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Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Rheumatoid Arthritis: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND & AIMS: Previous studies have shown a potential association between nonalcoholic fatty liver disease (NAFLD) and some immune-mediated inflammatory diseases, such as rheumatoid arthritis (RA), but this association has not been analyzed systematically. Therefore, we aimed to perform a systematic review and meta-analysis to ascertain a pooled prevalence estimate of NAFLD among patients with RA to fill this gap in knowledge.

METHODS: We conducted a literature search in PubMed, Embase, Web of Science, Scopus, and ProQuest, for observational studies published from inception to August 31, 2022, which reported prevalence of NAFLD in 100 or more adult (age, ≥18 y) patients with RA. To be included, NAFLD diagnosis was based on either imaging or histologic assessment. The results were presented as pooled prevalence, odds ratio, and 95% CI. The I^2 statistic was used to measure the heterogeneity between studies.

RESULTS: This systematic review included 9 eligible studies derived from 4 continents comprising 2178 patients (78.8% women) with RA. The pooled prevalence of NAFLD was 35.3% (95% CI, 19.9–50.6; I^2 = 98.6%; P < .001) in patients with RA. All studies used ultrasound for the diagnosis of NAFLD, except for 1 study that used transient elastography. The pooled prevalence of NAFLD in men with RA was significantly higher than in women with RA (35.2%; 95% CI,

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Mohammad Zamani (Conceptualization: Equal; Data curation: Equal; Formal analysis: Lead; Methodology: Equal; Writing – original draft: Equal)

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Rohit Loomba (Conceptualization: Equal; Funding acquisition: Lead; Methodology: Equal; Writing – review & editing: Equal)

24.0–46.5 compared with 22.2%; 95% CI, 17.9–26.58; P for interaction = .048). Each 1-unit increase in body mass index was associated directly with a 24% increased risk of NAFLD in RA patients (adjusted odds ratio, 1.24; 95% CI, 1.17–1.31; I^2 = 0.0%; P = .518).

CONCLUSIONS: Based on this meta-analysis, 1 in 3 patients with RA had NAFLD, which appears comparable with its overall prevalence among the general population. Clinicians should actively screen for NAFLD in patients with RA.

Keywords

Nonalcoholic Fatty Liver Disease; Rheumatoid Arthritis; Systematic Review

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disorder that principally affects the joints; however, extra-articular manifestations have been well described for this disease in the literature, including involvement of skin, eye, lung, renal, cardiac, nervous, and gastrointestinal systems.[1] Liver involvement is one of the clinical outcomes of RA that potentially can manifest as asymptomatic abnormal liver test results, autoimmune biliary diseases (such as primary biliary cirrhosis, or primary sclerosing cholangitis), metabolic liver diseases, autoimmune hepatitis, and/or nonalcoholic fatty liver disease (NAFLD).[2,3]

NAFLD is a condition defined as excess fat accumulation in the liver in individuals who consume little or no alcohol and do not have a secondary cause of hepatic steatosis.[4,5] This disease encompasses a spectrum of liver conditions ranging from nonalcoholic fatty liver, the nonprogressive form of NAFLD to nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD that can progress to cirrhosis, and hepatocellular carcinoma.[6,7] There are studies that have mentioned possible links between NAFLD and autoimmune/inflammatory conditions, such as inflammatory bowel disease (IBD); in our recent meta-analysis, we showed that the prevalence of NAFLD was 30.7% among patients with IBD, with a 2-fold higher risk of NAFLD in IBD patients vs healthy controls.[8] Previous studies also have reported various prevalence rates of NAFLD in patients with RA.[9,10] Systemic inflammation and use of steatogenic drugs (such as methotrexate, steroids) may explain NAFLD occurrence in RA patients.

However, there are limited data regarding the pooled estimate of the prevalence of NAFLD in patients with RA. Therefore, the purpose of the present study was to perform a comprehensive systematic review and meta-analysis using previously published surveys reporting the prevalence of NAFLD in RA patients. Our results hopefully will be useful to clinicians, pharmaceutical companies, and policy makers to develop better clinical guidelines, screening protocols, and public health policies for effective management strategies for both diseases.

Materials and Methods

Study Protocol

The current systematic review and meta-analysis was presented according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline.[11] The protocol of this

review was registered online in the International Prospective Register of Systematic Reviews in advance (CRD42022313449).

Information Sources and Search Strategy

We conducted a search in PubMed, Embase, Web of Science, Scopus, and ProQuest, for the literature published from inception to August 31, 2022, to collect the observational studies that reported the prevalence of NAFLD in RA patients, with no language limitations. We searched the related terms in the Medical Subject Headings database and finally chose the following terms as keywords, restricted to title/abstract: “rheumatoid arthritis” OR “rheumatoid arthritis” OR “rheumatic disease” OR “rheumatic diseases” AND “NAFLD” OR “nonalcoholic fatty liver” OR “non-alcoholic fatty liver disease” OR “nonalcoholic fatty liver disease” OR “fatty liver disease” OR “fatty liver” OR “steatosis” OR “NASH” OR “steatohepatitis.” We also manually checked the references of the captured articles for identifying other relevant studies.

Inclusion and Exclusion Criteria

Studies were considered eligible if they reported the prevalence of NAFLD in 100 or more adult (age, ≥18 y) patients with RA (diagnosed according to American College of Rheumatology (ACR) 1987 criteria or ACR/European League Against Rheumatism 2010 criteria).[12,13] The diagnosis of NAFLD was based on either imaging or histologic evidence of hepatic steatosis in individuals who consume little or no alcohol using the American Association for the Study of Liver Diseases NAFLD Practice Guidance.[5]

The exclusion criteria included the following: (1) case reports, reviews, editorials, and letters to the editor; (2) duplicates, or surveys investigating the same sample; (3) studies with insufficient information on NAFLD definition; (4) studies conducted on subjects with a specific condition (such as morbid obesity, transaminitis, and so forth); (5) surveys that included children; (6) articles with no extractable data on the main outcomes; and (7) full text not being available.

Study Selection and Data Extraction

The reports were evaluated for suitability by 2 independent investigators (M.Z. and S.A.-T.) by screening the titles and abstracts; full texts of the potential articles then were collected for more detailed examination. If necessary, the non-English articles were translated using Google Translate. If there were duplicate publications, the study with the most comprehensive details was chosen. Any discrepancies were resolved by consensus, and the kappa statistic was used for measurement of the agreement degree. The following data were extracted from the included articles into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA) by 2 authors (M.Z. and S.A.) independently: first author’s name, publication year, study location (country), diagnostic method of NAFLD, sample size, number of subjects by sex (if available), number of non-RA healthy controls (if available), RA-directed medication distribution, number of RA patients with NAFLD, number of RA patients with NASH (if available), and number of controls with NAFLD (if available). We also tried to extract the data regarding the risk factors for NAFLD (ie, odds ratios [ORs] with confounder adjustment), but there was adequate information only for body mass index

(BMI, kg/m^2) and methotrexate to be analyzed. We emailed the corresponding authors when the required information was not available.

Risk of Bias Assessment

We assessed the quality of the enrolled studies using the checklist proposed by Hoy et al.[14] This tool was designed for prevalence studies and has 9 queries about target population, sampling frame, selection of sample, response rate by subjects, method of data collection (eg, direct or proxy), case definition, study instrument, same mode of data collection, and numerators and dominators for the parameters. Each criterion has 2 potential responses, including "yes" (score, 0) or "no" (score, 1). The total scores would range from 0 to 9 for each study, and a higher score indicates a higher risk of bias and a lower quality.

Study Outcomes and Statistical Analysis

We combined the proportion of RA patients with concurrent NAFLD in each study to provide a pooled prevalence rate of NAFLD, using a random-effects model for providing more conservative estimates. We presented the values as percentages and 95% CI. In addition, we pooled the extracted adjusted ORs (aORs) for BMI and methotrexate to obtain overall estimates. The inconsistency index (I^2) test was used for assessment of the heterogeneity between the studies, which ranges from 0% to 100% and is categorized as low heterogeneity (25%–49%), moderate heterogeneity (50%–74%), and high heterogeneity (≥ 75%); to define a significant heterogeneity degree, the chi-squared test was used with a P value <.10.[15] Subgroup analyses were conducted according to sex, diabetes, hypertension, methotrexate use, and biologics use, and a P value (P for interaction) <.05 showed a significant difference between the subgroups. All statistical analyses were performed using STATA (StataCorp).

Results

Search Results, Study Selection, and Characteristics

Of 664 citations identified using the search strategy, full texts of 21 articles were obtained for eligibility assessment. Finally, a total of 9 eligible reports were included in this meta-analysis (Figure 1), containing 2178 patients with RA.[9,10,16–22] Excellent agreement was observed between the 2 reviewers for suitability investigation (kappa statistic = 0.84). All but 2 articles were published in English.[20,21] The publication date was between 2006 and 2022. Two studies were conducted in China,[21,22] 2 in Italy,[9,10] 1 in Japan,[20] 1 in Morocco,[17] 1 in Pakistan,[19] 1 in South Korea,[18] and 1 in the United States.[16] Regarding NAFLD criteria, significant alcohol consumption was defined as ≥30 g/d in men and ≥20 g/d in women in 6 studies,[9,10,17,18,20,22] >20 g/d in 2 studies,[16,19] and ≥140 g/wk in men and ≥70 g/wk in women in 1 study.[21] The baseline characteristics, as well as results of the quality assessment, of the 9 included studies are summarized in Table 1.

Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Rheumatoid Arthritis

An analysis of 9 studies comprising 2178 subjects showed that the pooled prevalence of NAFLD was 35.3% (95% CI, 19.9–50.6; I^2 = 98.6%; P < .001) in patients with RA (Figure 2). The highest prevalence was 84.3% (95% CI, 79.5–89.1) in Italy,[9] and the

lowest was 20.3% (95% CI, 14.3–26.0) in Pakistan.[19] All studies used ultrasound for the diagnosis of NAFLD, except 1 study that used FibroScan (Echosens).[20] Because of the high heterogeneity seen for our primary outcome, we tried to perform a sensitivity analysis by leave-one-out meta-analysis (removing the study by Erre et al[9]); the analysis showed that the pooled prevalence of NAFLD was 28.4% (95% CI, 22.3–34.5), with persistent high heterogeneity (I^2 = 91.2%; P < .001).

There was 1 study that compared the prevalence of NAFLD between 223 RA patients and 141 non-RA controls.[9] The prevalence of NAFLD was slightly higher in RA patients (84.3%; 95% CI, 78.9–88.8) than in controls (83.0%; 95% CI, 76.8–89.2). The OR for NAFLD in patients with RA compared with the control group was 1.10 (95% CI, 0.62–1.95).

One study reported the prevalence of NAFLD among RA patients according to NAFLD severity.[9] In this regard, the mild-to-moderate NAFLD was more prevalent than severe NAFLD in patients with RA (77.1%; 95% CI, 71.6–82.6; vs 7.2%; 95% CI, 3.8–10.6).

There was 1 study that reported the prevalence of NASH in patients with RA.[20] In that study, the frequency of NASH was n = 8 of the total 61 NAFLD cases, leading to a NASH prevalence of 7.8% (95% CI, 3.5–14.9) among RA patients.

Four studies were found that reported the prevalence of NAFLD in patients with RA according to sex.[10,18,19,21] Based on the analyses, the pooled prevalence of NAFLD in men with RA was significantly higher than in women with RA (35.2%; 95% CI, 24.0–46.5; compared with 22.2%; 95% CI, 17.9–26.58; P for interaction = .048). The OR for NAFLD in men vs women was 1.90 (95% CI, 1.07–3.37), with moderate heterogeneity between the studies (I^2 = 64.3%; P = .038) (Figure 3).

We also performed subgroup analyses based on diabetes,[10,18,20] hypertension,[10,18] methotrexate use,[10,18,20,21] and biologics use.[10,18,20,21] In this regard, the pooled prevalence of NAFLD was 53.9% (95% CI, 26.9–80.9; I^2 = 83.5%) in RA patients with diabetes (vs 36.6%; 95% CI, 16.0–57.2; I^2 = 94.7% in those without; P for interaction = .318), 26.3% (95% CI, 20.6–32.1; I^2 = 0.0%) in RA patients with hypertension (vs 29.6%; 95% CI, 18.4–40.7; I^2 = 64.9% in those without; P for interaction = .615), 29.2% (95% CI, 22.7–35.7; I^2 = 74.7%) in RA patients using methotrexate (vs 26.7%; 95% CI, 24.6–28.8; I^2 = 55.9% in RA patients not using methotrexate; P for interaction = .490), and 31.8% (95% CI, 17.6–46.0; I^2 = 69.8%) in RA patients using biologics (vs 36.9%; 95% CI, 18.8–54.8; I^2 = 93.1% in RA patients not using biologics; P for interaction = .664).

Factors Associated With Nonalcoholic Fatty Liver Disease in Patients With Rheumatoid Arthritis

There were 4 surveys that investigated the association between BMI (kg/m^2) and NAFLD in patients with RA using aORs.[9,10,18,21] Pooling these data indicated that each 1-unit increase in BMI was associated directly with a 24% increased risk of NAFLD in RA patients (aOR, 1.24; 95% CI, 1.17–1.31), without heterogeneity between the studies (I^2 = 0.0%; P = .518) (Figure 4A).

Based on 2 studies evaluating the association between methotrexate use and NAFLD in RA patients,[9,20] the pooled aOR for NAFLD in methotrexate users compared with nonusers was 1.28 (95% CI, 0.22–2.35), with no heterogeneity between the studies (I^2 = 0.0%; P = .571) (Figure 4B).

Discussion

The main finding of this systematic review and meta-analysis was that the prevalence of NAFLD in RA patients is approximately 36%. These data were derived from a diverse patient population residing on 4 continents. The pooled prevalence of NAFLD was approximately 2-fold higher in men with RA than in women with RA. Further studies are needed to examine the association between the presence of NASH, advanced fibrosis and cirrhosis in patients with RA, and whether disease severity in RA is linked to disease severity in NAFLD.

Probable connections between NAFLD and some immune-mediated inflammatory diseases have been proposed in previous studies; for instance, we recently indicated that the prevalence of NAFLD in IBD patients was roughly 31%,[8] which was a bit less than what we found among RA patients in the present study. It is noteworthy that we did not have enough data to compare NAFLD prevalence between RA and non-RA controls, so we cannot explicitly report an association between RA and NAFLD. Regarding the development of NAFLD in IBD patients, some potential leading factors have been reported, such as overexpression of proin-flammatory cytokines (eg, tumor necrosis factor α and interleukin 6) seen in both NAFLD and IBD,[23–26] and chronic exposure to steatogenic drugs (eg, methotrexate, corticosteroids).[27–29]

Our analyses showed that men with RA are at higher odds of NAFLD than women with RA. There are conflicting results on the differences in development of NAFLD between the 2 sexes. Although NAFLD is more prevalent in men vs women at younger ages, this trend changes conversely in older patients (especially after menopause), possibly due to the protective role of estrogen. Generally, sex differences in NAFLD can pertain to differences in sex hormones, genetic factors, sociocultural factors, and metabolic conditions.[8,30] The reasons men with RA are more likely to have NAFLD than women with RA should be further explored in experimental and epidemiological studies focusing on hormonal, genetic and social factors.

We acknowledge the following limitations. First, we tried to compare the prevalence of NAFLD between RA patients and healthy controls, but only 1 study reported this information, and therefore, we were not able to pool the data and determine the degree to which NAFLD risk is increased among patients with RA compared to those without RA; overall, our results on the association between RA and NAFLD should be interpreted with caution, and further research needs to clarify whether the risk of NAFLD increases in RA patients. Second, the individual studies included did not provide any useful data on the factors possibly associated with the severity of NAFLD in RA patients; further studies are needed to provide more granular data on medication use and disease severity of NAFLD in RA. Third, high heterogeneity was observed between the studies in some analyses (could

be explained by differences in study country, populations, and so forth), which may make it difficult to generalize an overall prevalence of NAFLD in patients with RA; of course, we tried to find the sources of heterogeneity by performing subgroup analyses based on sex, hypertension, diabetes, methotrexate, and biologics, but none of them could justify the heterogeneity. Overall, high heterogeneity for the estimates is not unexpected in the prevalence meta-analyses,[31] however, our results should be interpreted cautiously. Finally, studies included in this systematic review were from a broad range of years (2006–2022), during which the prevalence of NAFLD and the diagnosis approach could have changed; therefore, this issue needs to be considered when interpreting the results.

In conclusion, this systematic review and meta-analysis showed that 1 in 3 patients with RA experienced NAFLD, which appears comparable with its overall prevalence among the general population. Men with RA were more prone to have a concomitant diagnosis of NAFLD than women with RA. In addition, BMI was found as a potential risk factor for NAFLD in patients with RA. Further epidemiological studies are necessary to compare the NAFLD prevalence between patients with RA and those without. Moreover, it is recommended to clinicians who care for RA patients to carefully screen for NAFLD, especially if they have elevated BMI, to prevent further complications. Further studies are needed to assess the prevalence of NASH, fibrosis, and cirrhosis among patients with RA, and whether screening would be beneficial in this population.

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Conflicts of interest

This author discloses the following: Rohit Loomba serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen, Inc, Madrigal, Metacrine, Inc, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals, and Viking Therapeutics; has received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes, and Terns Pharmaceuticals; and is a co-founder of LipoNexus, Inc. The remaining authors disclose no conflicts.

Abbreviations used in this paper:

aOR	adjusted odds ratio
BMI	body mass index
IBD	inflammatory bowel disease
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OR	odds ratio

RA	rheumatoid arthritis

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What You Need to Know

Background

Previous studies have shown an association between rheumatoid arthritis (RA) and nonalcoholic fatty liver disease (NAFLD), but this association has not been analyzed systematically. Therefore, we conducted a literature search in 5 databases for observational studies that reported the prevalence of NAFLD in adult patients with RA.

Findings

Our analyses indicated that 1 in 3 patients with RA experienced NAFLD. We also found that the pooled prevalence of NAFLD was approximately 2-fold higher in men with RA than in women with RA. Finally, we observed that a higher body mass index potentially could be a risk factor for NAFLD in patients with RA.

Implications for patient care

There was a considerable prevalence of NAFLD in inflammatory bowel disease patients. It is recommended that clinicians who care for patients with RA carefully screen for NAFLD.

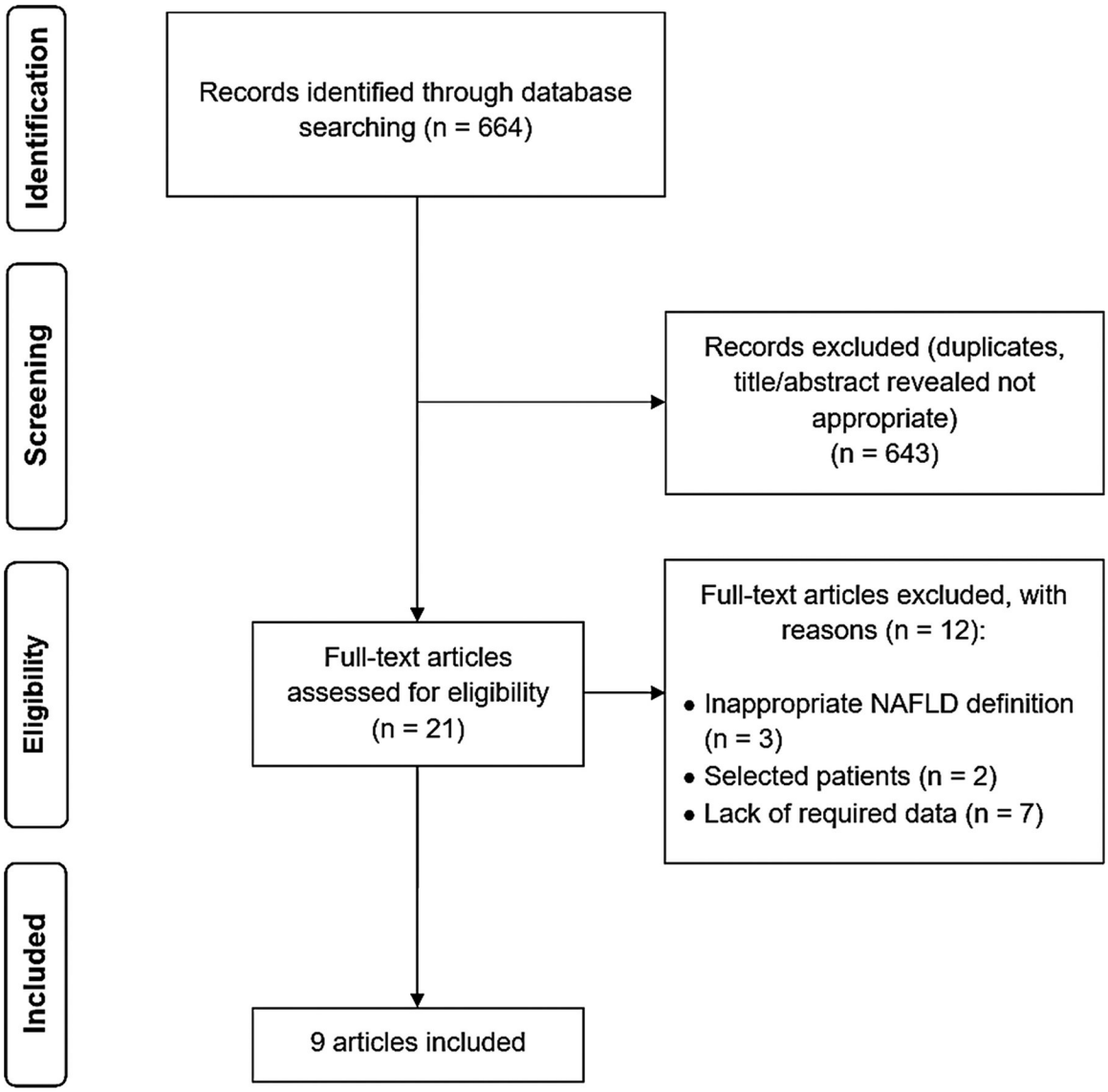

Figure 1.
Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram. NAFLD, nonalcoholic fatty liver disease.

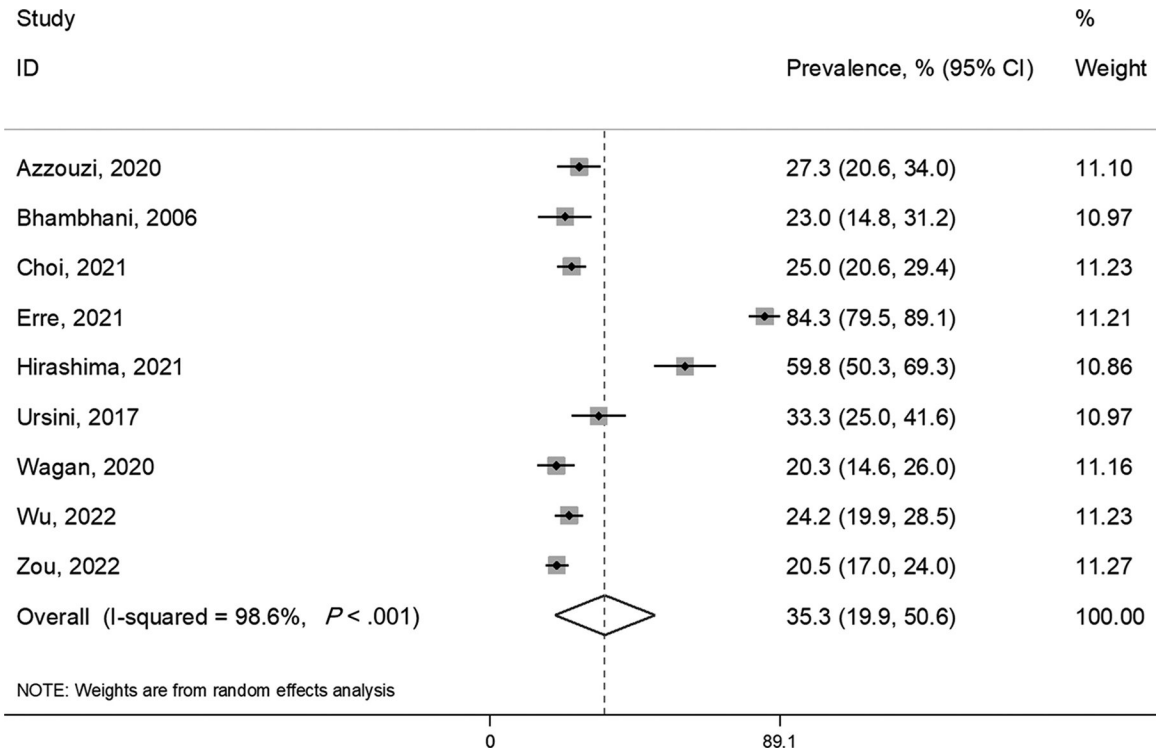

Figure 2.
Forest plot of the pooled prevalence of nonalcoholic fatty liver disease in patients with rheumatoid arthritis.

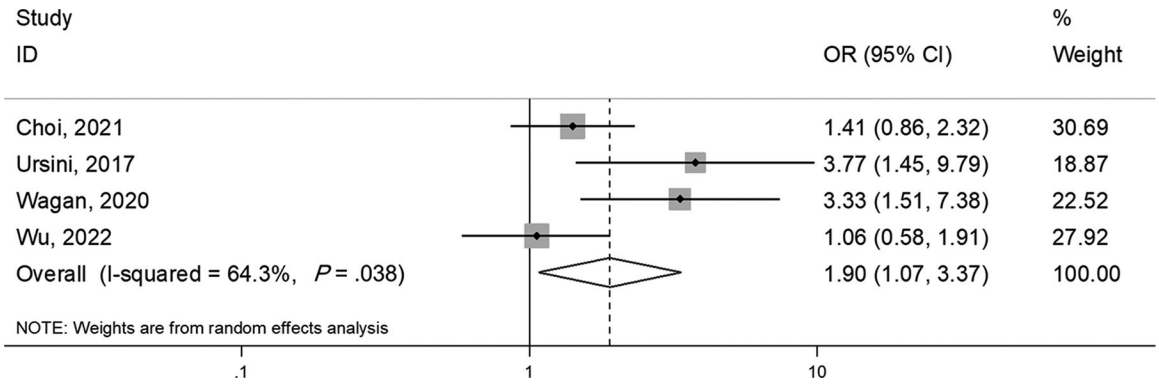

Figure 3.

Forest plot of the pooled odds ratio for nonalcoholic fatty liver disease in men with rheumatoid arthritis vs women with rheumatoid arthritis.

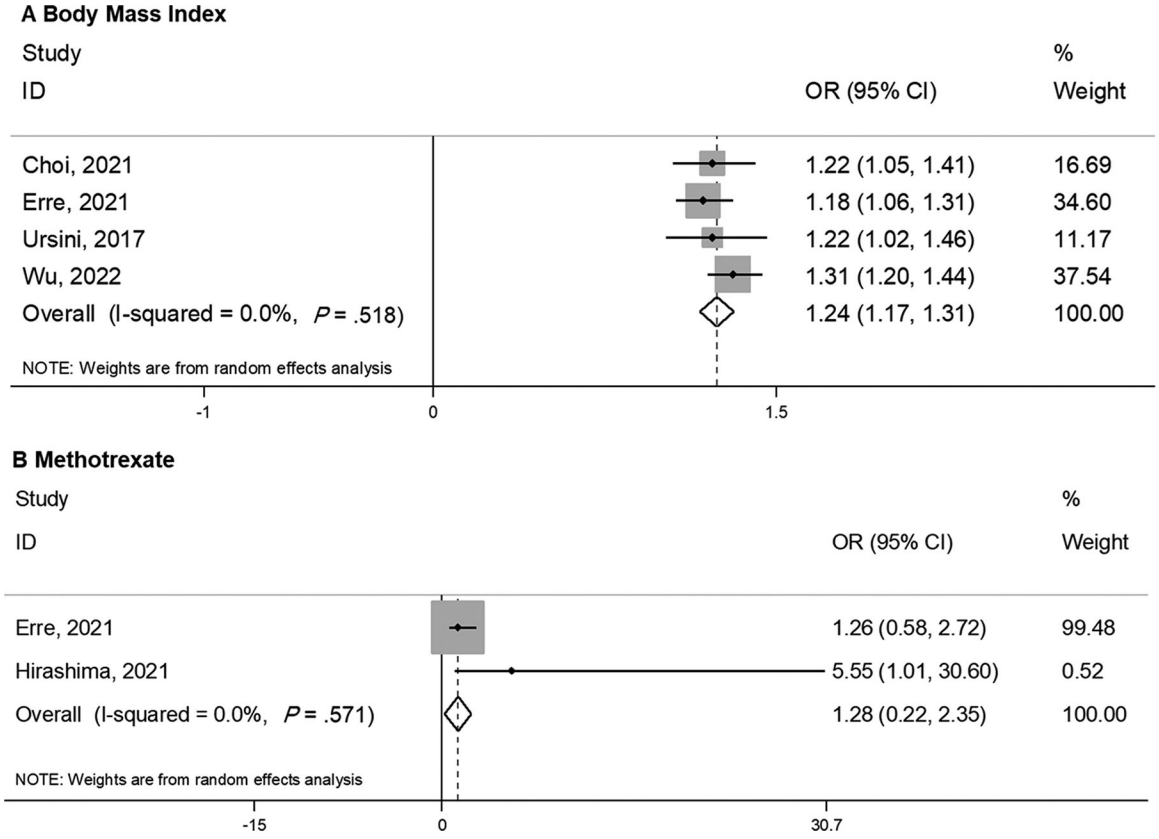

Figure 4.

Forest plots of the pooled odds ratios (ORs) for body mass index and methotrexate as potential risk factors for nonalcoholic fatty liver disease in patients with rheumatoid arthritis.

Table 1.

Baseline Characteristics of the Studies Included in the Systematic Review

Study	Country	Diagnostic method of NAFLD	Sample size	Men/ women	Prevalence of NAFLD, %	Risk of bias score	RA-directed medication distribution
Azzouzi et al,[17] 2020	Morocco	Ultrasound	172	17/155	27.3	4	NA
Bhambhani et al,[16] 2006	United States	Ultrasound	100	9/91	23.0	3	Methotrexate not initiated
Choi et al,[18] 2021	South Korea	Ultrasound	368	115/253	25.0	2	Methotrexate, 49.5%; hydroxychloroquine, 67.1%; leflunomide, 43.2%; sulfasalazine, 23.1%; tacrolimus, 6.0%; steroids, 51.6%; biologics, 6.5%
Erre et al,[9] 2021	Italy	Ultrasound	223	62/161	84.3	2	Methotrexate, 81.1%; leflunomide, 4.1%; TNF-α inhibitors, 20.2%; tocilizumab, 4.9%; abatacept, 1.8%; rituximab, 0.9%
Hirashima et al,[20] 2021	Japan	FibroScan	102	18/84	59.8	3	Methotrexate, 48.0%; steroids, 11.8%; biologics, 39.2%
Ursini et al,[10] 2017	Italy	Ultrasound	123	22/101	33.3	2	Methotrexate, 41.5%; leflunomide, 29.3%; hydroxychloroquine, 18.7%; biologics, 26.0%; steroids, 62.6%
Wagan et al,[19] 2020	Pakistan	Ultrasound	192	36/156	20.3	3	Methotrexate, 87.0%; hydroxychloroquine, 37.5%; sulfasalazine, 22.9%; leflunomide, 7.3%; steroids, 5.7%
Wu et al,[21] 2022	China	Ultrasound	385	72/313	24.2	3	Steroids, 54.3%; methotrexate, 59.5%; leflunomide, 48.6; hydroxychloroquine, 13.0%; sulfasalazine, 3.6%; cyclosporine, 6.5; biologics, 7.5%
Zou et al,[22] 2022	China	Ultrasound	513	111/402	20.5	3	Steroids, 51.1%; immunomodulators, 62.8%; biologics, 8.2%

NA, not available; NAFLD, nonalcoholic fatty liver disease; RA, rheumatoid arthritis; TNF-α, tumor necrosis factor α.