Clinical Biochemistry 88 (2021) 30–36

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

High-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide in acute heart failure: Data from the ACE 2 study

Kristian Berge [a,b], Magnus Nakrem Lyngbakken [a,b], Peder Langeland Myhre [a,b], Jon Brynildsen [a,b], Ragnhild Røysland [b,c], Heidi Strand [c], Geir Christensen [b,d], Arne Didrik Høiseth [a,b], Torbjørn Omland [a,b], Helge Røsjø [b,e,*]

[a] Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog, Norway
[b] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[c] Multidisciplinary Laboratory Medicine and Medical Biochemistry, Akershus University Hospital, Lørenskog, Norway
[d] Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway
[e] Division of Research and Innovation, Akershus University Hospital, Lørenskog, Norway

ARTICLE INFO

Keywords:
Troponin
Biomarker
Cardiovascular
Heart failure
HFpEF

ABSTRACT

Background: To assess if cardiac troponins can improve diagnostics of acute heart failure (AHF) and provide prognostic information in patients with acute dyspnea.

Methods: We measured cardiac troponin T with a high-sensitivity assay (hs-cTnT) in 314 patients hospitalized with acute dyspnea. The index diagnosis was adjudicated and AHF patients were stratified into AHF with reduced or preserved ejection fraction (HFrEF/HFpEF). The prognostic and diagnostic merit of hs-cTnT was compared to the merit of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Results: In the total population, median age was 73 (quartile [Q] 1–3 63–81) years and 48% were women. One-hundred-forty-three patients were categorized as AHF (46%) and these patients had higher hs-cTnT concentrations than patients with non-AHF-related dyspnea: median 38 (Q1-3 22–75) vs. 13 (4–25) ng/L; $p < 0.001$. hs-cTnT concentrations were similar between patients with HFrEF and HFpEF ($p = 0.80$), in contrast to NT-proBNP, which was higher in HFrEF ($p < 0.001$). C-statistics for discriminating HFpEF from non-AHF-related dyspnea was 0.80 (95% CI 0.73–0.86) for hs-cTnT, 0.79 (0.73–0.86) for NT–proBNP, and 0.83 (0.76–0.89) for hs-cTnT and NT-proBNP in combination. Elevated hs-cTnT remained associated with HFpEF in logistic regression analysis after adjusting for demographics, comorbidities and renal function. During median 27 months of follow-up, 114 (36%) patients died in the total population. Higher hs-cTnT concentrations were associated with increased risk of all-cause mortality after adjustment for clinical variables and NT-proBNP: hazard ratio 1.30 (95% CI 1.07–1.58), $p = 0.009$.

Conclusion: hs-cTnT measurements improve diagnostic accuracy for HFpEF and provide independent prognostic information in unselected patients with acute dyspnea.

1. Introduction

Cardiac troponins are cornerstone markers for diagnosis, risk stratification and selection of treatment strategy of acute coronary syndrome (ACS). Since cardiac troponin testing was implemented in U.S. [1] and European [2] guidelines for ACS twenty years ago, the diagnostic accuracy for ACS has greatly improved, due to novel high-sensitivity cardiac troponin (hs-cTn) assays with very low limit of detection. However, with increased sensitivity comes decreased specificity, and cardiac troponin elevations are present in numerous conditions such as aortic dissection, thromboembolic disorders, structural heart disease, and others [3].

Heart failure (HF) is a clinical syndrome characterized by dyspnea, peripheral edema and fatigue [4]. Diagnosing HF can be difficult due to overlapping symptoms with other conditions, and the phenotype of HF vary due to a broad spectrum of underlying pathophysiology. HF can be classified according to left ventricular systolic function, where ejection fraction (EF) < 40% is referred to as HF with reduced EF (HFrEF), EF

* Corresponding author at: Akershus universitetssykehus HF, Postboks 1000, 1478 Lørenskog, Norway.
E-mail address: helge.rosjo@medisin.uio.no (H. Røsjø).

https://doi.org/10.1016/j.clinbiochem.2020.11.009
Received 24 August 2020; Received in revised form 13 October 2020; Accepted 11 November 2020
Available online 25 November 2020

40–49% as HF with mid-range EF (HFmrEF), and EF ≥ 50% as HF with preserved EF (HFpEF). Acute HF (AHF) is defined as a rapid onset or worsening of symptoms and/or signs of HF, and has a poor outcome with 75% 5-year mortality for both HFrEF and HFpEF [5]. Numerous treatments have improved survival in chronic HFrEF, but no treatment has demonstrated improved survival in HFpEF [4]. Early diagnosis and treatment of underlying risk factors are therefore important to prevent progression of disease in HFpEF [6]. When suspecting AHF, European guidelines recommend measuring natriuretic peptides to be able to rule out AHF. Despite natriuretic peptides being significantly lower in HFpEF compared to HFrEF [7], the similar thresholds are recommended for both HFrEF and HFpEF. Key characteristics of HFpEF, such as atrial fibrillation (AF), obesity and impaired renal function also substantially influence natriuretic concentrations. Hence, natriuretic peptide testing has important limitations in diagnosing HFpEF [8]. Cardiac troponins, which are already available in most emergency departments (EDs), provide diagnostic [9] and prognostic [10] information for AHF. However, the majority of studies have predominantly included patients with HFrEF or undifferentiated AHF. Recent studies have also demonstrated elevated cardiac troponin concentrations in patients with HFpEF [11], and increased concentrations predict worse outcome [12]. Whether hs-cTnT measurements can improve diagnostic accuracy of HFpEF and provide prognostic information in patients presenting in the ED with dyspnea is largely unknown. Accordingly, in this study we hypothesized that hs–cTnT concentrations would provide (1) independent diagnostic information for HFpEF and (2) improve risk stratification among patients hospitalized with acute dyspnea.

2. Methods

2.1. Akershus cardiac examination (ACE) 2 study

The ACE 2 study was a prospective, single-center study at Akershus University Hospital conducted from June 2009 through November 2010. Study details have previously been reported [13]. In short, patients hospitalized due to acute dyspnea 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 disseminated malignant disease or other conditions 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 hospitalized with acute dyspnea, 314 patients were included in the final study cohort (Fig. 1). We performed the study in accordance with the Declaration of Helsinki and after approval from the Regional Ethics Committee. All study participants provided written consent before study inclusion.

2.2. Data collection

All participants completed a standardized questionnaire and clinical information was obtained directly from the ED physicians. We collected additional data from the hospital's electronic records, including blood pressure, heart rate, body temperature, respiratory rate and medical history. We defined known paroxysmal, persistent or chronic AF as history of AF, history of previous myocardial infarction or previous coronary intervention as coronary artery disease (CAD), and calculated body mass index (BMI) as body weight / [height × height] (kg/m^2). Left ventricular ejection fraction (LVEF) and signs of diastolic dysfunction were determined based on clinical routine transthoracic echocardiography.

2.3. Adjudication of diagnosis and follow-up data

An adjudication committee decided the index diagnosis for all patients in the cohort. The committee consisted of two senior physicians, who independently reviewed all relevant patient records, supplementary examinations, and follow-up data with median 464 days (quartile [Q] 304–705 days) between admission and adjudication. In cases of disagreement between the two adjudicators, discrepancy was resolved by consensus. Consistency between the adjudicators was measured with interrater reliability analysis using Kappa statistics. AHF diagnosis was made according to ESC guidelines and required worsening of typical symptoms of HF (e.g. dyspnea, edema, and fatigue), clinical signs of HF (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat), and objective evidence of structural or functional myocardial abnormality. Patients were diagnosed with HFpEF if they had symptoms and clinical signs of AHF combined with LVEF ≥ 50% and echocardiographic evidence of diastolic dysfunction (including pathologic mitral E/A, E deceleration time, E/é and left atrial enlargement). We did not differentiate between AHF patients with mid-range and reduced EF, and these patients were classified together as HFrEF. We obtained survival status on November 1st, 2012 from the hospital's electronic records, which are synchronized with Statistics Norway on a monthly basis.

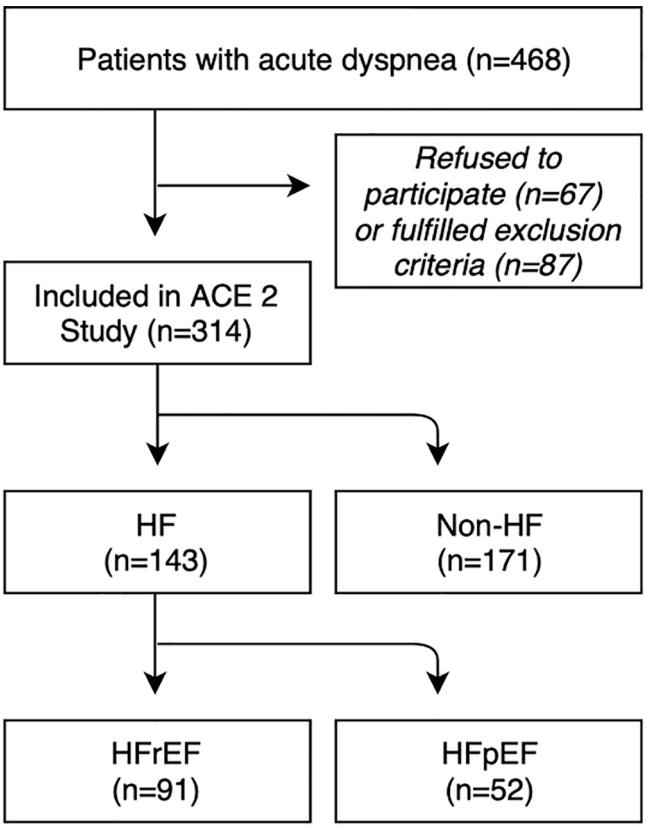

Fig. 1. Flow chart of the study.

2.4. Biochemical measurements

Blood samples were obtained within 24 hours of hospital admission in all patients, and day 2 (n = 231) and before discharge (n = 95) in a subgroup of the cohort. Samples were centrifuged, serum immediately frozen and stored at −80 °C before analysis. To measure cTnT concentrations, we used an hs assay (Elecsys TnT hs stat, Roche Diagnostics, Penzberg, Germany) as previously reported [14]. The assay has 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. hs-cTnT values below the limit of detection were assigned the value 3 ng/L. NT-proBNP was measured on a Cobas Platform (Roche Diagnostics, Basel, Switzerland) using the proBNP II assay, with a range of detection

from 5 to 35.000 ng/L. Measurements were performed without any prior freeze–thaw cycles, and other groups have previously reported excellent stability for both analytes regarding storage and freeze–thaw cycles with the assays used in our study [15,16]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [17].

2.5. Statistical analysis

Continuous normally distributed variables are presented as mean (standard error), and non-normally distributed variables, as assessed by Kolmogorov-Smirnov test (e.g. biomarkers), are presented as median (Q1-3). Differences were compared by the Mann-Whitney *U* test for non-normally distributed variables and by the Student's *t*-test for normally distributed variables. All biomarkers were transformed by the natural logarithm before analyses due to a right-skewed distribution. We presented dichotomous variables as absolute numbers and percentages, and compared categorical data by the Chi-square test. Associations with biomarker concentrations were assessed by univariable and multivariable linear regression analysis, whereas univariable and multivariable logistic regression analysis were used to determine predictors of HFrEF and HFpEF. When we compared non-AHF patients with the subgroups of AHF, patients with HFpEF were excluded when analyzing HFrEF patients and vice versa. We calculated the continuous net reclassification index with the R package PredictABEL [18] to assess the incremental value of biomarkers to basic diagnostic models for HFpEF and HFrEF. Variables in the basic diagnostic models were correlated with the respective diagnoses in multiple logistic regression analysis. The accuracy of biomarkers for diagnosis and prognosis was assessed by operating statistics curve (ROC) analysis with the area under the curve (AUC). The optimal cut-off values for the different biomarkers were found by the Youden index (*J*) method, and used to calculate the respective sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV). We stratified patients according to biomarker quartiles and constructed Kaplan-Meier survival curves to assess associations with mortality, and compared groups by the log-rank test. To identify independent predictors of all-cause mortality we calculated univariable and multivariable Cox proportional hazard regressions models. Analogously to the strategy of previous studies from this cohort [13], variables were included in multivariable analysis if they were significantly associated with the primary endpoint in univariable analyses. We used the Wilcoxon Signed-Rank Test to compare biomarker concentrations at different time points (delta values). When determining the hazard ratio (HR) of delta values, we adjusted for the baseline concentration by calculating HR for the ratio of delta change divided by the baseline concentration. We performed analyses with SPSS for Windows, version 23.0 (IBM Corp, Armonk, NY, USA), Medcalc for Windows, version 19.0 (MedCalc Software, Ostend, Belgium) and R for Windows (R Core Team, 2014).

3. Results

3.1. Patient characteristics

Of the 314 patients in the study, median age was 73 (Q1-3 63–81) years, 150 were women (48%) and 101 patients (32%) had a history of HF. AHF was adjudicated as the primary cause of hospitalization in 143 of 314 patients (46%). The adjudicator consensus of AHF diagnosis was 95% ($\kappa = 0.897$ [0.848–0.946]). Patients with AHF were typically older, more often male, and had more often previously established HF, AF, CAD, hypertension and diabetes mellitus (DM), were less often daily smokers and the prevalence of chronic obstructive pulmonary disease (COPD) was lower (Table 1). Among AHF patients, 91 patients had HFrEF and 52 patients had HFpEF (64% and 36% of the AHF population, respectively). Compared to patients with HFrEF, patients with HFpEF were older, more often women, and had lower prevalence of established HF diagnosis and CAD (Table 1).

3.2. hs-cTnT concentrations in diagnosing acute heart failure

Concentrations of hs-cTnT ranged from 3 to 900 ng/L in the total cohort with a median of 23 (Q1-3 10–42) ng/L. Old age, male sex, NYHA

Table 1
Baseline characteristics ACE2 cohort (n = 314).[a]

	Non-HF (n = 171)	AHF (n = 143)	*P*	HFrEF (n = 91)	HFpEF (n = 52)	*P*
Age, years	67 (61–77)	78 (68–83)	<0.001	74 (66–81)	81 (74–85)	0.003
Male sex	74 (43%)	90 (63%)	0.001	69 (76%)	21 (40%)	<0.001
BMI, kg/m^2	25 (21–30)	27 (22–29)	0.29	27 (22–29)	27 (22–30)	0.47
Smoking	55 (32%)	30 (21%)	0.08	23 (25%)	7 (14%)	0.10
NYHA class IV	71 (42%)	65 (46%)	0.48	42 (46%)	23 (44%)	0.82
LVEF	60 (50–60)	40 (30–55)	<0.001	35 (25–40)	55 (50–60)	<0.001
History of:						
HF	14 (8%)	87 (61%)	<0.001	72 (79%)	15 (29%)	<0.001
AF	28 (16%)	68 (48%)	<0.001	45 (50%)	23 (44%)	0.55
COPD	94 (55%)	61 (43%)	0.030	38 (42%)	23 (44%)	0.77
CAD	33 (19%)	77 (54%)	<0.001	61 (67%)	16 (31%)	<0.001
HT	51 (30%)	69 (48%)	0.001	39 (43%)	30 (58%)	0.09
DM	25 (15%)	43 (30%)	0.001	29 (32%)	14 (27%)	0.54
Vitals in the ED:						
Heart rate, bpm	94 (2)	92 (3)	0.19	93 (3)	91 (4)	0.82
sBP, mmHg	145 (2)	147 (3)	0.67	146 (4)	147 (4)	0.77
dBP, mmHg	78 (1)	82 (2)	0.12	84 (2)	78 (2)	0.09
Fever, ≥ 38 °C	28 (16%)	9 (6%)	0.008	6 (7%)	3 (6%)	0.85
Biomarkers:						
hs-cTnT on admission, ng/L	13 (4–25)	38 (22–75)	<0.001	35 (23–74)	39 (19–96)	0.79
hs-cTnT on day 2, ng/L	13 (5–27)	35 (22–71)	<0.001	36 (23–70)	35 (22–113)	0.71
hs-cTnT on discharge, ng/L	14 (4–26)	32 (16–48)	<0.001	28 (14–42)	34 (28–48)	0.49
NT-proBNP on admission, ng/L	348(119–1139)	3600(1601–8396)	<0.001	4308(2064–8738)	2293(704–4536)	<0.001
CRP, mg/L	22 (3–65)	13 (5–37)	0.044	13 (5–30)	17 (6–40)	0.26
eGFR, ml/min/1.73 m^2	87 (69–106)	66 (47–81)	<0.001	67 (45–81)	63 (47–82)	0.90

BMI, Body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; HT, hypertension; DM, diabetes mellitus; sBP, systolic blood pressure; dBP, diastolic blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate

[a] Data are presented as mean (SE), n (%), or median (Q1-Q3).

functional class IV, and greater NT-proBNP concentrations were associated with increasing hs-cTnT concentrations, and these variables in combination explained 54% of the variance of hs-cTnT concentrations in the total study population (Table 2). Compared with patients with non-AHF related dyspnea, AHF patients had higher concentrations of hs-cTnT: 38 (Q1-3 22–75) vs 13 (4–25) ng/L, p < 0.001; and NT-proBNP: 3600 (1601–8396) vs 348 (119–1139) ng/L, p < 0.001. hs-cTnT concentrations were comparable between HFpEF and HFrEF: 39 (19–104) vs. 35 (23–74) ng/L, p = 0.80, while NT-proBNP concentrations were lower in patients with HFpEF compared to HFrEF: 2293 (687–4569) vs 4308 (2064–8738) ng/L, p = 0.001.

In multivariable logistic regression analyses, history of HF and COPD, and hs-cTnT, NT-proBNP, and C-reactive protein concentrations were associated with AHF (Table 3). Elevated hs-cTnT (OR 2.52 [95% CI 1.56–4.07], p < 0.001) and NT-proBNP (1.42 [1.04–1.93], p = 0.028) concentrations, history of HF, and hypertension were associated with a diagnosis of HFpEF in our population (Supplementary Table 1). Adding hs-cTnT to a basic model for HFpEF that included NT-proBNP and clinical variables resulted in a net reclassification improvement of 0.51 (95% CI 0.46–0.56; p < 0.001). In contrast, hs-cTnT concentrations were not associated with HFrEF in multivariable analysis: OR 1.62 (95% CI 0.86–3.01), p = 0.13 (Supplementary Table 2).

AUC to diagnose AHF in the total cohort was 0.80 (95% CI 0.75–0.85) for hs-cTnT and 0.85 (0.81–0.89) for NT-proBNP (Supplementary Table 3). AUC for NT-proBNP to diagnose HFrEF was superior to hs-cTnT: 0.89 (0.85–0.93) vs. 0.80 (0.75–0.86), p = 0.003, while we found comparable AUCs for NT-proBNP and hs-cTnT to differentiate HFpEF from non-HF-related dyspnea: 0.79 (0.73–0.86) vs 0.80 (0.73–0.86), respectively, p = 0.95. The AUC to diagnose HFpEF for hs-cTnT and NT-proBNP combined was 0.83 (0.76–0.89).

3.3. hs-cTnT concentrations and prognosis in acute dyspnea

In total, 114 patients (37%) died during median 823 (Q1-3 471–998) days of follow-up. Stratifying all patients based on quartiles of hs-cTnT concentrations separated patients with a poor and favorable prognosis (p < 0.001 by log-rank test). Patients with both hs-cTnT and NT-proBNP concentrations above the median had significantly worse outcome compared to having both markers below median (Fig. 2; p < 0.001 by log-rank test). After adjustment for NT-proBNP and other risk indices, hs-cTnT concentrations at hospital admission were associated with mortality in the total cohort after adjustment for other covariates: HR 1.30 (95% CI 1.07–1.58) per 1 unit increase in $_{ln}$hs-cTnT (p = 0.009) (Table 4). For the total cohort, the AUC for hs-cTnT and NT-proBNP to predict mortality were comparable with AUC 0.70 (95% CI 0.64–0.75) and 0.67 (0.61–0.72), respectively, p = 0.32 (Supplementary Table 4).

In total 66 patients (46%) diagnosed with AHF died during follow-up. For these patients, the AUC for hs-cTnT was 0.65 (0.56–0.74) to predict mortality and the AUC of NT-proBNP was 0.67 (0.58–0.76). Higher concentrations of hs-cTnT were associated with mortality among AHF patients in unadjusted Cox regression analysis (p = 0.005), but this association was attenuated and no longer significant after adjustment for other risk indices and NT-proBNP (p = 0.15) (Supplementary Table 5). For non-AHF patients, we found hs-cTnT concentrations to be associated with mortality also in adjusted Cox regression analysis (p = 0.009) (Supplementary Table 6).

Table 2
Variables associated with increased hs-cTnT concentrations (n = 314).

	B	95% CI	P-value
Univariate linear regression			
Age	0.042	0.034–0.050	<0.001
Male sex	0.538	0.282–0.793	<0.001
BMI	−0.018	−0.036–0.001	0.06
Smoking	−0.447	−0.737–0.156	0.003
NYHA class IV	0.553	0.296–0.810	<0.001
History of:			
HF	0.834	0.569–1.098	<0.001
AF	0.589	0.312–0.865	<0.001
COPD	0.147	−0.115–0.408	0.27
CAD	0.762	0.501–1.022	<0.001
HT	0.563	0.301–0.825	<0.001
DM	0.427	0.113–0.742	0.008
$_{ln}$NT-proBNP	0.420	0.368–0.473	<0.001
$_{ln}$CRP	0.090	0.001–0.179	0.047
$_{ln}$eGFR	−1.129	−1.402–0.856	<0.001
Multivariable linear regression (backward selection) (r^2 = 0.54)			
Age	0.016	0.009–0.024	<0.001
Male sex	0.503	0.321–0.684	<0.001
NYHA class IV	0.326	0.141–0.510	0.001
$_{ln}$NT-proBNP	0.314	0.251–0.377	<0.001

Abbreviations as described in table 1.

Table 3
Variables associated with AHF as assessed by univariate and multivariable logistic regression analysis (n = 314).

	OR	95% CI	P-value	Wald
Univariate logistic regression				
Age	1.055	1.034–1.076	<0.001	27.65
Male sex	2.226	1.413–3.507	0.001	11.90
BMI	1.004	0.974–1.036	0.79	0.07
Smoking	0.560	0.335–0.937	0.027	4.88
NYHA class IV	1.174	0.750–1.837	0.48	0.49
History of:				
HF	17.422	9.172–33.093	<0.001	76.22
AF	4.630	2.749–7.799	<0.001	33.20
COPD	0.609	0.389–0.954	0.030	4.70
CAD	5.018	3.036–8.295	<0.001	39.57
HT	2.194	1.380–3.488	0.001	11.03
DM	2.511	1.442–4.373	0.001	10.58
$_{ln}$hs-cTnT	3.447	2.534–4.689	<0.001	62.13
$_{ln}$NT-proBNP	2.631	2.121–3.264	<0.001	77.46
$_{ln}$CRP	0.828	0.709–0.968	0.018	5.62
$_{ln}$eGFR	0.121	0.062–0.236	<0.001	38.45
Multivariable logistic regression (backward: LR)				
$_{ln}$hs-cTnT	2.387	1.540–3.701	<0.001	15.13
$_{ln}$NT-proBNP	2.142	1.579–2.907	<0.001	23.91
$_{ln}$CRP	0.521	0.392–0.694	<0.001	19.88
History of:				
HF	12.138	5.305–27.773	<0.001	34.94
COPD	0.357	0.171–0.746	0.006	7.51
HT	1.916	0.940–3.908	0.07	3.20

Abbreviations as described in Table 1.

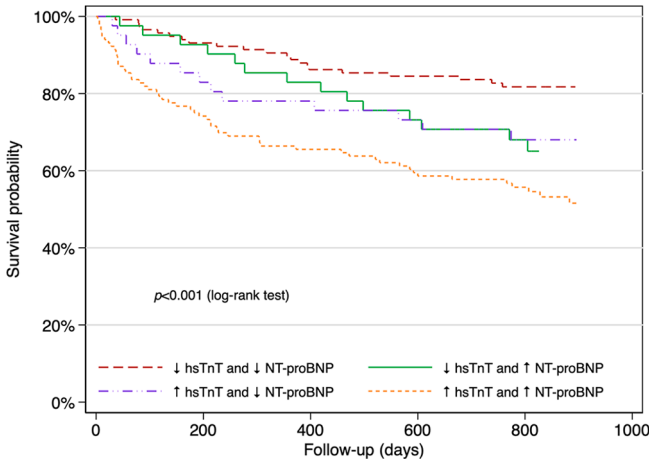

Fig. 2. Cumulative survival in patients with acute dyspnea stratified according to concentrations above or below median for hs-cTnT and NT-proBNP.

Table 4
Variables associated with all-cause mortality during follow-up as assessed by univariate and multivariable Cox proportional hazard regression analysis (n = 314).

	HR	95% CI	P-value
Univariate			
Age	1.048	1.031–1.066	<0.001
Male sex	0.997	0.691–1.440	0.99
BMI	0.930	0.899–0.961	<0.001
Smoking	0.957	0.628–1.460	0.84
NYHA class IV	1.858	1.283–2.691	0.001
History of:			
HF	1.951	1.345–2.828	<0.001
AF	1.713	1.176–2.495	0.005
COPD	2.146	1.457–3.161	<0.001
CAD	1.294	0.888–0.883	0.18
HT	1.271	0.876–1.844	0.21
DM	1.251	0.812–1.928	0.31
$_{ln}$hs-cTnT	1.560	1.346–1.808	<0.001
$_{ln}$NT-proBNP	1.369	1.224–1.530	<0.001
$_{ln}$CRP	1.112	0.983–1.256	0.09
$_{ln}$eGFR	0.522	0.342–0.798	0.003
Multivariable (backward: LR)			
$_{ln}$hs-cTnT	1.299	1.067–1.581	0.009
$_{ln}$NT-proBNP	1.174	1.020–1.351	0.025
Age	1.030	1.010–1.051	0.004
BMI	0.947	0.913–0.981	0.003
History of COPD	2.258	1.498–3.402	<0.001

Abbreviations as described in Table 1.

3.4. Serial hs-cTnT measurements in AHF

In the subgroup of patients with serial samples available, we found no significant change in hs-cTnT concentrations from baseline (median [Q1-3] 37.9 [22.1–83.8] ng/L) to day 2 (35.2 [21.9–76.3] ng/L, p = 0.22) among patients adjudicated as AHF. This was also the case when separating AHF patients into patients with HFrEF (33.2 [21.7–81.3] vs 32.6 [22.0–70.0] ng/L, p = 0.66) and HFpEF (41.2 [22.4–118.1] vs 35.3 [21.7–112.6] ng/L, p = 0.15). In contrast, we found a small reduction from baseline (24.0 [11.5–42.5] ng/L) to day 2 (22.3 [10.2–40.0] ng/L, p = 0.011) in the total study population with available serial samples. There was no association between decline in hs-cTnT concentrations and mortality in the total study population: HR 1.21 (95% CI 0.59–2.47), p = 0.60.

We also found a significant reduction in hs-cTnT concentrations from baseline to discharge in patients with serial samples: 27.1 (Q1-3 15.7–42.3) vs. 22.5 (8.7–36.9) ng/L, p = 0.001. The reduction from baseline to discharge did not predicted mortality: HR 1.00 (0.99–1.01), p = 0.60.

4. Discussion

The main result of this study is that hs-cTnT provides diagnostic information for HFpEF in an ED setting for patients presenting with acute dyspnea. In contrast, hs-cTnT concentrations did not add information to diagnose HFrEF, probably due to the excellent diagnostic accuracy of NT-proBNP in this population. Secondary, hs-cTnT improved risk stratification for the total population of ED patients presenting with acute dyspnea.

Cardiac troponins predict incident HF in both the general population [19] and among patients with established CAD [20]. Elevated cardiac troponin concentrations have also been found to predict mortality in both acute and chronic HF [10,21]. In line with this, U.S. guidelines recommend assessment of cardiac troponins on hospital admission in AHF (class IA) and in patients with chronic HF to assess risk of rehospitalization and death (class IIb) [22]. European guidelines also recommend measurement of cardiac troponins in patients with suspected AHF (class IC), primarily for detection of ACS as the underlying cause of AHF [4]. Despite being associated with the diagnosis of AHF [9], neither U.S. nor European guidelines recommend measurement of cardiac troponins to aid the diagnosis of AHF. It should be noted that currently none of the official HF guidelines recommend routine screening of hs-cTnT and natriuretic peptides unless there is suspicion of HF or ACS [4,22].

In our study, we found that median NT-proBNP concentrations were two-fold higher in patients with acute HFrEF compared to acute HFpEF. B-type natriuretic peptide production is known to be markedly influenced by cardiomyocyte stretch [23], which is higher in HFrEF patients with LV dilatation compared to HFpEF patients with preserved LV dimensions. Hence, we believe that lower wall stretch and -stress in acute HFpEF compared to HFrEF could partly explain the lower NT-proBNP concentrations found in our study, and also prior studies by other groups [24,25]. We also found hs-cTnT concentrations to be elevated in AHF patients, but in contrast to NT-proBNP, hs-cTnT concentrations were similar in HFpEF and HFrEF, and AUCs for hs-cTnT to diagnose these subgroups of AHF were comparable. Of note, hs-cTnT concentrations appear to be primarily associated with LV mass [26,27] and not so much LV systolic function, which indicate a link between cardiac troponin concentrations and HFpEF [28,29]. Other mechanisms could also contribute to the discrepancy between hs-TnT and NT-proBNP concentrations in HFrEF and HFpEF, including different release of cardiac troponin and B-type natriuretic peptides from atrial and ventricular cardiomyocytes.

Hospitalized HFpEF patients have elevated hs–cTnT concentrations [11], and we found that adding hs-cTnT to a diagnostic model of NT-proBNP and clinical variables reclassified patients to a correct diagnosis of HFpEF. This supports a potential of adding hs-cTnT measurements to NT-proBNP measurements in ED settings to identify HFpEF, which is attractive as the lower NT-proBNP concentrations in HFpEF patients also leads to more overlap and therefore inferior diagnostic accuracy for NT-proBNP to separate HFpEF patients from patients with non-HF-related dyspnea [24,25]. With the improved analytical performance of hs-cTnT assays, concentrations within reference intervals can now be measured in most healthy individuals, and concentrations below the 99th percentile still provide important diagnostic and prognostic information [30]. Instead of the old dichotomous interpretation of troponin levels as “positive” or “negative”, which is common for acute coronary syndrome, troponins should now be interpreted as a continuous variable and indicator of disease burden, particularly in the absence of coronary syndromes. In HF, troponins reflect different disease pathways than NT-proBNP [31] and might be useful as a supplement in the diagnostic workup of patients. When symptoms of HF are disproportionate with NT-proBNP concentrations, slightly elevated hs-cTnT concentrations could be an indicator of HF/HFpEF when ACS is excluded.

Cardiac troponins concentrations predict mortality across different populations, including patients with AHF [10] and acute exacerbation of COPD [32]. In our cohort, higher concentrations of both NT-proBNP and hs-cTnT at hospital admission independently predicted all–cause mortality. In unadjusted analysis, hs-cTnT was also predictive of all-cause mortality among the subset of AHF patients, but this association was attenuated when adjusted for NT-proBNP and clinical variables. This contrasts previous findings of hs-cTnT as a strong prognostic factor among patients with AHF [10], and the lack of independent association in our study may be due to limited power in this subset of patients. For patients with non-AHF-related dyspnea, hs-cTnT did predict mortality in adjusted analysis. This is in line with the BACH trial, with patients and setting comparable to our study. They also found that cardiac troponins predicted mortality among patients hospitalized due to acute dyspnea in the total cohort [33], and similar to our results, cardiac troponin was a stronger predictor of mortality among patients without AHF, compared to patients with AHF [34], in an ED setting. In line with this, several recent large studies have demonstrated particularly high mortality among patients with elevated cardiac troponin concentrations due to non-cardiac causes, such as pulmonary embolism, end-stage renal

disease, pneumonia, and central nervous system pathology [35,36]. Among these patients without acute cardiac disease, and particularly without ACS, we believe an elevated cardiac troponin concentration should be interpreted as the global burden of comorbidities with reduced organ level reserve and not as a marker of unstable CAD [35]. Pertinent to this point; our data could also be of relevance to understand the information provided by cardiac troponins in the recent pandemic of coronavirus-19 disease (Covid-19). Early reports have found increased mortality among elderly Covid-19 patients with comorbidities like hypertension and type 2 diabetes mellitus [37], which are clinical characteristics also common in our population. Hence, it might be wise to assess whether elderly Covid-19 patients with respiratory failure and high hs-cTnT concentrations might have concomitant, and often undiagnosed, HF/HFpEF.

4.1. Strengths and limitations

Strengths of the current study include a dedicated diagnostic adjudication committee with excellent agreement between the adjudicators. Biological specimens and patient related data were collected by dedicated study personnel in a uniform manner. hs-cTnT and NT-proBNP concentrations were measured at a core laboratory as a batch, thereby avoiding problems with variation in lab calibration over time. Limitations include relatively short follow-up, and single-center design with a moderate sample size. The limited sample size, particularly for the subgroup with acute HF, made the study underpowered to examine the prognostic value of hs-cTnT, specifically in patients with acute HF or HFrEF and HFpEF independently, and data should be interpreted in this context. There was no protocol for echocardiography and patients where the treating physician deemed AHF unlikely may not have received an echocardiogram, which is similar to the protocol of previous studies with unselected dyspneic patients [24]. All AHF patients had echocardiographic data available, either obtained during the current or recent hospitalization. A lack of cardiac imaging in the non-AHF population might have contributed to underdiagnosing of AHF, and particularly HFpEF, in which we have demonstrated that biomarkers are less sensitive.

5. Conclusion

In conclusion, we found that hs-cTnT provides useful diagnostic information among patients admitted to the ED with dyspnea. In particular, elevated hs-cTnT seems to be valuable in identifying patients with HFpEF. hs-cTnT also provides prognostic information for an unselected population with dyspnea, but a larger cohort is needed to examine the prognostic value of hs-cTnT for the subgroup of HF/HFrEF/HFpEF patients. Further studies are warranted to elucidate the pathophysiology of cardiac troponin release in patients with dyspnea, and especially in patients with HFpEF.

Funding

This work was supported by a research grant from the Norwegian Research Council [197992/B-07029] to TO and HR, and by internal grants from Akershus University Hospital [41810/340104].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to acknowledge the contribution by the Clinical Trial Unit, Division of Medicine, Akershus University Hospital, for patient inclusion and especially thank Vigdis Bakkelund, RN; Annika Lorentzen, RN; and Marit Holmefjord Pedersen, BSc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2020.11.009.

References

[1] T.J. Ryan, et al., ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction), J. Am. Coll. Cardiol. 28 (5) (1996) 1328–1428.
[2] L. Erhardt, Task force on the management of chest pain, Eur. Heart J. 23 (15) (2002) 1153–1176, https://doi.org/10.1053/euhj.2002.3194.
[3] M. Roffi, C. Patrono, J.-P. Collet, C. Mueller, M. Valgimigli, F. Andreotti, J.J. Bax, M.A. Borger, C. Brotons, D.P. Chew, B. Gencer, G. Hasenfuss, K. Kjeldsen, P. Lancellotti, U. Landmesser, J. Mehilli, D. Mukherjee, R.F. Storey, S. Windecker, 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC), Eur. Heart J. 37 (3) (2016) 267–315, https://doi.org/10.1093/eurheartj/ehv320.
[4] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, V. Falk, J.R. González-Juanatey, V.-P. Harjola, E.A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J.T. Parissis, B. Pieske, J.P. Riley, G.M.C. Rosano, L. M. Ruilope, F. Ruschitzka, F.H. Rutten, P. van der Meer, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the spec, Eur. J. Heart Fail. 18 (8) (2016) 891–975, https://doi.org/10.1002/ejhf.592.
[5] K.S. Shah, H. Xu, R.A. Matsouaka, D.L. Bhatt, P.A. Heidenreich, A.F. Hernandez, A. D. Devore, C.W. Yancy, G.C. Fonarow, Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction, J. Am. Coll. Cardiol. 70 (20) (2017) 2476–2486, https://doi.org/10.1016/j.jacc.2017.08.074.
[6] T.B. Horwich, G.C. Fonarow, Prevention of Heart Failure, JAMA Cardiol. 2 (1) (2017) 116, https://doi.org/10.1001/jamacardio.2016.3394.
[7] S.-H. Kang, J.J. Park, D.-J. Choi, C.-H. Yoon, I.-Y. Oh, S.-M. Kang, B.-S. Yoo, E.-S. Jeon, J.-J. Kim, M.-C. Cho, S.C. Chae, K.-H. Ryu, B.-H. Oh, Prognostic value of NT-proBNP in heart failure with preserved versus reduced EF, Heart 101 (23) (2015) 1881–1888, https://doi.org/10.1136/heartjnl-2015-307782.
[8] K. Bishu, et al., Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction, Am. Heart J. 164 (5) (2012) 763–770 e3.
[9] J.L., Januzzi Jr., et al., Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. Eur. Heart J., 2012. 33(18): p. 2265-71.
[10] W.F. Peacock IV, T. De Marco, G.C. Fonarow, D. Diercks, J. Wynne, F.S. Apple, A.H. B. Wu, Cardiac Troponin and Outcome in Acute Heart Failure, N. Engl. J. Med. 358 (20) (2008) 2117–2126, https://doi.org/10.1056/NEJMoa0706824.
[11] P.S. Jhund, et al., Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696, Circ. Heart Fail 7 (6) (2014) 953–959.
[12] P.L. Myhre, et al., Cardiac Troponin I and Risk of Cardiac Events in Patients With Heart Failure and Preserved Ejection Fraction, Circ. Heart Fail 11 (11) (2018), e005312.
[13] H. Rosjo, et al., Influence of glycosylation on diagnostic and prognostic accuracy of N-terminal pro-B-type natriuretic peptide in acute dyspnea: data from the Akershus Cardiac Examination 2 Study, Clin. Chem. 61 (8) (2015) 1087–1097.
[14] A.D. Hoiseth, et al., The influence of heart failure co-morbidity on high-sensitivity troponin T levels in COPD exacerbation in a prospective cohort study: data from the Akershus cardiac examination (ACE) 2 study, Biomarkers 21 (2) (2016) 173–179.
[15] M. Mansour, L. Clark, P.A. Kavsak, Effect of freeze-thaw and refrigeration conditions on high-sensitivity troponin T concentrations, Ann. Clin. Biochem. 49 (Pt 1) (2012) 101–102.
[16] W.L. Nowatzke, T.G. Cole, Stability of N-terminal pro-brain natriuretic peptide after storage frozen for one year and after multiple freeze-thaw cycles, Clin. Chem. 49 (9) (2003) 1560–1562.
[17] A.S. Levey, et al., A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group, Ann. Intern. Med. 130 (6) (1999) 461–470.
[18] S. Kundu, et al., PredictABEL: an R package for the assessment of risk prediction models, Eur. J. Epidemiol. 26 (4) (2011) 261–264.
[19] M.N. Lyngbakken, et al., Gender, High-Sensitivity Troponin I, and the Risk of Cardiovascular Events (from the Nord-Trondelag Health Study), Am. J. Cardiol. 118 (6) (2016) 816–821.
[20] T. Omland, et al., A sensitive cardiac troponin T assay in stable coronary artery disease, N. Engl. J. Med. 361 (26) (2009) 2538–2547.
[21] R. Latini, et al., Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure, Circulation 116 (11) (2007) 1242–1249.

[22] C.W. Yancy, et al., 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, Circulation 136 (6) (2017) e137–e161.
[23] E.R. Levin, D.G. Gardner, W.K. Samson, Natriuretic peptides, N. Engl. J. Med. 339 (5) (1998) 321–328.
[24] A.S. Maisel, et al., Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study, J. Am. Coll. Cardiol. 41 (11) (2003) 2010–2017.
[25] M. O'Donoghue, et al., The effects of ejection fraction on N-terminal ProBNP and BNP levels in patients with acute CHF: analysis from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, J. Card Fail 11 (5 Suppl) (2005) S9–S14.
[26] J.A. de Lemos, et al., Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population, JAMA 304 (22) (2010) 2503–2512.
[27] H. Rosjo, et al., Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy, Am. J. Cardiol. 108 (1) (2011) 88–91.
[28] P.L. Myhre, et al., Association Between Circulating Troponin Concentrations, Left Ventricular Systolic and Diastolic Functions, and Incident Heart Failure in Older Adults, JAMA Cardiol. (2019).
[29] M.N. Lyngbakken, et al., Cardiac Troponin I and T Are Associated with Left Ventricular Function and Structure: Data from the Akershus Cardiac Examination 1950 Study, Clin. Chem. 66 (4) (2020) 567–578.
[30] J.T. Saunders, et al., Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study, Circulation 123 (13) (2011) 1367–1376.
[31] N.E. Ibrahim, J.L. Januzzi Jr., Established and Emerging Roles of Biomarkers in Heart Failure, Circ. Res. 123 (5) (2018) 614–629.
[32] A.D. Hoiseth, et al., Elevated high-sensitivity cardiac troponin T is associated with increased mortality after acute exacerbation of chronic obstructive pulmonary disease, Thorax 66 (9) (2011) 775–781.
[33] A. Maisel, et al., Midregion prohormone adrenomedullin and prognosis in patients presenting with acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial, J. Am. Coll. Cardiol. 58 (10) (2011) 1057–1067.
[34] A. Maisel, et al., Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial, J. Am. Coll. Cardiol. 55 (19) (2010) 2062–2076.
[35] A. Kaura, et al., Association of troponin level and age with mortality in 250 000 patients: cohort study across five UK acute care centres, BMJ 367 (2019), l6055.
[36] C. Wu, et al., Causes of Troponin Elevation and Associated Mortality in Young Patients, Am. J. Med. 131 (3) (2018) 284–292 e1.
[37] W.J. Guan, et al., Clinical Characteristics of Coronavirus Disease 2019 in China, N. Engl. J. Med. (2020).