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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

Alan Maisel[1,2]*, Sean-Xavier Neath[2], Judd Landsberg[1,2], Christian Mueller[3], Richard M. Nowak[4], W. Frank Peacock[5], Piotr Ponikowski[6], Martin Möckel[7], Christopher Hogan[8], Alan H.B. Wu[9], Mark Richards[10], Paul Clopton[1], Gerasimos S. Filippatos[11], Salvatore Di Somma[12], Inder Anand[13], Leong L. Ng[14], Lori B. Daniels[9], Robert H. Christenson[15], Mihael Potocki[3], James McCord[4], Garret Terracciano[16], Oliver Hartmann[17], Andreas Bergmann[18], Nils G. Morgenthaler[7], and Stefan D. Anker[7,19]

[1]VA San Diego Healthcare System, San Diego, CA, USA; [2]University of California, San Diego, CA, USA; [3]University Hospital Basel, Basel, Switzerland; [4]Henry Ford Health System, Detroit, MI, USA; [5]The Cleveland Clinic, Cleveland, OH, USA; [6]Medical University, Faculty of Public Health, Wroclaw, Poland; [7]Charite, Campus Virchow-Klinikum, Berlin, Germany; [8]Virgina Commonwealth University, Richmond, VA, USA; [9]University of California, San Francisco, CA, USA; [10]University of Otago, Christchurch, New Zealand; [11]Athens University Hospital Attikon, Athens, Greece; [12]Sant'Andrea Hospital, University La Sapienza, Rome, Italy; [13]VA Minneapolis, MN, USA; [14]University of Leicester, and Leicester NIHR Cardiovascular Biomedical Research Unit, Leicester, UK; [15]University of Maryland School of Medicine, Baltimore, MD, USA; [16]University of California, San Diego School of Medicine, San Diego, CA, USA; [17]BRAHMS GmbH, Biotechnology Centre Hennigsdorf/Berlin, Germany; [18]Waltraut Bergmann Foundation, Hohen Neuendorf, Germany; and [19]Centre for Clinical and Basic Research IRCCS San Raffaele, Roma, Italy

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Aims Biomarkers have proven their ability in the evaluation of cardiopulmonary diseases. We investigated the utility of concentrations of the biomarker procalcitonin (PCT) alone and with clinical variables for the diagnosis of pneumonia in patients presenting to emergency departments (EDs) with a chief complaint of shortness of breath.

Methods and results The BACH trial was a prospective, international, study of 1641 patients presenting to EDs with dyspnoea. Blood samples were analysed for PCT and other biomarkers. Relevant clinical data were also captured. Patient outcomes were assessed at 90 days. The diagnosis of pneumonia was made using strictly validated guidelines. A model using PCT was more accurate [area under the curve (AUC) 72.3%] than any other individual clinical variable for the diagnosis of pneumonia in all patients, in those with obstructive lung disease, and in those with acute heart failure (AHF). Combining physician estimates of the probability of pneumonia with PCT values increased the accuracy to >86% for the diagnosis of pneumonia in all patients. Patients with a diagnosis of AHF and an elevated PCT concentration (>0.21 ng/mL) had a worse outcome if not treated with antibiotics ($P = 0.046$), while patients with low PCT values (<0.05 ng/mL) had a better outcome if they did not receive antibiotic therapy ($P = 0.049$).

Conclusion Procalcitonin may aid in the diagnosis of pneumonia, particularly in cases with high diagnostic uncertainty. Importantly, PCT may aid in the decision to administer antibiotic therapy to patients presenting with AHF in which clinical uncertainty exists regarding a superimposed bacterial infection.
Trial registration: NCT00537628

Keywords Acute heart failure • Procalcitonin • Pneumonia • Survival • Diagnosis

* Corresponding author. 3350 La Jolla Village Drive 151A San Diego, CA 92161, USA. Tel: +1 858 552 8585 x 7344, Fax: +1 858 552 7490, Email: amaisel@ucsd.edu

Introduction

The chief complaint of shortness of breath in patients presenting with suspected pneumonia requires a rapid accurate assessment so that early antibiotic therapy can be initiated and appropriate additional management implemented.[1,2] The diagnosis of pneumonia can be difficult in patients with pre-existing parenchymal lung disease because of baseline abnormal chest imaging, or in those presenting with an acute exacerbation of obstructive lung disease (AECOPD), bronchitis, or viral syndrome, because of overlapping symptoms. Detecting superimposed pneumonia in patients presenting with acute heart failure (AHF) is additionally difficult because of the non-specific nature of chest X-ray abnormalities in the setting of cardiogenic pulmonary oedema. Unfortunately, misdiagnoses may result in delayed or erroneous treatment potentially increasing adverse outcomes.[3,4] Procalcitonin (PCT) expression in parenchymal tissue is induced by bacterial infection. PCT is a diagnostic marker of severe bacterial infections. While PCT release is not organ specific, concentrations have been successfully used to diagnose and guide antibiotic therapy (initiation and cessation) in lower respiratory tract infections, pneumonia, and sepsis.[5,6] However, PCT has never been extensively studied for its ability to identify pneumonia or bacterial infection in the setting of AHF. We hypothesized that in patients presenting with a chief compliant of shortness of breath, PCT can significantly enhance the clinician's ability to diagnose pneumonia, whether occurring in isolation, or in the setting of AHF or of AECOPD. We also evaluated the association between PCT concentration, antibiotic treatment, and outcome in patients with a primary diagnosis of AHF, reasoning that overlapping symptoms of cough, shortness of breath, and abnormal chest imaging make this group uniquely challenging for clinicians with regards to the diagnosis of superimposed pneumonia, possibly leading to inappropriate antibiotic utilization.

Methods

The BACH (Biomarkers in Acute Heart Failure) trial was a prospective, 15-centre international study of 1641 patients presenting to the emergency department (ED) with a chief complaint of dyspnoea. All sites received local Institutional Review Board approval. The primary results have been reported elsewhere.[7]

Study population

A total of 1641 patients reporting shortness of breath upon presentation to the ED were enrolled from March 2007 to February 2008. Patients were excluded if they were under 18 years of age, unable to provide consent, had an acute ST-elevation myocardial infarction, were receiving haemodialysis, or had renal failure. The emergency physicians (EPs), blinded to the results of the investigational markers, assessed the patients enrolled in the study for the diagnosis of AHF or pneumonia using two separate visual analogue scales (VASs) and assigned a value of 0–100% clinical diagnostic certainty.

Confirmation of diagnosis

The gold standards for the diagnoses were determined by two cardiologists who independently reviewed all medical records and classified the likely diagnosis as heart failure (HF), pneumonia, a combination of both, or another diagnosis. Both were blinded to the other's assessments, investigational markers, and the EP's diagnosis. In the event of disagreement that could not be settled, a third adjudicator was used. In cases of suspected pneumonia, diagnosed using modified criteria from Fine *et al.* and Leroy *et al.*,[8,9] a single pulmonologist, blinded only to biomarker values, reviewed each case. All cases of pneumonia were required to have a new infiltrate on chest imaging in combination with microbiological proof of infection, or more than one of the major criteria. In cases of equivocal chest imaging (interstitial pattern, effusions), at least two major criteria were necessary. Community-acquired and healthcare-associated pneumonias were both recorded as pneumonia.

Biomarker assessment

Procalcitonin and other biomarkers were quantified with an automated sandwich immunoassay using TRACE technology described previously.[7] The PCT-sensitive KRYPTOR assay has a detection limit of 0.02 ng/mL and a functional assay sensitivity of 0.06 ng/mL. The inter-assay coefficient of variation for concentrations >0.3 ng/mL is $<6\%$. Samples were processed by personnel blinded from any patient data. White blood cell count (WBC) and C-reactive protein, if measured as part of the clinician's usual diagnostic workup, were potentially known to the clinician at the time of VAS determination.

Statistical analysis

Values are expressed as means and standard deviations, medians and interquartile ranges (IQR), or counts and percentages, as appropriate. Patients with and without pneumonia were compared with independent samples *t*-tests or Fisher's exact tests, as appropriate. Variables were log-transformed if appropriate.

Logistic regression was used to evaluate PCT for the diagnosis of pneumonia, for both uni- and multivariable analysis. To demonstrate independence from clinical variables, the added value of PCT on top of (i) a multivariable model with the seven most significant univariate variables and (ii) the physician-estimated probability of pneumonia was evaluated based on the likelihood ratio χ^2 test for nested models. The concordance index [C index or area under the curve (AUC)] is given as an effect measure for uni- and multivariable models. For multivariable models, a bootstrap-corrected version of the C index/AUC is given. For continuous variables, odds ratios (ORs) were standardized to describe the OR for a change of one IQR. The 95% confidence intervals (CIs) for risk factors and significance levels for χ^2 are given.[10] Net reclassification improvements (NRIs) were calculated for adding PCT based on categories which represent approximately the 15th and 85th percentile of the predicted probability for the model excluding PCT.[11] Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of PCT and multivariable models to compare their ability to predict pneumonia.

Cox proportional hazards regression was used to analyse the association of risk factors with survival in uni- and multivariable analyses. The C index is given as an effect measure. Survival curves plotted by the Kaplan–Meier method were used for illustration. For categorical variables, log-rank test *P*-values are given. To account for systematic differences between patients with and without antibiotic treatment, survival rates were adjusted for covariates.[10]

All analyses utilized a two-sided *P*-value of 0.05 for significance. All statistical analyses were performed using R version 2.5.1 (http://www.r-project.org) and Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Chicago, IL, USA).

Results

A total of 1641 patients were evaluated in the ED for shortness of breath, of which 6.8% (112) received a primary diagnosis of pneumonia, 34.6% (568) AHF, 12.2% (201) chronic obstructive pulmonary disease (COPD) exacerbation, 7.0% (130) asthma exacerbation, 6.5% (106) chest pain, 3.7% (61) bronchitis, 3.4% (55) arrhythmia, 2.4% (39) acute coronary syndrome, 2.3% (38) pulmonary embolism, 1.6% (27) influenza, and 18.5% (304) other diseases. A total of 155 patients (9.4%) with a primary or secondary diagnosis of pneumonia (112 as primary, and 43 as secondary) were combined. There were 407 patients (24.8%) diagnosed with an AECOPD (271 with COPD and 136 with asthma).

Patient characteristics in the pneumonia group and the non-pneumonia group are shown in *Table 1*. Patients with pneumonia were significantly more likely to have a past medical history of COPD and pneumonia, and a recent history of cough and night sweats. A past medical history of HF, coronary artery disease, myocardial infarction, and angioplasty was significantly more common in patients without pneumonia. PCT levels were obtained for 99.4% of all patients. PCT ranged from 0.02 to 349 ng/mL, with a median of 0.07 ng/mL and an IQR from 0.05 to 0.13 ng/mL. In healthy subjects, PCT plasma concentrations are typically $<$0.05 ng/mL.[12]

Procalcitonin for the diagnosis of pneumonia

Overall, 155 (9.4%) patients had a primary or secondary diagnosis of pneumonia. Twenty-nine of these had concurrent AHF and 17 had a concurrent AECOPD (13), asthma (2), or bronchitis (2). For patients with pneumonia, median PCT concentration was 0.18 ng/mL (IQR 0.07–0.58), and for patients without pneumonia PCT was 0.07 ng/mL (IQR 0.05–0.12). In total, 203 patients were on antibiotics upon entry. Their median PCT concentration was 0.08 ng/mL (IQR 0.05–0.20). A univariate logistic regression model for predicting the diagnosis of pneumonia was highly significant for PCT (χ^2 106.8, $P < 0.0001$, AUC 0.723). PCT predicted pneumonia equally well in the subgroup of patients with a history of lung disease (asthma or COPD) (AUC 0.713) and in patients presenting with an AECOPD or bronchitis (AUC 0.715), but slightly less in patients with concurrent AHF (AUC 0.641).

Multivariable analysis combining PCT values with clinical signs (*Table 2*) demonstrated that PCT contributed significantly to the prediction of pneumonia ($P < 0.0001$), adding independent information to clinical signs and increasing the AUC from 0.841 to 0.863 (χ^2 for adding PCT to the model 37.5, df = 1, $P < 0.0001$). Bootstrap-corrected AUCs were 0.834 for the model with clinical signs only and 0.857 for the model including PCT ($P < 0.0001$). Within this model, PCT was one of the strongest markers, together with temperature and recent history of cough. PCT was associated with a net reclassification improvement of 5.0% (95% CI 4.0–6.2%), based on risk categories representing approximately the 15th and 85th percentile of the predicted probability for the model including clinical signs only. Overall, the model including PCT moved 2.9% of pneumonia into a higher probability category, and 5.2% of non-pneumonia into a lower probability category.

Similarly, in a model incorporating both log-transformed PCT and physician-estimated probability, both variables contributed significantly to the prediction of pneumonia ($P < 0.0001$). PCT increased the AUC from 0.850 to 0.864 (χ^2 for adding PCT to the VAS 28.2, df = 1, $P < 0.0001$). The bootstrap-corrected AUC for the combined model including PCT was 0.863 ($P < 0.0001$), with an NRI of 5.0% (95% CI 4.0–6.2%). The model including PCT moved 2.1% of pneumonia into a higher probability category, and 5.3% of non-pneumonia into a lower probability category. *Figure 1* illustrates the predictive performance for PCT alone, the multivariable model including clinical signs, and the combined model including PCT using ROC curve analysis.

Chest X-ray was performed in 1445 patients (88%), of which 144 (10%) had definitive findings consistent with pneumonia [sensitivity and specificity 64.0% (95% CI 55.6–71.6%) and 95.7% (95% CI 94.4–96.6%), respectively]. PCT significantly added to the diagnostic value of the chest X-ray for the diagnosis of pneumonia, improving the AUC from 0.798 (chest X-ray alone) to 0.864 (chest X-ray and PCT) ($P < 0.0001$)). Importantly, PCT remained significant when the chest X-ray is included in the multivariable clinical signs model ($P < 0.0001$).

Total leucocyte count (WBC) was a moderate predictor for pneumonia, with an AUC of 0.69 (data not shown). This is consistent with findings from previous research.[13] PCT added significantly to the predictive value of WBC (added χ^2 74.5, $P < 0.0001$) indicating that PCT was better than and independent from WBC for predicting pneumonia. Adding (log-transformed) WBC to the multivariable model in *Table 2* does not affect the results (PCT remained significant, $P < 0.0001$). Due to the missing values in WBC, the available patients for the multivariable model were, however, significantly reduced.

Decreasing clinical uncertainty in difficult to diagnose pneumonia cases

At presentation, doctors were uncertain (defined as probability estimates between 21% and 80%) about the presence of pneumonia in 30% of patients ($n = 499$). In the 208 patients who presented with a PCT value $>$0.25 ng/mL, a concentration that predicts bacterial infection,[12] the EP-estimated probability of pneumonia was high ($>$80%) in only 15% of cases. The distributions of the physician probability estimates are illustrated in *Figure 2*. This figure also demonstrates how the uncertain category (labelled 'Medium') would be reduced by 82% if physician estimates were combined with a model ruling out pneumonia when PCT values were $<$0.25 ng/mL.

Procalcitonin and the decision to give antibiotics to patients presenting with acute heart failure

PCT was significantly associated with 90-day all-cause mortality for patients diagnosed with AHF ($P = 0.0024$). *Figure 3* illustrates this relationship in a Kaplan–Meier plot of PCT quintiles. Patients in the first quintile (PCT $<$ 0.05 ng/mL) had a 90-day survival rate of 92.0%, which fell to 80.5% (hazard ratio 2.6) for patients in the fifth quintile (PCT $>$ 0.21 ng/mL). One-fifth (20.8%) of these patients diagnosed with AHF were also

Table 1 Patient characteristics grouped by the presence or absence of pneumonia

Variables	*N*	Non-pneumonia (*n* = 1486)	Pneumonia (*n* = 155)	*P*-value
Demographics				
Age (years)	1641	63.5 ± 17.0	66.3 ± 15.8	0.0517
Male gender	1641	770 (51.8)	89 (57.4)	0.2049
Race	1626			0.0005
White		966 (65.6)	124 (80.5)	
Black		451 (30.6)	25 (16.2)	
Other		55 (3.7)	5 (3.2)	
Recent history				
Smoking	1593	420 (29.1)	49 (32.9)	0.3456
Wheezing	1543	430 (30.6)	38 (27.3)	0.4409
Cough	1603	811 (54.6)	137 (88.4)	<0.0001
Weight gain	1438	235 (17.9)	14 (10.9)	0.0497
Night sweats	1495	284 (20.9)	40 (29.2)	0.0294
Orthopnoea	1536	625 (44.8)	64 (45.7)	0.8587
Dyspnoea at rest	1605	719 (49.6)	76 (49.4)	1.0000
Exam variables				
Heart rate (b.p.m.)	1641	89.8 ± 23.6	101.6 ± 22.8	<0.0001
Systolic BP (mmHg)	1641	140.6 ± 30.4	133.5 ± 31.3	0.0055
Diastolic BP (mmHg)	1641	80.8 ± 18.2	74.9 ± 19.9	0.0002
BMI (kg/m^2)	1399	29.4 ± 8.9	27.0 ± 7.6	0.0034
Temperature (°C)	1576	36.70 ± 0.63	37.41 ± 1.00	<0.0001
Pulse oximetry (%)	1609	95.3 ± 5.3	93.2 ± 5.3	<0.0001
Rales	1624	452 (30.8)	72 (46.5)	0.0001
S3	1580	43 (3)	1 (0.7)	0.1175
Murmur	1604	226 (15.5)	28 (18.7)	0.3467
Elevated JVP	1539	256 (18.4)	15 (10.1)	0.0121
Oedema	1615	548 (37.5)	40 (26.1)	0.0060
Ascites	1579	38 (2.7)	3 (2)	0.7917
Wheezing	1619	397 (27.1)	55 (35.5)	0.0304
History variables				
Arrhythmia	1555	365 (25.9)	40 (27.2)	0.7671
Asthma	1594	289 (20.0)	29 (19.2)	0.9148
CRI	1584	222 (15.5)	24 (16.2)	0.8117
HF	1597	531 (36.7)	38 (25.5)	0.0069
CAD	1587	469 (32.6)	34 (23)	0.0159
COPD	1594	409 (28.4)	62 (40.8)	0.002
DM	1621	427 (29.1)	35 (22.7)	0.1104
Hyperlipidaemia	1549	529 (37.5)	41 (29.5)	0.0654
Hypertension	1614	987 (67.5)	93 (61.6)	0.1470
MI	1584	282 (19.7)	18 (11.9)	0.0214
Pneumonia	1536	196 (13.2)	64 (41.3)	0.0005
Pulmonary embolism	1604	75 (5.2)	10 (6.5)	0.4482
CABG	1615	141 (9.7)	17 (11.0)	0.5687
Angioplasty/stent	1602	194 (13.4)	10 (6.6)	0.0147
Stroke/CVA	1608	151 (10.4)	14 (9.0)	0.6774
Pacemaker/ICD	1616	144 (9.9)	18 (11.6)	0.4820
Prosthetic valve	1612	37 (2.5)	6 (3.9)	0.2935
Outpatient medications (known)				
Asprin	1616	526 (36.0)	48 (31.4)	0.2870
Clopidogrel	1617	124 (8.5)	7 (4.6)	0.1175
Warfarin	1615	232 (15.9)	25 (16.3)	0.9075

Continued

Table 1 *Continued*

Variables	N	Non-pneumonia (n = 1486)	Pneumonia (n = 155)	P-value
Beta-blockers	1613	580 (39.7)	47 (31.1)	0.0436
ACE inhibitors or ARBs	1616	622 (42.5)	58 (37.9)	0.3019
Calcium channel blockers	1614	329 (22.5)	40 (26.1)	0.3124
Statins	1617	485 (33.1)	32 (20.9)	0.0019
Diuretics	1618	713 (48.7)	61 (39.9)	0.0412
Digoxin	1617	111 (7.6)	9 (5.9)	0.5196
Aldosterone inhibitor	1615	139 (9.5)	10 (6.6)	0.3016
Anti-arrhythmics	1616	84 (5.7)	8 (5.3)	1.000
Nebulizer/inhaler	1613	497 (34.0)	64 (42.1)	0.0492
Steroids	1582	341 (23.8)	50 (33.3)	0.0127
Antibiotics	1614	161 (11.0)	42 (27.6)	<0.0001
Smoking cessation therapy	1577	27 (1.9)	1 (0.7)	0.5111
Other	1593	941 (65.2)	89 (59.3)	0.1523

Values are mean ± SD or *n* (%) and compared with independent samples *t*-test or Fisher exact tests, respectively.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CVA, cerebral vascular accident; DM, diabetes mellitus; HF, heart failure; ICD, implantable cardiac defibrillator; JVP, jugular venous pressure; MI, myocardial infarction.

Table 2 Prediction of pneumonia diagnoses (n = 155 events) from signs, physician-estimated probability of pneumonia (visual analogue scale), and procalcitonin concentration

Predictor	Univariable model results					Multivariable model results				
	OR	95%CI	χ^2	P-value	AUC	OR	95% CI	χ^2	P-value	AUC
Model with individual variables										
Temperature (°C)	2.2	1.9–2.5	124.1	<0.0001	0.709	1.8	1.5–2.1	45.5	<0.0001	
PCT (log, ng/mL)	1.9	1.7–2.1	106.8	<0.0001	0.723	1.6	1.4–1.9	38.7	<0.0001	
Cough (yes)	6.7	4.0–11.4	76.2	<0.0001	0.668	4.7	2.6–8.5	25.5	<0.0001	
Past pneumonia (yes)	4.7	3.3–6.7	65.0	<0.0001	0.647	3.7	2.4–5.7	34.5	<0.0001	
Heart rate (b.p.m.)	1.7	1.4–2.1	31.4	<0.0001	0.651	1.6	1.2–2.1	12.8	0.0004	
Rales (yes)	1.9	1.4–2.7	15.0	0.0001	0.578	1.5	1.0–2.3	3.3	0.0696	
Pulse oximetry (log, %)	0.9	0.8–0.9	12.2	0.0005	0.659	1.0	0.9–1.1	0.6	0.4397	
Diastolic BP (mmHg)	0.7	0.6–0.9	11.2	0.0008	0.580	0.7	0.5–0.9	7.2	0.0073	
Model with summary variable										
VAS pneumonia (%)	5.5	4.4–6.9	265.5	<0.0001	0.850	4.7	3.7–6.0	163.0	<0.0001	
PCT (log, ng/mL)	1.9	1.7–2.1	106.8	<0.0001	0.723	1.4	1.3–1.7	27.2	<0.0001	

Area under the curve (AUC) is bootstrap corrected for multivariable models.
BP, blood pressure; CI, confidence interval; OR, odds ratio; PCT, procalcitonin; VAS, visual analogue scale.

treated with antibiotics (excluding those already on antibiotics at the time of presentation), while only 5.1% (29) of those were ultimately diagnosed with pneumonia, suggesting the possibility of unnecessary antibiotic therapy. Additionally, in patients not treated with antibiotics on presentation, PCT predicted the possible need for antibiotic therapy during follow-up, representing a potential missed opportunity to treat: 33.0% of patients with PCT > with 17.3% of patients with PCT values <0.21 ng/mL ($P < 0.01$). Notably, of the 117 patients with PCT concentrations suggesting significant bacterial infection (>0.5 ng/mL), 38 (32%) did not receive antibiotic therapy. In this group, half were diagnosed with AHF, highlighting the difficulty of diagnosing superimposed bacterial infection in patients presenting with AHF.

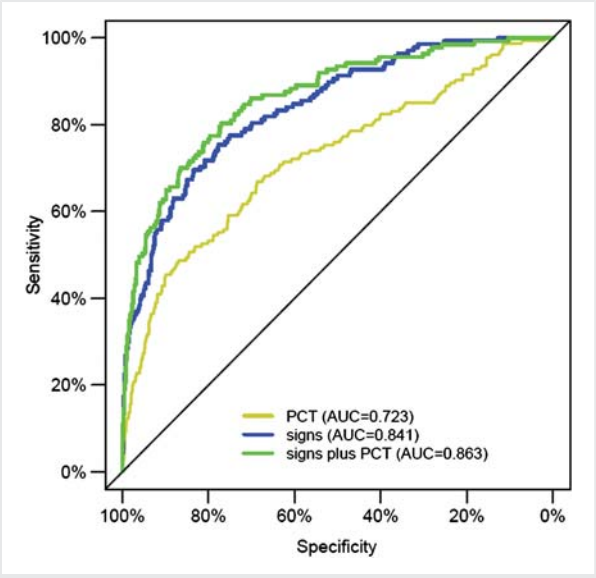

Figure 1 Receiver operating characteristic (ROC) curves for the diagnosis of pneumonia ($n = 155$ events), comparing procalcitonin (PCT), the multivariable model including clinical signs, as well as the clinical signs model plus PCT.

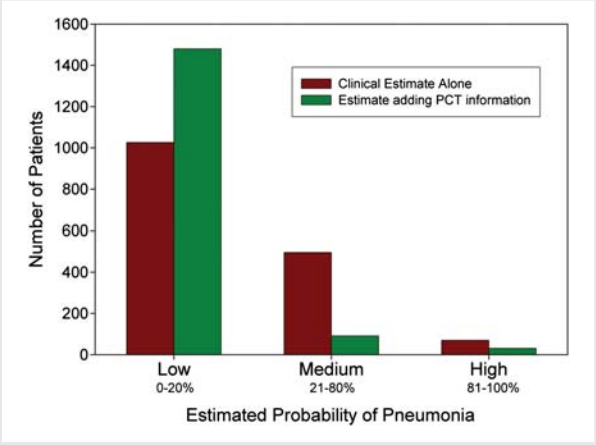

Figure 2 Distribution of patients based on physician-estimated probability of pneumonia (low, medium, and high) and how this distribution would shift if a procalcitonin (PCT) concentration of <0.25 ng/mL was adopted as a model to rule out pneumonia.

Procalcitonin, antibiotic administration, and survival in patients presenting with acute heart failure

Unadjusted data showed that patients treated with antibiotics had higher 90-day all-cause mortality than patients not treated ($P = 0.032$). After adjustment of covariates to control for group differences with respect to expected outcome, overall survival rates for AHF patients were not different whether or not they were treated with antibiotics ($P = 0.583$, *Figure 4A*). However, dividing the AHF patients into subgroups based on PCT concentration revealed survival differences between those treated or not treated with antibiotics. Patients with a PCT concentration >0.21 ng/mL had significantly worse survival if not treated with antibiotics ($P = 0.046$, *Figure 4B*). For AHF patients with PCT concentrations between 0.05 and 0.21 ng/mL, antibiotic treatment did not affect survival ($P = 0.36$, *Figure 4C*). AHF patients with low PCT values (<0.05 ng/mL, *Figure 4D*) had an increased mortality if they were treated with antibiotics ($P = 0.049$).

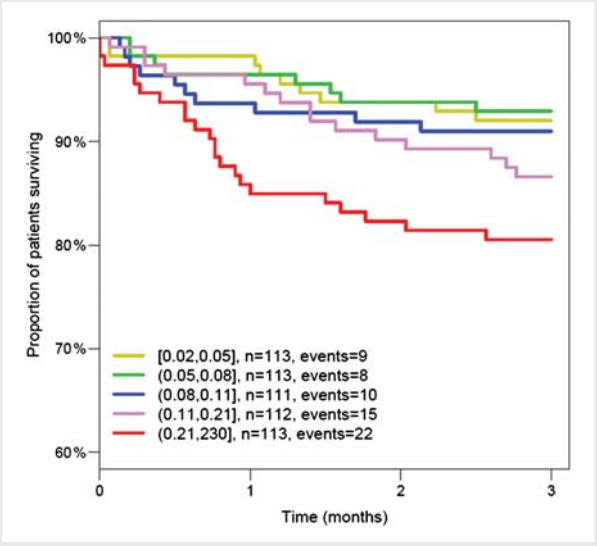

Figure 3 Kaplan–Meier plot of procalcitonin (PCT) quintiles for patients diagnosed with acute heart failure (AHF). PCT was significantly associated with 90-day all-cause mortality for patients diagnosed with AHF (Cox regression, χ^2 9.2, $P = 0.0024$).

The utility of procalcitonin combined with mid-regional pro atrial natriuretic peptide in the differential diagnosis of dyspneoa

Figure 5 illustrates schematically how the combination of mid-regional pro atrial natriuretic peptide (MR-proANP) [or brain natriuretic peptide (BNP)] and PCT can be used to diagnose acutely dyspnoeic patients with AHF and/or pneumonia: a PCT > 0.1 ng/mL together with an MR-proANP >350 pmol/L defined community-acquired pneumonia occurring with concomitant AHF; a PCT > 0.1 ng/mL with an MR-proANP <100 pmol/L defined community-acquired pneumonia alone, while an MR-proANP >350 pmol/L and a PCT <0.1 ng/mL defined HF alone. A similar algorithm can be deduced for BNP. The median and IQR for PCT and MR-proANP values in the four subgroups are listed in the legend of *Figure 5*.

Discussion

Differentiating the diagnosis of pneumonia from that of HF can be difficult, and disastrous consequences may occur from a mistake.[3,4] Moreover, detecting superimposed pneumonia in patients

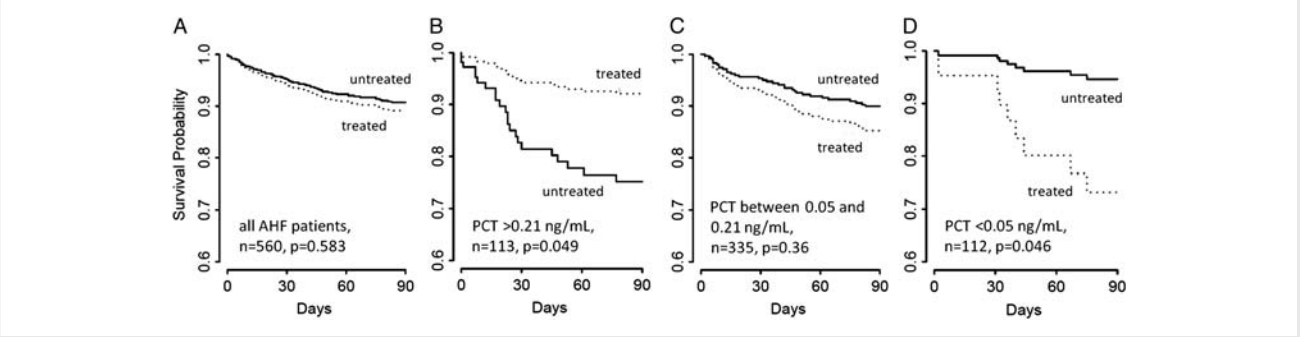

Figure 4 Kaplan–Meier plot for antibiotic treatment and all-cause mortality within 90 days for patients with acute heart failure (*A*; all AHF patients) and subgrouped by procalcitonin (PCT) quintiles: PCT > 0.21 ng/mL (*B*; highest quintile, $P = 0.049$), between 0.05 and 0.21 (*C*; $P = 0.36$, summarizing quintiles 2–4), and <0.05 ng/mL (*D*; lowest quintile, $P = 0.046$). Survival rate is adjusted for covariates; see Methods.

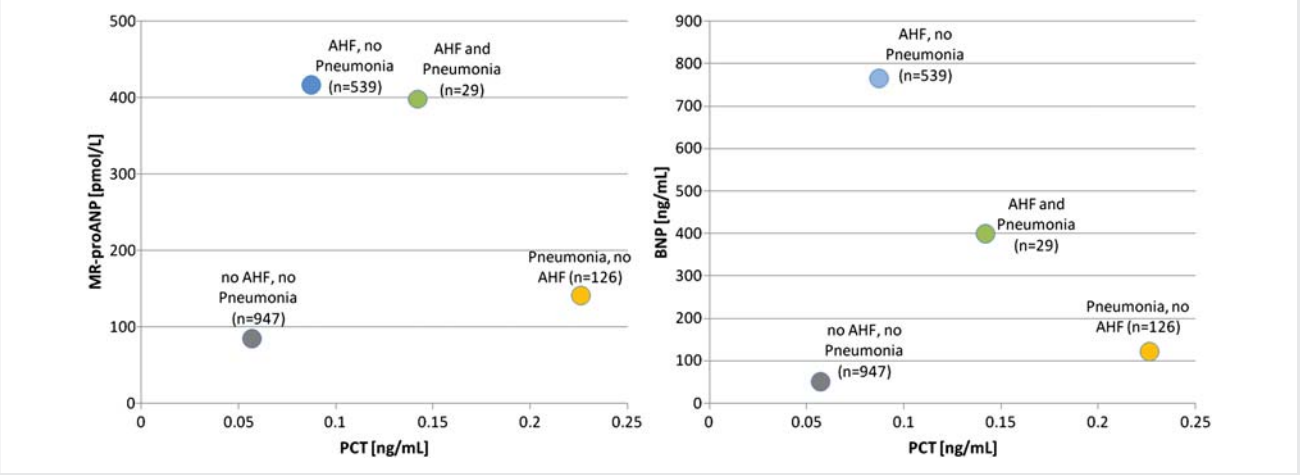

Figure 5 Median procalcitonin (PCT) and mid-regional pro atrial natriuretic peptide (MR-proANP) concentrations (left), as well as median PCT and brain natriuretic peptide (BNP) concentrations (right) for patients with acute heart failure (AHF) alone, pneumonia alone, AHF and pneumonia, and those without either condition. The median and interquartile range (IQR) for PCT (in ng/mL) in the four subgroups were as follows: no AHF, no pneumonia 0.06 (0.04–0.09); pneumonia, no AHF 0.23 (0.07–0.92); AHF, no pneumonia 0.09 (0.06–0.16); and AHF and pneumonia 0.14 (0.09–0.26). For MR-proANP (in pmol/L): no AHF, no pneumonia 84 (47–183); pneumonia, no AHF 141 (62–240); AHF, no pneumonia 417 (277–620); and AHF and pneumonia 398 (279–635). For BNP (in ng/mL): no AHF, no pneumonia 50 (20–166); pneumonia, no AHF 122 (37–292); AHF, no pneumonia 766 (409–1461); and AHF and pneumonia 400 (210–857).

presenting with AHF is additionally difficult because of the similar and therefore non-specific physical exam and chest X-ray abnormalities. This can also lead to great morbidity and mortality.[3,4] This study serves to highlight the difficulty clinicians face in diagnosing pneumonia in patients presenting with AHF.

In HF patients it is obviously important to identify those with the highest risk in order to improve outcome. Superimposed pulmonary disease has been shown to lead to increased morbidity and mortality in HF patients. Iverson and colleagues[14] have shown a clear link between lung function and outcome in HF patients by demonstrating the prognostic importance of spirometric variables, in addition to known risk factors, including self-reported COPD. These authors posit the knowledge that patients who have COPD may reduce the risk of overdosing diuretics due to misinterpretation of the primary underlying cause of dyspnoea. A similar argument can be made for those with pneumonia in our study.

Our results suggest that PCT provides additive diagnostic information in patients presenting with shortness of breath; models using PCT were robust when clinical uncertainty existed. Furthermore, our data speak to the potential utility of PCT in predicting clinical benefit from antibiotic treatment. Patients with a PCT concentration >0.21 ng/mL had significantly worse survival if not treated with antibiotics, and those with PCT values <0.05 ng/mL had an increased mortality if they were treated with antibiotics, suggesting that the risks of antibiotic administration may outweigh the benefits in this group. Taken together, these data suggest that the incorporation of PCT into the decision

to administer antibiotic therapy to patients presenting with AHF may impact survival.

Our data also demonstrate that combining PCT with MR-proANP, which was reported in this population to aid in the diagnosis of AHF,[7] holds promise for the categorization of acutely dyspnoeic patients into three groups mandating early therapy, specifically those with either HF alone, pneumonia alone, or both in combination. *Figure 5* shows the median PCT and MR-proANP/BNP concentrations in all patients, grouped by the presence or absence of pneumonia and AHF, and underscores how multiple biomarkers may be combined to assist in the diagnosis of clinically challenging overlapping disease states. Gheorghiade *et al.* and colleagues have previously proposed that a wide range of clinical and laboratory markers be used in combination to assess and grade congestion in acute HF more optimally in order to better direct management.[15] It could be argued that improved grading strategies, making optimal use of serum biomarkers, would be equally if not more important in the acute management of the undifferentiated dyspnoea that presents to EDs.

Limitations

There are several limitations of our study. Antibiotic treatment was neither randomized nor standardized in terms of type and dosage, and the analysis was post-hoc and not pre-specified. C-reactive protein measurements, which are frequently used in the differential diagnosis of HF vs. pneumonia, were not included in the analysis. Due to the lack of randomization, it is probable that sicker patients were also more likely to receive antibiotics, which probably explains the observed difference in risk of death. The number of patients ultimately diagnosed with both pneumonia and AHF was low, possibly reflecting our broad inclusion criteria of undifferentiated dyspnoea, consistent with the primary endpoint of the trial. This might also reflect a pre-selection bias of the on-site cardiologist responsible for making the initial assessment and therefore some cases of pneumonia might have escaped detection. This may also explain the slightly worse diagnostic performance in patients with concurrent AHF.

Hence our conclusions are exploratory and need validation in a randomized controlled trial. The rationale for carrying out this analysis in the large BACH dyspnoea trial was to evaluate whether PCT could aid in the decision to initiate antibiotics in patients with a primary diagnosis of AHF, where pneumonia occurs as a relevant but possibly less apparent co-morbidity. If this is proven, a logical next phase might then be a study treating according to biomarker stratification.

Another potential limitation is that the confirmation of diagnosis was performed by two independent cardiologists who made the final diagnosis. This method of diagnosis has the potential for bias of underreporting when two specialists from the same discipline are making the final diagnosis.

Clinical implications

This study extends the knowledge from previous work evaluating the clinical utility of PCT in the diagnosis and management of patients with suspected community-acquired pneumonia in the setting where AHF is also a possibility. There is a strong likelihood that PCT levels will help guide diagnostic therapeutic decisions with antibiotics. This needs to be tested in a large randomized interventional trial.

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