Kappa Free Light Chain Index Predicts Disease Course in Clinically and Radiologically Isolated Syndromes

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Abstract

Background and Objectives
To evaluate whether the kappa free light chain index (K-index) can predict the occurrence of new T2-weighted MRI lesions (T2L) and clinical events in clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS).

Methods
All consecutive patients presenting for the diagnostic workup, including CSF analysis, of clinical and/or MRI suspicion of multiple sclerosis (MS) since May 1, 2018, were evaluated. All patients diagnosed with CIS and RIS with at least 1-year follow-up were included. Clinical events and new T2L were collected during follow-up. The K-index performances in predicting new T2L and a clinical event were evaluated using time-dependent ROC analyses. The time to clinical event or new T2L was estimated using survival analysis according to the binarized K-index using an independent cutoff of 8.9, and the ability of each variable to predict outcomes was compared using the Harrell c-index.

Results
One hundred and eighty two patients (146 CIS and 36 RIS, median age 39 [30; 48] y-o, 70% females) were included with a median follow-up of 21 [13, 33] months. One hundred five (58%) patients (85 CIS and 20 RIS) experienced new T2L, and 28 (15%; 21 CIS and 7 RIS) experienced a clinical event. The K-index could predict new T2L over time in CIS (area under the curve [AUC] ranging from 0.86 to 0.96) and in RIS (AUC ranging from 0.84 to 0.54) but also a clinical event in CIS (AUC ranging from 0.75 to 0.87). Compared with oligoclonal bands (OCBs), the K-index had a better sensitivity and a slight lower specificity in predicting new T2L and clinical events in both populations. In the predictive model, the K-index was the variable that best predict new T2L in both CIS and RIS but also clinical events in CIS (c-index ranging from 0.70 to 0.77), better than the other variables, including OCB.

Discussion
This study provides evidence that the K-index predicts new T2L in CIS and RIS but also clinical attack in patients with CIS. We suggest adding the K-index in the further MS diagnosis criteria revisions as a dissemination-in-time biomarker.
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Glossary

AUC = area under the curve; CIS = clinically isolated syndrome; DIS = dissemination in space; DIT = dissemination in time; DMT = disease-modifying treatment; HR = hazard ratio; IgG = immunoglobulin G; KFLC = kappa free light chain; K-IF = KFLC intrathecal fraction; K-index = KFLC index; OCB = oligoclonal band; RIS = radiologically isolated syndrome; T2L = T2-weighted lesions.

Introduction

Immune-mediated and demyelinating CNS disorders represent an extensive range of diseases, some presenting with a first and unique flare-up and others with relapsing or progressive worsening courses. Multiple sclerosis (MS) is the most common chronic inflammatory and demyelinating disorder affecting young adults, with a female predominance. Several diagnosis criteria have been proposed and revised in the past 40 years, leading to a consensus on satisfying dissemination in space (DIS) and time (DIT) criteria to diagnose MS, both with equal performances.17,22 However, we lack data on the prognostic role of the K-index in patients presenting with CIS,23,24 and there are no data in RIS.

This study investigated whether the K-index could predict new clinical events and new T2L on follow-up MRI scans in patients presenting with CIS and RIS.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

According to French laws, the patients received transparent, fair, and appropriate research information, and written informed consent was obtained. The study was conducted following the Declaration of Helsinki and received approval from the institutional review board of the University Hospital of Nice (IRB number 2022 – EI-026).

Study Design

Based on prospectively acquired data, this retrospective study was conducted on patients referred to the MS tertiary center of Nice University Hospital, France. From May 1, 2018, to July 1, 2021, all consecutive patients older than 18 years presenting to our institution for a suspected MS diagnostic workup with at least 1-year follow-up and a CSF study were eligible. The patients were excluded from the analysis if they underwent lumbar puncture more than 6 months after the clinical event, if a disease-modifying treatment (DMT) was initiated before sampling (excepted for steroids), or if another diagnosis than CIS or RIS was made, including clinically definite MS. According to our institutional routine diagnostic workup, all patients underwent a brain and spinal cord 3T MRI, blood, and CSF analysis, including OCB determination and KFLC quantification. According to the standard of care, all patients had at least 1 clinical visit and 1 follow-up MRI per year. Medical electronic files of all eligible patients were recorded to collect demographic, clinical, biological, and MRI-needed data. Patients were then separated into groups according to their diagnosis: The CIS group comprised patients presenting with a first clinical demyelinating event, whatever their MRI and biological characteristics, and the RIS group formed patients presenting with typical MS-suggestive MRI T2L without a medical history of clinical events.
suggestive of demyelinating CNS disorder according to RIS
diagnosis criteria.8

Collected Data
For all included patients, the following data were recorded at
baseline: age, sex, time from the clinical event to blood and CSF
sampling, type of clinical demyelinating symptom, steroid use
before the workup, DIS location of T2L on the index brain and
spinal cord MRI, presence of gadolinium-enhancing T1-weighted
lesion on index MRI, CSF protein, and white blood cell counts.
CSF and serum albumin, IgG, OCB, and KFLC were recorded. At
every follow-up visit, the following data were recorded: clinical
attack occurrence suggestive of MS, presence of new T2L on MRI

MRI Analysis
All patients underwent brain and spinal cord MRI according
to routine care at baseline, with standardized MRI protocols25

| Table 1 Description of the Population According to Both CIS and RIS Groups |
|----------------------------------|------------------|------------------|
| **CIS, n = 146**                 | **RIS, n = 36**   |                  |
| **Age (y), median [Q1; Q3]**     | 38 [29; 46]      | 46 (33; 56)      |
| **Sex (female), n (%)**          | 96 (66)          | 31 (86)          |
| **No. of patients fulfilling the 2017 McDonald criteria, n (%)** | 78 (53) | — |
| **Type of the clinical event at sampling** |                  |                  |
| **Optic neuritis, n (%)**        | 40 (28)          | —                |
| **Myelitis, n (%)**              | 64 (44)          | —                |
| **Infratentorial attack, n (%)** | 37 (25)          | —                |
| **Steroid use before sampling, n (%)** | 12 (8)     | 0 (0)            |
| **Time of disease duration at sampling (d), median [Q1; Q3]** | 22 [7; 62] | — |
| **No. of patients with T2L in the location** |                  |                  |
| **Periventricular, n (%)**       | 94 (64)          | 36 (100)         |
| **Juxta/cortical, n (%)**        | 83 (57)          | 31 (86)          |
| **Infratentorial, n (%)**        | 76 (52)          | 13 (36)          |
| **Spinal cord, n (%)**           | 97 (66)          | 9 (25)           |
| **No. of patients with isolated symptomatic T2L, n (%)** | 55 (38) | — |
| **No. of patients with gadolinium-enhancing lesion, n (%)** | 62/130 (48) | 2/31 (6) |
| **No. of MRI/year/patient, median [Q1; Q3]** | 1.5 [1.1; 1.9] | 1.1 (0.8; 1.5) |
| **CSF protein count (g/L), median [Q1; Q3]** | 0.34 [0.27; 0.46] | 0.32 (0.26; 0.43) |
| **CSF WBC count (/mm³), median [Q1; Q3]** | 2 [0; 5] | 1 [0; 3] |
| **IgG index, median [Q1; Q3]**   | 0.68 [0.58; 1.00] | 0.61 (0.54; 0.98) |
| **Positive OCB status, n (%)**   | 79 (54)          | 16 (44)          |
| **K-index, median [Q1; Q3]**     | 37 [4; 106]      | 19 (3; 112)      |
| **Follow-up duration (mo), median [Q1; Q3]** | 20 [13; 33] | 25 (16; 35)      |
| **No. of patients with clinical attack during follow-up, n (%)** | 21 (14) | 7 (19) |
| **Time to clinical attack (mo), median [Q1; Q3]** | 10 [6; 13] | 19 (11; 38) |
| **No. of patients with DMT start before clinical attack, n (%)** | 69 (47) | 0 (0) |
| **No. of patients with new T2L during follow-up, n (%)** | 85 (58) | 20 (56) |
| **Time to new T2L (mo), median [Q1; Q3]** | 6 [3; 11] | 16 (9; 24) |
| **No. of patients with DMT start before new T2L, n (%)** | 20 (14) | 0 (0) |

Abbreviations: CIS = clinically isolated syndrome; DMT = disease-modifying treatment; IgG = immunoglobulin G; KFLC = kappa free light chain; RIS = radiologically isolated syndrome; WBC = white blood cell.
including 3D fluid-attenuated inversion recovery (FLAIR), T2-weighted, and T1-weighted images. Gadolinium-enhanced T1-weighted images were recorded for most participants (n = 161 (88%)). All images were obtained on a 3T field strength MRI with axial and sagittal 1-mm-thick slice. MRI reading and analysis were performed by 2 experienced neurologists-radiologists (L.M. and C.L.F.). All patients underwent at least a yearly brain MRI evaluation. According to clinical practice, some participants were evaluated more frequently depending on neurologists’ clinical assessment.

**Blood and CSF Analysis**

Blood and CSF were collected for all patients and analyzed in the Nice University Hospital immunology laboratory. Blood and CSF IgG, albumin, and KFLC were measured by turbidimetry with the analyzer Optilite (The Binding Site, Birmingham, UK) using the serum-free light chain immunoassay Freelite (The Binding Site, Birmingham, UK), according to the manufacturer’s instructions. Oligoclonal bands were determined by isoelectric focusing on agarose gel using subsequent immunoblotting using IgG-specific antibody staining (Hydrasys platform; Sebia, Lisses, France). Oligoclonal band patterns were evaluated by an experienced biologist and classified as positive (patterns II and III) or negative (other patterns). A cutoff of ≥ 2 CSF-restricted bands was used to define OCB positivity. The determination of intrathecal synthesis of KFLC was evaluated by the calculation of the K-index using the formula:

\[
K \text{-index} = \frac{(\text{CSF KFLC/serum KFLC})}{(\text{CSF albumin/serum albumin})}
\]

According to previously published data, a K-index of ≥8.9 was considered as positive.17

**Statistical Analysis**

Continuous variables were described by median and interquartile range (first and third quartiles) and categorical variables by count and percentage. The association of baseline covariates with the K-index was analyzed nonparametrically using the Wilcoxon rank-sum test for binary variables or the Kruskal-Wallis test for categorical variables with more than 2 levels.

The predictive performance of the quantitative K-index was analyzed using time-dependent ROCs to account for censored data: area under the curve (AUC) was calculated at different time points after diagnosis with a weighting by the inverse probability of the censoring approach. Optimal cutoffs at 12, 24, and 36 months were determined by maximizing the Youden index with a bootstrap method for the 95% CI. Sensitivity, specificity, positive predictive value, and negative predictive value were assessed at 12, 24, and 36 months using an independent K-index cutoff of 8.917 and for OCB. Diagnostic performances of our calculated K-index thresholds were not used for statistical analyses because of high heterogeneity (different cutoffs at each time point and large 95% CIs).

The time to first new T2L and clinical relapse were analyzed with survival curves estimated using the Kaplan-Meier method for the binarized K-index using the 8.9 cutoff17 and for OCB, with statistical significance assessed using the log-rank test. Univariate Cox regressions were constructed for each baseline covariate to determine the hazard ratio (HR) of the time to first new T2L and clinical relapse. The proportional hazard assumption was visually assessed using Schoenfeld residuals. The Harrell c-index was calculated to compare each variable based on the goodness of fit of the univariate model, ranging from 0.5 (not better than random) to 1 (perfect concordance). p Values less than 0.05 were considered statistically significant. Analyses were performed using R software, version 4.0.3,26 with the timeROC package for time-dependent ROC analysis.27

**Figure 1 Time-Dependent ROC Analyses**

The figure shows the ability of the K-index to predict over time (time-dependent AUC) new T2L occurrence in patients with CIS (panel A), new T2L occurrence in people with RIS (panel B), and clinical event occurrence in patients with CIS (panel C). Overall, the ability of the K-index to predict outcomes increases over time for CIS but decreases for RIS. The dashed lines show time-dependent CIs. AUC = area under the curve; CIS = clinically isolated syndrome; RIS = radiologically isolated syndrome; T2L = T2-weighted MRI lesions.
Table 2 Hazard Ratio of Key Variables and Their Concordance Index in Estimating the Risk of New T2L Occurrence in Patients With CIS

<table>
<thead>
<tr>
<th>No. Value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p Value</th>
<th>c-Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>——</td>
<td>——</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>146 Per 10 y increase</td>
<td>0.76 0.47–1.21</td>
<td>0.244</td>
<td>0.51</td>
</tr>
<tr>
<td>Age</td>
<td>146 Optic neuritis</td>
<td>0.60 0.48–0.73</td>
<td>&lt;0.001</td>
<td>0.67</td>
</tr>
<tr>
<td>Clinical event</td>
<td>146 Myelitis</td>
<td>0.56 0.32–1.01</td>
<td>0.051</td>
<td>0.59</td>
</tr>
<tr>
<td>No. of affected MS locations by T2L on baseline MRI scan</td>
<td>146 1</td>
<td>1.23 0.26–5.82</td>
<td>0.790</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>146 2</td>
<td>6.69 1.46–30.55</td>
<td>0.014</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>146 3 or 4</td>
<td>10.59 2.59–43.36</td>
<td>0.001</td>
<td>0.72</td>
</tr>
<tr>
<td>Gadolinium-enhanced T1 lesion on baseline MRI scan</td>
<td>130 Yes</td>
<td>1.40 0.89–2.19</td>
<td>0.144</td>
<td>0.55</td>
</tr>
<tr>
<td>K-index</td>
<td>146 Per 10 increase</td>
<td>1.06 1.04–1.07</td>
<td>&lt;0.001</td>
<td>0.77</td>
</tr>
<tr>
<td>Binarized K-index (&gt;8.9)</td>
<td>146 Positive</td>
<td>17.17 7.41–39.79</td>
<td>&lt;0.001</td>
<td>0.73</td>
</tr>
<tr>
<td>OCB</td>
<td>146 Positive</td>
<td>4.59 2.80–7.53</td>
<td>&lt;0.001</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Abbreviations: CIS = clinically isolated syndrome; K-index = kappa free light chain index; OCB = oligoclonal band; T2L = T2-weighted lesion.

Data Availability
Data not provided in the article because of space limitations may be shared (anonymized) at the corresponding author’s request for replicating procedures and results.

Results
Three hundred forty-four consecutive patients presented to our department during the study period for the diagnostic workup of a suspected MS, and 182 patients (146 CIS and 36 RIS) were included (eFigure 1, links.lww.com/NXI/A896 in supplementary material). One hundred and twenty-seven (70%) patients were women; the median age was 39 years (30; 48). Participants with CIS and RIS were comparable according to their CSF analysis and follow-up duration. People with RIS were older and more frequently women than patients with CIS in this cohort (Table 1).

Both participants with CIS and RIS had similar K-index values (median of 36.9 [4.1; 105.8] for CIS and 18.9 [3.1; 111.9] for RIS,

Figure 2 Survival Analysis Evaluating New T2L Occurrence in Patients With CIS According to Their Binary K-Index and OCB Status

The figure shows the time to new T2L in patients with CIS according to their positive (blue line) or negative (red line) K-index status (panel A) and their positive (blue line) or negative (red line) OCB status (panel B). OCB = oligoclonal band; T2L = T2-weighted MRI lesions.
and positive OCB status (54% for CIS and 44% for RIS, \( p = 0.393 \)). Positive OCB and K-index (binarized according to the 8.9 cutoff) were concordant in 149 (82%) patients. From the 33 (18%) remaining patients, most of them (n = 30) had a positive K-index with negative OCB. Detailed demographic, clinical, biological, and MRI data are provided in Table 1.

Of the 146 patients with CIS, 62 (48%) had at least 1 gadolinium-enhanced lesion on the baseline MRI scan, and 78 (53%) could be diagnosed with MS according to the 2017 McDonald criteria. From the 29 patients with CIS fulfilling the 2017 McDonald criteria because of OCB positivity (no or not reported T1 gadolinium-enhancing lesion), the median K-index value was 103.0 [53.6; 231.2], with a minimum value of 35.3.

At baseline, the K-index values significantly increased with the presence of a T1-weighted gadolinium-enhancing lesion (\( p = 0.049 \)), the number of MS DIS locations on MRI (\( p < 0.001 \)), and a positive OCB status (\( p < 0.001 \)) and decreased

### Table 3 Hazard Ratios of Key Variables and Their Concordance Index in Estimating the Risk of New T2L Occurrence in People With RIS

<table>
<thead>
<tr>
<th>No Value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>( p ) Value</th>
<th>c-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>36</td>
<td>0.44</td>
<td>0.15–1.31</td>
<td>0.142</td>
</tr>
<tr>
<td>Age</td>
<td>36 Per 10 y increase</td>
<td>0.69</td>
<td>0.46–1.03</td>
<td>0.071</td>
</tr>
<tr>
<td>Clinical event</td>
<td>146</td>
<td>Optic neuritis</td>
<td>0.59</td>
<td>0.17–2.09</td>
</tr>
<tr>
<td>Myelitis</td>
<td>146</td>
<td>0.80</td>
<td>0.29–2.26</td>
<td>0.667</td>
</tr>
<tr>
<td>No. of affected MS locations by T2L on baseline MRI scan</td>
<td>146</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3 or 4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gadolinium-enhanced T1 lesion on baseline MRI scan</td>
<td>130</td>
<td>Yes</td>
<td>0.88</td>
<td>0.36–2.12</td>
</tr>
<tr>
<td>K-index</td>
<td>146 Per 10 y increase</td>
<td>1.04</td>
<td>1.01–1.07</td>
<td>0.007</td>
</tr>
<tr>
<td>Binarized K-index (&gt;8.9)</td>
<td>146 Positive</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>OCB</td>
<td>146 Positive</td>
<td>2.56</td>
<td>0.99–6.60</td>
<td>0.053</td>
</tr>
</tbody>
</table>

**Abbreviations:** K-index = kappa free light chain index; OCB = oligoclonal band; RIS = radiologically isolated syndrome; T2L = T2-weighted lesion.

No HR could be estimated in clinical attack prediction for the variables “No. of affected MS locations by T2L on baseline MRI scan” and the “Binarized K-index” because no events occurred in one of the subgroups.

### Table 4 Hazard Ratios of Key Variables and Their Concordance Index in Estimating the Risk of Clinical Attack Occurrence in Patients With CIS

<table>
<thead>
<tr>
<th>No Value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>( p ) Value</th>
<th>c-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>146</td>
<td>0.44</td>
<td>0.15–1.31</td>
<td>0.142</td>
</tr>
<tr>
<td>Age</td>
<td>146 Per 10 y increase</td>
<td>0.69</td>
<td>0.46–1.03</td>
<td>0.071</td>
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<td>Clinical event</td>
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<td>0.17–2.09</td>
</tr>
<tr>
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<td>0.80</td>
<td>0.29–2.26</td>
<td>0.667</td>
</tr>
<tr>
<td>No. of affected MS locations by T2L on baseline MRI scan</td>
<td>146</td>
<td>1</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Gadolinium-enhanced T1 lesion on baseline MRI scan</td>
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<td>Yes</td>
<td>0.88</td>
<td>0.36–2.12</td>
</tr>
<tr>
<td>K-index</td>
<td>146 Per 10 y increase</td>
<td>1.04</td>
<td>1.01–1.07</td>
<td>0.007</td>
</tr>
<tr>
<td>Binarized K-index (&gt;8.9)</td>
<td>146 Positive</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>OCB</td>
<td>146 Positive</td>
<td>2.56</td>
<td>0.99–6.60</td>
<td>0.053</td>
</tr>
</tbody>
</table>

**Abbreviations:** K-index = kappa free light chain index; OCB = oligoclonal band; T2L = T2-weighted lesion.
with age ($p = 0.001$). The gender ($p = 0.074$) and the type of the clinical event ($p = 0.171$) did not statistically influence K-index values (eFigure 2, links.lww.com/NXI/A896 in supplementary material).

During the follow-up period (median of 21 months [13; 33]), 28 patients (15%) experienced a clinical event (21 CIS and 7 RIS), and 105 (58%) experienced at least 1 new T2L on follow-up MRI scans (85 CIS and 20 RIS). From the 69 patients with CIS for whom a DMT was started early after lumbar puncture, and before new clinical event occurrence, the median K-index was 72.5 [39.5; 214.6].

**K-Index Value Predicted New T2L in Patients With CIS**

According to time-dependent ROC analysis, the K-index had good prognostic performances to predict new T2L in CIS during follow-up, with AUC ranging from 0.86 [0.80; 0.92] at 12 months to 0.96 [0.91; 1.00] at 48 months (Figure 1A). The supplementary data show individual ROC at different time points (eFigure 3, links.lww.com/NXI/A896). The optimal cutoffs were 30.5 [11.6; 36.7] at 12 months, 14.9 [9.6; 40.9] at 24 months, and 13.6 [5.9; 46.6] at 36 months. According to Cox regression analysis, the hazard of new T2L in patients with CIS increased by 6% every time the K-index increased by 10 points (Table 2). Moreover, the K-index was the variable with the highest predictive performance (c-index of 0.77), compared with the number of DIS locations on T2-weighted images (c-index of 0.72), the presence of T1 gadolinium-enhancing lesion (c-index of 0.55), and the OCB status (c-index of 0.69) (Table 2).

When using the K-index as a binary variable (positive or negative according to the 8.9 cutoff value), the K-index had a better sensitivity (0.97–0.98 vs 0.70–0.82) and a slight lower specificity (0.55–0.79 vs 0.67–0.79) than OCB to predict new T2L over time in CIS (eTable 1, links.lww.com/NXI/A896 in supplementary material). Kaplan-Meier analyses showed that both OCB and the binarized K-index could predict the time to new T2L in patients with CIS ($p < 0.0001$, Figure 2).

**K-Index Value Predicted New T2L in People With RIS**

According to time-dependent ROC analysis, the K-index was able to predict new T2L in RIS, with AUC ranging from 0.84 [0.66; 1.00] at 12 months to 0.64 [0.43; 0.85] at 24 months (Figure 1B). The supplementary data show individual ROC at different time points (eFigure 4, links.lww.com/NXI/A896). The optimal cutoffs were 30.2 [21.2; 227.2] at 12 months and 17.7 [2.1; 227.2] at 24 months. According to Cox regression analysis, the hazard of new T2L in patients with RIS increased by 8% every time the K-index increased by 10 points (Table 3). Again, the K-index was the variable with the highest predictive performance (c-index of 0.70), compared with the number of DIS locations on T2-weighted images on baseline MRI scan (c-index of 0.54), the presence of T1 gadolinium-enhanced lesion (c-index of 0.58), and the OCB status (c-index of 0.62) (Table 3).

When using the K-index as a binary variable (positive or negative according to the 8.9 cutoff value), the K-index had a better sensitivity (0.97–0.98 vs 0.70–0.82) and a lower specificity (0.55–0.79 vs 0.67–0.79) than OCB to predict new T2L over time in RIS (eTable 2, links.lww.com/NXI/A896 in supplementary material). Kaplan-Meier analyses showed that both OCB and the binarized K-index could predict the time to new T2L in RIS ($p = 0.025$). Oligoclonal bands did not reach statistical significance for predicting new T2L in RIS ($p = 0.100$). Survival analyses are shown in supplementary material (eFigure 5).
K-Index Predicted Clinical Attack During Follow-up in Patients With CIS

According to time-dependent ROC analysis, the K-index had good prognostic performance to predict clinical attack in CIS, with AUC ranging from 0.75 [0.65; 0.85] at 12 months to 0.87 [0.74; 1.00] at 48 months (Figure 1C). As shown in Figure 1C, the AUC was stable over time. The supplementary data show individual ROC at different time points (eFigure 6, links.lww.com/NXI/A896). The obtained optimal cutoffs were 23.6 [20.0; 98.4] at 12 months and 9.6 [6.9; 80.5] at 24 months. According to Cox regression analysis, the hazard of clinical relapse in patients with CIS increased by 4% every time the K-index increased by 10 points (Table 4). The K-index was the variable with the highest predictive performance (c-index of 0.71), compared with the number of DIS locations on T2-weighted images on baseline MRI scan (c-index of 0.65), the presence of T1 gadolinium-enhanced lesion (c-index of 0.50), and the OCB status (c-index of 0.62) (Table 4).

When using the K-index as a binary variable (positive or negative according to the 8.9 cutoff value), the K-index had a better sensitivity (1.00 vs 0.68–0.77) and a lower specificity (0.35–0.42 vs 0.49–0.65) than OCB to predict new clinical events over time in CIS (eTable 3, links.lww.com/NXI/A896 in supplementary material). Kaplan-Meier analyses showed that the binarized K-index (p = 0.008) and OCB (p = 0.045) could predict the time to new clinical events in patients with CIS. Survival analyses are shown in Figure 3.

Discussion

In this prospective cohort of 146 patients with CIS and 36 patients with RIS, we show that the K-index measurement in the CSF is an exciting tool to predict the occurrence of new T2L at the early stages of MS spectrum disorders. The prediction extends to the clinical attack occurrence in patients with CIS. Of importance, we found that using the K-index as a continuous variable allows estimating the risk to fit the outcome (new T2L or clinical event) with a better concordance than a binarized K-index, reinforcing the use of a quantitative biomarker in such an approach.

Dedicated longitudinal studies focusing on the diagnostic performance of KFLC measurement to predict MS in patients presenting with early suggesting features (i.e., CIS and RIS) are still being determined.23,24,28,30 Most of these studies focused on the ability of the K-index to predict the occurrence of a second clinical event, but none specifically looked at whether the K-index could predict asymptomatic disease activity with the occurrence of new T2L. The 2017 McDonald criteria, used in clinical practice, specify that radiologic DIS and DIT, according to T2 or T1 gadolinium-weighted sequences, are enough to establish MS diagnosis and initiate specific DMT.6 Therefore, clinical relapse as the primary outcome of MS conversion does not reflect usual practice and could underestimate the K-index predictive value. However, given the low number of clinical attacks in our RIS group, we could not show whether the K-index could predict clinical attack in this population and extend to the 2017 McDonald criteria fulfillment.

To our knowledge, there is only one study that evaluates the diagnostic performance of the K-index in predicting MS according to either new T2L or clinical relapse.31 Based on the evaluation of 214 CIS patients, the authors found that using a positive K-index, based on a 5.9 or 6.6 cutoff values,18,31 had similar performances to OCB in predicting 2017 McDonald criteria fulfillment, with a slight increase in accuracy favoring the use of the K-index.23 We found similar results, although, in our prospective cohort, the K-index could predict new T2L and clinical relapse in patients with CIS with a better concordance than OCB. Compared with the previous study,23 we included all patients raising a suspicion of MS consecutively with a prospective evaluation of CSF parameters. Our follow-up duration is shorter (i.e., 2 years) but is counterbalanced by each patient’s yearly clinical and MRI assessment.

Our findings, associated with others23,24 together suggest that the K-index should be evaluated in clinical practice as a DIT-replacing biomarker. The unresolved question is how to use it in clinical practice. There is currently no consensus on the cutoff value to use to separate patients as having intrathecal KFLC synthesis or not having it.32,33 Our results show that optimal K-index cutoffs that best separate patients vary over time. Moreover, the CIs associated with our K-index cutoffs are wide. For these reasons, we chose to not analyze the diagnostic performances of our obtained cutoffs, focusing on an independent one established on a large cohort of patients.17 A main finding is that we show that by using an 8.9 K-index cutoff, none of the negative K-index CIS patients experienced a clinical event during follow-up, highlighting the good sensitivity of such a biomarker. Therefore, using a low K-index cutoff, it is 5.9, 6.6, or 8.9, was sufficient to discriminate patients at low risk of new T2L or clinical events in this cohort. In positive K-index patients, the risk could be graduated using the continuous K-index to increase specificity for MS diagnosis.

Our knowledge about KFLC measurement in RIS is poor. Two previous KFLC studies included people with RIS as MS or control populations, but did not analyze them separately.34,35 Even if our sample of RIS is small, we could find that the K-index could predict new T2L over time. Of interest, as for patients with CIS, higher K-index values were associated with a shorter time to new T2L. Unfortunately, we could not find an association between the K-index and the risk of clinical attack in RIS because of the low number of included patients. Therefore, RIS-dedicated studies should be performed, including more patients, to evaluate the clinical predictive role of the K-index. However, this result is of interest; at the same time, the RIS criteria have been revised,19 and asymptomatic radiologic activity (i.e., new T2L and/or new
T1 gadolinium-enhancing lesion) and the presence of OCB appear as a critical feature in diagnosing people with RIS.

This study has some strengths but also many limitations. Being a monocentric analysis, the K-index performances may be overestimated, and multicentric prospective studies must confirm these results. Nonetheless, our results are concordant with others, reinforcing their interest.

The median follow-up of our cohort was short. It may lead to underestimating the K-index predictive performance. At the same time, some patients, classified as “not fulfilling the outcome,” may present with new T2L or clinical attacks in the further years of follow-up. Even if the timeline is short, our results remained statistically significant with stable AUC over time, particularly for patients with CIS.

In our cohort, we reported that half of our patients had positive OCB (54% of CIS and 44% of RIS), which is lower than that usually reported.\(^1,15\) It might be explained by the interrater reliability of the isoelectric focusing method,\(^36\) reinforcing the need to use a fully automatized tool to measure intrathecal B-cell activity. Another explanation could be the prospective recruitment of this cohort. Some of our patients with CIS might be diagnosed retrospectively as having a monophasic idiopathic inflammatory demyelinating disease (i.e., idiopathic optic neuritis or myelitis),\(^5\) whereas 38% of our CIS cohort had a solitary symptomatic T2-weighted MRI lesion. We know that a small proportion of these patients may develop clinically definite MS.\(^37,38\) Still, they constitute the challenging part of patients for whom a prognostic biomarker is needed. Of importance, all patients with CIS with solitary T2-weighted images who experienced new T2L or clinical relapse had an elevated K-index.

Finally, DMT start was not taken into account as a confounding predictive factor. It has been performed deliberately for many reasons. First, DMT was started before new T2L occurrence in a small number of patients (n = 20). From these patients, the K-index value was elevated (median of 94.6). Therefore, some K-index–positive patients may be wrongly considered as not fulfilling the outcome, leading to an underestimation of the predictive value of the K-index. Second, in clinical practice, DMT start is made according to other known predictive factors such as the presence of T1 gadolinium-enhancing lesions or a high number of T2L. We show, in this study, that the K-index positively correlated with such MRI predictive biomarkers but also that it could predict the outcome with a better concordance. Third, all patients for whom a DMT was started in this study fulfilled the 2017 McDonald criteria. In clinical practice, the interest of using a biomarker to predict new T2L or clinical relapse is not needed in patients for whom a DMT can be started independently of such biomarker. Finally, it is difficult to assess the impact of DMT on the prognostic role of the K-index statistically, while it will require a very large cohort of patients, with some of them having a DMT and a negative K-index. Our cohort was too small to evaluate it.

Our study also has strengths. It has the advantage of being one of the first to evaluate the K-index as a predictive biomarker of asymptomatic new T2L. This outcome is relevant for clinical practice, although neurologists usually do not wait for another clinical event to identify DIT and treat patients as having MS. Moreover, our results align with others, identifying that the K-index is a highly sensitive biomarker to predict outcomes in CIS with very good performances and the first one using time-dependent ROC analyses to assess it. It reinforces the need for CSF analysis in diagnosing patients raising a suspicion of MS.

In conclusion, our study shows that the K-index reflects early disease course in MS spectrum disorders because it predicts new T2L in patients with RIS and MS (new T2L or clinical event) in patients with CIS. According to these findings and others, adding the K-index in the further revisions of MS diagnosis criteria should be discussed.

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Kappa Free Light Chain Index Predicts Disease Course in Clinically and Radiologically Isolated Syndromes


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