

Received: 2015.07.09  
Accepted: 2015.08.31  
Published: 2015.12.26

# Analysis of Clinically Relevant Factors for Pulmonary Hypertension in Maintenance Hemodialysis Patients

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Source of support:** Departmental sources

**Background:** Pulmonary hypertension (PH) is common in patients with maintenance hemodialysis (MHD) and is associated with high mortality. This study analyzed clinically relevant factors for pulmonary hypertension in MHD patients and the effect of serum pentraxin3 (PTX3) in the pathogenesis of PH to provide the basis for early diagnosis and treatment of MHD patients with PH.

**Material/Methods:** This study included 60 MHD patients (group A) and 30 healthy controls (group B). Group A was further divided into PH and non-PH groups. Clinical characteristics, auxiliary examination results and serum PTX3 level of the PH and non-PH groups were compared. Binary logistic regression was used to assess the risk factors for PH in MHD patients. ROC curve was applied to evaluate the diagnostic value of PTX3 in PH.

**Results:** The incidence rate of PH in MHD patients was 50%, and most presented as mild to moderate. Compared with the non-PH group, patients in PH group presented significantly longer atrial diameter, right ventricular diameter and main pulmonary artery diameter ( $P < 0.05$ ), as well as higher PTX3 and NT-proBNP level. Atrial diameter and PTX3 level were the risk factors for PH in MHD patients. AUC of PTX3 was 0.721 (95%CI: 0.590–0.851,  $P = 0.003$ ).

**Conclusions:** The prevalence of PH was higher in MHD patients and mostly presented as mild to moderate. Such patients often developed heart structural changes and cardiac ultrasound was highly recommended. Serum PTX3 level was significantly elevated and could be used as a marker of PH in MHD patients.

**MeSH Keywords:** **Hemodialysis Solutions • Methoxyflurane • White Coat Hypertension**

**Full-text PDF:** <http://www.medscimonit.com/abstract/index/idArt/895279>



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## Background

Pulmonary hypertension (PH) is a clinical condition characterized by persistent increase in pulmonary vascular resistance due to different pathogenesis. Its prevalence in patients with maintenance hemodialysis (MHD) was 18.8–68.8% [1]. Several studies have confirmed that PH is one of the risk factors associated with death in MHD patients [2,3]. Since PH is difficult to be found in early stages, early diagnosis and prevention of PH in MHD patients has recently become a research hotspot. It has been suggested that pentraxin3 (PTX3) might be a better biomarker for PH than brain natriuretic peptide [4]. We applied a cross-sectional study to investigate the clinical features of MHD patients with PH and the diagnostic value of PTX3 in these patients by comparing the PH and non-PH groups in order to screen MHD patients with PH for PH risk factor markers and to improve their prognosis.

## Material and Methods

### Research objects

#### MHD patients

Source of case: this study included 60 MHD patients from Beijing Chaoyang Hospital affiliated to the Capital Medical University in October 2013. The vascular access in MHD patients was autogenous arteriovenous internal fistula. Of the 60 MHD patients, there were 18 cases of diabetic nephropathy, 18 cases of primary chronic glomerulonephritis, 1 case of polycystic kidney, 7 cases of hypertension, 8 cases of drug-induced renal damage, 1 case of chronic pyelonephritis, and 7 cases with unknown reasons.

Inclusion criteria: a) Patients had received MHD for more than 3 months prior to the enrollment in this study; b) Older than 18 years old.

Exclusion criteria: a) Patients with malignant tumor; b) acute infection; c) acute myocardial infarction; d) chronic pulmonary disease; e) deep vein catheterization; f) immunosuppressant therapy; g) connective tissue diseases; h) hepatic disease; i) unwillingness to participate in the study.

PH diagnosis criteria: Echocardiography resting pulmonary artery systolic pressure that is tricuspid regurgitation differential pressure plus estimated right atrial pressure  $\geq 35$  mmHg is considered pulmonary hypertension. PH was defined as mild, PASP 35–45 mmHg; moderate, PASP 45–60 mmHg; or severe, PASP  $>60$  mmHg.

Therapeutic method: MHD patients received dialysis 3 times a week and 4 h each time on a dialysis machine (Fresenius 4008S, Germany) with heparin or low molecular heparin for anticoagulation. Polysulfone membranes with an area of 1.2–1.5 m<sup>2</sup> were used. Reverse osmosis water was applied as dialysis water. Bicarbonate was used as dialysate with a flow rate of 500 ml/min and blood flow volume of 200–300 ml/min. All enrolled patients received HD mode hemopurification through autogenous arteriovenous internal fistula.

#### Healthy controls

A total of 30 healthy controls were collected from the physical examination center in our hospital with normal hepatorenal function, blood routine, chest radiography and electrocardiogram.

#### Grouping

The subjects were divided into MHD group (group A) and healthy control (group B). Group A was further divided into the PH and non-PH groups (Table 1).

#### Main instruments

HWI thermostatic water bath was manufactured by Beijing medical equipment factory (Beijing, China). Low temperature centrifuge Eppendorf 541 SR was purchased from Eppendorf AG (Hamburg, Germany). Thermo automatic microplate reader and Thermo Scientific continuous pipette filler (Finnpipette) were purchased from Thermo Scientific (Fremont, CA, USA).

#### Blood sample collection

Blood was collected from healthy controls and MHD patients before dialysis. The blood was allowed to clot for 10–20 min at room temperature, and centrifuged at 2000–3000 rpm for

Table 1. Patients group.

Group	Group A	Group B	Total
Total number	60	30	90
PH group (PASP $\geq 35$ mmHg)	A1/30	–	–
Non-PH group (PASP $< 35$ mmHg)	A2/30	–	–

**Table 2.** Comparison of clinical features in MHD patients.

	PH (n=30)	Non-PH (n=30)	P value
Age (year)	62.3±12.9	61.2±12.9	0.742
Gender (male/female)	20/10	14/16	0.121
BMI (kg/m <sup>2</sup> )	23.0±3.9	21.3±6.4	0.245
Dialysis time (month)	58.8±47.6	54.6±47.6	0.734
Dehydration level (L)	2.8±1.1	2.4±1.0	0.100
spKt/V	1.4±0.3	1.5±0.4	0.403
Systolic pressure (mmHg)	148.6±14.0	148.8±19.3	0.962
Diastolic pressure (mmHg)	82.1±12.3	83.0±15.7	0.821
PASP (mmHg)	47.6±10.5	26.8±5.3	0.000

20 min. The supernatant was collected and stored at -70°C for PTX3 detection. The remaining part was sent for other tests.

### Observation index

#### Clinical information

Clinical information including primary illness, age, gender, height, weight, and BMI was collected. BMI=Weight (kg)/Height (m)<sup>2</sup>. Single pool urea clearance index (spKt/V) was applied to evaluate dialysis adequacy, and the Daugirdas formula was used for calculation:  $Kt/V = -\ln(R - 0.008t) + (4 - 3.5R) \times UF/W$ , where R is the ratio of BUN concentration after and before dialysis, t is the dialysis time (h), UF (L) is the ultrafiltration amount, and W (kg) is the body weight after dialysis.

#### Laboratory examination

Levels of serum albumin, creatinine, BUN, lipid and ferritin were detected. Intact parathyroid hormone (iPTH) was detected by the isotope chemiluminescence method. High sensitive C-reactive protein (hsCRP) was quantified by immunoturbidimetric tests. Amino-terminal pro-B natriuretic peptide (NT-proBNP) was determined by electrochemiluminescence. Hemoglobin in blood collected in EDTA anticoagulated tube was tested.

#### Cardiac ultrasound examination

MHD patients received ultrasonic cardiogram within 2 h after HD. The ultrasound was performed by two experienced ultrasonographers. Pulmonary artery systolic blood pressure was calculated as the quadrupling of tricuspid regurgitation differential pressure plus right atrium pressure.

#### PTX3 detection

Enzyme-linked immunosorbent assay (ELISA) was applied to detect PTX3 level according to the manufacture's manual (Beijing

Equation Company, Beijing, China). Briefly, 100 µl of diluted standard product was added into the corresponding reaction holes to prepare the standard curve. Samples (10 µl) were added into each hole. After washing the plate 5 times, 50 µl of enzyme reagent was added. The plate was washed 5 times again after incubated at 37°C for 30 min. 100 µl of color reagent was added to each hole and the plate was incubated at 37°C for 15 min. The reaction was terminated after adding 50 µl of termination liquid. The absorbance value (OD value) was measured at 450 nm wavelength. The concentration of each sample was calculated according to the OD value and the standard curve.

#### Statistical analysis

All statistical analyses were performed using SPSS17.0 software. Normality test was applied on continuous variables. Normally distributed continuous variables were presented as means and standard deviation ( $\bar{x} \pm SD$ ), whereas continuous variables with skewed distribution were presented with median (interquartile range). Demographic data were presented as constituent ratio. While t test and non-parametric test were used for the comparison between measurement data, chi-square test was applied for comparison between enumeration data. Binary logistic regression analysis was applied to analyze the correlation between PTX3 and PH. ROC curve was used to assess the diagnosis value of PTX3 for PH in MHD patients.  $P < 0.05$  was considered statistically significant.

## Results

### PH rates in MHD patients

A total of 60 MHD patients were enrolled in this study including 34 males and 26 females with an average age of 61.8±12.8 years. Among these patients, 30 patients (50%) developed PH, including 20 males and 10 females with an average age of 62.3±12.9 years. Among them, 14 cases (46.7%) were mild

**Table 3.** Comparison of serum PTX3 and auxiliary examination before dialysis.

	PH (n=30)	Non-PH (n=30)	P value
Serum albumin (g/L)	35.7±3.5	37.0±2.8	0.140
SCr before dialysis (umol/L)	743.3±212.8	786.1±149.6	0.371
BUN before dialysis (mmol/L)	21.2±5.8	21.7±4.5	0.669
Ca (mmol/L)	2.2 (2.1–2.4)	2.3 (2.2–2.4)	0.069
P (mmo/L)	1.7 (1.4–2.3)	1.9 (1.5–2.3)	0.339
Ca × P (mmol <sup>2</sup> /L <sup>2</sup> )	3.9 (2.8–5.0)	4.2 (3.6–5.1)	0.198
iPTH (pg/ml)	270.8±193.1	290.5±234.7	0.727
TCh (mmol/L)	4.2±1.0	4.7±1.0	0.056
TG (mmol/L)	1.9±1.4	2.0±1.1	0.896
HDL-C (mmol/L)	1.0±0.3	1.1±0.3	0.366
LDL-C (mmol/L)	2.3±0.8	2.5±0.7	0.220
Serum ferritin (ng/ml)	489.4±289.0	463.0±311.5	0.743
Hb (g/L)	115.6±12.4	119.3±13.3	0.270
NT-proBNP (pg/ml)	15972 (4888.3–35000)*	5811.0 (3162.8–13340.0)	0.018
hsCRP (mg/L)	2.9 (0.9–11.0)	2.6 (0.8–7.2)	0.534
PTX3 (ng/ml)	7.1±0.9*	6.3±1.1	0.002

\* P<0.05.

PH, 11 cases (36.7%) were moderate PH, and 5 cases (16.7%) were severe PH. A total of 30 patients (50%) presented no PH, including 14 males and 16 females with an average age of 61.2±12.9 years.

### Comparison of clinical characteristics between the PH and non-PH groups

#### Comparison of clinical features

No significant differences in age, gender, BMI, dialysis time, dehydration level, Kt/V, systolic pressure, and diastolic pressure was detected between the PH and non-PH groups (Table 2).

#### Comparison of auxiliary examination results

The level of PTX3 and NT-proBNP in the PH group was significantly higher compared with the non-PH group (P=0.002, and P=0.018, respectively) (Table 3). In addition, the PH group presented significantly higher levels of right atrium long and transverse diameter, pulmonary artery trunk diameter, right ventricular transverse diameter, and left atrial anterior and posterior diameter compared with the non-PH group (Table 4). Although the ejection fraction in the PH group was lower than that in the non-PH group, but there was no significant difference between the two groups (P=0.064).

#### Comparison of serum PTX3 level

As shown in Table 5, PTX3 level in group A was markedly higher than that in group B (P<0.001).

#### Correlation analysis between PTX3 and PH in MHD patients

As shown in Table 5, serum PTX3 level in the PH group was significantly higher than in the non-PH group. Multiple logistic regression analysis showed that PTX3, right atrial long diameter, and left atrial anterior and posterior diameter elevation were risk factors for PH in MHD patients (Table 6). The regression equation was  $\text{logit}(P) = 18.748 + 0.971 \text{ PTX3} + 0.174 \text{ right atrial long diameter} + 0.105 \text{ left atrial anterior and posterior diameter}$ .

#### Evaluation of the diagnostic values of PTX3, right atrial long diameter, and left atrial anterior and posterior diameter for PH by ROC curve

AUC of PTX3 was 0.721 (95%CI: 0.590–0.851, P=0.003). The best diagnostic cut-off point was 7.495, with sensitivity of 0.500 and specificity of 0.967. AUC of right atrial long diameter was 0.771 (95%CI: 0.651–0.891, P=0.000). The best diagnostic cut-off point was 47.85, with sensitivity of 0.667 and specificity of 0.767. AUC of left atrial anterior and posterior diameter was 0.668 (95%CI:

**Table 4.** Comparison of cardiac ultrasound in MHD patients.

	PH (n=30)	Non-PH (n=30)	P value
Right atrial long diameter (mm)	50.0±6.8*	44.3±5.6	0.001
Right atrial transverse diameter (mm)	37.4±7.6*	33.5±3.5	0.015
Pulmonary artery diameter (mm)	27.1±4.5*	24.7±2.2	0.012
Right ventricular transverse diameter (mm)	32.9±6.0*	29.7±3.5	0.013
Left ventricular transverse diameter (mm)	41.6±5.6	39.5±5.9	0.175
Left atrial anterior and posterior diameter (mm)	41.2±7.2*	36.5±6.2	0.009
Left ventricular end diastolic diameter (mm)	49.7±6.2	48.8±5.2	0.523
Left ventricular end systolic diameter (mm)	33.2±7.5	30.3±4.5	0.072
Ejection fraction (%)	66.0 (58.8–69.3)	67.5 (63.8–73.0)	0.064
Left ventricle posterior wall thickness (mm)	11.9±2.2	11.5±2.0	0.504
Interventricular septal thickness (mm)	12.6±2.7	12.1±1.7	0.336

\* P&lt;0.05.

**Table 5.** Comparison of serum PTX3 level in group A and B.

Group	Cases	Age (year)	Male/female (cases)	PTX3 (ng/ml)
Group A	60	61.8±12.8	34/26	6.8±1.1
Group B	30	60.6±12.1	16/14	5.0±0.9

**Table 6.** Binary logistic regression analysis of the risk factors for PH in MHD patients.

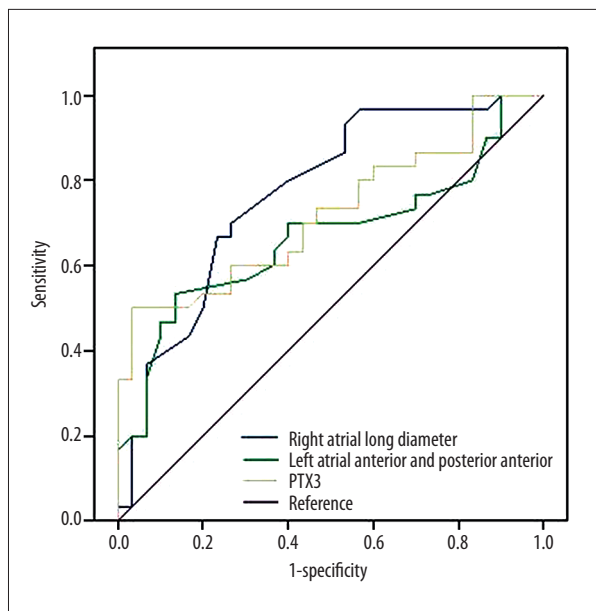
	OR	95% C.I.	P value
PTX3 (ng/ml)	2.64	1.259–5.536	0.010
Right atrial long diameter (mm)	1.19	1.044–1.357	0.009
Left atrial anterior and posterior diameter (mm)	1.111	1.001–1.232	0.047

0.526–0.808, P=0.026). The best diagnostic cut-off point was 42.15, with sensitivity of 0.467 and specificity of 0.867 (Figure 1).

## Discussion

MHD patients have high incidence of cardiovascular diseases (CVD) which is the first cause of death. As a type of CVD, PH has received a large amount of attention. The prevalence of PH in MHD patients ranges from 18.8% to 68.8% [1]. In MHD patients, volume load, left heart disease, endothelial dysfunction and inflammation state are involved in the occurrence and development of PH. PH is an independent risk factor of death in MHD patients. Besides the abovementioned factors, internal arteriovenous fistula and the biocompatibility of dialysis membrane are also involved in the occurrence of PH. Our study showed that PH incidence in MHD patients was 50%, which was consistent with previous reports.

In this study, MHD patients in the PH group showed more obvious cardiac structural changes compared with the non-PH group. PH induced right heart structural changes include right ventricular and atrial enlargement and pulmonary artery trunk diameter enlargement, resulting in the right heart failure. Right atrial long diameter is a risk factor for MHD patients with PH. ROC curve analysis showed that the sensitivity and specificity of right atrial long diameter on detecting PH were 0.667 and 0.767, respectively, when setting 47.85 mm as the boundary point. Left atrial diameter in the PH group was increased compared with the non-PH group, whereas the heart ejection fraction presented a downtrend, suggesting that PH is closely related to the left cardiac structure and function. Our result is consistent with previous findings that most PH in MHD patients are caused by left heart diseases [5]. When patients do not undergo right cardiac catheterization examination or fail to provide tricuspid regurgitation differential pressure, echocardiographic index supplies important information for the diagnosis



**Figure 1.** ROC curve of serum PTX3 level, right atrial long diameter, and left atrial anterior and posterior diameter.

of PH. NT-proBNP can be treated as a marker for left cardiac diastolic dysfunction in MHD patients, and is negatively correlated with left ventricular ejection fraction [6]. Additionally, NT-proBNP also has implication to volume status in MHD patients [7]. NT-proBNP in the PH group was substantially increased compared with the non-PH group, indicating that PH in MHD patients was closely associated with cardiac function and volume. Improving left heart function and reducing volume load are the basis for the treatment of PH in MHD patients.

PTX3 is one of the earliest discovered long-chain pentraxins and belongs to the pentraxin superfamily. Different from short chain pentraxin C-reactive protein (CRP), PTX3 can be produced by macrophages, neutrophils, dendritic cells, smooth muscle cells, endothelial cells and fibroblasts. It can also be generated by cumulus cells, glomerular mesangial cells, synovial cells and chondrocytes. PTX3 can bind to a variety of ligands including complement C1q, fibroblast growth factor 2, and P selectin to regulate a wide range of processes such as inflammation, angiogenesis, atherosclerosis, extracellular matrix formation and apoptotic cells scavenging [8]. Inflammatory stimulation can cause PTX3 overexpression in vascular endothelial cells, leading to PTX3 elevation in heart failure, vascular atherosclerosis, vasculitis, coronary heart disease, and ESRD. Consistent with previous literature [9], this study showed that serum PTX3 level was significantly increased in MHD patients, indicating that MHD patients might develop damages in endothelial function and inflammation. Several previous studies have implied that PTX3 may serve as a marker for PH, and this study confirmed that PTX3 was a risk factor for the occurrence

of PH in MHD patients. We speculated that PTX3 might participate in the occurrence of PH in MHD patients from the following three aspects:

PTX3 is closely associated with heart diseases. A study on patients with chronic kidney disease in stage 4–5 has suggested that PTX3 level is higher in patients with cardiovascular disease compared with patients with non-cardiovascular disease [10]. PTX3 elevation is independently associated with heart attack in patients with coronary heart disease [11]. PTX3 has shown an increasing trend with heart failure aggravation [12]. Heart disease can result in increasing left heart dysfunction and left atrial pressure increases, whereas PCWP elevation may cause PH. Studies have suggested that PH caused by left heart disease in MHD patients account for 65% of all PH cases [5]. Another study on 288 MHD patients has revealed that left atrial diameter is strongly associated with PH [2]. High PTX3 level may participate in the pathogenesis of PH in MHD patients by inducing left heart disease.

PTX3 is closely associated with vascular endothelial function. A response of vascular endothelial cells and smooth muscle cells to inflammatory stimuli can produce a large amount of PTX3. PTX3 co-cultured with human endothelial cells *in vitro* can lead to the synthesis of tissue factor. A study of non-dialysis patients with chronic stage 5 kidney disease has shown that PTX3 is independently correlated with flow-mediated dilation (FMD) [13]. Vascular endothelial dysfunction prevails in MHD patients, which is mainly presented as an imbalance between vasoconstrictor substance (such as endothelin 1) and diastolic material (such as nitric oxide). Endothelial dysfunction itself is also participated in PH, and can be confirmed by the following researches: a) it has been shown that in MHD patients with PH produced less nitric oxide compared with non-PH patients, whereas dialysis-induced nitric oxide in PH patients is increased more significantly [14]. b) Asymmetric dimethyl arginine (ADMA), a type of endogenous nitric oxide synthase inhibitor, has been confirmed to be independently correlated with PASP level in MHD patients. c) Mice with pulmonary hypertension secondary to congestive heart failure have presented endothelial dysfunction, vasodilation due to choline, and endothelin-1 receptor blocker-induced vasodilation enhancement [15]. PTX3 might participate in the occurrence of PH in MHD patients through impacting endothelial dysfunction.

PTX3 is closely related to inflammation. The process of dialysis can induce inflammation. PTX3 is significantly increased at 1 h since the beginning of dialysis and reaches the peak after 3 h, whereas TNF- $\alpha$  elevation is not so obvious [16]. PTX3 has been shown to strongly related to IL-1 $\beta$ , TNF- $\alpha$ , and fibrinogen in dialysis patients with chronic stage 5 kidney disease. These inflammatory markers are significantly elevated when the mononuclear cells are stimulated by endotoxin before hemodialysis, whereas there are no significant changes in the

levels of these factors when the mononuclear cells are stimulated by endotoxin after hemodialysis [17]. These findings imply that the process of dialysis activates inflammatory cells, and PTX3 can be served as a marker of inflammation. Serum level of IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 is increased in PH patients receiving maintenance hemodialysis, suggesting that chronic inflammation plays an important role in the occurrence of PH in MHD patients [18]. Therefore, PTX3 may participate in the occurrence PH in MHD patients through inflammation.

In summary, the prevalence of PH in MHD patients is high and PH is a risk factor of death in these patients. Early detection and treatment of PH will greatly improve their prognosis. PTX3 might participate in the pathogenesis of PH through endothelial dysfunction, inflammation, and cardiac functional changes in MHD patients. It can be served as a marker for screening PH. Moreover, PH patients often develop cardiac structure and

function changes. Thus, regular cardiac ultrasound is especially helpful for the diagnosis of PH in MHD patients. However, this cross-sectional study is limited by the small sample size and potential unclarified drug impact on the results of index measurement. Further investigation is needed in the future to confirm our findings.

## Conclusions

The prevalence of PH in MHD patients was high, and most presented as mild to moderate with coexisting heart structural changes. Regular cardiac ultrasound is needed for screening.

Serum PTX3 level was increased significantly in MHD patients.

PTX3 might serve as a risk factor marker for PH in MHD patients.

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