doi: http://dx.doi.org/10.11606/issn.1679-9836.v101i2e-155156 Rev Med (São Paulo). 2022 March-April;101(2):e-155156.

Review Article

Ocular manifestations of rheumatoid arthritis and autoantibodies positivity: a systematic review

Manifestações oculares da artrite reumatoide e positividade de autoanticorpos: uma revisão sistemática

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Losso TS, Wiens A. Ocular manifestations of rheumatoid arthritis and autoantibodies positivity: a systematic review / *Manifestações oculares da artrite reumatoide e positividade de autoanticorpos: uma revisão sistemática.* Rev Med (São Paulo). 2022 March-April;101(2):e-155156.

ABSTRACT: *Background*: Ocular involvement represents about 40% of extra-articular manifestations of Rheumatoid Arthritis, pointing to impairment in patients' quality of life. Anti-cyclic citrullinated peptide antibody and rheumatoid factor are serological markers to laboratorial diagnosis of disease. *Objective*: Identify main ocular manifestations of Rheumatoid Arthritis and its relationship between positivity of rheumatoid factor and anti-cyclic citrullinated peptide antibody, through a Systematic Review of literature. *Methods*: Systematic Review was conducted on database search, including: PubMed, Scopus, Web of Science and SciELO until January, 2018. Inclusion and exclusion criteria were applied and data of select studies were extracted and organized in tables and graphics. Methodological appraisal and statistical analysis, including meta-analyses, were performed. Selected studies were stored in software Endnote X8 student (Serial Number: 3151802521 e Product Key: L899B-8N8FJ-SX9JW-BEQ58-U9HCD). Statistical analyses were performed with Review Manager software version 5.3 (free software). *Results*: From 1,985 studies found by database search, four studies were selected and analyzed. Sicca syndrome and secondary Sjögren's syndrome represented about 50% of ocular manifestations. Meta-analyses applied in two studies demonstrated no statistical significative risk association between anti-cyclic citrullinated peptide and development of ocular manifestations. *Conclusion*: From extra-articular manifestations of Rheumatoid Arthritis, ocular manifestations correspond to a significative amount. Nevertheless, there were no statistical significative risk association between autoantibodies and these manifestations.

Keywords: Arthritis, rheumatoid; Rheumatoid factor; Cyclic citrullinated peptide; Keratoconjunctivitis sicca; Sjogren's syndrome.

RESUMO: *Contexto*: As manifestações oculares da artrite reumatoide representam cerca de 40% das manifestações extra-articulares, acarretando comprometimento da qualidade de vida. O fator reumatoide e o anticorpo contra peptídeos citrulinados cíclicos são marcadores sorológicos para diagnóstico laboratorial da doença. *Objetivo*: Identificar as principais manifestações oculares da artrite reumatoide e a sua relação com a positividade do fator reumatoide e anticorpo contra peptideos citrulinados cíclicos, através de uma revisão sistemática. *Métodos*: Uma revisão sistemática foi conduzida nas bases de dados: PubMed, Scopus, Web of Science e SciELO, até janeiro de 2018. Critérios de inclusão e exclusão foram aplicados e dados dos estudos selecionados foram extraídos e organizados em tabelas e gráficos. Avaliação metodológica e análise estatística, incluindo duas meta-análises, foram realizadas. Os estudos selecionados foram armazenados no Software Endnote X8 versão student (Serial Number: 3151802521 e Product Key: L899B-8N8FJ-SX9JW-BEQ58-U9HCD). Análises estatísticas foram realizadas com o *Software Review Manager* versão 5.3 (software gratuito). *Resultados*: Dos 1.985 estudos encontrados através da busca em bases de dados, quatro estudos foram incluídos. A síndrome sicca e síndrome de Sjögren secundária representaram cerca de 50% das manifestações oculares. Meta-análises aplicadas em dois estudos não identificaram associação de risco estatisticamente significativa entre o anticorpo contra peptideos citrulinados cíclicos e fator reumatoide e o desenvolvimento de manifestações oculares. *Conclusão*: As manifestações oculares da Artrite Reumatoide correspondem à significativa parcela das manifestações extra-articulares. No entanto, não foram constatadas associação de risco entre autoanticorpos e tais manifestações.

Palavras-chave: Artrite reumatoide; Fator reumatoide; Anticorpos anti-proteína citrulinada; Ceratoconjuntivite seca; Síndrome de Sjogren.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic and inflammatory autoimmune disease characterized by a deforming polyarthritis of small peripheral joints, however with potential manifestation in other sites. Extra-articular manifestations of RA can develop regardless of patients' age or gender, affect around 40% of total RA, in addition to be related to early morbidity and mortality[1,2,3,4,5,6].

Some predictors of extra-articular manifestations are suggested: male sex, HLA genes, severe articular disease, low functional capacity, smoking, disease duration, high values of inflammatory markers, autoantibodies such as rheumatoid factor (FR) and anti-cyclic citrullinated peptide antibody (anti-CCP)[1,2,3,4,5,6].

Ocular involvement of RA is variable and frequently affects anterior segment of the eye. Most described manifestations are keratoconjunctivis sicca, peripheral ulcerative keratitis, episcleritis, scleritis and retinal vasculitis. Because they present different potential of morbidity and poor visual outcome, like blindness, besides the possibility of emerging independently from other severe manifestations of articular and extra-articular disease, there are studies in the literature aiming to correlate ocular symptoms and autoantibodies[1,2,3,4,5,6].

Purposes of present study are to perform a systematic review (SR) of literature to identify and describe ocular manifestations in RA and its relationship with anti- CCP and RF positivity.

METHODS

This research was conducted in four selected databases: PubMed, Scopus, Web of Science and SciELO with an established search strategy consisting of keywords (controlled vocabulary search terms and free-text terms) about RA, ocular manifestations of RA, autoantibodies and study design. Keywords included Mesh terms and research was conducted until January, 2018. There weren't restrictions about year or journal of publication, authors, as well as there weren't used filters. Considering this breadth, grey literature was included in Scopus and Web of Science's search. Full electronic search strategy for all databases is present in Supplementary material.

From primary selected studies, after removal of duplicates, inclusion and exclusion criteria were applied in title and abstract reading. In sequence, studies whose filled inclusion criteria were selected for full-text reading. After that, studies that fulfilled eligibility criteria were included in the SR. All steps were carried in accordance with Cochrane Handbook for Systematic Reviews of Interventions and PRISMA flow diagram[7,8]. Cochrane Collaboration has defined an acronym for clinical questions construction. "P" refers to population studied, "I" to intervention to be assessed facing "C" comparator, aiming to identify the outcome "O", and "S" to identify studies' design[7,8].

In this research "P" refers to patients with diagnosed RA, "I" to RF and/or anti-CCP antibody positivity, "C" to RF and/or anti-CCP antibody negativity, "O" to ocular manifestations of RA and "S" to included studies in database search[7,8].

Study selection was made by two independent and blinded reviewers and discordance between them, during screening and full-text reading, was resolved by consensus.

Studies were included if they met following criteria: patients diagnosed with RA (above 16 years-old and according to 2010 American College of Rheumatology classification criteria or 1987 American Rheumatism Association classification criteria, in any disease stage or medications' treatment); positivity or negativity of RF and/or anti-CCP; ocular manifestations of RA; research in humans; studies written in Portuguese, English or Spanish; cohort, case-control, cross sectional and interventional studies[9,10].

Studies should include description of used methodology, cut off values, besides positivity, negativity and/or RF and anti-CCP values. They also should expose ocular manifestations analyzed and their relation to autoantibodies, through percentages, values, graphics, tables or in article's texts.

Studies were excluded if not presenting ocular manifestations' of RA; patients diagnosed with other autoimmune diseases (as Juvenile Rheumatoid Arthritis and Primary Sjögren's syndrome); patients diagnosed with other diseases or comorbidities which can present ocular symptoms; ocular diseases resulting from medication's use; absence of description of presence and values of RF and/or anti-CCP; absence of description of relationship between ocular manifestations and RF and/or anti-CCP; absence of methodological description and cut off values of RF and anti-CCP; narrative or systematic reviews, book chapters, case report, case series or workshops; studies written in languages other than Portuguese, English and Spanish.

From included studies, data was extract and organized in text, tables and graphics. Subsequently statistical analysis, including meta-analyses, were performed with studies which presented sufficient description of data and methodological appraisal and risk of bias were analyzed. Although this research was conducted according to Cochrane Handbook for Systematic Reviews of Interventions and PRISMA flow diagram, its protocol was not registered in database registry for systematic reviews [7,8].

Statistical methodology

Results of included studies were expressed as number and percentage to nominal variables, mean and standard deviation or median and interquartile range to quantitative variables[7,11]. Extracted data was organized in tables and graphics using Microsoft Office 2016.

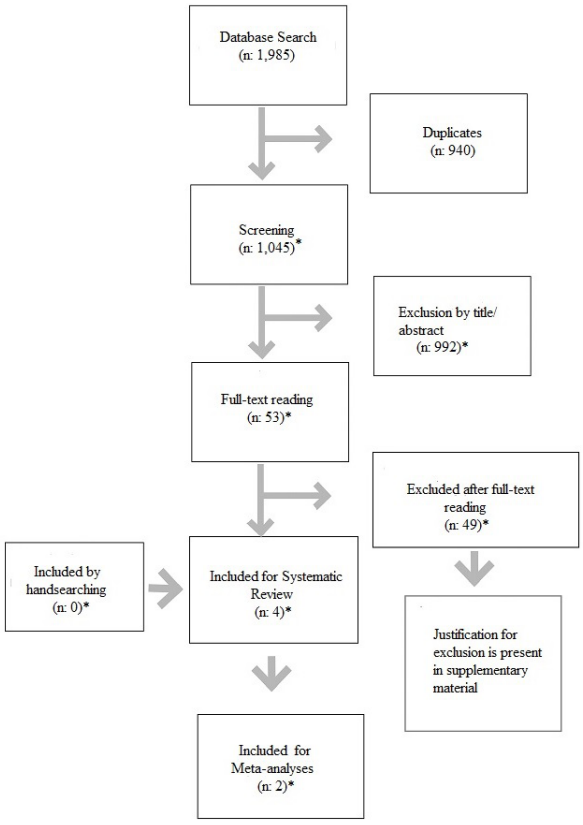
In order to analyze the role of autoantibodies in ocular manifestations of RA, it was performed two statistical analyses. The first one was an accuracy analysis of RF and anti-CCP in predicting presence of ocular manifestations, and the second one was two meta-analyses of association between anti-CCP and RF and development of secondary Sjögren's syndrome[7,11]. In accuracy analysis, it was calculated values of sensitivity, specificity, positive predictive value, negative predictive value and positive likelihood ratio of autoantibodies, presented with respective confidence intervals of 95% (CI95%). Statistical analysis was performed with BioEstat 5.3 program (free software)[11,12].

In meta-analyses, due to few included studies and small sample size, it was selected the Mantel-Haenszel method for dichotomic outcome. Risk ratio (RR) was chosen for effect measure for better understanding of results. It was applied a random-effect model considering clinical and methodological heterogeneity among included studies, and it was measured by I^2 test. Statistical analyses were performed with Review Manager software version 5.3 (free software)[7,13].

Methodological appraisal and risk of bias analysis were performed in accordance with Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies. This checklist included eight topics concerning inclusion and exclusion criteria of included participants, measurement of exposure, identification of confounding factors, strategies to deal with confounding factors, outcomes' measurement and statistical analysis used by authors. For each item, possible answers were "yes", "no", "unclear" or "not applicable[14].

RESULTS

From 4 databases selected, it was found 514 articles in PubMed, 1,230 in Scopus, 230 in Web of Science and 11 in SciELO, totalizing 1,985 articles. Subsequently, 940 duplicates were removed, resulting in 1,045 articles for screening by title and abstract. Inclusion and exclusion criteria were applied in this step. In sequence, 53 studies filled inclusion criteria for full-text reading. After that, four studies fulfilled eligibility criteria and were included in the SR. In order to complement initial research and broaden literature collection, reference handsearching of included studies were conducted, although without identification of additional articles. Figure 1 shows each operational step. Excluded studies, after full-text reading with justification, are present in Supplementary material[7,8].



Source: the author (2018).
Legend: * steps made by two blinded reviewers.

Figure 1. Operational steps in studies' selection

Three of included studies, (Salinas et al.[5], Alexiou et al.[15] and Gonzalez-Lopez et al.[16]), divided their samples of RA patients in groups with and without extra-articular manifestations of RA (EAM), with mean age, in years, between sixth and seventh decades and mean duration of RA, ranging from 5,9 to 12,4 years. Two articles, Salinas et al.[5] and Gonzalez-Lopez et al.[16], reported women and men population in each group, consequently, proportion of men: women were 1: 2,9 in both groups (with and without EAM), in first study, while in second one 1: 22,75 in EAM's group and 1: 8,3 in the other group[5,16]. Patients' clinical characteristics, in mentioned studies, are described in details in Table 1.

Table 1 – Clinical and laboratory characteristics of patients with and without extra-articular manifestations

Author / year	Clinical and laboratorial characteristics	With EAM	Without EAM
Alexiou et al.[15] 2008	Population, n (%)	95 (43,18)	125 (56,82)
	Female, n (%)	NR	NR
	Age (years, mean ± SD)	62,07 ± 12,4	60,8 ± 13,5
	Age at disease diagnosis	NR	NR
	Disease duration (years, mean ± SD)	11,6 ± 9,1	11,6 ± 10
	Anti-CCP + (n)	62/95	73/125
	Anti-CCP values (IU/ml, mean ± SEM)	99,1 ± 16,1	73,1 ± 10,2
	RF + (n)	66/95	75/125
	RF values (IU/ml, mean ± SEM)	265,0 ± 52,0	205,1 ± 40,6
Salinas et al.[5] 2013	Population, n (%)	74 (50)	74 (50)
	Female, n (%)	55 (74,32)	55 (74,32)
	Age (years, mean ± SD)	59,4 ± 12,1	59,5 ± 13,3
	Age at disease diagnosis (years, mean ± SD)	47 ± 12,3*	54,3 ± 14,5*
	Disease duration (years, mean ± SD)	12,4 ± 9,8*	5,9 ± 7*
	Anti-CCP + (n)	63/74*	43/74*
	Anti-CCP values (median, IQR)	116 (43,7-116,7)°	34 (2,7-35,7)°
	RF + (n)	67/74*	42/72*
	RF values (median, IQR)	108 (30-248)°	34,5 (2,7-114,5)°
Gonzalez-Lopez et al.[16] 2014	Population, n (%)	95 (42,22)	130 (57,78)
	Female, n (%)	91** (95,79)	116** (89,23)
	Age (years, mean ± SD)	54,82 ± 10,62*	50,75 ± 10,92*
	Age at disease diagnosis	NR	NR
	Disease duration (years, mean ± SD)	11,6 ± 9,69*	7,04 ± 6,57*
	Anti-CCP + (n)	NR	NR
	Anti-CCP values (IU/ml, mean ± SD). In 225 patients*	78,62 ± 104,86**	67,99 ± 74,14**
	RF + (n)	NR	NR
	RF values (IU/ml, mean ± SD). In 204 patients*	119,16 ± 220,03**	119,07 ± 252,69**

Included patients in Silva et al.[17] weren't divided in groups with and without EAM. Instead, demographic, clinical and laboratory features were analyzed as one group. Among 100 included participants, with mean age of 50 years, 88 were female. RA duration in years was 8 with standard deviation of 6,8 years, and mean age of disease onset was 42 years with standard deviation of 12,7 years[17].

Included articles studied RF and anti-CCP auto-antibodies, but mensuration was different among them, including manufacturer and technic aspects. Methodology used by each author were: In Alexiou et al.[15], IgM RF was measured by immuno-nephelometry (Dade-Behring®)

with cut off value of 15 IU/ml and anti-CCP by ELISA CCP2 kit (QUANTA lite IgG kit, INOVA®) with cut off value of 20 IU/ml. In Salinas et al.[5], RF was measured by immunoturbidimetry (without reporting of manufacturer) with positivity > 14 IU and anti-CCP was assessed by ELISA (Quanta Lite II, Inova diagnostics Inc®, San Diego, CA, USA) with negativity < 20 IU, low positivity 20-39 IU, intermediate positivity 40-59 IU and high positivity > 60 IU. In Gonzalez-Lopez, L. (2014), RF was measured by nephelometry (Dade Behring, DE®) with positivity > 20 IU/ml and anti-CCP by ELISA (DIASTAT, Axis-Shield Diagnostics Limited®, UK) with positivity ≥ 5 IU/ml. Finally, in Silva et al.[17] IgM RF was measured by immunoturbidimetry (Spinreact kit®) with positivity > 20 IU/ml and anti-CCP by ELISA (Immunoscan RA, EuroDiagnostica®) with negativity ≤ 25 IU/ml[5,15,16,17].

Studies described identified EAM, however, there wasn't total uniformity in methodology of detection and which manifestations were considered EAM. Alexiou et al. and Silva et al. cited EAM analyzed without describing used diagnostic criteria. Salinas et al.[5] described them as diagnosed by clinical examination and/or through complementary exams, while Gonzalez-Lopez et al.[16] used a protocol, including clinical judgement and/or complementary exams, for each EAM. Ocular manifestations of RA (OM) represented expressive proportion within EAM, as in Alexiou et al.[15], prevalence of sicca syndrome was 55,8%, and in Salinas et al.[5], 47,2%, while in Gonzalez-Lopez et al.[16], 61% for secondary Sjögren's syndrome. Silva et al.[17] reported 46% of secondary Sjögren's syndrome among all included patients[5,15,16,17].

EAM described in three of selected studies (Alexiou et al.[15], Salinas et al.[5] and Gonzalez-Lopez et al.[16]) can be listed in two subgroups, OM and non-ocular EAM. In Alexiou et al.[15], OM subgroup included scleritis, episcleritis and sicca syndrome while others were: rheumatoid nodules, serositis (pleural and pericardial fluids), pulmonary fibrosis, Felty's syndrome, Raynaud's phenomenon, vasculitis, and non-compressive neuropathy. Salinas et al.[5], described in OM subgroup: keratoconjunctivitis, xeropthalmia, scleritis, episcleritis, uveitis, retinal vasculitis and sicca syndrome. In non-ocular EAM: pericarditis (with or without effusion), ischemic cardiopathy, valvopathy, arrythmia, rheumatoid nodules (subcutaneous or in other organs), cutaneous vasculitis or in others organs, pleuritis with or without effusion, pulmonary fibrosis, bronchiolitis obliterans, non-compressive peripheral neuropathy, atlantoaxial subluxation, myositis, xerostomia, hepatitis, Felty's syndrome, anemia, glomerulonephritis and amyloidosis[5,15,16].

Finally, Gonzalez-Lopez et al.[16], described in OM subgroup: scleritis, episcleritis, uveitis, retinal vasculitis, keratoconjunctivis sicca and secondary Sjögren's syndrome. In non-ocular EAM subgroup: pericarditis, bronchiolitis obliterans, organizing pneumonia, pulmonary fibrosis, interstitial lung disease, Felty's syndrome, chronic anemia, major cutaneous vasculitis and vasculitis involving other organs, neuropathy, cervical myelopathy, glomerulonephritis, amyloidosis, xerostomia and subcutaneous rheumatoid nodules. Silva et al. described two EAM: subcutaneous nodules and secondary Sjögren's syndrome without dividing them between OM and non-ocular EAM[16,17].

Groups with and without EAM were also compared regarding presence and values of autoantibodies, except for Gonzalez-Lopez et al.[16], who didn't report all data of positivity or negativity for RF and anti-CCP in both groups. These percentages and values were compared between groups, but statistical tests and corresponding p values to evaluate statistical significance weren't described, by authors of included studies, in all analysis[5,15,16].

In Alexiou et al.[15], EAM group presented higher values and positive percentages for RF and anti-CCP compared to group without EAM, although differences between them weren't statistically significant or didn't have reported p values. In Salinas et al.[5], EAM group were identified with higher values and positivity for RF and anti-CCP compared to other group, and these differences were statistically significant, with $p < 0,05$, and statistical tests reported. In Gonzalez-Lopez et al.[16], RF and anti-CCP values weren't statistically different among groups, with $p > 0,05$ and statistical tests reported[5,15,16].

Concerning ocular manifestations, detailed manifestations were sicca syndrome in Alexiou et al.[15], xerophthalmia in Salinas et al.[5], and secondary Sjogren's syndrome in Gonzalez-Lopez et al.[16] and Silva (2006)[5,14,15,16]. In Alexiou et al.[15], comparing patients with sicca syndrome with those without EAM, authors identified anti-CCP positivity in 66% and 58,4%, respectively. Analyzing patients with sicca syndrome, 66% showed positivity and 34% negativity for anti-CCP. However, p values and statistical tests weren't reported for these analyses. In Salinas et al.[5], the group with xerophthalmia were anti-CCP positive in 83,1% against 43% in group without EAM, just as anti-CCP values were higher (150 IU, value in median) in the first group compared to the second one (34 IU, value in median). In this study, data for analysis of statistical significance was described. In Gonzalez-Lopez et al.[16], patients with secondary Sjogren's syndrome presented similar RF and anti-CCP positivity to patients without this syndrome and groups' difference didn't reach statistical significance, with $p > 0,05$ and statistical tests reported. In Silva et al.[17] 73,9% of patients with Sjögren's syndrome were anti-CCP positive and 89,1% RF positive, while 63% of patients without Sjögren's syndrome were anti-CCP positive and 92,6% RF positive, with statistical test reported and $p > 0,05$[5,15,16,17].

Statistical evaluation of included studies

According to described data reported by authors of included studies, autoantibodies' diagnostic validity tests were performed for sicca syndrome and anti-CCP

in Alexiou et al.[15], RF, anti-CCP and secondary Sjögren's syndrome for Gonzalez-Lopez et al.[16] and Silva et al.[17]. Salinas et al.[5] didn't report enough data for this statistical analysis. In line with results showed in Table 2, sensitivity values were lower than 75%, except for RF in Silva et al.[17], accuracy values were lower than 55% and positive likelihood ratios presented values near 1,0[5,11,15,16,17].

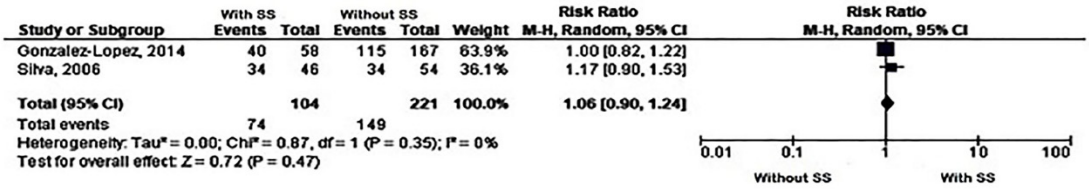
Table 2 – Autoantibodies' diagnostic validity tests for ocular manifestations of rheumatoid arthritis

Validity data	Alexiou et al.[15] (2008)	Gonzalez-Lopez et al.[16] (2014)		Silva et al.[17] (2006)	
	Anti-CCP (n: 220)	Anti-CCP (n: 225)	RF (n: 204)	Anti-CCP (n: 100)	RF (n: 100)
Sensibility -% (CI95%)	66 (53,3-78,8)	69 (57,1-80,9)	55,8 (42,3-69,3)	73,9 (61,2-86,6)	89,1*
Specificity-% (CI95%)	40,1 (32,7-47,6)	31,1 (24,1-38,2)	30,3 (23,0-37,6)	37 (24,2-49,9)	7,4*
PPV-% (CI95%)	25,9 (18,5-33,3)	25,8 (18,9-32,7)	21,5 (14,6-28,4)	50 (38,1-61,9)	45,1 (34,8-55,3)
NPV-% (CI95%)	78,8 (70,1-87,5)	74,3 (64,0-84,4)	66,7 (55,5-77,8)	62,5 (45,7-79,3)	44,4*
Accuracy-% (CI95%)	46,4 (39,8-53,0)	40,9 (34,5-47,3)	36,8 (30,1-43,4)	54 (44,2-63,8)	45 (35,2-54,8)
LR + (CI95%)	1,1 (0,88-1,39)	1 (0,82-1,22)	0,8 (0,61-1,04)	1,2 (0,90-1,53)	1 (0,85-1,09)

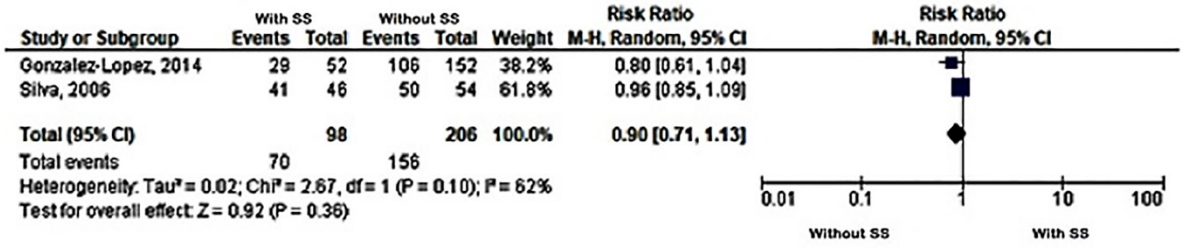
Results from Gonzalez-Lopez et al.1[6] and Silva et al.[17], presented data that allowed meta-analyses of association between autoantibodies, anti-CCP and RF, and secondary Sjögren's syndrome. Meta-analyses were conducted to evaluate anti-CCP and RF ability to predict development of secondary Sjögren's syndrome. Forest plot of anti-CCP and secondary Sjögren's syndrome is presented in Figure 2, while that of RF and this syndrome is presented in Figure 3[7,16,17].

Salinas et al.[5] didn't report enough data for these statistical analyses. In Alexiou et al.[15], available data concerned sicca syndrome, therefore, it wasn't possible to include it in these meta-analyses[5,15].

In the first Forest plot (Figure 2), RR for meta-analysis was 1,06 with CI95% of 0,90-1,24, with I^2 test of 0%. In the second Forest plot (Figure 3), RR for meta-analysis was 0,90 with CI95% of 0,71-1,13, with I^2 test of 62%[7,16,17].



Source: The author (2018).
Legend: Secondary Sjögren syndrome (SS), confidence interval of 95% (CI).
Figure 2 – forest plot of association between anti-cyclic citrullinated peptide antibody and secondary Sjögren's syndrome



Source: The author (2018).
Legend: Secondary Sjögren syndrome (SS), confidence interval of 95% (CI).
Figure 3 – Forest plot of association between rheumatoid factor and secondary Sjögren's syndrome

Methodological appraisal of included studies

Methodological evaluation of included studies in this SR was based on descriptions reported by each author. Salinas et al. and Gonzalez-Lopez et al. named themselves as cross-sectional studies and their methodological descriptions were compatible with this study design. Alexiou et al. described itself as retrospective and didn't detailed other information. Through analysis of methodological description, it was classified as cross-sectional. Silva et al. missed information about study design, thus, based on methodological description, it was classified as cross-sectional[5,15,16,17].

Built around these considerations, methodological and risk of bias analysis were made in accordance with Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies. This critical appraisal checklist is completely available in Supplementary Material[14].

Among included studies, Gonzalez-Lopez et al.[16] represented the most complete study, with greater number of answers "yes" and better description of methodological and statistical characteristics, otherwise, Alexiou et al. presented half of answers as "unclear", reflecting lack of methodological and statistical description. In second and third places of quality in methodological appraisal are, respectively, Salinas et al.[5] and Silva et al.[17]. Table 3 summarizes obtained responses[5,15,16,17].

Table 3 – Synthesis of methodological evaluation of included studies in this systematic review

Authos / Year	Possible answers				Total
	Yes	No	Unclear	Not applicable	
Alexiou et al.[15] (2008)	2	2	4	0	8
Salinas et al.[5] (2013)	5	0	3	0	8
Gonzalez-Lopez et al.[16] (2014)	7	0	1	0	8
Silva et al.[17] (2006)	3	2	3	0	8

Source: Adapted from Moola et al. (2017).

DISCUSSION

From studies included in this SR, it is noted that extra-articular manifestations of RA weren't rare and, among them, ocular manifestations represented an important portion. These findings are concordant with other studies present in literature. Cimmino et al.[18], studied 587 Italian RA patients and identified 42,9% of sicca syndrome within EAM, while Turesson et al.[4] verified 24,7% of keratoconjunctivitis sicca among EAM in a cohort study consisting of 609 RA patients in Rochester, Minnesota.

Main ocular manifestations of RA described in literature are, for anterior segment of the eye, keratoconjunctivitis sicca, peripheral ulcerative keratitis, anterior scleritis, episcleritis and, for posterior segment, posterior scleritis and retinal vasculitis. In this SR, evaluated ocular manifestations were sicca syndrome, xerophthalmia and secondary Sjögren's syndrome, which present a common element: dry eye or keratoconjunctivitis sicca[6,19,20]. This condition is chronic and demands continuous treatment, becoming one morbidity in RA patients[6,19,20].

Diagnostic accuracy analysis of anti-CCP and RF demonstrated that autoantibodies' positivity wasn't capable in predicting presence of sicca syndrome and secondary Sjögren's syndrome. This observation was based on analysis of three studies and available in sicca syndrome and secondary Sjögren's syndrome, failing in applying it to other ocular manifestations of RA[11,15,16,17].

Meta-analysis was conducted from two of selected studies. It showed absence of statistical significative risk association between anti-CCP and RF and secondary Sjögren's syndrome. However, same affirmation cannot be concluded for other ocular manifestations, since there wasn't available data, from included studies, for these analyses[7,16,17].

Main limitations of this SR were shortage of observational studies, concerning the proposed clinical question, in literature search; lack of standardization in autoantibodies' mensuration and ocular manifestations' definitions. There were not complete data availability from included studies in order to allow better comparability between them and better statistical analyses[5,15,16,17].

CONCLUSION

In this Systematic Review, ocular manifestations of Rheumatoid arthritis represented a considerable amount, about of 50%, and the main described were: sicca syndrome, xerophthalmia and secondary Sjögren's syndrome, presenting dry eye or keratoconjunctivitis sicca as a common element. Nevertheless, it was not found statistically significant risk association between rheumatoid factor and anti-CCP and these manifestations.

Authors participation: *Losso TS* and *Wiens A* - contributed in elaboration, correction and analysis of this research.
Acknowledgment: to Dr *Aristides Cruz* for participation in statistical analysis and to Dr *Magali Santiago Silva* for participation in methodological construction of this search.

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Submeted: 2019, February 23
Accepted: 2022, February 11