UDC 616.61-085.38-073.27:616.1]-07 https://doi.org/10.26641/2307-0404.2021.2.234513

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PREDICTORS OF CARDIOVASCULAR DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE VD STAGE TREATED WITH HEMODIALYSIS

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Цитування: Медичні перспективи. 2021. Т. 26, № 2. С. 59-66
Cited: Medicni perspektivi. 2021;26(2):59-66

Key words: *chronic kidney disease VD stage, hemodialysis, cardiovascular diseases, coronary artery disease, predictors*
Ключові слова: *хронічна хвороба нирок VД стадії, гемодіаліз, серцево-судинні захворювання, ішемічна хвороба серця, предиктори*
Ключевые слова: *хроническая болезнь почек VД стадии, сердечно-сосудистые заболевания, гемодиализ, ишемическая болезнь сердца, предикторы*

Abstract. Predictors of cardiovascular disease in patients with chronic kidney disease VD stage treated with hemodialysis. Shifris I.M., Dudar I.O., Krasiuk E.K., Shymova A.Yu. *The aim of the study was to establish the frequency and possible predictors of cardiovascular disease (CVD) in chronic kidney disease (CKD) VD stage patients, treated with hemodialysis, based on results of prospective observation. The prospective observational cohort study included 223 patients with CKD V D stage who were treated with hemodialysis (HD) during 2012-2019. The research was carried out in two stages. At the first stage, main demographic, laboratory and clinical characteristics of patients, including the frequency of CVD, at the time of beginning the study were examined. At the second stage, based on prospective studying of the dynamics of the frequency of CV pathology, an assessment of potential predictors of CVD in CKD V D stage patients treated with HD was made. Patients' characteristics determined at the beginning of the study were used as possible predictors. The average duration of prospective study was 35.5±17.8 months, cumulative – 579.3 patient-years. For determination of prognostic factors of CVD events, ROC-analysis, univariate and multivariate Cox proportional hazard regression analysis were done. The primary endpoint (newly diagnosed CVDs) was assessed at the end of the study. Statistical processing of the obtained results was performed using the MedCalc Statistical Software, version 19.3. During the study period, a significant increase of all CVD frequency by 80% ($p<0.001$) was stated, more than twice – of coronary heart disease (CHD; $p<0.001$) and atrial fibrillation (AF; $p=0.0039$). The incidence rate of CVD and CHD was 9.8 and 9.15 per 100-patient-years, respectively. The primary endpoint was observed in 92 (41.26%) patients: newly diagnosed CHD – in 53 patients, heart failure – in 12 patients, AF – in 9 patients, acute myocardial infarction – in 8 patients, other heart diseases – in 10 patients. Independent predictors on increased CVD risk in chronic kidney disease VD stage patients treated with hemodialysis are: age over 35 years, use of a central venous catheter as a vascular access during HD initiation, history of nasal MRSA collonization. On the other hand, serum albumin level of more than 36,6 g/l was associated with reduced risk.*

Реферат. Предикторы сердечно-сосудистых заболеваний у пациентов с хронической болезнью почек VД стадии, которые лечатся гемодиализом. Шифрис И.М., Дударь И.А., Красюк Э.К., Шимова А.Ю. *Целью работы было установить частоту и возможные предикторы сердечно-сосудистых заболеваний (ССЗ) у больных с хронической болезнью почек (ХБП) VД стадии, которые лечатся гемодиализом (ГД), по результатам проспективного наблюдения. В когортное проспективное открытое исследование было включено 223 пациента с ХБП VД ст., которые лечились ГД на протяжении 2012-2019. Исследование проведено в два этапа.*

На первом – проведено изучение основных демографических, лабораторных и клинических характеристик пациентов, в том числе и частоты ССЗ, на момент включения в исследование. На втором этапе, на основании проспективного изучения динамики частоты СС патологии, проведена оценка потенциальных предикторов ССЗ у пациентов с ХБП VД ст., которые лечатся ГД. В качестве возможных предикторов были использованы характеристики пациентов, определенные при включении в исследование. Средняя продолжительность проспективного наблюдения составила 35,5±17,8 месяца, кумулятивная – 579,3 пациенто-лет. Прогностическое значение факторов оценивали при помощи унивариантного и мультивариантного регрессионного анализа пропорциональных рисков Кокса, ROC-анализа. Первичную конечную точку (впервые выявленные ССЗ) оценивали на момент окончания исследования. Статистическая обработка полученных результатов проведена с помощью программы «MedCalc», Бельгия, версия 19.3. За время проспективного наблюдения констатировано достоверное увеличение частоты ССЗ на 80% (p< 0,0001), более чем в вдвое – ишемической болезни сердца (ИБС; p< 0,001) и фибрилляции предсердий (ФП; p=0,0039). Уровень первичной заболеваемости ССЗ и ИБС составил 9,84 и 9,15 на 100 пациенто-лет соответственно. Первичная конечная точка отмечена у 92 (41,26%) пациентов: впервые диагностированная ИБС – у 53 (23,77%), сердечная недостаточность – у 12 (5,4%), ФП – у 9 (4,04%), острый инфаркт миокарда – у 8 (3,6%), другие болезни сердца – у 10 (4,5%). Независимыми предикторами повышенного риска ССЗ у пациентов с ХБП VД ст., которые лечатся ГД, являются: возраст более 35 лет, использование центрального венозного катетера в качестве сосудистого доступа при инициации ГД, анамнез назальной колонизации MRSA. Вместе с тем, уровень сывороточного альбумина более 36,6 г/л способствует снижению риска.

Cardiovascular disease (CVD) remains the leading cause of death in the general population. To date, it has been proven that, on the one hand, the presence of chronic kidney disease (CKD) is one of the recognized independent risk factors for CVD, on the other - this group of diseases remains the leading cause of morbidity and mortality in patients with CKD. The incidence of CVD in patients with CKD reaches its maximum during treatment with dialysis renal replacement therapy (RRT) [8, 15]. According to available studies, the incidence of coronary heart disease (CHD) and heart failure (HF) is 42.3% and 40.4% in the population of patients undergoing hemodialysis (HD) in the United States. A similar rate for atrial fibrillation (AF) and acute myocardial infarction (AMI) is 19.6% and 14.0%, respectively [17].

According to the EURODOPPS study, the most common CVDs were coronary heart disease and heart failure, and their incidence in patients treated with HD in European countries was 36.6% and 20.5%, respectively. Other CVDs, according to the results of this study were registered in 33% of patients. CHD at the beginning of treatment with dialysis methods of RRT in the studied cohorts of patients is present in 25% of patients with CKD VD stage, CF – in more than 22% [8, 9].

The incidence of CVD, after the onset of treatment with dialysis methods of RRT, probably increases. In particular, according to N. Bansal, 2.2 years after the onset of treatment with dialysis methods of RRT, the proportion of patients with new cases of AMI and HF was 10.2% and 13.6%, respectively. The above is given special attention in view of the probable increase in the frequency of hospitalizations of patients in the dialysis population, the deterioration of the prognosis [5, 12].

The high frequency of this category of diseases is due to the high prevalence of traditional and non-traditional cardiovascular risk factors in the dialysis population. Among non-traditional, or uremic CVD risk factors, the most significant are hyperphosphatemia, secondary hyperparathyroidism, anemia, nutritional disorders, left ventricular hypertrophy (LVH), hyperhydration, the presence and type of vascular access, comorbid bacterial infections, asymptomatic carrier of methicillin-resistant S. aureus (MRSA) [1, 6, 11, 14, 16].

It should be noted that, despite the clinical significance of the problem, the number of available studies that analyze the risk factors for CVD in the population of patients with CKD VD stage is quite limited. In addition, more results were obtained by studying the problem in patients who are on the waiting list for kidney transplantation, which, to some extent, calls into question of their representativeness in relation to the entire dialysis population [5, 13]. According to leading experts, there is an urgent need for in-depth large-scale studies aimed at reducing the frequency of comorbid conditions in the population of patients with CKD VD stage, including CVD, based on a better study of risk factors for their occurrence [10].

The aim of the work is to establish the incidence and possible predictors of CVD in patients with CKD VD stage, who are treated with HD, based on the results of prospective observation.

MATERIALS AND METHODS OF RESEARCH

The cohort prospective open-label study included 223 patients with CKD VD, who were treated with hemodialysis during 2012-2019 at the Kyiv City Research and Practice Center for Nephrology and

Dialysis, which is the clinical base of the Department of Efferent Technologies of the Institute of Nephrology of the National Academy of Medical Sciences of Ukraine. The average duration of treatment of patients with HD at the time of inclusion in the study was 27.3±11.22 months.

All patients signed an informed consent to participate in the study. The study protocol was approved by the local ethics commission of the Institute of Nephrology of the National Academy of Medical Sciences of Ukraine. Criteria for inclusion of patients in the study were: age over 18 years, treatment with hemodialysis, the presence of permanent vascular access – arteriovenous fistula, the ability to adequately cooperate in the study. Exclusion criteria were: age <18 years, eKt/V <1.2 per HD session and/or duration of HD<12 hours/week, presence of rheumatic or congenital heart disease, history of kidney transplantation, hospitalization due to any cause and/or signs of infection during the month preceding inclusion in the study, fever, comorbid diseases in the acute phase, mental disorders, inability to adequately cooperate in the study.

The study was conducted in two stages. At the first stage, based on the analysis of medical records of dialysis patients, data on the presence of diabetes mellitus (DM), arterial hypertension (AH), secondary hyper parathyroidism (SHPT), coronary heart disease, heart failure, and other CVD diseases (uremic pericarditis, dysmetabolic cardiomyopathy, sinus tachycardia, non-rheumatic acquired heart defects – mitral valve prolapse, mitral valve insufficiency I-II st., aortic valve insufficiency I-II st., pulmonary artery valve insufficiency I-II st.), hyperhydration, anamnesis of MRSA colonization, type of initial vascular access, eKt/V, body mass index (BMI), electrocardiogram (ECG) results and echocardiography (EChCG).

Verification of AH diagnosis was performed in accordance with the Order of the Ministry of Health of Ukraine dated May 11, 2011 No. 280/44 “On approval of the standard and unified clinical protocols for medical care in the specialty “Nephrology” and adapted clinical guidelines “Treatment of patients with CKD VD stage”. AH in this population is defined as predialysis pressure >140/90 mm Hg. and post-dialysis pressure >130/90 mm Hg. in young patients and those whose life expectancy at HD is more than 3 years [4, 3]. In patients with clinical signs of hyperhydration (persistent edema, "paradoxical hypertension" – increased blood pressure in the second half of the HD session) the ultrasound evaluation of the subdiaphragmatic diameter of the inferior vena cava (DIVC) in the hepatic segment 30-60 minutes. after the end of the HD session was performed. Subdiaphragmatic DIVC more than 11 mm/m^2 is an objective criterion for hyperhydration [4, 3]. In addition, all patients at inclusion in the study underwent a routine laboratory examination to determine serum levels of hemoglobin, albumin, phosphorus, calcium, parathyroid hormone (PTH), ferritin, C-reactive protein (CRP). At the second stage of the study, a prospective study of new cases of AMI, coronary heart disease, heart failure, atrial fibrillation and determination of CVD predictors was conducted. All CVDs that were registered on the basis of consultative opinions of a cardiologist and/or discharge summaries of medical institutions (departments) of cardiac profile were analyzed. The primary endpoint identified in the study was the new nonfatal CVD. Prospective follow-up of patients was performed from the time of inclusion in the study until death, loss of contact with the patient or the end of the study on March 1, 2019, and its average duration was 35.5±17.8 months. The cumulative term of prospective observation is 579.3 patient-years (p/y).

Statistical processing of the obtained results was performed on a personal computer using the program "MedCalc", Ostend, Belgium (version 19.3 individual license with constant updating), taking into account the verification of indicators for normal distribution. Under normal distribution conditions, the data are given as mean values (M) and standard deviation (SD), medians (Me) and interquartile range [Q25; Q75] – in case of distribution different from normal. Indicators of qualitative features are given in the form of absolute and relative frequencies. Significance of differences was assessed according to the Student's criterion generally accepted in variation statistics (under conditions of normal distribution), non-parametric Mann-Whitney U-test (under conditions of distribution of indicators different from normal), criterion $\chi 2$. The difference in frequencies in the groups of paired observations was compared using the McNemar criterion $\chi 2$. All tests were two-tailed; for all types of analysis differences were considered statistically significant at $p<0.05$. To establish the predictive properties of the studied demographic, clinical and laboratory indicators identified at the beginning of the observation, univariate and multivariate Cox regression statistical analysis was used to determine the odds ratio (OR) of the primary endpoint. Statistically significant factors obtained by univariate analysis were used as variables in the multifactor model of Cox's proportional risks. Factors that remained significant in the multifactor analysis were interpre-

ted as independent predictors of new CVD in patients with CKD and treated with HD. The null hypotheses were tested at the significance level of $p \leq 0.05$ [2].

RESULTS AND DISCUSSION

Of the total number of cohort the surveyed, 72 (32.3%) were women and 151 (67.7%) – men. The mean age of patients in the study cohort was 49.4±14.03 years without statistically significant differences depending on gender (51.77±15.67 vs. 48.46±13.69 of women and men, respectively; p=0.1088). The most common cause of CKD stage V was glomerulonephritis – 111 patients (49.77%). The main clinical and laboratory parameters of patients involved in the study at the beginning of the observation are given in Table 1.

The frequency of CVD in the studied cohort of patients is presented in Table 2. Analysis of the incidence of CVD diseases at the beginning of the observation revealed that the most common condition is coronary heart disease. In general, it should be noted that at the beginning of the study, 115 CVDs were registered in 71 (31.8%) patients. In most patients, a combination of two comorbid CV conditions was observed. In particular, at the beginning of the observation coronary heart disease with heart failure was present in 19 (8.52%), coronary heart disease with other heart diseases – in 16 (7.2%), heart failure with AF – in 5 (2.24%) and HF with other heart diseases – in 4 (1.79%) patients. The results of the current study on the incidence of CVD at the beginning of the observation almost confirm the results obtained by scientists from the United States and Europe. In particular, in the studied cohort of patients treated with HD, the incidence of coronary heart disease in European countries was 23.3%. At the same time, the frequency of heart failure in the at HD of the US population was almost three times higher (40%) than in the cohort of HD patients studied by us [9, 17].

Table 1

General characteristics of the studied cohort (n=223)

Indicator	Value
Clinical data	
Cause of CKD VD stage DM (n /%)	53/23.8
eKt / V (M ± SD)	1.38±0.15
BMI (kg / m^2; M ± SD)	24.3±4.3
Type of vascular access at the onset of treatment with HD (AVF, n /%)	137/61.43
History of MRSA colonization (n /%)	76/34.1
LV ejection fraction (%, M ± SD)	54.36±8.8
Hyperhydration (n/%)	12/5.4
Hypertension (n /%)	194/86.9
Secondary hyperparathyroidism	114/51.12
Laboratory data, M±SD or Me [Q25; Q75]	
Albumin (g/l)	35.2±5.5
Hemoglobin (g/l)	87.0±16.2
Phosphorus (mmol/l)	2.29±0.56
Calcium (mmol/l)	2.28±0.26
CRP (mg/l)	6.2±1.7
Ferritin (ng/ml)	405 [284; 728]
Parathyroid hormone (pg/ ml)	834 [412; 1192]

Table 2

Structure and incidence of CVD in patients with CKD VD stage treated with HD (n=223)

Comorbid state	HD patients at the onset of the study (n/%)	HD patients at the end of follow-up (n/%)	Incidence rate (at 100 p/y)	p=
Total heart disease	71/31.8	128/57.4	9.84	< 0.0001
Coronary heart disease	52/23.3	105/47.1	9.15	< 0.0001
Heart failure	33/14.7	45/20.2	2.59	0.1264
Atrial fibrillation	6/2.7	15/6.7	1.55	0.0462
Myocardial infarction	5/2.24	13/5.8	1.38	0.0559
Other heart diseases	19/8.5	29/13.0	1.72	0.1254

Further analysis of the data given in Table 2 shows a probable increase during the observation period in both the incidence of CVD as a whole and the proportion of patients with individual comorbid conditions. A significant increase in the proportion of patients with CVD by 25.6% ($p<0.0001$), coronary heart disease by 23.8% ($p<0.0001$), AF by 4% ($p=0.0462$) was noted. Incidence of coronary heart disease (23.3% vs 47.1%; $\chi^2=53.0$, $p<0.001$) and AF (2.7% vs. 6.7%; $\chi^2=8.028$, $p=0.0039$) during the observation period has more than doubled. At the same time, the level of primary morbidity was significant only for coronary heart disease and the total number of CVD, being 9.15 per 100 patient-years and 9.84 per 100 patient-years, respectively. The results obtained in the course of our own research on the increase in the frequency of CVD over time in some way confirm the data presented in the work of N. Bansal [5]. Data on the increase in the incidence of CVD in HD patients with dialysis methods of RRT have been demonstrated by researchers from Canada. But the results of this study are based solely on the analysis of CV events that necessitated re-hospitalization and/or death of patients [12].

The primary endpoint was reached by 92 (41.25%) patients during 579.3 patient-years of follow-up. To determine the predictors of new CV events using regression analysis of Cox's risks, the demographic, clinical and laboratory characteristics of patients at the time of inclusion in the study were analyzed (Table 3).

Table 3

Results of univariate regression Cox's analysis for assessing the risk of reaching the primary endpoint of the study

Indicator	HR	95% CI	p
Age, years	1.0310	1.0155 - 1.0466	0.0001
Gender (male vs. female)	0.8840	0.5602 - 1.3949	0.5961
Albumin, g/l	0.8502	0.8131 - 0.8889	<0.0001
Hemoglobin, g/l	1.0011	0.9887 - 0.0137	0.8607
Phosphorus, mmol/l	1.9365	1.4563 - 2.5750	<0.0001
SRP, mg/l	1.0118	0.9921 - 1.0318	0.2425
Ferritin, ng/ml	1.0017	0.9977 - 1.0057	0.4057
Parathyroid hormone, pg/ml	0.9830	0.9602 - 1.0063	0.1514
LV ejection fraction,%	0.9998	0.9996 - 1.0000	0.0826
BMI, kg/m^2	1.0182	0.9721 - 1.0664	0.4461
Diabetes mellitus (yes against no)	3.6334	2.3417 - 5.6376	<0.0001
History of MRSA colonization (yes against no)	2.4919	1.6630 - 3.7340	<0.0001
Initial type of vascular access	3.3222	2.1815 - 5.0594	<0.0001

Notes: CVC – central venous catheter; AVF - arteriovenous fistula.

According to the results of uniivariate regression Cox's analysis it was determined that independent predictors of development of new CV events are: patient's age, MRSA status, initial type of vascular access and diabetes mellitus as a cause of CKD VD stage as well as serum albumin and phosphorus. Further, statistically significant factors were analyzed using multivariate regression Cox's model. The results obtained are shown in Table 4.

Table 4

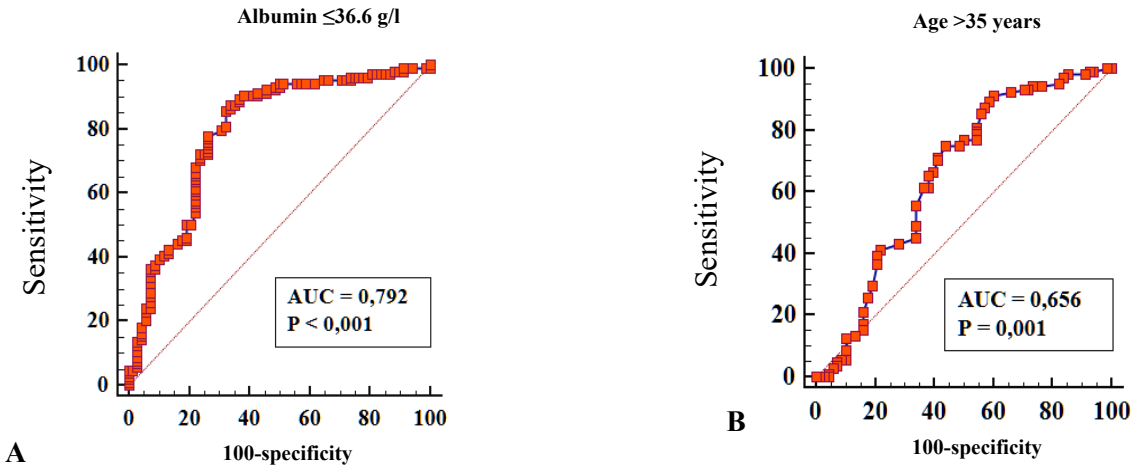
Results of multivariate step-by-step regression Cox's analysis for assessing the predictors of reaching the primary endpoint of the study

Indicator	HR	95% CI	p
Age, years	**1.0253**	**1.0063 - 1.0446**	**0.0088**
Albumin, g/l	**0.8837**	**0.8307 - 0.9400**	**0.0001**
History of MRSA colonization (yes against no)	**2.5661**	**1.4027 - 4.6945**	**0.0022**
Initial type of vascular access (CVC vs. AVF)	**2.5376**	**1.3662 - 4.7133**	**0.0032**

Notes: CEC – central venous catheter; AVF – arteriovenous fistula.

According to the results of multivariate step-by-step Cox's analysis, high prognostic values of HR (Hazard Ratio) for such independent predictors of non-fatal CVD in patients with CKD VD stage treated with HD are defined: patient's age, serum albumin, history of MRSA colonization and initial type of vascular access (χ^2 model =105,331, cc=4, p<0.001). Other independent changes that have been used as potential predictors of CVD (presence/absence of diabetes, serum phosphorus) are not included in the model and, accordingly, have no prognostic value.

Further, ROC-curves were constructed, which reflected the relationship between the development of new cases of CVD and continuous numerical variables included in the model for predicting new cases of CVD (Fig.).



ROC-curves of serum albumin use (A) and age (B) for the prognosis of new cases of CVD in patients with CKD V D st., treated with HD

Critical serum albumin levels ≤36.6 g/l (AUC=0.792; 95% CI: 0.724-0.850; sensitivity =87.50%; 95% CI) were optimally balanced in terms of sensitivity and specificity for predicting the achievement of the primary endpoint of the study: 79.6-93.2, specificity =66.18%, 95% CI: 53.7-77.2,

p<0.0001) and age of patients >35 years (AUC=0.656; 95% CI: 0.580-0.727; sensitivity =87.50%; 95% CI: 84.2-96.0; specificity =39.71%; 95% CI: 28.0-52.3; p=0.0006).

Thus, taking into account the results of ROC analysis, we can say that independent predictors of new CVD cases are: age over 35 years, use of CVC as a vascular access at the beginning of HD treatment and current/previous asymptomatic nasal MRSA carrier. At the same time, the level of serum albumin >36.6 g/l reduces the risk of new CVD in patients with CKD VD stage treated with HD.

CONCLUSIONS

1. The study showed a significant, almost double increase in incidence of CVD (p<0.0001) in patients with CKD VD stage treated with HD during 3-year follow-up (35.5±17.8 months).
2. According to the study, in the structure of CVD in patients with CKD VD stage treated with HD, both at the onset and end of the study CHD ranks first. An increase in the proportion of patients with coronary heart disease during prospective follow-up by 24% was revealed, the incidence rate is 9.15 per 100 patient-years.
3. Independent predictors of CVD in patients with CKD VD stage treated with HD, are: age over 35 years (HR=1.0253; 95% CI: 1.0063-1.0446), the use of the CV treated with HD C as a vascular access at the onset of treatment with HD (HR=2.5376; 95% CI: 1.3662-4.7133) and current/previous asymptomatic nasal MRSA carrier (HR=2.5661; 95% CI: 1.4027-4.6945). At the same time, the level of serum albumin >36.6 g/l reduces the risk (HR=0.8837; 95% CI: 0.8307-0.9400).
4. The method of risk assessment for patients with CKD VD stage is individualized, accessible in execution and interpretation and allows to stratify patients with increased risk of CVD by means of standard basic clinical and laboratory findings.

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

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The article was received
2020.12.23