

## CLINICAL-HEMATOLOGICAL FEATURES AND PROGNOSTIC SIGNIFICANT FACTORS IN PATIENTS WITH MULTIPLE MYELOMA

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**Summary:** The article presents the results of research, which are conducted for the first time among patients MM residents of Kirghizia. And specified features allow at an early stage diseases be suspected important diagnostic features of multiple myeloma (MM): anemia (in the range of 89 to 85g / l), early chronic renal failure high concentrations of creatinine, calcium, of the monoclonal of paraprotein (20% and above) in serum and the pathological plasmatic cells in the bone marrow punctate of (from the 14% and higher).

In dynamics observing the said signs are laboratory -diagnostic in markers MM, often among patients kirghiz nationalities and the contributing to factors high risk of disease progression.

According to the results of our study in patients MM kirghiz nationalities in 58-62% cases detected IgA- myeloma with manifestations chronic renal failure and most patients with poorer survival. This variant IgA-myeloma with light  $\kappa$ -chain has a high risk of progression. Patients suffering with multiple myeloma immunochemical variant IgA or A-myeloma is necessary of particular approach and required timely selection vysokodoznom of programs of chemotherapy and autologous bone marrow transplantation, or relationship or unrelated transplantation of hematopoietic stem cells in the presence of HLA- identical donor with aim achievements of the maximum effectiveness the treatment.

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Key words: multiple myeloma, anemia, monoclonal paraproteini, plasmatic cells, chronic renal failure, patients kirghiz nations.

### **Introduction**

Currently, multiple myeloma is a serious problem in health care, both abroad and in our country. The level morbidity this the pathology is about 1%. However, this not true indicators, because disease more often recognized at later stages, as there missing in blood, of the criteria, which are markers of malignancy especially in the early stages of its development.

Authors [6, 8] shown, that is most authentic indicator of activity cell proliferation is index the tags of plasma cells (IMPC), which is estimated by the number of cells in S-phase of the cell cycle, after a short incubation in vitro with such predecessors as 3H-thymidine or romdioksiuridin 5, as well as the number of Ki-67 positive cells and that the zip code is most valuable independent prognostic indicator at multiple myeloma.

It is well known, that for the determine the survival in prognosis of the disease is very important the value has the study of concentration b2-microglobulin. The level of this indicator depends on the mass tumors of myeloma cells and from the kidney function, which is has a important in the prognosis of the disease MM.

Several investigators proved, that the predictive influence largely determined close relationship with the t (4; 14) and t (14; 16), matter of fact 90% cases of myeloma with t (4; 14) and t (14; 16) as well also accompanied deletions 13th chromosome. The role of cytogenetic anomalies as factors of poor prognosis MM is was manifested most pronounced before the era of new therapeutic drugs. Data on the impact of certain genetic aberrations may be controversial and depend on the mode of treatment [9]. One of the manifestations of the biological activity of the tumors plasma cells (PC) is it the products of monoclonal immunoglobulin. In multiple myeloma usually detected typical M-gradient and / or protein Bence –Jones.

It should be noted, that in patients MM with increased levels immunoglobulin Ig A and Ig G light monoclonal chains are found in the urine of 50-60%, and in patients with increased levels immunoglobulin Ig D-myeloma the virtually almost at all. Extremely rare, chronic renal failure arises at patients with the absence of light chains in urine [2].

Very important is in the disease prognosis is also the definition the level of serum of an immunoglobulin (Ig).

Aim of this work: to study the features of the course Ig A-myeloma and to reveal of important clinical-laboratory parameters affecting the prognosis of the disease at patients with multiple myeloma kirghiz nationalities.

#### **MATERIALS AND STUDY METHODS:**

The overall group of patients make up 108 people (including 36 patients with of primary MM of them 34 - patients Russian-speaking population of residents Kirghizia and 2 patients(kirghiz nationalities), was the investigated in St. Petersburg NIIEM behalf L. Pasteur, the St. Petersburg clinical hospital of the Russian Academy of Sciences and Eurasian center oncohematology, immunology and therapy of since 2004 to 2012 years.

All the patients MM citizens of Kirghizia Republic, among them Russian-speaking population of residents Kirghizia - 86 patients, kirghiz nationalities - 22 patients, womens – 41, mens - 67, that have observed at the National Hospital under the Ministry of Health of the Kirghizia Republic, in Eurasian center oncohematology, immunology and therapy, patients with different stages currents and age from 33 to 90 years.

The diagnosis MM was installed the based on of standard criteria, including in classical triad plasmacytosis bone marrow no less 10%, varying degrees of bone damage from the osteoporosis prior to osteolysis, monoclonal protein in the blood and / or urine.

Each patient were taken into account into account clinical and laboratory parameters, stage of disease, age, gender.

Were determined by complete blood count with platelet count, total protein and its fractions were determined by conventional refractometric method, detection of M-gradient performed on the electropherogram, the concentration of creatinine by Jaffe method with using the of picric acid and NaOH, calcium levels was determined by mureksidnym method with the use reagent arsenazho-3, for investigations bone marrow puncture sternal and identified immunological variants [1,3] immunoglobulin products types heavy and light chains of immunoglobulins, typing of method of direct solid phase immunoassay.

Typing of 108 patients in the Laboratory of Immunology, National Center of Cardiology and Therapy Ministry of Health of Kirghizia Republic city Bishkek, on immunoglobulin Ig A, Ig M, Ig G, IgD, Ig E, and of these, 52 of patients (30 patients MM- Russian-speaking population of residents Kirghizia and 22 of patients kirghiz nationalities) since 1995 to 1999 years [4] were examined for immunoglobulins chains ( $\kappa$ ,  $\lambda$ ) in the laboratory hybridoma technology Federal Government Agency, Central Research Institute of Roentgenology and Radiology FAZSR, city St. Petersburg.

Air transportation and delivery was carried out to the laboratory hybridoma technologies Saint - Petersburg in the mini cooling boxes at  $-10^{\circ}\text{C}$ .

In the 22 patients kirghiz nationalities, were detected at the study in assays rarely occurring forms of variants immunoglobulin type Ig A  $\kappa$ -chains in the I-th stage at the 1 patient, the II-th stage- in 6 patients and in stage III - in 3 patients. Addition all 4 patients additionally were examined for immunoglobulin Ig D and Ig E. In this case are revealed increased titers of immunoglobulin Ig D in the I-th stage at 1 patient, in stage II at the 1 patient is revealed biklonalnaya tumor (IgA, Ig E) and the type of Ig D in 1 patient, in stage III in 1 patient Ig D. The remaining 8 patients with of products immunoglobulin IgG( $\kappa$ , $\lambda$ ).

Of the 86 of patients MM Russian-speaking population of residents Kirghizia revealed immunoglobulin Ig A  $\kappa$ -chain - in the I-th stage the 1 patient, in stage II - in the 1 patient, in stage III - in 3(three) of patients, with Ig E - in I-th stage -1(one) patient and Ig M - in 3(three) of patients with in stage III, non-secretory myeloma in the 1 patient in the I-th stage and in stage III the 1 patient. The remaining 75 patients with of products immunoglobulin IgG( $\kappa$ , $\lambda$ ).

In assessing results therapy of patients MM, were guided by the basic criteria of treatment effectiveness of patients with multiple myeloma developed by the National Cancer Institute of the United States, and the use of programs Moss proposed Finnish Leukemia Group 1989 year.

System staging MM proposed by [B.G.M.Durie. S.E.Salmon., 1975], on the present time it is generally accepted recognized, [7], and the supplemented system staging Durie-Salmon [5]

Table 1.

The distribution of patients with multiple myeloma of residents Kirghizia by stage of the currents and on the floor [ B.G.M. Durie.S.E.Salmon.,1975;2002.].

the total group patients n=108	multiple myeloma at patients kirghiz nationality by gender			multiple myeloma at patients Russian-speaking population of Kirghizia by gender		
	women n=22		the men	women n= 86		the men
stage I	2	(4)	2	7	(21)	14
stage II	3	(8)	5	12	(18)	6
stage III	4	(10)	6	13	(47)	34

The results of analysis of frequency of occurrence MM of patients kirghiz nationalities showed that in the I(first) stage and women, and Men suffer with equal frequency, and in patients MM Russian-speaking population of Kirghizia more often identified among men as compared to women

In the II-nd and III-her stage multiple myeloma more often is registered in men kirghiz nationalities as compared to women.

In the II-nd stage in patients with multiple myeloma Russian-speaking population of Kirghizia often is registered among women, and in stage III more frequently detected among men as compared to women (Table 1). As seen a large proportion of patients detected at late III stage because due to late of appealability patients.

MM the patients received, of accepted recognized programs.chemotherapy. Therapeutic plasma exchange prior to the of chemotherapy was performed for the patients with chronic renal failure.

Statistical processing of the results included the analysis of standard criteria. X<sup>2</sup>-square was used to assess significant differences in the occurrence of certain characteristics between the control group and patients MM. Determination of the "p" corresponding to the found znacheniyu. X<sup>2</sup>-square, with allowance for one degree of freedom. All mathematical calculations and statistical analysis of the overall study was performed using a personal computer using a software package for spreadsheets - "Microsoft – Excel M version 7.0 for Windows 95, for Windows-based 2010, Statistica-5.

## RESULTS AND DISCUSSION:

At primary of appealability of patients at diagnosis of conducted studies showed that the most often encountered Ig A-myeloma (Fig. 1), among MM patients the kirghiz nationalities the compared with patients MM Russian-speaking population of Kirghizia. And often in patients exhibit stage II, where in analyzes severe anemia (Hb 89; 85g / L ) and with lesions predominantly renal system (Fig. 2).

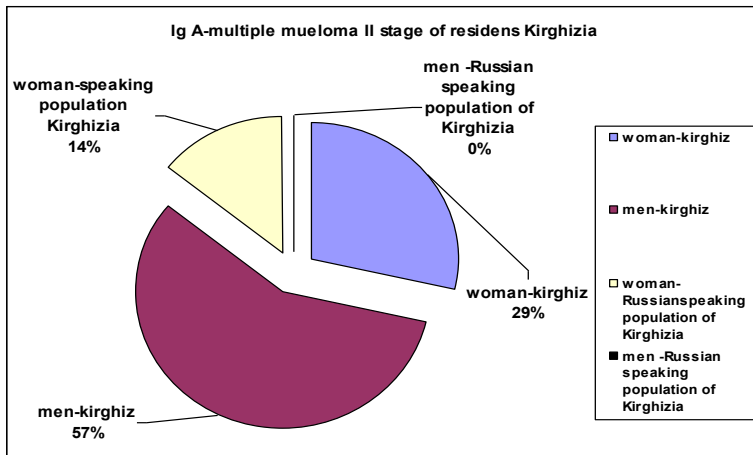


Figure 1. Residents of Kirghizia, patients multiple myeloma II stage with immunochemical variants Ig A-myeloma.

It is shown that more common among patients kirghiz ethnic nationalities of variant Ig A-myeloma among men - 57% of cases, women - 29%, and among women of Russian-speaking population Kirghizia -14% of cases, and among men Russian-speaking population of Kirghizia in our observation is not have met (Fig. 1)

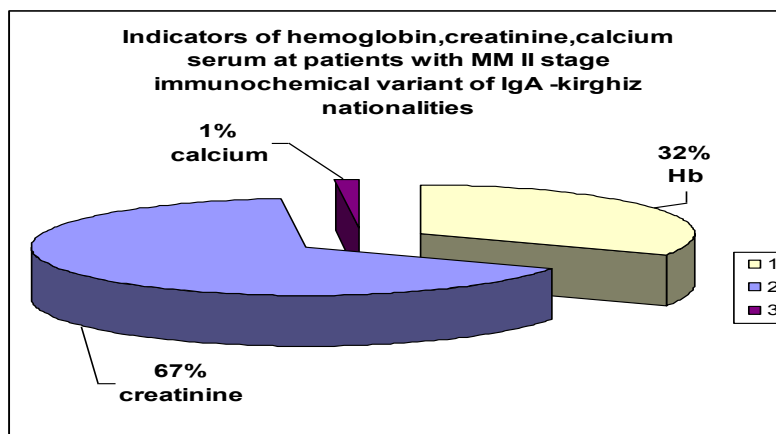


Figure 2. Showing of of hemoglobin, creatinine, and serum calcium at patients with multiple myeloma II stage immunochemical variant Ig A kirghiz nationalities

At patients multiple myeloma kirghiz nationalities of II stage immunochemical variant Ig A, the results are depicted in figure 2, where more often taped in blood count low content of hemoglobin level (anemia in 32% of cases) (from the Hb-89 g / L and below), in blood serum high indicators creatinine in 67% and of 1% calcium in the cases. The clinical manifestations were characterized with a pronounced anemic syndrome, ossalgicheskim syndrome, renal syndrome with expressed manifestations chronic renal failure.

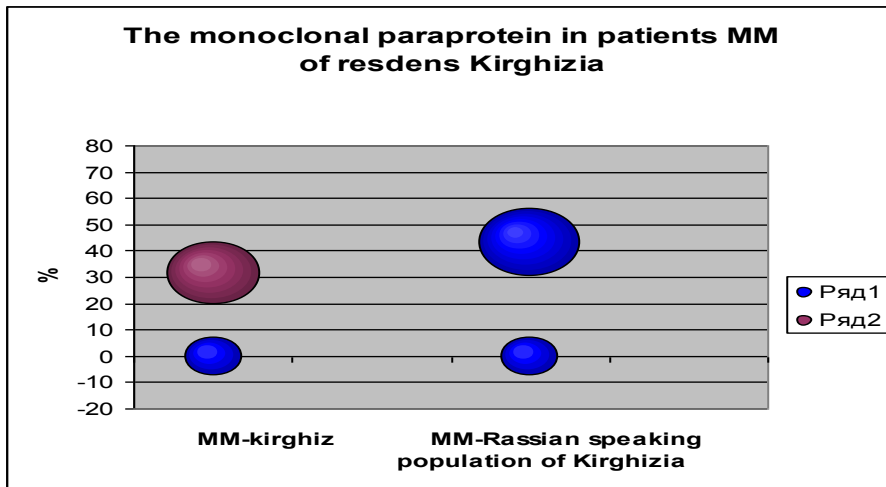


Figure.3. The monoclonal paraprotein in patients multiple myeloma of residents Kirghizia

\*Note: The a row 1 - the original; a row 2 - indicators of paraprotein.

In patients with MM of II stage among the Russian-speaking population of Kirghizia is revealed often a monoclonal paraprotein in serum (from the 32% and above), at which the course of the disease is less the malignant. In the comparison at patients with multiple myeloma of II stage immunochemical variant Ig A kirghiz ethnic nationalities, a monoclonal paraprotein is revealed often ( from the 20% and above), and in dynamic of observation titers secretion products more prone to the growth. Thus there is of abnormal proliferation of immunoglobulins and quite often an excess of other components of blood, which leads to hyperviscosity syndrome, in connection with which such of indicators titers markers of necessary to be considered how to with high risks of progression of disease MM and which is significantly affecting its prognosis (figure. 3).

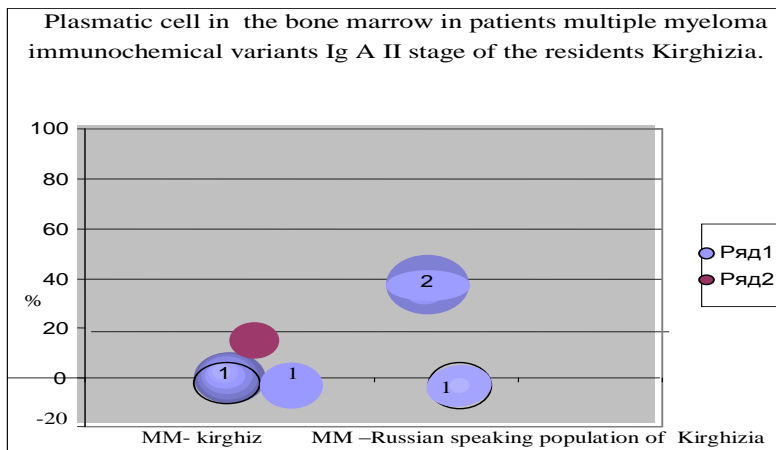


Figure. 4. Plasmatic cells in the bone marrow at patients with multiple myeloma II stage immunochemical variants Ig A of the residents Kirghizia.

\*Note: the row 1 - the original data, the row 2 - indicators of plasma cells in the bone marrow.

In primary of diagnosed multiple myeloma patients of II stage immunochemical variant Ig A of the kirghiz nationalities more often plasmatic cells of in the bone marrow revealed (from the > 14% and above) (Fig. 4). Despite such rather low parameter there is a trend inclination to rapid growth of plasma cells in the bone marrow and the prevalence of of tumor process, leading to the disease progression. And in dynamics of observation with unfavorable prognosis, patients with low survival more often likely to die from the complications of the underlying disease and joining infections. In the comparison group, according to our observations, in patients with multiple myeloma II stage Russian-speaking population of Kirghizia, often identified plasma cells in the bone marrow punctate of (from the > 30% and above), and the clinical course of proceeded less malignant. With timely conduct of the programs chemotherapy part of patients who have not had concomitant pathology, received response to therapy - a complete clinical-hematological remission, and accordingly survival rates were slightly higher.

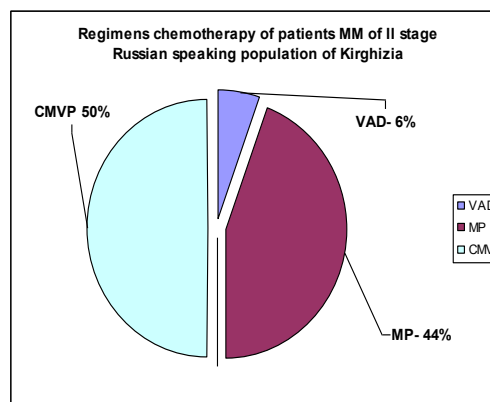
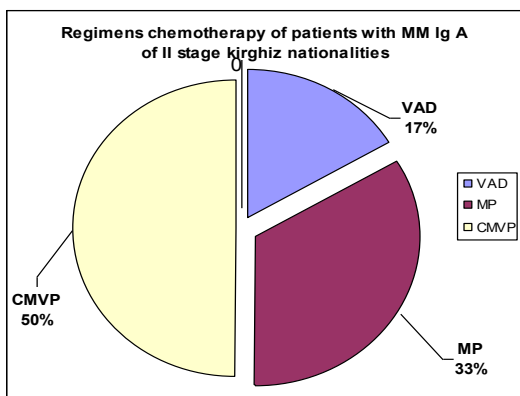


Figure 5A.Regimens chemotherapy of patients with MM of II stage Ig A kirghiz nationalities      Figure5B.Regimens chemotherapy of patients with MM of II stage Russian-speaking population of Kirghizia.

Apparently from figure 5A, MM patients stage II of immunochemical variant Ig A kirghiz nationalities the received programs of chemotherapy in 50% of cases CMVP- therapy , of the MP in 33% and VAD-therapy in 17% of cases.

Patients of II stage MM Russian-speaking population of Kirghizia, apparently from figure 5B, in the received programs of chemotherapy: in 50% cases therapy - CMVP, MR- in the 44% and VAD-therapy in 6% cases

The first diagnosed patients with MM stage II immunochemical variant Ig A kirghiz nationality with chronic renal failure before chemotherapy was conducted therapeutic plasmapheresis and VAD and CMVP- therapy with reply 4-month full clinical remission, on therapy MP was a partial answer, which significantly influenced the prognosis and survival of patients.

Patients with MM Russian-speaking population of Kirghizia II stage to therapy with MP gave full clinical-hematology remission on 8 months, and CMVP therapy - on the 9 months, on VAD therapy gave a partial answer.

According to estimates of results carried out therapy in patients with MM of II stage immunochemical variant Ig A the kirghiz nationalities, often the response to treatment gave on VAD and CMVP - therapy and it should be noted that the effectiveness from the carried out therapy influenced by individual to engineer therapy.

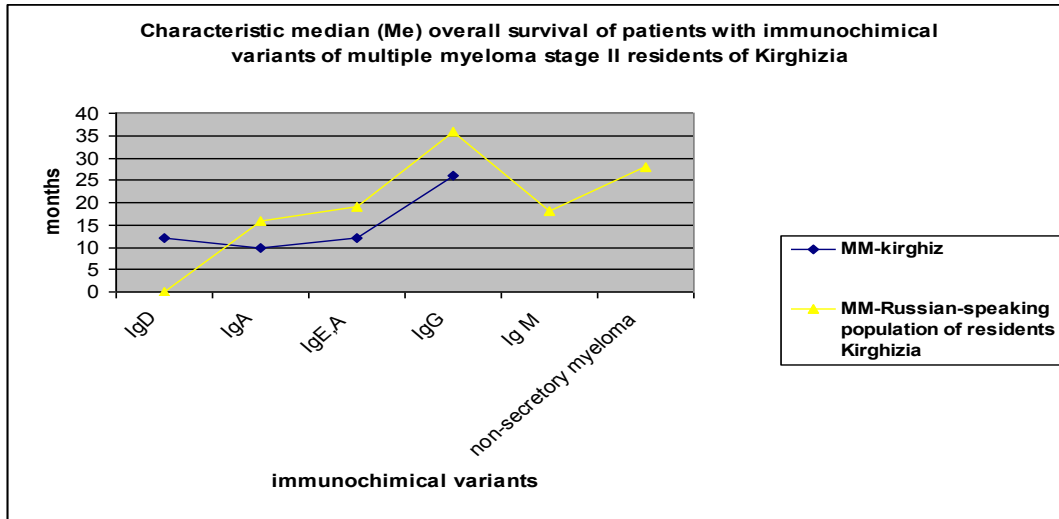


Figure 6. Characteristic median (Me) overall survival of patients with immunochimical variants of multiple myeloma stage II the residents of Kirghizia.

According to the results of our study as seen from the figure 6, shows, that with rare forms immunochimical variant MM in patients kirghiz ethnic often with Ig A-myeloma in the timely diagnosis and begun chemotherapy Me survival was reached 10 months, with Ig D- myeloma Me survival rates reached an average of 12-13 months, in the biklonalnoy tumor (Ig E, Ig A) to 11-12 months, in patients Me survival with Ig G-myeloma equal to 25-27 months. In comparison, patients with MM- Russian-speaking population of Kirghizia with Ig A- myeloma Me overall survival of patients is slightly higher and amounted to an average of 15-16 months, with IgE myeloma Me survival to 18-19 months, with Ig M-myeloma Me survival to 19 months, with non-secretory myeloma Me survival to 28-29 months and Ig G-myeloma Me overall survival reached an average of 37-38 months. Observation the shown that multiple myeloma patients with a rare form of immunochimical variant immunoglobulins overall survival is not was high, and in particular at Ig A -myeloma more malignant course of the disease, often with symptoms of chronic kidney failure combined with lower survival compared than is more often found IgG -myeloma and effectiveness of treatment depends on timely diagnosis and selection of therapy.



The progression of chronic renal failure can be slowed or halted only by the action of an effective chemotherapy so how complete normalization of renal function in this pathology is unlikely.

### **CONCLUSION:**

This necessary to pay attention the identification of criteria that can be regarded as markers of high risk of progression: the contents reliable laboratory diagnostic indicators MM plasma cells in the bone marrow punctate (from > 14%) and of the monoclonal paraprotein in the serum blood (20% and above) which in the dynamics of observation in patients with multiple myeloma immunochemical option Ig Ak-chains kirghiz nationality, course of the disease often associated with poorer survival.

It should be noted that patients with MM kirghiz nationalities found in 58-62% cases, Ig A-myeloma and on the moment primary of appealability is observed in assays anemia with kidney dysfunction.

In patients kirghiz nationalities suffering from MM more frequently with IgA -myeloma that allow to objectively evaluate the severity of the condition and predict the outcome of disease: is it content of plasma cells in the bone marrow punctate in the presence ( from 14% and above), of the monoclonal of paraprotein (from > 20% and above), concentrations levels creatinine, calcium in the serum and (below 89 g / L of hemoglobin).

Given the clinical and of hematological characteristics and of complications is needed timely choice programs of therapy.

The modern approach in treatment diseases of the MM should is to assess, depending on the stage currents immunochemical variant, early use of programm chemotherapy and planning programs of autologous bone marrow transplantation or peripheral stem cells , and or at the presence of HLA - identical donor - allogenic peripheral hemopoietic stem cell.

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