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Admission high-sensitivity troponin T and NT-proBNP for outcome prediction in acute heart failure

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ABSTRACT

Background: High-sensitivity troponin T (hs-TnT) reflects the severity of ongoing myocardial damage. In acute heart failure (AHF), its additive prognostic value over B-type natriuretic peptides is unclear.
Methods: Individual data of 1499 AHF patients with admission hs-TnT were collected from 3 cohorts.
Results: Patients (78 ± 10 years, 51% men, N-terminal fragment of pro-B-type natriuretic peptide – NT-proBNP - 5660 [2693–12,466], hs-TnT 43 ng/L [26–69]) experiencing in-hospital death ($n = 187$, 13%) had significantly higher hs-TnT and NT-proBNP on admission (both $p < 0.001$). Patients with hs-TnT ≥43 ng/L and NT-proBNP ≥5660 ng/L had a 2.7-fold higher risk of in-hospital death (relative risk - RR 2.7, 95% confidence interval - CI 1.7–4.5). Among discharged patients, 1024 deaths (81%) occurred over 11 months (4–22). In the whole population, hs-TnT ≥43 ng/L predicted all-cause death at 6, 12 and 24 months independently from NT-proBNP ≥5660 ng/L.
The best NT-proBNP cut-off for in-hospital mortality (4382 ng/L) independently predicted this endpoint, while the best hs-TnT cut-off (55 ng/L) did not. Patients with NT-proBNP ≥4382 ng/L and hs-TnT ≥55 ng/L had a 12-fold higher risk of in-hospital death (RR 11.7, 95% CI 6.9–19.7). The best hs-TnT cut-offs independently predicted all post-discharge outcomes.
Conclusions: The best NT-proBNP cut-off (4382 ng/L) independently predicts outcome, while the best hs-TnT (55 ng/L) does not; patients with both biomarkers ≥best cut-offs have a 12-fold higher risk of in-hospital mortality. Admission hs-TnT ≥43 ng/L and the best hs-TnT cut-offs hold independent prognostic significance for post-discharge outcome, while hs-TnT seems less predictive than NT-proBNP when considering absolute values.

1. Introduction

Heart failure (HF) is a leading cause of morbidity and mortality worldwide, and its burden is expected to increase with the aging population [1]. During the natural history of HF, the transition from compensated cardiac dysfunction to the acute symptomatic phase is defined as "new-onset HF" [2]. Afterwards, the clinical course of HF is marked by phases of acute decompensation, characterized by a significant morbidity and mortality, and strong predictors of death or readmission after discharge [2].

Abbreviations: ACCF/AHA, American College of Cardiology Foundation/American Heart Association; AHF, acute heart failure; AUC, area under the curve; CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, acute heart failure; HR, hazard ratio; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; NPV, negative predictive value; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; PPV, positive predictive value; ROC, receiver operating characteristics; RR, relative risk.

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Accurate prognostic stratification is crucial for patients with either new-onset or decompensated acute HF (AHF). On admission, accurate prediction of risk for in-hospital death may be leveraged for superior triage and may promote an enhanced therapeutic effort. For patients surviving the acute phase, a greater likelihood of future decompensation or death might imply need for closer follow-up, a more stringent indication to device or interventional therapy and more rapid titration of life-sparing drug therapies, possibly resulting in improved patient prognosis [2,3].

Circulating cardiac biomarkers may represent valid elements for risk stratification in AHF. In particular, B-type natriuretic peptides, cardiac hormones produced and secreted by ventricular cardiomyocytes, reflecting the severity of hemodynamic overload [4], and cardiac troponins (Tn) reflecting myocardial damage [5], are both central elements in the pathophysiology and clinical evolution of AHF.

Several papers have underscored the clinical utility of the assay of troponins for risk stratification in patients with AHF, as recently reviewed [6]. On the other hand, the assessment of the prognostic value of troponins is complicated by the existence of both traditional [7] and high-sensitivity (hs) assays [8], measuring either TnT [9] or TnI [10], the possibility to measure Tn at different time-points during hospitalization [11,12], and the small size of many cohorts [13,14]. Additionally, the need for a combined assessment of a natriuretic peptide and a hs-troponin for better prognostic stratification remains quite elusive. The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines issued a class I, level of evidence A recommendations for both NP and Tn measurement, though not explicitly state the need for a multi-marker strategy for risk prediction [15]. The latest European Society of Cardiology Guidelines even avoid considering biomarkers as possible tools for risk stratification in AHF [16].

To overcome these limitations, we analyzed a multi-center cohort AHF patients to explore the prognostic value of hs-TnT relative to N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP), and to search for reliable prognostic thresholds in the short- and long-term.

2. Methods

2.1. Patient population

In this retrospective analysis, individual patient data from 3 cohorts were collected: the Epidemiology of Acute Heart Failure in Emergency Departments (EAHFE) cohort ($n = 611$, 42%, enrolled from 2011 to 2014) [8], and 2 single-center populations from the Basel University Hospital, Basel, Switzerland ($n = 637$, 44%, enrolled from 2006 to 2015) and the Murcia University Hospital, Murcia, Spain ($n = 201$, 14%, enrolled from 2006 to 2010) [14]. The overall population included 1449 patients hospitalized for AHF, with hs-TnT measured on admission, and either experiencing in-hospital death or being followed-up at least for all-cause mortality. Patients with right HF due to pulmonary embolism were not included. The diagnosis of AHF was made when patients presented acutely with signs and symptoms of HF, which were attributed to a cardiac cause after a workup including natriuretic peptide testing. Patients with acute coronary syndromes (diagnosed according to the European Society of Cardiology Guidelines [17,18]), myocarditis, or cardiogenic shock were excluded. Patients received Guideline-recommended treatment for HF [15,16].

In all cohorts, serum samples for biomarker testing were obtained at presentation of patients to the emergency department. The only validated hs-TnT method (Roche Diagnostics®, Basel, Switzerland; limit of blank 3 ng/L, limit of detection 5 ng/L, 99th percentile value in apparently healthy individuals 14 ng/L) was used in all cohorts [19]. Admission NT-proBNP was available for 1218 patients (78%), and was measured through the ECLIA monoclonal method (Roche Diagnostics®). Estimated glomerular filtration rate (eGFR) was estimated through the Chronic Kidney Disease Epidemiology collaboration equation [20].

2.2. Statistical analysis

The analysis was performed using IBM SPSS Statistics (version 22, 2013) and R statistical software (http://www.r-project.org/, version 3.4.4). Normal distribution was assessed through the Kolmogorov-Smirnov test; variables with normal distribution were presented as mean ± standard deviation, while those with non-normal distribution as median and interquartile interval. Mean differences among groups were evaluated through the unpaired Student *t*-test. Categorical variables were compared by the Chi-square test with Yates correction. Together with median biomarker values on admission, the best cut-offs were searched through the Youden method. A prognostic model was defined, including all available variables with missing values in <5% of patients, excluding multicollinearity by calculating the variance inflation factor. This model included patient cohort, age, sex, new-onset vs. worsening HF, history of coronary artery disease (CAD), admission left ventricular ejection fraction (LVEF), New York Heart Association class, systolic blood pressure, heart rate, eGFR, plasma hemoglobin, sodium, white blood cell count, history of atrial fibrillation, hypertension, diabetes, COPD. The Fine-Gray model was used to account for mutually exclusive endpoints; non-cardiovascular death was considered as competing risk for cardiovascular death. NT-proBNP and hs-TnT values were $\log_2$-transformed, so that the hazard ratio expressed the increase in risk per each doubling of absolute biomarker values. Because the proportional hazard assumption in Cox model was not met, as demonstrated through the Schoenfeld Residuals Test, the prognostic value of median NT-proBNP and hs-TnT for in-hospital death and post-discharge outcome was evaluated in multivariate logistic regression analysis, considering the 6-, 12-, and 24-month timepoints. The net reclassification improvement and the integrated discrimination improvement were calculated to assess reclassification, with risk categories set at <10%, 10–30% and >30%. Two-tailed p values <0.05 were considered significant.

3. Results

3.1. Population characteristics and in-hospital outcome

The present study evaluated 1449 patients from 3 cohorts (**Supplemental Table 1**). Patients were aged 78 ± 10 years, 51% were men, and 45% had an history of CAD. Median LVEF was 50% (33–60). The index hospitalization was the first manifestation of HF in 31% of patients. Median eGFR was 46 mL/min/1.73 m^2 (32–68), while median hs-TnT and NT-proBNP concentrations were 43 ng/L (26–69) and 5660 (2693–12,466), respectively (Table 1).

In-hospital death occurred in 187 patients (13%). These patients were significantly older, more symptomatic on admission, with worse renal function and higher white blood cell count (possibly denoting pneumonia or other infections). The rates of in-hospital death were heterogeneous across cohorts, with patients from the EAHFE cohort having the highest rate (Table 1).

3.2. Median admission NT-proBNP and hs-TnT for the prediction of in-hospital death

Patients experiencing in-hospital death had significantly higher NT-proBNP and hs-TnT on admission (Fig. 1). The risk of in-hospital death increased by 32% per each doubling of NT-proBNP (HR 1.32, 95% confidence interval - CI 1.17–1.50, $p < 0.001$), and by 45% per each doubling of hs-TnT (HR 1.45, 95% CI 1.31–1.59, $p < 0.001$). When NT-proBNP and hs-TnT were added to the prognostic model specified in the Methods section, hs-TnT was independently associated with in-hospital death (HR 1.30, 95% CI 1.07–1.60; $p = 0.010$), whereas NT-proBNP was not ($p = 0.156$).

When added to the prognostic model above, neither NT-proBNP ≥5660 ng/L nor hs-TnT ≥43 ng/L were independent predictors of outcome (p values 0.882 and 0.206, respectively). Nevertheless, patients with NT-proBNP ≥5660 ng/L and hs-TnT ≥43 ng/L had a 2.7-fold higher risk of in-hospital death (relative risk - RR 2.7, 95% CI 1.7–4.5). Patients with only NT-proBNP ≥5660 ng/L had a similar risk than patients with both biomarkers <median (RR 1.0, 95% CI 0.4–2.0), while those with only hs-TnT ≥43 ng/L had a RR 1.9 (95% CI 1.0–3.4; Fig. 2). The combination of both biomarkers ≥median had a 67% sensitivity, 53% specificity, 93% positive predictive value (PPV), and 15% negative predictive value (NPV) for the prediction of in-hospital death (**Supplemental Table 2**).

3.3. Median admission hs-TnT and NT-proBNP as predictors of post-discharge outcome

Among the 1262 patients discharged, 1024 deaths (81%) were recorded over a median 11-month follow-up (4–22; **Supplemental Fig. 1**). Information on cardiovascular death was available for 792 patients (63%); among them, 415 experienced cardiovascular death (29%).

Table 1
Population characteristics on admission.

	Whole population (n = 1449)	In-hospital death (n = 187, 13%)	Alive at discharge (n = 1262, 87%)	p
Cohort (EAHFE, Swiss, Murcia; n, %)	611, 637, 201 (42, 44, 14)	137, 41, 9 (73, 22, 5)	474, 596, 192 (38, 47, 15)	**<0.001**
Age (years)	78 ± 10	80 ± 8	78 ± 10	**<0.001**
Men (n, %)	737 (51)	80 (43)	657 (52)	**0.016**
New-onset HF (n, %)	452 (31)	77 (41)	375 (30)	**0.001**
History of CAD (n, %)	656 (45)	57 (31)	599 (48)	**<0.001**
LVEF (%)	50 (33–60)	45 (30–57)	50 (33–60)	0.888
NYHA class (III, IV; n, %)	669, 747 (46, 52)	48, 130 (25, 70)	621, 613 (49, 49)	**<0.001**
SAP (mmHg)	137 (119–158)	128 (111–151)	138 (120–158)	**<0.001**
Heart rate (b.p.m.)	87 (74–105)	86 (75–103)	87 (73–106)	0.732
eGFR (mL/min/1.73 m^2)	46 (32–68)	42 (28–56)	47 (32–69)	**<0.001**
Hb (g/dL)	12.2 (11.0–13.7)	11.7 (10.7–13.2)	12.2 (11.0–13.7)	0.129
Sodium (mEq/L)	138 (136–141)	138 (133–141)	138 (136–141)	**0.036**
White blood cell count (cell/mm^3)	8450 (6838–10,833)	10,200 (8005–13,440)	8380 (6705–10,645)	**<0.001**
History of AF (n, %)	662 (46)	77 (41)	585 (46)	0.159
Hypertension (n, %)	1221 (84)	149 (80)	1072 (85)	**0.048**
Diabetes (n, %)	593 (41)	88 (47)	505 (40)	**0.069**
COPD (n, %)	384 (27)	47 (25)	337 (27)	0.633
NT-proBNP (ng/L)	5660 (2693–12,466)	10,244 (4738–22,180)	5433 (2544–11,634)	**<0.001**
hs-TnT (ng/L)	43 (26–69)	82 (37–237)	43 (26–75)	**<0.001**
Therapy at discharge				
ACEi/ARB (n, %)	925 (64)	–	853 (68)	–
BB (n, %)	781 (54)	–	731 (58)	–
MRA (n, %)	342 (24)	–	319 (25)	–
Diuretics (n, %)	1177 (81)	–	1076 (85)	–

ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AF, atrial fibrillation; BB, beta-blockers; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EAHFE, Epidemiology of Acute Heart Failure in Emergency Departments; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide; NYHA, New York Heart Association; SAP, systolic arterial pressure.
Significant p values are reported in bold.

The number of events at the different timepoints is provided in **Supplemental Table 3**. In the whole population ($n = 1449$), absolute NT-proBNP levels on admission appeared a stronger predictor of post-discharge outcome than hs-TnT values (Table 2), as confirmed through reclassification analysis (**Supplemental Table 4**). By contrast, when classifying patients according to the cut-offs above, admission hs-TnT ≥43 ng/L emerged as a strong, independent predictor of all-cause death at each timepoint (Table 2), with a better performance at risk reclassification analysis than NT-proBNP ≥5660 ng/L (**Supplemental Table 5**). A similar pattern was observed when categorizing patients according to median admission LVEF (<50% vs. ≥50%; **Supplemental Table 6**). The combination of NT-proBNP ≥5660 ng/L and hs-TnT ≥43 ng/L had a good sensitivity for outcome prediction at the different time-points (**Supplemental Table 2**).

3.4. Best cut-offs for outcome prediction

As an additional analysis, the best cut-offs for each endpoint were searched (**Supplemental Table 7**). When adding both NT-proBNP and hs-TnT to the prognostic model above, the best NT-proBNP cut-off for in-hospital mortality (4382 ng/L) independently predicted this endpoint, while the best hs-TnT cut-off (55 ng/L) did not. Patients with both NT-proBNP ≥4382 ng/L and hs-TnT ≥55 ng/L had an almost 12-fold higher risk of in-hospital mortality (RR 11.7, 95% CI 6.9–19.7).

The best hs-TnT cut-offs for all post-discharge endpoints were independent predictors of outcome, whereas, among the best NT-proBNP cut-offs, only the one for 6-month all-cause mortality independently predicted the corresponding endpoint (**Supplemental Table 7**).

4. Discussion

In a population of 1449 patients with either new-onset or decompensated AHF, those with both biomarkers assayed at admission ≥ median value (hs-TnT ≥43 ng/L and NT-proBNP ≥5660 ng/L) had a 2.7-fold higher risk of in-hospital death. When adding the best NT-proBNP and hs-TnT cut-offs (4382 ng/L and 55 ng/L, respectively) to baseline patient characteristics, only NT-proBNP ≥4382 ng/L independently predicted in-hospital mortality. Among discharged patients, admission hs-TnT ≥43 ng/L yielded strong independent prognostic significance for all-cause death at 6, 12 and 24 months, and for cardiovascular death at 24 months, while NT-proBNP ≥5660 ng/L was much less predictive. By contrast, hs-TnT seemed less predictive than NT-proBNP when considering absolute, log_2-transformed biomarker values. Finally, the best hs-TnT cut-offs independently predicted all post-discharge outcomes,

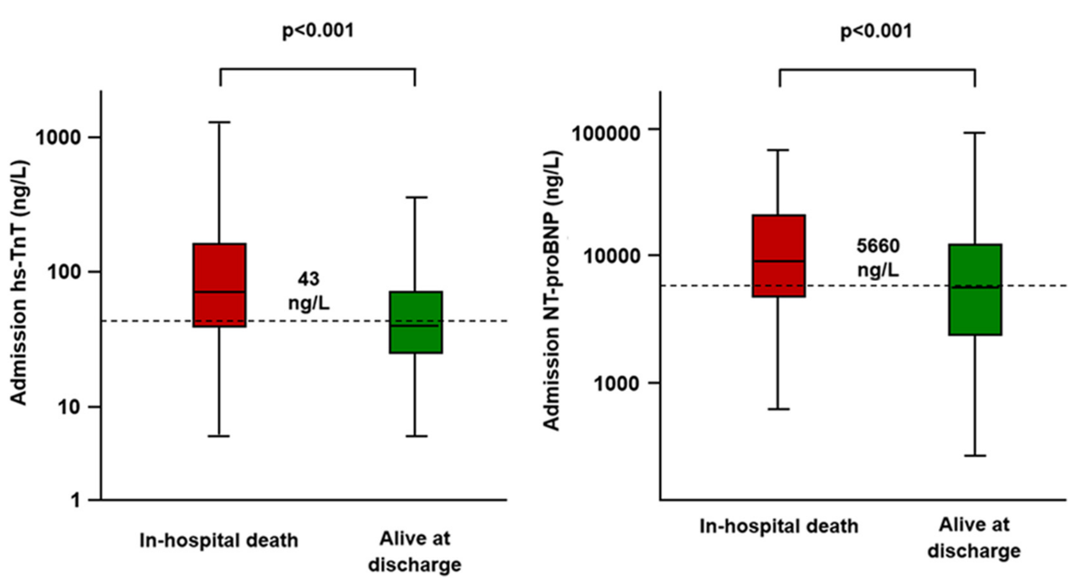

Fig. 1. Admission high-sensitivity troponin T (hs-TnT) and the risk of in-hospital death. Admission hs-TnT was significantly higher in patients dying during index hospitalization than in those surviving until discharge. Biomarker concentrations are log_{10}-transformed.

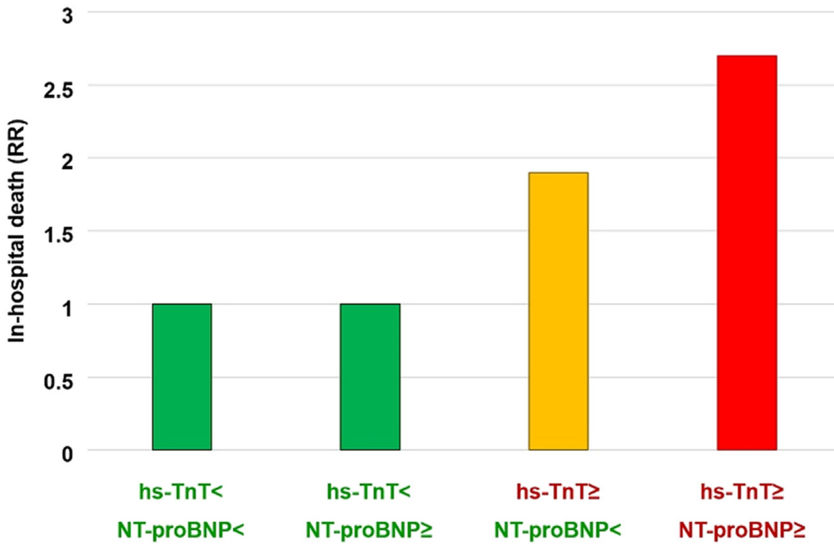

Fig. 2. Relative risk (RR) of in-hospital death according to high-sensitivity troponin T (hs-TnT) and N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) cut-offs. Patients were stratified according to median hs-TnT and NT-proBNP values (43 ng/L and 5660 ng/L, respectively).

while only the best NT-proBNP cut-off for 6-month all-cause mortality independently predicted its corresponding endpoint.

The rationale behind the ACCF/AHA Guideline recommendation for troponin measurement in AHF was largely to remind clinicians of the importance of searching for acute myocardial infarction as the underlying cause. In the setting of AHF not associated with acute coronary syndrome, Tn release seems to derive mostly from hemodynamic overload causing subclinical ischemia, with cell necrosis and possibly also non-necrotic release from suffering cells, as suggested mainly by experimental data [21–23]. The hemodynamic load is responsible for the increase in circulating B-type natriuretic peptides as well [24]. Both TnT and natriuretic peptides are excreted by the kidneys, and their circulating concentrations must be interpreted based on renal clearance [24,25].

Despite the A level of evidence for the ACCF/AHA recommendation [15], there is limited evidence to support troponin assessment for prognostic stratification, either alone or combined with natriuretic peptides. Except for the papers on the cohorts included in the present study [8,14], and a few small, single-center studies [14,15,26], the main source of information on the prognostic value of hs-TnT is the *post-hoc* analysis of the RELAX in in Acute Heart Failure (RELAX-AHF), which included a lower number of patients ($n = 1074$ with hs-TnT data at baseline), did not assess specifically in-hospital mortality, and evaluated patient outcome only up to 6 months [11]. Moreover, the additive prognostic value to NT-proBNP was considered only for cardiovascular death to 180 days [11].

We thus created an international, multi-center registry of real-world data to specifically analyze the prognostic value of hs-TnT compared to NT-proBNP, which is an established predictor of outcome in AHF. Contrary to previous studies, we assessed both absolute and dichotomized biomarker values, as cut-offs might be more readily employed by clinicians than absolute values. We evaluated the prognostic value of a single cut-off, namely median admission NT-proBNP or hs-TnT, which could be more easily remembered and used in current clinical practice than multiple cut-offs, but also the best cut-offs for each endpoint.

For the prediction of in-hospital death, absolute hs-TnT levels were more predictive than NT-proBNP. Among patients with only one biomarker ≥cut-off, those with hs-TnT ≥43 ng/L had a worse prognosis than those with only NT-proBNP ≥5660 ng/L, but neither median value was independently associated with outcome in a strong prognostic model. Furthermore, when assessing the best cut-off values, NT-proBNP ≥4382 ng/L, but not hs-TnT ≥55 ng/L, independently predicted in-hospital mortality. On the other hand, the risk of in-hospital death increased by almost 3 folds with both biomarkers were greater than or equal to median admission values, and almost 12 folds when NT-proBNP and hs-TnT were both ≥ best cut-offs. Therefore, the combined assessment of hs-TnT and NT-proBNP, on top of other clinical and laboratory variables, may identify a subset at higher risk of worse outcome

Table 2
Admission N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) cut-offs and outcome at 6, 12, 24 months.

		6 months			12 months			24 months		
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
All-cause death	NT-proBNP	1.25	1.08–1.45	**0.003**	1.31	1.14–1.51	<**0.001**	1.22	1.05–1.42	**0.008**
	hs-TnT	–	–	0.498	–	–	0.574	–	–	0.228
CV death	NT-proBNP	–	–	0.093	1.28	1.08–1.52	**0.005**	–	–	0.065
	hs-TnT	–	–	0.361	–	–	0.336	–	–	0.243
All-cause death	NT-proBNP ≥ 5660 ng/L	–	–	0.826	–	–	0.127	–	–	0.749
	hs-TnT ≥ 43 ng/L	1.73	1.17–2.54	**0.006**	1.60	1.11–2.33	**0.013**	1.89	1.27–2.82	**0.002**
CV death	NT-proBNP ≥ 5660 ng/L	–	–	0.686	1.86	1.15–3.01	**0.011**	–	–	0.144
	hs-TnT ≥ 43 ng/L	–	–	0.064	–	–	0.155	1.74	1.14–2.64	**0.010**

The whole population is considered ($n = 1449$). NT-proBNP and hs-TnT, considered either as absolute (log_2-transformed) values or dichotomized according to median values at baseline, were both added to the prognostic model including patient cohort, age, sex, new-onset vs. worsening heart failure (HF), history of coronary artery disease, admission left ventricular ejection fraction, New York Heart Association class, systolic blood pressure, heart rate, estimated glomerular filtration rate, plasma hemoglobin, sodium, white blood cell count, history of atrial fibrillation, hypertension, diabetes, chronic obstructive pulmonary disease.
Significant p values are reported in bold.

during hospital admission. This may allow an enhanced therapeutic effort tailored on the individual clinical phenotype.

After discharge, patients with hs-TnT ≥43 ng/L on admission had shorter event-free survival (especially when they had also NT-proBNP ≥median), and worse outcome at different time-points. This hs-TnT cut-off was predictive of all-cause mortality and long-term cardiovascular mortality. Therefore, the risk related to a greater extent of myocardial damage at hospitalization is likely to extend up to 2 years after discharge. It should be noted that concentrations of both troponin and natriuretic peptides predict ventricular remodeling in the long-term in patients with HF [27,28], suggesting the association between each biomarker and risk following discharge may in part be associated with this process. Notably, the hs-TnT cut-off (43 ng/L) had stronger prognostic value than NT-proBNP, which at the proposed cut-off (5660 ng/L) did not achieve independent prognostic significance at most timepoints. On the other hand, dichotomization of continuous variables may cause a loss of prognostic information, especially when the range of variation is large (as in the case of NT-proBNP) [29]. In fact, when considering absolute biomarker values, a strong prognostic value of NT-proBNP emerged, and this biomarker seemed to be more predictive than hs-TnT for post-discharge outcome.

Natriuretic peptides are established predictors of outcome in patients with AHF, and NT-proBNP cannot be replaced by hs-TnT as a tool for risk prediction, our results suggest that adding a hs-TnT measurement on admission allows to refine the prediction of in-hospital mortality and post-discharge outcome, especially when biomarker cut-offs are considered instead of absolute values. One possibility to further explore the additive prognostic value of hs-TnT is to examine if this biomarker provides additional prognostic information beyond a multi-parametric prognostic model developed to predict 1-year mortality and including NT-proBNP [30,31]. Moreover, dedicated studies are required to establish whether a therapeutic strategy informed by hs-TnT and/or NT-proBNP can improve patient prognosis in AHF.

Although our results provide short and longer-term prognostic information regarding NT-proBNP and hs-TnT in AHF, some limitations must be acknowledged. First, discharge biomarkers were not evaluated as they were available only for a small minority of patients, possibly reflecting the difficulty in performing serial biohumoral evaluations in a real-world setting. Second, information on therapies and causes of death during index hospitalization were not available for the majority of patients. Third, data on cardiovascular mortality was available only for 63% of the patients, and adjudication of the cause of death was not standardized across centers. Additionally, HF hospitalization was not assessed because of the high number of missing data. Therefore, all-cause death appears to be the more robust endpoint of this study. Fourth, the original cohorts differed with regard to many patient characteristics (as reported in **Supplemental Table 1**), and patient prognosis, with the EAHFE cohort (composed by older patients) having the higher rates of in-hospital mortality. Nevertheless, the assessment of individual patient data instead of pooled data should limit the impact of such heterogeneity, and study cohorts were included into the prognostic model for multivariable analysis. Fifth, overall mortality rates were quite high (83.5%) when considering both in-hospital death and death during the 11-month follow-up (4–22), possibly because of the quite advanced patient age. This could reduce the clinical applicability of these findings to the general population with AHF. Sixth, in the absence of established risk categories for reclassification analysis, they were set at <10%, 10–30% and >30% based on prior studies on HF biomarkers [32,33].

In conclusion, among patients admitted because of AHF, the combination of circulating NT-proBNP ≥5660 ng/L and hs-TnT ≥43 ng/L is associated to a 2.7-fold higher risk of in-hospital death. The best NT-proBNP cut-off (4382 ng/L) independently predicts outcome, while the best hs-TnT (55 ng/L) does not. Patients with both biomarkers ≥best cut-offs have an almost 12-fold higher risk of in-hospital mortality. Admission hs-TnT ≥43 ng/L holds strong independent prognostic significance for post-discharge outcome, notably all-cause death at 6, 12 and 24 months, and cardiovascular death at 24 months. Similarly, the best hs-TnT cut-offs for post-discharge outcome independently predict all endpoints, while only the best 6-month NT-proBNP cut-off independently predicts this endpoint. By contrast, hs-TnT seems less predictive than NT-proBNP when considering absolute, $\log_2$-transformed biomarker values. Overall, the assessment of NT-proBNP and hs-TnT refines prognostic stratification and helps identify patients at higher risk needing an enhanced, individualized therapeutic effort during hospital admission and after discharge.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.005.

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