

Comparison among different multiparametric scores for risk stratification in heart failure patients with reduced ejection fraction

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Abstract

Heart failure is a serious condition with high prevalence (about 2% in the adult population in developed countries, and more than 8% in patients older than 75 years). About 3–5% of hospital admissions are linked with heart failure incidents. The guidelines of the European Society of Cardiology for the diagnosis and treatment of acute and chronic heart failure have identified individual markers in patients with heart failure, including demographic data, aetiology, comorbidities, clinical, radiological, haemodynamic, echocardiographic and biochemical parameters. Several scoring systems have been proposed to identify adverse events, such as destabilizations, re-hospitalizations and mortality. This article reviews scoring systems for heart failure prognostication, with particular mention of those models with exercise tolerance objective definition. Although most of the models include readily available clinical information, quite a few of them comprise circulating levels of natriuretic peptides and a more objective evaluation of exercise tolerance. A literature review was also conducted to (a) identify heart failure risk-prediction models, (b) assess statistical approach, and (c) identify common variables.

Keywords

Risk prediction models, heart failure

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Few topics have received as much attention in medical literature over recent years as risk prediction in heart failure patients, especially in those with reduced ejection fraction (HFrEF). Estimation of prognosis in HFrEF is crucial,¹ for patients who are concerned about the probability of future events, for families who are worried about obligations, aspirations, fears, limitations, resources, and needs of relatives, and for physicians who like to decide the type and timing of additional tests or therapies with reliable and objective criteria.^{2,3}

A proper prognostic risk model for HFrEF

In theory, a multiparametric prognostic model should be as good as the variables from which it is derived. However, the relevance of individual prognostic

markers may vary according to the phase of the disease and the presence and value of accompanying variables – including non-cardiac comorbidities. Basic demographic and clinical variables such as age, gender, aetiology of disease and history of hospitalizations have a

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prognostic role. Their predictive value declines as heart failure becomes progressively more severe, and left ventricular ejection fraction (LVEF) also declines, although in several experiences female sex appears to be protective even in advanced stages of disease. In the general population, increased systolic blood pressure (SBP) and body mass index (BMI) are associated with worse outcomes;⁴ however, once HFrEF has developed, a reverse epidemiology is observed, and higher SBP and BMI are associated with lower risk.⁵ For example, a 10% reduction in mortality for each five-unit increase in BMI was seen in a large registry of acutely decompensated HFrEF.^{6,7} Impaired socioeconomic status has been shown to be a predictor of poor outcome,⁸ whereas the impact of race on mortality is controversial: some studies showed increased rates of hospitalization, while others exhibited a survival advantage in Black HFrEF patients.¹

Many univariate predictors, such as clinical features, New York Heart Association (NYHA) functional class, haemodynamic parameters, laboratory findings, several biomarkers, electrocardiographic and echocardiographic parameters, cardiac magnetic resonance imaging and coronary angiographic findings, have been shown to correlate with prognosis. Some findings at physical examination (e.g. third heart sound, increased jugular venous pressure) are associated with lower probability of survival, but their reproducibility is low since they are influenced by subjective appreciation.⁸ NYHA classification is also related to survival in HFrEF, but it depends also on subjective appreciation of symptoms by the patients. Several laboratory markers have revealed an independent association with prognosis.^{9–14} B-type natriuretic peptides (BNPs) have received most of the attention in recent years.^{14–16} The quartile of patients with the lowest N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in the placebo arm of the Valsartan Heart Failure Trial (Val-HeFT) had less than one-third the mortality (7.8%) of patients in the highest quartile (25.3%).¹⁷ NT-proBNP level at baseline and at discharge entered as independent markers of the risk of death in hospital and during follow-up, respectively, in a multicentre cohort of patients hospitalized for decompensated, advanced HFrEF.^{17–19} Many echocardiographic parameters of both right and left ventricular function show correlation with prognosis,^{20,21} of which LVEF is the most popular and probably the most relevant. Lower LVEF was associated with worse outcome in the CHARM programme: 1013 patients with an ejection fraction <23% had triple the all-cause mortality and quadruple the heart failure progression-related mortality of the 2795 patients with an ejection fraction >42%. When LVEF is severely reduced in all the

patients, indexes of right ventricular function may help in further risk stratification.^{22,23}

In HFrEF, oxygen consumption at peak exercise (peak VO_2) includes two relevant aspects related to impaired physiologic processes: cardiac output and the ability to extract oxygen from circulating blood. Peak VO_2 has been used for selection of heart transplant candidates for years.^{24,25} Excessive ventilatory response to exercise (measured as an elevated slope of ventilation per unit of carbon dioxide production (VE/ VCO_2 slope)) is a powerful risk predictor, perhaps secondary to abnormal cardiopulmonary reflexes; VE/ VCO_2 slope >34–36 identifies high risk patients, beyond peak VO_2 .²³ Thus, symptom-limited CPET relies on different gas exchange parameters that have, as individual factors, a prognostic impact.^{26–28}

Other variables that frequently resulted to have high predictive value in multiparametric scores were blood urea nitrogen and sodium.⁹ Cancer, acidosis expressed by arterial pH or blood lactate, and renal failure were highly predictive in case-control studies, but not in prognostic cohort studies. The opposite was seen with ejection fraction and BNP, which were found to be highly prognostic in cohort studies but not in case-control studies. In the advanced heart failure models, the strongest predictor variable was heart failure admissions.⁹

Beside characteristics of patients' clinical presentation, interventions have an impact on prognosis. HFrEF treatments significantly reduce mortality, and their effects on survival must be included in any discussion of prognosis.^{1,29,30} In the absence of evidence-based therapies, whatever the cause, patients become more critically ill. Being aware of the effects of therapies on the predicted mortality according to the Seattle Heart Failure Model (SHFM)³¹ led to an escalation of pharmaceutical or device-based therapy for 82% of observed patients. Implanted cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) are devices that may alter the outcome and course of the disease: ICD shows a 25–30% relative reduction in all-cause mortality in patients with myocardial infarction and reduced ejection fraction³² while in patients with wide QRS and left bundle branch block morphology CRT improves symptoms and survival.³³

Therapeutic options for refractory HFrEF are heart transplantation (HTx), left ventricular assist device (LVAD) and continuous intravenous inotropes. The average post-transplant survival is about 10–15 years, while destination therapy LVADs is followed by 5–10 years of survival in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database.³⁴ Various models have been proposed for assessment of outcomes after

LVAD placement. The INTERMACS classification describes patient pre-implant conditions. The INTERMACS 1 and 2 compared with 3 and 4 profiles demonstrated statistically significant 44% versus 11% mortality within 30 days after VAD placement, but later on INTERMACS 1 and 2 patients actually showed lower mortality than the 3 and 4 patients when considering only 30-day survivors.³⁵ A comparison of the INTERMACS, Destination Therapy Risk Score, Acute Physiology and Chronic Health Evaluation II, SHFM and Columbia risk scores in patients receiving a LVAD showed the SHFM risk score to have the strongest association with mortality.³⁶ Treatment with positive inotropic medications has an unquestionably deleterious effect.³⁷ HFREF patients dependent on continuous home dobutamine show a median survival as low as little months and a six-month mortality of 50%. Thus, long-term inotropes can be used cautiously only as a symptomatic therapy when other options are precluded.

In summary, allocating patients to one strategy or another is highly dependent on underlying survival expectation. As clinical practice guidelines continue to move toward personalized treatment recommendations that are tailored to the unique benefit–harm assessments of a given patient, integration of clinical risk prediction equations will remain essential for guiding absolute risk assessment. Predicting the future is an imperfect science: quantitative risk assessment is just the start, not the end, of a treatment decision. Risk estimates must be contextualized by clinicians.^{38,39} Table 1 summarizes the multidimensional risk stratification in HFREF.

Factors limiting the use in clinical practice of risk models

Why are risk models not used in clinical assessment? One major cause is the type of outcome. Risk models that are designed to predict the combined outcome of death or hospitalization, or of hospitalization only, had a poorer discriminative ability than those designed to predict cardiac or all-cause death. This may happen because differences in the probability of hospitalization are more difficult to foresee, and hospitalizations depend also on healthcare delivery organization;⁴⁰ therefore, non-fatal events are rarely included in risk score. Moreover, risk scores generally do not predict the mode of death and do not account for the associated changes in quality of life.³ Risk models for prognosis in advanced heart failure, for example, the Heart Failure Survival Score (HFSS) and the Metabolic Exercise Cardiac Kidney Index (MECKI) score, often refer to the combined outcome of death or HTx, and/or LVAD implant. This is motivated by the fact that both HTx and LVAD may be considered life-saving therapies that have the potential to change radically the destiny of these patients, especially when performed in an acute, emergency condition ('urgent' HTx, or LVAD with INTERMACS profile^{1–3}). However, performing HTx and LVAD depends not only on patients' medical characteristics, but also on individual choices (by the patient and by the medical staff), on non-medical characteristics (e.g. blood type 0 and large size reduce the probability of getting a HTx), and on events that may be considered causal (again, availability of a suitable donor) but in fact are also influenced by organization of healthcare (e.g. policy

Table 1. Acknowledged risk aspects in heart failure due to left ventricular systolic dysfunction.

Demographic data	Age, male, low socioeconomic status
Severity of heart failure	NYHA class, duration of HFREF, peak VO ₂ ; VE/VCO ₂ slope, distance at 6mWT
Clinical status	HR, SBP, fluid overload (rale pulmonary visceral congestion, peripheral oedema), hypotension, body weight reduction and frailty
Myocardial and LV dysfunction severity	LVEF, LV systolic and diastolic chamber size, filling pressure, LV hypertrophy, valvular disease (mitral regurgitation, aortic stenosis). RV and LA dimension, pulmonary pressure, dyssynchrony, area of hypo/akinesia, wide QRS complex, presumed infiltration or inflammatory, inducible ischaemia, poor viability
Biomarkers	Sodium, natriuretic peptide, plasma renin activity, aldosterone and catecholamines, endothelin-1, vasopressin; renal function, inflammatory, cardiac stress, cardiac damage markers. Metabolic and collagen and organ dysfunction markers
Cardiovascular co-morbidities	Diabetes, anaemia, atrial fibrillation, renal and hepatic dysfunction, COPD, depression, dementia, sleep apnoea.
Non-adherence	With recommended HFREF treatment
Events	HFREF hospitalization, aborted cardiac arrest, ICD shock

HFREF: heart failure reduced ejection fraction; LV: left ventricular; RV: right ventricle; LA: left atrium; NYHA: New York Heart Association; VO₂: oxygen consumption; VE/VCO₂ slope: ventilation (VE) and carbon dioxide production (VCO₂) slope; 6mWT: 6 min walking test; HR: heart rate; SBP: systolic blood pressure; LVEF: left ventricular ejection fraction; ICD: implanted cardioverter defibrillator; COPD: chronic obstructive pulmonary disease

for donor retrieval and allocation), and they vary widely from country to country.

Another source of heterogeneity is the clinical presentation of HFrEF patients: risk in chronic/acute, advanced/moderate HFrEF is different, and improvements have been seen between both inpatients and outpatients.³

Moreover, like most statistical analyses, risk scores perform well for large groups of individuals and for the intermediate term, but they perform very poorly for individuals and for the short term.³ A further complicating issue is the time horizon of risk scores, which may span from one to five years (the time horizon varied considerably among the studies identified, with few studies providing sufficient information to confirm robustness and generalizability to qualify the prognosis of individual patients), which may not be an adequate time frame in which to make lifestyle decisions, particularly in younger, less severely affected patients.³

Such a complex interplay cannot be reduced to the binary outcome of alive or dead.

Statistical techniques

Generation of a risk model requires to get access to a robust dataset and to apply several statistical techniques.^{29,39,40} Starting with a set of univariate predictors and applying a Cox proportional hazards model or logistic regression are the most used techniques (if patient follow-up is not uniform, a Cox-based analysis is the best statistical technique, while logistic regression analysis is most appropriate when follow-up is completed). Significant risk variables can be transformed by an equation into a continuous number, or one or more points may be attributed to individual significant factors, which are summed up to build the final score. Thresholds for defining low, intermediate and high-risk categories may be identified. Validation consists of analysis of the C statistic or area under the receiver-operator characteristic curve (AUC): assessment of the sensitivity and specificity of the predictive model.

The additional value of new proposed markers may be evaluated with several statistical approaches – such as the net reclassification and integrated discrimination improvement.¹ Moreover, to integrate risk prediction models into the decisional process and the healthcare management must be carried out keeping an eye on possible biases and on how missing data have been handled. In a review,³⁹ only 28% of the studies reported on how they handled missing data. This highlights the need for a significant improvement in the quality of data reporting.

Machine learning methods based on administrative claims offered limited improvement over logistic regression in predicting outcomes.⁴⁰ Inclusion of additional

clinical parameters from electronic medical records improved prediction for some outcomes. Models derived with reference to administrative data may be helpful in identifying high-risk target populations for deploying population-based interventions.

Comparison among risk models (with the adjunction of cardiopulmonary exercise testing variables)

The Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION)⁴¹ was a multicentre randomized controlled trial that tested the long-term safety and efficacy of aerobic exercise training plus evidence-based medical therapy versus evidence-based medical therapy alone in medically stable outpatients. The relationship between baseline clinical factors and the composite end point of death or all-cause hospitalization⁴¹ showed that exercise duration at the baseline cardiopulmonary exercise testing (CPET) was the most important predictor, while supplementary predictors were Kansas City Cardiomyopathy Questionnaire symptom stability score, serum urea nitrogen and male sex.⁴²

Several risk models for HFrEF mortality have been developed,² showing variable levels of success, and many of these models were developed and validated in selective cohorts of patients from clinical trials and may or may not perform in the same way in the so-called ‘real-world’ patients. Considering the aging of the population and the heterogeneity in clinical presentation and disease progression over time, a multiparametric approach is actually advocated as the best available strategy to predict HFrEF outcome. Because women are less represented in most clinical trials than men, risk models derived without validation in sex-specific cohorts may not have the same predictive accuracy as sex-specific heart failure risk models. A study was performed in 2225 advanced HFrEF patients; the 4 strongest predictors of outcome in both women and men were B-type natriuretic peptide, peak VO_2 by CPET, NYHA classification, and use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.⁴³ In addition, the UCLA model performed better than the SHFM³¹ and the HFSS.⁴⁴ A simple risk model assessing 4 clinical variables is well suited to provide prognostic information in HFrEF patients to verify whether the risk model was better with ejection fraction could be better in event-free survival.

In 2011, Goda et al. compared HFSS⁴⁵ and SHFM in a large cohort of HFrEF patients which were under evaluation for HTx candidacy and had undergone CPET: the AUCs were similar.⁴⁵ As the decision to

list ambulatory patients for HTx remains difficult, in 2012, Levy et al.⁴⁶ appraised whether the addition of peak VO₂ improved the predictive accuracy of the SHFM in 1240 outpatients; the outcomes were death/LVAD/urgent HTx, with patients being censored as alive at the time of elective transplant. The multivariate SHFM was a powerful predictor, and peak VO₂ added prognostic information. Conversely, in 2015, Dardas et al.⁴⁷ showed that integrating CPET variables or the 6-min walking distance with the SHFM improved only marginally the accuracy of risk predictions in 2152 ambulatory patients enrolled in HF-ACTION. Thus, CPET variables appear to be of particular relevance in the specific setting of advanced HFrEF.

The HFSS, SHFM and MECKI score were compared in a cohort of HFrEF patients that were able to perform symptom-limited CPET.⁴⁸ The MECKI score exhibited a greater prognostic accuracy in terms of combination of cardiovascular death, urgent HTx and LVAD implantation: the superiority of the MECKI score was evident at two-year follow-up and was also confirmed at four years. The accompanying editorial⁴⁹ stated that the MECKI model was judged in comparison with HFSS (peak VO₂ and clinical data) and SHFM (no CPET data), and, as peak VO₂ and VE/VCO₂ are used by clinicians for the transplant listing, it was not too surprising that this risk model was superior to a clinical risk model. Freitas et al.⁵⁰ compared the MECKI, SHFM, HFSS and MAGGIC risk models: all four models had a similar AUC for all-cause mortality at two years in 259 HFrEF patients. Therefore, a comparison between resting and exertional variables is in favour of the exercise ones in selected HFrEF cohorts and according to the outcome.

The MAGGIC risk model⁵¹ appeared to be more accurate than the CHARM and SHFM models in predicting one-year mortality at the population level: however, the reliability at the individual patient level was very poor. In a large number of chronic heart failure patients reported in the European Society of Cardiology Heart Failure Long-Term Registry,⁵² the MAGGIC risk model was more accurate. In a recent letter, MAGGIC and MECKI score were compared after cardiac rehabilitation in Holland:⁵³ the MECKI score showed an excellent performance in Dutch HFrEF patients, and the MECKI score can appropriately monitor time-dependent changes in risk estimates for adverse outcomes in HFrEF.

Conclusions

Each risk model has its own peculiarities, depending on the overall aim of the study, target population, length of follow-up, health procedures assessed, location of study and accessibility to study data. Time horizon

and sample size varied considerably among the studies identified, with few studies providing sufficient information to confirm robustness and generalizability to qualify the prognosis of individual patients. It is clear that there is a real need to integrate risk prediction models into healthcare management, but this must be carried out with an eye on bias and handling missing data. Comparing different risk models and accuracy of prognosis is a hard task. Most studies are exposed to criticisms relating to their construction.

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