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Multiple Cardiac Biomarker Testing Among Patients With Acute Dyspnea From the ICON-RELOADED Study

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ABSTRACT

Background: Among patients with acute dyspnea, concentrations of *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T, and insulin-like growth factor binding protein-7 predict cardiovascular outcomes and death. Understanding the optimal means to interpret these elevated biomarkers in patients presenting with acute dyspnea remains unknown.

Methods and Results: Concentrations of NT-proBNP, high-sensitivity cardiac troponin T, and insulin-like growth factor binding protein-7 were analyzed in 1448 patients presenting with acute dyspnea from the prospective, multicenter International Collaborative of NT-proBNP-Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department (ICON-RELOADED) Study. Eight biogroups were derived based upon patterns in biomarker elevation at presentation and compared for differences in baseline characteristics. Of 441 patients with elevations in all 3 biomarkers, 218 (49.4%) were diagnosed with acute heart failure (HF). The frequency of acute HF diagnosis in this biogroup was higher than those with elevations in 2 biomarkers (18.8%, 44 of 234), 1 biomarker (3.8%, 10 of 260), or no elevated biomarkers (0.4%, 2 of 513). The absolute number of elevated biomarkers on admission was prognostic of the composite end point of mortality and HF rehospitalization. In adjusted models, patients with one, 2, and 3 elevated biomarkers had 3.74 (95% confidence interval [CI], 1.26−11.1, $P = .017$), 12.3 (95% CI, 4.60−32.9, $P < .001$), and 12.6 (95% CI, 4.54−35.0, $P < .001$) fold increased risk of 180-day mortality or HF rehospitalization.

Conclusions: A multimarker panel of NT-proBNP, hsTnT, and IGBFP7 provides unique clinical, diagnostic, and prognostic information in patients presenting with acute dyspnea. Differences in the number of elevated biomarkers at presentation may allow for more efficient clinical risk stratification of short-term mortality and HF rehospitalization. (*J Cardiac Fail 2021;00:1−8*)

Concentrations of *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin T (hs-cTnT) are often tested among patients with suspected acute heart failure (HF) or myocardial infarction. Insulin-like growth factor binding protein-7 (IGFBP7) is a peptide hormone that induces cellular senescence via cell cycle arrest that has been increasingly implicated as a candidate biomarker for HF diagnosis.[1−4] Additionally, NT-proBNP and hs-cTnT as well as IGFBP7 have been

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implicated as important prognostic markers in patients presenting with acute dyspnea and HF.[1,5–7] Although many early studies of troponin in dyspnea utilized the original troponin assay, in recent years combining hs-cTnT with risk scoring systems has been implemented in emergency departments (EDs) for accelerated diagnostic pathways.[8] The routine assessment of NT-proBNP and hs-cTnT in patients with acute dyspnea is common in clinical practice, whereas the measurement of IGFBP7 as a clinically useful biomarker is a more recent discovery.[1,2] The information provided by multiplex assessment of these 3 biomarkers in those with acute dyspnea—a population with a broad range of clinical diagnoses—is likely complementary, but remains undefined. Understanding the optimal means to interpret the clinical profile of dyspneic patients using these 3 biomarkers, the meaning of biomarker elevations and their prognostic significance is an important step toward a multiplex approach to paneling multiple biomarkers for clinical use in acute dyspnea.

The usefulness of multiplex biomarker panels for patient evaluation and risk stratification has been studied in a breadth of cardiovascular diseases, including non-ST elevation acute coronary syndromes and incident HF in the ambulatory setting.[9,10] However, despite more than 2 decades of research dedicated to biomarkers in acute dyspnea and repeated calls for multimarker panels to refine the evaluation of patients presenting with acute dyspnea,[11,12] no widely accepted framework currently exists. Herein, we sought to evaluate the meaning of these 3 biomarkers among patients presenting with acute dyspnea from the International Collaborative of NT-proBNP-Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department (ICON-RELOADED) Study. To do so, we proposed to examine clinical characteristics of patients with elevation of 1 or more of these biomarkers and whether there are distinct clinical characteristics of patients presenting to the ED with acute dyspnea. We subsequently examined the prognostic meaning of elevations in these biomarkers. We hypothesized that differences in clinical profiles and prognosis would emerge based on variable patterns of biomarker elevation, which might inform important clinical differences and enhance discrimination for events soon after discharge.

Methods

Patient Population and Study Overview

The design and main results of the ICON-RELOADED trial have been published previously.[13,14] Briefly, the ICON-RELOADED trial was a prospective, multicenter clinical trial conducted across 19 study sites in North America that evaluated adults presenting to the ED with acute dyspnea. Adult subjects who presented to the ED between October 2015 and October 2016 with acute dyspnea and met the study inclusion and exclusion criteria were approached for enrollment. Major inclusion criteria included patients 22 years of age or older presenting to the ED with acute dyspnea, and major exclusion criteria included renal insufficiency with an estimated glomerular filtration rate of less than 15.0 mL/min/1.73 m^2 before enrollment or patients on hemodialysis. After informed consent was obtained, blood samples were collected, and clinical information was documented from the electronic medical record. Patients received a follow-up contact at approximately 6 months for assessment of hospitalization after index presentation. An adjudication committee blinded to biomarker concentrations judged the cause of the hospitalization as owing to HF or other causes, such as pneumonia, pulmonary embolism, or obstructive airway disease. Additionally, the adjudication committee judged rehospitalizations and deaths. All methods in this study were approved by the participating Institutional Review Boards.

Of the 1461 subjects enrolled in ICON-RELOADED, 1448 patients (99.1%) with complete biomarker data were included in the present analysis. Patients were classified into biomarker defined biogroups according to combinations of biomarker positivity as listed in Table 1. The biomarker cut-offs were chosen to reflect clinically relevant values: the cut-off for hs-cTnT was set at above (+) or below (−) the 99th percentile. The cut-off for NT-proBNP and IGFBP7 were set at above (+) or below (−) the median concentration for the group, individually previously reported as meaningful cut-points for outcome in the ICON-RELOADED cohort.[1] We compared the baseline characteristics of the medical history by biogroup, frequency of adjudicated HF diagnosis by biogroup, and finally evaluated outcomes (a composite of 180-

Table 1. Biogroup Assignment by Biomarker Combination.

Biogroup	hs-cTnT	IGFBP7	NT-proBNP	Subjects (%, *N*)
1	−	−	−	35.4% (513/1448)
2	−	+	−	9.2% (133/1448)
3	−	−	+	6.4% (92/1448)
4	+	−	−	2.4% (35/1448)
5	+	+	−	3.0% (43/1448)
6	−	+	+	7.4% (107/1448)
7	+	−	+	5.8% (84/1448)
8	+	+	+	30.5% (441/1448)

hs-cTnT, high-sensitivity cardiac troponin T; IGFBP7, insulin-like growth factor binding protein-7; NT-proBNP, N-terminal B-type natriuretic peptide

day mortality or adjudicated HF hospitalization) between groups.

Laboratory Evaluation

Concentrations of NT-proBNP (COBAS NT-proBNP assay, Roche Diagnostics, Mannheim, Germany) and hs-cTnT were measured using samples from index presentations, whereas IGFBP7 was measured in plasma samples from the same blood draw by using a precommercial COBAS Elecsys assay (Roche Diagnostics, Penzberg, Germany) by laboratory personnel blinded to clinical information. The detection method for IGFBP7 was a sandwich immunoassay developed using the Elecsys platform for electrochemiluminescence detection. Mouse monoclonal antibodies were generated and screened for specific detection of IGFBP7. The precision within-run coefficient of variation for IGFBP7 was 2% and a limit of detection of 0.01 ng/mL. For NTproBNP, the between-run coefficients of variation were 2.0% at 138 pg/mL and 1.8% at 4995 pg/mL; the limit of detection was 5 pg/mL. The hs-cTnT assay's limit of detection was 3 ng/L and between-run coefficients of variation were 3.4% and 2.6% at 27.4 ng/L and 2036 ng/L, respectively.

Statistical Analyses

Statistical analyses were performed on dichotomous variables according to the aforementioned cutoffs for NTproBNP, hs-cTnT, and IGFBP7. For display purposes, the characteristics of the study participants were summarized and described as categorical variables using counts and percentages. Normally distributed variables were expressed using means ± standard deviation and nonparametric variables were expressed using median (25th, 75th percentile).

An unadjusted Cox proportional hazards analysis was used to assess death or rehospitalization per elevation in biomarker by 6 months. The analyses were repeated for a model adjusted for age and sex, as well as a model which adjusted for age, sex, hypertension, diabetes, HF, and myocardial infarction. Comparisons between models were conducted and assessed for quality using Akaike information criterion (AIC). A *P* value of les than .05 was considered statistically significant. Statistical analysis was conducted using SAS (version 9.4).

Results

Baseline Characteristics

Baseline characteristics of all study subjects and for each biogroup are provided in **Table 2**. In general, study subjects were an average 56 years old and equally distributed between men and women; they had a high prevalence of hypertension, diabetes, and HF. The prevalence of adjudicated acute HF was 18.9% ($n = 274$).

In the absence of any elevated biomarkers on presentation, biogroup 1 was differentiated from the overall cohort by their younger age (46 years vs 56 years), female predominance (61.6% vs 49.2%), and lower overall prevalence of medical comorbidities. Conversely, individuals belonging to biogroup 8 had elevations in all 3 biomarkers and were differentiated from the overall cohort by their older age (67 years vs 56 years), White male predominance, and significant medical comorbidities, including higher rates of hypertension, HF, diabetes, coronary disease, and atrial fibrillation. They were also more likely to be prescribed loop diuretics and to be on guideline-directed medical therapies for HF.

Biogroups 2, 5, 6, and 8 were marked by the presence of elevated IGFBP7 and could be differentiated by their higher body mass index and increased prevalence of diabetes and hypertension. Biogroups 4, 5, 7, and 8 were marked by the presence of elevated hs-cTnT and could be differentiated by their higher prevalence of coronary artery disease and prior percutaneous coronary interventions. Biogroups 3, 6, 7, and 8 were marked by the presence of elevated NT-proBNP and could be differentiated by their higher prevalence of a prior HF diagnosis.

Of 441 patients with elevations in all 3 markers in biogroup 8, 218 patients (49.4%) were diagnosed with acute HF. This frequency of acute HF diagnosis in this group was higher than those with elevations in 2 biomarkers (18.8%, 44 of 234), one biomarker (3.8%, 10 of 260), or no elevated biomarkers (0.4%, 2 of 513). Differences between the remaining biogroups are demonstrated in Table 2.

Predictors of Mortality and HF Hospitalization

Across biogroups, the risk for the composite end point of mortality and HF rehospitalization is demonstrated in Fig. 1, which shows that biogroups with more abnormal biomarkers had a higher risk for the composite end point of death and HF hospitalization.

Next, considering various combinations of biomarkers in more specific detail, in unadjusted models, having 1, 2, and 3 elevated biomarkers (regardless of combination) was associated with a hazard ratio for the composite end point of 4.01 (95% confidence interval [CI] 1.50−10.7, $P = .006$), 14.6 (95% CI 6.17−34.7, $P < .001$), and 22.0 (95% CI 9.67−50.3, $P < .001$) per elevated biomarker. Further model adjustment is shown in Table 3; when the model was fully adjusted for age, sex, HF, myocardial infarction, hypertension, diabetes, atrial fibrillation, and estimated glomerular filtration rate, elevations in 1, 2, and 3 elevated biomarkers were

Table 2. Baseline Characteristics by Biogroup

Patient Characteristics	Overall (*N* = 1448)	1 (*n* = 513)	2 (*n* = 133)	3 (*n* = 92)	4 (*n* = 35)	5 (*n* = 43)	6 (*n* = 107)	7 (*n* = 84)	8 (*n* = 441)
Demographics									
Age	56.3 ± 15.6	46.0 ± 13.4	53.9 ± 12.3	54.0 ± 12.8	57.2 ± 12.9	61.6 ± 11.0	62.3 ± 11.7	59.0 ± 13.2	66.9 ± 13.3
Male	50.8% (735)	38.4% (197)	46.6% (62)	37.0% (34)	71.4% (25)	90.7% (39)	41.1% (44)	58.3% (49)	64.6% (285)
BMI (kg/m)	32.0 ± 9.23	32.0 ± 8.95	33.6 ± 10.7	30.0 ± 7.72	30.8 ± 6.16	34.1 ± 9.17	34.6 ± 9.29	29.1 ± 8.96	31.8 ± 9.38
Race									
Black or African American	36.6% (519)	49.7% (252)	35.4% (45)	35.2% (32)	51.5% (17)	35.7% (15)	26.2% (28)	28.8% (23)	24.8% (107)
White	59.5% (845)	46.7% (237)	59.1% (75)	58.2% (53)	48.5% (16)	64.3% (27)	71.0% (76)	66.3% (53)	71.3% (308)
Ethnicity									
Hispanic or Latino	13.6% (190)	18.3% (89)	22.7% (29)	9.1% (8)	5.9% (2)	2.4% (1)	14.3% (15)	5.0% (4)	9.7% (42)
Medical history/ comorbidities									
AF	14.9% (215)	3.3% (17)	0.8% (1)	8.7% (8)	5.7% (2)	9.3% (4)	30.8% (33)	9.6% (8)	32.5% (142)
CAD	21.4% (307)	5.1% (26)	14.0% (18)	15.2% (14)	22.9% (8)	27.9% (12)	25.2% (27)	30.5% (25)	40.8% (177)
COPD	27.4% (393)	17.0% (87)	20.5% (27)	36.3% (33)	44.1% (15)	48.8% (21)	24.8% (26)	40.7% (33)	34.5% (151)
CRT	1.7% (24)	0.2% (1)	0.8% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3.8% (4)	1.2% (1)	3.9% (17)
DM	28.6% (412)	18.2% (93)	31.6% (42)	13.2% (12)	25.7% (9)	32.6% (14)	36.2% (38)	23.2% (19)	42.0% (185)
HF	24.7% (351)	4.3% (22)	11.7% (15)	15.6% (14)	14.3% (5)	23.8% (10)	30.5% (32)	27.7% (23)	54.2% (230)
HTN	63.1% (910)	39.1% (200)	69.2% (90)	57.6% (53)	60.0% (21)	83.7% (36)	81.0% (85)	59.5% (50)	85.0% (375)
ICD	6.0% (86)	0.8% (4)	0.8% (1)	3.3% (3)	5.7% (2)	4.7% (2)	8.6% (9)	6.0% (5)	13.6% (60)
PAD	4.3% (61)	0.8% (4)	1.5% (2)	5.4% (5)	0.0% (0)	2.3% (1)	3.8% (4)	7.6% (6)	9.1% (39)
Prior CABG	6.7% (96)	0.0% (0)	3.1% (4)	4.3% (4)	0.0% (0)	7.0% (3)	4.7% (5)	13.4% (11)	15.7% (69)
Prior PCI	9.0% (128)	1.6% (8)	4.6% (6)	8.8% (8)	17.6% (6)	9.3% (4)	9.5% (10)	16.9% (13)	17.0% (73)
Prior MI	13.3% (188)	3.5% (18)	8.6% (11)	12.0% (11)	14.3% (5)	11.6% (5)	9.7% (10)	22.2% (18)	26.1% (110)
Renal failure	7.9% (114)	0.8% (4)	7.5% (10)	1.1% (1)	0.0% (0)	9.3% (4)	4.7% (5)	3.6% (3)	19.9% (87)
Medications									
ACEI/ARB	11.7% (170)	3.1% (16)	6.0% (8)	12.0% (11)	2.9% (1)	14.0% (6)	13.1% (14)	20.2% (17)	22.0% (97)
BB	16.4% (237)	4.7% (24)	10.5% (14)	15.2% (14)	5.7% (2)	18.6% (8)	25.2% (27)	21.4% (18)	29.5% (130)
MRA	3.2% (46)	0.0% (0)	1.5% (2)	1.1% (1)	0.0% (0)	4.7% (2)	2.8% (3)	2.4% (2)	8.2% (36)
Loop diuretic	22.2% (322)	1.6% (8)	5.3% (7)	14.1% (13)	2.9% (1)	23.3% (10)	29.9% (32)	22.6% (19)	52.6% (232)
Thiazide diuretic	3.0% (43)	1.6% (8)	5.3% (7)	4.3% (4)	2.9% (1)	9.3% (4)	1.9% (2)	2.4% (2)	3.4% (15)
Laboratory data									
Serum creatinine (mg/dL)	1.11 ± 2.28	1.03 ± 3.89	0.96 ± 0.36	0.83 ± 0.21	0.89 ± 0.22	1.14 ± 0.32	0.94 ± 0.25	0.87 ± 0.27	1.38 ± 0.96
BUN (mg/dL)	18.2 ± 12.3	12.9 ± 4.82	15.1 ± 7.45	13.6 ± 5.14	14.7 ± 4.94	17.9 ± 6.74	17.4 ± 9.42	16.2 ± 7.01	26.2 ± 16.9
eGFR (mL/min/1.73 m^2)	80.9 ± 44.1	97.7 ± 60.9	81.8 ± 23.8	91.6 ± 25.2	97.1 ± 45.7	74.5 ± 24.0	78.3 ± 22.3	93.1 ± 36.6	60.0 ± 26.3
hs-cTnT (pg/mL; median [25th, 75th])	10.4 (4.8, 25.6)	4.4 (2.9, 6.4)	7.2 (4.4, 9.2)	7.8 (4.3, 11.0)	19.9 (15.6, 25.4)	22.2 (16.3, 28.0)	9.7 (7.4, 12.1)	27.4 (18.6, 42.3)	32.7 (22.3, 51.1)
IGFBP7 (ng/mL, median [25th, 75th])	91.7 (75.2, 123.7)	73.7 (65.9, 81.8)	103.4 (96.7, 115.7)	79.6 (69.9, 85.9)	79.5 (74.1, 83.8)	107.2 (96.7, 122.6)	111.8 (101.6, 140.8)	83.1 (73.7, 87.8)	137.0 (115.8, 174.6)
NT-proBNP (pg/mL, median [25th, 75th])	153.9 (43.5, 1031.5)	38.3 (20.8, 69.9)	58.5 (26.8, 94.4)	296.7 (213.0, 439.9)	56.9 (25.9, 85.5)	81.6 (51.9, 108.0)	505.6 (279.4, 1092.0)	489.9 (275.9, 1363.0)	1829.0 (756.4, 4561.0)
Hospital disposition									
Admitted from ED to hospital	58.2% (843)	31.8% (163)	41.4% (55)	69.6% (64)	54.3% (19)	69.8% (30)	66.4% (71/107)	81.0% (68)	84.6% (373)
Hospital LOS (days)	3.87 ± 4.35	2.29 ± 2.43	2.61 ± 2.74	3.69 ± 5.04	3.10 ± 3.05	3.33 ± 3.18	3.43 ± 4.80	4.44 ± 4.49	4.83 ± 4.81
Adjudicated diagnosis									
Acute HF	18.9% (274)	0.4% (2)	3.0% (4)	6.5% (6)	0.0% (0)	7.0% (3)	29.9% (32)	10.7% (9)	49.4% (218)

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; HTN, hypertension; ICD, implantable cardioverter-defibrillator; IGFBP7, insulin-like growth factor binding protein-7; LOS, length of stay; MRA, mineralocorticoid receptor antagonist; MI, myocardial infarction; NT-proBNP, N-terminal B-type natriuretic peptide; PAD, peripheral artery disease; PCI, percutaneous coronary intervention. Percentages reported are out of patients per category with complete data available for analysis.

increasingly prognostic of the composite end point with hazard ratio of 3.74, 12.3, and 12.6, respectively (Table 3). The 3-biomarker model had a lower AIC compared to a model containing 2 biomarkers (AIC 1742.6 vs 1774.0)

Discussion

In this analysis of ICON-RELOADED, we studied the joint measurement of NT-proBNP, hs-cTnT, and IGFBP7 in a common clinical setting, and have added to current knowledge about how these biomarkers might best support clinical judgement. We evaluated a multimarker approach that not only allows for the identification of several key differences between clinical biogroups based on cardiac marker profiles, but also allows for rapid stratification of

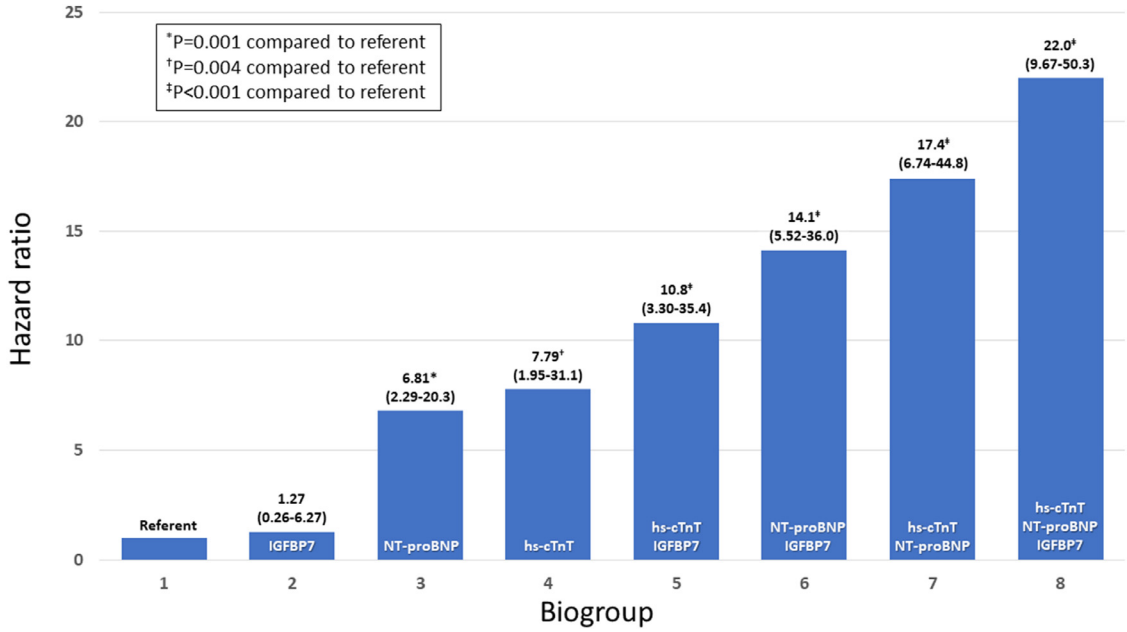

Fig. 1. Cox proportional hazard regression on composite end point of death and heart failure rehospitalization from discharge to 180 days by biogroup. Concentrations of N-terminal B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and insulin-like growth factor binding protein-7 (IGFBP7) were analyzed in 1448 patients presenting with acute dyspnea from the ICON-RELOADED Study. Eight biogroups were derived based on patterns in biomarker elevation at presentation and compared for differences in baseline characteristics. Unadjusted Cox proportional hazard regression are depicted per biogroup as compared with the reference biogroup 1.

differences in risk for adverse outcomes. Further, we found that elevations in NT-proBNP, hs-cTnT, and IGFBP7 were additive for prognosticating short term mortality and hospitalization, as well as in the diagnosis of acutely decompensated HF (Visual Take Home Graphic).

An examination of baseline characteristics by patient biogroup provides insights into the clinical significance of elevations in each individual biomarker. Patients belonging to the groups with elevation of NT-proBNP at presentation unsurprisingly had the highest prevalence of HF in their medical history. Similarly, patients belonging to groups 4, 5, 7, and 8 had elevations in hs-cTnT and had the highest prevalence of coronary artery disease and prior percutaneous coronary interventions. Interestingly, an examination of patients in groups 2, 5, 6, and 8 offered unique insights into the patients with elevations in IGFBP7. The peptide hormone IGFBP7 is implicated in cell cycle arrest in numerous disease states.[2–4] Many studies have associated IGFBP7 with obesity, diabetes, and aging; moreover, it has growing potential for its measurement in patients with HF for predicting disease progression and outcomes.[1,15,16] In the present analysis, patients with an elevated IGFBP7 had more diabetes and obesity than did the phenogroups without IGFBP7 elevation. This finding is congruent with studies of HF with preserved ejection fraction, where IGFBP7 has been associated with myocardial relaxation abnormalities and a phenotypic subset of patients with HF with preserved ejection fraction in whom metabolic syndromes, including diabetes and obesity, is prevalent.[15,16] In our present study, patients in biogroups with elevated IGFBP7 also had a higher prevalence of hypertension.

A key finding in this analysis was the significance of a 3-marker approach for short-term prognostication. Elevations in 1, 2, and 3 biomarkers were

Table 3. Cox Proportional Hazard Regression on Composite End Point of Death and Heart Failure Rehospitalization From Discharge to 180 Days After Discharge

Model	Hazard Ratio	95% Confidence Interval	*P* Value
Unadjusted			
Elevated 1 vs 0	4.01	1.50–10.7	.006
Elevated 2 vs 0	14.6	6.17–34.7	<.0001
Elevated 3 vs 0	22.0	9.67–50.3	<.0001
Age/sex adjusted			
Elevated 1 vs 0	4.26	1.59–11.4	.004
Elevated 2 vs 0	16.4	6.76–39.8	<.0001
Elevated 3 vs 0	25.7	10.8–61.2	<.0001
Fully adjusted*			
Elevated 1 vs 0	3.74	1.26–11.1	.017
Elevated 2 vs 0	12.3	4.60–32.9	<.0001
Elevated 3 vs 0	12.6	4.54–35.0	<.0001

*Model adjusted for age, sex, hypertension, diabetes, prior heart failure (HF), present HF, prior myocardial infarction, present myocardial infarction, estimated glomerular filtration rate, and atrial fibrillation.

increasingly predictive of not only HF diagnosis, but also short-term mortality and HF rehospitalization. In fact, simultaneous elevation in NT-proBNP, hs-cTnT, and IGFBP7 was 3 times more prognostic of mortality and HF rehospitalization at 6 months than was an elevation in NT-proBNP alone. These findings highlight how a single marker alone does not wholistically represent the complexity of the biochemical pathways involved in the pathophysiology of HF, but rather how the combined use of several biomarkers improves the characterization of patients with HF to better understand their prognosis and management. Interestingly, in this model, although the 3-biomarker model demonstrated a lower AIC, most of the prognostic potential was captured by an elevation in 2 biomarkers. Although the risk conferred in these groups was similar as compared to the reference group, the prevalence of HF was twice as high in the group with elevations in all 3 biomarkers. This finding is important; because currently only NT-proBNP and hs-cTnT are widely available in clinical practice. The findings in this study highlight the clinical usefulness of multiplex measurement of hs-cTnT and IGFBP7 alongside NT-proBNP to improve discrimination for cardiovascular risk in a group of patients with one of the most commonly assessed acute symptoms in the ED and further illustrate how risk assessment may be refined beyond NT-proBNP alone. A paneled approach for prognosis bears further evaluation either as categorical variables or modeled in a continuous fashion using a machine learning approach. Additionally, although speculative, an improved ability to discriminate risk between patients based on biomarker profiles may improve cost and should be evaluated in future studies.

It is important to note that the addition of biomarkers to clinical prediction models does not always result in marked increase in prognostic value.[17,18] This point has been particularly true in studies of biomarkers in acute HF, where besides certain biomarkers such as soluble ST2,[19–22] the addition of most other newer biomarkers to NT-proBNP have only modestly improved risk stratification profiles.[23–25] The proposed multimarker panel in the present study uniquely combines biomarkers across multiple pathophysiologic pathways (myocardial stretch, myocardial injury, and cellular senescence) and improves HF prognostication multifold. This point is further demonstrated in an examination of IGFBP7 in this cohort where elevation in IGFBP7 alone was of limited prognostic value as a marker of cellular senescence, but when added to biomarkers of myocardial stretch and injury, the prognostic yield increased multifold. And although multiplex cardiac biomarker testing has been shown to be of added value to single marker testing in population-based studies,[26,27] such testing among patients with acute dyspnea presenting to the ED setting (where biomarkers play an arguably greater role) lags behind. Thus, the fact that this analysis assesses a multimarker panel encompassing 3 pathophysiologic pathways in a large, diverse cohort of patients with dyspnea and without a prespecified HF diagnosis is an important contribution.

Although this analysis contributes to the current knowledge on diagnosis and prognosis in patients presenting with acute dyspnea, it is not without limitations. First, this analysis is subject to limitations of the ICON-RELOAD patient cohort, which have been noted previously, including its relatively small sample size and power for a multicenter study and the overall low percentage of patients presenting with acute HF.[1,14] A small sample size was particularly notable when examining patients in biogroups 4 and 5, who did not have elevations in NT-proBNP. This finding was anticipated, because elevations in NT-proBNP have many shared pathways for release, such that when NT-proBNP is elevated, other biomarkers will typically increase. Although the present analysis demonstrated this finding in a group of patients presenting with acute dyspnea, further translational insights are required to more granularly understand the additive clinical value of IGBFP7. Similarly, a better understanding of patients with elevations in just 1 biomarker pathway is warranted. Another limitation of the present study is that numerous models were compared without an adjustment for multiple comparisons, which could increase the possibility of type I errors. Additionally, complete echocardiographic data for the patients included in this analysis is not currently available, limiting the ability to make important distinctions between biogroups with respect to their underlying cardiac function and geometries. A further investigation of the changes in IGFBP7 and echocardiographic parameters of HF is required. Last, the selection of biomarker cut-offs was based on prior precedent and/or the central tendency of the present population and assessed in a dichotomous manner. Although this practice provides a more clinically relevant perspective for interpretation of our results, the use of absolute biomarker values as continuous variables and/or machine-learning derivation of optimal formulas for paneling results may be a more informative approach for biomarker-leveraged diagnosis and prognosis; nonetheless, for ease of clinical interpretation, this approach provides strikingly efficient prognostication. This analysis would benefit from external validation in similar, larger patient cohorts assessing NT-proBNP, hsTnT, and IGFBP7 in patients presenting with acute dyspnea, alongside other

exploratory and novel biomarkers across multiple pathophysiologic pathways implicated in HF.

Conclusions

In patients presenting to the ED with acute dyspnea, categorizing patients using a multimarker panel of NT-proBNP, hs-cTnT, and IGBFP7 results in biogroups with distinct clinical features. Additionally, patterns of these 3 biomarkers yield incremental prognostic information regarding 180-day mortality and HF rehospitalization. Elevations in 1, 2, and 3 biomarkers was increasingly predictive of both HF diagnosis and short-term outcomes, regardless of specific biomarker elevation. This 3-marker approach may prove useful for diagnosis and prognosis of patients presenting with acute dyspnea in a common clinical setting.

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