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MONOCYTE TO HIGH DENSITY LIPOPROTEIN RATIO AS CARDIOVASCULAR RISK FACTOR FOR PATIENTS WITH LONG STANDING RHEUMATOID ARTHRITIS AND ITS ASSOCIATION WITH DISEASE ACTIVITY USING SIMPLIFIED DISEASE ACTIVITY INDEX (S-DAI).

Original Research

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ABSTRACT

Background: Rheumatoid arthritis (RA), is a chronic auto-immune joint disorder in which the risk of cardiovascular disease (CVD) remains significantly heightened, attributed to an inflammation state. The aim of this study was to evaluate the association between MHR ratio and cardiovascular risk, as well disease activity measured with Simplified Disease Activity Index (S-DAI), in patients with long-standing RA.

Methods: This cross-sectional study was conducted at the Department of Rheumatology of Jinnah Postgraduate Medical Centre (JPMC), Karachi from January 2024 to June 2024. The rheumatoid arthritis was diagnosed using the 2010 ACR/EULAR Classification Criteria Score (score > 6). MHR ratio is the monocyte count (measured by the Sysmex 1000 Analyzer)/HDL levels. The disease activity was determined using the Simplified Disease Activity Index (S-DAI).

Results: The study sample included 68 patients with long-standing RA (mean age of 52.41 ± 10.96 years). Out of sixty-eight patients 75% were female and 25% were male. In association of cardiovascular risk factors with disease activity in patients with rheumatoid arthritis, the prevalence of obesity and diabetes mellitus was found to be higher in low activity (43.5%) and (38.5%). The prevalence of hypertension is the highest among those in the low activity group (42.9%).and decreases in moderate activity (14.3%). None of these risk factors including smoking ($p = 0.833$), obesity ($p = 0.983$) and Carotid plaque ($p = 0.780$) were found to be significant.

Conclusion: The findings of the study showed insignificant association of Monocyte to High-Density Lipoprotein (MHR) ratio with cardiovascular risk factors or disease activity in long-standing rheumatoid arthritis (RA). However, MHR may have predictive in other conditions, its role as a predictor in RA cardiovascular risk and disease severity has not yet been established.

Keywords: cardiovascular risk, chronic inflammation, disease activity index, dyslipidemia, high-density lipoprotein, inflammatory markers, monocyte to HDL ratio, rheumatoid arthritis, risk assessment, S-DAI, systemic inflammation, traditional cardiovascular risk factors.

INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune condition primarily affecting joints but may also be associated with extra-articular manifestations (1). It is estimated to affect 0.24 to 1% of world population with estimated annual incidence of 40 per 100,000 persons in United States (2). The prevalence of RA in Pakistan is estimated to be 0.5% of adult population (3). It is characterized by synovial inflammation and irreversible bone erosions, due to immune cells infiltration in the synovium resulting in inflammation and joint damage (4). Smoking is considered to be the most important environmental risk factor in development of RA, while most important genetic risk factor, the shared epitope alleles, reside in MHC class II region (5). HLA DR-4 is found in 70% of RA patients compared with 30% prevalence in controls (6). The pathological mechanisms implicated in pathogenesis of RA include post-translational citrullination of self-proteins, creating altered antigens which act as prime generators of autoimmune CD4+ T-cell response in RA patients.

Rheumatoid arthritis is also associated with various extra-articular manifestations including cardiovascular, pulmonary, renal and hematological diseases, due to inflammatory and autoimmune mechanisms (7). Cardiovascular disease is the most common cause of death in RA patients as it is associated with 50% increased cardiovascular mortality risk (7). Systemic inflammation in RA patients results in the development of focal arteries damage which leads to atherosclerotic plaque formation hence increasing risk of cardiovascular events (8). Various tools have been developed to assess the cardiovascular risk in RA patients including carotid ultrasound B-mode imaging (9). As cardiovascular events in RA occur due to chronic inflammation, investigators have also attempted to determine the role of hematological inflammatory markers in cardiovascular risk assessment (10). Monocytes act an essential part of the innate immune system in processes associated with inflammation and atherosclerotic plaque formation, while circulating high density lipoprotein (HDL) molecules act to suppress monocyte function. While clinicians have attempted to assess the efficacy of monocyte to HDL ratio (MHR) in predicting, very few investigators have done it in RA settings (11).

Romo-Cordero et al, reported that there was no significant difference in mean MHR values of RA patients compared to controls (12 ± 6 vs 11 ± 6). MHR significantly correlated with Systematic Coronary Risk Evaluation-2 (SCORE2) cardiovascular risk algorithm in patients with RA [SCORE2= 3.6 (1.8-5.8), p= < 0.001]. However, there was no significant association found between MHR and disease activity in terms of S-DAI score [SDAI 0.02(-0.02-0.06), p= 0.33] (12). Liu et al, studied the efficacy of MHR in stroke patients and reported that at cut-off level of 0.28, MHR had 66.01% sensitivity and 77.25% specificity with area under the curve value of 0.777. (13). It is evident from literature that MHR can be studied as a marker for cardiovascular risk though there is limited evidence available regarding its utility in RA patients (12, 13). As cardiovascular disease is the most common cause of mortality in patients with RA, it is important to determine the risk of cardiovascular events in cases of long-standing RA as appropriate lifestyle modifications and medical interventions may reduce cardiovascular events-related mortality in such patients. MHR may prove to be an inexpensive and readily available non-invasive tool in determining cardiovascular risk. Moreover, this study will also attempt to determine the association of MHR with disease activity.

METHODS

This cross-sectional study was undertaken at the Department of Rheumatology of Jinnah Postgraduate Medical Centre (JPMC), Karachi. A total of 68 patients were employed over a period of six months from January 2024 to June 2024 by using a non-probability, consecutive sampling approach. After obtaining the informed consent post explaining the risks and benefits associated with the study, patients with an age range of 18 to 60 years from either gender, diagnosed with rheumatoid arthritis having a disease duration of > 3 years were included to assess the monocyte to high-density lipoprotein ratio (MHR) as a cardiovascular risk factor for long-standing RA patients and its association with disease activity by using the Simplified Disease Activity Index (S-DAI). Patients with any heart-related complications (ischemic heart disease, heart failure or CVA), untreated infection, history of malignancy and hematological disorders, and taking any drugs causing myelosuppression, and pregnant women were excluded.

The rheumatoid arthritis was diagnosed using the 2010 ACR/EULAR Classification Criteria Score (score > 6). MHR ratio is the monocyte count (measured by the Sysmex 1000 Analyzer)/HDL levels. Their Cardiovascular Risk was evaluated using the Systemic Coronary Risk Evaluation-2 (SCORE-2) algorithm for South Asia by categorizing every patient on age, sex, smoking status, diabetes

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presence, cholesterol levels and systolic blood pressure. Based on the risk assessment findings, the patients were categorized as low risk (<5%), mild risk (5% - <10%), moderate risk (10% - <20%), high risk (20% - <30%), and very high risk (>30%). The disease activity was determined using the Simplified Disease Activity Index (S-DAI). All the gathered data was interpreted by using SPSS v.26. Descriptive statistics were reported in terms of mean ±standard deviation and frequency with percentage. Inferential statistics were calculated by using Chi-Square test at 5% level of significance.

RESULTS

Table 1 Demographic Characteristics of the Patients (n=68)

Variable	Frequency%
Gender	
Male	17 (25.0)
Female	51 (75.0)
Age, Mean ± SD= 52.41 ± 10.96 years	
20-50 Years	23 (33.8)
>50 Years	45 (66.2)
Body Mass Index, Mean ± SD= 25.82 ± 3.34 kg/m2	
20-26 Kg/m2	43 (63.2)
>26 Kg/m2	25 (36.8)

The study sample included 68 patients with long-standing RA (mean age of 52.41 ± 10.96 years). Out of sixty-eight patients 75% were female and 25% were male. Most patients, 66.2%, were > 50 years of age, whereas 33.8% were between the ages group of 20 to 50 years. The mean body mass index (BMI) was 25.82 ± 3.34 kg/m^2; among them 63.2% of patients had a BMI between 20 to 26 kg/m^2, while the remaining 36.8% had a BMI > 26 kg/m^2 as mentioned in Table 1.

Table 2 Cardiovascular Risk Factors and Disease Characteristics (n=68)

Duration of Disease, Mean ± SD= 8.12 ± 3.22 years	
4-8 years	44 (64.7)
>8 years	24 (35.3)
Baseline CRP, Mean ± SD= 2.89 ± 1.40 mg/L	
1.3-2.8 mg/L	40 (58.8)
>2.8 mg/L	28 (41.2)
Baseline ESR, Mean ± SD= 20.03 ± 7.67 mm/hr	
7-20 mm/hr	29 (42.6)
>20 mm/hr	39 (57.4)
IL-6, Mean ± SD= 5.15 ± 1.47 pg/mL	
3.2-5 pg/mL	40 (58.8)
>5 pg/mL	28 (41.2)
Monocytes to HDL-cholesterol ratio, Mean ± SD= 11.31 ± 3.77	

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Duration of Disease, Mean ± SD= 8.12 ± 3.22 years	
4-11	34 (50.0)
>11	34 (50.0)
Smoking Status, n (%)	
Yes	17 (25.0)
No	51 (75.0)
Obesity, n (%)	
Yes	23 (33.8)
No	45 (66.2)
Hypertension, n (%)	
Yes	28 (41.2)
No	40 (58.8)
Diabetes Mellitus, n (%)	
Yes	13 (19.1)
No	55 (80.9)
Dyslipidemia, n (%)	
Yes	36 (52.9)
No	32 (47.1)
Statins, n (%)	
Yes	21 (30.9)
No	47 (69.1)
Aspirin, n (%)	
Yes	8 (11.8)
No	60 (88.2)
Carotid Plaque, n (%)	
Yes	29 (42.6)
No	39 (57.4)
SDAI, n (%)	
Remission	16 (23.5)
Low Activity	30 (44.1)
Moderate Activity	12 (17.6)
Severe Activity	10 (14.7)

Table II represents the average disease duration in the study population was noted as 8.12 ± 3.22 years, with 64.7% of the patients having suffered from 4 to 8 years. Mean±SD of baseline C-reactive protein (CRP) was 2.89±1.30 mg/L; CRP levels of 58.8% of patients were

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lie between 1.3 and 2.8 mg/L, at considerably higher levels as compared with this rate in the entire patient population; mean ESR was 20.3 ±7.67 mm/hr and it exceeded >20 mm/hr in a total of 57.4%. The serum IL-6 levels of the patients were 5.15 ± 1.47 pg/mL, and 58.8% of the patients had a result of IL-6 ≤ 3.5 pg/mL. The mean monocyte/HDL cholesterol was documented as 11.31±3.77, and the level of this biochemical marker was > 11 among 50% of the patients. For cardiovascular risk factors, 25.0% of patients were smokers; 33.8% obese; 41.2% hypertensive and of these, 19.1% diabetic; and in dyslipidemia was noted in 52.9% with 42.6% patients had carotid plaque. The findings of Simplified Disease Activity Index (S-DAI) were reported that 23.5% were in remission from disease, and 14.7 % had severe activity.

Table 3 Distribution of Cardiovascular Risk Factors by Simplified Disease Activity Levels

Variables	Remission frequency (%age)	Low Activity frequency (%age)	Moderate Activity frequency (%age)	Severe Activity frequency (%age)	P-Value
Smoking, n (%)	5 (29.4)	6 (35.3)	3 (17.6)	3 (17.6)	0.833
Obesity, n (%)	6 (26.1)	10 (43.5)	4 (17.4)	3 (13.0)	0.983
Hypertension, n (%)	5 (17.9)	12 (42.9)	4 (14.3)	7 (25.0)	0.221
Diabetes Mellitus, n (%)	3 (23.1)	5 (38.5)	1 (7.7)	4 (30.8)	0.279
Dyslipidemia, n (%)	9 (25.0)	14 (38.9)	8 (22.2)	5 (13.9)	0.685
Statins, n (%)	4 (19.0)	8 (38.1)	5 (23.8)	4 (19.0)	0.670
Aspirin, n (%)	1 (12.5)	5 (62.5)	1 (12.5)	1 (12.5)	0.722
Carotid Plaque, n (%)	8 (27.6)	11 (37.9)	6 (20.7)	4 (13.8)	0.780

Table 3 shows the distribution of cardiovascular risk factors at remission, low, moderate and severe disease activity levels using the Simplified Disease Activity Index (S-DAI). Smoking was documented in 29.4% of remission patients, 35.3% low activity and 17.6% moderate / severe activities (p = 0.833). Obesity was commonly prevalent in the moderate activity group (43.5%) and less common in the severe activity group (13.0%; P = 0.983). Hypertension was noted in 42.9% of low activity group and 25.0% of severe activity (p = 0.221). Diabetes mellitus was noted in 30.8% patients with severe activity group and apparently least in moderate activity (7.7%; p = 0.279). In patients with low activity 38.9% suffered from a dyslipidemia vs. 13.9% of the very severe group (p = 0,685). There was no significant differ between low activity and severe activity cohorts in terms of presence of carotid plaque (37.9% vs 13.8%, p = 0.780). There were no statistically significant differences was noted between disease activity levels with respect to any of the cardiovascular risk factors.

DISCUSSION

The present study was designed to analyze the association between Monocyte to High Density Lipoprotein (HDL) ratio (MHR), a novel marker of cardiovascular risk, with long standing RA and its relation to their disease activity status as measured by the Simplified Disease Activity Index (S-DAI). Although cardiovascular disease is the leading cause of death in patients with RA, it likely represents only a small proportion of the chronic systemic inflammatory processes that promote dyslipidemia and atherogenesis (8). The aim of the present study was to investigate whether MHR, which is a new biomarker, is useful for determining cardiovascular risk and RA disease activity. The calculated mean MHR in the study population was 11.31 ± 3.77, which means that half of the participants had a value above 11. This is in agreement with the scarce evidence, for example a research of Romo-Cordero et al. reported similar mean MHR of RA patients compared to controls, however they found not statistical differences between both populations (12 ± 6 vs. 11 ± 6) [12]. Romo-Cordero, however, has also revealed that MHR correlated well with the SCORE2 cardiovascular risk algorithm in RA (p < 0.001), although our study showed no association between MHR and cardiovascular risk factors such as hypertension, diabetes, dyslipidemia and carotid plaque across different S-DAI levels.

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Liu et al. showed a good prediction of stroke outcomes using MHR with an AUC of 0.777 at a cut-off level of 0.28, suggesting promise for its use beyond RA in other cardiovascular diseases (13). Nevertheless, our investigation featured no distinguishing findings in regard to cardiovascular risk factors (history of smoking, obese patients and diabetes) associated with different severities of disease activity. For instance, smoking was present in 29.4% of patients in remission, but in 17.6% of those with moderate or severe disease activity ($p = 0.833$), suggesting that traditional cardiovascular risk factors may not closely align with RA disease activity (12). One of the most noteworthy findings of our study was the absence of any significant correlation between MHR and RA disease activity. While Romo-Cordero et al. similarly found no significant association between MHR and disease activity using S-DAI ($p = 0.33$) (12), our findings expand on this by exploring other cardiovascular risk factors and their distribution across disease activity levels. For example, we found no significant association between dyslipidemia and disease activity, with dyslipidemia affecting 38.9% of patients with low disease activity and 13.9% of those with severe disease ($p = 0.685$).

Our results aligned with those of Kocak et al., who reported that MHR was not significantly associated with disease severity in other inflammatory conditions such as ankylosing spondylitis, suggesting that the inflammatory mechanisms in different autoimmune diseases may affect the relationship between MHR and disease activity differently (14). The lack of significant association between MHR and disease activity across various inflammatory conditions raises questions about the generalizability of MHR as a biomarker for RA disease progression. These findings suggest that while MHR may be a useful biomarker for general cardiovascular risk in other conditions, its role in RA, particularly in relation to disease activity, is less clear. This supports the notion that RA's cardiovascular risk profile is multifactorial, driven by chronic inflammation as well as traditional cardiovascular risk factors such as hypertension, smoking, and dyslipidemia (7-10, 14-15). Our study's limitations include the relatively small sample size and cross-sectional design, which may limit the generalizability of the findings. Additionally, the absence of a control group prevents direct comparison with non-RA populations. Future longitudinal studies with larger sample sizes and control groups are needed to further clarify the role of MHR in RA-related cardiovascular risk.

CONCLUSION

The study concluded that the Monocyte to High-Density Lipoprotein (MHR) ratio did not show a significant association with cardiovascular risk factors or disease activity levels in patients with long-standing rheumatoid arthritis (RA). While cardiovascular disease remains a prominent cause of mortality in RA patients due to chronic inflammation, the use of MHR as a predictor for cardiovascular risk and disease severity in this context appears limited. These findings suggest that traditional cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, may not directly correlate with RA disease activity. Further longitudinal studies with larger sample sizes are necessary to validate the utility of MHR as a biomarker in RA-related cardiovascular risk assessment.

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