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Cardiovascular morbidity and mortality in patients treated with hemodialysis – epidemiological analysis

Kardiovaskularni morbiditet i mortalitet bolesnika na hemodijalizi: epdiemiološka analiza

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Abstract

Background/Aim. Cardiovascular diseases are the leading cause of death in patients treated with hemodialysis (HD). The annual cardiovascular mortality rate in these patients is 9%. Left ventricular (LV) hypertrophy, ischemic heart disease and heart failure are the most prevalent cardiovascular causes of death. The aim of this study was to assess the prevalence of traditional and nontraditional risk factors for cardiovascular complications, to assess the prevalence of cardiovascular complications and overall and cardiovascular mortality rate in patients on HD. **Methods.** We investigated a total of 115 patients undergoing HD for at least 6 months. First, a cross-sectional study was performed, followed by a two-year follow-up study. Beside standard biochemical parameters, we also determined cardiac troponins and echocardiographic parameters of LV morphology and function (LV mass index, LV fractional shortening, LV ejection fraction). The results were analyzed using the Student's *t* test and Mann-Whitney *U* test. **Results**. The patients with adverse outcome had significantly lower serum albumin ($p < 0.01$) and higher serum homocystein, troponin I and T, and LV mass index ($p < 0.01$). Hyperhomocysteinemia, anemia, hypertriglyceridemia and uncontrolled hypertension had the highest prevalence (86.09%, 76.52%, 43.48% and 36.52%, respectively) among all investigated cardiovascular risk factors. Hypertrophy of the LV was presented in 71.31% of the patients and congestive heart failure in 8.70%. Heart valve calcification was found in 48.70% of the patients, pericardial effusion in 25.22% and disrrhythmia in 20.87% of the investigated patients. The average annual overall mortality rate was 13.74%, while average cardiovascular mortality rate was 8.51%. **Conclusion**. Patients on HD have high risk for cardiovascular morbidity and mortality.

Key words:
cardiovascular diseases; morbidity; mortality; renal dialysis; risk factors; prevalence; hypertrophy, left ventricular; homocysteine.

Apstrakt

Uvod/Cilj. Kardiovaskularne bolesti su vodeći uzrok smrti bolesnika koji se leče hemodijalizom (HD). Jednogodišnja stopa kardiovaskularnog mortaliteta iznosi 9%, a od kardiovaskularnih poremećaja, kao uzročnici smrti najveću prevalenciju imaju hipertrofija leve komore (LK), ishemijska bolest srca i srčana slabost. Cilj rada bio je da se utvrdi prevalencija tradicionalnih i netradicionalnih faktora rizika od razvoja kardiovaskularnih komplikacija, prevalencija kardiovaskularnih komplikacija, kao i stopa opšteg i kardiovaskularnog mortaliteta bolesnika podvrgnutih HD. **Metode.** Ispitano je 115 bolesnika, koji su lečeni HD duže od šest meseci. Prvo, urađena je studija preseka, a zatim praćenje bolesnika u dvogodišnjem vremenskom periodu. Parametri ispitivanja, pored standardnih laboratorijskih analiza, uključili su srčane troponine i ehokardiografske parametre morfologije i funkcije LK: indeks mase LK, frakciono skraćenje LK, ejekcionu frakciju LK. Za statističku analizu dobijenih podataka korišćeni su Studentov *t* test i Mann-Whitney *U* test. **Rezultati.** Bolesnici sa nepovoljnim ishodom imali su visoko statistički značajno ($p < 0,01$) manje vrednosti albumina u serumu, kao i visoko statistički značajno ($p < 0,01$) veće vrednosti homocisteina, troponina I, troponina T i indeksa mase LK. Od ispitivanih faktora rizika najveću prevalenciju imali su hiperhomocisteinemija (86,09%), anemija (76,52%), hipertrigliceridemija (43,48%) i nekontrolisana hipertenzija (36,52%). Hipertrofiju LK imalo je 71,31%, a kongestivnu sistolnu srčanu insuficijenciju 8,70% bolesnika. Kalcifikaciju srčanih valvula imalo je 48,70%, perikardni izliv 25,22%, dok je poremećaj srčanog ritma imalo 20,87% ispitivanih bolesnika. Prosečna jednogodišnja stopa opšteg mortaliteta iznosila je 13,74%, a prosečna jednogodišnja stopa kardiovaskularnog mortaliteta 8,51%. **Zaključak.** Bolesnici na HD u visokom su riziku od razvoja kardiovaskularnog morbiditeta i mortaliteta.

Ključne reči:
srce, bolesti; morbiditet; mortalitet; hemodijaliza; faktori rizika; prevalenca; srce, hipertrofija leve komore; homocistein.

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Indtroduction

Cardiovascular diseases are the leading cause of death in patients on hemodialysis (HD). The annual mortality rate from cardiovascular disease in these patients is 9%. The major cardiovascular complications are left ventricular (LV) hypertrophy (LVH) (75%), ischemic heart disease (40%) and congestive hart failure (40%) [1]. High incidence of cardiovascular disease in patients on HD is related to high prevelence of traditional (hypertension, disturbed lipid metabolism, diabetes mellitus, cigarette smoking) and nontraditional (microinflammation, oxidative stress, hyperhomocysteinemia, secondary hyperparathyroidism) risk factors, which lead to increased atherosclerosis, plaque destabilization, myocardial fibrosis and valvular heart disease [2, 3].

Patients on hemodialysis are at higher risk for sudden cardiac death [4]. Hypertrophy of LV (present in 75% of patients on HD), fast electrolyte changes during HD (absence of potassium in dialysis solution), hyperkalemia, myocardial fibrosis and decreased coronary perfusion, all contribute significantly to the appearance of sudden cardiac death in these patients [4].

The aim of this study was to determine the prevalence of traditional and nontraditional (metabolic and hemodynamic) risk factors for the development of cardiovascular complications in patients on HD. Furthermore, we aimed to determine the prevalence of cardiovascular complications and overall and cardiovascular mortality rate in patients on regular HD.

Methods

This study was conducted at the Department of Hemodialysis, Clinic for Urology and Nephrology, Clinical Center of Kragujevac at Kragujevac, Serbia. The study included 115 patients (71 males and 44 females). All patients gave informed consent for participating 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/24 h and had various primary renal diseases.

We investigated the following variables: body mass index (BMI), hemoglobin concentration, hematocrit (Hct), arterial blood pressure (BP), arteriovenous shunt blood flow (Q_{AV}), serum homocystein (tHcy), serum C-reactive protein (CRP), total cholesterol, low-density lipoproteins LDL-cholesterol, high-density lipoproteins HDL-cholesterol and triglycerides, lipoprotein (a), calcium, phosphate, calcium-phosphate product (calcium × phosphate) and serum intact parathyroid hormone (iPTH) concentration.

Laboratory analysis

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

Serum urea was determined with complete enzymatic method (*urease-glutamate-dehydrogenase*), reference range being 3.5–7.5 mmol/l.

Hemoglobin concentration was measured by colorimetry, standard range was 110–180 g/l. Hematocrit was determined automatically with COULTER® A^C apparatus and from the formula: Hct(%) = (RBC × MCV)/10, where RBC – red blood cells and MCV – mean cell volume. Normal range was 0.35–0.60.

Serum albumin level was measured by photometric colour test with bromcresol green. The normal range was 38–46 g/l and concentration < 36 g/l suggested malnutrition.

Serum cholesterol was determined with enzymatic method (*cholesterol esterase –cholesterol oxidase*). Reference range was 3.37–6.48 mmol/l. Serum HDL lipoproteins concentration was measured by colorimetry. Reference range was 0.78–1.55 mmol/l. Serum LDL concentration was calculated from the formula: $C_{LDL} = C_{HOL\text{-}tot} - (TGL/2.2) - C_{HDL}$, where C_{LDL} is serum LDL concentration, $C_{HOL\text{-}tot}$ is total serum cholesterol, C_{HDL} is serum HDL concentration and TGL is serum triglycerides concentration. Reference range for LDL cholesterol was 2.39–4.08 mmol/l. Serum triglycerides were determined by enzymatic colorimetric method, normal range is 0–1.88 mmol/l. Serum lipoprotein (a) concentration was determined by the Behring Nephelometer System and N Latex Lp(a) reagent. Levels < 30 mg/dl were considered normal. Serum apolipoprotein AI (ApoAI) and apolipoprotein B (ApoB) levels were determined with N Antiserum to Human ApoAI (ApoAI) and N Antiserum to Human ApoB reagents respectively. Normal range for ApoAI was 1.25–2.15 g/l (women), 1.10–2.05 g/l (men), for ApoB was 0.55–1.25 g/l (women), 0.55–1.40 g/l (men). Reference range for apoB/apoAI ratio was 0.30–0.90 g/l for women and 0.35–1.00 g/l for men.

Serum calcium concentration was determined by photometric color test (Arseniko), reference range being 2.20–2.65 mmol/l. Serum phosphate was determined by photometric ultraviolet (UV) test, normal range being 0.80–1.45 mmol/l. Serum iPTH was determined by radioimmunoassay (IRMA). Normal iPTH concentration is 11.8–64.5 pg/ml for healthy individuals. Target levels for pateints on HD are below 200–300 pg/ml.

Homocystein concentration was measured by Fluorescence Polarization Immunoassay (FPIA) method. Levels > 15 μmol/l indicated hyperhomocysteinemia. Serum CRP was determined using the immunochemical nephelometric method, and calculated as mean value of two measurements in three months. Normal value was ≤ 5 mg/l.

Measurement of serum cardiac troponin T (cTnT) was based on electrochemiluminescence immunoassay technology (ElektroChemiLumineszenz ImmunoAssay – ECLIA method), by using the Roche Diagnostics troponin T kit. A level of > 0.1 ng/ml was considered positive for myocardial necrosis. Serum cardiac tropinin I (cTnI) was determined with ADV A × SYM cTnI immunoassay technology (*Abbott laboratories*). A level of > 0.15 ng/ml was considered positive for myocardial necrosis.

Echocardiography

The echocardiocraphic study was 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 megahertz (MHz) transducer probe, by a single experienced physician.

Left ventricular hypertrophy was determined by measuring the LV mass index (LVMi), which is normally ≤ 131 g/m^2 in men and ≤ 100 g/m^2 in women. Left ventricular mass index was calculated as follows:

$$\text{LVMi} = \frac{0.00083\,x\left[(LVEDD + IVSd + LVPWd)^3 - (LVEDD)^3\right] + 0.6}{BSA}\ \text{g/m}^2$$

Left ventricular end-diastolic volume index (iEDV), normally ≤ 90 ml/m^2 was quantified as:

$$\text{iEDV} = \frac{(LVEDD)^3\,x0.001047}{BSA}\ \text{ml/m}^2.$$

Abbreviations in the formulas stand for: IVSd - interventricular septal wall thickness in diastole (mm), LPWd – LV posterior wall thickness in diastole (mm), LVESD – LV end-systolic diameter (mm), LVEDD – LV end-diastolic diameter (mm), LVESV – LV end-systolic volume (ml), LVEDV – LV end-diastolic volume (ml), ET – ejection time (ms), BSA – body surface area (m^2).

Left ventricular hypertrophy was diagnosed when IVSd > 11 mm, LVPWd > 11 mm and LVMi > 131 g/m^2 for men and > 100 g/m^2 for women [5–7]. Concentric LVH existed when LV interventricuar septum thickness was > 11 mm in diastole, LV posterior wall thickness was > 11mm in diastole, LV internal diameter was < 4.7 mm in diastole, LVMi > 131 g/m^2 in males and > 100 g/m^2 in females, with normal LVFS and relative wall thickness (RWT) > 45% [5–7]. Determinants of LV eccentric hypertrophy were LVMi > 131 g/m^2 in males and > 100 g/m^2 in females, LV internal diastolic diameter > 57 mm, with normal LVFS and RWT ≤ 45% [5–7]. Left ventricular dilatation was diagnosed when internal LVEDD > 57 mm and iEDV > ml/m^2, with preserved systolic function and normal LVMi [5–7]. Echocardiographic findings of disturbed LV systolic function include LVFS ≤ 25% and LVEF ≤ 50% [5–7].

Arterial blood pressure was calculated as average value of twelve monthly measurements prior to laboratory and echocardiographic investigations. Hypertension exists when arterial BP is ≥ 140/90 mmHg in patients treated with antihypertensive drugs.

Arteriovenous shunt blood flow was determined with colour flow Doppler ultrasound, just before echocardiographic examination, on SHIMADZU-2200 machine, using the 7.5 MHz probe. Arteriovenous shunt blood flow was calculated as mean of three measurements on efferent vein, each performed 2–4 cm proximally to anastamosis. Target Q_{AV} for adequate dialysis is 300–800 ml/min.

Dialysis adequacy was assessed using Kt/Vsp index, calculated with 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 Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines delivered Kt/V should be ≥ 1.2.

Clinical definition of cardiovascular morbidity and mortality

Heart failure was characterized with presence of dyspnea and two of the following parameters: increased jugular venous pressure, rales, pulmonary hypertension or interstitial pulmonary edema confirmed on chest radiography [8].

Ischemic heart disease was defined as the presence of angina pectoris and/or a previous myocardial infarction. According to the American College of Cardiology and European Society of Cardiology myocardial infarction is characterized with spontaneous chest pain lasting over 20 minutes, accompanied by rise in cTnI level (cTnI ≥ 2 ng/mL), ST segment elevation ≥ 0,2 mV in leads V2–V3, or ≥ 0,1 mV in other leads, or presence of Q wave ≥ 1 mm and ≥ 30 ms wide in at least two consequent leads. *De novo* left bundle brunch block can also be a sign of acute myocardial infarction [8].

Infectious endocarditis was diagnosed based on the presence of either two major or one major and 3–5 minor Duke's criteria. The major criteria are: at least two positive blood cultures, new valvular regurgitation, positive echocardiogram (oscillating intracardiac mass on valve or supporting structures). The minor criteria include: patient predisposition, fever, vascular phenomenon, immunologic phenomenon, microbiological evidence (one positive blood culture) and echocardiographic finding consistent with infectious endocarditis but do not meet a major criterion as noted above [9, 10].

Causes of death in patients on HD were classified as cardiovascular events (acute myocardial infarction, congestive heart failure and sudden death) and non-cardiovascular events (infection/sepsis, neoplasm, unknown) [11].

Statistic analysis

Results were statistically analyzed with Student′s *t* test and Mann-Whitney *U* test. Values < 0.05 and < 0.01 were considered significant.

Results

Average age of 115 investigated patients was 53.30 ± 12.17 years, average time on dialysis 4.51 ± 4.01 years and average single pool modeling fractional clearance of body water of urea (Kt/Vsp) – Kt/Vsp 1.17 ± 0.23. General patients' data are shown in Table 1.

According to the results of a two-year follow-up period the patients were separated in two groups, 86 alive persons and 29 deceased. The patients with adverse outcome had significantly lower serum albumin levels and significantly higher serum tHcy, cTnT, cTnI and LVMi (Table 2).

Table 3 shows the prevalence of traditional risk factors for the development of cardiovascular complications in patients on HD. Hypertriglyceridemia (43.48%) and unregulated hypertension (36.5%) were the most prevalent risk factors in our group.

Table 1

General patients data

Variables	Outcome		Significance	*p*
	Alive (86 patients)	Deceased (29 patients)		
	$\bar{x} \pm SD$	$\bar{x} \pm SD$		
Sex (male/female)	56/30	15/14	$\chi^2_{emp} = 1.647$	0.199
Age (years)	52.47 ± 12.04	55.76 ± 12.41	$t_{emp} = -1.264$	0.209
Body mass index (kg/m^2)	22.76 ± 3.20	22.13 ± 3.15	$t_{emp} = 0.925$	0.357
Time on dialysis (years)	4.50 ± 4.20	4.55 ± 3.45	$Z_{emp} = -0.612$	0.541
Dialysis adequacy-Kt/Vsp*	1.18 ± 0.21	1.12 ± 0.29	$t_{emp} = 1.206$	0.230

*Single pool modeling fractional clearance of body water of urea (KT/V)

Table 2

Basic patients parameters based on outcome during the two-year follow-up

Variables	Outcome		Significance	*p*
	Alive (86 patients)	Deceased (29 patients)		
	$\bar{x} \pm SD$	$\bar{x} \pm SD$		
Systolic blood pressure (mmHg)	137.67 ± 20.39	139.48 ± 22.85	$t_{emp} = -0.401$	0.690
Diastolic blood pressure (mmHg)	83.95 ± 12.54	84.48 ± 14.10	$t_{emp} = -0.190$	0.849
Mean arterial pressure (mmHg)	101.86 ± 14.77	102.82 ± 16.19	$t_{emp} = -0.294$	0.769
Hemoglobin (g/l)	90.60 ± 14.74	86.90 ± 11.82	$t_{emp} = 1.227$	0.222
Hematocrit (%)	26.89 ± 4.44	25.98 ± 3.51	$t_{emp} = 0.997$	0.321
Total proteins (g/l)	73.38 ± 6.10	73.41 ± 6.49	$t_{emp} = 0.274$	0.784
Serum albumin (g/l)	41.31 ± 4.36	38.31 ± 4.71	$t_{emp} = 3.145$	0.002
Total cholesterol (mmol/l)	4.65 ± 1.11	4.50 ± 1.17	$t_{emp} = 0.653$	0.515
LDL*-cholesterol (mmol/l)	2.64 ± 0.82	2.56 ± 0.86	$t_{emp} = 0.422$	0.674
HDL†-cholesterol (mmol/l)	1.05 ± 0.28	1.07 ± 0.33	$t_{emp} = -0.284$	0.777
Triglycerides (mmol/l)	2.00 ± 1.18	1.78 ± 0.83	$t_{emp} = 0.968$	0.335
Lipoprotein (a) (g/l)	0.26 ± 0.26	0.28 ± 0.26	$Z_{emp} = -0.309$	0.757
Apolipoprotein A-I (mg/dl)	1.30 ± 0.26	1.28 ± 0.31	$t_{emp} = 0.405$	0.686
Apolipoprotein B (mg/dl)	1.05 ± 0.35	1.06 ± 0.30	$t_{emp} = -0.195$	0.845
C-reactive protein (mg/l)	5.17 ± 5.64	14.39 ± 13.89	$Z_{emp} = -1.150$	0.250
Homocystein (μmol/l)	22.25 ± 8.86	26.80 ± 8.42	$t_{emp} = -2.419$	0.017
Troponin T (ng/ml)	0.09 ± 0.12	0.30 ± 0.37	$Z_{emp} = -2.476$	0.013
Troponin I (ng/ml)	0.14 ± 0.46	0.35 ± 0.55	$Z_{emp} = -4.893$	0.0001
Left ventricular mass index (g/m^2)	138.02 ± 34.57	161.13 ± 53.61	$t_{emp} = -2.681$	0.008
End-diastolic volume index (ml/m^2)	98.46 ± 33.61	107.76 ± 37.18	$t_{emp} = -1.254$	0.212
Left ventricular fractional shortening (%)	33.01 ± 7.35	31.04 ± 8.70	$t_{emp} = 1.191$	0.236
Left ventricular ejection fraction (%)	68.86 ± 10.44	65.70 ± 12.79	$t_{emp} = 1.330$	0.186

*low-density lipoproteins; †high-density lipoproteins

Table 3

The prevalence of traditional risk factors for cardiovascular complications in patients on regular hemodialysis

Traditional risk factor	Percent of patients
Triglycerides (> 1.7 mmol/l)	43.48
Unregulated hypertension predialysis blood pressure (> 140/90 mmHg)	36.52
Total cholesterol (tChol > 5.2 mmol/l)	18.26
High density lipoproteins (HDL < 1.0 mmol/l)	20.87
Lipoprotein (a) [Lp(a) > 0.3 g/l]	29.57
Diabetes mellitus	11.30
Cigarette smoking	10.43
Body mass index (BMI > 25 kg/m^2)	4.35

Table 4 shows the prevalence of non-traditional risk factors for cardiovascular complications in patients on HD. Hyperhomocysteinemia and anemia had the highest prevalence (86.09% and 76.52%, respectively).

The prevalence of LV morphology alterations is shown in Table 5. Left ventricular hypertrophy was present in 71.31% (82) of the patients, while only 14.78% (17) had normal LV morphology. Disturbed systolic function, accompanied by symptoms and signs of congestive hart failure, was present in 8.70% of the patients, as shown in Table 6.

Valvular calcification was present in 48.70% (56) of the patients (Table 7), and pericardial effusion in 25.22% (29), as shown in Table 8.

Disrrhythmias were present in 20.87% (24) of the patients. Disrrhythmias due to impaired impulse generation (atrial fibrillation (4.35%), atrial flutter (0.87%), ventricular extrasystole (5.22%) and supraventricual extrasystole (0.87%) were more frequent than those involving impaired impulse conduction (complete right bundle branch block (1.74%), incomplete left bundle branch block (4.35%), sec-

Table 4

The prevalence of non-traditional risk factors for cardiovascular complications in patients on regular hemodialysis

Non-traditional risk factors	Percent of patients
Hemocystein (tHcy > 15 μmol/l)	86.09
Anemia (Hb < 110 g/l)	78.26
C reactive protein (CRP > 5 mg/l)	34.78
$Ca \times PO_4$ solubility product ($Ca \times PO_4 > 4.4$ mmol^2/l^2)	36.52
Phosphate ($PO_4 > 1.7$ mmol/l)	31.30
Secondary hyperparathyroidism (PTH > 300 pg/ml)	20.00
Arteriovenous shunt blood flow ($Q_{AV} > 1\,000$ ml/min)	9.57

Table 5

Echocardiographic assessment of left ventricular (LV) morphology in patients on regular hemodialysis

LV morphology	Percent of patients
Concentric LV hypertrophy	28.70
Eccentric LV hypertrophy	42.61
LV dilatation	13.91
Normal LV morphology	14.78

Table 6

Echocardiographic assessment of left ventricular (LV) systolic function in patients on regular hemodialysis

LV systolic function	Percent of patients
LV fractional shortening > 25% and LV ejection fraction > 50%	91.30
LV fractional shortening ≤ 25% and LV ejection fraction ≤ 50%	8.70*

*disturbed systolic function

Table 7

Echocardiographic assessment of heart valves calcification in patients on regular hemodialysis

Heart valve calcification (CVC)	Percent of patients
Mitral valve calcification	14.79
Aortic valve calcification	33.91
No CVC	51.30

Table 8

Echocardiographic assessment of pericardial effusion in patients on regular hemodialysis

Pericardiol effusion	Percent of patients
No pericardiol effusion	74.78
Present LVPW*	21.74
Present LVPW/RVAW†	3.48

*left ventricular posterior wall; †right ventricular anterior wall

ond degreee atrioventricular block (0.87%), as shown in Table 9.

Cardiovascular complications account for 62.7% of all deaths in patients on HD (Table 10). The average annual mortality rate in our patients was 13.74%, while the average annual cardiovascular mortality rate was 8.51% (Table 11).

Discussion

Patients on HD have 10–20 times greater risk of cardiovascular mortality compared to general population [12]. These patients are exposed to a number of traditional and nontraditional risk factors for cardiovascular complications [13, 14]. Traditional risk factors include hypertension, hyperlipidemia,

Table 9

Disrrhythmia in patients on regular hemodialysis

Disrrhythmia	Percent of patients
No dissrhythmia	79.13
Present disrrhythmia	20.87
- disturbed impulse generation (2/3 of the patients)	
- disturbed impulse conduction (1/3 of the patients)	

Table 10

Cause of death in patients on hemodialysis during two-year follow-up

Cause of death		Patients	
		n	%
Cardiovascular	sudden cardiac death *(Cardiac arrest cause ignota)*	5	17.24
	acute myocardial infarction	1	3.45
	pulmonary tromboembolism	2	6.90
	pericardial effusion	1	3.45
	disrrhythmia	3	10.34
	acute heart failure	3	10.34
	infectious endocarditis	1	3.45
	valvular heart 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
Total		29	100.00

Table 11

Overall and cardiovascular mortality rate in patients on hemodialysis during two-year follow-up

Mortality	Mortality rate		
	1st year	2nd year	Average biennial
Overall mortality	14 (12.17%)	15 (15.31%)	13.74%
Cardiovascular mortality	9 (7.83%)	9 (9.18%)	8.51%

cigarette smoking, diabetes and obesity. Nontraditional risk factors encompass a number of hemodynamic and metabolic factors. Hemodynamic factors include anemia, sodium and water retention, and increased shunt blood flow. Metabolic risk factors are hyperhomocysteinemia, oxidative stress, microinflammation and disturbed calcium and phosphate metabolism [13–17]. Our patients had similar distribution of cardiovascular risk factors as reported in other studies in patients on HD: 86.09% had hyperhomocysteinemia, 76.52% had anemia, 43.48% had hypertriglyceridemia and 36.52% had uncontrolled hypertension [18–23].

Left ventricular hypertrophy is a strong predictor of cardiovascular morbidity and mortality in patients on HD [24]. Increase of LVMi by ≥ 1,0 g/m^2/month is associated with increased risk of cardiovascular complications [24]. Left ventricular hypertrophy was present in 71.31% of our patients on HD. Similar rate of LVH on HD was reported by other authors [25–27]. In patients with normal LV volume (iEDV ≤ 90 ml/m^2) and normal systolic function (LVFS > 25%, LVEF > 50%), LVMi > 120 g/m^2 and LVMi/iEDV > 2.2 g/ml are independently associated with late mortality (death > 2 years following start of HD treatment) [28, 29]. Timely detection of risk factors and adequate treatment enable regression of LVH in patients on HD [30].

Aortic valve calcification is present in 28–58% of treated with patients on HD, while mitral valve calcification was found in 24%, as reported in previous studies [31]. In our study group, aortal valve calcification was found in 33.91% of patients and mitral valve calcification in 14.79%. Aortic valve calcification is associated with high peak transaortic blood flow, values ≥ 2.5 m/s indicating aortic stenosis [31]. Patients' age, time on dialysis, hyperphosphatemia and high calcium-phosphate product significantly contribute to the development of aortic valve calcification [31]. The annual incidence of hemodynamically significant aortic stenosis in patients on HD is 3.3% [32]. Aortic valve calcification leads to aortic stenosis, LV pressure overload and concentric LVH [31, 32]. Long term LV pressure overload caused by aortic stenosis leads to progression of LVH from adaptive to maladaptive stage, development of cardiomyopathy, myocyte loss and heart failure [32]. Mitral valve calcification causes left atrial dilatation and atrial fibrillation (absolute arrhythmia) [33, 34]. Secondary hyperparathyroidism, hyperphosphatemia and high calcium-phosphate product are associated with calcification of heart valves, coronary arteries and increased cardiovascular mortality [33, 34].

Intermitent atrial fibrillation is present in 16% of patients on HD [35]. It usually appears during HD session and stops spontaneously without therapeutic intervention 2–3 hours after the HD session. Propafenone was used successfully in both acute atrial fibrillation and as a prophylactic agent in patients on HD [36].

The prevalence of symptomatic pericardial disease in patients treated with HD is 11.8–21%. Mortality rate due to pericardial disease is 1.5% [37]. Pericardial effusion was present in 25.22% of our patients, while 3.48% of them had clinically significant effusion. Risk factors for development of pericarditis and pericardial effusion in end-stage renal disease patients are uremia, volume overload, malnutrition, inadequate HD, uncontrolled secondary hyperparathyroidism, high calcium-phosphate product and infection [37].

Risk factors for heart arrhythmia in patients treated with HD are: ischemic heart disease, LVH, congestive heart failure, pericardial effusion and electrolyte dysbalance [38]. The

prevalence of atrial disrrhythmia in end-stage renal disease patients on HD is 6%, atrial fibrillation being the most common [38]. Ischemic heart disease, LVH and mitral valve calcification are the most often correlated with atrial fibrillation [38]. The prevalence of ventricular extrasystole in our study group was 5.22%, and the prevalence of persistent atrial fibrillation was 4.35%.

Congestive heart failure, ventricular disrrhythmias, sudden cardiac death and acute myocardial infarction account for at least 40% of cardiovascular deaths in patients on HD [39]. The annual overall mortality rate in patients on HD is 6–16% and the annual cardiovascular mortality rate is 9% [39]. Our results show that annual overall mortality rate is 13.74% and average annual cardiovascular mortality rate is 8.51%. These results correspond with the mentioned published data [39].

The strategy for lowering overall and cardiovascular mortality in patients on HD should include identification and selection of high-risk patients, permanent evaluation of dialysis adequacy, maintaining better hemodynamic stability and electrolyte balance, and constant evaluation of prescribed cardioprotective therapy [39–41]. The strategy for identifying patients at high risk for cardiovascular complications and cardiovascular mortality should encompass determination of serum cardiac troponins, electrocardiographic markers, such as length of QTc interval and QTc-interval dispersion, and echocardiographic markers (LVMi) [35, 40–43].

Early detection of high-risk patients enables timely implementation of adequate therapeutic strategy. The primary therapeutic strategy for lowering cardiovascular mortality rate in patients on HD should include: antiaggregation therapy, control of lipid metabolism disorders and hypertension, while secondary therapeutic strategy includes coronary revascularisation and controle of heart rhythm disorders [44–48].

Conclusion

Patients on HD have high risk for cardiovascular morbidity and mortality. Hiperhomocysteinemia, anemia, hypertriglyceridemia and uncontrolled hypertension had the highest prevalence of cardiovascular risk factors among all investigated. Echocardiographic assessment for cardiovascular status in patients on HD identifies those with increased risk of cardiovascular complications, LVH, congestive heart failure, and heart valve calcification. Establishing the most sensitive parameters for identifying patients at risk for cardiovascular complications enables successfull treatment.

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