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The Influence of Body Mass Index on Clinical Interpretation of Established and Novel Biomarkers in Acute Heart Failure

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ABSTRACT

Background: Body mass index (BMI) is a known confounder for natriuretic peptides, but its influence on other biomarkers is less well described. We investigated whether BMI interacts with biomarkers' association with prognosis in patients with acute heart failure (AHF).

Methods and Results: B-type natriuretic peptide (BNP), high-sensitivity cardiac troponin I (hs-cTnI), galectin-3, serum neutrophil gelatinase-associated lipocalin (sNGAL), and urine NGAL were measured serially in patients with AHF during hospitalization in the AKINESIS (Acute Kidney Injury Neutrophil gelatinase-associated lipocalin Evaluation of Symptomatic Heart Failure) study. Cox regression analysis was used to determine the association of biomarkers and their interaction with BMI for 30-day, 90-day and 1-year composite outcomes of death or HF readmission. Among 866 patients, 21.2%, 29.7% and 46.8% had normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²) or obese (≥ 30 kg/m²) BMIs on admission, respectively. Admission values of BNP and hs-cTnI were negatively associated with BMI, whereas galectin-3 and sNGAL were positively associated with BMI. Admission BNP and hs-cTnI levels were associated with the composite outcome within 30 days, 90 days and 1 year. Only BNP had a significant interaction with BMI. When BNP was analyzed by BMI category, its association with the composite outcome attenuated at higher BMIs and was no longer significant in obese individuals. Findings were similar when evaluated by the last-measured biomarkers and BMIs.

Conclusions: In patients with AHF, only BNP had a significant interaction with BMI for the outcomes, with its association attenuating as BMI increased; hs-cTnI was prognostic, regardless of BMI. (*J Cardiac Fail* 2023;29:1121–1131)

Key Words: acute heart failure, body mass index, biomarker, natriuretic peptide, cardiac troponin.

Biomarkers have become an integral tool for the diagnosis, prognosis and management of heart failure (HF). The natriuretic peptides (NPs), B-type

natriuretic peptide (BNP) and its N-terminal fragment (N-Terminal Pro-[NT-proBNP]), are the prototypical HF biomarkers, and years of use and research

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have brought recognition to certain variables that can influence the interpretation of values in both acute and chronic HF.¹ Of these clinical variables, body mass index (BMI) has repeatedly been shown to influence the interpretation of NPs.^{2–5} It has been reported that NP levels are lower in obese patients because of decreased production and increased clearance due to adipose tissue dysfunction.^{6,7} Obesity is a known risk factor for the development of HF and is its major comorbidity.⁸ Hence, accurate interpretation of values in patients with HF and obesity is of significant clinical importance. Other biomarkers are available clinically or are being researched, and they reflect differing pathophysiological processes in HF, including myocardial injury, fibrosis and kidney impairment.⁹ These biomarkers have been attempted to be used in the early diagnosis of myocardial injury, renal dysfunction and risk stratification in patients with acute heart failure (AHF). BMI may also affect the value of these biomarkers, because obesity is associated with ischemic and nonischemic myocardial injury, inflammation and cardiorenal syndrome.^{10–12} However, there are limited data concerning how BMI affects interpretation.

The Acute Kidney Injury Neutrophil gelatinase-associated lipocalin Evaluation of Symptomatic Heart Failure Study (AKINESIS) is a prospective, international, multicenter study that was initially conducted to evaluate the utility of the serum and urine kidney-injury biomarker, neutrophil gelatinase-associated lipocalin (NGAL), in patients with AHF.¹³ From stored specimens, BNP, high-sensitivity cardiac troponin I (hs-cTnI), and galectin-3 (Gal-3) were measured. In this current analysis, we aimed to determine the correlation between BMI and BNP, hs-cTnI, Gal-3, and serum (sNGAL) and urine NGAL (uNGAL), and whether BMI significantly interacts with each biomarker's association with an outcome of death or HF readmission.

Methods

Study Population

The methods of AKINESIS have been described previously.¹³ The study was conducted from January 2011 through September 2013. Subjects at least 18 years of age, presenting to the emergency department or hospital with AHF, were screened for inclusion and enrolled. Subjects had to have 1 or more signs or symptoms of HF, including dyspnea on exertion, rales or crackles, galloping heart sound, jugular venous distention, orthopnea, paroxysmal nocturnal dyspnea, using more than 2 pillows to sleep, fatigue, edema, frequent coughing, a cough that produces mucous or blood-tinged sputum, or a dry cough when lying flat. In addition, subjects must

have received or planned treatment with intravenous diuretic agents. A value of BNP or NT-proBNP was not required for the inclusion. Exclusion criteria were: (1) acute coronary syndrome; (2) dialysis dependence or planned initiation of during the hospitalization; (3) organ transplantation; (4) enrollment in a drug-treatment study within the past 30 days or prior enrollment in this study; and (5) pregnancy or a member of a vulnerable population, as determined by the institutional review board. The study was approved by the institutional review boards at each study site, and each patient signed informed consent.

Originally, 927 patients were enrolled, of whom 52 did not have BMI data available at admission. Another 9 patients had BMIs < 18.5 kg/m² and were excluded for possible confounding of cachexia or frailty, leaving a total of 866 patients for this analysis. Patients were categorized into BMI categories of normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥ 30 kg/m²). Of these 866 patients, 837 participants had BNP measured, 829 had hs-cTnI measured, 843 participants had Gal-3 measured; 850 participants had serum NGAL (sNGAL) measured, and 772 participants had urine NGAL (uNGAL) measured.

Biomarkers

Biomarkers evaluated included BNP, hs-cTnI, Gal-3, sNGAL, and uNGAL. Details of these biomarkers have been published previously.¹⁴ uNGAL was analyzed alone and indexed to urine creatinine (uNGAL/uCr). uNGAL was evaluated in both manners, because urine biomarkers are frequently indexed to uCr to control for urine dilution; however, uCr itself can be dependent on BMI.¹⁵ Biomarkers were measured at admission, on hospital days 1, 2 and 3 and at discharge. When the results of biomarkers analyses were available at all time points, values at discharge were used as the last measured values. When the patients were discharged before day 3, or if missing values existed, the value at the last time point was used as the last measured value.

Outcome

The primary outcome was a composite of all-cause mortality or HF readmission as assessed at 30 days, 90 days and 1 year after enrollment. These outcomes were assessed by telephone follow-up or medical record review and were not centrally adjudicated.

Statistical Analysis

Patients' characteristics were compared by BMI category (normal, overweight, obese). Normally distributed variables are presented as means and

standard deviations (SD); non-normally distributed variables are presented as medians and 25th–75th percentiles; and categorical variables are presented as counts and percentages. Groups are compared by 1-way analysis of variance, the Mann-Whitney U test or the χ^2 test, as appropriate. A post hoc testing was performed for significant differences among groups by using Bonferroni correction. All biomarkers have skewed distribution, so they are log base-2-transformed so that higher levels can be interpreted as per 2-fold higher level of the biomarker.

To examine the relationship between each biomarker and BMI, the Spearman rank correlation coefficient was performed. Then we used linear regression, adjusting for age, sex, race, estimated glomerular filtration rate (eGFR), and atrial fibrillation, to obtain the unstandardized beta coefficients and 95% confidence intervals (CIs) for change in biomarker with increase in BMI.^{16,17} Next, we constructed a multivariable Cox model for each biomarker to obtain the hazard ratio (HR) and 95% CI for the outcome of death or HF readmission within the whole cohort. Variables in the model were selected based on prior literature and included age, sex, race, admission systolic blood pressure, atrial fibrillation, chronic obstructive pulmonary disease, diabetes, angiotensin converting enzyme-inhibitor or angiotensin receptor blocker use, beta-blocker use and admission eGFR, sodium, blood urea nitrogen and hemoglobin levels.^{18–20} In each model, we tested the biomarker*continuous BMI interaction; an interaction *P* value < 0.1 was considered significant. For illustrative purposes, the biomarkers with significant interactions were then evaluated in a multivariable Cox model within each category of BMI to show the trend of how biomarker associations change within clinically used BMI categories. Patients presenting with AHF have increased weight due to fluid overload, and that may lead to a falsely elevated BMI, so we performed analyses on both the 866 patients with admission BMIs available and on the 751 patients who had subsequent weights recorded during the hospitalization; we used their last recorded weight to calculate their last BMI, which may be more indicative of their dry weight. The last-measured BMI was analyzed with the last biomarker measurement performed on collected specimens. Only complete cases were used for analyses. For all comparisons and tests, a *P* value < 0.05 was considered significant, except as specified for interaction testing, where a *P* value < 0.10 was considered significant. We performed all statistical analyses in R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' Characteristics

The mean age of the whole cohort was 68.1 ± 13.9 years; 61.3% were men, and 61.7% were white individuals. Based on admission BMIs, 188 (21.2%), 263 (29.7%) and 415 (46.8%) had normal, overweight and obese BMIs, respectively (Table 1). As BMI increased across categories, age was significantly lower, whereas the prevalence of diabetes was significantly higher. Compared to normal and overweight patients, obese patients were less likely to be white individuals and had significantly higher systolic blood pressure, more prevalent edema and hypertension and use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers and higher dosages of loop diuretics within the first 3 days of hospitalization, and they had lower admission levels of blood urea nitrogen. Compared to patients with normal BMIs, obese patients had significantly higher diastolic blood pressure, higher prevalence of jugular venous distension and hyperlipidemia, and lower prevalence of atrial fibrillation. Compared to those with overweight BMIs, obese patients had significantly more prevalent orthopnea. Regarding biomarkers, as BMI category increased, the median admission BNP significantly decreased. Furthermore, overweight patients had significantly lower BNP levels than normal patients, and obese patients had significantly lower BNP levels than overweight patients. Obese patients had significantly lower hs-cTnI levels compared to normal and overweight patients. Other biomarker median-admission values were not significantly different.

Biomarker Changes With BMI

A Spearman rank correlation coefficient showed negative correlations between BNP and hs-cTnI levels; BMI on admission ($r = -0.37$; $P < 0.001$ for BNP and $r = -0.14$; $P < 0.001$ for hs-cTnI (Supplementary Fig. 1). Gal-3, sNGAL, uNGAL, and uNGAL/uCr were not significantly correlated with BMI ($r = -0.06$; $P = 0.077$ for Gal-3; $r = 0.05$; $P = 0.13$ for sNGAL; $r = 0.03$; $P = 0.47$ for uNGAL; and $r = 0.01$; $P = 0.76$ for uNGAL/uCr). In linear regression models adjusted for age, sex, race, admission eGFR, and atrial fibrillation, BNP and hs-cTnI were negatively associated with admission BMI, whereas sNGAL was positively associated with admission BMI (Fig. 1). Gal-3, uNGAL and uNGAL/uCr were not associated with admission BMI. When the last measured BMI was evaluated with the last measured biomarkers, findings were the same for BNP, hs-cTnI and sNGAL, but Gal-3 was positively associated with the last BMI. uNGAL and

Table 1. Baseline characteristics of patients by body mass index category

(n = Participants With Data Available)	Normal (n = 188)	Overweight (n = 263)	Obese (n = 415)
Age, years, mean \pm SD* (n = 860)	73.9 \pm 13.5	70.7 \pm 12.5	63.9 \pm 13.6
Men, n (%) (n = 866)	111 (59.0%)	177 (67.3%)	243 (58.6%)
White, n (%) [†] (n = 860)	131/186 (70.4%)	177/263 (67.3%)	223/411 (54.3%)
BMI, kg/m ² , median [IQR] (n = 866)	23.0 [21.6–24.0]	27.4 [26.0–28.5]	36.6 [32.9–41.9]
Systolic blood pressure, mmHg, mean \pm SD [‡] (n = 866)	134 \pm 29	137 \pm 28	145 \pm 30
Diastolic blood pressure mmHg, mean \pm SD [‡] (n = 866)	78 \pm 20	80 \pm 18	82 \pm 20
Heart rate, bpm, mean \pm SD (n = 866)	88 \pm 24	88 \pm 22	88 \pm 23
Shortness of breath, n (%) (n = 866)	130 (69.1%)	173 (65.8%)	289 (69.6%)
Orthopnea, n (%) [§] (n = 866)	114 (60.6%)	137 (55.9%)	285 (68.7%)
Edema, n (%) [†] (n = 866)	130 (69.1%)	182 (69.2%)	344 (82.9%)
Jugular venous distension, n (%) [‡] (n = 866)	67 (35.6%)	70 (26.6%)	80 (19.3%)
Hypertension, n (%) [†] (n = 866)	142 (77.5%)	201 (76.4%)	363 (87.5%)
Hyperlipidemia, n (%) [†] (n = 866)	81 (43.1%)	133 (50.6%)	238 (57.3%)
Diabetes, n (%) [*] (n = 866)	44 (23.4%)	97 (36.9%)	246 (59.3%)
Coronary artery disease, n (%) (n = 866)	82 (43.6%)	130 (49.4%)	184 (44.3%)
COPD, n (%) (n = 866)	51 (27.1%)	64 (24.3%)	117 (28.2%)
Tobacco use, n (%) (n = 866)	35 (18.6%)	49 (18.6%)	66 (15.9%)
Atrial fibrillation, n (%) [‡] (n = 866)	64 (34.0%)	70 (26.6%)	97 (23.4%)
ACEI/ARB, n (%) [†] (n = 866)	96 (51.1%)	165 (62.7%)	271 (65.3%)
Beta-blocker, n (%) (n = 866)	126 (67.0%)	186 (70.7%)	300 (72.3%)
Diuretic, n (%) (n = 866)	130 (69.1%)	178 (67.7%)	308 (74.2%)
Furosemide equivalent dose in first 3 days, mg/day, median [IQR] [†] (n = 866)	47 [27, 80]	53 [33, 100]	67 [40, 100]
Sodium, mEq/L, mean \pm SD (n = 860)	138 \pm 5	138 \pm 9	139 \pm 5
Hemoglobin, g/dL, mean \pm SD (n=863)	11.3 \pm 2.5	11.6 \pm 2.5	11.8 \pm 2.4
Creatinine, mg/dL, median [IQR] (n = 860)	1.16 [0.93–1.50]	1.20 [0.92–1.70]	1.18 [0.94–1.60]
eGFR, ml/min/1.73m ² , mean \pm SD (n = 860)	58.7 (25.1)	59.1 (26.4)	62.5 (27.5)
BUN, mg/dL, mean \pm SD [†] (n = 857)	36 \pm 32	34 \pm 31	28 \pm 20
BNP, ng/L, median [IQR]* (n = 837)	930 [447–1709]	653 [305–1181]	579 [148–829]
hs-cTnI, ng/L, median [IQR] [†] (n = 829)	30.5 [12.8–73.5]	28.3 [14.0–69.4]	21.9 [11.9–45.3]
Galectin-3, ng/mL, median [IQR] (n = 843)	26.1 [20.1–37.8]	26.1 [20.2–37.9]	24.7 [19.0–34.3]
sNGAL, ng/mL, median [IQR] (n = 866)	137.5 [80.1–214.1]	142.0 [88.4–240.1]	131.4 [81.7–249.0]
uNGAL, ng/mL, median [IQR] (n = 850)	11.7 [4.3–26.5]	13.4 [4.4–36.7]	12.5 [4.3–34.2]
uNGAL/uCr, ug/g, median [IQR] (n = 772)	28.1 [13.8–55.3]	25.9 [12.8–59.6]	24.8 [12.1–75.3]

Statistical significance in the post hoc analysis.

*Normal vs overweight and overweight vs obese BMI.

[†]Normal and overweight vs obese BMI.

[‡]Normal vs obese BMI.

[§]Overweight vs obese BMI. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; bpm, beats per minutes; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; hs-cTnI, high sensitivity cardiac troponin I; IQR, interquartile range; SD, standard deviation; sNGAL, serum neutrophil gelatinase associated lipocalin; uCr, urine creatinine; uNGAL, urine neutrophil gelatinase associated lipocalin.

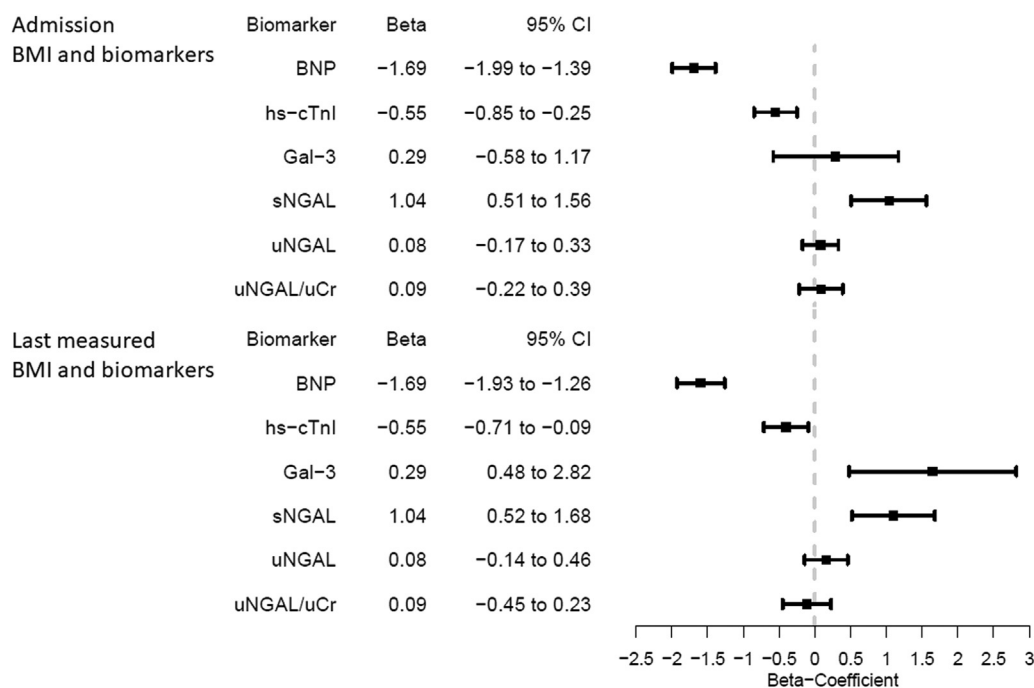


Fig. 1. Beta coefficients of biomarkers for body mass index in linear regression models adjusted for age, sex, race, admission eGFR, and atrial fibrillation, higher admission BMI was associated with lower BNP and hs-cTnI levels, whereas higher sNGAL levels were associated with higher admission BMIs. When the last measured biomarkers and BMIs were evaluated, higher BMI was associated with lower BNP and hs-cTnI, whereas higher sNGAL and Gal3 levels were associated with higher BMI. BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; hs-cTnI, high-sensitivity cardiac troponin I; sNGAL, serum neutrophil gelatinase associated lipocalin; uCr, urine creatinine; uNGAL, urine neutrophil gelatinase associated lipocalin.

uNGAL/uCr remained not associated with the last BMI.

Interaction of BMI With Biomarker Associations

Table 2 shows the composite of deaths or HF readmissions, deaths alone and HF readmissions alone at 30 days, 90 days or 1 year in each BMI category. The total number of those lost to follow-up was 7: 5 patients in the overweight category and 2 patients in the obese category. The incidence of the composite event was lower in higher BMI categories at all time points. The findings were the same when death alone was evaluated. There was no difference in HF readmissions between categories at any time points.

In a multivariable Cox model, admission BMI, higher BNP and higher hs-cTnI levels were associated with increased risks of death or HF readmission at all time points (Table 3). BNP on admission was associated with adjusted HR of 1.32 (95% CI, 1.12–1.56) for 30 days, 1.31 (95% CI, 1.16–1.48) for 90 days and 1.21 (95% CI, 1.11–1.32) for 1-year composite endpoint per 2-fold higher BNP. The hs-cTnI levels were associated with adjusted HR of 1.28 (95% CI, 1.16–1.43) for 30 days, 1.18 (95% CI, 1.09–1.28) for 90 days and 1.10 (95% CI, 1.04–1.17) for 1-year composite endpoint per 2-fold higher hs-cTnI. Higher

Gal-3 levels were associated with an increased risk of death or HF readmission only at 30 days, and higher uNGAL levels were associated with an increased risk of death or HF readmission only at 90 days. Only BNP had a significant interaction with admission BMIs for the composite endpoint at each time point, with the interaction term ranging from 0.983–0.992, indicating that the HR decreased exponentially approximately 1%–2% for each 1 kg/m² increase in BMI (Table 3). When the last BMI and biomarker measurements were used, associations were similar, except uNGAL was no longer associated with death or HF readmission at 90 days. BNP continued to have a significant interaction with BMI, whereas Gal-3 now had a significant interaction with last BMI at each time point. The interaction terms for last BNP and last BMI were similar to those at admission. For Gal-3, the interaction term ranged from 0.954–0.977, indicating that the HR decreased exponentially approximately 2%–5% for each 1 kg/m² increase in BMI (Table 3).

When admission BNP levels were evaluated within each category of admission BMI, its association with death or HF readmission at each time point decreased as BMI increased, and BNP was not associated with the death or HF readmission in obese patients (Fig. 2A). When evaluated by last measured

Table 2. Deaths or heart failure readmissions at 30 days, 90 days and 1 year by body mass index category

Death or HF readmission	Normal (n = 188)	Overweight (n = 263)	Obese (n = 415)	P value
30 days, n (%)	27 (14.4%)	25 (9.5%)	29 (7.0%)	0.02
90 days, n (%)	47 (25.0%)	44 (16.7%)	55 (13.3%)	<0.01
1 year, n (%)	84 (44.7%)	92 (35.0%)	110 (26.5%)	<0.01
Death	Normal (n = 188)	Overweight (n = 263)	Obese (n = 415)	P value
30 days, n (%)	13 (6.9%)	15 (5.7%)	11 (2.7%)	0.03
90 days, n (%)	28 (14.9%)	22 (8.4%)	18 (4.3%)	<0.01
1 year, n (%)	50 (26.6%)	51 (19.4%)	43 (10.4%)	<0.01
HF Readmission	Normal (n = 188)	Overweight (n = 263)	Obese (n = 415)	P value
30 days, n (%)	15 (8.0%)	10 (3.8%)	19 (4.6%)	0.10
90 days, n (%)	26 (13.8%)	26 (9.9%)	41 (9.9%)	0.30
1 year, n (%)	50 (26.6%)	50 (19.0%)	78 (18.8%)	0.06

HF, heart failure.

BNP and BMI, findings were similar, with no prognostic association of BNP in obese patients (Fig. 2B).

Last-measured Gal-3 levels had significant interactions with BMIs for outcomes at each time point. However, Gal-3 was significantly associated only with 30-day death or HF readmission in patients with normal BMIs and showed no association with other BMI categories at other time points (Supplementary Fig. 2).

Discussion

BMI is a well-described confounder of NPs in HF; however, BMI's interaction with NPs and other biomarkers in AHF is less well known. In this analysis, we found that higher BMI was associated with lower BNP and hs-cTnI levels and was associated with higher sNGAL and Gal-3 levels. Despite these associations, only BNP showed a significant interaction

Table 3. Multivariable Cox models for death or heart failure readmission at 30 days, 90 days, 1 year, with interaction between admission BMI and biomarker and last BMI and biomarker

Admission BMI and Biomarkers		BNP	hs-cTnI	Gal-3	sNGAL	uNGAL	uNGAL/uCr
30 days	Adjusted HR	1.32	1.28	1.52	1.20	1.07	1.04
	95% CI	(1.12–1.56)	(1.16–1.43)	(1.11–2.07)	(0.96–1.50)	(0.96–1.19)	(0.92–1.18)
	P value for interaction	0.02	0.81	0.50	0.40	0.31	0.66
	Interaction HR	0.983					
90 days	Adjusted HR	1.31	1.18	1.10	1.06	1.10	1.07
	95% CI	(1.16–1.48)	(1.09–1.28)	(0.85–1.43)	(0.89–1.26)	(1.02–1.19)	(0.98–1.17)
	P value for interaction	0.01	0.59	0.12	0.17	0.57	0.51
	Interaction HR	0.986					
1-year	Adjusted HR	1.21	1.10	0.97	1.00	1.02	0.99
	95% CI	(1.11–1.32)	(1.04–1.17)	(0.80–1.18)	(0.88–1.12)	(0.97–1.08)	(0.93–1.05)
	P value for interaction	0.05	0.61	0.12	0.88	0.13	0.34
	Interaction HR	0.992					
Last measured BMI and biomarkers	Adjusted HR	1.35	1.22	1.69	1.23	1.10	1.04
	95% CI	(1.13–1.62)	(1.08–1.37)	(1.06–2.70)	(0.96–1.59)	(0.97–1.26)	(0.90 to 1.20)
	P value for interaction	<0.01	0.63	0.08	0.32	0.76	1.00
	Interaction HR	0.981		0.962			
90 days	Adjusted HR	1.30	1.18	1.14	1.01	1.07	1.05
	95% CI	(1.14–1.47)	(1.08–1.28)	(0.80–1.64)	(0.84–1.22)	(0.97–1.17)	(0.94–1.16)
	P value for interaction	0.01	0.30	<0.01	0.86	0.99	0.88
	Interaction HR	0.987		0.954			
1 year	Adjusted HR	1.18	1.09	1.10	1.04	1.01	1.01
	95% CI	(1.09–1.29)	(1.02–1.16)	(0.84–1.44)	(0.91–1.18)	(0.95 to 1.08)	(0.94 to 1.08)
	P value for interaction	0.02	0.21	0.06	0.43	0.72	0.56
	Interaction HR	0.991		0.977			
	95% C	(0.984–0.998)		(0.953–1.001)			

BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; Gal3, galectin 3; hs-cTnI, high-sensitivity cardiac troponin I; HR, hazard ratio; sNGAL, serum neutrophil gelatinase associated lipocalin; uCr, urine creatinine; uNGAL, urine neutrophil gelatinase associated lipocalin.

Boldface type indicates statistical significance in adjusted HR.

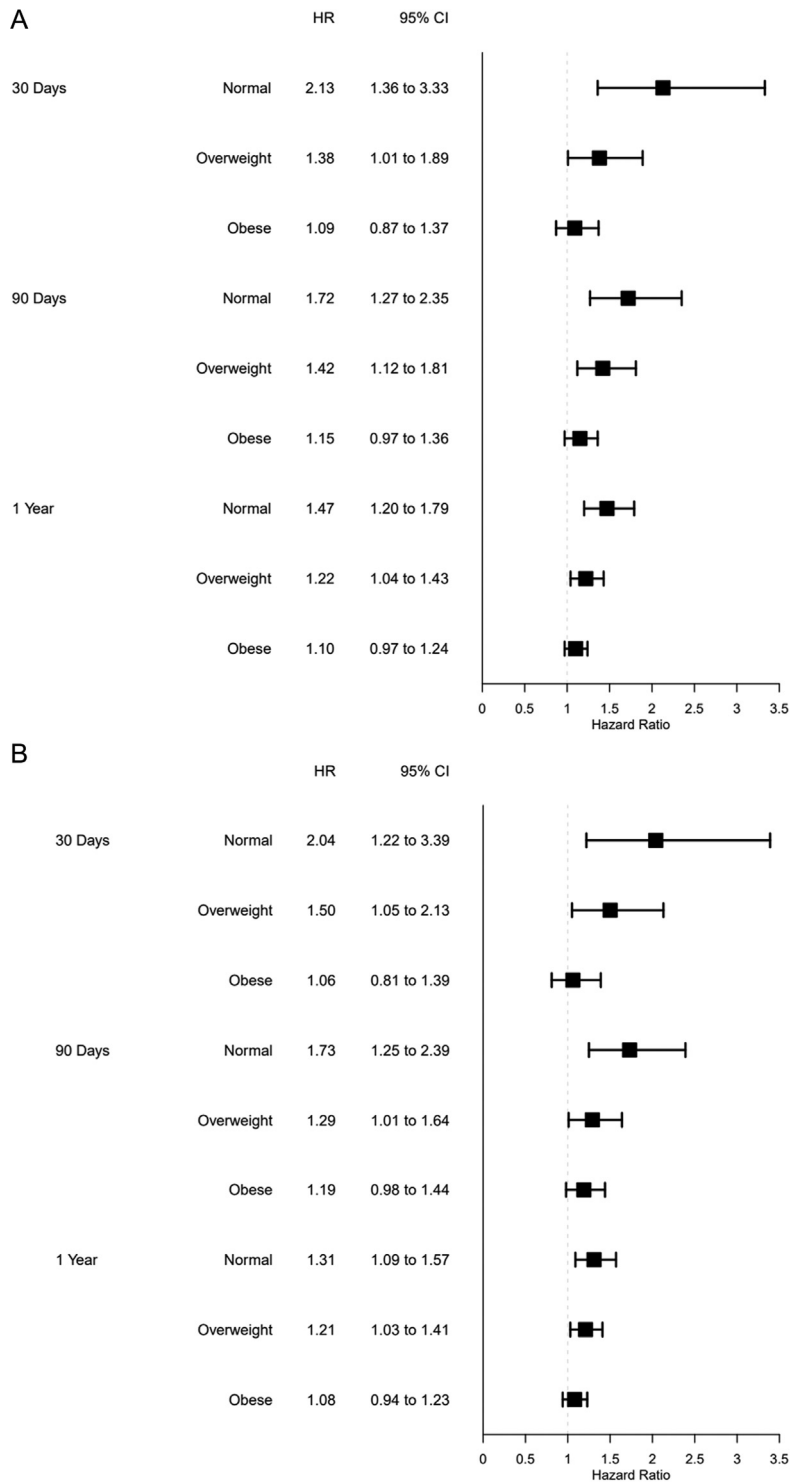


Fig. 2. Hazard ratios of BNP for death or heart failure hospitalization at differing follow-up times by BMI category. A, Analysis with admission BMI and BNP. B, Analysis with last measured BMI and BNP in multivariable Cox models. Hazard ratios of BNP for death or HF readmission at each time point decreased as admission BMI increased (A). BNP was not associated with the composite of death or HF readmission in obese patients. When evaluated by last-measured BNP and BMI, BNP was not associated with death or HF readmission in obese BMI categories (B). BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; HF, heart failure; HR, hazard ratio.

with BMI for the risk of death or HF readmission, on both hospital admission and the last-measured values during hospitalization. Conversely, higher hs-

cTnI levels were associated with an increased risk of death or HF readmission, irrespective of BMI. BNP's association with death or HF readmission

attenuated as BMI increased and was no longer associated with the composite outcome in obese patients. Therefore, even when obese patients are admitted due to AHF and with low BNP levels, that does not guarantee that they are at low risk for adverse events. This is also the case for the last-measured values when patients have been treated by decongestive therapy during hospitalization. For better risk stratification of patients with obese BMIs, another biomarker, which is not affected by BMI, such as hs-cTn, may be needed.

As other studies have shown, higher BMI was associated with lower BNP in our analysis. This finding is not novel, but we found that BNP's prognostication of death or HF readmission was significantly impacted by BMI in AHF, with BNP no longer prognostic for the composite outcome in obese patients. This finding differs from that of prior studies. Studies of outpatients with HF have given conflicting results concerning the interaction between BMI and NPs; some studies suggest that NPs are prognostic, regardless of BMI, and others show that NPs are not prognostic with higher BMIs.^{3,5,6,21} In AHF, prior studies did not find an interaction between BMI and NPs.^{2,4,22} However, these studies used different methodologies, such as dichotomizing BMI or excluding individuals with low NP levels, which may explain the differences in our findings from those of prior studies. Unlike those studies, our analysis showed a significant interaction between BMI and BNP for outcomes. Our findings are not impacted by some of the potential confounders in prior studies because the diagnosis of HF was made prospectively, independent of the levels of BNP, and it did not exclude patients with lower BNP levels. We also showed that the interaction between BNP and BMI for outcomes was consistent when last-measured values were analyzed. BNP value after treatment is more indicative of the patient's "dry" condition and more prognostic than the admission value.²³ Nevertheless, in obese patients assessed by the last-measured BMI, BNP value after the treatment was not associated with outcomes. Therefore, although about half of patients in our cohort with AHF were obese, special attention is needed when clinicians use BNP, both the admission and the discharge values, as a tool for risk stratification in this population.

Another intriguing finding from our analysis is the relationship between hs-cTnI and BMI. Prior studies reported that higher BMI was associated with higher troponin levels in patients without HF, whereas a prior study in patients with AHF found that troponin was not associated with BMI.^{22,24} We found that higher BMI was associated with lower troponin levels, a difference reflected primarily by lower hs-cTnI levels in obese patients compared to those with

normal and overweight BMIs. There are multiple possible explanations for this negative association. Obese patients may have had less severe HF, which is supported by the lower event rates in obese patients in our study, and that fits with the obesity paradox.²⁵ However, the obesity paradox may be restricted to older patients and those without diabetes, whereas the obese patients in our study were younger and more commonly had diabetes.^{26,27} Obese patients in the AKINESIS study may have had HF with preserved ejection fraction and with lower wall tension and possibly less myocardial injury.²⁸ Ejection fraction was not collected in several patients in the AKINESIS study, but the median BNP in obese patients in AKINESIS was notably elevated (579 ng/L), a range suggestive of reduced ejection fraction. Additionally, hs-cTn has been shown to be prognostic for heart failure with preserved ejection fraction, and the overall prognosis in HF is similar, regardless of ejection fraction; thus, a skewed HF population based on ejection fraction seems less likely or clinically significant for outcomes.^{29,30} Further research is needed to determine why obese patients have lower hs-cTnI levels, but its prognostic use without an interaction with BMI is of significant clinical importance. Currently, cTn has been reported to be a powerful predictor of poor prognosis, as hs BNP.³¹ Given the lack of prognostication value of BNP in obese patients, the use of cTn levels can be complementary and can improve risk stratification.

In our population with AHF, Gal-3's relation to BMI was complicated. Although we did not find a relationship between admission BMI and Gal-3, higher BMI was associated with a higher Gal-3 level at last measurement. Studies have shown that higher BMI is associated with higher Gal-3 levels; thus, this finding may more accurately reflect Gal-3's relationship to BMI in AHF.^{22,24} The lack of association at admission may result from the multiple factors influencing Gal-3 levels, such as inflammation and fibrosis, being confounded by the influence of fluid overload in BMI, which is uncovered only once congestion resolves. There was an interaction between last-measured Gal-3 and BMI for 30-day outcomes, and Gal-3 levels were prognostic in patients with normal BMIs, but the HRs for other time points were not significant. The influence of timing of measurements and an interaction with obesity may partially explain the limited prognostic ability of Gal-3 levels, which is in line with prior literature showing its variable prognostic utility.^{32,33}

Studies of patients both with and without AHF have shown that sNGAL increases with higher BMI, whereas small studies suggest that uNGAL may increase with higher BMI.^{22,34} These studies did not specifically evaluate whether BMI influences the

prognostic ability of NGAL in AHF. We did not find an association between uNGAL and BMI, either when we evaluated it alone or indexed it to uCr. Conversely, higher sNGAL was associated with higher BMI, a finding potentially connected to obesity-related inflammation.³⁵ sNGAL was not prognostic for death and HF readmission, and uNGAL largely lacked prognostic ability for death and HF readmission. For both biomarkers, these associations were not altered by BMI.

Our findings reaffirm the need to consider BMI in the interpretation of biomarkers in patients with AHF. In obese patients, the values of BNP and hs-cTnI can be lower, and those of sNGAL and Gal-3 can be higher. The interpretation of BNP for prognosis requires special attention, because its association with prognosis attenuates at higher BMIs and is no longer significant in obese patients. In contrast, clinicians may consider hs-cTnI for short- and long-term prognostication, regardless of BMI.

Limitations

We cannot exclude the possibility that other potential confounders were not identified or used, which may alter our findings. Additionally, although less than 5% of biomarker values were missing for most biomarkers, 11% of participants were missing uNGAL values; thus, findings may be biased due to loss of individuals without biomarkers or with missing variables. Signs and symptoms of AHF and administration of IV diuretics were requirements for entry into the AKINESIS study, but the diagnosis of AHF was not adjudicated. Additionally, echocardiography was not required for the study and was not available for a large proportion of individuals. Thus, we cannot exclude a possible misdiagnosis of HF or potential outcomes at higher BMIs' being driven by more patients with heart failure with preserved ejection fraction in this cohort. We assessed BMI at admission and later during hospitalization after diuretic therapy was given, but we may not have captured a true dry-weight BMI to evaluate biomarker interactions without the effect of fluid overload. Additionally, 25 patients died during hospitalization, which may have contributed to an immortal time bias. Therefore, findings based on the last BMI and last biomarker measurements should be interpreted cautiously. However, in clinical practice, physicians make risk assessments based on these biomarker values and the clinical findings of these timings; thus, our findings are clinically meaningful. There were also other analytical concerns, such as the correct functional form of the biomarkers in the Cox

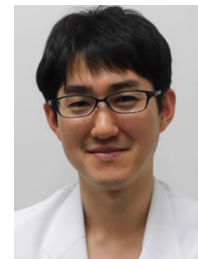
models, the missing data and the timeframe between the last biomarker and the last BMI.

Conclusions

In patients with AHF, higher BMI is associated with lower BNP and hs-cTnI levels and with higher sNGAL and Gal-3 levels. BMI significantly interacted with the prognostic ability of BNP, both on admission and after treatment during hospitalization, and for the outcome of death or HF readmission. This means that BNP is no longer prognostic in obese patients. Higher hscTnI levels predicted poor prognosis without being influenced by BMI, regardless of the timing of measurement; thus, they can be used in obese patients with AHF for risk stratification.

Lay Summary

Biomarkers' relationship with BMI should be considered in patients with AHF. In obese patients, values of BNP and hs-cTnI can be lower, and sNGAL and Gal-3 can be higher. In obese patients, BNP is no longer associated with outcomes of death or heart failure hospitalization, so alternative biomarkers may be needed for prognostication. Clinicians may consider using hs-cTnI because its association with outcomes did not vary with BMI.



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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.cardfail.2023.03.029](#).

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