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UTILITY OF NON-INVASIVE HEMATOLOGICAL BIOMARKERS IN NEWLY DIAGNOSED RHEUMATOID ARTHRITIS PATIENTS

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Doi: https://doi.org/10.52340/jecm.2024.03.02

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არაინვაზიური ჰემატოლოგიური ბიომარკერები რევმატოიდული ართრიტის მქონე ახლადდიაგნოსტირებულ პაციენტებში

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რეზიუმე

შესავალი: რევმატოიდული ართრიტი ქრონიკული აუტოიმუნური დარღვევაა, რომელსაც სინოვიუმის ქრონიკული ანთება ახასიათებს და სახსრის დაზიანებისა და სისტემური გართულებისკენ მივყავართ. რევმატოიდული არტრიტის სამკურნალო პირველი რიგის წამალი იმუნოსუპრესიული პრეპარატი მეტოტრექსატია. თუმცა პაციენტთა საგრძნობი რაოდენობა მეტოტრექსატის მიმართ რეზისტენტულია. სისხლის საერთო ანალიზიდან გამოთვლილი ბიომარკერები, როგორიცაა სისხლის წითელი უჯრედების განაწილების ფართობი (RDW), ჰემოგლობინისა და თრომბოციტების შეფარდება (HPR) და ჰემოგლობინ მონოციტების შეფარდება (HMR) სხვადასხვა ანთებითი მდგომარეობების დროს დაავადებისა და თერაპიაზე პასუხის მარკერებად გვევლინება. თუმცა ჯერჯერობით დადგენილი არ არის რევმატოიდული ართრიტის მქონე ახლადდიაგნოსტირებულ პაციენტებში ამ ბიომარკერების მეტოტრექსატით მკურნალობის გამოსავლის პროგნოზული ღირებულება.

მიზანი: კვლევის მიზანია რევმატოიდული ართრიტის მქონე ახლადდიაგნოსტირებულ პაციენტებში, მათ ვინც მეტოტრექსატით მკურნალობა დაიწყეს, RDW, HPR და HMR პროგნოზული ბიომარკერების პოტენციალის განსაზღვრა და დაავადების აქტიურობის ქულასთან (DAS-28) მათი კორელაციის დადგენა.

მეთოდები: კვლევაში ჩართული იყო 64 პაციენტი, რომლებიც დაიყო მეტოტრექსატ-რეზისტენტულ და მეტოტრექსატ-მგრძნობიარე ჯგუფებად, და 28 ასაკითა და სქესით შესაბამისი ჯანმრთელი ინდივიდები. სტანდარტული t-ტესტი იყო გამოყენებული ჯგუფებს შორის სპეციფიკური ბიომარკერების შესადარებლად. ორივე ჯგუფში RDW, HPR, HMR და DAS28 შორის კორელაციების დასადგენად Pearson-ის კორელაციის ტესტი იქნა გამოყენებული. ბიომარკერების პროგნოზული მნიშვნელობის შესაფასებლად მიმღების ოპერაციული მახასიათებლის (ROC) მრუდის ანალიზი ჩატარდა.

შედეგები: მეტოტრექსატ-რეზისტენტულ და მეტოტრექსატ-მგრძნობიარე ჯგუფებს შორის RDW-SD სარწმუნოდ განსხვავდება. სარწმუნო პოზიტიური კორელაცია შესწავლილ ბიომარკერებსა და DAS-28 შორის არც ერთ ჯგუფში არ დადგენილა. ROC მრუდების ანალიზი გვიჩვენებს, რომ მათ პროგნოზული ღირებულება არ აქვთ.

დასკვნა: RDW-SD-ის მომატებული დონე მეტოტრექსატ-რეზისტენტობის ადრეულ ინდიკატორად შეიძლება ჩაითვალოს ახლად დიაგნოსტირებულ პაციენტებში. ჩვენი კვლევით დადგინდა, რომ დაავადების აქტივობის მონიტორინგისთვის RDW-SD, HPR და HMR DAS-28-ს რევმატოიდული ართრიტის მქონე პაციენტებში ვერ ჩაანაცვლებს.

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation, which can lead to irreversible joint damage and disability if left untreated [1]. The disease activity in RA is typically assessed using clinical and laboratory parameters, such as the Disease Activity

Score of 28 joints (DAS-28), which incorporates swollen and tender joint counts, acute-phase reactant levels, and patient-reported outcomes [2]. In recent years, there has been growing interest in identifying the role of different complete blood count-derived (CBC) biomarkers that can serve as cost-effective, non-invasive tools across various medical conditions. Among these biomarkers, red cell distribution width (RDW), hemoglobin platelet ratio (HPR), and hemoglobin monocyte ratio (HMR) derived from complete blood count (CBC) measurements have emerged as promising candidates. RDW, a measure of the variation in the size of circulating red blood cells, has been shown to be an accessible and economical parameter that, together with other characteristics of the presentation and evolution of patients with COVID-19, can help determine the prognosis [3]. Interestingly, another study has shown that a preoperatively elevated standard deviation of RDW (RDW-SD) predicts favorable survival in patients with intrahepatic cholangiocarcinoma after curative resection [4]. RDW, along with other CBC-derived biomarkers such as neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios, has demonstrated good predictive value for early-phase severe acute pancreatitis (SAP) prediction, exhibiting the highest discriminatory capacity among other biomarkers and consequently indicating its potential as a convenient and reliable indicator for predicting SAP [5]. Similarly, HPR and HMR have garnered attention for their ability to reflect alterations in hematopoietic and inflammatory processes associated with various medical conditions. HPR, calculated as the ratio of hemoglobin to platelet count, has been proposed as a marker of developing radiation-induced trismus (RIT) among locally advanced nasopharyngeal carcinoma patients undergoing concurrent chemoradiotherapy (CCRT) [6]. Another study suggests that HPR combined with carcinoembryonic antigen (CEA) can increase diagnostic efficacy and may be a useful diagnostic marker for patients with rectal cancer [7]. Despite the growing body of evidence supporting the potential utility of these biomarkers, their utility in RA remains unclear. The correlation with DAS-28 scores as well as their predictive capabilities for treatment outcomes in newly diagnosed RA patients have not been investigated yet. Therefore, the main aim of this study was to investigate the associations between RDW, HPR, and HMR levels and DAS-28 scores in RA patients, as well as their predictive value for treatment response in individuals initiating methotrexate therapy, which serves as the standard initial treatment for RA.

Materials and Methods. Study population: This retrospective study involved 64 newly diagnosed patients with rheumatoid arthritis from the V. Tsitlanadze Scientific-Practical Center of Rheumatology in Tbilisi, Georgia, along with 28 age- and sex-matched controls who did not have any type of cancer, acute or chronic infections, or autoimmune diseases. To be included in the study, patients had to meet the diagnostic criteria for rheumatoid arthritis as established by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR). We gathered demographic information and detailed medical histories from each patient. Clinical and laboratory evaluations included recording the number of swollen and tender joints (SJC and TJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-CCP antibodies, complete blood count, and disease activity assessment using the DAS28 score. The DAS28 score was calculated using SJC, TJC, and ESR parameters. Patients were required to exhibit high disease activity (DAS28 > 3.2).

Exclusion criteria: Patients with diabetes, hypertension, renal failure, coronary artery disease, pulmonary disease, malignancy, infection, pregnancy or postpartum, granulomatous disease, or any inflammatory disorder were excluded from the study.

All patients were initiated on methotrexate with starting doses ranging from 7.5 to 15 mg weekly. The maximum titration was up to 25 mg weekly, as per standard clinical protocols.

Data collection: Complete blood count (CBC) data were collected from all patients. CBC measurements included hemoglobin, MCV, monocyte, and platelet counts, which allowed the calculation of RDW-SD, HPR, and HMR ratios. RDW-SD was calculated by dividing the standard deviation (SD) of the mean corpuscular volume (MCV) by the MCV and multiplying by 100. HPR and HMR were calculated as follows: hemoglobin count divided by platelets and monocytes, respectively.

Response assessment: After three months of treatment with methotrexate, patients underwent a reassessment to determine their response to the treatment. Based on disease activity markers such as

DAS-28, improvement in clinical symptoms, decrease in the number of tender and swollen joint counts, reduction of acute phase reactants (ESR and CRP), and better performance in vocational and avocational activities, patients were categorized into two groups: responders or non-responders. Those in the responder group (MTXS) who achieved remission or a significant reduction in disease activity continued their methotrexate treatment. Those in the non-responder group (MTXR), who did not achieve remission or showed inadequate improvement in disease activity were switched to treatment with tocilizumab, an interleukin-6 receptor inhibitor.

Statistical analysis: Statistical analyses were performed using Prism 9 and IBM SPSS Statistics for Windows, Version 26 (released 2010; IBM Corp., Armonk, New York, United States). Descriptive statistics were used to summarize patient demographics and baseline characteristics. All quantitative data were expressed as mean +/- standard deviation. Unpaired t-tests were used for group comparisons where appropriate. The statistical significance between groups for categorical variables was calculated using the chi-squared test. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for RDW-SD, HPR, and HMR in predicting treatment response. Pearson's correlation test was used for the correlation study. All tests were two-tailed. Differences below 0.05 were considered statistically significant.

Ethical considerations: The study protocol was approved by the Tbilisi State Medical University Biomedical Research Ethics Committee (approval number N1-2022/94). All participants provided informed consent before enrollment.

Table 1. Comparison between the study populations' baseline clinical and serological characteristics

	MTXS group n=37	MTXR group n =27	Control n=28	p^1	p^2	p^3
Age (years), (mean ± SD)	52.24±15.03	51.81±12.71	48.29±15.68	0.7380	0.5356	0.1821
Female, n (%)	33 (89.19%)	24 (88.89%)	20 (71.42%)	0.2217	0.1705	0.0655
DAS28	5.76±0.64	5.75±0.69		0.9625		
ANA positive (>1:80), n(%)	1 (2.7%)	5 (18.52%)	0 (0 %)	0.0164	0.0031	<0.0001
RF, n (%)	16 (43.24%)	27 (100%)	0 (0 %)	<0.0001	<0.0001	0.0001
Anti CCP, n (%)	27 (72.97%)	66 (96.30%)	0 (0 %)	0.0732	0.0035	0.0109
CRP (mg/L), (mean ± SD)	30.28±20.37	19.71±21.45		0.0493		
ESR (mm/h) (mean ± SD)	30.59±17.73	42.29±14.63		0.0130		
Neutrophils (10^3 cells/mL)	5.91±1.84	5.02±1.56	3.65±0.93	0.0455	<0.0001	<0.0001
Lymphocytes (10^3 cells/mL)	2.57±0.93	2.01±0.60	2.05±0.40	0.0084	0.0025	0.0905
Monocytes (10^3 cells/mL)	0.63±0.32	0.44±0.16	0.51±0.12	0.0053	0.0040	0.4022
Platelets (10^9 cells /mL)	313.22±92.67	326.1±69.04	248.93±43.93	0.5432	0.0003	<0.0001
RDW-SD	5.39±0.30	7.89±0.65	3.21±0.35	<0.0001	<0.0001	<0.0001
HPR	0.43±0.10	0.41±0.14	0.06±0.01	0.4364	<0.0001	<0.0001
HMR	258.68±176.51	329.93±166.11	28.30±5.10	0.1072	<0.0001	<0.0001

SD - Standard deviation, **DAS28** – Disease activity score for 28 joints, **ANA** - Antinuclear antibody, **Anti-CCP** – Anti-cycling citrullinated peptide antibody, **RF** – Rheumatoid factor, **CRP** – C reactive protein, **ESR** – Erythrocyte sedimentation rate, **RDW-SD – red cell distribution width** – standard deviation, **HPR** – Hemoglobin-platelet ratio, **HMR –** Hemoglobin-monocyte ratio. **p^1** – MTXS group vs. MTXR group, **p^2** –MTXR group vs. Control group, **p^3 –** MTXS vs. Control group.

Results. Table 1 summarizes the demographic, clinical, and laboratory data of studied subjects. Out of 64 enrolled patients, 57 were female and 7 were male. A total of 37 patients were included in the MTXS group, 27 patients in the MTXR group, and 28 age- and sex-matched individuals in the control group. The average age and gender distribution of the patients in the MTXS, MTXR, and control groups did not differ significantly. Statistically significant differences have been observed between the MTXR

and MTXS groups regarding RDW-SD, ESR, CRP, neutrophils, lymphocytes, and monocytes ($p<0.0001$, $p=0.0130$, 0.0493, 0.0455, 0.0084, and 0.0053 respectively). RDW-SD, along with ESR was substantially elevated in the MTXR group. Conversely, higher levels of CRP have been observed in the MTXS group. However, there was no statistically significant difference found between the groups in terms of DAS-28, HGR, and HMR ($p=0.9625$, 0.4364, and 0.1072 respectively). The correlation between RDW-SD, HPR, HMR, and DAS-28 was also studied, but no significant positive correlations were identified in either the MTXR or MTXS groups. The prognostic potential of studied CBC-derived biomarkers in predicting treatment outcomes among RA patients initiating methotrexate was assessed using Receiver Operating Characteristic (ROC) curve analysis. The ROC curve analysis demonstrated that the area under the curve (AUC) for each biomarker did not surpass the threshold indicative of predictive capability (Figure 1, Figure 2).

Figure 1. ROC curve analyzes the prognostic value of the Hemoglobin-Monocyte Ratio (HMR) in RA patients under MTX treatment

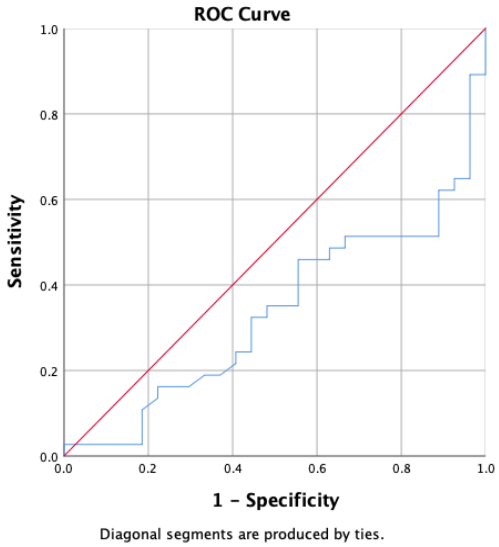


Figure 2. ROC curve analyzes the prognostic value of the Hemoglobin-Platelet Ratio (HPR) in RA patients under MTX treatment

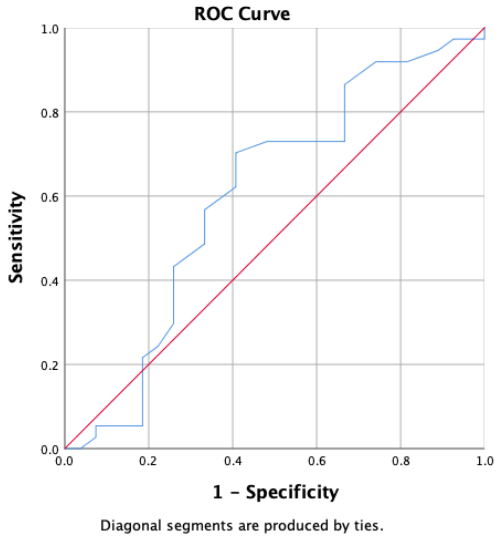
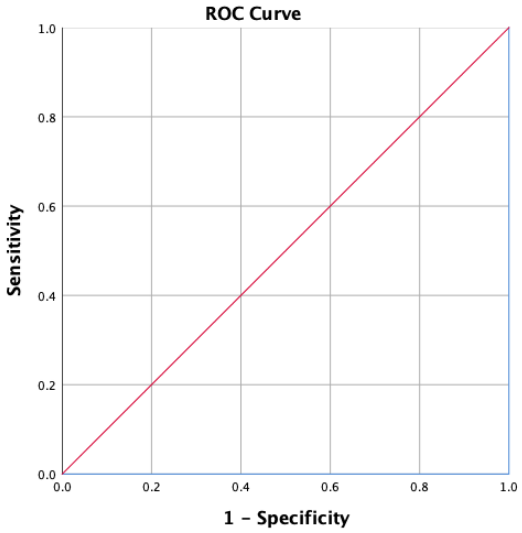


Figure 3. ROC curve analyzes the prognostic value of the red cell distribution (RDW) in RA patients under MTX treatment



Discussion: Rheumatoid arthritis represents a significant burden on global healthcare systems, with its chronic inflammatory nature often leading to joint damage and functional impairment if not effectively managed. In pursuit of improved treatment strategies and prognostic indicators, researchers have turned their attention to hematological biomarkers derived from routine CBC measurements. Among these biomarkers, RDW, HPR, and HMR have garnered interest for their potential utility in assessing disease activity and predicting treatment outcomes across various diseases. However, the specific relevance of these biomarkers in the context of RA has remained largely unexplored. Our study's primary and potentially pioneering finding is the identification of a statistically significant difference in RDW-SD between MTXR and MTXS groups. In the MTXR group, we observed a higher RDW-SD compared to the MTXS group ($p < 0.0001$) The observed difference in RDW-SD between the two groups may suggest a potential association between red blood cell morphology variability and methotrexate response in RA patients. Methotrexate, a cornerstone therapy in RA management, exerts its therapeutic effects through the inhibition of dihydrofolate reductase, thereby disrupting folate metabolism and ultimately suppressing immune-mediated inflammation. It is credible that variations in red blood cell morphology, as reflected by RDW-SD, could influence the efficacy of methotrexate therapy through as-yet-unknown mechanisms. One possible explanation for the observed difference in RDW-SD between MTXR and MTXS groups could be related to differences in systemic inflammation levels. RA is characterized by dysregulated immune responses and chronic inflammation, which can lead to alterations in red blood cell parameters, including RDW. Methotrexate resistance may be associated with heightened inflammatory activity, resulting in increased red blood cell variability as reflected by RDW-SD. Conversely, MTXS patients may exhibit lower levels of inflammation, leading to more stable red blood cell parameters and lower RDW-SD values. A similar finding has been demonstrated in a study of gastric cancer, where higher RDW-SD levels were associated with poor outcomes [8]. Additionally, genetic factors may play a role in mediating the relationship between RDW-SD and methotrexate response in RA patients. Genetic polymorphisms involved in folate metabolism and inflammation could potentially influence both RDW-SD values and individual responses to methotrexate therapy. Future studies incorporating genetic analyses may help elucidate the underlying genetic determinants of RDW-SD and its association with methotrexate resistance in RA. Furthermore, we investigated and found no significant correlation between RDW, HPR, and HMR levels and the DAS-28 in either group. This suggests that any of the biomarkers of interest cannot replace the DAS-28 to monitor disease activity and progression. Another study demonstrated a positive relationship between RDW, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and cardiac troponin I (cTnI) in acute myocardial infarction [9] and this underscores the need for further research in the direction of RA. Also, we have assessed the predictive capabilities of RDW-SD, HPR, and HMR for treatment outcomes in

newly diagnosed RA patients initiating methotrexate therapy. Our findings revealed that none of the examined CBC-derived biomarkers demonstrated predictive capability for treatment response. The AUC values for these biomarkers remained near or below the threshold of 0.5, indicative of outcomes no better than chance. These results, once again, highlight the limitations of RDW, HPR, and HMR as biomarkers in managing RA. The lack of predictive capability for treatment outcomes further underscores the complexity of RA pathogenesis and the need for multifaceted approaches to disease management. Although there is emerging data highlighting the predictive ability of those biomarkers in other medical settings [10], RA has its distinct inflammatory environment and underlying mechanisms, which may not be accurately represented by biomarkers that have demonstrated effectiveness in other diseases. Furthermore, variables such as age, gender, serological markers, concomitant medications, disease severity at the beginning of treatment, and lifestyle factors may interact with RDW, HPR, and HMR levels, impacting treatment response and complicating the interpretation of the study results.

When interpreting the results, it's important to consider the limitations of this study. These limitations include the relatively small sample size, data collection at a single medical center, and the retrospective nature of the study. It's important to note that these findings may not apply to patients who are receiving different treatment regimens or those at more advanced disease stages, as the study only looked at the use of methotrexate as the sole conventional disease-modifying antirheumatic drug (DMARD), along with short-term non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, for newly diagnosed patients.

Conclusion: We propose that there may be a relationship between an elevated RDW-SD and resistance to methotrexate in RA patients, suggesting that RDW-SD could be a novel, cost-effective, and easily measured parameter for predicting RA treatment outcomes at the start of treatment. We do not recommend using RDW-SD, HPR, and HMR as substitutes for DAS-28 for monitoring disease severity and activity. Our study emphasizes the need for ongoing research to identify reliable biomarkers to guide clinical decision-making and enhance outcomes for RA patients.

Conflict of interest: The authors of this article declare no conflicts of interest.

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UTILITY OF NON-INVASIVE HEMATOLOGICAL BIOMARKERS IN NEWLY DIAGNOSED RHEUMATOID ARTHRITIS PATIENTS

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SUMMARY

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation of the synovium, leading to joint damage and systemic complications. Methotrexate (MTX) is commonly used as a first-line treatment for RA due to its immunosuppressive properties. However, a significant proportion of patients exhibit resistance to MTX therapy. Lately, certain complete blood count (CBC) derived biomarkers such as red cell distribution width (RDW), hemoglobin platelet ratio (HPR), and hemoglobin-monocyte ratio (HMR) have emerged as promising indicators in various inflammatory conditions, providing insights into disease prognosis and therapeutic response. However, there is currently limited data available on the effectiveness of the abovementioned biomarkers as prognostic ones to predict treatment outcomes in newly diagnosed RA patients who are initiating MTX treatment.

Objective: This study aimed to determine the potential of RDW, HPR, and HMR as prognostic biomarkers in newly diagnosed RA patients commencing MTX therapy. Additionally, to investigate their possible correlation with the Disease Activity Score of 28 joints (DAS-28).

Methods: We conducted a comprehensive analysis involving 64 RA patients categorized into Methotrexate-resistant (MTXR) and Methotrexate-sensitive (MTXS) groups and 28 age- and sex-matched healthy individuals. Standard T-tests were used to compare specific biomarkers between MTXR, MTXS, and control groups. For the comparison of categorical variables between the groups Chi-square test was employed. We examined correlations with Pearson's correlation test between RDW, HPR, HMR, and DAS28 in both groups. To determine the predictive capabilities of these biomarkers, Receiver Operating Characteristic (ROC) curve analysis was performed.

Results: We identified statistically significant different RDW-SD values in MTXR and MTXS groups, according to an unpaired t-test. The RDW-SD was higher in the MTXR group compared to the MTXS. No significant positive correlations were identified between hematological biomarkers of interest and DAS-28 in either the MTXR or MTXS group. Additionally, The ROC curve analysis showed that their predictive capability was insignificant.

Conclusion: Elevated RDW-SD levels can be an early indicator of MTX resistance at the beginning of therapy in newly diagnosed RA patients. Additionally, based on our study cohort RDW-SD, HPR, and HMR cannot replace DAS-28 for assessing and monitoring disease activity in RA patients.

Keywords: Rheumatoid arthritis, RDW, HPR, HMR, Biomarkers