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Clinical usefulness of serum free light chains measurement in patients with multiple myeloma: comparative analysis of two different tests*

Przydatność kliniczna oznaczania stężenia wolnych łańcuchów lekkich u pacjentów ze szpiczakiem plazmocytowym: analiza porównawcza dwóch różnych testów

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: There are two commercially available tests for measurement of serum free light chains (sFLC) in multiple myeloma (MM) patients – Freelite and N Latex FLC. The aim of this study was to perform an assessment and direct comparison of the usefulness of the methods in routine clinical practice.

Methods: 40 refractory/relapsed MM patients underwent routine disease activity assessment studies, along with sFLC analysis using both assays. Correlation and concordance between the tests and sensitivity of studied methods of sFLC assessment were established. Special attention was focused on sFLC results in patients finally evaluated after completing the treatment.

Results: A weak correlation for the measurement of both κ [Passing–Bablok slope (PB) = 0.7681] and λ chains [(PB) = 1.542] was found. Using Bland–Altman plots, a bias of 0.0467 (κ) and -0.2133 (λ) between the measurements was documented. The concordance coefficient equaled 0.87 for κ, 0.62 for λ and 0.52 for κ/λ ratio. Ten patients had an abnormal Freelite assay κ/λ ratio and normal N Latex FLC κ/λ ratio. Three of these patients had negative serum protein electrophoresis results and fulfilled diagnostic criteria of stringent complete remission (sCR) according to N Latex FLC (but not according to Freelite). When the κ/λ ratio obtained by both methods was compared to patients' serum/urine protein electrophoresis and immunofixation results, sensitivity of Freelite and N Latex FLC was established to be 62.5% and 41%, respectively.

Conclusions: There was no strong correlation or concordance between the two assays, and the sensitivity in terms of sFLC detection was different. This may cause problems when diagnosis of sCR is considered.

Key words: **serum free light chains • multiple myeloma • Freelite • N Latex FLC • comparison**

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Introduction

Serum free light chain (sFLC) assessment has become a very important tool in clinical evaluation of multiple myeloma (MM) patients. Due to its sensitivity being higher than that of serum protein electrophoresis (SPEP), the assay has proven efficiency especially for light chain disease (LCD), oligo-secretory and non-secretory forms of MM – malignancies with low serum concentrations of monoclonal protein [1]. The production of monoclonal FLC is also characteristic for the majority of patients with symptomatic MM. For these reasons sFLC measurement was included in the International Myeloma Working Group (IMWG) guidelines as a recommended assay for diagnosis, prognosis and response assessment in different monoclonal gammopathies, from MGUS (Monoclonal Gammopathy of Undetermined Significance), to symptomatic MM [4]. The sFLC test's importance was recently highlighted by introduction of a new definition of symptomatic disease proposed by the IMWG. According to it, the sFLC ratio [involved FLC (iFLC)/uninvolved FLC (uFLC)] over 100 with concentration of iFLC higher than 100 mg/l is sufficient to diagnose MM and initiate cytotoxic therapy [16]. The evaluation of sFLC is also important in determining patients' response to treatment [6]. According to IMWG criteria [5], patients achieving complete remission (CR) who have a κ/λ ratio within the normal range and absence of clonal plasma cells in bone marrow, confirmed by immunohistochemistry or by low-sensitivity multiparametric flow cytometry [17], can be assigned to the stringent CR (sCR) group, with more favorable prognosis [9].

At the moment there are two commercial tests for sFLC measurement available on the market. The original assay, recommended by the guidelines is Freelite (The Binding Site Ltd, Birmingham, UK) [2]. The method has been used since 2001 and has been investigated in many studies ever since. The second, introduced in 2011, is N Latex FLC (Siemens, Germany) [18]. The main difference between them concerns the type of antisera used for binding FLC. Freelite uses polyclonal antibodies, whereas N Latex FLC uses a mixture of monoclonal antibodies. It implies uncertainty about comparability of the two assays. Lately, various studies addressing this issue have been published [3,7,10,13]. Their results are not entirely conclusive, and there is currently no agreement to use the assays interchangeably.

The aim of this study was to assess and compare both tests' usefulness in multiple myeloma patients treated with new drugs due to the active disease. Special attention was paid to the results of both tests in patients fulfilling other criteria of sCR.

Materials and Methods

Patient samples

Blood samples were taken from 40 randomly chosen patients with refractory/relapsed MM treated in the Department of Hematology and Bone Marrow Transplantation of the University Hospital of Lord's Transfiguration. Disease activity assessment was based on standard procedures including SPEP, urine protein electrophoresis (UPEP) and immunofixation (Ifix) along with sFLC concentration

Table 1 Clinical characteristic of patients included in the study

Parameter	Number of patients
Gender	
Female	23
Male	17
Age	
Median (years)	63
>65	12
Type of myeloma	
IgG (κ/ λ)	26 (22/4)
IgM (κ/ λ)	7 (5/2)
LCD (κ/ λ)	6 (2/4)
Solitary plasmocytoma	1
Renal function	
Normal	38
Impaired	2
Disease status	
With measurable monoclonal protein level	30
Complete remission	10

measurement by the Freelite and the N Latex FLC assays. Plasma cells clonality study was performed at the same time point as the sFLC assessment. It was determined by 4-color flow cytometry with the following antibody combination: CD38-fluorescein isothiocyanate/CD56-phycoerythrin/CD19-PerCP-Cy5.5/CD45-allophycocyanin and/or by bone marrow immunohistochemistry. In the latter case, the clonality was confirmed when the κ/λ ratio was >4:1 or <1:2, after counting at least 100 plasma cells [14]. Clinical characteristic of patients is summarized in Table 1.

sFLC analysis

Each serum sample was analyzed on a Siemens BN ProSpec nephelometer using particle-enhanced, high-specificity, homogeneous immunoassays (Freelite) and independently with the help of latex-enhanced immunonephelometry (N Latex FLC kappa and N Latex FLC lambda Assays). The analysis was performed according to protocols provided by the manufacturers, with precautions taken to avoid effects of antigen excess. Since there is no automatic antigen excess check for Freelite on Siemens nephelometers, two dilutions were tested, as recommended by The Binding Site's guidelines.

Reference ranges provided by the manufacturer were used in the analysis. In the case of the Freelite test it

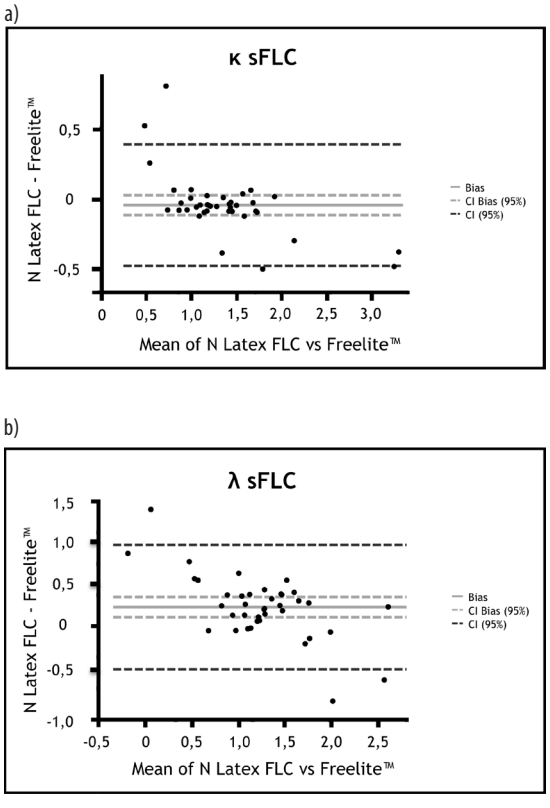


Fig. 1. Bland – Altman charts for logarithmic values of serum κ (a) and λ (b) free light chains. The bias equals -0.047 and 0.2133 for κ and λ measurement, respectively. A tendency to estimate higher values of λ sFLC by the N Latex FLC assay is shown

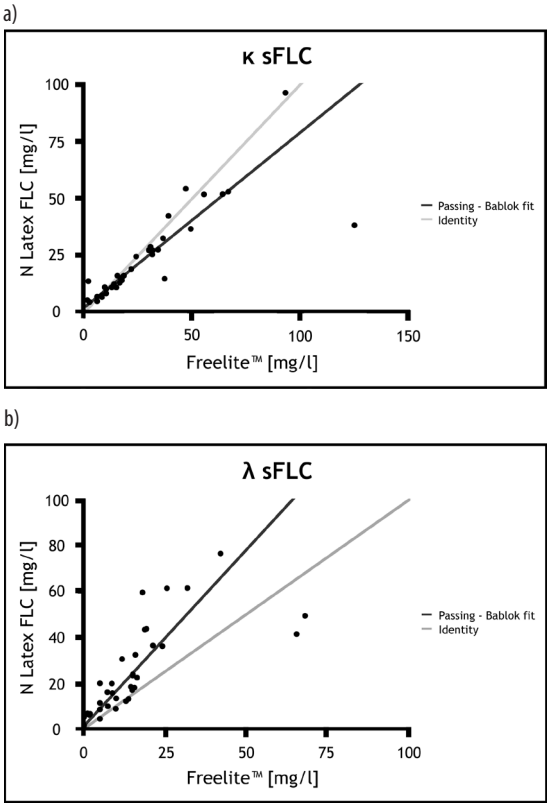


Fig.2. The serum free light chains (sFLC) concentration dependently from the assessment method used. Panels a) and b) show the Passing - Bablok analysis of κ and λ chains serum content in individual cases. The slope was equaled of 0.77 for κ sFLC and 1.54 for λ sFLC

was: for κ 3.3–19.4 [mg/l], for λ 5.71–26.3 [mg/l], and for κ/λ ratio 0.26–1.65. Respective values for the N Latex FLC test were: for κ chains 6.7–22.4 [mg/l], for λ chains 8.3–27.0 [mg/l], and for κ/λ ratio 0.31–1.56.

Comparison of methods

Absolute values of κ and λ chains concentrations obtained by the two methods were compared. We assessed concordance between qualitative results for κ, λ and κ/λ ratio. The results for κ and λ were grouped into three categories – low (below the reference range), normal, and high (above the reference range) – according to the manufacturer's reference ranges. For κ/λ ratio we used two categories – abnormal and normal. Clinical sensitivity was evaluated by comparing κ/λ ratio to SPEP/UPEP with Ifix results.

Statistical analysis

Methods were compared using Passing–Bablok regression (as recommended in Clinical and Laboratory Standards Institute guidelines EP09-A2-IR [11]) and Bland–Altman plots. For κ, λ and κ/λ results concordance correlation coefficient (CCC) and Cohen's kappa were determined. The strength of correlation was defined by the CCC result (>0.9 – almost perfect; >0.8-0.9 – substantial; >0.65-0.8 – moderate;

Table 2. Section a) - the results of concordance analysis of κ sFLC, λ sFLC and κ/λ ratio ranges obtained by the two studied methods. Section b) - detailed laboratory characteristic of the patients with normal κ to λ sFLC ratio by the N Latex FLC assay and an abnormal ranges by the Freelite™ test. In 7 out of 10 of these patients SPEP with immunofixation study confirmed the presence of clonal sFLC

a)

Test		Freelite™									
	κ sFLC	Low <3.3 mg/l	Normal 3.3 – 19.4 mg/l	High >19.4 mg/l	λ sFLC	Low <5.71 mg/l	Normal 5.71 – 26.3 mg/l	High >26.3 mg/l	κ/λ sFLC ratio	Normal 0.26 – 1.65	Abnormal
N Latex FLC	Low <6.7 mg/l	2	1	0	Low <8.3 mg/l	2	2	0	Normal 0.31 – 1.56	17	10
	Normal 6.7 - 22.4 mg/l	1	16	2	Normal 8.3 – 27 mg/l	0	20	0	Abnormal	0	13
	High >22.4 mg/l	0	0	18	High >27 mg/l	0	8	8			

κ sFLC Freelite™ vs N Latex FLC concordance = 0.87
λ sFLC Freelite™ vs N Latex FLC concordance = 0.62
κ/λ sFLC Freelite™ vs N Latex FLC concordance = 0.52

b)

			N Latex FLC				Freelite™							
N°	Gender	Age	κ [mg/l]	λ [mg/l]	κ/ λ ratio	κ/λ range	κ [mg/l]	λ [mg/l]	κ/λ ratio	κ/λ range	SPEP [mg/dl]	Ifix	Type of iFLC	Serum creatinine [μmol/l]
6	F	57	5.66	5.23	1.08	normal	1.66	0.254	6.54	abnormal	0	-	n.d.	94
11	F	41	14.3	16.1	0.89	normal	17.6	7.39	2.38	abnormal	0.8	+	κ	77
14	M	44	15.0	38.9	0.39	normal	37.3	273.0	0.14	abnormal	18.6	+	Λ	89
20	M	58	16.3	49.5	0.33	normal	15.5	68.2	0.23	abnormal	4.5	+	Λ	123
21	F	74	13.9	41.5	0.33	normal	2.09	65.6	0.03	abnormal	0	-	n.d.	102
27	F	60	24.7	30.6	0.81	normal	24.2	11.9	2.03	abnormal	0.5	+	κ	231
29	F	65	53.1	61.6	0.86	normal	66.7	32.0	2.08	abnormal	0.4	+	κ	82
32	F	68	25.6	23.4	1.09	normal	31.6	15.2	2.08	abnormal	0.2	+	κ	86
38	M	64	36.8	32.4	1.14	normal	49.4	16.0	3.09	abnormal	11.9	+	κ	98
40	M	64	16.1	15.7	1.03	normal	18.2	8.9	2.04	abnormal	0	-	n.d.	107

<0.65 – weak). The analysis was performed using GraphPad Prism and Analyse-it software.

Results

Comparison of absolute values

The results of κ and λ sFLC measurements analysis are given in Fig. 1 and 2. Bland–Altman plots showed a significant bias of 0.2133 for λ chains evaluation along with much lower bias of -0.0467 for κ chains. Passing–Bablok regression analysis documented a weak correlation between test results for both κ and λ sFLC measurements. Slope – the indicator of the proportional difference between the test results – equaled 0.77 (95% CI: 0.58–0.91) for κ and 1.54 (95% CI: 0.81–1.92) for λ.

Concordance analysis

According to κ and λ chains concentrations obtained by the two methods patients were classified into three groups, defined by reference ranges provided by the manufacturer and mentioned in the materials and methods section, with low, normal and high free light chains serum content. Concordance for these results was substantial for κ chains, with a concordance correlation coefficient

of 0.87 and Cohen's kappa of 0.84, while it was poor for λ, with the values of 0.62 and 0.57, respectively (Table 2a). For κ chain measurements there were only 2 patients with different results obtained by the two tests that were clinically significant (normal vs high). In the case of λ chains there were 8 such patients – with the result in the normal range according to Freelite and classified as high by the N Latex FLC test. κ/λ ratio was defined as normal or abnormal, according to reference ranges provided in the materials and methods section. The concordance between these results was poor, with a concordance correlation coefficient and Cohen's kappa of 0.52 and 0.53 (Table 2a). In the case of 10 patients κ/λ ratio analysis showed discrepant results. All of them were normal according to N Latex FLC and abnormal according to Freelite. Detailed analysis showed that 7 out of 10 of these patients were positive in SPEP as well as in Ifix studies (Table 2b). The remaining 3 patients had negative results of SPEP and Ifix. In one of these patients, the absence of clonal plasma cells was confirmed by immunohistochemistry, indicating that the patient achieved sCR, if we took the N Latex FLC result into consideration. However, relaying on the Freelite™ assay, none of these patients meet the sCR criteria.

SPEP/UPEP, Ifix results and κ/λ ratio assessment

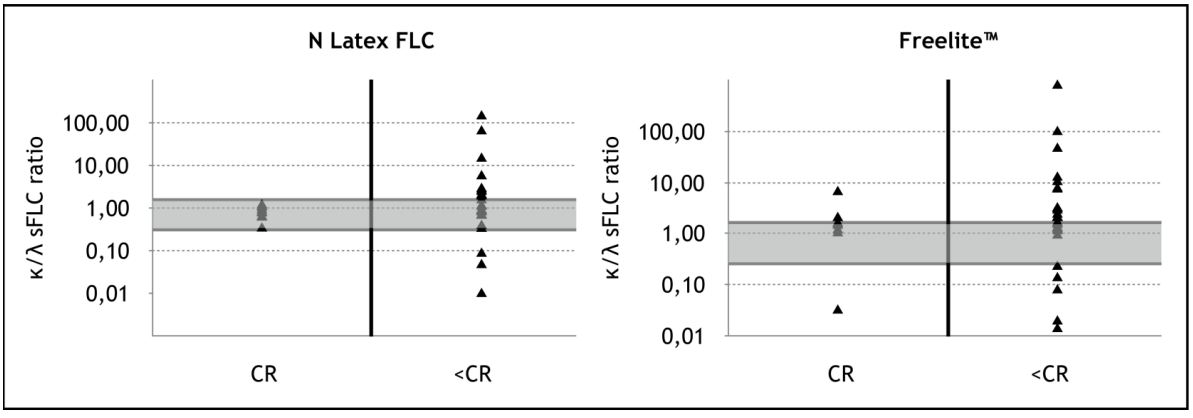
As an indicator of disease activity, κ/λ ratio obtained by the two methods was compared to patients' SPEP/UPEP and Ifix results (Table 3). Sensitivity of Freelite was 62.5% and that of N Latex FLC was 41%.

Discussion

Our study evaluates the usefulness of free light chains assessment by different tests in multiple myeloma patients receiving treatment, especially those who meet criteria of sCR. According to our knowledge, such an analysis has not been performed before.

To assess the concentration of sFLC, different assays and techniques are used. In both studied tests antibodies against κ and λ light chains' hidden epitopes

a)



b)

κ/λ sFLC ratio	N Latex FLC		Freelite™	
	Positive SPEP/UPEP and Ifix result	Negative SPEP/UPEP and Ifix result	Positive SPEP/UPEP and Ifix result	Negative SPEP/UPEP and Ifix result
Abnormal	**13**	0	**20**	3
Normal	19	**8**	12	**5**

Fig. 3. Section a) - FLC ratios obtained by the two methods in two groups of patients - those who achieved CR (negative SPEP and Ifix) and those who achieved response worse than CR. Gray zone indicates reference ranges for κ/λ FLC ratio. Section b) - clinical sensitivity of both assays, with SPEP/UPEP and Ifix results as a reference, equaled 62,5% for Freelite™ and 41% for N Latex FLC

are used [4]. In intact immunoglobulins these places are covered by the junction between light and heavy immunoglobulin chains and therefore are not accessible for antibodies. Targeting such antigens allows the assays to specifically measure only free light chains. Freelite contains polyclonal antibodies, produced by sheep immunized with κ or λ light chains obtained from urine of patients with light chain disease. The use of polyclonal antibodies allows one to recognize a wide variety of epitopes, which is essential in detection of such heterogeneous proteins as FLC. The disadvantage of this method is greater variation between reagent lots, although several studies claim that this effect is not highly significant [13]. In contrast, N Latex FLC uses monoclonal antibodies to bind hidden epitopes. The antibodies are obtained from mice immunized with free light chain Bence–Jones proteins. After immunization of mice the hybridoma cells are made from the mouse B cells and then the anti-κ and anti-λ clones are expanded. The downside of this approach is the possibility that monoclonal antibodies may not be able to recognize myriads of FLC epitopes [13]. However, there are studies proving that, when using N Latex FLC, such a situation does not occur very often [7]. In contrast to polyclonal-based tests, the monoclonal assay should retain high batch-to-batch consistency [15].

Only for κ chains measurements were the correlation and concordance satisfactory and the results of the two tests did not vary significantly – there were only 2 patients for whom different test results had clinical meaning (normal vs high). Both assays' comparability was much worse for assessing λ chains concentrations. As indicated by the Bland–Altman plots, N Latex FLC showed a tendency to estimate higher values of these sFLC than Freelite. This finding was confirmed by qualitative analysis – there were 8 patients with results within the normal range according to Freelite while being classified as 'high' by N Latex FLC. It influenced the ratio results – elevated λ diminished the final ratio value. As a result, some patients with κ iFLC, with its level elevated in both tests, achieved a normal κ/λ ratio according to N Latex FLC. Although the differences between the ratio values were not large, we could recognize such a pattern. We suggest that this discrepancy is influenced by λ chains' dimerization and polymerization, a common effect that can augment a reaction used in the nephelometric assay [8,12]. There is a possibility that N Latex FLC is more susceptible to this phenomenon.

Elevated sFLC ratio is among symptomatic disease defining criteria, and therefore the discrepancies between the tests could potentially lead to inappropriate diagnosis of multiple myeloma. Since our study was not performed on patients with newly diagnosed MM, or patients screened for monoclonal gammopathy, we can only speculate that the documented differences were not significant enough to affect patients with abundant FLC secretion, with sFLC ratio over 100 and with iFLC concentration higher than 100 mg/l.

From the clinical point of view, κ/λ ratio is the most important result. In our data this was the parameter that showed the highest discrepancy. In 10 out of 40 patients the results of sFLC ratio differed. All of them were classified as 'normal' by N Latex FLC and 'abnormal' by Freelite. Detailed analysis of SPEP/UPEP and Ifix study results showed that in 7 out of these 10 cases monoclonal protein was present. The remaining 3 patients had negative immunofixation, moreover, the absence of clonal plasma cells was also confirmed in one case. It either meant N Latex FLC assessed their sFLC concentration more accurately than Freelite and they achieved sCR or that Freelite was more accurate and they remained in CR. Since there is a significant difference in prognosis between patients who achieved sCR and CR, this question underlines a serious clinical issue [9].

When κ/λ ratio obtained by the two methods was compared to patients' SPEP/UPEP and Ifix results, Freelite showed higher sensitivity than N Latex FLC. Specificity analysis was not conducted, because, since sFLC assays can detect lower concentrations of proteins than electrophoretic tests, we found it impossible to determine whether the result is truly false positive.

In conclusion, our data confirmed that sensitivity of both assays in terms of sFLC detection differ. Therefore the clinical usefulness of using the two studied tests interchangeably and the cause of discrepancy between them should be further evaluated. This is especially important when sCR diagnosis is considered.

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