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Review

Gene polymorphism and serum level of RANKL among patients with rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

Receptor activator of nuclear factor-κB ligand (RANKL) is a key mediator linking inflammation to osteoclast activation and bone erosion in rheumatoid arthritis (RA). Evidence on circulating RANKL levels and RANKL (TNFSF11) polymorphisms in RA has been inconsistent. Web of Science, Scopus, and PubMed were searched from inception to December 2025 for clinical studies comparing patients with RA and healthy controls and reporting either serum/plasma RANKL concentrations and/or RANKL genotype/allele distributions. Mean differences (MD) were pooled for circulating RANKL, and odds ratios (OR) were pooled for polymorphisms under allelic, dominant, and recessive models. Ten studies (908 RA; 525 controls) were included for serum RANKL. Serum RANKL was higher in RA than controls (pooled MD 8.16, 95% CI 3.90–12.41). For genetic analyses, three SNPs were eligible for pooling. rs9533156 showed a significant association with RA in the allelic (C vs T: OR 0.82, 95% CI 0.70–0.97) and dominant models (CC+CT vs TT: OR 0.77, 95% CI 0.61–0.98). rs2277438 showed a borderline allelic association (OR 1.21, 95% CI 1.00–1.45) and model-dependent results for the recessive contrast with heterogeneity. RA is associated with increased circulating RANKL, while genetic associations appear SNP-specific, with the most consistent evidence observed for rs9533156. Larger, multi-ethnic studies with standardized biomarker measurements are needed.

Keywords: Genetic polymorphism, RANK Ligand, Rheumatoid arthritis, Biomarkers, Osteoprotegerin.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovitis, progressive cartilage destruction, and structural bone damage that can lead to disability and reduced quality of life. Although its clinical presentation is dominated by joint pain, swelling, and stiffness, RA is fundamentally a systemic immune disorder in which aberrant activation of innate and adaptive pathways sustains inflammation and reshapes tissue homeostasis [1-3]. One of the defining pathological features of RA is the tendency toward periarticular bone erosion, a process driven not only by inflammatory mediators but also by dysregulated bone remodeling within the joint microenvironment. Understanding the molecular signals that connect immune activation to osteoclast formation and bone resorption remains essential for explaining disease heterogeneity, identifying individuals at higher risk of severe structural damage, and refining prevention and treatment strategies [4-6].

Among the pathways that couple inflammation to skeletal destruction, the Receptor activator of nuclear factor-κB/Receptor activator of nuclear factor-κB ligand/osteoprotegerin (RANK/RANKL/OPG) axis occupies a central position. RANKL is a key osteoclastogenic factor that binds to its receptor RANK on osteoclast precursors and promotes their maturation and activity, while OPG acts as a soluble decoy receptor that counterbalances this effect. In RA, inflammatory cytokines and activated immune cells within the synovium can enhance RANKL expression, tipping the balance toward osteoclast activation and erosive damage [7-10]. Because RANKL is measurable in circulation, serum levels have been investigated as a potential biomarker reflecting disease activity, bone turnover, or propensity for structural progression. However, published findings are not fully consistent, likely due to variations in study populations, disease duration and treatment exposure, comorbidities, and laboratory assays. Clarifying whether RA is reliably associated with altered serum RANKL, and estimating the magnitude of any difference, could strengthen the rationale for biomarker-guided research and help interpret RANKL measurements across clinical contexts [2, 11].

In parallel, genetic variation may influence RA susceptibility and its skeletal manifestations by altering immune regulation, inflammatory set points, or expression of bone-remodeling mediators. Single nucleotide polymor-

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phisms (SNPs) within or near the RANKL gene have been explored as candidate variants that might modify risk of developing RA or affect downstream pathways involved in erosions [6, 10, 12]. Yet, individual genetic association studies often have limited sample sizes and are conducted in specific ancestries, making results prone to imprecision and population-specific effects. Moreover, the relationship between RANKL polymorphisms and circulating RANKL concentrations remains uncertain, and different genetic models (allelic, dominant, recessive) may yield different conclusions. Therefore, the present systematic review and meta-analysis aimed at comparing serum RANKL levels between patients with RA and healthy controls and to evaluate the association of commonly reported RANKL polymorphisms with RA risk.

2. Methods and Materials

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Systematic search

A comprehensive search was conducted in Web of Science, Scopus, and PubMed from inception through December 2025, using a combination of controlled vocabulary (e.g., Medical Subject Headings/ Elsevier's Life Science Thesaurus (MeSH/EMTREE), where applicable) and free-text keywords related to RANKL and rheumatoid arthritis. The search strategy combined RANKL terms ("receptor activator of nuclear factor kappa-B ligand" OR "RANKL" OR "Tumor Necrosis Factor Superfamily Member 11" OR "TNFSF11" OR "osteoprotegerin ligand" OR "OPGL" OR "TNF-Related Activation-Induced Cytokine" OR "TRANCE" OR "Osteoclast Differentiation Factor" OR "ODF") with rheumatoid arthritis terms ("rheumatoid arthritis" OR "RA") and, when relevant, biomarkers and genetic terms to capture both circulating levels and polymorphism studies ("serum" OR "plasma" OR "level" OR "concentration" OR "Enzyme-Linked Immunosorbent Assay" OR "ELISA" "expression" OR "polymorphism" OR "variant" OR "genotype" OR "allele" OR "single nucleotide polymorphism" OR "SNP"). The search was restricted to studies that compared patients with RA to healthy controls and reported either serum RANKL measurements and/or RANKL genotype/allele distributions. In addition, the reference lists of included articles and relevant reviews were manually screened to identify additional eligible studies.

2.2. Inclusion and eligibility criteria

Eligibility was defined using a PICO framework tailored to RANKL gene polymorphisms and serum RANKL levels in rheumatoid arthritis. We included full-text human clinical studies enrolling patients diagnosed with rheumatoid arthritis according to established criteria (e.g., American College of Rheumatology / European Alliance of Associations for Rheumatology (ACR/EULAR) or equivalent) and an appropriate healthy control group. The exposure of interest was either: (1) circulating RANKL measured in serum (or plasma when reported) using validated laboratory methods (e.g., ELISA or comparable immunoassays) with extractable summary statistics (mean and standard deviation/standard error, or data convertible to these), and/or (2) RANKL (TNFSF11) genetic variants, where studies reported genotype and/or allele distributions for extractable comparisons between RA and controls under standard genetic models (allelic, dominant, recessive). The primary outcomes were (a) the difference in serum RANKL levels between RA patients and controls and (b) the association between RANKL polymorphisms and RA susceptibility, expressed as odds ratios. We excluded animal or in vitro studies; case reports, reviews, editorials, and conference abstracts without complete data; studies without a healthy control group; pediatric-only cohorts; studies that assessed outcomes unrelated to RA; genetic studies lacking usable genotype/allele counts; biomarker studies that did not provide extractable quantitative RANKL data (or data convertible for pooling); and duplicate or overlapping datasets (in which case the most complete or most recent report was retained).

2.3. Data extraction and outcome measures

Data extraction was performed independently by two reviewers using a standardized, piloted form, and any discrepancies were resolved through discussion and, when needed, adjudication by a third reviewer. From each eligible study, we extracted: first author, publication year, country/setting, study design, diagnostic criteria for rheumatoid arthritis, sample size of RA and control groups, and key participant characteristics when reported (e.g., age and sex distribution). For the biomarker component, we recorded the biological matrix (serum or plasma), assay method and platform (e.g., ELISA and manufacturer if available), reporting units, and extractable quantitative data for RANKL in RA and controls (mean and dispersion measures such as Standard Deviation/Standard Error (SD/SE), or values convertible for meta-analysis). For the genetic component, we recorded the RANKL gene variant(s) investigated (SNP identifiers), genotyping method (if reported), and genotype and/or allele counts in cases and controls. We extracted or calculated study-level effect measures as appropriate, including mean differences for circulating RANKL and odds ratios with 95% confidence intervals for RA susceptibility under prespecified genetic models (allelic, dominant, and recessive). When studies reported results for multiple genetic contrasts or multiple datasets, we preferentially used the most complete dataset and harmonized the reference allele/genotype coding to ensure consistent direction of effect across studies; alternative contrasts or subgroup results were retained when available for descriptive reporting or potential sensitivity analyses.

2.4. Statistical analysis and data synthesis

Pooled estimates were calculated separately for serum RANKL levels and RANKL polymorphism–RA associations. For circulating RANKL, the effect size was expressed as the mean difference (MD) between rheumatoid arthritis patients and healthy controls, using study-level means and SDs (or values convertible to these). For genetic analyses, the association between each RANKL single nucleotide polymorphism and RA susceptibility was summarized as odds ratios (OR) with 95% confidence intervals (CI) under prespecified allelic, dominant, and recessive genetic models. When pooling ORs, logarithmic transformations of the ORs and their corresponding SEs were used for meta-analysis. Between-study heterogeneity was evaluated using the I^2 statistic and Cochran's Q test,

and pooled results were generated using fixed-effect and/or random-effects models as appropriate based on heterogeneity and the number of available studies. Forest plots were created to display individual study estimates, pooled effects, and heterogeneity measures for each outcome and genetic model. Where feasible, publication bias was explored using funnel plots, recognizing that formal assessment has limited power when few studies contribute to a given meta-analysis. All statistical analyses and figure generation were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio Inc., Boston, MA).

3. Results

Our initial search yielded 3,114 articles from PubMed, Scopus, and Web of Science, from which we eliminated 1,236 duplicates. After reviewing the titles and abstracts of the remaining 1,878 records, we retrieved 46 full-text articles for further evaluation. Ultimately, 13 studies [13-25] met our eligibility criteria and were included in the systematic review and meta-analysis (Fig. 1). Detailed characteristics of the included studies are summarized in Tables 1 and 2.

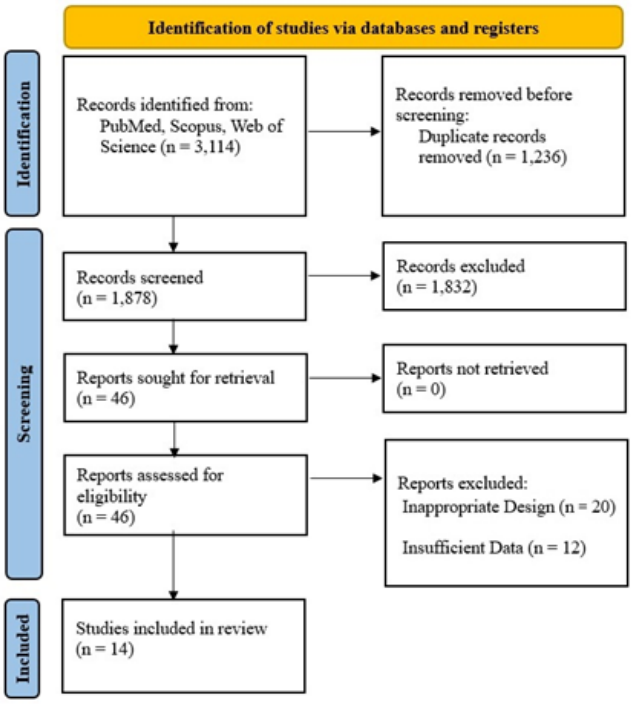


Fig. 1. PRISMA flow diagram for study selection.

Table 1. RANKL levels among the included studies.

Author	Year	Design	Country	Cases	Ct	RANKL Serum Level					
						RA			Control		
						M	SD	N	M	SD	N
Tan [14]	2010	RCS[1]	USA	23	24	6.4	6.1	23	2.6	1.8	24
Ellabban [15]	2012	CSS[2]	Egypt	24	13	40.23	55	24	36.8	33.2	13
Xu [16]	2014	CCS[3]	China	200	201	79.6	43.5	113	70.1	30.6	100
Mohamed [17]	2016	CCS	Egypt	172	176	10.8	8.92	172	2.86	2.65	176
Boman [19]	2017	CCS	Sweden	407	71	6.6	6.7	407	2.4	1.9	71
Li [20]	2020	CCS	China	60	20	336	275	60	103	31	20
Hussein [21]	2022	CCS	Egypt	60	30	240	159	16	148	14	5
Quaresma [22]	2023	CSS	Brazil	33	18	85	61	15	65	36	18
Balci [18]	2017	RCT[4]	Turkey	18	18	23.4	14.2	18	14.1	13.1	18
Mo[24]	2024	CCS	China	60	80	231	190	60	123.1	86	80

[1] RCS: Retrospective Cohort Study, [2] CSS: Cross-Sectional Study, [3] CCS: Case-Control Study, [4] RCT: Randomized Controlled Trial.

Table 2. RANKL polymorphism among the included studies.

Author	Year	Type	Polymorphism									
			RA					Control				
			C	T	CC	CT	TT	C	T	CC	CT	TT
Assmann [13]	2010	rs9533156	450	578	101	248	165	495	533	123	249	142
Mohamed [17]	2016	rs9525641	127	217	31	65	76	137	215	34	69	73
Arturo [23]	2024	rs9533156	65	123	13	39	42	110	158	22	66	46
			A	**G**	**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**
Assmann [13]	2010	rs2277438	820	192	342	136	38	860	164	360	140	12
Xu [16]	2014	rs3102735	342	58	146	50	4	313	63	131	51	6
		rs2277438	280	120	95	90	15	275	101	99	77	12
Pei [25]	2025	rs875625	287	351	71	145	103	298	362	76	146	108
			C	**G**	**CC**	**CG**	**GG**	**C**	**G**	**CC**	**CG**	**GG**
Xu [16]	2014	rs2073618	109	291	16	77	107	96	274	13	70	102
Arturo [23]	2024	rs9533155	117	71	44	29	21	121	147	44	33	57
Pei et al. [25]	2025	rs9533155	267	371	61	145	113	272	388	64	144	122
			G	**T**	**GG**	**GT**	**TT**	**G**	**T**	**GG**	**GT**	**TT**
Assmann [13]	2010	rs1054016	598	438	178	242	98	564	456	161	242	107

3.1. Study characteristics

For serum RANKL, the 10 included studies were conducted in the USA, Egypt, China, Sweden, Brazil, and Turkey, and included a mix of retrospective/clinical case–control and cross-sectional designs plus one randomized clinical trial. For genetics, polymorphism data were available for the following SNPs: rs9533156, rs9525641, rs2277438, rs3102735, rs875625, rs2073618, rs9533155, and rs1054016, with genotype and allele counts extracted for RA and control groups. Only rs9533156, rs2277438, and rs9533155 were reported by at least two studies and therefore could be meta-analyzed. The pooled meta-analysis of serum RANKL levels is presented in Fig. 2.

3.2. Serum RANKL levels

In the pooled analysis of serum RANKL, there were 908 patients with RA and 525 healthy controls. Individual studies generally showed higher mean serum RANKL levels in RA than controls, although the magnitude varied widely, ranging from small differences (e.g., Ellabban 2012) to very large differences (e.g., Li 2020 and Mo 2024). Forest plots for these associations are shown in Fig. 3.

3.3. Pooled mean difference

When results were pooled, serum RANKL levels were significantly higher in RA than in healthy controls under both fixed- and random-effects models. The fixed-effect pooled MD was 5.12 (95% CI 4.46 to 5.78; Z = 15.24; P < 0.0001). The random-effects pooled MD was 8.16 (95% CI 3.90 to 12.41; Z = 3.76; P = 0.0002). Between-study heterogeneity was substantial, with $Tau^2 = 18.621$, $Chi^2 = 84.13$ (degrees of freedom (df) = 9), P < 0.0001, and $I^2 = 89\%$. The prediction interval for the random-effects model was −2.77 to 19.08, indicating that while the average effect favored higher RANKL in RA, the true effect in a future comparable study could plausibly include little difference (or even lower levels), depending on population and study context. The forest plots summarizing these analyses are presented in Fig. 4.

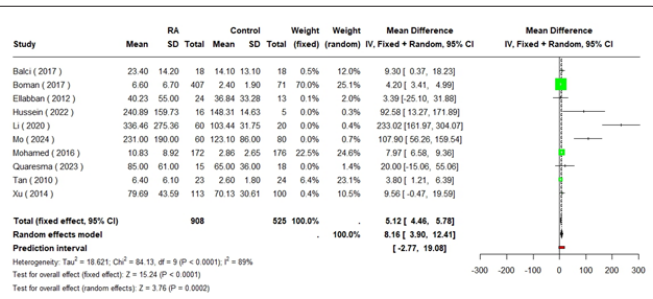


Fig. 2. Forest plot of pooled mean difference (MD) for serum RANKL levels (RA vs. healthy controls).

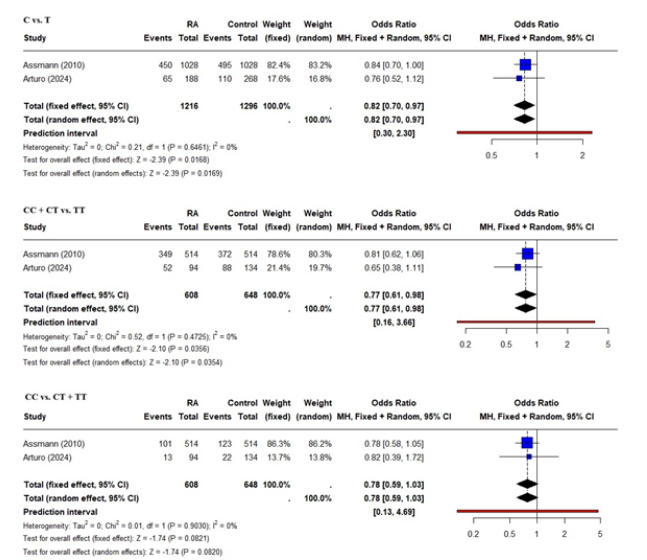


Fig. 3. Forest plot of pooled odds ratio (OR) for the association between rs9533156 polymorphism and rheumatoid arthritis: (A) allelic (C vs. T), (B) dominant (CC+CT vs. TT), and (C) recessive (CC vs. CT+TT) models.

3.4. RANKL polymorphisms

For the three SNPs reported by ≥2 studies (rs9533156, rs2277438, rs9533155), we synthesized associations using allelic, dominant, and recessive genetic models (as shown in our forest plots). For the remaining SNPs, data came from only one study each and were therefore not pooled. Forest plots depicting these results can be found in Fig. 5.

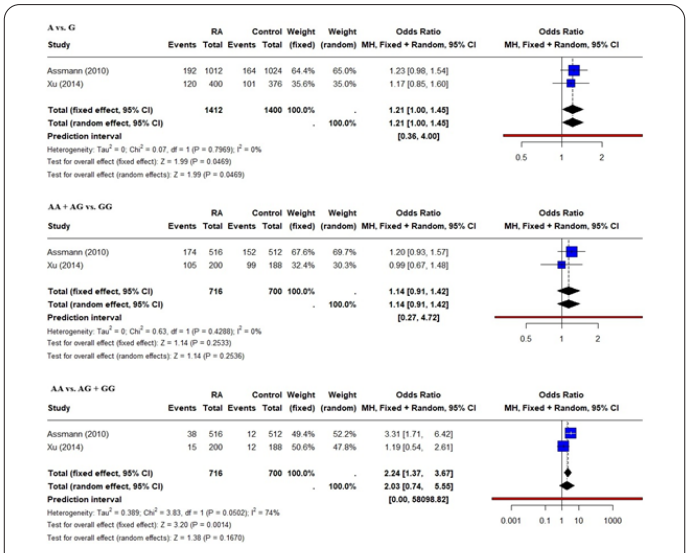


Fig. 4. Forest plot of pooled odds ratio (OR) for the association between rs2277438 polymorphism and rheumatoid arthritis: (A) allelic (A vs. G), (B) dominant (AA+AG vs. GG), and (C) recessive (AA vs. AG+GG) models.

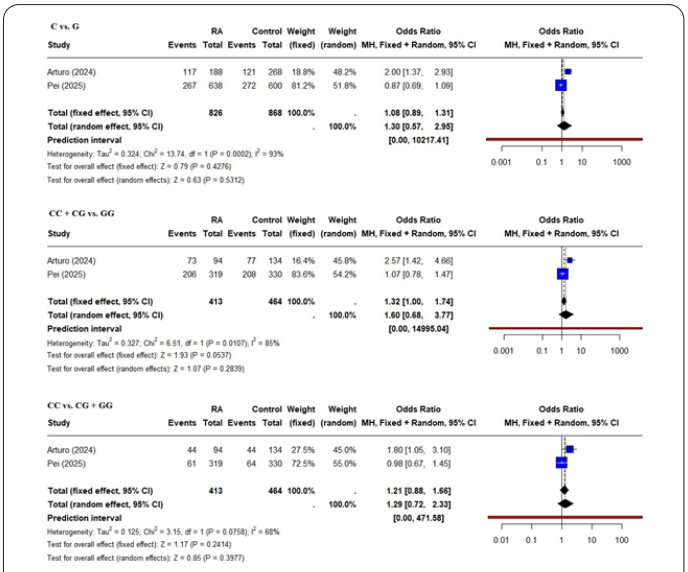


Fig. 5. Forest plot of pooled odds ratio (OR) for the association between rs9533155 polymorphism and rheumatoid arthritis: (A) allelic (C vs. G), (B) dominant (CC+CG vs. GG), and (C) recessive (CC vs. CG+GG) models.

3.5. rs9533156

Two studies (Assmann 2010 and Arturo 2024) contributed data for rs9533156. In the allelic comparison (C vs T), the pooled OR was 0.82 (95% CI 0.70 to 0.97) with I^2 = 0%, indicating no observed heterogeneity, and the overall effect was statistically significant (P≈0.017). In the dominant model (CC+CT vs TT), the pooled OR was 0.77 (95% CI 0.61 to 0.98) with I^2 = 0% and a significant overall effect (P≈0.036). In the recessive model (CC vs CT+TT), the pooled OR was 0.78 (95% CI 0.59 to 1.03) with I^2 = 0%, but the overall effect was not statistically significant (P≈0.082). Overall, rs9533156 showed evidence of an association with RA under the allelic and dominant models (OR<1), while the recessive model did not reach statistical significance.

3.6. rs2277438

Two studies (Assmann 2010 and Xu 2014) contributed data for rs2277438. In the allelic model, the pooled OR was 1.21 (95% CI 1.00 to 1.45) with I^2 = 0%, and the overall effect was borderline but statistically significant (P≈0.047). In the dominant model, the pooled OR was 1.14 (95% CI 0.91 to 1.42) with I^2 = 0%, and the overall effect was not significant (P≈0.253). In the recessive model, the fixed-effect pooled OR was 2.24 (95% CI 1.37 to 3.67) with statistical significance; however, heterogeneity was substantial (I^2 = 74%) and the random-effects pooled estimate was attenuated and not significant (OR = 2.03, 95% CI 0.74 to 5.55; P≈0.167), with a very wide prediction interval, reflecting major between-study uncertainty. Taken together, rs2277438 showed a weak/borderline allelic association, while conclusions for the recessive model were sensitive to heterogeneity and model choice.

3.7. rs9533155

Two studies (Arturo 2024 and Pei 2025) contributed data for rs9533155. In the allelic model (C vs G), the pooled effect was not statistically significant (fixed-effect OR = 1.08, 95% CI 0.89 to 1.31; random-effects OR = 1.30, 95% CI 0.57 to 2.95), and heterogeneity was very high (I^2 = 93%). In the dominant model (CC+CG vs GG), the fixed-effect estimate was borderline (OR = 1.32, 95% CI 1.00 to 1.74, P≈0.054), but the random-effects estimate was not significant (OR = 1.60, 95% CI 0.68 to 3.77) with high heterogeneity (I^2 = 85%). In the recessive model (CC vs CG+GG), neither fixed-effect (OR = 1.21, 95% CI 0.88 to 1.66) nor random-effects (OR = 1.29, 95% CI 0.72 to 2.33) pooling showed statistical significance, and heterogeneity remained moderate to high (I^2 = 68%). Overall, rs9533155 showed no clear evidence of association with RA across genetic models, and no consistent association across studies was observed due to substantial heterogeneity. A funnel plot to assess potential publication bias for the serum RANKL analysis is provided in Fig. 6.

3.8. Additional RANKL SNPs

Several SNPs were reported by only one study each (and therefore were not pooled): rs9525641 (Mohamed 2016), rs3102735 and rs2073618 (Xu 2014), rs875625 (Pei 2025), and rs1054016 (Assmann 2010). For these variants, our tables provide the allele and genotype distributions for RA and controls, but no meta-analytic summary estimate was produced due to the lack of replication across studies.

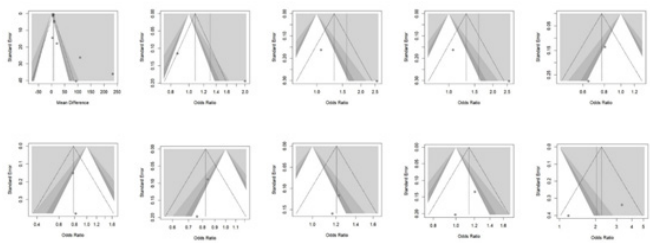


Fig. 6. Funnel plot for assessment of publication bias in studies reporting serum RANKL levels.

4. Discussion

This systematic review and meta-analysis aimed to clarify whether serum RANKL levels and RANKL gene polymorphisms are associated with rheumatoid arthritis (RA) compared with healthy subjects. Across 10 studies including 908 patients with RA and 525 controls, serum RANKL was higher in RA than in controls, with a significant pooled effect under both fixed-effect (MD 5.12, 95% CI 4.46–5.78) and random-effects models (MD 8.16, 95% CI 3.90–12.41), although heterogeneity was substantial (I^2 = 89%) and the prediction interval crossed the null (−2.77 to 19.08). In the genetic analyses (based on the SNPs reported by ≥2 studies), rs9533156 showed evidence of association with RA in the allelic (C vs T) and dominant (CC+CT vs TT) models with consistent effects across studies (I^2=0% in both), whereas rs2277438 showed a borderline allelic association and an unstable recessive-model result due to heterogeneity, and rs9533155 showed no clear association overall with very high heterogeneity between the two contributing studies.

When individual studies were examined, most reported higher mean serum RANKL levels in RA than in controls, but the size of the difference varied markedly, from small differences in some cohorts to very large differences in others. Our pooled analysis aligns with the overall direction seen in the majority of included studies by demonstrating higher circulating RANKL in RA, but it also highlights that the magnitude is not uniform across settings, which is reflected by the high I^2 and a prediction interval that includes small or null effects [2, 11].

This pattern suggests that differences in study populations (e.g., disease stage, inflammatory burden), laboratory methods, or treatment exposure likely influence measured RANKL levels and may explain why some single studies observed modest contrasts while others reported very large separations [26-28]. For rs9533156, the two eligible case–control studies reported effect estimates in the same direction (ORs <1 in the allelic and dominant contrasts), and our meta-analysis preserved this consistency by showing statistically significant pooled associations in both the allelic and dominant models with no heterogeneity (I^2=0%). In practical terms, our findings strengthen the inference suggested by the original reports: the association is not driven by one dataset alone and appears reproducible across at least two distinct populations. At the same time, the lack of a significant association in the recessive model indicates that the relationship may operate through carrier status rather than requiring homozygosity, although this interpretation remains tentative given the limited number of studies [29-31].

In contrast, our results for rs2277438 and rs9533155 mirror the mixed signals seen in the primary literature. For

rs2277438, the allelic results were consistent enough to yield a borderline pooled effect with minimal heterogeneity, but the recessive comparison showed pronounced between-study differences, one study suggesting a stronger homozygote effect while the other suggested a more modest or uncertain association, leading to divergent conclusions depending on whether fixed- or random-effects pooling was emphasized.

For rs9533155, the two contributing studies pointed in opposite directions for some contrasts (one indicating increased susceptibility and the other clustering near the null), which translated into very high heterogeneity and a non-significant pooled estimate. Collectively, these findings suggest that certain RANKL variants may be population-sensitive, potentially modified by ancestry, linkage disequilibrium patterns, or clinical factors such as therapy or disease phenotype.

RANKL is a central mediator linking immune activation to osteoclast differentiation and bone resorption, which makes it biologically plausible that elevated circulating RANKL accompanies RA and contributes to erosive disease. From a clinical perspective, a higher serum RANKL signal can be interpreted as an integrated readout of inflammatory cytokine activity and bone-remodeling imbalance; therefore, it has potential utility as a biomarker reflecting ongoing joint damage risk, particularly when interpreted alongside complementary markers (such as OPG) and imaging findings [32-34]. At the genetic level, polymorphisms within the RANKL locus may influence gene regulation or expression (directly or through linked variants), thereby shifting the threshold for osteoclast activation in inflammatory environments. Our pattern of findings, clear elevation of serum RANKL in RA plus selective genetic associations (more consistent for rs9533156 than for rs9533155), supports a model in which RANKL activity is important to RA biology, but genetic contribution may differ across variants and populations. Conceptually, combining genotype information (susceptibility or protective variants) with measured serum RANKL could improve risk stratification, help explain heterogeneity in erosive outcomes, and guide future studies testing whether genetic background modifies biomarker levels or treatment response in the RANKL pathway [35-37].

This study has several limitations. First, the serum RANKL meta-analysis showed substantial heterogeneity (I^2=89%), likely reflecting differences in assay methods, clinical characteristics, and treatment exposure across cohorts, and the prediction interval indicated that the effect size may vary widely between settings. Second, the polymorphism meta-analyses were based on only two studies per pooled SNP, which limits power, reduces the reliability of between-study variance estimates, and constrains exploration of ethnicity- or phenotype-specific effects. Finally, several potentially important analyses (e.g., subgrouping by disease activity, erosive status, medication use, or laboratory platform, and robust assessment of publication bias) were not feasible with the currently available number of studies and reporting detail.

Conclusions

In conclusion, this systematic review and meta-analysis indicate that serum RANKL levels are higher in patients with rheumatoid arthritis than in healthy subjects, supporting the involvement of the RANKL pathway in RA pathogenesis and bone-destructive processes. Genetic evidence was more variant-specific: rs9533156 showed a consistent association with RA in the allelic and dominant models with no detectable heterogeneity, whereas results for rs2277438 were modest and model-dependent, and rs9533155 showed no clear association and substantial inconsistency between studies. Overall, these findings suggest that dysregulation of RANKL is a reproducible feature of RA, while the contribution of RANKL polymorphisms may depend on the specific SNP and population studied; therefore, larger multi-ethnic studies with standardized biomarker measurement and unified genetic modeling are needed to confirm susceptibility signals and clarify how genetic variation relates to circulating RANKL levels and clinical severity.

Abbreviation

ACR/EULAR (American College of Rheumatology / European Alliance of Associations for Rheumatology); CCS (Clinical Case-Control Study); CI (Confidence Interval); CSS (Cross-Sectional Study); df (Degrees of Freedom); ELISA (Enzyme-Linked Immunosorbent Assay); EMTREE (Elsevier's Life Science Thesaurus); I^2 (I-squared statistic); MD (Mean Difference); MeSH (Medical Subject Headings); ODF (Osteoclast Differentiation Factor); OPG (Osteoprotegerin); OPGL (Osteoprotegerin Ligand); OR (Odds Ratio); PICO (Population, Intervention, Comparison, Outcome); PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses); RA (Rheumatoid Arthritis); RANK (Receptor Activator of Nuclear factor-κB); RANKL (Receptor Activator of Nuclear factor-κB Ligand); RCS (Retrospective Cohort Study); RCT (Randomized Controlled Trial); SD (Standard Deviation); SE (Standard Error); SNP (Single Nucleotide Polymorphism); TNFSF11 (Tumor Necrosis Factor Superfamily Member 11); TRANCE (TNF-Related Activation-Induced Cytokine)

Conflict of interest

The authors declare that they have no conflicts of interest related to this study.

Consent for publications

All authors have read and approved the final version of the manuscript and consent to its publication.

Availability of data and material

All data analyzed during this study are included in this published article.

Authors' contributions

P.S. contributed to the conception and design of the study, data acquisition, analysis, and drafting of the manuscript. A.S. participated in data extraction, statistical analysis, and critical revision of the manuscript. F.Y. supervised the study, contributed to study design and interpretation of data, and critically reviewed and finalized the manuscript. All authors read and approved the final manuscript.

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