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

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) *versus* 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% *versus* 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 1 year before/after initial MM-specific tests. Exclusion criteria were existence of end-organ damage (IMWG definitions) within 6 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 by the MHS laboratory (Table 1 A). Immunoparesis was defined as the presence of a low level of at least one immunoglobulin (Ig). Free light-chain κ (FLC-K), λ (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 in Table 1B, 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. χ^2 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 (HR) 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 (*Online Supplementary Figure S1*). 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. Table 1A presents the characteristics of non-MGUS patients and patients defined with LC-MGUS according to the IMWG *versus* 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 *versus* 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 (Table 1A). 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 68 mL/min/1.73 m², 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 eight (7.7%) individuals progressing to MM, compared to nine (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%)

Table 1A. Patient characteristics.

Variable	Control cohort N=4302	*IMWG definition N=1302	*iStopMM definition N=104	*P*[1]
Age in years at index, median (IQR)	65 (54-72)	70 (61-76)	64 (59-70)	<0.001
Age group in years, N (%)				<0.001
<70	2,845 (66)	648 (50)	74 (71)	-
>=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-chain 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
κ dominant, N (%)	0 (0)	1,078 (83)	84 (81)	0.6
λ 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 in months, median (IQR)	62 (39-91)	64 (36-76)	66 (39-75)	0.8

Table 1B. Free light-chain criteria.

FLC criteria	*IMWG definition	*iStopMM definition
FLC-R definition	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

[1]*P* value refers to the comparison of IMWG and iStopMM groups. IQR: interquartile range; eGFR: estimated glomerular filtration rate; FLC-R: free light-chain ratio; Ig: immunoglobulin; FLC-K: free light-chain κ; FLC-L: free light-chain λ; IMWG: International Myeloma Working Group. *Criteria for the IMWG and IStopMM definition are stated in Table 1B.

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 five (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 (Table 2), based on univariate analysis (*Online Supplementary Table S1*), 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 *versus* 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 Table 3 and guided by the findings of the univariate analysis (*Online Supplementary Table 2S*), 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

Table 2. Multivariate analysis for factors associated with progression to multiple myeloma.

Characteristic	HR	95% CI	*P*
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

HR: hazard ratio; CI: confidence interval; Ig: immunoglobulin; IMWG: International Myeloma Working Group.

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

Characteristic	HR	95% CI	*P*
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

HR: hazard ratio; CI: confidence interval; Ig: immunoglobulin; IMWG: International Myeloma Working Group.

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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Contributions
DS and IA contributed to the study design. ARB and IA supervised the study. ARB was responsible for statistical methodology. GM and DS were involved in data retrieval. DS, ARB, IA, YC and GM participated in data analysis. DS, ARB, IA, YC, TS and GM collectively contributed to writing the manuscript. All authors have read and approved the final version of the manuscript for submission.

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