# Serum 14-3-3η levels are increased and associated with a higher risk of osteoporosis in patients with rheumatoid arthritis: A meta-analysis

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**Abstract.** 14-3-3η can regulate the cell cycle, immunity, inflammation and the secretion of matrix metalloproteinases, while it may also be involved in the development of rheumatoid arthritis (RA) and promote bone injury. Therefore, the present meta-analysis focused on the dysregulated serum levels of 14-3-3η and its association with osteoporosis in patients with RA. Studies comparing the serum levels of 14-3-3η between patients with RA and healthy controls (HCs) or patients with RA with different bone mineral densities were retrieved from the EMBASE, Web of Science, PubMed and Cochrane databases. A total of 14 studies comprising 2,164 patients with RA and 1,136 HCs were included and analysed. Pooled analyses showed that the serum levels of 14-3-3η were enhanced in patients with RA compared with HCs [standardized mean difference (SMD): 1.34; 95% confidence interval (CI): 1.01-1.66; P<0.001]. In addition, the serum levels of 14-3-3η were also significantly higher in patients with RA with osteoporosis and osteopenia compared with those with normal bone mass (SMD: 1.96; 95% CI: 0.01-3.92; P=0.049 and SMD: 0.80; 95% CI: 0.09-1.52; P=0.028, respectively). Begg's and Egger's tests demonstrated that the publication bias for each evaluated indicator was low (all P>0.05). However, sensitivity analyses revealed that the findings were not very robust, which may be due to the omission of several individual studies. Overall, the present meta-analysis suggested that the serum levels of 14-3-3η were elevated and were associated with a higher risk of osteoporosis in patients with RA, thus supporting its potency as a circulating biomarker in the management of RA.

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*Key words:* rheumatoid arthritis, disease risk, osteoporosis, 14-3-3η, biomarker

## Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, autoimmune disease, which affects ~1% of the global population (1,2). This disease is commonly characterized by extraarticular involvement, such as cardiovascular disorders, interstitial lung disease and osteoporosis (3,4). Among the aforementioned complications, osteoporosis most commonly affects patients with RA. Previous meta-analyses including 227,812 RA cases revealed an estimated prevalence of osteoporosis in patients with RA of 27.6% (5,6). Several factors can be involved in the elevated risk of osteoporosis in patients with RA. These factors are mainly divided into two subtypes, namely direct disease-specific factors and indirect factors (7). The former factors include pathogenic autoantibodies, inflammation, bone erosion and the application of glucocorticoids, while smoking and vitamin D insufficiency are considered indirect factors associated with RA susceptibility (7-9).

14-3-3η is a highly conserved protein, which interacts with >200 functional proteins to activate or inhibit ligands of several significant signalling pathways. This protein is involved in regulating the cell cycle, cell apoptosis, mitogenic signalling transduction, immunity and inflammation (10-12). It has been also reported that 14-3-3η can positively regulate the expression of cytokines and enzymes, while it is involved in both local and systemic inflammation, thus promoting the development of RA. Correspondingly, several previous clinical studies indicated that the serum levels of 14-3-3η were elevated and it may therefore be considered a potential biomarker for the diagnosis of RA (13-15). Of note, other previous studies demonstrated that 14-3-3η led to upregulation of matrix metalloproteinase (MMP)-1 and MMP-9 and enhanced the expression of receptor activator of nuclear factor κB ligand to accelerate bone injury (16,17). In addition, several studies also revealed that the serum levels of 14-3-3η were associated with a higher risk of osteoporosis in patients with RA (13,18,19). However, another study argued that the serum levels of 14-3-3η were not different in patients with established RA compared with healthy controls (HCs) (20).

The present meta-analysis aimed to summarize the studies reporting the levels of serum 14-3-3η in patients with RA vs. HCs and/or the association between serum 14-3-3η levels and the risk of osteoporosis in patients with RA, thus providing a confirmative statement regarding the association between the serum levels of 14-3-3η and the risk of both RA and RA-related osteoporosis.

## Materials and methods

*Study search*. A systematic search in the EMBASE (embase.com), Web of Science (webofscience.com), PubMed (pubmed.ncbi.nlm.nih.gov) and Cochrane databases (www.cochranelibrary.com) was performed up to September 21, 2023 according to the PRISMA guidelines (21). Studies that compared the serum levels of 14-3-3η between patients with RA and HCs or in patients with RA with different bone mineral densities were included in the meta-analysis. The following searching terms were used: '14-3-3η', '14-3-3eta', '14-3-3', 'YWHAH', 'rheumatoid arthritis' and 'RA'. In addition, all references in the included articles were screened for other potentially related studies. The study research and selection were performed by RF, JZ, if disagreements occurred, a consultation from YSZ and decision was made after discussion.

*Inclusion criteria*. The inclusion criteria were as follows: i) Studies comparing the serum levels of 14-3-3η between patients with RA and HCs or in patients with RA with different bone mineral densities (normal bone mass, osteopenia and osteoporosis); ii) studies that determined the serum protein levels of 14-3-3η by ELISA; iii) those with access to full texts; iv) studies with extractable or evaluable data for analysis; and v) those which were published in the English language. Review articles, meta-analyses, case reports, comments, conference abstracts, letters, editorials or expert opinions were excluded.

*Data extraction and quality assessment*. Following study selection, two investigators (YX and LG) independently extracted and recorded data, such as first author name, publication year, study design, ethnicity, mean age, gender ratio, sample size and serum 14-3-3η levels. When any disagreements occurred, a third investigator (ZY) was invited for decision. The study quality was assessed independently by two investigators (RF and JZ) using the Newcastle-Ottawa scale criteria, containing three aspects (selection, comparability and outcome) (22). When any disagreements occurred, a third investigator (YSZ) was invited to make an adjudicative decision.

*Statistical analysis*. All analyses were carried out using Stata V.14.0 (StataCorp LP) software. Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were used for assessment. When the mean and standard deviation values were not reported in the included study, the data were converted from the median and quartile values (23,24). To avoid double-counting issues, when a study reported both early and established RA, the number of healthy subjects in the HC groups was divided correspondingly (equally in proportion to the number of early and established RA) (25). Heterogeneity was assessed using $I^2$ statistics. When heterogeneity was obtained ($I^2$>50.0% or P<0.05), the random-effects model was used. Publication bias was evaluated using the Begg's and Egger's tests. Sensitivity analyses were carried out by omitting one study at a time to evaluate the robustness of the results. P<0.05 was considered to indicate statistical significance.

## Results

*Inclusion of studies*. A total of 426 records were screened from the selected databases, including 200, 104, 86 and 36 studies from the EMBASE, Web of Science, PubMed and Cochrane databases, respectively. After removing any duplicated studies, a total of 184 studies were screened based on their title and abstract. Subsequently, studies with irrelevant topics, irrelevant data, letters, case reports, review articles, meta-analyses, manuscripts with no access to full data and not written in the English language were excluded. After reading the full texts of the remaining 15 articles, one study was excluded due to inaccessible data. Finally, a total of 14 studies were included in the meta-analysis (Fig. 1) (12-15,17-20,26-31). The characteristics of all included studies are listed in Table I. The quality of the enrolled studies was deemed acceptable (Table II).

*Comparison of 14-3-3η levels between patients with RA and HCs*. A total of 18 datasets were included in the meta-analysis and heterogeneity was observed among these studies. Pooled analysis with the application of the random-effects model indicated that the serum levels of 14-3-3η were significantly higher in patients with RA compared with those in HCs (P<0.001; Fig. 2). Subgroup analysis showed that 14-3-3η levels were markedly enhanced in patients with early RA (P<0.001; Fig. S1A), established RA (P<0.001; Fig. S1B) or RA of unknown duration (P<0.001; Fig. S1C) compared with the HC group.

*Comparison of 14-3-3η levels among patients with RA with osteoporosis, osteopenia and normal bone mass*. Among all studies included in the meta-analysis, five studies compared the serum levels of 14-3-3η between patients with RA with osteoporosis and those with normal bone mass (Fig. 3A), patients with RA-related osteopenia vs. those with normal bone mass (Fig. 3B) and patients with RA-related osteoporosis compared with those with RA-related osteopenia (Fig. 3C). However, heterogeneity was observed in these studies and therefore, the random-effects model was applied. In the pooled analysis, the levels of 14-3-3η were increased in patients with RA with osteoporosis (P=0.049; Fig. 3A) and osteopenia (P=0.028; Fig. 3B) compared with those with normal bone mass. A decreasing trend in 14-3-3η levels was observed in patients with RA with osteoporosis compared with those with osteopenia; however, statistical significance was not reached (P=0.082, Fig. 3C).

*Subgroup analysis*. Subgroup analysis was carried out based on study design and ethnicity. In terms of the 14-3-3η levels between patients with RA and HCs, the analysis revealed that the findings in each subgroup were similar to the main finding (all P<0.01; Table SI). Regarding the levels of 14-3-3η among patients with RA-related osteoporosis and osteopenia compared with those with normal bone mass, the pooled analysis showed that the findings in the subgroups of cohorts,

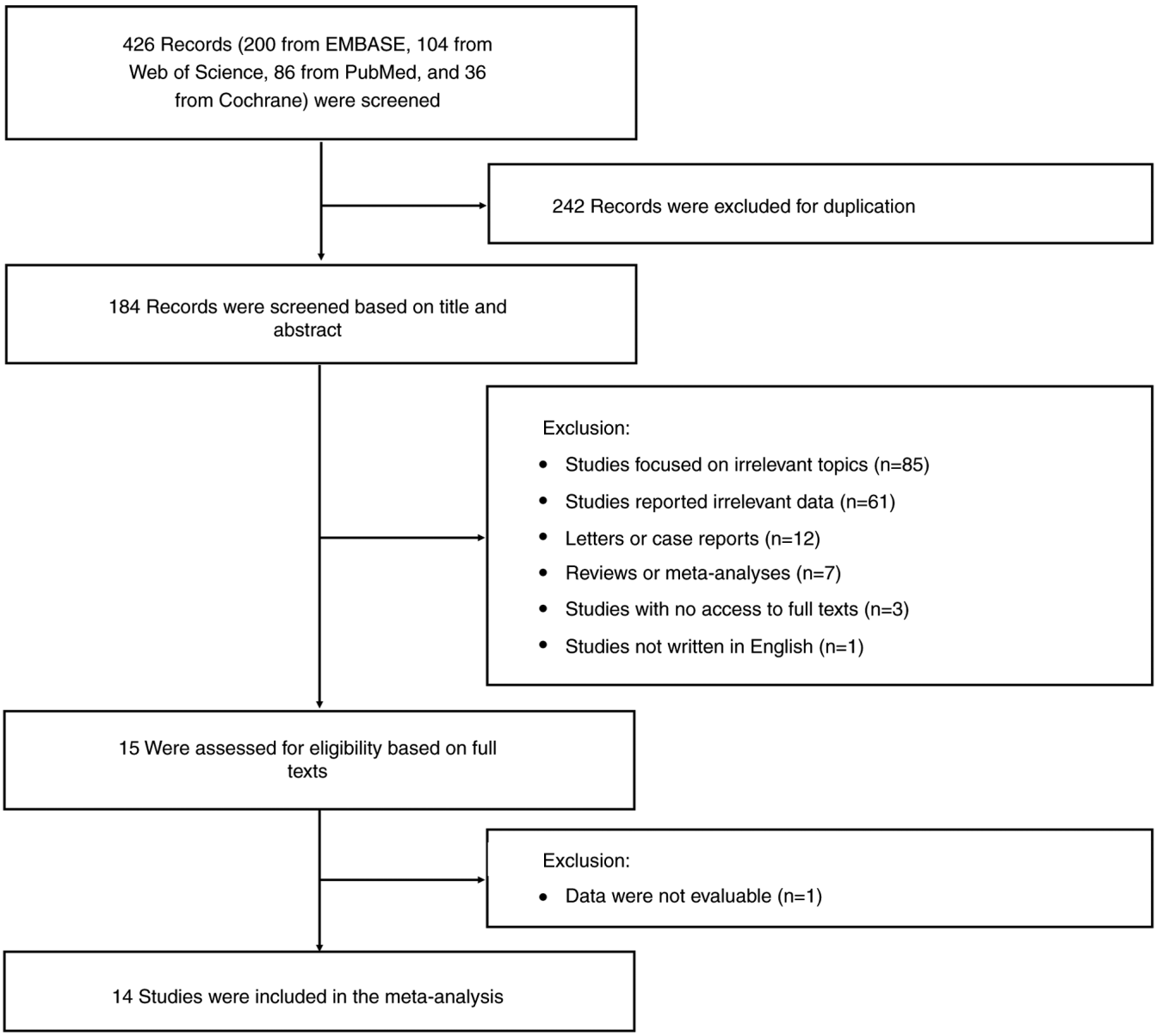


Figure 1. Flow diagram of research studies included in the meta-analysis.

cross-sectional studies and studies from Africa were similar to the main results (all P<0.001). Inconsistent results were only obtained in the subgroups of case-control studies and studies from Asia (all P>0.05; Table SI).

*Publication bias and sensitivity analysis*. Begg's and Egger's tests revealed that there was no publication bias in the current meta-analysis for any of the main findings (all P>0.05; Table III). Funnel plots also showed similar findings (Fig. S2). In the sensitivity analysis, the significance of the difference in 14-3-3η levels between patients with RA and HCs did not change, regardless of omitting any of the included datasets. However, the significance of the finding of the different serum levels of 14-3-3η between patients with RA with osteoporosis and those with normal bone mass changed from significant to insignificant after omitting any of the following datasets: Gong (a; early RA) (20), Sun (19), Zeng (18) and Adel (13) (Table IV). Consistently, the significance of the same finding between patients with RA-related osteopenia and those with normal bone mass changed from significant to insignificant after omitting the datasets provided by Sun (19) or Adel (13) (Table IV). Finally, after omitting the study by Gong (b) ('b' stood for established RA) (20), the serum levels of 14-3-3η became higher in patients with RA-related osteoporosis compared with those with osteopenia. However, the significance of the difference in findings between osteoporosis and osteopenia in RA did not change after omitting any of the other studies (Table IV).

## Discussion

14-3-3η is a member of the 14-3-3 family, which consists of intracellular chaperone proteins with a molecular weight of ~28 kDa (32). Benefiting from its subcellular amphipathic groove structure, 14-3-3η can interact with several proteins and participate in different cellular processes, such as signal

Table I. Characteristics of the studies included in the meta-analysis.

| First author, year | Study design | Ethnicity | Mean age, years | | Females/males | | Sample size | | Detection method for 14-3-3η protein | Assessment for 14-3-3η protein between RA and HCs | Assessment for 14-3-3η protein in RA with different bone mineral density | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | RA | HCs | RA | HCs | RA | HCs | | | | |
| Maksymowych, 2014 | Cohorts | Europe | 56 | 45 | 175/59 | 107/82 | 234 | 189 | ELISA | Yes | No | (17) |
| Maksymowych, 2015 | Cohorts | Europe | 56 | 58 | 190/59 | 40/15 | 249 | 55 | ELISA | Yes | No | (26) |
| Gong, 2017 | Case-control | Asia | 53 | 54 | 208/51 | 41/39 | 259 | 80 | ELISA | Yes | Yes | (20) |
| Mohamed, 2018 | Cohorts | Africa | 44 | 41 | 82/10 | 36/6 | 92 | 42 | ELISA | Yes | No | (27) |
| El-Sherif, 2019 | Cohorts | Africa | 45 | 33 | 48/2 | 11/3 | 50 | 14 | ELISA | Yes | No | (28) |
| Guan, 2019 | Cohorts | Asia | 61 | 59 | 71/23 | 25/15 | 94 | 40 | ELISA | Yes | No | (29) |
| Qu, 2019 | Cohorts | Asia | 50 | 49 | 74/42 | 62/54 | 116 | 116 | ELISA | Yes | No | (30) |
| Salman, 2019 | Cross-sectional | Asia | 53 | 52 | 36/9 | 36/9 | 45 | 45 | ELISA | Yes | No | (31) |
| Huang, 2020 | Case-control | Asia | 52 | 51 | 32/76 | 34/56 | 108 | 90 | ELISA | Yes | No | (14) |
| Sun, 2020 | Cross-sectional | Asia | 58 | NR | 179/106 | NR | 285 | NR | ELISA | No | Yes | (19) |
| Zeng, 2020 | Case-control | Asia | 54 | 54 | 83/30 | 57/20 | 113 | 77 | ELISA | Yes | Yes | (18) |
| Zhang, 2020 | Cohorts | Asia | 52 | 34 | 242/49 | 84/72 | 291 | 156 | ELISA | Yes | No | (12) |
| Hussin, 2021 | Case-control | Africa | 43 | 43 | 38/2 | 38/2 | 40 | 40 | ELISA | Yes | No | (15) |
| Adel, 2022 | Cohorts | Africa | 39 | 39 | 159/29 | 160/32 | 188 | 192 | ELISA | Yes | Yes | (13) |

RA, rheumatoid arthritis; HCs, healthy controls; NR, not reported.

Table II. Quality assessment according to Newcastle-Ottawa scale criteria.

| First author, year | Selection | Comparability | Outcome | Total score | (Refs.) |
|---|---|---|---|---|---|
| Maksymowych, 2014 | 4 | 2 | 2 | 8 | (17) |
| Maksymowych, 2015 | 3 | 2 | 2 | 7 | (26) |
| Gong, 2017 | 3 | 2 | 3 | 8 | (20) |
| Mohamed, 2018 | 3 | 2 | 2 | 7 | (27) |
| El-Sherif, 2019 | 3 | 2 | 2 | 7 | (28) |
| Guan, 2019 | 3 | 2 | 2 | 7 | (29) |
| Qu, 2019 | 4 | 2 | 2 | 8 | (30) |
| Salman, 2019 | 4 | 2 | 1 | 7 | (31) |
| Huang, 2020 | 4 | 2 | 2 | 8 | (14) |
| Sun, 2020 | 4 | 2 | 1 | 7 | (19) |
| Zeng, 2020 | 3 | 2 | 2 | 7 | (18) |
| Zhang, 2020 | 4 | 2 | 2 | 8 | (12) |
| Hussin, 2021 | 4 | 2 | 2 | 8 | (15) |
| Adel, 2022 | 4 | 2 | 2 | 8 | (13) |

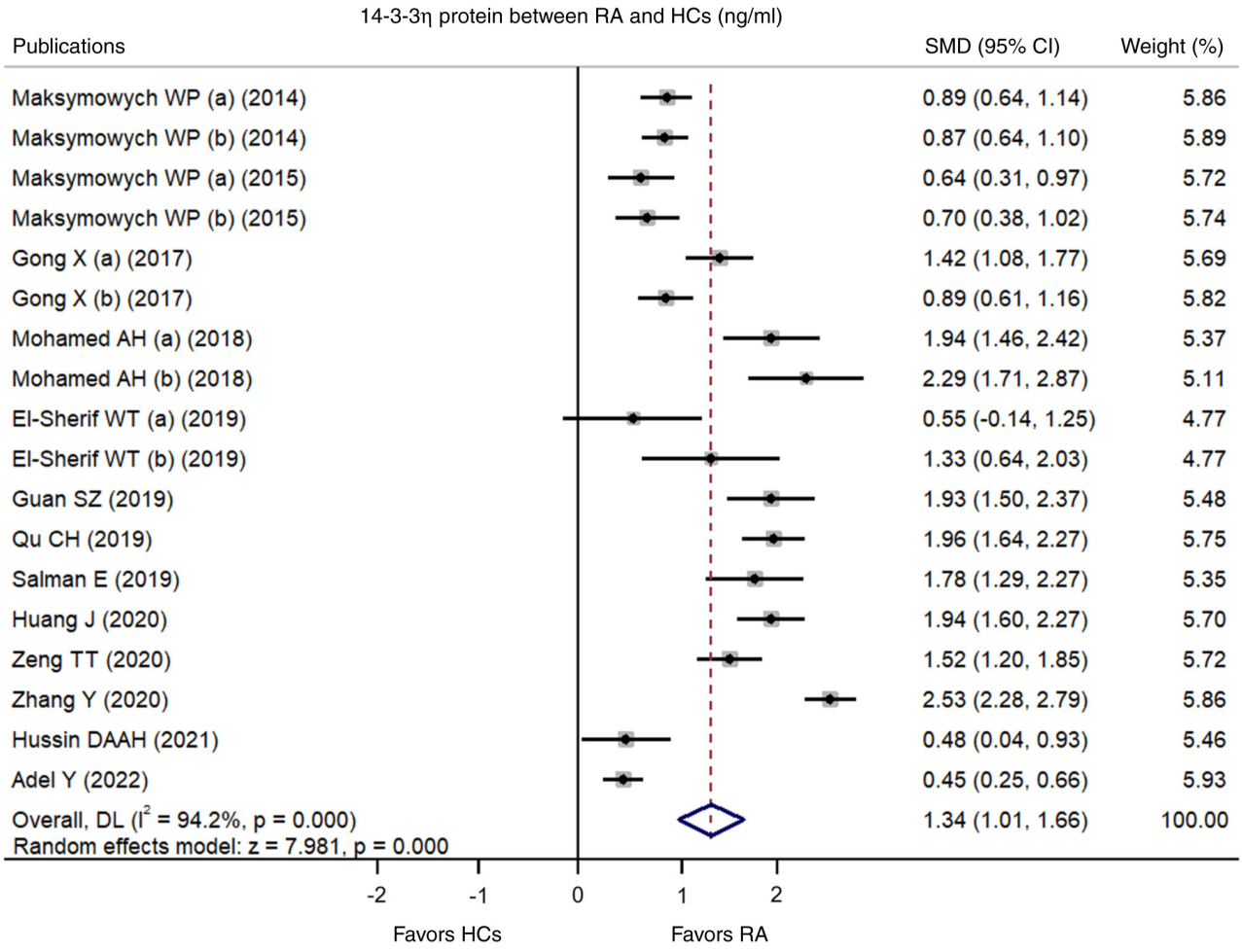


Figure 2. Pooled analysis comparing the serum levels of 14-3-3η between patients with RA and HCs. RA, rheumatoid arthritis; HCs, healthy controls; SMD, standardized mean difference.

transduction and protein synthesis (33). Several studies have been conducted to explore the role of 14-3-3η in the pathogenesis and progression of RA (34,35). For instance, a previous study demonstrated that 14-3-3η may be involved in the pathogenesis of RA via promoting the formation of invadosomes through regulating the forkhead box O3/Snail axis (34). In

Table III. Publication bias.

| Outcome | No. of included datasets | P-value (Begg's test) | P-value (Egger's test) |
|---|---|---|---|
| 14-3-3η protein between RA and HCs | 18[a] | 0.449 | 0.252 |
| 14-3-3η protein between osteoporosis and normal bone mass in RA | 5[b] | 0.221 | 0.142 |
| 14-3-3η protein between osteopenia and normal bone mass in RA | 5[b] | 0.462 | 0.307 |
| 14-3-3η protein between osteoporosis and osteopenia in RA | 5[b] | 0.462 | 0.330 |

[a]13 studies were included and 5 studies reported both early RA and established RA; [b]4 studies were included and 1 study reported both early RA and established RA. RA, rheumatoid arthritis; HCs, healthy controls.

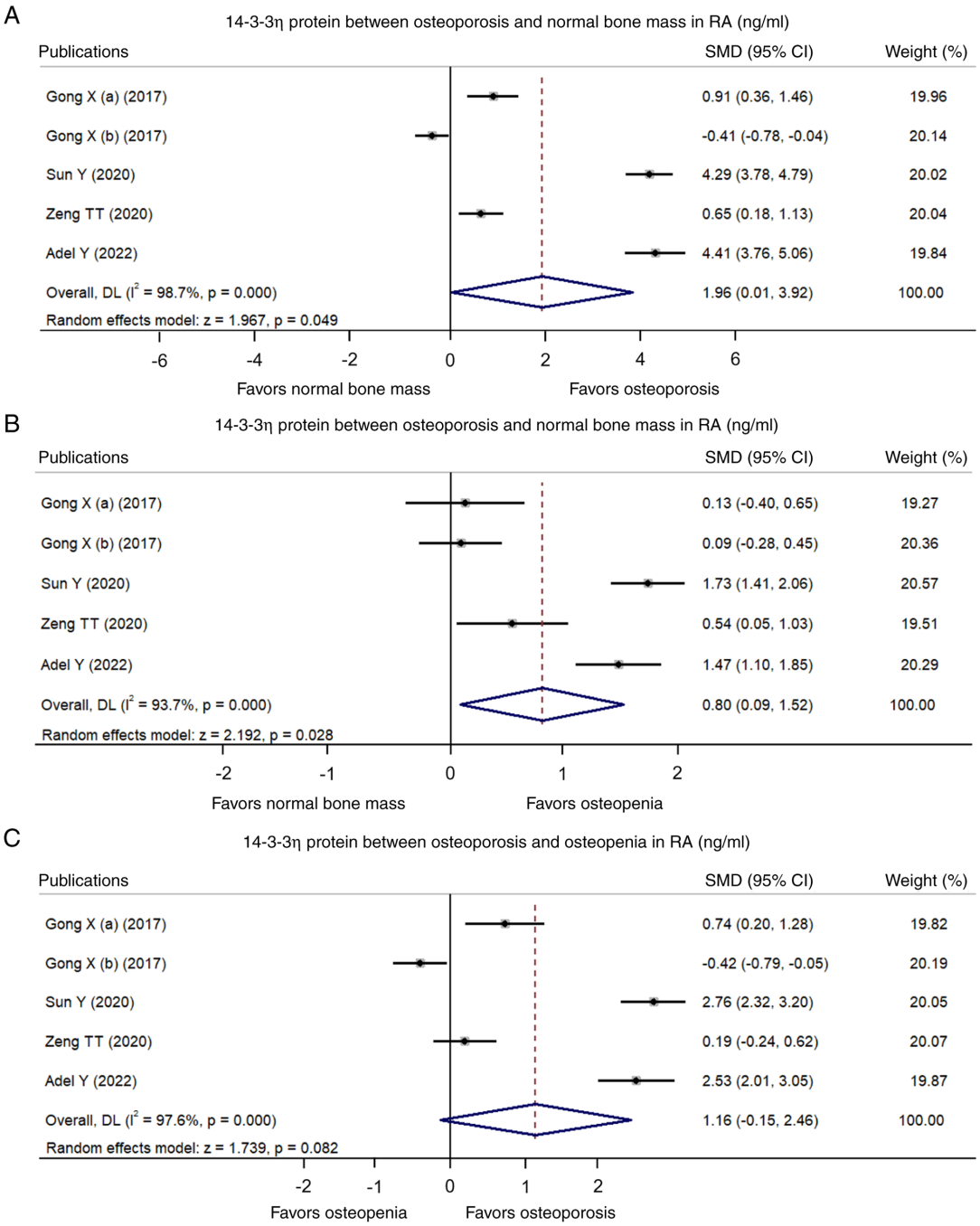


Figure 3. Pooled analysis of the serum levels of 14-3-3η among patients with osteoporosis and osteopenia and those with normal bone mass. Pooled analysis of 14-3-3η levels between patients with rheumatoid arthritis with (A) osteoporosis vs. those with normal bone mass, (B) osteopenia vs. normal bone mass and (C) osteoporosis vs. osteopenia. RA, rheumatoid arthritis; HCs, healthy controls; SMD, standardized mean difference.

Table IV. Sensitivity analysis.

A, 14-3-3η protein between RA and HCs, ng/ml

| Author, year of omitted study | Estimate, SMD | 95% CI | (Refs.) |
|---|---|---|---|
| Maksymowych[a], 2014 | 1.36 | 1.01-1.72 | (17) |
| Maksymowych[b], 2014 | 1.37 | 1.01-1.72 | (17) |
| Maksymowych[a], 2015 | 1.38 | 1.04-1.72 | (26) |
| Maksymowych[b], 2015 | 1.38 | 1.03-1.72 | (26) |
| Gong[a], 2017 | 1.33 | 0.98-1.68 | (20) |
| Gong[b], 2017 | 1.36 | 1.02-1.71 | (20) |
| Mohamed[a], 2018 | 1.30 | 0.96-1.64 | (27) |
| Mohamed[b], 2018 | 1.29 | 0.95-1.62 | (27) |
| Shovman[a], 2018 | 1.34 | 1.01-1.66 | (16) |
| Shovman[b], 2018 | 1.34 | 1.01-1.66 | (16) |
| El-Sherif[a], 2019 | 1.38 | 1.04-1.71 | (28) |
| El-Sherif[b], 2019 | 1.34 | 1.00-1.68 | (28) |
| Guan, 2019 | 1.30 | 0.96-1.64 | (29) |
| Qu, 2019 | 1.30 | 0.96-1.63 | (30) |
| Salman, 2019 | 1.31 | 0.97-1.65 | (31) |
| Huang, 2020 | 1.30 | 0.96-1.64 | (14) |
| Zeng, 2020 | 1.33 | 0.98-1.67 | (18) |
| Zhang, 2020 | 1.26 | 0.98-1.54 | (12) |
| Hussin, 2021 | 1.39 | 1.05-1.72 | (15) |
| Adel, 2022 | 1.39 | 1.07-1.71 | (13) |
| Combined | 1.34 | 1.01-1.66 | |

B, 14-3-3η protein between osteoporosis and normal bone mass in RA, ng/ml

| Omitted study | Estimate, SMD | 95% CI | (Refs.) |
|---|---|---|---|
| Gong[a], 2017 | 2.23 | -0.23-4.69 | (20) |
| Gong[b], 2017 | 2.56 | 0.53-4.59 | (20) |
| Sun, 2020 | 1.38 | -0.43-3.18 | (19) |
| Zeng, 2020 | 2.29 | -0.23-4.82 | (18) |
| Adel, 2022 | 1.36 | -0.65-3.37 | (13) |
| Combined | 1.96 | 0.01-3.92 | |

C, 14-3-3η protein between osteopenia and normal bone mass in RA, ng/ml

| Omitted study | Estimate, SMD | 95% CI | (Refs.) |
|---|---|---|---|
| Gong[a], 2017 | 0.96 | 0.16-1.76 | (20) |
| Gong[b], 2017 | 0.99 | 0.28-1.71 | (20) |
| Sun, 2020 | 0.56 | -0.13-1.26 | (19) |
| Zeng, 2020 | 0.86 | 0.00-1.73 | (18) |
| Adel, 2022 | 0.63 | -0.24-1.51 | (13) |
| Combined | 0.80 | 0.09-1.52 | |

D, 14-3-3η protein between osteoporosis and osteopenia in RA, ng/ml

| Omitted study | Estimate, SMD | 95% CI | (Refs.) |
|---|---|---|---|
| Gong[a], 2017 | 1.26 | -0.35-2.87 | (20) |
| Gong[b], 2017 | 1.55 | 0.25-2.86 | (20) |
| Sun, 2020 | 0.75 | -0.47-1.97 | (19) |

Table IV. Continued.

| D, 14-3-3η protein between osteoporosis and osteopenia in RA, ng/ml | | | |
|---|---|---|---|
| Omitted study | Estimate, SMD | 95% CI | (Refs.) |
| Zeng, 2020 | 1.40 | -0.23-3.03 | (18) |
| Adel, 2022 | 0.82 | -0.60-2.23 | (13) |
| Combined | 1.16 | -0.15-2.46 | |

[a]Study reported 14-3-3η protein in early RA; [b]study reported 14-3-3η protein in established RA. SMD, standardized mean difference; CI, confidence interval; RA, rheumatoid arthritis; HCs, healthy control.

another study, the serum levels of 14-3-3η were associated with an increased risk of RA and disease severity (35). Of note, emerging evidence has suggested that 14-3-3η serves a vital role in bone metabolism (13,19). For instance, a study revealed that 14-3-3η was negatively associated with procollagen type I N-propeptide, a bone remodelling-related marker (19). Another study indicated that 14-3-3η could predict the onset of osteoporosis in patients with RA (13). However, comprehensive studies evaluating the effect of 14-3-3η on modulating disease severity and bone remodelling in patients with RA are still lacking. Therefore, the current meta-analysis was carried out to address the above issues.

The present meta-analysis showed that the serum levels of 14-3-3η were higher in patients with RA compared with healthy subjects. In addition, the above results were also observed in both patients with early and established RA. This finding may be due to the fact that 14-3-3η, a member of the 14-3-3 family of proteins, could promote the expression of several transcription factors to activate the gene expression levels of immune response-related factors (36). Therefore, 14-3-3η was upregulated in patients with RA. Furthermore, the members of the 14-3-3 family may also be involved in the regulation of protein phosphorylation and recognition, thus further promoting autoimmunity. In addition, it has been reported that members of the 14-3-3 family can also regulate the proliferation and apoptosis of T and B cells, thus leading to the dysregulation of the immune system (36).

A previous study suggested that the levels of 14-3-3η were associated with those of MMP-1 and MMP-9. In addition, another study showed that 14-3-3γ, another homolog of 14-3-3η, was involved in osteoclastogenesis via regulating the NF-κB pathway (37). Therefore, the role of 14-3-3η in regulating osteogenesis and osteoclast-related pathology *in vitro* and the corresponding underlying mechanism have attracted increasing attention. However, the association between the levels of 14-3-3η and bone injury in patients with RA remains controversial (19,20). Therefore, the present meta-analysis was carried out to make a solid conclusion. The results demonstrated that 14-3-3η was highly expressed in both patients with RA-related osteoporosis and osteopenia compared with those with normal bone mass. The above findings may be due to the fact that 14-3-3η could regulate bone remodelling in patients with RA and promote the function of osteoclasts through several pathways, including the NF-κB signalling pathway and MMP family members (19,20,37). Therefore, 14-3-3η was upregulated in patients with RA with osteoporosis and osteopenia compared with patients with RA with normal bone mass. Of note, an increasing trend in the serum levels of 14-3-3η was observed in patients with RA with osteoporosis compared with those with osteopenia. However, statistical significance was not reached. This result was significantly influenced by the results reported by Gong *et al* (20), since the sensitivity analysis showed that the difference in the serum levels of 14-3-3η between patients with osteoporosis and those with osteopenia became statistically significant after omitting the aforementioned study. More specifically, the standard deviation was too high in the above study, ~2-fold higher than the mean value, and therefore, its results significantly affected the results of the current meta-analysis. Therefore, more studies are needed to verify the effect of 14-3-3η on the onset of osteoporosis and osteopenia in patients with RA. In terms of the relation of 14-3-3η and radiographic progression during follow-up in patients with RA, only one study reported that synovial fluid but not serum 14-3-3η predict absolute radiographic progression in patients with RA (38). Therefore, more studies are needed to investigate this issue.

Although the current study revealed novel findings, and the significant role of 14-3-3η in bone remodelling in patients with RA, there are still some non-ignorable limitations: i) Several contradictory results could affect the results of the present study. Therefore, further studies are needed. Sensitivity analysis indicated that the robustness of the meta-analysis was not steady enough, and therefore, the results should be further validated in future studies; iii) *in vitro* and *in vivo* studies are needed to clarify the role of 14-3-3η in regulating bone remodelling and its detailed underlying mechanism; iv) certain articles may have been missed that were not published in the databases used for the search of studies for the present meta-analysis, leading to potential publishing bias; v) further larger, well-designed prospective studies are needed to confirm the diagnostic value of 14-3-3η proteins in RA; vi) the studies analysed referred to patients with definite RA but not those hard to diagnose, leading to a greater diagnostic evaluation; and vii) the method to detect 14-3-3η in analysed studies was the same, i.e. ELISA, but the kits, sensitivity and range differed among studies, which may have affected the pooled findings.

In conclusion, the current study demonstrated that the serum levels of 14-3-3η were increased and were associated with a higher risk of osteoporosis in patients with RA,

thus supporting its potency as a circulating biomarker in the management of RA. However, further studies are needed to address these issues and confirm the value of 14-3-3η proteins in the diagnosis of RA.

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

RF and YZ contributed to the conception and design of the study. JZ, YX, LG and ZY contributed to data acquisition. RF, JZ and YZ performed the statistical analysis. All authors drafted and revised the manuscript. RF and YZ confirm the authenticity of all the raw data. All authors contributed to the article and have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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