BMC Immunology

RESEARCH

Open Access

Warning values of serum total kappa/lambda ratio for M-proteinemia

Jie Lu[1], Ying Zhu[1], Huifang Huang[1], Qian Yang[1] and Songnan Qi[1*]

Abstract

Background To introduce the serum total kappa/lambda ratio (K/L) in humoral immunity testing reports to improve the detection rate of M-proteinemia.

Methods 156 M protein-positive and 5464 M protein-negative samples confirmed by serum immunofixation electrophoresis(sIFE) were accumulated from January 2021 to December 2023 in the First Affiliated Hospital of Soochow University and the contents of immunoglobulins (IgG, IgA, IgM, kappa and lambda) were tested by Beckman IMMAGE800. All the samples were divided into two groups by time: the modeling group and the validation group. The K/L values in the modeling group were analyzed by SPSS 27.0 to get the receiver operating characteristic curve (ROC). Furthermore, a more in-depth analysis was conducted to verify the reliability of the optimal cutoff values in the validation group. In addition, the levels of immunoglobulins of another group including 106 patients with definite diagnosis of monoclonal gammopathy ranging from January 2021 to June 2024 were traced back to improve the diagnostic efficiency.

Results The optimal cutoff values of K/L were 2.31 and 1.43 corresponding to K-type and L-type M-proteinemia respectively by ROC analysis. The sensitivity and specificity were validated as 76.14% and 77.42%. False positives were mainly found in samples with systemic sclerosis (36.84%), hypohepatia (28.71%) and sicca syndrome (27.27%). While false negatives were mainly found in IgA monoclonal gammopathy (38.39%) and IgM monoclonal gammopathy (28.57%). Combining with the detection rules of IgG, IgA and IgM, the sensitivities for the diagnosis of immunoglobulin light chain amyloidosis(AL) and monoclonal gammopathy of undetermined significance(MGUS) can be increased to 83.33% and 85%.

Conclusions K/L > 2.31 and K/L < 1.43 can be used as warning values for M-proteinemia. In addition, the content of the heavy chain in IgA- or IgM-type M-proteinemia may be considered to improve the detection rate.

Keywords M-proteinemia, K/L, ROC, Plasma cell monoclonal, Cutoff

Background

M protein is an immunoglobulin produced by monoclonal proliferation of plasma cells or B lymphocytes. There are four categories of M protein: malignant M protein, which is commonly seen in multiple myeloma(MM), heavy chain disease, malignant lymphoma, lymphocytic leukemia, macroglobulinemia, etc.; secondary M protein; benign M protein; and M protein of unknown significance. M protein detection is of great significance in the diagnosis of MM, amyloidosis, and POEMS disorder (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes). The appearance of M protein in serum is called M-proteinemia [1]. Monoclonal proteins arise from the clonal expansion of antibody-secreting B cells or plasma

*Correspondence:
Songnan Qi
qisongnan@126.com
[1] Department of Clinical Laboratory, The First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu, China

cells and contribute to a large spectrum of disorders, including monoclonal gammopathy of undetermined significance(MGUS), immunoglobulin light chain amyloidosis(AL), cold agglutinin disease, monoclonal gammopathy of renal significance, and classic malignancies, such as MM and Waldenström macroglobulinemia [2].

The global incidence of MM has been increasing, particularly among men, people aged 50 years or older, and those from high-income countries [3]. Because the first clinical symptoms may have nothing to do with blood system diseases, patients may be treated in orthopedics, nephrology, gastroenterology, infection, cardiology, and other departments according to their clinical symptoms. In diseases with abnormal polyclonal proliferation of globulin, such as autoimmune and infectious diseases, it is easy to ignore the indication of globulin elevation, which makes the diagnosis of diseases such as amyloidosis and POEMS disorder more difficult. Therefore, early detection of M protein will improve the prognosis of patients with M-proteinemia [4, 5].

Immunoglobulin secreted by B cells and plasma cells is mainly composed of heavy chain and light chain, and the latter can be categorized into light chain kappa (K) and lambda (L). The concentration of normal human serum kappa light chain is about two times of that of lambda light chain. The serum total light chain (sTLC) includes the light chain bound to a heavy chain as part of an intact immunoglobulin and the free light chain in serum (serum free light chain (sFLC)). In malignancies such as MM, tumor cells can produce a large number of sTLC and sFLC, which cannot be completely cleared by the kidney, so that the sTLC and sFLC concentration exceeded the normal range. Therefore, both sTLC and sFLC levels are considered to be tumor markers in the diagnosis and monitoring of MM [6]. The sFLC ratio has been listed as a criteria for MM and related plasma cell disorders by International Myeloma Working Group [7]. However, there has been limited research on the serum total K/L value as an early warning of M-proteinemia [8]. In addition, studies have found that patients with MGUS have different degrees of risk for developing MM, Waldenström's macroglobulinemia, AL, or lymphoma [9, 10]. Thus, attention should be paid to the detection of all types of M protein. In addition to MM and B lymphoma, abnormal K/L values are also commonly seen in conditions such as immune deficiency, autoimmune disease(AID), infection, and non-B lymphoma [11, 12]. However, M-proteinemia differs from other types of abnormal light chain diseases is that most of the former have light chain restriction—that is, one parent chain is absolutely dominant. The purpose of this study was to investigate the early warning values of K/L for detecting M-proteinemia and determine reasonable cutoff values, according to which further serum immunofixation electrophoresis(sIFE) or serum protein electrophoresis(SPE) could be performed to increase the detection rate of M protein.

Samples and methods

Clinical data

Serum samples of patients were collected from January 2021 to December 2023 in the First Affiliated Hospital of Soochow University. The informed consent was obtained from all subjects. The positive samples included 156 patients characterized by M-proteinemia that were discovered for the first time. The presence of M protein was confirmed by sIFE. The negative samples included 4,722 patients in the negative diseases and 742 healthy persons. The inclusion criteria for the negative disease group were a clear diagnosis, no B-cell or plasma-cell clonal diseases, no M protein detected after sIFE or serum protein electrophoresis. The healthy negative group included patients with a healthy physical examination and non-elevated kappa and lambda levels. All the samples were divided into two groups, the samples from January 2021 to September 2022 were used as a modeling group for obtaining optimal cutoff values, and the samples from October 2022 to December 2023 were used as a validation group to verify the optimal cutoff values. The modeling group include 68 cases of positive samples and 3099 cases of negative samples. The validation group include 88 cases of positive samples and 2365 cases of negative samples. Another group including 106 patients with definite diagnosis of monoclonal gammopathy ranging from January 2021 to June 2024 were used for retrospective analysis to improve the diagnostic efficiency.

Specimen collection

Venous blood was collected into blood collection tubes with vacuum coagulation gel and centrifuged at 2,000 g for 7 min after coagulation, and the upper serum was separated.

Methods

Capillarys 2 Flexpiercing system (Sebia Inc., France) with its accessory kits was applied to conduct SPE while HYDRASYS 2 SCAN system (Sebia Inc., France) with its matched reagent was used for sIFE in this research. Furthermore, the contents of IgG, IgA, IgM, kappa and lambda were measured by the IMMAGE 800 analytical system (Beckman Coulter Inc., USA) with its accessory kits.

The reference intervals of IgG, IgA, IgM were set according to the Health Industry Standards of the

People's Republic of China as IgG 8.6–17.4 g/L, IgA 1.0–4.2 g/L, IgM 0.5–2.8 g/L.

The statistic software SPSS 27.0 was used to generate the receiver operating characteristic (ROC) curve based on the patient samples from January 2021 to September 2022. It should be mentioned that the Youden index (YI) used in this research was calculated by sensitivity and specificity analysis (the calculation formula is as follows: sensitivity + specificity-1). And finally, the K/L values corresponding to the maximum YI were chosen as the cutoff values for K- and L-type M proteins. Furthermore, according to the cutoff values, we analyzed the samples from October 2022 to December 2023 as a validation group. The unidentified positive validation group was classified according to heavy chain types—IgG positive (IgG+), IgA positive (IgA+), IgM positive (IgM+), and others (IgG-, IgA-, and IgM-negative)—and the proportions of these types bound to different light chains were calculated. The negative validation group was classified according to various disease, and the subgroups prone to false positives were further analyzed. In addition, the humoral immunity results of another 106 patients with definite diagnosis of monoclonal gammopathy ranging from January 2021 to June 2024 were traced back to compare the sensitivities of cut-offs for different diseases.

Results

ROC analysis

As shown in Fig. 1, blots judged as positive for M protein were cropped from the original images.

The type of monoclonal immunoglobulin can be determined by observing the presence of the dark, concentrated bands in each lanes. Each positive heavy chain has a corresponding light chain on the same horizontal line. If only the light chain is positive, it can be interpreted as a light chain-type M protein when other heavy chain such as IgD or IgE were ruled out. Two original images can be seen in supplementary material 1.

ROC curves were generated by K-positive M-proteinemia(K+) and L-positive M-proteinemia(L+) combined with M protein-negatives in modeling group separately. The optimal cutoff value for K + was K/L > 2.31(Youden Index 0.832) and for L + was K/L < 1.43(Youden Index 0.646). The ROCs are shown in Fig. 2.

As shown in Fig. 2, the area under the curve (AUC) was greater than 0.7 in both groups, indicating a high warning value. The AUC of K-type M protein (0.958) was larger than that of L-type M protein (0.886).

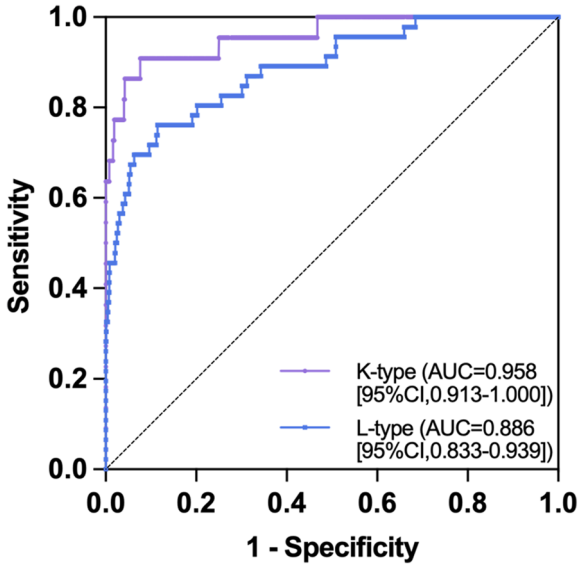

Fig. 2 Receiver operating characteristic curves of K- and L-type M protein

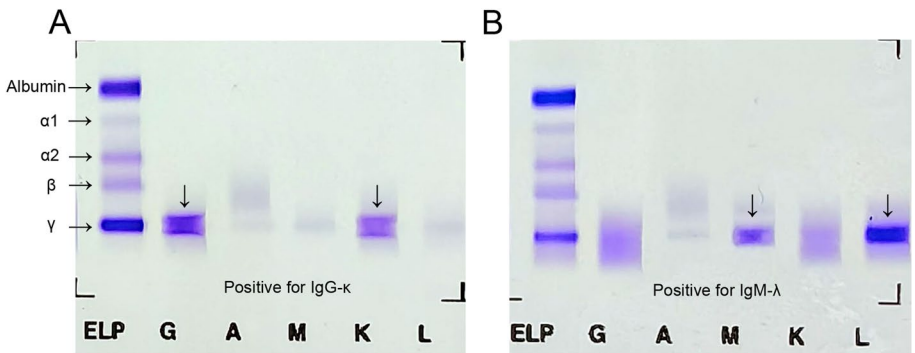

Fig. 1 Electrophoretic pattern of K-type IgG monoclonal gammopathy(A) and L-type IgM monoclonal gammopathy(B). Abbreviations: ELP, lane of serum protein electrophoresis (blots from top to bottom correspond to albumin, α1-globulin, α2-globulin, β-globulin and γ-globulin); G, lane of anti-IgG heavy chain; A, lane of anti-IgA heavy chain; M, lane of anti-IgM heavy chain; K, lane of anti-kappa light chain; L, lane of anti-lambda light chain

False-negative results analysis

The proportions of monoclonal IgG, IgA, IgM and others in the positive validation group were 53.41%, 20.45%, 15.91% and 10.22% respectively. The distribution of K/L values in different conditions are shown in Fig. 3.

Figure 3 (A) reveals that the K/L values of K-type and L-type M-proteinemia were obviously stratified. Figure 3 (B)shows the K/L values of K-type M-proteinemia grouped by different monoclonal heavy chain. In K-type M-proteinemia, IgG monoclonal gammopathy and IgM monoclonal gammopathy have more crossovers with NC. Figure 3 (C)shows the K/L values of L-type M-proteinemia grouped by different monoclonal heavy chain. In L-type M-proteinemia, IgA monoclonal gammopathy, IgM monoclonal gammopathy and others have more crossovers with NC.

The sensitivity of using K/L > 2.31 and K/L < 1.43 as cutoff values was verified to be 76.14% in the whole M protein-positive validation group. The false negative rates in different type of M-proteinemia are detailed in Fig. 4.

Figure 4 shows the false negative rates in different groups. As shown in the figure, the M protein-positive groups with heavy chain IgA and IgM have the highest probability of false negatives. The FNR of L-type M-proteinemia is much higher than K-type M-proteinemia.

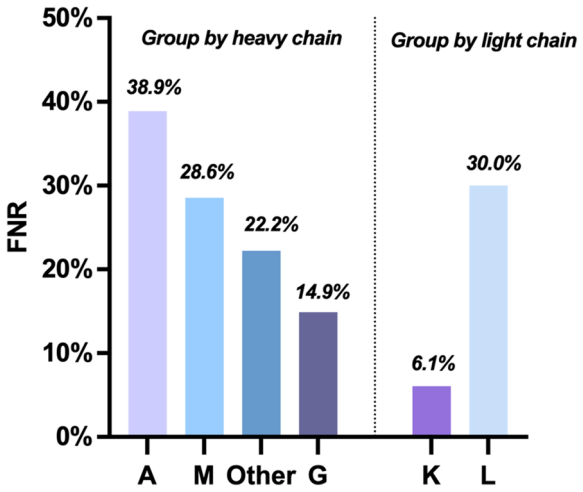

Fig. 4 False negative rates in different groups. Abbreviations: G, IgG monoclonal gammopathy; A, IgA monoclonal gammopathy; M, IgM monoclonal gammopathy; K, K-type M-proteinemia; L, K-type M-proteinemia; FNR: False negative rate

Further analysis of the heavy chain contents revealed that the individual increase of IgM content in all the IgM false negatives accounted for 71.4%, while the single increase of IgA content in all the IgA false negatives accounted for 35.7%.

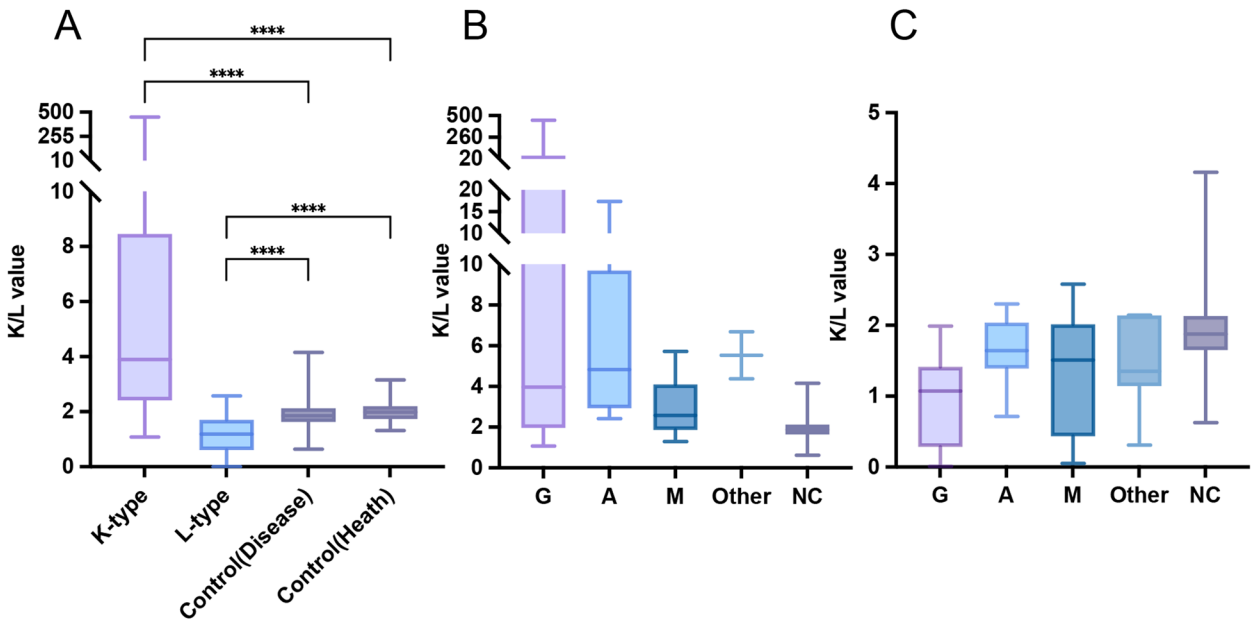

Fig. 3 Comparison of K/L values distribution in the whole validation group (**A**), K-type M-proteinemia (**B**) and L-type M-proteinemia (**C**). Abbreviations: G, IgG monoclonal gammopathy; A, IgA monoclonal gammopathy; M, IgM monoclonal gammopathy; NC, negative control in validation group. ****significant differences ($P < 0.0001$)

False-positive results analysis

The specificity of using K/L > 2.31 and K/L < 1.43 as cut-off values was verified to be 77.42% in the whole negative validation group. Patients in the negative validation group were grouped according to their disease. The K/L values of different diseases were compared with healthy people respectively. The detailed data are shown in Table 1.

As Table 1 shows, the K/L values of AID and infection are significantly different from health. To calculate the false positive rate(FPR) in different diseases, we further grouped autoimmunity diseases (AID) into 410 cases of systemic lupus erythematosus (SLE), 187 cases of connective tissue diseases(CTD), 132 cases of sicca syndrome (SS), 104 cases of rheumatoid arthritis(RA), 37 cases of dermatomyositis(DM), 38 cases of systemic sclerosis (SSC) and other AID. The highest FPR is 36.8%, occurred in SSC, then followed by 28.7% in hypohepatia and 27.3% in SS. The results are shown in Fig. 5.

Figure 5 shows that the FPR of K/L>2.31 is higher than K/L<1.43 in most disease groups and health group, while the FPR of K/L <1.43 is higher than K/L>2.31 in SLE group. In health group, the false-positive results occur mainly in K/L>2.31.

Table 1 Data summary of the negative validation group

Diagnose		Amount	Mean	SD	P
Health		345	2.00	0.32	
Diseases		2020	1.89	0.41	
	AID	1260	1.87	0.41	<0.001
	Cancer	225	1.94	0.36	0.058
	Hypohepatia	101	1.96	0.44	0.437
	Infection	147	1.89	0.38	<0.001
	TCL	187	1.96	0.44	0.313
	Other	100	1.82	0.42	<0.001

AID Autoimmunity diseases, TCL T-cell derived lymphoma, SD Standard deviation, P Independent sample T test compared with healthy people

Promotion of diagnostic efficiency

After combined K/L with immunoglobulin index, three possible screening conditions named A to C as listed below were designed based on the analysis of false negative and positive data: A: K/L < 1.43 or K/L > 2.31; B: Two or more indicators decrease among IgA, IgG and IgM; C: IgA or IgM alone elevate The data in validation group were checked under different coupled conditions for specificity. Furthermore, another 106 cases of confirmed diagnosis of monoclonal gammopathy were retroactively validated for sensitivities in different screening conditions. The results are shown in Table 2.

As shown in Table 2, K/L value combine with the contents of IgA, IgG and IgM can increase the sensitivity of M protein detection. However, when combined with condition B, patients with other hematological malignancies and those receiving immunosuppressive therapy should be excluded. Condition A combining with condition B can significantly improve the detection rate of AL, MGRS. While condition A combining with condition C can significantly improve the detection rate of MGUS. Only one sample with MM (non-secretory myeloma) was not detected under condition A.

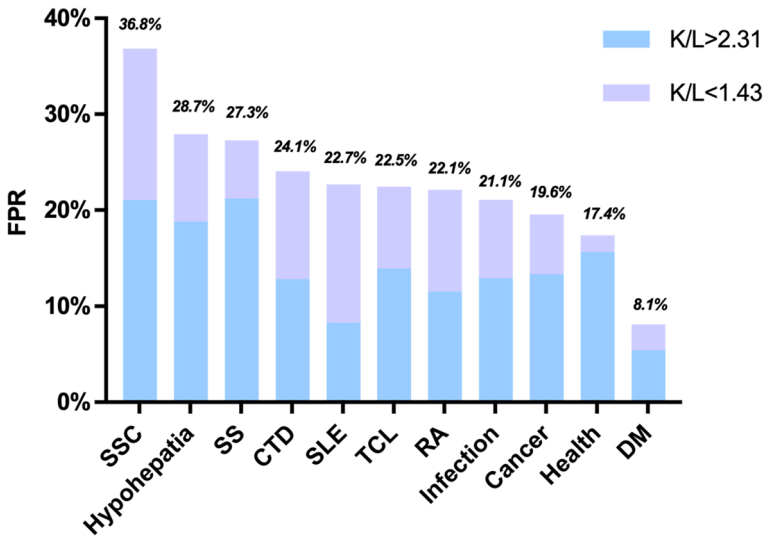

Fig. 5 False positive rates in different diseases. Abbreviations: FPR, false positive rate; SSC, systemic sclerosis; SS, sicca syndrome; CTD, connective tissue diseases; SLE, systemic lupus erythematosus; TCL, T-cell derived lymphoma; RA, rheumatoid arthritis; DM, dermatomyositis

Table 2 Validation results of different screening conditions

	MM	LPL	WM	SMM	MGRS	MGCS	MGUS	AL	
n	43	4	2	1	13	5	20	18	
Condition	Sensitivity %								Specificity%
A	97.67	100	100	100	69.23	80	75	66.66	77.42
A or B	100	100	100	100	76.92	80	80	83.33	72.9(Note)
A or C	97.67	100	100	100	76.92	80	80	66.66	70.95
Satisfies any of A, B and C	100	100	100	100	84.62	80	85	83.33	66.51

A, K/L < 1.43 or K/L > 2.31, *B* two or more indicators decrease among IgA, IgG and IgM, C, IgA or IgM alone elevate, *MM* Multiple myeloma, *LPL* Lymphoplasmacytic lymphoma, *WM* Waldenstrom macroglobulinemia, *SMM* Smoldering multiple myeloma, *MGRS* Monoclonal gammopathy of renal significance, *MGCS* Monoclonal gammopathy of clinical significance, *MGUS* Monoclonal gammopathy of undetermined significance, *AL* Amyloidosis

Note: The 85.76% new false negative patients were concentrated in TCL and patients receiving immunosuppressive therapy

Discussion

Patients with MM experience significant delays in diagnosis due to non-specific symptomatology. Early detection of this disease is of great significance for prognosis. Meanwhile, there are often different outcomes with different heavy chain type of M-proteinemia. At present, methods used to detect M protein are electrophoresis, sFLC assay, heavy/light chain(HLC) assay [13] and mass spectrometry [14, 15]. In terms of diagnostic accuracy, sFLC assay is outstanding, however, sFLC are usually performed in patients with clinical suspicion of monoclonal gammopathy, not appropriate for population screening due to the high cost and the poor comparability between the methodologies. Studies have found that reagent lot-to-lot variation of up to 45% for sFLC concentration and 32% for calculated sFLC ratio may affect proper monoclonal gammopathy monitoring [16]. By contrast, the methods of detecting serum total kappa and lambda are more mature and the results are more stable as the results can be traced to the reference material (ERM-DA470/IFCC). Meanwhile, serum total kappa and lambda are routinely measured in the majority of Chinese hospitals, which give serum total K/L a broader application field as a population screening indicator.

Changes in free light chains may affect the ratio of total serum light chains. The serum free light chain ratio is often outside of the normal reference range in several conditions, including chronic infection (osteomyelitis, endocarditis, HIV, EBV), inflammation, IgG4-related disease, autoimmune diseases (RA, SLE, Sjogren), neoplasm (lung, liver, gastric, rare T-cell lymphomas), liver disease (cirrhosis, chronic hepatitis) and renal failure [17]. In our study, we collected many of these diseases as a negative group. According to the results, K/L cutoffs of > 2.31 and < 1.43 for intercepting M protein showed AUCs of 0.958 and 0.886 respectively, with high early warning values. Moreover, when K/L > 2.31 and K/L < 1.43 were set at the same time, the specificity and sensitivity were reduced, which were verified to be 77.42%(specificity) and 76.14%(sensitivity) respectively for M protein detection. Thus, it is necessary to analyze the FNR and FPR in different conditions.

The proportions of monoclonal IgG, IgA, IgM and others in our positive validation group are 53.41%, 20.45%, 15.91% and 10.22%, which is consistent with the experimental result reported in literature [18]. We found that the FNR of L-type M protein (30.00%) is much higher than K-type (6.06%) on basis of K/L > 2.31 and K/L < 1.43. This may suggest a higher correlation between lambda light chain and M-proteinemia with low M-protein content, such as AL and MGUS [19]. In addition, K/L value is also related to different degrees of renal injury. The kappa FLCs are normally present in the serum as monomers, with a molecular mass of 22.5 kDa. Lambda FLCs frequently form dimers in the serum which increases their molecular mass to 45 kDa. The renal excretion of free kappa is much faster than free lambda. Serum FLC concentrations increased through the stages of decreasing eGFRs(Estimated glomerular filtration rate), which lead the increasing of K/Lvalue [20, 21]. As a result, L-type M proteinemia accompanied by renal impairment may not be easily detected. This was also verified in retrospective analysis, the sensitivity is lowest for AL(66.66%), followed by MGRS(69.23%) and MGUS(75%). Exclude very few cases with weakly positive expression in both light chain, the highest FNR was 38.89% for IgA monoclonal gammopathy, followed by 28.57% for IgM monoclonal gammopathy. This may be due to that the content of IgM or IgA is much lower than IgG in serum. However, there is a higher risk of disease progression in IgM and IgA MGUS than IgG [22, 23]. In consideration of this, we further analyzed the contents of gammopathy. We found that the individual increase of IgM content in all the IgM false negatives accounted for 71.4%, while the single increase

of IgA content in all the IgA false negatives accounted for 35.7%, in addition, there were 20% cases in the false negatives appeared at least two items decrease among IgA, IgG and IgM. So, another two rules are supplemented to improve the sensitivity: one rule is IgA or IgM alone elevate while the other is two or more indicators decrease among IgA, IgG and IgM. After combining all the above rules for M-protein detection, the sensitivities of AL, MGRS and MGUS can be significantly improved to 83.33%, 84.62% and 85%, respectively. However, patients with other hematological malignancies and those receiving immunosuppressive therapy should be excluded. In the research of Nasr SH et al., the sensitivity of SPE for AL was 54%, while the sensitivity was 81% accompanied by heavy chains [24]. Therefore, it is recommended to combine SPE and K/L value to improve specificity with the independent value increase of IgA or IgM. In addition, in the research of Nasr SH et al., the sensitivity of sFLC ratio for AL was 80% [24], which is much higher than total K/L for AL in our study. sTLC assay identify the light chain component of intact immunoglobulins and free light chains in serum while sFLC assay recognizes only the free light chain component. The presence of a polyclonal background prevents the sTLC assay from being able to distinguish clonality at < 4 g/L, whereas the sFLC assay can detect clonality at mg/L concentrations [25]. Therefore, for monoclonal light chain with lower content, the sFLC ratio has better sensitivity than the sTLC ratio.

In the validation group, the K/L values of AID and infection group are significantly different from health group ($P < 0.001$), meanwhile, we further grouped AID into SLE, CTD, SS, RA, DM, SSC to calculate the false positive rates. The false positive rate is highest in SSC (36.84%), followed by hypohepatia (28.71%) and SS (27.27%). What's interesting is that SS showed a FPR dominated by K/L > 2.31, which was very special in the AID we counted. In SLE, the false-positive results occurred mainly in K/L < 1.43. This may suggest the values of K/L in the development and prognosis of different autoimmune diseases. Yang D et al. mentioned in their paper that lambda light chains are frequently responsible for triggering the activation of inflammatory factors in autoimmune disorders, and an increase in their levels will cause various pathological changes in serum [26].

Because the Beckman IMMAGE800 immune-scattering turbidity ratio was used to measure the K/L values, the cutoff values obtained in this study can only be applied to Beckman IMMGE800 inspection and measurement systems, other detection systems require concrete verification (The K/L ratio may be slightly higher than other systems, the maximum deviation was 10.81%. Comparisons between the instruments are shown in supplementary material 2). Meanwhile, the number of positive cases and the disease types were limited, otherwise, the infection group was not distinguished between viral and bacterial. Thus, expanded statistical analyses should be conducted after setting the cutoff values.

Abbreviations

K/L	kappa/lambda ratio
sTLC	serum total light chain
sFLC	serum free light chain
ROC	Receiver operating characteristic
AUC	area under the curve
SPE	serum protein electrophoresis
sIFE	serum immunofixation electrophoresis
MGUS	monoclonal gammopathy of undetermined significance
AL	Immunoglobulin light chain amyloidosis
AID	autoimmune disease
SLE	systemic lupus erythematosus
CTD	connective tissue diseases
SS	sicca syndrome
RA	rheumatoid arthritis
DM	dermatomyositis
SSC	systemic sclerosis
FNR	False negative rate
FPR	False positive rate
MM	Multiple myeloma
LPL	lymphoplasmacytic lymphoma
WM	Waldenstrom macroglobulinemia
SMM	Smoldering multiple myeloma
MGRS	Monoclonal gammopathy of renal significance
MGCS	Monoclonal gammopathy of clinical significance
IFCC	International Federation of Clinical Chemistry

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12865-024-00664-6.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

We thank Dr Liang YT and Dr Bai DH for their assistance in revising the manuscript. We also thank all the participants in the study

Authors' contributions

All the authors contributed to this study. Lu J performed the whole research and wrote the manuscript. Zhu Y performed the experiments and analyzed the data. Huang HF and Yang Q contributed to the critical revision of the manuscript. Qi SN supervised the entire experiment and performed the final review of the article. All authors read and approved the final manuscript.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Soochow University (ethical review report number: 2024 – 077). All methods were carried out in accordance with relevant guidelines and regulations. The informed consent was obtained from all subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 11 March 2024 Accepted: 24 October 2024
Published online: 30 October 2024

References

1. Murray DL, Puig N, Kristinsson S, et al. <ArticleTitle Language="En">Mass spectrometry for the evaluation of monoclonal proteins in multiple myeloma and related disorders: an International Myeloma Working Group Mass Spectrometry Committee Report[J]. Blood cancer J. 2021;11(2):24.
2. Gao Y, Feng X et al. Prognostic significance of serum monoclonal proteins based on immunofixation electrophoresis in B-cell non-Hodgkin lymphoma [J]. Ann Hematol Published online Dec 20, 2023.
3. Huang J, Chan SC, Lok V, et al. The epidemiological landscape of multiple myeloma: a global cancer registry estimate of disease burden, risk factors, and temporal trends. Lancet Haematol. 2022;9(9):670–7.
4. Wang W, Li J, Yang Y et al. Update on the outcome of M-protein screening program of multiple myeloma in China: A 7-year cohort study. Cancer Med Published online Dec 22, 2023.
5. Seesaghur A, Petruski-Ivleva N, Banks VL, et al. Clinical features and diagnosis of multiple myeloma: a population-based cohort study in primary care[J]. BMJ open. 2021;11(10):52–9.
6. Zhai L, Zhao Y, Peng S, et al. Detection of the value of consecutive serum total light chain (sTLC) in patients diagnosed with diffuse large B cell lymphoma[J]. Ann Hematol. 2016;95(12):1999–2007.
7. Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma. Am Soc Clin Oncol Educ Book. 2016;35:e418–23.
8. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study [J]. Blood. 2009;113(541):2–7.
9. Khwaja J, D'Sa S, Minnema MC, Kersten MJ, Wechalekar A, Vos JM. IgM monoclonal gammopathies of clinical significance: diagnosis and management. Haematologica. 2022;107(9):2037–50. Published 2022 Sep 1.
10. Pang L, Rajkumar SV, Kapoor P, et al. Prognosis of young patients with monoclonal gammopathy of undetermined significance (MGUS). Blood Cancer J. 2021;11(2):26. Published 2021 Feb 1.
11. Lam CW, Chui SH, Leung NW, Li EK, Lai KN. Light chain ratios of serum immunoglobulins in disease. Clin Biochem. 1991;24(3):283–7.
12. Grimaldi LM, Castagna A, Maimone D, et al. Kappa light chain predominance in serum and cerebrospinal fluid from human immunodeficiency virus type 1 (HIV-1)-infected patients. J Neuroimmunol. 1991;32(3):259–68.
13. Keren DF, Schroeder L. Challenges of measuring monoclonal proteins in serum[J]. ClinicalChemistry Lab Med. 2016;54(6):947–61.
14. BarnidgeDR, Surendra D, Marina RA, et al. Phenotyping polyclonal kappa and lambda light chain molecular massdistributions in patient serum using mass spectrometry[J]. J ProteomeResearch. 2014;13(11):5198–205.
15. BarnidgeDR, Dispenzieri A, Merlini G, et al. Monitoring free light chains in serum using mass spectrometry[J]. ClinicalChemistry Lab Med. 2016;54(6):1073–83.
16. Lim SM, Wijeratne N, Choy KW, et al. A review of clinical guidelines, laboratory recommendations and external quality assurance programs for monoclonal gammopathy testing[J]. Crit Rev Clin Lab Sci. 2024;61(2):107–26.
17. Drayson M, Jennis T, Laketic-Ljubojevic I, et al. Laboratory practice is central to earlier myeloma diagnosis: Utilizing a primary care diagnostic tool and laboratory guidelines integrated into haematology services[J]. Br J Haematol. 2024;204(2):476–86.
18. Pontet F. A data base for 3000 monoclonal immunoglobulin cases and a new classification[J]. Clin Chim Acta. 2005;355(1/2):13–21.
19. Gertz MA. Immunoglobulin light chain amyloidosis: 2018 Update on diagnosis, prognosis, and treatment[J]. Am J Hematol. 2018;93(9):1169–80.
20. Hutchison CA, Cockwell, et al. Quantitative assessment of serum and urinary polyclonal free light chains in patients with type II diabetes: an early marker of diabetic kidney disease[J]. Expert Opin Ther Targets. 2008;12(6):667–76.
21. Rajkumar S, Vincent RA, Kyle, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance[J]. Blood. 2005;106(3):812–7.
22. Kyle RA, Themeau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance [J]. N Engl J Med. 2002;346:564–9.
23. Lomas OC, Mouhieddine TH, Tahri S, et al. Monoclonal gammopathy of undetermined significance (MGUS)—Not so asymptomatic after all [J]. Cancers. 2020;12(6):1554.
24. Nasr SH, Said SM, Valeri AM, et al. The diagnosis and characteristics of renal heavy-chain and heavy/light-chain amyloidosis and their comparison with renal light-chain amyloidosis[J]. Kidney Int. 2013;83(3):463–70.
25. Tietsche de Moraes Hungria V, Allen S, Kampanis P, Soares EM. Serum free light chain assays not total light chain assays are the standard of care to assess Monoclonal Gammopathies[J]. Rev Bras Hematol Hemoter. 2016;38(1):37–43.
26. Yang D, Yuan L, Ma X, et al. Histological study of Bactrian camel cryptorchidism and expression of immunoglobulin λ light chain in the testicular and epididymis of cryptorchid Bactrian camel[J]. Reprod Domest Anim. 2024;59(1):e14512.

Publisher's Note