

Diagnostic accuracy of IL-6, IL-10 and TNF- α cytokine levels in patients with mild cognitive impairment: Systematic review and meta-analysis

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Abstract

Introduction: There is growing evidence suggesting an association between Neurodegeneration and Inflammation playing a role in the pathogenesis of age-associated diseases, including Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). A systematic review and meta-analysis were performed to verify evidence on the diagnostic accuracy parameters of the inflammatory cytokines Interleukin-6 (IL-6), Interleukin-10 (IL-10) and Tumor Necrosis Factor (TNF- α). **Method:** A search of Medline, Scielo, Web of Science and Science Direct databases was performed and 9 observational studies associated with peripheral inflammatory biomarkers in CCL were identified. Mean (\pm SD) concentrations of these biomarkers and values of true positives (VP), true negatives (VN), false positives (FP) and false negatives (FN) for CCL and healthy controls (CS) were extracted from these studies. **Result:** Significantly higher levels of IL-10 were observed in subjects in the MCI group and Mini Mental State Examination (MMSE) scores were lower compared to CS. For the other investigations, no differences were found between the groups. Our meta-analysis for the TNF- α biomarker revealed high heterogeneity between studies in terms of sensitivity and specificity. **Limitations:** Lack of essential data in observational studies, which directly impacted the number of included studies. **Conclusion:** These findings do not support the involvement of inflammatory biomarkers for detection of MCI, although significant heterogeneity was observed. More studies are needed to evaluate the role of these cytokines in MCI, as well as in other stages of cognitive decline and all-cause dementias.

INTRODUCTION

The term Mild Cognitive Impairment (MCI) had its concept refined by Petersen e cols¹, who defined it for the first time as the initial stage of Alzheimer's Disease (AD) characterized predominantly by a decline in memory more than expected for a specific age, but not yet sufficient for the diagnosis of dementia. In 2004, this term was expanded and started to be described not only as a phase of AD, but was divided into four subtypes, thus covering other cognitive domains and being associated with other etiologies^{2,3}.

Prevalence studies show conversion rates from MCI to AD around 10 to 15% per year, while in normal individuals the evolution to AD is 1 to 2% per year, although an extensive variation in these rates is admitted in due to different methodological research strategies, different cognitive assessment instruments, age of the studied population and variability of operational diagnostic criteria^{3,4}.

Studies such as Petersen e cols⁵, evaluated the effectiveness of pharmacological treatments in MCI and point to possible ineffectiveness in reducing the chances of progression to dementia or probable Alzheimer's dementia. As a result, non-pharmacological treatments such as Transcranial Direct Current Stimulation

(tDCS) has gained significant attention as a possible intervention for the treatment of symptoms in MCI and AD, but the divergent results have led to uncertainties about the use of this non-invasive brain stimulation as a clinical therapy⁶. Benefits of drinks with high doses of flavonoids⁷, supplementation with B vitamins⁸, and with vitamin E, alone⁹ or combined with vitamin C¹⁰, also need to be further investigated, as their efficacy is uncertain and there is a low level of evidence.

In view of the discrepancies found, studies have sought to identify, with greater precision, useful biological biomarkers that can be correlated with mechanisms that may be involved in the development and progression of the severity of cognitive impairment¹¹, and thus, by believing that inflammatory processes are part of the AD brain pathology, studies show cytokines such as interleukin (IL)-6^{12,13,14,15}, as a marker of systemic inflammation that has been associated with cognitive decline, changes in brain morphology and increased risk of dementia, AD^{16,17}. Another potentially cited biomarker is tumor necrosis factor (TNF- α), an important mediator of systemic inflammation, activator of the central innate system, as well as other interleukins that modulate inflammation such as IL-2 and IL-10¹⁸. However, these findings are still confusing and of limited accuracy.

In this scenario, the assessment of inflammatory markers in individuals at risk of dementia, may reflect a more robust diagnostic measure and the conduct of this research aimed to seek evidence on the parameters of diagnostic accuracy of cytokines (IL-6, IL-10 and TNF- α) to resolve doubts and complement the detection of Mild Cognitive Impairment, thus providing support in clinical decision-making. We also sought to highlight possible gaps relevant to this topic present in the scientific literature that may highlight the need for new, more careful studies.

METHOD

study design

This is a systematic review with meta-analysis of observational studies. The protocol for this study was designed in accordance with the Preferred Reporting Items checklist for a systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA)¹⁹ and Cochrane recommendations Collaboration. In addition, it was registered with the International Prospective Register of ongoing Systematic Reviews - PROSPERO, under registration number ID: CRD42021254894.

Criteria for selection of studies

This review focused on observational studies in which serum levels of the markers of interest IL-6, IL-10 and TNF- α in plasma or serum of patients with Mild Cognitive Impairment were compared. For the meta-analysis, those studies that presented values of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) were considered, in addition to informing the blinding of participants and professionals involved in the diagnosis and performance of the tests blood.

Types of participants

Studies were selected that included participants of both sexes; aged [?] 50 years; diagnosed with Mild Cognitive Impairment, according to the criteria of Petersen et cols²⁰, and without a diagnosis of dementia according to the Diagnostic and Statistical Manual-IV (DSM-IV) and the National Institute of Neurology and Communication Disorder and Stroke -The Alzheimer's disease and Related Disorders Association Criteria (NINCDS-ADRDA)²¹.

Eligibility Criteria

Studies were included in this systematic review if they met the following eligibility criteria: (1) Our study included articles associated with inflammatory biomarkers (IL-6, IL-10, TNF- α) as predictors in the diagnosis of MCI; (2) studies must include healthy controls (HC) and MCI patients as participants; (3) have clearly described all inclusion and exclusion criteria; (4) describe diagnostic criteria and Neuropsychological tests for assessing cognitive function. No restrictions were used for CCL subtypes.

Exclusion criteria included: (1) articles that were associated with other diseases and disorders, such as vascular dementia, schizophrenia, depression, and others; (2) conference abstracts, letters to the editor, opinion pieces or editorials; (3) literature or systematic reviews; (4) Case studies without group-level statistics; (5) studies involving animals or works unrelated to the topic addressed were also excluded. All longitudinal studies were considered, provided they met the inclusion and quality criteria.

Search methods for identifying studies

Two researchers (BLLM and LLD) independently performed data collection using the mesh terms : “ Mild Cognitive Impairment ”, “ Cognitive Dysfunction ”, “ Inflammation mediators ”, “ Inflammation ”, “ Interleukins ” and other terms with a combination of Boolean Operators “AND” and “OR” in the following online databases: MEDLINE (*Medical Analysis and Retrieval System Online*) via PubMed ; Scielo (*Scientific Electronic Library Online*); Scopus (*Elsevier*); Web of Science (*now Clarivate Analytics*); and Science Direct, with no language restrictions to capture all possible relevant titles. Manual searches were also performed in the reference lists of included studies, related articles, article citations, and in the gray literature. All steps were completed by August 2022.

The selected studies were reassessed by the other authors (GKAL, GERM and ASSMS) to weigh the potentially eligible works and determine whether they actually met the selection criteria.

First, there was a reading of the abstracts and a second screening by reading the full text of the other articles. Disagreements were resolved by discussion and consensus with other reviewers, if necessary. All articles were managed in Rayyan Software (Intelligent Systematic Review) which was also used to remove duplicates. **Figure 1** shows the Flowchart (PRISMA) summarizing the study selection process.

Data extraction and tabulation

The articles that met the pre-established eligibility criteria were read independently by the researchers (GKAL, GERM and ASSMS) and carefully analyzed to obtain the results. Data were extracted using a spreadsheet with predefined categories, which consisted of general and individual information about each selected study, such as author, year of publication, demographic data of participants (sample size, age, gender, education), mean Mini- Mental State Examination (MMSE) score), values for the diagnostic tests of interest, and whether the sample was collected from serum or plasma. This instrument allowed each reviewer to extract data from the sample individually and facilitated the subsequent analysis of the data obtained. When there was no data or clarity of details, the authors of the studies were contacted for possible clarifications, but only one responded to the researchers’ request for data.

Data from selected studies were concatenated and analyzed. The analysis was carried out using the R version 4.2.1 *software* , freely available at <https://www.r-project.org/> . The significance level adopted throughout the analysis was 5%.

Quality assessment and risk of bias

Study quality was assessed using the tool developed by the University of Bristol known as QUADAS-2 (<https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/>) and recommended by the Cochrane Collaboration. The risk of bias in individual studies included 4 domains: (1) patient selection; (2) index test; (3) reference standard and (4) flow and time, analyzing the risk of bias and applicability in each category.

The results were incorporated into our sensitivity analysis, where only studies with low to moderate risk of bias were included. The evaluation was carried out using the Review Manager software version 5.3 and the result of the evaluation of each of the articles is presented in the form of a table.

Data analysis

At the end of the survey and data organization, a descriptive analysis of the study variables per group (CCL or Control) was performed using the mean and standard deviation as summary measures. After the

descriptive analysis, in order to choose the appropriate analysis methodology, the Shapiro-Wilk normality test was initially applied to test the null hypothesis that the data follow a normal distribution *versus* the alternative hypothesis that the data do not follow a normal distribution normal. Additionally, to test the hypothesis that there was no difference between the case and control groups for the study variables *versus* the alternative hypothesis that there was a difference between the case and control groups for the study variables, the Student t test for samples was used independent for variables with approximately normal distribution. For variables that do not follow an approximately normal distribution, the Wilcoxon -Mann-Whitney test was used to test this hypothesis.

The meta-analysis was performed according to the technique and sample type of each study (that is, by subgroups). Sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were measured with a 95% confidence interval based on the TP, TN, FP and FN rates that were extracted from the included studies.

Sensitivity, defined as the probability of a test result being positive when the disease exists (true positive rate) was calculated as $= TP / (TP + FN)$. Specificity, defined as the probability of a test result being negative when the disease is not present (true negative rate) was calculated as $= TN / (TN + TP)$. The PLR is the ratio of the probability of a positive test result given the presence of the disease to the probability of a positive test result given the absence of the disease, that is $= \text{true positive rate} / \text{false positive rate}$, or expressed as $\text{sensitivity} / (1 - \text{specificity})$. The NLR is the ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease, that is $= \text{false negative rate} / \text{true negative rate}$. SROC curves based on TP and FP rates were also constructed whenever possible to describe the relationship between test sensitivity and specificity.

The heterogeneity of the studies was established using the χ^2 test, with inconsistency values (I^2) greater than 50% considered moderate heterogeneity, and I^2 greater than 75% defined as high heterogeneity. Results with I^2 values greater than 50% were subjected to sensitivity analysis (that is, hypothetical removal of studies).

RESULTS

Identification of Studies

The search in the informed databases found a total of 11.392 articles, where 11.172 articles were identified after removing duplicates. Of these, 11.116 were excluded during the screening phase (reading the title and abstract) as they did not fit the research profile, with 56 records being fully evaluated. Finally, 9 studies that met the eligibility criteria established by the researchers were included in the systematic review, and of these, only two could be included in the meta -analysis. The report items that contemplate the process of identification and selection of studies are detailed in **Figure 1** .

Fig. 1 PRISMA flowchart summarizing study selection process

The included articles comprised a total of 2.436 participants where we can observe that a quantitative of 653 individuals were allocated in the CCL group, while 1.783 were allocated in the control group. The common information of most studies concerns the size and type of sample, age, sex, MMSE scores, serum IL-6, IL-10 and TNF- α values and are shown in **Table 1** .

Additionally, we note that the included studies were published between 2012 - 2019, and that four of them used plasma samples, four studies used serum samples, and one study did not specify the type of sample. Seven of the 9 studies included participants aged 60 years or older, and 2 had participants aged 50 years or older^{22,23}. Only one study did not specify the male/female ratio, but considering the others, a total of 1.279 men (339 cases and 940 controls) and 1.095 women (284 cases and 811 controls) can be observed. The study by Wennberg e cols²³ was the only one that did not use the MMSE as part of the neuropsychological assessment. Eight of the 9 studies evaluated serum levels of IL-6, four of IL-10 and six of TNF- α .

Table 1 : Data.

Study	Study	Type	Sample	Sample	Age	Age	% Women	% Women	MMSE	M
			case	ctrl	case	ctrl	case	ctrl	case	ct
²² Zhao 2012	²² Zhao 2012	serum	150	150	70.67	69.85	47.30	41.30	26.55	27
²³ Wennberg 2019	²³ Wennberg 2019	plasma	186	1416	79.70	71.90	40.90	47.30	-	-
²⁴ Shen 2019	²⁴ Shen 2019	plasma	57	57	68.77	67.77	31.58	31.58	25.82	29
²⁵ Magalhães 2017	²⁵ Magalhães 2017	serum	55	42	71.00	68.00	63.54	71.43	28.51	25
²⁶ King 2019	²⁶ King 2019	plasma	77	20	76.13	75.90	40.00	25.00	26.47	29
²⁷ Johansson 2017	²⁷ Johansson 2017	serum	11	18	72.00	76.00	54.54	44.44	28.00	29
²⁸ Kim 2017	us	us	29	28	75.03	72.00	61.50	57.10	23.62	27
²⁹ King 2017	plasma	plasma	58	20	77.05	75.90	45.76	25.00	26.45	29
³⁰ Dursun 2015	serum	serum	30	32	74.40	72.10	-	-	27.59	28

Comparison between groups

After carrying out the descriptive analyzes of the study variables that are available in **Table 2** , we can observe that there was a significant difference between the MMSE values of the CCL and control groups (p-value = 0.0065), so that the control group presented a higher mean value than the CCL group. There was also a significant difference between the IL-10 values of the CCL and control groups (p-value = 0.0126) so that individuals in the CCL group had a higher mean value than individuals in the control group. We can better observe the results obtained in the comparison between the groups of the main variables of the study in **Figure 2** .

Table 2 : Comparison of study variables between groups.

Variável	caso (n = 653)	controle (n = 1783)	p-valor
Idade	73,86 ± 3,51	72,158 ± 3,25	0,3020 ¹
% mulheres	48,14 ± 11,06	42,89 ± 16,07	0,4611 ¹
MMSE	26,63 ± 1,51	28,19 ± 1,29	0,0442 ^{1*}
IL-6	3,50 ± 2,91	2,37 ± 1,24	0,3735 ¹
IL-10	0,99 ± 0,08	0,62 ± 0,16	0,0126 ^{1*}
TNFα	5,64 ± 5,03	5,92 ± 4,11	0,8099 ²

*-significant results; 1- Student's t test for independent samples; 2- Wilcoxon -Mann- Whitney test

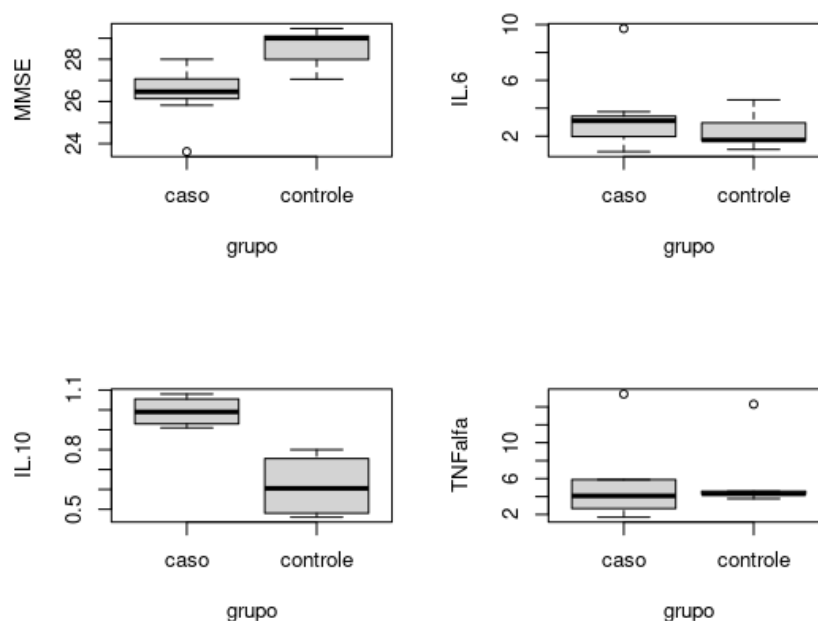


Figure 2 : Box - plot of the main study variables by group.

Quality Assessment

Studies were classified as moderate overall methodological quality according to QUADAS-2. All studies described patient selection methods and those included corresponded to the review question. Overall, the studies adequately reported the index and reference standard tests and how they were conducted and interpreted, but 6 of the 9 studies did not report blinding between those involved in clinical diagnosis and analyses, and only 5 studies specified the lower limits of detection for the evaluated markers, which entailed implications for the applicability domain.

Those who reported the interval between tests, whether patients received different index or standard trials, and full statistical analyzes performed, were thus judged to have low risk of bias for the flow and time domain. The remaining studies were classified as having an uncertain risk of bias for this domain. The entire summary of the methodological quality assessment can be seen in **supplementary figures 1 and 2**.

Meta-analysis

After selecting the studies, a diagnostic meta-analysis was performed for the inflammatory marker TNF- α , as a means of detecting MCI. The studies considered were Shen e cols²⁴ and Magalhães e cols²⁵. **Table 3** describes the sensitivity and specificity values of each study, as well as their respective 95% confidence intervals. We can observe that in the study carried out by Shen e cols²⁴, the method had a sensitivity of 0.836 and a specificity of 0.181, that is, we concluded that the method is more likely to be correct in detecting the disease in sick patients than detecting its absence in non-ill patients. In the study carried out by Magalhães e cols²⁵, the finding was in the opposite direction, so that a sensitivity of 0.321 was found, while the specificity was equal to 0.988, which indicates that the method is more effective in detecting the absence of the disease in non-ill patients than the presence of the disease. disease in patients. The results in **Table 3** can be seen graphically in **Supplementary Figures 3 and 4**, respectively.

Table 3 : Sensitivity and Specificity of the studies in the meta-analysis.

Study	sensitivity	specificity
Shen et al. 2019	0.836 [0.721; 0.910]	0.181 [0.103; 0.299]
Magalhas et al. 2017	0.312 [0.206; 0.443]	0.988 [0.898; 0.999]

Investigation of heterogeneity and publication bias

To check for heterogeneity between the sensitivity and specificity of the studies, the Chi-square test was used to test the null hypothesis that the studies have the same sensitivity or specificity *versus* the alternative hypothesis that the studies do not have the same sensitivity or specificity. In both cases, we obtained a p-value < 0.0001 , that is, we rejected the null hypotheses that the sensitivity and specificity of the studies are equal. Therefore, based on the sample and with 95% confidence, we conclude that the studies are heterogeneous in terms of sensitivity and specificity. It is important to determine the reason for the variation and understand whether it occurred by chance.

Table 4 : DOR, PLR+ and NRL- in the meta-analysis.

Study	ACHE	PLR	NRL
Shen et al. 2019	1.129 [0.430;2.961]	1.021 [0.865;1.206]	0.905 [0.407; 2.011]
Magalhas et al. 2017	38.636 [2.247; 664.439]	26.875 [1.662;434.454]	0.696 [0.581;0.832]

Table 4 describes the values of the odds ratio of diagnosis or *diagnosis odds ratio* (DOR), the likelihood ratio of a positive test (PLR) and the likelihood ratio of a negative test (NRL) from each study, as well as their respective 95% confidence intervals. The PLR ranges from one to infinity, and a PLR of one indicates that the probability of a positive test result is the same for patients with and without the disease. The NRL ranges from one to zero, and the closer the NRL is to zero, the lower the probability of disease in the presence of a negative test result. We can observe that in the study developed by Shen e cols²⁴, a PLR = 1.021 was obtained, indicating that the test was not very useful due to the fact that one belongs to the 95% confidence interval. In that same study, the NRL value was 0.905 and we also observed that one belongs to the confidence interval, indicating that the probability of the disease in the negative presence of the test is not small. In the study developed by Magalhães e cols²⁵, we observed a PLR value = 38.636, indicating that the test has a high probability of being positive in patients. We also have for this study the value of NRL = 0.696, indicating a low probability of detecting the disease in non-ill patients.

To verify whether the heterogeneity of the studies is due to random effects, the Q-Cochran test was used to test this hypothesis. The p-value found was 0.317, that is, we do not reject the hypothesis that the heterogeneity is in fact due to random factors, which is corroborated by the inconsistency measure (I^2) which was approximately 0%. We can also propose a ROC “curve”, keeping in mind that, in its classic use, the values are continuous, while in the diagnostic meta-analysis, each study corresponds to a point on the graph, thus not forming a proper curve. The elliptical ROC curve can be seen in **Figure 3**, in which the points indicate the sensitivity values and the false positive rate of each study, while the ellipse indicates the region of confidence for these values. The optimum point on the graph is the upper left corner, where the sensitivity value is close to one and the false positive rate is close to zero. Note that the study by Magalhães e cols²⁵ obtained a false positive value close to zero, while the study by Shen e cols²⁴ presented a false positive rate greater than 0.8.

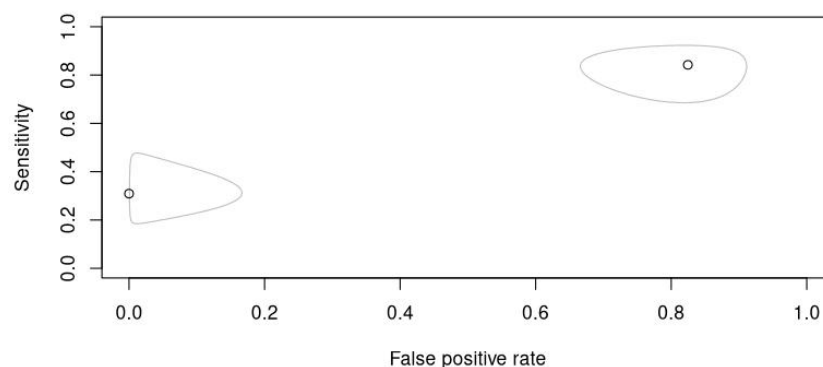


Figure 3 : Elliptical Roc curve for sensitivity and false positives.

DISCUSSION

In this study, we sought to provide evidence linking inflammation to CCL by investigating the diagnostic accuracy of three particular inflammatory markers, including pro-inflammatory IL-6, TNF- α and anti-inflammatory IL-10. However, it was not possible to verify the diagnostic accuracy due to discrepancies between the studies, in addition to the lack of essential data such as information on the rates of PT, TN, FP and NF, which were only reported by two authors.

Thus, the studies that were included in the meta-analysis for the inflammatory marker TNF- α as a way of detecting MCI, pointed to the conclusion based on the sample and with 95% confidence, that they are heterogeneous in terms of sensitivity and specificity of the tests performed. There was also no significant difference after descriptive analysis between the CCL and control groups for the TNF- α marker. This result is in line with that presented by³¹, where serum TNF- α levels increased significantly only in the early-onset and late-onset AD groups, and although these levels were higher in the CCL group than in the age-matched control group, it was not statistically significant. On the other hand, previous research observed a significant increase in serum TNF- α levels in patients with AD and also in the CCL group compared to healthy controls^{32,33,34}, which raises caution, as this is one of the main inflammatory cytokines produced by activated astrocytes and microglia and is increased in the affected brain regions of patients with AD³⁵.

Regarding IL-10, the study by Rosenberg e cols³⁶ reported that the increase in TNF- α levels stimulates the expression of IL-10, which is an anti-inflammatory cytokine capable of inhibiting its synthesis. In this research, IL-10 levels showed a significant difference between the values of the CCL and control groups (p-value = 0.0126) so that individuals in the CCL group had a mean value higher than those in the control group.

A meta-analysis evaluating the association between peripheral IL-6 levels in all-cause dementia found that higher concentrations of this inflammatory marker conferred an increased risk of developing AD. The authors highlight that peripheral inflammation can occur before clinical symptoms are present³⁷. In the study in question, no significant differences were observed in IL-6 levels between the CCL and control groups, which also corroborates the data by Bermejo e cols³⁸, where significantly elevated levels of IL-6 were found only in the plasma of patients with AD, while similar values were observed for the CCL group and healthy controls. One of the factors that can explain these results is that, in general, increased levels of IL-6 can be associated with several conditions, including aging itself³⁹.

To complement what has already been discussed, another important relationship to be observed is the association of the aforementioned biomarkers with the MMSE scores in these patients. Sharma e cols⁴⁰

did not find strong evidence of associations between inflammatory biomarkers and modified MMSE scores. Gezen et al.³¹ showed that patients with early-onset AD with low MMSE scores have high serum levels of the TNF- α marker. A significant difference between the MMSE values of the CCL and control groups (p -value = 0.0065) was found in this study, so that the control group had a higher mean value than the CCL group. However, further studies need to elucidate which inflammatory mechanisms directly influence the cognition of these individuals.

LIMITATIONS

This meta-analysis has strengths and limitations. Its strengths include comprehensive research methodology, as well as being the first study to assess the diagnostic accuracy of cytokines IL-6, IL-10, TNF- α as possible early markers in MCI. Furthermore, few studies presented robust analyzes in an attempt to detect possible inconsistencies in the evaluated tests and identify the reason for the high variation reported between them. Its limitations are inherent to observational studies that may affect researchers' ability to infer any causal relationship between inflammatory markers and CCL, as increased inflammatory levels can be both a cause and a consequence. Another limitation is the small number of studies included with little important data available, which made some comparisons unfeasible, restricting the exploration of potential sources of heterogeneity, such as comorbidities, level of physical activity, genetic factors, depression, among others that could elucidate the controversial results and better guide clinical practice.

CONCLUSION

In conclusion, this review found no evidence suggestive of increased peripheral levels of inflammatory markers in MCI patients. To confirm the findings of this meta-analysis, future observational studies including additional information from the participants are needed to provide a more adequate context, in addition to better assessing the differences in cutoff points between the developed analyses, which may be leading to the high degree of heterogeneity presented.

Conflict of interests

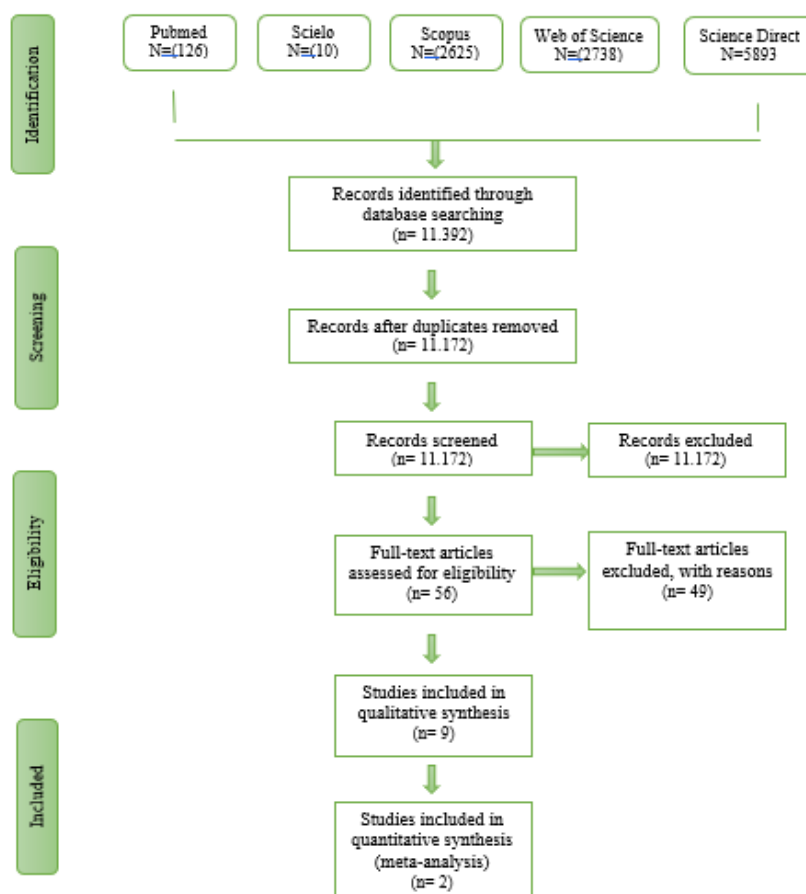
The authors claim that there are no conflicts of interest related to this research.

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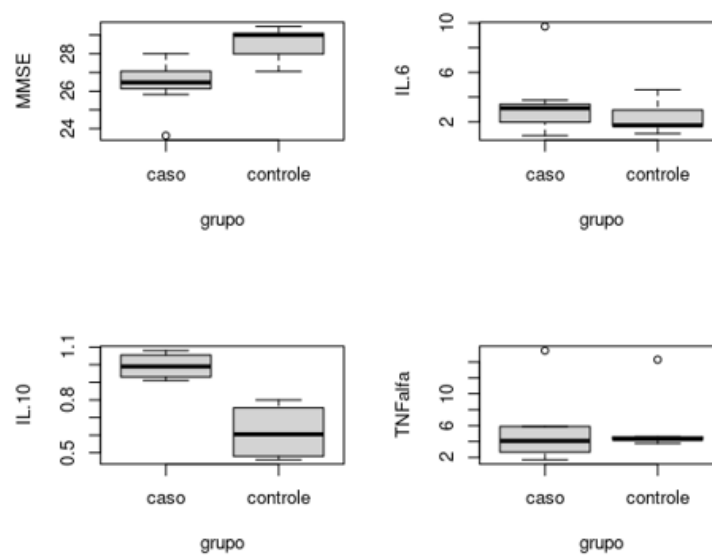


Figure 2: Box - plot of the main study variables by group.

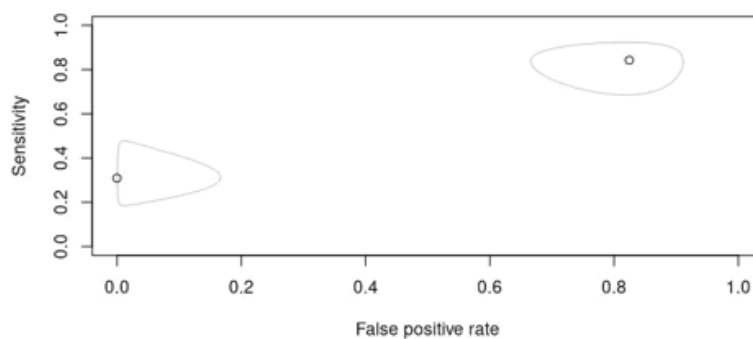


Figure 3: Elliptical Roc curve for sensitivity and false positives.

Table 1: Data.

Study	Type	Sample		Age		% Women		MMSE		IL-6		IL-10		TNF- α	
		case	ctrl	case	ctrl	case	ctrl	case	ctrl	case	ctrl	case	ctrl	case	ctrl
²² Zhao 2012	serum	150	150	70.67	69.85	47.30	41.30	26.55	27.06	1.86	1.72	-	-	-	-
²³ Wennberg 2019	plasma	186	1416	79.70	71.90	40.90	47.30	-	-	3.10	2.50	0.91	0.80	3.30	4.30
²⁴ Shen 2019	plasma	57	57	68.77	67.77	31.58	31.58	25.82	29.46	-	-	-	-	15.43	14.29
²⁵ Magalhães 2017	serum	55	42	71.00	68.00	63.54	71.43	28.51	25.80	3.75	3.40	1.08	0.71	4.86	3.76
²⁶ King 2019	plasma	77	20	76.13	75.90	40.00	25.00	26.47	29.10	2.07	1.70	1.03	0.50	1.70	4.30
²⁷ Johansson 2017	serum	11	18	72.00	76.00	54.54	44.44	28.00	29.00	0.88	1.04	-	-	-	-
²⁸ Kim 2017	us	29	28	75.03	72.00	61.50	57.10	23.62	27.41	9.72	4.60	-	-	5.89	4.60
²⁹ King 2017	plasma	58	20	77.05	75.90	45.76	25.00	26.45	29.10	3.11	1.66	0.95	0.46	2.66	4.26
³⁰ Dursun 2015	serum	30	32	74.40	72.10	-	-	27.59	28.57	-	-	-	-	-	-

Table 2: Comparison of study variables between groups.

Variável	caso (n = 653)	controle (n = 1783)	p-valor
Idade	73,86 \pm 3,51	72,158 \pm 3,25	0,3020 ¹
%			
mulheres	48,14 \pm 11,06	42,89 \pm 16,07	0,4611 ¹
MMSE	26,63 \pm 1,51	28,19 \pm 1,29	0,0442 ^{1*}
IL-6	3,50 \pm 2,91	2,37 \pm 1,24	0,3735 ¹
IL-10	0,99 \pm 0,08	0,62 \pm 0,16	0,0126 ^{1*}
TNF α	5,64 \pm 5,03	5,92 \pm 4,11	0,8099 ²

*-significant results; 1- Student's t test for independent samples; 2- Wilcoxon -Mann-Whitney test

Table 3: Sensitivity and Specificity of the studies in the meta-analysis.

Study	sensitivity	specificity
Shen et al. 2019	0.836 [0.721; 0.910]	0.181 [0.103; 0.299]
Magalhães et al. 2017	0.312 [0.206; 0.443]	0.988 [0.898; 0.999]

Table 4: DOR, PLR+ and NRL- in the meta-analysis.

Study	ACHE	PLR	NRL
Shen et al. 2019	1.129 [0.430;2.961]	1.021 [0.865;1.206]	0.905 [0.407; 2.011]
Magalhaes et al. 2017	38.636 [2.247; 664.439]	26.875 [1.662;434.454]	0.696 [0.581;0.832]