.673
Swollen Joint Count	0.545	0.398	0.179	-0.261	1.351
ESR (mm/hr)	0.077	0.035	**0.034**	0.006	0.148
CRP(mg/L)	0.150	0.096	0.126	-0.044	0.344
Rheumatoid Factor	0.045	0.054	0.414	-0.065	0.154
Anti-CCP	0.004	0.003	0.134	-0.001	0.010
Gender-Male	2.259	1.187	0.065	-0.144	4.663
BMI (kg/m^2)	-0.192	0.229	0.408	-0.656	0.272
DAS28-ESR	1.072	0.370	**0.006**	0.324	1.821
Current Smoker	3.523	1.699	0.045	0.084	6.962
Alcohol Intake	3.466	2.092	0.106	-0.769	7.701
Previous Fracture	6.911	1.398	**<0.0001**	4.080	9.742
Parent with Hip Fracture	-2.059	3.005	0.497	-8.143	4.025
Glucocorticoids	3.358	0.874	**0.0005**	1.588	5.128
Femur T-Score	-2.381	0.537	**<0.0001**	-3.468	-1.294
Lumbar Spine T-Score	-1.908	0.495	**0.0004**	-2.910	-0.906
Forearm T-Score	-1.603	0.457	**0.001**	-2.529	-0.678

Table IIB: Univariate regression analysis for association of FRAX score (for Major osteoporotic fracture) with various factors.

FRAX Score for Major Osteoporotic Fracture	Beta Co-efficient	Standard Error	p value	Lower Bound (95%)	Upper Bound (95%)
Age (years)	0.487	0.053	**<0.0001**	0.379	0.594
Duration (years)	0.957	0.106	**<0.0001**	0.742	1.172
Tender Joint Count	0.680	0.254	**0.011**	0.165	1.195
Swollen Joint Count	1.067	0.696	0.134	-0.342	2.477
ESR (mm/hr)	0.136	0.062	0.034	0.011	0.261
CRP (mg/L)	0.273	0.168	0.113	-0.068	0.614
Rheumatoid Factor	0.097	0.095	0.314	-0.095	0.288
Anti-CCP	0.009	0.005	0.078	-0.001	0.019
Gender Male	2.147	2.158	0.326	-2.221	6.515
BMI (kg/m^2)	-0.323	0.403	0.428	-1.140	0.493
DAS28 ESR	1.934	0.647	**0.005**	0.625	3.243
Current Smoker	3.099	3.113	0.326	-3.202	9.401
Alcohol Intake	3.158	3.776	0.408	-4.486	10.802
Previous Fracture	12.793	2.374	**<0.0001**	7.987	17.599
Parent with Hip Fracture	-2.564	5.303	0.632	-13.300	8.172
Glucocorticoids	5.702	1.558	**0.001**	2.547	8.857
Femur T-Score	-4.004	0.966	**0.0002**	-5.959	-2.049
Lumbar spine T-Score	-3.248	0.882	**0.001**	-5.033	-1.463
Forearm T-Score	-2.673	0.817	**0.002**	-4.327	-1.018

Table III: Multivariate regression analysis for independent predictors of FRAX score

FRAX score for Hip Fracture	Beta Co-efficient	Standard Error	p value	Lower Bound (95%)	Upper Bound (95%)
Age (years)	0.155	0.052	**0.006**	0.049	0.261
Duration (years)	0.126	0.133	0.348	-0.145	0.398
Tender Joint Count	0.118	0.092	0.206	-0.069	0.306
ESR (mm/hr)	-0.016	0.025	0.525	-0.066	0.034
Femur T-Score	-1.627	0.696	**0.0001**	-5.057	-1.326
Lumbar spine T-Score	-0.102	0.697	0.885	-1.528	1.324
Forearm T-Score	-0.116	0.448	0.798	-1.032	0.800
Current Smoker	2.653	0.866	**0.005**	0.881	4.425

younger population, a higher prevalence of osteoporosis was observed in patients with RA. Due to ethical considerations, healthy controls could not be subjected to DEXA scan and hence were not included in our study; thus data from studies in general population was used as control.

In our study, 34.61% females in pre-menopausal group had osteoporosis at any one site. In the study by Zahraa Nour in Egyptian cohort of 100 RA patients, prevalence of osteoporosis in pre-menopausal females was found as 45.8%[16], while in a study done in 394 RA patients in Norway, the prevalence was 6%[5]. These differences may be attributed to poor intake of vitamin D and calcium along with racial predilection, leading to earlier loss of BMD[17].

A significant negative correlation between disease activity measured by DAS28-ESR and T-score at femoral neck (r =-0.38, p = 0.015) was found in our study. 16 out of 18 patients with osteoporosis had DAS28-ESR suggestive of moderate or high disease activity. In a study done in Asian cohort by Katherine D. Wysham *et al*, low disease activity was associated with higher mean BMD at femoral neck (β 0.071, P = 0.020) similar to our findings[18].

Our study showed that BMD was lowest at Femur amongst the three sites in our patients. In a similar study in patients with RA, Sugiguchi S *et al* also found BMD of the femoral neck lower than lumbar spine[19].

In our study, the mean FRAX scores were 4.5 ± 5.18% for major osteoporotic fracture and 2.11 ± 2.95% for hip fracture with 22.50% of patients having FRAX scores above NOF cut-off to initiate anti osteoporotic treatment. In a similar observational cross-sectional study in North India, which included 185 cases of RA and 185 controls, it was observed that patients with RA were at a higher risk of developing major osteoporotic fracture (4.77 ± 5.04 *versus* 2.05 ± 1.84) and hip fracture (1.71 ± 2.81 *versus* 0.5 ± 0.95). They found that 15% of the RA patients and 5% of the control population had FRAX scores above cut-off for initiation of anti-osteoporotic treatment. Similar findings were reported by Meng *et al* in their study, which were comparable to our results[20,21].

Our study showed that age, disease duration, tender joint count, ESR, DAS28-ESR score, glucocorticoid intake and history of previous fracture had a significant positive correlation, while T-score at femur neck, lumbar spine and forearm had a significant negative correlation with FRAX scores. Current smoking showed a significant association with FRAX score for hip fracture. RF and ACPA levels did not show any correlation with fracture risk. However, multivariate analysis found only age, history of previous fracture, glucocorticoid intake, T-score at femoral neck and smoking as the independent predictors of FRAX score for major osteoporotic fractureor hip fracture.

In similar studies by Phuan-udom R *et al* and Meng *et al*, age, disease duration, glucocorticoid use and DAS28-ESR score were significantly associated with FRAX scores[21,22]. They also did not find correlation of RF and ACPA with fracture risk. Mukesh Sharma *et al* showed a significant association between history of previous fracture and parental history of hip fracture with higher FRAX scores, although it did not show any correlation between glucocorticoid use and fracture risk[20].

Many studies have shown an association between inflammatory markers like ESR and fracture risk[23-25]. It is possibly due to raised ESR causing accelerated loss of BMD and hence increased fracture risk.

A meta-analysis of 14 prospective cohort studies done by Zhen-Jie Wu *et al* in 2016 showed that the pooled relative risk for hip fracture in smoker vs non-smoker was 1.47 [95% CI (1.28 - 1.66), p = 0.05] which is compatible with our findings[26].

Our study had many limitations such as control population was not included due to ethical consideration regarding exposure of normal population to radiation during DEXA scan. The sample size was small and it was a single centre cross-sectional study. Patients were not followed-up, and it

was not known whether actual fracture did happen according to the calculated risk. Repeated FRAX scores are required to monitor the change in fracture risk since patients are on treatment and fracture risk may vary temporally.

Conclusions

The study concludes that patients with RA have increased prevalence of osteoporosis and are at higher risk of fracture. The 10 year risk of major osteoporotic and hip fracture calculated by FRAX score was high in these patients. Age, history of previous fracture, glucocorticoid intake and T-score at femoral neck were independent predictors of FRAX score for major osteoporotic fracture while age, history of previous fracture, current smoker and T-score at femoral neck were independent predictors of FRAX score for hip fracture. It is prudent to assess for fracture risk in patients with RA and initiate anti-osteoporotic measures.

Future long-term large prospective interventional studies are recommended to validate the FRAX score in RA patients.

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