MODELING THE CLINICAL PROFILE OF PATIENTS WITH HYPERTENSION AND ATRIAL FIBRILLATION BY SERUM NTpro-BNP LEVELS

Ivanov V.P., Zakrevska M.M.

National Pirogov Memorial Medical University, Vinnytsya, Vinnytsia, Ukraine

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ABSTRACT

Background. Hypertension and atrial fibrillation are a fairly common combination of heart pathology that occurs in the daily practice of a cardiologist. Associations of clinical laboratory and instrumental indicators with the levels of various biomarkers, in particular serum N-terminal fragment of brain natriuretic propeptide (NT-proBNP), are interesting and promising for scientific research and practical application.

The aim of the study was to simulate the clinical profiles of patients with hypertension and atrial fibrillation depending on the serum levels of NTpro-BNP.

Materials & Methods. 89 patients with stage II hypertension and various clinical forms of atrial fibrillation were included in the study. All patients underwent a general clinical examination, additional determination of NT-proBNP serum levels, and assessment of quality of life according to the Minnesota Living with Heart Failure Questionnaire (MLHFQ) for 2–3 days of hospital stay at against the background of selection of optimal therapy. Sequential statistical processing of the obtained data using Spearman's rank correlation analysis and multiple linear regression made it possible to create two clinical profiles of patients.

Results & conclusions. Thus, with a relatively high serum level of NTpro-BNP (≥810 ng/l), the following will be characteristic: hypertensive history >12 years; the presence of signs of left ventricular hypertrophy on the ECG according to the Sokolov-Lyon criteria; increase in the right atrium >36 mm and systolic pressure in the pulmonary artery >38 mm Hg according to Echocardiography; an increase in the average daily heart rate >110 per 1 min with Holter ECG monitoring; a decrease in the glomerular filtration rate <56 ml/min/1.73m^2 and an increase in the total MLHFQ score >27. The dominant markers of a relatively high level of NTpro-BNP were a decrease in quality of life, instrumental signs of hemodynamic overload of the right heart and clinically significant cardiorenal disorders. With a relatively low serum level of NTpro-BNP (≤220 ng/l), the following will be characteristic: hypertensive history anamnesis <8 years; lack of signs of the left ventricle hypertrophy on the ECG according to the Sokolov-Lyon criteria; the size of the right atrium <34 mm and/or the value of systolic pressure in the pulmonary artery <33 mm Hg according to Echocardiography; average daily heart rate with Holter ECG monitoring <92 per 1 minute; glomerular filtration rate >68 ml/min/1.73m^2 and the total MLHFQ score <21. The dominant markers of a relatively low level of NTpro-BNP were the absence of signs of left ventricular hypertrophy on the ECG and a balanced state of sympatho-adrenal activity by the nature of circadian regulation of heart rate.

Keywords: *atrial fibrillation; N-terminal fragment of brain natriuretic propeptide; clinical profile of patients.*

Corresponding author:
Zakrevska Maryna Mykhailivna – Postgraduate Student of the Department of Internal medicine No.3 at National Pirogov Memorial Medical University, Vinnytsya, Vinnytsia.
Address: Ukraine, 21018, Vinnytsya, Pyrohova str., 56, National Pirogov Memorial Medical University.
E-mail: DrZakrevska@ukr.net

Introduction

Hypertension and atrial fibrillation (AF) is a fairly common combination of heart pathology that occurs in the daily practice of a cardiologist [1]. The practical interest in such an association of diseases is primarily related to the high prevalence of both pathological conditions in the European population, the close connection of diseases with the de-

velopment of various cardiovascular events, including fatal ones, as well as a significant decrease in the quality of life of patients [2; 3].

Associations of clinical laboratory and instrumental indicators with the levels of various biomarkers are interesting and promising for scientific research and practical application, which not only characterize the specificity and severity of systemic processes occurring in the cardiovascular system, but also can be used to predict the course of diseases and certain standardization of clinical profiles of patients. One such biomarker is the serum N-terminal fragment of brain natriuretic propeptide (NT-proBNP) [4; 5].

The aim of the study was to simulate the clinical profiles of patients with hypertension and atrial fibrillation depending on the serum level of NTpro-BNP.

Materials and Methods

The study was conducted in accordance with the main provisions of the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research involving human subjects (2000) and the order of the Ministry of Health of Ukraine No.281 dated November 1, 2000. The research protocol was approved by the biomedical ethics commission of National Pirogov Memorial Medical University, Vinnytsya.

As part of an open observational randomized comparative study, 89 patients with stage II hypertension and various clinical forms of AF were examined. The average age in the studied contingent was (61.1±9.0) years. There were 39 men (43.8%) and 50 women (56.2%) in the study. All patients were examined and treated on the basis of the Municipal Institution of Vinnytsia Regional Clinical and Diagnostic Center for Cardiovascular Pathology during 2018–2021.

All patients underwent a general clinical examination in accordance with current international guidelines [3; 6; 7], additional determination of NT-proBNP serum levels and assessment of quality of life according to the MLHFQ (Minnesota Living with Heart Failure Questionnaire [8]) on day 2^{nd}–3^{rd} of hospital stay against the background selection of optimal therapy.

The levels of serum NT-proBNP were determined using the appropriate ELISA test systems (Critical Diagnostics, USA). The different levels of NT-proBNP and the selection of groups with a relatively low (RL, ≤220 ng/l), intermediate (Im, 221–809 ng/l) and relatively high (RH, ≥810 ng/l) levels were calculated by the method of variational statistics with determination of the median and interquartile range for the levels of biomarkers in the examined sample of patients (n=89). The RL level for this sample was defined as the value of the biomarker <25^{th} and RH – >75^{th} percentile, respectively. Instead, the Im level corresponded to the range of the indicator, which was between the 25^{th} and 75^{th} percentiles.

Statistical analysis was performed using Microsoft Excel (2016) and Statistica 12.0 (Statsoft, USA).

At the first stage of the analysis, in order to "filter" and select the most informative indicators, Spearman's rank correlation analysis was used between the actual biomarker serum levels (ng/l) and various clinical and instrumental indicators, as well as indicators of the quality of life according to the MLHFQ questionnaire.

Based on the results of the analysis, indicators that demonstrated statistically significant rank correlations ($p<0.05$) with the content of serum NT-proBNP were selected. These indicators were taken for the next analysis – multiple linear regression.

The serum level of NTpro-BNP was taken as the initial parameter of the multiple linear regression in points, where 1 point is RL, 2 points is Im, and 3 points is RH level, respectively.

When conducting a multiple regression analysis in order to determine the most informative combination of indicators, the procedure of stepwise inclusion of features ("Forward stepwise") was used. It allowed us to determine the combination with the largest coefficient of multiple regression – the coefficient of determination (R2). In addition, the beta coefficients (of the obtained parameters of the model, which demonstrate the nature and strength of the connection with the original parameter), the level of their statistical significance (p-value) and the strength of the influence of the parameters on the original parameter in points were determined. The latter was calculated as the ratio of the beta-coefficient of the parameter to the sum of the beta coefficients of all parameters of the model, multiplied by 100 and rounded to whole numbers.

To build a clinical profile of patients with different serum levels of NTpro-BNP we used two levels of the biomarker – RH and RL, which were previously determined for the examined sample of patients. In addition, threshold values of model parameters were calculated for each selected biomarker level, which made it possible to conduct a more detailed assessment of the clinical profile of patients. Threshold values of the parameters

were calculated as the values that determined the maximum informativeness (namely, the maximum value of the odds ratio of events – OR) in predicting separately RL and RH level of serum NTpro-BNP. For discrete values, the threshold values (in the case of a positive regression relationship) were taken as 0 points for RL and as 1 point for RH of the biomarker level, respectively.

Results and Discussion

Based on the results of Spearman's rank correlation analysis, those that demonstrated statistically significant rank correlations ($p<0.05$) with the NT-proBNP serum levels were selected from the wide variety of studied indicators (*Table 1*).

The indicators in *Table 1* were taken as the main parameters for multiple linear regression. The exceptions were the HM ECG indicators (HRday, HR24-hrs and CI – the ratio of day HR to night HR), which had the same clinical interpretation, so only the HRday indicator, which had the highest correlation coefficient, was taken for further regression analysis.

The results of multiple linear regression are shown in *Table 2*.

The rather high coefficient of multiple regression ($R^2=0.64$) with a significance level of $p=0.00002$ draws attention.

Therefore, analyzing the obtained data, it was observed that the model of the clinical profile of the patient based on the serum level of NTpro-BNP included 7 clinical and instrumental parameters, which revealed statistically significant regression relationships with the level of the biomarker ($p<0.05$):

1) duration of hypertensive medical history in years (beta=0.008; p=0.048);

2) the presence of signs of LV hypertrophy on the ECG according to the Sokolov-Lyon criteria (beta=0.106; p=0.008);

3–4) the size of RA in mm (beta=0.137; p=0.002) and STLa in mm Hg according to Echocardiography (beta=0.038; p=0.01);

5) HR_{day} per 1 minute according to the data of the HM ECG (beta=0.150; p<0.0001);

6) the value of GFR [ml/min/1.73m^2] (beta=-0.113; p=0.005);

7) the value of the total score according to the MLHFQ questionnaire (beta=0.193; p<0.0001).

Table 1. Statistically significant results of Spearman's rank correlation between various clinical and instrumental indicators and NTpro-BNP serum levels (ng/l)

Clinical and instrumental indicators	Spearman R	T(N-2)	P-value
Duration of hypertensive history, years	0.23	2.14	0.03
LV hypertrophy on ECG according to the Sokolov-Lyon criteria in points (1 point – yes, 0 – no)	0.32	3.10	0.002
FC according to NYHA	0.27	2.61	0.01
BMI, kg/m^2	-0.25	-2.42	0.02
RA according to EchoCG, mm	0.30	2.79	0.006
STLa according to EchoCG, mm Hg	0.29	2.75	0.007
Blockade of LAF of the LBB on ECG in points (1 point – yes, 0 – no)	0.24	2.22	0.02
HR_{day} according to HM ECG data, per 1 min	0.32	3.08	0.002
$HR_{24\text{-}hrs}$ according to HM ECG data, per 1 min	0.31	3.03	0.003
CI according to HM ECG data, um. unit	0.26	2.46	0.01
Daily number of VE according to HM ECG data	-0.27	-2.54	0.01
GFR, ml/min/1.73m^2	-0.28	-2.71	0.008
MLHFQ total score	0.41	4.56	<0.0001

Notes: LV – left ventricle; ECG – electrocardiography; HM – Holter monitoring; FC – functional class; BMI –body mass index; RA – right atrium size; EchoCG – echocardiography; STLa – systolic pressure in the pulmonary artery; LAF of the LBB – left anterior fascicle of the left bundle branch (His bundle); HRday and HR24-hrs are average daily and average 24-hours heart rate, respectively; CI – circadian index; VE – ventricular extrasystole; GFR – glomerular filtration rate; MLHFQ – Minnesota Living with Heart Failure Questionnaire.

Table 2. Results of multiple linear regression with the initial parameter of NTpro-BNP serum level in points

Model parameters	Beta-coefficient	P-value	Power of influence in points
Duration of hypertensive history, years	0.008	0.048	1
LV hypertrophy on ECG according to the Sokolov-Lyon criteria in points (1 point – yes, 0 – no)	0.106	0.008	14
RA according to EchoCG, mm	0.137	0.002	18
STLa according to EchoCG, mm Hg	0.038	0.01	5
HR_{day} according to HM ECG data, per 1 min	0.150	<0.0001	20
GFR, ml/min/1.73m^2	-0.113	0.005	15
MLHFQ total score	0.193	<0.0001	26

Notes:

Informativeness of the obtained model: coefficient of determination (multiple linear regression) – R^2=0.64; Fisher's actual test (F) = 56.73 at the appropriate level (df) = 3.16; level of significance (p) of the model = 0.00002; standard error of analysis according to the model (St. Error of estimate) = 0.04.

LV – left ventricle; ECG – electrocardiography; HM – Holter monitoring; RA – right atrium size; EchoCG – echocardiography; STLa – systolic pressure in the pulmonary artery; HRday – average daily heart rate; GFR – glomerular filtration rate; MLHFQ – Minnesota Living with Heart Failure Questionnaire.

Almost all indicators had a direct regression relationship with the serum level of NTpro-BNP (an increase in the serum level of the biomarker predicted an increase in the value of the indicator or a transition to a higher score), while only one parameter showed an inverse regression relationship with the level of the biomarker – the value of GFR [ml/min/1.73m^2]. The latter demonstrated that an increase in the serum level of NTpro-BNP predicted an actual decrease in the value of GFR and deterioration of the filtration function of the kidneys and vice versa.

The calculated influence of the parameters on the serum level of NTpro-BNP in points showed that the value of the total score according to the MLHFQ questionnaire (impact = 26 points), the average daily heart rate (20 points) and the size of the PP (18 points) had the greatest influence, in that time as the smallest – the value of STLa (5 points) and duration of hypertensive anamnesis (1 point). Such parameters as the value of GFR and the presence of LV hypertrophy on the ECG occupied an intermediate position – the impact was 15 and 14 points, respectively.

Thus, the analysis demonstrated that the level of quality of life, determined by the MLHFQ questionnaire adapted to patients with chronic heart failure, had the greatest impact on the serum level of NTpro-BNP; the nature of HRday regulation, which, first of all, reflected the activity of the sympatho-adrenal system and the nature of hemodynamic overload of the right heart, characterized by the echocardiogram size of RA. To a lesser extent, the effect on the biomarker level was found to be the nature of violations of the kidneys filtration function, which is a consequence of the cardiorenal continuum in patients with hypertension and is characterized by the value of GFR and the nature of structural damage to the LV myocardium, which is determined by signs of hypertrophy on the ECG (*Table 3*).

Analyzing the data in the Table 3, it was necessary to pay attention to the fact that the threshold values of the parameter determined for different serum levels of NTpro-BNP have different prognostic value in a priori prediction of different levels of the biomarker. For example, the duration of hypertensive history >12 years increases the a priori probability of RH level by 1.1 times, while history of <8 years – 1.6 times the probability of RL serum level of NTpro-BNP. The latter demonstrates that a short hypertensive history (<8 years) is more likely to predict the RL serum level of NTpro-BNP than a long hypertensive history (>12 years) – the RH level of the biomarker. Such logistics also apply to other parameters listed in the corresponding table.

Therefore based on the data we obtained, it should have been thought that in patients with hypertension and AF, regardless of its variant, in the

Table 3. Threshold values for parameters of the patient clinical profile model depending on the serum level of NTpro-BNP

Model parameters	Threshold values of parameters for different serum levels of NTpro-BNP	
	≥810 ng/l	**≤220 ng/l**
Duration of hypertensive history, years	>12 OR=15/14=1.1	<8 OR=18/11=1.6
LV hypertrophy on ECG according to the Sokolov-Lyon criteria in points (1 point – yes, 0 – no)	Yes OR=19/10=1.9	No OR=23/6=3.8
RA according to EchoCG, mm	>36 OR=21/8=2.6	<34 OR=17/12=1.4
STLa according to EchoCG, mm Hg	>38 OR=16/13=1.2	<33 OR=14/15=0.93
HR_{day} according to HM ECG data, per 1 min	>110 OR=18/11=1.6	<92 OR=20/9=2.2
GFR, ml/min/1.73m^2	<56 OR=20/9=2.2	>68 OR=16/13=1.2
MLHFQ total score	>27 OR=22/7=3.1	<21 OR=19/10=1.9

Notes: LV – left ventricle; ECG – electrocardiography; HM – Holter monitoring; RA – right atrium size; EchoCG – echocardiography; STLa – systolic pressure in the pulmonary artery; HRday – average daily heart rate; GFR – glomerular filtration rate; MLHFQ – Minnesota Living with Heart Failure Questionnaire.

case of a high serum level of NTpro-BNP (≥810 ng/l), the following clinical profile will be characteristic: hypertensive history >12 years; the presence of signs of LV hypertrophy on the ECG according to the Sokolov-Lyon criteria; increase in RA >36 mm and STLa >38 mm Hg according to Echocardiography; an increase in HR_{day} >110 per 1 min by HM ECG; a decrease in GFR <56 ml/min/1.73m^2 and an increase in the total score according to MLHFQ >27. The dominant markers of the NTpro-BNP serum level in these patients were a decrease in the quality of life, instrumental signs of hemodynamic overload of the right heart and clinically significant cardiorenal disorders.

In turn, in the case of low NTpro-BNP serum level (≤220 ng/l), the following clinical profile will be characteristic: hypertensive history <8 years; absence of signs of LV hypertrophy on ECG according to the Sokolov-Lyon criteria; the size of RA <34 mm and/or the size of STLa according to Echocardiography <33 mm Hg; HR_{day} by HM ECG <92 per 1 min; the value of GFR >68 ml/min/1.73m^2 and the total score according to MLHFQ <21. The dominant markers of RH of NTpro-BNP level in patients with hypertension and AF are the absence of signs of LV hypertrophy on the ECG (excludes the presence of significant structural lesions of the LV myocardium) and a balanced state of sympatho-adrenal activity by the nature of circadian heart rate regulation.

It is worth noting that the a priori clinical portrait of a patient with hypertension and AF and RL serum level of NTpro-BNP with a high probability implies, first of all, the absence of significant structural changes of the LV myocardium and signs of its hypertrophy on the ECG and not a high level of average HR_{day}.

Thus, in the absence of LV hypertrophy on the ECG, the chances of RL biomarker level are 3.3 times higher than when it is present, while at HR_{day} <92, it is 2.2 times higher compared to HR_{day} >92 per 1 min. In addition, the clinical portrait of a patient with hypertension and AF and RL serum level of NTpro-BNP implies a short history of hypertension (<8 years), no signs of hemodynamic overload of the right heart (RA <34 mm or/and STLa <33 mm Hg); absence of cardiorenal disorders (GFR >68 ml/min/1.73m^2) and mild deterioration of quality of life (total MLHFQ score <21).

Conclusions

1. Dominant markers of a relatively high level (≥810 ng/l) of serum N-terminal fragment of brain natriuretic propeptide in patients with hypertension and atrial fibrillation are a decrease in quality of life, instrumental signs of hemodynamic overload of the right heart, and clinically significant cardiorenal disorders.

2. The dominant markers of a relatively low level (≤220 ng/l) of serum N-terminal fragment of brain natriuretic propeptide in this contingent of patients are the absence of signs of left ventricular hypertrophy on the ECG and a balanced state of sympatho-adrenal activity by the nature of circadian regulation of heart rate.

In the future, it is planned to study an expanded range of biomarkers of cardiovascular disease and create a comprehensive clinical profile of the patient.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Data Transparency

The data can be requested from the authors.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

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