

Cerebrospinal fluid kappa free light chains versus kappa free light chain index as screening tests for multiple sclerosis

Lewis Wickham^{1,2}, Rachel Dale¹

¹Clinical Immunology, Cambridge University Hospitals NHS Foundation Trust

²School of Medical Sciences, The University of Manchester

Key words

Cerebrospinal fluid, kappa free light chains, kappa free light chain index, multiple sclerosis, oligoclonal banding

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system. The 2017 McDonald criteria¹ for MS state that cerebrospinal fluid (CSF) oligoclonal banding (OCB) provides evidence of intrathecal immunoglobulin synthesis and may substitute for dissemination in time to support a diagnosis. However, OCB analysis is labour-intensive and requires subjective interpretation. Measurement of CSF kappa free light chains (KFLC) has been shown to save time and perform comparably to OCB^{2,3}.

The objectives of this study were to:

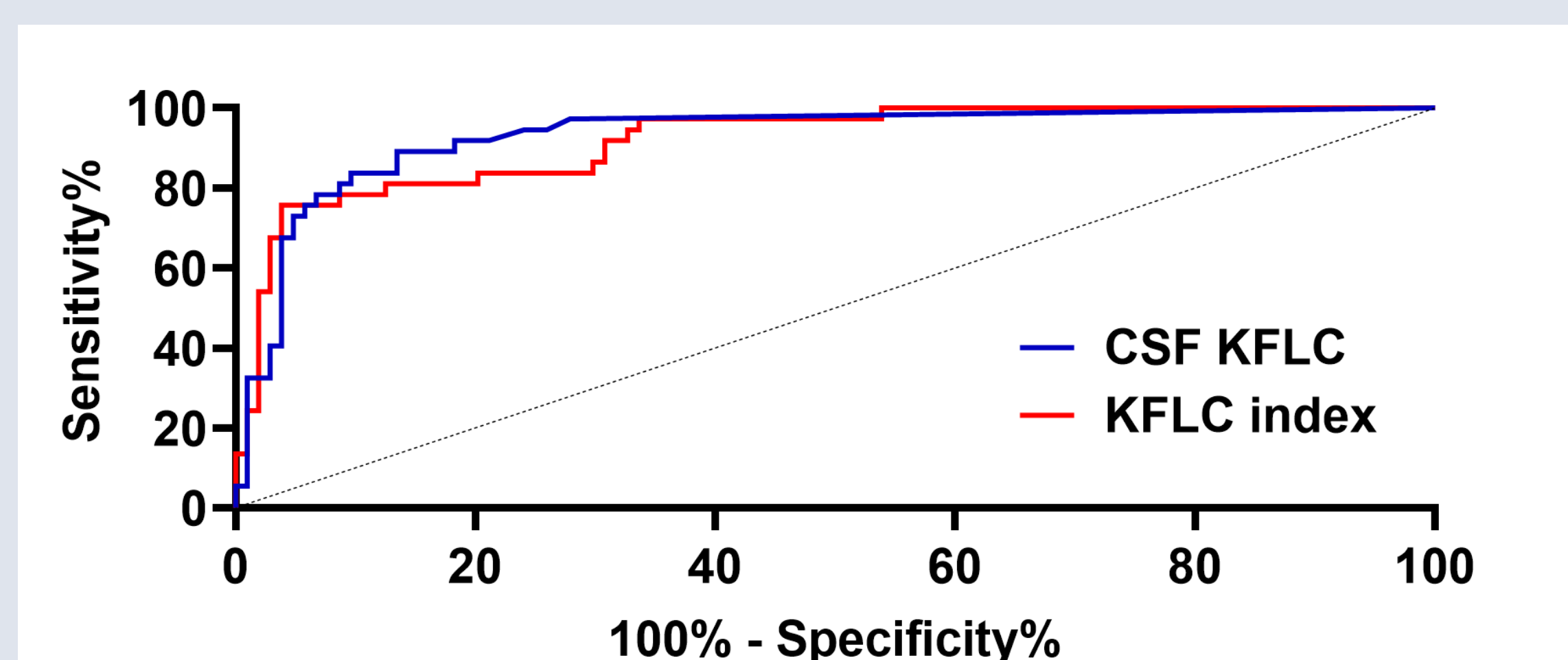
1. Compare the diagnostic accuracy of CSF KFLC, KFLC index and OCB analysis
2. Assess the performance characteristics of the KFLC assay
3. Analyse the costs associated with KFLC testing in an NHS diagnostic laboratory

Methods

The study included paired CSF and serum samples from 141 patients with suspected MS that had undergone OCB analysis at Addenbrooke's Hospital. Patients were classified by final diagnosis as 1) MS or 2) non-MS. We measured baseline KFLC and albumin concentrations by immunoturbidimetry using The Binding Site assays on the Optilite instrument. KFLC index was determined as (CSF KFLC/serum KFLC) ÷ (CSF albumin/serum albumin). We assessed diagnostic accuracy by receiver operating characteristic (ROC) curve analysis. Our stability study used aliquots of CSF and serum pools stored at 5°C and -20°C. Calculations compared the costs of our current and proposed practices.

Results

Both CSF KFLC and KFLC index displayed impressive diagnostic sensitivity and negative predictive value (NPV) at the given cutoffs, demonstrating their suitability as screening tests for MS (Fig. 1).



| Parameter | Cutoff | Sens.% | Spec.% | PPV% | NPV% |
|------------|--------------------------|--------|--------|------|------|
| OCB | ≥ 3 CSF-restricted bands | 97 | 91 | 80 | 99 |
| CSF KFLC | > 0.33 mg/L | 97 | 72 | 55 | 99 |
| KFLC index | > 4.26 | 97 | 66 | 51 | 99 |

Figure 1. ROC curve and summary of diagnostic performance for OCB, CSF KFLC and KFLC index.

CSF KFLC measurement was more accurate following sample storage at 5°C. This was due to deterioration of serum KFLC after 7 days of storage which noticeably affected KFLC index (Fig. 2).

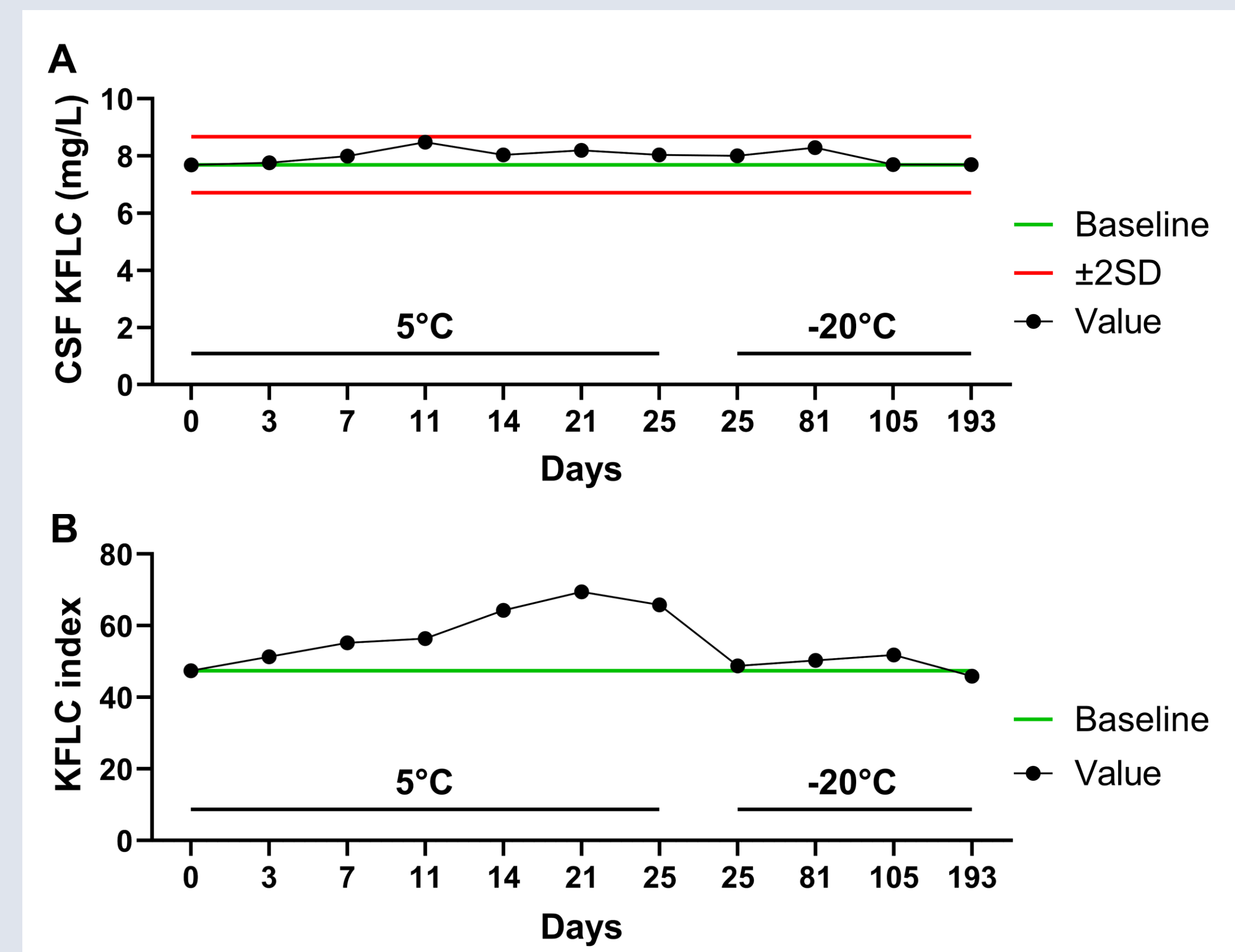


Figure 2. Stability of (A) CSF KFLC concentration and (B) KFLC index following storage of samples at 5°C and -20°C.

KFLC parameters are low-cost alternatives to OCB analysis. Testing for OCB in patients with CSF KFLC above the positive cutoff would save money versus OCB analysis alone (Table 1).

| Test | Material cost (per patient) | Staffing cost (per patient) | Total cost (per patient) | Cost per 100 patients |
|------------------------------|-----------------------------|-----------------------------|--------------------------|-----------------------|
| OCB | £22.28 | £7.15 | £29.43 | £2943 |
| CSF KFLC | £6.30 | £1.52 | £7.82 | £782 |
| KFLC index | £14.70 | £2.60 | £17.30 | £1730 |
| CSF KFLC + OCB for positives | – | – | – | £2136 |

Table 1. Estimated cost of analysis using different test combinations.

Conclusions

- Measurement of KFLC parameters allows rapid, low-cost testing for MS with high diagnostic sensitivity matching OCB analysis
- CSF KFLC measurement is simpler, cheaper, and more accurate following prolonged sample storage compared to KFLC index
- Integrating KFLC screening into clinical practice may reduce workload and costs without sacrificing diagnostic accuracy

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References

1. Thompson AJ, Banwell BL, Barkhof F et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* (2018) 17:162–173.
2. Christiansen M, Gjelstrup MC, Stilund M et al. Cerebrospinal fluid free kappa light chains and kappa index perform equal to oligoclonal bands in the diagnosis of multiple sclerosis. *Clin Chem Lab Med* (2018) 57:210–220.
3. Levraut M, Laurent-Chabalier S, Ayrignac X et al. Kappa Free Light Chain Biomarkers Are Efficient for the Diagnosis of Multiple Sclerosis: A Large Multicenter Cohort Study. *Neurol Neuroimmunol Neuroinflamm* (2023) 10:e200049.