Serum Pentraxin3: Its Relationship with left Ventricular Mass Index and its role as a Predictor for Cardiovascular Mortality in Hemodialysis Patients

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Abstract

Background: Serum pentraxin3 (PTX3) is one of the inflammatory markers found to be increased in chronic kidney disease (CKD) patients on hemodialysis (HD). The cardiovascular (CV) mortality rate is very high in CKD patients. While PTX3 is associated with left ventricular diastolic dysfunction in cardiac patients, there was no previous work, that studied the relationship between serum PTX3 and echocardiographic abnormalities in HD patients. **Aim:**The aim of the study is to assess the role of serum PTX3 as a risk factor for CV mortality and its relationship with left ventricular mass index (LVMI) in HD patients. **Subjects and methods:**This is a prospective study including seventy-four patients on regular hemodialysis in dialysis unit in the Internal medicine department at the Mansoura university hospital, and fifteen healthy subjects. All patients were followed for 24 months for overall and CV mortality. Also, serum high-sensitivity C-reactive protein (hs CRP), and PTX3, and LV echocardiographic parameters were assessed**. Results:** Serum PTX 3 was higher in HD patients than healthy subjects and significantly higher in deceased HD patients than the survived ones, also PTX3 correlated with LVMI. In the multivariate cox regression analysis, a serum PTX3 was shown to be an independent predictor for CV mortality. **Conclusions**:Serum pentraxin3 can be considered not only as a predictor for cardiovascular mortality but also as a marker for left ventricular hypertrophy in hemodialysis patients.

Keywords: Pentraxin3, hemodialysis, mortality, LVMI

Introduction

Chronic kidney disease (CKD) is one of the major health problems worldwide, with high prevalence and incidence. There was a high risk of cardiovascular-related mortality in CKD patients. Although elevated traditional risk factors as; age, cigarette smoking, hypertension, diabetes mellitus, and dyslipidemia in CKD patients could partially explain the pathophysiological mechanism of cardiovascular disease (CVD) in CKD patients, there were other issues which could not be explained as the severity of these CV complications ***(1)***. The existence of endothelial dysfunction was associated with inflammation and increase the risk for cardiovascular (CV) mortality in patients with and without uremia ***(2)***. The presence of low-grade inflammation had been a prominent feature of CKD, consequently, leading to CVD and protein-energy wasting (PEW) ***(3).*** However, there was evidence suggesting that pro-inflammatory cytokine upregulated in CKD, the exact causes of this were unknown. Various dialysis-related conditions such as catheters use (for vascular access), inefficient dialyzer membrane biocompatibility, contamination of dialysate, endotoxins exposure, and back-leak of dialysate through dialysis membrane in hemodialysis (HD) might enhance maintenance of low-grade inflammatory response ***(4)***.

Pentraxins (PTXs) are considered as a superfamily of highly conserved proteins, which are characterized by a multimeric mainly pentameric structure ***(5)***. There are two subclasses of pentraxins, short and long pentraxins according to the length and structure of the molecules. The classic short pentraxins include both C-reactive protein (CRP) and serum amyloid P (SAP), which are produced by inflammatory signals in the liver ***(5,6)***. PTX3 is expressed mainly extrahepatically ***(7);*** it is produced directly from injured tissues, and so reflects the inflammatory state ***(8)***. It is considered as a new acute-phase reactant, which is synthesized by different types of cells including macrophages, monocytes, neutrophils, fibroblasts, endothelial cells, and vascular smooth muscle cells. There is a correlation between PTX3 and increase risk of vascular events ***(9, 10).***

There is a gradual increase of PTX3 with the decline in glomerular filtration rate (GFR) which may be explained by an impaired clearance, due to the large molecular weight (40.6 kDa) of PTX, or to the increase of its

synthesis and release after stimulation in peripheral tissues ***(11).*** Additionally, serum PTX3 levels are increased in different diseases, like myocardial infarction, sepsis, rheumatoid arthritis, and inflammatory reaction in the kidney disease ***(7, 12).***

On the other hand, the echocardiographic abnormalities are common in CKD patients ***(13)***, particularly left ventricular abnormalities (LV), both structural and functional (***14)***. The most frequent finding is LV hypertrophy (***15)***. Hypertrophy is mainly due to volume and pressure overload in patients with ESRD ***(16).*** LV dilatation is less frequent as it takes more time and needs more volume and pressure overload ***(17).*** Cytokines appear to be the chief mediators of renal injury and are associated with the development of LVH (***18)***. As well as, serum PTX3 is significantly associated with high LVMI, and E/e values, which indicate left ventricular diastolic dysfunction (LVDD) in patients with or without heart failure, and GFR ranging from 56.3 ±21.9 to 69.5 ± 17.8 ml/ min/1.73m^2 without obvious uremia (***19)***. No previous works studied sPTX3 relationship with echocardiographic abnormalities in HD patients. The current study hypothesized that serum pentraxin 3 concentration was associated with LVMI abnormalities in HD patients, and had a significant role in the prediction of CV mortality in those patients.

Subjects and methods

Study design and population

The study design was a prospective cohort study, which included seventy-four patients (34 males, 40 females) with chronic renal failure on regular hemodialysis in the Internal medicine department at the Mansoura university hospital (dialysis unit), and 15 healthy subjects as a control group for comparative analysis. All studied HD patients were followed for 24 months (from January of 2015 to January of 2017) and the CV and overall cause deaths were observed during the study period. Cardiovascular mortality was defined as death due to coronary artery disease as; myocardial infarction, stroke, or heart failure (HF). Hemodialysis patients received regular HD treatment three times a week (3-4 h) per session using bicarbonate dialysate and synthetic Low flux membranes., **Inclusion criteria:** Patients older than 18 years on HD or for more than 6 months**. Exclusion criteria** were clinical signs of acute infection, active inflammatory diseases, chronic pulmonary disease, diabetic patients, and those treated with immunosuppressive drugs. All participants signed consent to be

included in the study, and the study was approved by the local ethical committee of the Mansoura faculty of medicine.

All participants were subjected to history taking, clinical examination with stress on, blood pressure (BP) measurement: SBP and DBP were measured pre hemodialysis, post hemodialysis and every hour during the session using a mercury sphygmomanometer, then the average of BP was calculated, body mass index (BMI) was calculated by the formula of (post-dialysis weight in kg per height in m^2), Framingham risk score (FRS) was used to investigate the risk of cardiovascular disease. FRS was calculated based on the six coronary risk factors including age, gender, total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol, systolic BP, and smoking habits (***20)*.**

Laboratory investigations

Complete blood count (CBC), serum creatinine, high-sensitivity C-reactive protein (hs-CRP), lipid profile, serum PTX3(s PTX3), and erythrocyte sedimentation rate (ESR) were done. Pentraxine-3 was assayed using Human Pentraxine-3 ELISA Kit, Sun Red, Germany. The principal of the assay was a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) ***(21).***

Echocardiography

An expert echocardiographer, who was unaware of the patients' data, performed echocardiographic measurements according to the recommendations of the American Society of Echocardiography ***(22).*** Patients were examined while lying on the left lateral position in a semi-dark room, the M-mode assessment was done using (Medison Sono Ace 4 X6) device. **LV mass** was calculated by using the Devereux formula, **LVM** was standardized by dividing it to body surface area (BSA) [LVM/BSA], then expressed as LVM index **(LVMI)** ***(23)***. and LVH was diagnosed as LVM/BSA >95 g/m^2in women and >115 g/m^2in men ***(24)***. Left Ventricle End Diastolic Dimension (LVEDD), Inter-Ventricular Septum at end- Diastole (IVSD), Ejection Fraction (%) EF, and E/A {the mitral early diastolic peak flow velocity (E)to late diastole velocity (A)} were assessed by conventional pulsed doppler, but E1/A1 ratio by tissue doppler to assess LV diastolic function. Myocardial performance index (MPI) was calculated by the sum of the isovolumic contraction and relaxation times divided by the ejection time. It is considered as a reliable parameter for the global LV function ***(25)***.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 22.0. Qualitative data were described using the number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, the standard deviation for parametric data after testing normality using the Kolmogorov-Smirnov test. The significance of the obtained results was judged at the (0.05) level.

Data analysis

Qualitative data:

the Chi-Square test was used for comparison of 2 or more groups & Fischer Exact test was used as a correction for the Chi-Square test when more than 25% of cells count less than 5 in 2*2 tables.

Quantitative data between groups:

Student t-test & Mann-Whitney U test were used to compare 2 independent groups for parametric & non-Parametric tests, respectively.

Spearman's correlation:

Spearman's rank-order correlation was used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and/or ordinal variables.

Kaplan-Meier test using log-rank x^2 **& Cox regression was used to** detect the effect of risk factors & predictors affecting Cardiovascular mortality with the calculation of hazard ratio.

Results

The current study included 74 patients (34 males, 40 females) with CKD on regular HD for more than 6 months and 15 healthy subjects as a control group. In the comparison of baseline laboratory data, table (1) shows that there was a highly significant decrease in serum calcium ($p < 0.001$), a significant increase in serum phosphorus and inflammatory markers (ESR, hs CRP, and s PTX3) in CKD patients than the healthy control group ($p < 0.001$), while there were non-significant changes in alkaline phosphatase levels in both groups.

The comparison of demographic data, and laboratory, and echocardiographic findings between HD patients who were deceased and survived were revealed in table (2). Deceased patients were older than survived ones. There were significantly lower Hb and serum albumin levels in patients who were deceased than those who survived. But there were significantly higher serum calcium, phosphorus, and alkaline phosphatase levels, all inflammatory markers (s PTX3, hs-CRP,

ESR), systolic BP, and values of echocardiographic parameters [LVM, LVMI, IVSD] in deceased than survived patients. However, gender, BMI, dialysis duration, number of patients with HCV positive AB, other echocardiographic parameters (EF%, E/A, E1/A1, MPI, LVDD) were comparable between the two groups.

Table 3 shows a highly significant negative correlation between Hb, and serum albumin levels and s PTX3. While, there was a significant positive correlation between serum creatinine, BUN, ESR, hs-CRP, and FRS and s PTX3. Also, there was a significant positive correlation between LVM, LVMI, and IVSD and s PTX3. However, there was a non-significant correlation between MPI and s PTX3.

Risk factors affecting CV survival among HD patients were shown in table 4. HD patients over fifty-year-old had a higher CV mortality risk. Hypercalcemia and elevated alkaline phosphatase levels were of greater risk of CV mortality and lower levels were linked with better survival. Increased inflammatory markers (hs CRP and s PTX3) were highly predictive of CV mortality during 24 months, also higher FRS values were associated with higher CV mortality risk. Kaplan Meier curve for overall survival among studied cases is presented in fig. (1). Survival after10 months was 89% and after 24 months was 79%. Mortality rate after 24 months was 21%. Sixteen deceased patients from overall cause mortality (9 males & 7 females) and included eleven had CV cause mortality (8 males & 3 females). Fig. (2) shows the Kaplan Meier curve for the effect of hs CRP on CV survival among studied HD cases. There was a significant decline in the survival curve in HD patients having hs CRP ≥28.6nmol/L. There was a significant decline in the survival curve in HD patients having pentraxin≥10 ng/ml (fig. 3).

Multivariate analysis shows cox regression for the prediction of CV mortality in HD patients. When six parameters with significant values in the Kaplan-Meier test were entered, only serum PTX3 was an independent predictor of mortality in HD patients with a highly significant value p: <0.001 (Table 5).

Table (1): Comparison of laboratory results between studied groups.

	Control (N=15)	HD Cases (N=74)	test of significance
Ca (mmol/L)	2.41±0.15	2.19±0.21	t=3.81 p<0.001*
Ph (mmol/L)	1.24±0.18	2.04±0.68	t=4.55 p<0.001*
Alkaline phosphatase (µkat/L)	1.5(0.92-2.75) (1.28-2.05)	1.86(0.98-6.68) (1.4 -2.47)	z=1.58 p=0.11
ESR (mm/hr)	10.0(7.0-16.0) (8.0-12.0)	29.0(8.0-59.0) (21.0-39.0)	z=5.51 p<0.001*
hS CRP (nmol/L)	5.43 (0.95-9.52) (2.86-6.67)	11.43 (1.9-57.14) (85.71-19.81)	z=4.67 p<0.001*
Pentraxin3 (ng/ml)	1.38(0.74-2.1) (0.95-1.54)	6.43(3.4-34.0) (5.0-8.22)	z=6.09 p<0.001*

HD: hemodialysis, Ca: calcium, Ph: phosphorus, ESR: Erythrocyte sedimentation rate, hs-CRP: high sensitivity c-reactive protein, t: Student t test Z: Mann -Whitney U test χ^2: Chi-Sqaure test, * statistically significant
Data are expressed as mean ±SD, Median (min-max) (interquartile range) or number and percentage

Table (2): Comparison of demographic, laboratory and echocardiographic findings among deceased and survived hemodialysis cases

	Survived n=58	Deceased n=16	test of significance
Age (years)	46.22±13.12	54.94±11.64	t=2.41 (p=0.02*)
Sex female	27(46.6)	7(43.8)	χ^2=0.04 (p=0.84)
male	31(53.4)	9(56.2)	
BMI (Kg/m2)	27.33±5.64	26.80±4.10	t=0.35 (p=0.73)
Dialysis duration (months)	36(7-120) (14-80.25)	54(13-120) (24-69)	z=1.05 (p=0.29)
Systolic BP (mmHg)	123.60±13.24	133.25±23.36	t=2.15(p=0.03*)
Hb (g/dl)	9.5 (0.9)	7.7 (0.6)	<0.001*
Serum albumin (g/L)	38 (4.0)	29(2.0)	<0.001*
Ca (mmol/L)	2.14±0.18	2.38±0.18	t=4.79 (p<0.001*)
Ph (mmol/L)	1.87±0.51	2.69±0.84	t=4.94 (p<0.001*)
Alkaline phosphatase (µkat/L)	1.67(0.98-4.42) (1.27-2.07)	3.48 (1.23-6.68) (2.62-4.87)	z=4.43 (p<0.001*)
ESR (mm/hr)	26(8-50) (18-34.25)	40(18-59) (33.25-52.75)	z=4.19 (p<0.001*)
hS CRP (nmol/L)	10.5±5.0	40.9±11.3	t=15.68 (p<0.001*)
Pentraxin3 (ng/dl)	5.9(3.4-10.0) (4.85-6.93)	18(9.7-34) (13.25-23)	z=6.08 (p<0.001*)
HCV (Ab positive)	28(48.3)	4(25.0)	χ^2=2.77 (p=0.09)
F score %	4(0-12) (0-6)	12(0-25) (6.5-16.75)	z=3.96 (p<0.001*)
LVM (g)	272.06±72.49	336.55±69.02	t=3.18 (p=0.002*)
LVMI (g/m^2)	152.42±39.01	178.40±33.26	t=2.43 (p=0.01*)
EF %	64.43±6.92	62.35±8.49	t=1.01 (p=0.32)
E/A	0.86(0.39-1.97) (0.69-1.25)	0.71(0.35-1.85) (0.53-1.06)	z=1.46 (p=0.15)
E1/A1	0.68(0.37-2.13) (0.54-1.22)	0.65(0.36-1.46) (0.56-1.26)	z=0.39 (p=0.69)
MPI	0.52±0.04	0.50±0.03	t=1.80 (p=0.06)
IVSD (ml)	1.08±0.13	1.24±0.09	t=4.46 (p<0.001*)
LVEDD (ml)	5.32±0.72	5.47±0.77	t=0.71 (p=0.48)

BMI: body mass index, BP: blood pressure, Hb: hemoglobin, Ca: calcium, Ph: phosphorus, ESR: Erythrocyte sedimentation rate, hs-CRP: high sensitivity c-reactive protein, HCV hepatitis c virus antibody positive, F score: Framingham risk score, LVM: left ventricular mass. LVMI: left ventricular mass index, EF: ejection fraction, E/A: the mitral early diastolic peak flow velocity (E)to late diastole velocity (A)} by conventional pulsed doppler, E1/A1: the mitral early diastolic peak flow velocity to late diastole velocity by tissue doppler, MPI: Myocardial performance index, IVSD: Inter-Ventricular Septum at end- Diastole , LVEDD: Left Ventricle End Diastolic Dimension t: Student t test Z: Mann -Whitney U test χ^2:Chi-Sqaure test * statistically significant, Data are expressed as mean ± SD, Median (min-max) (interquartile range) or number and percentage.

Table (3): Correlation between serum pentraxin3 and laboratory and echocardiographic parameters in hemodialysis patients.

		pentraxin 3(ng\ml) r(p)
Hb (gm/dl)	r(p)	-.609(0.0001)
S creatinine (µmol/L)	r(p)	.226(0.03)
BUN (mmol/L)	r(p)	.343(0.001)
Kt /V	r(p)	.203(0.083)
Uric acid (mmol/L)	r(p)	.121(0.258)
S albumin (g/L)	r(p)	-.623(0.0001)
F score %	r(p)	.719(<0.001)
ESR (mm/hr)	r(p)	0.38(0.001)
hs CRP (nmol/L)	r(p)	0.9(<0.001)
EF%	r(p)	-.095(0.420)
E/A	r(p)	-.053(0.657)
E1/A1	r(p)	.016(0.889)
MPI	r(p)	-.185(0.115)
IVSD (ml)	r(p)	.404**(<0.001)
LVEDD (ml)	r(p)	0.156(0.18)
LVM (gm)	r(p)	0.36(0.001*)
LVMI (g/m^2)	r(p)	.275*(0.018)

Hb: hemoglobin, S creatinine: serum creatinine, BUN: blood urea nitrogen, Kt/V: formula used for dialysis adequacy, S albumin: serum albumin, F score: Framingham risk score, ESR: erythrocyte sedimentation rate, hs CRP: high sensitivity C reactive protein, EF: ejection fraction, E/A: the mitral early diastolic peak flow velocity (E)to late diastole velocity (A)} by conventional pulsed doppler, E1/A1: E/A but by tissue doppler, MPI: Myocardial performance index, IVSD: Inter-Ventricular Septum at end- Diastole , LVEDD: Left Ventricle End Diastolic Dimension, LVM: left ventricular mass, LVMI: left ventricular mass index r: Pearson correlation coefficient, *: significant value<0.05

Table (4): Risk factors affecting cardio-vascular survival among studied cases

	% of censored cases	median survival time (95%CI)	log rank χ^2
Age/years			
≤50	12.8	22.97(22.01-23.93)	χ^2=4.02
>50	31.4	20.03(17.73-22.32)	p=0.045*
Sex Female	79.4	21.62(19.78-23.45)	χ^2=0.032
Male	77.5	21.55(19.85-23.24)	p=0.859
BMI (Kg/m2)			
underweight &normal	81.5	21.37(19.18-23.56)	χ^2=0.169
overweight & obese	76.6	21.70(20.2-23.20)	p=0.681
Systolic BP (mmHg)			
<130	83.3	22.19(20.78-23.59)	χ^2=1.475
≥130	71.9	20.78(18.60-22.96)	p=0.225
Calcium (mmol/L)			
Hypocalcemia (<2.1)	95.0	23.25(21.82-24.68)	χ^2=20.78
Normal level (2.1-2.37)	81.8	22.07(20.60-23.53)	p<0.001*
Hypercalcemia (>2.37)	30.0	16.10(11.51-20.69)	
Phosphorus (mmol/L)			
<1.13	80.0	21(15.74-26.26)	χ2=4.42
1.13-1.78	92.3	22.73(21.03-24.42)	p=0.11
>1.78	69.8	20.95(19.21-22.70)	
Alkaline phosphatase(µkat/L)			
Normal	94.4	23.33(22.55-24.12)	χ^2=35.46
high	35.0	16.85(13.55-20.15)	p=0.001*
ESR (mm/hr) Normal	100.0		χ^2=3.57
Abnormal	74.2	No statistics computed	p=0.059
hS CRP (nmol/L) < 28.6	95	23.38(22.66-24.11)	χ^2=73.03
≥ 28.6	7.1	13.86(10.19-17.53)	p=0.001*
Pentraxin3 (ng/ml)			
<10	98.3	23(22.69-24.0)	χ2=91.96
≥10	6.2	9.0(6.39-11.61)	p<0.001*
E/A			
<0.94	72.7	20.73(18.87-22.59)	χ^2=2.12
>0.94	86.7	22.83(21.55-24.12)	p=0.145
E1/A1			
<0.94	77.4	21.28(19.70-22.86)	χ^2=0.151
>0.94	81.0	22.33(20.54-24.13)	p=0.698
IVSD (ml)			
Normal	94.1	23.06(21.27-24.85)	χ^2=2.93
Abnormal	73.7	21.14(19.63-22.65)	p=0.087
LVDD (ml) Normal	86.2	22.10(20.27-23.94)	χ^2=1.55
Abnormal	73.3	21.24(19.58-22.91)	p=0.214
LVM(g) normal	100	no statistics computed	χ2=2.54
abnormal	75.4		p=0.111
F score % <10	91.9	23.04(22.18-23.9)	χ2=58.86
>10	8.3	10.0(3.0-20.18)	p<0.001*

Kaplan Meier curve, BMI: body mass index, ESR: erythrocyte sedimentation rate, hs CRP: high sensitivity C reactive protein, E/A: the mitral early diastolic peak flow velocity (E)to late diastole velocity (A)} by conventional pulsed doppler, E1/A1: E/A but by tissue doppler, IVSD: Inter-Ventricular Septum at end- Diastole, LVEDD: Left Ventricle End Diastolic Dimension, LVM: left ventricular mass.

Table (5): Cox regression for prediction of CV mortality among hemodialysis cases

	β	p	HR (95%CI)
Age/years			
≤50	0.401	0.532	Reference group
>50			1.49(0.424-5.26)
Calcium (mmol/L)			
Hypocalcemia (<2.1)			Reference group
Normal level (2.1-2.37)	-0.275	0.841	0.76(0.052-11.11)
Hypercalcemia (>2.37)	-0.590	0.686	0.554(0.032-9.65)
Alkaline phosphatase (µkat/L)			
normal	0.084	0.936	Reference group
high			1.09(0.14-8.45)
hs CRP (nmol/)			
normal	1.294	0.317	Reference group
Abnormal			3.65(0.289-45.99)
Pentraxin3(ng/ml)			
<10	4.43	0.001*	Reference group
≥10			84.09(6.82-100.8)
F score%			
<10	-0.730	0.410	Reference group
≥10			0.482(0.085-2.74)

HR: Hazard ratio, hs CRP: high sensitivity C reactive protein.

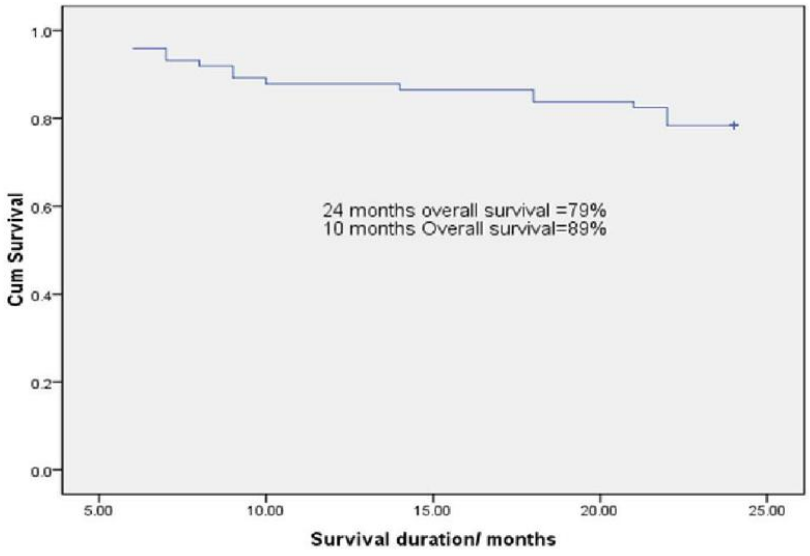

Figure (1): Kaplan Meier curve for the overall survival among hemodialysis cases

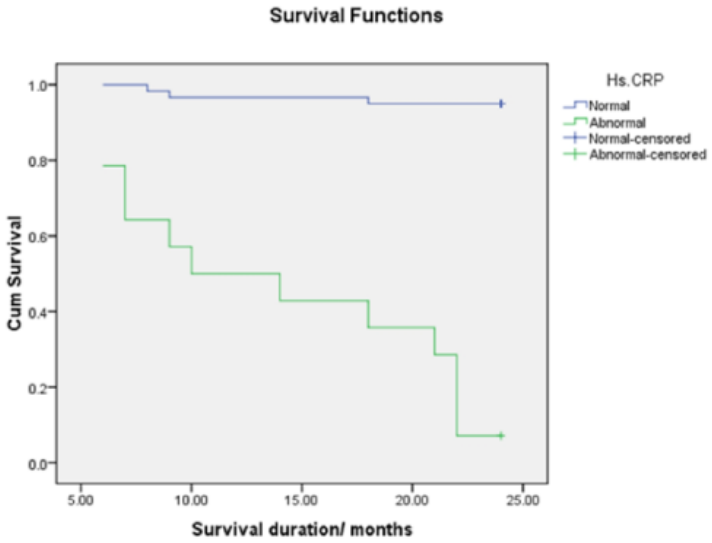

Figure (2): Kaplan Meier curve for the effect of high sensitivity CRP on cardiovascular survival among hemodialysis cases

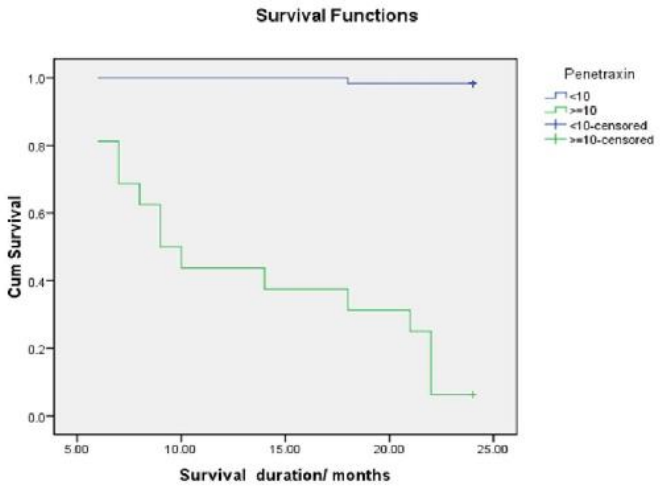

Figure (3): Kaplan Meier curve for the effect of serum pentraxin3 on cardiovascular survival among hemodialysis cases

Discussion

The mortality rate in end-stage renal disease (ESRD) patients is unacceptably very high, which is partially explained by increased traditional risk factors for CVD, so non-traditional risk factors like the persistent low grade of inflammation can play a role ***(11)***. PTX-3 is one of the inflammatory markers found to be elevated in CKD patients on HD ***(26)***. Various echocardiographic abnormalities are common on the left side of the heart among CKD patients ***(15)***. PTX3 was the significant marker correlated with

the presence of LVDD parameters in patients with and without HF ***(19).*** The exact relationship of PTX3 to echocardiographic changes in HD patients was not studied before. In the current study, we aimed to assess PTX3 association with CV mortality and with LVMI in HD patients

In the current study, there were higher levels of serum PTX3, and other inflammatory markers (ESR, hs CRP) in CKD patients on HD than in the healthy control group This agrees with previous studies, they found that PTX3 level was higher in uremic patients, as well as CRP and the other inflammatory biomarker ***(27)***, whether on dialysis or not ***(28- 31).***

Several studies have demonstrated that elevated levels of CRP, pentraxin-3 (PTX3), are associated with overall mortality and CV mortality in ESRD patients ***(32)***, and in HD patients ***(33, 34).*** Similarly, the current study found that serum levels of PTX3, other inflammatory markers (hs CRP, ESR) were significantly higher in the deceased HD group than survived ones. Additionally, in the current study, older patients, and those with significantly higher systolic BP or having higher levels of serum calcium, phosphate, and alkaline phosphatase, and higher F score in the deceased group, but there was no significant difference in BMI between deceased and survived HD groups. However, lower serum albumin and hemoglobin levels were associated with higher mortality rate in our HD group. In partial harmony, a previous study revealed similar results as regards; CRP, other inflammatory markers, and albumin but contrary to our results, lower levels of calcium and BMI were found in deceased HD patients when compared to survived ones ***(35).*** Moreover, several studies were in partial harmony with our work; the previous search showed that elder patients, and those with lower serum albumin, and higher CRP levels were more in deceased patients, but BMI, blood pressure, Hb, serum calcium, and phosphate levels were comparable in both groups ***(36).*** However, other research stated that female gender, lower serum albumin than 30 gm/l, Hb <10gm/dl, BMI <20kg/m2, EF <50% and presence of LVH were more in deceased than survived HD group, while, higher mean calcium, and lower albumin were more in deceased patients, which is in partial harmony with our results. But in contrary to our results, lower EF% was more in deceased patients, and age was comparable in both groups ***(37)***. These discrepancies of results might be explained by their different inclusion or exclusion criteria as; previous work studied

patients on HD from 90 days and included diabetic patients ***(35)***, which was different than our study. Also, another study included HD patients from 1 month from the start of dialysis and excluded patients with positive HBsAg or HCV ***(37).*** Furthermore, medical prescriptions and the use of central venous catheters weren't acknowledged in our study and this could be another explanation for the different results.

Left ventricular hypertrophy was the most common echocardiographic abnormalities among CKD patients; it was found to be associated with traditional risk factors, such as age, DM, and hypertension, and uremia-related risk factors, such as anemia and hypoalbuminemia ***(15)***. Moreover, the presence of LVH in ESKD patients had a negative prognostic value because it might lead to the development of heart failure, IHD, arrhythmias, and sudden death ***(38)***. Similarly, we found that higher values of LVM, LVMI, and IVSD, indicating LVH, were present in the deceased HD group than survived ones. This is in partial harmony with previous studies that revealed that the presence of LVH and EF%<50 % was more in the deceased HD group ***(37)*** or associated with increased poor CV outcome in ESKD patients ***(39, 38)***.

In the current study, serum PTX3 had a significant positive correlation with both (creatinine and BUN), inflammatory markers (hs CRP and ESR), and traditional CV risk factors (FRS). However, there was a significant negative correlation of PTX3 with hemoglobin, and serum albumin. On other hand, BMI had not correlated with PTX3 in HD groups. This agrees with previous studies ***(28, 34, 32, 27)***. On the contrary, other researchers found no significant correlation between PTX3 and CRP ***(40, 41),*** although this might be attributable to the different studied groups as; critically ill patients with liver cirrhosis ***(40)***, and patients with acute myocardial infarction ***(41).*** Additionally, in the current study, there was a significant positive correlation between PTX3 and IVSD, and LVM, while other Echocardiographic parameters had no significant association with sPTX3. Consequently, s PTX3 was correlated positively with LVH, which was a very common echocardiographic abnormality in HD patients ***(15).*** Several pathophysiologic mechanisms have a role in the development of LVH in uremic and nonuremic patients for example, anemia, volume overload, pressure overload, and other factors as microinflammation ***(42)***. Moreover, another study proved the

presence of an association of the inflammatory markers (CRP and IL6) and LVH in patients with HD ***(43).*** Whereas there was a positive correlation between s PTX3 and LVDD (EA) in nonuremic patients with heart failure and normal EF% ***(19)***, we found a positive correlation of PTX3 and LVH, but no significant correlation with MPI or (EA& E1A1), which assess global LV function and LV Diastolic Function, respectively. There were no previous studies were assessing the relation of s PTX3 and Echo parameters in HD patients.

Mortality remains very high in patients with ESRD ***(44).*** Moreover, cardiovascular disease was the major cause of death in HD patients ***(45, 46)***. The current prospective study design included seventy-four HD patients with a follow-up period of 24 months. Kaplan Meier curve for overall survival among HD patients was 89% at 10 months study period with mortality frequency of 11%, whereas survival after 2 years was 79% with a mortality frequency of 21%. This is nearby to the previous research that reported that the annual crude mortality rate of HD patients had been <10% in the past 2 decades ***(47),*** 18.5% for 24 months follow-up period ***(35)***, 19.8% ***(48)***.

By using the Kaplan-Meier test, increasing age, hypercalcemia, elevated alkaline phosphatase levels, serum PTX3≥10 ng/dl, serum Hs CRP≥28.6 nmol/L, and FRS ≥10 were found to be associated with higher mortality risk in HD patients and had shorter median survival time than lower values. This is in partial harmony with a previous study that found that all-cause and CV mortality were higher in the group of patients with serum PTX3 levels above the median value of 1.43 ng/ml ***(32)***.

On other hand, other authors studied the change of PTX3 levels and established that the stable high PTX-3 patients had a higher mortality risk than the stable low-PTX-3 group, the risk remained significantly higher after adjustments for age, sex, CVD, DM, vintage, and malnutrition. Also, they found that patients' group with increased and stable high-CRP levels had a higher mortality risk than the stable low group, these results confirm our statistics from a single baseline serum PTX3 level ***(49).***

To determine the most predictive variables associated with CV mortality with the calculation of hazard ratio in the current study, the six parameters with significant values in the Kaplan-Meier survival test were entered in cox regression analysis, only serum PTX3 was found to be a significant

predictor of CV mortality. In agreement with previous works reported that serum PTX3 concentration was a significant predictor of all-cause and CV mortality ***(32, 34, 50).***

On contrary to our results, another study found that a higher level of CRP (4th quartile) and lower levels of triglyceride (1st quartile) had an association with a higher risk of death in HD patients using survival regression analysis ***(35)***. Additionally, other researchers found that CRP and serum albumin were positively associated with mortality, even after adjusting comorbidities and laboratory values, also age, gender, WBC count were found to be significant predictors of mortality ***(51)***, these differences in results of multivariate analysis, might be attributable to dissimilar inclusion criteria in that study, which was restricted to patients in facilities that measure CRP routinely and patients with HD vintage>90 days, which was different than the current study. Furthermore, a previous study revealed that standard CRP assay presents a reasonable alternative to hs CRP assay in patients on HD and reported that CRP and hs CRP were significant predictors of mortality ***(52)***. This is contrary to the current study. Also, other works revealed that CRP was an independent predictor of both all-cause and CV mortality ***(53, 51).***

We concluded that there were elevated levels of serum PTX3 in HD patients, which correlated positively with inflammatory markers (ESR, hs CRP), FRS (CV risk score), and Echo parameters indicating LVH (LVM, LVMI, IVSD). Moreover, s PTX3 more than 10ng/ml was associated with lower median survival time among HD patients and were the most predictive risk factor indicating CV mortality in this group. Consequently, s PTX3 is an inflammatory marker that can be used for early detection of risky HD patients, as well as was considered as an indicator for LVH in these patients, though still there is a need for more study research to ascertain serum PTX3 relationship with echo parameters. The current study acknowledges some limitations as the low number of studied groups and short follow-up period. We recommend further studies with a large number of patients, prolonged follow-up period.

References

(1) Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clinical journal of the *American Society of Nephrology*. 2008; 3(2):505-21.

(2) Turkmen K, Erdur FM, Guney I, Ozbiner H, Toker A, Gaipov A, et al. Relationship between plasma pentraxin-3, neutrophil-to-lymphocyte ratio, and atherosclerosis in renal transplant patients. Cardiorenal medicine. 2012;2(4):298-307.

(3) Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. Kidney international. 2008 Feb 2;73(4):391-8.

(4) Ekdahl KN, Soveri I, Hilborn J, Fellström B, Nilsson B. Cardiovascular disease in hemodialysis: role of the intravascular innate immune system. *Nature Reviews Nephrology*. 2017;13(5):285-96.

(5) Garlanda C, Bottazzi B, Bastone A, Mantovani A. Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. Annu. Rev. *Immunol*. 2005; 23: 337-66.

(6) Agrawal A. CRP after 2004. *Molecular immunology*. 2005; 42(8):927-30.

(7) Pepys MB, Baltz ML. Acute-phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *In Advances in immunology* 1983; 34: 141-212.

(8) Abderrahim-Ferkoune A, Bezy O, Chiellini C, Maffei M, Grimaldi P, Bonino F, et al. Characterization of the long pentraxin PTX3 as a TNFα-induced secreted protein of adipose cells. Journal of lipid research. 2003 May 1;44(5):994-1000.

(9) Jenny NS, Arnold AM, Kuller LH, Tracy RP, Psaty BM. Associations of pentraxin 3 with cardiovascular disease and all-cause death: The Cardiovascular Health Study. *Arteriosclerosis, thrombosis, and vascular biology*. 2009; 29(4):594-9.

(10) Bonacina F, Baragetti A, Catapano AL, Norata GD. Long pentraxin 3: experimental and clinical relevance in cardiovascular diseases. *Mediators of inflammation.* 2013; 2013.

(11) Yao Q, Axelsson J, Stenvinkel P, Lindholm B: Chronic systemic inflammation in dialysis patients: an update on causes and consequences. *ASAIO J* 2004; 50: lii–lvii.

(12) Doni A, Michela M, Bottazzi B, Peri G, Valentino S, Polentarutti N, et al. Regulation of PTX3, a key component of humoral innate immunity in human dendritic cells: stimulation by IL-10 and inhibition by IFN-γ. Journal of leukocyte biology. 2006 Apr;79(4):797-802.

(13) Arjona Barrionuevo JD, Gonzáles Vargas-Machuca MF, Gómez Pulido F, Gil Sacaluga L, Gentil Govantes MA, Martínez-Martínez A. Transthoracic echocardiographic findings in patients with chronic kidney disease awaiting kidney transplantation. *Transplant Proc*. 2010;42(8):3123-5.

(14) Nardi E, Palermo A, Mule G, Cusimano P, Cottone S, Cerasola G. Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. *J Hypertens.* 2009;27(3):633–41.

(15) Pakfetrat M, Roozbeh J, Nikoo MH, Asem Z, Malekmakan L, Nikoo MA. Common echocardiography findings in pretransplant dialysis patients and their associations. Hong Kong *Journal of Nephrology*. 2013; 15(2):68-74.

(16) Hayashi SY, Rohani M, Lindholm B, Brodin LÅ, Lind B, Barany P, et al. Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging. Nephrology Dialysis Transplantation. 2006 Jan 1;21(1):125-32.

(17) Ganau A, Devereux RB, Roman MJ, De Simone G, Pickering TG, Saba PS, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. Journal of the American College of Cardiology. 1992 Jun 1;19(7):1550-8.

(18) Cottone S, Vadala A, Vella MC, Contorno A, Cerasola G. Comparison of tumor necrosis factor and endothelin-1 between essential and renal hypertensive patients. *J Hum Hypertens.* 1998; 12:351–354.

(19) Matsubara J, Sugiyama S, Nozaki T, Sugamura K, Konishi M, Ohba K, et al. Pentraxin 3 is a new inflammatory marker correlated with left ventricular diastolic dysfunction and heart failure with normal ejection fraction. Journal of the American College of Cardiology. 2011 Feb 15;57(7):861-9.

(20) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998; 97(18):1837-47.

(21) Moalli F, Jaillon S, Inforzato A, Sironi M, Bottazzi B, Mantovani A, et al. Pathogen recognition by the long pentraxin PTX3. Journal of biomedicine and biotechnology. 2011 Oct;2011.

(22) Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. Journal of the American Society of Echocardiography. 1989 Sep 1;2(5):358-67.

(23) Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. The American journal of cardiology. 1986 Feb 15;57(6):450-8.

(24) Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal-Cardiovascular Imaging. 2015 Mar 1;16(3):233-71.

(25) Shingu Y, Amorim P, Nguyen TD, Mohr FW, Schwarzer M, Doenst T. Myocardial performance (Tei) index is normal in diastolic and systolic heart failure induced by pressure overload in rats. European Journal of Echocardiography. 2010 Dec 1;11(10):829-33.

(26) Boehme M, Kaehne F, Kuehne A, Bernhardt W, Schröder M, Pommer W, et al. Pentraxin 3 is elevated in hemodialysis patients and is associated with cardiovascular disease. Nephrology Dialysis Transplantation. 2007 Aug 1;22(8):2224-9.

(27) Valente MJ, Rocha S, Coimbra S, Catarino C, Rocha-Pereira P, Bronze-da-Rocha E, et al. Long pentraxin 3 as a broader biomarker for multiple risk factors in end-stage renal disease: association with all-cause mortality. Mediators of inflammation. 2019 Jun 16;2019.

(28) Tong M, Carrero JJ, Qureshi AR, Anderstam B, Heimbürger O, Bárány P, et al. Plasma pentraxin 3 in patients with chronic kidney disease: associations with renal function, protein-energy wasting, cardiovascular disease, and mortality. Clinical Journal of the American Society of Nephrology. 2007 Sep 1;2(5):889-97.

(29) Yilmaz MI, Sonmez A, Ortiz A, Saglam M, Kilic S, Eyileten T, et al. Soluble TWEAK and PTX3 in nondialysis CKD patients: impact on endothelial dysfunction and cardiovascular outcomes. Clinical journal of the American Society of Nephrology. 2011 Apr 1;6(4):785-92.

(30) Oldani S, Finazzi S, Bottazzi B, Garlanda C, Baldassarre E, Valaperta S, et al. Plasma pentraxin-3 as a marker of bioincompatibility in hemodialysis patients. Journal of Nephrology. 2012 Jan 1;25(1):120-6.

(31) EL-Attar HA, Abaza MM, Gaber EW, EL-sharkawy RM. Serum profiles of pentraxin-3 and high sensitivity C-reactive protein in patients with chronic kidney disease treated with or without hemodialysis. *J Nephrol Ther*. 2017; 7:1.

(32) Krzanowski M, Krzanowska K, Gajda M, Dumnicka P, Dziewierz A, Woziwodzka K, et al. Pentraxin 3 as a new indicator of cardiovascular-related death in patients with advanced chronic kidney disease. Polskie Archiwum Medycyny Wewnętrznej= Polish Archives of Internal Medicine. 2017;127(3).

(33) Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *American journal of kidney diseases*. 2000;35(3):469-76.

(34) Suliman ME, Qureshi AR, Carrero JJ, Barany P, Yilmaz MI, Snaedal-Jonsdottir S, et al. The long pentraxin PTX-3 in prevalent hemodialysis patients: associations with comorbidities and mortality. QJM: An International Journal of Medicine. 2008 May 1;101(5):397-405.

(35) Sameiro-Faria MD, Ribeiro S, Costa E, Mendonça D, Teixeira L, Rocha-Pereira P, et al. Risk factors for mortality in hemodialysis patients: two-year follow-up study. Disease markers. 2013;35(6):791-8.

(36) Msaad R, Essadik R, Mohtadi K, Meftah H, Lebrazi H, Taki H, et al. Predictors of mortality in hemodialysis patients. The Pan African Medical Journal. 2019;33.

(37) Prabha D R, Prasad G. Predictors of mortality among patients on maintenance hemodialysis. *J NTR Univ Health Sci* 2016; 5:255-60

(38) Paoletti E, De Nicola L, Gabbai FB, Chiodini P, Ravera M, Pieracci L, et al. Associations of left ventricular hypertrophy and geometry with adverse outcomes in patients with CKD and hypertension. Clinical journal of the American Society of Nephrology. 2016 Feb 5;11(2):271-9.

(39) Collins AJ. Cardiovascular mortality in end-stage renal disease. *The American journal of the medical sciences.* 2003;325(4):163-7.

(40) Muller B, Peri G, Doni A, Torri V, Landmann R, Bottazzi B, et al. Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. Critical care medicine. 2001 Jul 1;29(7):1404-7.

(41) Peri G, Introna M, Corradi D, Iacuitti G, Signorini S, Avanzini F, et al. PTX3, A prototypical long pentraxin, is an early indicator of acute myocardial infarction in humans. Circulation. 2000 Aug 8;102(6):636-41.

(42) London GM. Left ventricular hypertrophy: why does it happen? *Nephrology Dialysis Transplantation*. 2003;18(suppl_8): viii2-6.

(43) Park CW, Shin YS, Kim CM, Lee SY, Yu SE, Kim SY, et al. Increased C-reactive protein following hemodialysis predicts cardiac hypertrophy in chronic hemodialysis patients. American journal of kidney diseases. 2002 Dec 1;40(6):1230-9.

(44) Pozzoni P, Del Vecchio L, Pontoriero G, Di Filippo S, Locatelli F. Long-term outcome in hemodialysis: Morbidity and mortality. *J Nephrol.* 2004;17(Suppl 8): S87–95.

(45) Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. The Lancet. 2012 Nov 10;380(9854):1662-73.

(46) Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. The Lancet. 2012 Nov 10;380(9854):1649-61.

(47) Nakai S, Iseki K, Itami N, Ogata S, Kazama JJ, Kimata N, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2009). Therapeutic Apheresis and Dialysis. 2012 Feb;16(1):11-53.

(48) Chandrashekar A, Ramakrishnan S, Rangarajan D. Survival analysis of patients on maintenance hemodialysis. *Indian J Nephrol*. 2014;24(4):206-13.

(49) Sjöberg B, Snaedal S, Stenvinkel P, Qureshi AR, Heimbürger O, Bárány P. Three-month variation of plasma pentraxin 3 compared with C-reactive protein, albumin, and homocysteine levels in hemodialysis patients. *Clinical kidney journal*. 2014; 7(4):373-9.

(50) Kones R: Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease a perspective. *Drug Des Devel Ther* 2010; 4: 383–413

(51) Bazeley J, Bieber B, Li Y, Morgenstern H, de Sequera P, Combe C, et al. C-reactive protein and prediction of 1-year mortality in prevalent hemodialysis patients. Clinical Journal of the American Society of Nephrology. 2011 Oct 1;6(10):2452-61.

(52) Helal I, Zerelli L, Krid M, ElYounsi F, Maiz HB, Zouari B, et al. Comparison of C-reactive protein and high-sensitivity C-reactive protein levels in patients on hemodialysis. Saudi Journal of Kidney Diseases and Transplantation. 2012 May 1;23(3):477.

(53) Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney international.* 1999;55(2):648-58.

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