Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.61.009567

On Mortality Risk Factors in Patients with End-Stage Chronic Kidney Disease Undergoing Hemodialysis

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ARTICLE INFO

Received: March 24, 2025

Published: April 02, 2025

Citation: Kholikov A Yu, Alimov A V, Alieva D A and Urmanova Yu M. On Mortality Risk Factors in Patients with End-Stage Chronic Kidney Disease Undergoing Hemodialysis. Biomed J Sci & Tech Res 61(2)-2025. BJSTR. MS.ID.009567.

ABSTRACT

Abbreviations: HD: Hemodialysis; BNP: Brain Natriuretic Peptide; CKD: Chronic Kidney Disease; CCI: Chronic Cerebral Ischemia; NII: Normalization of Intensive Indicators

Introduction

There is no consensus regarding the factors influencing mortality in patients undergoing hemodialysis (HD). According to the authors who searched PubMed, Embase, and Cochrane Central for studies assessing mortality risk factors in patients undergoing hemodialysis (HD), age (per 1 year), DM, pre-existing cardiovascular disease, CRP (higher vs. lower), ferritin In, adiponectin (per 10.0 μg/mL increase), HbA1c (higher vs. lower), TnT, and BNP were associated with an increased risk of all-cause mortality. BMI (per 1 kg/m^2 increase), hemoglobin (per 1 d/dL increase), albumin (higher vs. lower), TIBC, iron, ApoA2, and ApoA3 were associated with a decreased risk of all-cause mortality. Age (per 1-year increment), gender (women versus men), DM, previous CVD, duration of HD, ln ferritin, HDL, and HbA1c (higher versus lower) significantly increased the risk of cardiac death [1]. They noted that the risk of mortality and cardiac death in hemodialysis patients is influenced by multiple markers and factors. Among these risk factors, brain natriuretic peptide (BNP) occupies a special place. The authors' study in 2011 showed that BNP >1200 pg/ml as a marker of cardiac dysfunction and CRP ≧10 mg/l as a marker of inflammation identify patients with HD with an increased risk of CVD mortality. [2]. Univariate Cox regression analysis showed that the

following factors are predictors of all-cause mortality: hemoglobin (<110 g/l), phosphorus (>1.78 mmol/l), albumin (<40 g/l), C-reactive protein (CRP ≥ 10 mg/l), BNP (>1200 pg/ml) and cardiac ejection fraction (≤ 55%). Multivariate Cox regression analysis showed that only CRP ≥ 10 mg/L with a hazard ratio (HR) of 6.82 (95% CI 1.86-24.9, p = 0.004) and BNP > 1200 pg/mL with HR of 5.79 (95% CI 1.58-21.3, p = 0.004) were predictors of all-cause mortality. BNP > 1200 pg/mL with HR of 13.52 (95% CI 1.68-108.9, p = 0.014) was found to be an even stronger predictor of cardiovascular mortality than CRP ≥ 10 mg/L with HR of 6.53 (95% CI 1.35-31.6, p = 0.020).

High plasma BNP concentrations in HD patients have been associated with volume overload, left ventricular hypertrophy, CD, and T2DM. Plasma BNP concentration may be a useful parameter for assessing the risk of cardiac death in HD patients, providing prognostic information independent of other previously reported variables [3]. Cardiovascular disease is a major cause of morbidity and mortality in dialysis patients. The high incidence of cardiovascular disease in patients with chronic kidney disease (CKD) cannot be explained by traditional risk factors alone. Several studies have confirmed the association between vascular calcification and increased mortality [4]. The authors noted that the presence of vascular calcifications is a warning sign of increased cardiovascular risk. Simple vascular score is a simple method to assess this risk. In our study, increased incidence of vascular calcifications was directly correlated with older age and duration of hemodialysis. Standard radiography, echocardiography, and ultrasound imaging can be used to screen for vascular calcifications. Among these methods, radiography has the advantage of being widely available and easy to interpret. The authors investigated whether risk factors for mortality differ by gender in patients undergoing hemodialysis. Patients (n = 230; 118 women, 112 men) undergoing hemodialysis were followed up for 52 months to assess the incidence of death from cardiovascular or non-cardiovascular causes. Survival was compared using Cox regression analysis using age, T2DM, pre-existing coronary artery disease, troponin T, and C-reactive protein as covariates. A total of 120 participants (52.2%) died during 52 months of follow-up: 57 patients died from CVD, 35 patients died from infectious diseases.

Cox regression showed that age, pre-existing coronary artery disease, and troponin T were independent risk factors for all-cause mortality in both sexes. Analysis of men and women separately showed that T2DM and C-reactive protein appeared to be stronger risk factors for all-cause mortality in women. Cardiovascular mortality was predicted by troponin T in women (relative risk = 5.16, 95% CI: 1.67–15.88; p = 0.004) but not in men (relative risk = 1.69; 95% CI: 0.72–3.96; p = 0.23). Our study showed for the first time that the effect of risk factors on predicting CVD death is clearly gender-specific [5,6]. The aim of the study was to investigate risk factors for mortality in patients undergoing hemodialysis.

Material and Research Methods

The clinical material for the study included 150 patients with type 2 diabetes, examined and treated in RSNPMC Endocrinology M3 RUz from 2020 to 2022, who were on programmed hemodialysis. The duration of CKD ranged from 1 year of life to 15 years. Of these, there were 73 women and 77 men. The average age of men was 67 ± 4.2 years, and the average age of women was 64 ± 5.6 years. The control group consisted of 20 patients of the corresponding age. The number of hemodialysis sessions in patients varied from 2 to 16 According to the degree of chronic cerebral ischemia (CCI), patients were divided into 3 groups:

1 group – 50 (33.3%) patients with stage 5 diabetic nephropathy with grade 1 CCI;

2 group – 50 (33.3%) patients with stage 5 diabetic nephropathy with stage 2 CCI;

Group 3 - 50 (33.3%) patients with stage 5 diabetic nephropathy with stage 3 CCI.

Inclusion Criteria

patients with type 2 diabetes mellitus on programmed hemodialysis, with stage III chronic renal failure, stage 5 diabetic nephropathy.

Exclusion Criteria

pregnant women, children and young people with type 1 diabetes, patients with cardiovascular pathology before the diagnosis of type 2 diabetes, autoimmune thyroiditis (hypothyroidism). The obtained data were processed using the computer programs Microsoft Excel and STATISTICA_6. The reliability of differences in quantitative indicators (n>12) was determined using the Wilcoxon method for unrelated ranges; to determine the reliability of small samples (n<12), the nonparametric Fisher component randomization criterion for independent samples was used; for qualitative values, the Fisher-Irwin exact test was used.

Research Results

Table 1 shows the distribution of examined patients by gender and age. As can be seen from Table 1, patients in the age category from 60 to 74 years predominated among both men and women – 18/20 cases, respectively. Table 2 provides a comparison of mortality rates for 2001 and 2021 in patients with diabetes, depending on gender, age, and duration of program hemodialysis. In 2021, 262 patients with type 2 diabetes died in the Republic of Uzbekistan. Among the complications, 85 (32.4%) patients had respiratory failure from stage 1 to 5. As can be seen from Table 3, 39 patients had stroke among the causes of death, and 123 (46.9%) had cardiovascular events. That is, in 208 (79.4%) patients out of 262, the cause of death was acute cerebrovascular and acute cardiovascular failure. In both 2001 and 2021, among men (2001 - $\chi 2 = 81.8$; P = 0.0001, 2021 - $\chi 2 = 83.2$; P =

0.0001) and women (2001 - χ2 = 208.1; P = 0.0001, 2021 - χ2 = 173.9; P = 0.0001), patients over 60 years of age predominated. In most men (2001 - χ2=37.0; P=0.0001, 2021 - χ2=37.1; P=0.0001) and women (2001 - χ2=137.1; P=0.0001, 2021 - χ2=73.6; P=0.0001), mortality was recorded with a disease duration of more than 12 years. The analysis showed that in 2001, among the causes of death in women with type 1 diabetes, heart failure and stroke were 4 times more common, and 1.7 times more common were chronic renal failure. In 2009, no gender differences were found in the causes of death. The analysis of causes of death depending on gender and type of diabetes in 2001 and 2021 is presented in Table 2. In 2001, among the causes of death in women with type 2 diabetes, cardiovascular diseases were significantly more common (28.32% versus 6.64χ2=4.95; P=0.03), whereas in men gangrene (3.10% vs. 0.44%χ2=11.2; P=0.0001). Causes of death in women were also often AMI (6.64% vs. 1.77%χ2=0.26; P=0.61) and strokes (25.66% vs. 9.29%χ2=0.04; P=0.95), but the difference was not statistically significant. In 2021, the causes of death in women with type 2 diabetes were 2 times more often cardiovascular diseases (24.69% versus 12.35%) χ2=0.02; P=0.96) and CRF (3.70% versus 1.85%χ2=0.11; P=0.75) and 3.1 times - strokes (22.84% versus 7.41%χ2=1.66; P=0.20), but the difference was not significant.

Table 1: Distribution of patients by sex and age (WHO, 2017).

Age, Years	Number of Men	Number of Women
18-44 (young age)	41 (53.2%)	40 (54.8%)
45-59 (average age)	16 (20.8%)	11(15.0%)
60-74 (old age)	18 (23.4%)	20(27.5%)
75 and older (senior age)	2 (2.6%)	2 (2.7%)
Total: n = 150	77 (51.3%)	73(48.7%)

Table 2: Comparison of mortality rates for 2001 and 2021 in patients with diabetes, depending on gender, age and duration of program hemodialysis.

Complications, Stages	2001, n=257				2021, n=260			
	Men, n=74		Women,		Men, n=73		Women,	
	n	%	n	%	n	%	n	%
Type 2	65	87.9	161	88	71	28.7	176	71.3
Age								
Up to 30 years old	3	4.1	1	0.5	0	0	1	0.6
31-40 years old	-	-	4	2,2	2	2.8	1	0.6
41-50 years old	12	16.2	27	14.7	3	4.2	5	2.8
51-60 years old	9	12.1	28	15.3	15	21.1	26	14.8
Over 60 years old	50	67.6*	123	67.2*	51	71.9	143	81.2
Duration								
Up to 1 year	1	1.3	1	0.5	2	2.8	1	0.6
1 - 5 years	5	6.8	11	6	4	5.6	14	7.9
6-10 years	12	16.2	23	12.6	19	26.8	36	20.4
11 - 15 years old	26	35.1**	66	36.1**	21	29.6	57	32.5
16 years and over	30	40.5**	82	44.8**	25	35.2	68	38.6

Note: *reliability in relation to the number of patients under 60 years of age; **reliability in relation to the number of patients with diabetes duration of up to 10 years.

Table 3: Scale of the degree of risk factors for mortality in type 2 diabetes with stage 5 CKD.

Degree of Conditionality	OR Range	Factors
Tall	>3.0	SCF less than 15 ml/min, decreased BDNF level to 0.2-0.3 ng/ml, increased S100B more0.3mcg/l, increased NSE over 22 ng/ml, decreased intima media thickness MAG, increased urea, creatinine, low urine density, albuminuria, increased AU/Cr, low HDL, elevated triglycerides, hyperglycemia, elevated cholesterol, previous stroke, heart attack, Charcot foot, blindness, Hamilton scale score over 23 points, MMSE score below 10 points, WHOQol-BREF score less than 30 points
Average	2.0-3.0	SCF less than 15 ml/min, hyperglycemia, elevated urea, creatinine, elevated cholesterol; decreased BDNF level 0.6 -0.7 ng/ml, increased S100B 0.2-0.3mcg/l, NSE increase from 16 to 18 ng/ml, Hamilton scale score from 14 to 22 points, MMSE test score from 10 to 20 points, WHOQol-BREF questionnaire score from 30 to 50 points
Low	1.5-2.0	SCF from 15 to 25 ml/min; increased urea, creatinine, decreased BDNF level 0.8 -0.9 ng/ml, increased S100B 0.1 mcg/l, NSE increase from 8 to 15 ng/ml, Hamilton scale score from 0 to 13 points, MMSE test score more than 25 points, WHO-Qol-BREF questionnaire score less than 50 to 80 points

Note: MA – main arteries of the head, AU – albuminuria, Kr – creatinine.

When comparing the frequency of fatal cases depending on age (Table 4), it turned out that the majority of fatal cases both in 2001 and in 2021 occurred in the age period over 60 years. We see that, In DM 2, there is an increase in the incidence of mortality from CHF, MI, hyperglycemic coma and chronic renal failure. As a rule, the most common cause was SSN (in 2001 21.7% versus 1.8%χ2=41.4; P=0.0001; in 2021 - 35.2% versus 1.9% χ2=57.5; P=0.0001), AMI (in 2001 18.6% versus 1.3%χ2=35.6; P=0.0001; in 2009 - 8.6% versus 0.6% χ2=10.1; P=0.002), strokes (in 2001 30.9% versus 0.9%χ2=74.2; P=0.0001; in 2021 - 29.0% versus 1.2% χ2=46.6; P=0.0001). So, and The study of mortality and its causes depending on the duration of type 2 diabetes showed that both in 2001 and 2021 the overwhelming majority of deaths were observed with a diabetes duration of more than 10 years, the cause was cerebrovascular and cardiovascular pathology (76.5% and 79.42%, respectively). The study also revealed the average duration of the disease of deceased patients. Thus, in patients who died in 2001, the average duration of the disease was 12.5 ± 0.4 years (with type 1 diabetes 9.54 ± 1.91 years, with type 2 diabetes - 14.5 ± 1.12 years), and in patients who died in 2021 - 12.7 ± 0.8 years (8.9 ± 0.72 years and 15.9 ± 0.76 years, respectively), no significant difference was found between the indicators. The next stage of our work was the study of the prognosis of the development of complications using the method of normalization of intensive indicators (NII) of E.N. Shigan [1983].

Table 4: Comparative analysis of causes of mortality in patients with diabetes depending on gender.

	2001 Year				
	Type 2 Diabetes Mellitus				
	Men n=65			Women n=161	
	abs	%		abs	%
SSN	15	6.64		64	28.32*
OIM	4	1.77		15	6.64
Strokes	21	9.29		58	25.6
Coma of various genesis	-	-		2	0.88
Pneumonia	3	1.33		3	1.33
Cirrhosis	2	0.88		2	0.88
Oncological diseases	4	1.77		3	1.33
Gangrene of the lower extremities	7	3.1		1	0.44*
CRF	5	2.21		6	2.65
Pulmonary tuberculosis	-	-		1	0.44
Other diseases	4	1.77		6	2.65

	2021 Year				
	Type 2 Diabetes Mellitus				
	Men n=73			Women n=187	
	abs		%	abs	%
SSN	23		32.4	74	42.1
OIM	7		9.9	19	10.8
Strokes	9		12.7	30	17
Coma of various genesis	0		0	0	0
Pneumonia	3		4.2	8	4.5
Cirrhosis	2		2.8	1	0.6
Oncological diseases	2		2.8	3	1.7
Gangrene of the lower extremities	5		7	3	1.7
CRF	16		22	27	14.4
Pulmonary tuberculosis	0		0	0	0
Other diseases	5		6.8	15	8
Covid	5		7	10	5.7

Note: *reliability P<0.05.

Thus, an integrated assessment of the risk indicators of CVD in type 2 diabetes showed that those at greatest risk are those over 60 years of age (28.17%) with a disease duration of 16 years or more (35.58%) and those with bad habits, in particular smoking (17.87%). Next, we studied the degree of causality and the etiological proportion of RF mortality and developed a scale of the degree of causality and the etiological proportion of RF mortality in stage 5 CKD (Table 3). An integrated assessment of the risk indicators for CVD in type 2 diabetes showed that those at greatest risk are those over 60 years of age (28.17%) with a disease duration of 16 years or more (35.58%) and those with bad habits, in particular smoking (17.87%).

Discussion

Thus, the developed scale of the degree of causality and etiological proportion of RF mortality allowed us to identify factors in 3 degrees, which allows us to develop a set of measures to prevent complications and reduce the incidence of fatal outcomes.

Conclusions

1. A study of mortality and its causes depending on the duration of type 2 diabetes showed that in both 2001 and 2021, the overwhelming majority of deaths were observed with a diabetes duration of more than 10 years, the cause was cerebrovascular and cardiovascular pathology (76.5% and 79.4%, respectively).

2. An integrated assessment of the risk indicators of chronic cerebral ischemia in type 2 diabetes with stage V CKD showed that those at greatest risk are those over 60 years of age (28.17%) with a disease duration of 16 years or more (35.58%) and those with bad habits, in particular smoking (17.87%).

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.61.009567

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Submission Link: https://biomedres.us/submit-manuscript.php