fortune Journals

Review Article

ARCHIVES OF
CLINICAL AND
BIOMEDICAL RESEARCH
ISSN: 2572-5017

Use and Misuse of Serum Free Light Chain Assay: Challenging the Paradigms

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Abstract

Introduction: Lympho-plasmacytic neoplasms produce monoclonal immunoglobulins that may be intact immunoglobulins, light chains only, or intact immunoglobulins plus free light chains. Plasma cells generally produce more light chains than heavy chains and excess free light chains are detectable in serum and urine. Assays specific for free light chains have been available for about 25 years.

Observations and Interpretations: Monoclonal free light chains are pathogenic, whereas elevated polyclonal free light chains are markers of renal failure and inflammation. Abnormal ratio of serum free κ/ʎ chains has been used, erroneously, to diagnose monoclonal gammopathy. Urine examination is underutilized for evaluation of monoclonal free light chains. Diagnosis of monoclonal gammopathy of undetermined significance based on a κ/ʎ ratio of >1.65 has a 96% false positive rate; κ/ʎ ratio of >3.15 has a false positive rate of >80%. The requirement for a normal κ/ʎ ratio for stringent complete response is unsupported. Light chain escape in multiple myeloma probably does not exist. In monoclonal lesions, kappa chains occur at 4-5 times the concentration of lambda chains. Uninvolved kappa chains occur at twice the concentration of uninvolved lambda chains. Diagnostic criteria based on light chain quantity and ratio ought to be light chain type specific. The existing criterion for myeloma defining condition using light chain level of 100 mg/dL and ratio of involved to uninvolved light chain levels of >100 is untenable. Light chain predominant lesions have significantly worse prognoses. Screening for monoclonal gammopathy of undetermined significance is contraindicated. Modified immunofixation electrophoretic analyses can detect monoclonal free light chains with the sensitivity of mass spectrometry.

Recommendations:

a) There is an urgent need for simple assays, suitable for use in routine clinical laboratories, for identification and quantification of free monoclonal light chains.

b) Light chain predominant multiple myeloma lesions, both intact immunoglobulin as well as light chain only lesions, need to be identified as subtypes in clinical trials. Light chain predominant lesions have a 2-year shorter survival.

c) High sensitivity immunofixation electrophoretic assays for monoclonal light chains in serum and urine ought to precede bone marrow examination in initial diagnosis as well as in monitoring of monoclonal gammopathic lesions.

d) Abnormal κ/ʎ ratio is not diagnostic of monoclonal gammopathy and a normal ratio does not exclude monoclonal gammopathy. Diagnosis of a monoclonal gammopathic lesions ought to be supported by demonstration of a persistent, restricted mobility immunoglobulin in serum and/or urine, or a monoclonal population of plasma cells in bone marrow.

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Citation: Gurmukh Singh. Use and Misuse of Serum Free Light Chain Assay: Challenging the Paradigms. Archives of Clinical and Biomedical Research. 9 (2025): 461-472.

Received: October 25, 2025
Accepted: October 29, 2025
Published: November 06, 2025

Singh G., Arch Clin Biomed Res 2025
DOI:10.26502/acbr.50170490

Keywords: Multiple myeloma; Monoclonal gammopathy of undetermined significance; Light chain predominant multiple myeloma; Monoclonal free light chains; Myeloma defining conditions; Light chain escape; Stringent complete response, Serum free light chain assay; Urine immunofixation electrophoresis; FLC-Modified SIFE

Abbreviations: LC: Immunoglobulin Light Chain; MIg: Monoclonal Immunoglobulin; MG: Monoclonal Gammopathy; MGUS: Monoclonal Gammopathy Of Undetermined Significance; SMM: Smoldering Or Asymptomatic Multiple Myeloma; MM: Multiple Myeloma/ Plasma Cell Myeloma; LCMGUS: Light Chain MGUS

LCPMM = Light Chain Predominant MM; LCMM: Light Chain Multiple Myeloma; SIFE: Serum Immunofixation Electrophoresis; FLC-Modified SIFE: Free Light Chain Modified Serum Immunofixation Electrophoresis; UIFE: Urine Immunofixation Electrophoresis; FLCUIFE: Free LC UIFE

Introduction

Identification of epitopes specific for free immunoglobulin light chains has been a major development in immunology in the past 30 years. However, serum free light chain assay results have been misused. This communication addresses the proper and improper uses of this assay. In carrying out this review, I have been critical of the existing paradigms and at times may use terminology/words/phrases that could be considered belligerent, dismissive, adversarial, and not suitable for a scientific publication etc. Using my own publications to question the paradigms and opinions of ostensibly honorable organizations, e.g. International Myeloma Working Group (IMWG) may be considered problematic.

Background

Immunoglobulins constitute the dominant molecules in adaptive immune response. Through DNA rearrangement and somatic hypermutation, individuals can generate about 10^{16} different immunoglobulins. Immunoglobulins consist of two covalently linked heavy chains, of about 50 kilodalton each. Each heavy chain dimer is covalently linked to two light chains (LC) of about 25 kilodalton each. A given immunoglobulin molecule consists of only one type of heavy chain and one type of LC. There are five isotypes of heavy chains, namely, gamma, alpha, mu, epsilon, and delta, and two types of LCs namely kappa and lambda. These chains combine to produce ten different classes of immunoglobulins. IgG, IgA, IgM, IgE and IgD, each with either kappa or lambda LC [1,2].

Gamma heavy chain of IgG, the most abundant immunoglobulin isotype, has four subtypes with variations in physiological functions. Alpha heavy chain of IgA has two subtypes. IgA is the dominant immunoglobulin on mucosal surfaces. It usually occurs in dimeric form bound by J chain. Mucosal surface molecules also have the secretory piece. Mu heavy chain of IgM is larger than the gamma heavy chain. IgM usually occurs in pentameric form and is mostly confined to the intravascular space. IgM is usually the first immunoglobulin type to arise in response to an antigenic stimulus. The epsilon heavy chain of IgE is also larger than gamma heavy chain. While IgG, IgA and IgM are the primary molecules in defense against micro-organisms, IgE is associated with defense against parasites and is responsible for allergic reactions. Delta heavy chain, along with either kappa or lambda LC constitutes IgD. IgD is usually the first fully formed immunoglobulin in embryonic development, is mostly present on the surface of B-lymphocytes and serves as an antigen receptor. The heavy chains consist of 3-4 constant domains and a variable domain at the N-terminal [1].

The kappa and lambda LCs have one constant domain that is covalently linked to the first constant domain of heavy chain to form a Y shaped molecule. The N-terminal variable regions of LCs are contiguous with the variable regions of heavy chains to provide the prodigiously diverse antigen binding capacity [1]. Kappa LCs are slightly heavier than lambda LCs and free lambda LCs tend to form dimers. [2] Normal as well as neoplastic plasma cells usually produce more LCs than heavy chains. The excess free LCs can be detected in serum and urine [3,4].

Antisera specific to free LCs

Bradwell recognized that some epitopes on LCs are inaccessible when LCs are bound to heavy chains. By preparing antisera to such epitopes, The Binding Site developed an assay, FreeLite®, to measure free LCs in serum and other body fluids [2]. By evaluating the sera of blood donors and healthy individuals, Mayo clinic established reference ranges for free kappa and lambda LCs. They posited that the normal kappa/lambda (κ/λ) LC ratio ranged from 0.26 to 1.65. It became a common practice to label patients with results outside this range, even without a detectable monoclonal immunoglobulin (MIg), as having LC monoclonal gammopathy [5].

Natural preference for kappa chains over lambda chains

Kappa chains, and Kappa LC associated immunoglobulins occur in greater abundance than lambda chains and lambda LC associated immunoglobulins. In humans the kappa and lambda light chain associated immunoglobulins occur in a ratio of about 1.8:1. The corresponding ratio in mice is 19:1. This basal disparity in the abundance of kappa over lambda chains is further amplified during immune response or other immunological phenomena associated with inflammation, immune regeneration and clonal proliferation [6-10].

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DOI:10.26502/acbr.50170490

Monoclonal, polyclonal and oligoclonal immunoglobulins

Neoplastic disorders of the lympho-plasmacytic system are associated with monoclonal proliferation of cells, resulting in monoclonal immunoglobulins in body fluids. A nascent immune response may be associated with proliferation of a small number of clones that may be identifiable in serum by electrophoretic analysis [4,10]. Such oligoclonal phase gives way to the usual polyclonal pattern. Following stem cell transplantation, the implanted cells go through a phase of clonal proliferation that is frequently associated with the presence of multiple immunoglobulins of restricted mobility, oligoclones, detectable in serum by electrophoretic analysis [8-10]. Oligoclonal responses, physiological or following stem cell transplantation tend to be kappa dominant. Polyclonal hypergammaglobulinemia is usually associated with inflammatory disorders and may arise from an oligoclonal pattern or occur in parallel with an oligoclonal pattern.

Pathogenicity of free light chains

Monoclonal free light chains are pathogenic with the commonest lesion being tubular nephropathy. Other lesions caused by monoclonal light chains include amyloidosis, light chain deposition disease, systemic vasculitis and thrombotic microangiopathy [6].

Non-monoclonal/polyclonal free light chains are not pathogenic. These are present in abnormal quantities in renal failure, polyclonal hypergammaglobulinemia from any cause and inflammatory disorders. The poor prognosis associated with abnormal LC ratio reflects underlying pathology, not a deleterious effect of polyclonal free light chains.

Monoclonal gammopathy (MG)

Monoclonal gammopathic disorders consist of monoclonal gammopathy of undetermined significance (MGUS), smoldering or asymptomatic multiple myeloma (SMM) and the malignant disorder, multiple myeloma/plasma cell myeloma (MM) [4,11,12]. There has been considerable progress in the diagnosis, monitoring and treatment of MM in that the average survival has improved from 3 years to 10 years [13-15].

The majority of intact immunoglobulin MGUS are associated with a normal κ/λ ratio. Almost 90% of lambda chain-associated MGUS lesions have a normal κ/λ ratio [4,7-11]. The diagnostic criteria for MGUS include presence of MIg in serum at a concentration of <3.0 g/dL, < 10% plasma cells in bone marrow and lack of end-organ damage, usually referred to by the acronym, CRAB, i.e., Hypercalcemia, Renal failure, Anemia and Lytic bone lesion on x-ray examination [4,12,15]. The equivalent of MGUS of clinical significance has not been described for light chain MGUS (LCMGUS).

MG lesions may display distinctive characteristics based on the immunoglobulin type [14]. An additional variable is the amount of free monoclonal LCs secreted by the tumor. About 85% of MM lesions secrete intact immunoglobulins along with variable amounts of free monoclonal LCs. A small but not insignificant number of lambda chain associated MM lesions do not produce enough free monoclonal LCs such that the κ/λ ratio remains normal throughout the course of the disease [7,8]. About 18% of the intact immunoglobulin producing MM secrete a greater abundance of free monoclonal LCs and such lesions are called, LC predominant MM (LCPMM). This segregation based on the level of free monoclonal LCs is clinically important in that LCPMM lesions have worse prognosis [6,7]. Almost all IgD secreting MM are LCPMM and have poorer outcomes [8,16,17]. About 15% of MM lesions secrete LCs only, (LCMM) [17]. Within this group about 40% the lesions have higher levels of free monoclonal LCs and a shorter survival [8,17].

Based on the amount of free monoclonal LCs secreted by MG lesions in general, and MM lesions in particular, disorders can be subclassified as:

A. Intact immunoglobulins secreting MM:

1. LCPMM. These account for about 18% of the total intact immunoglobulin secreting lesions and have a two-year shorter survival [6,8]

B. LC only myelomas (LCMM):

1. LC Predominant LCMM. Forty percent of LCMM have serum free LC levels of >455 mg/dL and a more than 2-year shorter survival than conventional LCMM [6,8]

Documentation of monoclonality:

SFLC ratio is an inappropriate/inadequate/erroneous test to diagnose or rule out monoclonal gammopathy. Monoclonality of a plasma cell lesion can be documented by: (a) Demonstration of restricted mobility intact immunoglobulin or light chain in serum and/or urine by electrophoretic analysis. Higher sensitivity serum and urine immunofixation electrophoreses ought to precede bone marrow examination for documentation of a monoclonal lesion. (b) Mass spectrometry may be used in the identification of monoclonal immunoglobulins though high sensitivity immunofixation electrophoresis has equivalent sensitivity. (c) In non-secretory lesions and in detection of minimal residual disease, bone marrow examination by flow cytometry and nucleic acid analysis is appropriate.

Utility of Serum Free Light Chain (SFLC) assay

Along with the findings given above and the earlier observations that normal κ/λ ratio does not exclude MG and an abnormal ratio is not diagnostic of MG, leads to the conclusion that SFLC assay is useful only for diagnosing

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DOI:10.26502/acbr.50170490

and monitoring LCMM and LCPMM [6,8,16,17]. Elevated levels of polyclonal SFLC are generally a reflection of renal failure and inflammation. Inflammatory disorders are the likely explanation of poorer survival in patients with higher SFLC, with or without MGUS [4,8,18]. Elevated polyclonal SFLC levels are similar to C-reactive protein, ferritin levels and erythrocyte sedimentation rate in their association with chronic disorders.

Fallacy of Using Polyclonal SFLC Levels and Light Chain Ratios in Diagnosis

SFLC quantity and ratios of light chains have been used to diagnose LCMGUS; myeloma defining condition; stringent complete response in treatment of myeloma; and light chain escape. The fallacy of diagnosing immunoglobulin disorders by using SFLC levels and ratios are addressed below:

Light chain MGUS (LCMGUS)

MGUS lesions, like MM lesions, may produce LCs only. There are no generally agreed upon criteria for diagnosing LCMGUS. Detection of monoclonal LCs in serum and/or urine, with <10% plasma cells in bone marrow, without evidence of end-organ damage could be considered criteria for diagnosis of LCMGUS. An abnormal κ/λ ratio is not diagnostic of MG [4,7-9,19,20]. At a tertiary care center, 36% of the patients without evidence of MG had an abnormal κ/λ ratio with 87% of the specimens having kappa dominant abnormal ratio, i.e., κ/λ ratio >1.65 [4,7-9].

In patients with detectable MIgs, κ/λ ratio was falsely normal in about 27% of the 1,860 samples. The false negative rate was higher in lambda chains lesions (32%) than those with kappa chains (24%) [4,7-9]. Thus, given that 36% of patients have an abnormal κ/λ ratio without evidence of MG, and nearly 30% of patients with detectable MIgs have normal κ/λ ratio, it is unreasonable to diagnose LCMGUS from just an abnormal κ/λ ratio [4,7,19,20]. About half of LCMGUS disappear spontaneously [21]. The high spontaneous disappearance rate further questions the neoplastic nature of the lesions labeled as "MGUS" based on κ/λ ratio only and without any independent evidence of the existence of a MIg.

It was proposed that reactivity of The Binding Site polyclonal antiserum to free kappa LCs drifted and that the current assay may yield a higher reading for serum free kappa chains than the results from 20 years ago [22-24]. Even if the purported drift in kappa LC results is correct, the proposed revision for diagnosing Kappa MGUS to only when the κ/λ ratio is >3.0, or 3.15, without independent evidence of a MIg, is still erroneous[4,7,19,20]. It is also possible that the drift will reverse, necessitating another revision to the unreliable κ/λ ratio. More recently, the iStopMM group, that proposed the upper limit of normal κ/λ ratio as 3.15, published revised, age specific levels. The κ/λ ratio for <70-year-old persons being: 0.44-2.16, and that for >70-year-old persons being: 0.46-2.59. It is implied that patients with ratios outside this limit have LCMG, even though the authors presented no evidence that an abnormal κ/λ ratio was associated with a MIg, thus perpetuating the fallacy of using κ/λ ratio for diagnosing monoclonality [25].

In patients with MG, background levels of uninvolved kappa LCs are twice as high as the levels of uninvolved lambda LCs [8,11]. This explains, in part, that nearly 90% of lambda chain associated MGUS lesions have a normal κ/λ ratio [4,7]. Even in patients with SMM, about 60% of the lambda chain associated lesions have a normal κ/ʎ ratio. The levels of involved kappa LCs in patients with MG are 4-5-times higher than the levels of involved lambda LCs [8,11,26]. These observations explain the normal κ/λ ratio in the 25% of patients with detectable monoclonal lambda LCs in urine [11].

Using serum free light chain ratio to diagnose LCMGUS is erroneous.

In a retrospective study of 1740 urine specimens, a monoclonal light chain was detected in forty-eight, i.e., 2.76% (Kappa in 1.78% and Lambda in 0.98%) [19,20]. The range of κ/λ ratio and monoclonal LCs in urine are depicted in Table 1 (Modified from reference no. 19.) More lambda monoclonal LCs were detected in urines with a serum κ/λ ratio between 0.26 and 0.75 than those with a κ/λ ratio ≤0.25. More than one third of the kappa monoclonal LCs in urine were seen in specimens with κ/λ ratio of ≤1.65. It has already been noted and agreed that the initially proposed normal κ/λ ratio of 0.26 to 1.65 is not appropriate. In the latest iteration, Mayo Clinic recommended raising the upper limit of normal κ/λ ratio to 3.0 and iStopMM group recommended the upper limit to be 3.15, though they revised it further to a lower level [23-25]. More than 80% of the specimens with serum κ/λ ratio of > 3.0 or 3.15 have no evidence of a MG, hence using κ/λ ratio of >3.0 or >3.15 to diagnose LCMGUS would create a pseudo epidemic of kappa LCMGUS [19,20]. It warrants stressing that neither the Mayo Clinic nor the iStopMM group presented evidence of monoclonality in the specimens with the "abnormal" κ/λ ratios.

Unlike the concentration of intact immunoglobulins, there is no consensus on the level of monoclonal LCs required for a diagnosis of LCMGUS, LCSMM or LCMM. QUIET, FLC-Modified SIFE and Mass Spectrometry can provide an estimate of the concentration of monoclonal free LCs in serum, though none of these tests are in common use [27-33].

Singh G., Arch Clin Biomed Res 2025
DOI:10.26502/acbr.50170490

The following are the proposed criteria for diagnosis of LC lesions of MGUS, SMM and MM [12,34-36].

LCMGUS:

- Documentation of monoclonal LCs in serum and/or urine is essential. κ/λ ratio alone is inadequate for diagnosis. <10% plasma cells in bone marrow*, Lack of CRAB criteria
- Recommend monitoring renal function and level of monoclonal free LCs to assess the progress of disease

LCSMM:

- Monoclonal LCs in serum and/or urine. >10% plasma cells in bone marrow*. Lack of CRAB criteria
- Recommend monitoring renal function and level of monoclonal free LCs to assess the progress of disease. Involved LC concentration of >100 mg/L and ratio of involved to uninvolved LC of >100 has poor sensitivity of only 15.8% for identification of lesions likely to progress to multiple myeloma [4,8,36]. Multiple flaws in the study recommending this criterion have been identified, thus negating the validity of this criterion.

LCMM:

- Monoclonal LCs in serum and/or urine, >10% plasma cells in bone marrow and CRAB criteria

* Recommend strongly against bone marrow examination in LCMGUS and LCSMM unless there is progression of disease indicated by deterioration of renal function or levels of free monoclonal LCs or appearance of other CRAB criteria

Data from a previously published manuscript, are presented in Table 1, to highlight the infrequency with which isolated abnormal κ/λ ratios are associated with monoclonal LC in urine [19].

In 7 specimens with a κ/λ ratio <0.25, three of the 7, (42.9%) displayed free monoclonal light chain (FMLC) on UIFE. There were 45 specimens with κ/λ ratio from 0.26 to 0.75 and 12 of these 45, (26.7%) displayed a Lambda FMLC in urine. Of the 1688 specimens with κ/λ ratios from 0.75 to 352.79, two specimens (0.1%) displayed Lambda FMLC in urine. The κ/λ ratios for these two specimens were 1.56 and 2.28.

In the group of 1140 specimens with κ/λ ratio of ≤1.65, 16 specimens (1.4%) had Lambda FMLC in urine. Only one of 600 specimens with κ/λ ratio of ≥1.65 had urine containing Lambda FMLC.

The two specimens with Lambda FMLC in urine with κ/λ ratio > 0.75, both had polyclonal hypergammaglobulinemia. In the patient with κ/λ ratio of 1.56 the serum gamma globulin level was 2.42 g/dL, and the patient had nutritional deficiency neuropathy. The patient with κ/λ ratio of 2.28 had cirrhosis and sum of IgG, IgA and IgM equaled 2.2 gm/dL.

In brief, about 40% of specimens with a κ/λ ratio ≤0.25 had FMLC in urine. Lambda FMLC was very uncommon in the group with κ/λ ratio >0.75. Both patients in this rare group had polyclonal hypergammaglobulinemias that were kappa chain dominant hypergammaglobulinemias along with a monoclonal lambda light chain [9]. The polyclonal kappa free light chain concentrations far exceeded the concentrations of free monoclonal lambda light chains.

None of 335 specimens with κ/λ ratio ≤1.13 displayed Kappa FMLC in urine. In 806 specimens with κ/λ ratio ≥ 1.14 and ≤1.65 eight (1.0%) had Kappa FMLC on UIFE. Thus, in the 1140 specimens associated with κ/λ ratio ≤1.65, 8, (0.7%) displayed Kappa FMLC.

In 547 specimens with κ/λ ratio of 1.66 to 2.9, 13 (2.4%) had Kappa FMLC in urine. There were 53 specimens with κ/λ ratio of 3 to 353 and 10 of these (18.8%) displayed Kappa FMLC in urine. Six of seven specimens with κ/λ ratio ≥10 contained Kappa FMLC. The one negative specimen was from a patient with cirrhosis and renal failure. Both of

Table 1: UIFE results and serum κ/λ ratios. In 1740 specimens, results of UIFE and serum free light chain levels and κ/λ ratio were available. Other than the isolated presence of monoclonal light chain in urine, there was no evidence of a monoclonal lesion in these patients. The findings are explained below:

UIFE results from patients without evidence of MG, with κ/λ ratio, N=1740			
Total UIFE-0 with κ/λ ratio	**N=1740**	**Monoclonal Kappa N/%**	**Monoclonal Lambda N/%**
κ/λ ratio of ≤0.25	7	0/0	3/42.9
κ/λ ratio 0.26-0.75	45	0/0	12/26.7
κ/λ ratio of 0.26 to ≤1.65	1133	8/0.7	13/1.1
κ/λ ratio of 1.66 to 2.99	547	13/2.4	1/0.2
κ/λ ratio of >3 or >3.15 to 353	53	10/18.8	0
κ/λ ratio of 3 to 10	46	4/8.7	0
κ/λ ratio of 10 to 353	7	6/85.7	0

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DOI:10.26502/acbr.50170490

these pathologies can independently produce polyclonal hypergammaglobulinemia. Only four of the 46 (8.7%) specimens with κ/λ ratio ≥3.0 to <10 displayed Kappa FMLC in urine.

In brief, a κ/λ ratio of ≥10 was associated with FMLC in urine in 85.7% of the specimens None of the urine specimens with κ/λ ratio of ≤1.13 showed Kappa FMLC in urine. It warrants emphasis that > 80% of the urine specimens with a κ/λ ratio >3.0 or >3.15 did not display any FMLC and according to current criteria would be labeled, erroneously, as kappa MGUS and would account for a pseudo epidemic of kappa MGUS.

Myeloma defining conditions

The International Myeloma Working Group (IMWG) defined three categories of myeloma defining conditions for patients not meeting the usual criteria. These include (a) more than 60% plasma cells in bone marrow and (b) more than one bone lesion on MRI. Only the third criterion, based on SFLC levels and ratio, is relevant for this discussion. This criterion requires a SFLC of >100 mg/dL and a ratio of involved to uninvolved LC of >100. This measure appears to have been based on reference no 36. This LC-based criterion has a sensitivity of only 15.8% and the ROC curve (figure 1 of ref 36) is not meaningfully different from the diagonal [36]. In the ROC curve, the area under the curve is 0.55 with the diagonal being 0.5. A useful laboratory test is expected to have an area under the curve of >0.8. According to the authors, analysis of data provided a relevant ratio of involved to uninvolved LC of 91, however, the ratio was arbitrarily rounded up to 100, thus, the measure starts with a fudge factor of 10%. The authors stated that the kappa or lambda light chain designation of the lesions was based on κ/λ ratio. With specimens having a ratio <0.25 being designated as lambda and those with a ratio of >1.65 being labelled as kappa. They did not explain the status of specimens with ratio between 0.25 and 1.65. It is worth noting that about 60% of lambda chain associated SMM specimens have a normal κ/λ ratio and would thus have been excluded. [7] The authors did not describe the method used of measuring SFLCs. The methods cited as references have the lower limit of detection as 0.1 mg/dL. Thus, the values of 0.007 mg/dL for kappa and 0.04 mg/dL for lambda listed under "all patients" as the lower limit of the range of values could not possibly be correct. Their method lacks the sensitivity to measure such low values.

Additional issues of concern are noted below in the data presented in Table 1 of the relevant publication [36]. A part of Table 1 from the article is presented below [36]:

Patient characteristics at SMM diagnosis grouped according to FLC ratio ≥ 100 or < 100

Variables	*All patients*	*FLC ratio < 100*	*FLC ratio ≥ 100*	*P (95% CI)*
Median light chain concentration (mg/dl) Kappa	3.02 (0.007–761)	3.1	1.3	< 0.0005*
Lambda	1.26 (0.04–1715)	1.24	14.3	0.0001*

As has been observed by others, the background levels of kappa LC are more than twice the level of lambda LC, e.g., under *All patients*, the levels of kappa and lambda LC are 3.02 and 1.26 with a ratio of 2.4 [9,11]. Under the *FLC ratio <100* the kappa and lambda LC levels are 3.1 and 1.24 with a ratio of 2.5. This is meant to emphasize that in lambda lesions, the levels of lambda free light chain would have to be 2.4 to 2.5 times higher than the levels of kappa light chains to reach a ratio of involved to uninvolved light chain of 100. i.e., For a kappa lesion the level of SFLC would need to be only >126 to reach a ratio of 100 for involved to uninvolved LC levels. For lambda lesions the level of lambda free LC would have to be >302 to have a ratio of involved to uninvolved SFLC of >100. The figures under the heading, "*FLC ratio ≥ 100*" of 1.3 and 14.3 are implausible. The level of kappa median concentration, as listed at 1.3mg/dL, must be a misprint. However, even the level for lambda chain concentration of 14.3mg/dL under *FLC ratio>100* does not add up. How could the median level of lambda light chains be 14.3 for the group with a FLC ratio >100? As noted above, for the lambda lesions to reach a FLC ratio of 100 the levels of lambda LC would need to be >302. Thus, a median level of 14.3 for the group with FLC ratio >100 does not compute. Even if my assumption of using the kappa light chain level of 3.02 as the uninvolved light chain level is incorrect, for a ratio of 100 the level of uninvolved kappa light chain would have to be < 0.14. This level is below the limit of detection of the commercial assay. Given that the level of 14.3 is the median, it means that half of the specimens with ratio of 100 had levels lower than 14.3, further questioning the validity of the data. The designation of myeloma defining condition based on SFLC level and ratio is challenged here.

To complicate this issue further it is mentioned that the levels of kappa free LCs in patients with MG are 4-5-times higher than levels of involved lambda LC [8,9,11,26]. Levels of uninvolved kappa LC are twice or more as high as the levels of uninvolved lambda LCs [8,9,11,26]. Thus, LC concentration-based criterion for myeloma defining condition may have greater salience if the levels and ratios were LC type specific.

Stringent complete response

Response to treatment in myeloma is measured by agreed upon criteria [37,38]. Complete response is characterized

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DOI:10.26502/acbr.50170490

as: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow. Stringent complete response is complete response as defined above plus normal κ/λ ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

The requirement for normal κ/λ ratio is contested here. Following autologous stem cell transplantation in 84 patients with IgG lambda or IgA lambda MM, 15.5% of the patients displayed a kappa dominant abnormal κ/λ ratio in contrast to 13% displaying lambda dominant abnormal κ/λ ratio [10,11]. The 15.5% kappa dominant abnormal κ/λ ratios are obviously false positives and would interfere with interpretation of stringent complete response. The situation would be even worse for IgG kappa and IgA kappa MM lesions. The minimal false positive rate for abnormal κ/λ ratio would be 15.5% and likely much higher, as the 15.5% false positive kappa dominant κ/λ ratio occurred in the face of lambda chain associated lesion and had to overcome the expected high levels of free monoclonal lambda LCs. Thus, it is submitted that requiring a normal κ/λ ratio for stringent complete response is not supportable.

Light Chain escape

An implication of the recognition of LCPMM is related to the concept of LC escape. It has been proposed that some intact immunoglobulin MM lesions, recur, following treatment, as LCMM and the phenomenon has been referred to as LC escape [39]. However, in examining more than a thousand MM cases, no case of "LC escape" was observed (unpublished finding) that could not be explained by earlier detection of monoclonal LCs before intact MIg could be detected on relapse of MM in cases of LCPMM [40]. Thus, if an LC escape occurs, it must be exceeding rare [4,7,8]. Monitoring by measuring total serum free LC is inadequate as the assay is incapable of distinguishing between polyclonal and monoclonal LCs. If it could be demonstrated that the recurrent LC lesion has a different clonotype than the original MIg, that would strengthen the concept of LC escape.

Screening for MGUS is not only futile but harmful.

Even if strict criteria are used requiring demonstration of MIgs, and not just an abnormal κ/λ ratio, the logic of screening for an entity that is not treatable, nor transmissible is questionable. The outcomes in incidentally detected vs, screening detected MGUS are not different [41], A diagnosis of MGUS generates as much mental anguish and trauma as a diagnosis of MM [42]. There is a high rate of disappearance of LCMGUS. [21] Screening for MGUS generates only harm but there is no benefit [42,43].

Efforts are underway to distinguish high risk MGUS from indolent MGUS. One entity that may need to be considered is the sub-group of LC predominant MGUS. In the absence of an effective treatment, being able to identify high risk MGUS cases would not provide any benefit [44,45].

Conundrum of screening and early treatment

The current paradigm in cancer is to screen for early diagnosis and early treatment. While this philosophy has shown positive results in uterine carcinoma, Colo-rectal carcinoma, skin cancers and some lung cancers, there is controversy about improvement in results in other instances, e.g., breast cancer, and prostate cancer improvements being due to early detection vs. improvement in chemotherapeutics [46-51]. A similar issue of screening for early detection of recurrent malignancy has been shown to be without benefit but causes psychological and financial harm [52]. The issue of early diagnosis in MM is complicated by the fact that the disease has systemic pathology at the outset. There are no controlled trials for screening and early treatment of MM. A retrospective, observational investigation did not support a role for screening and early treatment of MM [53]. Treating patients with SMM has been recommended as it improved progression free survival. However, data showing improved overall survival is lacking [54]. Even in the case of MM, treatment with routinely used ASCT has not been shown, in randomized controlled trials, to improve overall survival [55]. The survival rate for MM has improved steadily over the past few decades, likely due to better drugs and not early diagnosis nor ASCT [56].

LC Predominant Monoclonal Gammopathic Disorders

As stated earlier, in MG disorders, free kappa LCs occur at 4-5 times greater average concentration than free lambda LCs [8,9,11,26]. A small but noticeable number of lambda chain associated MM lesions never display an abnormal κ/λ ratio due to inadequate production of excess free LCs [4,7,8]. Analysis of free LCs in MG disorders revealed that there are two populations that can be differentiated based on the concentration of free LCs [57-59]. The free LC concentration in mg/dL divided by the concentration of intact MIg in g/dL provided the best parameter for differentiation of high free LC producing lesions from the low producers. For kappa LC associated MM lesions the change point is 67 mg of free LC/dL per g of MIg/dL, and for lambda LC associated MM the corresponding Figure is 43.5 [57-59]. The corresponding values for the change point for MGUS and SMM for kappa chain associated lesions are 25.7 and 47.1 and for lambda chain associated lesions the corresponding values are 25.7 and 6.9.

LCPMM constitute about 18% of the total MM lesions and have significantly higher rates of renal failure, greater need for dialysis and correspondingly lower eGFR, and. a 2-year shorter survival [59]. As there are no effective treatments

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DOI:10.26502/acbr.50170490

specifically designed to lower the level of free monoclonal LCs and to prevent renal damage, it would be prudent to assess LCPMM lesions separately in any prospective clinical trials [8].

LCMM and free LC levels

The highest level of free LCs in patients with LCMM were subjected to change point analysis and the change point was 455 mg/dL. The lesions associated with higher levels had more than two years shorter survival than the lesions with levels lower than 455 mg/dL [59].

Assays for Free Monoclonal Light Chains

Reliance on the SFLC assay, despite its shortcomings, has persisted, in part, due to lack of a simple, reliable assay for quantification of free monoclonal LCs in body fluids, especially serum.

The following methods have been tried with varying success [27-33].

QUIET: Quantification by Ultrafiltration and Immunofixation Electrophoresis Testing method for serum free monoclonal LCs while feasible is not a method simple enough for adoption by the usual clinical laboratories. The method has a sensitivity of about 1.0 mg/dL and is specific for monoclonal LCs [27].

FLC-Modified SIFE: The conventional serum immunofixation electrophoresis (SIFE) was modified in two major respects. The whole serum, i.e., undiluted sample, was used as the inoculum rather than diluted serum as is usual case for SIFE. Antisera to free LCs were used in the immunofixation step. Helena Laboratories modified the equipment and procedure to the extent that the procedure now constitutes walk-away automation after loading the various items [32]. The method has a sensitivity of 1-2 mg/dL of free monoclonal LCs, similar to the sensitivity of mass spectrometry [28,29,33]. The sensitivity can be enhanced by duplicate or triplicate application of undiluted serum. Additional steps to increase sensitivity by enzymatic amplification are being explored [29], One of the Mass Spectrometry methods requires 30 repetitions of one step and still has a sensitivity of only 1-3 mg/dL [32].

MASS-FIX-MALDI: This patented method, used nanobody coated beads to extract immunoglobulins. The eluted material was subjected to MALDI-TOF analysis [29]. When serum specimens were tested in parallel between MASS-FIX MALDI and FLC-Modified SIFE, MASS-FIX MALDI missed monoclonal free LCs in more than half of the specimens that were positive by FLC Modified SIFE, in consonance with other laboratory and clinical data [28]. This assay has been withdrawn from the market.

Mass Spectrometry: Various versions of mass spectrometric analysis have been used successfully to quantify monoclonal free LCs in serum. The various mass spectrometry methods have a sensitivity of about 1-3 mg/dL and the sensitivity is comparable to the FLC-Modified SIFE [29-31].

Monoclonal free light chains in urine

Total free LCs can be measured in urine, however, more than one investigator concluded that such measurements do not add value [3,4]. Testing for monoclonal free LCs is urine is an important test as detection of monoclonal LCs in urine may be the only objective evidence of a MG. The following items in testing urine for monoclonal LCs are cogent:

A. A 24-hour urine, while desirable, is not essential. Random urine specimens are adequate for qualitative tests. [59]. First morning urine being naturally more concentrated is preferable

B. Concentrated urine specimens: A 100-fold concentration of urine is recommended for electrophoretic analysis, however, in patients with proteinuria a 100-fold concentration is not practical [61]. A 25-fold concentration is adequate for detection of monoclonal LCs [62]

C. Concentration by membrane filtration is the preferred method. Concentration by evaporation distorts the electrophoretic pattern due to high salt content [62]

D. Statements by "experts" notwithstanding, SFLC measurement is not a substitute for urine immunofixation electrophoresis (UIFE) [63-65]. A normal LC ratio does not exclude MG, and an abnormal ratio is not diagnostic of MG [4,7-9]. Detection of monoclonal LCs by UIFE is diagnostic of MG [19,20]

E. Recommending bone marrow examination, over UIFE, because "Urine examination is inconvenient and unreliable" is at best inappropriate [24]

The following methods have been used for detection of monoclonal LCs in urine: .

Conventional UIFE: Concentrated urine is subjected to immunofixation electrophoresis using conventional antisera to IgG, IgA, IgM, kappa and lambda LCs [66]. The anti LC antisera in conventional UIFE are not specific for free LCs and react with both free LCs and those bound to heavy chains. The reactivity of such sera to dimeric or polymeric LCs is variable [67]. Monoclonal free LCs usually migrate anodal to intact immunoglobulins; however, free monoclonal LCs may co-migrate with intact MIgs or even cathodal to it [67]. Monoclonal free LCs co-migrating with intact MIgs make it difficult to detect free monoclonal LCs in conventional UIFE [67].

MASS-FIX MALDI: A method similar to the MASS-FIX MALDI for serum was applied to urine analysis. However,

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DOI:10.26502/acbr.50170490

this method displayed lower sensitivity than conventional UIFE [68].

Free LC UIFE (FLC UIFE): This method is similar to conventional UIFE, except that antisera specific to free LCs were used rather than conventional anti-LC antisera [67]. This method improved the detection rate of monoclonal free LCs in urine by about 18% over that of conventional UIFE. The improved rate was due to better detection of free LCs co-migrating with intact MIgs and better reactivity with free LCs in general and dimeric LCs in particular.

Free LCs in other body fluids: Free LCs especially elevation of kappa free LCs in CSF are being promoted for the diagnosis of inflammatory conditions, e.g., multiple sclerosis [69,70]. However, this may not be specific to multiple sclerosis or CNS but the general tendency for kappa dominance in inflammatory conditions.

In summary

1. κ/λ ratio is not suitable for diagnosing or excluding MG. Even the revised upper limit of κ/λ ratio at 3.0 or 3.15 has more than 80% false positive results. An orthogonal assay capable of establishing monoclonality ought to be used before labeling a lesion as monoclonal
2. Urine examination, especially FLC UIFE, is essential for proper investigation of MG
3. FLC-Modified SIFE has a sensitivity similar to that of Mass Spectrometry in detecting monoclonal free LCs. The method warrants use in routine evaluation and monitoring of MG disorders and particularly in assessing minimal residual disease
4. Screening for MGUS is contraindicated. Screening for "early" diagnosis provides no benefit but induces unwarranted mental anguish and trauma. MGUS is not treatable, nor transmissible, nor a public health burden. About half of LCMGUS regress spontaneously. There is harm from screening, but no benefit. Using κ/λ ratio, without documenting monoclonality to diagnose MGUS is erroneous
5. Diagnosing myeloma defining condition by SFLC concentration and ratio of involved to uninvolved LC concentration is a deficient measure. Redefining the parameter using monoclonal LC type specific data is recommended. The approach taken for diagnosing light chain predominant MM is recommended for analysis of SMM lesions
6. Any future controlled trials of treatment of MM should segregate patients into LCPMM and conventional lesions. LCPMM has a two-year shorter survival than conventional lesions
7. Requiring a normal κ/λ ratio for diagnosis of stringent complete response is not supported by data
8. LC escape probably does not exist
9. Clinical significance of LC predominant MGUS and SMM remains to be ascertained

Conflict of interest: I serve as a consultant to Helena Laboratories, Sebia Inc, Diazyme Laboratories, Warm Springs GA medical center; and have applied for a patent for FLC-Modified SIFE method.

Funding: There is no external funding source.

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