RECOMMENDATIONS FOR USE OF FREE LIGHT CHAIN ASSAY IN MONOCLONAL GAMMOPATHIES

PREPORUKE ZA PRIMENU TESTA SLOBODNIH LAKIH LANACA KOD MONOKLONSKIH GAMAPATIJA

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Summary: The serum immunoglobulin free light chain assay measures levels of free κ and λ immunoglobulin light chains. There are three major indications for the free light chain assay in the evaluation and management of multiple myeloma and related plasma cell disorders. In the context of screening, the serum free light chain assay in combination with serum protein electrophoresis and immunofixation yields high sensitivity, and negates the need for 24-hour urine studies for diagnoses other than light chain amyloidosis. Second, the baseline free light chains measurement is of major prognostic value in virtually every plasma cell disorder. Third, the free light chain assay allows for quantitative monitoring of patients with oligosecretory plasma cell disorders, including AL, oligosecretory myeloma, and nearly two-thirds of patients who had previously been deemed to have non-secretory myeloma. In AL patients, serial free light chains measurements outperform protein electrophoresis and immunofixation. In oligosecretory myeloma patients, although not formally validated, serial free light chains measurements reduce the need for frequent bone marrow biopsies. In contrast, there are no data to support using free light chain assay in place of 24-hour urine electrophoresis for monitoring or for serial measurements in plasma cell disorders with measurable disease by serum or urine electrophoresis.

Keywords: serum free light chains, recommendations, free light chain assay, plasma cell disorders

Kratki sadržaj: Serumski test slobodnih lakih lanaca meri nivoe imunoglobulinskih slobodnih κ i λ lakih lanaca. Tri su glavne indicacije za primenu serumskog testa slobodnih lakih lanaca u proceni i lečenju multiplog mijeloma i srodnih plazma čelijskih poremećaja. U kontekstu skrininga, test slobodnih lakih lanaca u kombinaciji sa elektroforezom proteina seruma i imunofiksacijom doprinosi visokoj osetljivosti, čime se izbegava upotreba 24-časovnih urinarnih testova za otkrivanje amiloidoznih lakih lanaca. Referentna merenja slobodnih lakih lanaca imaju veliku prognošću vrednost za gotovo sve plazma čelijske poremećaje. Test slobodnih lakih lanaca omogućava kvantitativno praćenje bolesnika sa oligosekretornim plazma čelijskim poremećajima, uključujući primarnu, sistemsku AL amiloidozu, oligosekretorni mijelom, i oko 2/3 bolesnika sa nesekretornim multiplim mijelomom. Kod bolesnika sa primarnom, sistemskom AL amiloidozom, serijska merenja slobodnih lakih lanaca prevazilaze testove elektroforeze proteina i imunofiksacije. Kod bolesnika sa oligosekretornim mijelomom, iako neformalno validirana, serijska merenja slobodnih lakih lanaca unamanjuju potrebu za češtim biopsijama koštane srži. Nasuprot tome, ne postoji podrška za primenu testa slobodnih lakih lanaca umesto 24-časovne urinarnog elektroforeze za praćenje ili serijska merenja plazma čelijskih poremećaja, koja se mogu izmeriti serumskom ili urinarnom elektroforezom.

Ključne reči: serumski slobodni laki lanci, preporuke, test slobodnih lakih lanaca, plazma čelijski poremećaji

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List of used abbreviations: MG – monoclonal gammopathies; MGUS – monoclonal gammopathy of undetermined significance; MM – multiple myeloma; AL – amyloidosis; Ig – immunoglobulin; FLC – free light chains; PEP – protein electrophoresis; IE – immunoelectrophoresis; IFE – immunofixation electrophoresis; PCD – plasma cell disorders; kappa – κ; lambda – λ; dFLC - k/λ; FLC ratio; LCMM – light chain multiple myeloma; NSMM – non-secretory multiple myeloma; SMM – smoldering (asymptomatic) multiple myeloma; BMPC – bone marrow plasma cells; ISS – international staging system; CR – complete response; dFLC – difference between the involved and uninvolved FLC.


**Introduction**

The monoclonal plasmaproliferative disorders encompass a broad spectrum of diseases ranging from the often benign monoclonal gamopathy of undetermined significance (MGUS) to the potentially curable solitary plasmacytoma to the life-threatening conditions of multiple myeloma (MM) and light chain amyloidosis (AL) (Figure 1). For each of these diseases, measurements of circulating monoclonal immunoglobulins (Ig) have been the mainstay of diagnosis, prognosis and management. Until the 1990s, the repertoire of tests to document and measure the monoclonal Ig included electrophoresis (PEP), immunoelectrophoresis (IE), immunofixation electrophoresis (IFE), and nephelometric measurement of Ig heavy chains of serum. For most MGUS and MM patients, these measurements appeared to be sufficient; however, they were inadequate for the majority of patients with AL and more than 3% of myeloma patients with non-secretory or oligosecretory myeloma.

In the early 2000s an assay that measured serum Ig free light chains (FLC) was developed (1). This assay differentiated itself from prior light chain reagents that were called quantitative light chain measurements in that these novel polyclonal reagents were called quantitative light chain assays. Sensitive hemmagglutination assays showed reactivity to cells coated with the appropriate FLC at dilutions of >1:16,000, and no reactivity to light chains contained in intact Ig at dilutions of <1:2. The greater the specificity, the better one’s ability to quantitate κ and λ FLC in the presence of a large excess of serum IgG, IgA and IgM. In normal individuals and in the majority of patients with myeloma, most of the circulating light chain is bound to heavy chains – making less specific reagents a near surrogate for circulating heavy chain measurement (5). Katzmann et al. (4) defined the normal range using fresh and frozen sera from 127 healthy donors aged 21–62 years and frozen sera from 155 donors aged 51–90 years from the serum bank. The 95% reference interval for κ FLC was 3.3–19.4 mg/L, and that for λ FLC was 5.7–26.3 mg/L. For the κ/λ ratio, the 95% reference interval was 0.3–1.2 (Table I), but it was decided that the diagnostic range should include 100% of donors, making the normal diagnostic range for FLC κ/λ >0.26 –1.65. Using the 100% confidence interval increased the specificity of the test from 95% to 100%, with a drop in sensitivity from 98% to 97%. Patients with ratios greater than 1.65 contain excess κ FLC and

| Table I  | Serum reference ranges (4). |
|----------|-----------------------------|
|          | Mean Concentration (mg/L)   | Median Concentration (mg/L) | 95 Percentile Range (mg/L) |
| Normal Adult Serum |                       |                          |                             |
| Free κ   | 8.36                        | 7.30                      | 3.30–19.40                  |
| Free λ   | 13.43                       | 12.40                     | 5.71–26.30                  |
| κ/λ ratio| Mean Total range Median     |                           |                             |
|          | 0.63                        | 0.60                      | 0.26–1.65                   |
Figure 1 Development of the B-cell lineage and associated diseases.
are presumed to be producing clonal \( \lambda \) FLC. Patients with ratios less than 0.26 contain excess \( \lambda \) FLC and are presumed to be producing clonal \( \lambda \) FLC. The 100% confidence interval used reduces the likelihood that polyclonal activation of B cells will cause an abnormal ratio, but it is possible, and therefore the test must be interpreted in the context of clinical situation. If a patient is in the midst of an infection or a fare of a rheumatologic condition, the test should be repeated at a later date. Although the test is a major advance, it is not without its limitations (6). First, there can be significant lot-to-lot variation (19–20% CV) between batches of polyclonal FLC antisera that may result in variable immunoreactivity of individual monoclonal FLCs and inconsistent results (6). Second, some monoclonal light chains (particularly \( \kappa \) FLC) do not dilute in a linear fashion and may be underestimated in the absence of additional off line dilutions (6). Third, antigen excess can cause falsely low serum FLC results with nephelometric techniques, and manual dilution may be required for clinically suspicious samples (7). For large multi-institutional trials, serious consideration should be made for running samples at a centralized testing facility that performs lot-to-lot comparisons. Fourth, changes in amino acid sequence of the light chain may render certain light chain epitopes unrecognizable to the FLC reagents, but apparent on immunofixation or even electrophoresis (19). Conversely, extreme polymerization can cause an overestimation by as much as 10-fold.

### Limitations of urine measurements

Urine is traditionally used for testing but needs to be concentrated and analyzed by PEP or by IFE (20). These techniques are often inadequate for accurate detection of FLC. Additionally, the amount of FLC in the urine is influenced by renal tubular function since normal kidneys are very efficient in preventing protein leakage from the body. Only when the tumor production of FLC exceeds the resorptive capacity of the kidney does FLC appear in the urine in large amounts (21) (Figure 4).

### Role of the serum FLC assay in diagnosis

It is clear that having excess involving FLC or an abnormal \( rFLC \) is common in virtually all PCD (Table II). Historically, the gold standard for screening for PCD has been PEP with IFE of the serum and the urine. The most important screening study was done by Katzmann et al. (8). They asked whether the serum Ig FLC assay could replace urine IFE for...
Abnormal, %  99.5

80.8

93.5

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electrophoresis (8).

urinary monoclonal protein detected by immunofixation data base, 428 patients who had a protein related disorder. Within the Mayo Clinic PCD screening patients suspected of having a monoclonal protein disorder. The increased diagnostic sensitivity for the FLC assay in combination with serum PEP and serum IFE is sufficient to screen for pathological monoclonal PCD other than AL, which requires all the serum tests as well as the 24 hour urine IFE. If a diagnosis of a PCD is made, a 24 hour urine for PEP and IFE is essential for all patients.

Prognostic value of the serum FLC assay

The increased diagnostic sensitivity for the FLC diseases and the ability to eliminate urine in the diagnostic screen was somewhat predictable once the analytic sensitivity of the serum FLC assay was understood. A finding that emerged, but that was not entirely expected, was that baseline values of serum FLC can be used for prognostication (Table IV). The pathogenic rationale for this linkage is not well understood, but one possibility is that higher levels of FLC may be associated with IgH translocations (17) as well as increasing tumor burden (18, 22).

Table III  Four hundred and twenty-eight patients with urinary monoclonal protein detected by immunofixation electrophoresis (8).

| Laboratory test     | Abnormal, % |
|---------------------|-------------|
| Serum IFE           | 93.5        |
| Serum PEL           | 80.8        |
| Serum FLC           | 85.7        |
| Serum IFE or FLC ratio | 99.5        |

Figure 4  Changes in serum (dotted line) and urine (solid line) FLC with increasing tumor mass (NR = normal range).
Table IV  Uses of serum immunoglobulin FLC assay (18, 22–26).

| Screening in combination with IFE |
|-----------------------------------|
| Baseline values prognostic        |
| Monoclonal gammopathy of undetermined significance |
| Smoldering myeloma                |
| Symptomatic myeloma               |
| Plasma celloma                    |
| AL amyloidosis                    |

| Hematologic response              |
|-----------------------------------|
| AL amyloidosis                    |
| Non-secretory myeloma*            |
| Stringent complete response in multiple myeloma* |
| Light chain deposition disease    |
| (Personal experience of authors)  |

* Not yet validated

**Monoclonal gammopathy of undetermined significance**

Approximately 1/3 of MGUS patients have an abnormal rFLC and have a higher rate of progression than those who do not. Based on the size of the monoclonal protein peak, the isotype of the heavy chain, and the rFLC, a risk model for progression of MGUS to MM has been constructed (23). For the purpose of prognostic modeling, a rFLC of <0.25 or >4 was selected as abnormal. In addition to abnormal rFLC, on multivariate modeling an M-spike greater than or equal to 1.5 g/L and a heavy chain isotype other than IgG were associated with risk of progression to MM or related disorders. The risk of progression at 20 years for patients with 0, 1, 2 or 3 risk factors was 5%, 21%, 37%, or 58%, respectively.

**Smoldering (asymptomatic) multiple myeloma**

In addition to the use of FLC for prognosis in MGUS, baseline rFLC is useful for assessing prognosis for progression in smoldering MM (24). Baseline serum samples were available in 273 patients with SMM seen from 1970 to 1995. Abnormal rFLC predicted for higher rates of progression, and the best breakpoint for rFLC was less than or equal to 0.125 or greater than or equal to 8. The extent of abnormality of rFLC was independent of SMM risk categories defined by the number of bone marrow plasma cells (BMPC) and size of serum M proteins (24–26). A risk model was constructed, incorporating the best breakpoint of rFLC, BMPC ≥10%, and serum M protein ≥30 g/L. Patients with 1, 2, or 3 risk factors had 5-year progression rates of 25%, 51%, and 76% respectively.

**Solitary plasmacytoma**

In a cohort of 116 patients with solitary plasmacytoma the rFLC was retrospectively determined on serum collected at time of diagnosis. An abnormal ratio was present in 47% and associated with a higher risk of progression to myeloma (P=0.59). The risk of progression at 5 years was 44% in patients with an abnormal serum rFLC at diagnosis compared with 26% in those with a normal rFLC. One to two years following the diagnosis, a persistent serum M protein level of 0.5 g/dL or higher was an additional risk factor for progression to MM. A risk stratification model was constructed using the 2 variables of rFLC (normal or abnormal) and M protein level persistence at a level of 0.5 g/dL or greater. The low risk (n = 31), intermediate risk (n = 26), and high risk (n = 18) groups had 5 year progression rates of 13%, 26%, and 62%, respectively, respectively (P < 0.001) (27).

**Multiple myeloma**

Several studies have shown that baseline FLC is prognostic of survival in patients with newly diagnosed MM (28). Kyrtsonis et al. found that in 94 MM patients rFLC was prognostic. Median baseline rFLC was 3.6 in κ-MM patients and 0.02 in λ-MM. ‘High’ rFLC (worse than median) correlated with elevated serum creatinine and lactate dehydrogenase, extensive marrow infiltration and LCMM. The 5-year disease-specific survival was 82% and 30% in patients with rFLC less extreme or more extreme than median, respectively (R = 0.0001). The rFLC added to the International Staging System (ISS), with ISS stage 3 patients having a 5 year disease specific survival of 52% versus 16% depending on their rFLC. Van Rhee et al. have also demonstrated that among 301 patients enrolled to receive total therapy III, those with the highest levels of FLC – greater than 750 mg/L, which was the highest tercile – had the poorest outcomes. The highest baseline FLC levels were significantly associated with LCMM, elevated creatinine, beta-2-microglobulin, lactate dehydrogenase, and bone marrow plasmacytosis higher than 30%. Lastly, Snozek et al. (29) have also shown in a cohort of 790 patients diagnosed with active MM between 1995 and 1998 that baseline rFLC <0.03 or ≥32 (n=479) had inferior outcomes as compared to those with an rFLC between 0.03–32 (n=311), with median survival of 30 versus 39 months, respectively. When the abnormal rFLC was incorporated into a model using the cutoffs applied in the ISS (30) i.e. albumin <3.5 mg/L and serum β2-microglobulin ≥35 mg/L, it was found that rFLC was an independent risk factor. Patients with 0, 1, 2, or 3 adverse risk factors had significantly different overall survival, with median survival times of 51, 39, 30 and 22 months, respectively, P < 0.001.

**Immunoglobulin light chain amyloidosis (AL)**

In a cohort of 119 patients with AL undergoing peripheral blood stem cell transplantation, there was a significantly higher risk of death in patients with higher baseline FLC (hazard ratio 2.6, P< 0.04) (18). Base-
line FLC correlated with serum cardiac troponin levels, and higher FLC levels were associated with more organs involved by amyloid, suggesting that high FLC levels may be associated with more advanced disease.

*Recommendations for the use of the serum FLC assay in prognosis*

The serum FLC assay should be measured at diagnosis in all patients with MGUS, smoldering or active MM, solitary plasmacytoma, and AL amyloidosis (Table IV).

**Role of the FLC assay in response assessment**

Although FLC response can be considered in 3 contexts – oligosecretory diseases, LCMM, and measurable intact Ig disease – routine serial use of this assay can only be recommended for the first indication. As will be discussed below, to date there have been only a few studies that have validated the usefulness of serial FLC measurements, although efforts for standardizing the FLC response have been proposed. For serial measurements, either the involved FLC or the difference between the involved and uninvolved (dFLC) should be used. Aside from the time of diagnosis and in the context of documenting stringent complete response, the rFLC is not useful because of the not infrequently observed treatment related immunosuppression of the uninvolved (κ for monoclonal λ patients and λ for monoclonal κ patients) FLC during chemotherapy; the ratios generated when one of the FLC numbers is very low will be extreme, reflecting the degree of immunosuppression more than tumor burden (28).

*Recommendations for the use of the serum FLC assay in response assessment*

Serial FLC ascertainment should be routinely performed in patients with AL amyloidosis and MM patients with oligosecretory disease. It should also be done in all patients who have achieved a complete response (CR) to determine whether they have attained a stringent CR.

**Conclusion**

In summary, there are four major indications for the FLC assay in the evaluation and management of MM and related clonal PCD. In the context of screening for the presence of myeloma or related disorders, the serum FLC assay in combination with serum PEP and IF yields high sensitivity, and negates the need for 24-hour urine studies when screening for MM; once diagnosis of a PCD is made, 24-hour urine studies are required for all patients. Second, the FLC assay is of major prognostic value in virtually every PCD, including MGUS, SMM, active MM, immunoglobulin light chain amyloidosis (AL) and solitary plasmacytoma. Third, the FLC assay allows for quantitative monitoring of patients with oligosecretory PCD, including patients with AL, oligosecretory myeloma, and nearly two-thirds of patients who had previously been deemed to have non-secretory myeloma. In AL patients and patients with oligosecretory myeloma, measurement of FLC is essential. The FLC assay cannot replace the 24-hour urine PEP for monitoring myeloma patients with measurable urinary M proteins. Fourth, the rFLC is a requirement for documenting stringent complete response according the International Response Criteria. Although the serum FLC is a valuable assay in patients with PCD, there are technical limitations of the assay which make its use as a serial measurement potentially problematic including: lot-to-lot variation; assay imprecision; and instances in which it does not dilute in a linear fashion. The most important area for future investigation includes defining the clinical relevance of early FLC response or relapse in patients with measurable intact Ig or measurable urinary M proteins. Apart from initial diagnosis and documentation of stringent CR, its use is not advocated in these patients.

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