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ORAL ABSTRACTS

654.MGUS, AMYLOIDOSIS AND OTHER NON-MYELOMA PLASMA CELL DYSCRASIAS: CLINICAL AND EPIDEMIOLOGICAL

Revised Definition of Free Light Chains in Serum and Light Chain Monoclonal Gammopathy of Undetermined Significance: Results of the Istopmm Study

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Background: Serum free light chain (FLC) measurement, consisting of serum free kappa, serum free lambda, and a calculated FLC ratio (kappa/lambda), plays a pivotal role in the diagnosis, risk stratification and management of plasma cell disorders. Light chain monoclonal gammopathy of undetermined significance (LC-MGUS), is defined as abnormal FLC ratio with elevation of the involved FLC without evidence of heavy chain M protein or end-organ damage attributed to the plasma cell disorder. Several years ago, reference intervals for serum kappa (3.3-19.4 mg/L) and lambda (5.7-26.3 mg/L) FLC and FLC ratio (0.26-1.65) were defined in a small retrospective cohort (N = 282) of healthy individuals. Limitation of these reference intervals include inaccurate distributions among individuals with impaired kidney function. Recently, we addressed this matter in a large population-based study focusing on individuals with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m ^{2}, the results of which led to redefined reference intervals for patients with chronic kidney disease (Long et al, Blood Cancer J. 2022).

Here, using a large cohort (N=41,882) of screened individuals, we aimed to determine FLC reference intervals in individuals with normal kidney function (eGFR ≥ 60 mL/min/1.73m ^{2}).

Methods: Data were collected from the ongoing Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study, which focuses on population-based screening for MGUS. A total of 75,422 individuals aged ≥ 40 years (representing 51% of this age group in the Icelandic population) were screened for MGUS by serum protein electrophoresis, immunofixation, and serum FLC assay (Freelite®), and two-thirds of MGUS cases were randomized to active follow-up. Participants' eGFR was calculated using serum creatinine (CKD-EPI) closest to the time of screening. Participants with heavy chain M protein, known lymphoproliferative disorder, unknown eGFR or eGFR < 60 mL/min/1.73m ^{2}, were excluded. The 0.5 and 99.5 percentiles of kappa FLC, lambda FLC, and the FLC ratio distributions were assessed for the whole group, and subgroups of age, sex, and different levels of eGFR. A nonparametric bootstrapping method was used to calculate the 95% confidence intervals. Partitioning was determined based on the proportion of subgroups (age, sex and eGFR) outside the whole group reference interval.

Results: After application of the exclusion criteria, 41,882 participants were included for further analysis. The median (interquartile range, IQR) serum free kappa was 14.3 (11.6-17.8) mg/L, serum free lambda 14.2 (11.6-17.5) mg/L, and the FLC ratio was

1.02 (0.85-1.21). The median (IQR) age was 60 (52-68) years, eGFR 84 (74-94) mL/min/1.73 m ^{2}, and 43% were male. A strong correlation was found between age and serum kappa FLC ($\rho = 0.27$, $p < 0.001$), lambda FLC ($\rho = 0.14$, $p < 0.001$), and the FLC ratio ($\rho = 0.16$, $p < 0.001$). Use of standard reference intervals yielded abnormal results for 17.5%, 3.9%, and 4.5% of serum kappa, lambda, and FLC ratio determinations, respectively, and a prevalence of LC-MGUS of 2.0% (96% kappa and 4% lambda).

Based on these findings, we established new reference intervals for serum kappa and lambda FLC and FLC ratio, partitioned by age < 70 years and ≥ 70 years (Table). Utilizing the new reference intervals the crude prevalence of LC-MGUS was 0.3% (54% kappa and 46% lambda), yielding a relative decrease of 83%. Among the group of individuals diagnosed with LC-MGUS based on standard reference intervals who did not meet the diagnostic criteria using our revised reference intervals - none had progressed to a lymphoproliferative disorder after a median follow-up time of 42 months.

Conclusion: Based on prospective screening of more than 40,000 individuals and after 3.5 years of follow-up, we show that standard reference intervals for serum FLC and FLC ratio appear inaccurate for persons with preserved kidney function. We propose a revision of the reference intervals for serum FLC and FLC ratio, and a new definition of LC MGUS (Figure). Implementation of new reference intervals will decrease the rate of false positive diagnosis of LC-MGUS in individuals with preserved kidney function by more than 80%. This, in turn, will reduce the unnecessary psychological and financial burden driven by clinical evaluation and lifelong monitoring of these individuals.

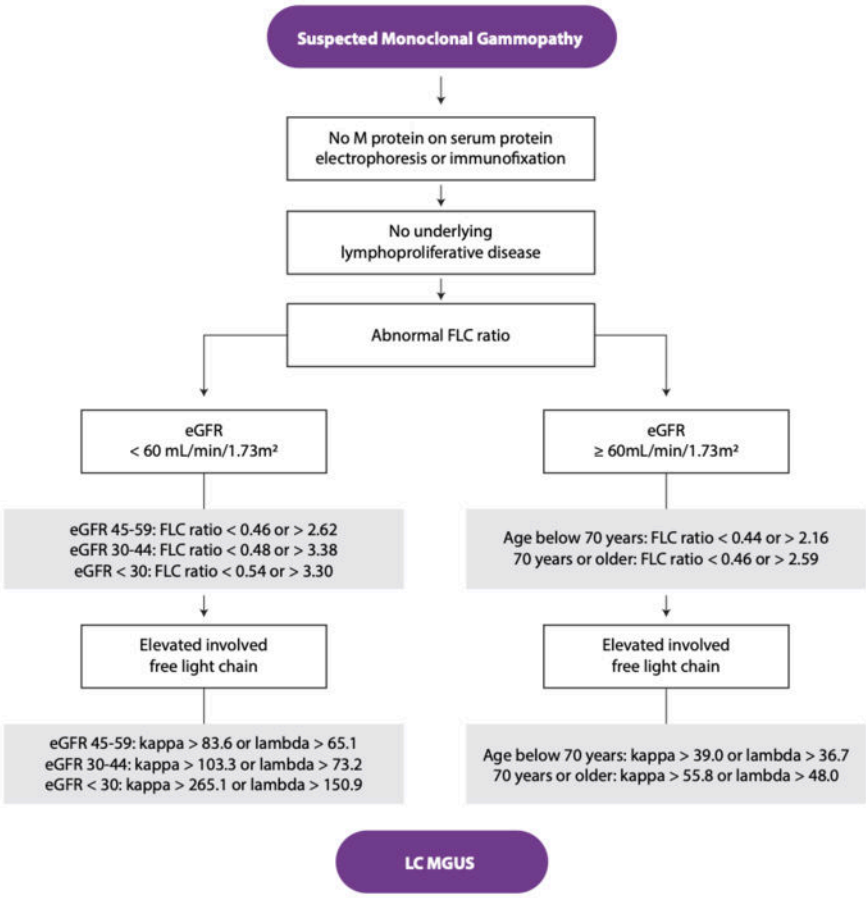
Disclosures Hultcrantz: *Amgen, Daiichi Sankyo, GlaxoSmithKline:* Research Funding; *Curio Science LLC, Intellisphere, Bristol Myer Squibb, GlaxoSmithKline:* Honoraria. **Harding:** *Bindingsite ltd.:* Current Employment, Membership on an entity's Board of Directors or advisory committees. **Landgren:** *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Adaptive:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Theradex:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Merck:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees. **Kristinsson:** *Celgene:* Research Funding; *Amgen:* Research Funding.

Table. Revised reference intervals for serum free kappa FLC, lambda FLC, and FLC ratio according to age

	New reference interval (0.5th to 99.5th percentile)		
	Kappa FLC (mg/L)	Lambda FLC (mg/L)	FLC ratio
Age < 70 years N=33,181	6.3–39.0	5.9–36.7	0.44–2.16
Age ≥ 70 years N=8,701	7.0–55.8	6.4–48.0	0.46–2.59

Standard reference intervals: Serum kappa FLC 3.3-19.4mg/L, lambda FLC 5.7-26.3mg/L, and FLC ratio 0.26-1.65. FLC, free light chain.

Figure. Revised definition of light chain monoclonal gammopathy of undetermined significance



All measurements of kappa and lambda FLC in mg/L. Involved FLC defined as high lambda with abnormally low FLC ratio and high kappa with elevated FLC ratio. LC-MGUS, light chain monoclonal gammopathy of undetermined significance; FLC, free light chain.

Figure 1

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