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REVIEW

Red Blood Cell Distribution Width: A Potential Inexpensive Marker for Disease Activity in Patients with Rheumatic Diseases; Scoping Review

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Background: Rheumatic diseases encompass a diverse group of autoimmune disorders that affect the joints and connective tissues. The red blood cell distribution width (RDW) has been widely investigated as an inflammatory marker. This scoping review aimed to explore the potential utility of RDW as an inexpensive marker for disease activity in patients with rheumatic diseases. By summarizing the available evidence, we aimed to determine whether RDW can serve as a reliable and accessible indicator of disease activity in these patients.

Methods: A comprehensive search was systematically performed across electronic databases, encompassing PubMed, Embase, and Web of Science. Studies have explored the relationship between RDW and disease activity in rheumatic diseases. Data extraction focused on the study characteristics, methodologies, and findings related to RDW as a disease activity marker.

Results: After removing duplicates, the initial search yielded 25 relevant studies. These studies encompassed a variety of rheumatic diseases, with rheumatoid arthritis being the most frequently studied condition. The association between RDW and disease activity was assessed by using various disease activity indices and clinical parameters. While some studies have reported a significant correlation between elevated RDW and disease activity, others have yielded inconclusive results.

Conclusion: From this review, we concluded that RDW is an inexpensive potential marker for the evaluation of disease activity in rheumatic diseases. RDW is promising as an inexpensive and readily available marker; however, its clinical utility in assessing disease activity in rheumatic conditions warrants more rigorous investigation through well-designed prospective studies.

Keywords: red blood cell distribution width, RDW, rheumatic diseases, disease activity, marker, scoping review

Introduction

Autoimmune disorders collectively referred to as rheumatic diseases impact a wide range of individuals globally, resulting in notable morbidity and diminished quality of life.[1] These conditions, including rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis, exhibit a chronic and often relapsing-remitting course characterized by inflammation of the joints, connective tissues, and other organ systems.[2] Accurate assessment of disease activity is paramount for guiding clinical management, adjusting treatment regimens, and evaluating therapeutic efficacy.[3]

Conventionally, disease activity in rheumatic diseases has been assessed using a combination of clinical evaluations, patient-reported outcomes, imaging studies, and various laboratory markers.[4] Such markers commonly encompass acute-phase reactants like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which serve as indicators of systemic inflammation.[4] However, the cost, accessibility, and potential fluctuations of these markers often pose challenges in the routine monitoring of disease activity.[5]

RDW, a parameter routinely reported in complete blood counts (CBC), quantifies the variation in the size of circulating red blood cells.[6] While RDW has traditionally been employed in the diagnosis of anemia, emerging evidence suggests that it may have broader implications beyond hematology.[7] Recent studies have proposed a potential association

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between elevated RDW levels and systemic inflammation, implicating its utility as an adjunctive marker for disease activity in various medical conditions including cardiovascular diseases, malignancies, and inflammatory disorders.[8,9]

In the context of rheumatic diseases, the concept of RDW as an inexpensive and easily accessible marker for disease activity holds promise.[10] A growing body of research has begun to explore the relationship between RDW and disease-activity indices specific to rheumatic conditions. However, the literature in this area remains fragmented, with variations in the study populations, methodologies, and reported outcomes.

The red blood cell distribution width (RDW) is related to red blood cell heterogeneity.[11] It is the most commonly used index for variation in red cell volume and can be used to detect subtle degrees of anisocytosis.[12] RDW is part of the automated full blood count (FBC) and is a routinely available parameter in hematological analyzers.[13]

In recent times, numerous studies have showcased a correlation between high RDW and the flare of inflammatory diseases, such as Behcet's disease[14] and systemic lupus erythematosus (SLE).[15]

This scoping review aimed to systematically compile and analyze the existing literature to determine the potential of RDW as a marker for disease activity in patients with rheumatic diseases. By synthesizing the available evidence, we sought to assess the consistency and strength of the association between RDW and disease activity, identify knowledge gaps, and provide insights into the feasibility of RDW as a supplemental tool for assessing disease activity in routine clinical practice.

Methodology

Study Design: This research was conducted as a scoping review, aiming to comprehensively explore the existing literature on the potential of red blood cell distribution width (RDW) as a marker for disease activity in patients with rheumatic diseases.

Research Question: The research Questions: The guide this scoping review are as follows.

- What is the extent of the existing research on the association between RDW and disease activity in patients with rheumatic diseases?
- What are the reported findings regarding the potential of RDW as a marker of disease activity in rheumatic diseases?

Search Strategy

A comprehensive search was conducted across electronic databases including PubMed, Embase, Web of Science, and Scopus. The search strategy included relevant keywords such as "red blood cell distribution width", "RDW", "rheumatic diseases", "disease activity", and related terms. Boolean operators (AND and OR) were used to refine the search. The search was restricted to articles published within a specified timeframe (last 5 years) to ensure the currency of the literature.

Inclusion and Exclusion Criteria

Articles that met the following criteria were included:

- Focusing on the association between RDW and disease activity in patients with rheumatic diseases.
- Human participants diagnosed with rheumatic diseases were included.
- Present original research findings, including cross-sectional, longitudinal, and retrospective studies.
- Articles published in English.

The Exclusion Criteria Were as Follows

- Studies unrelated to rheumatic diseases.
- Reviews, case reports, editorials, and conference abstracts.
- Studies not reporting relevant outcomes related to RDW and disease activity.

Data Extraction

Data were extracted using a standardized form, capturing information such as study characteristics (authors, publication year), study design, sample size, rheumatic disease types, disease activity indices used, RDW measurement methods, statistical analyses performed, and reported associations between RDW and disease activity.

RDW is Calculation

Red Blood Cell Distribution Width (RDW) is a measure of variation in the size of red blood cells (erythrocytes) in a blood sample. This was typically reported as a percentage. RDW is calculated using the following formula: RDW = (Standard Deviation of Red Blood Cell Volume ÷ Mean Cell Volume) × 100.[16]

The concept of "Standard Deviation of Red Blood Cell Volume" reflects the variation in sizes present among individual red blood cells, whereas "Mean Cell Volume" refers to the average size of red blood cells contained within the sample.

RDW is typically derived from a Complete Blood Count (CBC) examination, a diagnostic test that furnishes insights into the cellular constituents of the bloodstream, encompassing red blood cells. CBC measures various parameters, including hemoglobin concentration, hematocrit, and red blood cell indices, such as mean cell volume (MCV) and red cell distribution width (RDW).

Result

The positive associations observed between RDW and disease activity in a subset of studies suggest a potential link between elevated RDW levels and systemic inflammation in rheumatic diseases. However, the variability in methodologies, disease activity indices, and inconsistent findings across studies emphasizes the need for cautious interpretation and further investigation through well-designed prospective studies.

Rheumatoid Arthritis and RDW

Rheumatoid arthritis (RA) is a systemic autoimmune rheumatic disease that affects various tissues and organs and commonly involves synovial joints.[16,17] The guidelines set forth by the European League Against Rheumatism (EULAR) regarding the treatment of these individuals seek to manage disease activity or maintain patients in a state of remission with the goal of reducing the chances of complications.[18]

Although several different disease activity scores have been validated for RA, controversy exists regarding their accuracy in the assessment of disease activity, particularly in patients with fibromyalgia.[19]

Da Silva et al[20] have demonstrated a discrepancy between ultrasound synovitis scores and each of the Disease Activity Score 28 (DAS 28), the Simplified Disease Activity Index (SDAI) or the Clinical Disease Activity Index (CDAI) in the assessment of disease activity in patients with RA and concomitant fibromyalgia.

Another study showed that the presence of fibromyalgia results in higher disease activity scores in the absence of objective evidence of RA activity.[21]

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are common non-specific tests used to evaluate the acute phase response in RA. Many factors affect ESR levels, including age, sex, hypergammaglobulinemia, fibrinogen levels, rheumatoid factor, human immunodeficiency virus (HIV), and anemia.[22,23] However, CRP is expensive and not readily available in countries with financial and resource constraints, such as some African countries.[24]

Several recent studies have linked RDW to disease activity in patients with RA. Calabria et al[25] described a significant relationship between RDW and CRP, ESR, and disease activity score 28 (DAS28). This was present irrespective of age, sex, or disease duration.

Moreover, in a study of 110 RA patients, Yunchun et al[26] reported not only an association between RDW and the levels of inflammatory markers, but also a relationship between RDW and autoantibodies. In the same study, high levels of RDW were observed in patients with bone erosion.

Another study on patients with rheumatoid arthritis showed a significant association between RDW and DAS28, ESR, and CRP.[27]

A correlation analysis showed that RDW levels were positively associated with TNF-α and IL-6, and on the other hand, they were negatively associated with IL-10. Additionally, RDW was increased in patients with RA with active inflammation, suggesting that RDW may be a potential, convenient auxiliary marker for indicating the presence of an inflammatory process in patients with RA.[28]

Regarding cardiovascular diseases in patients with RA, increased RDW levels are related to endothelial progenitor cell depletion and mediators released from endothelial damage. Therefore, RDW may play a new role as a predictor of ischemic heart disease in RA patients.[29]

The relationship between RDW and cardiovascular diseases has been documented in many studies. A large retrospective study among unselected RA patients in the United States revealed that the proportion of RA patients with myocardial infarction was significantly higher in those with high RDW than in those with low RDW.[17]

Furthermore, Rodríguez et al[29] found that RDW measured at the onset of RA can be used as an early marker of cardiovascular risk in these patients, while it was associated with disease activity in patients with established disease. It is not clear whether this cardiovascular risk is a direct consequence of inflammation in RA.

A recent study examined RDW in individuals with rheumatoid arthritis (RA) and analyzed how baseline demographic and clinical factors might be linked to RDW levels. These findings indicate a notable increase in RDW levels in patients with RA.[30]

RDW and Systemic Lupus Erythematosus

Several studies have shown that RDW is correlated with the SLE Disease Activity Index (SLEDAI-2K), CRP level, and ESR.[31] Additionally, high RDW at the time of SLE diagnosis predicts poor outcomes.[32]

Another study showed a significant association between increased RDW and systemic lupus patients with very high activity compared to those with high activity.[33]

Vaya et al reported that SLE patients have higher RDW than healthy individuals and despite the presence of anemia in some SLE patients, high RDW has been found in SLE patients without anemia compared to healthy controls.[34] A recent UK study showed a significant relationship between RDW and fatigue levels in patients with SLE.[35]

RDW and Ankylosing Spondylitis (AS)

RDW is associated with disease activity in patients with ankylosing spondylitis.[36] In a case-control study by Sezgin et al, a notable distinction in RDW was observed between individuals with active ankylosing spondylitis (AS) characterized by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4 and those in a state of remission (BASDAI <4). Furthermore, RDW was positively correlated with ESR, CRP, and platelet levels.[27] Additionally, an Iraqi study revealed an association between increased RDW and disease activity in AS patients.

RDW and Primary Sjogren's Syndrome

Two studies examined RDW in patients with primary Sjögren syndrome. High RDW was shown to be associated with primary Sjogren's disease activity in one study, whereas another study reported that RDW can be used as a potential negative prognostic factor for the occurrence of pulmonary hypertension in patients with primary Sjogren's syndrome.[31,37]

RDW and Inflammatory Myopathies

Some studies have shown that RDW is positively related to the myositis disease activity assessment visual analog scale (MYOACT).[38] Another study found that RDW is independently related to myositis activity.[39]

RDW in Inflammatory Bowel Diseases (IBD)

Several studies have addressed the relationship between RDW and IBD. According to Yesil et al, RDW levels are higher in patients with inflammatory bowel disease (IBD) when compared to healthy controls, and these levels notably increase during periods of disease activity. Therefore, RDW may be used as a sensitive marker to assess disease activity in Crohn's disease.[40]

Another study of 74 patients with ulcerative colitis (UC) and 22 patients with Crohn's disease (CD) concluded that a high level of RDW is associated with UC activity, whereas in CD, CRP was found to be a significant indicator of disease activity.[41]

Oustamanolakis et al reported that RDW is elevated in patients with active IBD.[42] Another study showed that RDW is associated with disease activity in IBD, irrespective of the presence of anemia.[43]

RDW and Behçet's Disease

Among 236 patients with Behçet's disease (77 with active disease, 159 with inactive disease, and 72 controls), RDW, ESR, and CRP levels were found to be significantly elevated in patients with Behçet's disease than in the control group. They were also elevated in patients with active disease compared to those with inactive disease.[44]

A study published in 2012 reported that RDW is associated with disease activity in patients with Behçet's.[45]

RDW and Takayasu Arteritis

Currently, only two studies have examined the relationship between RDW and Takayasu arteritis. Liu et al reported that RDW may be a useful marker for the assessment of disease activity in Takayasu arteritis patients without anemia.[46] Another study reported a link between RDW and Takayasu arteritis disease activity.[36]

Atherosclerotic Cardiovascular Disease (ASCVD)

A recent study showed that RDW was positively associated with ASCVD 10-year scores and age. The ASCVD score did not change after spondyloarthritis treatment. Albumin levels negatively correlated with the ASCVD 10-year risk score. RDW and albumin levels were associated with CRP levels. ALC did not directly correlate with the ASCVD 10-year score but showed a tendency to be related to CVD, CVD events, and cardiac conduction irregularities. These results emphasize the need to further investigate RDW, albumin levels, and ALC as potential CVD predictors in patients.[47]

Discussion

This study explored the potential of red blood cell distribution width (RDW) as an inexpensive marker of disease activity in patients with rheumatic diseases. A synthesis of the available literature revealed a diverse landscape of studies examining the relationship between RDW and disease activity across various rheumatic conditions.[12–15] The discussion of these findings sheds light on the potential utility of RDW in assessing disease activity, highlights methodological variations, and highlights the need for further research.

A subset of the included studies demonstrated a positive association between elevated RDW levels and disease activity in rheumatic diseases.[16–29,48] This observation is in line with emerging evidence that RDW may serve as an indicator of systemic inflammation. Increased RDW has been linked to the release of pro-inflammatory cytokines and oxidative stress, both of which are hallmark features of autoimmune rheumatic diseases. These findings support the concept that RDW could potentially reflect the ongoing disease activity under these conditions.

Methodological variability was observed in the included studies. Variations in disease activity indices, RDW measurement techniques, and study populations contribute to the complexity of interpreting these findings. While some studies employed validated disease activity scores, others utilized clinical parameters or physician assessments, potentially introducing bias.[42] Moreover, variations in the laboratory methods for RDW measurement might affect the consistency and comparability of the results. These methodological challenges emphasize the importance of standardization in future research.

The potential of RDW as an inexpensive marker for disease activity holds promise in clinical practice. Routine complete blood counts (CBCs) are widely accessible, making RDW a convenient addition to the repertoire of disease activity markers.[49] Incorporating RDW into disease activity assessments could provide clinicians with an additional tool for monitoring patients, adjusting treatment strategies, and evaluating therapeutic efficacy.[50] However, the current body of evidence is not robust enough to warrant standalone use. Future research should address these gaps by conducting well-designed prospective studies, incorporating larger and more diverse patient populations, and employing standardized methodologies.

Here, we compare RDW with a few other recently introduced indices that are used in clinical practice or research to assess various aspects of health and disease.[39] These indices often serve as complementary markers to provide a more comprehensive understanding of different medical conditions, and include the following:

1. Neutrophil-to-Lymphocyte Ratio (NLR)
2. Platelet-to-Lymphocyte Ratio (PLR)
3. Mean Platelet Volume (MPV)
4. Red Cell Distribution Width to Platelet Ratio (RPR):
5. Monocyte-to-High-Density Lipoprotein Cholesterol Ratio (MHR)

Comparing RDW with these indices can reveal the associations between hematological parameters and various disease processes. Although RDW primarily reflects red blood cell size variability, indices such as NLR, PLR, and MPV provide insights into immune responses and platelet characteristics. Incorporating multiple indices, including RDW, into clinical assessments can offer a more comprehensive perspective on disease status and outcomes.

Abnormalities in RDW in different diseases indicate the underlying processes affecting red blood cell production, maturation, and turnover.[51] These abnormalities can result in elevated RDW, signifying increased cell size variability, or decreased RDW, indicating reduced variability. Although elevated RDW is more commonly discussed in disease contexts, decreased RDW can occur in conditions such as hereditary elliptocytosis, bone marrow disorders, and certain nutritional deficiencies. These abnormalities reflect intricate interactions among factors that influence erythropoiesis, iron metabolism, inflammation, and oxidative stress. Recognizing these mechanisms is essential for interpreting RDW values in clinical settings and for making informed diagnostic and treatment choices.

It's important to note that while these indices can provide valuable information, their clinical utility can vary depending on the specific disease context and the population being studied. Moreover, combining multiple indices should be performed cautiously, considering potential confounders and the complexity of the interactions between different biological systems.

This scoping review aims to offer a comprehensive assessment of the present research status regarding RDW as a prospective indicator for disease activity among individuals with rheumatic diseases. These findings will shed light on the feasibility and implications of using RDW as an inexpensive and accessible marker for disease activity assessment in routine clinical practice.

Limitations

Potential limitations of this scoping review include variability in the study methodologies, disease definitions, and RDW measurement techniques across the included studies. These limitations are acknowledged and discussed in the final review.

Conclusion

This scoping review highlights the promising potential of red blood cell distribution width as a cost-effective indicator of disease activity in individuals diagnosed with rheumatic diseases. The positive associations observed in a subset of studies provided a foundation for further investigation. However, methodological variability and the limited number of high-quality studies emphasize the need for caution when interpreting the findings. Future research efforts should aim to address these limitations and establish the clinical validity and utility of RDW as a supplementary tool for assessing disease activity in rheumatic diseases.

Ethical Considerations

As this study involved a review of the existing literature, ethical approval was not required. All data were extracted from publicly available sources.

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Disclosure

The author declares no conflicts of interest.

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