CLINICAL RESEARCH STUDY

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Diagnostic and Prognostic Utility of Procalcitonin in Patients Presenting to the Emergency Department with Dyspnea

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ABSTRACT

BACKGROUND: Among patients in the emergency department, dyspnea is a common complaint and can pose a diagnostic challenge. Biomarkers are used increasingly to improve diagnostic accuracy and aid with prognostication in dyspneic patients. The purpose of this study was to examine the clinical utility of serum procalcitonin (PCT) for the diagnosis of pneumonia in patients presenting to the emergency department with dyspnea. A secondary objective was to evaluate the prognostic value of PCT for death to 1 year.

METHODS: This study pooled the patient populations of 2 prospective cohorts that previously enrolled patients presenting to 2 urban emergency departments with dyspnea. A total of 453 patients had serum samples available for biomarker analysis. Clinician certainty for the diagnosis of acutely decompensated heart failure was reviewed. Discrimination, calibration, and net reclassification improvement for the diagnosis of pneumonia as well as fatal outcomes were considered. The main outcome was accuracy of PCT for diagnostic categorization of pneumonia. The prognostic value of PCT for survival to 1 year was a secondary outcome.

RESULTS: Pneumonia alone was diagnosed in 30 patients (6.6%), heart failure without pneumonia in 212 patients (47%), and both diagnoses in 30 patients (6.6%). Procalcitonin concentrations were higher in subjects with pneumonia (0.38 vs 0.06 ng/mL; $P < .001$). Area under the receiver operating characteristic curve for the diagnosis of pneumonia based on PCT was 0.84 (95% confidence interval [CI], 0.77-0.91; $P < .001$). Across all levels of clinician-based estimates of heart failure, PCT was sensitive and specific; notably, in patients judged with diagnostic uncertainty (n = 70), a PCT value of 0.10 ng/mL had the optimal balance of sensitivity and specificity (80% and 77%, respectively) for pneumonia. Adding PCT results to variables predictive of pneumonia resulted in a net reclassification improvement of 0.54 (95% CI, 0.24-0.83; $P < .001$) for both up- and down-reclassifying events. In adjusted analyses, elevated PCT was a predictor of 1-year mortality (hazard ratio 1.8; 95% CI, 1.4-2.3; $P < .001$) and was additive when elevated in conjunction with natriuretic peptides for this application.

CONCLUSION: In emergency department patients with acute dyspnea, PCT is an accurate diagnostic marker for pneumonia and adds independent prognostic information for 1-year mortality.

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KEYWORDS: Dyspnea; Heart failure; Natriuretic peptides; Pneumonia; Procalcitonin

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Of the 130 million annual visits to the emergency department, pneumonia and acutely decompensated heart failure rank among the top admitting diagnoses and represent the diagnoses with the largest number of 30-day all-cause readmissions, contributing to an estimated $4.3 billion in annual hospital costs.[1] In-hospital and 60- to 90-day mortality for heart failure are 8% and 13%, respectively,[2] and mortality is increased to 20% when a concomitant pneumonia is diagnosed.[3] Many patients presenting with dyspnea have multiple coexisting medical disorders that complicate their diagnosis and management. Diagnostic uncertainty in this setting is associated with longer hospital length of stay, increased costs, and higher likelihood for repeat hospitalization or death.[4] Further, delay of treatments, such as antibiotics in patients with pneumonia or diuretics for those with heart failure, has been associated with increased mortality.[5,6] Consequently, early and accurate diagnosis is critical. Studies have demonstrated that biomarkers may supplement judgment for diagnosis of heart failure[7,8]; for this application, the natriuretic peptides are now widely used. For correct diagnosis or exclusion of pneumonia, recent data have examined the potential value of procalcitonin (PCT).[9,10]

CLINICAL SIGNIFICANCE

- In emergency department patients with acute dyspnea, procalcitonin is an accurate diagnostic marker for pneumonia.
- When there is diagnostic uncertainty between the diagnosis of heart failure and pneumonia, procalcitonin provided good discrimination for the diagnosis and exclusion of pneumonia.
- Elevated procalcitonin is a predictor of 1-year mortality in patients with pneumonia and is additive when elevated in conjunction with the natriuretic peptides.

In healthy individuals, serum levels of PCT are undetectable. In states of bacterial infection, PCT messenger RNA is upregulated, whereas PCT production is attenuated by cytokines linked to viral infections[11,12]; PCT has thus been proposed as a diagnostic biomarker for bacterial infection. Although measurement of PCT has been examined in several clinical contexts, its use specifically in patients with acute dyspnea is less explored. In the Biomarkers in Acute Heart Failure (BACH) trial, data supportive of PCT to correctly identify or exclude pneumonia in patients with acute dyspnea were reported; additionally, PCT showed prognostic value for mortality prediction to 90 days from presentation. Therefore, we sought to rigorously examine the promising diagnostic and prognostic implications of PCT in patients with acute dyspnea.

METHODS

The institutional review boards at each institution approved of the study procedures (Partners Healthcare IRB, protocol no. 2003P000080).

Study Population

We examined the potential value of PCT in 2 populations of patients presenting to the emergency department setting, the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study[7] and the Biomonitoring and Cardiorenal Syndrome in Heart Failure (BIONICS-HF) study.[13] A study flow diagram is demonstrated in **Figure 1**.

The methods and primary results for the PRIDE study have been published previously.[7] In the PRIDE Study (a single-center study of acute dyspnea performed in Boston, Mass), at the time of emergency department evaluation, clinicians were asked for their impression for the presence of heart failure on a continuous scale from 0 ("absolutely certain not present") to 100% ("absolutely certain to be present").[14] Analytes previously tested include amino-terminal pro-B type natriuretic peptide (NT-proBNP), mid-regional pro-atrial natriuretic peptide (MR-proANP), mid-regional pro-adrenomedullin (MR-proADM),[15] and soluble (s)ST2.

The second cohort considered was the BIONICS-HF Study (NCT01570153).[13] This population was drawn from consenting patients aged ≥18 years who presented to the emergency department at either Massachusetts General Hospital (Boston) or Ospedale Sant'Andrea (Rome, Italy) with dyspnea due to heart failure. To be enrolled, the emergency department physician judged the patient as having certain heart failure.

As shown in **Figure 1**, from a potential total of 700 patients (599 patients from PRIDE and 101 patients from BIONICS-HF), 453 patients had available blood samples for biomarker analysis. Of these patients, 212 (47%) had a final diagnosis of heart failure, 30 (6.5%) had a primary diagnosis of pneumonia, and another 30 (6.5%) of the patients with heart failure had a secondary diagnosis of pneumonia, bringing the total to 60 (13%) patients with pneumonia. Follow-up to 1 year was 100% complete on all subjects in this analysis.

Determination of Diagnosis

The methods for determination of diagnosis have been published previously.[7] The diagnosis of pneumonia was based on local medical records and subsequently cross-verified according to clinical practice guidelines.[16,17] Managing physicians and adjudicators were blind to natriuretic peptide and PCT results.

Blood Analysis

The NT-proBNP analysis was performed with a commercially available immunoassay (Elecsys proBNP; Roche Diagnostics, Indianapolis, Ind).[7] Mid-regional-proANP,

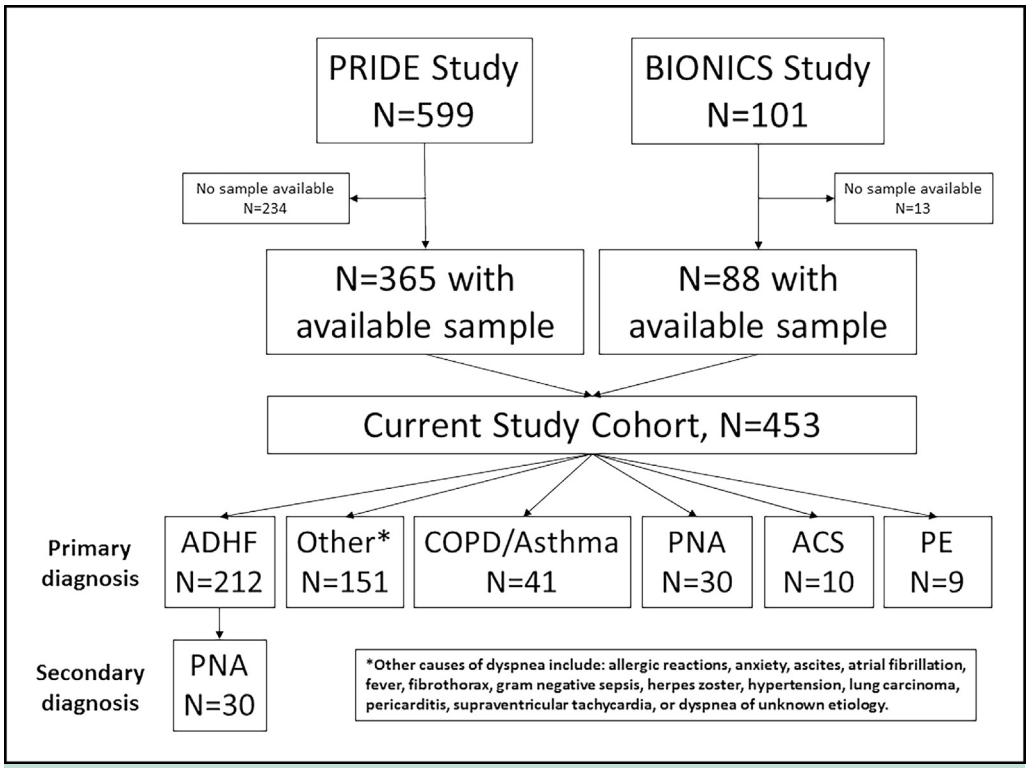

Figure 1 Flow diagram of the present study, including final diagnoses. ACS = acute coronary syndrome; ADHF = acutely decompensated heart failure; BIONICS = Biomonitoring and Cardiorenal Syndrome in Heart Failure; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism; PNA = pnuemonia; PRIDE = ProBNP Investigation of Dyspnea in the Emergency Department.

MR-proADM, and PCT were measured using a KRYPTOR System (BRAHMS AG, Hennigsdorf, Germany), whereas sST2 was assayed using a high-sensitivity enzyme-linked immunosorbent assay (Presage ST2; Critical Diagnostics, San Diego, Calif). The detection limit for PCT was 0.02 ng/mL; interassay coefficients of variation for PCT concentrations 0.30 ng/mL are below 6%. The intra-assay and interassay coefficients of variation for each marker have been reported previously.[7,15]

Statistical Analysis

Baseline characteristics of the study population, stratified by PCT concentration at presentation, were calculated. Continuous variables were summarized as mean ± standard deviation if normally distributed, whereas non-normally distributed continuous variables were summarized as median and interquartile range. Kolmogorov-Smirnov testing identified states of non-normality. Variables were compared using the Student *t* test or χ^2 test as appropriate, whereas the Mann-Whitney *U* test was used for continuous variables in the states of non-normality.

Diagnostic accuracy of PCT was assessed; performance of PCT at its optimal diagnostic threshold was assessed across clinician-expressed likelihood for the diagnosis of heart failure as the primary cause of dyspnea; as described by Green et al,[14] results on this scale between 25% and 75% were defined as clinical uncertainty. In those patients with dyspnea and estimates >75%, clinicians were leaning toward heart failure, whereas by proxy a percent likelihood <25% indicates clinical suspicion for an alternative diagnosis, such as pneumonia. Following this step, logistic regression models were developed to identify independent predictors of pneumonia. Odds ratios and 95% confidence intervals (CIs) were generated. All non-normal covariates were log-transformed. Logistic models were run for the multivariable model, once with PCT and once without PCT, with C-statistic for each step compared. After discrimination analysis, we considered continuous net reclassification improvement (NRI) as described by Pencina et al,[18] using 999 bootstrap replications to estimate the 95% CI for NRI.

To identify independent predictors of mortality, we used stepwise Cox proportional hazards modeling, including clinical variables as well as log-transformed results for NT-proBNP, MR-proANP, MR-proADM, sST2, and PCT. Variables with univariate significance ≤ .10 were considered for the multivariable model. The proportion of hazards was checked. C-statistics for models with and without PCT were calculated, and NRI was again measured. Cumulative hazard curves with PCT alone as well as together with MR-proANP were constructed. Last, outcomes as a function of PCT result and antibiotic prescription were assessed.

Table 1 Baseline Characteristics of the Study Subjects as a Function of Baseline Procalcitonin (PCT) Concentration

Characteristic	PCT < 0.10 ng/mL (n = 317)	PCT ≥ 0.10 ng/mL (n = 136)	*P* Value
Age	61.7 ± 17.1	72.7 ± 12.7	<.001
Sex (% male)	155 (48.9)	79 (58.1)	.09
Past history			
Diabetes mellitus	89 (28.1)	54 (39.7)	.02
Prior heart failure	81 (25.6)	58 (42.6)	<.001
Obstructive airway disease	36 (11.4)	33 (24.3)	.001
Hypertension	162 (51.1)	93 (68.4)	.001
Coronary artery disease	95 (30.0)	54 (39.7)	.06
Prior myocardial infarction	48 (15.1)	28 (20.6)	.20
Medications on presentation			
β-Blocker	140 (44.2)	75 (55.1)	.04
Loop diuretic	95 (30.0)	64 (47.1)	.001
Digoxin	29 (9.1)	18 (13.2)	.30
ACE inhibitor	73 (23.0)	34 (25.0)	.70
Angiotensin II receptor blocker	25 (7.9)	14 (10.3)	.50
Aldosterone antagonist	15 (4.7)	13 (9.6)	.08
Aspirin	120 (37.9)	57 (41.9)	.50
Nitrate	38 (12.0)	33 (24.3)	.002
Inhaled short-acting β-agonist	81 (25.6)	38 (27.9)	.70
Advair	25 (7.9)	23 (16.9)	.007
Steroid, systemic	16 (5.0)	5 (3.7)	.70
Antibiotics, chronic	4 (1.3)	6 (4.4)	.07
Inhaled long-acting β-agonist	13 (4.1)	10 (7.4)	.20
Inhaled anticholinergic	32 (10.1)	11 (8.1)	.60
Combivent	13 (4.1)	2 (1.5)	.30
Symptoms			
Paroxysmal nocturnal dyspnea	44 (13.9)	25 (18.4)	.30
Orthopnea	69 (21.8)	49 (36.0)	.002
Edema	72 (22.7)	51 (37.5)	.002
Chest pain	135 (42.6)	37 (27.2)	.003
Cough	116 (36.6)	54 (39.7)	.60
Fever	21 (7.5)	19 (22.4)	<.001
NYHA class			.002
I	39 (12.3)	7 (5.1)	
II	103 (32.5)	32 (23.5)	
III	94 (29.7)	41 (30.1)	
IV	81 (25.6)	56 (41.2)	
LVEF, last known	57 ± 17	55 ± 15	.07
Physical examination			
Temperature (°F)	96.7 ± 31.2	98.1 ± 30.7	.03
Body mass index (kg/m^2)	28.7 ± 6.6	28.5 ± 8.1	.30
Heart rate (beats/min)	84 ± 22	93 ± 24	<.001
Systolic blood pressure (mm Hg)	140 ± 31	137 ± 40	.09
Jugular venous distension	37 (11.7)	28 (20.6)	.02
S_3 gallop	5 (1.6)	2 (1.5)	1.0
Rales	89 (28.1)	80 (58.8)	<.001
Edema	92 (29.1)	63 (46.3)	.001
Chest radiography			
Interstitial edema	55 (17.4)	49 (36.0)	<.001
Infiltrate	38 (12.0)	33 (24.3)	.002
Cardiomegaly	15 (3.8)	35 (16.7)	<.001
Pleural effusion	45 (14.2)	46 (33.8)	<.001
Laboratory results, median (IQR)			
GFR (mL/min/1.73 m^2)	77.8 (60.0-94.1)	50.5 (35.1-72.3)	<.001
WBC	8.0 (6.5-10.4)	10.3 (7.3-13.3)	<.001
Hemoglobin (g/dL)	13.3 (12.0-14.7)	11.5 (10.0-12.8)	<.001
NT-proBNP (pg/mL)	388 (72-2395)	2685 (910-10091)	<.001

Table 1 Continued

Characteristic	PCT < 0.10 ng/mL (n = 317)	PCT ≥ 0.10 ng/mL (n = 136)	*P* Value
MR-proANP (pmol/L)	96.4 (36.2-249.4)	309.6 (157.4-552.4)	<.001
MR-pro ADM (nmol/L)	0.42 (0.20-0.83)	1.37 (0.84-2.22)	<.001
sST2 (ng/mL)	23.5 (13.7-44.3)	97.7 (51.0-190.1)	<.001

Values are number (percentage) or mean ± standard deviation, unless otherwise noted.

ACE = angiotensin-converting enzyme; GFR = glomerular filtration rate; IQR = interquartile range; LVEF = left ventricular ejection fraction; MR-proADM = mid-regional pro-adrenomedullin; MR-proANP = mid-regional pro-atrial natriuretic peptide; NT-proBNP = amino-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; sST2 = soluble ST2; WBC = white blood cell.

Receiver operating characteristic (ROC) analyses were performed using Analyse It software (Leeds, United Kingdom), whereas all other statistical analyses were performed using either PASW Statistics, version 17.0 (Chicago, Ill) or SAS (version 9.2; SAS Institute, Cary, NC). All *P* values are 2-sided, with a value of < .05 considered significant.

RESULTS

As noted and depicted in **Figure 1**, of the 453 patients in the present study, 212 (47%) had a final diagnosis of heart failure, 30 (6.5%) had a primary diagnosis of pneumonia, and another 30 (6.5%) of the patients with heart failure had a secondary diagnosis of pneumonia, bringing the total to 60 patients (13%) with pneumonia.

Baseline Characteristics

A PCT value of 0.10 ng/mL was found to have the best test-operating characteristics for the diagnosis of pneumonia. Baseline characteristics of the study population stratified by PCT value of <0.10 or ≥0.10 ng/mL are detailed in **Table 1**.

PCT and the Diagnosis of Pneumonia

Median [interquartile range] concentrations of PCT were higher in those with pneumonia (0.38 [0.12-1.40] ng/mL) compared with those without (0.06 [0.04-0.09] ng/mL; $P < .001$ for difference; **Supplemental Figure 1**, available online). **Supplemental Figure 2** (available online) depicts the various diagnoses and PCT concentrations measured in the study cohort. Notably, PCT concentrations were particularly highest in those with comorbid heart failure and pneumonia (0.62 [0.28-3.20] ng/mL); conversely, those with both heart failure and pneumonia (n = 30) had the highest concentrations of natriuretic peptides (results not shown).

In ROC curves, PCT had an area under the curve (AUC) of 0.84 (95% CI, 0.77-0.91; $P < .001$). An optimal PCT cut-off for the diagnosis of pneumonia was 0.10 ng/mL; at this threshold, PCT had an excellent balance of sensitivity, specificity, positive predictive value, and negative predictive value (NPV), as shown in **Table 2**. Notably, across clinician estimates for heart failure, PCT performed consistently and in a manner consistent with Bayesian probabilities (**Table 2**): when clinician estimate for heart failure likelihood was <25% (ie, less likely to be heart failure), PCT had highest specificity (85%), whereas in those patients judged to have >75% likelihood for heart failure (n = 139), PCT had highest sensitivity (95%) and NPV (99%); more than half (n = 74, 53.2%) of subjects judged as high likelihood for heart failure had PCT values <0.10 ng/mL. Finally, in challenging cases when clinician estimate of heart failure likelihood was between 25% and 75% (defined as "indecision"), PCT had balanced sensitivity and specificity.

When examining patients a posteriori in those with heart failure, PCT had an AUC of 0.92 (95% CI, 0.87-0.98; $P < .001$) for pneumonia; at 0.10 ng/mL, PCT had 97% sensitivity, 69% specificity, 36% positive predictive value, and 99% NPV, confirming utility to exclude pneumonia in those with heart failure; the threshold providing comparable specificity (97%) for pneumonia in heart failure was

Table 2 Operating Characteristics of Procalcitonin for the Diagnosis of Pneumonia in the Entire Group and in Previously Established Categories of Clinician-Estimated Likelihood for Heart Failure

Clinician Estimate of HF Likelihood	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall	78	80	39	96
Unlikely (<25%), n = 244, 33 pneumonia	70	85	42	95
Uncertain (25%-75%), n = 70, 10 pneumonia	80	77	36	96
Likely (>75%), n = 139, 17 pneumonia	95	57	27	99

In patients judged with low likelihood for heart failure (hence higher likelihood for pulmonary diagnoses), procalcitonin (PCT) had highest specificity for pneumonia, whereas in those with high likelihood for heart failure, PCT had excellent negative predictive value (NPV) for pneumonia. In those judged with indecision, PCT had an optimal balance of sensitivity and specificity.

HF = heart failure; NPV = negative predictive value; PPV = positive predictive value.

0.40 ng/mL. A possible strategy for using natriuretic peptides and PCT for evaluation of dyspnea is shown in Supplemental Figure 3 (available online).

In logistic regression to identify predictors of pneumonia, ln-transformed PCT remained as an independent variable in multivariable models (odds ratio 2.2; 95% CI, 1.4-3.6; Table 3); univariate results for predictors of pneumonia are shown in Supplemental Table 1 (available online). The C-statistic of the base clinical model without PCT was 0.94 (95% CI, 0.90-0.97), which rose to 0.95 (95% CI, 0.91-0.98) after PCT was added ($P = .35$).

Continuous NRI was performed comparing the model without PCT with a model incorporating PCT data. Addition of PCT results was associated with a significant NRI of 0.54 (95% CI, 0.24-0.83; $P < .001$). Overall, the model including PCT moved 25% of pneumonia into a higher probability category ($P = .08$), and 29% of non-pneumonia into a lower probability category ($P < .001$).

Predictors of Mortality

There were 40 deaths during the first 90 days, and 80 deaths by 1 year. Concentrations of presentation PCT were higher in 9- day decedents compared with survivors (0.13 [0.08-0.41] vs 0.06 [0.04-0.10] ng/mL; $P < .001$); in a similar manner, PCT values at presentation were higher in those dead at 1 year as well (0.12 [0.08-0.38] vs 0.06 [0.04-0.10] ng/mL; $P < .001$).

Univariate predictors of death at 90 days and 1 year are shown in Supplemental Table 2; multivariable predictors of death at 1 year are shown in Supplemental Table 3 (both available online). At 90 days, in adjusted models, presence of a heart murmur on examination (hazard ratio [HR] 3.5; 95% CI, 1.5-8.3; $P < .001$) as well as ln-transformed concentrations of sST2 (HR 3.0; 95% CI, 1.9-4.9; $P < .001$) emerged as predictors of 90-day mortality. At 1 year, PCT was an independent predictor death in adjusted models (HR 1.8; 95% CI, 1.4-2.3; $P < .001$), along with concentrations of MR-proANP (HR 1.8; 95% CI 1.2-2.6; $P = .004$).

To determine the incremental value of PCT beyond a base model, we again evaluated change in C-statistic; adding results for PCT increased the C-statistic for mortality from 0.77 to 0.80 ($P = .02$). Continuous NRI yielded a net reclassification improvement of 41% (95% bootstrap CI, 8-74; $P < .001$), exclusively driven by down-classification of risk in 44%.

In cumulative hazard analyses PCT $\geq$ 0.10 ng/mL was associated with higher cumulative hazard both at 90 days and 1 year (Figure 2). Because both PCT and MR-proANP were significant predictors of mortality at 1 year, we found greater precision in time to first event analyses considering the 2 in a multiple marker strategy using a previously derived threshold for MR-proANP (log−rank $P < .001$; Supplemental Figure 4, available online).[15]

Of the patients with pneumonia, the great majority (87.3%) were treated with antibiotics during their index hospitalization, whereas the minority (25.1%) of those without pneumonia also were treated. We found no association between outcome as a function of PCT concentration at presentation and subsequent antibiotic prescription status. Changing PCT thresholds did not affect the results (results not shown).

DISCUSSION

Among patients with acute dyspnea in the emergency department setting, we found PCT provided good discrimination for the diagnosis and exclusion of pneumonia, and both up- and down-classified likelihood for pneumonia diagnosis. Importantly, PCT concentrations allowed for accurate diagnosis and exclusion of pneumonia in those patients with comorbid heart failure; early recognition and treatment of such patients is of importance given their higher risk. Finally, PCT values were prognostic for death by 1 year, showing additive value with MR-proANP for this application.

Biomarkers are used increasingly in the routine practice of clinical medicine. A burgeoning literature has demonstrated occasionally conflicting utility of PCT in the diagnosis and management of infectious syndromes including pneumonia.[9,10,19-24] Our results are important, in that we not only showed that PCT provides useful discriminatory information for pneumonia, but does so in patients judged with clinical indecision, where PCT provided optimal operating characteristics. As would be expected on the basis

Table 3 Multivariable Predictors of a Diagnosis of Pneumonia Along with Operating Characteristics for the Diagnosis of Pneumonia

Variable	Odds Ratio (95% CI)	P Value	Sn (%)	Sp (%)	PPV (%)	NPV (%)
Aspirin use	0.26 (0.08-0.83)	.02	29	59	10	84
Chest radiograph infiltrate or pneumonia	12.5 (4.6-34.1)	<.001	51	90	45	92
Cough	6.1 (2.1-18.2)	.001	60	66	22	91
Fever	4.3 (1.5-12.7)	.009	38	93	47	92
PCT	2.2 (1.4-3.6)	.001	78	80	39	96
sST2	2.9 (1.6-5.3)	<.001	81	68	29	96

Both PCT and sST2 were entered as log-transformed variables. Operating characteristics for PCT and sST2 refer to optimal cut-offs of 0.10 ng/mL and 49 ng/mL, respectively.

CI = confidence intervals; NPV = negative predictive value; PCT = procalcitonin; PPV = positive predictive value; Sn = sensitivity; Sp = specificity; sST2 = soluble ST2.

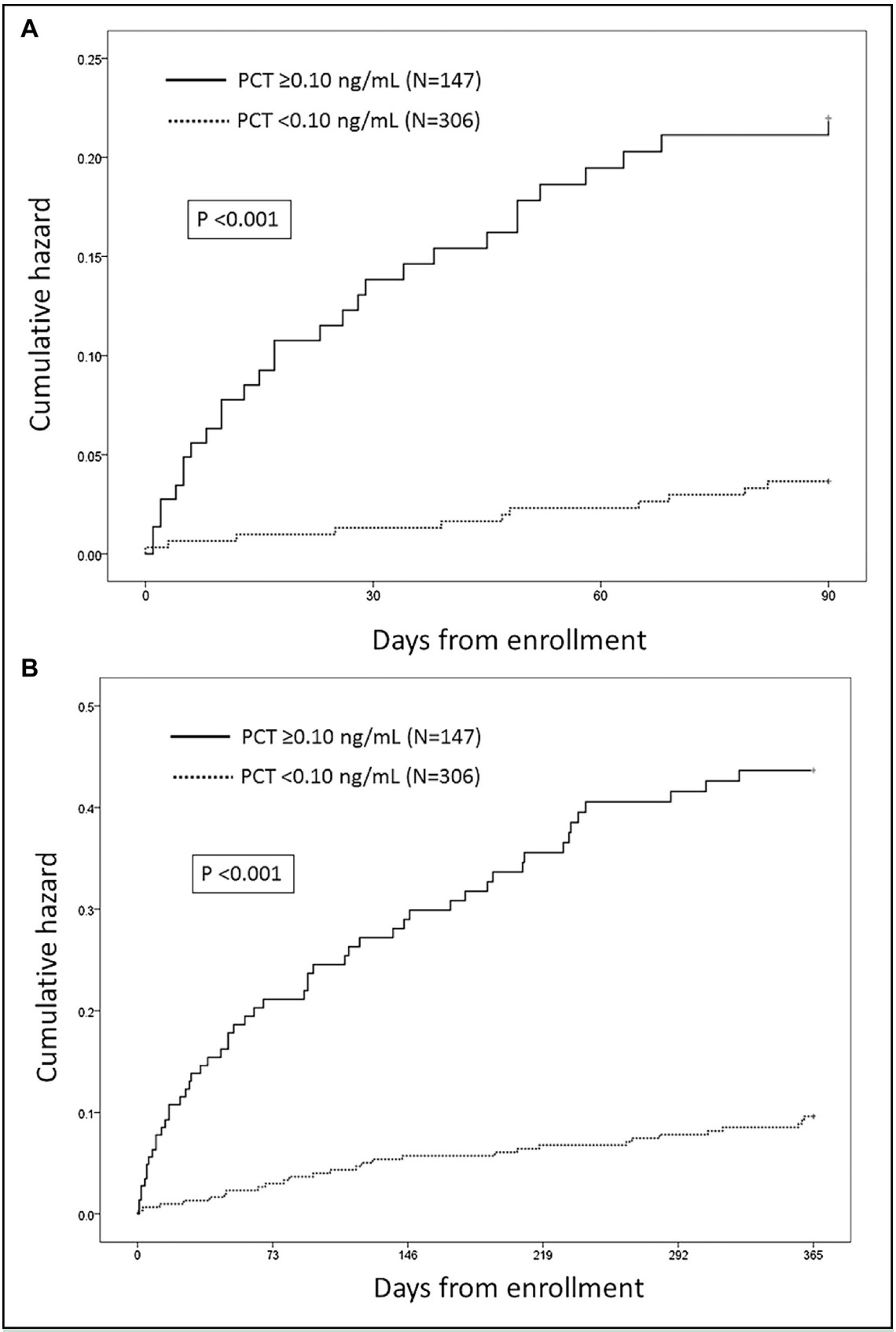

Figure 2 Cumulative hazard for death at (**A**) 90 days and (**B**) 1 year as a function of procalcitonin (PCT) concentrations.

of Bayesian considerations, in those patients considered at high likelihood for heart failure, PCT was very sensitive (providing excellent NPV to exclude pneumonia in a majority of such subjects), whereas in those with a low likelihood for heart failure (hence high likelihood for a pulmonary diagnosis), an elevated PCT was highly specific for pneumonia.

A notable finding in our study was, when measured alone or together with MR-proANP in a multimarker strategy, higher PCT values were associated with shorter time to first event in cumulative hazards analysis. Pneumonia risk models such as the CURB-65[25] and Pneumonia Severity Index[26] may be useful for triage decision making; however, their use may be cumbersome. Future efforts should compare the individual and additive value of PCT with established pneumonia risk scores; we lacked some variables in each model to examine this question in the present analysis.

Our results extend those of the BACH study with rigorous diagnostic and prognostic evaluation; although our findings are in alignment with BACH, we found higher AUC in ROC analyses (0.84 vs 0.72) and also a greater degree of reclassification in NRI assessment. Importantly, we extend the BACH prognosis assessment of PCT by adding substantially more complicated diagnostic assessment in those with heart failure, more complex survival analyses that include discrimination and NRI and show value of PCT out to a follow-up to 1 year, as opposed to 90 days, and we also compared PCT with a broader range of contemporary biomarkers.

A limitation of our study is its modest size, which limits the power of statistical calculations. The number of patients diagnosed with pneumonia was low relative to the number of patients with heart failure. Although both cohorts were studied prospectively with a priori power assumptions for their respective primary outcomes, our retrospective analysis for our primary and secondary outcomes occurred a posteriori. We lack serial measurement of PCT or other biomarkers. Last, we had few patients with elevated PCT that went untreated with antibiotics.

CONCLUSION

In an era of increasing clinical complexity and healthcare costs, biomarkers represent an important tool for both diagnostic and prognostic efficiency. The potential role for PCT is broad—from predicting mortality risk to optimizing diagnostic accuracy for pneumonia and guiding antimicrobial use in patients with concomitant heart failure. Our results support the diagnostic and prognostic value of PCT in acute dyspnea, adding substantially to clinical variables and other biomarkers for these applications.

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References

1. Hines AL, Barrett ML, Jiang HJ, Steiner CA. Conditions With the Largest Number of Adult Hospital Readmissions by Payer, 2011. Available at: www.ncbi.nlm.nih.gov/books/NBK206781/. Accessed October 26, 2014.
2. Rudiger A, Harjola VP, Müller A, et al. Acute heart failure: clinical presentation, one-year mortality and prognostic factors. *Eur J Heart Fail*. 2005;7(4):662-670.
3. Fonarow GC, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med*. 2008;168(8):847-854.
4. Ray P, Birolleau S, Lefort Y, et al. Acute respiratory failure in the elderly: etiology, emergency diagnosis and prognosis. *Crit Care*. 2006;10(3):R82.
5. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest*. 2009;136(5):1237-1248.
6. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA*. 1997;278(23):2080-2084.
7. Januzzi JL, Camargo CA, Anwaruddin S, et al. The N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *Am J Cardiol*. 2005;95(8):948-954.
8. Maisel AS, Krishnaswamy P, Nowak RM. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347(3):161-167.
9. Maisel A, Neath SX, Landsberg J, et al. Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *Eur J Heart Fail*. 2012;14(3):278-286.
10. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med*. 2011;39(9):2048-2058.
11. Linscheid P, Seboek D, Schaer DJ, Zulewski H, Keller U, Müller B. Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. *Crit Care Med*. 2004;32:1715-1721.
12. Nijsten MW, Olinga P, The TH, de Vries EG. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. *Crit Care Med*. 2000;28(2):458-461.
13. De Berardinis B, Gaggin HK, Magrini L, et al. Comparison between admission natriuretic peptides, NGAL and sST2 testing for the prediction of worsening renal function in patients with acutely decompensated heart failure. *Clin Chem Lab Med*. 2015;53(4):613-621.
14. Green SM, Martinez-Rumayor A, Gregory SA, et al. Clinical uncertainty, diagnostic accuracy, and outcomes in emergency department patients presenting with dyspnea. *Arch Intern Med*. 2008;168(7):741-748.
15. Shah RV, Truong QA, Gaggin HK, Pfannkuche J, Hartmann O, Januzzi JL. Mid-regional pro-atrial natriuretic peptide and pro-adrenomedullin testing for the diagnostic and prognostic evaluation of patients with acute dyspnoea. *Eur Heart J*. 2012;33(17):2197-2205.
16. Martinez-Rumayor A, Camargo CA, Green SM, Baggish AL, O'Donoghue M, Januzzi JL. Soluble ST2 plasma concentrations predict 1-year mortality in acutely dyspneic emergency department patients with pulmonary disease. *Am J Clin Pathol*. 2008;130(4):578-584.
17. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(Suppl 2):S27-S72.
18. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30(1):11-21.
19. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis*. 2007;7(3):210-217.

20. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426-435.
21. Heyland DK, Johnson AP, Reynolds SC, Muscedere J. Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. *Crit Care Med*. 2011;39(7):1792-1799.
22. Long W, Li L, Huang G, et al. Procalcitonin guidance for reduction of antibiotic use in patients hospitalized with severe acute exacerbations of asthma: a randomized controlled study with 12-month follow-up. *Crit Care*. 2014;18(5):471.
23. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med*. 2006;174(1):84-93.
24. Schuetz P, Christ-Crain M, Thomann R, Falconnier C. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections. *JAMA*. 2009;302(10):1059-1066.
25. Lim WS, Van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377-382.
26. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250.
27. Baggish AL, van Kimmendade R, Bayes-Genis A, Davis M, et al. Hemoglobin and N-terminal pro-brain natriuretic peptide: Independent and synergistic predictors of mortality in patients with acute heart failure: results from the International Collaborative of NT-proBNP (ICON) Study. *Clin Chim Acta*. 2007;381(2):145-150.
28. van Kimmendade R, Pinto YM, Bayes-Genis A, Lainchbury JG, Richards AM, Januzzi JL. Usefulness of intermediate amino-terminal prop-brain natriuretic peptide concentrations for diagnosis and prognosis of acute heart failure. *Am J Cardiol*. 2006;98(3):386-390.

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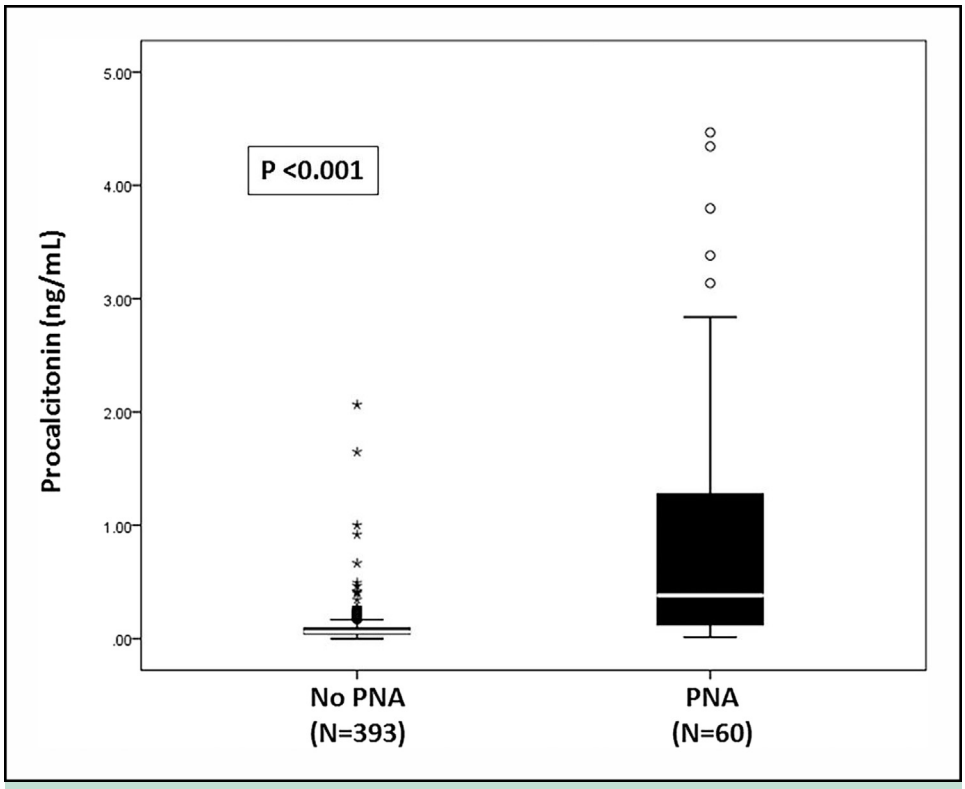
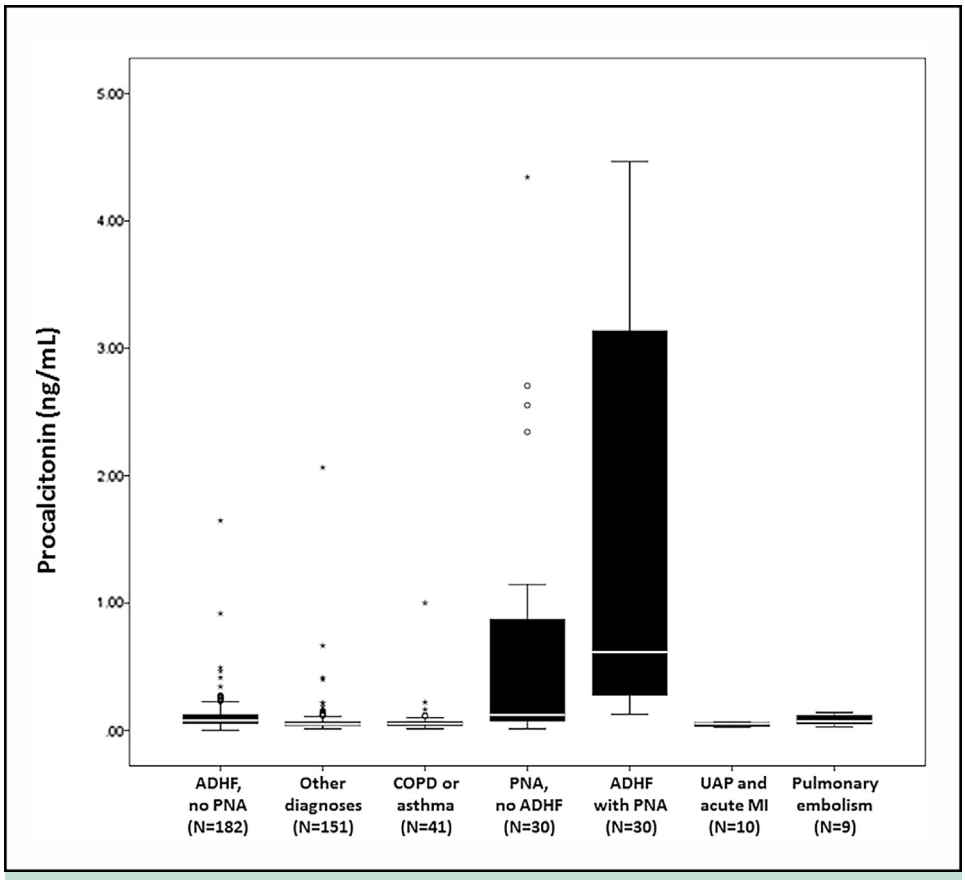
Authorship: All authors had access to the data and a role in writing the manuscript.

SUPPLEMENTAL DATA

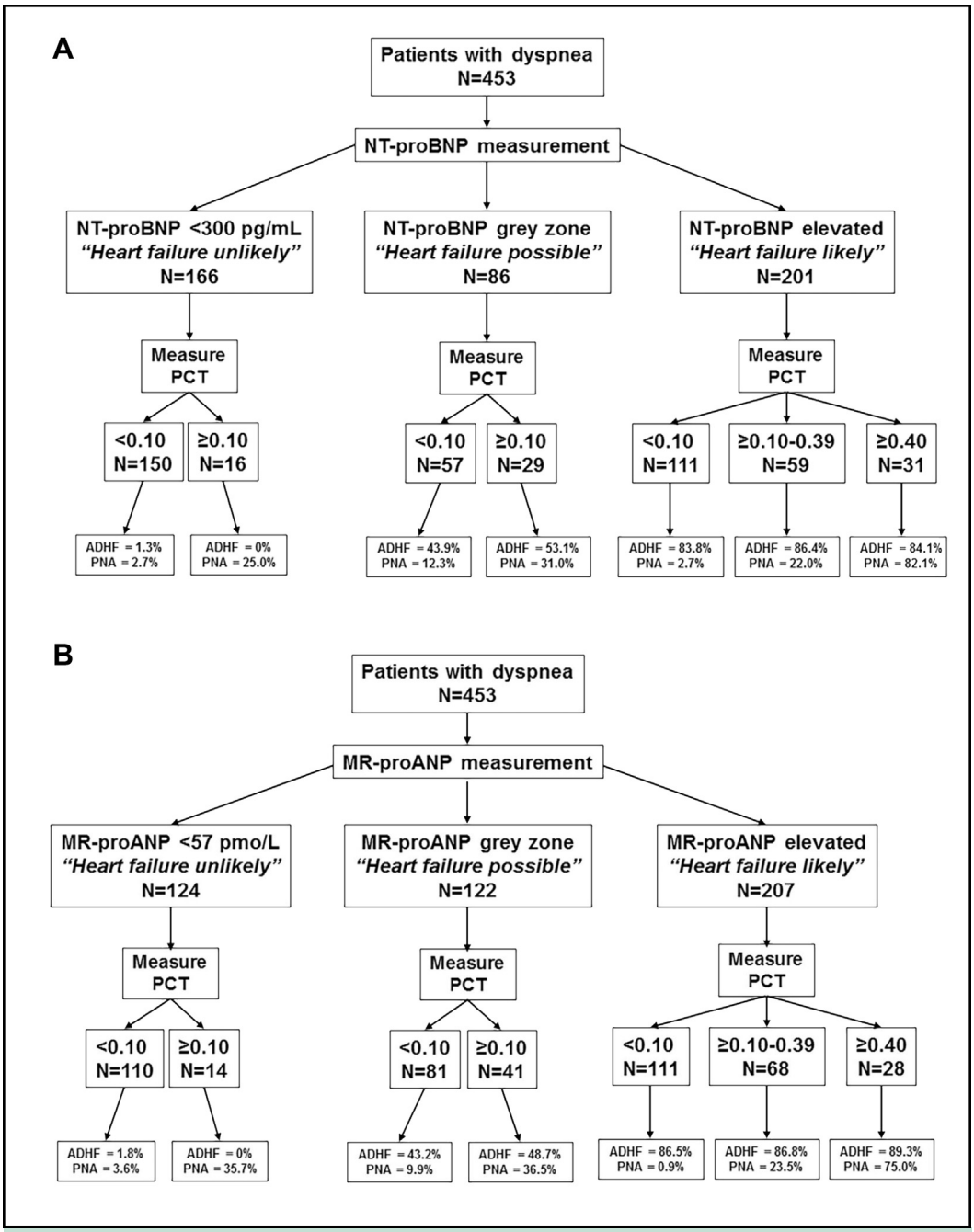
Supplemental figures and tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.06.037.



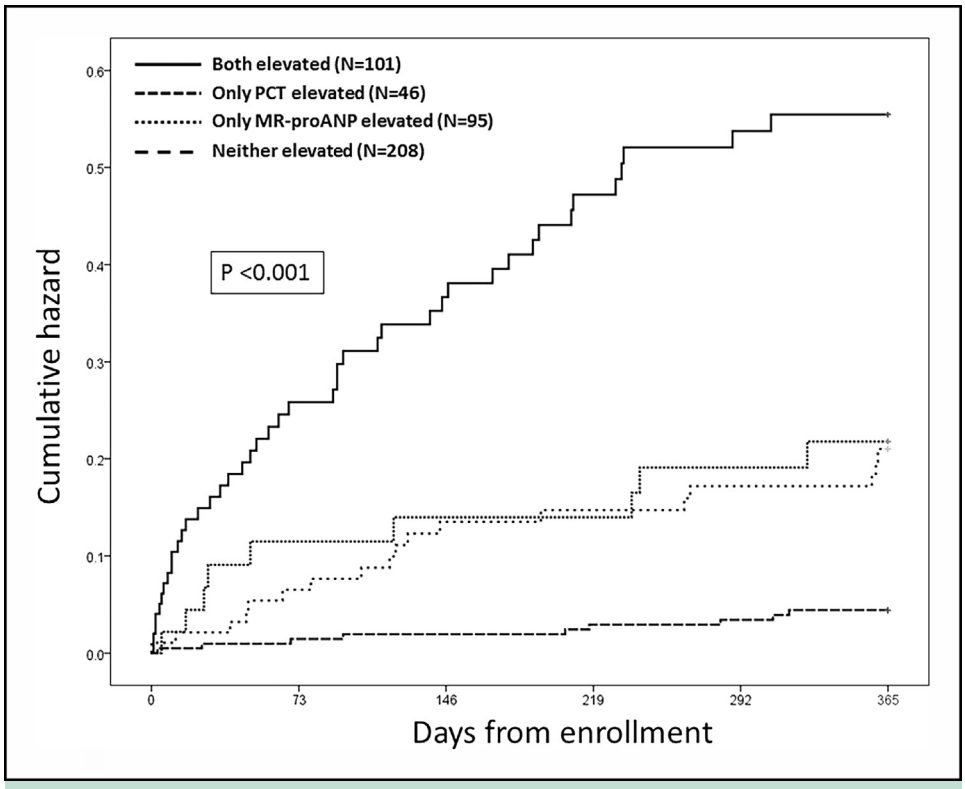
Supplemental Figure 1 Box and whisker plots of procalcitonin (PCT) as a function of pneumonia (PNA) vs alternative diagnosis. Median concentrations of procalcitonin were higher in those with pneumonia; boxes refer to the 25th and 75th percentiles, and whiskers the 5th and 95th percentiles. Outliers are shown as open circles, extremes as stars.



Supplemental Figure 2 Median concentrations of procalcitonin as a function of various diagnoses in the cohort. Values for procalcitonin were considerably higher in those with a diagnosis of pneumonia (PNA). Boxes refer to the 25th and 75th percentiles, and whiskers the 5th and 95th percentiles. Outliers are shown as open circles, extremes as stars. ADHF = acutely decompensated heart failure; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; UAP = unstable angina pectoris.



Supplemental Figure 3 Suggested diagnostic strategy for use of procalcitonin (PCT) in acute dyspnea, combining measurement with (**A**) amino-terminal pro-B type natriuretic peptide (NT-proBNP) or (**B**) mid-regional pro-atrial natriuretic peptide (MR-proANP). Using either natriuretic peptide, added use of procalcitonin allowed for even more refined identification or exclusion of heart failure (ADHF), pneumonia (PNA), or both diagnoses. Diagnostic cut-offs for NT-proBNP and MR-proANP are as previously defined.[15,27,28]



Supplemental Figure 4 Cumulative hazard for death at 1 year as a function of procalcitonin (PCT) and mid-regional pro-atrial natriuretic peptide (MR-proANP) concentrations. The 2 biomarkers provided additive prognostic value, reclassifying in time to first event analyses.

Supplemental Table 1 Univariate Predictors of a Final Diagnosis of Pneumonia

Univariate Variable	Odds Ratio (95% CI)	*P* Value
ACE	0.82 (0.43-1.6)	.55
ARB	0.49 (0.15-1.6)	.25
ASA	0.58 (0.32-1.0)	.07
Acutely decompensated HF	1.3 (0.76-2.2)	.34
Advair	2.0 (0.97-4.2)	.06
Aldactone	0.73 (0.21-2.5)	.62
β-Blocker	0.81 (0.47-1.4)	.43
CXR infiltrate or pneumonia	9.3 (5.1-16.8)	<.001*
CXR cephalization of vessels	2.1 (0.21-20.3)	.53
CXR interstitial edema	1.5 (0.86-2.8)	.15
CXR pleural effusion	1.7 (0.95-3.2)	.07
Chest pain	0.42 (0.22-0.79)	.007
Chronic antibiotics	4.3 (1.2-15.8)	.03
Combivent	0.43 (0.06-3.4)	.42
Cough	3.0 (1.7-5.1)	<.001*
Digoxin	1.3 (0.58-2.9)	.52
ECG LBBB	1.5 (0.58-3.7)	.41
ECG LVH	0.72 (0.16-3.2)	.67
ECG atrial fib flutter	1.8 (0.96-3.5)	.07
ECG sinus rhythm	0.64 (0.37-1.1)	.11
Edema	0.88 (0.50-1.6)	.66
Fever	8.0 (3.9-16.7)	<.001*
HCTZ	0.58 (0.17-2.0)	.38
HJR	0.72 (0.16-3.2)	.67
History of CAD	0.72 (0.40-1.3)	.28
History of COPD	1.9 (1.0-3.7)	.04
History of arrhythmia	1.1 (0.61-2.1)	.69
History of diabetes	0.77 (0.43-1.4)	.40
History of hypertension	0.77 (0.45-1.3)	.34
History of prior HF	1.1 (0.60-1.9)	.84
History of prior MI	0.58 (0.25-1.3)	.20
Hydralazine	0.88 (0.11-7.3)	.91
Inhaled anticholinergic	1.7 (0.79-3.8)	.17
Inhaled short acting β-agonist	2.1 (1.2-3.6)	.01
Inhaled corticosteroid	2.0 (0.85-4.5)	.12
Inhaled long acting β-agonist	1.3 (0.44-4.0)	.62
JVD	0.85 (0.38-1.9)	.69
Leukotriene modifier	0.88 (0.20-4.0)	.87
Loop diuretic	0.99 (0.57-1.7)	.97
Lower extremity edema	0.46 (0.23-0.94)	.03
Murmur	0.85 (0.37-2.0)	.70
Nitrate	0.76 (0.34-1.7)	.49
Orthopnea	1.2 (0.64-2.1)	.62
PND	1.2 (0.60-2.5)	.60
Pulmonary rales	2.8 (1.6-4.8)	<.001*
S4Gallop	1.2 (0.14-10.8)	.84
Sex	1.1 (0.65-1.9)	.69
Systemic steroid	2.6 (0.98-7.1)	.05
Wheezing	1.2 (0.68-2.3)	.47
Age, log-transformed	3.2 (1.1-9.1)	.03
BMI, log-transformed	0.34 (0.10-1.2)	.09
NT-proBNP, log-transformed	1.3 (1.1-1.5)	<.001*
BUN, log-transformed	1.6 (1.00-2.5)	.05
Creatinine, log-transformed	2.3 (1.2-4.3)	.01
MDRD creatinine clearance, log-transformed	0.49 (0.29-0.83)	.008
Diastolic BP, log-transformed	0.45 (0.12-1.7)	.24
ECG QRS duration, log-transformed	1.0 (0.34-3.2)	.95
Glucose, log-transformed	2.4 (1.3-4.7)	.009
Hb, log-transformed	0.29 (0.07-1.1)	.08
Last known EF, log-transformed	0.58 (0.26-1.3)	.18
PCT, log-transformed	3.3 (2.5-4.4)	<.001
MR proADM, log-transformed	2.5 (1.7-3.6)	<.001*
MR proANP, log-transformed	1.4 (1.1-1.8)	.005
Pulse, log-transformed	27.3 (8.2-91.0)	<.001*
Systolic BP, log-transformed	0.32 (0.12-0.89)	.03
Sodium, log-transformed	1.9 (0.22-15.6)	.56
ST2, log-transformed	3.6 (2.6-5.0)	<.001*
WBC, log-transformed	3.4 (1.9-6.1)	<.001*
NYHA: class II	1.1 (0.35-3.6)	.85
NYHA: class III	1.3 (0.41-4.2)	.65
NYHA: class IV	3.1 (1.0-9.2)	.05
NYHA: class I	1.0 (reference)	—
History of tobacco use: 1	0.33 (0.14-0.79)	.01
History of tobacco use: 2	0.58 (0.25-1.3)	.19
History of tobacco use: 3	0.51 (0.20-1.3)	.17
History of tobacco use: 0	1.0 (reference)	—

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASA = aspirin; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; ECG = electrocardiogram; EF = ejection fraction; Hb = hemoglobin; HCTZ = hydrochlorothiazide; HF = heart failure; HJR = hepatojugular reflex; JVD = jugular venous distention; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MDRD = Modification of Diet in Renal Disease; MI = myocardial infarction; NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnea; WBC = white blood cell.

*Indicates statistically significant.

Supplemental Table 2 Univariate Predictors of Mortality at 90 Days and 1 Year

Univariate Variable	90-Day Mortality Hazard Ratio (95% CI)	90-Day *P* Value	1-Year Mortality Hazard Ratio (95% CI)	1-Year *P* Value
ACE	1.4 (0.72-2.8)	.32	1.2 (0.72-1.9)	.51
ARB	0.87 (0.27-2.8)	.81	1.2 (0.58-2.5)	.63
ASA	1.4 (0.76-2.6)	.27	1.1 (0.71-1.7)	.63
Acutely decompensated HF	4.2 (2.0-8.8)	<.001*	3.9 (2.3-6.4)	<.001*
Advair	1.2 (0.47-3.1)	.71	1.2 (0.63-2.4)	.54
Aldactone	2.2 (0.87-5.7)	.10	2.4 (1.2-4.6)	.01
β-Blocker	2.4 (1.2-4.6)	.01	1.9 (1.2-2.9)	.007
CXR infiltrate or pneumonia	2.1 (1.1-4.3)	.03	1.3 (0.76-2.3)	.32
CXR cephalization of vessels	0	.99	1.3 (0.18-9.5)	.78
CXR interstitial edema	3.3 (1.8-6.1)	<.001*	3.0 (1.9-4.7)	<.001*
CXR pleural effusion	3.2 (1.7-6.0)	<.001*	2.7 (1.7-4.3)	<.001*
Chest pain	0.60 (0.30-1.2)	.16	0.76 (0.48-1.2)	.26
Chronic antibiotics	2.7 (0.65-11.2)	.17	2.7 (1.0-7.5)	.05
Combivent	0.72 (0.10-5.2)	.74	1.1 (0.36-3.6)	.83
Cough	0.62 (0.31-1.2)	.18	0.56 (0.34-0.93)	.02
Digoxin	2.3 (1.1-5.0)	.04	2.2 (1.3-3.9)	.005
ECG LBBB	1.5 (0.54-4.3)	.42	1.6 (0.76-3.3)	.22
ECG LVH	2.6 (0.92-7.2)	.07	2.5 (1.2-5.5)	.02
ECG atrial fib flutter	1.9 (0.91-3.8)	.09	1.8 (1.1-2.9)	.03
ECG sinus rhythm	0.39 (0.21-0.72)	.003*	0.56 (0.36-0.88)	.01
Edema	2.2 (1.2-4.2)	.01	2.1 (1.3-3.2)	.001
Fever	1.8 (0.63-5.5)	.27	1.8 (0.88-3.7)	.11
HCTZ	1.8 (0.69-4.5)	.24	1.9 (0.96-3.6)	.07
HJR	3.5 (1.4-8.8)	.009*	2.6 (1.2-5.7)	.01
History of CAD	1.4 (0.72-2.5)	.35	1.5 (0.99-2.4)	.05
History of COPD	1.2 (0.52-2.7)	.70	1.2 (0.67-2.1)	.55
History of arrhythmia	1.8 (0.92-3.4)	.09	1.7 (1.1-2.8)	.02
History of diabetes	1.5 (0.79-2.8)	.22	1.4 (0.92-2.3)	.12
History of hypertension	1.5 (0.78-2.8)	.23	1.5 (0.95-2.4)	.08
History of prior HF	2.1 (1.1-3.9)	.02	2.3 (1.5-3.6)	<.001*
History of prior MI	1.3 (0.59-2.8)	.54	1.2 (0.67-2.1)	.58
Hydralazine	1.5 (0.21-11.1)	.68	0.73 (0.10-5.2)	.75
Inhaled anticholinergic	0.49 (0.12-2.0)	.32	1.2 (0.59-2.4)	.63
Inhaled short acting β-agonist	0.69 (0.32-1.5)	.34	0.79 (0.47-1.3)	.37
Inhaled corticosteroid	0.62 (0.15-2.6)	.50	0.61 (0.22-1.7)	.34
Inhaled long acting β-agonist	0.46 (0.06-3.4)	.45	0.96 (0.35-2.6)	.94
JVD	2.3 (1.2-4.7)	.02	1.6 (0.92-2.8)	.10
Leukotriene modifier	0	.99	0.32 (0.04-2.3)	.26
Loop diuretic	1.5 (0.83-2.9)	.17	1.9 (1.2-2.9)	.006
Lower extremity edema	1.7 (0.87-3.1)	.12	1.7 (1.1-2.7)	.02
Murmur	2.1 (1.0-4.4)	.05	2.8 (1.7-4.5)	<.001*
Nitrate	1.6 (0.76-3.3)	.22	1.3 (0.74-2.3)	.38
Orthopnea	2.2 (1.2-4.2)	.01	2.2 (1.4-3.4)	<.001*
PND	1.2 (0.52-2.6)	.70	1.5 (0.90-2.6)	.12
Pulmonary rales	3.0 (1.6-5.6)	<.001*	2.5 (1.6-3.9)	<.001*
S3Gallop	5.8 (1.8-18.9)	.003*	4.8 (1.8-13.2)	.002
Sex	1.1 (0.61-2.1)	.69	1.0 (0.67-1.6)	.89
Systemic steroid	0.52 (0.07-3.8)	.52	1.7 (0.74-3.9)	.21
Wheezing	0.57 (0.24-1.3)	.20	0.72 (0.41-1.3)	.26
Age, log-transformed	22.8 (4.0-129.5)	<.001*	17.8 (5.5-57.7)	<.001*
BMI, log-transformed	0.20 (0.05-0.89)	.03	0.37 (0.14-1.0)	.06
NT-proBNP, log-transformed	1.5 (1.2-1.8)	<.001*	1.5 (1.3-1.7)	<.001*
BUN, log-transformed	2.6 (1.5-4.4)	<.001*	2.6 (1.8-3.7)	<.001*
Creatinine, log-transformed	1.9 (0.91-3.9)	.09	2.2 (1.3-3.6)	.003
MDRD creatinine clearance, log-transformed	0.50 (0.28-0.89)	.02	0.45 (0.30-0.66)	<.001*
Diastolic BP, log-transformed	0.50 (0.11-2.3)	.38	0.34 (0.11-1.0)	.05

Supplemental Table 2 Continued

Univariate Variable	90-Day Mortality Hazard Ratio (95% CI)	90-Day *P* Value	1-Year Mortality Hazard Ratio (95% CI)	1-Year *P* Value
ECG QRS duration, log-transformed	2.7 (0.81-9.2)	.10	2.2 (0.97-5.2)	.06
Glucose, log-transformed	1.6 (0.74-3.5)	.24	1.8 (1.1-3.1)	.03
Hb, log-transformed	0.14 (0.04-0.52)	.003	0.12 (0.05-0.29)	<.001*
Last known EF, log-transformed	0.39 (0.19-0.83)	.01	0.58 (0.33-1.0)	.06
PCT, log-transformed	1.5 (1.3-1.8)	<.001*	1.5 (1.3-1.7)	<.001*
MR proADM, log-transformed	3.5 (2.2-5.6)	<.001*	2.9 (2.1-3.8)	<.001*
MR proANP, log-transformed	2.3 (1.7-3.2)	<.001*	2.1 (1.7-2.6)	<.001*
Pulse, log-transformed	3.5 (1.0-12.0)	.04	1.8 (0.78-4.1)	.17
Systolic BP, log-transformed	0.64 (0.22-1.8)	.40	0.56 (0.29-1.1)	.09
Sodium, log-transformed	1.2 (0.36-4.0)	.77	0.82 (0.54-1.2)	.34
ST2, log-transformed	2.6 (1.9-3.5)	<.001*	2.2 (1.8-2.7)	<.001*
WBC, log-transformed	1.8 (0.99-3.2)	.05	1.4 (0.86-2.1)	.19
NYHA: class II	0.68 (0.17-2.7)	.59	0.75 (0.23-2.5)	.64
NYHA: class III	1.5 (0.43-5.4)	.51	2.7 (0.96-7.7)	.06
NYHA: class IV	2.1 (0.62-7.1)	.23	3.4 (1.2-9.6)	.02
NYHA: class I	1.0 (reference)	—	1.0 (reference)	—
History of tobacco use: 1	0.34 (0.15-0.79)	.01	0.46 (0.24-0.88)	.02
History of tobacco use: 2	0.24 (0.10-0.60)	.002	0.42 (0.22-0.81)	.01
History of tobacco use: 3	0.36 (0.14-0.98)	.05	0.42 (0.19-0.91)	.03
History of tobacco use: 0	1.0 (reference)	—	1.0 (reference)	—

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASA = aspirin; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CXR = chest x-ray; ECG = electrocardiogram; EF = ejection fraction; Hb = hemoglobin; HCTZ = hydrochlorothiazide; HF = heart failure; HJR = hepatojugular reflex; JVD = jugular venous distention; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MDRD = Modification of Diet in Renal Disease; MI = myocardial infarction; NYHA = New York Heart Association; PND = paroxysmal nocturnal dyspnea; WBC = white blood cell.

*Indicates statistically significant.

Supplemental Table 3 Multivariable Predictors of Death at 1 Year

Variable	Hazard Ratio (95% CI)	*P* Value
Hepatojugular reflux	3.5 (1.1-11.9)	.04
Murmur	4.8 (2.5-9.4)	<.001
Diastolic blood pressure	11.8 (3.1-44.8)	<.001
Systolic blood pressure	0.02 (0.003-0.14)	<.001
PCT	1.8 (1.4-2.3)	<.001
MR-proANP	1.8 (1.2-2.6)	.004

Continuous variables were log-transformed.