J Med Biochem 2011; 30 (4) DOI: 10.2478/v10011-011-0017-3

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 30: 293–301, 2011

Original paper
Originalni naučni rad

FREE LIGHT CHAINS OF IMMUNOGLOBULIN AS A PROGNOSTIC FACTOR FOR SOME PLASMAPROLIFERATIVE DISEASES

SLOBODNI LAKI LANCI IMUNOGLOBULINA KAO PROGNOSTIČKI FAKTOR KOD NEKIH PLAZMAPROLIFERATIVNIH BOLESTI

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Summary: Quantitation of monoclonal immunoglobulins and their fragments is used for monitoring the plasmaproliferative disease course and the effect of therapy. The aim of free light chains examination was to evaluate the significance of the FLC ratio as a prognostic factor for remission, progression and survival in different disease groups. The concentrations of immunoglobulins and free light chains were measured by an immunonephelometric method on a »SIEMENS« DADE BN II analyser with reagents (Freelite, The Binding Site, UK). In this examination 151 patients from 3 different disease groups: 1. Light chain disease or Bence Jones myeloma (37), 2. Biclonal gammopathy with FLC (23) and 3. Monoclonal gammopathy of undetermined significance (91), were investigated during a period of 7 years. The reference interval for FLC ratio is 0.26–1.65. According to the International Staging System for multiple myeloma, a serum FLC ratio of <0.03 or >32 was taken as abnormal. The patients with light chain disease and biclonal gammopathy with FLC with an abnormal FLC ratio and a combination of adverse risk factors (76.7%) had median survival times of 22–30 months, versus patients with a normal or slightly varied

Kratak sadržaj: Kvantitativno određivanje monoklonskih imunoglobulina i njihovih fragmenata koristi se za praćenje toka i terapijskog odgovora kod plazmaproliferativnih bolesti. Cilj određivanja slobodnih lakih lanaca imunoglobulina u serumu bolesnika jeste provera značaja njihovog količnika (κ/λ indeks) kao prognostičkog faktora remisije, progresije i preživljavanja. Koncentracije imunoglobulina i slobodnih lakih lanaca određivane su imunonefelometrijskom metodom na analizatoru SIEMENS DADE Behring II sa reagensima (FREELITE, The Binding Site, UK). U ispitivanje je uključen 151 bolesnik tokom perioda od 7 godina, koji su razvrstani u 3 grupe: 1. bolest lakih lanaca ili Bence Jones mijelom (37); 2. biklonalna gamapatija sa slobodnim lakim lancima (23) i 3. monoklonska gamapatija neutvrđenog značaja (91). Referentnim intervalom za κ/λ indeks smatraju se vrednosti 0,26–1,65. Prema Internacionalnom prognoznom indeksu za multipli mijelom, kao patološki uzet je κ/λ indeks <0,03 ili >32. Bolesnici iz prve dve grupe sa patološkim k/λ indeksom i kombinacijom nepovoljnih faktora rizika (76,7%) imali su prosečno vreme preživljavanja 22–30 meseci, nasu-

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List of abbreviations: Ig – immunoglobulin, HC – heavy chain, κ – kappa, λ – lambda, LC – light chain, MGUS – monoclonal gammopathy of undetermined significance, MM – multiple myeloma, WM – Waldenström's macroglobulinemia, LCD – light chain disease, LCDD – light chain deposit disease, BJ myeloma – Bence Jones myeloma, FLCs – serum free light chain, FLC ratio – κ/λ ratio, Ag – antigen, MG – monoclonal gammopathy, BG – biclonal gammopathy, TG – triclonal gammopathy, QG – quadriclonal gammopathy, Sn – sensitivity, Sp – specificity, PV – predictive value, PPV – positive predictive value, NPV – negative predictive value, ISS – International Staging System, MP protocol – Melphalan/Prednisone, MPT protocol – Melphalan/Prednisone/Thalidomide, CTD protocol – Cyclophosphamide/Thalidomide/Dexamethasone, VAD protocol – Vincristine/ Adriamycin/ Dexamethasone, SCT – stem-cell transplantation, SE – sedimentation of erythrocytes, 95% CI – 95% confidence interval, RR – relative risk, PD – progresive disease, Sβ2M – serum β2 microglobuluin, M – monoclonal, TP – true-positive, TN – true-negative, FP – false-positive, FN – false negative.

FLC ratio without adverse risk factors (23.3%) with median survival times of 39–51 months. About 38% of patients who had shown lowered free light chains values by more than 50% under therapy, achieved disease remission in the light chain disease and biclonal gammopathy with FLC groups. In the group of patients with monoclonal gammopathy of undetermined significance, 66.0% had a normal or slightly modified FLC ratio which corresponds to low and low-intermediate risk of disease progression, as opposed to 34.0% with an abnormal FLC ratio (<0.25 or >4) which corresponds to high and high-intermediate risk. An abnormal FLC ratio in the examined groups could be an independent risk factor for progression and poorer disease prognosis.

Keywords: free light chains, FLC ratio, plasmaproliferative disease, prognostic factor

prot bolesnicima sa fiziološkim ili neznatno izmenjenim κ/λ indeksom bez nepovoljnih faktora rizika (23,3%), sa prosečnim vremenom preživljavanja 39–51 mesec. Oko 38% bolesnika koji su pod terapijom imali sniženje κ/λ indeksa >50% su ostvarili remisiju bolesti. U grupi ispitanika sa MGNZ, 66,0% je imalo fiziološke ili neznatno izmenjene κ/λ indekse, što odgovara niskom i srednje niskom riziku progresije, nasuprot 34,0% sa patološkim κ/λ indeksom (<0,25 ili >4), što odgovara srednje visokom i visokom riziku progresije. Postojanje patološki značajnog κ/λ indeksa u ispitivanim grupama predstavlja nezavisan faktor rizika za progresiju bolesti i lošiju prognozu.

Ključne reči: slobodni laki lanci, κ/λ indeks, plazmaproliferativne bolesti, prognostički faktor

Introduction

Plasmocytes are the place of synthesis of the immunoglobulin (Ig) molecule, which consists of 2 heavy chains (HC) and 2 kappa (κ) or lambda (λ) polypeptide light chains (LC). Under normal conditions, the concentrations of polyclonal Free κ and λ Light Chains (FLC) are 3–19 and 5–26 mg/L, respectively. In abnormal conditions, such as benign or malignant forms of plasmaproliferative diseases – monoclonal gammopathies of undetermined significance (MGUS), multiple myeloma (MM) isotypes or Waldenstrom's macroglobulinemias (WM), one or several clones of B lymphocytes or plasmocytes synthesize only LC Ig, of κ or λ type in excessive amount. One version of MM is light chain disease (LCD) or Williams disease, which is often a synonym for the so-called Bence Jones (BJ) myeloma. Monospecific antisera to FLC Ig (»free« κ or λ) are used for the detection and identification of LC, and they react only with »hidden« antigens (Ag) on LC molecules. A patient can have two monoclonal (M) components and then we can talk about biclonal gammopathy (BG), and rare cases of triclonal gammopathy (TG) or quadriclonal gammopathy (QG) which are also described. In some cases, more than one clone may produce monoclonal gammopathies (biclonal or, very rarely, triclonal) (1). BG makes up 0.14–3% of all monoclonal gammopathies (MG). Patients with these homogenous M fractions in the electropherogram of serum or urine, which are called paraproteins, meet the diagnostic criteria for malignant plasmaproliferative diseases. Patients who do not meet the diagnostic criteria for MM, and without proof of any other lymphoproliferative disease are classified as MGUS (2). Concentrations of serum FLC (FLCs) are more sensitive, precise and accurate indicators for the detection, characterization and monitoring of the course of various types of paraproteinemia. Reference measurements of FLC are of great prognostic value for almost all plasma cell disorders (3). From a physiological point of view, serum tests for proteins of small molecular weight have clear advantage over urine tests. The advantage of FLCs determination is that the urine concentrations of filtered LC depend on variable re-absorption and decomposition in the renal proximal tubules. Concentrations of FLCs depend on the balance of secretion in plasma cells and renal clearance. FLCs are rapidly lost by means of glomerular filtration in the kidneys, with a serum half life of 2–6 hours, and they are metabolized in the proximal tubules of the kidneys. Under normal circumstances, small quantities of proteins pass from the kidney to the urinal tract (0.5–1.0 g/24 h), while in abnormal circumstances, approximately 10–30 g of FLC per day are filtrated into urine, and serum concentrations of FLC are increased several times, because the absorption mechanisms are saturated (4). Urine analysis is not a reliable proof that the concentration of synthesised FLC has changed. This fact is important, especially for older patients, because it is very hard to collect their urine samples during 24 hours, and the results can be unreliable (5). The reduction of the FLC ratio (κ/λ ratio) by more than 50% in relation to the beginning of therapy, together with the maintenance of unchanged values of intact monoclonal Ig, is the first indicator of good serologic response to the therapy administered during the treatment (6, 7).

The aim of the determination of FLC Ig in the patients' sera was to check the importance of their FLC ratio as a prognostic factor for remission, progression and survival in the examined groups of patients.

Patients and Methods

In this prospective clinical study the patients (n=151) were divided into 3 groups:

1. The group including patients with LCD or BJ myeloma (n=37).
2. The group including patients with BG with FLC (n=23).
3. The group including patients with MGUS (n=91).

Thorough clinical trials were done in all three groups, and on the basis of their results the examinees were classified according to the suspected

clinical diagnoses. Blood samples for protein diagnostics were taken in the morning hours in vacutainers, without anticoagulant, from the patients and outpatients of the Military Medical Academy. After the blood collection and spontaneous coagulation at room temperature, samples were centrifuged at 5000 rpm and analyses were done in fresh sera immediately, but some samples were kept at –20 °C for up to one month, and for longer periods they were stored at –70 °C. Quantitative determination of FLC and classes (isotypes) of Ig was done by an automated immunonephelometric method on a SIEMENS DADE Behring II analyzer with reagents (FREELITE, The Binding Site, UK), according to the instructions of the manufacturer in software programs for each analytical parameter.

Statistical analysis

The results obtained in connection with the utility of FLC as a disease prognostic marker are expressed as sensitivity (Sn) and specificity (Sp), along with their positive predictive value (PPV) and negative predictive value (NPV).

Results

The study included 151 patients in the period of seven years (from 2004 to 2010), divided into 3 groups. In the group of examinees with LCD or BJ myeloma, at the time they were diagnosed, 37/37 patients (100%) had FLC concentrations deviating from the reference interval (k=3.3–19.4; λ=5.71–26.3)

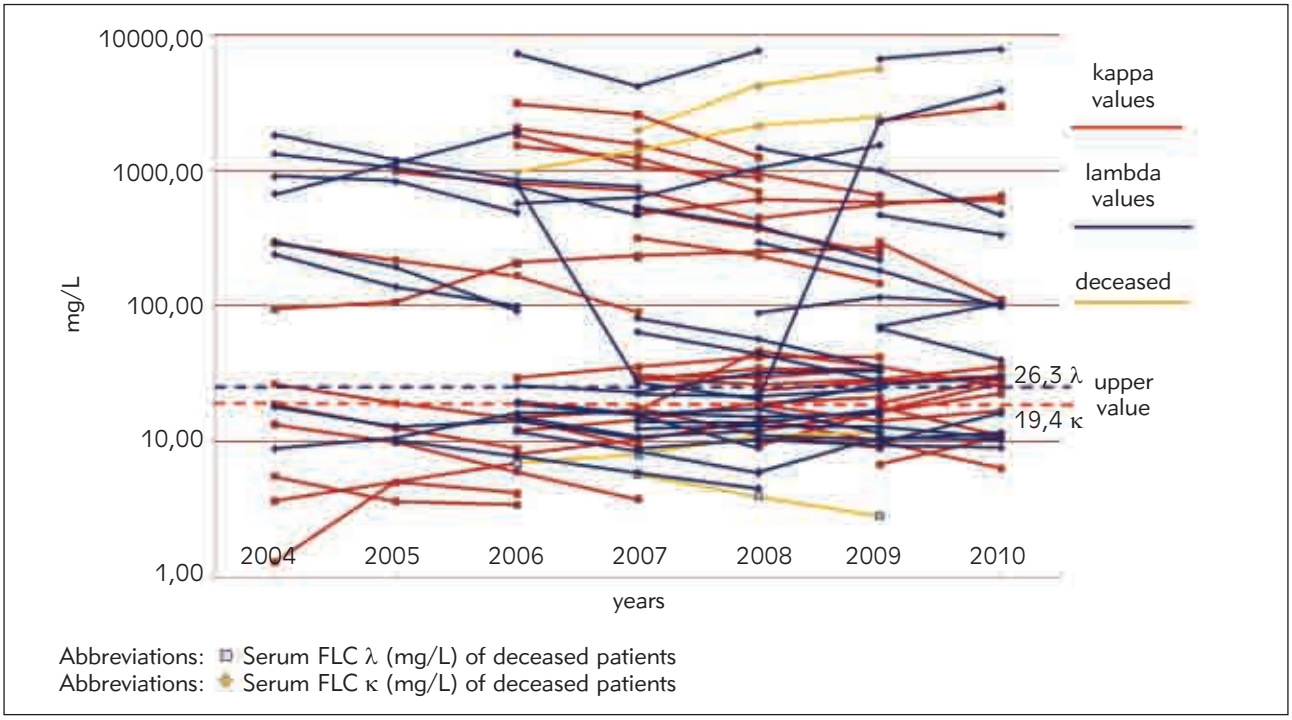

Figure 1 κ/λ-FLC in 37 patients with LCD (BJ myeloma).

Table I The risk factors and survival in 37 patients with LCD (BJ myeloma) according to ISS.

Type of LC Ig (No=number of patients)	FLC ratio	Sβ2M (g/L)	Serum albumin (g/L)	ISS – median survival	The relative risk of disease progression
κ (n=2) λ (n=1)	0.26–1.65 3/37 (8.1%)	<3.5	≥35	(0 risk factors ~ 51 month)	Low risk
κ (n=6) λ (n=1)	(<0.26 ili >1.65 7/37 (18.9%)	<3.5	≥35	(1 risk factor ~ 39 month)	Low intermediate risk
κ (n=3) λ (n=5)	<0.125 ili >8 8/37 (21.6%)	≥3.5–5	≥35	(2 risk factors ~ 30 month)	High intermediate risk
κ (n=9) λ (n=10)	<0.03 ili >32 19/37 (51.4%)	≥5	<35	(3 risk factors ~ 22 month)	High risk

Abbreviations: ISS – international staging system; LCD – light chain disease; BJ myeloma – Bence Jones myeloma; LC – light chain; Ig – immunoglobulin; FLC ratio – κ/λ ratio; Sβ2M – serum β2 microglobulin

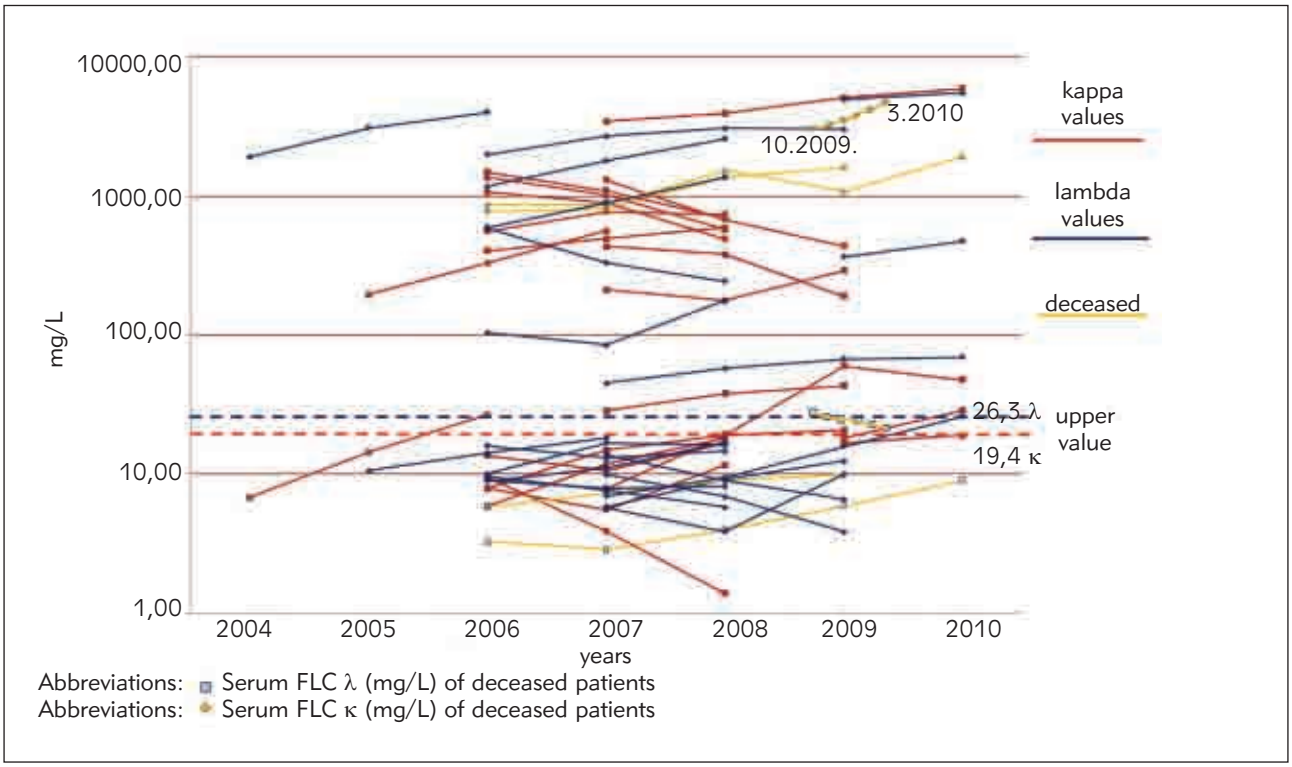

Figure 2 κ/λ-FLC in 23 patients with BG with FLC.

Table II The risk factors and survival in 23 patients with BG with FLC according to ISS.

BG with FLC (No=number of patients)	FLC ratio	Sβ2M (g/L)	Serum albumin (g/L)	ISS – median survival	The relative risk of disease progression
IgGλ-BJλ (n=1)	0.26–1.65 1/23 (4.4%)	<3.5	≥35	(0 risk factors ~ 51 month)	Low risk
IgGκ-BJκ (n=1) IgGλ-BJλ (n=1) IgAλ-BJλ (n=1)	(<0.26 ili >1.65 3/23 (13.0%)	<3.5	≥35	(1 risk factor ~ 39 month)	Low intermediate risk
IgGκ-BJκ (n=1) IgGλ-BJλ (n=1)	<0.125 ili >8 2/23 (8.7%)	≥3.5–5	≥35	(2 risk factors ~ 30 month)	High intermediate risk
IgGκ-BJκ (n=8) IgGλ-BJλ (n=4) IgAκ-BJκ (n=1) IgAλ-BJλ (n=4)	<0.03 ili >32 17/23 (73.9%)	≥5	<35	(3 risk factors ~ 22 month)	High risk

Abbreviations: ISS – international staging system; BG – biclonal gammopathy; FLC – free light chain; FLC ratio – κ/λ ratio; Sβ2M – serum β2 microglobulin

mg/L. Measured concentrations for FLC of κ-type are from 1.30 to 5650.00 (mg/L), and for FLC of λ-type from 2.82 to 7900.50 (mg/L). Graphic illustration is shown in *Figure 1*. Regarding sex, there were 16 women (43.2%) and 21 men (56.8%). Results show that 3 patients (8.1%) had FLC ratios within the reference interval (0.26–1.65), and 19 patients (51.4%) had high abnormal FLC ratios (<0.03 or >32). The remaining 8 patients (21.6%) had intermediate abnormal FLC ratios (<0.125 or >8), and 7 patients (18.9%) had low abnormal FLC ratios (<0.26 or >1.65) *(Table I)*. In the group of examinees with BG with FLC, at the time they were diagnosed, 23/23 patients (100%) had concentrations of FLC deviating from the reference interval. Measured concentrations for FLC of κ-type are from 3.30 to 5862.10 (mg/L), and for FLC of λ-type from 3.87 to 5451.00 (mg/L). Graphic illustration is shown in *Figure 2*. Regarding sex, there were 9 women (39.2%), and 14 men (60.8%). The results show that 1 patient (4.3%) had an FLC ratio within the reference interval (0.26–1.65), and 17 patients (73.9%) had high abnormal FLC ratios (<0.03 or >32). The remaining 2 patients (8.7%) had intermediate abnormal FLC ratios (<0.125 or >8), and

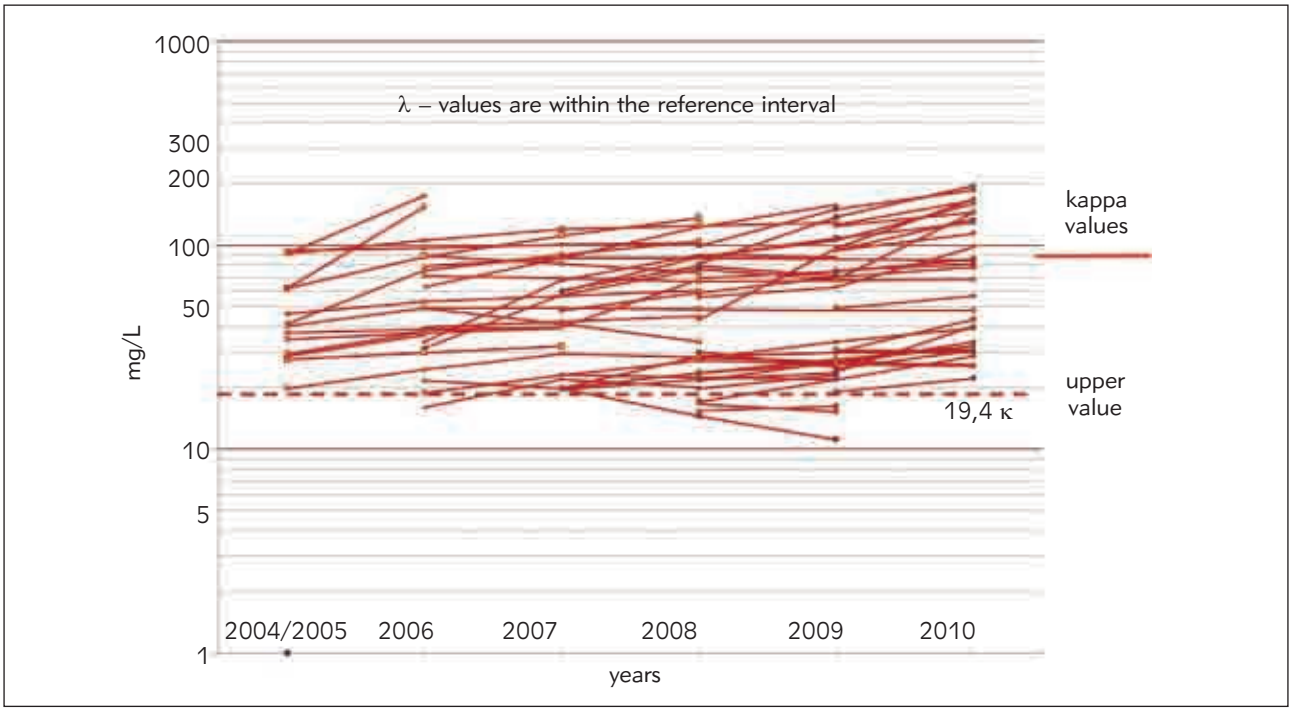

Figure 3 κ – values in 58 patients with MGUS.

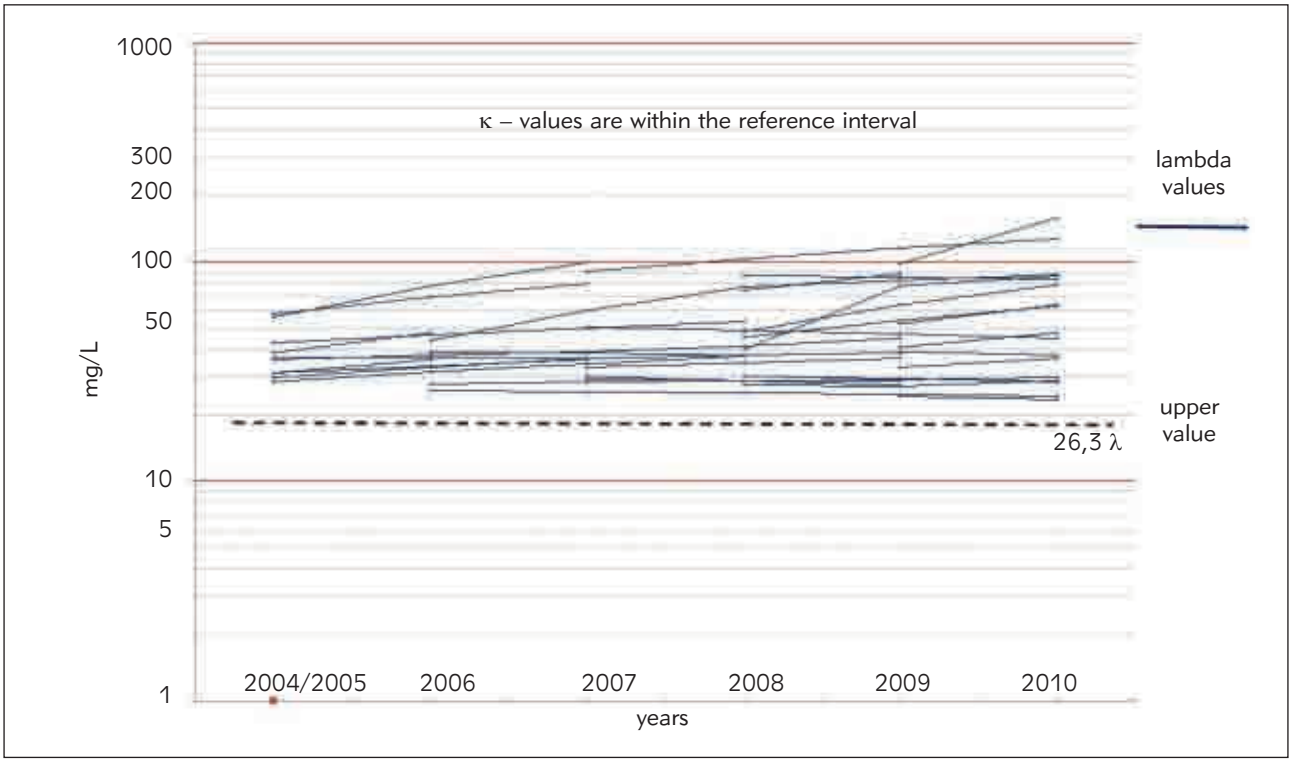

Figure 4 λ – values in 33 patients with MGUS.

3 patients (13.1%) had low abnormal FLC ratios (<0.26 or >1.65) *(Table II)*. In the group of examinees with MGUS, at the time they were diagnosed, 6/91 patients (6.6%) had concentrations of FLC that deviate from the reference interval. It was determined that 73 patients (80.2%) belong to the IgG class (isotype), 7 (7.7%) to the IgA class, 6 (6.6%) to the IgM class and 5 (5.5%) are biclonal. Measured concentrations for FLC of κ-type are from 3.20 to 237.31 (mg/L), and for FLC of λ-type from 1.61 to 159.00 (mg/L). Graphic

Table III Risk-stratification model to predict progression in 91 MGUS patients.

Ig isotype class (No=number of patients)	FLC ratio	Serum M-protein (g/L)	Relative risk (%)	Absolute risk of progression for years (%)
IgG (n=35) BG (n=1)	0.26–1.65 36/91 (39.5%)	<15	1 (Low risk)	5 (Low risk)
IgG (n=13) IgM (n=3) IgA (n=5) BG (n=3)	0.25–4 24/91 (26.4%)	<15	5.4 (Low intermediate risk)	21 (Low intermediate risk)
IgG (n=17) IgM (n=2) IgA (n=3) BG (n=3)	0.125–0.25 or 4–8 25/91 (27.5%)	≥15	10.1 (High intermediate risk)	37 (High intermediate risk)
IgG (n=4) IgM (n=1) IgA (n=1)	<0.125 or >8 6/91 (6.6%)	>15	28 (High risk)	58 (High risk)

Abbreviations: MGUS – monoclonal gammopathy of undetermined significance; Ig – immunoglobulin; BG – biclonal gammopathy; FLC ratio – κ/λ ratio; M – protein – monoclonal protein

Table IV Serum FLC characteristics at cut-off value in newly diagnosed plasmaproliferative disease patients.

Parameters	Test	Disease (D)		Sn (%)	Sp (%)	PPV (%)	NPV (%)
		(D^+) Malignant	(D^-) Benignant				
kappa or lambda (mg/L)	(T^+) > 200	(TP) 24	(FP) 0	100.0	71.0	40.0	100.0
	(T^-) 200	(FN) 36	(TN) 91				
Total (No)		60	91				

Abbreviations: TP = true-positive; FP = false-positive; FN = false-negative; TN = true-negative; Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value

illustration is shown in *Figures 3 and 4*. Regarding sex, there were 41 women (45.1%), and 50 men (54.9%). The results show that 60 patients (66.0%) had normal (0.26–1.65) or slightly modified FLC ratios (0.25–4), and 31 (34.0%) had abnormal values of serum LC and/or abnormal FLC ratios (0.125–0.25 or 4–8 and <0.125 or >8) *(Table III)*.

Statistical analysis of our data showed that Sn = 24/24 = 1, and the 95% confidence interval for Sn was 0.796–1.0, and for Sp = 91/127 = 0.71, and the 95% confidence interval for Sp was 0.629–0.792. We needed to achieve the probability that the test gives accurate diagnosis. Sn and Sp do not provide this information, so we used predictive values (PV) instead. The results show that positive predictive values (PPV) = 24/60 = 0.4, and the 95% confidence interval for PPV is 0.276–0.535. Negative predictive values (NPV) = 91/91 = 1, and the 95% confidence interval for NPV is 0.94–1.0 (*Table IV*).

Discussion

In our study, at the time they were diagnosed, 37/37 patients (100%) with BJ myeloma had abnormal concentrations of serum FLC, of the κ and/or λ type, as a result of kidney damage or bone marrow suppression. It was noticed that more than half of the examinees were BJ type k (54%) *(Table I)*. Similar information has been given by other authors, who have found that approximately 62% of BJ are type κ and 38% of BJ are type λ (8, 9). On the other hand, in the group of patients with BG with FLC, at the time they were diagnosed, 23/23 patients (100%) had abnormal concentrations of serum FLC, of the κ and/or λ type. Among the diseased in both groups there were slightly more men than women. During the study there were 2 patients with BJ myeloma and 3 patients with BG with FLC, whose concentrations of κ or λ LC were above 1600 mg/L, who died. Our results showed that all 5 patients who died belong to the λ isotypes. It is important to emphasize that the

patients from both groups with high concentrations of serum FLC >1000 mg/L, are at high risk of disease progression *(Figures 1* and *2)*. The disease was in an advanced stage at the time when patients were diagnosed. The tables (*Table I* and *Table II*) give the relative risks (RR) according to the ISS for myeloma (10) at the Mayo Clinic, USA. Our results are compatible with theirs, especially in the subgroups of BJ myeloma patients and BG with FLC with high RR. Five (8.3%) patients died of progressive disease (PD) during or after therapy and they could be considered as »low responders« to therapy. They all had an abnormal FLC ratio (<0.03 or >32) with median survival times of approximately 22 months. These data are similar to the literature (9, 10) and support the conclusion that the FLC ratio was a prognostic factor for remission, progression and survival in the examined groups.

In the consideration of the aim of the study, it was important for us to determine the significance of the FLC ratio, as a prognostic factor of remission, progression and survival in the examined groups. According to the International Staging System (ISS) (10), the values of FLC ratio in the initial diagnosis were taken as an important indicator of MM prognosis. In it, abnormal FLC ratio (<0.03 or >32), high β_2-microglobulin (≥ 3.5 g/L) or low serum albumin (< 35 g/L), are defined as adverse risk factors. Patients with any combination of 0, 1, 2 or 3 adverse risk factors, according to the above mentioned criteria, had significantly different FLC ratios of overall survival, with median survival times of: 51, 39, 30 and 22 months, respectively (P<0.001) (9). Median survival time in patients with 3 risk factors was less than half that in patients with 0 factors [median: 51 months with 0 factors, 39 months with 1 factor (P=0.13), 30 months with 2 factors (P=0.001) and 22 months with 3 factors (P<0.001)] (10). It is interesting that the FLC ratio most significantly contributed to the prognosis in patients in the II stage of MM (β_2-microglobulin= 3.5–5.5 mg/L, regardless of the albumin value, or albumin <35 g/L, β_2-microglobulin <3.5 mg/L). Based on the values of the FLC ratio, this stage is divided into two groups: patients with FLC ratio κ/λ <0.03 or >32 (P<0.021) and median survival times of approximately 30 months, and patients with FLC ratio from 0.03 to 32 and median survival times of approximately 39 months (11).

The results obtained with the immunonephelometric test for patients with BJ myeloma with a high or intermediate abnormal FLC ratio and a combination of adverse risk factors (73.0%), indicate that their median survival time is approximately 22–30 months, as opposed to the patients with a normal or slightly modified FLC ratio, without adverse risk factors (27.0%), with median survival times of approximately 39–51 months (*Table I*). Similar results were obtained in the group of patients with BG with FLC, where 82.6% patients with a high or intermediate abnormal FLC ratio and a combination of adverse risk factors, as opposed to 17.4% with a normal or slightly modified FLC ratio and without adverse risk factors *(Table II)*. Viewed from the laboratory aspect, BG, TG and QG are included in the so-called oligoclonal gammopathies, which are considered to be hardly detectable. All of this also confirmed that BJ myeloma is an incurable disease with a progressive course. Based on the information found in literature, after the patients are diagnosed (12), median survival time is approximately 3 years, and that is somewhat longer when compared to our results.

High concentrations of FLCs are the result of rapid growth and large aggressiveness of the tumor (13). Our results were confirmed in numerous clinical studies which indicate that the values of FLCs are of prognostic importance in patients with recently diagnosed or active MM (14, 15). High abnormal values of the FLC ratio in serum are caused by the synthesis of excessive quantity of FLC and disturbance of the normal balance of κ and λ secretion (16). The existence of an abnormal FLC ratio represents the main independent risk factor of disease progression (6).

During the monitoring, the examinees were submitted to some of the therapeutic protocols for MM: MP protocol (Melphalan/Prednisone) or MPT protocol (Melphalan/Prednisone/Thalidomide) for patients older than 65 years or younger than 65 years, but those were not candidates for autologous stem-cell transplantation (SCT). VAD protocol (Vincristine/Adriamycin/Dexamethasone) and CTD protocol (Cyclophosphamide/Thalidomide/Dexamethasone) were applied in patients yonger than 65 years, who were candidates for autologous SCT. Interferon and thalidomide were used as maintenance therapy after autologous SCT, in the last four (2007–10) years. From the first two groups (BJ myeloma and BG with FLC), approximately 38% of the patients who had the decrease of FLC ratio >50% under therapy achieved disease remission. The time of achievement of remission and the length of its duration determined the overall survival time (17). The values of FLC ratio are not significant indicators of the change of the disease course in relation to the basic Ig isotype in the group with MM, so their repeated laboratory determination is not indicated (18).

In the group of examinees with MGUS, the risk of progression increased if FLC ratio became extremely large, regardless of the quantity and type of MGUS. The explanation for the increased risk of malignant progression in patients with high concentrations of FLCs can be connected with the clonal evolution of plasma cells. All of this is confirmed by an observation that cytogenetic changes are connected with abnormal FLC in patients with MM (18, 19). At the time when they were diagnosed, 85/91 pati-

ents (93.4%) had abnormal concentrations of serum FLC, of the κ and/or λ type. Approximately one third of the patients with MGUS have an abnormal FLC ratio, and with that, a greater level of disease progression (19, 20). The results of our study confirmed this fact *(Table III)*. An FLC ratio of <0.25 or >4 was considered to be abnormal. According to the Risk Stratification Model to Predict Progression, an abnormal FLC ratio, M-protein≥15 g/L and HC isotype, on condition it is not IgG, are connected with the risk of progression of MGUS to MM, or related disorders. According to the information found in literature, the risk of progression during years for patients with risk factors 0, 1, 2 or 3 is: 5%, 21%, 37% or 58%, respectively. In a study done by Mayo Clinic, 73% of examinees were of IgG class, 14% IgM, 11% IgA and 2% were biclonal (21, 22). Our results show similar distribution of Ig classes, except for the IgM and IgA classes that are almost twice less present *(Table III)*. Serum FLC (κ and λ) in patients with MGUS did not have concentrations >200 mg/L. Statistically, this makes this group of examinees significantly different from the other two groups. However, progression of MGUS to MM can be predicted based on the overall clinical laboratory criteria (such as osteolytic lesions, sedimentation of erythrocytes (SE), serum β_2-microglobulin, serum M-protein).

The patients with MGUS should be monitored regularly, so as to identify the early signs of disease progression. The therapy is introduced only when the disease has developed (23). Today, it is a common practice to control all patients once per annum, to anticipate and prevent disease progression. Preferably, only patients with intermediate or high risk are controlled. Patients with low risk (approximately 40%), after repeated favorable results, need not have long term control (24). Numerous clinical studies indicate that the concentrations of FLC are increased in the sera of many patients with MGUS (25), which was confirmed by the results of our study (26). This further confirms the assumption that FLC in MGUS are pre-clinic dyscrasia of plasma cells with FLC.

In our study, the Sn (proportion of presentations with malignant disease that exhibit concentrations >200) is 24 of 24, or 100%. The Sp (proportion of presentations with benignant disease that do not have positive test >200) is 91 of 127, or 71%. Also, the PPV (percentage of patients with a positive test result who actually have the probability of malignant disease) is 24 of 60, or 40%. The NPV (percentage of patients with a negative test result who do not have the probability of malignant disease) is 91 of 91, or 100% (*Table IV*).

In conclusion, the existence of a significantly abnormal FLC ratio in the studied groups represents an independent risk factor for disease progression and thus for poorer prognosis. The reduction of FLC ratio and monoclonal Ig to normal values, under the influence of applied therapy, indicates good response of patients and adequate choice of therapy. Besides that, the relatively new immunonephelometric assay for the quantitative determination of FLC is the only specific, accurate and rapid laboratory test, especially for patients from the groups with LCD or BJ myeloma, BG with FLC and MGUS, and a valuable and important test for FLC evaluating, just like the quantification of other Ig isotypes in other MM cases.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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Received: December 20, 2010

Accepted: January 25, 2011