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# Kappa free light chains index in the differential diagnosis of Multiple Sclerosis from Neuromyelitis optica spectrum disorders and other immune-mediated central nervous system disorders

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ABSTRACT

The K free light chains index (K-FLC index) has been proposed as an alternative test for intrathecal immunoglobulin synthesis in MS diagnosis. Aim of the study was to assess the accuracy of the K-FLC index in differentiating MS from other immune-mediated CNS disorders and NMOSD.

Data were available from a cohort of 371 patients. K-FLC index was significantly higher in MS: MS mean K-FLC index 90.897 ± 134.198; NMOSD 17.992 ± 15.103; other immune-mediated CNS disorders 12.568 ± 24.440. The overall diagnostic accuracy of the K-FLC index was similar to intrathecal oligoclonal bands detection. However, as a quantitative variable, K-FLC index allowed easier discrimination of MS from other immune-mediated CNS disorders: highest K-FLC index values (> 100) were observed almost only in MS and are therefore strongly predictive of MS, in patients with the appropriate clinical presentation.

## 1. Introduction

Intrathecal synthesis of immunoglobulins (Ig) by plasma cells is a typical feature of Multiple Sclerosis (MS). The detection of intrathecal Ig synthesis either by quantitative or qualitative methods is important for the diagnosis of MS and is also a prognostic factor for the evolution of the disease (Thompson et al., 2018). The current gold standard in MS diagnosis is the assessment of oligoclonal IgG bands (OBs) in the cerebrospinal fluid (CSF) by isoelectrofocusing (IEF) followed by immunoblotting. However, the difficulties in the standardization of the test can limit its use in the diagnosis of the disease. The measurement of kappa free light chains index (K-FLC index) has been proposed as a faster, cheaper and easier alternative test for the detection of intrathecal immunoglobulin synthesis (Goffette et al., 2004; Presslauer et al., 2008; Kaplan et al., 2010; Presslauer et al., 2014).

Immunoglobulin light chains are produced in excess over heavy chains, and unbound free light chains (FLCs) can be normally measured in serum and CSF. FLCs levels in the CSF are a reliable parameter of plasma cells immunoglobulin production in the CNS. In a healthy state, the levels of FLCs in the CSF are low; however, their production is abnormally enhanced in pathological conditions with increased plasma cells activity, such as MS (Nakano et al., 2011).

The detection of CSF OBs is known to be not absolutely specific for MS. The presence of CSF OBs has also been described in several other inflammatory CNS disorders, autoimmune or infectious, many of which may mimic the clinical and radiological features of MS (Petzold, 2013). The lack of specificity of OBs detection is one of the reasons underlying the challenges in the diagnosis of MS; therefore, an accurate diagnostic workup confirming there is “no better explanation” is required, according to the current diagnostic criteria (Thompson et al., 2018).

Likewise, also the K-FLC index can be abnormally enhanced in non-MS CNS inflammatory disorders in which intrathecal Ig synthesis is increased. The aim of the present study was therefore to assess, on a large cohort of patients, the diagnostic accuracy of the K-FLC index in differentiating MS from other inflammatory CNS disorders (autoimmune or infectious) (OICDs) and from Neuromyelitis Optica Spectrum Disorder (NMOSD). Additional aims were to assess the diagnostic accuracy of the K-FLC index depending on age (in different age classes) and gender, and the sensitivity of the K-FLC index in correctly identifying OBs-negative MS patients.

## 2. Methods

Presence and number of OBs, serum and CSF albumin, serum and

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CSF IgG, serum and CSF kappa FLCs, serum and CSF lambda FLCs, IgG index and K-FLC index were recorded for all consecutive patients who underwent diagnostic lumbar puncture including intrathecal Ig synthesis assessment, for any reason, in a large University hospital (University Hospital A.O.U. Città della Salute e della Scienza di Torino) from 2016 to 2018.

MS diagnosis was based on the 2017 revision of the McDonald criteria (Thompson et al., 2018). NMOSD diagnosis was based on the 2015 International Panel for Neuromyelitis Optica Diagnosis (IPND) diagnostic criteria (Wingerchuk et al., 2015).

CSF and serum samples from all patients were brought to the same concentration of IgG (optimum concentration 20 mg/L in saline) and analyzed in the same run into adjacent electrophoretic trace. The qualitative detection and identification of oligoclonal bands was obtained using the Hydragel 9 CSF isofocusing (SEBIA). The technique used was the IEF on agarose gel system and semi-automatic Hydrasys, completed by immunofixation with peroxidase-labeled IgG antiserum. Each agarose gel contained in the kit consists of 18 tracks and enables comparative analysis of 9 pairs of CSF/serum IgG. Compared to the standard immunofixation approach, the use of enzyme-labeled antisera increases sensitivity 100 times over. Thus, IgG can be detected without concentrating CSF samples, even for IgG concentrations greater than or equal to 10 mg/l. CSF and serum immunofixation electrophoresis profiles of the same patient were compared visually by two independent dedicated Laboratory experts. The qualitative analysis by isoelectrofocusing and immunofixation of IgG allowed the classification of each sample in one of five different electrophoretic patterns.

The measurement of FLCs in CSF and serum of all patients was performed using the N Latex FLC (Siemens) on BNII nephelometric automated analyzer.

CSF indexes were extrapolated by using the following formulas: IgG index = QIgG/QAlb and K-FLC index = QK/QAlb where QIgG, QK and QAlb represent the ratios of serum and CSF IgG, kappa FCLs and albumin concentrations, respectively.

### 2.1. Statistical analysis

Comparisons between groups were performed using non-parametric tests (Kruskal-Wallis H test, Mann-Whitney *U* test). Correlation analysis was performed using the Spearman rank correlation test. Sensitivity and specificity were assessed by ROC analysis. The optimal threshold value for K-FLC index was estimated from the ROC curve (Youden Index). McNemar's test was used to compare the sensitivity and specificity of different diagnostic methods. Probability of MS diagnosis for increasing K-FLC index values was calculated with a logistic regression (dependent variabile MS diagnosis, independent variable K-FLC index). The statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

## 3. Results

Clinical and CSF data were available from 373 patients: mean age 46.3 years ± 18.9, sex ratio F:M 1.48 (Table 1). The patients were classified as follow: 37.5% (140) patients were diagnosed as MS/CIS (84.6% relapsing-remitting MS, 8.1% primary progressive MS, 7.3% CIS), 2.1% (8) as NMOSD (either AQP4 or MOG antibodies positive), 8.6% (32) as other immune-mediated CNS disorders (OICDs), either autoimmune (19 patients) (autoimmune encephalitis (LG1, NMDAR), neuroBehcet, neurosarcoidosis, acute disseminated encephalomyelitis) or infectious (13 patients) (viral encephalitis, viral myelitis, neuroborreliosis, brain abscess, viral meningitis), 9.9% (37) as Peripheral Nervous System (PNS) disorders (i.e. diabetic neuropathy, carential neuropathy, Guillain-Barré syndrome, chronic demyelinating inflammatory polyneuropathy, anti MAG antibodies neuropathy, anti GQ1b antibodies neuropathy, idiopathic neuropathy or radiculopathy), 41.8% (156) as non immune-mediated CNS disorders (i.e. neurodegenerative disorders, stroke, cervical spondilogenic myelopathy, metabolic encephalopathy, small vessel disease, brain tumors, epilepsy, prion encephalopathy, conversion disorder, migraine, vertigo).

**Table 1**
Demographic and clinical features of the study population.

| | Sex | Age | MS, RR | MS, PP | CIS | MS, EDSS |
|---|---|---|---|---|---|---|
| MS (140 patients) | 26.8% M, 73.2% F | Mean 40.5 ± 1.3 | 84.6% | 8.1% | 7.3% | Median 1.5, range 0–6.5 |
| NMOSD (8 patients) | 25.0% M, 75.0% F | Mean 53.2 ± 7.3 | | | | |
| Other immune-mediated CNS disorders (OICDs) (32 patients) | All OICDs 34.5% M, 65.5% F | Mean 51.2 ± 3.2 | | | | |
| | Autoimmune OICDs (19 patients) 29.4% M, 70.6% F | Mean 50.4 ± 17.9 | | | | |
| | Infectious OICDs (13 patients) 41.7% M, 58.3% F | Mean 51.3 ± 16.8 | | | | |
| PNS disorders (37 patients) | 62.5% M, 37.5% F | Mean 44.6 ± 4.3 | | | | |
| Non-immune mediated CNS disorders (156 patients) | 47.9% M, 52.1% F | Mean 50.4 ± 1.7 | | | | |

In all MS patients, lumbar puncture was performed at the time of the diagnosis, corresponding to the first demyelinating event: duration of disease was always < 3 months (except in primary progressive MS patients, in which it is typically difficult to exactly define retrospectically the moment of disease onset).
MS: Multiple Sclerosis; NMOSD: Neuromyelitis optica spectrum disorder; RR: relapsing-remitting; PP: primary progressive; CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale.

A statistically significant difference was shown in the mean K-FLC index between OBs positive and OBs negative patients (mean K-FLC index in OBs-positive patients 89.564 ± 130.099; mean K-FLC index in OBs negative patients 4.090 ± 9.760; $p < .0001$). K-FLC index correlated with all common measures of intrathecal inflammation: K-FLC index-IgG index correlation rho = 0.587, p < .0001; K-FLC index-OBs number correlation rho = 0.586, p < .0001).

On the whole study population, the K-FLC index showed a diagnostic accuracy for MS/CIS higher than the IgG index (K-FLC index AUC 0.939, 95% CI 0.910–0.968; sensitivity 90.4%, specificity 88.9% (Fig. 1); IgG index AUC 0.803, 95% CI 0.754–0.851; sensitivity 76%, specificity 67.3%) and comparable to CSF OBs (CSF OBs sensitivity 86.3%, specificity 89.4%; McNemar's test for comparison of CSF OBs to K-FLC index $p = .053$). The optimal K-FLC index cut-off threshold, calculated from the ROC curve, was 6.150. This value is similar to cut-off thresholds reported in previous studies (Presslauer et al., 2008; Leurs et al., 2019).

The K-FLC index was significantly higher in patients with MS/CIS compared to other patients groups (Table 2, Fig. 2, Fig. 3): MS/CIS mean K-FLC index 90.897 ± 134.198; NMOSD mean K-FLC index 17.992 ± 15.103; OICDs mean K-FLC index 12.568 ± 24.440; PNS disorders mean K-FLC index 2.479 ± 1.565; non immune-mediated CNS disorders mean K-FLC index 4.041 ± 7.748. Patients with non immune-mediated CNS disorders showed uniformly low K-FLC index, with the exception of 2 patients with CNS localization of mantle cell lymphoma that showed abnormally increased CSF FLCs levels (K-FLC

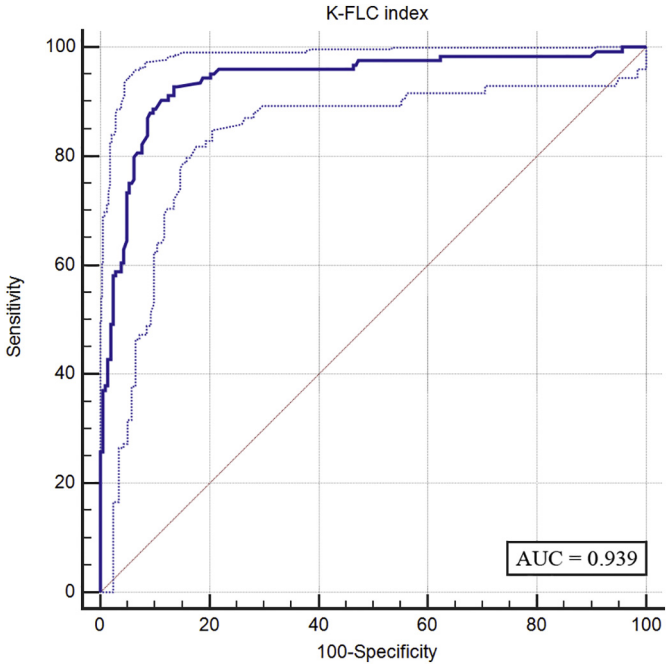


**Fig. 1.** ROC curve for K-FLC index, with 95% confidence intervals.

index 31.7 and 33.3); these were relapses in the CNS of a systemic disease that was otherwise in remission.

Higher K-FLC index in MS/CIS patients were determined by higher CSF kappa FLCs levels and CSF/serum kappa FLCs ratio in MS/CIS patients than in patients with NMOSD or OICDs (Fig. 2), reflecting higher intrathecal plasma cells activity in MS/CIS (MS/CIS mean CSF kappa FLCs 0.489 mg/dl ± 0.557; NMOSD mean CSF kappa FLCs 0.198 mg/dl ± 0.117; OICDs mean CSF kappa FLCs 0.199 mg/dl ± 0.407). Serum/CSF albumin ratio was instead not significantly different between these groups (Table 2).

The diagnostic accuracy of the K-FLC index was similar to CSF OBs in discriminating MS/CIS from OICDs (CSF OBs sensitivity 86.3%, specificity 62.1%; K-FLC index sensitivity 90.4%, specificity 69%; comparison of CSF OBs to K-FLC index, McNemar's test $p = .146$) or from NMOSD (CSF OBs sensitivity 86.3%, specificity 50.0%; K-FLC index sensitivity 91.2%, specificity 50.0%; comparison of CSF OBs to K-FLC index, McNemar's test $p = .179$). However, very high K-FLC index values were highly characteristic only of MS/CIS (Fig. 4):a K-FLC index above the 80th percentile (40.250) was observed almost only in MS/CIS patients (positive predictive value for MS/CIS 93.1%). A K-FLC index ≥100 showed 97.1% positive predictive value for MS/CIS (only exception being a patient with acute herpes virus 1 (HSV1) encephalitis) (Fig. 4).

A weak inverse correlation was observed between age and K-FLC index in MS/CIS patients (K-FLC index-age rho = − 0.245; $p = .006$). This was mainly due to the increase in the Q Alb (CSF/serum albumin ratio) with advancing age, because of higher CSF albumin and lower serum albumin. Consequently, the diagnostic accuracy of the K-FLC index was higher in patients with age ≤ 40 years (AUC 0.980, 95% CI 0.959–1.000; sensitivity 93.9% specificity 93.7%) than in patients with age > 40 years (AUC 0.903, 95% CI 0.848–0.957; sensitivity 86.4% specificity 85.9%).

Female MS/CIS patients showed higher mean K-FLC index than male MS/CIS patients; the difference however was not significant. No correlation was found between FLCs CSF levels or K-FLC index and EDSS. No significant difference in intrathecal plasma cell activity assessed by FLCs CSF levels was observed between relapsing-remitting and primary progressive MS patients, or in MS patients with clinical or radiological disease activity at the time of lumbar puncture if compared

**Table 2**
Summary of K-FLC index, CSF kappa FLCs, serum kappa FLCs, CSF albumin, serum albumin, IgG index, IEF, number of oligoclonal bands

| | | K-FLC CSF | K-FLC serum | Albumin CSF | Albumin serum | Q K | Q Alb | K-FLC index | IgG index | IEF (% positive) | Number of oligoclonal bands |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MS (140 patients) | | 0.479 mg/dl ± 0.548 | 1.293 mg/dl ± 0.457 | 30.250 mg/dl ± 40.130 | 4441.400 mg/dl ± 434.720 | 0.398 ± 0.478 | 0.007 ± 0.010 | 90.897 ± 134.198 | 0.980 ± 0.060 | 86.3% | 9.2 ± 0.5 |
| NMOSD (8 patients) | | 0.198 mg/dl ± 0.117[a] | 1.715 mg/dl ± 1.099[a] | 32.830 mg/dl ± 20.074[a] | 3748.17 mg/dl ± 536.925[a] | 0.116 ± 0.089[a] | 0.008 ± 0.006[a] | 17.992 ± 15.103 | 0.677 ± 1.247 | 57.1% | 6.6 ± 6.1 |
| Other immune-mediated CNS disorders (OICDs) (32 patients) | All OICDs | 0.199 mg/dl ± 0.407 | 1.528 mg/dl ± 0.808 | 38.410 mg/dl ± 26.187 | 4079.000 mg/dl ± 547.650 | 0.110 ± 0.173 | 0.009 ± 0.006 | 12.568 ± 24.440 | 0.680 ± 0.060 | 37.9% | 3.4 ± 0.9 |
| | Autoimmune OICDs (19 patients) | 0.103 mg/dl ± 0.188 | 1.479 mg/dl ± 0.702 | 33.000 mg/dl ± 18.293 | 4196.710 mg/dl ± 381.621 | 0.066 ± 0.106 | 0.008 ± 0.005 | 6.785 ± 9.446 | 0.566 ± 0.197 | 29.4% | 1.9 ± 4.6 |
| | Infectious OICDs (13 patients) | 0.333 mg/dl ± 0.580 | 1.596 mg/dl ± 0.968 | 46.080 mg/dl ± 33.902 | 3912.250 mg/dl ± 707.011 | 0.172 ± 0.229 | 0.011 ± 0.007 | 20.759 ± 35.578 | 0.850 ± 0.446 | 50.0% | 5.6 ± 6.0 |
| PNS disorders (37 patients) | | 0.045 mg/dl ± 0.079 | 1.473 mg/dl ± 0.712 | 53.850 mg/dl ± 46.874 | 4222.850 mg/dl ± 508.990 | 0.030 ± 0.040 | 0.013 ± 0.011 | 2.479 ± 1.565 | 0.620 ± 0.040 | 9.1% | 0.4 ± 0.3 |
| non-immune mediated CNS disorders (156 patients) | | 0.045 mg/dl ± 0.093 | 1.751 mg/dl ± 1.159 | 29.770 mg/dl ± 23.367 | 4136.140 mg/dl ± 576.860 | 0.027 ± 0.052 | 0.008 ± 0.009 | 4.041 ± 7.748 | 0.540 ± 0.020 | 3.6% | 0.3 ± 0.2 |

K-FLC index, CSF kappa FLCs, serum kappa FLCs, CSF albumin, serum albumin, IgG index, IEF, number of oligoclonal bands in MS, NMOSD, other immune-mediated CNS disorders, PNS disorders, non immune-mediated CNS disorders. Mean ± standard error.
MS: Multiple Sclerosis; NMOSD: Neuromyelitis optica spectrum disorder; K-FLC: k free light chains; IEF: isoelectrofocusing.
[a] For one NMOSD patient only the K-FLC index was available, but the data on CSF and serum K FLCs was missing.

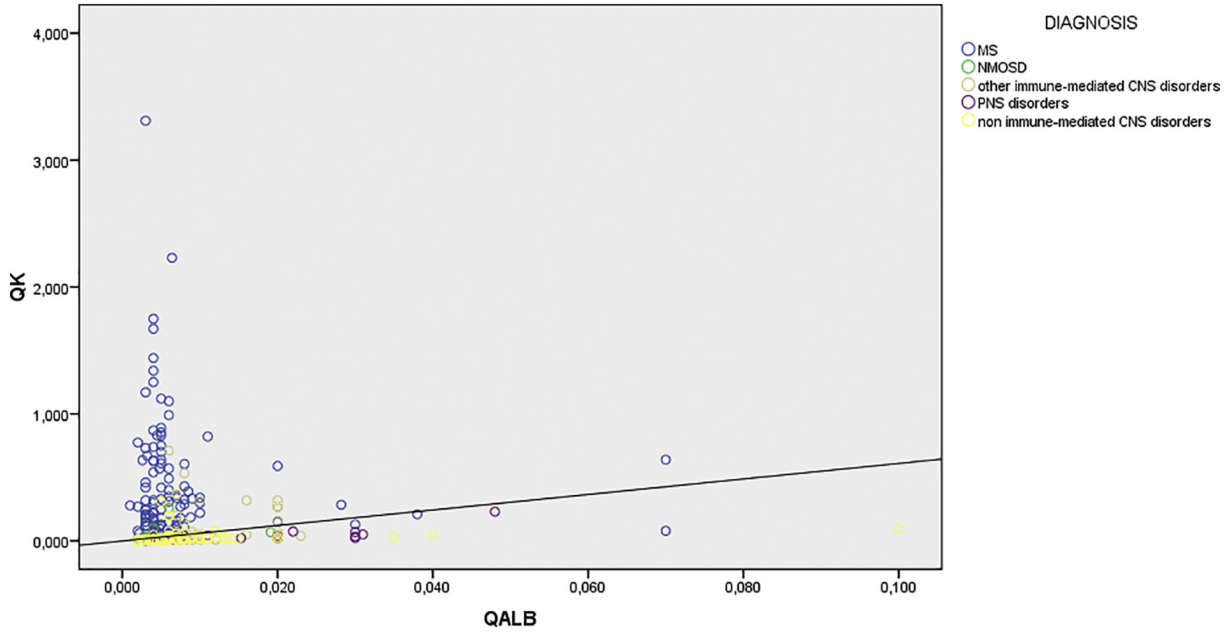


**Fig. 2.** K-FLC index (=QK/QAlb where QK and QAlb represent the ratios of serum and CSF albumin and kappa FCLs concentrations) in MS, NMOSD, immune-mediated CNS disorders, PNS disorders, non immune-mediated CNS disorders. The diagonal line is the optimal K-FLC index cut-off threshold, calculated from the ROC curve.

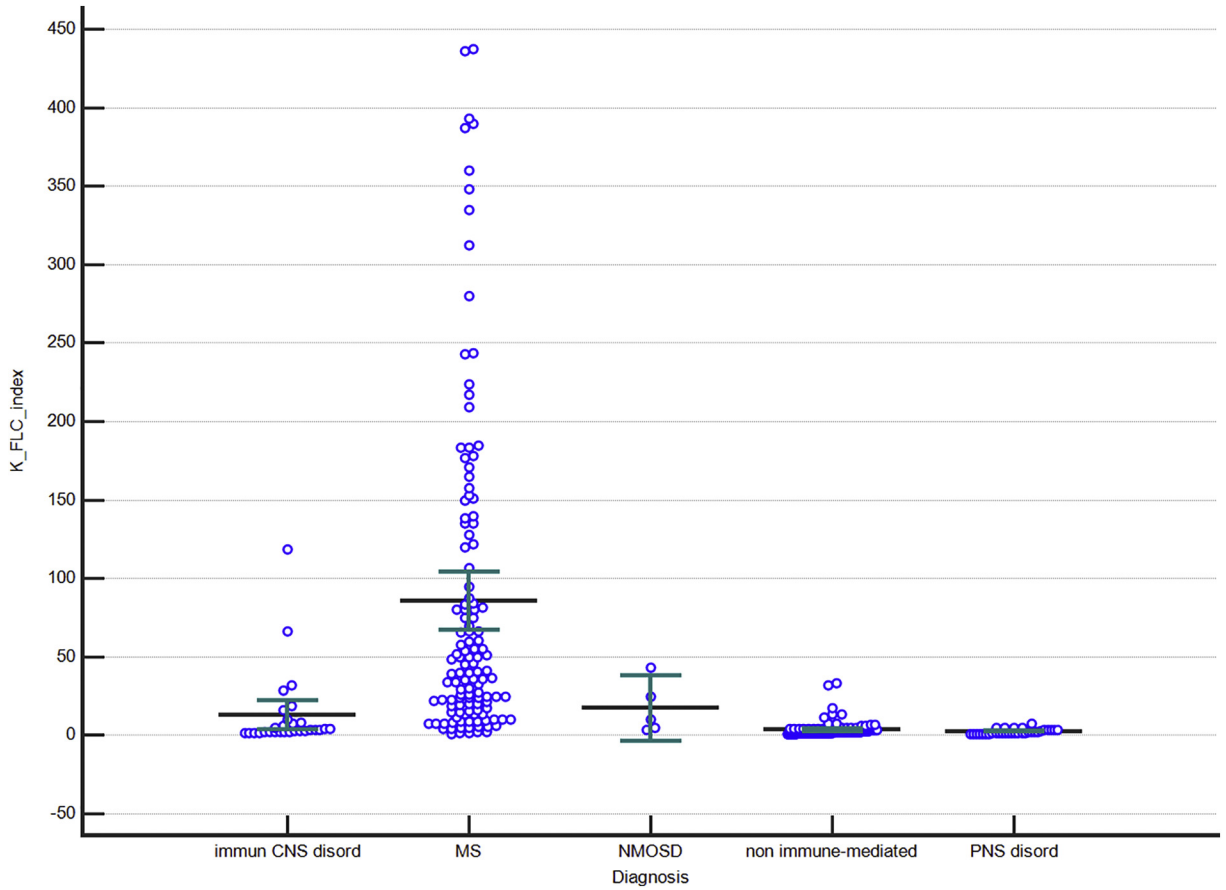


**Fig. 3.** K-FLC index in MS, NMOSD, immune-mediated CNS disorders, PNS disorders, non immune-mediated CNS disorders; horizontal lines represent mean and 95% confidence intervals.

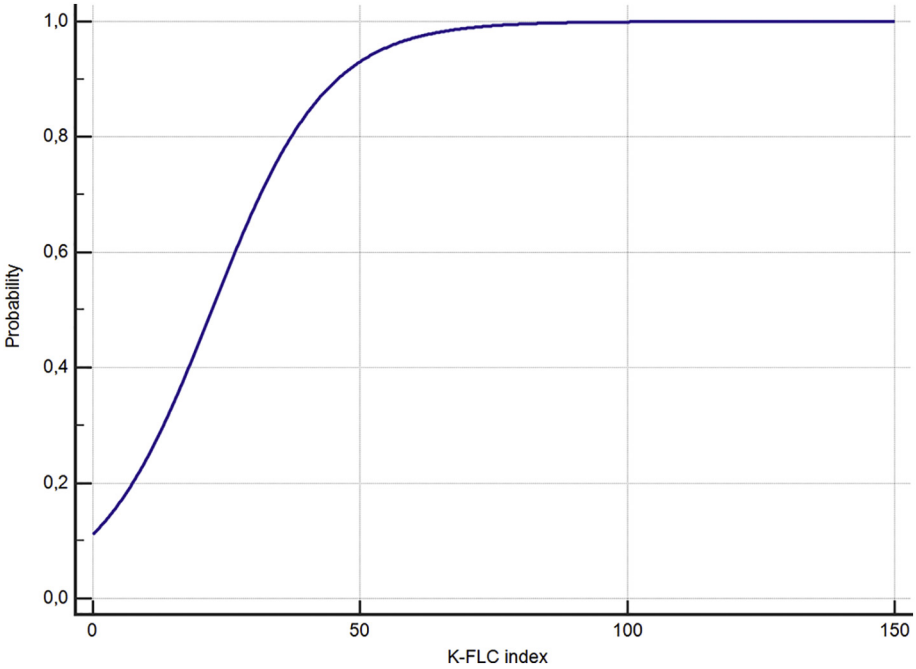


**Fig. 4.** Probability of MS diagnosis for increasing K-FLC index values (logistic regression; dependent variabile MS diagnosis, independent variable K-FLC index).

to patients with stable disease.

In OBs negative MS/CIS patients (17 patients), inclusion of K-FLC could have improved MS/CIS diagnosis, since the K-FLC index was abnormally increased in 9 patients (52.94%).

## 4. Discussion

The K-FLC index reliably detects intrathecal plasma cells activity and immunoglobulin synthesis in CNS inflammation. The demonstration of a high K-FLC index could represent an even more sensitive measure of intrathecal immunoglobulin production than OBs detection: FLCs, having low molecular weight, could diffuse more efficiently than the high-weight IgGs to the subarachnoid spaces (Goffette et al., 2004).

In MS patients the K-FLC index appears to be considerably higher than in OICDs. While in several inflammatory neurological disorders the intrathecal synthesis of FLCs is increased, MS patients show higher CSF FLCs levels and higher CSF/serum FLCs ratio than patients with OICDs or patients with NMOSD, and thus much higher mean K-FLC index.

As a quantitative variable, the K-FLC index appears to be superior to CSF OBs in discriminating MS from OICDs: while a degree of overlap in the K-FLC index exists between MS and OICDs, elevated K-FLC index values are highly characteristic only of MS. In our study, high K-FLC index values ($\geq$ 100) were only found in MS, with the exception of a patient with acute HSV1 encephalitis (whose clinical and radiological feature do not mimic MS). A high K-FLC index is therefore strongly predictive of MS in the appropriate clinical setting.

In non-inflammatory CNS disorders K-FLC index is uniformly low; one notable exception are patients with CNS localizations of mantle cell lymphoma, in which K-FLC index appears to be increased.

Our results confirm that the K-FLC index can accurately diagnose MS patients, with a sensitivity and specificity comparable to the detection of CSF OBs. This has been observed also in previous studies (Presslauer et al., 2008; Presslauer et al., 2014; Hassan-Smith et al., 2014; Duranti et al., 2013; Passerini et al., 2016; Crespi et al., 2019; Pieri et al., 2017; Bayart et al., 2018; Puthenparampil et al., 2018; Christiansen et al., 2018). The K-FLC index provides added diagnostic value in OBs negative MS patients, allowing detection of intrathecal immunoglobulin synthesis in more than half of OBs negative patients.

Therefore, the K-FLC index could represent an accurate alternative way to detect intrathecal synthesis in MS, besides the detection of OBs, adding diagnostic value to CSF examination.

By determining the K-FLC index, the technical drawbacks involved in OBs analysis, such as the requirement for skilled technicians to perform the technique as well as the experience required to interpret the gels and the lack of standardization (low interlaboratory reproducibility), can be avoided. Therefore, the K-FLC index is the most interesting alternative to OBs detection in MS diagnosis. Due to advances in technology, the K-FLC index can be measured quickly using an automated system so this test can be easily incorporated in the daily routine of immunology laboratories.

Two problems arise, however. The first one is the reproducibility of this technique: diagnostic accuracy has been defined in each laboratory on the basis of independently assessed cut-off thresholds. An effort should be made to establish shared protocols and, most importantly, a shared K-FLC index threshold should be identified on the basis of large series of cases.

The second problem is how to use this new biomarker in the frame of the "2017 revision of the McDonald MS Diagnostic Criteria" (Thompson et al., 2018). In this setting, the detection of OBs allows the demonstration of "dissemination in time" in a patient presenting with a typical first demyelinating episode. It also represents one of the three supporting conditions for primary progressive MS (being the others the MRI demonstration of lesions dissemination in the brain or in the spinal cord) in patients with 1 year disability progression. A large body of evidence demonstrating that this new biomarker has at least the same prognostic importance of OBs detection is therefore needed, before it could be considered equivalent in MS diagnosis.

## Declaration of Competing Interest

None.

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