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Mortality prediction in acute heart failure: scores or biomarkers?

Wussler Desiree[ab], Michou Eleni[a], Belkin Maria[a], Kozhuharov Nikola[ac], Diebold Matthias[ac], Gualandro Danielle M.[ad], Breidthardt Tobias[ab], Mueller Christian[a]

[a] Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Switzerland
[b] Department of Internal Medicine, University Hospital Basel, University of Basel, Switzerland
[c] Liverpool Heart and Chest Hospital, United Kingdom
[d] Heart Institute (InCor), University of Sao Paulo Medical School, Brazil

Summary

Acute heart failure (AHF) is a complex and heterogeneous syndrome not only associated with a concerning rise in incidence, but also with still unacceptably high rates of mortality and morbidity. As this dismal outcome is at least in part due to a mismatch between the severity of AHF and the intensity of its management, both in-hospital and immediately after discharge, early and accurate risk prediction could contribute to more effective, risk-adjusted management.

Biomarkers are noninvasive and highly reproducible quantitative tools that have improved the understanding of AHF pathophysiology. They can help guide the intensity of AHF management. In addition, using a statistical model to estimate risk from a combination of several predictor variables such as vital signs or demographics has gained more and more attention over recent years. In this context, the aim of a statistical model, which gives a so-called risk score, is to help clinicians to make more standardised decisions.

This review highlights recent advances and remaining uncertainties regarding risk stratification in AHF by characterising and comparing the potential of biomarkers and risk scores.

Keywords: *acute heart failure, biomarkers, risk scores, risk prediction*

Introduction

Acute heart failure (AHF) is a heterogeneous syndrome with a concerning rise in incidence [1, 2]. Equally, AHF is a growing social and economic burden in terms of its unacceptably high mortality rates and healthcare costs [3]. The dismal outcome of patients with AHF is at least in part due to a mismatch between risk assessment and the intensity of AHF management, both in-hospital and immediately after discharge [4–6]. Early and accurate risk prediction using clinical risk scores or biomarkers could contribute to more precise, risk-adjusted management [7, 8] (fig. 1).

Biomarkers quantify the pathophysiological processes central to a disease/syndrome and thereby provide a diagnostic and prognostic window [9–11]. Among the multitude of biomarkers evaluated in patients with AHF, natriuretic peptides (B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)), used as quantitative markers of haemodynamic stress and heart failure, are by far the most important. Their use has been extensively validated in large diagnostic and prognostic studies and is consistently given a class I recommendation for AHF diagnosis in current guidelines [12, 13]. In addition, BNP and NT-proBNP concentrations measured at hospital discharge help to predict mortality and AHF re-hospitalisation [14–16].

However, a single biomarker approach mostly quantifies one pathophysiologic pathway, and therefore risk stratification and adverse outcome prediction in AHF, a heteroge-

ABBREVIATIONS:

ADHERE	Acute Decompensated Heart Failure National Registry
AHF	acute heart failure
AHFI	Acute Heart Failure Index
ANP	atrial natriuretic peptide
BNP	B-type natriuretic peptide
CI	confidence interval
cTn	cardiac troponin
EHMRG	Emergency Heart Failure Mortality Risk Grade
ELAN	European coLlaboration on Acute decompeNsated heart failure
GDF-15	growth differentiation factor 15
GWTG-HF	Get With the Guidelines Heart Failure
HR	hazard ratio
MEESSI-AHF	Multiple Estimation of risk based on the emergency department Spanish Score In patients with AHF
MR-proADM	mid-regional pro-adrenomedullin
MR-proANP	mid-regional pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OHFRS	Ottawa Heart Failure Risk Scale
OR	odds ratio
sST2	soluble suppression of tumourigenicity 2

Correspondence:
Prof. Christian Müller, MD, Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, Petersgraben 4, CH-4031 Basel, Christian.mueller[at]usb.ch

neous syndrome with various phenotypes, is often limited [17, 18]. Accordingly, the estimation of risk from a combination of several predictors using a statistical model could improve accuracy [19–21]. Therefore, several prognostic models, so-called risk scores, incorporating clinical parameters such as vital signs, demographics, and often biomarkers, have been developed [7, 22–24].

This review highlights recent advances and remaining uncertainties regarding risk stratification in AHF by characterising and comparing the potential of biomarkers and risk scores.

Mortality prediction in AHF: biomarkers

What makes a biomarker useful?

Given the vast number of emerging biomarkers reported to be associated with mortality in AHF, five criteria may help put data on biomarkers into clinical perspective and aid assessment of their potential to ultimately improve patient management [18, 25–27]:

1. Pre-analytical and analytical aspects

   Often, pilot studies use dedicated blood sample preparation protocols that cannot be easily implemented into routine clinical practice, e.g. putting samples on ice immediately after blood draw or sample processing within minutes after blood draw [28]. This may be necessary for very unstable analytes, but would clearly reduce their utility in routine clinical practice. In addition, reasonable analytical precision needs to be demonstrated to ensure reproducibility of results. Turn-around time and the cost of measurement should also be reasonable.

2. Accuracy

   Biomarker concentration should provide high accuracy for prognosis. Some biomarkers have only modest accuracy as single variables but may provide some additional value in incomplete multivariable models [29]. As these models only rarely reflect integrated clinical judgment, physicians should remain critical whenever the new biomarker itself lacks high accuracy.

3. Incremental value

   In order to justify its possible application in routine clinical practice, a novel biomarker should add new and clinically useful information rather than restating information already available at the bedside or via the use of inexpensive, routinely available biomarkers. For instance, none of the thoroughly investigated renal biomarkers were able to convincingly demonstrate incremental value on top of old-fashioned creatinine for the early detection or prediction of acute kidney injury [30–32].

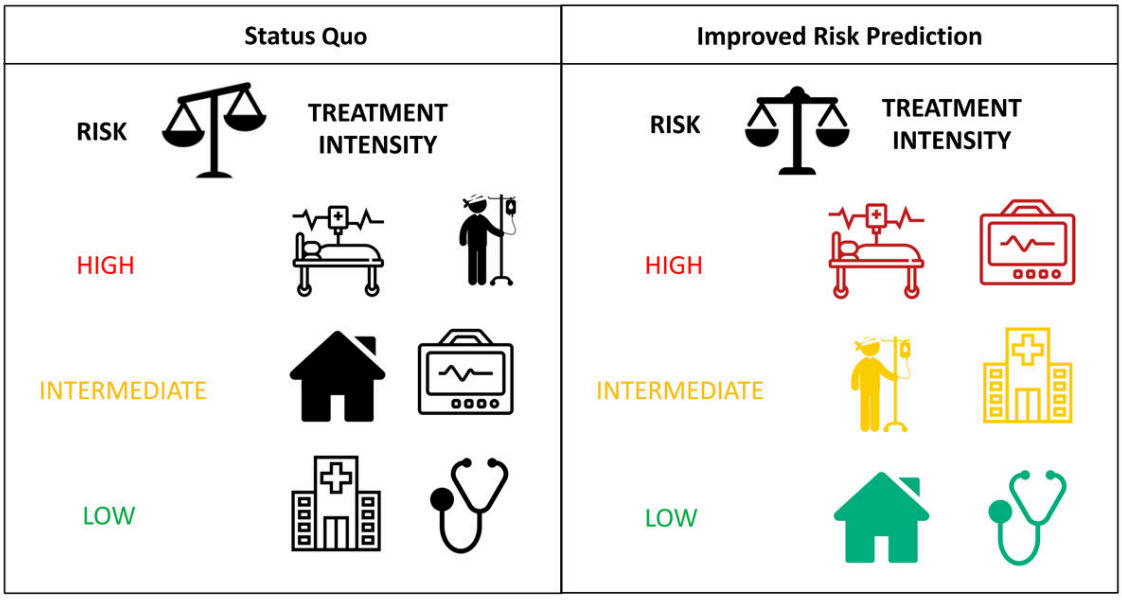
4. Understanding pathophysiology

   The organ and/or cells contributing predominately to systemic concentrations of many biomarkers are incompletely understood, e.g., for sST2 or GDF-15. This uncertainty makes it much less likely that a specific therapeutic intervention can be identified. It also raises the possibility that extra-cardiac production is dominant even in AHF [33, 34].

5. Guiding therapy (theragnostics)

   In order to plan clinical management, it is important to identify patients at very high risk. Ultimately, this information can only be used to alter outcomes if the very high risk is amendable by a change in manage-

Figure 1: Status quo shows the current mismatch between risk categories and the intensity of management both in-hospital and immediately after discharge. For example, a recent study showed that the majority of patients classified as low-risk using a heart failure risk score were hospitalised despite the fact that adjusted ambulatory follow-up might have been the more accurate approach [8]. **Improved risk prediction** using clinical risk scores or biomarkers could contribute to more effective, risk-adjusted management. Therefore, high-risk patients could be transferred to an intensive care unit with continuous monitoring (marked in red), intermediate-risk patients could be hospitalised or temporarily treated in an intermediate care unit (marked in yellow), whereas low-risk patients could be safely discharged home with an adjusted ambulatory follow-up (marked in green).



ment, e.g. more intense non-invasive monitoring while in hospital, more intense follow-up, or a specific modification of therapy. For instance, cardiac troponin concentrations are closely associated with mortality in AHF, but only when substantially elevated do they trigger a change in management, such as early coronary angiography when AMI is suspected as the AHF trigger.

Biomarkers involved in heart failure pathophysiology

Most biomarkers in current clinical evaluation can be assigned to one of the pathophysiologic pathways involved in the development and progression of heart failure [35] (fig. 2). The involvement of several pathophysiological pathways makes heart failure a complex, multiorgan disease with possible multiorgan failure due to proinflammatory activation, oxidative stress, ongoing ischaemia or unresolved congestion [36].

Haemodynamic stress and myocardial stretch

Natriuretic peptides

In response to volume or pressure overload and the resulting myocardial wall stress, the biologically inert NT-proBNP and biologically active BNP are enzymatically cleaved from their precursor proBNP [37]. Since their clinical introduction as markers of myocardial wall stress and HF, the rapid detection of AHF among patients presenting with acute dyspnoea has improved substantially [38–42]. Accordingly, the diagnostic use of natriuretic peptides has received a class I recommendation in both the European and American practice guidelines [12, 43].

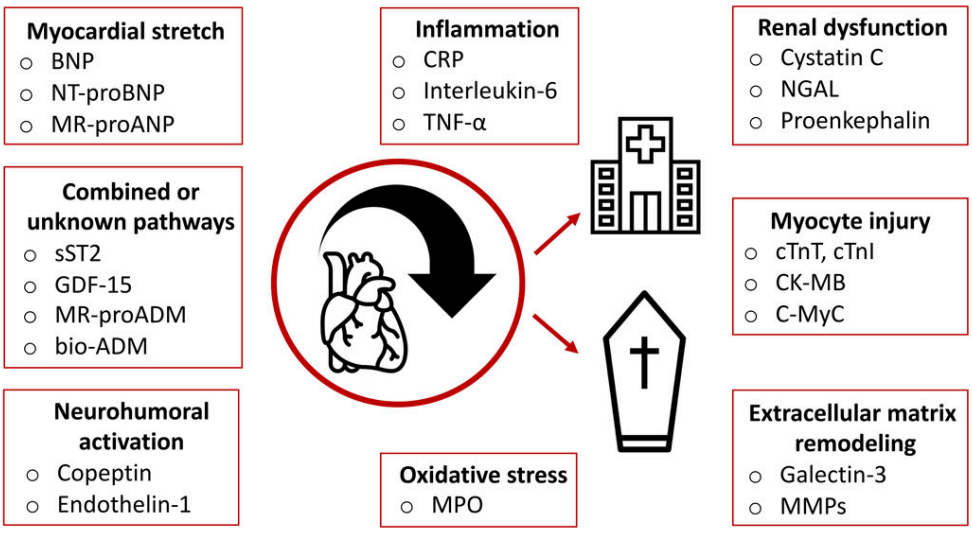
Besides their diagnostic value, BNP and NT-proBNP levels at hospital presentation are predictors of short- and long-term outcomes [14–16, 44–48]. For instance, in 48,629 AHF patients, BNP quartile was predictive of in-hospital mortality even after adjustment for common covariates [14]. However, the overall prognostic accuracy of BNP and NT-proBNP concentrations measured at presentation with AHF is only modest. When directly comparing pre-discharge values or the percentage change during hospitalisation with the admission values of natriuretic peptides, several studies have shown higher prognostic accuracy for measurements obtained during the course of hospitalisation [15, 49–53].

Both BNP and NT-proBNP concentrations are responsive to therapy during heart failure hospitalisation [15, 49–53]. Furthermore, the extent of decrease in plasma level is a strong predictor of outcome. For instance, in 171 AHF patients, treatment reduced BNP and NT-proBNP levels by more than 50% in survivors ($p < 0.001$), while in non-survivors treatment did not significantly impact natriuretic peptide levels [53]. However, since the introduction of sacubitril/valsartan, this concept must be reconsidered. By inhibiting neprilysin, sacubitril inhibits the degradation of BNP, thereby increasing its concentration in blood and to some extent uncoupling its decrease from successful therapy [54, 55]. In contrast, NT-proBNP concentration is still closely correlated with subjective and objective measures of clinical improvement in patients on sacubitril/valsartan [54, 56].

Natriuretic peptides other than BNP or NT-proBNP

Like the B-type natriuretic peptides, atrial natriuretic peptide (ANP) is released into circulation as a consequence of increased myocardial wall stress. However, due to its very short half-life of 2–5 minutes, only the measurement of its more stable precursor protein proANP makes it available for AHF diagnosis and prognosis in clinical practice [57]. In three large diagnostic studies, mid-regional pro-atrial natriuretic peptide (MR-proANP) showed comparable diagnostic and prognostic accuracy to NT-proBNP

Figure 2: Overview of the pathophysiological pathways involved in heart failure and the corresponding biomarkers with prognostic relevance.bio-ADM = bioactive adrenomedullin; BNP = B-type natriuretic peptide; CK-MB = creatine kinase myocardial band; C-MyC = cardiac myosin-binding protein C; CRP = C-reactive protein; cTnI = cardiac troponin I; cTnT = cardiac troponin T; GDF-15 = growth differentiation factor 15; MMP = matrix metalloproteinase; MR-proADM = mid-regional pro-adrenomedullin; MPO = myeloperoxidase; MR-proANP = mid-regional pro-atrial natriuretic peptide; NGAL = neutrophil gelatinase-associated lipocalin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST2 = soluble suppression of tumourigenicity 2; TNF-α = tumour necrosis factor alpha.



[58–60]. Although ANP, and therefore MR-proANP, are considered to be released predominately by the atria, which is hypothesised to provide an additional window to the heart to BNP and NT-proBNP, which are considered to be secreted mainly by the ventricles [61], combined use of MR-proANP with BNP or NT-proBNP has not yet been found to provide clinically relevant incremental diagnostic or prognostic value [58–60]. A reason might be that left atrial stress and right ventricular/right atrial stress may also play a role in stimulating BNP and NT-proBNP release. This was suggested in a recent study in patients with aortic stenosis, as the correlation between BNP and pulmonary capillary wedge pressure was stronger than that between BNP and left ventricular end-diastolic pressure [62].

Combined/unknown pathways

Soluble suppression of tumourgenicity 2 (sST2)

sST2 is one isoform of ST2, a protein which is part of the interleukin-1 receptor family and is released under conditions of myocardial and vascular strain [63]. sST2 concentrations have moderate prognostic accuracy in both acute and chronic heart failure and seem to provide incremental value in some multivariable models [29, 64–68]. Early changes in sST2 may also provide prognostic value. For instance, one study showed that non-survivors had higher sST2 admission levels (median 108 vs 69 ng/ml, $p < 0.01$) and also a lower decrease in sST2 (25% vs 42%, $p = 0.01$) during in-hospital treatment compared to survivors [66]. Additionally, sST2 concentrations appear to be responsive to therapy during HF hospitalisation [69, 70]. One of the main caveats regarding the use of sST2 is that its systemic concentrations seem to be the result of extra-cardiac production, with the predominant organ and/or cells yet to be identified [34]. This is in contrast to natriuretic peptides, whose cardiac production has been proven by studies measuring their trans-cardiac gradient [71, 72].

Growth differentiation factor 15 (GDF-15)

Similar pros and cons apply to GDF-15. The physiological expression of GDF-15 is mainly limited to the placenta and the prostate. However, the expression of GDF-15 in cardiomyocytes can be rapidly induced by inflammation or triggers of oxidative stress, including pressure overload in AHF [73]. Like sST2, GDF-15 concentrations are mainly the result of extra-cardiac production, with the predominant organ and/or cells yet to be identified [33]. Nevertheless, GDF-15 concentrations are strongly associated with death in multiple conditions, including AHF [74–76]. GDF-15 concentration was not modified by sacubitril/valsartan, whereas serelaxin administration was associated with greater decreases in GDF-15 compared to a placebo [75, 76].

Mid-regional pro-adrenomedullin (MR-proADM) and bioactive adrenomedullin (bio-ADM)

Adrenomedullin, a potent vasodilator with inotropic and natriuretic properties, is expressed in several tissues, such as the adrenal medulla, lungs and kidneys. Several studies have also shown a cardiac expression stimulated by both increased intracardiac filling pressure and volume overload [77, 78]. Adrenomedullin plasma levels are elevated in patients with chronic HF and correlate with disease severity [28, 77]. However, the clinical applicability of this biomarker is limited by the instability of the adrenomedullin plasma measurement. Therefore, MR-proADM, a more stable fragment from the same precursor as adrenomedullin, has emerged as a novel prognostic biomarker in AHF [58]. In addition, an assay exclusively measuring the biologically active amidated adrenomedullin (bio-ADM) is currently undergoing clinical evaluation [79].

Myocyte Injury

Cardiac troponin (cTn)

Most patients with AHF have cTn concentrations above the normal upper limit with a rise and/or fall even if AHF is not triggered by myocardial infarction. In the absence of evidence suggesting type 1 myocardial infarction, myocardial injury in patients with AHF [80] may have several different underlying pathophysiological processes, including cardiomyocyte apoptosis due to wall stress or toxicity related to inflammation [81]. The higher the cTn concentration in AHF, the higher the in-hospital and the long-term mortality, and the longer the length of stay [82–85]. Serial cTn measurements may allow monitoring of the response to therapy, and thereby provide additive information [85]. For instance, sacubitril/valsartan led to a 16% greater reduction in high-sensitivity cTnT concentration compared to enalapril after four weeks ($p < 0.001$) [70].

Extracellular matrix remodelling

Galectin-3

Galectin-3 belongs to a family of soluble lectins which play an important role in several pathophysiological processes such as inflammation and fibrosis. As these mechanisms are involved in the development of HF, a role of galectin-3 in HF pathophysiology has been suggested [86, 87]. In this context, recent studies have shown that galectin-3 is predictive of short-term mortality and rehospitalisation in patients presenting with AHF [88, 89]. However, two caveats apply to galactin-3. First, like sST2 and GDF-15, systemic galactin-3 concentrations in HF seem to depend mainly on extra-cardiac production [33]. Second, galactin-3 concentrations show a strong correlation with renal dysfunction. Therefore, at least some of their prognostic information may be purely a reflection of renal dysfunction [90].

Oxidative stress

Myeloperoxidase

Myeloperoxidase, a biomarker of inflammation and oxidative stress, is released from activated neutrophils, monocytes and from endothelial cells [91, 92]. Neutrophil activation and inflammation are associated with the development and progression of HF. Accordingly, myeloperoxidase levels are associated with increased mortality in AHF [93]. However, as oxidative stress is a rather unspecific element in AHF pathophysiology, the value of myeloperoxidase for AHF risk prediction appears comparably small.

Inflammation

C-reactive protein (CRP) and interleukin-6

Infectious diseases such as pneumonia are important and common precipitating factors in patients with AHF. However, even in the absence of an infection, mild increases in markers of systemic inflammation such as CRP or inter-

leukin-6 are common in AHF [94]. In this context, it has been hypothesised that mesenteric arterial hypoperfusion combined with increased mesenteric venous pressure results in bacterial translocation from the bowel to the bloodstream. Therefore, heart failure severity correlates with the extent of inflammation [95, 96].

CRP is a member of the pentraxin family and is mainly produced in the liver in response to systemic inflammation processes. Several studies have documented increased mortality in AHF patients with continuously increasing CRP concentrations [97–102]. This association persists after adjusting for common covariates, including BNP [102]. Similar observations have been made for interleukin-6: this cytokine has independently predicted all-cause mortality in several studies [103–105]. In conclusion, markers of inflammation are rather unspecific and therefore seem to be less useful as single marker strategies in AHF risk prediction. However, their combination with established cardiac biomarkers such as natriuretic peptides may provide incremental value.

Mortality prediction in AHF: risk scores

What makes a risk score useful in HF?

Given the vast number of emerging AHF risk scores, eight criteria may help put data on AHF risk scores into clinical perspective and aid assessment of their potential to ultimately improve patient management [19–21]:

1. Reliable clinical models should be developed using a large and high-quality dataset, possibly even one obtained from a multicentre study.
2. The model should be based on a sound statistical analysis plan. In this context, it is important to avoid statistical overfitting, particularly when multiple candidate predictor variables are used in a relatively small dataset.
3. A newly developed model must always be externally validated before its introduction to clinical practice can be considered. External validation using a dataset from a geographically different cohort is always preferred compared to a so-called time-dependent internal validation, which uses data from the same trial but obtained at a later time point as the derivation cohort.
4. Ideally, a score should be developed in the setting in which it will be clinically applied. As most AHF patients present to the emergency department for initial treatment [106], the derivation cohort for an AHF risk score should be recruited from the emergency department in order to provide early and accurate risk stratification.
5. Variables should be rapidly and routinely available and should assess disease severity as objectively as possible, rather than depend on the subjective judgment of a physician, to avoid interobserver variation.
6. Direct comparison of a new score with an established score in the same dataset is recommended to document prognostic equivalence or even superiority.
7. The accuracy of a risk score should be assessed by goodness of fit tests in the sense of near-optimal discrimination and calibration [107]. Furthermore, impact studies provide additional insights into a score´s impact on actual clinical decision-making and healthcare costs.
8. Geographical differences in AHF outcomes and the potential prognostic impacts of novel therapeutic agents such as sacubitril/valsartan mean that the performance of a risk score may vary depending on geographical region, and possibly also change over time [54, 108, 109]. Therefore, it should be feasible to update existing models by adjusting the intercept or adding novel predictors such as biomarkers [110].

Table 1 gives an overview of selected risk scores and their characteristics. Those scores that were derived in emergency department populations are highlighted. The depicted scores were chosen in order to assess the development of AHF risk scores over time and to compare different characteristics such as data source, sample size and predictor variables. Figure 3 directly compares the predictor variables of selected risk scores regarding their availability in the emergency department.

Risk scores without cardiac biomarkers as predictor variables

The Acute Decompensated Heart Failure National Registry (ADHERE)

The ADHERE decision tree consists of only three variables and was developed for predicting in-hospital mortality in AHF patients (table 1, fig. 3). Interestingly, the score incorporates serum creatinine and blood urea nitrogen as parameters, both of which reflect renal function. The underlying explanation could be that blood urea nitrogen is considered a marker of renal neurohumoral activation [118].

The c-statistic of the decision tree was 0.69 in the derivation cohort and 0.67 in the time-dependent internal validation cohort [112]. This discrimination is comparable with the performance of similar simple scores developed from smaller datasets [119]. Although the ADHERE decision tree cannot compete with other risk scores in terms of data source and acquisition, as it was derived from retrospectively analysed data from hospitalised AHF patients, the main advantage of this decision tool is its simple application, due to the use of only three objectively collectable and routinely available variables.

Acute Heart Failure Index (AHFI)

The AHFI was developed in a large, retrospective cohort study which constructed decision trees to identify patients at low risk of in-hospital mortality and serious medical complications [113]. The final prediction rule uses 21 variables, including demographics, clinical parameters, history variables and laboratory parameters. It identified 5758 (17.2%) patients as low-risk, of whom 1.4% experienced the combined primary outcome defined as in-hospital death or a predefined serious complication (table 1, fig. 3). A time-dependent internal validation and external validation in a single centre study showed slightly higher event rates in patients classified as low-risk: (1.7% and 2.5% vs 1.4%) [120, 121]. Like the ADHERE decision tool, the AHFI was derived retrospectively from administrative data, and furthermore, no measures of goodness of fit are giv-

en. However, its major disadvantage seems to be difficult handling due to a multitude of predictor variables.

Get With the Guidelines Heart Failure (GWTG-HF) risk score

The GWTG-HF risk score was derived from administrative data from hospitalised AHF patients for the prediction of in-hospital mortality [114]. Seven objective predictor variables routinely collectable at the time of admission were identified, and the constructed risk score showed an acceptable discrimination (c-statistic, 0.75) and calibration (Hosmer-Lemeshow = 0.242) when tested in the overall sample (table 1, fig. 3).

Even though the GWTGF-HF score, like the AHFI and the ADHERE decision tool, was derived from a large study population, data were again collected retrospectively from hospitalised patients. As an AHF risk score should be developed in the setting where it will be applied, data collection from the emergency department would be preferable.

Table 1: Summary of selected risk scores and their characteristics. Scores derived in ED populations are in bold type.

Risk score acronym	Data source and acquisition	Number of hospitals (country)	Sample size (derivation/ validation)	Model development	Data collection	No. variables included	Assessed risk	c-statistic (derivation/ validation)	External validation
Scores not including biomarkers as predictor variables									
EFFECT (2003) [111]	Administrative data (retrospective)	34 (derivation) 14 (validation) (Canada)	2624/1407	Logistic regression	Hospitalised patients	10/11†	30-day mortality 1-year mortality	0.80/0.79 (30-day mortality) 0.77/0.76 (1-year mortality)	No
ADHERE (2005) [112]	Administrative data (retrospective)	263 (United States)	33,046/32,229	Classification and regression tree	Hospitalised patients	3	In-hospital mortality	0.69/0.67	No
AHFI (2005) [113]	Administrative data (retrospective)	Pennsylvanian acute care centres (United States)	33,533/8384	Classification and regression tree	Hospitalised patients	21	In-hospital mortality and/or serious complications in survivors‡	Not given	Prospective validation in 259 patients in another US-American State
GWTG-HF (2010) [114]	Administrative data (retrospective)	198 (United States)	27,850/11,933	Logistic regression	Hospitalised patients	7	In-hospital mortality	0.75/0.75	No
Scores including biomarkers as variables									
EHMRG (2012) [22]	**Administrative data (retrospective)**	**86 (Canada)**	**7433/5158**	**Logistic regression**	**ED patients**	**10**	**7-day mortality**	**0.806/0.804**	**Administrative data from 6,708 patients in another Canadian state Two prospective cohort studies (Spain n = 2137; Switzerland n = 849)§**
OHFRS (2013) [23]	**Observational cohort study (prospective)**	**6 (Canada)**	**559/***	**Logistic regression**	**ED patients**	**10**	**Combined 14-/30-day endpoint¶**	**0.77/0.77***	**Clinical validation in 1,100 patients recruited in 6 Canadian EDs**
ADHF/NT-proBNP (2013) [115]	Administrative data (retrospective)	1 (derivation) 2 (validation) (Italy)	453/371	Logistic regression	Hospitalised patients	8	1-year mortality	0.839/0.768	No
ELAN-HF (2014) [116]	**Pooled data of 7 cohort studies (prospective)**	**7 (Europe)**	**1,301/***	**Cox regression**	**Hospitalised and ED patients**	**8**	**180-day mortality**	**0.76/–**	**Randomised trial of 325 patients in Italy**
STRATIFY (2015) [117]	**Observational cohort study (prospective)**	**4 (United States)**	**1033/***	**Logistic regression**	**ED patients**	**13**	**Combined 30-day endpoint‖**	**0.68/–**	**No**
MEESSI-AHF (2017) [7]	**Observational cohort study (prospective)**	**34 (Spain)**	**4867/3229**	**Logistic regression**	**ED patients**	**13 or less**	**30-day mortality**	**0.836/0.828**	**Prospective cohort study including 1572 patients in Switzerland**

ED = emergency department. Full names of risk scores: ADHERE = Acute Decompensated Heart Failure National Registry; ADHF/NT-proBNP = Acute Decompensated Heart Failure/N-terminal pro-B-type natriuretic peptide; AHFI = Acute Heart Failure Index; EFFECT = Enhanced Feedback For Effective Cardiac Treatment; EHMRG = Emergency Heart Failure Mortality Risk Grade; ELAN-HF = European coLlaboration on Acute decompeNsated Heart Failure; GWTG-HF = Get With the Guidelines Heart Failure; MEESSI-AHF = Multiple Estimation of risk based on the Emergency department Spanish Score In patients with AHF; OHFRS = Ottawa Heart Failure Risk Scale; STRATIFY = Improving Heart Failure Risk Stratification in the ED * Internal validation was performed using bootstrapping. † 10 predictor variables for the 30-day score and 11 for the one-year score. ‡ Serious complications include myocardial infarction, mechanical ventilation, resuscitation, ventricular fibrillation and reperfusion therapy during the index hospitalisation. § External validation was performed for the 30-day mortality prediction as the EHMRG was compared to the MEESSI-AHF risk score. ¶ The 14-/30-day endpoint includes 30-day all-cause mortality, admission to a critical care unit or readmission to the ED within 14 days, myocardial infarction or a major cardiac procedure such as coronary artery bypass grafting within 14 days of the initial ED presentation. ‖ The combined 30-day endpoint includes acute coronary syndrome, coronary revascularisation, emergent dialysis, intubation, mechanical cardiac support, cardiopulmonary resuscitation and death within 30-days of admission.

Figure 3: Overview of predictor variables included in selected risk scores.* Marked parameters of ELAN-HF were collected at hospital discharge.‡ The MEESSI-AHF score is also calculable with fewer than 13 variablesFull names of risk scores: ADHERE = Acute Decompensated Heart Failure National Registry; ADHF/NT-proBNP = Acute Decompensated Heart Failure/N-terminal pro-B-type natriuretic peptide; AHFI = Acute Heart Failure Index; EFFECT = Enhanced Feedback For Effective Cardiac Treatment; EHMRG = Emergency Heart Failure Mortality Risk Grade; ELAN-HF = European coLlaboration on Acute decompeNsated Heart Failure; GWTG-HF = Get With the Guidelines Heart Failure; MEESSI-AHF = Multiple Estimation of risk based on the Emergency department Spanish Score In patients with AHF; OHFRS = Ottawa Heart Failure Risk Scale; STRATIFY = Improving Heart Failure Risk Stratification in the EDACEI = angiotensin converting-enzyme inhibitor; ACS = acute coronary syndrome; BMI = body mass index; BP = blood pressure; BNP = B-type natriuretic peptide; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram. ED = emergency department; eGFR = estimated glomerular filtration rate; EMS = emergency medical service; HR = heart rate; LVEF = left ventricular ejection fraction = NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty

		EFFECT	ADHERE	AHFI	GWTG-HF	EHMRG	OHFRS	ADHF/NT-proBNP	ELAN-HF	STRATIFY	MEESSI-AHF	Total number of risk scores considering this variable
Demographics	Age	X			X	X			X	X	X	**6**
	Gender			X								1
	Race				X							1
	Transport by EMS					X						1
Clinical parameters	Systolic BP	X	X	X	X	X		X	X		X	**8**
	Diastolic BP									X		1
	HR			X	X	X	X					**4**
	HR during 3-minutes walking test											1
	Respiratory rate	X		X						X	X	**4**
	Oxygen saturation					X	X			X	X	**4**
	Temperature			X								1
	BMI									X		1
	Peripheral oedema								X			1
	NYHA class								*		X	2
	Low output symptoms										X	1
	Episode associated with ACS										X	1
	Need for supplemental O_2									X		1
	Barthel-Index Score											1
Prior history	Diabetes mellitus			X								1
	CAD			X								1
	Angina pectoris			X								1
	Cerebrovascular disease	X					X					2
	Dementia	X										1
	COPD	X			X			X				**3**
	Lung disease			X								1
	Hepatic cirrhosis	X										1
	Cancer	X				X						2
	Dialysis									X		1
	Prior intubation											1
	PTCA			X								1
	Outpatient ACEI									X		1
	Outpatient metolazone					X						1
Laboratory parameters	Hemoglobin	X						X				2
	White blood cell count			X								1
	eGFR							X				1
	Creatinine		X	X		X					X	**4**
	Potassium			X		X					X	3
	Sodium	X		X	X			X	X	X		**6**
	Blood urea nitrogen	X	X	X	X		X		*	X		**7**
	Glucose level			X								1
	Aterial pH			X								1
	Serum CO_2						X					1
Cardiac biomarkers	Cardiac troponin					X	X			X	X	**4**
	BNP/NT-proBNP						X	X	*	X	X	**5**
	Redution in BNP/NT-proBNP								*			1
Instrument based diagnostic	*ECG* : Signs of MI			X								1
	ECG : Ischemic changes			X			X					2
	ECG : QRS duration									X		1
	ECG: Hypertrophy of left ventricle										X	1
	Chest X-ray : Pulmonary congestion			X								1
	Chest X-ray: Pleural effusion			X								1
	Echo: LVEF											1
	Echo: Tricuspid regurgitation											1
	Total number of variables:	**11**	**3**	**21**	**7**	**10**	**10**	**8**	**8**	**13**	**13‡**	
	n objectively collected	11	3	17	7	10	9	6	6	12	8	
	n subjectively collected	0	0	4	0	0	1	2	2	1	5	
	n fast and routinely available (X)	11	3	21	7	10	8	6	4	13	12	

Risk scores including cardiac biomarkers as predictor variables

Emergency Heart Failure Mortality Risk Grade (EHMRG)

The EHMRG was derived from administrative data obtained from patients presenting with AHF to Canadian emergency departments [22]. A logistic regression model for seven-day mortality was constructed to identify 10 predictor variables which are objectively collectable and readily available at emergency department presentation. The EHMRG consists of vital signs, clinical features and laboratory parameters, including cTn as a cardiac biomarker (table 1, fig. 3). Goodness of fit tests show an excellent discrimination of the EHMRG in both the derivation (c-statistic, 0.806) and internal validation cohorts (c-statistic, 0.804).

Recently the EHMRG was externally validated and refined using administrative data obtained in another Canadian state. External validation showed an acceptable discrimination for seven-day mortality of the EHMRG score (c-statistic, 0.732) and its variables (c-statistic, 0.747). However, calibration of the prediction rule in the external validation cohort was not reported [122]. Interestingly, the authors assessed several scenarios to improve the model´s discrimination by introducing new variables and removing existing ones. The addition of natriuretic peptides improved the performance of the original prediction rule, as indicated by a significantly higher discrimination (c-statistic, EHMRG variables 0.747 vs 0.760; p = 0.007) and a net reclassification index of 0.268 (p <0.0001) for predicting seven-day mortality. In addition, the removal of cTn resulted in an impaired performance compared to the original EHMRG variables (c-statistic decrease from 0.747 to 0.740, p = 0.025; net reclassification index −0.269, p <0.0001). Furthermore, the EHMRG showed an acceptable discrimination when externally validated for the prediction of 30-day mortality in Spain (c-statistic, 0.741) [7] and Switzerland (c-statistic, 0.765) [8]. Strengths of the EHMRG include development in emergency department patients, use of routinely available variables and an external validation. Unfortunately, palliative patients are excluded from the EHMRG and data were not prospectively recorded.

Ottawa Heart Failure Risk Scale (OHFRS)

The OHFRS was developed in a small, prospective multicentre study including AHF patients presenting to the emergency department [23]. A logistic regression analysis was used to predict a composite endpoint including 30-day all-cause mortality and other adverse events such as admission to a critical care unit within 14 days of the index emergency department presentation. The 10 predictor variables included in the final risk scale were history variables, vital signs on admission and biomarkers such as cTn and NT-proBNP (table 1, fig. 3). Goodness of fit tests showed an acceptable discrimination (c-statistic, 0.77) and calibration (Hosmer-Lemeshow p = 0.75). Clinical validation was performed to explore the potential impact of the OHFRS on clinical practice [123]. This analysis showed that compared to clinical practice, using an admission threshold of an OHFRS >1 would have increased sensitivity for adverse event prediction in AHF patients (71.8% vs 91.8%) but would also have increased admission rates (57.2% vs 77.6%).

Despite development in the emergency department, an acceptable discrimination and a clinical validation, the OHFRS is limited by some disadvantages. In comparison to other described AHF risk scores, a uniform application in the emergency department seems unlikely due to many exclusion criteria (e.g., oxygen saturation at admission <85%, exclusion of inhabitants of a nursing home) and use of a three-minute walking test as a predictor variable, even though only few patients are physically capable of completing this task during an episode of AHF.

European coLlaboration on Acute decompeNsated Heart Failure (ELAN) score

The ELAN-HF score was designed for 180-day discharge prognostication in patients admitted for AHF. It used data assembled from prospective European cohort studies [116]. Unlike the other HF risk scores, the ELAN score includes predictor variables collected either at presentation or discharge (table 1, fig. 3). Therefore, it is not intended to provide early risk stratification in the emergency department, but rather is to be used for post-discharge risk stratification. In addition, some of the included predictor variables, such as the patients´ NYHA class, depend on the subjective judgement of the attending physician. Natriuretic peptides are incorporated twice, as NT-proBNP discharge levels, as well as NT-proBNP percentage change during hospitalisation. The model was externally validated in a small, single centre European randomised trial [116]. However, as no measures of discrimination or calibration are given, further studies are required for a comprehensive evaluation of the ELAN-HF score.

Improving Heart Failure Risk Stratification in the emergency department (STRATIFY) decision tool

The STRATIFY scale was developed in a prospective, multicentre study to identify AHF patients at a low risk of adverse events such as death or myocardial infarction within 30 days of emergency department presentation [117]. Thirteen predictor variables readily available at emergency department presentation, including cTnI and NTproBNP, were identified, and a nomogram was developed to assist estimation of the 30-day risk of adverse events. The overall calibration of the STRATIFY decision tool was 0.68 and results were confirmed by internal validation using bootstrapping (table 1, fig. 3). Advantages of the STATIFY decision tool include development in a prospective, multicentre study and the use of variables readily available within a short time after emergency department presentation. However, in comparison to other risk scores, the discrimination is rather poor, the scale was derived from a small dataset, and no external validation was performed.

Multiple Estimation of risk based on the Emergency department Spanish Score In patients with AHF (MEESSI-AHF)

The MEESSI-AHF risk score was derived to predict 30-day mortality in a large, prospective multicentre study of patients presenting with AHF to Spanish emergency departments [7]. The score consists of 13 variables which are partially subjectively collectable (symptoms of low output, NYHA class at admission) and partially objectively

collectable (cTn, natriuretic peptide level at admission) (table 1, fig. 3). A time-dependent internal validation was performed, confirming excellent discrimination (c-statistic, 0.828) and calibration (Hosmer-Lemeshow p = 0.122). Compared to the EHMRG, the MEESSI score shows a significantly better discrimination for 30-day mortality (c-statistic, 0.83 vs 0.75, p <0.001). In addition, external validation in a different country confirmed after recalibration an excellent discrimination (c-statistic, 0.80) and calibration (Hosmer-Lemeshow p = 0.23) after it was recalibrated by a simple adjustment of the intercept [8]. Major advantages of the MEESSI score include development in the emergency department in a large, prospective multicentre study. Furthermore, several reduced MEESSI models, calculable with fewer than 13 variables and still exhibiting good discrimination (c-statistic, 0.784 to 0.829), are available. In addition, its calculation is simplified by an already established online calculator, and external validation in a different country has been performed. Further studies to investigate the actual impact of the MEESSI-AHF risk score on clinical decision-making in the emergency department and healthcare costs are warranted.

Outlook

Future studies should focus on three aspects. First, gaining a better understanding of the pathophysiology of those biomarkers strongly associated with mortality in AHF, such as cTn, adrenomedullin, sST2 and GDF-15. This is a prerequisite for the identification and evaluation of targeted interventions aiming to mitigate the detrimental causal factors. Second, combinations of the most promising and best-validated risk score, currently the MEESSI score, with some of the novel biomarkers should be tested in large studies for possible incremental value. Third, scores are often time-consuming and burdensome to calculate. IT-based solutions need to integrate the calculation and display of these scores and the quantified risk within electronic healthcare records.

Conclusions

Early risk prediction plays a key role in the subsequent management of patients presenting with AHF, a heterogeneous syndrome associated with still unacceptably high rates of mortality and morbidity. In order to optimise risk prediction and the intensity of management, clinicians should be aware of the following concepts.

1. Biomarkers have improved the understanding of heart failure pathophysiology and can therefore contribute to adjusting the intensity of management in AHF.
2. Among the large variety of biomarkers currently available, natriuretic peptides and cTn seem the most promising in this indication.
3. However, as a heterogeneous syndrome with various phenotypes, a biomarker approach alone is insufficient for accurate risk prediction in AHF. Heart failure risk scores combining several predictor variables are more promising for helping clinicians to make decisions and customise the intensity of management.
4. Among the described risk scores, those combining demographics and clinical parameters with biomarkers in a model with fast and routinely available variables seem the most promising tools for early and accurate risk stratification in the emergency department.
5. For early risk stratification of patients with AHF in the emergency department, scores that were specifically derived and validated in emergency department cohorts should be used preferentially.
6. Besides biomarkers, age, systolic blood pressure, respiratory rate, oxygen saturation, creatinine, electrolytes and blood urea nitrogen are the most commonly used predictor variables in the described risk scores (fig. 3).
7. Among selected models, the MEESSI-AHF risk score currently seems to be the most promising tool for AHF risk prediction. This score was developed in the emergency department in a large derivation cohort, consists of fast and routinely available variables, exhibits highly accurate risk prediction and was externally validated in a different country from where it was developed.

Potential competing interests

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