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Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohort on Acute Heart Failure (MOCA) study

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ABSTRACT

Aim: This study aims to evaluate the incremental value of plasma biomarkers to traditional clinical variables for risk stratification of 30-day and one-year mortality in acutely decompensated heart failure (ADHF).
Methods and results: Through an international collaborative network, individual patient data on 5306 patients hospitalized for ADHF were collected. The all-cause mortality rate was 11.7% at 30 days and 32.9% at one year. The clinical prediction model (age, gender, blood pressure on admission, estimated glomerular filtration rate <60 mL/min/1.73 m^2, sodium and hemoglobin levels, and heart rate) had a c-statistic of 0.74 for 30-day mortality and 0.73 for one-year mortality. Several biomarkers measured at presentation improved risk stratification when added to the clinical model. At 30 days, the net reclassification improvement (NRI) was 28.7% for mid-regional adrenomedullin (MR-proADM; $p<0.001$) and 25.5% for soluble (s)ST2 ($p<0.001$). At one year, sST2 (NRI 10.3%), MR-proADM (NRI 9.1%), amino-terminal pro-B-type natriuretic peptide (NT-proBNP; NRI 9.1%), mid-regional proatrial natriuretic peptide (MR-proANP; NRI 7.4%), B-type natriuretic peptide (NRI 5.5%) and C-reactive protein (CRP; NRI 5.3%) reclassified patients with ADHF ($p<0.05$ for all). CRP also markedly improved risk stratification of patients with ADHF as a dual biomarker combination with MR-proADM (NRI 36.8% [$p<0.001$] for death at 30 days) or with sST2 (NRI 20.3%; [$p<0.001$] for one-year mortality).

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Conclusion: In this study, biomarkers provided incremental value for risk stratification of ADHF patients. Biomarkers such as sST2, MR-proADM, natriuretic peptides and CRP, reflecting different pathophysiologic pathways, add prognostic value to clinical risk factors for predicting both short-term and one-year mortality in ADHF.

1. Introduction

The care of patients with acutely decompensated heart failure (ADHF) is complex, involving clinical assessment and risk prediction as integral parts of daily clinical practice. Indeed, ADHF is associated with a very high mortality rate, and clinical risk stratification after hospitalization for ADHF remains a relevant challenge, in order to best identify those patients likely to encounter serious complications, and to potentially better allocate resources in order to mitigate this considerable risk. Several demographic and clinical factors, co-morbidities, and biochemical variables are associated with short- or mid-term mortality in ADHF, including measures of renal function and blood pressure as well as other relevant predictors [1–6]. In recent years, a growing focus has been given to novel blood-based biomarkers for their ability to risk stratify patients with ADHF, and with this, an abundance of different assays has emerged, many reportedly associated with increased mortality in heart failure [7,8].

Over the past several years, B-type natriuretic peptide (BNP) and its N-terminal precursor fragment (NT-proBNP) have become the biomarker "gold standards" for predicting risk, with studies demonstrating value of either test for risk stratification of ADHF [5,9–12]. Importantly, the value of natriuretic peptides as well as other novel markers has however been studied with variable depth. Indeed, the value of any biomarker for risk prediction in ADHF, analyzed in an unbiased and thorough manner, should clearly depend on the degree to which it adds to the prognostic information provided by standard risk factors and other available markers [13–15].

Accordingly, the purpose of this study was to equitably assess the individual and added value of various novel biomarkers to traditional clinical variables and to each other for risk stratification of patients with ADHF, using data from a large, collaborative global, multicenter patient cohort. Furthermore, we used the most recent and appropriate statistical tools, including reclassification and discrimination analyses.

2. Material and methods

The Multinational Observational Cohort on Acute heart failure (MOCA) study was performed in accordance with the ethical guidelines of the declaration of Helsinki and all patients provided written consent to the individual studies. In the MOCA database, individual patient data was coded without possibility of person identification. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.1. Study cohort

The study population comprised patients hospitalized for ADHF with at least one biomarker measured at presentation. Data and biomarker results were obtained either from participants enrolled in earlier studies and registries (n = 4323) [6,10,16–22] or from previously unpublished cohorts (n = 983). Patients presenting in emergency room (ED) or in cardiac care unit (CCU) with ADHF defined using standard criteria [23,24] and requiring hospitalization were eligible. Individual patients were included in the analysis if clinical parameters and biomarker data were available from presentation. In addition, mortality data at one year of follow-up was required for inclusion. Patients in this analysis were consecutively enrolled at the different sites, and all had ADHF confirmed for inclusion.

Twelve cohorts from 11 countries (Austria [n = 137], Czech Republic [n = 1917], Finland [n = 620], France [n = 199], Netherlands [n = 367], Italy [n = 213], Japan [n = 144], Spain [n = 107], Switzerland [n = 609], Tunisia [n = 187], and the United States [n = 597 for Cleveland, n = 209 for Boston]) provided individual patient data that were assembled for the study database, resulting in a large, global, and multicenter ADHF cohort.

2.2. Biomarker analysis

The database included available measurements of several plasma biomarkers reflecting different pathophysiological pathways in heart failure: cardiac stretch (BNP [various vendors], NT-proBNP [Roche Diagnostics], mid regional pro-atrial natriuretic peptide [MR-proANP, Thermo-Fisher Diagnostics]), vascular stress (mid-regional pro-adrenomedullin [MR-proADM, Thermo-Fisher Diagnostics]), inflammation (C-reactive protein [CRP, various vendors]), myocardial damage and remodeling (soluble [s]ST2, last generation of Presage ST2, Critical Diagnostics), and necrosis (Troponin [cTn] I, various vendors; cTnT, Roche Diagnostics). Biomarkers were either measured on admission by the local laboratory (at least one natriuretic peptide, CRP and one troponin) or in plasma generally stored at −80° (natriuretic peptides and all MR-proANP, MR-proADM and sST2).

2.3. Statistical methods and biomarker analysis

Clinical variables known to affect prognosis (age, gender, systolic [SBP] or diastolic [DBP] blood pressure, heart rate, impaired renal function [glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 estimated by the MDRD equation], sodium, and hemoglobin levels) were used to build a baseline model for mortality risk prediction in ADHF ("clinical model"), adding also a variable accounting for any difference between centers. As the increase in cardiovascular morbidity and mortality associated with renal dysfunction occurs mostly at eGFR-levels < 60 mL/min/1.73 m^2, this was selected as cut-off [25]. Gender, co-morbidities, impaired renal function and hyponatremia

Table 1
Characteristics of the study population (n = 5306).

	Value
Variables	
Age (years)	75 (65–81)
Male gender n = (%)	3002 (56.6)
Biological and hemodynamic status at admission	
RR (cpm)	23 (18–28)
SBP (mm Hg)	138 (117–160)
DBP (mm Hg)	80 (68–91)
Heart rate (bpm)	88 (73–106)
LVEF (%)	40 (26–55)
Co-morbidities n = (%)	
Diabetes mellitus	1832 (37.6)
COPD	807 (16.6)
Hypertension	3386 (68.1)
Chronic HF	2289 (47.4)
Atrial fibrillation	1292 (28.6)
Coronary artery disease	2814 (55.6)
Medication at admission n = (%)	
β-Blocker	2035 (50)
ACE inhibitor	1601 (46)
ARB	702 (20)
Diuretics	2016 (55)
Nitrates	980 (26)
Low dose aspirin	1495 (42)
Statins	922 (30)
Causes of ADHF (%)	
Acute coronary syndrome	36
Atrial fibrillation	12
Infection	23
Non-compliance	7
Not specified	22
Outcome n = (%)	
30-day mortality	611 (11.7)
One-year mortality	1745 (32.9)

Data given as mean numbers (n =), percentages (%) or median with interquartile range. NYHA = New York Heart Association, RR = respiratory rate, cpm = counts per minute, SBP = systolic blood pressure, DBP = diastolic blood pressure, bpm = beats per minute, LVEF = left ventricular ejection fraction, COPD = chronic obstructive pulmonary disease, HF = heart failure, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, eGFR = estimated glomerular filtration rate by modification of diet in renal disease formula.