

# Does Serum N-Terminal pro-Brain Natriuretic Peptide Level Predict the Severity of Angiographic Lesions in Patients with Acute Coronary Syndrome?

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## Abstract

**Background:** Serum N-terminal pro-brain natriuretic peptide (NT-proBNP), a polypeptide secreted by ventricular myocytes in response to stretch, was suggested as a predictor of adverse prognosis of the acute coronary syndrome (ACS). We examined the association between NT-proBNP level and angiographic findings in ACS patients to determine whether it could be used as a predictor of the severity of angiographic lesions.

**Methods:** This cross-sectional study was performed on 126 patients with chest pain or other ischemic heart symptoms suggestive of ACS. Venous blood samples were drawn to measure serum levels of NT-proBNP. Afterward, coronary angiography was performed and the patients were categorized into four groups according to the number of coronary vessels with significant stenosis. The severity of angiographic lesions was assessed with the Gensini scoring system.

**Results:** According to angiographic diagnosis, 11 (8.7%) patients had normal coronary arteries (no coronary artery disease [CAD]) and 115 (91.3%) had CAD, of whom 108 (85.7%) had obstructive CAD and 7 (5.6%) had minimal CAD. The serum NT-proBNP concentration was higher in the CAD group than in the non-CAD group ( $p$  value  $<0.01$ ). A progressive significant increase in the NT-proBNP concentration according to the Gensini score and the number of involved vessels was reported after adjustment for sex and age. Furthermore, the Receiver Operating Characteristic Curve (ROC) analysis indicated that an NT-proBNP cut-point of 400 pg/ml could predict obstructive CAD with a sensitivity of 65% and a specificity of 78%.

**Conclusion:** Higher levels of NT-proBNP among our ACS patients were associated with the severity of angiographic lesions in terms of both the Gensini score and the number of involved vessels. This finding underscores the potential role of NT-proBNP in predicting the severity of CAD before performing angiography.

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**Keywords:** Natriuretic peptide, brain • Acute coronary syndrome • Risk assessment

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## Introduction

Based on the World Health Organization (WHO) data, coronary artery disease (CAD) is the leading cause of death throughout the world.<sup>1</sup> CAD is also a worldwide epidemic, in which the risk of death decreases by early diagnosis and treatment. Acute coronary syndrome (ACS) results from an acute obstruction of a coronary artery and encompasses both myocardial infarction (MI) (ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation myocardial infarction [NSTEMI]) and unstable angina. ACS is a medical emergency and a major cause of hospitalization.<sup>2,3</sup>

Different methods such as Thrombolysis in myocardial infarction (TIMI) risk score and serum biomarkers like troponin, myeloperoxidase, creatine kinase (CK), CK-MB, and lactate dehydrogenase are employed to evaluate the prognosis and risk of ischemic events.<sup>4</sup> These methods also provide a basis for performing invasive diagnostic or therapeutic procedures such as coronary angiography. Since angiography is both expensive and associated with significant risks to the patient, identifying suitable patients for the intensive procedure, which requires intensive care, is both essential and cost-effective.<sup>5-8</sup>

B-type natriuretic peptide (BNP), a polypeptide secreted by ventricular myocytes during myocardial stretch, is used both as a prognostic and diagnostic biomarker of congestive heart failure.<sup>5-14</sup> It has also been suggested as the potential biomarker allied with adverse prognosis in ACS.<sup>13</sup>

In this study, we examined the association between serum BNP levels and angiographic findings in Iranian ACS patients to determine whether serum BNP had a potential role in predicting the severity of angiographic lesions and whether it could be used in coronary heart disease risk assessment.

## Methods

This cross-sectional, hospital-based study was performed on 126 patients with chest pain or other ischemic heart symptoms suggestive of ACS, who referred to the Catheterization Laboratory of Shariati Hospital, affiliated to Tehran University of Medical Sciences (TUMS) in Iran between January 2009 and January 2010. Patients who had one of the following symptoms were considered as ACS: 1) Patients with a recent increase in intensity, frequency, or duration of chest pain (crescendo angina); 2) Patients with sudden onset angina at rest or with minimal exertion; and 3) Patients with chest pain of one month's duration.

Patients with renal dysfunction (serum creatinine > 1.5 mg/dL), Body Mass Index (BMI) greater than 30 kg/m<sup>2</sup>, left ventricular ejection fraction (LVEF) below 40%, age below 75 years, and fever were excluded from the study.

Written informed consent was obtained from all the

patients, and the study protocol was approved by the Research Ethics Committee of TUMS. Demographic data such as age, sex, smoking habits, and history of diabetes hypertension were obtained through detailed history taking.

Venous blood samples were drawn to measure the serum levels of triglyceride (TG), high-density lipoprotein (HDL), cholesterol, low-density lipoprotein (LDL), N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations, troponin (cTnt), and high-sensitivity C-reactive protein (hs-CRP).

Serum NT-proBNP was measured using Stat Fax 3200 (Awareness) with the ELISA method. The cut point separating the normal and abnormal values for the serum levels of NT-proBNP was 208 pg/ml according to the company producing the laboratory kit (DRG Diagnostics Company, Germany).

Afterward, coronary angiography was performed by experienced cardiologists, and the patients were categorized into five groups according to angiographic findings as having left main disease, three-vessel disease, two-vessel disease, and one-vessel disease as well as patients without obvious stenosis. A diagnosis of obstructive coronary artery disease (CAD) was made when there was greater than 50% stenosis in one or more major coronary arteries. The severity of the angiographic lesions was evaluated using the Gensini scoring system.

The data were analyzed using the statistical package for Windows (SPSS16, Chicago, Inc). The normality of each variable distribution was determined by the Kolmogorov-Smirnov test. Variables with normal distribution were presented as Mean (Standard Deviation [SD]). Gensini score and serum NT-pro BNP were described as Median (25<sup>th</sup> -75<sup>th</sup> Percentile). The student t-test, the Mann-Whitney test, the Kruskal-Wallis test, and the chi-square test were used in analysis as appropriate. Correlations between variables were assessed using Spearman rank correlation. Linear regression analyses were used to evaluate the association between serum NT-proBNP and the severity of angiographic lesion with respect to both the Gensini score and the number of vessels with significant stenosis after adjustment for age and sex.

The Receiver Operating Characteristic (ROC) curve was drawn upon to determine a cut point for the serum level of NT-proBNP for predicting obstructive CAD. A p value less than 0.05 was considered statistically significant.

## Results

The study population consisted of 126 patients (75 men, 59.5%; 51 women, 40.5%) at a mean (SD) age of 55.37 (10.25) years within a range of 35 to 75. Troponin and NT-proBNP concentrations were measured in all the patients, and hs-CRP was measured in 92 (73%) patients. Among the patients, 102 (81%) had LVEF greater than 50% and 24 (19%) had 40 ≤ LVEF < 50.

Table 1. Patients' characteristics mean N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration, and the Gensini score

	Count (%)	Serum NT-proBNP level (pg/ml) Median (25 <sup>th</sup> – 75 <sup>th</sup> Percentile)	P value	Gensini score Median (25 <sup>th</sup> - 75 <sup>th</sup> Percentile)	P value
Gender			0.01		< 0.01
Male	75 (59.5%)	490.00 (354.00-666.00)		39.00 (15.00-69.00)	
Female	51 (40.5%)	327.00 (401.00-498.00)		16.00 (2.50-34.00)	
Hypertension			0.31		0.17
No	59 (46.8%)	467.00 (341.00-650.00)		38.50 (9.50-54.50)	
Yes	67 (53.2%)	450.00 (336.00-566.00)		22.50 (5.00-54.50)	
Smoking			< 0.01		0.06
No	78 (61.9%)	400.00 (327.00-508.25)		21.00 (4.00-54.75)	
Yes	48 (38.1%)	551.50 (376.50-802.25)		38.50 (15.87-54.12)	
Diabetes			0.45		0.16
No	90 (71.4%)	464.50 (334.50-651.00)		24.00 (4.00-51.87)	
Yes	36 (28.6%)	446.00 (355.50-496.00)		33.00 (15.50-59.62)	
Hyperlipidemia			0.77		0.36
No	48 (38.1%)	422.00 (336.00-611.25)		22.25 (5.12-47.75)	
Yes	78 (61.9%)	466.00 (346.50-605.50)		31.50 (7.62-56.25)	
ST segment deviation ( $\geq 0.5$ mv)			0.33		< 0.01
No	34 (27.0%)	425.50 (325.25-555.00)		12.50 (0.75-43.25)	
Yes	92 (73.0%)	464.50 (348.00-627.25)		33.00 (12.00-57.87)	
ACS crescendo			0.81		0.88
No	73 (58.4%)	467.00 (333.00-586.50)		32.00 (8.00-55.75)	
Yes	52 (41.6%)	426.50 (342.75- 637.75)		28.25 (5.12-52.62)	
ACS at rest			0.86		0.02
No	85 (67.5%)	463.00 (328.50-606.00)		21.00 (4.00-48.00)	
Yes	41 (32.5%)	424.00 (345.00-605.00)		38.00 (21.00-57.00)	
Unstable angina			< 0.01		< 0.01
No	55 (43.7%)	550.00 (390.00-720.00)		43.00 (24.00-64.00)	
Yes	71 (56.3%)	390.00 (302.00-502.00)		17.00 (2.50-42.00)	
STEMI			< 0.01		< 0.01
No	96 (76.2%)	400.00 (321.75-544.50)		21.00 (3.62-48.00)	
Yes	30 (23.8%)	575.00 (459.25-103.42)		44.00 (31.50-62.50)	
NSTEMI			0.41		0.05
No	101 (80.1%)	451.00 (336.00-586.50)		29.00 (4.00-50.50)	
Yes	25 (19.9%)	489.00 (341.50-680.50)		39.00 (16.50-65.50)	
TIMI risk			0.08		< 0.01
< 3	28 (22.2%)	394.00 (282.00-532.25)		3.25 (0.00-23.35)	
3-4	93 (73.8%)	476.00 (353.00-632.50)		34.50 (14.75-57.75)	
5-7	5 (4.0%)	628.00 (310.00-1402.00)		47.00 (17.00-84.50)	
CAD			< 0.01		< 0.01
Non-CAD	11 (8.7%)	354.00 (265.00-463.00)		0.00 (0.00-0.00)	
Minimal CAD	7 (5.6%)	287.00 (256.00-389.00)		1.50 (1.00-2.50)	
Obstructive CAD	108 (85.7%)	484.00 (352.50-627.25)		34.75 (16.25-56.75)	
Number of involved vessels			< 0.01		< 0.01
Without obvious stenosis	18 (14.3%)	315.00 (262.75-411.75)		0.00 (0.00-1.50)	
Single-vessel disease	30 (23.8%)	348.00 (307.50-478.50)		8.00 (4.00-23.62)	
Two-vessel disease	29 (23%)	484.00 (359.00-578.50)		27.50 (16.50-52.00)	
Three-vessel disease	47 (37.3%)	568.00 (426.00-979.00)		53.00 (39.00-66.00)	
Left main	2 (1.6%)	513.00 (360.00-666.00)		37.25 (20.00-54.50)	

ACS, Acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non-ST-segment myocardial infarction; TIMI, Thrombolysis in myocardial infarction; CAD, Coronary artery disease



Thirty-one (24.6%) patients were over 65 years of age. Thirty-eight (30%) patients presented with at least three risk factors for CAD. One hundred ten (87.3%) patients had used Aspirin in the previous 7 days. Serum cardiac biomarkers were elevated in 49 (38.9%) patients. Eighty-four (66.7%) patients had ST-segment deviation greater than 0.5 mm on the admission electrocardiogram (ECG). Sixteen (12.7%) patients had a history of documented ischemic heart disease. Fifty-six (44.4%) patients had at least two angina episodes in the previous 24 hours.

By summing the number of the factors presenting in each patient, we categorized them into different risk strata: low risk (TIMI score < 3); intermediate risk (scores 3 and 4); and high risk (scores 5, 6, and 7), which were seen in 28 (22.2%), 93 (73.8%), and 5 (4%) of the patients, respectively.

Table 1 illustrates the mean levels of N-proBNP concentrations and Gensini scores in the study population according to the different clinical characteristics and risk factors.

Among our study population, 71 (56.35%) patients presented with unstable angina and 55 (43.65%) with MI (30 [23.8%] with STEMI and 25 [19.8%] with NSTEMI). The median Gensini score and NT-proBNP concentration were significantly higher in the patients with MI than in those with unstable angina (43.00 and 550.00 pg/ml vs. 17.00 and 390.00 pg/ml, respectively; P value < 0.001).

According to angiographic diagnosis, 11 (8.7%) patients had normal coronary arteries (non-CAD) and 115 (91.3%) had CAD, of whom 108 (85.7%) had obstructive CAD and 7 (5.6%) had minimal CAD (non obstructive). Serum NT-proBNP concentration was significantly higher in CAD patients compared non-CAD group (the median of 442 pg/ml vs. 354pg/ml; p value < 0.01). This difference remain significant in patients with LVEF  $\geq$  50% [325.00 (253.25-497.50) Vs. 450.50 (341.25-564.00); P value = 0.04], as well as patients with 40%  $\leq$  LVEF < 50% [463.00 (440-486) Vs. 650.00 (396.00- 1294.00); P value = 0.25].

There were 18 (14.3%) patients without obvious stenosis in angiographic findings, 30 (23.8%) with one-vessel CAD, 29 (23%) with two-vessel CAD, 47 (37.3%) with three-vessel CAD, and 2 (1.6%) with left main involvement. A progressive and significant increase in the NT-proBNP concentration was associated with the number of coronary arteries involved (p value < 0.01). Figure 1 presents the median of serum NT-proBNP concentration by gender according to the number of coronary vessels involved.

There was a significant direct correlation between the serum level of NT-proBNP and the severity of angiographic lesions both in the Gensini score system and in the number of involved coronary vessels ( $r = 0.51$  for both; p value < 0.001). Afterward, via linear regression analysis we assumed NT-proBNP levels as the outcome and the severity of angiographic lesions as the covariates. Our result indicated that every one-unit increase in the Gensini score or the

number of involved coronary vessels was associated with 5.02 pg/ml (95%CI: 1.92-8.13) or 130.34 pg/ml (95%CI: 49.50-211.26) increase in the NT-proBNP level, independent of age and sex (p value < 0.01). Moreover, there was a strong correlation between the Gensini score and the number of involved vessels ( $r = 0.78$ ; p value < 0.001). High serum levels of troponin significantly correlated with the Gensini score and the number of involved coronary arteries with correlation coefficients of 0.38 and 0.26, respectively (p value 0.001).

Using spearman correlation analysis, we identified the factors that were directly associated with Gensini score; these factors were TIML score ( $r = 0.42$ , p value < 0.001), hs-CRP ( $r = 0.32$ , p value = 0.02), serum creatinine ( $r = 0.22$ , p value = 0.01), and total cholesterol ( $r = 0.18$ , p value = 0.04). Moreover, there was a significant reverse correlation between LVEF ( $r = -0.23$ , p value = 0.01) as well as gender ( $r = -0.33$ , p value = 0.0001) and the Gensini score. There was no significant association with age, BMI, smoking, HDL, TG, LDL, or dyslipidemia.

Regarding the patients' clinical presentations, a direct relation between unstable angina and the Gensini score was observed (p value = 0.0001). This association was significant in the patients with STEMI (p value = 0.026) but not in those with NSTEMI (p value = 0.096).

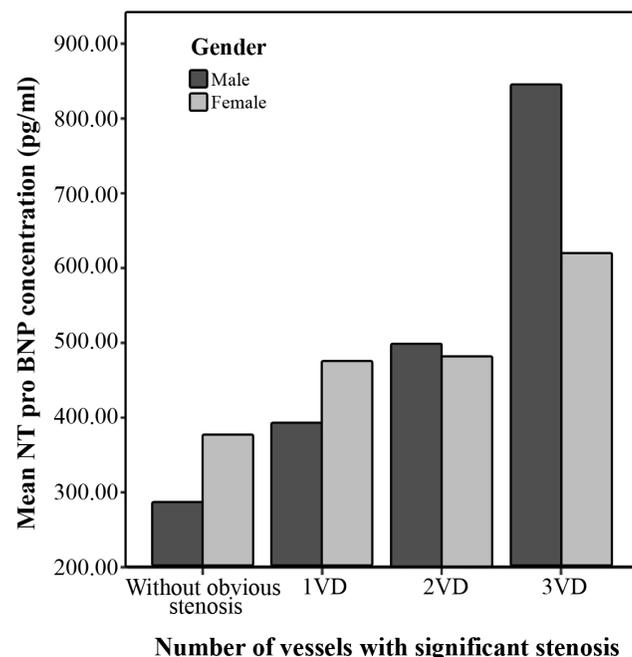


Figure 1. Median of N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration (pg/ml) according to the number of coronary vessels with significant stenosis

The cut-off levels of BNP to differentiate between the patients with obstructive CAD and those with non-obstructive CAD as determined by the ROC curve analysis are shown in

Table 2. The area under the ROC curve for NT-proBNP to predict obstructive CAD was 0.76 (p value < 0.001).

Table 2. The receiver operating characteristic (ROC) curve for various cut-off levels of B-type natriuretic peptide (BNP) in differentiating the patients with obstructive coronary artery disease from those with non-obstructive coronary artery disease\*

NT-proBNP level (pg/ml)	Sensitivity (95%CI)	Specificity (95%CI)	DOC
350	0.77 (0.69-0.85)	0.56 (0.33-0.79)	0.50
369	0.70 (0.61-0.79)	0.61 (0.38-0.84)	0.49
385	0.67 (0.58-0.76)	0.61 (0.38-0.84)	0.51
400	0.65 (0.56-0.74)	0.78 (0.59-0.97)	0.42 (cut off)
415	0.63 (0.54-0.72)	0.78 (0.59-0.97)	0.43
426	0.59 (0.50-0.68)	0.78 (0.59-0.97)	0.46
450	0.57 (0.48-0.66)	0.83 (0.66-1.0)	0.46

\*AUC: 0.76 (95% CI: 0.64 – 0.88), P value < 0.001

NT-proBNP, N-terminal pro-brain natriuretic peptide; DOC, Distance on curve equaling square root of (1-Sen) ^2+ (1-Spe) ^2; AUC, Area under curve

## Discussion

Chest pain is the most common reason for a referral to the emergency department. There are various criteria for determining the appropriate work-up procedures, including the TIMI score. However, NT-proBNP has never been used for the categorization of patients based on the corresponding risks.<sup>6, 12, 13</sup>

Previous studies have mainly supported measurement of NT-proBNP for the prediction and diagnosis of heart failure.<sup>9</sup> Be that as it may, there is limited published work to determine the value of this marker in the prediction and risk stratification of patients with CAD.<sup>13, 15, 16</sup> Hence, in the present study we assessed the serum NT-proBNP level in 126 patients presenting with ACS, who were candidates for coronary angiography, to determine the potential role of this marker in predicting the severity of angiographic lesions.

According to a large number of studies, there is a direct relationship between the NT-proBNP level and the severity of lesions found on angiography.<sup>6-8, 12, 17, 18</sup> This relationship is believed to be even more significant in patients with severe angiographic lesions and advanced LV dysfunction.<sup>6, 8, 18</sup>

Our findings chime in with those reported previously<sup>14</sup> insofar as we found a meaningful and direct relationship between the severity of angiographic lesions and the serum levels of NT-proBNP. This relationship was evident both vis-à-vis the Gensini score and the number of vessels with significant stenosis. The same meaningful relationship was found between the serum levels of hs-CRP, troponin T, and ST-deviation; however, the latter relationship was not in the

millimeters of ST-elevation (p value = 0.06). In addition, we found a significant reverse relationship between LVEF and NT-proBNP levels; hence, we did not include patients with LVEF below 40% in this study.

A study conducted on 2220 patients with unstable angina/NSTEMI by Sadanandan S et al.<sup>18</sup> declared an association between elevated NT-proBNP levels and tighter culprit stenosis, higher corrected TIMI frame count (CTFC), and left anterior descending coronary artery (LAD) involvement. By measuring the serum NT-proBNP level in patients with stable angina pectoris after exercise testing, Weber M et al.<sup>7</sup> demonstrated that this marker was elevated in these patients and that it had a close correlation with disease severity. The authors also reported that a cut-off level of 214 pg/mL could predict CAD with high accuracy. In contrast, the Peer A et al.<sup>15</sup> study revealed that the serum NT-proBNP level had no additive predictive value compared to the traditional risk factors in predicting CAD, although it was significantly associated with three-vessel disease after adjusting for sex, age, and classic risk factors. Likewise, Sattar N et al.<sup>16</sup> cautioned against the use of NT-proBNP for CHD risk prediction in healthy women and suggested that further studies with larger populations were needed to resolve this uncertainty.

In spite of the fact that patients with LVEF < 40% were excluded from this study, we found a meaningful reverse relationship between LVEF and serum levels of NT-proBNP. Meanwhile, CAD was associated with higher serum NT-pro BNP. In the present study, by categorizing patients into two groups based on their LVEF, we showed that this association remained significant particularly in patients with normal LV function (PV = 0.04). In patients with 40 ≤ LVEF < 50, the higher levels of serum NT-pro BNP in CAD patients were not significant. This could be explained by the small number of the patients in this group, which rendered the relationship non-meaningful (p value = 0.25). Along with the present result, another study indicated that serum NT-BNP was independently associated with adverse outcome of coronary disease in the presence or absence of preserved ejection fraction.<sup>19</sup>

The relation between the severity of angiographic lesions and cigarette smoking was not meaningful (p value = 0.058). Given the fact that we considered only those who currently smoke cigarettes as cigarette smokers and that the cardiovascular effects of cigarette smoking last for 3-5 years after a patient quits smoking, it would be fair to suggest the existence of a correlation between cigarette smoking and the severity of angiographic lesions.

It has been reported that the plasma levels of NT-proBNP can predict the severity of coronary vessel involvement and can be drawn upon for risk stratification.<sup>12-14</sup> Defining a cut-off value for NT-proBNP could help predict the severity of angiographic lesion; however, because these cut-off values vary due to different study cohorts, ethnicities, and



laboratory kits, we decided to determine the cut-point for serum levels of NT-proBNP in Iranian patients presenting with ACS by using the ROC curve. Based on the ROC curve analysis, a laboratory cut-point for obtaining the best predictive results for differentiating the obstructive CAD patients from the other patients was 400 pg/ml (sensitivity = 0.65 and 1-specificity = 0.22). Consequently, in the same way that the high serum level of troponin T is a criterion for determining risk, we can use the serum level of NT-pro BNP as another criterion for predicting the severity of coronary vessel involvement.

Studies with larger scopes, especially in high-risk subjects, are required to consider the serum NT-proBNP level as a biochemical marker in coronary heart disease risk assessment beyond the traditional risk factors so as to identify high-risk patients in early forms before clinical manifestation and predict the severity of CAD before performing angiography.

## Conclusion

Higher levels of NT-proBNP among our ACS patients were associated with the severity of angiographic lesions in terms of both the Gensini score and the number of involved vessels. This finding underscores the potential role of NT-proBNP in predicting the severity of CAD before performing angiography.

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