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Adopting the new iStopMM-based criteria for light-chain monoclonal gammopathy of undetermined significance: an ongoing debate

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Authors' disclosures

The authors declare that they have no conflicts of interest.

Contributions

D.S and I.A contributed to the study design. A.R.B and I.A supervised the study. A.R.B was responsible for statistical methodology. G.M and D.S were involved in data retrieval. D.S, A.R.B, I.A, Y.C and G.M participated in data analysis. D.S, A.R.B, I.A, Y.C, T.S, and G.M collectively contributed to writing the manuscript. All authors have read and approved the final version of the manuscript for submission.

Data sharing statement

The data that support the findings of this study are not publicly available.

The iStopMM (iS) project has recently proposed revised Free Light Chain (FLC) levels and criteria for diagnosing light-chain monoclonal gammopathy of undetermined significance (LC-MGUS). We investigated the prevalence of LC-MGUS, as well as the risk of progression to multiple myeloma (MM) in patients defined with LC-MGUS according to the international myeloma working group (IMWG) vs the iS criteria. We found that patients meeting the iStopMM criteria represented 8% of those meeting the IMWG criteria. Additionally, these patients exhibited a higher risk of progression to MM within 10 years: 7.7% vs 0.7% in patients who exclusively met the IMWG criteria, compared with 0.5% in patients without LC-MGUS ($p<0.001$). Our study validates the iS results on a large independent population, advocating for the adoption of the iS criteria for defining LC-MGUS.

LC-MGUS constitutes approximately 20% of all cases of MGUS.[1] This condition has the potential to progress to light-chain multiple myeloma (LC-MM),[2] and may also result in monoclonal gammopathy of renal significance (MGRS), potentially ending in renal failure.[3,4]

Timely detection of MGUS prior to MM diagnosis has been linked to decreased rates of end-organ damage and potentially, prolonged survival,[5–7] highlighting the importance of early and accurate diagnosis of MGUS including LC-MGUS.

Recent results from the iS study have cast doubt on the correctness of standard reference intervals for serum FLC level, particularly in individuals with impaired kidney function, proposing new reference intervals, and stricter criteria for diagnosing LC-MGUS.[8–10]

We investigated the prevalence of LC-MGUS and the risk of progression to MM and chronic kidney disease (CKD) in a real-world cohort of patients. The patients were defined according to the current IMWG definition[10] and the new iS criteria,[8] and were compared with patients who underwent a FLC test but were not defined as having LC-MGUS.

The current retrospective study (approved by Maccabi Healthcare Services [MHS] ethical committee) included patients registered in MHS, who underwent a FLC test for non-specific complains between 2007-2023, with no prior history of plasma cell dyscrasia or lymphoma.

Inclusion criteria were age ≥ 18 years, enrollment in MHS for ≥12 months before FLC testing (index date) and lack of monoclonal protein (M-protein) in serum protein electrophoresis (SPEP) and immunofixation (IFE) tests, performed within one year before/after initial MM-specific tests. Exclusion criteria were existence of end-organ damage

(IMWG definitions) within six months before/after the index date[10] and MM diagnosis within 6 months after first FLC test.

Patient characteristics and laboratory results at the index date were recorded from MHS laboratory. Immunoparesis was defined as the presence of a low level of at least one Ig. Free Light Chain Kappa (FLC-K), Lambda (FLC-L) levels, as well as the FLC ratio (FLC-R), were categorized and defined as normal versus abnormal according to the IMWG and the iS criteria, which proposed adjustments based on both age and estimated glomerular filtration (criteria are presented below Table1 ,providing patient characteristics).[8,10,11]

The definition of LC-MGUS relied on elevated levels of the appropriate LC and an abnormal FLC-R,[8,10,11] along with the absence of M-protein detection in SPEP or IFE analyses and the lack of MM-related organ damage prior to the first FLC test. Follow-up (FU) extended up to 10 years from the index test, with the first date of official MM diagnosis considered as an event.

Progression to MM was based on the appearance of this diagnosis in the medical records (ICD9 203.0) and the initiation of an anti-MM therapy. The development of renal failure was based on the appearance of a new diagnosis of CKD in patient's medical records,[12] reported ≥6 months after the index date (excluding patients who simultaneously progressed to MM).

Descriptive statistics (absolute numbers, percentages for categorical variables, and median and interquartile range (IQR) for continuous variables) were performed. Chi-square test and Mann-Whitney test were used for comparisons of proportions and medians across cohorts, respectively. Kaplan-Meier was used to present the cumulative diagnosis of MM. Univariate and multivariate Cox proportional hazards regression models were used to obtain hazard ratios and adjusted hazard ratios, respectively, for 10-year MM and CKD diagnoses.

Among the 11,239 patients who underwent a FLC test, 4,302 (38.3%) had normal FLC (control) and 1,406 (12%) met the IMWG criteria for LC-MGUS. A total of 5,531 patients were excluded (**Figure1S**). In total, 104 (7.4%) patients of those who met the IMWG criteria had also fulfilled the iS criteria, representing a decrease of 92% in LC-MGUS diagnosis. **Table1** presents the characteristics of non-MGUS patients and patients defined with LC-MGUS according to the IMWG vs the iS criteria. Patients who fulfilled the iS criteria were significantly younger ($p<0.001$) and had lower rates of hypertension, osteoporosis, and non-

insulin dependent diabetes (NIDDM). There was no significant difference in the incidence of immunoparesis between patients diagnosed with LC-MGUS by the iS vs the IMWG criteria.

The median FU period of our entire cohort was 62 (IQR 39-91) months, with no statistically significant differences in FU periods between the cohorts (**Table1**). In total, 17 (1.2%) patients who met the IMWG criteria progressed to MM. Their median age was 69 years, with a median eGFR of 68mL/min/1.73m^2, and 14 (82%) with elevated FLC-K levels. The estimated 10-year progression rate to MM was significantly higher in patients defined by iS criteria, with 8 (7.7%) individuals progressing to MM, compared to 9 (0.7%) in patients that exclusively met the IMWG criteria but not the iS criteria ($p<0.001$). In the non-LC-MGUS cohort, 23 (0.5%) individuals progressed to MM, a rate similar to that of patients who met only the IMWG criteria but not the iS criteria.

The development of CKD in patients that were not concomitantly diagnosed with MM was not significantly different between the study cohorts, with 5 (5.2%) patients officially diagnosed with CKD in the iS cohort, compared to 55 (4.2%) in the IMWG cohort and 169 (3.9%) in the control cohort ($p=0.7$).

Multivariate Cox regression analyses (**Table2**), based on univariate analysis (**Table1S**), confirmed that patients meeting the iS criteria had a significantly increased risk of progressing to MM compared to the control cohort (HR=15.4, $p<0.001$). In contrast, the risk of progression in patients defined with LC-MGUS according to the IMWG criteria alone was not significantly increased compared with that reported in the control cohort, with an HR of 1.44 ($p=0.4$). In line with that, risk of progression was significantly greater in the iS vs patients who met only the IMWG criteria (HR 11.1, $p<0.001$). IgA immunoparesis was also found to be associated with an increased risk of progression (HR 3.81, $p=0.026$).

The multivariate Cox regression analysis, as presented in **Table3** and guided by the findings of the univariate analysis (**Table2S**), identified IgG immunoparesis (HR 2.17, $p=0.004$) and hypertension (HR 1.41, $p=0.002$) to be associated with an increased likelihood of developing isolated CKD. However, patients meeting either the iS or the IMWG criteria did not exhibit a statistically significant elevation in the risk of CKD progression compared to the control cohort (HR 1.43, $p=0.3$ and HR 1.18, $p=0.2$ respectively). Moreover, there was no statistically significant difference observed between patients fulfilling the iS criteria and those meeting exclusively the IMWG LC-MGUS criteria in terms of CKD development (HR 1.41, $p=0.3$).

Analyzing a substantial cohort of patients who underwent MM-related tests for non-specific complaints, we observed that 92% of those meeting the IMWG criteria for LC-MGUS did not meet the iS criteria. These findings are consistent with the results reported by the iS prospective study, indicating an 83% decrease in the diagnosis of LC-MGUS when employing the proposed reference intervals. In agreement with these outcomes, the risk of developing MM was found to be significantly higher in the iS cohort compared to the IMWG cohort and the control cohort, which exhibited a similar risk to the IMWG cohort.

Despite the increased specificity of the iS criteria in identifying patients at higher risk for MM, it is noteworthy that these patients did not exhibit a significantly increased risk of developing CKD. This finding could be influenced by several factors, including the definitions used to characterize renal disease, which may not fully capture the range of kidney disorders associated with LC-MGUS. Additionally, differences in baseline characteristics between the IMWG and iS cohorts, particularly the younger age and lower rate of hypertension and NIDDM in the iS-defined cohort may have contributed to these findings.

Our study, while providing valuable insights, also has several limitations that should be acknowledged. The retrospective nature of the study design may introduce selection bias in selecting patients to undergo FLC testing. The reliance on medical records for data collection may lead to incomplete or inconsistent documentation. Moreover, the definitions used for LC-MGUS and CKD might not encompass all relevant cases, potentially affecting the generalizability of our findings.

Despite these limitations, this comprehensive real-world study, being the first to validate the iS criteria for LC-MGUS, underscores the necessity for further validation and the potential integration into clinical practice. The adoption of these stricter criteria would help alleviate the burden on healthcare resources and improve patient outcomes.

Future studies, validating these findings in larger, diverse populations are warranted.

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Table 1.Patient characteristics

Variable	**Control cohort** N=4302	***IMWG definition** N=1302	***iStopMM definition** N=104	**P-value**[1]
Age at index (years), median(IQR)	65 (54, 72)	70 (61, 76)	64 (59, 70)	<0.001
Age group, (years), n(%)				<0.001
Age < 70	2,845 (66)	648 (50)	74 (71)	
Age >= 70	1,457 (34)	654 (50)	30 (29)	
Sex, n(%)				0.8
Female	2,332 (54)	641 (49)	50 (48)	
Male	1,970 (46)	661 (51)	54 (52)	
Orthopedic consultation, n(%)	427 (9.9)	127 (9.75)	10 (9.6)	0.98
FLC-R result, median(IQR)	1.21 (1.02, 1.43)	1.88 (1.76, 2.09)	2.76 (2.26, 3.90)	<0.001
Immunoparesis, n(%)				0.4
No immunoparesis	3,001 (89)	980 (89)	83 (86)	
One chain immunoparesis	340 (10)	110 (10.0)	12 (12)	
Two chains immunoparesis	38 (1.1)	14 (1.3)	2 (2.1)	
IgA immunoparesis, n(%)	95 (2.3)	20 (1.6)	3 (3.0)	0.2
IgG immunoparesis, n(%)	95 (2.8)	10 (0.9)	1 (1.0)	0.6
IgM immunoparesis, n(%)	334 (8.5)	122 (10.0)	12 (12)	0.5
Kappa dominant, n(%)	0 (0)	1,078 (83)	84 (81)	0.6
Lambda dominant, n(%)	0 (0)	224 (17)	20 (19)	0.6
Hypertension, n(%)	2,284 (53)	841 (65)	55 (53)	0.017
Osteoporosis, n(%)	1,073 (25)	389 (30)	19 (18)	0.012
Diabetes, n(%)	1,115 (26)	477 (37)	24 (23)	0.005
eGFR at index, n(%)				<0.001
eGFR > 60	3,459 (80)	857 (66)	90 (87)	
45<eGFR<60	516 (12)	241 (19)	9 (8.7)	
30<eGFR<45	276 (6.4)	172 (13)	4 (3.8)	
0<eGFR<30	51 (1.2)	32 (2.5)	1 (1.0)	
Follow-up time (months), median(IQR)	62 (39, 91)	64 (36, 76)	66 (39, 75)	0.8

[1]P-value refers to the comparison of IMWG and iStopMM groups.

eGFR, Estimated Glomerular Filtration Rate; FLC-R, Free Light Chain Ratio; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IMWG, International Myeloma Working Group

FLC criteria	*IMWG definition	*iStopMM definition
FLC-R definition, mg/L	0.26–1.65	eGFR≥60 and age<70 years: <0.44 or >2.16; eGFR≥60 and age≥70 years:<0.46 or >2.59; eGFR 45–59:<0.46 or >2.62; eGFR 30–44:<0.48 or >3.38; eGFR<30:<0.54 or >3.3;
FLC-K definition, mg/L	3.3–19.4	eGFR≥60 and age<70 years: >39; eGFR≥60 and age≥70 years: >55.8; eGFR 45–59: >83.6; eGFR 30–44: >103.3; eGFR<30:> 265.1
FLC-L definition, mg/L	5.7–26.3	eGFR≥60 and age<70 years: >36.7; eGFR≥60 and age≥70 years: >48.0; eGFR 45–59: >65.1; eGFR 30–44: >73.2; eGFR<30: >150.9

Table 2. Multi-variate analysis for factors associated with progression to Multiple Myeloma

Characteristic	HR[1]	95% CI[1]	p-value
Study cohorts			
Control cohort	—	—	
IMWG definition	1.44	0.66, 3.13	0.4
iStopMM definition	15.4	6.87, 34.6	<0.001
IgA immunoparesis	3.81	1.17, 12.4	0.026

[1]HR = Hazard Ratio, CI = Confidence Interval

IgA, Immunoglobulin A; IMWG, International Myeloma Working Group

Table 3. Multivariate analysis for factors associated with progression of chronic kidney disease

Characteristic	HR[1]	95% CI[1]	p-value
Study cohort			
Control cohort	—	—	
IMWG definition	1.18	0.90, 1.53	0.2
iStopMM definition	1.43	0.70, 2.89	0.3
Hypertension	1.41	1.13, 1.76	0.002
IgG immunoparesis	2.17	1.29, 3.64	0.004

[1]HR = Hazard Ratio, CI = Confidence Interval

IgG, Immunoglobulin G; IMWG, International Myeloma Working Group

Supplementary data

Table 1S.Univariate analysis for factors associated with progression to Multiple Myeloma

Characteristic	N	HR[1]	95% CI[1]	p-value
Study cohort	5,708			
Control cohort		—	—	
IMWG definition		1.42	0.66, 3.09	0.4
iStopMM definition		15.6	6.96, 35.0	<0.001
Age > 70	5,708	2.83	1.50, 5.34	0.001
Sex	5,708			
Female		—	—	
Male		0.74	0.39, 1.39	0.4
Kappa dominant	5,708	2.25	1.17, 4.33	0.015
Lambda dominant	5,708	7.26	1.00, 52.3	0.05
Immunoparesis	4,580			
No immunoparesis		—	—	
One chain immunoparesis		1.25	0.44, 3.55	0.7
Two chains immunoparesis		2.78	0.38, 20.4	0.3
IgG immunoparesis	4,646	2.66	0.64, 11.1	0.2
IgA immunoparesis	5,424	3.73	1.15, 12.1	0.028
IgM immunoparesis	5,268	0.87	0.27, 2.82	0.8
Osteoporosis	5,708	1.77	0.93, 3.36	0.080

[1]HR = Hazard Ratio, CI = Confidence Interval

IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IMWG, International Myeloma Working Group

Table 2S. Univariate analysis for factors associated with progression of chronic kidney disease

Characteristic	N	HR[1]	95% CI[1]	p-value
Study cohort	5,668			
Control cohort		—	—	
IMWG definition		1.23	0.96, 1.57	0.10
iStopMM definition		1.65	0.88, 3.09	0.12
Age > 70 (years)	5,668	1.91	1.57, 2.32	<0.001
Sex	5,668			
Female		—	—	
Male		1.23	1.01, 1.49	0.037
Kappa dominant	5,668	1.44	1.13, 1.83	0.003
Lambda dominant	5,668	0.37	0.14, 1.28	0.46
Immunoparesis	4,546			
No immunoparesis		—	—	
One chain immunoparesis		1.47	1.06, 2.02	0.019
Two chains immunoparesis		1.66	0.74, 3.72	0.2
IgG immunoparesis	4,611	2.02	1.20, 3.38	0.008
IgA immunoparesis	5,384	1.78	1.04, 3.03	0.035
IgM immunoparesis	5,229	1.49	1.09, 2.02	0.011
Hypertension	5,668	1.29	1.05, 1.57	0.014
Diabetes	5,668	1.21	0.98, 1.48	0.073

[1]HR = Hazard Ratio, CI = Confidence Interval

IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IMWG, International Myeloma Working Group

Figure1S. Cohort of patients included in the study.