N Latex FLC ratio for definition of ultra-high-risk smoldering multiple myeloma (SMM)—validation of the FLC rule 100

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Guidelines and background

Smoldering multiple myeloma (SMM) is an asymptomatic precursor condition of multiple myeloma (MM). The condition is often discovered accidentally when M protein is found in serum or urine electrophoresis testing ordered for some other reason. Individuals with SMM have a 10% progression rate to symptomatic MM within the first 5 years after diagnosis. The progression rate drops to 3% within 5–10 years after diagnosis and further drops to 1% thereafter. Historically, treatment of patients with SMM was not indicated until they progressed to MM due to unacceptably high rates of treatment-related toxicity.

With the introduction of novel myeloma therapies offering high efficiency and improved tolerability, an intensive search for biomarkers was begun to identify patients who would benefit from early therapy. To intervene before the development of end-organ damage in MM, biomarkers are needed that accurately identify the subset of patients with SMM who have biological malignancy and are at imminent risk of progression. The International Myeloma Working Group (IMWG) reached a consensus that, if reliable biomarkers associated with a roughly 80% probability of progression (= positive predictive value [PPV]) to MM within 2 years were identified, such patients should be regarded as having MM. The experts further stipulated a specificity of 95% or greater and concluded that therapy should be offered to this ultra-high-risk group of SMM patients.[1] The experts involved in this definition pointed out that specificity is of much higher importance than sensitivity to avoid overtreatment.

The 2017 updated ESMO Clinical Practice Guidelines on Multiple Myeloma added a new, ultra-high-risk SMM subgroup as MM defining criteria with the indication for myeloma therapy. The so-called CRAB criteria, which define symptomatic MM, were supplemented by the SLiM criteria for definition of MM (see box below).[2]

ESMO clinical practice guidelines: diagnostic criteria for multiple myeloma[2]

Clonal BM plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:

- CRAB criteria: evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >177 µmol/L (>2 mg/dL)
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal or a hemoglobin value <100 g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
- SLiM criteria: any one or more of the following biomarkers of malignancy:
  - ≥60% clonal BM plasma cells
  - **Involved/uninvolved serum free light chain (FLC) ratio ≥100**
  - More than one focal lesion in MRI studies (each focal lesion must be ≥5 mm in size)

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For the diagnosis of SMM and MM, the ESMO guideline and the IMWG recommend the following tests:[2,3]

- Detection and evaluation of the monoclonal (M) component by:
  - Serum and/or urine protein electrophoresis (concentrate of 24-hour urine collection)
  - Nephelometric quantification of IgG, IgA, and IgM immunoglobulins
  - Characterization of the heavy and light chains by immunofixation
  - Serum FLC measurement
- Evaluation of bone marrow (BM) plasma cell infiltration
- Evaluation of lytic bone lesions
- Complete blood cell count, with differential serum creatinine, creatinine clearance, and calcium level

N Latex FLC Assays: French validation study in SMM patients

The updated IMWG and ESMO guidelines that include the FLC ratio of 100 or greater as a diagnostic criterion for MM are based on two studies in which FREELITE assays on the nephelometric Siemens Healthineers BN™ II System were used for FLC measurement.[1,4] Since those studies, several additional FLC assays have been cleared for diagnosis and monitoring of MM. However, FLC results obtained by different FLC assays, as well as FLC results obtained by the same assay but on different analyzers, must not be used interchangeably.[5]

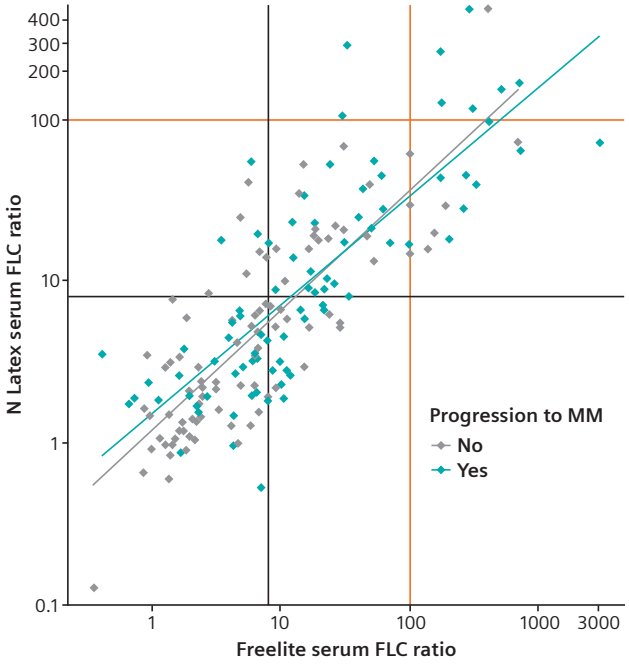
The predictive power of a particular assay and the appropriate cutoff for risk prediction cannot be determined by correlation analysis and require a well-defined SMM patient cohort with follow-up data for at least 2 years. For this reason, Henriot et al.[6] investigated the prognostic value of Siemens Healthineers N Latex FLC Assays in comparison to The Binding Site's FREELITE assays in a French cohort of 176 patients diagnosed with SMM according to the IMWG 2003 criteria. During the first 2 years after diagnosis, 62 patients (35%) progressed to symptomatic MM.

For both assays, the FLC ratio of involved to noninvolved FLC was calculated, and the performance of an FLC ratio of ≥100 to predict disease progression to symptomatic MM within the next 2 years was evaluated. Both assays had a similar ability to predict manifestation of MM, with a relative risk ratio of 1.99 for the N Latex FLC Assays and 2.04 for the FREELITE assays. The PPV and specificity were found to be higher for the N Latex FLC Assays (66.7%; 97.4%) compared to the FREELITE assays (56.5%; 91.2%).

Qualitative method comparison for the involved to noninvolved FLC ratio with a cutoff of 100 showed a 90% agreement rate (κ coefficient 0.39); the best agreement rate of 91.5% was obtained with a cutoff of 70 for the N Latex FLC Assays (κ coefficient 0.53).

	Cutoff	PPV	Specificity	Relative risk
N Latex FLC	100	66.7%	97.4%	1.99
FREELITE	100	56.5%	91.2%	2.04

Correlation analysis: FREELITE versus N Latex FLC ratio[6]



An N Latex FLC ratio ≥100 supports prognosis of disease progression in SMM patients with similar performance as observed for the FREELITE assays. However, the patients identified to be at very high risk by the two assays may differ.

In this study, the best sensitivity-to-specificity ratio for the N Latex FLC Assays was obtained with a cutoff ratio of 70.

It should be noted that the majority of patients with progressive disease within the first 2 years after diagnosis remain undetected (FLC ratio <100) by either the FREELITE or N Latex FLC assays.

FLC rule 100—What is the clinical evidence from published data?

In addition to the first two studies from the U.S. and Greece published in 2013, four more studies from the U.S., Denmark, and France on the FLC 'rule 100' have been published through 2019.

FREELITE	Total N (N with disease progression)	PPV	Specificity
Larson, 2013[1]	586 (205)	73%	97%
Kastritis, 2013*[4]	96 (12)	43%	98%
Waxman, 2015[7]	144	64%	N/A
Sørrig, 2016[8]	209 (28)	30%	N/A
Wu, 2018[9]	183 (71)	44%	90%
Henriot, 2019[5]	176 (62)	57%	91%
N Latex FLC	**Total N (N with disease progression)**	**PPV**	**Specificity**
Henriot, 2019[5]	176 (62)	67%	97%

**18-month outcome (all other studies were 24 months).*

The first and largest study from the Mayo Clinic[1] defining the ultra-high-risk SMM by an FLC ratio of ≥100 (and involved FLC ≥100 mg/L) did not reach the target of an 80% 2-year progression rate. However, the PPV of 73% determined in the Mayo Clinic study is the highest PPV result obtained so far; later studies performed between 2013 and 2018 reported PPVs of 30–64%.[4,6-9] The results presented by Henriot for both the N Latex FLC and FREELITE assays are well within the midrange of the PPV results obtained in the different studies, demonstrating that the N Latex FLC assays provided equivalent risk prognosis. For application of the FLC ratio ≥100 rule, high precision at the lower end of the measuring range is required, as the ratio is highly dependent on the precision of the very low-level, noninvolved free light chain.

In summary, in six studies published through 2019 addressing identification of ultra-high-risk SMM patients, an FLC ratio ≥100 identified such patients with a more modest progression rate than aimed for. Therefore, certain authors consider using an FLC ratio ≥100 as the sole criterion for treatment as active MM to be unjustified,[6] but they do recommend very close monitoring for these patients.

Abbreviations:
FLC: free light chains
MM: multiple myeloma
SMM: smoldering multiple myeloma
CRAB: calcium, renal, anemia, bone
SLiM: skelet, light chains, marrow
ESMO: European Society for Medical Oncology
IMWG: International Myeloma Working Group
PPV: positive predictive value

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