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Management of heart failure in the new era: the role of scores

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Aims **Heart failure is a widespread syndrome involving several organs, still characterized by high mortality and morbidity, and whose clinical course is heterogeneous and hardly predictable.**

In this scenario, the assessment of heart failure prognosis represents a fundamental step in clinical practice. A single parameter is always unable to provide a very precise prognosis. Therefore, risk scores based on multiple parameters have been introduced, but their clinical utility is still modest.

Methods **In this review, we evaluated several prognostic models for acute, right, chronic, and end-stage heart failure based on multiple parameters. In particular, for chronic heart failure we considered risk scores essentially based on clinical evaluation, comorbidities analysis, baroreflex sensitivity, heart rate variability, sleep disorders, laboratory tests, echocardiographic imaging, and cardiopulmonary exercise test parameters.**

Results **What is at present established is that a single parameter is not sufficient for an accurate prediction of prognosis in heart failure because of the complex nature of the disease. However, none of the scoring systems available is widely used, being in some cases complex, not user-friendly, or based on expensive or not easily available parameters.**

Conclusion **We believe that multiparametric scores for risk assessment in heart failure are promising but their widespread use needs to be experienced.**

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Introduction

Heart failure is a syndrome affecting several organs besides the cardiovascular system, including lungs, liver, muscles, kidney, brain, and the sympathetic system. Each of these organs participates in the disease severity and its prognosis. However, heart failure has a complex, heterogeneous clinical course,[1] characterized by periods of clinical stability and periods of decompensation, which are difficult to predict. Consequently, heart failure prognostication is nowadays a fine art and the assessment of prognosis is a fundamental step in clinical practice.[2]

Several prognostic indexes have been identified. They consider the clinical condition, such as the New York Heart Association (NYHA) classification[3] or various quality-of-life questionnaires,[4] or indexes dealing with a specific organ whose function is altered in heart failure, such as left ventricular ejection fraction (LVEF) or diameters for the heart,[2,3,5] glomerular filtration rate for the kidney,[1,6] brain natriuretic peptide (BNP) for fluid homeostasis,[7] catecholamine for the sympathetic nervous system,[5,8] alveolar capillary membrane diffusion for the lung,[9] or indexes dealing with exercise performance, such as the distance covered with the 6-minute walking test or peak VO_2,[1,5] VE/VCO_2 relationship,[1,10,11] or oxygen uptake efficiency slope[10,12] with cardiopulmonary exercise test,[11,13] just to mention some of the parameters proposed.

In recent years, it has become clear that a single parameter is, for prognosis, weaker than the effect of different parameters combined.[8,14,15] Indeed, several combinations of parameters either derived by a single test or by more tests have been evaluated, and several heart failure scores have been proposed.[1,3–5] The present review is dedicated to the analysis of the role of the

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different scores available for heart failure prognosis. Specifically, we will review prognostic scores for acute heart failure (AHF), right heart failure, and chronic heart failure. Regarding heart failure, we focused on scores that are based on clinical evaluation, comorbidity analysis, laboratory measurements, baroreflex sensitivity, heart rate variability, sleep abnormalities, echocardiographic findings, cardiopulmonary exercise test parameters, and finally we considered end-stage heart failure.

Acute heart failure

The European Society of Cardiology defines AHF as the rapid onset of symptoms and signs secondary to abnormal cardiac function in subjects with or without previous cardiac disease.[16] Nonetheless, other different definitions are currently applied for AHF, also referred to as acute decompensated heart failure or AHF syndromes.[17,18] Indeed, AHF is one of the leading causes of hospitalization, and a significant early readmission rate, as well a high mortality rate, has been reported in patients discharged following an AHF episode.[16–19]

The mechanisms underlying AHF vary from systolic to diastolic dysfunction, preload to afterload mismatch, and bradiarrhythmias to tachyarrhythmias.[18–21] Furthermore, concomitant cardiovascular and noncardiovascular diseases are common in this setting of patients and may precipitate the course of AHF and/or modify its pathophysiology.[22] Data from the Acute Decompensated Heart Failure National Registry (ADHERE), the Euro Heart Failure Survey, and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure demonstrated that most AHF episodes occur in elderly patients (over 70 years old) with a previous heart failure diagnosis.[23–25] These registries even supplied a detailed map of the most important comorbidities. Particularly, two-thirds of patients had a history of coronary artery disease, more than one-half had a hypertension history, one-third suffered from diabetes and/or chronic obstructive pulmonary disease, and approximately 20% showed renal dysfunction. Given the above-described heterogeneous scenario, a large number of variables have been found to stratify the AHF prognosis, including patient demographics, comorbidities, etiology, symptoms, vital signs, laboratory findings, diagnostic testing, and various pharmacological and nonpharmacological treatments. Notwithstanding, as happens in heart failure, also in AHF no single parameter supersedes others to such a large degree to be the sole predictor. Therefore, recent studies assessed all possible clinical, laboratory, and instrumental variables, thus allowing for the development and validation of mortality risk prediction models for hospitalized AHF patients. The EFFECT risk score, retrospectively obtained on 4000 hospitalized AHF patients[26] and validated on nearly 1000 patients,[27] identified 11 variables as independent predictors of mortality at both 30 days and 1 year (an electronic version of the score is available online at http://www.ccort.ca/CHFriskmodel.aspx). Particularly, it includes older age, lower systolic blood pressure (SBP), higher respiratory rate, higher blood urea nitrogen (BUN) level, hyponatremia, anemia, and some comorbidities such as cerebrovascular disease, chronic obstructive pulmonary disease, hepatic cirrhosis, dementia, and cancer, with an overall accuracy of 80% for 30-day mortality and 77% for 1-year mortality. Another interesting multiparametric scoring system comes from the analysis of the ADHERE data referring to more than 30,000 hospitalized AHF patients.[17] The analysis, starting from 39 univariate predictors, identified three single variables as providing the greatest amount of prognostic information regarding in-hospital mortality risk: BUN of at least 43 mg/dl, serum creatinine of at least 2.75 mg/dl, and SBP less than 115 mmHg (overall accuracy 67%). Supporting the importance of easily available variables such as SBP and renal function (especially BUN) in the risk stratification of newly hospitalized AHF patients, also the OPTIME-HF study confirmed that the best predictors of death at 2 months were lower SBP and elevated BUN together with older age, advanced NYHA class symptoms, and hyponatremia.[28]

Last, growing evidence now suggests that many other biomarkers, such as those of myocyte necrosis (i.e., cardiac troponin), inflammation (i.e., C-reactive protein), and left ventricular overload (i.e., BNP), should be added to the above-mentioned multiparametric approaches in order to improve their prognostic value.[29,30] However, a more in-depth discussion dealing with this topic can be found in the dedicated paragraph of this review.

Right heart failure in pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare disease characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular (RV) dilatation and dysfunction. Prognosis is strongly related to the ability of the RV to face increased afterload, and heart failure remains the main cause of death.[31,32]

Until few years ago, patients' risk stratification was mainly based on a single parametric approach due to the limitations derived from the rare nature of the disease. To improve our comprehension of this clinical tool, attention has recently turned to large multicenter cohorts of patients with longitudinal follow-up,[33] allowing a multiparametric approach to risk stratification. These registries facilitate our understanding of the predictive profile of the disease through the derivation and validation of risk scores.[34–36] Irrespective of the differences among the several methodological issues, all registries have demonstrated improved survival of patients with PAH compared with the National Institutes of Health registry,[37] established in 1981 before the modern treatment era.

The largest and most important among modern registries is the REVEAL US registry[34] (>2500 patients enrolled). Notably, the prognostic equation developed from the REVEAL registry is the only one that has been prospectively validated in an external incident cohort of PAH patients and translated into a simple risk score calculator that can be used in daily clinical practice.[38] The risk assessment is derived from a multivariable model and thus weights each risk factor as related with the others. Fourteen variables resulted associated with increased mortality: men aged older than 60 years, PAH associated with portal hypertension, PAH associated with connective tissue disease, family history of PAH, WHO functional class III/IV, renal insufficiency, resting SBP less than 110 mmHg, heart rate greater than 92 beats/min, right atrial pressure greater than 20 mmHg, 6MWT less than 165 m, BNP greater than 180 pg/ml, pulmonary vascular resistance greater than WU, DLCO less than 32%, and pericardial effusion. Another four variables were associated with increased 1-year survival: WHO functional class I, 6MWT greater than 440 m, BNP less than 50 pg/ml, and DLCO greater than 80%. Finally, 18 independent variables were used to create the risk calculator score, and five different clinical profiles were generated: low, average, moderately high, high, or very high risk. The discriminating power (c-index)[39] of the risk calculator is 0.724 (95% confidence interval, 0.677–0.773), that is comparable to those calculated for other widely used heart failure risk models: c-index of 0.725 for the Seattle Heart Failure Model[3] and 0.690 for the Heart Failure Survival Score.[5] The REVEAL risk score has been developed to be applicable at any timepoint of patients' assessment, regardless of PAH diagnosis, based on the most recent evaluation. Furthermore, the missing data indicator, included in the prognostic equation, allows clinicians to calculate risk profile even if data are unavailable for all of the predictive factors, improving the practice utility of the scoring.

Despite the limitations of its observational and uncontrolled nature, the risk score has been useful for transferring PAH condition from clinical trial populations to real-life patients and to make nonexpert clinicians aware of the unfavorable course of the disease.

To improve clinical management and patients' outcome, future research should move through larger collaborative cohorts, and results should be validated for time-dependent variables from a dynamic-assessment point of view and for different therapeutic strategy approaches.[40,41]

Chronic heart failure scores based on clinical evaluation, including comorbidity analysis

Despite major advances in the management of heart failure, mortality and readmission rates in the early post-discharge period have remained unchanged or slightly worsened during the last years.[42–44] A comprehensive assessment, including health status monitoring, targeted clinical examination (measurement of heart rate, blood pressure, and an evaluation of signs and symptoms of clinical congestion) and evaluation of comorbidities, may be the best strategy for identifying ambulatory heart failure patients at the highest risk of adverse outcome.[45,46] Health status assessment has proven to have prognostic value both in hospitalized and in ambulatory heart failure patients.[47,48] The Kansas City Cardiomyopathy Questionnaire seems to have a much greater sensitivity to changes in health status than other questionnaires used in patients with heart failure.[49] Clinical congestion may predispose heart failure patients to earlier and more frequent hospital admissions.[50] In a recent analysis of the EVEREST trial, it was demonstrated that the presence of rales and pedal edema at the first follow-up visit in patients recently hospitalized for worsening heart failure was associated with an increased risk of mortality and rehospitalization.[51] Concomitant disorders may complicate heart failure, adding further morbidity and mortality risk; thus, their identification and treatment is essential to implement specific and targeted therapies.[22] The development of predictive risk models for ambulatory heart failure patients can be helpful for providing this comprehensive assessment and for evaluating prognosis at the time of clinical evaluation. The 3-CHF score[52] and the HF-ACTION risk score[4] offer specific advantages over similar models and risk scores because they are applicable to a broad range of contemporary ambulatory heart failure patients. The variables included in these scores were selected because of their validated prognostic significance and easy detection. Some of predictors of 1-year mortality in the 3-CHF score are listed in Table 1. Moreover, the 3-CHF score is the first model validated in a large nontrial heart failure population that combines cardiac and noncardiac comorbidities commonly present in heart failure patients. The routine use of these predictive models with a risk score should be encouraged in order to provide a more comprehensive assessment and a better risk stratification of ambulatory patients with heart failure. The ability to identify high-risk patients is particularly important for scheduling closer follow-up programs for patients at the greatest risk, with the aim of a reduced hospitalization rate for worsening heart failure.

(1) Age (per decade increase)
  (a) Cardiac variables
    (i) NYHA class III–IV
    (ii) No RAS inhibitors
    (iii) Severe valve heart disease
    (iv) No beta blocker
    (v) Atrial fibrillation
    (vi) Left ventricular ejection fraction (per 5-unit increase)
  (b) Comorbid conditions

Table 1 Scores exclusively based on or including CPET variables

Authors	Score	Year	Variables included in the score	Endpoint
Scores including only CPET-derived parameters				
Myers *et al.*[11,85]		2008	VE/VCO_2 slope, $petCO_2$, OUES, HRR, peak VO_2 (ml/kg/min)	Cardiac-related mortality and composite outcome of death, transplantation, LVAD implantation, and CHF-related hospitalization
Guazzi *et al.*[10]	PROBE score	2010	EPB, VE/VCO_2 slope, peak VO_2 (ml/kg/min)	Cardiac-related mortality
Scores including parameters derived through different techniques but including CPET				
Aaronson *et al.*[5]	Heart Failure Survival Score (HFSS)	1997	Ischemic etiology, resting heart rate, LVEF, intraventricular conduction delay, mean resting blood pressure, serum sodium, peak VO_2 (ml/kg/min)	Event-free survival
Stempfle *et al.*[101]	Munich Score	2007	Ischemic etiology, SBP, LVEDD, the change in fractional shortening over 12 months (%), maximal workload at CPX	Event-free survival
O'Connor *et al.*[4]	HF-Action	2011	Exercise duration on CPX test, serum urea nitrogen, female gender, KCCQ symptom stability	Hospitalization/death
O'Connor *et al.*[4]	HF-Action	2011	Exercise duration on CPX test, serum urea nitrogen, female gender, BMI	Mortality
Agostoni *et al.*[1]	MECKI score	2012	Hemoglobin, sodium, MDRD, LVEF, VE/VCO_2, peak VO_2 (% pred)	Cardiovascular death and urgent heart transplant
Levy *et al.*[91]	Modified Seattle Heart Failure Score (SHFM)	2012	Peak VO_2, age, gender, weight, LVEF, SBP, hemoglobin, lymphocytes, uric acid, total cholesterol, sodium, QRS duration, implanted devices, medications, interventions, and NYHA classification	Death/LVAD implantation/urgent transplant
Kato *et al.*[102]		2013	Pulmonary capillary wedge pressure, right ventricle stroke work index, MELD-A, peak VO_2 (ml/kg/min)	Death/LVAD implantation/urgent transplant

BMI, body mass index; CPET, cardiopulmonary exercise test; CPX, cardiopulmonary exercise test; EPB, exercise periodic breathing (defined as an oscillatory pattern at rest that persisted for more than 60% of the exercise test duration at an amplitude greater than 15% of the average resting value); HRR, heart rate recovery; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; MELD-A, Model for End-stage Liver Disease-albumin level; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; $petCO_2$, end-tidal pressure of CO_2; SBP, systolic blood pressure; VO_2, oxygen uptake.

(vii) Diabetes with target organ damage
(viii) Hemoglobin (per 0.5 g/dl increase)
(ix) Serum creatinine

Chronic heart failure scores based on laboratory evaluation

Heart failure management could be improved by prognostic scores including laboratory parameters, individually or in combination with other readily available clinical and instrumental information.[53] For instance, an incremental prognostic value of the addition of BNP to the Seattle Heart Failure Model (SHFM) has been demonstrated in an elderly heart failure population.[54,55] Moreover, a further improvement in the discriminative capacity of this modified model was achieved after the addition of prealbumin.[55]

The prognostic capacity of several laboratory variables has been broadly demonstrated and accepted: troponins as signs of myocyte injury and predictors of left ventricular end-diastolic dysfunction in heart failure patients with chronic kidney disease;[56] natriuretic peptides, BNP and its amino-terminal pro-peptide (NTproBNP) as predictors of left ventricular systolic dysfunction and adverse outcome, and as good diagnostic and prognostic markers of heart failure importantly integrated into the clinical practice;[57–60] creatinine, creatinine clearance, sodium, uric acid, cystatin C, and hemoglobin as expressions of kidney damage in heart failure (the so-called ''cardiorenal syndrome''). Another laboratory marker of kidney involvement is the neutrophil gelatinase-associated lipocalin (NGAL); a meta-analysis by Haase *et al.* demonstrated that NGAL is an early predictor of subclinical acute kidney injury in heart failure, more efficient than creatinine.[61] However, at present, no score includes NGAL among its parameters. Also MR proADM in the BACH trial was shown to be a specific marker of prognosis in patients with heart failure.[62]

In 2005, Adlam *et al.*[53] developed a simple scoring system, using clinical information and BNP.

More recently, some investigators evaluated the incremental usefulness of multiple conventional biomarkers,[63] each assessing a different pathophysiological mechanism of heart failure.

A multimarker score based on seven laboratory variables (creatinine, creatinine clearance, sodium, uric acid, hemoglobin, BNP, hs-CRP) was assessed by Niizeki *et al.* in 2009,[63] by establishing the optimal cutoff value for each biomarker and categorizing patients into three risk strata.

The same scoring method was adopted in four other multibiomarker risk models: the MUSIC score[64] predicts

mortality considering eGFR, sodium, NTproBNP, troponin, hemoglobin, and GGT in combination with other demographic, clinical, echocardiographic, 12-lead ECG, and 24-h Holter monitoring variables; Richter *et al.*[65] included NTproBNP and a set of eight novel biomarkers representative of different biological pathways: inflammation, chemotaxis and immunological activation, oxidative stress, cell proliferation and growth, angiogenesis, remodeling, and fibrogenesis as well as apoptosis; Bjurman *et al.*[66] generated a risk score based exclusively on age, troponin T, and cystatin C, which improves prognostic assessment especially in patients with NTproBNP levels between 2000 and 8000 ng/l; finally, Fontanive *et al.*[67] combined eGFR less than ml/min and NTproBNP levels above the median with other demographic, clinical, and echocardiographic parameters.

Barlera *et al.*[68] represented instead their final risk model with a nomogram that can be easily used to estimate the risk of death for individual patients and that includes uricemia and eGFR as laboratory parameters.

Chronic heart failure scores based on baroreflex sensitivity, heart rate variability, and sleep abnormalities

Growing evidence is available on the relationship between sleep disorders and heart failure.

It should not be disregarded that sleep-related breathing disorders (SRBD) are highly prevalent in heart failure patients, with both central and obstructive sleep apneas being frequently observed in these patients. Central sleep apnea is more common than obstructive sleep apnea in heart failure patients and, when combined, they affect 40–60% of patients.[69,70] In recent years, SRBD have been reported to have an important added prognostic value in heart failure patients, in particular when they are associated with periodic breathing during exercise.[12] Specifically, Corra *et al.*[12] reported three classes of risk in heart failure patients: a) low risk [absence of exercise-induced periodic breathing and apnea/hypopnea index (AHI = number of apneas and hypopneas per hour of sleep) $\leq$30/h]; b) intermediate risk (presence of either exercise-induced periodic breathing or AHI > 30/h); c) high risk (presence of both exercise-induced periodic breathing and AHI > 30/h). Although full video-polysomnography remains the gold standard for diagnosis, an increasing number of limited diagnostic systems (cardiorespiratory monitoring) are available to meet the high clinical demand.[71] AHI combined with nocturnal oxygen saturation behavior, which can be evaluated by the oxygen desaturation index (number of desaturation episodes per hour of sleep) and by mean and minimum values of SaO_2 during the night, is a widely used parameter able to quantify the severity of SRBD.

Several methods are available to assess the arterial baroreflex function in the laboratory, but an important step forward in the investigation of the arterial baroreflex in humans is represented by techniques that analyze the sensitivity of spontaneous baroreflex control of heart rate, that is, techniques based on the analysis of spontaneously occurring blood pressure and heart rate fluctuations.[72,73] The possible clinical relevance of reduced baroreflex sensitivity as well as of a depressed heart rate variability in heart failure patients has been suggested.[74]

Proper use of the analyses based on fractals and chaos theory to qualify or quantify the characteristics of heart rate time series is a reliable index of physiological systems in many clinical studies,[75] including heart failure patients.[76]

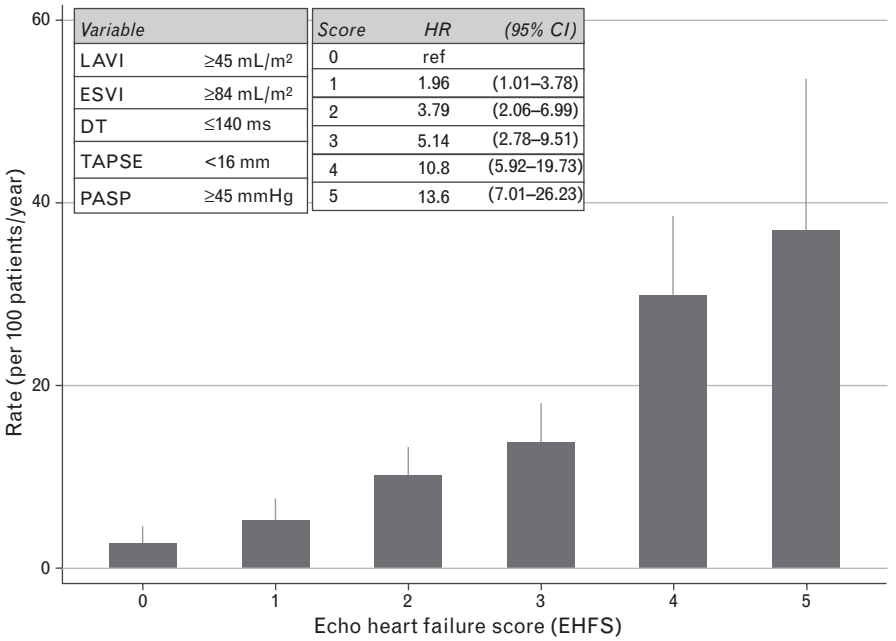
However, a multidisciplinary approach must be implemented to identify scores able to optimize the prognostic role of SRBD, heart rate variability, and baroreflex sensitivity in heart failure patients.

Chronic heart failure scores based on echocardiographic imaging

Transthoracic echocardiography is routinely acquired in heart failure patients, providing useful information for patient management and prognostic stratification.[77] Several echocardiographic parameters have been proposed as predictors of outcome in heart failure, including left atrial volume, left ventricular (LV) remodeling, LVEF, transmitral flow, mitral regurgitation severity, RV function, PAH, LV dyssynchrony, 2D-strain, and tissue-Doppler parameters.[77–84] However, it is not clear which one is a truly strong, independent predictor of mortality in heart failure, or whether there is an incremental prognostic advantage in combining several of these variables. Furthermore, the clinical scoring systems available have not included echocardiographic information in their algorithms other than LVEF.[3,4,52,64]

Carluccio *et al.* studied survival of 747 consecutive patients with stable systolic heart failure. Comprehensive echocardiography was performed at the initial clinical evaluation.[2] By multivariable Cox model, five independent predictors of mortality were identified among the 14 initial possible echocardiographic variables (LV end-systolic volume index; left atrial volume index; deceleration time of E velocity; pulmonary artery systolic pressure; and TAPSE). The Echo Heart Failure Score (EHFS) was then derived by assigning the value of 1 to each independent predictor when present, and 0 when it was absent, and then by summing the numbers. The mortality rate (per 100 patients/year) significantly increased with EHFS ranging from 0 to 5 (Fig. 1; $P < 0.0001$), with a mortality hazard ratio of 3.58 (95% confidence interval 2.74–4.78) for EHFS of at least 3. More importantly, the addition of EHFS to a base model including independent clinical predictors of all-cause mortality (age, NYHA class >II, heart rate, anemia, no beta-blocker or ACE inhibitor therapy, and plasma levels

Fig. 1



Risk stratification of all-cause mortality in patients with systolic heart failure according to EHFS score. From Carluccio *et al.*[2] Reproduced with permission.

of natriuretic peptides) resulted in an incremental predictive power (increase in C statistic from 0.74 to 0.81, $P < 0.0001$), with a 36% increased probability of death in subjects without events (Fig. 2). Therefore, the EHFS was able to identify heart failure patients at very high risk of mortality, and to reclassify as at high risk those patients otherwise defined at intermediate risk on the basis of clinical and laboratory parameters.[2]

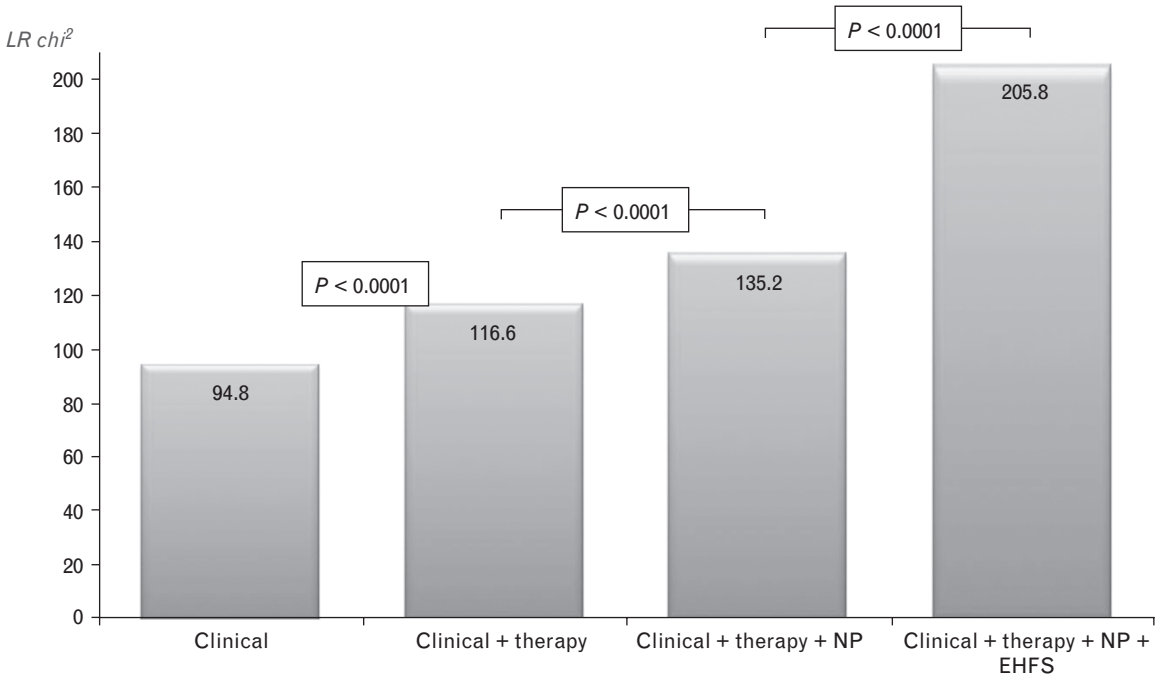
LVEF did not enter the final model because of several reasons including: a) the peculiar distribution of variables and events in the cohort of patients studied; b) the strict dependence of LVEF on heart rate – so that an almost normal LVEF may be observed in severe heart failure patients treated with high doses of beta-blockers; and c) the evidence that LVEF is unrelated to stroke volume. This result suggests that stratification of systolic heart failure patients based on LVEF alone may be inaccurate, and that parameters of RV (dys)function (TAPSE) and pulmonary artery systolic pressure, as well as a short deceleration time of E velocity – important landmarks in the progression from uncomplicated LV dysfunction to congestive heart failure – should be taken into account to better characterize the hemodynamic profile of patients, independently of the severity of LV systolic dysfunction.

The EHFS may offer promising applications for clinical use: 1) it is based upon variables that can be easily measured at the outpatient clinic or echo lab: measurements derived from new technologies (i.e., 2D-Strain, dyssynchrony, etc.) were purposely avoided in order to build a prediction model based on parameters most commonly measurable in a clinical setting and in the largest number of echo labs; 2) it can integrate the clinical scoring systems available; and 3) it could be useful for serial follow-up evaluations.

Chronic heart failure scores based on cardiopulmonary exercise test

Cardiopulmonary exercise test (CPET) provides several parameters with a relevant prognostic capacity for patients with heart failure, including oxygen uptake (VO_2), carbon dioxide production (VCO_2), and ventilation-derived parameters on top of blood pressure and heart rate. Moreover, oxygen pulse and peak VO_2, according to the Fick equation, are used to estimate peak exercise stroke volume and cardiac output, respectively. However, cardiac output can be noninvasively measured during exercise by inert gas methods. Moreover, VO_2 is also used for the measurement of cardiac power, which is the product of peak VO_2 and SBP and holds a strong prognostic capacity.[85] Indeed, since the mid-1990s, consensus guidelines have recommended the use of CPET in the management of patients with heart failure,[11] in association with other clinical and instrumental data. However, these guidelines exclusively considered peak VO_2 among all the variables of CPET; only in recent years has a broader appreciation of CPET occurred,[11] so that, among the criteria for heart transplantation, a pivotal role on top of peak VO_2 has been assigned to VE/

Fig. 2



Clinical = Age>70; NYHA class>2; HR>70 bpm, Anemia

Therapy = No-ACEI; No-Betablockers

Incremental predictive power through the addition of the EHFS score to independent clinical predictors of all-cause mortality. EHFS, Echo Heart Failure Score; NYHA, New York Heart Assoication.

VCO_2,[1,11,86] which is an index of ventilatory inefficiency reflecting ventilation/perfusion mismatching in the lungs.

Scoring systems can be classified in scores including only CPET-derived parameters and scores that comprehend data obtained through different techniques, including CPET variables (Table 1).

Risk stratification based solely on CPET variables seems to be limited because such an approach does not make efficient use of routinely obtained clinical measures of known prognostic capacity.[5] However, the accuracy of VE/VCO_2 slope derived from CPET for predicting outcomes in heart failure patients is well established.[11,86]

The Metabolic Exercise test data combined with Cardiac and Kidney Indexes, the MECKI score,[1] have been recently validated (Table 1). The MECKI score combines easy-to-obtain laboratory and echocardiographic variables with CPET parameters, considering in particular not only peak VO_2, as done in HFSS,[5] but also indexes of ventilatory inefficiency. An algorithm for the immediate calculation of the MECKI score, defining the risk of cardiovascular death and urgent heart transplant at 2 years, is now available online (http://www.cardiologicomonzino.it/en/Pages/MeckiScore.aspx).

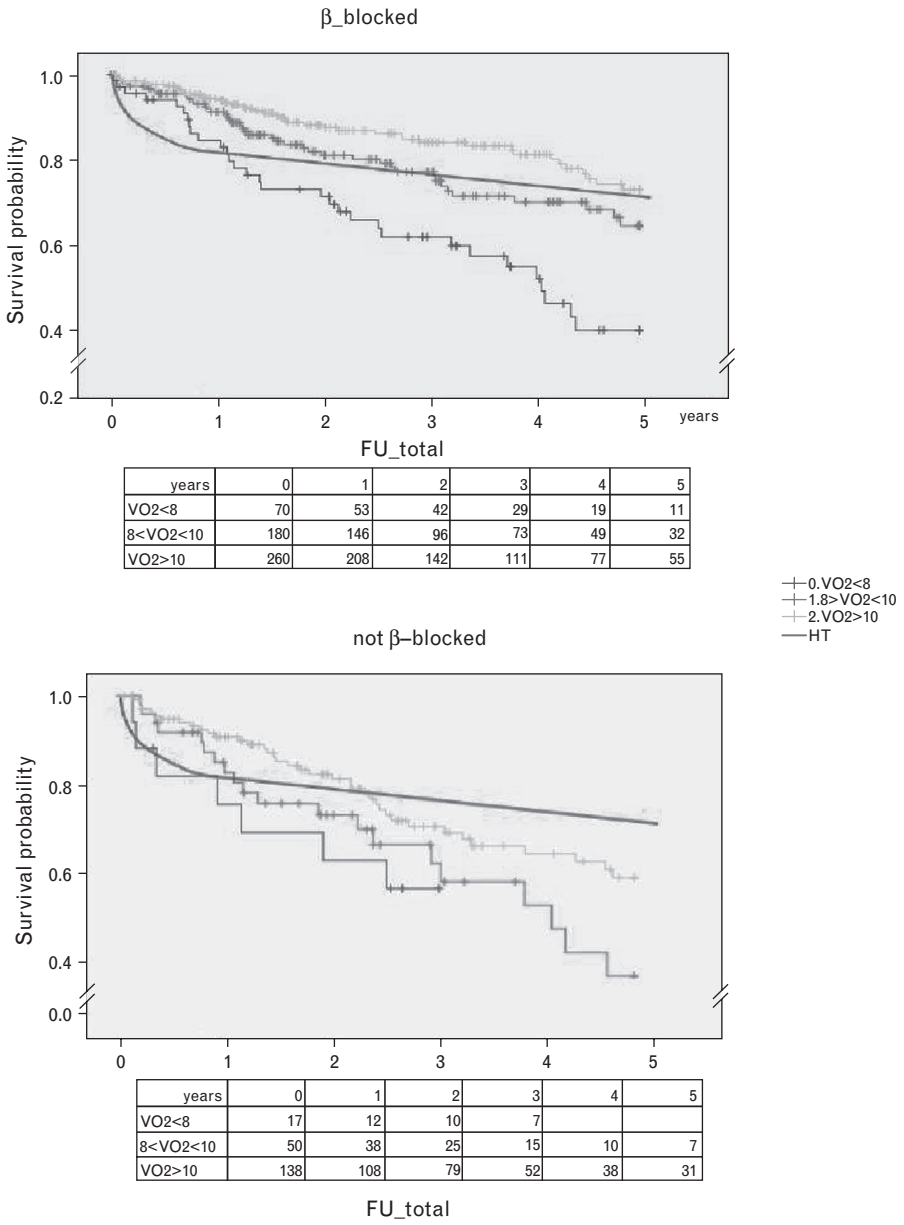
Furthermore, it has been demonstrated that an unidentified anaerobic threshold during maximal CPET is an independent negative prognostic variable in heart failure.[87]

End-stage heart failure: intra-aortic balloon pump, left ventricular assist device, and transplantation

For selected patients with end-stage heart failure, transplantation remains the gold-standard treatment, with long-term survival. However, the risk stratification of patients with end-stage heart failure is a critical component of the transplant candidate selection process.

A peak VO_2 of 14 ml/kg/min, or less than 50% of the predicted value for age and gender during anaerobic exercise, suggests patients who will potentially benefit from heart transplantation (HT);[88] in the era of β-blocker therapy, the value of peak VO_2 associated with a worse prognosis has been reduced to 12 ml/min/kg.[89] However, the progressive improvement of heart failure patients' survival due to new therapies requires a continuous reevaluation of prognosis through peak VO_2. In fact, it has been recently demonstrated that, even though peak VO_2 keeps on allowing a risk stratification of heart failure

Fig. 3



Survival (death/urgent HT) of beta-blocked/non beta-blocked patients grouped for peak VO_2. Red line = survival rate of post-HT patients. HT, heart transplantation. From Cattadori *et al.*[90] Reproduced with permission.

patients regardless of the presence of β-blocker therapy, patients on optimized medical therapy benefit from HT only if severely intolerant to exercise (peak VO_2 <8 ml/kg/min); on the contrary, heart failure patients with severe exercise limitation not on β-blocker therapy show a worse survival rate than post-HT patients (Fig. 3).[90]

The combination of several noninvasive measures can contribute to the prognosis estimation. Seven risk factors have been used and validated in patients undergoing transplant evaluation in the HFSS.[5] Patients in medium-risk and high-risk groups (according to this score) should be considered for HT. Although this score was made before the widespread use of β-blockers, it also provides an effective risk stratification in patients on β-blockers.[91] The HFSS is not validated for patients hospitalized with AHF.

Another score – the SHFM[3] – is a validated multivariate risk model that uses NYHA classification to assess functional capacity rather than peak VO_2. Levy *et al.*[92] have

Table 2 INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) scale for classifying patients with advanced heart failure

Profiles	Definition	Description
INTERMACS 1	*"Crash and burn"*	Hemodynamic instability in spite of increasing doses of catecholamines and/or mechanical circulatory support with critical hypoperfusion of target organs (severe cardiogenic shock)
INTERMACS 2	*"Sliding on inotropes"*	Intravenous inotropic support with acceptable blood pressure but rapid deterioration of kidney function, nutritional state, or signs of congestion
INTERMACS 3	*"Dependent stability"*	Hemodynamic stability with low or intermediate, but necessary due to hypotension, doses of inotropics, worsening of symptoms, or progressive kidney failure
INTERMACS 4	*"Frequent flyer"*	Temporary cessation of inotropic treatment is possible, but the patient presents frequent symptom recurrences and typically with fluid overload
INTERMACS 5	*"Housebound"*	Complete cessation of physical activity, stable at rest, but frequently with moderate water retention and some level of kidney dysfunction
INTERMACS 6	*"Walking wounded"*	Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity
INTERMACS 7	*"Placeholder"*	Patient in New York Heart Association functional class II or III with no current or recent unstable water balance

recently demonstrated that the addition of peak VO_2 provides further prognostic information across the spectrum of the SHFM, but changes in decisions regarding transplant listing mainly occur in moderate-risk patients. Furthermore, combining HFSS and SHFM improves predictive ability.[93]

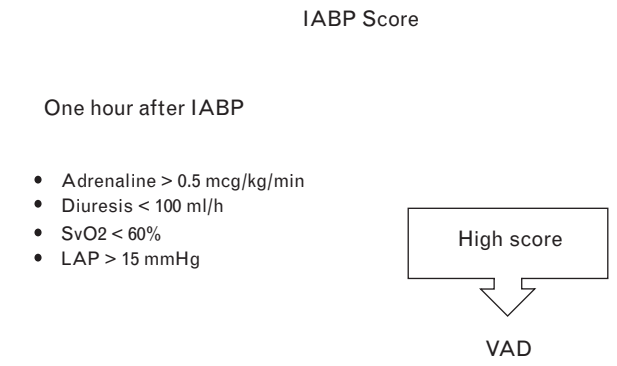
The addition of iodine-123 meta-iodobenzylguanidine imaging to the SHFM improves risk stratification in patients considered for ICD, CRT-D, left ventricular assist device (LVAD), and HT.[94]

However, the most widely used classification for patients with severe heart failure is the Intermacs classification, which is based on simple clinical parameters (Table 2).

In patients who suffer from low cardiac output syndrome despite intra-aortic balloon pump (IABP) support, ventricular-assist devices (VADs) have been used to achieve circulatory recovery. Some patients are bridged to HT; others receive a VAD as permanent therapy.

To verify the indications and timing of the VAD implantation in patients who received an IABP, Hausmann *et al.*[95] measured the hemodynamic parameters 1 hour after IABP insertion and then calculated a new score, the ''IABP score'' (0 to 5 points) (Fig. 4). In patients with a high ''IABP score'' and poor survival prognosis, the VAD implantation should be considered.

Fig. 4



Variables considered in IABP score to identify patients at high risk who may benefit from VAD implantation. IABP, intra-aortic balloon pump; VAD, ventricular-assist device. Data from Hausmann *et al.*[95]

Patients with severe heart failure being considered for destination LVAD therapy often have advanced age or noncardiac morbidities that make them ineligible for transplantation.

Several risk assessment tools have been developed to predict also postoperative complications and mortality in these patients.[96–99] In addition, bleeding during implantation of mechanical circulatory support is the most common perioperative complication.

The Model for End-Stage Liver Disease predicts events in cirrhotic subjects undergoing major surgery[100] and may offer similar prognostication in LVAD candidates with comparable degrees of multisystem dysfunction. It identifies LVAD candidates at high risk of perioperative bleeding and mortality.[101] This score is a weighted sum of serum creatinine, bilirubin, and the international normalized ratio with a minimum score set at 6 and no set maximum.[101]

Considering the difficulties in defining end-stage heart failure, in estimating prognosis in the individual patient, and the continuing evolution of available therapies, new scores for risk assessment in end-stage heart failure should be experienced.

Conclusion

At present, a single parameter is clearly not sufficient for a precise prognosis in heart failure due to the composite nature of the syndrome. Several scoring systems have been proposed and validated, but their clinical use, if any, is limited to specific settings. Unfortunately, an easy-to-calculate, cheap, adaptable to all heart failure patients and, most importantly, precise prognostic tool is still not available. Thus, prognostic stratification of heart failure patients should be evaluated in a hierarchical clinical and diagnostic framework, comprehensive of multiple prognostic indicators, and not limited to a single specific score.

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