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VARIANTS OF URIC ACID METABOLISM AND THEIR IMMUNE AND MICROBIOTA ACCOMPANIMENTS IN PATIENTS WITH NEUROENDOCRINE-IMMUNE COMPLEX DYSFUNCTION

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ВАРІАНТИ МЕТАБОЛІЗМУ СЕЧОВОЇ КИСЛОТИ ТА ЇХ ІМУННІ Й МІКРОБІОТНІ ЗВ'ЯЗКИ У ПАЦІЄНТІВ З НЕЙРОЕНДОКРИННО-ІМУННОЮ КОМПЛЕКСНОЮ ДИСФУНКЦІЄЮ

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ВАРИАНТЫ МЕТАБОЛИЗМА МОЧЕВОЙ КИСЛОТЫ И ИХ ИММУННЫЕ И МИКРОБИОТНЫЕ СВЯЗИ У ПАЦИЕНТОВ С НЕЙРОЭНДОКРИННО-ИММУННОЙ КОМПЛЕКСНОЙ ДИСФУНКЦИЕЙ

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Summary/Резюме

Background. Previously, we found a wide range of uric acid exchange parameters and functional relationships of uricemia and uricosuria with the parameters of immunity in healthy rats analyzed. We continued our research along the same lines in the clinical observation of patients, who came to the Truskavets' spa for the rehabilitation treatment. Relationships between uricemia and uricosuria, on the one hand, and immunity and microbiota parameters, on the other hand, have been identified. The purpose of this study is to further explore these relationships using the cluster and discriminant analyses. *Material and Methods.* The object of observation were 34 men and 10 women aged 24-70 years old, who came to the Truskavets' spa for the rehabilitation treatment of chronic pyelonephritis combined with cholecystitis in remission. The serum and daily urine levels of the uric acid by uricase method

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were determined. Immune status evaluated on a set of I and II levels recommended by the WHO. The condition of microbiota is evaluated on the results of sowing of feces and urine. *Results*. Cluster analysis revealed 4 variants of uric acid metabolism by deviating uricosuria and uricemia from the norm in Z-scores. In 34% of individuals, moderate hypouricosuria (-0,97±0,11 Z) is combined with a lower borderline uricemia (-0,53±0,20 Z). In 25% of patients, lower-border uricemia (-0,70±0,22 Z) is accompanied by marked hyperuricosuria (+3,87±0,25 Z). In 24% of people, moderately elevated uricosuria (+1,26±0,14 Z) is combined with completely normal uricemia (+0,09±0,16 Z). Finally, in 17%, a similar level of uricosuria (+1,17±0,19 Z) is combined with marked hypouricemia (-1,89±0,14 Z). Discriminant analysis revealed 12 parameters of immunity and 5 parameters of microbiota, by which the clusters of uric acid metabolism are identified with 94,3 %% accuracy.

Conclusion. Endogenous uric acid has a modulating overall beneficial effect on a number of immune and microbiota parameters in both healthy rats and people with neuroendocrine-immune complex dysfunction on background of chronic inflammatory diseases.

Keywords: *Uricemia, Uricosuria, Immunity, Microbiota, Relationships, Humans.*

Передумови. Раніше ми виявили широкий діапазон параметрів обміну сечової кислоти та проаналізували функціональні зв'язки урикемії і урикозурії з параметрами імунітету у здорових щурів. Ми продовжували наше дослідження за тими ж напрямками у клінічному спостереженні за пацієнтами, які прибували на курорт Трускавець на реабілітаційне лікування. Було виявлено зв'язки між урикемією та урикозурією, з одного боку, і імунітетом та параметрами мікробіоти, з іншого. *Метою* цього дослідження є подальше вивчення цих зв'язків за допомогою кластерного та дискримінантного аналізів. *Матеріал та методи.* Об'єктом спостереження були 34 чоловіки та 10 жінок у віці 24-70 років, які прибули на курорт Трускавець на реабілітаційне лікування хронічного пієлонефриту, поєднаного з холециститом, у стадії ремісії. Визначали рівень сечової кислоти в сироватці та добовій сечі уриказним методом. Імунний статус оцінювали за набором тестів I та II рівнів, рекомендованих ВООЗ. Стан мікробіоти оцінено за результатами посіву калу та сечі уніфікованими методами. *Результати*. Кластерний аналіз виявив 4 варіанти метаболізму сечової кислоти за відхиленнями урикозурії та урикемії від норми у Z-одиницях. У 34% осіб помірна гіпоурикозурія (-0,97±0,11 Z) поєднується з нижньопограничною урикемією (-0,53±0,20 Z). У 25% пацієнтів нижньопогранична урикемія (-0,70±0,22 Z) супроводжується вираженою гіперурикозурією (+3,87±0,25 Z). У 24% людей помірно підвищена урикозурія (+1,26±0,14 Z) поєднується з цілком нормальною урикемією (+0,09±0,16 Z). Нарешті, у 17% осіб аналогічний рівень урикозурії (+1,17±0,19 Z) поєднується із вираженою гіпоурикемією (-1,89±0,14 Z). Дискримінантний аналіз виявив 12 параметрів імунітету та 5 параметрів мікробіоти, за сукупністю яких кластери метаболізму сечової кислоти ідентифікуються з точністю 94,3%. *Висновок.* Ендогенна сечова кислота чинить модулюючий загалом сприятливий вплив на ряд параметрів імунітету та мікробіоти як у здорових щурів, так і у людей з дисфункцією нейроендокринно-імунного комплексу на тлі хронічних запальних захворювань.

Ключові слова: *урикемія, урикозурія, імунітет, мікробіота, кореляції, люди.*

Предпосылки. Ранее мы выявили широкий диапазон параметров обмена мочевой кислоты и проанализировали функциональные связи урикемии и урикозурии с параметрами иммунитета у здоровых крыс. Мы продолжили наши исследования в том

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же направлении в клинических исследованиях за пациентами, которые прибывали на курорт Трускавец для реабилитационного лечения. Были выявлены связи между урикемией и урикозурией, с одной стороны, и иммунитетом и параметрами микробиоты, с другой. *Целью исследования* было дальнейшее изучение этих связей с использованием кластерного и дискриминантного анализов. Материал и методы. Объектом наблюдения были 34 мужчины и 10 женщин в возрасте 24-70 лет, которые прибыли на курорт Трускавец для реабилитационного лечения хронического пиелонефрита в сочетании с холециститом, в стадии ремиссии. Определили уровень мочевой кислоты в сиворотке и суточной моче уриказным методом. Иммунный статус оценивали наборами тестов I и II уровней, рекомендованных ВОЗ. Состояние микробиоты оценили по результатам посева кала и мочи унифицированными методами. *Результаты*. По результатам кластерного анализа выявили 4 варианта метаболизма мочевой кислоты по отклонениям урикозурии и урикемии от нормы в Z-единицах. У 34% пациентов умеренная гипоурикозурия (-0,97±0,11 Z) сочетается с нижнепограничной урикемией (-0,53±0,20 Z). У 25% пациентов нижнепограничная урикемия (-0,70±0,22 Z) сопровождается выраженной гиперурикозурией (+3,87±0,25 Z). У 24% людей умеренно подвышена урикозурия (+1,26±0,14 Z) сочетается с вполне нормальной урикемией (+0,09±0,16 Z). Наконец, у 17% пациентов аналогичный уровень урикозурии (+1,17±0,19 Z) сочетается с выраженной гипоурикемией (-1,89±0,14 Z). Дискриминантный анализ выявил 12 параметров иммунитета и 5 параметров микробиоты, по совокупности которых кластеры метаболизма мочевой кислоты идентифицируются с точностью 94,3%. Вывод. Эндогенная мочевая кислота оказывает модулирующее в целом благоприятное влияние на ряд параметров иммунитета и микробиоты как у здоровых крыс, так и у людей с дисфункцией нейроэндокринно-иммунного комплекса на фоне хронических воспалительных заболеваний.

Ключевые слова: *урикемия, урикозурия, иммунитет, микробиота, корреляции, люди.*

Introduction

Previously, we found a wide range of uric acid metabolism parameters grouped into four clusters [5] and functional relationships of uricemia and uricosuria with the parameters of immunity in female rats analyzed [6,7]. We continued our research along the same lines in the clinical observation of patients, who came to the Truskavets' spa for the rehabilitation treatment. The canonical correlation analysis revealed that raw uricemia determines by 28% nine parameters of immunity (relative blood content of pan-lymphocytes and their $CD4^+$-, $CD56^+$-, 0-populations, relative content of polymorphonuclear neutrophils, intensity and completeness of their phagocytosis Staph. aureus and their bactericidal capacity, saliva content of IgG) as well as bacteriuria and content in E. coli feces. Uricemia, normalized by sex and age, determines by 25% another constellation of immunity parameters (relative $CD8^+$ T-lymphocytes content, CIC, E. coli phagocytosis intensity and completeness, Staph. aureus phagocytosis activity and completeness) as well as content in E. coli feces with impaired enzymatic activity and Klebsiela&Proteus. Instead, uricosuria determines only four parameters of immunity and only by 11,5% [8].

The purpose of this study is to further explore the relationship between uric acid metabolism and immunity parameters, as well as microbiota parameters, which in turn are closely linked to immunity [23].

Material and methods

The object of observation were 34 men and 10 women aged 24-70 years old, with neuroendocrine-immune complex dysfunction on the background of chronic pyelonephritis combined with cholecystitis in remission, documented in a previous study

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[18,19]. The survey was conducted twice, before and after ten-day balneotherapy (drinking Naftussya bioactive water three times a day, ozokerite applications, mineral baths every other day) [10].

The serum and daily urine levels of the Uric acid by uricase method were determined. The analyzes were carried out according to the instructions described in the manual [4]. The analyzers "Pointe-180" ("Scientific", USA) were used with appropriate sets.

In portion of capillary blood we counted up Leukocytogram (LCG) (Eosinophils, Stub and Segmentonucleary Neutrophils, Lymphocytes and Monocytes) and calculated two variants of Adaptation Index as well as two variants of Strain Index by IL Popovych [2,16].

Strain Index-1 = $[(Eo/3,5-1)^2 + (SN/3,5-1)^2 + (Mon/5,5-1)^2 + (Leu/6-1)^2]/4$

Strain Index-2 = $[(Eo/2,75-1)^2 + (SN/4,25-1)^2 + (Mon/6-1)^2 + (Leu/5-1)^2]/4$

Immune status evaluated on a set of I and II levels recommended by the WHO as described in the manuals [11,14]. For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD8, CD22 and CD56 from company "Granum" (Kharkiv) with visualization under light microscope with immersion system. Subpopulation of T cells with receptors high affinity determined by test of "active" rosette formation. The state of humoral immunity judged by the concentration in serum circulating immune complexes (by polyethylene glycol precipitation method) and Immunoglobulins classes M, G, A (ELISA, analyser "Immunochem", USA). In addition, the saliva level of secretory IgA, IgA and IgG was determined as well as lysozime (by bacteriolysis of Micrococcus lysodeikticus).

We calculated also the Entropy (h) of Immunocytogram (ICG) and Leukocytogram (LCG) using formulas [17,20,24], adapted from classical CE Shannon's formula [22]:

$hICG = -[CD4 \cdot \log_2 CD4 + CD8 \cdot \log_2 CD8 + CD22 \cdot \log_2 CD22 + CD56 \cdot \log_2 CD56]/\log_2 4$

$hLCG = -[L \cdot \log_2 L + M \cdot \log_2 M + E \cdot \log_2 E + SNN \cdot \log_2 SNN + StubN \cdot \log_2 StubN]/\log_2 5$

Parameters of phagocytic function of neutrophils estimated as described by SD Douglas and PG Quie [3] with moderately modification by MM Kovbasnyuk [13,21]. The objects of phagocytosis served daily cultures of Staphylococcus aureus (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and Escherichia coli (O55 K59) as typical representative of Gram-negative Bacteria. Both cultures obtained from Laboratory of Hydro-Geological Regime-Operational Station JSC "Truskavets'kurort". Take into account the following parameters of Phagocytosis: activity (percentage of neutrophils, in which found microbes - Hamburger's Phagocytic Index PhI), intensity (number of microbes absorbed one phagocytes - Microbial Count MC or Right's Index) and completeness (percentage of dead microbes - Killing Index KI). On the basis of the recorded partial parameters of Phagocytosis, taking into account the Neutrophils (N) content of 1 L blood, we calculated the integral parameter - Bactericidal Capacity of Neutrophils (BCCN) by the formula [10]:

$BCCN\ (10^9\ Bact/L) = N\ (10^9/L) \cdot PhI\ (\%) \cdot MC\ (Bact/Phag) \cdot KI\ (\%) \cdot 10^{-4}$

In addition, the blood level of cytokines IL-1, IL-6 and TNF-б was determined (by the ELISA with the use of analyzer "RT-2100C" and corresponding sets of reagents from "Diactone", France). The condition of Microbiota is evaluated on the results of sowing of feces and urine.

Norms are borrowed from the Instructions and Database of the Truskavets' Scientific School of Balneology.

Results processed by methods of cluster [1] and discriminant [12] analyses, using the software package "Statistica 5.5".

Results and Discussion

Preliminary examination revealed a

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wide dispersion of both the concentration of Uric Acid in serum and its excretion in the urine (normalized by sex and age [8]), as was the case in healthy female rats [5]. This prompted us to re-apply cluster analysis (k-mean clustering method [1]).

As a result, four groups of persons were created, significantly different from each other in parameters of Uric Acid exchange (Table 1), while the differences between the members of each group were much smaller (Table 2).

The location of the members of the four clusters on the plane of uricemia and uricosuria is visualized in Fig. 1.

In 34% of individuals (20 males and 10 females), moderate hypouricosuria is combined with lower-grade uricemia, which is why the cluster is labeled S±E-. In 25% of patients (18 men and 4 women), lower-border uricemia is accompanied by marked hyperuricosuria (S-E2+ cluster). In 24% of people (16 men and 5 women), moderately elevated uricosuria is associated with completely normal uricemia (S±E+ cluster). Finally, in 17% (14

Table 1

Cluster Means and Euclidean Distances between Clusters
Distances below diagonal, Squared distances above diagonal

	Cluster No. 1 (21)	Cluster No. 2 (15)	Cluster No. 3 (30)	Cluster No. 4 (22)
Uric Acid Serum, Z	+0,09	-1,89	-0,53	-0,70
Uric Acid Excretion, Z	+1,26	+1,17	-0,97	+3,87
No. 1	0,00	1,95	2,68	3,71
No. 2	1,40	0,00	3,21	4,34
No. 3	1,64	1,79	0,00	11,72
No. 4	1,93	2,08	3,42	0,00

Table 2

Members of Clusters and Distances from Respective Cluster Center

Cluster Number 1 contains 21 cases

	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.
	C_22	C_26	C_29	C_31	C_34	C_36	C_40	C_50	C_51	C_54	C_58	C_59	C_73	C_78	C_79	C_80
Distance	0,58	0,81	1,18	0,97	0,22	0,38	0,57	0,31	0,8	0,79	0,51	0,76	0,91	0,69	0,52	0,81
	Case No.	Case No.	Case No.	Case No.	Case No.											
	C_7	C_10	C_13	C_15	C_17											
Distance	0,52	0,78	0,46	0,4	0,49											

Cluster Number 2 contains 15 cases

	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.
	C_2	C_3	C_21	C_24	C_27	C_30	C_39	C_43	C_46	C_47	C_56	C_65	C_72	C_85	C_87
Distance	0,53	0,32	1,04	0,66	0,48	0,95	0,68	0,64	0,51	0,31	0,69	0,49	0,73	0,4	0,64

Cluster Number 3 contains 30 cases

	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.
	C_52	C_53	C_60	C_62	C_63	C_64	C_66	C_74	C_75	C_76	C_77	C_81	C_82	C_83	C_84
Distance	0,67	0,86	0,42	0,52	0,67	0,64	0,33	0,97	0,78	0,62	0,41	0,92	0,69	0,49	1,11
	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.
	C_4	C_6	C_8	C_9	C_12	C_16	C_18	C_19	C_23	C_32	C_33	C_38	C_41	C_42	C_48
Distance	1,15	0,61	0,78	2,19	0,38	1,3	0,9	0,74	0,67	0,57	0,08	1,01	0,91	0,81	1,3

Cluster Number 4 contains 22 cases

	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.
	C_1	C_5	C_11	C_14	C_20	C_25	C_28	C_35	C_37	C_44	C_45	C_49	C_55	C_57	C_61	
Distance	0,92	0,88	0,75	0,61	0,92	0,73	0,72	0,6	1,03	2,15	1,17	0,33	0,8	1,5	2,02	
	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.	Case No.									
	C_67	C_68	C_69	C_70	C_71	C_86	C_88									
Distance	0,85	0,58	0,56	0,81	0,65	0,88	1,77									

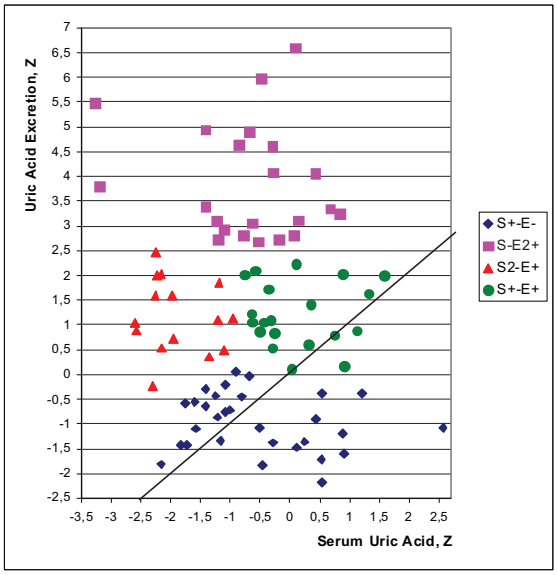

Fig. 1. Normalized levels (Z-scores) of uricemia (X-line) and uricosuria (Y-line) in patients of different clusters

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Table 3

Discriminant Function Analysis Summary for Variables of Uric Acid Exchange, Immunity and Microbiota

Step 21, N of vars in model: 19; Grouping: 4 grps; Wilks' Λ: 0,00478; approx. $F_{(57)}$=17,3; $p<10^{-6}$

Variables currently in the model	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)	Wilks Λ	Par-tial Λ	F-re-move (3,7)	p-le-vel	Toler an-cy	Norm Cv/σ (30)
Serum Uric Acid, mM/L Z	0,322 -0,53	0,249 -1,89	0,371 +0,09	0,316 -0,70	0,0063	0,758	7	10^{-3}	0,658	0,365 0,116
Uric Acid Excr, mM/24 h Z	2,27 -0,97	3,88 +1,17	3,94 +1,26	5,94 +3,87	0,039	0,123	157	10^{-6}	0,647	3,00 0,250
Popovych's Strain Index-1, points	0,13	0,16	0,25	0,13	0,005	0,953	1,1	0,362	0,754	0,067 0,722
Killing Index vs Staph. aureus, %	47,9	47,9	53,0	49,5	0,0049	0,98	0,4	0,72	0,312	58,9 0,142
Lysozime Saliva, mg/L	171	171	172	167	0,0059	0,804	5,4	0,002	0,249	180 0,168
Phagocytose Index vs Staph. aureus, %	98,96	99,00	99,00	98,54	0,0057	0,843	4,1	0,01	0,318	98,3 0,018
Pan-Lymphocytes of Blood, %	33,9	35,8	31,7	34,6	0,0055	0,868	3,3	0,025	0,306	32,0 0,174
Phagocytose Index vs E. coli, %	99,43	98,80	99,13	98,40	0,0057	0,845	4	0,011	0,295	98,3 0,012
Erythrocyturia, points	0,12	0,08	0,07	0,12	0,0051	0,935	1,5	0,212	0,662	0 **0,10**
IgA Saliva, mg/L	144	142	135	118	0,0054	0,887	2,8	0,047	0,215	415 0,241
Bifidobacterium faeces, lg CFU/g	5,66	5,40	5,49	5,74	0,0055	0,867	3,4	0,023	0,016	6,94 0,011
Lactobacillus faeces, lg CFU/g	6,38	6,14	6,31	6,48	0,0053	0,902	2,4	0,078	0,015	8,10 0,015
Leukocyturia, lg/mL	3,44	3,19	3,26	3,44	0,0056	0,855	3,7	0,015	0,237	3,00 0,070
IgG Serum, g/L	15,6	14,5	15,1	14,4	0,0053	0,911	2,2	0,101	0,694	12,75 0,206
Bacteriuria, points	0,27	0,43	0,22	0,28	0,0054	0,881	3	0,037	0,243	0 **0,24**
Bactericidity vs Staph. aureus, 10^9 Bacteria/L	94,5	90,6	103,0	93,8	0,0055	0,877	3,1	0,034	0,233	105,7 0,100
Entropy of Immunocytogram	0,956	0,964	0,967	0,967	0,0052	0,927	1,7	0,171	0,459	0,960 0,059
Interleukin-6, ng/L	5,49	5,27	5,20	5,44	0,0051	0,929	1,7	0,182	0,202	4,25 0,324
Microbial Count vs E. coli, Bacteria/Phagocyte	64,6	62,8	65,3	63,5	0,0051	0,938	1,5	0,233	0,32	54,7 0,194

Note. For some variables instead Cv is **SD**.

Table 4

Variables of Leukocytogram and Phagocytosis, currently not in the model

Variables	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)	Wilks Λ	Par-tial Λ	F-re-move (3,7)	p-le-vel	Toler an-cy	Norm Cv/σ (30)
Leukocytes of Blood, 10^9/L	5,67	5,48	5,55	5,91	0,0048	0,993	0,14	0,93	0,257	5,00 0,100
Polymorphonucleary Neutrophiles of Blood, %	54,6	52,7	55,8	53,2	0,0048	0,995	0,1	0,96	0,073	55,0 0,100
Stubnucleary Neutrophiles of Blood, %	2,78	2,56	2,54	2,69	0,0047	0,987	0,29	0,83	0,469	4,25 0,147
Eosinophiles of Blood, %	3,30	2,97	3,80	3,25	0,0046	0,972	0,63	0,6	0,624	2,75 0,318
Monocytes of Blood, %	5,40	6,00	6,18	6,32	0,0047	0,99	0,23	0,88	0,689	6,0 0,083
Microbial Count vs Staph. aur, Bact/Phagoc.	62,0	64,0	63,1	60,7	0,0048	0,994	0,14	0,94	0,275	61,6 0,160
Killing Index vs E. coli, %	45,9	44,0	51,0	48,8	0,0048	0,996	0,09	0,96	0,114	62,0 0,156
Bactericidity vs E. coli, 10^9 Bacteria/L	94	80	100	97	0,0048	0,997	0,06	0,98	0,075	99 0,100

men and 1 woman), a similar level of uricosuria is combined with marked hypouricemia (S2-E+ cluster).

Discriminant analysis (forward stepwise [12]) was conducted to identify exactly the parameters of immunity and microbiota, which together described four clusters differ from each other. The program included in the discriminant model, in addition, by definition, uricemia and uricosuria, 8 immune parameters of blood, 2 of saliva, 2 so-called informative parameters, 2 parameters of feces microbiota and 3 parameters of urine that characterize chronic pyelonephritis (Table 3).

Outside the model appeared 8 variables of Leukocytogram and Phagocytosis (Table 4), 6 of Humoral Immunity (Table 5), 5 of Cellular Immunity (Table 6), 3 Proinflammatory factors (Table 7), 4 Informative variables (Table 8), as well as 6 variables of feces and urine Microbiota (Table 9).

The discriminant variables are ranked by criterion Lambda (Table 10).

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Table 5

Variables of Humoral Immunity, currently not in the model

Variables	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)	Wilks Λ	Par-tial Λ	F-re-move (3,7)	p-le-vel	Toler an-cy	Norm Cv/σ (30)
CD22+ B-Lymphocytes, %	22,7	23,9	23,8	24,5	0,0047	0,991	0,2	0,9	0,363	20,0 0,175
Circulating Immune Complexes, units	35	33	40	35	0,0047	0,986	0,32	0,81	0,729	45 0,389
IgA Serum, g/L	1,85	1,64	1,85	1,67	0,0047	0,977	0,51	0,67	0,485	1,875 0,167
IgM Serum, g/L	1,50	1,40	1,47	1,40	0,0047	0,976	0,52	0,67	0,718	1,15 0,239
Secretory IgA Saliva, mg/L	496	496	503	472	0,0047	0,978	0,49	0,69	0,189	622 0,153
IgG Saliva, mg/L	42,2	42,8	41,6	41,3	0,0046	0,967	0,73	0,54	0,227	36 0,222

Table 6

Variables of Cellular Immunity, currently not in the model

Variables	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)	Wilks Λ	Par-tial Λ	F-re-move (3,7)	p-level	Toler ancy	Norm Cv/σ (30)
CD4+CD3+ T-helper Lymphocytes, %	32,6	32,3	30,0	28,3	0,0046	0,967	0,73	0,54	0,001	39,5 0,082
CD8+CD3+ T-cytolytic Lymphocytes, %	23,3	21,2	23,4	23,7	0,0047	0,983	0,37	0,78	0,613	23,5 0,138
CD3+ T-active Lymphocytes, %	29,0	29,7	28,4	28,6	0,0047	0,978	0,5	0,69	0,648	30,0 0,167
CD56+ Natural Killer Lymphocytes, %	18,9	20,7	20,4	21,2	0,0047	0,982	0,4	0,76	0,24	17,0 0,172
0-Lymphocytes of Blood, %	2,5	1,8	2,4	2,3	0,0048	0,996	0,09	0,97	0,295	0 **5,56**

Table 7

Variables of Proinflammatory factors, currently not in the model

Variables	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)	Wilks Λ	Par-tial Λ	F-re-move (3,7)	p-level	Toler ancy	Norm Cv/σ (30)
Interleukin-1, ng/L	4,58	5,34	4,74	4,81	0,005	0,975	0,560	0,650	0,522	4,51 0,173
Tumor Necrosis Factor-α, ng/L	6,21	5,87	5,76	6,13	0,005	1,000	0,000	1,000	0,648	4,90 0,326
C-Reactive Protein, ng/L	2,60	2,46	2,41	2,57	0,005	1,000	0,000	1,000	0,485	2,18 0,324

Table 8

Informative Variables, currently not in the model

Variables	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)	Wilks Λ	Par-tial Λ	F-re-move (3,7)	p-level	Toler ancy	Norm Cv/σ (30)
Entropy of Leukocytogram	0,647	0,653	0,651	0,660	0,0048	0,997	0,07	0,98	0,659	0,681 0,070
Popovych's Strain Index-2, points	0,18	0,21	0,39	0,18	0,0047	0,978	0,5	0,69	0,088	0,065 0,618
Popovych's Adaptation Index-1, points	1,17	1,16	1,07	1,06	0,0047	0,98	0,45	0,72	0,469	1,70 0,147
Popovych's Adaptation Index-2, points	0,84	0,82	0,81	0,77	0,0046	0,971	0,64	0,59	0,524	1,70 0,147

Next, the 19-dimensional space of discriminant variables transforms into 3-dimensional space of canonical roots. The canonical correlation coefficient is for Root 1 0,950 (Wilks' Λ=0,030; $\chi^2_{(57)}$=264; $p<10^{-6}$), for Root 2 0,678 (Wilks' Λ=0,312; $\chi^2_{(36)}$=88; $p<10^{-5}$) and for Root 3 0,650 (Wilks' Λ=0,577; $\chi^2_{(17)}$=41; p=0,0008). The major root contains 85,4% of discriminative properties, the second 8,0% and the third 6,6%.

Table 11 presents standardized (normalized) and raw (actual) coefficients for discriminant variables. The calculation of the discriminant root values for each person as the sum of the products of raw coefficients to the individual values of discriminant variables together with the constant enables the visualization of each patient in the information space of the roots.

Table 12 shows the correlation coefficients of discriminant variables with canonical discriminant Roots, the cluster centroids of Roots, and the normalized values of the discriminant variables as well as variables currently not in the model but worth the attention.

As we can see, the major root is uniquely interpreted as uricosuria. Together with it, the root condenses information on the entropy of the immunocytogram (ICG) and, in the reverse way, the intensity of ph-

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Table 9

Variables of Microbiota, currently not in the model

Variables	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)	Wilks Λ	Par-tial Λ	F-re-move (3,7)	p-le-vel	Toler an-cy	Norm Cv/σ (30)
E. coli faeces, lg CFU/g	8,28	8,28	8,23	8,28	0,005	1,000	0,000	1,000	0,613	8,66 0,030
Attenuated E. coli faeces, %	60	66	53	56	0,005	0,997	0,080	0,970	0,110	17,4 1,0
Hemolytic E. coli faeces, %	13	26	20	10	0,005	0,976	0,520	0,670	0,432	0 **25**
Klebsiela&Proteus faeces, %	11,2	8,8	18,2	13,1	0,005	0,982	0,400	0,750	0,146	10 0,500
Bacteriuria, lg CFU/mL	1,19	1,79	1,05	1,21	0,005	0,976	0,530	0,670	0,077	0 **0,98**
Leukocyturia, points	0,15	0,10	0,15	0,19	0,005	0,977	0,500	0,680	0,162	0 **0,15**
Erhytrocyturia, lg/mL	3,09	3,01	2,94	3,13	0,005	0,982	0,400	0,750	0,172	2,70 0,095

Table 10

Summary of Stepwise Analysis for Variables of Uric Acid Exchange, Immunity and Microbiota

Variables currently in the model	F to enter	p-level	Λ	F-va-lue	p-level
Uric Acid excretion, Z-score	154	10^{-6}	0,154	154	10^{-6}
Serum Uric Acid level, Z-score	13,5	10^{-6}	0,104	58,3	10^{-6}
Popovych's Strain Index-1, points	2,3	0,079	0,095	36,1	10^{-6}
Killing Index vs Staphylococcus aureus, %	2,1	0,108	0,089	26,8	10^{-6}
Lysozime Saliva, mg/L	2,2	0,096	0,082	21,8	10^{-6}
Phagocytose Index vs Staphylococcus aureus, %	2,3	0,084	0,075	18,6	10^{-6}
Pan-Lymphocytes of Blood, %	2,2	0,09	0,069	16,4	10^{-6}
Phagocytose Index vs Escherichia coli, %	2,0	0,119	0,064	14,7	10^{-6}
Erythrocyturia, points	2,2	0,096	0,059	13,5	10^{-6}
IgA Saliva, mg/L	1,6	0,208	0,056	12,3	10^{-6}
Bifidobacterium faeces, lg CFU/g	1,7	0,167	0,052	11,5	10^{-6}
Lactobacillus faeces, lg CFU/g	1,6	0,194	0,049	10,7	10^{-6}
Leukocyturia, lg/L	1,4	0,254	0,046	10,0	10^{-6}
IgG Serum, g/L	1,3	0,29	0,044	9,4	10^{-6}
Bacteriuria, points	1,8	0,161	0,041	9,0	10^{-6}
Bactericidity vs Staphyl. aureus, 10^9 Bacteria/L	2,8	0,046	0,036	8,8	10^{-6}
Entropy of Immunocytogram	1,1	0,338	0,005	19,0	10^{-6}
Interleukin-6, ng/L	1,5	0,21	0,005	18,1	10^{-6}
Microbial Count vs E. coli, Bacteria/Phagocyte	1,5	0,233	0,005	17,3	10^{-6}

Table 11

Standardized and Raw Coefficients and Constants for Variables of Uric Acid exchange, Immunity and Microbiota

Coefficients	Standardized			Raw		
Variables	Root 1	Root 2	Root 3	Root 1	Root 2	Root 3
Uric Acid excretion, Z-score	1,223	0,017	0,043	1,523	0,021	0,054
Serum Uric Acid level, Z-score	0,083	-0,832	-0,123	0,088	-0,889	-0,131
Popovych's Strain Index-1, points	0,002	-0,242	-0,28	0,012	-1,292	-1,493
Killing Index vs Staph. aureus, %	0,062	-0,356	-0,074	0,007	-0,042	-0,009
Lysozime Saliva, mg/L	0,204	-0,14	-1,296	0,03	-0,021	-0,193
Phagocytose Index vs Staph. aur,, %	0,563	0,247	-0,683	0,478	0,21	-0,58
Pan-Lymphocytes of Blood, %	-0,661	0,239	0,188	-0,086	0,031	0,025
Phagocytose Index vs E. coli, %	-0,327	-0,061	0,931	-0,247	-0,046	0,703
Erythrocyturia, points	-0,049	-0,148	0,455	-0,493	-1,506	4,621
IgA Saliva, mg/L	-0,704	0,399	0,06	-0,02	0,012	0,002
Bifidobacterium faeces, lg CFU/g	-1,357	0,214	4,01	-1,165	0,184	3,443
Lactobacillus faeces, lg CFU/g	1,355	-0,15	-3,68	0,949	-0,105	-2,577
Leukocyturia, lg/L	-0,381	-0,056	0,987	-0,571	-0,084	1,479
IgG Serum, g/L	-0,301	-0,203	0,238	-0,081	-0,055	0,064
Bacteriuria, points	-0,051	0,937	-0,463	-0,21	3,855	-1,903
Bactericidity vs Staph. aur, 10^9 Bac/L	-0,279	0,689	-0,766	-0,011	0,028	-0,031
Entropy of Immunocytogram	-0,344	0,274	-0,095	-12,89	10,26	-3,568
Interleukin-6, ng/L	-0,475	0,365	0,522	-1,808	1,389	1,986
Microbial Count vs E. coli, Bact/Phag	0,072	0,091	0,654	0,008	0,011	0,077
			Constants	7,317	-38,510	-3,494
			Eigenvalues	9,266	0,850	0,732
			Cumulative Prop.	0,854	0,933	1,000

agocytosis by neutrophils of both bacteria, the content of IgA and lysozyme in saliva and IgG in serum. Such uricous-immune relationships are visualized (Fig. 2) by the localization of members of the S±E- cluster in the negative zone of the root axis, reflecting the combination of hypouricosuria with a slight neg-entropy of ICG, on the one hand, and maximally for sampling increased phagocytosis activity against E. coli and IgG content in serum while minimally for sampling reduced IgA content in saliva, on the other hand.

Instead, in the positive zone of the axis localized members of the cluster S-E2+, in which hyperuricosuria is accompanied by a slightly increased ICG entropy, minimal for the sample increase in serum IgG, lack of activation of phagocytosis and maximum for the sample decrease in IgA and lysozyme saliva content.

The members of the other two clusters with equally moderate hyperuricosuria occupy an intermediate quasi-zero zone of the axis, reflecting the intermediate state of these immune parameters.

By adding monocytes and T-helper cells not included in the model, we obtain immuno-enhancing and immuno-suppressive patterns for uricosuria (Fig. 3).

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Table 12

Correlations Variables-Canonical Roots, Means of Roots and Z-scores of Variables of Uric Acid exchange, Immunity and Microbiota

Variables	Correlations Variables-Roots			S±E-III (30)	S2-E+ II (15)	S±E+ I (21)	S-E2+ IV (22)
Root 1 (85,4%)	R 1	R 2	R 3	-3,51	-0,09	+0,61	4,27
Uric Acid excretion	0,768	0,13	0,161	-0,97	+1,17	+1,26	+3,87
Entropy of Immunocytogram	0,057	-0,013	-0,099	-0,07	+0,07	+0,13	+0,13
Monocytes	currently not in model			-1,22	0,00	+0,36	+0,65
Phagocytose Index vs E. coli	-0,097	-0,106	-0,048	+0,96	+0,42	+0,70	+0,09
IgA Saliva	-0,095	0,061	-0,108	-2,71	-2,73	-2,80	-2,97
Lysozime Saliva	-0,073	-0,042	-0,18	-0,28	-0,31	-0,27	-0,42
Phagocytose Index vs Staph. aureus	-0,043	0,009	-0,121	+0,37	+0,40	+0,39	+0,14
IgG Serum	-0,041	-0,075	0,023	+1,10	+0,65	+0,89	+0,64
$CD4^+CD3^+$ T-helper Lymphocytes	currently not in model			-2,12	-2,21	-2,93	-3,47
Root 2 (8,0%)	R 1	R 2	R 3	-0,18	+1,82	-0,99	-0,04
Uric Acid Serum	-0,008	-0,743	-0,05	-0,53	-1,89	+0,09	-0,70
Killing Index vs Staph. aureus	0,033	-0,181	-0,186	-1,25	-1,32	-0,70	-1,12
Bactericidity vs Staph. aureus	0,003	-0,163	-0,118	-1,06	-1,43	-0,25	-1,12
Bactericidity vs E. coli	currently not in model			-0,50	-1,92	+0,14	-0,20
$CD8^+CD3^+$ T-cytolytic Lymphocytes	currently not in model			-0,06	-0,71	-0,04	+0,06
Microbial Count vs E. coli	-0,014	-0,103	-0,026	+0,94	+0,76	+0,99	+0,83
Leukocyturia, lg	-0,004	-0,061	0,177	+0,89	+0,39	+0,51	+0,88
Lactobacillus faeces	0,008	-0,05	0,069	-1,19	-1,35	-1,24	-1,12
Bifidobacterium faeces	0,002	-0,043	0,106	-1,13	-1,35	-1,27	-1,09
Bacteriuria, points	0,003	0,308	-0,033	+1,11	+1,75	+0,93	+1,17
Bacteriuria, lg	currently not in model			+1,21	+1,82	+1,07	+1,23
Attenuated E. coli faeces	currently not in model			+2,47	+2,79	+2,07	+2,21
Interleukin-1	currently not in model			+0,09	+1,06	+0,29	+0,38
Pan-Lymphocytes	0,005	0,175	0,095	+0,34	+0,68	-0,05	+0,40
Root 3 (6,6%)	R 1	R 2	R 3	+0,59	-0,74	-1,16	+0,81
Popovych's Strain Index-1	0,01	-0,135	-0,287	+1,29	+1,87	+3,83	+1,28
Klebsiela&Proteus faeces	currently not in model			+0,23	-0,24	+1,64	+0,62
Erythrocyturia, points	-0,006	-0,023	0,271	+1,22	+0,80	+0,75	+1,23
Interleukin-6	0,014	-0,061	0,112	+0,90	+0,74	+0,69	+0,86
Tumor Necrosis Factor-α	currently not in model			+0,82	+0,62	+0,54	+0,77
C-Reactive Protein	currently not in model			+0,60	+0,39	+0,32	+0,55

Table 13

Squared Mahalanobis Distances between Clusters, F-values (df=19,7) and p-levels

Clusters	S±E+ I	S2-E+ II	S-E2+ IV	S±E-III
S±E+ I (21)	0	9,1	19,5	21,7
S2-E+ II (15)	3,1 10^{-3}	0	26,2	18,3
S-E2+ IV (22)	8,3 10^{-6}	9,1 10^{-6}	0	63,7
S±E- III (30)	10,6 10^{-6}	7,1 10^{-6}	32,1 10^{-6}	0

Table 14

Coefficients and Constants for Classification Functions of Clusters

Clusters	S±E+ I	S2-E+ II	S-E2+ IV	S±E- III
Variables	p=0,239	p=0,170	p=0,250	p=0,341
Uric Acid excretion, Z-score	-5,524	-6,483	0,233	-11,67
Serum Uric Acid level, Z-score	-66,14	-68,88	-67,14	-67,53
Popovych's Strain Index-1, points	-67,95	-72,32	-72,26	-71,73
Killing Index vs Staph. aureus, %	6,538	6,41	6,506	6,458
Lysozime Saliva, mg/L	-0,192	-0,363	-0,499	-0,678
Phagocytose Index vs Staph. aureus, %	118,4	118,5	119,3	115,7
Pan-Lymphocytes of Blood, %	-5,873	-5,732	-6,143	-5,459
Phagocytose Index vs E. coli, %	69,08	69,51	69,67	71,34
Erythrocyturia, points	-150,3	-152,2	-144,3	-141,3
IgA Saliva, mg/L	-1,631	-1,588	-1,699	-1,537
Bifidobacterium faeces, lg CFU/g	-12,09	-9,259	-9,291	-1,077
Lactobacillus faeces, lg CFU/g	-13,36	-15,21	-14,74	-21,76
Leukocyturia, lg/L	238,1	239	239,1	243
IgG Serum, g/L	0,326	0,271	0,129	0,739
Bacteriuria, points	138,8	149,4	138,7	139,7
Bactericidity vs Staph. aureus, 10^9 Bacteria/L	-1,871	-1,796	-1,948	-1,856
Entropy of Immunocytogram	3605	3637	3552	3658
Interleukin-6, ng/L	580,9	586,6	579,1	592,8
Microbial Count vs E. coli, Bacter/Phagocyte	-6,096	-6,036	-5,897	-5,985
Constants	-13393	-13514	-13427	-13468

The separation of the last two clusters occurs along the axis of the second root, which represents inverted uricemia. The upper position of the members of the S2-E+ cluster reflects a combination of hypouricemia in them with a maximum for sampling inhibition of the completion of Staph. aureus phagocytosis, a minimum of Leukocyturia and activation of the intensity of E. coli phagocytosis, as well as maximum reduction in the microbiota of beneficial Lactobacillus and Bifidobacterium, which are inversely related to the root. Instead, panlymphocytes and bacteriuria (estimated on a one-point scale [10]) levels, which are directly related to the root, are maximal for sampling.

The lower position of the S±E+ cluster members reflects a combination of normal uricemia with normal or less reduced/elevated levels of the listed immunity parameters and microbiota negatively/positively associated with the second root.

Taking into account not included in the model T-cytolytic lymphocytes, bacteri-

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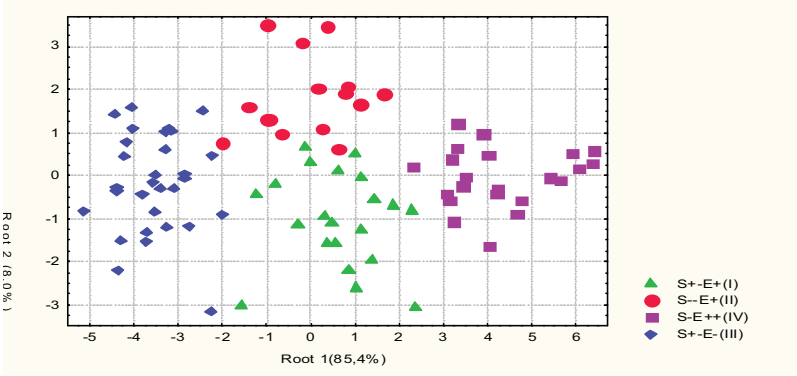

Fig. 2. Scatterplot of patients from differ clusters in space of first and second Roots

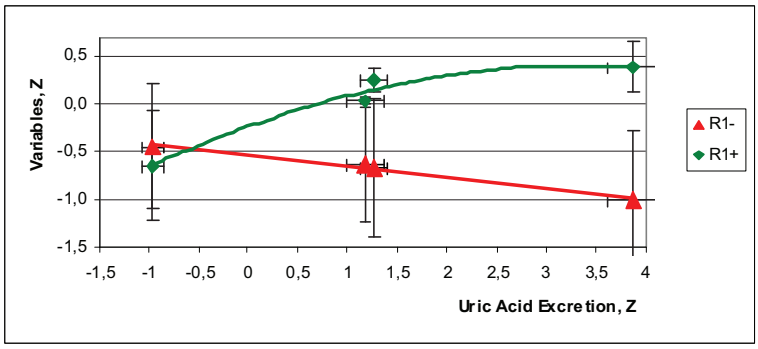

Fig. 3. Patterns of Immunity parameters, the information of which is condensed in the first Root

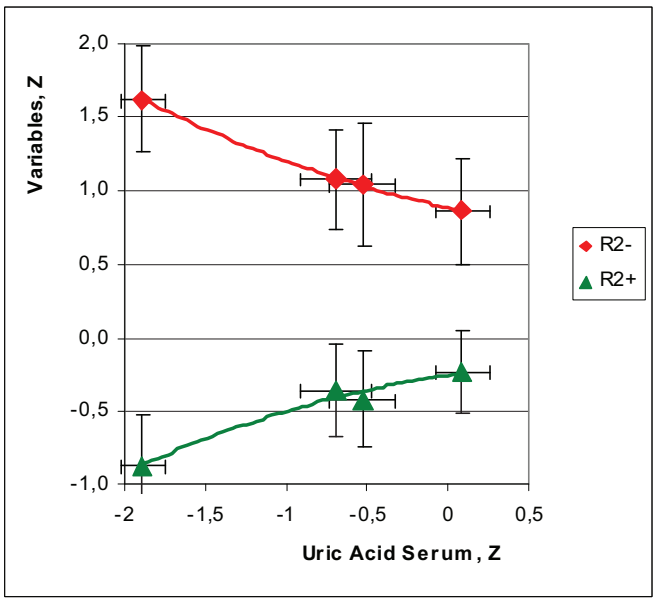

Fig. 4. Patterns of Immunity parameters, the information of which is condensed in the second Root

cidal activity against E. coli, row bacteriuria, relative content of E. coli with impaired enzymatic activity in the microbiota and plasma IL-1 level, we have formed immuno-enhancing and immuno-suppressive patterns of uricemia (Fig. 4).

In the information space of the two roots, which together condense 93,4% of the discriminatory information, all four clusters are visually clearly separated, with some exceptions (Fig. 2).

Additional delimitation of the members of the S±E+ cluster occurs along the axis of the third root, due to the maximum elevated Popovych's Strain Index-1, the relative content in microbiota of the Klebsiela&Proteus and Erythrocyturia, instead of the minimally increased levels of proinflammatory factors (Figs. 5 and 6).

In general, cluster delineation is highly reliable (Table 13).

The same discriminant variables can be used to identify the belonging of one or another person to one or another cluster. This purpose of discriminant analysis is realized with the help of classifying functions (Table 14).

We can retrospectively recognize members of III cluster unmistakably, of IV cluster with one error, but of I and II clusters with two errors (Table 15).

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Table 15

Classification Matrix for Clusters
Rows: Observed classifications; Columns: Predicted classifications

Clusters	Percent correct	S±E+ I	S2-E+ II	S-E2+ IV	S±E- III
		p=0,239	p=0,170	p=0,250	p=0,341
I	90,5	**19**	2	0	0
II	86,7	1	**13**	0	1
IV	95,5	1	0	**21**	0
III	100	0	0	0	**30**
Total	94,3	21	15	21	31

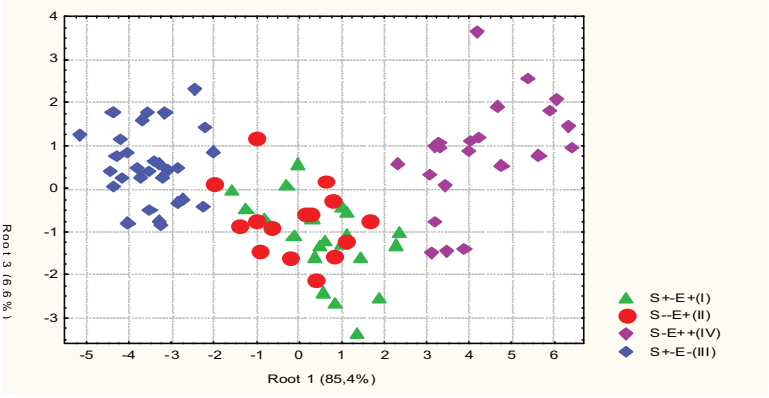

Fig. 5. Scatterplot of patients from differ clusters in space of first and third Roots

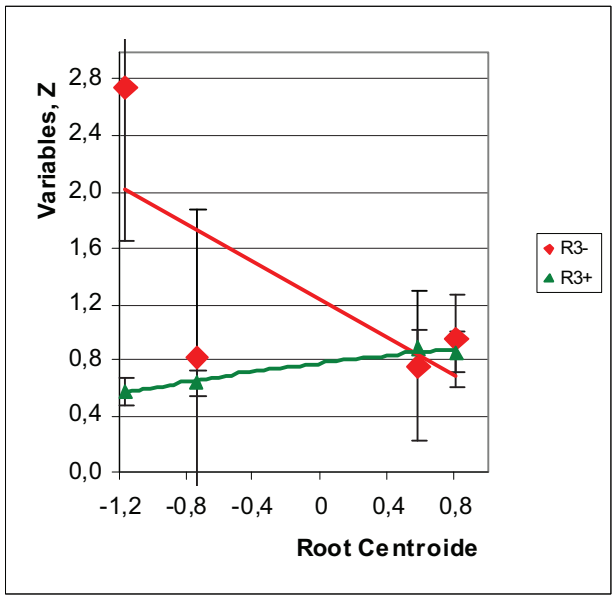

Fig. 6. Patterns of Immunity parameters, the information of which is condensed in the third Root

Accordance to ethics standards

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

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