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Association between the NLRP3 rs10157379 and rs10754558 genetic variants with rheumatoid arthritis activity, autoantibodies, and inflammatory biomarkers

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Abstract

Background

The contribution of *NLRP3* variants to rheumatoid arthritis (RA) pathogenesis remains unclear.

Objective

To investigate the association of the *NLRP3* rs10754558 C > G and rs10157379 C > T variants with RA disease activity, rheumatoid factor (RF), anti-cyclic citrullinated peptide (ACPAs) antibodies, and inflammatory biomarkers.

Methods

The study included 262 patients with RA and 168 controls. Disease activity was assessed using the Disease Activity Score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR) and categorized as remission (< 2.6) or moderate/severe activity (≥ 2.6). *NLRP3* variants were genotyped by real-time polymerase chain reaction. RF, ACPAs, C-reactive protein (CRP), white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), WBC-to-hemoglobin ratio (WHR), and lymphocyte-to-CRP ratio (LCR) were evaluated.

Results

The TT genotype of the rs10157379 variant, under the recessive model, was associated with an increased likelihood of active disease [odds ratio (OR): 2.96, 95% confidence interval (95% CI): 1.16–7.59, p = 0.023], whereas the TC genotype showed a protective effect under codominant and overdominant models (OR: 0.28, 95% CI: 0.10–0.75, p = 0.011 and OR: 0.36, 95% CI: 0.16–0.82, p = 0.011, respectively). Carriers of the CC or CG genotypes of rs10754558 exhibited higher LCR values compared with GG carriers. Carriers of the TT genotype of rs10157379 showed higher WHR than TC carriers. Both variants were not associated with RF or ACPAs seropositivity.

Conclusion

The *NLRP3* rs10157379 appears to modulate RA disease activity and inflammatory profiles, whereas neither the rs10157379 nor the rs10754558 variants was associated with RF and ACPAs. These findings support a role for *NLRP3* genetic variability in RA disease activity and in the inflammatory integrative biomarkers.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that primarily affects synovial joints, leading to progressive bone damage, functional disability, and an increased risk of cardiovascular events [1]. RA susceptibility arises from a complex interplay between genetic and environmental factors. The strongest associations include female sex, a family history of RA, the presence of the human leukocyte antigen (HLA)-shared epitope, tobacco smoking, mucosal inflammation, and microbial influences [2].

RA pathogenesis is characterized by synovial membrane hyperplasia driven by the infiltration of inflammatory cells, including T and B lymphocytes, macrophages, neutrophils, and dendritic cells. This cellular influx promotes excessive production of proinflammatory cytokines and proteolytic enzymes, which drive chronic inflammation and joint destruction. Key cytokines implicated in RA include tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), and receptor activator of nuclear factor kappa-B ligand (RANKL). These mediators activate synovial fibroblasts and chondrocytes, enhance the secretion of collagen-degrading enzymes, and promote osteoclast differentiation, ultimately resulting in cartilage and bone erosion [3, 4].

The diagnosis of RA often relies on the detection of autoantibodies, particularly rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPAs), which are also important prognosis biomarkers [5, 6]. In addition, elevated levels of acute-phase reactants, such as C-reactive protein (CRP), and increased erythrocyte sedimentation rate (ESR) are widely used to assess systemic inflammation and disease activity [5].

Inflammasomes play a critical role in inflammation by orchestrating innate immune responses and contributing to tissue homeostasis; however, their dysregulation can exacerbate inflammatory diseases [7]. Among these complexes, the Nucleotide-binding, oligomerization domain (NOD)-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome is activated by a wide range of endogenous and exogenous stimuli, including damage-associated molecular patterns (DAMPs), mitochondrial-derived reactive oxygen species (ROS), and proinflammatory cytokines. Upon activation, NLRP3 promotes caspases-1-dependent maturation of IL-1β and IL-18, thereby triggering inflammatory signaling and pyroptotic cell death [8]. Inappropriate activation of the NLRP3 inflammasome has been implicated in several autoimmune diseases, including RA [9, 10]. Increased NLRP3 expression has been detected in synovial tissue, peripheral blood, and $CD4^+$ T cells from patients with RA [11, 12].

The *NLRP3* gene is located on chromosome 1 (1q44), has nine exons and over 60 SNVs that are associated with different levels of activation of the complex, such as gain or loss of function [13] and is likely linked to susceptibility, worse prognosis, and RA activity [10, 14]. The SNP rs10754558 G > C is located in the 3'unstraletd region (3'UTR) of the *NLRP3*, a key region of post-transcriptional regulation that can affect mRNA stability and interaction with the microRNA-146a binding sites leading to an increase in *NLRP3* expression [15] and has been associated with different diseases [9, 10, 14, 16–29].

The *NLRP3* rs10754558 has been investigated for its potential role in RA susceptibility, disease activity, and therapeutic response [9, 27–29]. Higher ACPAs titers at RA diagnosis have been reported in patients lacking the C allele of the rs10754558 C > G variant [10]. However, studies failed to confirm the association of the NLRP3 rs10754558 and RA susceptibility [10], RF production, disease activity, and bone erosions [28]. Therefore, the role of the *NLRP3* rs10754558 variant in the susceptibility and severity is inconsistent in different ethnic backgrounds [9, 11, 26, 27].

The *NLRP3* rs10157379 T > C variant is located in an intronic region and is unclear how it may affect the gene function. This variant has been evaluated in different diseases, including renal cell carcinoma [21], chronic kidney disease [22], and severe acute respiratory syndrome after SARS-CoV-2 infection [23]. At the best of our knowledge, there are currently no data regarding the *NLRP3* rs10157379 variant in individuals with RA.

The assessment of RA disease activity commonly relies on inflammatory biomarkers such as ESR, CRP, and composite indices including the Disease Activity Score in 28 joints (DAS28). However, these measures present limitations, particularly in patients with low disease activity or clinical remission [30]. In this context, novel hematological indices derived from routine blood counts, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have emerged as reliable and accessible potentially indicators of RA disease activity. Elevated NLR and PLR values are associated with increased systemic inflammation and have been positively correlated with DAS28, ESR, and CRP [31, 32]. Nevertheless, while some studies support the utility of NLR and PLR as inflammatory markers of RA, others suggest that these indices may not independently reflect disease activity [33, 34]. Similarly, the lymphocyte-to-CRP ratio (LCR) has gained increasing attention as a biomarker of systemic inflammation in various clinical settings [35–38], although its role in RA not yet been elucidated. The white blood cell (WBC)-to-hemoglobin ratio (WHR) is another emerging inflammatory biomarker that reflects the combined effects of systemic inflammation and anemia [39, 40]. Notably, higher WHR values have shown promise as a cost-effective tool for monitoring RA disease activity [41], particularly in routine clinical practice [42].

Given the established role of *NLRP3* genetic variants in RA pathogenesis and the potential utility of hematological inflammatory biomarkers, this study hypothesizes that patients carrying the *NLRP3* rs10754558 GG genotype, previously associated with increased inflammasome expression, exhibit higher RA disease activity. In addition, inflammatory biomarkers derived from routine blood counts, including NLR, PLR, LCR, and WHR may correlate with RA disease activity. Considering the influence of ethnic variability on hematological parameters. this study aimed to investigate the association between *NLRP3* rs10754558 and rs10157379 genetic variants, RA disease activity, RF, ACPAs, and inflammatory biomarkers in a Brazilian population.

Methods

Subjects

This prospective case-control study included 383 adult individuals of both sexes, aged 18 to 70 years, comprising 225 patients with RA and 158 individuals without RA who served as controls.
Patients were followed at the Rheumatology Outpatient Clinic of the Specialty Outpatient Clinic of Londrina University Hospital (AEHU), Londrina, Paraná, Brazil. Participants were consecutively recruited between February 2022 and February 2023, and the groups were controlled for sex, age, and ethnicity. The diagnosis of RA was established according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [5].

Disease activity was assessed using the DAS28 and ESR results (DAS28-ESR) and categorized with remission/low activity (DAS28-ESR < 2.6), moderate/high disease activity (DAS28-ESR ≥ 2.6). Moreover, when DAS28 ESR >5.1, it was also categorized as high disease activity [43].

The exclusion criteria for both patients and controls included the presence of other autoimmune diseases, acute or chronic infectious diseases, neoplasms, chronic kidney disease, and alcoholism. The sample size was not calculated a priori and was determined by convenience sampling of the eligible patients with RA attending during the study period.

Epidemiological, Demographic, Anthropometric, and Clinical Data

Information on epidemiological, demographic, anthropometric, medical history, and RA treatment were obtained during clinical evaluations performed by a rheumatologist using a standardized assessment questionnaire. Anthropometric measurements included body weight, measured to the nearest 0.1 kg using an electronic scale with participants wearing light clothing and no shoes, and height, measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as the ratio of weight in kilograms to height in meters squared.

Inflammatory and Immunological Biomarkers

Total WBC and platelet counts were analyzed using automated methods. ESR was assessed with an automated system (Ves-Matic™· CUBE 30, DIESSE, Siena, Italy). High-sensitivity CRP (hsCRP) and RF levels were determined through turbidimetry (C8000™ Abbott Laboratory, Abbott Park, IL, USA). ACPAs levels were measured using chemiluminescence microparticle immunoassay (Architect™, Abbott Laboratory, Abbott Park, IL, USA). RF and ACPAs levels were considered positive when values were equal to or exceeded 30 U/mL and 5 U/mL, respectively. High positivity was defined as levels greater than three times the upper limit of normal [5]. The inflammatory biomarkers NLR, PLR, LCR, WHR were determined.

NLRP3 Genotyping

The *NLRP3* genetic variants rs10157379 T>C and rs10754558 C>G were evaluated by qualitative real-time polymerase chain reaction (qPCR) using the TaqMan™ method. For this purpose, Taqman™ SNP Genotyping Assay 40X (Applied Biosystems, Foster City, CA, USA) containing two primers and two allele-specific TaqMan™ MGB probes with a reporter dye at the 5' end (VIC™ or FAM™) and TaqMan™ Universal Genotyping Master Mix (Applied Biosystems, Foster City, CA, USA) were used. For the rs10157397 variant (C 30076082_30), the primer was ntTTCTGTATTTCTATTTTTCCTGCCT**[C/T]**GTAGACACCAAAGAGCTTAAAAAAC

and for the rs10754558 variant (C 26052028_10), the primer was
GACAATGACAGCATCGGGTGTTGTT**[C/G]**TCATCACAGCGCCTCAGTTAGAGGA

(Applied Biosystems, Foster City, CA, USA). The fluorescence levels of the real-time polymerase chain reaction products were evaluated by the QuantSudio™ equipment (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

Categorical variables were expressed as absolute numbers (n) and percentages (%) and analyzed using the chi-square test or Fisher's exact test. Continuous variables were expressed as median with interquartile range (IQR) and analyzed using the Mann-Whitney test. The Hardy-Weinberg equilibrium was determined for both variants. Associations between *NLRP3* variants and study variables were evaluated using codominant, recessive, dominant, and overdominant genetic models. Associations between the *NLRP3* variants and inflammatory biomarkers were analyzed using the Kruskal-Wallis test with Tukey's post hoc analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Statistical significance was defined as a p value of less than 0.05. Analyses were conducted using SPSS for Windows, version 24.0 (SPSS 31 Inc. Chicago, IL, USA).

Results

Characteristics of RA patients and controls

A total of 383 individuals were evaluated and divided in two study groups: 225 patients with RA and 158 healthy controls. **Table 1** summarizes the epidemiological, demographic, clinical, and laboratory parameters obtained from patients with RA and controls. Patients with RA were older than controls (p<0.001), exhibited higher frequency of use antihypertensive therapy, hypertension, and

metabolic syndrome. Most of the patients (172/76.4%) presented considered remission/low disease activity (DAS28-ESR< 2.6), and 26 (11.5%) presented DAS28-ESR > 5.1. Most of them showed seropositivity to the RF (50.2%) and ACPAs (59.1%), and no extra-articular symptoms (88.4%). The patients were using prednisone (69.8%), methotrexate (65.3%), leflunomide (41.3%), antimalarials (38.7%), TNF inhibitors (25.8%), and anti-CD20 (1.3%) therapies.

NLRP3 rs10754558 C>G and rs10157379 T>C variants and autoantibodies

The frequency of the *NLRP3* rs10754558 and rs10157379 variants was in Hardy-Weinberg Equilibrium. The *NLRP3* variants were not associated with RF and ACPAs status, as showed in **Tables 2** and **3,** respectively.

NLRP3 rs10754558 C>G and rs10157379 T>C variants and disease activity

The association between *NLRP3* rs10754558 C>G and rs10157379 T>C variants with RA disease activity (DAS28-ESR <2.6 *versus* ≥2.6), in codominant, dominant, recessive, and overdominant genetic models are shown in **Table 4**. Patients carrying the rs10157379 TC genotype, in codominant model, showed lower disease activity compared with those carrying the TT genotype (OR: 0.28; 95%CI: 0.10-0.75, p=0.011), as well as in overdominant model compared with those carrying the TT+CC genotypes (OR: 0.36; 95%CI: 0.16-0.82, p=0.016). Moreover, patients carrying the TT genotype, in recessive model, exhibited higher disease activity than those carrying the TC +CC genotypes (OR: 2.96; 95%CI: 1.16-7.59, p=0.023). The NLRP3 rs10754558 CG genotype, in codominant model, showed a trend toward the possible protector effect for the disease activity (p=0.065).

NLRP3 rs10754558 C>G and rs10157379 T>C variants and inflammatory biomarkers

The association between the *NLRP3* rs10754558 C>G and rs10157379 T>C variants and some inflammatory biomarkers, such as NLR, PLR, WHR, and LCR are presented in **Tables 5** and **6,** respectively. For the rs10754558 C>G variant, it was found that CC and CG genotypes showed LCR approximately 3 times higher than GG genotype. In other words, it means that patients carrying the GG genotype showed higher CRP values than lymphocyte count (p<0.05). For the rs10157379 T>C variant, it was demonstrated that the WHR were significantly different between the patients carrying the TT and TC genotypes, with those carrying the TT genotype exhibited higher WHR than those carrying the TC genotype. For the CC genotype, no significant difference was observed.

Discussion

The main finding of the present study was the association between the *NLRP3* rs10157379 T > C variant and RA disease activity. In the recessive model, the *NLRP3* 10157379 TT genotype was associated with a threefold increased likelihood of disease activity, while the TC genotype, under codominant and overdominant models, was associated with a protective effect, showing approximately 3.57- and 2.77-fold higher odds of being in remission, respectively. This result was unexpected, considering that the T > C substitution has been described as a gain-of-function variant, with the C allele potentially enhancing NLRP3 expression and consequently, the inflammatory response [15]. One possible explanation is that the heterozygous TC genotype may exert a regulatory or compensatory effect, possibly through allele-specific expression or post-transcriptional mechanisms that result in a more balanced inflammasome response.

Interestingly, the best fit in our analyses was found under an overdominant model, suggesting a potential heterozygote effect (heterosis), in which intermediate levels of NLRP3 expression could modulate inflammasome activation more efficiently. Such effects have been described in other complex immune-mediated conditions, where heterozygosity may confer a functional advantage through balanced expression of proinflammatory mediators [44]. Therefore, the CG heterozygous genotype may result in a better phenotype than the CC and GG homozygous genotypes, and the intermediate NLRP3 levels may be optimal to modulate specific signaling pathways [45]. However, we interpret the overdominant association as a hypothesis-generating result that warrants further investigation in larger and independent RA cohorts to confirm whether heterozygosity indeed confers a differential protective profile.

In the present study, no significant association was observed between the *NLRP3* rs10754558 variant and RA disease activity as well as between the *NLRP3* rs10157379 and rs10754558 variants with RF, and ACPAs autoantibodies. Although ACPAs are associated with a worse prognosis in RA patients [5], the specific *NLRP3* rs10754558 and rs10157379 *NLRP3* genetic variants investigated in this study do not appear to directly influence the production of this autoantibodies. Our results corroborate the findings of previous study that showed no association between the *NLRP3* 10754558 variant and RF, the development of bone erosions, and disease activity when measured by DAS28 [28]. However, previous study reported an association between the *NLPR3* rs10754558, rs35829419, and rs4612666 variants with susceptibility, worse prognosis, and RA activity; moreover, the study showed that the titer of ACPAs during diagnosis of RA was high in the absence of the C allele of rs10754558 C > G variant in RA patients [10]. These findings highlight the complexity of NLRP3 regulation in

RA and suggest that the relationship between *NLRP3* genetic variants and disease activity may have dual or context-dependent roles in disease pathogenesis

Other interesting and original results obtained in the present study were the association between the *NLPR3* variants and two of the integrative inflammatory biomarkers. The *NLRP3* rs10157379 variant was associated with WHR and the *NLRP3* rs10754558 variant was associated with LCR. For the rs10754558 variant, it was found that the CC and CG genotypes presented the LCR approximately 3 times higher than the GG genotype, i.e., patients carrying the CC and CG genotypes showed higher immune regulation that those carrying the GG genotype. With respect to the *NLRP3* rs10157379, patients carrying the TT genotype showed higher WHR than those carrying the TC genotype. This result appears to be consistent with the association obtained between the TT genotype, in the recessive model, and the 3-fold higher odds of presenting RA disease activity.

Due to the heterogeneity of RA, the markers such as CRP and ESR exhibit certain limitations in their capacity to assess disease activity. There arises a need to find new biomarkers capable of assessing inflammation and the insights into the disease dynamics. LCR is a relatively integrative new biomarker that combines the assessment of lymphocyte count, which reflects immune cell function and regulation, with CRP, a well-established marker of acute inflammation. LCR has gained attention as an indicator of systemic inflammation in neoplastic diseases [36, 37] and has emerged as a valuable biomarker for the early detection and prediction of severe conditions such as coronavirus disease 2019 (COVID-19) [35] and sepsis [38]. While several lines of evidence support that NLR, PLR, and WHR were higher in RA patients than controls, and in patients with active RA compared to those with inactive RA [32, 33, 46, 47], at the best of our knowledge, LCR was not reported in patients with RA.

The association between the *NLRP3* rs10157379 TT genotype with higher values of WHR underscores the elevated WBC counts in RA that is a marker of disease activity and severity and the decreased hemoglobin in patients with RA. A mechanist explanation is that *NLRP3* rs10157379 TT genotype may increase the NLRP3 expression and should increase the inflammatory cytokines such as IL-1β, IL-18, and further, IL-6 and TNF-α, which drive leukocyte production and activation. In patients with RA, the inflammasome's activation leads to a pro-inflammatory environment characterized by elevated levels of both neutrophils and pro-inflammatory cytokines like IL-1β. The IL-1β and IL-18 cytokines affect the recruitment and function of neutrophils and lymphocytes in the context of active systemic inflammation. Lymphopenia may also occur due to the sequestration of lymphocytes in inflamed tissues or the suppression of their production. It can be caused by the disease process itself, but is also commonly induced by treatments like glucocorticoids and conventional or biological DMARDs. Moreover, it was described a perturbation of the T cell repertoire in RA [48]. Anemia of inflammation begins with the activation of the immune system and the subsequent release of cytokines that leads to an elevation of hepcidin, responsible for hypoferremia, and a suppression of erythropoiesis due to lack of iron [41, 42].

Anemia of inflammation is commonly observed in patients with chronic infections and autoimmune diseases, in which inflammation was easily detectable and sustained, particularly, in RA patients with active disease, as result chronic inflammation [41, 42]. Therefore, these evidences may explain, in part, the association between the *NLRP3* 10157379 TT genotype with the higher WHR compared with the TC genotype. The presence of the T allele could increase the inflammatory status, increasing the WBCs count and decreasing the hemoglobin levels. The WHR is an emerging inflammatory biomarker which reflects systemic inflammation (through WBC) and anemia (through hemoglobin).

Limitations of the present study must be addressed. First, the case-control design that does not allow establishing the causal relationship between the study variables; second, the sample size may limit the statistical power to detect associations with smaller effect sizes or gene-gene/environment interactions; third, most RA patients were on remission/low disease activity and on various treatment regimens that introduces variability on biomarker levels and disease activity scores; fourth, the possibility of variations in the erythrocyte, neutrophil, lymphocyte, and platelet counts in response to short- and long-term therapies with methotrexate, a drug with myelotoxicity effect used by the most RA patients included in the study [49]. Additionally, the study did not account for other genetic factors that could interact with immune response components and environmental factors. However, one strength of the study was that some possible confounding variables, such as medication use, sex, age, ethnicity, and smoking were controlled in the statistical analysis considering that sex-hormones [50], age [51], and smoking [52] exert specific effects in inflammasome and the other variables of the study.

To the best of our knowledge, this is the first study to investigate the *NLRP3* rs10157379 variant specifically in the disease activity, FR, ACPAs, and the integrate hematological biomarkers among patients with RA, which limits direct comparison with previous literature. From a translational perspective, if confirmed in independent cohorts, the rs10157379 variant—particularly in heterozygous form—may hold potential as a genetic biomarker for disease activity stratification or for identifying patients more likely to achieve remission. This could contribute to the development of more personalized treatment strategies targeting the inflammasome axis in RA. Further studies

integrating gene expression, protein function, and larger patient cohorts are needed to elucidate the molecular mechanisms involved and to assess the potential of this variant as a biomarker for disease activity or therapeutic response in RA.

Conclusion

Taken together, mechanistic insights suggest that the *NLRP3* rs10157379 and rs10754558 genetic variants may genotype-specific effects on inflammatory pathways. In the recessive model, the TT genotype of the *NLRP3* rs10157379 variant was associated with a 2.96-fold increased likelihood of presenting disease activity. In contrast, the TC genotype, in the codominant and overdominant models, was associated with a 3.57- and 2.77-fold greater chance, respectively, of being in remission from RA. Regarding the rs10754558 variant, individuals with the CC and CG genotypes exhibited higher LCR compared to those with the GG genotype. Conversely, patients carrying the GG genotype had higher LCR. For the rs10157379 variant, patients with the TT genotype also showed higher WHR than those with the TC genotype. However, neither of the *NLRP3* variants was associated with RF or ACPAs levels. Future longitudinal and functional studies are warranted to validate these findings and to explore additional genetic and environmental factors in RA pathophysiology.

Declarations

Author Contribution

All authors whose names appear on the submission of the manuscript made substantial contributions to the conception or design of the work, or the acquisition, analysis, and interpretation of data, drafted the work or revised the manuscript (text, tables, and references), approved the version submitted to the Immunologic Research. The major contributions are detailed bellow:

Beatriz Neves Bruniera: Methodology, investigation; formal analysis, writing

Tainah Mendes Ahrens: Methodology, investigation

Eduarda dos Santos: Methodology, investigation

Tatiana Mayumi Veiga Iriyoda: Methodology, investigation, writing,

Marcell Alysson Batisti Lozovoy: Methodology, investigation, formal analysis, writing,

Andrea Name Colado Simão: Conceptualization, formal analysis

Edna Maria Vissoci Reiche: Conceptualization, writing, editing, supervision.

Ethics approval

This study was conducted after approval by the Institutional Research Ethics Committees of University of Londrina, Paraná, Brazil (CAAE: 37420820.0.0000.5231). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The studied participants were informed about the present research, and a written consent form was taken from all of them before their enrollment. Moreover, all the authors and co-authors participated and contributed sufficiently in the research, and all of them concur with the submission. The manuscript has been approved by the responsible authorities where the work was carried out. The authors also concur that, if accepted, the manuscript shall not be published elsewhere in the same form in either the same or any other language, without the consent of the Editor-in Chief of the **Immunologic Research.**

Standards for reporting

The manuscript was prepared taking into account the recommendations of the guidelines hosted by the Strengthening the Reporting of Observational studies in Epidemiology (STROBE). STROBE is used for observational studies (cohort, case-control, or cross-sectional designs) according to the STROBE statement (www.strobe-statement.org)

Data availability

The dataset generated during and/or analyzed during the current study will be available from E.M.V.R. upon reasonable request and once the dataset has been fully exploited by the authors.

Competing Interests and Funding

The authors declare that they have no competing interest. None of the authors are involved in the publication process or have a financial or other beneficial interest in the products or concepts mentioned in the submitted manuscript.

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Tables

Table 1 Demographic, clinical, and immunological characteristics of the patients with rheumatoid arthritis and healthy controls

Variables		Controls (n=158)		Patients (n=225)		p value
		n	%	n	%	
Ethnicity	Caucasian	121	76.6	163	72.4	0.363
	Non-Caucasian	37	23.4	62	27.6	
Sex	Female	127	80.4	189	84.0	0.359
	Male	31	19.6	36	16.0	
Smoking	No	141	89.2	191	84.9	0.217
	Yes	17	10.8	34	15.1	
Antihypertensive	No	129	90.2	133	59.1	0.000*
	Yes	14	9.8	92	40.9	
MetS	No	131	83.4	132	59.7	0.000*
	Yes	26	16.6	89	40.3	
Hypertension	No	118	88.7	118	52.7	0.000*
	Yes	15	11.3	106	47.3	
DAS ESR <2.6	No	-	-	53	23.6	
	Yes	-	-	172	76.4	
Rheumatoid factor	Negative	-	-	112	49.8	
	Positive	-	-	113	50.2	
ACPAs	Negative	-	-	92	40.9	
	Positive	-	-	133	59.1	
Extrarticular manifestations	No	-	-	199	88.4	
	Yes	-	-	26	11.6	

Categorical variables were expressed as absolute number (n) and percentage (%). Continuous variables were expressed as median and interquartile range. DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; ACPAs: anti-citrullinated peptide antibodies; MetS: Metabolic syndrome; *Chi-square test significant at the 0.05 level.

Table 2 Association between *NLRP3* rs10754558 C>G and rs10157379 T>C genetic variants and anti-citrullination peptide antibodies (ACPAs) in patients with rheumatoid arthritis

		ACPAs					
Genetic Variant		Negative (n=92)		Positive (n=133)		p value	
		n	%	n	%		
NLRP3 rs10754558 C>G							
Codominant	CC	33	35.9	43	32.3		
	CG	46	50.0	72	54.1	0.822	
	GG	13	14.1	18	13.5		
Recessive	CC+CG	79	85.8	115	86.5	0.898	
	GG	13	14.1	18	13.5		
Dominant	CG+GG	59	64.1	90	67.7	0.581	
	CC	33	35.9	43	32.3		
Overdominant	CC+GG	46	50.0	61	45.9	0.541	
	CG	46	50.0	72	54.1		
NLRP3 rs10157379 T>C							
Codominant	TT	31	33.7	40	30.1		
	TC	43	46.7	67	50.6	0.830	
	CC	18	19.6	26	19.5		
Recessive	TT+TC	74	80.4	107	80.4		
	CC	18	19.6	26	19.5	0.998	
Dominant	TC+CC	61	66.3	93	69.9		
	TT	31	33.7	40	30.1	0.566	
Overdominant	TT+CC	49	53.3	66	49.6		
	TC	43	46.7	67	50.6	0.592	

The categorical variables were expressed as absolute numbers (n) and percentages (%).

ACPAs: anti-citrullinated peptide antibodies

Table 3 Association between *NLRP3* rs10754558 C>G and rs10157379 T>C genetic variants and rheumatoid factor in patients with rheumatoid arthritis

		Rheumatoid Factor				
Genetic Variant		Negative (n=112)		Positive (n=113)		
						p value
		n	%	n	%	
NLRP3 rs10754558 (C>G)						
Codominant	CC	44	39.3	32	28.3	
	CG	55	49.1	63	55.8	0.198
	GG	13	11.6	18	15.9	
Recessive	CC+CG	99	88.4	95	84.1	0.347
	GG	13	11.6	18	15.9	
Dominant	CG+GG	68	607	81	71.7	0.082
	CC	44	393	32	28.3	
Overdominant	CC+GG	57	509	50	44.2	
	CG	55	491	63	55.8	0.381
NLRP3 rs10157379 (T>C)						
Codominant	TT	37	33.0	34	30.1	
	TC	54	48.2	56	49.6	0.883
	CC	21	18.8	23	20.4	
Recessve	TT+TC	91	81.3	90	79.6	0.762
	CC	21	18.8	23	20.4	
Dominant	TC+CC	75	67.0	79	69.9	
	TT	37	33.0	34	30.1	0.226
Overdominant	TT+CC	58	51.8	57	50.4	
	TC	54	48.2	56	49.6	0.840

The categorical variables were expressed as absolute numbers (n) and percentages (%).

Table 4 Association between *NLRP3* rs10157379 and rs10754558 variants and the rheumatoid arthritis activity measured using DAS28 ESR

		DAS ESR ≥2.6					
Genetic Variant		No		Yes		OR (95%CI)	p value
		n	%	n	%		
NLRP3 rs10754558							
	CC	9	24.3	43	40.6	Reference	
Codominant	CG	24	64.9	52	49.1	0.43 (0.17-1.05)	0.065
	GG	4	10.8	11	10.4	0.58 (0.14-2.39)	0.452
Dominant	CC+CG	33	89.2	95	89.6	Reference	
	GG	4	10.8	11	10.4	0.98 (0.27-3.51)	0.975
Recessive	CG+GG	28	75.7	63	59.4	Reference	
	CC	9	24.3	43	40.6	2.20 (0.92-5.24)	0.074
Overdominant	CC+GG	13	35.1	54	50.9	Reference	
	CG	24	64.9	52	49.1	0.49 (0.22-1.10)	0.085
NLRP3 rs10157379							
	TT	7	18.9	43	40.6	Reference	.
Codominant	TC	23	62.2	41	38.7	0.28 (0.10-0.75)	0.011
	CC	7	18.9	22	20.8	0.51 (015-1.73)	0.286
Dominant	TT+TC	30	81.1	84	79.2	Reference	
	CC	7	18.9	22	20.8	1.14 (0.42-3.07)	0.790
Recessive	TC+CC	30	81.1	63	59.4	Reference	
	TT	7	18.9	43	40.6	2.96 (1.16-7.59)	0.023
Overdominant	TT+CC	14	37.8	65	61.3	Reference	
	TC	23	62.2	41	38.7	0.36 (0.16-0.82)	0.016

Data expressed as absolute numbers (n) and percentages (%). Logistic regression analysis controlled for medication use, sex, age, ethnicity, and smoking.

Table 5 Association between the *NLRP3* rs10754558 C>G genetic variant and the inflammatory biomarkers in patients with rheumatoid arthritis

	CC			CG			GG		
	Median	IQR		Median	IQR		Median	IQR	
NLR	2.3786	1.5820	3.5149	2.1901	1.4861	3.0682	2.0702	1.7654	3.1818
PLR	143.3529	108.6951	186.6240	138.6948	107.3590	188.9567	137.0668	107.3928	178.7234
WHR	509.0866	383.3711	685.0833	504.3247	412.0370	611.9596	518.0180	439.7059	730.4965
LCR	987.4056[ab]	548.2801	2650.2500	913.3590[ab]	382.6029	2443.3862	333.9011[b]	218.5090	874.1026

Data expressed as median and interquartile range (IQR). Kruskal-Wallis and Tukey tests. Statistical significance: $p<0.05$. a=No statistic significant difference between CC and CG genotypes. b= statistic significant difference between CC and GG, as well as CG and GG genotypes. NLR: Neutrophil/Lymphocyte ratio; PLR: Platelets/Lymphocyte ratio; WHR: White blood cell/Hemoglobin ratio; LCR: Lymphocyte/C-reactive protein ratio. CC: homozygous genotype of the major allele; CG: heterozygous genotype of the variant allele; GG: homozygous genotype of the variant allele.

Table 6 Association between the *NLRP3* rs10157379 T>C genetic variant genotypes and the inflammatory biomarkers in patients with rheumatoid arthritis

	TT			TC			CC		
	Median	IQR		Median	IQR		Median	IQR	
NLR	2.3100	1.5557	3.2628	2.1767	1.6519	3.0555	2.1303	1.4159	3.2593
PLR	141.3201	108.5714	181.3149	142.3144	113.4144	193.0010	120.3762	101.2346	148.8604
WHR	540.6191[a]	439.7059	705.4795	480.0265[a]	374.0667	567.4143	519.3277	422.2222	646.1538
LCR	699.1268	337.9200	1636.4653	987.4056	483.2136	2601.0712	956.8245	513.5821	1747.5524

Data expressed as median and interquartile range (IQR). Kruskal-Wallis and Tukey tests. Statistical significance: $p<0.05$. a= Statistic significant difference between TT and CT genotypes; NLR: Neutrophil/Lymphocyte ratio; PLR: Platelets/Lymphocyte ratio; WHR: White blood cell/Hemoglobin ratio; LCR: Lymphocyte/C-reactive protein ratio. TT: homozygous genotype of the major allele; TC: heterozygous genotype of the variant allele; CC: homozygous genotype of the variant allele.