NL Neurology Letters

Review Article

https://doi.org/10.61186/nl.3.3.50

Diagnostic value of kappa free light chain and kappa index in Multiple Sclerosis: a systematic review and meta-analysis

Fardin Nabizadeh[1, 2, *, **], Mobin Mohamadi[1, 2, **], Tahereh Maleki[3], Parya Valizadeh[3], Fatemeh Sodeifian[4]

1- School of Medicine, Iran University of Medical Sciences, Tehran, Iran
2- Alzheimer's Disease Institute, Tehran, Iran
3- School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
4- Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran

Received 12 May 2024; **Revised** 29 June 2024; **Accepted** 18 September 2024; **Published** 27 September

Abstract

Background: It was found in previous studies that abnormal cerebrospinal fluid (CSF) κFLC (kappa free light chain) and κ index levels were associated with increased probability of CIS conversion to Multiple sclerosis (MS) and also accurate diagnosis. However, still, the value of κFLC and κ index for MS diagnosis remains controversial. In this systematic review and meta-analysis study, we aimed to evaluate the diagnostic value of CSF κFLC and κ index for MS.

Methods: Three electronic databases including PubMed, Scopus, and Web of Science were searched for published literature and reviewed abstracts. We included studies that measured and reported CSF κFLC level or κ index in adults with MS.

Results: After a two-step review, 31 studies with a total of 9324 subjects were included in our qualitative and quantitative synthesis. Our analysis showed that the overall sensitivity and specificity of CSF κFLC in the diagnosis of MS from other groups was 85% (CI: [0.77- 0.90]) and 90% (CI: [0.82- 0.95]). Further analysis for the κ index demonstrated sensitivity and specificity of 90% (CI: [0.88- 0.92]) and 87% (CI: [0.84- 0.90]) for detecting MS from all other groups. Meta-analysis showed that the sensitivity and specificity of the κ index in the diagnosis of MS from other groups was 91% (CI: [0.89- 0.92]) and 86% (CI: [0.83- 0.88]) while the area under the curve (AUC) was 0.94 when the cut-off point was lower than 8. Also, at the cut-off point>8, the sensitivity and specificity were 87% (CI: [0.80- 0.91]) and 90% (CI: [0.81- 0.95]) and AUC was 0.93.

Conclusion: Our meta-analysis revealed that both the κFLC and κ index are effective biomarkers for distinguishing MS from other neurological diseases. Our results also showed that the κ index is significantly higher in MS patients compared to patients with other inflammatory and non-inflammatory neurological diseases. Thus, we strongly recommend incorporating the κ index into MS diagnosis protocols.

Keywords: Multiple sclerosis, kappa free light chain, diagnosis, kappa index, κ, Oligoclonal IgG bands

* **Correspondence author** Fardin Nabizadeh, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
Email: fardinnabizade1378@gmail.com

**Equal contribution

Cite this article as: Nabizadeh, F., Mohammadi, M., Maleki, T., Valizadeh, P., Sodeifian, F. Diagnostic value of kappa free light chain and kappa index in Multiple Sclerosis: a systematic review and meta-analysis. Neurology Letters, 2024; 3(2): 50-63. doi: 10.61186/nl.3.3.50.

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), affecting over 2 million people worldwide. Both humoral- and cell-mediated immunity are involved in the pathogenesis of the disease. The first symptoms of MS are presented as isolated flare known as clinically isolated syndrome (CIS) (1, 2). CIS is commonly manifested as partial myelitis, unilateral optic neuritis, motor or sensory symptoms of the brain hemisphere, or brain stem syndrome. Some patients presenting CIS develop MS in the following years; however, other groups of patients would not

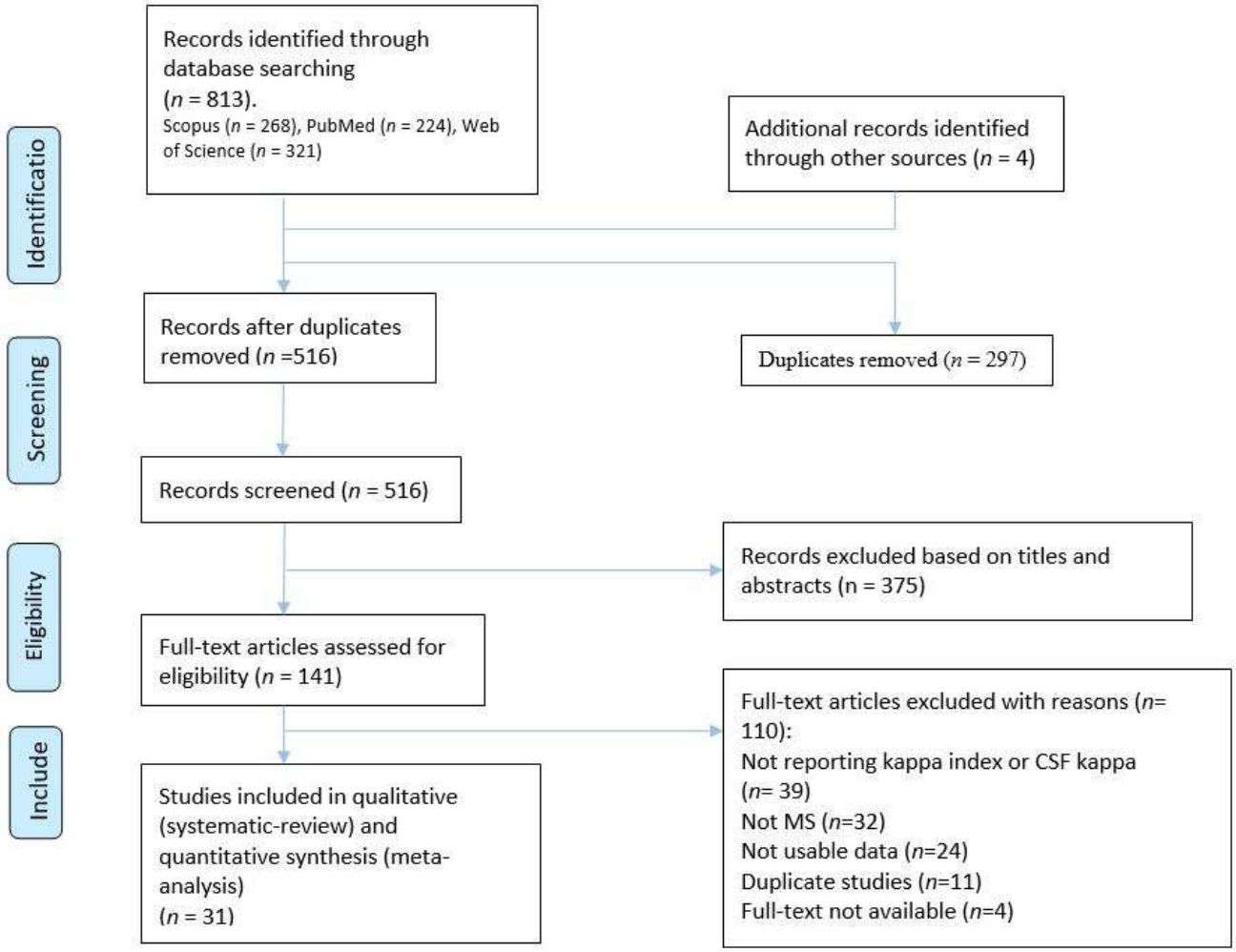

Figure 1. PRISMA flow diagram depicting the flow of information through the different phases of a systematic review

develop MS over time (3). A major number of MS patients have a remission period after disease relapse and with disease progression, relapse periods occur more frequently with shorter duration of remission periods (3, 4). Early diagnosis of MS is critical since earlier administration of immune modulatory drugs decelerates MS progression and associated cognitive and disability (5-7).

During neuroinflammatory processes in MS, plasma cells synthesize intrathecal immunoglobulin (Ig). Oligoclonal IgG bands (OCB) of cerebrospinal fluid (CSF) are detected by isoelectric focusing (IEF) and immunoblotting or immunofixation in the next step (8, 9). The latest update to the diagnostic criteria for MS advocates for a multimodal approach that combines clinical findings, CSF analysis, and magnetic resonance imaging (MRI) data to enable a more accurate diagnosis. The revised McDonald criteria stipulate that the identification of two or more OCBs in the CSF serves as a key parameter for the diagnosis of MS (10). Nonetheless, this technique has several constraints that include susceptibility to subjective interpretation, being cost-prohibitive, possessing qualitative rather than quantitative characteristics, as well as requiring considerable labor investments (11-13). Moreover, the specificity of OCB is low, since the intrathecal synthesis of IgG bands occurs in many other neuroinflammatory diseases not just in MS (14). Therefore, it is required to identify additional CSF biomarkers to facilitate earlier diagnosis of MS.

An alternative biomarker with high prognostic and diagnostic power is free light chains (FLC) including kappa (κ) and lambda (λ) FLCs which are synthesized by plasma cells in CSF. Several studies have previously determined FLCs as an alternative biochemical biomarker for the diagnosis of MS (15-17). The presence of κFLC and λFLC in CSF has been known since 1980. (18). During inflammation, immunoglobulins and excess of κ and λ light chains are produced by mobilized B lymphocytes in CSF (19). Healthy individuals have a low concentration of FLCs in the serum and CSF, but their concentration increases during inflammatory processes (20). In addition to κFLC in CSF, κ index (CSF/ serum κFLC divided by CSF/ serum albumin) increased in patients with MS compared to healthy individuals (21). However, still, the value of κFLC quantification for MS diagnosis remains controversial

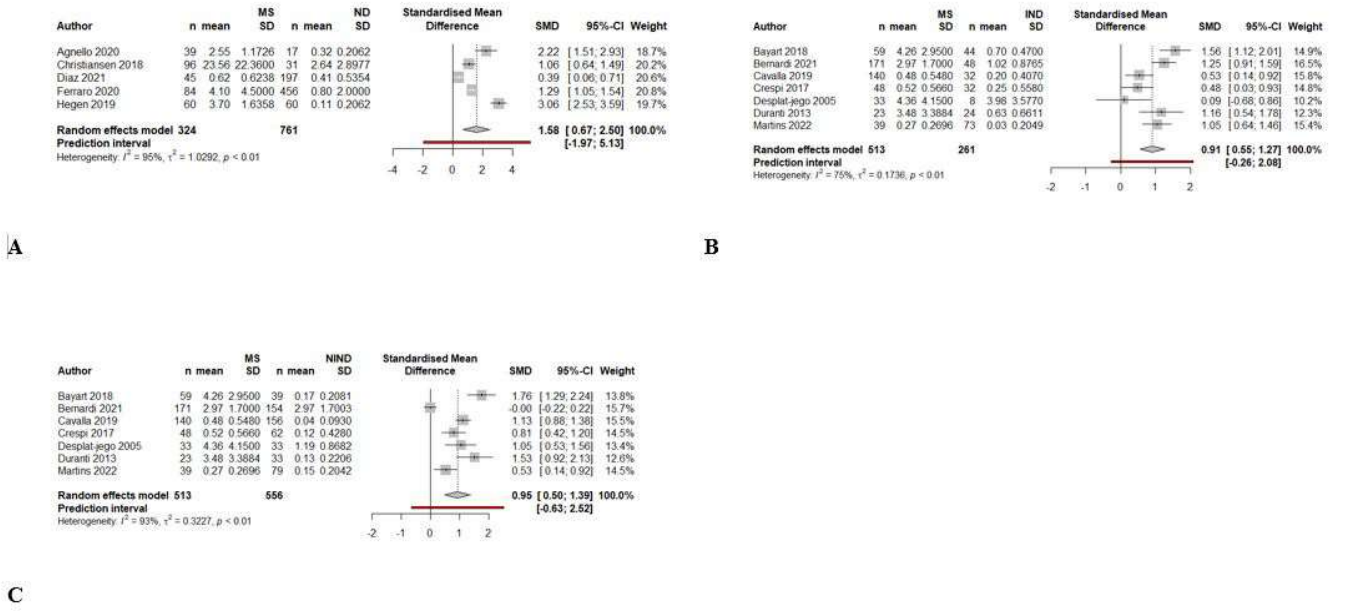

Figure 2. Forest plot of CSF κFLC levels in MS compared to ND (A), IND (B), and NIND (C)

and some studies reported that it is less valuable than OCB testing (22-24). This could be due to the different number of participants, different measurement assays, and different administered cut-off values. Rosenstein et al. conducted a study revealing the potential of κFLC as a viable diagnostic tool for MS, with comparable accuracy rates regarding sensitivity and specificity when compared to OCBs (25). Consistently, a recent meta-analysis study indicated that there is no significant difference in diagnostic accuracy of κFLC and OCBs (26).

Early detection of MS presents a vital aspect in managing the disease, leading to better prognosis and improved clinical outcomes. The development of a diagnostic test that effectively detects the presence of MS at the initial stages of the disease could significantly aid in improving patient management strategies. To this end, the search for novel diagnostic tools and methods has been an active area of research in recent years. It was found in previous studies that abnormal CSF κFLC and κ index levels were associated with an increased probability of CIS conversion to MS and also accurate diagnosis of MS (22, 27). Moreover, quantitative κFLC analysis could demonstrate immunological differences between MS and other inflammatory diseases (28, 29). Recently, a systematic review and meta-analysis investigated the diagnostic value of CSF κFLC in MS (30), however since the κ index showed higher accuracy in discriminating MS from CIS and other neuroinflammatory diseases, there is a lack of comprehensive review on the role of κ index in MS diagnosis. In this systematic review and meta-analysis study, we aimed to evaluate the diagnostic value of CSF κFLC and κ index for MS.

Method and Materials

The current systematic review and meta-analysis were performed according to the Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) consensus statement (25).

Literature search strategy

Three electronic databases including PubMed, Scopus, and Web of Science were searched for published literature and reviewed abstracts. The search strategy was built around concepts of "free light chain", "kappa", and "Multiple Sclerosis". Also, the reference list of articles was reviewed to identify additional potential studies.

Eligibility criteria

The eligible studies should meet the following criteria: 1) Measured and reported CSF κFLC level or κ index in adults with MS, 2) existence of a comparing group (e.g., control, CIS, Neuromyelitis optica spectrum disorders (NMOSD), Neurological diseases (ND). Non-inflammatory neurological diseases (NIND), inflammatory neurological diseases (IND), and …), 3) the number of participants more than 10, 4) defined diagnostic criteria. Moreover, the papers had to describe CSF sampling and storage techniques to ensure sufficient quality. There was no language restriction. Also, patients with any subtypes, disease duration, disability, and comorbidities were included.

Study selection

The studies were screened in the two-step process by two independent investigators (T.M, M.M). First, the title and abstracts retrieved from online databases were screened, and irrelevant studies were excluded. Then, the full text of remained papers was carefully reviewed, and included studies were selected based on our eligibility criteria. Any disagreements through the screening were resolved by consultation with the third researcher (F.N).

Data extraction

Table1. Demographic, clinical characteristics, and findings of included studies

Author	Year	Country	Study design	Preanalytical conditions	Measuring equipment (reactive)	Type of MS	Sample size	Mean age
Agnello et al.	2020	Italy	Cross-sectional	−80°C	Freelite	RRMS, PPMS, and CIS	56	MS: 32, ND:68
Ayrignac et al.	2020	France	Retrospective cross-sectional	NR	NR	NR	42	NR
Bayart et al.	2018	Belgium	Cross-sectional	NR	FreeLite	RRMS, PPMS, and SPMS	142	45.8
Bernardi et al.	2021	Italy	Cohort	Centrifuged (10min 3000g and 2000g), stored (−20°C, −40°C, or −80°C)	Freelite MX	NR	406	37 median
Cavalla et al.	2019	Italy	Cross-sectional	Optimum concentration 20 mg/L in saline	N Latex FLC (Siemens) on BNII nephelometric automated analyzer	RRMS, PPMS, and CIS	373	46.3
Christiansen et al.	2018	Denmark	Prospective cross-sectional	Rutine samples (-70˚C)	FreeLite	RRMS, PPMS, and CIS	230	40 median
Crespi et al.	2017	Italy	Cross-sectional	NR	N Latex FLC kappa/lambda Kit and BN II System	NR	150	51
Crespi et al.	2021	Italy	Cross-sectional	NR	BN II nephelometer	NR	667	72.9
Desplat-jego et al.	2005	France	Cross-sectional	−80◦C until FLC assays	BN II nephelometer	RRMS/PMS	89	35 median
Diaz et al.	2021	Spain	Cross-sectional	−80◦C	Freelite Mx	NR	252	44.12
Duell et al.	2020	Sweden	Cross-sectional	NR	BN II nephelometer	RRMS	112	43
Duranti et al.	2013	Italy	Cross-sectional	−20 °C	BN Prospec automated analyzer	NR	80	50
Ferraro et al.	2020	Italy	Cross-sectional	centrifuged at 3000 rpm for 10 min and stored in	analyzed with IEF on an agarose gel	NR	540	38

Gudowska-Sawczuk et al.	2020	Poland	Cross-sectional	−80 ◦C	NR	RRMS	76	NR
Hassan-Smith et al.	2014	UK	Cross-sectional	-80 °C	BN II nephelometer	RRMS/ PPMS	160	RRMS: 40, PPMS:51
Hegen et al.	2019	Austria	Cross-sectional	NR	FreeLite	NR	120	39
Leurs et al.	2018	Netherlands, Spain, France, Belgium, Hungary, Italy, Poland, Turkey, Denmark, Serbia, Austria, and Switzerland	Cross-sectional	2 hours at −80°C	FreeLite	RRMS/SPMS/PPMS	745	38
Martins et al.	2022	Portugal	Cross-sectional	− 80 ◦C	BN II	NR	191	44
Mene´ndez-Valladares et al.	2015	Spain	Cross-sectional	− 80 ◦C	Siemens BN II analyzer	RRMS	176	45.7
Passerini et al.	2016	Italy	Cross-sectional	CSF and serum samples were centrifuged 10 min at 800 rpm and 10 min at 3000 rpm, and were stored at −20◦C	BNII	NR	100	37.4
Perez et al.	2019	Italy	Cross-sectional	NR	NR	NR	160	37.7
Pieri et al.	2017	Italy	Cross-sectional	−80 °C	BN Prospec	NR	176	NR
Presslauer et al.	2008	Austria	Cross-sectional	−80 °C	FreeLite	RRMS/ PPMS	438	NR
Presslauer et al.	2015	Austria/ Germany	Cross-sectional	centrifugation after the blood samples were allowed to clot for ⩾ 30 minutes	FreeLite	NR	180	39
Puthenparampil et al.	2018	Italy	Retrospective cross-sectional	−80 °C	FreeLite and BNII	RRMS	107	NR
Rosenstein et al.	2021	Sweden	Cross-sectional	NR	N Latex FLC kappa kit	RRMS, PPMS, CIS, and SPMS	327	41

Saadeh et al.	2022	USA	Cross-sectional	−20°C or −80°C	BNII nephelometric	NR	Retrospective:702, Prospective:657	Retrospective:54.3, Prospective: 56.5
Senel et al.	2019	Germany	Cross-sectional	NR	FreeLite	NR	1224	37
Valencia-Vera et al.	2017	Spain	Cross-sectional	−20 °C/ centrifugation after the blood samples were allowed to clot for ≥30 min	FreeLite and BN ProSpec	NR	122	NR
Vasilj et al.	2018	Croatia	Cross-sectional	An aliquot of serum and CSF was stored at +4 °C until 7 days, and another was stored at -20 °C until 30 days	BNII nephelometric	NR	151	NR
Vecchio et al.	2020	Italy	Cross-sectional	NR	BNII nephelometric	RRMS, PPMS, CIS, and SPMS	373	51.1

NR, Not Reported; MS, Multiple Sclerosis; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; CIS, clinically isolated syndrome

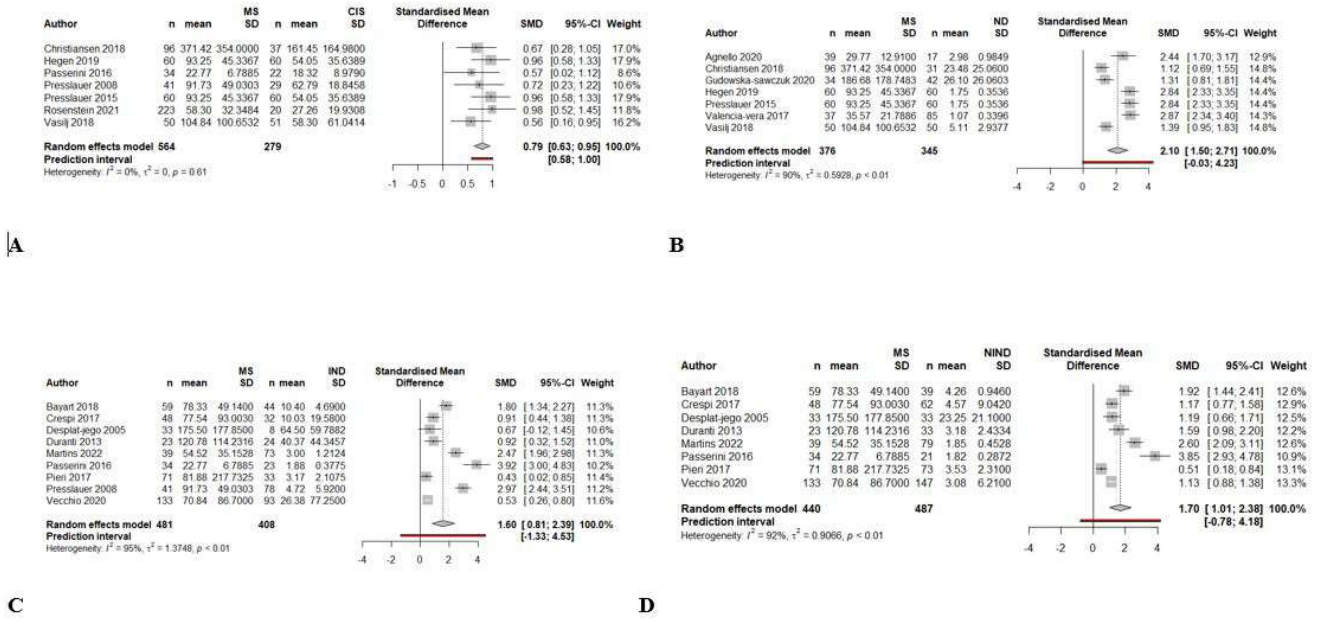

Figure 3. Forest plot of κ index in MS compared to CIS (A), ND (B), IND (C), and NIND (D)

The following information was manually extracted from the eligible studies by the same investigators (T.M, M.M): Study's demographics, preanalytical condition, measuring equipment, the subtype of MS, age, number of subjects in each group, mean κ index, SD of κ index, mean CSF κFLC, SD of CSF κFLC, proposed cutoff, sensitivity, specificity, and AUC. The final data was reviewed by a third researcher (F.N).

Quality assessments

The risk of bias among included studies was assessed using studies the quality assessment of diagnostic accuracy studies (QUADAS-2) criteria (26).

Statistical analysis

The statistical analysis was performed using R 4.1.2 software. For diagnostic test accuracy (DTA) analysis, the number of patients in each control (n1) and experimental (n2) groups, sensitivity (Se), and specificity (Sp) were collected from each study. Then similar data was put into the same subgroups based on the control type MS type pairs for pooling. Using collected data (n1, n2, Se & Sp) contingency table was created and true positive (TN), true negative (TN), false positive (FP), and false negative were calculated. These parameters were used in the "madad" function to calculate the confidence interval for each study's reported Se & SP and also calculate pooled sensitivity and specificity and their respective confidence intervals (CI) using the "Wilson" approach for univariate analysis. The results of the univariate analysis are reported in forest plots for both Se and SP for each subgroup.

A bivariate approach (Reitsma et al) has been used to estimate sensitivity and specificity across studies accounting for between-study heterogeneity. Results are provided as Receiver Operating Curve (ROC) for each study and their CIs are illustrated. Also, a Summary Receiver Operating Curve is calculated for the bivariate model with CI and predictive interval indicated.

To examine the effect of cut-off used for serum κ index in MS-total group subgroup analysis was performed, dividing the studies into two subgroups with "cut-off less than 8" and "cut-off greater than 8" and their pooled Se & Sp and Area under the curve (AUC) was calculated for comparison.

To see if there is a meaningful difference in CSF κFLC level and κ index between MS patients and control groups a random effect model was used to pool standardized mean difference (SMD) in different subgroups and results are reported in forest plots with pooled effect size, CI and predictive interval.

Results

Study selection

Eight hundred and thirteen studies were identified via database search (Figure 1). After duplicate removal, 516 papers were screened. Finally, after a two-step review, 31 studies with a total of 9324 subjects were included in our qualitative and quantitative synthesis (27-57).

Among the included studies, 30 were cross-sectional (27-30, 32-57), and one was cohort (31). The demographical and clinical characteristics of the included studies are summarized in Table 1. According to the results of the QUADAS-2 assessment, the risk of bias was low among the included studies (Table 2).

The mean difference of the CSF κFLC and κ index

We compared the level of CSF κFLC in MS patients with IND, NIND, and ND. Our results demonstrated that the level of CSF κFLC was significantly higher in MS patients compared to ND

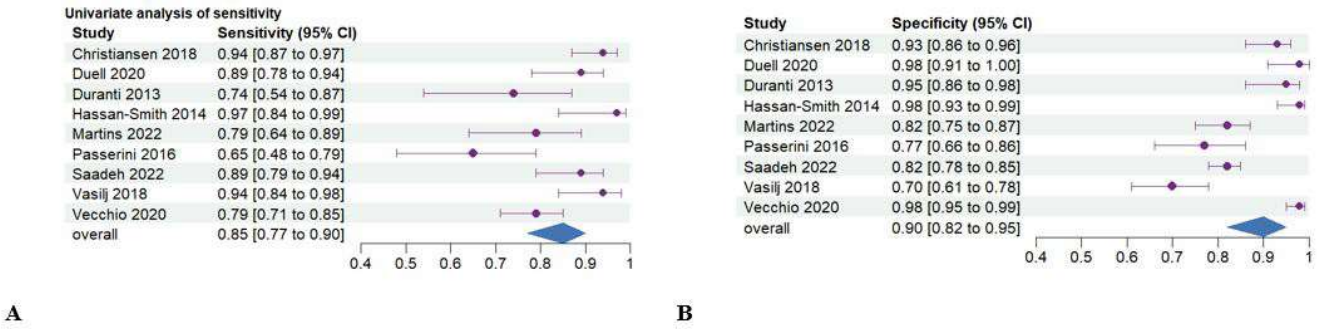

Figure 4. Forest plot of sensitivity (A) and specificity (B) of CSF κFLC levels in detecting MS from other groups

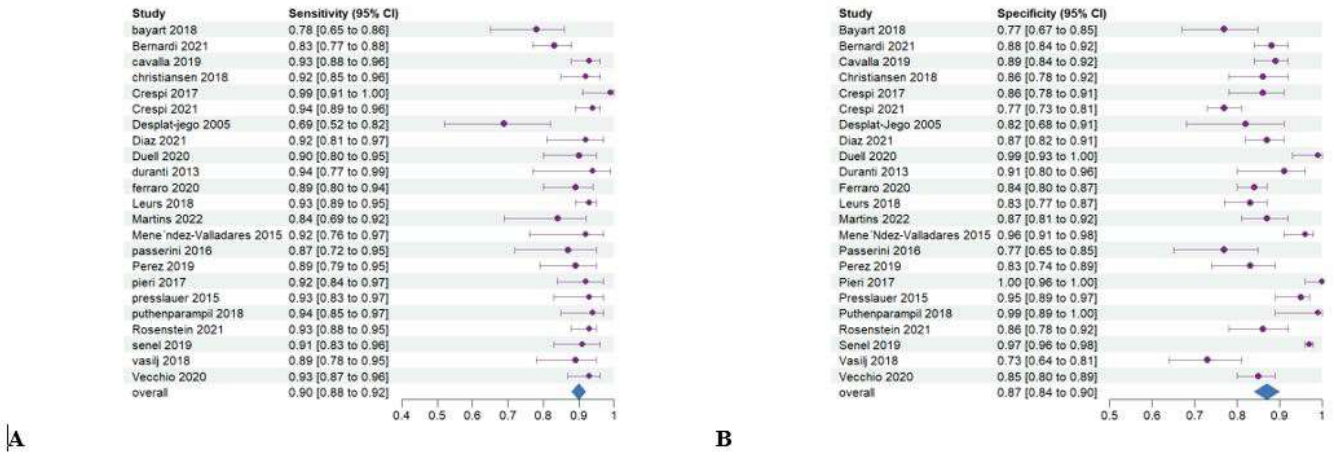

Figure 5. Forest plot of sensitivity (A) and specificity (B) of κ index in detecting MS from other groups

	cut-off	sensitivity	specificity	AUC
1	cut-off < 8	0.91 [0.89 to 0.92]	0.86 [0.83 to 0.88]	0.94
2	cut-off > 8	0.87 [0.80 to 0.91]	0.90 [0.81 to 0.95]	0.93

Figure 6. Sensitivity and specificity of κ index in detecting MS from other groups based on cut-off points

subjects (SMD = 1.58 [0.67, 1.5], I2= 95%, prediction interval= [-1.97, 5.13]) (Figure 2). Moreover, we compared the level of CSF κFLC in MS vs IND patients. We found a higher level of CSF κFLC in MS patients (SMD = 0.91 [0.55, 1.27], I2= 75%, prediction interval= [-0.26, 2.08]). Also, the level of CSF κFLC was significantly higher in MS patients when compared to NIND subjects (SMD = 0.95 [0.50, 1.39], I2= 93%, prediction interval= [-0.63, 2.52]).

The data were subjected to additional analysis to investigate the κ index difference in MS patients compared to individuals with IND, NIND, ND, and CIS. It was found that the κ index was significantly higher in MS patients compared to subjects with CIS (SMD = 0.79 [0.63, 0.95], I2= 0%, prediction interval= [0.58, 1.0]) (Figure 3). It is interesting to note that the prediction interval for future studies was close to our confidence interval and it was well above zero. Also, the κ index was significantly higher in MS patients compared to patients with ND (SMD = 2.1 [1.50, 2.71], I2= 90%, prediction interval= [-0.03, 4.23]). Furthermore, our analysis showed that the mean standardized κ index in MS patients was 1.60 higher than individuals with IND (SMD = 1.60 [0.81, 2.39], I2= 95%, prediction interval= [-1.33, 4.53]). Meta-analysis of MS vs NIND patients showed a higher κ index in subjects with MS

Table2. Results of risk of bias assessments of included studies

	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Agnello et al.	Low	Unclear	Low	Low
Ayrignac et al.	Low	Low	Low	Low
Bayart et al.	Unclear	Low	Low	Unclear
Bernardi et al.	High	Low	Low	Low
Cavalla et al.	Low	Low	Low	Unclear
Christiansen et al.	High	Unclear	Low	Low
Crespi et al.	Low	High	Unclear	Low
Crespi et al.	Low	Low	Low	Low
Desplat-jego et al.	Low	Low	Low	Low
Diaz et al.	Low	Low	Low	Unclear
Duell et al.	Low	Low	Low	Low
Duranti et al.	Unclear	High	Low	Low
Ferraro et al.	Low	Low	Low	Low
Gudowska-Sawczuk et al.	Low	Unclear	Low	High
Hassan-Smith et al.	High	Low	Low	Low
Hegen et al.	Unclear	Low	Low	Low
Leurs et al.	Low	High	Low	Low
Martins et al.	Low	Low	Low	Low
Mene´ndez-Valladares et al.	Low	Unclear	Low	Unclear
Passerini et al.	Low	Low	Low	Low
Perez et al.	Low	Low	Unclear	Low
Pieri et al.	Unclear	Low	Low	Low
Presslauer et al.	Unclear	Low	Low	Low
Presslauer et al.	High	Low	Low	Low
Puthenparampil et al.	Low	Low	Unclear	Low
Rosenstein et al.	Low	Low	Low	Low
Saadeh et al.	High	Low	Low	Low
Senel et al.	Low	Unclear	Low	Unclear
Valencia-Vera et al.	Low	Low	Low	Unclear
Vasilj et al.	Low	Low	High	Low
Vecchio et al.	Unclear	Low	Low	Low

Table3. Results of pooled sensitivity, specificity, and AUC calculated using bivariate analysis

	sensitivity	specificity	AUC
CSF κFLC for detecting MS from all other groups	0.855 [0.777 to 0.909]	0.910 [0.822 to 0.957]	0.931
κ index for detecting MS from all other groups	0.901 [0.878 to 0.920]	0.876 [0.841 to 0.904]	0.943
κ index for detecting MS from ND	0.929 [0.865 to 0.964]	0.816 [0.743 to 0.881]	0.937

κFLC, kappa free light chain; ND, Neurological diseases; AUC, Area under the curve

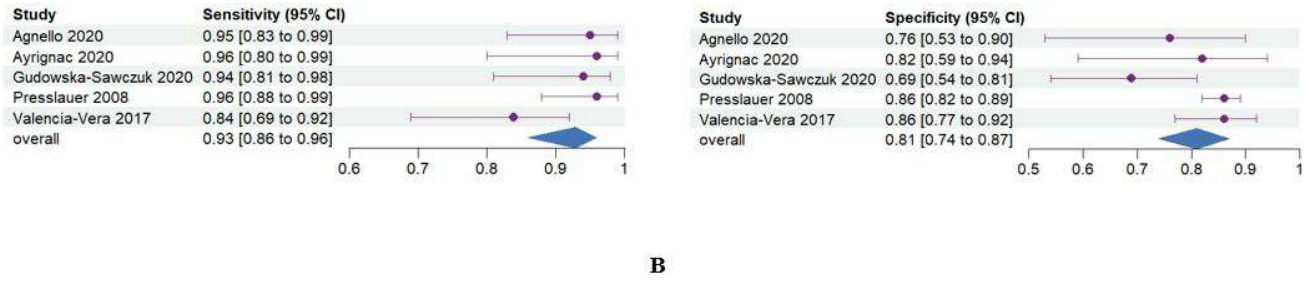

Figure 7. Forest plot of sensitivity (A) and specificity (B) of κ index in detecting MS from ND

(SMD = 1.70 [1.01, 2.38], I2= 92%, prediction interval= [-0.78, 4.18]).

Diagnostic accuracy of CSF κFLC and κ index

Our analysis showed that the overall sensitivity and specificity of CSF κFLC in the diagnosis of MS from other groups was 85% (CI: [0.77- 0.90]) and 90% (CI: [0.82- 0.95]) (Figure 4).

Further analysis for the κ index demonstrated sensitivity and specificity of 90% (CI: [0.88- 0.92]) and 87% (CI: [0.84- 0.90]) for detecting MS from all other groups (Figure 5). We performed a sub-group analysis based on the proposed cut-off points for the κ index among included studies. Meta-analysis showed that the sensitivity and specificity of the κ index in the diagnosis of MS from other groups was 91% (CI: [0.89- 0.92]) and 86% (CI: [0.83- 0.88]) while the AUC was 0.94 when the cut-off point was lower than 8 (Figure 6). Also, at the cut-off point>8, the sensitivity and specificity were 87% (CI: [0.80-0.91]) and 90% (CI: [0.81- 0.95]) and AUC was 0.93.

Moreover, we attempt to investigate the diagnostic accuracy of the κ index in the detection of MS from ND patients and our analysis showed 93% sensitivity (CI: [0.86- 0.96]) and specificity of 81% (CI: [0.74- 0.87]) (Figure 7). Also, the results of the bivariate analysis are presented as SROC in figure 8. Also pooled sensitivity, specificity and AUC calculated using bivariate analysis are shown in Table 3. The area under the curve (AUC) was high in every calculated group for κ index and CSF κFLC. Regarding the small confidence interval, small prediction interval, and high AUC, specificity, and sensitivity values of the κ index; it can be concluded that the κ index is a potential biomarker to distinguish MS from other (Neurological) diseases with great accuracy and high reliability (small confidence and predictive intervals).

Also, the results of the bivariate analysis are presented as SROC in figure 8.

Discussion

Our meta-analysis revealed statistically significant elevations in the CSF κFLC and κ index MS patients compared to IND, NIND, and ND groups. Our results also demonstrate that the κ index was significantly higher in MS patients compared to subjects with CIS. In the latter finding, we observed minimal heterogeneity and a small prediction interval, which implies that this finding is highly reliable and replicable in future studies. Notably, the measurement of the κ index holds potential significance for evaluating and managing CIS, which is a preliminary episode of demyelinating symptoms that may or may not progress into MS (64). Early and precise risk stratification is essential as it enables the prompt initiation of appropriate treatment (65).

Our diagnostic test accuracy meta-analysis found that the κ index had a pooled sensitivity and specificity of 90% and 87% for differentiating MS from other groups. The subgroup analysis revealed that the κ index demonstrated acceptable diagnostic capability in determining MS from other neurologic disorders (AUC>0.9). However, it was noted that the κFLC index showed slightly lower sensitivity than the κ index, making it a less optimal choice as a screening tool. However, the specificity of CSF κFLC was marginally higher than the κ index. Further subgroup meta-analysis suggested that a cut-off value of less than 8 for the κ index results in a higher sensitivity, which is desirable when considering its use as a screening tool.

Growing evidence indicates that B cells play a critical role in the progression of MS by contributing to its inflammatory and neurodegenerative elements (66, 67) via the interplay of both antibody-dependent and antibody-independent pathways (68, 69). OCBs reflect the presence of groups of immunoglobulins, and the presence of two or more of them in the CSF, when the exact bands are not detectable in the corresponding serum, is a hallmark of a humeral inflammatory response within CNS detected by flow cytometry (70, 71). Several studies have reported a correlation between the presence of OCBs and the extent of disability experienced by MS patients (72, 73). These findings highlight the importance of OCBs as a potential biomarker in the prognosis of MS (74, 75). The gold-standard method for detecting inflammation within the CNS has been the assessment of OCBs (76, 77). The OCBs change during COVID-19, and other comorbidities related to insulin resistance is reported by several studies (78-80).

The presence of locally synthesized κFLCs in the CNS of MS patients serves as an additional marker of an ongoing intrathecal inflammatory response (81, 82). Measuring the levels of κFLC and albumin in both CSF and serum enables the

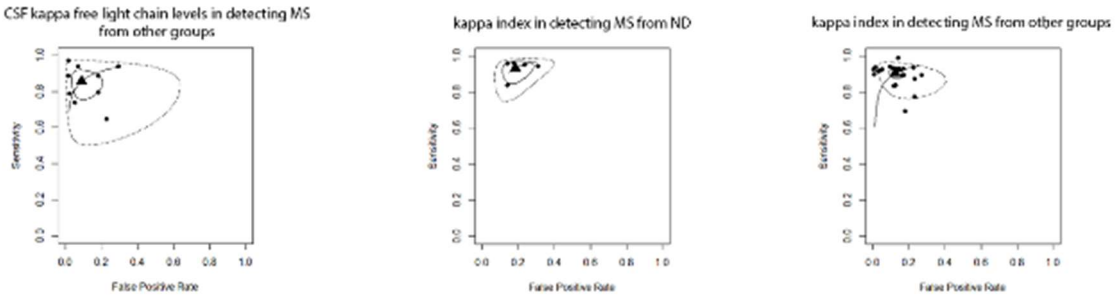

Figure 8. SROC curve of the Retisma model. Triangle: summary point. Circle: individual studies. Solid closed curve: 95% confidence interval of summary point. Dashed closed curve: 95% prediction interval. Solid line: curve proposed by Rutter & Gatsonis.

determination of intrathecal κFLC production through the calculation of the κ index, which also includes information on blood-brain barrier permeability (83, 84). In recent years, the κ index has gained increasing recognition as a quantitative diagnostic tool in MS, offering a potential alternative to the traditional OCB measurement (85, 86). This index possesses several methodological advantages over OCBs, including automation, independence from subjective interpretation, quantifiability, ease of performance, and cost-effectiveness (21, 25). κFLC measurement is also effective in predicting the risk of a subsequent clinical episode in patients presenting with an initial clinical manifestation of demyelination (87-91). Previous studies have shown that the κ index is an effective diagnostic tool for both CIS, with comparable sensitivity and specificity to the OCB (58, 92-94). In a different study, the κ index is shown to be more sensitive yet less specific than OCB for detecting MS. However, according to another study, the absence of high κFLC levels is more valuable in excluding MS, while OCBs are more crucial for establishing the diagnosis (84). Overall, according to the existing literature and our meta-analysis, we recommend incorporating the κ index measurement as the initial screening step in the diagnostic algorithms for patients with suspected MS and CIS (33, 95). An MRI diagnosis of MS involves detecting lesions or abnormalities in the brain and spinal cord, which appear as bright or dark spots on the scan, indicating areas where the immune system has damaged the protective myelin sheath around nerves (96).

Our meta-analysis had a few limitations, mainly inherent to the nature of the original studies that were included. For instance, administering corticosteroids before sample collection in some of the included studies may affect the serum κFLC concentrations (89, 97) and introduce bias in results. However, the lack of detail on corticosteroid consumption status prevented us from conducting a meta-regression. Also, using different versions of McDonald's criteria to define subgroups among included studies might be a source of bias. Additionally, the results of our meta-analysis were limited by substantial heterogeneity present in the majority of subgroup analyses. However, the subgroup analysis comparing CIS and MS demonstrated low levels of heterogeneity, which enhances the credibility of the results obtained. Regarding the strengths of our study, it is noteworthy that it is the largest meta-analysis conducted on the existing evidence and the first to perform subgroup analysis on differences in κFLC and κ index levels between MS and other commonly misdiagnosed conditions, namely IND and CIS. Additionally, this meta-analysis utilized the SMD statistic to control for the impact of the different methodologies employed in the included original studies.

The current body of research supports the significance of κFLC and κ index as predictors of MS progression (98, 99). However, additional studies are required to confirm the prognostic value of κFLC and κ index in MS. Future studies are also needed to investigate the correlation between κFLC levels, disease activity, and treatment response in MS patients, as well as to determine the diagnostic utility and treatment guiding potential of κFLC. Additionally, Future studies with higher statistical power should be conducted to establish a reliable guideline and universal cut-off for using the κ index as a diagnostic or screening tool in clinical practice.

Conclusion

Our meta-analysis revealed that both the κFLC and κ index are effective biomarkers for distinguishing MS from other neurological diseases. Our results also showed that the κ index is significantly higher in MS patients compared to CIS and other IND patients. Thus, we strongly recommend incorporating the κ index into MS diagnosis protocols.

Deceleration

Funding

We do not have any financial support for this study.

Conflict of interest

The author declares no conflict of interest regarding the publication of this paper.

Ethical approval

Not applicable

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

This manuscript has been approved for publication by all authors.

Author Contributions

FN, MM, PV, and FS: Designed the study, analyzed the data, and wrote the paper; FN, MM and TM: collected data and interpreted the data, and wrote the draft version of the manuscript. The manuscript was revised and approved by all authors.

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