Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance


We hypothesized that the presence of monoclonal free kappa or lambda immunoglobulin light chains in monoclonal gammopathy of undetermined significance (MGUS), as detected by the serum free light chain (FLC) assay increases the risk of progression to malignancy. Of 1384 patients with MGUS from Southeastern Minnesota seen at the Mayo Clinic from 1960 to 1994, baseline serum samples obtained within 30 days of diagnosis were available in 1148. At a median follow-up of 15 years, malignant progression had occurred in 87 (7.6%) patients. An abnormal FLC ratio (kappa-lambda ratio < 0.26 or > 1.65) was detected in 379 (33%) patients. The risk of progression in patients with an abnormal FLC ratio was significantly higher compared with patients with a normal ratio (hazard ratio, 3.5; 95% confidence interval [CI], 2.3-5.5; \( P < .001 \)) and was independent of the size and type of the serum monoclonal (M) protein. Patients with an abnormal serum FLC ratio, non-immunoglobulin G (non-IgG) MGUS, and a high serum M protein level (≥ 15 g/L) had a risk of progression at 20 years of 58% (high-risk MGUS) versus 37% with any of these risk factors (high-intermediate risk), 21% with one risk factor (low-intermediate risk), and 5% when none of the risk factors were present (low risk). (Blood. 2005; 106:812-817)

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell proliferative disorder found in approximately 3% of the general population 50 years of age and older.1 The hallmark of MGUS is the presence of a monoclonal immunoglobulin in the serum, commonly referred to as a monoclonal (M) protein. By definition, patients with MGUS have a serum M protein less than 30 g/L, bone marrow plasma cells less than 10%, and no anemia, hypercalcemia, lytic bone lesions, or renal failure that would be indicative of a malignant plasma cell disorder.2-4 Since MGUS is asymptomatic, diagnosis is usually the result of a screening serum protein electrophoresis performed as part of a diagnostic work up by primary-care providers. MGUS is associated with progression to multiple myeloma or related malignancy at a rate of 1% per year.5,6 Thus the risk of malignancy for a 50-year-old patient with a 25-year life span is 25%. However, the risk of progression does not diminish even after 25 to 35 years, making lifelong follow-up by primary-care providers necessary in all persons diagnosed with MGUS.5,7

Since myeloma is incurable and has a median survival of only 3 to 4 years,8-10 delaying or preventing the progression of MGUS assumes great significance. However, given the potential adverse effects of prophylactic approaches and the duration for which such interventions will be needed, only patients at a high risk for progression can be considered candidates for testing preventive strategies. Conversely, low-risk patients must not be subjected to potentially harmful or expensive tests or preventive interventions. It is therefore important to identify risk factors that can accurately predict the subset of patients with the greatest likelihood of progression. Unfortunately, such risk factors have been very difficult to identify. In a large population-based study of MGUS, we evaluated more than 13 potential risk factors, but only the size and type of M protein (IgM and IgA subtypes) were predictive of progression.5 In another study, Cesana and colleagues reported that a bone marrow plasma cell percentage of 6% to 9% carried twice the risk of progression compared with marrow involvement that is 5% or less.11 Clearly, additional laboratory predictors of progression of MGUS to myeloma are needed.

A novel, highly sensitive serum free light chain (FLC) assay is now available for clinical practice.12 It allows quantification of free kappa (\( \kappa \)) and lambda (\( \lambda \)) chains (ie, light chains that are not bound to intact immunoglobulin) secreted by plasma cells. An abnormal kappa-lambda FLC ratio indicates an excess of one light chain type versus the other, and is interpreted as a surrogate for clonal expansion based on extensive testing in healthy volunteers, and patients with myeloma, amyloidosis, and renal dysfunction.13,14

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S.V.R., R.A.K., J.A.K., A.R.B., and L.J.M.III participated in the study concept, data analysis, study design, and writing of the report; M.F.P., D.R.L., and T.M.T. were involved in data collection, data analysis, and manuscript review; A.D. was involved in data analysis and manuscript review; R.J.C. was involved in performing the free light chain assays, data collection, and manuscript review. An Inside Blood analysis of this article appears in the front of this issue.

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The assay is performed on automated chemistry analyzers, is widely available, and is commonly used to monitor patients with oligo-secretory or nonsecretory myeloma and primary amyloidosis, as well as patients with the light-chain only form of myeloma. The presence of a monoclonal FLC in MGUS may be a marker of clonal evolution in the neoplastic plasma cell since it likely indicates a loss of control over the proportion of heavy and light chains synthesized. We undertook this study to test the hypothesis that an abnormal FLC ratio at baseline is a risk factor for the progression of MGUS to malignancy.

Materials and methods

The study cohort was derived from persons who resided in the 11 counties in southeastern Minnesota who met previously established diagnostic criteria for MGUS at the Mayo Clinic from January 1, 1960, through December 31, 1994. Of 1384 patients with MGUS diagnosed during this period, a cohort whose baseline characteristics, methods of detection, follow-up, and risk of progression have been well described by us earlier,11 1148 patients who had cryopreserved serum samples collected within 30 days of the MGUS diagnosis were studied. Follow-up was through the review of each patient’s complete medical records at the Mayo Clinic. The study was approved by the Mayo Institutional Review Board.

The FLC level in serum collected at the time MGUS was first recognized was determined on all 1148 patient samples using the FLC assay (Freelite; The Binding Site, Birmingham, United Kingdom) performed on a Dade-Behring Nephelometer (Deerfield, IL). It consists of 2 separate measurements, one to detect free-kappa (normal range, 3.3-19.4 mg/L) and the other to detect free-lambda (normal range, 5.7-26.3 mg/L) light chains. In addition to measuring the absolute levels of FLC, the test also allows the assessment of clonality based on the ratio of kappa-lambda light chains.

Table 1. Clinical characteristics of 1148 southeastern Minnesota patients with monoclonal gammopathy of undetermined significance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>622 (54)</td>
</tr>
<tr>
<td>Female</td>
<td>526 (46)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>0-49</td>
<td>66 (6)</td>
</tr>
<tr>
<td>50-59</td>
<td>123 (11)</td>
</tr>
<tr>
<td>60-69</td>
<td>286 (25)</td>
</tr>
<tr>
<td>70+</td>
<td>673 (59)</td>
</tr>
<tr>
<td>Serum monoclonal protein heavy chain type</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>806 (70)</td>
</tr>
<tr>
<td>IgA</td>
<td>135 (12)</td>
</tr>
<tr>
<td>IgM</td>
<td>182 (16)</td>
</tr>
<tr>
<td>Biclonal</td>
<td>25 (2)</td>
</tr>
<tr>
<td>Serum monoclonal protein level, g/L</td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>287 (25)</td>
</tr>
<tr>
<td>6-10</td>
<td>229 (20)</td>
</tr>
<tr>
<td>11-20</td>
<td>604 (53)</td>
</tr>
<tr>
<td>21-30</td>
<td>28 (2)</td>
</tr>
</tbody>
</table>

The assay is performed on automated chemistry analyzers, is widely available, and is commonly used to monitor patients with oligo-secretory or nonsecretory myeloma and primary amyloidosis, as well as patients with the light-chain only form of myeloma. The presence of a monoclonal FLC in MGUS may be a marker of clonal evolution in the neoplastic plasma cell since it likely indicates a loss of control over the proportion of heavy and light chains synthesized. We undertook this study to test the hypothesis that an abnormal FLC ratio at baseline is a risk factor for the progression of MGUS to malignancy.

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chain levels (normal reference range, 0.26-1.65). Patients with a kappa-lambda FLC ratio less than 0.26 are typically defined as having monoclonal lambda FLC and those with ratios greater than 1.65 are defined as having a monoclonal kappa FLC. If the FLC ratio is greater than 1.65, kappa is considered to be the “involved” FLC and lambda the “uninvolved” FLC, and vice versa if the ratio is less than 0.26.

The normal reference range of 0.26 to 1.65 for the free-kappa–lambda ratio in the FLC assay reflects a higher serum level of free-lambda light chains than would be expected given the usual kappa-lambda ratio of 2 for intact immunoglobulins. This occurs because the renal excretion of free kappa (which exists usually in a monomeric state) is much faster than free lambda (which is usually in a dimeric state).13,14

FLCs

The prognostic effect of abnormal kappa-to-lambda FLC ratio on progression of MGUS was studied. We also examined whether the risk of progression varied depending on the extent to which the FLC ratio was abnormal. To estimate the continuous risk effect of the FLC ratio, a smoothing spline as previously described17 was used in univariate and multivariate Cox proportional hazards models. The risk of progression depending on extent to which the FLC ratio was abnormal was also estimated after adjusting for the size of the serum monoclonal protein to the mean monoclonal protein level. The primary end point was progression to multiple myeloma or a related disorder. Progression endpoints were examined both as cumulative probability of progression and cumulative incidence. The former was computed using an ordinary Kaplan-Meier estimate19 where patients who die are censored; curves were compared using the log-rank test. The effects of potential risk factors on progression rates were examined using a Cox proportional hazards model.18 The cumulative incidence curve, on the other hand, explicitly accounts for death from other causes (such as cardiovascular disease, cerebrovascular disease, or unrelated malignancy) as a competing risk and was estimated using the method of Gooley.20

Results

Clinical characteristics

The median age at diagnosis of MGUS was 72 years. The median serum M protein at diagnosis was 12 g/L. Urine electrophoresis and immuno-electrophoresis or immunofixation was done in 370 patients. Of these, a monoclonal light chain was detected in 110 patients (98%) of the patients. A higher proportion of patients with a positive urinary monoclonal protein had an abnormal FLC ratio (55%) compared with patients with no detectable monoclonal proteins in the urine (32%) (P < .001).

Outcomes

These 1148 patients were followed for a total of 8982 person years (median, 15 years). There were 783 patients (68%) who were followed until death. During this period of observation, 87 (7.6%) patients experienced progression: multiple myeloma (53 patients), IgM lymphoma (17 patients), primary amyloidosis (6 patients), macroglobulinemia (6 patients), chronic lymphocytic leukemia (3 patients), and plasmacytoma (2 patients). The cumulative probability of progression was 9% at 10 years, 20% at 20 years, and 30% at 25 years, or approximately 1% per year (Figure 1). Because patients who die are censored, the upper curve in this figure reflects the probability that a patient who has not died of other causes will experience plasma cell progression at each point in the follow-up; it therefore represents the natural history of the disease assuming patients do not die of other causes prior to progression. The risk of progression is lower if competing causes of death are taken into account, 11.2% at 25 years, as illustrated by the lower curve in Figure 1A.

Risk of progression based on FLC assay

In a Cox proportional hazards model, the risk of progression in patients with an abnormal FLC ratio was significantly higher compared with patients with a normal ratio (hazard ratio, 3.5; 95% confidence interval, 1.1-10.2).

Table 2. Absolute risk of progression of MGUS to myeloma or related disorders based on the serum FLC ratio

<table>
<thead>
<tr>
<th>Time of follow-up</th>
<th>Absolute risk of progression, % of patients (95% CI)</th>
<th>Risk based on FLC (kappa-lambda) ratio using the current diagnostic reference range</th>
<th>Risk based on increasingly abnormal FLC (kappa-lambda) ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal ratio 0.26-1.65*</td>
<td>Abnormal ratio &lt; 0.26 or &gt; 1.65†</td>
<td>FLC ratio 0.25-4§</td>
</tr>
<tr>
<td>5 y</td>
<td>2.5 (1.3-3.8)</td>
<td>8 (4.8-11)</td>
<td>3.1 (1.9-4.4)</td>
</tr>
<tr>
<td>10 y</td>
<td>5.3 (3.2-7.4)</td>
<td>16.7 (11.4-21.7)</td>
<td>6.4 (4.4-8.4)</td>
</tr>
<tr>
<td>15 y</td>
<td>6.6 (4.9-8.4)</td>
<td>29.9 (21.1-37.8)</td>
<td>9.6 (6.5-12.6)</td>
</tr>
<tr>
<td>20 y</td>
<td>12.6 (4.5-20.7)</td>
<td>35 (23.6-45.1)</td>
<td>15.8 (8.5-22.7)</td>
</tr>
<tr>
<td>Cumulative annual rate of progression, %/y</td>
<td>0.6</td>
<td>1.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*p = 769.
†p = 379.
§p = 977.
‡p = 95.
¶p = 76.
IgA, IgM, or biclonal IgA plus IgM 2.6 (1.7-4.0)
Serum M protein size 2.4 (1.7-3.5)
Abnormal FLC ratio 2.6 (1.7-4.2)

(Figure 1B).

corresponding rates at 20 years were 35% and 13%, respectively
an abnormal ratio compared with 5% with a normal ratio;
corresponding rates at 20 years were 35% and 13%, respectively
(Figure 1B).

There was a good correlation between increasingly abnormal
FLC ratio and the relative risk of progression (Figure 2A). The
absolute risk of progression at 5, 10, 15, and 20 years for varying
FLC ratios is given in Table 2.

An increased risk of progression was also noted when the
analysis was done using absolute levels of serum FLC. Patients
with elevated levels of kappa or lambda FLC had a significantly
higher risk of progression compared with those with lower levels
(hazard ratio, 2.1; 95% CI, 1.3-3.5; P = .002). There were 61
patients (5%) who had suppressed levels of the uninvolved FLC in
the absence of elevated involved FLC levels; no increased risk of
progression was seen in this group (hazard ratio, 1.2; 95% CI,
0.5-2.6; P = .65).

Of 379 patients with an abnormal FLC ratio, the abnormal ratio
was due to elevated involved FLC alone in 309 patients; the risk of
progression in this group was significantly higher compared with
patients with a normal ratio (hazard ratio, 3.5; 95% CI, 2.2-5.5;
P < .001). An abnormal ratio was solely due to suppressed
uninvolved FLC in 32 patients whereas it was due to combined
elevated involved FLC and suppressed uninvolved FLC in 20
patients. The hazard ratio for the risk of progression in these 2
groups was 1.4 and 10.5, respectively, but interpretation is
restricted by the small sample size. An abnormal FLC ratio
occurred with normal levels of both uninvolved and involved
FLC in 18 patients.

### Table 3. Multivariate analysis of prognostic factors for progression of monoclonal gammopathy of undetermined significance

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio (95% confidence interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal FLC ratio</td>
<td>2.6 (1.7-4.2)</td>
</tr>
<tr>
<td>Serum M protein size</td>
<td>2.4 (1.7-3.5)</td>
</tr>
<tr>
<td>IgA, IgM, or biclonal IgA plus IgM</td>
<td>2.6 (1.7-4.0)</td>
</tr>
</tbody>
</table>

*P < .001 for each variable.

The effect of an abnormal FLC ratio on risk of progression was
independent of the size of the M protein, as illustrated in Figure 2B,
which has been adjusted for the size of the serum M protein. After
adjusting for the size and type of the serum M protein on
multivariate analysis, the hazard ratio for progression associated
with an abnormal FLC ratio was only slightly reduced (hazard
ratio, 2.6; 95% CI, 1.7-4.2; P < .001) as delineated in Table 3. In
this multivariate model the hazard ratio for the size of the serum M
protein was 2.4 (P < .001) and that for a non–IgG type MGUS was 2.6
(P < .001).

### Risk stratification model for MGUS

The FLC ratio added additional prognostic value to all 3 subgroups
of MGUS stratified by the 2 known prognostic factors, the size and
type of M protein (Table 4). We constructed a model for predicting
the risk of progression of MGUS based on the size of the serum M
protein, the type of immunoglobulin, and the presence of an
abnormal FLC ratio (< 0.26 or > 1.65). The use of these 3 risk
factors identified 4 cohorts of patients with MGUS with significa-
cantly different rates of progression (Table 4; Figure 3). In fact,
when competing causes of death are taken into account, the true
time risk of progression decreases to 2% for patients in the
low-risk group.

### Discussion

The term “MGUS” was first coined at the Mayo Clinic more than
25 years ago,24 and our studies have shown that the risk of
progression of MGUS to myeloma or related malignancy is
approximately 1% per year.5-7 However, distinguishing the patient
with a stable monoclonal gammopathy from one in whom multiple
myeloma or related disorders will eventually develop is difficult
when MGUS is originally recognized. Moreover, there is no
decline in the risk of progression over time,5,6 necessitating lifelong
follow-up, usually performed by primary-care providers. Patients
are referred to hematologists typically in the face of a rising M

### Table 4. Risk-stratification models to predict progression of monoclonal gammopathy of undetermined significance to myeloma or related disorders

<table>
<thead>
<tr>
<th>Risk group</th>
<th>No. patients</th>
<th>Relative risk, 95% CI</th>
<th>Absolute risk of progression at 20 years, %</th>
<th>Absolute risk of progression at 20 years accounting for death as a competing risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of FLC ratio to known prognostic categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (serum M protein &lt; 15 g/L and IgG subtype)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FLC ratio</td>
<td>449</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal FLC ratio</td>
<td>142</td>
<td>7.4</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Intermediate risk (either serum M protein ≥ 15 g/L or non-IgG subtype)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FLC ratio</td>
<td>278</td>
<td>1</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Abnormal FLC ratio</td>
<td>184</td>
<td>2.2</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td>High risk (serum M protein ≥ 15 g/L and non-IgG subtype)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal FLC ratio</td>
<td>42</td>
<td>1</td>
<td>37</td>
<td>23</td>
</tr>
<tr>
<td>Abnormal FLC ratio</td>
<td>53</td>
<td>1.5</td>
<td>58</td>
<td>27</td>
</tr>
<tr>
<td>Risk stratification model incorporating all 3 predictive factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (serum M protein &lt; 15 g/dL, IgG subtype, normal FLC ratio [0.26-1.65])</td>
<td>449</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low-intermediate risk (any 1 factor abnormal)</td>
<td>420</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>High-intermediate risk (any 2 factors abnormal)</td>
<td>226</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>High risk (all 3 factors abnormal)</td>
<td>53</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
</tbody>
</table>
protein on follow-up, or when other symptoms and signs suggestive of myeloma or related malignancy develop.

Given the uncertainty that follows the diagnosis of MGUS and the need for long-term follow-up, clinical management would be greatly enhanced by identification of factors that more accurately predict progression or stability. We recently conducted a small case-control study to determine if the presence of an abnormal FLC ratio was associated with progression of MGUS.22 There were 47 patients with MGUS who had progression to myeloma or related disorder who served as cases, while 50 patients with MGUS without evidence of disease progression served as controls. The presence of an abnormal FLC ratio was associated with a 2.5-fold increased risk of progression. Given the significant clinical implications of this finding, the present study was undertaken with the goal of validating and confirming these findings in a large, well-established population-based cohort of patients with MGUS in whom long-term follow-up was available.5

The results of this study confirm our hypothesis that an abnormal FLC ratio is an important risk factor for progression and is independent of the size and type of the serum M protein, 2 known prognostic factors.3 The relative risk of progression is related to the extent to which the ratio is abnormal. We also show that the size and type of the M protein and the serum FLC ratio can be combined to yield a powerful risk-stratification model for the progression of MGUS. This model identifies a group of patients with low-risk MGUS (constituting almost 40% of the cohort) who have only a 5% risk of progression at 20 years, and a lifetime risk of 2% when competing causes of death are taken into account. Clearly, this group of patients can be reassured to a great extent. In fact, the serum M protein levels may need to be rechecked in this group only if symptoms of myeloma or related disorder become apparent. On the other hand, the smaller group of high-risk patients needs to be monitored more closely before pathologic fractures, hypercalce-mia, renal failure, paraplegia from extramedullary plasmacytoma, primary amyloidosis, overwhelming infection, or other serious complications develop.

Another goal of the study was to identify patients in whom prophylactic interventions can be justified. Low-risk patients should clearly be excluded from preventive strategies and trials that typically carry adverse effects and cost. However, even in the high-risk group with both a high serum M protein and an abnormal FLC ratio, the risk of progression is only 3% per year, making it hard to justify preventive strategies. It is important in this context to realize that 3% percent of the general population over the age of 50 years has MGUS, whereas the annual incidence of myeloma is only 4 per 100,000,23 and that the vast majority of patients with MGUS (approximately 75%-90%)24 will not develop myeloma or a related disorder in their lifetime. A risk of progression of 3% per year is, in our opinion, insufficient to warrant large preventive trials in MGUS in the absence of effective drugs with low long-term toxicity. Clearly, additional risk factors are needed, and we are currently exploring factors such as bone marrow microvesSEL density, marrow angiogenic potential, and presence of circulating plasma cells in predicting progression of MGUS. The high-risk patients with MGUS identified in this study will serve as the base from which additional risk factors can identify a suitable cohort for chemoprevention trials.

Recent studies show that loss of heavy chain expression in myeloma is related to cytogenetic events in the heavy chain locus on chromosome 14 (14q32).24 We hypothesize that clonal evolution of the neoplastic plasma cell may be marked by imbalance in heavy and light chain production, and the results of this study lend support to this theory. Whether the expression of excess clonal FLCs in MGUS evolves from a cell that has undergone additional cytogenetic changes, or represents a clone that has aberrant light chain overexpression from the outset, needs further investigation.

The serum FLC assay used in this study is currently used clinically to monitor response to therapy in patients with myeloma who present with unmeasurable levels of monoclonal protein in serum and urine protein electrophoresis studies (oligo-secretory or nonsecretory disease).12 In these patients, the serum FLC levels are often elevated, decreasing the need for serial bone marrow biopsies. It is also used in a similar manner in patients with primary amyloidosis who often have low or unmeasurable levels of monoclonal protein by electrophoresis.15 The FLC assay is also being investigated as a replacement to 24-hour urine electrophoresis studies to monitor light chain excretion in the urine.14,16 Criteria to assess response using the serum FLC assay have been proposed,25 but need further validation.

The presence of an abnormal FLC ratio is a clinically and statistically significant predictor of progression in MGUS. We identify a low-risk subset of patients with MGUS with a remarkably small lifetime risk of progression in whom less frequent follow-up can be justified. Since this subset accounts for almost 40% of all patients, this is a finding of significant importance for the management of MGUS.

References


