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Prognostic value of cardiac biomarkers and National Early Warning Score 2 in acute dyspnoea

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ABSTRACT

Objective Patients hospitalised with acute dyspnoea due to acute heart failure (AHF) have a grave prognosis, but the European Society of Cardiology guidelines recommend no system to risk stratify these patients. The prognostic value of combining National Early Warning Score (NEWS) 2 and established cardiac biomarkers is not known.

Methods We measured high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and calculated NEWS2 in 314 patients with acute dyspnoea within 24 hours of hospitalisation. Their prognostic merits were assessed in the total cohort and for the subgroup with AHF separately.

Results The median age was 73 (quartile (Q) 1–3, 63–81) years, 48% were women and 143 patients (46%) were hospitalised with AHF. The 114 patients (36%) who died during follow-up (median 823 days, Q1–3, 471–998) had higher concentrations of hs-cTnT (62 vs 33 ng/L, p<0.001) and NT-proBNP (6995 vs 2605 ng/L, p<0.001), and higher NEWS2 (6.1 vs 4.5 points, p<0.001), compared with survivors. Patients with increased vs low NEWS2 clinical risk had higher mortality rates in adjusted analyses in the total cohort (HR 2.11, 95% CI 1.28 to 3.48) and in patients with AHF (HR 2.00, 95% CI 1.54 to 2.60). NEWS2 provided incremental prognostic information compared with biomarkers alone for the total cohort: area under the curve 0.72 vs 0.70, p=0.042, and for the subpopulation with AHF: 0.70 vs 0.67, p=0.014.

Conclusion NEWS2 predicts long-term mortality in patients hospitalised due to acute dyspnoea and the subgroup with AHF and provide incremental prognostic information to hs-cTnT and NT-proBNP.

Key questions

What is already known about this subject?

- N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) can predict long-term mortality in patients hospitalised with heart failure (HF).
- Several prognostic models combining clinical variables with blood biomarkers have been developed and validated for hospitalised HF patients but are either cumbersome in use or have suboptimal accuracy.

What does this study add?

- We have demonstrated that the clinical scoring system National Early Warning Score (NEWS) 2 can predict long-term prognosis for patients hospitalised with acute dyspnoea and the subgroup with acute HF, and provide incremental prognostic information to NT-proBNP and hs-cTnT.

How might this impact on clinical practice?

- NEWS2, used alone or in combination with NT-proBNP and hs-cTnT, can help to identify high-risk patients hospitalised with acute dyspnoea or acute HF, who might benefit from more aggressive treatment and prompt follow-up consultations after discharge.
- As NEWS2 is already implemented in clinical practice in the United Kingdom and an increasing number of countries across Europe, the long-term prognostic accuracy of this system can prove valuable for many clinicians due to its availability.

INTRODUCTION

Patients with acute dyspnoea represent almost 1 in 10 patients admitted to emergency departments (ED).[1] Heart failure (HF) is the dominating cause and contribute to a third to half of the hospitalisations.[2 3] Hospitalisation for acute HF (AHF) is associated with a grave prognosis as one in three will die within the first year, which is more than twice the mortality rates seen in chronic HF.[4] Guidelines for highly prevalent diseases such as acute exacerbation of chronic obstructive pulmonary disease (AECOPD), acute coronary syndromes and community-acquired pneumonia all recommend specific prognostic scoring systems to identify high-risk patients, but the European Society of Cardiology (ESC) HF guidelines lack such recommendations for AHF.[5] Notably, the ESC HF guidelines also lack recommendations to use biomarkers for post-discharge risk stratification of HF patients. This in spite of numerous studies validating the accuracy of biomarkers to predict long-term mortality for hospitalised

HF patients, particularly using cardiac troponins[6] and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurements.[7] In contrast, American HF guidelines[8] recommend using both risk scoring systems (class IIa recommendation) and to measure cardiac troponins and NT-proBNP to establish a prognosis after discharge.

In Europe, the clinical scoring system National Early Warning Score (NEWS) has gained traction the last decade to detect serious illness and clinical deterioration, and the revised edition NEWS2 is now widely implemented in both hospital EDs and wards.[9] The system was originally designed by the Royal College of Physicians of London as a standardised way to predict cardiac arrest, unanticipated intensive care unit admission or death within 24 hours, and has later also been validated as superior to other systems for prediction of long-term mortality in general ED populations and for patients with respiratory distress.[10] The system assigns an aggregated score based on vital parameters, which is subclassified into a low, low-medium, medium and high clinical risk. However, NEWS2 depends on symptoms, which for AHF closely correlate with fluid overload,[5] but not necessarily cardiac output and mortality. The utilisation and accuracy of NEWS2 to predict mortality have so far not been studied in acute HF patients. We hypothesise that NEWS2 can be an easy and readily available tool to prognosticate patients hospitalised with acute dyspnoea and AHF, and that it can provide incremental prognostic information to the established cardiac biomarkers high-sensitivity cardiac troponin T (hs-cTnT) and NT-proBNP.

METHODS

Akershus Cardiac Examination 2 Study

The ACE 2 Study was a prospective single-centre cohort study investigating the diagnostic and prognostic properties of established and novel biomarkers in patients admitted with acute dyspnoea. Study details have previously been published in full.[11] In short, the study was conducted at Akershus University Hospital from June 2009 to November 2010. Patients hospitalised due to acute dyspnoea were included if they were ≥18 years of age and able to provide informed consent. Dedicated study personnel screened for eligible patients during the daily morning briefings at the ED, and additional blood sampling was done within 24 hours. Patients with short life expectancy, as well as patients who had gone through major surgery, acute myocardial infarction, or coronary intervention within the last 2 weeks, were excluded. Of 468 patients hospitalised with acute dyspnoea, 314 patients were included in the final study cohort (figure 1). There was no patient or public involvement at the time the study was conducted (2009–2010).

Data collection

All patients completed a standardised questionnaire and clinical information was obtained directly from the ED physician. Additional data were collected from the hospital's electronic records, including data collected prior to and/or after the current hospitalisation when available. Medical history was dichotomised, with all temporal patterns of atrial fibrillation (AF) being defined as AF, and previous myocardial infarction and/or coronary intervention being defined as coronary artery disease (CAD). Body mass index (BMI) was calculated as body weight/[height ×height] (kg/m^2). Left ventricular ejection fraction (LVEF) and diastolic dysfunction were determined based on clinical routine transthoracic echocardiography. NEWS2 was retrospectively calculated based on vital parameters registered in the ED, and included data on respiratory rate, oxygen saturation, hypercapnic respiratory failure, need of supplemental oxygen, systolic blood pressure, heart rate, consciousness and body temperature. Variables were assigned a point value from 0 to 3 based on degree of abnormality and summed up. An aggregated score of 0–4 was assigned low risk, a score of 3 (full score) in any individual parameter was assigned low-medium risk, an aggregated score of 5–6 was assigned medium risk, and an aggregated score of 7 or more was assigned high risk, as described by The Royal College of Physicians of London.[9]

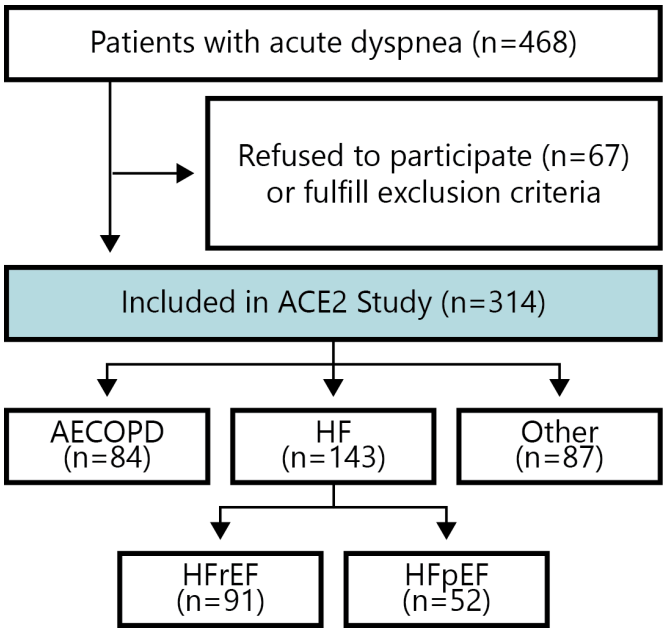

Figure 1 Flow chart of the study. ACE2, Akershus Cardiac Examination 2; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HF, heart failure; HFrEF, HF with reduced EF; HFpEF, HF with preserved EF.

Adjudication of diagnosis and follow-up data

The index diagnosis of the hospitalisation was adjudicated by two senior physicians who had access to all data in the hospital's electronic journal system. The adjudicators reviewed all relevant data individually and in cases of disagreement, the diagnosis was decided by consensus. HF diagnoses were based on ESC HF guidelines, requiring worsening of typical symptoms and clinical signs, and objective evidence of structural or functional myocardial abnormality, and subdivided according

to LVEF. Patients with EF ≥50% and echocardiographic evidence of altered structure or dysfunction (including pathologic mitral E/A, E deceleration time, E/e' and left atrial enlargement) were diagnosed with HF with preserved EF (HFpEF). In this study we did not include the intermediate group HF with mildly reduced EF (EF 40%–50%), and these patients were pooled with the group with EF <40% as HFrEF patients. We obtained survival status on 1 November 2012, from the hospital's electronic records, which are monthly synchronised with Statistics Norway.

Biochemical measurements

Blood samples were collected within 24 hours of hospitalisation. Test tubes were centrifuged, and serum was immediately frozen and stored at −80°C. Measurements were performed without prior freeze-thaw cycles, ensuring excellent stability for both analytes as previously reported.[12 13] hs-cTnT concentrations were measured with a high sensitivity Roche assay (Elecsys TnT hs stat, Roche Diagnostics, Penzberg, Germany) with a range of detection from 3 to 10 000 ng/L, a 10% coefficient of variation of 13 ng/L, and a 99th percentile in healthy individuals of 14 ng/L. Values below the limit of detection were assigned the value 3 ng/L. NT-proBNP was measured with the pro-BNP II assay from Roche (Roche Diagnostics, Basel, Switzerland), with a range of detection from 5 to 35.000 ng/L. Glomerular filtration rate was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation. [14]

Statistical analysis

Continuous variables are presented as median (IQR) and compared with the Mann-Whitney U. Dichotomous variables are presented as absolute numbers (percentage) and compared with the χ^2 test. We calculated correlations with the Spearman rank method. Univariate and multivariable linear regression were used to assess association between explanatory variables and NEWS2, whereas univariate and multivariable Cox regression were used to identify predictors of all-cause mortality. In both cases, we used backward selection on all the significant variables from univariate regression to establish the final explanatory model, analogously to the strategy of previous studies from this cohort.[11] We base this approach on the purposeful selection of covariates for models with dichotomised outcomes as described by Hosmer and Lemeshow.[15] The prognostic accuracy of NEWS2 was assessed as a continuous variable, as a categorical variable with the four recommended clinical risk groups (1) low risk; (2) low-medium risk; (3) medium risk; (4) high risk, and as a dichotomous variable (low risk vs low-medium, medium, and high risk). Kaplan-Meier survival curves were stratified by NEWS2 clinical risk, and differences in survival rates were tested by the log-rank test. The accuracy for biomarkers and NEWS2 to predict mortality were assessed by receiver operating characteristic curve (ROC) analysis with the area under the curve (AUC). For 11 of the 314 patients, respiratory rate was missing when calculating NEWS2. For these cases, we used multiple imputation with predictive mean matching for the five closest neighbours with five imputations per missing variable. All biomarkers were transformed by the natural logarithm before analyses due to a right-skewed distribution. We used two-tailed tests and considered p<0.05 significant. Kappa statistics were used to calculate consistency between the adjudicators. All analyses were performed with Stata (V.16, StataCorp). We used the TRIPOD checklist when writing our report.[16]

RESULTS

Patient characteristics

In total, 314 patients were included in the current study. Forty-eight per cent were women, median age was 73 (Q1–3, 63–81) years, median BMI 26 (22–30) kg/m^2 and 27% were current smokers (table 1).Thirty-two per cent had a history of HF and 49% of chronic obstructive pulmonary disease (COPD). In total, 143 of 314 hospitalised patients (46%) were adjudicated with AHF, with a consensus rate of 95% (κ=0.897 (0.848–0.946)). AHF patients were older, more often male and had more comorbidities than patients with non-HF-related dyspnoea. HFpEF (n=52) patients were more often older females with de novo HF and had lower prevalence of established CAD compared with HFrEF patients (n=91) (online supplemental table 1). We report discharge medication for the HF patients in online supplemental table 2.

NEWS2 and cardiac biomarkers on hospital admission

The NEWS2 ranged from 0 to 12 with median 5 (Q1–3, 3–7). In adjusted analysis, New York Heart Association class IV, history of COPD and higher C-reactive protein and hs-cTnT concentrations were associated with increasing NEWS2 (online supplemental table 3). The distribution of vital parameters contributing to the total NEWS2 were mostly similar between the different causes of acute dyspnoea; AHF, AECOPD or other (table 1), and between HFpEF and HFrEF (online supplemental table 4). Patients with AHF had higher peripheral oxygen saturation (94% vs 91%, p<0.001) and lower temperature (36.8°C vs 37.2°C, p<0.001), compared with patients with AECOPD. We found no significant differences for respiratory rate, supplemental oxygen, systolic blood pressure, heart rate or consciousness. In total, patients with AHF had lower NEWS2 (5.1), compared with AECOPD patients (5.9; p=0.039). Among AHF patients, the HFpEF group had lower peripheral oxygen saturation and higher temperature (online supplemental table 4).

The median concentration of NT-proBNP was 1926 ng/L (Q1–3, 446–5468) for the total cohort, 3600 (1601–8396) for AHF and 379 ng/L (171–1008) for AECOPD. With a similar pattern, hs-cTnT was 27 ng/L (16-53) in the total cohort, and 38 ng/L (22-75) and 18 ng/L (10-28) for AHF and AECOPD, respectively. The concentrations and prognostic accuracies of hs-cTnT and NT-proBNP in this cohort have previously been reported.[17] hs-cTnT

Table 1 Baseline characteristics ACE2 cohort (n=314)†

	Total n=314	AHF n=143	AECOPD n=84‡	Other n=87‡
Age	73 (63–81)	78 (68–83)	68 (63–77)***	65 (48–78)***
Male sex	164 (52%)	90 (63%)	35 (42%)**	39 (45%)**
BMI	26 (22–30)	27 (22–29)	24 (19–28)**	26 (23–31)
Smoking	85 (27%)	30 (21%)	28 (33%)*	27 (31%)
NYHA class IV	136 (43%)	65 (45%)	47 (56%)	24 (28%)**
History of				
HF	101 (32%)	87 (61%)	9 (11%)***	5 (6%)***
AF	96 (31%)	68 (48%)	15 (18%)***	13 (15%)***
COPD	155 (49%)	61 (43%)	84 (100%)***	10 (11%)***
CAD	111 (35%)	78 (55%)	23 (27%)***	10 (11%)***
HT	120 (38%)	69 (48%)	26 (31%)*	25 (29%)**
DM	68 (22%)	43 (30%)	9 (11%)***	16 (18%)*
Biomarkers at ED				
hs-cTnT (ng/L)	27 (16–53)	38 (22–75)	18 (10–28)***	8 (3–23)***
NT-proBNP (ng/L)	1926 (446–5468)	3600 (1601–8396)	379 (171–1008)***	280 (88–1293)***
CRP (mg/L)	16 (6–40)	13 (5–37)	26 (6–50)*	15 (3–90)
eGFR (mL/min/1.73 m^2)	74 (55–99)	66 (47–81)	91 (71–107)***	85 (69–104)***
Vitals at ED				
RR (per minute)	24 (18–28)	24 (18–28)	24 (20–30)	22 (16–28)
O2 saturation (%)	93 (89–96)	94 (90–97)	91 (88–94)***	94 (91–97)
Supplemental O2	136 (43%)	64 (45%)	49 (58%)*	23 (26%)**
Systolic BP (mm Hg)	142 (127–161)	144 (123–166)	144 (130–161)	138 (128–151)
HR (beats per minute)	90 (78–108)	88 (74–109)	97 (82–111)	90 (75–105)
Altered mental state	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Temperature (°C)	37.0 (36.6–37.4)	36.8 (36.4–37.3)	37.2 (36.8–37.7)***	37.1 (36.6–37.6) **
NEWS2	5 (3–7)	5 (3–7)	6 (3–8)*	4 (2–6)*

*P<0.05; **p<0.01; ***p<0.001.
†Data are presented as n (%) or median (Q1–Q3).
‡Compared with AHF group.
.ACE, Akershus Cardiac Examination; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AF, atrial fibrillation; AHF, acute heart failure; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; hs-cTnT, high-sensitivity cardiac troponin T; HT, hypertension; NEWS2, National Early Warning Score 2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RR, respiratory rate.

correlated with respiratory rate, the need of supplemental oxygen, systolic blood pressure and total NEWS2, whereas NT-proBNP correlated with respiratory rate, peripheral oxygen saturation, the need of supplemental oxygen, systolic blood pressure and temperature (online supplemental table 5). The correlation coefficient between NEWS2 and hs-cTnT was 0.30 (p<0.001) and the correlation coefficient between NEWS2 and NT-proBNP was 0.20 (p<0.001).

Predictors of long-term mortality

One-hundred and fourteen patients (36%) died during a median follow-up time of 823 days (Q1–3, 471–998). NEWS2 as a continuous variable, hs-cTnT and NT-proBNP all predicted mortality in unadjusted analysis. hs-cTnT (HR 1.35, 95% CI 1.12 to 1.61) and NEWS2 (HR 1.08, 95% CI 1.02 to 1.16) were also significant in multivariable analysis, while the association was attenuated and no longer significant for NT-proBNP in the final multivariable model (table 2).

By stratifying patients according to NEWS2 clinical risk groups, we found that the lowest risk group had the highest survival rates (figure 2A; p<0.001 by the log rank test). The association between elevated NEWS2 clinical risk and survival was significant in both unadjusted (HR 2.74, 95% CI 1.66 to 4.51 for elevated compared with low clinical risk, p for trend <0.001) and adjusted analyses (HR 2.11, 95% CI 1.28 to 3.48, p for trend=0.034) (online supplemental table 6). NEWS2 predicted mortality independent of cardiac biomarker concentrations, and patients with elevated NEWS2 risk grade in combination

Table 2 Variables associated with all-cause mortality during follow-up

	HR	95% CI
Univariate		
NEWS2	1.14	1.07 to 1.22
Age	1.05	1.03 to 1.07
Male sex	1.00	0.69 to 1.44
BMI	0.93	0.90 to 0.96
Smoking	0.96	0.63 to 1.46
NYHA class IV	1.86	1.28 to 2.69
History of		
HF	1.95	1.35 to 2.83
AF	1.71	1.18 to 2.50
COPD	2.15	1.46 to 3.16
CAD	1.29	0.89 to 1.88
HT	1.27	0.88 to 1.84
DM	1.25	0.81 to 1.93
Biomarkers at ED		
$_{ln}$hs-cTnT	1.56	1.35 to 1.81
$_{ln}$NT-pro-BNP	1.37	1.22 to 1.53
$_{ln}$CRP	1.11	0.98 to 1.26
$_{ln}$eGFR	0.52	0.34 to 0.80
Multivariable		
NEWS2	1.08	1.02 to 1.16
Age	1.03	1.01 to 1.05
BMI	0.94	0.91 to 0.98
$_{ln}$hs-cTnT	1.35	1.12 to 1.61
History of HF	1.57	1.05 to 2.36
History of COPD	2.11	1.39 to 3.20

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; HT, hypertension; NEWS2, National Early Warning Score 2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

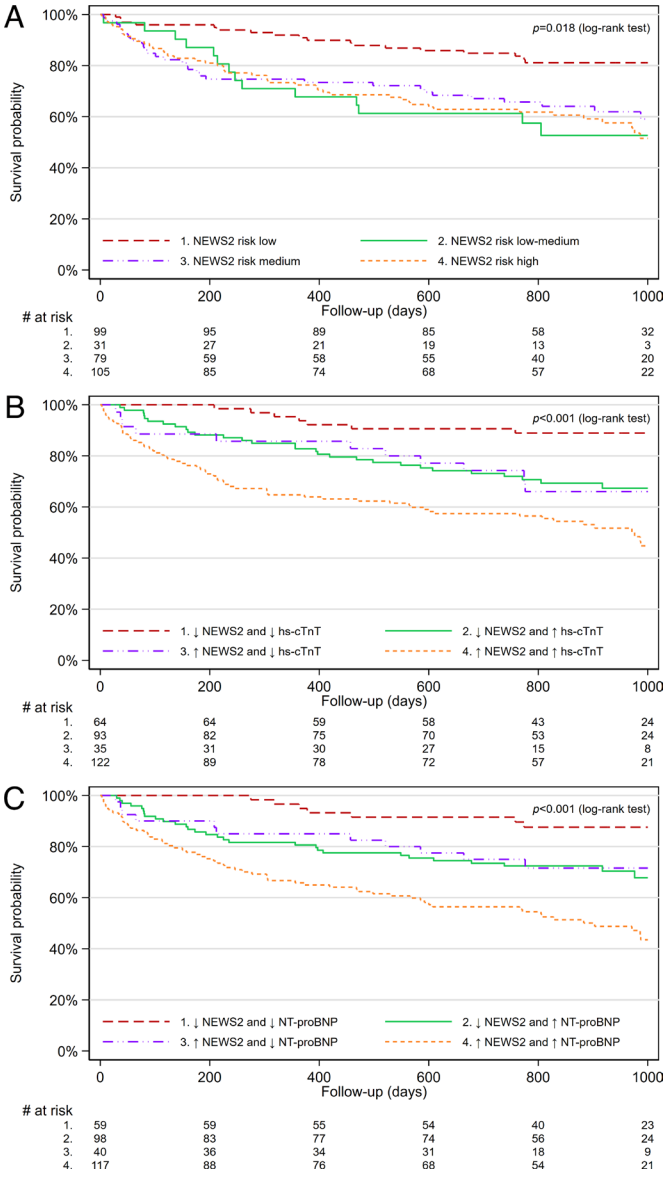

Figure 2 Survival rates stratified by (A) NEWS2 clinical risk, (B) low vs elevated NEWS2 clinical risk and concentrations of hs-cTnT above vs below median, (C) low vs elevated NEWS2 clinical risk and concentrations of NT-proBNP above vs below median. hs-cTnT, high-sensitivity cardiac troponin T; NEWS2, National Early Warning Score; NT-prBNP, N-terminal pro-B-type natriuretic peptide

with concentrations of hs-cTnT (figure 2B) and/or NT-proBNP (figure 2C) above the median (n=149) had the highest mortality rate during follow-up, with a HR of 5.64 (95% CI 2.45 to 12.97), compared with those with low NEWS2 clinical risk and cardiac biomarkers below the median (n=50) (online supplemental table 6). Among the variables contributing to NEWS2, higher respiratory rate (HR 1.07, 95% CI 1.04 to 1.09) and lower systolic blood pressure (HR 0.99, 95% CI 0.98 to 0.99) predicted mortality in adjusted analyses (online supplemental table 6). The ROC-AUC of NEWS2 to predict mortality was 0.64 (95% CI 0.58 to 0.71), which was not statistically different from hs-cTnT 0.69 (95% CI 0.64 to 0.75, p for comparison=0.22) or NT-proBNP at 0.67 (95% CI 0.61 to 0.73, p for comparison=0.64).

Among the subgroup of patients with AHF, 66 patients (46%) died. In unadjusted analysis for this subgroup, NT-proBNP (HR 1.53, 95% CI 1.24 to 1.89), hs-cTnT (HR 1.37, 95% CI 1.10 to 1.71) and NEWS2 (HR 1.12, 95% CI 1.03 to 1.22) predicted mortality (online supplemental table 7). Among these, only NT-proBNP still predicted mortality in multivariable analysis (HR 1.46, 95% CI 1.17 to 1.83). Stratifying patients by NEWS2 clinical risk also predicted mortality for the subgroup with AHF (p=0.018 by the log-rank test, (online supplemental figure). Adding NEWS2 to both biomarkers resulted in a higher AUC for mortality compared with the two biomarkers alone for the total cohort (AUC 0.72, 95% CI 0.66 to 0.78 vs 0.70,

95% CI 0.64 to 0.75, p for comparison=0.042), and for the subpopulation with AHF (AUC 0.70, 95% CI 0.60 to 0.78 vs 0.67, 95% CI 0.58 to 0.76, p for comparison=0.014) (online supplemental table 8). The prognostic accuracy of NEWS2 was higher for HFpEF compared with HFrEF (AUC 0.80, 95% CI 0.68 to 0.93 vs 0.56 95% CI 0.43 to 0.68, p for comparison=0.005) (online supplemental table 8).

DISCUSSION

In this retrospective analysis of the prospective cohort study ACE 2, we found that NEWS2 predicted long-term mortality among an unselected group of patients presenting to the ED with acute dyspnoea, as well as for the subgroup of patients with AHF. These associations were significant for both patients with high and low concentrations of the cardiac biomarkers hs-cTnT and NT-proBNP, and patients with elevated NEWS2 risk in combination with high concentrations of hs-cTnT and/or NT-proBNP had the worst prognosis, with 60% mortality after 3 years. For patients with low NEWS2 clinical risk and one or both cardiac biomarkers below the median the mortality rate after 3 years was about 10%. In line with this, we found that adding NEWS2 on top of cardiac biomarkers in a prediction model improved long-term risk stratification.

NEWS2 starts rising when disease directly or indirectly affects the cardiopulmonary system or causes new confusion or fever. In patients with AHF, symptoms are primarily a result of fluid accumulation and/or redistribution, ultimately resulting in congestion.[5 18] The mechanisms behind the congestion are triggered by cardiac dysfunction and peripheral hypoxia, and include several neurohumoral pathways such as activation of the sympathetic nervous system, the renin–angiotensin–aldosterone system and the arginine-vasopressin system.[19] This gradually elevates cardiac filling and venous pressures until the threshold for clinical symptoms and signs is reached, with dyspnoea, tachycardia, hypertension or hypotension dependent on cardiac reserve, and tachypnoea as result. In our data, lower systolic blood pressure and higher respiratory rate at admission were the significant predictors of mortality among the vital parameters registered at the ED.

Thirty-six per cent of the patients in our cohort died during the median follow-up time of 823 days, whereof 22% died the first year. This is slightly higher than previous studies reporting a 1-year mortality of 15%–16%.[7 20] For patients with AHF, the 1-year mortality rate in our cohort was comparable to previous studies with 28% compared with 24%–38%,[21 22] and underlining that the prognosis of AHF is worse than many common cancers.[23] Within the first year after a HF hospitalisation, the cumulative mortality rate will reach one in three, and within 5 years almost two in three.[24] Though many risk score systems have been developed to identify AHF patients at particularly high risk, none have been endorsed by ESC HF guidelines, partly due to being cumbersome in use in an ED setting. We found that patients with elevated NEWS2 risk grade had a three times higher mortality rate after 3 years of follow-up, compared with those with a low NEWS2 clinical risk grade, suggesting that NEWS2 can be a valuable tool for long-term risk prediction in patients with acute dyspnoea and AHF.

The increased mortality risk seen in patients with elevated NEWS2 was independent of the concentrations of the cardiac biomarkers hs-cTnT and NT-proBNP, which are known predictors of short-term and long-term mortality.[6 7 25 26] Patients with elevated NEWS2 clinical risk and one or both cardiac biomarkers above median had the highest mortality rate with more than five times the mortality risk, compared with those with low NEWS2 clinical risk and cardiac biomarkers below the median. The utilisation of NEWS2 in combination with cardiac blood biomarkers might thus be a simple and effective way to identify high-risk AHF patients at discharge, and similar strategies have been demonstrated effective in other cohorts for NEWS in combination with D-dimer[20] and infections markers.[27] An additional value of using NEWS2 with cardiac biomarkers comes from its availability, as NEWS2 already is implemented in a large proportion of European hospitals.

NEWS2 had the highest prognostic accuracy for patients with HFpEF, which is a patient group where effective treatment options are missing. In contrast to HFrEF, which is dominated by ischaemic aetiology[28] and have a number of pharmacological treatments to improve survival and reduce the risk of rehospitalisation,[5] no treatment option has improved survival for HFpEF patients. Whether improved prognostication in HFpEF patients, possibly by using NEWS2 on hospital admission, may better identify a subgroup that better respond to pharmacological therapy will have to be explored in additional trials.

Strengths and limitations

In this study, we used an adjudication committee consisting of two independent experienced physicians to set the index diagnoses according to current guidelines, which provided an excellent consensus between the adjudicators. All relevant data were collected in a uniform matter by dedicated study personnel, and hs-cTnT and NT-proBNP concentrations were measured at a core laboratory as a batch to avoid variation in lab calibration over time. As limitations, this study had moderate sample size and a single-centre design. Respiratory rate, which was one of the variables used to calculate NEWS2, was missing in 11 of 314 patients. This was handled by imputing missing values based on the other NEWS2 variables and outcome, and imputations did not significantly change any results compared with analyses of original datasets. Even though adjudication consensus was excellent in this study, some of the non-AHF patients in the study never underwent echocardiography, which could have contributed to underdiagnosis of AHF.

CONCLUSION

NEWS2 clinical risk predicts long-term mortality in patients hospitalised due to acute dyspnoea, and the combination of NEWS2 with the established cardiac biomarkers hs-cTnT and NT-proBNP provide incremental prognostic accuracy.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Regional Comittees for Medical Research Ethics South East Norway. Reference number for ethics approval: S-08824d 2008/21288 09/418. Participants gave informed consent to participate in the study before taking part.

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