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Inflammatory factors and restless legs syndrome: A systematic review and meta-analysis

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ABSTRACT

The possible role of inflammatory factors in the pathogenesis of restless legs syndrome (RLS) is not well understood. Because several inflammatory diseases have shown an association with the risk for RLS, the measurement of serum/plasma levels of inflammatory factors has been a matter of a scarce number of studies. We performed a systematic review and a meta-analysis to assess the possible association of serum/plasma levels of inflammatory markers with the risk for RLS. Our results showed a significant trend towards higher serum/plasma C reactive protein (CRP) levels and higher neutrophil-to-lymphocyte (NLR) ratio in patients diagnosed with RLS than in controls, although statistical significance disappeared after applying the random-effects model. Further studies are needed to confirm the suggested possible role of inflammatory factors in the pathogenesis of RLS.

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1. Introduction

Also known as Willis-Ekbom disease (WED), restless legs syndrome (RLS) is a highly prevalent [1] sensorimotor syndrome with well-established diagnostic criteria [2]. Genetic factors should likely play an important role in the etiology of RLS, since linkage studies in families with RLS have identified at least 8 susceptibility loci [3], and genome-wide association studies (GWAS) and further meta-analyses identified 21 susceptibility genes to date [3–5].

While the main neurochemical features found in RLS are dopaminergic dysfunction and iron deficiency, with a possible contribution of adenosinergic, GABAergic, and glutamatergic neurotransmission systems [6], and oxidative stress [6–8]. The possible role of inflammatory factors in the etiopathogenesis of RLS is suggested by the association of several inflammatory and autoimmune diseases, including chronic liver disease [9], Sjogren's syndrome [9], rheumatoid arthritis [9], sarcoidosis [9], systemic lupus erythematous [9], inflammatory bowel disease [9,10], multiple sclerosis [11], mastocytosis [12], and chronic obstructive pulmonary disease [13], to the risk for RLS, and the description of patients suffering from recurrent and severe RLS always coinciding with infectious-inflammatory conditions [14]. Moreover, induction of RLS related to infectious agents such as *Borrelia* [15], *Streptococcus* [16], *Mycoplasma* [16], *Herpesvirus varicella-zoster* [17], and *SARS CoV2* [18] has been reported; a higher than expected prevalence of RLS in patients with leprosy [19], tuberculosis [20], or Creutzfelt-Jakob disease [21]; and increased risk for RLS in patients with infections by *Helicobacter pylori* [22,23], and COVID 19 [24,25]. However, data from an initial study describing increased risk for RLS in patients with *Human immunodeficiency virus* (*HIV*) infection [26], were not confirmed in another two studies [27,28]. Finally, the so-called "long-COVID state" increased the prevalence of RLS in women [29]. In addition, it has been described improvement of RLS symptoms by steroids [30,31].

However, inflammatory aspects of RLS have been a matter of only a few studies. In this systematic review and meta-analysis, we try to analyze the results of published studies aimed at establishing the possible role of inflammatory factors in the etiopathogenesis of RLS.

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Abbreviations

BMI	body mass index
c-aAb	cytokine-specific autoantibodies
COVID	coronavirus disease
CRP	C reactive protein
GABA	gamma-aminobutyric acid
GM-CSF	granulocyte-macrophage colony-stimulating factor
GWAS	Genome-wide association studies
hsCRP	high-specific C reactive protein
HIV	Human immunodeficiency virus
IFN-α	interferon-alpha
IL	interleukin
iRLS	idiopathic restless legs syndrome
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NFKB	nuclear factor kappa-B
NLR	Neutrophil-to-lymphocyte ratio
NOS	Newcastle-Ottawa scale
PLMS	periodic limb movements during sleep
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RLS	restless legs syndrome
SARS CoV2	severe acute respiratory syndrome coronavirus 2
TNF-α	Tumor necrosis factor α
WOS	Web of Science
WED	Willis-Ekbom disease

2. Methods

2.1. Search strategy and criteria for eligibility of studies

We have carried out a literature search using 3 several well-known Databases (PubMed, EMBASE, Web of Science-WOS-Main Collection) from the period between 1966 and August 19, 2022. For this purpose, we crossed the term "restless legs syndrome" with "inflammation" (49, 219, and 201 items found in PubMed, EMBASE, and WOS, respectively), "inflammatory factors" (21, 3, and 71 found in PubMed, EMBASE, and WOS, respectively), "inflammatory markers" (12, 10, and 27 items found in PubMed, EMBASE, and WOS, respectively), "C reactive protein"" (22, 103, and 73 items found in PubMed, EMBASE, and WOS, respectively), "cytokines" (27, 21, and 31 items found in PubMed, EMBASE, and WOS, respectively), "interleukins"" (10, 1, and 4 items found in PubMed, EMBASE, and WOS, respectively), tumor necrosis factor alpha" (6, 7, and 21 items found in PubMed, EMBASE, and WOS, respectively), neutrophil-to-lymphocyte ratio" (4, 8, and 11 items found in PubMed, EMBASE, and WOS, respectively), and "infection" (111, 744, and 234, respectively). Through the complete search, a total of 785 references were obtained, all of which were manually examined one by one by the 4 authors, who selected for consensus only those strictly related to the analyzed topic. This was done without applying any restrictions related to the language of the publications and excluding abstracts and duplicate publications. Fig. 1 shows the flowchart for the selection of eligible studies, which was carried out following the PRISMA guidelines [32].

2.2. Studies selection and methodology used for review and the meta-analyses

Table 1 summarizes the methodology, and the main results of the studies included in the systematic review. We performed a meta-analysis of those inflammatory markers that were the subject of at least 3 studies, This condition was met by serum/plasma levels of (C reactive protein/high-specific C reactive protein) CRP-hsCRP in patients with RLS compared with controls, by patients with chronic kidney disease that compares with those without RLS, and by the neutrophil-to-lymphocyte ratio (NLR) in patients with RLS compared with controls, the results of which have been summarized in Tables 2–4. We extracted the following data: first author, year of publication, country, study design, and quantitative measures. The Newcastle-Ottawa Scale [53] was used to analyze the risk for bias. Serum/plasma CRP/hsCRP levels were converted to mg/L and NLR was expressed as a quotient. The meta-analysis, which followed the PRISMA [32] (Table S1) and the MOOSE guidelines [54] (Table S2) was carried out by using the R software package meta [55]. Due to the heterogeneity across studies, we applied the random-effects model and used the inverse variance method for the meta-analytical procedure. The statistical power to detect differences in mean values (alpha = 0.05) for the pooled samples was calculated when stated in the text.

3. Results

3.1. Studies assessing serum/plasma CRP levels

The results of studies assessing serum/plasma CRP or hsCRP levels in patients diagnosed with RLS compared with healthy controls are summarized in Table 2. Two studies described higher serum/plasma levels in patients with iRLS [40,46], while another 5 did not find significant differences [33,35,38,42,43]. The results of the pooled data from these studies showed significantly higher CRP levels in RLS, but this statistical significance disappeared either when the common effect model (P = 0.137) or the random effects model (P = 0.860) was used (Table 2, Fig. 2). Interestingly, Trotti et al. [56], in a study that included 137 untreated patients with RLS who underwent a polysomnographic study, showed an association between increased serum/plasma hsCRP levels and the odds for severe periodic leg movements of sleep (PLMS).

Table 3 summarizes the results of studies assessing serum/plasma levels of CRP or hsCRP in patients with end-stage or chronic kidney disease with RLS compared with those without RLS. A single study showed higher serum and a correlation between hsCRP and RLS severity [48], while other 3 studies [47,49,50], showed non-significant differences. The results of the pooled data from these studies showed non-significant differences in serum/plasma CRP levels between patients with RLS and patients without RLS, both using the common effects (P = 0.558) or the random-effects (P = 0.732) models (Table 3, Fig. 3). Finally, one study involving pediatric patients showed a non-significantly higher frequency of patients with hsCRP concentration ≥1 mg/L in the group of patients with RLS compared with those without RLS [53].

Mandal et al. [30] showed a lack of significant differences in serum/plasma hsCRP levels in patients with chronic obstructive pulmonary disease with and without RLS.

3.2. Studies assessing neutrophil-to-lymphocyte ratio (NLR)

The results of studies assessing NLR in patients diagnosed with RLS compared with healthy controls are summarized in Table 4. Two cross-sectional studies [37,43] and one prospective longitudinal one [47] showed higher NLR in RLS than in controls, although

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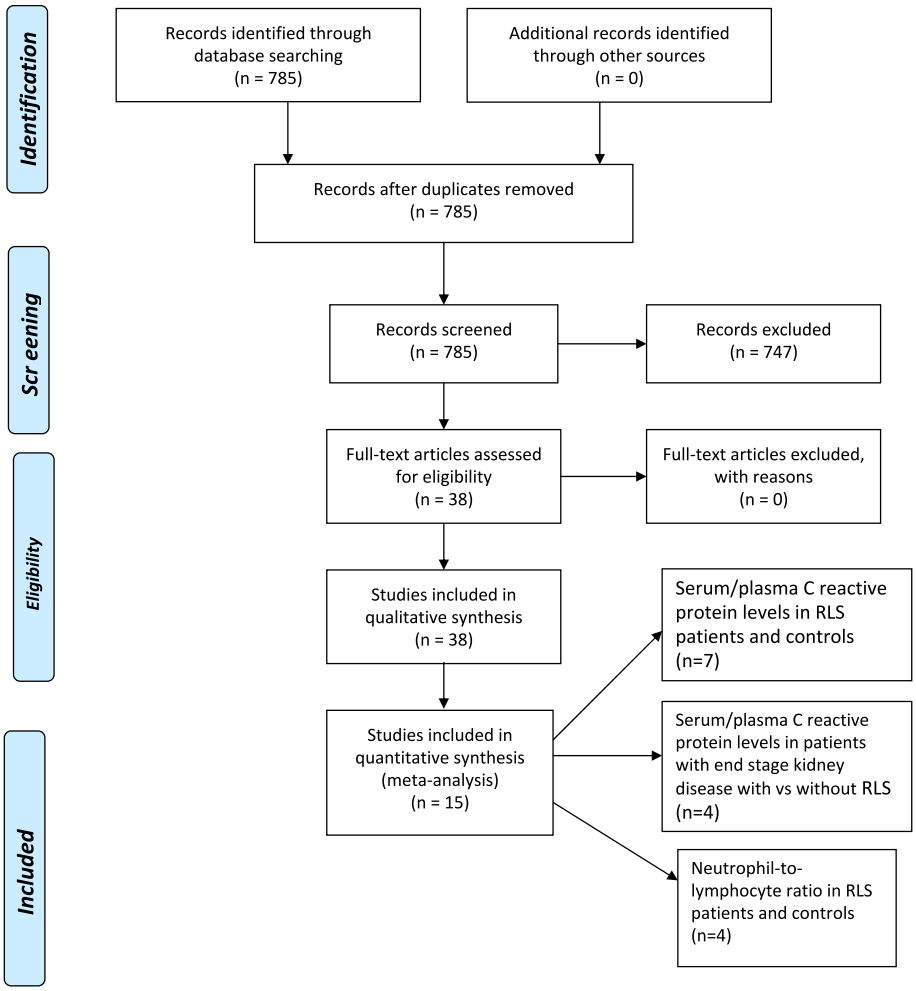

Fig. 1. Flowchart for the selection of eligible studies analyzing serum/plasma levels inflammatory factors in patients with restless legs syndrome.

in the latter of these the statistical significance disappeared after adjusting for sex, age, body mass index, and smoking status [45]. Another cross-sectional study showed similar values in the two study groups [37]. The results of the pooled data of these studies showed a significantly higher NLR ratio in RLS patients when compared with healthy controls when using the common effects model ($P < 0.0001$), but the statistical significance disappeared when the random-effects model ($P = 0.135$) was applied (Table 4, Fig. 4).

3.3. Studies assessing serum/plasma levels of cytokines

Two cross-sectional studies showed higher serum/plasma levels of tumor necrosis factor α (TNF-α) levels in RLS patients compared with controls [38,43], and one of them also showed increased serum/plasma levels of interleukin 1β (IL-1β) and IL-6 [43]. In contrast, another cross-sectional study showed similar plasma cytokine-specific autoantibodies (c-aAb) against IL-1α, IL-6, IL-10, and GM-CSF (granulocyte-macrophage colony-stimulating factor) in patients with RLS and in controls, a higher frequency of c-aAb against IFN-α (interferon-alpha) in RLS patients, and significantly higher plasma suPAR (soluble urokinase-type plasminogen activator receptor) levels in patients with severe RLS (although the latter disappeared after adjusting for sex, age, body mass index, and smoking status) [43].

According to Trotti et al. [56], IL-6 and TNF-α were not related to the presence of PLMS in RLS patients. Serum IL-6 levels were increased in patients with end-stage kidney disease and RLS compared with those without RLS [48] and were similar in patients with hematologic malignancies with and without RLS [52].

Finally, Hennessy et al. [57], in an association study involving a short series of individuals, described an association of several polymorphisms in the IL-1β IL-17α genes, but a lack of association of polymorphisms of other IL, IFN, TNF-α, and nuclear factor kappa-B (NFKB) genes with the risk for RLS in patients with HIV infection.

3.4. Proteomic studies

Three serum/plasma [39,41,44] and one cerebrospinal fluid [34] proteomic studies, involving a short series of participants, showed up-regulation or down-regulation of several proteins involved in inflammatory processes in patients with RLS compared with controls (Table 1).

4. Discussion and conclusions

The possible role of inflammatory factors in the pathogenesis, or their possible value as markers of RLS remains to be determined. Data regarding the results of serum/plasma CRP levels are controversial. The results of the current meta-analysis suggest an association between this value and the risk for RLS, that was not

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Table 1
Studies addressing serum/plasma inflammatory markers in patients with RLS compared with controls and in patients with several diseases and with RLS, compared with those without RLS. NOS Newcastle-Ottawa Scale.

Patients with iRLS compared with controls				
AUTHORS, YEAR [REF]	STUDY DESIGN	TYPE OF STUDY	MAIN FINDINGS	NOS quality score
Kim et al., 2010 [33]	Measurement of serum CRP levels in a random sample of 714 subjects (59 with RLS and 655 without RLS)	Longitudinal community-based epidemiological study involving 61,730 Korean individuals	• Similar serum CRP levels in RLS patients and controls.	8
Patton et al., 2013 [34]	Proteomic analysis in cerebrospinal fluid samples from 6 iRLS and 5 age- and sex-matched controls subjects.	Cross-sectional, hospital-based, case-control study	• Increased CSF levels of Cystatin C, Lipocalin-type Prostaglandin D2 Synthase, Vitamin D binding Protein, and β-Hemoglobin, • Decreased CSF levels of Apolipoprotein A1 and α-1-acid Glycoprotein in RLS patients	4
Benediktsdottir et al., 2010 [35]	Measurement of serum CRP and IL-6 levels in random samples from the general population (1344 individuals, 205 with RLS and 1139 without RLS)	Prospective study using the national registries of inhabitants of Reykjavik, Iceland, and Uppsala, Sweden,	• Similar serum CRP and IL-6 levels in RLS patients and controls.	7
Varım et al., 2016 [36]	Measurement of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) In 75 RLS patients and 56 controls.	Cross-sectional, hospital-based, case-control study	• Patients with RLS showed a significantly higher NLR than controls	5
Tak & Sengul, 2018 [37]	Measurement of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) In 62 RLS patients and 40 controls.	Cross-sectional, hospital-based, case-control study	• Similar NLR and PLR in RLS patients and controls.	5
Auvinen et al., 2018 [38]	Measurement of serum CRP and TNF-α levels in 396 "healthy" subjects without depression (98 with and 198 without RLS)	Cross-sectional, hospital-based, case-control study	• Similar serum CRP and TNF-α levels in patients with and without RLS.	6
Bellei et al., 2018 [39]	Proteomic analysis in plasma samples from 34 iRLS and 17 age- and sex-matched controls subjects.	Cross-sectional, hospital-based, case-control study	• Up-regulation of alpha-1B-glycoprotein, alpha-1-acid glycoprotein 1, haptoglobin, complement C4-A, and immunoglobulin kappa constant in RLS patients • Up-regulation of kininogen-1, immunoglobulin heavy constant alpha 1, and immunoglobulin lambda constant 2 in patients with severe RLS. • Down-regulation of complement C3 in RLS patients and alpha-1-antitrypsin in patients with severe RLS.	5
Olgun Yazar et al., 2019 [40]	Measurement of serum hsCRP and hsCRP/albumin ratio in 197 iRLS patients and 183 controls	Cross-sectional, hospital-based, case-control study	• Patients with iRLS had significantly higher serum hsCRP and hsCRP/albumin ratio, and lower albumin levels than controls.	6
Shin et al., 2020 [41]	Proteomic analysis in serum samples from 7 iRLS and 6 age- and sex-matched control subjects.	Cross-sectional, hospital-based, case-control study	• Up-regulation of alpha-2 macroglobulin precursor, complement C3, beta-2-glycoprotein I apolipoprotein H, plasma kallikrein 120 (PK-120) precursor, and chain A, Vitamin D binding protein • Down-regulation of complement C4A, alpha-2 HS glycoprotein, and coagulation factor XII.	4
Reyhani & Kabeloglu, 2021 [42]	Measurement of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) monocyte-to-high-density lipoprotein cholesterol ratio (MHR), and serum CRP levels in 102 RLS patients and 51 controls.	Cross-sectional, hospital-based, case-control study	• Significantly higher NLR and similar PLR, MHR, and serum CRP levels in RLS patients compared with controls.	5
Uslu et al., 2021 [43]	Measurement of plasma levels of hsCRP and serum levels of cytokines in 29 iRLS patients and 65 healthy control subjects.	Cross-sectional, hospital-based, case-control study	• Similar plasma hsCRP in iRLS patients and controls. • Higher serum IL-1β, IL-6, and TNF-α levels in iRLS patients	5
Mondello et al. [44],	Proteomic analysis in serum samples from 12 iRLS and 10 age- and sex-matched control subjects.	Cross-sectional, hospital-based, case-control study	• Increased serum levels of apolipoprotein C-II, leucine-rich alpha-2-glycoprotein 1, FLJ92374, extracellular matrix protein 1, and FLJ93143 - in iRLS patients. • Decreased serum levels of vitamin D-binding protein, FLJ78071, alpha-1-antitrypsin, CD5 antigen-like, haptoglobin, fibrinogen alpha chain, complement factor H-related protein 1, platelet factor 4, and plasma protease C1 inhibitor in iRLS patients	5
Dowsett et al., 2021 [45]	Measurement of neutrophil-to-lymphocyte ratio (NLR) in 13,055 subjects (661 with RLS and 12,394 without RLS)	Cross-sectional study in Danish blood donors	• Patients with RLS showed a significantly higher NLR than controls, although this did not remain after adjusting for sex, age, alcohol consumption, smoking status, and BMI	8
Dowsett et al., 2022 [46]	Measurement of plasma levels of CRP (170 with RLS and 3394 without RLS), soluble urokinase-type plasminogen activator receptor (suPAR) (126 with RLS and 4420 without RLS), and five c-aAb against IL-1α	Cross-sectional study in subsets of Danish blood donors	• RLS showed significantly higher plasma CRP levels (that remained after adjusting for sex, age, BMI, and smoking status).	8

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Table 1 (*continued*)

Patients with iRLS compared with controls				
AUTHORS, YEAR [REF]	STUDY DESIGN	TYPE OF STUDY	MAIN FINDINGS	NOS quality score
	(interleukin-1 alpha), IL-6, IL-10 (interleukin-10), IFN-α(interferon-alpha) and GM-CSF (granulocyte-macrophage colony-stimulating factor) (75 with and 1403 without RLS).		• RLS patients with frequent RLS symptoms showed significantly higher plasma suPAR levels (that disappeared after adjusting for sex, age, BMI, and smoking status) • A higher frequency of RLS patients showed higher caAb against IFN-α	
Patients with chronic kidney disease with vs without RLS				
AUTHORS, YEAR [REF]	**STUDY SETTING**	**TYPE OF STUDY**	**MAIN FINDINGS**	
La Manna et al., 2011 [47]	Measurement of serum or plasma CRP and fibrinogen levels, and erythrocyte sedimentation rate, in 100 patients with ESKD (31 with and 69 without RLS).	Cross-sectional, Hospital-based, case-control study	• Similar CRP levels in both study groups • Significantly higher fibrinogen levels and erythrocyte sedimentation rate in patients with RLS	6
Higuchi et al., 2015 [48]	Measurement of serum levels of high sensitivity CRP (hsCRP) and IL-6 in 157 patients with ESKD (33 with and 124 without RLS).	Cross-sectional, Hospital-based, case-control study	• Significantly higher serum levels of hsCRP and IL-6 in the RLS group. • Serum hsCRP levels were correlated with RLS severity.	6
Nasiri et al., 2015 [49]	Measurement of serum CRP levels in 74 patients with ESKD (62 with and 12 without RLS).	Cross-sectional, Hospital-based, case-control study	• Similar CRP levels in both study groups	4
Kaya et al., 2015 [50]	Measurement of serum CRP levels in 232 patients with ESKD (37 with and 195 without RLS).	Cross-sectional, Hospital-based, case-control study	• Similar CRP levels in both study groups	6
Riar et al., 2019 [51]	Measurement of serum hsCRP levels in 116 pediatric patients with chronic KD (19 with and 97 without RLS).	Cross-sectional, Hospital-based, case-control study	• RLS prevalence tended to be non-significantly higher in the group "with inflammation" (hsCRP concentration ≥1 mg/L) compared with those "without inflammation"	5
Patients with other diseases with vs without RLS				
AUTHORS, YEAR [REF]	**STUDY SETTING**	**TYPE OF STUDY**	**MAIN FINDINGS**	
Mandal et al., 2016 [30]	Measurement of serum levels of high sensitivity CRP (hsCRP) in 76 patients with chronic obstructive pulmonary disease (20 with and 56 without RLS).	Cross-sectional, Hospital-based, case-control study	• Significantly higher serum levels of hsCRP in the RLS group.	5
Chandra et al., 2019 [52]	Measurement of serum levels of IL-6 in 66 patients with hematologic malignancies (4 with and 62 without RLS).	Cross-sectional, Hospital-based, case-control study	• Similar serum IL-6 levels in patients with RLS and without RLS.	5

Table 2
Studies addressing serum/plasma C reactive protein of high specific C reactive protein levels (mg/L) in patients with RLS and healthy controls (HC).

AUTHOR, YEAR [REF]	RLS PATIENTS N	RLS PATIENTS mean ± SD	HC N	HC mean ± SD	Difference of means (95% C·I.), P
Kim et al., 2010 [33]	59	1.9 ± 3.6	655	2.3 ± 6.5	0.40 (−1.28 to 2.08); 0.641
Benediktsdottir et al., 2010 [35]	205	1.4 ± 1.5	1139	1.5 ± 1.5	0.10 (−0.12 to 0.32); 0.380
Auvinen et al., 2018 [38]	98	2.8 ± 0.8	198	3.1 ± 0.4	0.30 (0.16–0.44); <0.0001
Olgun Yazar et al., 2019 [40]	197	2.1 ± 1.8	183	1.6 ± 1.2	−0.50 (−0.81 to −0.19); 0.0017
Reyhani et al., 2021 [42]	102	0.4 ± 0.4	51	0.2 ± 0.2	−0.20 (−0.32 to −0.08); 0.001
Uslu et al., 2021 [43]	29	1.1 ± 2.1	65	1.8 ± 1.7	0.70 (−0.11 to 1.51); 0.090
Dowsett et al., 2022 [46]	170	0.74 ± 1.11	3394	0.52 ± 0.80	−0.22 (−0.35 to −0.09); 0.0006
TOTAL SERIES	**860**	**1.50 ± 1.78**	**5685**	**1.06 ± 2.52**	**−0.44 (-6.15 to -0.27) < 0.0001. Random effects model P = 0.832**

confirmed with the random-effects model, although these findings could be related to the high statistical weight of one of the related works [46], and the lack of homogeneity of the total sample. On the other hand, serum/plasma CRP levels did not differ significantly between patients with RLS compared with those without RLS in patients with chronic kidney disease, and patients with chronic obstructive pulmonary disease. However, the description of an association between serum hsCRP levels and the risk for PLMS in RLS patients [56] points to this protein as a possible marker, at least for this particular symptom.

The results of the meta-analysis of the studies that analyzed the NLR showed a significant increase in this value in patients with RLS compared to healthy controls by using the common-effects model, which was not confirmed with the random-effects model. Serum/plasma levels of cytokines have been addressed by only a few studies, although two of them showed increased TNF-α in RLS

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Table 3
Studies addressing serum/plasma C reactive protein of high specific C reactive protein levels (mg/L) in patients with chronic kidney disease with and without RLS.

AUTHOR, YEAR [REF]	PATIENTS WITH RLS N	PATIENTS WITH RLS mean ± SD	PATIENTS WITHOUT RLS N	PATIENTS WITHOUT RLS mean ± SD	Difference of means (95% C·I.), P
La Manna et al., 2011 [47]	31	1.2 ± 1.2	69	0.8 ± 0.8	−0.40 (−0.80 to 0.00); 0.052
Higuchi et al., 2015 [48]	33	2.6 ± 1.92	124	1.7 ± 1.54	−0.9 (−1.52 to 1.03); 0.005
Nasiri et al., 2015 [49]	62	1.03 ± 0.75	12	2.28 ± 0.82	1.25 (0.77−1.73); <0.0001
Kaya et al., 2015 [50]	37	5.2 ± 6.27	195	6.3 ± 9.73	1.1 (−2.17 to 4.38); 0.509
TOTAL SERIES	**163**	**2.33 ± 3.57**	**400**	**3.80 ± 7.28**	**1.47 (0.30 to 2.64); 0.0142. Random effects model P = 0.693**

Table 4
Studies addressing neutrophil-to-lymphocyte ratio (NLR) in patients with RLS and healthy controls (HC).

AUTHOR, YEAR [REF]	RLS PATIENTS N	RLS PATIENTS mean ± SD	HC N	HC mean ± SD	Difference of means (95% C·I.), P
Varım et al., 2016 [36]	75	1.96 ± 0.66	56	1.67 ± 0.68	−0.29 (−0.52 to −0.06); 0.015
Tak & Sengul, 2018 [37]	62	1.80 ± 1.10	40	2.01 ± 0.67	0.21 (−0.17 to 0.59); 0.281
Reyhani & Kabeloglu, 2021 [42]	102	2.4 ± 1.4	51	1.7 ± 0.9	−0.70 (−1.13 to −0.27); 0.001
Dowsett et al., 2021 [45]	661	1.80 ± 0.55	12,394	1.72 ± 0.55	−0.08 (−0.12 to −0.04); 0.0003
TOTAL SERIES	**900**	**1.88 ± 0.77**	**12,541**	**1.72 ± 0.55**	**−0.16 (-0.20 to -0.12); < 0.0001 Random effects model P = 0.088**

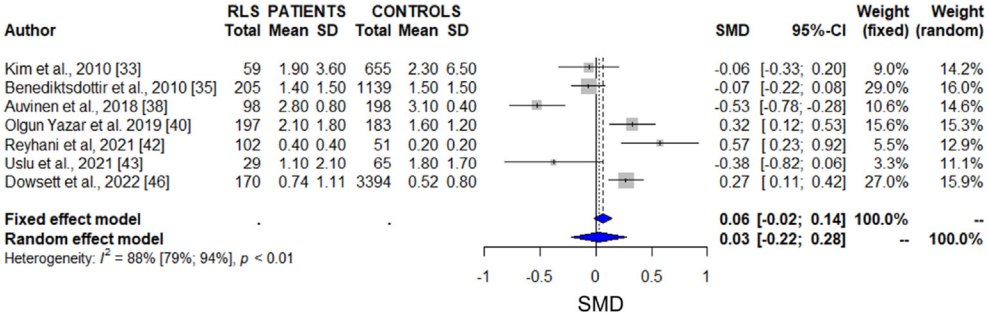

Fig. 2. Meta-analysis of studies measuring serum/plasma C reactive protein (CRP) levels in patients with RLS and controls.

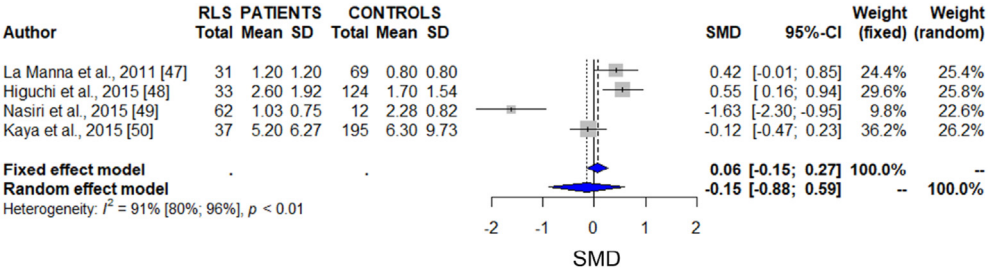

Fig. 3. Meta-analysis of studies measuring serum/plasma C reactive protein (CRP) levels in patients with end-stage kidney disease with vs. without RLS.

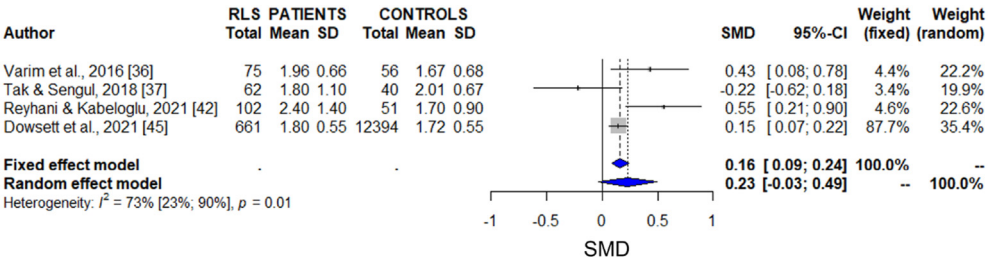

Fig. 4. Meta-analysis of studies measuring neutrophil-to-lymphocyte ratio (NLR) in patients with RLS and controls.

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patients [38,43]. Finally, the results of proteomic studies [34,39,41,44], although they should be considered preliminary, point towards the possibility of a possible role of several inflammatory factors in the pathogenesis of RLS.

In summary, despite previous publications suggesting the increased risk for RLS of patients with different inflammatory diseases [9–14], including infectious diseases [15–29], and the described response of RLS symptoms to steroids [30,31], current data on the possible role of inflammatory factors in the risk for RLS or their value as markers of this disease are not well established. Data from the current meta-analysis showed a non-significant trend towards a possible role of CRP and NLR but, due to the heterogeneity of the results between different series, the results are inconclusive. On the other hand, the possible implication of TNF-α, suggested by two studies (TNF-α and other cytokines were excluded from the meta-analysis because the minimum of studies required was 3) [38,43], and of other inflammatory factors, suggested by proteomic studies (data obtained from these studies are heterogeneous, with small sample size, and none of the proteins were detected in at least 3 studies) [34,39,41,44], awaits confirmation with future replication studies.

Practice points

- Inflammatory factors could hypothetically play a role in RLS because RLS is frequently associated with inflammatory and autoimmune diseases.
- Studies assessing serum/plasma C reactive protein (CRP) levels have shown a non-significant trend towards an increase of this value in patients with iRLS compared with controls.
- Studies assessing the neutrophil-to-lymphocyte ratio (NLR) have shown a significant increase in this value in patients with iRLS, which disappeared after applying the random-effects model.
- Despite proteomic studies that have shown up- or down-regulation of proteins involved in inflammatory processes, data from these studies should be considered preliminary.

Research agenda

We suggest that future studies trying to establish the possible role of inflammatory factors in the pathogenesis of RLS should fulfill, at least, the following conditions.

- Design as prospective and multicentre studies with a long-term follow-up period.
- Recruitment of a large number of patients diagnosed with iRLS according to standardized criteria [1] (both with and without family history RLS, exclusion of secondary causes of RLS should be obligatory), and matched healthy controls not fulfilling clinical criteria for the diagnosis of RLS and without a family history of RLS or other movement disorders.
- Performance of periodic clinical evaluations in the iRLS patients involved in the study (these should include the International RLS group rating scale - (IRLSGRS). Subjects included as healthy controls should also be evaluated periodically for the eventual development of RLS symptoms during the follow-up period (in this case, they should be included in the iRLS group after excluding causes of secondary RLS)
- Collection of plasma/serum and cerebrospinal in iRLS patients and controls (previous to starting treatment for RLS in iRLS patients) for the measurement of multiple potential inflammatory markers should be desirable.
- It should be desirable the obtention of blood DNA from the iRLS patients and controls for genetic studies related to different inflammatory biomarkers (however, previously to the obtention of samples, it should be useful to consult with the GWAS catalog for the National Human Genome Research Institute and European Bioinformatics Institute and look up all the genetic alleles associated with RLS and then see if these alleles are also associated with specific immunological-inflammatory diseases)

Institutional review board statement

Not required because this article is a review.

Data availability statement

All data relating to the current study, intended for reasonable use, is available from J.A.G. Agúndez (University Institute of Molecular Pathology Biomarkers, University of Extremadura -UNEx ARADyAL Instituto de Salud Carlos III, Av/de la Universidad S/N, E10071 Cáceres. Spain) and F.J. Jiménez-Jiménez (Section of Neurology, Hospital del Sureste, Arganda del Rey, Madrid, Spain).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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