ORIGINAL ARTICLE

Prognostic value of novel biomarkers compared with detailed biochemical evaluation in patients with heart failure

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KEY WORDS

biochemical tests, biomarkers, heart failure, prognosis

ABSTRACT

INTRODUCTION The assessment of prognosis is crucial for the clinical management of patients with heart failure (HF).

OBJECTIVES The aim of the study was to evaluate the usefulness of novel biomarkers for the assessment of prognosis in patients with HF, compared with a detailed assessment based on routine laboratory tests.

PATIENTS AND METHODS The study included 179 patients with HF. In all patients, routine laboratory tests were performed and selected biomarkers were measured (N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, growth hormone, myeloperoxidase, metaloproteinase 9, procollagen type III, soluble ST2, insulin growth factor, and neutrophil gelatinase-associated lipocain). The primary endpoint was death or urgent heart transplantation, while the secondary endpoints encompassed primary endpoints plus cardioverter intervention or hospitalization for HF.

RESULTS The mean age of the study group was 52.5 years (91% were men). Most patients had advanced HF. During a 6-month follow-up, 21 primary endpoints and 63 secondary endpoints were recorded. A multiple regression analysis showed that of all laboratory variables and biomarkers, only uric acid and sodium were independent predictors of primary endpoints, and only estimated glomerular filtration rate had a predictive value for secondary endpoints. None of the biomarkers were a significant prognostic factor in the study population.

CONCLUSIONS Biomarkers do not outweigh the value of standard laboratory tests. Routine laboratory workup allows to assess multiorgan damage and provides the most significant prognostic data. Biochemical tests should remain the gold standard for the assessment of prognosis in patients with HF.

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Received: February 24, 2015.
Revision accepted: May 22, 2015.
Published online: May 28, 2015.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2015; 125 (6): 434-442

INTRODUCTION Heart failure (HF) is a complex disease syndrome with an unfavorable prognosis. Based on the recent data, HF survival has improved; however, from the population's perspective, the percentage of HF death has been at best stable in recent years, if not showing a slight increase.[1] An accurate evaluation of patients' prognosis is crucial for guiding the clinical management and identification of high-risk subjects who should be candidates for advanced therapy.[2] There have been numerous attempts to develop proper risk prediction algorithms. The majority of them employ well-established clinical and demographic variables; however, they do not fully reflect the overall risk.[3] It is not clear why risk scores developed with the factors from one population cannot be easily applied to others. Moreover, it should be stressed that some of the risk scores were established about 20 years ago. Thus, taking into consideration the complexity and variability of HF,

it seems justified to search for new prognostic methods incorporating new variables.

The progression of HF is influenced by numerous different pathological processes including neurohormonal activation, oxidative stress, inflammation, and vascular and myocardial remodeling along with renal or liver impairment.[4] Therefore, there is a growing interest in including a diverse biomarker profile reflecting the undergoing pathological processes into the prediction algorithm.[5] Such an approach appears promising; however, it is not obvious whether the new biomarkers can fully outweigh the biochemical evaluation used in every day clinical practice.

The aim of this prospective study was to evaluate the usefulness of both laboratory evaluation and new biomarkers to provide a deeper insight into prognostic factors in patients with HF. To test this hypothesis, we selected several biomarkers reflecting diverse biological pathways observed in HF.

PATIENTS AND METHODS

The study included 179 subsequent subjects with systolic HF who were admitted to the Department of Heart Failure and Transplantology of the Institute of Cardiology between June 2011 and December 2012. Similarly to other studies, we did not differentiate between stable and decompensated HF.[2,6-8] The study protocol was approved by the Bioethics Committee of the Institute of Cardiology, and each participant gave informed consent to participate in the study. The inclusion criterion was systolic dysfunction based on an echocardiographic evaluation in the previous 2 years (ejection fraction [EF] <45% and symptoms of HF). Subjects who were unable to give their consent or suffered from any other conditions or diseases that might have influenced their survival were excluded from the study. All the included patients were referred to the department owing to decompensation of HF or for elective evaluation. They underwent standard treatment and diagnostic procedures according to their managing physicians. Detailed clinical information was obtained at the time of enrollment. All blood samples were collected within the first 48 hours from the initial day of hospitalization between 7 AM and 9 AM and delivered immediately to a laboratory for further processing. Routine laboratory evaluation, as recommended by the European Society of Cardiology (ESC) guidelines on HF,[9] was conducted on the daily basis, and the rest of the samples after centrifugation were stored at –80°C until the assay. All biomarkers and biochemical parameters were analyzed using the same blood samples.

Similarly to other studies,[10] we considered either all-cause mortality or heart transplantation as primary endpoint. Secondary composite endpoint included death, heart transplantation, justified antiarrhythmic cardioverter-defibrillator intervention, or hospitalization for HF. Events during the follow-up were verified during control visits or, if the patient did not show up, through a phone call. In the case of missing data, the survival status was confirmed via the National Statistical Office.

Biomarker testing and routine laboratory tests

Serum insulin like growth factor 1 (IGF-1) was assayed using a radioimmunoassay (IGF1-RIACT; Cisbio Bioassays, Codolet, France). The detection limit was set at 1 ng/ml. Intra- and interassay coefficients of variation (CVs) were 3.8% and 8.2%, respectively. To determine serum intact amino-terminal propeptide of type III (PIIINP) procollagen, the UniQ PIIINP RIA kit was used (Orion Diagnostica Oy, Espoo, Finland). The limit of detection of the assay was about 0.3 μg/l. Intra- and interassay CVs were 7.0% and 7.2%, respectively. Serum neutrophil gelatinase-associated lipocain (NGAL) was determined with sandwich NGAL enzyme-linked immunosorbent assay (ELISA) kit (BioPorto Diagnostics A/S, Gentofte, Denmark). Quantitative estimation of human active matrix metalloproteinase 9 concentrations in serum samples was performed using a highly specific Quantikine ELISA (R&D Systems, Minneapolis, Minnesota, United States). The limit of quantitation of the assay was about 0.16 ng/ml. Intra- and interassay CVs were 2.9% and 7.8%, respectively. Human soluble ST2 was determined using a specific Quantikine ELISA. The limit of detection of the assay was 5.1 pg/ml. Intra- and interassay CVs were 5.6% and 7.1%, respectively. To assess myeloperoxidase (MPO) levels, the ARCHITECT MPO assay was used (Diagnostics, Abbott Park, Illinois, United States). It is an automated chemiluminescent microparticle immunoassay using the Chemiflex technology. Growth hormone was assessed using IMMULITE 2000 Growth Hormone, a solid-phase, 2-site chemiluminescent immunometric assay. Troponin I was measured with a microparticle electrochemiluminescence immunoassay using the Architect system (Abbott Laboratories, Abbott Park, Illinois, United States), with a limit of detection of 0.01 ng/ml. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was determined with an electrochemistry assay using a Cobas 6000 instrument (Roche Diagnostics, Mannheim, Germany). High-sensitivity C-reactive protein (hsCRP) was analyzed with an immunoturbidimetric assay using the Cobas 6000 instrument. Functional sensitivity of the assay was about 0.03 mg/dl and the limit of detection was 0.015 mg/dl. Serum creatinine was determined with an enzymatic assay with Cobas 6000. Creatinine clearance was calculated using the Cockcroft–Gault formula. All other biochemical parameters (cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, uric acid, alanine transaminase, and bilirubin) were analyzed with Cobas 6000, using enzymatic or colorimetric methods. The parameters of the complete blood count were evaluated by Sysmex 4500 using fluorescent flow cytometry and hydrodynamic focusing.

TABLE 1 Baseline characteristics of the study group

Variables	Values
age, y	52.6 ±11.4
men	90.5
body mass index, kg/m^2	27.8 ±4.3
heart rate, bpm	73.7 ±12.4
systolic blood pressure, mmHg	107.6 ±13.5
diastolic blood pressure, mmHg	67.2 ±11.3
left ventricular ejection fraction	23.8 ±9.2
left ventricular end-diastolic diameter, mm	74.9 ±10.4
left ventricular end-systolic diameter, mm	66.4 ±11.4
NYHA class I/II/III/IV	6.2/35.8/46.8/11.2
ischemic etiology of heart failure	49.7
history of heart failure, y	7.5 ±7.1
implantable cardioverter-defibrillator	57.5
cardiac resynchronization therapy	18.9
comorbidities, % of patients reporting this condition	
atrial fibrillation (paroxysmal or permanent)	54.7
ischemic heart disease	51.4
hypertension	40.8
thyroid abnormalities	20.7
renal dysfunction	18.9
liver dysfunction or cholelithiasis	16.8
peptic ulcer disease	16.2
diabetes mellitus	15.6
chronic obstructive pulmonary disease	11.2
peripheral vascular disease	10.1
cerebrovascular disease	9.5
gout	8.3
urolithiasis	6.7
average number of comorbidities, n	3.3 ±2.4
medication use, % of patients taking medication	
ACEI/ATII blockers	82.6/9.2
β-blockers	96.7
aldosterone antagonists	84.9
digoxin	64.6
diuretics	91.6
statins	51.4
anticoagulation	51.4
aspirin	39.1
IV catecholamines during hospitalization	13.9
IV diuretics during hospitalization	16.2

Data are presented as means ± standard deviation or percentage of patients.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ATII, angiotensin II receptor blockers; NYHA, New York Heart Association

Statistical analysis Baseline characteristics of the study group were presented as a percentage for dichotomous variables or means and standard deviations for continuous variables. Medians and interquartile ranges were used for biomarkers and laboratory test results. Logistic regression was used to evaluate significant predictors of survival plus transplantation or composite endpoint. Stepwise mixed analysis was based on the variables that showed an association with the endpoint at a *P* level of less than 0.05. The limits for entering and staying in the model were set at a *P* level of less than 0.05 for stepwise analysis. Data from the stepwise mixed analysis were used to develop the final model. All tests were 2-sided and a *P* value of less than 0.05 was considered significant.

RESULTS The study included 179 subjects. During a 6-month follow-up, 21 primary endpoints (11 deaths and 10 transplantations) and 63 secondary endpoints were recorded. The baseline characteristics of the study group are presented in TABLE 1. The mean age on enrollment was 52.5 ±11.4 years, and men constituted the majority of the population. Most participants reported various comorbidities, with coronary artery disease, atrial fibrillation (paroxysmal or permanent), and hypertension being the most prevalent. Moreover, renal failure and thyroid abnormalities were recorded in nearly one-fifth of the patients, while pulmonary diseases, peripheral vascular or cerebrovascular diseases, and joint problems were less common. The mean number of comorbidities exceeded 3. Most of the patients were in a more advanced New York Hear Association (NYHA) class, and NYHA class III was the most prevalent. Because the mean duration of HF exceeded 7 years, it can be assumed that most patients had a long history of HF. In nearly 50% of the cases, ischemic etiology of HF was recorded. The baseline results of basic laboratory tests and biomarkers are presented in TABLE 2. Of blood count parameters, red blood cell distribution width (RDW) was high, while hemoglobin levels, leukocyte count, and neutrophil percentage were within the reference range. Renal function, based on the average estimated glomerular filtration rate (eGFR), was normal in the majority of patients. Sodium levels were normal but uric acid was elevated. Liver function tests revealed slightly increased bilirubin levels and normal alanine transaminase levels.

The assessment of biomarkers showed that almost all of the biomarkers in the majority of the patients were within the reference range. Only the median levels of NT-proBNP were almost 20-fold higher than the normal level. On the other hand, hsCRP levels w not increased in most patients.

A logistic regression analysis showed that only a few variables were significantly correlated with primary or secondary endpoints. Both endpoints were significantly associated with well-established biomarkers such as NT-proBNP and ST2. However, none of the remaining biomarkers showed a significant correlation with the outcome. The only exception was NGAL, which predicted the secondary endpoint. Of the biochemical markers, those associated with renal, liver, and, to some extent, hematological abnormalities were predictive of future events. Nevertheless, on the basis of the stepwise analysis, all of the biomarkers were excluded from the multiple logistic regression model. For both endpoints, the markers

TABLE 2 Routine laboratory tests and biomarkers at baseline

Features	Values[a]
RDW, %	14.8 (13.7–15.9)
hemoglobin, G/dl	14.6 (13.5–15.5)
hematocrit, l/l	0.44 (0.41–0.47)
leukocytes, G/l	7 (5.9–8.3)
neutrophils, %	61.6 (35.5–68.7)
eGFR, ml/min/1.73 m^2	69.2 (55.5–83.0)
LDL cholesterol, mmol/l	2.54 (1.98–3.62)
total cholesterol, mmol/l	4.3 (3.5–5.3)
HDL cholesterol, mmol/l	1.1 (0.9–1.3)
troponin I, ng/ml	0.013 (0.004–0.031)
uric acid, μmol/l	445 (374–520)
sodium, mmol/l	141 (138–143)
ALT, U/l	24 (18–36)
bilirubin, μmol/l	18.3 (11.4–25.1)
NT-proBNP, pg/ml	2116 (947–3971)
soluble ST2, ng/ml	17.45 (12.1–28.5)
metalloproteinase 9, ng/ml	558 (410–764)
high-sensitivity CRP, mg/dl	0.3 (0.1–0.7)
procollagen III, µg/l	6.0 (4.2–7.8)
IGF-1, ng/ml	135 (108–179)
GH, ng/ml	0.35 (0.11–1.06)
NGAL, ng/ml	162 (114–210)
mieloperoxidase, pmol/l	1258 (836–1830)

Data are presented as median and interquartile range.

a each of the biochemical parameter and biomarker available in at least 80% and 91% of the subjects, respectively

Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GH, growth hormone; HDL, high--density lipoprotein; IGF-1, insulin growth factor 1; LDL, low-density lipoprotein; NGAL, neutrophil gelatinase-associated lipocain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RDW, red blood cell distribution width

of water–electrolyte imbalance and renal abnormalities remained significant predictors of future outcomes in the context of a wide biochemical evaluation. For sodium and eGFR, a negative association was documented, while uric acid was a positive predictor of future events. Based on the receiver-operating characteristic curve analysis, the area under the curve was 0.78 for primary endpoint and 0.64 for secondary endpoint, indicating a significant ability to assess patients' risk (TABLES 3 and 4).

DISCUSSION The available risk scores for predicting prognosis in patients with HF are primarily based on clinical or hemodynamic parameters. In recent years, novel biomarkers have been included in the evaluation of HF patients with the aim to improve clinical assessment and better visualize disease progression. However, our results showed that the selected novel biomarkers did not provide any additional prognostic information to that obtained using established biochemical markers of end-organ damage or metabolic disturbances.

Predicting the disease course and the risk of future adverse events is a pivotal task in clinical medicine.[2] The scores should be simple and easily accessible for clinical practitioners.[11] Multiple attempts have been undertaken to improve risk prediction by adding multiple biomarker panels to clinical risk scores for community-based cohorts, yielding conflicting results.[12-14] Once cardiovascular disease such as HF is established, the strategy to predict prognosis is not so well defined. Nevertheless, it is crucial for planning clinical management and patient care.

One of the first concepts incorporating novel biomarkers has been proposed by Braunwald et al.[4] In a recent review by Kalogeropoulos et al.,[15] the authors stated that the main question in biomarker strategy is whether the addition of a tested marker modifies patients' risk profile in a clinically significant way. In the majority of standard models, there is a considerable variability in clinical adjustment. It ranges from an elementary set of known risk factors (eg, age, sex, NYHA class, or some of the diagnostic test results)[2,16] to a comprehensive set of variables or established models (the Seattle Heart Failure Score or the Heart Failure Survival Score).[3] The prognostic utility of 1 or more HF biomarkers has been analyzed in a number of previous studies. Numerous

TABLE 3 Predictors of death or heart transplantation in univariate or multivariate logistic regression analysis

	Single logistic regression[a]			Stepwise mixed analysis[b]	Multiple logistic regression[c]		
	OR	95% CI	*P* value	*P* value	OR	95% CI	*P* value
RDW	1.361	1.117–1.657	0.002	0.1	–	–	–
% of neutrophils	1.064	1.010–1.120	0.02	0.7	–	–	–
bilirubin	1.057	1.019–1.097	0.003	0.3	–	–	–
soluble ST2	1.019	1.006–1.033	0.005	0.2	–	–	–
uric acid	1.006	1.002–1.009	0.001	0.0002	1.006	1.002–1.009	0.002
NT-proBNP	1.000	1.000–1.000	0.01	0.4	–	–	–
eGFR	0.963	0.936–0.990	0.008	0.07	–	–	–
sodium	0.811	0.71–0.91	0.0009	0.04	0.79	0.68–0.89	0.0003
HDL cholesterol	0.144	0.031–0.671	0.01	0.3	–	–	–

a only significant variables are presented
b only variables with a *P* value of less than 0.05 in the stepwise analysis were used in the final multiple regression model
c area under the curve = 0.78

Abbreviations: CI, confidence interval; OR, odds ratio; others, see **TABLE 2**

scores presented a positive association with a predefined outcome,[16-18] but still their clinical value remains a matter of debate.[2,19,20] In studies evaluating the risk reclassification with regard to biomarker use in patients with HF, the advantage of redefining the risk was established.[21-24] However, it must be stressed that the studies did not include a wide range of biochemical tests, which are easily available for practitioners. The same is true for most of the other studies evaluating biomarkers that ignored a more in-depth evaluation regarding renal or liver function, metabolic abnormalities, or hematological changes.[12,16,25] In a critical review, the authors raised concerns with regard to inconsistency in developing prognostic models, with some of the studies using stepwise analysis with data at hand, while others adopting literature-based information.[15] Another aspect is population heterogeneity with different stages of HF and also the diversity of prespecified outcomes used.[15]

Although natriuretic peptides and some other biomarkers, such as CRP and troponin, are available for most practitioners, still a wide range of biomarkers are used only by well-equipped centers. Therefore, even if prognostic significance of these biomarkers was confirmed and even though they would improve our understanding of HF pathology, they would not be useful in everyday care of HF patients. Another important issue is the high cost of biomarkers.

According to the ESC and American guidelines, a precise laboratory evaluation including biochemical tests and complete blood count remains the gold standard in HF patients. Out of an extensive range of tested biomarkers, natriuretic peptides are widely accepted, while other parameters are considered as potentially useful.[3,26]

Our population was homogenous with regard to the definition of systolic heart failure proposed by the guidelines on HF.[26] The age of our population, although younger than expected, was similar to that reported by other investigators.[2,16] The etiology of HF was balanced between ischemic versus nonischemic. In our study, most of the well-known prognostic factors were associated with survival or composite endpoint, in accordance with previous reports.[6,21,23,27-31]

The novel biomarkers of different pathological pathways, which we subjectively selected for analysis, did not show any significant association with prognosis, with the exception of NT-proBNP and ST-2, which have a well-established role in predicting risk in HF population.[21,25,32,33] Hence, they lost their significance in favor of the standard tests when adjusted for other routine laboratory variables. It is hard to explain this, particularly considering the available evidence showing the benefit of novel biomarkers. However, when analyzing the data on biomarkers, the biological variability should be considered. This issue was addressed by Wu et al.,[34] who reported a surprisingly high reference change value within a day. For natriuretic peptides, the range was between –28% and 39%, simultaneously with week-to week variability from –66% to 198%. ST2 seemed more stable, with week-to-week variance from –26% to 34%, though still presenting potentially confounding strength.[34] It cannot be excluded that changes in those cardiovascular biomarkers may be secondary to multiorgan damage, the assessment of which was very limited in the majority of biomarker studies.

RDW has recently emerged as a potentially useful prognostic marker. High RDW is a typical finding in the setting of impaired red blood cell production or elevated red cell damage.[35] Activation of proinflammatory cytokines in HF might inhibit erythropoietin-induced red cell maturation and thus produce an increased variability, indicated by higher RDW. Thus RDW might be the marker of an increased inflammatory response in HF.[35,36] The effect of RDW on prognosis is not clear; however, it is hypothesized that it reflects a combination of inflammation and iron metabolism.[36] RDW is regarded by some authors as a more powerful

TABLE 4 Predictors of death or heart transplantation or implantable-cardioverter defibrillation or hospitalization for heart failure in univariate and multivariate logistic regression analyses

	Single logistic regression[a]			Stepwise mixed analysis[b]	Multiple logistic regression[c]		
	OR	95% CI	*P* value	*P* value	OR	95% CI	*P* value
RDW	1.238	1.049–1.461	0.01	0.13	–	–	
soluble ST2	1.013	1.000–1.026	0.04	0.27	–	–	
NGAL	1.006	1.001–1.011	0.02	0.49	–	–	
NT-proBNP	1.000	1.000–1.000	0.04	0.55	–	–	
eGFR	0.970	0.952–0.989	0.002	0.001	0.98	0.95–0.99	0.02
sodium	0.86	0.78–0.93	0.0003	0.22	–	–	
total cholesterol	0.732	0.551–0.972	0.03	0.12	–	–	
LDL cholesterol	0.673	0.472–0.961	0.03	0.17	–	–	

a only significant variables are presented
b only variables with a *P* value of less than 0.05 in the stepwise analysis were used in the final multiple regression model
c area under the curve = 0.64

Abbreviations: see **TABLES 2** and **3**

predictor than hemoglobin,[37] which was also the case in our study. Considering low cost and wide availability, RDW should be measured in all subjects with HF.

Renal dysfunction is one of the most commonly reported comorbidities in HF, also in Polish population.[38,39] It is considered to play a crucial role in the pathophysiology of heart dysfunction.[40] The interaction between kidney and heart diseases is bidirectional and is known as cardiorenal syndrome. It may be stated that renal insufficiency in HF reflects reduced tissue perfusion. Impaired survival in patients with either baseline reduction of eGFR or progressive worsening of renal function in HF has been reported in the last 2 decades, and the SOLVD trial[41] was one of the first clinical studies confirming the significance of this interaction. Nevertheless, in a recent publication, Loffler et al.[42] observed that in properly treated chronic HF, worsening renal function in itself may not reflect poor prognosis. Still the baseline eGFR was a strong negative predictor of prognosis in this population. The magnitude of prognostic effect of reduced eGFR is well illustrated by a systematic review showing a much higher risk of mortality in patients with moderate or severe reduction in eGFR, with a hazard ratio of 2.3 for the severe reduction.[43] In a recent large meta-analysis based on 85 studies, Damman et al.[40] investigated the significance of renal dysfunction at baseline or worsening renal function in HF. They reported that severe renal impairment and worsening renal failure resulted in 117% and 95% higher risk of death, respectively. Despite the fact that the prognostic and pathophysiological role of renal insufficiency is well documented, its significance remains underappreciated.[35] Our results confirm the complex interplay between the cardiovascular system and other system organs. Modification of Diet in Renal Disease and other equations used in the previous studies on renal function[35] are easy to apply in clinical practice. Therefore, the assessment of renal function using the eGFR should never be neglected in everyday practice.

NGAL is a newer renal biomarker, highly upregulated in the early stage of renal injury. In our study, it lost its significance after adjustment for other parameters such as eGFR. It might have been too late to detect early renal injury, given that a relatively high percentage of our patients had advanced HF.

Sodium is another well-established marker potentially reflecting neurohormonal activation, particularly of the renin–angiotensin–system, upregulation of the sympathetic system, and increased vasopressin levels. The neurohormonal activation reduces both sodium and water excretion by limiting distal water delivery caused by lowering GFR and by increasing proximal sodium and water reabsorption resulting in water–electrolyte imbalance and expanding ventricular load. Also, it cannot be excluded that hyponatremia is simply a marker of high vasopressin levels and in fact just an epiphenomenon of a greater degree of HF severity.[44] Higher sodium excretion related to a more intensive use of diuretics in advanced HF leading to electrolyte disturbances should be also recognized. The usefulness of hyponatremia as an unfavorable prognostic marker has been confirmed in numerous studies and registries.[6,29,45] In a recent study, hyponatremia was significantly associated both with all-cause death and cardiovascular death and with rehospitalization. The effect was observed in the short term and increased risk persisted in the long term.[44] Thus, our data showing sodium levels as the strongest predictor of prognosis are in accordance with previous reports. As this test is commonly available, it should be given the priority in HF patients. Despite the fact that it is associated with poor prognosis, it has not been confirmed that correction of sodium levels improves survival.

The assessment of liver function in HF patients is another important issue. In fact, these tests are often ignored. In the CHARM trial,[46] elevated bilirubin was a strong predictor of adverse outcome.

However, the exact mechanism of the liver–heart interaction has to be investigated in future studies.[47] As the cardiorenal interaction plays a significant role in HF, renal impairment obscures the role of liver dysfunction.

The negative effect of low lipid levels in HF, known as reversed epidemiology, was noticed previously.[7] It was suggested that it might reflect a protective role by modifying inflammatory markers in HF.[48] On the other hand, low LDL cholesterol might be a marker of disease severity, as advanced HF is characterized by increased metabolic demand and energy consumption.[7]

An interesting observation is that the fraction of leukocytes provides additional prognostic information. In fact, it was already demonstrated that low lymphocyte count was predictive of all-cause mortality or heart transplantation,[49] later confirmed in the population from the EVEREST trial.[30] The mechanism is not entirely clear, but this may be due to splanchnic congestion causing enteric loss of lymphocytes. The activation of cytokines responsible for reduction of lymphocytes indirectly, presumably by apoptotic mechanisms, has been also suggested.[30]

Although we did not confirm the role of MPO, regarded as a marker of oxidative stress,[4] we demonstrated an independent prognostic value of uric acid, indirectly suggesting this pathological process. Despite the fact that hyperuricemia is associated with reduced cardiac output and diuretic use due to impaired excretion, it is recognized to reflect more than simply the hemodynamic status.[8,27,50] Higher uric acid levels are a marker of enhanced xanthine oxidase activity in HF,[27,50,51] which is an important source of oxygen free radicals.[50] Uric acid is already an established prognostic factor in HF.[27,50] However, it is unclear whether uric acid is an active player or bystander in the pathophysiology of HF.[51] Thus, our study, which showed a predominance of uric acid over novel biomarkers, along with the markers of kidney function, confirms previous observations.

Study limitations Our study has several limitations. A relatively small group of patients and the lack of a reference group should be acknowledged. Despite the fact that all of the subjects had their blood sample taken, we were not able to obtain full profiles of the routine laboratory and biomarker tests for each individual participant. Nevertheless, we are confident about our results. Similar problems were also reported by other researchers. As our study population was recruited from subsequent patients admitted to our department, some of them were unstable and required inotropic support, while the remaining patients were relatively stable. On the other hand, it provided an opportunity to evaluate patients presenting with mild-to-severe HF. The selection of biomarkers that cannot fully reflect the pathological pathways in HF is another limitation.

Conclusions It has been demonstrated that from the prognostic point of view, the most important task is careful and extensive laboratory evaluation of every patient with HF. Based on our results, biomarkers provided valuable prognostic data but did not outweigh laboratory tests. However, the selection of biomarkers for evaluation might have affected the results. Nevertheless, a well-planned diagnostic evaluation, available in almost every laboratory, must remain the most important stage of everyday practice and should not be replaced by novel, more sophisticated methods. Data obtained from standard laboratory tests revealing multiorgan involvement provide the most valuable prognostic information for HF patients.

Contribution statement TR and JK conceived the idea for the study and contributed to the design of the research. TR, JJ, AK, PL, MS-M, and GJ-W were responsible for data collection.TR, AK, PL, PR, and TZ performed analysis and interpretation of the data. TR obtained funding and supervised the study. The statistical analysis was performed by PK. AK, PL, PR, JK, MS-M, PK, and TZ were involved in the critical revision of the manuscript for important intellectual content. All authors edited and approved the final version of the manuscript.

Acknowledgments The study was supported by intramural research funding from the Institute of Cardiology (grant No. 2.31/VII/II; to TR).

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ARTYKUŁ ORYGINALNY

Znaczenie prognostyczne nowych biomarkerów w porównaniu ze szczegółową oceną biochemiczną pacjentów z niewydolnością serca

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SŁOWA KLUCZOWE

biomarkery, niewydolność serca, oznaczenia biochemiczne, rokowanie

STRESZCZENIE

WPROWADZENIE Ocena prognostyczna chorych z niewydolnością serca (NS) ma zasadnicze znaczenie w planowaniu dalszego postępowania terapeutycznego.

CELE Celem prezentowanej pracy była ocena przydatności nowych biomarkerów w ocenie rokowania pacjentów z NS w porównaniu ze szczegółową oceną na podstawie badań laboratoryjnych.

PACJENCI I METODY Badaniem objęto grupę 179 pacjentów z NS. U wszystkich pacjentów wykonywano rutynowe badania laboratoryjne, a także przeprowadzono oznaczenia wybranych biomarkerów (N-końcowy peptyd natriuretyczny typu B, wysokiej czułości białko C-reaktywne, hormon wzrostu, mieloperoksydaza, metaloproteinaza 9, prokolagen typu III, rozpuszczalna forma ST2, insulinopodobny czynnik wzrostu 1 i lipokalina związana z żelatynazą neutrofili). Głównym punktem końcowym był zgon lub transplantacja serca w trybie pilnym, natomiast wtórne punkty końcowe obejmowały wszystkie zdarzenia głównych punktów końcowych oraz interwencję kardiowertera albo hospitalizację z powodu NS.

WYNIKI Średni wiek badanej populacji wynosił 52,5 lat (91% stanowili mężczyźni). Większość chorych była w zaawansowanych stadiach NS. W trakcie 6 miesięcy obserwacji zarejestrowano 21 głównych oraz 63 wtórnych punktów końcowych. Na podstawie analizy wielu zmiennych stwierdzono, że spośród wszystkich danych laboratoryjnych oraz biomarkerów jedynie kwas moczowy i sód były niezależnymi czynnikami rokowniczymi wystąpienia głównych punktów końcowych oraz jedynie szacunkowy współczynnik filtracji kłębuszkowej miał istotną wartość predykcyjną dla wtórnych punktów końcowych. Żaden z biomarkerów nie był istotnym czynnikiem prognostycznym w badanej populacji.

WNIOSKI Biomarkery nie przewyższają wartości prognostycznej standardowych oznaczeń laboratoryjnych. Rutynowa diagnostyka laboratoryjna umożliwia ocenę uszkodzenia wielonarządowego, dostarczając jednocześnie najistotniejszych danych dotyczących rokowania. Ocena biochemiczna powinna pozostać złotym standardem w ocenie rokowania pacjentów z NS.

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Praca wpłynęła: 24.02.2015.
Przyjęta do druku: 22.05.2015.
Publikacja *online*: 28.05.2015.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2015; 125 (6): 434-442