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Effect of gender and age serum level of N-terminal pro-Brain natriuretic peptide and echocardiographic findings in patient with ACS

Wafa M. Merza, phD[(1)]
[1]*Department of basic sience, Collage of dentistry, University of Baghdad*

Background: Acute Coronary Syndrome is one of the commonly diagnosed life threatening condition as of *now. Hence it is necessary to diagnose early and assess the severity of disease as soon as possible. This study is done to prove the correlation of cardiac marker NT-pro BNP in Acute Coronary Syndrome.*
Aim: To estimate the serum level of N-terminal pro-Brain natriuretic peptide levels in Acute coronary syndrome. Also to find the association of serum NT-pro-BNP levels and echocardiographic parameter in patients with age and gender.
Materials and Methods: 70 patients of age group between 25 to 84 of both sexes who got admitted within 24 hours after onset of symptoms and diagnosed as Acute Coronary Syndrome in Baghdad Medical College & Hospital at baghdad medical city during the period of November 2019 to August 2020). The levels of NT-Pro BNP were measure in blood with Rapid NT-Pro BNP Assay kit.
Results: *This study included 70 patients with mean±SD of age was (58.77±11.45) years they divided into two groups: Male group and female group. The control group included 20 healthy persons with mean age (33.47±12.58) years and ranged from (20-58) years. patients mean age was significantly higher than control group mean age(P-value =0.0149). There was a significant increase in the frequency of ACS among males in comparison to females (P-value =0.0027). The patients with ACS were found to have significantly higher mean (± SEM) value of serum NT-PROBNP concentrations (p=0.0144) as compared with mean (± SEM) value of serum control group. There were significant difference in mean(± SEM) value of serum NT-PROBNP concentration, left atrium diameter, E/e and deceleration time between male and female groups (P-value=0.0273). The mean(± SEM) value of serum NT-PROBNP concentrations and deceleration time were found significantly higher in Female group than Male group, (P-value=0.0466, P-value=0.0377 respectively), while mean(± SEM) of left atrium diameter and E/e value were found significantly higher in Male group than in Female group, (P-value=0.026, P-value=0.042 respectively). There were non-significant difference in mean (± SEM)value of serum NT-PRO BNP concentrations, hs-troponin I, hs-CRP, diameter of left atrium, deceleration time and ejection fraction among quartile groups, (P-value >0.5). There were significant difference in mean(± SEM) values of E/e among quartile groups, (P-value=0.041). There was highly significant difference in mean(± SEM) values of isovolumic relaxation time among quartile groups, (P-value=0.011).*
Conclusion: NT-pro BNP is reliable biomarker in diagnosing ACS age and gender *affect serum* NT-pro BNP and echocardiographic parameter
Keywords: Acute Coronary Syndromes, NT-pro BNP, cardiac markers.

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I. Introduction

Acute coronary syndromes caused by sudden blockage of a coronary artery. According to degree and location of blockage it ranges from unstable angina to non–ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and sudden cardiac death.1

The root cause of ACS is unstable plaque within the coronary arteries. Rupture of coronary plaque causes their thrombogenic contents to become exposed to the circulation. This leads to platelet activation, initiation of the coagulation cascade and other physiological effects resulting in myocardial ischemia. A second class of MI, type 2, is related to a supply/demand mismatch resulting from coronary spasm, high or low blood pressure, anemia, arrhythmia or stenosis due to a fixed atherosclerotic lesion 2. Although ACS is the predominant etiology for cardiac necrosis, it is important to note that there are several other etiologies that also cause myocardial ischemia 3, type 3 MI describes patients who suffer from cardiac sudden death, and types 4a, 4b, and 5 MI are related to interventional procedures. Regardless of the pathobiology, myocardial necrosis due to myocardial ischemia is designated as MI 1,2.

BNP differs from other biomarkers used for risk-stratification in ACS, such as troponin and creatine kinase-MB, in that it is a counter-regulatory hormone that may play an active role in the response to ischemic injury. The level of BNP may reflect the size or severity of the ischemic insult, even when myocardial necrosis has not occurred4.

II. Materials and Methodology

This study is conducted among 70 patients of age group between 30 to 84 of both sexes who got admitted within 12 hours after onset of symptoms and diagnosed as Acute Coronary Syndrome (STEMI, NSTEMI & Unstable Angina) in Baghdad Medical College &medical city Hospital, during the period of November 2019 to August 2020 Laboratory Investigations includes blood urea serum creatinine to rule out frank renal failure. Other investigations includes serial ECG monitoring, Echocardiography, blood levels of Troponin T Within 12 hours of the onset of symptoms, the levels of NT-Pro BNP were measure in blood with Rapid NT-Pro BNP Assay kit. Description of the NT proBNP Rapid Assay Kit: The strips are coated with canine antibodies to human NT pro terminal end of brain Natriuretic peptide. It is a semi quantitative assay and it gives the measurement as 500pg/ml. Values below 100pg/ml was considered as minimal or insignificant and values above 100 pg/ml considered significant. Significant values in the range of 100-500pg/ml is taken as moderately elevated and values above 500pg/ml were taken as moderately elevated.

III. Results

Clinical data

This study included 70 patients with mean±SD of age was (58.77±11.45) years ranged from (25-84) years divided into two groups: Male group included 52(74.3%) patients, and female group included 18 (25.7%) patients.

The control group included 20 healthy persons with mean age (33.47±12.58) years and ranged from (20-58) years, divided into two groups male group included 10 (50%) persons and female group included 10 (50%) persons, table(1),(2).

patients mean age was significantly higher than control group mean age(P-value =0.0149). There was a significant increase in the frequency of ACS among males in comparison to females (P-value =0.0027).

Table (1)Frequency distribution of total study sample by age**.**

	Control	patients	P-value
Mean± SD	33.47±12.58	58.77±11.45	0.0149 **
SE	1.49	1.36	--
Min	20	25	--
Max	58	84	--
C.V%	37.6089	19.48	--

Table (2) Frequency distribution of total study sample by gender.

Sex	Control		patients	
	No.	%	No.	%
Male	10	50	52	74.3
Female	10	50	18	25.7
Total	20	100	70	100
P-value	---	1.00 NS	---	0.0027 **

Biochemical markers in Acute Coronary Syndrome (ACS) patients and control group

Serum level of NT-PRO Brain Natriuretic Peptide (NT-PROBNP), (hs-TnI) and (hs-CRP) were compared between the patients group and the control group using analysis of variance (ANOVA) and t-test of significant as in table (3). The patients with ACS were found to have significantly higher mean (± SEM) value of serum NT-PROBNP concentrations (p=0.0144) as compared with mean (± SEM) value of serum control group, the mean (± SEM) value of serum hs-troponin I concentrations did not differ significantly (p=0.372) as compared with mean (± SEM) value of serum control group, and significantly higher mean (± SEM) value of serum hs-CRP concentrations (p=0.002) as compared with mean (± SEM) value of serum control group.

Table (3) Comparison between patients & control according to biochemical markers.

Group	No.	Mean ± SEM Mean ± SD		
		NT-PROBNP (ng/L)	**TnI: Troponin I (ng/L)**	**CRP:C-Reactive protein (mg/L)**
Patients	70	203.95 ± 21.42 203.95 ±179.21	8.10 ± 0.87 8.10 ±7.27	12.73 ± 0.97 12.73 ±8.11
Control	20	107.79 ± 4.23 107.79 ±18.91	7.74 ± 0.48 7.74 ±2.14	0.316 ± 0.143 0.316 ±O.63
T-test value **P-value**	--	34.782 ** 0.0144	1.973 NS 0.372	3.019 *** 0.00252
** (P≤0.01), *** (P≤0.001), NS: Non-significant (p >0.05).				

- Results expressed as Mean (+ SEM).
- Results expressed as Mean (± SD).

Gender

The table (4) shows effect of gender on biochemical markers & echocardiographic finding, study patients divided into Male (n = 52) and Female (No. = 18) groups, there were significant difference in mean(± SEM) value of serum NT-PROBNP concentration, left atrium diameter, E/e and deceleration time between two groups(P-value=0.0273). The mean(± SEM) value of serum NT-PROBNP concentrations and deceleration time were found significantly higher in Female group than Male group, (P-value=0.0466, P-value=0.0377 respectively), while mean(± SEM) of left atrium diameter and E/e value were found significantly higher in Male group than in Female group, (P-value=0.026, P-value=0.042 respectively). The mean(± SEM) value of serum hs-troponin I , hs-CRP concentrations, isovolumic relaxation time and ejection fraction were non significantly higher in Female group than Male group.

Table (4) Effect of gender on biochemical markers & echocardiographic Finding.

Parameters	Gender Mean ± SEM		P-value
	Male (No. = 52)	**Female(No. = 18)**	
NT-PROBNP (ng/L)	178.21 ± 18.43	278.33 ± 25.06	0.0466 *
hs-TnI: Troponin I (ng/L)	6.81 ± 0.71	11.84 ± 1.03	0.215 NS
hs-CRP: C-reactive protein (mg/L)	12.53 ± 0.84	13.15 ± 0.92	0.792 NS
LAD: Left atrium diameter (cm)	3.71 ± 0.05	3.37 ± 0.08	0.026 *
E/e	10.10 ± 0.26	7.79 ± 0.12	0.042 *
IVRT: Isovolumic relaxation time (ms)	87.97 ± 7.53	89.44 ± 12.96	0.762 NS
DT: Deceleration time(ms)	181.94 ± 7.62	228.61 ± 11.79	0.0377 *
EF%: Ejection fraction	48.73 ± 6.91	53.33 ± 8.06	0.681 NS
* (P≤0.05), NS: Non-significant.			

Age

The table (5) shows effect of age grouping on biochemical parameters and echocardiographic findings, the study patients were divided into four quartiles. There were non-significant difference in mean (± SEM)value of serum NT-PRO BNP concentrations, hs-troponin I, hs-CRP, diameter of left atrium, deceleration time and ejection fraction among quartile groups, (P-value >0.5). There were significant difference in mean(± SEM) values of E/e among quartile groups, (P-value=0.041). There was highly significant difference in mean(± SEM) values of isovolumic relaxation time among quartile groups, (P-value=0.011).

Table (5) Effect of age grouping on biochemical markers & echocardiographic Finding.

Parameters	Age group (year) Mean ± SEM				P-value
	Quartile1 30-40 No.=3	Quartile2 41-50 No.=11	Quartile3 51-60 No.=26	Quartile4 >60 No.=29	
NT-PRO BNP(ng/L)	150.10± 43.54	203.69± 70.23	182.77± 25.57	225.50± 38.38	0.799 NS
hsTnI:TroponinI (ng/L)	5.38± 0.248	7.74± 1.97	8.29± 1.65	8.46± 1.32	0.918 NS
hs-CRP:C-reactive protein (mg/L)	17.00± 3.78	14.07± 1.82	11.60± 1.78	13.05± 1.54	0.662 NS
LAD: Left atrium diameter (cm)	3.6133± 0.24835	3.77± 0.15	3.48± 0.12	3.68± 0.12	0.514 NS
E/e	4.66± 0.66	11.52± 1.74	8.96± 0.51	9.79± 0.70	0.038*
IVRT:Isovolumic relaxation time (ms)	148.66± 40.71	73.45± 4.98	86.84± 4.90	89.68± 4.74	0.001**
DT: Deceleration time (ms)	219.00± 35.23	182.27± 28.80	174.23± 13.05	212.68± 11.47	0.193 NS
EF%:Ejection fraction	46.00± 6.65	48.72± 3.26	49.80± 2.36	50.27± 1.941	0.921 NS

* (P≤0.05), ** (P≤0.01),NS: Non-significant.

Statistical Analyses

SPSS version 16 was used in analysis of the data. The cardiac markers were expressed as mean± standard errors. ANOVA tests were used to compare between different cardiac markers. A p-value less than 0.05 were considered statistically significant.

IV. Discussion

Age is a strong risk factor for atherosclerotic diseases in western countries. The mortality and morbidity rates begin to increase after the age of 45 years in males and 55 years in females as reported by Walsh JM et al. (1995).[5]

Although atherosclerosis is typically a progressive disease, it usually does not become clinically manifested until middle age or later. Between ages 40 and 60 (years) the incidence of myocardial infarction increases five fold and death rates from IHD rise with each decade even into advanced ages.[6]

In the present study, the majority of patients who developed UA and AMI were above the age of 40 years and there was a significant increase in the frequency of IHD with increasing age, the mean age (years) for patients was (58.77±11.45) table(1). This result was the same as that of Ibrahim (2007) [7] who found that mean age for patients with IHD in Erbil was 58 years and this indicated that most of the patients were in their middle age. This result also agree with a study of Mackness et al. (2008) who stated that as you get older, your risk for atherosclerosis increases.[8] Atherogenesis was considered with distinct chronologic phases. The first phase, initiation occurs all too frequently during childhood or adolescence, then the nascent lesion which enters a phase of progression, that generally considered to occur during young adulthood through middle life. Ultimately, atherosclerotic disease becomes manifested with either chronic, stable symptoms or thrombotic complications such as acute myocardial infarction or ischemic stroke. Traditionally, the latter phase of atherothrombosis, complication occurs in the middle-age or in elderly individuals .[9]

patients mean age was higher than control mean age, theoretically patients mean age must be same as control mean age, but practically is impossible to find old age persons without thyroid disease, heart disease, kidney disease, pulmonary disease, diabetes, inflammatory disease, liver disease and arthritis together.

Its also found that the frequency of male patients group were (74.3%) patients, and female group were (25.7%) patients, table(2). So there was a significant increase in the frequency of MI and UA among males in comparison to females, these results agree with the study reported by Villar et al. (2008) who found greater incidence of CVD in men and postmenopausal women compared with premenopausal women implies a vasoprotective phenotype of females, which may be influenced by sex hormones. These hormones, particularly estrogen, have modulator effects on the endothelium and circulating cells that have been implicated in vascular inflammation and in the development of CVD. [10]

The present study showed that a significant positive correlation between serum NT-PROBNP concentrations and serum hs-TnI concentrations in patients with ACS, the cause may be: increase serum NT-

PROBNP concentrations indicate presence of heart muscle ischemia, prolonged ischemia leads to muscle necrosis and releasing of Troponin I , there were no previous studies that express the cause of this result , the result here disagree with B.Vergèsa et al.[11] who found Nt-proBNP was negatively associated with peak plasma troponin level (P=0.0002).

The present study result showed significant difference in mean±SE value of serum NT-PROBNP levels among quartiles age groups, this result agree with following studies:

Seon Gyu Choi et al.[12] reported that: NT-proBNP concentrations of older patients were significantly higher than those of young patients. Fazlinezhad et al.[13] reported that : slight positive relation between BNP levels of AMI patients and age (P = 0.01, r = 0.39). A striking increase in mean and upper centile values for NT-proBNP with age has been reported in healthy volunteers. After multivariate adjustment, a 10 year increase in age was associated with a 1.4-fold increase in pro-peptide concentration.[14] In animal studies, an increase in natriuretic peptide gene expression has been documented with advancing age.[15] Furthermore, the increase in natriuretic peptide concentrations with age may reflect a higher prevalence of subclinical cardiac disease in healthy older people. Of all the major clinical predictors such as age, admission symptoms of HF, parameters related to the infarct size, including biochemical measurements (maximal CK-MB activity, maximal creatinine and CRP concentrations) and echocardiographic assessments, the differences among three BNP groups were present only according to age, the time from the start of symptoms to admission, TIMI Risk Score and LVEF. Plasma BNP, serum creatinine concentration, LVEF and age were predictive only in univariate analysis. It is worth noting that even BNP was not an independent predictor of mortality. Based on the previous reports, these parameters are known to be strong and independent predictors of mortality in patients with HF and coronary artery disease, including acute phase of MI [16]. Agnieszka et al.[17] reported that only age finally became an independent risk factor: in multivariate analysis neither BNP, creatinine concentration, nor LVEF were predictive. The mechanisms for age-related differences in natriuretic peptides are also not fully understood, but may include both increased secretion secondary to structural changes in the heart, and decreased clearance.[18]

Gender

The mean(± SEM) value of serum NT-PROBNP concentrations was found significantly higher in Female than Male groups, table (5).This result agree with the following studies:

L Lorgis et al.[19] reported that the proportion of women was higher in the upper age quarter and the proportion of women had an independent impact on pro-peptide concentrations whatever the age group. The physiological basis for this sex related difference is unclear. Astimulatory effect of female sex hormones has been reported in experimental studies,[20] and production of B-type natriuretic peptide may be sensitive to oestrogen regulation.[21]

As presented in the current study, Yoshida et al reported that female MI patients had significant higher BNP levels, than male MI patients, independent from their age.[22] However, A. Fazlinezhad1[13] in their study showed there was no significant difference between the genders in mean of BNP level, which may be due to the smaller number of patients as a limitation.

V. Conclusion:

NT-pro BNP is reliable biomarker in diagnosing ACS age and gender affect serum *NT-pro BNP and echocardiographic parameter*

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Conclusion Our study shows that the NT-pro BNP is reliable biomarker in diagnosing not only STEMI & NSTEMI but also in unstable angina. NT-PRO BNP was a useful biochemical marker in the diagnosis` of ischemia. NT-PRO BNP was more sensitive than troponine I for diagnosis of ischemia.
NT-PRO BNP was a viable parameter in diffrentiating between diastolic dysfunction stages in ischemia.

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