Med Glas (Zenica) 2025;22(1)
https://doi.org/10.17392/1882-22-01

Med Glas (Zenica)

ORIGINAL ARTICLE

Which accessible clinical features and laboratory findings might predict methotrexate success in children with juvenile idiopathic arthritis in Bosnia and Herzegovina?

Adisa Čengić[1*], Velma Selmanović[1], Sniježana Hasanbegović[1], Hamza Izeta[2], Lamija Zečević[3], Nejra Džananović[3]

[1]Pediatric Clinic, Clinical Centre of the University of Sarajevo, Bosnia and Herzegovina; [2]Health Centre of Canton Sarajevo, Bosnia and Herzegovina; [3]Clinical Immunology, Clinical Centre of the University of Sarajevo; Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To determine whether demographic data, clinical features, and laboratory variables at disease onset can predict the response to methotrexate in juvenile idiopathic arthritis (JIA) patients.
Methods A cohort of 143 newly diagnosed JIA patients initially treated with methotrexate was enrolled in this study. Demographic, clinical, and laboratory parameters were analysed using univariate and multivariate logistic regression to identify predictors of response to methotrexate. The variables included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets, IgA, IgG, the number of active joints and age at disease onset. Treatment response was assessed at six months, with patients classified as responders (those who achieved clinically inactive disease according to the American College of Rheumatology - ACR criteria) or non-responders.
Results Poor response to methotrexate was associated with the number of active joints (p=0.0001; OR=2.7), baseline levels of CRP (p=0.044; OR=1.138), IgA (p =0.004; OR=2.159), and platelet count (p=0.01; OR=1.05). IgG level (P=0.236) did not correlate with the treatment response.
Conclusion We identified widely available and clinically acceptable biomarkers that can be utilized as predictive indicators of response to methotrexate in JIA patients.

Keywords: chronic joint inflammation, response, treatment

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an umbrella term for a heterogeneous group of inflammatory joint diseases in childhood predominantly affecting musculoskeletal system (bones, joints, cartilage, tendons, ligaments, muscles), but could involve other organs and tissues (1). The disease targets the synovial layer, leading to swelling, pain and stiffness in the joint. This process can spread to nearby tissues. Both innate and adaptive immune system are involved in autoimmune process in genetically predisposed patients (2).

Modern paediatric rheumatology embraces a cutting-edge, individualized treatment approach, optimizing medication efficacy to achieve inflammation control, inactive disease, and preserve joint function (3). The prognosis for children with JIA has significantly improved over the last two to three decades owing to expansion of knowledge in the field of paediatric rheumatology (4). Effective management requires comprehensive analysis of disease severity, likelihood of achieving remission, therapeutic resistance, and the risk of relapse. Accurate estimation of these factors plays a crucial role in guiding optimal treatment and medication choices, significantly impacting the effectiveness of therapeutic interventions (5).

Medication modalities include disease modifying agents, mostly methotrexate (MTX), leflunomide, and sulfasalazine, as well as growing number of biologicals targeting different inflammatory mediators (1). Low-dose weekly MTX is one of the most commonly used first-line agents in the treatment of JIA (3). A treatment decision usually relies on an accurate combined clinical, laboratory and radiology assessment of the disease (6).

There have been various attempts to identify clinical predictors of response to MTX in children with arthritis. In children with high disease activity or poor prognostic factors, MTX is recommended to be used as a first-line drug with or without a biological agent in addition (7). There is considerable variation in clinical response to MTX among JIA patients (8). Regardless of significant expansion of knowledge, rheumatologist still do not know why some patients respond and the others do not respond successfully to MTX, pointing to the need of finding a specific biomarker. Gene polymorphisms failed to reliably explain the treatment response to MTX (9). Ideally, individualized successful drug selection early in the course of the disease would result in rapid and complete disease control. Early identification of these markers can guide the need for more aggressive treatment strategies, including the prompt introduction of biologic agents (5).

***Corresponding author:** Adisa Čengić
Phone: +387 33 566 428; fax: +387 33 566 400
E-mail: adisaus@yahoo.com
ORCID: https://orcid.org/0009-0003-7763-3463

Submitted: 26. Jul. 2024. Revised: 03 Sep. 2024. Accepted: 04 Sep. 2024.

From both a clinical and public health perspective, it is crucial to identify markers linked to poor prognosis and resistance to non-biologic disease-modifying antirheumatic drugs (DMARDs) in paediatric JIA patients.

Numerous studies have delved into predictive models for assessing inadequate responses to methotrexate (10), but to the best of our knowledge, none have been published on children with JIA in B&H.

The aim of this study was to uncover potential biomarkers for MTX response among the demographic, clinical, and laboratory parameters collected at the onset of JIA in children in Bosnia and Herzegovina.

PATIENTS AND METHODS

Patients and study design

A retrospective cohort study involving 143 patients with juvenile idiopathic arthritis (JIA) was conducted at the Paediatric Clinic of the Clinical Centre of the University of Sarajevo from April 2019 to March 2023. This patient cohort represents a diverse geographic population from across the Federation of Bosnia and Herzegovina (FB&H). The diagnosis of JIA was confirmed according to the International League of Associations for Rheumatology (ILAR) criteria (11), which define the disease as arthritis persisting for more than six weeks in patients under 16 years of age, after ruling out all other known causes of arthritis, including infections, malignancies, and other autoimmune diseases. Arthritis was diagnosed based on the presence of at least two of the following criteria: inflammatory pain, restricted range of motion, and/or joint swelling (1). Patients with systemic JIA were not enrolled in the study due to severe systemic inflammatory features of the disease and different treatment recommendations, which include early introduction of biologics (12).

This study was conducted in accordance with the principles outlined in the Helsinki declaration. Parents or guardians of all research subjects had signed a pre-prepared informed consent form before blood samples were taken.

An ethical approval was granted by the Ethics Committee of the Clinical Centre of the University of Sarajevo and the Ethics Committee of the School of Medicine of the University of Sarajevo.

Methods

The study's inclusion criteria were patients treated with MTX during the first six months following the diagnosis. This treatment was supplemented with non-steroidal anti-inflammatory drugs (ibuprofen, naproxen and indomethacin) and/or a single dose of intra-articular steroids (triamcinolone hexacetonide) per affected joint. Systemic corticosteroids were restricted to the dose of 0.5 mg/kg of body weight, administered exclusively during the initial two months of MTX therapy.

At the onset of the disease, demographic factors (gender and age at onset), clinical features (number of active joints), and laboratory parameters erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets, IgA and IgG were recorded.

After six months of the treatment with MTX all patients underwent a detailed rheumatologic exam and repeated laboratory findings. Based on these assessments, the patients were classified as responders or non-responders. Responders were defined as those who achieved clinically inactive disease according to the American College of Rheumatology Provisional Criteria for Defining Clinical Inactive Disease and Clinical Remission (referred to as the Wallace Criteria) (13). Clinically inactive disease was determined by the following criteria: no active arthritis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or CRP; and a physician global assessment (PhGA) indicating no disease activity, with morning stiffness lasting less than 15 minutes. Non-responders were identified as those who did not achieve clinically inactive disease after six months of treatment and required the addition of either non-biological or biological disease-modifying antirheumatic drugs (DMARD).

Statistical analysis

Nominal and ordinal variables were analysed using the χ^2 test. For continuous variables, the symmetry of their distribution using the Kolmogorov-Smirnov test was firstly assessed. If the distribution deviated statistically significantly ($p<0.05$) from the symmetric (Gaussian) distribution, the median and interquartile range to display the mean values and measure of dispersion was used, and compared them using non-parametric tests (Mann-Whitney U test). Otherwise, the independent t-test and presented average values with the arithmetic mean and standard deviation were used. Correlations between variables were assessed using Spearman's rho.

Univariate binary logistic regression was used to examine the influence of individual variables on binary prediction (response to therapy), specifically the likelihood of a worse therapeutic outcome. Variables that showed a statistically significant influence in the univariate analysis were then examined using multivariate binary logistic regression. The reliability of the model was tested with a series of statistical tests: the Hosmer and Lemeshow test, Cox & Snell R^2, and Nagelkerke R^2. The threshold for statistical significance was set at $\alpha=0.05$. Decisions regarding the acceptance or rejection of hypotheses were based on the p value ($p\geq\alpha$ indicated hypothesis acceptance, $p<\alpha$ indicated hypothesis rejection). The results were presented in absolute and relative numbers, statistical values with the use of statistical indicators, and displayed in simple and comprehensible tables.

RESULTS

The studied population consisted of 143 JIA patients, 80 (56%) were girls and 63 (44%) were boys; the average age was 9.2±4.6 years.

The most prevalent subtype of JIA was oligoarticular arthritis, 65 (45.5%), followed by polyarticular rheumatoid factor (RF) negative JIA, 44 (30.8%), enthesitis related arthritis, 24 (16.8%) and polyarticular RF positive JIA, seven (4.9%), while psoriatic arthritis was detected in three (2.1%) patients (Table 1).

After six months of initial treatment, the patients were divided into two groups based on their therapeutic response: the first group consisted of 71 children who achieved inactive disease, while the second group included 72 patients who remained with active disease despite MTX treatment.

Table 1.Demographic data and subtypes of juvenile idiopathic arthritis (JIA)

Variable	No (%) of children
Female/male (N=143)	56 (80)/44 (63)
Median age disease onset (years)	9,2±4,6
Subtypes of JIA (n=143)	
oJIA	65 (45.5)
pJIA RF-	44 (30.8)
pJIA RF+	7 (4.9)
ERA	24 (16.8)
psJIA	3 (2.1)

oJIA, oligoarticular juvenile idiopathic arthritis; pJIA, polyarticular juvenile idiopathic arthritis; RF -, rheumatoid factor negative; RF +, rheumatoid factor positive; ERA, enthesitis related arthritis; psJIA, psoriatic juvenile idiopathic arthritis

Univariate regression analysis revealed no significant predictive effect of the patient's age on the treatment outcome (p=0.452; OR (95% CI) 0.973 (0.907-1.045). Similarly, gender did not demonstrate a statistically significant influence on therapeutic outcomes (p=0.150; OR (95% CI) 0.150 (0.838-3.171).

ESR was a significant predictor of treatment outcome (0.0001); for every 10 mm/h increase in ESR, the likelihood of not responding to initial therapy rises 1.6 times (OR=1.6). Elevated CRP level was associated with a poorer response (p=0.044); a 10 mg/L increase in CRP level correlated with 14% higher likelihood of inadequate response to MTX (OR=1.138). Platelet count emerged as a statistically significant predictor of therapeutic outcome (p=0.01); each 10-unit increase in platelet count raises the chance of non-response by 5% (OR=1.0). There was a statistically significant difference in serum IgA level between the two patient groups (p=0.004); an increase of one unit in IgA level was associated with a twofold increase in the likelihood of not responding to MTX (OR=2.159). IgG level did not exhibit a statistically significant effect on therapeutic outcome (p=0.236) (Table 2).

Table 2.Predictive value of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelets count, IgA and IgG on treatment response

Variable	OR (95% CI)	p
ESR	1.649 (1.294-2.100)	0.001
CRP	1.138 (1.003-1.291)	0.044
Platelets	1.052 (1.012-1.094)	0.010
IgA	2.159 (1.274-3.661)	0.004
IgG	1.057 (0.964-1.159)	0.236

OR, odds ratio; CI, confidence interval

In the responder group, 36 patients had arthritis in one joint, 24 in two joints, eight in three joints, and four patients in four joints. None of the patients in this group had arthritis affecting five or more joints. Conversely, in the non-responder group, eight patients had arthritis in one joint, 23 in two joints, 17 in three joints, five in four joints, and eight patients had arthritis affecting five or more joints.

The number of affected joints demonstrated a statistically significant impact on therapeutic outcome (p=0.0001). For each additional affected joint, the likelihood of not responding to MTX increases nearly threefold (OR = 2.7).

DISCUSSION

Modern rheumatology treatments aim to optimally control inflammation, achieve complete disease remission, and maintain full functional capacity and productivity. These advancements have significantly improved the prognosis for children with JIA. Effective strategic decision-making in the treatment of juvenile idiopathic arthritis (JIA) is vital for ensuring successful outcomes (14). Methotrexate is a cornerstone in the initial treatment of JIA, known for its excellent safety profile and cost-effectiveness (15).

The aim of this study was to determine whether demographic data and clinical and laboratory variables at disease onset can predict the response to MTX in patients with JIA.

The analysis of the demographic characteristics revealed that neither the children's age at JIA diagnosis nor the gender significantly influence the occurrence of therapeutic resistance in our study, which is consistent with findings from previous studies (16).

Our analysis indicated that ESR was a significant predictor of poor therapeutic response. Elevated inflammation, as reflected by ESR, is linked to higher disease activity and serves as an effective indicator of poor outcome to initial immunomodulatory therapy, such as methotrexate (17–19).

The American College of Rheumatology includes C-reactive protein (CRP), an acute-phase protein, alongside with ESR in its recommendations for monitoring disease activity in JIA (13). Our study confirms that elevated CRP levels were linked to therapeutic resistance, aligning with findings from previous research (20). During systemic inflammation, the liver produces pro-inflammatory cytokines that stimulate megakaryocytes in the bone marrow, leading to an increased release of platelets (21). Prior studies have demonstrated that in patients with rheumatoid arthritis, platelets infiltrate the synovial fluid (22). Reactive thrombocytosis, a common symptom of inflammation in JIA, is often associated with more severe inflammatory processes, particularly in polyarticular and systemic forms of the disease (23). Given the established role of platelets in inflammatory arthritis, our results indicated that platelet count can be a valuable marker for predicting poor therapeutic responses. This finding aligns with the study by Vakiloi et al (24).

At the time of the JIA diagnosis, IgA levels were notably higher in patients who required an aggressive immunomodulatory therapy after six months of treatment, indicating therapeutic resistance. This finding aligns with previous research on the correlation between IgA level and therapeutic response (25,26). IgG level increased during the active phase of JIA, with notable differences observed between active and inactive disease states (27). In our cohort, IgG level did not significantly influence treatment outcome, which is inconsistent with the findings of Stoll et al. (28). Our study further highlights that the degree of therapeutic resistance is closely associated with the number of affected joints, demonstrating a statistically significant correlation; the patients with a higher number of joints exhibiting signs of arthritis were more likely to be non-responders to MTX. Our results are in accordance with previous studies (3,6,29),

In developing countries, where access to treatment varies widely, identifying affordable and accessible indicators of dis-

ease prognosis is crucial. These parameters can guide therapeutic decisions and ensure that all children receive the best possible care.

With ongoing advancements in molecular biology and biomarker research, we anticipate the development of algorithms capable of predicting individualized risks related to the disease progression, complications, and joint damage. Such advancements are expected to optimize the treatment process for each JIA patient, enabling more precise and effective management and improving their overall quality of life (30).

A major limitation of the study was that we did not compare treatment responses across different JIA subtypes. Future research should focus on monitoring therapeutic responses to MTX within each specific JIA group.

Assessing patients as having more severe form of JIA using simple parameters is crucial for ensuring timely and effective treatment, especially at the primary care level. Early intervention, such as prompt treatment of infections and regular checkups, are vital for these patients, who, due to systemic inflammation and immunosuppressive therapy, are at a higher risk of infections. This study aims to provide valuable insights not only for rheumatologists but also for primary care physicians, highlighting the importance of a serious and informed approach to managing JIA patients.

In conclusion, our research suggests that poor response to methotrexate among JIA patients is associated with the number of active joints, baseline levels of CRP, level of IgA and platelet count. Categorizing patients with more MTX- resistant forms of JIA based on easily accessible analyses is crucial for ensuring timely and effective treatment. Further prospective studies with a larger cohort of patients across different JIA subtypes are necessary to validate our findings.

ACKNOWLEDGEMENTS

Our greatest appreciation goes to the patients who participated in this study, as well as to their parents.

AUTHOR CONTRIBUTIONS

Conceptualization, A.Č. and S.H.; methodology, A.Č.; software, I.H.; validation, A.Č., S.H., V.S., L.Z., N.Dž. and H.I.; formal analysis, A.Č. and H.I.; investigation, A.Č.; resources, A.Č., V.S., L.Z. and N.Dž.; data curation, A.Č., V.S. AND H.I.; writing—original draft preparation, A.Č.; writing—review and editing, A.Č., V.S. and H.I.; visualization, H.I.; supervision, S.H. and V.S.; project administration, A.Č.; funding acquisition, A.Č. All authors have read and agreed to the published version of the manuscript.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

REFERENCES

1 Barut K, Adrovic A, Şahin S, Kasapçopur Ö. Juvenile Idiopathic Arthritis. Balk Med J 2017;34;(2):90–101. doi: 10.4274/balkanmedj.2017.0111.

2 Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw RA. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol Online J 2021;19;(1):135. doi: 10.1186/s12969-021-00629-8.

3 Martini A, Lovell DJ, Albani S, Brunner HI, Hyrich KL, Thompson SD, et al. Juvenile idiopathic arthritis. Nat Rev Dis Primer 2022;8;(1):5. doi: 10.1038/s41572-021-00332-8.

4 Schoemaker CG, Swart JF, Wulffraat NM. Treating juvenile idiopathic arthritis to target: what is the optimal target definition to reach all goals? Pediatr Rheumatol Online J 2020;18;(1):34. doi :10.1186/s12969-020-00428-7.

5 Bridges JM, Mellins ED, Cron RQ. Recent progress in the treatment of non-systemic juvenile idiopathic arthritis. Fac Rev 2021;10:23. doi: 10.12703/r/10-23.

6 Rezaei E, Hogan D, Trost B, Kusalik AJ, Boire G, Cabral DA, et al. Clinical and associated inflammatory biomarker features predictive of short-term outcomes in non-systemic juvenile idiopathic arthritis. Rheumatol Oxf Engl 2020; 59;(9):2402–11. doi :10.1093/rheumatology/kez615.

7 Tan J, Renton WD, Whittle SL, Takken T, Johnston RV, Tiller G, et al. Methotrexate for juvenile idiopathic arthritis. Cochrane Database Syst Rev 2024;2;(2):CD003129. doi: 10.1002/14651858.CD003129.pub2.

8 Shoop-Worrall SJW, Lawson-Tovey S, Wedderburn LR, Hyrich KL, Geifman N, CLUSTER Consortium. Towards stratified treatment of JIA: machine learning identifies subtypes in response to methotrexate from four UK cohorts. EBioMedicine 2024;100:104946. doi: 10.1016/j.ebiom.2023.104946.

9 Roszkiewicz J, Smolewska E. In the Pursuit of Methotrexate Treatment Response Biomarker in Juvenile Idiopathic Arthritis-Are We Getting Closer to Personalised Medicine? Curr Rheumatol Rep 2017;19;(4):19. doi: 10.1007/s11926-017-0646-8.

10 Mo X, Chen X, Li H, Li J, Zeng F, Chen Y, et al. Early and Accurate Prediction of Clinical Response to Methotrexate Treatment in Juvenile Idiopathic Arthritis Using Machine Learning. Front Pharmacol 2019;10:1155. doi :10.3389/fphar.2019.01155.

11 Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31;(2):390–2.

12 Barut K, Adrovic A, Sahin S, Tarcin G, Tahaoglu G, Koker O, et al. Prognosis, complications and treatment response in systemic juvenile idiopathic arthritis patients: A single-center experience. Int J Rheum Dis 2019;22;(9):1661–9. doi: 10.1111/1756-185X.13649.

13 Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N, Childhood Arthritis Rheumatology Research Alliance, et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res 2011; 63;(7):929–36. doi: 10.1002/acr.20497.

14 Guzman J, Oen K, Tucker LB, Huber AM, Shiff N, Boire G, et al. The outcomes of juvenile idiopathic arthritis in

children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis 2015; 74;(10):1854–60. doi: 10.1136/annrheumdis-2014-205372.
15 Ferrara G, Mastrangelo G, Barone P, La Torre F, Martino S, Pappagallo G, et al. Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting. Pediatr Rheumatol Online J 2018;16;(1):46. doi: 10.1186/s12969-018-0255-8.
16 Batu ED, Sönmez HE, Gülhan B, Arıcı ZS, Topaloğlu R, Bilginer Y. Predictors of methotrexate response in Turkish children with oligoarticular and polyarticular juvenile idiopathic arthritis. Turk J Pediatr 2017;59;(1):6–12. doi: 10.24953/turkjped.2017.01.002.
17 Bulatovic M, Heijstek MW, Van Dijkhuizen EHP, Wulffraat NM, Pluijm SMF, de Jonge R. Prediction of clinical non-response to methotrexate treatment in juvenile idiopathic arthritis. Ann Rheum Dis 2012;71;(9):1484–9. doi: 10.1136/annrheumdis-2011-200942.
18 Onel KB, Horton DB, Lovell DJ, Shenoi S, Cuello CA, Angeles-Han ST, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Rheumatol Hoboken NJ 2022;74;(4):553–69. doi: 10.1002/art.42037.
19 Yanagimachi M, Naruto T, Hara T, Kikuchi M, Hara R, Miyamae T, et al. Influence of polymorphisms within the methotrexate pathway genes on the toxicity and efficacy of methotrexate in patients with juvenile idiopathic arthritis. Br J Clin Pharmacol 2011;71;(2):237–43. doi: 10.1111/j.1365-2125.2010.03814.x.
20 Alberdi-Saugstrup M, Zak M, Nielsen S, Herlin T, Nordal E, Berntson L, et al. High-sensitive CRP as a predictive marker of long-term outcome in juvenile idiopathic arthritis. Rheumatol Int 2017;37;(5):695–703. doi: 10.1007/s00296-017-3657-x.
21 Scherlinger M, Richez C, Tsokos GC, Boilard E, Blanco P. Author Correction: The role of platelets in immune-mediated inflammatory diseases. Nat Rev Immunol 2023; 23;(6):409. doi: 10.1038/s41577-023-00869-7.
22 Cafaro G, Bartoloni E, Alunno A, Gerli R. Platelets: a potential target for rheumatoid arthritis treatment? Expert Rev Clin Immunol 2019;15;(1):1–3. doi:10.1080/1744666X.2019.1544071.
23 Wallimann M, Bouayed K, Cannizzaro E, Kaiser D, Belot A, Merlin E, et al. Disease evolution in systemic juvenile idiopathic arthritis: an international, observational cohort study through JIRcohort. Pediatr Rheumatol Online J 2023;21;(1):96. doi: 10.1186/s12969-023-00886-9.
24 Vakili M, Ziaee V, Moradinejad MH, Raeeskarami SR, Kompani F, Rahamooz T. Changes of Platelet Indices in Juvenile Idiopathic Arthritis in Acute Phase and After Two Months Treatment. Iran J Pediatr 2016;26;(3):e5006. doi: 10.5812/ijp.5006.
25 Moradinejad MH, Rafati AH, Ardalan M, Rabiei M, Farghadan M, Ashtiani MTH, et al. Prevalence of IgA deficiency in children with juvenile rheumatoid arthritis. Iran J Allergy Asthma Immunol 2011;10;(1):35–40.
26 Abdukhakimova D, Dossybayeva K, Almukhamedova Z, Mukusheva Z, Assylbekova M, Zhangabylova D, et al. Serum immunoglobulin A (IgA) levels in children affected with Juvenile Idiopathic Arthritis. Heliyon 2023;9;(7): e17479. doi: 10.1016/j.heliyon.2023.e17479.
27 Rayhan SM, Laila K, Rahman SA. Serum Immunoglobulin Concentrations in Juvenile Idiopathic Arthritis Cases during Active and Inactive Disease States. Open J Rheumatol Autoimmune Dis 2024;14;(02):49–59. doi: 10.4236/ojra.2024.142006.
28 Stoll ML, Li Q-Z, Zhou J, Punaro M, Olsen NJ. Elevated IgG autoantibody production in oligoarticular juvenile idiopathic arthritis may predict a refractory course. Clin Exp Rheumatol 2011;29;(4):736–42.
29 Rypdal V, Guzman J, Henrey A, Loughin T, Glerup M, Arnstad ED, et al. Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis: part 1-results of the Canadian model in the Nordic cohort. Arthritis Res Ther 2019; 21;(1):270. doi: 10.1186/s13075-019-2060-2.
30 Huang HYR, Wireko AA, Miteu GD, Khan A, Roy S, Ferreira T, et al. Advancements and progress in juvenile idiopathic arthritis: A Review of pathophysiology and treatment. Medicine (Baltimore) 2024;103;(13):e37567. doi: 10.1097/MD.0000000000037567.