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ACTIVATION OF CHRONIC INFLAMMATION AND COMORBIDITY IN END-STAGE RENAL DISEASE PATIENTS TREATED WITH CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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Ключевые слова: *хроническая болезнь почек, постоянный амбулаторный перитонеальный диализ, провоспалительные цитокины, коморбидность, смертность*

Abstract. Activation of chronic inflammation and comorbidity in end-stage renal disease patients treated with continuous ambulatory peritoneal dialysis. Shifris I.M., Dudar I.O., Driyanska V.E., Shymova A.U. *The aim of the work was to determine the blood serum pro-inflammatory cytokine profiles and to study their relationship with comorbidity and mortality in end-stage renal disease (ESRD) patients treated with continuous ambulatory peritoneal dialysis (CAPD). Ninety three ESRD patients treated with CAPD during 2012-2019 were included in the cohort prospective open study. The study was conducted in two stages. At the first stage, the determination of TNF-α and IL-6 levels was conducted and study of comorbidity, its quantitative assessment, baseline clinical and laboratory parameters was made. A modified polymorbidity index (MPI) which determined the quantitative assessment of comorbidity was calculated as the number of diseases per one patient excluding ESRD and its reasons. At the second stage, considering the baseline values of the studied cytokines, a prospective study of the dynamics of the prevalence of comorbid pathology, the value of MPI and mortality rate was carried out. The average duration of prospective follow-up was 26.4±6.8 months. Serum cytokines levels were determined by ELISA. Statistical analysis was performed by using "MedCalc", version 19.1.7. (Ostend, Belgium). Serum levels of TNF-α and IL-6 were significantly higher in PD-patients with 5 or more comorbid diseases. Levels of TNF-α>13.0 pg/ml have a negative effect on the dynamics of prevalence of heart failure (HF) and coronary heart disease (CHD), number of comorbid conditions in CAPD-patients. The proportion of the dead with a level of TNF-α>13.0 pg/ml was by three times higher, and deaths from cardiovascular events are almost by 10 times higher than patients who had a level of TNF-α≤13.0 pg/ml. Serum levels of IL-6>23.4 pg/ml are associated with a significant increase in number of comorbid conditions, prevalence of bacterial infections and overall and infectious mortality. Independent predictors of comorbidity and overall mortality in patients with ESRD who are treated with CAPD are serum levels of TNF-α, IL-6 and albumin. Serum levels of TNF-α and albumin are predictors of fatal cardiovascular events, and serum levels of IL-6 are predictors of fatal infectious events.*

Реферат. Активация хронического воспаления и коморбидность у пациентов с хронической болезнью почек VД ст., которые лечатся постоянным амбулаторным перитонеальным диализом. Шифрис И.М., Дударь И.А., Дриянская В.Е., Шимова А.Ю. *Целью работы было определение сывороточных профилей провоспалительных цитокинов и изучение их связи с коморбидностью и смертностью больных с хронической болезнью почек (ХБП) VД ст., которые лечатся постоянным амбулаторным перитонеальным диализом (ПАПД). В когортное проспективное открытое исследование было включено 93 пациента с ХБП VД ст., которые лечились ПАПД на протяжении 2012-2019. Исследование проведено в два этапа. На первом – проведено определение уровней ФНО-α и ИЛ-6 и изучение коморбидных заболеваний, количественной оценки коморбидности, основных клинико-лабораторных показателей на момент включения в исследование. Для количественной оценки коморбидности вычислялся модифицированный индекс полиморбидности (МИП) – количество заболеваний на одного больного, без учета ХБП VД ст. и ее причины. На втором этапе, с учетом определенных в начале исследования значений исследуемых цитокинов, проведено проспективное исследование динамики распространенности коморбидной патологии, значения МИП и уровня смертности. Средняя продолжительность проспективного наблюдения составила 26,4±6,8 месяца. Определение содержания цитокинов (ФНО-α, ИЛ-6) в сыворотке крови проводили методом иммуноферментного анализа (ELISA). Статистическая обработка полученных результатов проведена с помощью программы «MedCalc», версия 19.1.7. Сывороточные уровни ФНО-α и ИЛ-6 были достоверно выше у ПД пациентов с 5-тью и более коморбидными заболеваниями. Уровни ФНО-α> 13,0 пг/мл негативно влияют на динамику распространенности сердечной недостаточности и ИБС, способствуют увеличению количества коморбидных состояний у пациентов, которые лечатся ПАПД. Удельный вес умерших пациентов с уровнем ФНО-α>13,0 пг/мл в три раза выше, а умерших от сердечно-сосудистых событий выше почти в 10 раз, чем пациентов с уровнем ФНО-α ≤13,0 пг/мл. Сывороточные уровни ИЛ-6>23,4 пг/мл ассоциируются с достоверным увеличением количества коморбидных состояний, удельного веса бактериальных инфекций, общей и инфекционной смертности. Независимыми предикторами коморбидности и общей смертности у больных с ХБП Д ст., которые лечатся ПАПД, являются сывороточные уровни ФНО-α, ИЛ-6 и альбумина, предикторами фатальных сердечно-сосудистых событий - сывороточные уровни ФНО-α и альбумина, инфекционных - сывороточные уровни ИЛ-6.*

In most countries, including Ukraine peritoneal dialysis (PD), ranks second in the structure of renal replacement therapy (RRT) [11]. Despite the presence of certain advantages of PD compared with hemodialysis (HD), primarily related to the stability of hemodynamics, the survival rates of patients treated with PD and the method itself remain unsatisfactory [2]. This encourages the world medical community to study the factors that worsen the individual prognosis. Among the latter, clinicians pay special attention to the study of comorbidity and the factors associated with its development and prevalence in the population of patients with CRD VD stage. According to numerous studies, increased production of pro-inflammatory immune mediators, the most significant of which are tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), is a catalyst for the development of comorbid states. In particular, it was found that chronic

inflammation plays a leading role in the development of early atherosclerosis, which, in turn, is a pathogenetic factor in the occurrence of fatal and serious non-fatal cardiovascular (CV) comorbid conditions in patients with CRD VD stage treated with PD [5, 9, 7, 6].

Proinflammatory cytokines perform a protective function, as they provide migration to the site of inflammation of effector cells (neutrophils, macrophages), stimulate their phagocytic and bactericidal activity, onset the start of antigen-specific immune response. At the same time, elevated plasma TNF-α, according to Eunjung Kang et al. is a significant risk factor for bacterial infections, especially pneumonia in patients with CRD VD stage. Moreover, according to the results of this study, no relationship was established between plasma levels of TNF-α and IL-6 and markers of nutritional status, in particular serum albumin, serum creatinine and body mass index (BMI) [12]. However, other researchers note that the processes of chronic inflammation lead to nutritional disorders, which result in an increased risk of comorbid bacterial infections [10].

It should be noted that the occurrence of comorbid diseases in patients with CRD VD stage are accompanied by increased catabolism and exacerbates chronic inflammation. A number of studies demonstrate that elevated levels of pro-inflammatory cytokines in the initiation of PD treatment are associated with high mortality in patients with CRD VD stage [4]. Activity of chronic inflammation in patients with CRD VD stage is traditionally determined by serum/plasma cytokine levels and associated with metabolic, dialysis and other factors. Among the latter, the study of the association with nutritional disorders, age, residual renal function (RRF) and the main cause of CRD continues [4, 7, 12].

Finally, most of the available research concerns the analysis of the level of pro-inflammatory mediators of immunity, their prognostic significance in certain comorbid conditions, mainly associated only with cardiovascular events. Studies on the relationship between chronic inflammation and total comorbidity are quite limited, and in the PD population of patients – absent.

The aim of the study was to determine the serum profile of TNF-α and IL-6 and to investigate their relationship with comorbidity and mortality of patients with CRD VD stage treated with continious ambulatory peritoneal dialysis (CAPD).

MATERIALS AND METHODS OF RESEARCH

The cohort prospective open-label study included 93 patients with CRD VD stage who were treated with CAPD during 2012-2019 at Kyiv City Research and Practice Center for Nephrology and Dialysis, which is the clinical base of the Institute of Nephrology of the National Academy of Medical Sciences of Ukraine. CAPD sessions were performed using Dianeal PD solution with glucose monohydrate content of 1.36% M/OB / 13.6 mg/ml and 2.27% M/OB / 22.7 mg/ml in double bags of 2.0 l. The inclusion of patients in the study was performed after signing the Informed Consent to participate in the study. The study was conducted in accordance with the Law of Ukraine "On Medicinal Products" and the Declaration of Helsinki of the last revision. Criteria for inclusion of patients in the study were: age over 18 years, PD treatment, the ability to adequately cooperate in the study process. Exclusion criteria were: age <18 years, total weekly K/V<1.7, hospitalization for any cause and/or sign of infection during the month preceding the study, inability to cooperate adequately during the study. Of the total number there were 38 (40.86%) women, the average age – 55.05±15.6 years and 55 (59.14%) men, the average age – 56.2±13.96. By type of kidney damage, patients with non-diabetic glomerular – 62 (66.7%), diabetic and non-glomerular – 22 (23.6%) and 9 (9.7%), respectively dominated. The average duration of PD treatment at the time of inclusion in the study was 16.6±9.5 months.

The study was conducted in two stages. At the first stage, serum levels of proinflammatory cytokines (TNF-α and IL-6) were determined, comorbid status was analysed as well as basic clinical and laboratory parameters (hemoglobin, albumin, total global score (TGS), RRF, body mass index) at the time inclusion in the study. All comorbid conditions registered on the basis of clinical observation, monitoring of laboratory and instrumental studies, consultative opinions of allied specialists, available abstracts from medical histories and other data from the outpatient card were analyzed as well. For the quantitative characterization of comorbidity, a modified polymorbidity index (MPI) was calculated – the number of diseases / one patient, taking into account the homogeneity of the studied population without taking into account the existing CRD and its main cause [3]. At the second stage of the study, taking into account the values of the studied cytokines determined at the onset of the study, a prospective study of the prevalence of the most common comorbid pathology, the value of MPI and the proportion of deaths was carried out. The mean duration of prospective follow-up was 26.4±6.8 months. The primary endpoint was death from any cause. Patients were monitored until the

initial endpoint, loss of contact with the patient or the end of the study on March 1, 2019.

Serum cytokine levels (TNF-α and IL-6) were determined by ELISA on a "SunRise TouchScreen" analyzer using commercially available "Vector Best" test systems (RF). The limits of the reference values were obtained on the basis of the results of a study of 25 relatively healthy individuals. The studies were performed in the laboratory of immunology of the Institute of Nephrology of the National Academy of Medical Sciences of Ukraine.

Statistical processing of the obtained results was performed on a personal computer using the program "MedCalc", licensed version 19.1.7 [8], taking into account the verification of indicators for normal distribution. Under normal distribution conditions, mean values (M) and standard deviation (SD) were evaluated. Significance of differences was assessed according to the generally accepted in variation statistics: Student's test (under normal distribution conditions), non-parametric Mann-Whitney U-test (under conditions of distribution of indicators other than normal), χ^2. The difference was considered significant at a significance level of $p<0.05$. In order to determine the prognostic values of TNF-α and IL-6, ROC analysis was performed with determining the area of the ROC curve and assessing the sensitivity and specificity. The Pearson correlation coefficient was used to measure the linear relationship between the variables. Associations between dependent and independent variables were analyzed by stepwise multifactor regression analysis. The null hypotheses were tested at the significance level of $p\leq0.05$ [1].

RESULTS AND DISCUSSION

The main clinical and laboratory parameters of the examined cohort of patients at the onset of the study are shown in Table 1.

Table 1

General clinical and laboratory characteristics of the studied patients (n=93)

Indicators	Values
Hemoglobin (g/l; M ± SD)	**84.96±12.78**
Albumin (g/l; M ± SD)	**32.36±4.65**
BMI (kg/m^2; M ± SD)	**25.23±4.89**
RRF, (ml/min / 1.73 m^2; M ± SD)	**3.29±2.96**
TGS, points (M ± SD)	**5.60±1.87**
Comorbid states (n/%)	
Anemia	**89 / 95.7**
Hypertension (AH)	**87 / 93.6**
Secondary hyperparathyroidism (SHPT)	**41 / 44.92**
Coronary heart disease (CHD)	**29 / 31.18**
Diseases of the gastrointestinal tract (GIT)	**28 / 30.11**
Chronic obstructive pulmonary disease (COPD)	**16 / 17.2**
Heart failure (HF)	**26 / 27.96**
Peripheral vascular disease (PVD)	**31 / 33.33**
Cerebrovascular diseases (CVD)	**30 / 32.26**
MPI (points; n/%)	
Low (1-2)	**7 / 7.53**
Medium (3-4)	**53 / 56.99**
High (≥5)	**33 / 35.48**
M ± SD	**4±1.2**

Comparative analysis of the average concentrations of proinflammatory mediators in the serum confirmed the available data on a significant increase in the studied cytokines in the population of patients with CRD VD stage compared with the indicators of the reference group of healthy donors (Table 2) [5, 6, 7, 9, 12].

The study of the levels of these mediators depending on the value of MPI allowed to establish a significant increase in the content of both TNF-α and IL-6 in the serum of patients with 5 or more comorbidities (Table 3).

Table 2

TNF-α and IL-6 content in the serum of PD patients

Indicator	Cytokine levels (pg/ml; M ±SD)		p
	conditionally-healthy donors (n=25)	PD-patients (n=93)	
TNF -α	3.1±1.92	16.93±10.07	<0.0001
IL-6	5.87±3.88	24.34±11.77	<0.0001

In the study of the correlation between the quantitative assessment of comorbidity and clinical and laboratory findings of PD patients, the presence of a significant positive relationship with the serum content of TNF-α and IL-6, moderate inverse relationship with albumin and TGS, weak inverse one – with the level of hemoglobin and RRF was established (Table 4).

Table 3

TNF-α and IL-6 content in the serum of PD patients depending on quantitative assessment of comorbidity

Показник, пг/мл; M ±SD	Сумарний показник коморбідності (бали)			p_1	p_2	p3
	MPI 1-2 points (n=7)	MPI 3-4 points (n=53)	MPI ≥5 points (n=33)			
TNF-α	7.36±2.26	12.76±8.46	26.71±12.19	0.1	0.0001	<0.0001
IL-6	7.96±2.83	15.96±11.34	42.7±18.64	0.07	<0.0001	<0.0001

Notes: p_1 = difference of indicators from MPI value: 1-2 points against 3-4 points, p_2 = difference of indicators from MPI value: 1-2 points against ≥5 points, p_3 = difference of indicators from MPI value: 3-4 points against ≥5 points.

Considering the presence of a significant reliable correlation between the studied proinflammatory mediators of inflammation and MPI, it is arguably a certain role of these cytokines in the pathogenesis of comorbidity in patients with CRD VD stage treated with CAPD.

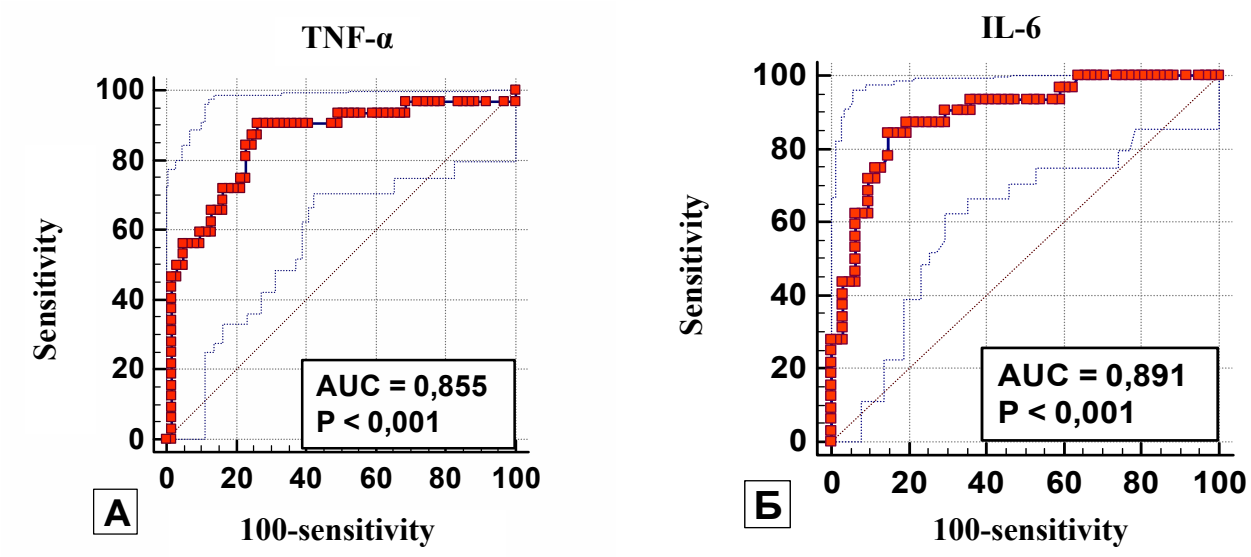
The identified patterns became the basis for determining the prognostic potential of pro-inflammatory markers of chronic inflammation to assess the course of CRD VD stage. Accordingly, at the second stage of the study with the help of ROC-analysis, the optimal cut-off points for the studied cytokines were determined, which characterize the presence of ≥5 comorbid diseases in PD patients (Fig.). It was found that increase in the serum of TNF-α>13.0 pg/ml (AUC=0.855; 95% CI: 0.766-0.919; sensitivity =90.62%; 95% CI: 75-98; specificity =73.77%; 95% CI: 60.9-84.2; p<0.0001) and the level of IL-6 ->23.4 pg/ml (AUC=0.891, 95% CI 0.810-0.946, sensitivity =84.37%, 95% CI: 67.2-94.7, specificity =85.25%, 95% CI: 73.8-93.0, p<0.0001) have the best operational characteristics.

Table 4

Results of correlation analysis between MPI values and clinical and laboratory parameters

Correlating signs			Correlation indices	
			r	p
MPI(points)	TNF-	α (pg/ml)	0.6043	<0.0001
		IL-6 (pg/ml)	0.6311	<0.0001
		Hemoglobin (g/l)	-0.2671	0.0097
		Albumin (g/l)	-0.4018	0.0001
		BMI (kg/m^2)	-0.1056	0.3138
		TGS (points)	-0.3837	0.0001
		RRF (ml/min/1.73 m^2)	-0.2943	0.0042
		Duration of PD (days)	0.04599	0.6616

Based on the identified critical levels of pro-inflammatory markers of chronic inflammation, the proportion of the most common comorbid pathology, the value of MPI, the number and causes of fatalities was analyzed. The results of the analysis of the studied clinical parameters depending on the serum level of TNF-α are shown in Table 5.



ROC-curves of TNF-α (A) and IL-6 (B) use for prognosis high comorbidity in patients of the study population

The analysis allowed us to state that both at the onset and at the end of the observation there is a probable difference in the proportion of AH depending on the serum levels of TNF-α determined on the basis of ROC analysis. The data obtained by us to some extent correspond to the results of the study by Lee J.K. et al. [6]. The latter concerns a probably higher prevalence of CVD at high levels of TNF-α. The current study shows a statistically significant increase, over the observation period, the proportion of HF in patients with TNF-α>13.0 pg/ml, namely 30.2% at the time of inclusion

in the study against 51.2% at the end of the observation (p=0.044). There is a significant increase in the proportion of ICD, which is 39.5% vs. 55.8%, but p=0.133. It should be noted that, regardless of the level of TNF-α, in the course of time, the proportion of all comorbid states tended to increase. However, the value and dynamics of changes in the value of MPI clearly demonstrates a sufficient load of comorbidities in the study population, which is probably higher at the level of TNF-α>13.0 pg/ml, both at the onset and at the end of observation. Special emphasis should be placed on increasing the MPI during the observation period by almost 23% in patients with serum levels of this pro-inflammatory mediator >13.0 pg/ml (5.9±0.94 vs. 4.8±0.92; p<0, 0001). Probably higher, provided that the critical levels of TNF-α are exceeded, there is a total mortality (OR – 6.618, 95% CI: 2.645-16.559; p=0.0001). At the same time, the analysis depending on the cause allowed to state statistically significant differences only for CV fatal events. The proportion of deaths from comorbid CVD is almost 10 times higher in patients with TNF-α>13.0 pg/ml than with serum level of TNF-α≤13.0 pg/ml (OR - 15,6923, 95% CI: 3.361 - 73.269; p=0.0005).

The results of the analysis of the studied clinical indicators depending on the serum level of IL-6 are shown in Table 6.

Table 5

Evaluation and dynamics of clinical indicators of PD patients depending on the serum level of TNF-α

Indicator	PD patients at the beginning of the study		p	PD patients at the end of the observation		p
	TNF-α (pg/ml)			TNF-α (pg/ml)		
	≤13.0 (n=50)	>13.0 (n=43)		≤13.0 (n=50)	>13.0 (n=43)	
Comorbid states (n /%)						
Anemia	45/92	43/100	0.059	44/88	43/100	0.0195
AH	44/88	43/100	0.0195	42/84	43/100	0.006
SHPT	20/40	21/48.8	0.44	21/42	25/58.1	0.124
CHD	12/24	17/39.5	0.11	14/28	24/55.8	0.044
GIT diseases	13/26	15/34.9	0.354	14/28	16/37.2	0.347
COPD	7/14	9/20.9	0.382	8/16	11/25.6	0.255
HF	13/26	13/30.2	0.654	13/26	22/51.2	0.013
PVD	15/30	16/37.2	0.465	16/32	18/41.9	0.326
CVD	14/28	15/34.9	0.476	15/30	22/51.2	0.038
Bacterial infections				16/32	19/44.2	0.229
MPI (M ± SD)	3.25±0.91	4.8±0.92	<0.001	3.65±0.89	5.9±0.94	<0.001
Cases of death during the observation period (n /%)						
HD				2/4	17/39.5	<0.001
Infections				5/10	7/16.3	0.369
CVD				2/4	3/6.9	0.537
Others				2/4	1/2.33	0.651
Total number				11/22	28/65.1	<0.001

Analysis of the value and dynamics of changes in MPI, depending on the determined serum levels of IL-6, shows that this indicator is probably higher, both at the onset and at the end of the observation, at the level of IL-6>23.4 pg/ml. At the same time, the increase in MPI during the observation period is less intense than in the study of changes depending on the level of TNF-α and makes up 14% (5.7±0.98 vs. 5.0±0.94; p=0.0033).

Table 6

Evaluation and dynamics of clinical indicators of PD patients depending on the serum level of IL-6

Indicators	PD patients at the onset of study		p	PD patients at the end of observation		p
	IL-6 (pg/ml)			IL-6 (pg/ml)		
	≤23.4 (n=58)	>23.4 (n=35)		≤23.4 (n=58)	>23.4 (n=35)	
Comorbid states (n/%)						
Anemia	55/94.8	34/97.1	0.59	53/91.4	34/97.1	0.28
AH	54/93.1	33/94.3	0.82	53/91.37	32/91.42	0.99
SHPT	19/32.76	22/62.9	0.005	22/37.9	24/68.57	0.004
CHD	15/25.86	14/40.0	0.156	20/34.48	18/51.42	0.109
GIT diseases	16/27.58	12/34.28	0.49	18/31.03	15/42.86	0.25
COPD	9/15.17	7/20.0	0.55	10/17.24	9/25.71	0.33
HF	14/24.13	12/34.28	0.29	18/31.03	17/48.57	0.093
PVD	17/29.3	14/40.0	0.29	18/31.03	16/45.7	0.156
CVD	16/27.6	13/37.1	0.34	19/32.76	18/51.42	0.077
Bacterial infections	-	-	-	15/25.9	20/57.14	0.003
MPI (M ± SD)	3.35±0.83	5.0±0.94	<0.001	3.86±1.17	5.7±0.98	<0.001
Cases of death during the observation period (n /%)						
HD				10/15.5	9/28.57	0.128
Infections				2/3.45	10/28.57	0.0005
CVD				4/5.15	1/5.71	0.549
Others				3/1.72	-	-
Total number				19/32.7	20/57.14	0.021

During the follow-up period, episodes of bacterial infections occurred in 35 PD patients, in the vast majority of whom serum IL-6 levels exceeded >23.4 pg/ml (20/57.1% vs. 15/25.9%; p=0.003; OR – 15.6923, 95% CI: 3.361 – 73.269; p=0.0005). The analysis of death cases allowed to establish a similar trend. Bacterial infections cause almost 13% of fatal consequences, probably a higher proportion of cases in patients with IL-6 levels >23.4 pg/ml (OR – 11.20, 95% CI: 2.2846 – 54.9069; p=0.0029). Probable differences were also found in the analysis of total mortality (OR – 3.0175, 95% CI: 1.2768 – 7.1314; p=0.0118). The results obtained in the course of our own research in some way confirm the data obtained by Eunjung Kang et al. [12]. However, this applies only to an

increase in the level of the studied proinflammatory markers of chronic inflammation in PD patients with bacterial infections. In contrast to the researchers, we did not obtain a significant difference in serum levels of both TNF-α (15.416±11.807 vs. 17.824±13.257; p=0.575) and IL-6 (36.442±29.147 vs. 20.691±21.264; p=0.076), depending on the type of infection (systemic against PD-associated), which occurred during the observation period.

Taking into account the purpose of our study and to assess the significance of the studied indicators, a step-by-step multifactor regression analysis was performed, where the dependent variables were the values of MPI, total, cardiovascular and infectious mortality. The independent variables were the duration of PD treatment, serum levels of albumin, hemoglobin, TNF-α, IL-6, BMI, RRF and TGS (Table 7).

According to the results of multifactor regression analysis, it was found that the total comorbidity and total mortality of patients with CRD VD stage treated with CAPD are associated with serum levels of TNF-α, IL-6 and albumin. Cardiovascular mortality in this population is dependent on serum levels of TNF-α and albumin, infectious mortality – only on serum levels of IL-6.

Table 7

The results of step-by-step multifactor regression analysis

Variable		Statistical index				R^2,%
dependent	independent	b	sb	t	P	
MPI	IL-6. pg/ml	0.07046	0.00407	6.698	<0.0001	
	TNF-α. pg/ml	0.03563	0.00797	4.471	<0.0001	62
	Albumin. g/l	-0.05122	0.02306	-2.221	0.0291	
Total mortality	IL-6. pg/ml	0.01042	0.00169	6.145	<0.0001	
	TNF-α. pg/ml	0.01997	0.00299	6.682	<0.0001	64
	Albumin. g/l	-0.02148	0.00747	-2.877	0.0050	
CV mortality	TNF-α. pg/ml	0.01146	0.00364	3.151	0.0022	
	Albumin. g/l	-0.02214	0.00908	-2.438	0.0168	28
Infectious mortality	IL-6. pg/ml	0.00723	0.00146	4.965	<0.0001	21

Notes: b – regression coefficient, sb – standard error of regression coefficient, R^2,% – coefficient of determination.

CONCLUSIONS

1. According to the study, serum levels of proinflammatory cytokines TNF-α and IL-6 in patients with CRD VD stage treated with CAPD are likely to be higher in the presence of 5 or more comorbid diseases (p<0.001).
2. The presence of a significant positive reliable correlation between MPI and the levels of the studied proinflammatory mediators of inflammation and a significant inverse - with the level of albumin, hemoglobin, TGS, RRF is indirect confirmation of the role of chronic inflammation activation in the pathogenesis of comorbidity of patients with CRD VD stage treated with CAPD.
3. It is established that serum TNF-α levels >13.0 pg/ml have a strong negative impact on the dynamics of the proportion of heart failure and ICD, contribute to an increase of almost a quarter in the number of comorbid conditions in patients with CRD VD stage treated with CAPD. The proportion of deceased patients with TNF-α levels >13.0 pg/ml is three times higher, and deaths from CV events are almost 10 times higher as compared to patients with TNF-α level ≤13.0 pg/ml.
4. Serum levels of IL-6 >23.4 pg/ml are associated with a probable increase in the number of comorbid conditions, the proportion of comorbid bacterial infections, total and infectious mortality during the observation period.
5. Independent predictors of comorbidity, general, cardiovascular and infectious mortality of patients with CRD VD stage treated with CAPD are

determined. For comorbid status and total mortality, these are serum levels of TNF-α, IL-6 and albumin. Predictors of CV fatal events are serum levels of TNF-α and albumin, of infectious – serum levels of IL-6.

Conflict of interest. The authors declare no conflict of interest.

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