Renal Impairment Risk Factors in Patients with Type 2 Diabetes

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Abstract. The article presents the Kaplan-Meier analysis, which estimates the cumulative survival function at the time of occurrence of each outcome. In order to predict the risk of an event for the object under consideration and assess the influence of independent variables on this risk, a Cox regression was built, which is also called the Cox proportional hazards model. The capabilities of these methods have been demonstrated using a real example of the analysis of risk factors affecting renal outcome in patients with type 2 diabetes mellitus (DM). A retrospective study of 82 patients with type 2 DM complicated by chronic kidney disease (CKD) stage 1-3 with the level of albumin excretion in urine A1-A2 was conducted. During the observation period, 26.8% of patients showed a decrease in glomerular filtration rate (GFR) below 60 ml / min / 1,73 m2 and an increase in the albumin-creatinine ratio (A/Cr) above 3 mg / mmol. In this regard, patients were divided into two groups depending on the presence of signs of CKD. We studied the main clinical and laboratory parameters: anthropometric, hemodynamic, the level of compensation for carbohydrate metabolism, serum creatinine, urine creatinine, urine albumin, and lipid metabolism. The indicator of intrarenal vascular resistance: resistive index (RI) of the right segmental artery was determined. It has been established that risk factors of impaired renal function in patients with type 2 diabetes are age, duration of diabetes, obesity, level of carbohydrate metabolism compensation and resistance index. The most informative indicator is the resistance index of 0,70 and higher. This indicator can be taken as a criterion for renal prognosis.

Keywords. Diabetes mellitus type 2, chronic kidney disease, glomerular filtration rate, renal circulatory, doppler ultrasound, resistive index.

1 Introduction

Chronic kidney disease (CKD) is the leading microvascular complication in patients with type 2 diabetes mellitus (DM) [1, 2]. Currently, the diagnosis of diabetic kidney damage is mainly based on clinical and laboratory parameters. According to the recommendations of national and foreign expert groups to clarify the stage of kidney damage in diabetes, it is necessary to determine the glomerular filtration rate (GFR) and the level of albumin excretion in the urine [3, 4]. These indicators characterize both

structural and functional changes in the kidneys, but they do not predict the rate of progression of diabetic kidney damage. It is known that the risk factors for the development and progression of deterioration of renal function are unsatisfactory compensation of diabetes mellitus, long duration of the disease, impaired intrarenal hemodynamics, arterial hypertension, hyperlipidemia [5]. However, it is still difficult to predict the renal prognosis, since there are additional causes of the loss of renal filtration capacity. So, according to some authors, Doppler ultrasound, namely, the determination of the index of intrarenal vascular resistance, can detect hemodynamic disturbances in the early stages of renal disease and prevent the onset or progression of renal failure in patients with diabetes [6-8]. In addition, R. Ikee et al found a pronounced relationship between histopathological parameters and the level of the resistance index (RI) in patients with type 2 diabetes [9]. H. Xu et al., in 2017, conducted a study in which, using renal Doppler sonography, revealed that microvascular disorders are an early marker of nephrosclerosis, even before the detection of morphological changes in mice with induced type 2 diabetes [10]. Thus, the search for additional risk factors will expand the understanding of the pathogenesis of diabetic kidney damage, and will allow developing effective approaches to prevent the progression of CKD.

Purpose of the study is to identify risk factors for deteriorating renal function and determine the possibility of using RI as a criterion for predicting renal outcome in patients with type 2 diabetes.

2 Materials and Methods

From October 2015 to December 2019, 82 patients with type 2 diabetes were under observation. During the observation period, 26,8% of patients showed a decrease in GFR below 60 ml/min/1,73 m2 and an increase in the albumin-creatinine ratio (A/Cr) above 3 mg/mmol. In this regard, the patients were divided into two groups: 1st - 60 patients (39 men and 21 women), who had a GFR higher or equal to 60 ml/min/1,73 m2 and A/Cr from 0,2 to 1,8 mg/mmol. 2nd - 22 patients (18 men and 4 women), who had GFR below 60 ml/min/1,73 m2 and A/Cr from 5 to 16,4 mg/mmol. The main clinical and laboratory parameters were studied: anthropometric, hemodynamic, level of carbohydrate metabolism compensation, serum creatinine, urine creatinine, urine albumin, lipid metabolism indicators. All patients underwent a Doppler study of one of the segmental arteries of the right kidney. The index RI of intrarenal vascular resistance was determined. The diagnosis of CKD was established based on the determination of GFR using the CKD-EPI formula and the calculation of A/Cr in accordance with the recommendations of the International Society of Nephrology (KDIGO). Statistical processing of the experimental data was carried out using the STATISTICA 10 software and included methods of variation statistics, correlation analysis, and nonparametric tests (Mann-Whitney, Ro-Spearman) [11]. The analysis of factors affecting renal outcome was carried out in several stages. At the first stage, a statistically significant difference in the studied parameters was revealed. Threshold values were generated for each selected factor. At the second stage, a one-way analysis of renal outcome according to Kaplan-Meier using a long-rank test was performed [12].

At the final stage, multivariate analysis was carried out using the Cox regression model. The magnitude of the relative risk was determined with the indication of 95% confidence interval (CI). Sample data are presented in the form Me [Xmin; Xmax], where Me is the median of the sample data, [Xmin; Xmax] is the range of the sample. In paired comparisons, the level of significance $\alpha = 0.05$ is accepted.

3 Results and Discussion

The study revealed that patients with type 2 diabetes with signs of CKD (group 2) were older compared to group 1 (65 [60;70] vs 56[50;63] years, p2,1=5,5*10-8, respectively). In addition, they differed in a longer duration of the disease (15[10;23] vs 6[5;8] years, p2,1=0,0001, respectively). The presence of obesity (31[29;33] vs 29[26;32] kg/m2, p2,1=0,009, respectively); a higher level of glycated hemoglobin (HbA1c) (9,0[7,8;10,0] vs 7,9[6,9;8,9] %, p2,1=0,002, respectively) and a higher RI value (0,71[0,67;0,73] vs 0,66[0,61;0,69], p2,1=0,000001, respectively) (tabl. 1).

Table 1. Clinical and laboratory characteristics of the examined groups, Me [xmin; xmax].

Index	1 group DM without CKD (n=60)	2 group DM with CKD (n=22)	p
Duration of diabetes, years	6 [5; 8]	15 [10; 23]	0,0001*
Age, years	56 [50; 63]	65 [60; 70]	$5,5*10^{-8}$*
BMI, kg/m^2	29 [26; 31]	31,0 [29; 33]	0,009*
BP(S), mm Hg	140 [130; 145]	140 [135; 145]	0,125
BP(D), mm Hg	90 [80; 100]	90 [80; 100]	0,420
Heart rate, blows/minute	72 [70; 75]	73 [72; 77]	0,187
HbA1c, %	7,9 [6,9; 8,9]	9,0 [7,8; 10,0]	0,002*
Fasting glycemia, mmol/l	7,4 [6,4; 8,6]	7,6 [6,6; 9,0]	0,123
Cholesterol, mmol/l	4,1 [3,4; 5,2]	4,5 [3,7; 5,7]	0,125
Triglycerides, mmol/l	1,4 [1,1;2,7]	1,5 [1,2; 2,2]	0,745
Albumin/creatinine ratio, mg/mmol	0,4 [0,2; 1,8]	2,3 [5,0; 16,4]	$1,20*10^{-6}$*
Blood creatinine, μmol/l	70 [64;80]	109 [84; 127	$4,5*10^{-9}$*
GFR (CKD-EPI), ml/min/1,732	92 [81; 104]	48 [37; 59]	$2,52*10^{-10}$*
RI	0,66 [0,61; 0,69]	0,71 [0,67; 0,73]	0,00002*

Legend: Me – sample median; [xmin; xmax] – sample span; * – difference with the 2 group, p<0,05.

In the general group of the surveyed, a relationship was found between serum creatinine and: age (ρ=0,38, p=0,0001), the duration of diabetes (ρ=0,35, p=0,0004), BMI (ρ=0,28, p=0,005), RI (ρ=0,41, p=0,0001). And also between GFR and: age (ρ=-0,55, p=0,002), BMI (ρ=-0,30, p=0,0001), HbA1c (ρ=-0,32, p=0,001), RI (ρ=-0,38, p=0,001), relationship between A/Cr and: RI (ρ=0,30, p=0,001), HbA1c (ρ=0,31, p=0,001) (see Fig. 1).

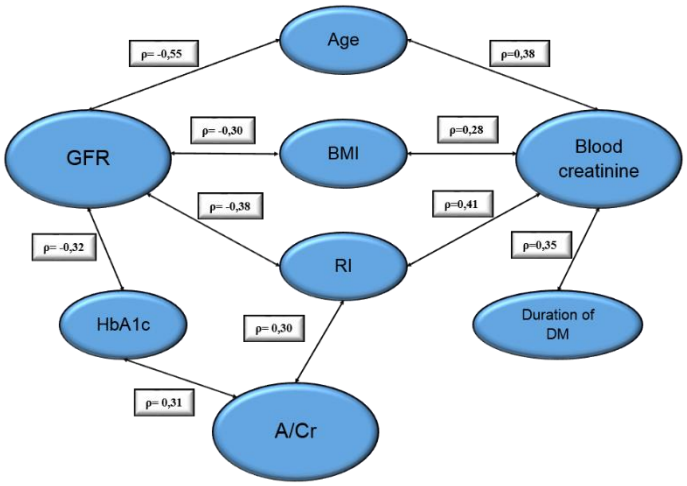

Fig. 1. Correlation pleiad of relationships between renal parameters and characteristics of patients with diabetes.

For univariate analysis of renal outcome using the Kaplan-Meier method, patients were divided into two groups depending on the duration of diabetes mellitus: duration of diabetes <10 years and duration of diabetes ≥10 years. This threshold value was chosen because it is known that the development of irreversible morphological changes begins 10 years after the onset of DM [13]. Deterioration of renal function during the follow-up period was found equal to 40% in the group with DM duration ≥10 years (p = 0,0001) (see Fig. 2).

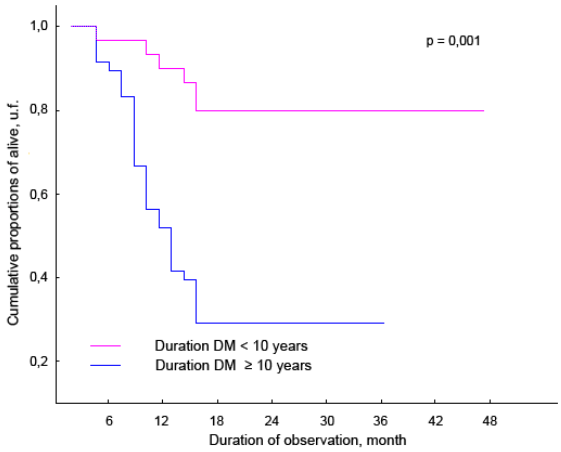

Fig. 2. Survival depending on the duration DM.

For BMI, the upper limit of 30 kg/m2 is taken as the threshold value in accordance with the standards of the World Health Organization (WHO). Two groups of patients were identified. In the group with BMI ≥30 kg/m2, the deterioration of renal function was 45% (p = 0,0001) (see Fig. 3).

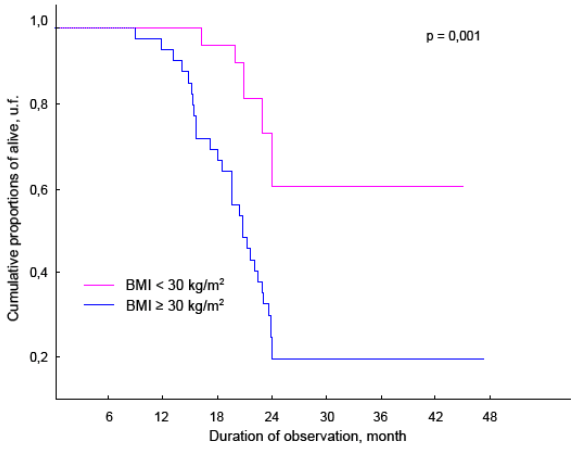

Fig. 3. Survival by BMI.

For HbA1c, the threshold was 8% based on algorithms for specialized medical care for patients with diabetes [3]. Two groups of patients were identified. Deterioration of renal

function during the observation period was detected in the group with HbA1c ≥8% and amounted to 45% (p = 0,001) (see Fig. 4).

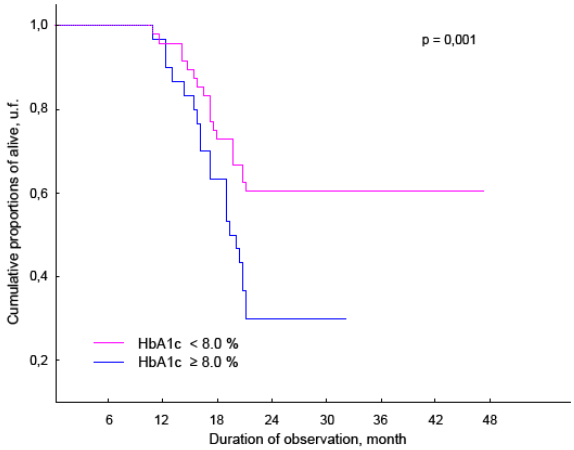

Fig. 4. Survival based on HbA1c.

For age, the upper limit of the norm of 60 years (elderly age) was taken as a threshold value and 2 groups of patients were identified. In the group of patients aged ≥60 years, the deterioration of renal function was 50% (p = 0.0001) (see Fig. 5).

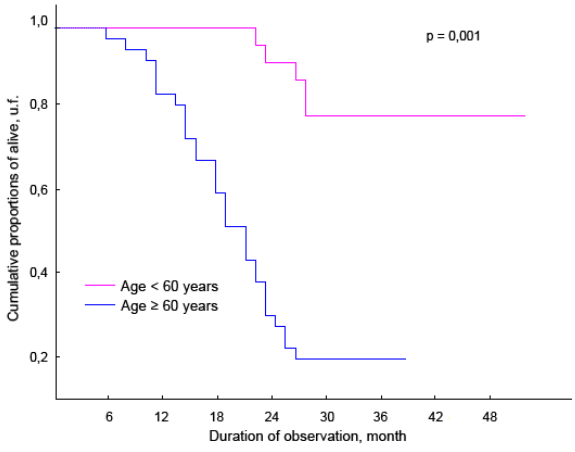

Fig. 5. Survival by age.

It is known that an increase in the resistance index values above 0,70 indicates a decrease in renal function in patients with type 2 DM [6]. Patients by RI were divided into two groups: RI <0,70 and RI ≥ 0,70. Deterioration of renal function over the

observation period was found in the group with RI ≥ 0,70 and amounted to 60% (p = 0,001) (see Fig. 6).

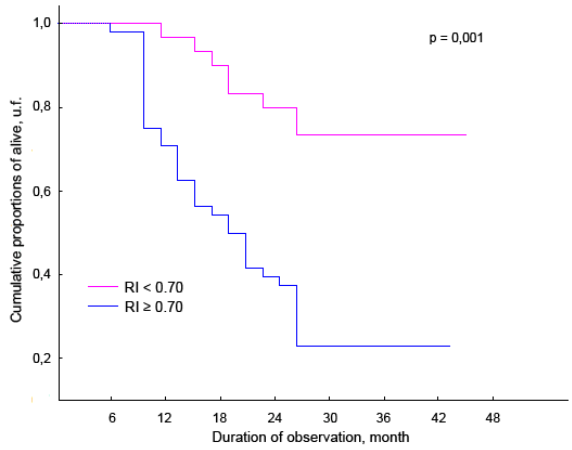

Fig. 6. Survival depending on RI.

At the final stage, a Cox model was formed, which was based on all factors affecting the renal outcome identified at the previous stages: age, duration of the disease, BMI, HbA1c, RI. The analysis showed that a significant risk factor for deterioration of renal function is RI≥0,70 (Er=1,9; CI=1,6–2,3; p=0,001) (see Fig.7). In particular, patients with a high RI had a 1,9 times greater risk of death than patients with normal values.

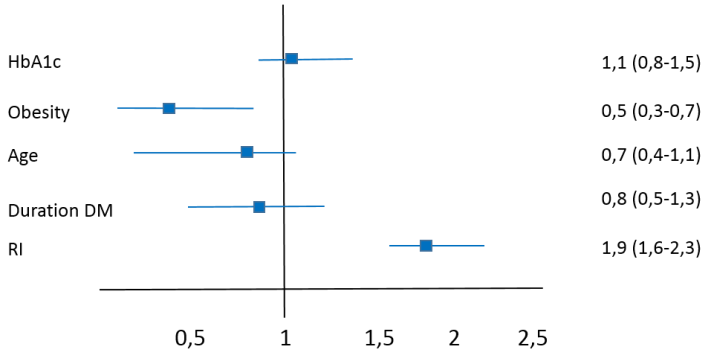

Fig. 7. RI ≥0,70 the most significant risk factor for deteriorating kidney function.

In conclusion, would like to note that the complexity of the problem we are solving required a more sophisticated method of statistical analysis. Along with analysis of variance, logistic regression, survival analysis takes a significant place. This is a method by which, over a certain period of time, the patterns of the appearance of a

certain outcome in representatives of the observed sample are studied. There are several mathematical and statistical methods that can be used to analyze survival, in cases where there is incomplete information about the sample: using life tables, the Kaplan-Meier method, Cox regression and Cox regression with time-dependent predictors [14]. In this article, we examined the possibility of using the Kaplan-Meier method and Cox regression on a real example of analyzing risk factors affecting renal outcome in patients with type 2 DM.

4 Conclusions

Thus, using the Kaplan-Meier method and Cox regression, we confirmed that the risk factors for deteriorating renal function in patients with type 2 diabetes are:

- age,
- duration of diabetes,
- obesity,
- level of compensation of carbohydrate metabolism,
- index of resistivity.

According to the results of multivariate analysis in the Cox model, the most significant factor for predicting renal outcome is a resistance index equal to 0,70 and higher. The definition of this indicator can be used for non-invasive diagnosis and assessment of kidney damage in patients with type 2 diabetes.

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