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Research paper

Novel and established biomarkers to complement risk scores in patients with acute decompensated heart failure – a pilot study

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ABSTRACT

Study Objective: There are several risk scores for mortality in patients with acute decompensated heart failure (ADHF) such as the European Collaboration on Acute Decompensated Heart Failure Score (ELAN-HF Score), the ADHF/NT-proBNP-Score or A2B-Score (age, anemia, BNP). The aim of this study was to evaluate the predictive value of such risk scores with and without addition of novel cardiorenal biomarkers.
Design & Setting: Single-center, exploratory prospective cohort study at the University Hospital Heart Centre Brandenburg.
Participants: Forty-four adult patients hospitalized for ADHF.
Interventions: Measurement of established and novel biomarkers at hospital admission including N-terminal-pro brain natriuretic peptide (NT-pro-BNP), troponin T, creatinine, cystatin C, soluble suppression of tumorigenicity 2 (sST2), Neprilysin, Dickkopf-3 (DKK3), interleukin-6 (IL-6), growth differentiation factor-15 (GDF-15), Galectin-3, Progranulin and urine neutrophil gelatinase-associated lipocalin (uNGAL).
Main Outcome Measures: Analysis of predictive indices of ELAN-HF, ADHF/NT-proBNP and A2B-Scores for 90-day mortality with and without adding biomarkers. AUC <0.8 was considered as fair, ≥ 0.8 as good and > 0.9 as excellent predictive value.
Results: Median age was 78.0 (25th–75th percentiles 69.3–83.8) years, 50 % (22/44) were female. Twelve patients (27.3 %) died within 90 days after discharge. All three risk scores were higher in non-survivors and showed fair AUC for 90-day mortality (ELAN-HF: 0.792 [0.639–0.901], $p = 0.003$; ADHF-NT-proBNP score: 0.749 [0.559–0.938], $p = 0.012$; A2B score: 0.734 [0.541–0.927], $p = 0.017$). Adding troponin T, cystatin C-based estimated glomerular filtration rate (eGFR) or uNGAL to risk scores was associated with an area under the curve (AUC) >0.80 for all models. Combination of troponin T, cystatin C-based eGFR and uNGAL increased risk scores to AUC >0.91.
Conclusion: These findings imply that further evaluation of the addition of a panel of cardiorenal biomarkers to ADHF risk scores is warranted.

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1. Introduction

Episodes of worsening symptoms and signs, e.g., dyspnea, peripheral edema and physical weakness characterize the clinical course of patients with acute decompensated heart failure [1]. Acute decompensated heart failure (ADHF) is one of the leading causes for hospital admissions [2,3]. Mortality in patients aged 65 years or more ranges from 25 % to 40 % one year after an episode of ADHF [4–6]. Cardiorenal syndrome (CRS) further increases the risk of all-cause and cardiovascular death [7,8]. This is reflected in the use of established cardiac and renal function biomarkers in risk scores for mortality in patients with ADHF.

Since NT-proBNP is a common diagnostic biomarker in ADHF, the Acute decompensated heart failure/n-terminal-pro brain natriuretic peptide (ADHF/NT-proBNP) (ADHF/NT-proBNP) Score is a well applicable risk model. Scrutinio et al. analyzed the effect of adding NT-proBNP to the reference model on risk classification and developed the ADHF/NT-proBNP Score for the prediction of 1-year mortality in hospitalized patients with advanced decompensated heart failure [9,10]. In 2015, the score was reevaluated for short-term mortality and showed an area under the curve (AUC) of 0.82 for the prediction of 90-day mortality [11]. The European Collaboration on Acute Decompensated Heart Failure Score (ELAN-HF) Score for mortality within 180-days after discharge was derived from a large prospective cohort study of patients hospitalized for ADHF [12,13]. The products were summed and prospectively applied to each patient in both the derivation cohort as well as in the validation cohort to provide individual estimates of mortality within 180-days [12,13]. Numerous studies have demonstrated that a relative NT-proBNP reduction at discharge for ADHF is a significant predictor of readmissions and mortality [12,14,15].

In 2019, Nakada et al. developed the simple, easy to determine Age, anemia, brain natriuretic peptide (A2B) Score for patients with ADHF to predict 2-year mortality after discharge [16]. The A2B Score divided patients into four risk groups [16]. Recently, the score was validated in another Japanese cohort [17]. The A2B score seems to be useful even when brain natriuretic peptide was substituted with NT-proBNP [17].

In recent years, various risk scores have been developed for patients with ADHF. So far, none is considerably better than the others and only a few scores are generally recognized and clinically applicable. Thus, one of the remaining challenges for improved treatment of patients with ADHF is the refinement of risk scores. Novel cardiorenal biomarkers show potential in identifying acute kidney injury and some as prognostic markers [18,19]. The aim of this pilot study was to investigate whether novel cardiorenal biomarkers including NGAL and Neprilysin or established parameters such as troponin T improve the predictive values of validated risk scores such as ELAN-HF score, ADHF/NT-proBNP score and A2B score for 90-day mortality.

2. Materials and methods

2.1. Study population and design

In this single-center, prospective pilot study, we enrolled 50 adult patients admitted to the University Hospital Heart Centre Brandenburg for ADHF between October 2019 and October 2021. In 44 patients complete biomarker measurement was available at the time of hospital admission or the day thereafter. Inclusion criteria were the presence of ADHF, the need for intravenous diuretic therapy and a written informed consent. Exclusion criterion was incomplete data regarding the biomarker results. The study was approved by the local ethics committee (E-01-20,190,603, date of approval 18.09.2019). All patients included in the study agreed to participate in the study by providing written informed consent.

2.2. Data collection and definitions

Medical records were reviewed for demographics (age, gender, blood pressure, medication), comorbidities, e.g. arterial hypertension, chronic kidney disease (CKD), diabetes, atrial fibrillation, echocardiographic data, e.g. left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), tricuspid annular plane systolic excursion (TAPSE) and routine laboratory data, e.g. NT-proBNP, troponin T and serum creatinine as well as length of stay in hospital. The creatinine or cystatin C-based eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. [20]. Diuretic non-responsiveness was defined as an increase in diuretic dose within three days. Follow-up was performed 90-days after discharge by telephone visits for rehospitalization and all-cause mortality within 90-days. The primary endpoint of this exploratory study was the absolute difference and 95 % confidence interval of AUC of each risk score with and without addition of novel cardiorenal biomarkers to predict all cause 90-day mortality.

2.3. Risk scores for mortality

The ADHF/NT-proBNP Score is a risk score for the prediction of 1-year mortality using the following parameters: Age, LVEF, creatinine-based eGFR, presence of chronic obstructive pulmonary disease (COPD), systolic blood pressure (SBP), serum sodium, hemoglobin, NT-proBNP, presence of moderate or severe tricuspid regurgitation and previous hospitalization for heart failure $\leq$6 month prior the index admission [10] (**Table Appendix A1**). Score-based prediction rule was developed from a logistic regression model by using an integer-based scoring system. The variables selected in the multivariable NT-proBNP algorithm were used to build the risk score; continuous variables were replaced by categorized versions with well-defined thresholds [10].

The ELAN-HF Score uses the following parameters to predict 180-day mortality after discharge: NT-proBNP levels at discharge, dynamics of NT-proBNP levels during hospitalization, age $\geq$ 75 years, peripheral edema, systolic blood pressure (SBP) $\leq$115 mmHg, hyponatremia on admission, serum urea at discharge $\geq$15 mmol/l and New York Helath Association (NYHA) class $\geq$III at discharge [12] (**Table Appendix A1**). To calculate the ELAN-HF score, each variable in the multivariate model was multiplied by its regression coefficient.

The A2B-Score is a simple risk score to predict 2-year mortality of patients with ADHF [16]. It uses the following parameters: age, anemia and BNP and groups the patients into four risk categories (**Table Appendix A1**).

2.4. Biomarkers analyses

Immediately after collection, blood samples were transferred to EDTA or serum tubes and centrifuged at 4 °C and 3500 rpm for 15 min. The supernatant plasma or serum, respectively, was then aliquoted into three 1000 µl portions per sample in 2 ml tubes, and frozen at −80 °C until further processing. Established serum biomarkers (NT-proBNP, troponin T, creatinine, C-reactive protein (CRP), electrolytes, glucose levels, bilirubin, hemoglobin, urea) were measured at admission by the in-house clinical laboratory as previously described [21]. Novel cardiorenal biomarkers were measured in urine including neutrophil gelatinase-associated lipocalin (uNGAL) (Human Lipocalin-2/NGAL ELISA, BioVendor, Eching, Germany), Neprilysin (Human Neprilysin DuoSet ELISA, R&D Systems Minneapolis, USA), Dickkopf-3 (DKK3) (Human DKK3 DuoSet ELISA, R&D Systems Minneapolis, USA) and Interleukin-6 (IL-6) (ECLIA, Roche Diagnostics Mannheim, Germany) and in serum, including cystatin C (immunoturbidimetric assay, Roche Diagnostics Mannheim, Germany) NGAL, Neprilysin (Human Neprilysin DuoSet ELISA, R&D Systems Minneapolis, USA), Growth Differentiation Factor 15 (GDF-15) (Human GDF-15 DuoSet ELISA, R&D Systems Minneapolis, USA), soluble Suppression of Tumorgenicity 2 (sST2) (Human sST2/IL-33R DuoSet ELISA R&D Systems, Minneapolis, USA), Galectin 3 (Human Galectin 3 DuoSet ELISA, R&D Systems Minneapolis, USA) and Progranulin (Human Progranulin DuoSet ELISA, R&D Systems

Minneapolis, USA). Enzyme linked immunosorbent assays (ELISA) were performed in accordance with instructions supplied by the manufacturer. In short, serum samples and standard proteins were added to the multiwell plate coated with the respective capture antibody and incubated for 2 h. Plates were then washed using washing buffer (Tween 20, Sigma Aldrich, St. Louis, MO, USA) and phosphate buffered saline solutions. In the next step, a biotin-labelled antibody was added to each well and incubated for another 2 h. ELISA plates were washed another time, and a streptavidin-horseradish-peroxidase solution was added. After adding tetramethylbenzidine (Sigma Aldrich, St. Louis, MO, USA), a color reaction was achieved. Optical density was measured at 450 nm on an ELISA plate reader (iMark Microplate Absorbance Reader, Bio-Rad Laboratories, Vienna, Austria or TriStar^2 S LB 942, Berthold Technologies, Germany).

2.5. Statistical analysis

The sample size was based on our previous publication [21]. In this study, 50 patients were required to investigate a correlation between Soluble Suppression of Tumorigenicity 2 (sST2) and the fluid status using bivariate non-normal distributed correlation analysis (Spearman correlation coefficient: > 0.5, α: 0.05, power: 0.8).

Variables are described using medians and 25th to 75th percentiles for continuous measures, and proportions for categorical measures. Comparisons between groups were performed using chi-square or Fisher's exact test for categorical variables, and Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate. We assessed the discriminative ability and performance of candidate biomarkers and risk scores to predict 90-day mortality in a stepwise approach: First, the AUC of the receiver operator characteristics (ROC) based on biomarker concentrations measured at admission was calculated separately for each marker. The predictive performance of the risk assessment models is reported as AUC with a 95 % confidence interval (CI). We defined an AUC <0.8 as fair, ≥ 0.8 as good and > 0.9 as excellent predictive value. Thereafter, we sequentially included each biomarker separately into the risk model to exclude interaction. In the final step, the biomarkers with AUC >0.70 were all together included into the risk model. To compare the AUC-ROCs, obtained with and without adding biomarkers, the Hanley/McNeil method was used. An absolute difference of AUC of each risk score with and without addition of novel cardiorenal biomarkers to predict all cause 90-day mortality of >0.1 AUC units was considered to be relevant. Statistical analysis was performed using IBM SPSS Statistics software version 28.0 including R 4.0 extension (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

Forty-four patients with ADHF and full biomarker data were included in the study. The median age of patients was 78.0 (25th–75th [69.3–83.8]) years, 50 % (22/44) were female. Most patients presented with arterial hypertension (86.3 %, 38/44), chronic kidney disease (63.6 %, 28/44) and atrial fibrillation (72.7 %, 32/44) (Table 1). The median length of stay in hospital was 8.5 days (6.0–12.3). Out of the forty-four patients, twelve patients (27.3 %) died during the 90-days follow-up period. Median survival time from admission of those who died was 48.0 days (12.3–65.3) (Table 2). (See Table 1.)

3.2. Patient characteristics in survivors and non-survivors

Patients who did not survive 90-days after index hospital stay were older (83.5 years [73.3–88.8] vs. 76.0 years [69.0–82.0], $p = 0.034$), more often female (75.0 % vs. 40.6 %, $p = 0.042$) and presented more frequently with chronic kidney disease (100 % vs. 50 %, $p < 0.001$) but less frequently with arterial hypertension (66.7 % vs. 93.8 %, $p = 0.020$) compared to patients who survived (Table 1). Diastolic blood pressure at admission was 89.0 mmHg (73.0–97.0) in survivors compared to 60.5 mmHg (58.3–85.0) in those who died within 90-days ($p = 0.007$). Echocardiographic parameters and medication were similar in both

Table 1
Baseline characteristics.

	Overall (n = 44)	Non-Survivors (n = 12)	Survivors (n = 32)	p-value
Demographics				
Age, years	78.0 (69.3–83.8)	83.5 (73.3–88.8)	76.0 (69.0–82.0)	0.034
Female, n (%)	22 (50.0 %)	9 (75.0 %)	13 (40.6 %)	0.042
Body weight, kg	84.7 (70.8–107.3)	87.9 (65.5–115.5)	83.0 (73.0–99.2)	0.884
SBP, mmHg	135.0 (123.0–147.0)	129.5 (108.3–140.3)	136.0 (123–150)	0.242
DBP, mmHg	83.0 (66.0–92.0)	60.5 (58.3–85.0)	89.0 (73.0–97.0)	0.007
Heart rate, bpm	80.0 (71.8–95.0)	76.0 (69.0–90.0)	80.0 (70.0–98.0)	0.494
Risk Score				
ELAN-HF, points	4.0 (3.0–7.0)	6.5 (5.0–8.0)	4.0 (3.0–5.0)	0.002
ADHF/NT-proBNP, points	39.7 (22.7–57.4)	55.1 (39.7–69.3)	30.7 (19.6–46.3)	0.010
A2B, points	4.0 (3.0–5.0)	5.0 (4.0–5.0)	4.0 (3.0–4.0)	0.017
Comorbidities				
Arterial hypertension, n (%)	38 (86.3 %)	8 (66.7 %)	30 (93.8 %)	0.020
CKD, n (%)	28 (63.6 %)	12 (100.0 %)	16 (50.0 %)	<0.001
Atrial fibrillation, n (%)	32 (72.7 %)	8 (66.7 %)	24 (75.0 %)	0.580
Diabetes, n (%)	21 (47.7 %)	8 (66.7 %)	13 (40.6 %)	0.124
Congestive heart disease, n (%)	21 (47.7 %)	7 (58.3 %)	14 (43.8 %)	0.388
Previous MI, n (%)	12 (27.3 %)	4 (33.3 %)	8 (25.0 %)	0.580
Hypercholesterolemia, n (%)	16 (36.4 %)	4 (33.3 %)	12 (37.5 %)	0.798
Type of heart failure, n (%)				
right-sided heart failure	11 (25.0 %)	4 (33.3 %)	7 (21.9 %)	0.123
left-sided heart failure	14 (31.2 %)	1 (8.3 %)	13 (40.6 %)	
biventricular heart failure	19 (43.2 %)	7 (58.3 %)	12 (37.5 %)	
NYHA II, n (%)	27 (61.4 %)	7 (58.3 %)	20 (62.5 %)	0.995
NYHA III, n (%)	11 (25.0 %)	3 (25.0 %)	8 (25.0 %)	
Chronic obstructive pulmonary disease, n (%)	8 (18.2 %)	1 (8.3 %)	7 (21.9 %)	0.413
Peripheral vascular disease, n (%)	4 (9.1 %)	1 (8.3 %)	3 (9.4 %)	>0.99

Table 2
Patient outcomes.

	Overall (n = 44)	Non-Survivors (n = 12)	Survivors (n = 32)	p-value
Survival time, days (IQR)		48.0 (12.3–65.3)		
Hospital length of stay, days (IQR)	8.5 (6.0–12.3)	12.0 (7.0–17.3)	8.0 (6.0–11.8)	0.049
Diuretic non-responsiveness	23 (52.3 %)	5 (41.7 %)	18 (56.3 %)	0.524
Successful decongestion*	9 (20.5 %)	1 (8.3 %)	8 (25 %)	0.404

IQR = interquartile range; differences were calculated using chi-square or Fisher's exact test for categorical variables, and Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate.

* Defined as absence of signs of volume overload on day three (i.e., no more than trace edema, no pleural effusion, and no ascites).

groups (Table 1).

Patients who did not survive 90 days had a longer stay in hospital (12.0 days [7.0–17.3]) compared to patients who survived (8.0 days [6.0–11.8], p = 0.049) (Table 2). There were no differences in the absence of peripheral leg edema on day three of decongestive therapy between non-survivors and survivors. Also, diuretic non-responsiveness (increase in diuretic dose within three days) was comparable between both patient groups (non-survivors 41.7 % vs survivors 56.3 %, p = 0.524).

3.3. Biomarkers in survivors and non-survivors

Non-survivors had higher values of NT-proBNP, serum urea and troponin T and lower concentrations of hemoglobin compared to survivors at admission (Table 3). Among novel cardiorenal biomarkers, only concentrations of cystatin-C based eGFR were different in survivors and non-survivors (Table 3). Predictive value for mortality was an AUC <0.7 for all novel biomarkers assessed, except for cystatin-C based eGFR [AUC 0.770 (0.597–0.895)] and uNGAL [AUC 0.701 (0.511–0.851)] (Table 4).

3.4. Risk scores with and without addition of biomarkers

All three risk scores evaluated for 90-day mortality were higher in patients who did not survive compared to those who did (Table 1). Without addition of biomarkers, all risk scores assessed showed fair AUC-ROC for 90-day mortality (ELAN-HF: 0.792 [0.639–0.901], p = 0.003; ADHF-NT-proBNP score: 0.749 [0.559–0.938], p = 0.012; A2B score: 0.734 [0.541–0.927], p = 0.017) (Table 5).

Adding troponin T or cystatin C-based eGFR or uNGAL showed good AUC >0.80 for all models, however absolute difference of AUC compared to each risk score alone was not relevant (<0.1 AUC units). The combination of troponin T, cystatin C-based eGFR and uNGAL added to all risk scores showed excellent AUC >0.91 with relevant absolute difference of AUC-ROC compared to each risk score alone (Table 5, Fig. 1a-c). However, absolute AUC-ROC differences of novel versus standard risk models did not reach statistical significance.

4. Discussion

In this study, we assessed the predictive value of risk scores for mortality in patients with ADHF with and without the addition of novel and established cardiorenal biomarkers. All three risk scores were higher in non-survivors and showed fair predictive value for 90-day mortality. Adding troponin T or cystatin C-based eGFR or uNGAL to risk scores was associated with good predictive value for all models. The addition of troponin T, cystatin C-based eGFR and uNGAL to risk scores had an excellent predictive value.

Previous studies have validated the utility of risk scores such as ELAN-HF and ADHF/NT-proBNP in predicting outcomes in ADHF patients by relying on established markers like NT-proBNP and creatinine [10,12]. However, the limitations of these scores in accurately predicting outcomes, especially in high-risk populations, have prompted exploration into additional biomarkers [18,19]. Our study aligns with the growing body of evidence suggesting that novel biomarkers reflecting cardiac and renal stress may provide complementary information to existing scores [22–24]. The results of this pilot study provide preliminary evidence supporting the potential clinical utility of incorporating novel cardiorenal biomarkers into existing risk scores for patients with ADHF. We assessed the predictive value of risk scores with and without the addition of novel and established cardiorenal biomarkers. All three risk scores without addition of cardiorenal

Table 1
(cont.) Baseline characteristics.

	Overall (n = 44)	Non-Survivors (n = 12)	Survivors (n = 32)	p-value
Medication				
ACE-inhibitor, n (%)	17 (38.6 %)	3 (25.0 %)	14 (43.8 %)	0.255
AT-1 antagonists, n (%)	38 (86.4 %)	10 (83.3 %)	28 (87.5 %)	0.719
Betablocker, n (%)	38 (86.4 %)	10 (83.3 %)	28 (87.5 %)	0.719
Neprilysin-inhibitor, n (%)	4 (9.1 %)	2 (16.7 %)	2 (6.3 %)	0.267
Thiazide, n (%)	39 (88.6 %)	10 (83.3 %)	29 (90.6 %)	0.497
Loop diuretics, n (%)	39 (88.6 %)	10 (83.3 %)	29 (90.6 %)	0.497
Torasemide, mg	15.0 (10.0–30.0)	30.0 (15.0–40.0)	12.5 (10.0–22.5)	0.016
Allopurinol, n (%)	14 (31.8 %)	6 (50.0 %)	8 (25.0 %)	0.112
Metformin, n (%)	6 (13.7 %)	1 (8.3 %)	5 (15.6 %)	>0.99
Echocardiographic parameter				
LVEF, %	40.0 (30.0–52.8)	36.0 (25.0–52.5)	45.0 (30.0–53.5)	0.435
LVEDD, mm/m^2	50.0 (45.3–58.8)	45.5 (38.8–49.0)	54.0 (47.5–60.0)	0.045
RVD1, mm	39.0 (36.0–46.5)	39.0 (38.0–47.0)	39.0 (35.0–47.0)	0.592
TAPSE, mm	15.0 (13.0–20.0)	13.5 (8.8–18.5)	16.0 (13.0–20.0)	0.269
LA size, cm^2	26.3 (21.0–34.8)	27.1 (22.1–36.2)	25.0 (20.7–35.0)	0.462
RA size, cm^2	26.0 (20.5–30.4)	21.9 (15.2–32.3)	26.8 (20.8–30.7)	0.386

SBP = systolic blood pressure, DBP = diastolic blood pressure, CKD = chronic kidney disease, MI = myocardial infarction, NYHA = New York Health Association, LVEF = left ventricular ejection fraction, LVEDD = left ventricular enddiastolic diameter, RVD = right ventricular diameter, TAPSE = tricuspid annular plane systolic excursion, LA = left atrium, RA = right atrium; differences were calculated using chi-square or Fisher's exact test for categorical variables, and Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate.

Table 3
Laboratory values at admission.

	Overall (n = 44)	Non-Survivors (n = 12)	Survivors (n = 32)	p-value
Routine laboratory values at admission				
Serum creatinine, µmol/l	125.0 (98.0–156.3)	137.5 (126.8–218.5)	119.5 (88.0–150.5)	0.011
Serum creatine-based eGFR, ml/min	43.0 (32.5–59.5)	30.0 (18.5–40.3)	50.0 (36.0–71.0)	<0.001
Urea, mmol/l	11.2 (8.3–14.8)	14.7 (13.8–25.0)	9.1 (7.1–11.9)	<0.001
Hemoglobin, mmol/l	7.7 (6.7–8.5)	6.8 (6.5–7.6)	8.0 (7.4–8.6)	0.008
NT-proBNP, pg/ml	5256 (3331–9208)	7345 (5141–10,187)	4297 (2468–5991)	0.037
Troponin T, pg/ml	40.7 (23.3–60.5)	56.2 (41.1–83.9)	32.9 (18.1–52.8)	0.005
CRP, mg/l	5.7 (2.5–20.1)	5.9 (3.3–17.0)	4.4 (1.9–18.3)	0.254
Glucose levels, mmol/l	6.8 (5.5–9.5)	7.8 (5.3–14.3)	6.4 (5.5–8.2)	0.246
Sodium, mmol/l	139.1 (137.2–141.8)	139.0 (132.8–142.3)	138.7 (137.1–140.8)	0.880
Potassium, mmol/l	4.3 (4.1–4.7)	4.3 (4.0–5.1)	4.2 (4.0–4.6)	0.679
Bilirubin, micromol/l	13.3 (10.3–18.5)	12.8 (8.9–25.7)	15.5 (11.2–19.3)	0.648
Cardiorenal biomarkers at admission				
Cystatin C-based eGFR, ml/min	31.0 (21.0–53.0)	23.5 (14.5–31.3)	34.0 (25.5–58.5)	0.012
GDF-15 in Serum, ng/ml	2442.2 (1519.2–3704.2)	3069.7 (2097.2–4399.1)	2210.9 (1450.5–3827.5)	0.156
sST2 in Serum, ng/ml	35.2 (17.3–46.8)	29.2 (23.3–53.4)	34.4 (16.3–45.7)	0.359
Neprilysin in Serum, ng/ml	345.8 (147.4–829.6)	151.7 (103.4–849.6)	305.4 (157.4–663.9)	0.743
Galectin 3 in Serum, ng/ml	1.6 (0.6–4.3)	2.5 (0.8–4.1)	1.1 (0.4–4.1)	0.453
Progranulin in Serum, ng/ml	34.0 (29.2–44.2)	30.8 (29.4–49.0)	34.8 (26.5–44.4)	0.805
IL-6 in Urine, pg/ml	7.1 (3.4–20.1)	5.7 (2.9–18.6)	9.1 (3.6–21.2)	0.782
NGAL in Urine, ng/ml	3.4 (1.6–6.1)	7.6 (1.5–21.0)	2.4 (1.4–4.4)	0.100
Neprilysin in Urine, ng/ml	468.0 (180.4–775.1)	291.3 (51.7–510.3)	488.5 (229.6–818.4)	0.123
DKK3 in Urine, ng/ml	14.8 (8.9–18.6)	11.8 (7.5–18.9)	16.1 (10.2–19.3)	0.375

eGFR = estimated glomerular filtration rate, NT-proBNP = N-terminal-pro brain natriuretic peptide, CRP = C-reactive protein, GDF-15 = growth differentiation factor-15, sST2 = soluble suppression of tumorigenicity 2, IL-6 = interleukin-6, NGAL = neutrophil gelatinase-associated lipocalin, DKK3 = Dickkopf 3; differences were calculated using chi-square or Fisher's exact test for categorical variables, and Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate.

Table 4
ROC analysis for mortality.

Variable	AUC-ROC	95 % CI (lower limit)	95 % CI (upper limit)	SE	p-value
*ELAN-HF, points	0.792	0.639	0.901	0.082	0.003
*ADHF/NT-proBNP, points	0.749	0.559	0.938	0.097	0.012
*A2B, points	0.734	0.541	0.927	0.099	0.017
Routine biomarker not yet included in above mortality risk scores					
Troponin T	0.774	0.626	0.921	0.075	0.006
Novel cardiorenal biomarkers not included in established mortality risk scores					
Serum markers					
Cystatin C-based eGFR	0.770	0.597	0.895	0.084	0.001
GDF-15	0.648	0.468	0.829	0.092	0.107
sST2	0.597	0.411	0.783	0.095	0.306
Galectin 3	0.587	0.404	0.771	0.094	0.351
Neprilysin	0.536	0.323	0.749	0.109	0.740
Progranulin	0.473	0.266	0.679	0.105	0.105
Urine markers					
NGAL	0.701	0.511	0.851	0.037	0.113
Neprilysin	0.674	0.489	0.826	0.037	0.114
DKK3	0.594	0.382	0.806	0.108	0.386
IL-6	0.468	0.272	0.664	0.112	0.765

eGFR = estimated glomerular filtration rate, GDF-15 = growth differentiation factor-15, sST2 = soluble suppression of tumorigenicity 2, NGAL = neutrophil gelatinase-associated lipocalin, DKK3 = Dickkopf 3, IL-6 = interleukin-6.
* as published without troponin T and novel cardiorenal biomarkers.

biomarkers were higher in non-survivors but showed only fair predictive value for 90-day mortality. Adding troponin T or cystatin C-based eGFR or uNGAL to risk scores was associated with good predictive value (AUC >0.80) for all models. The addition of all three biomarkers - troponin T, cystatin C-based eGFR and uNGAL - to risk scores showed an excellent predictive value (AUC >0.91). These findings underscore the potential of these biomarkers to refine risk assessment.

Several studies have been published to stratify mortality risk for patients suffering from ADHF. Using data from a multicenter registry study, Fonarow et al. developed the Acute Decompensated Heart Failure National Registry (ADHERE) risk decision tree, which requires blood urea nitrogen (BUN), systolic blood pressure and serum creatinine [25]. Furthermore, in a multicenter prospective study by Peterson et al. the authors developed the "Get with the Guidelines Heart Failure Risk Score" providing an AUC of 0.75 for in-hospital mortality [26]. However, ADHERE risk tree and "Get with the Guidelines Heart Failure Risk Score" only predict the risk of in-hospital mortality. With regards to intermediate and long-term risk, the 2003 established Heart Failure Risk Scoring System by Lee et al. reached an AUC of 0.80 for the prediction of 30-day mortality and an AUC of 0.77 for the prediction of 1-year mortality [27]. Besides age, BUN, hyponatremia and hemoglobin, the score requires data on vital signs such as blood pressure and respiratory rates [27]. The score by Novack et al. is based on a minimal set of admission routine laboratory tests (including albumin, sodium, blood urea, uric acid, white blood cell counts) and basic patient data (age, sex, history of myocardial infarction, dyslipidemia, arterial hypertension, diabetes, history of bypass surgery, atrial fibrillation, COPD and dementia) [28]. For the prediction of 30-day mortality, the addition of five routine laboratory tests results to a set of clinical and demographic characteristics improved the AUC-ROC from 0.76 to 0.81 for 30-days and from 0.72 to 0.76 for one-year mortality prediction [28]. However, most scores rely on the use of routine laboratory parameters as well as extensive clinical parameter [10,12,26–28]. As to date, the predictive accuracy of the statistical models used for risk prediction of mortality had only an acceptable discriminatory value (AUC ≤0.81) [26–28].

Here, we explored three more established risk scores that use NT-proBNP or BNP as a parameter: ADHF/NT-proBNP Score, ELAN-HF Score and A2B Score. These risk scores do not include further cardiorenal biomarkers besides NT-proBNP and BNP, respectively, and only show fair predictive value as well. Troponin T, cystatin C and uNGAL reflect cardiac and renal function and we were able to show an AUC improvement after the addition. These findings may be explained at

Table 5
ROC analysis for mortality and risk scores with and without biomarkers included.

Score	ELAN-HF		ADHF/NT-proBNP		A2B	
	AUC	p-value*	AUC	p-value*	AUC	p-value*
	0.792	0.003	0.749	0.012	0.734	0.017
	(0.639-0.901)		(0.559–0.938)		(0.541–0.927)	
	SE 0.082		SE 0.097		SE 0.099	
	PLUS biomarker		PLUS biomarker		PLUS biomarker	
Troponin T	0.844	0.371	0.789	0.602	0.813	0.414
	(0.699–0.938)		(0.635–0.899)		(0.662–0.916)	
	SE 0.073		SE 0.086		SE 0.090	
Cystatin C-based eGFR	0.808	0.417	0.788	0.495	0.778	0.439
	(0.640–0.921)		(0.617–0.907)		(0.606–0.900)	
	SE 0.064		SE 0.084		SE 0.079	
NGAL in Urine	0.848	0.953	0.804	0.932	0.728	0.647
	(0.674–0.951)		(0.623–0.924)		(0.539–0.872)	
	SE 0.091		SE 0.098		SE 0.120	
Troponin T + Cystatin C-based eGFR + NGAL in Urine	0.933	0.124	0.916	0.130	0.916	0.097
	(0.752–0.994)		(0.729–0.990)		(0.729–0.990)	
	SE 0.05		SE 0.062		SE 0.062	
Difference between areas	0.134		0.147		0.193	
	(−0.037–0.306)		(−0.043–0.337)		(−0.037–0.424)	

eGFR = estimated glomerular filtration rate, NGAL = neutrophil gelatinase-associated lipocalin.
* Hanley & McNeil.

least in part by the complementary role in the pathophysiology of ADHF.

Troponin release has been documented during hospitalization in patients with ADHF [29]. It is a parameter of myocardial necrosis and apoptosis and is spilled into the bloodstream when cardiomyocytes demise [30]. This occurs in acute myocardial infarction as well as in chronic myocardial damage due to coronary artery disease or altered cardiac stress during heart failure. Altered cardiac stress leads to ventricular remodeling due to changes in hemodynamics and activation of the renin angiotensin aldosterone system [31]. As a structural protein in cardiomyocytes, troponin T also correlates with the extent of remodeling [32]. Moreover, an impaired renal function with reduced excretion of troponin leads to increased plasma levels [33]. The more advanced dysfunction of heart and kidney are, the higher the risk of mortality is.

Cystatin C is produced by nucleated cells. It is freely filtered and reabsorbed by the kidney and is not influenced by muscle mass, nutritional status, age or gender. Therefore, it is an excellent parameter to assess kidney function in older people. A study by Segarra et al. suggests that the use of an equation based on cystatin C is superior to CKD-EPI in estimating GFR of hospitalized patients [34]. In the context of cardiorenal syndrome, cystatin C-based eGFR is an earlier and more precise parameter to depict prognosis determining kidney injury [34].

Produced by neutrophils, NGAL is a marker of kidney injury and rises in plasma and urine in the case of tubular damage [35]. In the context of ADHF, hemodynamic and thus renal perfusion deteriorates which leads to tubular injury. Studies showed plasma NGAL to be a predictor for mortality in patients with heart failure and CKD [36]. Elevated levels of uNGAL on the first day of admission were related to the development of clinical acute kidney injury and are independently associated with poor prognosis [37–40].

The addition of novel biomarkers, particularly those reflecting both cardiac and renal function, to established ADHF risk scores could enable more precise risk stratification. This may facilitate earlier and more targeted interventions for high-risk patients, potentially improving clinical outcomes by allowing for more individualized treatment plans. Specifically, incorporating markers like troponin T, cystatin C-based eGFR, and uNGAL could help identify patients who are at elevated risk of short-term mortality despite having stable conventional biomarker profiles.

A risk score determined from parameters upon admission or over the course of the first hours of therapy is important. This is why we calculated A2B Score, ADHF/NT-pro-BNP Score and ELAN-HF Score with parameters upon admission and furthermore added cardiorenal biomarkers with an excellent predictive value. This could lead to more aggressive monitoring and timely therapeutic interventions in the hospital setting as early as possible.

Our study confirmed the predictive value of uNGAL, cystatin C and troponin T for mortality [41–44]. To the best of our knowledge, this is the first study to show that adding established and novel cardiorenal biomarkers to preexisting risk scores for patients with ADHF improved their predictive ability.

The study results are limited by its single-center design and small sample size. ELAN-HF Score, ADHF/NT-proBNP Score and A2B Score were designed to predict 180-day respectively 1-year and 2-year mortality. However, the prediction period for mortality in our study was 90 days. Biomarker selection was based on pathophysiological considerations, however, was not complete. Survivors presented significantly more frequently with arterial hypertension. We assess this as a statistical random error due to the small sample size of our study. On the side of non-survivors, in contrast, we observe significantly lower diastolic blood pressure values and a greater blood pressure amplitude as a sign of arterial vascular stiffness with a high proportion of patients diagnosed with heart failure with reduced ejection fraction. This may lower the proportion of arterial hypertension in non-survivors in our cohort.

Integrating novel biomarkers into risk scores may also help optimize resource allocation in healthcare settings by identifying patients who could benefit most from intensive care and follow-up. For instance, patients identified as high-risk through enhanced scoring models might be prioritized for advanced heart failure therapies or close post-discharge monitoring, potentially reducing rehospitalization rates and overall healthcare costs, whereas low risk patients could be followed via telemedicine.

Future studies with larger, more diverse populations are needed to confirm the findings of this study and determine the clinical utility of adding novel biomarkers to ADHF risk scores. Moreover, the therapeutic guidance and the cost-effectiveness of such an approach and its impact on patient-centered outcomes should be explored. Additionally,

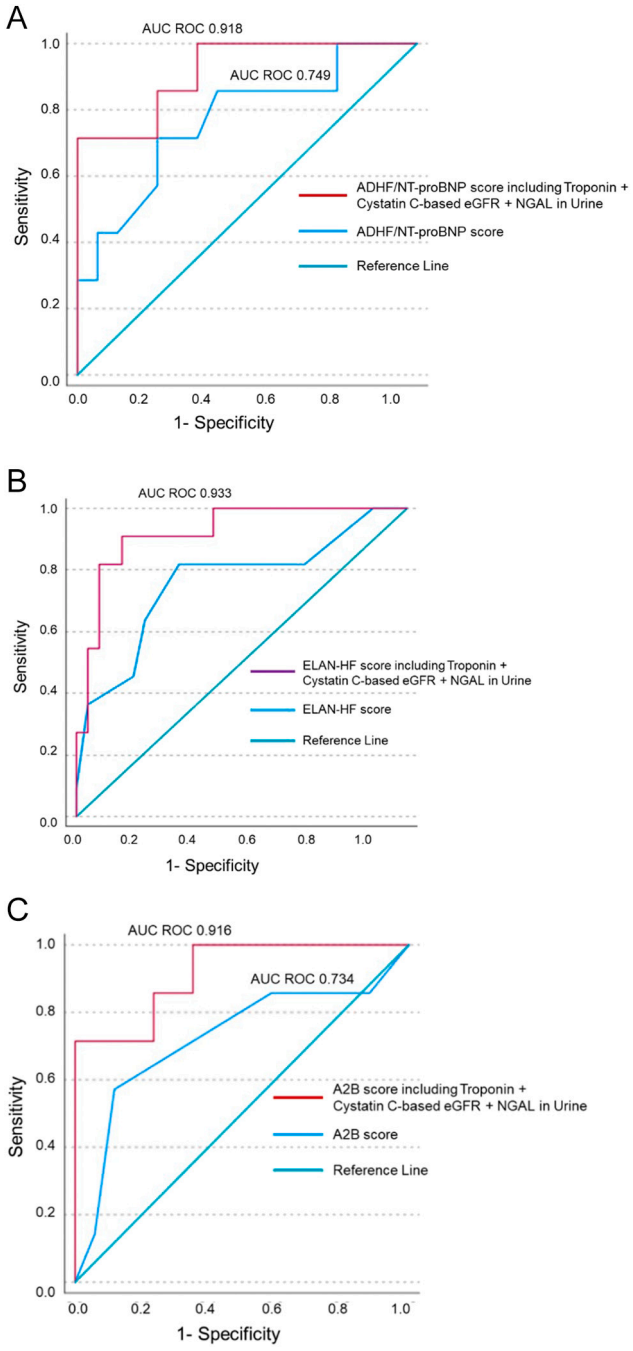

Fig. 1. Receiver operating characteristic (ROC) curves of
A) ELAN-HF-Score
B) ADHF/NT-proBNP-Score and
C) A2B-Score with and without a combination of biomarkers (troponin T, cystatin C-based eGFR and NGAL in urine) for predicting mortality.

longitudinal studies could provide insights into how these biomarkers change over time and how such changes correlate with clinical outcomes.

5. Conclusions

ELAN-HF Score, ADHF/NT-proBNP Score and A2B-Score predicted mortality in patients with ADHF. Adding one of the biomarkers troponin T, cystatin C-based eGFR or uNGAL or all four improved risk models. An adjusted risk score may significantly improve existing ADHF risk scores and potentially contribute to more accurate risk stratification and favorable clinical outcomes. Further research is needed to fully elucidate the clinical implications of incorporating these biomarkers into ADHF-risk scores.

CRediT authorship contribution statement

Valentin Hähnel: Writing – original draft, Visualization, Formal analysis. **Victoria Meretz:** Investigation. **Christian Butter:** Writing – review & editing, Supervision. **Vera Paar:** Formal analysis. **Christoph Edlinger:** Writing – review & editing, Data curation. **Michael Lichtenauer:** Writing – review & editing, Formal analysis. **Ronald Biemann:** Methodology, Data curation. **Berend Isermann:** Methodology, Data curation. **Meike Hoffmeister:** Investigation, Formal analysis. **Michael Haase:** Visualization, Methodology, Conceptualization. **Anja Haase-Fielitz:** Methodology, Formal analysis, Conceptualization. **Marwin Bannehr:** Writing – review & editing, Software, Formal analysis, Conceptualization.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Brandenburg Medical School (E-01-20,190,603, date of approval 18.09.2019). Informed consent was obtained from all subjects involved in the study.

Declaration of competing interest

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Appendix A

Table A1
Variables included in mortality risk score.

Variable	ELAN-HF Score	ADHF/NT-proBNP Score	A2B Score
NT-proBNP	+	+	+
Age	+	+	+
LVEF		+	
Moderate-severe TR		+	
Peripheral edema	+		
Systolic blood pressure	+	+	
Hyponatremia / serum sodium	+	+	
Serum urea	+	+	
Serum creatinine-based eGFR		+	
NYHA class III/IV	+		
Hemoglobin		+	+
HF-related hospitalization		+	
COPD		+	

ELAN-HF Score.

The score uses the following parameters: absolute NT-proBNP at discharge: 1500–5000 pg/ml,1; 5001–15,000 pg/ml, 3; >15,000 pg/ ml, 4 points / Other risk markers (1 point each) were as follows: NT-proBNP reduction of ≤30 % from admission to discharge / aged ≥75 years at admission / presence of peripheral edema at admission / systolic blood pressure ≤ 115 mmHg at admission / hyponatremia (sodium <135 mmol/l) at admission / serum urea of ≥15 mmol/l at discharge / New York Heart Association class III or IV at discharge.

ADHF/NT-proBNP Score.

The score uses the following parameters: age < 70 years, 0; ≥ 70 years, 3 points / N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels: < 5000 pg/ml, 0; 5000–15,000 pg/ml, 1; 15,000 pg/ml, 2 points / Chronic obstructive pulmonary disease (COPD): Absent: 0; present: 3 points / Estimated glomerular filtration rate (eGFR): ≥ 60 ml/min/1.73 m^2: 0; 30–59 ml/min/1.73 m^2, 2; < 30 ml/min/1.73 m^2, 4 points / Serum sodium concentration: ≥ 136 mmol/l: 0; 130–135 mmol/l, 1; < 130 mmol/l: 3 points / Hemoglobin levels: ≥ 12 g/dl: 0; 10–11.9 g/dl: 1; < 10 g/dl: 3 points / Left ventricular ejection fraction (LVEF): ≥ 40 %: 0; < 40 %: 2 points / Tricuspid regurgitation: None or mild: 0; Moderate or severe: 3 points.

A2B Score.

The score uses the following parameters: age (<65 years, 0; 65–74 years, 1; ≥75 years, 2 points) / anemia (hemoglobin ≥12 g/dl, 0; 10–11.9 g/dl, 1; <10 g/dl, 2), and BNP (<200 pg/ml, 0; 200–499 pg/ml, 1; ≥500 pg/ml, 2) and groups the patients into four risk categories.

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