Prevalence of Metabolic Syndrome in Patients With Rheumatoid Arthritis: An Updated Systematic Review and Meta-Analysis

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Introduction: Rheumatoid arthritis (RA) due to systemic inflammation and insulin resistance increases the risk of cardiovascular disease and reduces life expectancy. In order to develop cardiac death prevention strategies, it is necessary to estimate the prevalence of metabolic syndrome (MetS) in these patients.

Methods: This systematic review and meta-analysis was performed to estimate the prevalence of MetS among patients with RA. International databases (i.e., Scopus, PubMed, Web of Science, and Google Scholar) were searched during the period of October 1 and October 10, 2012. Heterogeneity among the included studies was assessed through the Cochrane Q test statistics and $I^2$ test. Finally, a random-effects meta-analysis model was computed to estimate the pooled prevalence of MetS.

Results: Sixty-one articles with 96 groups and a sample size of 13,644 people were analyzed. The pooled prevalence of MetS was 32% (95% CI: 29.6–34.4). The highest prevalence of MetS is related to studies conducted in Asia (32.7%, 95% CI: 29–36.3) and Europe (32.7%, 95% CI: 27.5–37.9) and the lowest Prevalence was also related to studies conducted in Africa (28%, 95% CI: 28.8–32.2). The prevalence of MetS in men was 33% (95% CI: 26–39) and 34% (95% CI: 29–40) in women. Findings by diagnostic criteria showed that the highest and lowest prevalence of MetS was related to ATP III (37.5%, 95% CI: 30.9–44.2) and EGIR (14.4%, 95% CI: 10.5–18.5), respectively.

Conclusions: MetS is highly prevalent in patients with RA and identification of high-risk patients is necessary to prevent cardiovascular mortality.

Keywords: metabolic syndrome, rheumatoid arthritis, prevalence, systematic review, meta-analysis

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology characterized by systemic symptoms, especially joint involvement and deformity (1). Patients with rheumatoid arthritis are at high risk for cardiovascular disease and premature death due to systemic inflammation, which reduces their life expectancy by 5 to 10 years (2, 3). Rheumatoid arthritis is associated with insulin resistance, dyslipidemia, and changes in adipokines profiles that are components of the metabolic syndrome (MetS) (4).
Insulin resistance is a constant risk factor for cardiovascular disease and the central mechanism in metabolic syndrome, which is present in 70% of patients with RA (5, 6).

MetS, also known as syndrome X and insulin resistance syndrome, refers to a set of cardiovascular risk factors (obesity, glucose intolerance, dyslipidemia, and high blood pressure) that can lead to cardiovascular disease (7). MetS increases cardiovascular outcomes and mortality by 2 and 1.5 times, respectively (8, 9). The increased risk of cardiovascular disease in patients with rheumatoid arthritis has been well established, so that the European League Against Rheumatism (EULAR) recommends that screening and management of cardiovascular risk in these patients be performed immediately (10, 11).

Various studies have shown that the prevalence of metabolic syndrome in these patients varies between 10 and 56% (12, 13). In this systematic review and meta-analysis, the cumulative prevalence of metabolic syndrome in patients with rheumatoid arthritis has been estimated.

**METHODS**

**Search Strategy**

The present systematic review and meta-analysis study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). To access articles examining the prevalence of metabolic syndrome in patients with rheumatoid arthritis, a comprehensive search with no data limit was performed in the following databases: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search was conducted between October 1 and October 10, 2021. All article published until August 30, 2021 were included. Articles were searched with keywords (“Metabolic Syndrome”[Mesh] OR “Metabolic Syndrome”[tiab] OR “Insulin Resistance Syndrome”[tiab] OR “Metabolic X Syndrome”[tiab] OR “Dysmetabolic Syndrome”[tiab] OR “Reaven Syndrome”[tiab] OR “Metabolic Cardiovascular Syndrome”[tiab]) AND (“rheumatic diseases”[Mesh] OR “Arthritis, Rheumatoid”[Mesh] OR “Rheumatic disease”[tiab] OR “Rheumatism”[tiab] OR “Rheumatoid Arthritis”[tiab] OR “Rheumatic symptom”[tiab]) AND (“Prevalence”[Mesh] OR “Prevalence”*[tiab] OR “Period Prevalence”*[tiab] OR “Point Prevalence”*[tiab]). The reference lists of the included articles were also reviewed to find other eligible articles.

**Selection of Studies and Data Extraction**

All observational studies published in English that reported the prevalence or frequency of metabolic syndrome in patients with rheumatoid arthritis were analyzed. Interventional, review, and replication studies, as well as studies investigating the prevalence of metabolic syndrome in other rheumatic diseases, were excluded. According to the inclusion and exclusion criteria, the titles and abstracts of the articles were independently reviewed by two researchers and the required information such as first author, year of publication, country of study, sample size, prevalence or frequency of metabolic syndrome in patients with rheumatoid arthritis were extracted and recorded in a pre-prepared form. To evaluate the quality of articles, the modified Newcastle-Ottawa Scale (NOS) was used, which has three main sections. The first part, rated on a scale of one to five stars, focuses on the methodological quality of each study (i.e., sample size, response rate, and sampling technique). The second section considers the comparability of the study cases or cohorts with a possibility of two stars to be gained. The last section is concerned with the outcomes and statistical analysis of the original study with a possibility of three stars to be gained. Two authors extracted the information and evaluated the methodological quality of the articles, independently. Any disagreements between the two reviewers were resolved consensus (15, 16).

**Statistical Analysis**

Point estimation and 95% confidence interval (CI) of metabolic syndrome due to binomial distribution formula and heterogeneity between studies was evaluated by Cochran Q test with a significance level of less than 0.1 and I² index. The degree of heterogeneity was assessed using the I² index. Heterogeneities were divided into three categories: less than 25% (low heterogeneity), 25 to 75% (moderate heterogeneity) and more than 75% (high heterogeneity). Pooled prevalence was estimated using a random-effects model. Subgroup analysis was performed based on diagnostic criteria and continent. To investigate the potential publication bias, funnel plot based on Egger’s regression test was used. Univariate meta-regression was used to investigate the relationship between the prevalence of metabolic syndrome and the year of study and the mean age of patients. Data analysis was performed using Stata software version 16.

**RESULTS**

In the initial search, 938 potentially relevant articles were retrieved. Of these articles, 431 articles were excluded due to duplications and removing duplicate articles, 507 articles remained. The titles and abstracts of the remaining articles were reviewed and 411 irrelevant articles were removed. Of the remaining 96 articles, 34 articles were deleted for not reporting the prevalence of MetS (Figure 1).

**Study Characteristics**

In this study, 62 articles with a sample size of 13,644 people were analyzed, the characteristics of which are listed in Table 1. Most studies were performed in Morocco (n = 9) and Iran (n = 9). Most studies were based on NCEP/ATP III (n = 42) and IDF (n = 21) diagnostic criteria. Thirty-nine studies were conducted in Asia, 25 in Europe, 18 in the United States and 14 in Africa. All selected articles had good methodological quality.

The prevalence of MetS in patients with rheumatoid arthritis was 32% (95% CI: 29.6–34.4%). The prevalence of metabolic syndrome was 33% (95% CI: 26–39%) in men and 34% (95% CI: 29–40%) in women. The findings demonstrated that the highest prevalence of MetS was related to studies in Asia (32.7%, 95% CI: 29–36.3%) and Europe (32.7%, 95% CI: 27.5–37.9%) and the lowest prevalence was related to studies in Africa (28%, 95% CI: 22.8–33.2%) (Figure 2). Findings by diagnostic criteria
of metabolic syndrome showed that the highest and lowest prevalence were related to ATP III (37.5%, 95% CI: 30.9–44.2%) and EGIR (14.4%, 95% CI: 10.5–18.5%) criteria, respectively (Table 2).

**Meta-Regression**

The results of meta-regression showed that the prevalence of MetShad increased significantly with increasing age (in studies in the Americas) \( p = 0.006 \) (Figure 3). Also, the prevalence of MetS over time in studies in Asia was significantly increased \( p = 0.024 \). Also, publication bias was not significant in the analyzed studies \( p = 0.569 \).

**DISCUSSION**

The results of this study showed that one third of patients with RA have MetS. The results of a previous meta-analysis of 38 articles (with 70 groups) between 2007 and 2016 showed that the prevalence of MetS in patients with RA was 30.65%, which is almost consistent with the results of the present study (71). The reason for the high prevalence of metabolic syndrome in these patients can be attributed to traditional risk factors such as smoking, body mass index, gender, dyslipidemia and hypertension, although the role of continuous inflammation and activation of endothelial cells cannot be ignored (41). Inflammatory cytokines such as TNFα also reduce insulin function and facilitate insulin resistance (2). On the other hand, these patients use non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to control the disease, which can cause metabolic disorders such as high blood pressure, obesity and diabetes (27). Serum levels of some biomarkers associated with metabolic syndrome, adipokines such as adiponectin, and biomarkers of endothelial cell activation and inflammation may appear to be useful in predicting cardiovascular risk in patients with RA (72).

The highest prevalence of metabolic syndrome was related to studies in Asia and Europe and the lowest prevalence was related to studies in Africa. Given that nutritional, ethnic and sociodemographic status are the determinants of the prevalence of metabolic syndrome, the reason for this finding can be attributed to these differences in these communities.
### TABLE 1 | Characteristics of included articles.

| First author          | Year | Country     | Sample size | Mean age | RA patients (%) | Diagnostic criteria | Total | Male | Female |
|-----------------------|------|-------------|-------------|----------|-----------------|---------------------|-------|------|--------|
| **First author** | **Year** | **Country** | **Sample size** | **Total** | **M/F** | **Diagnostic criteria** | **Mean age** | **RA patients (%)** | **Total** | **Male** | **Female** |
| Turgunova et al. (17) | 2021 | Kazakhstan  | 101         | 31/70    | IDF  | 40.5 | - | - | - | - |
| Hee et al. (18)      | 2021 | Singapore  | 561         | 0/561    | NCEP/ATP III | 44.9 | - | - | - | - |
| Giraud et al. (19)   | 2021 | France     | 75          | 20/55    | WHO  | 59.2 | 28 | - | - | - |
| Kong et al. (20)     | 2021 | China      | 717         | 152/565  | CDS  | 61   | 31.2 | - | - | - |
| Cioffi et al. (21)   | 2021 | Italy      | 228         | -        | IDF  | 58   | 15  | - | - | - |
| Mobini et al. (13)   | 2020 | Iran       | 200         | -        | NCEP/ATP III | 54.5 | - | - | - | - |
|                    |      |            |             |          | IDF  | 56   | - | - | - | - |
| Garcia-Chagollan et al. (4) | 2020 | Mexico     | 216         | 22/194   | NCEP/ATP III | 46  | 30.6 | - | - | - |
| Xu et al. (22)       | 2020 | Korea      | 247         | 48/199   | NCEP/ATP III | 58  | 15   | - | - | - |
| Shaikh et al. (23)   | 2020 | Pakistan   | 104         | 10/94    | NCEP/ATP III | 33.4 | 32.7 | - | - | - |
| Ozkul et al. (24)    | 2019 | Turkey     | 50          | 11/39    | IDF  | 56.9 | 36  | - | - | - |
| Mulumba et al. (3)   | 2019 | Congo      | 75          | 15/60    | NCEP/ATP III | 51.8 | 25.3 | - | - | - |
| Ene et al. (25)      | 2019 | Romania    | 120         | 31/89    | IDF-NCEP/ATP III | 52.7 | 39.2 | 45.2 | 37.1 | - |
| Naidu et al. (26)    | 2019 | India      | 114         | 21/93    | NCEP/ATP III | 44.8 | 31.6 | - | - | - |
| Kuriya et al. (27)   | 2019 | USA        | 1543        | 443/1100 | WHO  | 54   | 30.8 | 42 | 26 | - |
| Akbal et al. (28)    | 2019 | Turkey     | 53          | 12/41    | ATP III | 51  | 47.1 | - | - | - |
| Aleksic et al. (29)  | 2019 | Serbia     | 81          | 19/62    | IDF  | 59.7 | 54.3 | - | - | - |
| Mobini et al. (30)   | 2018 | Iran       | 140         | 25/115   | NCEP/ATP III | 44.7 | 31.4 | - | - | - |
|                    |      |            |             |          | IDF  | 35   | - | - | - | - |
| Gomes et al. (7)     | 2018 | Brazil     | 338         | 31/307   | NCEP/ATP III | 53.5 | 51.3 | - | - | - |
| Burggraaf et al. (31)| 2017 | Netherland | 212         | 65/147   | NCEP/ATP III | 54  | 40.1 | - | - | - |
| Slimani et al. (32)  | 2017 | Algeria    | 249         | 36/213   | NCEP/ATP III | 50.1 | 13.9 | 14.3 | 13.8 | - |
| Pandey et al. (33)   | 2017 | India      | 84          | 18/66    | ATP III 2004 | 44.8 | 39.2 | - | - | - |
| Ostojic et al. (34)  | 2016 | Serbia     | 36          | 6/30     | -      | 36  | 30.6 | - | - | - |
| Lee et al. (35)      | 2016 | Korea      | 598         | 110/488  | AHA/NHLBI | 63.6 | 36.4 | 34.5 | 36.9 | - |
| Hugo et al. (36)     | 2016 | France     | 57          | 15/42    | IDF  | 57.6 | 24  | 25 | 24 | - |
| Zafar et al. (37)    | 2016 | Pakistan   | 384         | 97/277   | NCEP/ATP III | 43.8 | 31.3 | 18.5 | 35.5 | - |
| Oliveira et al. (38) | 2016 | Brazil     | 107         | 0/107    | NCEP/ATP III | 55.5 | 51.4 | - | 51.4 | - |
|                    |      |            |             |          | IDF  | 53.4 | - | 53.4 | - | - |
| Muller et al. (39)   | 2016 | Estonia    | 91          | 66/25    | NCEP/ATP III | 51.6 | 35   | - | - | - |
| Dihingia et al. (40) | 2016 | India      | 72          | 6/66     | NCEP/ATP III | 41.5 | 16.7 | - | - | - |
| Ghazaly et al. (41)  | 2015 | Egypt      | 80          | 13/67    | ATP III | 40.7 | 50  | 53 | 49.2 | - |
| Salamon et al. (42)  | 2015 | Croatia    | 583         | 100/483  | ATP III | 59  | 43.1 | 40 | 43.7 | - |
| Tantayakom et al. (43)| 2015 | Thailand   | 267         | 31/236   | NCEP/ATP III | 59  | 16.1 | 12.9 | 16.5 | - |
| Parra-Salcedo et al. (44)| 2015 | Mexico     | 160         | 18/142   | AHA/NHLBI | 38.1 | 28  | - | - | - |
|                    |      |            |             |          | IDF  | 18   | - | - | - | - |
|                    |      |            |             |          | NCEP/ATP III | 24  | - | - | - | - |
| Craciun et al. (12)  | 2014 | Romania    | 51          | 7/44     | IDF-AHA | 55.2 | 19  | 10.5 | 82.4 | - |
|                    |      |            |             |          | NCEP/ATP III | 23  | - | - | - | - |
|                    |      |            |             |          | IDF  | 18   | - | - | - | - |
|                    |      |            |             |          | AHA  | 14   | - | - | - | - |
| Bilecik et al. (45)  | 2014 | Turkey     | 100         | 0/100    | IDF  | 52   | 33  | - | 33 | - |
| Ozmen et al. (46)    | 2014 | Turkey     | 52          | 15/37    | NCEP/ATP III | 51  | 17.3 | - | - | - |
| Kumar et al. (47)    | 2014 | India      | 54          | 6/48     | IDF  | 46   | 29  | - | - | - |
|                    |      |            |             |          | NCEP/ATP III | 31  | - | - | - | - |
| First author | Year | Country | Sample size | Diagnostic criteria | Mean age | RA patients (%) |
|--------------|------|---------|-------------|---------------------|----------|-----------------|
|              |      |         | Total/M/F   |                     |          | RA patients (%) |
|              |      |         |              |                     |          | Total/M/F       |
| Abourazzak et al. (48) | 2014 | Morocco | 179/22/157 | IDF, NCEP/ATP III, AACE 2003 | 49       | 30.7/-/-        |
| Salinas et al. (49) | 2013 | Argentina | 409/69/340 | ATP III, IDF, NCEP/ATP III 2003 | 55.5     | 30/62/23.8     |
| Abdul-Qahhar et al. (50) | 2013 | Iraq | 203/41/162 | NCEP/ATP III 2004, IDF, WHO | 46.9     | 51.2/12/92      |
| Rostom et al. (51) | 2013 | Morocco | 120/10/110 | NCEP/ATP III 2001, IDF, WHO | 49       | 30.8/10/32.7    |
| Lee et al. (52) | 2013 | Korea | 84/0/84 | NCEP/ATP III | 50.6     | 19/-/19         |
| Ormseth et al. (53) | 2013 | USA | 162/18/144 | ATP III | 54       | 26/-/-          |
| Karakoc et al. (1) | 2012 | Turkey | 54/7/47 | IDF, NCEP/ATP III 2004, WHO | 49.8     | 42.6/-/-        |
| Marka et al. (54) | 2012 | Slovakia | 87/4/83 | IDF, NCEP/ATP III 2001, WHO | 58.8     | 48.3/-/-        |
| Da Cunha et al. (55) | 2012 | Brazil | 283/50/233 | NCEP/ATP III 2004, WHO | 56.8     | 39.2/-/-        |
| Goshayeshi et al. (56) | 2012 | Iran | 120/14/106 | NCEP/ATP III 2001, WHO | 45.5     | 45.2/-/-        |
| Baker et al. (57) | 2012 | USA | 499/83/416 | IDF, NCEP/ATP III 2001, WHO | 49.5     | 10.6/-/-        |
| Crowson et al. (58) | 2011 | USA | 232/58/174 | NCEP/ATP III 2001, WHO | 58.8     | 33/36/32        |
| Sahebari et al. (59) | 2011 | Iran | 120/14/106 | IDF, NCEP/ATP III 2001, WHO | 45.5     | 30.8/28.6/41.5  |
| Karimi et al. (60) | 2011 | Iran | 92/0/92 | NCEP, WHO | 48.3     | 27.2/-/-        |
| Mok et al. (61) | 2011 | Hong Kong | 699/133/566 | JS 2009, WHO | 53.3     | 20/-/-          |
| Dao et al. (62) | 2010 | Vietnam | 105/0/105 | IDF, NCEP/ATP III 2004, WHO | 56.3     | 40.9/-/-        |
| Raterman et al. (63) | 2010 | Netherlands | 236/79/157 | NCEP, WHO | 62.1     | 19.9/-/-        |
| Solomon et al. (64) | 2010 | South Africa | 291/32/259 | NCEP/ATP III 2001, WHO | 27.2     | 31.3/-/-        |
| Giles et al. (65) | 2010 | USA | 131/51/80 | NCEP/ATP III 2001, WHO | 61       | 36/-/-          |
| Santos et al. (66) | 2010 | Portugal | 98/0/98 | ATP III, WHO | 49.2     | 25.5/-/-        |
| Toms et al. (67) | 2009 | UK | 387/105/282 | IDF, NCEP/ATP III 2004, WHO | 63.1     | 45.3/52.7/42.6 |
| Chung et al. (2) | 2008 | USA | 66/18/48 | WHO | 59       | 42/-/-          |
| Zonana-Nacach et al. (68) | 2008 | Mexico | 107/- | NCEP/ATP III, WHO | 42.9     | 18.7/-/-        |
| Karvounaris et al. (69) | 2007 | Greece | 200/53/147 | ATP III, WHO | 63       | 44/39.6/45.6   |
| Montagna et al. (70) | 2007 | Italy | 45/3/42 | NCEP/ATP III, WHO | 53.8     | 55.5/-/-        |
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FIGURE 2 | Forest plot of the pooled prevalence of MetS in patients with RA in Europe.

TABLE 2 | Subgroup prevalence of MetS among patients with RA.

| Subgroups | Number of studies | Prevalence (95% CI) | Between studies | Subgroup |
|-----------|------------------|---------------------|----------------|----------|
|           |                  |                     | \(P_{heterogeneity}\) | \(Q\) | \(I^2\) | \(P_{heterogeneity}\) | \(I^2\) |
| Continent |                  |                     |                |         |       |               |       |
| Asia      | 39               | 32.7 (29–36.3)      | 91.2%          | 0.001   | 505.13 | 2.39          | 0.495 |
| Europe    | 25               | 32.7 (27.5–38)      | 93.37%         | 0.001   | 418.57 |                |       |
| America   | 18               | 32.3 (27–37.5)      | 94.66%         | 0.001   | 345.11 |                |       |
| Africa    | 14               | 28 (22.8–33.2)      | 88.24%         | 0.001   | 155.11 |                |       |
| Criteria  |                  |                     |                |         |       |               |       |
| WHO       | 8                | 25.2 (20–30.4)      | 81%            | 0.004   | 42.19  | 79.69         | 0.001 |
| IDF       | 21               | 35.2 (29.4–41.1)    | 93.1%          | 0.017   | 482.13 |                |       |
| JS        | 4                | 33.5 (21–48)        | 96.6%          | 0.015   | 128.65 |                |       |
| NCEP/ATP III | 42               | 32 (28.5–35.5)      | 91.2%          | 0.012   | 518.62 |                |       |
| ATP III   | 8                | 37.5 (31–44)        | 85.9%          | 0.007   | 47.09  |                |       |
| AACE      | 4                | 26.2 (17.3–35.2)    | 87.8%          | 0.007   | 25.17  |                |       |
| EGIR      | 3                | 14.4 (10.5–18.4)    | 36.75          | 0.001   | 2.92   |                |       |

WHO, World Health Organization; IDF, International Diabetes Federation; EGIR, European Group against Insulin Resistance; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel; AACE, American Association of Clinical Endocrinologists; AHA/NHLBI, The American Heart Association / National Heart, Lung, and Blood Institute; JS, Joint Statement.
In a study by Park et al. (73) the prevalence of metabolic syndrome in Korean and American adults was compared, and the results showed that the prevalence of metabolic syndrome and all its components (except low high density lipoprotein-cholesterol) was higher in American adults than in Korean. The two groups were not different in terms of blood pressure (73). The results of our study differ from those of Park et al. (73); in that they examined the prevalence of metabolic syndrome among patients with rheumatoid arthritis, not the general population. Therefore, further studies in this regard seem necessary.

The highest and lowest prevalence of metabolic syndrome were related to ATP III and EGIR criteria, respectively. In all diagnostic criteria, blood pressure, triglycerides, HDL cholesterol and fasting glucose are measured, and the difference between them is in the selection of the cut-off points and the measure of obesity. In WHO and EGIR criteria, the presence of hyperinsulinemia as an indicator of insulin resistance is the starting point, while in ATP III, the number of abnormalities is considered (69). These differences have led to different prevalence being reported in a group of patients (same patients) based on different criteria, so appropriate standards should be used to diagnose MetS in different regions. In a meta-analysis performed to estimate the prevalence of metabolic syndrome in postmenopausal women, the highest prevalence of metabolic syndrome was based on the ATP III screening criterion (74). The prevalence of metabolic syndrome increased significantly with age (in studies in the Americas). The prevalence of metabolic syndrome in the general population also increases with age (27), which can be due to redistribution of adipose tissue, weight gain, insulin resistance, and lipid changes (75).

Given that the prevalence of metabolic syndrome in patients with rheumatoid arthritis has not been studied in some countries and therefore has not been analyzed, the findings of this study should be generalized with caution worldwide.

**CONCLUSION**

Metabolic syndrome is so common in patients with RA that one-third of these patients have MetS, so identifying at-risk patients is essential to prevent cardiovascular events.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article-supplementary material, further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

WC: concept, design, and drafting of the manuscript. WC, MP, and XT: acquisition, analysis, or interpretation of data. XT: critical revision of the manuscript for important intellectual content. MP: statistical analysis. All authors gave their final approval of this version of the manuscript.

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