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CLINICAL STUDY

Aortic pulse wave velocity is a strong predictor of all – cause and cardiovascular mortality in chronic dialysis patients

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Abstract

Background/Aims: The aim of this study was to investigate all-cause and cardiovascular mortality in chronic hemodialysis patients (CHP) and to identify the determinants of mortality predictors. *Methods*: In this study with 3 years of follow-up period, we studied a cohort of 80 CHPs. Mean age at entry was 59.3 ± 11.8 years (duration of dialysis 5.47 ± 5.16 years). At entry, together with standard clinical and biochemical analyses, pulse wave velocity (PWV) was determined from time diversity propagation of the common carotid artery and common femoral artery flow signals by Doppler ultrasound. *Results*: The mean PWV (m/s) was presented at entry: in survived (12.5 ± 2.01) and deceased (13.13 ± 1.70) patients. The PWV cutoff point (by ROC curves) was 11.8. The regression coefficients (b) and Exp (b) hazard ratio coefficients of covariates in Cox-regression survival analysis in all-cause and CV outcomes was: PWV ($b = 0.2617$, Exp[b] = 1.2992, $p = 0.0027$; $b = 0.3569$, Exp[b] = 1.4289, $p = 0.0005$), CRP ($b = 0.0776$, Exp[b] = 1.0807, $p = 0.0001$; $b = 0.0832$, Exp[b] = 1.0868, $p = 0.0001$) and albumin ($b = -0.1302$, Exp[b] = 0.8779, $p = 0.0089$; $b = -0.1881$, 0.8285, $p = 0.0030$), respectively. Relative risk for exposed groups according to all-cause and CV events was 4.2976 (95% CI = 1.6051–11.5071) and 14.3590 (95% CI = 1.6051–11.5071), $p = 0.0037$, respectively. *Conclusions*: We conclude that PWV, CRP and serum albumin are strong independent predictors of overall and CV mortality in patients undergoing dialysis.

Keywords

Albumin, arterial stiffness, cardiovascular mortality, CRP, survival

History

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Introduction

As the heart contracts, the aortic valve opens and blood is pumped into the aorta and the systemic circulation. Aorta receives pressure spreading from the walls of the heart to its own walls. Dilated aorta wall generates a pressure wave that travels along the arterial tree. Its velocity is more pronounced than blood travel velocity. The speed of these pressure waves is known as pulse wave velocity (PWV). It measures the speed of generated pressure propagation, not the displacement of blood fluid.

PWV is a measure of arterial stiffness. Arterial stiffness describes the reduced capability of an artery to expand and contract in response to pressure changes.[1] PWV is inversely correlated with arterial distensibility and relative arterial compliance. A high percentage of all cardiovascular diseases are associated with stiffening of the arteries, a direct consequence of atherosclerosis. Increased arterial stiffness is the result of many contributing factors, such as atherosclerosis, vascular calcification and changes in collagen/elastin ratio content in the vessel wall. The increase in artery wall stiffness is noticeable from the beginning of the arteriosclerosis process, before anatomical changes and clinical manifestations are observed.

Atherosclerosis is the most frequent cause of cardiovascular morbidity in patients with end-stage renal disease (ESRD). Patients with ESRD face a particularly high risk of cardiovascular disease and total mortality.[2] Accelerated arteriosclerosis is a major risk to long-term survivors on maintenance hemodialysis.[3] Myocardial infarction and cerebrovascular events occupy an important place in the mortality of these patients. The cardiovascular mortality rate of chronic dialysis patients (CHPs) is approximately 20 times higher than that of the general population, and the cerebrovascular death rate is nearly 10 times higher.

The arterial system in ESRD patients undergoes structural remodeling very similar to changes with aging, and is characterized by diffuse dilation, hypertrophy and stiffening of the aorta and major arteries. In comparison with non-uremic patients, the intima-media thickness of major central arteries is increased in ESRD patients.[4]

In recent years, many studies have also provided that circulating biomarkers such as albumin and C-reactive protein (CRP) are in strong independent correlation with PWV.

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To the contrary, tissue biomarkers such as vascular calcification or arterial stiffness are signs of true tissue damage, rather than circulating biomarkers risk factors. PWV, as measure of arterial stiffness, reflects the cumulative exposure to damaging factors that have harmed the cardiovascular system.

Detection of arterial stiffness provides physicians with useful prognostic information for cardiovascular mortality, independent of traditional cardiovascular (CV) risk factors, because the traditional CV risks do not accurately predict survival in CHP patients.[5] The aim of this study was to investigate all-cause and cardiovascular mortality in chronic hemodialysis patients and to identify the determinants of mortality predictors.

Methods

The study was designed as a longitudinal prospective analysis in 80 chronic hemodialysis (HD) patients who underwent noninvasive PWV measurements and standard clinical and laboratory procedures at baseline accompanied by 36-months follow-up period.

Patients

A cohort of 80 chronic HD patients (53 men and 27 women) was studied between December 2009 and December 2012. Mean age at entry was 59.3 ± 11.8 years, their mean body mass index (BMI) was $23.5 \pm 3.6\,kg/m^2$. Twenty patients were smokers, 37 were hypertonic and 16 were diabetics. The mean duration of the dialysis therapy was 5.47 ± 5.16 years. Patients were eligible for entry into the study if they had been on HD for at least 3 months and if they had no clinical manifestation of cardiovascular disease (stroke, myocardial infarction and peripheral vascular occlusion) at least 6 months before entering in the study.

The underlying renal diseases were: chronic glomerulonephritis in 19 patients (23.75%), interstitial nephritis in 11 (13.75%), diabetic nephropathy in 9 (11.25%), nephroangiosclerosis in 7 (8.75%), adult polycystic kidney disease in 6 (7.5%), obstructive nephropathy in 5 (6.25%) and other and unknown etiology in 23 (28.75%).

The patients had been on regular hemodialysis using a low-flux synthetic membrane, at a blood flow rate of 180–200 mL/min via their arteriovenous fistulas. The HD session was tailored (4–5 hours, three times a week) to achieve a $Kt/V \geq 1.2$ (1.22 ± 0.32). A bicarbonate dialysate was used at flow rate of 500 mL/min in each patient. A strict bacteriological standard was ensuring by continuous monitoring of water quality. In accordance with the needs, patients were receiving erythropoietin and iron supplements for maintaining the hemoglobin level according the recommendations of 110–120 g/L. For maintaining the serum phosphate under 1.8 mmol/L, patients were using calcium carbonate tablets of 1 g as an alternative phosphate binder. Antihypertensive therapy with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) was initiated or continued at all participants when systolic pressure exceeded 140 mmHg, or the diastolic pressure exceeded 90 mmHg.

All patients gave informed consent to participate in the study. No patient had an acute infection, congestive heart failure, or a malignancy at entry into study. All participants signed an informed consent and the study was approved by the Ethics Committee of our institution.

Cardiovascular outcomes

Cardiovascular (CV) mortality was defined as death whose cause was one of the following CV events or sudden death: cerebrovascular disease (stroke), peripheral vascular disease, arrhythmia, congestive heart failure or myocardial infarction.

Assessment

We used a pulsed-Doppler ultrasound with a linear array 7.5 MHz probe (Toshiba SSA-340 A, Toshiba Medical System Co., Tokyo, Japan) synchronized with ECG. The examination began with the patient in a supine position after locating the CCA with B-mode at the supraclavicular level (1–2 cm of the bifurcation) and locating the CFA midway the ante superior crest of the iliac bone and the pubic bone (in the groin). Two Doppler waves were recorded transcutaneously at the base of the neck for the right CCA and over the right CFA. Although it is not possible to analyze the carotid and femoral waves simultaneously, they can be normalized separately with the electrocardiogram (ECG) getting.[6] PWV measurements were taken under the same conditions during both examinations, after the second dialysis session (second and third dialysis-free days represent the time point when PWV is very close to the weekly middle value) in supine position after resting for at least 10 minutes, including a constant room temperature of 19–21 °C. Baseline PWV was determined and patients were followed three years for outcomes.

We used three parameters to calculate the PWV by foot to foot method: T1 – time delay, from ''R-wave'' of ECG to point A (foot of the CCA wave), T2 – time delay from ''R-wave'' of ECG to point B (foot of the CFA wave) and distance D measured from the sternal notch (CCA) to the groin (CFA). The foot of the wave is defined at the end of diastole, when the steep rise of the waveform begins. Path length (distance D) was defined by direct anthropometric measurement of the distance between suprasternal notch (fossa jugularis sternalis) and groin.

The measurement of carotid-femoral PWV was made by dividing the D by the ΔT, so-called TT (Transit Time). Time diversity ΔT was calculated by the time differences T1 and T2 yield the time delay: $\Delta T = T2 - T1$. The speed of pulse wave (V) was calculated by standard equation for the speed: V (m/s) = S (m)/ΔT (s). Hence, PWV = D/Δt (m/s). The time diversity of electric (ECG) and Doppler (CCA and CFA) signals is shown in Figure 1.

Clinical and biochemical parameters (urea, creatinine, hemoglobin, total protein, albumin, cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, C-reactive protein [CRP] and fibrinogen) were determined in all participants using standard laboratory procedures, performed on a Cobas Mira S Analyzer (Roche Diagnostics, Holliston, MA). Blood was drawn immediately before the start of a dialysis session in a fasting state. Mean values obtained from six consecutive measurements during the 6 months (every month) before PWV measurements were used in the analysis.

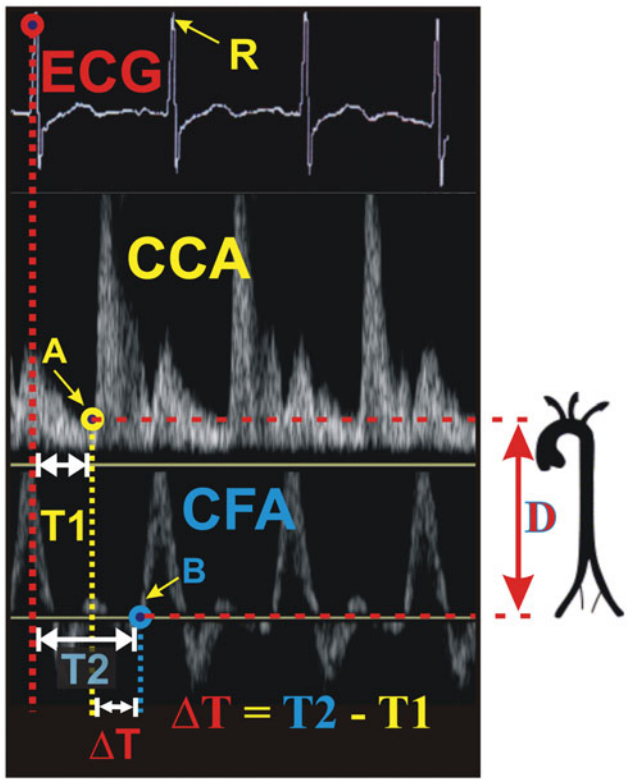


Figure 1. PWV determination: time diversity of electrocardiographic and Doppler signals. CCA, common carotid artery; CFA, common femoral artery; ΔT, transit time; D, carotid-femoral distance.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (IBM Co., Armonk, NY). Box-and-whisker plots exploratory graphics were created using MedCalc for Windows, version 12.2.1.0 (MedCalc Software, Ostend, Belgium). Results are presented as mean ± SD unless otherwise stated. Comparisons between groups were performed using the unpaired Student's *t*-test. All tests were two-sided. A value of $p < 0.05$ was considered to indicate statistical significance. Discrimination, the ability of a model to distinguish between patients who survive and patients who die (all-cause or cardiovascular) was assessed using receiver operating characteristic (ROC) curve analysis. If the area under curve is more than 0.5, the model had discriminatory power. Survival rates were analyzed using Kaplan–Meier survival curves. The Cox proportional hazards model was used to identify the independent determinants of mortality predictors. Baseline variables PWV and biochemical markers were added into the model. Backward stepwise elimination was applied to remove the insignificant variables. In order to avoid multicollinearity because 2 variables had VIF (variance inflation factor) around or greater than 5, we removed one of the variables from the regression model.

Results

Baseline characteristics of the participants

From December 2009 to December 2012, PWV measurements and other demographic and laboratory examinations were successfully conducted on 80 CHPs (at baseline) with a mean follow-up of 30.69 ± 9.93 months. Patients' demographics and clinical characteristics determined at the start of the study are shown in Table 1.

Demographic characteristics (gender, age, BMI, duration of dialysis, diabetes, hypertension and smoking status), circulating biomarkers (urea, creatinine, albumin protein status, lipid status and inflammatory factors) and PWV as crucial tissue biomarkers are shown in Table 1.

Table 1. Demographic and clinical variables in CHPs at baseline.

Variables	Values
Demographic characteristics	
Gender, male, *N* (%)	53 (66.25)
Age, years	59.3 + 11.8
BMI, kg/m^2	23.40 ± 3.60
Duration of dialysis, years	5.47 ± 5.16
Diabetes mellitus, *n* (%)	16 (20)
Hypertension, *n* (%)	37 (46.20)
Smokers, *n* (%)	20 (25)
Biochemistry	
Urea, mmol/L	20.89 + 5.25
Creatinine, mmol/L	730.61 ± 204.11
Hemoglobin, g/l	111.7 + 18.2
Total protein, g/L	67.30 + 6.33
Albumin, g/L	38.44 + 4.90
Cholesterol, mmol/L	4.25 + 1.16
LDL-cholesterol, mmol/L	2.3510.97
HDL-cholesterol, mmol/L	1.21 + 0.51
Triglycerides. mmol/L	1.42 + 0.61
C-reactive protein, mg/L	9.37 ± 7.63
Fibrinogen, g/L	4.37 ± 1.59
PWV, m/s	12.50 ± 2.01

Table 2. Causes of death in 23 chronic hemodialysis patients during three-year follow-up.

Cause of death	Number of patients (%)
Cardiovascular event	17 (73.90)
Myocardial infarction	4 (17.39)
Arrhythmia	2 (8.69)
Stroke	3 (13.04)
Congestive heart failure	2 (8.69)
Ventricular fibrillation	1 (4.35)
Pulmonary edema	2 (8.69)
Sudden cardiac death	3 (13.04)
Other causes	6 (26.10)
Malignant tumors	2 (8.69)
Diabetic coma	1 (4.35)
Gastrointestinal bleeding	1 (4.35)
Ketoacidosis	1 (4.35)
Infections	1 (4.35)

Follow-up and outcomes

During the 3-year follow-up period, 23 deaths (13 male and 10 female) were recorded, including 17 cardiovascular (10 male and 7 female) and 6 noncardiovascular events (3 male and 3 female) (Table 2).

The mean aortic PWV in the CHPs at baseline was: 12.50 ± 2.01 m/s (range 8.2–18.2), male 12.5 ± 2.3 m/s (range 8.2–18.2), female 12.4 ± 1.4 m/s range (8.9 ± 14.3).

Table 3. Comparison of clinical variables between patients who died and those who survived.

Variables	$N=57$	$N=23$	p
Demographic characteristics			
Gender, male, N (%)	40 (70.17)	13 (56.52)	0.299
Age, years	56.54 ± 11.96	66.13 ± 8.34	<0.001
BMI, kg/m^2	23.67 ± 3.42	23.77 ± 4.10	0.911
Duration of dialysis, years	5.79 ± 5.59	4.69 ± 3.92	0.392
Diabetes mellitus, n (%)	9 (15.78)	7 (30.43)	0.215
Hypertension, n (%)	26 (45.61)	11 (47.82)	1.000
Smokers, n (%)	17 (29.8)	3 (13.04)	0.157
Biochemistry			
Urea, mmol/L	21.58 ± 5.28	19.19 ± 4.86	0.105
Creatinine, µmol/L	757.30 ± 218.47	$664.46 + 147.26$	0.065
Hemoglobin, g/L	114.44 ± 18.29	104.95 ± 16.49	0.034
Total protein, g/L	67.87 ± 6.34	65.88 ± 6.85	0.218
Albumin, g/L	39.42 ± 4.75	36.03 ± 4.51	0.004
Cholesterol, mmol/L	4.29 ± 1.24	4.21 ± 1.09	0.788
LDL-cholesterol, mmol/L	$1.99 + 0.75$	2.50 ± 1.01	0.015
HDL-cholesterol, mmol/L	1.32 ± 0.47	1.17 ± 0.53	0.217
Triglycerides. mmol/L	1.40 ± 0.52	1.44 ± 0.79	0.791
C-reactive protein, mg/L	7.47 ± 3.26	14.09 ± 12.22	<0.001
Fibrinogen, g/L	$4.12 + 1.24$	$4.98 + 2.32$	0.225
PWV, m/s	11.26 ± 2.37	13.13 ± 1.70	<0.001

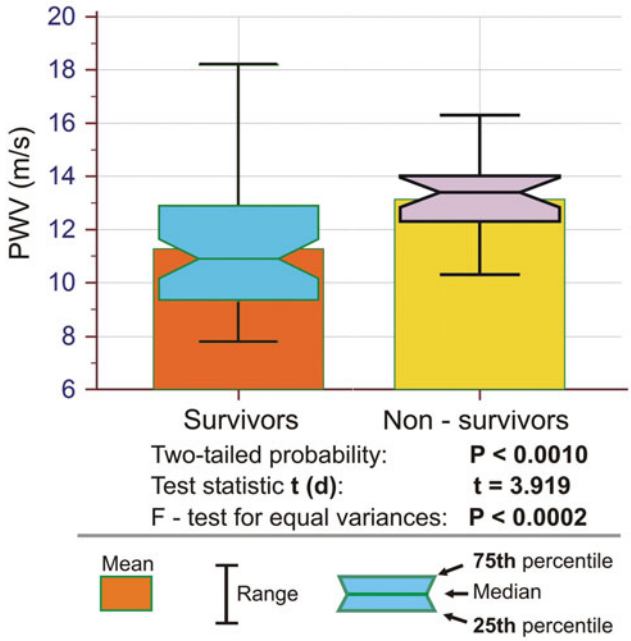


Figure 2. Mean values and distribution of PWV in 57 survivors and 23 nonsurvivors (A t test for unpaired data, two-tailed probability).

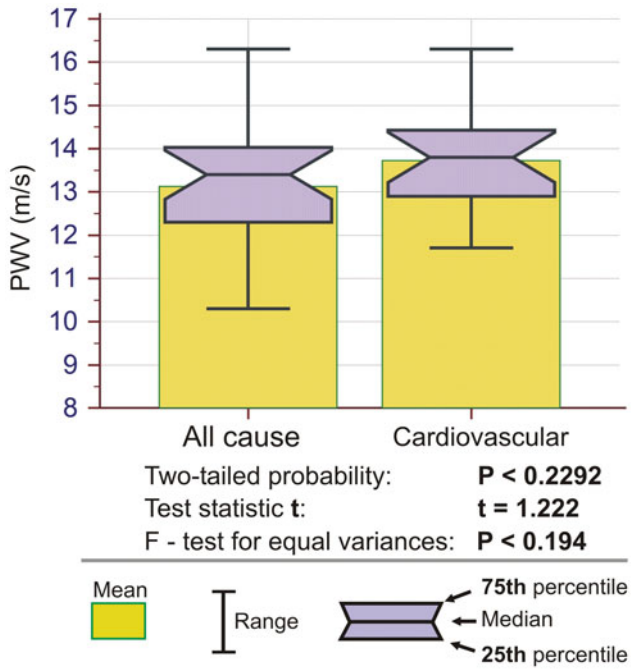


Figure 3. Mean values and distribution of PWV in deceased patients (23 all-causes vs. 17 cardiovascular) during three-year follow-up. A t test for unpaired data, two-tailed probability).

Patients outcomes comparison

Demographic and clinical variables in the patients who died and those that survived are shown in Table 3.

In the deceased group, age was significantly greater ($p<0.001$). Significantly greater in the same group were: CRP ($p<0.001$), PWV ($p<0.001$) and LDL-cholesterol ($p=0.015$). In the deceased group, albumin ($p=0.004$) and hemoglobin (0.034) were significantly lower. Total protein, total cholesterol, HDL-cholesterol, urea and creatinine were also lower in the deceased group. Duration of dialysis was lower than that in the survival group, but not significantly ($p=0.392$).

The mean PWV in survived CHPs was 11.26 ± 2.37 m/s and mean PWV in died CHPs was 13.13 ± 1.70 m/s. Before we made a decision about which test to use for comparison PWVs between the survivors and nonsurvivors groups, we made variance ratio (F test). As result from the data we got by variance ratio of 1.93 (5.627/2.915) and significance level of $p=0.091$, as well as from the different number of participants (53 survivors and 23 nonsurvivors) in the groups, we decided to use t test for unpaired data. When assuming unequal variances (Figure 2), we present Welch-test statistic as $t(d)$. In comparison with survivors, nonsurvivors had a significantly higher median PWV (13.4 m/s vs. 10.9 m/s, respectively) and significantly higher mean value for PWV (13.13 m/s and 11.26 m/s, respectively, $p<0.001$).

Patients mortality comparison

The mean PWV in deceased patients (overall death) was 13.13 ± 1.70 m/s and mean PWV in deceased patients from cardiovascular disease cause was 13.72 ± 1.24 m/s. Because of the unequal number of the participants in both the examined groups (23 vs. 17) and the variance ratio test (F test) results (variance ratio 1.894, $p=0.194$), we made t test for unpaired data (Figure 3). There is no statistical significance between mean PWV in all-cause and cardiovascular cause ($p=0.2292$). There is no statistically significance between median PWV in deceased from all-cause and CV mortality (13.4 m/s vs. 13.8, respectively, $p=0.285$) too.

Estimation of cutoff point

We used discrimination, the ability of a model to distinguish patients who survived and who died. We assessed them by receiver operating characteristic (ROC) curve analysis.

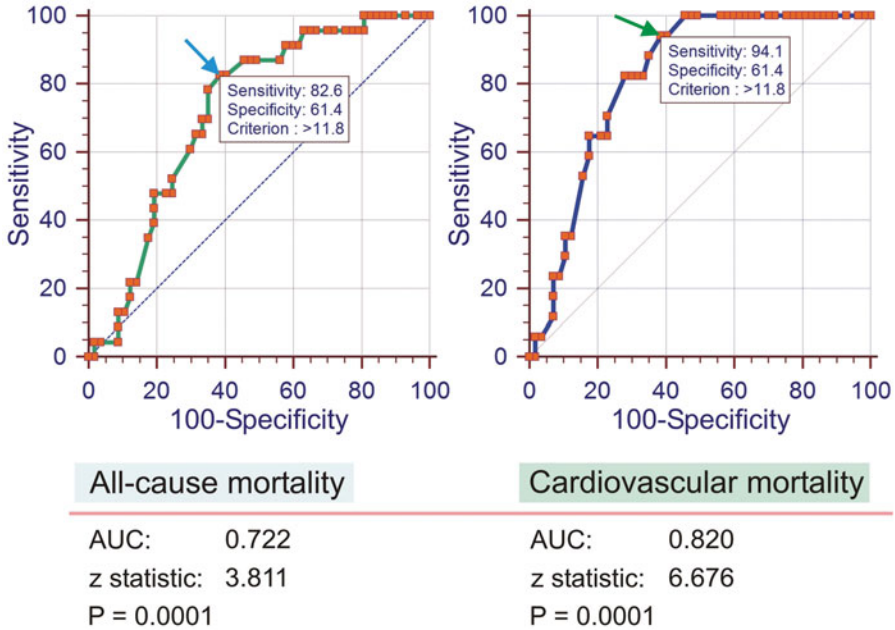


Figure 4. Receiver operating characteristics (ROC) curves for PWV as a predictor of death (all-cause and cardiovascular mortality).

Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold (PWV in the detection of cardiovascular and overall mortality).

Area under curve was 0.722, z-statistic was 3.811 and significance level p was smaller than 0.0001 (area = 0.5) in ROC curve for PWV as a predictor of all-cause mortality. The 95% confidence interval for the mean was 0.610–0.816. The PWV cutoff point value where the sensitivity and specificity were highest (82.6% and 61.4%, respectively) was 11.8 m/s. The results we got by ROC curve analysis in MedCalc 12.2.1.0. for cardiovascular event among CHPs were: area under curve (0.820), z statistic (6.676) and significance level ($p < 0.0001$). The 95% confidence interval for the mean was 0.714–0.900. The PWV cutoff point, for group with cardiovascular cause of death, where the sensitivity and specificity were highest (94.1% and 61.4%, respectively) was 11.8 m/s (Figure 4).

Comparing the ROC curves we got following results: difference (0.098), standard error (0.075), z statistic (1.302) and significance level ($p = 0.193$). There is no statistically significant difference between PWV cutoff point estimated by ROC curves for PWV as a predictor of death in all cause and cardiovascular mortality.

Creation of subgroups and comparison between them

Using this PWV value as a cutoff point, the patients were divided into two subgroups according to the mean value of PWV at baseline. Subgroup 1 included patients with PWV $\geq$ 11.8 m/s and subgroup 2 consisted of patients with PWV values below the cutoff point (PWV < 11.8 m/s). We analyzed a total of 80 chronic hemodialysis patients. PWV greater than or equal to cutoff point of 11.8 m/s was found in as many as 42 patients (25 male, 17 female). Thirty-eight patients (28 male, 10 female) had PWV less than 11.8 m/s.

The mean PWV in 42 patients from subgroup 1 was 13.65 ± 1.32 m/s (95% CI for the mean was 13.234–14.061). The mean PWV in 38 patients from subgroup 2 was 9.76 ± 1.29 m/s (95% CI for the mean was 9.332–10.183). Patients from both subgroups were predominantly male (59.52% in subgroup 1 and 73.68% in subgroup 2). In the subgroup 1, age was significantly greater ($p < 0.001$). Significantly greater in the same subgroup were: duration of dialysis ($p = 0.003$), C-reactive protein ($p = 0.010$), fibrinogen ($p = 0.024$) and PWV ($p < 0.001$), but HDL-cholesterol was significantly lower ($p = 0.042$). Total protein and albumin were also lower in the subgroup 1, but not significantly ($p = 0.421$ and $p = 0.250$, respectively). Urea, creatinine, cholesterol, LDL-cholesterol and triglycerides were also assessed in both subgroup; there were no statistically significant differences among them. Their values were greater in subgroup 1, than in another subgroup 2.

The comparison of mean PWV values between two subgroups by t test for unpaired data is presented in Figure 5. The mean, range, 25th and 75th percentiles, t statistic (13.245), F value for equal variances ($p = 0.877$) and two-tailed probability ($p < 0.0001$) are also shown (Figure 5). There was high statistically significance between the mean PWV in the subgroup 1 and subgroup 2 (13.65 ± 1.32 and 9.76 ± 1.29, $p < 0.001$).

In the CHPs with PWV above the cutoff value (subgroup 1, $n = 42$) there were 19 lethal outcomes (45.23%): 16 cardiovascular events (38.09%) and 3 non-cardiovascular (7.14%). Four lethal outcomes (10.52%) were registered in group with PWV below the cutoff value (subgroup 2, $n = 38$): 1 cardiovascular event (2.63%) and 3 (7.89%) from another, non-cardiovascular etiology.

Relative risk for exposed groups according to all-cause events was 4.2976 (95% CI = 1.6051–11.5071), $p = 0.0037$, z statistic was 2.902. There was a about 4-fold increased risk in subgroup 1, and this increase is statistically significant ($p = 0.0037$). Relative risk for exposed groups according cardiovascular events was 14.3590 (95% CI = 2.0063–102.7686), $p = 0.0080$, z statistic was 2.653. There was a about 14-fold increased risk in subgroup 1, and this increase is statistically significant ($p = 0.0080$).

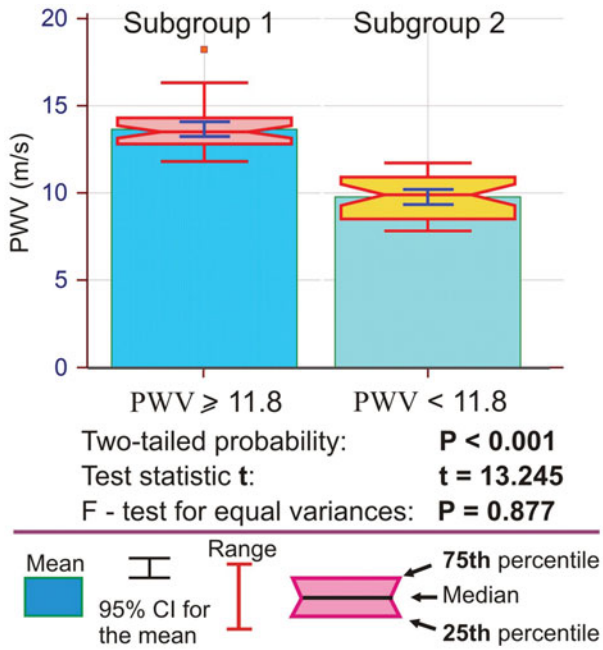


Figure 5. Mean values and distribution of PWV in two subgroups according PWV cutoff. A *t* test for unpaired data, two-tailed probability.

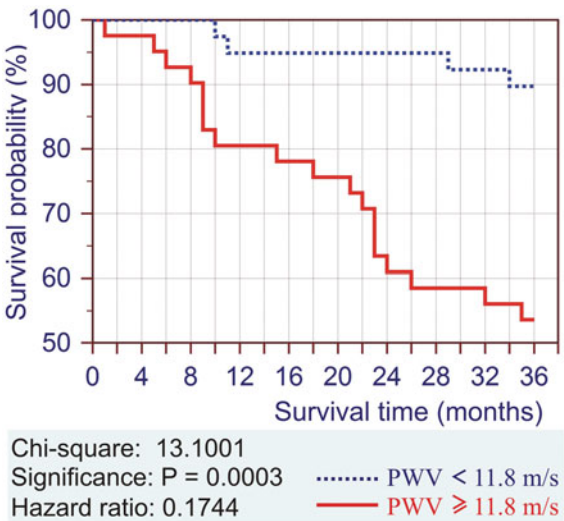


Figure 6. Kaplan–Meier estimates of survival of hemodialysis patients during three-year follow-up with respect of PWV cutoff value.

Kaplan–Meier survival

A plot of the Kaplan–Meier estimate of the survival function presented as series of horizontal steps of declining magnitude, approaching the true survival function in CHPs is shown in Figure 6. Vertical drop indicates an event.

When we compared 2 survival curves (subgroup 1 [PWV $\geq$ 11.8 m/s] and subgroup 2 [PWV $<$ 11.8 m/s], Logrank test) we got these results: Chi-square = 13.1001; DF = 1; Significance = 0.0003; Hazard ratio = 0.1744, 95% CI (0.0767–0.3965). Significantly higher mortality was observed in patients with PWV $\geq$ 11.8 m/s ($p < 0.001$) (Figure 7).

When we compared 2 survival curves (all-cause and cardiovascular, Logrank test) we got these results: Chi-square = 0.9129; DF = 1; Significance = 0.3393; Hazard ratio = 0.7391, 95% CI (0.3977–1.3737).

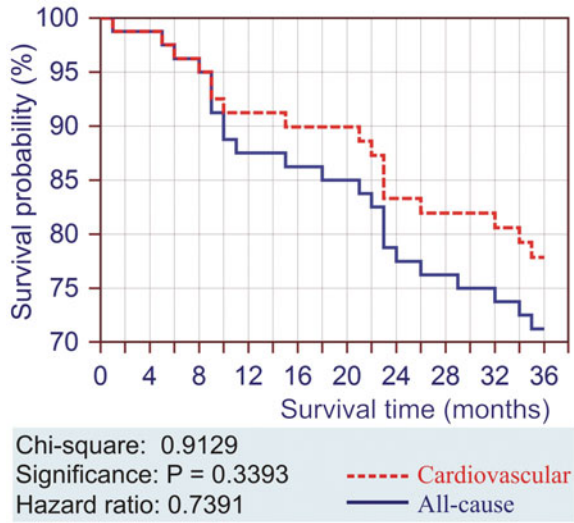


Figure 7. Kaplan–Meier estimates of survival of hemodialysis patients during three-year follow-up according causes of death.

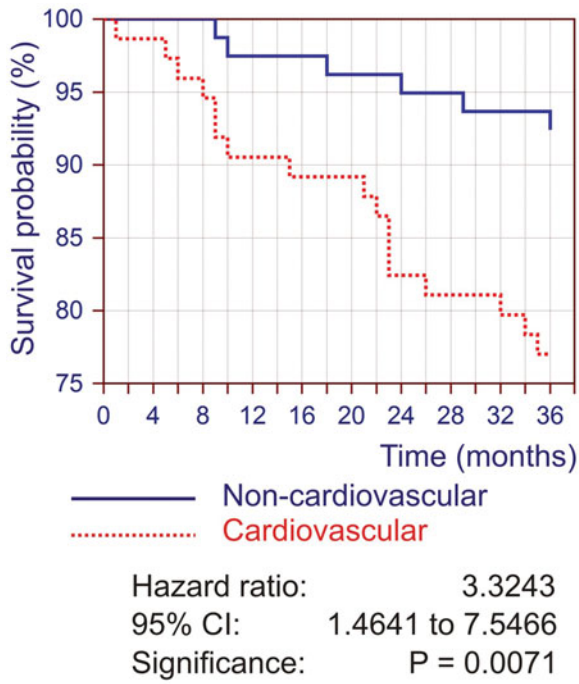
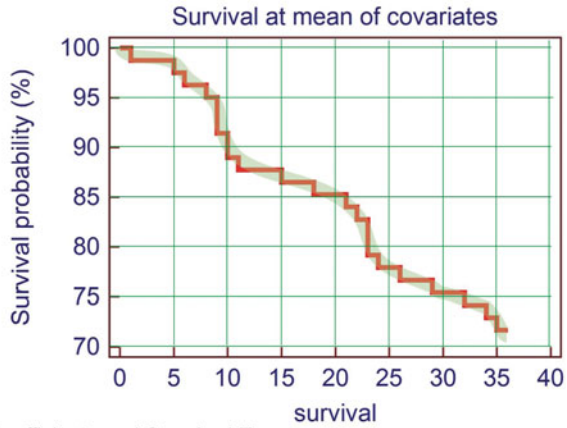


Figure 8. Kaplan–Meier estimates of survival of hemodialysis patients during three-year follow-up according non-cardiovascular or cardiovascular events (comparison of survival curves (Logrank test).

We did not find statistically significant difference between all-cause and cardiovascular mortality in CHPs. When we compared survival curves plotted by 6 non-cardiovascular outcomes and 17 cardiovascular events, we got these results: Chi-square = 7.243, DF = 1, $p = 0.0071$, Hazard ratio = 3.324 and 95% CI = 1.4661–7.5477, Endpoint *n*: observed 6.0 and 17; Expected *n*: 12.4 and 10.6 (comparison of survival curves, Logrank test). This curves plot is presented in Figure 8.

Cox-regression analysis

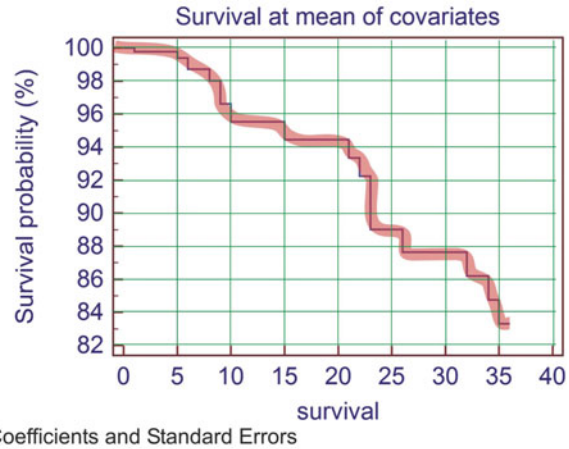
Assessments (regression coefficient [b], hazard ratio coefficient Exp [b], *p* value, standard error [SE] and 95% CI



Coefficients and Standard Errors

Covariate	b	SE	P	Exp(b)	95% CI of Exp(b)
PWV	0.2617	0.0873	**0.0027**	1.2992	1.0957 to 1.5403
CRP	0.0776	0.0198	**0.0001**	1.0807	1.0040 to 1.1233
Albumin	-0.1302	0.0498	**0.0089**	0.8779	0.7966 to 0.9674

Figure 9. Cox-regression survival analysis (predictors of all-cause outcome).



Coefficients and Standard Errors

Covariate	b	SE	P	Exp(b)	95% CI of Exp(b)
PWV	0.3569	0.1027	**0.0005**	1.4289	1.1696 to 1.7457
CRP	0.0832	0.0211	**0.0001**	1.0868	1.0430 to 1.1325
Albumin	-0.1881	0.0633	**0.0030**	0.8285	0.7322 to 0.9375

Figure 10. Cox-regression survival analysis (predictors of cardiovascular outcome).

[confidence interval] of Exp [b]) of independent predictors for all-cause outcome after Cox-regression model analysis are shown in Figure 9.

During the follow-up period, 23 deaths were recorded. According to the Cox-regression analysis, the significant covariates retained by the model (backward stepwise) were only PWV, CRP and albumin (Figure 9).

Covariates with positive regression coefficients (b), PWV (0.2617) and CRP (0.0776) are associated with increased hazard and decreased survival times, i.e. as predictors (PWV and CRP) increases, the hazard of the all-cause events and the predicted survival duration decreases. Albumin, as covariate with negative regression coefficient (b) (−0.1302), indicates decreased hazard and increased survival time. The predictor PWV has an Exp (b) hazard ratio coefficient of 1.2992. The hazard ratio (HR) increases by 1.2992 (29.92%) with each unit increase in PWV. The HR increases by 1.0807 (8.07%) with each unit increase of CRP, too. Albumin indicate hazard ratio decreased by 1.14 (1/0.8779) or 13.9% with each unit increase by self. Predictor variable coefficients of statistical significance p values followed the order of: CRP (0.0001), PWV (0.0027) and albumin (0.0089).

Assessments (regression coefficient [b], hazard ratio coefficient Exp [b], p value, standard error [SE] and 95% CI [confidence interval] of Exp [b]) of independent predictors for cardiovascular outcome after Cox-regression model analysis are shown in Figure 10.

During the follow-up period, 17 cardiovascular deaths occurred. Because of the strong inter correlation of age with PWV ($r = 0.599$, $p < 0.0001$) we did not enter age in both Cox-regression analysis. According to the Cox-regression analysis, the significant covariates retained by the model (backward stepwise) were only PWV, CRP and albumin (Figure 10).

Covariates with positive regression coefficients (b), PWV (0.3569) and CRP (0.0832) are predictors of the cardiovascular events. They indicate decreased hazard and increased survival time. Albumin, as covariate with negative regression coefficient (b) (−0.1881), indicate decreased hazard and increased survival time. The predictor PWV has an Exp (b) hazard ratio coefficient of 1.4289. The HR increases by 1.4289 (42.89%) with each unit increase in PWV and increases by 1.0868 (8.68%) in CRP. Albumin indicate hazard ratio decreased by 1.2070 (1/0.8285) or 20.7% with each unit increase by self. Covariate coefficients of statistical significance p values followed the order of: CRP (0.0001), PWV (0.0005) and albumin (0.0030).

The mean values of covariates are taken as referent values for comparison when calculating the Exp (b) hazard ratio coefficients: PWV (11.8), CRP (9.37) and albumin (38.44) in all-cause mortality Cox-regression analysis; PWV (11.8), CRP (9.57) and albumin (38.40) in cardiovascular mortality Cox-regression analysis. A reference value of PWV covariate is identical with its cut-off point of 11.8 m/s.

Discussion

In this prospective observational cohort study with 3 years of follow-up, we studied a cohort of 80 chronic hemodialysis patients with a mean follow-up of 30.69 ± 9.93 months. Each participant was subjected to noninvasive diagnostic Doppler ultrasonography and blood biochemistry tests.

Among the different methods of evaluating arterial stiffness, the most widely used in the literature is aortic PWV, specifically in the area running from the aortic arch or common carotid artery (CCA) to the common femoral artery (CFA). Typically, the pulse wave is detected by pressure transducers or arterial tonometry, but we used Doppler ultrasonography for PWV determination.

The purpose of this study was to investigate all-cause and cardiovascular mortality in the patients undergoing hemodialysis and to identify the determinants of mortality predictors. Cardiovascular disease still remains the main cause of death in chronic hemodialysis patients. Are the traditional risks factors for atherosclerosis sufficient alone to describe high prevalence of CV disease in this condition? The traditional

risk factors for atherosclerosis (age, elevated blood pressure, smoking status, low levels of HDL cholesterol, high levels of LDL cholesterol and triglycerides, obesities and diabetes) interact to initiate atherosclerosis and promote the development of CV disease have enhanced our ability to assess risk in individual patient. In addition, understanding of new, so-called novel risk factors (C-reactive protein, homocysteine, plasma fibrinogen, interleukin-10, impaired glucose tolerance and metabolic syndrome) and when these are included along with the classic risk factors in assessing the global risk profile, may improve ability to predict future risk precisely. In uremic patients, traditional risk factors are added to specific, disease-related (inflammation and malnutrition) and treatment-related risk factors (incompatibility of dialysis membrane and dialysis adequacy).[7]

The start point for making visible differences in circulating and tissue markers of atherosclerosis, between survived and nonsurvival participants, is to compare them. Statistical significance of some demographic and biochemical markers in survived/died hemodialysis patients may play a crucial role in initiating the detection of factors associated with the genesis of atherosclerosis. We found statistically significant difference in: ages (<0.001), hemoglobin (0.034), albumin (0.004), LDL-cholesterol (0.015), CRP (0.001) and PWV (<0.001) between both groups (survived vs. nonsurvival, see Table 3). Higher absolute creatinine concentration (757.30 vs. 664.46, survived/died respectively) in survived group was associated with greater use of dialysis, but lower overall mortality in adjusted analyses.[8] The relative risk of death was lower in patients with higher levels of serum creatinine.[9] The multivariate Cox-regression analysis in many studies demonstrated that ESRD patients with CRP $\geq$ 10 mg/L, decrease of 1 g/L in serum albumin and PWV $\geq$ 12 m/s were associated with increased risk of cardiovascular and over-all mortality. Hemodialysis patients with low hemoglobin (<110 g/L) and albumin (<40 g/L) are at more risk for early deaths than patients with normal hemoglobin and albumin.[10]

In the present study, we measured PWV, which is as a marker of aortic stiffness, since it is related to the square root of the vessels elasticity modulus and to the thickness/radius ratio. The PWV determined from foot-to-foot transit time in the aorta offers a simple, reproducible, and noninvasive evaluation of regional aortic stiffness.[11] PWV is a direct method for measuring aortic stiffness. It is a simple, non-invasive and robust method, easy to implement in clinical practice. Comparing the PWV results in survivors (11.26 ± 2.37 m/s) and nonsurvivors (13.13 ± 1.70 m/s), we got significantly ($p < 0.001$) higher PWV in deceased patients. PWV in deceased patients from cardiovascular disease is more pronounced, it is equal to 13.72 ± 1.24 m/s ($p < 0.001$). At first sight, it is not very big difference, only about two and half meters. But, if we know the fact, that an increase of aortic PWV by 1 m/s correspond to an age, sex and risk factor adjusted, risk increase of 14%, 15% and 15% in total CV events, CV mortality and all-cause mortality, respectively, the abovementioned fact is not for underestimation. An increase in aortic PWV by 1 SD (standard deviation) was associated with respective increases[12] of 47%, 47% and 42%.

Comparison of PWV among deceased patients from all-cause and cardiovascular mortality did not present statistical significance ($p < 0.2292$). Because of that fact, we had to find another way of division and comparison between CHPs, taking into account the value of PWV in the patients with lethal outcome, independently of cause for that event. The most relevant way of structuring the comparison groups, in order to obtain the statistical significance between them is grouping by cutoff PWV value. The point with highest pair of sensitivity and specificity on ROC curves for PWV as a predictor of death (Figure 4) was identical (PWV = 11.8 m/s) for both cause of death in CHPs, with more pronounced sensitivity in prediction of cardiovascular mortality than an overall mortality (94.1 vs. 82.6, respectively). Despite these small differences in ROC curves, however, no statistical significant difference is registered between them with respect of reason of cause of mortality.

We found that the PWV cutoff point of 11.8 m/s was predictive of increased mortality in our CHPs, especially for cardiovascular mortality. However, different studies have determined different cutoff points of PWV that were predictive of increased overall and cardiovascular mortality. The cutoff point of 12 m/s or greater was chosen based upon a study demonstrating this to be the level associated with clinically significant negative prognosis in patients with ESRD.[13] Considering the fact that the mean value of PWV is 8.3 m/s and median of 8.2 m/s (mean age 61.0 years) in the general population,[14] the majority of patients with ESRD could be considered to have increased arterial stiffness and elevated PWV (our results: PWV = 12.50 m/s, mean age 59.3) as results of accelerated atherosclerosis. Because this fact is common in CHPs, increased arterial stiffness has recently become intensively investigated as a major novel cardiovascular risk factor. It is well known that vessels stiffen as age increases because of an overproduction of abnormal collagen fibers and a relative loss of elastin in the extracellular matrix of arteries.[15] In the present study, age at inclusion was a strong predictor of cardiovascular and overall mortality, but this parameter did not enter the multivariate Cox analysis partly because of its strong inter correlation with PWV ($r = 0.599$, $p < 0.0001$). PWV value was also positively correlated with patient age in other studies that estimate the PWV and got similar to our results ($r = 0.592$, $p = 0.0001$).

When we considered the PWV of 11.8 m/s as relevant cutoff point speed, for all-cause and especially for cardiovascular mortality prediction, we made two different subgroups. There was statistically significant differences between subgroup 1 and subgroup 2 ($p < 0.001$) according PWV value (13.65 ± 1.32 vs. 9.76 ± 1.29 respectively). Age, HDL-cholesterol, CRP and fibrinogen also show statistically significant differences when we compared between this two subgroup, too (Table 4). A plot of the Kaplan–Meier estimate of the survival function as the function of cutoff PWV (Logrank test) present significantly higher mortality in patients with PWV $\geq$ 11.8 m/s ($p < 0.001$, Figure 6). The conclusion is that, the two survival curves (PWV < 11.8 m/s and PWV $\geq$ 11.8 m/s) differ significantly, or that the grouping variable has a significant influence on survival time.

Consider the facts that mean PWV (13.65 ± 1.32 m/s), mean fibrinogen concentration (4.7 ± 1.63 g/L), mean CRP (11.43 ± 9.63 mg/L) and mean HDL-cholesterol (1.09 ± 0.43 mmol/L) the majority of patients with PWV

Table 4. Demographic and biochemistry characteristics of chronic dialysis patients by cutoff point of PWV.

	PWV (m/s)		
	Subgroup 1	Subgroup 2	
	>11.8	<11.8	*p*
Demographic characteristics	N = 42	N = 38	
Gender, male, *N* (%)	25 (59.52)	28 (73.68)	0.238
Age, years	65.97 ± 9.72	51.92 ± 9.29	<0.001
BMI, kg/m^2	23.57 ± 3.56	23.85 ± 3.69	0.731
Duration of dialysis, years	7.07 ± 6.09	3.71 ± 3.12	0.003
Diabetes mellitus, *n* (%)	9 (21.43)	7 (18.42)	0.786
Hypertension, *n* (%)	15 (35.71)	22 (57)	0.072
Smokers, *n* (%)	5 (11.9)	12 (31.57)	0.054
Biochemistry			
Urea, mmol/L	21.48 ± 5.42	20.24 + 5.05	0.294
Creatinine, μmol/L	734.18 ± 170.82	726.66 ± 237.88	0.870
Hemoglobin, g/l	113.95 + 19.86	109.24 ± 16.09	0.250
Total protein, g/L	66.75 ± 5.85	67.90 ± 6.85	0.421
Albumin, g/L	37.84 ± 4.92	39.11 ± 4.87	0.250
Cholesterol, mmol/L	4.29 ± 1.24	4.21 + 1.09	0.761
LDL-cholesterol, mmol/L	2.55 ± 1.04	2.18 ± 0.87	0.090
HDL-cholesterol, mmol/L	1.09 ± 0.43	1.32 ± 0.56	0.042
Triglycerides. mmol/L	1.45 ± 0.66	1.37 ± 0.56	0.563
C-reactive protein, mg/L	11.43 ± 9.63	7.10 ± 3.37	0.010
Fibrinogen, g/L	4.70 ± 1.93	3.9 ± 0.98	0.024
PWV, m/s	13.65 ± 1.32	9.76 ± 1.29	<0.001

greater than or equal to 11.8 m/s (subgroup 1) could be considered to have rigid blood vessels, chronic inflammation, suggesting that inflammation may be involved in arterial stiffening. Anti-inflammatory strategies may, therefore, be of benefit in reducing arterial stiffness and thus cardiovascular risk, especially in patients with premature arterial stiffening.[16]

Elevated serum triglycerides and low level of HDL-cholesterol, reported as elevated serum triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL) constitute a risk for insulin resistance and increased arterial stiffness is evident in subgroup 1 (TG/HDL = 1.5 ± 0.88) than in subgroup 2 (TG/HDL = 1.32 ± 0.81).[17]

There was a more than 4-fold increased relative risk for lethal outcomes (all-causes mortality) in subgroup 1 with more stiffened arteries (PWV ≥ 11.8 m/s, P = 0.0037). Relative risk for exposed groups according cardiovascular lethal outcomes was a about 14-fold increased risk in subgroup 1 (PWV < 11.8 m/s, P = 0.0080). Taking into consideration above mentioned arguments, it remains to be demonstrated whether PWV, which is a major determinant of arterial stiffness, has any independent prognostic relevance for all-cause and CV mortality. Several mechanisms may explain the association between increased PWV and CV mortality. Arterial stiffness is a cause of premature return of reflected waves in late systole, increasing central pulse pressure and the load on the ventricle, reducing ejection fraction and increasing myocardial oxygen demand. Arterial stiffness is correlated with atherosclerosis probably through the effects of cyclic stress on arterial wall thickening.[17] Significant increase in mortality was evidenced in patients belonging to the 1 group, especially when we compared CV to non-CV events (Logrank test) by cutoff PWV. Comparison of two plotted curves according to CV and non-CV (Figure 8) give a hazard ratio of 3.3243 ($p = 0.0071$) for significant increase in CV mortality.

According to the Cox-regression analysis, the significant covariates with positive regression coefficients were PWV and CRP, as predictors which increased the hazard and decreased survival times of all-cause and cardiovascular lethal outcomes. Albumin, as predictor with negative regression coefficient, decreased the hazard and increased survival time of all-cause and cardiovascular lethal outcomes.

The HR of CV mortality were higher for high aortic PWV (subgroup 1, PWV ≥ 11.8 m/s) compared with low aortic PWV subjects from subgroup 2 (HR = 1.43). The HR of CV mortality for an increase in aortic PWV by 1 m/s was 1.43, corresponding to a risk increase of 42.89%. The HR increases by 1.30 with each unit increase of aortic PWV, corresponding to a risk increase of 29.92% in all-cause outcomes. The significance of the impact of increased PWV is apparent when we show the values of relative risk for exposed groups: more than 14-fold increased risk according CV lethal outcomes and about 4-fold increased risk according all-cause lethal outcomes, comparing two subgroups (PWV cutoff 11.8 m/s). The HR of CV mortality for an increase in CRP by each unit was 1.09 corresponding to a risk increase of 8.68%. The HR increases by 1.08 with each unit increase of CRP, corresponding to a risk increase of 8.07% in all-cause outcomes. Albumin indicate HR decreased by 1.21 (20.7%) and 1.14 (13.9%) with each unit increase by self, in CV and all-cause lethal outcomes, respectively.

Hypoalbuminemia is associated with poor prognosis in patients with certain chronic diseases, such as end-stage renal disease and cancer. Like the authors of previous studies of patients with renal disease,[18] we found that the serum albumin concentration was the powerful independent predictor of all-cause (HR = 1.14, $p = 0.009$) and CV death (HR = 1.21, $p = 0.003$). The close correlation between lower serum albumin and increased PWV might be explained by the fact that hypoalbuminemia was associated with increased oxidative stress in dialysis patients. Using plasma protein thiol oxidation and protein carbonyl formation as inductor of oxidative, Danielski et al.[18] found that oxidative stress was significantly elevated in hypoalbuminemia group compared with normoalbuminuria group. Increased oxidative stress, in turn, could accelerate atherosclerosis process with the consequence of arterial stiffness increase.

When evaluating the role of an elevated s-CRP as a predictor of mortality, it should be pointed out that inflammation might be involved both in factors predisposing to malnutrition or hypoalbuminemia and to atherosclerotic CVD. Proinflammatory cytokines can adversely affect nutrition by inducing proteolysisin muscle, increasing energy expenditure, and inhibiting appetite.[19] They also reported that CRP was negatively correlated with albumin, suggesting that inflammation had induced hypoalbuminemia as part of the acute-phase response. The malnourished patients also had higher plasma levels of lipoprotein (a) and fibrinogen, two acute-phase reactants considered to be independent atherogenic factors in the general population.[20] Because malnutrition (albumin, 20.7% HR), inflammation (CRP, 42.9% HR) and increased arterial stiffness (PWV, 8.68% HR) are significant independent risk factors of mortality that frequently coincide, one might expect that the CV death risk (%) should increase in patients with more than one of these

factors present. Several recent studies have confirmed that inflammation, as reflected by elevated levels of serum CRP or proinflammatory cytokines, are significant independent predictors of mortality in hemodialysis patients.[21]

Importantly, the predictive value of increased arterial stiffness is larger in patients with higher risk disease states, such as renal disease. Although for each patient group exact values may differ slightly, for an increase in aortic PWV of 1 m/s or of 1 SD, the risk increases by more than 10% or 40%, (all-cause and CV mortality) respectively. Aortic PWV may represent a surrogate end point, which may in fact indicate in which patients the traditional CV risk factors translate into real risk. Summary comparative results from meta-analysis of the predictive value of aortic stiffness (carotid-femoral PWV) for all-cause and CV events are presented by Vlachopoulos et al.[22] – HR: 1.63 for CV, 1.61 for all-cause mortality;[11] HR: 1.44 for CV, 1.35 for all-cause mortality;[23] HR: 1.20 for CV, 1.14 for all-cause mortality.[24]

The principal finding of our study was that joint effects of PWV, CRP and serum albumin were strongly and independently predictive of outcome in CHP. Whether enhanced arterial stiffness is a risk factor contributing to the development of CV disease or is a marker of established CV disease is a matter of debate.[25] The salient finding of our study was that, in CHPs, PWV was a strong independent predictor of over-all and cardiovascular mortality with high-level performance values, assessed by simple, indirect, reproducible and noninvasive evaluation of regional arterial stiffness.

Limitations

This study had several limitations. Firstly, the critical factors during PWV estimations were the transit time (ΔT) and the length of the vascular segment (D). Underestimation of measured travel path may result with error during transcutaneous access of vessels, especially in tortuous aorta in elderly patients. Second, we had no data of circulating and tissue markers at the time of overall and cardiovascular death event. The third limitation is that, no invasive catheter measurements, which are considered the gold standard, were acquired in this study. However, PWV has previously been validated against pressure catheters.[26]

In conclusion, the current study's findings suggest that PWV as measure of arterial stiffness, CRP as a prototypical positive acute phase protein and serum albumin as a negative acute phase protein are strong independent predictors of overall and CV mortality in patients undergoing dialysis. A standard PWV cutoff point in CHP should be further investigated and estimated by large clinical studies. By incorporating PWV measurements into standard regular diagnostic assessments for CV and clinic estimation, the patients who are at increased CV risk can be pinpointed earlier, with a recommendation for preventive appropriate stiffness reduction therapy starting.

Declaration of interest

No potential conflict of interest relevant to this article reported.

References

1. Marina C, Phil C. Role of arterial stiffness in cardiovascular disease. *J R Soc Med Cardiol.* 2012;1:4–11.
2. Zaccali C, Mallamaci F, Tripepi G. Traditional and emerging cardiovascular risk factors in end-stage renal disease. *Kidney Int Suppl.* 2003;6:105–110.
3. Safar ME, Henry O, Meaume S. Aortic pulse wave velocity: an independent marker of cardiovascular risk. *Am J Geriatr Cardiol.* 2002;11:295–304.
4. London GM, Marchais SJ, Metivier F, Pannier B. Vascular and cardiac remodeling in end-stage renal disease. *Nefrologia.* 1997;18: 17–21.
5. Antonio B, Emiliana F, Carlo R. Arterial stiffness in chronic kidney disease: the usefulness of a marker of vascular damage. *Int J Nephrol.* 2011;5:73–78.
6. Calabia J, Torguet P, Garcia M, et al. Doppler ultrasound in the measurement of pulse wave velocity: agreement with the Complior method. *Cardiovasc Ultrasound.* 2011;9:1–13.
7. Selim G, Stojceva-Taneva O, Ivanovski N, et al. Inflammation and anaemia as predictors of cardiovascular mortality in hemodialysis patients. *Hippokratia.* 2007;11(1):39–43.
8. Wilson FP, Yang W, Feldman HI. Predictors of death and dialysis in severe AKI: the UPHS-AKI cohort. *Clin J Am Soc Nephrol.* 2013;8(4):527–537.
9. Goya SW, Geral AS, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke.* 1997;28:557–563.
10. Anees M, Ibrahim M. Anemia and hypoalbuminemia at initation of hemodialysis risk factor for survival of dialysis patients. *JCPSP.* 2009;19(12):776–780.
11. Blacher J, Asmar R, Djane S, et al. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension.* 1999;5:1111–1117.
12. Nichols WW, O'Rourke MF, Vlachopoulos C. Properties of the arterial wall. In: McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London: Edward Arnold; 1990:77–114.
13. Covic A, Haydar AA, Bhamra-Ariza P, et al. Aortic pulse wave velocity and arterial wave reflections predict the extent and severity of coronary artery disease in chronic kidney disease patients. *J Nephrol.* 2005;18:388–396.
14. Noriko I, Ryo M, Hideshi K, et al. Aortic pulse wave velocity predicts cardiovascular mortality in middle-aged and elderly Japanese men. *Circ J.* 2009;73:549–553.
15. Sipahiogly MH, Kucuk H, Unal A, et al. Impact of arterial stiffness on adverse cardiovascular outcomes and mortality in peritoneal dialysis patients. *Perit Dialysis Int.* 2012;32:73–80.
16. McEniery C., Yasmin, Maki-Petaja KM, et al. C-reactive protein is associated with arterial stiffness in apparently healthy individuals. *Arteriosclerosis Thrombosis Vascular Biol.* 2004;5:969–974.
17. Shimizu Y, Nakazato M, Sekita T, et al. Association of arterial stiffness and diabetes with triglycerides-to-HDL cholesterol ratio for Japanese men: the Nagasaki Islands study. *Atherosclerosis.* 2013;2:491–500.
18. Danielski M, Ikizler TA, McMonagle E, et al. Linkage of hypoalbuminemia, inflammation, and oxidative stress in patients receiving maintenance hemodialysis therapy. *Am J Kidney Dis.* 2003;42(2):286–294.
19. Chang HR, Bistrian B. The role of cytokines in the catabolic consequences of infection and injury. *J Parenter Enteral Nutr.* 1997;22:156–166.
20. Qureshi AR, Rashid AQ, Divino-Filho JC, et al. Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. *J Am Soc Nephrol.* 2002;13:28–36.
21. Owen WF, Lowrie EG. C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int.* 1998;54:627–636.
22. Vlachopoulos C, Aznaouridus K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *JAMA.* 2010; 55(13):1318–1327.
23. Shoji T, Emoto M, Shinohara K, et al. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *JASN.* 2001;12(10):2117–2124.

24. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation,* 2005;111:3384–3390.
25. El-Sayed H, Kevin RJ, Alan BM, Jean MS, Richard DW. Measuring aortic pulse wave velocity using high-field cardiovascular magnetic resonance: comparison of techniques. *J Cardiovasc Magn Reson.* 2010;12:26–31.
26. Blacher J, Guerin A, Pannier B, Marchais S, Safar M, London G. Impact of aortic stiffnesss on survival in end-stage renal disease. *Circulation.* 1999;99:2434–2439.