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Plasma Bioactive-Adrenomedullin as a Prognostic Biomarker in Acute Heart Failure

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Abstract

Objective—To evaluate the prognostic performance of a new biomarker, plasma bioactive adrenomedullin (bio-ADM), for short-term clinical outcomes in acute heart failure.

Methods—A multicenter prospective cohort study of adult emergency department (ED) patients suspected of having acute heart failure was conducted to evaluate the association between plasma bio-ADM concentration and clinical outcomes. The primary outcome was a composite of the following within 30 days: death, cardiac arrest with resuscitation, respiratory failure, emergency dialysis, acute coronary syndrome, hospitalization >5 days, and repeat ED visit or hospitalization. Prognostic accuracy was evaluated with a non-parametric receiver operating characteristic (ROC) curve. Additionally, a multivariable logistic regression model was constructed to assess the additive prognostic performance of bio-ADM while adjusting for other biomarkers routinely used clinically, including BNP, cardiac troponin I, creatinine, and sodium concentration.

Results—Two hundred forty-six patients were enrolled, including 85 (34.6%) patients with the primary outcome. Plasma bio-ADM concentrations were higher among patients who experienced the primary outcome (median: 80.5 pg/ml; IQR: 53.7 pg/ml, 151.5 pg/ml) compared to those who did not (median: 54.4 pg/ml; IQR: 43.4 pg/ml, 78.4 pg/ml) ($p < 0.01$). Area under the ROC curve was 0.70 (95% CI: 0.63, 0.75). After adjusting for the other biomarkers, plasma bio-ADM remained a strong predictor of the primary outcome (adjusted odds ratio per IQR change: 2.68; 95% CI: 1.60, 4.51).

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Conclusions—Bio-ADM concentrations at the time of ED evaluation for acute heart failure were predictive of clinically-important 30-day outcomes, suggesting bio-ADM is a promising prognostic marker for further study.

1. INTRODUCTION

Acute heart failure (AHF) is one of the most common illnesses treated in emergency departments (EDs) in the United States (US).[1] After establishing an AHF diagnosis and initiating treatment, a major clinical decision facing emergency physicians is whether to pursue hospitalization for in-patient management.[2] Approximately 80% of patients diagnosed with AHF in US EDs are hospitalized.[1] Hospitalization allows for close observation and titration of intravenous medications, but is also associated with substantially higher cost than outpatient management and places patients at risk for nosocomial complications, such as infections, delirium, and falls.[2-5] Ideally, hospitalization would be reserved for patients at high risk for short-term severe complications of AHF, such as respiratory and renal failure, and those needing specific in-patient therapies, such as intravenous vasoactive medications.[2-3] However, ensuring clinical stability and estimating the risk of severe short-term outcomes is problematic with existing prognostic tools. This prognostic uncertainty plays a significant role in the high admission rate for AHF patients.[1-3. 6]

A prognostic biomarker that accurately identified AHF patients at high risk for short-term complications would be invaluable for guiding management decisions, particularly decisions regarding hospitalization. Natriuretic peptides, such as B-type natriuretic peptide (BNP), are widely used as diagnostic biomarkers for AHF, but their prognostic performance is suboptimal.[7,8] While patients with an elevated cardiac troponin, renal dysfunction, and hyponatremia are at increased risk for severe outcomes, a subset of patients without these risk factors also experiences adverse events, suggesting additional biomarkers are needed.[9-12]

Adrenomedullin is a vasodilatory peptide that is elevated in patients with chronic heart failure and may also acutely rise in AHF.[13-15] Elevated levels of mid-region pro-adrenomedullin (MR-proADM), a stable fragment derived from the same precursor peptide as adrenomedullin, have previously been shown to predict 90-day mortality among patients presenting with acute shortness of breath, including those with AHF.[8,16] MR-proADM measurement does not distinguish between biologically-active amidated adrenomedullin and the non-functional adrenomedullin variant containing a glycine-extended C-terminal residue. Recently, a sandwich immunoassay has been developed to specifically measure the biologically-active form of adrenomedullin—bio-active adrenomedullin (bio-ADM)—making it feasible to use it as a biomarker in clinical medicine.[17-19] Due to the need for better prognostic markers in AHF and a biologically-plausible association between bio-ADM and AHF severity, we evaluated the prognostic accuracy of plasma bio-ADM for predicting severe, short-term clinical outcomes in patients evaluated in the ED for AHF.

2. METHODS

2.1. Study Design

We conducted a multicenter prospective cohort study to evaluate plasma bio-ADM as a prognostic biomarker in adults presenting to the ED with signs and symptoms consistent with AHF at two university-affiliated tertiary care EDs and two community EDs in the US. We studied single measurements of bio-ADM in plasma collected at the time of initial ED presentation. This study utilized a subset of patients recruited for the STRATIFY and DECIDE studies.[20] Methodological details of patient recruitment and enrollment have been reported previously.[20] The local Institutional Review Boards of the participating sites approved the study. All enrolled patients provided written informed consent for participation.

2.2. Study Population

We randomly selected 250 patients enrolled in the STRATIFY/DECIDE cohort between July 20, 2007 and February 4, 2011.[20] Enrolled patients presented to the ED with acute cardiopulmonary symptoms, met the Modified Framingham Criteria for AHF,[20] and were clinically suspected of having AHF. To ascertain if AHF was truly the cause of each patient's acute symptoms, a panel of three cardiologists reviewed the medical record of each enrolled patient's ED visit and subsequent hospitalization. Each cardiologist classified the primary cause of symptoms as *AHF* or *not AHF*. Two cardiologists initially reviewed each case. If classification by the initial two cardiologists were discordant, a third cardiologist reviewed the case, with the final diagnosis based on majority. Inter-rater agreement between the initial two reviewers was calculated with Cohen's Kappa. The prognostic accuracy of bio-ADM was evaluated both in the full study population (*Suspected AHF Population*) and separately in the subset of patients who had AHF confirmed based on the cardiologists' review (*Confirmed AHF Population*).

2.3. Biomarker Measurement

Trained research personnel collected and banked plasma from patients in the ED. Samples were frozen within two hours and stored at −80°C. Plasma bio-ADM concentrations were measured by investigators blinded to clinical data at Sphingotec GmbH (Hennigsdorf, Germany). The bio-ADM assay has been previously described.[19] In brief, it is a one-step sandwich chemiluminescence immunoassay, based on Acridinium NHS-ester labeling for the detection of human ADM in unprocessed, neat plasma. It employs two mouse monoclonal antibodies, one directed against the midregion (solid phase), and the other directed against the amidated C-terminal moiety of ADM (labeled antibody). The assay employs 50 μL of plasma samples/calibrators and 200 μL of labeled detection antibody. The analytical assay sensitivity is 2 pg/ml. In prior work,[19] the median bio-ADM concentration of 200 healthy adults was 20.7 pg/mL; the 99th percentile was 43.0 pg/mL.

Patients also had additional, standard-of-care biomarkers measured while in the ED, including BNP, cardiac troponin I, creatinine, and sodium concentration.

2.4. Outcomes

Research personnel ascertained outcomes 30 days (+/− 2 days) after the index ED visit via phone interviews and medical record review. Two categories were evaluated: severe clinical outcomes and healthcare utilization outcomes. A severe clinical outcome was defined as the occurrence of ≥ 1 of the following events: death; cardiac arrest with return of spontaneous circulation; respiratory failure with intubation; emergency dialysis; and acute coronary syndrome. [21] Healthcare utilization outcomes included: hospital length of stay (LOS) greater than 5 days, return ED visit for AHF within 30 days, and repeat hospitalization for AHF within 30 days. Five days was chosen to denote prolonged LOS because this represents the median hospital LOS for AHF in the US.[1]

The primary study outcome was a composite of all severe clinical and healthcare utilization outcomes. In secondary analyses, we separately evaluated severe clinical outcomes without the healthcare utilization outcomes.

2.5. Data Analysis

2.5.1. Unadjusted Analyses—In the primary analysis, we evaluated the prognostic accuracy of plasma bio-ADM concentration in the Suspected AHF Population (all enrolled patients) for a composite of all 30-day outcomes. Bio-ADM concentrations in patients who experienced ≥ 1 outcome were compared to those who did not experience any outcomes with the Wilcoxon Rank Sum Test. A non-parametric receiver operating characteristic (ROC) curve was constructed to display the performance of bio-ADM to discriminate between patients who did and did not experience a 30-day outcome. We also used the 25^{th}, 50^{th}, and 75^{th} percentile of bio-ADM concentration in the study population as cut-points, and calculated the proportion of patients with bio-ADM levels above and below these cut-points who experienced the primary outcome.

Secondary analyses were also performed after limiting study outcomes to the severe clinical outcomes and limiting the study population to the Confirmed AHF Population. Therefore, three secondary analyses were conducted: 1) severe clinical outcomes in the Suspected AHF Population; 2) all 30-day outcomes in the Confirmed AHF Population; and 3) severe clinical outcomes in the Confirmed AHF Population.

2.5.2. Multivariable Biomarker Model—A multivariable logistic regression model was constructed to assess the additive prognostic performance of bio-ADM while adjusting for other biomarker results, including BNP, cardiac troponin I, creatinine, and sodium concentration. Data for bio-ADM, BNP, cardiac troponin I and creatinine were logarithmically transformed (log-10) due to highly skewed distributions. The study population for this model included Suspected AHF patients who had non-missing data for all five biomarkers. The dependent variable was a composite of all 30-day outcomes. Independent variables included: bio-ADM log-10 transformed, BNP log-10 transformed, cardiac troponin I log-10 transformed, creatinine log-10 transformed, and serum sodium concentration. To allow for comparisons of odds ratios (ORs) among the biomarkers, we reported ORs associated with one interquartile range (IQR) change in each biomarker level. To quantify the relative strength of association for each of the biomarkers with the outcome,

we removed one biomarker from the full regression model at a time and calculated the added value of each biomarker based on the likelihood ratio chi-square test for nested models. A higher likelihood ratio chi-square statistic for a particular biomarker indicated greater contribution to the overall model.

Statistical analyses were conducted with STATA 12.0 (College Station, TX).

3. RESULTS

3.1. Patient Characteristics

Two hundred fifty patients were randomly selected from the STRATIFY/DECIDE cohort[20] for this study. Four patients were excluded, including three patients with insufficient data to classify whether their symptoms were due to AHF and one patient who had insufficient plasma for bio-ADM measurement; the remaining 246 patients were included as the Suspected AHF Population (Figure 1; Table 1). Of these 246 patients, 124 (50.4%) were confirmed to have AHF based on the cardiologist review and were considered the Confirmed AHF Population. The initial two cardiologists agreed on whether AHF was the cause of symptoms in 224 (91.1%) cases [Kappa = 0.82 (standard error: 0.060)].

3.2. Suspected AHF Population

Among the 246 patients in the Suspected AHF Population, 85 (34.6%) met the primary outcome by experiencing at least one of the 30-day outcomes; 18 (7.3%) patients had a severe clinical outcome (Table 2).

3.2.1. All 30-Day Outcomes (Primary Outcome)—Plasma bio-ADM concentration was higher in patients who experienced at least one 30-day outcome (median: 80.5 pg/ml; IQR: 53.7 pg/ml, 151.5 pg/ml) compared to those who did not (median: 54.4 pg/ml; IQR: 43.4 pg/ml, 78.4 pg/ml) ($p < 0.01$). Area under the ROC curve was 0.70 (95% CI: 0.63, 0.75) (Figure 2a). The 25^{th}, 50^{th}, and 75^{th} percentile of plasma bio-ADM concentration in the Suspected AHF population was 46.4 pg/ml, 60.7 pg/ml, and 92.5 pg/ml, respectively. Proportions of patients with bio-ADM concentrations above and below each of these cut-points who experienced the composite outcome are shown in Table 3.

3.2.2. Severe Clinical Outcomes—After limiting the outcome of interest to only severe clinical outcomes, plasma bio-ADM concentration was significantly higher in patients who experienced the outcome (median: 89.9; IQR: 53.5 pg/ml, 186.6 pg/ml) compared to those who did not (median: 59.5 pg/ml; IQR: 45.8 pg/ml, 89.7 pg/ml) ($p = 0.01$). Area under the ROC curve was 0.68 (95% CI: 0.62, 0.74) (Figure 2b). Bio-ADM levels for patients with no outcomes, healthcare utilization outcomes, and severe clinical outcomes are illustrated in Figure 3.

3.3. Confirmed AHF Population—Among the 124 patients in the Confirmed AHF Population, 71 (57.3%) experienced at least one of the 30-day outcomes, including 13 (10.5%) with a severe clinical outcome (Table 2). Plasma bio-ADM concentration was higher in those who experienced at least one of the 30-day outcomes (median: 91.8 pg/ml; IQR: 56.0 pg/ml, 167.8 pg/ml) than those who did not (median: 69.7 pg/ml; IQR: 46.4

pg/ml, 84.6 pg/ml) ($p < 0.01$). Area under the ROC curve was 0.67 (95% CI: 0.59, 0.76) (Figure 2c). When only considering severe clinical outcomes, bio-ADM remained a predictor of outcomes (Figure 2d).

3.4. Multivariable Biomarker Model—The multivariable logistic regression model included 151 patients in the Suspected AHF Population who had ED measurements for all five biomarkers; 61(40.4%) of these patients experienced the composite 30-day outcome. Both bio-ADM (aOR per one IQR change: 2.68; 95% CI: 1.60, 4.51) and BNP (aOR per one IQR change: 3.06; 95% CI: 1.34, 7.00) were significantly associated with the outcome in the multivariable model, with bio-ADM (likelihood ratio chi-square: 17.70) contributing more to overall model fit than BNP (likelihood ratio chi-square: 7.56) (Table 4).

4. DISCUSSION

This is the first study to evaluate plasma bio-ADM in patients with AHF and suggests it may be a useful prognostic biomarker. Our study has two important findings. First, higher bio-ADM levels were associated with increased risk for important 30-day outcomes. Second, bio-ADM was an independent risk factor for clinical outcomes in a multivariable model including other biomarkers clinicians currently use when evaluating AHF patients, including BNP, cardiac troponin I, creatinine, and sodium concentration. This suggests potential complementary roles for bio-ADM and BNP in the risk stratification of AHF patients.

We evaluated the predictive performance of plasma bio-ADM for several short-term outcomes. Initially, we used a composite of a broad range of outcomes clinicians find important when deciding on disposition for a patient in the ED.[2,3,6,22-24] These outcomes included mortality, morbidity and healthcare utilization, such as prolonged hospitalization and repeat presentations for AHF. The rationale for including healthcare utilization outcomes stems from the concept that ED AHF patients who undergo a prolonged hospitalization or rapidly return to the hospital after an ED visit are likely poor candidates for outpatient management. Acknowledging hospital length of stay and repeat presentations may be driven by factors other than AHF severity, we also evaluated the prognostic performance of bio-ADM for an outcome limited to severe clinical events, including 30-day mortality, cardiac arrest, respiratory failure, emergency dialysis and acute coronary syndrome. Bio-ADM maintained similar prognostic performance both with (ROC AUC = 0.70) and without (ROC AUC = 0.68) healthcare utilization endpoints included in the composite outcome of interest.

Providing clinicians with rapid and accurate prognostic information for AHF patients at the time of ED evaluation has the potential to improve clinical care.[2,20,23,24] Currently, approximately 80% of patients with suspected AHF in US EDs are hospitalized with little attention to an individual patient's risk for clinical decompensation or potential benefit of hospitalization.[1,2,20,23,24] A reliable prognostic biomarker could help guide clinicians to an aggressive management strategy with intravenous medications and hospitalization selectively for AHF patients most likely to benefit from it.

Due to the heterogeneity of AHF, involvement of multiple organ systems, and diverse precipitants leading to acute decompensation, no single biomarker provides comprehensive risk stratification.[22] Accounting for this broad range of physiological disturbances with a multi-biomarker panel for AHF prognosis may be an approach to improve risk stratification. Bio-ADM is a promising new candidate for an AHF biomarker panel. It is a mediator of vascular control and marker of vascular dysregulation, which is a hallmark of AHF exacerbations.[10] While it has similar biological activity to the natriuretic peptides, bio-ADM responds to different stimuli in the peripheral circulation, and therefore likely provides complementary information to BNP.[10] Prior work suggests cardiac troponin, renal function, and serum sodium concentration may also help differentiate high- and low-risk patients with AHF.[9-11] Initial evaluation in this study suggests bio-ADM provides predictive information independent of these other markers. Additional work with larger cohorts is indicated to explore how bio-ADM may be incorporated into a panel of multiple biomarkers for AHF risk stratification.

4.1. Limitations

This study was a secondary analysis of the a multicenter cohort study.[20] This was a relatively small study conducted at a four hospitals in the US. Additional study with larger sample sizes and diverse settings is needed to further adjust for potential confounders and more thoroughly evaluate the additive prognostic information provided by bio-ADM above other markers. Single measurements of bio-ADM were evaluated in this study; evaluation of serial measurements is planned.

5. CONCLUSIONS

In this study of 246 ED patients with suspected AHF, single measurements of plasma bio-ADM were significantly associated with clinically-important 30-day outcomes. Bio-ADM is a promising new biomarker that may add important prognostic information for patients with AHF. Further study is indicated to robustly evaluate bio-ADM in larger sample sizes, both as a single biomarker and as a component of multi-marker panels.

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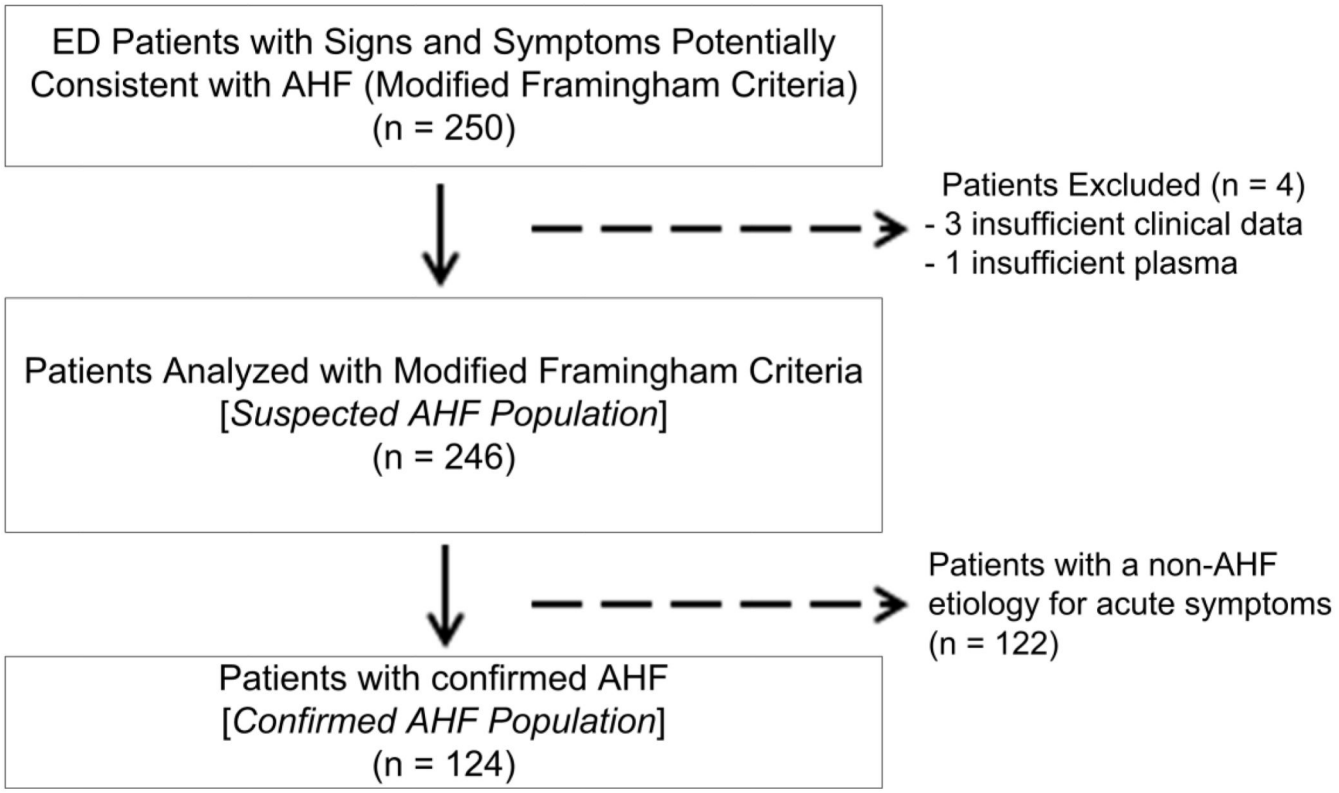

Figure 1.
Flow diagram of patient enrollment.

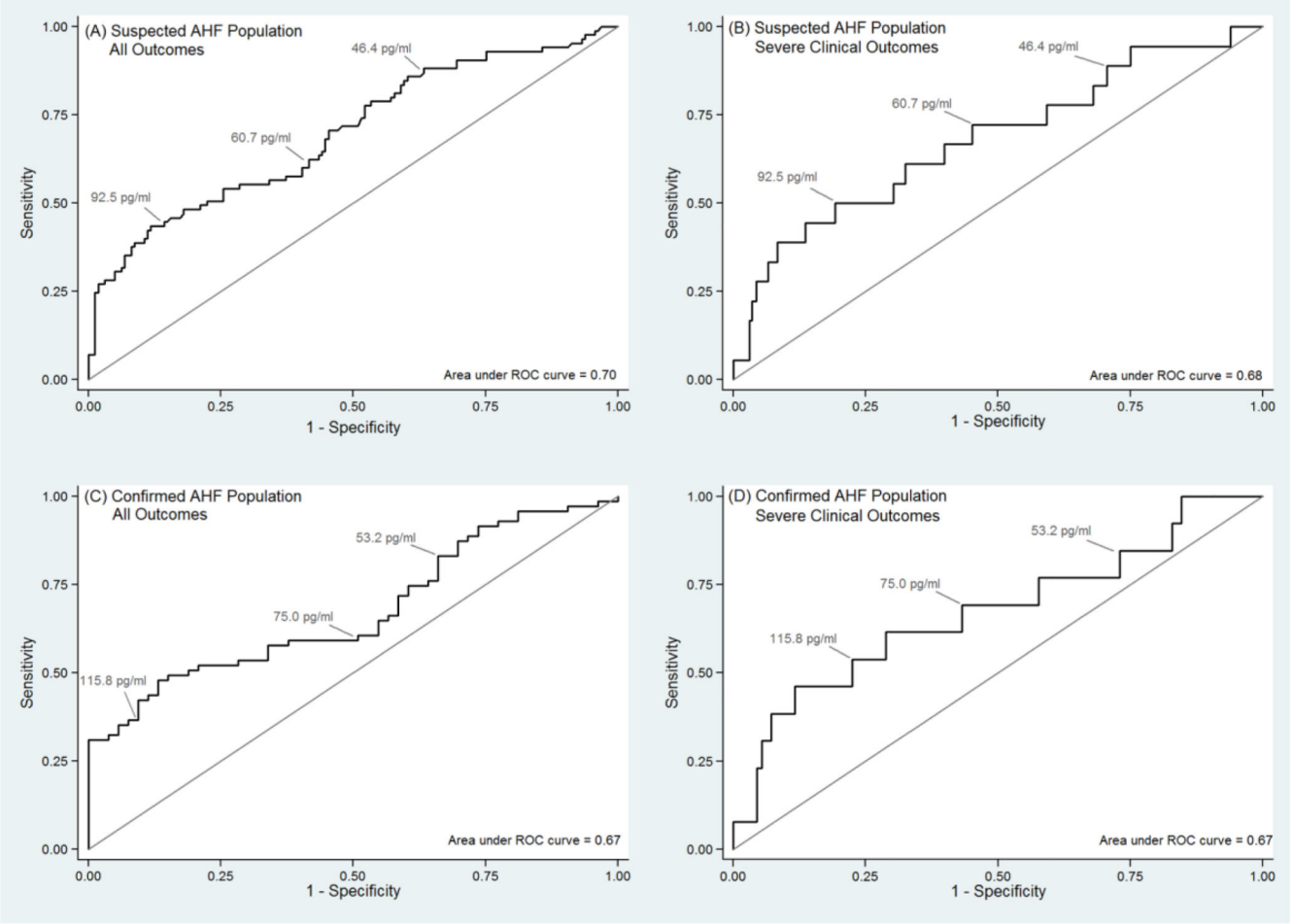

Figure 2.

Receiver operating characteristic (ROC) curves showing the predictive performance of bioactive adrenomedullin (bio-ADM) to identify patients with the study outcomes: (A) Suspected Acute Heart Failure (AHF) Population with a composite of all 30-day outcomes; (B) Suspected AHF Population with only severe clinical outcomes; (C) Confirmed AHF Population with a composite of all 30-day outcomes; (D) Confirmed AHF Population with only severe clinical outcomes. The 25th, 50th, and 75th percentiles of bio-ADM concentration for each population are displayed on the ROC plots.

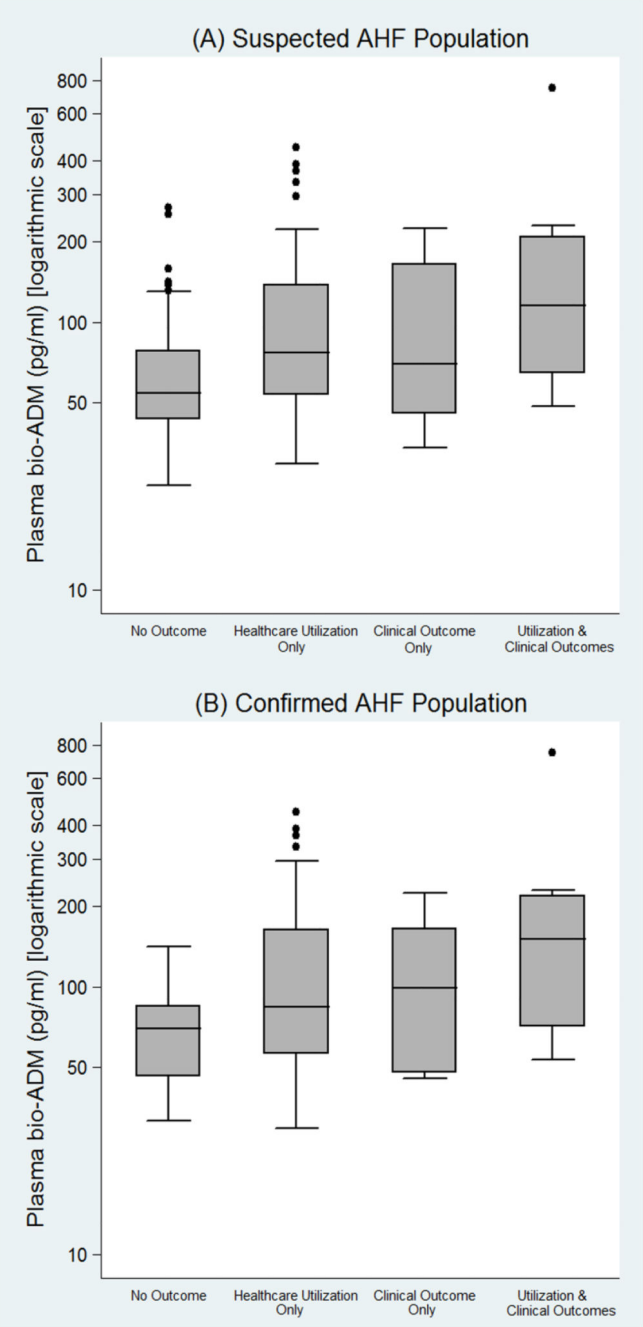

Figure 3.

Box plots of plasma bioactive adrenomedullin (bio-ADM) concentration, by outcome category among the (A) Suspected Acute Heart Failure (AHF) Population, and (B) Confirmed AHF Population. The y-axis of each plot is displayed on a logarithmic scale. The center of each box plot represents the median, with the box denoting the interquartile range (IQR), the upper and lower whiskers representing 1.5-times the IQR above and below the

75% percentile and 25% percentile, respectively, and dots noting outliners beyond the whiskers.

Table 1

Patient characteristics.

Characteristic	Suspected AHF Population (n = 246)	Confirmed AHF Population (n = 124)
Age, median (IQR), years	62 (53, 74)	65 (56, 76.5)
Female, n (%)	106 (43.1)	43 (34.7)
Race / Ethnicity		
White, non-Hispanic	160 (65.0)	72 (58.1)
Hispanic	1 (0.4)	0
Black	84 (35.2)	52 (41.9)
Other	1 (0.4)	0
Medical Insurance (primary)		
Private insurance	62 (25.2)	32 (25.8)
Medicare	127 (51.6)	66 (53.2)
Medicaid	33 (13.4)	16 (12.9)
None	24 (9.8)	10 (8.1)
Presenting Vital Signs		
Systolic BP, median (IQR)	144 (127, 172)	148 (131, 179)
Heart Rate, median (IQR)	89 (77, 104)	94 (78, 109)
Respiratory Rate, median (IQR)	20 (18, 24)	20 (18, 24)
Oxygen Saturation, median (IQR)	96 (94, 98)	96 (92, 98)
Presenting Symptoms		
Shortness of breath	147 (59.8)	73 (58.9.)
Chest pain	54 (22.0)	18 (14.5)
Orthopnea	167 (68.2)	83 (67.5)
Fatigue	203 (82.5)	89 (79.0)
Medical History		
Body Mass Index, median (IQR)	30.7 (25.5, 38.1)	30.0 (24.9, 36.1)
Current smoker, n (%)	41 (16.7)	20 (16.1)
Chronic heart failure, n (%)	145 (58.9)	85 (68.6)
Prior myocardial infarction, n (%)	75 (30.5)	40 (32.3)
Valvular heart disease, n (%)	51 (20.7)	25 (20.2)
Hypertension, n (%)	188 (76.4)	99 (79.8)
Diabetes Mellitus, n (%)	106 (43.1)	57 (46.0)
Chronic pulmonary disease, n (%)	79 (32.1)	27 (21.8)
Chronic renal disease, n (%)	45 (18.3)	26 (21.0)
Laboratory Results		
Sodium, median (IQR) [meq/L]	139 (137, 141)	140 (138, 141)
Creatinine, median (iQr) [mg/dL]	1.2 (0.92, 1.70)	1.40 (1.13, 1.90)

Characteristic	Suspected AHF Population (n = 246)	Confirmed AHF Population (n = 124)
Blood urea nitrogen, median (IQR) [mg/dL]	20 (12, 30)	22 (15, 34)
Hemoglobin, median (IQR) [g/dL]	12.4 (11.0, 13.6)	12.4 (10.8, 13.7)
Cardiac Troponin I, median (IQR) [ng/ml]	0.01 (0, 0.04)	0.03 (0.01, 0.06)
B-type natriuretic peptide, median (IQR) [pg/ml]	329 (82, 1005)	863 (410, 1718)
Admitted to Hospital, n (%)	199 (80.9)	119 (96.0)

AHF: acute heart failure

IQR: interquartile range

Table 2

Patient outcomes.

30-Day Outcome	Suspected AHF Population (n = 246)	Confirmed AHF Population (n = 124)
Severe Clinical Outcomes		
Death	14 (5.7)	10 (8.1)
Cardiac Arrest with ROSC	4 (1.6)	4 (3.2)
Respiratory Failure	2 (0.8)	1 (0.8)
Emergency Dialysis	2 (0.8)	2 (1.6)
Acute Coronary Syndrome	2 (0.8)	1 (0.8)
≥ 1 severe clinical outcome (secondary outcome)	**18 (7.3)**	**13 (10.5)**
Healthcare Utilization Outcomes		
Hospital Length of Stay > 5 days	65 (26.4)	54 (43.6)
Return ED Visit for AHF	20 (8.1)	19 (15.3)
Return Hospitalization for AHF	19 (7.7)	18 (14.5)
≥ 1 healthcare utilization outcome	78 (31.7)	66 (53.2)
≥ 1 Any 30-Day Outcome (primary outcome)	**85 (34.6)**	**71 (57.3)**

AHF: acute heart failure

ROSC: return of spontaneous circulation

ED: emergency department

Table 3

Proportion of patients who experienced a composite of all 30-day outcomes based on bio-ADM concentration cut-points. Selected bio-ADM cut-points represent the 25th, 50th, and 75th percentile of bio-ADM concentration in the study populations.

bio-ADM cut-point	bio-ADM < cut-point		bio-ADM ≥ cut-point	
	Patients, n	Patients with Outcome, n (%)	Patients, n	Patients with Outcome, n (%)
Suspected AHF Population (N=246)				
46.4 pg/ml [25th %tile]	61	10 (16.4)	185	75 (40.5)
60.7 pg/ml [50th %tile]	123	32 (26.0)	123	53 (43.1)
92.5 pg/ml [75th %tile]	185	47 (25.4)	61	38 (62.3)
Confirmed AHF Population (N=124)				
53.2 pg/ml [25th %tile]	31	13 (41.9)	93	58 (62.4)
75.0 pg/ml [50th %tile]	62	29 (46.8)	62	42 (67.7)
115.8 pg/ml [75th %tile]	93	45 (48.4)	31	26 (83.9)

bio-ADM: bioactive adrenomedullin

CI: confidence interval

Table 4

Results of univariate and multivariate logistic regression models evaluating five biomarkers as predictors of the composite 30-day outcome in patients evaluated for acute heart failure. Adjusted odds ratio (OR): OR adjusted for all other biomarkers. Added likelihood ratio (LR) chi-square: added value analysis based on nested regression models.

Variable	df	Univariate			Multivariate		
		LR Chi-square	p	OR (95% CI)	Added LR Chi-square	p	Adjusted OR (95% CI)
Log10 bio-ADM (per IQR change)	1	20.52	<0.001	2.62 (1.65, 4.17)	17.70	<0.001	2.68 (1.60, 4.51)
Log10 BNP (per IQR change)	1	12.75	<0.001	3.24 (1.62, 6.52)	7.56	0.006	3.06 (1.34, 7.00)
Log10 Troponin I (per IQR change)	1	2.20	0.138	1.45 (0.88, 2.40)	0.15	0.70	1.12 (0.63, 1.98)
Log10 Creatinine (per IQR change)	1	1.73	0.188	1.25 (0.89, 1.76)	0.42	0.52	0.88 (0.58, 1.31)
Sodium (per IQR change)	1	0.59	0.444	1.16 (0.78, 1.74)	1.70	0.19	1.34 (0.86, 2.08)

Log10: data transformed logarithmically using base-10

df: degrees of freedom

LR: likelihood ratio

OR: odds ratio

CI: confidence interval

bio-ADM: bioactive adrenomedullin

BNP: B-type naturetic peptide