

### Pentraxin 3 in Hemodialysis Patients: Relationship to Co-morbidities

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**Abstract:** Hemodialysis (HD), despite being the most common treatment modality for end stage renal disease (ESRD); the mortality rate in HD patients from co-morbidities still remains higher than 20-50 % per year. The aim of this study was to measure the plasma level of pentraxin 3 (PXT3) in patients on maintenance HD and to assess its relationships to co-morbidities such as malnutrition and associated co-morbid diseases. This case-control study included 50 HD patients, 30 ESRD patients and 30 healthy controls. HD patients were classified into different subgroups according to the Davies co-morbidity index and malnutrition score. Plasma pentraxin3 (PTX3) was analyzed by a sandwich ELISA technique. Plasma level of PTX3 reached its highest levels in HD patients followed by ESRD patients as compared to healthy controls. Moreover, within the different subgroups, the highest levels and the highest odd ratio of PTX3 were detected in the subgroups having the highest Davies co-morbidity index, or the highest malnutrition score as compared to the other subgroups. At a cutoff 0.6 ng/mL, PTX3 was able to discriminate HD patients with low Davies co-morbidity index from those with both medium and high Davies co-morbidity index with a diagnostic sensitivity of 92.5% and a diagnostic specificity of 70.0%. Meanwhile, the best cutoff of plasma PTX3 for discriminating patients with mild malnutrition from severe and moderate malnutrition was 0.6 ng/mL with a diagnostic sensitivity 90.9% and a diagnostic specificity 41.2%. In conclusion: Pentraxin 3 appears to be a clinically useful marker for early identification of patients with renal failure on maintenance HD who are at substantially increased risk of morbidity. These patients may require care and aggressive follow-up in more specialized units. Such patients would also probably benefit from early referral to a renal transplant center for consideration of candidacy for transplantation and expedited evaluation

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#### Introduction

It is generally admitted that alterations in the immune and host defense system occur in patients with end-stage renal disease (ESRD). Moreover a chronic inflammatory condition, associated with a state of malnutrition and cardiovascular complications are often prevalent in hemodialysis (HD) patients and could be responsible for more than 50% of the morbidity and mortality observed in these patients<sup>(11,19)</sup>.

Pentraxin 3 (PTX-3) is a long pentraxin structurally related to, although distinct from, classic short pentraxins, such as CRP and serum amyloid P<sup>(12)</sup>. PTX-3 is the first cloned long pentraxin as an interleukin-1b (IL-1b)-inducible gene in endothelial cells and a tumor necrosis factor (TNF- $\alpha$ )-a stimulated gene (TSG14) in fibroblasts. PTX-3 expression occurs in a variety of cell types, including endothelial cells, mononuclear phagocytes, dendritic cells, smooth muscle cells, fibroblasts, adipocytes and epithelial cells in response to inflammatory cytokines<sup>(8,14)</sup>. A dramatic increase in the levels of PXT3 have been reported in critically ill patients, with a gradient from systemic inflammatory response syndrome to septic shock, in addition to several other diseases as acute

coronary syndrome, acute respiratory distress syndrome, lung disease and eclampsia<sup>(14,17)</sup>.

**Aim Of The Work:** The aim of this work was to measure the plasma level of pentraxin 3 (PXT3) in patients on maintenance hemodialysis and to assess its relationships to co-morbidities such as malnutrition and associated co-morbid diseases.

#### Subjects And Methods:

##### Subjects:

This study was conducted at the internal medicine department and the renal dialysis unit of Ain Shams University Hospitals. All participants granted their consent to share in this study.

##### **Group I: Hemodialysis Patients (n = 50):**

This group included fifty (50) adult patients with ESRD who were on maintenance hemodialysis for more than 3 months. They were 26 females and 24 males who were recruited from the renal dialysis unit at Ain Shams university hospitals.

Patients of this group were further categorized according to Davis Co-morbidity index into low, medium and high co-morbidity subgroups<sup>(7)</sup>. Moreover, patients were classified according to the malnutrition score into 3 classes; mild malnutrition,

moderate malnutrition and severe malnutrition subgroups<sup>(4)</sup>.

**Group II: ESRD Patients (n = 30):**

This group included thirty (30) adult patients with ESRD defined by a glomerular filtration rate (GFR) < 15mL/min and who did not start any renal replacement therapy. They were 13 females and 17 males, who were recruited from the internal medicine department at Ain Shams University Hospitals.

**Group III: Healthy Controls (n= 30):**

This group included thirty (30) age - and sex-matched healthy subjects serving as a control group. They were 16 females and 14 males.

**Exclusion criteria:** Patients who received inadequate hemodialysis (defined as a urea reduction ratio >65 %) or who were on maintenance hemodialysis for less than 3 months and patients with acute infections were excluded from the study<sup>(3)</sup>.

All participants in this study were subjected to full history taking and clinical examination with special emphasis on the nutritional state, DM, obstructive pulmonary disease, cardiovascular complications, collagen diseases, peripheral ischemia, malignancy, the assay of plasma pentraxin 3 (PTX3) and routine laboratory investigations (Hemoglobin concentration, ESR, hs CRP, FBS, 2 h PP blood sugar, liver profile, serum urea and creatinine). In addition, group I was subjected to the estimation of efficiency of hemodialysis by the calculation of urea reduction ratio (URR), assessment of co-morbidity score according to Davies co-morbidity index and calculation of malnutrition score. Finally, group II was subjected to the measurement of the GFR by the calculation of the corrected creatinine clearance.

**Sampling:**

-Five milliliters of fasting morning venous blood (predialysis in case of group I) were withdrawn under complete aseptic conditions from each participant. Three mL of them were collected in a sterile dry vacutainer; serum was then separated by centrifugation and was used for the immediate assay of serum urea and creatinine. The remaining two mL were collected into an EDTA tube for the immediate estimation of hemoglobin concentration followed by sample centrifugation at 1000 xg for 15 minutes within 30 minutes of collection. The separated plasma was stored at -70°C for subsequent assay of plasma PTX3.

-For group II patients, a 24-hour urine sample was collected for the immediate measurement of GFR measured as corrected creatinine clearance in addition group I patients were subjected to a post-dialysis venous blood sample collection for assay of serum urea.

**Methods:**

**A) Analytical Methods:**

**1- Assay of serum urea and both serum and urinary creatinine** was performed on Synchron CX-9 autoanalyser (Beckman Instruments Inc., Scientific Instruments Division, Fullerton, CA92634-3100, USA).

**2- Hemoglobin concentration** was done using Max M Coulter (Beckman Coulter, Inc., 22 RaioJuste-Olivier, 1260 Nyon-Switzerland).

**3- Plasma Pentraxin 3 (PTX3)** was carried by a sandwich a commercially available ELISA kit provided by Quantikine R&D International, Inc. (R&D International, Inc., 614 McKinly Place N.E., Minneapolis, MN55413 USA). The detection limit is 100 pg/mL and inter assay variability is 8%-10%. In this technique, a streptavidin-coated plate is incubated with a biotinylated monoclonal antibody specific for PTX3. Plate wells are washed and pretreated standards and samples are added to the wells. Any PTX3 present is bound by the immobilized biotinylated antibody. After washing away any unbound substance, an enzyme-linked conjugate specific for PTX3 is added to the wells. Following a wash to remove any unbound conjugate, a substrate solution is added to the wells and color develops in proportion to the amount of PTX3 bound. The color development is stopped and the intensity of the color is measured. A standard curve was constructed and from which concentration of PTX3 (ng/mL) was deduced by interpolation<sup>(9)</sup>.

**B) Methods of Calculated Parameters:**

**1- Calculation of urea reduction ratio (URR)** by the following equation:

$$URR = \{(\text{pre dialysis blood urea nitrogen "BUN"} - \text{post dialysis BUN}) / \text{pre dialysis BUN}\} \%^{(10)}$$

**2- Calculation of corrected creatinine clearance** by the following equation:

$$[\text{urine creatinine} \times \text{urine volume} / \text{serum creatinine}] \times [1.73 / \text{S.A} \times 1440]^{(13)}$$

**3- Davies Co-morbidity Index Score:** the score assigns 1 point for each of the following conditions; ischemic heart disease, left ventricular dysfunction, peripheral vascular disease, malignancy, diabetes, collagen vascular disease, and other significant pathology (e.g., chronic obstructive pulmonary disease). The theoretical range is zero to seven. Accordingly, patients were categorized into; patients with low Davies Co-morbidity index score (score 0), patients with medium Davies Co-morbidity index score (score from 1-3) and patients with high Davies Co-morbidity index score (score more than 3)<sup>(5)</sup>.

**4- Malnutrition Score** was applied to assess the degree of malnutrition based on five parameters [ body mass index (BMI), mid-upper arm circumference (MUAC), hemoglobin level, clinical examination for signs of nutritional deficiencies and gastrointestinal tract (GIT) manifestations]. Each

parameter was given a score ranging from 3-6. The total score of malnutrition score ranged from a minimum of 15 to a maximum of 30, and accordingly patients were divided into; patients with no malnutrition (score 15 - > 21), patients with mild malnutrition (score 21- < 24), patients with moderate malnutrition (score 24- >27) and patients with severe malnutrition (score 27-30)<sup>(4)</sup>.

**C) Statistical Methods:** statistical analysis was carried out on personal computer using SPSS software version 8, USA. Non-parametric data were expressed as median and interquartile range (IQR). Comparative statistics was done by Kruskal- Wallis test, Wilcoxon's rank sum and Chi-squared test. The Odds ratio was calculated in order to study the relationship between two characteristics Receiver operating characteristic curve (ROC) analysis was applied to assess the overall diagnostic performance of PTX3 in the study.  $P > 0.05$  was considered non significant,  $P < 0.05$  was considered significant and  $P < 0.01$  conclusion and recommendation: was considered highly significant.

### Results

The results obtained in the present study are presented in tables (1-5) and figures (1 and 2).

Descriptive and comparative statistics of the various measured parameters in the different studied groups are shown in **table (1)**. A significant difference was found between the three groups as compared to each other regarding serum urea, hemoglobin and plasma PTX3 ( $p < 0.001$ ), while a non significant difference was found between the three groups as regards age and sex ( $p > 0.05$  respectively). Meanwhile, a significant difference was found regarding serum creatinine in control group when compared to either HD or ESRD patient groups ( $p < 0.001$  respectively).

The descriptive and comparative statistics between the different HD patient subgroups regarding

plasma PTX3 are shown in tables (2 and 3). When HD patients were classified according to the Davies co-morbidity index, a highly significant difference was found between the three subgroups as regards plasma level of PTX3 ( $p < 0.001$ ), being highest in patients with high co-morbidity index and lowest in patients with low co-morbidity index (median 36 ng/mL vs 0.6 ng/mL). Classification of HD patients according to the malnutrition score revealed the presence of a highly significant difference in plasma PTX3 only between patients with severe malnutrition as compared to either those with mild or moderate malnutrition ( $p < 0.001$  respectively), being highest in the former subgroup (median 41.5 ng/dL vs 0.95 and 1.2 ng/dL).

In the present study, the odds ratio for plasma PTX3 were calculated in order to study the degree of its association with each of Davis co-morbidity index and malnutrition score (Table 4). The analysis showed that plasma PTX3 was significantly associated with high odds ratio for Davis co-morbidity index (odds ratio 28;  $p > 0.001$ ) and malnutrition score (odds ratio 7;  $p > 0.05$ ).

The study of the diagnostic performance of plasma PTX3 in the discrimination between different HD subgroups revealed that the best ROC cutoff of plasma PTX3 in discriminating patients with high and medium Davis co-morbidity index from those with low Davis co-morbidity index was 0.6 ng/mL with a diagnostic efficacy of 86.0%, sensitivity 92.5%, specificity 70%, PPV 92.5%, NPV 70.0%, and AUC 0.92 (Table 5 and figure 1). Meanwhile when patients were classified according to the malnutrition score, a cutoff 0.6 ng/mL was found to discriminate patients with severe and moderate malnutrition from those with mild malnutrition with diagnostic efficacy of 74%, sensitivity 90.9%, specificity 41.2%, PPV 75%, NPV 70%, and AUC 0.75 (Table 5 and figure 2).

**Table (1):** Descriptive and comparative statistics of the measured parameters between different studied groups

Parameters Parameters	Group I (n=50)	Group II (n=30)	Control (n=30)	Group I vs Control	Group I Vs Group II	Group II Vs Control
	Median(IQR)	Median(IQR)	Median(IQR)			
Age (years)	53.5 (44.5-63.3)	50 (37.5-58)	51 (49-60.5)	$z$ 0.57 $p > 0.05$	$z$ 0.52 $p > 0.05$	$z$ 0.25 $p > 0.05$
Sex	M 48%	M 56.7%	M 46.7%	$\chi^2$ -0.01 $p > 0.05$	$\chi^2$ 0.27 $p > 0.05$	$\chi^2$ -0.16 $p > 0.05$
	F 52%	F 43.3%	F 53.3%			
Urea (mg/dL)	181 (105-223)	90 (60-100)	20 (15-25)	$z$ 8.78 $p < 0.001$	$z$ 13.72 $p < 0.001$	$z$ 7.06 $p < 0.001$
Creatinine (mg/dL)	9.1 (7.8-12.8)	10.1 (8.5-13.0)	0.5 (0.4-0.8)	$z$ 25.90 $p < 0.001$	$z$ -1.60 $p > 0.05$	$z$ 18.55 $p < 0.001$
Hb (g/dL)	9.2 (8.9-10.6)	11.4 (9.6-12.9)	12.4 (11.3-13.0)	$z$ - 6.15 $p < 0.001$	$z$ -4.83 $p < 0.001$	$z$ -10.37 $p < 0.001$
Pentraxin 3 (ng/mL)	2.3 (0.9-33.0)	0.8 (0.6-1.5)	0.4 (0.3-0.5)	$z$ 5.71 $p < 0.001$	$z$ 4.85 $p < 0.001$	$z$ 4.35 $p < 0.001$

Group I: Hemodialysis patients; Group II: ESRD patients; Hb: hemoglobin;

IQR: Interquartile range;  $p > 0.05$ : Non-significant difference;  $p < 0.001$ : Highly significant difference.

**Table (2):** Descriptive and comparative statistics of PTX3 levels among different HD patient subgroups according to Davis co-morbidity index and malnutrition score

Parameters	PTX3 Median (IQR)	Test of Significance	
		H	p
<b>Davies co-morbidity index</b>			
Low (n=10)	0.6(0.5-0.9)	45.0	>0.001
Medium (n=15)	1.4(0.7-3.0)		
High (n= 25)	36.0(10.0-40.0)		
<b>Malnutrition Score</b>			
Mild (n=16)	0.95(0.5-3.0)	46.9	>0.001
Moderate (n=20)	1.2(0.7-6.0)		
Severe (n=14)	41.5(25.0-60.0)		

PTX3: pentraxin 3; IQR: interquartile range; p >0.001: highly significant difference.

**Table (3):** Between- two groups- comparison of PTX 3 levels in the different HD patient subgroups according to Davis co-morbidity index and malnutrition score

Parameters	PTX3	
	Z	p
<b>Davies co-morbidity index</b>		
Low vs Medium	-2.50	>0.05
Low vs High	-4.38	>0.001
MediumvsHigh	-4.49	>0.001
<b>Malnutrition Score</b>		
Mild vs Moderate	-1.55	<0.05
Mildvs Severe	-4.14	>0.001
ModerateVs Severe	-3.92	>0.001

PTX3: pentraxin 3; HD: hemodialysis; P <0.05: non-significant difference  
p>0.05: significant difference; p >0.001: highly significant difference.

**Table (4):** Odds ratio of pentraxin 3 in different HD patient subgroups

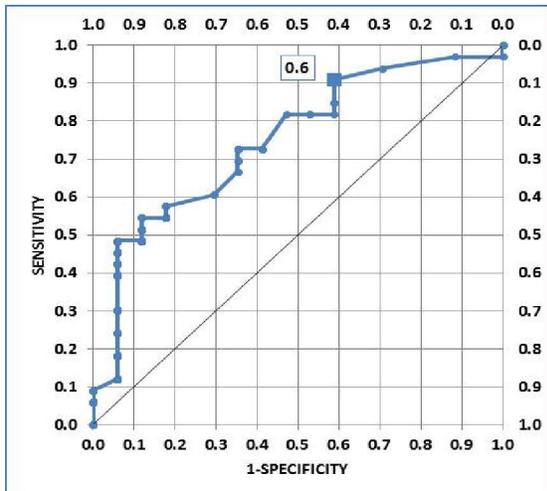
	Odds Ratio	95% CI		p
		Lower	Upper	
<b>Davis co-morbidity score</b>				
High and medium vs low	28.78	4.79	172.82	<0.001
<b>Malnutrition score</b>				
Severe and moderate vs mild	7.00	1.52	32.33	>0.05

95% CI: 95% confidence interval; H.D.: hemodialysis;  
p<0.05: significant difference; p >0.001: highly significant difference

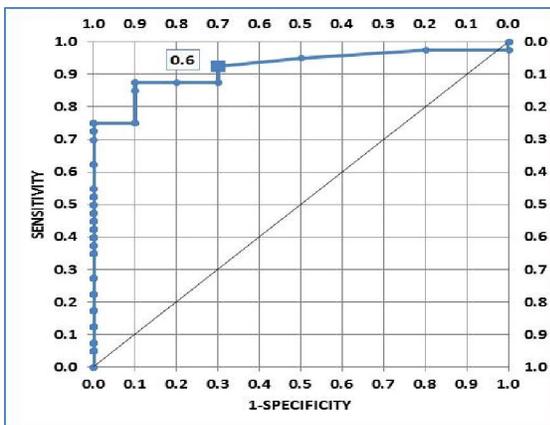
**Table (5):** Diagnostic performance of pentraxin 3 levels in different H.D. patient subgroups according to Davis co-morbidity index and malnutrition score

Parameter	ROC Cutoff ng/mL	Diagnostic Sensitivity %	Diagnostic Specificity%	Positive Predictive Value %	Negative Predictive Value %	Diagnostic Efficiency %
<b>Davies co-morbidity score</b>						
High and medium Vs low	0.6	92.5	70.0	92.5	70.0	86.0
<b>Malnutrition score</b>						
Severe and moderate Vs mild	0.6	90.9	41.2	75.0	70.0	74.0

HD: hemodialysis; ROC: receiver operating characteristic.



**Figure (1):** ROC curve analysis showing the diagnostic performance of PTX3 for discriminating patients with high and medium Davis co-morbidity index from those with low Davis co-morbidity index.



**Figure (2):** ROC curve analysis showing the diagnostic performance of PTX3 for discriminating patients with severe and moderate malnutrition score from those with mild malnutrition score.

## Discussion

In the present study, plasma PTX3 demonstrated higher levels among ESRD group as compared to controls. This finding was supported by a study performed by **Zhou et al.**<sup>(19)</sup> showing the ability of PTX-3 to bind to the C1q component of the complement cascade and to participate in the clearance of apoptotic cells; hence suggesting an important role for PTX-3 in the regulation of inflammatory reactions and innate immunity. In addition, because PTX-3 is produced from vascular endothelial cells and macrophages, PTX-3 levels may directly reflect the inflammatory status.

The present study revealed the presence of higher plasma PTX3 levels in HD patients than in

those with ESRD. This finding were strengthened by **Boehme et al.**<sup>(1)</sup>, **Tong et al.**<sup>(18)</sup> and **Oldani et al.**<sup>(14)</sup> who demonstrated the ability of HD procedure itself to exaggerate the already present pro-inflammatory state likely by the bio-incompatibility from HD membrane, exposure to exotoxins from dialysate water and infected vascular access during the extracorporeal procedure. As a consequence, an increase in different pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and IL-17 occurs with subsequent enhanced over-expression of PTX3 in primary proximal tubular epithelial cells (PTECs), primary mesangial cells and renal fibroblasts, followed by its release into the systemic circulation in high concentrations. Being produced locally at the site of inflammation, the PTX3 level is believed to be a true independent indicator of disease activity<sup>(12, 16)</sup>.

Aiming to evaluate the relationship between the plasma PTX3 level and the co-morbid diseases, HD patient group was divided according to Davies co-morbidity index into three subgroups (low, medium and high Davies co-morbidity index)<sup>(7)</sup>. Accordingly, the highest level of PTX3 was detected in the high Davies co-morbidity index followed by the medium Davies co-morbidity index then the low Davies co-morbidity index. Similar data were reported by **Davies et al.**<sup>(6)</sup> and **Suliman et al.**<sup>(17)</sup>, who added that the association between PTX3 and co-morbidities is not surprising as the chronic inflammation may increase the pro-oxidant activity usually in generalized tissue damage which could definitely trigger the occurrence of co-morbid diseases such as ischemic heart disease, left ventricular dysfunction, peripheral vascular disease, malignancy, diabetes, systemic collagen disease and other significant pathology (e.g., chronic obstructive pulmonary disease, cirrhosis), in HD patients.

In order to evaluate the relationship between the level of plasma PTX3 and the degree of severity of malnutrition in HD patients, the HD patients were divided according to malnutrition score into mild, moderate and severe subgroups<sup>(4)</sup>. Accordingly, the plasma level of PTX3 was significantly higher in, severe malnutrition subgroup than in moderate or mild malnutrition. These finding were in accordance with that of **Suliman et al.**<sup>(17)</sup> and **Bonanni et al.**<sup>(2)</sup> who mentioned that the occurrence of malnutrition in HD patients is not entirely accounted for by inadequate nutrient intake but increases progressively along with the loss of residual renal function. Moreover, the uremia-induced alterations in both protein metabolism (negative protein balance and negative energy balance) and gastrointestinal tract function (anorexia, hiccups, nausea, vomiting, uremic fetor associated with unpleasant taste, mucosal ulceration, peptic ulcer, diarrhea due to antibiotic treatment, and constipation)

can exaggerate the malnutrition status, which in turn aggravates the inflammation leading to a decrease synthesis of negative acute-phase proteins (albumin, pre albumin, transferrin, retinol binding protein and insulin growth factor-1) by liver.

In the present study, the degree of association between PTX3 level and each of Davies co-morbidity index and malnutrition score was evaluated by the calculation of the odds ratios. The analysis showed that high plasma PTX3 was significantly associated with high odds ratio for high Davies co-morbidity index and severe malnutrition score (odd ratio 28 and 7 respectively).

In the present study, assessment of the diagnostic performance of plasma PTX3 in discriminating between different HD subgroups was assessed. The best plasma PTX3 cutoff for discriminating patients with low Davies co-morbidity index from those with both medium and high Davies co-morbidity index was 0.6 ng/mL. This cutoff showed a diagnostic sensitivity of 92.5%, diagnostic specificity of 70.0%, negative predictive value of 70.0%, positive predictive value of 92.5%, the diagnostic efficacy of 86.0% and an AUC of 0.92. Meanwhile, the best cutoff of plasma PTX3 for discriminating patients with mild malnutrition from severe and moderate malnutrition was 0.6 ng/mL with diagnostic sensitivity 90.9%, diagnostic specificity 41.2%, negative predictive value 70.0%, positive predictive value 75.0%, diagnostic efficacy 74.0% and an AUC was 0.75.

In conclusion: Pentraxin 3 appears to be a clinically useful marker for early identification of patients with renal failure on maintenance HD who are at substantially increased risk of morbidity. These patients may require care and aggressive follow-up in more specialized units. Such patients would also probably benefit from early referral to a renal transplant center for consideration of candidacy for transplantation and expedited evaluation.

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