INPLASY PROTOCOL

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Corresponding author:
Yun Gao

gaoyun@ncu.edu.cn

Author Affiliation:
Nanchang University.

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Relationship between LGALS3 gene rs4644 and rs4652 polymorphisms and susceptibility to rheumatoid arthritis: a meta-analysis and trial sequential analysis

Yang, CS[1]; Tian, Y[2]; Tian, HK[3]; Wen, LQ[4]; Gao, Y[5].

Review question / Objective: **In recent years, many studies on the influence of LGALS3 rs4644 and rs4652 polymorphisms and rheumatoid arthritis risk have been conducted, but the results are controversial. The aim of this study was to conduct a meta-analysis and trial sequential analysis (TSA) of the relationship between LGALS3 rs4644 and rs4652 polymorphisms and susceptibility to rheumatoid arthritis.**
Eligibility criteria: **Case–control studies that were published online were expected to be included, regardless of sex, race, and age. The studies were required to have at least two groups – an RA case group and a healthy control group – and provide the number of specific genotypes for both groups. Studies that did not involve human participants were excluded. In cases where the data were duplicated in multiple publications, we selected the earliest publication for inclusion in the analysis. Studies with incomplete data that could not be obtained even after contacting the corresponding author were excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 April 2023 and was last updated on 24 April 2023 (registration number INPLASY202340082).

INTRODUCTION

Review question / Objective: **In recent years, many studies on the influence of LGALS3 rs4644 and rs4652 polymorphisms and rheumatoid arthritis risk have been conducted, but the results are controversial. The aim of this study was to conduct a meta-analysis and trial sequential analysis (TSA) of the relationship between LGALS3 rs4644 and rs4652 polymorphisms and susceptibility to rheumatoid arthritis.**

Condition being studied: **The aim of this study was to conduct a meta-analysis and**

trial sequential analysis (TSA) of the relationship between LGALS3 rs4644 and rs4652 polymorphisms and susceptibility to rheumatoid arthritis. The included original studies were required to have at least two groups – an RA case group and a healthy control group – and provide the number of specific genotypes for both groups. The first author, publication year, country, and the number of sample for each genotype in each group were also recorded.

METHODS

Search strategy: Embase, Web of Science, PubMed, Wanfang (Chinese), VIP (Chinese), and CNKI (Chinese) databases were used for article retrieval. The keywords used in the database searches included LGALS3, "galectin 3" [MeSH], rheumatoid arthritis, and "arthritis, rheumatoid" [MeSH]. Articles that met the inclusion criteria were retrieved from the database establishment to 1 March 2023.

Participant or population: The included original studies were required to have at least two groups – an RA case group and a healthy control group – and provide the number of specific genotypes for both groups.

Intervention: CC, CA and AA genotypes of LGALS3 gene rs4644 and rs4652 polymorphisms.

Comparator: CC vs AA, CC+CA vs AA, CC vs CA+AA, CC vs CA, CA vs AA, C vs A.

Study designs to be included: Case–control studies that evaluated the relationship between LGALS3 gene rs4644 and rs4652 polymorphisms and susceptibility to rheumatoid arthritis were included. After article screening, data extraction and quality evaluation, meta-analysis was conducted using RevMan software. Sensitivity analysis was conducted by one-by-one exclusion method. Publication bias analysis was conducted by Stata software using Begg's and Egger's test. Trial sequential analysis was conducted using TSA software.

Eligibility criteria: Case–control studies that were published online were expected to be included, regardless of sex, race, and age. The studies were required to have at least two groups – an RA case group and a healthy control group – and provide the number of specific genotypes for both groups. Studies that did not involve human participants were excluded. In cases where the data were duplicated in multiple publications, we selected the earliest publication for inclusion in the analysis. Studies with incomplete data that could not be obtained even after contacting the corresponding author were excluded.

Information sources: Embase, Web of Science, PubMed, Wanfang (Chinese), VIP (Chinese), and CNKI (Chinese) databases.

Main outcome(s): Results: Seven case–control studies from four articles were included in the analysis. For rs4644, the CC vs. AA, CC vs. CA + AA, and C vs. A all outcomes showed odds ratios (ORs) < 1 and P-values < 0.05. For rs4652, the CC + CA vs. AA, CA vs. AA, and C vs. A all outcomes showed ORs > 1 and P-values < 0.05. The dependability of the conclusions of the meta-analysis was not likely to be affected by publication bias. Sensitivity analysis and TSA revealed that the conclusions were somewhat unstable and had the chance of false negatives or false positives owing to the limited number of included samples.

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of each included article. The methodological quality and potential risk of bias of the case–control studies were mainly evaluated using the NOS. These evaluations were performed independently by two authors of our paper, and any conflict was resolved with the assistance of a third party.

Strategy of data synthesis: RevMan 5.4, StataMP 17, and TSA 0.9.5.10 beta were used to perform statistical analysis in this study. The significance threshold for statistical tests was set at 0.05. P-values were used to measure heterogeneity. A

fixed-effects model was selected for the meta-analysis because the P-value was greater than 0.05 in the heterogeneity test, indicating that there was no significant heterogeneity. Conversely, a random-effects model was used when considerable heterogeneity was observed. After the meta-analysis, the pooled odds ratios (ORs), P-values, and 95% confidence intervals (95% CIs) were reported. A one-by-one exclusion procedure was applied to perform the sensitivity analysis. Begg's and Egger's tests were used to assess publication bias. TSA was used to examine random errors, such as false negatives and positives, in repeatedly updated meta-analyses and to determine the required sample size to provide robust results.

Subgroup analysis: N/A.

Sensitivity analysis: A one-by-one exclusion procedure was applied to perform the sensitivity analysis.

Country(ies) involved: China, Iran, India.

Keywords: LGALS3; rheumatoid arthritis; gene polymorphism; meta-analysis; trial sequential analysis.

Contributions of each author:
Author 1 - Changsen Yang.
Author 2 - Ye Tian.
Author 3 - Haokun Tian.
Author 4 - Lequan Wen.
Author 5 - Yun Gao.