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CARDIOVASCULAR MORTALITY IN HEMODIALYSIS PATIENTS: CLINICAL AND EPIDEMIOLOGICAL ANALYSIS

KARDIOVASKULARNI MORTALITET KOD BOLESNIKA NA HEMODIJALIZI: KLINIČKA I EPIDEMIOLOŠKA ANALIZA

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Summary: Cardiovascular diseases are the leading cause of death in hemodialysis (HD) patients. The annual cardiovascular mortality rate in these patients is 9%, with left ventricular (LV) hypertrophy, ischemic heart disease and heart failure being the most prevalent causes of death. The aim of this study was to determine the cardiovascular mortality rate and estimate the influence of risk factors on cardiovascular mortality in HD patients. A total of 115 patients undergoing HD for at least 6 months were investigated. Initially a cross-sectional study was performed, followed by a two-year follow-up study. Beside the standard biochemical parameters, C-reactive protein (CRP), homocysteine, cardiac troponins (cTn) and the echocardiographic parameters of LV morphology and function (LV mass index, LV fractional shortening, LV ejection fraction) were determined. Results were analyzed using Cox regression analysis, Kaplan-Meier and Log-Rank tests. The average one-year cardiovascular mortality rate was 8.51%. Multivariate Cox regression analysis identified increased CRP, cTn T and I, and LV mass index as independent risk factors for cardiovascular mortality. Patients with cTnT > 0.10 ng/mL and CRP > 10 mg/L had significantly higher cardiovascular mortality risk ($p < 0.01$) than patients with cTnT > 0.10 ng/mL and CRP ≤ 10 mg/L and those with cTnT ≤ 0.10 ng/mL and CRP ≤ 10 mg/L ($p < 0.01$). HD patients with high cTnT and CRP have a higher cardiovascular mortality risk.

Keywords: C-reactive protein, cardiovascular mortality, hemodialysis, risk factors, troponin T

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Kratak sadržaj: Kardiovaskularne bolesti su vodeći uzrok smrti bolesnika koji se leče hemodijalizom. Jednogodišnja stopa kardiovaskularnog mortaliteta iznosi 9%, a od kardiovaskularnih bolesti najveću prevalenciju imaju hipertrofija leve komore, ishemijska bolest srca i srčana slabost. Cilj rada je bio da se utvrdi stopa kardiovaskularnog mortaliteta i da se ispita uticaj faktora rizika na razvoj kardiovaskularnog mortaliteta kod bolesnika na hemodijalizi. Ispitano je 115 bolesnika koji se leče hemodijalizom duže od šest meseci. Prvo je obavljena studija preseka, a zatim praćenje bolesnika u dvogodišnjem vremenskom periodu. Parametri ispitivanja obuhvatili su koncentraciju C-reaktivnog proteina, homocisteina, srčanog troponina T i I, kao i ehokardiografske parametre morfologije i funkcije leve komore. Za statističku analizu dobijenih podataka korišćeni su Coxova regresiona analiza, Kaplan-Meierov test i Log-Rankov test. Utvrđeno je da prosečna jednogodišnja stopa kardiovaskularnog mortaliteta iznosi 8,51%. Multivarijantna Coxova regresiona analiza je pokazala da su povećana koncentracija C-reaktivnog proteina, srčanog troponina T i I, i povećan indeks mase leve komore nezavisni faktori rizika za nastanak kardiovaskularnog mortaliteta. Bolesnici kod kojih je koncentracija srčanog troponina T – cTnT > 0,10 ng/mL i koncentracija CRP > 10 mg/L imaju statistički veoma značajno ($p < 0,01$) veći rizik od kardiovaskularnog mortaliteta u odnosu na bolesnike kod kojih je cTnT > 0,10 ng/mL i CRP ≤ 10 mg/L i statistički veoma značajno ($p < 0,01$) veći rizik od kardiovaskularnog mortaliteta u odnosu na bolesnike koji imaju cTnT ≤ 0,10 ng/mL i CRP ≤ 10 mg/L. Bolesnici koji se leče hemodijalizom kod kojih je povišena koncentracija srčanog troponina T i C-reaktivnog proteina imaju povećan rizik od kardiovaskularnog mortaliteta.

Ključne reči: faktori rizika, C-reaktivni protein, troponin T, kardiovaskularni mortalitet, hemodijaliza

Introduction

Cardiovascular diseases are the leading cause of death in hemodialysis (HD) patients. The high incidence and prevalence of cardiovascular diseases in HD patients are related to high blood pressure, disturbed lipid metabolism, oxidative stress, microinflammation, hyperhomocysteinemia, anemia, secondary hyperparathyroidism and vascular shunt flow (1–5). The annual cardiovascular mortality rate in these patients is 9%, with left ventricular hypertrophy (LVH), ischemic heart disease and congestive heart failure being the most prevalent causes (5).

HD patients are at high risk of sudden cardiac death due to LVH, disturbed coronary circulation, decreased coronary reserve, increased sympathetic activity and angiotensin II plasma concentration and fast electrolyte changes during HD (potassium, calcium, magnesium) (6–9).

The strategy for lowering cardiovascular mortality rate in HD patients should include early identification of high-risk patients, permanent evaluation of dialysis adequacy and individually tailoring dialysis conditions, as well as maintaining better hemodynamic stability and electrolyte balance (6–9). Identifying patients at high risk for cardiovascular complications and cardiovascular mortality is based on measuring serum C-reactive protein (CRP), homocysteine, cardiac troponins (cTn) T and I, and determining relevant echocardiographic markers (LV mass index – LVMi, end-diastolic LV volume index – iEDV and LV ejection fraction – LVEF) (6–9).

Early detection of high-risk patients enables timely implementation of adequate therapeutic strategy. The primary therapeutic strategy for lowering the cardiovascular mortality rate in HD patients should include antiaggregation therapy, statins and beta-blockers, while the secondary therapeutic approach includes coronary revascularisation and percutaneous implantation of cardioverter defibrillator (6–9).

The aim of this study was to determine the cardiovascular mortality rate and estimate the influence of risk factors on cardiovascular mortality in HD patients.

Patients and Methods

A group of 115 patients, treated at the Department of Hemodialysis of the Clinic of Urology and Nephrology, Clinical Center »Kragujevac« in Kragujevac, was studied. All patients gave informed consent for participation in the study, according to the Declaration of Helsinki. All subjects were hemodynamically stable and on standard bicarbonate HD for over 6 months, with diuresis < 200 mL/24h. None of them had either clinical or echocardiographic signs of acute coronary syndrome or congestive heart failure three months prior to the initiation of this study. Initially a cross-section study was performed, followed by a two-year follow-up period.

The following variables were determined in order to assess their influence on cardiovascular morbidity: systolic and mean arterial pressure, serum hemoglobin, albumin, cholesterol, homocysteine, CRP, cTn T and I concentrations and dialysis adequacy (Kt/Vsp).

Laboratory analysis

Blood samples for laboratory analyses were drawn after 12 hours of overnight fasting, before the dialysis session and heparin administration.

Serum urea was determined with the complete enzymatic method (urease-glutamate-dehydrogenase), the reference range being 3.5–7.5 mmol/L. Serum albumin level was measured by the photometric colour test with bromcresol green. The normal range was 38–46 g/L and a concentration of < 36 g/L suggested malnutrition. Total serum cholesterol was determined with an enzymatic method (*cholesterol esterase – cholesterol oxidase*). The reference range was 3.37–6.48 mmol/L.

Serum CRP was determined using the immunoturbidimetric method. CRP was calculated as the mean value from two measurements taken within three months. Normal value was ≤ 5 mg/L, while values > 10 mg/L suggest microinflammation. All parameters were analyzed using the Olympus 640 analyzer (Olympus, Munich, Germany).

Hemoglobin concentration was measured by colorimetry, on an HmX Coulter Hematology analyzer, Beckman Coulter, and the standard range was 110–180 g/L. Total serum homocysteine concentration was measured by the FPIA (Fluorescence Polarization Immunoassay) method. Levels > 15 mmol/L indicated hyperhomocysteinemia.

Measurements of serum cTnT were performed based on the electrochemiluminescence immunoassay technology (ECLIA method – *ElectroChemi-Luminescence ImmunoAssay*), using the Roche Diagnostics troponin T kit. A level of > 0.1 ng/mL was considered positive for myocardial necrosis. Serum cTnI was determined using immunoassay technology (CMIA method – *ChemiLuminescence Immuno-Assay*), Architect system, *Abbott Laboratories*, USA. A level of > 0.15 ng/mL was considered positive for myocardial necrosis.

Echocardiography

The echocardiographic examinations were performed 15 to 20 hours after the dialysis session, in order to avoid end-diastolic LV diameter alterations induced by the interdialytic volume gain. All studies were performed on a SHIMADZU-2200 ultrasound machine, with a 2.5 MHz transducer probe, by a single experienced physician.

Left ventricular hypertrophy was determined by measuring the left ventricular mass index-LVMi.

Normal values are ≤131 g/m^2 for men and ≤ 100 g/m^2 for women (10–12). Left ventricular fractional shortening (LVFS), representing a measure of systolic function, is normally 42 ± 8% (10–12). Left ventricular ejection fraction (LVEF) was determined as a marker of LV systolic function. Reference range for LVEF is 67 ± 9% (10–12).

Arterial blood pressure was calculated as average value of twelve monthly measurements, taken prior to laboratory and echocardiographic investigations.

Dialysis adequacy was assessed based on the Kt/Vsp index, calculated from Daugridas second-generation formula:

$$Kt/Vsp = \ln(C_2/C_1 - 0.008 \times T) + (4 - 3.5 \times C_2/C_1) \times UF/W,$$

where C_1 stands for predialysis serum urea, C_2 – postdialysis serum urea (mmol/L), T – treatment time (h), UF – ultrafiltration (L), W – body weight after dialysis (kg). According to K/DOQI guidelines delivered Kt/V should be ≥ 1.2.

Clinical definition of cardiovascular morbidity and mortality

Causes of death in HD patients were classified as cardiovascular events (acute myocardial infarction, congestive heart failure and sudden death) and non-cardiovascular events (infection/sepsis, neoplasm, unknown) (13).

Statistic analysis

Results were statistically analyzed using Cox univariate and multivariate regression analyses, Kaplan-Meier test and Log-Rang test. Values < 0.05 and < 0.01 were considered significant.

Results

This two-year prospective follow-up study included 115 patients (71 males and 44 females), average age 53.30 ± 12.17 years, average time on dialysis 4.51 ± 4.01 years and average Kt/Vsp 1.17 ± 0.23. General patient data are shown in *Table I*.

Cardiovascular causes of death made up for 62.07% of all deaths during the follow-up period (*Table II*). The average all-cause annual mortality rate was 13.74%, while the average cardiovascular annual mortality rate was 8.51% (*Table III*).

Increased CRP, cTnT, cTnI and LVMi ($p < 0.01$), as well as decreased LVEF ($p < 0.05$) were identified as the risk factors significantly related to cardiovascular mortality using the Cox univariate regression analysis (*Table IV*).

Multivariate Cox regression analysis identified increased CRP ($p < 0.01$), cTnT ($p < 0.05$), cTnI (p

Table I Demographic, anthropometric, clinical and biochemical data of the study population.

Demographic, anthropometric, clinical and biochemical data		Basic statistical parameters
		Mean ± SD
Number		115
Sex (male/female)		71/44
Age (years)		53.30 ± 12.17
Body mass index (kg/m^2)		22.60 ± 3.18
Time on dialysis (years)		4.51 ± 4.01
Kt/Vsp index		1.17 ± 0.23
Systolic blood pressure (mmHg)		138.13 ± 20.95
Mean arterial blood pressure (mmHg)		102.10 ± 15.07
Serum albumin (g/L)		40.55 ± 4.62
Serum total cholesterol (mmol/L)		4.61 ± 1.12
Hemoglobin (g/L)		89.67 ± 14.10
Serum C-reactive protein (mg/L)		7.50 ± 9.34
Serum homocysteine (mmol/L)		23.06 ± 8.58
Serum troponin T (ng/mL)		0.14 ± 0.23
Serum troponin I (ng/mL)		0.20 ± 0.48
Left ventricular mass index (g/m^2)		143.85 ± 41.21
End-diastolic volume index (mL/m^2)		100.80 ± 34.62
Left ventricular ejection fraction (%)		68.06 ± 11.11
Causes of end-stage renal disease	Diabetic nephropathy	12 (10.44%)
	Chronic pyelonephritis	19 (16.52%)
	Hypertensive nephropathy	21 (18.26%)
	Chronic nephropathy	7 (6.09%)
	Chronic glomerulonephritis	35 (30.43%)
	Obstructive nephropathy	4 (3.48%)
	Polycystic renal disease	15 (13.04%)
	Balkan endemic nephropathy	2 (1.74%)

Table II Mortality causes in the study population.

Cause of death		Two-year follow-up
Cardiovascular	Sudden cardiac death	5 (17.24%)
	Acute myocardial infarction	1 (3.45%)
	Pulmonary thromboembolism	2 (6.90%)
	Pericardial effusion	1 (3.45%)
	Disturbances of cardiac rhythm	3 (10.34%)
	Acute cardiac insufficiency	3 (10.34%)
	Infectious endocarditis	1 (3.45%)
	Valvular disease	1 (3.45%)
	Cerebrovascular insult	1 (3.45%)
Non-cardiovascular	Pneumonia	2 (6.90%)
	Sepsis	3 (10.34%)
	Neoplasm	2 (6.90%)
	Gastrointestinal bleeding	3 (10.34%)
	Acute abdomen	1 (3.45%)
Overall		29 (100%)

Table III All-cause and cardiovascular mortality rates in maintenance hemodialysis patients during the two-year follow-up period.

MORTALITY	MORTALITY RATE		
	Annual		Average
All-cause	14 (12.17%)	15 (15.31%)	13.74%
Cardiovascular	9 (7.83%)	9 (9.18%)	8.51%

Table IV Cox univariate regression analysis of risk factors for cardiovascular mortality.

Variable	Cox regression analysis					
	B	S.E.	Exp B	95% CI for Exp B		Significance (p)
				Lower	Upper	
Albumin	–0.080	0.046	0.923	0.843	1.011	0.085
Cholesterol	–0.122	0.231	0.885	0.563	1.391	0.597
Hemoglobin	–0.025	0.019	0.975	0.940	1.012	0.188
C-reactive protein	0.065	0.019	1.065	1.026	1.106	0.001
Homocysteine	0.011	0.027	1.011	0.960	1.065	0.683
Troponin I	0.860	0.270	2.363	1.391	4.014	0.001
Troponin T	1.765	0.622	5.840	1.725	19.770	0.005
Systolic blood pressure	0.008	0.012	1.008	0.985	1.032	0.481
Mean arterial blood pressure	0.009	0.016	1.009	0.978	1.042	0.566
Kt/Vsp index	–1.604	1.190	0.201	0.020	2.072	0.178
LVMi	0.013	0.004	1.013	1.004	1.022	0.004
iEDV	0.008	0.006	1.008	0.996	1.021	0.188
LVEF	–0.046	0.019	0.956	0.920	0.993	0.019

LVMi – left ventricular mass index, iEDV – end-diastolic volume index, LVEF – left ventricular ejection fraction

Table V Cox multivariate regression analysis of risk factors for cardiovascular mortality.

Variable	Cox regression analysis					
	B	S.E.	Exp B	95% CI for Exp B		Significance (p)
				Lower	Upper	
C-reactive protein	0.069	0.022	1.071	1.025	1.119	0.002
Troponin I	0.603	0.304	1.828	1.007	3.320	0.047
Troponin T	1.649	0.834	5.200	1.014	26.671	0.048
LVMi	0.009	0.004	1.009	1.000	1.017	0.046
LVEF	–0.038	0.021	0.963	0.924	1.003	0.072

LVMi – left ventricular mass index, LVEF – left ventricular ejection fraction

Table VI The influence of serum troponin T and C-reactive protein on hemodialysis patients' survival during the two-year follow-up period (cardiovascular mortality).

Variable	Survival rate				Log Rank significance (p)			
	6 M	12 M	18 M	24 M				
cTnT > 0.10 ng/mL i CRP > 10 mg/L	83.88%	71.40%	64.26%	56.23%	P	1	2	3
cTnT > 0.10 ng/mL i CRP ≤ 10 mg/L	92.31%	84.62%	80.77%	66.52%	2	0.83 0.3610	/	/
cTnT ≤ 0.10 ng/mL i CRP > 10 mg/L	100.00%	100.00%	87.51%	87.51%	3	2.18 0.1400	0.99 0.3208	/
cTnT ≤ 0.10 ng/mL i CRP ≤ 10 mg/L	100.00%	100.00%	100.00%	98.36%	4	28.32 0.00001	19.88 0.0001	3.75 0.0528

M – month, P – parameter, Parameter 1: cTnT > 0.10 ng/mL and CRP > 10 mg/L, Parameter 2: cTnT > 0.10 ng/mL and CRP ≤ 10 mg/L, Parameter 3: cTnT ≤ 0.10 ng/mL and CRP > 10 mg/L, Parameter 4: cTnT ≤ 0.10 ng/mL and CRP ≤ 10 mg/L

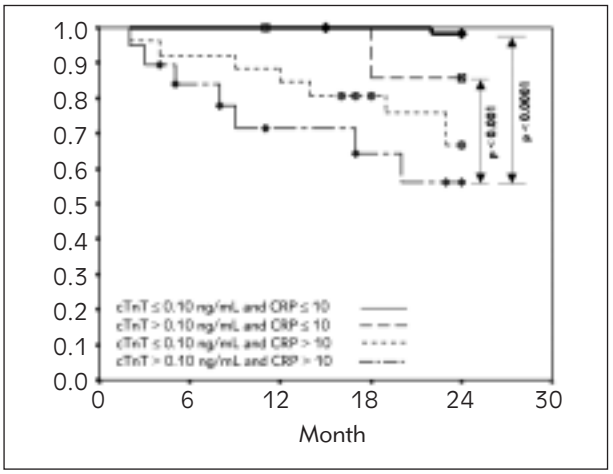

Figure 1 The influence of troponin T and C-reactive protein on hemodialysis patients' survival during the two-year follow-up period (cardiovascular mortality).

< 0.05) and LVMi ($p < 0.05$) as independent risk factors for cardiovascular mortality (*Table V*).

Patients with cTnT > 0.10 ng/mL and CRP > 10 mg/L at baseline had significantly ($p < 0.01$) higher cardiovascular mortality risk than patients with cTnT > 0.10 ng/mL and CRP ≤ 10 mg/L, and those with cTnT ≤ 0.10 ng/mL and CRP ≤ 10 mg/L (*Table VI* and *Figure 1*).

Discussion

The high incidence of cardiovascular disease in HD patients is related to the high prevalence of traditional (hypertension, disturbed lipid metabolism, diabetes mellitus, cigarette smoking) and non-traditional (microinflammation, oxidative stress, hyperhomocysteinemia, secondary hyperparathyroidism) risk factors, which lead to increased atherosclerosis, plaque destabilization, myocardial fibrosis and valvular heart disease (15, 16).

Hemodialysis patients are at higher risk for sudden cardiac death. Ischemic heart disease, LV hypertrophy, cardiac failure, disturbed myocardial ultrastructure and function, increased sympathetic activity and fast electrolyte shifts during HD all contribute significantly to the appearance of sudden cardiac death in these patients (6, 17). The average annual cardiovascular mortality rate in HD patients in this study of 8.51% is similar to the 9% reported by other authors (17, 18). Increased CRP, cTnT, cTnI and LVMi were identified as independent risk factors for cardiovascular mortality in our study group.

Early detection of HD patients at high risk for cardiovascular mortality enables timely initiation of adequate preventive treatment measures (19). Possible methods for identifying these patients in the clinical environment include tests for assessing microinflammation, coronary plaque instability and rupture risk (CRP) and markers of cardiac ischemia and tissue damage (cTn) (20–23). Due to the complexity of their condition, in HD patients it is necessary to determine several outcome markers (24–26). Simultaneous determination of CRP and cTnT enables identification of patients with increased cardiovascular risk who should be submitted to further diagnostic monitoring and aggressive treatment of cardiovascular risk factors (26–28). During the two-year follow-up period, patients with serum cTnT > 0.10 ng/mL and CRP > 10 mg/L had a significantly higher cardiovascular mortality rate than those with cTnT ≤ 0.10 ng/mL and CRP ≤ 10 mg/L. Several previous studies also showed that HD patients with cTnT > 0.10 ng/mL and CRP > 10 mg/L had the lowest survival rate (27–30).

The alarming rate of cardiovascular events in dialysis patients demands accurate risk profiling to identify individuals at greater risk and therefore needing intensive surveillance and treatment in order to prevent cardiovascular morbidity and mortality and improve the patients' quality of life (31–36).

In conclusion, the patients on maintenance HD with increased serum levels of cardiac troponin T and C-reactive protein have higher risk of cardiovascular mortality demanding additional diagnostic surveillance and close therapeutic monitoring.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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