Received: 28 October 2023 | Revised: 15 March 2024 | Accepted: 19 March 2024

DOI: 10.1002/jha2.886

eJHaem

British Society for Haematology

RESEARCH ARTICLE

The choice of serum-free light chain analysis method could potentially have clinical consequences for myeloma patients

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Funding information
The Department of Research, Education and Innovation, Södra Älvsborg Hospital (SÄS) Borås, Grant/Award Number: sas-981725

Abstract

Multiple myeloma (MM) is a disease, that at times poses diagnostic and monitoring challenges. Over the last decades laboratory methods have been expanded with serum free light chain (FLC) analysis. Alerted by two index cases with clinical impact due to failure of the FLC analysis to indicate a disease progression, we aimed to identify any clinical consequences due to known differences between FLC analysis methods. We applied two FLC analysis methods (Freelite Binding Site [FBS] and N-Latex Siemens [NLS]) on all patients with MM and monoclonal gammopathy of uncertain significance diagnosed/followed up at Södra Älvsborg Hematology Unit, from April to December 2022. From a total of 123 patients with malignant plasma cell disorder, we identified five cases (4.1%) where solely the FBS method, as opposed to NLS, urine and serum electrophoresis, could support diagnosis or detect progression. The consequences of this discrepancy included not only change of diagnosis or delayed therapy but also change of treatment. Our findings indicate that a stronger awareness of the potential weaknesses of different FLC methods is needed, which calls for a closer collaboration between clinical chemists and hematologists.

KEYWORDS
disease progression, hematology, immunoglobulin light chains, monoclonal gammopathy of undetermined significance, multiple myeloma, paraproteinemia

1 | INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder that can present diagnostic and monitoring challenges, even now in an era of improved diagnostic methods [1, 2] and increasingly efficient therapies prolonging survival [3]. Core components in the diagnostic and monitoring methods for MM are the serum and urine electrophoreses that measure monoclonal immunoglobulin in serum and κ-, λ-chains in urine (Bence Jones proteinuria) respectively. These biomarkers are a diagnostic criterium for a majority of the plasma cell disorders, pointing towards these diseases in a clinical investigation, and may also serve as prognostic features during follow-up, where changes in concentrations could indicate disease progression or treatment response. Although easily accessible, not all MM patients will present with these biomarkers [1–3]. Also, over the course of the malignant plasma cell disorder (primarily myeloma),

the production of M-protein may be diminished or completely lost [4].

The implementation of serum-free light chain (FLC) analysis has become a valuable addition to the clinician's toolset. Some of the benefits are, 1) diagnosis and monitoring of oligo-secretory plasma cell disorders, 2) distinction between plasma cell disorders requiring treatment (MM) and those with a watch-and-wait approach (monoclonal gammopathy of uncertain significance [MGUS] and smoldering myeloma [SMM]), and 3) detection of FLCs in serum with regards to their potentially debilitating effect on renal function. The specific FLC criteria for plasma cell disorders are clarified in the updated guidelines of the International Myeloma Working Group (IMWG)[5, 6].

In the wake of the introduction of FLC analysis in the clinical setting [7–9], the development of different (competing) methods for the detection and quantification of FLC [10–13], revealed some common analytical challenges [14]. The most alarming was the poor correlation between different methods [15]. So far, this has led to the common recommendation by researchers that the same method of FLC analysis should be utilized for monitoring patients since concentration values, and consequently ratios and differences over time, can vary widely between assays [16, 17].

Initially, there was only one method available for measuring FLC, the Serum Freelite (The Binding Site Group Ltd., Freelite Binding Site [FBS]) method [7, 8]. It is widely used in Europe and the United States and is the method on which the IMWG has based its serum-FLC diagnostic and prognostic criteria. The method carried some technical challenges, primarily the issue of antigen excess [18], which required experienced vigilance and time-consuming reevaluations and corrections. When alternative methods for FLC analysis were made available, hospitals in the Västra Götaland region (VGR) of Sweden (comprising 1.7 million inhabitants), among other regions in Sweden, looked for a method with less of the issues seen with the FBS method. In 2017, Södra Älvsborg Hospital, in the VGR, adopted the N-Latex (Siemens Healthineers) (NLS) method [10], for its perceived advantages when compared to the FBS method.

In 2020, we noticed two separate clinical cases (Table 4 and Table S1) where patients developed severe disease progression with significant and debilitating clinical consequences for the patients, without fair warning from the monitoring analyses of FLC. A great discrepancy was detected in the assessment of FLC with the NLS method compared to serum electrophoresis. To further evaluate this discrepancy, samples were analyzed also with the FBS method. These analyses showed a much higher level of the involved FLC, and the results were in line with what the serum electrophoresis had signaled. One of the patients suffered severe renal failure which led to life-long hemodialysis, whereas the other patient experienced progressive renal failure, overall deterioration of the general physical status, and later death.

The purpose of this study was to compare two methods for FLC analysis, the formerly used FBS and the currently used NLS, in a real-life setting at the hematology unit at Södra Älvsborg Hospital. With a regimen of double testing for FLC, we aimed to discover patients at risk of suffering the same consequences as the two index cases, and to find out if and when, one or both, FLC methods are essential for diagnosing MM disease and assessing its response during follow-up.

TABLE 1 **Patient characteristics**. One case with IgM-type paraprotein had multiple plasmacytomas. Only light chain means the patient did not have measurable levels of the four immunoglobulin types, only light chains in either urine or serum or in both urine and serum. In a couple of cases, one MM and one MGUS, paraproteinemia was detected in the gamma region but could not be further specified, nor could their clonal type be determined. In one case of IgG-M-protein, the clonal type could not be assessed and the FLC was normal. In another case with MM in complete remission since 1996, neither type nor clonality of M-protein could be recovered, and the κ-, λ-, light chains have remained normal since the introduction of FLC-measurement.

	n (%)
Included patients	175
Male	99 (57)
Female	76 (43)
Median age *years* (range)	*74 (32–92)*
Plasma cell disorders	175
MM	110 (63)
SMM	5 (2.9)
Plasmacytoma	7 (4.0)
Plasma cell leukemia	1 (0.6)
MGUS	48 (27)
AL	4 (2.3)
Paraprotein type	175
IgA	31 [18]
IgD	2 (1.1)
IgG	117 (67)
IgM	1 (0.6)
Only light chain	21 [12]
Gamma region	2 (1.1)
Undetermined	1 (0.6)
Clonal type	175
Clonal Type: kappa (κ)	106 (61)
Clonal Type: lambda (λ)	65 (37)
Clonal Type: undetermined	4 (2.2)

Abbreviations: AL, light chain amyloidosis; FLC, free light chain; IgA, immunoglobulin A; IgD, immunoglobulin D; IgG, immunoglobulin G; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering myeloma.

2 | METHODS

2.1 | Patient selection

From April 21, 2022, to December 31, 2022, all referred, investigated, or monitored patients regarding MGUS and malignant plasma

TABLE 2 **Outcome of Freelite Binding Site (FBS) and N-Latex Siemens (NLS) comparisons**. The table demonstrates number of cases where either of the two FLC methods, FBS and NLS detect at least a three times higher level than the other, in at least one of the three applications of FLC results, 1) involved light chain concentration, 2) involved/non-involved light chain ratio, and 3) increase in difference between involved and non-involved light chain. For five patients the ≥ 3:1 difference is deemed clinically relevant because it had a significant impact on the clinical outcome for the patient. This is further clarified in Table 3.

	n (%)
Included double tested	175 (100)
≥3:1 difference in result between FLC-methods	31 [18]
MM, SMM, plasmacytoma, and plasma cell leukemia	24 [14]
FBS > NLS	16 (9.1)
NLS > FBS	8 (4.6)
MGUS	7 (4.0)
FBS > NLS	4 (2.3)
NLS > FBS	3 (1.7)
Clinically relevant ≥3:1 difference	5 (2.9)
MM, SMM, plasmacytoma, and plasma cell leukemia	5 (2.9)
FBS 3:1 > NLS	5 (2.9)
NLS 3:1 > FBS	0
MGUS	0
FBS > NLS	0
NLS > FBS	0

Abbreviations: FBS, Freelite Binding Site; FLC, free light chain; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NLS, N-Latex Siemens; SMM, smoldering myeloma.

cell disorders at the Hematology unit of Södra Älvsborg Hospital, were potential study candidates. All patients, for whom the clinician requested an analysis of serum FLC, were tested with two methods (see below). The aim was to perform double testing at each requested FLC analysis. Study patients were then identified retrospectively by checking all double tested against all patients that were diagnosed or followed up at the Hematology unit during the study period. Patients were diagnosed and/or regularly assessed during follow-up according to the diagnostic and prognostic criteria in the IMWG guidelines [5, 6]. In total 896 (768 with malignant plasma cell disorder, 99 with MGUS, and 29 with AL-amyloidosis) double tests were performed on the included patients with a median of seven tests per patient with malignant plasma cell disorder, a median of two tests per patient with MGUS and a median of eight tests per patient with AL-amyloidosis.

Patients where the M-protein was of an IgM-type in MGUS or indolent lymphoma were excluded. This was also the case for patients with multiple myeloma only monitored with a significant M-protein and for those treated with bispecific antibodies where the therapy led to unmeasurable FLC.

2.2 | Laboratory analysis of M-protein and FLCs

Blood sampling and urine collection were conducted routinely as part of clinical investigations or follow-up procedures. However, during the study period, a portion of the serum samples were fresh frozen at −80°C, reserve samples were primarily used to perform extra analyses and adjustments whenever there were clear or suspected signs of estimation issues, including antigen excess. Serum FLC analysis was conducted with two different assays, the polyclonal FBS and the monoclonal NLS method. A BN Prospec Nephelometer (Siemens Healthineers) was used for both assays. All patients analyzed for FLC, were also analyzed for total serum immunoglobulin (IgG, IgA, and IgM) concentrations, using Alinity c (Abbott Laboratories). Serum/urine protein electrophoresis (S/uPEP) and immunofixation, for assessment of M-protein and Bence-Jones-proteinuria, were performed with agarose gels on the Hydrasys 2 Scan (Sebia, Lisses, France) and Alinity c (Abbott Laboratories). Serum-M-Protein was measured in g/L. Reference values for FLC-analyses were: **NLS**: S-FLC κ 6.7–22.4 mg/L, S-FLC λ mg/L 8.3–27.0 mg/L, κ/λ-ratio 0.31–1.56, **FBS**: S-FLC κ 3.3–19 mg/L, and S-FLC λ 5.7–26 mg/L, κ/λ-ratio 0.3–1.7, $\Delta\ \kappa{-}\lambda$ (absolute difference between κ and λ) mg/L. Urine protein analysis: tU-Albumin mg/24 h, U-Albumin mg/L, tU-κ mg/24 h, U-κ mg/L, tU-λ mg/24 h, and U-λ mg/L.

2.3 | Data analysis

M-protein and double-tested FLC data were registered and checked against other standard laboratory data, patient chart registries, and skeletal surveys when necessary. The first step of comparing FLC data between the FBS and NLS methods aimed to determine cases where there was a ≥3:1 difference in FLC concentration levels of involved(inv)-FLC, or a ≥3:1 difference in FLC-ratio, or a ≥3:1 difference in increase of difference between involved and non-involved FLC, at least once (for patients tested more than once) and the first time it is observed (for patients tested more than once). Secondly, a patient chart review was performed to confirm diagnosis and response, according to the IMWG criteria [5, 6], to determine cases where diagnosis and/or response assessment rested only on FLC (-concentrations, or -ratio, or -an increase of difference), and excluding cases where FLC simply was not necessary to take adequate clinical action (i.e. other clinical features sufficed to assess diagnosis or response). The purpose was to identify cases where a difference between the two FLC methods had a clinical consequence, for example, a change of diagnosis, a therapeutic delay with the development of debilitating symptoms (skeletal lesions, renal failure), or the opposite, a timely therapeutic intervention to prevent a clinical consequence.

3 | RESULTS

3.1 | Patient characteristics

In total, 199 patients had an investigation, treatment, follow-up, or second opinion assessment, due to diagnosed or suspected plasma cell

TABLE 3 **Relevant cases from April to December 2022**. The table summarizes the clinical consequence of the difference in measurement between the FBS and NLS methods for the identified five cases. Only FBS results meet the diagnostic or prognostic criteria (according to International Myeloma Working Group guidelines) to prompt adequate and timely action and to reveal a diagnostic delay.

Case	Analysis	Clinical consequence
1	NLS-FLC fails to signal MM disease progression	Delayed therapy, fracture
2	NLS-FLC is not enough to meet MDE criteria, only diagnosed as SMM	Delayed correct diagnosis (MM), exclusion from SMM clinical study
3	NLS-FLC is not enough to meet malignant plasma cell disorder criteria, only diagnosed as MGUS	Delayed diagnosis (plasma cell leukemia), acute renal and respiratory failure
4	Only FBS-FLC supports MM diagnosis and later disease progression	Timely onset of therapy and later therapy adjustment
5	Only FBS-FLC supports MM disease progression	Timely onset of therapy

Abbreviations: FBS, Freelite Binding Site; FLC, free light chain; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NLS, N-Latex Siemens; SMM, smoldering myeloma.

disorder during the study period, and 175 met the inclusion criteria. Fifteen patients were excluded due to not being double-tested with both FLC methods along with nine double-tested.

Patient characteristics are presented in Table 1. The male/female ratio was balanced, and the median age was representative of the study population. The malignant plasma cell disorder patients ($n = 123$) include 109 MM, five SMM, eight plasmacytoma, and one plasma cell leukemia patient. Twenty-four (20%) of the MM-patients had unmeasurable levels of whole M-protein monitored with serum electrophoresis during the observation period.

3.2 | Outcome of FBS and NLS comparisons

Thirty-one patients were identified who had a relative difference of ≥ 3:1 in involved FLC levels or inv/non-inv FLC ratio at diagnosis (where the FLC level is a myeloma defining event [MDE] criteria at diagnosis)[5] or ≥ 3:1 difference in the increase of difference between involved and non-involved chain during follow-up [6]. Twenty-four patients with a malignant plasma cell disorder (MM, SMM, plasmacytoma, and plasma cell leukemia) and seven with MGUS (Table 2). In 5 verified cases (4.1% of the included patients with malignant plasma cell disorder), the ≥ 3:1 difference was clinically relevant (Table 3 and Tables S2–S7), revealing a diagnostic delay with serious clinical consequence (two cases), an earlier assessment of disease progression and timely shift or onset of therapy (two cases), and a change of diagnosis and follow-up routines (one case). The assessment of diagnosis, or disease progression in these five cases rested entirely on the FLC measurement from one of the two methods (FBS), that is, there were no other clinical features to indicate the diagnosis or the disease progression. Renal insufficiency as a potential consequence of myeloma (creatinine > 177 μmol/L) was observed in five of 31 patients with a significant difference in FLC between methods. Only the index case had end stage renal insufficiency that could have affected the FLC-levels [19], however that patient had improved FLC levels with a lesser difference between FLC methods during the observation period and was hence not part of the 31 identified cases.

3.3 | Case reports

The first index case detected is described in Table 4, whereas index case 2 and the relevant cases 1–5 detected during the study period (Table 3) are detailed in Tables S2–S7.

3.4 | Index case 1

3.4.1 | 68-year-old male with MM diagnosed in 2015 (no previous medical conditions)

At diagnosis in 2015, the patient presented with progressing fatigue, anemia (Hb 82 g/L), acute renal failure (creatinine 511 μmol/L), S-Albumin 41 g/L, S-Calcium 2.68 mmol/L, S-IgA λ 1 g/L, S-κ 16.1 mg/L, S-λ 17000 mg/L (FBS method), tU-Albumin 46 mg/24 h, tU-κ < 6.11 mg/L, and tU-λ 16448 mg/24 h. Bone marrow biopsy showed an extensive plasma cell infiltration and a skeletal CT survey revealed multiple osteolytic lesions. The first two lines of therapy resulted in a very good partial response (VGPR). The renal function partially recovered (creatinine around 200 μmol/L) whereas S-κ, S-λ and κ/λ-ratio normalized. There were no other remaining signs or symptoms of MM-related organ impairment or MDEs.

In late February 2020, the patient was hastily admitted to the hospital, due to frequent diarrhea, anemia, and acute deterioration of the chronic renal insufficiency, creatinine 1300 μmol/L, and urgent hemodialysis was initiated. There was an increase in the involved serum light chain (S-κ 21.7 mg/L and S-λ 250 mg/L with the NLS method), however, the serum electrophoresis indicated a much higher level of λ-chains. Samples were sent to neighboring NÄL Hospital utilizing the FBS method, which yielded significantly higher λ-levels (S-λ 30800 mg/L). Urine analysis revealed a Bence-Jones proteinuria (tU-Albumin 132 mg/24 h, tU-κ 20 mg/24 h, tU-λ 9018 mg/24 h, and tU-Protein 280 mg/24 h). Further, a bone marrow aspirate revealed 12% plasma cells, an increased serum lactate dehydrogenase 9.5 μkat/L, and the presence of +1q21 mutation in the cytogenetic FISH analysis (stage III myeloma, according to R-ISS [2]). The patient was

TABLE 4 Index case 1. Clinical parameters monitored for Index case 1.

Variable	Feb 2020	Mar 2020	Jul 2020	Apr 2021	May 2021	Jun 2021	May 2022	Dec 2022
M-protein	1	<1	0	5	7	0	0	0
-type	IgA λ	IgA λ	n/a	λ	λ	n/a	n/a	n/a
N-Latex Siemens								
κ	21.7	31.2	68.6	63	22.3	48.1	77.3	88.6
λ	250	39.8	78.4	67	105	46.4	84.2	81.7
κ/λ	0.09	0.78	0.88	0.94	0.21	1	0.92	1.1
$\Delta\kappa$–λ	228	9	10	4	83	2	13	8
Freelite Binding Site								
κ	19.8	24.9	8.,2	76	n/a	n/a	102	122
λ	30800	754	32.7	3470	14800	169	39	61
κ/λ	<0.01	0.03	2.51	0.02	n/a	n/a	2.6	2,0
$\Delta\kappa$–λ	30780	729	50	3394	n/a	n/a	63	61
Urine analysis								
tU-Albumin	132	284	38 mg/L	51 mg/L	121	84	–	–
tU-κ	20	22	15 mg/L	34 mg/L	11	57	–	–
tU-λ	9018	282	6.9 mg/L	519 mg/L	9688	64	–	–
Clinical Features								
Hb	80	87	106	88	68	81	89	116
Leucocytes	7.7	3.29	6.73	8.84	11.1	1.62	8.9	3.5
Thrombocytes	222	33	139	272	132	116	101	63
Creatinine	1300	778	509	508	603	345	558	550
Calcium	2.31	–	2.32	2.48	2.81	2.34	2.46	2.53
Lesion	n/a	yes[†]	n/a	n/a	n/a	n/a	n/a	n/a
Symptom	yes[‡]	yes[‡]	no	no	no	no	no	no
Therapy								
-type	–	VTD	VTD	Btz/Dex	–	PCD	PCD	PCD

M-Protein g/L, -type (immunoglobulin type and clonal type κ or λ of M-protein), **Serum free light chain analysis-N-Latex Siemens**: κ 6.7–22.4 mg/L, λ 8.3–27.0 mg/L, κ/λ 0.31–1.56, $\Delta\kappa$–λ mg/L, **-Freelite Binding-Site**: κ 3.3–19 mg/L, and λ 5.7–26 mg/L, κ/λ 0.3–1.7, $\Delta\kappa$–λ mg/L, **Urine protein analysis**: tU-Albumin, tU-κ, and tU-λ mg/24 h. Results reported in mg/L instead of mg/24 h when insufficiently collected total-24h-urine volume, **Clinical Features**: Hb 117–153 g/L, Leucocytes 3.5–8.8 × 10^9/L, Thrombocytes 165–387 × 10^9/L, Creatinine 60–105 mmol/L, Calcium 2.15–2.50 µmol/L, Lesion (skeletal) yes, no, or n/a, Symptom (disease-related symptoms, primarily pain, but also fatigue, neuropathy, etc.) yes or no.

Abbreviations: BtzDex, bortezomib, dexamethasone; Hb, hemoglobin; IgA, immunoglobulin A; M-protein, monoclonal immunoglobulin, paraprotein; n/a, not assessed; PCD, pomalidomide, cyclophosphamide, dexamethasone; tU, total-24h-urine; VTD, bortezomib, thalidomide, dexamethasone.; $\Delta\kappa$–λ, absolute difference between kappa and lambda; κ, kappa; κ/λ, kappa/lambda-ratio; λ, lambda.

[†]Multiple skeletal lesions, both new and known deteriorated lesions compared to previous assessments in 2015.

[‡]Diarrhea and fatigue, however no pain.

started on third-line therapy including maintenance therapy, again attaining VGPR, but unfortunately had to remain on permanent hemodialysis, keeping the creatinine concentrations fluctuating around 500 µmol/L.

In April 2021 serum electrophoresis revealed 5 g/L of serum-free λ chains, which did not match what the FLC-analysis (NLS) had measured, so again samples were sent to NÄL lab conforming significantly higher levels of serum free λ chains (3470 mg/L) using the FBS method. This immediately prompted a shift in therapy which eventually proved efficient against the disease, attaining VGPR for the fourth time.

4 | DISCUSSION AND CONCLUSIONS

Our study revealed five cases where the only means for diagnosis or detecting disease progression was FLC analysis and where only one (FBS) of the two parallel applied methods served to detect the relevant changes.

The introduction of methods measuring FLCs in serum has been important in facilitating the diagnosis and monitoring of multiple myeloma. Even though the FBS method was the first to see a wider use [7–9], to this day, there is no gold standard method for analyzing serum

FLCs [15, 20]. Where the polyclonal FBS method had a tendency for both overestimation and underestimation, with issues such as antigen excess [18], the monoclonal methods such as NLS [10] were introduced to achieve more consistent results, less sensitive to antigen excess and potentially superior for disease monitoring. This prompted a change of method from FBS to NLS in several hospitals in Sweden in 2017.

The discrepancies detected between FLC methods have been described earlier [20]. Studies have demonstrated that all available methods display a high degree of correlation at the lower normal and close to normal ranges and a significant degree of discrepancy at higher concentration levels [21], highlighting the issue of non-interchangeability between the methods, and at the same time pushing for further research. There are many possible reasons for the discrepancy, instrument- and calibrator-associated [22], assay-related [20], difference in reference intervals, or analytical difficulties connected to the presence of renal failure [23]. Renal insufficiency due to myeloma may affect the levels of FLC but not the κ/λ-ratio [23]. Also, none of the relevant 31 cases had end-stage kidney disease [19]. We have no indications of specific assay batch problems, since the discrepancy when present occurred repeatedly during the observation period in a fraction of the patients, and not across the whole study population. Furthermore, there was no sign of or reason to suspect machine-related issues since both assays were run on the same nephelometer. Laboratory diligence along with parallel testing with both serum electrophoresis and FLC analysis, enabled the discovery of discrepant FLC measurement in 2020, proving on the one hand the importance of serum electrophoresis, and on the other hand, revealing the insufficiency of FLC methods. Although our findings demonstrate an advantage for one of the FLC methods, only a validating study at another center could potentially support our results.

To the best of our knowledge, this is the first study to describe clinical consequences for patients due to the reported issues with FLC analysis. Even if the study has a limited number of patients, we can show clinical, relevant discrepancies in a substantial number of cases. The intention of the authors is to point toward this issue, and we recommend constant vigilance and close collaboration between laboratory and clinical physicians, particularly for cases of malignant plasma cell disorder relying primarily on FLC analysis for diagnosis and monitoring, regardless of the choice of method for FLC analysis.

AUTHOR CONTRIBUTIONS

Ljupco Veskovski, Ingvar Jakobsson, Ulf-Henrik Mellqvist, and Per-Ola Andersson conceived and designed the study concept. All authors acquired, analyzed, or interpreted the data. Ljupco Veskovski drafted the manuscript and all authors critically revised and finally approved the submitted version.

ACKNOWLEDGMENTS

Christina Suhonen and Annika Falk at the Laboratory for Clinical Chemistry SÄS Borås were essential for identifying the discrepant index cases that formed the basis of this study. Karin Appelgren was involved in the identification of significant discrepant cases at the Department of Clinical Chemistry, Sahlgrenska University Hospital, Göteborg. This work was supported by The Department of Research, Education and Innovation, Södra Älvsborg Hospital (SÄS) Borås, funded the study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article. Additional data can be made available upon request.

ETHICS STATEMENT

The study was approved by the Swedish Ethical Review Authority (Dnr 2022–05485–01).

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Veskovski L, Jakobsson I, Andersson P-O, Gustafsson T, Sedigh A, Knut-Bojanowska D, et al. The choice of serum-free light chain analysis method could potentially have clinical consequences for myeloma patients. eJHaem. 2024;5:455–61. https://doi.org/10.1002/jha2.886