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MINIREVIEWS

Predicting mortality in patients with acute heart failure: Role of risk scores

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Abstract

Acute heart failure is a leading cause of hospitalization and death, and it is an increasing burden on health care systems. The correct risk stratification of patients could improve clinical outcome and resources allocation, avoiding the overtreatment of low-risk subjects or the early, inappropriate discharge of high-risk patients. Many clinical scores have been derived and validated for in-hospital and post-discharge survival; predictive models include demographic, clinical, hemodynamic and laboratory variables. Data sets are derived from public registries, clinical trials, and retrospective data. Most models show a good capacity to discriminate patients who reach major clinical end-points, with C-indices generally higher than 0.70, but their applicability in real-world populations has been seldom evaluated. No study has evaluated if the use of risk score-based stratification might improve patient outcome. Some variables (age, blood pressure, sodium concentration, renal function) recur in most scores and should always be considered when evaluating the risk of an individual patient hospitalized for acute heart failure. Future studies will evaluate the emerging role of plasma biomarkers.

Key words: Acute heart failure; Prognosis; Scoring; Risk stratification; Outcome

Core tip: We present a review of the most relevant scores developed for the risk stratification of patients hospitalized for acute heart failure. For each score, the strengths, weaknesses, statistical pertinence and applicability in a real-world situation are evaluated. Furthermore, we revisit the general criteria and statistical metrics that should be considered in the design and analysis of prognostic studies.

INTRODUCTION

Acute heart failure (AHF) is a complex and hetero-geneous clinical syndrome defined as the rapid onset or change in symptoms and signs of heart failure requiring immediate medical attention and urgent therapy[1]. It is a leading reason for hospitalization and is burdened by high short-(intra-hospital) and long-term (6 to 12 mo) mortality.

Most often, the first triage of patients with AHF is performed in the emergency department (ED), where these patients present to receive initial care. Then, on the basis of the clinical profile and risk stratification, patients are discharged, admitted to a medical ward or cardiac division, or transferred to an intensive care unit. At the end of hospitalization, a structured follow-up is planned to reduce the risk of early rehospitalization (a major issue in health care system) and improve long-term survival.

Therefore, the risk stratification of patients with AHF is a pivotal medical task aimed to improve the outcome of patients with AHF and the efficiency of the health care delivery system. Physicians involved in the care of acute heart failure patients should be able to evaluate the risk profile especially in two critical turning points: (1) at the time of hospital admission, for choosing the best hospital setting according to the risk profile and for identifying low-risk patients who can be safely discharged to home, thus pursuing both the best outcome of patients and the correct allocation of resources; and (2) at the time of discharge, for planning disease management of patients for a given risk profile, and for the selection of patients suitable for more advanced therapies.

Physicians always determine an initial prognosis by integrating the patient's characteristics, clinical signs and laboratory tests. The prediction is inherently multivariable; however, the relative weight that a doctor assigns to each variable, which relies on his clinical judgment, previous experiences, personal beliefs and, eventually, on his current mood, could be inaccurate and misleading.

Even the most skilled physician might incorrectly estimate the risk of death in heart failure patients or be uncertain about prognosis[2]. Furthermore, the precision of risk estimate based on clinical judgment might be reduced by the urgency of making a critical decision in the case of more severe clinical scenarios[3-5]. An incorrect prognosis might generate a mismatch between intensity of care and the risk profile of the patient.

Risk score are multivariable predictive models in which relative weights are assigned to each variable in order to calculate the probability that a specific event (death, rehospitalization) will occur in the future. They are tools that help doctors estimate prognosis in a more unbiased way, translating the result of prognostic studies in clinical practice.

Beyond the benefit to an individual patient, the research of valid prognostic models is fundamental for public health policy, for comparative effectiveness and health service research, for quality of care outcome assessment, for health technology assessment of therapies and laboratory tests, and for studying new approaches, mechanisms and targets for clinical trials[6].

Methodological issue and critical points of risk stratification of AHF patients

A risk model is the final output of prognostic research, which is a three-step course that calls for (1) development studies aimed to identify relevant predictors entering the model and their relative weights. In this phase the performance of the models estimated by evaluating the calibration and the discrimination, and the model is adjusted for overfitting; an internal validation should be performed by bootstrapping techniques in the same population from which the model is derived; (2) external validation studies, in which the model is validated in new populations; and (3) impact studies designed to evaluate if the decision making for a single patient, driven by the risk status assigned according to the predictive model, could improve clinical outcome[7].

Correct statistical metrics should be used for reporting prognostic studies. To measure the ability of a model to discriminate patients for a binary outcome, the C-statistic (equivalent to the area under the receiver operating characteristics curve) is calculated[8]; it ranges from 0.50 (no discrimination) to 1 (perfect discrimination).

Calibration measures the correlation between observed and predicted events, and it is generally assessed with the Hosmer-Lemeshow statistic[9]. Recently, the standardization of reporting of a multivariable prediction model has been proposed[10]. Many reasons make the development of a prognostic score in the setting of acute heart failure a challenging task.

The validity of a risk score depends on the population from which it is derived and on the choice of the variables; AHF syndromes include different clinical scenarios: (1) decompensated HF and worsening chronic heart failure; (2) pulmonary oedema; (3) cardiogenic shock; (4) hypertensive HF; and (5) right HF[11]. Moreover, each class could undergo a further classification; for example, worsening chronic heart failure patients could have preserved or reduced ejection fraction as well. It is unlikely that the same prognostic model could fit miscellaneous clinical patterns, as each of one is endowed with peculiar physiopathological aspects.

Another relevant issue is the source of the data set from which the model is derived. Community-based settings and clinical trial populations are often very divergent; the latter generally includes younger people with a lower rate of co-morbidities that might have a relevant role in driving prognosis, especially in older

Table 1 Main risk scores in acute heart failure							
Risk score	Data source	Publication year	Sample size (derivation)	Sample size (validation)	Validation	Model development	Endpoint
In-hospital mortality							
ADHERE[15]	Registry	2005	33046	32229	External	Classification trees	In-hospital mortality
AHFI[16]	Statewide databases	2005	33533	8384	External	Classification trees	In-hospital mortality and complications
OPTIMIZE-HF[19]	Registry	2008	37548	181830	Internal/external	Logistic regression model	In-hospital mortality
GWTG-HF[20]	Registry	2010	27850	11933	Internal/external	Logistic regression model	In-hospital mortality
EHMRG[21]	Population-based cohort	2012	7433	5158	Internal/external	Logistic regression model	7 d mortality
PROTECT[23]	Clinical trial	2012	2015	1435	Internal/external (clinical trial population)	Cox proportional hazards model	Composite endpoint of death, worsening heart failure or heart failure rehospitalization
Post-discharge mortality							
EFFECT[24]	Community	2003	2624	1407	Internal/external	Logistic regression model	30 d mortality/1 yr mortality
OPTIME-CHF[25]	Clinical trial	2004	949	-	Internal	Cox proportional hazards model	60 d mortality
OPTIMIZE-HF[26]	Registry	2008	4402	949/433	Internal/external (clinical trial population)	Cox proportional hazards model	60-90 d post-discharge mortality
APACHE-HF[27]	Community (single centre)	2014	824	-	-	Cox proportional hazards model	90 d mortality
ELAN[28]	Pooled data of seven cohorts	2014	1301	325	External (clinical trial population)	Cox proportional hazards model	180 d mortality
ADHF/NT-proBNP[29]	Community	2013	453	371	External	Logistic regression model	1 yr mortality
ESCAPE[30]	Clinical trial	2010	433	471	Internal/external (clinical trial population)	Cox proportional hazards model	6 mo mortality

ADHERE: Acute decompensated heart failure national registry; AHFI: Acute heart failure index; OPTIMIZE-HF: Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; GWTG-HF: Get with the guidelines-heart failure; EHMRG: Emergency heart failure mortality risk grade; PROTECT: Placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function; EFFECT: Enhanced feedback for effective cardiac treatment; OPTIME-CHF: Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure; APACHE-HF: Acute physiology and chronic health evaluation in heart failure; ADHF/NT-proBNP: Acutely decompensated heart failure n-terminal pro-brain natriuretic peptide; ESCAPE: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness; ELAN: European collaboration on acute decompensated heart failure.

populations. The external validity of a model derived from clinical trial is, at minimum, controversial.

Another critical point is the choice of variables used to calculate the score. A huge number of determinants of survival for AHF have been studied; many variables have been associated with prognosis in univariate and multivariate analysis, including clinical characteristics, hemodynamic markers, serum biomarkers, and medication use[12]. If a stepwise selection is used, then the availability of so many variables could lead to the inclusion of too many parameters in the model, causing overfitting, with the model generating random error or noise and resulting in a spurious prognostic association.

A model that has been overfit will have a poor predictive performance in other populations. Parsimony in the number of parameters and developing the simplest model with the highest accuracy are proper ways to improve the applicability of the model to other populations[13]. In AHF syndrome, clinical, laboratory and

hemodynamic variables might suddenly change during the clinical course. Some variables could be associated with short-term improvement but worse long-term survival (for example, use of inotropic drugs); therefore, the timing of data collection and the timeline for the endpoint survey are pivotal.

RISK SCORES
Several prognostic models combining different variables have been developed to predict in-hospital mortality and to estimate outcomes between 30 d up to 6 mo post-discharge. Table 1 summarizes methodological characteristics of the risk scores, Table 2 the variables entering different models, and Table 3 the models' performances.

In-hospital risk models
Acute decompensated heart failure national

Table 2 Variables used in the risk score models

Risk score	Variables
ADHERE[15]	BUN, creatinine, SBP
AHFI[16]	Gender, CAD, diabetes, lung disease, SBP, HR, respiratory rate, temperature, blood urea nitrogen, sodium, potassium, white blood cell count, acute myocardial infarction o myocardial ischemia at ECG, pulmonary congestion or pleural effusion on radiographic examination
OPTIMIZE-HF[19]	Creatinine, sodium, age, HR, liver disease, previous CVA/TIA, peripheral vascular disease, race, left ventricular systolic dysfunction, COPD, SBP, previous HF hospitalization
GWTG-HF[20]	Older age, low SBP, elevated heart rate, presence of COPD, and non-black race
EHMRG[21]	HR, creatinine, systolic blood pressure initial oxygen saturation, serum troponin
PROTECT[23]	BUN, respiratory rate, HR, albumin, cholesterol, diabetes, previous HF hospitalization
EFFECT[24]	Age, SBP, BUN, sodium concentration, cerebrovascular disease, dementia, COPD, hepatic cirrhosis, cancer, hemoglobin
OPTIME-CHF[25]	Age, BUN, SBP, sodium, NYHA class
OPTIMIZE–HF[26]	Age, weight, SBP, serum creatinine, history of liver disease, history of depression history of reactive airway disease
APACHE-HF[27]	Mean blood pressure, HR, serum sodium, serum potassium, creatinine, haematocrit, Glasgow coma scale, age
ELAN[28]	NT-proBNP at discharge, NT-proBNP reduction, age, peripheral oedema, SBP, sodium, serum urea, NYHA class
ADHF/NT-proBNP risk score[29]	COPD, SBP, eGFR, serum sodium, hemoglobin, NT-proBNP; left ventricular ejection fraction, tricuspid regurgitation
ESCAPE[30]	Age, BUN, six-minute walk test, sodium, CPR/mechanical ventilation, diuretic dose at discharge, no-blocker at discharge, BNP

BUN: Blood urea nitrogen; SBP: Systolic blood pressure; CAD: Coronary heart disease; HR: Heart rate; CVA: Cerebral vascular accident; COPD: Chronic obstructive pulmonary disease; CPR: Cardiopulmonary resuscitation; eGFR: Estimated glomerular filtration rate; NT-proBNP: N-terminal brain natriuretic peptide; ADHERE: Acute decompensated heart failure national registry; AHFI: Acute heart failure index; OPTIME-CHF: Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure; EHMRG: Emergency heart failure mortality risk grade; EFFECT: Enhanced feedback for effective cardiac treatment; OPTIMIZE-HF: Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; PROTECT: Placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function; GWTG-HF: Get with the guidelines-heart failure; APACHE-HF: Acute physiology and chronic health evaluation in heart failure; ADHF/NT-proBNP: Acutely decompensated heart failure n-terminal pro-brain natriuretic peptide; ESCAPE: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness; ECG: Electrocardiogram; TIA: Transient ischemic attack; ELAN: European collaboration on acute decompensated heart failure.

Table 3 Performances of risk scores

Risk score	Calibration	C-statistic (derivation cohort)	C-statistic (validation cohort)	Low-risk group mortality (%)	High-risk group mortality (%)
In-hospital mortality					
ADHERE[15]	NV	0.75	0.75	2.1	21.9
AHFI[16]	NV	NA	0.59	0.3	NA
OPTIMIZE-HF[19]	NV[1]	0.75	0.746	NA	NA
GWTG-HF[20]	Calibrated	0.75	0.75	0.4	9.7
EHMRG[21]	Calibrated	0.80	0.803	0.3	8.2
PROTECT[23]	Calibrated	0.67	0.67	4.8[1]	28.7[2]
Post-discharge mortality					
EFFECT[24]	Calibrated	0.80 (30 d)	0.79 (30 d)	0.4 (30 d)	59 (30 d)
		0.77 (1 yr)	0.76 (1 yr)	7.8 (1 yr)	78.8 (1 yr)
OPTIME-CHF[25]	NV[1]	0.77	0.76	2	30
OPTIMIZE-HF[26]	NV	0.72	NA	NA	NA
APACHE-HF[27]	NV	0.78			20[2]
ELAN[28]	NV	0.77	NA	3.6	51.1
ADHF/NT-proBNP risk score[29]	Calibrated	0.84	0.77	3.7	89.5
ESCAPE[30]	NV[1]	0.76	0.65[3]	7	100

[1]A graphic plot of the predicted *vs* observed probability of outcome was reported; [2]Relative risk of death in the high-risk group *vs* the low-risk group; [3]In the validation cohort, the model did not include brain natriuretic peptide and diuretic dose. NA: Not available; NV: Calibration was not verified by statistical tests; ADHERE: Acute decompensated heart failure national registry; AHFI: Acute heart failure index; OPTIMIZE-HF: Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; GWTG-HF: Get with the guidelines-heart failure; OPTIME-CHF: Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure; EHMRG: Emergency heart failure mortality risk grade; EFFECT: Enhanced feedback for effective cardiac treatment; BNP: Brain natriuretic peptide; ADHF/NT-proBNP: Acutely decompensated heart failure n-terminal pro-brain natriuretic peptide; ESCAPE: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness; PROTECT: Placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function; ELAN: European collaboration on acute decompensated heart failure.

registry: The "acute decompensated heart failure national registry" (ADHERE) provides a risk stratification model to predict in-hospital mortality in patients admitted with acutely decompensated heart failure[14].

The authors analysed the clinical, demographic and biochemical data of 33046 patients from the Acute Decompensated Heart Failure National Registry in order to develop a risk stratification model. The model

was prospectively tested using data from 32229 hospitalizations, which comprised the validation cohort. Statistical analysis revealed that blood urea nitrogen (BUN) level of 43 mg/dL or higher was the best single predictor for mortality. The second best predictor was admission systolic blood pressure (SBP) < 115 mmHg. Serum creatinine levels of 2.75 mg/dL or higher provided additional prognostic value in patients with BUN levels $\geq$ 43 mg/dL and SBP $\leq$ 115 mmHg. The authors employed the CART method to derive a risk tree identifying acutely decompensated heart failure (ADHF) patients at low, intermediate and high risk for in-hospital mortality in the validation cohort. Heart rate and age did not improve the risk stratification of patients in the final algorithm.

Finally, ROC curves were used to assess the accuracy of the models. The study provided a useful and validated tool for mortality risk stratification by employing signs and laboratory data evaluated on hospital admission. The combination of two different markers of renal function confirms the established link between the heart and kidney and thus the association between clinical outcomes and markers of renal function[15]. Mortality in the low- and high-risk group was 2.1% and 22%, respectively.

The ADHERE algorithm was derived from a real-world population, the model was adequately validated in an additional cohort of patients, and it meets parsimony criteria requiring only three variables, which are easily measured at the time of hospital admission. A major criticism of the ADHERE algorithm is that the registry entries reflect individual hospitalizations, and repeated hospitalizations of the same patient are entered as separated records. This is a clear violation of the fundamental research principle of independence of experimental units, which limits the internal validity of the study. Another limit is the overly high mortality of the low-risk group in comparison with other models. However, the ADHERE algorithm might allow for immediate and simple triage at admission in the emergency department, not requiring complex calculations.

AHF index: Auble *et al*[16] analysed 33533 patients admitted from the ED with a diagnosis of heart failure. The authors derived a prediction rule to identify patients at low-risk of in-hospital death and serious medical complications. The proposed prediction rule resulted from a combination of demographic, biochemical and non-invasive diagnostic tools.

The performance of this algorithm, named the AHF index, was further examined, and the index was validated in an independent group of 8383 patients admitted to the ED with heart failure, with respect to inpatient mortality, serious medical complications before hospital discharge, and 30 d mortality. The mortality rates in the low-risk group were significantly higher in the validation cohort compared to the two derivation cohorts (0.7%-1.7% *vs* 0.3%)[17,18].

Organized program to initiate lifesaving treatment in hospitalized patients with HF: Beginning with an analysis of a national hospital-based registry and quality improvement program [organized program to initiate lifesaving treatment in hospitalized patients with HF (OPTIMIZE-HF) registry], predictors of in-hospital mortality were identified, and a practical risk-prediction tool of in-hospital mortality that is applicable in routine clinical practice for patients hospitalized for heart failure was derived. The identification of the most important predictors from the multivariate logistic regression analysis allowed the development of a point scoring system to predict in-hospital mortality. The ability of the logistic regression model to discriminate mortality was tested by a classification and regression tree (CART) analysis. The model combined multiple variables, and the final risk-prediction normogram included age, heart rate, SBP, serum creatinine, serum sodium, primary cause of admission (heart failure or other), and left ventricular systolic dysfunction. For each value of each variable, a score associated with the probability of in-hospital mortality is calculated. The model had a good performance, with a C-statistic of 0.75; however, no validation of the score has been reported[19].

Get with the guidelines-HF: Another useful risk model has been provided by the American Heart Association's "get with the guidelines-heart failure" programme. The score combines clinical variables to predict in-hospital mortality. The programme involved 39783 patients, with a derivation sample of 27850 and a validation sample of 11933 patients, and can be applied to heart failure patients, with both preserved and reduced left ventricular ejection fraction. The proposed score combined 7 clinical factors routinely collected at the time of admission. The 7 predictor variables (older age, low SBP, elevated heart rate, presence of chronic obstructive pulmonary disease, and non-black race) were identified in the multivariate model. The estimation of in-hospital mortality can be carried out by summing points assigned to each predictor, with a total score ranging from 0 to 100. The inclusion of race among the predictors might limit the application of the model in different countries. The risk score had good discrimination: C-index was 0.75 in both derivation and validation data set.

In-hospital mortality in the lower and higher risk group was 0.4% and 9.7%, respectively. The model was thought to be helpful in patient triage and in the use of evidence-based therapy in the highest-risk patients, reducing resource allocation in those at low risk[20].

Emergency heart failure mortality risk grade: Lee DS *et al*[21] proposed a multivariate risk index for 7-d mortality using initial vital signs, clinical and presenting features and readily available laboratory tests, with the aim of predicting acute mortality and guiding acute clinical decision making for patients with HF who present to the ED. The derivation cohort was comprised of 7433

patients, and the validation cohort was comprised of 5158 patients. The authors developed the "emergency heart failure mortality risk grade" (EHMRG), which comprises multiplicative and additive variables with an available online calculator. The EHMRG encompassed all patients presenting to the ED, regardless of whether they were hospitalized or discharged, providing a useful tool to guide hospitalization-*vs*-discharge decisions based on prognosis. A higher heart rate and creatinine concentration, a lower SBP and oxygen saturation, and non-normal serum troponin levels were associated with an increased mortality risk and were entered into the score. The area under the receiver-operating characteristic curves of the model was 0.805 for the derivation data set and 0.826 for the validation data set. Despite the fact that left ventricular ejection fraction and natriuretic peptide analysis have been validated as predictive variables in both acute and chronic heart failure, they were not included in the model because they are not frequently assessed in the ED.

Placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function: The international "placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function" (PROTECT) trial enrolled 2033 patients hospitalized with AHF and mild or moderate impairment of renal function[22]. Of the 2033 patients, 2015 had complete data for the analysis, and a risk score was developed for predicting the composite endpoint (death, worsening heart failure, rehospitalization for HF) at 7 d; points assigned to each predictor were summed, for a total point score ranging from 0 to 100 points. All variables employed were collected within 24 h of admission. The strongest predictor of the outcome was higher BUN concentration. Other predictors of an adverse outcome were lower values of serum albumin, serum cholesterol, and SBP, as well as higher heart and respiratory rates. The variables employed in the model demonstrate the role of metabolic status, neurohormonal activation and reduced cardiac performance in influencing patient outcomes. The model underwent an external validation in a study population of another clinical trial; the C-index in the derivation and validation population was 0.67.

The study population of the derivation data set was enrolled in the trial with strict inclusion and exclusion criteria: Patients taking inotropic agents and those with severe pulmonary disease, recent ischemia or preserved ejection fraction were not included; therefore, the applicability of the PROTECT risk score to a wide range of community-based populations is limited[23].

Post-discharge risk models
In addition to prediction of in-hospital mortality, attempts to assess short-, medium- and long-term prognosis, as well as the risk of events, in patients hospitalized for AHF, has led to the proposal of different risk models.

Enhanced feedback for effective cardiac treatment: The "enhanced feedback for effective cardiac treatment" study analysed multiple variables available at the time of hospital presentation of more than 4000 patients hospitalized for heart failure. The authors identified predictors of mortality, and they developed and validated a model that could predict all-cause 30 d and 1 year mortality. Age, lower SBP, higher respiratory rate, higher BUN level, hyponatremia, and co-morbidities were independent predictors of mortality at both 30 d and 1 year. Very low risk scores (< 60) identified patients with a mortality rate of 0.4% at 30 d and 7.8% at 1 year. Patients with very high-risk scores (> 150) had a mortality rate of 59% at 30 d and 78.8% at 1 year. The authors suggested the importance of assessing selected variables during the first hours of hospital presentation in order to help the physician to identify patients with a high risk of events and optimize patient management[24].

Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure: The data from the "outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure" (OPTIME-CHF) study were analysed to develop a model predicting the post-discharge outcome of inpatients hospitalized for acute decompensated heart failure[25].

A multivariate model allowed the assessment of variables predictive of mortality or the composite endpoint of death and re-hospitalization at 60 d. Age, lower SBP, New York Heart Association class IV symptoms, elevated BUN, and decreased sodium were predictors of death at 60 d. The C-index for mortality at 60 d was 0.77. As for other models derived from clinical trials, the populations used to derive the models represent only a subgroup of AHF patients; the study populations have consisted entirely of patients with reduced ejection fraction, whereas patients with renal dysfunction or who required inotropes were excluded from the studies.

OPTIMIZE-HF: O'Connor *et al*[26] developed a clinical model predictive of short-term clinical outcome in patients discharged after hospitalization for HF. The authors employed logistic regression analysis that initially included 45 potential variables and finally identified 8 significant risk factors to predict the risk of mortality within 60 d after discharge, with a C-index of 0.72. Co-morbidities (liver disease, depression, reactive airway disease) have a major role in the score.

In addition to the risk score, the study confirmed the

importance of evidence-based therapies prescribed at discharge; β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blocker and lipid-lowering therapies were associated with decreased mortality and rehospitalization.

Acute physiology and chronic health evaluation in HF: This score, constructed by Okazaki *et al*[27] includes all factors significantly predictive of survival after discharge and assigns one point for each factor. The parameters considered in the scoring system are the mean blood pressure, pulse, sodium, potassium, creatinine, haematocrit, age and glasgow coma scale; these parameters exhibited a high sensitivity and specificity and an adequate area under the curve. The score was able to predict all-cause death or readmission due to heart failure at 90 d. The study did not include NYHA class, left ventricular ejection fraction, BUN, hemoglobin and brain natriuretic peptide (BNP), which has been found to be predictive of prognosis in previous studies. Acute physiology and chronic health evaluation in HF has other major limitations: It was derived from a single centre population, all patients were admitted to an intensive care unit for respiratory or circulatory support, and the score has not been validated.

European collaboration on acute decompensated-HF: The data from seven cohorts of prospective studies of patients admitted due to acutely decompensated heart failure were pooled by Salah *et al*[28] to develop a predictive discharge score based on different predictors of mortality, including the absolute value at discharge and percentage reduction of NT-proBNP. The European collaboration on acute decompensated-HF score assigned one point for each factor but 3 points for n-terminal (NT)-proBNP values at discharge ranging from 5001 to 15000 pg/mL and 4 points for values > 15000 pg/mL. The score showed that the absolute values of NT-proBNP at discharge and the percentage reduction during hospitalization, combined with other established risk markers, might improve the risk stratification for adverse events within 180 d after discharge.

ADHF/NT-proBNP risk score: Confirming the relevance of natriuretic peptide measurements in patients with acutely decompensated heart failure, Scrutinio *et al*[29] studied the improvement in the risk reclassification of patients with AHF by adding NT-proBNP to other common clinical variables. The authors proposed the ADHF/NT-proBNP risk score, with a possible total score ranging from 0 to 22. The score proved to be effective in predicting one-year mortality in patients hospitalized for acutely decompensated heart failure, providing clinicians with a validated and easy-to-use predictive tool in daily clinical practice. Adding NT-proBNP to the reference model did not improve discrimination, but resulted in significant risk reclassification.

Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: The evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness (ESCAPE) trial enrolled 433 patients hospitalized with ADHF, and it analysed the relationship between clinical factors at discharge and 6 mo mortality. The aim of the analysis was to create a score, potentially useful to identify patients at high and low risk of recurrent events. Among the variables analysed, a high discharge BNP level showed the strongest association with death. The proposed score included 8 variables, with 1 point possible for each variable, except for BUN and BNP, for which additional points were assigned for the highest value, with a maximum 13 possible points. The C-index for 6 mo mortality was 0.78 in the derivation data set, but it was reduced to 0.65 in the validation population[30].

CLINICAL APPLICATIONS AND FUTURE DIRECTIONS

The great number of validated prognostic models, each combining different variables, suggests how difficult it is to estimate risk in patients with AHF. Nevertheless, efforts to develop risk models are justified by the evidence that the risk of in-hospital mortality, early post-discharge mortality, and re-hospitalization remains high[31]. Approximately 12%-15% of patients hospitalized for AHF die within 12 wk, and 30% of these patients die within 12 mo of admission[32].

The accurate estimation of risk is essential for proper in-hospital and post-discharge treatment plans and outpatient follow-up. Nevertheless, despite all the proposed prognostic models, the clinical application remains challenging, and clinical scores are not considered part of the standard of care[33].

A major limit of the risk scores approach is that these tools evaluate a "class risk", that is to say, the risk of a cohort of patients sharing common characteristics. In addition, the scores' applicability in evaluating the risk of an individual patient remains elusive. Lemeshow demonstrated that valid predictive models might produce markedly different prognosis for an individual[34], suggesting that they should not be used for individual patient decision making. Due to the great number of prognostic variables, the discordance between prognosis for an individual by different scores might be substantial.

Risk stratification by scoring methods should support rather than replace medical judgment in the clinical decision making process concerning the single patient. Physicians involved in the care of patients with AHF should be familiar with a number of risk scores and should choose the most suitable on the basis of the patient's profile according to the characteristics of the derivation population of the score.

Beyond the evaluation of an individual patient, risk scores are useful tools for managing the process of care, defining diagnostic and therapeutic pathway,

and identifying possible subjects to include in a clinical trial. In patients with chronic advanced heart failure, the Heart Failure Survival Score was able to identify medium- and high-risk patients who benefit from heart transplantation in comparison with a low-risk group in which heart transplantation was not associated with a survival benefit[35]. Currently, no study has evaluated if allocation of patients, driven by risk status according to a predictive model, could improve the clinical outcome in acute heart failure, and currently, no pharmacological intervention has been able to reduce mortality in AHF. Appropriate risk stratification could allow targeting of patients who could benefit from established or new therapies.

Even if the phenotypic heterogeneity of AHF patients makes difficult to find a risk model suitable for all patients, some parameters recur in most of the models. Age, low blood pressure, reduced cardiac performance, low sodium renal concentration due to neurohormonal activation, and decreased renal function are included in most risk models.

Notably, baseline renal dysfunction is a relevant predictor of short and long-term outcome in AHF patients. Worsening renal function, which occurs in 20%-30% of patients hospitalized for AHF, is associated with a poor outcome[36], and the possible role of new therapies for AHF in patients with worsening renal function has recently been investigated[37].

Regarding biomarkers, the role of natriuretic peptides is well-known, and it has a significant prognostic value at both baseline and discharge. Nevertheless, new plasma biomarkers are continuously being identified and validated but have yet to enter in clinical practice[38-41]. In the MOCA trial, biomarkers such as sST2, MR-proADM, natriuretic peptides and CRP provided incremental value for risk stratification of ADHF patients when added to a clinical variables-based model. Further studies are needed to determine if a multi-marker strategy could improve the prognosis and outcome of acute heart failure patients[42].

How to choose a risk score? To choose a risk score, statistical and methodological pertinence should be evaluated. Models have a high grade of evidence when they are derived from large community or registry populations, when they have been validated in an external population, and when they show good discrimination (c-statistic > 0.70) in both derivation and validation cohorts; eventually, adequate calibration is crucial.

Clinicians should be suspicious of risk models derived from clinical trials and that were not validated in an external population and that were not calibrated. Risk models in which in-hospital mortality is the outcome must be used at the time of hospital admission. Obviously, when patients with AHF are admitted to the emergency department, risk stratification based on models with few easily measurable variables is preferred. Risk models that evaluate long-term mortality are useful during hospitalization and at discharge to plan the follow-up or to select patients for advanced therapies.

CONCLUSION

Scores for the risk stratification of AHF patients are useful tools that might support, not replace, clinical judgment and supply a rational approach for prognostication of the individual patient. Further studies are necessary to evaluate if the outcome of patients with acute heart failure can be improved with the use of these tools.

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