

Free Kappa and Lambda Light Chains in Plasma Cell Dyscrasias

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ABSTRACT

Automated serum kappa (κ) and lambda (λ) free light chain (FLC) immunoassay may be used as a rapid screening tool for multiple myeloma and other light chain diseases as it is more sensitive and robust than serum protein electrophoresis (SPE) and urine immunofixation electrophoresis (IFE). Serum FLC enables earlier diagnosis and evaluation of tumour response to therapy. Serum FLC testing has been incorporated into an international guideline for all newly diagnosed plasma cell cancers for diagnosis, prognosis, monitoring and assessing treatment.

Keywords: free light chains, myeloma panel, screening

SYNONYMS

Kappa (κ) free light chain (FLC), Lambda (λ) FLC, multiple myeloma (MM), light-chain multiple myeloma (LCMM), non secretory MM (NSMM), smouldering MM (SMM), amyloidosis (AL), light chain deposition disease (LCDD), monoclonal gammopathy of undetermined significance (MGUS)

SPECIMEN

Serum or plasma (collected in heparin or EDTA) may be used. The serum or plasma should be separated from the red blood cells as soon as possible and analysed. Specimens that cannot be assayed immediately should be stored at 2–8°C or -20°C. Specimens remain stable for up to 4 days at 2–8°C. Frozen specimens should not be subjected to repeated freeze and thaw cycles.

The 24-hour urine FLC test is not recommended for screening of monoclonal proteins^{1–4}. A 24-hour urine sample is difficult to collect and must be concentrated properly to ensure a good analytical result. FLC levels are elevated in the blood long before being detected in the urine. Under normal circumstances, proteins are filtered rapidly through the renal glomeruli and reabsorbed in the proximal tubules so blood FLC level must be grossly

elevated before the absorption mechanisms are overwhelmed. Thus, urine SPE and serum FLC levels do not correlate well.

INDICATIONS

▪ Suspected Plasma Cell Dyscrasia (PCD)

The current gold standard for evaluation of PCD is IFE. However, in most labs, IFE is usually performed only in the presence of a monoclonal band so LCCM, LCDD and AL may be missed. Urine IFE is not ideal as FLCs are cleared by the kidneys and would show up in overwhelming levels. The International Myeloma Working Group has recommended a serum panel consisting of serum FLC, SPE and IFE for monoclonal plasma disorders for all patients except AL for which a 24-hour urine IFE is required^{2,3}.

Serum κ and λ FLC assays are useful in the diagnosis of patients with suspected PCD^{4–8,16}. Using a 100% confidence interval, the reference range for the κ/λ ratio has been set at 0.26–1.65; patients with κ/λ ratio greater > 1.65 and < 0.26 are presumed to be having excess κ and λ light chains, respectively⁹. The frequency of abnormal serum FLC (κ/λ) ratio has been estimated to be 96% for symptomatic MM, 88–90% for smouldering MM, 68% for non-secretory MM (NSMM), and 33–44% for monoclonal gammopathy of undetermined significance

(MGUS)^{3,8}. In contrast, abnormal serum FLC is detected in light chain disorders – 100% for LCMM, 91–98% for amyloidosis (AL), and 93% for light chain deposition disease (LCDD)^{3,8}. It is notable that LCMM accounts for 15% of newly MM cases and AL which is 20% as common as MM may be missed in conventional SPE as the monoclonal band may not be exhibited^{6,10}.

▪ Monitoring PCD

Baseline FLC is prognostic and increased serum FLC is an independent adverse prognostic factor for both event free and overall survival, and subsequent serial measurements enable quantitative monitoring of the patients^{3,6,11,12}. The European Group for Blood and Bone Marrow Transplant / International Bone Marrow Transplant Registry (EBMT/IBMTR) has incorporated the response criteria for the serum FLC assay to assess treatment response in PCD patients:

- complete response if FLC ratio is normal
- partial response if FLC decreases by $\geq 50\%$
- progressive disease if FLC increase by > 10 mg/dL^{3,6,13}.

Serum FLC provides for a more rapid evaluation of tumour response to therapy than intact immunoglobulin as its half life is 2–6 hours compared to 6 days for IgA and 20–25 days for IgG¹⁶.

▪ MGUS

An increasingly abnormal FLC (κ/λ) ratio in MGUS may reflect progression to MM. SFLC is also used to identify patients who may benefit from prophylactic interventions since approximately 1% of MGUS progresses to MM per year and 33% of these patients have abnormal FLC ratios¹⁴.

▪ Residual PCD disease

Even when SPE and IFE are negative, patients can still have residual PCD. In such cases the SFLC may be abnormal due to its higher sensitivity¹⁶.

METHODOLOGY

Most automated systems use the same commercial reagents from The Binding Site Ltd but results are not comparable as the analytical systems use different method principles, such as immunoturbidimetry and immunonephelometry¹⁵.

LIMITATIONS

Test results should be interpreted in context with other clinical findings and the limitation of the analytical system. Abnormal FLC levels may be recorded in immune suppression or stimulation, reduced renal clearance and lymphoproliferative disorders. Serum FLC may not correspond to electrophoresis results as approximately 10% patients with intact immunoglobulin myeloma may be missed as they do not produce FLC; and SPE would be more useful in these patients^{15,16}. Non-linearity in κ FLC dilution and antigen excess in the sample may result in analytical errors².

ADDITIONAL INFORMATION

Serum FLC by itself has a high diagnostic sensitivity in addition to being able to produce same session results often within an hour. Abnormal or borderline FLC (κ/λ) results may be followed up with IFE for confirmation and further work up.

In a survey of 428 patients at Mayo Clinic with positive urine IFE, 93.5% of the cohort were identified by serum IFE, 80.8% by SPE, 85.7 % by serum FLC and 99.5% if all three tests (SPE, serum IFE and FLC) were done.^{2,6} In another 110 Mayo patients with AL, the diagnostic performance of serum FLC is 91% compared with 69% for serum IFE and 83% for urine IFE while a combination of all 3 assays improved the detection rate to 99%^{2,6}.

SFLC is not easily available here as the only manufacturer, The Binding Site Inc (UK), is not represented and the cost is prohibitive. Nonetheless, measurement of total light chains (TLC) in serum is available on all the automated immunoassay instruments and is a reasonable surrogate for FLC¹⁷. However, this approach is less useful as the detection limit on these TLC assays is 100-fold less than SFLC (< 1.0 mg/L) and slightly inferior to IFE (100 mg/L).

CONCLUSION

The utility of serum FLC is clear^{18–20} and it is technically more robust than electrophoresis, which is very operator-dependent though this has been mitigated somewhat by automated systems. The International Myeloma Working Group 2011 now recommends a myeloma panel including IFE, SPE, and serum FLC in all patients with newly diagnosed plasma cell dyscrasias³. The clinical community

should keep abreast of this development especially with regards to FLC.

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