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ROLE OF AUTONOMOUS AND ENDOCRINE FACTORS IN IMMUNOTROPIC EFFECTS OF NITROGENOUS METABOLITES IN PATIENTS WITH CHRONIC PYELONEPHRITIS

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Abstract

Background. We have previously shown that nitrogenous metabolites have immunomodulatory effects in healthy rats and humans as well as patients with dysfunction of neuroendocrine-immune complex, encephalopatia and chronic pyelonephritis. The purpose of this study is clarification of the role of neuro-endocrine factors in their immunotropic activity in patients with chronic pyelonephritis. **Materials and Methods**. The object of observation were 17 men (aged 24-70 years) with chronic pyelonephritis in remission. The plasma levels and urinary excretion of nitrogenous metabolites as well as parameters of immunity and its neuro-endocrine regulation twice (on admission and after balneotherapy at the Truskavets' Spa) was performed. **Results**. Judging by the multiple correlation coefficient, uricosuria exhibits maximal neuro-endocrine activity (R=0,780), followed by bilirubinemia (R=0,742), creatinineuria (R=0,692), uricemia (R=0,636), creatinineemia (R=0,632), urea excretion (R=0,536), instead urea plasma correlate with neuro-endocrine parameters insignificantly (R=0,360). Nitrogenous metabolites together determine the state of neuro-endocrine regulation by 94,2%, which, in turn, determine the state of immunity by 99,9%. **Conclusion**. Nitrogenous metabolites carry out immunomodulation in different ways: directly through aryl hydrocarbon (bilirubin), toll-like and adenosine (uric acid) receptors of immunocytes; through modulation of the activity of neurons of the autonomous nervous system and endocrinocytes with subsequent neuro-endocrine immunomodulation; and also, apparently, due to an off-receptor effect on neurons, endocrinocytes and immunocytes (urea and creatinine).

Keywords: **bilirubin, uric acid, urea, creatinine, immunity, HRV, adaptation hormones, relationships, chronic pyelonephritis.**

INTRODUCTION

We have previously shown that nitrogenous metabolites have immunomodulatory effects, both in healthy rats [11,12,30] and humans [21] as well as patients with dysfunction of neuroendocrine-immune complex [13,14,36], encephalopatia [20] and chronic pyelonephritis [22]. The purpose of this study is clarification of the role of neuro-endocrine factors in immunotropic activity of nitrogenous metabolites in patients with chronic pyelonephritis.

MATERIAL AND METHODS

The object of observation were 17 men (aged 24-70 years) with chronic pyelonephritis in remission. The examination was performed twice, before and after a 9-11-day course of balneotherapy: bioactive water Naftussya (3 ml/kg one hour before meals three times a day) and in half an hour additionally water "Mariya" in the same dose as well as application of Ozokerite on the lumbar region (temperature 45^0C, exposure 30 minutes, every other day, 5 procedures) and baths with mineral water (Cl^--SO_4^{2-}-Na^+-Mg^{2+} containing salt concentration 25 g/L, temperature 36-37^0C, duration 8-10 minutes, every other day, 5 procedures) [29].

The plasma and urinary levels of uric acid (by uricase method), urea (by urease method by reaction with phenol hypochlorite) and creatinine (by Jaffe's color reaction by Popper's method) as well as plasma bilirubin (by diazoreaction using the Jedrashik-Kleghorn-Grof method), adaptation hormones and parameters of HRV and immunity was performed.

The biochemic analyzes were carried out according to the instructions described in the manual [7]. The analyzers “Pointe-180” ("Scientific", USA) and “Reflotron” (Boehringer Mannheim, BRD) were used with appropriate sets.

Plasma levels of major hormones of adaptation [4,8,9,10]: Cortisol, Testosterone, Aldosterone, Triiodothyronine and Calcitonin we determined by the ELISA with the use of analyzer “RT-2100C” and corresponding sets of reagents from “Алкор Био”, XEMA Co., Ltd and DRG International Inc.

State of autonomous nervous system evaluated by parameters of HRV. ECG recorded during 7 min in II lead by hardware-software complex "CardioLab+HRV" ("KhAI-Medica", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. Baevskiy’s parameters: heart rate (HR), the mode (Mo), the amplitude of mode (AMo), the variational swing (MxDMn). Temporal parameters (Time Domain Methods): the standart deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 ms (pNN_{50}), triangular index (TNN). Spectral parameters (Frequency Domain Methods): power spectral density (PSD) bands of HRV: high-frequency (HF, range 0,40÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,040÷0,015 Hz) and ultralow-frequency (ULF, range 0,015÷0,003 Hz). Calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index (CI)=(VLF+LF)/HF), Baevskiy’s Stress Index (BSI) and Activity of Regulatory Systems Index (BARSI) [2,3,15,34].

Immune status evaluated on a set of I and II levels recommended by the WHO as described in the manuals [18,24,26]. For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD25, CD8, CD22 and CD56 from company "Granum" (Kharkiv) with visualization under light microscope with immersion system. Subpopulation of T cells with receptors high affinity (T-active) determined by test of “active” rosette formation. The state of humoral immunity judged by the concentration in serum of Circulating Immune Complexes (by polyethylene glycol precipitation method) and

Immunoglobulins classes M, G, A (ELISA, analyser "Immunochem", USA). In addition, the levels of IL-1, IL-6 and C-RP was determined (by the ELISA with the use of analyzer "RT-2100C" and corresponding set of reagents from "Diactone", France).

The set of immune parameters of saliva was IgG, IgA, secretory IgA (ELISA, analyser "Immunochem", USA) and Lysozyme. The activity of the latter was evaluated by the bacteriolysis of Micrococcus lysodeicticus test (nephelometric method) [18].

Parameters of phagocytic function of neutrophils estimated as described by SD Douglas & PG Quie [5] with moderately modification by MM Kovbasnyuk [23]. 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 [29]:

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

In portion of capillary blood we counted up Leukocytogram (LCG) (Eosinophils, Rod-shaped and Polymorphonucleary Neutrophils, Lymphocytes and Monocytes). On the basis of these elements, IL Popovych's Strain and Adaptation indices were calculated [10,32].

We calculated also the Entropy (h) of Immunocytogram (ICG) and Leukocytogram (LCG) using IL Popovych's formulas [27,28] derived from classical CE Shannon's formula [35]:

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

$$hLCG = - [L \bullet \log_2 L + M \bullet \log_2 M + E \bullet \log_2 E + PMNN \bullet \log_2 PMNN + RSN \bullet \log_2 RSN]/\log_2 5$$

Results processed by using the software package "Statistica 64".

RESULTS AND DISCUSSION

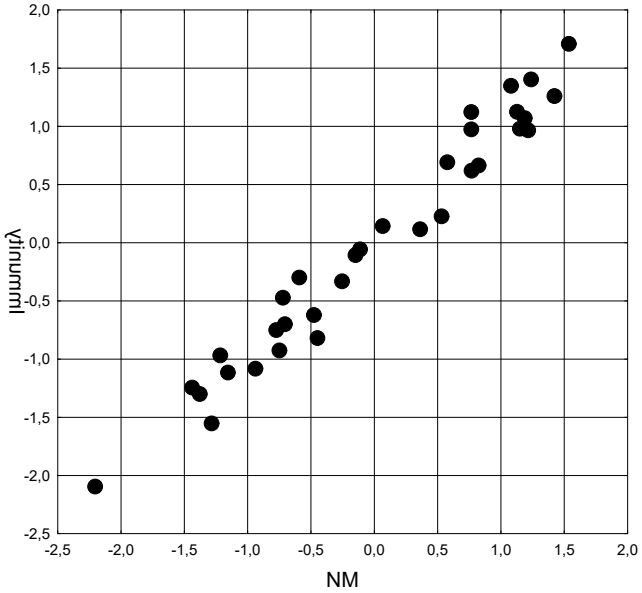
Following the accepted algorithm, we first created a matrix of correlations between nitrogenous metabolites and immune parameters (Table 1, see Appendix).

At the next stage, the canonical correlation between the parameters of nitrogenous metabolites, on the one hand, and the parameters of immunity, on the other hand, was analyzed. The program identified two pair of canonical roots. Nitrogen root of first pair receives the maximum factor load from the plasma bilirubin, much smaller, but unidirectional from urea, creatinine and uric acid as well as from the excretion of urea and creatinine, while the factor load from uricosuria is negligible (Table 2).

Table 2. Factor load on first pair of canonical roots of nitrogenous metabolites and immunity parameters in patients with chronic pyelonephritis

Left set	Root 1
Bilirubin Plasma, µM/L	0,714
Urea Plasma, mM/L	0,436
Creatinine Plasma, µM/L	0,444
Uric acid Plasma, mM/L	0,392
Urea Excretion, mM/24h	0,355
Creatinine Excretion, mM/24h	0,136
Uric acid Excretion, mM/24h	-0,024
Right set	**Root 1**
IgM Serum, g/L	-0,604
Lysozime Saliva, mg/L	-0,391
IgG Serum, g/L	-0,249
$CD22^+$ B- Lymphocytes, %	-0,220
Entropy of Immunocytogram	-0,192
Pan-Lymphocytes, %	-0,027
Pan-Leukocytes, 10^9/L	0,388
Rod-shaped Neutrophils, %	0,365
IgA Serum, g/L	0,295
Popovych's Strain Index-2, units	0,231

The immune root of the first pair presents the parameters subject to **downregulation** or **upregulation.** In general, this immune constellation is determined by nitrogenous metabolites by 96.4% (Fig. 1).



R=0,982; R^2=0,964; $\chi^2_{(133)}$=192; p=0,0007; Λ Prime<10^{-4}

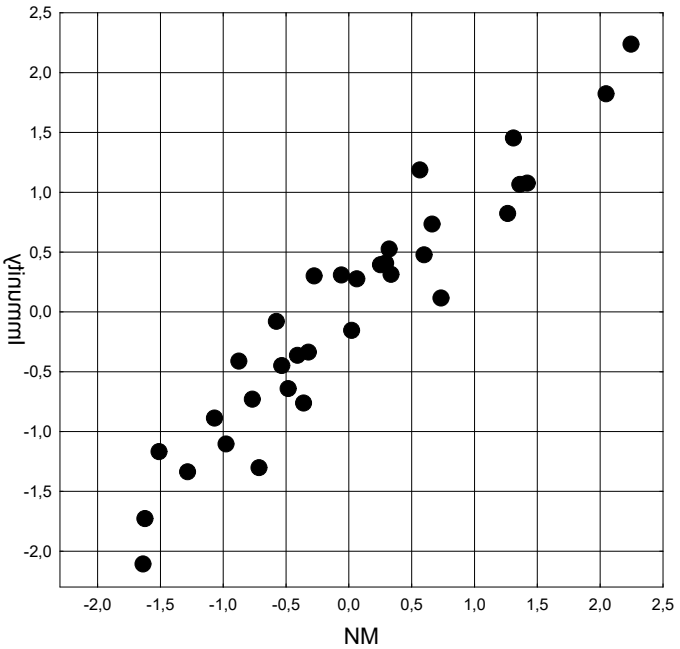
Fig. 1. Scatterplot of canonical correlation between Nitrogenous Metabolites (X-line) and the Immunity (Y-line) in patient chronic pyelonephritis. First pair of Roots

Nitrogen root of second pair receives the maximum factor load from the uricemia as well as unidirectional from excretion of the nitrogenous metabolites. Instead, the levels of metabolites in plasma give factor loadings with the opposite sign (Table 3).

Table 3. Factor load on second pair of canonical roots of nitrogenous metabolites and immunity parameters in patients with chronic pyelonephritis

Left set	Root 2
Uric acid Plasma, mM/L	-0,718
Urea Excretion, mM/24h	-0,441
Uric acid Excretion, mM/24h	-0,233
Creatinine Excretion, mM/24h	-0,217
Urea Plasma, mM/L	0,436
Creatinine Plasma, µM/L	0,323
Bilirubin Plasma, µM/L	0,309
Right set	**Root 2**
Microbial Count for Staph. aureus, Bac/Phag	-0,581
$CD8^+$ T-cytolytic Lymphocytes, %	-0,533
$CD4^+$ $CD25^+$T-regulatory Lymphocytes, %	-0,523
Microbial Count for E. coli, Bac/Phagocyte	-0,517
Phagocytose Index vs Staph. aureus, %	-0,425
Entropy of Immunocytogram	-0,382
IgM Serum, g/L	-0,294
Killing Index vs E. coli, %	-0,270
$CD22^+$ B- Lymphocytes, %	-0,230
Popovych's Strain Index-2, units	0,216
Rod-shaped Neutrophils, %	0,201
Phagocytose Index vs E. coli, %	0,194
Lysozime Saliva, mg/L	0,157
$CD3^+$ T-active Lymphocytes, %	0,149
IgA Serum, g/L	0,141
Polymorphonuclear Neutrophils, %	0,090

The immune root of the second pair presents another constellation of the parameters subject to **upregulation** or **downregulation.** In general, these immune variables are determined by nitrogenous metabolites by 90,3% (Fig. 2).



R=0,950; R^2=0,903; $\chi^2_{(108)}$=130; p=0,071; Λ Prime<10^{-3}

Fig. 2. Scatterplot of canonical correlation between Nitrogenous Metabolites (X-line) and the Immunity (Y-line) in patients with chronic pyelonephritis. Second pair of Roots

In the next step of the analysis, a regression model was constructed for each nitrogenous metabolite by stepwise exclusion until the maximum level of adjusted R^2 was reached.

As expected, based on the previous results, uric acid showed the maximum immunotropic activity among nitrogenous metabolites. Uricosuria positively correlates with the **relative** PSD of LF band (Fig. 3) as a generally recognized HRV-marker of **sympathetic** tone [3,15,34], as well as with the parameter inverse to the Mode HRV (Table 5), which reflects the level of circulating catecholamines [2,25]. In contrast to the relative value, the **absolute** value of PSD of LF band is interpreted ambiguously. LF power may be produced by both the vagal and sympathetic, and blood pressure regulation via baroreceptors, primarily by the vagal [33] or by baroreflex activity alone [6]. In resting conditions, the LF band reflects baroreflex activity and not cardiac sympathetic innervation [34]. In this study, we found, firstly, that the correlation between the relative and absolute values of LF band is insignificant (r=0,24); secondly, that LF ($msec^2$) is positively correlated with HRV-markers of vagal tone: RMSSD (r=0,69) and pNN_{50} (r=0,64) but negatively with the sympathetic marker AMo (r=-0,59).

Instead, with the relative PSD of VLF band, the correlation of uricosuria is **inverse** (Fig. 4). Just now Valle-Mandragon del L et al [41] showing that during hemodialysis angiotensin II had a positive correlation with VLF (r=0,390) and with LF/HF (r=0,359) and a negative correlation with LF (r=-0,262) and HF (r=-0,383) bands. Earlier it was reported that low VLF power has been correlated with low levels of testosterone, while other biochemical markers, such as those mediated by the hypothalamic–pituitary–adrenal axis (e.g., cortisol), have not [40]. There are opinions that VLF band directly reflects both vagal and sympathetic tone [1] or vagal tone only [38] as well as saliva testosterone level [40] while inversely - renin-angiotensin-aldosterone system activity [1,40]. In this study, we found that relative PSD of VLF band weakly inversely correlated with HRV-markers of vagal tone: RMSSD (r=-0,31) and pNN_{50} (r=0,35).

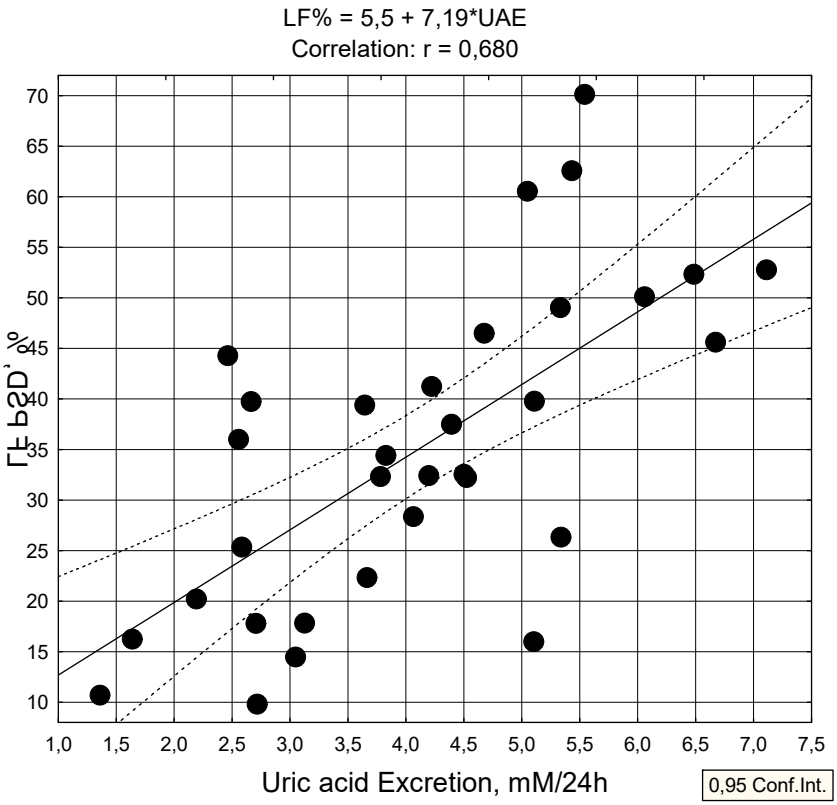


Fig. 3. Scatterplot of correlation between Uricosuria (X-line) and relative PSD of LF band of HRV (Y-line) in patients with chronic pyelonephritis

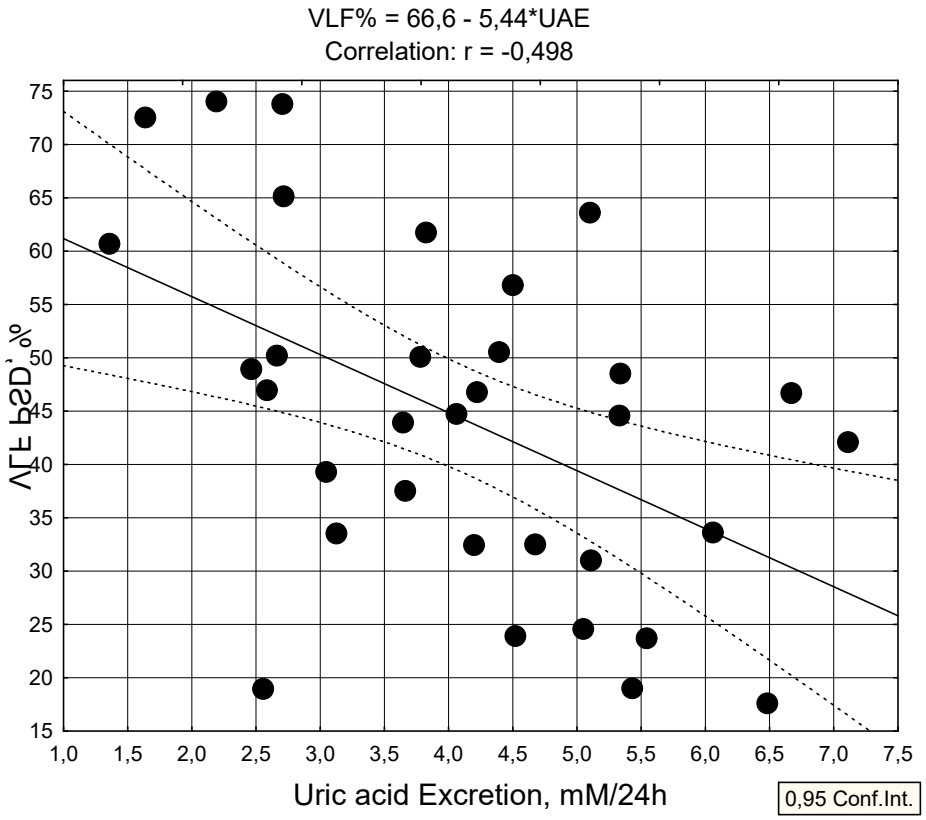


Fig. 4. Scatterplot of correlation between Uricosuria (X-line) and relative PSD of VLF band of HRV (Y-line) in patients with chronic pyelonephritis

Table 5. Regression Summary for Uricosuria, mM/24h
R=0,780; R^2=0,608; Adjusted R^2=0,535; $F_{(5,3)}$=8,4; p=0,00007

N=33		Beta	St. Err. of Beta	B	SE of B	$t_{(27)}$	p-level
Variables	r		Intercpt	1,425	2,292	0,62	0,539
LF/TP, %	**0,68**	1,620	0,608	0,153	0,058	2,66	0,013
1/Mode HRV, msec^{-1}	**0,41**	-0,245	0,132	-0,0024	0,0013	-1,85	0,075
LF/(LF+HF), %	**0,35**	-0,821	0,461	-0,060	0,033	-1,78	0,086
PSD LF band, msec^2	**0,28**	0,233	0,145	0,00054	0,00034	1,61	0,120
VLF/TP, %	**-0,50**	0,749	0,445	0,069	0,041	1,68	0,104

It seems that urocosuria acts as both a sympatho(adreno)mimetic and a cholinomimetic. The rate of integral determination of autonomous regulation is 60,8% (Table 5).

Instead, uricemia clearly downregulates vagal tone (Fig. 5 and Table 6) and causes a sympathotonic shift in the sympatho-vagal balance, the marker of which is the Baevskyi's Stress Index (Fig. 6).

In addition, uricemia downregulates plasma testosterone level (Fig. 7), possibly mediated by VLF band, which is consistent with the cited authors [40].

The measure of such neuro-endocrine modulation is 40,4% (Table 6).

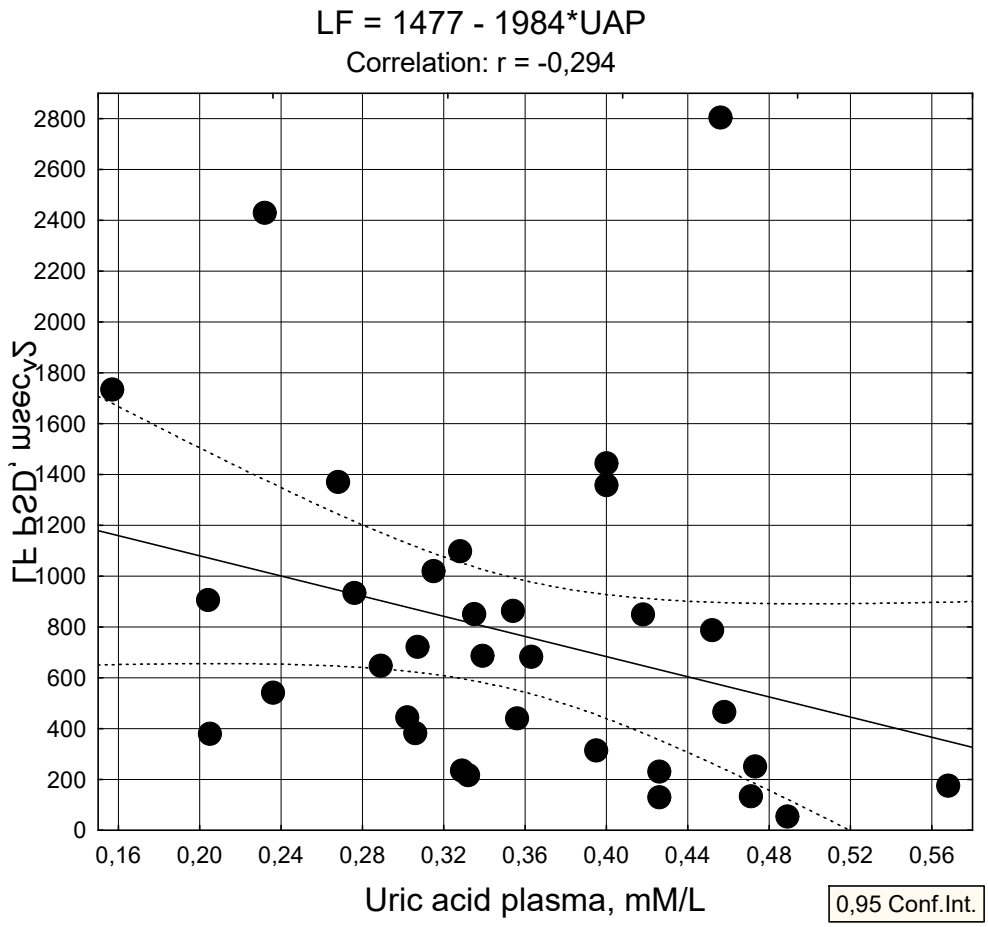


Fig. 5. Scatterplot of correlation between Uricemia (X-line) and PSD of LF band of HRV (Y-line) in patients with chronic pyelonephritis

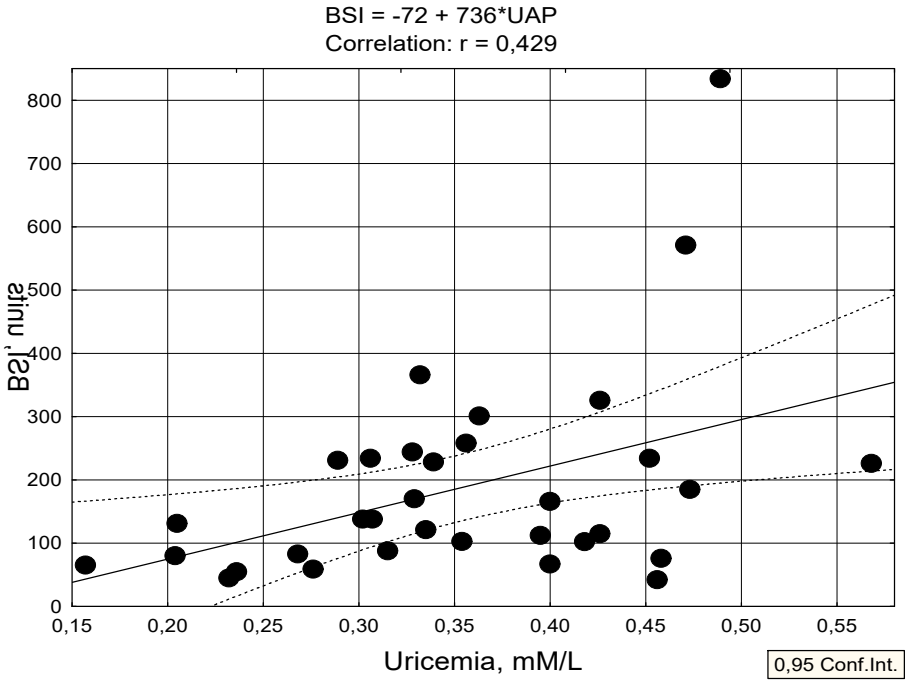


Fig. 6. Scatterplot of correlation between Uricemia (X-line) and Baevskiy's Stress Index of HRV (Y-line) in patients with chronic pyelonephritis

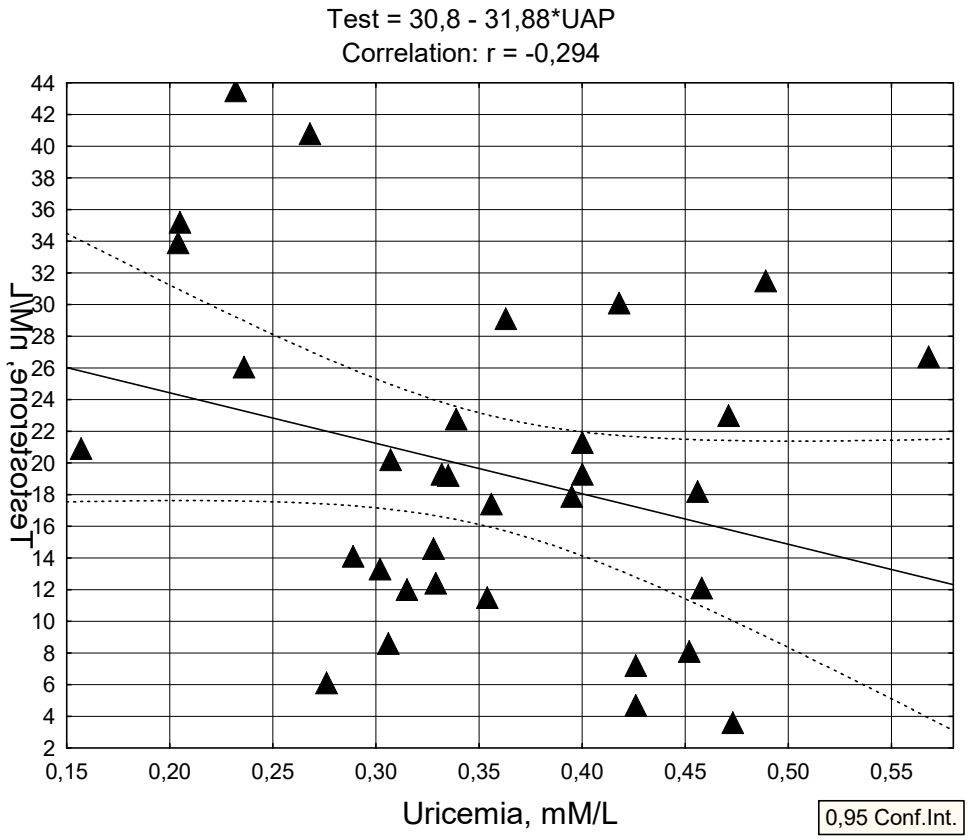


Fig. 7. Scatterplot of correlation between Uricemia (X-line) and Testosterone plasma level (Y-line) in patients with chronic pyelonephritis

Table 6. Regression Summary for Uricemia, mM/L
R=0,636; R^2=0,404; Adjusted R^2=0,294; $F_{(5,3)}$=3,7; p=0,012

N=33		Beta	St. Err. of Beta	B	SE of B	$t_{(27)}$	p-level
Variables	r		Intercpt	0,261	0,107	2,45	0,021
Stress Index HRV, un.	**0,43**	0,676	0,253	0,0004	0,0001	2,67	0,013
MxDMn HRV, msec	**-0,37**	-0,388	0,328	-0,0006	0,0005	-1,18	0,247
PSD LF band, msec²	**-0,29**	-0,406	0,314	-0,00006	0,000047	-1,29	0,207
Testosterone, nM/L	**-0,29**	-0,371	0,162	-0,0034	0,0015	-2,29	0,030
SDNN HRV, msec	**-0,26**	0,997	0,429	0,0053	0,0023	2,33	0,028

Bilirubinemia is negatively correlated with the definite vagal marker pNN50 (Fig. 8), but positively with the definite sympathetic marker AMo and probable VLFr (Fig. 9), as well as with ULF band HRV (Table 7). The interpretation of the latter is still missing in the available literature [34]. In this sample, the ULF band is positively correlated with the vagal markers: MxDMn (r=0,55), RMSSD (r=0,51) and pNN50 (r=0,43), but negatively with the sympathetic marker LFnu (r=-0,27), so it is colored as an HRV marker of vagal tone.

In general, bilirubinemia determines the listed HRV parameters by 50,1% (Table 7).

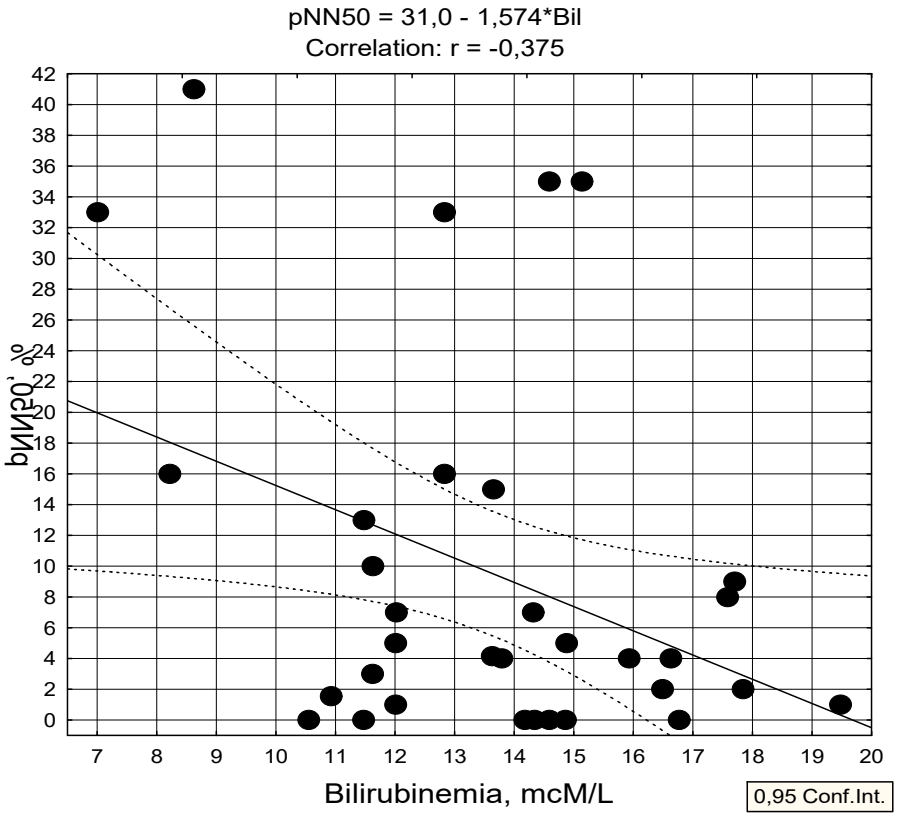


Fig. 8. Scatterplot of correlation between plasma Bilirubin (X-line) and pNN_{50} of HRV (Y-line) in patients with chronic pyelonephritis

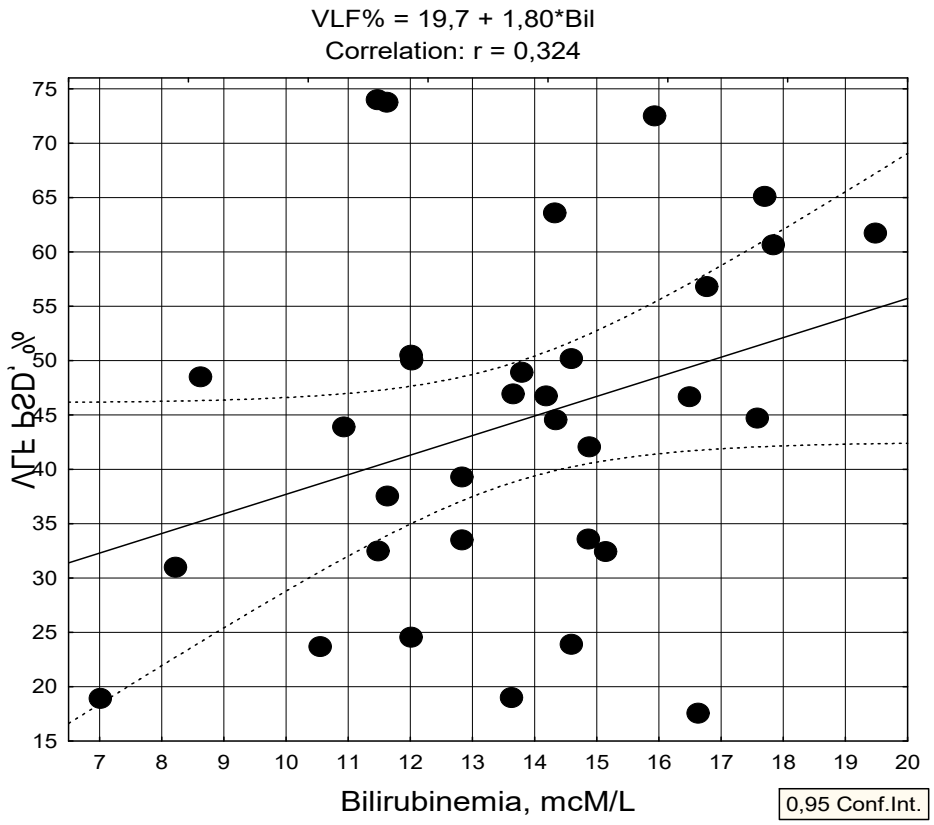


Fig. 9. Scatterplot of correlation between plasma Bilirubin (X-line) and relative PSD of VLF band of HRV (Y-line) in patients with chronic pyelonephritis

Table 7. Regression Summary for Bilirubinemia, µM/L
R=0,742; R^2=0,551; Adjusted R^2=0,487; $F_{(4,3)}$=8,6; p=0,00012

N=33		Beta	St. Err. of Beta	B	SE of B	$t_{(28)}$	p-level
Variables	r		Intercpt	8,859	2,212	4,01	10^{-3}
pNN_{50} HRV, %	**-0,38**	-0,412	0,173	-0,0982	0,0413	-2,38	0,025
PSD ULF band, msec^2	**0,34**	0,665	0,142	0,0111	0,0024	4,69	10^{-4}
VLF/TP, %	**0,32**	0,293	0,138	0,0527	0,0248	2,13	0,042
Amplitude of Mode HRV, %	**0,29**	0,254	0,159	0,0462	0,0289	1,60	0,121

Creatinine excretion is positively correlated with a number of markers of sympatho-vagal balance, as well as plasma levels of testosterone and triiodothyronine (Figs. 10-11 and Table 8), determining such a neuro-endocrine constellation by 47,8%.

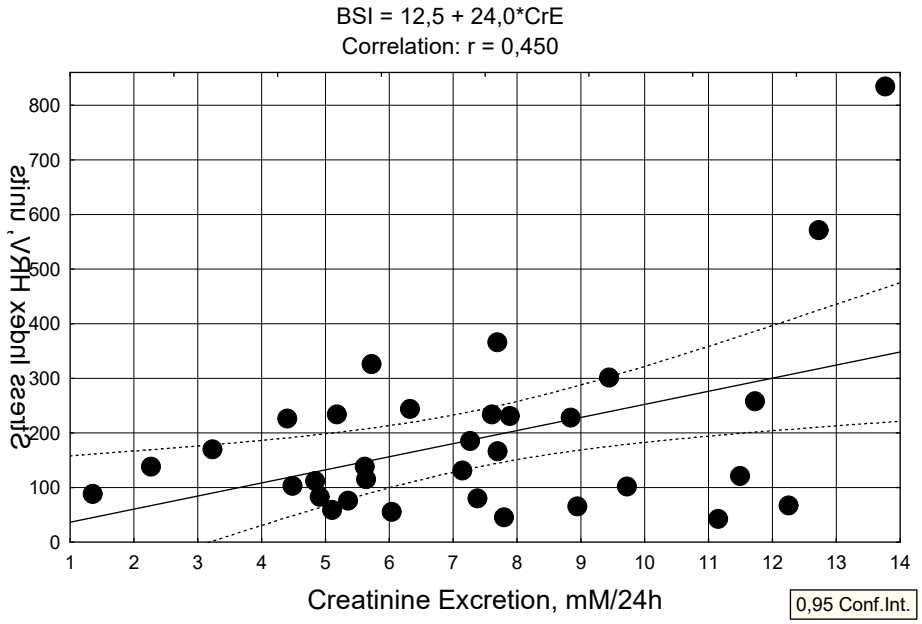


Fig. 10. Scatterplot of correlation between Creatinineuria (X-line) and Baevskiy's Stress Index of HRV (Y-line) in patients with chronic pyelonephritis

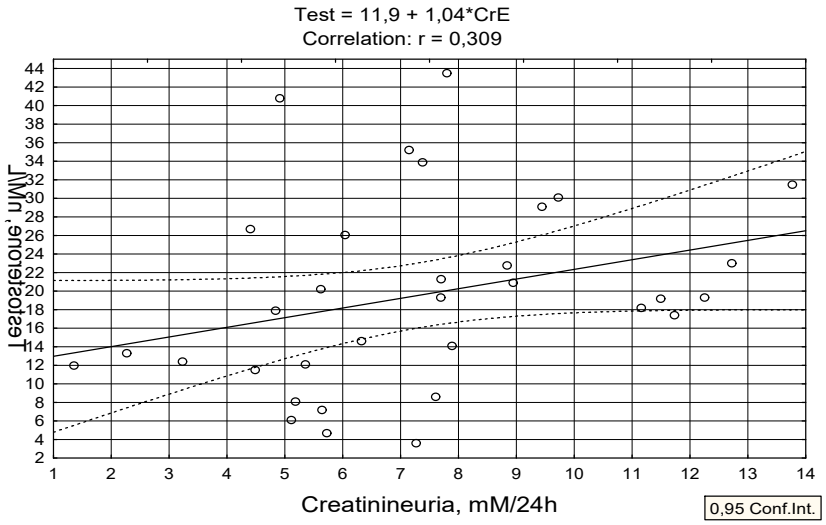


Fig. 11. Scatterplot of correlation between Creatinineuria (X-line) and plasma Testosterone level (Y-line) in patients with chronic pyelonephritis

Table 8. Regression Summary for Creatinineuria, mM/24h
R=0,692; R^2=0,478; Adjusted R^2=0,382; $F_{(5,3)}$=5,0; p=0,0024

N=33		Beta	St. Err. of Beta	B	SE of B	$t_{(27)}$	p-level
Variables	r		Intercpt	31,60	20,45	1,54	0,134
Stress Index HRV, un.	**0,45**	0,353	0,153	0,0066	0,0029	2,30	0,029
1/Mode HRV, msec^{-1}	**0,38**	-0,996	0,588	-0,021	0,012	-1,69	0,102
Heart Rate, beats/min	**0,34**	-0,682	0,581	-0,173	0,148	-1,17	0,251
Testosterone, nM/L	**0,31**	0,369	0,152	0,109	0,045	2,43	0,022
Triiodothyronine, nM/L	**0,27**	0,243	0,144	1,097	0,654	1,68	0,105

Instead, the level of creatinine **in plasma** (Table 9) correlates with markers of sympatho-vagal balance in the opposite way, that is, it downregulates the level of circulating catecholamines. Downregulation was also detected in relation to vagal tone, as evidenced by the negative correlation of RMSSD. Regarding the effect of plasma creatinine on sympathetic tone, the situation is ambiguous: with one sympathetic marker (LFr), the correlation is negative, but with the other (VLFr), it is positive. By the way, these HRV parameters are negatively correlated (r=-0,64). The rate of determination of this constellation of HRV parameters by creatinineemia is 39,9%.

Table 9. Regression Summary for Creatinineemia, µM/L
R=0,632; R^2=0,399; Adjusted R^2=0,288; $F_{(5,3)}$=3,6; p=0,013

N=33		Beta	St. Err. of Beta	B	SE of B	$t_{(27)}$	p-level
Variables	r		Intercpt	266,6	92,6	2,88	0,008
VLF/TP, %	**0,37**	-0,294	0,291	-0,2163	0,2141	-1,01	0,321
Heart Rate, beats/min	**-0,30**	-1,218	0,658	-1,2040	0,6503	-1,85	0,075
1/Mode HRV, msec^{-1}	**-0,27**	-0,762	0,628	-0,0612	0,0504	-1,21	0,235
LF/TP, %	**-0,25**	-0,502	0,280	-0,3819	0,2130	-1,79	0,084
RMSSD HRV, msec	**-0,29**	-0,766	0,252	-0,5350	0,1763	-3,04	0,005

Urea excretion is positively correlated with one of the markers of sympathetic tone (Fig. 12) and the plasma level of cortisol, but negatively with the plasma level of calcitonin (Fig. 13). The determination of this neuro-endocrine constellation is small, but still statistically significant (Table 10).

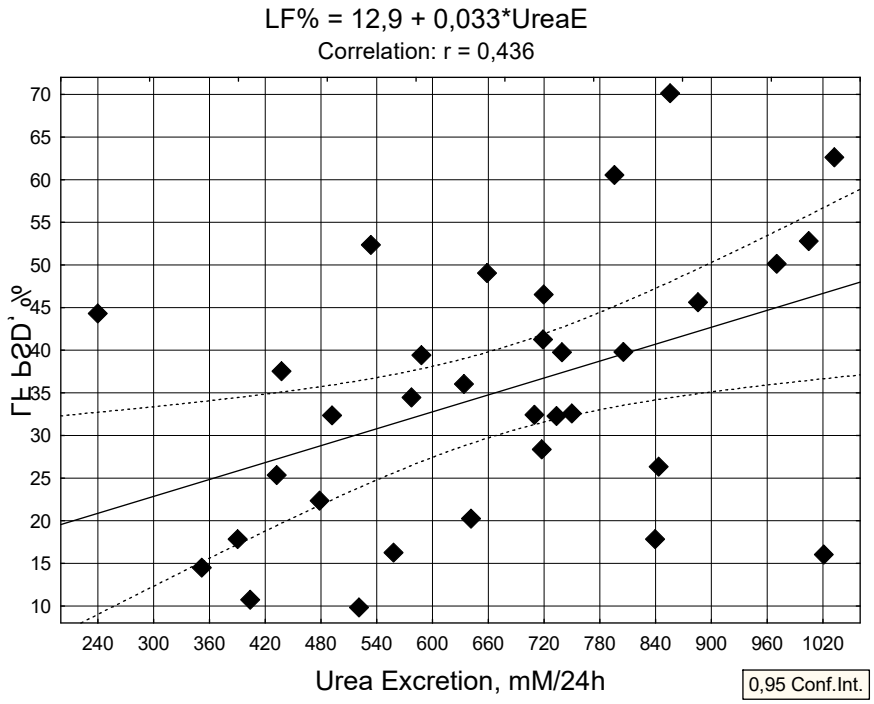


Fig. 12. Scatterplot of correlation between Urea Excretion (X-line) and relative PSD of LF band of HRV (Y-line) in patients with chronic pyelonephritis

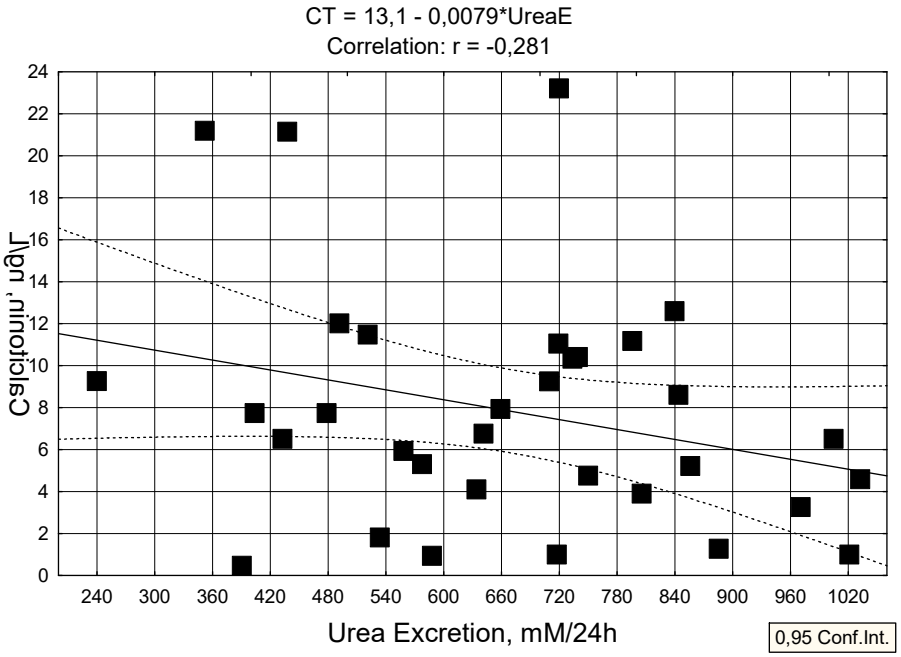


Fig. 13. Scatterplot of correlation between Urea Excretion (X-line) and Calcitonin plasma level (Y-line) in patients with chronic pyelonephritis

Table 10. Regression Summary for Urea Excretion, mM/24h
R=0,536; R^2=0,288; Adjusted R^2=0,210; $F_{(3,3)}$=3,9; p=0,0186

N=33		Beta	St. Err. of Beta	B	SE of B	$t_{(29)}$	p-level
Variables	r		Intercpt	447,4	122,5	3,65	0,001
LF/TP, %	**0,44**	0,407	0,157	5,372	2,077	2,59	0,015
Cortisol, nM/L	**0,28**	0,204	0,163	0,199	0,159	1,25	0,221
Calcitonin, ng/L	**-0,28**	-0,187	0,164	-6,673	5,847	-1,14	0,263

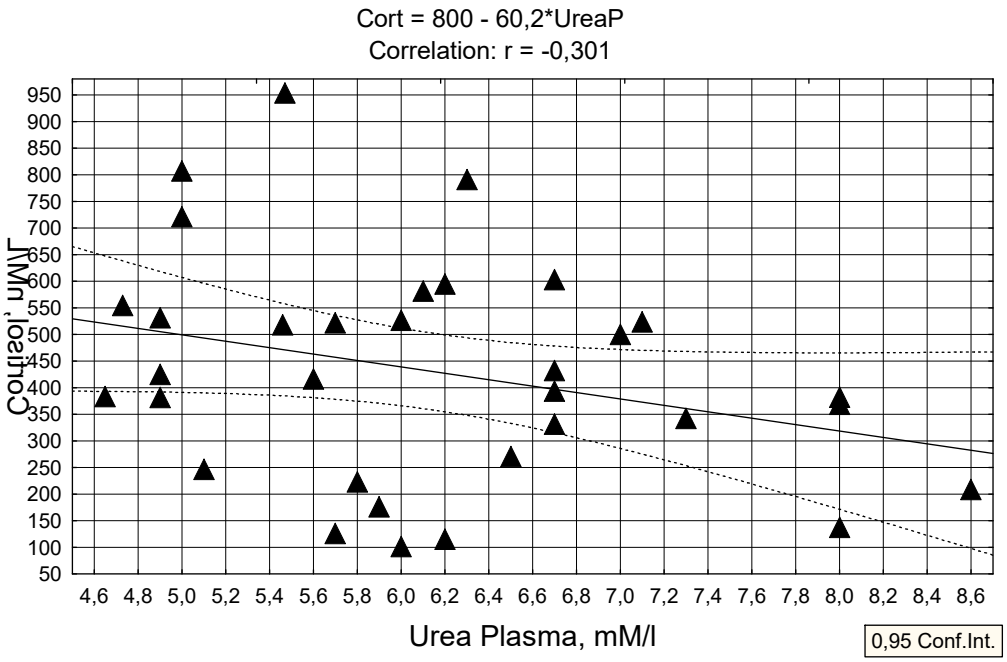


Fig. 14. Scatterplot of correlation between Urea (X-line) and Cortisol (Y-line) plasma levels in patients with chronic pyelonephritis

Instead, plasma urea correlates with cortisol in the opposite way, similar to the creatinineuria/creatininemia situation. A weak positive correlation with triiodothyroninemia was also revealed. In general, the influence of plasma urea on hormone levels, not to mention HRV parameters, is statistically insignificant (Table 11).

Table 11. Regression Summary for Urea Plasma, mM/L
R=0,360; R^2=0,129; Adjusted R^2=0,071; $F_{(2,30)}$=2,23; p=0,125

N=33		Beta	St. Err. of Beta	B	SE of B	$t_{(30)}$	p-level
Variables	r		Intercpt	6,184	0,668	9,26	10^{-6}
Cortisol, nM/L	**-0,30**	-0,269	0,173	-0,0013	0,0009	-1,56	0,129
Triiodothyronine, nM/L	**0,24**	0,199	0,173	0,3116	0,2703	1,15	0,258

At the next stage, the canonical correlation between nitrogenous metabolites, on the one hand, and neuro-endocrine parameters, on the other hand, was analyzed (Table 12).

Table 12. Matrix of correlations between nitrogenous metabolites and neuro-endocrine parameters included in canonical model

	Correlations, left set with right set						
variable	Bil	Urea E	Urea P	CrP	UAP	CrE	UAE
T3	-0,053	0,016	0,242	-0,227	-0,199	0,271	0,012
Cortisol	0,063	0,281	-0,301	-0,083	0,169	0,002	0,221
Calcitonin	-0,172	-0,281	0,033	-0,049	-0,040	-0,169	-0,196
Testosterone	-0,161	0,136	0,109	-0,022	-0,294	0,309	0,062
BSI	0,270	0,149	-0,023	-0,051	0,429	0,450	0,091
Mode	-0,153	-0,273	0,172	0,265	-0,154	-0,376	-0,414
AMo	0,286	0,155	-0,012	0,006	0,399	0,296	0,149
MxDMn	-0,072	0,083	0,144	-0,028	-0,366	-0,070	0,119
HR	0,096	0,322	-0,184	-0,296	0,142	0,344	0,426
SDNN	-0,091	-0,069	0,078	-0,218	-0,257	-0,019	-0,023
RMSSD	-0,309	-0,111	-0,027	-0,291	-0,099	0,051	-0,072
PNN50	-0,375	-0,092	-0,024	-0,274	-0,035	0,101	-0,064
ULF	0,344	-0,104	-0,019	-0,188	0,018	0,082	-0,093
LF	-0,126	0,145	0,051	-0,337	-0,294	0,153	0,284
IC	0,258	0,048	0,078	0,301	-0,048	-0,208	-0,029
VLF%	0,324	-0,159	0,066	0,365	0,213	-0,182	-0,498
LF%	-0,150	0,436	-0,067	-0,248	-0,228	0,219	0,680
LFNU	0,167	0,340	-0,005	0,060	-0,084	0,085	0,351

At the next stage, the canonical correlation between nitrogenous metabolites, on the one hand, and neuro-endocrine parameters, on the other hand, was analyzed (Table 12). Based on the results of the analysis, two pairs of canonical roots were formed.

The factor structure of the nitrogenous root of the first pair is formed by positive loads from bilirubinemia and uricemia and negative loads from the excretion of uric acid and urea, as well as, to a minimal extent, from plasma urea (Table 13).

For convenience, the components of the neuro-endocrine root of the first pair are placed not by rank and sign, as usual, but by the features of correlations with the components of the nitrogenous root.

The first constellation consists of 4 HRV parameters, which are **upregulated** by both bilirubinemia and uricemia, while LF band and testosterone are subject to **downregulation** by both metabolites. Given the literature data that bilirubin is an agonist of aryl hydrocarbon receptors, and uric acid is an agonist of adenosine receptors, which are expressed by many types of cells, in particular, immunocytes, endocrinocytes, and neurons [20,30], we assume that both metabolites activate neurons of sympathetic nuclei (locus coeruleus, rostral ventrolateral medulla, sympathetic ganglia) and/or inhibit neurons of the nuclei of the vagus nerve (ambiguous, dorsal vagal nucleus, cardial ganglia); activation of the neuroendocrine cells of the medullar zone of the adrenal glands is also possible. Inhibition of the release of testosterone is theoretically possible by both a direct effect on Leydig cells and components of the hypothalamic-pituitary-gonadal axis.

ULF band and plasma cortisol level **upregulated** by bilirubin only, that is, probably through aryl hydrocarbon receptors of neurons of the nuclei of the vagus nerve and endocrinocytes of the fascicular zone of the adrenal glands or components of the hypothalamic-pituitary-corticoadrenal axis respectively.

Interestingly, some markers of vagal tone (pNN50 and RMSSD) are **downregulated** only by bilirubin, while others (MxDMn and SDNN) are **downregulated** only by plasma uric acid. We tend to explain this situation with the notion that the first pair of HRV parameters are

considered to be indisputable markers of vagal tone, while the second one reflects primarily the total effect of autonomic regulation, and vagal tone to a lesser extent [2,34].

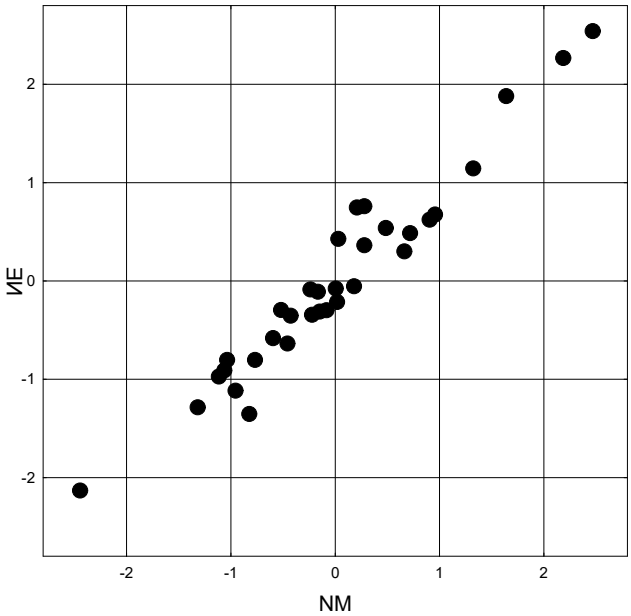
The other two markers of sympathetic tone (LFr and LFnu) are **upregulated** by uricosuria, that is, also due to adenosine receptors of neurons of sympathetic nuclei.

Finally, plasma levels of calcitonin and triiodothyronine are upregulated by urea excretion and plasma levels, respectively. In view of the lack of information about the existence of urea receptors, we refrain from making assumptions about possible mechanisms.

In general, bilirubin, uric acid and urea determine the constellation of neuro-endocrine parameters by 94,2% (Fig. 15).

Table 13. Factor load on first pair of canonical roots of nitrogenous metabolites and neuro-endocrine parameters in patients with chronic pyelonephritis

Left set	**Root 1**
Bilirubin Plasma, μM/L	**0,651**
Uric acid Plasma, mM/L	**0,598**
Uric acid Excretion, mM/24h	**-0,460**
Urea Excretion, mM/24h	**-0,286**
Urea Plasma, mM/L	**-0,060**
Right set	**Root 1**
VLF/TP, %	**0,471**
Amplitude of Mode HRV, %	**0,367**
Stress Index HRV, units	**0,455**
1/Mode HRV, $msec^{-1}$	**0,115**
PSD LF band, $msec^2$	**-0,309**
Testosterone, nM/L	**-0,228**
PSD ULF band, $msec^2$	**0,351**
Cortisol, nM/L	**0,060**
pNN_{50} HRV, %	**-0,151**
RMSSD HRV, msec	**-0,142**
MxDMn HRV, msec	**-0,343**
SDNN HRV, msec	**-0,157**
LF/TP, %	**-0,496**
LF/(LF+HF), %	**-0,133**
Calcitonin, ng/L	**-0,099**
Triiodothyronine, nM/L	**-0,092**



R=0,970; R^2=0,942; $\chi^2_{(126)}$=185; p=0,0005; Λ Prime<10^{-4}

Fig. 15. Scatterplot of canonical correlation between nitrogenous metabolites (X-line) and neuro-endocrine parameters (Y-line) in patients with chronic pyelonephritis. First pair of Roots

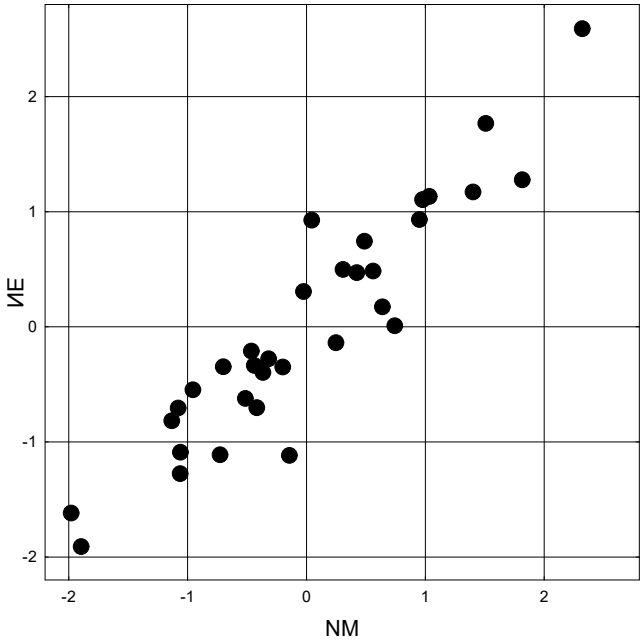
And where is creatinine? Together with bilirubin, it forms the factor structure of the nitrogenous root of the second pair (Table 14). The VLF band and the associated centralization index are **upregulated** by both plasma metabolites, and the marker of sympathetic tone LFnu only by bilirubin. On the other hand, the undisputed markers of vagal tone (pNN_{50} and RMSSD) are **downregulated** by both metabolites, while the two controversial vagal markers (LF and SDNN) are **inhibited** only by creatinine, and calcitonin is **downregulated** only by bilirubin. Finally, plasma levels of triiodothyronine and testosterone are **upregulated** by creatinine excretion.

Regarding the inhibition of calcitonin release, speculations are possible with Ah receptors of C-cells of the thyroid gland and/or afferent terminals [37,39]. Instead, the mechanism of regulatory influence of creatinine, as well as urea, remains without discussion due to the complete lack of information about the existence of the corresponding receptors. The only rational explanation is a toxic effect on the corresponding cells, but it is broken by the fact that this contingent does not have uremia.

In general, bilirubin and creatinine determines the constellation of neuro-endocrine parameters by 87,1% (Fig. 16).

Table 14. Factor load on first pair of canonical roots of nitrogenous metabolites and neuro-endocrine parameters in patients with chronic pyelonephritis

Left set	Root 2
Creatinine Plasma, μM/L	-0,665
Bilirubin Plasma, μM/L	-0,296
Creatinine Excretion, mM/24h	0,472
Right set	Root 2
(VLF+LF)/HF as Centralization	-0,491
VLF/TP, %	-0,330
LF/(LF+HF), %	-0,325
pNN_{50} HRV, %	0,550
RMSSD HRV, msec	0,524
PSD LF band, $msec^2$	0,385
SDNN HRV, msec	0,356
Calcitonin, ng/L	0,210
Triiodothyronine, nM/L	0,564
Testosterone, nM/L	0,290



R=0,933; R^2=0,871; $\chi^2_{(102)}$=131; p=0,027; Λ Prime<10^{-3}

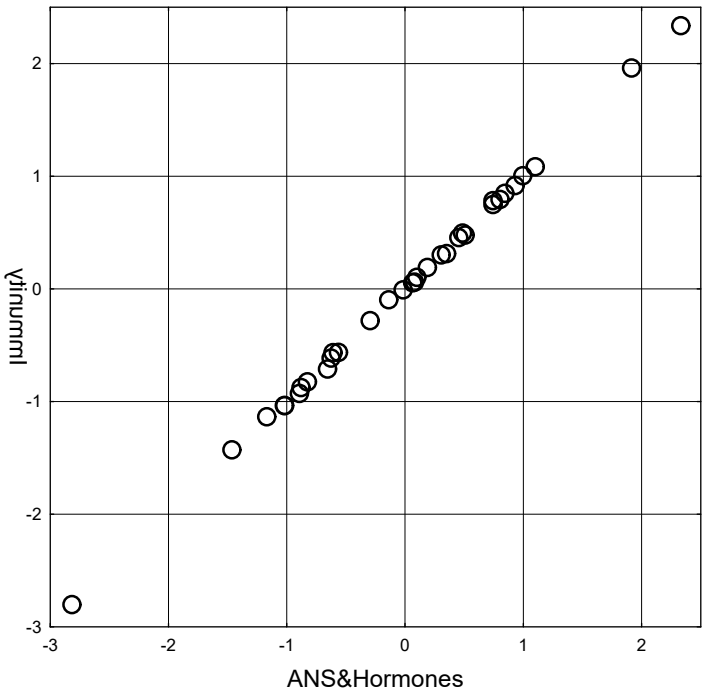
Fig. 16. Scatterplot of canonical correlation between nitrogenous metabolites (X-line) and neuro-endocrine parameters (Y-line) in patients with chronic pyelonephritis. Second pair of Roots

At the final stage, the canonical correlation between the selected neuro-endocrine parameters associated with nitrogenous metabolites, on the one hand, and the parameters of immunity, on the other hand, was analyzed. The program identified only one significant pair of canonical roots. Neuro-endocrine root receives negatively factor loads from vagal tone and calcitonin, and opposite in sign - from sympathetic tone and testosterone, triiodeththyronine and cortisol (Table 15). The factor structure of the immune radical is formed by 19 parameters of immunity.

Table 15. Factor load on canonical roots of neuro-endocrine regulation and immunity in patients with chronic pyelonephritis

Left set	R
pNN_{50} HRV, %	-0,569
SDNN HRV, msec	-0,374
Calcitonin, ng/L	-0,327
PSD LF band, $msec^2$	-0,170
LF/(LF+HF), %	0,569
LF/TP, %	0,396
Baevskiy's Stress Index HRV, units	0,358
Testosterone, nM/L	0,263
Triiodothyronine, nM/L	0,174
Cortisol, nM/L	0,097
Right set	R
IgM Serum, g/L	-0,554
Pan-Lymphocytes, %	-0,474
Entropy of Immunocytogram	-0,370
$CD22^+$ B- Lymphocytes, %	-0,338
Microbial Count for E. coli, Bacteria/Phag	-0,311
Killing Index vs E. coli, %	-0,279
Phagocytose Index vs Staph. aureus, %	-0,229
IgG Serum, g/L	-0,220
Phagocytose Index vs E. coli, %	-0,123
Popovych's Strain Index-2, units	-0,105
$CD8^+$ T-cytolytic Lymphocytes, %	-0,105
Lysozime Saliva, mg/L	-0,060
Microbial Count for St. aur., Bac/Phagocyte	-0,058
Pan-Leukocytes, 10^9/L	-0,056
$CD4^+$ $CD25^+$T-regulatory Lymphocytes, %	-0,027
Polymorphonuclear Neutrophils, %	0,553
IgA Serum, g/L	0,219
Rod-shaped Neutrophils, %	0,161
$CD3^+$ T-active Lymphocytes, %	0,044

A detailed analysis of neuro-endocrine connections in line with the concept of the neuro-endocrine-immune complex [4,9,10,17,19,31,32,37,39] will be carried out in the next article. For now, allow us to conclude this article by stating the fact of **almost linear** dependence between neuro-endocrine and immune sets (Fig. 17).



R=0,9997; R^2=0,9994; $\chi^2_{(228)}$=344; p=10^{-6}; Λ Prime=10^{-6}

Fig. 17. Scatterplot of canonical correlation between neuro-endocrine parameters (X-line) and the Immunity (Y-line) in patients with chronic pyelonephritis

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975 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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APPENDIX

Table 1. Matrix of correlations between nitrogenous metabolites and immunity parameters in patients with chronic pyelonephritis

Variable	Correlations N=33						
	Bil	CrP	UAP	CrE	UAE	Urea E	Urea P
CD25	-0,16	-0,06	0,48	-0,05	0,07	0,12	-0,04
IL-6	0,05	-0,01	0,09	0,19	-0,01	-0,08	0,04
CRP	-0,25	0,21	-0,01	0,08	0,02	0,08	0,19
IL-1	0,12	0,07	-0,38	-0,02	0,00	-0,14	-0,02
SIgA	0,06	0,09	-0,09	0,28	-0,15	-0,22	0,02
IgG S	-0,13	-0,06	-0,25	0,04	-0,11	0,10	-0,20
Lys S	-0,24	-0,06	-0,11	0,26	-0,19	-0,28	-0,04
IgA S	-0,09	-0,09	-0,31	0,19	-0,18	-0,21	-0,10
Phl St A	-0,11	0,08	0,39	0,10	-0,18	0,03	-0,27
MC St A	-0,26	-0,09	0,38	0,20	-0,09	0,24	-0,38
KI St A	0,16	-0,26	0,34	0,01	-0,15	-0,01	0,06
Phl E C	0,00	0,14	-0,01	0,08	-0,21	-0,30	0,09
MC E C	-0,37	-0,07	0,21	0,10	0,08	0,39	-0,28
KI EC	0,14	-0,12	0,46	-0,00	-0,07	-0,00	0,18
H LCG	-0,10	0,26	0,27	0,11	-0,14	0,17	0,22
BCC St A	0,14	-0,23	0,26	0,22	0,08	0,26	-0,13
BCC E C	0,10	-0,20	0,39	0,15	0,17	0,30	0,02
Leuk	0,26	0,14	0,03	0,09	0,24	0,29	0,23
PMNN	0,16	-0,28	-0,25	0,23	0,36	0,16	-0,11
RSN	0,32	0,14	-0,03	0,12	-0,08	0,10	0,17
Eos	-0,01	0,25	0,18	0,06	-0,02	0,19	0,26
Mon	-0,24	-0,11	0,22	0,12	0,06	0,16	-0,08
Lymph	-0,14	0,24	0,17	-0,29	-0,38	-0,26	0,05
PSI-1	0,01	-0,10	-0,06	-0,07	-0,14	-0,13	-0,04
PSI-2	0,16	0,17	-0,01	-0,07	-0,13	0,01	0,31
PAI-1	0,28	-0,24	-0,09	0,15	0,24	-0,10	-0,17
PAI-2	0,24	-0,12	-0,08	0,20	0,18	0,02	-0,21
CD4	0,17	-0,07	-0,36	-0,01	-0,05	-0,02	-0,09
CD8	-0,12	-0,16	0,42	-0,09	0,06	0,16	-0,15
CD22	0,02	-0,36	0,01	-0,22	0,13	-0,12	-0,43
CD3 act	0,03	0,03	-0,18	-0,25	0,04	-0,13	-0,03
CIC	0,18	0,03	0,28	0,18	-0,01	-0,09	0,11
IgG	0,01	-0,25	-0,05	0,05	-0,03	-0,22	-0,06
IgA	0,45	0,14	0,09	0,09	0,10	-0,11	0,18
IgM	-0,65	-0,29	0,04	0,05	-0,05	-0,02	-0,19
CD56	-0,00	0,21	-0,16	0,10	-0,03	-0,14	0,21
0-Lymph	-0,06	0,38	0,04	0,22	-0,11	0,09	0,45
H ICG	0,02	-0,44	0,14	-0,19	0,11	-0,06	-0,49

Table 4. Matrix of correlations between nitrogenous metabolites and endocrine&HRV parameters in patients with chronic pyelonephritis

Variable	Correlations N=33						
	Bil	CrP	UAP	ECr	EUA	UreaE	UreaP
Bil	1,00	0,07	0,11	0,06	-0,00	-0,08	0,26
CrP	0,07	1,00	0,08	-0,25	-0,38	-0,20	0,52
UAP	0,11	0,08	1,00	0,18	-0,16	0,12	0,10
ECr	0,06	-0,25	0,18	1,00	0,47	0,54	0,12
EUa	-0,00	-0,38	-0,16	0,47	1,00	0,65	-0,03
Urea E	-0,08	-0,20	0,12	0,54	0,65	1,00	0,05
Urea P	0,26	0,52	0,10	0,12	-0,03	0,05	1,00
PTA	0,10	0,11	0,23	0,06	-0,13	-0,09	0,04
Aldosterone	-0,07	0,12	0,12	0,12	-0,12	-0,12	0,10
T3	-0,05	-0,23	-0,20	0,27	0,01	0,02	0,24
Cortisol	0,06	-0,08	0,17	0,00	0,22	0,28	-0,30
Calcitonin	-0,17	-0,05	-0,04	-0,17	-0,20	-0,28	0,03
Testosterone	-0,16	-0,02	-0,29	0,31	0,06	0,14	0,11
BSI	0,27	-0,05	0,43	0,45	0,09	0,15	-0,02
BARSI	0,11	-0,20	-0,03	0,40	0,18	0,25	0,05
TNN	-0,22	0,11	-0,33	-0,14	-0,13	-0,17	0,13
Mode	-0,15	0,27	-0,15	-0,38	-0,41	-0,27	0,17
AMo	0,29	0,01	0,40	0,30	0,15	0,16	-0,01
MxDMn	-0,07	-0,03	-0,37	-0,07	0,12	0,08	0,14
HR	0,10	-0,30	0,14	0,34	0,43	0,32	-0,18
SDNN	-0,09	-0,22	-0,26	-0,02	-0,02	-0,07	0,08
RMSSD	-0,31	-0,29	-0,10	0,05	-0,07	-0,11	-0,03
PNN50	-0,37	-0,27	-0,04	0,10	-0,06	-0,09	-0,02
TP	-0,06	-0,26	-0,19	0,11	-0,01	-0,02	0,06
ULF	0,34	-0,19	0,02	0,08	-0,09	-0,10	-0,02
VLF	0,09	-0,07	-0,22	-0,02	-0,21	-0,11	0,10
LF	-0,13	-0,34	-0,29	0,15	0,28	0,15	0,05
HF	-0,23	-0,27	-0,02	0,14	-0,05	-0,07	0,03
LF/HF	0,11	0,06	-0,18	-0,08	0,31	0,21	-0,03
(VLF+LF)/HF	0,26	0,30	-0,05	-0,21	-0,03	0,05	0,08
HHRV	-0,01	-0,30	-0,07	0,20	0,05	-0,22	-0,11
ULF%	0,47	-0,01	0,19	-0,05	-0,19	-0,20	-0,12
VLF%	0,32	0,36	0,21	-0,18	-0,50	-0,16	0,07
LF%	-0,15	-0,25	-0,23	0,22	0,68	0,44	-0,07
HF%	-0,39	-0,15	-0,05	-0,02	-0,13	-0,26	0,04
LFNU	0,17	0,06	-0,08	0,08	0,35	0,34	-0,01