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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Prognostic factors in heart failure — are they all equally important?

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INTRODUCTION. WHY DO WE NEED PROGNOSTIC FACTORS IN HEART FAILURE?

The prevalence of heart failure (HF) is constantly growing, posing major clinical, social, and economic challenges. Not only does HF lead to a premature death, but it also results, through diminished functional capacity, frequent disease exacerbations, and repeated hospitalisations, in worse quality of life, loss of work productivity, and substantial direct and indirect costs to the public healthcare system [1].

Despite significant advancements in both pharmacological and interventional treatment of HF, including cardiac implantable electronic devices, mechanical circulatory support, percutaneous procedures for severe valvular disease, as well as the introduction of new inotropic, rate-limiting, and vasodilative agents, prognosis in overt HF remains poor [1]. Moreover, after a period of decline in the rates of HF mortality, crude death rates from HF in Poland seem to be rising [2]. Thus, recognition of predictors of an unfavourable outcome in HF is crucial for two major reasons. First, in clinical practice, alertness for the presence of such predictors allows early identification of patients at the highest risk of events, followed by intensified monitoring and implementation of adequate, individualised preventive and therapeutic measures (including, in the most advanced cases, selection of candidates for mechanical circulatory support or heart transplantation [HTx]). Secondly, knowledge of prognostic factors specific for HF adds to our understanding of the pathophysiological background of this complex clinical entity, enhancing the possibility for the development of new, targeted therapies.

WHAT MAKES A "GOOD" PROGNOSTIC FACTOR?

Dynamic research in the field of HF has led to identification of a vast number of demographic, clinical, and laboratory (e.g. biochemical, echocardiographic, genetic) prognostic factors. However, while some of them are of undeniable significance, either due to their imminent clinical consequences and clear therapeutic implications (e.g. signs of volume overload and/or peripheral hypoperfusion, low left ventricular ejection fraction [LVEF], occurrence of ventricular tachycardia) or proven diagnostic and prognostic value (e.g. B-type natriuretic peptide [BNP], N-terminal pro-BNP [NT-proBNP]), others might not be such powerful predictors of clinical outcomes, carrying relatively little additional information (e.g. biomarkers of subclinical inflammation) or might not be as useful due to their low accessibility in the clinical setting (e.g. most biomarkers of neurohormonal activation other than BNP/NT-proBNP) [3]. From a clinician's perspective, in order to be practically relevant, a predictor should not only identify high-risk individuals, but should also be easily obtainable in most patients (e.g. physical examination, electrocardiogram, basic laboratory parameters) and associated with some therapeutic implications, i.e. either 1) enable risk stratification and qualification of patients to evidence-based therapies (e.g. low LVEF as an indication for cardioverter-defibrillator implantation for primary prevention of sudden cardiac death, LVEF and QRS duration used for qualification for cardiac resynchronisation), 2) guide the type and intensity of pharmacotherapy (e.g. clinical symptoms and signs of volume overload, echocardiographic indices of high left ventricular [LV] filling pressures and/or elevated estimated pulmonary pressure, BNP-guided therapy), or 3) constitute a modifiable risk factor that might be subjected to specific treatment.

RISK STRATIFICATION IN HEART FAILURE

The 2016 European Society of Cardiology (ESC) guidelines on HF name over 70 predictors of unfavourable outcome in HF patients [3]. A modified list of prognostic factors in HF is presented in Table 1. Understandably, the abundance of those variables: 1) derives from complex pathophysiological pathways of HF development as well as from the fact that advanced HF affects function of other critical organs, and 2) denotes the need for more comprehensive means of assessment of prognosis in these patients because no single parameter is sufficient on its own. Thus, different risk scores, encompassing various numbers of predictive variables, have been proposed for risk stratification in HF [4–22]. A recent meta-analysis reported as many as 117 models, using 249 different variables [20]. Separate scales were derived for prognostic evaluation in acute and chronic HF (Table 2 and Table 3, respectively). Different risk models were designed to assess different clinical endpoints, for example for patients with acute HF some models were developed for the estimation of in-hospital mortality (Table 2), some for the estimation of post-discharge mortality (e.g. EFFECT model [8], OPTIME-CHF model [9], ESCAPE risk score [10], ADHF/NT-proBNP risk score [11]), and some for the estimation of a composite endpoint including death, worsening HF, and HF rehospitalisation (e.g. PROTECT risk model [12]). Some of the risk scores were derived from large (e.g. ADHERE [4], AHFI [5], OPTIMIZE-HF [6], GWTG-HF [7], MAGGIC [15]) and some from relatively small (e.g. ESCAPE [10], Frankenstein et al. [16]) HF populations. Some, including three models most commonly used in chronic HF (Heart Failure Survival Score, HFSS [13], Seattle Heart Failure Model, SHFM [14], and MAGGIC HF Risk Calculator [15]), were validated in independent cohorts of HF patients [22–25]. Some of the models are in the form of point scoring systems (e.g. GWTG-HF [7], EFFECT [8], ESCAPE [10]), while others are in the form of simple (ADHERE [4]) or complicated (AHFI [5]) risk trees. A few are available as interactive online calculators (e.g. SHFM [14], MAGGIC HF Risk Calculator [15], GWTG-HF Risk Score [7]).

So far, in validation cohorts, most models have shown only modest to moderate accuracy (with C statistic ranging from approximately 0.6 to 0.8) in predicting mortality in HF [22–26]. Furthermore, although their performance seems

Table 1. Markers of unfavourable outcome in heart failure (according to [3], modified)

Demographic data	Older age, male sex, low socio-economic status
Medical history	Ischaemic aetiology, longer HF duration, previous HF hospitalisation, adequate and inadequate high-energy ICD interventions, non-compliance to evidence-based HF therapies (β-blockers, RAAS inhibitors)
Clinical status	Advanced NYHA class, high resting heart rate, low SBP, clinical signs of volume overload (e.g. pulmonary congestion, peripheral oedema, jugular vein dilatation, hepatomegaly) and of peripheral hypoperfusion, Cheyne-Stoke ventilation, lower BMI, frailty
Electrocardiogram	Wide QRS complex, ventricular arrhythmia, atrial fibrillation
Cardiac imaging, including echocardiography	LV systolic dysfunction (low LVEF, reduced GLS), LV dilatation, LV hypertrophy, severe LV diastolic dysfunction, pseudonormal/restrictive LV filling pattern, left atrial dilatation, pulmonary hypertension, right ventricle dilatation and dysfunction, dyssynchrony, severe valvular disease, large territory of non-viable myocardium or of inducible ischaemia in imaging stress testing, late gadolinium enhancement in CMR
Exercise testing	Short 6-minute walk test distance, reduced VO_2peak and high VE/VCO_2slope in cardiopulmonary exercise test
Biomarkers (obtainable in clinical practice)	High natriuretic peptides, elevated cardiac troponins, low sodium, low haemoglobin, low ferritin, high uric acid, markers of end-organ dysfunction (creatinine/eGFR, urea/BUN, liver enzymes), inflammatory markers (hsCRP, WBC, NLR)
Other biomarkers (derived from pre-clinical and clinical studies; both established and emerging)	Of neurohormonal activation (plasma renin activity, aldosterone, catecholamines, vasopressin, copeptin, adrenomedullin) Of cardiac damage/fibrosis/remodelling (galectin-3, ST2, syndecan-1, TIMPs, PIIINP, homocysteine) Of endothelial dysfunction (endothelin-1, endothelial apoptotic microparticles) Of subclinical inflammation/oxidative stress (IL-6, TNF-α, osteoprotegerin, annexin) Metabolic markers (adiponectin, resistin) Other (cystatin C, urinary kidney injury molecule-1, GDF 15, surfactant protein B, microRNAs)
Genetic testing	Lamin A/C — LMNA mutations (especially non-missense mutations), phospholamban (PLN) mutation
Non-cardiac co-morbidities	Previous stroke/TIA, peripheral artery disease, diabetes, anaemia, iron deficiency, COPD, sleep apnoea (both central and obstructive), kidney/liver dysfunction, depression

BMI — body mass index; BUN — blood urea nitrogen; CMR — cardiac magnetic resonance; COPD — chronic obstructive pulmonary disease; eGFR — estimated glomerular filtration rate; GDF 15 — growth/differentiation factor 15; GLS — global longitudinal strain; HF — heart failure; hsCRP — high-sensitivity C-reactive protein; ICD — implantable cardioverter-defibrillator; IL-6 — interleukin 6; LV — left ventricle; LVEF — left ventricular ejection fraction; NLR — neutrophil-to-lymphocyte ratio; NYHA — New York Heart Association; PIIINP — N-terminal propeptide of type III collagen; RAAS — renin-angiotensin-aldosterone system; RNA — ribonucleic acid; SBP — systolic blood pressure; TIA — transient ischaemic attack; TIMPs — tissue inhibitors of metalloproteinases; TNF-α — tumour necrosis factor alpha; VE/VCO_2 — minute ventilation/carbon dioxide production; VO_2peak — peak oxygen uptake; WBC — white blood cell count

acceptable at the population level, they do not reliably predict one-year outcome of an individual patient [26]. The discriminatory ability of the models for prediction of HF hospitalisation appears to be even lower than that for estimation of the risk of death [20, 21]. Finally, no evidence from randomised clinical trials exists to support the superiority of any of these models in qualification for HTx or any other specific therapy. Thus, none of them has been recommended for the selection of candidates for HTx or LV assist device by the current guidelines, although the 2013 American guidelines generally advise the use of validated multivariable risk scores (mainly SHFM for chronic HF, and ADHERE model for acute HF) to estimate prognosis in HF patients [3, 27].

VALUES OF DIFFERENT PROGNOSTIC FACTORS

As depicted in Tables 2 and 3, the presented risk scales differ significantly both in the number of variables included in each model (from two to over a dozen) and in the types of variables used, i.e. some use only basic clinical parameters and biomarkers, while others (some of the models developed for chronic HF) include more sophisticated parameters (e.g. from cardiopulmonary exercise testing) or data on pharmacotherapy. However, an analysis of predictive factors from Tables 2 and 3 allows for identification of variables included in the models more often than others: age, sex, heart rate (HR), systolic blood pressure (SBP), New York Heart Association (NYHA) class, LVEF, kidney function, and sodium

Table 2. Selected risk models for the assessment of in-hospital mortality in acute heart failure

	ADHERE [4]	AHFI [5]	OPTIMIZE-HF [6]	GWTG-HF [7]
Demographic variables		Sex	Age	Age Race
Co-morbidities		CAD/coronary angiography Diabetes Chronic lung disease		COPD
Clinical presentation	SBP	SBP Heart rate Respiratory rate Temperature ACS (ECG) Pulmonary congestion/pleural effusion (X-ray) Arterial pH	SBP Heart rate HF as a primary cause of hospitalisation	SBP Heart rate
Echocardiography			LVEF < 40%	
Biomarkers	BUN Creatinine	BUN Creatinine Sodium Potassium Glucose WBC	Creatinine Sodium	BUN Sodium

The four presented models were chosen because they were derived from the largest cohorts.
ADHERE — Acute Decompensated Heart Failure National Registry; AHFI — Acute Heart Failure Index; OPTIMIZE-HF — Organised Programme to Initiate Lifesaving Treatment in Hospitalised Patients with Heart Failure; GWTG-HF — Get with the Guidelines-Heart Failure; ACS — acute coronary syndrome; BUN — blood urea nitrogen; CAD — coronary artery disease; COPD — chronic obstructive pulmonary disease; ECG — electrocardiogram; LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; WBC — white blood cell count

concentration. Other strong predictors of death in HF, consistently reported across different models, include diabetes, BNP/NT-proBNP concentration, weight or body mass index, and exercise capacity [4–22].

Of all prognostic variables, LVEF and NYHA class belong to the most useful and powerful predictors of long-term HF outcomes. Notably, it is well recognised that correlation of those two parameters is not very strong, partly because: 1) stroke volume depends not only on LVEF but also on LV end-diastolic volume and LV loading conditions, 2) LV filling pressures are related not only to its systolic but also to its diastolic function, and 3) LVEF as a sole parameter does not fully reflect LV systolic function [3]. The association of LVEF with survival is not linear as it is most markedly expressed in patients with severely reduced LVEF; once elevated above 45% LVEF does not further contribute to the estimation of cardiovascular outcomes in HF [28].

Having identified predictors with the strongest relation to mortality in HF, it seems important to distinguish between factors which themselves influence HF outcomes (and may therefore constitute potential targets for future therapies) and variables which, albeit found to be associated with HF prognosis, are not causally related to the clinical course of HF, serving rather as surrogate markers. Biomarkers of the renin–angiotensin–aldosterone (RAA) system and sympathetic activation are an excellent example of the first group. Pharmacologic inhibition of these two neurohormonal systems is the cornerstone of HF treatment. Mild-to-moderate anaemia, on the other hand, seems more a representative of the second group than a direct cause of adverse events in HF, despite the fact that the association between anaemia and mortality in HF is well established [29–31]. In HF patients, anaemia is probably a marker of: 1) accumulation of factors which are themselves important predictors of unfavourable outcomes in HF (such as older age, malnutrition, frailty, and higher non-cardiac co-morbidity burden, including chronic kidney disease), both by their direct influence and due to our tendency to under-prescribe evidence-based HF therapies in such patients, 2) iron deficiency, which might itself aggravate skeletal and heart muscle dysfunction, and 3) more advanced HF stages because anaemia in severe HF might result from subclinical inflammation (anaemia of chronic disorders) as well as from haemodilution in patients with fluid retention [31, 32]. These assumptions are supported by the fact that iron supplementation (in both anaemic and non-anaemic HF patients), but not darbepoetin or erythropoietin treatment, has led to an improvement in functional capacity and a reduction in hospitalisations for symptom deterioration in HF [33–35].

Table 3. Selected risk models for the assessment of long-term prognosis in chronic heart failure

	Heart Failure Survival Score [13]	Seattle Heart Failure Model [14]	MAGGIC Heart Failure Risk Calculator [15]	Frankenstein et al. [16]	PACE risk score [17]***	SHOCKED predictors [18] ***
Demographic variables		Age Sex	Age Sex	(Different cutoffs depending on sex)	Age	Age
Medical history	Ischaemic aetiology	Ischaemic aetiology	HF duration			
Co-morbidities			Diabetes COPD Current smoking		Peripheral artery disease	AF Diabetes CKD COPD
Clinical status	Heart rate MAP	NYHA class SBP Weight	NYHA class SBP BMI			NYHA class
ECG	QRS > 0.12 s					
ECHO	LVEF	LVEF	LVEF		LVEF	LVEF
Exercise testing	VO_2peak*			6MWT		
Biomarkers	Sodium	Sodium Uric acid Cholesterol Haemoglobin Lymphocytes	Creatinine	NT-proBNP	Creatinine	
Therapy		Beta-blocker** ACE-I** ARB** Aldosterone antagonist** Diuretic dose Statin Allopurinol ICD/CRT**	Beta-blocker ACE-I/ARB	(Different cutoffs depending on beta--blocker usage)		

*In the model by Zugck et al. [19] VO_2 peak was replaced by 6MWT distance; additionally, a two-variable model containing only LVEF and VO_2peak or LVEF and 6MWT was shown to be superior
**Enables assessment of the impact of the index intervention on long-term survival
***In patients after ICD implantation
6MWT — 6-minute walk test; ACE-I — angiotensin-converting-enzyme inhibitor; AF — atrial fibrillation; ARB — angiotensin II receptor blockers; BMI — body mass index; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronisation therapy; ECG — electrocardiogram; ECHO — echocardiography; HF — heart failure; ICD — implantable cardioverter-defibrillator; LVEF — left ventricular ejection fraction; MAP — mean arterial pressure; NT-proBNP — N-terminal pro B-type natriuretic peptide; NYHA — New York Heart Association; SBP — systolic blood pressure; VO_2peak — peak oxygen uptake

Nevertheless, it is not always possible to unequivocally differentiate the two groups of predictors (independent causes vs. surrogate markers) from one another. Hyponatraemia was proven to be a major predictor of in-hospital and long-term mortality and morbidity, irrespective of age or LVEF, and across a diverse spectrum of HF patients (hospitalised and ambulatory; with reduced and with preserved LVEF) [5, 6, 13, 14, 20, 21, 36]. Undoubtedly, the presence of hyponatraemia in HF patients is related to disease severity, and is primarily triggered by reduced cardiac output leading to activation of the sympathetic and the RAA system, and — finally — to an increased secretion of vasopressin [36]. Diuretic treatment may further aggravate hyponatraemia in HF patients. However, whether hyponatraemia itself worsens the clinical course of HF or whether it merely reflects HF severity is unclear. The fact that hyponatraemia remains a strong prognosticator in multivariate analyses in different cohorts of HF patients might suggest its causative relationship with HF outcomes [5, 6, 13, 14, 20, 21, 37]. The observed association of low sodium concentration with hypotension seems bidirectional: hyponatraemia is, on one hand, an indirect result of reduced cardiac output (as described above), but, on the other hand, may itself further decrease SBP and facilitate fluid shift from the intravascular space to the interstitial compartment. This exacerbates fluid retention and end-organ hypoperfusion,

and aggravates kidney dysfunction in HF patients [36]. Nevertheless, therapy with tolvaptan, a vasopressin type 2 receptor antagonist, did not reduce long-term mortality or morbidity in patients hospitalised for HF [38].

PROGNOSTIC FACTORS IN DIFFERENT HEART FAILURE SUBPOPULATIONS

Heart failure is a complex clinical entity with different underlying aetiologies and a wide spectrum of clinical manifestations with regard to symptom severity (different NYHA functional classes), haemodynamic profile (presence/absence of congestion and/or peripheral hypoperfusion), and clinical presentation (acute vs. chronic HF, HF with reduced LVEF [HFrEF] vs. HF with preserved LVEF [HFpEF], right-ventricular HF, hypertensive HF). It may be anticipated that the magnitude of impact of each of the prognostic factors from Table 1 on survival in HF may vary depending on the clinical setting (e.g. hospitalised vs. ambulatory patients), HF aetiology (ischemic vs. non-ischaemic), HF type (HFrEF vs. HFpEF), and other patient characteristics (e.g. age, sex, race, concomitant diseases). For example, as presented in Tables 2 and 3, different predictors were proven to be significant for outcome assessment in acute and chronic HF. Variables such as HR and SBP have been included in most models for acute HF (but not in all models for chronic HF), while NYHA class and LVEF have been predominantly used in chronic HF models [4–22, 39]. On the other hand, age, sodium concentration and indices of kidney dysfunction have been strong, independent predictors both in acute and in chronic HF patients [4–22, 37, 40].

The second important HF classification is based on the value of LVEF. Recently, along with HFrEF and HFpEF, the 2016 ESC guidelines — similarly to the American document — have distinguished a third HF entity: HF with mid-range LVEF [3, 27]. Differences in patient characteristics and clinical course of HFrEF and HFpEF have long been acknowledged and well proven [3]. In terms of prognosis, patients with HFpEF are more frequently hospitalised due to non-cardiovascular causes compared to HFrEF patients, and all-cause mortality seems to be higher in HFrEF than in HFpEF, as demonstrated by a meta-analysis including randomised clinical trials — although contradictory results were brought by epidemiological studies and registries, suggesting similar prognosis in both HF subgroups [41–43]. Some prognostic factors in both HF subpopulations also differ; understandably, as mentioned above, LVEF is an important predictor of clinical outcomes in HFrEF but not in HFpEF [41–44]. Non-cardiac co-morbidities bear more prognostic significance in the context of HFpEF than HFrEF [3, 42]. Finally, no evidence-based HFrEF treatment has proven beneficial in HFpEF [41–43]. A separate score (I-PRESEVE Score) for risk stratification in HFpEF was developed [45].

Another HF population that seems distinct in terms of prognostic factors comprises patients with HF and concomitant atrial fibrillation (AF). Compared to HF patients in sinus rhythm, HF patients with AF were reported to have higher short- and long-term mortality, as well as higher rate of hospital readmissions [18, 46, 47]. Such unfavourable prognosis of HF patients with accompanying AF may result both from the fact that AF is a marker of older age and more advanced HF with higher left atrial pressures, and from further impairment of cardiac function by AF. As increased HR is associated with reduced survival in HF, it might be anticipated that the key mechanism leading to an excess of deaths in HF patients with concomitant AF is mainly due to increased ventricular rate, and that rate-limiting pharmacotherapy should improve the prognosis in those patients. However, hitherto studies have shown that in HF patients with concomitant AF: 1) ventricular rate of below 70 bpm is related to worse outcomes, and 2) treatment with beta-blockers has failed to reduce mortality and morbidity in patients with reduced LVEF [3, 48, 49]. There is no clear recommendation regarding either target HR or the use of beta-blockers in this population [3]. However, most recently, a potential benefit of beta-blocker treatment in HF patients with AF was implied [50].

CONCLUSIONS

Despite identification of many modern markers of adverse outcomes and development of sophisticated algorithms for the estimation of HF prognosis, clinical decision-making in HF (including indications to pharmacological treatment and cardiac implantable electronic devices) is still predominantly based on a few basic parameters, such as the presence of HF symptoms (NYHA class), LVEF, and QRS complex duration and morphology. Nevertheless, with our growing understanding of the course and pathophysiology of HF, new perspectives arise with a potential for a more precise evaluation of prognosis in an individual patient, followed by the selection of an individually tailored treatment.

Conflict of interest: *none declared*

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