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Pan-Immune Inflammation Value in Newly Diagnosed Rheumatoid Arthritis Patients Initiating Methotrexate Treatment

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a persistent autoimmune condition characterized by synovial inflammation, culminating in joint deterioration and systemic implications. Methotrexate (MTX) is the primary therapeutic intervention for RA initiation due to its immunomodulatory properties. Nevertheless, resistance to MTX therapy is observed in a notable subset of patients. The Pan-Immune Inflammation Value (PIV) has recently emerged as a prospective biomarker in various inflammatory contexts, furnishing prognostic insights and indications of therapeutic response. Derived from routine complete blood count parameters, PIV has garnered significant interest as a prognostic biomarker across a spectrum of medical conditions, encompassing cancer to septic shock. Despite this, there exists a paucity of data regarding the efficacy of PIV as a prognostic biomarker for predicting treatment outcomes in newly diagnosed RA patients initiating MTX therapy.

Objectives: This study aims to assess the potential utility of PIV as a prognostic biomarker in newly diagnosed RA patients undergoing MTX therapy. Additionally, the study explores the plausible correlation between PIV and the Disease Activity Score of 28 joints (DAS-28).

Methods: A comprehensive analysis encompassing 64 RA patients, stratified into Methotrexate-resistant (MTXR) and Methotrexate-sensitive (MTXS) cohorts, along with 28 age- and sex-matched healthy individuals, was conducted. ANOVA analyses were employed to evaluate variations in hematological biomarkers among the groups. Standard T-tests facilitated the comparison of specific biomarkers among MTXR, MTXS, and control groups. The Chi-square test was utilized to compare categorical variables among the groups. Pearson's correlation test was also employed to explore correlations between PIV and DAS28 in both cohorts. Receiver Operating Characteristic (ROC) curve analysis was performed to ascertain the predictive capacity of PIV.

Results: An unpaired t-test revealed no statistically significant difference in PIV (p=0.16) between the MTXR and MTXS groups. Similarly, no significant positive correlations were discerned between PIV and DAS-28 in the MTXR or MTXS groups (p=0.15 and 0.33, respectively). Furthermore, ROC curve analysis revealed insignificance in the predictive capability of PIV.

Conclusions: Based on our findings, we cannot advocate for the utilization of PIV as a predictor of methotrexate response in newly diagnosed RA patients. Moreover, our study cohort underscores the inadequacy of PIV as a replacement for DAS-28 in assessing disease activity among RA patients.

Keywords: Methotrexate resistance; novel biomarker; rheumatoid arthritis; pan-immune inflammation value (PIV).

BACKGROUND

Rheumatoid arthritis (RA) stands as a chronic autoimmune disorder characterized by persistent synovial inflammation, culminating in joint degradation and systemic complications.[1] Methotrexate (MTX) is frequently employed as the primary therapeutic modality for RA due to its immunosuppressive properties. Nonetheless, a notable subset of patients exhibits resistance to MTX therapy, resulting in disease advancement and unfavorable clinical outcomes. The Pan-Immune Inflammation Value (PIV) has recently emerged as a promising biomarker across various inflammatory contexts, providing insights into disease prognosis and therapeutic response. Derived from routine complete blood count parameters, PIV has garnered significant attention as a prognostic biomarker across a spectrum of medical conditions, spanning from cancer to septic shock. A comprehensive literature review reveals compelling evidence supporting its utility in predicting therapeutic response and clinical outcomes in diverse patient populations. Notably, in the context of septic shock, a study elucidates the prognostic significance of PIV, as it correlates with longer survival rates in affected patients.[2] By incorporating PIV into clinical practice, healthcare providers can identify patients at elevated risk of adverse outcomes, facilitating timely interventions to enhance survival rates and optimize patient care. Moreover, investigations examining the predictive value of PIV in neoadjuvant immunochemotherapy for esophageal squamous cell carcinoma underscore its potential in forecasting treatment efficacy and clinical outcomes.[3] Pre-treatment PIV emerges as a valuable tool for risk assessment, enabling personalized therapeutic strategies and improving patient prognosis in this complex clinical scenario. In the oncology realm, PIV has demonstrated prognostic significance across various cancer types, including extensive-stage small-cell lung cancer and hepatocellular carcinoma.[4,5] Baseline PIV levels predict

clinical outcomes, offering valuable insights into disease progression and guiding treatment decision-making. Additionally, PIV exhibits promise in predicting survival rates in patients with operable breast cancer.[6] Furthermore, elevated PIV levels have been associated with reduced glomerular filtration rate (GFR) in patients with lupus nephritis, suggesting its potential as a novel biomarker for assessing GFR reduction risk and the necessity for intensive treatment in these patients.[7] PIV, amalgamating diverse markers of inflammation and immune system cells, shows promise as a prognostic tool for various pediatric conditions, including respiratory distress syndrome in preterm infants and pediatric acute-onset neuropsychiatric syndrome (PANS).[8] In rheumatoid arthritis, PIV has emerged as a valuable marker for evaluating remission and active disease compared to healthy individuals. It can also aid in assessing disease activity in patients with active rheumatoid arthritis.[9] However, there remains limited data concerning the effectiveness of PIV as a prognostic biomarker for predicting treatment outcomes in newly diagnosed RA patients initiating MTX therapy. Therefore, this study aims to ascertain the potential of PIV as a prognostic biomarker of MTX treatment outcomes in the abovementioned cohort. Additionally, the study aims to investigate the potential correlation between PIV and the Disease Activity Score of 28 joints (DAS-28), a widely utilized tool for assessing disease activity in patients with rheumatoid arthritis.[10]

METHODS

Study population

This retrospective study comprised 64 newly diagnosed rheumatoid arthritis patients recruited from the V. Tsitlanadze Scientific-Practical Center of Rheumatology in Tbilisi, Georgia. Additionally, 28 age- and sex-matched controls without a history of cancer, acute or chronic infections, or autoimmune disorders were included. Patients meeting the diagnostic criteria for rheumatoid arthritis established by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) were eligible for inclusion.

Demographic data and comprehensive medical histories were collected for each participant. Clinical and laboratory evaluations included documentation of swollen and tender joint counts (SJC and TJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, rheumatoid factor (RF) status, anti-cyclic citrullinated peptide (anti-CCP) antibody levels, complete blood count (CBC) and assessment of disease activity using the 28-joint disease activity score (DAS28). Disease activity was defined as high if the DAS28 score exceeded 3.2

Exclusion criteria

Patients with comorbidities such as diabetes, hypertension, renal failure, coronary artery disease, pulmonary disorders, malignancy, infections, pregnancy or postpartum status, granulomatous diseases, or any other inflammatory conditions were excluded from the study.

All patients were initiated on methotrexate therapy with initial doses ranging from 7.5 to 15 mg weekly, with titration up to a maximum of 25 mg weekly following standard clinical protocols.

Data collection

Complete blood count (CBC) data were obtained from all participants. CBC parameters included neutrophil, lymphocyte, monocyte, and platelet counts, enabling the calculation of the Pan-Immune Inflammation Value (PIV). PIV was computed using the formula: (neutrophil count × platelet count × monocyte count) / lymphocyte count.

Response assessment

Following three months of methotrexate treatment, patients underwent reassessment to evaluate treatment response. The response was determined based on various disease activity markers, including the Disease Activity Score of 28 joints (DAS28), improvement in clinical symptoms, reduction in tender and swollen joint counts, decrease in acute phase reactants (erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP] levels), and enhanced performance in vocational and avocational activities. Patients were categorized into two groups: responders (MTXS) and non-responders (MTXR). Responders achieved either remission or a substantial reduction in disease activity and continued methotrexate treatment. In contrast, non-responders who did not achieve remission or showed inadequate improvement were switched to tocilizumab therapy, an interleukin-6 receptor inhibitor.

Statistical analysis

Statistical analyses were conducted using Prism 9 and IBM SPSS Statistics for Windows, Version 26. Descriptive statistics summarized patient demographics and baseline characteristics, with quantitative data presented as mean ± standard deviation. Group comparisons were made using unpaired t-tests and analysis of variance (ANOVA) as appropriate. The chi-squared test assessed statistical significance between groups for categorical variables. Receiver operating characteristic (ROC) curve analysis determined optimal cut-off values for PIV in predicting treatment response. Pearson's correlation test investigated correlations. All tests were two-tailed, with p-values < 0.05 considered statistically significant.

Ethical Consideration

The study protocol received approval from the Tbilisi State Medical University Biomedical Research Ethics Committee (approval number N1-2022/94). All participants provided informed consent prior to enrollment.

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RESULTS

Out of 64 enrolled patients, 57 were female, and seven were male. Thirty-seven patients were included in the MTXS group, 27 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 ESR, CRP, neutrophils, lymphocytes, and monocytes (p=0.01, 0.05, 0.05, 0.01, and 0.01, respectively). However, no statistically significant difference was found between the groups regarding DAS-28 and PIV (p=0.96 and 0.16, respectively).

Table 1 summarizes the studied subjects' demographic, clinical, and laboratory data.

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

	RA patients n=64	MTXS group n=37	MTXR group n =27	Control n=28	p^1	p^2	p^3
Age (years), (mean ± SD)	52.06 ±14.00	52.24 ± 15.03	51.81 ± 12.71	48.29 ± 15.68	0.74	0.54	0.18
Female, n (%)	57 (89.06%)	33 (89.19%)	24 (88.89%)	20 (71.42%)	0.22	0.17	0.07
DAS28	5.76 ± 0.66	5.76 ± 0.64	5.75 ± 0.69		0.96		
ANA positive (>1:80), n (%)	5 (9.3%)	1 (2.7%)	5 (18.52%)	0 (0 %)	0.02	0.00	<0.0001
RF, n (%)	43 (67.19%)	16 (43.24%)	27 (100%)	0 (0 %)	<0.0001	<0.0001	0.00
Anti CCP, n (%)	53 (82.81%)	27 (72.97%)	66 (96.30%)	0 (0 %)	0.07	0.00	0.01
CRP (mg/L), (mean ± SD)	25.82±21.32	30.28±20.37	19.71±21.45		0.05		
ESR (mm/h) (mean ± SD)	34.83±17.48	30.59±17.73	42.29±14.63		0.01		
Neutrophils (10^3 cells/mL)	5.53±1.77	5.91±1.84	5.02±1.56	3.65±0.93	0.05	<0.0001	<0.0001
Lymphocytes (10^3 cells/mL)	2.34±0.85	2.57±0.93	2.01±0.60	2.05±0.40	0.01	0.00	0.09
Monocytes (10^3 cells/mL)	0.55±0.28	0.63±0.32	0.44±0.16	0.51±0.12	0.01	0.00	0.40
Platelets (10^9 cells /mL)	318.7±83.16	313.22±92.67	326.1±69.04	248.93±43.93	0.54	0.00	<0.0001
PIV	498.30±403.40	559.42±449.74	559.40±449.70	241.84±139.29	0.16	0.00	0.00

Abbreviations: ANA, antinuclear antibody; Anti-CCP, anti-cycling citrullinated peptide antibody; CRP, C reactive protein; DAS28, disease activity score for 28 joints; ESR, erythrocyte sedimentation rate; p1, MTXS group vs. MTXR group; p2, MTXS group vs. MTXR group vs. Control group; p3, overall RA patients vs. Control group; PIV, pan-immune inflammation value; RF, rheumatoid factor; SD, standard deviation.

An ANOVA analysis showed significant differences between the MTXS, MTXR, and control groups in PIV (p=0.02). However, no statistically significant difference was observed in terms of PIV (p=0.17) between the MTXR and MTXS groups, according to an unpaired t-test. The relationship between PIV and DAS-28 was also studied, but no significant positive correlations were identified in the MTXR or MTXS groups (p=0.15 and 0.33, respectively) (Tab.2).

TABLE 2. Correlation between DAS-28 and PIV in MTXR and MTXS group

	MTXR	MTXS
	DAS 28 versus PIV	
Pearson correlation coefficient (r)	*0.26*	*-0.17*
P value	*0.18*	*0.33*

Abbreviations: DAS28, disease activity score for 28 joints; MTXR, methotrexate non-responders; MTXS, methotrexate responders; PIV, pan-immune inflammation value.

Prognostic Assessment of PITAB.3V

The prognostic potential of PIV in predicting treatment outcomes among RA patients initiating methotrexate was assessed using Receiver Operating Characteristic (ROC) curve analysis. Table 3 and Figure 1 display the results of ROC curve analysis for PIV.

The ROC curve analysis showed that PIV's predictive capability was insignificant, as the AUC value was 0.564 (Tab.3).

TABLE 3. ROC Analysis Results of PIV

Area Under the Curve				
			Test Result Variable(s): PIV	
Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.564	0.072	0.388	0.422	0.706

Abbreviations: PIV, pan-immune inflammation value

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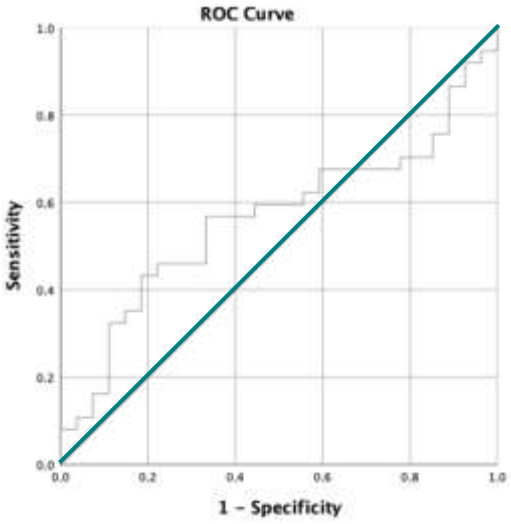
FIGURE 1. ROC curve analyzes the prognostic role of pan-immune inflammation value (PIV) in RA patients under MTX treatment



DISCUSSION

Rheumatoid arthritis (RA) poses a multifaceted challenge involving cellular and humoral immune responses in its pathogenesis. Current research endeavors to identify dependable biomarkers for evaluating treatment response in RA patients. While it is established that immune system precursor cells, like neutrophils and platelets, contribute to disease and ensuing inflammation by producing cytokines, chemokines, and growth factors, our comprehension of specific hematological biomarkers derived from complete blood count (CBC) remains limited. Investigating the role of Pan-Immune Inflammation Value (PIV) in RA patients initiating Methotrexate treatment may enhance our understanding of managing this complex disease. Our study's findings do not support PIV as a reliable predictor of Methotrexate therapy outcomes or suggest a positive correlation between PIV and DAS-28. Notably, literature regarding the correlation between PIV and DAS-28 in RA patients is scarce. Tutan's report highlights PIV's efficacy in distinguishing between remission and active RA compared to healthy individuals, with a positive correlation with DAS-28. However, our findings contradict these observations.

The discrepancy between our study and previous research raises pertinent discussion points. Firstly, the lack of correlation between PIV and DAS28 in our cohort may stem from variations in patient populations, disease characteristics, or methodological differences. These variations could encompass differences in patient demographics or treatment protocols. Secondly, the absence of PIV's predictive capacity in discerning treatment outcomes, particularly in predicting Methotrexate response, challenges its utility as an RA biomarker. This suggests that factors beyond PIV, such as genetic predisposition or disease heterogeneity, influence treatment response.

Study limitations must be acknowledged when interpreting these findings. These include the relatively small sample size, data collection from a single medical center, and the study's retrospective nature. Additionally, using Methotrexate as the sole treatment modality in newly diagnosed patients may limit generalizability to patients on different regimens or with advanced disease stages. Factors like age, gender, serological markers, concomitant medications, and lifestyle may interact with PIV levels, complicating treatment response interpretation.

CONCLUSIONS

Based on our findings, we cannot support the use of PIV as a predictor of methotrexate response in newly diagnosed RA patients. Also, our study cohort has shown that it cannot substitute DAS-28 for assessing and monitoring disease activity in RA patients. Due to conflicting data in the literature, further research is needed to understand the factors that affect PIV levels and their association with treatment outcomes in RA. Standardization and validation of PIV assays in large cohorts are necessary to ensure their reliability and validity for clinical use. This will ultimately optimize outcomes in RA patients.

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