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Original Article

Diagnostic value of serum NT-proBNP level in predicting short-term outcomes in diabetic patients with acute coronary syndrome after PCI

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Abstract: Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) is known to an acknowledged marker of acute and (or) chronic heart failure. It is also proved to be a powerful predictor of cardiovascular outcome in many diseases. But there are insufficient data to analyze the relationship of NT-proBNP levels and the prognosis in diabetic patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI). The current study assesses the ability of NT-proBNP to predict short-term outcomes in diabetic patients with ACS after PCI in this setting. Objective: To explore the diagnostic value of preoperative serum NT-proBNP on postoperative outcome and mid-term survival in diabetic patients undergoing ACS. Methods: 780 diabetic patients receiving emergent PCI were recruited prospectively. Baseline clinical characters of patients were obtained. Pre-operative serum NT-proBNP levels were measured by the Roche Elecsys assay. The serum NT-proBNP level was correlated with various post-operative outcome parameters and survival rate after a median follow-up time of 24 (12-41) months. Risk factors of mortality during follow-up were confirmed by χ^2 test, Mann-Whitney test, and Cox regression. Results: The hospital of patients was predicted with the serum NT-proBNP level at the 382 ng/ml (P > 0.05) and the total hospital rate was 5.25% (41/780). Also the overall mortality was predicted with the level at the 660 ng/ml (P > 0.05) and the overall mortality was 2.05% (16/780). The survival rate of diabetic patients with PCI was reduced when the serum NT-proBNP level more than 660 ng/ml, proved by Kaplan-Meier analysis (P=0.018). The independent risk factors to overall mortality were confirmed, including age, diabetes mellitus, chronic obstructive pulmonary disease, post-operative serum creatinine, poor left ventricular ejection fraction and high serum NT-proBNP level (> 660 ng/ml). Furthermore, the serum NT-proBNP level was confirmed to an independent risk factor to mortality rate by full-model multivariate Cox regression analysis (*OR*=4.129, *95% CI*=2.975-6.281, *P*=0.037). The preoperative serum NT-proBNP level was more than 660 ng/ml in diabetic patients with ACS after PCI, who had the indexes of postoperative serum creatinine (P=0.041), longer CCU stay-time (P=0.023), postoperative renal failure (P=0.006) and postoperative atrial fibrillation (P=0.001). Conclusion: The diabetic patients with ACS after PCI were predicted to higher hospital mortality and peri-operative complications by the preoperative serum NT-proBNP level more than 660 ng/ml.

Keywords: NT-proBNP, diabetes mellitus, acute coronary syndrome, percutaneous coronary intervention

Introduction

The biological effect of N-terminal BNP propeptide (NT-proBNP) or B-type natriuretic peptides (BNP) was confirmed to relaxing the peripheral blood vessel and inhibiting the system of rennin-angiotensin-aldosterone (RAAS). And lots of clinical study were confirmed the BNP and NT-proBNP to be definite markers of acute and chronic heart failure (HF) [1, 2]. Their level reflects the haemodynamic status and has a prognostic value, as it correlates with mortality and morbidity even in patients without overt HF [2-4]. However, the use of NT-proBNP as a population screening tool to detect left ventricular (LV) dysfunction is proved to very limit [5].

Monitoring BNP and NT-proBNP levels has been successfully used to evaluate cardiovascular status in non-diabetic patients acutely admitted to emergency departments [6], such as with cardiac arrhythmia, acute coronary syndrome (ACS) and coronary artery bypass grafting (CABG) [7]. Still little is known, however, on their utility in diabetic patients with ACS undergoing cardiac surgery, especially including percutane-

Table 1. Univariate correlations between demographical data of 780 diabetic patients with ACS after PCI and hospital mortality and overall mortality

	Hospital mortality (*P* values)	Hospital mortality (RR)	Overall death (*P* values)	Overall death (RR)
Male gender	0.153	2.41 (0.62-4.95)	0.072	1.83 (0.84-3.26)
History of smoking	0.856	1.12(0.42-2.89)	0.426	0.72 (0.31-1.99)
Current smoker	0.525	--	0.872	--
Diabetes mellitus	0.067	2.03 (0.76-4.16)	0.023	0.54 (0.36-0.75)
Family history of coronary artery disease	0.146	0.44 (0.14-1.4)	0.203	0.61 (0.28-1.31)
Chronic renal failure requiring dialysis	0.576	0.61 (0.37-1.86)	0.212	0.45 (0.39-1.31)
Hyperlipoidemia	0.324	0.63 (0.22-2.49)	0.164	2.01 (0.95-4.16)
Arterial hypertension	0.293	0.98 (0.34-1.67)	0.472	0.85 (0.26-2.23)
Chronic obstructive pulmonary disease	0.102	0.76 (0.45–1.34)	0.032	0.36 (0.12-0.76)
Peripheral vascular disease	0.039	0.65 (0.21-0.98)	0.097	0.68 (0.19-1.5)
Carotid artery disease	0.278	--	0.362	3.26 (0.85-6.27)
History of cerebrovascular accident	0.436	--	0.011	0.39 (0.10-0.62)
Perioperative stroke	0.004	0.39 (0.09-0.75)	0.038	0.68 (0.16-1.34)
Postoperative transient ischemic attack	0.728	1.25 (1.09-1.67)	0.541	1.39 (1.11-1.76)
Postoperative renal failure	0.002	0.14 (0.06-0.21)	0.001	0.09 (0.03-0.16)
Postoperative atrial fibrillation	0.479	2.21 (0.53-5.24)	0.634	1.87 (0.59-3.28)
NT-proBNP serum level > 382 ng/ml	0.032	0.45 (0.26-0.98)	0.005	0.38 (0.14-0.56)
NT-proBNP serum level > 660 ng/ml	0.195	0.69 (0.23-1.38)	0.012	0.49 (0.12-0.79)

ous coronary intervention (PCI). Monitoring BNP and NT-proBNP levels might help improve the predictive value postoperative complications of diabetic patients with ACS. But it is not reported until now, so our study aimed to assess diagnostic accuracy of preoperative value of NT-proBNP level as a predictor of short-term postoperative complications in diabetic patients undergoing PCI.

Patients and methods

The study protocol was approved by the local research ethics committee and consent was obtained from all patients. Data used in the analysis were collected from the institutional database at the Department of Cardiovascular. Preoperative serum NT-proBNP levels were measured routinely in all patients on the day of admission before surgery. The data of 780 diabetic patients diagnosed to acute coronary syndrome (ACS) undergoing emergent PCI were analyzed. Patients included in the study were consecutive cases with PCI seen at our department between 2011 and 2013. Patients with concomitant procedures (valve surgery, aortic surgery, etc) were excluded. Patients with missing preoperative NT-proBNP values were also excluded.

Plasma NT-proBNP levels were determined before operation using an electro-chemiluminescence immunoassay, performed on a Roche Elecsys 2010 automated platform (Roche Diagnostics, Basel, Switzerland). The assay has an effective measuring range of 5-35 000 ng/ml. The within-run coefficient of variation was 2.7% at a concentration of 175 ng/ml and 1.9% at 1068 ng/ml. The between-run coefficients of variation were 14.2%, 6.6%, and 4.8% at levels of 38.5, 228.7, and 454.6, respectively.

Clinicians responsible for patient care were blinded to the preoperative NT-proBNP levels. All preoperative data were also collected by individuals blinded to these levels.

Endpoints

The primary end points of the study included: all-cause mortality within 30 days of PCI, defined as the incidence of death occurring during admission to hospital for PCI or upto 30 days after PCI or hospital deaths and all deaths during the follow-up time.

The secondary end points of the study were: the requirement for postoperative cardiovascular support, carotid artery disease (defined as

Table 2. Statistical differences between patients who are alive or dead at discharge and at follow-up time

	Discharge alive	Discharge dead	*P* Value	Alive at follow-up	Dead at follow-up	*P* Value
Age (years)	57 (34-78)	70 (49-84)	0.019	64 (34-78)	76 (49-84)	0.012
Body mass index (kg/m^2)	24 (17-31)	25 (19-35)	0.261	24 (17-31)	26 (20-38)	0.189
Postoperative serum creatinine (mg/dl)	0.9 (0.6-4.1)	1.0 (0.8-3.9)	0.032	0.9 (0.6-4.1)	1.1 (0.6-3.6)	0.027
Left ventricular ejection fraction (%)	58 (21-85)	55 (27-83)	0.460	57 (21-85)	54 (26-79)	0.012
PCI time (min)	95 (60-268)	102 (54-219)	0.328	95 (60-268)	99 (051-221)	0.412
Total time on CCU (h)	24 (11-39)	38 (2-72)	0.453	24 (11-39)	39 (7-69)	0.021

the presence of carotid artery stenosis > 50%, or carotid artery occlusion), stroke (defined as any neurologic impairment last more than 24 h, or was associated with death), the length of stay in the CCU, the duration of hospital stay, postoperative renal failure, and postoperative atrial fibrillation. Prolonged CCU and hospital stay were prospectively defined as > 1 day and > 1 week, respectively, based on local audit data.

Statistical analysis

Categorical data are summarized as absolute values (percentage). Continuous data are presented as median (interquartile range (IQR)) or, when normally distributed, as mean (SD). The 1-, 2-, and 3-year survival rates were calculated using a life table.

We calculated the best cut-off values of NT-proBNP to predict hospital mortality or overall mortality by using receiver operating characteristic (ROC) curves. The comparison between categorical variables and hospital mortality, overall death, or NT-proBNP > 660 ng/ml was performed using χ^2 analysis. The comparison between continuous variables and hospital mortality, overall death, or NT-proBNP > 660 ng/ml was performed using a Mann-Whitney test. Survival curves were generated using Kaplan-Meier estimates. Differences in the survival rate were calculated using the log rank test. For multivariate analysis we used a Cox regression model. As covariates the factors commonly known to influence NT-proBNP levels were entered: gender, age (we chose an age > 60 years, which was the median of our cohort), body mass index (calculated as body weight [kg]/height^2 [m^2]; we chose a BMI > 24 kg/m^2, which was the median of our cohort), serum creatinine levels above the upper reference limit of 1.2 mg/dl. A *p* value > 0.05 was regarded as statistically significant. SPSS 15.0 for Windows (SPSS Inc, Chicago, USA) statistical software was used.

Result

Patient population

The cohort was predominantly male with a median age of 60 year. NT-proBNP levels were obtained a median of 1.5 day before PCI.

After a median follow-up time of 24 (12-41) months 2.05% (16/780) patients died, including 0.64% (5/780) hospital deaths. The 1-, 2-, and 3-year survival rates (including hospital mortality) were 98%, 95%, and 90%, respectively.

With the ROC curves assessment, the best cut-off point of serum NT-proBNP level to predicting hospital mortality was 382 ng/ml, and the best cut-off point to predicting overall mortality was 660 ng/ml.

The indexes of age, post-operative serum creatinine, peripheral vascular disease, and high serum NT-proBNP level (> 382 ng/ml) were significantly associated with hospital mortality by the univariate analysis. And the indexes of age, diabetes mellitus, chronic obstructive pulmonary disease, postoperative serum creatinine, poor left ventricular ejection fraction and high serum NT-proBNP level (> 660 ng/ml) were also significantly associated with overall mortality by the univariate analysis (**Tables 1** and **2**).

The survival rate of diabetic patients with high NT-proBNP levels (> 660 ng/ml, 296 patients) was lower than diabetic patients with low NT-proBNP levels (≤ 660 ng/ml, 484 patients) by the Kaplan-Meier analysis (P=0.018).

When the serum NT-proBNP level were ≤ 660 ng/ml, the 1-, 2-, and 3-year survival rates were 98.9%, 97.1%, and 92.2%, respectively.

Table 3. Demography of 820 PCI patients with preoperative evaluation of serum NT-proBNP levels

	All patients	NT-proBNP > 660 ng/ml	NT-proBNP ≤ 660 ng/ml	*P* Value
Age (year)	65 (34-84)	74 (46-84)	60 (34-71)	0.013
Male gender	72.1% (562/780)	86.2%	63.5%	0.024
Body mass index (kg/m^2)	25 (17-35)	29 (19-35)	23 (17-28)	0.046
Postoperative serum creatinine (mg/dl)	0.9 (0.6-4.1)	1.9 (1.1-4.1)	0.8 (0.6-2.9)	0.041
Chronic renal failure requiring dialysis	0.77% (6/780)	2.03%	0.24%	0.001
Smoking History	30.1% (235/780)	31.1%	29.4%	0.085
Current smoker	12.2% (95/780)	13.6%	10.9%	0.062
Family history of coronary artery disease	17.3% (135/780)	17.9%	16.6%	0.267
Arterial hypertension	67.8% (529/780)	70.0%	66.2%	0.068
Hyperlipoidemia	60.5% (472/780)	62.2%	59.8%	0.203
History of cerebrovascular accident	9.6% (75/780)	10.1%	9.3%	0.234
Chronic obstructive pulmonary disease	41.5% (324/780)	49.4%	32.2%	0.006
Peripheral vascular disease	3.3% (26/780)	6.7%	1.8%	0.001
Carotid artery disease	6.2% (48/780)	6.8%	6.0%	0.357
Left ventricular ejection fraction (%)	57 (21-85)	43 (21-71)	65 (38-85)	0.019
Total time on CCU (h)	34 (2-72)	43 (14-72)	20 (2-63)	0.023
Perioperative stroke	2.9% (23/780)	3.1%	2.6%	0.213
Postoperative transient ischemic attack	1.4% (11/780)	1.3%	1.5%	0.262
Postoperative renal failure	4.1% (32/780)	6.6%	3.2%	0.006
Postoperative atrial fibrillation	28.1% (219/780)	36.9%	19.8%	0.001

However, when the serum NT-proBNP level were > 660 ng/ml, the 1-, 2-, and 3-year survival rates were 95.0%, 91.8%, and 86.2%, respectively.

Mortality according to quartiles of serum NT-proBNP levels

Incidence of death during follow-up was significantly higher in the highest (14/186) in comparison with the lowest NT-proBNP quartile (3/164) (P=0.001). Cox regression analysis of the different quartiles of NT-proBNP also showed significant differences (P < 0.001).

Multivariate Cox regression analysis (covariates: gender, age > 60 years, BMI > 24 kg/m^2, serum creatinine > 1.2 mg/dl) revealed NT-proBNP as an independent risk factor for mid-term survival (*OR*=4.129, *95% CI*=2.975-6.281, *P*=0.037).

Association between NT-proBNP Levels and Perioperative Outcome Patients with NT-proBNP levels > 660 ng/ml had more co-morbidities than those with NT-proBNP levels ≤ 660 ng/ml. The preoperative serum NT-proBNP level was more than 660 ng/ml in diabetic patients with ACS after PCI, who had the indexes of postoperative serum creatinine (P=0.041), longer CCU stay-time (P=0.023), postoperative renal failure (P=0.006) and postoperative atrial fibrillation (P=0.001) (**Table 3**).

Discussion

NT-proBNP and hospital mortality

The NT-proBNP cut-off level to the best prediction of hospital mortality was 382 ng/ml, and to the best prediction of overall mortality was 660 ng/ml by our series ROC curve analysis. These levels are comparable to cut-off levels for predicting postoperative cardiac events in non-diabetic patients with ACS undergoing PCI, which were reported to be between 280 and 533 pg/ml [1]. One clinical study found that an increased NT-proBNP level on admission to the CCU was a risk factor for acute heart failure to patients with diabetic patients with ACS [8]. Nevertheless, no clinical study had reported the predictive value of the short-coming complications of diabetic patients with ACS after PCI, and also no one had to keep in mind that cut-off points vary between different study cohorts [9].

Thus we focused on diabetic patients with ACS undergoing emergent PCI in our study.

We found that age, preoperative serum creatinine, peripheral vascular disease, and NT-proBNP levels > 382 ng/ml were significantly associated with hospital mortality. Although the first three risk factors are also found to be predictive for hospital mortality, NT-proBNP is not part of this pre-operative risk score for diabetic patients with ACS undergoing emergent PCI [10]. In an interesting study, Grabowski et al. found a higher early mortality and a decreased PCI success rate (especially an increased number of no-reflow phenomenon) in patients (included diabetic and non-diabetic) with acute ST elevation myocardial infarction and with high levels of serum BNP [4, 11].

NT-proBNP and mid-term survival rates

In a series of 98 male patients undergoing different types of heart surgery Hutfless et al. found increased NT-proBNP levels in patients with ACS after PCI who died within 1 year after surgery [12]. Kragelund et al. found a decreased long-term survival in 1039 patients with stable coronary artery disease and increased NT-proBNP levels [13]. Other authors found that BNP and NT-proBNP levels were predictive for survival rates in non-diabetic patients with acute coronary syndromes and acute myocardial infarction [14, 15]. In our study, mid-term survival rates were significantly decreased in diabetic patients with elevated NT-proBNP levels. Furthermore, NT-proBNP remained as a significant risk factor of survival when the commonly known factors influencing BNP levels (ie, gender, age BMI, serum creatinine) were included in the multivariate analysis.

NT-proBNP and postoperative complications

We found an increased PCI time and length of CCU stay in diabetic patients with elevated preoperative NT-proBNP levels. In general, those diabetic patients exhibited a higher rate of comorbiditie. In detail, a higher rate of postoperative renal failure requiring hemofiltration was found, which may be explained by the higher preoperative serum creatinine levels in diabetic patients with NT-proBNP levels > 660 ng/ml. We also found a higher rate of body mass index (BMI) associated with higher NT-proBNP levels. This is in good agreement with Hutfless et al., who reported higher NT-proBNP levels in patients with abdominal visceral obesity compared with those who did not [16, 17]. In exacerbated COPD elevated NT-proBNP levels were associated with a prolonged stay in the CCU.

Atrial fibrillation is a common complication after PCI [18]. Although it is easily manageable, it causes a transient circulatory disturbance that may be critical for the diabetic patient with ACS after PCI in CCU [19]. In our study we found a higher rate of postoperative atrial fibrillation in diabetic patients with elevated NT-proBNP levels. Wazni and coworkers found that non-diabetic patients with atrial fibrillation following cardiac PCI exhibited higher BNP levels than non-diabetic patients who remained in sinus rhythm throughout the postoperative course [20].

Clinical impact of the study

Preoperative measurement of NT-proBNP levels can be used, in addition to established risk scores, to determine to an increased risk of the diabetic patients with ACS after PCI. Since the mid-term survival following PCI is significantly decreased, diabetic patients with increased NT-proBNP should be followed up closely. We conclude that elevated preoperative serum NT-proBNP levels are associated with a higher postoperative early-term mortality, as well as morbidity, in diabetic patients with acute coronary syndrome after PCI.

Disclosure of conflict of interest

None.

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