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PROGNOSTIC VALUE OF PENTRAXIN3 IN ACUTE CORONARY SYNDROME

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ABSTRACT

Purpose: Pentraxin 3(PTX3) is a recently identified member of the pentraxin family that is increased in acute coronary syndrome (ACS).

The aim of this study was to assess the value of PTX3 in acute coronary syndrome by comparing it with serum hs CRP (highly sensitive CRP) and troponin I (TnI) together with its prognostic value.

Material and Methods: The study was conducted on 61 patients from the ICU divided into three groups Group 1: myocardial infarction(n=18), Group 2: unstable angina (n=19), Group 3: stable angina (n=24) these groups were compared to 15 healthy controls.

All participants received clinical assessment, PTX 3,TnI,hs CRP and lipid profile.All patients were followed up for six months after discharge.

Results: The statistical differences between cardiac groups and control in the lipid profile($p<0.001$) PTX 3, TnI, hsCRP were significantly higher in the myocardial infarction group compared to other groups ($p <0.001$).

Using (ROC) curves AUC for PTX3 -hs CRP -Tn I (0.962,0.916,0.922) pentraxin showed the highest validity.

The cut-off point for the ROC on follow-up was 3.75 for pentraxin with a sensitivity of 66.7 % and 0.708 for TnI with sensitivity 60%.

Conclusions: PTX3 is a sensitive and specific biomarker for the diagnosis of ACS exhibiting additional prognostic value when measured with TnI.

Key words: acute coronary syndrome, pentraxin 3, Troponin, hsCRP

1. INTRODUCTION

The onset of acute coronary syndrome (ACS) involves rupture or erosion of atherosclerotic plaques in coronary arteries. The microembolization of platelet aggregates and components of the disrupted plaque are believed to be responsible for the release of myocardial markers in many of these patients. Although biomarkers for ischemic myocardial damage, such as troponin-T (TnT), have been clinically utilised to diagnose ACS,the diagnostic sensitivity and specificity for ACS, especially at the earliest stage, remain insufficient.[1-2].

Pentraxin-3 (PTX3) has emerged as a novel marker thought to be more specific for vascular inflammation than other proteins in the pentraxin family such as C-reactive protein (CRP). Higher PTX3 levels are associated with worse cardiovascular (CV) outcomes after acute coronary syndromes, independently of CRP.[3-4]

Pentraxin-3 is also associated with increased risk of CV death among elderly persons without established CV disease (CVD).[5]

The biologic plausibility of its role in CVD risk is supported by its localisation in atherosclerotic plaques,[4] and the higher concentration of PTX3, but not CRP, in the coronary sinus of patients with heart failure (HF).[6]

Contradictory results regarding the value of PTX3 as a predictor of adverse outcomes among persons with acute coronary syndrome has not been well studied.

The aim of our study was to assess the value of PTX3 compared with other cardiac inflammatory markers in acute coronary syndrome and its prognostic value

2. PATIENTS AND METHODS

The present study included 61 patients presenting with chest pain or chest discomfort, occurring within 24 hours prior to admission, to the medical ICU in Kasr El Aini hospital.

The patients were categorised into 3 groups according to the ECG findings and cardiac enzymes:

Group 1: included 18 patients with acute myocardial infarction. Sixteen of the patients presented with STEMI (diagnosed by persistent ST segment elevation of at least 0.1mV in at least 2 contiguous leads evolving

into pathological Q waves) and 2 with NSTEMI (diagnosed by depressed ST segment of at least 0.5mV in at least 2 contiguous leads evolving or not into pathological waves). Acute myocardial infarction was defined as a cardiac troponin- I level > 0.1 ng/mL of the upper reference limit on admission or 8 h after admission.

Group 2: included 19 patients with unstable angina. Twelve of the patients presented with ECG showing inverted T waves of at least 0.1mV in at least 2 contiguous leads, 5 presented with flat T waves and 2 with right bundle branch block.

Group 3: included 24 patients with stable angina. All of the patients were free of recent ECG changes.

In addition, 15 healthy volunteers as a control group (group 4) were included in the study.

Informed consent was obtained from all participants prior to participation.

Exclusion criteria

1- Patients with renal impairment (serum creatinine > 1.3mg/dl).
2- Malignant diseases, inflammatoryconditions, autoimmune diseases and diabetes mellitus.
3- Patients with vasospastic angina, symptomatic peripheral vascular disease or stroke.

Methods

This study was performed into in 2 stages

Stage 1; cross sectional study of 3 groups of patients

Stage 2; prospective study 6 month follow up for cardiac event

A thorough history was obtained from all patients, including demographic data (age, gender and smoking), history of hypertension, diabetes mellitus, previous similar attacks, symptoms suggestive of coronary artery disease or symptoms suggestive of ventricular dysfunction. Furthermore, physical examination to assess any cardiac abnormality and an electrocardiogram were performed for all patients on admission.

All patients underwent follow-up for 6 months after admission via a telephone call. A cardiac event was defined as cardiac death, rehospitalisation for ACS, or rehospitalisation for worsening heart failure.

Laboratory Analysis

Venous blood samples were drawn at the time of admission to analysis the seru[illegible]uman serum C - reactive protein (hs-CRP), serum cardiac troponin I, plasma pentraxin3, serum total cholesterol, Triglycerides, HDL, LDL and serum creatinine.

Methodology

- The plasma PTX3 concentrations were measured via a newly developed enzyme-linked immunosorbent assay (ELISA). This assay can measure plasma PTX3 concentration linearly between 0.1 and 20 ng/mL. The coefficient of variation for the PTX3 assay was 3.7% at 0.2 ng/mL and 1.4%at 2.2 ng/mL.[7]
- The serum hs CRP levels were measured using the high-sensitivity CRP-Latex X2 Seikeen Assay Kit.[8]
- The serum troponin I level was measured using a Stratus CS analyser and the serum creatinine was measured with an enzyme method using Liqitech Creatinine PAP II. The coefficient of variation for the hs CRP assay was 5.1% at 0.17 mg/L and 2.5% at 1.88 mg/L while that for the troponin I assay was 9.0% at 0.12 ng/mL and 5.1% at 6.3 ng/mL.[9]
- The coefficient of variation for the creatinine assay was 2.3% at 0.2 mg/dL and 1.4% at 3.2 mg/dL.[10]
- The estimated glomerular filtration rate (GFR) was calculated with the following formula :(194 × Age 0.287 × Serum creatinine concentrations).[11]

3. RESULTS

The present study included 61 patients who were categorized into 3 groups according to the ECG findings and cardiac enzymes:

The demographic data of the studied groups was the following mean of age in years ± SD in group 1 (56.39 ± 10.16), in group 2 (55.06 ±7.44), in group 3 (61.11 ± 12.49) in control group (57.67± 7.95).

The sex distribution Female /Male ratio was (9/9) in group 1, (8/11) in group 2, (9/15) in group 3 and in control group (7/8).

Smoking (n) % in group 1 (8) 45%, in group 2 (9) 50%, in group 3 (15) 63%.

Hypertension(n)% in group 1 (7) 38.9%, in group 2 (10) 56.3%, in group 3 (11) 40.7%

Mean hypertension duration in months in group 1 (32.6 ± 15.33), in group 2 (27.10 ± 26.63), in group 3 (36.11 ± 28.69).

The fraction of patients with a history of coronary artery disease in group 1 was (7) 38.9%, in group 2 (13) 68.42%, in group 3 (23) 95.8%.

The laboratory data of the studied groups are shown in table 1.

Table 1. The laboratory data of the studied groups

Groups / Variables	Group 1: Myocardial infarction (mean±SD)	Group 2: Unstable angina (mean±SD)	Group 3: Stable angina (mean±SD)	Group 4: Control (mean±SD)
Serum Cholesterol(mg/dl)	218.43± 27.3 (a)	209± 36.48 (a)	209 ± 36.52 (a)	148.5± 20.54 (b)
Serum TG(mg/dl)	95.01± 13.43 (a)	91.8 ± 11.64 (a)	91.58± 14.88 (a)	78.31±8.88 (b)
Serum HDL(mg/dl)	38.8± 6.94 (a)	34.48± 4.9 (a)	36.27± 5.96 (a)	50.33± 5.75 (b)
Serum LDL(mg/dl)	160.63±29.33 (a)	165.6±34.04 (a)	149.43 ± 37.95 (a)	78.24± 19.02 (b)
Serum Pentraxin3 (1.2n/l)	6.02± 1.55 (a)	3.58± 0.88 (b)	2.52 ± 1.13 (b)	0.87± 0.32 (c)
Serum Troponin-I (<1n/l)	5.15±3.38 (a)	0.83± 0.088 (b)	0.78 ± 0.051 (b)	0.02 ± 0.01 (c)
Serum hs-CRP (1.1 mg/l)	9.29 ± 3.14 (a)	3.17 ± 1.69 (b)	3.07 ± 1.16 (b)	1.06±0.48 (c)

**different initials means statistically significant difference*

The lipid profiles of the cardiac groups did not differ, while the control statistically differed from the cardiac group (p<0.001).

The levels of Pentraxin 3, Troponin –I and hsCRP were significantly higher in the myocardial infarction group compared to the unstable and stable angina (p <0.001). However, groups2-3 did not statistically differ.

Group I showed positive correlation between pentraxin 3, troponin I and hs CRP (p = 0.005 r=0.63/ p<0.001 r= 0.819).

Group II showed positive correlation between pentraxin 3 and troponin (p=0.05 r=0.631).

Group III showed positive correlation between pentraxin 3 and troponin(p=0.001 r=0.624), pentraxin 3 and hs CRP (p<0.001, r=0.717) and Troponin and hsCRP (p=0.001 r=0.592).

The correlation between biomarkers of cardiac damage are shown in table 2.

Table 2. Correlation between biomarkers of cardiac damage

group	pentraxin		troponin		hs CRP	
groupI	p	r	p	r	p	r
pentraxin 3	-	-	0.05*	0.631	<0.001*	0.819
troponin	0.05*	0.631	-	-	0.12	0.581
group II						
pentraxin 3	-	-	0.008*	0.633	0.65	0.472
troponin	0.008*	0.631	-	-	0.012	0.61
group III						
pentraxin 3	-	-	0.001*	0.624	<0.001*	0.717
troponin	0.001*	0.624	-	-	0.001*	0.592

**statsticaly significant <0.05*

Table 3. Results of ROC curve comparing different matkers

marker	cut off value	AUC	senstivity	specificity	PPV	NPV	TA
pentraxin	4.06	0.962	94.4%	86.2%	68.0	98	88.2
troponin	0.36	0.916	94.4%	70.7%	51.4	100	77.6
hsCRP	4.150	0.922	88.9%	75%	53.3	95.7	79

AUC:Area under the curve

PPV:Positive predictive value

NPV:Negative predictive value

TA: Total area

Figure 1 compares the diagnostic validity of PTX3 with those of Troponin and hs CRP using a receiver operating characteristic (ROC) curve for myocardial infarction against control shown in fig 1.

The diagnostic validity in acute myocardial infarction versus other groups is compared in table 3 for all cardiac enzymes.

The AUC values of Pentraxin, CRP and serum troponin were (96.2, 92.2 and 91.6) respectively, showing that the validity of the ROC curve of pentraxin was highest for unstable angina versus the control AUC for hs CRP, pentraxin and troponin I (1.0.971 and 1, respectively).

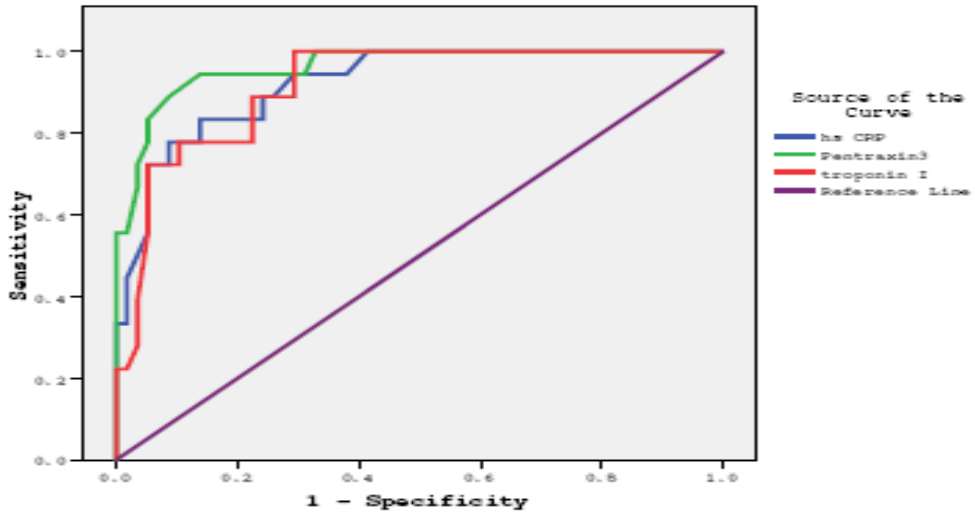

Fig. 1. *(ROC) curve for cardic markers in myocardial infarction against control*

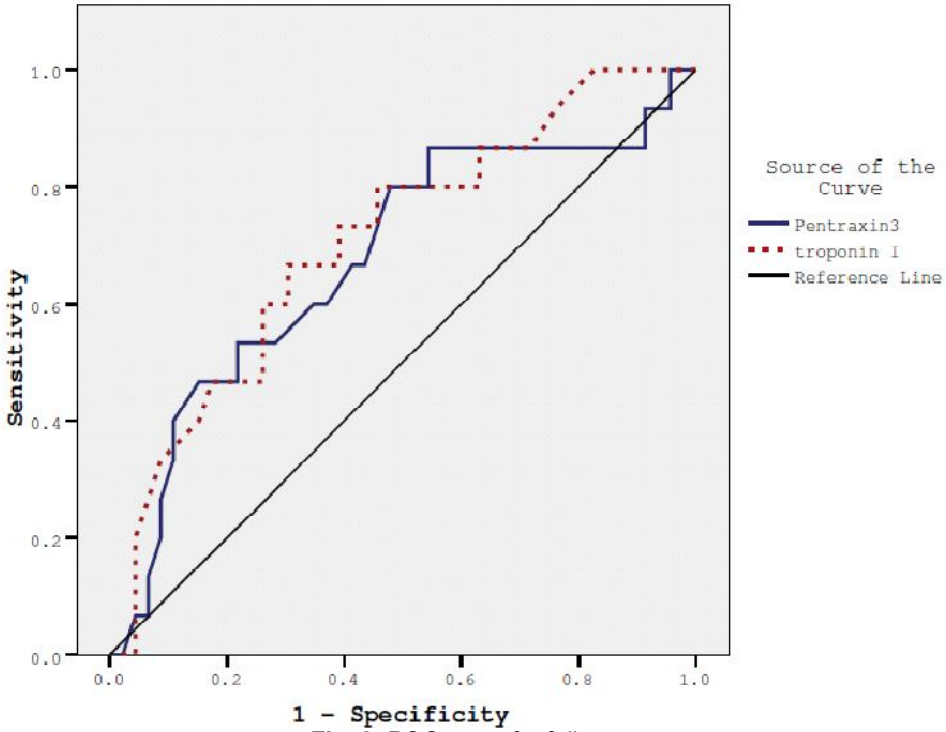

Fig. 2. *ROC curve for follow up*

Predictors of 6-month cardiac events

All patients were followed up for 6 months via telephone call to assess the following outcomes:

re-admission (8 myocardial infarction, 2 unstable angina, total n=10) 16.4% and death (n=5) 8.2%

The incidence of cardiac events was higher in patients with high pentraxin level ≥4 ng/ml

Thus troponin I more reliably predicted outcome than pentraxin 3.

We studied the predictive probability of different variable to detect out come, including (age, sex, PTX3, TnI, duration of illness and triglyceride level) And predicted Probability score from 0-1.

Higher scores indicated worse outcomes.The ROC curve analysis for follow up is shown in fig (2).

The cut off value of pentraxin was (3.75 AUC 0.677) with a sensitivity of 66.7%

The cut-off point of TnI was (0.708 AUC 0.708) with a sensitivity of 60%

The hsCRP level did not correlate with the prognosis.

Thus, pentraxin 3 is a strong independent biomarker for acute coronary syndrome with a high diagnostic sensitivity and superior to other inflammatory markers.

Using pentraxin with troponin is a better predictor for acute coronary syndrome than pentraxin alone over a 6 month duration.

4. DISCUSSION

The importance of circulating markers of cardiac damage in acute MI for early diagnosis and prognostic stratification has expanded from markers of cardiac myocyte necrosis such as creatine kinase,[1-2] and troponins,[12-13] to markers of inflammation such as the short pentraxin, CRP and serum amyloid A protein (SAP) (Inflammatory mediators are intimately associated with the cascade of events leading to atherosclerotic plaque initiation, development, and rupture. [14-15]

However the clinical value of inflammatory biomarkers, is limited as many of them lack specificity regarding cardiovascular pathologies, and they often yield only moderate prognostic value. PTX3 has been suggested as a promising candidate biomarker in this context. PTX3 is produced at the site of injury and might therefore be a useful indicator of localised cardiovascular inflammatory processes.[16-23]

In the present study, the mean values of serum total cholesterol, TG, HDL or LDL cholesterol did not statistically significantly. In agreement with these results, Kume et al 2011 found that the serum total cholesterol, HDL, LDL cholesterol and TG levels were not significantly differ between acute coronary syndrome and non-acute coronary syndrome patients.[24]

Our results showed that the mean values of serum pentraxin3 were elevated in all cardiac groups. The mean values of serum pentraxin3 were statistically significantly higher in all of the cardiac groups compared to the control group ($p<0.001$).

The mean serum pentraxin3 levels in patients in group I (myocardial infarction) were statistically significantly higher than those of both group 2 (unstable angina) ($p<0.001$) and group 3 (stable angina) ($p<0.001$).

The mean values of pentraxin3did not statistically differ between group 2 and group 3 ($p=0.051$).

In agreement with our results the expression of PTX3 was found to be increased in patients with myocardial infarction. [4-6-19]

Peri et al 2000, observed that PTX3 peaked at a median of 7.5 hrs in patients with acute myocardial infarction and returned to normal after 3 days (14).

Inoue et al 2007(6), found that the level of serum PTX3 increased in patients with unstable angina. These findings led to the investigation of PTX3 expression levels as a potential prognostic indicator of disease. Matsui et al, 2010,[4] found that the expression of pentraxin ± 3.1ng/ml in patients with UA/NSTEMI was an independent predictors for cardiac events over 6 months which were defined as cardiac death, rehospitalisation for acute coronary syndrome, or rehospitalisation for worsening heart failure. Latini et al 2007 found that the level of PTX3 rapidly increased after unstable angina or acute myocardial infarction and that a level of PTX3 of exceeding 10.73 ng/ml was a predictor of 3 month mortality in patients with acute MI. [4]

Eggres et al found that the PTX3 levels in NSTE-ACS patients were significantly higher compared to healthy controls.[22]

Notably, the PTX3 levels in patients with ST-elevation myocardial infarction have been described as being almost twice as high.This findings supports the notion that PTX3 levels correlate with the amount of injured myocardium as also suggested by the association between the levels of PTX3and cTnT.19

In our study we found correlation between troponin I and pentraxin 3 in acute myocardial infarction group ($p=0.05, r=0.631$).

Norma et-al reported high level of circulating PTX3 in the early phase of AMI (within 6 h of the onset of clinical symptoms). The PTX3 level returns to normal values 48 h after the onset of symptoms; the concentration does not vary in matched healthy controls or in patients with chronic stable angina. [23]

In our study, the PTX3 levels did not significantly correlat with any of the parameters of the lipid profile. Similar results were also recorded by Kume et-al 2011.[24]

We compared the diagnostic sensitivity and specificity of pentraxin3 for acute myocardial infarction, unstable angina and stable angina with those of troponin I and hs-CRP using ROC curves. The sensitivity and specificity of pentraxin3 for the diagnosis of AMI appeared to be higher than those of troponin and hs-CRP. The AUC values for pentraxin3, troponinI and hs-CRP were 0.962, 0.916 and 0.922 respectively. In the myocardial infarction group, the ROC curves of the sensitivity and specificity for PTX3 were 94 % and 86% respectively. These values were 94% and 70% respectively for troponin I and 88% and 75% respectively for hs-CRP.

Matsui et al. found that the PTX3 levels exceeding 3.1 ng/mL in patients with UAP/non-ST-elevation MI (n = 204) was predictive of the occurrence of a 6-month cardiac event, including cardiac death, rehospitalisation for ACS, and rehospitalisation for worsening heart failure [matsui], while Latini et al. have showed that PTX3 levels exceeding 10.73 ng/mL predicted 3-month mortality in patients with AMI (n = 724).[4]

The plasma concentration of PTX3, but not hsCRP, remained an independent predictor of cardiac events in a stepwise multivariate Cox regression analysis that included 18 well-known clinical and biochemical predictors of ACS outcome. Moreover, a comparison of the cardiac event rate and Kaplan–Meier analyses according to the median values of these markers showed that PTX3 could better stratify high- and low-risk patients. These findings suggest that the measurement of plasma PTX3 may represent a more effective means for early risk stratification compared to hsCRP in patients with UA/NSTEMI as reported previously in patients with ST-segment elevation myocardial infarction.[4]

The prognostic values of PTX3 for future acute myocardial infarction (AMI) and mortality, in patients with ACS without ST elevation and ST elevation AMI have also been demonstrated.[3-4]

Kume et al 2011 compared the diagnostic sensitivity and specificity of PTX3 for ACS with other biomarkers, such as TnT and H-FABP. The ROC curves clearly indicated that the sensitivity and specificity of PTX3 were higher, than TnT and H-FABP, for the diagnosisof ACS, STEACS or AMI.

The diagnostic sensitivity and specificity of PTX3, and H-FABP, were compared in all subjects and the TnT-negative subpopulation. Diagnostic specificity and sensitivity of PTX3 were similar between the whole ACS population and the TnT-negative ACS subpopulation, indicating that PTX3 would provide additional diagnostic information for ACS, when measured in combination with TnT. [19]

In addition to different endpoint definitions, the rather long time interval between symptom onset and blood sampling (approximately 15 h) in GUSTO IV might partly explain part of these discrepant findings. PTX3 has been described to peak at 7.5 h in myocardial infarction.Thus earlier measurements and/or a larger amount of injured myocardium than commonly found in NSTE-ACS may be needed to prove a stronger association of this biomarker with outcome. [25]

M. Eggers et al showed that the median PTX3 levels of NSTE-ACS patients were significantly higher than those of healthy controls (3.8 vs. 1.9 µg/L; $p < 0.001$). The PTX3 levels in patients with NSTE-ACS were independently related to female sex and the cardiac troponin T levels, but not to age or cardiovascular risk factors. The PTX3 levels were higher in patients who died within 1 year but did not emerge as an independent predictor of 1-year mortality (adjusted OR 1.2 [95 % CI 0.6–2.3]).

This finding was in contrast to CRP (adjusted OR 1.5 [95 % CI 1.1–2.3]). Neither PTX3 nor CRP showed significant discriminative value regarding mortality prediction.

Conclusions: The PTX3 levels are elevated in NSTE-ACS. However, the prognostic information provided by PTX3 levels is limited and inferior compared to CRP. Thus our data, thus, do not support the measurement of PTX3 in patients with NSTE-AC. [22]

The clinical and prognostic implications of circulating pentraxin 3 levels in non ST-elevation acute coronary syndrome were determined. The PTX3 levels were only weakly related to the 1-year mortality, and failed to provide prognostic value in a model adjusted for age and sex. This finding was in contrast to CRP which remained independently predictive even following adjustment for other predictors of mortality. [22]

Notably, CRP was not independently prognostic in our study in agreement with mantovani, norta, peri [17-19].

Further investigations are required to explore the application of this approach to a broad spectrum of patients presenting with chest pain and a low to intermediate probability of ACS. Moreover, serial measurements of PTX3 might be useful for evaluating changes in the inflammatory status, estimating risk during the follow-up period, and directing in- and out-patient treatments.

Further studies are needed to clarify the role of the repetitive measurement of PTX3 before and after treatment with drugs such as aspirin and statin for determining the prognosis of patients with UA/NSTEMI. In a large population.

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