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The Prognostic Role of Bwiomarkers in Patients with Chronic Heart Failure

Objective — Investigate the role of biomarkers in the prognosis of the clinical course of the disease in patients with chronic heart failure (CHF) of different NYHA functional classes (FC).

Materials and Methods — The study included 132 patients with CHF: Group 1 was composed of 70 patients with NYHA FC II CHF, and Group 2 included 62 patients with FC III-IV CHF. The patients underwent clinical, instrumental, functional, and laboratory measurements, which included serum concentrations of NT-proBNP, ST-2, galectin-3, and C-reactive protein. Patients were examined at baseline and at 3, 6, and 12 mos of follow-up. The following cardiac complications were used as endpoints: urgent hospitalization due to decompensated CHF, heart transplantation, cardiovascular death. Endpoints were registered during the 12-mo follow-up period.

Results — Endpoints were recorded for 58 patients (44%) of the total sample of patients with CHF: 38 patients were urgently hospitalized, 10 patients underwent heart transplantation, 10 patients died. Cardiac complications were recorded at a higher rate in patients with FC III-IV CHF (63% vs. 27% of patients with FC II; p<0.001). In FC II CHF patients, the incidence of cardiac complications was significantly correlated with NT-proBNP blood concentrations (Rpb=0.53; p=0.023), left ventricular end-diastolic volume (LVEDV) (Rpb=0.50; p=0.044), and mitral regurgitation (Rpb=0.53; p=0.038). Cardiac complications in patients with FC III-IV CHF were associated with ST-2 (Rpb=0.52; p=0.004) and galectin-3 (Rpb=0.46; p=0.009) blood concentrations, and with systolic pulmonary artery pressure (PAP) (Rpb=0.41; p=0.014). Unlike other laboratory measurements, galectin-3 concentrations were significantly correlated with type 2 diabetes mellitus (DM2) (Rpb=0.40; p=0.003). In this study, correlation analysis and evidence of significant differences in the concentrations of biomarkers provided a rationale for identifying potential predictors of severe cardiac complications during medium- and long-term follow-up periods in patients with CHF of different severity: NT-proBNP concentrations in FC II patients; ST-2 and galectin-3 serum concentrations in FC III-IV patients; galectin-3 concentrations in patients with CHF and DM2.

Conclusion — NT-proBNP blood concentrations are associated with CHF severity and serious cardiac complications in patients with FC II CHF within the following 12 mos. The poor prognosis of FC III-IV CHF is associated with the concentration of the ST-2 biomarker. The blood concentration of galectin-3 is a significant predictor of poor prognosis in patients with CHF and DM2. Predictors of the adverse course of CHF of varying severity were differentiated. For FC II CHF, NT-proBNP >1723 pg/ml or, if NT-proBNP <1 723 pg/mL, then EDV >311 ml. For FC III-IV CHF, ST-2 >67 ng/mL or, if ST-2 <67 ng/mL, then PAP >61 mm Hg. Galectin-3 has a prognostic value for the clinical course of the disease at different follow-up periods in patients with CHF and DM2: galectin-3 concentrations >16 ng/mL and 13-16 ng/mL are risk factors for mid- and long-term cardiac complications, respectively.

Keywords — Chronic heart failure; prognostic criteria; biomarkers

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Biomarkers are currently given a prominent role in assessing the severity and prognosis of chronic heart failure (CHF). It should be noted, however, that none of the existing biomarkers can be fully indicative of the risk of occurrence or progression of CHF. Nor are they indicative of the disease stage or the likelihood of adverse clinical outcomes. Thus, a differentiated approach to the comprehensive utilization of cardiac biomarkers and the findings of clinical and instrumental examinations appears promising. This approach should significantly increase the accuracy of diagnosis and prognosis. Selecting the optimal number of tests, including measurements of clinical, hemodynamic, and laboratory variables, is necessary for accurate diagnosis and prognosis.

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Material and Methods

The study included 132 patients with CHF: Group 1, 70 patients with NYHA functional class (FC) II CHF; Group 2, 62 patients with FC III-IV CHF.

The following echocardiographic variables were measured: left ventricular (LV) end-diastolic dimension, LV end-systolic dimension, LV end-diastolic volume (EDV), LV end-systolic volume, LV ejection fraction (EF), the transverse and longitudinal sizes of the right atrium and right ventricle, right ventricular EF, pulmonary artery pressure (PAP), volume of mitral regurgitation, and anterior-posterior, transverse, and longitudinal dimensions of the left atrium. The laboratory determinations included serum concentrations of NT-proBNP, ST-2, galectin-3, and C-reactive protein (CRP). Patients were examined at baseline and at 3, 6, and 12 mos of follow-up.

The following cardiac complications were used as endpoints: urgent hospitalization due to decompensated CHF, heart transplantation, cardiovascular death. The endpoints were registered during a 12-mo follow-up period.

Quantitative values are presented as medians (Me) and quartile ranges (LQ = the 25th percentile, UQ = the 75th percentile). Nominal indicators are presented as relative frequencies, expressed as percentages (P). Differences between quantitative data of two independent samples were evaluated with the nonparametric Mann-Whitney test. Contingency tables and Pearson's chi-squared test were used to compare group data with binary values. Correlation analyses were performed to identify relationships between clinical outcomes, baseline blood concentrations of the laboratory markers, and intracardiac hemodynamic values. Correlations, beginning from moderate, were considered significant if >0.30. For this correlation analysis, the resultant variable, i.e., clinical outcome during a particular period, was represented as a binary value: 0 = favorable course of the disease, 1 = detected and documented cardiac complications. The correlation coefficients were used to estimate the direction and strength of relationships between variables. The point-biserial correlation coefficient (Rpb) was used to evaluate relationships between binary and quantitative variables. The rank-biserial correlation coefficient (Rrb) reflected relationships between binary and sequential variables, and the Spearman correlation coefficient (Rs) reflected relationships between quantitative variables.

A classification tree (CT), i.e., a decision tree, was used to determine the factors associated with an adverse course of the disease during the 12-mo follow-up period. CTs provide a means to represent decision rules in a coherent, hierarchical structure. Stages in the CT creation:

1) select a forecast accuracy criterion;
2) select a type of branching;
3) determine when further branching should be stopped i.e., the algorithm stopping criterion;
4) construct a CT and determine its suitable size;
5) evaluate the CT.

In this study, the classifiers were built with a minimum error of false classification. The Classification and Regression Trees (CART) algorithm of one-way branching was used. The Factor Analysis Classification Tree (FACT) was selected as the stopping rule for the branching process. The fraction of objects in the terminal nodes was set as 0 and 1. Prognostic variables branched until all leaf nodes were reached, or until the number of objects of a predicted class in the node was less than the predetermined fraction of the total number of patients in this class. Each CT component was evaluated from 0 to 100 depending on its degree of contribution to the prognosis.

The triple cross-validation method was used to select the decision tree of an appropriate size and to evaluate it. The specified value 3 determined the number of random subsamples (of equal size where possible), which were formed from the baseline or training sample using a random number generator. The cost of cross-validation (CV-cost) or a fraction of incorrectly classified objects was calculated for all three test samples. The total CV-cost is presented as the mean and the standard deviation to characterize the degree of the cost range. If the mean CV-cost was less than in the training sample, the CT was considered valid.

The quality of the CT classification was evaluated by two main parameters: recognition accuracy (RA) and error. RA is the ratio of correctly classified objects to the total number of objects in a given node. The error is the ratio of objects incorrectly classified during the training process to the total number of objects in the training dataset. The prognostic effectiveness of the CT was evaluated by the following parameters: 1) sensitivity, the frequency of assigning individuals with an adverse outcome to the subgroup of patients with cardiac complications; 2) specificity, the frequency of classifying individuals with a favorable outcome to the subgroup of patients without cardiac complications.

The critical level of significance for all tests and criteria was taken to be 0.05, i.e., differences were considered statistically significant at $p<0.050$.

Results

Endpoints were registered in 58 patients, representing 44% of the total sample of patients with CHF. 38 patients were urgently hospitalized, 10 patients underwent heart transplantation, and 10 patients died. Cardiac complications were recorded at a higher frequency in Group 2 patients with FC III-IV CHF, 63% vs. 27% of Group 1 patients with FC II ($p<0.001$). In Group 1, the incidence of all adverse outcomes was 14% in the first 6 mos and 13% ($p=0.863$) in 6 to 12 mo period. In Group 2, cardiac complications developed in 29% of patients by the 6th mo and in 34% of patients after 6 more

months of follow-up (p=0.550). The FC II and FC III-IV groups differed significantly in the incidence of cases that reached endpoints within 6 mos and after 6 more months of follow-up (p=0.037 and p<0.001, respectively).

The incidence of cardiac complications in FC II CHF patients significantly correlated with NT-proBNP blood concentrations (Rpb=0.53; p=0.023), left ventricular end-diastolic volume (LVEDV) (Rpb=0.50; p=0.044), and mitral regurgitation (Rpb=0.53; p=0.038). Cardiac complications in patients with FC III-IV CHF were associated with ST-2 (Rpb=0.52; p=0.004) and galectin-3 (Rpb=0.46; p=0.009) blood concentrations, and with systolic pulmonary artery pressure (PAP) (Rpb=0.41; p=0.014). Unlike other laboratory measurements, galectin-3 concentrations were significantly correlated with type 2 diabetes mellitus (DM2) (Rpb=0.40; p=0.003).

The patients with CHF were divided retrospectively after the 12-mo follow-up period into subgroups 1a and 2a having favorable course of the disease or into subgroups 1b and 2b with occurrence of the endpoints in the medium- and long-term follow-up periods.

Fig. 1 shows that in the favorable course of the disease, baseline NT-proBNP blood concentrations were higher in subgroup 2a patients with FC III-IV CHF, 2144 (797-2930) pg/mL vs. 625 (183-1042) pg/mL in subgroup 1a (p=0.002). Subgroups 1b and 2b did not differ in concentrations of this cardiac biomarker, 1820 (1051-2207) pg/mL and 2122 (1017-2930) pg/mL, respectively (p=0.713). The baseline NT-proBNP concentrations in patients with FC II CHF and endpoints registered within 12 mos of follow-up were significantly higher than in patients without severe cardiac complications (p=0.004). Subgroups 2a and 2b of patients with FC III-IV CHF did not differ in baseline NT-proBNP concentrations (p=0.784).

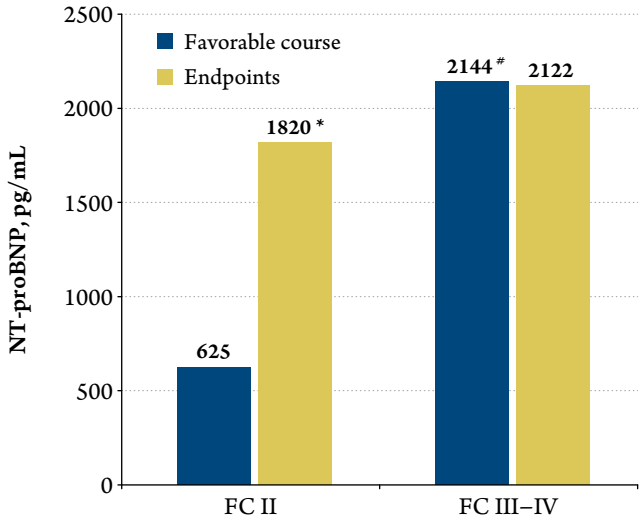
As shown in Fig. 2, the baseline ST-2 concentration in subgroup 2b patients was 40.5 ng/mL, which was significantly higher than that in subgroup 2a (p=0.029). The clinical course of FC II CHF in Group 1 patients was not associated with ST-2 concentrations, since there was no statistically significant difference between subgroups 1a and 1b (p=0.814).

A comparative analysis of the galectin-3 concentrations produced results similar to those of ST-2. Blood concentrations of the galectin-3 biomarker were highest in Group 2b patients with FC III-IV CHF and having serious cardiac complications within 12 mos after the baseline examination (p=0.028; Fig 3.). This Group 2b value was also significantly higher than those of Groups 1a and 1b.

Given that galectin-3 correlated significantly with DM, the subsample of patients with CHF and DM2 was further analyzed. The proportion of patients with DM was 28% of the total number of examined patients with CHF. Of these, more than 90% were patients with FC III-IV CHF. The course of the disease in 73% of patients with DM was adverse (Fig. 4), and 55.6% of all cardiac complications in DM patients developed during the first 6 mos after the baseline examination.

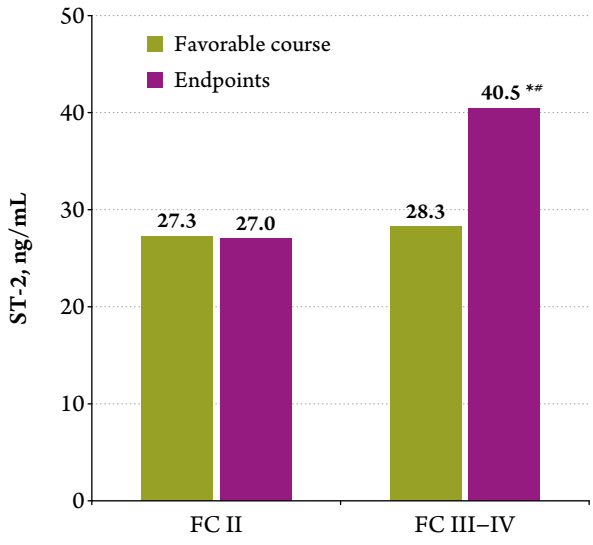
In CHF with DM2, baseline galectin-3 blood concentrations significantly correlated with the rate of endpoint occurrence by the 6th mo of follow-up (Rpb=0.85; p<0.001) and, also, in the long-term follow-up period (Rpb=0.88 p<0.001). Galectin-3

Figure 1. Baseline NT-proBNP concentrations in chronic heart failure patients with or without adverse clinical outcomes within 12 mos of follow-up



* – significant differences with subgroups 1a and 2a (p<0.05);
# – significant differences with FC II (p<0.05).
FC – functional class; NT-proBNP – natriuretic peptide.

Figure 2. Baseline ST-2 concentrations in chronic heart failure patients with favorable or adverse clinical outcomes within 12 mos of follow-up



*– significant differences with subgroups 1a and 2a (p<0.05);
– significant differences from FC II (p<0.05).
FC – functional class.

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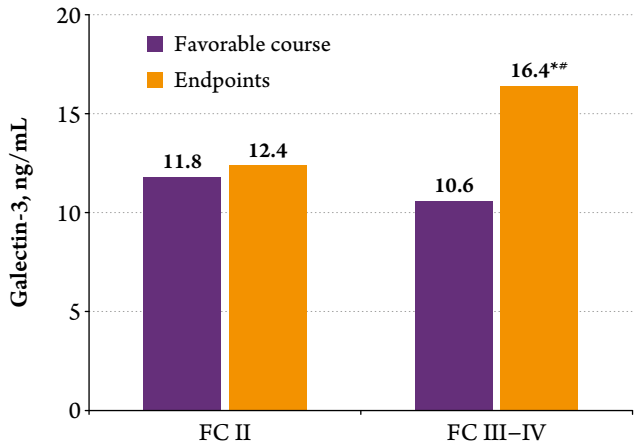
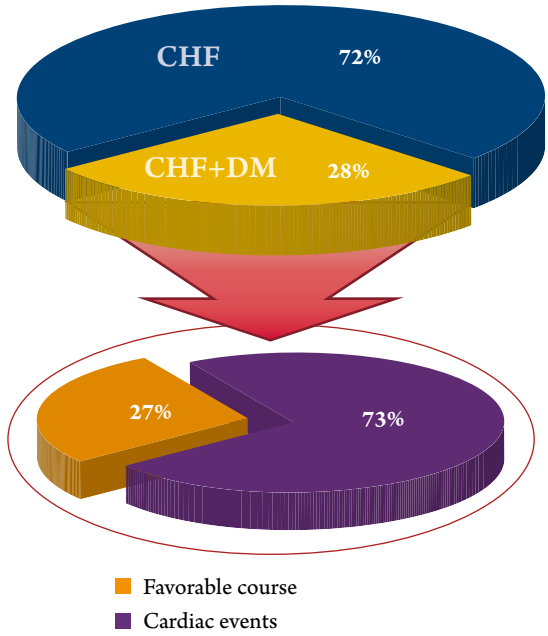
Figure 3. Baseline galectin-3 blood concentrations in chronic heart failure patients with favorable and adverse clinical outcomes within 12 mos of follow-up



* – significant differences with subgroups 1a and 2a ($p<0.05$);
\# – significant differences from FC II ($p<0.05$).
FC – functional class.

Figure 4. The relative incidence of cardiac complications in patients with CHF and concomitant DM2



CHF, chronic heart failure;
DM, diabetes mellitus.

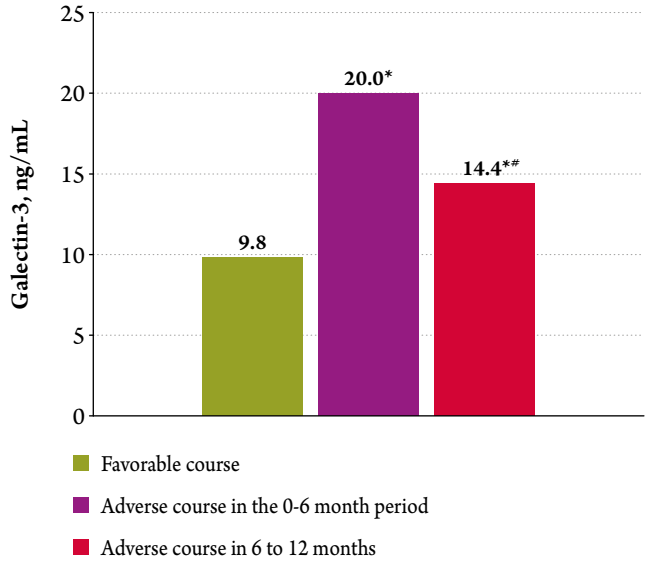
concentrations in patients with DM directly depended on the body mass index (Rpb=0.49; p=0.043).

Fig. 5 shows the baseline concentrations of galectin-3 in the favorable course of the disease and in the occurrence of medium- and long-term endpoints. Patients with cardiac complications in the first 6 mos of follow-up had the highest concentrations of this marker at baseline, 20.0 (17.0-27.4) ng/mL. Patients with a favorable course of the disease had the lowest concentrations, 9.8 (8.9-12.5) ng/mL. Patients with cardiac complications registered from the 6th to the 12th mo of the follow-up period had a baseline galectin-3 of 14.4 (13.4-15.3) ng/mL. All subgroups of patients with CHF and DM defined by the clinical course of the disease were significantly different ($p<0.020$).

In this study, the results of correlation analysis and the significant differences in the concentrations of biomarkers in patients, as grouped by CHF FC and by the nature of the disease course, provided a rationale for establishing potential laboratory predictors of severe cardiac complications likely to occur during medium- and long-term follow-up periods in patients with CHF of different severity. These predictors are NT-proBNP concentrations in FC II patients, ST-2 and galectin-3 serum concentrations in FC III-IV patients, and galectin-3 concentrations in patients with CHF and DM2.

The risk factors for the development of cardiac complications in patients with CHF of varying severity were identified by utilizing CTs. The cut-off values and the sequence of evaluation of the predictors were determined to identify patients at risk. FC II CHF patient CT (CT #1) represented in Fig. 6 had three terminal nodes, two branches, and included NT-proBNP concentrations and LVEDV. Initially, patients with adverse course of the disease were identified using NT-

Figure 5. Galectin-3 concentrations in patients with DM2 depending on the nature of the disease course within 12 mos of follow-up



* – significant differences with the favorable course of the disease;
\# – significant differences in terms of adverse outcomes.
DM – diabetes mellitus.

proBNP RA=71.4%. The cut-off value of the marker was 1 723 pg/mL. If the NT-proBNP concentration was less than the cut-off value, cardiac complications were associated with LVEDV >311 mL (RA=85.7). The resulting CT had an excellent prognostic performance, sensitivity =91.7%, specificity =92.1%, and classification accuracy = 92%.

The mean cross-validation value of CT #1 (0.32±0.080), calculated by the classification errors in the generated test samples, did not exceed the value of the training sample (0.393).

CT #2 constructed for patients with FC III-IV CHF showed that, of all biomarkers analyzed, ST-2 blood levels had prognostic value (Fig. 7). When this marker exceeded 67 ng/mL, patients with RA 83.3% were classified as likely to have adverse outcomes within 12 mos of follow up.

When ST-2 concentrations were >67 ng/mL, PAP had discriminatory power. With PAP more than 61 mm Hg, RA of endpoint occurrence in patients with FC III-IV CHF was 90%. Among the predictors in CT #2, PAP had the highest rank significance (100 points). The overall accuracy of prognosis using the ST-2 and PAP markers was 87.1%, with prognosis accuracy of the favorable course of the disease 88.2% and the occurrence of endpoints 85.7%. Triple cross-validation confirmed the adequacy of CT #2, where the mean value of cross-validation for the test samples (0.137±0.050) was less than that of the baseline sample (0.139).

CT containing a single marker, galectin-3 blood concentrations, was chosen for patients with CHF and concomitant DM2 using a brute-force search for all possible combinations in the laboratory and echocardiographic parameter array performed in this study. The resulting CT #3 diagram is shown in Fig. 8.

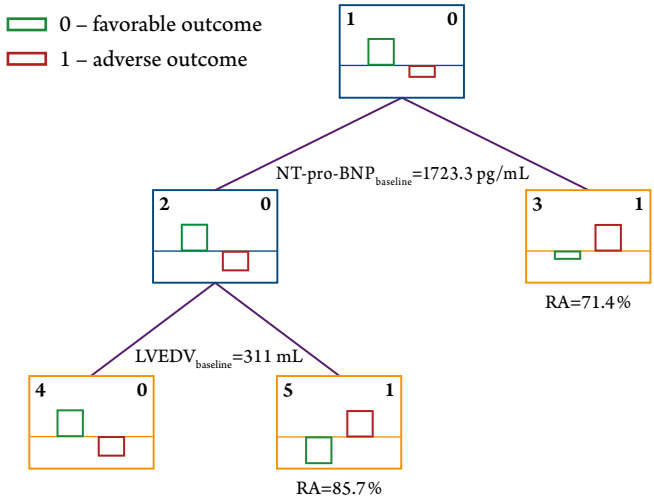
The accuracy of the prognosis of cardiac complications in patients with CHF and DM2 was 86.7% for the first 6 mos and 85.7% for 6 to 12 mos. The triple cross-validation confirmed the validity of CT #3, where the error value of the training sample was 0.154 and the mean value of the test samples was 0.084±0.010.

Potential factors affecting the adverse course of the disease in patients with CHF of varying severity were identified among the laboratory cardiac markers already at the stage of a priori power analysis. NT-proBNP concentrations reflected the severity of CHF only in the favorable course of the disease. A relationship between the NT-proBNP concentrations and CHF FC was absent in patients with severe cardiac complications within 12 mos of follow-up. In FC II CHF, the NT-proBNP blood concentrations were associated with an endpoint occurrence in the medium- and long-term follow-up periods. In FC III-IV patients, this cardiac marker had no prognostic value, because high concentrations of NT-proBNP were observed in all patients regardless of further clinical outcome. The baseline concentration of NT-proBNP in patients with FC II CHF with cardiac complications was comparable to that of patients with severe FC III-IV CHF. Most high-profile medical associations recommend measuring natriuretic peptide concentrations for CHF diagnosis, treatment control, and prognosis of CHF.

Mechanical factors, including ventricular hypertrophy and dilation, increased left or right ventricular end-diastolic pressure, development of pulmonary hypertension, neurohumoral factors including renin, noradrenaline, angiotensin-II, and ischemic factors stimulate the active release of BNP from cardiomyocytes [1, 2].

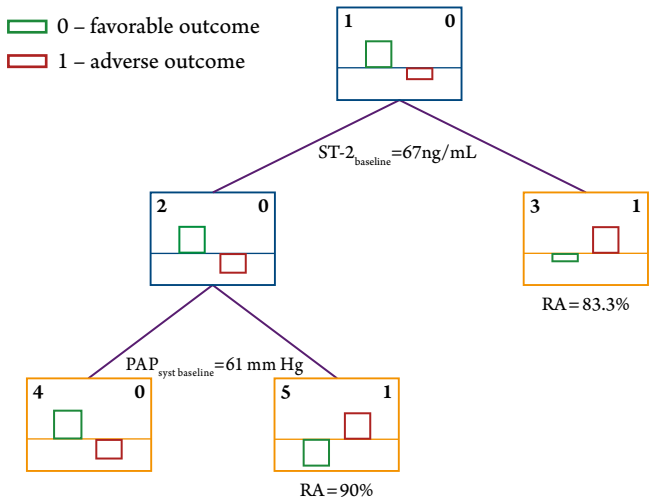
ST-2 is associated with the nature of the course of FC III-IV CHF. Although there is not a close relationship between the severity of CHF and ST-2, this marker can be used as a prognostic factor in patients with FC III-IV CHF. The increase in ST-2 blood concentrations is associated with increased myocardial wall stress due to volume/pressure overload,

Figure 6. Classification tree (CT) of patients with FC II chronic heart failure according to the presence and absence of significant cardiac events within 12 mos of follow-up (CT #1)



NT-proBNP – natriuretic peptide; FC – functional class; LVEDV – left ventricular end-diastolic volume; RA – recognition accuracy.

Figure 7. Classification tree (CT) of patients with FC III-IV chronic heart failure according to the presence and absence of significant cardiac events within 12 mos of follow-up (CT #2)



PAP_{syst} – systolic pulmonary artery pressure; FC – functional class; RA – recognition accuracy.

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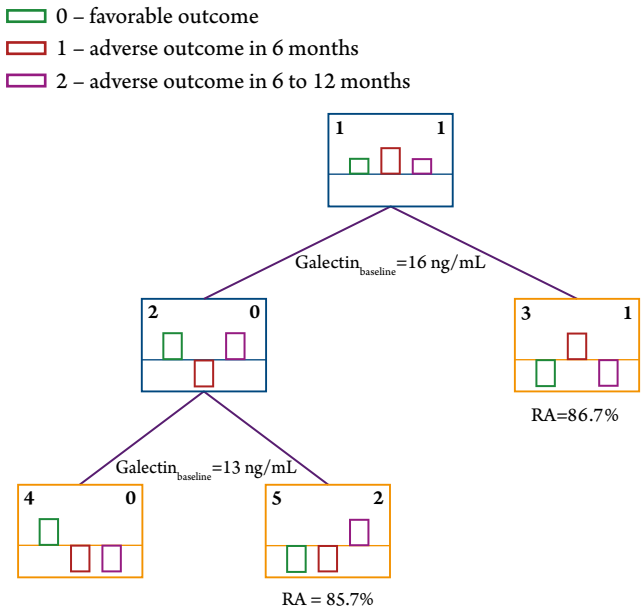
Figure 8. Classification tree (CT) of patients with chronic heart failure and concomitant diabetes mellitus by the presence and absence of significant cardiac events within 12 mos of follow-up (CT #3)



RA – recognition accuracy.

stiffness, and ventricular hypertrophy [3, 4]. Generally, ST-2 is considered a biomarker with strong prognostic potential in CHF [2, 5]. As with ST-2, the baseline concentrations of galectin-3 were significantly higher in patients with FC III CHF that developed cardiac complications within 12 mos of follow-up. The possibility of using galectin-3 as a CHF biomarker is being discussed by the scientific community. A number of studies have confirmed the prognostic value of galectin concentrations in peripheral blood of patients with CHF [6-9]. Furthermore, several reports demonstrated close association of galectin-3 concentrations with markers of myocardial fibrosis [5, 7-12]. There is evidence that galectin-3 has higher prognostic value than NT-pro-BNP in the short-term prognosis of CHF progression and of other cardiovascular complications, particularly in patients with severe CHF [12-14]. However, NT-pro-BNP is superior to galectin-3 as diagnostic tool in CHF.

Our data on the prognostic value of galectin-3 in patients with CHF and concomitant CD are consistent with the results of a large cohort study, PREVEND (Prevention of Renal and Vascular END stage), that investigated the correlation between galectin-3 concentrations and risk factors for cardiovascular disease, and the prognostic power of the biomarker for cardiovascular and total mortality [4, 15]. According to our results, galectin-3 concentrations were closely correlated with such factors as body mass index, arterial hypertension, lipid composition of the blood, and kidney function. The study of patients with extracardiac pathologies also showed a direct relationship between galectin-3 concentrations and obesity, DM2, and increased incidence of cardiovascular events within the first 12 mos [16, 17]. However, galectin-3 is still not widely used in clinical practice. Investigation of plasma concentrations of this laboratory parameter as a biological marker of adverse prognosis is a promising direction for research.

Our results showed that the use of biomarkers in patients with CHF must be differentiated according to CHF severity and comorbidities. The combined administration of laboratory tests and clinical instrumental examinations improves the accuracy of the prognosis in CHF.

Conclusion

NT-proBNP blood concentrations are associated with the severity of CHF and with severe cardiac complications in patients with FC II CHF within the following 12 mos. A poor prognosis of FC III-IV CHF is associated with concentrations of ST-2. The blood concentration of galectin-3 is a significant prognostic criterion in patients with CHF and with DM2.

Predictors of adverse course of CHF of varying severity were differentiated. For FC II CHF, NT-proBNP >1723 pg/mL or, if NT-proBNP <1723 pg/mL, then EDV >311 mL. For FC III-IV CHF, ST-2 >67 ng/mL or, if ST-2 <67 ng/mL, then PAP >61 mm Hg.

Galectin-3 has a prognostic value for the assessment of the clinical course of CHF in different follow-up periods in patients with CHF and DM2: galectin-3 concentrations >16 ng/mL and 13-16 ng/mL are risk factors for mid- and long-term cardiac complications, respectively.

No conflict of interest is reported.

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