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Assesment of Damage in Juvenile Idiopathic Arthritis: Single Center Experience

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Abstract

After biological treatment options, quality of life and articular functions in patients with Juvenile Idiopathic Arthritis (JIA) have been maintained close to normal. It is essential to evaluate the activation and the articular and extra-articular damage during the disease course. This study aimed to evaluate the damage status and factors affecting JIA patients who were followed up in our clinic. Two hundred four JIA patients who had been followed up for two years or more were included. The data of the patients were collected retrospectively. Demographic data, comorbid diseases, laboratory data (at baseline and during follow-up), disease activity during the follow-up period, and treatments were evaluated. Disease activities, quality of life, and Juvenile Arthritis Damage Index articular(JADI-A) and extra-articular (E) were evaluated at the final examination. Factors affecting JADI-A and E were assessed by univariate and multivariate logistic regression analysis. In this study,127 (62.6%) of the patients were female. The median age was 13 (IQR: 11-16), and the age at diagnosis was 7 (IQR: 4-10) years. The median follow-up time was 5 (IQR: 4-8) years. Ninety-two (45.3%) patients had comorbid diseases. JADI-A scores were median:0(min-max: 0-24), JADI-E scores were median:0(min-max:0-4) in whole study population. In multivariate analysis, the mean annual attacks number [OR: 1,759 (CI: 1,300-2,379], p: <0,001), mean annual eritrocyte sedimantation rate (ESR) [OR: 1,072 (CI: 1,021-1,125), p: 0.005], duration of metotrexate usage [OR: 1.029 (CI: 1.013-1.046, p: 0.001] and biological drug usage [OR: 5.810 (CI: 1.296-26.054), p: 0.022) were effective on JADI-A scores. The CRP value at the first admission [OR: 1.007 (CI: 1,000-1,014), p: 0.037], the mean annual ESR value [OR: 1,051 (CI: 1,008-1,095), p: 0.019] were found to be effective on the JADI-E scores. The ideal cut-off point of the annual attacks number and mean annual ESR affecting JADI-A scores were 1.38 [AUC: 0.734 (0.641-0.828), p: 0.001] and 14.32 [AUC: 0.617 (0.514-0.721), p: 0.027], respectively. The ideal cut-off point of the CRP value at the first admission and mean annual ESR value affecting JADI-E scores were 13,25 [AUC: 0,662 (0,541-0,782), p: 0,009], and 15,10 [AUC: 0.674(0.567-0.780), p: 0.002], respectively. Steroid related complications such as, obesity in 12 (5.9%), hirsutism in 3 (1.5%), transient adrenal suppression in 14 (6.9%), 8 (3.9%), and osteoporosis determined in 7 (3.4%) patients. We have shown that parameters used routinely can be helpful to predict damage. We also think that new criteria should be added to the scoring.

Keywords: Juvenile, arthritis, damage

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Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common cause of chronic arthritis in childhood. There are seven subgroups according to the International leag of Rheumatism (ILAR) classification.[1] The prognosis and morbidity are different in each group. The primary aim of the treatment is to eliminate active disease, normalize joint function, maintain normal growth and prevent long-term joint damage. Treatment protocols were developed over the years. In 2011, the first protocol was published by the American College of Rheumatology (ACR).[2] In 2013, the treatment guideline was updated for the systemic JIA.[3] Finally, in 2019, treatment was revised for groups other than systemic JIA.[4] Biological therapies, which started to be used after 2000, have changed morbidity and mortality. The morbidity is associated with both articular and extra-articular complications. Untreated synovial inflammation causes permanent damage to joint components and may result in joint ankylosis. Cardiovascular complications, amyloidosis, growth retardation, delayed puberty developed due to chronic inflammation. Uveitis can cause eye complications such as vision loss, cataracts, and glaucoma. Depending on the steroids usage, osteoporosis, adrenal suppression, diabetes mellitus (DM) may develop. It is essential to evaluate the disease activation and the articular and extra-articular damage during the disease course.[5] The Juvenile Arthritis Damage Index (JADI) is a comprehensive assessment tool of articular and extra-articular damage in children with JIA. It is calculated by the physician based on the physical examination and clinical history. The index has two parts, JADI-A, which evaluates joint damage, and JADI-E, which evaluates extra-articular damage.[6]

Highlights

- Articular and extra-articular damage secondary to disease or treatment may be seen in JIA.
- The JADI index is the damage assessment tool used in JIA.
- Having persistent high inflammatory markers is a risk factor for a high JADI index.

This study aimed to evaluate the damage status and the affecting factors of the articular and extra-articular damage in JIA patients.

Material and Method

A total of 204 JIA patients under the age of 18, disease duration more than two years, and still in follow-up were included in the study. Diagnostic information, subgroups, anthropometric data, number and location of affected joints, systemic findings, presence of uveitis, comorbid diseases, and family history were recorded. The white blood cells (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, anti-nuclear antibody (ANA), HLA-B27, rheumatoid factor (RF), Anti- cyclic citrullinated peptide (anti-CCP) were recorded. During the follow-up period, frequency of disease flares, nonsteroid anti-inflammatory (NSAI) drug, and intraarticular steroid (IAS) usage, uveitis attacks, steroid dose (mg/kg/year), mean WBC, ESR, and CRP values were calculated per year. The JIA treatments and durations were recorded. The activity scores, assessment of health quality of life of the patients, and damage scores were evaluated at the last examination. JADAS was calculated for oligo JIA and poly JIA, JSpADAS for enthesitis-related arthritis (ERA), and sJADAS for systemic JIA patients.[7-9] Quality of life score was evaluated with the children's health quality of life (CHAQ) score.[10] Anthropometric data, partial damage, ankylosis, and prosthetic joints were detected in the final examination. JADI-A and E scores were calculated from the collected data.[11] In the JADI-A, 36 joints were evaluated for the presence of damage. Each damaged joint was scored on a 2-point scale (1: partial damage, 2: severe damage, ankylosis, or prosthesis). The maximum total score was 72. In the JADI-E, 13 items were evaluated in five different organs/systems. Ocular (If the patient has had eye surgery, it was scored as 2 for each eye. If the patient developed legal blindness, the score was 3). Cutaneous (subcutaneous atrophy as a result of the intra-articular corticosteroid injection, stria rubrae), endocrine (diabetes mellitus, growth failure, pubertal delay), non-articular musculoskeletal (fractures or vertebral collapses due to osteoporosis, significant abnormality of the vertebral curve as a result of leg-length discrepancy or hip contracture, significant leg length discrepancy or growth abnormality of a bone segment, avascular necrosis of bone, severe muscle atrophy) findings, and secondary amyloidosis were evaluated. Each item was scored as either 0 or 1, according to whether the damage was present, respectively. The maximum total score was 17. Malnutrition, obesity, hirsutism, adrenal suppression, osteoporosis, and development of MAS not included in JADI-E score were recorded.[6]

Statistical Analysis:

Statistics 22.0 (IBM Corp. Armonk, New York, USA) statistical package program was used. Shapiro-Wilk and Kolmogorow-Smirnow Normality test and Q-Q graphs were used to determine whether the data showed normal distribution. Results are given as median (min-max) and quarterly (IQR). In evaluating variables between groups, categorical data were evaluated with the chi-square test; continuous data were evaluated with the normal distribution, one-way analysis of variance ANOVA, and those that did not show the normal distribution were evaluated with the Kruskal Wallis test. Univariate and multivariate logistic regression analysis was performed to assess the factors affecting the JADI-A and JADI-E scores. The risk coefficient and 95% confidence interval were given, and the p-value was accepted as <0.05. The significant cut-off point of the continuous data, the area under the curve, sensitivity, and specificity values were calculated.

Results

Demographic Data of the Patients

Two hundred and four patients with JIAwere included in the study. A hundred and twenty-seven (62.6%) of the patients were female, and 75 (36.9%) were male. The median age was 13 years (IQR: 11-16), and the age at diagnosis was 7 (IQR: 4-10) years. The median follow-up period was 5 (IQR:4-8) years. A total of 92 (45.3%)

patients had comorbid disease. The median age at diagnosis of comorbid disease was 8 (IQR:4-11), and the follow-up period was 5 (IQR:2-9) years. The most common comorbid disease was FMF (n:44). A total of 54 (26.6%) patients had a family history of rheumatologic disease.The demographic data of patients were analyzed separately according to JIA subtypes (**Table 1**).

Clinical Evaluation at Initial Period

The median weight standard deviation score (SDS) was -0.19 (IQR:-0.80-0.50), height SDS was -0.07 (IQR:-1.10-0.40) at the time of diagnosis. The median number of affected joints was 2 (IQR:1-4). Patients who developed uveitis in the first year were detected in oligo, poly, and ERA subgroups. The initial laboratory findings represented in Table 1. The ANA was performed in 96 (47.3%) patients, and it was found to be positive in 90 (44.3%) patients. The HLA-B27 was performed in 92 (45.3%) patients, and positivity was detected in 30 (14.8%) patients. Rheumatoid factor was measured in 83 (40.9%) patients, and positivity was detected in 4 (2%) patients. Anti-CCP was examined in 18 (8.9%) patients, and positivity was detected in 1 (0.5%) (**Table 1**).

Clinical and Laboratory Evaluation in Follow-up Period

The median number of attacks per year was 1 (IQR: 0.50-1.76). It was 2,33 (IQR:1,25-4,37) in poly JIA group. The annual steroid requirement was calculated as 0.92 (IQR:0-5.94) mg/kg/year. Steroid amounts was 22,15 (IQR:5,80-71,81) mg/kg/year in the systemic JIA group. The annual median ESR was 11.81 (IQR:6.46-20.8) mm/h. It was 25 (IQR:18,30-40,15) mm/h in the systemic JIA subgroup. The annual median CRP was 4.72 (IQR: 2.50-8.73) mg/L. It was 11,92 (IQR:8,38-35,09) mg/L in the systemic JIA subgroup. The clinical and laboratory characteristics of the patients during the follow-up are detailed for the subgroups in **Table 2**.

Table 1.
Demographic, clinical and laboratory parameters of the patients at first diagnose

Variables	JIA subgroups						
	Total (n=204)	Systemic (n=17)	Oligoarticular (n=82)	Polyarticular (n=42)	ERA (n=55)	Psoriatic (n=5)	Undifferentiated (n=3)
Age (year)	13 (11-16)	13 (12-14.5)	12 (10-15)	12 (10-15)	15 (13-17)	16 (13-17)	16 (12-16)
Age of diagnosis (year)	7 (4-10)	8 (3.5-10)	6 (3-9)	6 (2-9·5)	9.5 (7.75-11)	12 (6-13)	10 (9-10)
Sex (F/M), n/%	127/75 (62.6/36.9)	12/5 (70.6/29.4)	47/35 (57.3/42.7)	31/10 (75.6/24.4)	30/24 (55.6/44.4)	4/1 (80/20)	3/0 (100)
Disease duration (year)	5 (4-8)	6 (3-8)	6 (4-7)	5 (3-8)	5 (3-7)	4 (4-7.5)	6 (3-6)
Weight SDS	-0.19 (-0.80-0.50)	0.40 (-0.40-1)	-0.30 (-0.80-0.10)	-0.20 (-1.09-0.70)	-0.02 (-0.82-1)	0.70 (-0.43-1.80)	-0.30 (-0.51- (-0.30)
Height SDS	-0.07 (-1.10-0.40)	0 (-0.76-0.64)	-0.40 (-1.20-0.20)	0 (-0.50-0.70)	0 (-0.81-0.82)	-0.60 (-1.17-1.25)	-0.30 (-0.42- (-0.30)
Number of joint	2 (1-4)	2 (0.5-3)	2 (1-2)	6 (4.5-8)	2 (1-3.25)	4 (2-5)	6 (2-6)
Uveitis at first year, n	15	0	8	5	2	0	0
HGB (g/dL)	11.9 (10.8-13)	10.4 (9.7-11.95)[a]	12.3 (11.4-13)[a]	11.4 (10.4-12)	12 (11.2-13.2)	12 (10.5-12)	12.9 (12.9-13.0)
WBC/mm³	9170 (7290-11835)	15712 (9605-19905)[a,b,c]	9320 (7312-11490)[a]	8874 (7022-12135)[b]	8865 (6947-10492)[c]	10625 (8650-10625)	7570 (6840-7570)
PLTx10³/mm³	377 (301-448)	469 (298-750)	340 (293-480)	410 (318-553)	375 (302-420)	395 (275-395)	309 (300-309)
ESR (mm/h)	27 (8.5-55)	65 (33.5-103)[a,b]	19 (5.5-37)[a]	44 (16.2-74.7)	22 (7-45)[b]	35 (4-35)	4 (3-4)
CRP (mg/L)	11.3 (3.3-46.2)	104 (19-148)[a,b,c]	5·4 (3.1-21)[a]	25.9 (5.5-52.6)[b]	7.35 (3.17-31.2)[c]	3 (1-3)	3.4 (2.1-3.4)
Ferritin (mg/dL)	239 (40-2867)	401 (71-3929)	NA	NA	NA	NA	NA
ANA (+/-), %	90/96 (44.3/47.3)	2/12 (11.8/70.6)	45/34 (54.9/41.5)	24/15 (58.5/36.6)	17/30 (31.5/55.6)	1/3 (20/60)	1/2 (33.3/66.7)
HLA-B27(+/-), %	30/92 (14.8/45.3)	1/2 (5.9/11.8)	2/43 (2.4/52.4)	2/15 (4.9/36.6)	23/27 (42.6/50)	2/2 (40/40)	-/0
RF (+/-), %	4/83 (2/40.9)	0/3 (-/17.6)	NA	2/33 (4.9/80.5)	0/17 (0/31.5)	0/1 (0/20)	NA
Anti-CCP(+/-),%	1/18 (0.5/8.9)	0/1 (-/5.9)	NA	1/9 (2.4/24.4)	0/2	NA	NA
CD (n, %)	92 (45.3)	9 (52.9)	37 (45.1)	16 (39)	27 (50)	1 (20)	2 (66.7)
Age of CD diagnose (year)	8 (3.75-11)	8 (7-12)	8 (2-10)	6 (2-12)	9 (5-11)	15 (15-15)	8.5 (8-8.5)
Duration of CD (year)	5 (2-9)	2 (1-6.5)	5 (2-10)	3 (2-7)	5 (3-9)	2 (2-2)	5.5 (3-5.5)
Family history of RD, n (%)	54 (26.6)	2 (11.8)	20 (24.4)	8 (19.5)	19 (35.2)	3 (60)	2 (66.7)

All parameters were given median and Interquartile range. a, b, c: There was a statistically differences between same latters. ANA: Antinuclear antibody, Anti-CCP: Anti-Cyclic Citrullinated peptide antibodies, CD: Comorbid Disease, CRP: C reactive protein, ESH: Erythrocyte sedimentation rate, HGB: Hemoglobin, PLT: Platelets, RD: Rheumatologic disease, RF: Rheumatoid factor, SDS: Standard deviation score, WBC: White blood cells,

Table 2.
Clinical and laboratory parameters during the disease course

Parameters	Total (n=204)	JIA subgroups Systemic (n=17)	Oligoarticular (n=82)	Polyarticular (n=42)	ERA (n=55)	Psoriatic (n=5)	Undifferentiated (n=3)
Number of attacks/year	1 (0.50-1.76)	1 (0.50-0.75)[a]	0.77 (0.50-1.21)[b]	2.33 (1.25-4.37)[a,b,c]	1 (0.40-1.80)[c]	1.40 (0.87-2.12)	0.85 (0.33-0.85)
Number of NSAI usage/year	0.21 (0.14-0.33)	0.09 (0-0.33)	0.25 (0.16-0.28)	0.20 (0.10-0.33)	0.25 (0.19-0.33)	0.25 (0.10-0.25)	0.16 (0-0.16)
Dose of steroid (mg/kg/year)	0.92 (0-5.94)	22.15 (5.80-71.81)[a,b,c,d,e]	0 (0-4.50)[a]	5.58 (0.56-14.83)[b]	0 (0-1.44)[c]	0 (0-6.37)[d]	0[e]
IAS usage/year	0 (0-0.4)	0 (0-0.08)	0.28 (0-0.50)[a]	0 (0-0.30)	0 (0)[a]	0 (0-0.37)	0
Number of Uveitis attacks/year	55	1	34	15	5	0	0
HGB/year, g/dL	12.8 (12.20-13.47)	12.64 (11.98-13.05)	12.8 (12.28-13.61)	12.51 (11.9-13.2)	13 (12.17-13.56)	12.85 (12.65-13.71)	13.5 (12.7-13.5)
WBC/mm³/ year	7845 (7035-8990)	9454 (8543-11073)[a,b,c]	7846 (7067-8938)[a]	7878 (6969-9219)[b]	7447 (6870-8377)[c]	7200 (6481-8350)	7696 (7069-7696)
PLT/ mm³/ year	333 (290-382)	368 (289-403)	318 (278-379)	338 (303-377)	335 (292-377)	330 (267-422)	268 (250-268)
ESR/year, mm/h	11.81 (6.46-20.8)	25 (18.30-40.15)[a,b,c]	9.54 (5.45-17.21)[a]	14.40 (9.57-23.60)[b]	11.98 (6.93-19.70)[c]	11.3 (7.25-32.95)	8.2 (5.6-8.2)
CRP/year, mg/L	4.72 (2.50-8.73)	11.92 (8.38-35.09)[a,b,c,d]	3.70 (1.99-5.42)[a]	6.6 (3.16-9.96)[b]	5 (2.82-8.55)[c]	2.85 (1.11-4.45)[d]	2.13 (1.51-2.13)
Ferritin/year, mg/dl		71.90 (37.82-1392)					

All parameters were given median and Interquartile range. a, b, c, d: There was a statistically differences between same latters. CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, HGB: Hemoglobin, IAS: Intra-articular steroids, PLT: Platelets, WBC: White blood cells

Biological and Non-Biological DMARDs

Non-biological DMARD treatment was applied to 185 (91.1%) of our patients. Methotrexate was the most common non-biologic DMARD (97%). The median duration of methotrexate was 36 (IQR:22-58) months. The number of patients using biological therapy was 98 (48.3%). Psoriatic Arthritis (60%) and poly JIA (63.4%) had the highest rates treated with biological therapy. TNF -α blockers were the most common performing biological drugs were detected 96 (80.6%) times.

Comorbid diseases were detected in 45.3% of the patients. Forty-four patients had familial Mediterranean fever, the most common comorbid disease. Other diseases were Behçet's disease, atopic dermatitis, inflammatory bowel disease, and epilepsy. Colchicine was the most common drug for comorbid diseases.

Evaluation of Disease Activity Scores and JADI Scores

Disease activity scores of the patients at the last examination are shown in **Table 3**. Sixty-five partially damaged joints were detected in JADI-A scores at last visit. Out of the 39 (60%) were in the poly JIA. The ankylosed joint count was 22. Out of the 9 (40.9%) were detected in oligo JIA.

In the JADI-E index, eye involvement was present in a total of 10 (4.9%), partial vision loss in 6 (2.9%), and surgical application in 5 (2.5%) patients. Cataract and visual loss were highest in the systemic JIA subgroup (17.6%, 5.9%). Among the cutaneous findings, 8 (3.9%) patients had stria rubrae, and 2 (1%) patients had scar atrophy secondary to intra-articular injection. Among endocrine disorders, short stature was observed in 20 (9.8%), delayed puberty in 2 (1%), and secondary diabetes mellitus in 1 (0.5%) patients. Among the musculoskeletal system complications, vertebral fractures in 5 (2.5%), limb length differences in 4 (2%), avascular necrosis in 5 (2.5%), amyloidosis in 3 (1.5%) (secondary to FMF) were detected. The JIA subtype in patients with avascular necrosis was oligoarticular JIA in 2, ERA in 2, and polyarticular JIA in 1. localization of necrosis was femoral head in 4 patients and was mandibular condyle in 1 patient. The median cumulative prednisolone dose was 80 mg, maximum cumulative prednisolone dose was 875 mg in these patients. Only one patient did not use steroids.

Malnutrition, obesity, hirsutism, adrenal suppression, osteoporosis, and development of MAS, which were not included in the JADI scoring, were also evaluated. Malnutrition in 20 (9.8%), obesity in 12 (5.9%), hirsutism in 3 (1.5%), transient adrenal suppression in 14 (6.9%), 8 (3.9%), osteoporosis and MAS determined in 7 (3.4%) patients (**Table 3**).

Evaluation of Factors Affecting JADI-A and JADI-E Score

The analysis was performed by univariate and multivariate models. JIA subtype, gender, age at diagnosis, duration of JIA, presence of comorbid disease, duration of comorbid disease, family history of the rheumatological disease, number of affected joints and laboratory parameters, annual number of attacks and NSAI drug usage, median annual steroid amount, mean annual laboratory parameters, DMARD use and duration, biological use and duration were evaluated. In multivariate analysis,

annual number of attacks [OR:1,759 (CI:1,300-2.379]), (p:<0.001), mean annual ESR [OR:1,072 (CI:1,021-1,125),p:0.005] , duration of MTX use [OR: 1.029 (GA: 1.013-1.046, p:0.001]) and the use of biological drugs [OR: 5,810 (GA: 1.296-26.054), (p: 0.022)) were detected independent risk factors affecting on JADI-A score (**Table 4**). On JADI-E score, in multivariate analysis, the CRP value at the first admission [OR: 1.007 (GA:1,000-1.014), p: 0.037], the mean annual ESR value [OR:1.051 (GA:1.008-1.095)), p:0.019] were detected as independent risk factors (**Table 5**).

Determination of Cut-off Points of Factors Affecting JADI-A and JADI-E

The ideal cut-off point for the number of attacks per year, which affects the JADI-A score, was detected at 1.38. There was a significant [AUC:0.734 (0.641-0.828),p:0.001] effect on the JADI-A score (**Table 6, Figure 1**). Sensitivity was calculated as 69% and specificity as 72%.

The median annual ESR ideal cut-off point, which affects the JADI-A score, was detected at 14.32. There was a significant [AUC:0.617 (0.514-0.721), p:0.027] effect on the JADI-A score (**Table 6, Figure 1**). The sensitivity was calculated as 58% and the specificity as 58%.

The ideal cut-off point for CRP at first admission, which affects the JADI-E score, was 13.25. There was a significant [AUC:0.662 (0.541-0.782), p:0.009] effect on the JADI-E score (**Table 6, Figure 1**). Sensitivity was calculated as 57% and specificity as 56%. The annual mean ESR ideal cut-off point was 15.10, which affected the JADI-E score. There was a significant [AUC:0.674 (0.567-0.780), p:0.002] effect on the JADI-E score (**Table 6, Figure 1**). Sensitivity was calculated as 63% and specificity as 63%.

Table 3.
Disease activity scores and JADI-A and JADI-E scores at last visit

Variables	JIA subgroups						
	Total (n=204)	Systemic (n=17)	Oligoarticular (n=82)	Polyarticular (n=42)	ERA (n=55)	Psoriatic (n=5)	Undifferentiated (n=3)
JADAS	NA	NA	0 (0-29)	0 (0-21)	NA	0	0
JSpADAS	NA	NA	NA	NA	0 (0-9)	NA	NA
sJADAS	NA	0 (0-21)	NA	NA	NA	NA	NA
CHAQ	0 (0-1.30)	0 (0-1.25)	0 (0-1.25)	0 (0-1.3)	0 (0-1)	0 (0-0)	0 (0-0)
JADI-A	0 (0-24)	0 (0-14)	0 (0-5)	0 (0-24)	0 (0-4)	0 (0-1)	0 (0-0)
Number of partially damaged joints (n/%)	65 (100)	17 (26.15)	5 (7.69)	39 (60)	7 (10.76)	1 (1.53)	0
Number of ankylosed joints (n/%)	22 (100)	2 (9.09)	9 (40.90)	8 (36.36)	3 (13.63)	0	0
Prosthesis (n/%)	1 (0.5)	0	0	1 (2.4)	0	0	0
JADI-E	0 (0-4)	0 (0-2)	0 (0-3)	0 (0-4)	0 (0-1)	0	0
EYE							
Cataract	10 (4.9)	3 (17.6)	4 (4.9)	1 (2.4)	2 (3.6)	0	0
Vision loss	6 (2.9)	1 (5.9)	4 (4.9)	0	1 (1.8)	0	0
Surgery	5 (2.5)	0	3 (3.7)	1 (2.4)	1 (1.8)	0	0
Blindness	0	0	0	0	0	0	0
CUTANEOUS							
Striae rubrae	8 (3.9)	2 (11.8)	2 (2.4)	3 (7.1)	1 (1.8)	0	0
Atrophy after IAS	2 (1)	0	1 (1.2)	1 (2.4)	0	0	0
ENDOCRINE							
Growth failure	20 (9.8)	3 (17.6)	7 (8.5)	5 (11.9)	5 (9.1)	0	0
Pubertal delay	2 (1)	0	1 (1.2)	0	2 (3.6)	0	0
Diabetes Mellitus	1 (0.5)	0	0	0	1 (1.8)	0	0
MUSCULOSKELETAL							
Muscle atrophy	0	0	0	0	0	0	0
Vertebral fracture	5 (2.5)	0	2 (2.4)	1 (2.4)	2 (3.6)	0	0
Small extremity	4 (2)	0	2 (2.4)	1 (2.4)	1 (1.8)	0	0
Avascular necrosis	5 (2.5)	0	2 (2.4)	1 (2.4)	2 (3.6)	0	0
Amyloidosis	3 (1.5)	0	2 (2.4)	1 (2.4)	0	0	0
OTHERS							
Malnutrition	20 (9.8)	1 (5.9)	7 (8.5)	4 (9.5)	8 (14.5)	0	0
Obesity	12 (5.9)	1 (5.9)	3 (3.7)	3 (7.1)	3 (5.5)	1 (25)	0
Hirsutism	3 (1.5)	1 (5.9)	0	2 (4.8)	0	0	0
Adrenal suppression	14 (6.9)	4 (23.5)	2 (2.4)	6 (14.3)	2 (3.6)	0	0
Cushingoid appearance	12 (5.9)	7 (41.2)	1 (1.2)	3 (7.1)	1 (1.8)	0	0
Osteoporosis	8 (3.9)	3 (17.6)	1 (1.2)	2 (4.8)	2 (3.6)	0	0
MAS	7 (3.4)	7 (41.2)	0	0	0	0	0

All parameters were given median (minimum-maximum). CHAQ: Childhood Health Assessment Questionnaire, JADAS: Juvenile Arthritis Disease Activity Score, JADI-A: Juvenile Arthritis Damage Index-artcular JADI-E: Juvenile Arthritis Damage Index-extra-articular, JSpADAS: Juvenile Spondyloarthropahy Disease Activity Score, sJADAS: Systemic Juvenile Arthritis Disease Activity Score, MAS: Macrophage activation Syndrome, NA: Not assessed

Table 4.
Factors affecting JADI-A score

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	P value	OR	95% CI	P value
JIA subgroups	1.322	1.005-1.739	0.046	1.266	0.793-2.020	0.323
Sex	1.035	0.489-2.188	0.929			
Age of diagnosis	0.966	0.877-1.065	0.491			
Disease duration	1.065	0.945-1.200	0.299			
Presence of comorbidity	0.804	0.391-1.655	0.554			
Duration of comorbidity	0.961	0.837-1.103	0.567			
Family history	0.923	0.412-2.066	0.845			
First HGB (gr/dl)	0.802	0.635-1.013	0.064			
First WBC/mm³	1.000	1.000-1.000	0.245			
First PLT/x10³/mm³	1.000	1.000-1.000	0.781			
First ESR (mm/h)	1.012	1.000-1.025	0.047	0.999	0.978-1.020	0.939
First CRP (mg/L)	1.003	0.996-1.010	0.399			
Affected joint number at fist admission	1.219	1.100-1.352	0.000	1.023	0.847-1.236	0.813
Attacks number/ year	1.634	1.292-2.067	0.000	1.759	1.300-2.379	<0.001
NSAI usage/ year	0.345	0.041-2.923	0.329			
IAS/ year	1.853	0.669-5.129	0.235			
Steroid/year (mg/kg)	1.014	0.999-1.029	0.064			
HGB/ year(gr/dl)	0.798	0.546-1.166	0.244			
WBC/year/mm³	1.000	1.000-1.000	0.404			
PLT/year/mm³	1.002	0.997-1.006	0.542			
ESR/year(mm/h)	1.049	1.013-1.085	0.006	1.072	1.021-1.125	0.005
CRP/year/(mg/L)	1.021	0.993-1.050	0.143			
DMARD usage	0.271	0.035-2.116	0.213			
Duration of MTX	1.020	1.008-1.033	0.001	1.029	1.013-1.046	0.001
Biologic drug usage	0.214	0.092-0.498	0.000	5.810	1.296-26.054	0.022

HGB: Hemoglobin, WBC: White blood cells, PLT: Platelets, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein

Table 5.
Factors affecting JADI-E score

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	P value	OR	95% CI	P value
JIA subgroups	1.085	0.797-1.476	0.605			
Sex	1.193	0.526-2.705	0.673			
Age of diagnosis	1.077	0.969-1.197	0.167			
Disease duration	0.996	0.871-1.139	0.955			
Presence of comorbidity	0.749	0.341-1.646	0.471			
Duration of comorbidity	0.865	0.728-1.027	0.097			
Family History	2.621	0.870-7.895	0.087			
First HGB (gr/dl)	0.913	0.727-1.147	0.433			
First WBC/mm³	1.000	1.000-1.000	0.005	1.000	1.000-1.000	0.162
First PLT/mm³	1.000	1.000-1.000	0.788			
First ESR (mm/h)	1.018	1.005-1.031	0.006	0.995	0.974-1.017	0.667
First CRP (mg/L)	1.011	1.004-1.017	0.002	1.007	1.000-1.014	0.037
Affected joint number at fist admission	1.036	0.926-1.160	0.534			
Attacks number/ year	1.061	0.849-1.327	0.601			
NSAI usage/ year	0.237	0.023-3.182	0.300			
IAS/ year	0.712	0.195-2.601	0.608			
Steroid/ year (mg/m²)	1.023	1.007-1.038	0.005	1.008	0.988-1.029	0.421
HGB/ year(gr/dl)	0.880	0.588-1.318	0.537			
WBC/year/mm³	1.000	1.000-1.001	0.003	1.007	0.989-1.026	0.443
PLT/year/mm³	1.000	0.995-1.005	0.977			
ESR/year/(mm/h)	1.068	1.029-1.108	0.000	1.051	1.008-1.095	0.019
CRP/year/(mg/L)	1.035	1.003-1.068	0.031	0.978	0.934-1.024	0.339
DMARD usage	0.757	0.164-3.494	0.721			
Duration of MTX	0.999	0.984-1.013	0.838			
Biologic drug usage	0.817	0.376-1.775	0.609			

HGB: Hemoglobin, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, PLT: Platelets, WBC: White blood cells

Table 6.
JADI-A and E affecting factors cut point values

Variable	Cut of value	AUC	%95 CI	p	% Sensitivity	% Specificity
JADI-A						
Attacks/year	1.38	0.734	0.641-0.828	0.001	0.694	0.726
Mean ESR/year	14.32	0.617	0.514-0.721	0.027	0.583	0.589
JADI-E						
First CRP	13.25	0.662	0.541-0.782	0.009	0.577	0.566
Mean ESR/year	15.10	0.674	0.567-0.780	0.002	0.633	0.632

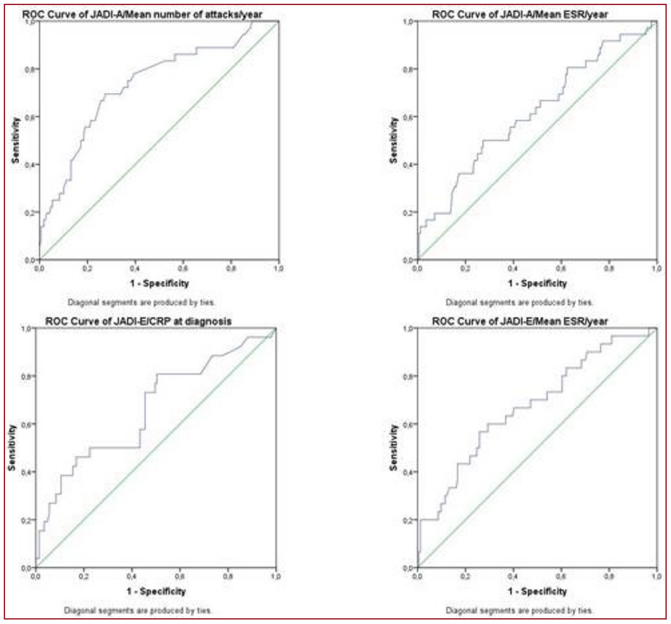

Figure 1. The ideal cut-off points affected JADI-A and E scores

Discussion

This is the first study evaluating the damage status of patients with JIA in Turkey during the biological era. The median JADI-A score was detected 0 (0-24), and the median JADI-E score was 0 (0-4). Viola et al. found JADI-A score median 0 (0-39) and JADI-E median 0 (0-7)) in 2005.[11] Their study involved 158 patients and patients with a mean follow-up period of 7.3 years.[11] Later in 2016, Menon et al.[12] evaluated 1064 patients diagnosed with systemic, oligo and poly JIA with an average of 2 years of follow-up. They determined the JADI-A score as 0 (0-52) and the JADI-E score as 0 (0-6). In our patients, the maximum values were found to be lower than in other studies in the literature. The reasons may be that the study was performed in the biological era and the ease of reach to health care providers.

Comorbid diseases whose had 45.3% of the patients were evaluated in this study. FMF was the most common comorbid disease. Patients with FMF and JIA were reported that they had more destructive arthritis.[13] The ankylosing spondylitis accompanying FMF has been reported as 12.9% in adult studies.[14,15] Our previous study detected that patients with ERA accompanying FMF showed less classical FMF and ERA findings.[16] Therefore, delayed diagnosis and therapy may affect joint destructions in JIA with FMF patients. But our results did not show that comorbid disease was a risk factor for the JADI-A score.

We found that the annual number of attacks and the median annual ESR values were independent risk factors for the JADI-A scores. In addition, it was determined that the duration of MTX usage was longer, and the rate of biological usage was higher in patients with high JADI-A. This result may be an indirect indication that long-term activation increases the articular damage.

Although the sensitivity and specificity were not high, attacks count per year and ESR value may predict articular damage. Menon et al. reported that the articular damage was higher in systemic JIA, and the damage increased with disease duration in systemic JIA and poly JIA.[12] In the study performed in Indian and Italian patients with systemic JIA, articular damage was higher in Indian patients. It was thought due to delays in diagnosis, lack of a multidisciplinary approach, long-term steroid usage, and difficulties in accessing biological drugs.[17] Although the JIA subtype did not appear statistically significant in our patients, the most damaged joints were in the systemic JIA and poly JIA. Giancana et al.[18] evaluated the damage indices of patients who received MTX between 1986 and 1999 and those who received biologics between 2000 and 2017. Joint damage was found to be lower in patients in the biological era.[19]

We found that the CRP value at admission and the median annual ESR were independent risk factors for the JADI-E score. Although its sensitivity and specificity were not high, CRP and ESR values may predict extra-articular damage. Previous studies have shown that the most common extra-articular injuries include growth retardation, muscle atrophy, and short leg length.[17] In our study, short stature (9.8%), cataract (4.9%), and striae (3.9%) were the most common extra-articular damages, respectively—all of these damages related to steroid therapy. Makearlani et al. found that 39% of patients with JIA had growth retardation after three years.[19] Patients with systemic JIA constitute 90% of these patients, and the median duration of glucocorticoid treatment was 46 weeks. Another study published in 2020 reported that patients with poly and systemic JIA who received six months of relatively short-term glucocorticoid treatment were prone to low weight and delayed puberty.[20]

Malnutrition, obesity, hirsutism, adrenal suppression, osteoporosis, which are not included in the JADI-E score, were also evaluated in our study. All of these complications are associated with steroid therapy. But, the annual steroid amount was not detected as an independent risk factor in the multivariate analysis. This may be due to the shorter steroid therapy duration due to DMARDs and biologic agents. A German study reported that high-dose steroid therapy was less performed in systemic JIA after the 2000s than before.[21]

Adrenal suppression was present in 6.9% (14) of our patients, most of which were patients with systemic and poly JIA. In the literature, adrenal suppression has been reported in approximately half of the patients using steroids with rheumatological disease.[22] It was recommended to control adrenal suppression during the steroid reduction phase of treatment.[23]

In our study, osteoporosis was detected at a rate of 3.9%. The causes of osteoporosis in JIA patients are inflammation, glucocorticoid therapy, and immobilization. In other words, JIA itself is a significant risk factor for decreased bone mineral density. Rodd et al. detected 6% vertebral fracture in 6% of pediatric rheumatology patients using steroids, 36.7% of these patients were JIA, and half of them were systemic JIA.[23] Le Blanche et al.[24] showed that 0.5 mg/kg/day steroid dose increased two times the risk of fracture. The control of inflammation, mobilization, and discontinuing GC treatment as soon as possible decrease the risk of osteoporosis. In another study, the factors affecting the progression of patients with systemic

JIA were evaluated. It has been shown that the dose and duration of steroids did not affect the prognosis.[25] An IL-1 receptor antagonist in patients with systemic JIA to reduce the steroid-related JADI-E score was recommended to achieve and maintain the inactive disease.[26]

Osteonecrosis was detected in 2.5% of our patients. Osteonecrosis can be associated with short and long-term steroid use. Steroid-induced osteonecrosis in children has been extensively studied in hematological diseases, and information on rheumatological diseases is limited.[27]

Topical and systemic use of glucocorticoids causes ocular side effects. The use of topical steroids, especially for more than three months, increases the risk of cataracts.[28] Likewise, systemic steroid use increases the risk of cataracts and ocular hypertension. Cataracts occurred in 4.9% of our patients, and half of them underwent surgical intervention. Both steroid side effects and JIA-related uveitis affect the ocular complications. The timely use of DMARDs and biological drugs prevent ocular complications.[29]

India mainly published studies related to the JADI index. In a 2008 study, JADI was detected as a useful index to measure articular and extra-articular damage in ERA. But, it did not adequately reflect lower extremity joint damage, enthesitis, and spinal damage.[29] It has been suggested to include the spine, foot joints, and enthesitis score in JADI to increase usefulness in ERA.[30] Even though they were not included in the JADI-E index, steroid-related side effects such as obesity, adrenal suppression, cushingoid appearance, osteoporosis without fracture were observed in a considerable number of patients in our study.

There are some limitations of our study. Data were obtained retrospectively from the medical records. The activity scores during the follow-up period could not be achieved. The reasons were that the scoring calculations have changed over the years, and especially the incomplete recording of VAS scores. However, all evaluation parameters were obtained at the last examination. In our study, the annual number of attacks, annual median inflammatory markers, drugs, and their doses were calculated in detail. These are the strength of our work.

In our study, we evaluated the damage status of our patients in the biological period. We have shown that parameters used routinely can be helpful to predict disease related damage. We also think that obesity, adrenal suppression, cushingoid appearance, osteoporosis without fracture should be added to the damage scoring as new criteria.

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Ethics Committee Approval: The study was carried out with the permission of Erciyes University Ethics Committee (Date: 12.02.2020, Decision No: 2020/104).

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Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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